Clinical Study Protocol VT-002 Amendment 4

A 3-Arm, Multicenter, Randomized, Double-Masked, Crossover Safety and Efficacy Study of BRIMOCHOL™ PF (Carbachol/Brimonidine Tartrate Fixed-Dose Combination) Topical Ophthalmic Solution vs. Carbachol PF Monotherapy Topical Ophthalmic Solution vs. Brimonidine Tartrate Monotherapy Topical Ophthalmic Solution in Subjects with Emmetropic Phakic or Pseudophakic Presbyopia

Sponsor:	Visus Therapeutics, Inc. [redacted]
Medical Monitor:	[redacted]
Development Phase:	3
IND number:	150905
Clinical Trial Compliance:	This clinical trial will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Council for Harmonisation (ICH) and all applicable federal and local regulations.
Version and Date:	Version 5.1/ 4 Apr 2023

Signature Page

Sponsor Signatory:

eSignature on file

[redacted]

Date

Principal Investigator Signature Page

Protocol Title	A 3-Arm, Multicenter, Randomized, Double-Masked, Crossover Safety and Efficacy Study of BRIMOCHOL™ PF (Carbachol/Brimonidine Tartrate Fixed-Dose Combination) Topical Ophthalmic Solution vs. Carbachol PF Monotherapy Topical Ophthalmic Solution vs. Brimonidine Tartrate Monotherapy Topical Ophthalmic Solution in Subjects with Emmetropic Phakic or Pseudophakic Presbyopia
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I, the undersigned, have read this protocol and agree to personally supervise conduct of this protocol in accordance with ethical principles as outlined in the ICH guidelines on GCP, any applicable laws and requirements (including Part 54: Financial Disclosure by Clinical Investigators) and any additional conditions mandated by a regulatory authority and/or Institutional Review Board (IRB).

I acknowledge that I am responsible for the overall study conduct; I approve of and will comply with all conditions, instructions, and restrictions described in this protocol. I am aware that my adherence to the above protocol is mandatory and that any changes in the protocol or consent form, except those necessary to eliminate apparent immediate hazards to human subjects, must first be approved in writing by Visus Therapeutics, Inc., and the respective IRB.

I also agree that all information provided to me by Visus Therapeutics, Inc., including this document, Investigator's Brochure, case report form, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be related in confidence to the IRB. I also understand that reports of information about the study or its progress will not be provided to anyone not involved in the study other than to the Principal Investigator, or in confidence to the IRB or to the Food and Drug Administration (FDA) or other legally constituted authority.

Principal Investigator Signature	Date

Printed Name	Institution	City, State

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LIST OF ABBREVIATIONS

_M	Mesopic
_P	Photopic
ADL	Activities of daily living
AE	Adverse event
ALR	Alternating logistic regression
AUC	Area under the curve
$AUC_{0\text{-}8h}$	Area under the curve from Hour 0 to Hour 8
BAK	Benzalkonium chloride
BUCDVA	Binocular uncorrected distance visual acuity
BUCNVA	Binocular uncorrected near visual acuity
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CV	Coefficient of variation
D	Diopters
eCRF	Electronic case report form
EDC	Electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized Estimating Equations
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IOL	Intraocular lens
IOP	Intraocular pressure
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive response technology
NRS	Numeric rating scale
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MUCDVA	Monocular uncorrected distance visual acuity
MUCNVA	Monocular uncorrected near visual acuity
PD	Pharmacodynamics
PF	Preservative free
PI	Principal Investigator
PP	Per-protocol
PT	Preferred term
OD	Oculus dexter (right eye)
OD/OS	Each eye separately
OS	Oculus sinister (left eye)
OU	Both eyes at the same time
ROW	Rest of world

SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SSRI	Selective serotonin reuptake inhibitor
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event

1 PROTOCOL SUMMARY AND SCHEDULE

1.1 Protocol Summary

Protocol Number	VT-002
Title	A 3-Arm, Multicenter, Randomized, Double-Masked, Crossover Safety and Efficacy Study of BRIMOCHOL™ PF (Carbachol/Brimonidine Tartrate Fixed-Dose Combination) Topical Ophthalmic Solution vs. Carbachol PF Monotherapy Topical Ophthalmic Solution vs. Brimonidine Tartrate Monotherapy Topical Ophthalmic Solution in Subjects with Emmetropic Phakic or Pseudophakic Presbyopia
Brief Title	Phase 3 Safety and Efficacy Study BRIMOCHOL PF vs. Carbachol PF Monotherapy Topical Ophthalmic Solutions vs. Brimonidine Tartrate Monotherapy Topical Ophthalmic Solution in Subjects with Emmetropic Phakic or Pseudophakic Presbyopia
Sponsor	Visus Therapeutics, Inc.
Development Phase	3
Purpose and Rationale	Presbyopia is an inevitable, age-related, gradual loss in the ability to focus at intermediate and near targets without spectacle or surgical correction due to a progressive loss of elasticity in the crystalline lens. Pharmacologic miosis with cholinergic agents such as pilocarpine has been well-established to improve near visual acuity and depth of focus in presbyopic individuals but the duration of action has been limited. Carbachol is a more potent and durable cholinergic agent than pilocarpine. Additionally, nonclinical studies in rabbits conducted by Visus suggest that the addition of an alpha-2 agonist to carbachol results in an approximately 42% increase in area under the curve (AUC) compared with carbachol alone providing a greater and more durable miotic effect than with carbachol alone. This increased activity due to brimonidine was also demonstrated in a recently completed Phase 2 crossover clinical study conducted by Visus which compared BRIMOCHOL with the preservative benzalkonium chloride (BAK), BRIMOCHOL without BAK (BRIMOCHOL™ PF [Carbachol 2.75% / Brimonidine Tartrate 0.1% Fixed-Dose Combination] Topical Ophthalmic Solution, hereafter BRIMOCHOL PF), and Carbachol without BAK (Carbachol PF 2.75% Monotherapy Topical Ophthalmic Solution, hereafter Carbachol PF). [redacted]

	[redacted]
Study Objectives	• To demonstrate the efficacy, safety, tolerability, [redacted] fixed-dose combination BRIMOCHOL PF (Carbachol PF 2.75%/brimonidine tartrate 0.1% fixed-dose combination) compared with its individual components: Carbachol PF 2.75% monotherapy and brimonidine tartrate 0.1% monotherapy topical ophthalmic solutions in subjects with emmetropic phakic or pseudophakic presbyopia • To evaluate the pharmacodynamic effect on pupil size of the fixed-dose combination BRIMOCHOL PF compared with the individual components Carbachol PF 2.75% monotherapy and brimonidine tartrate 0.1% monotherapy topical ophthalmic solutions in subjects with emmetropic phakic or pseudophakic presbyopia
Study Design	After signing the Informed Consent Form (ICF) and meeting all eligibility criteria at the Screening Visit and Visit 2 (Hour 0), subjects will be randomly assigned to treatment sequences that include each of the three study treatments. Each subject will receive each of the three treatments from Visit 2 to Visit 4 according to the order specified in the sequence randomly assigned to the subject. [redacted]

	Sites have the option to schedule a Pre-Screening Visit to confirm pupil size eligibility only. An abbreviated ICF must be signed for this Visit. The Pre-Screening Visit may be done on a separate day from Screening/Visit 1; however, if it is completed on a separate day, the pupil size measurements should be repeated at Screening/Visit 1. The full Study ICF must be signed. [redacted]
Study Treatments	All subjects will be randomized to receive a single drop instilled in each eye with one of the following treatments at each dosing visit such that all subjects receive each of the 3 treatments: • BRIMOCHOL™ PF (carbachol 2.75%/brimonidine tartrate 0.1% fixed-dose combination) Topical Ophthalmic Solution • Carbachol PF 2.75% monotherapy Topical Ophthalmic Solution • Brimonidine tartrate 0.1% monotherapy Topical Ophthalmic Solution
Study Population	[redacted] with visually significant emmetropic phakic or pseudophakic presbyopia, and until approximately 152 subjects are complete.
Inclusion Criteria	A subject must meet the following criteria at Visit 1 and Visit 2 (pre-dose assessment) to be eligible for inclusion in the study: 1. Male or female in good general health 2. Age 45 to 80 years, inclusive 3. Phakic in both eyes or Pseudophakic in one or both eyes following uncomplicated cataract surgery with monofocal intraocular lens (IOL) placement "in the bag" no less than 6 months prior to screening [redacted] 5. Visual Acuity/Refraction: a. Monocular uncorrected near visual acuity (MUCNVA) of [redacted] ETDRS letters (Snellen equivalent of [redacted] or worse) in each eye under mesopic conditions; b. Binocular uncorrected near visual acuity (BUCNVA) of [redacted] ETDRS letters (Snellen equivalent of [redacted] or worse) under mesopic conditions; c. Binocular near visual acuity improvement [redacted] letters at 40 cm [redacted] with BUCNVA under mesopic conditions; d. Monocular uncorrected distance visual acuity (MUCDVA) of [redacted] ETDRS letters (Snellen equivalent of [redacted] or better) in each eye under photopic conditions; and e. Spherical equivalent by manifest refraction not greater than ±0.50 D and cylinder not greater than 0.50 D. 6. Intraocular pressure (IOP) ≥10 mm Hg and ≤21 mm Hg 7. Media clarity, pupillary dilation, and subject cooperation sufficient for adequate ophthalmic visual function testing and anatomic assessment 8. Normal retina and optic nerve examination

	9. Not receiving eye drops in either eye other than topical artificial tears no more than twice a day 10. Females of childbearing potential must agree to use one of the following methods of birth control from the date they sign the informed consent form (ICF) until after the last study visit (Visit 4 or Exit): a. Abstinence, when it is in line with the preferred and usual lifestyle of the subject b. Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy (vasectomy procedure must have been conducted at least 60 days prior to the Screening Visit or confirmed via sperm analysis) c. Barrier method (e.g., condom or occlusive cap) with spermicidal foam/gel/film/cream, AND either hormonal contraception (oral, implanted, or injectable) or an intrauterine device or system. Note: Non-childbearing potential is defined as surgical sterilization (i.e., bilateral oophorectomy, hysterectomy, or tubal ligation) or postmenopausal (defined as not having a period for at least 12 consecutive months prior to Screening). 11. Able to give informed consent and willing and able to comply with all study visits and examinations.
Exclusion Criteria	A subject who meets any of the following criteria will be excluded from the study: 1. Current use (within 4 weeks of Visit 1) or likely need for distance refractive correction or the use of contact lens at any time during the study 2. Narrow iridocorneal angles (Shaffer grade ≤2 on gonioscopy examination or Van Herick grade ≤2 by slit-lamp exam) or previous iridotomy 3. Iris or pupil abnormalities 4. History of hyphema, microhyphema, cyclodialysis, iridodynesis, or trauma to either eye 5. Use of systemic or topical antihistamines 48 hours prior to on-site study visits, anticholinergics (including tricyclic antidepressants or monoamine oxidase inhibitors; however, use of selective serotonin reuptake inhibitor [SSRI] is acceptable) or cholinergics (including pilocarpine [e.g., VUITY] or cevimeline), alpha-1 agonists (including tetryzoline, oxymetazoline, phenylephrine, pseudoephedrine, methoxamine, mephentermine, cirazoline, benzphetamine), and alpha-2 agonists (including methyldopa, brimonidine, clonidine, dipivefrin, guanabenz) within 90 days prior to Visit 1 or at any time during the study 6. Use of systemic alpha-antagonists (including phenoxybenzamine, phentolamine, alfuzosin, doxazosin, terazosin, tamsulosin, prazosin, and yohimbine) within 90 days prior to visit 1 or at any time during the study 7. Participation in other investigational drug or device clinical trials within 30 days prior to Visit 1 or planning to participate in any other investigational drug or device clinical trials within 30 days of study completion. This includes interventional clinical trials investigating the use of a pharmacologic agent for the treatment of cataract or presbyopia. 8. Any other ocular pathology requiring treatment with topical prescription ophthalmic drops or intravitreal injection (e.g., glaucoma, allergic conjunctivitis, retinal disease). Note: Mild dry eye requiring only topical artificial tears up to 2 times a day is acceptable. 9. Concurrent use of temporary or permanent punctal plugs or history of punctal cautery in one or both eyes

	10. Corneal abnormalities in either eye that interfere with visual acuity or measurement of IOP including total corneal staining grade of >1 and central corneal staining >0 on the National Eye Institute (NEI) corneal grading scale 11. Congenital or traumatic cataracts or congenital aphakia, central lens opacity on visual axis. 12. History of intraocular surgery other than uncomplicated cataract surgery. Note: Prior LASIK refractive surgery at least 12 months prior is acceptable if the subject meets all other eligibility criteria. 13. For phakic subjects, phacodynesis or subluxation of the lens or suspected loose zonules 14. For pseudophakic subjects, complicated cataract surgery resulting in capsular tear, placement of IOL outside the bag (e.g., sulcus, scleral or iris fixation or anterior chamber placement) or yttrium aluminum garnet (YAG) capsulotomy or an axial length of ≥25 mm 15. History of uveitis 16. Diagnosis of glaucoma or ocular hypertension or IOP of >21 mm Hg or pseudoexfoliation in either eye 17. Any active ocular or peri-ocular infection; any history of recurrent or chronic infection, including herpetic infection, in either eye 18. Current or previous retinal detachment or retinal pathology including age-related macular degeneration 19. Concurrent disease in either eye that could require medical or surgical intervention during the study period 20. Known to be immunocompromised or receiving immunosuppression 21. History of allergic reaction to the investigational product or any of its components 22. Women who are pregnant or lactating 23. Unwilling or unable to give informed consent 24. Any disease or medical condition that, in the opinion of the Investigator, would prevent the subject from participating in the study or might confound study results 25. Previous participation in the Visus VT-003 clinical trial.

