

Short Title

COMPASS-XT

Long Title

AN OBSERVATIONAL MULTICENTER CLINICAL STUDY TO ASSESS THE LONG-TERM SAFETY OF THE CYPASS MICRO-STENT IN PATIENTS WITH PRIMARY OPEN ANGLE GLAUCOMA WHO HAVE COMPLETED PARTICIPATION IN THE COMPASS TRIAL (TMI-09-01-E)

1 TITLE PAGE

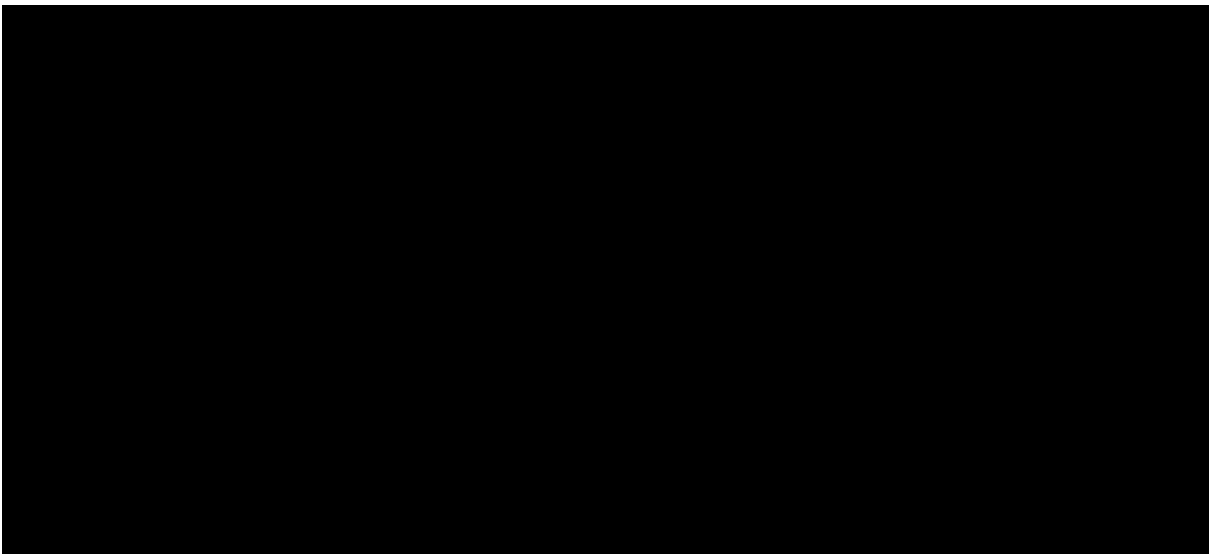
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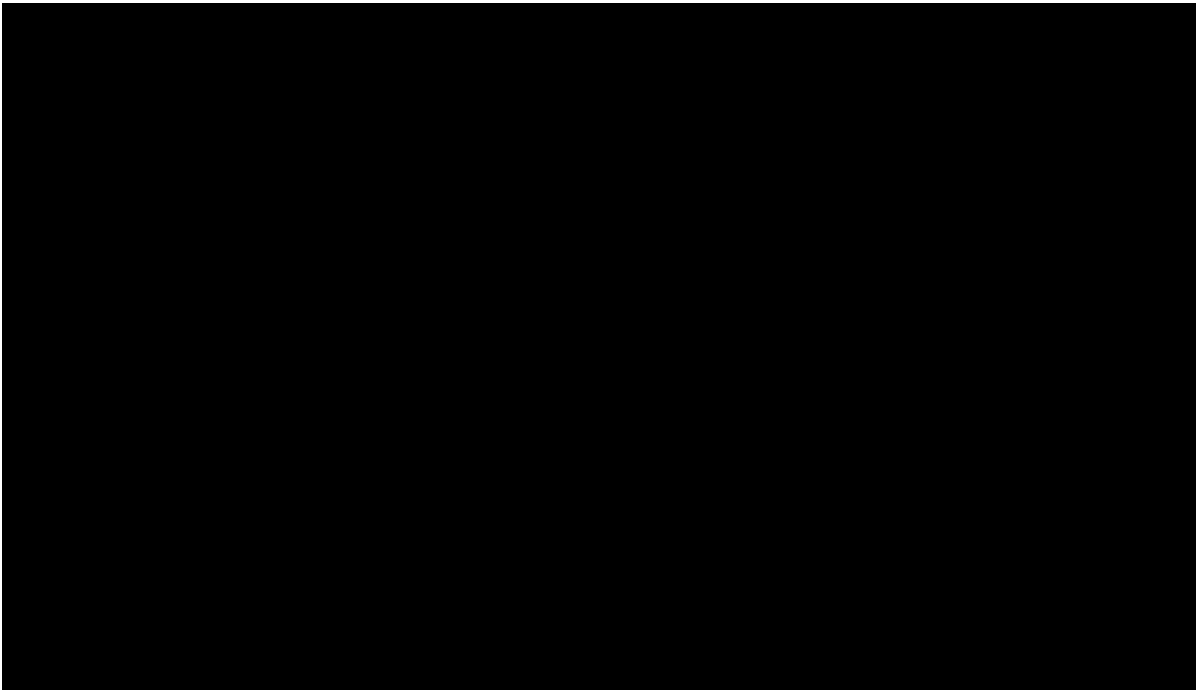
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Test Product(s): CyPass

Approvals: See last page for electronic approvals to Archive

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**AN OBSERVATIONAL MULTICENTER CLINICAL STUDY TO ASSESS THE LONG-TERM
SAFETY OF THE CYPASS MICRO-STENT IN PATIENTS WITH PRIMARY OPEN ANGLE
GLAUCOMA WHO HAVE COMPLETED PARTICIPATION IN THE COMPASS TRIAL
(TMI-09-01-E)**

THE COMPASS TRIAL EXTENSION (COMPASS-XT)

SPONSOR:

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6201 SOUTH FREEWAY
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GLAUCOMA WHO HAVE COMPLETED PARTICIPATION IN THE COMPASS TRIAL
(TMI-09-01-E)**

THE COMPASS TRIAL EXTENSION (COMPASS-XT)

1 PERSONNEL AND FACILITIES

STUDY SPONSOR:

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2 ABBREVIATIONS

AAO	American Academy of Ophthalmology
AC	anterior chamber
ADE	adverse device effect
AE	adverse event
ALT	argon laser trabeculoplasty
ANOVA	analysis of variance
BCVA	best corrected visual acuity
CAI	carbonic anhydrase inhibitor
CCT	central corneal thickness
C:D	cup-to-disc ratio
CF	count fingers
CI	confidence interval
D	diopter
dB	decibel
DSEK	Descemet stripping endothelial keratoplasty
ECD	endothelial cell density
ECL	endothelial cell loss
eCRF	electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
HM	hand motion
HVF	Humphrey visual field (perimeter)
ICD	informed consent document
ICF	informed consent form
IDE	investigational device exemption
IOL	intraocular lens
IOP	intraocular pressure
IRB	institutional review board
KM	Kaplan-Meier
LogMAR	logarithm of minimal angle of resolution
LP	light perception
LTF	lost to follow-up
MD	mean deviation
MGD	meibomian gland disease
MIGS	minimally invasive glaucoma surgery
NLP	no light perception
OAG	open-angle glaucoma
OCT	optical coherence testing
OD	right eye
OS	left eye
OU	both eyes
OVD	ophthalmic viscosurgical device

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PAS	peripheral anterior synechiae
PCO	posterior capsular opacification
PDR	proliferative diabetic retinopathy
POAG	primary open-angle glaucoma
SAE	serious adverse event
SAP	statistical analysis plan
SLT	selective laser trabeculoplasty
SOP	standard operating procedure
TFBUT	tear film break-up time
TLR	total letters read
UADE	unanticipated adverse device effect
VA	visual acuity
VF	visual field

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3 STUDY SYNOPSIS

3.1 Study Objective

The purpose of this research study is to evaluate the long-term safety of the CyPass Micro-Stent in subjects who have completed Study Protocol TMI-09-01.

3.2 Study Population

The study population will consist of up to 480 eyes of 480 subjects who completed 24 month follow-up in study Protocol TMI-09-01 and meet study eligibility criteria.

3.3 Study Design

This is a multicenter, observational study with no planned interventions. Both prospective and retrospective data on participating subjects may be collected in the study.

3.4 Study Outcomes

3.4.1 Primary Outcome - Safety

- Rate of occurrence of sight-threatening AEs

3.4.2 Secondary Outcomes - Safety

- Best Corrected Visual Acuity (BCVA)
- Rate of occurrence of ocular adverse events (AE)
- Slit lamp, gonioscopy and fundus findings
- Visual field mean deviation (MD)
- Central corneal thickness
- Central corneal endothelial cell density (ECD)
- Rate of occurrence of CyPass movement, defined as a change by at least 1 in the number of CyPass rings visible (e.g., from 0 rings to 1 ring or from 3 rings to 2 rings) that does not result in clinical sequelae (e.g., secondary surgical intervention to modify device position, corneal endothelial touch by device, corneal edema leading to loss of BCVA > 2 lines at the last postoperative visit in comparison with preoperative BCVA, progressive ECL, erosion of device through sclera, or device obstruction requiring secondary surgical intervention), and that is not attributable to:
 - variations in gonioscopic viewing angle or illumination,
 - changes in angle anatomy due to concomitant findings such as resolution of hyphema,
 - changes in anterior chamber depth, or
 - development of focal peripheral anterior synechiae.

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3.4.3 Secondary Outcomes – Effectiveness

- Mean change in intraocular pressure (IOP)
- Proportion of subjects who are not using ocular hypotensive medication with $\geq 20\%$ reduction in IOP from baseline in the COMPASS Trial
- Proportion of subjects who are not using ocular hypotensive medication with IOP ≥ 6 mmHg and ≤ 18 mmHg

3.5 Schedule of Visits

Subjects are to be evaluated at 36 months, 48 months and 60 months post-randomization in study protocol TMI-09-01 (See [APPENDIX 1](#) – Schedule of Events and Procedures).

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4 INTRODUCTION AND RATIONALE

4.1 The CyPass Micro-Stent

As shown in Figure 1 below, the CyPass Micro-Stent is a polyimide tube with a fenestrated through-lumen. The length of the CyPass device is 0.250" (6.35 mm). The device has a 0.012" (0.30 mm) inner diameter and 0.017" (0.43 mm) outer diameter. The CyPass Micro-Stent, when implanted as directed, is designed to allow outflow of aqueous fluid from the AC of the eye (where the device proximal end resides) through and around the distal end of the tube into the supraciliary and suprachoroidal spaces.



Figure 1
CyPass Micro-Stent

4.2 Protocol Background and Rationale

Protocol TMI-09-01, also known as the COMPASS Trial, was a prospective, randomized, comparative multicenter study to assess the safety and effectiveness of the CyPass Micro-Stent in subjects with primary open angle glaucoma who were undergoing cataract surgery. In the study, a total of 505 subjects were randomized to one of two treatment groups, as follows: The CyPass group underwent cataract surgery and received the CyPass Micro-Stent, while the Control group underwent cataract surgery alone. All subjects randomized were followed for 2 years postoperatively.

The study was performed in 2 phases. During the initial phase, 75 subjects were randomized. After FDA review of 3 month or longer postoperative data on these subjects, approval was granted for enrollment and randomization of the remaining 430 subjects in the study expanded phase. Enrollment in the initial study phase began in September 2009 and ended in August 2010. Enrollment in the expanded phase of the study began in July 2011 and the last study subject was randomized in March 2013.

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Subjects enrolled in the COMPASS Trial were examined at 2 preoperative visits to confirm eligibility for study participation. The first visit (Screening Visit) involved a comprehensive ophthalmic examination. Subjects qualifying after completion of the Screening Visit were required to discontinue use of ocular hypotensive medication, or “washout”, for a pre-established period to remove the medication from their system. After washout, subjects returned for a Baseline Visit during which they were re-evaluated and additional baseline data was collected to confirm continued eligibility. Subjects who qualified after the Baseline Visit were scheduled for cataract surgery. After completion of uncomplicated cataract surgery, subjects were randomized intraoperatively to either the CyPass group or the Control group. Subjects were asked to return for examination at postoperative Day 1, Week 1, Month 1, Month 3, Month 6, Month 12, Month 18 and Month 24.

