Official title: A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of SCD-044 in the Treatment of Moderate to Severe Atopic Dermatitis

Document: Study Protocol

NCT number: NCT04684485

Document date: 10 April 2023

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF SCD-044 IN THE TREATMENT OF MODERATE TO SEVERE ATOPIC DERMATITIS

CLINICAL STUDY PROTOCOL

Protocol Number: SCD-044-19-16

[redacted]

Protocol Version Date: April 10, 2023

Study Managing Lead: Taro Pharmaceuticals U.S.A., Inc.

[redacted]

Eudra Ct No.: 2022-001934-12

UTN: U1111-1289-7887

Sponsor: Sun Pharmaceutical Industries Ltd.

Developmental phase of study: 2b

[redacted]

[redacted]

[redacted]

PRINCIPAL INVESTIGATOR AGREEMENT

I have carefully read and understand the foregoing protocol SCD-044-19-16 “A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF SCD-044 IN THE TREATMENT OF MODERATE TO SEVERE ATOPIC DERMATITIS” and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR) and local regulatory guidelines. I will attempt to complete the study within the time designated.

I will ensure that the rights, safety and welfare, of Subjects under my care are protected. I will ensure control of the drugs under investigation in this study.

I will provide copies of the protocol and all other study-related information supplied by the Sponsor to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study.

I agree to keep records on all Subject information (case report forms, shipment and drug return forms and all other information collected during the study) and drug disposition in accordance with Food and Drug Administration (FDA) regulations.

I will not enroll any Subjects into this protocol until IRB approval and Sponsor approval are obtained.

Principal Investigator	**Signature, Date**

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LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALC	Absolute Lymphocyte Counts
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ACR	American College of Rheumatology
AST	Aspartate aminotransferase
ATS	American Thoracic Society
ATWS	Active Treatment Worst Case
AUC	Area under the concentration-time curve
AV block	Atrioventricular block
BL	Baseline
BP	Blood pressure
bpm	beats per minute
BSA	Body Surface Area
CFR	Code of Federal Regulations
Cmax	Maximum Concentration/Maximum Observed Concentration
CMH	Cochran-Mantel-Haenszel
CNS	Central Nervous System
COPD	Chronic obstructive pulmonary disease
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
Ctrough	lowest concentration reached by a drug before the next dose
DLQI	Dermatology Life Quality Index
DM	Data Management
DMARD	Disease Modifying Anti-rheumatic drug
EASI	Eczema Area and Severity Index
EC	Ethics Committee
ECG	Electrocardiography
ED	Early Discontinuation
EDC	Electronic Data Capture
e.g.	exempli gratia, “for example”, “such as”
EoS	End-of-Study
EOT	End of Treatment
EU	European Union
EU Ct No.	European Union Clinical Trial Register number
FEV	Forced expiratory volume
FDA	Food and Drug Administration
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
GLP	Good Laboratory Practice
HAQ	Health Assessment Questionnaire
HBsAg	Surface antigen of the hepatitis B virus (HBV)
hCG	Human Chorionic Gonadotropin
HEENT	Head, Eyes, Ears, Nose and Throat
HIV	Human immunodeficiency virus
hr	Hour
HR	Heart rate
hrs	Hours
HDL	High-density lipoproteins
ICF	Informed Consent Form
IGA	Investigator Global Assessment
ICH	International Conference on Harmonization
ID	Identification
IRB	Institutional Review Board
IUD	Intrauterine Device
ICH	International Conference on Harmonization
IGA	Investigator’s Global Assessment
INR	International Normalized Ratio
IND	Investigational New Drug
IP (IMP)	Investigational (Medicinal) Product
IR	Infrared

IRT	Interactive Response Technology
ITT	Intent To Treat
IV	Intravenous
Kg	Kilogram
LDL	Low-density lipoprotein
L/kg	Litre per kilogram
LOCF	Last Observation Carried Forward
mg	Milligram
mL	Millilitre
mm	millimeter
MCV	Mean Corpuscular Volume
MM	Medical Monitor
Mm Hg	millimeter of mercury
msec	millisecond
NCE	New Chemical Entity
NDA	New Drug Application
ng	Nanogram
NK cell	Natural Killer cell
NOAEL	No Observed Adverse Effect Level
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
NYHA	New York Heart Association
OCT	Optical Coherence Tomography
OTC	Over the Counter
PFT	Pulmonary Function Test
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	Principal Investigator
POEM	Patient Oriented Eczema Measure
PtGA	Patient Global Assessment of Disease Activity
PtA-P	Patient Global Assessment of Pain
[redacted]	[redacted]
PML	Progressive Multifocal Leukoencephalopathy
PP	Per Protocol
PRES	Posterior Reversible Encephalopathy Syndrome
PT	Prothrombin time
aPTT	Activated partial thromboplastin time
PUVA	psoralen and ultraviolet A
QRS	A combination of the Q wave, R wave and S wave
QT	QT Interval (the time from the start of the Q wave to the end of the T wave)
QTcF	QT corrected Fridericia's formulas
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCORAD	SCORing Atopic Dermatitis
S1P	Sphingosine-1-phosphate
S1PR1	Sphingosine-1-phosphate Receptor 1
SPARC	Sun Pharma Advanced Research Company Limited
SPIL	Sun Pharmaceutical Industries Ltd.
SUSAR	Suspected Unexpected Serious Adverse Reactions
t1/2	Half-Life
TBL	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
TIA	Transient Ischemic Attack
Tmax	Time to Maximum Plasma Concentration
vIGA-AD™	Validated Investigator Global Assessment scale for Atopic Dermatitis (also vIGA)
VAS	Visual Analogue Scale
VZV	Varicella Zoster Virus
ULN	Upper Limit of Normal
UTN	Universal Trial Number
UV-B	type B ultraviolet
WBC	White Blood Cell
PP-NRS	Peak Pruritus Numeric Rating Scale
µg/mL	Microgram Per Milliliter
µg•h/mL	Microgram Times Hour Per Milliliter
µM	Micro Molar

STUDY SYNOPSIS

Protocol Number: SCD-044-19-16

Title of Study: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF SCD-044 IN THE TREATMENT OF MODERATE TO SEVERE ATOPIC DERMATITIS

Sponsor: Sun Pharmaceutical Industries Ltd

[redacted]

Start of the study: in North and Latin America: June 2021 [first participant enrolled]
in Europe: July 2023 [anticipated open for recruitment]

End of the study: the study is expected to be concluded upon final collection of data for all outcome measures and adverse events, including safety follow up (last participant's last visit).

Investigational Products:
SCD-044 Tablets [redacted] (Low dose)
SCD-044 Tablets [redacted] (Intermediate dose)
SCD-044 Tablets [redacted] (High dose)
SCD-044 Tablets [redacted])

Control: Placebo of SCD-044 product

Treatment Duration: The study treatment period will last up to 32 weeks

Dose and Mode of Administration: [redacted] according to a randomization scheme and [redacted] schedule.

Objectives:

Primary Objective:

- To determine the effect of SCD-044 treatment on moderate to severe atopic dermatitis, as measured by proportion of subjects showing at least 75% improvement in Eczema Area and Severity Index (EASI) at Week 16.

Secondary Objectives:

- To evaluate the efficacy of SCD-044 as measured by validated Investigator's Global Assessment (vIGA) of disease severity
- To evaluate the efficacy of SCD-044 as measured by Peak Pruritus Numeric Rating Scale (PP-NRS)
- To evaluate the efficacy of SCD-044 as measured by SCORing Atopic Dermatitis (SCORAD)
- To evaluate the efficacy of SCD-044 as measured by Patient Oriented Eczema Measure (POEM)
- To evaluate the efficacy of SCD-044 as measured by change in body surface area (BSA) involvement over the treatment period
- To assess the effect of SCD-044 on quality of life, as measured by Dermatology Life Quality Index (DLQI)
- To assess the effect of SCD-044 on Patient Global Impression of Severity (PGIS)
- To assess the effect of SCD-044 on Patient Global Impression of Change (PGIC)
- To assess the safety and tolerability of SCD-044 in subjects with moderate to severe atopic dermatitis

[redacted]

[redacted]

Design: Subjects in this randomized, double-blind, placebo controlled, parallel-group, multiple-center study will be assigned to treatment with the investigational products or placebo control according to a randomization scheme and [redacted] schedule:

- **Part I** (16 weeks): Subjects will be randomized to Placebo, Low dose [redacted] Intermediate dose [redacted] or High dose [redacted]

[redacted]

[redacted]

Phone or in person contacts may be scheduled [redacted] to collect information on concomitant medication, compliance with the study drug use, health changes (AEs & AESI), queries for PML and PRES and to provide instructions.

[redacted]

Subjects will be admitted into the study after informed consent has been obtained. An Unscheduled Visit is allowed at any time, for any reason, if in the Investigator's opinion it is warranted. If a Subject is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit and all procedures scheduled for Early Discontinuation will be performed. If the Unscheduled Visit is not an Early Discontinuation Visit (i.e., the Subject will continue to take part in the study), then all procedures scheduled for that Unscheduled Visit will be performed. Subjects who are discontinued early from the study must attend the Follow-up [redacted] weeks after the date of Early Discontinuation.

Study Population:

Key Inclusion Criteria

1. Males and non-pregnant non-lactating females ≥ 18 years of age providing written informed consent prior to any study-related procedures.
2. Diagnosis of chronic atopic dermatitis for ≥ 1 year at Screening and Baseline based on Eichenfield revised criteria of Hanifin and Rajka

[redacted]

Key Exclusion Criteria

1. Female Subjects who are pregnant, nursing or planning to become pregnant during study participation or within 6 months of completing the study.

[redacted]

[redacted]

5. Known organ complications of Diabetes mellitus such as reduced renal function, significant retinal pathology or neuropathy.
6. History or presence of uveitis

[redacted]

[redacted]

Number of Subjects:

Approximately 240 subjects will be enrolled in the study [redacted] to the following treatment groups:

- Placebo of SCD-044
- SCD-044 Tablets [redacted] (Low dose)
- SCD-044 Tablets [redacted] (Intermediate dose)
- SCD-044 Tablets [redacted] (High dose)

[redacted]

A subset of eligible subjects will participate in photographic evaluation

At Baseline, subjects will be randomized to 4 treatment groups [redacted]

Criteria for Evaluation:

Following assessments will be performed by the investigator according to the schedule of assessments:

Efficacy:

- Eczema Area and Severity Index (EASI), validated Investigator's Global Assessment (vIGA-AD™, abbreviated as vIGA), Body Surface Area (BSA), and SCORing Atopic Dermatitis (SCORAD).
- Subjects will be asked to complete DLQI, POEM, PGIS, PGIC, and PP-NRS.

[redacted]

[redacted]

Study Endpoints:

Primary:

- Proportion of subjects who achieve ≥75% overall improvement in EASI score from Baseline to Week 16

Key Secondary:

- Proportion of subjects who achieve score of '0' (clear) or '1' (almost clear) on a 5-point, vIGA scale [redacted]

Other Secondary:

[redacted]

- Proportion of subjects who achieve ≥4-point improvement in PP-NRS from Baseline to Weeks [redacted] 32

[redacted]

- Proportion of subjects who achieve SCORAD 50 and SCORAD 75 response from Baseline to Week [redacted] 32
- Change from Baseline in quality of life measured by DLQI scores to Week [redacted] 32

- Change from Baseline in percent BSA with atopic dermatitis measured to Week 32
- Change from Baseline in POEM score to Week d 32
- Proportion of subjects who achieve ≥4-point improvement from Baseline in the frequency of itching recorded in PP-NRS to 32
- Proportion of subjects with improvement in PGIC from Baseline to Week 32
- Change in PGIS of disease from Baseline to Weeks 32

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1. INTRODUCTION AND BACKGROUND

Atopic dermatitis (AD) is a chronic, inflammatory skin disease that affects approximately 18 million adults and 13% of children in the United States. It is characterized by red, itchy, and scaly rashes that are typically on the face, arms, and legs, but may occur anywhere on the body. Scratching of pruritic lesions can also lead to lichenification. While its etiology is unknown, risk factors include family history of atopic diseases and genetics. A child has a higher chance of developing AD if the parent has AD, asthma, or allergic rhinitis. The condition can be worsened by triggers such as stress and allergens. It usually begins during the first few years of life and its severity may fluctuate overtime, with flares and symptoms continuing into adulthood.[1]

The diagnosis of AD is based on chronic or relapsing history and clinical examination of the features of pruritus, and typical morphology and distribution pattern of lesions specific to age.[2,3,4] Minor features including xerosis, early age of onset, and secondary skin infections of *Staphylococcus aureus* and *Herpes simplex* can also support diagnosis. Treatments include skin care management, elimination of exacerbating factors, moisturizers, antihistamines, antidepressants, corticosteroids, phototherapy, immunosuppressants, and biologics. Antibiotics are used to treat secondary infections. Because AD can also cause distress, the appropriate therapy depends on the severity of the disease as well as its effect on the patient's quality of life.

Topical corticosteroid (TCS) is the first-line therapy for managing acute *flare*. Although TCS is effective for controlling acute *flare*, it may not be clinically safe to use TCS for longer than 1 to 2 weeks because of side effects like skin atropy, acne, purpura etc. After initial therapy with TCS, topical calcineurin inhibitors (TCI, e.g. tacrolimus or pimecrolimus) can be prescribed for maintenance therapy, which can be used up to 6 months or 1 year. The most common side-effect of topical calcineurin inhibitors (TCI) is a burning sensation on the skin where the drug is applied topically along with other common side effects like nasopharyngitis, respiratory tract infection and headache.

[redacted]

Sun Pharmaceutical Industries Limited (SPIL) is developing a S1P1 receptor agonist, SCD-044, to treat moderate to severe atopic dermatitis. SCD-044 is a potent S1P1 [redacted]

S1PR1 modulation and the resulting lymphocyte sequestration have potential for treating [redacted] AD, psoriasis, [redacted]

SCD-044 has shown efficacy in preclinical models of AD. SCD-044 was evaluated for safety and tolerability in Phase 1 clinical study. The safety and tolerability of SCD-044 following administration of single and multiple doses is demonstrated. In addition, pharmacodynamics effect of SCD-044 was evaluated in Phase 1 study. SCD-044 caused clinically meaningful reduction in lymphocyte counts with acceptable safety profile in the Phase I study. The reduction in lymphocytes is anticipated to result in therapeutic benefit in treatment of AD.

The current study is a Phase IIb dose ranging study to assess the efficacy and safety of SCD-044 in treatment of moderate to severe AD.

[redacted]

[redacted]

2. OBJECTIVES

The objectives of this study are as follows:

Primary Objective:

- To determine the effect of SCD-044 treatment on moderate to severe atopic dermatitis, as measured by proportion of subjects showing at least 75% improvement in Eczema Area and Severity Index (EASI) at Week 16.

Secondary Objectives:

- To evaluate the efficacy of SCD-044 as measured by validated Investigator's Global Assessment (vIGA) of disease severity
- To evaluate the efficacy of SCD-044 as measured by Peak Pruritus Numeric Rating Scale (PP-NRS)
- To evaluate the efficacy of SCD-044 as measured by SCORing Atopic Dermatitis (SCORAD)
- To evaluate the efficacy of SCD-044 as measured by Patient Oriented Eczema Measure (POEM)
- To evaluate the efficacy of SCD-044 as measured by change in body surface area (BSA) involvement over the treatment period
- To assess the effect of SCD-044 on quality of life, as measured by Dermatology Life Quality Index (DLQI)
- To assess the effect of SCD-044 on Patient Global Impression of Severity (PGIS)
- To assess the effect of SCD-044 on Patient Global Impression of Change (PGIC)
- To assess the safety and tolerability of SCD-044 in subjects with moderate to severe atopic dermatitis

[redacted]

[redacted]

3. STUDY OVERVIEW

Start of the study: in North and Latin America: [redacted]
in Europe: [redacted]

End of the study: the study is expected to be concluded upon final collection of data for all outcome measures and adverse events, including safety follow up (last participant's last visit).

Subjects in this randomized, double-blind, placebo controlled, parallel-group, multiple-center study will be assigned to treatment with the investigational products or placebo control according to a randomization scheme and [redacted] schedule.

- **Part I** ([redacted] Subjects will be randomized to Placebo, Low dose [redacted] Intermediate dose [redacted] or High dose [redacted] of SCD-044 in [redacted] to assess primary and secondary endpoints [redacted]
- **Part II** [redacted]
- [redacted]

[redacted]

[redacted]

Phone or in person contacts may be scheduled for [redacted] and corresponding [redacted] visits to collect information on concomitant medication, compliance with the study drug use, health changes (AEs & AESI), queries for PML and PRES and to provide instructions.

[redacted]

Subjects will be admitted into the study after informed consent has been obtained. An Unscheduled Visit is allowed at any time, for any reason, if in the Investigator's opinion it is warranted. If a Subject is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit and all procedures scheduled for Early Discontinuation will be performed. If the Unscheduled Visit is not an Early Discontinuation Visit (i.e., the Subject will continue to take part in the study), then all procedures scheduled for that Unscheduled Visit will be performed. [redacted]

A subset of eligible subjects will participate in photographic evaluation.

[redacted]

The assigned Investigational Product will be administered orally [redacted]. Subjects will be required to use diaries to document the date of study treatments, any missed treatments and the occurrence of all adverse events.

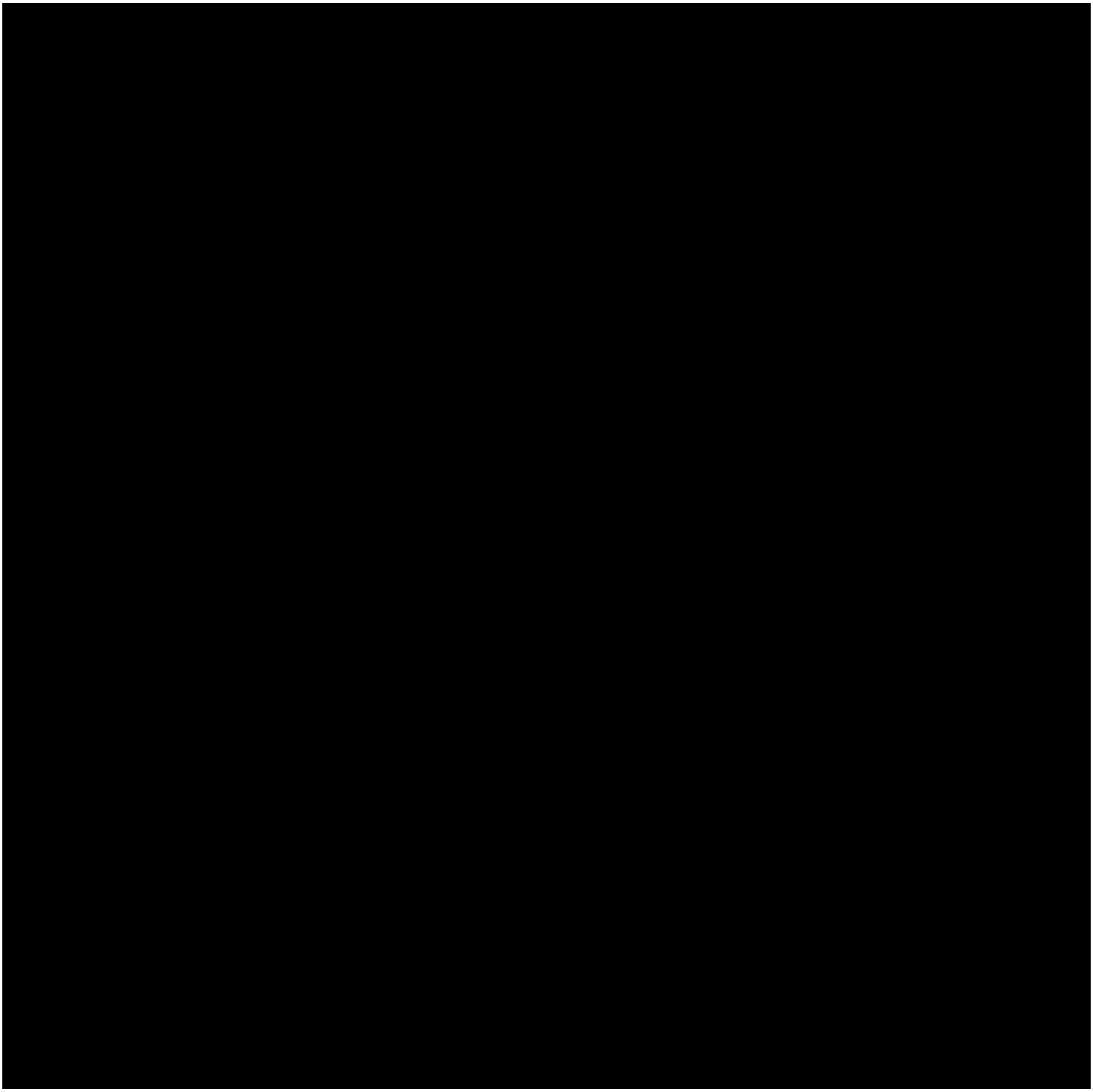
[redacted]

If the Principal Investigator or designee determines that the Subject's condition has worsened to the degree that it is unsafe for the Subject to continue in the study, the Subject may be discontinued from the study as a treatment failure and the Subject may be treated using the standard care.

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

4. STUDY POPULATION

4.1 Number of Subjects

Approximately 240 subjects will be enrolled in the study in a [redacted] the following treatment groups:

- Placebo of SCD-044 product [redacted]
- SCD-044 Tablets [redacted] (Low dose)
- SCD-044 Tablets [redacted] (Intermediate dose)
- SCD-044 Tablets [redacted] (High dose)

[redacted]

4.2 Inclusion Criteria

1. Males and non-pregnant non-lactating females ≥ 18 years of age providing written informed consent prior to any study-related procedures.
2. Diagnosis of chronic atopic dermatitis for ≥ 1 year at Screening and Baseline based on Eichenfield revised criteria of Hanifin and Rajka [redacted]
3. Moderate to severe atopic dermatitis at Screening and Baseline defined as:

[redacted]

[redacted]

4.3 Exclusion Criteria

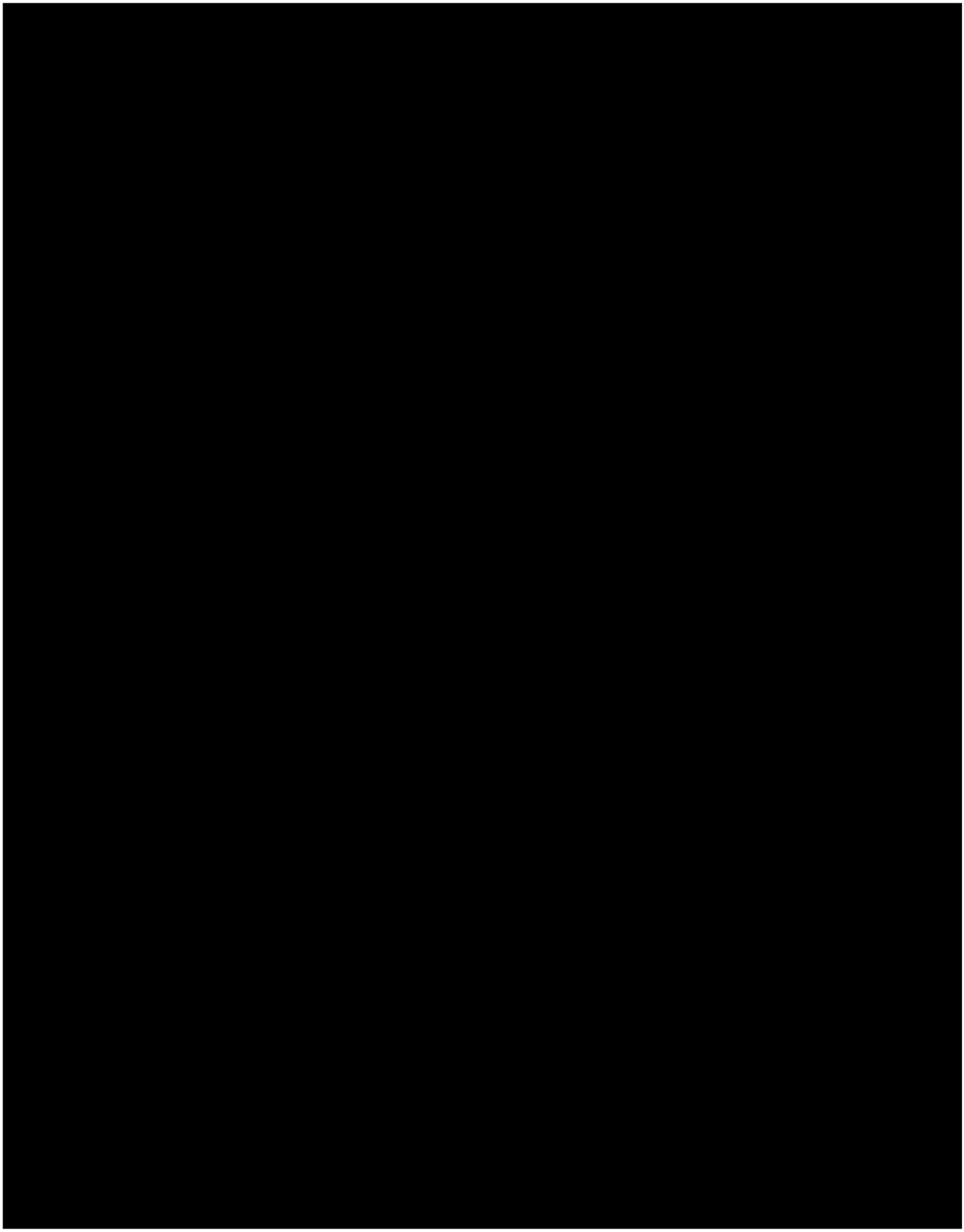
1. Female Subjects who are pregnant, nursing or planning to become pregnant during study participation or within 6 months of completing the study.

