A PHASE 3 RANDOMIZED, DOUBLE-MASKED, CONTROLLED TRIAL TO ESTABLISH THE SAFETY AND EFFICACY OF INTRAVITREOUS ADMINISTRATION OF FOVISTA™ (ANTI PDGF-B PEGYLATED APTAMER) ADMINISTERED IN COMBINATION WITH EITHER AVASTIN® OR EYLEA® COMPARED TO AVASTIN® OR EYLEA® MONOTHERAPY IN SUBJECTS WITH SUBFOVEAL NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

PROTOCOL NO: OPH1004B

(Supersedes Protocol No: OPH1004A)

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1 GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine aminotransferase
AMD	Age-Related Macular Degeneration
AST	Aspartate aminotransferase
BUN	Blood Urea Nitrogen
CATT	Comparison of AMD Treatments Trials
CNV	Choroidal Neovascularization
CRF	Case Report Form
DA	Disc Area
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
EC	Endothelial Cell
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
ETDRS	Early Treatment Diabetic Retinopathy Study
EW	Early Withdrawal
FA	Fluorescein Angiography
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl-Transferase
IB	Investigator Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IOP	Intraocular Pressure
IRB	Institutional Review Board
NLP	No Light Perception
NV	Neovascular
NYHA	New York Heart Association
OCT	Optical Coherence Tomography
OU	Both eyes
PDGF	Platelet Derived Growth Factor
PDT	Photodynamic Therapy
RC	Reading Center
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SE	Study Eye
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SHRM	Subretinal Hyper-Reflective Material
TLP	Thermal Laser Photocoagulation
ULN	Upper Limit of Normal
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell
WHO	World Health Organization

2 SUMMARY OF PROTOCOL OPH1004B

SYNOPSIS	
TITLE:	A phase 3 randomized, double-masked, controlled trial to establish the safety and efficacy of intravitreous administration of Fovista™ (Anti PDGF-B pegylated aptamer) administered in combination with either Avastin® or Eylea® compared to Avastin® or Eylea® monotherapy in subjects with subfoveal neovascular age-related macular degeneration.
OBJECTIVES:	The objectives of this study are to evaluate the safety and efficacy of Fovista™ (E10030) intravitreous administration when administered in combination with either Avastin® or Eylea® compared to Avastin® or Eylea® monotherapy in subjects with subfoveal choroidal neovascularization secondary to age-related macular degeneration (AMD).
STUDY DESIGN:	Subjects will be randomized in a 1:1 ratio to the following dose groups: • Fovista™ 1.5 mg/eye + Avastin® 1.25 mg/eye or Eylea® 2 mg/eye • Fovista™ sham + Avastin® 1.25 mg/eye or Eylea® 2 mg/eye Within each of the above dose groups, subjects will be randomized in a 1:1 ratio to either Avastin® 1.25 mg/eye or Eylea® 2 mg/eye. Subjects randomized to receive Avastin will be treated with active Fovista™ or sham in combination with Avastin® monthly for 24 months. Subjects randomized to receive Eylea will be treated with active Fovista™ or sham in combination with Eylea® every month for the first 3 doses (Day 1, Month 1, and Month 2) and every other month thereafter (i.e., Months 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22). Therefore, subjects randomized to receive Avastin® will be treated with active Fovista™ or sham in combination with Avastin® for a total of 24 administrations. Subjects randomized to receive Eylea® will be treated with active Fovista™ or sham in combination with Eylea® for a total of 13 administrations. All subjects will have a final follow-up visit at Month 24.
ENDPOINTS:	<u>Primary Efficacy Endpoint</u>: The primary efficacy endpoint is the mean change in visual acuity (ETDRS letters) from baseline at the Month 12 visit. <u>Safety Endpoints:</u> Safety endpoints include adverse events, vital signs, ophthalmic variables [ophthalmic examination, intraocular pressure (IOP), fluorescein angiogram (FA), optical coherence tomography (OCT)], ECG, and laboratory variables.

SYNOPSIS	
PLANNED SAMPLE SIZE:	Approximately 622 subjects will be randomized into one of the two treatment cohorts (311 subjects per dose group).
SUBJECT SELECTION:	Subjects of either gender aged 50 years or above diagnosed with subfoveal choroidal neovascularization secondary to AMD.
FORMULATION:	Fovista™ (E10030)  Avastin® (bevacizumab) Avastin® is a preservative-free, clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution supplied in a single-use glass vial containing 100 mg in 4 mL, of which 0.05 mL will be administered for intravitreal injection. The 100 mg product is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. Avastin is presented in a 4 mL vial and should be used without further dilution. The vial is considered single use and should not be used on any additional study subjects or non-study patients. Avastin® should be administered in accordance with the procedure described in this protocol. Eylea® (aflibercept) Eylea® is a preservative-free colorless to pale yellow sterile solution, supplied in a single-use glass vial designed to deliver 0.05 mL of Eylea® (40 mg/mL in 10mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2). Eylea® should be used without further dilution and administered in accordance with the package insert.
INVESTIGATIONAL DRUG DOSAGE:	Subjects randomized to active drug will receive between 13 and 24 injections of Fovista™ 1.5 mg/eye.

3 STUDY ASSESSMENTS

Year 1

Assessment	SCR	Day 1[1]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Informed Consent	X													
Medical & Ophthalmic History, Performance status	X													
Vital Signs/ Physical Exam[2]	X	X						X						X
12-Lead ECG	X													X
Protocol refraction and visual acuity using ETDRS chart[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tonometry[3,4,5]/Ophthalmologic Examination[3,6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Color Fundus Photographs[3]	X	*						X						X
Fluorescein Angiogram[3]	X	*						X						X
Optical Coherence Tomography (OCT)[3]	X	*			X			X			X			X
Laboratory Tests (hematology, chemistry, urinalysis)	X							X						X
Serum pregnancy test (if applicable)	X													
Visual Function Questionnaire (VFQ-25)		X			X			X			X			X
Randomization		X*												
Subjects Randomized to Fovista™/Sham + Avastin®		X	X	X	X	X	X	X	X	X	X	X	X	X
Subjects Randomized to Fovista™/Sham + Eylea®		X	X	X		X		X		X		X		X
3-Day Post-Injection Telephone Safety Check		A/E	A/E	A/E	A	A/E	A	A/E	A	A/E	A	A/E	A	A/E
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[7]		X	X	X	X	X	X	X	X	X	X	X	X	X

[1]Day 1 assessments should be performed within 14 days of Screening.

[2]Physical examination is performed at Screening, and at the investigator's discretion thereafter. Vital Signs are performed at all indicated timepoints.

[3]Ocular assessments are performed at Screening, Months 6, 12, 18 and Month 24/Early Withdrawal on both eyes (OU). Ocular assessments at all other study visits are performed on the study eye (SE) only.

[4]Goldmann applanation tonometry must be performed at Screening. The tonopen may be used at other times, however Goldmann applanation tonometry must be used to verify any IOP ≥30mm Hg occurring more than 30 min post-injection, or any IOP ≥30 mmHg at any other time.

[5]Tonometry should be measured prior to the first injection, at least 30 minutes after the first injection, and at least 30 minutes after the Fovista™/sham injection, and at any additional times as specified by the Intravitreous Administration Protocol (see Section 17.5).

[6]Ophthalmic exam should be performed twice at the injection visits; once prior to the first injection, and again after the second injection.

[7]Adverse events are to be recorded starting after the first dose of study drug.

*Under certain conditions (i.e. significant anatomic change or significant change in VA since Screening as defined in Section 10.2.2.1), ocular imaging must be repeated before randomization can be considered. See **Section 10.2.2.1, Reconfirmation of Eligibility at Day 1**, for details.

VISIT WINDOWS: It is essential that subjects adhere to their prescheduled study visits within the following visit windows – Months 1 to 24: ± 7 days.

A = Avastin Subjects Only, A/E= Avastin and Eylea Subjects

STUDY ASSESSMENTS (CONTINUED)

Year 2

Assessment	Month 13	Month 14	Month 15	Month 16	Month 17	Month 18	Month 19	Month 20	Month 21	Month 22	Month 23	Month 24	Early Withdrawal
Informed Consent													
Medical & Ophthalmic History, Performance status													
Vital Signs/ Physical Exam[2]						X						X	X
12-Lead ECG												X	X
Protocol refraction and visual acuity using ETDRS chart[3]	X	X	X	X	X	X	X	X	X	X	X	X	X
Tonometry[3,4,5]/Ophthalmologic Examination[3,6]	X	X	X	X	X	X	X	X	X	X	X	X	X
Color Fundus Photographs[3]						X						X	X
Fluorescein Angiogram[3]						X						X	X
Optical Coherence Tomography (OCT)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Tests (hematology, chemistry, urinalysis)						X						X	X
Serum pregnancy test (if applicable)													
Visual Function Questionnaire (VFQ-25)						X						X	X
Randomization													
Subjects Randomized to Fovista™/Sham + Avastin®	X	X	X	X	X	X	X	X	X	X	X		
Subjects Randomized to Fovista™/Sham + Eylea®		X		X		X		X		X			
3-Day Post-Injection Telephone Safety Check	A	A/E	A	A/E	A	A/E	A	A/E	A	A/E	A		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[7]	X	X	X	X	X	X	X	X	X	X	X	X	X

[1]Day 1 assessments should be performed within 14 days of Screening.
[2]Physical examination is performed at Screening, and at the investigator's discretion thereafter. Vital Signs are performed at all indicated timepoints.
[3]Ocular assessments are performed at Screening, Months 6, 12, 18 and Month 24/Early Withdrawal on both eyes (OU). Ocular assessments at all other study visits are performed on the study eye (SE) only.
[4]Goldmann applanation tonometry must be performed at Screening. The tonopen may be used at other times, however Goldmann applanation tonometry must be used to verify any IOP ≥30mm Hg occurring more than 30 min post-injection, or any IOP ≥30 mmHg at any other time.
[5]Tonometry should be measured prior to the first injection, at least 30 minutes after the first injection, and at least 30 minutes after the Fovista™/sham injection, and at any additional times as specified by the Intravitreous Administration Protocol (see Section 17.5).
[6]Ophthalmic exam should be performed twice at the injection visits; once prior to the first injection, and again after the second injection.
[7]Adverse events are to be recorded starting after the first dose of study drug.
*Under certain conditions (i.e. significant anatomic change or significant change in VA since Screening as defined in Section 10.2.2.1), ocular imaging must be repeated before randomization can be considered. See **Section 10.2.2.1, Reconfirmation of Eligibility at Day 1**, for details.

VISIT WINDOWS: It is essential that subjects adhere to their prescheduled study visits within the following visit windows – Months 1 to 24: ± 7 days.

A = Avastin Subjects Only, A/E= Avastin and Eylea Subject

4 INTRODUCTION

4.1 Age-Related Macular Degeneration (AMD)

Age-related macular degeneration is a disease characterized by progressive degenerative abnormalities in the macula of the eye, a small area in the central portion of the retina. It is characteristically a disease of individuals >50 years of age and is the leading cause of visual loss in developed countries. In the United States, it is estimated that approximately 6% of individuals 65-74 years of age, and 20% of those older than 75 years of age are affected with AMD [1]. Because of the increasing life expectancy in developed and developing countries, the elderly sector of the general population is expected to rise at a greater rate in the coming decades. While 1 of 8 Americans was considered to be elderly in 1994, it is expected that 1 of 5 will fall into this category in 2030. Using U.S. Census Bureau projections, the number of Americans over 65 years of age will more than double to 80 million by the middle of this century [2]. In the absence of adequate prevention or treatment measures, the number of cases of AMD with visual loss is expected to grow accordingly.

Age-related macular degeneration is classified into one of two general subgroups**:** the non-neovascular (non-exudative or dry) form of the disease and the neovascular (exudative or wet) form of the disease. The non-neovascular form of AMD is more prevalent, accounting for approximately 90% of all AMD cases, and is often characterized by a slow degeneration of the macula resulting in atrophy of the central retina with gradual vision loss over a period of years. By contrast, neovascular AMD, although less prevalent, commonly causes sudden, often substantial, loss of central vision and is responsible for most cases of severe loss of visual acuity in this disease [3]. This type of AMD results when abnormal blood vessels (neovascularization) proliferate under and/or within the retina. These blood vessels leak blood and fluid into the retina, which results in rapid vision loss. The end stage of the disease is scarring with irreversible destruction of the central retina.

The current FDA approved pharmacologic therapies for wet AMD target and inhibit Vascular Endothelial Growth Factor (VEGF). VEGF is an endothelial cell survival factor and a mitogen. Endothelial cells are a key component of neovascular tissue. All approved anti-VEGF agents for wet AMD are administered by the intravitreal route of administration. These include Lucentis® (ranibizumab), Eylea® (aflibercept), and Macugen® (pegaptanib sodium) [4, 5, 6, 7]

In addition, although not labeled by the FDA for the treatment of neovascular AMD, the anti-VEGF agent Avastin® (bevacizumab) is currently used to treat the ~50% of eyes with neovascular AMD in the United States. A multicenter, prospective, randomized trial, funded by the US National Eye Institute, "The Comparison of Age-Related Macular Degeneration Treatments Trials" (CATT) demonstrated that monthly dosing with Avastin® 1.25 mg (0.05 mL) was non-inferior to monthly dosing of Lucentis® for eyes with neovascular AMD [8].

Avastin®, Lucentis®, and Eylea®, on average, all improve the visual outcomes in eyes with neovascular AMD. The primary mechanism of action of these anti-VEGF agents is to decrease the intraretinal and subretinal fluid associated with abnormal blood vessels. Despite maximal therapy with intravitreal monotherapy anti-VEGF agents, majority of subjects do not achieve significant visual gain (≥ 15 letters of vision), and approximately 20% to 30% lose additional vision from baseline.

Neovascular proliferation is the key step in wet AMD development. These abnormal vessels consist of endothelial cells, pericytes, and inflammatory cells. Two factors that play important roles in proliferation and maintenance of abnormal blood vessels are VEGF and Platelet Derived Growth Factor (PDGF). VEGF is an endothelial cell survival factor and a key mediator in the process of neovascularization. It is also one of the most potent inducer of vascular permeability in biologic systems.

PDGF is a growth factor responsible for pericyte survival, maturation and regulation.

The neovascularization process is complex and anti-VEGF resistance may result from multiple mechanisms including endothelial cell protection by pericytes. Simultaneous and selective inhibition of both VEGF and PDGF has the potential to have significantly more impact on abnormal vessels than inhibition of the VEGF alone [9].

4.2 Vascular Endothelial Growth Factor (VEGF), Platelet Derived Growth Factor (PDGF) and Neovascular AMD

A number of distinct cytokine growth factors are known to be involved in the complex process of angiogenesis [10]. Of those factors, VEGF, a homodimeric protein, has high specificity for vascular endothelium and its major tyrosine kinase receptors are selectively expressed on vascular endothelium. VEGF stimulates endothelial cells to proliferate, migrate and protect them from apoptosis [11].

PDGF is another growth factor which has been implicated in ocular neovascularization. A total of four different genes encode four different PDGF polypeptide chains (PDGF-A, PDGF-B, PDGF-C, and PDGF-D). Each of these bind to their receptors as a homodimer i.e. PDGF-AA, PDGF-BB, PDGF-CC, and PDGF-DD. In addition, a heterodimer PDGF AB is also encoded [12, 13]. Neovascular endothelial cells secrete Platelet Derived Growth Factor B (PDGF-BB), which binds to its PDGF receptor β (PDGFR- ββ) on pericytes (mural cells). PDGF-BB signaling is critical for pericyte survival, maturation and regulation.

PDGF plays a major role during embryonic development, where they are of crucial importance for the development of certain types of mesenchymal cell types (muscle, blood, connective tissue, vascular system, heart, much of the kidney and dermis of the skin). In the adult, PDGF stimulates wound healing and regulates the interstitial fluid pressure in tissues. Overactivity of PDGF has been implicated in certain malignancies, as well as in other diseases involving excessive cell growth, including atherosclerosis and fibrotic conditions and ocular neovascularization [13, 14]. The sequence homology of PDGF is highly conserved across species. Rat and rabbit PDGF sequences bear remarkable similarities to the human cytokine [15, 16]. This is important in the extrapolation of animal data to humans.

PDGF upregulation has been demonstrated in the chick chorioallantoic membrane assay [17], the mouse corneal pocket assay [18] and in tumors [19]. It is also well established that PDGF plays a role in pericyte recruitment [20].