Study protocol TMI-09-01-E, the COMPASS Extension Trial, is designed to collect safety data beyond 24 months postoperatively for subjects who completed study protocol TMI-09-01. [REDACTED]

[REDACTED] Study enrollment was initiated April 2016.

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5 STUDY OBJECTIVES

The purpose of this research study is to evaluate the long-term safety of the CyPass Micro-Stent in subjects who completed Study Protocol TMI-09-01.

5.1 Study Outcomes

5.1.1 Primary Outcome – Safety

- Rate of occurrence of sight-threatening AEs

5.1.2 Secondary Outcomes - Safety

- Best Corrected Visual Acuity (BCVA)
- Rate of occurrence of ocular adverse events (AE)
- Slit lamp, gonioscopy and fundus findings
- Visual field mean deviation (MD)
- Central corneal thickness
- Central corneal endothelial cell density (ECD)
- Rate of occurrence of CyPass movement, defined as a change by at least 1 in the number of CyPass rings visible (e.g., from 0 rings to 1 ring or from 3 rings to 2 rings) that does not result in clinical sequelae (e.g., secondary surgical intervention to modify device position, corneal endothelial touch by device, corneal edema leading to loss of BCVA > 2 lines at the last postoperative visit in comparison with preoperative BCVA, progressive ECL, erosion of device through sclera, or device obstruction requiring secondary surgical intervention), and that is not attributable to:
 - variations in gonioscopic viewing angle or illumination,
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 - changes in anterior chamber depth, or
 - development of focal peripheral anterior synechiae.

5.1.3 Secondary Outcomes – Effectiveness

- Mean change in intraocular pressure (IOP)
- Proportion of subjects who are not using ocular hypotensive medication with $\geq 20\%$ reduction in IOP from baseline in the COMPASS Trial
- Proportion of subjects who are not using ocular hypotensive medication with IOP ≥ 6 mmHg and ≤ 18 mmHg

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6 STUDY DESIGN

Study Protocol TMI-09-01-E is a multicenter observational study. Up to 480 subjects randomized in the COMPASS Trial at up to 24 investigational sites may participate. Study data through 5 years post-randomization in the COMPASS Trial will be collected for subjects who consent to participate.

**7 STUDY POPULATION****7.1 Subject Inclusion Criteria**

To be included in the study, individuals must meet each eligibility criterion presented as follows:

1. Participated in, and completed, Study Protocol TMI-09-01.
2. Is able to understand study requirements and willing to follow study instructions
3. Is willing to return for required study follow-up visits.

7.2 Subject Exclusion Criteria

The presence of any of the following characteristics will exclude individuals from study participation:

1. Systemic disease that, in the opinion of the Investigator, would put the subject's health at risk and/or prevent completion of required study visits.
2. Early termination from Study Protocol TMI-09-01.

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8 STUDY PROCEDURES

8.1 Subject Entry

Participants who completed Protocol TMI-09-01 (the COMPASS Trial) will be asked to enroll in the study. The investigator or designee will explain the study purpose, procedures and responsibilities to the potential participant and provide sufficient opportunity to ask questions, while allowing adequate time for consideration of the information provided. Upon participant confirmation of interest, written informed consent will be obtained and the subject will be enrolled in the study. One copy of the informed consent document (ICD) will be retained with the subject's medical records and one copy will be provided to the subject.

8.2 Study Visits

All subjects enrolled will return for defined follow-up visits through 60 months post-randomization in the COMPASS Trial. The number of scheduled study visits required will be dependent on the date of subject randomization in the COMPASS Trial. Data collected from each study visit will be recorded on an electronic Case Report Form (eCRF).

8.2.1 36 Month Postoperative Visit

This visit will occur at postoperative day 1095 ± 90 days. The following information will be captured for the study eye at this visit:

- Manifest refraction and ETDRS BCVA
- Slit lamp biomicroscopy
- Goldmann tonometry
- Dilated fundus examination and C:D ratio assessment
- Visual field mean deviation
- Gonioscopy examination (CyPass-implanted eyes only)
- Central corneal pachymetry
- Specular microscopy
- Ocular hypotensive medications
- AE assessment
- Subject Symptom Questionnaire

In the event a subject is enrolled who is more than 36 months postoperative, retrospective data for the 36-month follow-up period, if available, may be collected from review of the subject's medical chart.

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8.2.2 48 Month Postoperative Visit

This visit will occur at postoperative day 1460 ± 90 days. The following information will be captured for the study eye at this visit:

- Manifest refraction and ETDRS BCVA
- Slit lamp biomicroscopy
- Goldmann tonometry
- Dilated fundus examination and C:D ratio assessment
- Visual field mean deviation
- Gonioscopy examination (CyPass- implanted eyes only)
- Central corneal pachymetry
- Specular microscopy
- Ocular hypotensive medications
- AE assessment
- Subject Symptom Questionnaire

In the event a subject is enrolled who is more than 48 months postoperative, retrospective data for the 48-month follow-up period, if available, may be collected from review of the subject's medical chart.

8.2.3 60 Month Postoperative Visit

This visit must occur at postoperative day 1825 ± 90 days. The following information will be captured for the study eye at this visit:

- Manifest refraction and ETDRS BCVA
- Slit lamp biomicroscopy
- Goldmann tonometry
- Dilated fundus examination and C:D ratio assessment
- Visual field mean deviation
- Gonioscopy examination (CyPass-implanted eyes only)
- Central corneal pachymetry
- Specular microscopy
- Ocular hypotensive medications
- AE assessment
- Subject Symptom Questionnaire

In the event a subject is enrolled who is more than 60 months postoperative, retrospective data for the 60-month follow-up period, if available, may be collected from review of the subject's medical chart.

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The examinations required at each study visit are outlined and summarized in [APPENDIX 1](#) (Schedule of Events and Procedures) and a description of examination methodology is provided in [APPENDIX 2](#) (Examination Procedures, Tests, Equipment and Techniques).

8.3 Unscheduled Visits

Unscheduled visits are clinic visits not specified in the protocol when the subject returns for examination due to a complaint regarding the study eye or a surgical procedure performed on the study eye. No specific testing is required at unscheduled visits; rather, the investigator and/or qualified investigational staff will perform the examinations or procedures necessary to evaluate the subject at these visits. Clinical data from unscheduled visits will be recorded on the relevant eCRF.

8.4 Subject Disposition**8.4.1 Discontinued Subjects**

Subjects who exit the study prior to completion are considered to be “discontinued”. Subjects may be discontinued due to:

- Onset or progression of systemic disease that, in the opinion of the investigator, would put the subject’s health at risk or compromise the subject’s ability to return for necessary follow-up visits, or
- Administrative reasons (e.g., voluntary withdrawal or loss to follow-up)

The sponsor should be promptly notified of subject discontinuation and the relevant eCRF should be completed for this subject.

If a subject does not return for a scheduled study visit, the investigational site will make a minimum of 3 documented attempts via telephone, email, or regular mail to contact the subject. If the subject does not reply to any of these attempts, the site will send a letter to the subject using certified mail, with a request for notification of receipt. If a subject continues to be non-responsive to these follow-up attempts, the subject will be considered to be lost to follow-up.

8.4.2 Completed Subjects

Completed subjects are those who are not discontinued from the study prior to completion of required scheduled visits.

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9 STATISTICAL METHODS

The objective of this study is to collect long-term safety data regarding the CyPass Micro-Stent in subjects who completed the COMPASS Trial. The primary outcome is the occurrence of sight-threatening AEs. Other study outcomes include the rate of occurrence of ocular AEs in the study eye, BCVA, slit lamp, gonioscopy and fundus examination findings, central corneal thickness, central corneal ECD. Study outcomes will be analyzed as follows.

9.1 Sight Threatening Ocular Adverse Events

Sight-threatening AEs include, but are not limited to, BCVA loss of ≥ 3 lines, endophthalmitis, corneal decompensation, severe retinal detachment, severe choroidal hemorrhage, severe choroidal detachment and aqueous misdirection. A non-parametric time to event Kaplan-Meier (K-M) analysis for the sight-threatening AE rate at 5 years will be provided by treatment group. This method accounts for all information that discontinued patients contribute to the rate of the primary safety event up to the point at which that patient discontinues (i.e., is censored). The cumulative Kaplan-Meier probability that a subject experienced a sight-threatening AE will be completed for each treatment group. To aid in the interpretation of the results, the annualized rates for each year and over the five (5) year period will be calculated.

9.2 Ocular Adverse Events

The number of subjects reporting at least 1 AE of a given type will be summarized. AEs not listed that occur during the study will be added to the summary of AEs. Each AE will be summarized by incidence, percentage and 95% confidence interval.

9.3 Central Corneal Pachymetry

Central corneal pachymetry data collected at baseline, 12 month and 24 month postoperative visits in Protocol TMI-09-01 and collected in this protocol will be summarized with N, mean, standard deviation, minima, median, and maxima. A 95% confidence interval will be provided for the change and percentage change from baseline. Change between 2 consecutive visits will also be summarized.

9.4 Central Corneal Endothelial Cell Density

Endothelial cell density (ECD) data collected at baseline, 3 month, 6 month, 12 month and 24 month postoperative visits in Protocol TMI-09-01 and in this protocol will be summarized with N, mean, standard deviation, minima, median, and maxima for each treatment arm. A 95% confidence interval will be provided for the change and percentage change in ECD from baseline. The change between 2 consecutive visits will also be summarized.

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9.5 Best Corrected Visual Acuity

Best Corrected Visual Acuity (BCVA) data collected at the subject baseline, 12 month and 24 month postoperative visits in Protocol TMI-09-01 and in this protocol will be summarized as counts and percentages with 95% confidence intervals for subjects who have BCVA 20/20 or better, 20/25 or better, 20/32 or better, 20/40 or better and worse than 20/40. Also, shift tables from baseline will be presented with counts, percentages, and 95% confidence intervals.

9.6 Slit Lamp, Gonioscopy and Fundus Exam Findings

Slit lamp, gonioscopy, and fundus examination findings at scheduled follow-up visits will be tabulated such that the number and percentage of subjects in each category and 95% confidence intervals for the percentages will be summarized by scheduled follow-up visit.

9.7 Visual Field Loss Mean Deviation

The visual field mean deviation (MD) testing data collected at baseline, 3 month, 6 month, 12 month and 24 month postoperative visits in Protocol TMI-09-01 and in this protocol will be summarized with N, mean, standard deviation, minima, median, and maxima. A 95% confidence interval will be provided for the change and percentage change from baseline.

9.8 Intraocular Pressure

The N, mean, standard deviation, minima, median, and maxima for change in IOP will be presented for each study visit, along with a 95% confidence interval on the mean change. The number and proportion of subjects who are not using ocular hypotensive medication with $\geq 20\%$ reduction in IOP from baseline in the COMPASS Trial will also be presented at each study visit, along with a 95% confidence interval. Finally, the number and proportion of subjects who are not using ocular hypotensive medication with IOP ≥ 6 mmHg and ≤ 18 mmHg will be presented at each study visit, along with a 95% confidence interval.

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10 ADVERSE EVENTS

All ocular AEs occurring in the study eye must be reported on the relevant eCRF. Adverse events will be categorized by degree of harm to the subject (mild, moderate, or severe) and the relationship to the CyPass Micro-Stent. Since there are no aspects of the study that can affect both eyes, only serious adverse events observed in the fellow eye must be reported. Serious non-ocular AEs will also be captured on the relevant eCRF throughout the course of the study.

