STUDY PROTOCOL

[redacted]

A Multicentre Dispensing Clinical Evaluation of MiSight® Lenses

A three-year multicentre, parallel-group, controlled, double-masked, randomised clinical trial to quantify the effectiveness of CooperVision Inc.'s MiSight® (omafilcon A) soft (hydrophilic) contact lens in slowing the rate of progression of juvenile-onset myopia.

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PROTOCOL CHANGE HISTORY

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1 BACKGROUND INFORMATION

Myopia is a significant public health problem, affecting at least 33% of adults in the United States.[1] Epidemiological studies provide strong evidence that the prevalence of myopia has increased in the U.S.[2] in the past decade and also worldwide.[3] The most rapid increase has been in East Asian countries where it has reached epidemic proportions affecting over 80% of adults in some regions, such as Hong Kong, Taiwan and Singapore.4-6

The myopic eye has an increased risk of developing ocular pathology that may lead to vision loss, including retinal detachment, glaucoma, cataract and myopic retinopathy.7 The following studies illustrate that the contribution of myopic retinopathy to impaired vision can be high. The Rotterdam Study, of 6775 subjects aged 55 years or older, found that, for persons younger than 75 years, myopic degeneration was one of the two leading causes of impaired vision.8 In a study population of 3021 participants, 40 years or older, in Tajimi City, Japan, myopic macular degeneration was the leading cause of monocular blindness.9 The Beijing Eye Study, with 3251 participants aged 40 or older, found the prevalence of myopic retinopathy increased significantly with refractive error from 3.8% in eyes with refractive errors lower than 4 dioptres of myopia to 89.6% in eyes with at least 10 dioptres of myopia.[10]

There is considerable evidence from animal studies that emmetropization is an active rather than a passive process and that eye growth is mediated by visual signals.[11] For example, when a minus lens is placed in front of the eye, it imposes hyperopic defocus on the visual system causing eye growth to increase and the eye to grow longer in order to bring the retina back to the focal plane. Conversely, a plus lens imposes myopic defocus which slows eye growth and results in hyperopic refractive errors.

This observed induction of myopic refractive errors with imposed hyperopic defocus underlies the hypothesis that hyperopic defocus resulting from under-accommodation during near work may be a driving factor in the development and progression of myopia in susceptible individuals. Accommodative lag is considered to be an important factor in the pathogenesis of myopia because of the association between myopia progression and near work.[12-16] Some studies indicate that myopes tend to have a larger lag of accommodation compared to emmetropes[17-21] and larger accommodative lags have been linked to both the development[22-24] and progression of myopia.[18,20,25,26]

Several treatment paradigms for slowing myopia progression have been evaluated in intervention studies, however most therapies have demonstrated small treatment effects that last for relatively short periods of time or have significant side effects.[27] Among the optical treatments investigated for controlling myopia progression, progressive addition lenses (PALs) have been used as a means to decrease accommodative lag during near work.[28,29] While these trials yielded statistically significant but clinically small treatment effects, subgroup analyses show significantly larger benefits for children with near esophoria and larger lags of accommodation indicating that the rationale of reducing accommodative lag has some merit.[29,30]

Further evidence of the potential for this treatment paradigm to slow myopia progression is provided by several small studies examining the effectiveness of bifocal and multifocal soft contact lenses as myopia control treatments in children and young adults, with these studies reporting larger treatment effects than seen in spectacle lens studies.[31-35] Two of the latter studies were particularly successful, one comparing bifocal to SVD soft contact lens wearers reported a 72% reduction in the bifocal lens group[31], while the other found a 67% reduction in myopia progression when multifocal spectacles lens wearers were switched to multifocal contact lenses.[33] In addition, a mono-vision spectacle lens trial, in which the dominant eye was fully corrected for distance and the fellow eye was under corrected such that the latter

eye experienced myopic defocus (a focal point located in front of the retina) for both distance and near objects, demonstrated significantly slower myopia progression in the under-corrected eye versus the fully corrected eye.[36]

Orthokeratology (ortho-k) is an alternative contact lens treatment that may also have the potential to reduce myopia progression. This technique uses reverse geometry RGP contact lenses to remodel the anterior corneal surface to temporarily reduce the refractive error in low to moderate myopes.[37,38] Two recent longitudinal studies reported slower progression of myopia (slower increase in ocular axial length) in subjects treated with overnight ortho-k compared to subjects wearing either spectacle correction or soft contact lenses. [39,40]

One theory to explain the slowing of myopia progression with ortho-k is the conversion of relative peripheral hyperopia to relative peripheral myopia that results as a consequence of the corneal reshaping occurring with this treatment. Lending support to this theory, several studies have reported differences in peripheral refractive errors between myopes, emmetropes and hyperopes across the horizontal meridian with myopes usually showing relative hyperopia in the periphery, and emmetropes and hyperopes showing relative myopia in the periphery.[41-46]

Previous studies have shown that children are capable of wearing many current modalities of contact lenses: daily wear RGP contact lenses,[47-49] orthokeratology contact lenses,[39,40] and soft contact lenses, including daily disposable contact lenses.[50-53]

Because myopia typically develops at ages younger than 10 years and because progression rates are higher in younger children, it is felt that a successful myopia control treatment should target this highly susceptible population.[54-58]

In a small scale cross-over study, Anstice and Phillips applied dual-focus (DF) design contact lenses, which allow clear distance vision and myopic defocus simultaneously, to children aged 11 to 14 years (inclusive), The mean change in spherical equivalent refraction (SER) with DF lenses (-0.44±0.33 D) was less than with single vision distance (SVD) lenses (-0.69±0.38 D; $P < 0.001$).The mean increase in axial length was also less with DF lenses (0.11±0.09 mm) than with SVD lenses (0.22±0.10 mm; $P < 0.001$). [35]

The purpose of this study is to quantify the effectiveness of DF contact lenses (commercial name 'MiSight®') for slowing juvenile-onset myopia progression in a three year, multicentre, parallel-group, controlled, double-masked randomised clinical study.

1.1 Investigational Product

The investigational (test) product, MiSight®, and the control lenses, CooperVision Proclear® 1-Day, are both soft (hydrophilic) contact lenses composed of omafilcon A material.

The test product is investigational in the United States, and areas of Asia Pacific but cleared for distribution in Canada and Europe (CE marked).

The Proclear® contact lens has been cleared for distribution in the United States [redacted] It is currently available on the market for the correction of refractive error in non-aphakic persons with non-diseased eyes that are myopic or hyperopic and exhibit astigmatism of 2.00D or less that does not interfere with visual acuity. Both the test and control lenses will be used following a daily wear, daily disposable modality.

The investigators should only use lenses provided by the sponsor or the CRO. If during the study, the subject's refraction changes such that they can no longer wear any of the lens powers available for study, they will need to be exited from the study.

Table 1: Lens Names and Descriptions

	Test	Control
Lens type	MiSight ®	Proclear ® 1-Day
Manufacturer	CooperVision, Inc.	CooperVision, Inc.
Diameter/ base curve (mm)	14.2 / 8.7	14.2 / 8.7
Sphere powers available for study (D)	-0.75 to -6.00 (0.25 steps)	
Wear regimen	Daily wear	Daily wear
Replacement schedule	Daily disposable	Daily disposable

1.2 Summary of Non-clinical Studies

Non-clinical studies conducted on the MiSight® lens material are summarised in the Investigator's Brochure (separate document).

1.3 Potential Risks and Benefits for Human Subjects

1.3.1 General Risks of Contact Lens Wear

This is considered a significant risk study based on US FDA guidance and non-significant risk study based on ISO guidelines due to the fact that study subjects will be wearing the lenses on a daily wear basis and the contact lens has been approved (CE marked) for sale in Europe.[59,60] The risk is also reduced based on the results of biocompatibility testing and the history of the Proclear® 1-Day lenses which are currently approved and marketed.

The general risks associated with contact lens wear have been established through device evaluations and market reporting. The risks may include discomfort, dryness, aching or itching eyes, excessive tearing, discharge, hyperaemia and variable or blurred vision. More serious risks include photophobia, iritis, corneal oedema, corneal neovascularisation and corneal ulcers.

1.3.2 Paediatric Risks of Contact Lens Wear

Several studies have demonstrated that children in the study age group are mature enough to safely and successfully wear contact lenses.[48,49,51-53,61] There were no serious adverse events reported during the 3-month CLIP study.[51] This study of 8 to 12 year old children wearing soft contact lenses for the first time, also reported no significant changes in corneal staining, hyperaemia, tarsal abnormalities or corneal oedema. A small but significant increase in conjunctival staining was observed at the 1-week and 1-month visits, which decreased at the 3-month visits suggesting an adaption period for contact lens wear. [51]

Similar findings were reported in a 3-month study of 8 to 11 year old children in Singapore.[61] There were three adverse events (all due to chalazion), and significantly more limbal and bulbar hyperaemia and corneal staining at follow-up visits compared to baseline, however no instances were greater than Grade 2 (0-4 scale).

Less than 8% of children wearing soft lenses in previous myopia control studies displayed adverse events.[45,52] In addition, the incidence of these events, was similar between spectacle and contact lens wearers.[52] None of the events was serious, and all of them resolved without

permanent decrease in best corrected visual acuity.[45,52] For instance, in the 3-year ACHIEVE study, nine contact lenses wearers out of a total of 484 subjects (247 of whom received lenses) experienced 13 adverse events, all of which resolved without permanent decrease in best corrected visual acuity.[52]

Concerns regarding the risks of contact lens wear in children have recently been raised by Wang *et al*. who reported that contact lenses accounted for 23% of the medical device-associated adverse events among paediatric patients.[62] However, most of the contact lens related injuries were considered superficial and preventable, resulting from alteration of recommended wearing or replacement schedules and non-compliance with contact lens care regimens. Any such potential risks to the subjects in the current study will be mediated by proper training and education in successful and safe contact lens wear. Parents will be trained in insertion and removal of the lenses, contact lens care for daily disposable lenses and in identifying signs and symptoms that could be indicative of potential contact lens related problems. The lenses will be dispensed only after the subject demonstrates an ability to insert and remove the contact lenses. Additional training sessions will be provided if this is not accomplished during the randomisation and dispensing visit. Subjects will be provided with a more than adequate supply of contact lenses to discourage re-use of lenses in the event that a lens is torn or lost during normal usage.

1.3.3 Potential Benefits of Contact Lens Wear

The participants in both study groups may benefit from contact lens wear due to quality of life improvements associated with wearing contact lenses compared to spectacles for refractive error correction. Contact lens wear has been found to notably improve how children feel about their appearance and participation in activities.[63] Contact lens wear has also been found to improve the self-perception of 8 to 11 year old myopic children in terms of physical appearance, athletic competence and social acceptance.[64] In addition, myopic children younger than 12 years old report better vision related quality of life when wearing contact lenses compared to glasses.[65]

The potential benefits of the test contact lenses to the subjects are the possibility of slowed myopia progression[31-35]

There are also potential benefits of contact lens wear for myopia control compared to other treatment paradigms.[66] Unlike PALs, where children may not be using the near portion of the lens,[67] a child's reading behaviour when wearing the test lens does not need to be altered. In addition, contact lens wear does not involve the same degree of adverse ocular and systemic side effects compared to pharmacological treatments, such as atropine and pirenzepine, which have been found to be clinically successful in slowing myopia progression.[68-70]

1.4 Description of Treatment Period

Following the signing of the informed consent and assent documents, a baseline examination will be done to determine eligibility. Eligible subjects who wish to continue with the study will be dispensed study lenses and return for follow-ups at 1 week, 1, 6, 12, 18, 24, 30 and 36 months.

1.5 Statement of Compliance

This clinical study is designed to be in conformance with the ethical principles in the Declaration of Helsinki, with the ICH guidelines for Good Clinical Practice (GCP) and all applicable local regulations.

1.6 Study Population

The eligible study population will include up to 300 subjects (in order for 174 to finish) who require bilateral vision correction. The study population are myopic children aged 8 to 12 years old inclusive at the baseline examination, with -0.75 to -4.00 D of myopia and less than 1.00 D of astigmatism. Subjects must meet the eligibility criteria and provide written informed assent and have written informed consent of their parent or guardian. A minimum of 50% of the study population should be in the 8-10 year old group.

The study will take place at up to six investigational sites across North America, Europe and Asia Pacific including schools and colleges of optometry and ophthalmology clinics. Each site will enrol 50 eligible subjects (minimum 40 – maximum 60). Study sites will be selected based on the experience of the site investigator and staff in conducting clinical trials, the availability of potential study subjects, and the interest of the site in performing the trial.

1.7 References

- 21 CFR Part 812 Investigational Device Exemptions
- Declaration of Helsinki
- ICH E6 - International Conference on Harmonisation; Good Clinical Practice
- ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects

2 STUDY OBJECTIVE AND PURPOSE

The primary objective of this study is to quantify the effectiveness of the test lens, MiSight®, in slowing the rate of progression of juvenile-onset myopia compared to a conventional soft contact control lens (CooperVision Proclear® 1-Day), while providing comparable comfortable, clear vision. This objective will be achieved by conducting a randomised clinical trial comparing myopia progression, as measured by cycloplegic autorefraction and axial length, in children treated with MiSight® versus children treated with Proclear® 1-Day. The comparison will allow quantification of the effect of MiSight® on myopia progression during 3 years of follow-up.

[redacted]

3 CLINICAL STUDY DESIGN

3.1 Primary Endpoints

3.1.1 Primary Safety Endpoints

An assessment of non-inferiority will be made between the test and control lenses in the cumulative incidence of objective findings, including biomicroscopic findings and adverse events.