[redacted]

[redacted]

5. Known organ complications of Diabetes mellitus such as reduced renal function, significant retinal pathology or neuropathy.
6. History or presence of uveitis

[redacted]



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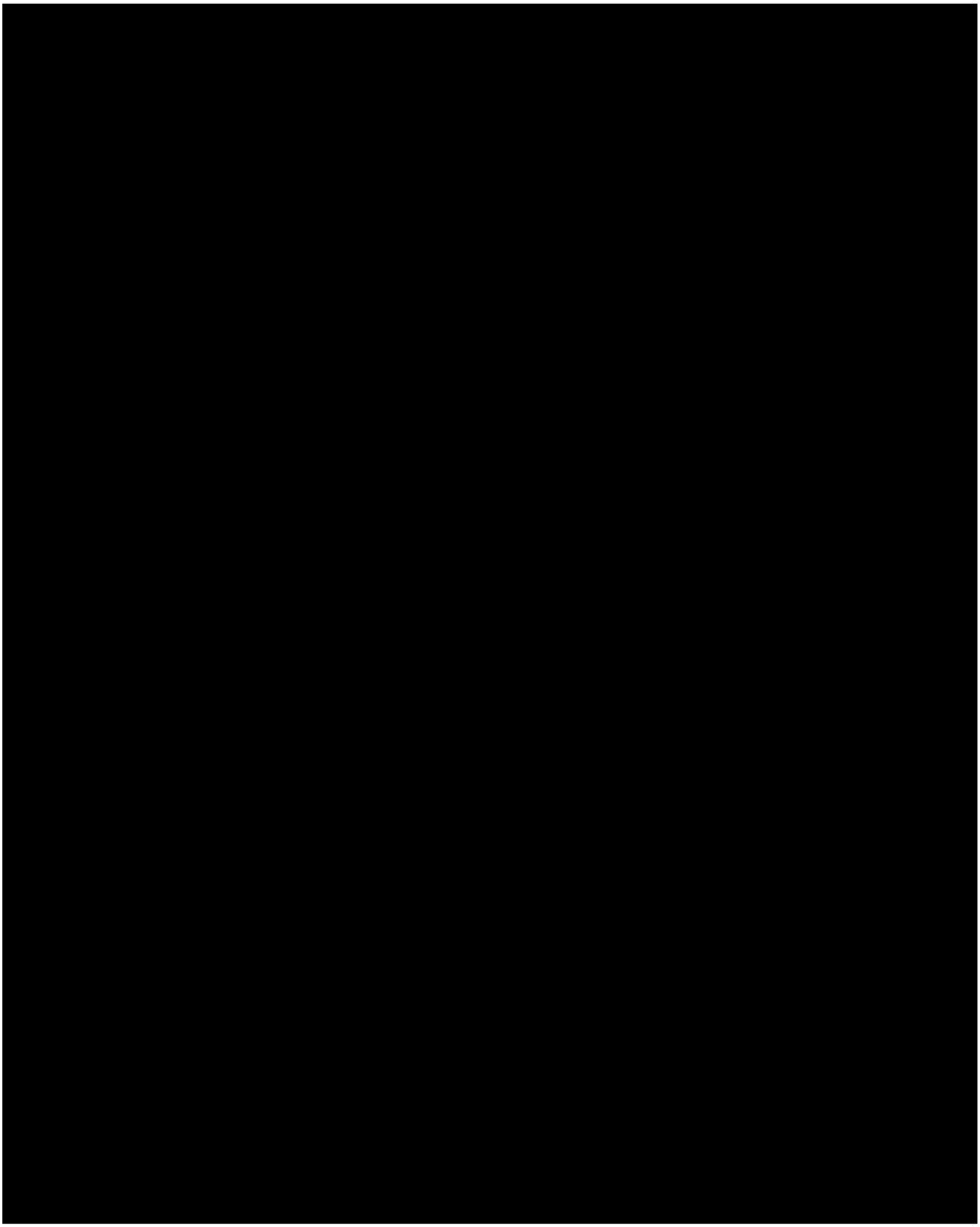

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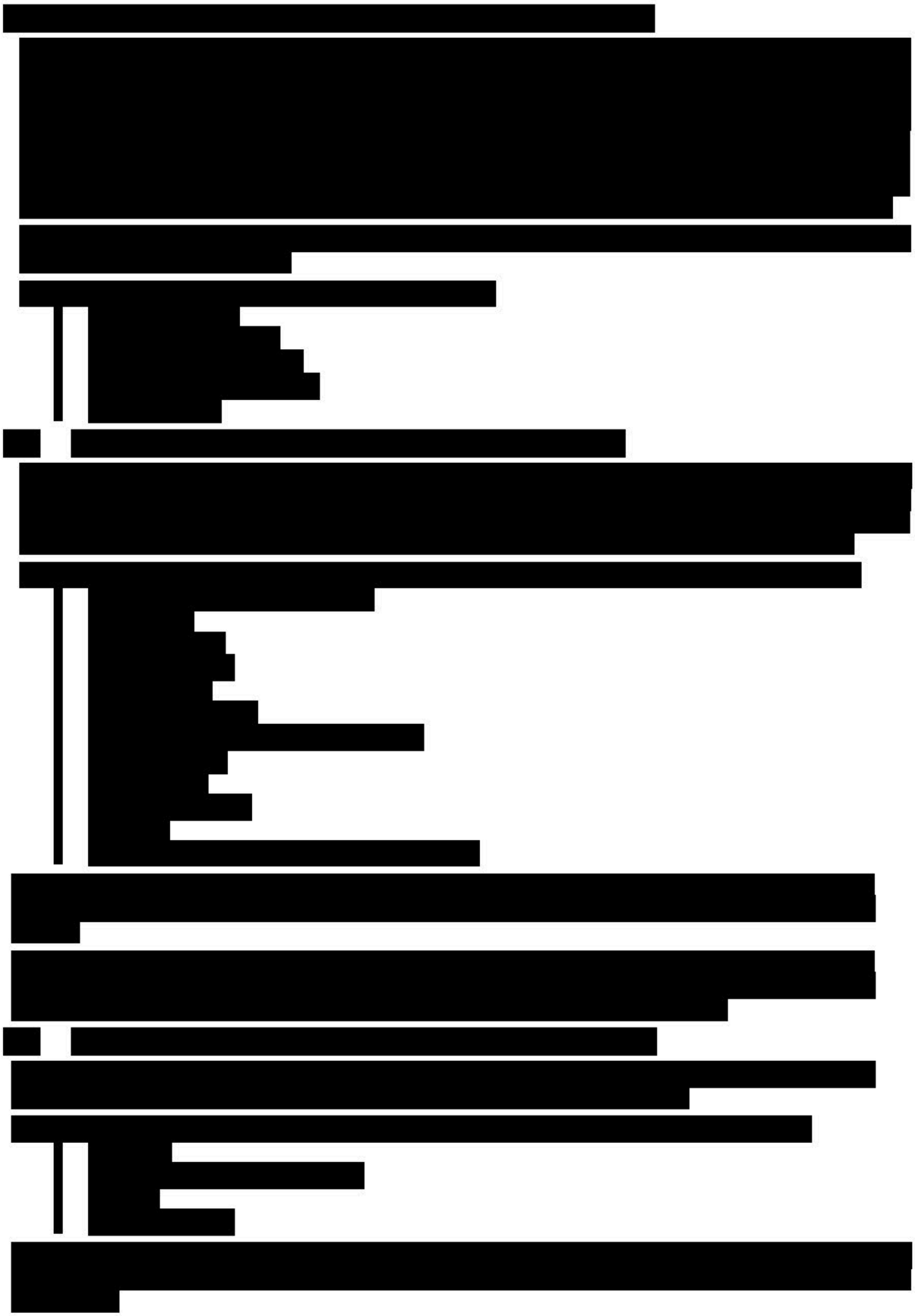

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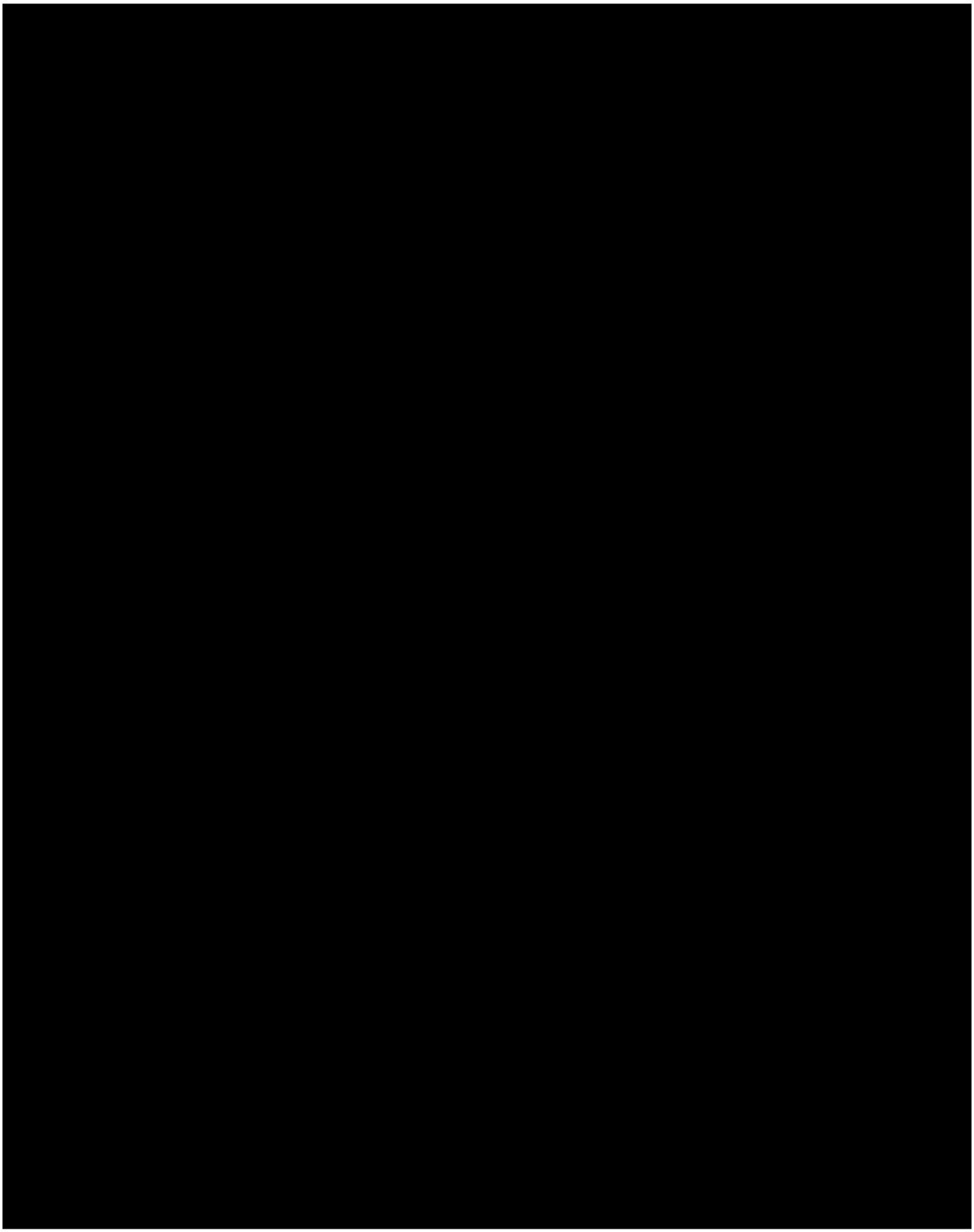
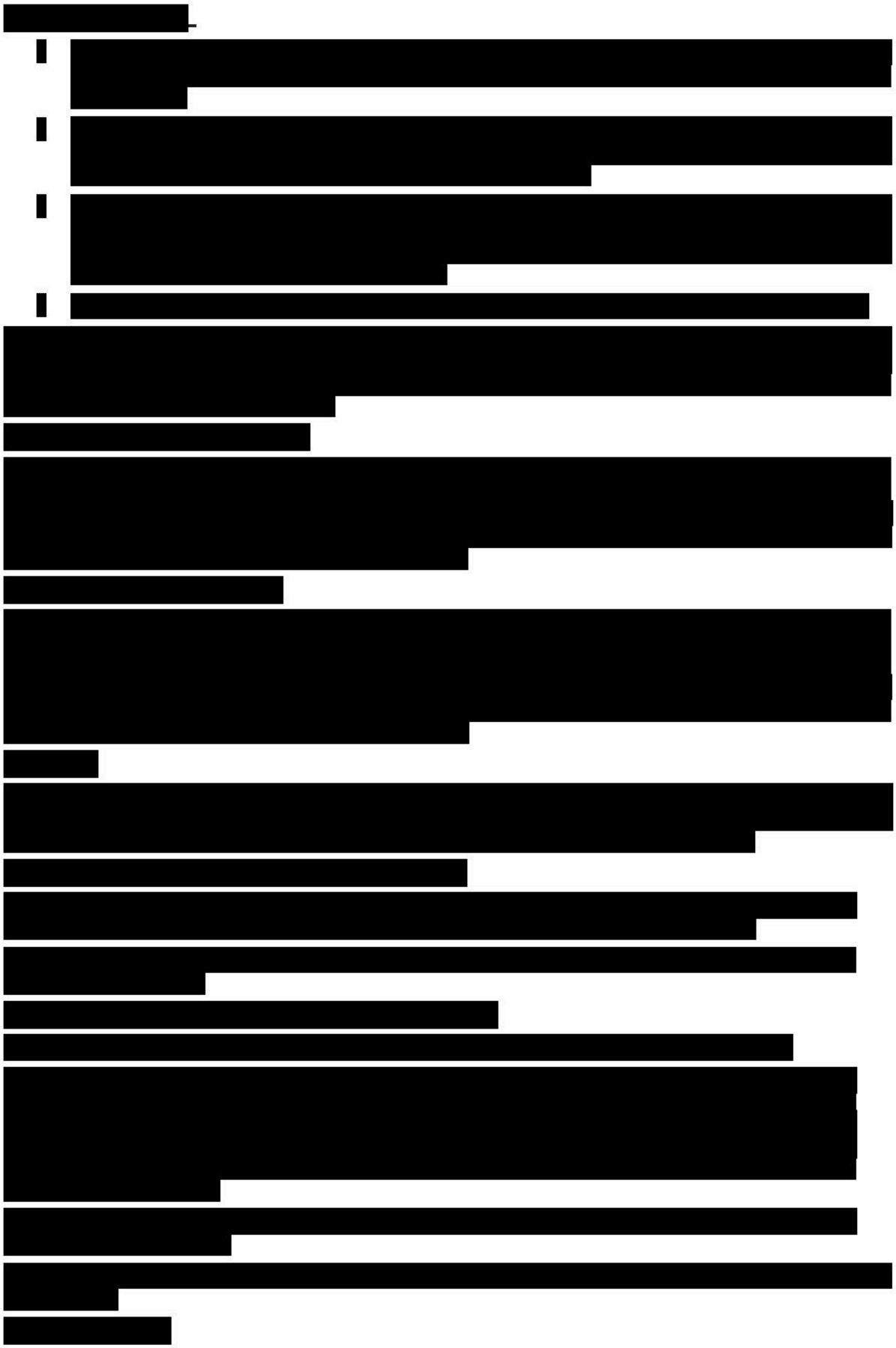
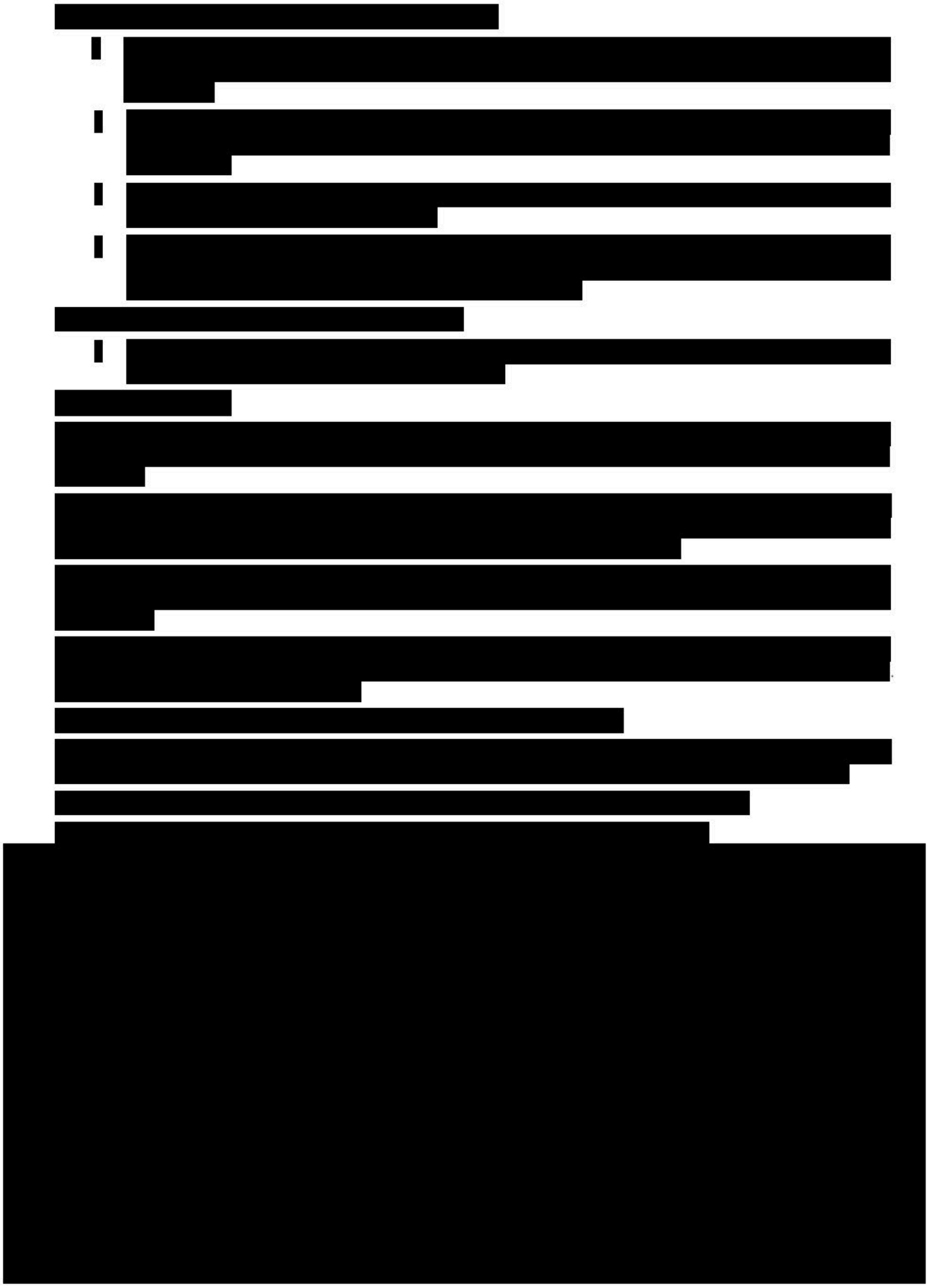






[redacted]

[redacted]

6 STUDY EVALUATIONS

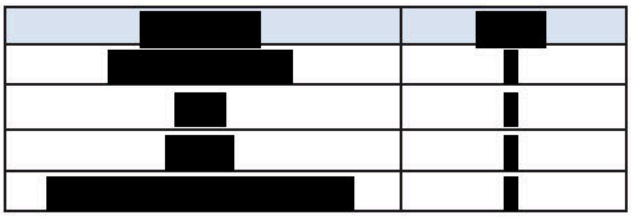
6.1 Efficacy

Efficacy assessments should be performed by the investigator or a designee who is appropriately trained and experienced in the assessment of atopic dermatitis patients.

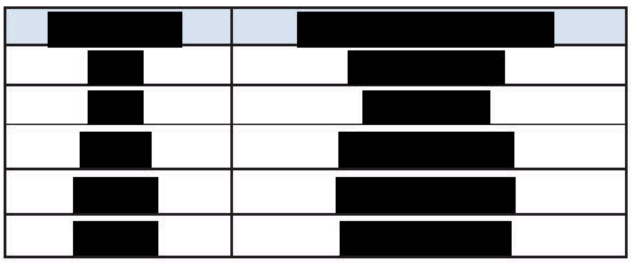
Preferably a [redacted] qualified Investigator or designee at each clinical site will perform focused area assessments (vIGA, EASI, SCORAD, BSA) for each Subject [redacted]

6.1.1 Dermatology Life Quality Index (DLQI)[15]

At the study visits [redacted] subjects will be asked to complete a 10-item questionnaire to measure how much the skin problem has affected subject's life over the past week. [redacted]. Subject will be instructed to complete the DLQI before the subject is interviewed for adverse event monitoring. [redacted]



The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired:



6.1.2 Patient Global Impression of Severity (PGIS)[16]

At the study visits [redacted] subjects will be asked to assess their overall impression of disease severity over the past week using a scale of None, Mild, Moderate or Severe. (Appendix VI)

6.1.3 Patient Global Impression of Change (PGIC)[17]

At the study visits [redacted]) subjects will be asked to assess if there has been an improvement or decline in clinical status using a 5-point scale depicting a patient's rating of overall improvement. [redacted]

6.1.4 Peak Pruritus Numeric Rating Scale (PP-NRS)[18]

At the study visits [redacted] subjects will be asked to assess severity of itching caused due to atopic dermatitis [redacted]

[redacted]

6.1.5 Validated Investigator Global Assessment (vIGA)[19]

At Screening and Baseline, to be eligible for inclusion in the study, subjects must have a definite clinical diagnosis of atopic dermatitis of at least moderate severity [redacted] as an overall assessment of all atopic dermatitis lesions.