Ocular conditions or diseases present at the time of study enrollment in Study Protocol TMI-09-01 will be considered as “baseline”. Changes in a chronic condition or disease that are consistent with natural disease progression are not considered to be AEs. The status of AEs that were “ongoing” at subject exit from Study Protocol TMI-09-01 will be evaluated at the time of enrollment in this study. Events that remain ongoing and that meet the AE definitions for this protocol will be documented as AEs in this study

10.1 Ocular Adverse Events

Ocular AEs that might reasonably be expected to occur include, but are not limited to, the following:

- BCVA loss of 2 lines (10 letters) or more on the ETDRS chart in comparison with the best BCVA reported in Study Protocol TMI-09-01
- Any 2-point worsening in slit lamp examination findings (other than cells and flare) to “severe or “very severe”, which is not associated with a pre-existing condition
- Chronic anterior uveitis, defined as inflammation of Grade 1+ or worse persisting for more than 3 months post-operatively or that recurs less than 3 months after discontinuation of anti-inflammatory treatment
- Endophthalmitis
- Presence of flat anterior chamber requiring anterior chamber reformation
- Presence of a shallow chamber with iridocorneal apposition without lens/cornea touch
- Corneal edema
- Corneal decompensation
- Corneal opacification
- Hyphema, which is > 2 mm in size
- Retinal detachment
- Proliferative vitreoretinopathy
- Other retinal complications (e.g., dialysis, flap tears)
- Increase in C:D ratio of ≥ 0.3 units in comparison with the 24-month C:D ratio reported in Study Protocol TMI-09-01
- A confirmed worsening in visual field mean deviation (MD) of ≥ 2.5 dB compared to the 24-month visual field MD determined in Study Protocol TMI-09-01
- Suprachoroidal hemorrhage
- Choroidal effusion requiring surgical drainage

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- Choroidal effusion or detachment with at least a partially hemorrhagic component that obstructs vision or causes pain (including both peripheral and “kissing” choroidal detachments) lasting longer than 30 days
- Hypotonic maculopathy
- Macular edema (including cystoid macular edema and diabetic macular edema)
- Choroidal folds
- Other maculopathy
- Clinically significant hypotony, which is defined as IOP < 6 mmHg that results in maculopathy; flat anterior chamber requiring reformation; corneal folds; onset or worsening of with-the-rule astigmatism by ≥ 1 Diopter or rotation of against-the-rule to with-the-rule astigmatism by ≥ 1 Diopter; choroidal effusion requiring surgical drainage; suprachoroidal hemorrhage or BCVA loss of ≥ 2 lines
- Mean (or median) IOP ≥ 10 mmHg higher than the subject’s baseline mean unmedicated diurnal IOP reported in Protocol TMI-09-01
- CyPass device obstruction by iris, vitreous, lens, fibrous overgrowth, fibrin or blood
- CyPass device malfunction
- CyPass device malposition or dislodgement, defined as CyPass positioning after deployment such that:
 - The device is not in the supraciliary space, or
 - There is a clinical sequela resulting from device position including, but not limited to:
 - Secondary surgical intervention to modify device position (e.g., repositioning, proximal end trimming or explantation)
 - Corneal endothelial touch by device
 - Corneal edema leading to loss of BCVA > 2 lines at the last postoperative visit in comparison with preoperative BCVA
 - Progressive ECL, defined as reduction in endothelial cell count of 30% or more relative to baseline ECD value
 - Erosion of device through sclera
 - Device obstruction requiring secondary surgical intervention.
- CyPass device exposure or extrusion
- Other events that necessitate unplanned intraocular surgical re-intervention (other than Nd:YAG capsulotomy), which includes, but is not limited to CyPass explantation, CyPass repositioning, CyPass trimming, planned CyPass lumen occlusion and treatment of elevated IOP that is not satisfactorily managed using ocular hypotensive medication
- Significant ptosis
- Atrophy/phthisis
- Wound dehiscence, which is defined as persistent aqueous leak or fistula formation
- Vitreous hemorrhage
- Chronic ocular pain, which is defined as continuous pain documented at 2 visits at least 30 days apart not associated with a pre-existing condition
- Significant foreign body sensation

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- Any 2-point worsening of an ocular symptom questionnaire report to “severe” or “very severe”, which is not associated with a pre-existing condition

10.2 Sight-Threatening Ocular Adverse Events

Sight-threatening AEs include, but are not limited to endophthalmitis, corneal decompensation, BCVA loss ≥ 3 lines, severe retinal detachment, severe choroidal hemorrhage, severe choroidal detachment and aqueous misdirection.

10.3 Grading of Adverse Events

Adverse events will be categorized by degree of harm to the subject using the 3-point scale below:

- Mild: Discomfort noticed, but there is no disruption of normal daily activity
- Moderate: Discomfort is sufficient to reduce or affect normal daily activity
- Severe: Incapacitation as evidenced by the inability to work or perform normal daily activity

10.4 Follow-up of Adverse Events

Adverse events will be followed until resolution or stabilization of the event.

10.5 Expedited Reporting of Adverse Events

Serious adverse events (SAE) require expedited reporting to the sponsor or designee regardless of relationship to the CyPass Micro-Stent. An AE is classified as SERIOUS if it:

- Caused or led to death
- Was life-threatening (i.e., the AE placed the subject at immediate risk of death)
- Required or prolonged inpatient hospitalization (i.e., the AE required at least a 24-hour inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay)
- Was sight-threatening, or otherwise disabling (i.e., the AE resulted in a substantial disruption of the subject's ability to carry out normal life functions)
- Resulted in a congenital anomaly/birth defect (i.e., an adverse outcome in a child or fetus of a subject due to participation in this study)
- Does not meet any of the above serious criteria but jeopardized the subject by requiring medical or surgical intervention to prevent one of the outcomes listed above.

All SAEs must be reported immediately (within 24 hours) of the Investigator's or site's awareness.

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with the CyPass Micro-Stent, that has not been previously identified. UADEs must be reported within 24 hours of the Investigator's or site's awareness.

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Adverse device effects (ADE) and/or device malfunctions that do not meet seriousness criteria and/or are anticipated must be reported within 10 calendar days of the Investigator's or site's awareness.

If product is returned in relation to an AE, a printed copy of the completed relevant AE eCRF must be included with the product return.

Reports should be submitted via the sponsor's electronic data capture (EDC) system. Document all relevant information such as concomitant medications, Discharge summary, Autopsy report, Certificate of Death etc. associated with the AE as part of the subject narrative, if applicable. Should the EDC system become non-operational, complete a paper copy of the relevant eCRF and fax to the sponsor at [REDACTED] in accordance with the timelines stated above. Once the EDC system becomes operational; enter the reported information into the EDC system. Additional relevant information after initial reporting must be entered into the eCRF promptly after the data become available.

11 STUDY MONITORING

Study monitoring will be performed in accordance with the sponsor's clinical standard operating procedures (CSOP). A combination of central and on-site monitoring activities will be utilized to confirm study site adherence to the study protocol and associated regulatory requirements, as well as to confirm appropriate reporting of study AEs. Observations from on-site monitoring visits and resulting action items will be documented and maintained in the study master file.

12 ETHICAL AND REGULATORY CONSIDERATIONS

This protocol was designed, and will be conducted in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later amendments. Basic responsibilities of the study sponsor, investigators and overseeing Institutional Review Board(s) (IRB) are as noted below:

12.1 Sponsor Responsibilities

The sponsor is responsible for maintaining clinical study records and reports as noted below for at least 2 years following study termination or completion. The Sponsor will make these records available for audit and review by FDA as requested by the Agency.

Clinical Study Records:

- AEs and UADEs
- Signed Investigator Agreements and Investigator *Curriculum Vitae* (CV)
- Financial disclosure information under 21 CFR Part 54
- Study eCRFs

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- Study-related correspondence

Clinical Study Reports:

- Written evaluation of any UADEs will be provided to all Investigators, IRBs and FDA within 10 working days of receipt of notice of the event
- Written notice of withdrawal of IRB approval will be provided to all Investigators, IRBs and FDA within 5 working days
- Annual study progress reports to all IRBs (if required by the IRB, progress reports will be submitted at greater frequency than annual)
- Annual progress reports to FDA
- Final report to all IRBs and FDA within 6 months of study termination or completion

12.2 Investigator Responsibilities

Each principal investigator is required to sign an Investigator Agreement, which documents the investigator's obligations with respect to protocol adherence, subject informed consent, and safety event reporting. By signing the Investigator Agreement, the investigator acknowledges his/her commitment to the sponsor that he/she will comply with the protocol and study obligations. All investigators must participate in a protocol review conducted by the sponsor or designated representative. No changes in this protocol can be made without the written approval of the sponsor and the overseeing IRB(s).

The investigator is responsible for the subject informed consent process and for confirming that all subjects provide written informed consent prior to enrollment in the study and that those subjects enrolled conform to study protocol eligibility criteria.

The investigator is responsible for maintaining clinical study records and reports as noted below for at least 2 years following study termination or completion. The Investigator will make these records available for audit and review by the Sponsor, IRB and/or FDA as requested.

Clinical Study Records:

- Study protocol and any amendments
- Subject source documents (e.g., medical records) including case history, documentation that informed consent was obtained prior to study participation, and description of circumstances if informed consent was not obtained
- Subject eCRFs
- Signed and dated ICDs for each subject
- Study-related correspondence

Clinical Study Reports:

- Continuing review reports to IRB and Sponsor, at least annually or as required by IRB
- Any other records required by the IRB

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12.3 Institutional Review Board Responsibilities

This protocol and the subject ICD must be reviewed and approved by an IRB operating in accordance with local procedures and 21 CFR Parts 50, 56, and 812 before enrollment of subjects. The Investigator is responsible for maintaining IRB approval for the study protocol and ICD and for keeping the IRB informed of protocol amendments and AEs in accordance with IRB requirements.

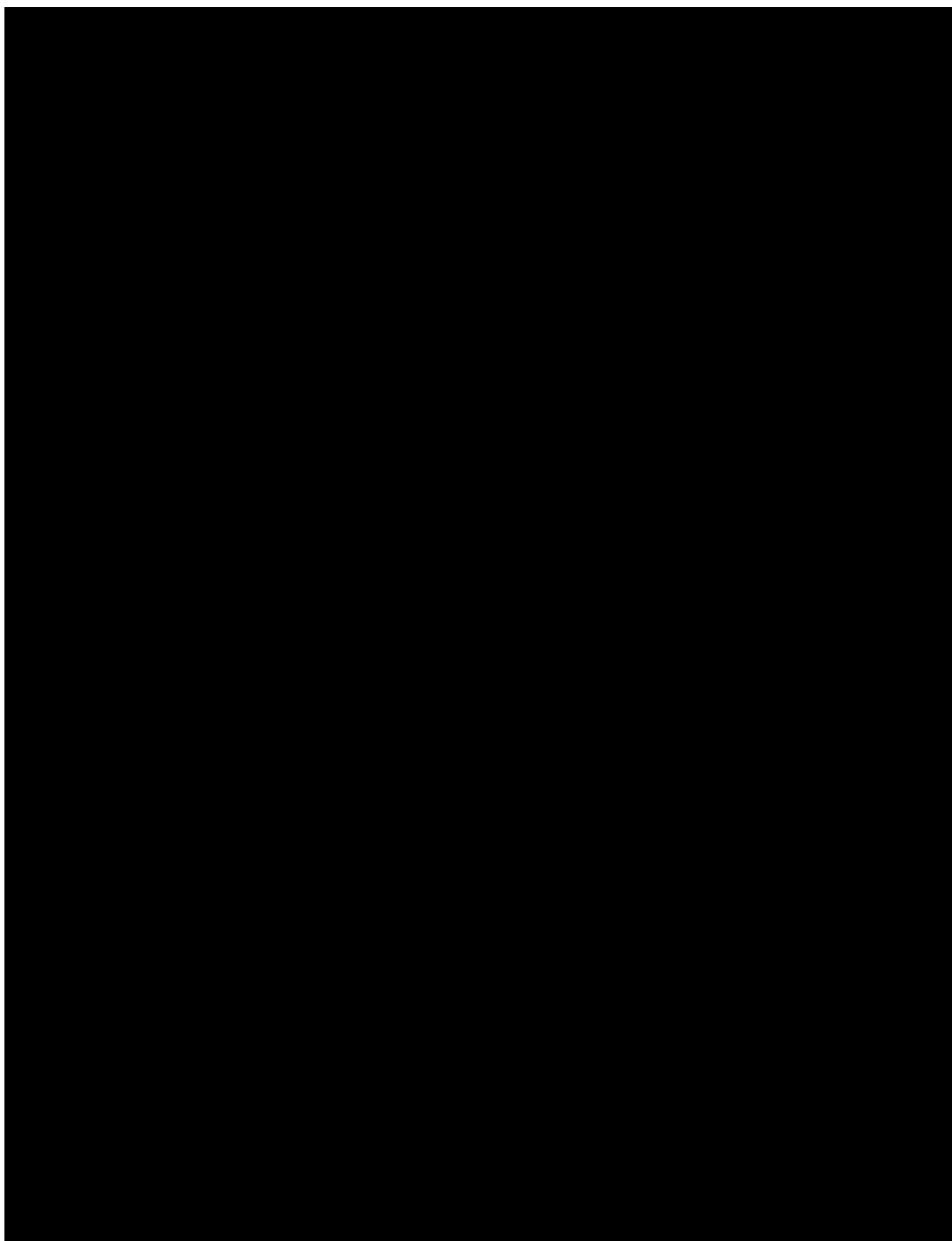
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APPENDIX 1
SCHEDULE OF EVENTS AND PROCEDURES

