CLINICAL PROTOCOL

Protocol Amendment 3 Version Date: 19 April 2017
Protocol Amendment 2 Version Date: 12 August 2016
Protocol Amendment 1 Version Date: 14 March 2016
Original Final Version Date: 16 February 2016

Open-Label Rollover Study for Continuing Valbenazine (NBI-98854) Administration for the Treatment of Tardive Dyskinesia

Protocol No.: NBI-98854-1506

Development Phase: 3b

Sponsor: Neurocrine Biosciences, Inc.
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SIGNATURES:

I agree to conduct this study in accordance with the requirements of this Clinical Protocol and also in accordance with the following:

- Established principles of Good Clinical Practices (GCP) (Harmonized)
- United States (US) Code of Federal Regulations (CFR); US Food and Drug Administration (FDA)

CLINICAL STUDY TITLE:

Open-Label Rollover Study for Continuing Valbenazine (NBI-98854) Administration for the Treatment of Tardive Dyskinesia

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As Agreed:

_____ _____

Principal Investigator Signature Date

PRINCIPAL INVESTIGATOR:

_____

(Print Principal Investigator Name)

SITE:

_____

(Print Site Name)

Accepted for the Sponsor:

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1. SYNOPSIS

Title of Study: Open-Label Rollover Study for Continuing Valbenazine (NBI-98854) Administration for the Treatment of Tardive Dyskinesia

Study Number: NBI-98854-1506

Study Centers: Approximately 40 centers in United States.

Objectives:

The objectives of this study are:

- To provide continued access to valbenazine for the treatment of tardive dyskinesia (TD) in approximately 150 subjects with schizophrenia, schizoaffective disorder or mood disorder who have completed a Phase 3 valbenazine study.
- To collect long-term safety and tolerability data in subjects receiving valbenazine (40 mg or 80 mg) administered once daily for up to 72 weeks (18 months).

Study Design: This rollover study will provide subjects who completed a Phase 3 valbenazine (NBI-98854) study open-label access to valbenazine for the treatment of TD until valbenazine is anticipated to be available commercially or they complete 72 weeks of treatment. In addition, this study is designed to collect long-term safety and tolerability data as well as subject-reported information following chronic administration of valbenazine in subjects with TD.

This is a rollover study with open-label, fixed-doses of valbenazine (40 mg or 80 mg) administered once daily (qd) for a total of up to 72 weeks of treatment. This study will allow enrollment of approximately 150 medically stable male and female subjects with TD who had previously participated in and completed the NBI-98854-1304 or NBI-98854-1402 Phase 3 study. Subjects can have their final NBI-98854-1304 or NBI-98854-1402 visit on the same day as Day 1 for this rollover study provided they sign the current study's informed consent before the final NBI-98854-1304 or NBI-98854-1402 visit. This will allow certain safety assessments to be used for both studies. The safety assessment results that can apply to both studies include physical examinations (including weight), vital signs, and electrocardiograms (ECG).

All subjects must sign an informed consent form (ICF) prior to the conduct of any study-related procedures, including washout of medications disallowed in the study. Before subjects can provide informed consent, the investigator (or designee) must determine whether the subject has the capacity to provide consent for participation using the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC). Only subjects who are deemed to have the capacity to provide consent may sign the ICF.

On Day 1, eligible subjects will receive a supply of valbenazine 40 mg qd for the first 4 weeks of the treatment period. On Day 2, valbenazine will be administered at home (in the presence of their caregiver, if applicable) in the morning or evening. After Day 2, the subject will be directed to take their dose at about the same time each day (eg, morning or evening).

At the end of Week 4, the investigator may escalate the subject's dose to 80 mg qd or continue with the subject's current dose (40 mg qd). A dose escalation will be allowed at the end of Week 4 based on the physician investigator's (or designee's) assessments of the safety and tolerability of valbenazine as well as clinical impression of TD.

At any time after dose escalation, the investigator may decrease the dose to 40 mg if the subject is unable to tolerate the dose increase. The subject will continue at this dose (40 mg) until the end of the treatment period (end of Week 72). Subjects who are unable to tolerate the starting dose of 40 mg or the resumption of 40 mg will be discontinued from the study.

Subjects will return to the clinical site every 4 weeks for assessments and dispensation of valbenazine. Subjects who do not want to continue in the study will be terminated from the study. The final assessments will be performed at the end of Week 72 or upon early termination. The clinic visits after Day 1 will have a visit window of -7 or +2 days.

Study Population: Approximately 150 medically stable adult male and female subjects with clinical diagnosis of schizophrenia or schizoaffective disorder with neuroleptic-induced TD or mood disorder with neuroleptic-induced TD will be enrolled. This study will only enroll subjects who express an interest in continuing to receive or re-initiate valbenazine and had previously participated in and completed the NBI-98854-1304 or NBI-98854-1402 study. Subjects must be psychiatrically stable as determined clinically by the physician investigator, including a Brief Psychiatric Rating Scale (BPRS) score of <50 at Day 1.

Duration of treatment and study participation: The expected duration of study participation for each subject is up to 72 weeks.

Investigational product, dosage, and mode of administration: Valbenazine will be supplied in capsule form containing 40 mg (free base equivalent) of NBI-98854 as the ditosylate salt. The doses that will be used in this study are: 40 mg qd taken as one valbenazine 40 mg capsule and 80 mg qd taken as two valbenazine 40 mg capsules. The subjects must swallow the capsules with at least 4 oz. of water and can take valbenazine with or without food. Valbenazine may be taken in the morning or evening. The subject will be directed to take their dose at about the same time each day. If treatment is interrupted for ≤5 missed consecutive doses, subjects are allowed to resume with their current dose regimen (40 mg qd or 80 mg qd). If treatment is interrupted for >5 missed consecutive doses, subjects should contact the investigator before resuming treatment; subjects deemed clinically stable by the investigator may resume with their current dose regimen (40 mg qd or 80 mg qd).

Reference therapy, dosage, and mode of administration: Not applicable.

Criteria for evaluation:

Efficacy:

- Clinical Global Impression of TD-severity (CGI-TD-severity) will be completed by the investigator at baseline (Day 1) and at the end of Weeks 12, 24, 36, 48, 60, and 72 or upon early termination.

Safety:

Safety and tolerability will be monitored throughout the study and will include the following assessments:

- Adverse events.
- Clinical laboratory tests (hematology, clinical chemistry, and urinalysis).
- Vital signs (including orthostatic blood pressure and pulse).
- Physical examinations.
- 12-lead electrocardiogram.
- Suicidal ideation and behavior – evaluated using the Columbia-Suicide Severity Rating Scale (C-SSRS).

Additional assessments:

- Patient Satisfaction Questionnaire will be completed by the subject at baseline (Day 1) and at the end of Weeks 12, 24, 36, 48, 60, and 72 or upon early termination.
- The Social Functioning Scale (SFS) will be completed by the subject at baseline (Day 1) and at the end of Weeks 12, 24, 36, 48, 60, and 72 or upon early termination.

Statistical methods: Efficacy, safety, tolerability, and additional assessments will be summarized using descriptive statistics.

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
β-hCG	β-human chorionic gonadotropin
BMI	Body mass index
BPRS	Brief Psychiatric Rating Scale
CDS	Clinical Drug Safety
CFR	Code of Federal Regulations
CGI-TD-severity	Clinical Global Impression of Tardive Dyskinesia-Severity
C_{max}	Maximum plasma concentration
CNS	Central nervous system
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
DSM	Diagnostic and Statistical Manual of Mental Disorders
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report forms
EDC	Electronic Data Capture
EDTA K_2	Dipotassium ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GGT	Gamma-glutamyl transferase
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
IUD	Intrauterine device
IWRS	Interactive Web Response System
MAOI	Monoamine oxidase inhibitors
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NBI	Neurocrine Biosciences, Inc.
OTC	Over the counter
qd	Once daily
QTcF	Corrected QT interval using Fridericia's formula
RDW	Red cell distribution width
SAE	Serious adverse event
SAP	Statistical analysis plan

SD	Standard deviation
SEM	Standard error of the mean
SFS	Social Functioning Scale
SOC	System organ class
TD	Tardive dyskinesia
TEAE	Treatment-emergent adverse event
UBACC	University of California, San Diego Brief Assessment of Capacity to Consent
UDS	Urine drug screen
ULN	Upper limit of normal
US	United States
VMAT2	Vesicular monoamine transporter 2
WBC	White blood cell
WHO Drug	World Health Organization Drug Dictionary

3. ETHICS

The study will be conducted in accordance with Neurocrine Biosciences, Inc. (NBI) standards that meet regulations relating to Good Clinical Practices (GCP). These standards respect the following guidelines:

- Good Clinical Practice: Consolidated Guideline (International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996).
- United States (US) Code of Federal Regulations (CFR) regulating clinical studies (21 CFR parts 50, 54, 56, 312, and 314).

The ethical requirements of Institutional Review Boards/Ethics Committees (IRBs/ECs) and the Informed Consent Forms (ICFs) are discussed in Section 13.

4. INTRODUCTION

4.1. Background

Tardive dyskinesia (TD) is a neurological condition characterized by involuntary movements of the orofacial region (ie, tongue, lips, jaw, face), limbs, and trunk. TD develops with chronic neuroleptic drug use and often persists after discontinuation of the offending medication. Only a small proportion of patients who are treated with dopamine receptor blocking drugs develop this syndrome. While isolated case reports of TD after short-term exposure exist, most often TD emerges after long-term neuroleptic treatment over months to years. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines chronic exposure to neuroleptics and duration of symptoms as the basis for TD diagnosis. In addition to duration and amount of neuroleptic exposure, other risk factors for TD appear to include older age, schizophrenia, and cognitive impairment (Margolese et al, 2005). TD can be disabling, lead to bodily harm (eg, lip or tongue lacerations, falls), interfere with activities of daily living, and result in social isolation.

The pathophysiology of TD is not fully understood; however, post-synaptic dopamine hypersensitivity in the striatum is the most prominent feature (Margolese et al., 2005). Dysregulation of dopaminergic systems is an integral component of several CNS disorders, including other hyperkinetic movement disorders and conditions such as schizophrenia and bipolar disorder. The transporter protein vesicular monoamine transporter 2 (VMAT2) plays an important role in presynaptic dopamine release, regulating monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release. The differential expression of VMAT2 in human brain (versus endocrine tissue) makes agents that selectively target VMAT2 potentially useful for the treatment of CNS disorders (Weihe and Eiden, 2000).

4.2. Valbenazine (NBI-98854)

NBI-98854 (valbenazine tosylate) is a highly selective, orally active VMAT2 inhibitor and is currently under development at Neurocrine Biosciences, Inc. (NBI) for the treatment of tardive dyskinesia (TD) and Tourette syndrome (TS).

In nonclinical studies, NBI-98854 appears to cause little or no cytochrome P450 (CYP) enzyme inhibition or induction at pharmacologically relevant concentrations. Metabolism of NBI-98854 is characterized by hydrolysis of NBI-98854 to NBI-98782, and CYP3A4/5-dependent mono-oxidation to NBI-136110. All 3 entities, namely, NBI-98854, NBI-98782, and NBI-136110, have the ability to bind to and inhibit VMAT2. However, NBI-98782 is the most potent and appears to be responsible for the majority of the observed pharmacological activity of VMAT2 inhibition. NBI-98854 delivers NBI-98782 in a controlled fashion with limited peak-to-trough plasma concentration fluctuation and low pharmacokinetic (PK) variability that should limit adverse events (AEs) associated with excessive monoamine depletion. Repeat-dose nonclinical toxicology studies conducted in mice, rats, and dogs have revealed no adverse effects at doses of 60 mg/kg/day in the mouse, 3 mg/kg/day in the rat and 15 mg/kg/day in the dog. Additionally, cardiovascular, pulmonary, and central nervous system (CNS) safety pharmacology studies have also been conducted, where the no observed adverse effect level (NOAEL) was equal to or exceeded the 15 mg/kg level seen in repeat dose toxicology studies. NBI-98854 had a modest negative effect on rat fertility at 10 mg/kg/day (NOAEL of 3 mg/kg/day). The NOAEL for embryo/fetal development in rats and rabbits was 15 mg/kg/day and 50 mg/kg/day, respectively. There was no evidence of teratogenicity in rats or rabbits. Finally, NBI-98854 was negative in in vitro mutagenicity assays (namely, Ames and chromosomal aberration) and an in vivo rat micronucleus test.

Thirteen clinical studies with NBI-98854 have been completed to date: 9 Phase 1 studies, 8 in healthy male and female elderly and nonelderly subjects, and 1 in hepatically impaired adults; and 4 Phase 2 studies in subjects with TD and a clinical diagnosis of schizophrenia or schizoaffective disorder, mood disorder, or gastrointestinal (GI) disorder. In addition, preliminary data are available for the 6-week, placebo-controlled period for the ongoing Phase 3 study NBI-98854-1304 in subjects with TD and a clinical diagnosis of schizophrenia or schizoaffective disorder, or mood disorder. A total of 510 subjects have received at least 1 dose of NBI-98854 and 246 received placebo in these studies.

Clinical PK data indicate that when administered orally under fasted conditions, NBI-98854 appeared to be rapidly absorbed with maximum plasma concentration being reached within 1 hour. An active metabolite, NBI-98782, was formed gradually with maximum plasma concentration typically being reached 4 to 10 hours after dosing. Plasma concentrations for both NBI-98854 and NBI-98782 appeared to decline after reaching maximal concentration and both exhibited an apparent terminal half-life of approximately 20 hours in non-elderly adult subjects and 23 to 28 hours in elderly subjects. Coadministration of ketoconazole (strong CYP3A4/5 inhibitor) with NBI-98854 caused an approximate 1.5- and 1.7-fold increase in C_{max} of NBI-98854 and NBI-98782, respectively. Coadministration of NBI-98854 and rifampin (strong CYP3A4/5 inducer) led to an approximate 29% and 72% decrease in C_{max} and $AUC_{0-\infty}$, respectively, for NBI-98854, and an approximate 50% and 77% decrease, respectively, for NBI-98782 compared with administration of NBI-98854 alone. For NBI-136110, concomitant administration with rifampin led to a 50% increase in C_{max} and a 68% decrease in $AUC_{0-\infty}$ compared with administration of NBI-98854 alone. Administration in subjects with hepatic impairment resulted in a C_{max} of NBI-98854 of 1.46- and 1.65-fold greater in subjects with moderate and severe hepatic impairment, respectively, than in subjects with normal hepatic function.

NBI-98854 has been generally well tolerated in single doses up to 300 mg and in multiple doses of up to 100 mg. In Phase 2 studies and the interim analysis from one Phase 3 study, treatment-emergent adverse events (TEAEs) were reported by 42.8% and 36.4% of NBI-98854 and placebo subjects, respectively. AEs reported in ≥2% of NBI-98854 subjects and at a higher incidence than placebo included somnolence, headache, fatigue, vomiting, dry mouth, akathisia, and fall. Suicidal ideation was reported in a similar percentage of subjects receiving NBI-98854 or placebo (2.0% and 1.9%, respectively). Most TEAEs were mild or moderate in intensity. Two deaths have been reported in clinical studies; 1 subject who received placebo died due to cardiopulmonary arrest secondary to myocardial infarction and the second subject died possibly due to a cardiovascular event (treatment remains blinded). No treatment-emergent serious AEs (SAEs) have been reported in Phase 1 studies. In Phase 2 studies and the interim analysis from one Phase 3 study, SAEs were reported in 17 subjects (4.9%) who received NBI-98854 and 6 subjects (2.8%) who received placebo. There were no clinically important differences in the number or types of SAEs reported across dose groups. Only 1 SAE (acute hepatitis) was assessed by the investigator as possibly related to study drug. No cardiovascular, laboratory, or vital sign related safety signals have been identified. Increases in serum prolactin above normal laboratory ranges have been noted, but there have been no TEAEs associated with hyperprolactinemia. In general, depression, drug-induced akathisia, and drug-induced parkinsonism did not worsen during treatment with NBI-98854.

Results from Phase 2 studies indicated an improvement in the Abnormal Involuntary Movement Scale (AIMS) score after 6 weeks of continuous dosing with either NBI-98854 50 mg once daily, continuous dosing with NBI-98854 100 mg once daily for 2 weeks followed by continuous dosing with NBI-98854 50 mg once daily for 4 weeks (NBI-98854-1201; preliminary data), 6 weeks of titrated doses from 25 mg up to 75 mg NBI-98854 once daily (NBI-98854-1202). Preliminary results from the 6-week placebo-controlled treatment period in the Phase 3 study (NBI-98854-1304) indicated a statistically significant improvement in the AIMS dyskinesia total score mean change from baseline for the NBI-98854 80 mg group compared with placebo. Similar results were also observed for the NBI-98854 40 mg group. Results from an open-label safety extension with dosing up to 12 weeks (NBI-98854-1201) showed continued benefit in subjects who continued taking NBI-98854 50 mg daily and also in subjects originally assigned to placebo who went on to receive NBI-98854 50 mg once daily for the 6 weeks of open-label treatment. Results from the 6 week dose-titration study (NBI-98854-1202) showed a statistically significant reduction in the AIMS dyskinesia total score in the NBI-98854 group compared to placebo. A statistically significant higher responder rate (ie, ≥50% improvement in AIMS dyskinesia total score from baseline) was also observed in the NBI-98854 group compared with placebo.

4.3. Study and Dose Rationale

All subjects in the current study will have previously received valbenazine 40 mg to 80 mg for 42 to 48 weeks in a Phase 3 valbenazine study (NBI-98854-1304 or NBI-98854-1402). In the current study, subjects will receive a starting dose of valbenazine 40 mg once daily (qd) for 4 weeks. At the end of Week 4, the investigator may escalate the subject's dose to 80 mg qd or continue with the subject's current dose (40 mg qd). A dose escalation will be allowed at the end of Week 4 based on the physician investigator's (or designee's) assessments of the safety and tolerability of valbenazine as well as clinical impression of TD.

