Janssen Research & Development

Statistical Analysis Plan

A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Adult Subjects Assessed to be at Imminent Risk for Suicide

Protocol 54135419SUI3001; Phase 3

JNJ54135419 (esketamine)

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AMENDMENT HISTORY

The SAP, originally approved on 23 November 2018 has been revised. The following is a list of changes made to the SAP, along with the rationale for each change:
1) Section 2.2.1 Analysis Phase Start and End Dates: Start and end dates for the F/U phase are only defined for subjects who completed the DB phase and continued into the F/U phase (including a visit in the F/U phase or an adverse event in the F/U phase). Any assessment (including an adverse event) after the DB completion date is considered as in the F/U phase for the subjects who completed the DB phase.
2) Section 2.5.4 Follow-up Analysis Set: The Follow-up analysis set is defined as all subjects who entered the follow-up phase or had provided adverse event data after the double-blind phase.
3) Section 5.3.2 Analysis Methods: in addition to the Hodges-Lehmann estimate, the treatment effect will also be estimated using least square means based on an ANCOVA model on the actual change with factors for treatment, analysis center, standard of care antidepressant treatment as randomized (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy) and baseline CGI-SS-R (unranked) as a covariate. A point estimate and 95% confidence interval for the treatment difference will be provided.

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASA	American Society of Anesthesiologists
AST	aspartate aminotransferase
BHS	Beck Hopelessness Scale
BMI	body mass index
BP	Blood Pressure
CADSS	Clinician Administered Dissociative States Scale
C-CASA	Columbia Classification Algorithm for Suicide Assessment
CGI-SR-I	Clinical Global Impression – Imminent Suicide Risk
CGI-SR-LT	Clinical Global Impression – Long-term Suicide Risk
CGI	Clinical Global Impression
CGI-SS-R	Clinical Global Impression – Severity of Suicidality - Revised
CI	confidence interval
DB	Double-blind
ECG	electrocardiogram
ER	Emergency Room
EQ-5D-5L	EuroQol Group; 5 dimension; 5 level
EQ-VAS	EuroQol Group: visual analogue scale
FDA	Food and Drug Administration
FoST	frequency of suicidal thinking
F/U	Follow-up
GCP	Good Clinical Practice
HPA	hypothalamic-pituitary-adrenal
HR	heart rate
HRUQ	Healthcare Resource Use Questionnaire
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IWRS	interactive web response system
LOCF	last observation carried forward
MADRS	Montgomery Asberg Depression Rating Scale
MDD	major depressive disorder

MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Psychiatric Interview
MMRM	Mixed-effects model using repeated measures
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
NDE	natural direct effect
NIE	natural indirect effect
PR	pulse rate
QLDS	Quality of Life in Depression Scale
QTc	corrected QT
QTcB	QT corrected according to Bazett's formula
QTcF	QT corrected according to Fridericia's formula
RC	Remote contact
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
SIBAT	Suicide Ideation and Behavior Assessment Tool
TEAE	treatment-emergent adverse event
TEMA	treatment-emergent markedly abnormal
TSQM-9	treatment satisfaction questionnaire for medication
ULN	upper limit of normal

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses for Study 54135419SUI3001.

1.1. Trial Objectives

Primary Objective

The primary objective is to evaluate the efficacy of intranasal esketamine 84 mg compared with intranasal placebo in addition to comprehensive standard of care in reducing the symptoms of MDD, including suicidal ideation, in subjects who are assessed to be at imminent risk for suicide, as measured by the change from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS) total score at 24 hours post first dose.

Key Secondary Objective

The key secondary objective is to assess the efficacy of intranasal esketamine compared with intranasal placebo in reducing severity of suicidality as measured by the clinical global impression of severity of suicidality revised version (CGI-SS-R) at 24 hours post first dose.

Other Secondary Objectives

The other secondary objectives are:

- To evaluate the efficacy of intranasal esketamine compared with intranasal placebo in remission of MDD (defined as MADRS total score ≤12) at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25).
- To evaluate the efficacy of intranasal esketamine compared with intranasal placebo in reducing symptoms of MDD as assessed by the MADRS total score at 4 hours post first dose on Day 1, and through the end of the double-blind treatment phase (Day 25).
- To assess the efficacy of intranasal esketamine compared with intranasal placebo in reducing severity of suicidality as measured by the CGI-SS-R at 4 hours post first dose on Day 1, and through the end of the double-blind treatment phase (Day 25).
- To assess the efficacy of intranasal esketamine compared with intranasal placebo in achieving resolution of suicidality as measured by the score of 0 (normal, not at all suicidal) or 1 (questionably suicidal) of the CGI-SS-R at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25).
- To assess the efficacy of intranasal esketamine compared with intranasal placebo in reducing imminent suicide risk as measured by the clinical global impression of imminent suicide risk (CGI-SR-I) at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25).
- To assess the impact of intranasal esketamine compared with intranasal placebo on the following patient-relevant concepts through the end of the double-blind treatment phase (Day 25)
  - Hopelessness as measured by Beck Hopelessness Scale (BHS)

  - Health related quality of life and health status, using the European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level (EQ-5D-5L)
  - Health related quality of life using the Quality of Life in Depression Scale (QLDS)
  - Treatment satisfaction using the Treatment Satisfaction Questionnaire for Medication (TSQM-9)
  - Patient-reported suicidality using the Suicidal Ideation and Behaviors Assessment Tool (SIBAT), including Module 5 My Risk, Question 3 (patient-reported frequency of suicidal thinking)
- To assess the safety and tolerability of intranasal esketamine during the double-blind treatment phase and the follow-up phase, with special attention given to the following assessments:
  - Potential effects on suicidal ideation and behavior using the SIBAT
  - On dosing days:
    - Effect on heart rate, blood pressure, respiratory rate, and blood oxygen saturation
    - Effect on alertness and sedation using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale
    - Treatment-emergent dissociative symptoms using the Clinician Administered Dissociative States Scale (CADSS)
- To assess the pharmacokinetics of intranasal esketamine.

Exploratory Objectives

The exploratory objectives are:

- To evaluate the efficacy of intranasal esketamine compared with intranasal placebo in reducing symptoms of MDD as assessed by the MADRS total score and remission rate through the end of the follow-up phase (Day 90).
- To assess the efficacy of intranasal esketamine compared with intranasal placebo in reducing severity of suicidality as measured by the CGI-SS-R and resolution of suicidality through the end of the follow-up phase (Day 90).
- To assess the efficacy of intranasal esketamine compared with intranasal placebo in reducing imminent suicide risk as measured by the CGI-SR-I through the end of the follow-up phase (Day 90).
- To assess the impact of intranasal esketamine compared with intranasal placebo through the end of the follow-up phase (Day 90) on the following patient-relevant concepts:
  - Hopelessness (BHS)
  - Health related quality of life and health status (EQ-5D-5L)
  - Health related quality of life (QLDS)
  - Subject treatment satisfaction (TSQM-9)

- To assess the effect of intranasal esketamine compared with intranasal placebo on the SIBAT Module 3 My Current Thinking through the double-blind treatment (Day 25) and follow-up (Day 90) phases.
- To assess medical resource utilization as measured by the Healthcare Resource Use Questionnaire (HRUQ) of intranasal esketamine compared with intranasal placebo through the end of the follow-up phase (Day 90), including 30-day and 60-day readmission, and emergency room visits related to MDD and suicidality.
- To evaluate whether pretreatment concentrations or post-treatment change in MDD-related biomarkers (eg, hypothalamic-pituitary-adrenal [HPA] axis function, immune system activation, growth factors, metabolic markers) correlate with clinical response or non-response as measured by the MADRS, following intranasal administration of esketamine.

1.2. Trial Design

This is a randomized, double-blind, placebo-controlled, multicenter study. A target of 224 male and female subjects, 18 to 64 years of age, with MDD presenting to an emergency room (ER) or other permitted setting and assessed to be at imminent risk for suicide will be enrolled in this study.

The study will consist of a screening evaluation performed within 48 hours prior to the Day 1 intranasal dose (if possible, screening should occur within 24 hours prior to the Day 1 intranasal dose), immediately followed by a 25-day double-blind treatment phase (Day 1 to 25), and a 65-day follow-up phase (Day 26 to Day 90). The total study duration for each subject will be approximately 13 weeks.

On Day 1 of the double-blind treatment phase, approximately 224 subjects will be randomized in a 1:1 ratio to 1 of 2 treatments: intranasal esketamine 84 mg (n = 112) or intranasal placebo (n = 112), administered two times per week for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25). Randomization will be stratified by study center and by the physician's assessment of the subject's need of standard of care antidepressant treatment (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy); the standard of care will be determined prior to randomization on Day 1.

The first dose of study medication will be administered in the ER or other permitted setting, including the inpatient psychiatric unit. All subjects will be treated in the context of comprehensive standard clinical care, including hospitalization and the initiation or optimization of antidepressant treatment, which will be determined by the treating physician(s). The standard of care antidepressant treatment will be initiated or optimized for all subjects on Day 1.

After the first dose (ie, starting with the Day 4 dose or later), a one-time dose reduction to intranasal esketamine 56 mg or intranasal placebo is allowed if a subject is unable to tolerate the intranasal esketamine 84 mg or placebo dose assigned at randomization. No further dose adjustment is allowed during the double-blind treatment phase.

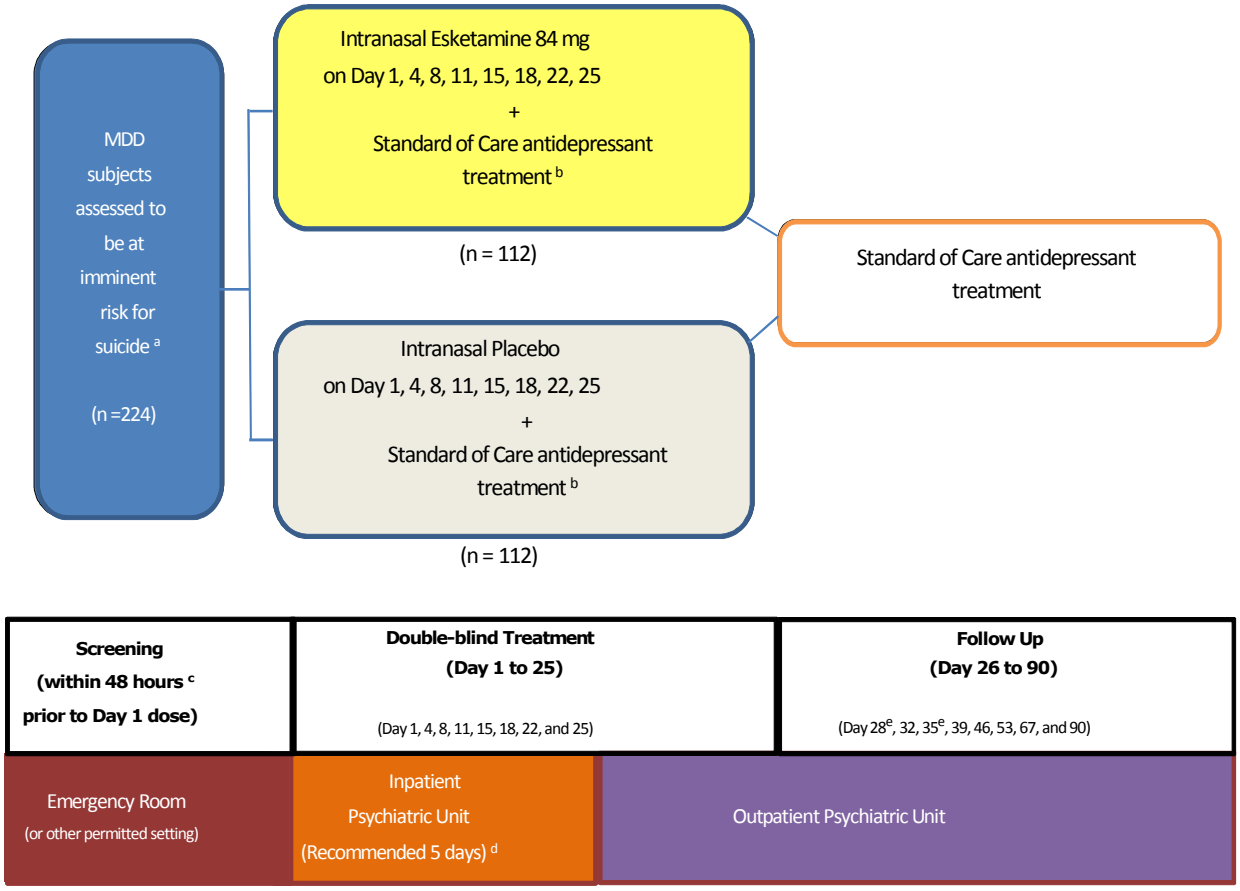
Dose titration/adjustments of newly initiated or optimized standard of care antidepressant treatment should occur during the first 2 weeks of double-blind treatment (ie, by Day 15), with

doses remaining stable thereafter through the end of the double-blind phase (Day 25). During the follow-up phase, the antidepressant treatment will be managed based on clinician's judgment.

Subjects will remain in the inpatient psychiatry unit for a recommended duration of 5 days, with shorter or longer hospitalizations permitted if clinically warranted per local standard of care. Discharge before 5 days must be discussed and approved by the sponsor's medical monitor. Following discharge from the inpatient psychiatric unit, subsequent visits for the double-blind treatment phase will be conducted twice-weekly at an outpatient psychiatric facility through Day 25. During the follow-up phase, subjects will be monitored twice weekly for the first two weeks (Days 28, 32, 35, and 39) after study drug treatment. Subjects will then be followed up weekly for the next two weeks (Days 46 and 53) and every two weeks for the rest of the follow-up period (Days 67 and 90).

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



[a] Randomization will be stratified by study center and by the physician's assessment of the subject's need of standard of care antidepressant treatment (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy); the standard of care will be determined prior to randomization on Day 1.
[b] Standard of care antidepressant treatment will be initiated or optimized on Day 1.
[c] If possible, screening should be performed within 24 hours prior the Day 1 intranasal dose.
[d] Discharge before 5 days must be discussed and approved by the sponsor's medical monitor.
[e] Remote contact

1.3. Statistical Hypotheses for Trial Objectives

The primary hypothesis is that, in addition to comprehensive standard of care, intranasal esketamine 84 mg is superior to intranasal placebo in rapidly reducing the symptoms of MDD, including suicidal ideation, as assessed by the change from baseline in the MADRS total score at 24 hours post first dose in subjects who are assessed to be at imminent risk for suicide.

1.4. Sample Size Justification

The maximum sample size for this study was calculated assuming an effect size of 0.45 for the MADRS total score at 24 hours post first dose (Day 2), a two-sided significance level of 0.050, and a drop-out rate at 24 hours of 5%. Approximately 112 subjects will need to be randomized to each treatment group to achieve 90% power. The effect size used in this calculation was based on results of the ESKETINSUI2001 study where the effect size for the change from baseline to Day 2 was 0.65 (mean difference between treatment groups of -7.2 and a pooled SD of 11.02) for MADRS total score. Given that the ESKETINSUI2001 study was a Phase 2 study carried out in only one country, the maximum sample size for this Phase 3 study was determined using a smaller effect size of 0.45 to allow for greater variability that can be expected for a study conducted globally.

1.5. Randomization and Blinding

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by study center and by the physician's assessment of the subject's need of standard of care antidepressant treatment (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy); the standard of care will be determined prior to randomization on Day 1. This stratification is aimed at balancing treatment groups within the standard of care antidepressant treatment to be initiated or optimized on Day 1, as antidepressant monotherapy and antidepressant plus augmentation therapy may be differentially effective. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kits for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the treatment assignment (eg, study drug plasma concentrations, treatment allocation) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding. To minimize the risk of unblinding the treatment assignment during the study, different raters will perform efficacy and safety assessments. Clinicians who perform MADRS and SIBAT will be different than those who evaluate vital signs, MOAA/S, CADSS, and adverse events. Raters for the MADRS and SIBAT assessment will not be allowed to access or to review subject safety records; therefore, they will not provide clinical care for subjects. Clinical care of subjects will be performed by clinicians at the study site who are not MADRS and CGI-SS-R/SIBAT raters. Adherence to this procedure will be monitored and enforced during the study.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed.

To maintain the blinding of intranasal study medication, the esketamine and placebo intranasal devices will be indistinguishable.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Pooling Algorithm for Analysis Centers

Pooling may be conducted only for randomized subjects only if a sufficient number of subjects are not randomized to a site. If necessary, within each region (North America, Europe, Asia, Other) small study centers with fewer than 4 randomized subjects will be combined for the purpose of analysis. These small centers will be ordered according to the total number of subjects and then sequentially using the center number. The pooling will be carried out sequentially beginning with the smallest center. The size of any pooled analysis center should be as large as possible and not be larger than the size of the largest center in the region. If the number of small centers is large, and one pooled analysis center cannot include all small centers, then the second (or more) pooled analysis center(s) will be formed after the first one is filled with as many small centers as possible. Pooled sites as described are called analysis centers and will be used in the analyses as center effect.

2.2. Analysis Phases

There are 2 analysis phases defined in this study: Double-blind and Follow-up (post treatment). Each analysis phase has its own analysis reference start date.

2.2.1. Analysis Phase Start and End Dates

Double-Blind Phase

The DB start date is the date of the first dose of double-blind medication. The DB end date is the maximum of the date of the last visit (excluding remote contact visit) in the double-blind phase and the date of early treatment termination. For randomized subjects who did not receive any medication in the double-blind phase, both the DB start date and end date are missing.

Follow-up Phase

Start and end dates for the F/U phase are only defined for subjects who completed the DB phase and continued into the F/U phase (including a visit in the F/U phase or an adverse event in the F/U phase). The analysis reference start date of the follow-up analysis phase is the day after the reference end date for the double-blind analysis phase. The analysis reference end date is the date of the last visit (excluding remote contact visit) in the follow-up phase for subjects who discontinued in F/U phase but had remote contact on Day 90. Otherwise, it is the maximum of the last follow-up visit date and the end of trial date.

2.2.2. Study Reference Start and End Dates

The overall reference start date for the study is defined as the date of the first dose of DB medication (the date is missing for screened subjects who did not receive a dose of DB medication). The overall reference end date for the study is the end of trial date including the last follow-up visit.

2.2.3. Study Day and Relative Day

Study day is calculated relative to the overall reference start date for the study. Relative day is calculated relative to the analysis reference start date of the analysis phase in which the data are captured.

Study day for an event on or after the start of the study is calculated as:

Event date-study start date+1.

Study day for an event prior to the start of the study is calculated as:

Event date-study start date

Relative day for an event on or after a reference start date is calculated as:

Event date - reference start date + 1.

Relative day for an event prior to a reference start date is calculated as:

Event date - reference start date.

2.3. Baseline and End Point

The double-blind baseline value will be the last observation before receiving the first dose of the study drug in the double-blind phase.

The double-blind end point value will be the final post baseline value assessed during the double-blind phase.

2.4. Visit Windows

As subjects do not always adhere to the protocol visit schedule (including permitted visit windows), the following rules are applied to assign actual visits to protocol visits. Listed below are the visit windows for analysis and the target days for each visit. The reference day is Study Day 1 (which is the first day that any study drug was taken in the double-blind phase).

If a subject has 2 or more scheduled or unscheduled visits in one visit window, the visit closest to the target day will be used as the protocol visit for that visit window. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

All assignments will be made in chronological order. Once a visit is assigned to a visit window, it will no longer be used for a later time point except for the end point. Listed below are the visit windows and the target days (if applicable) for each visit defined in the protocol for all phases (Table 1).