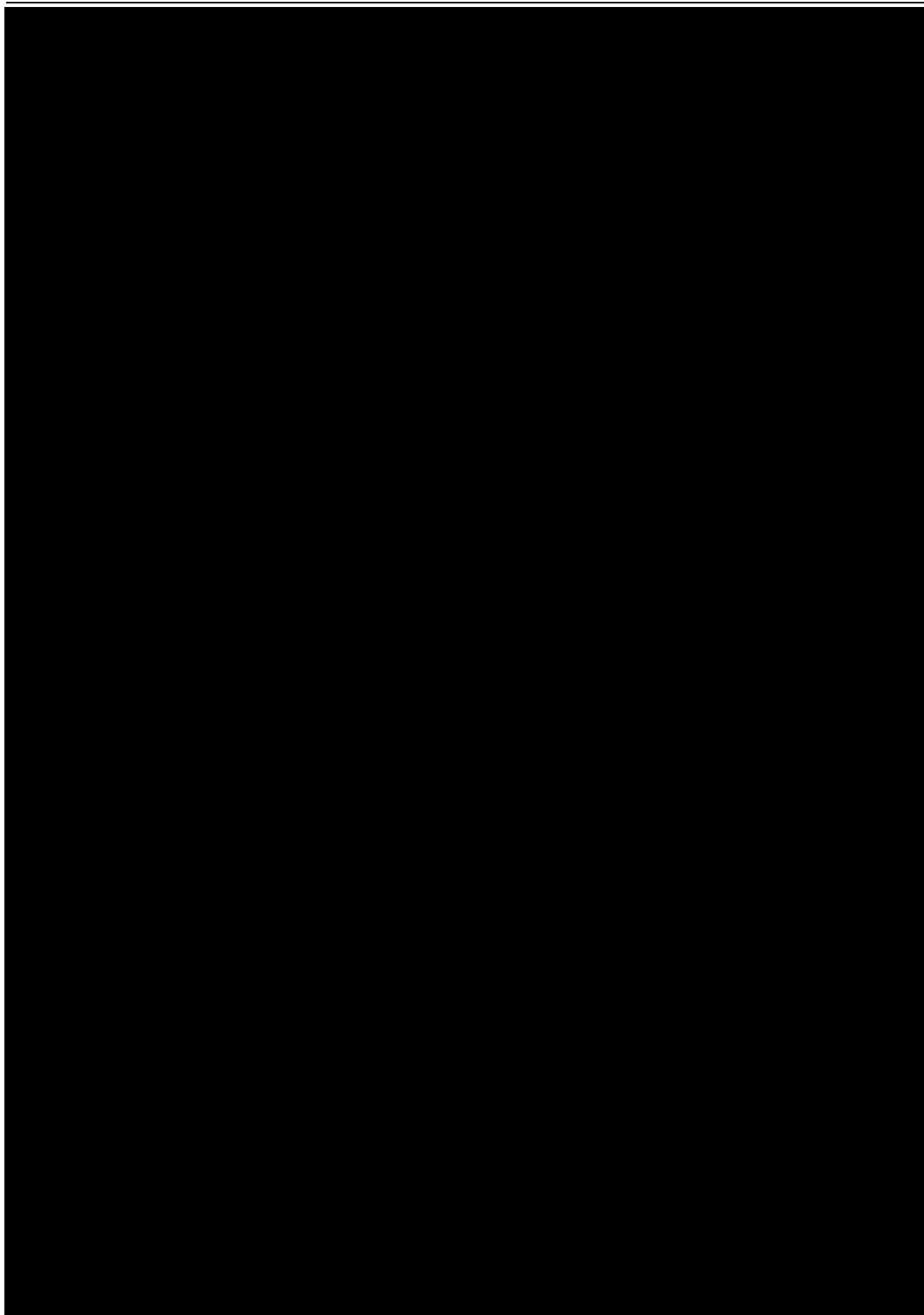
PROCEDURE/EXAMINATION ¹	36 Mo 1095 ± 90 DAYS POSTOPERATIVE	48 Mo 1460 ± 90 DAYS POSTOPERATIVE	60 Mo 1825 ± 90 DAYS POSTOPERATIVE
Informed Consent	X		
Medical History Update	X	X	X
Ocular Hypotensive Medications	X	X	X
Manifest Refraction	X	X	X
BCVA (ETDRS), based on Total Letters Read	X	X	X
IOP (using Goldmann Tonometry)	X	X	X
Slit Lamp Biomicroscopy	X	X	X
Gonioscopy (only for subjects in the CyPass group)	X	X	X
Dilated Fundus Exam, including Cup to Disc (C:D) Ratio	X	X	X
Central Corneal Thickness (using Pachymetry)	X	X	X
Specular Microscopy (ECD)	X	X	X
AE Assessment	X	X	X
Visual Field (Humphrey 24-2 SITA Standard)	X	X	X
Subject Symptom Questionnaire	X	X	X

