Clinical Study Protocol

A Well-Controlled, Fixed-Dose Study of TEV-50717 (Deutetrabenazine) for the Treatment of Tics Associated with Tourette Syndrome

Study Number TV50717-CNS-30060

NCT03571256

Protocol with Amendment 03 Approval Date: 05 May 2019

Clinical Study Protocol with Amendment 03

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A Well-Controlled, Fixed-Dose Study of TEV-50717 (Deutetrabenazine) for the Treatment of Tics Associated with Tourette Syndrome

A Study to Test if TEV-50717 is Effective in Relieving Tics Associated with Tourette Syndrome

Efficacy and Safety Study TV50717-CNS-30060 (Phase 3)

IND number: 127692; NDA number: NA; BLA number: NA;
EudraCT number: 2017-002976-24

EMA Decision number of Pediatric Investigation Plan: Not applicable

Article 45 or 46 of 1901/2006 does not apply

Original Protocol Approval Date: 13 July 2017

Protocol Amendment 03 Approval Date: 05 May 2019

Sponsor

Teva Branded Pharmaceutical
Products R&D, Inc.
41 Moores Road
Frazer, Pennsylvania 19355
United States of America

Teva's Development Partner
Nuvelution TS Pharma, Inc.
101 Main Street, 12th Floor
Cambridge, Massachusetts 02142
United States of America

Confidentiality Statement

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Council for Harmonisation (ICH); United States (US) Code of Federal Regulations (CFR), and European Union (EU) Directives and Regulations (as applicable in the region of the study); national country legislation; and the sponsor's Standard Operating Procedures (SOPs).

This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Branded Pharmaceutical Products R&D, and Nuvelution TS Pharma, INC, and/or its affiliates. The recipient agrees that no information contained herein may be published or disclosed without written approval from the sponsor.

AMENDMENT HISTORY

The protocol for Study TV50717-CNS-30060 (original protocol dated 13 July 2017) has been amended and reissued as follows:

Amendment 03	05 May 2019 78 patients randomized/enrolled to date
Amendment 02	25 March 2019 50 patients randomized/enrolled to date
Amendment 01	20 November 2017 No patients randomized/enrolled to date

The Summary of Changes to the Protocol includes the corresponding reason/justification for each change and is provided in Section 15.

INVESTIGATOR AGREEMENT

Original Protocol Dated 13 July 2017

Amendment 03 Dated 05 May 2019

IND number: 127692; EudraCT number: 2017-002976-24

EMA Decision number of Pediatric Investigation Plan: Not applicable

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A Well-Controlled, Fixed-Dose Study of TEV-50717 (Deutetrabenazine) for the Treatment of Tics Associated with Tourette Syndrome

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol with Amendment 03 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes agreement with this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national or local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the investigational medicinal product (IMP) that were furnished to me by the sponsor to all physicians and other study personnel reporting to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the study. I agree to keep records on all patient information, IMP shipment and return forms, and all other information collected during the study, in accordance with national and local Good Clinical Practice (GCP) regulations as well as all other national and international laws and regulations.

Principal Investigator	**Signature**	**Date**

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	Signature	Date
[redacted]	[redacted]	5 May 2019

COORDINATING INVESTIGATOR AGREEMENT

Original Protocol Dated 13 July 2017

Amendment 03 Dated 05 May 2019

IND number: 127692; EudraCT number: 2017-002976-24

EMA Decision number of Pediatric Investigation Plan: Not applicable

Article 45 or 46 of 1901/2006 does not apply

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Coordinating Investigator [redacted]

Title: [redacted]

Address of Investigational Center: [redacted]

Tel: [redacted]

Coordinating Investigator	Signature	Date
[redacted]	[redacted]	05/08/2019

COORDINATING INVESTIGATOR AGREEMENT

Original Protocol Dated 13 July 2017

Amendment 03 Dated 05 May 2019

IND number: 127692; EudraCT number: 2017-002976-24

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Coordinating Investigator [redacted]

Title: [redacted]

Address of Investigational Center: [redacted]

Tel: [redacted]

Coordinating Investigator	**Signature**	**Date**
[redacted]	[redacted]	May 5, 2019

CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS

Sponsor's Authorized Representative	[redacted]
Legal Representative of the Sponsor in the EU	[redacted]
For protocol issues, contact the following study leaders (right) **Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study**	[redacted] Tel [redacted] Email: [redacted] [redacted] Tel: [redacted]
Study Principal Investigator	[redacted] Tel: [redacted] [redacted] Tel: [redacted]
For medical issues, contact the following physicians (right) **Sponsor's Representative of Global Patient Safety and Pharmacovigilance** For **serious adverse events:** Send by email to the local safety officer/contract research organization (LSO/Syneos Health). The email address will be provided in the serious adverse event report form. In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.	[redacted] USA Tel: [redacted] Cell: [redacted] Email: [redacted] [redacted]

	[redacted]
For operational issues, contact the Head of Operations listed (right) **Sponsor's Clinical Operations Contact**	[redacted]
For serious adverse events	Send by e-mail to the local safety officer (LSO)/Syneos Health. The email address will be provided in the serious adverse event report form. In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.
Central Institutional Review Board	Copernicus Group IRB 1 Triangle Drive Durham, NC 27709 USA
Central Clinical Laboratory	Q2 Solutions (Quest) LLC 27027 Tourney Road, Suite 2E Valencia, CA 91355 USA

Electronic Data Capture	Medidata RAVE (through Syneos Health)
Contract Research Organization	Syneos Health, LLC 1030 Sync Street Morrisville, NC 27560 USA
Central Electrocardiogram Evaluation	ERT 1818 Market Street 10th Floor Philadelphia, PA 19103 USA
Integrated Response Technology	Endpoint 55 Francisco Street, Suite 200 San Francisco, CA 94133 USA
ePRO, eCOA, and Scales Training	Bracket Global, LLC 575 East Swedesford Road, Suite 200 Wayne, PA 19087 USA

CLINICAL STUDY PROTOCOL SYNOPSIS

Study TV50717-CNS-30060

Title of Study: A Well-Controlled, Fixed-Dose Study of TEV-50717 (Deutetrabenazine) for the Treatment of Tics Associated with Tourette Syndrome

Sponsor: Teva Branded Pharmaceutical Products R&D, Inc., 41 Moores Road, Frazer, Pennsylvania 19355 United States of America

Sponsor's Development Partner: Nuvelution TS Pharma, INC., 601 Gateway Boulevard Suite 1270, South San Francisco, California 94080, United States of America

Investigational New Drug (IND) Number: 127692

EudraCT Number: 2017-002976-24

EMA Decision number of Pediatric Investigation Plan: Not applicable

Article 45 or 46 of 1901/2006 does not apply

Name of Test Investigational Medicinal Product (IMP): TEV-50717 (previously SD-809)

EudraVigilance (EV) code for the IMP, if applicable: SUB179485

Type of the Study: Efficacy and Safety Study (Phase 3)

Indication: Treatment of Tourette syndrome (TS)

Is this study conducted to investigate the New Use of an approved, marketed product? Yes

Number of Investigational Centers Planned: Approximately 55

Countries Planned: North America, Latin America, Australia, Ukraine, South Korea, and Europe

Planned Study Period: Planned start in January 2018 with a duration of approximately 17 months

Number of Patients Planned (total): 150 (50 per treatment arm; TEV-50717 [high]:TEV-50717 [low]: placebo randomized 1:1:1 ratio)

Study Population: Male and female patients between 6 and 16 years of age (inclusive) with tics associated with Tourette syndrome

Primary and Secondary Objectives and Endpoints

The purpose of the study is to determine whether TEV-50717 is effective in the treatment of tics associated with TS in male and female patients between 6 and 16 years of age.

Objectives	Endpoints
The **primary objective** of the study is to evaluate the efficacy of fixed doses of TEV-50717 to reduce motor and phonic tics associated with Tourette Syndrome (TS).	The primary efficacy endpoint is the change in the Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS) from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients.
Secondary objectives	The secondary efficacy endpoints are as follows: 1. change in the Tourette Syndrome-Clinical Global Impression (TS-CGI) score from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients 2. change in the TTS of the YGTSS from baseline to week 8 for low-dose TEV-50717 and placebo will be tested 3. change in the TS-CGI score from baseline to week 8 between low-dose TEV-50717-treated patients and placebo-treated patients 4. change in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) score from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients 5. change in the TS-PGII score from baseline to week 8 between low-dose TEV-50717-treated patients and placebo-treated patients 6. change in the Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life- scale (C&A-GTS-QOL) activities of daily living (ADL) subscale from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients 7. change in the C&A-GTS-QOL ADL subscale from baseline to week 8 between low-dose TEV-50717-treated patients and placebo-treated patients The hierarchy of testing of secondary endpoints regarding dose level to control type I error is specified in the section entitled **"**Analysis of Key Secondary Endpoints."

Exploratory Endpoints:

[redacted]

Safety Endpoints:

Objectives	Endpoints
A **secondary objective** is to evaluate the safety and tolerability of TEV-50717.	The safety endpoints are as follows: • incidence of adverse events • observed values and changes from baseline in vital signs • observed values and change from baseline in the Children's Depression Inventory Second Edition (CDI-2; Parent and Self-report Profiles) • observed values in the children's Columbia Suicide Severity Rating Scale (C-SSRS) • observed values and changes from baseline in electrocardiogram (ECG) parameters and shifts from baseline for clinically significant abnormal findings • observed values and changes from screening in clinical laboratory parameters (hematology, chemistry, and urinalysis) In addition to routine monitoring of adverse events, clinical laboratory

Objectives	Endpoints
	parameters, 12-lead ECGs and safety scales, an independent Data Monitoring Committee will monitor safety during the conduct of the study.

Pharmacokinetic Endpoint:

The pharmacokinetics of the alpha-dihydrotetrabenazine (α-HTBZ) and beta-dihydrotetrabenazine (β-HTBZ) metabolites of TEV-50717 will be explored based on sparse sampling (2 samples) at week 8.

General Study Design: This is a Phase 3, randomized, double-blind, placebo-controlled, 8-week treatment study in which patients with tics associated with TS will be invited to participate. Patients will be randomized to low-dose TEV-50717, high-dose TEV-50717, or placebo (1:1:1). The target dose for each patient receiving TEV-50717 will be based on the group to which they are randomized, body weight at baseline, and cytochrome P450 2D6 (CYP2D6) impairment status. Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor or are a CYP2D6 poor metabolizer based on blinded assessment of CYP2D6 genotype at baseline. CYP2D6 status will be used by Interactive Response Technology (IRT) for randomization into the study.

Prescreening period (up to 3 months before baseline): For patients who require discontinuation of certain prohibited concomitant medications 3 months before baseline (depot neuroleptics, botulinum toxin, or tetrabenazine), informed consent/assent, depending on the child's age, as appropriate, should be obtained prior to discontinuing the prohibited medication.

Screening period (up to 31 days): After informed consent/assent, depending on the child's age, as appropriate, is obtained, patients who are stable from a medical and psychiatric standpoint will undergo a screening evaluation, including medical history, physical and neurological examination, laboratory testing, and 12-lead ECG, along with rating scales to assess severity, frequency, and impairment of tics and comorbid TS symptoms and behavioral status. The Mini International Neuropsychiatric Interview for Children and Adolescents (MINI Kid), is a short questionnaire (largely yes/no questions) to screen for clinically significant underlying psychiatric illness that may affect the subject's eligibility. The assessment will focus on detecting major depression, mania/hypomania, obsessive/compulsive disorder, alcohol and substance abuse, attention deficit hyperactivity and conduct disorders, and psychotic disorders.

At the discretion of the investigator, the screening visit may be divided into 2 visits to reduce the burden on patients. If the screening visit is divided into 2 visits, the blood sample should be obtained during the first of the 2 visits. Patients will return to the clinic on day 1 for baseline procedures and to re-confirm eligibility. Patients may be rescreened 1 time if there is a change in the status of the patient regarding eligibility for the study. (Note: Details of rescreening must be approved and documented by the medical monitor and/or Clinical Surveillance and Training [CST] team.)

YGTSS Rater Certification: All investigators and sub-investigators who will be administering the YGTSS from screening through the end of study visit must undergo and pass a Rater Certification Program which will be provided separately from this protocol. Every effort must be made to ensure that the same certified rater administers the YGTSS to a specific patient at all visits, especially at the baseline and week 8/early termination visits. However, if due to

unforeseen circumstances the same rater is absolutely unavailable to complete a visit rating, the YGTSS can be administered only by another certified individual from that study site.

Treatment period (8 weeks): Patients who continue to remain eligible for participation in the study will be randomized at the baseline visit (day 1) and will receive blinded IMP to begin that same day (day 1) with food. Tablets should be taken with food (eg, a snack) and should not be taken on an empty stomach. Patients and their caregiver/adult will interact regularly with the clinical research staff, either by telephone contact or clinic visit to assure adherence with study procedures and to evaluate safety and efficacy. To this end, clinic visits will be performed at weeks 2, 4, and 8 after baseline, in order to evaluate safety; assess tic severity with the YGTSS, TS-CGI, TS-PGII, and the C&A-GTS-QOL; and perform safety rating scales to augment adverse event reporting, concomitant medication usage, clinical laboratory examination, and 12-lead ECGs. Telephone contacts will occur at the end of weeks 1, 3, 6, and 7.

As this is a fixed-dose study, patients will undergo dose escalation (ie, forced titration) to their target dose over the first 4 weeks of treatment. If a patient experiences depression, suicidal ideation or behavior, anxiety, akathisia, parkinsonism, or somnolence, or any other adverse event that interferes with daily activity, or any adverse event that is related to IMP, a single dose reduction is permitted. The investigator must discuss any further dose adjustments (eg, holding the dose or doses) with the medical monitor.

In case of such an adverse event, the investigator will determine if a dose reduction or suspension is necessary. If a determination is made that a dose reduction or suspension is required, the medical monitor must be contacted. All available information, including the patient and caregiver/adult reports of adverse events, the clinical assessment of safety by the investigator, and information from rating scales should be incorporated in the decision. This reduced dose will become the patient's dose for the remainder of the study.

Patients will return to the clinic at week 8 for the final on-treatment assessment of safety and efficacy. At this visit, patients will undergo a complete evaluation, including performance of all efficacy measures, including assessment of tic severity with the YGTSS; and complete safety testing, including physical and neurological examination, safety laboratory testing, 12-lead ECG, and all rating scales. In addition, patients will undergo pharmacokinetic sampling at week 8, at which time 2 pharmacokinetic specimens will be obtained 2 to 3 hours apart. Prior to the clinic visit on week 8, patients will be reminded to record in their diary the start time of their last meal and the time of their last dose of study medication before the week 8 visit. The site will document the date and time of the sample collection.

Follow-up: All patients will discontinue IMP at the week 8 visit and will return 1 week later for evaluation of safety and tic reduction (week 9).

Patients who complete the study may be eligible to begin participation in an open-label safety extension study of TEV-50717 (Study TV50717-CNS-30047). For this study, the follow-up period is defined as 1 week of washout for patients who will participate in the open-label safety extension Study TV50717-CNS-30047 and 2 weeks after the last dose of IMP (1 week after the end of the washout period) for patients who will not roll over into the open-label safety extension Study TV50717-CNS-30047. Patients not participating in the open-label safety extension study for TEV-50717 will have a follow-up telephone contact for safety evaluation 1 week after the end of the treatment period (2 weeks after their last dose of IMP).

Prohibited drugs will remain the same during the washout period for patients who will participate in the open-label extension Study TV50717-CNS-30047. Patients who will not participate in the extension study may begin/resume tic therapy medication after the first week of the washout period.

Brief Summary of Study Design for the Trial Registry(s):

Standard placebo-controlled, double-blind study design (TEV-50717 [low dose and high dose] vs. placebo in a 1:1:1 ratio) was chosen to determine whether IMP treatment results in a statistically significant effect on the tics in patients with TS.

Method of Randomization and Blinding: Patients will be randomly assigned to receive treatment with TEV-50717 (low dose, high dose) or matching placebo in a 1:1:1 ratio using an IRT based on their baseline weight and CYP impairment status. The patients will be stratified into 2 age groups (6- to 11-years and 12- to 16-years). The sponsor will monitor enrollment in age strata to ensure there is adequate representation in each stratum. Patients and investigators will remain blinded to treatment assignment during the study. In addition, the sponsor's clinical personnel and all vendors (with the exception of the IRT vendor and the bioanalytical sample analysis vendor) involved in the study will be blinded to the IMP identity until the database has been locked for analysis and the treatment assignments are revealed. However, if a prioritized sample analysis is needed, bioanalytical personnel may be unblinded. After unblinding of this study, the study site may remain blinded to patient treatment assignments until completion of the safety extension Study TV50717-CNS-30047.

Investigational Medicinal Products: Dose, Pharmaceutical Form, Route of Administration, and Administration Rate

Test IMP: TEV-50717 (previously SD-809), deutetrabenazine

Daily Dose of IMP by Baseline Body Weight Category, CYP2D6 Impairment, and Study Week

Dose group **Baseline weight (kg)**	**Daily dose (mg) at the start of visit/week**[a]			
	Week 1 (Days 1-7)	**Week 2 (Days 8-14)**	**Week 3 (Days 15-21)**	**Week 4 main dose (Days 22-28) to Week 8 main dose (Days 50-56)**
Low dose				
≥40	12	24	30	36
≥40, CYP impaired	6	12	18	18
30 to <40	6	12	18	24
30 to <40, CYP impaired	6	12	12	12
20 to <30	6	12	18	18
20 to <30, CYP impaired	6	6	6	6
High dose				
≥40	12	24	36	48

Dose group Baseline weight (kg)	Daily dose (mg) at the start of visit/week[a]			
	Week 1 (Days 1-7)	Week 2 (Days 8-14)	Week 3 (Days 15-21)	Week 4 main dose (Days 22-28) to Week 8 main dose (Days 50-56)
≥40, CYP impaired	6	15	24	30
30 to <40	12	24	30	36
30 to <40, CYP impaired	6	12	18	18
20 to <30	12	18	24	30
20 to <30, CYP impaired	6	12	12	12

[a] Administration of a given dose will take place throughout the days indicated. The new dose starts the morning after the telephone contact or the morning after the clinic visit.

CYP impaired=patients who are receiving a strong CYP2D6 inhibitor or who are a CYP2D6 poor metabolizer.

Placebo IMP: Placebo tablets match TEV-50717 tablets

Duration of Patient Participation and Maximal Exposure to IMP: This study will consist of a prescreening period of up to 3 months, a screening period of up to 31 days, an 8-week double-blind treatment period, and a follow-up period. For this study, the follow-up period is defined as 1 week of washout for patients who will participate in the open-label safety extension Study TV50717-CNS-30047 and 2 weeks after the last dose of IMP (1 week after the end of the washout period) for patients who will not roll over into the open-label safety extension Study TV50717-CNS-30047. Patients who complete the study may be eligible 1 week after their last dose of IMP to begin participation in an open-label safety extension study of TEV-50717. Patients not participating in the open-label safety extension study for TEV-50717 will have a follow-up telephone contact to evaluate safety 2 weeks after their last dose of IMP. Patients are expected to participate in this study for its entire duration, which is a minimum of 11 weeks and a maximum of 14 weeks.

Study Duration: Approximately 17 months from January 2018

End of Study: End of study is defined as the date of the week 10 telephone contact with the last participant.

Plans for Treatment or Care after the Patient Has Ended Participation in the Study: Patients who complete the study may be eligible to begin participation in an open-label safety extension study of TEV-50717 (Study TV50717-CNS-30047).

Inclusion Criteria: Patients may be included in the study only if they meet all of the following criteria:

a. Patient is 6 to 16 years of age, inclusive, at baseline.
b. Patient weighs at least 44 pounds (20 kg) at baseline.
c. Patient meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V™) diagnostic criteria for TS and, in the opinion of the investigator, patient, and caregiver/adult, the patient's active tics are causing distress or impairment.

d. Patient has a TTS of 20 or higher on the YGTSS at screening and baseline.
e. Patient is able to swallow study medication whole.
f. Patient and caregiver/adult are willing to adhere to the medication regimen and to comply with all study procedures.
g. Patient is in good general health, as indicated by medical and psychiatric history as well as physical and neurological examination.
h. In the investigator's opinion, the patient and caregiver/adult have the ability to understand the nature of the study and its procedures, and the patient is expected to complete the study as designed.
i. Patient and caregiver/adult provided written informed consent/assent, depending on the child's age, as appropriate, according to local regulations.
j. Females who are postmenarchal or ≥12 years of age may be included only if they have a negative beta-human chorionic gonadotropin (β-HCG) test at baseline or are sterile.
k. Females who are postmenarchal or ≥12 years of age whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study (ie, starting at screening) and for 30 days or 5 half-lives, whichever is longer after last dose of IMP.
l. The patient must be willing and able to comply with study restrictions and to remain at the clinic for the required duration during the study period and willing to return to the clinic for the follow-up evaluation as specified in this protocol.

Exclusion Criteria: Patients will be excluded from participating in this study if they meet any of the following criteria:

a. Patient has a neurologic disorder other than TS that could obscure the evaluation of tics.
b. The patient's predominant movement disorder is stereotypy (coordinated movements that repeat continually and identically) associated with autism spectrum disorder.
c. Patient has clinically significant obsessive-compulsive disorder (OCD) at baseline that, in the opinion of the investigator, is the primary cause of impairment.
d. Patient has clinically significant depression at screening or baseline.

   Note: Patients receiving antidepressant therapy may be enrolled if on a stable dose for at least 6 weeks before baseline.
e. Patient has a history of suicidal intent or related behaviors within 2 years of screening:
   - previous intent to act on suicidal ideation with a specific plan, irrespective of level of ambivalence, at the time of suicidal thought
   - previous suicidal preparatory acts or behavior
f. Patient has a history of a previous actual, interrupted, or aborted suicide attempt.
g. Patient has a first-degree relative who has completed suicide.
h. Patient has a confirmed diagnosis of bipolar disorder, schizophrenia, or another psychotic disorder.

i. Patient has a DSM diagnosis based on the Mini International Neuropsychiatric Interview For Children and Adolescents Inventory at screening that, in the opinion of the investigator, makes the patient unsuitable for the study.

j. Patient has received Comprehensive Behavioral Intervention for Tics for TS or Cognitive Behavioral Therapy for OCD within 4 weeks of screening.

k. Patient has received any of the following concomitant medications for tics within the following specified exclusionary windows of first dose:

- within 3 months: depot neuroleptics, botulinum toxin, or tetrabenazine
- within 4 weeks: cannabidiol oil and valbenazine
- within 21 days: reserpine
- within 14 days: neuroleptics (oral), typical and atypical antipsychotics, metoclopramide, levodopa, and dopamine agonists

  Note: Use of stimulant medications, including amphetamine, methylphenidate, and lisdexamfetamine, is allowed if primary use is for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), dosing has been stable for at least 2 weeks before screening, and no changes to dose or frequency are anticipated during the course of the study.

  Note: Use of atomoxetine is allowed if the primary use is for the treatment of ADHD, dosing has been stable for at least 4 weeks before screening, and no changes to dose or frequency are anticipated during the course of the study.

  Note: Use of benzodiazepines is allowed if primary use is not for tics and dosing has been stable for at least 4 weeks before screening.

  Note: Use of topiramate (up to 200 mg/day) is allowed if dosing has been stable for at least 4 weeks before screening.

  Note: Use of guanfacine or clonidine is allowed regardless of indication (ie, if prescribed for tics or TS) if the dosing has been stable for at least 4 weeks before screening and no changes to dose or frequency are anticipated during the course of the study. If discontinuation of either medication is anticipated due to ineffectiveness, poor tolerability, or patient/caregiver preference, discontinuation should occur 4 or more weeks prior to the screening visit.

l. Patient has received treatment with deep brain stimulation, transmagnetic stimulation, or transcranial direct current stimulation within 4 weeks of the screening visit for reduction of tics.

m. Patient has a QT interval corrected for heart rate using Fridericia's formula (QTcF) interval value >450 msec (males) or >460 msec (females), or >480 msec (with right bundle branch block) on a 12-lead electrocardiogram (ECG) at screening, or requires treatment with drugs known to prolong the QT interval.

n. Patient has a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure.

o. Patient has evidence of hepatic impairment, as indicated by the following:

- aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 × the upper limit of the normal range (ULN) at screening
- alkaline phosphatase (ALP) or total bilirubin >2 × ULN at screening

Note: Patients with Gilbert's syndrome are eligible to participate if approved by the medical monitor.

Note: Patients with abnormalities in 2 or more of the following clinical laboratory parameters must be approved for enrollment by the medical monitor: AST, ALT, ALP, and total bilirubin.

p. Patient has evidence of clinically significant renal impairment, indicated by a serum creatinine >1.5 × ULN at screening.
q. Patient has received a monoamine oxidase inhibitor within 14 days of the baseline visit.
r. Patient has a known allergy to any of the components of the IMP product.
s. Patient has participated in an investigational drug or device study and received IMP/intervention within 30 days or 5 drug half-lives of baseline, whichever is longer.
t. Patient is a pregnant or lactating female or plans to be pregnant during the study.
u. Patient has a history of or acknowledges alcohol-related disorder in the previous 12 months, as defined in the DSM-V™.
v. Patient has a positive urine drug screen test result or is unable to refrain from substance abuse throughout the study.

Statistical Considerations

Sample Size Rationale: It is estimated that approximately 50 patients per arm will enable a power of at least 90% to detect a beneficial standardized effect of 68% or more when the TEV-50717 arm is compared to placebo (difference of 6.5 in the change from baseline to week 8 in TTS, assuming a standard deviation of 9.5 in each arm) in a 2-sided type I error rate of 5% after accounting for potential dropouts.

Analysis of Primary Endpoint: The primary efficacy endpoint for this study is the change in the TTS of the YGTSS from baseline to week 8 between high-dose TEV-50717-treated and placebo-treated patients. The primary analysis will be a mixed-model repeated-measures model with the change in the TTS as the dependent variable. The model will include fixed effects for treatment group, week (3 levels: weeks 2, 4, and 8), and the treatment group-by-week interaction. The baseline TTS, region, and age group at baseline (2 levels: 6 to 11 years, 12 to 16 years) will be included as covariates. The unstructured covariance matrix for repeated observations within patients will be used. The least squares means of the change in TTS from baseline at week 8 will be compared between the high-dose treatment arm and the placebo arm using a 2-sided test at the alpha = 0.05 level of significance. In addition, actual values and changes in the TTS from baseline to each visit will be summarized using descriptive statistics.

Analysis of Key Secondary Endpoints: A hierarchical (fixed-sequence) testing approach will be used for the analysis of the key secondary endpoints. If an endpoint is not statistically significant, confirmatory hypothesis testing will not be carried out on the remaining hypotheses, and remaining hypotheses will be considered exploratory rather than confirmatory. The following analyses of key secondary endpoints will be conducted:

1. The change from baseline to week 8 in TS-CGI will be analyzed using a similar model as the primary analysis; however, instead of change in YGTSS TTS as the dependent variable and baseline YGTSS TTS as a covariate, the corresponding TS-CGI values will be used. The comparison between high-dose TEV-50717 and placebo will be tested.
2. Using the same model as for the primary analysis, the comparison between the change in the TTS of the YGTSS from baseline to week 8 for low-dose TEV-50717 and placebo will be tested.
3. Using the same model as described in endpoint #1 above for TS-CGI, the comparison between the change in the TS-CGI values from baseline to week 8 for low-dose TEV-50717 and placebo will be tested.
4. The change from baseline to week 8 in TS-PGII will be analyzed using a Cochran-Mantel-Haenszel row mean score test with modified ridit scoring controlling for age group. The comparison between high-dose TEV-50717 and placebo will be tested.
5. Using the same model as described in endpoint #4 above for TS-PGII, the comparison between the change in the TS-PGII values from baseline to week 8 for low-dose TEV-50717 and placebo will be tested.
6. The change from baseline to week 8 in C&A-GTS-QOL ADL subscale will be analyzed using a similar model as the primary analysis; however, instead of change in YGTSS TTS as the dependent variable and baseline YGTSS TTS as a covariate, the corresponding C&A-GTS-QOL ADL subscale values will be used. The comparison between high-dose TEV-50717 and placebo will be tested.
7. Using the same model as described in endpoint #6 above for C&A-GTS-QOL ADL subscale, the comparison between the change in the C&A-GTS-QOL ADL subscale scores from baseline to week 8 for low-dose TEV-50717 and placebo will be tested.

Exploratory Analyses:

[redacted]

Multiple Comparisons and Multiplicity: The hierarchical testing method will be used to maintain the experiment-wise type I error of 5% level for the primary and key secondary analyses. The primary efficacy endpoint will first be tested at the 5% type I error level. If the p-value of the primary analysis is ≤0.05, the secondary hypotheses will be tested in the order listed for the analysis of key secondary endpoints until either an analysis produces a p-value >0.05 or all analyses result in a p-value ≤0.05.

Analysis of Pharmacokinetic Endpoint: Samples collected for pharmacokinetic analysis will be quantified for α-HTBZ and β-HTBZ metabolite plasma concentrations and will be pooled with previous data and analyzed using population pharmacokinetic techniques. Analysis methods will be detailed in a separate population pharmacokinetic analysis plan. Exploratory pharmacokinetic/pharmacodynamic (PD) analysis may be performed on PD/safety endpoints.

Safety Analyses: All adverse events will be coded using the Medical Dictionary for Regulatory Activities. Each patient will be counted only once in each preferred term or system organ class category for the analyses of safety. Summaries will be presented for all adverse events, adverse events determined by the investigator to be related to study treatment, serious adverse events, and adverse events causing withdrawal from the study. Summaries will be presented by treatment group and for all patients. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

Observed values and changes from baseline in laboratory results and vital signs will be summarized descriptively.

Observed values in ECG parameters will be summarized, and counts and percentages of abnormal findings will be presented. In addition, the number and percentage of patients with on-treatment QTcF values >450, >480, or >500 msec and change from baseline >30 or >60 msec will be presented.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with IMP.

Observed values in the C-SSRS and observed values and changes from baseline in the CDI-2 (Parent and Self-report Profiles) will be presented by treatment group for all patients.

Sensitivity Analysis: Sensitivity analyses of primary and key secondary endpoints will be conducted using the per-protocol analysis set. Sensitivity analyses for missing data and the statistical model will be provided in the statistical analysis plan.

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Abbreviation	Term
α-HTBZ	alpha-dihydrotetrabenazine
β-HTBZ	beta-dihydrotetrabenazine
β-HCG	beta-human chorionic gonadotropin
λ_z	apparent plasma terminal elimination rate constant
ADHD	Attention Deficit Hyperactivity Disorder
ALT	alanine aminotransferase (SGPT)
ALP	alkaline phosphatase
AST	aspartate aminotransferase (SGOT)
AUC	area under the plasma concentration-time curve
AUC_{0-t}	area under the plasma concentration-time curve from time 0 to the time of the last measurable IMP concentration
AUC_{0-tmax}	area under the plasma concentration-time curve from time 0 to the time of median t_{max}
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time 0 to infinity
BLA	Biological License Application
BMI	body mass index
BP	blood pressure
CA	Competent Authority
CDI-2	Children's Depression Inventory Second Edition
CDMS	clinical data management system
CFR	Code of Federal Regulations (USA)
CGI-C	Clinical Global Impression of Change
CIOMS	Council for International Organizations of Medical Sciences
CL/F	apparent total plasma clearance (except for metabolites)
C_{max}	maximum observed concentration
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CST	Clinical Surveillance and Training

Abbreviation	Term
CTA	Clinical Trial Application
CTFG	Clinical Trial Facilitation Group
[redacted]	[redacted]
CYP	cytochrome P4502D6
C&A-GTS-QOL	Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life scale
DMC	Data Monitoring Committee
DSM-V™	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EC	Ethics Committee
ECG	electrocardiogram
EMA	European Medicines Agency
ERA	European Regulatory Affairs
EU	European Union
EudraCT	European Clinical Trials
EV	EudraVigilance
GCP	Good Clinical Practice
GCO	Global Clinical Operations
GPSP	Global Patient Safety and Pharmacovigilance
GQA	Global Quality Assurance
GRA	Global Regulatory Affairs
[redacted]	[redacted]
HD	Huntington disease
IB	Investigator's Brochure
ICF	informed consent form
ICH	The International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IND	Investigational New Drug
INN	international nonproprietary name
IRB	Institutional Review Board
ITT	intent-to-treat
LAM	lactational amenorrhea methods

Abbreviation	Term
LSO	local safety officer
MAA	Marketing Authorisation Application
MINI Kid	Mini International Neuropsychiatric Interview for Children and Adolescents
mITT	modified intent to treat
MTD	maximum tolerated dose
[redacted]	[redacted]
n	number
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIMP	Non-Investigational Medicinal Products
NOAEL	no-observed-adverse-effect level
OCD	obsessive-compulsive disorder
OTC	over-the-counter
PD	pharmacodynamics
PGx	pharmacogenetics
PND	postnatal day
PP	per-protocol
QTcF	QT interval corrected for heart rate using Fridericia's formula
RA	Regulatory Affairs
RSI	reference safety information
RTSM	Randomization and Trial Supply Management
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOP	Standard Operating Procedure
SpO_2	saturation of peripheral oxygen
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	elimination half-life
TD	tardive dyskinesia
TS	Tourette syndrome
TS-CGI	Tourette Syndrome-Clinical Global Impression
TS-PGII	Tourette Syndrome-Patient Global Impression of Impact
[redacted]	[redacted]
TTS	Total Tic Score

Abbreviation	Term
UDS	urine drug screen
ULN	upper limit of normal
US	United States (of America)
USA	United States of America
V	visit
VAS	visual analog scale
V_z/F	apparent total volume of distribution (except for metabolites)
[redacted]	[redacted]
W	week
WHO	The World Health Organization
WHO Drug	World Health Organization Drug Dictionary
YGTSS	Yale Global Tic Severity Scale

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Introduction

Tourette syndrome (TS) is a neurodevelopmental disorder characterized by multiple motor and phonic tics that frequently co-occurs with a variety of behavioral and psychiatric problems (Jankovic 2001, Jankovic and Kurlan 2011). Studies have suggested that the prevalence estimates of TS among children vary widely from 0.4% to 5% in community samples (Bitsko et al 2014). Tics are classified as either simple or complex; simple motor tics include eye blinks, shoulder shrugs, while simple vocal tics include grunting, coughing, and sniffing. Complex motor tics include touching/tapping and walking in patterns, while complex vocal tics include echolalia (repeating another's speech) and coprolalia (shouting obscenities or profanities) (Jankovic 2001, Shaw and Coffey 2014). TS was thought to be a psychogenic disorder until improvement with neuroleptics was first observed in the 1960s, leading to the theory of central dopaminergic hyperactivity as a possible mechanism of tics associated with TS. When the symptoms impair function, most physicians utilize alpha adrenergic drugs (guanfacine and clonidine), typical neuroleptics (haloperidol, pimozide, and fluphenazine), or atypical neuroleptics (olanzapine, ziprasidone, and aripiprazole) to control tics (Gilbert and Jankovic 2014, Wijemanne et al 2014). In the United States of America (USA), haloperidol and pimozide are approved for the treatment of tics associated with TS, while aripiprazole carries a broader indication of "for the treatment of TS". Neuroleptics have the potential for serious adverse effects, including tardive dyskinesia (TD), which typically manifests as an irreversible orofacial stereotypy, and other forms of hyperkinetic movement disorder (Waln and Jankovic 2013). Up to 25% of adults chronically treated with dopamine receptor antagonists (neuroleptics; including the so-called "atypical" neuroleptics, such as aripiprazole) eventually develop TD (Jankovic 1995, Pasricha et al 2006, Peña et al 2011). Although elderly individuals, especially women, are particularly susceptible to developing TD, this iatrogenic condition may also rarely occur in children (Mejia and Jankovic 2010). Tetrabenazine, which depletes dopamine presynaptically, has been shown to be effective in treating the tics associated with TS (Jain et al 2006, Jankovic 2015, Jankovic and Beach 1997, Kenney et al 2007, Paleacu et al 2004, Porta et al 2008), but has not been documented to cause TD in clinical use.

While generally effective in reducing the tics of TS, tetrabenazine is associated with frequent adverse events, including somnolence, nausea, depression, insomnia, and parkinsonism, that may limit its utility. Moreover, tetrabenazine is an immediate-release formulation with the following limitations: (1) adverse events of tetrabenazine, such as somnolence, akathisia, and anxiety, are often associated with peak concentration after dosing; (2) the active metabolites have short half-lives, with the attendant requirement to dose the immediate-release formulation frequently; and (3) the active metabolites alpha-dihydrotetrabenazine (α-HTBZ) and beta-dihydrotetrabenazine (β-HTBZ) are either primarily (α) or exclusively (β) metabolized by cytochrome P450 2D6 (CYP2D6). Polymorphisms in the CYP2D6 gene necessitate genotyping to prevent poor metabolizers from experiencing significantly greater exposure to the active drug moiety than extensive metabolizers (Mehanna et al 2013).

To address the limitations of commercial tetrabenazine (XENAZINE®), Auspex, a wholly owned subsidiary of Teva Pharmaceutical Products R&D, Inc, developed deutetrabenazine (referred to

as TEV-50717, previously SD-809) that is eliminated more slowly than tetrabenazine. TEV-50717 has been shown to reduce plasma fluctuation and dosing frequency and thus has the potential to improve overall tolerability as compared to that of tetrabenazine. Data in patients receiving TEV-50717 for the treatment of chorea associated with Huntington disease (HD) demonstrate a favorable safety profile with low rates of neuropsychiatric adverse events. In TS patients with troublesome motor and phonic tics, preliminary efficacy and safety data for TEV-50717 have been generated in an open-label, Phase 1b pilot study (Study SD-809-C-17). Results of this study are summarized in Section 1.3.2.2 and support further development of TEV-50717 for treatment of tics associated with TS.

TEV-50717 was approved for the treatment of chorea associated with HD and for the treatment of TD on 03 April 2017 and 30 August 2017, respectively.

The purpose of the study is to determine whether TEV-50717 is effective in the treatment of tics associated with TS in male and female patients between 6 and 16 years of age.

1.2. Name and Description of Investigational Product

TEV-50717 (deutetrabenazine), the investigational medicinal product (IMP), is a vesicular monoamine transporter 2 (VMAT2) inhibitor with the chemical name (RR, SS)-1,3,4,6,7,11b-hexahydro-9, 10-di(methoxy-d3)-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-one. TEV-50717 tablets are available in the following dose strengths: 6, 9, 12, 15, and 18 mg, all of which are identical in size, shape, and color (white). The IMP will be supplied in 40-count tablets per dose strength per blister pack.

1.3. Findings from Nonclinical and Clinical Studies

Brief summaries of nonclinical pharmacology, pharmacokinetics, and toxicology studies and clinical studies are provided in the following sections. More detailed information is provided in the Investigator's Brochure (IB).

1.3.1. Nonclinical Studies

The key nonclinical study findings are provided below, with details available in the IB.

1.3.1.1. Nonclinical Pharmacology

TEV-50717 is a selectively deuterium-substituted VMAT2 inhibitor structurally related to tetrabenazine. The metabolites formed from TEV-50717 (α-HTBZ and β-HTBZ) are potent inhibitors of VMAT2 binding, with K_i values of 3.8 and 22 nM, respectively, that are similar to previously reported values of their corresponding non-deuterated forms (Scherman et al 1988). Off-target binding occurs at a similar extent with deuterated and non-deuterated α-HTBZ and β-HTBZ. TEV-50717 and tetrabenazine in male rats at doses resulting in similar systemic exposure to the test articles (α-HTBZ and β-HTBZ) produced similar, expected, exaggerated central nervous system pharmacological effects. In particular, the adverse event of catalepsy, a known response in rats to drugs which reduce central nervous system dopamine concentrations (Fuenmayor and Vogt 1979), was similar in magnitude after TEV-50717 and tetrabenazine administration.

1.3.1.2. Nonclinical Pharmacokinetics and Drug Metabolism

In human liver S9, the metabolite profile of TEV-50717 overlapped with that of tetrabenazine. In a clinical comparative human [^{14}C]-absorption, distribution, metabolism, and excretion and mass-balance study, the approximately 22 metabolites of TEV-50717 were also metabolites of tetrabenazine. Thus, previous clinical experience with tetrabenazine provides predictive information about the safety of TEV-50717 and its metabolites.

Tetrabenazine, α-HTBZ, and β-HTBZ, and by extension, their deuterated forms, do not inhibit or induce cytochrome P450 (CYP) isoenzymes at clinically relevant concentrations (XENAZINE Prescribing Information 2015). M1, a minor metabolite that may circulate in greater concentrations as a metabolite of TEV-50717 as compared to tetrabenazine, is neither an inhibitor of major CYP isozymes or transporters nor an inducer of CYP isozymes. M4, a major metabolite of tetrabenazine and TEV-50717 is neither an inhibitor of major CYP isozymes or transporters nor an inducer of CYP isozymes.

1.3.1.3. Toxicology

General and Reproductive Adult Toxicology: Oral administration of TEV-50717 in rats reduced body weight gain, increased mammary hyperplasia, and produced estrous cycle changes, all of which occurred with tetrabenazine at doses that produced similar systemic exposures to test articles and metabolites. Mammary and estrus effects are likely consequences of reduced central dopamine and subsequent increased prolactin, consistent with information in the XENAZINE (tetrabenazine) label. Oral administration of TEV-50717 in pregnant rats did not produce test article-related embryofetal toxicities, even at doses that led to reduced body weight gain in dams. Oral administration of metabolite M1 to pregnant rats from gestational days 6 to 17 produced no test article-related maternal or fetal toxicities.

Genetic Toxicology: TEV-50717 and its α-HTBZ and β-HTBZ metabolites were negative in in vitro studies for mutagenicity (bacterial reverse mutation, or the Ames test) and for chromosomal structural aberrations in human peripheral blood lymphocytes. Oral doses of TEV-50717 were negative for inducing micronuclei in the bone marrow of treated mice.

Juvenile Toxicology: The effects of TEV-50717 on juvenile development was assessed in male and female rats with oral dosing from weaning (postnatal day [PND] 21) to PND 71, similar to human dosing from Year 2 through early adolescence and overlapping with TEV-50717 oral dosing in a general adult toxicology study. The effects of M1 was assessed in male and female juvenile rats from PND 25 to PND 70 with a recovery phase and postdosing reproductive assessment.

TEV-50717 produced no test-article-related effects on learning and memory functions, on histopathology assessments, on reproductive capacity (male and female fertility, estrus cyclicity), or on intrauterine survival of embryos from matings during recovery from test article administration. Adversely reduced body weight gain and adverse clinical observation of tremors and in-cage hyperactivity were all noted in previous studies with adult rats; these effects have not predicted adult clinical intolerance to TEV-50717. The highest dose level of M1 (50 mg/kg/day) produced no test article-related toxicities (clinical observations, changes in body weight gain, clinical pathology, histopathology, ophthalmology, and performance in learning and memory tests).

The NOAEL (no-observed-adverse-effect level) for toxicities in juvenile rats is lower than that in adults; however, the total (α+β)-HTBZ exposure multiples or safety margins comparing rat to humans at the adult and juvenile age categories are similar. The potential for increased sensitivity to the effects of TEV-50717 in pediatric patients is mitigated by 2 factors. First, the effects of TEV-50717 on behavior and weight gain recovered with cessation of test article administration in the juvenile rat toxicology study. Second, the clinical significance of tremors and reduced body weight gain in rats dosed with TEV-50717 are unclear because these findings were not adverse events of note in adults or adolescent patients. While hypoactivity in rats has the potential to relate to clinical observations of somnolence, this adverse effect is controlled with dose reduction. In clinical comparison, the adverse event profile of tetrabenazine in adult patients is qualitatively similar to patients from approximately 22 months to 18 years of age (Jain et al 2006, Kenney et al 2007, Porta et al 2008).