At any time after dose escalation, the investigator may decrease the dose to 40 mg if the subject is unable to tolerate the dose increase. The subject will continue at this dose (40 mg) until the end of the treatment period (end of Week 72). Subjects who are unable to tolerate the starting dose of 40 mg or the resumption of 40 mg will be discontinued from the study.

Clinical data from TD subjects administered repeated doses of valbenazine from 12.5 mg to 100 mg per day indicate that valbenazine is generally well tolerated and associated with dose-related efficacy. Exposure-response analysis indicates that a steady state maximum plasma concentration (C_{max}) of 20 to 40 ng/mL NBI-98782 is an appropriate plasma concentration range for efficacy.

Valbenazine doses of 40 mg and 80 mg are associated with exposure to the active metabolite, NBI-98782, in the target range of 20 to 40 ng/mL when administered initially as 40 mg qd and adjusted upward to 80 mg qd if dyskinesia persists after several weeks of treatment. These doses have been selected to provide exposure associated with acceptable tolerability and robust efficacy. Doses below 40 mg are well tolerated but offer dyskinesia reduction comparable to placebo. Doses above 80 mg afford little incremental benefit but increase the risk of adverse events (AEs) reflecting extension of VMAT2 pharmacology. Because many subject-specific factors appear to influence tolerability and efficacy, clinicians will be required to start all subjects at 40 mg, the lower of the two doses.

5. STUDY OBJECTIVES

The objectives of this study are:

- To provide continued access of valbenazine for the treatment of tardive dyskinesia (TD) in approximately 150 subjects with schizophrenia, schizoaffective disorder or mood disorder who have completed a Phase 3 valbenazine study.
- To collect long-term safety and tolerability data in subjects receiving valbenazine (40 mg or 80 mg) administered once daily for up to 72 weeks (18 months).

6. STUDY DESIGN

This rollover study will provide subjects who completed a Phase 3 valbenazine study open-label access to valbenazine for the treatment of TD until valbenazine is anticipated to be available commercially or they complete 72 weeks of treatment. In addition, this study is designed to collect long-term safety and tolerability data as well as subject-reported information following chronic administration of valbenazine in subjects with TD.

This is a rollover study with open-label, fixed-doses of valbenazine (40 mg qd or 80 mg qd) for a total of up to 72 weeks of treatment. This study will allow enrollment of approximately 150 medically stable male and female subjects with TD who had previously participated in and completed the NBI-98854-1304 or NBI-98854-1402 Phase 3 study. Subjects can have their final NBI-98854-1304 or NBI-98854-1402 visit on the same day as Day 1 for this rollover study provided they sign the current study's informed consent before the final NBI-98854-1304 or NBI-98854-1402 visit. This will allow certain safety assessments to be used for both studies. The safety assessment results that can apply to both studies include physical examinations

(including weight), vital signs, and electrocardiograms (ECG). Other Day 1 assessments (including safety labs) must be collected for the current study (even if the subject is completing the final visit for the previous study). The study will be conducted in approximately 40 centers in the US. A schematic of the study design is shown in Figure 1.

All subjects must sign an ICF prior to the conduct of any study-related procedures, including washout of medications disallowed in the study. Before subjects can provide informed consent, the investigator (or designee) must determine whether the subject has the capacity to provide consent for participation using the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC; Jeste et al., 2007). A copy of the UBACC is provided in Appendix 16.1. Only subjects who are deemed to have the capacity to provide consent may sign the ICF.

On Day 1, eligible subjects will receive a supply of valbenazine 40 mg qd for the first 4 weeks of the treatment period. On Day 2, valbenazine will be administered at home (in the presence of their caregiver, if applicable) in the morning or evening. After Day 2, the subject will be directed to take their dose at about the same time each day (eg, morning or evening).

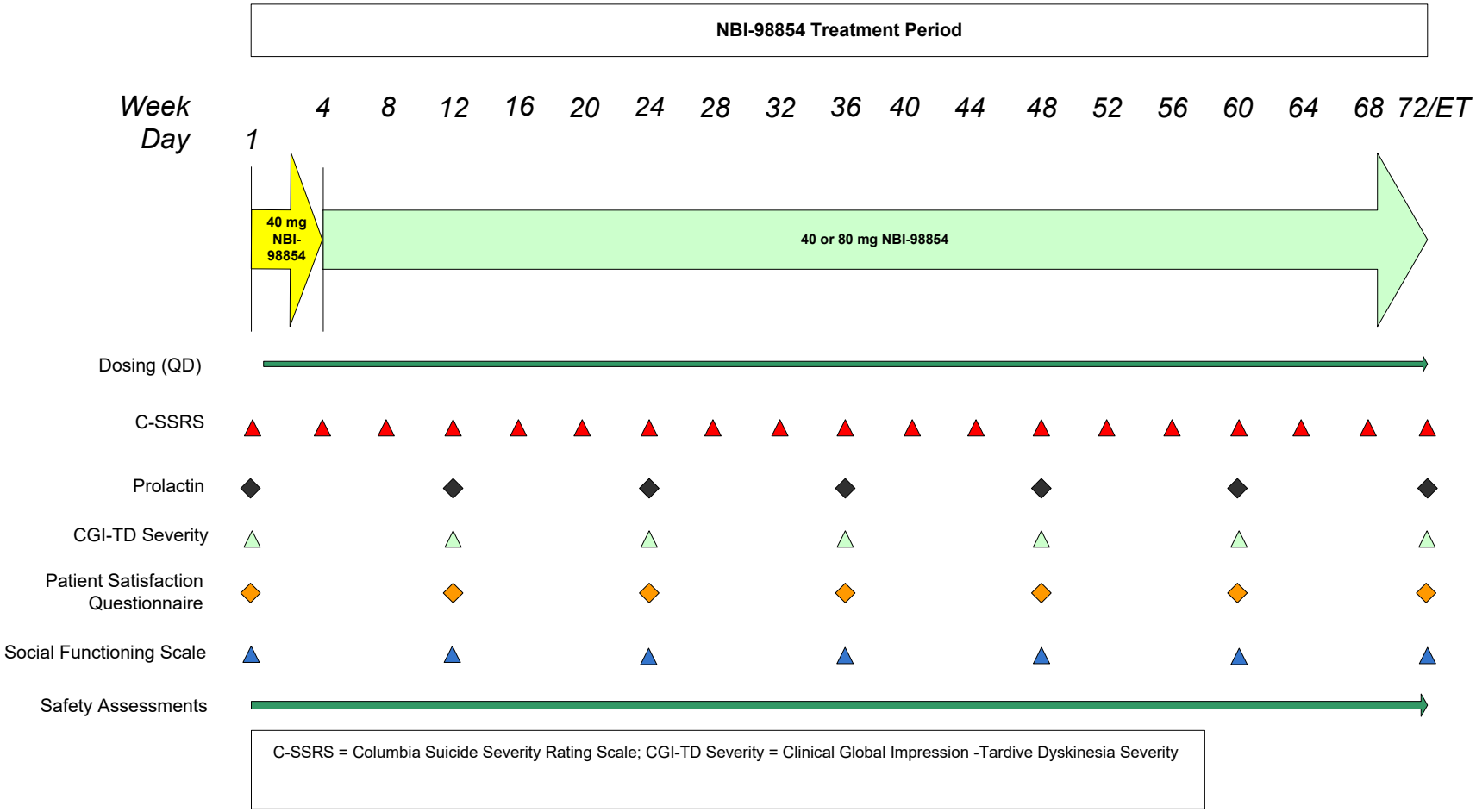
At the end of Week 4, the investigator may escalate the subject's dose to 80 mg qd or continue with the subject's current dose (40 mg qd). A dose escalation will be allowed at the end of Week 4 based on the physician investigator's (or designee's) assessments of the safety and tolerability of valbenazine as well as clinical impression of TD.

At any time after dose escalation, the investigator may decrease the dose to 40 mg if the subject is unable to tolerate the dose increase. The subject will continue at this dose (40 mg) until the end of the treatment period (end of Week 72). Subjects who are unable to tolerate the starting dose of 40 mg or the resumption of 40 mg will be discontinued from the study. If treatment is interrupted for ≤5 missed consecutive doses, subjects are allowed to resume with their current dose regimen (40 mg qd or 80 mg qd). If treatment is interrupted for >5 missed consecutive doses, subjects should contact the investigator before resuming treatment; subjects deemed clinically stable by the investigator may resume with their current dose regimen (40 mg qd or 80 mg qd).

Subjects will return to the clinical site every 4 weeks for assessments and dispensation of valbenazine. Subjects who do not want to continue in the study will be terminated from the study. The final assessments will be performed at the end of Week 72 or early termination.

The clinic visits after Day 1 will have a visit window of -7 or +2 days.

Figure 1: Study Design Schematic



7. STUDY POPULATION

This study will include approximately 150 medically stable adult male and female subjects with clinical diagnosis of schizophrenia or schizoaffective disorder with neuroleptic-induced TD or mood disorder with neuroleptic-induced TD. This study will only enroll subjects who express an interest in continuing to receive or re-initiate valbenazine and had previously participated in and completed the NBI-98854-1304 or NBI-98854-1402 study. Subjects must be psychiatrically stable as determined clinically by the physician investigator, including a Brief Psychiatric Rating Scale (BPRS) score of <50 at Day 1.

7.1. Subject Inclusion Criteria

To participate in this study, subjects must meet the following criteria:

1. Be male or female aged 18 to 85 years (inclusive).
2. Have participated in and completed the NBI-98854-1304 or NBI-98854-1402 Phase 3 study. Subjects can have their final NBI-98854-1304 or NBI-98854-1402 visit on the same day as Day 1 for this rollover study provided they sign the current study's informed consent before the final NBI-98854-1304 or NBI-98854-1402 visit.
3. Subjects of childbearing potential must agree to use hormonal or two forms of nonhormonal contraception (dual contraception) consistently throughout the study and until 30 days after the last dose of valbenazine.

Acceptable methods of contraception include the following:

- Condom with spermicide (cream, spray, foam, gel, suppository, or polymer film).
- Diaphragm with spermicide (with or without condom).
- Cervical cap with spermicide (with or without condom).
- Vaginal sponge impregnated with spermicide used with a condom.
- Intrauterine device (IUD).
- Hormonal contraception taken for at least 3 months prior to Day 1.

The following subjects are not required to use contraception:

- Subjects who practice total abstinence from sexual intercourse as the preferred lifestyle (periodic abstinence is not acceptable).
- Female subjects with partners or male subjects who had been vasectomized at least 3 months prior to Day 1.
- Female subjects who have been postmenopausal for at least 1 year prior to Day 1.
- Female subjects who are surgically sterile (ie, bilateral oophorectomy, hysterectomy, or bilateral tubal ligation) at least 3 months prior to Day 1.

4. Female subjects who have not been postmenopausal for at least 1 year must have a negative urine pregnancy test on Day 1.

5. Maintenance medication(s) for schizophrenia or schizoaffective disorder, mood disorders, and other nonprohibited concurrent medications (see Section 8.8.1) should be at a stable dose (including no changes to the dose and frequency of ongoing medications and no discontinuation of medications) for a minimum of 30 days before Day 1. Benzodiazepines must be at a stable dose for 2 weeks before Day 1. This criterion will be satisfied if the investigator can confirm prior and current medications and doses through reliable subject-reported information (eg, subject provides a list of medications and doses).
6. Subjects with a diagnosis of schizophrenia or schizoaffective disorder who are not using antipsychotic medication must have a stable psychiatric status as clinically determined by the investigator. Subjects with a diagnosis of bipolar disorder must be on stable dose of mood stabilizer(s) (eg, lithium, valproate, or olanzapine) for a minimum of 30 days before Day 1.
7. Be in good general health and expected to complete the study as designed.
8. Have a body mass index (BMI) of 18 to 42 kg/m^2 (inclusive) on Day 1. (BMI is defined as the subject's weight in kg divided by the square of the subject's height in meters.)
9. Have adequate hearing, vision, and language skills to perform the procedures specified in the protocol.
10. Have voluntarily provided informed consent and have signed an ICF indicating that the purpose of the study has been explained, and are willing and able to adhere to the study regimen and procedures described in the ICF. Subjects must also have been deemed capable of providing consent to study participation using the UBACC prior to signing the ICF.
11. Have a negative urine drug screen (UDS) (negative for amphetamines, barbiturates, benzodiazepine, phencyclidine, cocaine, opiates, and cannabinoids) at Day 1 (UDS kit results conducted at the clinical site), except for any subject receiving a stable dose of barbiturates, benzodiazepines, or opiates. Subjects with positive cannabinoid results may be allowed to participate in the study provided that the subject is given thorough counseling and agrees to refrain from using cannabinoids for the duration of his/her study participation.
12. Have a negative alcohol breath test on Day 1.
13. Be willing to provide authorization for access to personal health information in conjunction with US Health Insurance Portability and Accountability Act (HIPAA).

7.2. Subject Exclusion Criteria

Subjects will be excluded from the study if they:

1. Have an active clinically significant unstable medical condition within 30 days prior to Day 1.
2. Have history of severe hepatic impairment or have chronic elevation of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5 times upper limit of normal (ULN).
3. Have clinically significant parkinsonism (eg, tremor, rigidity, bradykinesia, balance/gait issues) as assessed by the investigator.

4. Have a known history of substance dependence, or substance (drug) or alcohol abuse within 3 months prior to Day 1 (nicotine and caffeine dependence are not exclusionary), as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) (eg, DSM-IV).
5. Have a significant risk of suicidal or violent behavior. Subjects with any suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the Columbia-Suicide Severity Rating Scale (C-SSRS) in the 3 months prior to Day 1 (using Screening/Baseline version) will be excluded.
6. Have BPRS total score of ≥50 on Day 1.
7. Have a known history of neuroleptic malignant syndrome.
8. Have a known history of long QT syndrome or cardiac arrhythmia.
9. Have an electrocardiogram (ECG) QT interval corrected for heart rate using corrected QT interval using Fridericia's formula (QTcF) of >450 msec (males) or >470 msec (females) on Day 1 or the presence of any clinically significant cardiac abnormality.
10. Receive any excluded concomitant medication.
11. Have a hematologic malignancy or solid tumor diagnosed within 3 years prior to Day 1, with the exception of localized skin cancer or carcinoma in situ of the cervix.
12. Have received an investigational drug (other than valbenazine) within 30 days prior to Day 1 or plan to use an investigational drug (other than valbenazine) during the study.
13. Have a blood loss ≥550 mL or donated blood within 30 days prior to Day 1.
14. Have an allergy, hypersensitivity, or intolerance to tetrabenazine.
15. Are currently pregnant or breastfeeding.

7.3. Subject Identification and Replacement of Subjects

Subjects will be identified by their unique subject number and initials (first, middle, last). The subject initials and subject number will be noted on electronic case report forms (eCRFs), all source documentation, laboratory documents, and ECG tracings. Subjects who discontinue from the study after the initiation of dosing will not be replaced.

7.4. Randomization

Subjects will not be randomized in this study.

8. EVALUATIONS

8.1. Schedule of Assessments

Table 1 summarizes the frequency and timing of all study assessments and procedures. Subjects will provide written informed consent before any study-related procedures are performed, including the cessation of prohibited concomitant medications. Subject-related activities and events including specific instructions, procedures, concomitant medications, dispensing of

valbenazine, and descriptions of AEs will be recorded in the appropriate source documents and eCRFs.

Table 1: Schedule of Assessments

Procedure	Baseline	Open-Label Valbenazine Treatment Period																		
Week[a]	Day 1[b]	DAY 2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72/ET[c]
Visit[a]	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Informed consent/ UBACC	X																			
Inclusion/exclusion criteria	X																			
Medical and surgical history	X																			
Physical examination (including weight)	X				X			X			X			X			X			X
Height	X																			
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead electrocardiogram[d]	X		X		X			X			X			X			X			X
Pregnancy test[e]	X (S,U)		X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)	X (U)
Clinical laboratory tests[f]	X				X			X			X			X			X			X
Urine drug screen[g]	X																			
Alcohol breath test	X																			
Serum prolactin	X				X			X			X			X			X			X
BPRS	X																			
C-SSRS[h]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-TD-severity	X				X			X			X			X			X			X
Patient Satisfaction Questionnaire	X				X			X			X			X			X			X
Social Functioning Scale	X				X			X			X			X			X			X
Daily valbenazine dosing at home[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense valbenazine[j]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Valbenazine accountability[k]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event monitoring	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Outpatient clinic visit	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations and footnotes appear on the following page.

Definitions: BPRS=Brief Psychiatric Rating Scale; CGI-TD-severity=Clinical Global Impression of Tardive Dyskinesia-Severity; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; QTcF=corrected QT interval using Fridericia's formula; S=serum; U=urine; UBACC=University of California, San Diego Brief Assessment of Capacity to Consent.

[a] The visits after Day 1 will have a visit window of -7 or +2 days.

[b] For subjects completing the final NBI-98854-1304 or NBI-98854-1402 visit on the same day as Day 1, the NBI-98854-1304 or NBI-98854-1402 assessments for physical examination (including weight), vital signs, and ECG will be used for Day 1.

[c] Final visit for subjects who complete the study (or early termination).

[d] A standard 12-lead ECG will be conducted after the subject has rested supine for at least 5 minutes. The ECG parameters that will be assessed include heart rate, QT interval, QTcF, PR interval, and QRS duration based on the ECG machine readings.

[e] Pregnancy tests are only required for female subjects who are not postmenopausal for at least 1 year prior to Day 1. Urine and serum pregnancy tests will be conducted at Day 1. The urine pregnancy test result on Day 1 will be used to confirm eligibility.

[f] Clinical laboratory tests include hematology, clinical chemistry, and urinalysis. All blood samples will be obtained under non-fasted conditions.

[g] Urine drug screen (UDS) collected on Day 1 will be analyzed by the central lab. In addition, a UDS kit provided by the central lab will be used at the clinical site to confirm eligibility on Day 1. A UDS using a kit provided by the central lab may be conducted at the clinical site at any time during the study if the subject is suspected of substance or drug abuse.