¹ All ophthalmic procedures/examinations will be performed on the study eye only

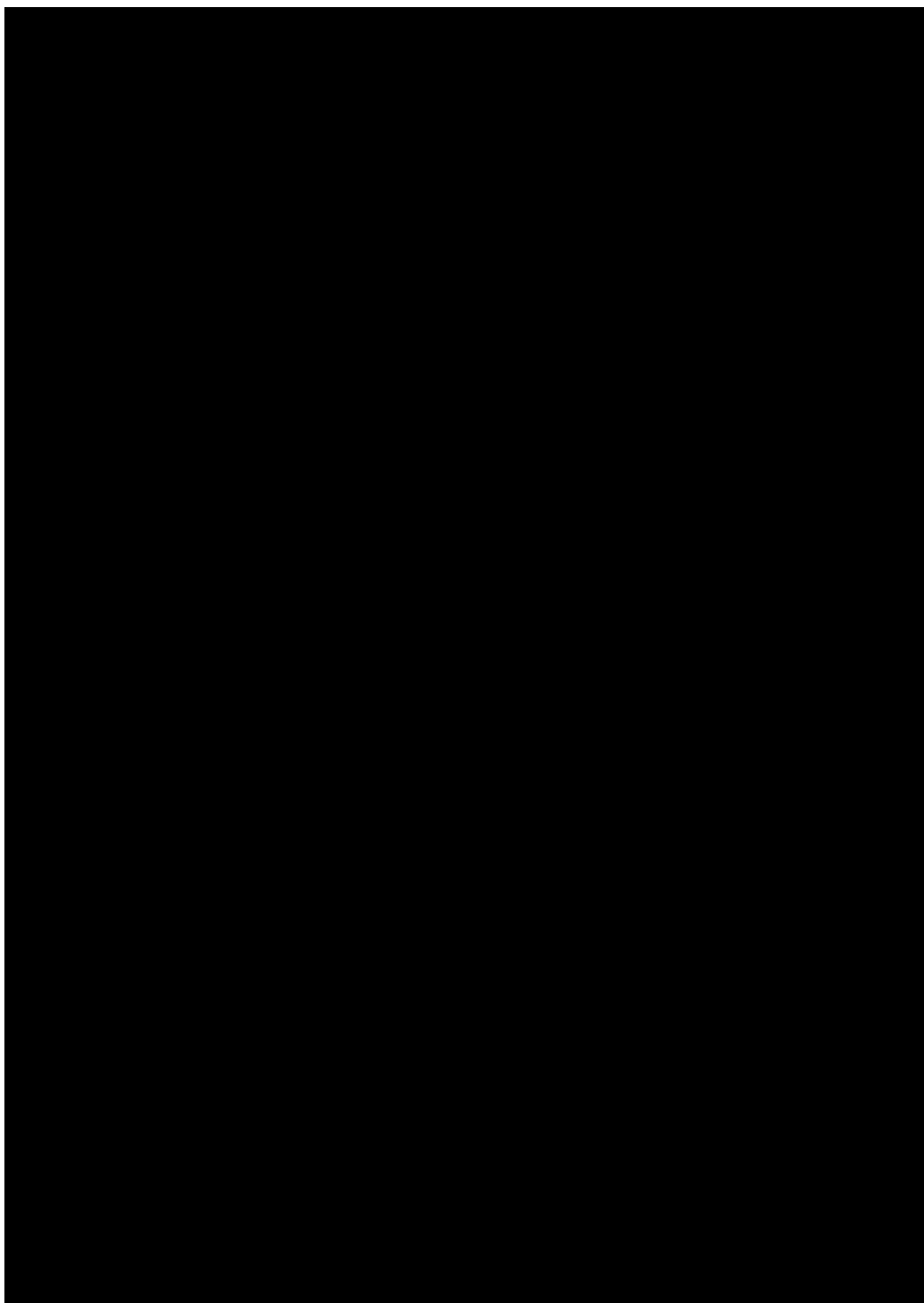
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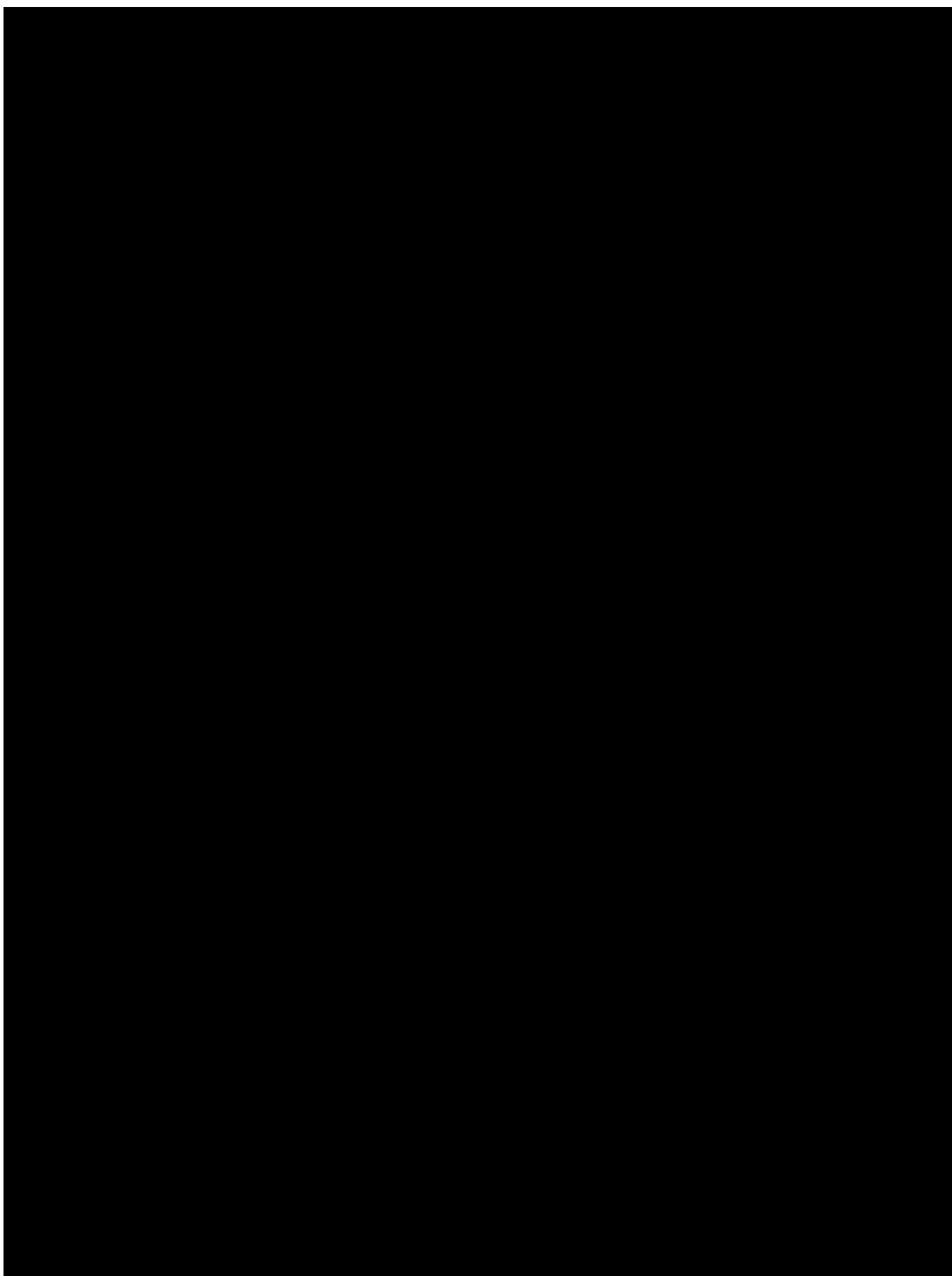
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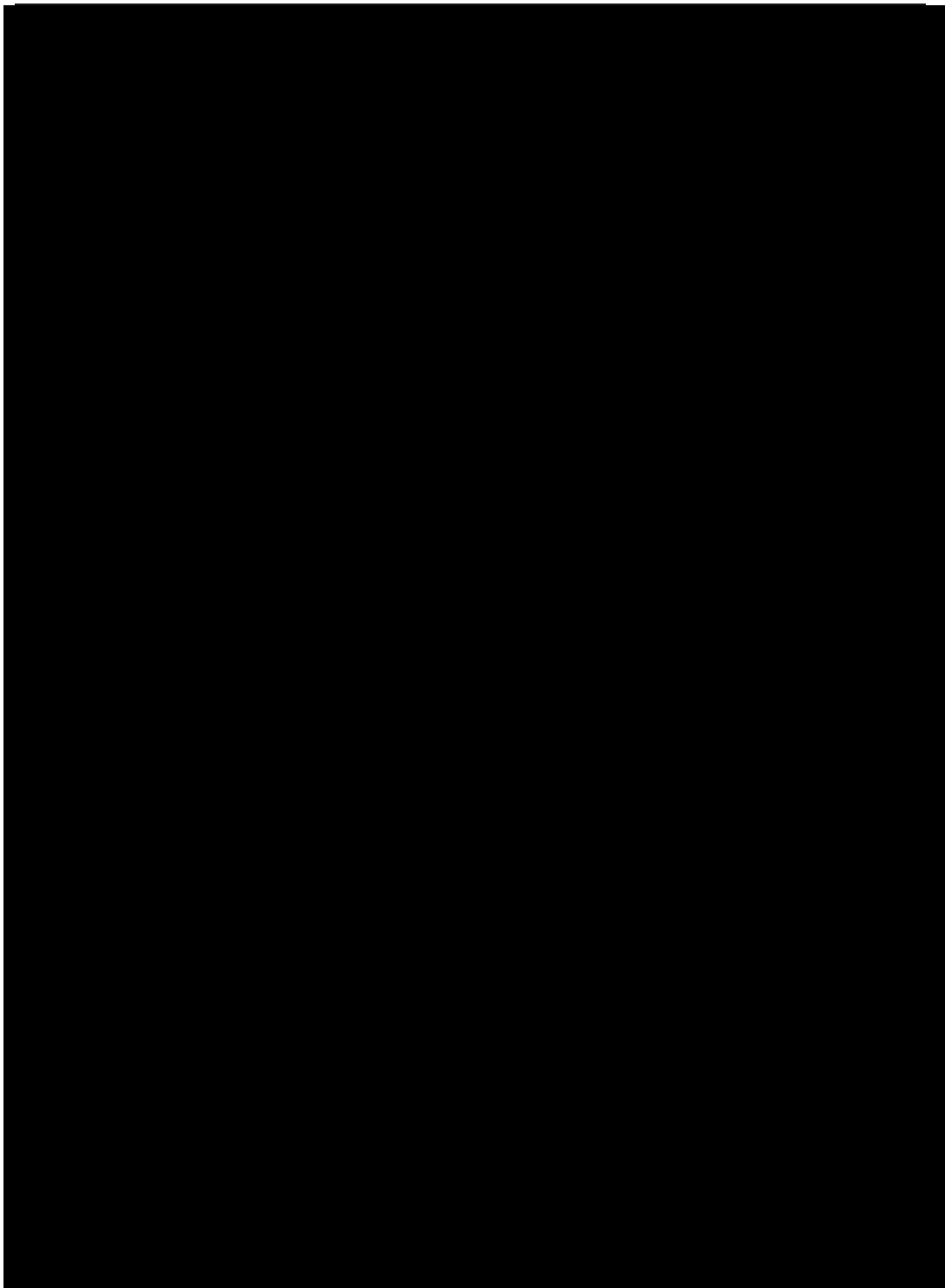
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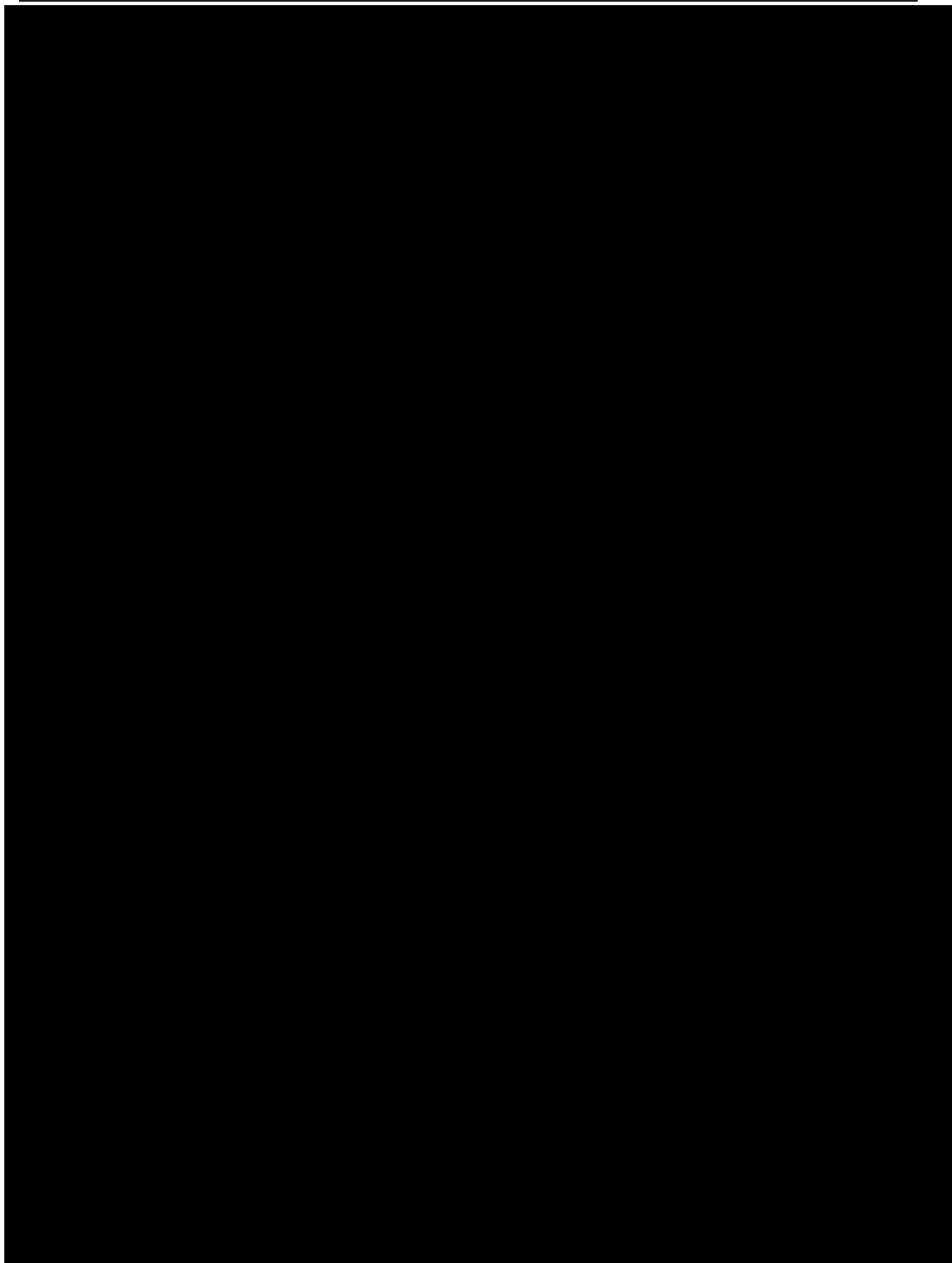
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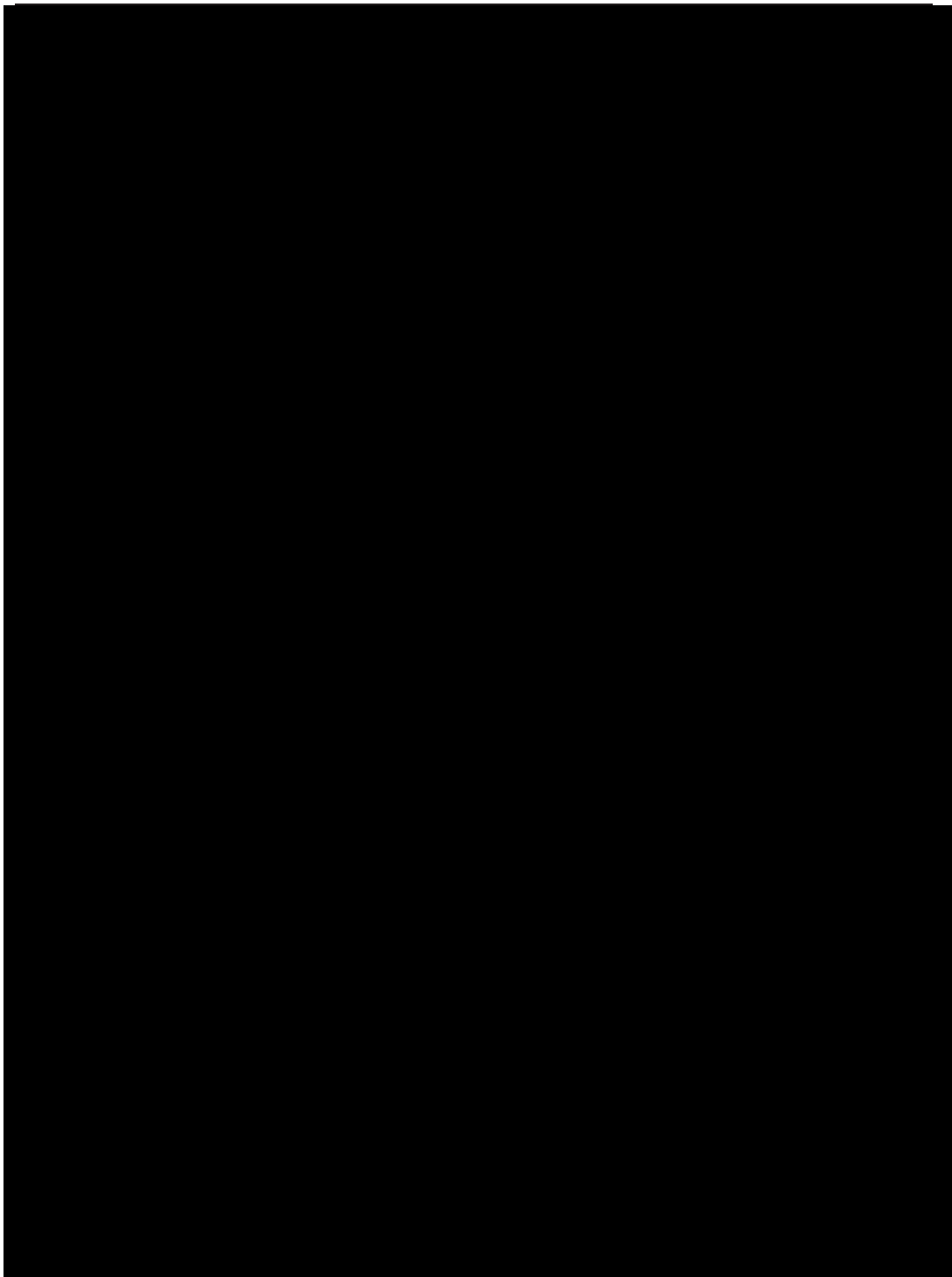