1.3.2. Clinical Studies

The clinical development plan for TEV-50717 to date includes:

- [redacted]
- [redacted]
- 1 completed Phase 3 pivotal study for the treatment of chorea associated with HD
- 1 completed Phase 3 long-term safety study in patients with HD
- 2 completed Phase 2/3 and Phase 3 studies in patients with TD
- [redacted]
- 1 completed Phase 1b study in patients with TS
- [redacted]
- [redacted]

Further details may be found in the IB.

1.3.2.1. Clinical Pharmacology Studies

Seven Phase 1 clinical pharmacology studies were conducted in healthy adult subjects. In addition, sparse pharmacokinetic sampling was included in the Phase 3 studies with HD and TD patients where a population pharmacokinetic analyses including these data have been performed to extensively evaluate both the pharmacokinetics and pharmacokinetic-pharmacodynamic relationship of TEV-50717. A summary of the clinical pharmacology findings is provided in the IB.

Pharmacometric analyses of the active metabolites of TEV-50717 based on the Phase 1 clinical pharmacology in healthy adult volunteers were performed to support dose selection and pharmacokinetic characterization in a pediatric population. Subsequently, a further pharmacometric analysis of active metabolites following administration of TEV-50717 to adolescent TS patients with tics (Study SD-809-C-17) was recently completed. The results of these analyses are described in Section 1.3.2.3.

1.3.2.2. Clinical Safety and Efficacy Studies

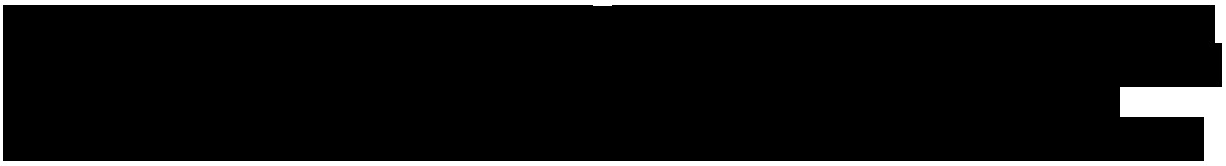
TEV-50717 has a pharmacologic activity indistinguishable from tetrabenazine, a VMAT2 inhibitor with established efficacy in treating the motor and phonic tics associated with TS.

[redacted]

1.3.2.3. Pharmacometrics Analysis of TEV-50717 Active Metabolites to Support Dose Selection and Pharmacokinetic Characterization in a Pediatric Population

Population pharmacokinetic modeling of the TEV-50717 active metabolites α-HTBZ and β-HTBZ has been performed throughout the clinical development program. Based on robust pharmacokinetic sampling data obtained in healthy volunteers in the Phase 1 program, a structural population pharmacokinetic model was developed to guide dose selection for HD patients with chorea (SD-809-CLN-076) and subsequently optimized to better describe the absorption/bioconversion profile of α-HTBZ and β-HTBZ (Study SD-809-CLN-077).

Employing the structural model defined in Study SD-809-CLN-077, sequential and sparse pharmacokinetic sampling data obtained from Study SD-809-C-17 were combined with the Phase 1 data employed in Study SD-809-CLN-077 to estimate the exposure total of (α+β)-HTBZ in adolescent patients (age 12 to 18 years) with TS and to simulate exposure in adolescent and pediatric patients (age 6 to 11 years) with and without concomitant use of a strong CYP2D6 inhibitor across a range of doses (Appendix A). Population model parameters were re-estimated for the combined Phase 1 and adolescent data obtained from patients in Study SD-809-C-17. The model was used to simulate total (α+β)-HTBZ exposures across a range of body weights corresponding to a pediatric and adolescent population according to the Centers for Disease Control growth charts.



This analysis provides the basis for the dosing recommendations in Section 5.1.

1.4. Known and Potential Benefits and Risks to Patients

1.4.1. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product

Additional information regarding benefits and risks to patients may be found in the IB and the United States prescribing information for AUSTEDO™ (deutetrabenazine).

2. STUDY OBJECTIVES AND ENDPOINTS

This is a Phase 3 study to evaluate the efficacy and safety of deutetrabenazine (TEV-50717) tablets for the reduction of motor and phonic tics associated with TS in children and adolescents 6 through 16 years of age.

2.1. Primary and Secondary Study Objectives and Endpoints

The primary and secondary study objectives and endpoints are:

Objectives	Endpoints
The **primary objective** of the study is to evaluate the efficacy of fixed doses of TEV-50717 to reduce motor and phonic tics associated with TS.	The primary efficacy endpoint is the change in the Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS) from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients.
Secondary objectives	The secondary efficacy endpoints are as follows: 1. change in the TS-CGI score from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients 2. change in the TTS of the YGTSS from baseline to week 8 for low-dose TEV-50717 and placebo will be tested 3. change in the TS-CGI score from baseline to week 8 between low-dose TEV-50717-treated patients and placebo-treated patients 4. change in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) score from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients 5. change in the TS-PGII score from baseline to week 8 between low-dose TEV-50717-treated patients and placebo-treated patients 6. change in the Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life- scale (C&A-GTS-QOL) activities of daily living (ADL) subscale from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients 7. change in the C&A-GTS-QOL ADL subscale from baseline to week 8 between low-dose TEV-50717-treated patients and placebo-treated patients The hierarchy of testing of secondary endpoints regarding dose level to control type I error is specified in the section entitled "Analysis of Key Secondary Endpoints."

2.1.1. Justification of Primary Endpoint

[redacted]

2.2. Exploratory Endpoints

[redacted]

2.3. Safety Endpoints

Objectives	Endpoints
A **secondary objective** is to evaluate the safety and tolerability of TEV-50717.	The safety endpoints are as follows: • incidence of adverse events • observed values and changes from baseline in vital signs • observed values and change from baseline in the Children's Depression Inventory Second Edition (CDI-2; Parent and Self-report Profiles) • observed values in the children's Columbia Suicide Severity Rating Scale (C-SSRS) • observed values and changes from baseline in electrocardiogram (ECG) parameters and shifts from baseline for clinically significant abnormal findings • observed values and changes from screening in clinical laboratory parameters (hematology, chemistry, and urinalysis) In addition to routine monitoring of adverse events, clinical laboratory parameters, 12-lead ECGs and safety scales, an independent Data Monitoring Committee will monitor safety during the conduct of the study.

2.4. Pharmacokinetic Endpoint

The pharmacokinetics of the α-HTBZ and β-HTBZ metabolites of TEV-50717 will be explored based on sparse sampling (2 samples) at week 8.

3. STUDY DESIGN

3.1. General Study Design and Study Schematic Diagram

This is a Phase 3, randomized, double-blind, placebo-controlled, 8-week treatment study in which patients with tics associated with TS will be invited to participate. Patients will be randomized to low-dose TEV-50717, high-dose TEV-50717, or placebo (1:1:1). The target dose for each patient receiving TEV-50717 will be based on the group to which they are randomized, body weight at baseline, and cytochrome P450 2D6 (CYP2D6) impairment status. Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor or are a CYP2D6 poor metabolizer based on blinded assessment of CYP2D6 genotype at baseline, which will be used only by IRT for randomization into the study.

Prescreening period (up to 3 months before baseline): For patients who require discontinuation of certain prohibited concomitant medications 3 months before baseline (depot neuroleptics, botulinum toxin, or tetrabenazine), informed consent/assent, depending on the child's age, as appropriate, should be obtained prior to discontinuing the prohibited medication.

Screening period (up to 31 days): After informed consent/assent, depending on the child's age, as appropriate, is obtained, patients who are stable from a medical and psychiatric standpoint will undergo a screening evaluation, including medical history, physical and neurological examination, laboratory testing, and 12-lead ECG, along with rating scales to assess severity, frequency, and impairment of tics and comorbid TS symptoms and behavioral status. The Mini International Neuropsychiatric Interview for Children and Adolescents, or MINI Kid, is a short questionnaire (largely yes/no questions) to screen for clinically significant underlying psychiatric illness that may affect the subject's eligibility. The assessment will focus on detecting major depression, mania/hypomania, obsessive/compulsive disorder, alcohol and substance abuse, attention deficit hyperactivity and conduct disorders, and psychotic disorders.

At the discretion of the investigator, the screening visit may be divided into 2 visits to reduce the burden on patients. If the screening visit is divided into 2 visits, the blood sample should be obtained during the first of the 2 visits. Patients will return to the clinic on day 1 for baseline procedures and to re-confirm eligibility. Patients may be rescreened 1 time if there is a change in the status of the patient regarding eligibility for the study. (Note: Details of rescreening must be approved and documented by the medical monitor and/or Clinical Surveillance and Training [CST] team.)

Treatment period (8 weeks): Patients who continue to remain eligible for participation in the study will be randomized at the baseline visit (day 1) and will receive blinded IMP to begin that same day (day 1). Tablets should be taken with food (eg, a snack) and should not be taken on an empty stomach. Patients and their caregiver/adult will interact regularly with the clinical research staff, either by telephone contact or clinic visit to assure adherence with study procedures and to evaluate safety and efficacy. To this end, clinic visits will be performed at weeks 2, 4, and 8 after baseline to evaluate safety; assess tic severity with the YGTSS, TS-CGI, TS-PGII, and the C&A-GTS-QOL; and perform safety rating scales to augment adverse event reporting, concomitant medication usage, clinical laboratory examination, and 12-lead ECGs. Telephone contacts will occur at the end of weeks 1, 3, 6, and 7.

As this is a fixed-dose study, patients will undergo dose escalation (ie, forced titration) to their target dose over the first 4 weeks of treatment. If a patient experiences depression, suicidal ideation or behavior, anxiety, akathisia, parkinsonism, or somnolence, or any other adverse event that interferes with daily activity, or any adverse event that is related to IMP, a single dose reduction is permitted. The investigator must discuss any further dose adjustments (eg, holding the dose or doses) with the medical monitor.

In case of such an adverse event, the investigator will determine if a dose reduction or suspension is necessary. If it is determined that a dose reduction or suspension is required, the medical monitor must be contacted. All available information, including the patient and caregiver/adult reports of adverse events, the clinical assessment of safety by the investigator, and information from rating scales should be incorporated in the decision. This reduced dose will become the patient's dose for the remainder of the study.

Patients will return to the clinic at week 8 for the final on-treatment assessment of safety and efficacy. At this visit, patients will undergo a complete evaluation, including performance of all efficacy measures (including assessment of tic severity with the YGTSS), and complete safety testing (including physical and neurological examination, safety laboratory testing, 12-lead ECG, and all rating scales). In addition, patients will undergo pharmacokinetic sampling at week 8, at which time 2 pharmacokinetic specimens will be obtained 2 to 3 hours apart. Prior to the clinic visit on week 8, patients will be reminded to record in their diary the start time of their last meal and the time of their last dose of study medication before the week 8 visit. The site will document the date and time of the sample collection.

Follow-up: All patients will discontinue IMP at the week 8 visit and will return 1 week later for evaluation of safety and tic reduction (week 9).

Patients who complete the study may be eligible to begin participation in an open-label safety extension Study TEV-50717 (Study TV50717-CNS-30047). For this study, the follow-up period is defined as 1 week of washout for patients who will participate in the open-label safety extension Study TV50717-CNS-30047 and 2 weeks after the last dose of IMP (1 week after the end of the washout period) for patients who will not roll over into the open-label safety extension Study TV50717-CNS-30047. Patients not participating in the open-label safety extension study for TEV-50717 will have a follow-up telephone contact for safety evaluation 1 week after the end of the treatment period (2 weeks after their last dose of IMP).

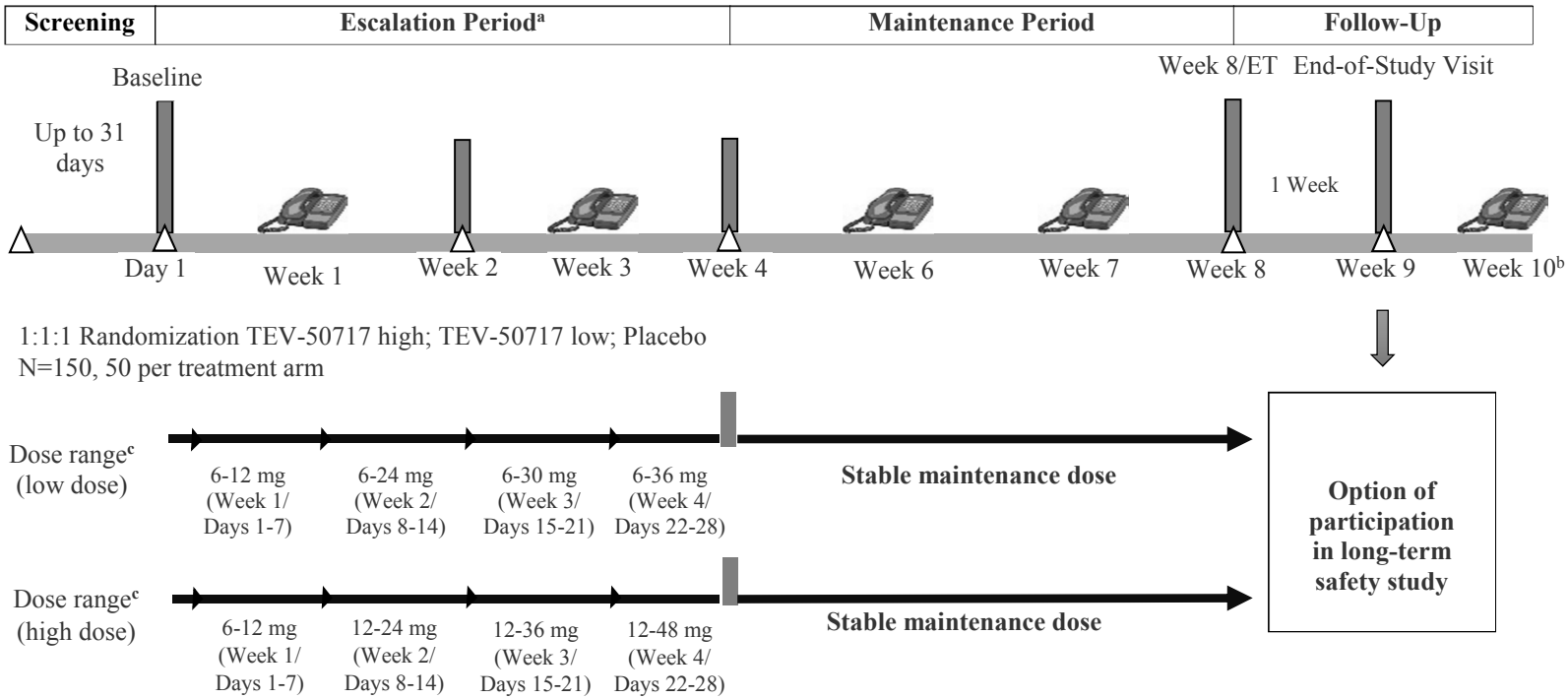
The end of study is defined as the date of the week 10 telephone contact with the last participant.

Prohibited drugs will remain the same during the washout period for patients who will participate in the open-label extension Study TV50717-CNS-30047. Patients who will not participate in the extension study may begin/resume tic therapy medication after the first week of the washout period.

The study duration will be approximately 17 months from January 2018.

The study schematic diagram is presented in Figure 1.

Figure 1: Overall Study Schematic Diagram



[a] If a stable dose is reached before the indicated time, the patient should continue taking that dose for the remainder of the escalation period and throughout the maintenance period. See Table 1 for the maximum dose of IMP and escalation by CYP impairment status, week, and baseline body weight category.

[b] This is a telephone contact for safety evaluation, required only for patients who will not participate in the open-label safety extension study for TEV-50717.

[c] Ranges account for different dosing schedules for patients with baseline weight ≥40 kg; ≥40 kg, CYP impaired; 30 to <40 kg; 30 to <40 kg, CYP impaired; 20 to <30 kg; and 20 to <30 kg, CYP impaired. See Table 1 for daily dose by category.

CYP=cytochrome P4502D6; CYP impaired=patients who are receiving a strong CYP2D6 inhibitor or who are a CYP2D6 poor metabolizer; ET=early termination visit.

Note: An unscheduled visit will require a clinic visit.

3.2. Planned Number of Patients and Countries

The number of evaluable patients is planned to be 150. Details on sample size are given in Section 9.

The study is planned to be conducted in approximately 10 countries in approximately 55 investigational centers. The study is expected to start in January 2018 and last for approximately 17 months.

3.3. Justification for Study Design and Selection of Population

Standard placebo-controlled, double-blind study design (TEV-50717 [low dose and high dose] vs placebo in a 1:1:1 ratio) was chosen to determine whether IMP treatment results in a statistically significant effect on tics in patients with TS.

The population to be studied includes children and adolescents, 6 through 16 years of age. Per eligibility criteria, the participants' tics need to be troublesome and cause distress or impairment based on the assessment of the patient, parent/guardian, and investigator. Based on these criteria, this is a study population in need of treatment.

3.4. Drug Administration

IMP will be administered as follows:

- IMP should be swallowed whole and taken with food (eg, a snack) and should not be taken on an empty stomach.
- Dosing will be based on body weight and CYP2D6 impairment status at the baseline visit, as shown in Table 1.
- The total daily dose, as provided in Table 1, is divided into a twice-daily administration. Two tablets will be taken twice daily starting at day 1 per Table 1. Daily doses will be administered twice daily, approximately 8 to 10 hours apart during the day. Depending on the dose and arm assigned, TEV-50717 tablets and/or placebo tablets will be taken to maintain the blind. A minimum of 6 hours should elapse between doses. If a patient misses a dose, and it is within 6 hours of their next dose, the missed dose should be skipped.
- After week 1, dose escalations may not occur more frequently than once every 5 days.
- The dose of IMP will be escalated weekly during the escalation period, according to Table 1.
- In the case of an adverse event, the investigator is permitted to perform a single dose reduction of 6 mg. **The investigator must discuss any further dose adjustments (eg, holding the dose or doses) with the medical monitor.**
- During the titration period, the dose of the IMP will be adjusted weekly according to Table 1. Investigators will be blinded to CYP status, with a dose cap for poor metabolizers prespecified by the IRT.

IMP will be packaged in blister packs and provided for patients to take at home (see Section 5.1).

Table 1: Daily Dose of IMP by Baseline Body Weight Category, CYP2D6 Impairment, and Study Week

Dose group Baseline weight (kg)	Daily dose (mg) at the start of visit/week[a]			
	Week 1 (Days 1-7)	**Week 2 (Days 8-14)**	**Week 3 (Days 15-21)**	**Week 4 main dose (Days 22-28) to Week 8 main dose (Days 50-56)**
Low dose				
≥40	12	24	30	36
≥40, CYP impaired	6	12	18	18
30 to <40	6	12	18	24
30 to <40, CYP impaired	6	12	12	12
20 to <30	6	12	18	18
20 to <30, CYP impaired	6	6	6	6
High dose				
≥40	12	24	36	48
≥40, CYP impaired	6	15	24	30
30 to <40	12	24	30	36
30 to <40, CYP impaired	6	12	18	18
20 to <30	12	18	24	30
20 to <30, CYP impaired	6	12	12	12

[a] Administration of a given dose will take place throughout the days indicated. The new dose starts the morning after the telephone contact or the morning after the clinic visit.
CYP impaired=patients who are receiving a strong CYP2D6 inhibitor or who are a CYP2D6 poor metabolizer.

Pharmacokinetic data will be reviewed at the week 8 visit. Evaluation of pharmacokinetic data will include review of the measurement of plasma concentrations of TEV-50717 (deutetrabenazine), α-HTBZ, β-HTBZ, and other metabolites, as required.

3.5. Stopping Rules for the Study

There are no formal rules for early termination of this study. During the conduct of the study, serious adverse events will be reviewed (Section 7.1.5) as they are reported from the investigational centers to identify safety concerns.

The study may be terminated by the sponsor for any reason at any time. For example, the sponsor should terminate the study in the event of the following:

- new toxicological or pharmacological findings or safety issues that invalidate the earlier positive benefit-risk assessment
- discontinuation of the development of the IMP

3.6. Schedule of Study Procedures and Assessments

Study procedures and assessments with their time points are presented in Table 2. During a visit, study procedures and assessments should be performed in the order specified in the study manual. Detailed descriptions of each method of procedures and assessments are provided in Section 6 (efficacy assessments), Section 7 (safety assessments), and Section 8 (pharmacokinetic and other assessments). Study procedures and assessments by visit are listed in Appendix B.

Table 2: Study Procedures and Assessments

	Prescreening	Screening	BL[a]	Escalation period (weeks)				Maintenance period (weeks)			Follow-up (weeks)		Unscheduled
Study week[b]	**Up to 3 months**	**Up to 31 days**	**Day 1**	**1 (Day 7)**	**2 (Day 14)**	**3 (Day 21)**	**4 (Day 28)**	**6 (Day 42)**	**7 (Day 49)**	**8/ ET[c] (Day 56)**	**9 (Day 63)**	**10[d] (Day70)**	
Visit window (days)			**0**	**±3 days**							**±3 days from week 8**		
Informed consent/assent	X	X											
Randomization			X										
Clinic visit		X[e]	X		X		X			X	X		X
Telephone contact				X		X		X	X			X	
Dose escalation[f]				X	X	X							X[g]
Eligibility criteria		X	X										
Medical and psychiatric history		X											
Demographics		X											
Vital signs and weight[h]		X	X[i]		X		X[i]			X[i]	X		X
Physical examination		X								X			X[j]
Neurological examination		X								X			X[j]
Height		X								X			
12-Lead ECG[k]		X	X				X			X			X[j]
PK blood sampling										X[l]			
Chemistry / hematology / urinalysis		X								X			X[j]

Table 2: Study Procedures and Assessments (Continued)

	Prescreening	Screening	BL[a]	Escalation period (weeks)				Maintenance period (weeks)			Follow-up (weeks)		Unscheduled
Study week[b]	**Up to 3 months**	**Up to 31 days**	**Day 1**	**1 (Day 7)**	**2 (Day 14)**	**3 (Day 21)**	**4 (Day 28)**	**6 (Day 42)**	**7 (Day 49)**	**8/ ET[c] (Day 56)**	**9 (Day 63)**	**10[d] (Day70)**	
Visit window (days)			**0**	**±3 days**							**±3 days from week 8**		
Urine drug screen		X								X			X[j]
CYP2D6 genotype[m]		X											
β-HCG test[n]		X	X				X			X			X[j]
MINI Kid[o]		X											
CDI-2 (Parent and Self-report Profiles)[p]		X	X		X		X			X	X		X[j]
C-SSRS (Children's Baseline/Screening)[q]		X											
C-SSRS (Children's Since Last Visit)[q]			X		X		X			X	X		X[j]
YGTSS[r s]		X	X		X[t]		X			X	X[t]		
TS-CGI[s]			X		X		X			X	X		
TS-PGII[s]			X		X		X			X	X		
[redacted]			X		X		X			X	X		
[redacted]			X		X		X			X	X		
[redacted]			X				X[u]			X	X[u]		
C&A-GTS-QOL[q]			X				X			X			X[j]
Dispense IMP[v]			X		X		X						X[j]
Collect IMP					X		X			X			X[j]

Table 2: Study Procedures and Assessments (Continued)

	Prescreening	Screening	BL[a]	Escalation period (weeks)				Maintenance period (weeks)			Follow-up (weeks)		Unscheduled
Study week[b]	**Up to 3 months**	**Up to 31 days**	**Day 1**	**1 (Day 7)**	**2 (Day 14)**	**3 (Day 21)**	**4 (Day 28)**	**6 (Day 42)**	**7 (Day 49)**	**8/ ET[c] (Day 56)**	**9 (Day 63)**	**10[d] (Day70)**	
Visit window (days)			**0**	**±3 days**							**±3 days from week 8**		
Assess IMP accountability / compliance / supply				X[w]	X	X[w]	X	X[w]	X[w]	X			X[j]
Assess AEs		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X

[a] The baseline visit (day 1) will occur the same day as the scheduled first dose of the IMP (day 1).
[b] Assessment will be performed at the end of study week (±3 days).
[c] For patients who withdraw prematurely, an early termination visit should be conducted as soon as possible after the last dose of IMP. In addition, all patients who discontinue early will have a follow-up telephone contact for safety evaluation 2 weeks after their last dose of IMP; evaluations will be as described for week 10.
[d] This visit is a telephone contact for safety evaluation, required only for patients who will not roll over into the open-label safety extension study for TEV-50717.
[e] The screening visit may be conducted over 2 separate visits at the discretion of the investigator. If the screening visit is divided into 2 visits, the blood sample should be obtained during the first of the 2 visits.
[f] Patients will be provided with a diary at baseline, week 2, week 4, and at unscheduled visits, to record critical information on dosing. The date and time of the last dose of study medication before the week 8 visit should be recorded in the diary by the patient or caregiver/adult. The site will document the date and time of the sample collection. Prior to the clinic visit on week 8, patients will be reminded to record the start time of their last meal and the time of their last dose in their diary.
[g] Dose escalation will only occur during the dose escalation period (ie, from week 1 to week 4).
[h] Weight must be measured with shoes and outerwear off.
[i] Orthostatic blood pressure and pulse will be measured after patient is in standing position for at least 3 minutes.
[j] Assessment will be completed at investigator's discretion.
[k] All ECGs will be performed after at least 5 minutes of rest in a supine or semi-supine position.
[l] Two samples will be collected. The first sample will be collected upon arrival at the clinic. The second sample will be collected within 2 to 3 hours after the first PK sample collection. Patients with early morning visits (ie, within 2 hours of their scheduled AM dosing) should take their IMP dose in the clinic after the first PK sample is collected.

[m] The patient's genotype for CYP2D6 will be blinded during the conduct of the study, except for the sample analysis and IRT vendor.

[n] For females who are postmenarchal or ≥12 years of age, a urine test will be administered at baseline and at week 4, while a serum test will be administered at screening, week 8, and if clinically indicated.

[o] MINI Kid (children and adolescents) modules to be used are Major Depressive Episode (Module A), (Hypo) Manic Episode (Module D), OCD (Module J), Alcohol Dependence/Abuse (Module L), Substance Dependence/Abuse (Non-alcohol; Module M), ADHD (Module O), Conduct Disorder (Module P), and Psychotic Disorders and Mood Disorders with Psychotic Features (Module R).

[p] Children 6 years of age at baseline will not complete the self-report version; the caregiver/adult will complete the parent version.

[q] For children 13 years of age and under, interviews may be performed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information.

[r] Input from the caregiver/adult is required.

[s] The YGTSS, TS-CGI, TS-PGII, and [redacted] questionnaires should be performed before any blood draws or ECG assessments.

[t] Perform assessment of Severity Ratings of the questionnaire. Inventory portions (ie, "Motor Tic Symptom Checklist" and "Phonic Tic Symptom Checklist" do not need to be performed).

[u] Perform the Severity Ratings of OCD symptoms (Questions 1 through 10) only. Checklist does not need to be performed.

[v] Contact IRT and dispense IMP and patient diary. Study drug will be dispensed in the clinic; patients will receive doses for 2 weeks (current dose level and next dose level) to cover the telephone contacts during escalation. See Table 1 for baseline weight-based dosing titration. At week 4, patients will receive doses for 4 weeks of treatment.

[w] The site needs to discuss the drug status during the telephone contacts to ensure that the patient has adequate tablets, inform the patient if they should escalate, and remind them to bring completed blister packs to the next in-clinic visit.

AE=adverse event; ADHD=Attention Deficit Hyperactivity Disorder; β-HCG=beta-human chorionic gonadotropin; BL=baseline visit; CDI-2=Children's Depression Inventory Second Edition (Parent and Self-report Profiles); C-SSRS=Columbia Suicide Severity Rating Scale; [redacted]; CYP2D6=cytochrome P450 2D6; ECG=electrocardiogram; ET=early termination visit; C&A-GTS-QOL=Child and Adolescent Gilles de la Tourette Syndrome–Quality of Life- scale; IMP=Investigational Medicinal Product; IRT=Interactive Response Technology; MINI Kid=Mini International Neuropsychiatric Interview For Children and Adolescents; OCD=obsessive-compulsive disorder; PK=pharmacokinetic; TS-CGI=Tourette Syndrome-Clinical Global Impression; TS-PGII=Tourette Syndrome-Patient Global Impression of Impact; [redacted]; YGTSS=Yale Global Tic Severity Scale.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow patients to be randomized/enrolled are not granted by Teva (Appendix C).

4.1. Patient Inclusion Criteria

Patients may be included in this study only if they meet all of the following criteria:

a. Patient is 6 to 16 years of age, inclusive, at baseline.
b. Patient weighs at least 44 pounds (20 kg) at baseline.
c. Patient meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V™) diagnostic criteria for TS and, in the opinion of the investigator, patient, and caregiver/adult, the patient's active tics are causing distress or impairment.
d. Patient has a TTS of 20 or higher on the YGTSS at screening and baseline.
e. Patient is able to swallow study medication whole.
f. Patient and caregiver/adult are willing to adhere to the medication regimen and to comply with all study procedures.
g. Patient is in good general health, as indicated by medical and psychiatric history as well as physical and neurological examination.
h. In the investigator's opinion, the patient and caregiver/adult have the ability to understand the nature of the study and its procedures, and the patient is expected to complete the study as designed.
i. Patient and caregiver/adult provided written informed consent/assent, depending on the child's age, as appropriate, according to local regulations.
j. Females who are postmenarchal or ≥12 years of age may be included only if they have a negative beta-human chorionic gonadotropin (β-HCG) test at baseline or are sterile. Definitions of sterile are given in Appendix E.
k. Females who are postmenarchal or ≥12 years of age whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study (ie, starting at screening) and for 30 days or 5 half-lives, whichever is longer after the last dose of IMP. Further details are included in Appendix E.
l. The patient must be willing and able to comply with study restrictions and to remain at the clinic for the required duration during the study period and willing to return to the clinic for the follow-up evaluation as specified in this protocol.

4.2. Patient Exclusion Criteria

Patients will not be randomized/enrolled in this study if they meet any of the following criteria:

a. Patient has a neurologic disorder other than TS that could obscure the evaluation of tics.

b. The patient's predominant movement disorder is stereotypy (coordinated movements that repeat continually and identically) associated with autism spectrum disorder.

c. Patient has clinically significant obsessive-compulsive disorder (OCD) at baseline that, in the opinion of the investigator, is the primary cause of impairment.

d. Patient has clinically significant depression at screening or baseline.

Note: Patients receiving antidepressant therapy may be enrolled if on a stable dose for at least 6 weeks before baseline (see Table 9 for prohibited antidepressants).

e. Patient has a history of suicidal intent or related behaviors within 2 years of screening:

   – previous intent to act on suicidal ideation with a specific plan, irrespective of level of ambivalence, at the time of suicidal thought

   – previous suicidal preparatory acts or behavior

f. Patient has a history of a previous actual, interrupted, or aborted suicide attempt.

g. Patient has a first-degree relative who has completed suicide.

h. Patient has a confirmed diagnosis of bipolar disorder, schizophrenia, or another psychotic disorder.

i. Patient has a DSM diagnosis based on the Mini International Neuropsychiatric Interview For Children and Adolescents Inventory at screening that, in the opinion of the investigator, makes the patient unsuitable for the study.

j. Patient has received Comprehensive Behavioral Intervention for Tics for TS or Cognitive Behavioral Therapy for OCD within 4 weeks of screening.

k. Patient has received any of the following concomitant medications for tics within the following specified exclusionary windows of first dose:

   – within 3 months: depot neuroleptics, botulinum toxin, or tetrabenazine

   – within 4 weeks: cannabidiol oil and valbenazine

   – within 21 days: reserpine

   – within 14 days: neuroleptics (oral), typical and atypical antipsychotics (see Appendix H, Table 9), metoclopramide, levodopa, and dopamine agonists

Note: Use of stimulant medications, including amphetamine, methylphenidate, and lisdexamfetamine, is allowed if primary use is for the treatment of ADHD, dosing has been stable for at least 2 weeks before screening, and no changes to dose or frequency are anticipated during the course of the study.

Note: Use of atomoxetine is allowed if the primary use is for the treatment of ADHD, dosing has been stable for at least 4 weeks before screening, and no changes to dose or frequency are anticipated during the course of the study.

Note: Use of benzodiazepines is allowed if primary use is not for tics and dosing has been stable for at least 4 weeks before screening.

Note: Use of topiramate (up to 200 mg/day) is allowed if dosing has been stable for at least 4 weeks before screening.

Note: Use of guanfacine or clonidine is allowed regardless of indication (ie, if prescribed for tics or TS) if the dosing has been stable for at least 4 weeks before screening and no changes to dose or frequency are anticipated during the course of the study. If discontinuation of either medication is anticipated due to ineffectiveness, poor tolerability, or patient/caregiver preference, discontinuation should occur 4 or more weeks prior to the screening visit.

l. Patient has received treatment with deep brain stimulation, transmagnetic stimulation, or transcranial direct current stimulation within 4 weeks of the screening visit for reduction of tics.

m. Patient has a QT interval corrected for heart rate using Fridericia's formula (QTcF) interval value >450 msec (males) or >460 msec (females), or >480 msec (with right bundle branch block) on a 12-lead electrocardiogram (ECG) at screening, or requires treatment with drugs known to prolong the QT interval (see Appendix H, Table 10 for a complete list of prohibited QT-prolonging drugs).

n. Patient has a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure.

o. Patient has evidence of hepatic impairment, as indicated by the following:

- aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 × the upper limit of the normal range (ULN) at screening
- alkaline phosphatase (ALP) or total bilirubin >2 × ULN at screening

Note: Patients with Gilbert's syndrome are eligible to participate if approved by the medical monitor.

Note: Patients with abnormalities in 2 or more of the following clinical laboratory parameters must be approved for enrollment by the medical monitor: AST, ALT, ALP, and total bilirubin.

p. Patient has evidence of clinically significant renal impairment, indicated by a serum creatinine >1.5 × ULN at screening.

q. Patient has received a monoamine oxidase inhibitor within 14 days of the baseline visit.

r. Patient has a known allergy to any of the components of the IMP product.

s. Patient has participated in an investigational drug or device study and received IMP/intervention within 30 days or 5 drug half-lives of baseline, whichever is longer.

t. Patient is a pregnant or lactating female, or plans to become pregnant during the study.

u. Patient has a history of or acknowledges alcohol-related disorder in the previous 12 months, as defined in the DSM-V™.

v. Patient has a positive urine drug screen test result or is unable to refrain from substance abuse throughout the study.

4.3. Withdrawal Criteria and Procedures for the Patient

In accordance with the Declaration of Helsinki (and in accordance with the applicable country's acceptance), each patient is free to withdraw from the study at any time. The investigator also has the right to withdraw a patient from the study if any of the following events occur:

a. intercurrent illness
b. adverse events (any patient who experiences an adverse event may be withdrawn from the study or from study treatment at any time at the discretion of the investigator or sponsor as indicated in Section 7.1.7)
c. pregnancy (see Section 7.3)
d. other reasons concerning the health or well-being of the patient
e. lack of cooperation
f. post-baseline QTcF value >500 msec or change from baseline >60 msec (as described in Section 7.1.7). The investigator should repeat the ECG assessment twice and compare the average of the 2 pre-treatment QTcF values (baseline and screening) to the average of the 3 post-baseline QTcF values. The IMP must be stopped for any confirmed post-baseline QTcF value >500 msec or increase from baseline >60 msec.
g. when a blind is broken due to safety concerns (see Section 5.10.2). If a patient is unblinded by mistake, the investigator should discuss with the medical monitor whether or not the patient should be withdrawn.
h. if the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn from the study (Section 5.7).

In addition, a patient may be withdrawn from the study as described in Sections 3.5, 5.10, 5.7, 7.1.7, and Appendix B.

Should a patient decide to withdraw after administration of IMP, or should the investigator decide to withdraw the patient, all efforts will be made to complete and report all observations up to the time of withdrawal. A complete final evaluation of the patient's withdrawal should be made as soon as possible after the last dose of IMP, and an explanation should be given as to why the patient is withdrawing or being withdrawn from the study. Assessments to be conducted at the early termination visit are described in Appendix B.

The reason for and date of withdrawal from the study must be recorded on the source documentation and transcribed onto the CRF. If a patient withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an adverse event or a potentially clinically significant abnormal laboratory test result, monitoring will be continued at the discretion of the investigator (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the IMP or study procedure is made). The specific event or test result must be recorded on the source documentation and transcribed onto the CRF.

All patients who discontinue early will have a follow-up telephone contact for safety evaluation 2 weeks after their last dose of IMP (Appendix B).

4.4. Replacement of Patients

A patient who is enrolled but does not complete the treatment period will not be replaced.

4.5. Rescreening

A patient who is screened but not enrolled may be rescreened 1 time if there is a change in the status of the patient regarding eligibility for the study. (Note: Details of rescreening must be approved and documented by the medical monitor and/or Clinical Surveillance and Training [CST] team.)

If the patient is rescreened, an informed consent/assent form (ICF) will need to be resigned.

4.6. Screening Failure

Screening failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized/enrolled in the study. Minimal information includes but is not limited to demography, screening failure details, eligibility criteria, and any serious adverse events.

5. TREATMENTS

5.1. Investigational Medicinal Products Used in the Study

IMP is defined as the test IMPs, reference IMPs, and matching placebo IMPs to the respective test and reference IMPs.

5.1.1. Test Investigational Medicinal Product

The investigational product is a matrix formulation and is designed as a tablet to be administered with food (eg, a snack) and should not be taken on an empty stomach. The IMP is coated with a white polymer coating to aid in swallowing. TEV-50717 tablets have been manufactured according to current Good Manufacturing Practice regulations. TEV-50717 tablets will be supplied as 6-, 9-, 12-, 15-, and 18-mg tablets and will be packaged in blister packs and labeled according to applicable regulatory guidelines. Each blister pack (40-count tablets per dose strength per blister pack) will contain a sufficient supply of drug until the next specified visit/telephone contact, plus overage to account for potential delays in study visits.

Additional details may be found in the IB for TEV-50717.

5.1.1.1. Starting Dose and Dose Levels

Two active-dose levels were selected for this study. The target population, children 6 to 16 years of age, inclusive, will vary considerably in body weight. There will also be varying impairment of the drug metabolizing enzyme CYP2D6, whether from use of certain concomitant medications that inhibit the enzyme or genetic predisposition to poor metabolism of CYP2D6 substrates.

5.1.1.2. Dose Modification and Dose Stratification

As this is a fixed dose study, patients will undergo dose escalation (ie, forced titration) to their target dose over the first 4 weeks of treatment (see Section 3.4 and Table 1). If a patient experiences depression, suicidal ideation or behavior, anxiety, akathisia, parkinsonism, or somnolence, or any other adverse event that interferes with daily activity, or any adverse event that is related to IMP, a single dose reduction is permitted. The investigator must discuss any further dose adjustments (eg, holding the dose or doses) with the medical monitor.

In case of such an adverse event, the investigator will determine if a dose reduction or suspension is necessary. If a determination is made that a dose reduction or suspension is required, the medical monitor must be contacted. All available information, including the patient and caregiver/adult reports of adverse events, the clinical assessment of safety by the investigator, and information from rating scales should be incorporated in the decision. This reduced dose will become the patient's dose for the remainder of the study.

5.1.2. Placebo Investigational Medicinal Product

Placebo tablets match TEV-50717 tablets. The packaging will be the same as described for TEV-50717 above.

Table 3: Investigational Medicinal Products Used in the Study

IMP name	Test IMP	Placebo IMP	Reference IMP (None)
Trade name and INN, if applicable, or company-assigned number	TEV-50717 (previously SD-809), deutetrabenazine	Not applicable	Not applicable
Formulation	film-coated tablet	film-coated tablet	Not applicable
Unit dose strength(s) / Dosage level(s)	TEV-50717 tablets are available in the following dose strengths: 6, 9, 12, 15, and 18 mg, all of which are identical in size, shape, and color (white). IMP will be supplied in 40-count tablets per dose strength per blister pack	Not applicable	Not applicable
Route of administration	oral	oral	Not applicable
Dosing instructions	The total daily dose, as provided in Table 1, is divided into a twice-daily administration. Two tablets will be taken twice daily starting at day 1 per Table 1. Daily doses will be administered twice daily, approximately 8 to 10 hours apart during the day. Depending on the dose and arm assigned, TEV-50717 tablets and/or placebo tablets will be taken to maintain the blind. A minimum of 6 hours should elapse between doses. If a patient misses a dose, and it is within 6 hours of their next dose, the missed dose should be skipped. Tablets should be swallowed whole and taken with food (eg, a snack) and should not be taken on an empty stomach.	The total daily dose, as provided in Table 1, is divided into a twice-daily administration. Two tablets will be taken twice daily starting at day 1 per Table 1. Daily doses will be administered twice daily, approximately 8 to 10 hours apart during the day. Depending on the dose and arm assigned, TEV-50717 tablets and/or placebo tablets will be taken to maintain the blind. A minimum of 6 hours should elapse between doses. If a patient misses a dose, and it is within 6 hours of their next dose, the missed dose should be skipped. Tablets should be swallowed whole and taken with food (eg, a snack) and should not be taken on an empty stomach.	Not applicable
Packaging	IMP will be provided in blister packs	Placebo IMP will be provided in blister packs	Not applicable
Manufacturer	[redacted]	[redacted]	Not applicable

IMP=Investigational Medicinal Product

5.2. Preparation, Handling, Labeling, Storage, and Accountability for IMPs

5.2.1. Storage and Security

The investigator or designee must confirm appropriate temperature conditions have been maintained for all IMPs received and any discrepancies are reported and resolved before use of the IMPs.

The IMP (TEV-50717 and the placebo) should be stored protected from light, at a controlled room temperature, 20°C to 25°C (68°F to 77°F); however, storage between 15°C and 20°C (59°F and 68°F) is acceptable if there is no alternative. The IMP should be stored in a dry, securely locked, substantially constructed cabinet or enclosure with access limited to authorized staff.

Diversion is considered to have occurred when the legal supply chain of prescription analgesic medicinal products is broken, and medicinal products are transferred from a licit to an illicit channel of distribution or use.

5.2.2. Labeling

Supplies of IMPs will be labeled according to the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be translated into the local language.

5.2.3. Accountability

Each IMP shipment will include a packing slip listing the contents of the shipment, return instructions, and any applicable forms.

The investigator is responsible for ensuring that deliveries of IMPs and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with the local regulations, and used in accordance with this protocol.

Only patients enrolled in the study may receive IMPs, and only authorized staff at the investigational center may supply or administer IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions or appropriate instructions with access limited to the investigator and authorized staff at the investigational center.

The investigator (or designee) will instruct the patient to store the IMP according to the instructions on the label, if applicable; or will give instructions in an appropriate form.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

A record of IMP accountability (ie, IMP and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Empty, partially used, and unused blister packs IMP will be disposed of, as agreed with the sponsor/development partner.

5.3. Justification for Investigational Medicinal Products

5.3.1. Justification for Dose of Test Investigational Medicinal Product

As body weight and CYP2D6 impairment are known predictors for exposure to the active circulating metabolites of TEV-50717, the "high" and "low" doses will represent a target exposure (area under the plasma concentration-time curve [AUC], maximum observed concentration (C_{max}) rather than a fixed milligram amount of drug. The high dose targets a mean (CV%) AUC of approximately 1500 ng▪hr/mL (60%) and a mean (CV%) C_{max} of approximately 100 ng/mL (39%). These targets were chosen as they represent exposure in another population (HD patients) receiving up to 48 mg/day that was associated with robust efficacy and favorable tolerability. The low dose group targets a mean (CV%) AUC of approximately 1000 ng▪hr/mL (60%) and a C_{max} of approximately 80 ng/mL (39%). Based on Phase 3 studies in both HD and TD patients, exposures associated with an AUC of approximately 1000 ng▪hr/mL are still anticipated to be efficacious.