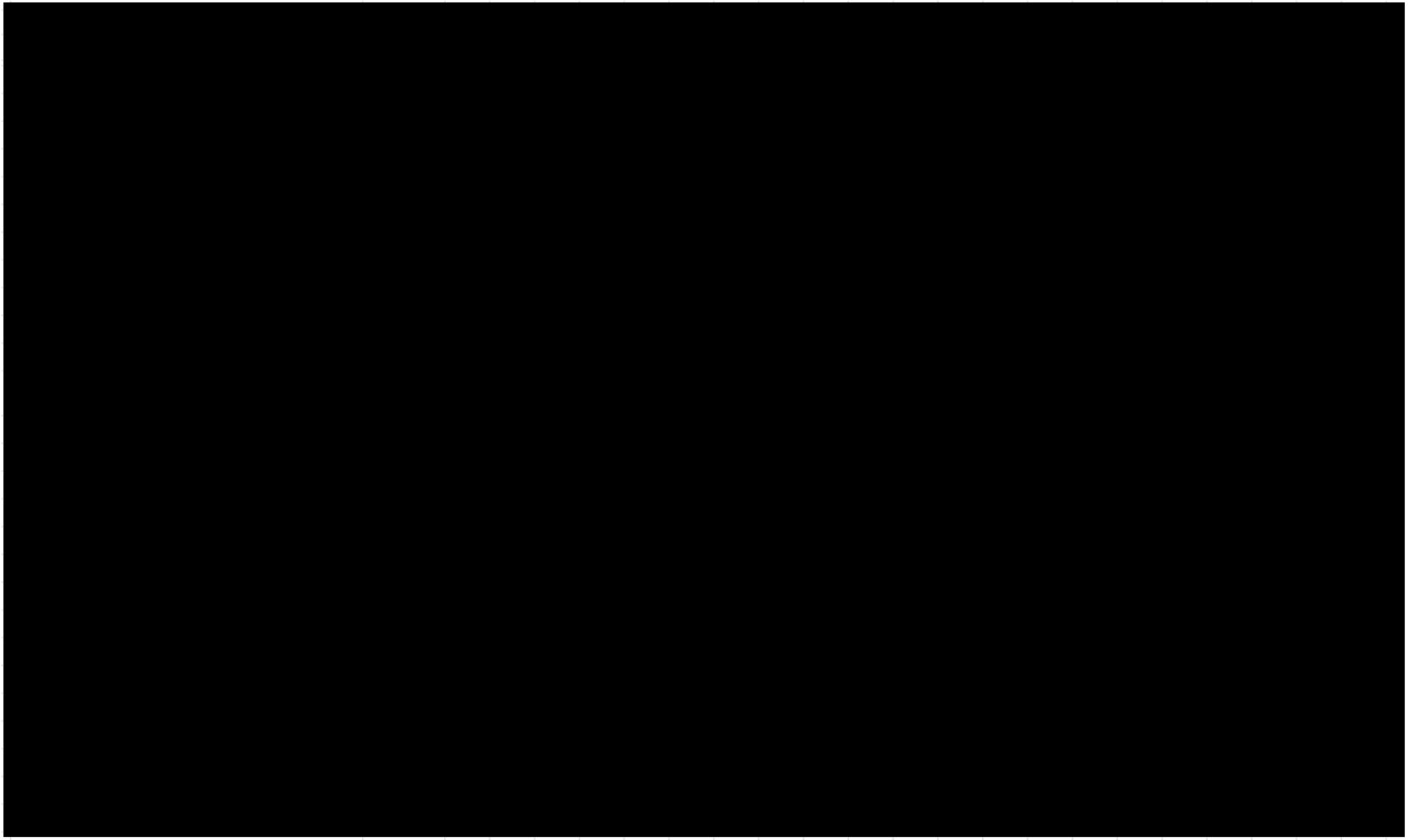
Efficacy Assessments	Primary Efficacy Endpoints for the US FDA (Gated) A treatment responder is defined as a subject who has a ≥15 ETDRS letter gain from Baseline in binocular uncorrected near visual acuity (BUCNVA) without a ≥5 ETDRS letter loss in binocular uncorrected distance visual acuity (BUCDVA) using both eyes under mesopic conditions. Baseline at each dosing visit will be the pre-dose assessment at Hour 0 of the visit. At a visit, each subject's responder status will be [redacted] The superiority of BRIMOCHOL PF over both monotherapies will be established if its proportion of responders at Hour 1 is statistically greater than each monotherapy (brimonidine tartrate and Carbachol PF) at the 5% significance level. Additionally, the comparisons for BRIMOCHOL PF against Carbachol PF at subsequent timepoints will be gated to control the overall type I error at 5% in the following fixed-sequence order: 1. BRIMOCHOL PF vs brimonidine tartrate at Hour 1 and BRIMOCHOL PF vs Carbachol PF at Hour 1 as the co-primary comparisons [redacted] Primary Efficacy Endpoint for Rest of the World (ROW) An area under the curve ($AUC_{0\text{-}8h}$) defined as a weighted average of changes from Baseline in ETDRS letters of BUCNVA using both eyes under mesopic conditions [redacted] will be the primary efficacy endpoint for ROW. The superiority of BRIMOCHOL PF over both monotherapies will be established if its mean AUC is statistically greater than each monotherapy at the 5% significance level. [redacted]
Safety Assessments	Safety Endpoints • Ocular and non-ocular AEs, Slit-Lamp Biomicroscopy, Intraocular Pressure, Dilated Ophthalmoscopy • Proportion of subjects with a ≥15 letters loss in mesopic MUCNVA at 40 cm in either eye

	• Proportion of subjects with a ≥15 letters loss in mesopic BUCDVA at 4 M using both eyes
Other Assessments	Pharmacodynamic (PD) Endpoints: • Change from Baseline in pupil size in each eye, the average, the minimum, and the maximum of the two eyes at all timepoints for both mesopic and scotopic measurements • [redacted]
General Statistical Methods and Types of Analyses	Analysis Populations • *Safety Population:* All subjects who receive at least 1 dose of IP. Subjects will be analyzed as treated. • *Modified Intent-to-Treat (mITT) Population:* All subjects who are randomized and receive at least 1 dose of IP. Subjects will be analyzed as randomized. • *Per-Protocol Population (PP):* All mITT subjects who comply with the protocol without major protocol deviations/violations deemed to potentially affect study treatment effect. [redacted] Efficacy Analyses [redacted]

	[redacted] [redacted] [redacted] [redacted] [redacted] PD Analyses: The observed and change from Baseline values of pupil size in each eye, the average between eyes, the minimum between eyes, and the maximum between eyes at all timepoints will be summarized with descriptive statistics by treatment, visit, and nominal time. At each timepoint, a mixed-effect model to compare BRIMOCHOL PF with each monotherapy will be performed. Safety Analyses: Safety assessments will be analyzed with the safety population. AEs will be summarized by system organ class (SOC) and preferred term (PT), presenting the number and percentage of subjects having treatment-emergent AEs (TEAEs). Severity and relationship to IP will be listed as appropriate. The safety endpoints that compare event rates between groups may be similarly performed using the methods as outlined above for efficacy endpoints. [redacted] [redacted]

	Sample Size Calculation  [redacted] will be enrolled to complete 152 subjects.

1.2 Schedule of Visits and Procedures



2 BACKGROUND

2.1 Presbyopia

Presbyopia is an inevitable, age-related, gradual loss in the ability to focus at intermediate and near targets without spectacle or surgical correction due to a progressive loss of elasticity in the crystalline lens. Symptoms of presbyopia include blurred vision, ocular discomfort/headache, fatigue/drowsiness from near work, increased working distance (arms too short), and need for brighter light for reading. In childhood, an amplitude of accommodation of 12 diopters (D) is typical (Benzoni 2012). Amplitude of accommodation declines linearly at a rate of about 0.3 D per year, falling below a threshold at which near vision is noticeably impaired by approximately 40 to 45 years of age. An estimated 1.27 billion people have presbyopia globally, and this number is projected to increase to 1.78 billion people by 2050 (Frick 2015), including virtually all adults >50 years old.

Therapeutic approaches to presbyopia cover a spectrum of nonsurgical to surgical techniques (Moarefi 2017). Non-invasive methods of correcting presbyopia (e.g., bifocal, or multifocal progressive addition lenses) can be effective, but many patients are dissatisfied for cosmetic or other reasons and desire independence from spectacles. Various surgical techniques have been applied on the cornea, lens, or sclera (Gil-Cazorla 2016). However, surgery is invasive and difficult to reverse in the event of complications or patient dissatisfaction. Moreover, surgical corrections usually require that patients choose for one eye to be corrected for distance and one for near, or monovision. Many patients do not like this outcome as this leaves them without binocular vision or depth perception at distance and near (Goertz 2014, McDonnell 2003). There is currently one Food and Drug Administration (FDA)-approved drug product to treat presbyopia, VUITY (pilocarpine 1.25%), with a limited duration of action.

2.2 Investigational Products

Visus Therapeutics, Inc. (Visus) is developing BRIMOCHOL™ PF (Preservative Free) (carbachol 2.75% / brimonidine tartrate 0.1% fixed-dose combination) Topical Ophthalmic Solution (hereafter BRIMOCHOL PF) and Carbachol PF 2.75% Monotherapy Topical Ophthalmic Solution (hereafter Carbachol PF) eye drop for improvement in near visual acuity in emmetropic phakic and pseudophakic presbyopia.

The active pharmaceutical ingredients carbachol and brimonidine tartrate are currently approved for topical ophthalmic use. Both carbachol and brimonidine tartrate have been used extensively in ophthalmic applications and the approved products have been administered chronically at higher total daily doses than that in the BRIMOCHOL PF combination product.

Five Investigator-initiated trials of a pharmacy-compounded formulation of BRIMOCHOL containing up to 3.0% carbachol and 0.2% brimonidine tartrate were conducted in presbyopic subjects; the results of 4 of these studies are published (Abdelkader 2015, 2016, 2018, 2019). These studies evaluated pupillometry and near visual acuity across a range of carbachol concentrations from 1.5% to 3.0%, the effects of BRIMOCHOL in older and younger presbyopes and in pseudophakes, the occurrence of tachyphylaxis over 3 months, and whether the fixed-dose

combination demonstrated contribution of elements, i.e., that the combination is more effective than the individual monotherapies. These studies were not conducted by Visus.

In brief, the studies concluded there was a dose-response to carbachol concentration with the 3% carbachol giving the greatest peak and duration of effect on pupil size and near visual acuity (Abdelkader 2019). Commercially available carbachol and brimonidine tartrate were given concomitantly 5 minutes apart or as the fixed-dose BRIMOCHOL PF combination. The combination was more effective than carbachol and brimonidine tartrate given as monotherapy (Abdelkader 2016), suggesting contribution of elements. No tachyphylaxis was noted over 3 months of daily dosing and clinical response was comparable in subjects older or younger than 50 years of age and in pseudophakes (Abdelkader 2015). Additionally, there were no reports of headache in the largest of these studies in 57 subjects (Abdelkader 2019), suggesting that the addition of brimonidine tartrate may have mitigated the incidence of headache, which is a common adverse event (AE) associated with the use of cholinergic agents alone.