Pericyte recruitment is part of the maturation process in blood vessel development. Pericytes intimately cover the endothelial cells and lead to a mature blood vessel phenotype. Once the pericyte cell population is well established, the effectiveness of anti-VEGF agents at destabilizing blood vessels is greatly reduced. This anti-VEGF resistance is imparted by pericytes being a major source of survival factors (i.e. VEGF-A) to the endothelial cells. PDGF-B, secreted at high levels specifically by the growth of endothelial cells in neo-vessels, leads to the recruitment of pericytes to the newly formed vessels. The primary receptor for PDGF-B in the eye, PDGFR-β, is expressed on recruited pericytes. Disruptions of the PDGF-B/PDGFR-β receptor system by either blocking agents or gene knock-out result in pericyte loss along with extensive vascular defects that include microaneurysms, vascular permeability and non-functional vessels. In addition, it has been shown that the interruption of the PDGF-B/PDGFR-β receptor system in combination with anti-VEGF strategies result in vessel regression [9]. Whereas disruption of the

pericyte-endothelial association in more established neovessels can result in vessel regression, it has not affected the normal fully established vasculature. The reason for this difference in sensitivity is not known but points to pathological neovascularization being in a dynamic state, shifting between periods of vessel growth and maturation. This evidence suggests that altering the PDGF-B/ PDGFR-β receptor system in combination with anti-VEGF agents may cause regression of abnormal blood vessels in neovascular AMD while preserving the normal vascular architecture, thereby yielding an effective anti-angiogenesis therapy.

4.3 Fovista™ (E10030)

The evidence implicating PDGF in several serious diseases has made PDGF antagonists highly desirable, and the first clinically useful antagonists are now available. The best-characterized PDGF antagonists are macromolecules (antibodies, soluble receptor domains or DNA aptamers) which bind to PDGF isoforms and prevent them from binding to receptors, or low molecular weight receptor kinase inhibitors [21]. The most well-characterized PDGF receptor kinase inhibitor is STI571 (Imatinib, Gleevec™), which inhibits, in addition to PDGF alpha- and beta-receptors, the kinases of the stem cell factor receptor, Abl and Arg [22].

In a highly powered, randomized controlled Phase 2 trial combining Fovista™ with an anti-VEGF agent in the treatment of neovascular AMD, combination therapy

proved superior in terms of mean visual gain when compared to eyes that were treated with anti-VEGF monotherapy [23].

4.3.1 NonClinical Efficacy

The preclinical data demonstrating the anti-angiogenic properties of Fovista™ are described in detail in the Investigator Brochure (IB).

4.3.2 NonClinical Pharmacokinetics of Fovista™

Further information regarding the pharmacokinetic properties of Fovista™ is described in detail in the Investigator Brochure (IB).

4.3.3 Toxicology

A variety of nonclinical toxicity studies with Fovista™ have been completed, including genetic toxicology and chronic repeat-dose intravitreal studies in rabbit and dogs up to 6 and 9 months in duration, respectively. All of the pivotal safety studies were performed in accordance with the FDA's Good Laboratory Practice Regulations (21 CFR Part 58). The results of the Fovista™ toxicity studies are presented in detail in the Investigator Brochure (IB). Overall, there were no ocular or systemic safety issues in the Fovista™ toxicology program that would preclude the intravitreous administration of Fovista™ at the dose level, frequency and duration intended for this clinical trial.

4.4 Clinical Data

A total of 22 subjects who met inclusion/exclusion criteria were treated in a Phase 1

study (OPH1000). Subjects were enrolled in a repeat-dose escalation scheme of three monthly intravitreal injections of Fovista™ (0.03, 0.3, 1.5 or 3.0 mg/eye) in combination with Lucentis® 0.5 mg/eye. Fovista™ combined with Lucentis® was well tolerated. No dose limiting toxicities or drug-related adverse events were reported at any of the dose levels investigated. Visual acuity and anatomic data suggested potential bioactivity associated with regression of the neovascular membrane.

A phase 2, randomized, prospective, double-masked, controlled trial (OPH1001) has recently been completed in subjects with subfoveal neovascular lesions secondary to AMD. Subjects received six monthly intravitreous injections of Fovista™ given in combination with Lucentis®. In this parallel group, multicenter study, 449 subjects were randomized in a 1:1:1 ratio to the following dose groups: Fovista™ 0.3 mg/eye + Lucentis® 0.5 mg/eye, Fovista™ 1.5 mg/eye + Lucentis® 0.5 mg/eye, or Fovista™ sham + Lucentis® 0.5 mg/eye.

Combination therapy proved superior in terms of mean visual gain when compared to eyes that were treated with anti-VEGF monotherapy. The combination of Fovista™ (1.5 mg) and Lucentis® met the pre-specified, alpha protected primary endpoint of superiority in mean visual acuity gain compared to ranibizumab monotherapy (10.6 ETDRS letters at week 24, compared to 6.5 letters, p=0.019). Additionally, a dose-response curve was observed. The combination of Fovista™ (0.3 mg) with Lucentis® demonstrated an increase in mean vision of 8.8 letters, while the combination of Fovista™ (1.5 mg) with Lucentis® demonstrated an increase in mean vision of 10.6 letters. The mean change in vision change over time demonstrated superiority for the combination groups at each measured timepoint and was sustained, with increasing differentiation of the curves at study closure.

[redacted]

Combination therapy was well tolerated. The most common ocular adverse events were, as expected in intravitreal studies, related to the intravitreal preparation and injection procedure and not drug-related, e.g., conjunctival hemorrhage, punctate keratitis, and eye pain. There were no events of endophthalmitis, retinal detachment, retinal tear or iatrogenic traumatic cataract after a total of 4431 intravitreal injections (1776 administrations of Fovista™ and 2655 administrations of Lucentis®). As expected, the mean IOP increased after each intravitreal injection consistent with the volume effect. However, mean IOP in all arms returned to pre-injection level at the next visit, including at the end of the study. The systemic safety profile of Fovista™/Lucentis® was similar to that of Lucentis® monotherapy.

Additional information regarding the clinical data for Fovista™ is described in detail in the Investigator Brochure (IB).

4.5 Trial Rationale

There is widespread acceptance that the main therapeutic benefit of anti-VEGF mono-therapy is its potent anti-permeability property. This is consistent with VEGF being the most potent inducer of permeability [24]. The current clinically available anti-VEGF agents (Lucentis®, Avastin® and Eylea®) have all demonstrated similar therapeutic benefit in multiple clinical studies [4, 5, 6, 8]. However, despite maximal anti-VEGF therapy (e.g. increased dosage/regimen), additional efficacy has not been observed [25]. Based on this, it appears that a “ceiling” of anti-VEGF effect has been reached and an unmet need persists. Furthermore, anti-VEGF monotherapy does not lead to the regression of the pathologic neovascular (NV) tissue. Therefore, stability of the NV complex ensues despite continued treatment, which may limit significant visual gain in majority of treated subjects. Hence, targeted pharmacotherapeutic strategies inducing NV regression coupled with resolution of permeability in wet AMD may result in enhanced visual outcome.

Neovascularization is a normal process involved in embryonic development and tissue repair but becomes pathological when blood vessels proliferate into abnormal tissues (i.e. tumors), avascular cornea, or the subretinal space. The

proliferation, invasion, and migration of the NV vessels are coordinated by a complex molecular mechanism involving growth factors, cytokines, and their associated receptors. The diverse set of signaling pathways involved in wet AMD indicate the need for a multi-targeted pharmacotherapy approach for its treatment.

The NV tissue consists of endothelial cells (EC), pericytes, and inflammatory cells (i.e. occasional macrophages). Based on current understanding, the NV process involves the formation of angiogenic sprouts from existing capillaries growing into the avascular space. These sprouts are led by tip cell filopodia. VEGF is a master switch for NV involved in the activation, survival, and proliferation of EC and has been found at the tip of the angiogenic sprout. Following the formation of the EC angiogenic sprout, the newly formed vessels attract and are coated by pericytes leading to NV maturation.

Pericytes are derived via differentiation of mural cells. Their presence on capillaries leads not only to NV support and stabilization but also promotes endothelial cell survival through chemical signaling and physical interactions including pericyte production of VEGF [26]. The endothelial survival signaling by integrated pericytes is critical and may explain the resistance of the NV tissue to VEGF withdrawal, i.e. lack of NV regression to monotherapy anti-VEGF treatment [26]. Therefore, stripping of pericytes combined with anti-VEGF therapy may lead to regression of NV vessels and further improvement of visual outcome.

The coating of the NV endothelial cells by pericytes is initiated by endothelial cell expression of the paracrine platelet derived growth factor B (PDGF-B), which forms the homo dimer PDGF-BB. The EC expressed PDGF-B is retained proximally by heparin sulfate proteoglycan with the highest concentration in the cells at the tip of the angiogenic sprout. The recognition of the proximally retained PDGF-BB by the PDGFR-β receptor on pericytes initiates the proliferation and migration of the pericytes along the growing neovascularization. The importance of PDGF-B/PDGFR-β interaction in the pericyte recruitment and capillary maturation has been demonstrated through gene knockout, ectopic delivery of competing PDGF-B, blocking the PDGF-B/PDGFR-β interaction by external agents, or deletion of the PDGF-B heparin sulfate proteoglycans binding motif [27,28]. At the angiogenic sprout, the attachment and maturation of pericytes follows the proliferation of endothelial cells (both in time and space) [28,29].

The importance of the PDGF–B/PDGFR-β interaction in pericyte recruitment, maturation, and resistance to anti-VEGF mediated regression has been

demonstrated in animal models [9]. These studies show that blocking the PDGF–B/PDGFR-β interaction leads to lack of pericyte coverage, abnormal/leaking blood vessels, inhibition of NV capillary maturation, and neonatal lethality [30,31]. Specifically, animal injury models of corneal and choroidal neovascularization (CNV) have demonstrated that administration of agents that block the PDGF-B/PDGFR-β interaction leads to pericyte stripping from the pathological neovasculature [9]. Further, co-administration of anti-VEGF and anti-PDGF agents leads to a greater NV inhibition than either agent alone. More importantly, such combination induces NV regression as well.

Established mature, non-pathological vascularization is unaffected with inhibitors of the PDGF-B/PDGFR- β interaction. A decreased PDGF-B dependency on pericytes residing on mature host vessels may be related to differential PDGFR-β receptor expression on these cells or the nature of pericyte-EC associations in each situation. In the mature host vascular bed (non-pathologic vascular tissue), Sphingosine-1-phosphate (SP1) mediated N-Cadherin and Gap junction activated TGF-β1 leads to a stabilized pericyte-EC interaction and mural cell differentiation [32]. In addition, in the mature host vasculature, the pericytes and EC share a common basement membrane with individual pericytes contacting multiple endothelial cells. Conversely, pericytes involved in pathological neovascularization appear to have an abnormal morphology with a looser association to the underlying EC vasculature [33].

Fovista™ (E10030) is a PDGF-B antagonist with high specificity and affinity in the form of a pegylated oligonucleotide (aptamer). In vitro and in vivo studies using this compound in combination with an anti-VEGF agent have demonstrated its effectiveness at preventing the formation of NV vessels as well as stripping of pericytes leading to regression of established NV vessels [28].

The Phase 2 Fovista™ study demonstrated superiority of Fovista™ (1.5mg) /Lucentis® combination therapy compared to Lucentis® monotherapy. At the commencement of this phase 2b trial, Eylea was not available in the market and was therefore not included as an anti-VEGF agent. In addition, the data from the CATT trial establishing the non-inferiority of Avastin® to Lucentis® was not available. Well powered, randomized, controlled, prospective comparative trials of monotherapy anti-VEGF agents in wet AMD have failed to show superiority of any of the anti-VEGF agents. Fovista's pharmaceutical activity as measured via the level of gene expression, using real-time PCR, as a function of binding to the

cellular receptors reveal that the specific anti-VEGF in the combination does not affect its individual activities.

5 TRIAL OBJECTIVES

5.1 Objectives

The objectives of this study are to evaluate the safety and efficacy of Fovista™ intravitreous administration when administered in combination with either Avastin® or Eylea® compared to Avastin® or Eylea® monotherapy in subjects with subfoveal choroidal neovascularization secondary to age-related macular degeneration (AMD).

5.2 Endpoints

Primary Efficacy Endpoint:

The primary efficacy endpoint is the mean change in visual acuity (ETDRS letters) from baseline at the Month 12 visit.

Secondary Efficacy Endpoints:

Refer to Statistical Methods (Section 11) for enumeration of the secondary efficacy parameters.

Safety Endpoints:

- Adverse events (AEs)
- Vital signs (pulse, systolic and diastolic blood pressure)
- Ophthalmic variables (IOP, ophthalmic examination, fluorescein angiograms and OCT)
- ECG (12-lead)
- Laboratory variables (blood: hematology, renal function, hepatic function, and electrolytes; urinalysis)

6 TRIAL DESIGN

Subjects will be randomized in a 1:1 ratio to the following dose groups:

- Fovista™ 1.5 mg/eye + Avastin® 1.25 mg/eye or Eylea® 2 mg/eye
- Fovista™ sham + Avastin® 1.25 mg/eye or Eylea® 2 mg/eye

Within each of the above dose groups, subjects will be randomized in a 1:1 ratio to either Avastin® 1.25 mg/eye or Eylea® 2 mg/eye.

Subjects randomized to receive Avastin will be treated with active Fovista™ or sham in combination with Avastin® monthly for 24 months.

Subjects randomized to receive Eylea will be treated with active Fovista™ or sham in combination with Eylea® every month for the first 3 doses (Day 1, Month 1 and Month 2) and every other month thereafter (i.e., Months 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22).

Therefore, subjects randomized to receive Avastin® will be treated with active Fovista™ or sham in combination with Avastin® for a total of 24 administrations. Subjects randomized to receive Eylea® will be treated with active Fovista™ or sham in combination with Eylea® for a total of 13 administrations.

All subjects will have a final follow-up visit at Month 24.

7 PROCEDURES

7.1 Procedures for Refraction and Vision Testing

Refraction and Vision Testing will be performed at all time points specified in Section 10.2 “Trial Assessments”. Retroilluminated modified Ferris-Bailey ETDRS (Early Treatment Diabetic Retinopathy Study) charts are used starting at 4 meters (see Appendix 17.3).

When protocol refraction and best-corrected visual acuity measurement is required by the trial protocol, this will be performed only by certified visual acuity examiners ***masked to the previous visual acuity measurement and to whether or not the subject has been assigned to active treatment or control***. The examiner will be supplied with the previous protocol refraction only.

7.2 Tonometry

Tonometry will be performed at all time points specified in Section 10.2 “Trial Assessments”. Tonometry should be performed before the first injection and at least 30 minutes after each injection. For the post-injection tonometry, proper care should be taken to minimize the risk of contamination.

Goldmann applanation tonometry must be performed at Screening. Tonopens may be used at all other timepoints, but Goldmann applanation tonometry must be used to verify IOP for a post-injection reading of ≥ 30 mm Hg occurring more than 30 minutes post-injection, or for a reading of ≥ 30 mm Hg at any other time.

7.3 Ophthalmologic Examination

The following examinations will be performed at all time points specified in Section 10.2 “Trial Assessments”.

- Inspection of the eyelids
- Examination of the extra-ocular muscle movement
- Inspection of the cornea
- Examination of the anterior chamber for inflammation (Appendix 17.1)
- Examination of the pupils
- Examination of the iris
- Inspection of the lens
- Inspection of the vitreous body (Appendix 17.2)
- Inspection of the retina and optic disc

7.4 Fundus Photography and Fluorescein Angiography

Color fundus photographs and fluorescein angiography (FA) will be performed at all time points specified in Section 10.2 “Trial Assessments”. A Reading Center (RC) will confirm eligibility of subjects prior to enrollment. All color fundus photos and FAs that are collected at protocol-specified times must be sent to the RC as specified in the RC procedure manual. The RC will provide instructions for the color fundus photographs and FA procedures.

7.5 Optical Coherence Tomography

Optical Coherence Tomography (OCT) will be performed at all time points specified in Section 10.2 “Trial Assessments”. The RC will provide instructions for the OCT procedures, including which OCT reports must be sent to the RC.

7.6 Laboratory Tests

The following laboratory tests will be performed as specified in Section 10.2 “Trial Assessments”:

- Hematology: hemoglobin, platelet count, WBC and differential
- Coagulation profile: PT, PTT (baseline only)
- Renal Function: serum creatinine and BUN
- Hepatic function: serum bilirubin, alkaline phosphatase, GGT, SGOT/AST and SGPT/ALT
- Electrolytes: sodium, potassium, chloride, bicarbonate, calcium and phosphate
- HbA1c (baseline only)
- Complete Urinalysis (including specific gravity, protein, blood, etc.)
- Serum pregnancy test (if of child-bearing potential)

If a laboratory value outside of the normal range is judged as clinically significant by the Investigator, the Investigator will repeat the laboratory determination as judged appropriate to ensure the validity of the abnormal result. If any clinically significant abnormal results are noted, the tests are to be repeated until the results are normal, are no longer considered clinically significant by the investigator, or an explanation for the change is obtained.

7.7 Vital Signs, Physical Examination and Performance Status (ECOG)

A physical examination will be performed at Screening and at the Investigators’ discretion thereafter. Assessment of vital signs will be performed at all time points specified in Section 10.2 “Trial Assessments”.

Performance Status (ECOG) will be assessed at Screening in accordance with Appendix 17.4.

7.8 12-Lead ECG

A 12-lead ECG will be performed at all time points specified in Section 10.2 “Trial Assessments”.