5.3.2. Justification for Use of Placebo Investigational Medicinal Product

A standard placebo-controlled, double-blind study design (TEV-50717 [low dose and high dose] vs placebo in a 1:1:1 ratio) was chosen to determine whether IMP treatment results in a statistically significant effect on the tics of patients with TS. As TS is not a progressive neurological disorder, and available treatments are for symptomatic control, the use of placebo is justified in a short-term study where safety is carefully monitored. Moreover, a placebo control is ideal for characterizing the efficacy and safety of an experimental agent in a new study population.

5.4. Treatment after the End of the Study

Patients who complete the study may be eligible to begin participation in an open-label safety extension study of TEV-50717 (Study TV50717-CNS-30047). Patients not participating in the open-label safety extension study for TEV-50717 will have a follow-up telephone contact for safety evaluation 1 week after the end of the treatment period (2 weeks after their last dose of IMP).

5.5. Restrictions

Medications prohibited before and/or during the study are described in Section 5.6.

While patients receiving strong CYP2D6 inhibitors such as paroxetine, fluoxetine, and bupropion at baseline may be enrolled into this study, the removal of strong CYP2D6 inhibitors during treatment is discouraged as this would have an effect on exposure to active circulating drug. If the removal of a strong CYP2D6 inhibitor is required from a clinical perspective, the medical monitor should be contacted so an appropriate change in IMP can be made. The addition of a strong CYP inhibitor is prohibited. The use of quinidine and terbinafine are prohibited (see Appendix H, Table 11).

Restrictions in regard to sexual activity and required laboratory values are provided in the inclusion and exclusion criteria.

As with other VMAT2 inhibitors (tetrabenazine, reserpine), patients should be advised that the concomitant use of alcohol or other sedating drugs with TEV-50717 may have additive effects and cause or worsen somnolence. Given the age of the study population, the use of alcohol during this study is prohibited.

Patients should be advised not to drive a car or operate dangerous machinery until they understand how TEV-50717 affects them.

Use of illicit drugs is prohibited from the time of signing of the informed consent/assent form and throughout study participation.

Patients may not donate blood from the time of informed consent/assent, while taking the IMP, and for 14 days after the last dose.

5.6. Prior and Concomitant Medication or Therapy

Any prior or concomitant medication a patient has had within 3 months before IMP administration and up to the end of study, including follow-up, will be recorded on the CRF. Generic or trade name, indication, dose, and start and end dates of the administered medication will be recorded. The sponsor will encode all medication according to the World Health Organization (WHO) drug dictionary (WHO Drug).

At each clinic visit after the screening visit, the investigator will ask patients whether they have taken any medications (other than IMP), including over-the-counter medications, vitamins, or herbal or nutritional supplements, since the previous visit. Parents/patients will be instructed during the course of the study to notify the investigator if any new medication is prescribed, including over-the-counter medications. Any prescribed medication should be reviewed with the investigator. Indication, dosage, and start and end dates should be entered on the CRF.

The medical monitor must be contacted if a patient is receiving (or has to begin or stop receiving during the study) a medication that is associated with QTc prolongation or that is a known strong CYP inhibitor. Allowed strong CYP inhibitors at baseline are shown in Appendix H, Table 8. Addition of a strong CYP inhibitor is prohibited.

Prohibited antipsychotic drugs are listed in Appendix H, Table 9. Prohibited medications that are associated with QTc prolongation are listed in Appendix H, Table 10.

Concomitant medication and treatment will be monitored throughout the study.

5.7. Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance until completion of the IMP administration according to the protocol or discontinuation from IMP. A check of compliance with IMP intake will be performed during each visit after the IMP has been dispensed; and IMP accountability records will be completed.

If the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn from the study. The IEC/IRB should be notified as required by national and local regulations.

Exposure to IMP will be assessed as required.

5.8. Temporary Discontinuation of Investigational Medicinal Product

Dose Reduction

If a patient experiences a "clinically significant" adverse event that is attributed to IMP, the investigator will determine if a dose reduction or suspension is necessary. Dose adjustments should be made based on all available information, including the patient and caregiver/adult reports of adverse events and tic reduction, the clinical assessment of safety and efficacy by the investigator, and information from rating scales. In the case of an adverse event, the investigator is permitted to perform a single dose reduction of 6 mg. **The investigator must discuss any further dose adjustments (eg, holding the dose or doses) with the medical monitor.**

If the determination that a patient requires a dose reduction or suspension is made during a telephone contact, an unscheduled clinic visit should be conducted as soon as practicable thereafter.

Dose Suspension

Suspension of study medication for up to 1 week, if warranted for patient safety, is allowed. If the patient restarts study medication within 7 days of suspension, the full dose of TEV-50717 may be resumed without titration. **Suspensions of study medication for adverse events must be reviewed with the medical monitor before therapy is restarted**. If a subject's serum potassium or magnesium were tested and found to be below the lower limit of normal and clinically significantly, the laboratory test should be repeated at least once. If the abnormality in the repeated laboratory test is consistent with the prior laboratory test, the IMP must be suspended. The Medical Monitor must be contacted to determine the appropriate investigation and treatment. TEV-50717 may only be restarted once serum potassium or magnesium have normalized.

The reason for a dose reduction or suspension must be clearly documented.

If a dose reduction or suspension occurs before a scheduled clinic visit, the clinic visit will be postponed so that efficacy evaluations can be performed at least 5 days after the change.

The patients who restart IMP treatment will follow the visit schedule as outlined in Table 2. Patients who withdraw from the study will proceed as described in Section 4.3.

5.9. Randomization and Blinding

This is a Phase 3, randomized, double-blind, placebo-controlled, 8-week-treatment study in which patients with tics associated with TS will be invited to participate. Patients will be randomized to either TEV-50717 (low-dose, high-dose) or matching placebo in a 1:1:1 ratio using an Interactive Response Technology (IRT) based on their baseline weight and CYP impairment status. The patients will be stratified into 2 age groups (6 to 11 years and 12 to 16 years). Patients and investigators will remain blinded to treatment assignment during the study.

Patients will be centrally randomly assigned to the treatment groups by means of a computer-generated randomization list after confirmation of all eligibility criteria. The creation of the randomization list will be under the responsibility and oversight of Syneos Health.

In addition, the sponsor's clinical personnel and all vendors (with exception of the IRT vendor and the bioanalytical sample analysis vendor) involved in the study will be blinded to the IMP identity until the database is locked for analysis and the treatment assignment revealed. After unblinding of this study, the study site may remain blinded to patient treatment assignments until completion of the safety extension Study TV50717-CNS-30047.

The randomization list and treatment will be assigned to the relevant treatment groups through a qualified service provider (ie, via IRT). The generation of the medication list and management of the IRT system will be done by a qualified service provider under the oversight of Nuvelution TS Pharma, INC (referred to hereafter as Nuvelution TS Pharma).

The staff member at the investigational center who will dispense the IMP will not know the treatment given to each patient.

5.10. Maintenance of Randomization and Blinding

Patients will be randomly assigned to receive treatment with TEV-50717 (low dose, high dose) or matching placebo in a 1:1:1 ratio using an IRT based on their baseline weight and CYP impairment status. The patients will be stratified into 2 age groups (6- to 11-years and 12- to 16-years). The sponsor will monitor enrollment in age strata to ensure there is adequate representation in each stratum. Patients and investigators will remain blinded to treatment assignment during the study. In addition, the sponsor's clinical personnel and all vendors (with the exception of the IRT vendor and the bioanalytical sample analysis vendor) involved in the study will be blinded to the IMP identity until the database has been locked for analysis and the treatment assignments are revealed. However, if a prioritized sample analysis is needed, bioanalytical personnel may be unblinded.

5.10.1. Maintenance of Randomization

Patient randomization codes will be maintained in a secure location within Syneos Health. At the time of analysis, when treatment codes are needed, the Syneos Health statistician assigned to the study will make a request to unblind, and will receive the unblinded codes and unblinded IMP assignment according to the processes defined in the relevant Standard Operating Procedure.

5.10.2. Blinding and Unblinding

Blinded pharmacokinetic data may be assessed during the study. For patients who have pharmacokinetic sample bioanalysis or data analysis conducted, the individuals responsible for sample bioanalysis and other responsible personnel will know who received active IMP and who received placebo during the study (of those patients only). Personnel responsible for bioanalysis will be provided with the randomization code to facilitate the analysis. However, the personnel responsible for bioanalysis and pharmacokinetic data analysis will not have access to clinical safety and efficacy data, and will provide concentration data to other personnel in a manner that will not identify individual patients (ie, a dummy patient identifier will be linked to the concentration data of an individual patient).

For information about personnel who may be aware of IMP assignments, see Section 5.9. These individuals will not be involved in the conduct of any study procedures or assessment of any adverse events.

In case of a serious adverse event, pregnancy, or in cases when knowledge of the IMP assignment is needed to make treatment decisions, the investigator may unblind the patient's IMP assignment as deemed necessary, mainly in emergency situations. Individual randomization codes, indicating the IMP assignment for each randomized patient, will be available to the investigator(s) or pharmacist(s) at the investigational center via the Randomization and Trial Supply Management (RTSM), both via telephone and internet. If possible, the sponsor should be notified of the event before breaking of the code. If this is not possible, the sponsor should be notified immediately afterwards and the patient's IMP assignment should not be given. Breaking of the randomization code can always be performed by the investigational center without prior approval by the sponsor.

When a blind is broken, the patient will be withdrawn from the study and the event will be recorded on the CRF. However, if a patient is unblinded by mistake, the investigator should discuss with the medical monitor whether or not the patient should be withdrawn. The circumstances leading to the breaking of the code should be fully documented in the investigator's study files and in the patient's source documentation. Assignment of IMP should not be recorded in any study documents or source document.

In blinded studies, for an adverse event defined as a suspected unexpected serious adverse reaction (SUSAR) (ie, reasonable possibility; see Section 7.1.4), Global Patient Safety and Pharmacovigilance (GPSP) may independently request that the blind code be broken (on a case-by-case basis) to comply with regulatory requirements. The report will be provided in an unblinded manner for regulatory submission. If this occurs, blinding will be maintained for the investigator and for other personnel involved in the conduct of the study and analysis and reporting of the data.

5.10.3. Data Monitoring Committee

During the conduct of this study, an IDMC will review accumulating safety and efficacy data on a regular basis to ensure the continuing safety of the study patients and study conduct issues.

The iDMC will be composed of independent physicians with expertise in the relevant therapeutic field and other relevant experts, such as a statistician. The iDMC will receive safety data periodically, which will be presented by masked treatment groups. They will have the right to recommend modification of the study for safety reasons.

iDMC sessions can be open or closed. During open sessions, representatives of the sponsor may be present, and information is provided and discussed in a blinded fashion. During closed sessions, the only participants are members of the iDMC and the designated unblinded statistician (if approved to be present).

If there is a request to unblind any individual treatment assignment, a written request from the IDMC (as a committee), signed by the IDMC chairperson, should be made to the unblinded statistician. The appropriate medical and operational personnel will be notified but will not receive the unblinded treatment information. Any use of unblinded treatment assignments should be clearly documented and reported to the sponsor at study termination.

The IDMC chairperson will communicate with Nuvelution TS Pharma in regard to issues resulting from the conduct and clinical aspects of the study. Nuvelution TS Pharma and Syneos Health will work closely with the committee to provide the necessary data for review.

The conduct and specific details regarding the IDMC sessions and requests to unblind any blinded treatment assignment are outlined in the IDMC charter.

5.11. Total Blood Volume

The total volume of blood to be collected for each patient in this study is approximately 35 mL, as detailed in Table 4.

Table 4: Blood Volumes

Type of samples	Volume per sample	Total number of samples	Total volume (maximum)
Clinical laboratory (chemistry/hematology)	10 mL	2	20 mL
Pharmacokinetic	5 mL	1 time point (week 8) × 2 samples	10 mL
CYP2D6 genotyping	3 mL	1	3 mL
Optional pharmacogenetic sample	2 mL	1	2 mL
Total			**35 mL**

CYP2D6=cytochrome P450 2D6.
Note: beta-human chorionic gonadotropin testing (in females who are postmenarchal or ≥12 years of age) is included in the clinical laboratory sample.

6. ASSESSMENT OF EFFICACY

Site-administered efficacy scales include YGTSS and [redacted], and self-administered efficacy scales include [redacted] TS-PGII, [redacted], and C&A-GTS-QOL.

6.1. Primary Efficacy Measure and Justification

The primary efficacy measure is the TTS of YGTSS.

The YGTSS is administered at screening; baseline; and weeks 2, 4, 8, and 9:

- Complete assessment (Checklist and Severity Ratings) at screening, baseline, and weeks 4 and 8
- Severity Ratings assessment only at weeks 2 and 9
- Input from caregiver/adult is required for all subjects irrespective of age

The choice of YGTSS (specifically the TTS) as a primary efficacy measure is supported by its wide use in clinical practice for the evaluation of symptoms associated with TS and its successful use in the Phase 1b Study SD-809-C-17 (Section 1.3.2.2).

The YGTSS rating scale is a semi-structured clinician rating instrument that provides an evaluation of the number, frequency, intensity, complexity, and interference of motor and phonic tics (Leckman et al 1989). The items pertaining to the tic ratings are scored on 2 subscales: Motor Tics and Vocal Tics. Behaviors are rated on a 6-point scale. The scale has a look-back period of 1 week. Additionally, the scale assesses the severity of tics, which includes overall impairment of the patient, and combines motor and visual tic information into a TTS score. A GSS can then be determined by combining the patient's severity rating with the TTS.

A reference sample is provided in Appendix I.

6.2. Key Secondary Efficacy and Exploratory Measures

6.2.1. Tourette Syndrome–Clinical Global Impression

The TS-CGI is administered at baseline and at weeks 2, 4, 8, and 9. The TS-CGI scale is a 7-point Likert scale that allows the clinician to use all available information to assess the impact of tics on the patient's quality of life. The TS-CGI is rated as follows: 1 (normal), 2 (borderline), 3 (mild), 4 (moderate), 5 (marked), 6 (severe), and 7 (extreme).

A reference sample is provided in Appendix N.

6.2.2. Tourette Syndrome-Patient Global Impression of Impact

The TS-PGII is administered at baseline and weeks 2, 4, 8, and 9. Input from the caregiver/adult is permitted.

The TS-PGII is a single-item questionnaire that asks the patient to assess their degree of impact due to current tics. The TS-PGII uses a 5-point scale, ranging from not at all (1) to very much (5), to assess overall response to therapy. In general, patient-rated global measures of change

have face validity and have been shown to correlate with disability for a number of chronic conditions.

A reference sample is provided in Appendix O.

6.2.3. [redacted]

[redacted]

6.2.4. Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life Scale

The C&A-GTS-QOL is administered at baseline, week 4, and week 8. Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information.

The C&A-GTS-QOL is a 27-item questionnaire specific to TS patients that asks the patient to assess the extent to which their quality of life is impacted by their symptoms. The C&A-GTS-QOL contains 6 subscales (cognitive, coprophenomena, psychological, physical, obsessive-compulsive, and ADL) and uses a 5-point Likert scale ranging from no problem to extreme problem. Patients will also be asked how satisfied they feel overall with their life at that moment by using a VAS scale between 0 and 100 (Su et al 2017).

A reference sample is provided in Appendix Q.

6.2.5. [redacted]

[redacted]

6.2.6. [redacted]

[redacted]

6.2.7. [redacted]

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel by evaluating: reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, physical examination findings (including body weight and height measurements), use of concomitant medications, neurological examination, C-SSRS, and CDI-2.

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study, or of any concurrent disease, whether or not considered related to the IMP, TEV-50717. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events.

Accordingly, an adverse event can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions (Note: A condition recorded as pre-existing that is intermittently symptomatic [eg, headache] and that occurs during this study should be recorded as an adverse event.)
- drug interactions
- events occurring during diagnostic procedures or during any washout period of this study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event, or require medical treatment or further diagnostic work-up, or are considered by the investigator to be clinically significant (Note: Abnormal laboratory test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events.)

7.1.2. Recording and Reporting of Adverse Events

For recording of adverse event, the study period is defined for each patient as the time period from signature of the informed consent/assent form to the end of the follow-up period. For this study, there will be 1 week of washout for patients who will participate in the open-label safety extension Study TV50717-CNS-30047 and 2 weeks after the last dose of IMP for patients who will not roll over into the open-label safety extension Study TV50717-CNS-30047.

For subjects who experience an adverse event or serious adverse event after signing a prescreening ICF for Study TV50717-CNS-30060, the event will be documented in the subject source documents and Electronic Data Capture (EDC) systems. For serious adverse events, the serious adverse event form must be completed in addition, and the serious adverse event must be reported immediately to the sponsor (Section 7.1.5.3.1). If the subject attends the screening visit, the adverse event or serious adverse event identified during the prescreening period will be considered medical history. For data entry purposes in EDC, the stop date for the prescreening adverse event or serious adverse event will be the date of the screening visit, and the start date for the associated medical history will be the date of the screening visit.

All adverse events that occur during the defined study period must be recorded both on the source documentation and the CRF, regardless of the severity of the event or judged relationship to the IMP. For serious adverse events, the serious adverse event form must be completed and the serious adverse event must be reported immediately (Section 7.1.5.3.1). The investigator does not need to actively monitor patients for adverse events after the defined period. Serious adverse events occurring to a patient after the treatment of that patient has ended should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

At each contact with the patient, the investigator or designee must question the patient about adverse events by asking an open-ended question such as “Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe.” All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, on the serious adverse event form.

The clinical course of each adverse event will be monitored at suitable intervals until resolved, stabilized, or returned to baseline; or until the patient is referred for continued care to a health care professional; or until a determination of a cause unrelated to the IMP or study procedure is made.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding IMP, treatment administered, and outcome for each adverse event must be recorded both on the source documentation and the CRF.

The relationship of each adverse event to IMP and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

Further details are given in the safety monitoring plan.

7.1.3. Severity of an Adverse Event

The severity of each adverse event must be recorded as 1 of the following:

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

7.1.4. Relationship of an Adverse Event to the Investigational Medicinal Product

The relationship of an adverse event to the IMP is characterized as follows:

Table 5: The Relationship of an Adverse Event to the IMP

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the IMP.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the IMP. • It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the IMP. • It does not reappear or worsen when the IMP is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the administration of IMP cannot be ruled out with certainty.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the IMP. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear after discontinuation of the IMP, yet an IMP relationship clearly exists. • It follows a known pattern of response to the IMP.

7.1.5. Serious Adverse Events

An additional blood sample for the measurement of IMP concentration should be collected, if possible, from each patient experiencing a serious adverse event leading to discontinuation of IMP at any time during the study. If study center personnel are unable to obtain a blood sample in a timely fashion, this should be discussed with the medical monitor to determine whether the sample still needs to be obtained.

For recording of serious adverse event, the study period is defined for each patient as that time period from signature of the informed consent/assent form to the end of the follow-up period as defined in Section 7.1.2. Serious adverse events occurring in a patient after the end of the follow-up period should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

7.1.5.1. Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- results in death
- is life-threatening adverse event (ie, the patient was at risk of death at the time of the event); it does not refer to an event which hypothetically might have caused death if it were more severe
- requires inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event

  Hospitalizations scheduled before the patient and caregiver/adult signed the informed consent/assent form will not be considered serious adverse events, unless there was worsening of the pre-existing condition during the patient's participation in this study
- results in persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- is a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition

  Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event

All occurrences of possible drug-induced liver injury that meet Hy's law criteria, defined as all of the below, must be reported by the investigator to the sponsor as a serious adverse event:

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase of >3x the upper limit of normal (ULN)
- total bilirubin increase of >2x ULN
- absence of initial findings of cholestasis (ie, no substantial increase of alkaline phosphatase [ALP])

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.

7.1.5.2. Expectedness

A serious adverse event that is not included in the Adverse Reaction section of the relevant reference safety information (RSI) by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The RSI for this study is the IB.

A serious adverse event that is not included in the listing of adverse reactions in the RSI by its specificity, severity, outcome, or frequency is considered an unexpected adverse event.

For the purpose of SUSAR reporting, the version of the IB at the time of occurrence of the SUSAR applies.

7.1.5.3. Reporting a Serious Adverse Event

7.1.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events that occur during the study, regardless of judged relationship to administration of the IMP, must be reported by the investigator according to the instructions provided on the serious adverse event form. The event must be reported within 24 hours of when the investigator learns about it. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor patients for adverse events once this study has ended.

Serious adverse events occurring to a patient after the last administration of IMP of that patient has ended should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the LSO or designee (a CRO in a country without a sponsor LSO) (contact information is in the Clinical Study Personnel Contact Information section); the LSO will forward the report to the sponsor's GPSP.

The following information should be provided to record the event accurately and completely:

- study number
- investigator and investigational center identification
- patient number
- onset date and detailed description of adverse event
- investigator's assessment of the relationship of the adverse event to the IMP (no reasonable possibility, reasonable possibility)

Additional information includes:

- age and sex of patient
- date of first dose of IMP
- date and amount of last administered dose of IMP
- action taken
- outcome, if known

- severity
- explanation of assessment of relatedness
- concomitant medication (including doses, routes of administration, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death
  - cause of death (whether or not the death was related to IMP)
  - autopsy findings (if available)

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the IMP, study procedures, and to underlying disease.

Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigator within 24 hours of when it becomes known to the same address as the initial report.

For all countries, the sponsor's GPSP will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/Extensible Markup Language (XML) file to the LSO/CRO for submission to the competent authorities, IEC/IRBs, and investigators, according to regulations. The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

Blinding will be maintained for all study personnel. Therefore, in case of a SUSAR, only the LSO/CRO will receive the unblinded report for regulatory submission; the others will receive a blinded report.

Note: Although pregnancy is not a serious adverse event, the process for reporting a pregnancy is the same as that for reporting a serious adverse event, but using the pregnancy form (see Section 7.2).

7.1.5.3.2. Sponsor Responsibility

If a serious unexpected adverse event is believed to be related to the IMP or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of TEV-50717 and the appropriate competent authorities (and IEC/IRB, as appropriate).

In addition to notifying the investigators and competent authorities (and IEC/IRB, as appropriate), other action may be required, including the following:

- altering existing research by modifying the protocol
- discontinuing or suspending the study

- modifying the existing consent/assent form and informing all study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to TEV-50717

7.1.6. Protocol-Defined Adverse Events of Special Interest

No protocol-defined adverse events of special interest were identified for this study.

7.1.7. Withdrawal Due to an Adverse Event

Any patient who experiences an adverse event may be withdrawn from the study or from study treatment at any time at the discretion of the investigator. If a post-baseline QTcF value >500 msec or change from baseline >60 msec is found, the investigator should repeat the ECG assessment twice and compare the average of the 2 pre-treatment QTcF values (baseline and screening) to the average of the 3 post-baseline QTcF values. The IMP must be stopped for any confirmed post-baseline QTcF value >500 msec or increase from baseline >60 msec. If a patient is withdrawn wholly or in part because of an adverse event, both the adverse events page and termination page of the CRF will be completed at that time.

In addition, a blood sample should be obtained for the measurement of IMP concentrations, if possible. The patient will be monitored at the discretion of the investigator (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the IMP or study procedure is made). The investigator must inform the clinical project physician/clinical leader as soon as possible of any patients who are being considered for withdrawal due to adverse event(s). Additional reports must be provided when requested.

If a patient is withdrawn from the study for multiple reasons that include adverse events, the termination page of the CRF should indicate that the withdrawal was related to an adverse event. An exception to this requirement will be the occurrence of an adverse event that, in the opinion of the investigator, is not severe enough to warrant discontinuation but that requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be need to take a prohibited medication, not the adverse event.

7.1.8. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure patient safety, after the event has stabilized or treatment has been administered (or both), the investigator or other physician in attendance must contact the physician identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study.

7.2. Psychometric Rating Scales

Site-administered safety scales include the MINI Kid and C-SSRS, and self-administered safety scales include CDI-2.

7.2.1. Mini International Neuropsychiatric Interview for Children and Adolescents

Select MINI Kid modules are administered at screening only. Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information.

The MINI Kid is a short questionnaire to be administered by a trained clinician. The MINI Kid assesses symptoms of psychiatric disorders as outlined in the International Classification of Diseases-10 and the DSM-V™ in children 6 to 17 years of age by self-report. For children under 13 years old, the patient may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale, and the caregiver/adult is encouraged to participate when needed. The MINI Kid version 6 is composed of 24 modules overall, and questions are largely yes-or-no questions. The current study will focus on 8 modules: Major Depressive Episode (Module A), (Hypo) Manic Episode (Module D), OCD (Module J), Alcohol Dependence/Abuse (Module L), Substance Dependence/Abuse (Non-alcohol; Module M), ADHD (Module O), Conduct Disorder (Module P), and Psychotic Disorders and Mood Disorders with Psychotic Features (Module R).

A reference sample is provided in Appendix I.

7.2.2. Columbia-Suicide Severity Rating Scale

The C-SSRS children's baseline/screening scale assesses past and current suicidal ideation and behaviors to determine suicide risk and is administered at screening. C-SSRS children's SLV scale is administered at baseline and at weeks 2, 4, 8, and 9. Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information. The C-SSRS is an interview by trained study personnel.

Suicidal ideation

- Patients with a positive C-SSRS suicidal ideation score on either items 1 or 2 or a change on the CDI-2 Parent or Self-Report Profiles consistent with increasing depressive symptoms must be 1) discussed with the medical monitor, 2) re-evaluated within 2 to 3 days in a clinic visit, and 3) treated according to the investigator's medical judgment. Consultation with a child and adolescent psychiatrist or licensed child/adolescent mental health provider is advised, followed by close ongoing monitoring.
- If patients endorse or report a C-SSRS suicidal ideation level of 3, 4, or 5, subjects will be evaluated immediately by the study investigator and referred for psychiatric evaluation. The medical monitor will be immediately consulted. If it is determined by the investigator, after consultation with the medical monitor and the consulting psychiatrist, that exposure to the IMP may have contributed to this change in C-SSRS and/or increased depressive symptoms, IMP will be immediately discontinued and the patient terminated from the study. In cases where it is determined that IMP did not contribute to changes in depression or suicidality, the investigator will consult with

the medical monitor, the consulting psychiatrist, and/or sponsor to determine whether the patient should continue in the study.

Suicidal behavior

- Actual attempt:
  - If patients report any suicidal behavior that is an actual attempt as assessed in the C-SSRS, they will be evaluated immediately by the study investigator, referred for psychiatric evaluation, and terminated from the study.
- Interrupted attempt, aborted attempt, or Preparatory Acts or Behavior:
  - If patients report any suicidal behavior that is interrupted, aborted, or preparatory as assessed in the C-SSRS, they will be evaluated immediately by the study investigator and referred for psychiatric evaluation. In cases where it is determined in the psychiatric evaluation that IMP did not contribute to changes in suicidal behavior, the investigator will consult with the medical monitor, the consulting psychiatrist, and/or sponsor to determine whether the patient should continue in the study.

A reference sample is provided in Appendix K.

7.2.3. Children's Depression Inventory, Second Edition

The CDI-2 (Parent and Self-report Profiles) is administered at screening; baseline; and weeks 2, 4, 8, and 9. As the CDI-2 is designed for children 7 to 17 years of age, children 6 years of age at baseline will not complete the self-report version; the caregiver/adult will complete the parent version.

The CDI-2 Self-report is a 28-item self-report questionnaire assessing depressive symptoms in children 7 to 17 years of age with basic reading and comprehension skills. In the CDI-2, children are asked to choose 1 of 3 statements that most closely aligns with their feelings in the previous 2 weeks. The questionnaire covers both the major and minor symptoms of depression as outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (Sun and Wang 2015).

The CDI-2 Parent is a 17-item questionnaire administered to parents to assess depression-related behaviors observed in their children. In the CDI-2 Parent, parents are asked to rate their child's behaviors in the past 2 weeks on a 4-point Likert scale from "not at all" to "much or most of the time". The questionnaire allows for the division of depressive symptoms into functional problems and emotional problems (Sun and Wang 2015).

A reference sample is provided in Appendix J.

7.3. Pregnancy

Any female patient becoming pregnant during the study will discontinue IMP.

All pregnancies of female patients participating in the study that occur during the study, or within 14 days after the end of the study, are to be reported immediately to the individual identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the sponsor (LSO/CRO) with the completed pregnancy form. The

process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (see Section 7.1.5.3).

The investigator is not required to report patients who are found to be pregnant between screening and baseline, provided no IMP was given. All female patients who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous, elective, or voluntary abortion). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after withdrawal from the study will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy in the female patient participating in the study does not continue to term, 1 of the following actions will be taken:

- For a spontaneous abortion, report as a serious adverse event.
- For an elective abortion due to developmental anomalies, report as a serious adverse event.
- For an elective abortion **not** due to developmental anomalies, report on the pregnancy form; do not report as an adverse event.

7.4. Medication Error and Special Situations Related to the Investigational Medicinal Products

Any administration of IMP that is not in accordance with the study protocol should be reported on the CRF either as a violation, if it meets the violation criteria specified in the protocol (Appendix C), or as a deviation, in the patients source documents, regardless of whether or not an adverse event occurs as a result.

The following are types of medication errors and special situations:

1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.
2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied. Any dose of IMP (whether the test IMP or placebo), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor.
3. Misuse: Situations where the IMP is intentionally and inappropriately used not in accordance with the authorized product information.
4. Abuse: Persistent or sporadic, intentional excessive use of IMP which is accompanied by harmful physical or psychological effects.
5. Off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the authorized product information.

6. Occupational exposure: Exposure to an IMP, as a result of one's professional or non-professional occupation.
7. Breastfeeding: Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk.

7.5. Clinical Laboratory Tests

All clinical laboratory test results outside of the reference range will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

The clinical significance of the laboratory value will be evaluated by the criteria described in the laboratory manual and by the judgement of the investigator. A laboratory test result that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event, and monitored as described in Section 7.1.2. An event may include a laboratory or diagnostic test abnormality (once confirmed by repeated testing) that results in the withdrawal of the patient from the study, the temporary or permanent withdrawal of IMP, or further diagnostic work-up. (Note: Abnormal laboratory or diagnostic test results at the screening visit that preclude a patient from entering the study or receiving IMP are not considered adverse events.).

Table 6: Clinical Laboratory Tests

Serum Chemistry	Hematology	Urinalysis
calcium phosphorus sodium potassium chloride creatinine glucose magnesium BUN total cholesterol uric acid Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Lactate dehydrogenase (LDH) Alkaline phosphatase (ALP) bicarbonate or carbon dioxide total protein albumin total bilirubin direct bilirubin	hemoglobin hematocrit red blood cell (RBC) count mean cell volume platelet count white blood cell (WBC) count, and differential count – Absolute neutrophil count (ANC) – polymorphonuclear leukocytes (neutrophils) – lymphocytes – eosinophils – monocytes – basophils	protein glucose ketones blood (hemoglobin) pH specific gravity microscopic – bacteria – RBCs – WBCs – casts – crystals

7.5.1. Serum Chemistry, Hematology, and Urinalysis

Clinical laboratory tests (serum chemistry, hematology, and urinalysis) will be performed at the time points detailed in Table 2. Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are provided in Table 6.

7.5.2. Other Clinical Laboratory Tests

7.5.2.1. Human Chorionic Gonadotropin Tests

β-HCG tests in serum or urine will be performed for all females who are postmenarchal or ≥12 years of age as detailed in Table 2 and, if clinically indicated. Any female patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.3.

7.5.2.2. Urine Drug Screen

A urine drug screen (UDS) will be performed at the time points specified in Table 2. The UDS detects the presence of drugs prohibited according to the laboratory manual. If a given parameter cannot be tested using urine, an alternative matrix (eg, serum) may be considered acceptable. The sponsor's medical expert must be made aware in advance of, and provide approval for, drug screen parameters to which this will apply.

A positive result for any of the above drugs or their metabolites, without medical explanation, will preclude the patient from enrollment or continued participation in the study.

7.5.2.3. Cytochrome P450 2D6 Genotyping

One 3-mL sample for CYP2D6 genotyping will be collected from all patients in the study at screening. Sample testing results will not be provided to the study team until the study is unblinded.

This assessment potentially includes the association analysis of the variation in CYP2D6 gene with clinical treatment responses to the IMP (eg, efficacy, pharmacokinetic, tolerability, and safety features or disease susceptibility and severity features).

7.6. Physical Examinations

Physical examination, including height and weight, general appearance, skin, head, eyes, ears, nose, throat, neck, lymph nodes, cardiovascular, respiratory, musculoskeletal, abdominal, and extremities will be performed at the time points detailed in Table 2.

Weight must be measured with shoes and outerwear off.

Any physical examination finding that is judged by the investigator as a clinically significant (except at the screening visit) will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

7.7. Vital Signs

Vital signs (pulse, BP, body temperature, and respiratory rate) will be measured at the time points detailed in Table 2. All vital signs results outside of the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

Before BP and pulse are measured, the patient must rest in a supine or semi-erect/seated position for at least 5 minutes. (The same position and arm should be used each time vital signs are measured for a given patient.) For any abnormal vital sign value, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event, and monitored as described in Section 7.1.2.

7.8. Electrocardiography

A 12-lead ECG will be recorded at the time points detailed in Table 2. All ECGs will be performed after at least 5 minutes rest in a supine or semi-supine position. A qualified physician at a central diagnostic center will be interpreting the ECG.

All ECG results outside of the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

Any ECG finding that is judged by the investigator as clinically significant (except at the screening visit) will be considered an adverse event, recorded on the source documentation and in the CRF, and monitored as described in Section 7.1.2.

If a post-baseline QTcF value >500 msec or change from baseline >60 msec is found, the investigator should repeat the ECG assessment twice and compare the average of the 2 pre-treatment QTcF values (baseline and screening) to the average of the 3 post-baseline QTcF values. The IMP must be stopped for any confirmed post-baseline QTcF value >500 msec or increase from baseline >60 msec.

7.9. Assessment of Suicidality

TEV-50717 is considered to be central nervous system (CNS)-active. In addition, there have been some reports of suicidal ideation or behavior as reported in the product label when it has been given to some patients with certain conditions. The sponsor considers it important to monitor for such events before and during this clinical study.

Some CNS-active IMPs may be associated with an increased risk of suicidal ideation or behavior when given to some patients with certain conditions. Although this IMP or other similar medicinal products in this class have not been shown to be associated with an increased risk of suicidal thinking or behavior when given to this study population, the sponsor considers it important to monitor for such events before or during this clinical study.

The study population being administered TEV-50717 should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing TEV-50717 in participants who experience signs of suicidal ideation or behavior; detailed recommendations are provided in Section 7.2.2.

Baseline assessment of suicidal ideation and behavior and treatment-emergent suicidal ideation and behavior will be assessed during the study using the Columbia-Suicide Severity Rating Scale described in Section 7.2.2.

Depression and Suicidality as an Adverse Event

Families and caregivers of subjects will be instructed to monitor patients for any changes in or new onset of depressive symptoms; unusual changes in mood, cognition, or behavior; or onset of and/or changes in suicidal ideation or behavior, and to report such symptoms immediately to the study investigator. Telephone contacts and clinic visits also allow opportunities for investigators to assess adverse events.

If a relevant change in status is identified, patients will be seen immediately for an unscheduled visit by the study investigator and discussed with the medical monitor. The patient will be referred for further psychiatric evaluation if there is any suspected suicidal ideation with any level of intent, suicidal behavior, or clinical findings suggesting that the patient may be dangerous to self or others, and/or experiencing depression. The investigator will record these symptoms as an adverse event of depression and/or suicidality. If it is determined by the investigator, after consultation with the medical monitor and the consulting psychiatrist, that exposure to the IMP may have contributed to the adverse event of depression or suicidality, IMP will be immediately discontinued and the patient will be terminated from the study. Follow up with a pediatric psychiatrist or licensed child and adolescent mental health clinician will be arranged.

In cases where it is determined that IMP did not contribute to the adverse event of depression or suicidality, the investigator will consult with the medical monitor and/or sponsor to determine whether the patient should continue in the study.

A reference sample is provided in Appendix K.

7.10. Neurological Examinations

Neurological examination, including mental status, cranial nerves, motor system (strength, tone, and posture), coordination, gait and balance, tendon reflexes, and sensation, will be performed at the time points detailed in Table 2. Any neurological examination finding that is judged by the investigator as a potentially clinically significant change (worsening) compared with the screening value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

7.11. Concomitant Medication or Treatment

Concomitant therapy or medication usage will be monitored throughout the study. Parents/patients will be instructed during the course of the study to notify the investigator if any new medication is prescribed/administered, including over-the-counter medications. Any prescribed/administered medication should be reviewed with the investigator.

Medications that are allowed, provided that conditions outlined in the table are met, are shown in Appendix H, Table 7. The tables for allowed and prohibited medications are not comprehensive and may not include all possible concomitant medications.

The medical monitor must be contacted if a patient is receiving (or has to begin or stop receiving during the study) a medication that is associated with QTc prolongation or that is a known strong CYP inhibitor, or if there are any questions regarding any medication not listed in Appendix H.

Prohibited medications that are associated with QTc prolongation are listed in Appendix H, Table 10, while prohibited antipsychotic drugs are listed in Appendix H, Table 9.

7.12. Methods and Time Points of Assessing, Recording, and Analyzing Safety Data

All adverse events will be reviewed on a periodic basis by the clinical project physician/medical monitor according to the safety monitoring plan (eg, scheduled safety reviews for TEV-50717) as preliminary safety databases become available.

Methods and time points of assessing safety data are discussed in Section 3.6. Procedures for recording safety data are discussed in Appendix S, and methods of analyses are discussed in Section 9.7.

8. ASSESSMENT OF PHARMACOKINETICS / PHARMACODYNAMICS

8.1. Pharmacokinetic Assessment

Blood samples will be obtained for the measurement of plasma concentrations of TEV-50717 (deutetrabenazine), α-HTBZ, β-HTBZ, and other metabolites, as required.

Blood sampling for pharmacokinetics will be performed at the week 8 visit. Two samples will be collected. The first sample will be collected upon arrival at the clinic. The second sample will be collected 2 to 3 hours after the first pharmacokinetic sample collection. The time between samples should be maximized in order to provide the most useful information. Patients with early morning visits (ie, within 2 hours of their scheduled AM dosing) should take their dose in the clinic after the first pharmacokinetic sample is collected.

Patients will be provided with a diary to provide critical information on dosing at baseline, week 2, week 4, and at unscheduled visits. The date and time of the last dose of study medication before the week 8 visit should be recorded in the diary by the patient or caregiver/adult. The site will document the date and time of the sample collection. Prior to the clinic visit at week 8, patients will be reminded to record the start time of their last meal and the time of their last dose in their diary.

Blood samples (5 mL) will be collected via venipuncture for plasma concentration measurements of TEV-50717 and metabolites or other analytes.

The dates and times of IMP administration and the date and time of each pharmacokinetic sample will be recorded on the source documentation and transcribed onto the CRF.

An exploratory analysis of the pharmacokinetics of active metabolites on the pharmacodynamics or safety endpoints may be performed.

Additional details regarding sampling and handling as well as shipment and analysis of samples will be provided in the laboratory manual.

8.2. Pharmacodynamics Assessment

Exposure-response (eg, pharmacodynamic [PD] and/or safety endpoints) may be assessed if the appropriate data are available.

8.3. Pharmacogenetics

8.3.1. CYP2D6 Genotyping/Pharmacogenetics

At the screening visit, a blood sample (3 mL) will be obtained for analysis of CYP2D6 genotype. The patient's genotype for CYP2D6 will remain blinded during the conduct of the study. If the patient elects for pharmacogenetics (PGx) evaluation on the optional informed consent/assent, a PGx sample (2 mL) will be obtained and stored for exploratory PGx evaluation. This PGx assessment will investigate the relationship between subjects' genetic variability and study outcomes. Candidate genes included in this assessment may be related to, or hypothesized to be

related to, pharmacokinetics, safety features, drug mechanism of action, Tourette syndrome, or related diseases. The final list of genes to be evaluated will be determined at the time of analysis to be able to account for the most current research.

9. STATISTICS

This section describes the statistical analysis as foreseen at the time of planning the study. Changes, additions, and further details about the analyses will be described in the statistical analysis plan. After finalization of the statistical analysis plan, any additional analyses or changes to analyses that may be required will be fully disclosed in the CSR.

9.1. Sample Size and Power Considerations

It is estimated that approximately 50 patients per arm will enable a power of at least 90% to detect a beneficial standardized effect of 68% or more when the TEV-50717 arm is compared to placebo (difference of 6.5 in the change from baseline to week 8 in TTS, assuming a standard deviation of 9.5 in each arm) in a 2-sided type I error rate of 5% after accounting for potential dropouts.

9.2. Analysis Sets

9.2.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all randomized patients, regardless of whether or not a patient took any IMP. In this population, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

9.2.2. Modified Intent-to-Treat Analysis Set

The modified intent-to-treat (mITT) analysis set is a subset of the ITT analysis set including only patients who receive at least 1 dose of IMP and who have both a baseline and at least 1 postbaseline YGTSS assessment.

In the mITT analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received. All primary and secondary analyses will be based on the mITT set.

9.2.3. Safety Analysis Set

The safety analysis set will include all randomized patients who receive at least 1 dose of IMP.

In the safety analysis set, treatment will be assigned based on the treatment the patients actually received, regardless of the treatment to which they were randomized, unless otherwise specified.

9.2.4. Per-Protocol Analysis Set

The per-protocol analysis set will include patients who are compliant with study medication (80% to 105%), have a YGTSS assessment at baseline and at weeks 2, 4, and 8, and who have not taken prohibited concomitant medications as indicated in exclusion criterion, and who have no major protocol deviations that affect the validity of the efficacy measurements. The list of protocol deviations will be reviewed before unblinding, and major protocol deviations that could affect the primary and secondary variables will be determined.

9.2.5. Additional Analyses Sets

The pharmacokinetic analysis set will include those patients from the safety analysis set who have sufficient data to be included in the population pharmacokinetic analysis.

9.3. Data Handling Conventions

For all variables, only the observed data from the patients will be used in the statistical analyses, ie, there is no plan to estimate missing data, unless otherwise specified. For the sensitivity analysis of the primary and key secondary efficacy endpoints, detailed data imputation rules will be described in the statistical analysis plan.

9.4. Study Population

The mITT analysis set (see Section 9.2.2) will be used for all efficacy summaries and analyses unless otherwise noted. The safety analyses set will be used for all safety summaries. Sensitivity analyses of primary and key secondary endpoints will be conducted using the per-protocol analysis set. Summaries will be presented by treatment group and for all patients.

9.4.1. Patient Disposition

Data from patients screened; patients screened but not randomized (and reason not randomized); patients who are randomized; patients randomized but not treated (and reason); patients in the ITT, safety, and other analysis sets; patients who complete the study; and patients who withdraw from the study will be summarized using descriptive statistics. Data from patients who withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics.

9.4.2. Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including medical history, prior medications, and ECG findings, will be examined to assess the comparability of the treatment groups and will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented, if necessary.

9.5. Efficacy Analysis

9.5.1. Primary Endpoint

The primary efficacy endpoint is the change in the TTS of the YGTSS from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients.