Please see the Investigator Brochure (IB) for additional information on the nonclinical and clinical support for BRIMOCHOL PF development.

3 RATIONALE FOR THE STUDY AND STUDY DESIGN

3.1 Therapeutic Rationale for BRIMOCHOL PF and Carbachol PF in Presbyopia

In recent years, various miotics have been investigated alone or in combination with one or more other agents as treatments for presbyopia (Benozzi 2012, Karanfil 2017, Renna 2017). Until recently, there are two currently marketed miotic agents in the US: pilocarpine (Isopto® Carpine [Prescribing Information]) for the lowering of intraocular pressure (IOP) and carbachol (MIOSTAT® 0.01% [Prescribing Information]) for obtaining miosis during surgery. Carbachol was also marketed as ISTOPO® CARBACHOL (Prescribing Information) for the lowering of IOP for more than 50 years but was withdrawn from the market for commercial and not safety reasons. Carbachol is generally regarded as a stronger and longer-acting miotic than pilocarpine (Gelatt 1984) with a dosing frequency of up to 3 times daily rather than up to 4 times daily for pilocarpine. Recently, VUITY® (pilocarpine 1.25%) was approved for the treatment of presbyopia. The efficacy of VUITY for the treatment of presbyopia was demonstrated in two 30-Day Phase 3, randomized, double-masked, vehicle-controlled studies, namely GEMINI 1 (NCT03804268) and GEMINI 2 (NCT03857542). A total of 750 participants aged 40 to 55 years old with presbyopia were randomized (375 to VUITY group) in the two studies and participants were instructed to administer one drop of VUITY or vehicle once daily in each eye. In both studies, the proportion of participants gaining 3 lines or more in mesopic, high contrast, binocular distance corrected near visual acuity (DCNVA), without losing more than 1 line (5 letters) of corrected distance visual acuity (CDVA) with the same refractive correction was statistically significantly greater in the VUITY group compared to the vehicle group at Day 30, Hour 3. Statistical significance was not achieved in both studies at Hour 6.

Both carbachol and pilocarpine are parasympathomimetic agents that induce miosis by promoting contraction of the iris sphincter muscle through activation of muscarinic receptors. However, both miotics also contract the ciliary muscle. It is through this effect on the ciliary muscle that miotics can reduce IOP by putting traction on the scleral spur and uveoscleral meshwork, thereby increasing aqueous outflow (Nardin 1966). It is also by this mechanism that miotics cause their main AEs: browache/headache (a referred pain from the ciliary muscle contraction/spasm) and a decrease in distance acuity by inducing a myopic shift (Poinoosawmy 1976).

Brimonidine tartrate is a selective alpha-2 adrenergic agonist that works presynaptically in the management of elevated IOP to inhibit the release of norepinephrine (Kato 2018) at the nerve terminals, thereby decreasing aqueous production, episcleral venous pressure and improving uveoscleral outflow. By inhibiting norepinephrine's release, brimonidine tartrate's main effect on the pupil is to inhibit contraction of the iris dilator muscle, which is classically stimulated as part of the fight or flight sympathetic response or, more commonly, under dark lighting to let more light into the eye.

Pupil size is modulated continuously by the opposing parasympathetic and sympathetic pathways in response to ambient lighting, accommodation, and overall sympathetic tone. The pharmacologic effects of targeting both the parasympathetic and sympathetic pathways by combining a cholinergic with an alpha-2 agonist on the pupil may be more pronounced, particularly under mesopic conditions, than observed when only one pathway is pharmacologically altered. Indeed, results of the prior clinical studies of BRIMOCHOL referenced above suggest the addition of an alpha-2 agonist leads to a more robust and durable miosis and improvement in near visual acuity over monotherapy alone. [redacted] It may be primarily by this mechanism that the prior referenced clinical study (Abdelkader 2016) demonstrated this apparent contribution of elements. Nonclinical studies conducted by Visus have demonstrated that the fixed-dose combinations BRIMOCHOL and BRIMOCHOL PF not only displayed a contribution of elements in rabbits over the individual monotherapies formulated similarly on pupil size, but that iris/ciliary body carbachol C_{max} and area under the curve (AUC) concentrations are approximately 42% higher with the combination than carbachol alone (data on file).

Finally, prior ex vivo studies in bovine ciliary muscle suggest alpha-2 receptors inhibit the contraction of cholinergically innervated ciliary muscle that does not occur when the ciliary muscle is at rest (Kubo 1992) and may explain the absence of reported headache in prior clinical trials (Abdelkader 2019). The potential to minimize the ciliary body-induced AEs of browache/headache, myopic shift, and IOP changes associated with cholinergics alone supports the further rationale for combining an alpha-2 agonist with a cholinergic agent.

[redacted]

3.2 Study Rationale

The present study has been designed as a crossover study to compare the safety and efficacy of the fixed-dose combination BRIMOCHOL PF compared with its individual components (Carbachol PF and brimonidine tartrate monotherapies), at multiple timepoints up to 8 hours after a single dose in each eye.

[redacted]

3.3 Rationale for Dose and Regimen Selection

To gain market authorization of a combination product, the sponsor must demonstrate superiority of the combination product over the individual components. Accordingly, the efficacy of BRIMOCHOL PF in improving near visual acuity is being compared to Carbachol PF and Brimonidine tartrate in this study. The doses, formulations and posology were successfully evaluated in Phase 2. All IP are to be dosed not more than once daily in both eyes.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Study Objectives

- To demonstrate the efficacy, safety tolerability, [redacted] fixed-dose combination BRIMOCHOL PF (Carbachol PF 2.75% brimonidine tartrate 0.1% fixed-dose combination) compared with its individual components: Carbachol PF 2.75% monotherapy and brimonidine tartrate 0.1% monotherapy topical ophthalmic solutions in subjects with emmetropic phakic or pseudophakic presbyopia

- To evaluate the pharmacodynamic effect on pupil size of the fixed-dose combination BRIMOCHOL PF compared with the individual components Carbachol PF 2.75% monotherapy and brimonidine tartrate 0.1% monotherapy in subjects with emmetropic phakic or pseudophakic presbyopia

4.2 Study Endpoints

4.2.1 Efficacy Endpoints

Primary Efficacy Endpoints for the US FDA: Proportion of Treatment Responders

A treatment responder is defined as a subject who has a ≥15 ETDRS letter gain from Baseline in binocular uncorrected near visual acuity (BUCNVA) without a ≥5 ETDRS letter loss in binocular uncorrected distance visual acuity (BUCDVA) using both eyes under mesopic conditions. The Baseline for each dosing visit will be the pre-dose assessment at Hour 0 of the visit. [redacted]

Primary Efficacy Endpoint for Rest of the World (ROW): Mean of AUCs

An area under the curve ($AUC_{0\text{-}8h}$) is defined as a weighted average of changes from Baseline in ETDRS letters of BUCNVA using both eyes under mesopic conditions for a subject across [redacted] at a visit. The Baseline for each dosing visit will be the pre-dose assessment at Hour 0 of the visit.

[redacted]

- [redacted]

[redacted]

4.2.2 *Safety Endpoints*

- Ocular and non-ocular AEs, Slit-Lamp Biomicroscopy, Intraocular Pressure, Dilated Ophthalmoscopy
- Proportion of subjects with a ≥15 letters loss in mesopic MUCNVA at 40 cm in either eye
- Proportion of subjects with a ≥15 letters loss in mesopic BUCDVA at 4 M using both eyes

4.2.3 *Pharmacodynamic (PD) Endpoints*

- Change from Baseline in pupil size in each eye, the average, the minimum, and the maximum of the two eyes at all timepoints at all timepoints for both mesopic and scotopic measurements
- [redacted]

4.2.4 [redacted]

- [redacted]

[redacted]

5 STUDY DESIGN

5.1 Study Design

This is a 3-arm, multicenter, randomized, crossover, Phase 3 safety and efficacy study in [redacted] with visually significant emmetropic phakic or pseudophakic presbyopia, and until approximately 152 subjects are complete at study sites in the United States.

After signing the Informed Consent Form (ICF) and meeting all eligibility criteria at the Screening Visit and Visit 2 (Hour 0), subjects will be randomly assigned to treatment sequences that include each of the three study treatments over the course of 4 study visits for up to approximately 45 days. The study design is shown schematically in Figure 1, and the schedule of visits and procedures in Section 1.2.

Sites have the option to schedule a Pre-Screening Visit to confirm pupil size eligibility. An abbreviated ICF must be signed for this Visit. The Pre-Screening Visit may be done on a separate day from Screening/Visit 1; however, if it is completed on a separate day, the pupil size measurements must be repeated at the Screening/Visit 1. The full Study ICF must be signed.

The Study Visits are:

- Visit 1 (-14 to -1 days): [redacted]
- Visit 2: [redacted]
- Visit 3: [redacted]
- Visit 4/Exit: [redacted]

[redacted]

[redacted]

[redacted]

IP will be topically administered at the clinic by the unmasked study site personnel with a single drop in both eyes at approximately [redacted] treatments (Visits 2, 3, and 4).

Visual function will be assessed [redacted]

Figure 1: Study Design Schematic

[redacted]

5.2 Beginning and End of Study

A subject is considered enrolled in the study when they have provided written, informed consent.

A subject is considered to have completed the study after they have completed Visit 4.

From the time the subject signs the ICF to Study Exit; they will participate in the study for approximately 45 days.

A subject is considered to have discontinued after they have withdrawn consent or has been discontinued under the conditions specified in Section 6.3.

[redacted]

6 STUDY POPULATION

[redacted] with visually significant emmetropic phakic or pseudophakic presbyopia and until approximately 152 subjects are complete at approximately 18 sites are planned to be enrolled in this study.

6.1 Inclusion Criteria

A subject must meet the following criteria at [redacted] to be eligible for inclusion in the study:

1. Male or female in good general health
2. Age 45 to 80 years, inclusive
3. Phakic in both eyes

   or

   Pseudophakic in one or both eyes following uncomplicated cataract surgery with monofocal intraocular lens (IOL) placement "in the bag" no less than 6 months prior to screening

[redacted]

5. Visual Acuity/Refraction:
   a. Monocular uncorrected near visual acuity (MUCNVA) of [redacted] ETDRS letters (Snellen equivalent of [redacted] or worse) in each eye under mesopic conditions;
   b. Binocular uncorrected near visual acuity (BUCNVA) of [redacted] ETDRS letters (Snellen equivalent of [redacted] or worse) under mesopic conditions;
   c. Binocular near visual acuity improvement [redacted] letters at 40 cm [redacted] with BUCNVA under mesopic conditions;
   d. Monocular uncorrected distance visual acuity (MUCDVA) of [redacted] ETDRS letters (Snellen equivalent of [redacted] or better) in each eye under photopic conditions; and
   e. Spherical equivalent by manifest refraction not greater than ±0.50 D and cylinder not greater than 0.50 D.
6. Intraocular pressure (IOP) ≥10 mm Hg and ≤21 mm Hg
7. Media clarity, pupillary dilation, and subject cooperation sufficient for adequate ophthalmic visual function testing and anatomic assessment
8. Normal retina and optic nerve examination
9. Not receiving eye drops in either eye other than topical artificial tears no more than twice a day
10. Females of childbearing potential must agree to use one of the following methods of birth control from the date they sign the informed consent form (ICF) until after the last study visit (Visit 4 or Exit):
    a. Abstinence, when it is in line with the preferred and usual lifestyle of the subject

b. Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy (vasectomy procedure must have been conducted at least 60 days prior to the Screening Visit or confirmed via sperm analysis)

c. Barrier method (e.g., condom or occlusive cap) with spermicidal foam/gel/film/cream, AND either hormonal contraception (oral, implanted, or injectable) or an intrauterine device or system.

Note: Non-childbearing potential is defined as surgical sterilization (i.e., bilateral oophorectomy, hysterectomy, or tubal ligation) or postmenopausal (defined as not having a period for at least 12 consecutive months prior to Screening).