3.1.2 Primary Quantification of Effectiveness Endpoints

- The progression of myopia will be less for the test lens group compared to the control lens group. The progression of myopia will be defined as the magnitude of change in spherical equivalent refractive error relative to baseline (see Section 6.1)

- The progression of myopia will be less for the test lens group compared to the control lens group. The progression of myopia will be defined as the change in axial length relative to baseline, as the progression of myopia has been shown to be associated with increases in axial length (see Section 6.1).[28]

3.2 Secondary Endpoints

3.2.1 Secondary Safety Endpoints

- [redacted]

3.3 Clinical Study Design

This study is a multicentre, parallel-group, controlled, double-masked (subject and investigator), randomised clinical trial with a duration of three years.

3.3.1 Study Design Rationale

Previous, small scale studies have indicated some beneficial effect in slowing myopia progression from the use of bifocal lenses compared with single visions lenses.[31-35] As noted earlier, one such study involving a DF lens found more than a one-third reduction in myopia. However, most previous studies have been relatively short (≤1 year) and the important question remains as to whether this inhibitory effect persists beyond the first year. It is therefore the intention to run this study for three years.

Several study designs are available for testing the effectiveness of myopia control treatments. A classic cross-over design has been used with a previous study of DF lenses, however this design is not appropriate for a longer term evaluation. Aside from the inordinately long study duration, by the time of switching to the other treatment, the child would be at a different stage of development. Contralateral eye comparisons have also been undertaken but there is an obvious risk of inducing unwanted anisometropia. A parallel group design has therefore been selected as the best option.

For the control treatment, soft contact lenses of similar back surface design and material as the test lens have been selected. As well as facilitating masking, this allows for specific testing of the effect of the DF optics on myopia control and rules out possible confounding factors. It is not felt necessary to have an additional control group of spectacle wearers as a previous study has noted similar myopia progression between single vision soft contact lenses and spectacles.[52]

A large enough sample size has been planned so as to maintain a large study group even after the inevitable drop-outs. Nevertheless, the drop-out rate for children in soft contact lens studies has been relatively low.[50-53] Based on the findings of previous studies, it is calculated that this will allow enough subjects completing the study to test for statistically as well as clinically significant differences between groups (see Section 8.1).

3.4 Study Bias Control

3.4.1 Randomisation

Each enrolled subject will be assigned a subject number prior to being randomised. Eligible subjects will be sequentially randomised into either the test or control group (1:1 ratio). [redacted]

[redacted]

3.4.2 Masking

Several steps will be taken to keep the investigators, subject and parents/guardians masked to the assigned lens:

- Subjects will be identified by subject numbers, which are unrelated to study lens assignments.
- Study lenses will be labelled such that the identity of the study lens group is not revealed. Therefore sites must only dispense lenses for the study that have been provided by the sponsor or CRO.
- If for any reason the investigator needs to be unmasked to the lens type the study subject is wearing, they should follow the decoding procedures which will be present in the investigator study binder.

3.5 Study Treatment Description

3.5.1 Study Treatment Wearing Time

Each dispensed subject will be asked to wear their lenses for a minimum of 10 hours per day for at least 6 days per week. Wearing time should not exceed 15 hours per day. The lenses are to be removed each night (daily wear use only). Subjects must not sleep in their lenses. The lenses should be discarded at the end of each wearing period and a fresh pair inserted the next day.

3.5.2 Study Treatment Packaging and Storage

3.5.2.1 Study Treatment Packaging

The test lenses and the control lenses will be shipped in blister packs containing a buffered saline packaging solution. The label strip is marked with the lens power, base curve, diameter, lot number and expiration date. The lens package or packing slip is marked with the lens power, base curve, diameter, lot number and lens code. In addition, the packaging for all study lenses will indicate that the product is for use in this investigational study only.

3.5.2.2 Study Treatment Storage

Lens materials and solutions provided by the Sponsor for this study should be stored at room temperature, separately from general office supplies and provided only to study subjects. Study lenses must be maintained in an area of restricted access and separated from the normal office lens storage to avoid possible mix-up. Access to all study materials must be limited to the site personnel for study purposes only.

3.6 Study Duration and Schedule of Visits

Subjects who are willing to participate will be examined at a baseline visit. If the subject is eligible, and wishes to continue with the study they will be asked to return for another visit (1-7 days after baseline) for lens insertion and removal training. Study lenses will also be dispensed (test or control, according to randomisation – see separate document) at this visit.

After Baseline and the subject is randomised to study lenses, follow-up visits will be conducted at the intervals shown in Table 2.

Table 2: Visit Schedule

Scheduled Follow up Visits	Acceptable Range
Dispensing and I&R training	1-7 days from Baseline
1-week	7 days ± 2 days from dispensing
1 month	30 days ± 4 days from dispensing
6 months	180 days ± 7 days from dispensing
12 months	360 days ± 14 days from dispensing
18 months	540 days ± 21 days from dispensing
24 months	720 days ± 30 days from dispensing
30 months	900 days ± 37 days from dispensing
36 months	1080 days ± 44 days from dispensing

If, at any of the follow-ups, the subject is unable to wear the study lenses for a minimum of 10 hours a day for at least 6 days a week, they will not be discontinued from the study, but the data from these subjects may be analysed separately.

Visits that fall outside of the acceptable range will be counted as unscheduled visits for analysis purposes.

3.6.1 Missed Visits

If a scheduled study visit is missed, a follow-up form for that visit must be completed with the subject identification and investigator/site information. The follow-up visit that has been missed must be identified and the 'missed visit' box checked on the CRF. The reason for the missed visit should be written in the comments section of the CRF. The remainder of the CRF should have a line drawn diagonally across the page to indicate that no information was collected. The form should be signed by the investigator.

3.7 Study Discontinuation

The clinical study may be discontinued by the sponsor or IRB/IEC at any time if, in the opinion of the sponsor or IRB/IEC, it is in the best interest of the study participants or for any other reason. If the decision is made to discontinue the study, the sites will be notified to call in the study subjects and perform a final study examination, collect all of the study materials and complete study exit forms and documentation.

At any time during the study, an investigator may determine that it is not in the best interest of the subject to continue in the study and discontinue that subject from the study. Subjects may also withdraw from the study at any time of their own volition. Specific criteria and procedures for study discontinuation and withdrawal are found in Section 4.4.

3.8 Study Product Accountability

The applicable study initiation documents (including but not limited to: investigator agreement, Statement of Investigator, IRB/IEC approval, protocol signature document, financial disclosure form, etc.) must be received by the CRO before investigational materials can be shipped to the investigational site. If applicable, approval from the appropriate regulatory

authorities must be obtained before shipping lenses to the investigational site. For example FDA IDE approval is required before lenses can be shipped to the sites.

All study lenses will be sent to the investigational site by the CRO (see page 1). An initial bank of lenses will be sent to the investigational site for initial dispensing and then any additional lenses required will be ordered from the CRO.

All study lenses must be inventoried upon receipt, recorded on the Lens Accountability Form [redacted] by the investigational site and stored in a secure area, segregated from any other materials, and issued only as directed in the protocol. The investigational site must document the dispensing and return (unused lenses only) of each investigational lens for each subject using the Lens Dispensing Forms provided in each subject's study record [redacted]

Study sites will not be required to retain any packaging from used lenses.

Study subjects must discontinue wearing the study lenses at the exit visit and all used lenses must be discarded. All unused lenses must be returned to the study site and recorded on the subject's Lens Dispensing Form.

Study product accountability will be checked by the study monitor (assigned by the sponsor or CRO) during site monitoring. All unused lenses, returned from subjects or never dispensed to the study subjects, must be available to the study monitor for verification of lens accountability at the completion of the study. Any discrepancies in study lens accountability must be explained by the investigator. After the study monitor has verified product accountability, any unused materials will be returned to the CRO or the sponsor at the end of the study unless the investigator is otherwise directed by the CRO or the study sponsor. All product returned to the CRO or sponsor will be documented on the Lens Accountability Form.

3.9 Maintenance/Breaking of Randomisation Codes

Randomisation codes will be maintained by the CRO. The codes will not be broken until the time of data analysis unless it becomes necessary to do so sooner due to an Adverse Event or product problem.

3.10 Recording of Source Data

Unless otherwise stated, the study case report forms (CRFs) will serve as source data documents for this study.

The CRFs will be completed at the time of the visit and then sent to the CRO (listed on page 1 of protocol) within 7 days of the study visit (see Sections 10.4 and 12.1).

Note: If study information is collected using an automated piece of equipment, the information should be recorded directly from the instrument display to the CRF or from an instrument printout if there is no display. The CRF will become the source document if there is no printout. If a printout is obtained from the instrument, the original printout must be placed into the subject's study record as a source document with the subject number and date of recording noted on the printout. The two anonymised copies of the printout that are attached to the CRFs will not be considered source documents (see Section 12.1).

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Subject Recruitment

The eligible study population will include up to 300 myopic children who require bilateral vision correction. Potential subjects will be identified from the investigators' clinic database records and/or will be actively recruited by advertisements, brochures, emails or mailed letters to the parents of children in the target age range who wear glasses.

4.2 Inclusion Criteria

Prior to being considered eligible to participate in this study, each subject MUST:

1. Be between 8 and 12 years of age inclusive at the baseline examination.
2. Have:
   a. read the Informed Assent,
   b. been given an explanation of the Informed Assent,
   c. indicated an understanding of the Informed Assent and
   d. signed the Informed Assent Form.
3. Have their parent or legal guardian:
   a. read the Informed Consent,
   b. been given an explanation of the Informed Consent,
   c. indicated an understanding of the Informed Consent and
   d. signed the Informed Consent Form.
4. Along with their parent or guardian, be capable of comprehending the nature of the study, and be willing and able to adhere to the instructions set forth in this protocol.
5. Along with their parent or guardian, agree to maintain the visit schedule and be able to keep all appointments as specified in the study protocol for the duration of the study (see Visit Schedule, Section 3.5).
6. Agree to accept either the control or test lens as assigned by the randomisation scheme.
7. Agree to wear the assigned contact lenses for a minimum of 10 hours per day, at least 6 days per week, for the duration of the 3 year study and to inform the study investigator if this schedule is interrupted. (Wearing time may be modified by the study staff for health reasons.)
8. Possess wearable and visually functional eyeglasses.
9. Be in good general health, based on his/her and parent's/guardian's knowledge.
10. Have best-corrected visual acuity by manifest refraction of +0.10 logMAR (20/25 Snellen equivalent) or better in each eye.
11. Meet the following refractive criteria determined by cycloplegic autorefraction at baseline:
    a. Spherical Equivalent Refractive Error (SERE): between -0.75 and -4.00 D inclusive.
    b. Astigmatism: $\leq$ -0.75 D
    c. Anisometropia: < 1.00D

4.3 Exclusion Criteria

Subjects may not be considered eligible if **ANY** of the following apply:

1. Subject has previously or currently wears contact lenses or rigid gas permeable contact lenses, including orthokeratology lenses.
2. Subject appears to exhibit poor personal hygiene (that in the investigator's opinion might prevent safe contact lens wear).
3. Subject is currently or within 30 days prior to this study has been an active participant in another clinical study.
4. Parent / guardian or close relative is a member, of the office staff, including the investigator(s).
5. Current or prior use of bifocals, progressive addition lenses, atropine, pirenzepine or ANY other myopia control treatment.
6. Subject was born earlier than 30 weeks or weighed less than 1500g (3.3lb) at birth.
7. Regular use of ocular medications (prescription or over-the-counter), artificial tears, or wetting agents.
8. Current use of systemic medications which may significantly affect contact lens wear, tear film production, pupil size, accommodation or refractive state. Such as, but not limited to: long term use of nasal decongestants (for example, pseudoephedrine, phenylephrine), antihistamines (for example, chlorpheniramine, diphenhydramine), Prednisolone or Ritalin (methylphenidate).
9. A known allergy to fluorescein, benoxinate, proparacaine or tropicamide.
10. A history of corneal hypoesthesia (reduced corneal sensitivity), corneal ulcer, corneal infiltrates, ocular viral or fungal infections or other recurrent ocular infections.
11. Strabismus by cover test at far (4 m) or near (40 cm) wearing distance correction.
12. Known ocular or systemic disease such as, but not limited to: anterior uveitis or iritis, episcleritis or scleritis, glaucoma, Sjogren's syndrome, lupus erythematosus, scleroderma, or diabetes.
13. Any ocular, systemic or neuro-developmental conditions that could influence refractive development. Such as, but not limited to: persistant pupillary membrane, vitreous hemorrhage, cataract, corneal scarring, ptosis eyelid hemangiomas, Marfan's Syndrome, Down's syndrome, Ehler's-Danlos syndrome, Stickler's syndrome, ocular albinism, retinopathy of prematurity.
14. Keratoconus or an irregular cornea.
15. Biomicroscope findings that would contraindicate contact lens wear including, but not limited to:
    a. corneal scars within the visual axis
    b. neovascularisation or ghost vessels $\geq$ 1.5 mm in from the limbus
    c. Any active anterior segment ocular disease that would contraindicate contact lens wear.
    d. giant papillary conjunctivitis of Grade 2 or worse
    e. allergic or seasonal conjunctivitis (if the study investigator believes it could significantly interfere with maintaining the specified contact lens wearing schedule)
    f. clinically significant (Grade 3 or 4) abnormalities of the anterior segment, lids, conjunctiva, sclera or associated structures.
16. The investigator for any reason considers that it is not in the best interest of the subject to participate in the study.

To be eligible to begin the study, a subject must have ALL of the inclusion criteria and NONE of the exclusion criteria present.

4.4 Subject Discontinuation Criteria and Procedures

A subject's study participation may be discontinued at any time if, in the opinion of the subject, the investigator, the IRB/IEC, or the sponsor, it is in the best interest of the subject. A subject may withdraw or be withdrawn from the study at any time of their own volition. Upon discontinuation or withdrawal from the study, subjects must return all unused study lenses to the investigator.