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval (Day)	Target Time Point (Relative Day)
MADRS	DB	1	Baseline (DB)	≤1; pre-dose	1
		1	Day 1 (DB): 4H	1	1
		2	Day 2 (DB)	2	2
		4	Day 4 (DB)	3 - 6	4
		8	Day 8 (DB)	7 - 9	8
		11	Day 11 (DB)	10 - 12	11
		15	Day 15 (DB)	13 - 16	15
		18	Day 18 (DB)	17 - 19	18
		22	Day 22 (DB)	20 - 23	22
		25	Day 25 (DB): Predose	24 - end of DB	25
		25	Day 25 (DB): 4H	24 - end of DB	25
		DB final visit	End Point (DB)	Day 1 (DB): 4H - end of DB	
		Day 25 RC[a]	Day 25 (RC)	use Day 25 RC visit	25
	F/U	28	Day 28 (F/U)	Day 1 (F/U) - 4	3
		32	Day 32 (F/U)	5 - 10	7
		39	Day 39 (F/U)	11 - 17	14
		46	Day 46 (F/U)	18 - 24	21
		53	Day 53 (F/U)	25 - 34	28
		67	Day 67 (F/U)	35 - 53	42
		90	Day 90 (F/U)	54 - end of F/U	65
		F/U final visit	End Point (F/U)	Day 1 (F/U) - end of F/U	
		Day 90 RC[a]	Day 90 (RC)	use Day 90 RC visit	65
SIBAT Module 1	DB	1	Baseline (DB)	≤1; pre-dose	1
SIBAT (Modules 3, 5, 6 and 7)	DB	1	Baseline (DB)	≤1; pre-dose	1
		1	Day 1 (DB): 4H	1	1
		2	Day 2 (DB)	2	2
		4	Day 4 (DB)	3 - 6	4
		8	Day 8 (DB)	7 - 9	8
		11	Day 11 (DB)	10 - 12	11
		15	Day 15 (DB)	13 - 16	15
		18	Day 18 (DB)	17 - 19	18
		22	Day 22 (DB)	20 - 23	22
		25	Day 25 (DB)	24 - end of DB	25
		DB final visit	End Point (DB)	Day 1 (DB): 4H - end of DB	
	F/U	32	Day 32 (F/U)	Day 1 (F/U) - 10	7
		39	Day 39 (F/U)	11 - 17	14
		46	Day 46 (F/U)	18 - 24	21
		53	Day 53 (F/U)	25 - 34	28
		67	Day 67 (F/U)	35 - 53	42
		90	Day 90 (F/U)	54 - end of F/U	65
		F/U final visit	End Point (F/U)	Day 1 (F/U) - end of F/U	
SIBAT Module 4	DB	8	Day 8 (DB)	1 - 9	8
		11	Day 11 (DB)	10 - 12	11
		15	Day 15 (DB)	13 - 16	15
		18	Day 18 (DB)	17 - 19	18
		22	Day 22 (DB)	20 - 23	22
		25	Day 25 (DB)	24 - end of DB	25
		DB final visit	End Point (DB)	Day 8 (DB) - end of DB	
	F/U	32	Day 32 (F/U)	Day 1 (F/U) - 10	7
		39	Day 39 (F/U)	11 - 17	14
		46	Day 46 (F/U)	18 - 24	21
		53	Day 53 (F/U)	25 - 34	28
		67	Day 67 (F/U)	35 - 53	42
		90	Day 90 (F/U)	54 - end of F/U	65
		F/U final visit	End Point (F/U)	Day 1 (F/U) - end of F/U	
SIBAT (Module 8)	DB	1	Baseline (DB)	≤1; pre-dose	1

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval (Day)	Target Time Point (Relative Day)
		2	Day 2 (DB)	2	2
		8	Day 8 (DB)	3 - 10	8
		15	Day 15 (DB)	11 - 19	15
		25	Day 25 (DB)	20 - end of DB	25
		DB final visit	End Point (DB)	2 - end of DB	
	F/U	32	Day 32 (F/U)	Day 1 (F/U) - 13	7
		46	Day 46 (F/U)	14 - 29	21
		67	Day 67 (F/U)	30 - 53	42
		90	Day 90 (F/U)	54 - end of F/U	65
		F/U final visit	End Point (F/U)	Day 1 (F/U) - end of F/U	
SIBAT (Module 2)	DB	1	Baseline (DB)	≤1; pre-dose	1
		8	Day 8 (DB)	2 - 10	8
		15	Day 15 (DB)	11 - 19	15
		25	Day 25 (DB)	20 - end of DB	25
		DB final visit	End Point (DB)	2 - end of DB	
	F/U	90	Day 90 (F/U)	Day 1 (F/U) - end of F/U	65
BHS	DB	1	Baseline (DB)	≤1	1
		8	Day 8 (DB)	2 - 16	8
		25	Day 25 (DB)	17 - end of DB	25
		DB final visit	End Point (DB)	2 - end of DB	
	F/U	46	Day 46 (F/U)	Day 1 (F/U) - 42	21
		90	Day 90 (F/U)	43 - end of F/U	65
		F/U final visit	End Point (F/U)	Day 1 (F/U) - end of F/U	
QLDS/ EQ-5D-5L	DB	1	Baseline (DB)	1	1
		2	Day 2 (DB)	2	2
		11	Day 11 (DB)	3 - 17	11
		25	Day 25 (DB)	18 - end of DB	25
		DB final visit	End Point (DB)	2 - end of DB	
	F/U	46	Day 46 (F/U)	Day 1 (F/U) - 42	21
		90	Day 90 (F/U)	43 - end of F/U	65
		F/U final visit	End Point (F/U)	Day 1 (F/U) - end of F/U	
TSQM-9	DB	11	Day 11 (DB)	1 - 17	11
		25	Day 25 (DB)	18 - end of DB	25
		DB final visit	End Point (DB)	1 - end of DB	
	F/U	46	Day 46 (F/U)	Day 1 (F/U) - 42	21
		90	Day 90 (F/U)	43 - end of F/U	65
		F/U final visit	End Point (F/U)	Day 1 (F/U) - end of F/U	
Nasal examination	DB	Screening	Baseline (DB)	≤1	≤1
		25	Day 25 (DB)	2 - end of DB	25
		DB final visit	End Point (DB)	2 - end of DB	
Vital signs	DB	Screening	Screening	≤1; pre-dose	≤1
		1	Baseline (DB)	≤1; pre-dose	1
		1	Day 1 (DB): Predose Day 1 (DB): 40M Day 1 (DB): 1H Day 1 (DB): 1.5H	1	1
		4	Day 4 (DB): Predose Day 4 (DB): 40M Day 4 (DB): 1H Day 4 (DB): 1.5H	2 - 5	4
		8	Day 8 (DB): Predose Day 8 (DB): 40M Day 8 (DB): 1H Day 8 (DB): 1.5H	6 - 9	8
		11	Day 11 (DB): Predose Day 11 (DB): 40M	10 - 12	11

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval (Day)	Target Time Point (Relative Day)
			Day 11 (DB): 1H Day 11 (DB): 1.5H		
		15	Day 15 (DB): Predose Day 15 (DB): 40M Day 15 (DB): 1H Day 15 (DB): 1.5H	13 - 16	15
		18	Day 18 (DB): Predose Day 18 (DB): 40M Day 18 (DB): 1H Day 18 (DB): 1.5H	17 - 19	18
		22	Day 22 (DB): Predose Day 22 (DB): 40M Day 22 (DB): 1H Day 22 (DB): 1.5H	20 - 23	22
		25	Day 25 (DB): Predose Day 25 (DB): 40M Day 25 (DB): 1H Day 25 (DB): 1.5H	24 - end of DB	25
		DB final visit	End Point (DB)	Day 1 (DB): 40M - end of DB	
	F/U	90	Day 90 (F/U)	Day 1 (F/U) - end of F/U	65
ECG	DB	Screening	Baseline (DB)	≤1; pre-dose	≤1
		1	Day 1 (DB): 1H	1	1
		8	Day 8 (DB): 1H	2 - 16	8
		25	Day 25 (DB): 1H	17 - end of DB	25
		Maximum (DB)	Maximum (DB)	Day 1 (DB): 1H - end of DB	
		DB final visit	End Point (DB)	Day 1 (DB): 1H - end of DB	
Pulse oximetry[b] MOAA/S[c] (predose and every 15 minutes to 1.5H) CADSS (predose, 40M, 1.5H)	DB	1	Day 1	1	1
		4	Day 4	2 - 5	4
		8	Day 8	6 - 9	8
		11	Day 11	10 - 12	11
		15	Day 15	13 - 16	15
		18	Day 18	17 - 19	18
		22	Day 22	20 - 23	22
		25	Day 25	24 - end of DB	25
Body weight	DB	Screening	Baseline (DB)	≤1	≤1
		25	Day 25 (DB)	2 - end of DB	25
		DB final visit	End Point (DB)	2 - end of DB	
	F/U	90	Day 90 (F/U)	Day 1 (F/U) - end of F/U	65
Height	DB	Screening	Baseline (DB)	≤1	≤1
Hematology, Chemistry, Urinalysis	DB	Screening	Baseline (DB)	≤1	≤1
		25	Day 25 (DB)	2 - end of DB	25
		DB final visit	End Point (DB)	2 - end of DB	

[a] Subjects who discontinue with reasons other than withdrawal of consent, lost to follow up, or death will be contacted remotely at 3 days after the last dose of intranasal study medication (if the date of the Early Termination visit is less than 3 days after the last dose of intranasal study medication) and on Day 25 for MADRS assessment. Day 25 remote contact (RC) will only be used as part of sensitivity analysis for MADRS total score at Day 25

[b] If oxygen saturation levels are <93% at any time during the 1.5 hour postdose interval, pulse oximetry will be recorded every 5 minutes until levels return to ≥93% or until the subject is referred for appropriate medical care, if clinically indicated.

[c] If the MOAA/S score is ≤3 at any time during the 1.5 hour postdose interval, the MOAA/S will be performed every 5 minutes until a score of 4 is reached (at which point a frequency of every 15 minutes can be resumed until t=+1.5 hours post dose).

2.5. Analysis Sets

Subjects will be classified into the following analysis sets: all randomized, full, safety and follow-up.

For each analysis set described below subjects who received an incorrect treatment will be analyzed under the planned treatment.

2.5.1. All Randomized Analysis Set

This analysis set will include all subjects who were randomized (i.e., subjects who reported a randomization date, or were assigned a randomization number) regardless of whether treatment was received. This analysis set will be used for summarizing the overall study completion/withdrawal information.

2.5.2. Full Efficacy Analysis Set

The efficacy analyses of data in the double-blind phase will be based on the full efficacy analysis set. The full efficacy analysis set is defined as all randomized subjects who received at least 1 dose of double-blind study medication and have both a baseline and a post-baseline evaluation for the MADRS total score or CGI-SS-R.

2.5.3. Safety Analysis Set

Safety analyses for the double-blind phase will be performed on the Safety analysis set. It will include all randomized subjects who received at least 1 dose of study drug in the double-blind phase.

Screen failures and randomized subjects who received no double-blind study medication will be excluded from the safety analysis set.

2.5.4. Follow-up Analysis Set

The Follow-up analysis set is defined as all subjects who entered the follow-up phase or had provided adverse event data after the double-blind phase. This analysis set will be used for both efficacy and safety analyses.

2.6. Definition of Subgroups

Analyses will be provided for the primary endpoint, change from baseline in MADRS total score, and the key secondary endpoint, change from baseline in CGI-SS-R using the following subgroups.

- Sex
- Race (White, Black, Asian, Other)
- Age Group (18-34 years, 35-54 years, 55-64 years)

- Region: North America (includes United States), Europe (includes Bulgaria, Estonia, Germany, Hungary, South Africa, Spain), and Asia (includes Malaysia, Republic of Korea and Taiwan)
- Country (Bulgaria, Estonia, Germany, Hungary, Malaysia, Republic of Korea, South Africa, Spain, Taiwan, United States)
- Baseline MADRS total score (≤/> median)
- Standard of care antidepressant treatment as randomized (antidepressant monotherapy, or antidepressant plus augmentation therapy)
- Baseline SIBAT: Prior Suicide Attempt (Yes, No) (Module 1: "I have made one or more attempts to end my life")
- Baseline Suicide attempt within the last month (Yes, No)

2.7. Incomplete/Missing Dates for Adverse Events

Treatment-emergent adverse events (TEAEs) for the double-blind phase are those events with an onset date/time on or after the start of double-blind study medication and occurred on or before the end of the double-blind phase. Adverse events (AEs) for the follow-up phase are those events with an onset date on or after the start of the follow-up phase and occurred on or before the end of the follow-up phase. A conservative approach will be used to handle the missing dates for AEs.

Onset Date

If the onset date of an adverse event is missing day only, it will be set to:

i) First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of DB start date

ii) The day of DB start date, if the month/year of the onset of AE is the same as month/year of the DB start date and month/year of the AE resolution date is different

iii) The day of DB start date or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the DB start date and month/year of the AE resolution date are the same.

If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:

i) January 1 of the year of onset, as long as this date is after the DB start date.

ii) DB start date, if this date is the same year that the AE occurred.

A completely missing onset date of an adverse event will be set to the DB start date.

Resolution Date

The missing day of resolution of an adverse event will be set to the last day of the month of resolution.

If the resolution date of an adverse event is missing both day and month, it will be set to the earlier of the date of withdrawal, study completion, or December 31 of the year.

A completely missing resolution date of an adverse event that is not recorded as ongoing will be set to the date of withdrawal or study completion.

2.8. Imputation Rules for Missing AE Time of Onset/Resolution

If the time of onset is missing, it will be imputed as follows:

i) 00:00 if the date of onset is after DB start date

ii) The time of intranasal medication start in the double-blind treatment phase, if the date is the same as DB start date.

If the time of resolution is missing, it will be set to 23:59.

If a missing time is associated with a partial or missing date, the date will be imputed first prior to imputing the time.

3. DATA MONITORING COMMITTEE REVIEW

3.1. Independent Data Monitoring Committee

An external Independent Data Monitoring Committee (IDMC) will be established and will provide recommendations about stopping or continuing the study based on safety. The IDMC will monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study. The committee will meet every 6 months to review safety data. After the reviews, the IDMC will make recommendations regarding the continuation of the study. The details of the safety analysis for the IDMC are provided in a separate IDMC SAP for Safety Monitoring. Roles and responsibilities for the IDMC are detailed a separate IDMC charter.

The IDMC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. The IDMC responsibilities, authorities, and procedures will be documented in its charter.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics (Table 2) and psychiatric history at baseline (Table 3) will be summarized by treatment group for the Safety and Full Efficacy analysis sets. Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation [SD],

median, minimum, and maximum). Categorical variables will be summarized using a frequency distribution with the number and percentage of subjects in each category.

Table 2: Demographic Variables and Baseline Characteristics

Continuous Variables:

- Age (years)
- Baseline weight (kg)
- Baseline height (cm)
- Baseline BMI (kg/m^2) calculated as Weight (kg)/[Height (m)]^2

Categorical Variables:

- Age (18-34 years, 35-54 years, 55-64 years)
- Sex (male, female)
- Race[a] (White, Black or African American, Asian, American Indian or Alaskan native, Native Hawaiian or other Pacific islander, other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Baseline BMI (underweight <18.5 kg/m^2, normal 18.5-<25 kg/m^2, overweight 25-<30 kg/m^2, obese ≥30 kg/m^2)
- Standard of Care Antidepressant Treatment as Randomized (monotherapy, augmentation)
- Standard of Care Antidepressant Treatment as Actually Received (monotherapy, augmentation, initial monotherapy followed by augmentation therapy)
- Country

[a] If multiple race categories are indicated, then Race is recorded as "Multiple".

Table 3: Psychiatric History at Baseline Variables

Continuous Variables:

- Baseline MADRS total score
- Baseline MADRS item 10 (suicide)
- Baseline BHS total score

Categorical Variables:

- Baseline CGI-SS-R
- Baseline CGI-SR-I
- Baseline MINI (B3 and B10 Current Status): think about suicide (Y/N), frequency (occasionally, often, very often) and intensity (mild, moderate, severe); Intend to act on thoughts of killing yourself (Y/N)
- Baseline SIBAT: Prior Suicide Attempt (Yes, No) (Module 1: "I have made one or more attempts to end my life")
- Baseline SIBAT: Patient Reported Global Assessment of Suicide Risk (Module 5, Question 3: "Which of the following ratings best describes your thinking about suicide right now")
- Baseline Suicide attempt within the last month (Y/N)

4.2. Disposition Information

The distribution of the number of subjects who are randomized, receive double-blind treatment, and complete the double-blind phase will be presented by treatment group. In addition, the distribution of treatment termination reasons will be presented. These summaries will be provided for the All Randomized and Safety analysis sets. A subject will be considered to have completed the double-blind phase if he or she has completed assessments through Day 25.

The distribution of the number of subjects who completed the study, including the follow-up phase, will be presented by treatment group. The reasons for discontinuation will be summarized.

4.3. Extent of Exposure

The total duration of the double-blind phase is defined as time between the first and the last day of study medication in the double-blind phase.

Descriptive statistics (N, mean, SD, median, and range) of total duration will be presented by treatment group for the Full and Safety analysis sets. A frequency distribution showing the number of days a subject was dosed during the double-blind phase will be provided. In addition, the number and percent of subjects who decreased their dose during the double-blind phase will be provided.

4.4. Protocol Deviations

Deviations that occurred during the study will be tabulated for the All Randomized analysis set by treatment group. Major deviations will be tabulated as they are grouped prior to unblinding in the following categories: Entered but did not satisfy criteria; Received a disallowed concomitant treatment; Received wrong treatment or incorrect dose; Developed withdrawal criteria but not withdrawn; Other. More categories may be included depending on the nature of the protocol deviation.

4.5. Prior and Concomitant Medications

The number and percent of subjects receiving prior antidepressant and antipsychotic medications will be summarized by treatment group for the Safety analysis set.

The number and percent of subjects who receive concomitant therapies will be summarized by treatment group using the generic term of the medication for the Safety analysis set and for the Follow-up analysis set. The use of benzodiazepines and lithium during the double-blind phase and the follow-up phase will be summarized separately. The standard of care antidepressant treatment during the double-blind phase and the follow-up phase will also be summarized.

5. EFFICACY

The efficacy variables for this study are listed in Table 4.