9.5.2. Key Secondary Endpoints

1. Change in the TS-CGI score from baseline to week 8 between high-dose TEV-50717 treated patients and placebo treated patients
2. Change in the TTS of the YGTSS from baseline to week 8 for low-dose TEV-50717 and placebo will be tested

3. Change in the TS-CGI score from baseline to week 8 between low dose TEV-50717-treated patients and placebo-treated patients
4. Change in the TS- PGII score from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients
5. Change in the TS-PGII score from baseline to week 8 between low-dose TEV-50717-treated patients and placebo-treated patients
6. Change in the C&A-GTS-QOL ADL subscale from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients
7. Change in the C&A-GTS-QOL ADL subscale from baseline to week 8 between low-dose TEV-50717 treated patients and placebo treated patients

9.5.3. Exploratory Endpoints

9.5.4. Safety Endpoints

9.5.5. Planned Method of Analysis

The mITT analysis set (Section 9.2.2) will be used for all efficacy analyses. Summaries will be presented by treatment group.

9.5.5.1. Primary Efficacy Analysis

The primary efficacy endpoint for this study is the change in the TTS of the YGTSS from baseline to week 8 between high-dose TEV-50717-treated and placebo-treated patients. The primary analysis will be a mixed-model repeated-measures model with the change in the TTS as the dependent variable. The model will include fixed effects for treatment group, week (3 levels: weeks 2, 4, and 8), and the treatment group-by-week interaction. The baseline TTS, region, and age group at baseline (2 levels: 6 to 11 years, 12 to 16 years) will be included as covariates. The unstructured covariance matrix for repeated observations within patients will be used. The least squares means of the change in TTS from baseline at week 8 will be compared between the high-dose treatment arm and the placebo arm using a 2-sided test at the alpha = 0.05 level of significance. In addition, actual values and changes in the TTS from baseline to each visit will be summarized using descriptive statistics.

9.5.5.2. Sensitivity Analysis

Sensitivity analyses for missing data and the statistical model will be provided in the statisitical analysis plan.

9.5.5.3. Key Secondary Efficacy Analyses

A hierarchical (fixed-sequence) testing approach will be used for the analysis of the key secondary endpoints. If an endpoint is not statistically significant, confirmatory hypothesis testing will not be not carried out on the remaining hypotheses, and remaining hypotheses will be considered exploratory rather than confirmatory. The following analyses of key secondary endpoints will be conducted:

1. The change from baseline to week 8 in TS-CGI will be analyzed using a similar model as the primary analysis; however, instead of change in YGTSS TTS as the dependent variable and baseline YGTSS TTS as a covariate, the corresponding TS-CGI values will be used. The comparison between high-dose TEV-50717 and placebo will be tested.
2. Using the same model as for the primary analysis, the comparison between the change in the TTS of the YGTSS from baseline to week 8 for low-dose TEV-50717 and placebo will be tested.
3. Using the same model as described in endpoint #1 above for TS-CGI, the comparison between the change in the TS-CGI values from baseline to week 8 for low-dose TEV-50717 and placebo will be tested.
4. The change from baseline to week 8 in TS-PGII will be analyzed using a Cochran-Mantel-Haenszel-row mean score test with modified ridit scoring controlling for age group. The comparison between high-dose TEV-50717 and placebo will be tested.
5. Using the same model as described in endpoint #4 above for TS-PGII, the comparison between the change in the TS-PGII values from baseline to week 8 for low-dose TEV-50717 and placebo will be tested.
6. The change from baseline to week 8 in the C&A-GTS-QOL ADL subscale will be analyzed using a similar model as the primary analysis; however, instead of change in YGTSS TTS as the dependent variable and baseline YGTSS TTS as a covariate, the

corresponding C&A-GTS-QOL ADL subscale values will be used. The comparison between high-dose TEV-50717 and placebo will be tested.

7. Using the same model as described in endpoint #6 above for the C&A-GTS-QOL ADL subscale, the comparison between the change in the C&A-GTS-QOL ADL subscale scores from baseline to week 8 for low-dose TEV-50717 and placebo will be tested.

9.5.5.4. Exploratory Analyses

[redacted]

9.6. Multiple Comparisons and Multiplicity

The hierarchical testing method will be used to maintain the experiment-wise type I error of 5% level for the primary and key secondary analyses. The primary efficacy endpoint will first be tested at the 5% type I error level. If the p-value of the primary analysis is ≤0.05, the secondary hypotheses will be tested in the order listed for the analysis of key secondary endpoints until either an analysis produces a p-value >0.05 or all analyses result in a p-value ≤0.05.

9.7. Safety Analysis

Safety endpoints for this study are as follows:

- adverse events and concomitant medications: from the signing of the informed consent/assent form through follow-up, inclusive of all visits and telephone contacts
- physical examination: screening and week 8
- neurological examination: screening and week 8
- vital signs: screening; baseline; and weeks 2, 4, 8, and 9
  Note: orthostatic blood pressure and pulse at baseline and weeks 4 and 8
- children's C-SSRS
  - baseline/Screening scale: screening
  - since Last Visit scale: baseline, and weeks 2, 4, 8, and 9
- CDI-2 (Parent and Self-report Profiles): screening; baseline; and weeks 2, 4, 8, and 9
- 12-Lead ECG: screening, baseline, and weeks 4 and 8
- clinical laboratory tests (serum chemistry, hematology, and urinalysis): screening and week 8
- pregnancy testing: screening, baseline, and week 8
- drug screen: screening and week 8

Safety analyses will be performed on the safety analysis set (Section 9.2.3).

9.7.1. Safety Analysis

All adverse events will be coded using the Medical Dictionary for Regulatory Activities. Each patient will be counted only once in each preferred term or system organ class category for the analyses of safety. Summaries will be presented for all adverse events, adverse events determined by the investigator to be related to study treatment, serious adverse events, and adverse events causing withdrawal from the study. Summaries will be presented by treatment group and for all patients. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

Observed values and changes from baseline in laboratory results and vital signs will be summarized descriptively.

Observed values in ECG parameters will be summarized, and counts and percentages of abnormal findings will be presented. In addition, the number and percentage of patients with

on-treatment QTcF values >450, >480, or >500 msec and change from baseline >30 or >60 msec, will be presented.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with IMP.

Observed values in the C-SSRS and observed values and changes from baseline in the CDI-2 (Parent and Self-report Profiles) will be presented by treatment group for all patients.

9.8. Tolerability Analysis

Tolerability was not specifically defined.

9.9. Pharmacokinetic Analysis

Blood samples will be obtained for the measurement of plasma concentrations of TEV-50717 (deutetrabenazine), α-HTBZ, β-HTBZ, and other metabolites, as required.

Blood sampling for pharmacokinetics will be performed at the week 8 visit. Two samples will be collected. The first sample will be collected upon arrival at the clinic. The second sample will be collected within 2 to 3 hours after the first pharmacokinetic sample collection. The time between samples should be maximized in order to provide the most useful information. Patients with early morning visits (ie, within 2 hours of their scheduled AM dosing) should take their dose in the clinic after the first pharmacokinetic sample is collected.

Patients will be provided with a diary to provide critical information on dosing at baseline, week 2, week 4, and at unscheduled visits. The date and time of the last dose of study medication before the week 8 visit should be recorded in the diary by the patient or caregiver/adult. The site will document the date and time of the sample collection. Prior to the clinic visit on week 8, patients will be reminded to record the start time of their last meal and the time of their last dose in their diary.

Plasma samples for both α-HTBZ and β-HTBZ metabolite concentrations will be pooled with previous data and analyzed using population pharmacokinetics techniques. The population pharmacokinetics analysis will result in a final structural model that best describes the data. A covariate assessment will evaluate the relationship between potential covariates (ie, body weight, age, height, etc.) and concentrations of α-HTBZ and β-HTBZ metabolites. The final population pharmacokinetic analysis will be included in a separate report.

9.10. Planned Interim Analysis

There will be no formal interim analysis.

9.11. Reporting Deviations from the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the statistical analysis plan, the CSR, or any combination of these, as appropriate, and in accordance with applicable national, local, and regional requirements and regulations.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Refer to Appendix C for information regarding quality control and quality assurance. This includes information about protocol amendments, deviations, responsibilities of the investigator to study personnel, study monitoring, and audit and inspection.

Refer to Appendix R for the definition of a clinical product complaint and investigator responsibilities in the management of a clinical product complaint.

11. COMPLIANCE STATEMENT

This study will be conducted in full accordance with the ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice E6 and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [21CFR] Parts 11, 50, 54, 56, 312, and 314, Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use). Any episode of noncompliance will be documented.

The investigator is responsible for performing the clinical study in accordance with this protocol and the applicable GCP guidelines referenced above for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this clinical study in accordance with the protocol will be documented in separate clinical study agreements with the sponsor and other forms as required by national competent authorities in the country where each investigational center is located.

The investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the clinical study; and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the involved clinical study personnel must be familiar with the background and requirements of the study; and with the properties of the IMPs as described in the IB or prescribing information.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the clinical study at that investigational center and for contacts with study management, with the Independent Ethics Committee/Institutional Review Board (IEC/IRB), and with competent authorities.

See Appendix D for the ethics expectations of informed consent or assent, competent authorities and independent ethics committee and institutional review board, confidentiality regarding study patients, and requirements for registration of the clinical study.

12. DATA MANAGEMENT AND RECORD KEEPING

See Appendix S for information regarding data management and record keeping. This includes direct access to source data and documents, data collection, data quality control, and archiving of CRFs and source documents.

13. FINANCING AND INSURANCE

A separate clinical study agreement, including a study budget, will be signed between each principal investigator and Syneos Health before the IMP is delivered.

The patients in this clinical study are insured in accordance with applicable legal provisions. The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions. Excluded from the insurance coverage are eg, damages to health, and worsening of previous existing disease that would have occurred or continued if the patient had not taken part in the clinical study.

The policy of Clinical Trials Insurance will be provided to the investigational centers by the sponsor.

For covered clinical studies (see 21CFR54), the investigator will provide the sponsor with financial information required to complete Food and Drug Administration (FDA) 3454 form. Each investigator will notify the sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

14. REFERENCES

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15. SUMMARY OF CHANGES TO PROTOCOL

15.1. Amendment 03 Dated 05 May 2019

The primary reason for this amendment is [redacted]

This amendment is considered to be substantial (ie, requires approval by Competent Authority, IEC, and/or IRB) by the sponsor's Authorized Representative. Other nonsubstantial changes have been made to the protocol (and protocol synopsis, as appropriate). These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

Original text with changes shown	New wording	Reason/Justification for change
Global		
Number of Patients Planned (total): ~~174 (58~~150 (50 per treatment arm)	**Number of Patients Planned (total):** 150 (50 per treatment arm)	Upon further review, study sample size has been reverted back to the original sample size prior to Amendment 02.
1.1 Introduction		
Studies have suggested that ~~up to 7%~~the prevalence estimates of ~~school~~TS among children ~~fulfill the diagnostic criteria for TS~~ vary widely from 0.4% to 5% in community samples (~~Kurlan et al 2002~~Bitsko et al 2014).	Studies have suggested that the prevalence estimates of TS among children vary widely from 0.4% to 5% in community samples (Bitsko et al 2014).	Updated the prevalence estimates of TS among children upon further literature review for accuracy
3.2 Planned Number of Patients and Countries		
The number of evaluable patients is planned to be ~~174~~150.	The number of evaluable patients is planned to be 150.	Enrollment number has been decreased back to the original sample size prior to Amendment 02.
5.10.1 Maintenance of Randomization		
Patient randomization codes will be maintained in a secure location within Syneos Health~~, Biometrics~~. At the time of analysis, when treatment codes are needed, the Syneos Health statistician assigned to the study will make a request to unblind, and will receive the unblinded codes and unblinded IMP assignment according to the processes defined in the relevant Standard Operating Procedure.	Patient randomization codes will be maintained in a secure location within Syneos Health. At the time of analysis, when treatment codes are needed, the Syneos Health statistician assigned to the study will make a request to unblind, and will receive the unblinded codes and unblinded IMP assignment according to the processes defined in the relevant Standard Operating Procedure.	Updated direction on how/who will maintain patient randomization
9.1 Sample Size and Power Considerations		
It is estimated that approximately ~~58~~50 patients per arm will enable a power of at least 90% to detect a beneficial standardized effect of ~~63~~68% or more when the TEV-50717 arm is compared to placebo (difference of ~~6.0~~6.5 in the change from baseline to week 8 in TTS, assuming a standard deviation of 9.5 in each arm) in a 2-sided type I error rate of 5% after accounting for potential dropouts.	It is estimated that approximately 50 patients per arm will enable a power of at least 90% to detect a beneficial standardized effect of 68% or more when the TEV-50717 arm is compared to placebo (difference of 6.5 in the change from baseline to week 8 in TTS, assuming a standard deviation of 9.5 in each arm) in a 2-sided type I error rate of 5% after	Updated the sample size back to the expected enrollment number prior to Amendment 02. The statistical considerations were updated per most current assumptions.

Original text with changes shown	New wording	Reason/Justification for change
~~The sample size for this study has been increased from 150 total patients (50 patients per arm) to 174 total patients (58 patients per arm). This adjustment is based solely on external data (ie, valbenazine Phase 2 study results, efficacy of TEV-50717 in the treatment of HD and TD, and ABILIFY® Phase 3 data). Data from the ongoing TEV-50717 Phase 2/3 and Phase 3 studies, TV50717-CNS-30046 and TV50717-CNS-30060, are blinded and were not used to inform the sample size calculation.~~	accounting for potential dropouts.	
9.5.5.2 Sensitivity Anlaysis		
Sensitivity analyses for missing data~~,~~ and the statistical model~~, and for the increase in sample size,~~ will be ~~conducted as detailed~~provided in the statisitical analysis plan.	Sensitivity analyses for missing data and the statistical model will be provided in the statisitical analysis plan.	The definition of the sensitivity analysis was updated to remove any mention of increased sample size, now that we have reverted back to the original sample size prior to Amendment 02.
14 References		
Bitsko RH, Holbrook JR, Visser SN, et al. A National Profile of Tourette Syndrome, J Dev Behav Pediatr 2014;35(5):317-22. ~~Kurlan R, Como PG, Miller B, Palumbo D, Deeley C, Andresen EM, et al. The behavioral spectrum of tic disorders: a community-based study. Neurology 2002;59(3):414-20.~~	Bitsko RH, Holbrook JR, Visser SN, et al. A National Profile of Tourette Syndrome, J Dev Behav Pediatr 2014;35(5):317-22.	Upon further literature review, an updated reference has been included to more accurately present the prevalence estimates of TS among children.

15.2. Amendment 02 Dated 25 March 2019

The primary reasons for this amendment are to increase study sample size and update corresponding statistical considerations; include additional nonclinical data observed in rat toxicology studies; further clarify procedures to be carried out during the screening and enrollment periods (eg, informed consent/assent stipulations); update requirements on drug storage, accountability, and security; update/clarify patient inclusion criteria, exclusion criteria, and withdrawal criteria; [redacted]; provide updates on allowed and prohibited medications; and include additional guidance for evaluation and management of suicidal ideation, suicidal behavior, and depression.

This amendment is considered to be substantial (ie, requires approval by Competent Authority, IEC, and/or IRB) by the sponsor's Authorized Representative. Other nonsubstantial changes have been made to the protocol (and protocol synopsis, as appropriate). These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

Original text with changes shown	New wording	Reason/Justification for change
Global		
Informed consent/assent ~~or assent~~, depending on the child's age, as appropriate, is obtained	Informed consent/assent, depending on the child's age, as appropriate, is obtained	Update made for clarity on expectations surrounding obtaining informed consent and/or assent, dependent upon the child's age
Patients and their ~~parent/legal guardian~~caregiver/adult…	Patients and their caregiver/adult…	Updated terminology surrounding the patient's caregiver/adult to encompass all scenarios of individuals caring for this population
Title Page		
~~601 Gateway Boulevard~~ ~~Suite 1270~~ ~~South San Francisco, California 94080~~ 101 Main Street, 12th Floor Cambridge, Massachusetts 02142	101 Main Street, 12th Floor Cambridge, Massachusetts 02142	Address update
This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Branded Pharmaceutical Products R&D, and Nuvelution TS Pharma, INC, and/or its affiliates. © ~~2017~~2019 Teva Branded Pharmaceutical Products R&D, Inc. and Nuvelution TS Pharma, INC. All rights reserved.	This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Branded Pharmaceutical Products R&D, and Nuvelution TS Pharma, INC, and/or its affiliates. © 2019 Teva Branded Pharmaceutical Products R&D, Inc. and Nuvelution TS Pharma, INC. All rights reserved.	Updates included per Teva's current Confidentiality Statement template text
Clinical Laboratory and Other Departments and Institutions		
Sponsor's Authorized Representative [redacted]	**Sponsor's Authorized Representative** [redacted]	Update to Sponsor representatives and points of contact

Original text with changes shown	New wording	Reason/Justification for change
[redacted] **Legal Representative of the Sponsor in the EU** [redacted] **<u>For protocol issues, contact the following study leaders (right)</u>** **Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study** [redacted] **<u>For medical issues, contact the following physicians (right)</u>** **Sponsor's Representative of Global Patient Safety and Pharmacovigilance** For **serious adverse events:** [redacted]	**Legal Representative of the Sponsor in the EU** [redacted] **For protocol issues, contact the following study leaders (right)** **Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study** [redacted] **For medical issues, contact the following physicians (right)** **Sponsor's Representative of Global Patient Safety and Pharmacovigilance** For **serious adverse events:** [redacted]	

Original text with changes shown	New wording	Reason/Justification for change
[redacted]	[redacted]	

Original text with changes shown	New wording	Reason/Justification for change
[redacted] **For serious adverse events** Send by email to the local safety officer (LSO)/ Syneos Health. The email address will be provided in the serious adverse event report form. In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction. **Central Institutional Review Board** Copernicus Group IRB 1 Triangle Drive Durham, NC 27709 USA **Central Clinical Laboratory** Q2 Solutions (Quest) LLC	[redacted] **For serious adverse events** Send by email to the local safety officer (LSO)/ Syneos Health. The email address will be provided in the serious adverse event report form. In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction. **Central Institutional Review Board** Copernicus Group IRB 1 Triangle Drive Durham, NC 27709 USA **Central Clinical Laboratory** Q2 Solutions (Quest) LLC 27027 Tourney Road, Suite 2E Valencia, CA 91355 USA	

Original text with changes shown	New wording	Reason/Justification for change
27027 Tourney Road, Suite 2E Valencia, CA 91355 USA **Electronic Data Capture** Medidata RAVE (through Syneos Health) **Contract Research Organization** Syneos Health, LLC 1030 Sync Street Morrisville, NC 27560 USA **Central Electrocardiogram Evaluation** ERT 1818 Market Street 10th Floor Philadelphia, PA 19103 USA ~~**Bioanalytical Pharmacokinetics Evaluation**~~ ~~Information will be included in the Trial Master File~~ ~~**Randomization and Trial Supply Management (RTSM) vendor**~~ ~~Endpoint~~ **Integrated Response Technology** Endpoint 55 Francisco Street, Suite 200 San Francisco, CA 94133 USA **ePRO, eCOA, and Scales Training** Bracket Global, LLC 575 East Swedesford Road, Suite 200 Wayne, PA 19087 USA	**Electronic Data Capture** Medidata RAVE (through Syneos Health) **Contract Research Organization** Syneos Health, LLC 1030 Sync Street Morrisville, NC 27560 USA **Central Electrocardiogram Evaluation** ERT 1818 Market Street 10th Floor Philadelphia, PA 19103 USA **Integrated Response Technology** Endpoint 55 Francisco Street, Suite 200 San Francisco, CA 94133 USA **ePRO, eCOA, and Scales Training** Bracket Global, LLC 575 East Swedesford Road, Suite 200 Wayne, PA 19087 USA	
Synopsis		

Original text with changes shown	New wording	Reason/Justification for change
Countries Planned: North America, Latin America, ~~Turkey~~Australia, Ukraine, South Korea, and Europe	**Countries Planned:** North America, Latin America, Australia, Ukraine, South Korea, and Europe	Updated list of countries for inclusion
1.1 Introduction		
To address the limitations of commercial tetrabenazine (XENAZINE®), Auspex, a wholly owned subsidiary of Teva Pharmaceutical Products R&D, Inc, ~~has~~ developed ~~a deuterated form of tetrabenazine~~deutetrabenazine (referred to as TEV-50717 ~~or~~, previously SD-809) that is eliminated more slowly than tetrabenazine.	To address the limitations of commercial tetrabenazine (XENAZINE®), Auspex, a wholly owned subsidiary of Teva Pharmaceutical Products R&D, Inc, developed deutetrabenazine (referred to as TEV-50717, previously SD-809) that is eliminated more slowly than tetrabenazine.	Minor updates to streamline background on drug product

Original text with changes shown	New wording	Reason/Justification for change
1.3.1.3 Toxicology		
The NOAEL (no-observed-adverse-effect level) for toxicities in juvenile rats is lower than that in adults; however, the total (α+β)-HTBZ exposure multiples or safety margins comparing rat to humans at the adult and juvenile age categories are similar. The potential for increased sensitivity to the effects of TEV-50717 in pediatric patients is mitigated by 2 factors. First, the effects of TEV-50717 on behavior and weight gain recovered with cessation of test article administration in the juvenile rat toxicology study. Second, the clinical significance of tremors and reduced body weight gain in rats dosed with TEV-50717 are unclear because these findings were not adverse events of note in adults or adolescent patients. While hypoactivity in rats has the potential to relate to clinical observations of somnolence, this adverse effect is controlled with dose reduction. In clinical comparison, the adverse event profile of tetrabenazine in adult patients is qualitatively similar to patients from approximately 22 months to 18 years of age (Jain et al 2006, Kenney et al 2007, Porta et al 2008).	The NOAEL (no-observed-adverse-effect level) for toxicities in juvenile rats is lower than that in adults; however, the total (α+β)-HTBZ exposure multiples or safety margins comparing rat to humans at the adult and juvenile age categories are similar. The potential for increased sensitivity to the effects of TEV-50717 in pediatric patients is mitigated by 2 factors. First, the effects of TEV-50717 on behavior and weight gain recovered with cessation of test article administration in the juvenile rat toxicology study. Second, the clinical significance of tremors and reduced body weight gain in rats dosed with TEV-50717 are unclear because these findings were not adverse events of note in adults or adolescent patients. While hypoactivity in rats has the potential to relate to clinical observations of somnolence, this adverse effect is controlled with dose reduction. In clinical comparison, the adverse event profile of tetrabenazine in adult patients is qualitatively similar to patients from approximately 22 months to 18 years of age (Jain et al 2006, Kenney et al 2007, Porta et al 2008).	Added no-observed-adverse-effect level for toxicities
1.3.2 Clinical Studies		
• 7~~6~~ completed Phase 1 studies in healthy adult volunteers • 2 ongoing Phase 1 studies in healthy adult volunteers • 1 ~~ongoing~~completed Phase 3 long-term safety study in patients with HD • 2 ongoing Phase 2/3 and Phase 3 studies in	• 7 completed Phase 1 studies in healthy adult volunteers • 2 ongoing Phase 1 studies in healthy adult volunteers • 1 completed Phase 3 long-term safety study in patients with HD • 2 ongoing Phase 2/3 and Phase 3 studies	The clinical development plan for TEV-50717 has been updated to reflect the most current program information

Original text with changes shown	New wording	Reason/Justification for change
patients with TS • 1 ongoing Phase 3 long-term safety study in patients with TS	in patients with TS • 1 ongoing Phase 3 long-term safety study in patients with TS	
2 Study Objectives and Endpoints		
This is a Phase ~~2~~/3 study to evaluate the efficacy and safety of deutetrabenazine (TEV-50717) tablets for the reduction of motor and phonic tics associated with TS in children and adolescents 6 through 16 years of age.	This is a Phase 3 study to evaluate the efficacy and safety of deutetrabenazine (TEV-50717) tablets for the reduction of motor and phonic tics associated with TS in children and adolescents 6 through 16 years of age.	This study is a Phase 3 study, not a Phase 2/3 study
2.2 Exploratory Endpoints (other sections affected: 9.5.3 Exploratory Endpoints)		
Exploratory Endpoints: • [redacted]	[redacted]	[redacted]
3.1 Study Design		
Screening period (up to 31 days): At the discretion of the investigator, the screening visit may be divided into 2 visits to reduce the burden on patients. If the screening visit is divided into 2 visits, the blood sample should be obtained during the first of the 2 visits. Patients will return to the clinic on day 1 for baseline procedures and to re-confirm eligibility. Patients may be rescreened 1 time if there is a change in the status of the patient regarding eligibility for the study. (Note: Details of rescreening must be approved and	Screening period (up to 31 days): At the discretion of the investigator, the screening visit may be divided into 2 visits to reduce the burden on patients. If the screening visit is divided into 2 visits, the blood sample should be obtained during the first of the 2 visits. Patients will return to the clinic on day 1 for baseline procedures and to re-confirm eligibility. Patients may be rescreened 1 time if there is a change in the status of the patient regarding	Updates to the study design included to specify screening procedures and to provide further guidance to investigators in the situation that a patient experiences certain types of adverse events

Original text with changes shown	New wording	Reason/Justification for change
documented by the medical monitor and/or Clinical Surveillance and Training [CST] team.) Treatment period (8 weeks): As this is a fixed-dose study, patients will undergo dose escalation (ie, forced titration) to their target dose over the first 4 weeks of treatment. If a patient experiences ~~either a protocol-defined "important neuropsychiatric adverse event" or a serious adverse event that is related to IMP, a single dose reduction is permitted. An "important neuropsychiatric adverse event" includes the following:~~ depression, suicidal ideation or behavior, anxiety, akathisia, parkinsonism, ~~and~~or somnolence, or any other adverse event that interferes with daily activity~~.~~, or any adverse event that is related to IMP, a single dose reduction is permitted. The investigator must discuss any further dose adjustments (eg, holding the dose or doses) with the medical monitor.	eligibility for the study. (Note: Details of rescreening must be approved and documented by the medical monitor and/or Clinical Surveillance and Training [CST] team.) Treatment period (8 weeks): As this is a fixed-dose study, patients will undergo dose escalation (ie, forced titration) to their target dose over the first 4 weeks of treatment. If a patient experiences depression, suicidal ideation or behavior, anxiety, akathisia, parkinsonism, or somnolence, or any other adverse event that interferes with daily activity, or any adverse event that is related to IMP, a single dose reduction is permitted. The investigator must discuss any further dose adjustments (eg, holding the dose or doses) with the medical monitor.	
Section 3.2 Planned Number of Patients and Countries (other sections effected: Section 9.1 Sample Size and Power Considerations and Figure 1: Overall Study Schematic Diagram)		
The number of evaluable patients is planned to be ~~150~~174.	The number of evaluable patients is planned to be 174.	Updated enrollment numbers. See further justification provided in Section 9.1 of the this summary of changes.
3.4 Drug Administration (other section effected: 5.1.2 Placebo Investigational Medicinal Product [Table 3])		
3.4 ~~Dose Escalation Procedures~~ Drug Administration • ~~To preserve the blinding, 2~~ The total daily dose, as provided in Table 1, is divided into a twice daily administration. Two tablets will be taken twice daily starting at day 1 per Table 1… • ~~Dose reductions, if required, should be in increments~~	**3.4 Drug Administration** • The total daily dose, as provided in Table 1, is divided into a twice daily administration. Two tablets will be taken twice daily starting at day 1 per Table 1… • In the case of an adverse event, the	Section heading updated per request from Regulatory Authorities Dosing information and dose reduction guidelines were clarified

<table>
<tr><th>Original text with changes shown</th><th>New wording</th><th>Reason/Justification for change</th></tr>
<tr><td>~~of 6 mg.~~ ~~If more than 1 dose reduction is required for an adverse event, the medical monitor must be notified.~~ In the case of an adverse event, the investigator is permitted to perform a single dose reduction of 6 mg. The investigator must discuss any further dose adjustments (eg, holding the dose or doses) with the medical monitor.

Table 1: Daily Dose of IMP by Baseline Body Weight Category, CYP2D6 Impairment, and Study Week
<table><tr><th>Dose group
Baseline weight (kg)</th><th>Daily dose (mg) at the start of visit/week[a]</th></tr></table>[a] Administration of a given dose will take place throughout the days indicated. The new dose starts the morning after the telephone contact or the morning after the clinic visit.</td><td>investigator is permitted to perform a single dose reduction of 6 mg. The investigator must discuss any further dose adjustments (eg, holding the dose or doses) with the medical monitor.

Table 1: Daily Dose of IMP by Baseline Body Weight Category, CYP2D6 Impairment, and Study Week
<table><tr><th>Dose group
Baseline weight (kg)</th><th>Daily dose (mg) at the start of visit/week[a]</th></tr></table>[a] Administration of a given dose will take place throughout the days indicated. The new dose starts the morning after the telephone contact or the morning after the clinic visit.</td><td>Footnote “a” was added to Table 1 to provide further clarity on dosing expectations</td></tr>
<tr><td colspan="3">Section 3.6: Table 2: Study Procedures and Assessments</td></tr>
<tr><td>Note: Week 4 assessments were previously captured underneath the “Maintenance Period” incorrectly. Week 4 assessments have been moved underneath the “Escalation Period.”
[e] The screening visit may be conducted over 2 separate visits at the discretion of the investigator. If the screening visit is divided into 2 visits, the blood sample should be obtained during the first of the 2 visits.
[f] Patients will be provided with a diary at baseline, week 2, week 4, and at unscheduled visits, to record critical information on dosing.</td><td>Note: Week 4 assessments were previously captured underneath the “Maintenance Period” incorrectly. Week 4 assessments have been moved underneath the “Escalation Period.”
[e] The screening visit may be conducted over 2 separate visits at the discretion of the investigator. If the screening visit is divided into 2 visits, the blood sample should be obtained during the first of the 2 visits.
[f] Patients will be provided with a diary at baseline, week 2, week 4, and at unscheduled visits, to record</td><td>Week 4 was placed under the correct study period

Dose escalation is allowed through week 4

Updated footnotes to include that blood samples should be obtained during the first screening visit (if 2 screening visits are required), to include</td></tr>
</table>

Original text with changes shown	New wording	Reason/Justification for change
[g] Dose escalation will only occur during the dose escalation period (ie, from week 1 to week ~~3~~4). [v] Contact IRT and dispense IMP and patient diary. Study drug will be dispensed in the clinic; patients will receive doses for 2 weeks (current dose level and next dose level) to cover the telephone contacts during escalation. See Table 1 for baseline weight-based dosing titration. At week 4, patients will receive doses for 4 weeks of treatment.	critical information on dosing. [g] Dose escalation will only occur during the dose escalation period (ie, from week 1 to week 4). [v] Contact IRT and dispense IMP and patient diary. Study drug will be dispensed in the clinic; patients will receive doses for 2 weeks (current dose level and next dose level) to cover the telephone contacts during escalation. See Table 1 for baseline weight-based dosing titration. At week 4, patients will receive doses for 4 weeks of treatment.	specific timepoints for diary dispensing, to clarify the dose escalation period, and to provide guidance on dispensing of IMP
4.1 Patient Inclusion Criteria (other sections affected: Appendix D Ethics)		
f. Patient and ~~parent/legal guardian~~caregiver/adult are willing to adhere to the medication regimen and to comply with all study procedures. h. In the investigator's opinion, the patient and ~~parent/legal guardian~~caregiver/adult have the ability to understand the nature of the study and its procedures, and the patient is expected to complete the study as designed. i. Patient and parent/legal guardian provided written informed consent/assent, depending on the child's age, as appropriate, according to local regulations ~~(eg, the patient has provided written assent and/or co-consent, as appropriate)~~.	f. Patient and caregiver/adult are willing to adhere to the medication regimen and to comply with all study procedures. h. In the investigator's opinion, the patient and caregiver/adult have the ability to understand the nature of the study and its procedures, and the patient is expected to complete the study as designed. i. Patient and parent/legal guardian provided written informed consent/assent, depending on the child's age, as appropriate, according to local regulations.	Updated language in the inclusion criteria to encompass all scenarios of individuals caring for this population and for alignment across the protocol
4.2 Patient Exclusion Criteria (other sections affected: Appendix H Allowed and Prohibited Medications)		
k. Patient has received any of the following concomitant medications for tics within the following specified exclusionary windows of ~~screening~~first dose: → within 4 weeks: cannabidiol oil and valbenazine Note: Use of stimulant medications, including amphetamine, methylphenidate, and lisdexamfetamine, is allowed if primary use is for the treatment of ADHD, dosing has been stable for at least 2 weeks before screening, and no changes to dose or	k. Patient has received any of the following concomitant medications for tics within the following specified exclusionary windows of first dose: → within 4 weeks: cannabidiol oil and valbenazine Note: Use of stimulant medications, including amphetamine, methylphenidate, and lisdexamfetamine, is allowed if primary use is for the	Added cannabidiol oil and valbenazine as concomitant medications Included notes for various different concomitant medications and stipulations Added monoamine oxidase

Original text with changes shown	New wording	Reason/Justification for change
frequency are anticipated during the course of the study. Note: Use of atomoxetine is allowed if the primary use is for the treatment of ADHD, dosing has been stable for at least 4 weeks before screening, and no changes to dose or frequency are anticipated during the course of the study. Note: Use of guanfacine or clonidine is allowed regardless of indication (ie, if prescribed for tics or TS) if the dosing has been stable for at least 4 weeks before screening and no changes to dose or frequency are anticipated during the course of the study. If discontinuation of either medication is anticipated due to ineffectiveness, poor tolerability, or patient/caregiver preference, discontinuation should occur 4 or more weeks prior to the screening visit. q. Patient has received a monoamine oxidase inhibitor within 14 days of the baseline visit.	treatment of ADHD, dosing has been stable for at least 2 weeks before screening, and no changes to dose or frequency are anticipated during the course of the study. Note: Use of atomoxetine is allowed if the primary use is for the treatment of ADHD, dosing has been stable for at least 4 weeks before screening, and no changes to dose or frequency are anticipated during the course of the study. Note: Use of guanfacine or clonidine is allowed regardless of indication (ie, if prescribed for tics or TS) if the dosing has been stable for at least 4 weeks before screening and no changes to dose or frequency are anticipated during the course of the study. If discontinuation of either medication is anticipated due to ineffectiveness, poor tolerability, or patient/caregiver preference, discontinuation should occur 4 or more weeks prior to the screening visit. q. Patient has received a monoamine oxidase inhibitor within 14 days of the baseline visit.	inhibitor as part of the exclusion criteria
4.3 Withdrawal Criteria and Procedures for the Patient		
The investigator also has the right to withdraw a patient from the study ~~in the event of~~ if any of the following events occur: a. intercurrent illness b. adverse events (any patient who experiences an adverse event may be withdrawn from the study or from study treatment at any time at the discretion of the investigator or sponsor as indicated in Section 7.1.7) c. pregnancy (see Section 7.37.3)~~, or~~ d. other reasons concerning the health or well-being of the patient ~~or in the event of~~ e. lack of cooperation~~. If a~~	The investigator also has the right to withdraw a patient from the study if any of the following events occur: a. intercurrent illness b. adverse events (any patient who experiences an adverse event may be withdrawn from the study or from study treatment at any time at the discretion of the investigator or sponsor as indicated in Section 7.1.7) c. pregnancy (see Section 7.3) d. other reasons concerning the health or well-being	Updated format and withdrawal criteria due to adverse event

Original text with changes shown	New wording	Reason/Justification for change
f. post-baseline QTcF value >500 msec or change from baseline >60 msec ~~is found, the~~ (as described in Section 7.1.7). The investigator should repeat the ECG assessment twice and compare ~~to~~ the average of the 2 pre-treatment QTcF values (baseline and screening) to the average of the 3 post-baseline QTcF values. The IMP must be stopped for any confirmed post-baseline QTcF value >500 msec or increase from baseline >60 msec. g. when a blind is broken due to safety concerns (see Section 5.10.2). If a patient is unblinded by mistake, the investigator should discuss with the medical monitor whether or not the patient should be withdrawn. h. if the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn from the study (Section 5.7).	of the patient e. lack of cooperation f. post-baseline QTcF value >500 msec or change from baseline >60 msec (as described in Section 7.1.7). The investigator should repeat the ECG assessment twice and compare the average of the 2 pre-treatment QTcF values (baseline and screening) to the average of the 3 post-baseline QTcF values. The IMP must be stopped for any confirmed post-baseline QTcF value >500 msec or increase from baseline >60 msec. g. when a blind is broken due to safety concerns (see Section 5.10.2). If a patient is unblinded by mistake, the investigator should discuss with the medical monitor whether or not the patient should be withdrawn. h. if the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn from the study (Section 5.7).	
4.5 Rescreening		
A patient who is screened but not enrolled may be rescreened ~~once~~1 time if there is a change in the status of the patient regarding eligibility for the study ~~patient's medical background, a modification of study entry criteria, or other relevant change~~. (Note: Details of rescreening must be approved and documented by the ~~study~~medical monitor and/or Clinical Surveillance and Training [CST] team.) If the patient is rescreened, an informed consent/assent form (ICF) will need to be resigned.	A patient who is screened but not enrolled may be rescreened 1 time if there is a change in the status of the patient regarding eligibility for the study. (Note: Details of rescreening must be approved and documented by the medical monitor and/or Clinical Surveillance and Training [CST] team.) If the patient is rescreened, an informed consent/assent form (ICF) will need to be resigned.	Provided further details rescreening activities and process

Original text with changes shown	New wording	Reason/Justification for change
5.1.1.2 Dose Modification and Dose Stratification		
As this is a fixed-dose study, patients will undergo dose escalation (ie, forced titration) to their target dose over the first 4 weeks of treatment (see Section 1.1 and Table 1). If a patient experiences ~~either a protocol-defined "important neuropsychiatric adverse event" or a serious adverse event that is related to IMP, a single dose reduction is permitted. An "important neuropsychiatric adverse event" includes the following:~~ depression, suicidal ideation or behavior, anxiety, akathisia, parkinsonism, or~~and~~ somnolence, or any other adverse event that interferes with daily activity~~.~~, or any adverse event that is related to IMP, a single dose reduction is permitted. The investigator must discuss any further dose adjustments (eg, holding the dose or doses) with the medical monitor.	As this is a fixed-dose study, patients will undergo dose escalation (ie, forced titration) to their target dose over the first 4 weeks of treatment (see Section 1.1 and Table 1). If a patient experiences depression, suicidal ideation or behavior, anxiety, akathisia, parkinsonism, or somnolence, or any other adverse event that interferes with daily activity, or any adverse event that is related to IMP, a single dose reduction is permitted. The investigator must discuss any further dose adjustments (eg, holding the dose or doses) with the medical monitor.	Updated dose modification language to provide additional guidance to the investigator
5.2.1 Storage and Security (other sections affected: Appendix G HANDLING, LABELING, STORAGE, AND ACCOUNTABILITY FOR IMP)		
The IMP (TEV-50717 and the placebo) ~~must~~should be stored protected from light, at a controlled room temperature, ~~15~~20°C to ~~30~~25°C (~~59~~68°F to ~~86~~77°F); however, storage between 15°C and 20°C (59°F and 68°F) is acceptable if there is no alternative. The IMP should be stored in a dry, securely locked, substantially constructed cabinet or enclosure with access limited to authorized staff.	The IMP (TEV-50717 and the placebo) should be stored protected from light, at a controlled room temperature, 20°C to 25°C (68°F to 77°F); however, storage between 15°C and 20°C (59°F and 68°F) is acceptable if there is no alternative. The IMP should be stored in a dry, securely locked, substantially constructed cabinet or enclosure with access limited to authorized staff.	Updated temperature range for storage of the IMP
5.2.3 Accountability		
Empty, partially used, and unused blister packs IMP will be ~~returned to the sponsor or designee~~disposed of, as agreed with the sponsor/development partner.	Empty, partially used, and unused blister packs IMP will be disposed of, as agreed with the sponsor/development partner.	Updated guidance surrounding disposal practices for the IMP
5.5. Restrictions (other sectins affected: Appendix H ALLOWED AND PROHIBITED MEDICATIONS)		
The use of quinidine and terbinafine are prohibited (see Appendix H, Table 11).	The use of quinidine and terbinafine are prohibited (see Appendix H, Table 11).	Added quinidine and terbinafine to the list of prohibited medications
5.8 Temporary Discontinuation of Investigational Medicinal Product		

Original text with changes shown	New wording	Reason/Justification for change
Dose Reduction ~~**If more than 1 dose reduction is required for an adverse event, the medical monitor must be notified.**~~ In the case of an adverse event, the investigator is permitted to perform a single dose reduction of 6 mg. **The investigator must discuss any further dose adjustments (eg, holding the dose or doses) with the medical monitor.** **Dose Suspension** Suspension of study medication for up to 1 week, if warranted for patient safety, is allowed. If the patient restarts study medication within 7 days of suspension, the full dose of TEV-50717 may be resumed without titration. **Suspensions of study medication for adverse events must be reviewed with the medical monitor before therapy is restarted**. If a subject's serum potassium or magnesium ~~falls below the lower limit of normal~~ were tested and found to be below the lower limit of normal and clinically significant, the laboratory test should be repeated at least once. If the abnormality in the repeated laboratory test is consistent with the prior laboratory test, IMP must be suspended. ~~**Similarly, suspensions for more than 7 days must be reviewed by the medical monitor to determine if there is adequate time for patients to be reiterated and complete study evaluations.**~~	**Dose Reduction** In the case of an adverse event, the investigator is permitted to perform a single dose reduction of 6 mg. **The investigator must discuss any further dose adjustments (eg, holding the dose or doses) with the medical monitor.** **Dose Suspension** Suspension of study medication for up to 1 week, if warranted for patient safety, is allowed. If the patient restarts study medication within 7 days of suspension, the full dose of TEV-50717 may be resumed without titration. **Suspensions of study medication for adverse events must be reviewed with the medical monitor before therapy is restarted**. If a subject's serum potassium or magnesium were tested and found to be below the lower limit of normal and clinically significant, the laboratory test should be repeated at least once. If the abnormality in the repeated laboratory test is consistent with the prior laboratory test, the IMP must be suspended.	Updated dose reduction and dose suspension text to provide further guidance
5.10.1 Maintenance of Randomization		
Patient randomization codes will be maintained in a secure location ~~at the service provider contracted to generate the codes. At the time of analysis (after the end of study), after receiving unblinding request from Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant Standard Operating Procedure (SOP).~~ within Syneos Health, Biometrics. At the time of analysis, when treatment codes are needed, the Syneos	Patient randomization codes will be maintained in a secure location within Syneos Health, Biometrics. At the time of analysis, when treatment codes are needed, the Syneos Health statistician assigned to the study will make a request to unblind and will receive the unblinded codes.	Updated guidance on the maintenance of randomization and the process for requesting unblinded codes

<table>
<tr><th>Original text with changes shown</th><th>New wording</th><th>Reason/Justification for change</th></tr>
<tr><td><u>Health statistician assigned to the study will make a request to unblind and will receive the unblinded codes.</u></td><td></td><td></td></tr>
<tr><td colspan="3">5.10.2 Blinding and Unblinding</td></tr>
<tr><td><u>However, if a patient is unblinded by mistake, the investigator should discuss with the medical monitor whether or not the patient should be withdrawn.</u></td><td>However, if a patient is unblinded by mistake, the investigator should discuss with the medical monitor whether or not the patient should be withdrawn.</td><td>Provided further guidance to the investigator in the situation that a patient is unblinded by mistake</td></tr>
<tr><td colspan="3">5.11 Total Blood Volume (other sections affected: 7.5.2.3 Cytochrome P450 2D6 Genotyping)</td></tr>
<tr><td>Table 4: Blood Volumes
<table>
<tr><th>Type of samples</th><th>Volume per sample</th><th>Total number of samples</th><th>Total volume (maximum)</th></tr>
<tr><td>Clinical laboratory (chemistry/hematology)</td><td>10 mL</td><td>2</td><td>20 mL</td></tr>
<tr><td>Pharmacokinetic</td><td>5 mL</td><td>1 time point (week 8) × 2 samples</td><td>10 mL</td></tr>
<tr><td>CYP2D6 genotyping</td><td><s>5</s><u>3</u> mL</td><td>1</td><td><s>5</s><u>3</u> mL</td></tr>
<tr><td><u>Optional pharmacogenetic sample</u></td><td><u>2 mL</u></td><td><u>1</u></td><td><u>2 mL</u></td></tr>
<tr><td>Total</td><td></td><td></td><td>35 mL</td></tr>
</table></td><td>Table 4: Blood Volumes
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<tr><td>Clinical laboratory (chemistry/hematology)</td><td>10 mL</td><td>2</td><td>20 mL</td></tr>
<tr><td>Pharmacokinetic</td><td>5 mL</td><td>1 time point (week 8) × 2 samples</td><td>10 mL</td></tr>
<tr><td>CYP2D6 genotyping</td><td>3 mL</td><td>1</td><td>3 mL</td></tr>
<tr><td>Optional pharmacogenetic sample</td><td>2 mL</td><td>1</td><td>2 mL</td></tr>
<tr><td>Total</td><td></td><td></td><td>35 mL</td></tr>
</table></td><td>Updated the blood draw volumes and included optional pharmacogenetic sample</td></tr>
<tr><td colspan="3">6.2.5 Yale Global Tic Severity Scale</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>

Original text with changes shown	New wording	Reason/Justification for change
[redacted]	[redacted]	[redacted]
7.1.2 Recording and Reporting of Adverse Events		
For subjects who experience an adverse event or serious adverse event after signing a prescreening ICF for Study TV50717-CNS-30060, the event will be documented in the subject source documents and Electronic Data Capture (EDC) systems. For serious adverse events, the serious adverse event form must be completed in addition, and the serious adverse event must be reported immediately to the sponsor (Section 7.1.5.3.1). If the subject attends the screening visit, the adverse event or serious adverse event identified during the prescreening period will be considered medical history. For data entry purposes in EDC, the stop date for the prescreening adverse event or serious adverse event will be the date of the screening visit, and the start date for the associated medical history will be the date of the screening visit.	For subjects who experience an adverse event or serious adverse event after signing a prescreening ICF for Study TV50717-CNS-30060, the event will be documented in the subject source documents and Electronic Data Capture (EDC) systems. For serious adverse events, the serious adverse event form must be completed in addition, and the serious adverse event must be reported immediately to the sponsor (Section 7.1.5.3.1). If the subject attends the screening visit, the adverse event or serious adverse event identified during the prescreening period will be considered medical history. For data entry purposes in EDC, the stop date for the prescreening adverse event or serious adverse event will be the date of the screening visit, and the start date for the associated medical history will be the date of the screening visit.	Added language on reporting of adverse events after subjects sign a prescreening ICF
7.1.5 Serious Adverse Events		
An additional blood sample for the measurement of IMP concentration should be collected, if possible, from each patient experiencing a serious adverse event leading to discontinuation of IMP at any time during the study. If study center personnel are unable to obtain a blood sample in a timely fashion, this should be discussed with the medical monitor to determine whether the sample still needs to be obtained.	An additional blood sample for the measurement of IMP concentration should be collected, if possible, from each patient experiencing a serious adverse event leading to discontinuation of IMP at any time during the study. If study center personnel are unable to obtain a blood sample in a timely fashion, this should be discussed with the medical monitor to determine whether the sample still needs to be obtained.	Added language to specify that an additional blood sample should be collected, if possible, from each patient who experiences a serious adverse event
7.1.5.3.1 Investigator Responsibility		
To satisfy regulatory requirements, all serious adverse events that occur during the study, regardless of judged relationship to administration of the IMP, must be reported ~~to the sponsor~~ by	To satisfy regulatory requirements, all serious adverse events that occur during the study, regardless of judged relationship to administration of the IMP,	Updated guidance for investigator reporting of adverse events

Original text with changes shown	New wording	Reason/Justification for change
the investigator according to the instructions provided on the serious adverse event form.	must be reported by the investigator according to the instructions provided on the serious adverse event form.	