4.4.1 Reasons for Discontinuation

The following is a list of possible reasons for discontinuation or withdrawal from the study. Any associated findings will be fully documented on the Follow-up Form and the Exit Form will be completed. Subjects will be followed until resolution of contact lens related complications. Subjects who discontinue for any reason will not be replaced.

i. Protocol Completion: The subject has completed the protocol specified visit schedule.

ii. Not Dispensed: The subject was not dispensed either the test or control lenses. The reason they are not dispensed may include but are not limited to:

   a. [redacted]

   b. Be unable to demonstrate competent lens handling and understanding of safety precautions of contact lens wear after two dispensing visits.

iii. Adverse Event: The subject has been reported to have an adverse event and was discontinued due to the adverse event.

iv. Objective Ocular Findings: The subject may be permanently discontinued from the study due to positive biomicroscope findings or other objective ocular findings that are not specifically cited as adverse events. Depending on the severity of the condition and on the judgment of the study investigator some conditions would result in temporary discontinuation until resolution. The reason for discontinuation should indicate whether the biomicroscope findings were related or not related to the study lenses.

v. [redacted]

vii. Subject or Parent/Guardian Decision: The subject (or their parent/guardian) may decide to discontinue from the study for whatever reason. The reason must be recorded in the comments section of the exit form.

viii. Protocol Violation: The subject will be discontinued if they are repeatedly found to be in violation of the study protocol.

ix. Instillation of Topical Ocular Medication: Topical ocular medications and/or artificial tears may be prescribed by the investigator for a limited duration (less than four weeks) to treat a transient condition. The subject will discontinue lens wear during this time, but may remain an active subject (at the discretion of the investigator) following the resumption of

lens wear (and discontinuation of the topical medication or artificial tears). If the subject needs to be out of lens wear for more than four weeks, the investigator should contact the CRO who will liaise with the sponsor to decide if this subject can continue in the study after resumption of lens wear.

x. The subject will be discontinued if he or she elects to use a topical ocular medication, artificial tears or wetting agent during the study that the study investigator has not approved (see section 5.4).

xi. Power requirement outside study lens power range: The subject will be discontinued if his or her refraction changes such that their required contact lens power is outside of the power range of the study.

xii. Lost to Follow-Up: The subject cannot be contacted to return for follow-up or exit from the study. For a subject to be classified as "lost to follow-up" there must be attempts to reach the subject by email and phone, followed by postal correspondence requiring a signed return receipt. These attempts will be documented in the subject's study record.

4.4.2 Data to be Collected

A follow-up exam should be completed for each subject on the date of the discontinuation (scheduled or unscheduled follow-up). If the subject is lost to follow-up, the exit form should be completed with the date of the last study examination as the exit date. If the reason for discontinuation is anything other than study completion, an explanation should be provided.

4.4.3 Follow-up Required

Subjects who are discontinued from the study for reasons 4.4.1.iii or 4.4.1.iv above must be followed until the condition has resolved, returned to pre-study status, or warrants no further follow-up before being discontinued from the study.

If resolution has not occurred within 6 weeks after the study end date, the subject will be exited from the study, but must continue to be followed until the condition has resolved, returned to pre-study status or warrants no further follow-up.

5 TREATMENT OF SUBJECTS

The following data will be collected as noted in the Study Visit Plan (Appendix B).

NOTE: All study examinations and evaluations MUST be done using the procedures and scales provided in [redacted] DO NOT use other procedures, scales or equipment without prior authorisation from the sponsor or CRO, even if they are equivalent.

- Case history
- Biological parental non-cycloplegic autorefraction (if one or both parents do not give consent to undergo this procedure or are not present, parental refractive status may be recorded from a recent prescription)
- Lensometry of subject's habitual prescription
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Biomicroscopy and fluorescein assessment
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Complications and adverse events

[redacted]

5.1 Study Visits

5.1.1 Initial Visits

5.1.1.1 Informed Assent/Consent

Prior to being evaluated, the subject and his/her parent/guardian must have the study explained to them; read or have the informed assent and consent documents read to them and indicate understanding of the documents.

The consent and assent documents will be provided to subjects in the official language of the country of each study site. Additional languages may be available if requested by the site and agreed by the sponsor via the CRO. The content of the consent and assent documents may vary slightly from country to country, based on the requirements of the respective IRB/IEC. The investigator must ensure that they use only the consent form which has been approved

by both the sponsor and the IRB/IEC/Health Authority (if appropriate). [redacted]

The investigator or designee will explain the study purpose, procedures, and subject responsibilities to the potential subject and his/her parent/guardian. The subject's willingness and ability to fulfil the study's requirements will be determined.

If the subject agrees to participate in the study, written informed consent will be obtained from the parent or guardian and written informed assent will be obtained from the subject. The assent and consent forms will be signed and dated in the presence of the investigator's staff after opportunity has been given for discussion, questions or concerns by the subject and his or her parent/guardian.

The investigator and the person who explained the informed assent and consent must also sign the documents. The original documents will be retained in the subject's records, and copies will be provided to the parent/guardian.

[redacted]

5.1.1.2 Baseline Exam

Following the signing of the informed consent, the subject will be assigned a chronological subject number from the Subject Number Table [redacted] and will be considered enrolled onto the study at this point. The baseline examination data will be collected and the eligibility criteria reviewed. If the subject meets all of the inclusion criteria and none of the exclusion criteria are present, the subject can continue in the study. If the subject is found to be ineligible, he/she will be discontinued from the study at this time and considered a screen fail. If the subject does not have a pair of sunglasses at the visit, then a pair of disposable mydriatic glasses should be given to them to wear home.

If the subject is eligible, he/she will be randomised into either the test or control lens group for trial lens fitting. The lenses will be identified by a code to maintain masking of the subject and the study investigators.

5.1.2 Dispensing Visit

The dispensing visit will be 1-7 days after the baseline visit. The assigned study lenses will be fitted according to the fitting guide [redacted]

[redacted]

[redacted] The parent/guardian and the subject will be instructed about proper lens insertion and removal techniques, contact lens hygiene and signs and symptoms of contact lens related problems that should be immediately

reported to the study investigator. Each subject and parent/guardian should receive a copy of the study lens patient instructions [redacted]

Study lenses will not be dispensed until the subject is capable of inserting and removing the lenses independently and has demonstrated sufficient understanding of safe contact lens wear. Extra visits will be scheduled if the subject is not successful during the first Dispensing Visit.

If the subject is not successful with insertion/removal, if there are any findings that temporarily contraindicate lens wear, if different lens parameters are required, or the subject temporarily cannot be dispensed for some other reason, a new dispensing visit should be scheduled. New lenses should be ordered, if applicable.

If the lenses cannot be dispensed at the second dispensing visit, the subject must be discontinued from the study at this time. [redacted]

If the subject's condition fits the definition of an Adverse Event, an Adverse Event form must be completed and the subject followed until the event has resolved.

If possible, the subject's follow up visit appointments for the next year should be made at the completion of the Dispensing visit.

5.1.3 Follow-up Visits (at 1-week, 1-, 6-, 12-, 18-, 24-, 30- and 36-months)

The first follow up visit occurs 1 week after the successful completion of the dispensing visit. The remaining follow up visits will occur at 1-month and 6 months after dispensing and then at 6 month intervals from the date of the dispensing visit for up to 3 years. It is important for data analysis that visits fall within the designated visit windows (see Section 3.5).

Outcome data [redacted] axial length) [redacted] will be collected at the 12 monthly follow-up visits. In addition, the adherence to contact lens wear will be assessed at all visits and the need for a prescription change will be evaluated and subject safety will be monitored. At each follow up visit, the investigator will ask the subject and parent/guardian to report any symptoms, problems and complaints that have been experienced since the last visit. [redacted]

Study procedures will be performed as described in the study visit plan [redacted]

[redacted]

At the 36 month visit, the subject and their parent/guardian will complete a Subject Study Completion Form [redacted]

5.1.4 Unscheduled Visits

Each time a subject is examined outside a regularly scheduled study visit, a follow-up visit examination must be completed with the visit identified as Unscheduled by completing an unscheduled visit form. The visit examination must be as complete as possible and the reason for the unscheduled visit must be recorded.

Additional visits, designated as unscheduled problem visits, may take place between regularly scheduled visits to address problems with contact lenses, visual symptoms, ocular health or any safety concerns. Other unscheduled visits, as required to ensure patient health and safety, may occur at the discretion of the study investigator. [redacted]

[redacted]

[redacted]

5.2 Lens Replacements/Parameter Changes

Prescription changes will be made when the difference in subjective refraction between the current and the most recent prescription (in at least one eye) [redacted].

If the appropriate lens powers are not available at the office, investigators should immediately order lenses to minimise the amount of time spent wearing an incorrect prescription. While waiting for the new lenses subjects should continue to wear their current study lenses

If there has been no change to the study lens prescription, the lenses may be posted by registered mail to the subject (i.e. the parcel must be signed for to confirm receipt). [redacted]

All lens parameter changes during the study must be documented on the Lens Dispensing Form [redacted] The investigator must record the reasons for the replacements. When study lenses are replaced, the used lenses must be discarded. Any unused lenses must be returned by the study subject to the investigator and documented.

5.3 Study Completion

Subjects will have completed the study after completing the 36 month visit. When the subject is exited an Exit Form must be completed, with the reason being listed as study completion. The subject and their parent/guardian will complete a Subject Study Completion Form [redacted]

The study will be considered complete when all subjects have either completed the 36 month visit or been discontinued for other reasons. Copies of all remaining completed subject forms must be forwarded to the CRO at this time. The investigator is responsible for accounting for all investigational product received. The study monitor will perform a site visit after the end of the study to check accountability for all investigational products, inventory any remaining investigational product and to make sure that all study materials have been/are returned to the CRO or the sponsor. Completion and retention of case report forms and other study documents not verified at previous monitoring visits will be verified at this time.

5.4 Medications/Treatments Permitted and Not Permitted During the Study

5.4.1 Contact Lens Care

Subjects will be instructed to dispose of their contact lenses every night and insert a new pair of lenses in the morning; therefore contact lens cleaning, soaking and disinfecting products should not be required. If the contact lenses must be removed briefly during the day for swimming or other activities then the subject should throw the lenses away and replace with a new pair afterwards. Therefore subjects should always carry a spare pair of contact lenses and spectacles in case the contact lenses need to be removed for any reason when not at home.

Preservative free rewetting/comfort drops may be used in this study as needed to lubricate and rewet lenses.

While wearing lenses, the use of any other over-the-counter artificial tears is NOT PERMITTED during the study, but after lens removal, is permitted if required.

5.4.2 Ocular Medications

The use of topical ocular medications is contraindicated at all times during this study unless prescribed as part of a treatment for an adverse event. The use of any ocular medications to treat conditions that arise will require temporary suspension of lens wear, an adverse event report, and evaluation of the subject for discontinuation from the study.

For any adverse event where lens wear is suspended, an unscheduled follow-up evaluation of the subject must be performed before allowing the subject to return to lens wear. Subjects may not return to lens wear until all topical ocular medications have been discontinued and a documented exam has verified the resolution of the adverse event.

5.4.3 Concomitant Medications

Changes in concomitant medications from those recorded at the initial visit should be indicated on the follow-up visit forms by checking 'Yes' on the concomitant medication question and recording the change in the comments section.

5.5 Procedures for Monitoring Subject Adherence

To track compliance, subjects will be asked their average contact lens wearing times, average number of days lenses are worn per week and about their contact lens experience at each follow-up visit. [redacted]

6 ASSESSMENT OF EFFECTIVENESS

6.1 Quantification of Effectiveness Parameters

The first primary outcome measure for progression of myopia, is defined as the magnitude of change in the spherical equivalent refractive error relative to baseline. [redacted]

[redacted]

The second primary outcome measure for progression of myopia, is defined as the magnitude of change in axial length relative to baseline, as the progression of myopia has been shown to be associated with increases in axial length[redacted]

[redacted] rom these data it can be confirmed that there were no substantial changes in corneal curvature over the duration of the study and therefore, any differences in refractive error are due to differences in axial length.

6.2 [redacted]

[redacted]

7 ASSESSMENT OF SAFETY

7.1 Safety Parameters

The primary safety measure is the comparison of objective findings, including biomicroscopic findings and adverse events between the test lens and the control lens. The test lens is currently approved for use and is on the market in Europe and therefore no safety issues are expected with this contact lens [redacted] However, the cumulative incidence of objective findings, including biomicroscopic findings and adverse events with the test lens group should be less than or equal to the control lens group, i.e. the test lens group will be statistically non-inferior to the control lens group with an odds ratio less than 1.33 [redacted]

[redacted]

7.2 Recording and Analysis of Safety Parameters

Biomicroscope evaluations will be performed at every visit in accordance with the Study Visit Plan [redacted] Analysis will be done in accordance with the plan presented in Section 8.

7.3 Adverse Event and Device Deficiencies

7.3.1 Adverse Event Descriptions

An adverse event (AE) is any unfavourable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

Serious Adverse Events: Those events that are vision-threatening and result in permanent impairment of a body function or permanent damage to a body structure.

Examples include, but are not limited to:

- Presumed Microbial keratitis (MK)/infectious corneal ulcer
- Permanent decrease of ≥ 2 lines in Snellen best spectacle corrected visual acuity (BSCVA)
- Central or paracentral corneal opacity
- Corneal neovascularisation within the central 6 mm (Grade 4)
- Uveitis
- Endophthalmitis
- Hypopyon
- Hyphema
- Iritis

Significant Adverse Events: Those events that usually are symptomatic but are non-vision-threatening and result in temporary impairment of a body function or temporary damage to a body structure.