Table 4: Efficacy Variables

Efficacy Variable		Endpoint
MADRS	• Change in MADRS total score from Baseline to 24 hours post first dose	Primary
	• Remission of MDD (MADRS total score ≤12) at 4 hours and 24 hours post first dose, and through the end of the DB treatment phase (Day 25)	Secondary
	• Change in MADRS total score from Baseline to 4 hours post first dose and through the end of the DB treatment phase (Day 25)	Secondary
	• Change in MADRS total score from Baseline through the end of the follow-up phase (Day 90)	Exploratory
	• Remission of MDD (MADRS ≤12) through the end of the follow-up phase (Day 90)	Exploratory
	• Response rates (at least 50% improvement from baseline) at 4 hours and 24 hours post first dose, and through the end of the DB treatment (Day 25) and follow-up phases (Day 90)	Exploratory
	• Change in MADRS individual item from Baseline through the end of the DB treatment (Day 25) and follow-up phases (Day 90)	Exploratory
SIBAT – CGI-SS-R	• Change in CGI-SS-R from Baseline to 24 hours post first dose	Key Secondary
	• Change in CGI-SS-R from Baseline to 4 hours post first dose and through the end of the DB treatment phase (Day 25)	Secondary
	• Resolution of suicidality (CGI-SS-R score of 0 or 1) at 4 hours and 24 hours post first dose, and through the end of the DB treatment phase (Day 25)	Secondary
	• Change in CGI-SS-R from Baseline through the end of the follow-up phase (Day 90)	Exploratory
	• Resolution of suicidality (CGI-SS-R score of 0 or 1) through the end of the follow-up phase (Day 90)	Exploratory
SIBAT – CGI-SR-I	• Change in CGI-SR-I from Baseline to 4 hours and 24 hours post first dose, and through the end of the DB treatment phase (Day 25)	Secondary
	• Change in CGI-SR-I from Baseline through end of the follow-up phase (Day 90)	Exploratory
BHS	• Change in BHS total score from Baseline through the end of the DB treatment phase (Day 25)	Secondary
	• Change in BHS total score from Baseline through the end of the follow-up phase (Day 90)	Exploratory
EQ-5D-5L, EQ-VAS, and health status index	• Change in EQ-5D-5L dimension scores, the sum score, EQ-VAS and health status index from Baseline through the end of the DB treatment phase (Day 25)	Secondary
	• Change in EQ-5D-5L dimension scores, the sum score, EQ-VAS, health status index from Baseline through the end of the follow-up phase (Day 90)	Exploratory
QLDS	• Change in QLDS from Baseline through the end of the DB treatment phase (Day 25)	Secondary
	• Change in QLDS from Baseline through the end of the follow-up phase (Day 90)	Exploratory

Table 4: Efficacy Variables

Efficacy Variable		Endpoint
TSQM-9	• TSQM-9 score of effectiveness, convenience and global satisfaction domains through the end of the DB treatment phase (Day 25)	Secondary
	• TSQM-9 score through the end of the follow-up phase (Day 90)	Exploratory
SIBAT – Module 3 (My Current Thinking)	• Change in SIBAT– Module 3 (My Current Thinking) from Baseline through the end of the DB treatment (Day 25) and follow-up (Day 90) phases	Exploratory
SIBAT – Module 5 (My Risk) Question 3	• Change in SIBAT – Module 5 (My Risk) Question 3 from Baseline through the end of the DB treatment phase (Day 25)	Secondary
SIBAT – Module 7 (Global Clinical Impression) FoST	• Change in SIBAT – Module 7 (Global Clinical Impression) FoST from Baseline through the end of the DB treatment phase (Day 25)	Secondary
	• Change in SIBAT – Module 7 (Global Clinical Impression) FoST from Baseline through the end of the follow-up (Day 90) phase	Exploratory
SIBAT – CGI-SR-LT	• Change in CGI-SR-LT from Baseline through the end of the DB treatment (Day 25) and follow-up (Day 90) phases	Exploratory
SIBAT – Module 8 (Clinical Judgment of Optimal Suicide Management)	• Change in SIBAT – Module 8 (Clinical Judgment of Optimal Suicide Management) from Baseline through the end of the DB treatment (Day 25) and follow-up (Day 90) phases	Exploratory
SIBAT - Module 2 (My Risk/Protective Factors)	• Change in SIBAT - Module 2 (My Risk/Protective Factors) from Baseline through the end of the DB treatment phase (Day 25)	Exploratory

5.1. Analysis Specifications

5.1.1. Level of Significance

Statistical analysis tests will be conducted at a two-sided 0.050 level of significance unless specified otherwise.

The multiplicity, with regard to testing multiple endpoints (the primary and the key secondary), will be controlled by a fixed sequence testing procedure, ie, the key secondary hypothesis will be tested only after the null hypothesis for the primary endpoint is rejected.

Two-sided p-values will only be presented for the primary and key secondary endpoint (provided primary endpoint is significant). Point estimates of the treatment differences and 95% CIs will be presented for all other endpoints.

5.1.2. Data Handling Rules

For endpoints using analysis of covariance (ANCOVA), the last observation carried forward (LOCF) method will be applied to the MADRS, CGI-SS-R, CGI-SR-I, BHS, and QLDS score for the double-blind and follow-up phases. If a subject does not enter the follow-up phase, double-blind observations will not be carried forward into the follow-up phase.

The last post baseline observation during the double-blind phase will be carried forward as the "End Point" for the double-blind phase. The last post baseline observation in the follow-up phase will be carried forward as the "End Point" for the follow-up phase. Besides the observed cases and the end point assessment, the LOCF values will be created for intermediate post-baseline time points as well. These imputed time points will be labeled 'DAY X (DB) LOCF' or 'Day X (F/U) LOCF'.

5.1.3. Imputation Methods for Missing Items

Imputation of missing individual item scores will apply to MADRS and is described in Section 5.2.1. For all other scales where multiple items are summed to create a total, if any item of the scale is missing on one visit, the total score for that scale at that visit will be left blank.

5.1.4. Change from Baseline

For all efficacy variables, changes from baseline will be determined over time for both the double-blind and the follow-up phases, using double-blind baseline.

5.2. Primary Efficacy Endpoint

5.2.1. Definition

The primary efficacy endpoint is the change in MADRS total score from Baseline (Day 1, predose) to 24 hours post first dose in the double-blind phase. The baseline assessment and assessments during the follow-up phase use a 7 day recall period, the Day 1 and Day 25 4-hours post dose assessment uses a 4 hour recall period, the Day 2 24-hour post dose assessment uses a 24 hour recall period, and the other assessments in the double-blind phase use a since last assessment recall period. The MADRS consists of 10 items that cover all of the core depressive symptoms (apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, and suicidal thoughts). For the MADRS performed at 4-hours post dose on Day 1 and 25, the MADRS scores for the sleep item recorded predose on the same day will be carried forward. Each item is scored from 0 (item is not present or is normal) to 6 (severe or continuous presence of the symptom). A total score (0 to 60) is calculated by adding the scores of all 10 items. For each item as well as the total score, a higher score represents a more severe condition. If 2 or more items are missing, no imputation will be performed and the total score will be left missing. Otherwise, the total score will be calculated as the sum of the items present multiplied by the ratio of the maximum possible number of items (i.e., 10) to the number of items present.

5.2.2. Primary Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 4 components:

Population: subjects with MDD who are at imminent risk of suicide, as defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population;

Variable: change from baseline to 24 hours post first dose (Day 2) in MADRS total score (see Section 5.2.1);

Intervention Effect: the effect of the initially randomized treatment that would have been observed had all subjects remained on their treatment until Day 2 of the double-blind phase;

Summary Measure: the difference in variable least square means.

The primary analysis will be based on the full efficacy analysis set and the MADRS total scores collected at Day 2.

5.2.3. Analysis Methods

The primary efficacy endpoint, change from Baseline (Day 1, predose) to 24 hours post first dose (Day 2) in MADRS total score, will be analyzed using an analysis of covariance (ANCOVA) model, with factors for treatment (placebo or esketamine 84 mg), analysis center, standard of care antidepressant treatment as randomized (antidepressant monotherapy or antidepressant plus augmentation therapy), and baseline MADRS total score as a continuous covariate. Since subjects are hospitalized at the time of the primary endpoint, it is anticipated that missing data will be infrequent. However, if a subject has a MADRS total score at a time earlier than 24 hours post first dose but does not have the 24 hour value, the earlier value will be used for the primary efficacy analysis (ie, LOCF). The treatment effects will be estimated using least square means. A point estimate and 95% confidence interval for the treatment difference, along with the associated p-value will be provided. In addition, descriptive statistics (N, mean, SD, median, minimum and maximum) of the primary efficacy variable will be provided by analysis center. The cumulative distribution function for any percent improvement from baseline to 24 hours in MADRS total score will be graphically presented.

Descriptive statistics (N, mean, SD, median, minimum and maximum) for the MADRS total score and the change from baseline will be provided for both the observed case and LOCF data during the double-blind and follow-up phases. The ANCOVA model, as described above, will also be used to analyze all other post baseline time points for both observed case and LOCF data. Point estimates and 95% confidence intervals for the treatment differences will be provided. An additional analysis at Day 25 including remote contact data for subjects who discontinue during the double-blind phase using this ANCOVA model will be performed.

Both observed case data and LOCF means (±standard error [SE]), mean changes (±SE) from baseline, and least square mean changes (±SE) from baseline will be presented graphically for the double-blind and follow-up phases.

Model Assumptions

The normality and equal variance assumptions underlying the primary ANCOVA model will be assessed graphically for the MADRS total score at 24 hours post first dose. Residuals from the primary model will be plotted against the predicted values and a QQ plot of the residuals versus the expected quantiles of the standard normal distribution will be presented. If either the equal variance or the normality assumption appears to be grossly violated, other methods including an

ANCOVA on ranks model or an appropriate transformation of the primary endpoint might be considered.

MMRM

To assess the sensitivity of the results of the ANCOVA analysis at End Point (DB) and End Point (F/U), a mixed-effects model using repeated measures (MMRM) based on observed case data will be performed comparing treatments for the change from Baseline (Day 1, predose) to each assessment in the double-blind and follow-up phases, including Day 25 (DB) and Day 90 (F/U), in MADRS total score. The model will include baseline MADRS total score as a continuous covariate, and day, treatment, analysis center, standard of care antidepressant treatment as randomized (antidepressant monotherapy or antidepressant plus augmentation therapy), and day-by-treatment interaction as fixed effects, and a random subject effect. The within-subject variance between visits will be estimated via an unstructured variance-covariance matrix. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) with separate subject random effect. Comparison of esketamine versus placebo will be performed using the appropriate contrast. Point estimates and 95% confidence intervals for the treatment differences will be provided for each timepoint.

Sensitivity Analysis for Missing Data

If the overall missingness of the primary endpoint at 24 hours is above 5%, then additional sensitivity analyses that rely on Missing Not at Random assumptions will be performed to assess the robustness of the primary analysis and MMRM results. These analyses include a jump to reference multiple imputation as well as a delta adjustment multiple imputation analysis (including the establishment of the tipping point), which assumes a worsening of the MADRS scores after treatment discontinuation.

Subgroup Analyses

Forest plots will be provided displaying analysis results for each subgroup listed in Section 2.6. The point estimate of the treatment difference and its 95% confidence interval for each subgroup will be based on an ANCOVA analysis for the primary endpoint using the appropriate contrast. The model will include factors for treatment, analysis center, standard of care antidepressant treatment as randomized (antidepressant monotherapy or antidepressant plus augmentation therapy), subgroup and treatment-by-subgroup, and baseline MADRS total score as a covariate. The terms in the models will be adjusted for the subgroup of baseline MADRS total score (≤/> median). Baseline MADRS total score (as a continuous covariate) will not be included in the model when the dichotomized baseline MADRS total score is included in the model.

Individual Item Analyses

At each time point during the double-blind and follow-up phases, a frequency distribution of the MADRS individual item scores will be provided. Descriptive statistics (N, median, minimum and maximum) for these scores and the changes from baseline will be provided. The treatment

difference will be estimated for each item using the Hodges-Lehmann estimate, which is the median of all possible paired differences for the change from baseline for individual item. Hodges-Lehmann estimates and the corresponding 95% CI for the treatment differences will be provided for each timepoint.

5.3. Key Secondary Endpoint

5.3.1. Definition

One module of the SIBAT includes the Clinical Global Impression – Severity of Suicidality – Revised (CGI-SS-R). The key secondary endpoint is the change in CGI-SS-R from Baseline (Day 1, predose) to 24 hours post first dose in the double-blind phase. The CGI-SS-R summarizes the clinician's overall impression of severity of suicidality. The CGI-SS-R rating will be based on the totality of information available to the clinician, including information from the SIBAT. This rating operates like numerous other CGI-severity scales that have been used in other psychiatric studies. These instruments have shown clinical validity and sensitivity to change. The CGI-SS-R rating is scored on a 7-point scale from 0 (normal, not at all suicidal) to 6 (among the most extremely suicidal patients).

5.3.2. Analysis Methods

The analysis of the key secondary efficacy endpoint, change from baseline for CGI-SS-R at 24 hours post first dose (Day 2), will be performed for LOCF data using an ANCOVA model on the ranks of change with factors for treatment, analysis center, standard of care antidepressant treatment as randomized (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy) and baseline CGI-SS-R (unranked) as a covariate. The associated p-value will be provided. The treatment difference will be estimated using the Hodges-Lehmann estimate, which is the median of all possible paired differences for the change from baseline for CGI-SS-R at 24 hours. The Hodges-Lehmann estimate and the corresponding 95% CI for the treatment difference will be provided. The treatment difference will also be estimated using least square means based on an ANCOVA model on the actual change with factors for treatment, analysis center, standard of care antidepressant treatment as randomized (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy) and baseline CGI-SS-R (unranked) as a covariate. A point estimate and 95% confidence interval for the treatment difference will be provided. The cumulative distribution function for any improvement and percent improvement from baseline to 24 hours in CGI-SS-R will be graphically presented.

The multiplicity, with regard to testing multiple endpoints (the primary and the key secondary), will be controlled by a fixed sequence testing procedure, ie, the key secondary hypothesis will be tested only after the null hypothesis for the primary endpoint is rejected.

At each time point during the double-blind and follow-up phases, a frequency distribution of the CGI-SS-R score and changes from baseline will be provided for both the observed case and LOCF data. In addition, descriptive statistics (N, median, minimum, and maximum) for these scores and the changes from baseline will be provided for both the observed case and LOCF data. Hodges-Lehmann estimates and the corresponding 95% CI for the treatment differences will be provided for each timepoint. ANCOVA model on the change from baseline for both

LOCF and observed case data will be performed for each time point as an additional exploratory analysis.

Both observed case data and LOCF frequency distributions will be presented graphically using stacked bar charts for baseline, 4 hours post first dose, 24 hours post first dose, and Day 25.

Item Response Modeling

Item response modeling will be used to estimate treatment difference using an odds ratio [redacted] See Attachment 5. The analysis of CGI-SS-R will be performed based on the change from baseline for CGI-SS-R at 4 hours and 24 hours post first dose.

[redacted]

This [redacted] model, [redacted] will be estimated jointly by Bayesian modelling with Gibbs sampling method[8] to take into account the uncertainty of estimation in each separate model[9]. Non-informative priors are used for parameters. R (version 3.3) will be used for this analysis with JAGS (version 4.2) via R-package R2jags. The posterior median estimate and 95% credible interval of the odds ratio will be reported.

Subgroup Analyses

Forest plots will be provided displaying analysis results for each subgroup listed in Section 2.6. The median estimate of the treatment difference in terms of odds ratio and its 95% credible interval for each subgroup will be based on item response modelling for the key secondary endpoint using the appropriate contrast. The model will include factors for treatment, analysis center, standard of care antidepressant treatment as randomized (antidepressant monotherapy or antidepressant plus augmentation therapy), subgroup and treatment-by-subgroup, and baseline latent CGI-SS-R score as a covariate.

Mediation Analysis

Mediation analysis will be performed to examine the mediating role of depressive symptoms assessed by change from baseline in MADRS total score on change from baseline in CGI-SS-R provided that both endpoints demonstrate a statistically significant difference between esketamine and placebo. In the mediation analysis framework, natural direct effect can be conceived of as independent treatment effect on the outcome (i.e., change in CGI-SS-R) that is

above and beyond its effect on the mediator (i.e., change in MADRS total score); controlled direct effect can be conceived of as the independent treatment effect on the outcome controlling the mediator at a fixed level; and natural indirect effect can be conceived of as a treatment effect on the outcome that is mediated by its effect on the mediator.

Two analyses are suggested to assess the extent to which change in CGI-SS-R may be mediated by or independent of change in MADRS total score based on observed data for Day 2. The analyses will consider change in CGI-SS-R as an ordinal variable and change in MADRS total score as a continuous variable.

- Parametric Counterfactual Approach: this approach introduced by VanderWeele et.al[2] provides closed-form analytic expressions for controlled direct effect (CDE) on the odds ratio scale, for category j,

  $$CDE(m) = \frac{P(Y_{am} \leq j|c)}{P(Y_{am} > j|c)} \Big/ \frac{P(Y_{a^*m} \leq j|c)}{P(Y_{a^*m} > j|c)}$$

  where m is given level of mediator M, a and a^* are two levels of treatment group A, c is a set of covariates, Y_{am} is the outcome when $A = a$, $M = m$. The controlled direct effect can be expressed as the exponential of a linear combination of the coefficients based on a proportional odds model of the outcome.

  The analysis will be based on the proportional odds model of change in CGI-SS-R from baseline with factors for treatment, analysis center, standard of care antidepressant treatment as randomized (antidepressant monotherapy or antidepressant plus augmentation therapy), change from baseline in MADRS total score and baseline CGI-SS-R as a covariate. Estimate of the controlled direct effect will be obtained by plugging in the estimated coefficient values and the mean level of change in MADRS total score into the analytic expressions. Under the proportional odds model, the controlled direct effect will be constant across different levels of change in CGI-SS-R.

- Simulation-based Counterfactual Approach: this approach introduced by Imai et.al[3] obtains natural direct effect (NDE) and natural indirect effect (NIE) on the difference scales using numerical simulations, for category j,

  $$NDE = P\left(Y_{aM_{a*}} = j\middle|c\right) - P\left(Y_{a*M_{a*}} = j\middle|c\right)$$

  $$NIE = P\left(Y_{aM_{a}} = j\middle|c\right) - P\left(Y_{aM_{a*}} = j\middle|c\right)$$

  where $Y_{aM_{a*}}$ is the outcome when $A = a$ and M is set to M_{a*}, the level it would have been under treatment group $A = a^*$.

  The approach uses non-parametric bootstrapping to construct the point estimate for natural direct effect and natural indirect effect from the bootstrap sampling distribution. The p-value is based on a percentile bootstrap method. The original data will be stratified by analysis center, and for each analysis center a random sample equal in size to the original one will be

drawn. The abovementioned proportional odds model for change in CGI-SS-R and an ANCOVA model for change in MADRS total score will be used for each bootstrapped sample. The ANCOVA model will include factors for treatment, analysis center, standard of care antidepressant treatment as randomized (antidepressant monotherapy or antidepressant plus augmentation therapy), and baseline CGI-SS-R score (unranked) as a covariate.

Mediation analysis may also be performed to examine the mediating role of severity of suicidality assessed by change from baseline in CGI-SS-R on change from baseline in MADRS total score, provided both endpoints demonstrate a statistically significant difference between esketamine and placebo. The simulation-based counterfactual approach described above would be used to assess the extent to which change in MADRS total score may be mediated by or independent of change in CGI-SS-R based on observed data for Day 2.

5.4. Other Secondary and Exploratory Variables

5.4.1. Remission of MDD

5.4.1.1. Definition

A subject is defined to be in remission of MDD (yes=1 and no=0) at a given time point if the MADRS total score is ≤12. Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered to be in remission.

5.4.1.2. Analysis Methods

Frequency distributions of subjects meeting criteria for remission will be provided at each time point during the double-blind and follow-up phases. The estimates of the treatment difference in proportions and the 95% CIs will be reported at each time point.

5.4.2. Responder

5.4.2.1. Definition

The percentage change from baseline at Day X is calculated as 100*(MADRS total score at Day X – Baseline MADRS total score)/(Baseline MADRS total score). Negative percent changes in MADRS total score indicate improvement (e.g., percent change ≤-50% indicates improvement ≥50%).

A subject is defined a responder (yes=1 and no=0) at a given time point if the percent improvement in MADRS total score is ≥50%. Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered a responder.

5.4.2.2. Analysis Methods

Frequency distributions of subjects who achieve a response will be provided at each time point during the double-blind and follow-up phases. The estimates of the treatment difference in proportions and the 95% CIs will be reported at each time point.

