

VGFT-OD-0706 Week 24 Topline Results

Title: A Double-Masked, Randomized, Controlled Study of the Safety, Tolerability and Biological Effect of Repeated Intravitreal Administration of VEGF Trap-Eye in Patients with Diabetic Macular Edema (DME)

Protocol: VGFT-OD-0706.03; March 20, 2009

Study Drug: VEGF Trap-Eye

Sponsor: Regeneron Pharmaceuticals, Inc.

Statistician: Ke Yang, Ph.D.

Study Director: Alyson Berliner, M.D., Ph.D.

Clinical Monitor: Lisa Miglietta

Date: February 1, 2010

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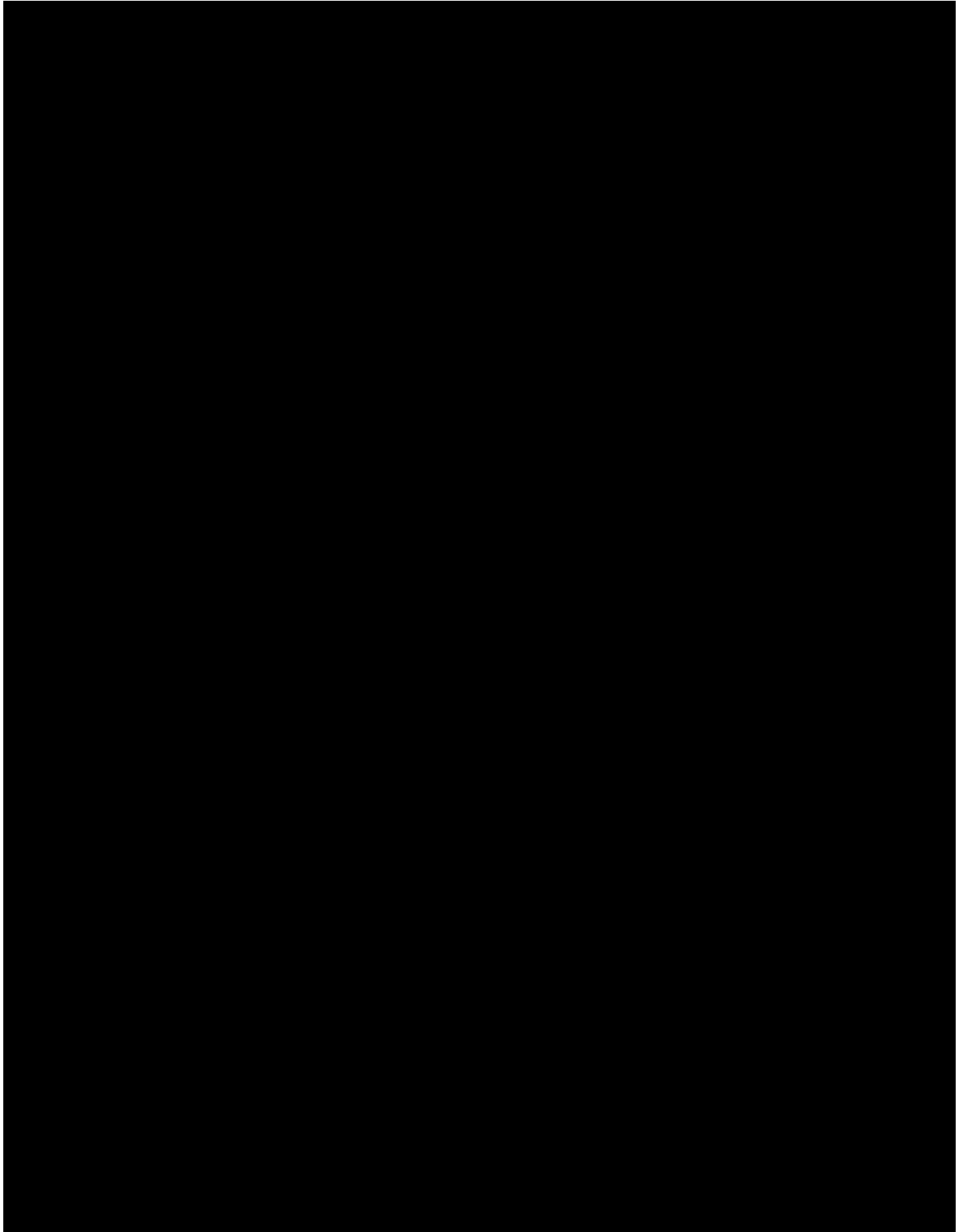
Document's type	Document Reference	Effective Date	Page
Standard	BDM-STD-ST5-1.0	December 15, 2008	2/33

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1. OVERVIEW

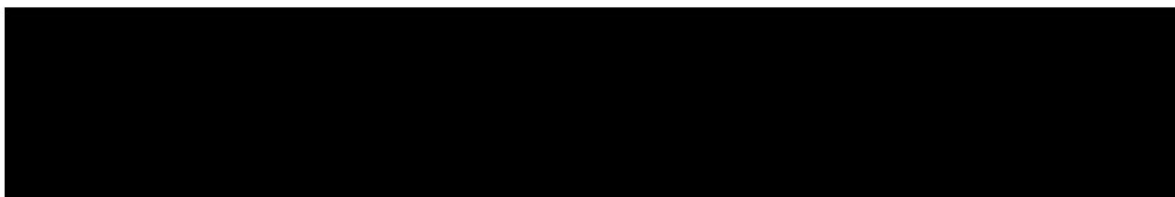
The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of the study prior to the database lock. The SAP is intended to be a comprehensive and detailed description of strategy and statistical technique to be used to realize the analysis of data for VGFT-OD-0706 study.

1.1 STUDY OBJECTIVES

1.1.1 PRIMARY OBJECTIVES



1.1.2 SECONDARY OBJECTIVES



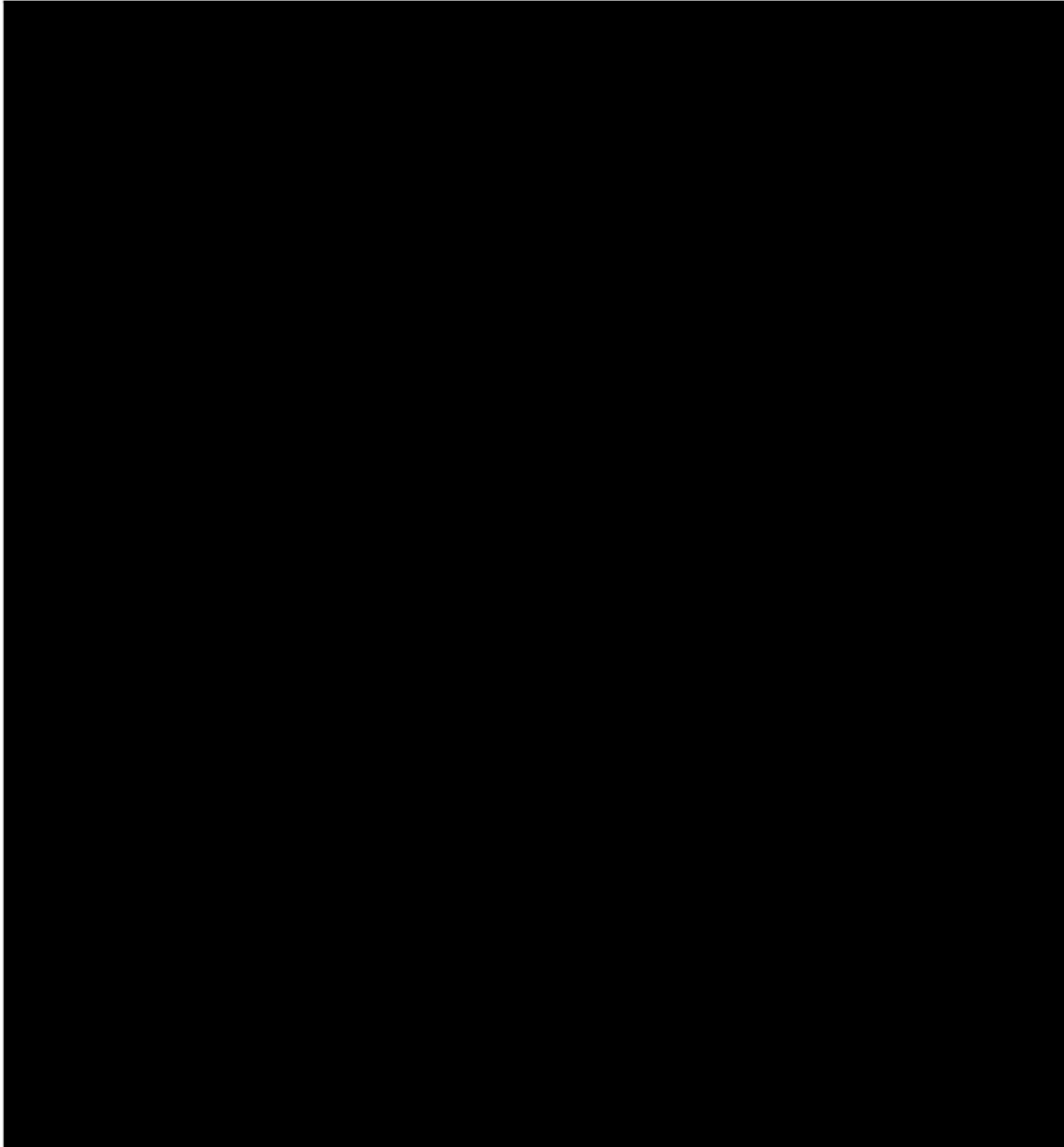
1.2 TRIAL DESIGN

VGFT-OD-0706 is a Phase 2, double-masked, randomized, multi-center clinical trial. Subjects will be randomized in a 1:1:1:1:1 ratio to one of the following treatment arms:

1. 0.5 mg VEGF Trap-Eye every 4 weeks (0.5q4) out to Week 52
2. 2.0 mg VEGF Trap-Eye every 4 weeks (2.0q4) out to Week 52
3. 2.0 mg VEGF Trap-Eye, 3 initial monthly doses, then every 8 weeks, (2.0q8) out to Week 52
4. 2.0 mg VEGF Trap-Eye, 3 initial monthly doses then PRN (2.0 PRN) as needed according to protocol re-treatment criteria out to Week 52
5. Laser photocoagulation (focal laser using modified ETDRS technique); out to Week 52; subjects in this arm will also receive sham injections every 4 weeks (approximately 2 laser treatments are expected)

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2. POPULATIONS OF ANALYSIS

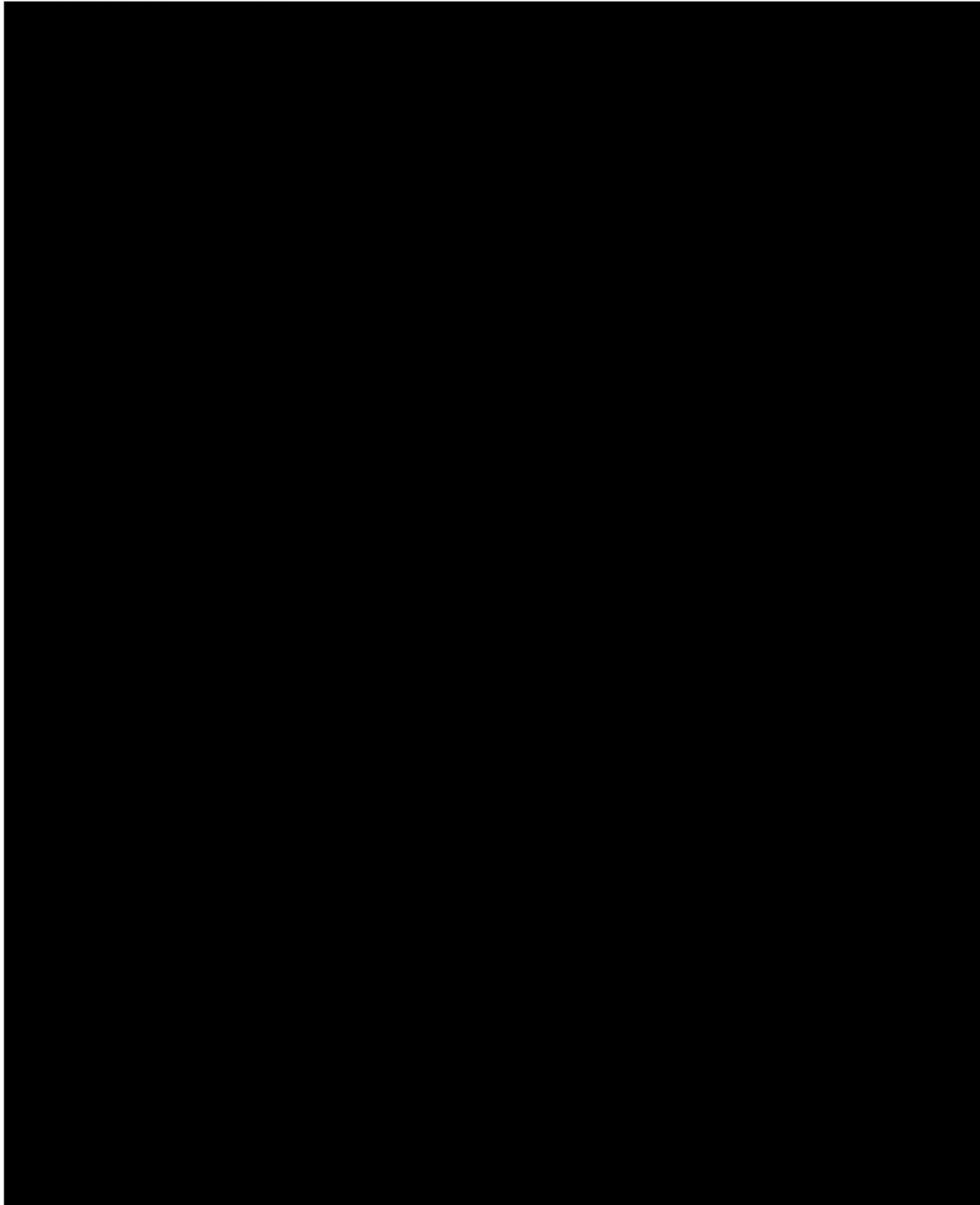
In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9

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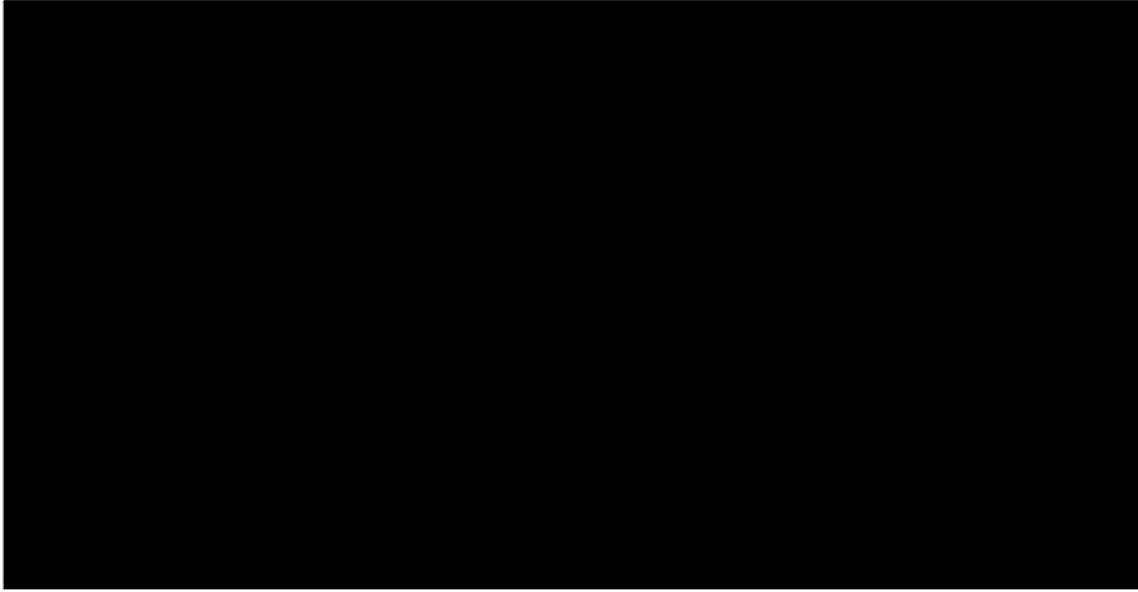
Statistical Principles for Clinical Trials (1998), the following population of analysis will be used for all statistical analysis.



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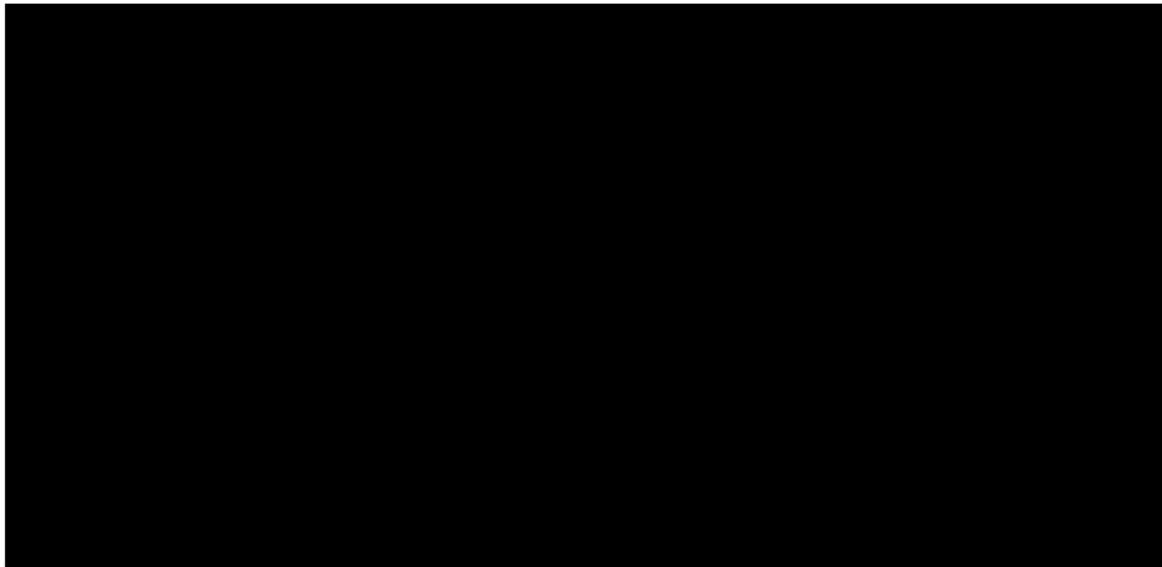
3. VARIABLES OF ANALYSIS