11. Able to give informed consent and willing and able to comply with all study visits and examinations

6.2 Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Current use (within 4 weeks of Visit 1) or likely need for distance refractive correction or the use of contact lens at any time during the study
2. Narrow iridocorneal angles (Shaffer grade ≤2 on gonioscopy examination or Van Herick grade ≤2 by slit-lamp exam) or previous iridotomy
3. Iris or pupil abnormalities
4. History of hyphema, microhyphema, cyclodialysis, iridodynesis, or trauma to either eye
5. Use of systemic or topical antihistamines 48 hours prior to on-site study visits, anticholinergics (including tricyclic antidepressants or monoamine oxidase inhibitors; however, use of selective serotonin reuptake inhibitor [SSRI] is acceptable) or cholinergics (including pilocarpine [e.g., VUITY] or cevimeline), alpha-1 agonists (including tetryzoline, oxymetazoline, phenylephrine, pseudoephedrine, methoxamine, mephentermine, cirazoline, benzphetamine), and alpha-2 agonists (including methyldopa, brimonidine, clonidine, dipivefrin, guanabenz) within 90 days prior to Visit 1 or at any time during the study.
6. Use of systemic alpha-antagonists (including phenoxybenzamine, phentolamine, alfuzosin, doxazosin, terazosin, tamsulosin, prazosin, and yohimbine) within 90 days prior to visit 1 or at any time during the study
7. Participation in other investigational drug or device clinical trials within 30 days prior to Visit 1 or planning to participate in any other investigational drug or device clinical trials within 30 days of study completion. This includes interventional clinical trials investigating the use of a pharmacologic agent for the treatment of cataract or presbyopia.
8. Any other ocular pathology requiring treatment with topical prescription ophthalmic drops or intravitreal injection (e.g., glaucoma, allergic conjunctivitis, retinal disease).

[redacted]

9. Concurrent use of temporary or permanent punctal plugs or history of punctal cautery in one or both eyes

10. Corneal abnormalities in either eye that interfere with visual acuity or measurement of IOP including total corneal staining grade of >1 and central corneal staining >0 on the National Eye Institute (NEI) corneal grading scale

11. Congenital or traumatic cataracts or congenital aphakia, central lens opacity on visual axis.

12. History of intraocular surgery other than uncomplicated cataract surgery.

    Note: Prior LASIK refractive surgery at least 12 months prior is acceptable if the subject meets all other eligibility criteria.

13. For phakic subjects, phacodynesis or subluxation of the lens or suspected loose zonules

14. For pseudophakic subjects, complicated cataract surgery resulting in capsular tear, placement of IOL outside the bag (e.g., sulcus, scleral or iris fixation or anterior chamber placement) or yttrium aluminum garnet (YAG) capsulotomy or an axial length of ≥25 mm

15. History of uveitis

16. Diagnosis of glaucoma or ocular hypertension or IOP of >21 mm Hg or pseudoexfoliation in either eye

17. Any active ocular or peri-ocular infection; any history of recurrent or chronic infection, including herpetic infection, in either eye

18. Current or previous retinal detachment or retinal pathology including age-related macular degeneration

19. Concurrent disease in either eye that could require medical or surgical intervention during the study period

20. Known to be immunocompromised or receiving immunosuppression

21. History of allergic reaction to the investigational product or any of its components

22. Women who are pregnant or lactating

23. Unwilling or unable to give informed consent

24. Any disease or medical condition that, in the opinion of the Investigator, would prevent the subject from participating in the study or might confound study results

25. Previous participation in the Visus VT-003 clinical trial

6.3 Subject Discontinuation

A subject may discontinue the study at any time during the study for any reason. When possible, the following assessments should be assessed at the Exit Visit: pregnancy test, AEs, concomitant

medications, vital signs, pupillometry, BUCNVA_M, BUCDVA_M, MUCNVA_M, slit-lamp biomicroscopy, IOP, and dilated ophthalmoscopy.

[redacted]

A subject may be withdrawn from the study if the Investigator or the Sponsor determines that it is unsafe for the subject to continue in the study. Discontinuation will be made at the discretion of the Investigator or at the subject's request.

A subject may be discontinued due to a change in compliance with an inclusion/exclusion criterion that is clinically relevant and affects subject safety, occurrence of AEs, occurrence of pregnancy, or administration of non-permitted concomitant medication that might affect subject safety or study assessments/objectives. If a subject is discontinued for a reason that is related to coronavirus disease 2019 (COVID-19), it should be recorded as such.

When possible, the Sponsor should be notified before the subject is discontinued. Subjects who are discontinued from the study during a study Visit should have the Exit procedures completed when possible. The date the subject is withdrawn from the study and the reason for discontinuation will be recorded on the subject's electronic case report form (eCRF).

A subject is considered to have been lost to follow-up if they cannot be contacted by the Investigator. The Investigator will document efforts to attempt to reach the subject twice and will send a certified letter before considering the subject lost to follow-up. The end of participation for a subject lost to follow-up is documented as the delivery/return date of the certified letter.

7 TREATMENTS

7.1 Study Treatment

7.1.1 Randomization/Treatment Assignment

Subjects who provide informed consent will be assigned a subject number. Subjects will be randomly assigned to all three of the crossover treatment arms of BRIMOCHOL PF, Carbachol PF, and brimonidine (at Visits 2, 3, and 4).

7.1.2 Study Treatment

Each subject will receive a single dose of IP topically administered in both eyes in a masked fashion according to the assigned treatment randomization.

- BRIMOCHOL PF (Carbachol PF 2.75%/brimonidine tartrate 0.1% fixed-dose combination) Topical Ophthalmic Solution
- Carbachol PF 2.75% monotherapy Topical Ophthalmic Solution
- Brimonidine tartrate 0.1% monotherapy Topical Ophthalmic Solution

7.1.3 Masking/Unmasking

Investigators, study site staff (except for the unmasked site personnel), and subjects will remain masked to the treatment assignment for the duration of the study. An unmasked study site personnel will be responsible for receipt of IP shipments, dispensing, disposition, and dosing of all IP to maintain this masking. The unmasked study personnel will avoid discussing the color of the IP with the Investigator, other study site personnel, and the subject.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unmask study treatment records at the site(s) to verify that randomization/dispensing has been done accurately.

In case of an emergency, the Investigator has the sole responsibility for determining if the unmasking of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unmasking is warranted, the Investigator should make every effort to contact the Sponsor prior to unmasking a subject's treatment assignment unless this could delay emergency treatment of the subject. If a subject's treatment assignment is unmasked, the Sponsor must be notified within 24 hours after breaking the masking. The date and reason that the masking was broken must be recorded in the source documentation and case report form, as applicable.

The Sponsor/designee may unmask the treatment assignment for any subject with a serious adverse event (SAE). If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy.

7.2 Investigational Product Preparation and Dispensing

IP should only be handled by the unmasked study site personnel, including receipt and confirmation of new inventory. This person will be identified on the delegation of authority as the unmasked study site personnel.

At Visit 2 (Randomization), after confirmation of eligibility, the unmasked study site personnel will request for a randomization and kit assignment and a kit number will be dispensed. At subsequent treatment Visits (Visits 3 and 4), the unmasked study site personnel will do the same to request the next kit assignment.

The unmasked study site personnel will locate the dispensed kit number on the outer carton for the assigned kit and will open and remove the inner foil pouch. They will then confirm that the kit number on the pouch matches the kit number on the carton and will proceed to open the pouch to remove one vial for subject treatment. After the first vial has been removed and dispensed from a kit, the unmasked study site personnel will continue to dispense vials from that kit number until all vials have been used.

[redacted]

A single drop of IP is instilled in each eye (a single vial contains sufficient IP to treat both eyes). The subject will be asked to keep their eyes gently closed for approximately one minute. Site personnel may gently dab the subject's face with tissue if necessary; subjects are not allowed to do this themselves to prevent wiping away medication.

After dosing is complete, the unmasked study site personnel will immediately remove the used vial from the room. Refer to the IP Manual for full dosing and dispensation instructions.

7.2.1 Investigational Product Packaging and Labeling

[redacted]

7.2.2 Investigational Product Storage

IP inventory storage conditions can be found in the IP Manual.

A calibrated temperature thermometer with minimum and maximum capability must be used to monitor the temperature. A temperature log must be recorded throughout the study, logging the minimum and maximum temperature once every business day.

7.2.3 Investigational Product Compliance and Accountability

The Investigator is responsible for overseeing their overall IP accountability, ensuring that an accurate accounting of the number of IP (vials) inventory is received from the Sponsor, the number of units used to dose study subjects, and the number of units returned to inventory through the duration of the study.

IP accountability records must be readily available for inspection by the study monitor and are open to inspection by regulatory authorities at any time.

Only the unmasked site personnel should handle the IP and receipt of IP shipments. The shipment will be inspected to verify the number and condition of the IP received and confirm receipt of the consignment.

7.2.4 Return and Disposal of Investigational Product

At the completion of the study, all unused IP inventory will be returned to the designated depot for reconciliation and destruction.

7.3 Permissible Concomitant Medications/Treatments

Any medication (including ocular and over-the-counter) taken at least once within 28 days prior to the Screening Visit and during the study period will be recorded in electronic data capture (EDC), including the reason for its use.

Any medication taken during the study (Screening to Visit 4/Exit) will be recorded in EDC as a concomitant medication.

7.4 Prohibited Concomitant Medications/Treatments

Medications/treatments that are prohibited prior to Visit 1 (Screening) are identified in the exclusion criteria (Section 6.2).

Use of any of the following is prohibited during the study:

- An investigational drug (other than BRIMOCHOL PF or Carbachol PF) or device for any indication
- Use of systemic or topical antihistamines 48 hours prior to on-site study visits (including alpha-1 agonists: tetryzoline, oxymetazoline, phenylephrine, pseudoephedrine).
- Use of systemic anticholinergics (including tricyclic antidepressants or monoamine oxidase inhibitors; however, use of selective serotonin reuptake inhibitor [SSRI] is acceptable]) or cholinergics (including pilocarpine [e.g., VUITY] or cevimeline) or alpha-2 agonists (including brimonidine, dipivefrin) within 90 days prior to visit 1 or at any time during the study.
- Use of systemic alpha-antagonists (including methoxamine, mephentermine, cirazoline, benzphetamine, methyldopa, clonidine, guanabenz, phenoxybenzamine, phentolamine, alfuzosin, doxazosin, terazosin, tamsulosin, prazosin, and yohimbine) within 90 days prior to visit 1 or at any time during the study.
- [redacted]

8 STUDY VISIT SCHEDULE AND PROCEDURES

The schedule of visits and procedures is provided in Section 1.2. Details of the examinations and procedures are provided in the **Procedure Manual**.

Any delays in visits or assessments that are related to COVID-19 should be documented as such.

All subjects must sign the study ICF before beginning any screening procedures, and a copy of the ICF must be given to the subject. The Investigator or designee must record the date when the ICF was signed in the subject's medical records.

After signing the ICF, it is acceptable to perform procedures to prioritize pupil size measurement for eligibility confirmation and then return to the recommended order listed to complete the Screening Visit. Details of the Screening options are provided in the **Procedure Manual.**

[redacted]

The procedures should occur in the order presented below where possible, with the exception of pupil size eligibility. Sites have the option to schedule a Pre-Screening Visit to confirm pupil size eligibility. An abbreviated ICF must be signed for this Visit. The Pre-Screening Visit may be done on a separate day from Screening/Visit 1; however, if it is completed on a separate day, the pupil size measurements should be repeated at the Screening/Visit 1. The full Study ICF must be signed. The measurement obtained during the Screening Visit must meet eligibility requirements.

8.1 Visit 1: Screening (-14 to -1 Days)

1. Informed consent
2. Demographics
3. Medical, ophthalmic, surgical history
4. Physical assessment by body system

   Note: The body systems will be reviewed with the subject, and abnormal reports will be documented in the subject's EDC under Medical History.

5. Urine pregnancy test for females of childbearing potential
6. AEs (Section 9.1)
7. Concomitant medications (Sections 7.3 and 7.4)

8. Vital signs
9. Manifest refraction (OD/OS)
10. [redacted]
11. Dark adaptation
12. [redacted]
13. [redacted]
14. [redacted]
15. [redacted]
16. [redacted]
17. [redacted]
18. Slit-lamp biomicroscopy (OD/OS) [redacted]
19. IOP measurement (OD/OS) after slit-lamp biomicroscopy
20. Dilated ophthalmoscopy (OD/OS) after all assessments
21. [redacted]

[redacted]

8.2 Visit 2: (Randomization), Visit 3, and Visit 4/Exit

Note: Visit 3 and Visit 4 windows: minimum of 3 days but no more than 16 days from the previous Visit.