7.9 Visual Function Questionnaire-25

The Visual Function Questionnaire (or VFQ-25) is a 25-question quality of life questionnaire created by the National Eye Institute to measure the influence of visual disability on general health and functioning. The VFQ-25 will be administered by site personnel and performed at all time points specified in Section 10.2 “Trial Assessments”.

8 SUBJECT POPULATION

8.1 Sample Size

Approximately 311 subjects will be enrolled in each cohort, for a total of 622 subjects in the study.

8.2 Inclusion Criteria

Subjects must meet the following criteria to be eligible to participate in this study.

8.2.2 General Inclusion Criteria

8.2.2.1 Subjects of either gender aged ≥ 50 years.

8.2.2.2 Performance Status ≤ 2 according to Eastern Cooperative Oncology Group (ECOG) / World Health Organization (WHO) scale (Appendix 17.4).

8.2.2.3 Women must agree to be using two forms of effective contraception, be post-menopausal for at least 12 months prior to trial entry, or surgically sterile; if of child-bearing potential, a serum pregnancy test must be performed within 14 days prior to the first injection with a negative result. The two forms of effective contraception must be implemented during the trial and for at least 60 days following the last dose of test medication.

8.2.2.4 Provide written informed consent.

8.2.2.5 Ability to comply with study and follow-up procedures and return for all trial visits.

8.3 Exclusion Criteria

Subjects will ***not be eligible for the trial*** if any of the following criteria are present in the study eye or systemically:

8.3.1 Ophthalmic Exclusion Criteria

8.3.1.1 Any prior treatment for AMD in the study eye prior to the Day 1 visit, except oral supplements of vitamins and minerals.

8.3.1.2 Any prior intravitreal treatment in the study eye prior to the Day 1 visit, regardless of indication (including intravitreal corticosteroids).

8.3.1.3 More than 50% of the total lesion size made up of scarring or atrophy as determined by fundus photography with or without fluorescein angiography, with or without OCT. Subjects with any subfoveal scar or subfoveal atrophy directly below the center of the fovea are excluded.

8.3.1.4 More than 50% of the total lesion size consisting of subretinal hemorrhage.

8.3.1.5 Presence of retinal angiomatous proliferation (RAP).

8.3.1.6 Presence of significant serous pigment epithelial detachments (PEDs), such as large PEDs that constitute greater than 50% of the total lesion or have a vertical height of ≥ 400 µm. Presence of pure PED without subretinal hyper-reflective material.

8.3.1.7 Presence of pigment epithelial tears or rips.

8.3.1.8 Presence of intraocular inflammation (≥ trace cell or flare), significant epiretinal membrane (causing distortion of macular anatomy and/or opacification), significant vitreomacular traction (causing distortion of macular anatomy), macular hole (full or partial thickness) or vitreous hemorrhage.

8.3.1.9 Aphakia or absence of the posterior capsule. Absence of an intact posterior capsule is allowed if it occurred as a result of YAG laser posterior capsulotomy in association with prior posterior chamber IOL implantation.

8.3.1.10 History of idiopathic or autoimmune-associated uveitis in either eye.

8.3.1.11 Significant media opacities, including cataract, which might interfere with visual acuity, assessment of toxicity, or fundus photography in the study eye. Subjects should not be entered if there is likelihood that they will require cataract surgery in the study eye in the next 12 months.

8.3.1.12 Presence of other causes of choroidal neovascularization, including pathologic myopia (spherical equivalent of -8 diopters or more, or axial length of 25mm or more), the ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, and multifocal choroiditis.

8.3.1.13 Any intraocular surgery or thermal laser within three (3) months of trial entry. Any prior thermal laser in the macular region, regardless of indication.

8.3.1.14 Any ocular or periocular infection in the past twelve (12) weeks.

8.3.1.15 History of any of the following conditions or procedures in the study eye: Rhegmatogenous retinal detachment, pars plana vitrectomy, filtering surgery (e.g. trabeculectomy), glaucoma drainage device, corneal transplant.

8.3.1.16 Previous therapeutic radiation in the region of the study eye.

8.3.2 General Exclusion Criteria

8.3.2.1 Any of the following underlying conditions or diseases including:

- A definitive diagnosis of diabetes mellitus or diabetic retinopathy (regardless of HbA1c level)
- HbA1c value of ≥6.5%*
  *If the HbA1c value is ≥ 6.5% and ≤ 6.9%, and the patient has no signs or symptoms of diabetes mellitus, has a normal creatinine, has no diabetic retinopathy and no glycosuria, then the patient may have an oral glucose tolerance test (OGTT) at the discretion of the investigator. If the 2-hour glucose value on OGTT is <200 mg/dL (<11.1mmol/L), then the patient may be enrolled.[1]
- History of other disease, metabolic dysfunction, physical examination finding or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications.
- History or evidence of severe cardiac disease (e.g., NYHA Functional Class III or IV - see Appendix 17.6), history or clinical evidence of unstable angina, acute coronary syndrome, myocardial infarction or coronary artery revascularization within 6

[1] The OGTT will be performed at a local laboratory as follows: (1) A fasting baseline plasma glucose is drawn; (2) the patient is administered 75 gm oral dextrose; (3) a 2-hour plasma glucose level is drawn. FDA form 1572 must be amended to include the local laboratory, and the local laboratory certification and OGTT normal values must be collected and appropriately filed by the site.

months, or ventricular tachyarrythmias requiring ongoing treatment.

- Stroke (within 12 months of trial entry).
- Any major surgical procedure within one month of trial entry.

8.3.2.2 Any treatment with an investigational agent in the 60 days prior to randomization for any condition.

8.3.2.3 Known serious allergies to the fluorescein dye used in angiography (mild allergy amenable to treatment is allowable), or to the components or formulation of either Fovista™ or Avastin® or Eylea®.

9 TRIAL MEDICATION

9.1 Drug Supply

9.1.1 Fovista™

Fovista™ (E10030) drug substance is a pegylated aptamer [redacted]

[redacted]

9.1.2 Avastin®

Bevacizumab (Avastin®) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay systems. Avastin® contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Avastin® has an approximate molecular weight of 149 kD. Avastin® is produced in a mammalian cell (Chinese Hamster Ovary) expression system in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product and the solution is preservative free.

9.1.3 Eylea®

Aflibercept injection (Eylea®) is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration. Aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, consisting of an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa. Aflibercept is produced in recombinant Chinese Hamster Ovary (CHO) cells.

9.2 Dose and Administration

9.2.1 Preparation

Fovista™, Avastin® and Eylea® will be injected without dilution.

Fovista™ is supplied in a single-use glass vial as noted in Section 9.1.1 above. To prepare for injection of Fovista™, use the 19 gauge filter needle (supplied in the

injection kit) and a new 1-mL sterile syringe (supplied) to withdraw about 0.2 mL of Fovista™ from the glass vial using aseptic technique. Remove the filter needle and replace it with the sterile 27 gauge injection needle (supplied). Expel any air bubbles and adjust the injection volume to 0.05 mL (50 μL). The procedure for sham Fovista™ injection is described in Section 17.5.

Avastin® injection is a preservative-free, clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution supplied in a single-use glass vial containing 100 mg in 4 mL, of which 0.05 mL will be administered for intravitreal injection. The 100 mg product is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. Using aseptic technique, 0.2 mL of the Avastin® injection vial contents are withdrawn through a 5-micron 19-gauge filter needle attached to a 1-cc tuberculin syringe. The filter needle should be discarded after withdrawal of the vial contents and should not be used for intravitreal injection. The filter needle should be replaced with a sterile 30-gauge × 1/2-inch needle for the intravitreal injection. The contents should be expelled until the plunger tip is aligned with the line that marks 0.05 mL on the syringe.

The Avastin vial is for single use. Any Avastin remaining in the vial is non-sterile and may not be used to treat any additional study subjects or non-study patients.

Eylea® is a sterile, clear, and colorless pale yellow solution. Eylea® is supplied as a preservative-free, sterile, aqueous solution in a single-use, glass vial designed to deliver 0.05 mL (50 microliters) of Eylea® (40 mg/mL in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2). Using aseptic technique, all (0.28 mL) of the aflibercept injection vial contents are withdrawn through a 5-micron 19-gauge filter needle attached to a 1-cc syringe. The filter needle should be discarded after withdrawal of the vial contents and should not be used for intravitreal injection. The filter needle should be replaced with a sterile 30-gauge × 1/2-inch needle for the intravitreal injection. The contents should be expelled until the plunger tip is aligned with the line that marks 0.05 mL on the syringe.

9.2.2 Treatment Regimen and Duration

Subjects randomized to active drug will receive 18-24 injections of Fovista™ 1.5 mg/eye.

9.2.3 Administration of Trial Drug

The method for intravitreous administration of Fovista™, Avastin® and Eylea® is described in detail in Appendix 17.5.

9.2.4 Storage

The investigator, or an approved representative (e.g. pharmacist), will ensure that all trial drugs are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. Store Fovista™, Eylea® and Avastin® under standard refrigeration conditions (2-8°C; 36-46°F); do not freeze. All vials should be protected from light and stored in the original carton or clinical kit, as provided, until the time of use. Avastin® vials should not be shaken.

9.3 Previous or Concomitant Therapy

Previous treatment for AMD in the study eye prior to Day 1 is not permitted except for oral supplements of vitamins and minerals.

Any treatment with any investigational agent for any condition in the 60 days prior to Screening, or treatment with an investigational agent for any condition during the trial, is not permitted.

Treatment for AMD in the fellow eye during the study with an approved product is permitted at any time. Although not labeled for the treatment of wet AMD, bevacizumab (Avastin®) is also allowed in the fellow eye at the discretion of the investigator.

10 TRIAL CONDUCT

10.1 Subject Enrollment

Before recruitment of subjects into the trial, written Institutional Review Board (IRB) or Ethics Committee (EC) approval of the protocol and informed consent must be obtained.

Subjects who meet the eligibility criteria and have provided written informed consent will be enrolled in the trial. If any inclusion or exclusion criteria are not met, treatment with trial drug should not commence without prior written approval from Ophthotech Corp. or its designee.

10.2 Trial Assessments

Written informed consent must be obtained before any of the Screening procedures listed below are performed. However, if a routine office procedure (e.g. FA, OCT) is performed to diagnose AMD independent of this clinical trial, and subsequently the subject provides informed consent for this study, these procedures performed prior to informed consent may be used as screening assessments for this study, provided the 14-day period of screening evaluations is respected and provided the assessments are acceptable to the standards of the study, including the Reading Center. An explanation of the trial and discussion of the possible risks and discomforts will be given by the investigator. Only those subjects who fulfill all eligibility criteria will be entered into the trial.

Ocular assessments performed at Screening, Month 6, Month 12, Month 18 and Month 24 (and at an Early Withdrawal visit if performed) should be performed on both eyes (OU). Ocular assessments at all other study visits are performed on the study eye (SE) only.

The following assessments will be performed during the study.

10.2.1 Screening Assessments

The following Screening evaluations, as outlined in the Study Assessments Chart (see Section 3), will be performed ***within 14 days*** prior to Day 1. Screening assessments can be broken into 2 days if necessary.

- Informed consent
- Medical history
- Ophthalmologic history (OU)
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Ophthalmologic Examination and Goldmann Applanation Tonometry (OU)
- Vital Signs /Physical Examination/Performance Status (ECOG)

- ECG
- Color fundus photographs (OU)
- Fluorescein Angiograms (FA) (OU, transit study eye)
- Optical Coherence Tomography (OCT) (OU)
- Laboratory Tests
- Serum pregnancy test within 14 days of first injection (if applicable)
- Concomitant Medication Assessment

10.2.2 On-Trial Assessments

The following evaluations, as outlined in the Study Assessments Chart (see **Section 3**), will be performed on the days specified below.

Note:

- ***Concomitant Medications should be assessed at every study visit.***
- ***Adverse events (AEs) should be assessed starting at Day 1 after the first dose of trial drug.***

10.2.2.1 Reconfirmation of Eligibility at Day 1

To remain eligible for randomization on Day 1, the following two criteria must be met:

1. There is NO SIGNIFICANT ANATOMICAL CHANGE by clinical examination between the Screening visit and Day 1 (i.e. large subretinal hemorrhage, RPE rip, pigment epithelial detachment).

2. VISUAL ACUITY at Day 1 is WITHIN INCLUSION CRITERIA (Snellen equivalent 20/63 to 20/200) and WITHIN 5 LETTERS (better or worse) of the SCREENING VA.

   OR

   VISUAL ACUITY at Day 1 is WITHIN INCLUSION CRITERIA (Snellen equivalent 20/63 to 20/200) and WITHIN 6-10 LETTERS (better or worse) of the SCREENING VA, and repeat clinical examination and OCT imaging – both as judged and documented by the investigator – does NOT reveal:

- A significant anatomical change since the Screening visit (for example, large subretinal hemorrhage, RPE rip, pigment epithelial detachment), or
- An increase in central retinal thickness on OCT of ≥ 50 microns, or
- Any increase in "intraretinal" foveal fluid

If the patient is randomized, the repeat OCT (and FA, if taken) must be submitted to the Reading Center to be used as the new study baseline.

If the clinical examination and OCT imaging reveal any of the above findings, the patient must NOT be randomized.

If the Snellen VA equivalent at Day 1 is GREATER THAN 10 ETDRS LETTERS (better or worse) different from the SCREENING VA, the patient must NOT be randomized.

If the Snellen VA equivalent at Day 1 is NO LONGER WITHIN THE INCLUSION CRITERIA (Snellen equivalent 20/63 to 20/200), the patient must NOT be randomized.

10.2.2.2 Day 1 Visit

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic Examination (SE)
- Vital Signs
- Visual Function Questionnaire-25
- Randomization
- Avastin® or Eylea® Treatment
- Fovista™/Sham Treatment

Post-injection

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.3 Day 3 (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.4 Month 1 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Avastin® or Eylea® Treatment
- Fovista™/Sham Treatment

Post-injection

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.5 Month 1 + 3 Days (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.6 Month 2 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Avastin® or Eylea® Treatment
- Fovista™/Sham Treatment

Post-injection

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.7 Month 2 + 3 Days (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.8 Month 3 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Optical Coherence Tomography (OCT) (SE)

- Visual Function Questionnaire-25

Subjects Randomized to Receive Avastin®

- Avastin® Treatment
- Fovista™/Sham Treatment
-

Post-injection – Subjects who received Avastin + Fovista™/Sham Only

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.9 Month 3 + 3 Days (±1 day) – Subjects who received Avastin + Fovista™/Sham Only

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.10 Month 4 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Avastin® or Eylea® Treatment
- Fovista™/Sham Treatment

Post-injection

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.11 Month 4 + 3 Days (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.12 Month 5 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)

Subjects Randomized to Receive Avastin®

- Avastin® Treatment

- Fovista™/Sham Treatment

Post-injection– Subjects who received Avastin + Fovista™/Sham Only

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.13 Month 5 + 3 Days (±1 day) – Subjects who received Avastin + Fovista™/Sham Only

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.14 Month 6 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Vital Signs
- Color fundus photographs (OU)
- Fluorescein Angiograms (FA) (OU, transit study eye)
- Optical Coherence Tomography (OCT) (OU)
- Laboratory Tests
- Visual Function Questionnaire-25
- Avastin® or Eylea® Treatment
- Fovista™/Sham Treatment

Post-injection

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.15 Month 6 + 3 Days (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.16 Month 7 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)

- Tonometry and Ophthalmologic examination (SE)

Subjects Randomized to Receive Avastin®

- Avastin® Treatment
- Fovista™/Sham Treatment

Post-injection – Subjects who received Avastin + Fovista™/Sham Only

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.17 Month 7 + 3 Days (±1 day) – Subjects who received Avastin + Fovista™/Sham Only

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.18 Month 8 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Avastin® or Eylea® Treatment
- Fovista™/Sham Treatment

Post-injection

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.19 Month 8 + 3 Days (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.20 Month 9 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Optical Coherence Tomography (OCT) (SE)
- Visual Function Questionnaire-25

Subjects Randomized to Receive Avastin®

- Avastin® Treatment
- Fovista™/Sham Treatment

Post-injection – Subjects who received Avastin + Fovista™/Sham Only

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.21 Month 9 + 3 Days (±1 day) – Subjects who received Avastin + Fovista™/Sham Only

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.22 Month 10 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Avastin® or Eylea® Treatment
- Fovista™/Sham Treatment

Post-injection

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.23 Month 10 + 3 Days (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.24 Month 11 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)

Subjects Randomized to Receive Avastin®

- Avastin® or Treatment
- Fovista™/Sham Treatment

Post-injection – Subjects who received Avastin + Fovista™/Sham Only

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.25 Month 11 + 3 Days (±1 day) – Subjects who received Avastin + Fovista™/Sham Only