At the Screening and the study visits [redacted] the investigator will perform an overall assessment of all atopic dermatitis lesions [redacted]

[redacted]

6.1.6 Body Surface Area (BSA)

At Screening and Baseline, to be eligible for inclusion in the study, subjects must have a definite clinical diagnosis of atopic dermatitis [redacted]

At the screening and the study visits 2 [redacted] the investigator will assess both the % BSA affected with atopic dermatitis and extent of involvement for the [redacted]

At the study visits [redacted] the investigator will assess extent of involvement for the SCORAD [redacted]

6.1.7 Patient Oriented Eczema Measure (POEM)[21]

At study visits [redacted], subjects wll be asked to complete a 7-item questionnaire about their atopic dermatitis over the past [redacted]

Each of the seven questions carries equal weight [redacted]

[redacted]

6.1.8 Eczema Area and Severity Index (EASI)[22]

At Screening and Baseline, to be eligible for inclusion in the study, [redacted]

[redacted]

[redacted]

Based on gross morphological findings, scores will be assigned on a 4-point scale ['0' (absent), '1' (mild), '2' (moderate) and '3' (severe)] for each clinical sign. [redacted]

6.1.9 SCORing Atopic Dermatitis (SCORAD)[23]

At study visits [redacted] the investigator will assess the extent and severity of atopic dermatitis using the SCORAD.

[redacted]

[redacted]

6.5 Diagnosis of Atopic Dermatitis

At Screening and Baseline, to be eligible for inclusion in the study, subjects must have a definite clinical diagnosis of chronic atopic dermatitis for at least 1 year as defined by [redacted] of Hanifin and Rajka (see Table 3).[3]

Note: It is acceptable for the first diagnosis of atopic dermatitis (done ≥ 1 year prior to Screening) to be based on [redacted] or the criteria of Hanifin and Rajka (Table 4).[4]

Table 3: Eichenfield revised criteria of Hanifin and Rajka for diagnosis of AD

Essential features (must be present):

• Pruritus
• Eczema (acute, subacute, chronic)
  ▪ Typical morphology and age-specific patterns*
  ▪ Chronic or relapsing history
 	
*<u>*Patterns include:*</u>

1. Facial, neck, and extensor involvement in infants and children 2. Current or previous flexural lesions in any age group 3. Sparing of the groin and axillary regions
IMPORTANT FEATURES—Seen in most cases, adding support to the diagnosis:
• Early age of onset • Atopy ▪ Personal and/or family history ▪ Immunoglobulin E reactivity • Xerosis
ASSOCIATED FEATURES—These clinical associations help to suggest the diagnosis of atopic dermatitis but are too nonspecific to be used for defining or detecting atopic dermatitis for research and epidemiologic studies:
• Atypical vascular responses (eg, facial pallor, white dermographism, delayed blanch response) • Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis • Ocular/periorbital changes • Other regional findings (eg, perioral changes/periauricular lesions) • Perifollicular accentuation/lichenification/prurigo lesions
EXCLUSIONARY CONDITIONS—It should be noted that a diagnosis of atopic dermatitis depends on excluding conditions, such as:
• Scabies • Seborrheic dermatitis • Contact dermatitis (irritant or allergic) • Ichthyoses • Cutaneous T-cell lymphoma • Psoriasis • Photosensitivity dermatoses • Immune deficiency diseases • Erythroderma of other causes

Table 4: Diagnostic features of atopic dermatitis by Hanifin and Rajka

basic features (must have 3 or more)
• Pruritus • Typical morphology and distribution: Flexural lichenification or linearity in adults Facial and extensor involvement in infants and children • Chronic or chronically-relapsing dermatitis • Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)
and minor features (must have 3 or more)
1. Xerosis **2.** Ichthyosis/palmar hyperlinearity/keratosis pilaris **3.** Immediate (type I) skin test reactivity **4.** Elevated serum IgE **5.** Early age of onset **6.** Tendency toward cutaneous infections (esp. *Staph. Aureus* and *Herpes simplex*)/impaired cell-mediated immunity **7.** Tendency toward non-specific hand or foot dermatitis **8.** Nipple eczema **9.** Cheilitis **10.** Recurrent conjunctivitis **11.** Dennie-Morgan infraorbital fold **12.** Keratoconus **13.** Anterior subcapsular cataracts **14.** Orbital darkening **15.** Facial pallor/facial erythema

16. Pityriasis alba
17. Anterior neck folds
18. Itch when sweating
19. Intolerance to wool and lipid solvents
20. Perifollicular accentuation
21. Food intolerance
22. Course influenced by environmental/emotional factors
23. White dermographism/delayed blanch

[redacted]

7.1.1 [redacted] Screening Visit [redacted]

Potential subjects will be screened during a [redacted] period prior to randomization. CRO/Sponsor's approval is required on a case-by-case basis for an extension of the Screening Period to obtain all test results and to re-screen a subject. [redacted] The new informed consent/assent is not required, unless an amended or revised informed consent/assent is introduced during the study.

The following procedures will be performed at Screening:

1. **Written informed consent will be obtained**. Subjects must have provided IRB approved written informed consent. Subjects will be given the approved ICF describing the study and any risks associated with participation. The Subject will be allowed as much time as needed to read and understand the information presented in the consent form. Appropriate study personnel will be available to answer any questions the Subject might have regarding the study or study-related procedures. If the Subject chooses to participate in the study, he or she will be asked to sign and date the consent form and will be provided with a copy for his or her records. The ICF must be signed by the Subject before any protocol assessments can be undertaken.
2. Demographics will be collected, including date of birth, gender, race and ethnicity.
3. A compliance with applicable inclusion and exclusion criteria will be reviewed. (See Sections 4.2, 4.3)
4. After confirming the eligibility, the Subject will be assigned a screening number.
5. A complete medical history will be obtained for the Subject's current and past medical conditions. Significant medical history should include, but not be limited to, evidence of hypertension, lipid disorders, obesity*, heart attack, stroke, congestive heart failure, kidney disease, and auto immune disease and diabetes. Significant surgical history should include, but not be limited to, removal of blockage from an artery and gallbladder removal. (See Section 5.1)

   * Obesity = BMI ≥30 (as defined by Metropolitan Life Insurance Company Chart)
6. A complete list of current and past (within the previous 30 days) medications will be obtained for each Subject. (See Section 5.8)
7. A physical examination will be performed. At a minimum, the physical examination will include the following: height, weight, assessment of general appearance, comprehensive skin examination, HEENT, heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, and extremities. (See Section 5.2)
8. A urinalysis dipstick will be performed and evaluated at a site (See Section 5.5)
9. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
10. Blood samples will be collected for Hematology, Lipid Profile, Chemistry, Coagulation profile, Serology, QuantiFERON Gold test, and Serum pregnancy test for women of childbearing potential (See Section 5.5)
11. Any AEs occurring after signing Informed Consent should be reported (See Section 5.9)
12. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
13. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
14. A 12-lead electrocardiogram (ECG) will be performed (See Section 5.12)
15. A pulmonary function test will be performed or scheduled with an external expert (See Section 5.6)
16. An ophthalmologic examination including OCT will be performed or scheduled with an external expert (See Section 5.7)
17. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.

18. The overall status of the Subject's atopic dermatitis will be assessed using the validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA). (See Section 6.1.5). [redacted].
19. Eczema Area and Severity Index (EASI) will be evaluated. [redacted]
20. Body Surface Area (BSA) involvement will be assessed. [redacted]

[redacted]

7.1.2 [redacted] Baseline Visit [redacted]

If the Screening assessment was completed more than 2 weeks prior:

1. A physical examination will be performed. At a minimum, the physical examination will include the following: height, weight, assessment of general appearance, comprehensive skin examination, HEENT, heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, and extremities. (See Section 5.2)
2. A urinalysis dipstick will be performed and evaluated at a site (See Section 5.5)
3. A blood sample(s) will be collected for Hematology, Lipid Profile, Chemistry, and Coagulation (See Section 5.5)

The following procedures will be performed at Baseline:

4. Compliance with the inclusion and exclusion criteria, including results of laboratory evaluations, a pulmonary function test, and an ophthalmologic examination will be reviewed.
5. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.5)
6. After confirming the eligibility, the Subject will be assigned a randomization number using Interactive Response Technology (IRT). (see Section 8.4.1)
7. The Subject's diary provided at the previous visit will be collected and reviewed.
8. A medical history will be updated with any changes of the Subject's health since the previous study visit. (See Section 5.1)
9. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.8)
10. A [redacted] sample will be collected for [redacted] sample (See Section 6.3)
11. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
12. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
13. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
14. Subject Reported Assessments will be collected for:
    [redacted]
15. Focused Area Assessments will be performed for:
    - Validated Investigator Global Assessment (vIGA) (See Section 6.1.5)
    [redacted]

16. A whole-body photography – *for subjects consenting for photography* (See Section 6.4)
17. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)

19. Study drug administration in a clinic before 12 noon (See Section 8.5)

21. A general safety review before discharge

Note: Contact for should be scheduled at least 3 days after .

7.1.3 Visit

The following procedures will be performed at

1. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.5)
2. Subject Reported Assessments will be collected for:
3. Focused Area Assessments will be performed for:
   - Validated Investigator Global Assessment (vIGA) (See Section 6.1.5)

The following procedures will be performed by an independent safety team:

4. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
5. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
6. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
7. The Subject's diary provided at the previous visit will be collected and reviewed.
8. The returned study drugs will be counted
9. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 4.5 and 5.8)

10. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
11. A blood sample(s) will be collected for (See Section 5.5):
    - Hematology (total WBC count with differential counts including ALC and ANC)
    - Chemistry

[redacted]

13. The following will be dispensed during [redacted]
    - The study drug assembled for [redacted]
    - A diary card with instructions and to record the study drug use, health changes and concomitant medication

    [redacted]
14. A general safety review before discharge

[redacted].

7.1.4 [redacted] Visit [redacted]

The following procedures will be performed at [redacted]

1. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.5)
2. Focused Area Assessments will be performed for:
    - Validated Investigator Global Assessment (vIGA) (See Section 6.1.5)
    - Eczema Area and Severity Index (EASI) (See Section 6.1.8)
    - SCORing Atopic Dermatitis (SCORAD) (See Section 6.1.9)
    - Body Surface Area (BSA) (See Section 6.1.6)

[redacted]

3. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
4. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
5. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
6. The Subject's diary provided at the previous visit will be collected and reviewed.
7. The returned study drugs will be counted
8. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 4.5 and 5.8)
9. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
10. A blood sample(s) will be collected for Hematology and Chemistry (See Section 3.1 and 5.5)
11. Independent Safety Assessor review:

- Safety Lab Alerts
- As available
    i. Lab results
    ii. Exam results

The following procedures will be performed prior a subject discharged from a clinic:

12. The following will be dispensed during
    - The study drug assembled for
    - A diary card with instructions and to record the study drug use, health changes and concomitant medication
13. A general safety review before discharge

7.1.5 Visit

The following procedures will be performed at

1. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.5)
2. Subject Reported Assessments will be collected for:
3. Focused Area Assessments will be performed for:
    - Validated Investigator Global Assessment (vIGA) (See Section 6.1.5)
4. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
5. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
6. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
7. An ophthalmologic examination including OCT will be performed or scheduled with an external expert (See Section 5.7)
8. The Subject's diary provided at the previous visit will be collected and reviewed.
9. The returned study drugs will be counted
10. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 4.5 and 5.8)
11. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
12. A sample will be collected for (See Section 3.1 and 5.5)
13. A sample will be collected for sample (See Section 6.3)

[redacted]

The following procedures will be performed prior a subject discharged from a clinic:

15. The following will be dispensed during Visit 9:
    - The study drug assembled for Visit 9
    - A diary card with instructions and to record the study drug use, health changes and concomitant medication
    - [redacted]
16. A general safety review before discharge

[redacted]

7.1.6 [redacted] Visit [redacted]

The [redacted] must be scheduled in a morning to allow the dosing before 12 noon.

The following procedures will be performed at [redacted]

1. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.5)
2. Subject Reported Assessments will be collected for:
   - [redacted]
3. Focused Area Assessments will be performed for:
   - [redacted]

[redacted]

5. A whole body photography – *for subjects consenting for photography* (See Section 6.4)

[redacted]

6. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
7. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
8. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
9. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
10. The Subject's diary provided at the previous visit will be collected and reviewed.
11. The returned study drugs will be counted
12. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 4.5 and 5.8)
13. The Subject's body weight will be measured while the Subject is lightly clothed (e.g., no coat or shoes)

14. A urinalysis dipstick will be performed and evaluated at a site (See Section 5.5)
15. A [redacted] sample will be collected for [redacted] (See Section 3.1 and 5.5)
16. A [redacted] sample will be collected for [redacted] (See Section 6.3)
17. A blood sample will be collected within one hour before dosing for [redacted] (See Section 5.14)

[redacted]

19. Study drug administration in a clinic before 12 noon (See Section 8.5)
20. The following will be dispensed during [redacted]
    - The study drug assembled for Visits 10, 11, 12, and 13
    - A diary card with instructions and to record the study drug use, health changes and concomitant medication

    [redacted]
21. A general safety review before discharge

[redacted]

7.1.7 [redacted] Visit [redacted]

[redacted]

1. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
2. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
3. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
4. The Subject's diary provided at the previous visit will be collected and reviewed.
5. The returned study drugs will be counted
6. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 4.5 and 5.8)
7. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)

8. A blood sample will be collected for Hematology (See Section 3.1 and 5.5)

[redacted]

10. The following will be dispensed during [redacted]
    - The study drug assembled for [redacted]
    - A diary card with instructions and to record the study drug use, health changes and concomitant medication

    [redacted]
11. A general safety review before discharge

[redacted]

7.1.8 [redacted] Visit [redacted]

The following procedures will be performed at [redacted]

1. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.5)
2. Subject Reported Assessments will be collected for:

   [redacted]
3. Focused Area Assessments will be performed for:
   - Validated Investigator Global Assessment (vIGA) (See Section 6.1.5)

   [redacted]
4. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
5. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
6. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
7. The Subject's diary provided at the previous visit will be collected and reviewed.
8. The returned study drugs will be counted
9. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 4.5 and 5.8)
10. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
11. A blood sample(s) will be collected for Hematology and Chemistry (See Section 3.1 and 5.5)
12. A blood sample will be collected within one hour before dosing for [redacted] (See Section 6.2)
13. Study drug administration in a clinic before 12 noon (See Section 8.5)

[redacted]

[redacted]

The following procedures will be performed prior a subject discharged from a clinic:

15. The following will be dispensed during [redacted]
    - UPT to be performed at [redacted] – *for female Subjects of childbearing potential*
    - The study drug assembled for [redacted]
    - A diary card with instructions and to record the study drug use, health changes and concomitant medication

    [redacted]
16. A general safety review before discharge

[redacted]

7.1.9 [redacted] Visit [redacted]

The following procedures will be performed at [redacted]

1. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.5)
2. Subject Reported Assessments will be collected for:

   [redacted]
3. Focused Area Assessments will be performed for:
   - Validated Investigator Global Assessment (vIGA) (See Section 6.1.5)

   [redacted]

The following procedures will be performed by an independent safety team:

4. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
5. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
6. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
7. The Subject's diary provided at the previous visit will be collected and reviewed.
8. The returned study drugs will be counted
9. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 4.5 and 5.8)
10. A blood sample(s) will be collected for Hematology and Chemistry (See Section 3.1 and 5.5)
11. [redacted] will be collected within [redacted] hour before dosing for [redacted] (See Section 6.2)
12. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)

[redacted]

[redacted]

14. Study drug administration in a clinic before 12 noon (See Section 8.5)

The following procedures will be performed prior a subject discharged from a clinic:

15. The following will be dispensed during [redacted]
    - The study drug assembled for [redacted]
    - A diary card with instructions and to record the study drug use, health changes and concomitant medication

    [redacted]
16. A general safety review before discharge
17. On-site [redacted] (Study Day 225 ± 3 Days) will be scheduled and the Subject will be instructed to bring the Study Product (used, unused, and partially used packs), emollient, and Subject diary with him or her to this visit.

7.1.10 [redacted] End of Treatment Visit [redacted]

The [redacted] must be scheduled in a morning to allow the dosing before 12 noon.

The following procedures will be performed at [redacted]

1. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.5)
2. Subject Reported Assessments will be collected for:

   [redacted]
3. Focused Area Assessments will be performed for:
   - Validated Investigator Global Assessment (vIGA) (See Section 6.1.5)

   [redacted]
4. A whole body photography – *for subjects consenting for photography* (See Section 6.4)

[redacted]

5. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
6. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
7. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
8. The Subject's diary provided at the previous visit will be collected and reviewed.
9. The returned study drugs will be counted
10. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 4.5 and 5.8)
11. A physical examination will be performed. At a minimum, the physical examination will include the following: height, weight, assessment of general appearance, comprehensive skin examination, HEENT, heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, and extremities. (See Section 5.5)
12. A urinalysis dipstick will be performed and evaluated at a site (See Section 5.5)

13. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
14. A blood sample(s) will be collected for [redacted]
15. A [redacted] sample will be collected for [redacted] sample (See Section 6.3)
16. A [redacted] sample will be collected within [redacted] hour before dosing for [redacted] (See Section 5.14)
17. A 12-lead electrocardiogram (ECG) will be performed (See Section 5.12)
18. A pulmonary function test will be performed or scheduled with an external expert (See Section 5.6)
19. An ophthalmologic examination including OCT will be performed or scheduled with an external expert (See Section 5.7)
20. Study drug administration in a clinic before 12 noon (See Section 8.5)

[redacted]

The following procedures will be performed prior a subject discharged from a clinic:

22. The following will be dispensed during [redacted]
    - A diary card with instructions and to record health changes and concomitant medication
    - [redacted]
23. A general safety review before discharge

[redacted]

7.1.11 [redacted] Follow-up Visit [redacted]

The following procedures will be performed at [redacted]

1. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.5)

[redacted]

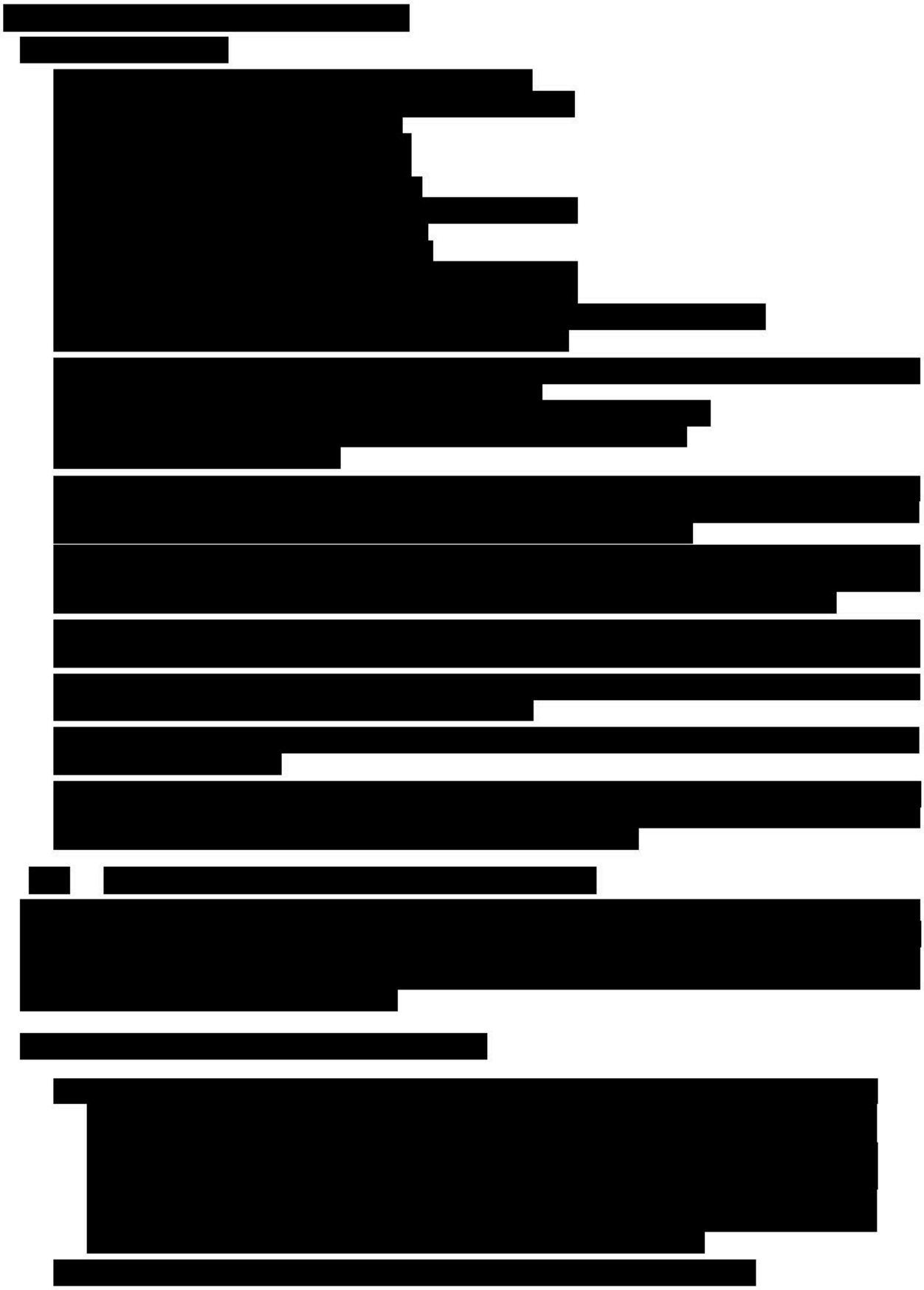
2. The Subject's diary provided at the previous visit will be collected and reviewed.
3. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 4.5 and 5.8)
4. A blood sample(s) will be collected, if needed for Hematology, Chemistry, and Coagulation profile that were abnormal and clinically significant at [redacted] (EOT) (See Section 5.5)
5. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
6. A 12-lead electrocardiogram (ECG) will be performed, if needed (See Section 5.12)
7. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
8. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)