5.4.3. Resolution of Suicidality

5.4.3.1. Definition

A subject is defined to have achieved resolution of suicidality (yes=1 and no=0) at a given time point if the CGI-SS-R score is 0 (normal, not at all suicidal) or 1 (questionably suicidal). Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered to have resolution of suicidality.

5.4.3.2. Analysis Methods

Frequency distributions of subjects meeting criteria for resolution of suicidality will be provided at each time point during the double-blind and follow-up phases. The estimates of the treatment differences in proportions and 95% CIs will be reported.

5.4.4. CGI-SR-I

5.4.4.1. Definition

One module of the SIBAT includes the Clinical Global Impression of Imminent Suicide Risk (CGI-SR-I). The CGI-SR-I is a scale summarizing the clinician's best assessment of the likelihood that the subject will attempt suicide in the next 7 days. The CGI-SR-I rating is scored on a 7-point scale from 0 (no imminent suicide risk) to 6 (extreme imminent suicide risk).

5.4.4.2. Analysis Methods

At each time point during the double-blind and follow-up phases, a frequency distribution of the CGI-SR-I score and change from baseline will be provided for both the observed case and LOCF data. In addition, descriptive statistics (N, median, minimum, and maximum) for these scores and the changes from baseline will be provided for both the observed case and LOCF data. Hodges-Lehmann estimates and the corresponding 95% CI for the treatment differences will be provided for each timepoint.

As described in Section 5.3.2 the posterior median estimate and 95% credible interval of odds ratio from item response modeling will be reported at 4 hours and 24 hours post first dose.

Both observed case data and LOCF frequency distributions will be presented graphically using stacked bar charts for baseline, 4 hours post first dose, 24 hours post first dose, and Day 25.

5.4.5. BHS

5.4.5.1. Definition

The BHS (Attachment 2) is a self-reported measure to assess one's level of negative expectations or pessimism regarding the future. It consists of 20 true-false items that examine the respondent's attitude over the past week by either endorsing a pessimistic statement or denying an optimistic statement; 9 are keyed false and 11 are keyed true. These items fall within 3 domains: (1) feelings about the future; (2) loss of motivation; and (3) future expectations. For every statement, each response is assigned a score of 0 or 1. The total BHS score is a sum of item

responses and can range from 0 to 20, with a higher score representing a higher level of hopelessness. Total scores that range from 0 to 3 are considered within the normal range, scores 4 to 8 identify mild hopelessness, scores 9 to 14 identify moderate hopelessness, and scores greater than 14 identify severe hopelessness.

The BHS will be administered using a recall period of the last 7 days.

5.4.5.2. Analysis Methods

Changes from baseline over time in BHS total score will be analyzed based on observed case data using MMRM as described in Section 5.2.3. In addition, the same ANCOVA model described in Section 5.2.3 will be performed for both observed case and LOCF data. The estimates of treatment differences based on the least square means and 95% CIs will be provided for each model.

Descriptive statistics (N, mean, SD, median, minimum and maximum) for the BHS total score and the change from baseline will be provided for both the observed case and LOCF data during the double-blind and follow-up phases.

Both observed case data and LOCF mean values and changes from baseline over time will be graphically presented for the double-blind and follow-up phases.

5.4.6. EuroQol Group; 5 Dimension; 5 Level (EQ-5D-5L)

5.4.6.1. Definition

The EQ-5D-5L (EuroQol Group - 5 Dimension - 5 Level) is a standardized 2-part instrument for use as a measure of health outcome, primarily designed for self-completion by respondents. It essentially consists of the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ-VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each of the 5 dimensions is divided into 5 levels of perceived problems (Level 1 indicating no problem, Level 2 indicating slight problems, Level 3 indicating moderate problems, Level 4 indicating severe problems, and Level 5 indicating extreme problems).

The subject selects an answer for each of the 5 dimensions considering the response that best matches his or her health “today.” The descriptive system can be represented as a health state. The EQ-VAS self-rating records the respondent’s own assessment of his or her overall health status at the time of completion, on a scale of 0 (the worst health you can imagine) to 100 (the best health you can imagine).

The time taken to complete the questionnaire varies with age, health status, and setting but is likely to be around 1 minute.

Individual scores from the 5 dimensions will be used to obtain a weighted health status index as shown below:

(i) Scores from each dimension will be combined to obtain a 5L profile score or health state: eg, a score of 1 for each dimension will give a 5L profile score of 11111. Dimension scores will be combined in the following order: Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression

(ii) The value set of the Health Status Index for various values of 5L profile scores is published for Canada in the following website: https://www.ncbi.nlm.nih.gov/pubmed/26492214

(iii) The Canadian value set will be used to get the HSI values for all the countries participating in the study

In addition, a sum score will be derived as follows: The scores of the five dimensions (values 1-5) will be added (sums between 5 and 25). From this score, subtract 5 (range 0-20) and multiply by 5 (range 0-100)

5.4.6.2. Analysis Methods

Descriptive statistics of actual values and changes from baseline by treatment group will be provided for the dimension scores, weighted EQ-5D health status index, the EQ-VAS, and the sum score at each time point for the double-blind and follow-up phases.

Individual dimension responses will be summarized at each visit using a frequency distribution by treatment group for the double-blind and follow-up phases. Graphical presentations will also be provided using bar charts for baseline, 24 hours post first dose, and Day 25.

5.4.7. QLDS

5.4.7.1. Definition

The QLDS is a disease specific patient-reported outcome designed to assess health related quality of life in patients with MDD, ie, it captures the impact of depression and its treatment from the patient's perspective. The instrument has a recall period of "at the moment", contains 34-items with "true"/"not true" response options and takes approximately 5-10 minutes to complete. The score range is from 0 (good quality of life) to 34 (very poor quality of life). It has been shown to have acceptable psychometric properties and sensitivity to change.

5.4.7.2. Analysis Methods

Changes from baseline over time in QLDS score will be analyzed based on observed case data using MMRM as described in Section 5.2.3. In addition, the same ANCOVA model described in Section 5.2.3 will be performed for both observed case and LOCF data. The estimates of treatment differences based on the least square means and 95% CIs will be provided for each model.

Descriptive statistics (N, mean, SD, median, minimum and maximum) for the QLDS score and the change from baseline will be provided for both the observed case and LOCF data during the double-blind and follow-up phases.

Both observed case data and LOCF mean values and change from baseline over time will be graphically presented for the double-blind and follow-up phases.

5.4.8. TSQM-9

5.4.8.1. Definition

The TSQM-9 is a 9-item generic patient reported outcome instrument to assess patients' satisfaction with medication. It is derived from the longer TSQM Version 1.4 and covers 3 domains of effectiveness, convenience and global satisfaction. The instrument is scored by domain with scores ranging from 0-100 where a lower score indicates lower satisfaction. The recall period is "the last 2-3 weeks".

5.4.8.2. Analysis Methods

Descriptive statistics (N, mean, SD, median, minimum and maximum) for the TSQM-9 domain scores will be provided during the double-blind and follow-up phases.

5.4.9. SIBAT – Module 2 (My Risk/Protective Factors), Module 3 (My Current Thinking), Module 5 (My Risk) Question 3, Module 7 (Global Clinical Impression) FoST, CGI-SR-LT, and Module 8 (Clinical Judgment of Optimal Suicide Management)

5.4.9.1. Definition

Module 2 (My Risk/Protective Factors), Module 3 (My Current Thinking), Question 3 (patient-reported frequency of suicidal thinking) in Module 5 (My Risk), Module 7 (Global Clinical Impression) Assessment of Frequency of Suicidal Thinking (FoST), and CGI-SR-LT from the SIBAT will be used to assess patient and clinician reported suicidality. Module 2 (My Risk/Protective Factors) asks patients to describe how they have acted or felt in the past 7 days. Each of the first 21 items has 6 response options ranging from "Never" to "All the time". A total score is calculated by adding the scores of the first 21 questions (Attachment 3). Module 3 consists of 48 patient-reported items about their current thinking and takes approximately 7 minutes to complete. Each item has 6 response options ranging from "Strongly disagree" to "Strongly agree". A total score is calculated by adding the scores of all 48 items with higher values indicating higher symptomatology (Attachment 3). Question 3 from Module 5 asks patients to describe their thinking about suicide right now. There are 5 response options ranging from "I have no suicidal thoughts" to "I have suicidal thoughts all of the time." Module 7 FoST is a clinician-reported global impression with response options of "Never", "Rarely", "Sometimes", "Often", "Most of the time", and "All of the time." The CGI-SR-LT is a scale summarizing the clinician's best assessment of subjects' long-term risk for suicide. The CGI-SR-LT rating is scored on a 7-point scale from 0 (no suicide risk in the long term) to 6 (extreme risk for suicide in the long term). Module 8 asks clinicians about their assessment of the best clinical management for the subject. The score range is from 1 (No special management needed) to 11 (Not ratable).

5.4.9.2. Analysis Methods

Frequency distributions for Question 3 from Module 5 (My Risk), Module 7 (Global Clinical Impression) FoST, CGI-SR-LT and Module 8 (Clinical Judgment of Optimal Suicide Management) will be provided during the double-blind and follow-up phases. In addition, descriptive statistics for these scores, Module 3 (My Current Thinking) total score and Module 2 (My Risk/Protective Factors) total score and the changes from baseline will be provided.

6. SAFETY

6.1. Adverse Events

Adverse events (AEs) are coded using the MedDRA dictionary (version 19.1 or above). Treatment-emergent adverse events (TEAEs) that occurred in the double-blind phase will be summarized by system organ class, preferred term, and treatment group. Adverse events that occurred in the follow-up phase will be summarized separately. In addition, separate summaries will be provided for AEs that occurred after DB phase for subjects who discontinued from DB phase and AEs that occurred after follow-up phase for subjects who discontinued from follow-up phase. Data listings will be provided for AEs with onset date after the end of trial date. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Adverse events occurring in different phases of the study are defined as below:

- Treatment-emergent adverse events during the double-blind phase are defined as AEs with an onset during the double-blind phase. In other words, treatment-emergent AE during the double-blind phase should satisfy the condition: Double-blind start date/time ≤ AE onset date/time ≤ double-blind end date. If onset time is missing and AE onset date is the same as the double-blind start date, the AE is defined to be treatment emergent in the double-blind phase.
- Adverse events during the follow-up phase are defined as AEs with an onset during the follow-up phase. AEs during the follow-up phase should satisfy the condition: follow-up phase start date ≤ AE onset date ≤ follow-up phase end date.

A TEAE is an event that is new in onset or increased in severity following treatment initiation. An event that starts prior to and ends after the initiation of study medication will be considered treatment-emergent only if the severity increases after the start of medication. Adverse events will not be considered treatment-emergent if they occur or increase in severity during the follow-up phase.

In addition, AEs will be summarized by severity and relationship to study drug using the preferred term. For the summaries of AEs by severity/relationship to study drug, the observation with the most severe occurrence/closest relationship to study drug will be chosen if there is more than one incident of an adverse event reported during the analysis phase by the subject. The proportion of TEAEs occurring on dosing days and the proportion of TEAEs that occur on dosing days with same day resolution will be summarized. Duration and resolution time of severe TEAEs will also be summarized.

Serious AEs (SAEs) and AEs that lead to study discontinuation will be summarized separately by treatment group, system organ class, and preferred term. TEAEs leading to dose reduction or interruption due to intranasal study medication will also be summarized. Data listings will also be generated for deaths, other SAEs, and discontinuations due to AEs.

The TEAEs potentially related to suicidality (preferred terms: Completed suicide, Depression suicidal, Intentional overdose, Intentional self-injury, Multiple drug overdose intentional, Poisoning deliberate, Self injurious behavior, Self-injurious behaviour, Self-injurious ideation, Suicidal behaviour, Suicidal behavior, Suicidal ideation, Suicide attempt) will be summarized.

Adverse Events of Special Interest

Clinically relevant TEAEs of special interest will be examined separately grouped in the following categories:

- Suggestive of abuse potential (Aggression, Confusional state, Decreased activity, Dependence, Disorientation, Dissociation, Dissociative disorder, Dizziness, Drug abuse, Drug abuser, Drug dependence, Drug use disorder, Drug detoxification, Drug diversion, Drug rehabilitation, Drug tolerance, Drug tolerance increased, Drug withdrawal convulsions, Drug withdrawal headache, Drug withdrawal syndrome, Euphoric mood, Feeling abnormal, Feeling drunk, Feeling of relaxation, Hallucination, Hallucination, auditory, Hallucination, gustatory, Hallucination, olfactory, Hallucination, synaesthetic, Hallucination, tactile, Hallucination, visual, Hallucinations, mixed, Inappropriate affect, Mental impairment, Product tampering, Psychomotor hyperactivity, Psychotic disorder, Rebound effect, Somatic hallucination, Somnolence, Substance abuser, Substance dependence, Substance use, Substance use disorder, Substance-induced mood disorder, Substance-induced psychotic disorder, Thinking abnormal, Withdrawal arrhythmia, Withdrawal syndrome);
- Increased blood pressure (Blood pressure increased, Blood pressure diastolic increased, Blood pressure systolic increased, Hypertensive crisis, Hypertensive emergency, Hypertension)
- Increased heart rate (Heart rate increased, Tachycardia)
- Transient dizziness/vertigo (Dizziness, Dizziness exertional, Dizziness postural, Dizziness procedural, Procedural dizziness, Vertigo, Vertigo labyrinthine, Vertigo positional, Vertigo CNS origin);
- Impaired cognition (Cognitive disorder);
- Cystitis (Allergic cystitis, Chemical cystitis, Cystitis, Cystitis erosive, Cystitis haemorrhagic, Cystitis interstitial, Cystitis noninfective, Cystitis ulcerative, Cystitis-like symptom);
- Anxiety (Anticipatory anxiety, Anxiety, Anxiety disorder);
- Anticipated Dosing-related AEs (Anxiety, Anticipatory anxiety, Dissociation, Dizziness, Dizziness postural, Feeling abnormal, Feeling drunk, Nausea, Somnolence, Vertigo, Vomiting).

The number and percentage of subjects taking concomitant medication for dissociation events (preferred term of Dissociation) at any time during the double-blind phase will be provided. In

addition, number of occurrences of TEAEs of suggestive of abuse potential will be summarized by intranasal dosing session.

In addition, a summary of treatment-emergent AEs of cardiac safety (preferred terms: cardiac flutter, electrocardiogram QT prolonged, palpitations, seizure, sudden cardiac death, sudden death, syncope, torsade de pointes, ventricular arrhythmia, ventricular fibrillation, ventricular flutter, ventricular tachycardia) will be provided.

6.2. Clinical Laboratory Tests

Descriptive statistics (N, mean, SD, median and range) for observed values and changes from baseline will be provided for clinical laboratory tests (hematology, chemistry and urinalysis) at each scheduled time point in the double-blind phase.

Clinical laboratory tests that meet the criteria for markedly abnormal will be listed by subject for the double-blind and follow-up phases. The incidence of treatment-emergent markedly abnormal laboratory values that occurred at any time during the double-blind phase will be presented. Clinical laboratory test values will be considered "treatment-emergent markedly abnormal" (TEMA) using the criteria defined by the Sponsor (Janssen Research & Development, LLC) listed in Attachment 1. The identification of TEMA laboratory values is based on the post-baseline value being out of range while the baseline value is either missing or within the range given in Attachment 1. If post-baseline laboratory results are above the upper limit and the baseline value is below the lower limit, then the post-baseline abnormality will also be considered TEMA. The same applies to the post-baseline value being below the lower limit with the baseline value being above the upper limit.

The incidence of subjects with ALT or AST values >3*upper limit of normal (ULN) will be presented. Additionally, incidence of hepatic toxicity (Hy's Law[4]) defined as ALT or AST values >3*ULN AND total bilirubin values >2*ULN will be presented. Similar to the markedly abnormal analysis, only subjects with baseline ALT or AST values ≤3*ULN (AND baseline total bilirubin values ≤2*ULN for hepatic toxicity) (or if baseline value is missing) will be eligible for these analyses.

6.3. Vital Signs, Weight, and BMI

Descriptive statistics for values and changes from baseline at each scheduled time-point during the double-blind and follow-up phases will be presented for blood pressure (systolic and diastolic), pulse (heart) rate, respiratory rate, oxygen saturation, weight, temperature, and BMI. In addition, descriptive statistics of pulse rate and blood pressure (systolic and diastolic) values, changes and percent changes from predose will be provided for each dosing day. Frequency distributions of maximum percent increase from predose and time of maximum percent increase will also be presented for blood pressure. Descriptive statistics of maximum increase and maximum percent increase from predose will be provided for blood pressure for each dosing day. Note that if the maximum value within a phase occurs at multiple time points, the earliest time point is selected.

The proportion of subjects who have a treatment-emergent abnormality, as defined in Table 5 below, will be presented for the double-blind phase. The double-blind baseline will be used to determine abnormal values. A listing of subjects meeting any of the criteria will also be provided for the double-blind phase.

Table 5: Treatment-Emergent Abnormality Categories for Vital Signs

	Post-baseline value outside of normal limit if:	
Vital Parameter	Abnormally low	Abnormally high
Pulse (bpm)	A decrease from baseline of ≥15 to a value ≤50	An increase from baseline of ≥15 to a value ≥100
Systolic BP (mmHg)	A decrease from baseline of ≥20 to a value ≤90	An increase from baseline of ≥20 to a value ≥180
Diastolic BP (mmHg)	A decrease from baseline of ≥15 to a value ≤50	An increase from baseline of ≥15 to a value ≥105

BP = blood pressure

The proportion of subjects who experienced treatment-emergent markedly elevated blood pressure (systolic BP≥180 or diastolic BP≥110) at any time during the double-blind phase will be summarized by treatment group and hypertension status.

Mean (+/-SE) values for systolic BP, diastolic BP and heart rate will be summarized and presented graphically over the double-blind phase by treatment group and hypertension status. In addition, for subjects with hypertension who receive antihypertensive medication, the same tables and graphs will be summarized by medication type (beta-blockers, multiple agents (beta blockers + others), all other agents and none).

A listing of subjects with oxygen saturation less than 93% will be provided.

6.4. Nasal Examination

Targeted nasal examinations (including the upper respiratory tract/throat) will be conducted by a qualified healthcare practitioner. The objective of the examination at Screening is to rule out any subjects with anatomical or medical conditions that may impede drug delivery or absorption.

Subsequent examination will consist of a visual inspection of the nostrils, nasal mucosa, and throat for nasal erythema, rhinorrhea, rhinitis, capillary/blood vessel disruption and epistaxis and graded as follows: absent, mild, moderate, or severe.

Abnormalities observed during the targeted nasal examinations at screening and post-baseline will be summarized and listed by treatment group.

6.5. Electrocardiogram

The ECG variables that will be analyzed include heart rate (HR), respiratory rate (RR), pulse rate (PR) interval, QRS interval, QT interval and corrected QT (QTc) intervals. The QTc intervals will include the QTcB (Bazett) and QTcF (Fridericia).

The maximum post-baseline value during the double-blind phase will be computed for each ECG parameter using data from both scheduled and unscheduled visits.

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. Summary tables for values and changes from baseline will be presented at each time point during the double-blind phase.

The frequency of treatment-emergent abnormalities will be tabulated and presented for the double-blind phase. The identification of treatment-emergent abnormal ECG values is based on the post-baseline value (a value occurring after the first study drug administration) being out of range while the baseline value is either missing or within the limits given in Table 6. If post-baseline ECG results are above the upper limits (abnormally high) and the baseline value is below the lower limits (abnormally low), then the post-baseline abnormality will also be considered treatment-emergent. The same applies to the post-baseline value being below the lower limits (abnormally low) with the baseline value being above the upper limits (abnormally high). Abnormal ranges for the HR, PR, QRS and QT intervals are given in Table 6.