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.26 Month 12 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Vital Signs
- ECG
- Color fundus photographs (OU)
- Fluorescein Angiograms (FA) (OU, transit study eye)
- Optical Coherence Tomography (OCT) (OU)
- Laboratory Tests
- Visual Function Questionnaire-25
- Avastin® or Eylea® Treatment
- Fovista™/Sham Treatment

Post-injection

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.27 Month 12 + 3 days (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.28 Month 13 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)

- Optical Coherence Tomography (OCT) (SE)

Subjects Randomized to Receive Avastin®

- Avastin® or Treatment
- Fovista™/Sham Treatment

Post-injection – Subjects who received Avastin + Fovista™/Sham Only

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.29 Month 13 + 3 days (±1 day) – Subjects who received Avastin + Fovista™/Sham Only

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.30 Month 14 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Optical Coherence Tomography (OCT) (SE)
- Avastin® or Eylea® Treatment
- Fovista™/Sham Treatment

Post-injection Tonometry - at least 30 minutes after each injection (SE)

- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.31 Month 14 + 3 Days (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.32 Month 15 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Optical Coherence Tomography (OCT) (SE)

Subjects Randomized to Receive Avastin®

- Avastin® or Treatment
- Fovista™/Sham Treatment

Post-injection – Subjects who received Avastin + Fovista™/Sham Only

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.33 Month 15 + 3 days (±1 day) – Subjects who received Avastin + Fovista™/Sham Only

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.34 Month 16 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Optical Coherence Tomography (OCT) (SE)
- Avastin® or Eylea® Treatment
- Fovista™/Sham Treatment

Post-injection

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.35 Month 16 + 3 days (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.36 Month 17 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Optical Coherence Tomography (OCT) (SE)

Subjects Randomized to Receive Avastin®

- Avastin® Treatment
- Fovista™/Sham Treatment

Post-injection – Subjects who received Avastin + Fovista™/Sham Only

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.37 Month 17 + 3 Days (±1 day) – Subjects who received Avastin + Fovista™/Sham Only

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.38 Month 18 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Vital Signs
- Color fundus photographs (OU)
- Fluorescein Angiograms (FA) (OU, transit study eye)
- Optical Coherence Tomography (OCT) (OU)
- Laboratory Tests
- Visual Function Questionnaire-25
- Avastin® or Eylea® Treatment
- Fovista™/Sham Treatment

Post-injection

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.39 Month 18 + 3 days (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.40 Month 19 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Optical Coherence Tomography (OCT) (SE)

Subjects Randomized to Receive Avastin®

- Avastin® or Treatment
- Fovista™/Sham Treatment

Post-injection – Subjects who received Avastin + Fovista™/Sham Only

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.41 Month 19 + 3 days (±1 day) – Subjects who received Avastin + Fovista™/Sham Only

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.42 Month 20 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Optical Coherence Tomography (OCT) (SE)
- Avastin® or Eylea® Treatment
- Fovista™/Sham Treatment

Post-injection

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.43 Month 20 + 3 Days (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.44 Month 21 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Optical Coherence Tomography (OCT) (SE)

Subjects Randomized to Receive Avastin®

- Avastin® Treatment
- Fovista™/Sham Treatment

Post-injection – Subjects who received Avastin + Fovista™/Sham Only

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.45 Month 21 + 3 days (±1 day) – Subjects who received Avastin + Fovista™/Sham Only

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.46 Month 22 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Optical Coherence Tomography (OCT) (SE)
- Avastin® or Eylea® Treatment
- Fovista™/Sham Treatment

Post-injection

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.47 Month 22 + 3 days (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.48 Month 23 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Optical Coherence Tomography (OCT) (SE)

Subjects Randomized to Receive Avastin®

- Avastin® or Treatment
- Fovista™/Sham Treatment

Post-injection – Subjects who received Avastin + Fovista™/Sham Only

- Tonometry - at least 30 minutes after each injection (SE)
- Ophthalmologic Exam - at least 30 minutes after the second injection (SE)

10.2.2.49 Month 23 + 3 Days (±1 day) – Subjects who received Avastin + Fovista™/Sham Only

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.2.50 Month 24 (±7 days)

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Vital Signs
- ECG
- Color fundus photographs (OU)
- Fluorescein Angiograms (FA) (OU, transit study eye)
- Optical Coherence Tomography (OCT) (OU)
- Laboratory Tests
- Visual Function Questionnaire-25

10.2.2.51 Early Withdrawal

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Vital Signs
- ECG
- Color fundus photographs (OU)

- Fluorescein Angiograms (FA) (OU, transit study eye)
- Optical Coherence Tomography (OCT) (OU)
- Laboratory Tests
- Visual Function Questionnaire-25

Adverse events are recorded up until 30 days after the last dose of study drug or until the last follow up visit of the trial, whichever comes later. An adverse event that is ongoing at the last follow-up study visit is required to be followed up until the event resolves or stabilizes at a level acceptable to the Investigator and/or Sponsor. If the subject still presents with any treatment-related toxicity, the follow-up period will be extended until return to baseline status or until the condition has stabilized.

10.3 Withdrawal from Trial

Subjects have the right to withdraw from the trial at any time for any reason. The Investigator (after consultation with the Sponsor) or Sponsor also have the right to withdraw subjects from the trial in the event of concurrent illness, adverse events, treatment-failure after a prescribed procedure, protocol violations, cure, administrative or other reasons.

Final trial assessments as outlined in the Study Assessments Chart, Section 3, should be performed on all subjects who withdraw. Subjects who withdraw due to an adverse event should be followed until resolution of the adverse event, or an adequate explanation for the event is obtained.

Subjects who withdraw for any reason should have assessments performed according to the Early Withdrawal schedule. If an alternative treatment for AMD is initiated, the subject will no longer be evaluated according to this protocol.

10.4 Trial Discontinuation

The reason for a subject discontinuing from the trial will be recorded in the case report form. A discontinuation occurs when an enrolled subject ceases participation in the trial, regardless of the circumstances, prior to completion of the protocol. The investigator must determine the primary reason for discontinuation. A discontinuation must be reported immediately to the clinical monitor or his/her designated representative if it is due to a serious adverse event (SAE) (see Section

12.4). The final evaluation required by the protocol will be performed at the time of trial discontinuation. The investigator will record the reason for trial discontinuation, provide or arrange for appropriate follow-up (if required) for such subjects, and document the course of the subject's condition.

Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Ophthotech Corp.

11 STATISTICAL METHODS

11.1 Experimental Design

Subjects will be randomized in a 1:1 ratio to the following dose groups:

- Fovista™ 1.5 mg/eye + Avastin® 1.25 mg/eye or Eylea® 2 mg/eye
- Fovista™ sham + Avastin® 1.25 mg/eye or Eylea® 2 mg/eye

Within each of the above dose groups, subjects will be randomized in a 1:1 ratio to either Avastin® 1.25 mg/eye or Eylea® 2 mg/eye.

Subjects will be treated with active Fovista™ or sham in combination with Avastin®

Subjects randomized to receive Avastin will be treated with active Fovista™ or sham in combination with Avastin® monthly for 24 months.

Subjects randomized to receive Eylea will be treated with active Fovista™ or sham in combination with Eylea® every month for the first 3 doses (Day 1, Month 1, and Month 2) and every other month thereafter (i.e., Months 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22).

Therefore, subjects randomized to receive Avastin® will be treated with active Fovista™ or sham in combination with Avastin® for a total of 24 administrations. Subjects randomized to receive Eylea® will be treated with active Fovista™ or sham in combination with Eylea® for a total of 13 administrations.

All subjects will have a final follow-up visit at Month 24.

11.2 Endpoints

11.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change in visual acuity (ETDRS letters) from baseline to the Month 12 visit.

11.2.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints of the trial include:

- The proportion of subjects in each treatment group gaining 20 or more ETDRS letters from baseline at the Month 12 visit.
- The proportion of subjects in each treatment group gaining 25 or more ETDRS letters from baseline at the Month 12 visit.
- The proportion of subjects in each treatment group losing 5 or more ETDRS letters from baseline at the Month 12 visit.
- The mean change in visual acuity (ETDRS letters) from baseline at the Month 6 visit.

11.2.3 Safety and Tolerability Endpoints

Safety and tolerability endpoints are:

- All adverse events reported, whether or not deemed related to the injection procedure or study treatment
- All serious adverse events (SAE), whether or not deemed related to the injection procedure or study treatment
- Laboratory data (blood: hematology, renal function, hepatic function, and electrolytes; urinalysis)
- Ophthalmic variables (IOP, ophthalmic examination, fluorescein angiograms and OCT)
- Vital sign measurements
- ECG

11.3 Number of Subjects

11.3.1 Sample Size Required

For the primary endpoint (the mean change in visual acuity from baseline at Month 12) the Fovista™/Avastin® or Eylea® treatment arm will be compared to the Sham/ Avastin® or Eylea® treatment arm. [redacted] To account for dropouts, approximately 311 subjects will be recruited in each group, for a total of approximately 622 subjects enrolled.

[redacted]

11.4 Randomization Procedure

Subjects will be centrally allocated to one of the two treatment groups, and further allocated to one of the two treatments (Avastin® or Eylea®) [redacted]

[redacted]

11.5 Masking Procedures

Treatment with Fovista™ 1.5 mg/eye or Fovista™ sham is double-masked, i.e., the study staff (except for unmasked personnel, see below) and the patient will not be aware of the treatment assignment. Treatment with Avastin® or Eylea® will be administered in an open-label manner; however the visual acuity examiner will not be aware of this treatment assignment.

It is the responsibility of the Principal Investigator to ensure that the physician assessing adverse events, the VA examiner, all masked study personnel and the subject remain masked to the subject's treatment assignment of Fovista™ 1.5 mg/eye or Fovista™ sham.

The masking procedures for this protocol are similar to those of The Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) [8], sponsored by the National Eye Institute of the United States National Institutes of Health. There are different levels of masking within the study. The Refractionist and Visual Acuity Examiner are masked to the treatment assignment of Fovista™ 1.5 mg/eye or Fovista™ sham. The unmasked injector (ophthalmologist) and designated unmasked assistant(s) (if needed) are unmasked to treatment assignment. The masked assessor (ophthalmologist) will perform all other physician assessments including the relationship of all adverse events to study drug, including those noted by the unmasked injector.

11.5.1 Visual Acuity Assessments

Since this is a double-masked study, subjects and staff at the investigational site, particularly the visual acuity examiners, will be masked to the subject's treatment assignment of Fovista™ 1.5 mg/eye or Fovista™ sham. Additionally, the study staff and the patient should not inform the visual acuity examiner if the patient is being treated with Avastin® or Eylea®. All visual acuity assessments will be performed by the trial refractionist/ophthalmologist, who will be masked to the subject's treatment as well as previous visual acuity assessments. The trial refractionist/ophthalmologist will be supplied only with the subject's most recent protocol refraction.

To ensure that the visual acuity examiner remains masked to the assignment to Avastin® or Eylea®, an important task of the study coordinator is to remind the patient not to discuss the drug they are receiving with the visual acuity examiner. Similarly, clinic staff must be reminded not to discuss the assignment to Avastin® or Eylea® with Visual Acuity Examiner prior to each examination.

11.5.2 Injections

Each clinical site is required to have a minimum of 2 ophthalmologists – the unmasked injector and the masked assessor. The unmasked injector will perform

the Fovista™/Sham injection as well as the post-injection ophthalmic exam and tonometry measurements. Either ophthalmologist may perform the Avastin® or Eylea® injection. The unmasked injector and designated unmasked assistants (if needed) are not permitted to be involved in the conduct of the study in any other manner and are not to communicate with any other personnel or subjects regarding the treatment assignment. Once the unmasked injector or unmasked assistant breaks the seal on the masked drug kit, no masked study personnel can be present until after the injections are complete and the drug kit and components (vial, syringe, needles) have been disposed of by the unmasked injector/unmasked assistant; only the empty drug kit box and the tear-off part of the vial label are saved. The masked assessor will perform all other physician assessments including the relationship of all adverse events to study drug, including those noted by the unmasked injector.

11.5.3 Statistical Analyses

All statistical analyses will be performed by a statistical office independent of the study Sponsor. The Sponsor and the subjects will remain masked to treatments until the end of the study, except if safety considerations justify breaking the code for individual subjects.

11.5.3.1 Analysis upon all Subjects Completing Month 12

When all enrolled subjects have either completed 12 months of treatment or discontinued from the study, an analysis will be conducted to assess results for the primary and secondary endpoints (at the primary time point, Month 12). Results will be made available to select individuals within the sponsor organization to provide executive oversight and for regulatory and legal purposes, e.g., public dissemination of results as required by U.S. business law. Individual patient treatment regimens will not be made available to investigators or to individuals directly involved in the conduct of the trial in order to preserve appropriate masking.

11.6 Analytical Considerations

11.6.1 Analytical Plan and Significance Levels

The primary efficacy endpoint is the mean change in visual acuity (ETDRS letters) from baseline to the Month 12 visit.

The methods for imputation of post-baseline, missing data will be specified in the Statistical Analysis Plan. Among the approaches, Last Observation Carried Forward (LOCF), all observed data, a mixed model repeated measure approach (MMRM), multiple imputation and other analyses will be considered as deemed appropriate. The Statistical Analysis Plan will specify the details of this approach.

Additional details regarding analyses will be provided in a separate Statistical Analysis Plan.

11.6.2 Descriptive Statistics

Descriptive statistics will be provided to document baseline and on-trial comparability, including demographic information, treatment administration, and protocol violations.

11.6.3 Efficacy Analysis

Primary Endpoint

Comparisons of the mean change in visual acuity in ETDRS letters between Fovista™/Avastin® or Eylea® and Sham/Avastin® or Eylea® for the primary endpoint will be made using analysis of covariance with baseline visual acuity as a covariate, stratified by (blocking on) lesion subtype (>50% classic vs. ≤50% classic).

Secondary Endpoints

Analysis methodology for secondary endpoints will be specified in a separate Statistical Analysis Plan.

11.6.4 Safety Analysis

The safety analysis will be conducted on all subjects who had at least one administration of trial drug.

Adverse events will be summarized using MedDRA terms. The incidence and severity of adverse events will be listed and grouped by body system.

All laboratory data will be listed and values falling outside normal ranges will be identified. Summary statistics (i.e., mean, median, standard deviation, minimum and maximum) will be presented for all continuous variables.

Summary statistics will be given on the number of subjects for whom the trial medication had to be permanently stopped.

11.6.5 Subset Analyses

The trial is not sized to test for the presence of treatment by subset interactions. Thus true treatment by subset interactions will likely be missed, unless they are quite substantial. Conversely, should any particular subset of subjects seem to benefit more or less from therapy than the total population, this will not be taken as evidence of a true treatment by subset interaction, given the likelihood that such an observation could be due to chance alone. With these caveats in mind, exploratory subset analyses may be performed.

12 ADVERSE EVENTS

12.1 Definition of Adverse Events

An Adverse Event (AE) is defined as follows: Any untoward medical occurrence in a patient or subject including unfavorable and unintended signs, symptoms or disease temporally associated with the use of a medicinal product and which does not necessarily have to have a causal relationship to this treatment.

Adverse events include illnesses with onset during the trial, or exacerbations of pre-existing illnesses. Exacerbation of pre-existing illness is defined as a significant increase in the severity of the illness as compared to the start of the trial, and should be considered when a subject requires new or additional treatment for that illness. Lack of or insufficient clinical response or efficacy should not be recorded as an adverse event.

In addition, clinically significant changes in objective findings (e.g., laboratory, ECG, X-ray, physical examination) should also be considered as to whether they are adverse events. The criteria for determining whether an objective finding should be reported as an adverse event are as follows:

1. Associated with accompanying symptoms; and/or
2. Requires medical/surgical intervention; and/or

3. Leads to a change in trial dosing or discontinuation from the trial, significant additional concomitant drug treatment or other therapy; and/or
4. Leads to any of the outcomes included in the definition of a serious adverse event; and/or
5. Is considered to be an adverse event by the investigator or Sponsor.

Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

12.2 Assessment and Reporting of Adverse Events

Adverse events will be recorded starting after the first dose of trial drug and continuing until 30 days after the last dose or until the last follow-up visit required by the protocol, whichever comes later. An adverse event that is ongoing at the last follow up study visit is required to be followed up until the event resolves or stabilizes at a level acceptable to the investigator and/or Sponsor.

All adverse events spontaneously reported, elicited or observed by the investigators will be recorded. The events will be recorded in the source documents and onto the adverse event pages of the case report form, including date of onset and resolution, severity, relationship to trial treatment and determination of “serious”.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

The investigator will take all therapeutic measures necessary for resolution of the adverse event. Any medication necessary for treatment of the adverse event must be recorded in the subject’s source documents and on the appropriate pages of the subject’s case report form.

To assist with grading of adverse event severity, the following definitions are provided:

Mild = Aware of sign or symptom, but easily tolerated;

Moderate = Discomfort enough to cause interference with usual activity;

Severe = Incapacitating with inability to work or do usual activity;

Adverse events are assessed as either related to the intravitreous injection procedure (eyelid speculum, anesthetic drops, mydriatic drops, antibiotic drops, povidone-iodine drops or flush, subconjunctival injection of anesthetic, intravitreous injection), termed "injection procedure-related", or to study drug (Fovista™, Avastin® or Eylea®).