Original text with changes shown	New wording	Reason/Justification for change
7.2.2 Columbia-Suicide Severity Rating Scale		
Suicidal ideation • Patients with a positive C-SSRS suicidal ideation score on either items 1 or 2 or a change on the CDI-2 Parent or Self-Report Profiles consistent with increasing depressive symptoms must be 1) discussed with the medical monitor, 2) re-evaluated within 2 to 3 days in a clinic visit, and 3) treated according to the investigator's medical judgment. Consultation with a child and adolescent psychiatrist or licensed child/adolescent mental health provider is advised, followed by close ongoing monitoring. • If patients endorse or report a C-SSRS suicidal ideation level of 3, 4, or 5, subjects will be evaluated immediately by the study investigator and referred for psychiatric evaluation. The medical monitor will be immediately consulted. If it is determined by the investigator, after consultation with the medical monitor and the consulting psychiatrist, that exposure to the IMP may have contributed to this change in C-SSRS and/or increased depressive symptoms, IMP will be immediately discontinued and the patient terminated from the study. In cases where it is determined that IMP did not contribute to changes in depression or suicidality, the investigator will consult with the medical monitor, the consulting psychiatrist, and/or sponsor to determine whether the patient should continue in the study. Suicidal behavior • Actual attempt: If patients report any suicidal behavior that is an actual attempt as assessed in the C-SSRS, they will be evaluated immediately by the study investigator,	Suicidal ideation • Patients with a positive C-SSRS suicidal ideation score on either items 1 or 2 or a change on the CDI-2 Parent or Self-Report Profiles consistent with increasing depressive symptoms must be 1) discussed with the medical monitor, 2) re-evaluated within 2 to 3 days in a clinic visit, and 3) treated according to the investigator's medical judgment. Consultation with a child and adolescent psychiatrist or licensed child/adolescent mental health provider is advised, followed by close ongoing monitoring. • If patients endorse or report a C-SSRS suicidal ideation level of 3, 4, or 5, subjects will be evaluated immediately by the study investigator and referred for psychiatric evaluation. The medical monitor will be immediately consulted. If it is determined by the investigator, after consultation with the medical monitor and the consulting psychiatrist, that exposure to the IMP may have contributed to this change in C-SSRS and/or increased depressive symptoms, IMP will be immediately discontinued and the patient terminated from the study. In cases where it is determined that IMP did not contribute to changes in depression or suicidality, the investigator will consult with the medical monitor, the consulting psychiatrist, and/or sponsor to determine	Added guidance on how to handle suicidal ideation and suicidal behavior descriptions as identified by the C-SSRS

Original text with changes shown	New wording	Reason/Justification for change
referred for psychiatric evaluation, and terminated from the study. • Interrupted attempt, aborted attempt, or Preparatory Acts or Behavior: If patients report any suicidal behavior that is interrupted, aborted, or preparatory as assessed in the C-SSRS, they will be evaluated immediately by the study investigator and referred for psychiatric evaluation. In cases where it is determined in the psychiatric evaluation that IMP did not contribute to changes in suicidal behavior, the investigator will consult with the medical monitor, the consulting psychiatrist, and/or sponsor to determine whether the patient should continue in the study.	whether the patient should continue in the study. Suicidal behavior • Actual attempt: If patients report any suicidal behavior that is an actual attempt as assessed in the C-SSRS, they will be evaluated immediately by the study investigator, referred for psychiatric evaluation, and terminated from the study. • Interrupted attempt, aborted attempt, or Preparatory Acts or Behavior: If patients report any suicidal behavior that is interrupted, aborted, or preparatory as assessed in the C-SSRS, they will be evaluated immediately by the study investigator and referred for psychiatric evaluation. In cases where it is determined in the psychiatric evaluation that IMP did not contribute to changes in suicidal behavior, the investigator will consult with the medical monitor, the consulting psychiatrist, and/or sponsor to determine whether the patient should continue in the study.	
7.9 Assessment of Suicidality		
Consideration should be given to discontinuing TEV-50717 in participants who experience signs of suicidal ideation or behavior~~.~~; detailed recommendations are provided in Section 7.2.2. ~~Families and caregivers of participants being treated with TEV-50717 should be instructed to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such~~	Consideration should be given to discontinuing TEV-50717 in participants who experience signs of suicidal ideation or behavior; detailed recommendations are provided in Section 7.2.2. Depression and Suicidality as an Adverse Event Families and caregivers of subjects will be instructed to monitor patients for any changes in or new onset of depressive symptoms; unusual changes in mood,	Added further descriptions and guidance on depression and suicidality assessed as adverse events

Original text with changes shown	New wording	Reason/Justification for change
~~symptoms immediately to the study investigator.~~ Depression and Suicidality as an Adverse Event Families and caregivers of subjects will be instructed to monitor patients for any changes in or new onset of depressive symptoms; unusual changes in mood, cognition, or behavior; or onset of and/or changes in suicidal ideation or behavior, and to report such symptoms immediately to the study investigator. Telephone contacts and clinic visits also allow opportunities for investigators to assess adverse events. If a relevant change in status is identified, patients will be seen immediately for an unscheduled visit by the study investigator and discussed with the medical monitor. The patient will be referred for further psychiatric evaluation if there is any suspected suicidal ideation with any level of intent, suicidal behavior, or clinical findings suggesting that the patient may be dangerous to self or others, and/or experiencing depression. The investigator will record these symptoms as an adverse event of depression and/or suicidality. If it is determined by the investigator, after consultation with the medical monitor and the consulting psychiatrist, that exposure to the IMP may have contributed to the adverse event of depression or suicidality, IMP will be immediately discontinued and the patient will be terminated from the study. Follow up with a pediatric psychiatrist or licensed child and adolescent mental health clinician will be arranged. In cases where it is determined that IMP did not contribute to the adverse event of depression or suicidality, the investigator will consult with the medical monitor and/or sponsor to determine whether the patient should continue in the study.	cognition, or behavior; or onset of and/or changes in suicidal ideation or behavior, and to report such symptoms immediately to the study investigator. Telephone contacts and clinic visits also allow opportunities for investigators to assess adverse events. If a relevant change in status is identified, patients will be seen immediately for an unscheduled visit by the study investigator and discussed with the medical monitor. The patient will be referred for further psychiatric evaluation if there is any suspected suicidal ideation with any level of intent, suicidal behavior, or clinical findings suggesting that the patient may be dangerous to self or others, and/or experiencing depression. The investigator will record these symptoms as an adverse event of depression and/or suicidality. If it is determined by the investigator, after consultation with the medical monitor and the consulting psychiatrist, that exposure to the IMP may have contributed to the adverse event of depression or suicidality, IMP will be immediately discontinued and the patient will be terminated from the study. Follow up with a pediatric psychiatrist or licensed child and adolescent mental health clinician will be arranged. In cases where it is determined that IMP did not contribute to the adverse event of depression or suicidality, the investigator will consult with the medical monitor and/or sponsor to determine whether the patient should continue in the study.	
7.11 Concomitant Medication or Treatment		
The tables for allowed and prohibited medications are not comprehensive and may not include all possible concomitant	The tables for allowed and prohibited medications are not comprehensive and may not include all possible	Included a few more details on the list of concomitant

Original text with changes shown	New wording	Reason/Justification for change
medications. The medical monitor must be contacted if a patient is receiving (or has to begin or stop receiving during the study) a medication that is associated with QTc prolongation or that is a known strong CYP inhibitor~~.~~, or if there are any questions regarding any medication not listed in Appendix H.	concomitant medications. The medical monitor must be contacted if a patient is receiving (or has to begin or stop receiving during the study) a medication that is associated with QTc prolongation or that is a known strong CYP inhibitor, or if there are any questions regarding any medication not listed in Appendix H.	medications
8.1 Pharmacokinetic Assessment ((other sections affected: 9.9 Pharmacokinetic Analysis)		
Patients will be provided with a diary to provide critical information on dosing at baseline, week 2, week 4, and at unscheduled visits~~to provide critical information on dosing before the week 8 visit~~.	Patients will be provided with a diary to provide critical information on dosing at baseline, week 2, week 4, and at unscheduled visits.	Updated language to provide further clarity on which visits a diary would be dispensed
8.3.1 CYP2D6 Genotyping/Pharmacogenetics		
At the screening visit, a blood sample (~~5 to 6~~3 mL) will be obtained for analysis of CYP2D6 genotype. The patient's genotype for CYP2D6 will remain blinded during the conduct of the study. If the patient elects ~~this option~~for pharmacogenetics (PGx) evaluation on the optional informed consent/assent, a PGx sample (2 mL) will be obtained and~~ the remaining sample will be~~ stored for exploratory PGx evaluation.	At the screening visit, a blood sample (3 mL) will be obtained for analysis of CYP2D6 genotype. The patient's genotype for CYP2D6 will remain blinded during the conduct of the study. If the patient elects for pharmacogenetics (PGx) evaluation on the optional informed consent/assent, a PGx sample (2 mL) will be obtained and stored for exploratory PGx evaluation.	Updated the volume of blood to be drawn for the analysis of CYP2D6 genotype at baseline and included additional details on the PGx blood sample for subjects who elect this option
9.1 Sample Size and Power Considerations		
It is estimated that approximately 58~~50~~ patients per arm will enable a power of at least 90% to detect a beneficial standardized effect of 63% or more when the TEV-50717 arm is compared to placebo (difference of 6.0 ~~of 6.5 points or more~~ in the change from baseline to week 8 in TTS, ~~when the high dose TEV-50717 arm is compared to placebo~~assuming a standard deviation of 9.5 in each arm) ~~and~~in a 2-sided type I error rate of 5% after accounting for potential dropouts. The sample size for this study has been increased from 150 total patients (50 patients per arm) to 174 total patients (58 patients per arm). This adjustment is based solely on external	It is estimated that approximately 58 patients per arm will enable a power of at least 90% to detect a beneficial standardized effect of 63% or more when the TEV-50717 arm is compared to placebo (difference of 6.0 in the change from baseline to week 8 in TTS, assuming a standard deviation of 9.5 in each arm) in a 2-sided type I error rate of 5% after accounting for potential dropouts. The sample size for this study has been increased from 150 total patients (50 patients per arm) to 174 total patients (58 patients per arm). This adjustment is	Recently, a Phase 2 study assessing the safety and efficacy of valbenazine in the treatment of pediatric and adolescent TS patients (T-FORCE GOLD study) failed to meet its primary efficacy objective. The details on the results from this study have not yet been made public. Based on this negative

Original text with changes shown	New wording	Reason/Justification for change
data (ie, valbenazine Phase 2 study results, efficacy of TEV-50717 in the treatment of HD and TD, and ABILIFY® Phase 3 data). Data from the ongoing TEV-50717 Phase 2/3 and Phase 3 studies, TV50717-CNS-30046 and TV50717-CNS-30060, respectively, are blinded and were not used to inform the sample size calculation.	based solely on external data (ie, valbenazine Phase 2 study results, efficacy of TEV-50717 in the treatment of HD and TD, and ABILIFY® Phase 3 data). Data from the ongoing TEV-50717 Phase 2/3 and Phase 3 studies, TV50717-CNS-30046 and TV50717-CNS-30060, respectively, are blinded and were not used to inform the sample size calculation.	efficacy outcome, the sample size assumptions for Study TV50717-CNS-30046 were re-evaluated using data external to the ongoing TEV-50717 Phase 3 TS program. After review of the standardized effect in the TEV-50717 placebo-controlled pivotal studies in HD and TD and in collaboration with the scientific advisors to the TEV-50717 TS program (ie, Dr. Jankovic, Dr. Coffey, and Dr. Jimenez-Shahed), a treatment effect of 6.0 difference in TTS reflecting a 63% beneficial standardized effect was deemed to be a more appropriate assumption to base the sample size calculation.
9.2.1 Intent-to-Treat Analysis Set		
The intent-to-treat (ITT) analysis set will include all randomized patients, regardless of whether or not a patient took any IMP. ~~A patient is considered enrolled according to the status reported in the database. All efficacy analyses will be based on the ITT analysis set~~In this population, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.	The intent-to-treat (ITT) analysis set will include all randomized patients, regardless of whether or not a patient took any IMP. In this population, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.	Updated details on the intent-to-treat analysis set
9.2.4 Per-Protocol Analysis Set		

Original text with changes shown	New wording	Reason/Justification for change
The per-protocol analysis set will include patients who are compliant with study medication (80% to 105%), have a YGTSS assessment at baseline and at weeks 2, 4, and 8, and who have not taken prohibited concomitant medications as indicated in exclusion criterion~~.~~, and who have no major protocol deviations that affect the validity of the efficacy measurements. The list of protocol deviations will be reviewed before unblinding, and major protocol deviations that could affect the primary and secondary variables will be determined.	The per-protocol analysis set will include patients who are compliant with study medication (80% to 105%), have a YGTSS assessment at baseline and at weeks 2, 4, and 8, and who have not taken prohibited concomitant medications as indicated in exclusion criterion, and who have no major protocol deviations that affect the validity of the efficacy measurements. The list of protocol deviations will be reviewed before unblinding, and major protocol deviations that could affect the primary and secondary variables will be determined.	Updated the definition of the per-protocol analysis set
9.3 Data Handling Conventions		
For all variables, only the observed data from the patients will be used in the statistical analyses, ie, there is no plan to estimate missing data, unless otherwise specified. ~~Detailed~~For the sensitivity analysis of the primary and key secondary efficacy endpoints, detailed data imputation rules will be described in the statistical analysis plan.	For all variables, only the observed data from the patients will be used in the statistical analyses, ie, there is no plan to estimate missing data, unless otherwise specified. For the sensitivity analysis of the primary and key secondary efficacy endpoints, detailed data imputation rules will be described in the statistical analysis plan.	Updated language pertaining to data imputation rules described in the statistical analysis plan
9.3.1 Handling Withdrawals and Missing Data		
~~Missing data will not be imputed, unless otherwise specified.~~	Not applicable	Removed section, as it was determined that this subsection was already covered under existing Section 9.3
9.5.5.1 Primary Efficacy Analysis		
The baseline TTS, region, and ~~baseline~~ age group at baseline (2 levels: 6 to 11 years, 12 to 16 years) will be included as covariates.	The baseline TTS, region, and age group at baseline (2 levels: 6 to 11 years, 12 to 16 years) will be included as covariates.	Elaborated statistical analysis and covariates planned for the primary endpoint
9.5.5.2 Sensitivity Analysis		
Sensitivity analyses for missing data, the statistical model, and for the increase in sample size, will be conducted as detailed in the statisitical analysis plan. ~~To assess the robustness of the primary efficacy analysis, the~~	Sensitivity analyses for missing data, the statistical model, and for the increase in sample size, will be conducted as detailed in the statisitical analysis plan.	Removed specific analysis details and updated the protocol to state that sensitivity analysis will be

Original text with changes shown	New wording	Reason/Justification for change
~~following additional analyses will include:~~ • ~~Using the same repeated measures model as described for the primary analysis, the groups will be compared using the per-protocol population.~~ • ~~The primary analysis at week 8 will be repeated on a complete data set using multiple imputation methodology for imputing missing data using a missing not at random (MNAR) missing data assumption to investigate when statistical significance disappears.~~ ~~Data will be imputed for patients missing data at week 8 using the predictive mean matching multiple imputation method (Heitjan and Little 1991, Schenker and Taylor 1996). Under a missing-not-at-random data assumption, patients treated with TEV-50717 who discontinue the study for any reason other than "Lost to Follow-Up" will have their missing data at week 8 imputed. Only placebo patients will be included in the imputation model, while all other patients will have data imputed from a model derived from their assigned treatment group. The imputation model will include age group at baseline, baseline TTS score, and TTS scores at all visits up to week 8 where the TTS is scheduled to be collected. The resulting complete, imputed datasets will each be analyzed using the same model as the primary analysis model, and the resulting statistics combined using methodology provided by Rubin (1987) and Little and Rubin (2002). Details on imputing missing data and combining inferences from the resultant datasets will be provided in the statistical analysis plan.~~		provided in the statistical analysis plan

<table>
<tr><th>Original text with changes shown</th><th>New wording</th><th>Reason/Justification for change</th></tr>
<tr><td colspan="3">13. FINANCING AND INSURANCE</td></tr>
<tr><td>A separate clinical study agreement, including a study budget, will be signed between each principal investigator and ~~the sponsor (or the CRO designated by the sponsor)~~ Syneos Health before the IMP is delivered.</td><td>A separate clinical study agreement, including a study budget, will be signed between each principal investigator and Syneos Health before the IMP is delivered.</td><td>Administrative update</td></tr>
<tr><td colspan="3">Appendix B STUDY PROCEDURES AND ASSESSMENTS BY VISIT</td></tr>
<tr><td>Not Applicable</td><td>The study procedures and assessments by visit have been updated to align with all changes as noted within with the Schedule of Assessments and study design of Protocol TV50717-CNS-30060 Amendment 02.</td><td>Updated all study procedures and assessments to align with all changes per this amendment. Additional guidance text for the sites was provided.</td></tr>
<tr><td colspan="3">Appendix H ALLOWED AND PROHIBITED MEDICATIONS</td></tr>
<tr><td>Table 11 Other Prohibited Drugs
<table>
<tr><th>Generic</th><th>Class/clinical use</th><th>Note</th></tr>
<tr><td>Cannabidiol oil</td><td>Cannabis</td><td>Also includes other forms of cannabinoids</td></tr>
<tr><td>Valbenazine</td><td>Vesicular monoamine transporter 2 inhibitor</td><td>Ingrezza off-label</td></tr>
<tr><td>Quinidine</td><td>Class I antiarrhythmic agent</td><td>Strong CYP2D6 inhibitor</td></tr>
<tr><td>Terbinafine</td><td>Antifungal medication</td><td>Weak CYP2D6 inhibitor</td></tr>
</table>
CYP2D6=cytochrome P450 2D6.</td><td>Table 11 Other Prohibited Drugs
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</table>
CYP2D6=cytochrome P450 2D6.</td><td>Updated Appendix H to include a table for other prohibited drugs</td></tr>
<tr><td colspan="3">Appendix R Pharmacokinetic Samples</td></tr>
<tr><td>~~Specimen Sampling and Handling~~
~~For plasma collection, 5 mL of blood will be collected into~~</td><td>Not Applicable</td><td>Removed Appendix R</td></tr>
</table>

Original text with changes shown	New wording	Reason/Justification for change
~~lithium heparin tubes and processed to plasma. Blood samples will be centrifuged (1500g, approximately 10 minutes, at 0 to 5°C) between 5 minutes and 1 hour after sampling. If a refrigerated centrifuge is not available, samples should be chilled before centrifugation. Other measures should be taken as appropriate to prevent samples from heating significantly during centrifugation. Separated plasma will be transferred in approximately equal portions in 2 opaque, labeled, polypropylene tubes (Sets A and B).~~ ~~For serum collection, samples will be collected in Vacutainer tubes containing no anticoagulant and allowed to set at room temperature for between 1 and 1.5 hours to allow for serum separation to occur. Samples will then be centrifuged (1500g, approximately 10 minutes, at 0 to 5°C). If a refrigerated centrifuge is not available, samples should be chilled before centrifugation. Other measures should be taken as appropriate to prevent samples from heating significantly during centrifugation. Separated serum will be transferred in approximately equal portions in 2 opaque, labeled, polypropylene tubes (Sets A and B).~~ ~~Labels for samples should include study number, patient randomization number, period, nominal collection time, Set A or B, and indication that they are pharmacokinetic samples. Samples will be stored at a temperature from -20 or below in an upright position for a maximum of 2 weeks until they are shipped to the central laboratory.~~ ~~Shipment and Analysis of Samples~~ ~~Serum or plasma samples for all patients will be shipped from the investigational center to the central laboratory, where they will be stored until shipped to the sponsor or designee for analysis. Samples will be stored in an upright position at -20ºC until assayed. The central laboratory will be notified before the shipment of the samples and will be sent the shipping~~		

Original text with changes shown	New wording	Reason/Justification for change
~~information when the samples are shipped. An electronic file containing sample demographics will be emailed to the bioanalytical laboratory and the sponsor's representatives from bioanalytical departments for each shipment.~~ ~~Set A samples will be transported with a temperature data logger and frozen with dry ice sufficient for 4 days, by next day courier to the central laboratory.~~ ~~Set B samples will be sent either to the same laboratory as that for Set A samples on a subsequent day by next day courier, or be retained at the investigational center until the study is completed and the CSR has been issued (unless shipment to another facility is requested by the sponsor). Instructions as to the disposition of the Set B samples will be provided by the sponsor.~~ ~~Sample shipments should be sent no later in the week than Wednesday morning for next day delivery. Samples are not to arrive on the weekend.~~ ~~Samples will be analyzed using an appropriate validated method. Timing of the initiation of sample analysis will be determined by the sponsor's representatives of bioanalytical departments responsible for the bioanalysis while keeping the study blinding, if any, intact.~~		

15.3. Amendment 01 Dated 20 November 2017

The primary reason for this amendment is to change aspects of the conduct, some IMP administration procedures, include concomitant medications, participating countries, acceptable contraceptive methods, analysis of the data, and clinical study personnel.

This amendment is considered to be substantial (ie, requires approval by CA, IEC, and/or IRB) by the sponsor's Authorized Representative. Other nonsubstantial changes have been made to the protocol (and protocol synopsis, as appropriate). These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

Original text with changes shown	New wording	Reason/Justification for change
Global		
Nuvelution TS Pharma, INC.	Nuvelution TS Pharma, INC	Name update
Not applicable	Tourette Syndrome-Patient Global Impression of Impact (TS-PGII)	Added TS-PGII to assessments
Gilles de la Tourette Syndrome - Quality of Life scale (GTS-QOL)	Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life scale (C&A-GTS-QOL)	Updated to Gilles de la Tourette Syndrome children and adolescents scale
Screening period (up to 31 days ~~4 weeks ; minimum of 3 days~~)	Screening period (up to 31 days)	Updated to clarify the screening period duration
May be interviewed ~~in conjunction~~separately or jointly	May be interviewed separately or jointly	Updated to conduct of interview
Baseline/day ~~0~~ 1 visit	Baseline/day 1 visit	Updated to clarify visit day of baseline visit
Clinical Laboratory and Other Departments and Institutions		
[redacted]	[redacted]	Update to Sponsor representatives and points of contact

Original text with changes shown	New wording	Reason/Justification for change
[redacted]	[redacted]	
Synopsis		
Not applicable	Sponsor's Development Partner: Nuvelution TS Pharma, Inc., 601 Gateway Boulevard Suite 1270, South San Francisco, California 94080, United States of America	Added Sponsor Development Partner
Countries Planned: ~~Approximately 10 in~~ North America, ~~South~~Latin America, Turkey, Ukraine, South Korea, and Europe	**Countries Planned:** North America, Latin America, Turkey, Ukraine, South Korea, and Europe	Updated to more specifically list the countries/regions planned for the study
1.1 Introduction		
~~TEV-50717 was granted breakthrough status for treatment of TD by the FDA based on the results of Study SD-809-C-18, and NDA 209885 was granted priority review status.~~ TEV-50717 was approved for the treatment of chorea associated with HD and for the treatment of TD on 03 April 2017 and 30 August 2017, respectively.	TEV-50717 was approved for the treatment of chorea associated with HD and for the treatment of TD on 03 April 2017 and 30 August 2017, respectively.	Updated to account for approval of TD in August 2017.
2.1 Primary and Secondary Study Objectives and Endpoints		
The secondary efficacy endpoints are as follows: 1. change in the ~~Tourette Syndrome Clinical Global Impression (~~TS-CGI~~)~~ score from baseline to week 8 between high-dose TEV-50717 treated patients and placebo treated patients 2. change in the TTS of the YGTSS from baseline to week 8 for	The secondary efficacy endpoints are as follows: 1. change in the TS-CGI score from baseline to week 8 between high-dose TEV-50717 treated patients and placebo treated patients 2. change in the TTS of the YGTSS from baseline to week 8 for low dose TEV-50717 and placebo will be tested	Additional secondary efficacy endpoints were included for analysis. Changes were made to existing secondary

Original text with changes shown	New wording	Reason/Justification for change
low dose TEV-50717 and placebo will be tested 3. change in the TS-CGI score from baseline to week 8 between low dose TEV-50717 treated patients and placebo treated patients ~~2.~~4. change in the Tourette Syndrome-Patient Global Impression of [redacted] Impact (TS-[redacted] PGII) score from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients 5. change in the TS-PGII score from baseline to week 8 between low-dose TEV-50717-treated patients and placebo-treated patients 6. change in the Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life- scale (C&A-GTS-QOL) ~~physical/~~activities of daily living (ADL) subscale from baseline to week 8 between high-dose TEV-50717 treated patients and placebo treated patients ~~3.~~7. change in the C&A-GTS-QOL ADL subscale from baseline to week 8 between low-dose TEV-50717 treated patients and placebo treated patients The hierarchy of testing of secondary endpoints regarding dose level to control type I error is specified in the section entitled "Analysis of Key Secondary Endpoints."	3. change in the TS-CGI score from baseline to week 8 between low dose TEV-50717 treated patients and placebo treated patients 4. change in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) score from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients 5. change in the TS-PGII score from baseline to week 8 between low-dose TEV-50717-treated patients and placebo-treated patients 6. change in the Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life- scale (C&A-GTS-QOL) activities of daily living (ADL) subscale from baseline to week 8 between high-dose TEV-50717 treated patients and placebo treated patients 7. change in the C&A-GTS-QOL ADL subscale from baseline to week 8 between low-dose TEV-50717 treated patients and placebo treated patients The hierarchy of testing of secondary endpoints regarding dose level to control type I error is specified in the section entitled "Analysis of Key Secondary Endpoints."	efficacy endpoints. (ie, [redacted] was removed from secondary efficacy endpoints)
2.2 [redacted]		
3.1 Study Design		
Treatment period (8 weeks): Patients who continue to remain eligible for participation in the study will be randomized at the baseline visit (day ~~0~~1) and will receive blinded IMP to begin ~~taking the next morning (~~that same day (day 1). Tablets should be taken with food	Treatment period (8 weeks): Patients who continue to remain eligible for participation in the study will be randomized at the baseline visit (day 1) and will receive blinded IMP to begin that same day (day 1). Tablets should be taken with food (eg, a snack)	Updated to align with Table of Assessments and procedures. Dosing information adjusted

Original text with changes shown	New wording	Reason/Justification for change
(eg, a snack) and should not be taken on an empty stomach. Patients and their parent/legal guardian will interact regularly with the clinical research staff, either by telephone contact or clinic visit to assure adherence with study procedures and to evaluate safety and efficacy. To this end, clinic visits will be performed at weeks 2, 4, and 8 after baseline to evaluate safety; assess tic severity with the YGTSS, TS-CGI, TS-PGII, and the [redacted] C&A GTS-QOL; and perform safety rating scales to augment adverse event reporting, concomitant medication usage, clinical laboratory examination, and 12 lead ECGs. Telephone contacts will occur at the end of weeks 1, 3, 6, and 7.	and should not be taken on an empty stomach. Patients and their parent/legal guardian will interact regularly with the clinical research staff, either by telephone contact or clinic visit to assure adherence with study procedures and to evaluate safety and efficacy. To this end, clinic visits will be performed at weeks 2, 4, and 8 after baseline to evaluate safety; assess tic severity with the YGTSS, TS-CGI, TS-PGII, and the C&A-GTS-QOL; and perform safety rating scales to augment adverse event reporting, concomitant medication usage, clinical laboratory examination, and 12-lead ECGs. Telephone contacts will occur at the end of weeks 1, 3, 6, and 7.	slightly. Assessments and the scales to be used at weeks 2, 4, and 8 were updated per changes made to the endpoints.
3.4 Dose Escalation Procedures		
IMP will be administered as follows: • IMP should be swallowed whole and taken with food (eg, a snack) and should not be taken on an empty stomach. • ~~Daily doses will be administered twice daily in 2 divided doses, approximately 8 to 10 hours apart during the day.~~ Dosing will be based on body weight and CYP2D6 impairment status at the baseline visit, as shown in Table 1. • To preserve blinding, 2 tablets will be taken ~~in the morning and again in the evening~~ twice daily starting at ~~week 4~~ day 1 per Table 1. Daily doses will be administered twice daily, approximately 8 to 10 hours apart during the day. Depending on the dose and arm assigned, TEV-50717 tablets and/or placebo tablets will be taken to maintain the blind. A minimum of 6 hours should elapse between doses. If a patient misses a dose, and it is within 6 hours of their next dose, the missed dose should be skipped. • After week 1, d~~D~~ose escalations may not occur more frequently than once every 5 days. • The dose of IMP will be escalated weekly during the escalation period, according to Table 1. • Dose reductions, if required, should be in increments of 6 mg. If more than 1 dose reduction is required for an adverse event, the medical monitor must be notified. • During the titration period, the dose of the IMP will be adjusted weekly according to Table 1. Investigators will be blinded to CYP status, with a dose cap for poor metabolizers prespecified by the IRT. IMP will be packaged in blister packs and provided for patients to	IMP will be administered as follows: • IMP should be swallowed whole and taken with food (eg, a snack) and should not be taken on an empty stomach. • Dosing will be based on body weight and CYP2D6 impairment status at the baseline visit, as shown in Table 1. • To preserve blinding, 2 tablets will be taken twice daily starting at day 1 per Table 1. Daily doses will be administered twice daily, approximately 8 to 10 hours apart during the day. Depending on the dose and arm assigned, TEV-50717 tablets and/or placebo tablets will be taken to maintain the blind. A minimum of 6 hours should elapse between doses. If a patient misses a dose, and it is within 6 hours of their next dose, the missed dose should be skipped. • After week 1, dose escalations may not occur more frequently than once every 5 days. • The dose of IMP will be escalated weekly during the escalation period, according to Table 1. • Dose reductions, if required, should be in increments of 6 mg. If more than 1 dose reduction is required for an adverse event, the medical monitor must be notified. • During the titration period, the dose of the IMP will be adjusted weekly according to Table 1. Investigators will be blinded to CYP status, with a dose cap for poor metabolizers prespecified by the IRT. IMP will be packaged in blister packs and provided for patients to take at home (see Section 5.1).	Updated to account for the latest IMP administration instructions and guidance.

Original text with changes shown	New wording	Reason/Justification for change
take at home (see Section 5.1).		
Section 3.6: Table 2: Study Procedures and Assessments		
Not applicable	Table 2 was updated in alignment with the changes made to the protocol. Study days were added to increase clarity/timing of assessments. The visit window was increased to ±3 days between week 1 to week 10. Assessments and footnotes were adjusted/edited	Table 2 was updated to be consistent and aligned with the changes made to the protocol
4.1 Patient Inclusion Criteria		
j. Females who are postmenarchal or ≥12 years of age may be included only if they have a negative β- HCG test at baseline or are sterile. Definition of sterile is given in Appendix E. k. Females ~~of childbearing potential~~who are postmenarchal or ≥12 years of age whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study (ie, starting at screening) and for 30 days or 5 half lives, whichever is longer after last dose of IMP. Further details are included in Appendix E.	j. Females who are postmenarchal or ≥12 years of age may be included only if they have a negative β- HCG test at baseline or are sterile. Definition of sterile is given in Appendix E. k. Females who are postmenarchal or ≥12 years of age whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study (ie, starting at screening) and for 30 days or 5 half lives, whichever is longer after last dose of IMP. Further details are included in Appendix E.	Update to females "of childbearing potential." Newly defined as females who are postmenarchal or ≥12 years of age (in alignment with updated Appendix E)
4.2 Patient Exclusion Criteria		
m. Patient has a QTcF value >450 msec (males) or >460 msec (females), or >480 msec (with right bundle branch block) on a 12-lead electrocardiogram (ECG) at screening~~.~~, or requires treatment with drugs known to prolong the QT interval (see Appendix H Table 10 for a complete list of prohibited QT-prolonging drugs). t. Patient has a history of or acknowledges alcohol ~~or substance abuse~~ related disorder in the previous 12 months, as defined in the DSM-5.	m. Patient has a QTcF value >450 msec (males) or >460 msec (females), or >480 msec (with right bundle branch block) on a 12-lead electrocardiogram (ECG) at screening, or requires treatment with drugs known to prolong the QT interval (see Appendix H Table 10 for a complete list of prohibited QT-prolonging drugs). t. Patient has a history of or acknowledges alcohol-related disorder in the previous 12 months, as defined in the DSM-5.	Update to include a list of prohibited QT prolonging medications. Latest DSM-5 language included as well
5.1.2 Placebo Investigational Medicinal Product		
(Table 3. Dosing instructions [Test IMP]) To preserve blinding, 2 tablets will be taken twice daily starting at day 1 per Table 1. Daily doses will be administered twice daily~~in 2 divided doses~~, approximately 8 to 10 hours apart during the day. ~~In order to preserve blinding, 2 tablets will be taken in the morning and again in the evening starting at week 3~~Depending on the dose and arm assigned, TEV-50717 tablets and/or placebo tablets will be taken to maintain the blind. A minimum of 6 hours should elapse between doses. If a patient misses a dose, and it is within 6 hours of their next	(Table 3. Dosing instructions [Test IMP]) To preserve blinding, 2 tablets will be taken twice daily starting at day 1 per Table 1. Daily doses will be administered twice daily, approximately 8 to 10 hours apart during the day. Depending on the dose and arm assigned, TEV-50717 tablets and/or placebo tablets will be taken to maintain the blind. A minimum of 6 hours should elapse between doses. If a patient misses a dose, and it is within 6 hours of their next dose, the missed dose should be skipped. Tablets should be swallowed whole and taken with food	Updated Table 3 to clarify dosing instructions for test and placebo IMP Updated Table 3 to reflect the manufacturer of Placebo IMP

Original text with changes shown	New wording	Reason/Justification for change
dose, the missed dose should be skipped. Tablets should be swallowed whole and taken with food (eg, a snack) and should not be taken on an empty stomach. (Table 3. Dosing instructions [Placebo IMP]) To preserve blinding, 2 tablets will be taken twice daily starting at day 1 per Table 1. Daily doses will be administered twice daily~~in 2 divided doses~~, approximately 8 to 10 hours apart during the day. ~~In order to preserve blinding, 2 tablets will be taken in the morning and again in the evening starting at week 3~~Depending on the dose and arm assigned, TEV-50717 tablets and/or placebo tablets will be taken to maintain the blind. A minimum of 6 hours should elapse between doses. If a patient misses a dose, and it is within 6 hours of their next dose, the missed dose should be skipped. Tablets should be swallowed whole and taken with food (eg, a snack) and should not be taken on an empty stomach. (Table 3. Manufacturer [Placebo IMP]) ~~Not applicable~~Norwich Pharmaceuticals, Inc. (Referenced as NPI or Norwich) 6826 State Highway 12 Norwich, NY 13815	(eg, a snack) and should not be taken on an empty stomach. (Table 3. Dosing instructions [Placebo IMP]) To preserve blinding, 2 tablets will be taken twice daily starting at day 1 per Table 1. Daily doses will be administered twice daily, approximately 8 to 10 hours apart during the day. Depending on the dose and arm assigned, TEV-50717 tablets and/or placebo tablets will be taken to maintain the blind. A minimum of 6 hours should elapse between doses. If a patient misses a dose, and it is within 6 hours of their next dose, the missed dose should be skipped. Tablets should be swallowed whole and taken with food (eg, a snack) and should not be taken on an empty stomach. (Table 3. Manufacturer [Placebo IMP]) Norwich Pharmaceuticals, Inc. (Referenced as NPI or Norwich) 6826 State Highway 12 Norwich, NY 13815	
5.2.3 Accountability		
A record of IMP accountability (ie, IMP and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Empty, partially used, and unused blister packs IMP will be ~~disposed of per site policy, or~~ returned to the sponsor or designee, as agreed with the sponsor.	A record of IMP accountability (ie, IMP and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Empty, partially used, and unused blister packs IMP will be returned to the sponsor or designee, as agreed with the sponsor.	Updated to clarify management of unused blister packs IMP
5.5. Restrictions		
While patients receiving strong CYP2D6 inhibitors (paroxetine, fluoxetine, and bupropion) at baseline may be enrolled into this study, the ~~addition or~~ removal of strong CYP2D6 inhibitors during treatment is discouraged as this would have an effect on exposure to active circulating drug. If the ~~addition or~~ removal of a strong CYP2D6 inhibitor is required from a clinical perspective, the medical monitor should be contacted so an appropriate change in IMP can be made. The addition of a strong CYP inhibitor is prohibited.	While patients receiving strong CYP2D6 inhibitors (paroxetine, fluoxetine, and bupropion) at baseline may be enrolled into this study, the removal of strong CYP2D6 inhibitors during treatment is discouraged as this would have an effect on exposure to active circulating drug. If the removal of a strong CYP2D6 inhibitor is required from a clinical perspective, the medical monitor should be contacted so an appropriate change in IMP can be made. The addition of a strong CYP inhibitor is prohibited.	Updated to reflect prohibition of the addition of a strong CYP inhibtor during treatment.
5.6 Prior and Concomitant Medication or Therapy		
At each clinic visit after the screening visit, the investigator will ask	At each clinic visit after the screening visit, the investigator will	Updated to account for

Original text with changes shown	New wording	Reason/Justification for change
patients whether they have taken any medications (other than IMP), including over-the-counter medications, vitamins, or herbal or nutritional supplements, since the previous visit. Parents/patients will be instructed during the course of the study to notify the investigator if any new medication is prescribed, including over-the-counter medications. Any prescribed medication should be reviewed with the investigator. Indication, dosage, and start and end dates should be entered on the CRF. The medical monitor must be contacted if a patient is receiving (or has to begin or stop receiving during the study) a medication that is associated with QTc prolongation or that is a known strong CYP inhibitor. Allowed strong CYP inhibitors at baseline are shown in Appendix H Table 8. Addition of a strong CYP inhibitor is prohibited. Prohibited antipsychotic drugs are listed in Appendix H Table 9. Prohibited medications that are associated with QTc prolongation are listed in Appendix H Table 10.	ask patients whether they have taken any medications (other than IMP), including over-the-counter medications, vitamins, or herbal or nutritional supplements, since the previous visit. Parents/patients will be instructed during the course of the study to notify the investigator if any new medication is prescribed, including over-the-counter medications. Any prescribed medication should be reviewed with the investigator. Indication, dosage, and start and end dates should be entered on the CRF. The medical monitor must be contacted if a patient is receiving (or has to begin or stop receiving during the study) a medication that is associated with QTc prolongation or that is a known strong CYP inhibitor. Allowed strong CYP inhibitors at baseline are shown in Appendix H Table 8. Addition of a strong CYP inhibitor is prohibited. Prohibited antipsychotic drugs are listed in Appendix H Table 9. Prohibited medications that are associated with QTc prolongation are listed in Appendix H Table 10.	the patient guidelines on handling additional prescriptions during the study. Added link to prohibited medications that are associated with QTc prolongation.
5.8 Temporary Discontinuation of Investigational Medicinal Product		
If more than 1 dose reduction is required for an adverse event, the medical monitor ~~should~~must be notified. The patients who restart IMP treatment will follow the visit schedule as outlined in ~~the protocol~~ Table 2. Patients who withdraw from the study will proceed as described in Section 4.3.	If more than 1 dose reduction is required for an adverse event, the medical monitor must be notified. The patients who restart IMP treatment will follow the visit schedule as outlined in Table 2. Patients who withdraw from the study will proceed as described in Section 4.3.	Updated to reflect necessity of notifying medical monitor during dose reduction. Updated link to visit schedule scheme.
5.11 Total Blood Volume		
Not applicable	Table 4 column header updated to reflect inclusion of data for maximum total volume. Footnotes revised to reflect update to definition of female subjects who are to undergo gonadotropin testing.	Table 4 column header and footnotes updated. Revised to account for update to definition of females “of childbearing potential”; newly defined as females who are postmenarchal or ≥12 years of age (in alignment with updated Appendix E)
6.2.2. Tourette Syndrome-Patient Global Impression of Impact		
Not applicable	Section 6.2.2 added to reflect description for the additional assessment, Tourette Syndrome- Patient Global Impression Impact	Added section for additional assessment