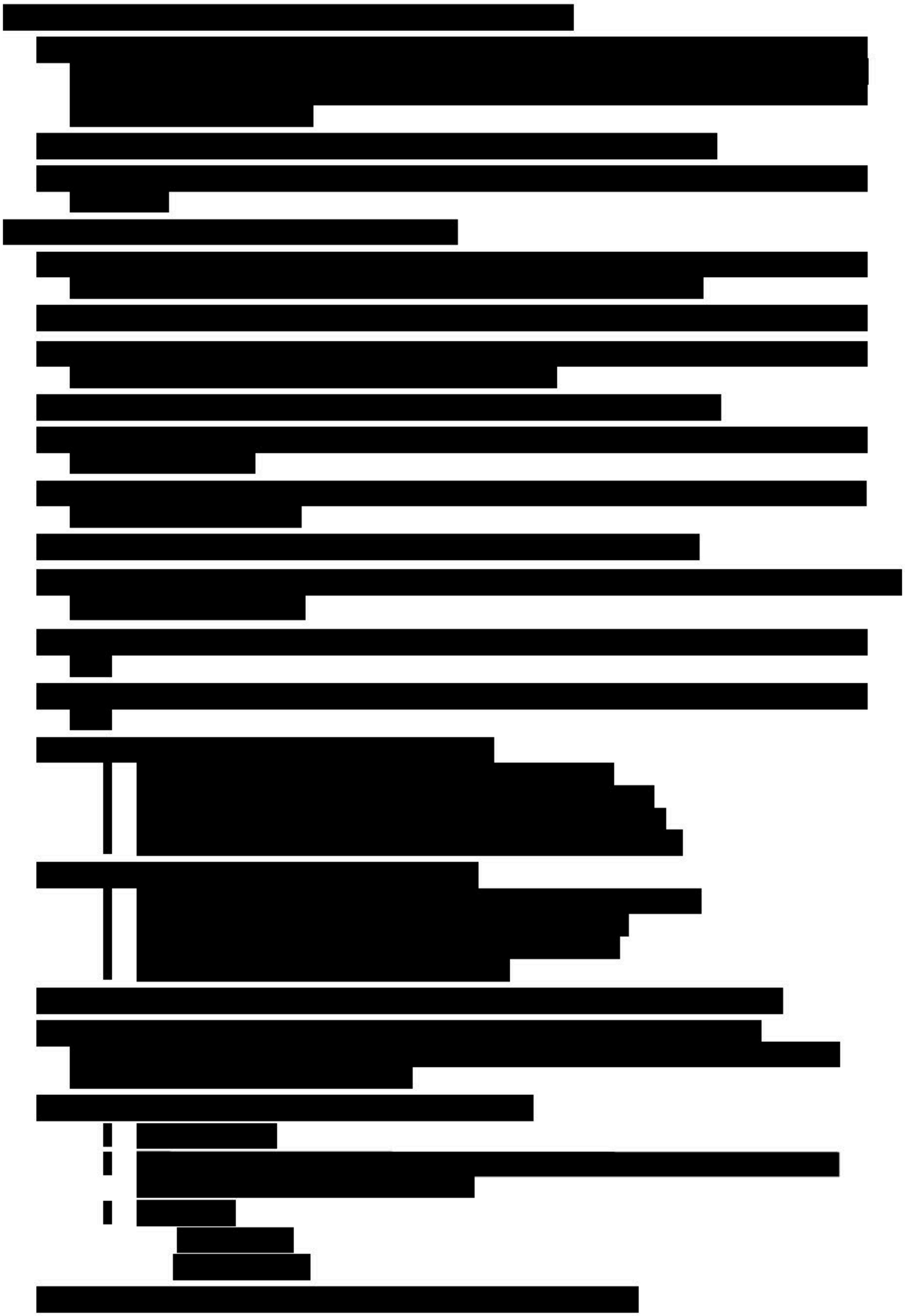
9. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)

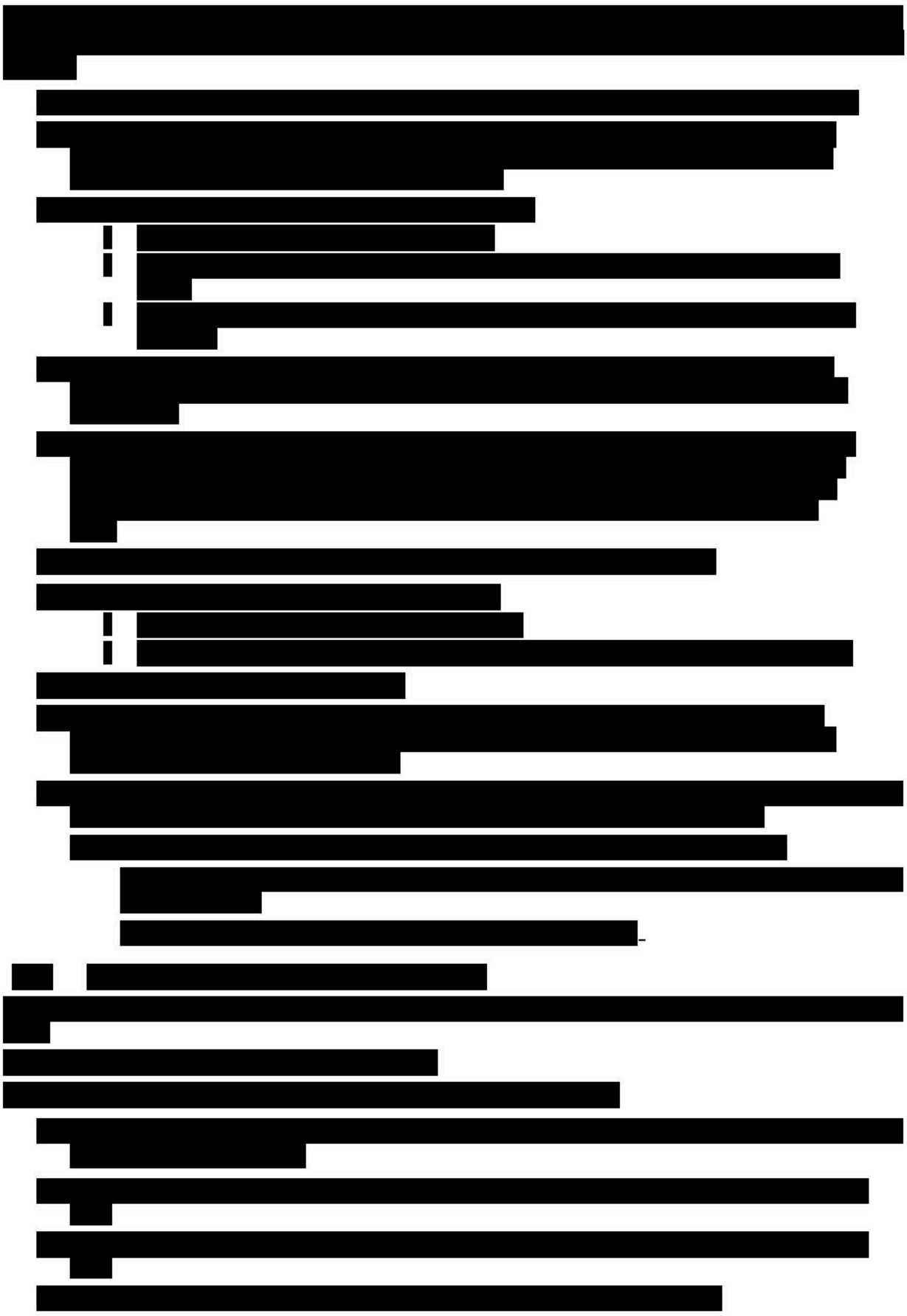
[redacted]

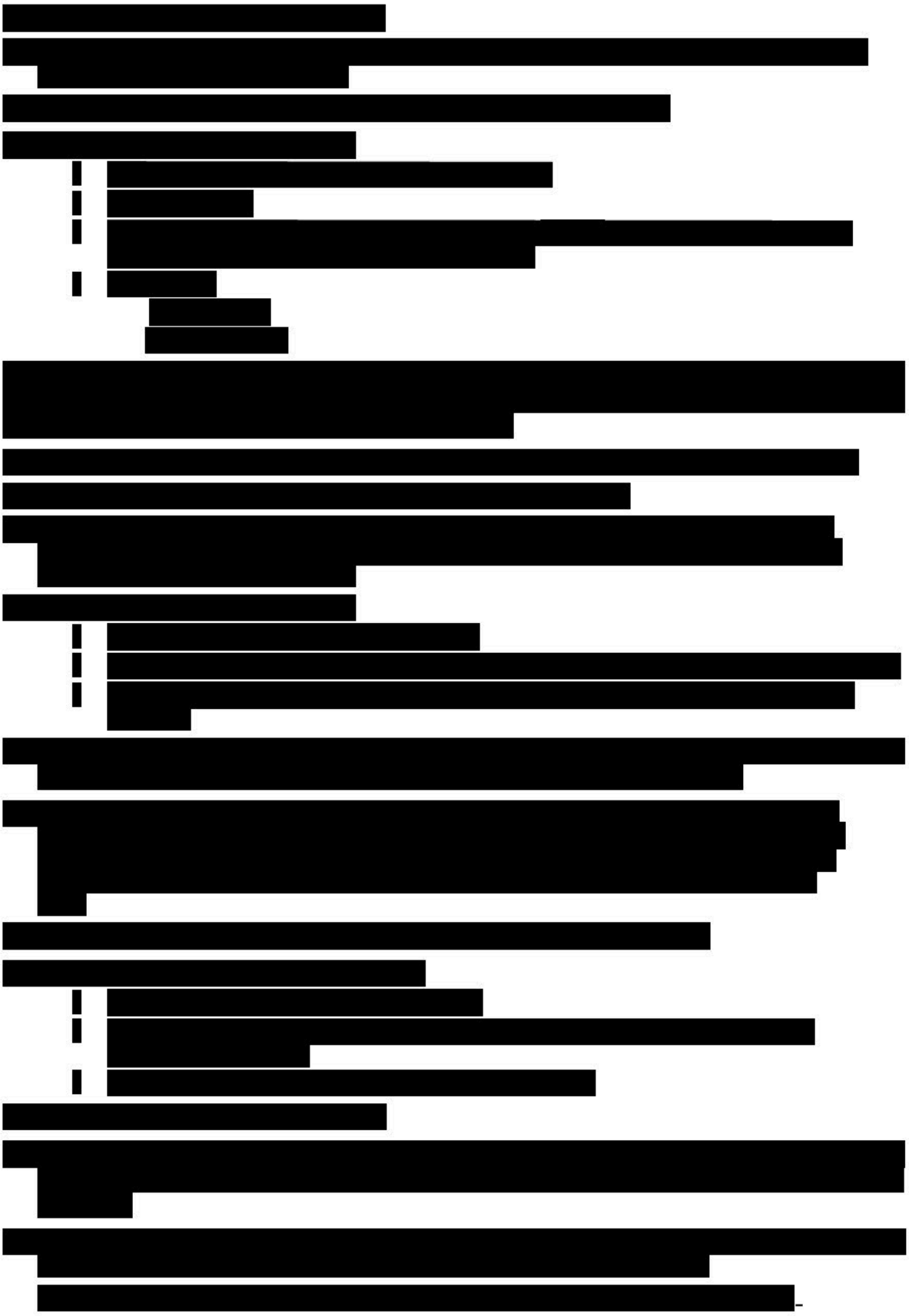
11. A general safety review before discharge

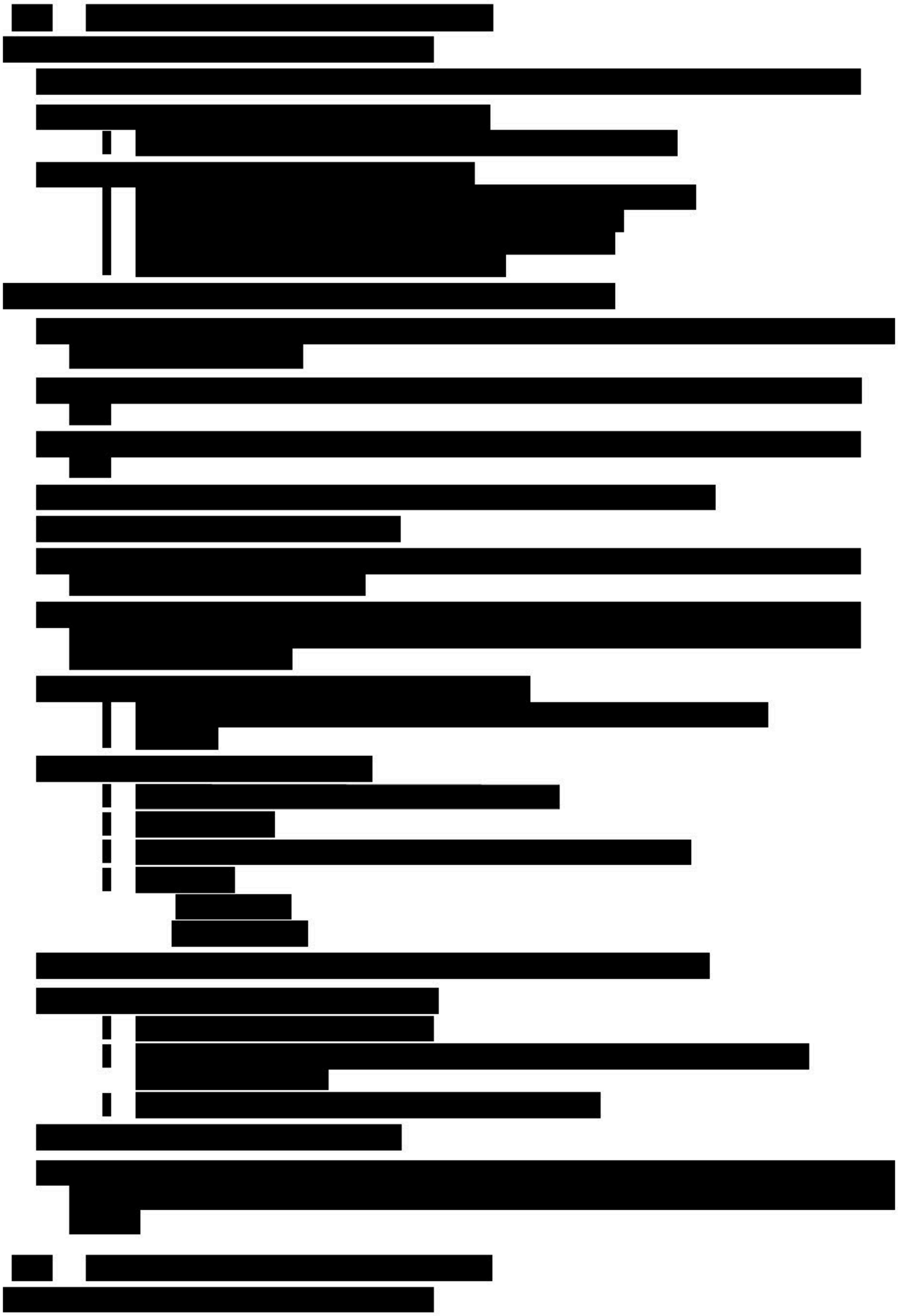
[redacted]