Examples include, but are not limited to:

- Peripheral non-infectious ulcer
- Symptomatic corneal infiltrative events
- Superior epithelial arcuate lesions (SEALs)
- Any temporary loss of ≥ 2 lines of BSCVA (for ≥ 2 weeks)
- Corneal staining ≥ Grade 3
- Corneal neovascularisation ≥ Grade 2
- Any event which necessitates temporary lens discontinuation ≥ 2 weeks

Non-Significant Adverse Events: Those conditions that are usually asymptomatic, non-vision-threatening and usually do not result in impairment of a body function or damage to a body structure.

Examples include, but are not limited to:

- Non-Significant Infiltrative Events (< Grade 2 and non-symptomatic)
- Papillary conjunctivitis Grade 2 (only if a change of 2 grades from baseline)
- Blepharitis
- Meibomianitis
- Contact dermatitis
- Localised allergic reactions
- Conjunctivitis: bacterial, viral, allergic
- Any corneal event which necessitates temporary lens discontinuation ≥ 1 day and < 2 weeks (e.g. in the event of mild to moderate corneal staining, lens wear may be discontinued for 24 hours)

7.3.2 Adverse Event Recording and Reporting

Any AE observed by the investigator or reported by the subjects will be documented on the appropriate Follow-Up CRF (which may be at a scheduled visit or an unscheduled visit), Adverse Event forms and Infiltrative Event form ([redacted] One form should be completed per eye, therefore two forms should be completed for a bilateral event. When an AE is initially discovered, page one of the adverse event form should be completed as well as the 'Treatment / Action' section on page 2. Care should be taken to describe the condition accurately. The AE codes [redacted] should be used to indicate the diagnosis. The diagnosis should be separate from the evaluation that the event is or is not related to the device. For example, the diagnosis is a peripheral ulcer or a peripheral infiltrate. The diagnosis should never be CLPU (Contact Lens Peripheral Ulcer) or CLPI (Contact Lens Peripheral Infiltrate).

The classification examples in Section 7.3.1 above should be carefully reviewed to determine AE severity and reporting requirements.

All Serious or Significant AEs must be reported within 24 hours to the Medical Monitor by phone or fax or email [redacted] and to the IRB/IEC within 10 days, via the method specified by the IRB/IEC, unless otherwise specified by the IRB/IEC. If applicable, Serious Adverse Events will be reported to the appropriate regulatory authorities within 10 days unless otherwise specified by the regulatory authority. Serious Adverse event will be reported to the FDA following the IDE reporting procedures.

The report should include copies of the appropriate Follow-Up (scheduled or unscheduled) and Adverse Event Form and any other supporting documentation available at the time. The report should comment on whether or not the AE was considered study lens related.

If the subject experiences an AE in which an ocular infection is suspected, the appropriate ocular structures and lens (if being worn) **must** be cultured. All infiltrates with ≥ Grade 3 staining must be cultured and the Infiltrative Event Form completed. If the lens is not being worn and has been saved and stored in a lens case, the lens and lens case should be cultured. Procedures for culturing are included in [redacted] Culture reports should be retained in the subject's study records.

Copies of any culture reports or records/reports from consulting practitioners (with the subject's name blacked out and subject's ID added to the report) should also be submitted to the CRO and the IRB/IEC as soon as possible to become part of the Adverse Event Record. If possible photos of the event should be taken.

An Adverse Event Review Committee independent of the investigator will conduct an evaluation of any significant or serious AE. The committee will determine the final classification of each of these for the purposes of the final report.

[redacted]

Non-significant AEs should also be recorded on the Adverse Event Form [redacted] and reported to the CRO in a timely manner.

7.3.3 Adverse Event Follow-up and Closure

At each adverse event follow-up, the follow-up section on the adverse event form and a corresponding unscheduled Follow-up Form (scheduled or unscheduled depending on the

visit type) must be completed. The minimum procedures to be completed at an unscheduled visit are shown in the unscheduled column of the Study Visit Plan table [redacted]

The subject must be followed until the condition has resolved, returned to pre-study status, or warrants no further follow-up. At that time, the outcome section of the Adverse Event form with a corresponding Follow-up Form (scheduled or unscheduled depending on the visit type) must be completed. Subjects required to discontinue lens wear may not return to lens wear until all ocular medications have been discontinued and a follow up visit, slit lamp and final Adverse Event form have been completed. The investigator should use his/her best judgment as to whether the subject should continue with study lens wear following an AE. If the subject needs to be out of lens wear for more than four weeks, the investigator should contact the CRO who will liaise with the sponsor to decide if this subject can continue in the study after resumption of lens wear. If the subject is exited, an Exit form must be completed.

As follow-up information for serious and significant AEs becomes available, this information should be forwarded to the CRO and the IRB/IEC. A complete set of documentation including all Case Report Forms and external reports should be submitted to the IRB/IEC at the time of resolution.

If resolution has not occurred within 6 weeks after the study end date, the subject will be exited from the study, but must continue to be followed until the condition has resolved, returned to pre-study status or warrants no further follow-up.

All adverse events will be listed and analysed in the final clinical report.

7.3.4 Device Deficiencies

For the purpose of this protocol device deficiencies are defined as any inadequacy of the contact lenses with respect to its identity, quality, durability, reliability, safety, or performance.

All device deficiencies should be documented on the CRFs. The investigator should assess and document on the CRF whether the device deficiency would have led to a serious adverse event if:

a) Suitable action had not been taken

b) Intervention had not been made, or

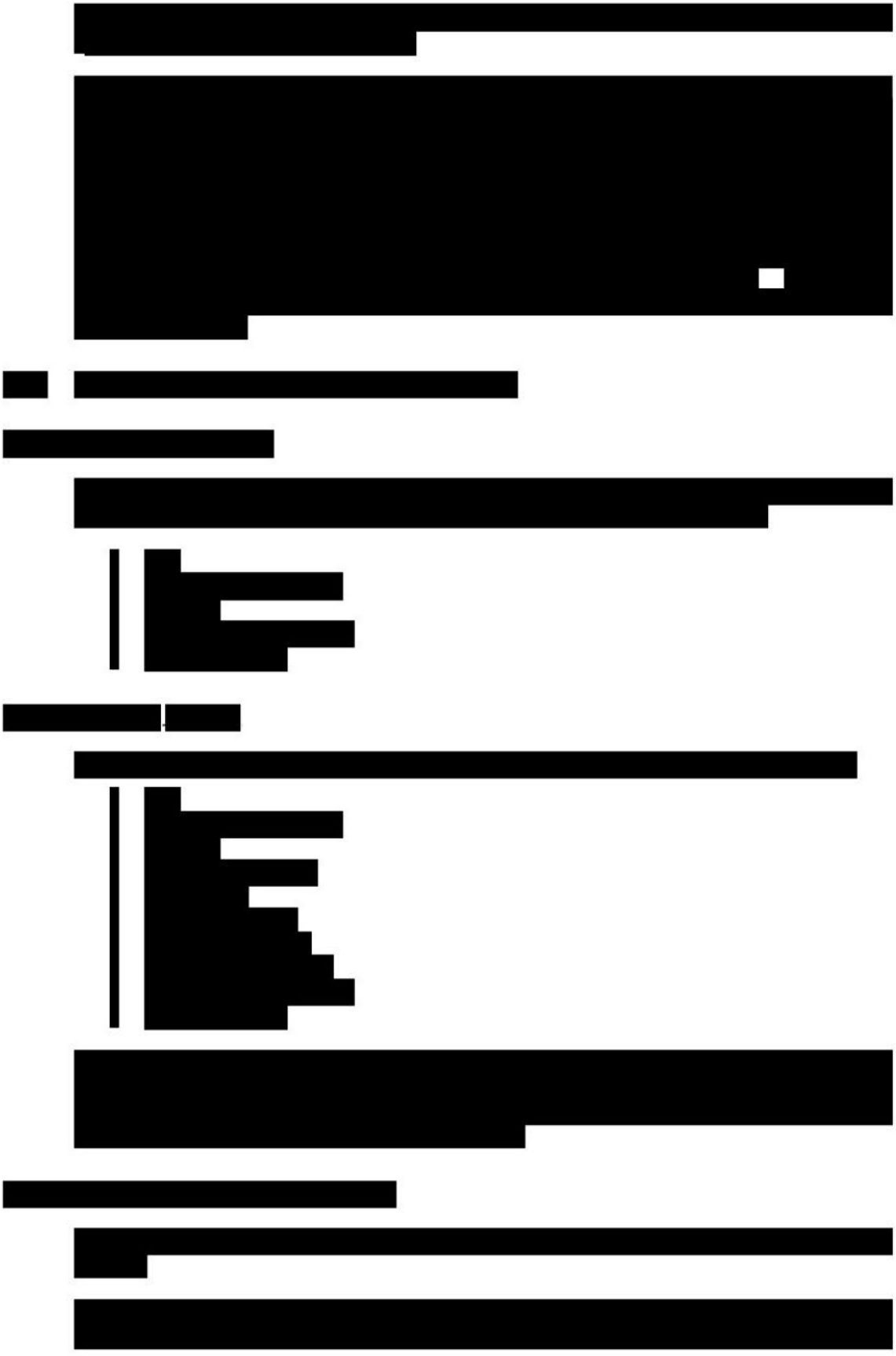
c) Circumstances had been less fortunate.

The CRO is responsible to immediately notify Sponsor of these events for reporting review. The CRO will notify the sites if the IRB/IEC needs to be notified

[redacted]

[redacted]

beneficial, but one or more sites show the treatment to be detrimental, then the variance will



[redacted]

9 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

9.1 Monitoring

Investigational site monitoring will be performed by a qualified study monitor identified by the Sponsor or the CRO. On-site visits will be completed at each site at least once a year. It is expected however, that there will be more than one visit in the first year. The frequency and procedure of the monitoring visits will be documented in the monitoring plan which is in a separate document. The investigator will allow the study monitor and sponsor representatives or IRB/IEC to observe procedures and inspect study records and subjects' medical records throughout the study to verify protocol compliance, case report completeness and investigational material accountability. Should the investigator be found to be non-compliant and unwilling or unable to convert noncompliant practices, the CRO in consultation with the Sponsor will terminate that investigator's role in the investigation and the IRB/IEC will be notified.

9.2 Audits

The Investigator shall permit the CRO, the Sponsor, the IRB/IEC and the appropriate regulatory authorities to inspect its facilities, equipment, and study-related records, data and other documents upon reasonable notice. In addition, the regulatory authorities or the IRB/IEC may conduct such inspections as they deem necessary at any time whether or not advanced notice is given by them. The Investigator agrees to notify the Sponsor or CRO within 24 hours (or as soon as reasonably practicable) of the start of any unannounced inspection by the IRB/IEC or the regulatory authorities or of the receipt from the IRB/IEC or the regulatory authorities of a notice of inspection whether given in writing or orally. If such notice is in writing, a copy with any attachments thereto shall be provided to the CRO or the Sponsor.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Standard Operating Procedures

The sponsor and CRO will manage the trial according to applicable written Standard Operating Procedures (SOPs) to ensure that the trial is conducted and data are generated, documented (recorded) and reported in compliance with the protocol, GCP and applicable regulatory requirements.

10.2 Agreements

Agreements made by the sponsor or CRO with the investigational sites or other parties involved in the clinical trial will be in writing, as part of the protocol or in separate agreements or documents.

10.3 Monitoring

10.3.1 Site Qualification Visit

Qualified personnel or consultants of the sponsor (including the study monitor) will meet with investigators prior to the initiation of the study in order to review the adequacy of the potential subject population, facilities, and equipment with respect to the needs of the study and to familiarise the investigator with the study protocol. Further details about the procedure of this visit can be found in the monitoring plan which is in a separate document.

10.3.2 Site Initiation Visit

Qualified personnel or consultants of the sponsor (including the study monitor) will monitor the site before the initiation of subject enrolment to ensure all investigators and study staff are fully trained in ICH GCP guidelines and the protocol. Further details about the procedure of this visit can be found in the monitoring plan which is in a separate document.

10.3.3 Interim Monitoring Visits and Consultation

Interim monitoring visits and telephone, fax, mail and email consultation will be performed during the course of the study to ensure the proper progress and documentation of the study findings. The schedule of monitoring visits will be based on the rate of enrolment and number of subjects enrolled at each site and shall ensure that the site is complying with ICH GCP, that subjects are being properly selected and that study data are being correctly recorded.

Further details about the procedure of this visit can be found in the monitoring plan which is in a separate document.

10.3.4 Close-out Monitoring Visit

Qualified personnel or consultants of the sponsor (including the study monitor) will visit the clinical site for formal close-out when all subjects have completed the final visit of the study to collect any outstanding forms and to ensure accountability of contact lenses and all study supplies. An Investigator Study Completion Form will be completed by the investigator (see the CRFs held in a separate document). Further details about the procedure of this visit can be found in the monitoring plan which is in a separate document.

10.4 Data Collection and Entry

All of the data collection protocols will be standardised through study documentation, uniform study forms and uniform criteria for subject recruitment, including independent confirmation of eligibility by the CRO. Study personnel will be trained before collecting study data.

The CRFs will be completed at the time of the visit. [redacted]. All forms will be reviewed for completeness and evident recording errors will be rectified by contacting the appropriate clinical site. Double-entry routines will be utilised to reduce data entry errors, and computerised editing routines will be used to identify missing, invalid, inconsistent, or questionable data entries for verification prior to data analysis. These data issues will be resolved by contacting the relevant clinical site. All data files will be backed up routinely, with weekly backups stored at an alternative location.