Original text with changes shown	New wording	Reason/Justification for change
6.2.3 Tourette Syndrome-Patient Global Impression of Severity		
[redacted]	[redacted]	
6.2.4 Child and Adolescent Gilles de la Tourette Syndrome - Quality of Life Scale		
The C&A-GTS-QOL is administered at baseline, week 4, and week 8. Children 13 years of age and under ~~must~~may be interviewed ~~in conjunction~~separately or jointly with the ~~parent/legal guardian~~caregiver/adult as appropriate or defined by the scale. The C&A-GTS-QOL is a 27-item questionnaire specific to TS patients that asks the patient to assess the extent to which their quality of life is impacted by their symptoms. The C&A-GTS-QOL contains ~~4~~6 subscales (cognitive, coprophenomena, psychological, physical, ~~obsessional~~obsessive-compulsive, and ~~cognitive~~ADL) and uses a 5-point Likert scale ranging from no problem to extreme problem. Patients will also be asked how satisfied they feel overall with their life at that moment by using a VAS scale between 0 and 100 (~~Cavanna~~Su et al ~~2008~~2017).	The C&A-GTS-QOL is administered at baseline, week 4, and week 8. Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. The C&A-GTS-QOL is a 27-item questionnaire specific to TS patients that asks the patient to assess the extent to which their quality of life is impacted by their symptoms. The C&A-GTS-QOL contains 6 subscales (cognitive, coprophenomena, psychological, physical, obsessive-compulsive, and ADL) and uses a 5-point Likert scale ranging from no problem to extreme problem. Patients will also be asked how satisfied they feel overall with their life at that moment by using a VAS scale between 0 and 100 (Su et al 2017).	Updated to account for changes to name and definition of Gilles de la Tourette Syndrome children and adolescents scale Subscale details were updated
6.2.6. [redacted]	[redacted]	Updated to reflect changes in how the assessment is expected to be administered
6.2.7. [redacted]	[redacted] add relevant information.	Updated to reflect changes in how the assessment is expected to be administered
7.1.1. Definition of an Adverse Event		
~~In this study, any adverse event occurring after the clinical study~~	(Note: Abnormal laboratory test results at the screening visit that	Deleted statement on

Original text with changes shown	New wording	Reason/Justification for change
~~patient has signed the informed consent form should be recorded and reported as an adverse event.~~ (Note: Abnormal laboratory ~~or diagnostic~~ test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events.)	preclude a patient from entering the study or receiving study treatment are not considered adverse events.)	adverse event recording after signing of informed consent form
7.1.2. Recording and Reporting of Adverse Events		
For this study, there will be 1 week of washout for patients who will participate in the open-label safety extension study TV50717-CNS-30047 and 2 weeks after the last dose of IMP ~~(1 week after the end of the washout period)~~ for patients who will not roll over into the open-label safety extension study TV50717-CNS-30047. Further details are given in the safety monitoring plan.	For this study, there will be 1 week of washout for patients who will participate in the open-label safety extension study TV50717-CNS-30047 and 2 weeks after the last dose of IMP for patients who will not roll over into the open-label safety extension study TV50717-CNS-30047. Further details are given in the safety monitoring plan.	Updated details on last dose of IMP. Added direction to safety monitoring plan for further information.
7.1.5. Serious Adverse Events		
For recording of serious adverse event, the study period is defined for each patient as that time period from signature of the informed consent form to the end of the follow-up period as defined in Section 7.1.2.	For recording of serious adverse event, the study period is defined for each patient as that time period from signature of the informed consent form to the end of the follow-up period as defined in Section 7.1.2.	Added link to related section
7.1.5.2. Expectedness		
A serious adverse event that is not included in the Adverse Reaction section of the relevant reference safety information (RSI) by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The RSI for this study is ~~provided in Appendix B of~~ the IB. A serious adverse event that is not included in the ~~reference safety information~~listing of adverse reactions in the ~~IB~~RSI by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. ~~The sponsor's Global Patient Safety and Pharmacovigilance will determine the expectedness for all serious adverse events.~~ For the purpose of SUSAR reporting, the version of the IB at the time of occurrence of the SUSAR applies.	A serious adverse event that is not included in the Adverse Reaction section of the relevant reference safety information (RSI) by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The RSI for this study is the IB. A serious adverse event that is not included in the listing of adverse reactions in the RSI by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. For the purpose of SUSAR reporting, the version of the IB at the time of occurrence of the SUSAR applies.	Updated to reflect new definition of unexpected adverse events
7.1.5.3.1. Investigator Responsibility		
Blinding will be maintained for ~~the people who are involved directly in the~~all study personnel. Therefore, in case of a SUSAR, only the LSO/CRO will receive the unblinded report for regulatory submission; the others will receive a blinded report.	Blinding will be maintained for all study personnel. Therefore, in case of a SUSAR, only the LSO/CRO will receive the unblinded report for regulatory submission; the others will receive a blinded report.	Updated to clarify blinding for all study personnel

Original text with changes shown	New wording	Reason/Justification for change
7.1.7. Withdrawal Due to an Adverse Event		
Any patient who experiences an adverse event may be withdrawn from the study or from study treatment at any time at the discretion of the investigator. ~~If a patient is withdrawn from the study~~If a post-baseline QTcF value >500 msec or change from baseline >60 msec is found, the investigator should repeat the ECG assessment twice and compare the average of the 2 pre-treatment QTcF values (baseline and screening) to the average of the 3 post-baseline QTcF values. The IMP must be stopped for any confirmed post-baseline QTcF value >500 msec or increase from baseline >60 msec. If a patient is withdrawn wholly or in part because of an adverse event, both the adverse events page and termination page of the CRF will be completed at that time.	Any patient who experiences an adverse event may be withdrawn from the study or from study treatment at any time at the discretion of the investigator. If a post-baseline QTcF value >500 msec or change from baseline >60 msec is found, the investigator should repeat the ECG assessment twice and compare the average of the 2 pre-treatment QTcF values (baseline and screening) to the average of the 3 post-baseline QTcF values. The IMP must be stopped for any confirmed post-baseline QTcF value >500 msec or increase from baseline >60 msec. If a patient is withdrawn wholly or in part because of an adverse event, both the adverse events page and termination page of the CRF will be completed at that time.	Added guideline for IMP discontinuation due to prolonged QTcF
7.1.8. Overdose of IMP		
~~7.1.8. Overdose of IMP~~ ~~Any dose of TEV-50717 (whether the investigational product or a placebo), whether taken intentionally or unintentionally, in excess of that prescribed during the given time period must be immediately reported to the sponsor. When the identification of the IMP must be known, the investigator must follow the procedures outlined in Section 5.10.~~	Section deleted	Section deleted
7.2.2. Columbia-Suicide Severity Rating Scale		
The C-SSRS children's baseline/screening scale ~~(that collects the history of~~assesses past and current suicidal ideation and behaviors to determine suicide~~)~~ risk and is administered at screening. C-SSRS children's SLV scale is administered at baseline and at weeks 2, 4, ~~6,~~8, and 9~~, 12, and 13~~. Children 13 years of age and under ~~must~~may be interviewed ~~in conjunction~~separately or jointly with the ~~parent/legal guardian.~~caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, parent/legal guardian involvement is strongly encouraged. Questions should be directed to the child, but the ~~parent/legal guardian~~caregiver/adult should be encouraged to add relevant information. ~~The C-SSRS (Posner et al 2009) is a Food and Drug Administration (FDA) endorsed questionnaire to screen for suicidality in trials of central nervous system–active compounds (in September 2010).~~ The C-SSRS is an interview by trained study personnel.	The C-SSRS children's baseline/screening scale assesses past and current suicidal ideation and behaviors to determine suicide risk and is administered at screening. C-SSRS children's SLV scale is administered at baseline and at weeks 2, 4, 8, and 9. Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, parent/legal guardian involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information. The C-SSRS is an interview by trained study personnel.	Updated to reflect changes to definition and administration of the C-SSRS

Original text with changes shown	New wording	Reason/Justification for change
7.2.3. Children's Depression Inventory, Second Edition		
The CDI-2 (parent and self-report versions) is administered at screening; baseline; and weeks 2, 4, ~~6~~,8, and 9~~, 12, 13~~.	The CDI-2 (parent and self-report versions) is administered at screening; baseline; and weeks 2, 4, 8, and 9.	Updated to reflect changes to definition and administration of the CDI-2
7.3. Pregnancy		
Any female patient becoming pregnant during the study will discontinue IMP. All pregnancies of ~~females~~ female patients participating in the study that occur during the study, or within 14 days ~~of completion~~ after the end of the study, are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the investigator must provide the sponsor (LSO/CRO) with the completed pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (see Section 7.1.5.3). ~~Any female patient becoming pregnant during the study will discontinue treatment. All patients who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous or voluntary termination). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after termination from the study will be reported as an adverse event or serious adverse event, as appropriate.~~ The investigator is not required to report patients who are found to be pregnant between screening and baseline, provided no ~~protocol-related procedures were applied~~ IMP was given. ~~Since there is no evidence of teratogenicity, genotoxicity, fetotoxicity, or spermatotoxicity for this IMP, female partners will not be required to sign an ICF to monitor the outcome of the pregnancy.~~	Any female patient becoming pregnant during the study will discontinue IMP. All pregnancies of female patients participating in the study that occur during the study, or within 14 days after the end of the study, are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the investigator must provide the sponsor (LSO/CRO) with the completed pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (see Section 7.1.5.3). The investigator is not required to report patients who are found to be pregnant between screening and baseline, provided no IMP was given.	Updated guidelines on managing pregnancies during the course of the study
7.5.2.1 Human Chorionic Gonadotropin Tests		
Any female patient who becomes pregnant during the study will ~~discontinue treatment~~be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.3.	Any female patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.3.	Updated action taken with IMP in case of pregnancy during the course of the

Original text with changes shown	New wording	Reason/Justification for change
		study
7.6. Physical Examinations		
Any physical examination finding that is judged by the investigator as ~~a~~ clinically significant (except at the screening visit) will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.	Any physical examination finding that is judged by the investigator as clinically significant (except at the screening visit) will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.	Added exception to assessment of clinically signficant adverse event
7.9. Assessment of Suicidality		
Baseline assessment of suicidal ideation and behavior and treatment-emergent suicidal ideation and behavior will be assessed during the study using the Columbia-Suicide Severity Rating Scale described in Section 7.2.2.	Baseline assessment of suicidal ideation and behavior and treatment-emergent suicidal ideation and behavior will be assessed during the study using the Columbia-Suicide Severity Rating Scale described in Section 7.2.2.	Added link to related section
7.10. Neurological Examinations		
Not applicable	**7.10. Neurological Examinations** Neurological examination, including mental status, cranial nerves, motor system (strength, tone, and posture), coordination, gait and balance, tendon reflexes, and sensation, will be performed at the time points detailed in Table 2. Any neurological examination finding that is judged by the investigator as a potentially clinically significant change (worsening) compared with the screening value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.	Section added to reflect additional assessments
7.11. Concomitant Medication or Treatment		
Not applicable	**7.11. Concomitant Medication or Treatment** Concomitant therapy or medication usage will be monitored throughout the study. Parents/patients will be instructed during the course of the study to notify the investigator if any new medication is prescribed/administered, including over-the-counter medications. Any prescribed/administered medication should be reviewed with the investigator. Medications that are allowed, provided that conditions outlined in the table are met, are shown in Appendix H Table 7. The medical monitor must be contacted if a patient is receiving (or has to begin or stop receiving during the study) a medication that is associated with QTc prolongation or that is a known strong CYP inhibitor. Prohibited medications that are associated with QTc prolongation are listed in Appendix H Table 10, while prohibited antipsychotic drugs are listed in Appendix H Table 9.	Section added to reflect additional assessments

Original text with changes shown	New wording	Reason/Justification for change
7.12. Methods and Time Points of Assessing, Recording, and, Analyzing Safety Data		
Not applicable	**7.12. Methods and Time Points of Assessing, Recording, and Analyzing Safety Data** All adverse events will be reviewed on a periodic basis by the clinical project physician/medical monitor according to the safety monitoring plan (eg, scheduled safety reviews for TEV-50717) as preliminary safety databases become available. Methods and time points of assessing safety data are discussed in Section 3.6. Procedures for recording safety data are discussed in Appnedix T, and methods of analyses are discussed in Section 9.7.	Section added to reflect additional assessments
8.1. Pharmacokinetic Assessment		
Not applicable	**8.1. Pharmacokinetic Assessment**	Subheading added to further specify assessments
8.2. Pharmacodynamic Assessment		
Not applicable	**8.2. Pharmacodynamics Assessment** Exposure-response (eg, pharmacodynamic [PD] and/or safety endpoints) may be assessed if the appropriate data are available.	Subsection added to reflect additional assessment
8.3. Pharmacogenetics		
Not applicable	**8.3. Pharmacogenetics**	Subsection added for further specification of assessments
8.3.1. CYP2D6 Genotyping/Pharmacogenetics		
~~**8.1.1.**~~ **8.3.1. CYP2D6 ~~Genotype~~Genotyping/Pharmacogenetics** At the screening visit, a blood sample (5 to 6 mL) will be obtained for analysis of CYP2D6 genotype. The patient's genotype for CYP2D6 will remain blinded during the conduct of the study. If the patient elects this option on the optional informed consent, the remaining sample will be stored for exploratory pharmacogenetics (PGx) evaluation. This PGx assessment will investigate the relationship between subjects' genetic variability and study outcomes. Candidate genes included in this assessment may be related to, or hypothesized to be related to, pharmacokinetics, safety features, drug mechanism of action, Tourette syndrome, or related diseases. The final list of genes to be evaluated will be determined at the time of analysis to be able to account for the most current research.	**8.3.1. CYP2D6 Genotyping/Pharmacogenetics** At the screening visit, a blood sample (5 to 6 mL) will be obtained for analysis of CYP2D6 genotype. The patient's genotype for CYP2D6 will remain blinded during the conduct of the study. If the patient elects this option on the optional informed consent, the remaining sample will be stored for exploratory pharmacogenetics (PGx) evaluation. This PGx assessment will investigate the relationship between subjects' genetic variability and study outcomes. Candidate genes included in this assessment may be related to, or hypothesized to be related to, pharmacokinetics, safety features, drug mechanism of action, Tourette syndrome, or related diseases. The final list of genes to be evaluated will be determined at the time of analysis to be able to account for the most current research.	Added guidelines and administration of genotyping

Original text with changes shown	New wording	Reason/Justification for change
9.5.2. Key Secondary Endpoints		
1. Change in the TS-CGI score from baseline to week 8 between high-dose TEV-50717 treated patients and placebo treated patients 2. Change in the TTS of the YGTSS from baseline to week 8 for low-dose TEV-50717 and placebo will be tested ~~2~~3. Change in the TS-[redacted]CGI score from baseline to week ~~8~~ 8 between low dose TEV-50717-treated patients and placebo-treated patients 4. Change in the TS- PGII score from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients 5. Change in the TS-PGII score from baseline to week 8 between low-dose TEV-50717-treated patients and placebo-treated patients ~~3~~6. Change in the C&A-GTS-QOL ~~physical/activities of daily living~~ADL subscale from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients 7. ~~Additional Efficacy~~Change in the C&A-GTS-QOL ADL subscale from baseline to week 8 between low-dose TEV-50717 treated patients and placebo treated patients.	1. Change in the TS-CGI score from baseline to week 8 between high-dose TEV-50717 treated patients and placebo treated patients 2. Change in the TTS of the YGTSS from baseline to week 8 for low-dose TEV-50717 and placebo will be tested 3. Change in the TS-CGI score from baseline to week 8 between low dose TEV-50717-treated patients and placebo-treated patients 4. Change in the TS- PGII score from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients 5. Change in the TS-PGII score from baseline to week 8 between low-dose TEV-50717-treated patients and placebo-treated patients 6. Change in the C&A-GTS-QOL ADL subscale from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients 7. Change in the C&A-GTS-QOL ADL subscale from baseline to week 8 between low-dose TEV-50717 treated patients and placebo treated patients.	Additional secondary efficacy endpoints were included for analysis. Changes were made to existing secondary efficacy endpoints. (ie, [redacted] was removed from secondary efficacy endpoints)
9.5.3. [redacted]		

Original text with changes shown	New wording	Reason/Justification for change
patients who have a reduction of 6 or more points in the [redacted]	[redacted]	
9.5.5.2. Sensitivity Analysis		
At week ~~12~~8	At week 8	Updated timepoints to be aligned with protocol guidelines
9.5.5.3. Key Secondary Efficacy Analyses		
1. The change from baseline to week 8 in TS-CGI will be analyzed using a similar model as the primary analysis; however, instead of change in YGTSS TTS as the dependent. 3. Using the same model as described in endpoint #1 above for TS-CGI, the comparison between the change in the TS-CGI values from baseline to week 8 for low-dose TEV-50717 and placebo will be tested. 4. The change from baseline to week 8 in TS-[redacted]PGII will be analyzed using a ~~similar model as the primary analysis; however, instead of change in YGTSS TTS as the dependent variable and baseline YGTSS TTS as a covariate, the corresponding [redacted] values will be used~~Cochran-Mantel Haenszel-row mean score test with modified ridit scoring controlling for age group. The comparison between high-dose TEV-50717 and placebo will be tested. 5. Using the same model as described in endpoint #4 above for TS-[redacted]GII, the comparison between the change in the TS-PGII values from baseline to week 8 for low-dose TEV-50717 and placebo will be tested. 6. The change from baseline to week 8 in the C&A-GTS-QOL	1. The change from baseline to week 8 in TS-CGI will be analyzed using a similar model as the primary analysis; however, instead of change in YGTSS TTS as the dependent. 3. Using the same model as described in endpoint #1 above for TS-CGI, the comparison between the change in the TS-CGI values from baseline to week 8 for low-dose TEV-50717 and placebo will be tested. 4. The change from baseline to week 8 in TS-PGII will be analyzed using a Cochran-Mantel Haenszel-row mean score test with modified ridit scoring controlling for age group. The comparison between high-dose TEV-50717 and placebo will be tested. 5. Using the same model as described in endpoint #4 above for TS-PGII, the comparison between the change in the TS-PGII values from baseline to week 8 for low-dose TEV-50717 and placebo will be tested. 6. The change from baseline to week 8 in the C&A-GTS-QOL ADL subscale will be analyzed using a similar model as the primary analysis; however, instead of change in YGTSS TTS as the dependent variable and baseline YGTSS TTS as a	Additional efficacy analysis removed. Updated to account for changes made to existing secondary efficacy endpoints.

Original text with changes shown	New wording	Reason/Justification for change
ADL subscale will be analyzed using a similar model as the primary analysis; however, instead of change in YGTSS TTS as the dependent variable and baseline YGTSS TTS as a covariate, the corresponding C&A-GTS-QOL ADL subscale values will be used. The comparison between high-dose TEV-50717 and placebo will be tested. 7. Using the same model as described in endpoint #6 above for the C&A-GTS-QOL ADL subscale, the comparison between the change in the C&A-GTS-QOL ADL subscale scores from baseline to week 8 for low-dose TEV-50717 and placebo will be tested. ~~**9.5.6.4. Additional Efficacy Analysis**~~	covariate, the corresponding C&A-GTS-QOL ADL subscale values will be used. The comparison between high-dose TEV-50717 and placebo will be tested. 7. Using the same model as described in endpoint #6 above for the C&A-GTS-QOL ADL subscale, the comparison between the change in the C&A-GTS-QOL ADL subscale scores from baseline to week 8 for low-dose TEV-50717 and placebo will be tested.	
9.5.5.4 [redacted]		

Original text with changes shown	New wording	Reason/Justification for change
will be included as the covariate.	of interest will be included as the covariate.	
Appendix B. Study Proecuderes and Assessments by Visit		
• TS-CGI • TS-PGII (Note: Input from the caregiver/adult is permitted.) • [redacted] • [redacted] • [redacted] • C&A-GTS-QOL	• TS-CGI • TS-PGII (Note: Input from the caregiver/adult is permitted.) • [redacted] • [redacted] • [redacted] • C&A-GTS-QOL	Updated to reflect additional assessments
Appendix E. Females of Chilbdearing Potenial and Birth Control Method		
Appendix E. FEMALES OF CHILDBEARING POTENTIAL AND BIRTH CONTROL METHODS ~~AND PREGNANCY TESTING~~ ~~Contraception recommendations and pregnancy testing should encompass all IMPs as well as non-investigational medicinal products, eg, background therapy, and the measures to be followed should be based on the medicinal product with highest risk. Assessment of likelihood of possible interaction between IMP or concomitant medications and hormonal contraception should be conducted. Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method, eg, CYP 4A inducers. In case of suspected interaction, hormonal contraceptive alone may not be sufficient. In the absence of clinical pharmacokinetic interaction study data in IMPs with demonstrated or suspected human teratogenicity/fetotoxicity, recommendation for use of hormonal contraceptives should be thoroughly justified by the sponsor. Additional contraceptive methods, including supplementary barrier methods, may be considered.~~ **Females of childbearing potential are defined as:** • not surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile • ~~not postmenopausal~~ • ~~**Description**~~who are postmenarchal or ≥12 years of	**Appendix E. FEMALES OF CHILDBEARING POTENTIAL AND BIRTH CONTROL METHODS** **Females of childbearing potential are defined as:** • not surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile • who are postmenarchal or ≥12 years of age **Highly effective birth control methods:** Highly effective birth control methods are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered. Such methods include: • Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least 1 month before the first dose of IMP • Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; these should be initiated at least 1 month before the first dose of IMP **Unacceptable birth control methods:** Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable	Updated section for brevity. Clarified definition of "females of childbearing potential". Updated guidelines for application/adminitration of of birth control methods. Updated information for acceptable and unacceptable birth control methods. Updated guidelines for pregnancy testing in female patients.

Original text with changes shown	New wording	Reason/Justification for change
~~**different**~~age **Highly effective birth control methods:** Highly effective birth control methods are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered. Such methods include: • Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least ~~7 days (for IMPs without suspected teratogenicity/genotoxicity) and 1 month (for IMPs potentially teratogenic/genotoxic)~~1 month before the first dose of IMP • Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; these should be initiated at least ~~7 days (for IMPs without suspected teratogenicity/genotoxicity) and 1 month (for IMPs potentially teratogenic/genotoxic)~~1 month before the first dose of IMP ~~**Acceptable birth control methods:**~~ ~~Acceptable birth control methods that result in a failure rate of more than 1% per year include: progestogen-only oral hormonal contraception for which the inhibition of ovulation is not the primary mode of action; male or female condom with or without spermicide; cap, diaphragm, or sponge with spermicide. The combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable but not highly effective methods of birth control.~~ **Unacceptable birth control methods:** Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together. ~~**Male contraception:**~~ ~~Male patients must always use a condom, except in cases of no genotoxicity; or no demonstrated or suspected human teratogenicity/fetotoxicity.~~	methods of contraception. Female condom and male condom should not be used together.	

Original text with changes shown	New wording	Reason/Justification for change
~~**Vasectomy:**~~ ~~Use of contraceptive methods applies also to vasectomized men, because of the risk associated with transfer of a drug via seminal fluid.~~ ~~**Contraception for female partners of male study participants:**~~ ~~Female partners (who are not pregnant) of male study participants must use contraception for non-pregnant women of childbearing potential until the end of relevant systemic exposure in case of IMPs with genotoxicity or IMPs with no genotoxicity but demonstrated or suspected human teratogenicity/fetotoxicity.~~ ~~**Pregnancy tests in women of childbearing potential:**~~ ~~7. Conduct monthly pregnancy testing from first dose of IMP until last dose of IMP and additional 30 days in case the IMP does not have a marketing authorization and has suspected human teratogenicity/genotoxicity/fetotoxicity. Conduct monthly pregnancy testing and in case the IMP has a marketing authorization, if the IMP has a demonstrated or suspected human teratogenicity/genotoxicity/fetotoxicity according to Risk Safety Information. Shorter testing intervals are to be considered depending on drug dosing schedule.~~ ~~**Pregnancy tests in women of childbearing potential:**~~ ~~1. Consider additional pregnancy testing, but at least at the end of relevant systemic exposure., in case of possible human teratogenicity/fetotoxicity. This refers to IMPs, for which human data on pregnancies is limited or not available, there is no suspicion of human teratogenicity based on class effects or genotoxic potential, and nonclinical reproductive toxicity studies of relevance for early human pregnancy show positive findings that do not generate a strong suspicion of human teratogenicity/ fetotoxicity.~~ ~~2. For IMPs with unlikely risk of human teratogenicity/fetotoxicity, additional pregnancy testing is generally not necessary. This refers to IMPs for which assessment of the completed necessary nonclinical studies does not indicate teratogenicity/ fetotoxicity in early pregnancy and human data are not available or do not contradict these findings or there is already sufficient		

Original text with changes shown	New wording	Reason/Justification for change
~~evidence for lack of risk based on human data.~~ **~~Pregnant female partners of male study participants:~~** ~~Male study participants must use condoms during intercourse if their female partners are pregnant.~~		
Appendix G. Handling, Labeling, Storage, and Accountability for IMP		
Empty, partially used, and unused IMP will be ~~disposed of per site policy, or~~ returned to the sponsor or its designee, as agreed with the sponsor.	Empty, partially used, and unused IMP will be returned to the sponsor or its designee, as agreed with the sponsor.	Updated guidelines for management of partially used or unused IMP
Appnedix H. List of Allowed and Prohibited Medications		
	Table 10 added to reflect list of prohibited QTc prolonging drugs	Added table to provide list of prohibited QTc prolonging drugs
Appendix Q. Child and Adolescent Gilles de la Tourette Syndrome - Qualityf of Life - Scale for Patients Aged 6 to 12 Years (C&A-GTS-QOL 6-12) and 13 to 18 Years (C&A-GTS-QOL 13-18)		
	Appendix revised to reflect updates on questionnaire	Revised questionnaire to account for updates to assessment

APPENDIX A.DISTRIBUTION OF AUG BY WEIGHT CATEGORIES AND CYP2D6 STATUS

Figure 2: Distribution of AUC of Total (α+β)-HTBZ for Selected Doses Based on Weight Categories

APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT

1. **Procedures for Prescreening (Up to 3 Months)**

The prescreening visit will take place not more than 3 months before the baseline visit. The following procedure will be performed at prescreening:

- obtain written informed consent/assent, depending on the child's age, as appropriate, before any study-related procedures are performed

2. **Procedures for Screening (Up to 31 days)**

The screening visit will take place up to 31 days before the baseline visit. A patient who is screened but not enrolled may be rescreened 1 time if there is a change in the status of the patient regarding eligibility for the study. (Note: Details of rescreening must be approved and documented by the medical monitor and/or Clinical Surveillance and Training [CST] team.)

The Yale Global Tic Severity Scale (YGTSS) questionnaire should be performed before any blood draws or electrocardiogram (ECG) assessments. All investigators and sub-investigators who will be administering the YGTSS from screening through the end of study visit must undergo and pass a Rater Certification Program which will be provided separately from this protocol. Every effort must be made to ensure that the same certified rater administers the YGTSS to a specific patient at all visits, especially at the baseline and week 8/early termination visits. However, if due to unforeseen circumstances the same rater is absolutely unavailable to complete a visit rating, the YGTSS can be administered only by another certified individual from that study site. The following procedures will be performed at screening:

- obtain written informed consent/assent, depending on the child's age, as appropriate, before any study-related procedures are performed
- conduct clinic visit (may be conducted over 2 separate visits at the discretion of the investigator [Note: If the screening visit is divided into 2 visits, the blood sample should be obtained during the first of the 2 visits.])
- review eligibility (inclusion and exclusion) criteria
- review medical and psychiatric history
- review demographics information
- measure vital signs (pulse, blood pressure [BP], body temperature, and respiratory rate) and weight (Note: Weight must be measured with shoes and outerwear off.)
- perform full physical and neurological examinations (including height)
- perform 12-lead ECG (Note: ECG will be performed after at least 5 minutes rest in a supine or semi-supine position)
- perform clinical laboratory tests, including chemical, hematological, and urine analyses
- perform urine drug screen (UDS)

- obtain a blood sample (3 mL) for analysis of CYP2D6 genotype
- perform a serum pregnancy (beta-human chorionic gonadotropin [β-HCG]) test (only in females who are postmenarchal or ≥12 years of age)
- administer the following questionnaires (Note: For Mini International Neuropsychiatric Interview for Children and Adolescents [MINI Kid] and Columbia Suicide Severity Rating Scale [C-SSRS], children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information. The YGTSS questionnaire should be performed before any blood draws or ECG assessments.):
  - MINI Kid (Note: The following modules will be used: Major Depressive Episode [Module A], [Hypo] Manic Episode [Module D], obsessive-compulsive disorder [OCD; Module J], Alcohol Dependence/Abuse [Module L], Substance Dependence/Abuse [Non-alcohol; Module M], Attention Deficit Hyperactivity Disorder [ADHD; Module O], Conduct Disorder [Module P], and Psychotic Disorders and Mood Disorders with Psychotic Features [Module R])
  - Children's Depression Inventory Second Edition (CDI-2), Parent and Self-report Profiles (Note: Children 6 years of age at baseline will not complete the self-report version; the caregiver/adult will complete the parent version.)
  - C-SSRS (children's baseline/screening)
  - YGTSS (Input from the caregiver/adult is required.)
- assess of adverse events
- review medication history and concomitant medications

3. **Procedures Before Administration of Investigational Medicinal Product (Baseline, Day 1)**

Patients who meet the inclusion and exclusion criteria at screening will continue to the day 1 visit, when baseline assessments will be conducted. The YGTSS, Tourette Syndrome-Clinical Global Impression (TS-CGI), Tourette Syndrome-Patient Global Impression of Impact (TS-PGII), and [redacted] questionnaires should be performed before any blood draws or ECG assessments.

The following procedures will be performed at the day 1 visit/baseline:

- randomization
- conduct clinic visit
- review eligibility (inclusion and exclusion) criteria
- measure vital signs (orthostatic pulse and BP [after standing for at least 3 minutes], body temperature, and respiratory rate) and weight (Note: Weight must be measured with shoes and outerwear off.)

- perform 12-lead ECG (Note: ECG will be performed after at least 5 minutes rest in a supine or semi-supine position.)
- perform serum pregnancy (β-HCG) test (only in females who are postmenarchal or ≥12 years of age)
- administer the following questionnaires (Note: For C-SSRS, [redacted] and Child and Adolescent Gilles de la Tourette Syndrome - Quality of Life scale (C&A-GTS-QOL), children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information. The YGTSS, TS-CGI, TS-PGII, and [redacted] questionnaires should be performed before any blood draws or ECG assessments.):
  - CDI-2, Parent and Self-report Profiles (Note: Children 6 years of age at baseline will not complete the self-report version; the caregiver/adult will complete the parent version.)
  - C-SSRS (children's Since Last Visit [SLV])
  - YGTSS (Input from the caregiver/adult is required.)
  - TS-CGI
  - TS-PGII (Input from the caregiver/adult is permitted.)
  - [redacted]
  - [redacted]
  - [redacted]
  - C&A-GTS-QOL
- dispense investigational medicinal product (IMP) (patients will receive doses for 2 weeks [current dose level and next dose level] to cover the telephone contacts)
- provide patients with a diary to record critical information on dosing
- assess of adverse events
- review concomitant medications

4. **Procedures During Administration of Investigational Medicinal Product**

   a. **Escalation Period (Weeks 1 and 3) and Maintenance Period (Week 6)**

Patients who meet the inclusion and exclusion criteria at screening will continue to visit 1, when baseline assessments will be conducted. The YGTSS, TS-CGI, TS-PGII, and [redacted] questionnaires should be performed before any blood draws or ECG assessments.

The following procedures will be performed at weeks 1, 3, and 6:

- telephone contact
- dose escalation (weeks 1 and 3 only)
- assess IMP accountability/compliance/supply
- assess of adverse events
- review concomitant medications

b. Escalation Period (Week 2)

The following procedures will be performed at week 2:

- conduct clinic visit
- dose escalation
- measure vital signs (pulse, BP, body temperature, and respiratory rate) and weight (Note: Weight must be measured with shoes and outerwear off.)
- administer the following questionnaires (Note: For C-SSRS, [redacted], [redacted], and C&A-GTS-QOL, children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information. The YGTSS, TS-CGI, TS-PGII, and [redacted] questionnaires should be performed before any blood draws or ECG assessments.):
  - CDI-2, Parent and Self-report Profiles (Note: Children 6 years of age at baseline will not complete the self-report version; the caregiver/adult will complete the parent version.)
  - C-SSRS (Children's SLV)
  - YGTSS (Input from the caregiver/adult is required.)
  - TS-CGI
  - TS-PGII (Note: Input from the caregiver/adult is permitted.)
  - [redacted]
  - [redacted]
- dispense IMP and patient diary
- collect IMP
- assess IMP accountability/compliance/supply
- assess of adverse events
- review concomitant medications

c. Escalation Period (Week 4)

The following procedures will be performed at week 4:

- conduct clinic visit
- measure vital signs (orthostatic pulse and BP [after standing for at least 3 minutes], body temperature, and respiratory rate) and weight (Note: Weight must be measured with shoes and outerwear off.)
- perform 12-lead ECG (Note: ECG will be performed after at least 5 minutes rest in a supine or semi-supine position.)
- perform serum pregnancy (β-HCG) test (only in females who are postmenarchal or ≥12 years of age)
- administer the following questionnaires (Note: For C-SSRS, [redacted], and C&A-GTS-QOL, children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information. The YGTSS, TS-CGI, TS-PGII, and [redacted] questionnaires should be performed before any blood draws or ECG assessments.):
  - CDI-2, Parent and Self-report Profiles (Note: Children 6 years of age at baseline will not complete the self-report version; the caregiver/adult will complete the parent version.)
  - C-SSRS (Children's SLV)
  - YGTSS (Note: Input from the caregiver/adult is required.)
  - TS-CGI
  - TS-PGII (Note: Input from the caregiver/adult is permitted.)
  - [redacted]
  - [redacted]
  - [redacted]
  - C&A-GTS-QOL
- dispense IMP and patient diary (prior to the clinic visit on week 8, patients will be reminded to record the start time of their last meal and the time of their last dose of study medication before the week 8 visit)
- collect of IMP
- assess IMP accountability/compliance/supply
- assess adverse events

- review concomitant medications

d. Maintenance Period (Week 7)

The following procedures will be performed at week 7:

- telephone contact
- assess IMP accountability/compliance/supply
- assess adverse events
- review concomitant medications

e. Maintenance Period/Early Termination (Week 8)

Dosing requirements for the week 8 visit must be followed to ensure appropriate pharmacokinetic sample collection. Patients with early morning visits (ie, within 2 hours of their scheduled AM dosing) should take their dose in clinic after the first pharmacokinetic sample is collected. The date and time of the last dose of study medication before the week 8 visit should be recorded in the diary by the patient or caregiver/adult. The site will document the date and time of the sample collection. Prior to the clinic visit on week 8, patients will be reminded to record the start time of their last meal and the time of their last dose in their diary. The following procedures will be performed at week 8/early termination:

- conduct clinic visit
- measure vital signs (orthostatic pulse and BP [after standing for at least 3 minutes], body temperature, and respiratory rate) and weight (Note: Weight must be measured with shoes and outerwear off.)
- perform full physical and neurological examinations (including height)
- perform 12-lead ECG (Note: ECG will be performed after at least 5 minutes rest in a supine or semi-supine position.)
- obtain pharmacokinetic blood samples (Two samples will be collected. The first sample will be collected upon arrival at the clinic. The second sample will be collected within 2 to 3 hours after the first PK sample collection. Patients with early morning visits (ie, within 2 hours of their scheduled AM dosing) should take their IMP dose in the clinic after the first PK sample is collected.)
- perform clinical laboratory tests, including chemical, hematological, and urine analyses
- perform UDS
- perform serum pregnancy (β-HCG) test (only in females who are postmenarchal or ≥12 years of age)
- administer the following questionnaires (Note: For C-SSRS, [redacted] and C&A-GTS-QOL, children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should

be encouraged to add relevant information. The YGTSS, TS-CGI, TS-PGII, and [redacted] questionnaires should be performed before any blood draws or ECG assessments.):

- CDI-2, Parent and Self-report Profiles (Note: Children 6 years of age at baseline will not complete the self-report version; the caregiver/adult will complete the parent version.)
- C-SSRS (children's SLV)
- YGTSS (Input from the caregiver/adult is required.)
- TS-CGI
- TS-PGII (Input from the caregiver/adult is permitted.)
- [redacted]
- [redacted]
- [redacted]
- C&A-GTS-QOL

- collect IMP
- assess IMP accountability/compliance/supply
- assess adverse events
- review concomitant medications

5. Follow-up (Weeks 9 and 10)

The YGTSS, TS-CGI, TS-PGII, and [redacted] questionnaires should be performed before any blood draws or ECG assessments.

The following procedures and assessments will be performed at the follow-up weeks 9 and 10 (±3 days from week 8):

The following procedures will be performed at week 9:

- conduct clinic visit
- measure vital signs (pulse, BP, body temperature, and respiratory rate) and weight (Note: Weight must be measured with shoes and outerwear off.)
- administer the following questionnaires (Note: For C-SSRS, [redacted], [redacted], and C&A-GTS-QOL, children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information. The YGTSS, TS-CGI, TS-PGII, and [redacted] questionnaires should be performed before any blood draws or ECG assessments.):

- CDI-2, Parent and Self-report Profiles (Note: Children 6 years of age at baseline will not complete the self-report version; the caregiver/adult will complete the parent version.)
- C-SSRS (Children's SLV)
- YGTSS (Input from the caregiver/adult is required. Perform assessment of Severity Ratings of the questionnaire. Inventory portions [ie, "Motor Tic Symptom Checklist" and "Phonic Tic Symptom Checklist"] do not need to be performed.)
- TS-CGI
- TS-PGII (Note: Input from the caregiver/adult is permitted.)
- [redacted]
- [redacted]
- [redacted] (Perform the Severity Ratings of OCD symptoms [Questions 1 through 10] only. Checklist does not need to be performed.)

- assess adverse events
- review concomitant medications

The following procedures will be performed at week 10:

- telephone contact
- assess adverse events
- review concomitant medications

6. Unscheduled Visits

An unscheduled visit may be performed at any time during the study at the patient's request and as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded on the CRF, as well as any other data obtained from procedures and assessments.

The following procedures will be performed at every unscheduled visit:

- conduct clinic visit
- measure vital signs (pulse, BP, body temperature, and respiratory rate) and weight (Note: Weight must be measured with shoes and outerwear off.)
- assess adverse events
- review concomitant medications

The following procedures will be performed at the investigator's discretion:

- perform full physical and neurological examinations
- perform 12-lead ECG (at the investigator's discretion) (Note: ECG will be performed after at least 5 minutes rest in a supine or semi-supine position.)

- perform clinical laboratory tests, including chemical, hematological, and urine analyses
- perform UDS
- perform serum pregnancy (β-HCG) test (only in females who are postmenarchal or ≥12 years of age)
- administer the following questionnaires:
  - CDI-2, Parent and Self-report Profiles (Note: Children 6 years of age at baseline will not complete the Self-report version; the caregiver/adult will complete the Parent version.)
  - C-SSRS (Children's SLV; Note: Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information.)
  - C&A-GTS-QOL
- dispense IMP and patient diary, if applicable
- collect IMP
- assess IMP accountability/compliance/supply

Other procedures and assessments may be performed at the discretion of the investigator.

APPENDIX C.QUALITY CONTROL AND QUALITY ASSURANCE

Protocol Amendments and Protocol Deviations

Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/IRB and national and local competent authorities, as applicable, except when necessary to address immediate safety concerns to the patients or when the change involves only nonsubstantial logistics or administration. The principal investigator at each investigational center, the coordinating investigator (if applicable), and the sponsor will sign the protocol amendment.

Protocol Deviations

Any deviation from the protocol that affects, to a significant degree, (a) the safety, physical, or mental integrity of the patients in the study and/or (b) the scientific value of the study will be considered a protocol violation. Protocol deviations may include non-adherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to IMP administration; use of prohibited medications. Protocol deviations will be identified and recorded by investigational center personnel in the CRF. All protocol deviations will be reported to the responsible IEC/IRB, as required.

When a protocol violation is reported, the sponsor will determine whether to withdraw the patient from the study or permit the patient to continue in the study, with documented approval from the medical expert. The decision will be based on ensuring the safety of the patient and preserving the integrity of the study.

Changes in the inclusion and exclusion criteria of the protocol are **not** prospectively granted by the sponsor. If investigational center personnel learn that a patient who did not meet protocol inclusion and exclusion criteria was entered in a study, they must immediately inform the sponsor of the protocol violation. If such patient has already completed the study or has withdrawn early, no action will be taken but the violation will be recorded.

Information to Study Personnel

The investigator is responsible for giving information about the study to all personnel members involved in the study or in any element of patient management, both before starting the study and during the course of the study (eg, when new personnel become involved). The investigator must ensure that all study personnel are qualified by education, experience, and training to perform their specific task. These study personnel members must be listed on the investigational center authorization form, which includes a clear description of each personnel member’s responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study personnel, including the investigator, and for ensuring they comply with the protocol.

Study Monitoring

To ensure compliance with GCP guidelines, the study monitor or representative is responsible for ensuring that patients have signed the informed consent form and the study is conducted according to applicable Standard Operating Procedures (SOPs), the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the sponsor and the investigator. The main responsibilities of the study monitor(s) are to visit the investigator before, during, and after the study to ensure adherence to the protocol, that all data are correctly and completely recorded and reported, and that informed consent/assent, depending on the child's age, as appropriate, is obtained and recorded for all patients before they participate in the study and when changes to the consent form are warranted, in accordance with IEC/IRB approvals.

The study monitor(s) will contact the investigator and visit the investigational center according to the monitoring plan. The study monitor will be permitted to review and verify the various records (CRFs and other pertinent source data records, including specific electronic source document relating to the study) to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded.

As part of the supervision of study progress, other sponsor personnel may, on request, accompany the study monitor on visits to the investigational center. The investigator and assisting personnel must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected during the course of these monitoring visits or provided in follow-up written communication.

Audit and Inspection

The sponsor may audit the investigational center to evaluate study conduct and compliance with protocols, SOPs, GCP guidelines, and applicable regulatory requirements. The sponsor's Global Clinical Quality Assurance, independent of Global Specialty Development, is responsible for determining the need for (and timing of) an investigational center audit.

The investigator must accept that competent authorities and sponsor representatives may conduct inspections and audits to verify compliance with GCP guidelines.

APPENDIX D.ETHICS

Informed Consent/Assent

The investigator, or a qualified person designated by the investigator, should fully inform the patient and parent/legally acceptable representative of all pertinent aspects of the study, including the written information approved by the IEC/IRB. All written and oral information about the study will be provided in a language as nontechnical as practical to be understood by the patient. The patient should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documents.