4. STATISTICAL METHODS

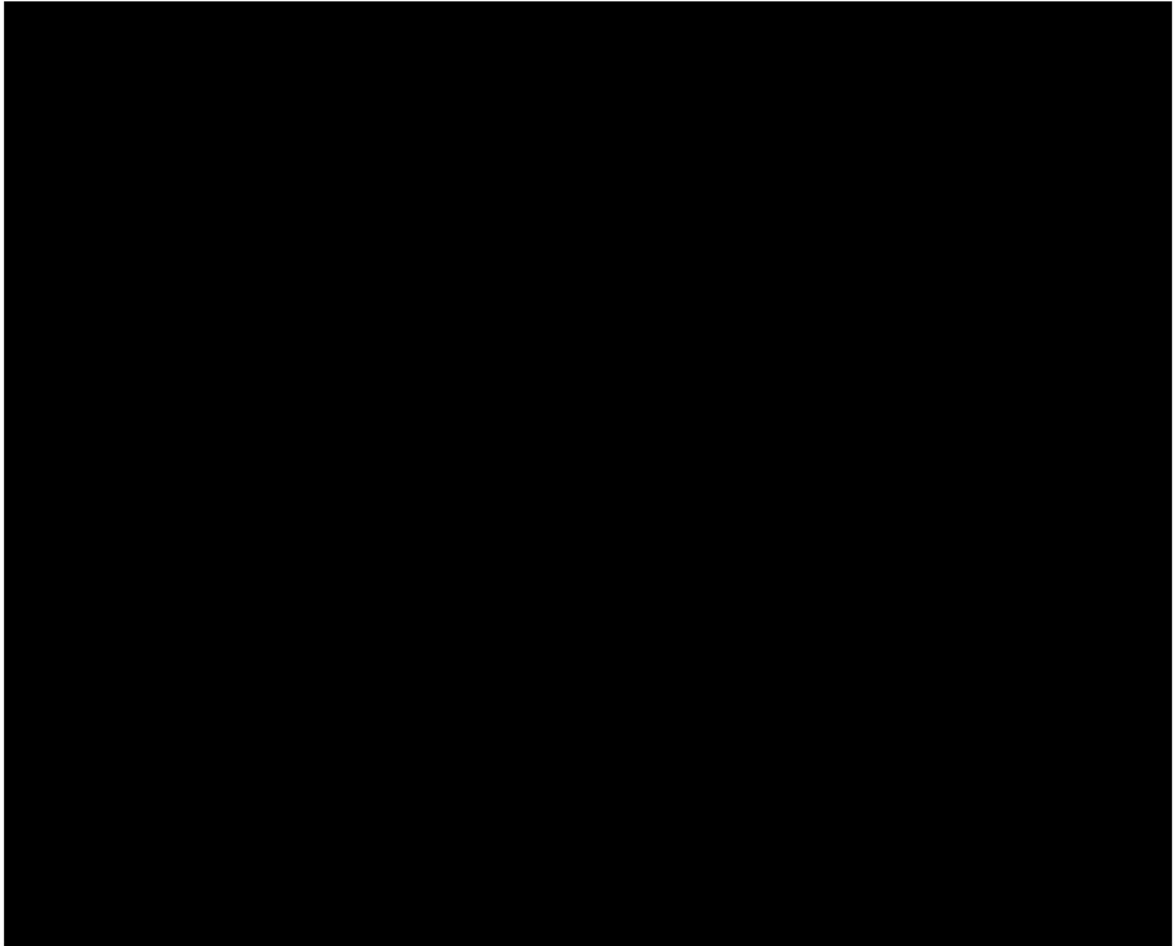
4.1 ANALYSIS OF EFFICACY DATA

4.1.1 PRIMARY EFFICACY ANALYSIS

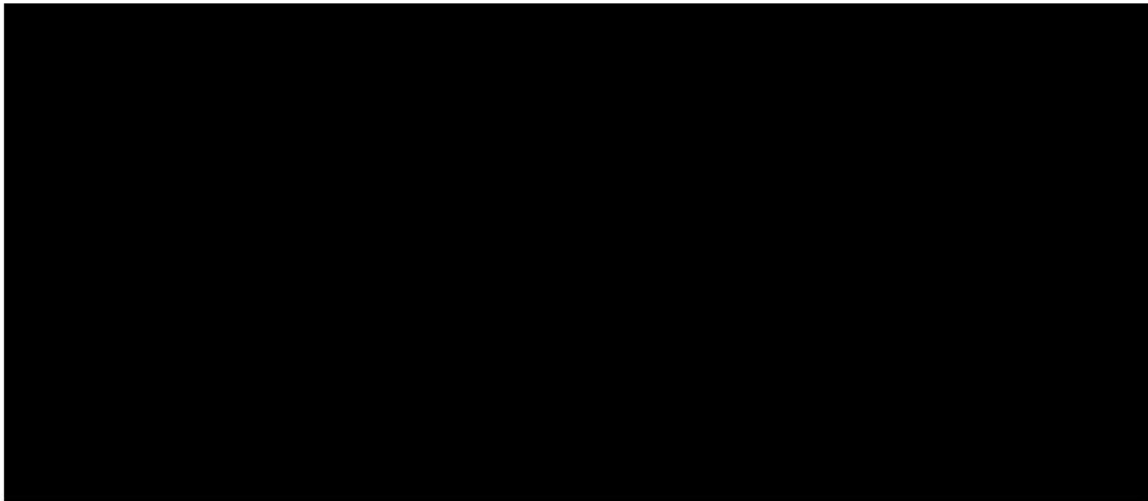


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4.1.2 SECONDARY EFFICACY ANALYSIS



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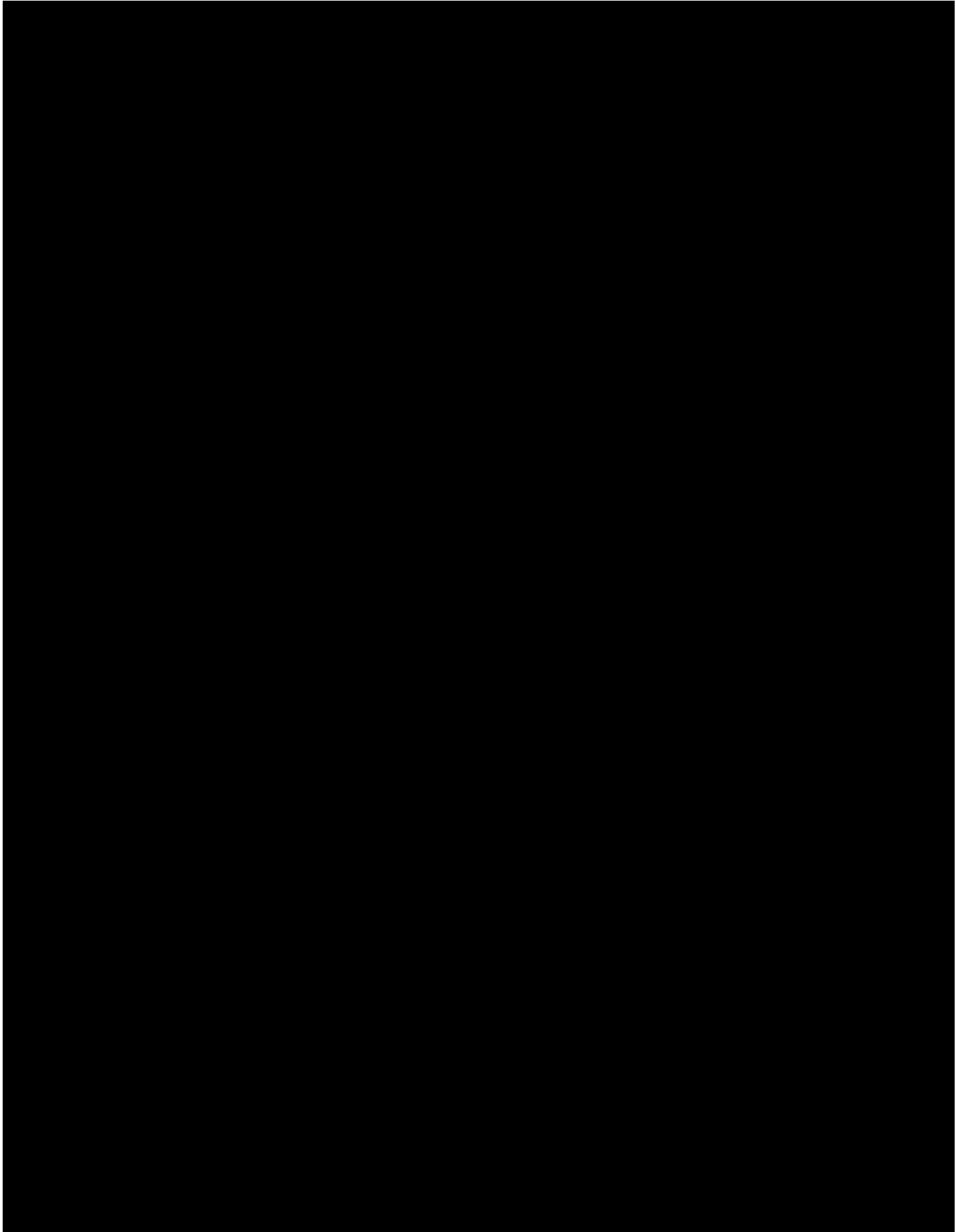
4.2 ANALYSIS OF SAFETY DATA

Safety data will be analyzed as treated on safety analysis set. Safety and tolerability of all treatments and doses will be examined.

5. DATABASE LOCK

The database up to Visit 9 (Week 24) was locked on January 26, 2010 for primary analysis.