The relationship to the intravitreous injection procedure or to study drug will be assessed using the following definitions:

Not Related = There is not a reasonable possibility that the adverse event is related to the injection procedure or to the study drug.

Related = There is a reasonable possibility that the adverse event is related to the injection procedure or to the study drug.

12.3 Definition of Serious Adverse Events

A serious adverse event is any event that:

1. Results in death;
2. Is life-threatening (immediate risk of death);
3. Results in inpatient hospitalization or prolongation of existing hospitalization;
4. Results in a persistent or significant disability/incapacity; or
5. Results in congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient/subject and may

require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

A life-threatening adverse event is any event that places the patient/subject at immediate risk of death from the reaction as it occurred; i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Disability is a substantial disruption of a person's ability to conduct normal life functions.

Hospitalization is defined as any formal inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission also includes transfer within the hospital to an acute/intensive care inpatient unit (e.g., from the psychiatric wing to a medical floor, from a medical floor to the coronary care unit).

- Inpatient admission does not include the following:
    - Emergency Room/Casualty Department visits
    - Outpatient/same-day/ambulatory procedures and observation/short-stay units
    - Hospice facilities and Respite care (e.g., caregiver relief)
    - Rehabilitation facilities, skilled nursing facilities, nursing homes, custodial care facilities
- Inpatient admission in the absence of a precipitating, treatment-emergent, clinical adverse event may meet criteria for "seriousness" but is not an adverse event and thus is not subject to immediate reporting to the Sponsor. For example:
    - Admission for treatment of a pre-existing condition not associated with the development of a new adverse event or with a worsening of the pre-existing condition (e.g., for work-up of persistent pretreatment lab abnormality)
    - Social admission (e.g., subject has no place to sleep)
    - Optional admission not associated with a precipitating clinical adverse event (e.g., yearly physical, elective cosmetic surgery)

12.4 Assessment and Reporting of Serious Adverse Events

Serious adverse events will be recorded starting after the first dose of trial drug and continuing until 30 days after the last dose or until the last follow-up visit required by the protocol, whichever comes later. Any serious adverse event occurring at any other time after completion of the trial must be promptly reported if a causal relationship to trial drug is suspected.

If a serious adverse event occurs, the Sponsor is to be notified within 24 hours of awareness of the event by the investigator. In particular, if the serious adverse event is fatal or life-threatening, notification to the Sponsor must be made regardless of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports.

All Serious Adverse Events must be reported by FAX

to the Sponsor or Designee within 24 hours.

FAX NUMBER:

Refer to the "Safety Contact List" provided separately

12.5 Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee will review patient safety data during the course of the trial.

12.6 Exposure in Utero

If any trial subject becomes or is found to be pregnant while receiving trial drug, the investigator must contact the Sponsor. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The Sponsor will inform the site of the information to be provided.

12.7 Abnormal Laboratory Results

If a clinically significant laboratory value occurs, the investigator will repeat the laboratory determination as judged appropriate until the abnormality is resolved, is no longer considered clinically significant by the investigator, or an explanation for the change is obtained.

13 RESPONSIBILITIES

13.1 Emergency Equipment

All participating sites should have emergency resuscitation equipment available, including at a minimum, an Ambu bag, IV tubing, D5W IV fluid, oxygen, and epinephrine 1:1000, and Diphenhydramine Hydrochloride (Benadryl). It is each center's responsibility to ensure that all equipment is within specifications for the duration of the trial. Each center should have written policies regarding resuscitation procedures.

13.2 Case Report Forms and Trial Documentation

The investigator will complete the appropriate case report form pages within 3 business days following completion of each procedure or evaluation.

All data recorded on case report forms will be supported by source documents. For certain trial parameters, with prior written agreement by the trial sponsor and monitor, the case report form may be used to record source data.

All source documents will be made available to Ophthotech Corp. clinical monitors during scheduled monitoring visits, to auditors during any audits requested by Ophthotech Corp., and to regulatory agencies during inspections.

The investigator will maintain a Trial File containing all trial related documentation required by Good Clinical Practice (GCP). This Trial File will be reviewed periodically for completeness by Ophthotech Corp.'s clinical monitors and must be made available to auditors and regulatory agencies.

All case report forms and original source documents including ocular images should be stored for a minimum of two years after a marketing application has been approved, or two years after formal discontinuation of development of the investigational drug, or five years after completion of the trial, whichever is longer. Documents should not be destroyed without the permission of Ophthotech Corp. In the event of the Principal Investigator leaving the clinical site, it is the Principal Investigator's responsibility to notify Ophthotech Corp. in writing and to designate which trial material will be transferred at the clinical site.

13.3 Drug Accountability/Storage Conditions

The investigator is responsible for the accountability of all used and unused trial medication and for recording and documenting the drug storage temperature at arrival and throughout the trial. Drug accountability records will be reviewed during monitoring visits. Adequate drug accountability records include documentation of all trial drug supplies received, dispensed to trial subjects, and returned to Ophthotech Corp.

At the end of the trial, all drug supplies and documentation will be reviewed and verified by the trial monitors. The sites will be instructed to destroy unused trial drug supplies when the trial is completed, or the site may choose to return the drug to an Ophthotech Corp. contracted drug management facility for destruction. If the drug is destroyed at the site, the drug accountability form must be completed and sent to Ophthotech Corp. for archiving.

13.4 Protocol Compliance

Ophthotech Corp. will not compensate the Investigator for evaluation of cases in which the procedures and evaluations are conducted in a manner other than that specified by the protocol.

Under certain circumstances, individual protocol criteria may be waived by Ophthotech Corp. and in agreement with the investigator. Any such waiver will be documented in writing and provided to the investigator by Ophthotech Corp.

13.5 Ethical Aspects

Local Regulations/Declaration of Helsinki

The investigator will ensure that this trial is conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, South Africa, and Scotland) and with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The trial must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (May 9th 1997) and with local law if it affords greater protection to the subject. For studies conducted in the USA or under US IND, the investigator will additionally ensure adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CFR,

subchapter D, part 312, “Responsibilities of Sponsors and Investigators”, part 50, “Protection of Human Subjects”, and part 56, “Institutional Review Boards”.

13.6 Institutional Review Board (IRB) or Ethics Committee (EC) Approval and Informed Consent

The investigator is responsible for obtaining approval of the trial protocol, informed consent, and any advertising used for subject recruitment from the appropriate IRB/EC prior to initiating the trial. The investigator will forward the following documents prior to commencement of subject enrollment:

- IRB/EC approval documentation
- Approved trial subject informed consent
- A list of IRB/EC members, or statement of compliance

Prior to enrollment, written informed consent must be obtained from each subject or his/her legally authorized representative. The informed consent must contain all of the elements prescribed by the relevant regulatory authorities and must be appropriately signed, dated and witnessed. **Any changes by the Investigator or local IRB/EC to the sample consent provided by the Sponsor must be approved by the Sponsor before initiating enrollment.**

13.7 Clinical Trial Insurance

Ophthotech Corp. has insurance coverage for medicine-induced injury and other liabilities incurred during clinical trials with its compounds.

13.8 Trial Report and Publications

The trial will be documented in a final report, which will contain appropriate statistical analysis and medical overview. No individual site or investigator may publish or present any results from the trial until a joint, multi-center publication of the trial results is made by Sponsor in conjunction with various participating investigators and appropriate sites contributing data and comments. Subsequently, individual investigators may request to publish or present results from the trial; however, approval will be at the sole discretion of the Sponsor. Should the foregoing language be in conflict with the language addressing publication in the clinical trial agreement, the language in the clinical trial agreement will prevail.

14 MONITORING

The investigator will permit representatives of Ophthotech Corp. to review all case report forms, trial documentation, and subject medical records at regular intervals throughout the trial. These monitoring visits are for the purpose of verifying protocol compliance, subject safety, and the adequacy of data collected.

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16 SIGNATURE PAGE

Signatures confirm that this protocol OPH1004B has been carefully read and fully understood, and that there is agreement to comply with the conduct and terms of the trial specified herein in compliance with Good Clinical Practice and all other regulatory requirements.

PROTOCOL OPH1004B: "A phase 3 randomized, double-masked, controlled trial to establish the safety and efficacy of intravitreous administration of Fovista™ (Anti PDGF-B pegylated aptamer) administered in combination with either Avastin® or Eylea® compared to Avastin® or Eylea® monotherapy in subjects with subfoveal neovascular age-related macular degeneration."

Trial Sponsor: **Ophthotech Corporation**

17 APPENDICES

17.1 Method for Evaluating Anterior Chamber Inflammatory Activity

17.1.1 Examination

1. The pupils will be maximally dilated.
2. A slit-lamp biomicroscope will be used with a one by two mm^2 beam at an angle of 30-45°. The number of cells within this wedge will be counted.
3. The grade of anterior chamber inflammatory activity is determined.

17.1.2 Standardized Description of Anterior Chamber Activity

Anterior chamber activity will be graded on a scale of 0, trace, 1+, 2+, 3+, and 4+.

The grading is as follows:

0	None
Trace	<5 cells in wedge
1+	5 - 10 cells in wedge
2+	11 - 20 cells in wedge
3+	21 - 50 cells in wedge
4+	>50 cells in wedge

Hogan MJ, Kimura SJ, Thygeson P. Signs and symptoms of Uveitis. I. Anterior uveitis. Am J Ophthalmol 1959; 47:155-170.

17.2 Method for Evaluating Vitreous Inflammatory Activity

All subjects will have the standard fundus examination followed by evaluation for inflammatory activity in the vitreous.

17.2.1 Marking

The clarity of the optic nerve head, retinal vessels, and the nerve fiber layer are used as landmarks for the marking criteria.

17.2.2 Examination

1. The pupils will be maximally dilated.
2. An indirect ophthalmoscope and a 20+ diopter aspheric lens will be used as the standard.
3. Standard fundus examination is performed with the last view being over the disc and surrounding retina.
4. Inflammatory activity is evaluated by the examiner by determining which standardized description most closely resembles the vitreal haze seen through the indirect ophthalmoscope.

17.2.3 Standardized Description of Vitreous Inflammation

Vitreous activity will be graded on a scale of 0, 1+, 2+, 3+, and 4+.

The grading is as follows[1]:

0	No evident vitreal haze at all.
1+	Minimal haze. Optic nerve head and retinal vessels are both clearly defined.
2+	Retinal vessels are visible, but not clearly defined.
3+	Optic nerve head is visible but the borders are blurry, and cannot see vessels.
4+	Optic nerve head is obscured.