11 ETHICAL CONSIDERATIONS

11.1 IRB/IEC/Health Authority Approval

Approval of the study protocol and informed consent document must be obtained from an appropriate legally constituted IRB/IEC and appropriate Health Authority* (if required, for example FDA IDE approval) before investigational materials can be shipped and the study initiated. Renewal of this approval must be obtained as required by the IRB/IEC/Health Authority (such as the FDA IDE approval), but at least on an annual basis. The IRB/IEC/Health Authority must be informed of all serious and significant AEs within the time frame specified in the IRB/IEC/Health Authority approval letter and must approve modifications to the Protocol, the Informed Consent Form, or the Case Report Forms (if required). In addition, advertisements for subject recruitment must be approved by the IRB/IEC/Health Authority (if required) and Sponsor prior to dissemination or use. A final report of the investigator's study results must be submitted to the IRB/IEC/Health Authority on completion of the study along with other reports as required in the study design and by the IRB/IEC/Health Authority.

11.2 Informed Consent and Assent

A legally constituted assent document must be explained to, read, understood and signed by each study subject prior to the subject being enrolled in the study. A legally constituted consent document must be explained to, read, understood and signed by a parent or legal guardian of the subject prior to the subject being enrolled in the study. The individual explaining the Informed Assent and Consent must have full knowledge of the protocol and

have been authorised by the investigator and must also sign the documents. The investigator will also sign the consent form and depending on the local regulatory considerations, other signatures may be required. One copy of each document will be provided to each subject's parent/guardian and the original will be retained by the investigator in the subject's file and the subject will be considered enrolled onto the study at this point. No subjects can be exposed to the study materials prior to the proper execution of the Informed Assent and Consent Forms.

12 DATA HANDLING AND RECORDKEEPING

12.1 Case Report Form Completion/Correction

Ballpoint pen with permanent black or blue ink must always be used when recording data on Case Report Forms and other study-related documents (pencil and felt-tip pen may NOT be used). Writing on Case Report Forms should be done firmly and legibly to ensure that carbonless copies can easily be read. Site personnel must review all CRF copies (white originals and "non carbon" copies) prior to submission to ensure that information is complete and legible and that any changes have been properly made. To correct any errors, cross through once and initial and date the correction in the margin. DO NOT ERASE OR USE WHITE OUT OR ANY OTHER CORRECTION FLUIDS. If necessary explain the reason for the change. There must be no stray marks or "write-throughs" on the yellow CRF copies that obscure or confuse the data, which will be the study record at the site. The original forms must be legible and complete prior to submission to the CRO.

Note: if study information is collected using an automated piece of equipment, the information should be recorded directly from the instrument display to the CRF or from an instrument printout if there is no display. The CRF will become the source document if there is no printout. If a printout is obtained from the instrument, the original printout should be placed into the subject's study record and the printout becomes the source document for that piece of information. Two copies of the printout should be made with the subject name or any identifying information removed. One copy should be attached to the CRF that is sent to the CRO and the other is attached to the site copy of the CRFs.

Corrections or changes to information on any study documents, CRFs, source documents, Lens accountability forms, Lens dispensing forms etc. must conform to the following procedure: strike through the item to be corrected with a single line (the item should still be readable), write the corrected information as close to the original information as possible and initial and date the change. If necessary explain the reason for the change.

CRFs should be submitted to the CRO according to the instructions [redacted] The white originals of all completed case report forms (except Informed Consent) will eventually be submitted to the CRO. Yellow "carbon" copies will be retained at the site. Informed Consent and Assent form originals should stay at the site, and copies should be given to subjects.

If a scheduled visit is missed, the appropriate Case Report Form must be completed with the subject ID, and investigator initials and site. The follow-up visit that has been missed must be identified and the "missed visit" box checked on the CRF. If information is available, note the reason for missing the visit in the Comments section. The remainder of the CRF should have a line drawn diagonally across the page to indicate that no information was collected. The form should be signed by the investigator. As close to the visit window as possible, an Unscheduled Visit should be completed and sufficient lenses dispensed till the next follow-up visit [redacted]

12.2 Archiving and Record Retention

All study records as listed below will be maintained by the Investigator for a minimum period of two years following notification by the sponsor or designee that the device has been approved for marketing or that the study has been withdrawn from the approval process. If the study lenses have been cleared for distribution in the region of the study site, then the Investigator should keep the study records until notified by the sponsor. Note: if state, local or international laws or regulations require a longer retention period, the records should be retained for the appropriate additional time. The investigator will not destroy any study documents without first gaining permission from either the CRO or the sponsor.

- A copy of the signed Statement of Investigator
- A copy of the approved Protocol and Protocol Signature document
- A copy of the approved Informed Consent Form and Assent Form used for this study.
- Copies of the signed Informed Consent Forms and Assent Forms for each subject enrolled in the study
- Copies of all completed Case Report Forms for each subject enrolled into the study
- Copies of all records relating to AEs, including but not limited to: Case Report Forms, culture reports, records and reports from outside practitioners, healthcare facilities and laboratories.
- Source documents, which are defined as all records containing original study subject information, examination results, etc.
- All records of investigational product accountability (shipping, receipt, dispensing and return forms)
- A copy of IRB/IEC approval and all correspondence
- All correspondence records (written, electronic and oral) related to this study
- The Statement of Financial Disclosure for the Investigator and all Co-Investigators

Sites that use the CRFs and source documents as patient records must retain copies of the visit information for the time that is appropriate for their individual state requirements.

13 PUBLICATION POLICY AND CONFIDENTIALITY

13.1 Publication

The trial results will be reported on the NIH website, www.ClinicalTrials.gov. In addition, it is the intention of the sponsors to publish the findings of the study in a refereed scientific journal.

13.2 Confidentiality

This study is confidential in nature. The Investigator shall make no public statement, whether in written, oral or electronic form, relating to the CRO, the Sponsor, the substances, materials, products and devices being investigated or the Study itself without obtaining the prior written consent of the CRO and the Sponsor.

All information gathered during this study is proprietary and should be made available only to those directly involved in the study who have a need to know.

Authorised recipients of this data include:

- Investigator and co-investigator(s)
- Other allied health care personnel necessary for the conduct of the study
- IRB/IEC personnel
- Sponsor representatives
- Contract Research Organisation
- Designated study monitor
- Designated medical monitor
- FDA or other government regulatory agencies

All above personnel who are provided with data concerning this study will be informed of its confidential and proprietary nature. Release of this data (through presentation, publication or other written or oral communication) to other than the above listed personnel requires the prior written permission from the study Sponsor. Study investigators and all office personnel are prohibited from acknowledging participation in the study to individuals and organisations except those listed above. This includes sales representatives and other departments or subsidiaries of the sponsor without the direct written permission of the sponsor.

14 INVESTIGATOR RESPONSIBILITIES

- Regulatory Authority approval: The investigator is responsible for ensuring compliance to the appropriate regulatory procedures for their country and the applicable FDA IDE requirements (21CFR 812.100 and 812.110)
- IRB/IEC Approval: the investigator is responsible for the following:
  - Approval for the study and all sub-investigators (the CRO will assist with the initial submission).
  - Annual renewal of the study approval.
  - Reporting to the CRO within 5 working days if the IRB/IEC withdraws approval for the investigator's part of the study.
- Informed Assent and Consent: must be appropriately obtained and documented for each study subject.
- Compliance: the approved study Protocol (and any amendments, if applicable) and instructions from the CRO or the Sponsor must be followed. The Investigator is responsible to ensure compliance with all applicable federal, national, state and local laws and regulations and guidelines applicable to clinical investigators and to the use of investigational devices in humans.
- Reporting of Protocol Deviations: the investigator should not make changes to the Study without prior written approval of the CRO, the IRB/IEC and the Sponsor unless necessary to eliminate an apparent immediate hazard to subjects in the study. Protocol deviations should be reported within 24 hours of the occurrence to the CRO and the Sponsor and within 5 working days to the IRB/IEC.
- Adverse Event Reporting: The investigator is responsible for reporting all serious and significant AEs to the medical monitor within 24 hours and to the IRB/IEC within 10 days of discovery (unless otherwise specified by the IRB/IEC). Non-significant AEs should be reported to the CRO within the normal timeframes for CRF submission.
- Study Lens Control & Documentation: Investigational lenses must be kept in an area of limited access and may only be used for study subjects in accordance with the study protocol and other procedures. Receipt, dispensing, and return must be documented.
- Proper Record-keeping: CRFs and other study documents must be completed, corrected (if needed) and maintained according to the study protocol and other study procedures and instructions.

- Inspections: cooperation with the Sponsor, CRO, monitors, IRB/IEC and the appropriate regulatory authorities for inspection of the study site.
- Study Reports
  - Interim study reports must be provided to the IRB/IEC at a frequency required by the individual IRB/IEC, but not less than annually.
  - A final report must be provided to the Sponsor/CRO and the IRB/IEC upon completion of the study.
  - Any other reports as required by the Sponsor, IRB/IEC and the appropriate regulatory authorities.

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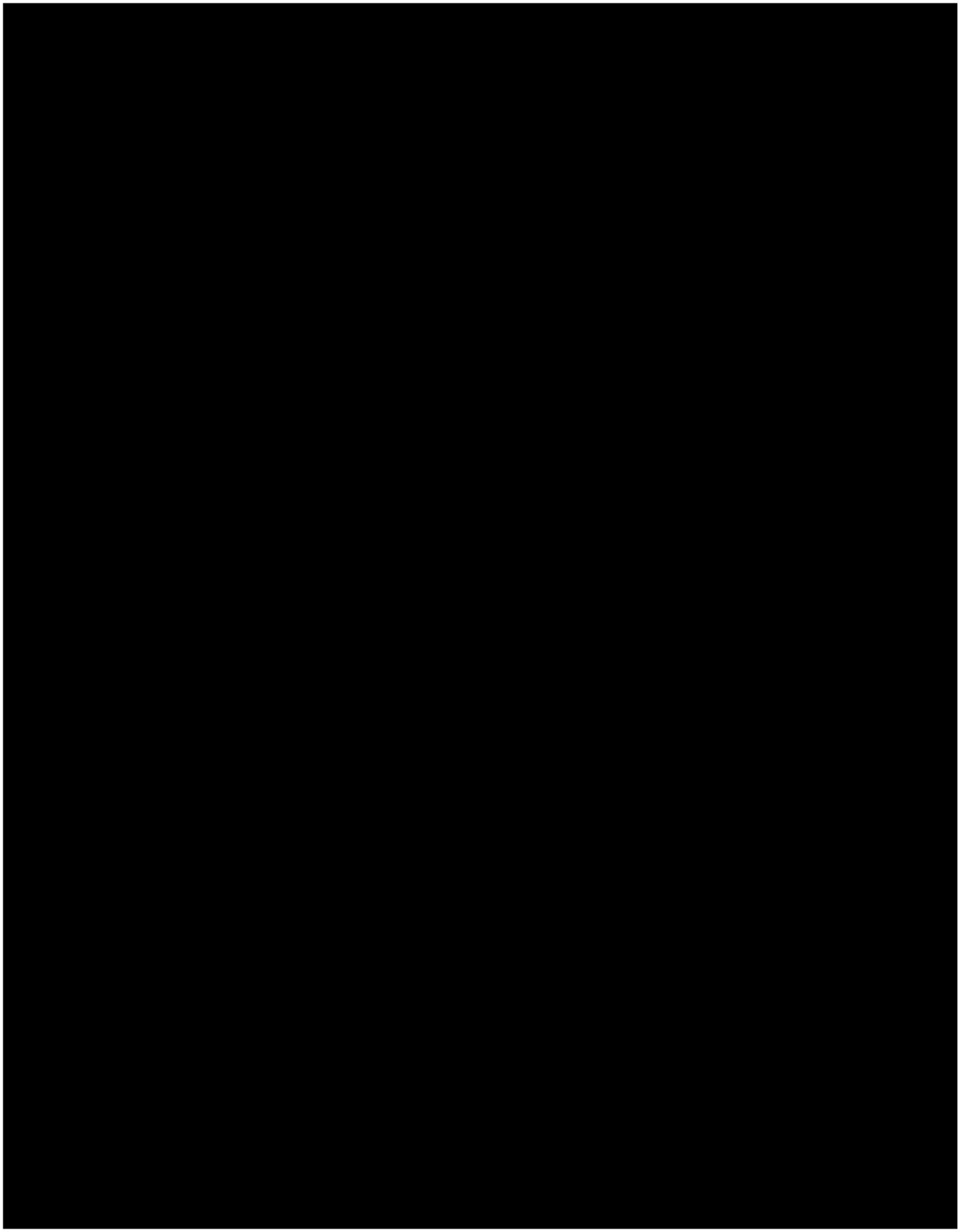