Table 6: Limits for HR, PR, QRS and QT Interval Abnormality

ECG parameter	Abnormally Low	Abnormally High
HR (bpm)	≤50	≥100
PR interval (msec)	--	≥210
QRS interval (msec)	≤50	≥120
QT interval (msec)	≤200	≥500

Based on the maximum QTc value for each subject during the double-blind phase (separate for each QTc correction) the incidence of abnormal QTc values and changes from baseline will be summarized by treatment group. Criteria for abnormal corrected QT intervals and changes from baseline are given in Table 7 and are derived from the ICH E14 Guidance[1] (the same criteria apply to all QT corrections).

Table 7: Criteria for Abnormal QTc Values and Changes From Baseline

Parameter	Classification	Criteria
Clinically Significant QTc Value	No	≤500
	Yes	>500
QTc change from baseline	No concern	≤30
	Concern	>30 - 60
	Clear concern	>60
QTc value	Normal	≤450
	>450 - 480	>450 - ≤480
	>480 - 500	>480 - ≤500
	>500	>500

These criteria are based on ICH E14 Guideline

The proportion of subjects with treatment emergent abnormalities will be presented for the double-blind phase. Listings of subjects with abnormalities will be provided for the double-blind and follow-up phases.

6.6. Other Safety Parameters

6.6.1. Modified Observer's Assessment of Alertness/Sedation (MOAA/S)

The MOAA/S will be used to measure treatment-emergent sedation with correlation to levels of sedation defined by the American Society of Anesthesiologists (ASA) continuum. The MOAA/S scores range from 0 [No response to painful stimulus; corresponds to ASA continuum for general anesthesia] to 5 [Readily responds to name spoken in normal tone (awake); corresponds to ASA continuum for minimal sedation].

On each intranasal dosing day, the MOAA/S will be performed every 15 minutes from predose to 1.5 hours postdose.

If the score is ≤3 at any time during the 90 minute postdose interval, the MOAA/S will be performed every 5 minutes until a score of 4 is reached (at which point a frequency of every 15 minutes can be resumed until t = 90 minutes postdose).

If a subject does not have a score of at least 5 at t = 90 minutes postdose, the subject should continue to be monitored. For subjects with a score of 4, the assessment should be repeated every 15 minutes. And for subjects with a score of ≤3, the assessment should be repeated every 5 minutes until the score returns to 5 or the subject is referred for appropriate medical care, if clinically indicated.

Descriptive statistics of the MOAA/S score and changes from pre-dose will be summarized at each scheduled time point. In addition, the proportion of subjects experiencing sedation (score less than or equal to 3) will be presented by treatment group during the double-blind phase.

Mean MOAA/S scores will be presented graphically for each dosing day.

6.6.2. Clinician Administered Dissociative States Scale (CADSS)

The Clinician Administered Dissociative States Scale (CADSS) is an instrument for the measurement of present-state dissociative symptoms and will be administered to assess treatment-emergent dissociative symptoms. On each dosing day, the CADSS will be performed predose, and at 40 minutes and 1.5 hours postdose. The CADSS comprises 23 subjective items and participant's responses are coded on a 5-point scale (0 = "Not at all", 1 = "Mild", 2 = "Moderate", 3 = 'Severe" and 4 = "Extreme"). If any CADSS items are scored zero at 40 minutes, these items will not need to be repeated at 1.5 hours postdose. These zero scores at 40 minutes will be carried forward to 1.5 hours. The CADSS is divided into 3 components using the following scoring method:

Component	Questions	Range
Depersonalization	Sum of 3, 4, 5, 6, 7, 20, 23	0-28
Derealization	Sum of 1, 2, 8, 9, 10, 11, 12, 13, 16, 17, 18, 19, 21	0-52
Amnesia	Sum of 14, 15, 22	0-12
Total Score	Sum of 1 through 23	0-92

For the total score and each component, a higher score represents a more severe condition.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) of the total scores and component scores at each time point and visit, along with change from the pre-dose time point within each visit, will be presented.

In addition, the proportion of subjects with an increase in CADSS total score from the pre-dose value at any visit during the double-blind phase will be presented by treatment group.

Mean changes in CADSS total score from pre-dose value will be presented graphically for each dosing day. Boxplots of CADSS total score over time will be also be provided.

6.6.3. Columbia Classification Algorithm for Suicide Assessment (C-CASA)

Responses from the SIBAT will be mapped to corresponding categories of the C-CASA (Columbia Classification Algorithm for Suicide Assessment) 2012 Plus.[5,6] If a subject maps to multiple categories at the same visit, then the most severe category will be considered as their C-CASA category for that visit. Attachment 4 contains the mapping algorithm. The first post baseline mapping will occur at Day 8 since that is the first post baseline visit with responses to each of the modules used in the mapping. Using the C-CASA 2012 Plus, potentially suicide-related events will be classified using the following 18 categories:

Suicidal Ideation (SI-1 to SI-X)

SI-1: Passive Suicidal ideation

SI-2: Active Suicidal Ideation: Non-specific (no method, intent or plan)

SI-3: Active Suicidal Ideation: method, but no intent or plan

SI-4: Active Suicidal Ideation: method and intent, but no plan

SI-5: Active Suicidal Ideation: method, intent and plan

SI-X: Active Suicidal Ideation: other

Suicidal Behavior (SB-1 to SB-5)

SB-1: Completed Suicide

SB-2: Suicide Attempt

SB-3: Interrupted Suicide Attempt

SB-4: Aborted Suicide Attempt

SB-5: Preparatory acts towards imminent suicidal behavior

Self-Injurious Behavior (SIB-1 to SIB-2)

SIB-1: Self-Injurious Behavior Without Suicidal Intent

SIB-2: Self-Injurious Behavior, Intent unknown

Not Enough Information / Other (13-16)

13: Not enough information (fatal)

14: Not enough information (non-fatal)

15: Other (accidental, psychiatric medical), no deliberate self-harm

16: No suicidal ideation or behavior

17: Not mapped to categories above

A frequency distribution of the 18 categories at each scheduled time point by treatment will be provided. In addition, the proportion of subjects classified in a more severe C-CASA category compared the baseline category at any visit during the double-blind and follow-up phases will be presented by treatment group.

The most severe category for each subject will also be summarized into one of four broad categories: No suicidal ideation or behavior/Other/Not enough information, Self-Injurious behavior, Suicidal ideation, and Suicidal behavior. A frequency distribution of the most severe category during the double-blind and follow-up phases will be summarized by treatment group. Shifts from the baseline visit to the most severe category during the double-blind and follow-up phases will be summarized by treatment group.

7. PHARMACOKINETICS/PHARMACODYNAMICS

Details of the pharmacokinetic and pharmacodynamic analysis are provided in a separate document.

8. BIOMARKER/PHARMACOGENOMIC ANALYSES

Details of biomarker and pharmacogenomic analyses are provided in a separate document.

9. HEALTH ECONOMICS

9.1. Healthcare Resource Use Questionnaire (HRUQ)

Medical resource utilization data, associated with medical encounters, will be collected using the Healthcare Resource Use Questionnaire (HRUQ) on an ongoing basis whenever an encounter

occurs. The HRUQ includes information regarding utilization of healthcare services (including the timing and type of serves), enabling changes in level and quantity of services to be considered as a variable in economic models.

Frequency distributions and descriptive statistics (N, mean, SD, median, minimum and maximum) for the HRUQ, including 30-day and 60-day readmission, and emergency room visits related to MDD and suicidality, will be provided during the double-blind and follow-up phases. A summary of the duration of the initial hospitalization will also be provided.

10. RELATIONSHIP BETWEEN CGI-SS-R AND OTHER RELEVANT CLINICAL ENDPOINTS

The relationship between changes in CGI-SS-R scores and changes in relevant endpoints will be evaluated to demonstrate sensitivity to changes in severity of suicidality as assessed by the CGI-SS-R. The SIBAT CGI-SS-R was designed to comprehensively evaluate the severity of suicidality by taking into account a broad range of suicide ideation and behavior. The CGI-SS-R was designed to detect changes in suicidality over short periods of time (i.e., hours). The CGI-SS-R has face validity; the category ratings are directly interpretable as different levels of severity of suicidality. The correlation between changes in CGI-SS-R scores and changes in the MADRS total, MADRS suicidal ideation item, and the SIBAT Module 7 (Global Clinical Impression) FoST will be presented.

REFERENCES

1. International Conference on Harmonization (ICH) Tripartite Guideline E14. London: s.n., 2005. pp. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic for non-antiarrhythmic drugs.
2. VanderWeele, T.J., Zhang, Y., Lim, P. (2016). Mediation analysis with an ordinal outcome. Epidemiology, 27(5):651-5.
3. Imai K, Keele L, Tingley D (2010). A general approach to causal mediation analysis. Psychological Methods, Vol. 15, No. 4, pp. 309–334
4. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). [2009] Guidance for industry drug induced liver injury: premarketing clinical evaluation. Available: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf.
5. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164:1035-1043.
6. United States Food and Drug Administration, United States Department of Health and Human Services. Guidance for Industry: Suicidality: Prospective Assessment of Occurrence in Clinical Trials, Draft Guidance. August 2012. Revision 1. Available: http://www.fda.gov/downloads/Drugs/Guidances/UCM225130.pdf
7. Fox, Jean-Paul. Bayesian item response modeling: Theory and applications. Springer Science & Business Media, 2010.
8. Plummer, Martyn. "JAGS: A program for analysis of Bayesian graphical models using Gibbs sampling." Proceedings of the 3rd international workshop on distributed statistical computing. Vol. 124. 2003.
9. Wong, Wan Ling, et al. "Accounting for Standard Errors of Vision-Specific Latent Trait in Regression Models Accounting for SEs in Regression Models." Investigative ophthalmology & visual science 55.9 (2014):5848-5854.

ATTACHMENTS

Attachment 1: Criteria of Markedly Abnormal Laboratory Values

Laboratory Parameter	Markedly Abnormal Limits	
	Low	High
Alanine aminotransferase (ALT) (SGPT) [U/L]	N/A	200
Alanine aminotransferase (ALT) (SGPT) [U/L]	N/A	>3X ULN
Albumin [g/L]	24	60
Alkaline phosphatase [U/L]	N/A	250
Aspartate aminotransferase (AST) (SGOT) [U/L]	N/A	250
Aspartate aminotransferase (AST) (SGOT) [U/L]		>3X ULN
Basophils [%]	N/A	6
Bicarbonate [mmol/L]	15.1	34.9
Bilirubin, total [µmol/L]	N/A	51.3
Blood urea nitrogen [mmol/L]	N/A	17.9
Calcium [mmol/L]	1.5	3
Chloride [mmol/L]	94	112
Creatine kinase (U/L)	N/A	990
Creatinine [µmol/L]	N/A	265.2
Eosinophils [%]	N/A	10
Erythrocytes (RBC) [x1012/L] -- female	3.0	5.5
-- male	3.0	6.4
Gamma glutamyl transferase [U/L]	N/A	300
Glucose [mmol/L]	2.2	16.7
Hemoglobin [g/L]	80	190
Hematocrit [fraction] -- female	0.28	0.50
-- male	0.24	0.55
Lactate Dehydrogenase [U/L]	N/A	500
Leukocytes(WBC) [x109/L]	2.5	15.0
Lymphocytes [%]	10	60
Monocytes [%]	N/A	20
Neutrophils, segmented [%]	30	90
Phosphate [mmol/L]	0.7	2.6
Platelet count [x109/L]	100	600
Potassium [mmol/L]	3.0	5.8
Protein, total [g/L]	50	N/A
Sodium [mmol/L]	125	155
Urate [µmol/L]	89.2	594.8
Urine pH	N/A	8.0
Hy's Law criteria:		
Alanine aminotransferase (ALT) (SGPT) [U/L] or Aspartate aminotransferase (AST) (SGOT) [U/L]		>3X ULN
AND		

Bilirubin, total [µmol/L]	>2X ULN

Note: The same limits apply to both males and females unless gender is indicated;
N/A = Not applicable.

Attachment 2: Beck Hopelessness Scale Scoring

Add the number of responses appearing in the green cells. This is the total score.

1.	I look forward with hope and enthusiasm	T	F
2.	I might as well give up because there is nothing I can do about making things better for myself	T	F
3.	When things are going badly, I am helped by knowing that they cannot stay that way forever	T	F
4.	I can't imagine what my life would be like in ten years	T	F
5.	I have enough time to accomplish the things I want to do	T	F
6.	In the future, I expect to succeed in what concerns me most	T	F
7.	My future seems dark to me	T	F
8.	I happen to be particularly lucky, and I expect to get more of the good things in life than the average person	T	F
9.	I just can't get the breaks, and there's no reason I will in the future	T	F
10.	My past experiences have prepared me well for the future	T	F
11.	All I can see ahead of me is unpleasantness rather than pleasantness	T	F
12.	I don't expect to get what I really want	T	F
13.	When I look ahead to the future, I expect that I will be happier than I am now	T	F
14.	Things just won't work out the way I want them to	T	F
15.	I have great faith in the future	T	F
16.	I never get what I want, so it is foolish to want anything	T	F
17.	It's very unlikely that I will get any real satisfaction in the future	T	F
18.	The future seems vague and uncertain to me	T	F
19.	I can look forward to more good times than bad times	T	F
20.	There's no use in really trying to get anything I want because I probably won't get it.	T	F

Attachment 3: SIBAT Module 2 and Module 3 Scoring

SIBAT Module 2: Each of the first 21 items of SIBAT Module 2 has 5 response options: "Never", "Rarely", "Sometimes", "Often", "Most of the time" and "All the time", with the corresponding scores listed below. The total score is calculated by adding the scores of the first 21 items.

	Over the past 7 days…	***Scoring Algorithm***					
1	*...I have felt hopeful.*	5	4	3	2	1	0
2	*...I have felt agitated.*	0	1	2	3	4	5
3	*...I have felt happy.*	5	4	3	2	1	0
4	*...my life has felt empty.*	0	1	2	3	4	5
5	*...I have felt valued by others.*	5	4	3	2	1	0
6	*...my emotions have been stable.*	5	4	3	2	1	0
7	*...I have wanted to end my life.*	5	4	3	2	1	0
8	*...I have felt hopeless.*	0	1	2	3	4	5
9	*...I have felt calm.*	5	4	3	2	1	0
10	*...I have felt depressed.*	0	1	2	3	4	5
11	*...my life has felt fulfilled.*	5	4	3	2	1	0
12	*...I have felt worthless.*	0	1	2	3	4	5
13	*...I have gotten angry easily.*	0	1	2	3	4	5
14	*...my sleep has been good.*	5	4	3	2	1	0
15	*...I have had sudden, unexpected urges to take my life.*	0	1	2	3	4	5
16	*...I have felt anxious.*	0	1	2	3	4	5
17	*...my relationships with others have been good.*	5	4	3	2	1	0
18	*...I have felt isolated from others.*	0	1	2	3	4	5
19	*...I have thought about killing myself.*	0	1	2	3	4	5
20	*...I have wanted to hurt other people.*	0	1	2	3	4	5
21	*...I have heard a voice telling me to kill myself.*	0	1	2	3	4	5

SIBAT Module 3: Each of the 48 items of SIBAT Module 3 has 6 response options: “Strongly Disagree”, “Disagree”, “Slightly Disagree”, “Slightly Agree”, “Agree”, “Strongly Agree”, with the corresponding scores listed below. The total score is calculated by adding the scores of the 48 items.

1	*I am glad to be alive.*	5	4	3	2	1	0
2	*I feel worthless.*	0	1	2	3	4	5
3	*It is difficult to control my urges to end my life.*	0	1	2	3	4	5
4	*I feel powerless to improve my situation.*	0	1	2	3	4	5
5	*My spiritual/religious beliefs prevent me from ending my life.*	5	4	3	2	1	0
6	*I wish to die in my sleep in the near future.*	0	1	2	3	4	5
7	*My concern for others prevents me from ending my life.*	5	4	3	2	1	0
8	*If I developed a life-threatening illness, I would make every effort to overcome it.*	5	4	3	2	1	0
9	*Nothing in life gives me pleasure.*	0	1	2	3	4	5
10	*I have been shamed and should die.*	0	1	2	3	4	5
11	*I feel so depressed that I would be better off dead.*	0	1	2	3	4	5
12	*I think I will end my life within the next year.*	0	1	2	3	4	5
13	*I feel lonely.*	0	1	2	3	4	5
14	*My emotional distress is so severe that I want to end my life.*	0	1	2	3	4	5
15	*I feel so stressed that it would be better if I were dead.*	0	1	2	3	4	5
16	*People or forces in the world want me to be dead.*	0	1	2	3	4	5
17	*I feel guilty about things I have done.*	0	1	2	3	4	5
18	*Others would be better off if I were dead.*	0	1	2	3	4	5
19	*There is no future for me.*	0	1	2	3	4	5
20	*I worry that there will be no one to help care for me.*	0	1	2	3	4	5
21	*I fantasize about ending my life.*	0	1	2	3	4	5
22	*I have life goals that are important to me.*	5	4	3	2	1	0
23	*I wish I were dead.*	0	1	2	3	4	5
24	*I feel trapped in my current unhappy situation.*	0	1	2	3	4	5
25	*I am a good person.*	5	4	3	2	1	0
26	*My life is hopeless and ending my life is the only way out.*	0	1	2	3	4	5
27	*There is a greater purpose for my life.*	5	4	3	2	1	0
28	*My thoughts are mixed up and I am confused.*	0	1	2	3	4	5
29	*I want to make my life a better one.*	5	4	3	2	1	0
30	*I feel neglected.*	0	1	2	3	4	5

31	*Death is the only solution to my problems.*	0	1	2	3	4	5
32	*Some people in my life give me happiness.*	5	4	3	2	1	0
33	*I am fully prepared to end my life.*	0	1	2	3	4	5
34	*Helping others gives my life purpose.*	5	4	3	2	1	0
35	*Nobody will care if I am dead.*	0	1	2	3	4	5
36	*I want to stay alive.*	5	4	3	2	1	0
37	*My physical pain is so severe that I want to end my life.*	0	1	2	3	4	5
38	*My emotional (mental) pain is so severe that I want to end my life.*	0	1	2	3	4	5
39	*I want to spend more time alone.*	0	1	2	3	4	5
40	*I feel anxious much of the time.*	0	1	2	3	4	5
41	*I feel agitated much of the time.*	0	1	2	3	4	5
42	*I feel frightened much of the time.*	0	1	2	3	4	5
43	*I am talented and skilled.*	5	4	3	2	1	0
44	*I feel in control of my life.*	5	4	3	2	1	0
45	*I am a burden to others.*	0	1	2	3	4	5
46	*I am scared of dying.*	5	4	3	2	1	0
47	*I have troubling thoughts that I cannot control.*	0	1	2	3	4	5
48	*I am having a crisis in my life.*	0	1	2	3	4	5