[h] The "Screening/Baseline" version should be used at baseline (Day 1) and "Since Last Visit" version should be used at all subsequent visits.

[i] Starting on Day 2, subjects will self-administer valbenazine daily (in the morning or evening, at approximately the same time each day) at home in the presence of their caregiver (if applicable).

[j] Subjects will receive a 4-week supply of valbenazine on Day 1 and will need to return to clinical site every 4 weeks to obtain a 4-week supply of valbenazine.

[k] At the end of Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72 subjects will return all unused valbenazine, and a compliance check will be performed by counting the capsules returned at the visit.

8.2. Baseline Assessments

8.2.1. Brief Psychiatric Rating Scale (BPRS)

The BPRS is a clinician-rated tool designed to assess the severity of psychopathology in patients with schizophrenia and other psychotic disorders (Overall and Gorham, 1962, 1988). The BPRS includes 18 items that address somatic concern, anxiety, emotional withdrawal, conceptual disorganization, guilt feelings, tension, mannerisms and posturing, grandiosity, depressive mood, hostility, suspiciousness, hallucinatory behaviors, motor retardation, uncooperativeness, unusual thought content, blunt affect, excitement, and disorientation.

The severity of each of the 18 items of the BPRS is rated on a scale of 1 (not present) to 7 (extremely severe) (total score range: 18 to 126). Higher scores represent greater symptom severity.

The investigator or other qualified clinical site personnel will administer and score the scale at baseline (Day 1), and subjects must have a BPRS total score <50 to be eligible for study participation (see exclusion criterion #6). A copy of the BPRS is provided in Appendix 16.2.

8.3. Efficacy Assessment

8.3.1. Clinical Global Impression of Tardive Dyskinesia-Severity (CGI-TD-severity)

The CGI-TD-severity, which is based on a 7-point scale (range: 1=normal, not at all ill to 7=among the most extremely ill patient), will be used to rate the overall global severity of TD. This scale is a modification of a scale developed by the Psychopharmacology Research Branch of the National Institute of Mental Health (Guy, 1976). A copy of the CGI-TD-severity is provided in Appendix 16.3.

The investigator or qualified clinician designee (eg, psychologist or social worker) will rate the scale at the scheduled times. If possible, the same person should rate the CGI-TD-severity at all visits.

The CGI-TD-severity will be completed by the investigator at baseline (Day 1) and during the treatment period at the end of Weeks 12, 24, 36, 48, 60, and 72 (final study visit or upon early termination).

8.4. Safety Assessments

Concomitant medication use and AEs will be monitored throughout the study as described in Section 8.8.1 and Section 10, respectively. Additional safety assessments are described in the following sections.

Any abnormal vital sign measurement, clinical laboratory test, physical examination finding, or ECG parameter deemed clinically significant by the investigator will be repeated as needed, including test results obtained on the final study visit or upon early termination, until the value returns to baseline (or within normal limits), or the investigator deems the abnormality to be of no clinical significance. If the investigator determines that a subject has a clinically significant finding of treatment-emergent depression, suicidal ideation, psychiatric symptoms (based upon

the C-SSRS or clinical assessment), the finding will be documented as an AE, and appropriate psychiatric evaluation and intervention will be provided.

For subjects completing the final NBI-98854-1304 or NBI-98854-1402 visit on the same day as Day 1, the NBI-98854-1304 or NBI-98854-1402 assessments for physical examination (including weight), vital signs, and ECG will be used for Day 1.

8.4.1. Medical and Surgical History

A general medical and surgical history will be obtained at baseline (Day 1).

The subject's psychiatric history will be documented and will include the subject's age at first diagnosis of schizophrenia or schizoaffective disorder or mood disorder, and age at TD diagnosis. If necessary, subject age at onset can be estimated by the investigator based upon available clinical information.

8.4.2. Physical Examination Including Neurological Assessment, Height, and Weight

A complete physical examination will consist of an assessment of the following: general appearance; skin and mucosa; head, eyes, ears, nose, throat; lymph nodes; chest/lungs; cardiovascular; abdomen; extremities; musculoskeletal; and neurological system.

A physical examination including weight will be conducted at baseline (Day 1) and during the treatment period at Weeks 12, 24, 36, 48, 60, and 72 (final study visit or upon early termination). Height will be recorded at baseline (Day 1) only. Height and weight will be recorded with subjects wearing ordinary indoor clothing without shoes. Height and weight will be used to calculate the BMI (kg/m^2).

8.4.3. Vital Sign Measurements

Vital sign measurements, including orthostatic systolic and diastolic blood pressure, orthostatic pulse rate, respiratory rate (supine), and oral body temperature will be measured at the visits stated below. Blood pressure will be measured using a calibrated automatic blood pressure cuff after the subject has been supine for at least 5 minutes and after approximately 2 minutes of standing. The automatic blood pressure cuff will also provide pulse rate measurement.

Vital sign measurements will be collected at baseline (Day 1) and during the treatment period at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72 (final study visit or upon early termination).

8.4.4. Electrocardiogram

A standard 12-lead ECG will be recorded in triplicate (1 to 3 minutes apart) after the subject has rested supine for at least 5 minutes. The ECG parameters that will be assessed include HR, PR interval, QRS duration, QT interval, and QTcF (machine readings or calculated). Additionally, the occurrence of de- and re-polarization and rhythm disorders or other abnormalities will be assessed. Based on the review of these parameters, the investigator or designee will note if the ECG is Normal, Abnormal Not Clinically Significant, or Abnormal Clinically Significant. If the ECG is Abnormal Clinically Significant, the investigator or designee will provide a description of the abnormality recorded on the AE eCRF.

The 12-lead ECG recordings will be conducted at baseline (Day 1) and during the treatment period at Weeks 4, 12, 24, 36, 48, 60, and 72 (final study visit or upon early termination).

8.4.5. Clinical Laboratory Assessments

All clinical laboratory tests will be analyzed by a central laboratory (unless otherwise noted below), which will provide instructions and supplies to the clinical site staff before study initiation. Laboratory samples will be collected in the following approximate amounts: 4 mL for hematology, 4mL for hemoglobin A1c (HbA1c), and 5 mL for clinical chemistry (includes serum pregnancy test at baseline).

The routine laboratory tests (hematology, clinical chemistry, and urinalysis) will be performed under non-fasted conditions at baseline (Day 1) and during the treatment period at Weeks 12, 24, 36, 48, 60, and 72 (final study visit or upon early termination).

The following clinical safety laboratory assays will be performed:

Hematology: complete blood count including white blood cell (WBC) count with differential, red blood cell count, hemoglobin, hematocrit, platelet count, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), red cell distribution width (RDW), and mean platelet volume (MPV). A sample for HbA1c will also be collected (approximately 4 mL in dipotassium ethylenediaminetetraacetic acid [EDTA K_2]).

Clinical Chemistry: sodium, potassium, calcium, magnesium, chloride, blood urea nitrogen, bicarbonate, creatinine, uric acid, albumin, alkaline phosphatase, lactate dehydrogenase, AST, ALT, gamma-glutamyl transferase (GGT), creatine kinase, total bilirubin, total cholesterol, triglycerides, total protein, and glucose.

Urinalysis: specific gravity, nitrite, ketones, protein, urobilinogen, glucose, bilirubin, leukocyte esterase, occult blood, and pH; microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive for protein, leukocyte esterase, or blood.

The following additional laboratory tests will be performed:

Urine Drug Screen: UDS collected at baseline (Day 1) will be analyzed by the central lab for amphetamines, barbiturates, benzodiazepines, phencyclidine, cocaine, opiates, and cannabinoids. In addition, a UDS kit provided by the central lab will be used at the clinical site to confirm eligibility at baseline (Day 1). A UDS using a kit provided by the central lab may be conducted at the clinical site at any time during the study if the subject is suspected of substance or drug abuse. Subjects with a positive cannabinoid result may be allowed to participate in the study provided that the subject is given thorough counseling and agrees to refrain from using cannabinoids for the duration of his/her study participation. Subjects receiving a chronic and stable dose of benzodiazepines, barbiturates, or opiates are allowed into the study (refer to Section 8.8.1).

Alcohol: An alcohol breathalyzer test will be conducted at baseline (Day 1) at the clinical site to confirm eligibility. This test may be randomly performed at any time during the study at the investigator's discretion.

Pregnancy Test: Pregnancy tests will be performed throughout the study for female subjects who are not postmenopausal for at least 1 year. A serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) will be conducted for all female subjects on Day 1 (as part of clinical chemistry) and analyzed by the central laboratory. A urine pregnancy test will be performed at the clinical site at baseline (Day 1) to confirm eligibility, as well as at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72 (final study visit or upon early termination).

Prolactin: Blood samples to determine serum prolactin concentration will be collected at baseline (Day 1) and during the treatment period at Weeks 12, 24, 36, 48, 60, and 72 (final study visit or upon early termination). Approximately 5 mL of blood will be collected into a serum separator tube. Serum prolactin samples will be shipped to a central laboratory for analysis.

For any abnormal tests deemed clinically significant, repeat analysis will be performed until the cause of the abnormality is determined or until the value returns to baseline (or within normal limits), or the investigator deems the abnormality to be of no clinical significance.

8.4.6. Estimated Total Blood Sample Volume Required by the Study

The estimated total blood sample volume for each subject is presented in Table 2. These estimates include samples to be collected during baseline and the treatment period (or upon early termination).

Table 2: Estimated Total Blood Sample Volume

Parameter	Number of Samples Required	Approximate Volume (mL)	Approximate Total Volume (mL)
Clinical chemistry[a]	7	5	35
Hematology	7	4	28
HbA1c	7	4	28
Prolactin	7	5	35
Approximate Maximum Total Blood Sample Volume per Subject (mL):			**126**

[a] Includes pregnancy test for female subjects at baseline (Day 1).

8.4.7. Assessment of Suicidal Ideation and Behavior – Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a validated instrument to prospectively assess suicidal ideation and behavior (http://www.cssrs.columbia.edu). There are versions of the questionnaire designed for use at baseline (Day 1: Screening/Baseline version) and visits throughout the study (Since Last Visit version). All versions of the C-SSRS include a series of screening questions related to suicidal ideation and suicidal behavior. Subject responses of 'yes' to one or more screening questions will prompt additional questions that evaluate frequency and intensity of suicidal ideation and/or behavior. Subjects with any suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the C-SSRS in the 3 months prior to Day 1 (using Screening/Baseline version) should be excluded (see exclusion criterion #5). A copy of the C-SSRS (Screening/Baseline and Since Last Visit) is provided in Appendix 16.4.

The C-SSRS will be administered and scored by the investigator or other qualified clinical site personnel who have completed C-SSRS certification. The C-SSRS will be administered at

baseline (Day 1) and during the treatment period at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72 (final study visit or upon early termination). The "Screening/Baseline" version of the scale will be used to evaluate subject eligibility at baseline (Day 1) and the "Since Last Visit" version will be used at all other visits.

If at any time after baseline (Day 1) the subject's response to the suicidal ideation section of the C-SSRS is worse than the baseline (Day 1) assessment (past 3 months), it will be documented as an AE. All suicidal behaviors will be documented as an AE. Appropriate psychiatric evaluation and intervention will be provided for any treatment-emergent suicidal behavior or clinically significant suicidal ideation.

8.5. Additional Assessments

8.5.1. Patient Satisfaction Questionnaire

Subjects will evaluate their satisfaction with valbenazine treatment by choosing 1 of 5 responses (very satisfied, somewhat satisfied, neither satisfied nor dissatisfied, somewhat dissatisfied, or very dissatisfied). The Patient Satisfaction Questionnaire will be completed by the subjects at baseline (Day 1) and during the treatment period at Weeks 12, 24, 36, 48, 60, and 72 (final study visit or upon early termination). A copy of the Patient Satisfaction Questionnaire is provided in Appendix 16.5.

8.5.2. Social Functioning Scale

The Social Functioning Scale (SFS; Birchwood et al, 1990) is a 79-item scale designed to assess social functioning. Abilities and performance in seven areas are assessed: social engagement, interpersonal communication, activities of daily living, recreation, social activities, competence at independent living, and occupation/employment. Raw scores of the subscales are converted to scale score equivalents with a mean of 100 and an SD of 15. This scale has been shown to be a reliable, valid, and sensitive measure of social functioning (Birchwood et al. 1990).

The SFS will be completed by the subject at baseline (Day 1) and during the treatment period at the end of Weeks 12, 24, 36, 48, 60, and 72 (final study visit or upon early termination). A copy of the SFS is provided in Appendix 16.6.

8.6. Specific Period Information

Study visits during the treatment period at the end of weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72 (or upon early termination) will have a visit window of -7 or +2 days.

8.6.1. Baseline (Day 1)

For subjects completing the final NBI-98854-1304 or NBI-98854-1402 visit on the same day as Day 1, the NBI-98854-1304 or NBI-98854-1402 assessments for physical examination (including weight), vital signs, and ECG will be used for Day 1.

The following evaluations and tasks will be performed at baseline (Day 1):

- The ICF will be reviewed with subjects. The UBACC will then be administered. Only subjects who are deemed to have the capacity to provide consent may sign the ICF. The ICF must be signed prior to any additional study procedures.
- Assess inclusion/exclusion criteria.
- Collect medical and surgical history.
- Perform a physical examination (including height and weight without shoes; perform BMI calculation).
- Perform alcohol breath test.
- Perform UDS using kit provided by central laboratory.
- Perform urine pregnancy test for all female subjects who are not postmenopausal for at least 1 year.
- Perform 12-lead ECG in triplicate (1 to 3 minutes apart).
- Collect vital signs, including orthostatic systolic and diastolic blood pressure, orthostatic pulse rate, respiratory rate, and oral body temperature.
- Perform serum pregnancy test (β-hCG) for all female subjects who are not postmenopausal for at least 1 year.
- Collect blood sample for hematology and clinical chemistry.
- Collect blood sample for serum prolactin.
- Collect urine sample for urinalysis.
- Record prior medications.
- Administer C-SSRS (Screening/Baseline version).
- Administer CGI-TD-severity.
- Administer Patient Satisfaction Questionnaire and SFS.
- Administer BPRS.

After completion of these assessments, if the subject is eligible for the study the clinical site will access the Interactive Web Response System (IWRS) to obtain an identification number for a kit containing a 4-week supply of valbenazine to be dispensed to the subject. At this point, the subject will be considered enrolled in the study.

Enrolled subjects will:

- Be monitored for AEs.
- Be instructed to take valbenazine at home (in the presence of their caregiver, if applicable) at approximately the same time each day (eg, morning or evening) beginning the following day (Day 2). Valbenazine may be taken with or without food and must be swallowed with at least 4 oz. of water.

- Be instructed to contact the clinical site immediately without waiting for the next scheduled visit to report AEs or before starting any new medication.
- Be instructed to return to the clinical site in approximately 4 weeks for their next visit.
- Be instructed to return all unused valbenazine and packaging at the next scheduled visit.

8.6.2. Treatment Period

8.6.2.1. Day 2

Beginning on Day 2, subjects will take valbenazine at home (in the presence of their caregiver, if applicable) in the morning or evening; subsequent doses should be taken at approximately the same time each day. Valbenazine may be taken with or without food and must be swallowed with at least 4 oz. of water.

8.6.2.2. End of Week 4

The following procedures will be conducted at the end of Week 4 (-7 or +2 days):

- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and oral body temperature.
- Perform urine pregnancy test for all female subjects who are not postmenopausal for at least 1 year.
- Perform 12-lead ECG in triplicate (1 to 3 minutes apart).
- Administer C-SSRS (Since Last Visit version).
- AE monitoring.
- Record concomitant medications.
- Valbenazine accountability.

<u>Dose Titration Assessment:</u>

At the end of Week 4, a dose escalation will be allowed based on the physician investigator's (or designee's) assessments of safety and tolerability of valbenazine as well as clinical impression of TD.

The investigator may decrease the dose to 40 mg at any time after the end of Week 4 (including between scheduled study visits) for any subject who is unable to tolerate the 80 mg dose. These subjects will receive 40 mg for the remainder of the treatment period or will be discontinued from the study if they are unable to tolerate the 40 mg dose.

Once a determination of dose escalation or maintenance is made, the IWRS will be accessed to obtain an identification number for a kit containing a 4-week supply of valbenazine to be dispensed to the subject. For subjects who have a dose increase, the investigator will inform the subject that a dose reduction to 40 mg is allowed if the subject is unable to tolerate the 80 mg dose.

Subjects will be reminded:

- To take valbenazine at home (in the presence of their caregiver, if applicable) at approximately the same time each day (eg, morning or evening). Valbenazine may be taken with or without food and must be swallowed with at least 4 oz. of water.
- To contact the clinical site immediately without waiting for the next scheduled visit to report AEs or before starting any new medication.
- To return to the clinical site in approximately 4 weeks for their next scheduled visit.
- To return all unused valbenazine and packaging at the next scheduled visit.

8.6.2.3. End of Weeks 8, 16, 20, 28, 32, 40, 44, 52, 56, 64, and 68

The following procedures will be conducted at the end of Weeks 8, 16, 20, 28, 32, 40, 44, 52, 56, 64, and 68 (-7 or +2 days for each visit):

- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and oral body temperature.
- Perform urine pregnancy test for all female subjects who are not postmenopausal for at least 1 year.
- Administer C-SSRS (Since Last Visit version).
- AE monitoring.
- Record concomitant medications.
- Valbenazine accountability.

The investigator may decrease the dose to 40 mg at any time after the end of Week 4 (including between scheduled visits) for any subject who is unable to tolerate the 80 mg dose. These subjects will receive 40 mg for the remainder of the treatment period or will be discontinued from the study if they are unable to tolerate the 40 mg dose.