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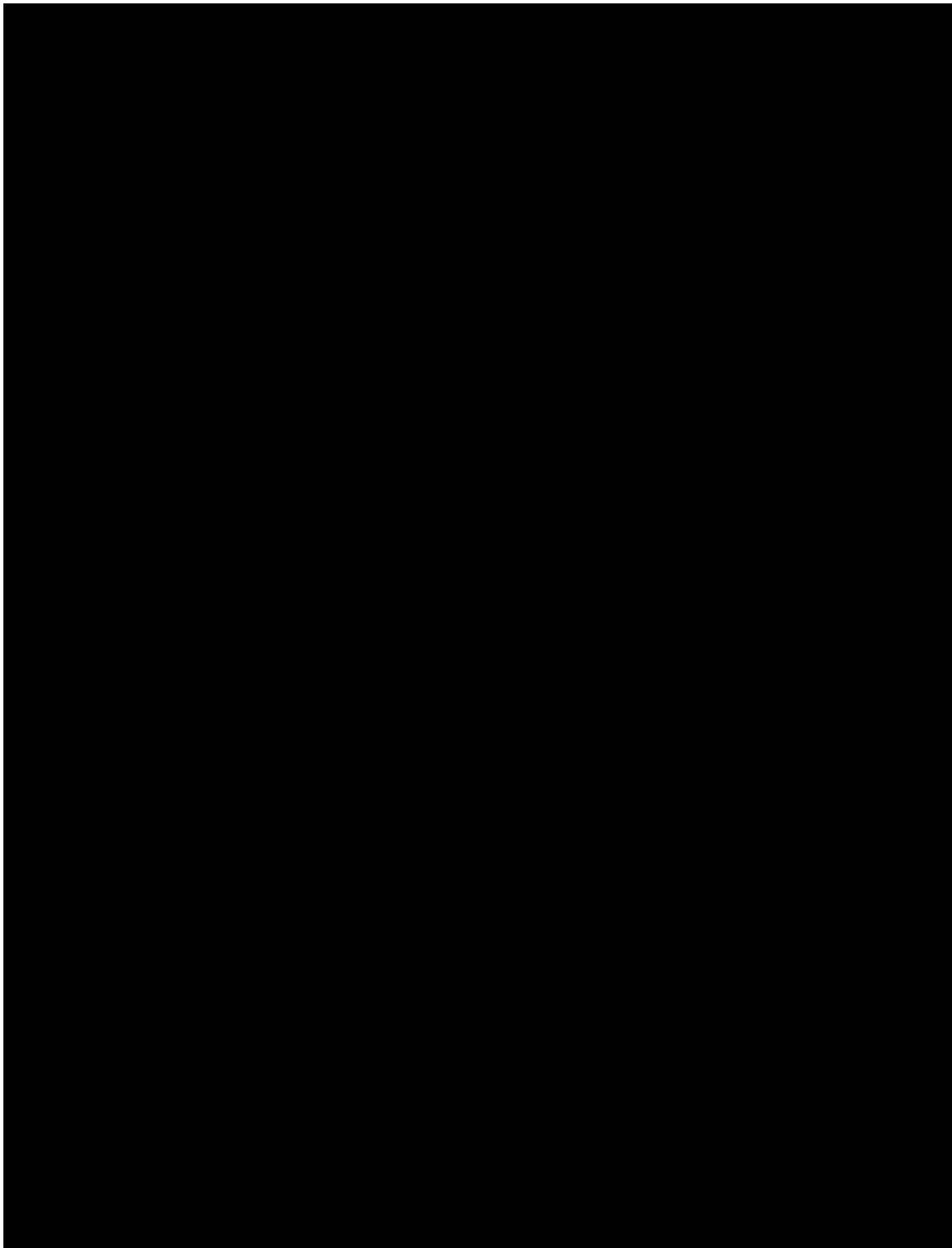
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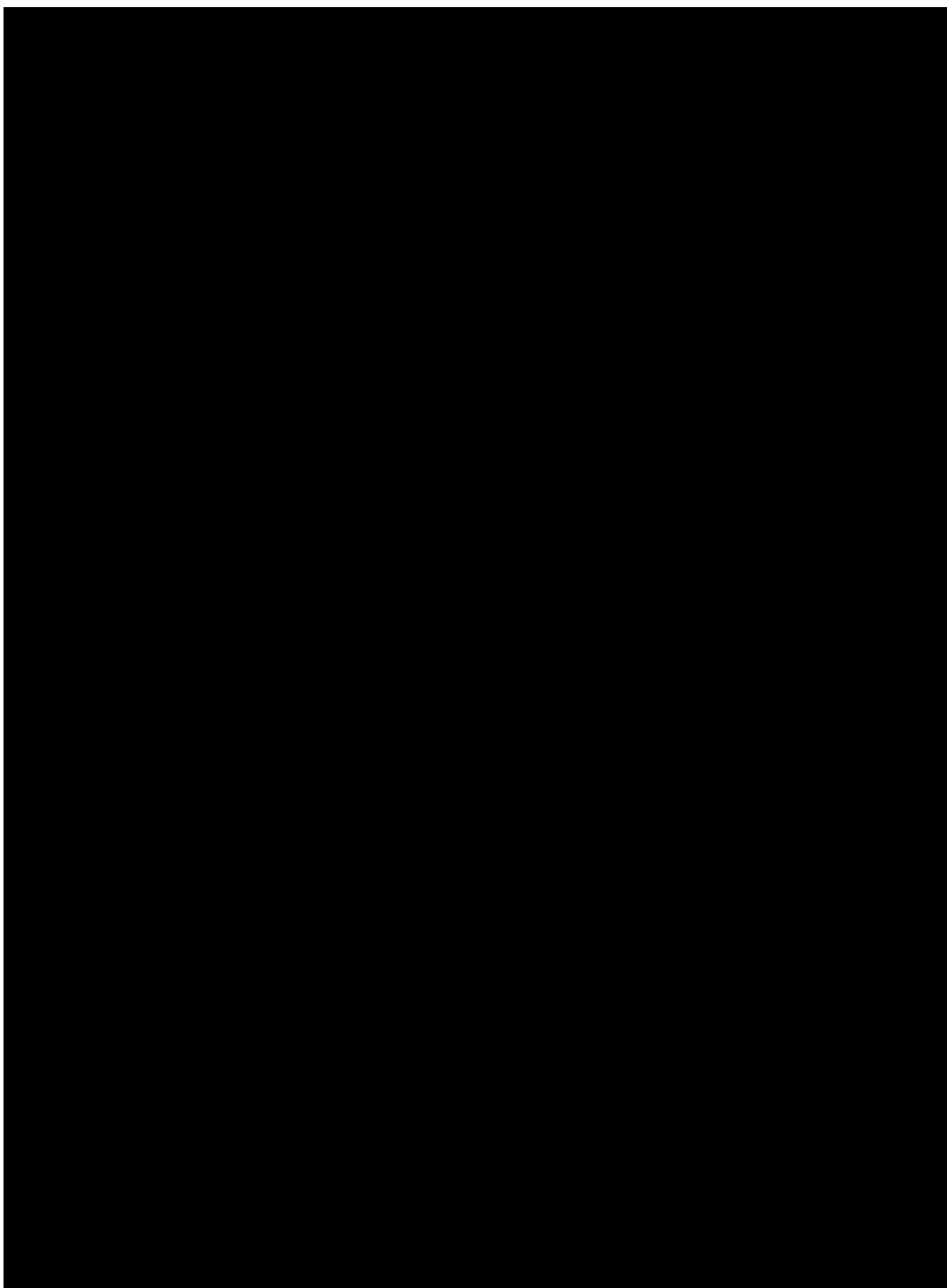
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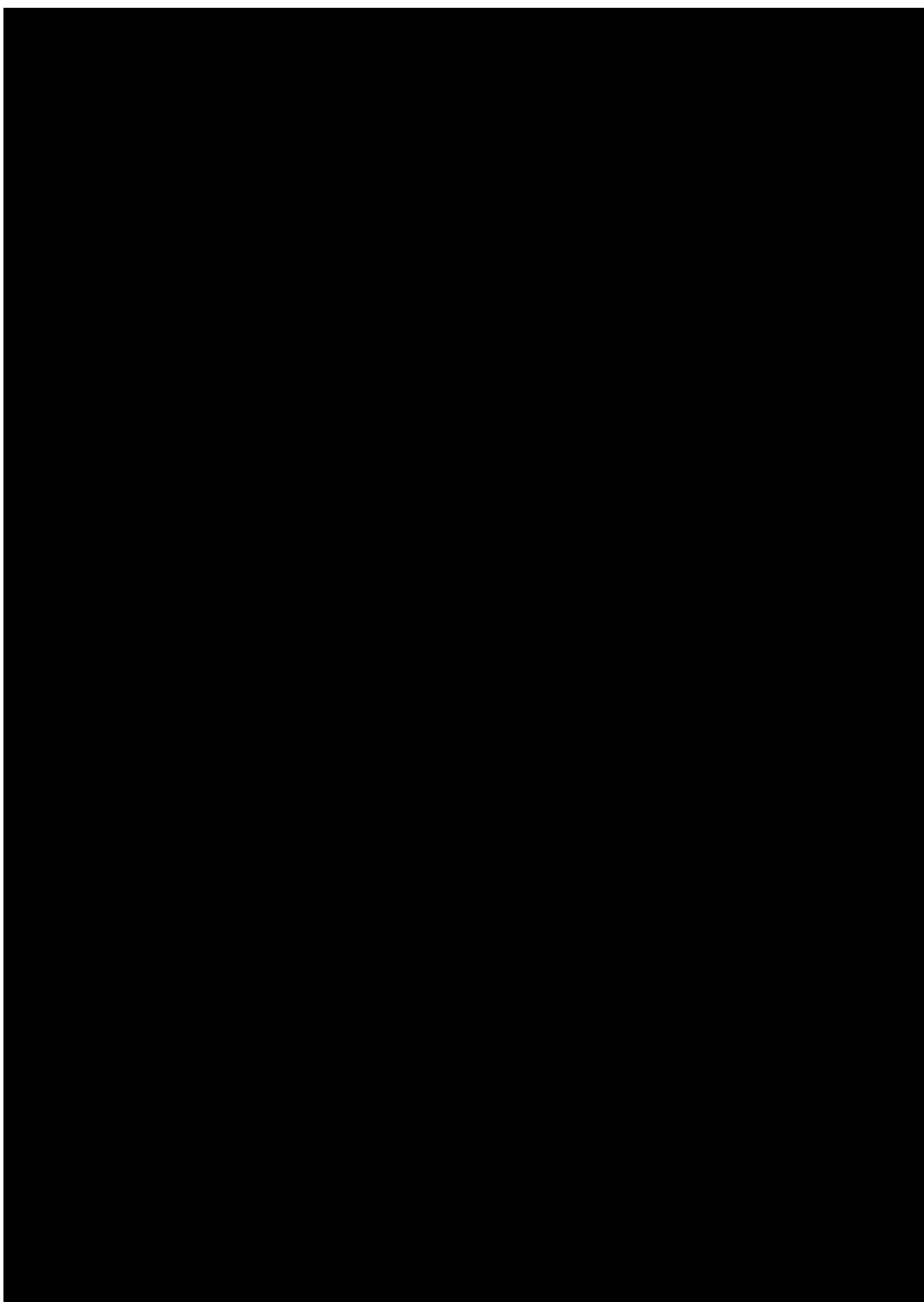
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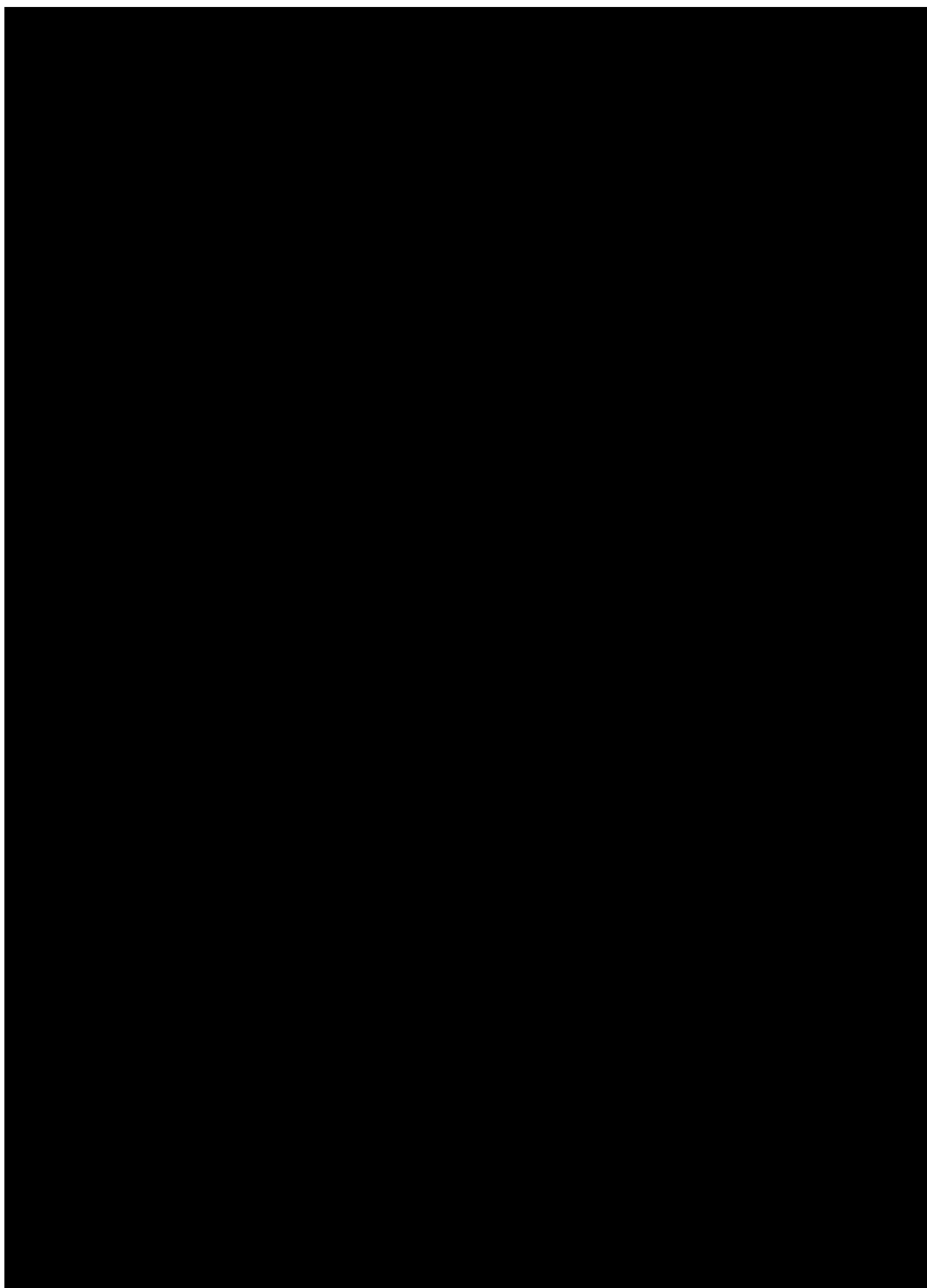
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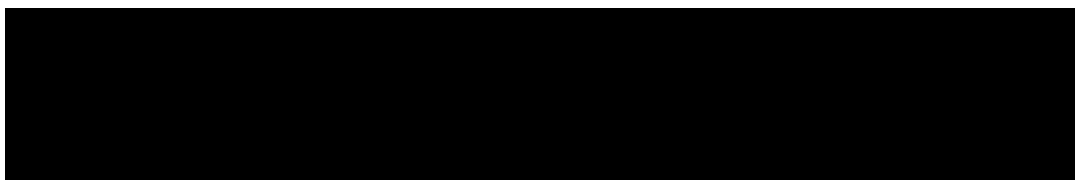
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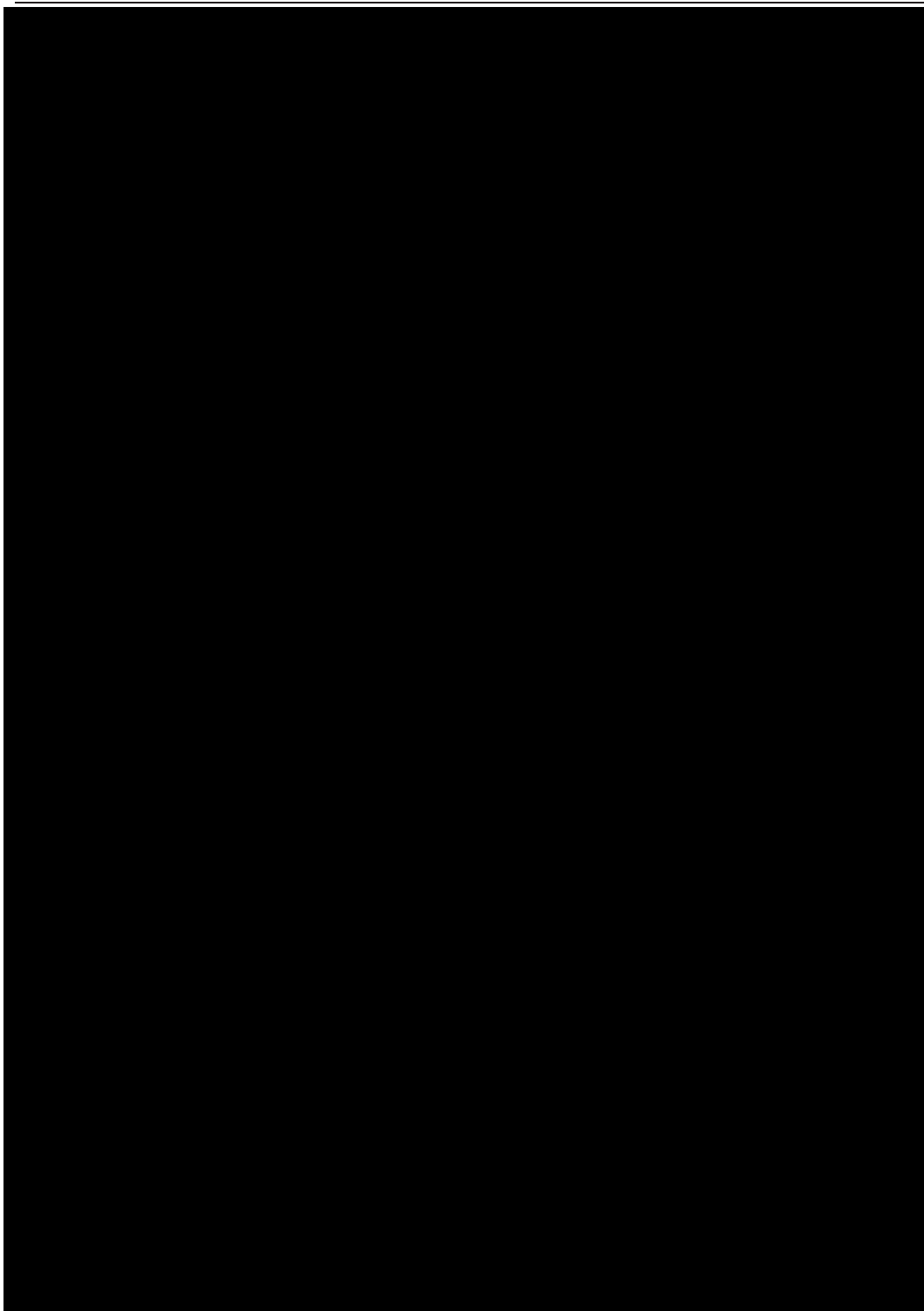