Attachment 4: SIBAT Mapping to the C-CASA 2012 Plus

	C-CSSRS / Expanded C-CASA Code Number	2012 C-CASA Plus Category
1	SI-1	Passive Suicidal ideation
2	SI-2	Active Suicidal Ideation: Non-specific (no method, intent or plan)
3	SI-3	Active Suicidal Ideation: method, but no intent or plan
4	SI-4	Active Suicidal Ideation: method and intent, but no plan
5	SI-5	Active Suicidal Ideation: method, intent and plan
X	SI-X	Active Suicidal Ideation: other
6	SB-1	Completed Suicide
7	SB-2	Suicide Attempt
8	SB-3	Interrupted Suicide Attempt
9	SB-4	Aborted Suicide Attempt
10	SB-5	Preparatory acts towards imminent suicidal behavior
11	SIB-1	Self-Injurious Behavior Without Suicidal Intent
12	SIB-2	Self-Injurious Behavior, Intent unknown
13	Other	Not enough information (fatal)
14	Other	Not enough information (non-fatal)
15	Other	Other (accidental, psychiatric medical), no deliberate self-harm
16	Other	No suicidal ideation or behavior
17	Other	Not mapped

Baseline

	C-CSSRS / Expanded C-CASA Code Number	2012 Expanded C-CASA Category	How SIBAT maps to 2012 C-CASA Plus Categories Lifetime (BASELINE)
1	SI-1	Passive Suicidal ideation	Inclusion: About Me: #17 = Yes Or My Current Thinking: #6, or 10, or 11, or 15, or 18, or 23, or 31 = Slightly Agree/Agree/Strongly Agree Or My Risk: #1 = 1/2/3/4 Or Exclusion: About Me: #18 = Yes Or My Risk/Protective Factors: #7, 15, or 19 = rarely, sometimes, often, most of the time, all the time Or My Current Thinking #3, 12, 14, 21, 26, 33, 37 or 38 = Slightly Agree/Agree/Strongly Agree Or My Risk: #2 or 3 = 1 /2 /3 /4 Or My Risk: #4 = 2 /3 /4 Or My Risk: #5 = 3 / 4

	C-CSSRS / Expanded C-CASA Code Number	2012 Expanded C-CASA Category	How SIBAT maps to 2012 C-CASA Plus Categories Lifetime (BASELINE)
2	SI-2	Active Suicidal Ideation: Non-specific (no method, intent or plan)	Inclusion: About Me: #18b = Yes Or My Risk/Protective Factors: #7, 15, or 19 = rarely, sometimes, often, most of the time, all the time Or My Current Thinking: #3, 12, 14, 21, 26, 33, 37, or 38 (Slightly Agree/Agree/Strongly Agree) Or My Risk: #2 or 3 = 1 /2 /3 /4 Or My Risk: #5 = 3 / 4 Exclusion: About Me: #18c or 18d or 18g or 18h or 18j or 18k = Yes Or My Risk: #4 = 2 /3 /4
3	SI-3	Active Suicidal Ideation: method, but no intent or plan	Inclusion: About Me: #18 and 18d = Yes Exclusion: About Me: #18c, or 18g or 18h or 18j or 18k = Yes Or My Risk: #4 = 2 /3 /4
4	SI-4	Active Suicidal Ideation: method and intent, but no plan	Inclusion: About Me: #18 and 18c = Yes or My Risk: #4 = 2 /3 /4 AND About Me 18d = Yes Exclusion: About Me: #18g or 18h or 18j or 18k = Yes
5	SI-5	Active Suicidal Ideation: method, intent and plan	Inclusion: About Me: #18 and 18c = Yes or My Risk: #4 = 2 /3 /4 AND About Me 18d=Yes AND About Me (18g or 18h or 18j or 18k) = Yes Exclusion: None
X	SI-X	Active Suicidal Ideation: Other	Inclusion: About Me: #18b = Yes Or My Risk/Protective Factors: #7, Or 15, Or 19 = rarely, sometimes, often, most of the time, all the time Or My Current Thinking: #3, OR 12, OR 14, OR 21, OR 26, OR 33, OR 37, OR 38 (Slightly Agree/Agree/Strongly Agree) Or My Risk: #2 = 1/2/3/4 Or My Risk: #3 = 1 /2 /3 /4 Or My Risk: #4 = 2 /3 /4 Or My Risk: #5 = 3 / 4 Or About Me: #18c or 18d or 18g or 18h or 18j or 18k = Yes Exclusion: Map to any of the following categories: SI-2, OR SI-3, OR SI-4, OR SI-5
6	SB-1	Completed Suicide	Inclusion: Not Applicable
7	SB-2	Suicide Attempt	Inclusion: About Me: #18L = Yes Exclusion: None
8	SB-3	Interrupted Suicide Attempt	Inclusion: About Me: #18v= Yes Exclusion: None
9	SB-4	Aborted Suicide Attempt	Inclusion: About Me: #18s = Yes Exclusion: None

	C-CSSRS / Expanded C-CASA Code Number	2012 Expanded C-CASA Category	How SIBAT maps to 2012 C-CASA Plus Categories Lifetime (BASELINE)
10	SB-5	Preparatory acts towards imminent suicidal behavior	Inclusion: About Me: #18i or 18j= Yes Exclusion: None
11	SIB-1	Self-Injurious Behavior Without Suicidal Intent	Inclusion: About Me: #19 = Slightly Agree/Agree/Strongly Agree Exclusion: None
12	SIB-2	Self-Injurious Behavior, Intent unknown	Inclusion: About Me: #19 'not sure' Exclusion: None
13	Other	Not enough information (fatal)	Inclusion: Not Applicable Exclusion: None
14	Other	Not enough information (non-fatal)	Inclusion: Not Applicable Exclusion: None
15	Other	Other (accidental, psychiatric medical), no deliberate self-harm	Inclusion: About Me: (#14 or 15 = Yes) AND (#18L = No AND #19 = Never) Exclusion: None
16	Other	No suicidal ideation or behavior	Inclusion: My Current Thinking: # 12 and 23 = Disagree/Strong Disagree Exclusions: About Me: #17 or #18 = Yes Or My Risk/Protective Factors: #7, 15, and 19 = rarely, sometimes, often, most of the time, all the time Or My Current Thinking #3 or 6 or 10 or 11 or 12 or 14 or 15 or 18 or 21 or 23, or 26, or 31, or 33 or 37 or 38 = Slightly Agree/Agree/Strongly Agree Or My Risk: #1 or 2 or 3 = 1 /2 /3 /4 Or My Risk: #4 = 2 /3 /4 Or My Risk: #5 = 3 / 4
17	Other	Not Mappable	Y: If mapping to C-CASA Code Number 1 and 2 and 3 and 4 and 5 and 6 and 7 and 8 and 9 and 10 and 11 and 12 and 13 and 14 and 15 and 16 and X = No or missing, then YES N: If not YES, then NO

Initial Most Severe category:
SI: 5 > 4 > X > 3 > 2 > 1
SB: 6 > 7 > 8 > 9 > 10
SIB: 12 > 11

Overall severity determination: 6 > 7 > 8 > 9 > 10 > 5 > 4 > X > 3 > 2 > 1 > 12 > 11 > 13 > 14 > 16 > 15 > 17

If both inclusion and exclusion criteria are met, the exclusion criterion takes precedence over the inclusion criterion and the mapping condition is NOT met.

Post-Baseline

	C-CSSRS / Expanded C-CASA Code Number	2012 Expanded C-CASA Category	How SIBAT maps to 2012 C-CASA Plus Categories Post Baseline
1	SI-1	Passive Suicidal ideation	Inclusion: My Current Thinking: #6, or 10, or 11, or 15, or 18, or 23, or 31 = Slightly Agree/Agree/Strongly Agree Or My Risk: #1 = 1/2/3/4 Exclusion: My Risk/Protective Factors: #7, 15, or19 = rarely, sometimes, often, most of the time, all the time Or My Current Thinking #3, 12, 14, 21, 26, 33, 37 or 38 = Slightly Agree/Agree/Strongly Agree Or My Actions: #10 = Yes Or My Risk: #2 or 3 = 1 /2 /3 /4 Or My Risk: #4 = 2 /3 /4 Or My Risk: #5 = 3 / 4
2	SI-2	Active Suicidal Ideation: Non-specific (no method, intent or plan)	Inclusion: My Risk/Protective Factors: #7, 15, or 19 = rarely, sometimes, often, most of the time, all the time Or My Current Thinking: #3, 12, 14, 21, 26, 33, 37, or 38 = Slightly Agree/Agree/Strongly Agree Or My Actions: #10 a = Yes Or My Risk: #2 or 3 = 1 /2 /3 /4 Or My Risk: #5 = 3 / 4 Exclusion: My Actions: #10b or 10c or 10d or 10g = Yes, or #10e is any answer other than 'NO' Or My Risk: #4 = 2 /3 /4
3	SI-3	Active Suicidal Ideation: method, but no intent or plan	Inclusion: My Actions: #10c = Yes Exclusion: My Actions: #10b or 10d or 10g = Yes, or #10e is any answer other than 'NO' Or My Risk: #4 = 2 /3 /4
4	SI-4	Active Suicidal Ideation: method and intent, but no plan	Inclusion: My Actions: (# 10b or 10g = Yes) or My Risk: #4 = 2 /3 /4 AND My Actions 10c = Yes Exclusion: My Actions: #10d = Yes, or #10e is any answer other than 'NO'
5	SI-5	Active Suicidal Ideation: method, intent and plan	Inclusion: My Actions: (# 10b or 10g = Yes) or My Risk: #4 = 2 /3 /4 AND My Actions 10c = Yes AND My Actions (#10d = Yes or #10e is any answer other than 'NO') Exclusion: None

	C-CSSRS / Expanded C-CASA Code Number	2012 Expanded C-CASA Category	How SIBAT maps to 2012 C-CASA Plus Categories Post Baseline
X	SI-X	Active Suicidal Ideation: other	Inclusion: My Risk/Protective Factors: #7, or 15, or 19 = rarely, sometimes, often, most of the time, all the time Or My Current Thinking: #3, OR 12, OR 14, OR 21, OR 26, OR 33, OR 37, or 38 (Slightly Agree/Agree/Strongly Agree) Or My Actions: #10 a = Yes Or My Risk: #2 or 3 = 1 /2 /3 /4 Or My Risk: #4 = 2 /3 /4 Or My Risk: #5 = 3 / 4 Or My Actions: #10b or 10c or 10d or 10g = Yes, or #10e is any answer other than 'NO' Exclusion: Map to any of the following categories: SI-2, OR SI-3, OR SI-4, OR SI-5
6	SB-1	Completed Suicide	Inclusion: Introduction: Response 1a1 Exclusion: None
7	SB-2	Suicide Attempt	Inclusion: Introduction: Response 1a4 Or My Actions: #3 or 5 = Yes Exclusion: None
8	SB-3	Interrupted Suicide Attempt	Inclusion: My Actions: #8 = Yes Exclusion: None
9	SB-4	Aborted Suicide Attempt	Inclusion: My Actions: #7= Yes Exclusion: None
10	SB-5	Preparatory acts towards imminent suicidal behavior	Inclusion: My Actions: # 10f or 10g = Yes Exclusion: None
11	SIB-1	Self-Injurious Behavior Without Suicidal Intent	Inclusion: My Actions: # 2 = Yes AND #3 = No Or My Actions: # 4 = Yes AND #3 = No Or My Actions: #9= Yes Exclusion: None
12	SIB-2	Self-Injurious Behavior, Intent unknown	Inclusion: My Actions: (Either #2 or 4 = Yes) AND #3 = Uncertain) Or My Actions: #9 = Uncertain Exclusion: None
13	Other	Not enough information (fatal)	Inclusion: Introduction: Response 1a2 or 1a3 Exclusion: None
14	Other	Not enough information (non-fatal)	Inclusion: Introduction: Response 1a6 Exclusion: None
15	Other	Other (accidental, psychiatric medical), no deliberate self-harm	Inclusion: My Actions: #1 = No Or My Actions: #1 = Yes AND (My Actions #2 and 3 = No) Or Introduction: Response 1a5 Exclusion: None

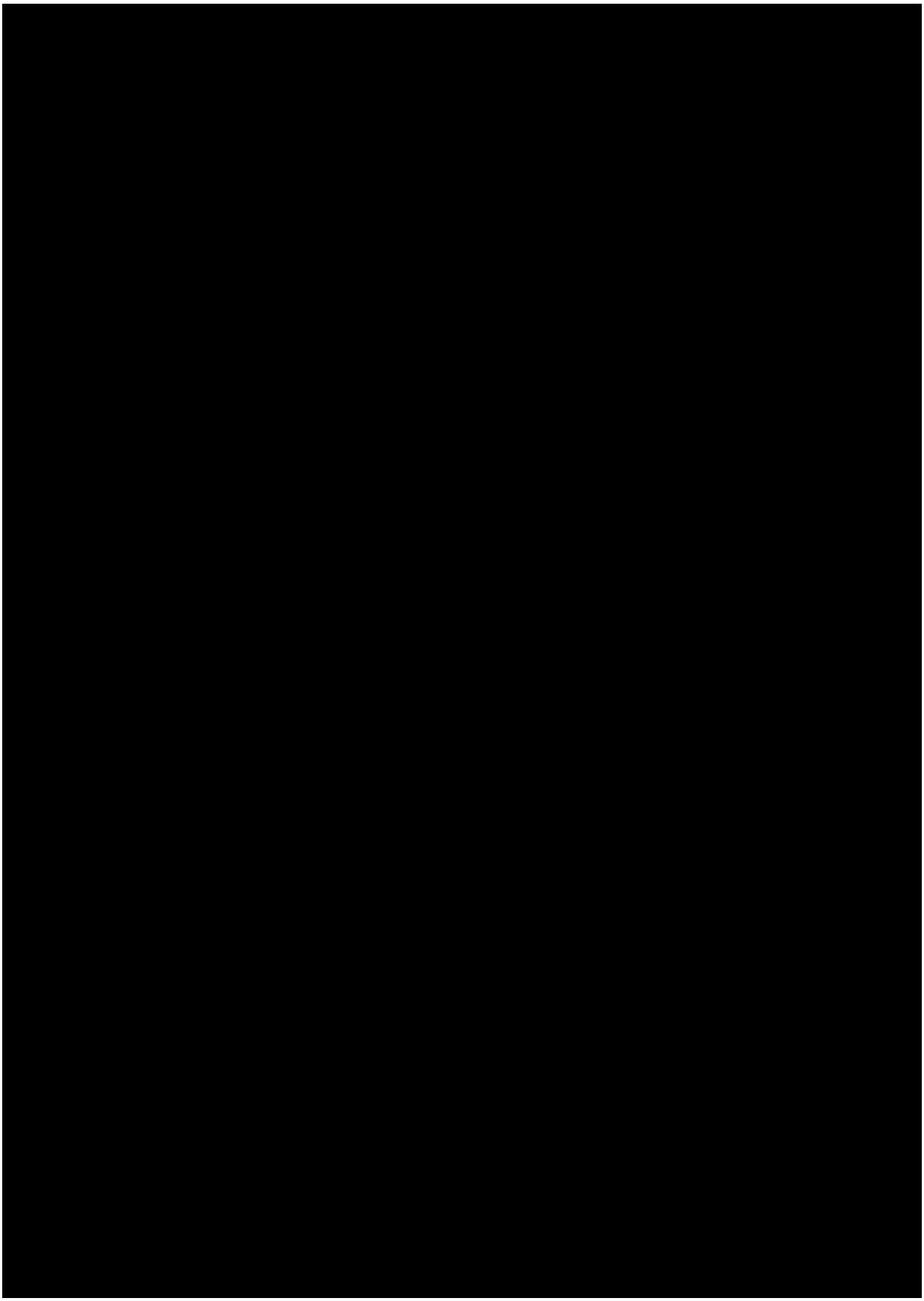
	C-CSSRS / Expanded C-CASA Code Number	2012 Expanded C-CASA Category	How SIBAT maps to 2012 C-CASA Plus Categories Post Baseline
16	Other	No suicidal ideation or behavior	Inclusion: My Current Thinking: #12 and 23 = Disagree/Strong Disagree Exclusion: My Risk/Protective Factors: #7, 15, or 19 = rarely, sometimes, often, most of the time, all the time Or My Current Thinking #3 or 6 or 10 or 11 or 12 or 14 or 15 or 18 or 21 or 23, or 26, or 31, or 33 or 37 or 38 = Slightly Agree/Agree/Strongly Agree Or My Actions: #3 or 5 or 7 or 8 or 10 = Yes Or My Risk: #1 or 2 or 3 = 1 /2 /3 /4 Or My Risk: #4 = 2 /3 /4 Or My Risk: #5 = 3 / 4
17	Other	Not mapped	Y: If mapping to C-CASA Code Number 1 and 2 and 3 and 4 and 5 and 6 and 7 and 8 and 9 and 10 and 11 and 12 and 13 and 14 and 15 and 16 and X = No or missing, then YES N: If not YES, then NO

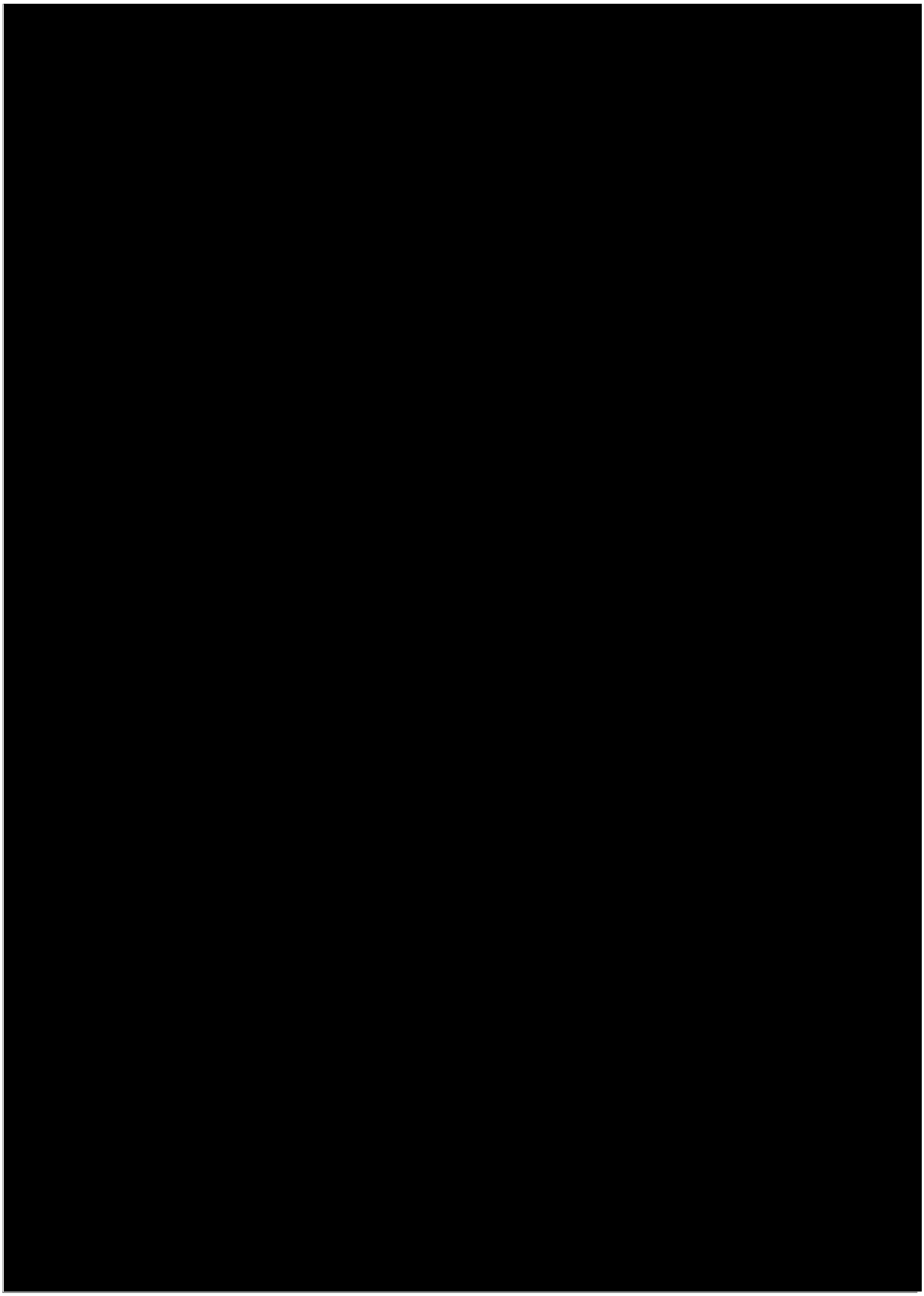
Initial Most Severe category:
SI: 5 > 4 > X > 3 > 2 > 1
SB: 6 > 7 > 8 > 9 > 10
SIB: 12 > 11