A personally signed and dated informed consent will be obtained from the parent/legally acceptable representative, and a signed and dated assent, depending on the child's age, as appropriate, will be obtained from each patient (if the patient is able) before any study specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The patient's willingness to participate in the study will be documented in the informed consent form, which will be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The investigator will keep the original informed consent/assent forms, depending on the child's age, as appropriate, and copies will be given to the patients. It will also be explained to the patients that the patient is free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment.

The investigator, or a qualified person designated by the investigator, should fully inform the patient and each parent/legally acceptable representative of all pertinent aspects of the study, including the written information approved by the IEC/IRB. All written and oral information about the study will be provided in a language as nontechnical as practical to be understood by the each parent/legally acceptable representative and the patient. The patient and each parent/legally acceptable representative should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documents.

A personally signed and dated informed consent form will be obtained from each parent/legally acceptable representative, and a signed and dated assent and/or co-consent form will be obtained from each patient (if the patient is able) before any study specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained; according to IEC/IRB requirements. The forms will be signed and dated also by the person who conducted the informed consent discussion. The investigator will keep the original informed consent and assent forms, and copies will be given to the patients (and each parent/legally acceptable representative). It will also be explained to the patients (and each parent/legally acceptable representative) that they are free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment.

Competent Authorities and Independent Ethics Committees/Institutional Review Boards

Before this study starts, the protocol will be submitted to the national competent authority and to the respective IEC/IRB for review. As required, the study will not start at a given investigational

center before the IEC/IRB and competent authority (as applicable) for the investigational center give written approval or a favorable opinion.

Confidentiality Regarding Study Patients

The investigator must ensure that the privacy of the patients, including their identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification number.

Personal medical information may be reviewed for the purpose of patient safety or for verifying data in the source and the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, Global Quality Assurance (GCA), or competent authorities. Personal medical information will always be treated as confidential.

Registration of the Clinical Study

In compliance with national and local regulations and in accordance with Teva standard procedures, this clinical study will be registered on trials registry websites.

APPENDIX E.

APPENDIX F. LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the investigational center.

The following actions must be taken if a patient fails to return to the investigational center for a required study visit:

- The investigational center must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- In cases in which the patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of 'lost to follow-up'.

APPENDIX G. HANDLING, LABELING, STORAGE, AND ACCOUNTABILITY FOR IMP

Storage and Security

The investigator or designee must confirm appropriate temperature conditions have been maintained for all IMPs received and any discrepancies are reported and resolved before use of the IMPs.

The IMP (TEV-50717 and the placebo) should be stored protected from light, at a controlled room temperature, 20°C to 25°C (68°F to 77°F); however, storage between 15°C and 20°C (59°F and 68°F) is acceptable if there is no alternative. The IMP should be stored in a dry, securely locked, substantially constructed cabinet or enclosure with access limited to authorized staff.

Diversion is considered to have occurred when the legal supply chain of prescription analgesic medicinal products is broken, and medicinal products are transferred from a licit to an illicit channel of distribution or use.

Labeling

Supplies of IMPs will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on GCP and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be translated into the local language.

Accountability

Each IMP shipment to the site will include a packing slip listing the contents of the shipment, drug return instructions, and any applicable forms.

The investigator is responsible for ensuring that deliveries of IMP and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with the local regulations, and used in accordance with this protocol.

A record of IMP accountability (ie, IMP and other materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Empty, partially used, and unused blister packs will be disposed of, as agreed with the sponsor/development partner.

APPENDIX H. ALLOWED AND PROHIBITED MEDICATIONS

Table 7: Allowed Medications

Generic/Drug Class	Brand name	Condition
Stable Medications Allowed According to Inclusion/Exclusions Criteria		
Hormonal birth control	-	Must be receiving stable treatment (including dose) for at least 3 months before screening.
Antidepressants (not listed in Table 8)	-	Must be receiving stable treatment (including dose) for at least 6 weeks before baseline.
Benzodiazepines	-	Primary use must not be for tics; dosing must have been stable for at least 4 weeks before screening. **Note: PRN (as needed) use is prohibited.**
Topiramate (up to 200 mg/day)	-	Must be receiving stable treatment (including dose) for at least 4 weeks before screening.
Guanfacine	INTUNIV®, TENEX®	Allowed, regardless of indication (ie, if prescribed for tics or Tourette syndrome). Must be receiving stable treatment (including dose) for at least 4 weeks before screening and no changes to dose or frequency are anticipated during the course of the study. If discontinuation of guanfacine is anticipated due to ineffectiveness, poor tolerability, or patient/caregiver preference, discontinuation should occur 4 or more weeks prior to the screening visit.
Clonidine	CATAPRES®, CLONIDINE ER®, KAPVAY®, CATAPRES-TTS®	Allowed, regardless of indication (ie, if prescribed for tics or Tourette syndrome). Must be receiving stable treatment (including dose) for at least 4 weeks before screening and no changes to dose or frequency are anticipated during the course of the study. If discontinuation of clonidine is anticipated due to ineffectiveness, poor tolerability, or patient/caregiver preference, discontinuation should occur 4 or more weeks prior to the screening visit.
Stimulants		Include amphetamine, methylphenidate, and lisdexamfetamine. Primary use is for the treatment of ADHD; dosing must have been stable for at least 2 weeks before screening, and no changes to dose or frequency are anticipated during the course of the study.
SNRIs/NRIs		Includes atomoxetine. Primary use is for the treatment of ADHD;

Generic/Drug Class	Brand name	Condition
Stable Medications Allowed According to Inclusion/Exclusions Criteria		
		dosing must have been stable for at least 4 weeks before screening, and no changes to dose or frequency are anticipated during the course of the study.
Additional Medications Allowed with Pre-Approval from Medical Monitor		
Inhaled beta2 adrenergic agonists	-	Asthma
Guaifenesin	DURATUSS G®, GANIDIN NR®, GG 200 NR®, GUAIFENESIN LA®, LIQUIBID®, MUCO-FEN 1200®, ORGANIDIN NR®, Q-BID LA®, ROBITUSSIN®, SCOT-TUSSIN®	Cold symptoms
Antihistamines	-	Allergies
Melatonin	Melatonin Time Release, Health Aid Melatonin, VesPro Melatonin, SGard	Insomnia

ADHD=Attention-deficit/hyperactivity disorder; NRI=norepinephrine reuptake inhibitor; SNRIs=serotonin-norepinephrine reuptake inhibitor.
Note: No dosing changes can be made during the study.

Table 8: Allowed Strong CYP Inhibitors at Baseline

Generic	Brand name	Class/clinical use
Bupropion	APLENZIN®, BUDEPRION SR®, BUPROBAN®, FORFIVO XL®, WELLBUTRIN®, WELLBUTRIN SR®, WELLBUTRIN XL®, ZYBAN®, ZYBAN ADVANTAGE PACK®, BUDEPRION XL®, CARMUBINE®, CLORPRAX®, ELONTRIL®, QUOMEM®, VOXRA®, WELLBUTRIN®, ZYNTABAC®	Antidepressant (aminoketone)
Fluoxetine	PROZAC®, PROZAC WEEKLY®, SARAFEM®, RAPIFLUX®, SELFEMRA®, PROZAC PULVULES®, ADOFEN® (BRAINPHARMA, SPAIN), AFFEX®, ANDEPIN®, APO-FLUOXETINE®, ASTRIN®, AUGORT®, AZUR®, BELLZAC®, BIOXETIN®, BIOZAC®, CLEXICLOR®, CLORIFLOX®, DAGRILAN®, DEFLUOX®, DEPREKS®, DEPRENON®, DEPREX®,DEPREXEN®, DEPREXETIN®, DEPREXIN®, DEPSET®, DIESAN®, DIGASSIM®, DINALEXIN®, DOCFLUOXETINE®, DOCUTRIX®, EXOSTREPT®, FEFLUZIN®, FELICIUM®, FELICIUM®, FLOCCIN®, FLONITAL®, FLORAK®, FLOTINA®, FLOXET®, FLUCTIN®, FLUCTINE®, FLUCTINE®, BFLUESCO®, FLUMIREX®, FLUNEURIN®, FLUNISAN®, FLUOCALM®, FLUOCIM®, FLUOCIM®, FLUOGAL®, FLUOX®, FLUOXA®, FLUOX-BASAN®, FLUOXELICH®, FLUOXEMED®, FLUOXEMERCK®, FLUOXENORM®, FLUOXE-Q®, FLUOXEREN®, FLUOXETINE CAPSULES® BP 2014, FLUOXETINE CAPSULES® USP 36, FLUOXETINE DELAYED-RELEASE CAPSULES® USP 36, FLUOXETINE ORAL SOLUTION® BP 2014, FLUOXETINE ORAL SOLUTION® USP 36, FLUOXETINE TABLETS® USP 36, FLUOXGAMMA®, FLUOXIBENE®, FLUOXIFAR®, FLUOXIN®, FLUOXIN®, FLUOXISTAD®, FLUOXITYROL®,	Antidepressant (selective serotonin reuptake inhibitor)

Generic	Brand name	Class/clinical use
	FLUOXONE®, FLUOX-PUREN®, FLUOXSTAD®, FLUSOL®, FLUSTAD®, FLUVAL®, FLUVAL®, FLUX®, FLUXADIR®, FLUXEMED® (PROMED, POL.), FLUXET®, FLUXIL®, FLUXOMED®, FLUXONIL®, FLUZAC®, FLUZAK®, FOKESTON®, FONTEX®, FOXETEVA®, FRAMEX®, FULSAC®, FYSIONORM®, GEROZAC®, GRINFLUX®, HAPILUX®, IBIXETIN®, IPSUMOR®, LECIMAR®, LOKSETIN®, LURAMON®, MAGRILAN®, MILEZIN®, MIZAC®, MOTIVONE®, MUTAN®, NODEPE®, NODEPE®, NORZAC®, NUFLUO®, OLENA®, ORTHON®, PORTAL®, PORTAL®, PORTAL®, POSITIVUM®, PRODEP®, PROFLUSAK®, PROSIMED®, PROZAC®, PROZAMEL®, PROZATAN®, PROZEP®, PROZIT®, PROZIT®, PSIPAX®, RENEURON®, SALIPAX®, SALIPAX®, SARTUZIN®, SELECTUS®, SEREZAC®, SERONIL®, SEROSCAND®, SOFELIN®, STEPHADILAT-S®, STRESSLESS®, TARGET®, THIRAMIL®, TUNELUZ®, XEREDIEN®, XETIRAN®, ZAFLUOX®, ZAXETINA®, ZEDPREX®, ZINOVAT®	
Paroxetine	BRISDELLE®, PAXIL®, PAXIL CR®, PEXEVA®, ACTAPAROXETINE®, ADEPRESS®, ALLENOPAR®, APARO®, APO-PAROX®, ARAPAXEL®, ARKETIS®, ARKETIS®, AROPAX®, AROPAX®, AS-PAROKS®, CASBOL®, DENERVAL®, DEROXAT®, DEXANTOL®, DROPAX®, DROPAXIN®, EUTIMIL®, FROSINOR®, LIMSA®, MOTIVAN®, NOKTURN®, NOPRILEX®, OXEPAR®, OXET®, PALUXETIL®, PARETIN®, PAREXAT®, PAROCETAN®, PAROGEN®, PAROLET®, PAROLICH®, PAROMERCK®, PARONEX®, PAROSAT®, PAROSER®, PAROTUR®, PAROX®, PAROXALON®, PAROXAT®, PAROXEDURA®, PAROXETINE TABLETS® BP 2014, PAROXETINE TABLETS® USP 36, PAROXETOP®, PAROXIA®, PAROXINOR®, PAXERA®, PAXERATIO®, PAXETIL®, PAXIL®, PAXINOL®, PAXPAR®, PAXT®, PAXTIN®, PREXAT®, REMOOD®, REXETIN®, RITLEMI®, SERESTILL®, SEREUPIN®, SEROXAT®, SOLBEN®, STILIDEN®, TABERIL®, TAGONIS®, VOLTAK®, XETANOR®, XETIN®, ZANOXINA®, ZURIA®	Antidepressant (selective serotonin reuptake inhibitor)

CYP=cytochrome P450; IMP=investigational medicinal product
Note: The use of these medications will affect the maximum daily dose of IMP, as shown in Table 1.

Table 9: Prohibited Antipsychotic Drugs

Typical/first generation antipsychotics		Atypical/second generation antipsychotics	
Generic	**Brand name**	**Generic**	**Brand name**
Chlorpromazine	THORAZINE®, LARGACTIL®, JUVEN TOS®, LARGATREX®, AMINAZIN®, CHLORACTIL®, CHLORAZIN®, CLONACTIL®, DIMINEX BALSAMICO®, FENACTIL®, HIBERNAL®, MEGAPHEN®, PLEGOMAZIN®, PROPAPHENIN®, PROZIN®, SOLIDON®, ZULEDIN®	Aripiprazole	ABILIFY®, ABIZOL®, AMDOAL®, ARIFAY®, ARIPA®, BRISKING®, CUREXOL®, FIXMENT®, IGNIS®, MADEPZOL®, RIMA-FIX®, ZOLERIP®
Haloperidol	HALDOL®, SERENACE®, ALASED®, ALOPERIDIN®, BIOPERIDOLO®, BUTERIDOL®, DOZIC®, DURAPERIDOL®, ELAUBAT®, FORTUNAN®, HALDOL®, HALONEURAL®, HALOPER®, LEPTOL®,	Asenapine maleate	SAPHRIS®, SYCREST®

Typical/first generation antipsychotics		**Atypical/second generation antipsychotics**	
Generic	**Brand name**	**Generic**	**Brand name**
	NORODOL®, OVOCTEROL®, SEDAPERIDOL®, SENORM®, SERENACE®, SERENELFI®, SEVIUM®, SIGAPERIDOL®, VESADOL®, VESALIUM®, DECALDOL®, NORODOL®, SENORM®		
Loxapine	LOXAPAC®, LOXITANE®, DESCONEX	Clozapine	CLOZARIL®, AZALEPROL®, AZALEPTIN®, CLONEX®, CLOPIN®, CLOSASTENE®, CLOZALUX®, DENZAPINE®, ELCRIT®, FAZACLO®, KLOZAPOL®, LANOLEPT®, LEPONEX®, NEMEA®, OZAPIM®, ZAPONEX®
Molindone	MOBAN®	Iloperidone	FANAPT®
Perphenazine	TRILAFON®, DECENTAN®, ETAPERAZIN®, FENTAZIN®, LONGOPAX®, MINITRAN®, MUTABASE®, MUTABON®, TRIPHENAZE®, TRIPTAFEN®	Lurasidone	LATUDA®
Pimozide	ORAP® ANTALON®, NOROFREN®, OPIRAN®, PIRIUM®	Olanzapine	ZYPREXA®, AEDON®, APSICO®, APZET®, ARENBIL®, ARKOLAMYL®, ASTERILON®, ATYZYO®, BLOONIS®, CAPRILON®, CLINGOZAN®, DECOLAN®, ELYNZA®, FORDEP®, FREDILAN®, KOZYLEX®, LANZAFEN®, LANZAPIN®, LAZAPIX®, LERNUP®, MITAB®, NAKOZAP®, NEWZYPRA®, NIOLIB®, NORMITON®, NORPEN ORO®, NYKOB®, NYZOL®, OFANS®, OFERTA®, OLAFER®, OLAN®, OLANZARAN®, OLAPIN®, OLAZAX®, OLSTADRYN®, OZILORMAR®, ROLYPREXA®, TIZINA®, XAPRITX®, ZALASTA®, ZAPRIS®, ZERPI®, ZIPRODEC®, ZOLAFREN®, ZONAPIR®, ZYPADHERA®
Prochlorperazine	COMPAZINE®, STEMETIL®, TEMENTIL®	Olanzapine / fluoxetine	SYMBYAX®
Thioridazine	MELLARIL®, MELLERETTE®, MELLERETTEN®, RIDERIL®, SONAPAX®, THIORIL®, TISON®, VISERGIL®, DETRIL®, ELPERIL®, MELERIL®, MELLERETTES®, MELLERIL®, MELZINE®, THIODAZINE®, THIOZINE®, VISERGIL®	Paliperidone	INVEGA®, CILAG®, XEPLION®
Thiothixene	NAVANE®, ORBINAMON®	Quetiapine	SEROQUEL®, ALZEN®, ATROLAK®, BIQUELLE®, DERIN®, EBESQUE®, GENTIAPIN®, ILUFREN®, KEFRENEX®, KETIRON®, KWETAPLEX®, NEURORACE®, NOTIABOLFEN®,

Typical/first generation antipsychotics		**Atypical/second generation antipsychotics**	
Generic	**Brand name**	**Generic**	**Brand name**
			PINAPAZ®, QUENTAPIL®, QUENTIAX®, QUETATIEFI®, QUETEPER®, QUETEX®, QUETIAFAIR®, QUETIALAN®, QUETIAMYLAN®, QUETROP®, RAIKAR®, RIZMUL®, ROCOZ®, SEOTIAPIM®, SEQUASE®, SEROPIA®, SEROQUEL®, SEROQUIN®, SEROTIAPIN®, SETININ®, SONDATE®, TEVAQUEL®, VIKETO®, VUTIF®, XEROQUEL®, ZALURON®
Trifluoperazine	STELAZINE®, ESKAZINE®, JALONAC®, JATRONEURAL®, JATROSOM®, MODALINA®, OXYPERAZINE®, PARMODALIN®, PARSTELIN®, STELABID®, STELAZINE®, TERFLUZINE®	Risperidone	RISPERDAL®, ALEPTAN®, ARKETIN®, ATORNIL®, BELIVON®, CALMAPRIDE®, DIAFORIN®, DISAPERID®, ITRAXEL®, LOTIN®, NECLAV®, PERDIN RIPAX®, RISFARMAL®, RISPAL®, RISPATAL®, RISPEMYLAN®, RISPEN®, RISPENON®, RISPE-Q®, RISPERDALCONSTA®, RISPERDALORO®, RISPERDOC®, RISPERGER®, RISPERIGAMMA®, RISPERSTAD®, RISPEVA®, RISPIMEDICA®, RISPOLIN®, RISPONE®, SMISSEN®

Typical/first generation antipsychotics		**Atypical/second generation antipsychotics**	
Generic	**Brand name**	**Generic**	**Brand name**
Promethazine-containing compounds	PHENERGAN®-CONTAINING COMPOUNDS, ATOSIL®, BOIPULMONALE SIMPLE®, CREMA ANITALLERGICA ANTIPRURIGINOSA®, FARGAN®, FENERGAN TOPICO®, RECTOQUINTYL-PROMETHAZINE®, TUSSISEDAL®, ACTITHIOL ANTIHIST®, ALGOTROPYL®, ALLERFEN®, ANTIHEMORROIDAL®, ARTU®, ATOSIL®, BEXOL®, BOIPULMONALE SOL®, BRONCATAR®, BRONCONAIT®, CHOLIGRIP NA NOC®, CIGARETTES ET POUDRE FUMANTERGYL®, CLOSIN®, COLDREX NITE®, COLDREX NITE®, DIPHERGAN®, DOBACEN PLUS®, DOLSOM®, DUPLAMIN®, EUSEDON MONO®, FARGANESSE®, FENAZIL®, FENERGAN®, FRINOVA®, HEMOTRIPSIN®, INSOMNYL®, JUVEPIRINE A LA PROMETHAZINE®, LINERVIDOL®, LYSEDIL®, MEDISED®, NARDYL PAMERGAN P100®, PAXELADINE NOCTEE®, PETIGAN MIRO®, PHENERGAN®, PHENHALAL®, PHENSEDYL®, PHENSEDYL PLUS®, PIPOLPHEN®, PIPOLZINE®, POLFERGAN®, PROMKIDDI®, PRONEURIN®, PROTHIAZINE EXPECTORANT®, PRURIDERM ULTRA®, PSICOSOMA®, Q-MAZINE®, QUINTOPAN ENFANT®, RHINATHIOL PROMETHAZINE®, RONPIRIN COLD REMEDY®, SAYOMOL®, SOMINEX®, SOPORIL®, SUGARCETON®, TACHINOTTE®, TARDYL®, THESIT P®, TIEUCALY®, TITANOX®, TIXYLIX®, TRANSMER®, ZIZ®	Tiapride	HIPOKIN®, SEREPRILE®, TIAGER®, TIAPRID PMCS®, TIAPRIDAL®, TIAPRIDE PMCS®, BOINLIL®, CUCKOOL 10%®, DELPRAL®, GRAMALIL®, GRAMALIL 10%®, GRINOLART®, ITALPRID®, LUO YI®, NEURELARK®, SEREPRID®, SEREPRILE®, SHANG YAN®, TIALAREAD®, TIALAREAD 10%®, TIAPRA®, TIAPRALAN®, TIAPRID-1 A PHARMA®, TIAPRID AbZ®, TIAPRID AL®, TIAPRID HEXAL®, TIAPRIDA GENERIS®, TIAPRIDAL®, TIAPRID-CT®, TIAPRIDE 10% SAWAI®, TIAPRIDE CT®, TIAPRIDE FUDAN FUHUA®, TIAPRIDE HYDROCHLORIDE AMEL®, TIAPRIDE MYLAN®, TIAPRIDE RATIOPHARM®, TIAPRIDE SANDOZ®, TIAPRIDE SAWAI®, TIAPRIDEX®, TIAPID-NEURAXPHARM®, TIAPRID-RATIOPHARM®, TIAPRIM®, TIAPRIM 10%®, TIAPRIZAL®, TIARYL®, TIARYL 10%®, TIAZET®
		Ziprasidone	GEODON®, ZELDOX®, ZYPSILAN®
Fluphenazine	PROLIXIN®, PROLIXIN DECANOATE®, PROLIXIN ENANTHATE®, PERMITIL®		

Note: This table does not apply after the first week of the washout period for patients not rolling over to the open-label extension study (Study TV50717-CNS-30047).

Table 10: Prohibited QTc Prolonging Drugs

Generic	Class/clinical use	Note
Azithromycin[a]	Antibiotic/bacterial infection	
Chloroquine/Mefloquine	Anti-malarial/malaria infection	
Clarithromycin[b]	Antibiotic/bacterial infection	
Domperidone	Anti-nausea/nausea	Not available in USA
Droperidol	Sedative; anti-nausea/anesthesia adjunct, nausea	
Erythromycin[b]	Antibiotic; gastrointestinal (GI) stimulant; GI motility	
Moxifloxacin	Antibiotic/bacterial infection	
Sevoflurane	Anesthetic, general/anesthesia	
Probucol	Antilipemic/hypercholesterolemia	Not available in USA
Sparfloxacin	Antibiotic/bacterial infection	Not available in USA

[a] Allowed dose of azithromycin is up to 500 mg/day
[b] Systemic use only. Topical use is allowed.
USA=United States of America.

Table 11: Other Prohibited Drugs

Generic	Class/clinical use	Note
Cannabidiol oil	Cannabis	Also includes other forms of cannabinoids
Valbenazine	Vesicular monoamine transporter 2 inhibitor	Ingrezza off-label
Quinidine	Class I antiarrhythmic agent	Strong CYP2D6 inhibitor
Terbinafine	Antifungal medication	Weak CYP2D6 inhibitor

CYP2D6=cytochrome P450 2D6.

APPENDIX I. MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW FOR CHILDREN AND ADOLESCENTS

The sample provided in this appendix is for reference only.

Modules:

Major Depressive Episode (Module A),

(Hypo) Manic Episode (Module D),

OCD (Module J),

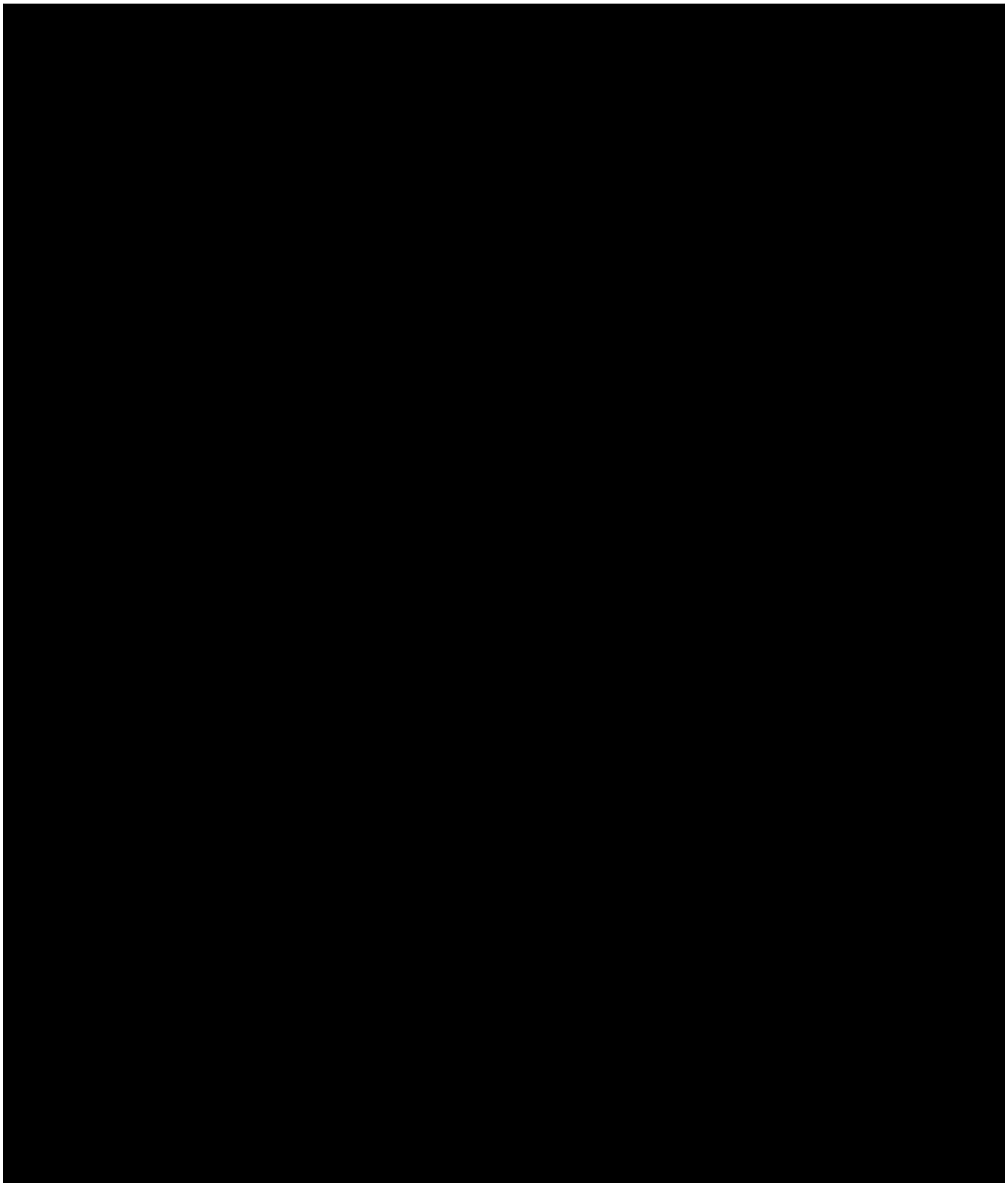
Alcohol Dependence/Abuse (Module L),

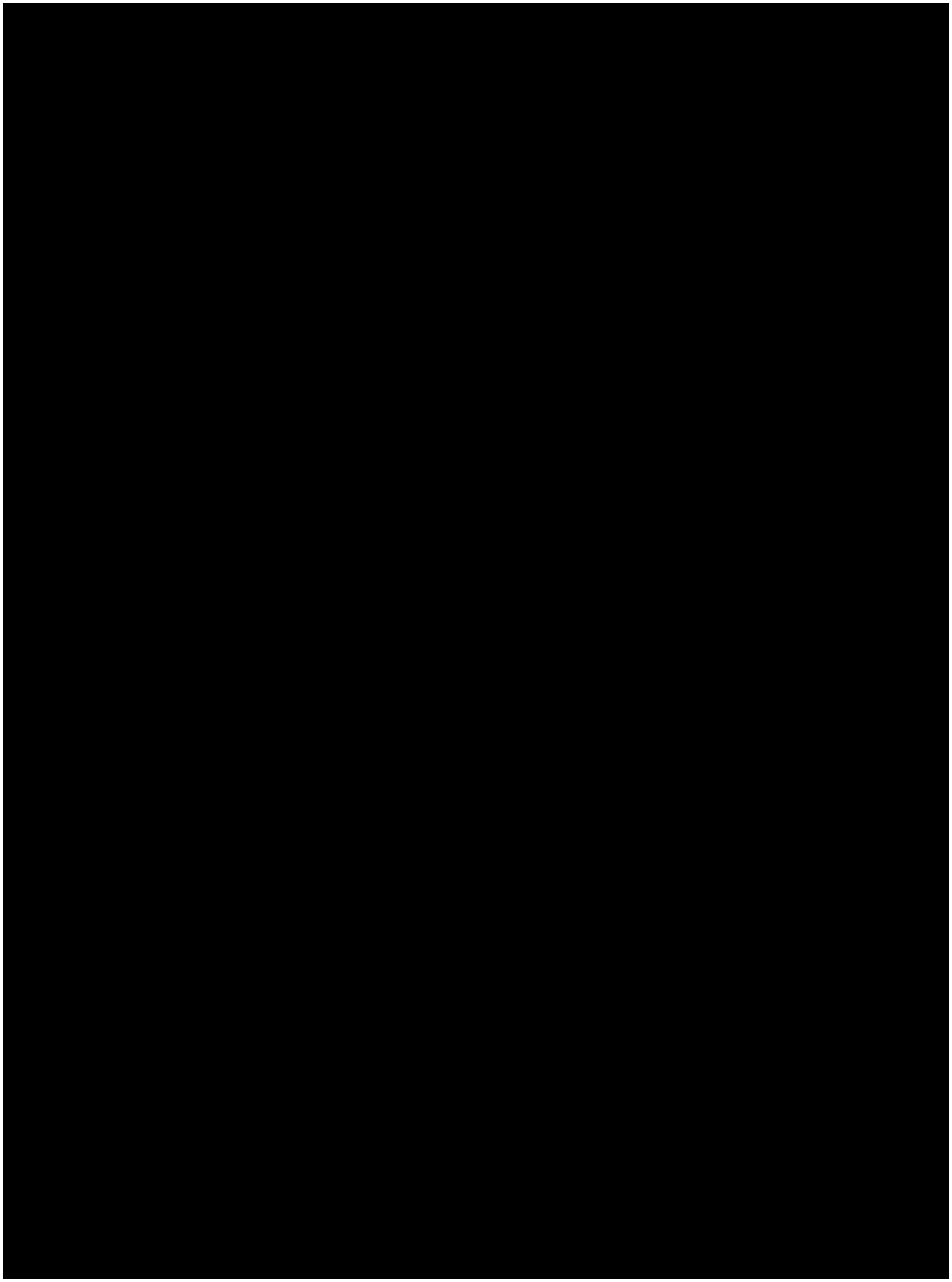
Substance Dependence/Abuse (Non-alcohol; Module M),

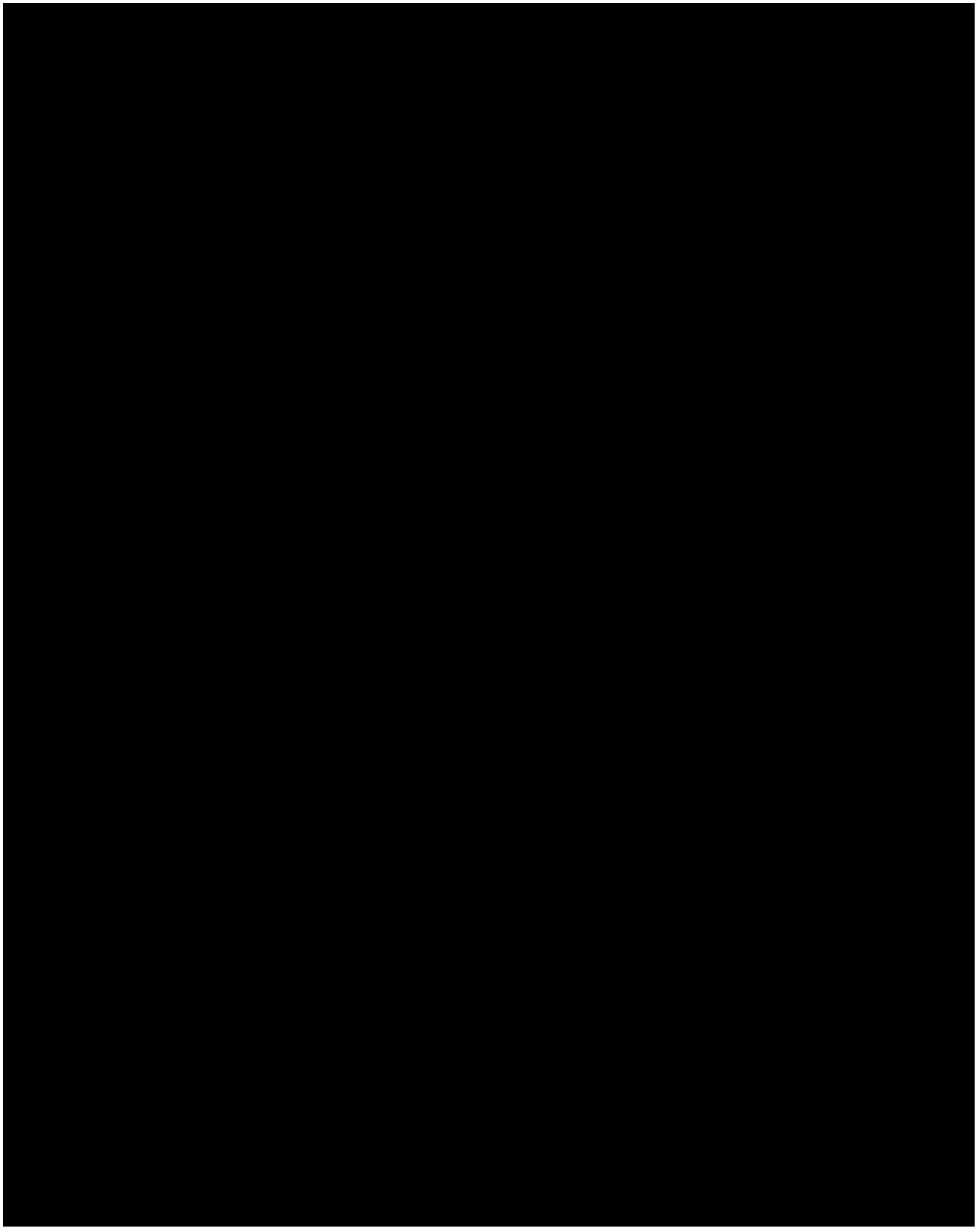
ADHD (Module O),

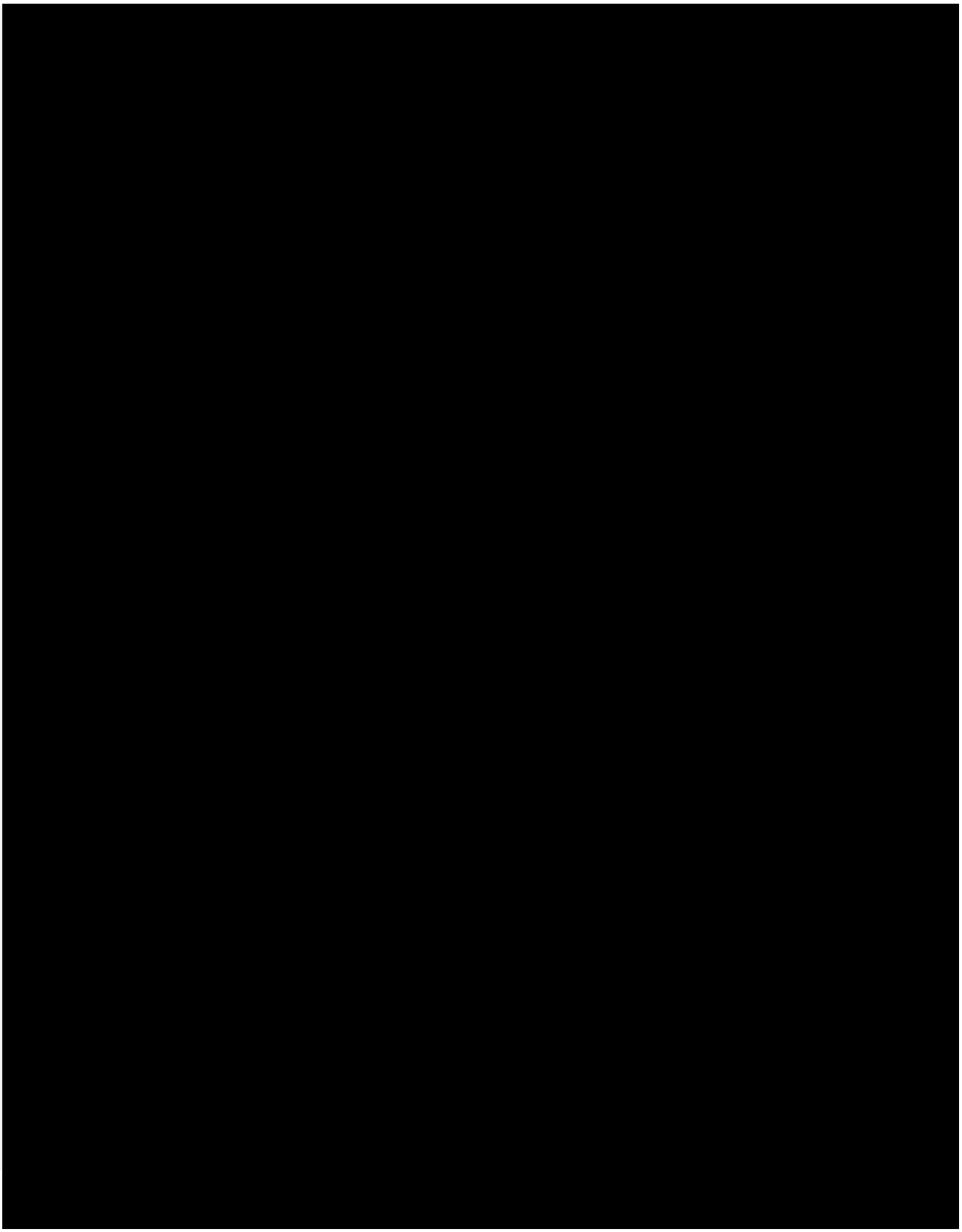
Conduct Disorder (Module P), and

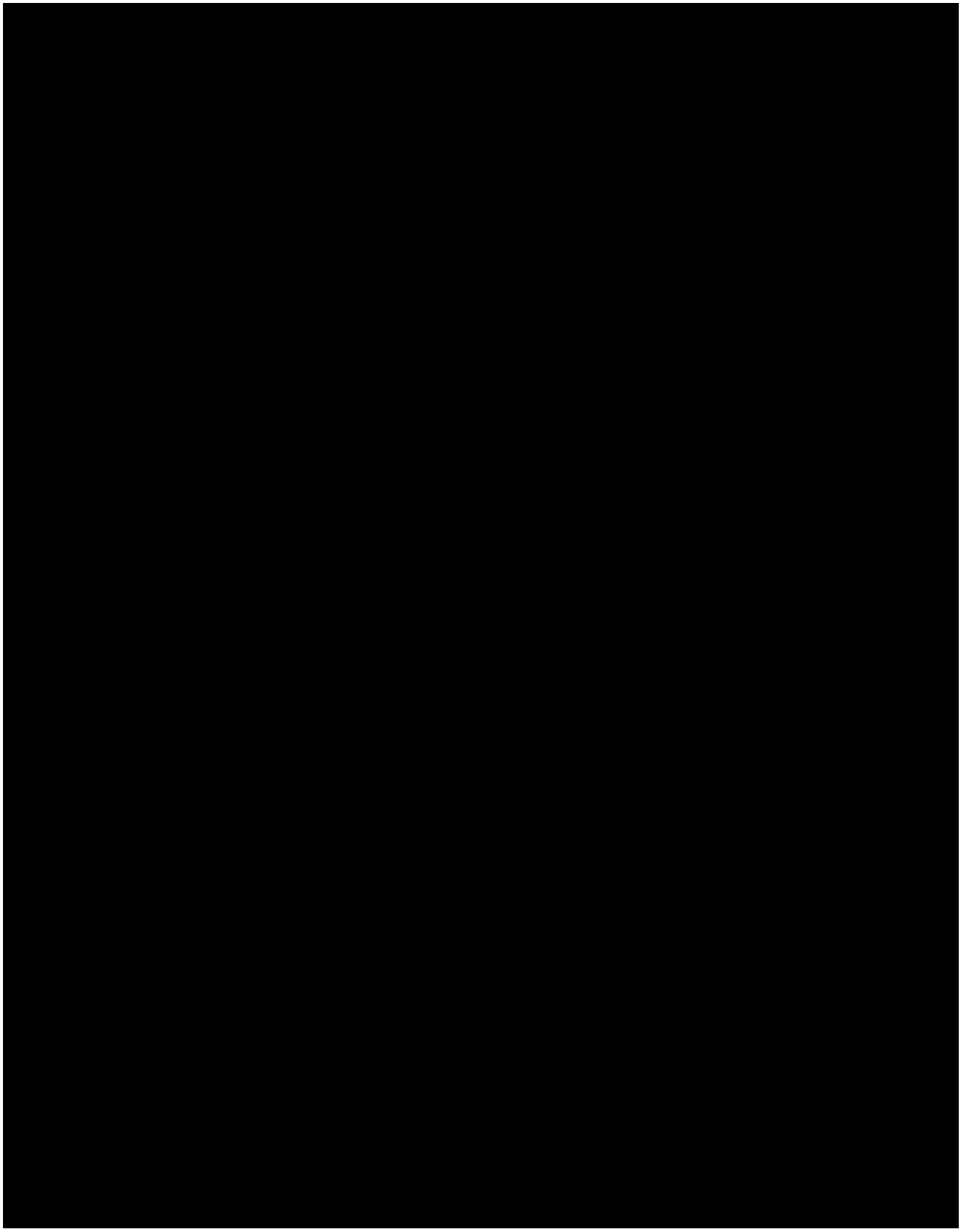
Psychotic Disorders and Mood Disorders with Psychotic Features (Module R).