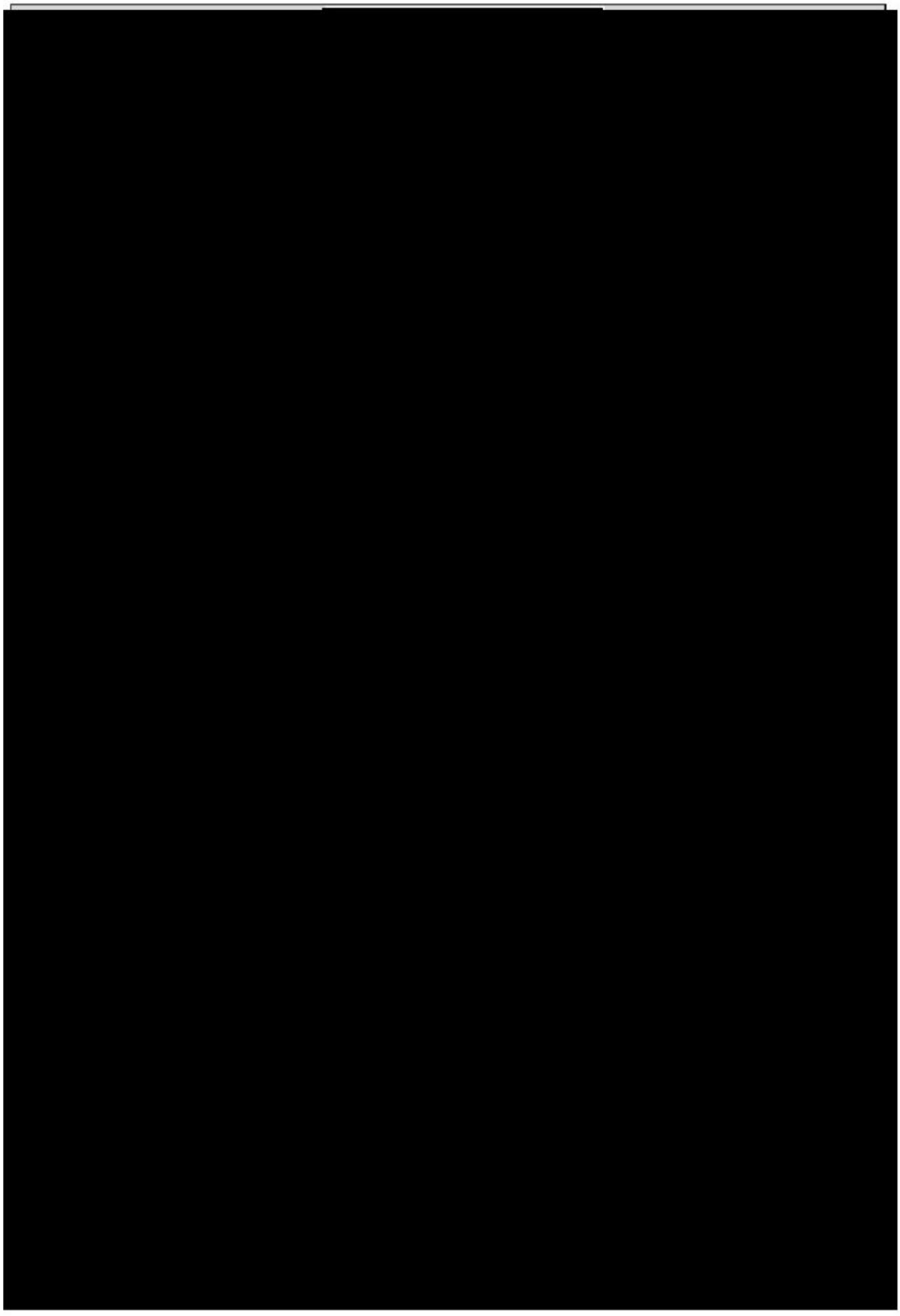

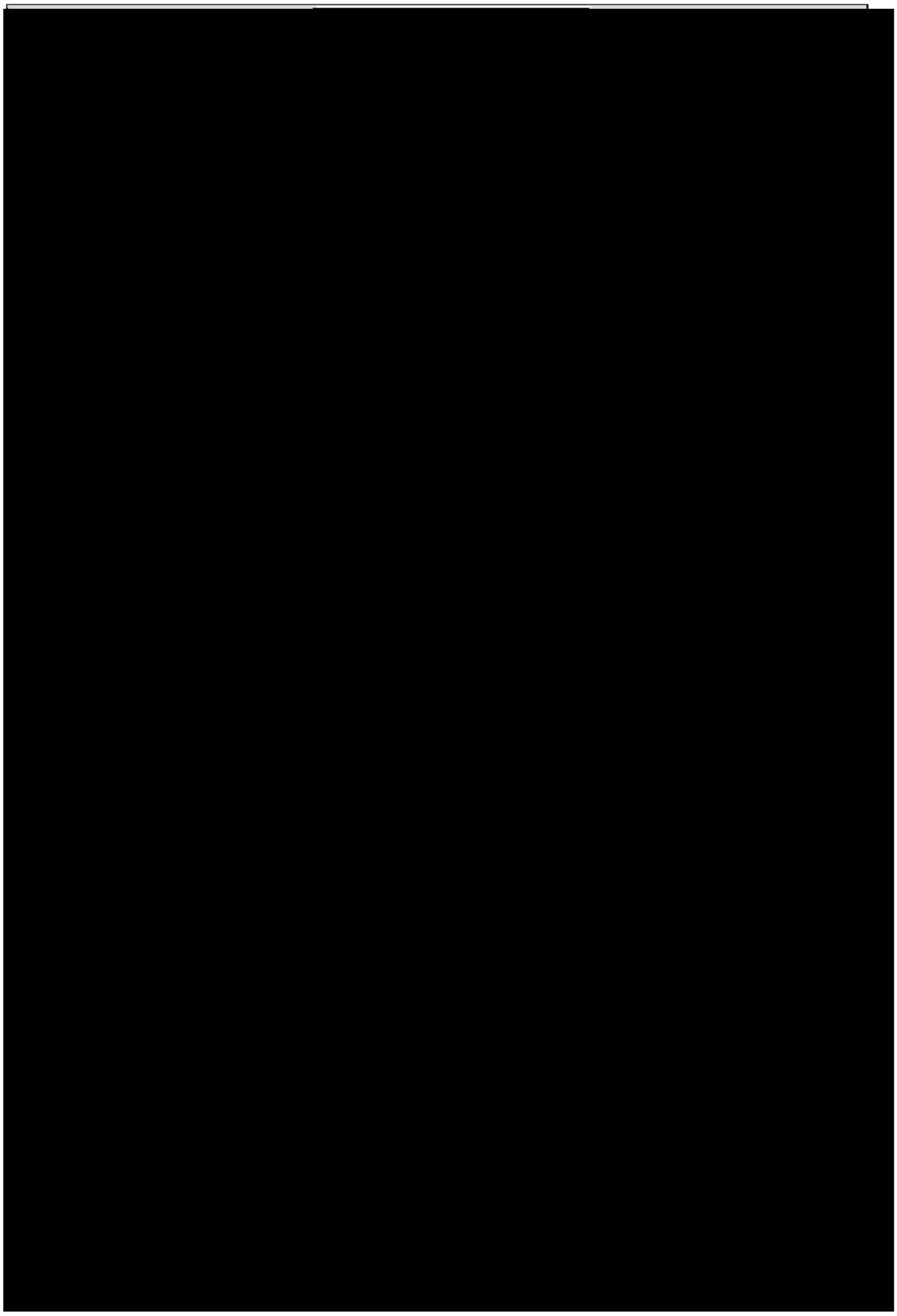

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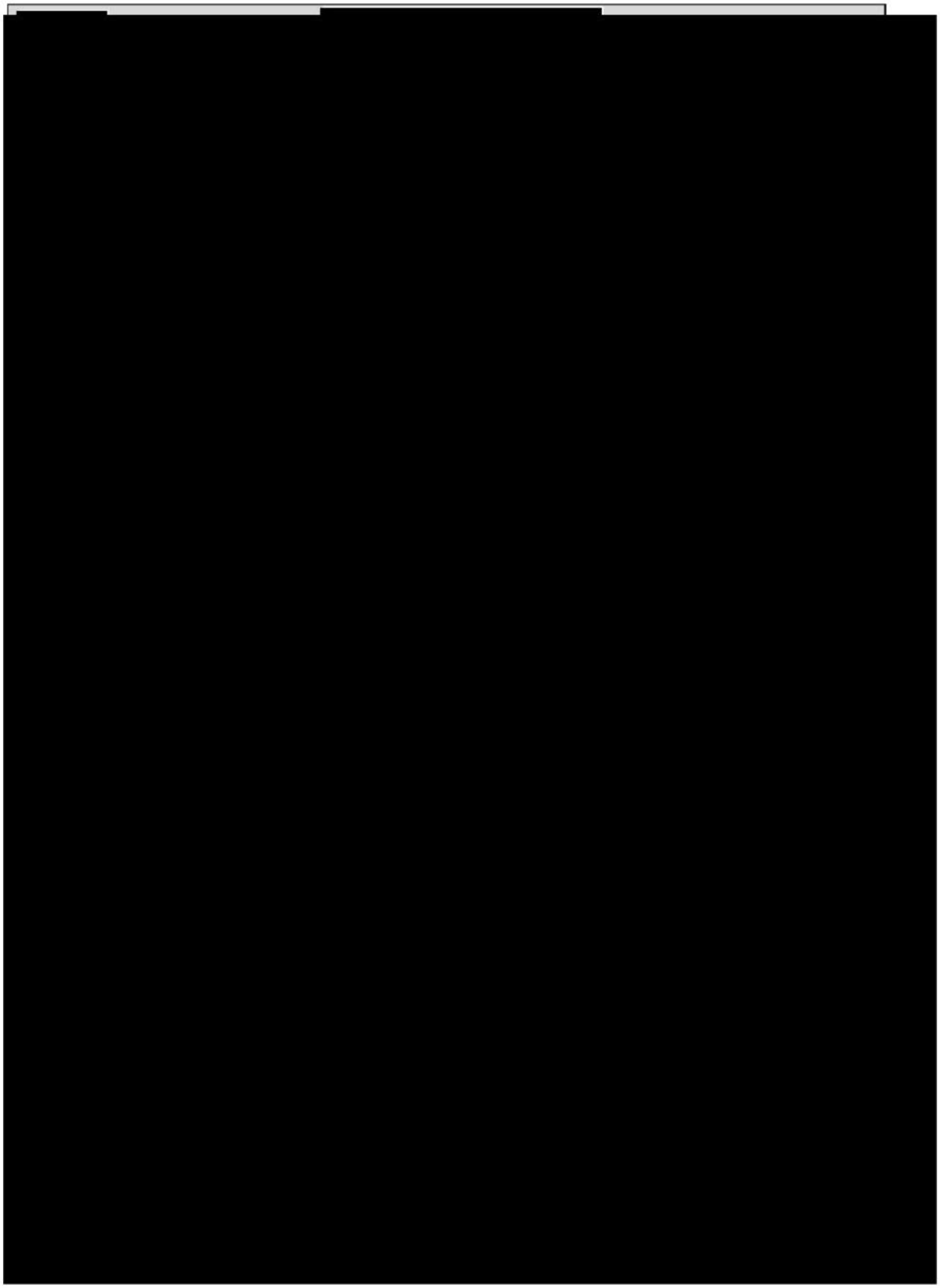