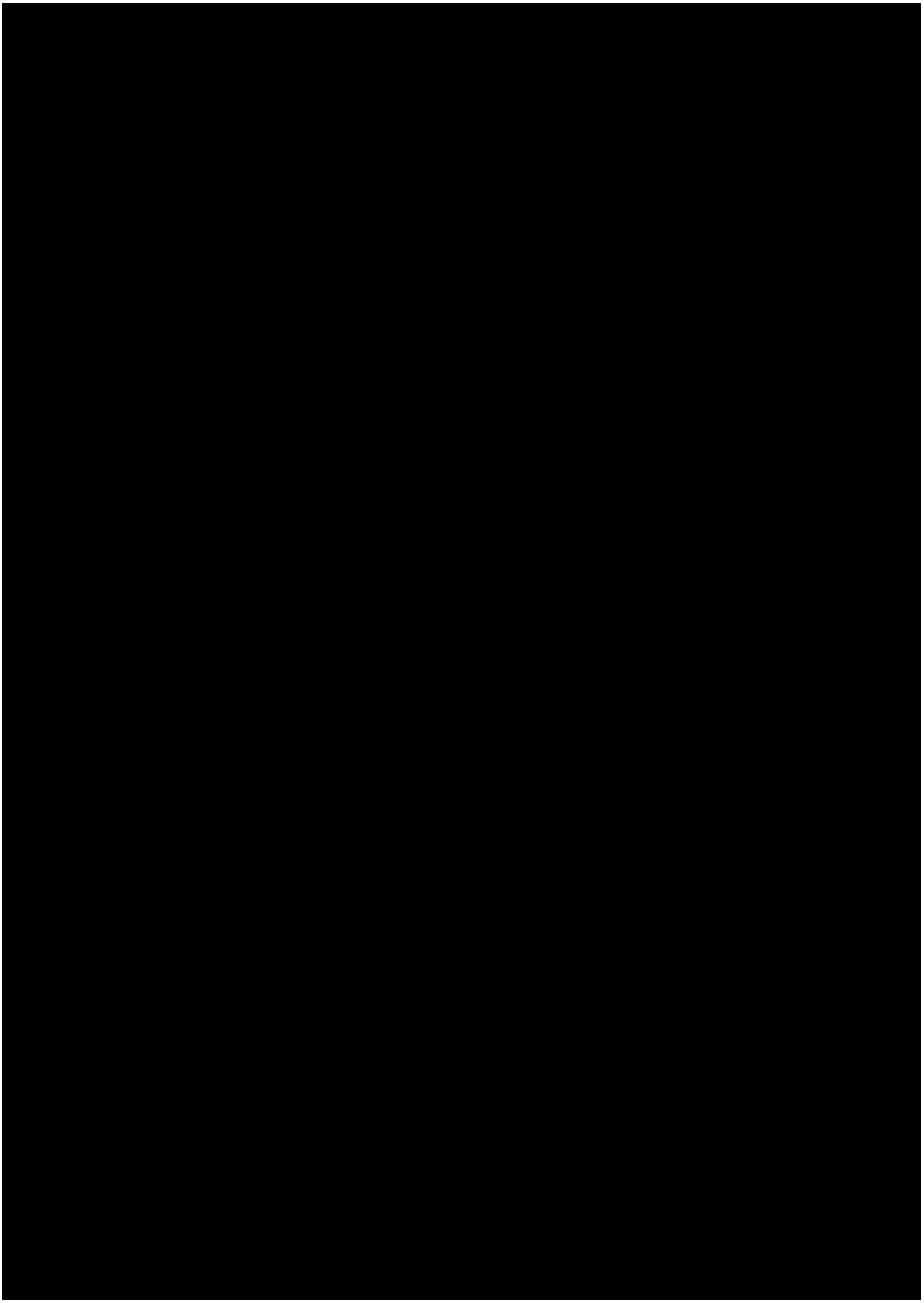
Overall severity determination: 6 > 7 > 8 > 9 > 10 > 5 > 4 > X > 3 > 2 > 1 > 12 > 11 > 13 > 14 > 16 > 15 > 17

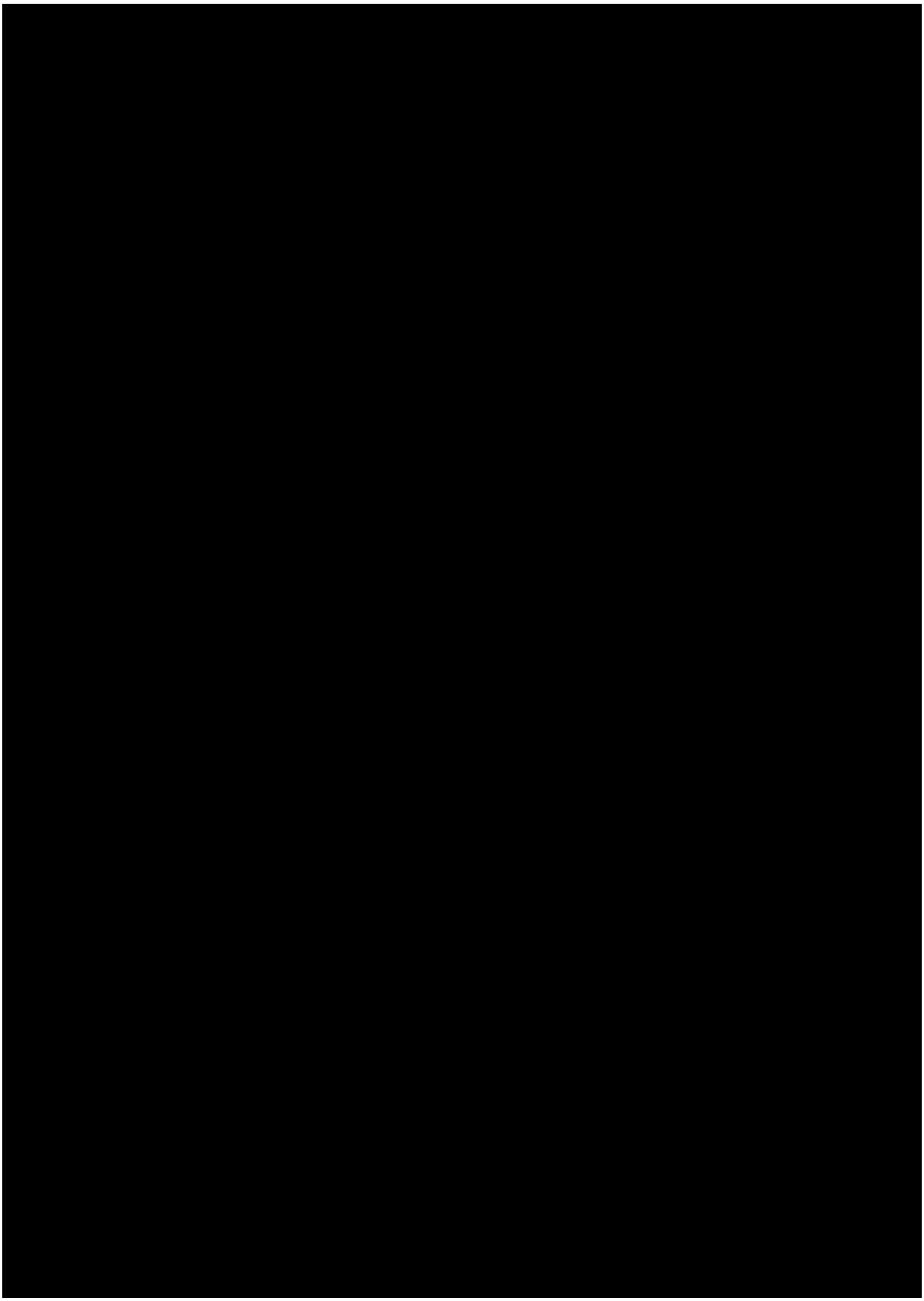
If both inclusion and exclusion criteria are met, the exclusion criterion takes precedence over the inclusion criterion and the mapping condition is NOT met.

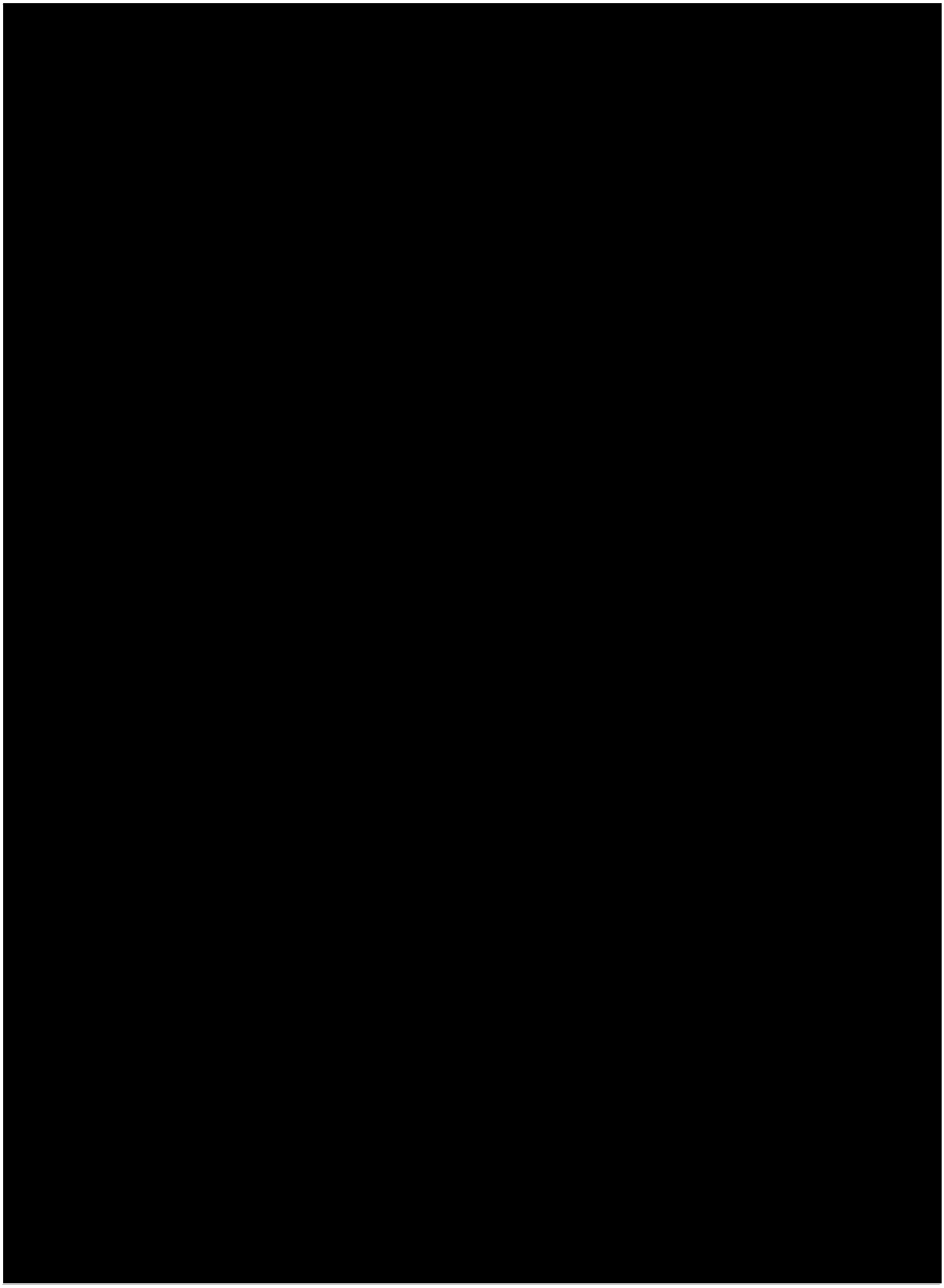
[redacted]