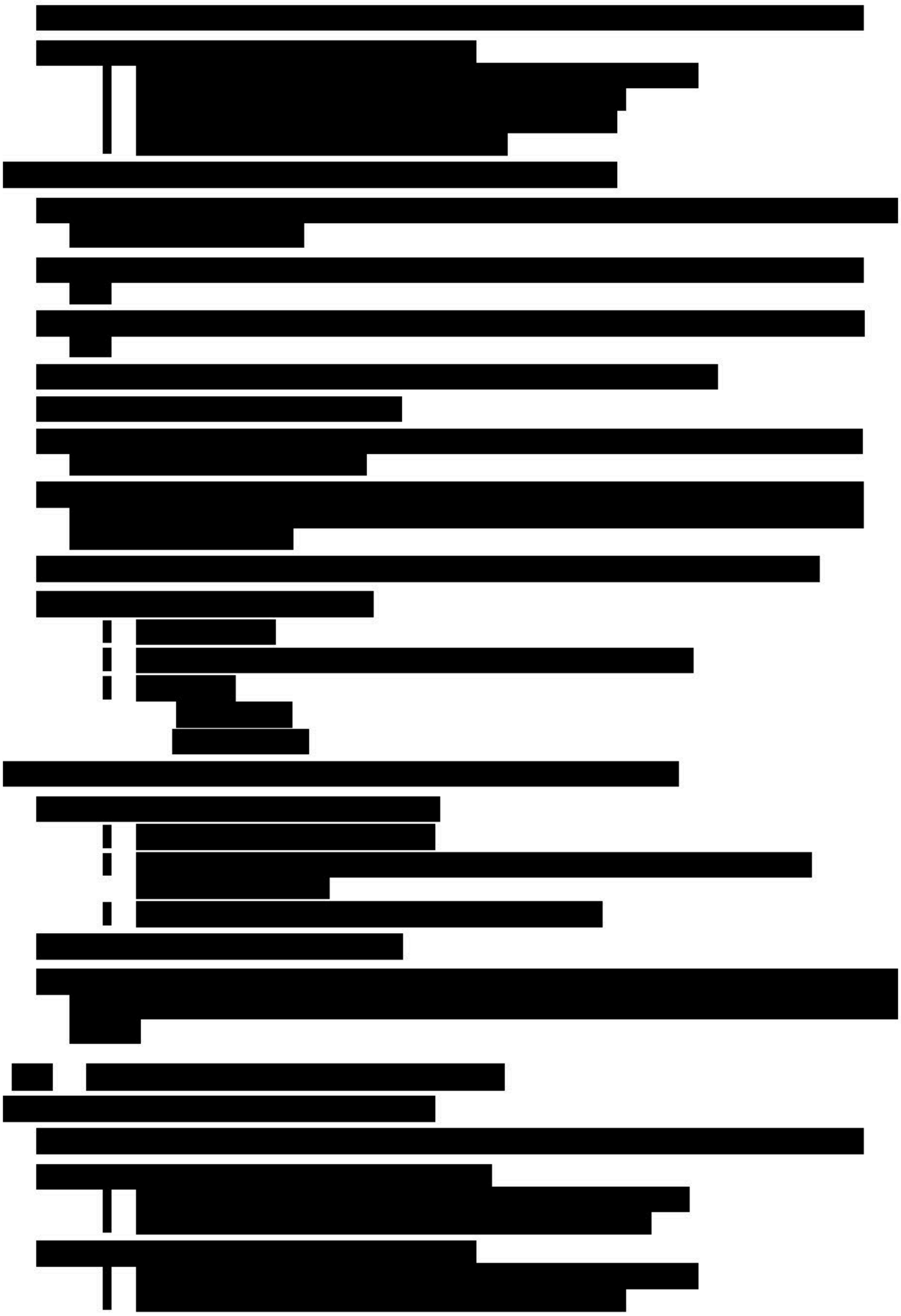


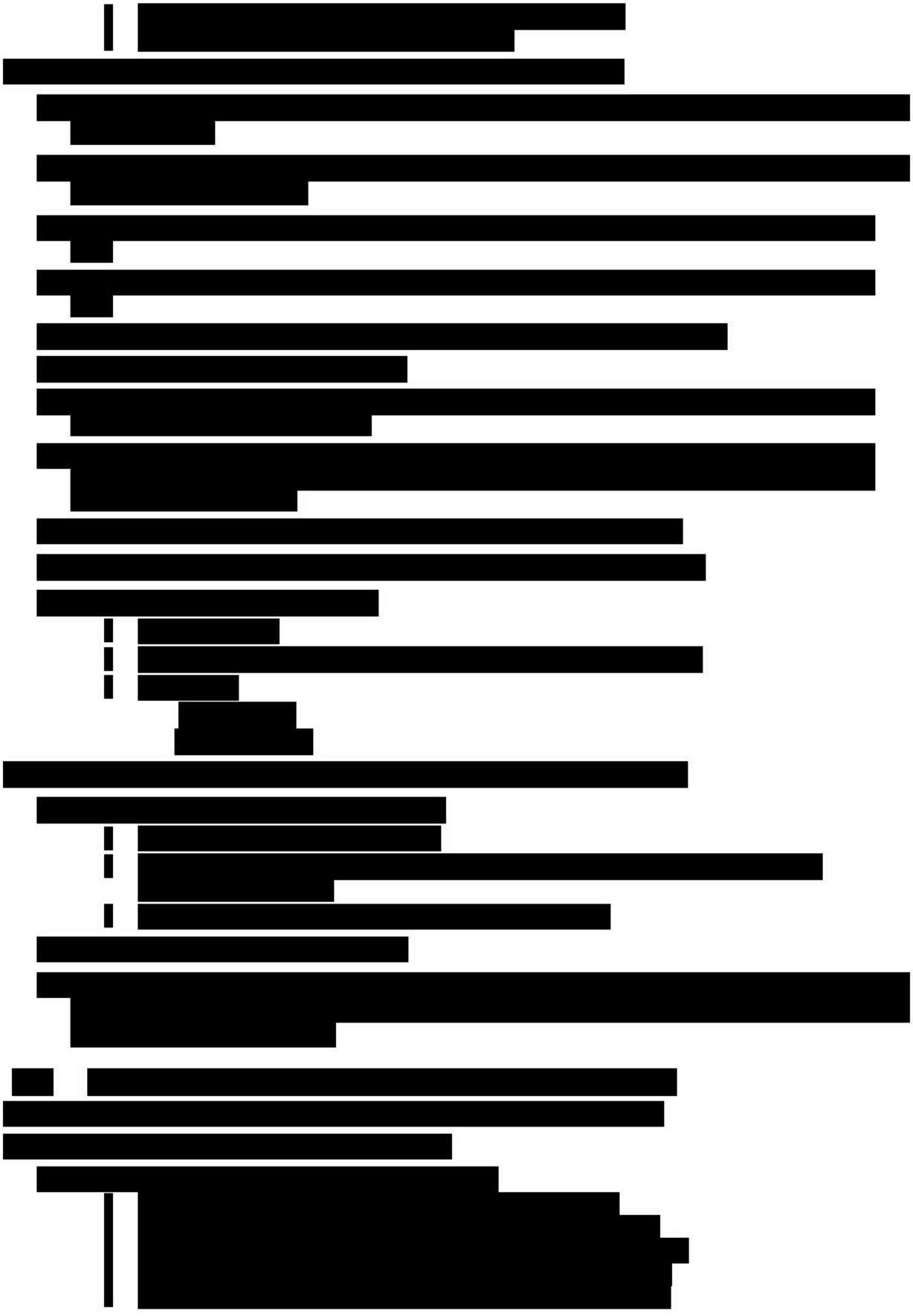


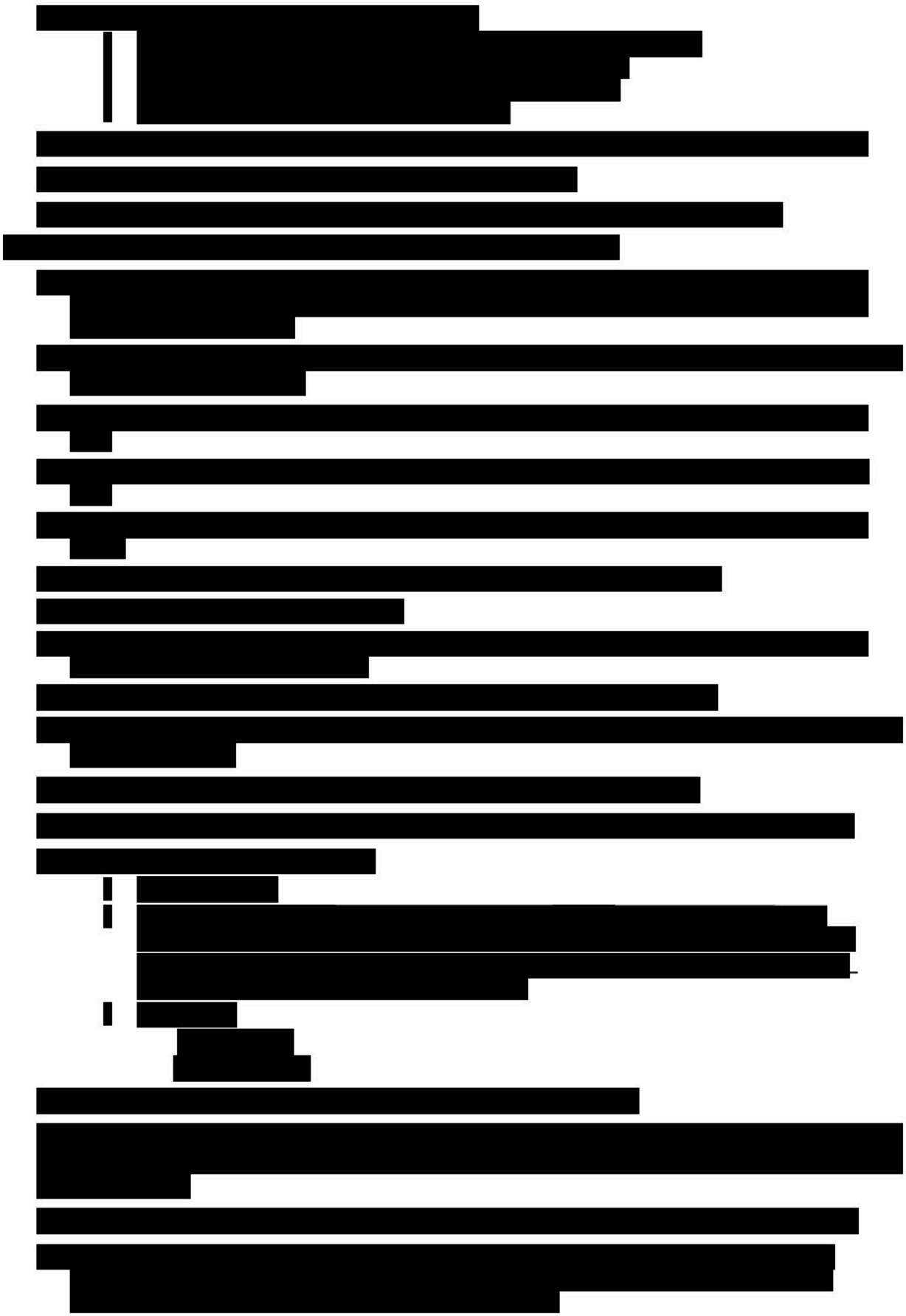


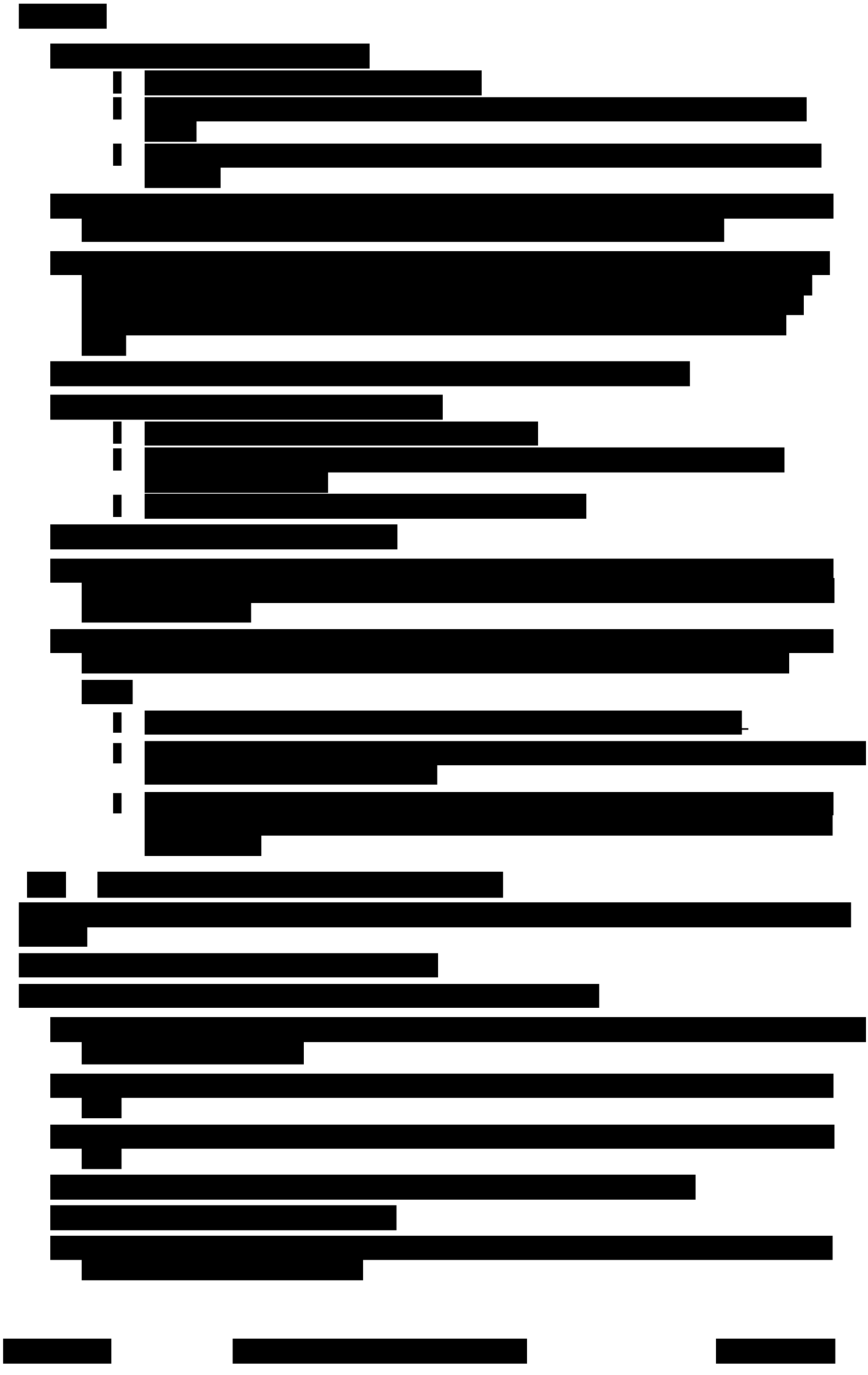


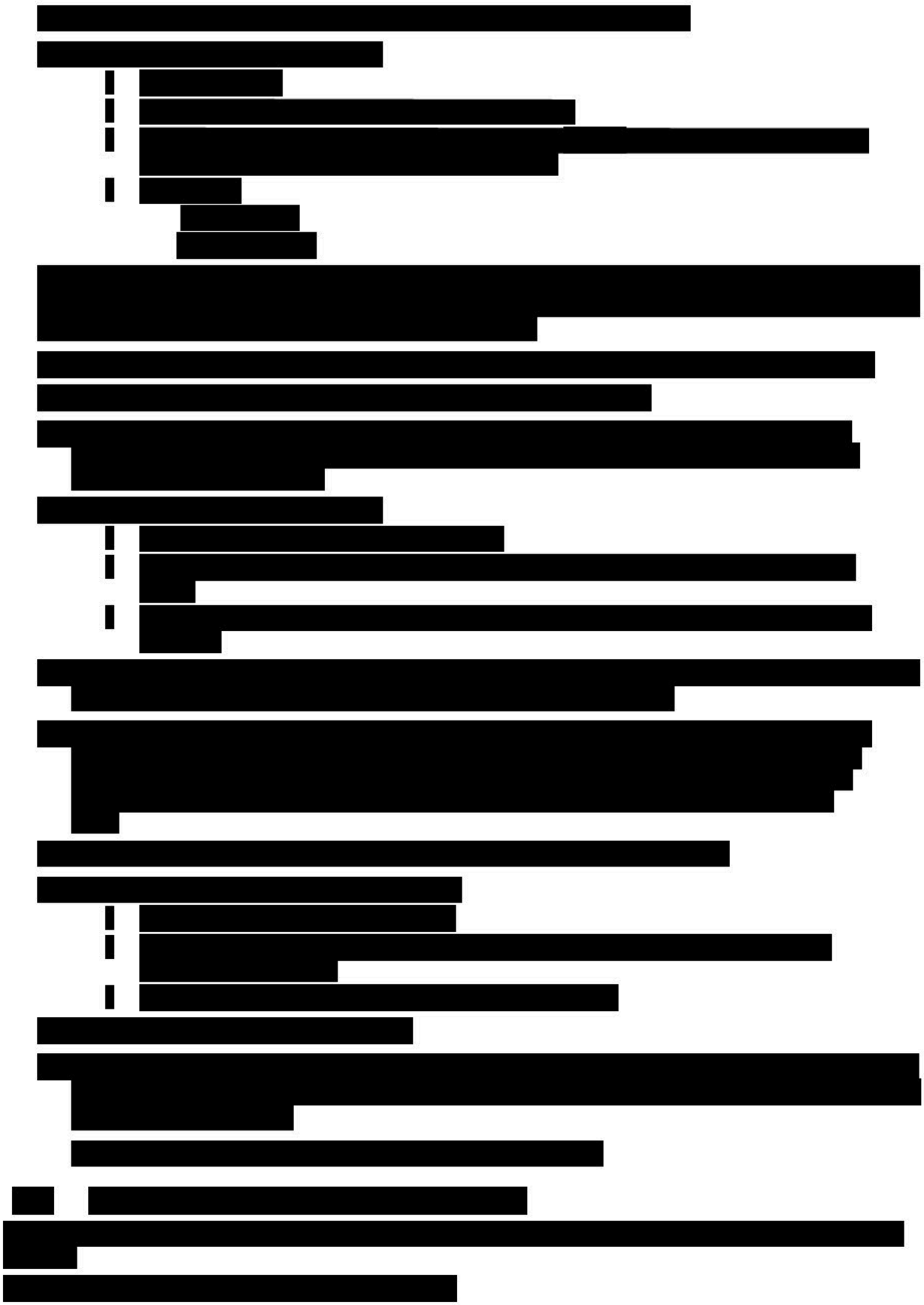


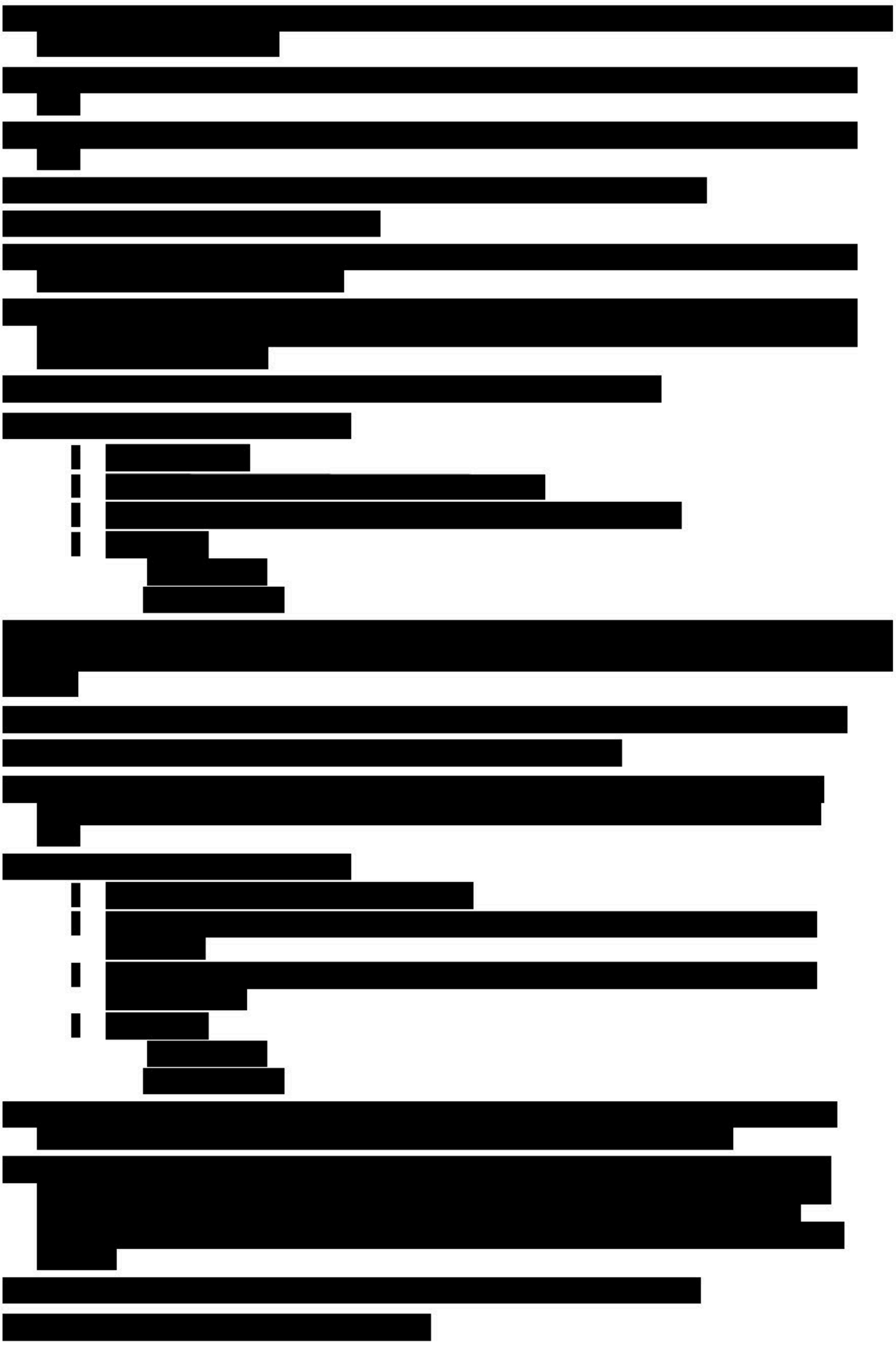


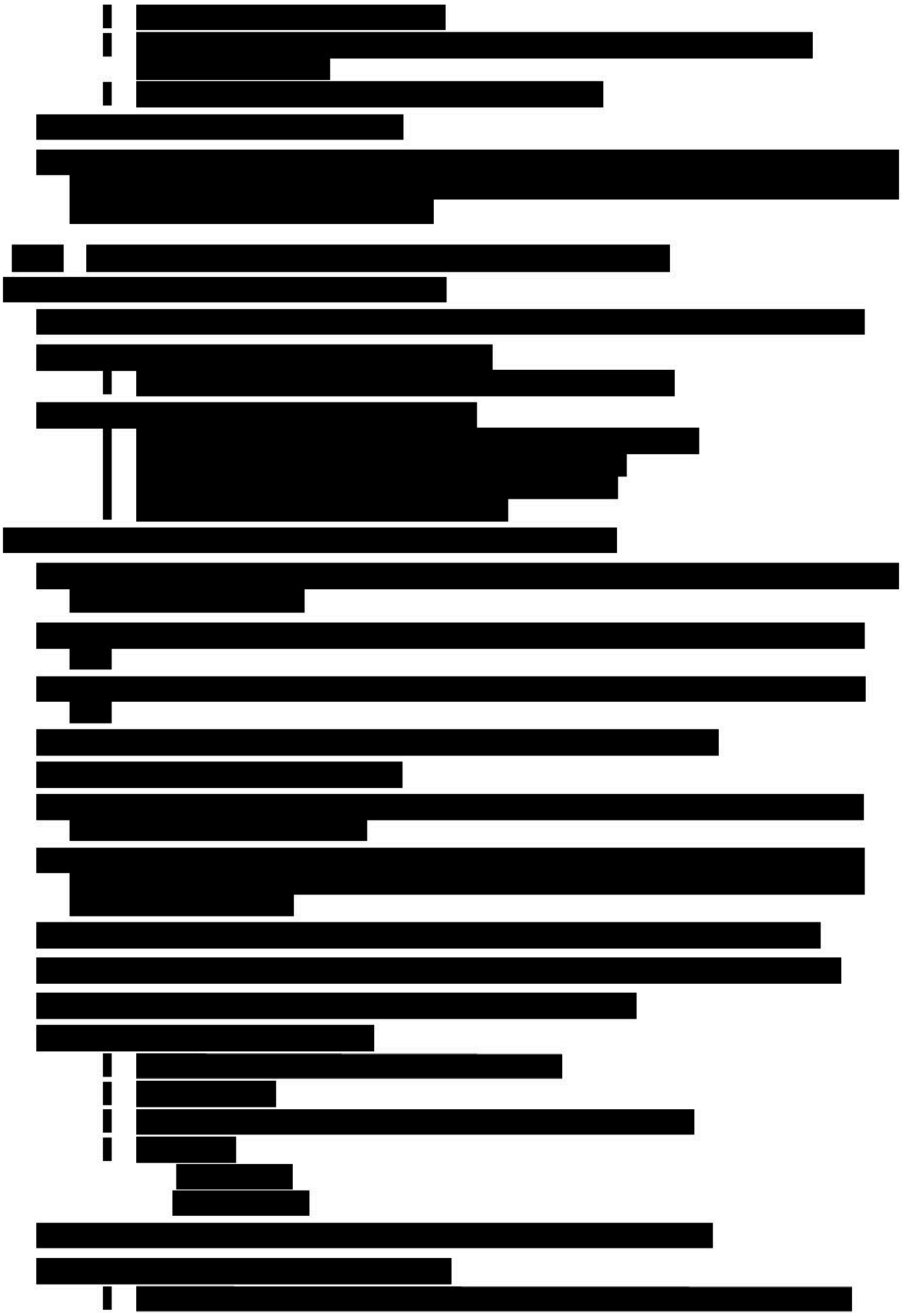


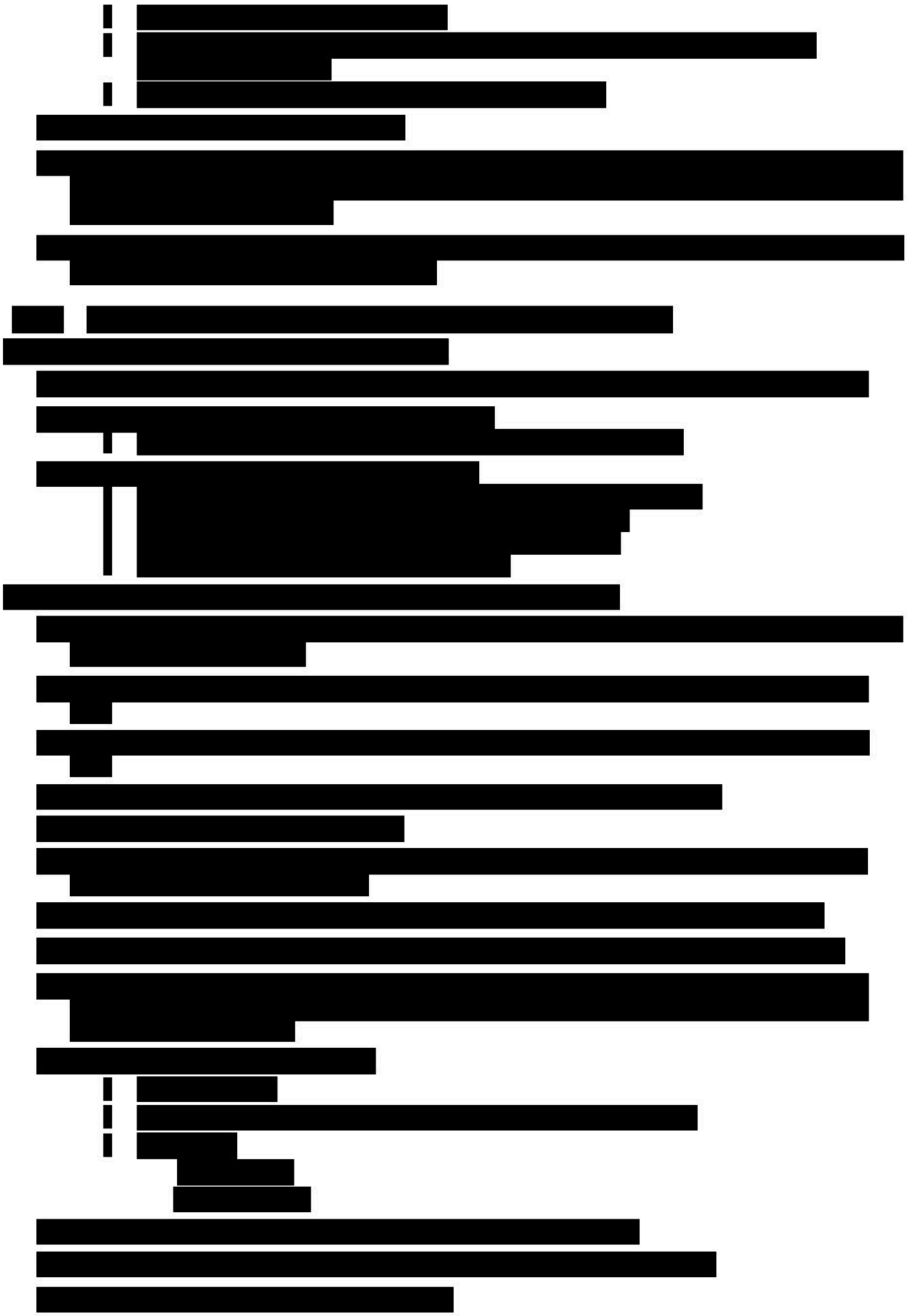


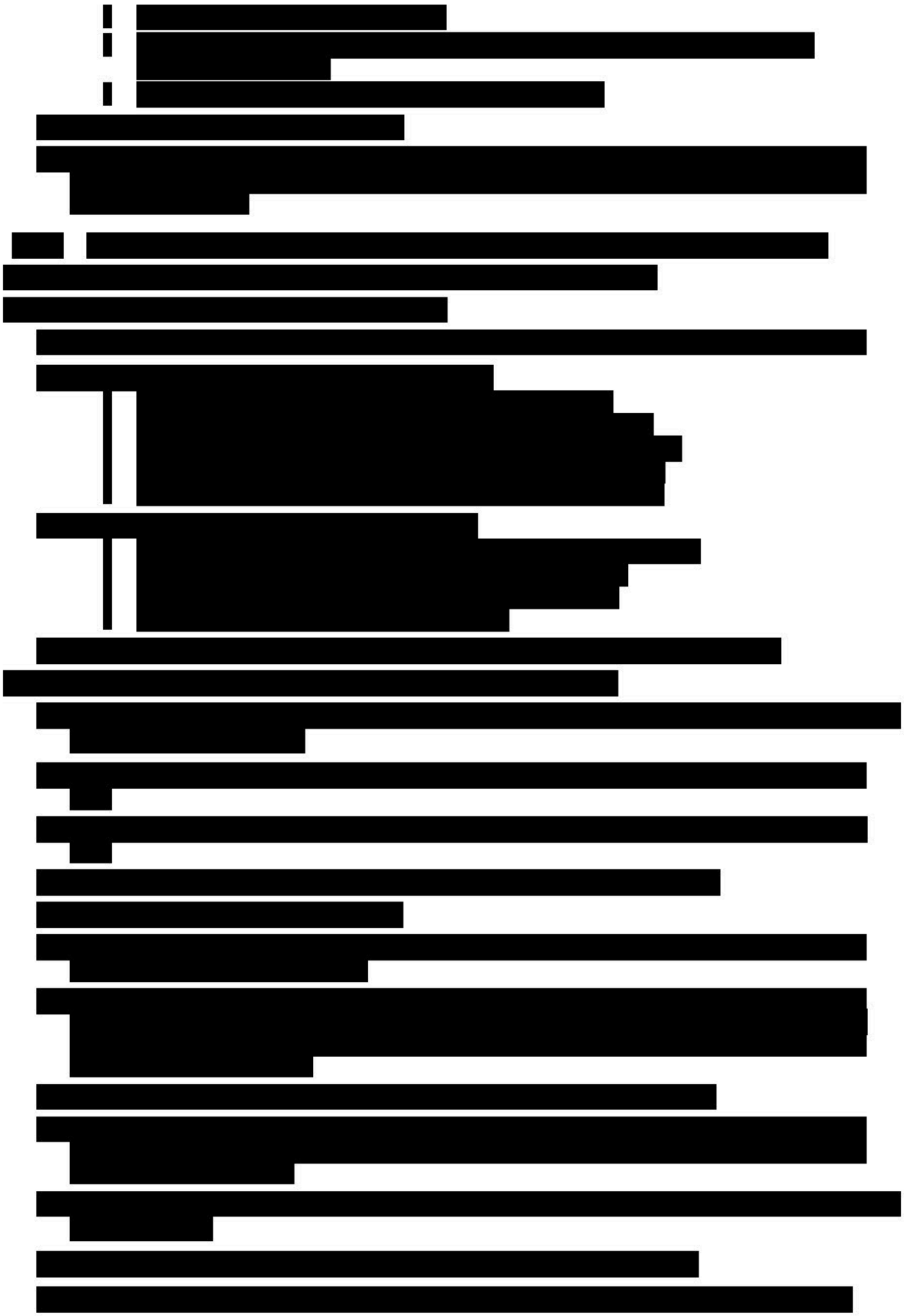


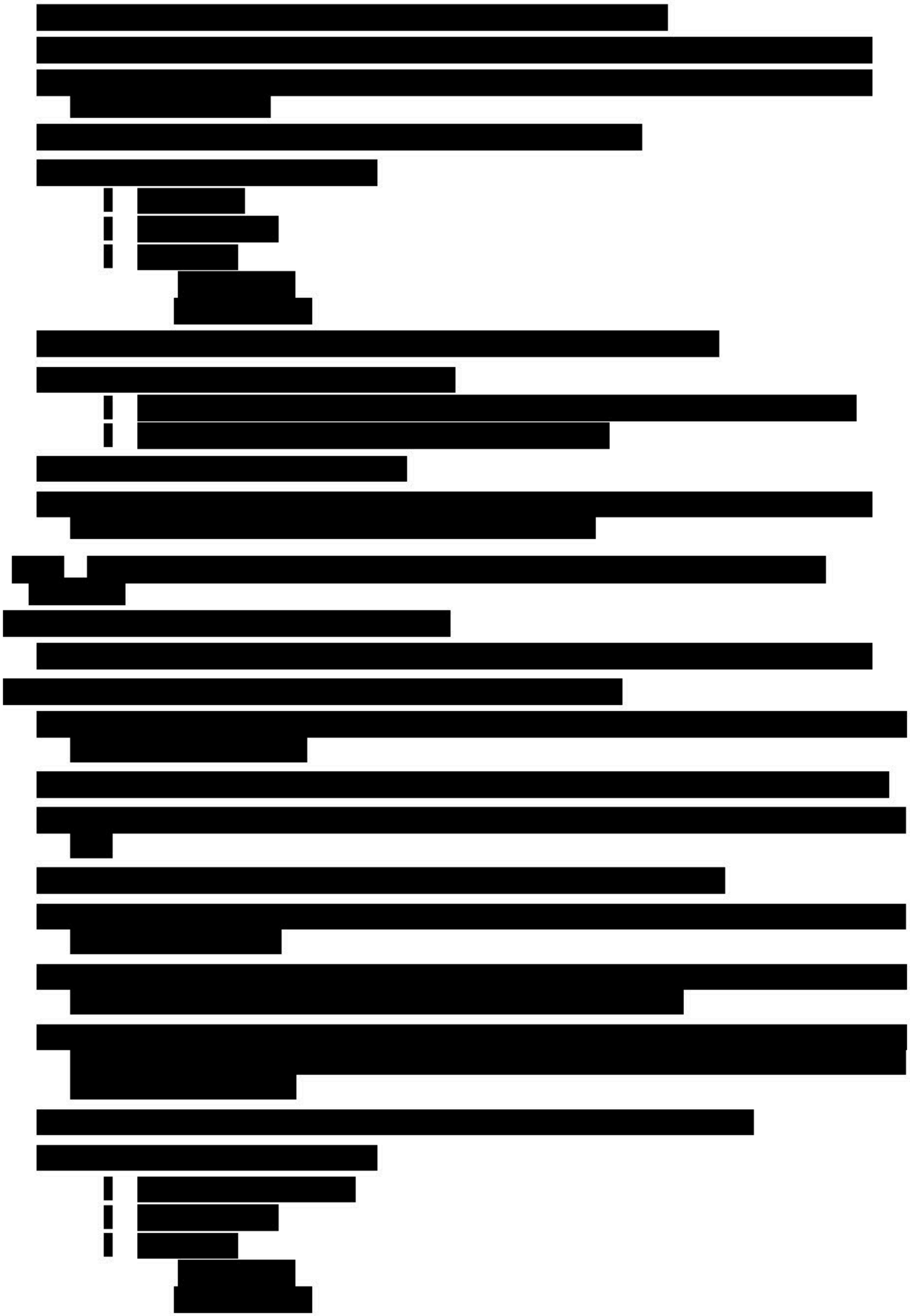


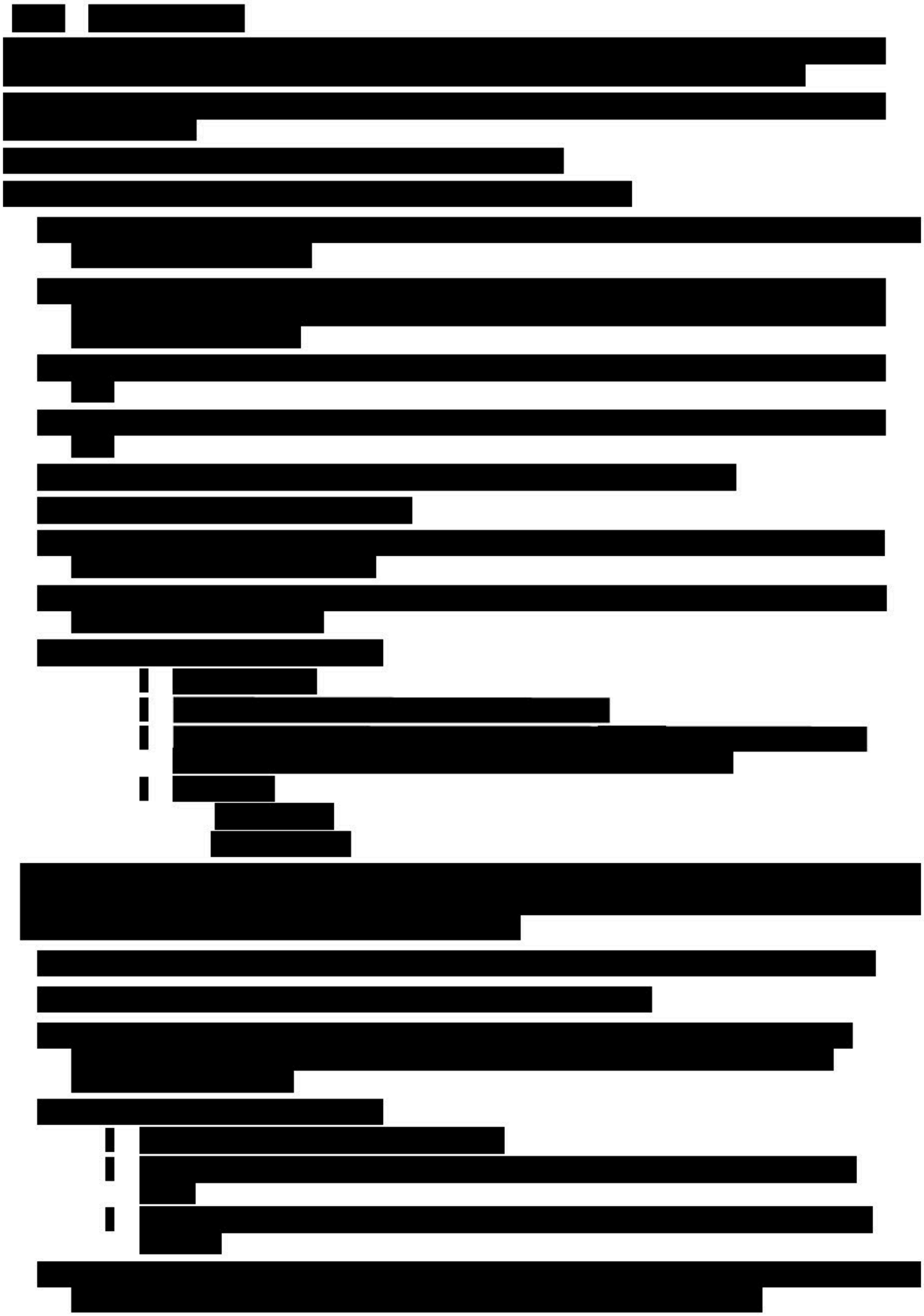












[redacted]

INVESTIGATIONAL PRODUCT

8.1 Description

All study medications will be dispensed by and returned to a qualified dispenser designated by the Principal Investigator. The investigational product will be dispensed only from the institution(s) approved by an Institutional Review Board.

The Investigational Product will be supplied by the Sponsor. The following treatments will be self-administered or administered by the Subject's caregiver during this study.

Investigational Products:	SCD-044 Tablets [redacted] (Low dose) SCD-044 Tablets [redacted] (Intermediate dose) SCD-044 Tablets [redacted] (High dose) [redacted]
Control:	Placebo of SCD-044 product

[redacted]

8.3 Packaging and Labeling

In order to maintain the study blind the randomization schedule will be generated by a third party. Randomization will be performed according to a computer-generated randomization scheme. Only one Subject number will be assigned to each Subject. The Subject will maintain the same number throughout the study. The Investigational Product will be identically labeled and packaged such that neither the Subject nor any Investigator can identify the treatment.

[redacted]

[redacted]

Details of the IMP packaging and labelling for the European region will be separately described in the IMP manual.

8.4 Treatment Assignment

The subject study identification number will correspond to a computer-generated randomization schedule assigning that number to one of the study treatment groups in Part I. [redacted]

8.4.1 Randomization

The subject numbers at the site will be assigned by an Interactive Response Technology (IRT) using global data across all sites and identification numbers available at a site. [redacted]

8.5 Administration of Investigational Product

At study visits 2 through 16, Investigational Product will be dispensed to randomized Subjects along with a diary. Each Subject will also receive written study instructions, which detail the proper administration method of the Investigational Product and general study instructions.

The study medication should be taken [redacted] preferably at the same time each day before 12 noon [redacted] The doses should be taken with approximately 240 mL (8 oz.) of water.

Investigational Product will be used for approximately [redacted] days.

Subjects will be required to use diaries to document the date of doses, any missed doses, emollient use, and the occurrence of all adverse events.

At each visit during the study, the Investigator or designee should review proper use of the Investigational Product.

[redacted]

[redacted]

8.6 Assessment of Compliance

Compliance with scheduled use of Investigational Product and emollient will be determined from the Subject's diary. Subjects will be instructed to bring their daily diary, emollient, and used and unused study drug containers at all scheduled visits or Early Discontinuation Visit to allow for tablet count and compliance checks. Subjects will also be asked to record in a daily diary the date when they took the study drug and applied emollient. In addition, Subjects will be instructed to document all AEs on the diary.

[redacted]

8.7 Investigational Product Accountability

It is the responsibility of the Principal Investigator to ensure that the current disposition of the Investigational Product is maintained at each study site where Investigational Product is inventoried and dispensed. When a drug shipment is received at a study site, the Principal Investigator or the Principal Investigator's Designee must inventory the drug and sign the receipt form provided with the shipment. The receipt form should be emailed as per instructions provided on the receipt. A copy of the receipt should remain at the site.

The Investigator will not supply study test articles to any person not enrolled in this study, or to any physician or scientist except those named as sub-investigators.

A Drug Accountability Log will assist study site staff in maintaining inventory records of study drug.

Subjects must return used, partially used or unused Investigational Product so that any remaining drug supplies can be accounted for and noted in the Drug Accountability Log.

A certified copy of the Drug Accountability Log must be provided to the study monitor at the conclusion of the study and the original should remain at the study site.

8.8 Return of Clinical Supplies

All used and unused containers of Investigational Product may be returned to the Drug Labeling, Packaging and Shipping Facility for destruction or be destructed at the site after study close-out and final drug accountability is reconciled.

[redacted]

[redacted]

9.1.4 Rationale for the Use of Comparator

A placebo control arm is included to demonstrate that the investigational products are active and as a parameter that the study is sufficiently sensitive to detect differences between products.

9.1.5 Rationale for Study Endpoints

The primary endpoint will be the proportion of subjects with at least 75% improvement in EASI at Week 16. Duration of 16 Weeks is considered adequate to detect a clinically meaningful difference between placebo and active treatment and is consistent with previous studies in this indication. Proportion of subjects achieving validated Investigator Global Assessment (vIGA) of "clear" or "almost clear" with at least a two-grade reduction from baseline to Week 16 will be a key secondary end-point.

[redacted]

9.3 Blinding and Unblinding Procedures

In order to maintain the study blind the randomization schedule will be generated by a third party. Randomization will be performed according to a computer-generated randomization scheme. [redacted]

[redacted]

9.5 Datasets to be Analyzed

Three analysis populations will be used in the analysis of the clinical data:

1. A Safety Population subject is any individual who was randomized into the study and dispensed study drug.
2. The ITT Population includes all randomized subjects regardless of whether they received the investigational product.
3. The Per Protocol (PP) Population includes all ITT subjects who meet all inclusion/exclusion criteria and have no protocol violations that affect proper administration of the treatment or accurate evaluation of its effectiveness.

Additionally, the Screen Fail subjects will be summarized, including reasons for removal.

9.6 Demographics and Baseline/Randomization Characteristics

Demographic and baseline/randomization characteristics will be summarized descriptively by treatment group for the ITT, PP, and Safety Populations.

9.7 Safety Assessment

Safety Assessments will include vital signs, physical examination, adverse events (AEs), laboratory tests, ECG monitoring, pulmonary function tests, ophthalmologic exams.

The safety of SCD-044 will be evaluated by:

- Incidence, seriousness and severity of all adverse events
- Shifts from baseline in hematology and laboratory tests
- Incidence of AEs of special interest (AESI)
- [redacted]

The extent of exposure will be summarized using descriptive statistics. No inferential analyses are planned.

Incidence of all adverse events reported during the study will be summarized using the MedDRA dictionary by System Organ Class and Preferred Term, by treatment group, severity, and relationship to study drug.

An AE is considered treatment emergent if it was not present prior to the first dose of treatment or, if it was present, it worsened in severity or treatment attribution.

Safety analyses will be performed on the Safety Population. All safety data will be listed by treatment and subject in data listings. AEs will also be summarized by actual dose at time of onset of the AE to account for possible dose reductions over the course of the study.

9.8 Efficacy Assessment

Primary endpoint:

- Proportion of subjects who achieve ≥75% overall improvement in EASI score from Baseline to Week 16

Key Secondary endpoint:

- Proportion of subjects who achieve score of '0' (clear) or '1' (almost clear) on a 5-point, vIGA scale [redacted] Week 16

Other Secondary endpoints:

- Percent change in EASI score from Baseline to Week [redacted] 32
- [redacted]
- Change in mean EASI score from Baseline to Week [redacted] 32
- [redacted]
- Proportion of subjects who achieve ≥4-point improvement in PPI-NRS from Baseline to Week [redacted] 32
- [redacted]
- Proportion of subjects who achieve SCORAD 50 and SCORAD 75 response from Baseline to Weeks [redacted] 32
- Change from Baseline in quality of life measured by DLQI scores to Week [redacted]
- [redacted]
- Change from Baseline in percent BSA with atopic dermatitis measured to Week [redacted] 32
- Change from Baseline in POEM score to Week [redacted] 32

- Change in PGIS of disease from Baseline to Week 32

Efficacy Analysis

The primary and key secondary efficacy variables will be analyzed using a test, using the Intent-to-Treat (ITT) Population. Additional details will be included in the SAP.

Sensitivity Analyses

For sensitivity testing, the primary and key secondary endpoints analyses will also be performed using the per protocol (PP) population.

Additional sensitivity analyses will be performed for the primary efficacy variable using the following populations:

- The Intent-to-Treat (ITT) Population using Last-Observation-Carried-Forward imputation (LOCF)
- The Per Protocol (PP) Population, using Observed Cases (OC)
- The Intent-to-Treat (ITT) Population, active treatment worst case (ATWC), defined as all missing assessments in the placebo group defaulted to responder but missing assessments in active treatment arm defaulted to nonresponder. Full tipping point analysis methods will be discussed in the SAP.

Additional details of the statistical approach will be provided in the statistical analysis plan.

[redacted]

9.9 Concomitant Medication

The start and stop date of concomitant medication use during the study will be provided in the data listings in addition to the reason for the medication use.

9.10 Summary of Subjects who terminate prematurely

Reasons for premature termination will be summarized by treatment group.

[redacted]

[redacted]

10. ADVERSE EVENTS

10.1 Reporting of Adverse Events

Any untoward medical occurrence in a Subject or clinical-trial Subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, clinically significant abnormal laboratory finding or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Any adverse event associated with the use of a drug in humans, whether or not considered product-related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action. Reporting an adverse event does not necessarily reflect a conclusion that the product caused or contributed to the adverse event.