17.2.4 References

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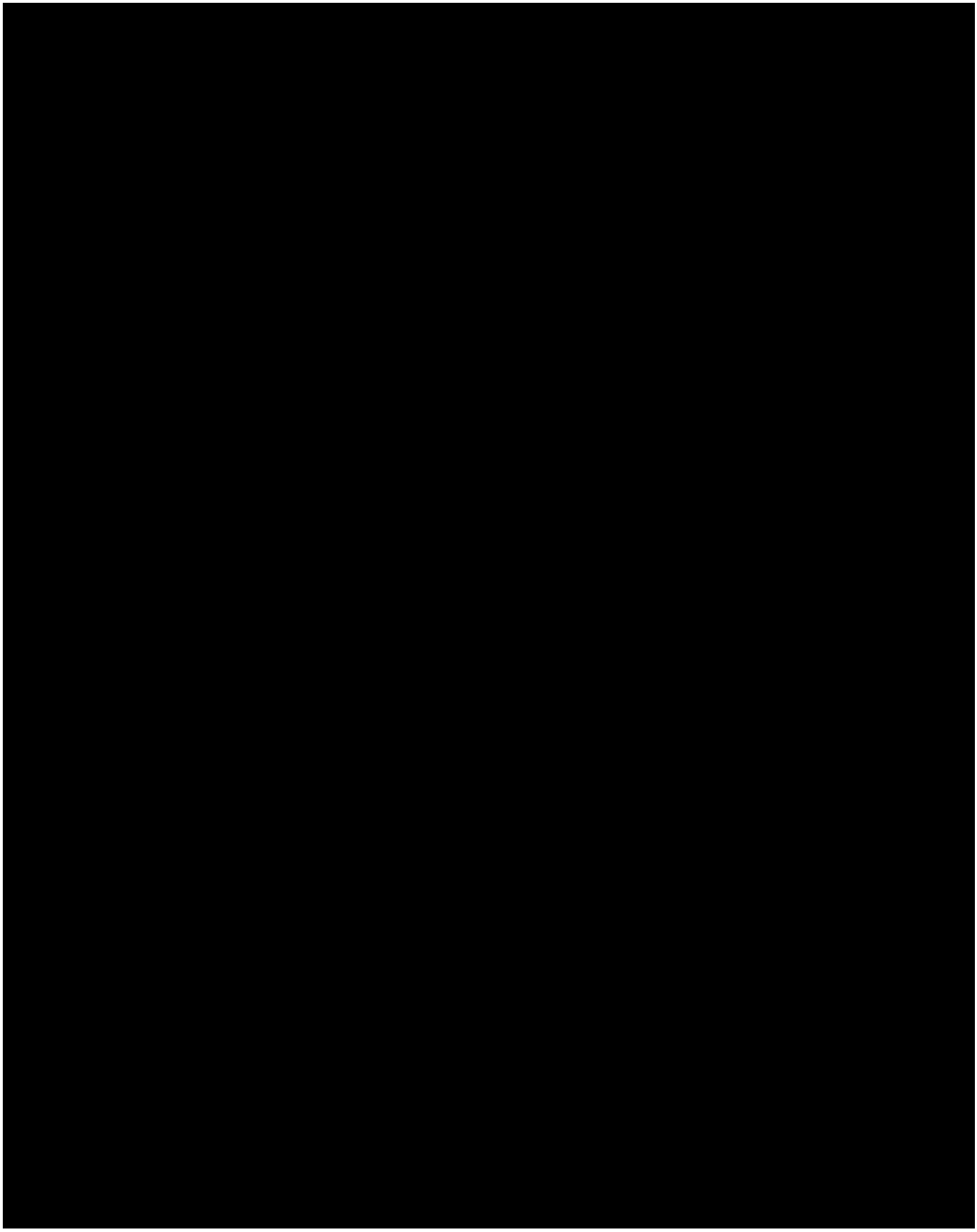
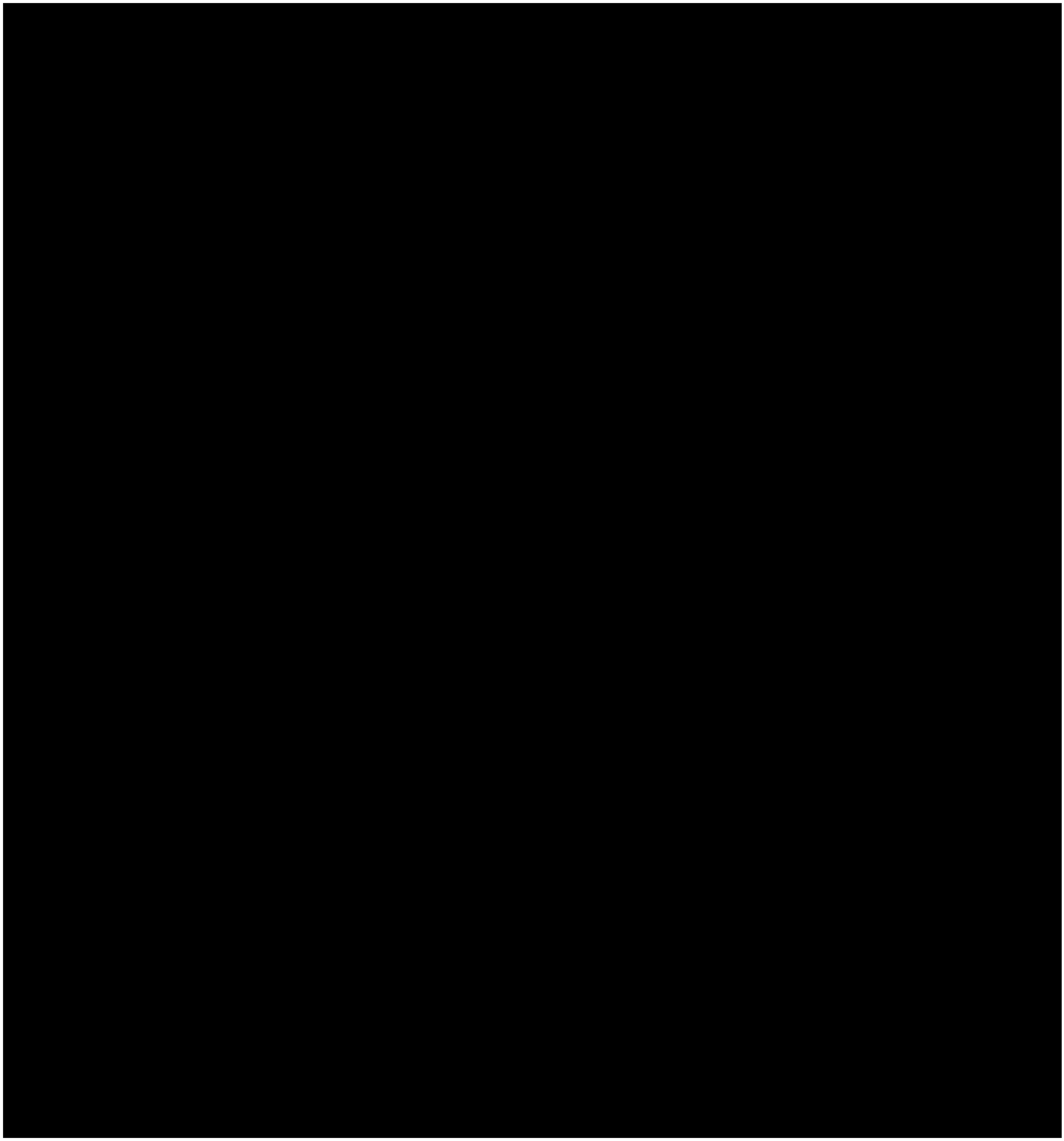
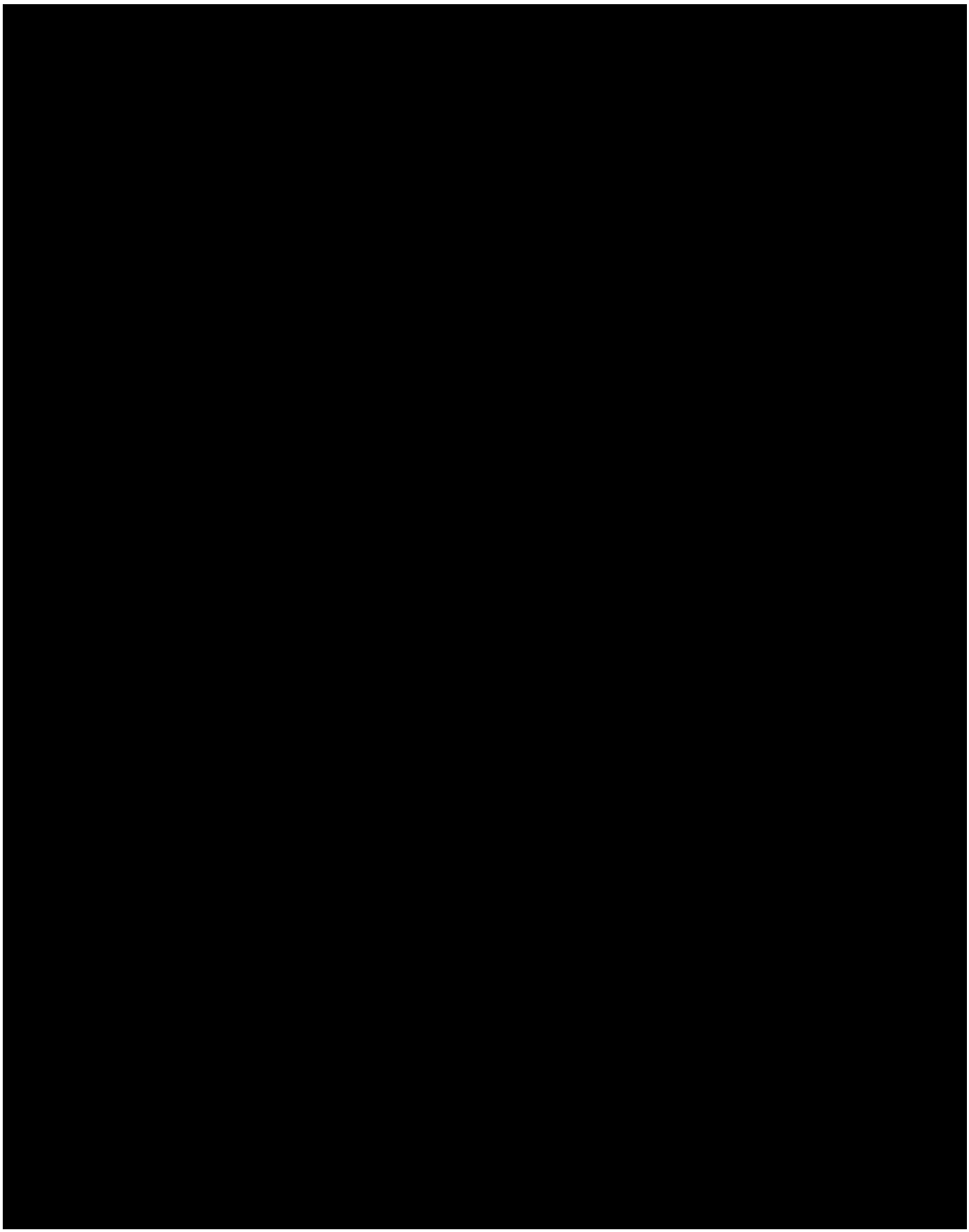
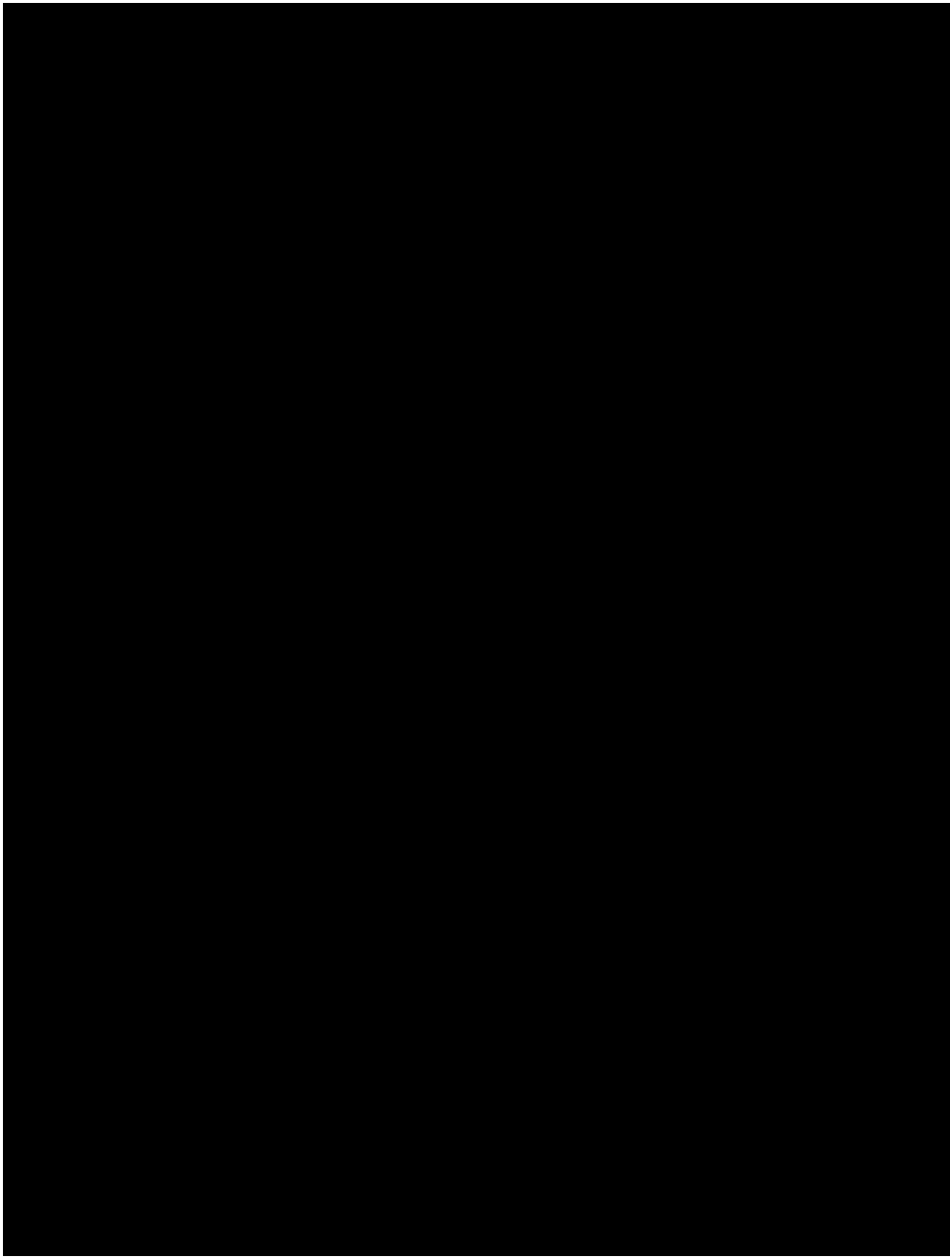
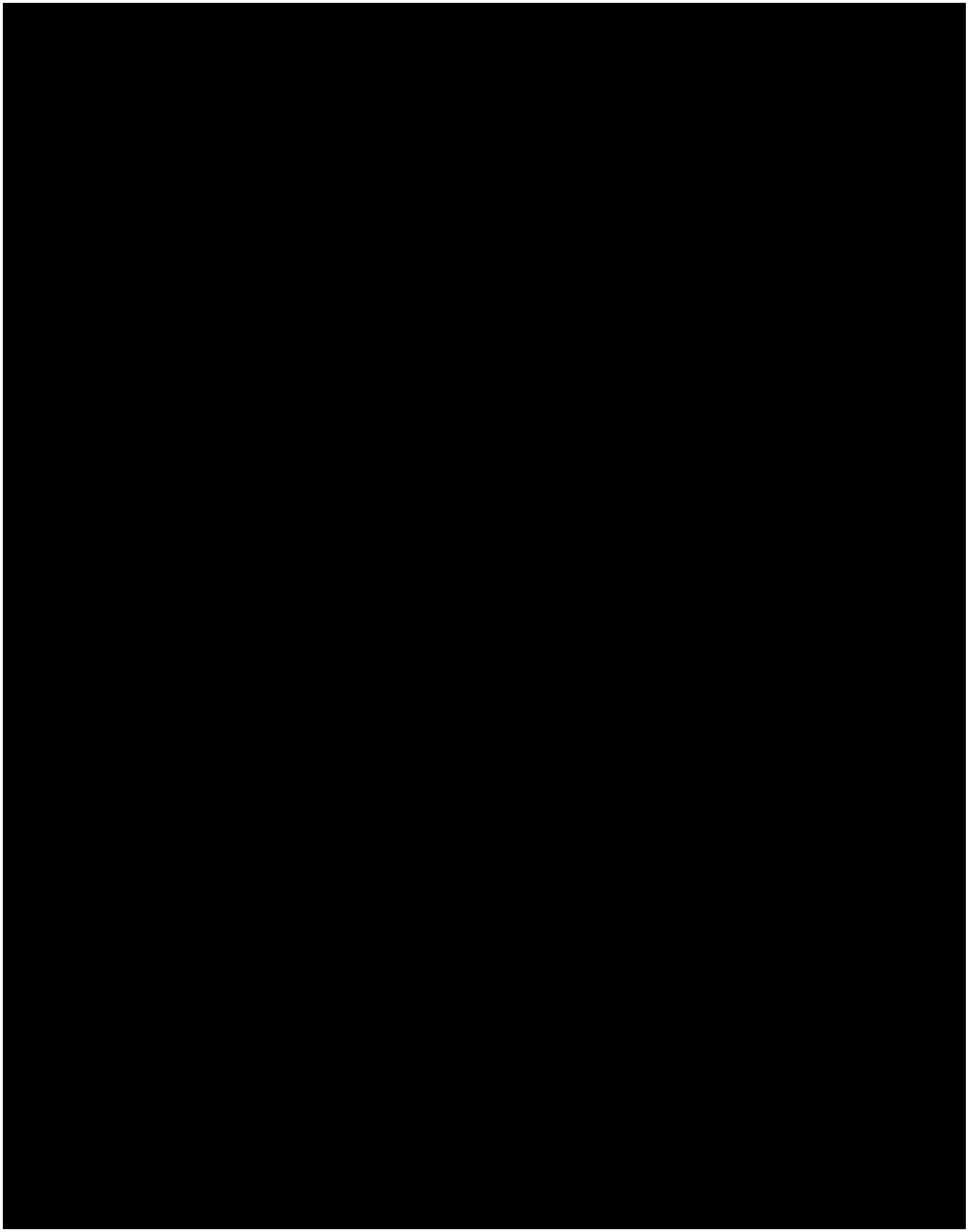
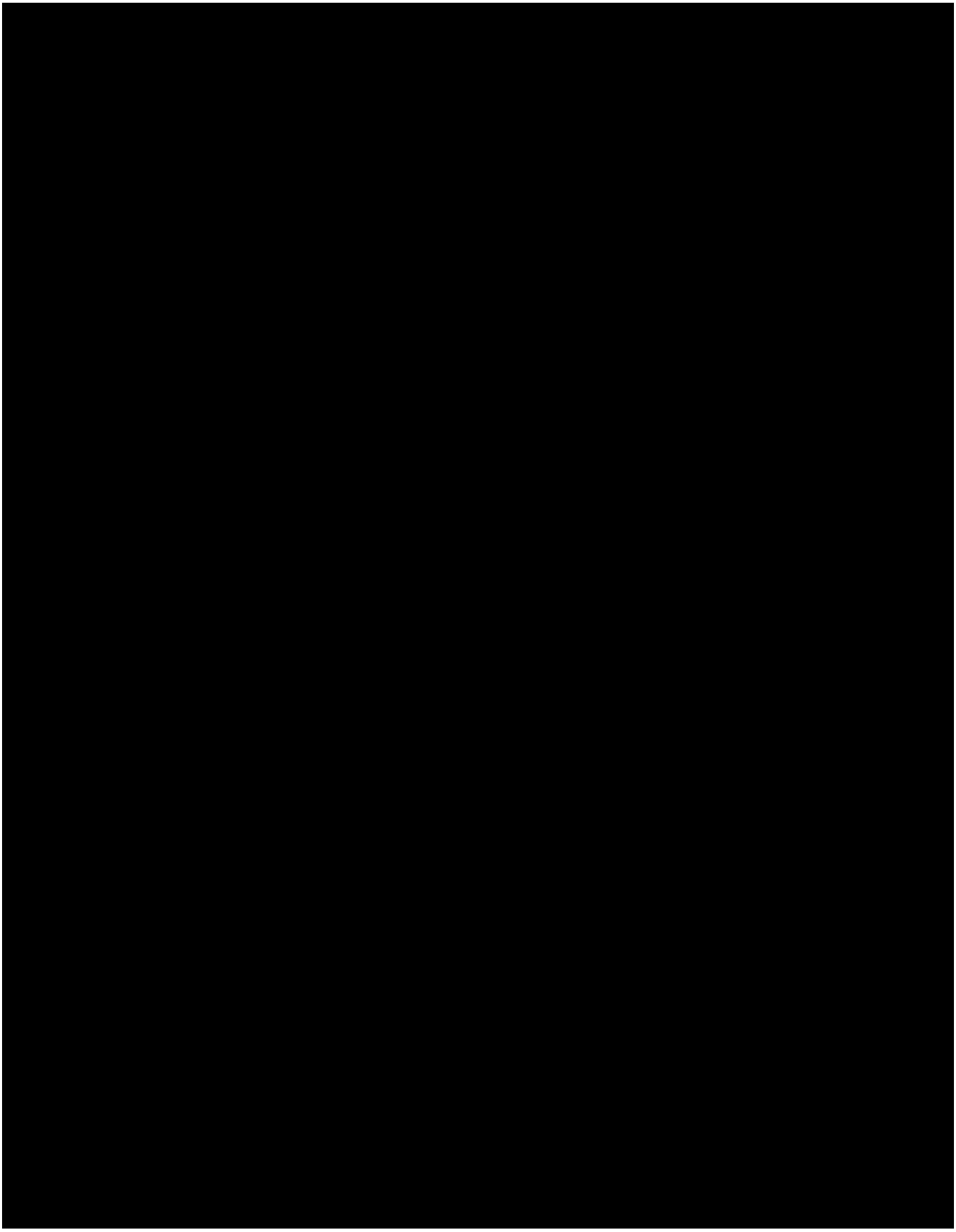