6. RESULTS



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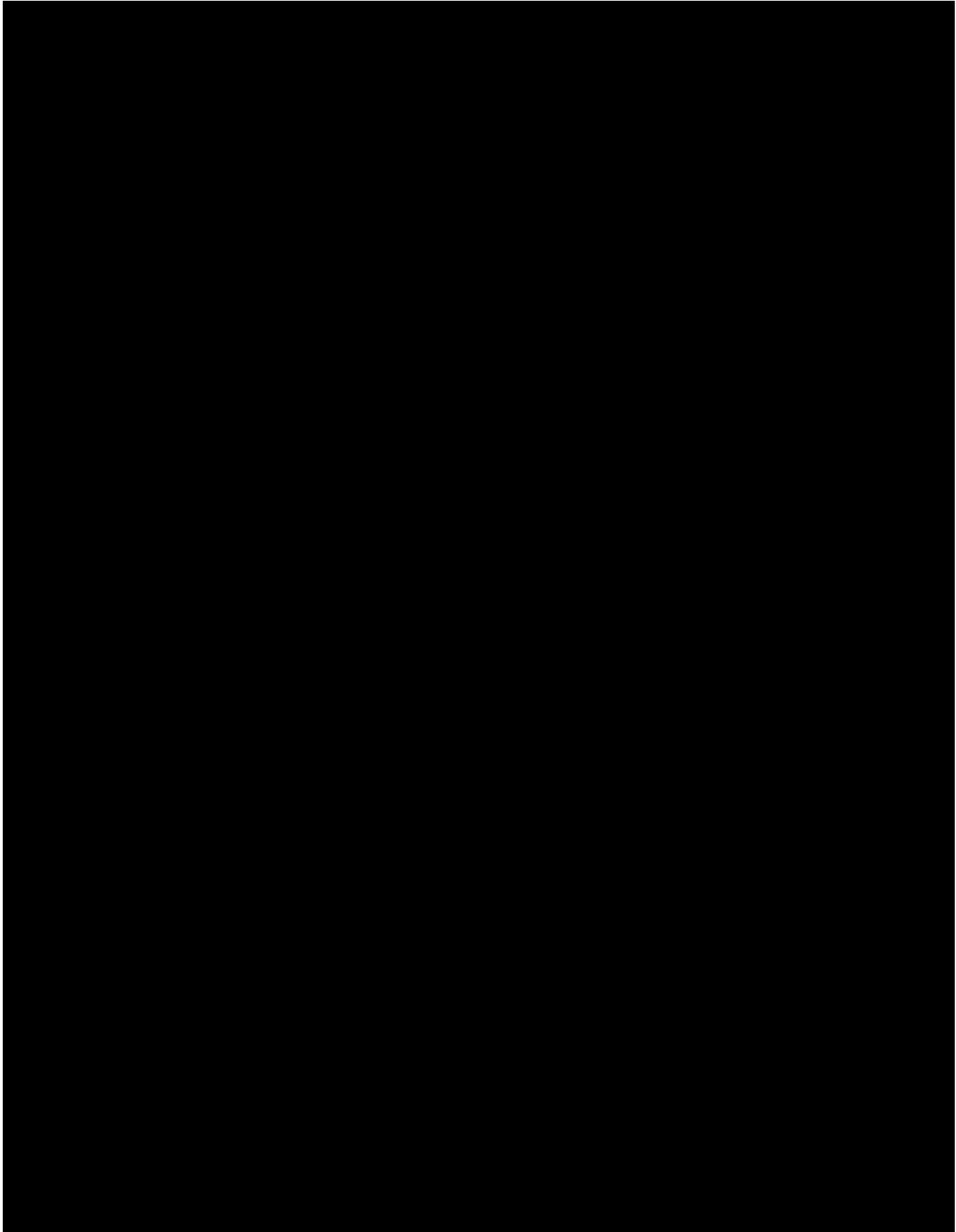
There were 221 subjects randomized, 2 of them were not treated. There were 219 subjects in full Analysis set and safety set, 189 subjects in per protocol set.

6.1.2 STUDY DISPOSITION

Table 2 Main Reason for Premature Discontinuation

	Laser (N=44)	0.5q4 (N=44)	2.0q4 (N=44)	2.0q8 (N=44)	2.0PRN (N=45)	All (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%)	39 (88.6%)	41 (91.1%)	201 (91.0%)
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	1 (2.3%)	0	2 (0.9%)
Death	0	1 (2.3%)	1 (2.3%)	1 (2.3%)	0	3 (1.4%)
Subject Lost To Follow-Up	0	1 (2.3%)	1 (2.3%)	2 (4.5%)	2 (4.4%)	6 (2.7%)
Termination Of Study By Sponsor	0	0	0	0	0	0
Treatment Failure	2 (4.5%)	0	0	0	0	2 (0.9%)
Other	0	0	0	0	0	0

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6.1.4 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Table 4 Demographics

	Laser (N=44)	0.5q4 (N=44)	2.0q4 (N=44)	2.0q8 (N=42)	2.0PRN (N=45)	ALL (N=219)
Sex						
n	44	44	44	42	45	219
Male	27 (61.4%)	24 (54.5%)	27 (61.4%)	22 (52.4%)	29 (64.4%)	129 (58.9%)
Female	17 (38.6%)	20 (45.5%)	17 (38.6%)	20 (47.6%)	16 (35.6%)	90 (41.1%)
Race						
n	44	44	44	42	45	219
White	38 (86.4%)	41 (93.2%)	41 (93.2%)	36 (85.7%)	41 (91.1%)	197 (90.0%)
Black	4 (9.1%)	3 (6.8%)	1 (2.3%)	2 (4.8%)	1 (2.2%)	11 (5.0%)
Asian	1 (2.3%)	0	0	1 (2.4%)	2 (4.4%)	4 (1.8%)
Native Hawaiian or Other Pacific Islander	1 (2.3%)	0	0	0	0	1 (0.5%)
Other	0	0	2 (4.5%)	1 (2.4%)	1 (2.2%)	4 (1.8%)
Multi-Racial	0	0	0	2 (4.8%)	0	2 (0.9%)
Ethnicity						
n	44	44	44	42	45	219
Hispanic or Latino	8 (18.2%)	13 (29.5%)	16 (36.4%)	5 (11.9%)	14 (31.1%)	56 (25.6%)
Not Hispanic or Latino	36 (81.8%)	31 (70.5%)	28 (63.6%)	37 (88.1%)	31 (68.9%)	163 (74.4%)
Ethnicity*Race						
Hispanic or Latino						
White	8 (18.2%)	13 (29.5%)	15 (34.1%)	3 (7.1%)	13 (28.9%)	52 (23.7%)
Other	0	0	1 (2.3%)	0	1 (2.2%)	2 (0.9%)

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	Laser (N=44)	0.5q4 (N=44)	2.0q4 (N=44)	2.0q8 (N=42)	2.0PRN (N=45)	ALL (N=219)
Multi-Racial	0	0	0	2 (4.8%)	0	2 (0.9%)
Not Hispanic or Latino						
White	30 (68.2%)	28 (63.6%)	26 (59.1%)	33 (78.6%)	28 (62.2%)	145 (66.2%)
Black	4 (9.1%)	3 (6.8%)	1 (2.3%)	2 (4.8%)	1 (2.2%)	11 (5.0%)
Asian	1 (2.3%)	0	0	1 (2.4%)	2 (4.4%)	4 (1.8%)
Native Hawaiian or Other Pacific Islander	1 (2.3%)	0	0	0	0	1 (0.5%)
Other	0	0	1 (2.3%)	1 (2.4%)	0	2 (0.9%)
Age (year)						
n	44	44	44	42	45	219
Mean (SD)	64.0 (8.12)	62.3 (10.70)	62.1 (10.50)	62.5 (11.49)	60.7 (8.66)	62.3 (9.92)
Median	63.5	63.5	62.0	64.0	61.0	63.0
(Min: Max)	(48: 78)	(37: 87)	(34: 87)	(29: 82)	(40: 84)	(29: 87)
Height (cm)						
n	44	43	44	42	45	218
Mean (SD)	168.25 (10.72)	166.40 (10.72)	167.97 (10.46)	167.78 (10.57)	169.66 (10.39)	168.03 (10.53)
Median	170.18	166.37	167.64	166.37	167.64	167.64
(Min: Max)	(145.5: 188.0)	(142.2: 184.0)	(145.0: 188.0)	(149.0: 188.0)	(153.7: 200.7)	(142.2: 200.7)

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Table 5 Baseline Characteristics

	Laser (N=44)	0.5q4 (N=44)	2.0q4 (N=44)	2.0q8 (N=42)	2.0PRN (N=45)	All (N=219)
Prior Treatment						
Anti-VEGF	10 (22.7%)	5 (11.4%)	10 (22.7%)	6 (14.3%)	6 (13.3%)	37 (16.9%)
Laser	22 (50.0%)	21 (47.7%)	23 (52.3%)	28 (66.7%)	26 (57.8%)	120 (54.8%)
Pan Retinal Photocoagulation	4 (9.1%)	4 (9.1%)	3 (6.8%)	9 (21.4%)	2 (4.4%)	22 (10.0%)
Steroids	12 (27.3%)	8 (18.2%)	7 (15.9%)	10 (23.8%)	9 (20.0%)	46 (21.0%)
Baseline ETDRS						
n	44	44	44	42	45	219
Mean (SD)	57.6 (12.47)	59.3 (11.16)	59.9 (10.07)	58.8 (12.23)	59.6 (11.06)	59.0 (11.35)

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	Laser (N=44)	0.5q4 (N=44)	2.0q4 (N=44)	2.0q8 (N=42)	2.0PRN (N=45)	All (N=219)
Baseline Central Retinal Thickness (um)						
n	44	44	44	42	45	219
Mean (SD)	440.6 (145.41)	426.1 (128.29)	456.6 (134.95)	434.8 (111.83)	426.6 (152.37)	436.9 (134.81)

Diabetic Retinopathy Severity

None	1 (2.3%)	0	3 (6.8%)	0	0	4 (1.8%)
Mild	1 (2.3%)	2 (4.5%)	4 (9.1%)	3 (7.1%)	5 (11.1%)	15 (6.8%)
Moderate	29 (65.9%)	20 (45.5%)	25 (56.8%)	21 (50.0%)	25 (55.6%)	120 (54.8%)
Severe	12 (27.3%)	20 (45.5%)	11 (25.0%)	11 (26.2%)	14 (31.1%)	68 (31.1%)
Proliferative	1 (2.3%)	2 (4.5%)	1 (2.3%)	7 (16.7%)	1 (2.2%)	12 (5.5%)
n	44	44	44	42	45	219
Mean (SD)	3.3 (0.65)	3.5 (0.66)	3.1 (0.85)	3.5 (0.86)	3.2 (0.68)	3.3 (0.76)

Diabetic Type

Type 1	6 (13.6%)	1 (2.3%)	3 (6.8%)	4 (9.5%)	2 (4.4%)	16 (7.3%)
Type 2	39 (88.6%)	43 (97.7%)	41 (93.2%)	38 (90.5%)	43 (95.6%)	204 (93.2%)