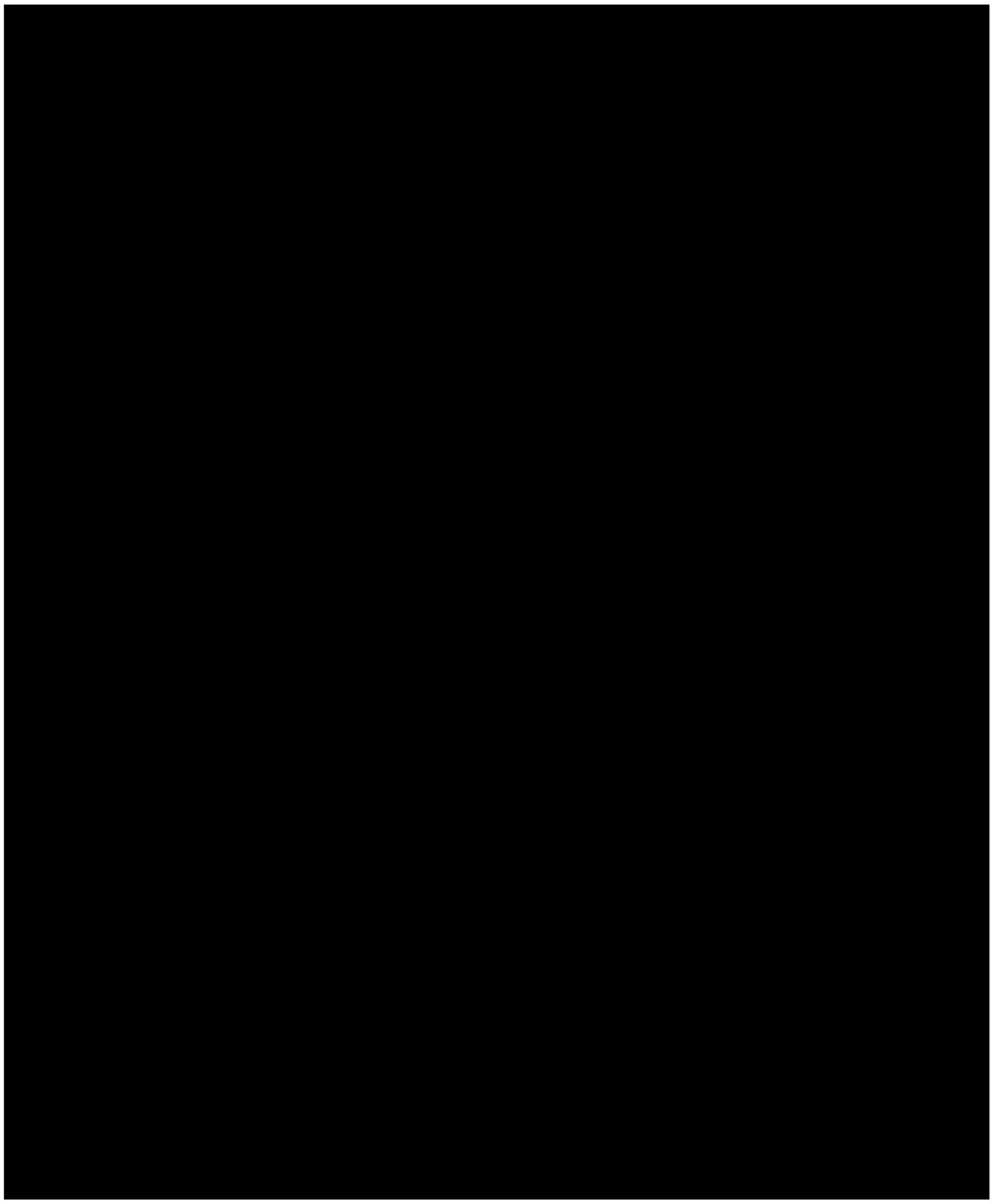

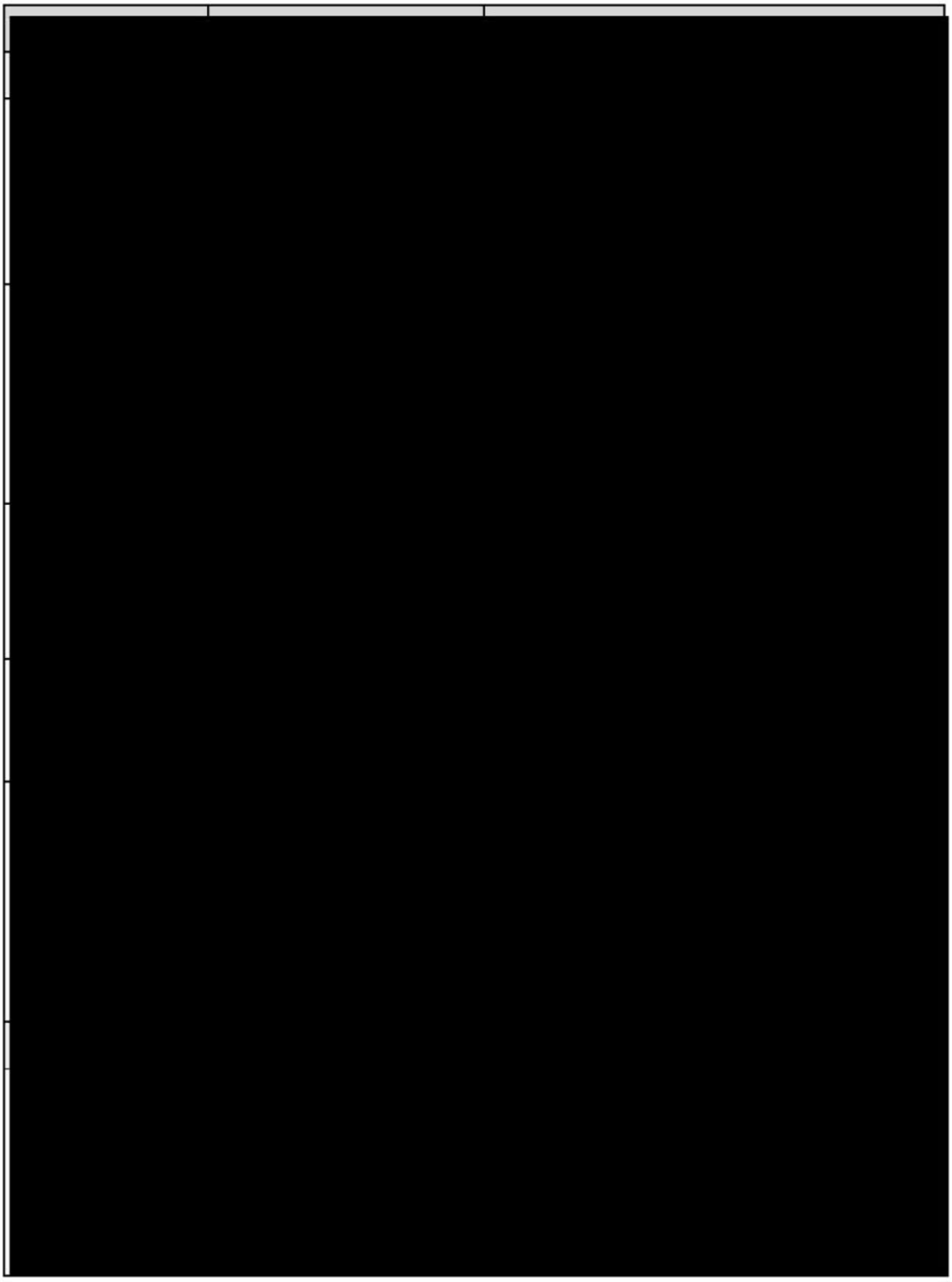

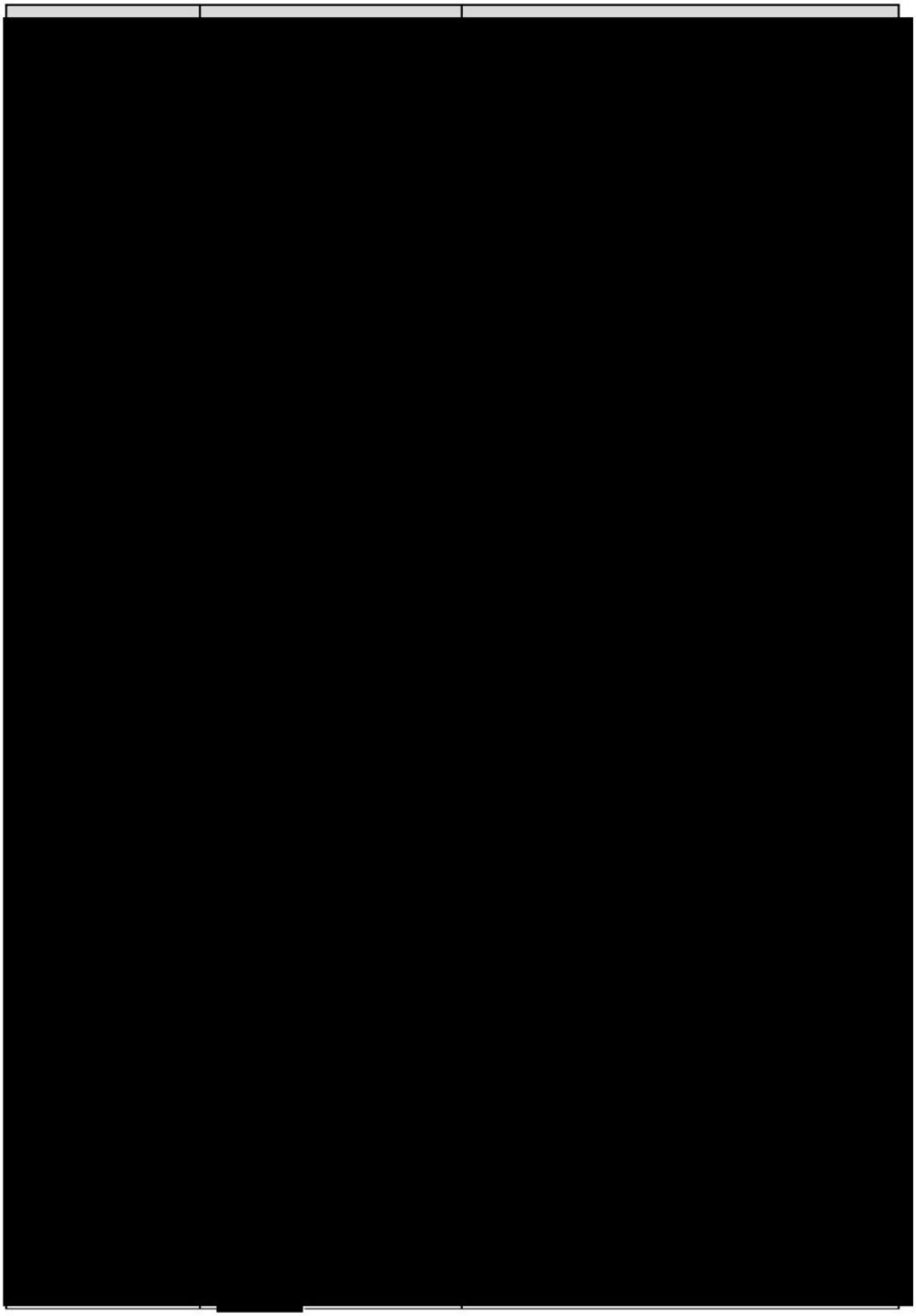

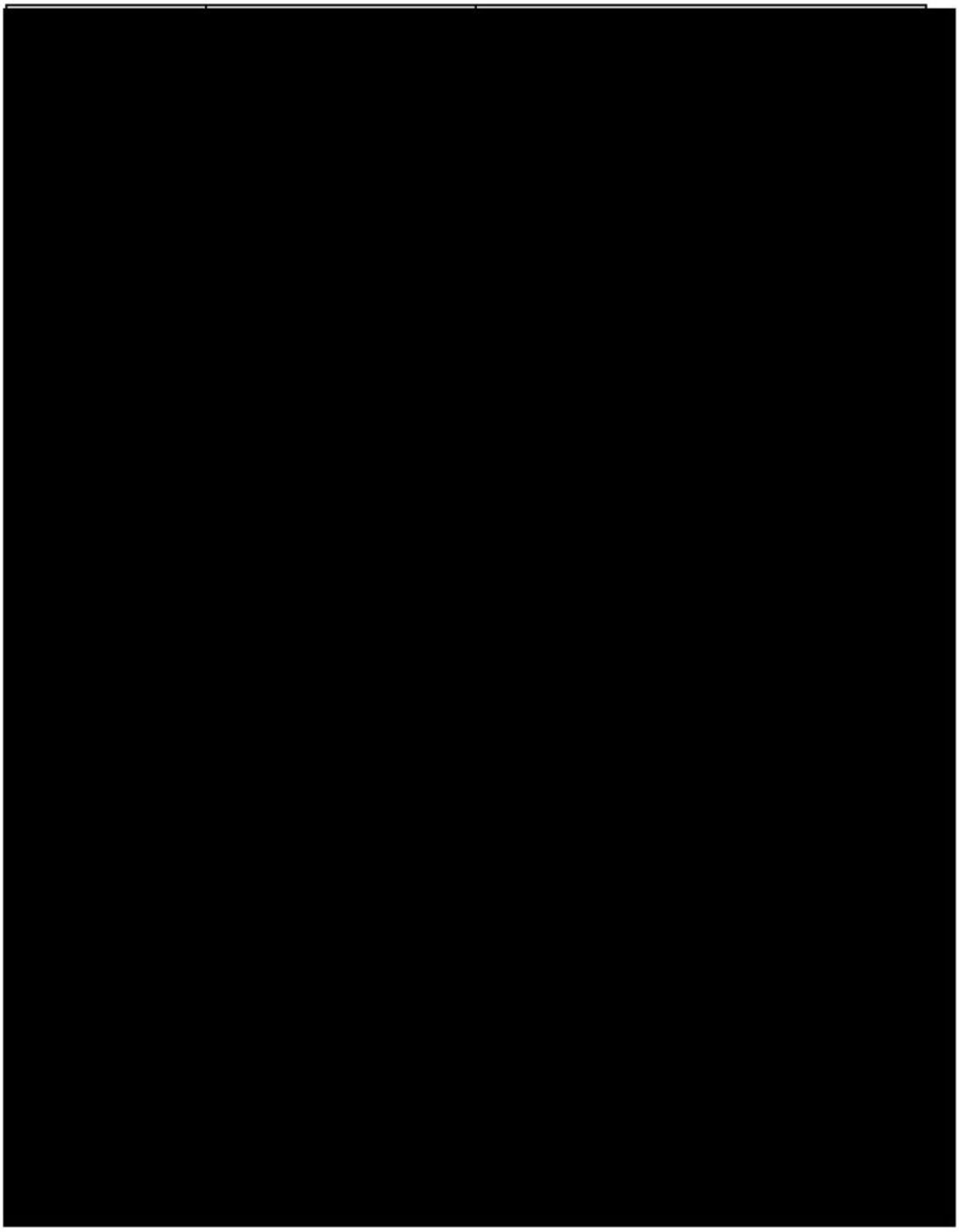

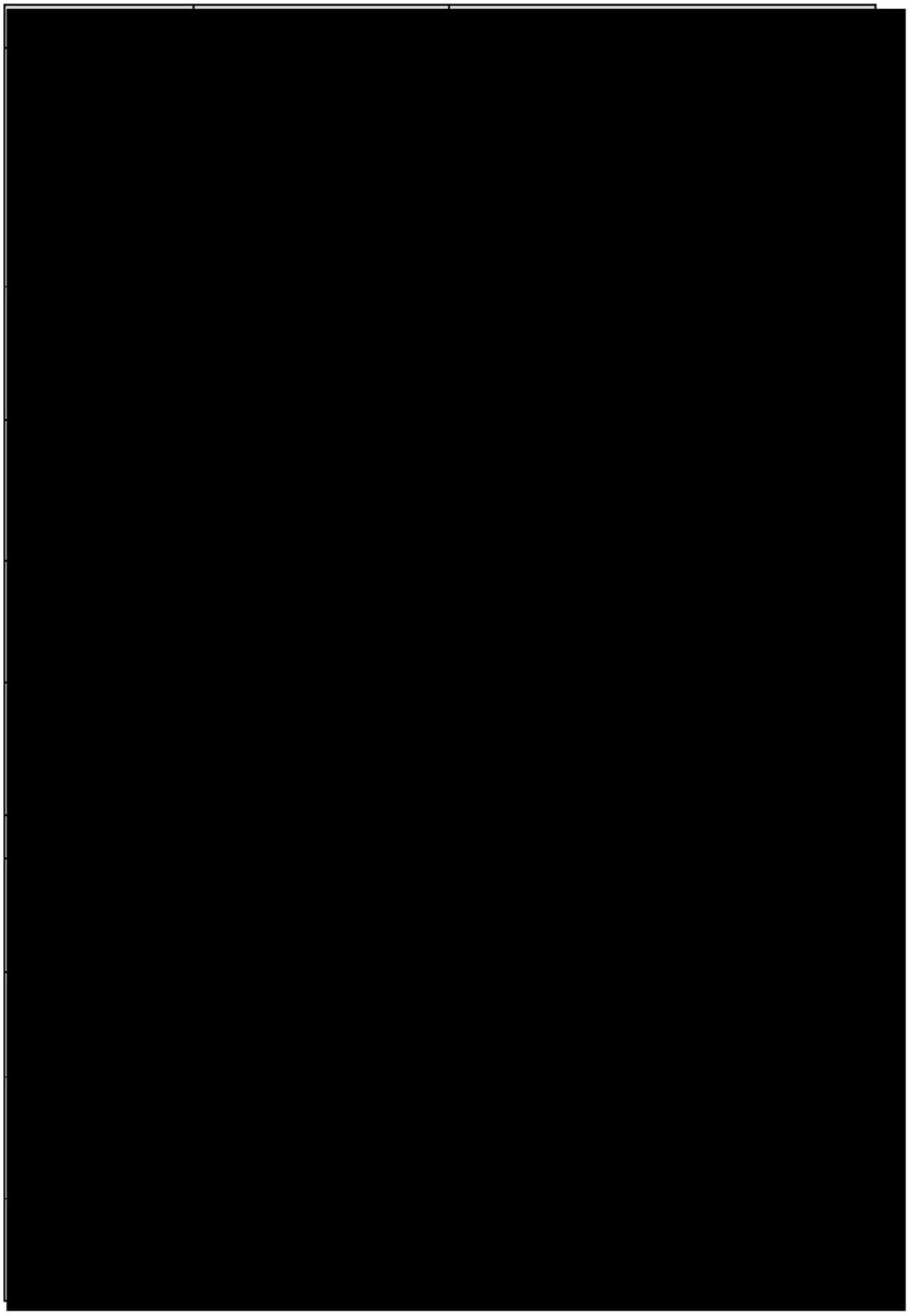

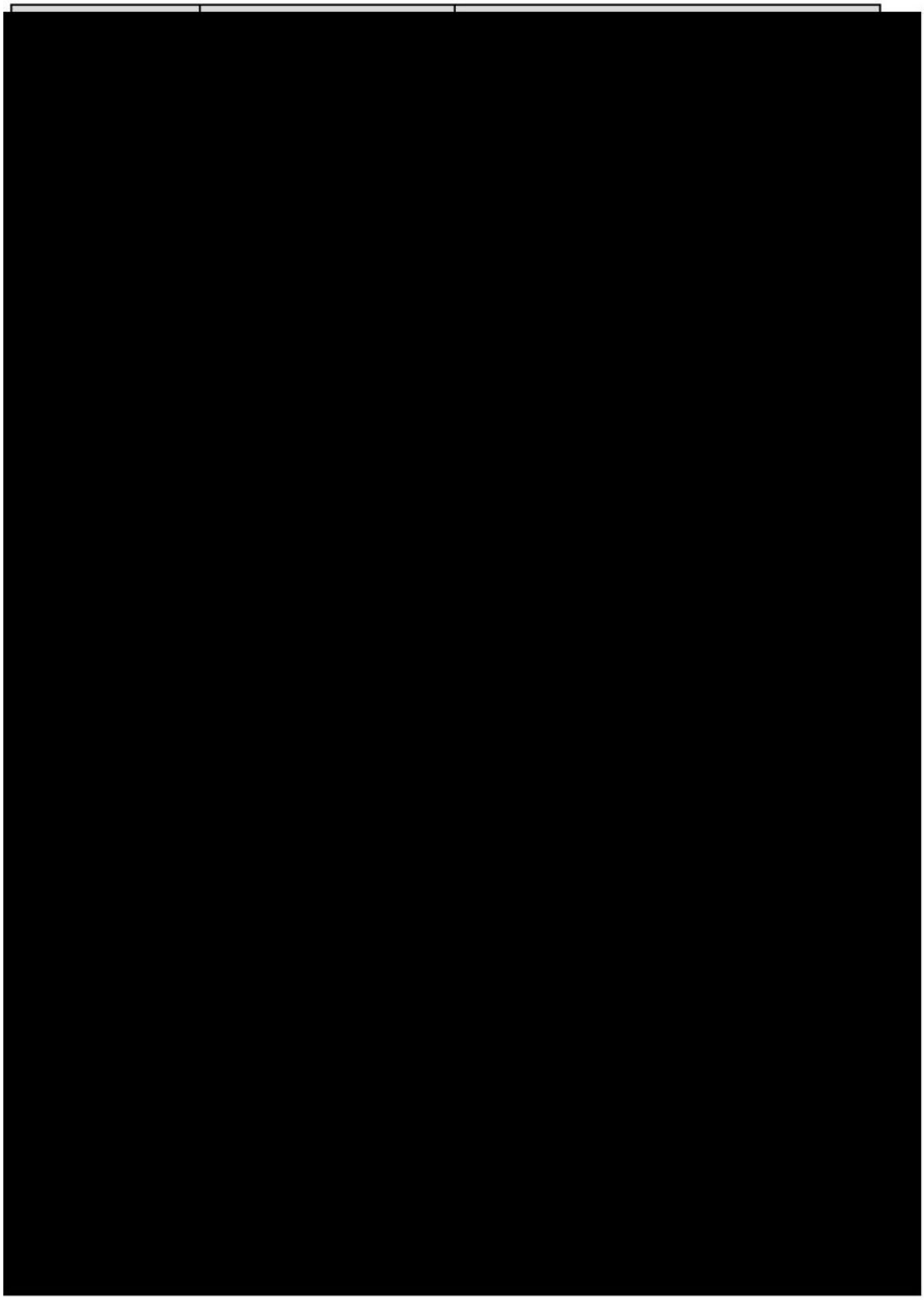