Once a determination of dose maintenance or reduction (for subjects who had their dose escalated to 80 mg at the end of Week 4), the IWRS will be accessed to obtain an identification number for a kit containing a 4-week supply of valbenazine to be dispensed to the subject. For subjects receiving 80 mg, the investigator will inform the subject that a dose reduction to 40 mg is allowed if the subject is unable to tolerate the 80 mg dose.

At each visit, subjects will be reminded:

- To take valbenazine at home (in the presence of their caregiver, if applicable) at approximately the same time each day (eg, morning or evening). Valbenazine may be taken with or without food and must be swallowed with at least 4 oz. of water.
- To contact the clinical site immediately without waiting for the next scheduled visit to report AEs or before starting any new medication.
- To return to the clinical site in approximately 4 weeks for their next scheduled visit.
- To return all unused valbenazine and packaging at the next scheduled visit.

8.6.2.4. End of Weeks 12, 24, 36, 48, and 60

The following procedures will be conducted at the end of Weeks 12, 24, 36, 48, and 60 (-7 or +2 days for each visit):

- Perform a physical examination (including weight without shoes).
- Perform 12-lead ECG in triplicate (1 to 3 minutes apart).
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and oral body temperature.
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Collect blood sample for serum prolactin.
- Perform urine pregnancy test for all female subjects who are not postmenopausal for at least 1 year.
- Administer C-SSRS (Since Last Visit version).
- Administer CGI-TD-severity.
- Administer Patient Satisfaction Questionnaire and SFS.
- AE monitoring.
- Record concomitant medications.
- Valbenazine accountability.

The investigator may decrease the dose to 40 mg at any time after the end of Week 4 (including between scheduled visits) for any subject who is unable to tolerate the 80 mg dose. These subjects will receive 40 mg for the remainder of the treatment period or will be discontinued from the study if they are unable to tolerate the 40 mg dose.

Once a determination of dose maintenance or reduction (for subjects who had their dose escalated to 80 mg at the end of Week 4) is made, the IWRS will be accessed to obtain an identification number for a kit containing a 4-week supply of valbenazine to be dispensed to the subject. For subjects receiving 80 mg, the investigator will inform the subject that a dose reduction to 40 mg is allowed if the subject is unable to tolerate the 80 mg dose.

<u>At each visit, subjects will be reminded:</u>

- To take valbenazine at home (in the presence of their caregiver, if applicable) at approximately the same time each day (eg, morning or evening). Valbenazine may be taken with or without food and must be swallowed with at least 4 oz. of water.
- To contact the clinical site immediately without waiting for the next scheduled visit to report AEs or before starting any new medication.
- To return to the clinical site in approximately 4 weeks for their next scheduled visit.
- To return all unused valbenazine and packaging at the next scheduled visit.

8.6.2.5. End of Week 72 (Final Study Visit or Early Termination)

The following procedures will be conducted at the end of Week 72 (final study visit or upon early termination) (-7 or +2 days):

- Perform a physical examination (including weight without shoes).
- Perform 12-lead ECG in triplicate (1 to 3 minutes apart).
- Collect vital signs, including orthostatic systolic and diastolic blood pressures, orthostatic pulse rate, respiratory rate, and oral body temperature.
- Collect blood sample for hematology and clinical chemistry.
- Collect urine sample for urinalysis.
- Collect blood sample for serum prolactin.
- Perform urine pregnancy test for all female subjects who are not postmenopausal for at least 1 year.
- Administer C-SSRS (Since Last Visit version).
- Administer CGI-TD-severity.
- Administer Patient Satisfaction Questionnaire and SFS.
- AE monitoring.
- Record concomitant medications.
- Valbenazine accountability.
- Instruct female subjects of childbearing potential to continue using contraception until 30 days after the last dose of valbenazine (see inclusion criterion #3).

8.7. Duration

The expected duration of study participation for each subject is up to 72 weeks.

8.8. Restrictions

8.8.1. Prior and Concomitant Medications

All prescription and over-the-counter (OTC) medications, including dietary and herbal supplements, taken by subjects during the 30 days before Day 1 and during the study will be collected.

Medications to treat psychiatric and medical conditions: All coexistent diseases or conditions will be treated in accordance with prevailing medical practice. Maintenance medication(s) for schizophrenia or schizoaffective disorder, mood disorders, and other nonprohibited concurrent medications should be at a stable dose (including no changes to the dose and frequency of ongoing medications and no discontinuation of medications) for a minimum of 30 days before Day 1. Benzodiazepines must be at a stable dose for 2 weeks before Day 1. Investigators should document doses of current medication through medical or pharmacy

records, confirmation with the subject's caregivers (if applicable), or through reliable subject-reported information (eg, provide a list of medications and doses).

Washout of Prohibited Medications: Subjects should discontinue prohibited medications for at least 30 days before undergoing Day 1 procedures provided they sign an ICF before discontinuation.

Prohibited medications: The following medications are prohibited from 30 days prior to Day 1 (unless otherwise stated) until the final visit (or early termination) as described below:

- Antiemetics: Metoclopramide, prochlorperazine, and promethazine are prohibited.
- Cytochrome P450 (CYP) 3A4 inducers: Strong inducers of CYP3A4 (eg, phenobarbital, rifabutin, rifampin, primidone, St. John's Wort) are prohibited.
- Dopamine agonists and precursors: Dopamine receptor agonists (eg, ropinirole) and precursors (eg, carbidopa/levodopa) are prohibited.
- Monoamine oxidase inhibitors (MAOIs): All MAOIs (eg, isocarboxazid, phenelzine, selegiline, tranylcypromine) are prohibited.
- VMAT2 Inhibitors: VMAT2 inhibitor medications (eg, tetrabenazine, reserpine) are prohibited, except for valbenazine.

8.8.2. General and Dietary Restrictions

Subjects must agree to adhere to the following prohibitions and restrictions during the study in order to be eligible to participate:

- Not to use any prohibited concomitant medication (Refer to Section 8.8.1).
- Limit alcohol use to less than 7 drinks per week during the course of the study.
- Not to donate blood during the study and for 4 weeks after completion of the study.
- Not to participate in an investigational drug study for at least 30 days after the last dose of valbenazine or 30 days after study completion, whichever is longer.

8.9. Withdrawal Criteria

8.9.1. Reasons for Withdrawal

Subjects are free to discontinue their participation in the study at any time. The investigator must withdraw any subject from the study if that subject requests to be withdrawn or becomes pregnant.

The investigator must withdraw the subject from the study if the subject experiences any of the following:

- If the type, frequency, or severity of any AE become unacceptable/intolerable.
- QTcF value >500 msec (confirmed by a cardiologist).

- If the subject exhibits suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the C-SSRS.
- Is lost to follow up.
- Subject is confirmed to be pregnant.

The investigator or NBI may withdraw the subject from the study for other reasons as described below. These should be discussed on a case-by-case basis with the NBI medical monitor (or designee) prior to withdrawing the subject from the study.

- Develops a clinically significant laboratory or ECG abnormality.
- Requires a medication that is prohibited by the protocol (refer to Section 8.8.1).

All subjects prematurely discontinuing the study, regardless of cause, must have all early termination assessments performed (see Section 8.6.2.5).

8.9.2. Handling of Withdrawals

If a subject prematurely withdraws from the study, either at his/her request or at the investigator's discretion, the investigator will record the reason for withdrawal on the relevant eCRF. All subjects who withdraw from the study prematurely must have all early termination assessments performed (unless the subject has withdrawn consent and refuses further intervention).

It is crucial to obtain follow-up data for any subject withdrawn because of an AE, abnormal laboratory test, vital sign measurement, physical examination, or ECG finding. Every effort must be made to undertake safety follow-up procedures.

8.9.3. Sponsor's Termination of Study

NBI reserves the right to discontinue the study at any time for clinical or administrative reasons. Such a termination must be implemented by the investigator, if instructed to do so by NBI in a time frame that is compatible with the subjects' well-being.

9. VALBENAZINE

9.1. Valbenazine Drug Supplies

NBI or its designee will provide the clinical site with valbenazine sufficient for the study, with the corresponding certificates of analysis.

The valbenazine capsule is a pearlescent purple opaque cap/pearlescent white opaque body, hard gelatin No. 1 size capsule with an axial orientated printed black bar, containing 40 mg (free base) NBI-98854 ditosylate salt. Subjects must swallow valbenazine capsule(s) with at least 4 oz. of water.

9.2. Supply, Storage, and Return (Drug Accountability)

9.2.1. Drug Packaging and Labeling

All packaging and labeling operations will be performed according to Good Manufacturing Practice and GCP rules. Valbenazine will be sent to an authorized staff member at the clinical site. The authorized clinical site staff member must confirm receipt of valbenazine to NBI or its designee via the IWRS.

Valbenazine will be supplied as capsules in child-resistant bottles. Each bottle will contain 30 capsules of valbenazine 40 mg. Subjects will be provided with enough valbenazine for 28 days of dosing plus 2 extra days of dosing (ie, 1 bottle for subjects receiving 40 mg and 2 bottles for subjects receiving 80 mg).

Each bottle will be labeled with a single panel label and secured with tamper evident seals. Label text will include but is not limited to the protocol number, dosage form, route of administration, valbenazine kit number, Sponsor name and address, storage condition and the statement "Caution – New Drug: Limited by Federal (or US) Law to Investigational Use".

9.2.2. Valbenazine Storage and Return

Valbenazine capsules must be stored at controlled room temperature (20˚C to 25˚C or 68˚F to 77˚F) under the conditions specified in the Investigator's Brochure and in a locked area accessible only to the pharmacist (or designee) until dispensing. Excursions outside this range will be allowed provided they meet the following conditions:

- Storage between refrigerated conditions (2˚C or 36˚F) and CRT (25˚C or 77˚F) for an unspecified length of time.
- Storage at temperatures above 25˚C (77˚F) but no more than 30˚C (86˚F) for up to 3 months.
- Storage at temperatures above 30˚C (86˚F) but no more than 40˚C (104˚F) for up to 24 hours.

Valbenazine should be stored and inventoried according to applicable state and federal regulations and study procedures.

Written documentation to account for valbenazine and drug packaging materials (bottles) is mandatory; all unused valbenazine and drug packaging materials must be kept in a secure location for final accountability and reconciliation. Returned valbenazine and drug packaging materials must be accounted for on a valbenazine return form provided by NBI or the designee. The investigator must provide a written explanation for any destroyed or missing valbenazine or drug packaging materials.

Returns will be shipped to NBI or its designee at the completion of the study according to instructions provided by NBI or its designee. Valbenazine return forms must be completed for

the shipment of returns and sent with the valbenazine and drug packaging materials. One copy of the valbenazine return form will be retained in the investigator's study file.

All returned valbenazine and drug packaging materials should be stored, inventoried, reconciled, and returned according to applicable state and federal regulations and study procedures.

9.2.3. Blinding

This is an open-label study.

9.3. Valbenazine Administration

The valbenazine doses that will be used in this study are 40 mg (taken as one 40 mg capsule) and 80 mg (taken as two 40 mg capsules). Subjects will self-administer valbenazine (in the presence of their caregiver, if applicable) at approximately the same time each day. Subjects may take valbenazine with or without food and must swallow it with at least 4 oz. of water every day during the treatment period. If treatment is interrupted for ≤5 missed consecutive doses, subjects are allowed to resume with their current dose regimen (40 mg qd or 80 mg qd). If treatment is interrupted for >5 missed consecutive doses, subjects should contact the investigator before resuming treatment; subjects deemed clinically stable by the investigator may resume with their current dose regimen (40 mg qd or 80 mg qd).

9.4. Valbenazine Compliance and Accountability

Subjects will bring all unused valbenazine and empty drug packaging material to the clinical site at each visit for drug accountability and reconciliation by clinical site personnel. A compliance check will be performed by counting the capsules returned at each scheduled visit.

The quantity of valbenazine dispensed, used, and returned will be recorded on a dispensing log or otherwise documented. The quantity of valbenazine lost or destroyed must also be accounted for and documented. The designated pharmacist or qualified personnel will be responsible for maintaining accurate records of the quantity and dates of all valbenazine supplies received, dispensed, and returned.

9.5. Valbenazine Drug Return

Written documentation to account for valbenazine and drug packaging materials is mandatory; all unused valbenazine and drug packaging materials must be kept in a secure location for final accountability and reconciliation. Returned valbenazine and drug packaging materials must be accounted for on a valbenazine return form provided by NBI or the designee. The investigator must provide a written explanation for any destroyed or missing valbenazine or drug packaging materials.

Returns will be shipped to NBI or its designee at the completion of the study according to instructions provided by NBI or its designee. Valbenazine return forms must be completed for the shipment of returns and sent with valbenazine and drug packaging materials. One copy of the valbenazine return form will be retained in the investigator's study file.

All returned valbenazine and drug packaging materials should be stored, inventoried, reconciled, and returned according to applicable state and federal regulations and study procedures.

10. ADVERSE EVENTS

All AEs, whether observed by the investigator, reported by the subject, noted from laboratory findings, or by other means, will be recorded from the time the subject has signed the ICF until the subject's final study visit (Week 72 or upon early termination). Note, AEs and serious adverse events (SAEs) will be collected for enrolled subjects only.

10.1. Definition

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. During the study, clinically significant adverse changes in clinical status, ECGs, laboratory values (not associated with an AE or concurrent medical condition), or physical examinations are considered AEs. Any subject complaint associated with such an abnormal finding will also be reported as an AE.

Adverse events include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of conditions present at the start of the study; (2) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction.

Subjects should be questioned in a general way, without asking about the occurrence of any specific symptom. The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms. Following questioning and evaluation, all AEs, whether believed by the investigator to be related or unrelated to valbenazine, must be documented in the subject's medical records, in accordance with the investigator's normal clinical practice and on the AE eCRF. Each AE is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to valbenazine.

The following are not considered AEs:

- Continuous persistent disease/symptom present before valbenazine administration, unless it unexpectedly progresses, or increases in severity following valbenazine administration.
- Pregnancy (see Section 10.5).

10.1.1. Intensity of Adverse Events

Adverse events must be graded for intensity. An intensity category of mild, moderate, or severe, as defined in Table 3, must be entered on the AE eCRF. It should be noted that the term "severe" used to grade intensity is not synonymous with the term "serious."

Table 3: Intensity of Adverse Events

Grade	Intensity
Mild	An adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	An adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
Severe	An adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.1.2. Relationship to Valbenazine

The investigator will document his/her opinion of the relationship of the AE to treatment with valbenazine using the criteria outlined in Table 4. An AE is deemed associated with the use of valbenazine "if there is a reasonable possibility that the drug caused the AE" (otherwise referred to as a suspected adverse reaction). Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE (Title 21 CFR 312.32 [a]).

Table 4: Relationship of Adverse Events to Valbenazine

Relationship	Description
Definite	A reaction that follows a reasonable temporal sequence from administration of the drug or in which the drug level has been established in body fluids or tissue; that follows a known or expected response pattern to the suspected drug; and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure.
Possible	An adverse event in which there is reasonable possibility that the drug caused the event. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the adverse event.
Unlikely	A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known or suspected response pattern to the suspected drug; but that could reasonably be explained by known characteristics of the subject's clinical state.
Not Related	Any event that does not meet the above criteria.

10.2. Recording Adverse Events

For enrolled subjects, each AE will be listed as a separate entry on an AE eCRF. The investigator will provide information on dates and times of onset and resolution, intensity, seriousness, frequency, action(s) taken, changes in valbenazine usage, relationship to valbenazine, and outcome.

The following categories of medical events that could occur during participation in a clinical study must be reported within 24 hours to NBI or designee:

- SAE, including death (see Section 10.4).
- Pregnancy (see Section 10.5).

10.3. Post-Study Follow-Up of Adverse Events

All AEs, including clinically significant changes in ECGs, physical examination findings, or isolated clinically significant laboratory findings must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up. If resolved, a resolution date should be documented on the eCRF.

Adverse events ongoing at the final visit or at early termination will be followed for as long as necessary to adequately evaluate the subject's safety or until the event stabilizes or resolves or until the subject is lost to follow-up. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals, as is practical.

10.4. Serious Adverse Events

All SAEs will be recorded from the time the subject has signed the ICF until 30 days after the last dose of investigational product or until the subject begins taking commercial product, whichever comes first.

10.4.1. Definition of a Serious Adverse Event

An SAE is any AE that results in any of the following outcome:

- Death.
- A life-threatening AE. Life-threatening means that the subject was, in the view of the investigator or Sponsor, at immediate risk of death from the reaction as it occurred. It does not mean that hypothetically the event might have caused death if it occurred in a more serious form.
- Inpatient hospitalization or prolongation of existing hospitalization. Hospitalization for elective treatment or a pre-existing condition that did not worsen during the clinical investigation is not considered an AE. Hospitalization or nursing home admission for the purpose of caregiver respite is not considered an AE. Complications that occur during hospitalization are AEs, and if a complication prolongs hospitalization, the event is considered serious. Treatment in a hospital emergency room is not a hospitalization.
- A persistent or significant incapacity or substantial disruption of a person's ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization. These events may be considered serious when, based on appropriate medical judgment, they may jeopardize the health of the subject and may require medical or surgical intervention to prevent one of the outcomes listed. Any other event thought by the investigator to be serious should also be reported, following the reporting requirements detailed in this section. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias,

convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.4.2. Managing Serious Adverse Events

Subjects experiencing an SAE or an emergency situation will be examined by a physician as soon as possible. The physician in attendance will do whatever is medically needed for the safety and well-being of the subject. The subject will remain under observation as long as medically indicated. Appropriate laboratory studies will be conducted until all parameters return to normal or are otherwise explained or stable. The subject will be followed until the SAE resolves or until the subject is medically stabilized. The investigator (or designee) will notify the Medical Monitor (and the IRB, if necessary) immediately (within 24 hours) of the SAE and the outcome of the SAE.

If an investigator becomes aware of an SAE within the time of informed consent until 30 days after the last dose of investigational product or until the subject begins taking commercial product, whichever comes first, then the event must be documented and reported as described in Section 10.4.3.