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6.2 EFFICACY

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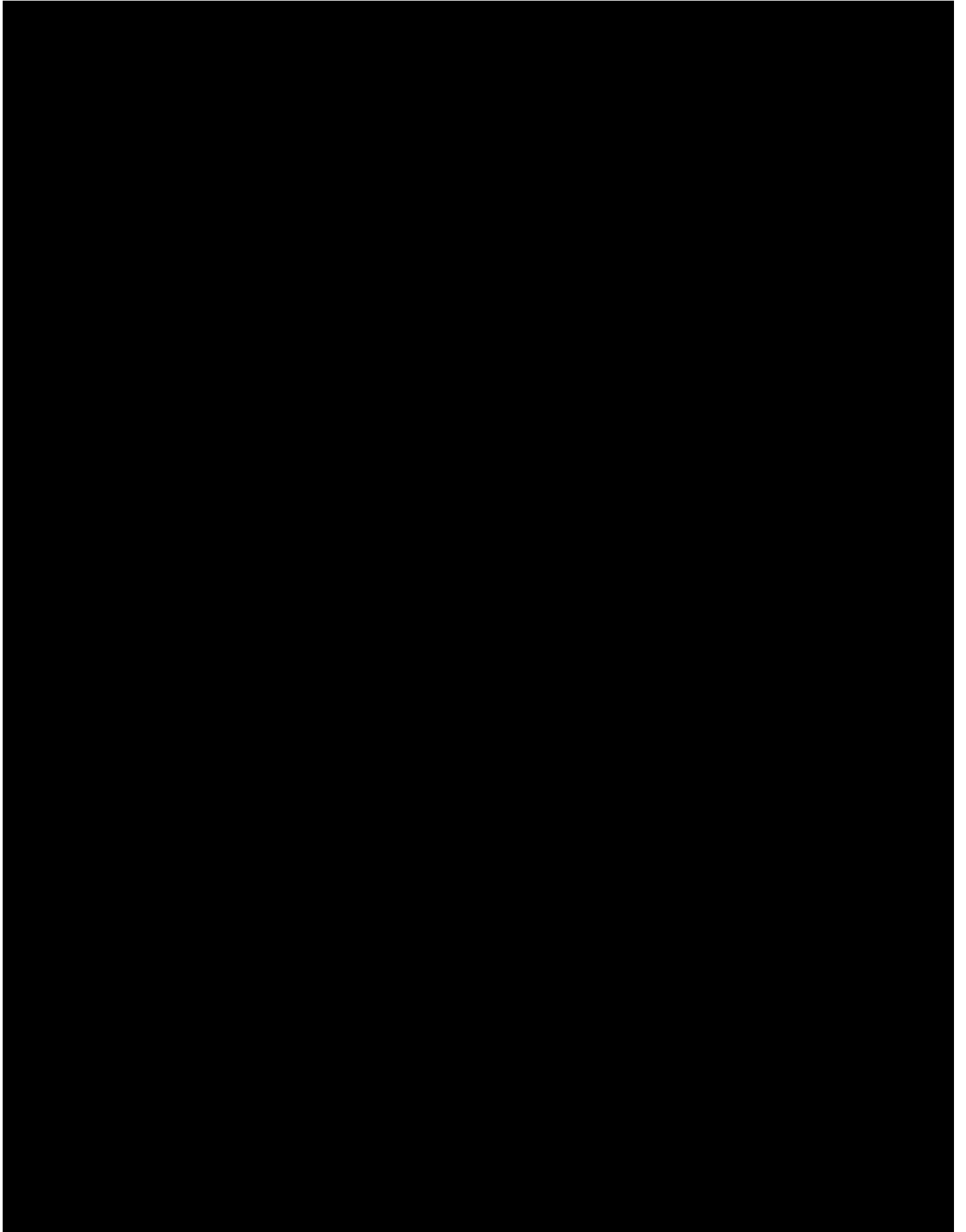
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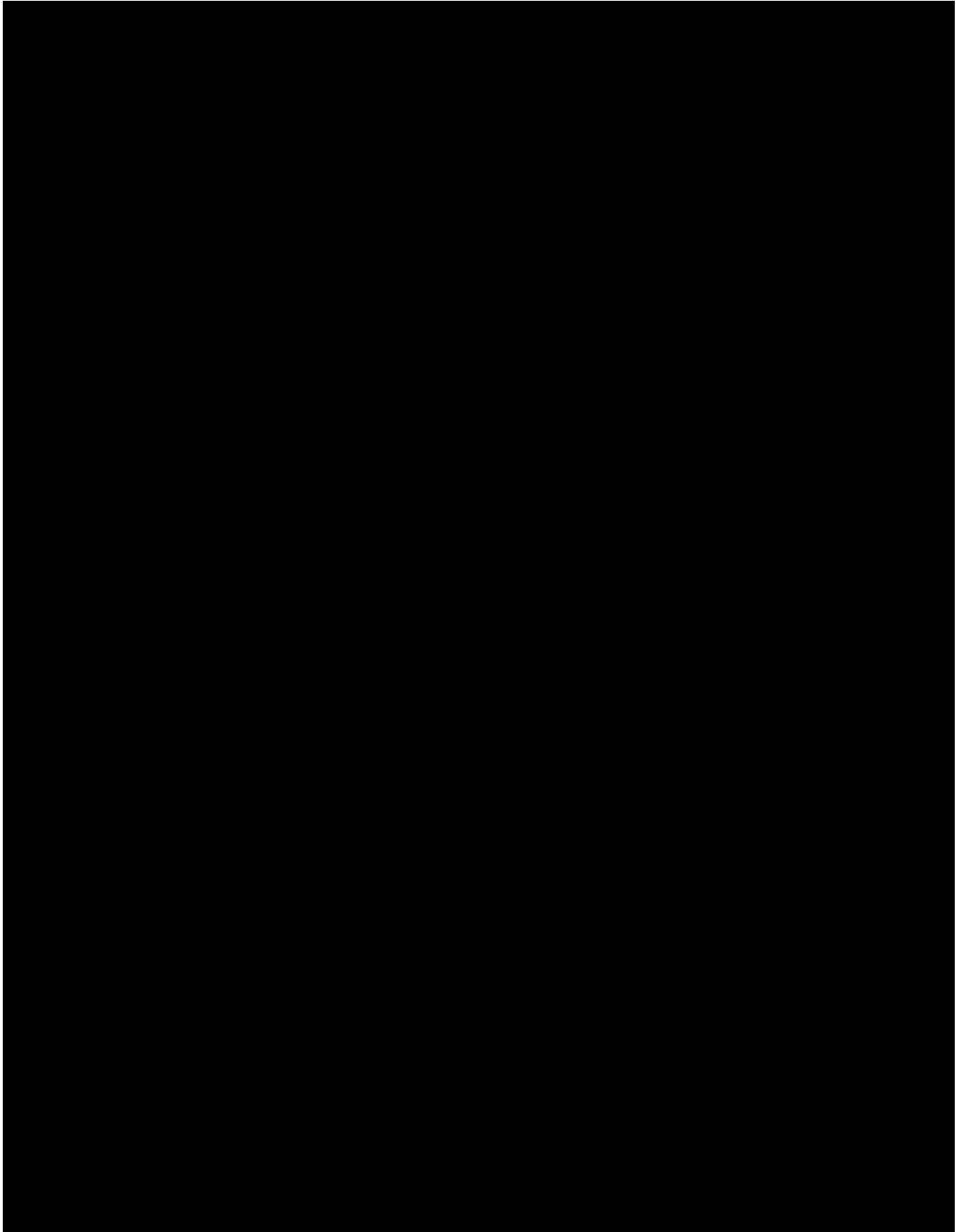
6.2.1 PRIMARY EFFICACY ENDPOINT

Table 6 Primary Analysis of Change from Baseline in BCVA at Week 24

	Laser (N=44)	0.5q4 (N=44)	2.0q4 (N=44)	2.0q8 (N=42)	2.0PRN (N=45)
Baseline					
n	44	44	44	42	45
Mean (SD)	57.6 (12.47)	59.3 (11.16)	59.9 (10.07)	58.8 (12.23)	59.6 (11.06)
Week 24					
n	44	44	44	42	45
Mean (SD)	60.1 (17.62)	67.9 (14.90)	71.3 (11.02)	67.3 (12.39)	69.9 (10.93)
Week 24 Change from Baseline					
n	44	44	44	42	45
Mean (SD)	2.5 (16.14)	8.6 (14.64)	11.4 (8.67)	8.5 (7.50)	10.3 (7.52)

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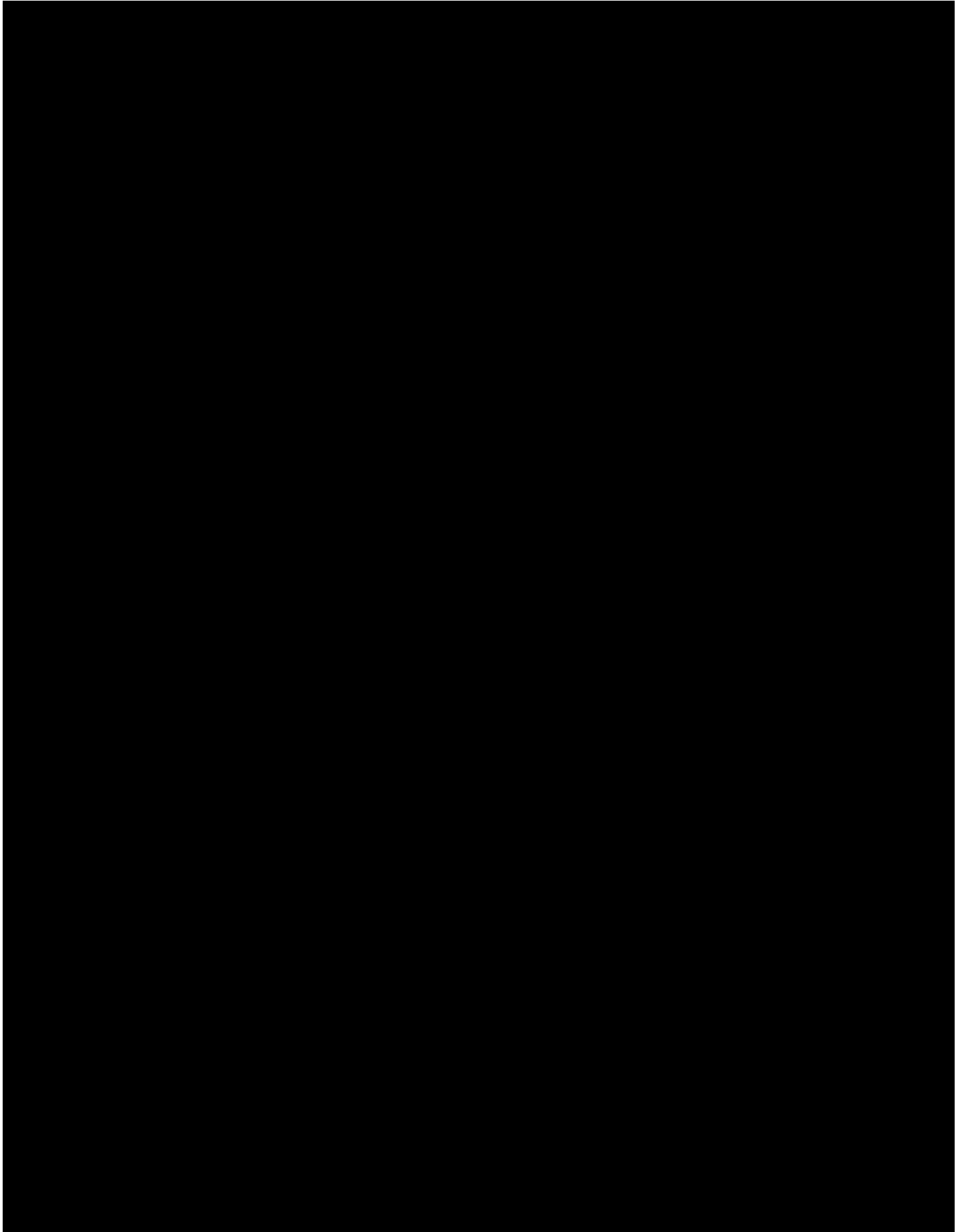
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Table 9 Analysis of Change from Baseline in Central Retinal Thickness at Week 24