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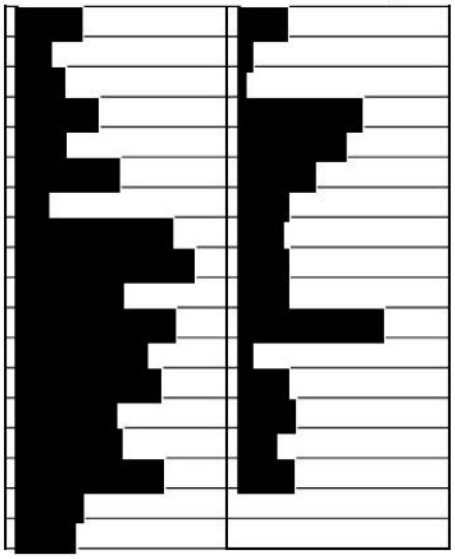

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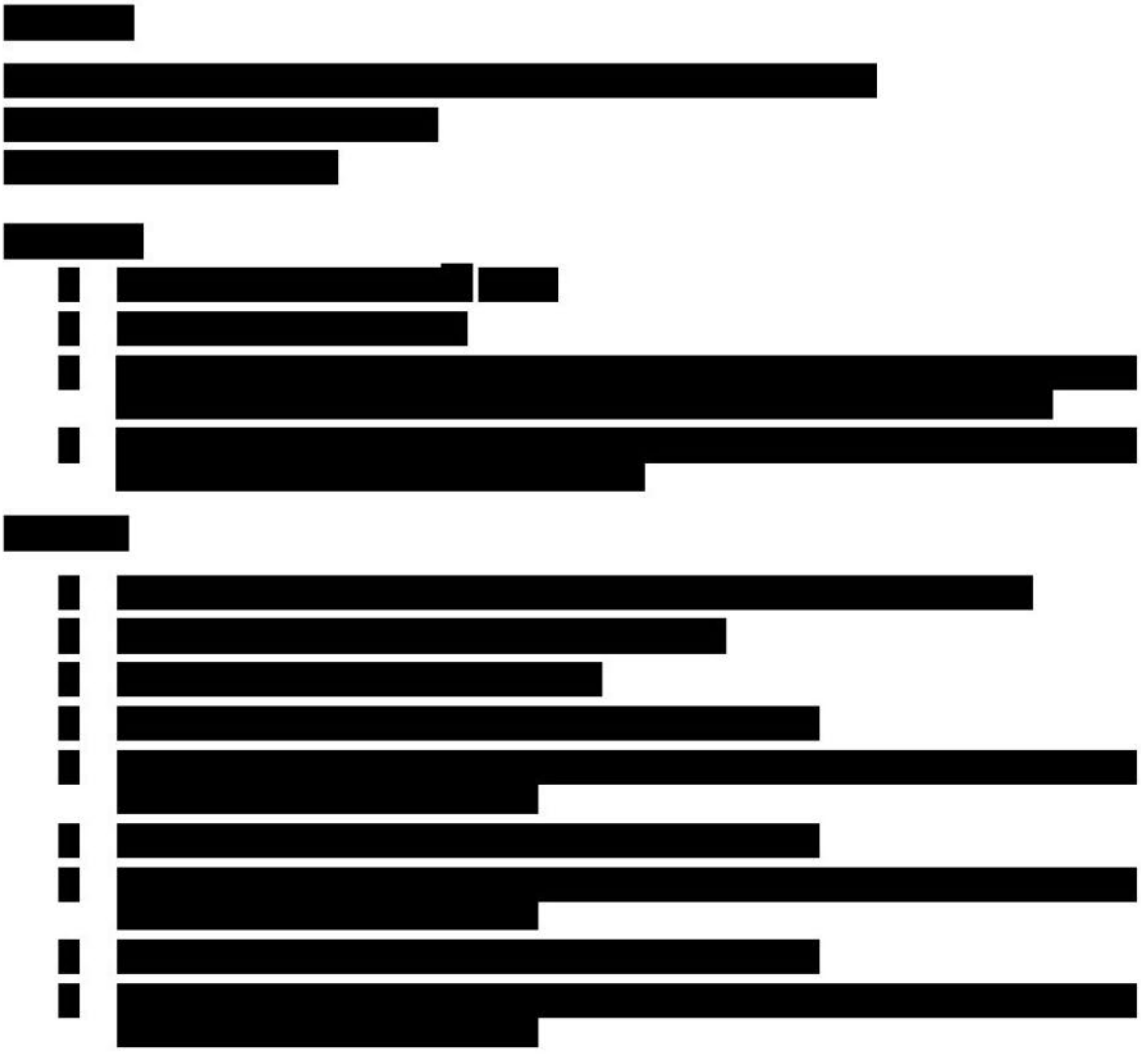

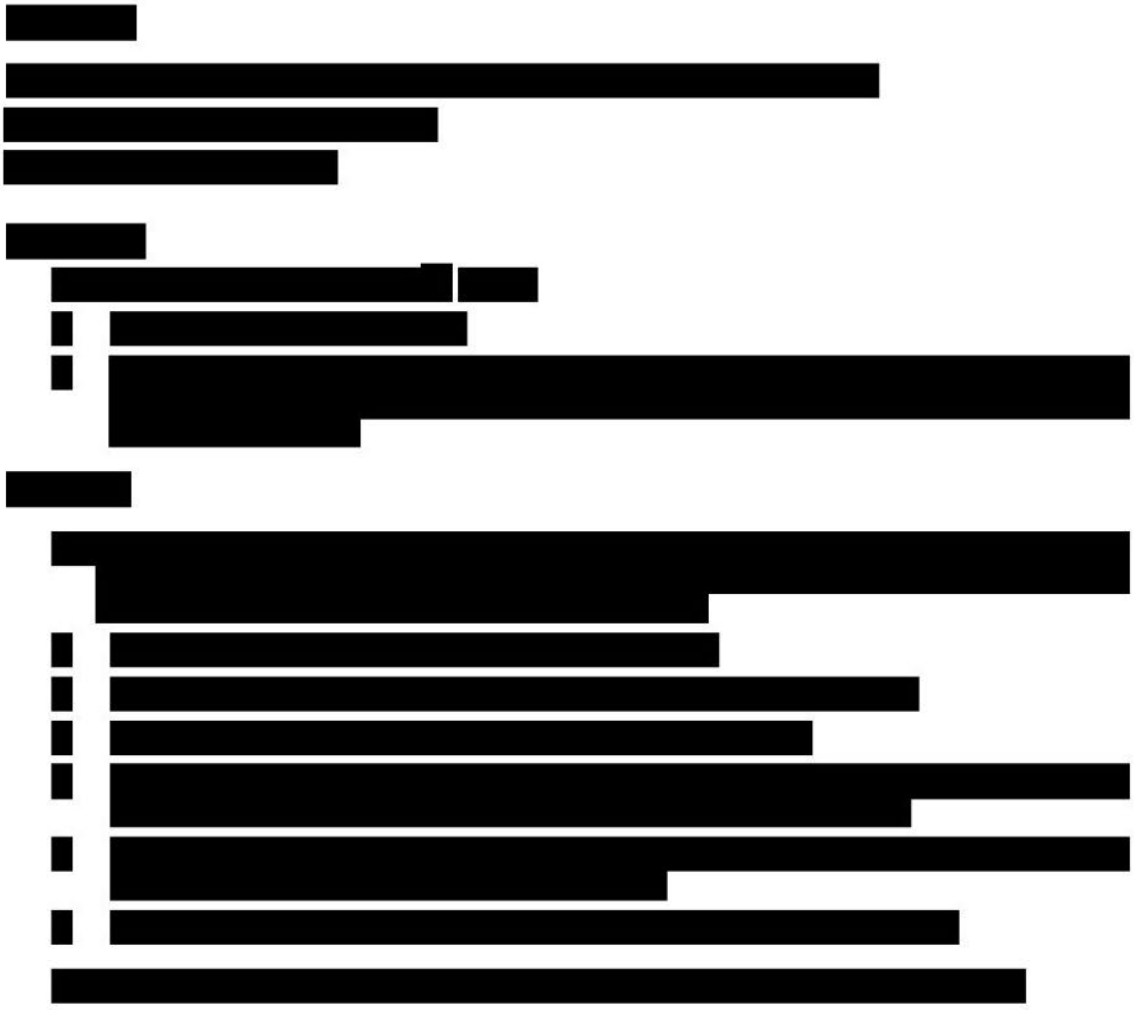

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