10.4.3. Reporting Serious Adverse Events and Other Immediately Reportable Events

Serious AEs and other immediately reportable events (defined in Section 10.2) must be reported within 24 hours of first knowledge of the event by study personnel to the NBI Medical Monitor or NBI Clinical Drug Safety (CDS) Department. Serious AEs and pregnancies must be followed by a fax or email of the SAE or Pregnancy Form. It is important that the investigator provide his or her assessment of relationship to valbenazine at the time of the initial SAE report.

For SAEs and other immediately reportable events, contact CDS:

CDS telephone:
CDS facsimile:
CDS e-mail:
NBI Medical Monitor: **Telephone:**
Cell phone:

10.4.4. Expedited Safety Reports

NBI or its representatives will submit an Expedited Safety Report for any suspected adverse reaction (as defined in Section 10.1.2) that is considered both serious and unexpected within 15 calendar days and for any unexpected fatal or life-threatening experience within 7 calendar days via telephone or facsimile; or according to country-specific regulations.

NBI or its representatives will send copies of each safety report submitted to regulatory authorities to the investigators. The safety report must be submitted to the appropriate IRB as soon as possible. Documentation of the submission to the IRB and receipt by the IRB (if applicable) must be retained for each safety report.

10.5. Pregnancy

Pregnancy is neither an AE nor an SAE unless the criteria for an SAE are met. However, all pregnancies in female subjects who received valbenazine will be followed to assess for congenital anomaly. Subjects must be counseled at all visits to continue using hormonal or 2 forms of nonhormonal contraception (see inclusion criterion #3 in Section 7.1) until 30 days after the last dose of valbenazine. If at any time between the time the subject signs the ICF and the last visit, a subject believes she is pregnant, the subject will be instructed to return to the clinical site within 24 hours and undergo a serum pregnancy test to confirm pregnancy.

All confirmed pregnancies in subjects who received valbenazine must be immediately reported to NBI (see Section 10.4.3 for contact information), followed by fax or email of the pregnancy form to NBI CDS. A first trimester ultrasound will be required for all confirmed pregnancies. Pregnancies in subjects who received valbenazine will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

11. DOCUMENTATION OF DATA

11.1. Case Report Forms

The CRF data for this study are being collected with an electronic data capture (EDC) system ( ) provided by . The EDC system and the study-specific eCRFs will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, , while the validation of the study specific eCRFs will be conducted by NBI and the required documentation will be maintained in the Trial Master File.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by authorized study personnel in the EDC system, with the exception of data captured in an electronic format, which will be loaded electronically into the appropriate eCRFs. All data entered into the eCRF will be supported by source documentation. The eCRF for each subject must be reviewed by the investigator and signed on the appropriate eCRF page(s). This should be done as soon as possible after the subject completes the study.

The investigator or an authorized member of the investigator's staff will make any necessary additions/corrections to the eCRF. All change information, including the date, person performing the corrections, and reason for the change will be available via the electronic audit trail, which is part of the EDC system. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by NBI (or designee). NBI will also be allowed access to all source documents and medical records pertinent to the study in order to verify eCRF entries. The Principal Investigator will review the eCRFs for completeness and accuracy and enter his or her electronic signature on the eCRFs as evidence thereof.

 will provide access to the NBI portal of the EDC system for the duration of the study through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at

that time as a durable record of the site's eCRF data. Although not required, the investigator may make paper printouts from that media.

All clinical work conducted under this protocol is subject to GCP regulations. This includes an inspection by NBI and/or health authority representatives at any time. The Principal Investigator will agree to the inspection of study -related records by health authority representatives and/or NBI.

11.2. Data Capture, Review, and Validation

Data entered in the EDC system will be verified against the source data by NBI (or designee). Any discrepancies will be corrected on-line by authorized site personnel. After completion of the entry process, automated (computer-generated) logic checks will run in order to identify items such as inconsistent study dates. In addition, manual review/checks may be performed by NBI on the data. Any inconsistencies/errors/omissions identified will be sent to the site (via an electronic query) for the necessary corrections to be made to the eCRF. Once entered and saved in an eCRF, data immediately become part of the study database and are available to NBI.

11.3. Coding Dictionaries

Adverse events and medical history will be coded using the chosen version of the Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be coded using the chosen version of the World Health Organization Drug Dictionary (WHO Drug).

12. STATISTICAL AND ANALYTICAL PLAN

Descriptive statistical methods will be used to summarize the data from this study. The term "descriptive statistics" refers to the number of subjects (n), mean, median, standard deviation (SD), standard error of the mean (SEM), minimum, and maximum for continuous variables; and refers to the number and/or percentage of subjects (or events) for categorical variables. Data summaries will include tables, figures, and listings.

12.1. Analysis Sets

Analysis sets, which represent subsets of the study population defined for analysis-related purposes, will be described in detail in the study Statistical Analysis Plan (SAP). The SAP will be developed subsequent to the development of this protocol, but before finalizing the study database.

12.2. Sample Size Determination

The sample size for this study is based on practical considerations and not on a statistical power calculation.

12.3. Handling of Missing Data

In general, all available study data will be included in relevant data displays, including any available data for subjects with incomplete or missing data. Specific rules for handling missing data values will be identified in the SAP.

12.4. Disposition of Subjects

A summary of subject disposition will be prepared that displays the number of subjects who were enrolled and completed the study. The number of subjects who did not complete the study will be displayed both overall and by reason for discontinuation.

12.5. Demographics and Baseline Subject Characteristics

Demographic data and subject baseline characteristics will be summarized with descriptive statistics.

12.6. Valbenazine Dosing and Compliance

The estimated number of doses of valbenazine taken during the 4-week intervals between consecutive scheduled visits during the treatment period will be summarized with descriptive statistics by visit. The cumulative estimated number of doses taken through Week 72 will be summarized also. Additionally, the number of subjects who have a dose reduction will be summarized.

12.7. Efficacy Data

12.7.1. CGI-TD-Severity

Descriptive statistics will be presented for CGI-TD-severity score at each assessment and for the changes from baseline (Day 1) to each assessment after Day 1.

12.8. Safety Data

Treatment-emergent AEs (TEAEs), categorized by system organ class (SOC) and preferred term as defined by MedDRA, will be summarized. A TEAE is defined as any AE that occurs after the first dose of valbenazine through the final study visit. Any AE that occurred before the first dose of valbenazine will be considered a pretreatment AE.

The TEAE tables will include the number of events, number of unique subjects experiencing each event, and percentage of subjects experiencing each event.

AEs will be also be tabulated in terms of the number and percentage of subjects experiencing events by intensity and relationship to valbenazine.

Separate listings will be generated for pretreatment AEs, TEAEs, SAEs and deaths, and AEs leading to premature discontinuation from the study.

Clinical laboratory, vital signs, physical examination, and ECG data will be summarized with descriptive statistics and frequency tables as appropriate. Prior and concomitant medications will be presented in data listings.

12.9. Additional Assessments

12.9.1. Patient Satisfaction Questionnaire

Descriptive statistics will be presented for Patient Satisfaction Questionnaire score at each assessment and for the changes from baseline (Day 1) to each assessment after Day 1.

12.9.2. Social Functioning Scale

Descriptive statistics will be presented for SFS score at each assessment and for the changes from baseline (Day 1) to each assessment after Day 1.

12.10. Additional Analyses

Additional analyses may be performed for this study.

12.11. Interim Analysis

An interim analysis is not planned for this study.

13. REGULATORY AND ETHICAL ISSUES

13.1. General Legal References

The study will be carried out according to the provision of the US CFR, the US Food and Drug Administration (FDA), and the International Conference on Harmonisation Guidelines for GCP. All clinical work conducted under this protocol is subject to GCP rules. This includes an inspection by NBI or its representative, health authority, or IRB representatives at any time. The investigator must agree to the inspection of study-related records by health authority representatives and/or NBI or its designee.

13.2. Institutional Review Board/Ethics Committee

The final approved protocol and the ICF will be reviewed by the IRB/EC at the clinical site. The committee's decision concerning conduct of the study will be sent in writing to the investigator and a copy will be forwarded to NBI. The investigator agrees to make any required progress reports to the IRB/EC, as well as reports of SAEs, life-threatening problems, or death.

13.3. Protocol Adherence – Amendments

The protocol must be read thoroughly and the instructions must be followed exactly. Any changes in the protocol will require a formal amendment. Such amendments will be agreed upon and approved in writing by the investigator and NBI. The IRB will be notified of all amendments to the protocol. Amendments to the protocol will not be implemented until written IRB approval has been received.

13.4. Required Documents

The investigator must provide NBI or its designee with the following documents before the enrollment of any subject (copies should be kept by the investigator in the investigator's study regulatory binder):

- Signed copy (original) of the protocol signature page.
- Completed and signed statement of investigator (Form FDA 1572).
- Financial disclosure documentation as required.
- Curriculum vitae and current medical license of the investigator and sub-investigators.

- Letter of approval from the IRB/EC for both protocol and ICF.
- Copy of the IRB/EC approved written ICF to be used.
- Laboratory documents (certifications/accreditations, normal ranges) if not provided by a central laboratory.

13.5. Informed Consent

All subjects will provide their written informed consent before the performance of any study-related procedures.

Each subject's chart will include the signed ICF for study participation. When the study treatment is completed and the eCRF has been monitored, the ICF will be kept in the investigator's central study file. Regulatory authorities may check the existence of the signed ICF in this central study folder if not having done so during the study.

13.6. Study Monitoring

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include telephone calls and on-site visits. During the on-site visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor will also perform drug accountability checks and may periodically request review of the investigator study file to ensure completeness of documentation in all respects of clinical study conduct.

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period. The investigator or appointed delegate will receive the study monitor during these on-site visits, will cooperate in providing the documents for inspection, and respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the regulatory agencies.

13.7. Quality Assurance

The study will be conducted in accordance with NBI's standard operating procedures designed to ensure that all procedures are in compliance with GCP and FDA Guidelines and according to national law. Quality assurance audits may be performed at the discretion of NBI.

13.8. Record Retention

Federal regulations require that records of drug disposition, eCRFs, and all reports of this investigation shall be retained by the investigator for a minimum of 2 years after notification by NBI that the regulatory authorities have been notified of the study's termination, or 2 years after approval of the marketing application. If the investigator is unable to retain the study documents for the required amount of time, NBI must be informed of the individual who will be assuming this responsibility.

13.9. Confidentiality

NBI or its designee, and the clinical site affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, all data will be identified only by an identification number and, where applicable, subject initials.

All information concerning this study and which was not previously published is considered confidential information. This confidential information shall remain the sole property of NBI; it shall not be disclosed to others without written consent of NBI; and shall not be used except in the performance of this study.

The information compiled during the conduct of this clinical study is also considered confidential and may be disclosed and/or used only by NBI as they deem necessary. To allow the use of the information derived from this clinical study and to ensure compliance to current federal regulations, the investigator is obliged to furnish NBI with the complete test results and all data compiled in this study.

14. STUDY COMMENCEMENT AND DISCONTINUATION

Subject entry should not begin until after the required regulatory documents are confirmed as received and the Initiation Visit has occurred. All personnel expected to be involved in the conduct of the study will undergo orientation to include review of study protocol, instructions for eCRF completion, AE reporting, and overall responsibilities including those for drug accountability and study file maintenance.

If the study is discontinued, all subjects should undergo a complete follow-up examination. Any clinically relevant finding, including laboratory values of potential clinical concern, and adverse experiences will be followed until they resolve or return to a clinically acceptable level.