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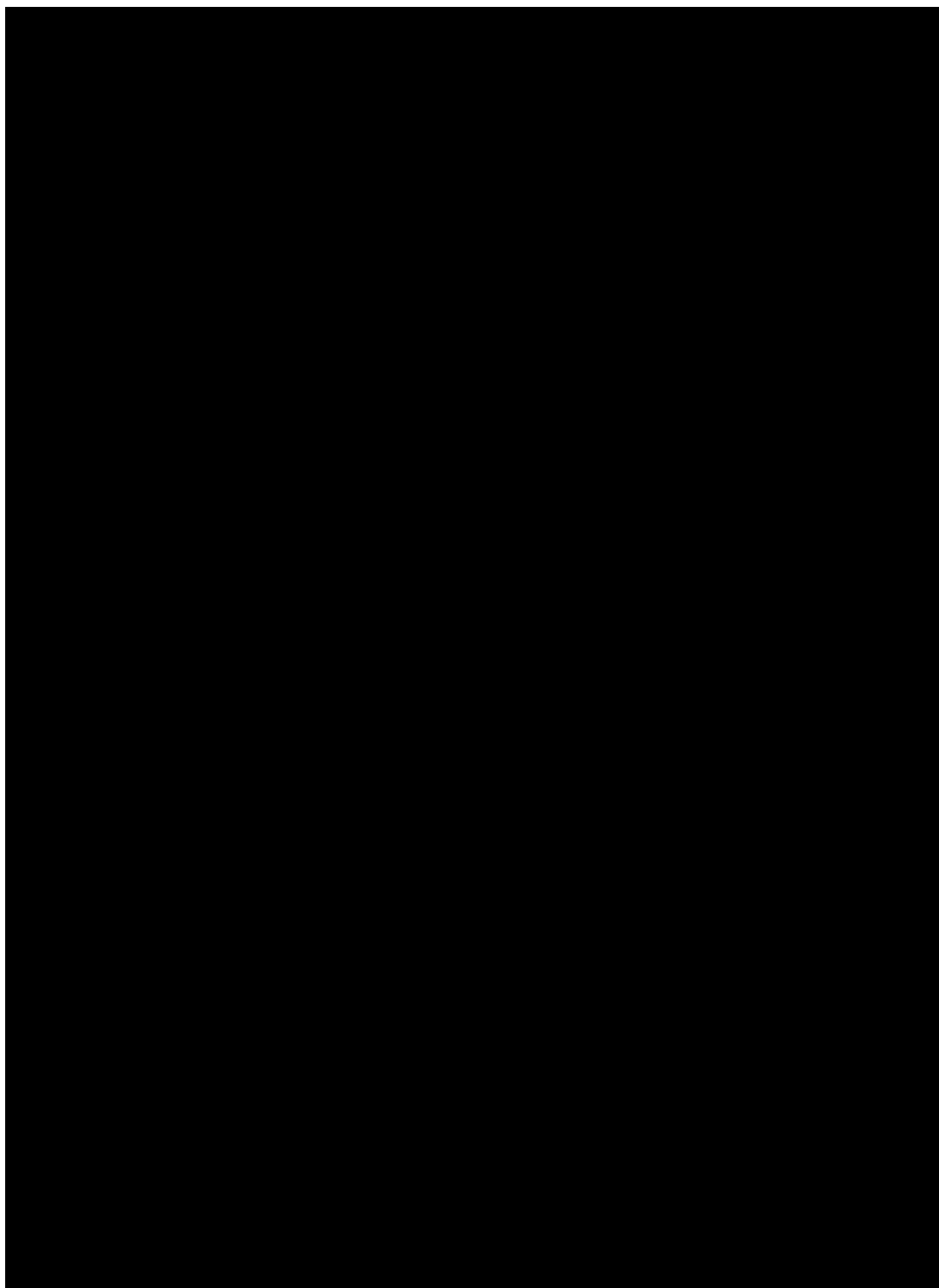
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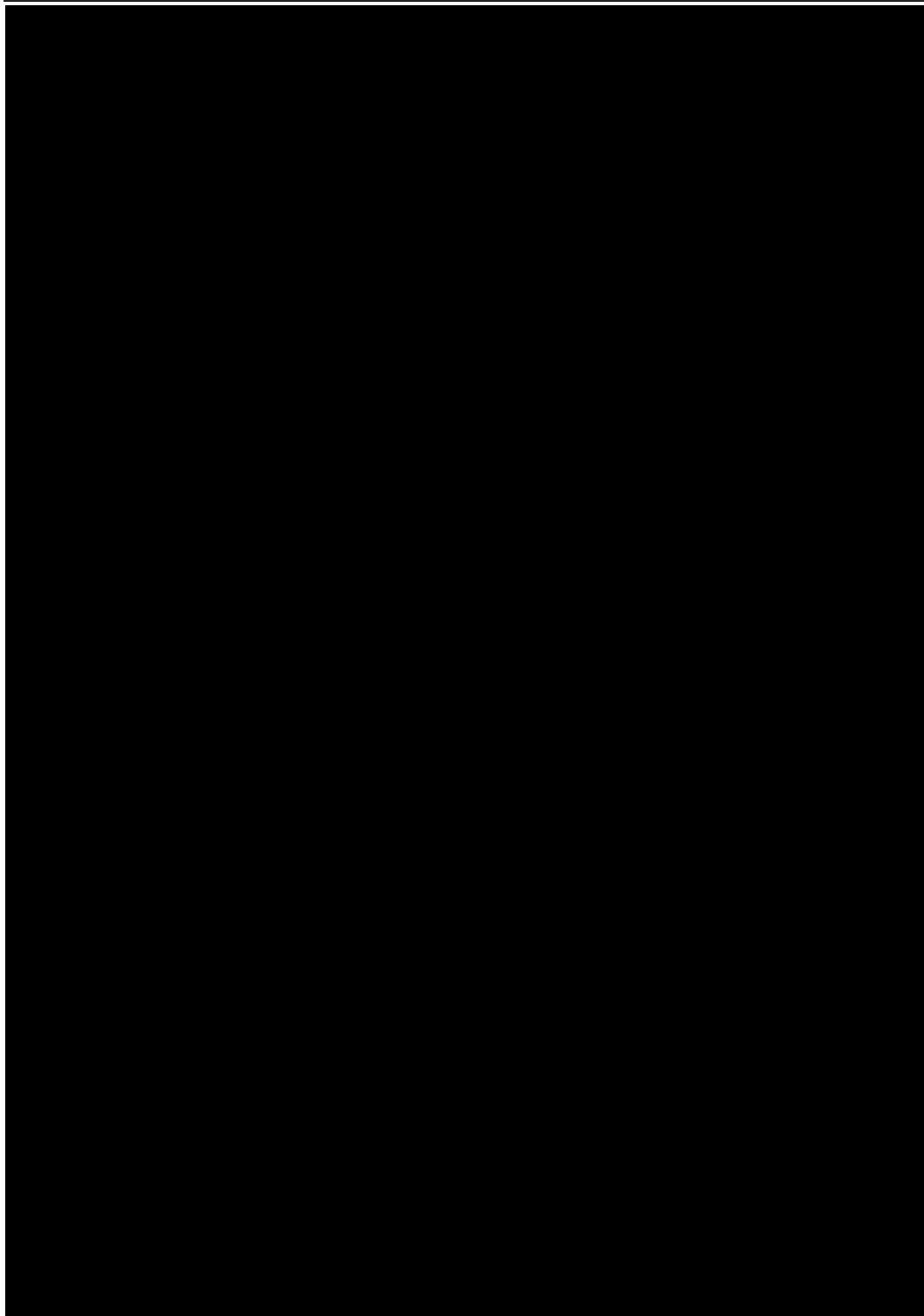
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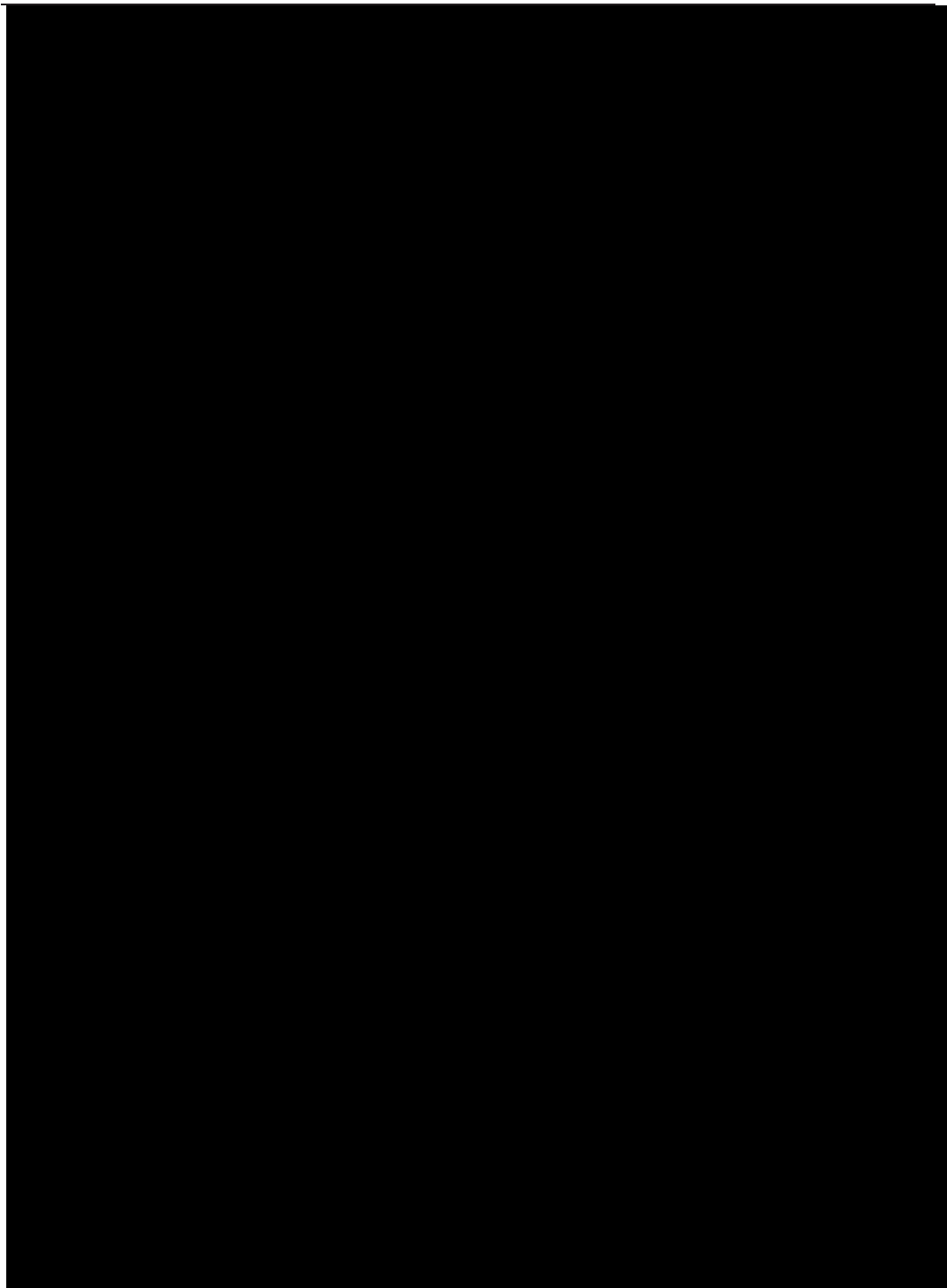
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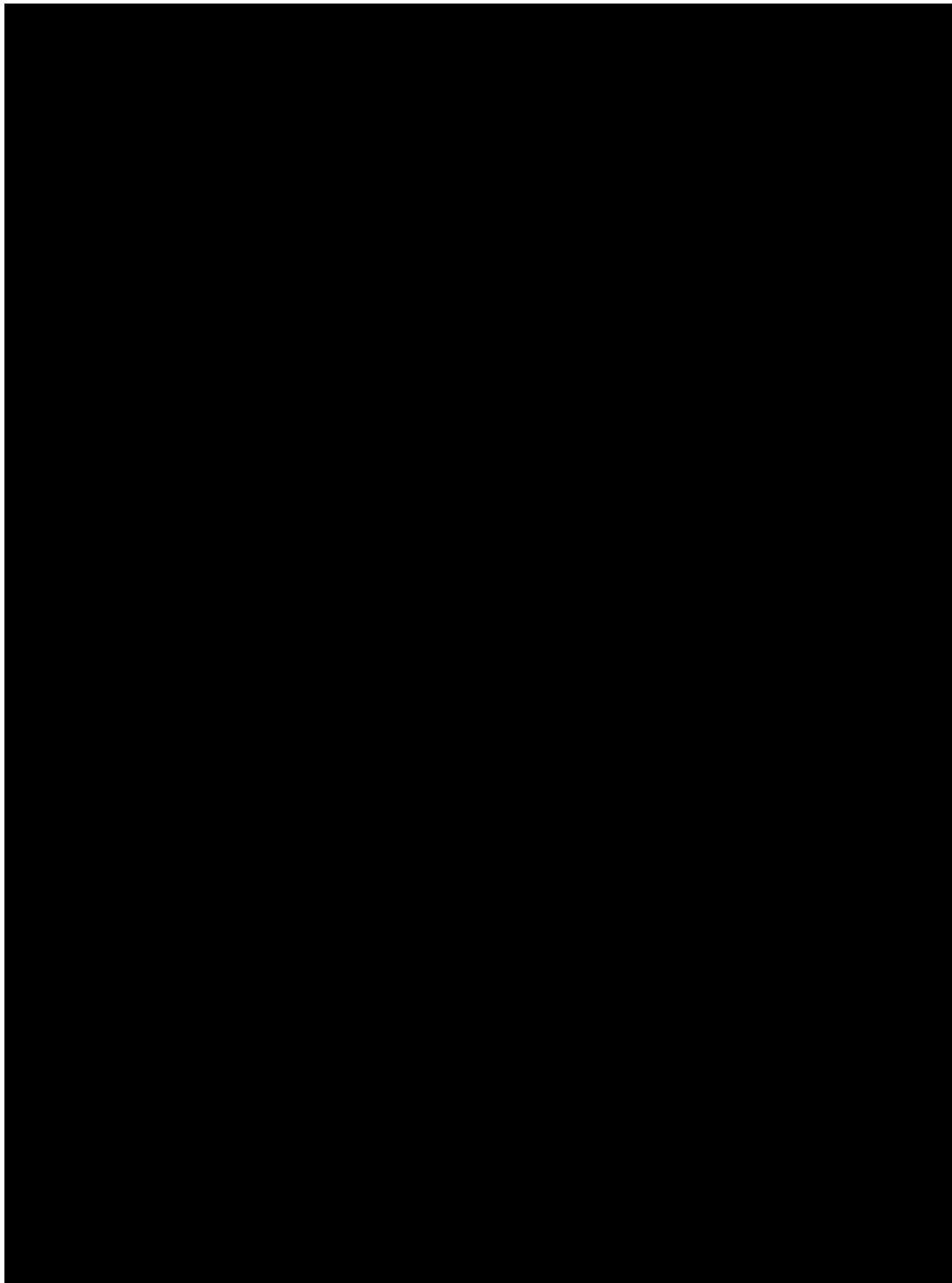
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**APPENDIX 4
INVESTIGATOR SIGNATURE PAGE**