Category	Laser (N=44)	0.5q4 (N=44)	2.0q4 (N=44)	2.0q8 (N=42)	2.0PRN (N=45)
Baseline					
n	44	44	44	42	45
Mean (SD)	440.6 (145.41)	426.1 (128.29)	456.6 (134.95)	434.8 (111.83)	426.6 (152.37)
Week 24					
n	43	44	43	41	44
Mean (SD)	372.0 (160.18)	281.5 (103.72)	262.2 (96.73)	306.2 (114.03)	272.5 (109.43)
Week 24 Change from Baseline					
n	43	44	43	41	44
Mean (SD)	-67.9 (135.17)	-144.6 (110.65)	-194.5 (143.04)	-127.3 (141.78)	-153.3 (132.17)

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6.3 SAFETY

6.3.1 TREATMENT EMERGENT ADVERSE EVENTS

Table 11 Summary of Ocular Treatment Emergent Adverse Events of Study Eye

System Organ Class 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)
Total number of reported such events	51	66	41	69	64	240
Number (proportion) of subjects who reported such events	21 (47.7%)	26 (59.1%)	20 (45.5%)	23 (54.8%)	19 (42.2%)	88 (50.3%)
Headache	10	12	8	12	10	42
Nausea	8	10	6	10	8	32
Dizziness	7	9	5	9	7	31
Abdominal pain	6	8	4	8	6	28
Diarrhea	5	7	3	7	5	25
Constipation	4	6	2	6	4	22
Flatulence	3	5	1	5	3	17
Indigestion	3	4	2	4	3	16
Stomach pain	3	4	2	4	3	16
Upper respiratory tract infection	2	3	1	3	2	11
Back pain	2	3	1	3	2	11
Joint pain	2	3	1	3	2	11
Extracranial bruit	2	3	1	3	2	11
Headache, tension	2	3	1	3	2	11
Headache, migraine	2	3	1	3	2	11
Headache, unspecified	2	3	1	3	2	11
Headache, stress	2	3	1	3	2	11
Headache, sinus	2	3	1	3	2	11
Headache, cervicogenic	2	3	1	3	2	11
Headache, exertion	2	3	1	3	2	11
Headache, menstrual	2	3	1	3	2	11
Headache, postural	2	3	1	3	2	11
Headache, idiopathic	2	3	1	3	2	11
Headache, chronic	2	3	1	3	2	11
Headache, episodic	2	3	1	3	2	11
Headache, tension, chronic	2	3	1	3	2	11
Headache, tension, episodic	2	3	1	3	2	11
Headache, tension, unspecified	2	3	1	3	2	11
Headache, tension, stress	2	3	1	3	2	11
Headache, tension, sinus	2	3	1	3	2	11
Headache, tension, cervicogenic	2	3	1	3	2	11
Headache, tension, exertion	2	3	1	3	2	11
Headache, tension, menstrual	2	3	1	3	2	11
Headache, tension, postural	2	3	1	3	2	11
Headache, tension, idiopathic	2	3	1	3	2	11
Headache, tension, chronic	2	3	1	3	2	11
Headache, tension, episodic	2	3	1	3	2	11
Headache, tension, unspecified	2	3	1	3	2	11
Headache, tension, stress	2	3	1	3	2	11
Headache, tension, sinus	2	3	1	3	2	11
Headache, tension, cervicogenic	2	3	1	3	2	11
Headache, tension, exertion	2	3	1	3	2	11
Headache, tension, menstrual	2	3	1	3	2	11
Headache, tension, postural	2	3	1	3	2	11
Headache, tension, idiopathic	2	3	1	3	2	11
Headache, tension, chronic	2	3	1	3	2	11
Headache, tension, episodic	2	3	1	3	2	11
Headache, tension, unspecified	2	3	1	3	2	11
Headache, tension, stress	2	3	1	3	2	11
Headache, tension, sinus	2	3	1	3	2	11
Headache, tension, cervicogenic	2	3	1	3	2	11
Headache, tension, exertion	2	3	1	3	2	11
Headache, tension, menstrual	2	3	1	3	2	11
Headache, tension, postural	2	3	1	3	2	11
Headache, tension, idiopathic	2	3	1	3	2	11
Headache, tension, chronic	2	3	1	3	2	11
Headache, tension, episodic	2	3	1	3	2	11
Headache, tension, unspecified	2	3	1	3	2	11
Headache, tension, stress	2	3	1	3	2	11
Headache, tension, sinus	2	3	1	3	2	11
Headache, tension, cervicogenic	2	3	1	3	2	11
Headache, tension, exertion	2	3	1	3	2	11
Headache, tension, menstrual	2	3	1	3	2	11
Headache, tension, postural	2	3	1	3	2	11
Headache, tension, idiopathic	2	3	1	3	2	11
Headache, tension, chronic	2	3	1	3	2	11
Headache, tension, episodic	2	3	1	3	2	11
Headache, tension, unspecified	2	3	1	3	2	11
Headache, tension, stress	2	3	1	3	2	11
Headache, tension, sinus	2	3	1	3	2	11
Headache, tension, cervicogenic	2	3	1	3	2	11