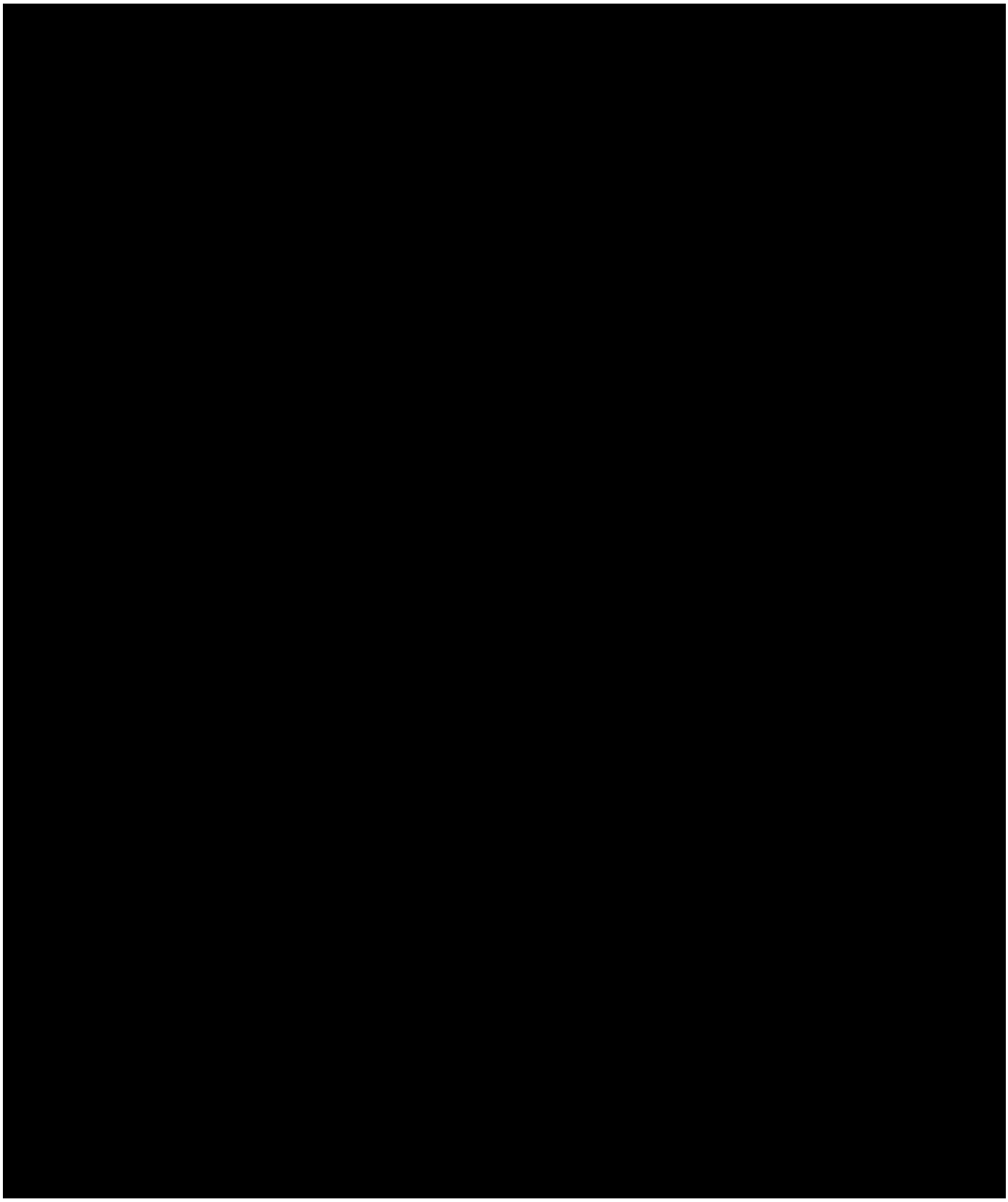


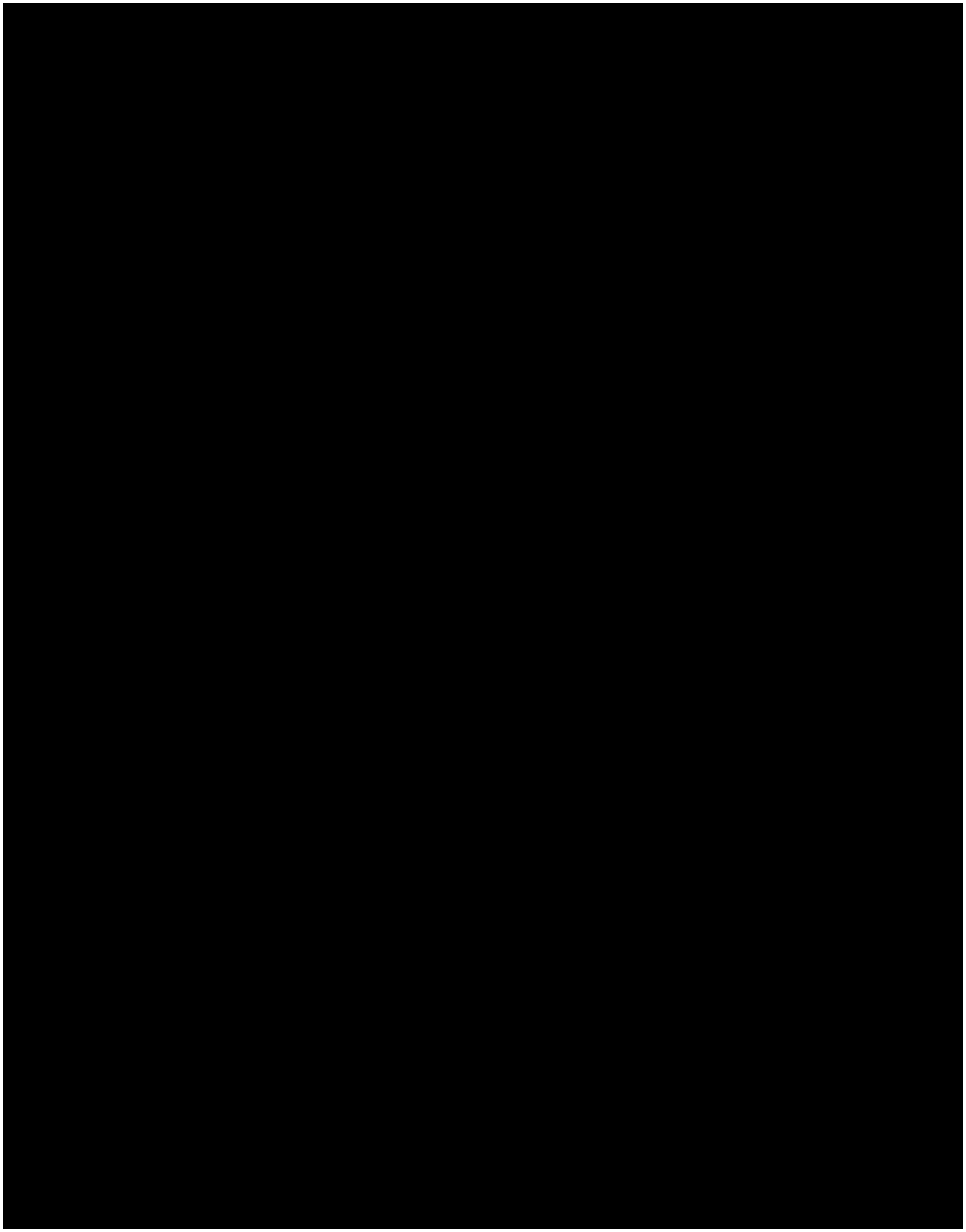


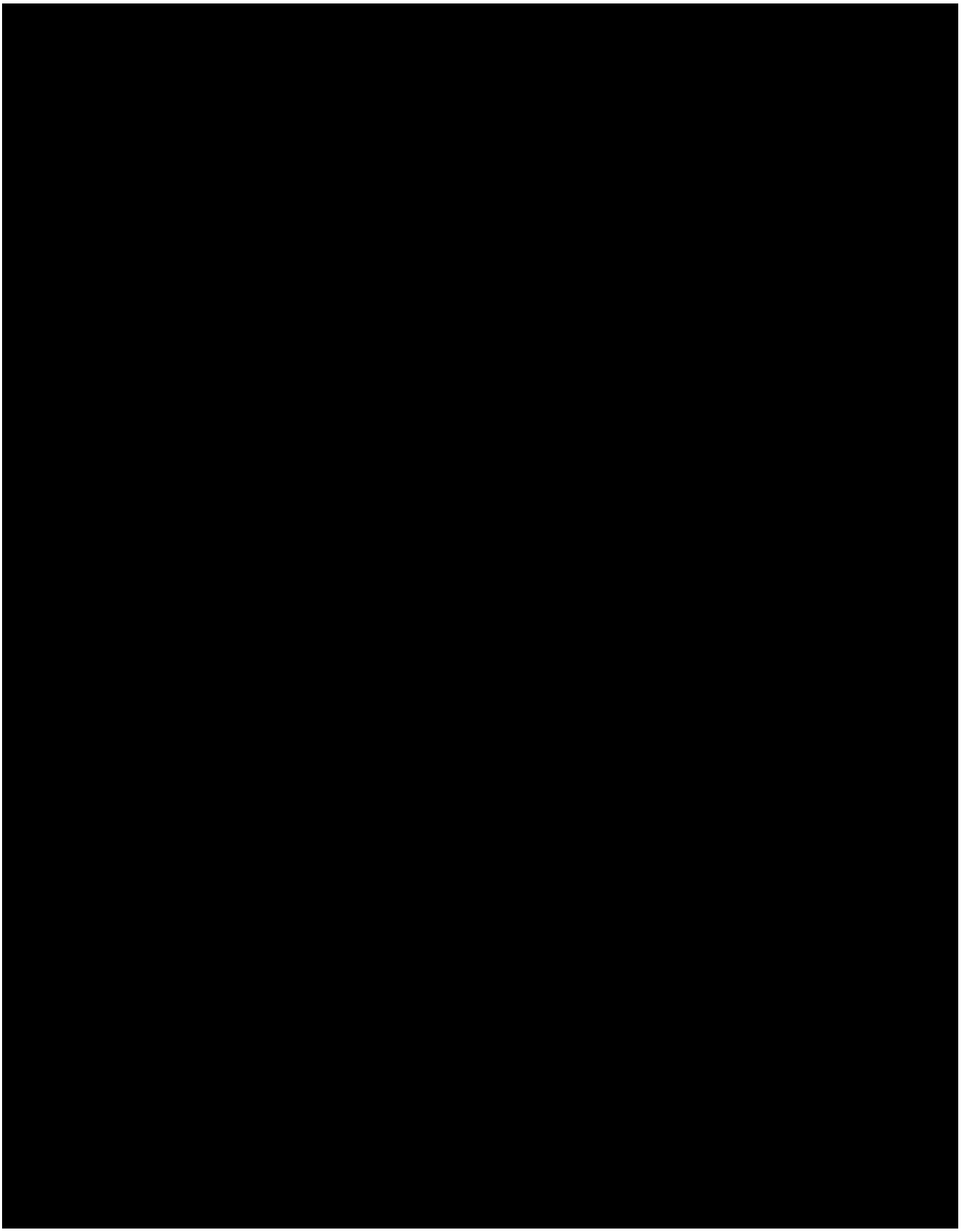












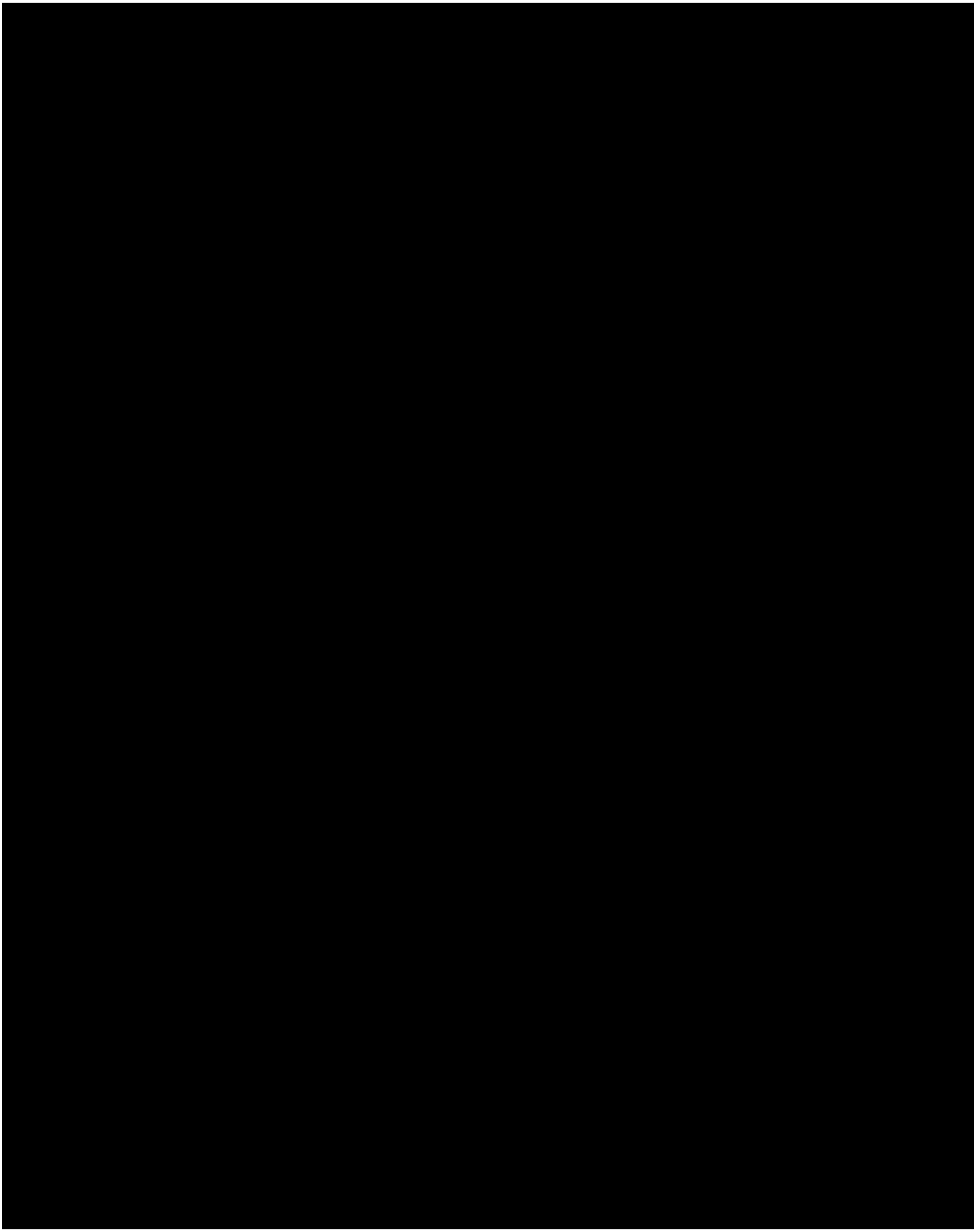
17.4 ECOG/WHO Performance – Karnofsky Performance Status Scales

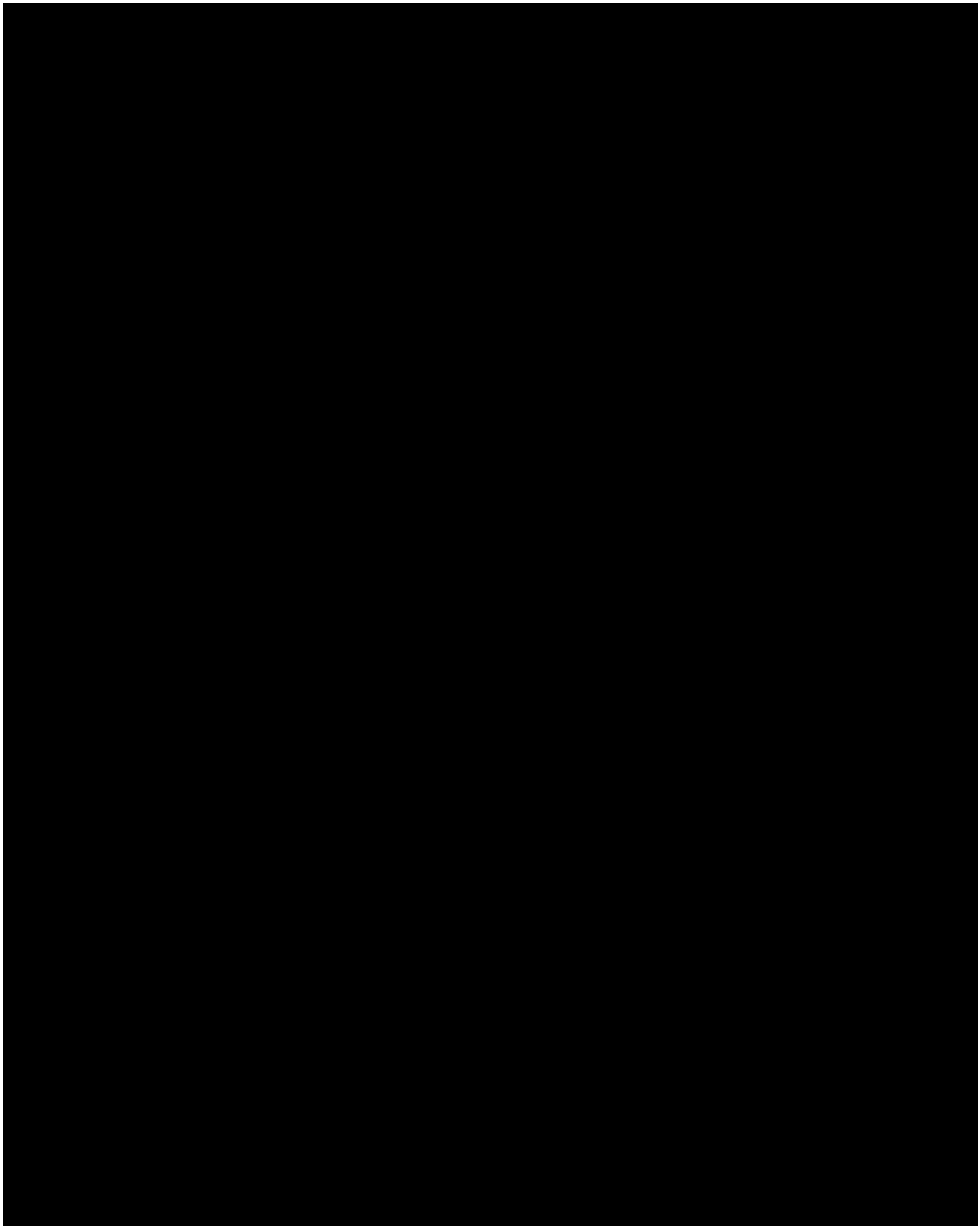
The Eastern Cooperative Oncology Group (ECOG) / World Health Organization (WHO) scale for assessment of the subject's functional ability.