I have read and agree to follow the study procedures as outlined in this protocol.

Investigator Name (Printed)

Investigator Signature

Date

CONFIDENTIAL - DO NOT COPY

This protocol contains confidential proprietary information with respect to Alcon products and clinical trials. I agree to hold this information in confidence and not to disclose it to any third parties for a period of three years from the date of this agreement, or until this information becomes a matter of public knowledge or until a formal agreement for that purpose has been entered into by the parties.

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**PROTOCOL TMI-09-01-E
VERSION G**

**AN OBSERVATIONAL MULTICENTER CLINICAL STUDY TO ASSESS THE LONG-TERM
SAFETY OF THE CYPASS MICRO-STENT IN PATIENTS WITH PRIMARY OPEN ANGLE
GLAUCOMA WHO HAVE COMPLETED PARTICIPATION IN THE COMPASS TRIAL
(TMI-09-01-E)**

THE COMPASS TRIAL EXTENSION (COMPASS-XT)

SPONSOR:

**ALCON LABORATORIES
6201 SOUTH FREEWAY
FORT WORTH, TX 76134-2099**

I have reviewed and approve the elements of this clinical study protocol.

[Redacted signature area]

26 October 2016
Date

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**PROTOCOL TMI-09-01-E
VERSION G**

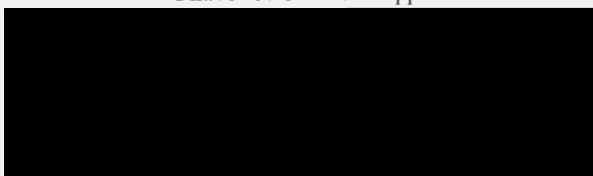
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THE COMPASS TRIAL EXTENSION (COMPASS-XT)

SPONSOR:

**ALCON LABORATORIES
6201 SOUTH FREEWAY
FORT WORTH, TX 76134-2099**

I have reviewed and approve the elements of this clinical study protocol.



27 Oct 2016
Date

**TRANSCEND CYPASS MICRO-STENT
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**PROTOCOL TMI-09-01-E
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SPONSOR:

**ALCON LABORATORIES
6201 SOUTH FREEWAY
FORT WORTH, TX 76134-2099**

I have reviewed and approve the elements of this clinical study protocol.

[Redacted signature]

11 Nov 2016
Date

**TRANSCEND CYPASS MICRO-STENT
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THE COMPASS TRIAL EXTENSION (COMPASS-XT)

SPONSOR:

**ALCON LABORATORIES
6201 SOUTH FREEWAY
FORT WORTH, TX 76134-2099**

I have reviewed and approve the elements of this clinical study protocol.

MD, COMPASS Study Medical Monitor

October 28, 2016

Date

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FORT WORTH, TX 76134-2099**

I have reviewed and approve the elements of this clinical study protocol.

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[Redacted signature block] M.D.

10/28/20

Date