All adverse events, whether observed by an Investigator or Study Coordinator or reported by the Subject, whether related to study drug or not related to study drug, shall be documented in the Subject records, together with details, i.e., date of onset, description of the AE, the duration and intensity of each episode, the action taken, the relationship to the Investigational Product and the degree of severity, the seriousness, date of resolution, and the outcome.

[redacted]

The Principal Investigator or designee must strive to follow the Subject until the adverse event has resolved or becomes clinically insignificant, or stabilized or the Subject is lost to follow-up. The Principal Investigator or designee must immediately report to the Contract Research Organization, by telephone and follow-up in writing, all study drug discontinuations due to adverse events.

Assessment of Severity

The intensity or severity of an adverse event (AE) is characterized as:

- Mild: an AE that is easily tolerated
- Moderate: an AE sufficiently discomforting to interfere with daily activity
- Severe: an AE that prevents normal daily activities

Relationship to Study Medication

The relationship is characterized as:

- Not Related: This applies to any AE that is clearly not related to use of the study drug.
- Possible: This means the association of the AE with the study drug is unknown; however, a relationship between drug and event cannot be ruled out.
- Probable: There is a reasonable temporal relationship between the use of the study drug and the AE. Based upon the Principal Investigator or designee's clinical experience, the association of the event with the study drug seems likely.
- Definite: The AE occurs following the application of the study drug and it cannot be reasonably explained by any known characteristics of the Subject's clinical state, environmental or toxic factors or other modes of therapy administered to the Subject. It disappears or decreases upon discontinuation of the study drug and reappears on a re-challenge of the investigational product.

10.2 Pregnancy

Female Subjects of childbearing potential must have been using and must agree to continue to use accepted methods of birth control, throughout the study. All female Subjects are considered to be of childbearing potential unless they are premenarchal, have been surgically sterilized or have been postmenopausal for at least 1 year. Tubal ligation is not considered equivalent to female sterilization. Women with a history of tubal ligation are still considered females able to become pregnant and must complete a pregnancy test. Alternatively, any of the following methods of birth control are acceptable: oral or injectable contraceptives, contraceptive patches, [redacted] (stabilized for at least 3 months), [redacted] (vaginal contraceptive), [redacted] (contraceptive implant), double barrier methods (e.g. condom and spermicide), IUD, tubal ligation, Essure or abstinence with a 2nd acceptable method of birth control should the Subject become sexually active. Prior to study enrollment women of child bearing potential must be advised of the importance of avoiding pregnancy during study participation.

A negative result of a pregnancy test having a minimum sensitivity of at least 50mIU/ml for hCG should be obtained from each applicable visit. Pregnancy testing will be performed at applicable study visits and the results of all pregnancy tests (positive or negative) will be documented.

If following initiation of study treatment, it is subsequently discovered that a study Subject is pregnant or may have been pregnant at the time of Investigational Product exposure, the Investigational Product will be permanently discontinued. The Principal Investigator or designee must immediately notify the CRO of this event.

Protocol-required procedures for study discontinuation and follow-up must be performed on the Subject. Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the Principal Investigator must report to the sponsor follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of eight weeks after birth.

10.3 Serious Adverse Events

An **Adverse Event or Suspected Adverse Reaction** is considered ''serious'' if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life threatening adverse event; (Note: the term "life-threatening" as used here refers to an event in which the Subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)
- In-Subject hospitalization or prolongation of existing hospitalization

  (A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health or if the hospitalization is clearly not associated with an AE (e.g., hospitalization due to social / logistic reason) are not to be considered as SAEs)
- A persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions)

- A congenital anomaly/birth defect
- Any "other" important medical event

Important medical events that may not result in death, be life-threatening or require hospitalization may be considered Serious Adverse Events when, based on appropriate medical judgment, they may jeopardize the Subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Regardless of the above, any additional adverse events, which the Principal Investigator or designee considers significant, should be immediately reported to the Contract Research Organization.

SAE reporting by the Investigator:

Any Serious Adverse Event, whether deemed drug-related or not, must be reported by the Investigator to the Contract Research Organization (CRO) within 24 hours after the Principal Investigator or Study Coordinator becomes aware of its occurrence. The Principal Investigator or the Principal Investigator's Designee must complete an SAE Form and email it to the Contract Research Organization, along with the subject's Adverse Events, Medical History, and Concomitant Medications Log within 24 hours of notification of the event.

The Principal Investigator or the Principal Investigator's Designee must be prepared to supply the following information:

a. Principal Investigator Name and Site Number
b. Subject I.D. Number
c. Subject initials and date of birth
d. Subject Demographics
e. Clinical Event
   1) Diagnoses and Description
   2) Date of onset
   3) Severity
   4) Treatment
   5) Medical records, hospitalization/discharge records
   6) Relationship to study drug
   7) Action taken regarding study drug
f. **If the AE was Fatal or Life-threatening**
   1) Cause of death (whether or not the death was related to study drug)
   2) Autopsy findings (if available)
   3) Death Certificate

The Principal Investigator must provide a follow-up written report within **5 calendar days** of reporting the event to the CRO. The written report must contain a full description of the event and any sequelae. Subjects who have had an SAE must be followed clinically until all parameters (including laboratory) have either returned to normal or are stabilized. The Investigator must also report follow-up information if it becomes known to the Investigator.

SAE reporting by the CRO:

The CRO must notify the [redacted] Study Manager and Sponsor Drug Safety Department **within 24 hours** of the initial notification of the event. Documentation should be sent to Taro's SAE Coordinator and Sponsor Drug Safety listed below:

[redacted]

[redacted]

[redacted] Study Manager and/or Sponsor Drug Safety Department must receive any follow-up [redacted] of receipt by CRO.

10.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

An **Adverse Event or Suspected Adverse Reaction** is considered a SUSAR if it is serious, unexpected, and suspected. Prior to reporting to the applicable Regulatory Authorities, the Sponsor will evaluate the available evidence and to judge the likelihood that the drug actually caused the adverse event. The SUSAR must be reported to FDA within 15 days, or if fatal or life threatening, within 7 days, by the Sponsor. The Sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event. Additionally, potential Hy's law cases will be reported as SUSARs.

The Sponsor is responsible for reporting of suspected unexpected serious adverse reactions and notifying the relevant regulators (including the authorities in the EEA via EudraVigilance and the IRBs/IECs) and the Investigator sites within the specified timeframes of all SUSARs, as applicable per local requirements

The applicable Regulatory Authorities shall be notified by Sponsor Safety Physician of any SUSAR, as per local Regulatory Authorities guidelines and timeframe specified as per local regulation.

All participating Investigators, EC/IRB and other stakeholders shall be notified of any SUSAR by CRO's Medical Monitor as per local regulatory requirement.

10.5 Adverse Events of Special Interest (AESI)

AESI should be reported by a site to the CRO using an SAE form within 24 hours of awareness. The CRO must notify the [redacted] Study Manager and Sponsor Drug Safety within 24 hours of the initial notification of the event.

10.6 Post-study Events

Any AE/SAE that occurs up until the follow-up visit, or if the follow-up visit does not occur within the defined time window, then 4 weeks post the end of treatment visit or 4 weeks post the last dose of study drug for subjects with early discontinuation, should be reported and included in the safety analysis of the study.

Any AE/SAE which occurs past this date will be reported if it is considered related to study drug by the Investigator.

11. ETHICS

This study will be conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and will be consistent with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable regulatory requirements (including EU CT Regulation 536/2014). The study will be conducted in compliance with the protocol.

The rights, safety and well-being of the study Subjects are the most important considerations and should prevail over interests of society and science.

The Sponsor ensures that local regulatory requirements are met before the start of the study. The Sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any RA approvals required prior to release of IP for shipment to the site.

11.1 Informed Consent

The Principal Investigator must ensure that Subjects are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical studies in which they volunteer to participate. The principles of Informed Consent, according to FDA Regulations and ICH GCP will be followed. A copy of the proposed consent form must be submitted to the IRB, together with the protocol, for approval. Prior to beginning of the study, the Principal Investigator must have the IRB's written approval

of the written informed consent form and any other information to be provided to Subjects.