15. REFERENCES

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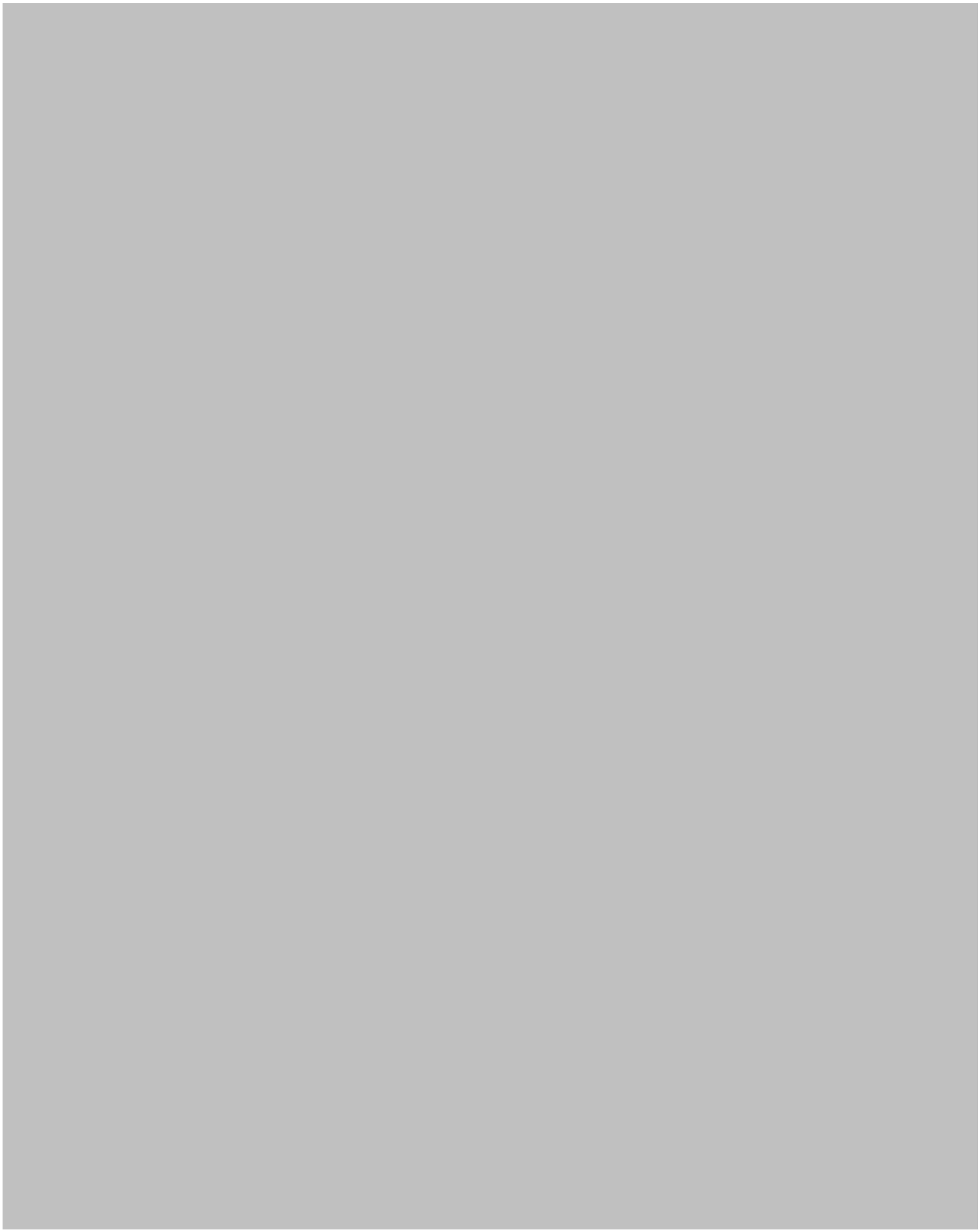
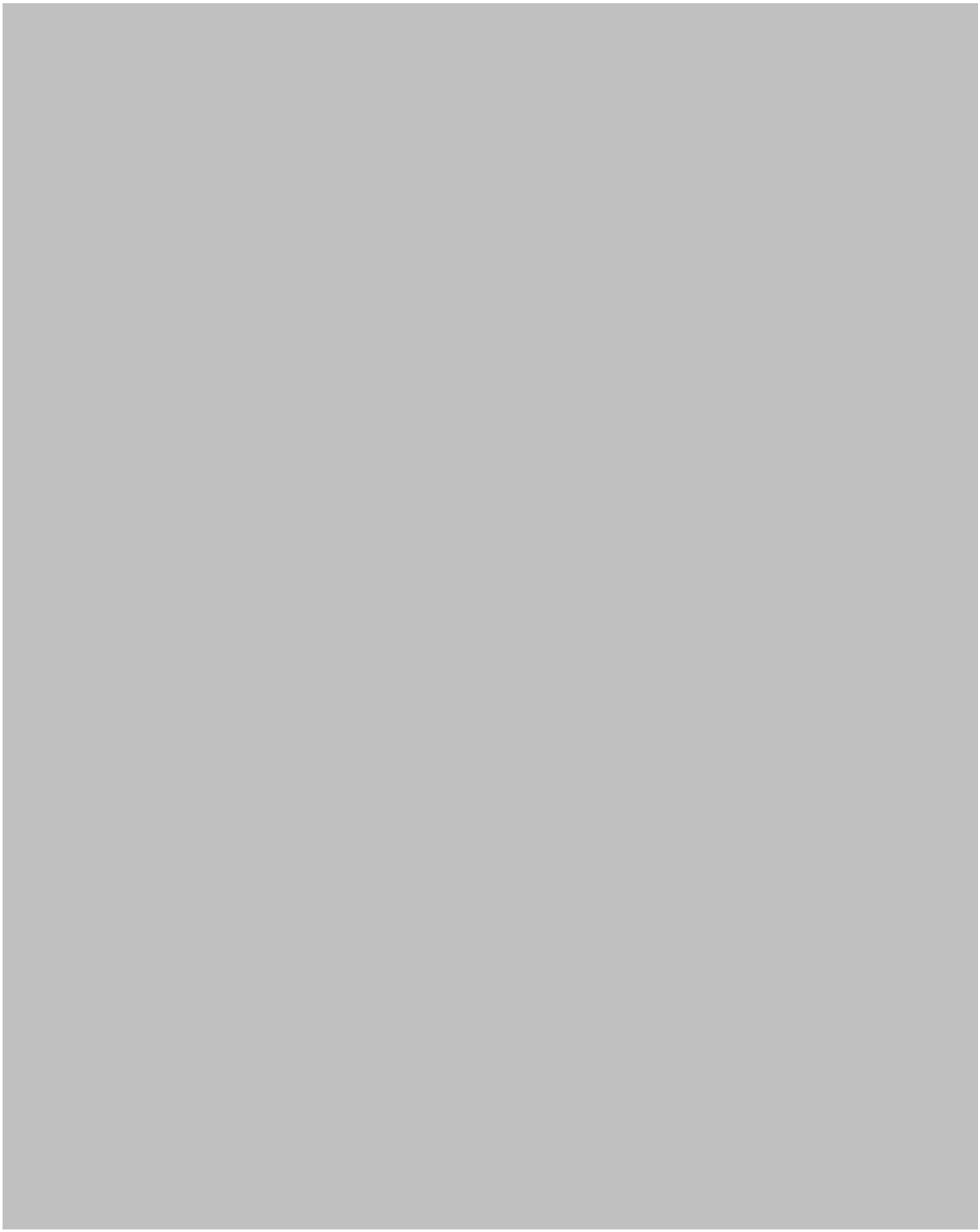
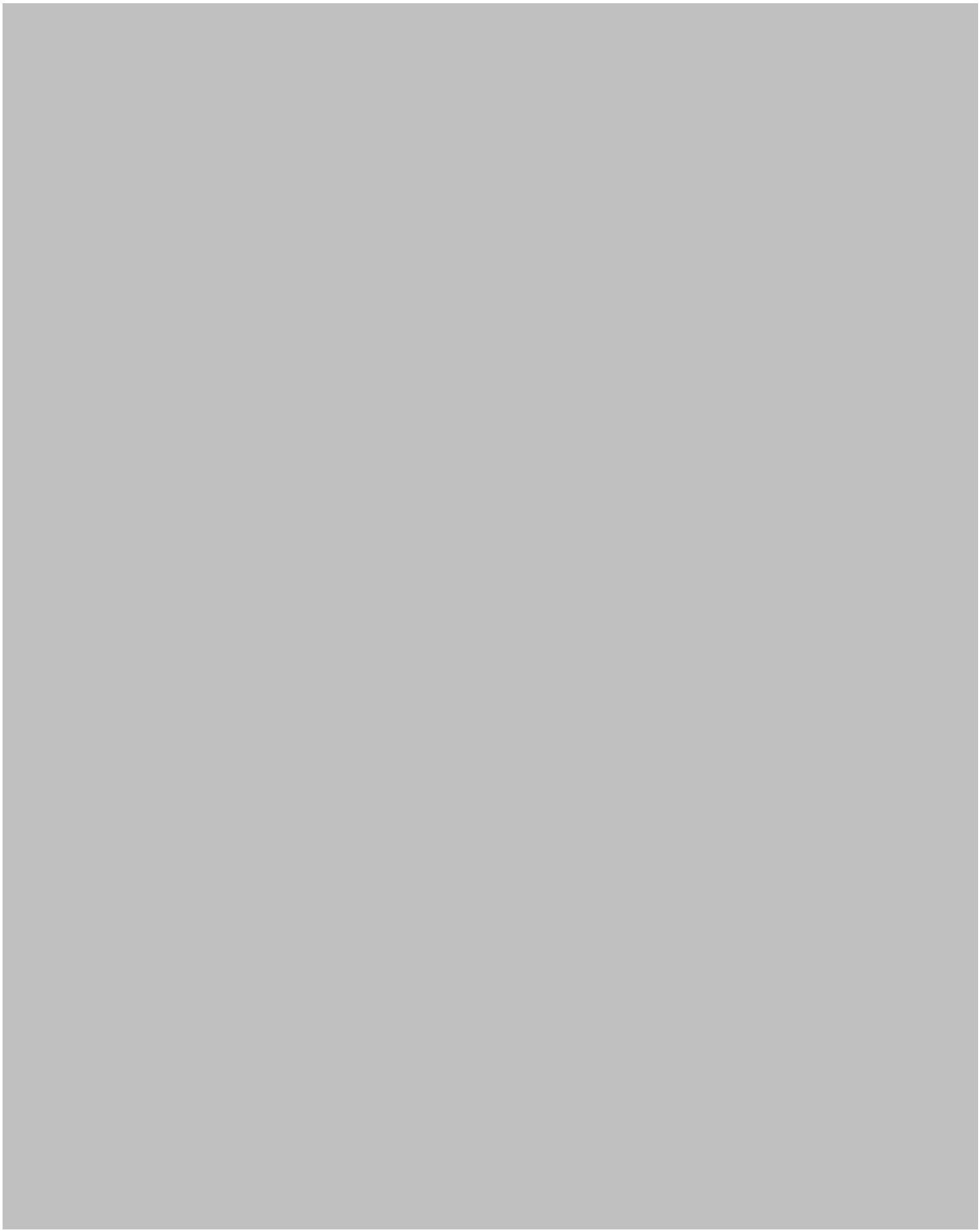
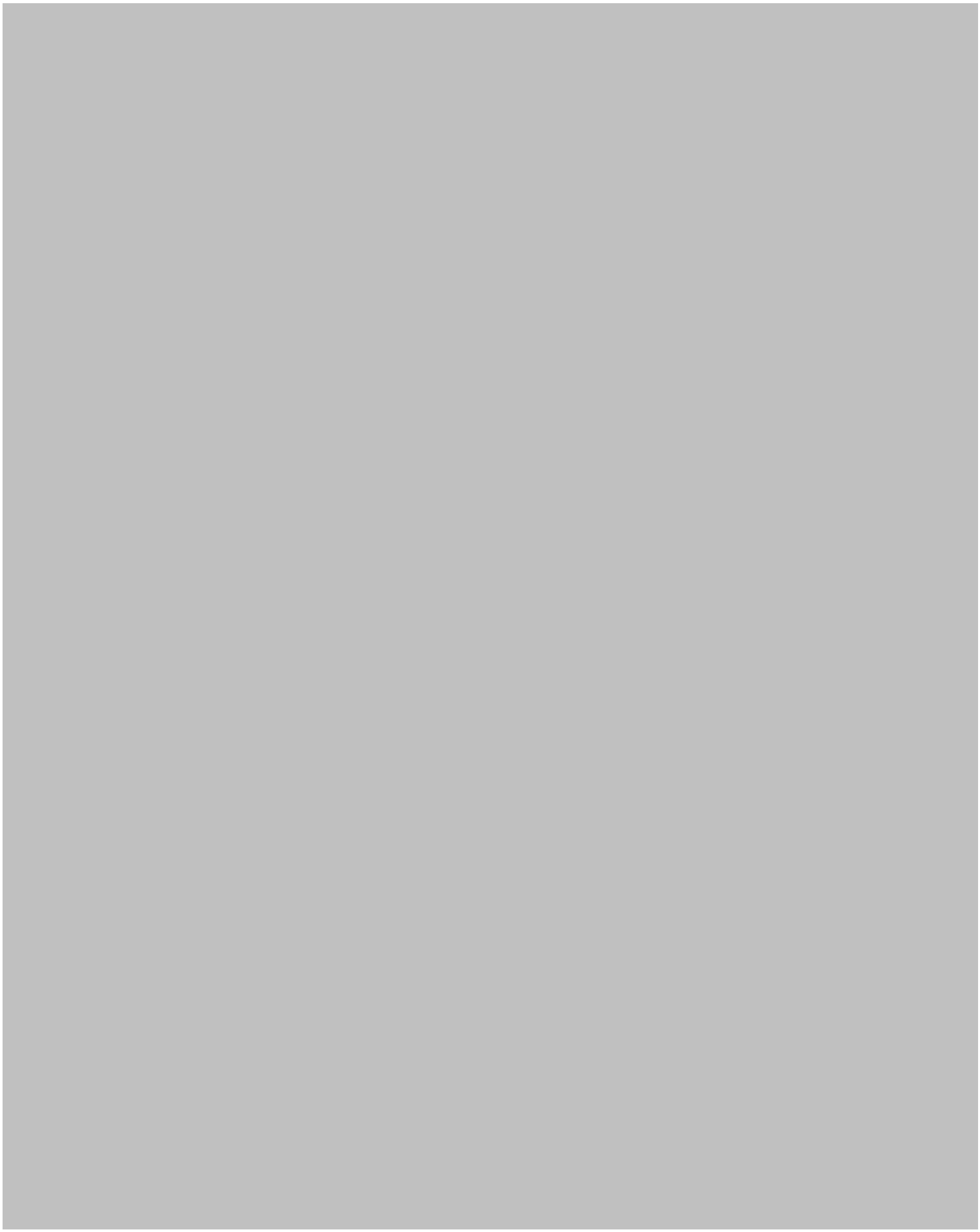
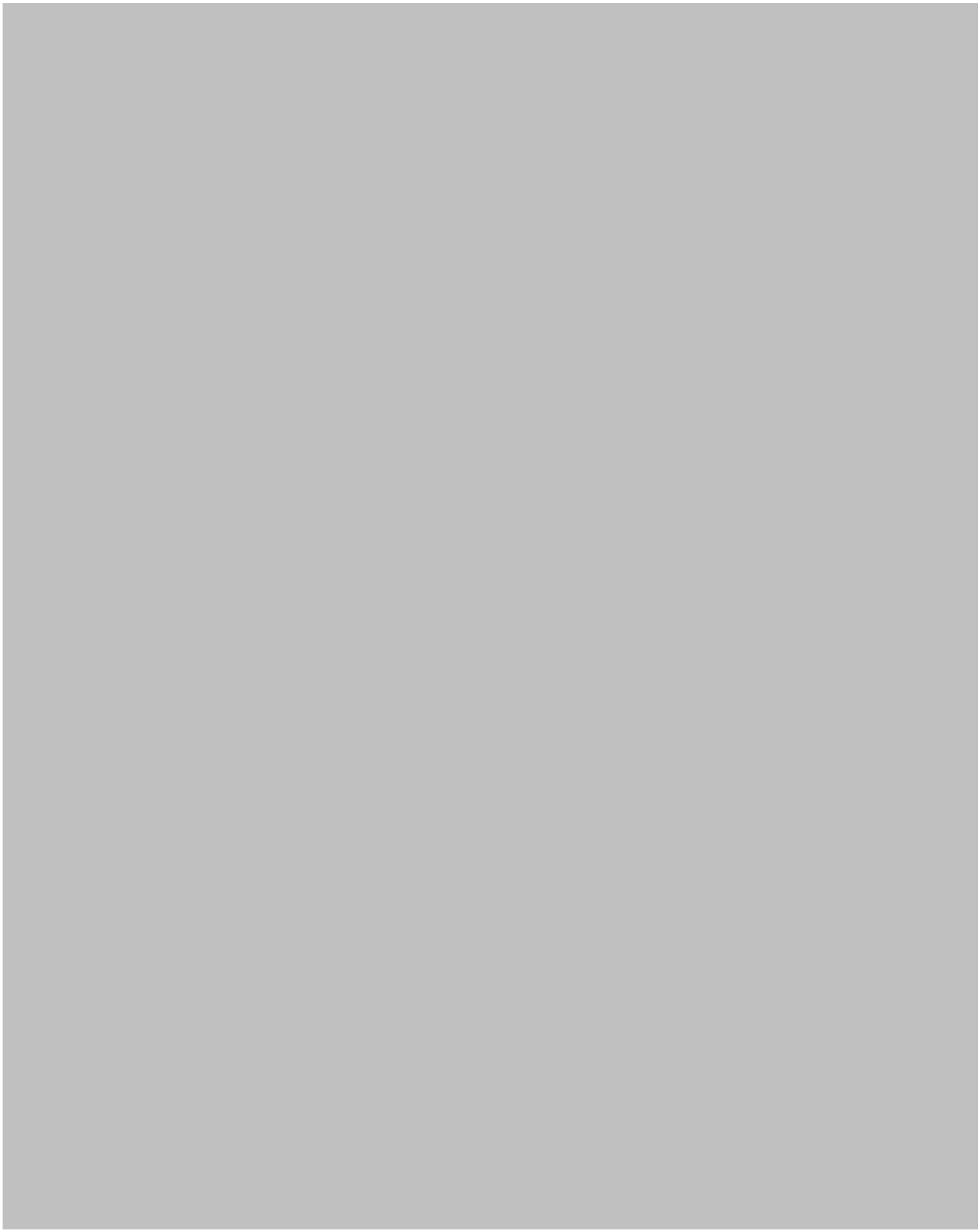
16. APPENDICES