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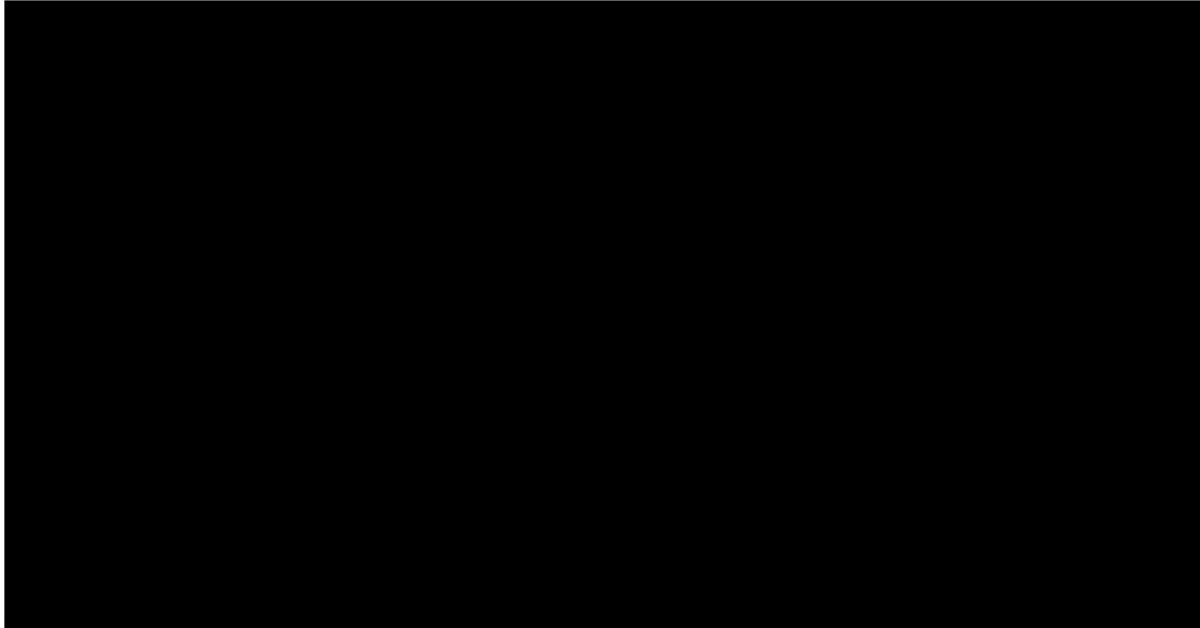
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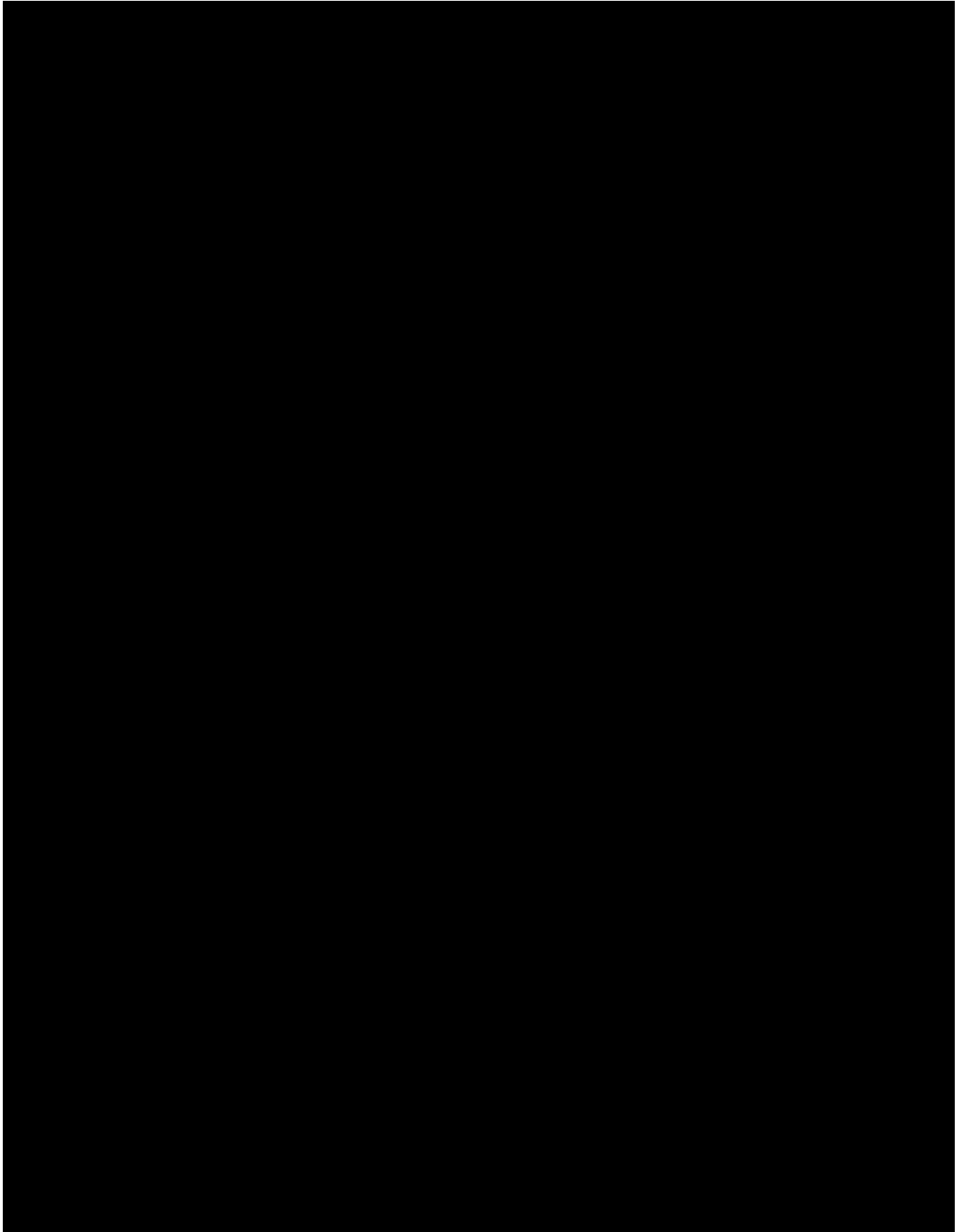
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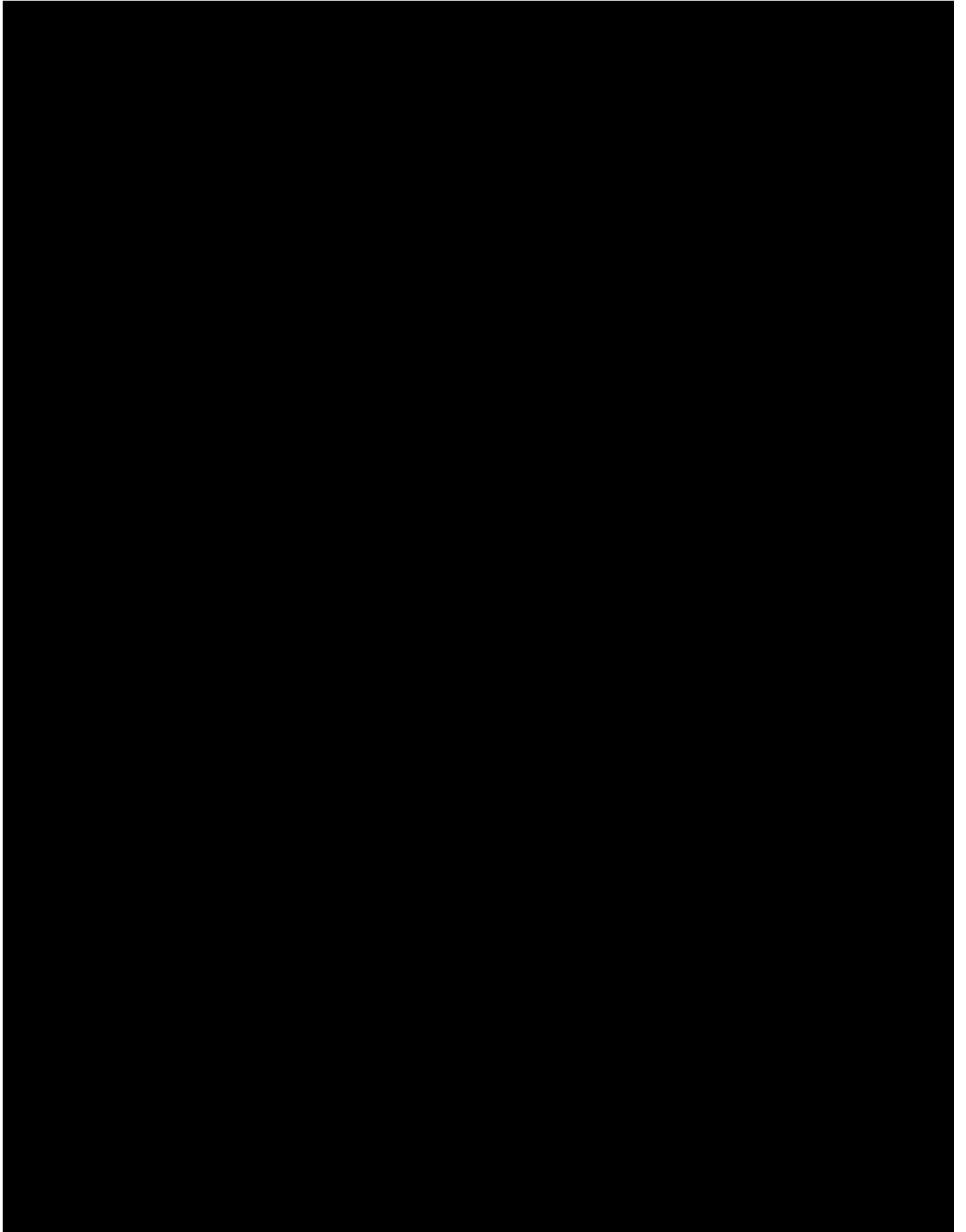
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System Organ Class Preferred Term	Laser (N=44)	0.5q4 (N=44)	2.0q4 (N=44)	2.0q8 (N=42)	2.0PRN (N=45)	All VGFT (N=175)
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CONFIDENTIAL - PROTECTIVE ORDER MATERIAL