[redacted]

1. Update medical, ophthalmic, surgical history
2. At **Visit 4/Exit only**, urine pregnancy test for females of childbearing potential
3. AEs (Section 9.1)
4. Concomitant medications (Sections 7.3 and 7.4)
5. Vital signs

[redacted]

[redacted]

8. [redacted]

   a. Dark adaptation

   b. [redacted]

   c. [redacted]

   d. [redacted]

   e. [redacted]

   f. [redacted]

9. IRT kit assignment / randomization

10. IP instillation [redacted]

11. Dark adaptation [redacted]

12. [redacted]

13. [redacted]

14. Manifest refraction (OD/OS) ***ONLY*** *if subject experiences moderate distance vision loss*

15. [redacted]

16. [redacted]

17. [redacted]

18. Slit-lamp biomicroscopy (OD/OS) with corneal staining after all visual function assessments [redacted]

19. IOP measurement (OD/OS) after slit-lamp biomicroscopy [redacted]

20. At **Visit 4/Exit only**, dilated ophthalmoscopy (OD/OS) after all assessments [redacted]

21. [redacted]

22. At **Visit 4/Exit only**, Study exit

9 SAFETY MONITORING AND REPORTING

9.1 Adverse Events

9.1.1 Definition and Reporting

An AE is defined as any untoward medical occurrence in a subject or clinical investigational subject who has signed an ICF that does not necessarily have a causal relationship with this treatment.

AEs include:

- Unfavorable changes in general condition
- Subjective or objective signs/symptoms
- Concomitant diseases or accidents
- Clinically relevant adverse changes in laboratory parameters observed in a subject during a clinical study
- Persistent loss of ≥3 lines of distance or near visual acuity

AEs comprise all disturbances of general health status, subjective and objective disease symptoms (including laboratory abnormalities), and accidents observed in the context of a clinical trial, irrespective of a possible causal relationship with the administration of the trial substance. Events occurring in the framework of a clinical trial during drug-free and post-treatment periods are also to be designated as AEs.

AE information may be volunteered by the subject or solicited by study personnel through non-leading questions, such as "How are you feeling?"

Subjects will be queried for resolution of ongoing AEs or until any unresolved AEs are judged by the Investigator to have stabilized or if lost to follow-up. Resolution of all AEs will be promptly documented by the site in the subject's eCRF.

All AEs regardless of causality will be reported by the Investigator to the Medical Monitor through the 30-day period after the last dose of study treatment.

Any AE related to COVID-19 must be recorded as such.

9.2 Serious Adverse Events

9.2.1 Definitions

An SAE is any untoward medical occurrence at any dose that results in any of the following outcomes:

- Death
- A life-threatening event (i.e., puts the subject, in the view of the Principal Investigator (PI), at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical event that may require medical or surgical intervention to prevent one of the above outcomes

An unexpected adverse drug event is any adverse drug event, the specificity or severity of which is not consistent with the current IB.

An AE is associated with the use of the drug if a reasonable possibility exists that the drug may have caused the event.

9.2.2 Reporting

SAEs that are unexpected and related to BRIMOCHOL PF and/or Carbachol PF are reportable to Regulatory Authorities. All SAEs, regardless of causality will be reported by the Investigator to the Medical Monitor through the 30-day period after the last dose of study treatment. Deaths and SAEs occurring after the 30-day safety follow-up period AND considered related to study treatment or study procedures must also be reported.

Report all SAEs (initial and follow-up information) on an SAE form and send the form to the Sponsor or designee within 24 hours of the discovery of the event or information (see below). The Sponsor or designee may request follow-up and other additional information from the

Investigator (e.g., hospital admission or discharge notes, laboratory results). SAEs will be followed up through resolution, stabilization, or treatment termination.

Report all deaths with the primary cause of death as the SAE term, as death is the outcome of the event, not the event itself. If an autopsy was performed, report the primary cause of death on the autopsy report as the SAE term. Forward autopsy and postmortem report(s) to the Sponsor or designee, as outlined above.

If study treatment is discontinued, temporarily suspended, or the dose reduced because of an SAE, include this information in the SAE report.

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that qualify for mandatory expedited reporting to regulatory authorities where the SAE is suspected to be caused by the study treatment and is considered unexpected (i.e., not defined as expected in the current IB clinical study protocol, or approved labeling for marketed drugs). In this case, the Sponsor or designee will report to the relevant regulatory authorities and forward a formal notification describing the SUSAR to Investigators, according to regulatory requirements. Each Investigator must then notify his or her institutional review board (IRB) of the SUSAR as required by local regulatory authorities and in accordance with IRB policy.

Preplanned surgeries or procedures for pre-existing known medical conditions for which a patient requires hospitalization is not reportable as a serious adverse event and should be listed in medical history.

9.2.3 Classification of Severity of Adverse Event

The severity of AEs will be categorized, as shown below.

Categorization of Severity of Adverse Events

Mild	The event is minor and does not cause significant discomfort to subject or change in activities of daily living (ADL); subject is aware of symptoms, but symptoms are easily tolerated.
Moderate	The event is an inconvenience or concern to the subject and causes interference with ADL, but the subject is able to continue with ADL.
Severe	The event significantly interferes with ADL and the subject is incapacitated and/or unable to continue with ADL.
Potentially life-threatening	An event/reaction in which the subject was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe.

9.2.4 Relationship to Investigational Product

The Investigator will make a determination of the relationship of the AE to the IP using a 4-category system (not related, possible, probable, definite), as shown below.

Categorization for Determining Relationship of AEs to Study Treatment	
Not related	An AE that does not follow a reasonable temporal sequence from administration of the drug and that can be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment.
Possible	An AE that follows a reasonable temporal sequence from the administration of the drug (including the course after withdrawal of the drug) and that cannot be excluded as being possibly caused by the drug (e.g., existence of similar reports attributed to the drug and/or its analogues; reactions attributable to the pharmacological effect of the drug), although other factors such as underlying disease, complications, concomitant drugs, or concurrent treatment are presumable.
Probable	An AE that follows a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug) and that can be excluded as being possibly caused by other factors, such as underlying disease, complications, concomitant drugs, or concurrent treatment.
Definite	An AE that follows a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug), follows a known or hypothesized cause–effect relationship, and (if appropriate) satisfies the following: • Positive results obtained in drug sensitivity tests. • Toxic level of the drug present in blood or other body fluids.

9.2.5 Ocular Events of Special Interest

For this study medically important events comprise the following ocular events, which are of special interest and by default are to be reported as SAEs:

- Acute angle glaucoma or moderate to severe increase in IOP of >25 mm Hg
- Retinal tear or detachment

9.3 Pregnancies

Females of childbearing potential must have a negative urine pregnancy test at Visit 1 to participate. If a female has a positive urine pregnancy test during the study, the subject will be withdrawn from the study and the Investigator will notify IQVIA and/or the Sponsor within 24 hours of knowledge of the positive pregnancy test.

The pregnancy will be followed to term and/or outcome, and this outcome must be reported to the Sponsor. A pregnancy is not regarded as an AE or SAE unless the birth results in a congenital anomaly/birth defect, or there is suspicion that the study treatment may have interfered with the effectiveness of a contraceptive medication or method.

10 DATA COLLECTION AND MANAGEMENT

10.1 Data Confidentiality

All data collected during the study will be recorded in the subject's eCRF. To maintain confidentiality, subjects will be identified only by Subject Number and initials.

10.2 Site Monitoring

The Sponsor or designee (e.g., Clinical Research Associate [CRA]) will be responsible for monitoring this clinical trial. The CRA will monitor the study conduct, proper eCRF and source documentation completion and retention, and accurate IP accountability. To this end, the CRA will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. The Investigator will grant access to all documents (related to the study and subjects) at any time these are requested. In turn, the CRA will adhere to all requirements for subject confidentiality as outlined in the ICF. The Investigator and study staff will be expected to cooperate with the CRA, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

10.3 Data Collection

All primary source data or copies thereof (e.g., laboratory records, eCRFs, data worksheets, correspondence, photographs, and computer records) that are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report will be retained in the clinic archives.

11 STATISTICAL METHODS AND DATA ANALYSIS

Data analysis will be performed according to the Sponsor's or designee's standard operating procedures. A detailed statistical analysis plan (SAP) will be provided prior to database lock.

Unless otherwise stated, continuous variables will be summarized using the number of subjects, mean, standard deviation (SD), median, minimum, and maximum; and categorical variables will be summarized using the frequency count and the percentage of subjects in each category. Unless otherwise specified, the Baseline for each efficacy and PD endpoint at each dosing visit is defined as the pre-dose assessments at Hour 0 of the visit.

All subject study data collected in the eCRFs and other media will be presented in data listings.

11.1 Analysis Sets

11.1.1 Safety Population

All subjects who receive any amount of IP will be included in the safety population. Subjects will be analyzed as treated.

11.1.2 Modified Intent-to-Treat (mITT) Population

All randomized subjects who receive at least 1 dose of IP will be included in the modified intent-to-treat (mITT) population. Subjects will be analyzed as randomized.

11.1.3 Per-Protocol Population

All mITT subjects who comply with the protocol without major protocol deviations/violations deemed to potentially affect study treatment effect will be included in the PP population. [redacted]

11.2 Efficacy Analyses

[redacted]

Primary Efficacy Endpoints for the US FDA

A treatment responder is defined as a subject who has a ≥15 ETDRS letter gain from Baseline in BUCNVA without a ≥5 ETDRS letter loss in BUCDVA using both eyes under mesopic conditions.

Primary Efficacy Endpoint for Rest of the World (ROW)

The ROW primary efficacy endpoint will be an $AUC_{0\text{-}8h}$ defined as a weighted average of changes from Baseline in ETDRS letters of BUCNVA using both eyes under mesopic conditions

[redacted]

[redacted]

[redacted]

11.3 Pharmacodynamic Analyses

The PD endpoint is the change from Baseline in pupil size in each eye, the average between eyes, the minimum between eyes, and the maximum between eyes at all timepoints.

[redacted]

11.4 Safety Analyses

Safety assessments will be analyzed with the safety population. The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code AEs by system organ class (SOC) and preferred term (PT). A treatment-emergent adverse event (TEAE) is a post-treatment AE where:

- there is no pre-treatment AE of the same MedDRA primary SOC and PT during the study; or
- there is a pre-treatment AE of the same MedDRA primary SOC and PT during the study, and the maximum severity during the post-treatment period is greater than that during the pre-treatment period

The number and percentage of subjects reporting TEAEs will be tabulated by primary SOC and PT for each treatment. TEAEs will be further classified by severity and relationship to IP in the summaries. Given that subjects are to be treated with different treatments at Visits 2, 3, and 4, an AE will be considered as a TEAE and attributed to a particular treatment if the AE has a new starting date or a severity worsening date after receiving the treatment and before receiving the subsequent treatment.

The safety endpoints that compare event rates between groups may be similarly performed using the methods as outlined above for efficacy endpoints.

Vital signs and the safety variables associated with ocular assessments (e.g., visual acuity, slit--lamp biomicroscopy, and IOP) will be summarized by treatment for each visit using appropriate descriptive statistics.

[redacted]

11.6 Sample Size Calculation

Sample size and power consideration is based on the procedure given by Connor (1987). The response rates of a paired population are denoted in the table below:

[redacted]

[redacted] will be enrolled to complete 152 subjects.

12 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

12.1 Regulatory and Ethical Compliance

The study will be conducted in accordance with the International Council for Harmonisation Good Clinical Practice (ICH GCP) guidelines, principles enunciated in the Declaration of Helsinki, and all applicable FDA regulations.

12.2 Responsibilities of the Investigator and IRB

This protocol, the ICF, and all relevant supporting data must be submitted to the IRB for approval. IRB approval of the protocol, the ICF, any advertisement used to recruit study subjects must be obtained before initiating the study.

The PI is responsible for keeping the IRB advised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, at least once a year. The PI is also responsible for notifying the IRB of any reportable AEs that occur during the study.

12.3 Informed Consent Procedures

At the first visit, prior to initiation of any study-related procedures, subjects must give their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits. The ICF must be signed and dated by the subject prior to study participation. A copy of the ICF must be provided to the subject. Signed consent forms must remain in the subject's study file and be available for verification by the Sponsor or its representative at any time.