Informed consent will be obtained from all Subjects using the following procedure: Subjects must have provided IRB approved written informed consent. Prior to initiating screening for the study, Subjects will be given the approved ICF describing the study and any risks associated with participation. The Subject will be allowed as much time as needed to read and understand the information presented in the consent form. Appropriate study personnel will be available to answer any questions the Subject might have regarding the study or study-related procedures. If the Subject chooses to participate in the study, he or she will be asked to sign and date the consent form and will be provided with a copy for his or her records. The ICF must be signed by the Subject before any protocol assessments can be undertaken. Each Subject's signed informed consent must be kept on file by the Principal Investigator.

11.2 Institutional Review Board

Before study initiation, the Principal Investigator must have written and dated approval from the IRB for the protocol, consent form, Subject recruitment materials and any other written information to be provided to Subjects.

Any changes to the protocol as well as a change of the Principal Investigator, which is approved by the Sponsor, must also be approved by the site's IRB and documentation of this approval provided to the Sponsor/designee. Records of the IRB review and approval of all documents pertaining to this study must be kept on file by the Principal Investigator and are subject to inspection during or after completion of the study. All SAEs must also be reported to the IRB.

Periodic status reports must be submitted to the IRB at least annually, as well as notification of completion of the study and a final report within one (1) month of study completion or discontinuation or per the local ethics committee requirements. A copy of all reports submitted to the IRB must be sent to the Sponsor/designee.

The Principal Investigator will ensure that an IRB that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study.

11.3 Subject Confidentiality

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive personal information is handled in accordance with local data protection laws (including, but not limited to, HIPAA and GDPR). Appropriate consent for collection, use, and disclosure and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws.

Participant names will not be supplied to the sponsor or its designee. Only the participant number will be recorded in the study database; if the participant's name appears on any other document (eg laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with appropriate technical and organizational measures as required by local data protection laws.

The monitor(s), the auditor(s), IRB/IEC, and the regulatory authority(ies), will be granted direct access to the Subject's original medical records for verification of the clinical trial procedures and/or data, without violating the confidentiality, to the extent permitted by the applicable laws and regulations and that by signing a written informed consent form, the Subject or the Subject's legally acceptable representative is authorizing such access.

The identifying the Subject will be kept confidential and, to the extent permitted by the applicable laws and regulations, will not be made publicly available. If the results of the trial are published, the Subject's identity will remain confidential.

11.4 Indemnity/Liability and Insurance

The Sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the CRO/Investigator as necessary.

12. DOCUMENTATION

12.1 Site Regulatory Documents Required for Initiation

The following documents will be received by the CRO prior to the initiation of the study:

1. Completed and signed FDA Form 1572
2. Current curricula vitae, signed and dated for the Principal Investigator and each Sub-Investigator named in the FDA Form 1572 (current within 2 years)
3. Current medical licenses of the Principal Investigator and Sub-Investigators named in FDA Form 1572
4. Documentation of IRB approval of this study protocol, Principal Investigator and informed consent form
5. Current IRB membership list or roster
6. A copy of the protocol agreement page signed by the Principal Investigator
7. Non-disclosure Agreements for the Principal Investigator and Sub-Investigators named in FDA Form 1572
8. Financial Disclosure Statement for the Principal Investigator and each Sub-Investigator named in FDA Form 1572.
9. Statement of Non-Debarment

12.2 Maintenance and Retention of Records

It is the responsibility of the Principal Investigator to maintain a comprehensive and centralized filing system of all relevant documentation.

Copies of all pertinent records will be retained by the Principal Investigator for at least two years following final approval of the drug and/or notification from the Sponsor. These regulatory documents should be retained for a longer period if required by local regulatory authorities. These records include documents pertaining to the receipt and return of drug supplies, IRB, informed consent, source documents. No documents shall be transferred from the site or destroyed without first notifying the Sponsor. If the Principal Investigator withdraws from the study, the records shall be transferred to a mutually agreed upon designee. Notice of such transfer will be given in writing to the Sponsor.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories designed to document all observations and other data pertinent to the investigation on each individual treated with the Investigational Product or entered as a control in the investigation.

12.3 Data Collection and Reporting

Data for individual Subjects will be collected on source documents. The data management system will be Electronic Data Capture (EDC). The Investigator and his/her study site personnel will be responsible for transferring data to the electronic Case Report Forms (eCRFs). The Investigator is required to verify that all of the requested information is accurately recorded in the eCRFs. All information requested in the eCRFs needs to be supplied, including subject identification, date(s), assessment values, etc., and any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documents.

Source documents such as the clinic chart are to be maintained separately from the eCRF in order to allow data verification. Because of the potential for errors, inaccuracies and illegibility in transcribing data into eCRFs, originals of laboratory and other test results must be kept on file. Source documents and copies of test results must be available at all times for inspection by the study monitor. The following should also be available for review:

1. Subject Screening Log – reflecting the reason any Subject screened for the study was found to be ineligible

2. Delegation of Authority / Study Personnel Signature Log – all site personnel will be listed along with their responsibilities and signatures; to be maintained at the site throughout the study
3. Monitoring Log – the date and purpose of all monitoring visits by the Sponsor/Designee will be documented
4. Enrollment Log – documenting Subject initials and start and end dates for all Subjects enrolled
5. Drug Inventory/Packing Slip – reflecting the total amount of drug shipped to the site and received and signed for by the Principal Investigator
6. Drug Accountability Log – reflecting the total amount of Investigational Product dispensed to and returned by each Subject
7. Informed Consent Form and Assent Form – which must be available for each Subject and be verified for proper documentation

The study monitor will be responsible for reviewing and verifying the data recorded in the eCRFs, utilizing the original source documentation and will query discrepant findings. The Investigator and study site personnel will be responsible for answering all queries. All queries issued by the data management personnel will be answered by site personnel and verified by the monitor.

Electronically generated data like laboratory results, ECG results etc. could be directly integrated with or transferred to the clinical database.

[redacted]

12.4 Primary Source Documents

The Principal Investigator must maintain primary source documents supporting significant data for each Subject's medical notes. These documents, which are considered "source data", should include documentation of:

- Demographic information
- Evidence supporting the diagnosis/condition for which the Subject is being studied
- General information supporting the Subject's participation in the study
- General history and physical findings
- Hospitalization or Emergency Room records (if applicable)
- Each study visit by date, including any evaluations, relevant findings/notes by the Principal Investigator(s), occurrence (or lack) of adverse events and changes in medication usage, including the date the study drug commenced and completed.
- Any additional visits during the study
- Any relevant telephone conversations with the Subject regarding the study or possible adverse events
- An original, signed informed consent form or assent form for study participation

The Principal Investigator must also retain all Subject specific printouts/reports of tests/procedures performed as a requirement of the study.

12.5 Study Monitoring

The study will be monitored by representatives of the Contract Research Organization to assess compliance with ICH-GCP and applicable regulations. The Principal Investigator will be visited by a monitor prior to the study and at regular intervals during the course of the study. These visits are for the purposes of verifying adherence to the protocol. The investigators and institutions involved in the clinical trial are to permit clinical trial-related monitoring, including provision of direct access to source data and documents.

The study monitor will review the informed consent/assent forms and verify eCRF entries by comparing them with the source documents (hospital/clinic/office records) that will be made available for this purpose. The monitor will review the maintenance of regulatory documentation and drug accountability.

The monitor will review on a regular basis the progress of the study with the Principal Investigator and other site personnel.

eCRF sections may be monitored during these visits. At the end of the study, a closeout monitoring visit will be performed. Monitoring visits will be arranged in advance at a mutually acceptable time with site personnel. Sufficient time must be allowed by the site personnel for the monitoring of eCRFs and relevant source documents. The Study Coordinator and/or Principal Investigator should be available to answer questions or resolve data clarifications. Adequate time and space for these visits should be made available by the Principal Investigator.

12.6 Data and Safety Monitoring Board

An independent DSMB has been established for periodic review of safety data for this study. The composition and responsibilities of the DSMB are described in the DSMB Charter. The DSMB has access to study un-blinded data.

12.7 Audits and Inspections

During the course of the study and/or after it has been completed, one or more site visits may be undertaken by auditors as authorized representatives of the Sponsor. The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with the protocol, recognized GCP guidelines and all applicable regulations.

Additionally, the study may be inspected by regulatory agencies. These inspections may take place at any time during the course of the study and/or after it has been completed.

The investigators and institutions involved in the clinical trial are to permit clinical trial-related audits and regulatory inspections, including provision of direct access to source data and documents.

THE INVESTIGATOR MUST NOTIFY THE CONTRACT RESEARCH ORGANIZATION and SPONSOR PROMPTLY OF ANY INSPECTIONS SCHEDULED BY REGULATORY AUTHORITIES, AND PROMPTLY FORWARD COPIES OF INSPECTION REPORTS TO THE SPONSOR.

12.8 Modifications to the Protocol

The procedures defined in the protocol will be carefully reviewed to ensure that all parties involved with the study fully understand the protocol. In order to ensure the validity of the data, no violations from the protocol, with minimal exceptions, may be made unless the issue is broad enough to warrant revision of the protocol. Such revisions must be submitted to and have documented approval from the Sponsor and the IRB/regulatory agency, as applicable, prior to implementation.

The only circumstance in which an amendment may be initiated without prior IRB approval is to eliminate apparent immediate hazards to a Subject or Subjects. However, the Principal Investigator must notify the Sponsor immediately and the IRB within 5 working days after implementation.

All protocol violations will be reported on the protocol violation log and included in the study reports. A protocol violation is defined as any change, deviation, or departure from the study design or procedures of research project that is NOT approved by the IRB prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations.

The sponsor will notify the authorities as applicable (in line with country/region requirements) about a serious breach of the regulations or of the version of the protocol applicable at the time of the breach. A ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical trial.

12.9 Completion of Study

The Principal Investigator is required to sign the eCRFs and all other relevant data and records to the Contract Research Organization.

The Principal Investigator is expected to submit a final report to the IRB and the Sponsor within one (1) month of study completion or discontinuation.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs/IECs, the regulatory authorities, and any Contract Research Organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements.

Study results reporting:

The Sponsor will provide Clinical Study Report (or its summary) to the regulatory agencies, as applicable, in timeframe in line with country requirements.

For the EU countries: irrespective of the outcome of the clinical trial, the Sponsor will submit a summary of the intermediate results, as well final results of the clinical study to the relevant EU clinical study database (the Clinical Trials Information System [CTIS] database at https://euclinicaltrials.eu/home) in a timely manner. As appropriate, the final study results posting this will be accompanied by a summary written in a manner that is understandable to laypersons.

12.10 Data Protection in the European Economic Area

The Sponsor, as Data Controller, ensures that all processing activities involving personal data performed in the scope of this Study are compliant with, but not limited to, the requirements set by EU General Data Protection Regulation (GDPR 679/2016), its subsequent amendments and any additional national laws on Data Protection, recommendations, and guidelines as applicable

The Sponsor will take adequate measures to comply with the applicable rules on the protection of personal data, specifically regarding the implementation of the organizational and technical arrangements aiming to avoid unauthorised access, disclosure, dissemination, alteration, or loss of information and processed personal data. Similarly, measures will be taken to implement and for ensuring confidentiality of records and personal data of subjects.

In case of the occurrence of any data breach, the Sponsor will immediately apply relevant measures to mitigate the risks to data of subjects as appropriate in relation to the specific context of the data breach, taking into account its source, underlying intentions, possibilities of recovery etc. Any data breach presenting risks to the rights and freedoms of data of subjects will be reported to the relevant supervisory data protection authority within 72 hours of the Sponsor becoming aware of the data breach

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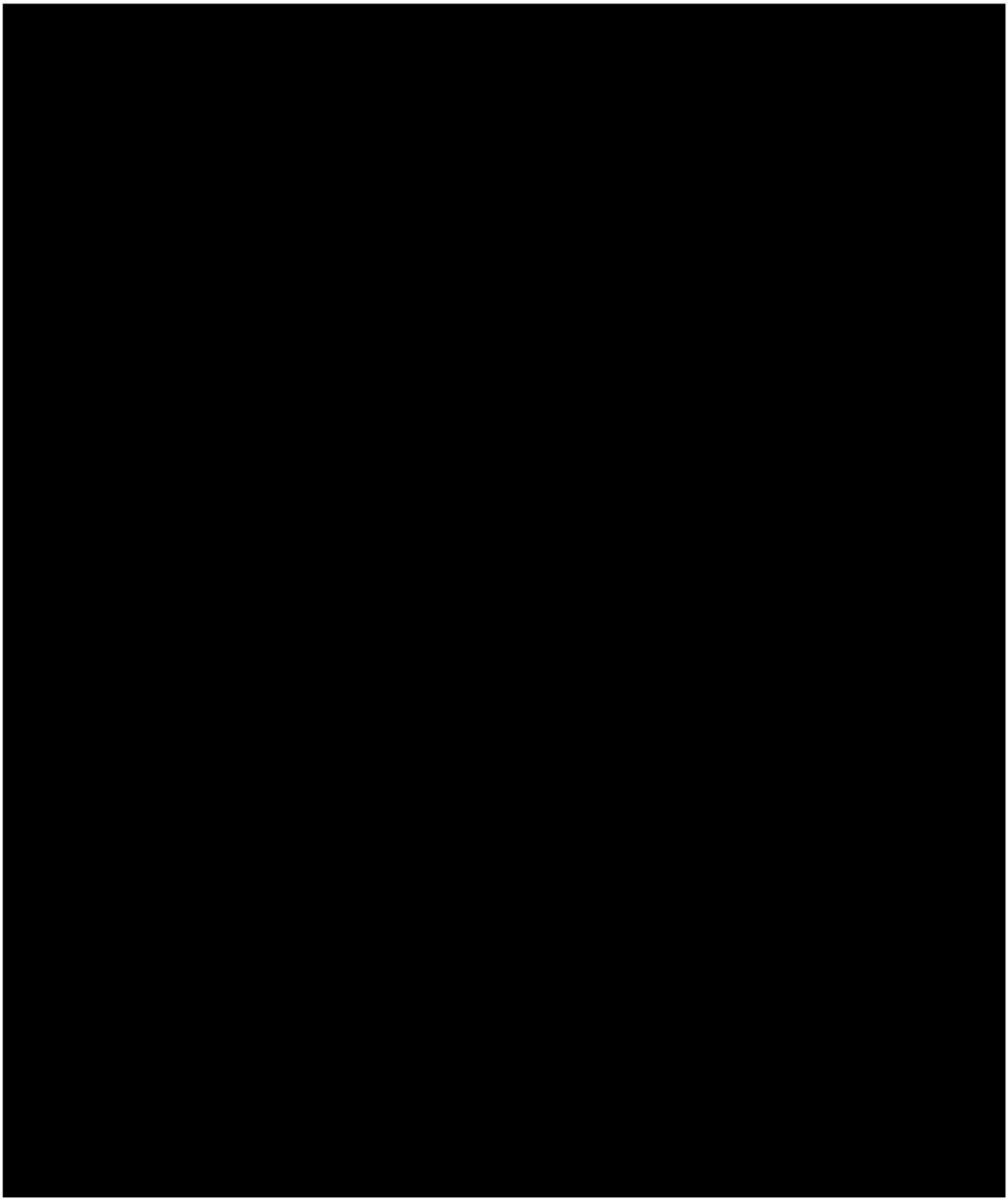
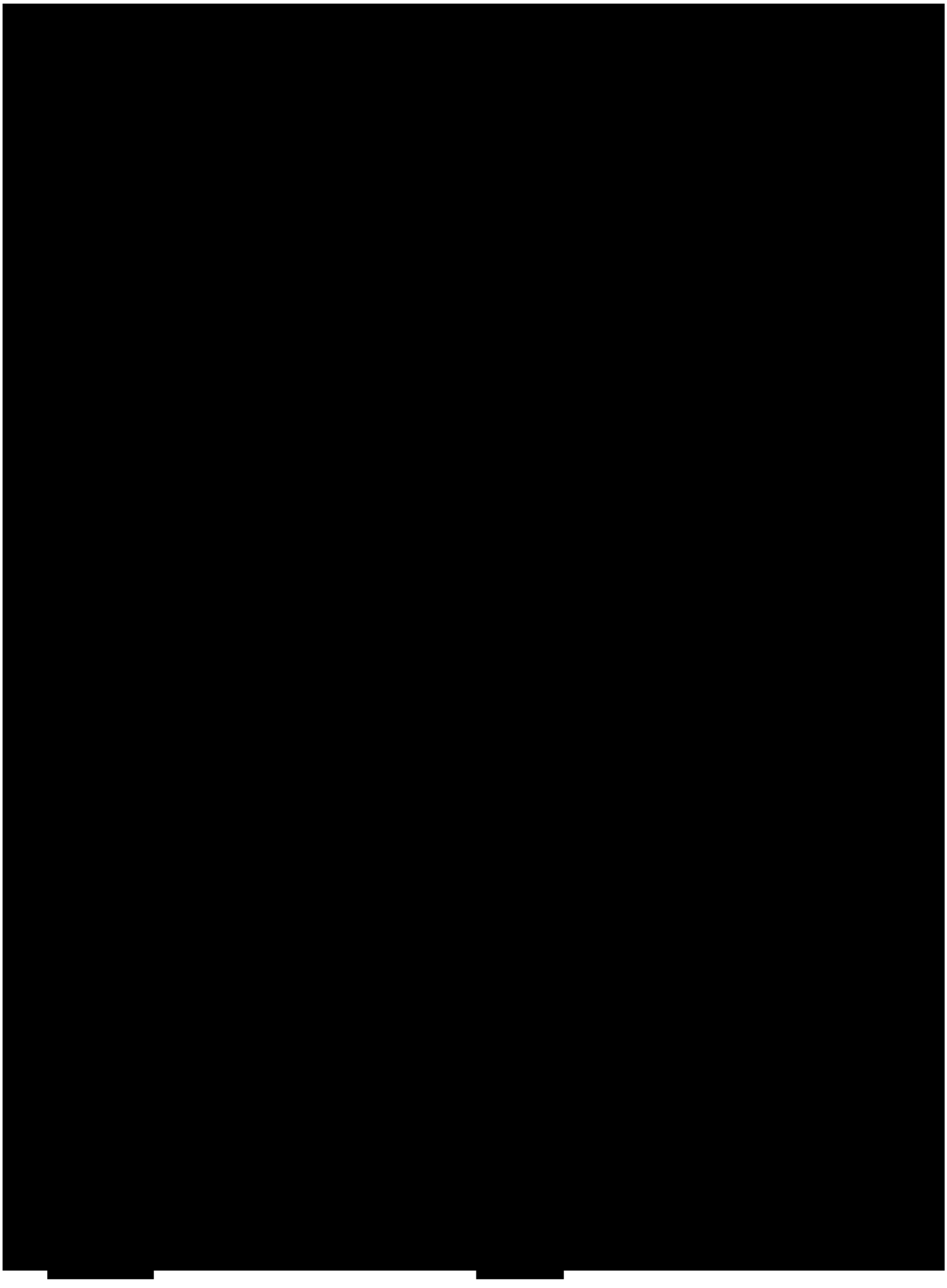
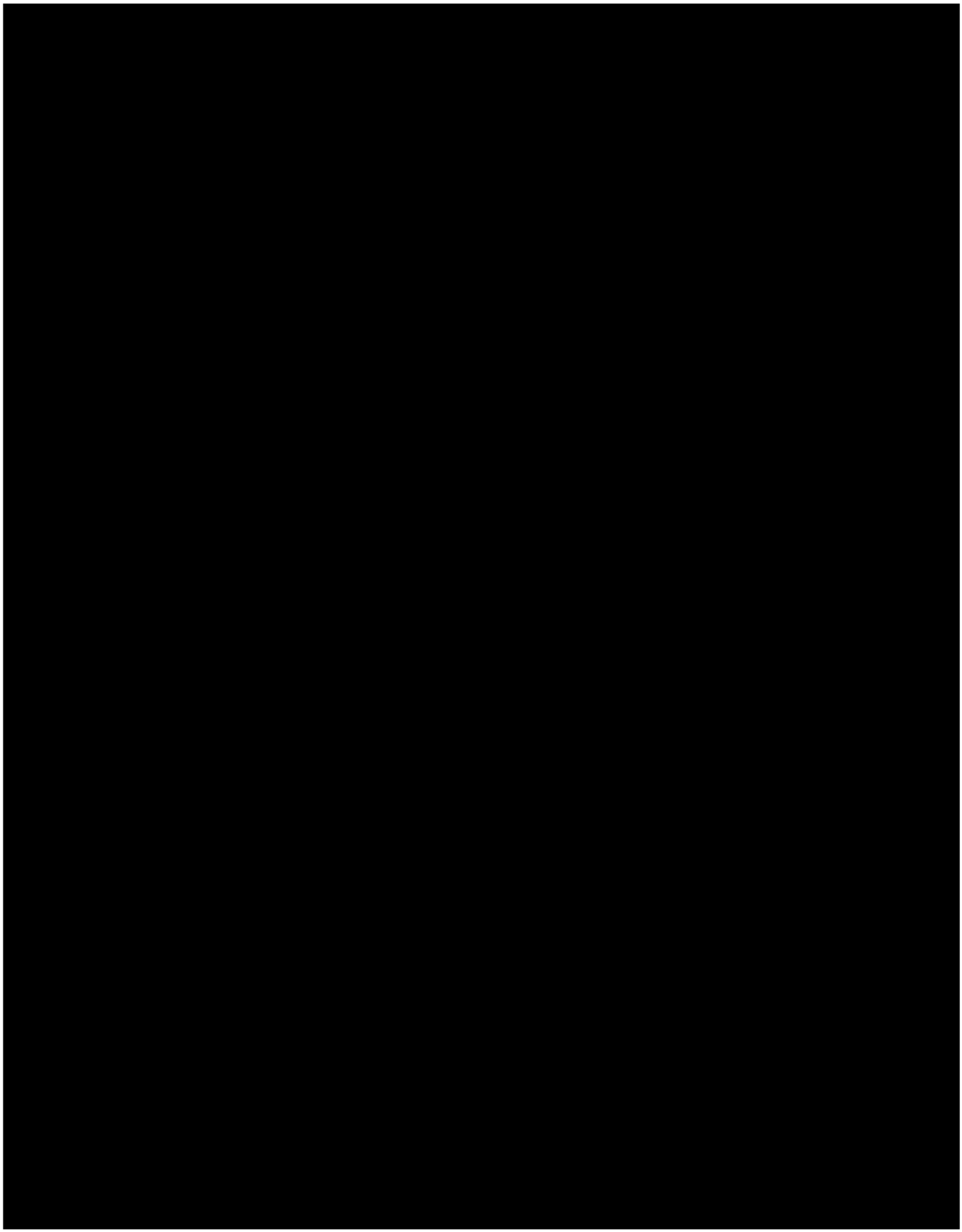
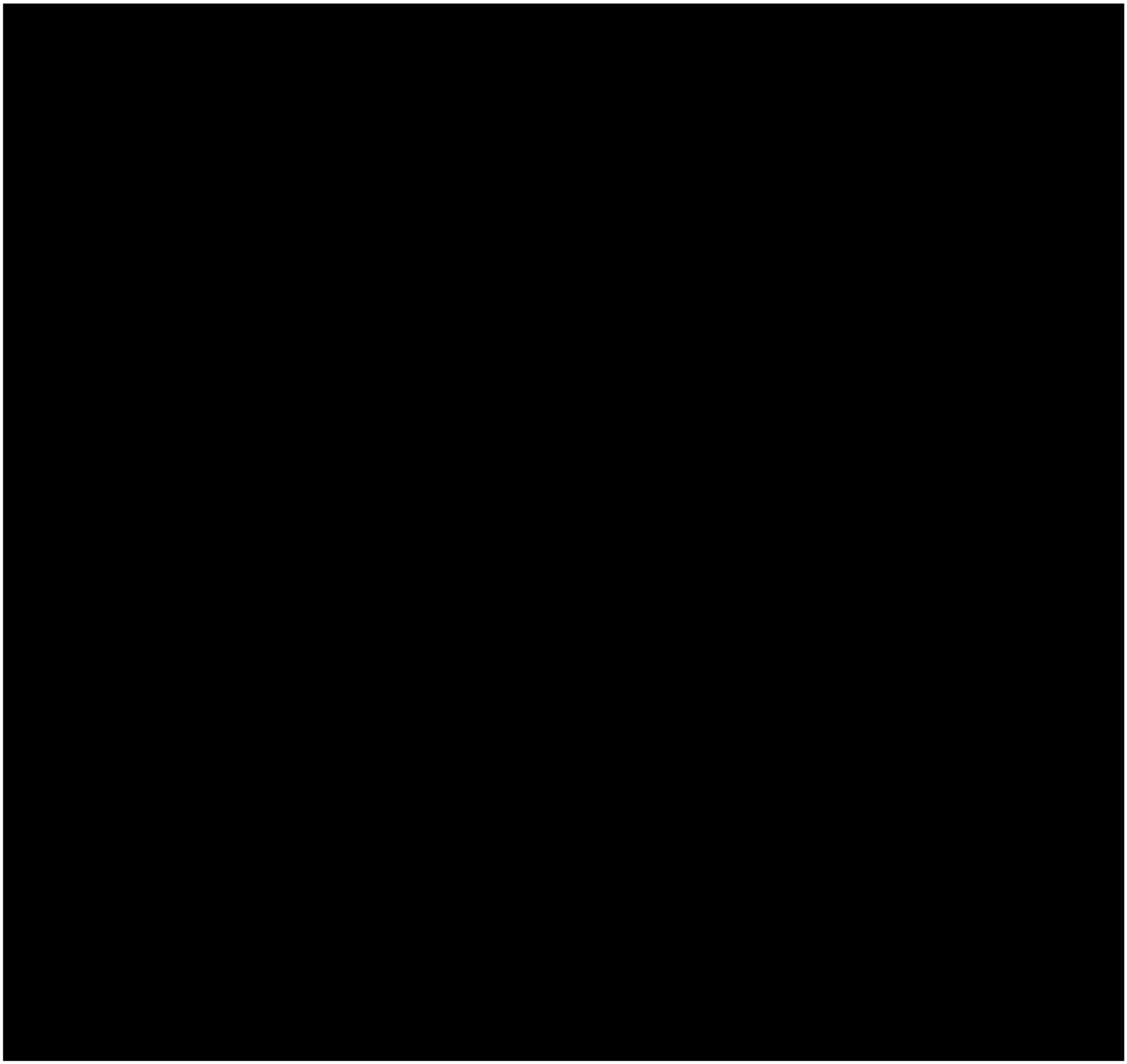