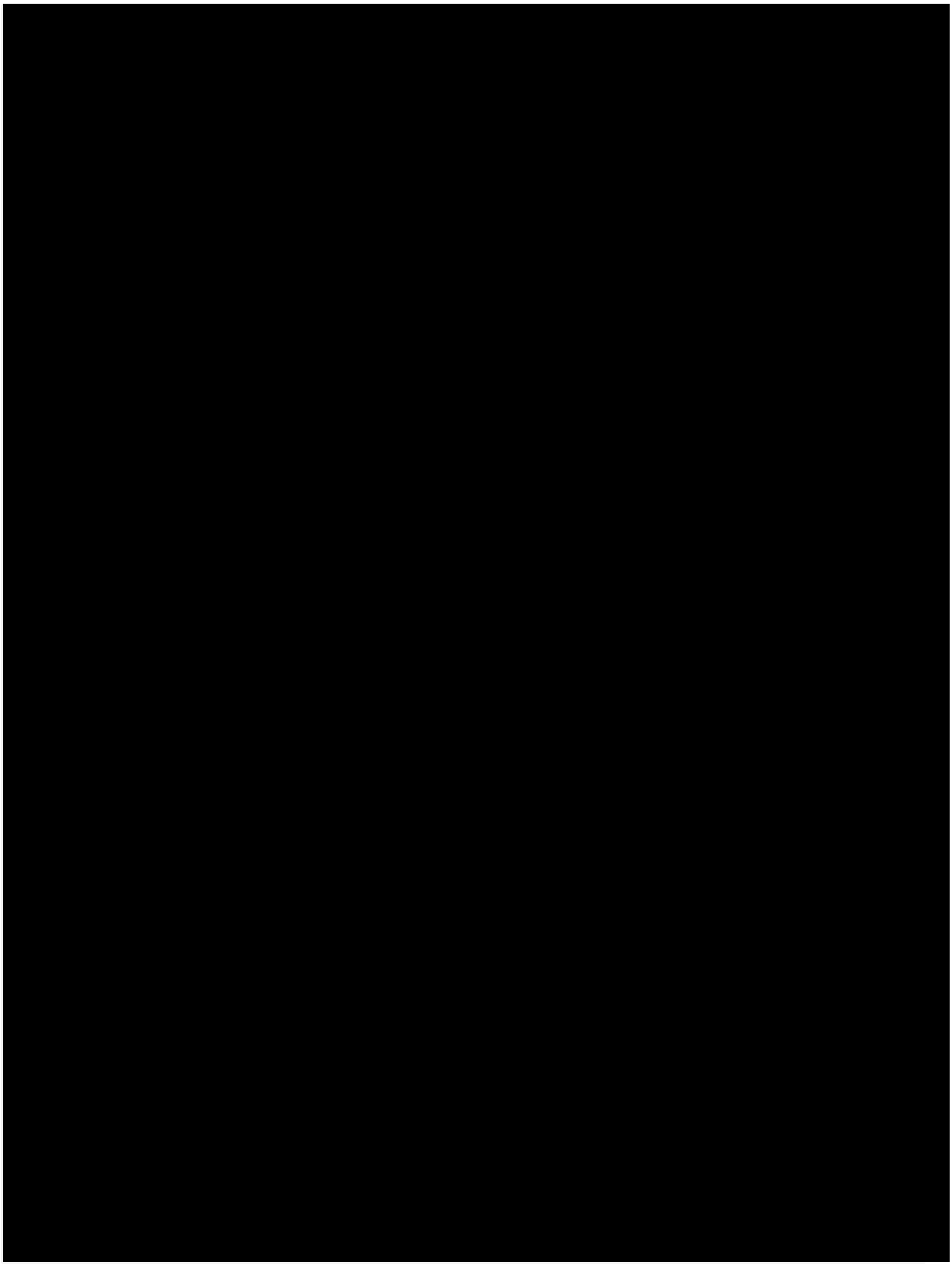


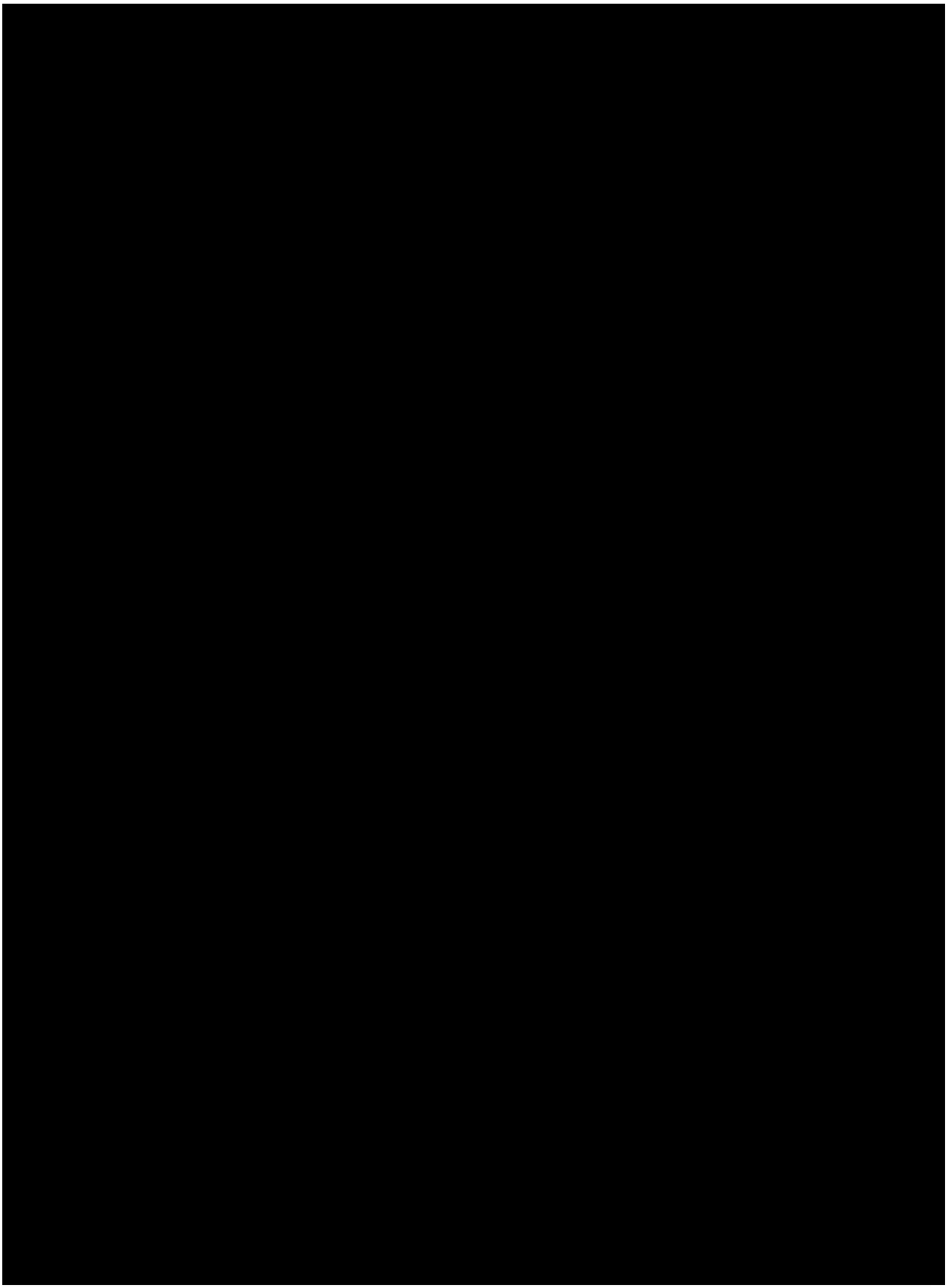


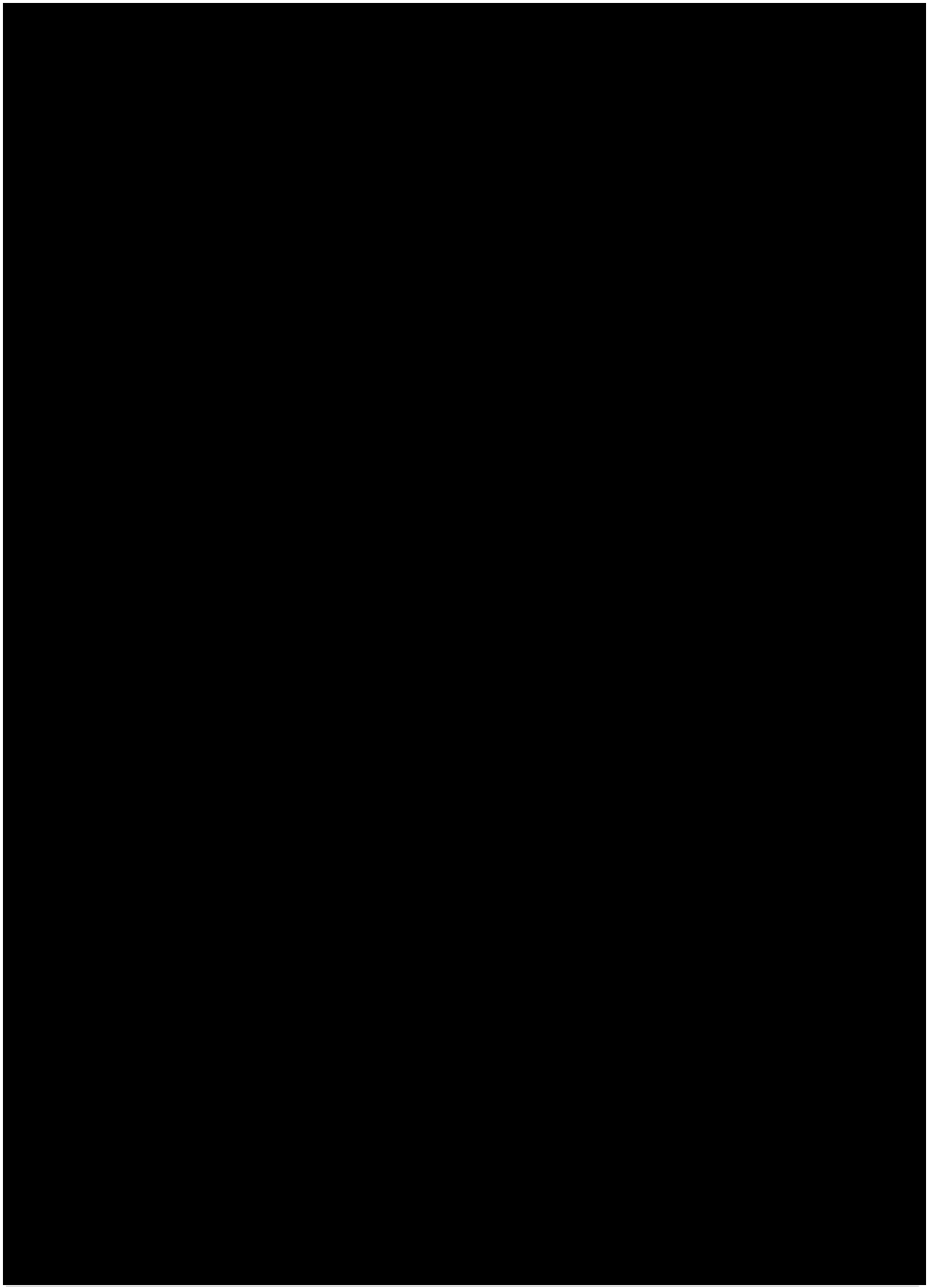


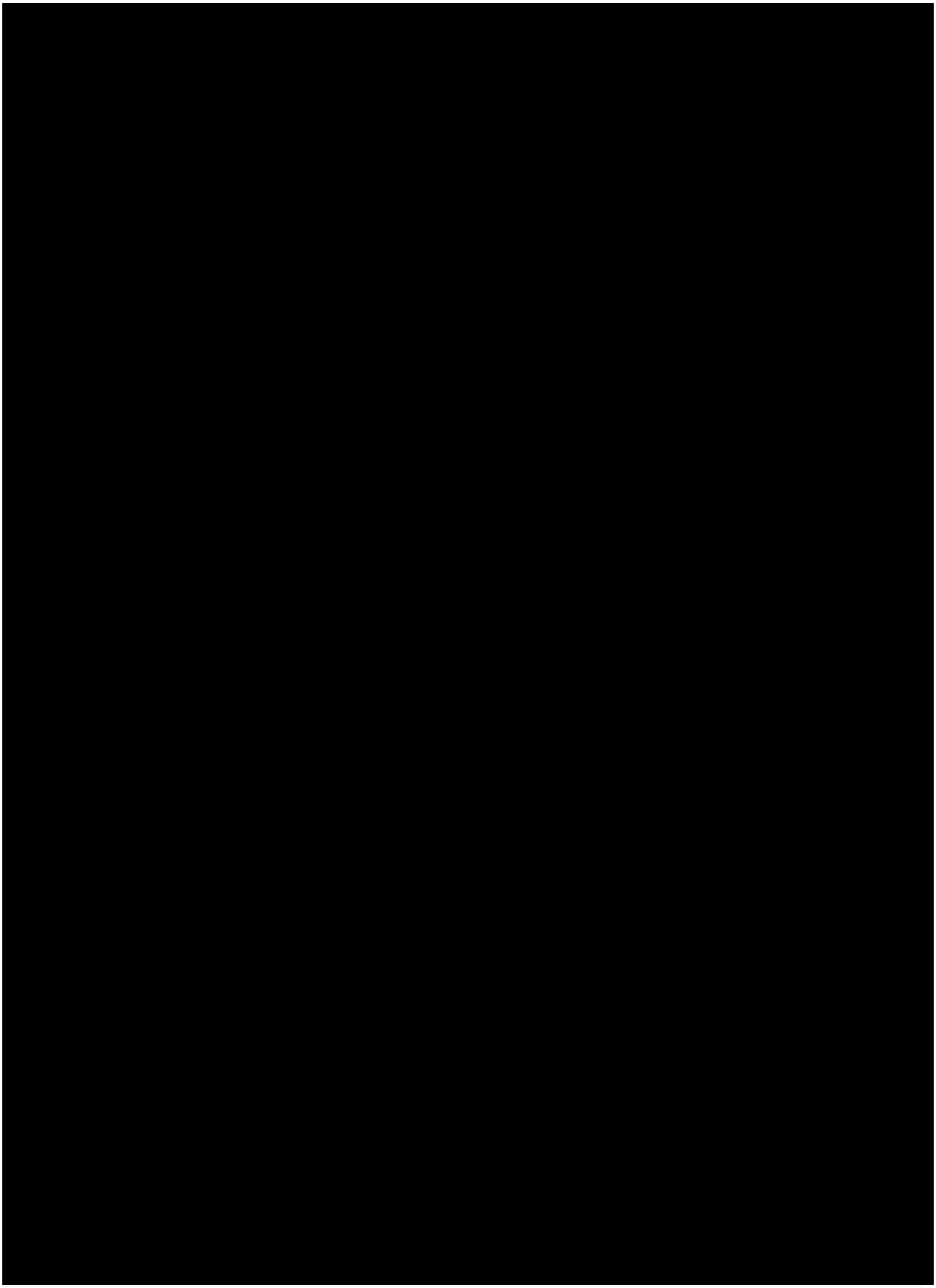


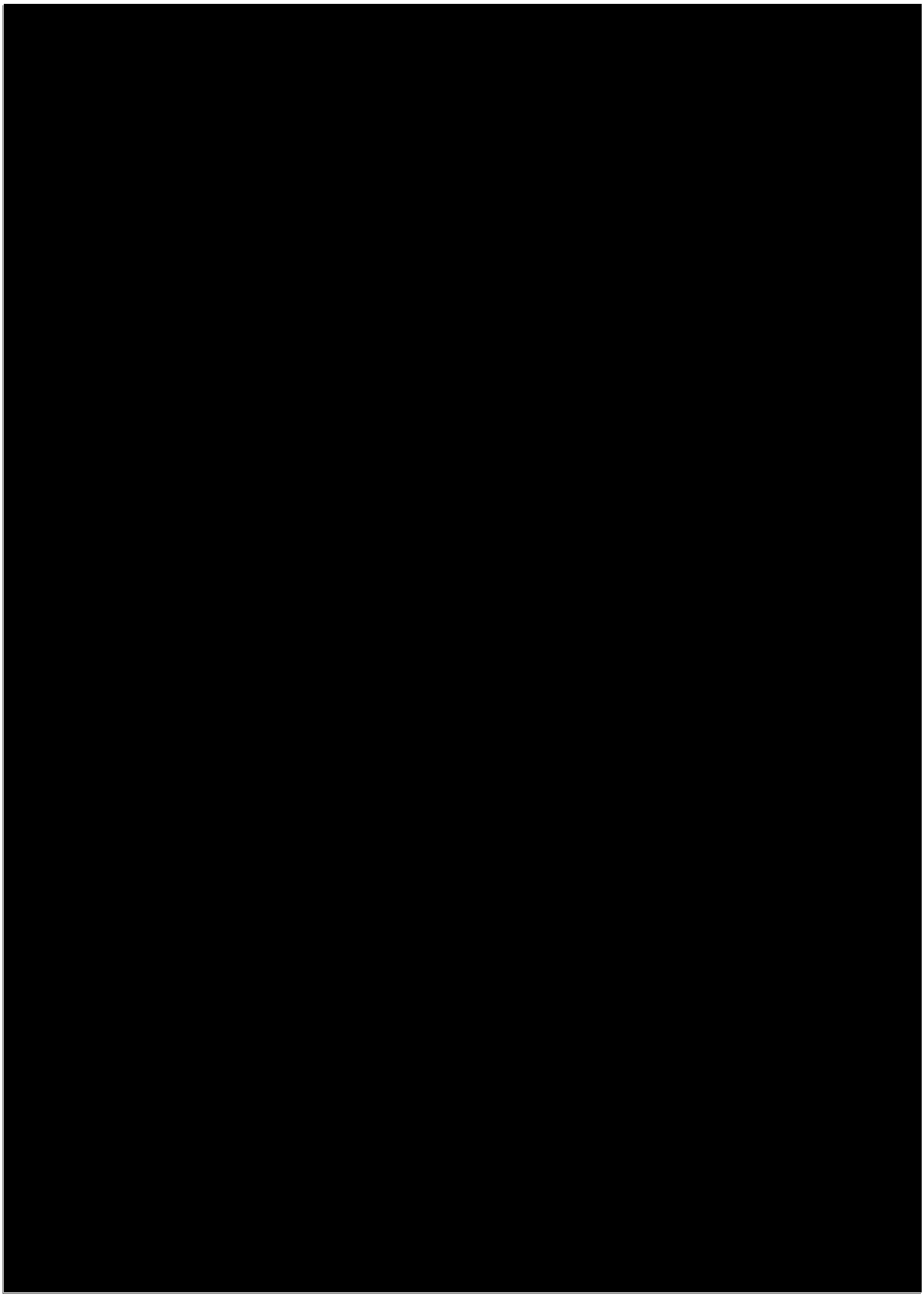


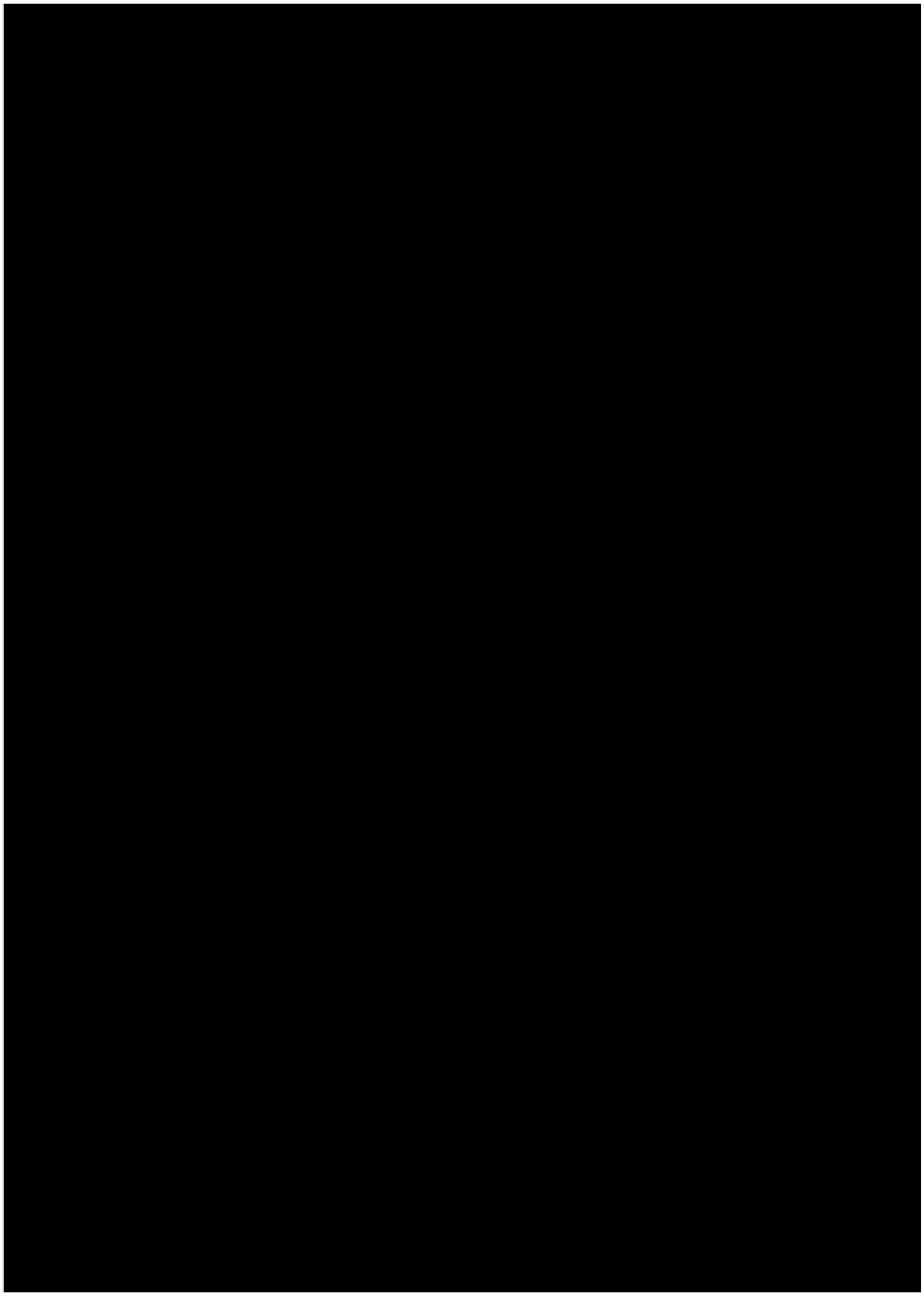


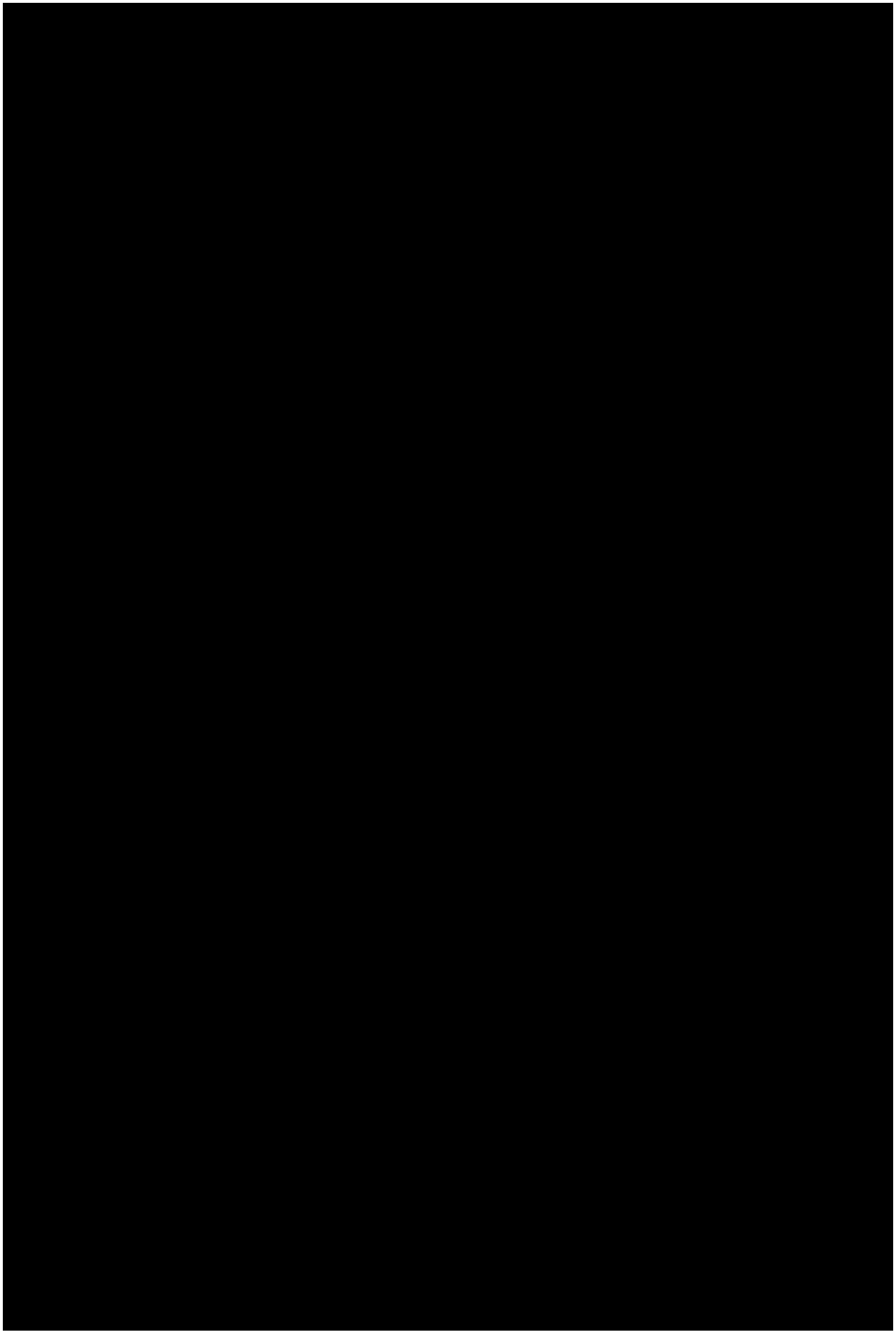












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