12.4 Publication of Study Protocol and Results

Visus will retain ownership of all data. All proposed publications based on this study will be subject to the Sponsor's approval requirements.

12.5 Study Documentation, Recordkeeping, and Retention of Documents

All study data will be captured using an EDC system. All source documents, records, and reports will be retained by the clinic.

All primary source data or copies thereof (e.g., eCRFs, data worksheets, correspondence, and computer records) that are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report will be retained in the clinic archives.

The Investigator must retain study documents for a period of 2 years following the date a marketing application is approved for the study product for the indication for which it is being investigated; or if no application is to be filed or if the application is not approved for such

indication until 2 years after the investigation is discontinued and the FDA is notified. The site should not destroy records until authorized to do so by Visus.

12.6 Confidentiality of Study Documents and Subject Records

All information provided regarding the study, as well as all information collected or documented during the study, will be regarded as confidential. The Investigator agrees not to disclose such information in any way without prior written permission from the Sponsor.

Any publication of the results, either in part or in total (articles in journals or newspapers, oral presentations, abstracts, etc.) by the Investigator or their representative(s), shall require prior notification and review, within a reasonable time frame, by the Sponsor, and cannot be made in violation of the Sponsor's confidentiality restrictions or to the detriment of the Sponsor's intellectual property rights.