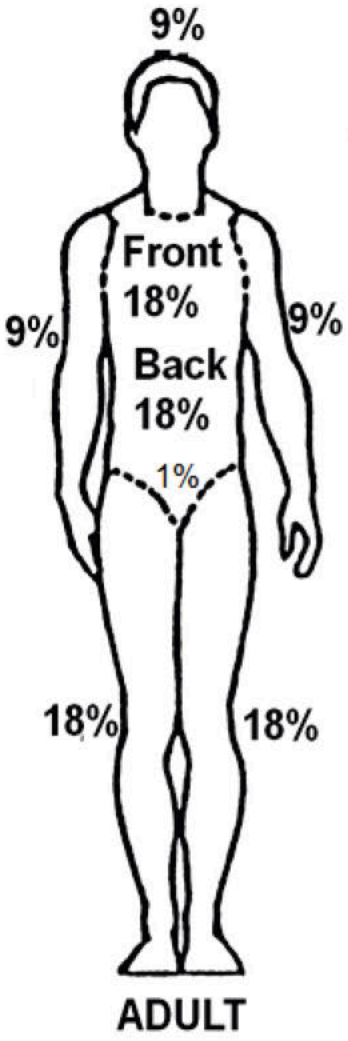


APPENDIX II: BODY SURFACE AREA (BSA)

[redacted]

The [redacted] provides a general estimation of total BSA for several anatomic areas. The Investigator may then visually estimate the proportion of the involved skin within each anatomic area and calculate the total percentage of BSA affected. Calculate to the nearest whole percentage.

Part	Adult body % of total
Head	9%
Genitalia	1%
Arm	9%
Leg	18%
Anterior trunk	18%
Posterior trunk	18%



Handprint method (to determine % BSA affected and extent of involvement for EASI):

To estimate the % BSA Affected and extent of involvement for EASI, the investigator should use the handprint method of approximation: the patient's handprint (palm and fingers together) represents approximately one percent (1%) of his/her BSA.

The total number of handprints for each body region of head and neck, upper limbs, trunk (including axillae and groin) and lower limbs (including buttocks) equals: 10, 20, 30, and 40, respectively.

The % BSA affected by atopic dermatitis is the percent total of affected areas for all four regions of the body.

Body region	Total number of handprints in body region	Surface area of body region equivalent to one handprint
Head and neck	10	10%
Upper limbs	20	5%
Trunk (includes axillae and groin)	30	3.33%
Lower limbs (includes buttocks)	40	2.5%

Note: The EASI will exclude scalp, palms, and soles from the assessment/scoring.

APPENDIX III: PATIENT ORIENTED ECZEMA MEASURE (POEM) EXAMPLE

Please circle one response for each of the seven questions below about your eczema. Please leave blank any questions you feel unable to answer.

1. Over the last week, on how many days has your skin been itchy because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

2. Over the last week, on how many nights has your sleep been disturbed because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

3. Over the last week, on how many days has your skin been bleeding because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

4. Over the last week, on how many days has your skin been weeping or oozing clear fluid because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

5. Over the last week, on how many days has your skin been cracked because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

6. Over the last week, on how many days has your skin been flaking off because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

7. Over the last week, on how many days has your skin felt dry or rough because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

Total POEM Score (Maximum 28): _____

APPENDIX IV: DERMATOLOGY LIFE QUALITY INDEX (DLQI) EXAMPLE

The aim of this questionnaire is to measure how much your skin problem has affected your life over the **past week.** Please check ☑ one box for each question.

1	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐		
2	Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐		
3	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
4	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
5	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
6	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
7	Over the last week, has your skin prevented you from **working** or **studying**? If "No", over the last week how much has your skin been a problem at **work** or **studying**?	Yes No A lot A little Not at all	☐ ☐ ☐ ☐ ☐	Not relevant	☐
8	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
9	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
10	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐

APPENDIX V: ECZEMA AREA AND SEVERITY INDEX (EASI) SOURCE DOCUMENT EXAMPLE

Areas[1]	Extent[2]		Severity of Signs[3]			
	Score	% involvement	Erythema	Induration/papulation	Excoriation	Lichenification
Head/neck	0	☐ 0				
	1	☐ 1 - 9%	☐ 0 (None)	☐ 0 (None)	☐ 0 (None)	☐ 0 (None)
	2	☐ 10 – 29%	☐ 1 (Mild)	☐ 1 (Mild)	☐ 1 (Mild)	☐ 1 (Mild)
	3	☐ 30 – 49%	☐ 2 (Moderate)	☐ 2 (Moderate)	☐ 2 (Moderate)	☐ 2 (Moderate)
	4	☐ 50 – 69%	☐ 3 (Severe)	☐ 3 (Severe)	☐ 3 (Severe)	☐ 3 (Severe)
	5	☐ 70 – 89%				
	6	☐ 90 – 100%				
Trunk (including the genital area)	0	☐ 0				
	1	☐ 1 - 9%	☐ 0 (None)	☐ 0 (None)	☐ 0 (None)	☐ 0 (None)
	2	☐ 10 – 29%	☐ 1 (Mild)	☐ 1 (Mild)	☐ 1 (Mild)	☐ 1 (Mild)
	3	☐ 30 – 49%	☐ 2 (Moderate)	☐ 2 (Moderate)	☐ 2 (Moderate)	☐ 2 (Moderate)
	4	☐ 50 – 69%	☐ 3 (Severe)	☐ 3 (Severe)	☐ 3 (Severe)	☐ 3 (Severe)
	5	☐ 70 – 89%				
	6	☐ 90 – 100%				
Upper extremities	0	☐ 0				
	1	☐ 1 - 9%	☐ 0 (None)	☐ 0 (None)	☐ 0 (None)	☐ 0 (None)
	2	☐ 10 – 29%	☐ 1 (Mild)	☐ 1 (Mild)	☐ 1 (Mild)	☐ 1 (Mild)
	3	☐ 30 – 49%	☐ 2 (Moderate)	☐ 2 (Moderate)	☐ 2 (Moderate)	☐ 2 (Moderate)
	4	☐ 50 – 69%	☐ 3 (Severe)	☐ 3 (Severe)	☐ 3 (Severe)	☐ 3 (Severe)
	5	☐ 70 – 89%				
	6	☐ 90 – 100%				
Lower extremities (including the buttocks)	0	☐ 0				
	1	☐ 1 - 9%	☐ 0 (None)	☐ 0 (None)	☐ 0 (None)	☐ 0 (None)
	2	☐ 10 – 29%	☐ 1 (Mild)	☐ 1 (Mild)	☐ 1 (Mild)	☐ 1 (Mild)
	3	☐ 30 – 49%	☐ 2 (Moderate)	☐ 2 (Moderate)	☐ 2 (Moderate)	☐ 2 (Moderate)
	4	☐ 50 – 69%	☐ 3 (Severe)	☐ 3 (Severe)	☐ 3 (Severe)	☐ 3 (Severe)
	5	☐ 70 – 89%				
	6	☐ 90 – 100%				

The assessed parameters are inserted into a table (example shown below for age≥8 years). The final EASI score ranges from 0-72.

Body region	Erythema	Edema/papulation	Excoriation	Lichenification	Area score	Multiplier	Score
Head/neck	(+	+	+	)	x	x 0.1	
Trunk	(+	+	+	)	x	x 0.3	
Upper extremities	(+	+	+	)	x	x 0.2	
Lower extremities	(+	+	+	)	x	x 0.4	
The final EASI score is the sum of the 4 region scores							_____ (0 – 72)

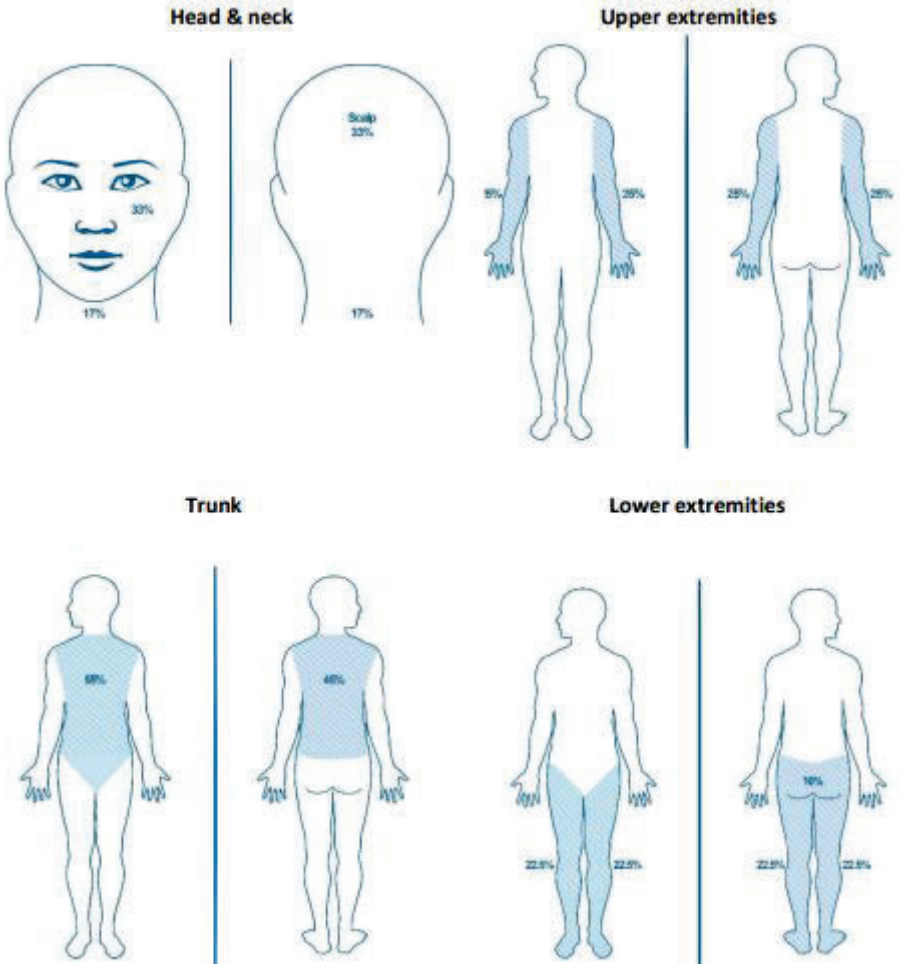
How to use EASI:

1. Select a body region

2. Assess the extent of eczema in that body region

Each body region has potentially 100% involvement. Using the table below, give each respective body region a score of between 0 and 6 based on the percentage involvement. Precise measurements are not required.

To aid in your body region grading you can use the diagrams below.

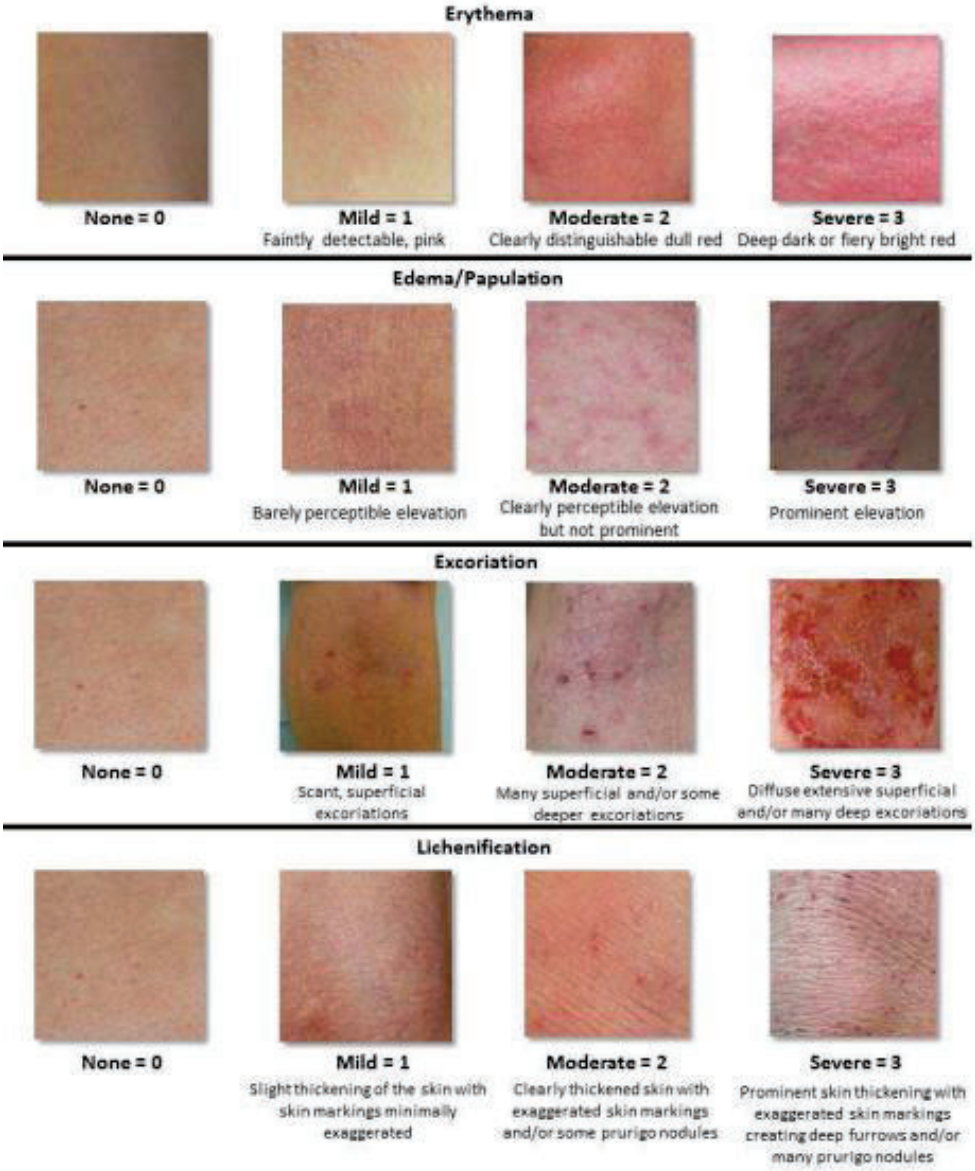


3. Assess the severity of each of the four signs in that body region: erythema, edema/papulation, excoriation, and lichenification

Grade the severity of each sign on a scale of 0 to 3.

- Take an average of the severity across the involved region.
- Half points (1.5 and 2.5) may be used. 0.5 is not permitted – if a sign is present it should be at least mild (1)
- Palpation may be useful in assessing edema/papulation as well as lichenification

To aid your severity grading, a photographic atlas of suggested categories is available below.



Remember: Include only inflamed areas in your assessment; do not include xerosis (dryness), ichthyosis, keratosis pilaris, urticaria, infection (unless there is underlying eczema), or post inflammatory pigmentation changes.

APPENDIX VI: PATIENT GLOBAL IMPRESSION OF SEVERITY (PGIS) EXAMPLE

Please choose the response below that best describes the severity of your atopic dermatitis over the **past week**.

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe

APPENDIX VII: PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC) EXAMPLE

Please choose the response below that best describes the overall change in your atopic dermatitis since you started taking the study medication: Please check ☑ one box only	
☐	Much better
☐	A little better
☐	No Change
☐	A little worse
☐	Much Worse

APPENDIX VIIIa: PEAK PRURITUSNUMERIC RATING SCALE (PP-NRS) EXAMPLE

Severity of Pruritus

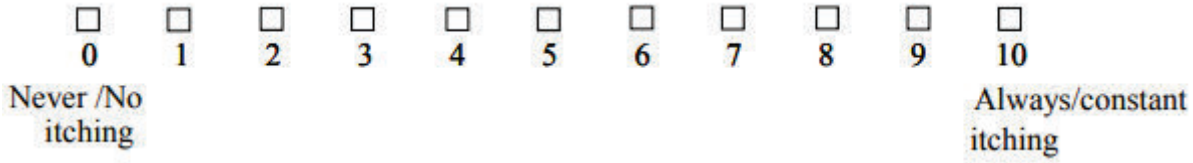
On a scale of 0 to 10, with 0 being “no itch” and 10 being “worst itch imaginable”, how would you rate your itch at the worst moment during the previous 24 hours?

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
No itch										Worst itch imaginable

APPENDIX VIIIb: FREQUENCY OF ITCHING DUE TO ATOPIC DERMATITIS EXAMPLE

Frequency of Pruritus

Select the number that best describes frequency of itching due to atopic dermatitis over the past 24 hours (check one number only).



APPENDIX IX: SCORING ATOPIC DERMATITIS (SCORAD) EXAMPLE

Area (A)
To determine extent, the sites affected by eczema are shaded on a drawing of a body. The [redacted] is used to calculate the affected area (A) as a percentage of the whole body (Appendix II).

Body area	Extent	Maximum
Head and neck		9%
Upper limbs		9% each
Lower limbs		18% each
Anterior trunk		18%
Back		18%
Genitals		1%
Total (A):		100%

Add the scores for each area. The total area is 'A', which has a possible maximum of 100%.

Intensity (B)
A representative area of eczema is selected. In this area, the intensity of each of the following signs is assessed as none (0), mild (1), moderate (2) or severe (3).

- Redness
- Swelling
- Oozing/crusting
- Scratch marks
- Skin thickening (lichenification)
- Dryness (this is assessed in an area where there is no inflammation)

The intensity scores are added together to give 'B' (maximum 18).

Representative Area of Eczema					
Redness	Swelling	Oozing/crusting	Scratch marks	Skin thickening (lichenification)	Dryness (this is assessed in an area where there is no inflammation)
☐ 0 (None) ☐ 1 (Mild) ☐ 2 (Moderate) ☐ 3 (Severe)	☐ 0 (None) ☐ 1 (Mild) ☐ 2 (Moderate) ☐ 3 (Severe)	☐ 0 (None) ☐ 1 (Mild) ☐ 2 (Moderate) ☐ 3 (Severe)	☐ 0 (None) ☐ 1 (Mild) ☐ 2 (Moderate) ☐ 3 (Severe)	☐ 0 (None) ☐ 1 (Mild) ☐ 2 (Moderate) ☐ 3 (Severe)	☐ 0 (None) ☐ 1 (Mild) ☐ 2 (Moderate) ☐ 3 (Severe)

Subjective symptoms (C)
Subjective symptoms (itch and sleeplessness), are each scored by the patient or relative using a visual analogue scale where 0 is no itch (or no sleeplessness) and 10 is the worst imaginable itch (or sleeplessness). These scores are added to give 'C' (maximum 20).

SCORAD =	A/5 +	7B/2 +	C
=	+	+	

The maximum score is 103.

Subjective symptoms (C)

Note: Please ensure that the line is 100 mm in length after printing the source document and measuring the distance

Instructions for the subject

Itch:

No itch — Worst imaginable itch

Sleeplessness:

No sleeplessness — Sleeplessness

APPENDIX X: PROTOCOL FOR ORTHOSTATIC (POSTURAL) VITAL SIGN MEASUREMENT EXAMPLE

Procedure[14]

1. Assess by verbal report and observation the subject's ability to stand.
2. Have subject lie in bed with the head flat for a minimum of 5 minutes.
3. Measure the blood pressure and the pulse while the subject is supine.
4. Instruct subject to stand.
   - Ask subject about dizziness, weakness, or visual changes associated with position change. Note diaphoresis or pallor.
   - If subject is unable to stand, sit patient upright with legs dangling over the edge of the bed.
   - The subject should be permitted to resume a supine position immediately if syncope or near syncope develops.
5. Measure the blood pressure and pulse measurements 2-5 minutes after subject stands. Support the forearm at heart level when taking the blood pressures to prevent inaccurate measurement.
6. Assist subject back to bed in a position of comfort.
7. Document vital signs and other pertinent observations. Note all measurements taken and the position of the subject during each reading.
8. Report all findings, including all sets of blood pressure and pulse results, and whether the subject experienced pallor, diaphoresis, or faintness when upright, to the independent safety assessor

☐ **Pre-dose** ☐ **Post-dose**

subject's position	pulse rate* (bpm)	systolic BP(mmHg)	diastolic BP (mmHg)	observations associated with position change	Evaluation (change +/- from supine values) *decline of ≥20mm Hg in systolic BP = orthostatic hypotension* *decline of ≥10mm Hg in diastolic BP = orthostatic hypotension* *increase of at least 30bpm in pulse rate may suggest hypovolemia*
Supine (after the Subject is rested for at least 5 minutes)					
2-5 minutes after subject stands				☐dizziness ☐weakness ☐visual changes ☐diaphoresis ☐pallor ☐other:	change (+/-) in pulse rate (bpm): _____ change (+/-) in systolic BP (mmHg) : _____ change (+/-) in diastolic BP (mmHg) : _____ ☐ orthostatic hypotension ☐ suggested hypovolemia

* Pulse rate to be measured [redacted] by counting the number of heart beats over 60 seconds (the pulse rate should not be extrapolated after counting for part of 60 seconds).

If needed, at the independent safety assessor's discretion, pulse rate and BP may be measured in triplicate (at 1-2 minute intervals). Report the lowest value.