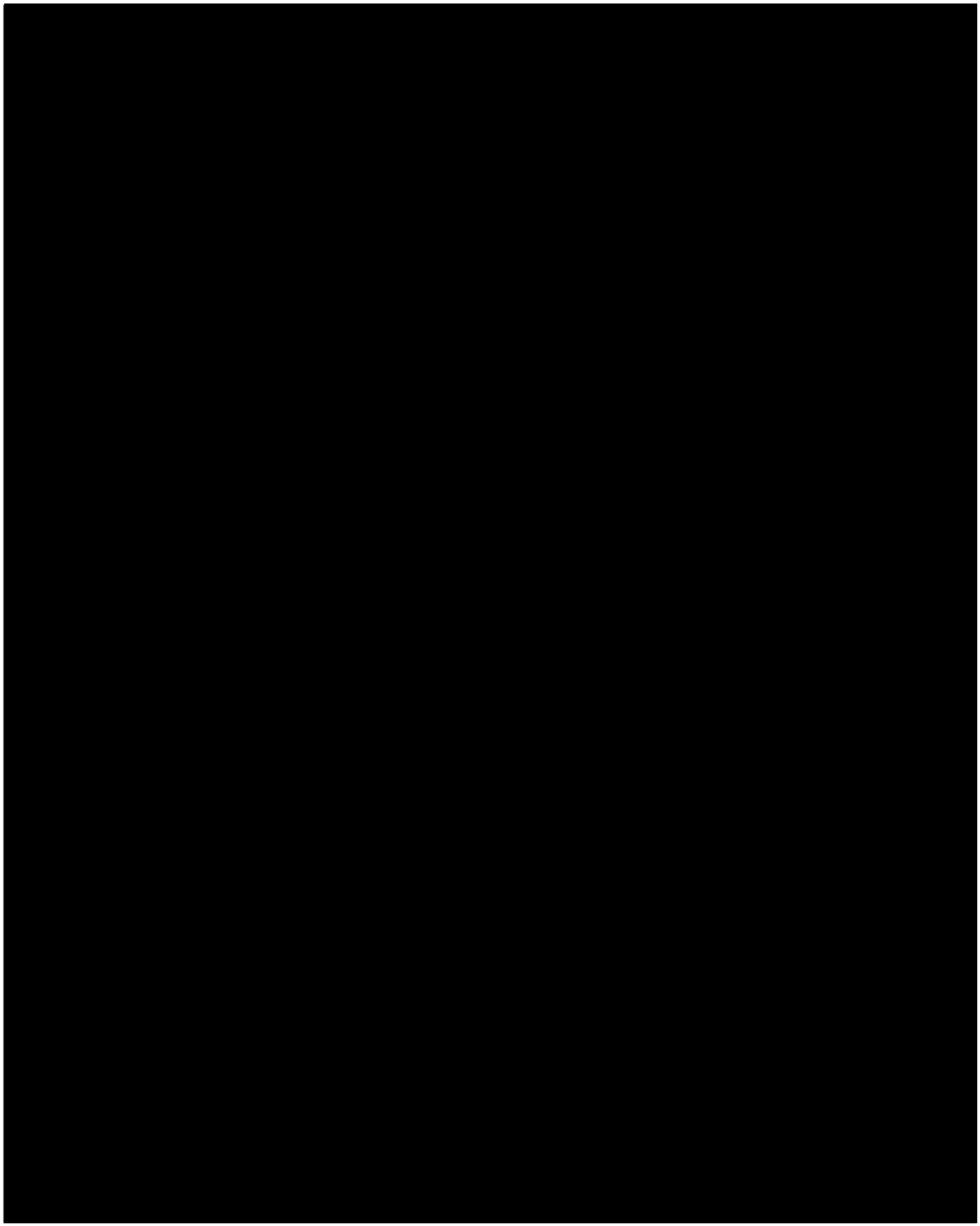
ECOG (Zubrod)		Karnofsky	
Score	**Description**	**Score**	**Description**
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or do active work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled; hospitalization indicated. Death not imminent.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick; hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly

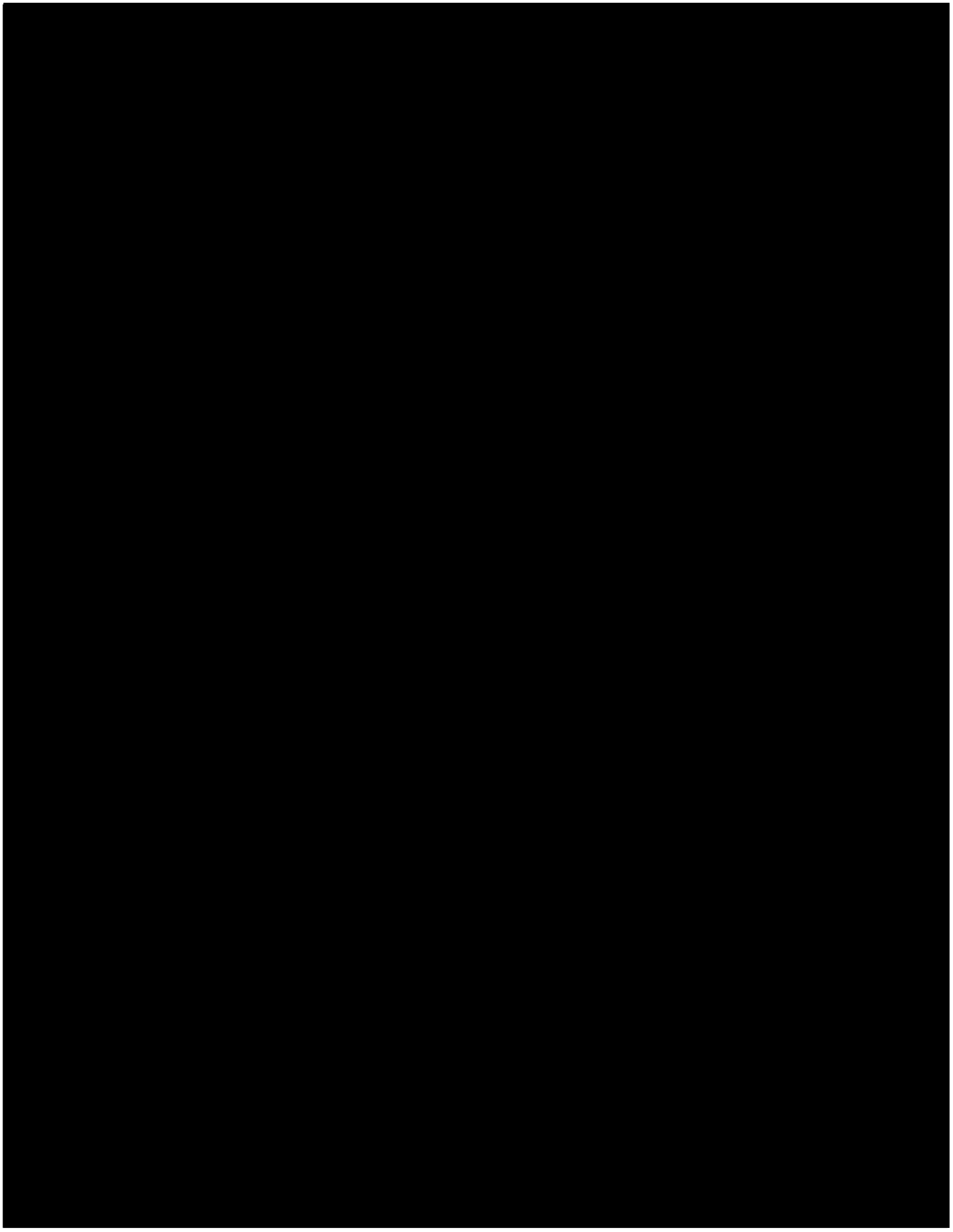
Cancer Therapy Evaluation Program, Common Toxicity Criteria, Version 2.0, DCTD, NCI, NIH, DHHS, Revised March 23, 1998

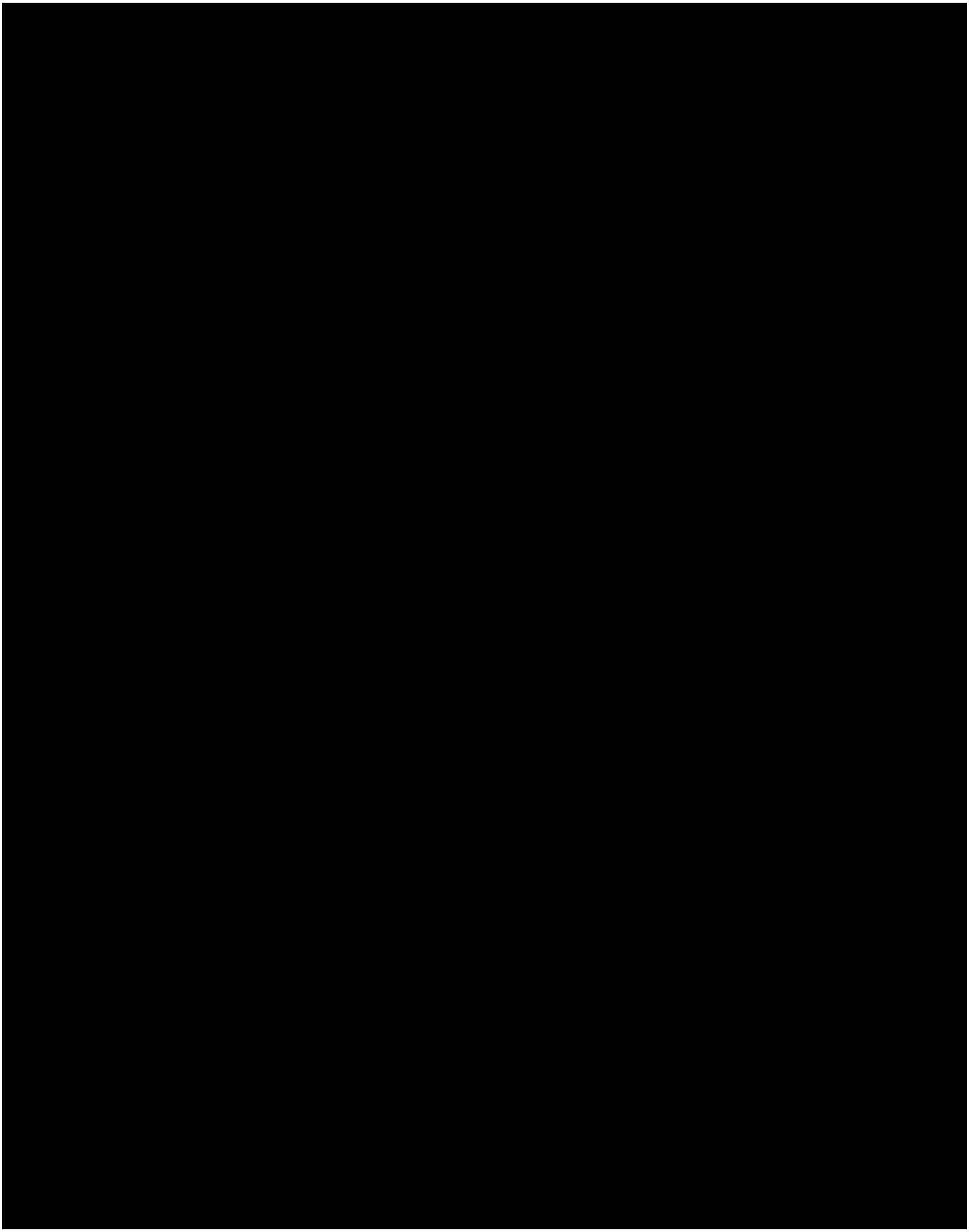
Karnofsky DA, et al., Cancer 1: 634–656. 1948

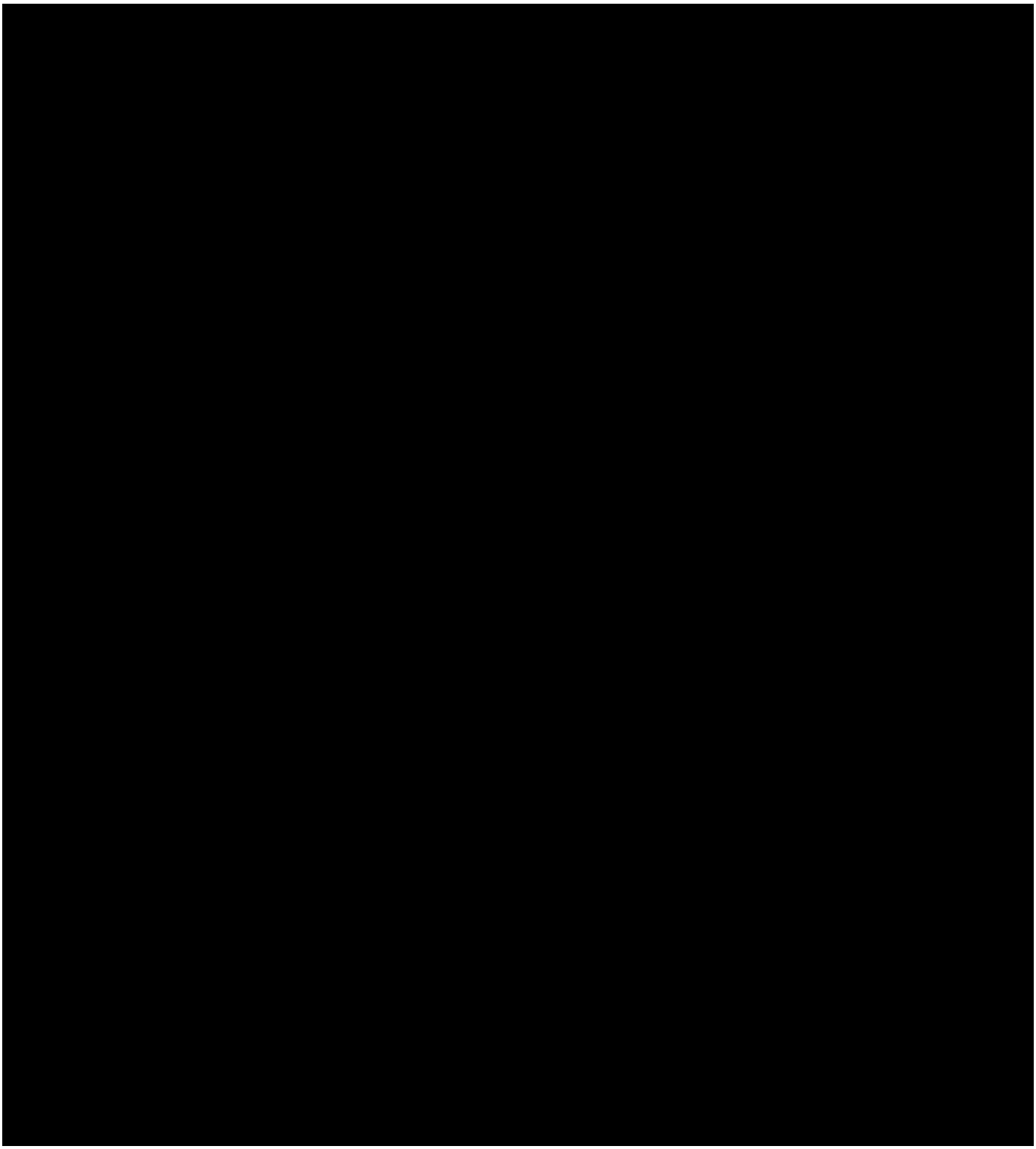












17.6 NYHA Functional Classifications

Class	Subject Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea (shortness of breath).
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea (shortness of breath).
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.