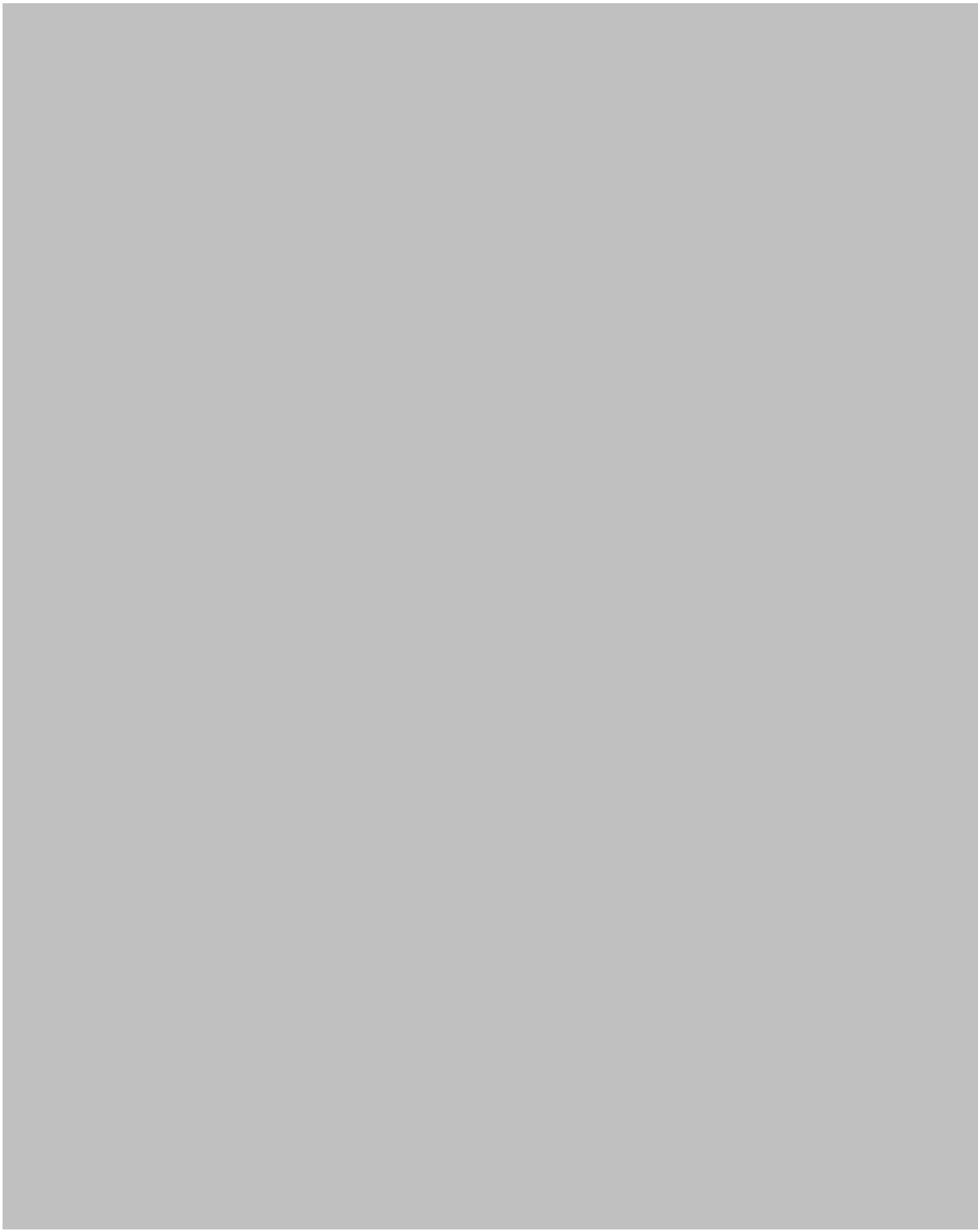


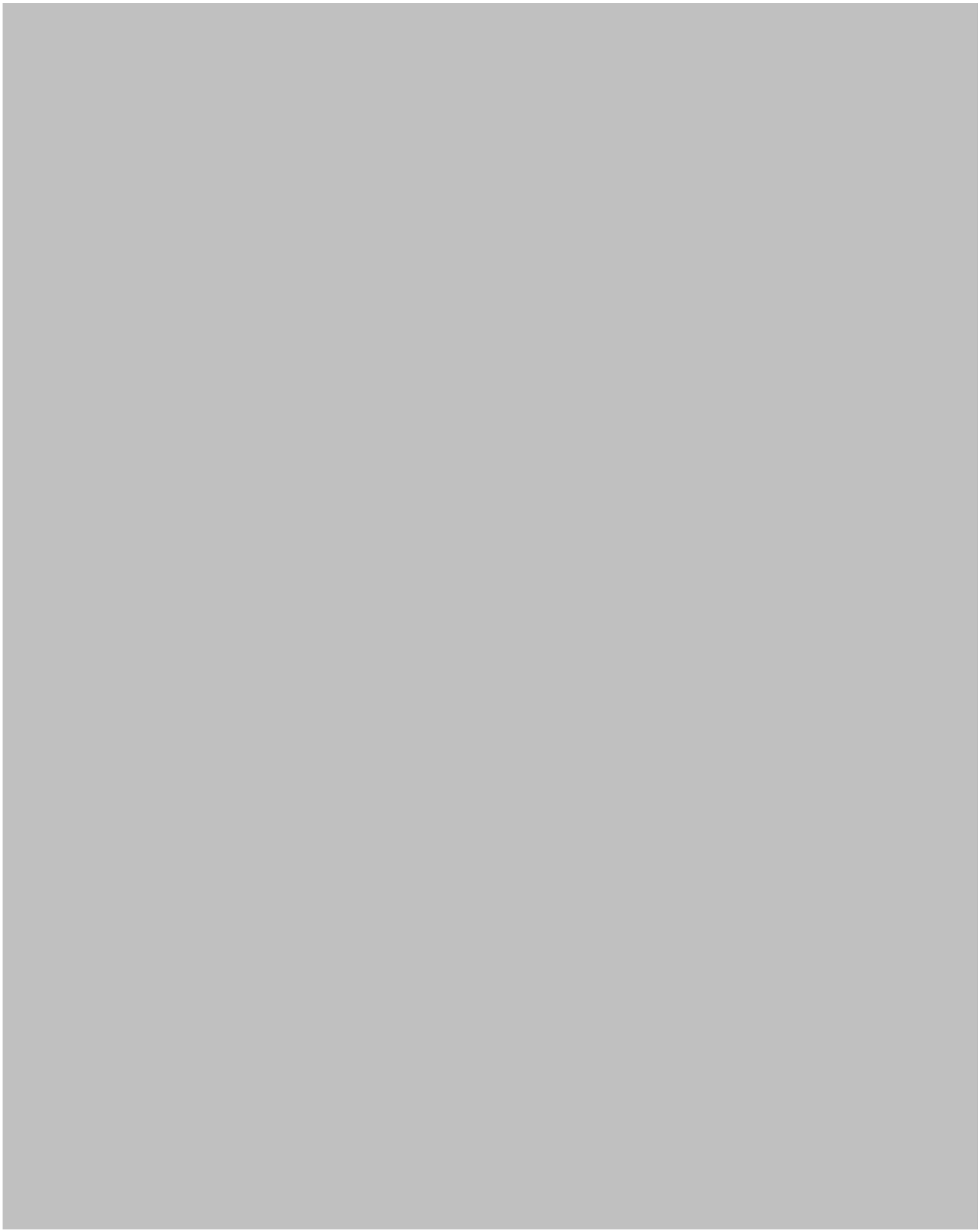


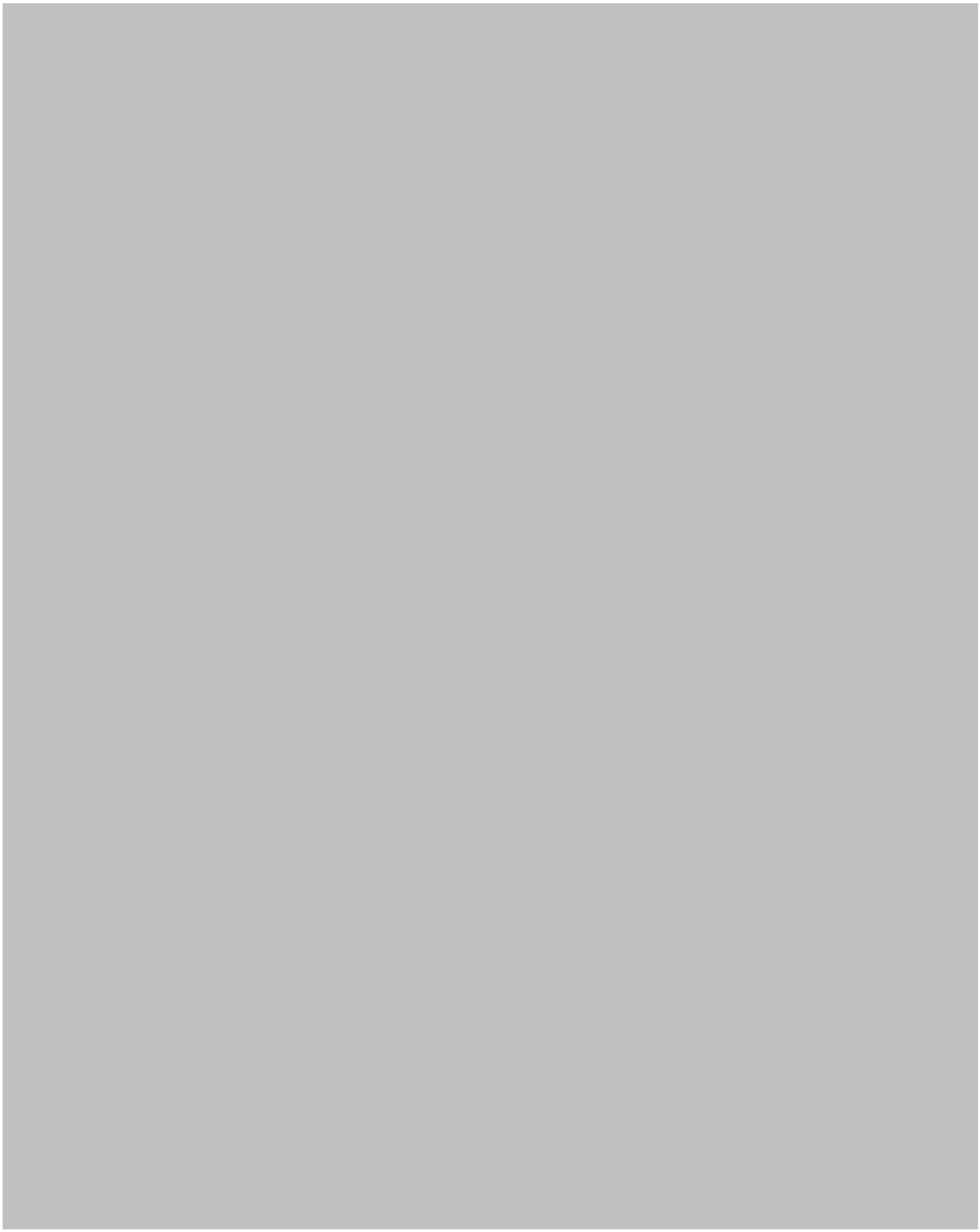


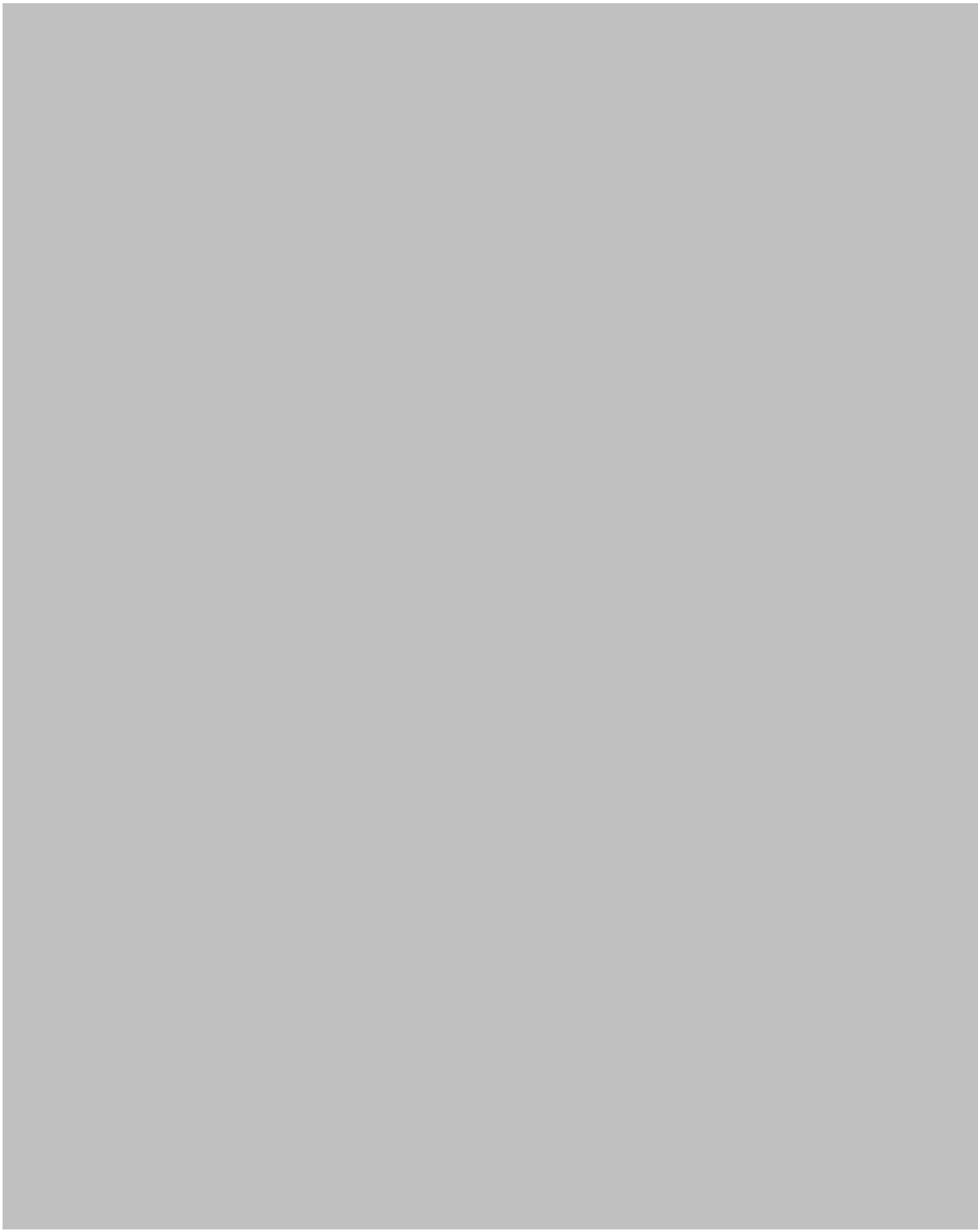


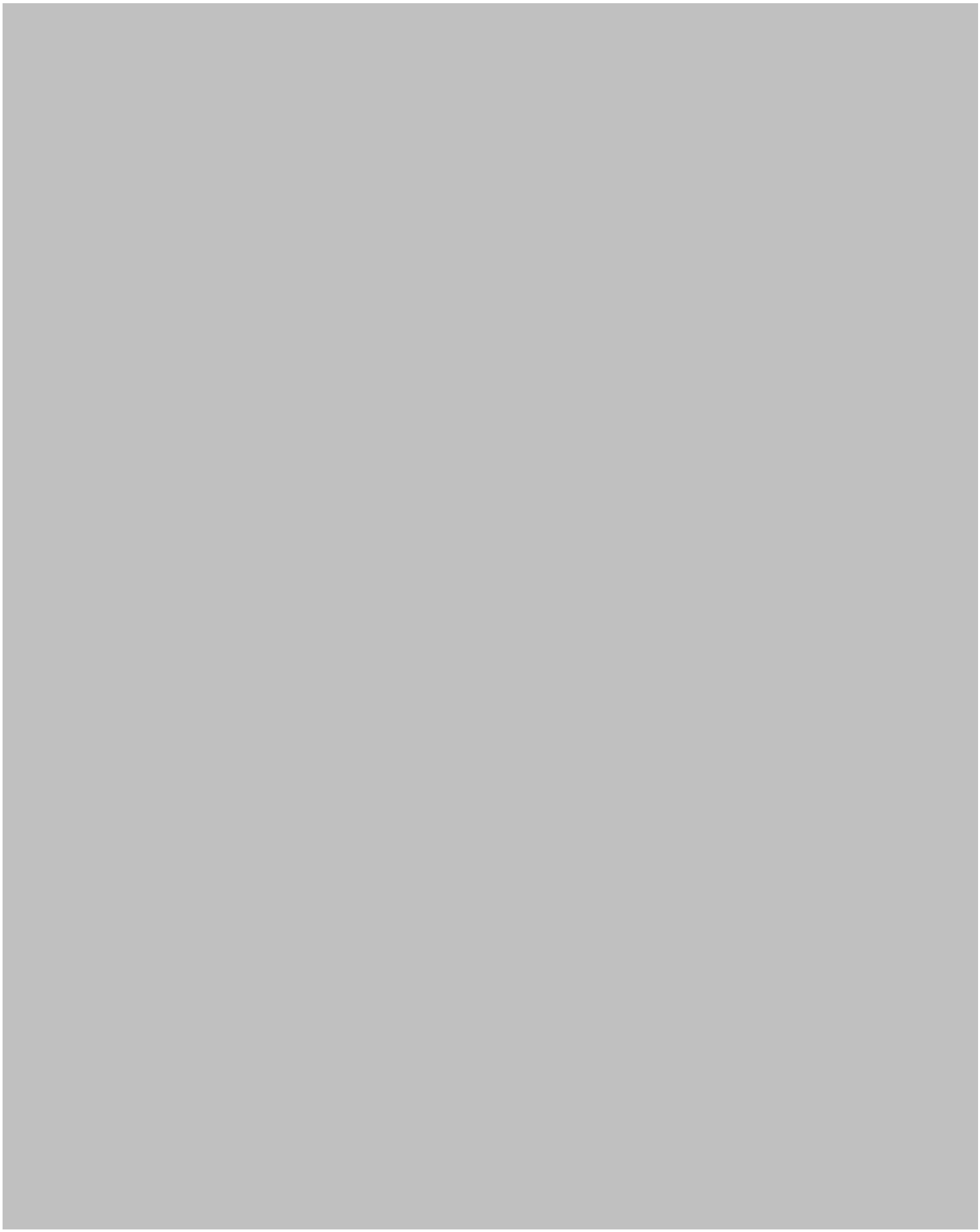


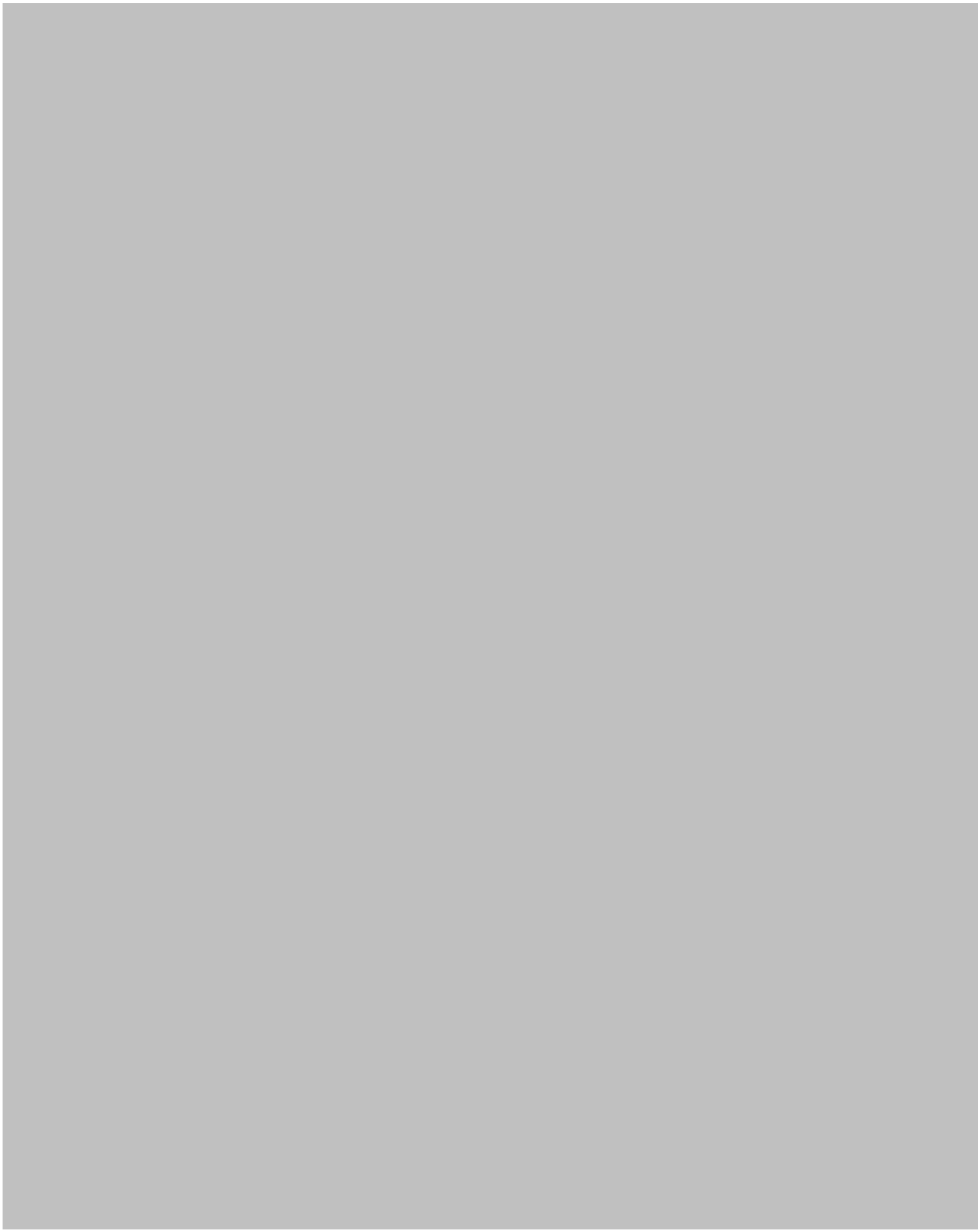