The results from Screening and data collected during the study will be recorded in the subject's eCRF. To maintain confidentiality, subjects will be identified only by numbers and initials.

12.7 Monitoring and Quality Assurance

During the study, the Sponsor, an IQVIA Biotech CRA, or designee may complete routine monitoring visits to review protocol compliance, assess IP accountability, and ensure the study is being conducted according to regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality.

Further details of the study monitoring will be outlined in a clinical monitoring plan (CMP). Regulatory authorities of domestic and foreign agencies, the Sponsor, and IQVIA Biotech Quality Assurance and/or its designees may carry out on-site inspections and/or audits that may include source data checks. Therefore, direct access to the original source data will be required for inspections and/or audits.

All inspections and audits will be carried out considering data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

12.8 Protocol Adherence

The Investigator must adhere to the protocol as detailed in this document and agree that the Sponsor must approve any changes to the protocol prior to seeking approval from the IRB. There will be no alterations in the protocol without agreement between the Sponsor and the Investigator. There will be no alterations in the protocol affecting subject safety without the express written approval of the Sponsor, Investigator, and the IRB.

12.9 Study Termination

The study may be stopped at a study site at any time by the Investigator. The Sponsor may stop the study (and/or the study site) for any reason with appropriate notification.

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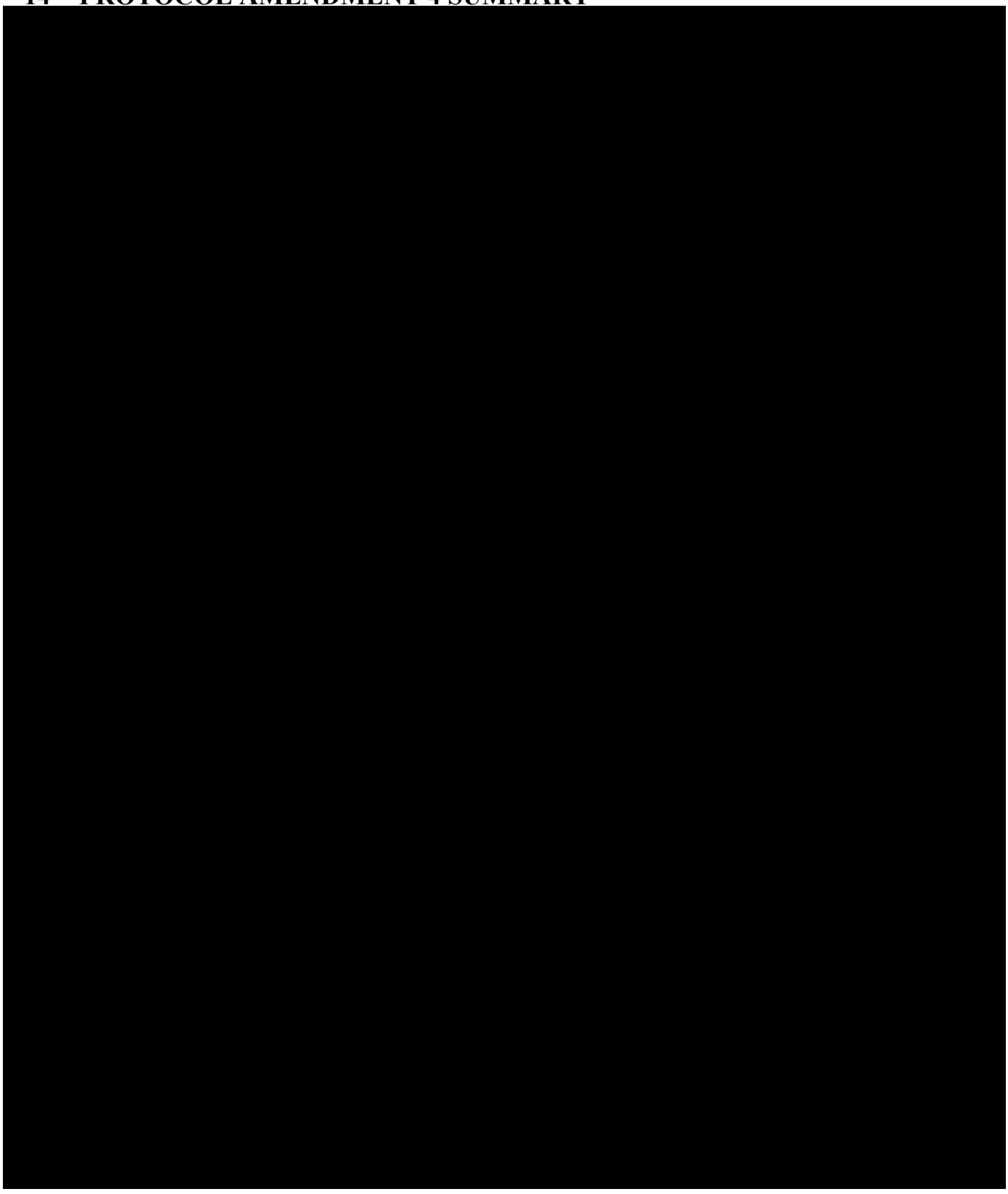
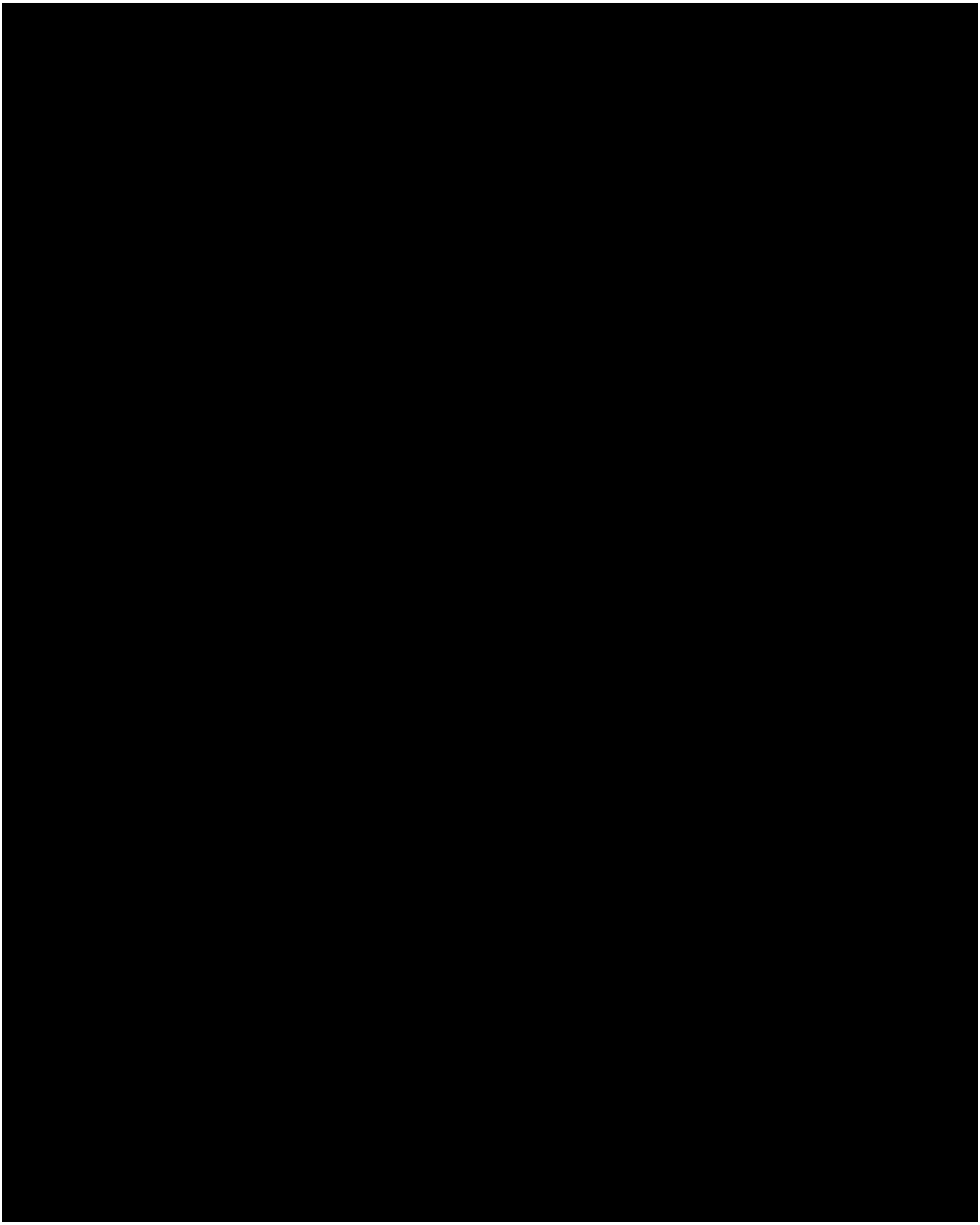
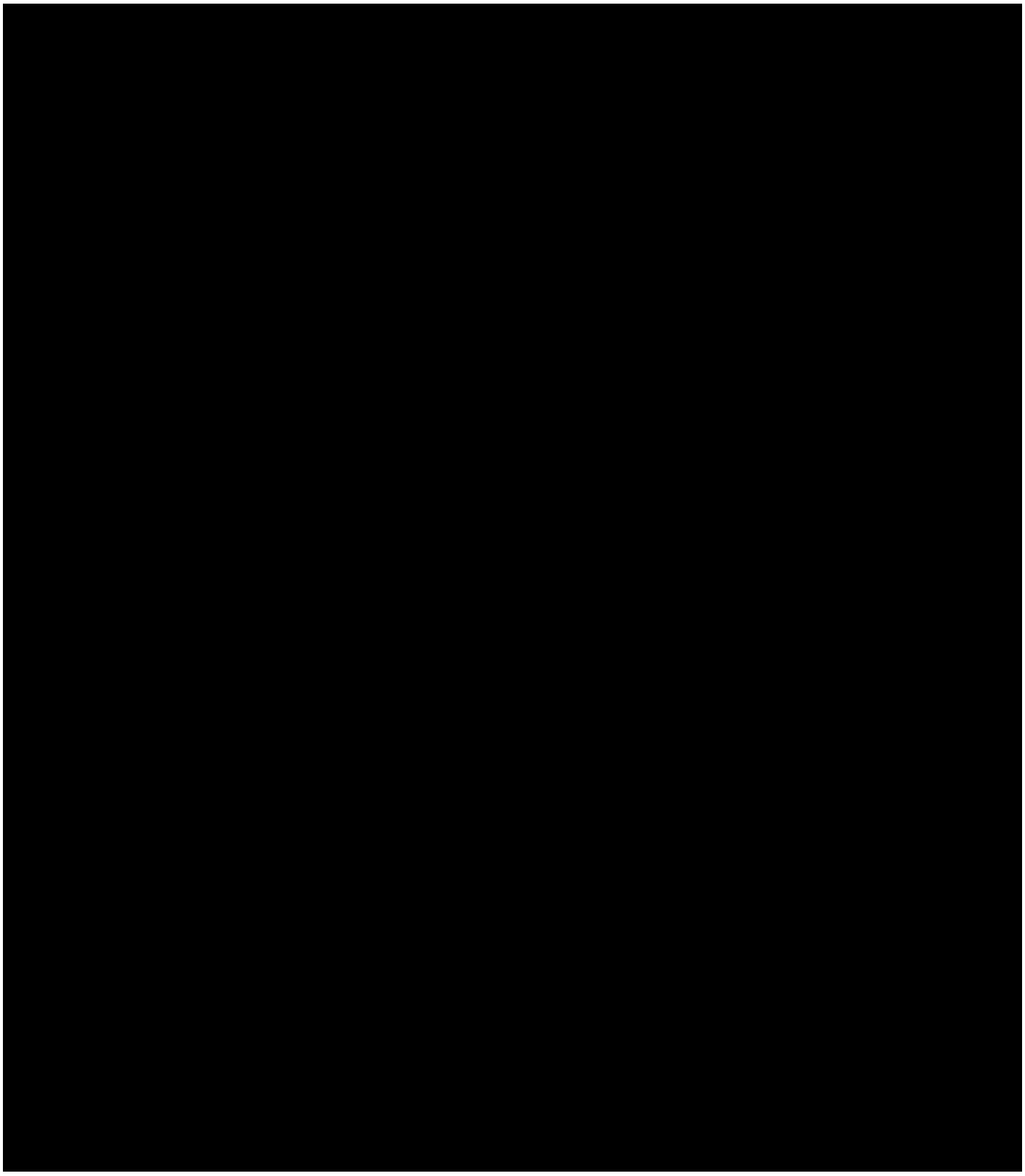
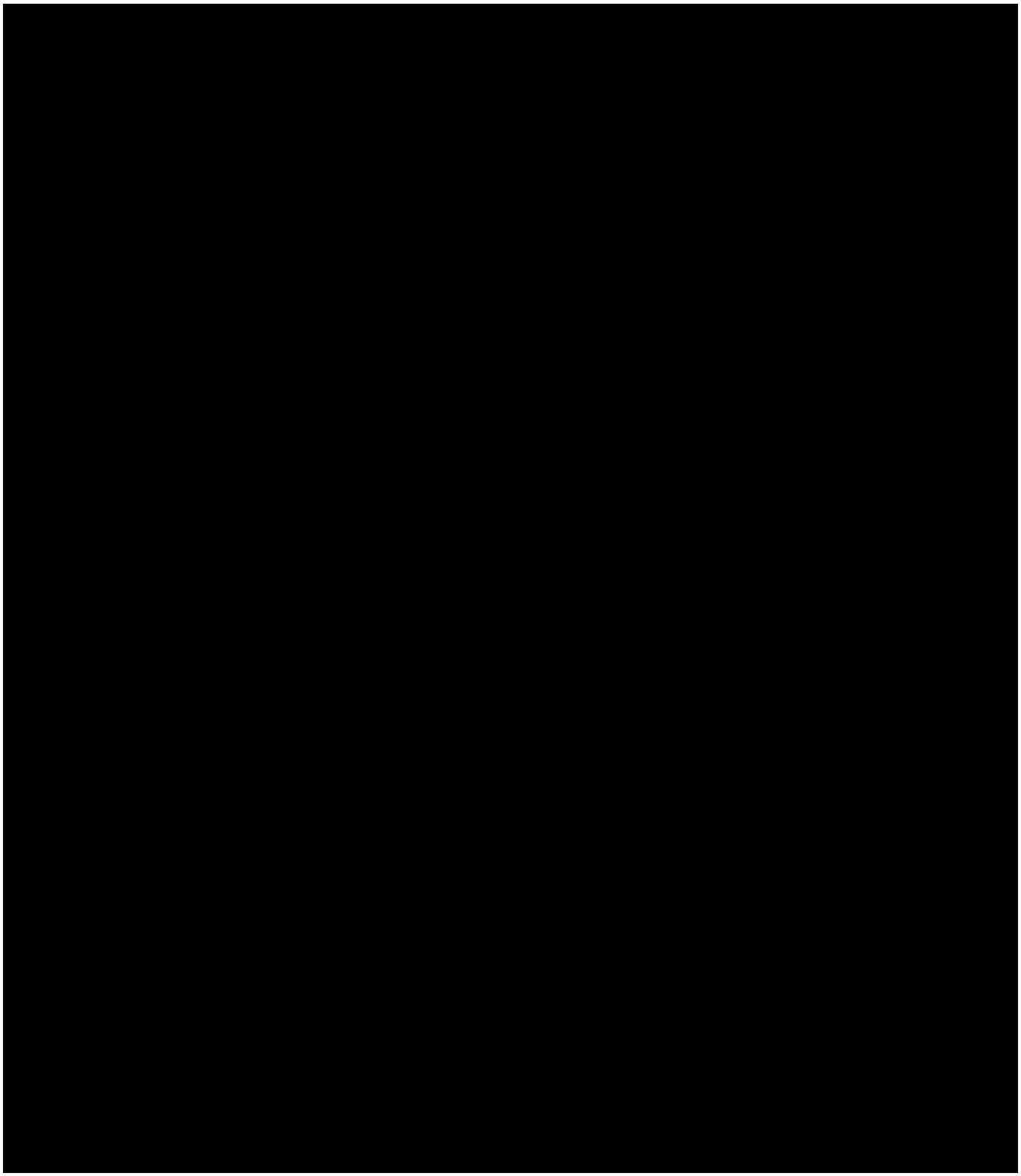
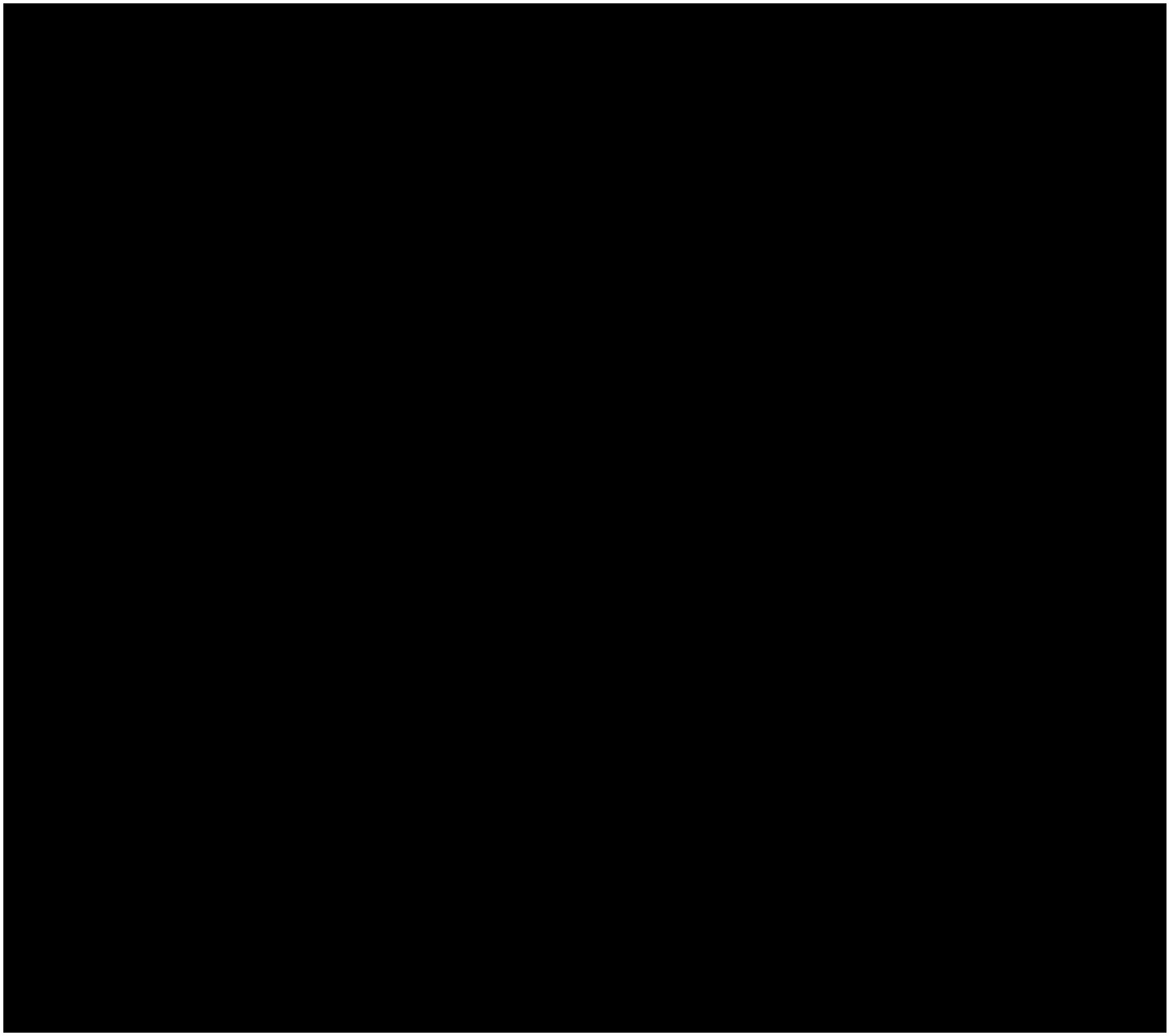
14 PROTOCOL AMENDMENT 4 SUMMARY