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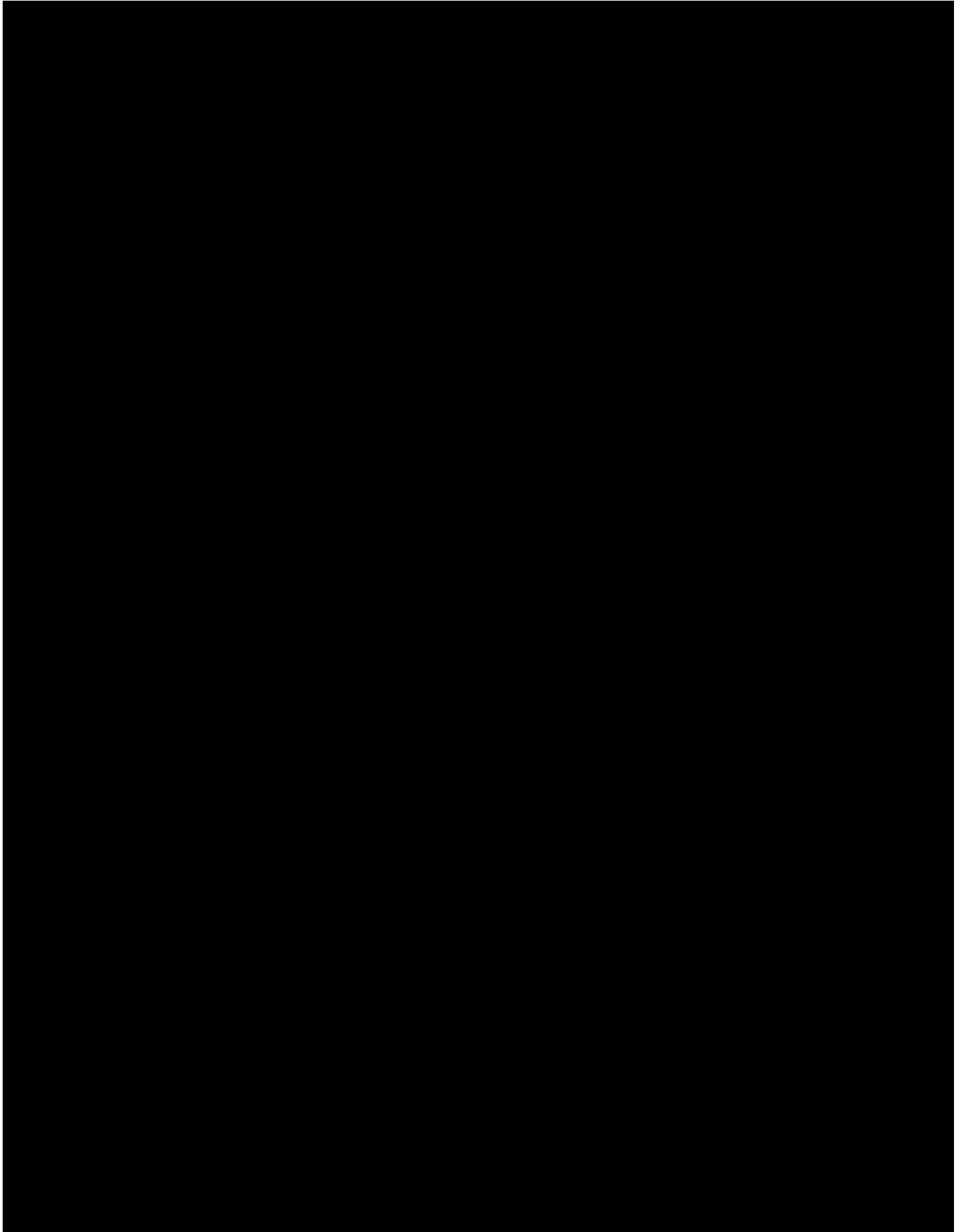
VGFT-OD-0706
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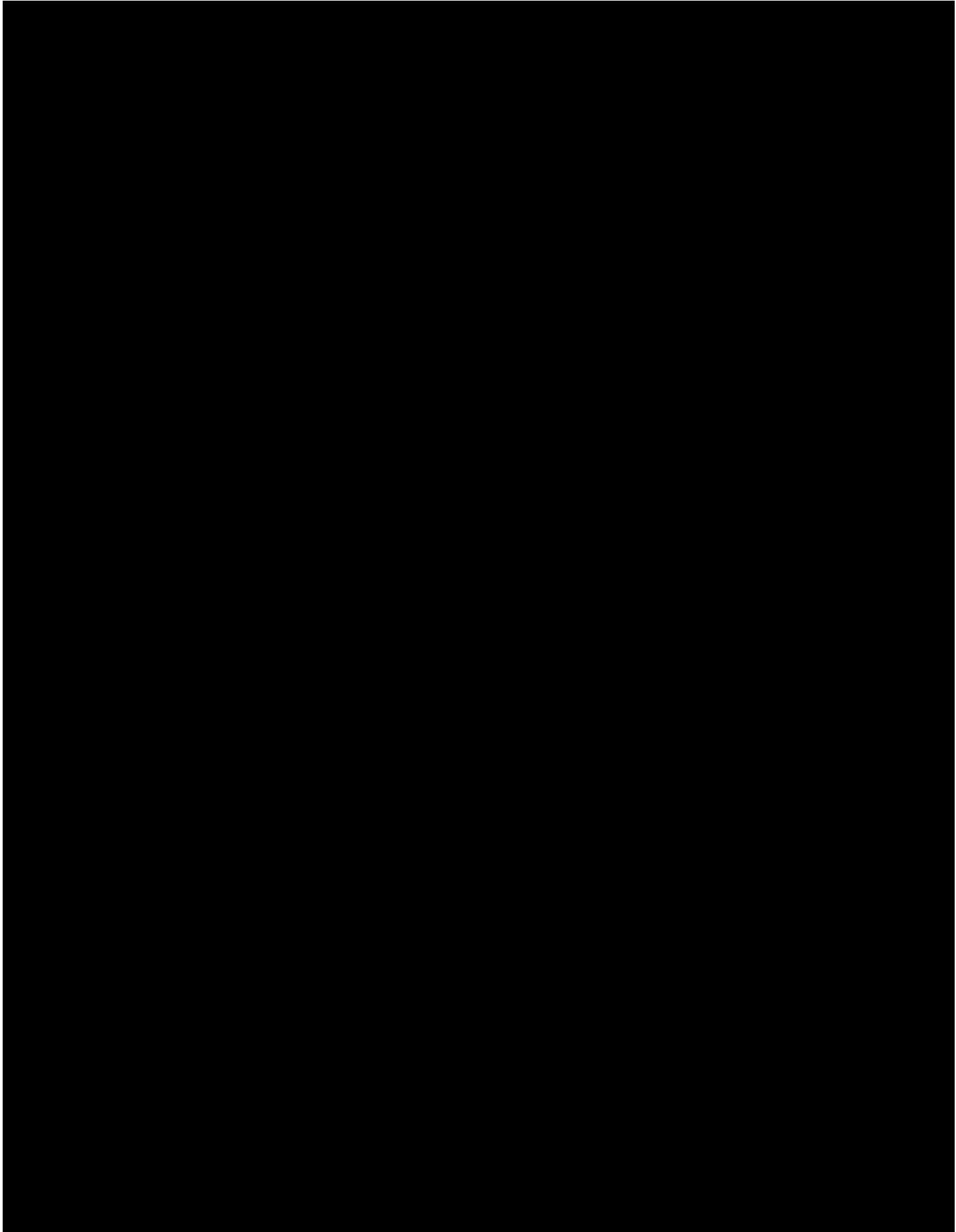
6.3.2 SERIOUS ADVERSE EVENTS

Table 13 Summary of Serious Ocular Adverse Events of Study Eye

System Organ Class 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)
Total number of reported such events	3	1	1	1	1	4
Number (proportion) of subjects who reported such events	3 (6.8%)	1 (2.3%)	1 (2.3%)	1 (2.4%)	1 (2.2%)	4 (2.3%)
Infections and infestations	0	0	1 (2.3%)	0	1 (2.2%)	2 (1.1%)
Endophthalmitis	0	0	1 (2.3%)	0	1 (2.2%)	2 (1.1%)
Eye disorders	3 (6.8%)	1 (2.3%)	0	0	0	1 (0.6%)
Uveitis	0	1 (2.3%)	0	0	0	1 (0.6%)
Diabetic retinal oedema	1 (2.3%)	0	0	0	0	0
Visual acuity reduced	1 (2.3%)	0	0	0	0	0
Vitreous haemorrhage	1 (2.3%)	0	0	0	0	0
Injury, poisoning and procedural complications	0	0	0	1 (2.4%)	0	1 (0.6%)
Corneal abrasion	0	0	0	1 (2.4%)	0	1 (0.6%)

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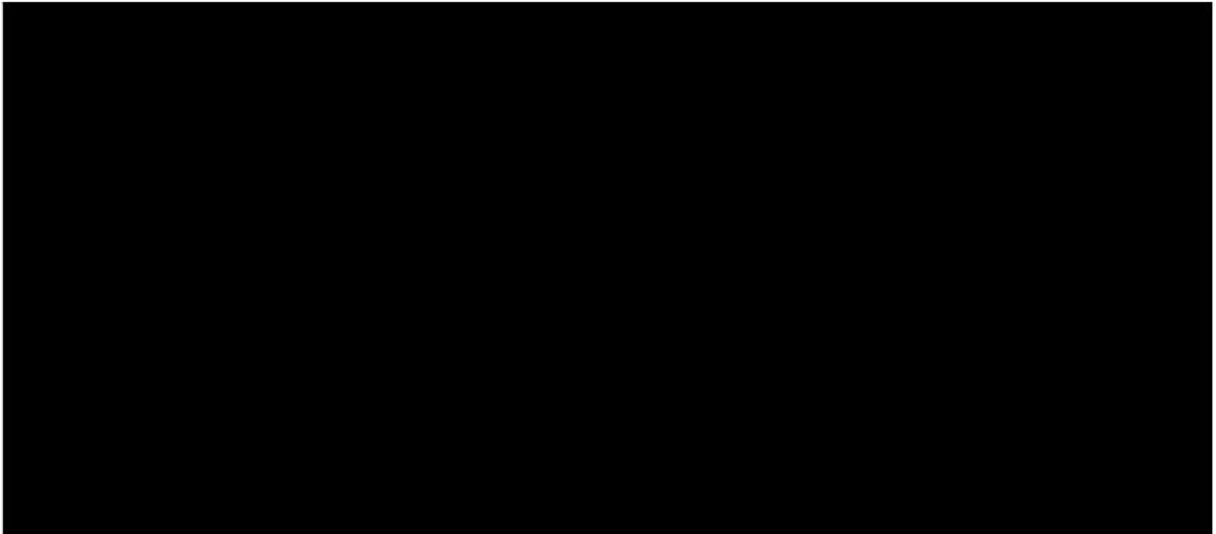


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6.3.3 DISCONTINUATION DUE TO AE



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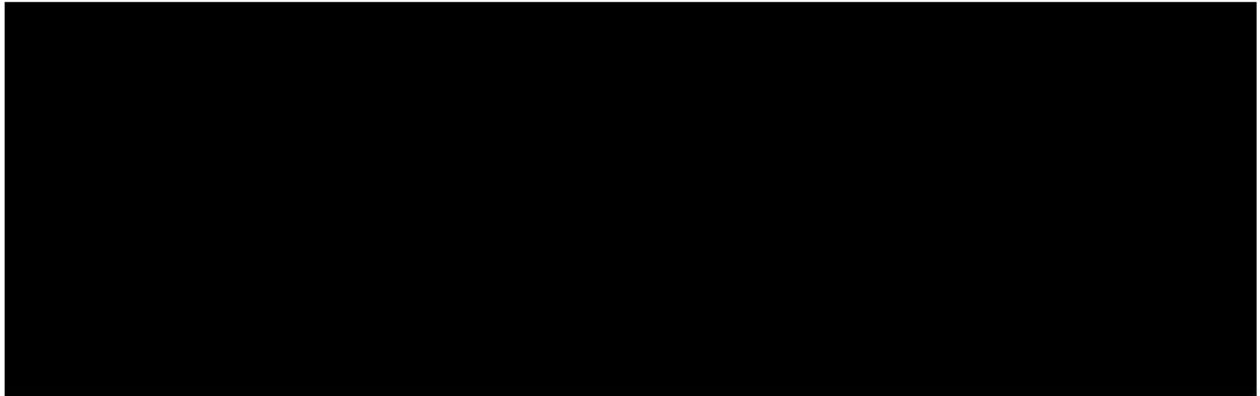
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6.3.4 DEATHS



7. SUMMARY



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