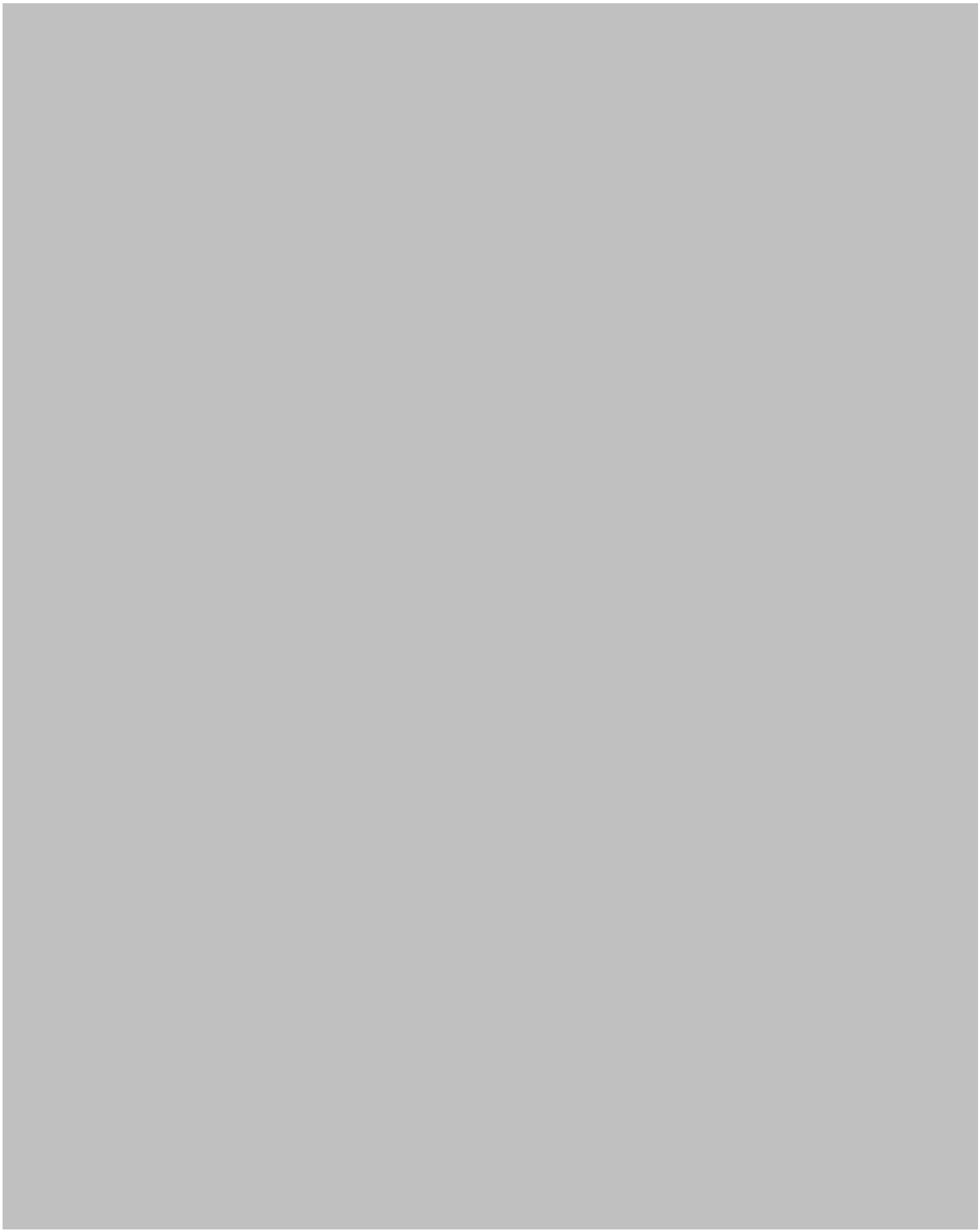


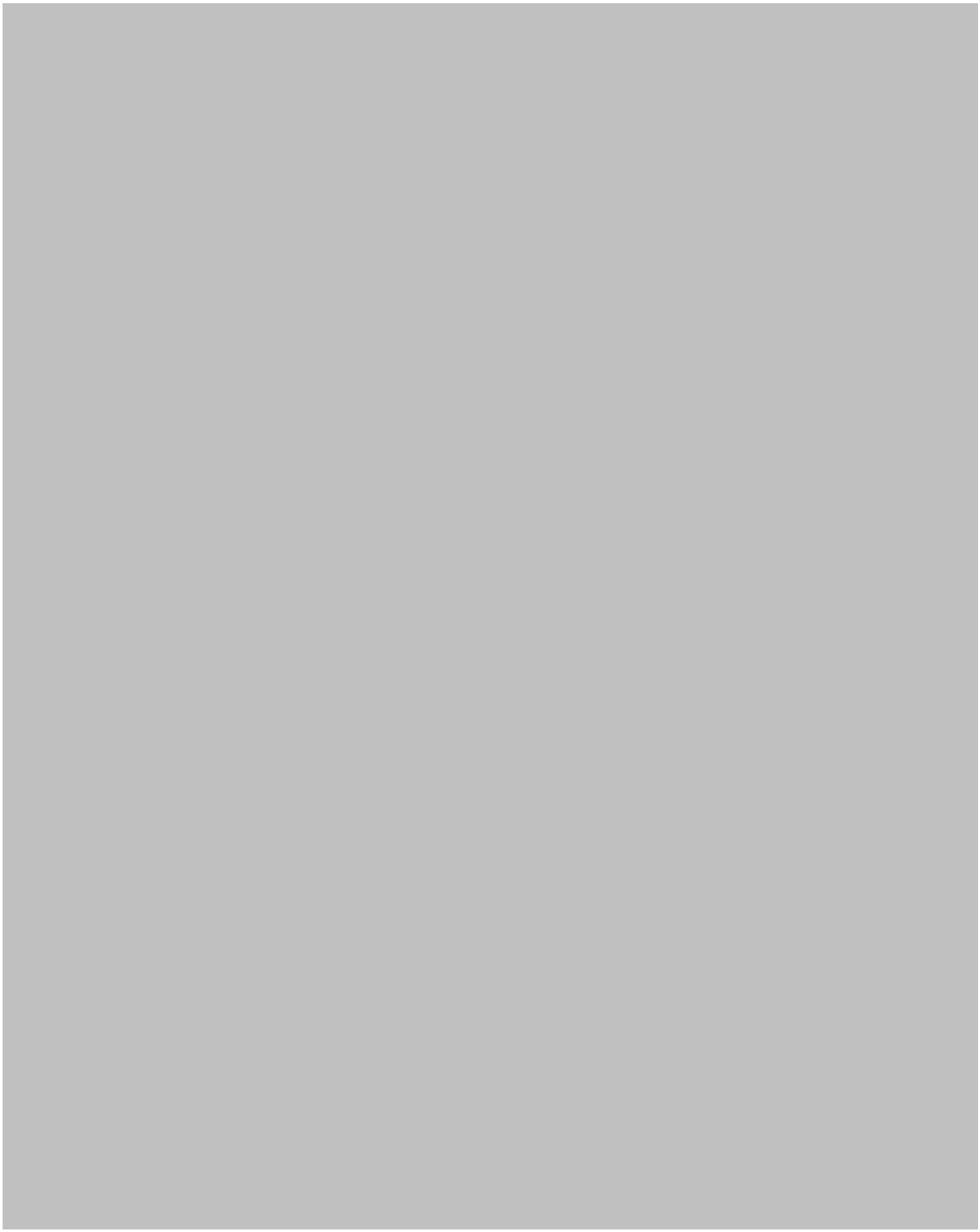


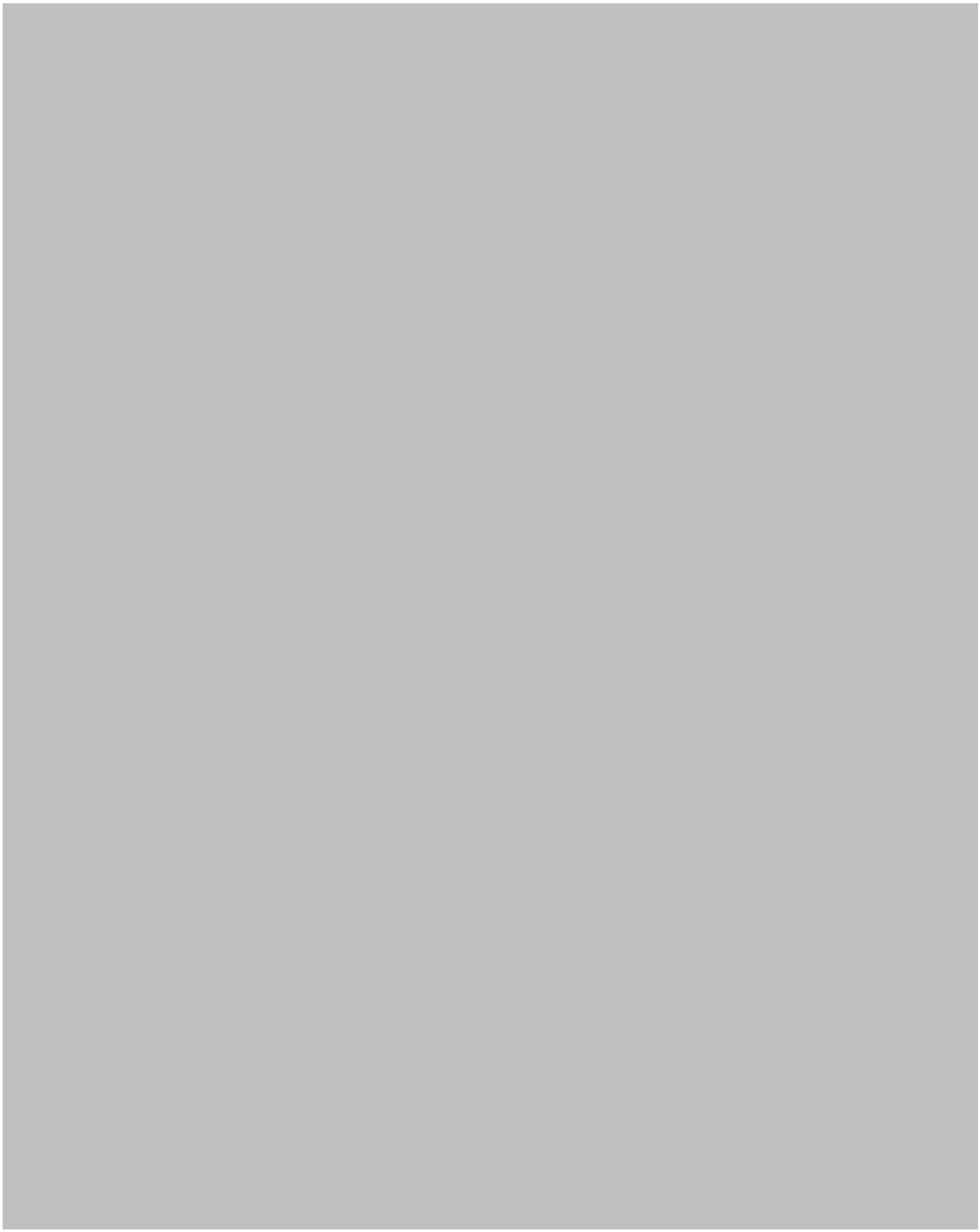


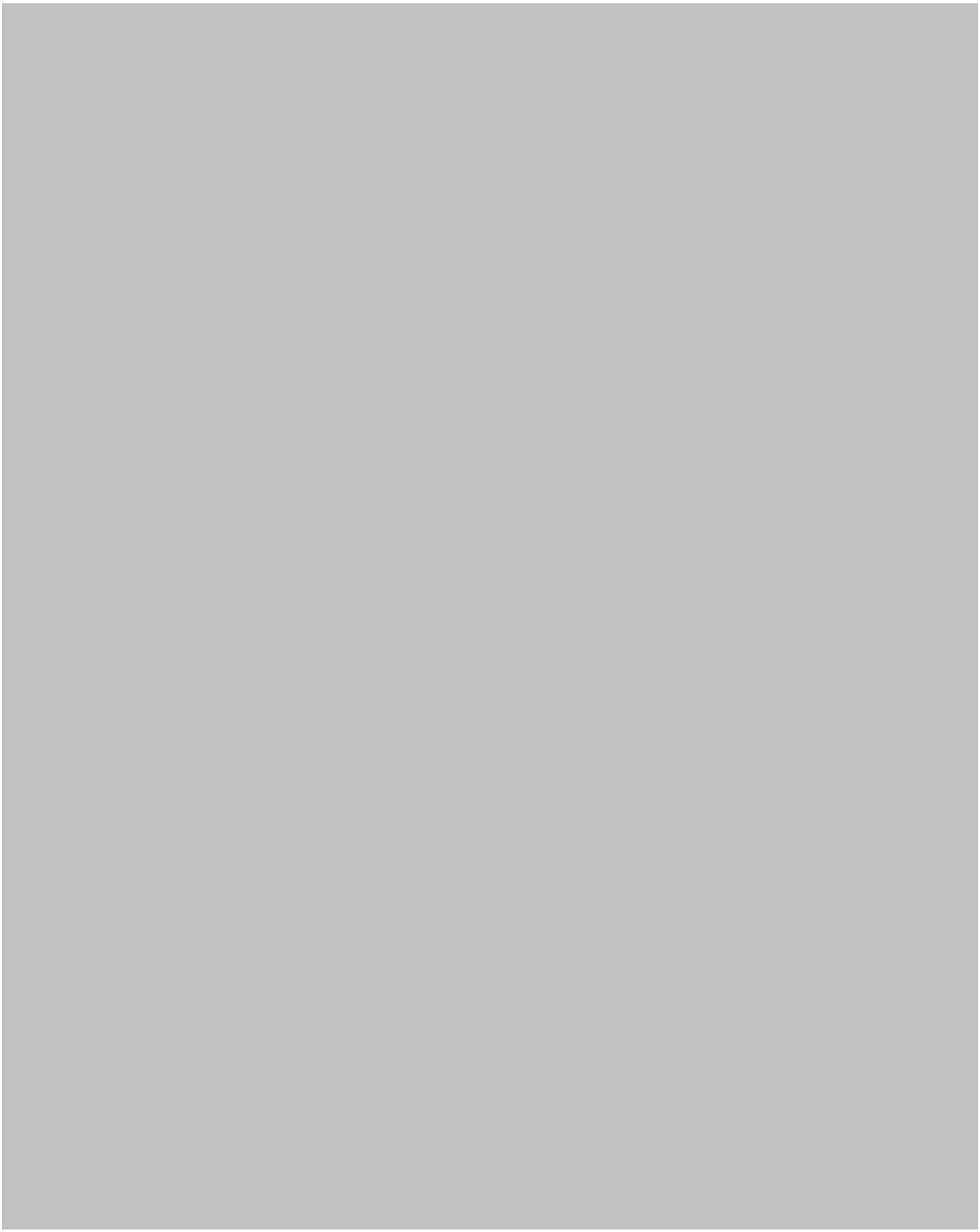


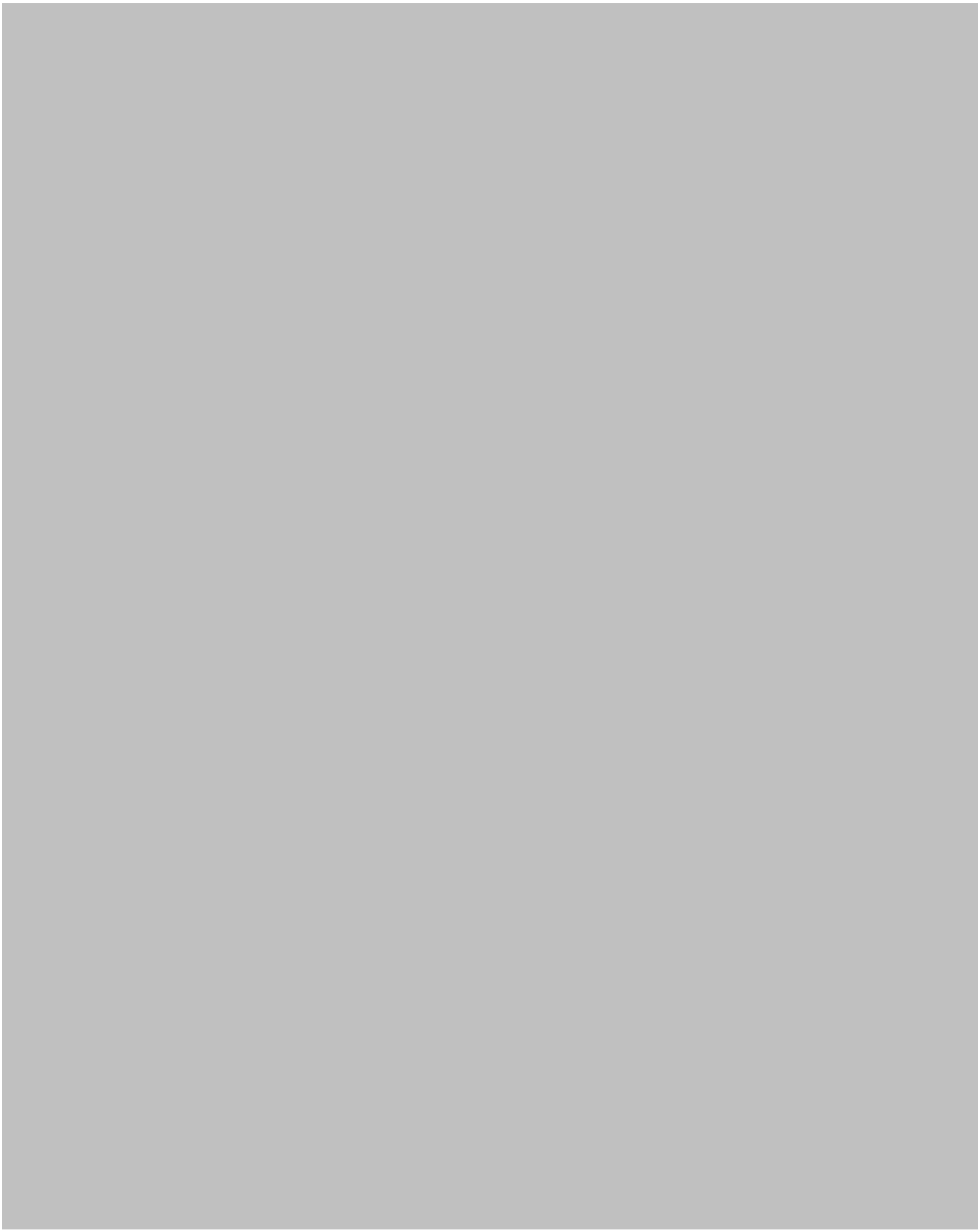












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