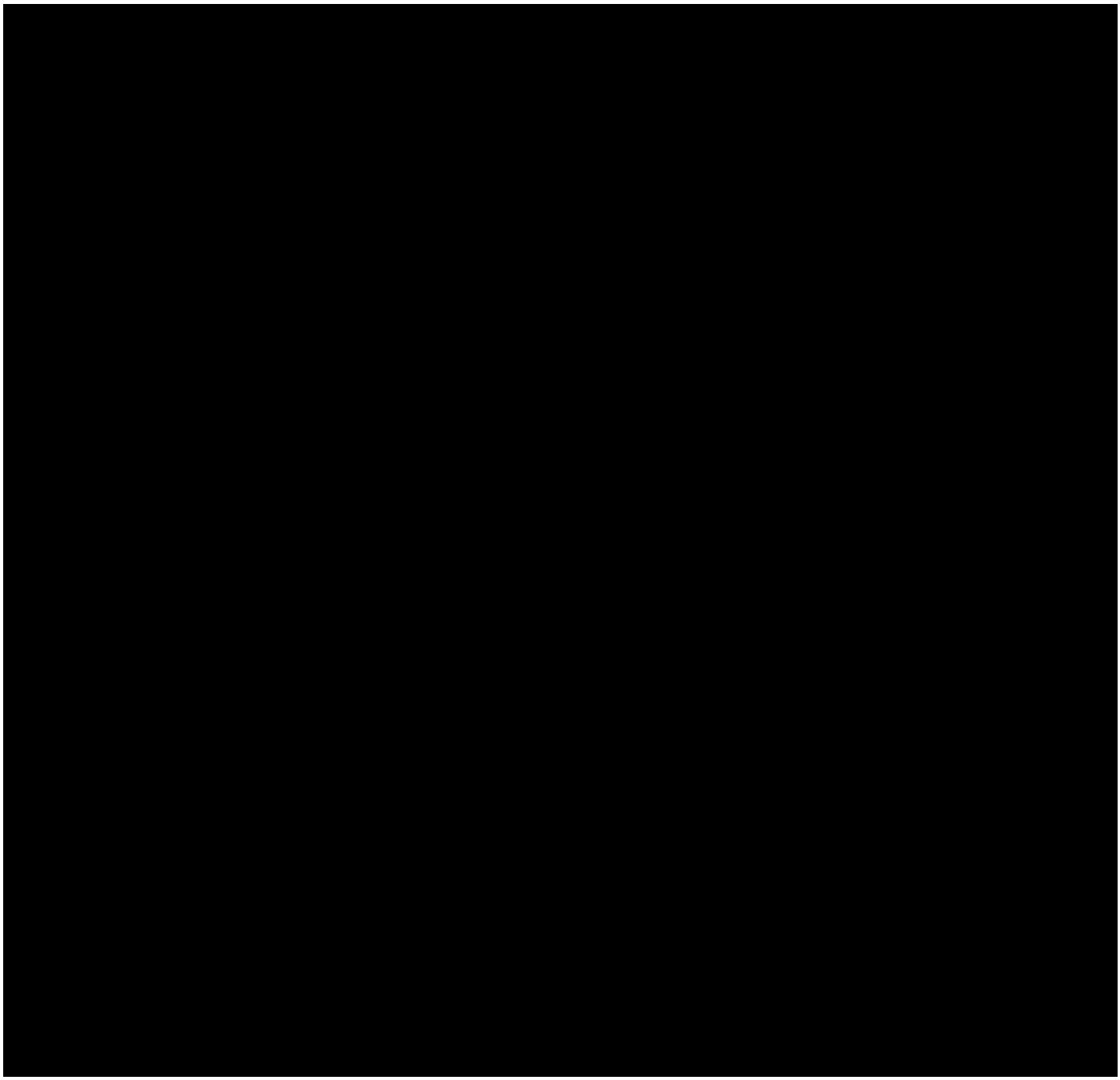


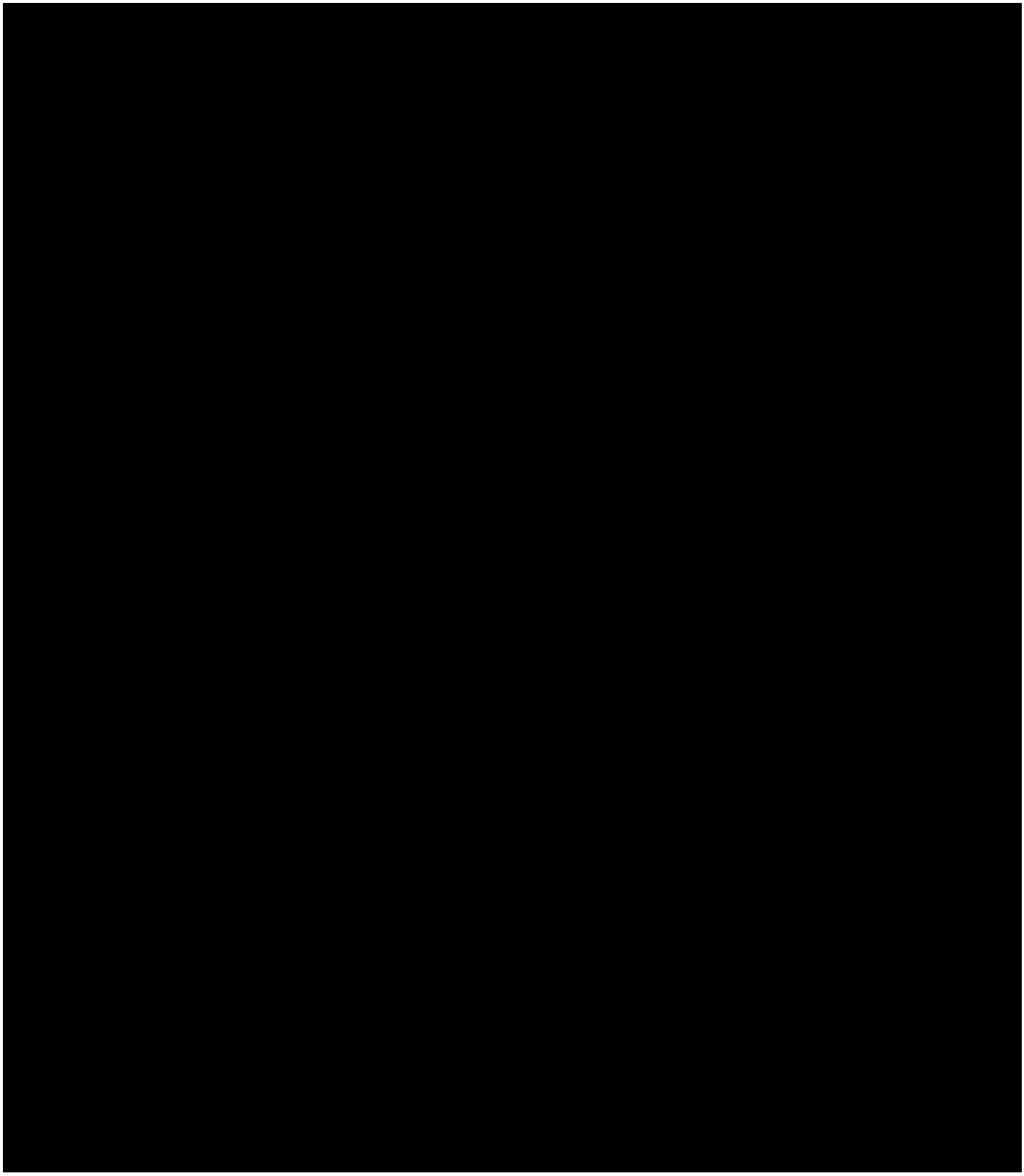




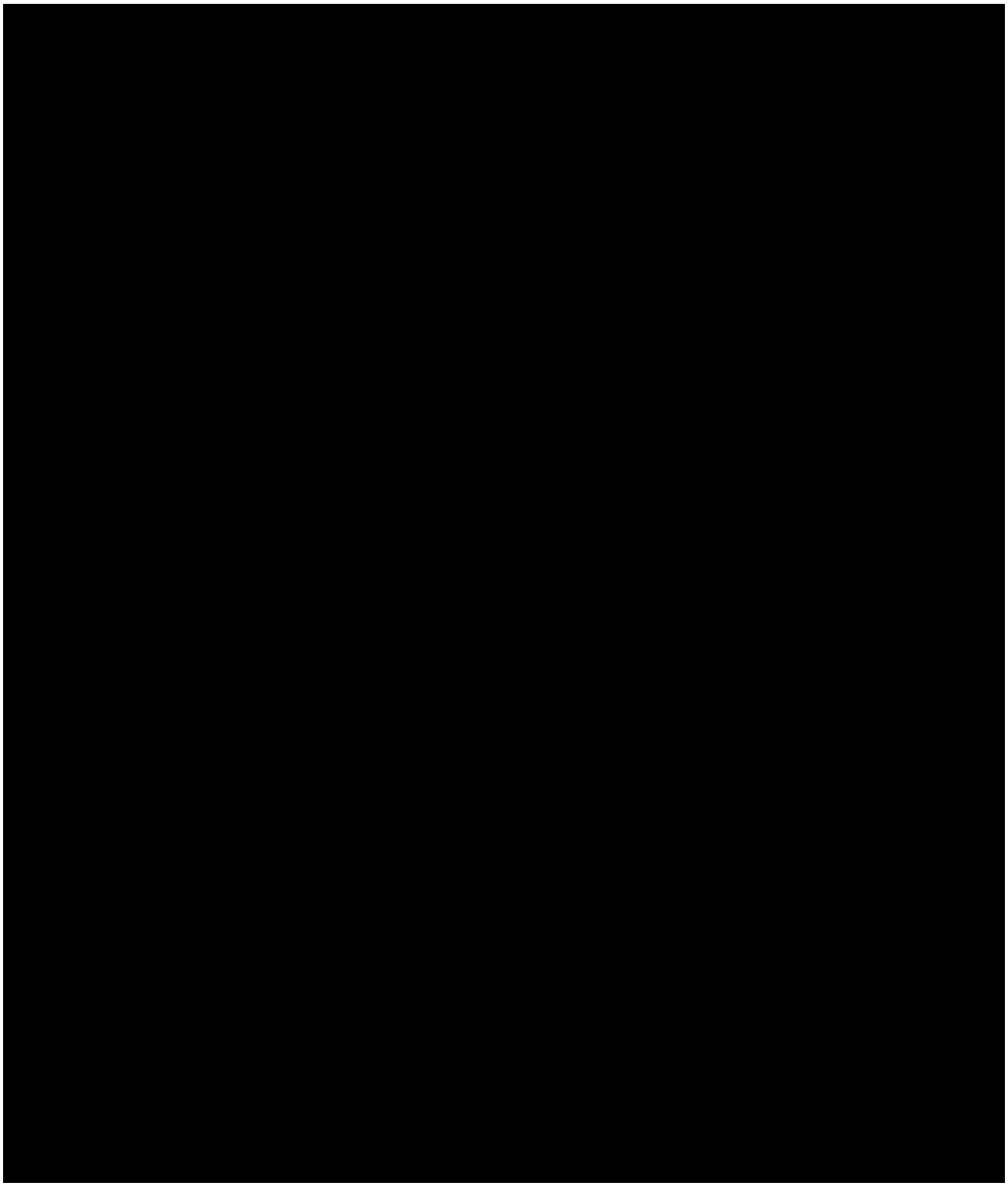




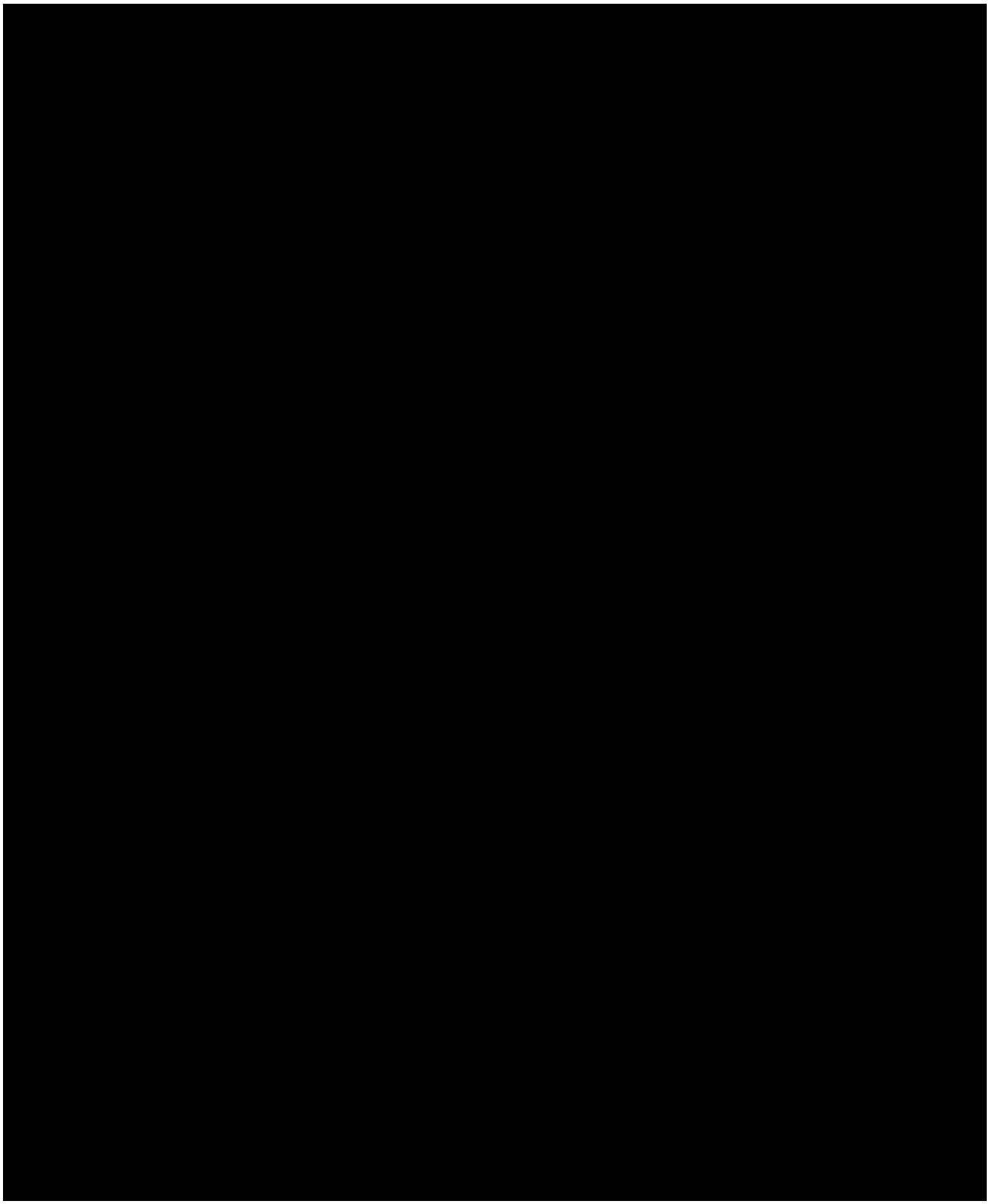




15 PROTOCOL AMENDMENT 3 SUMMARY



16 PROTOCOL AMENDMENT 2 SUMMARY



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17 PROTOCOL AMENDMENT 1 SUMMARY