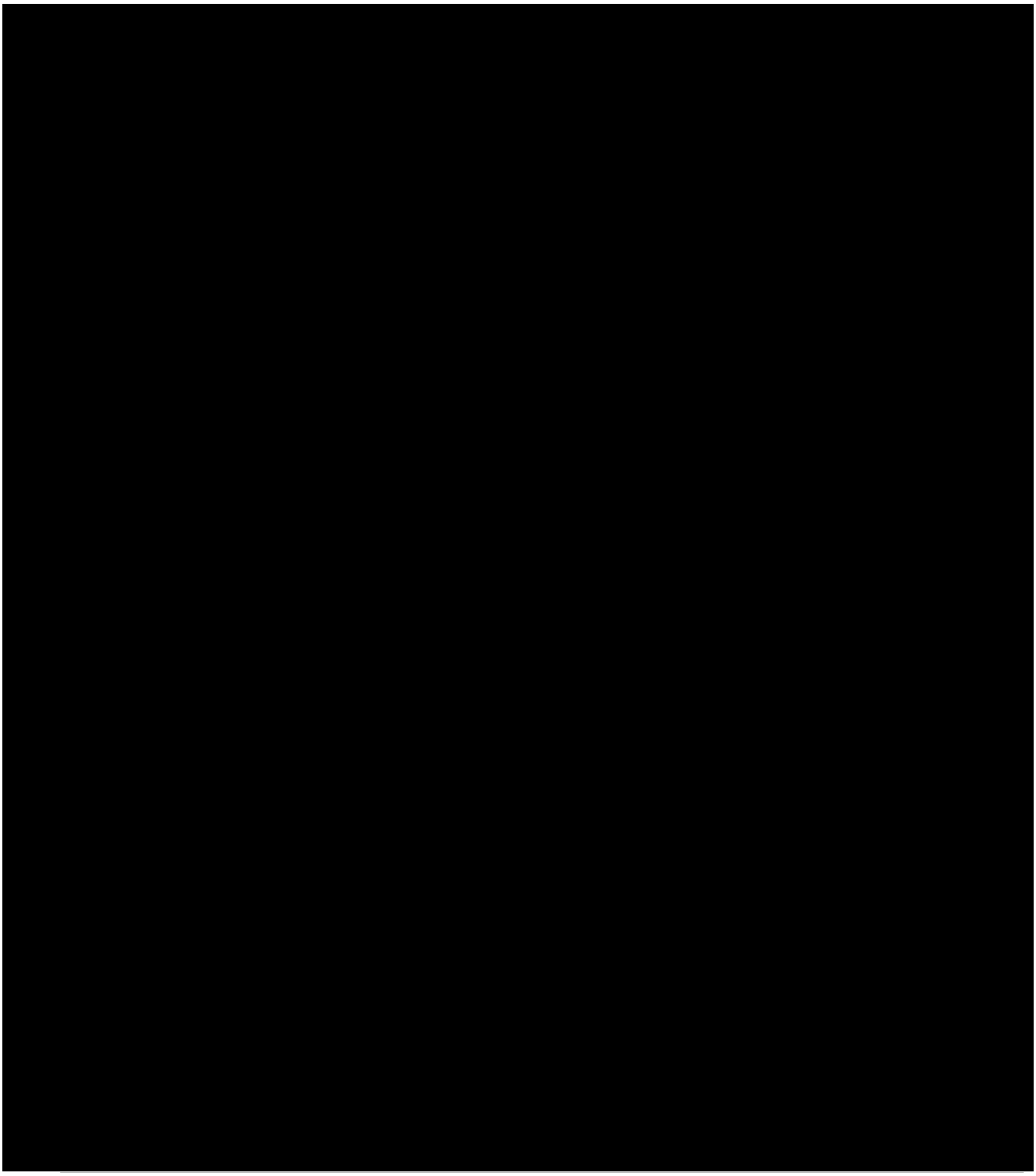


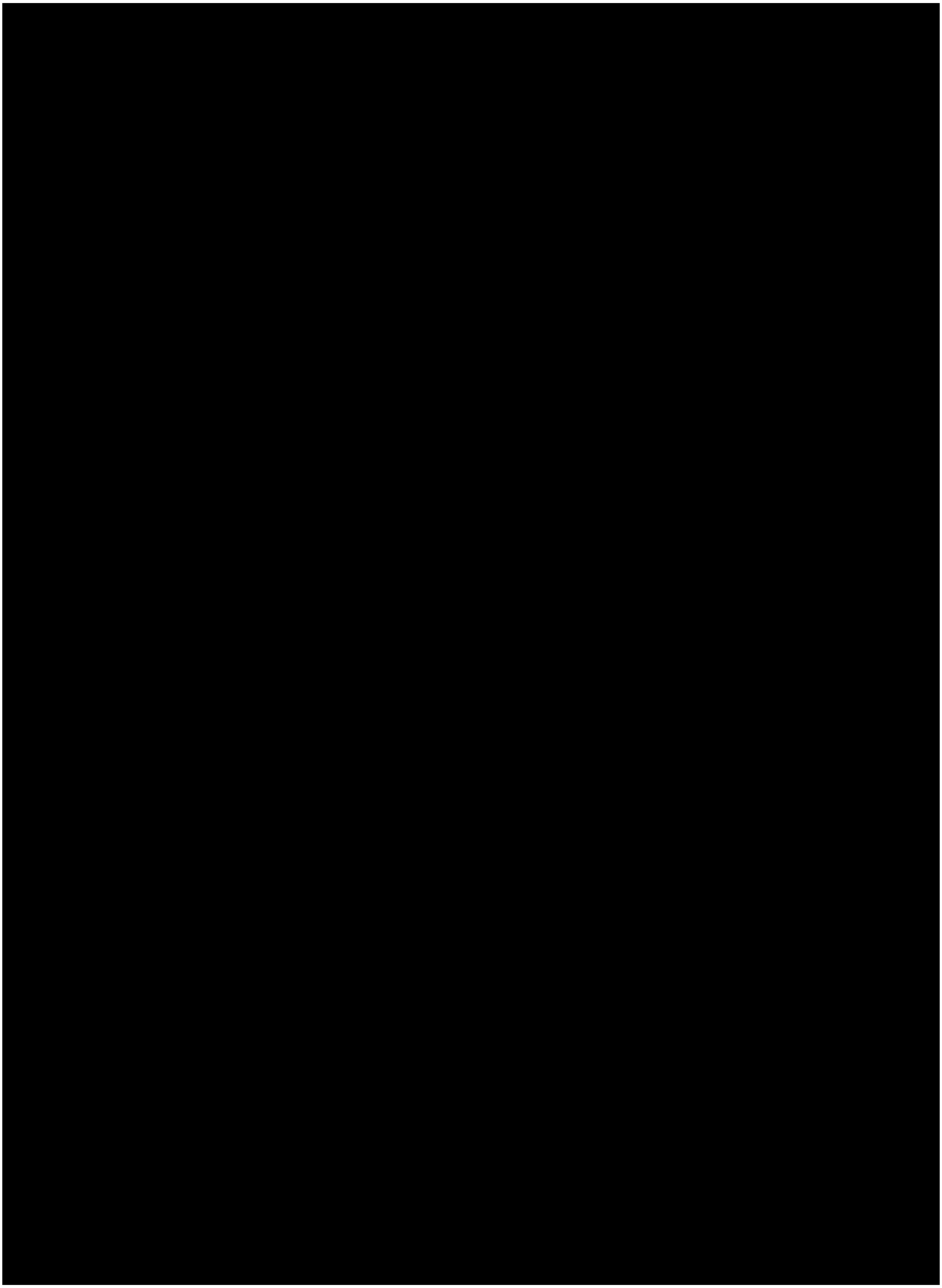


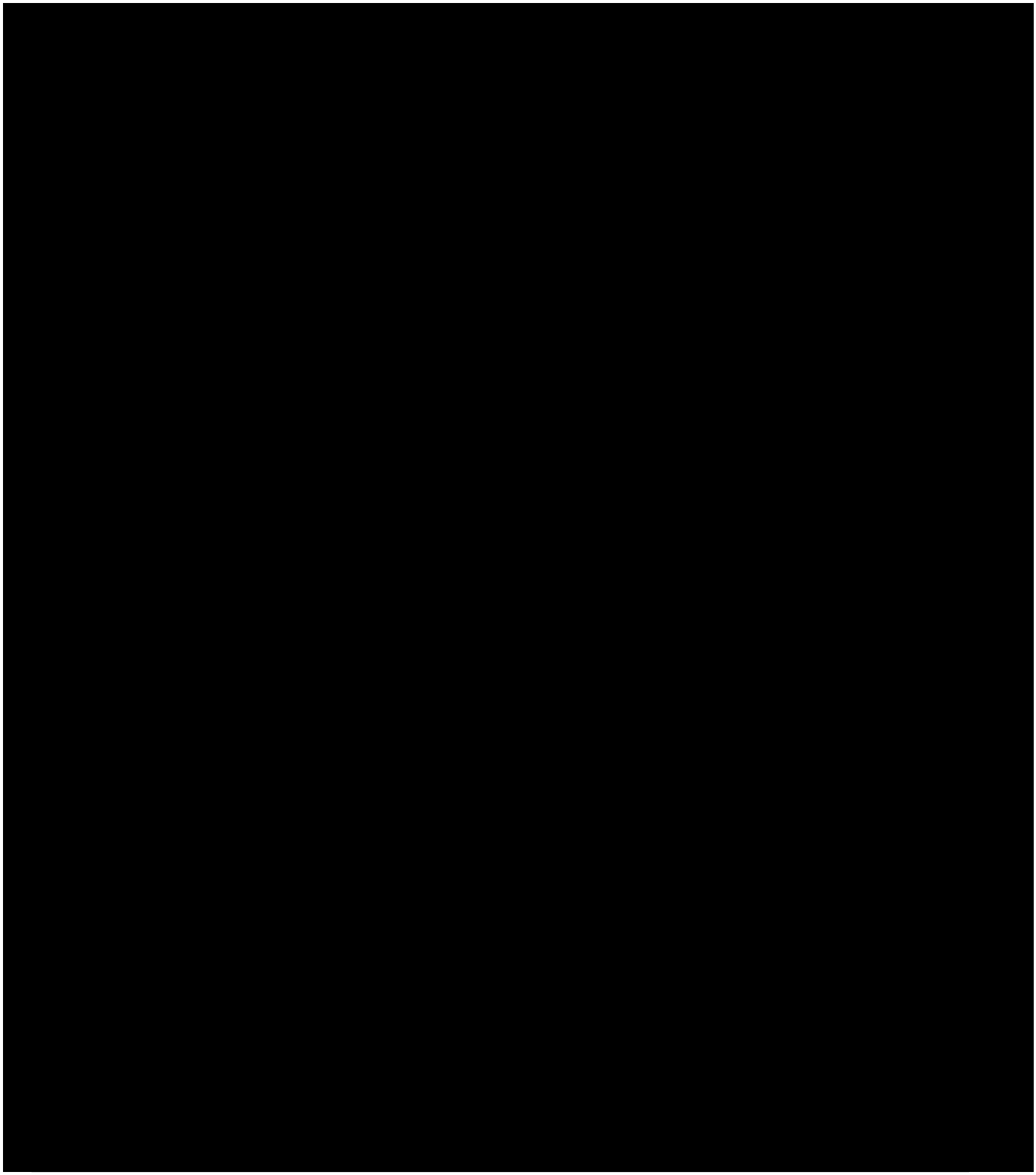


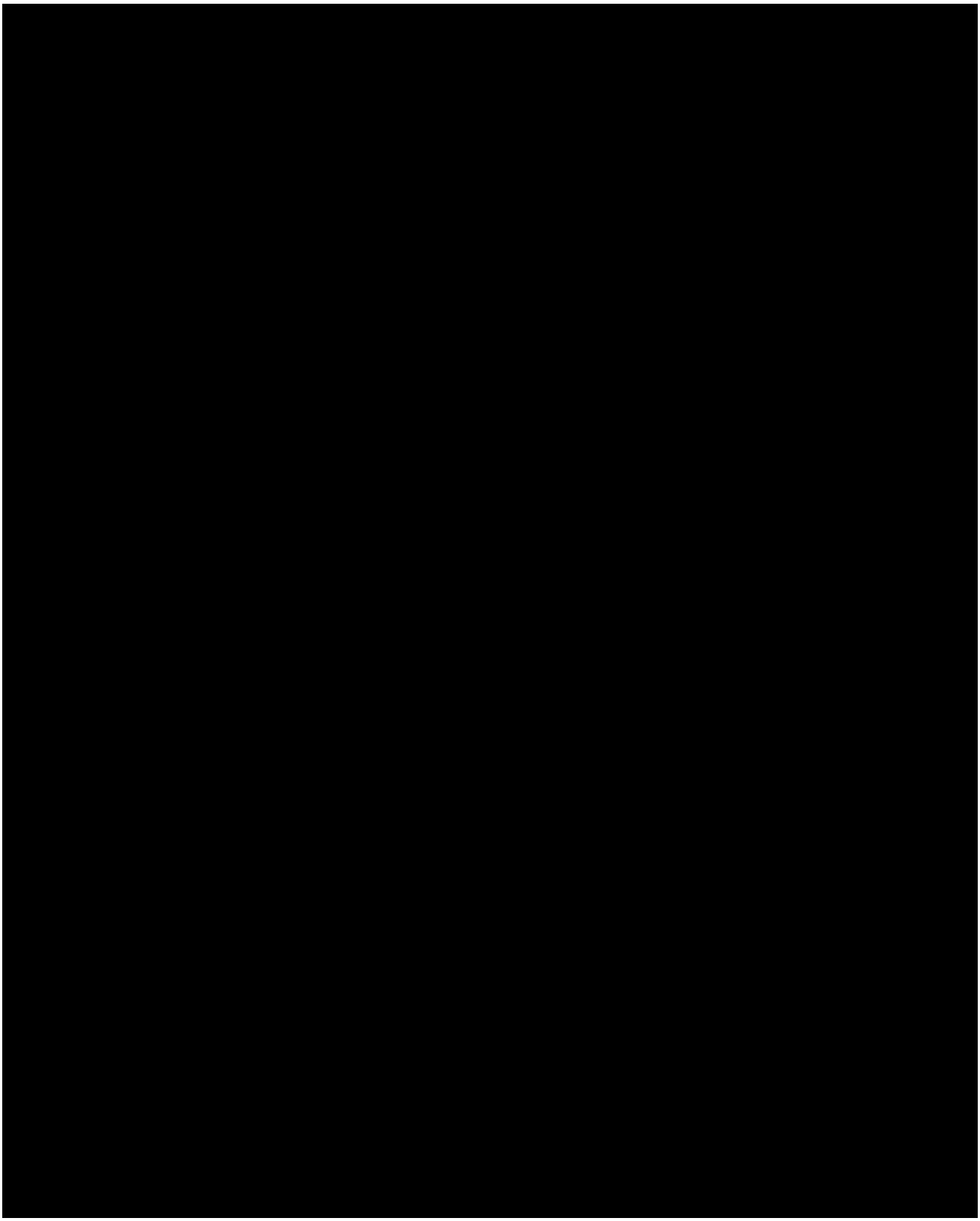


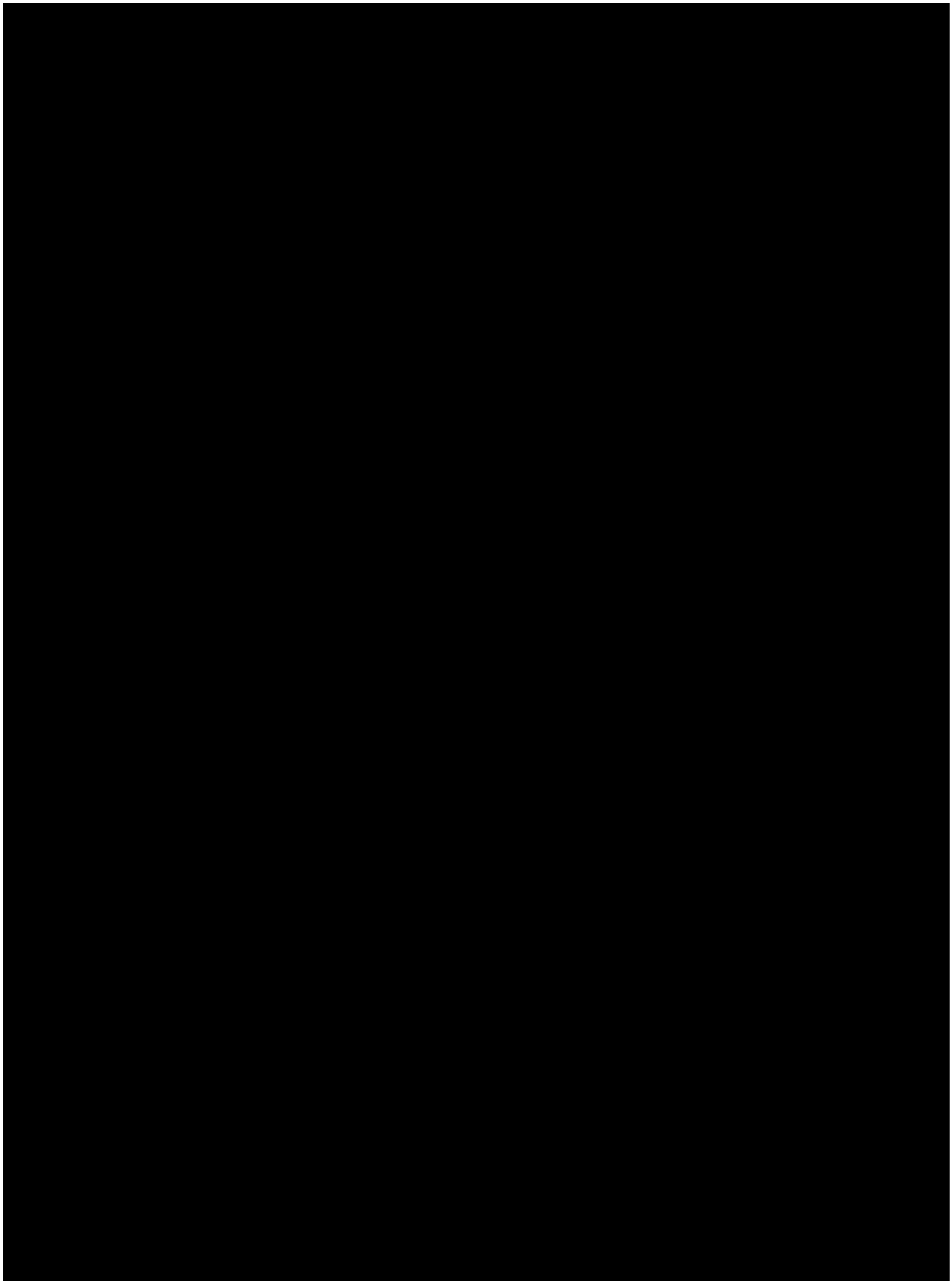


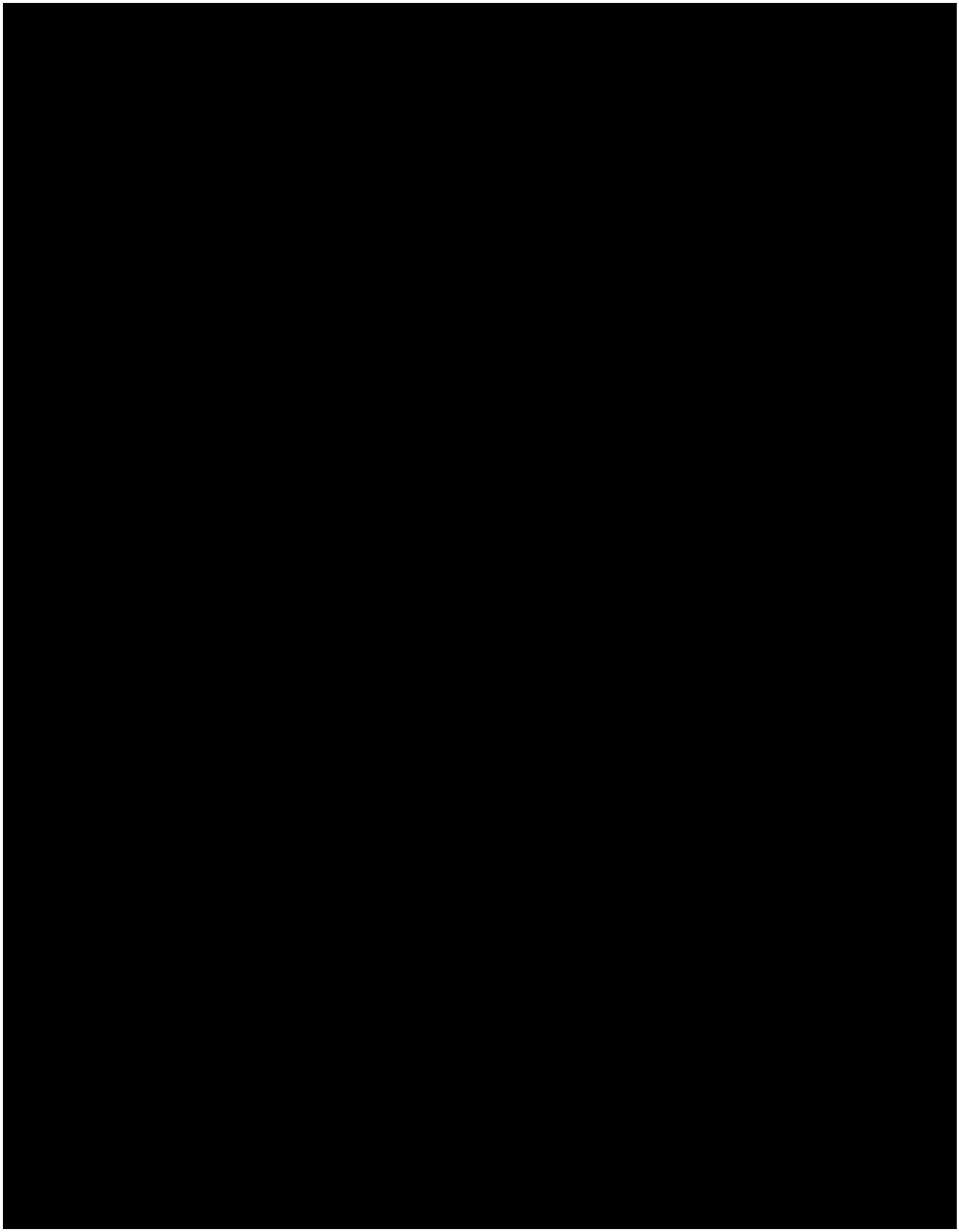


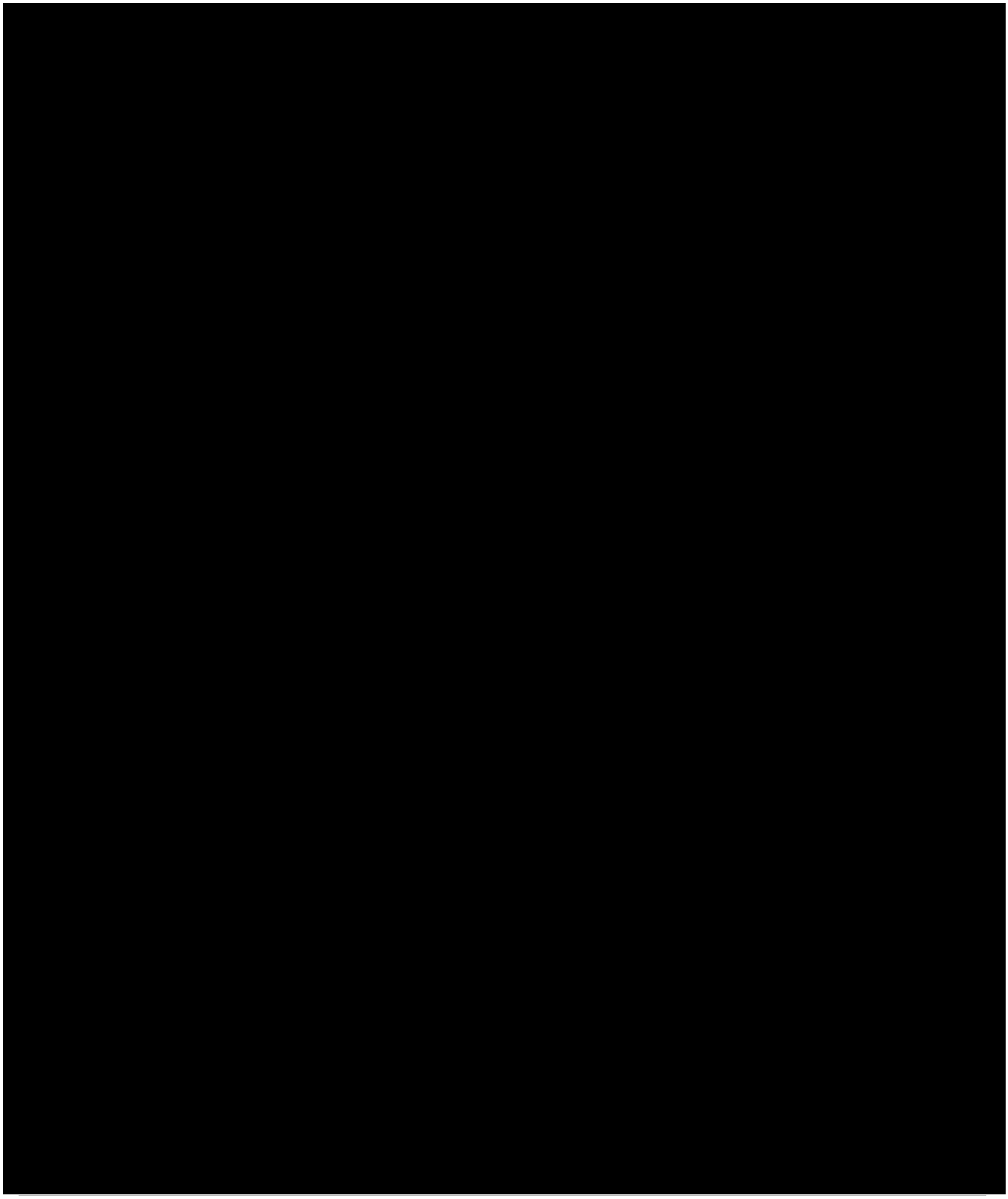


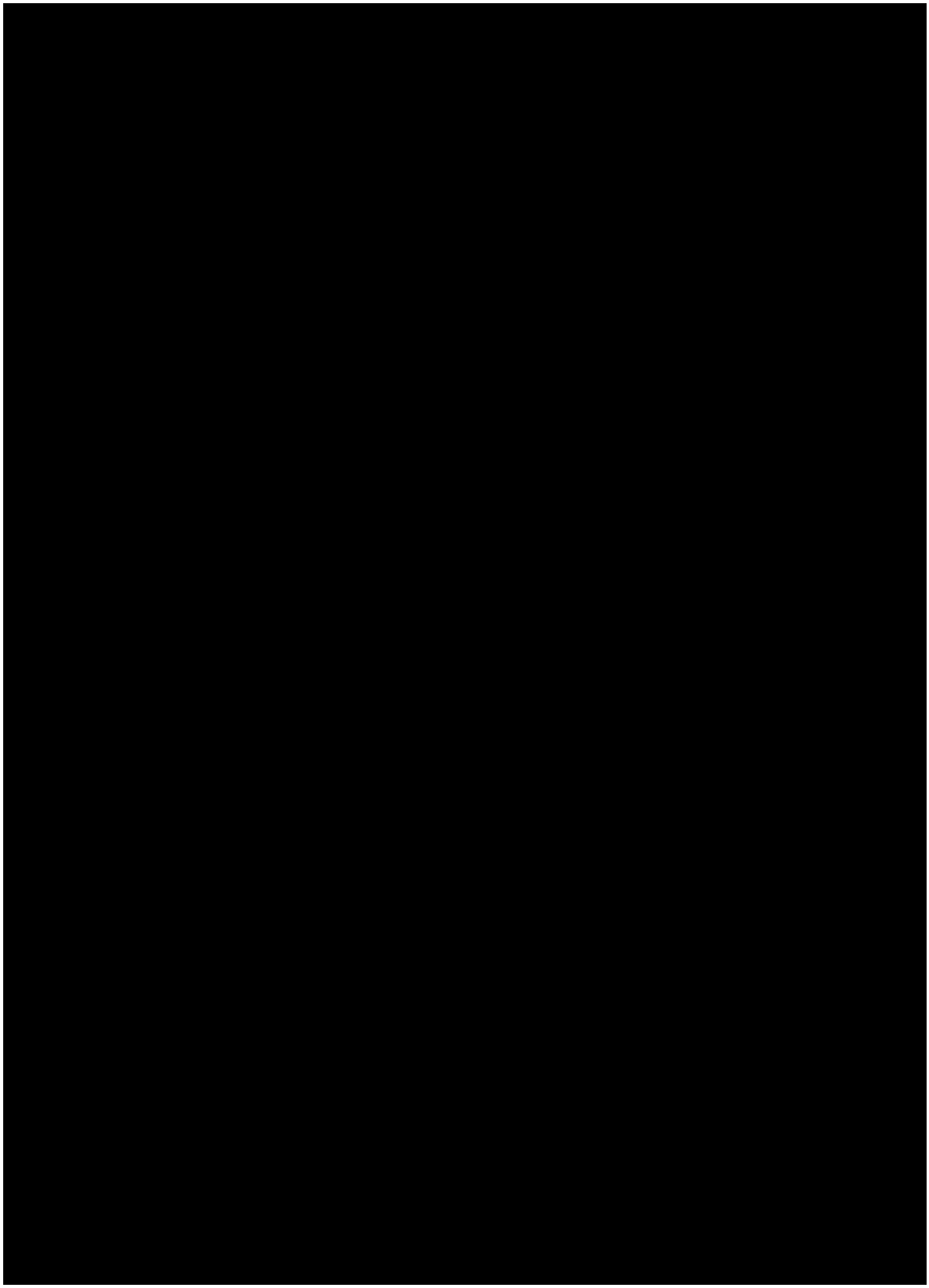












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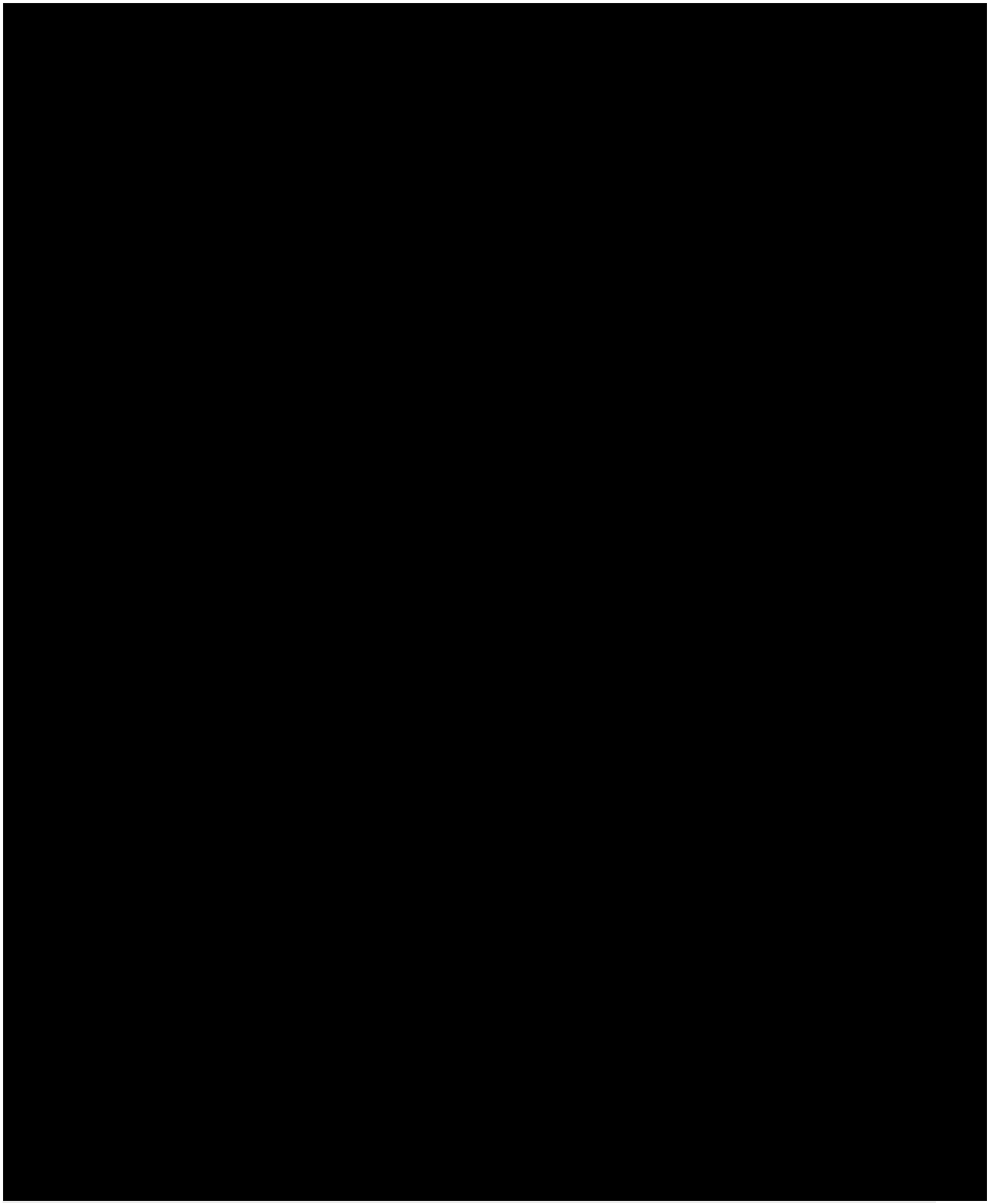

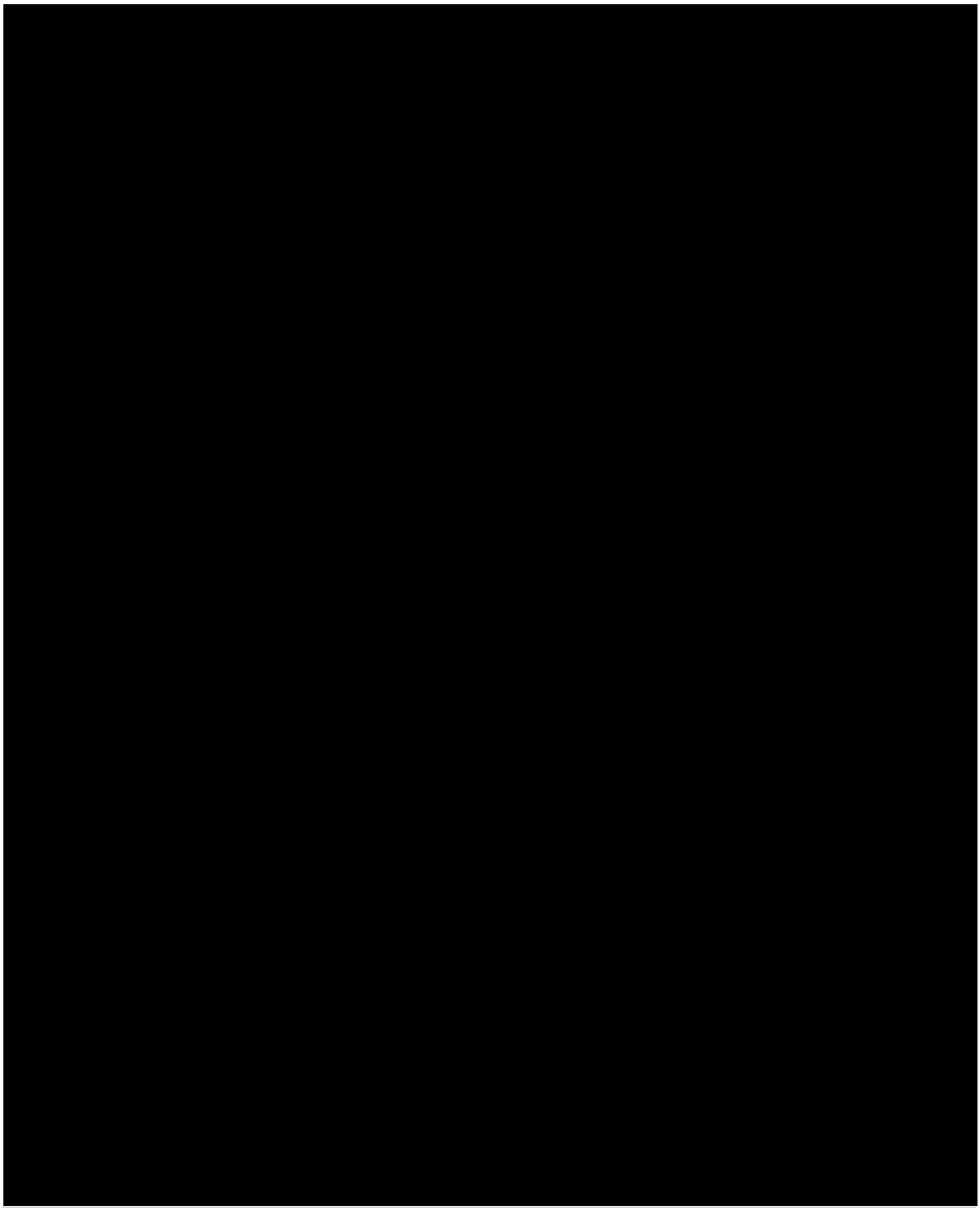

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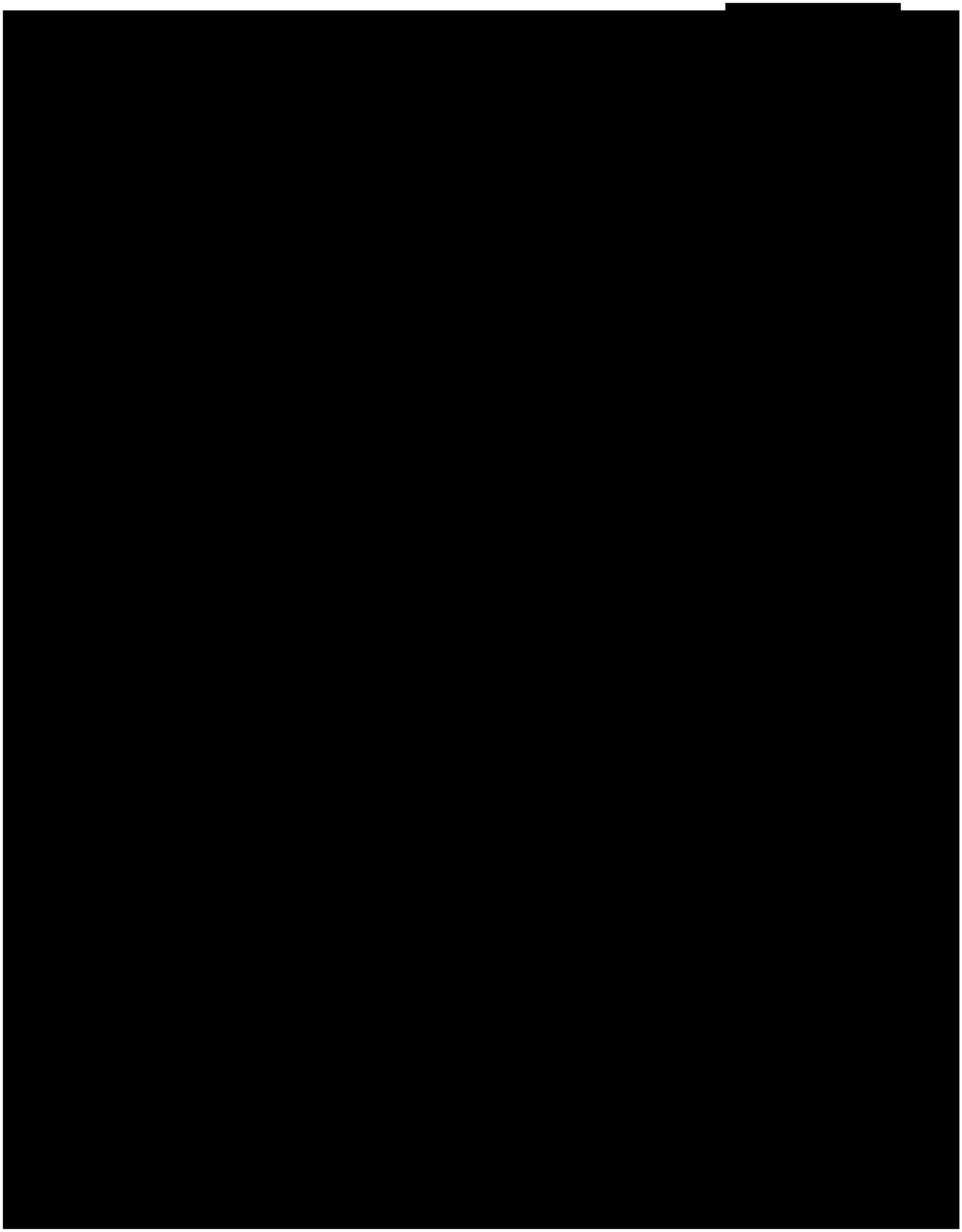

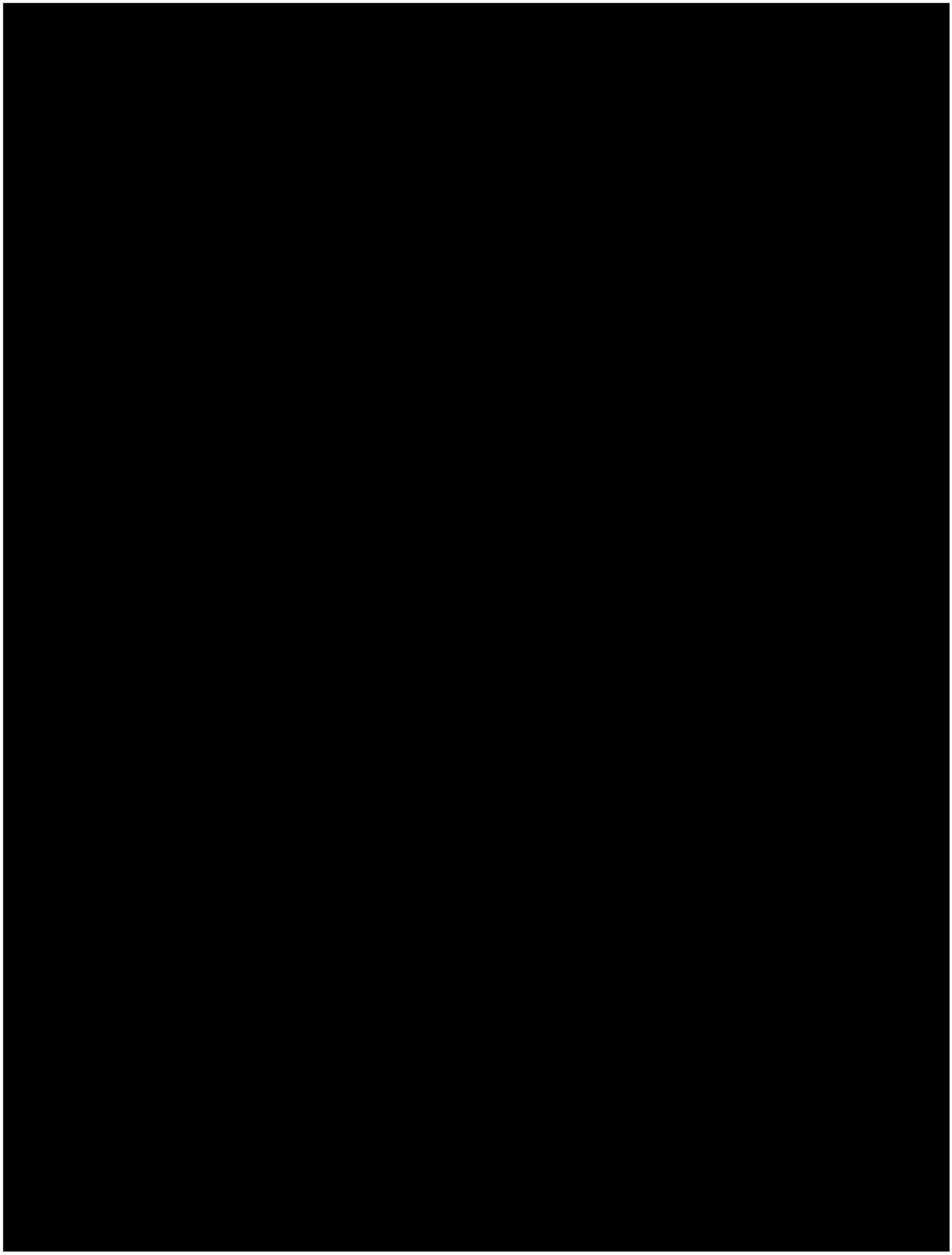

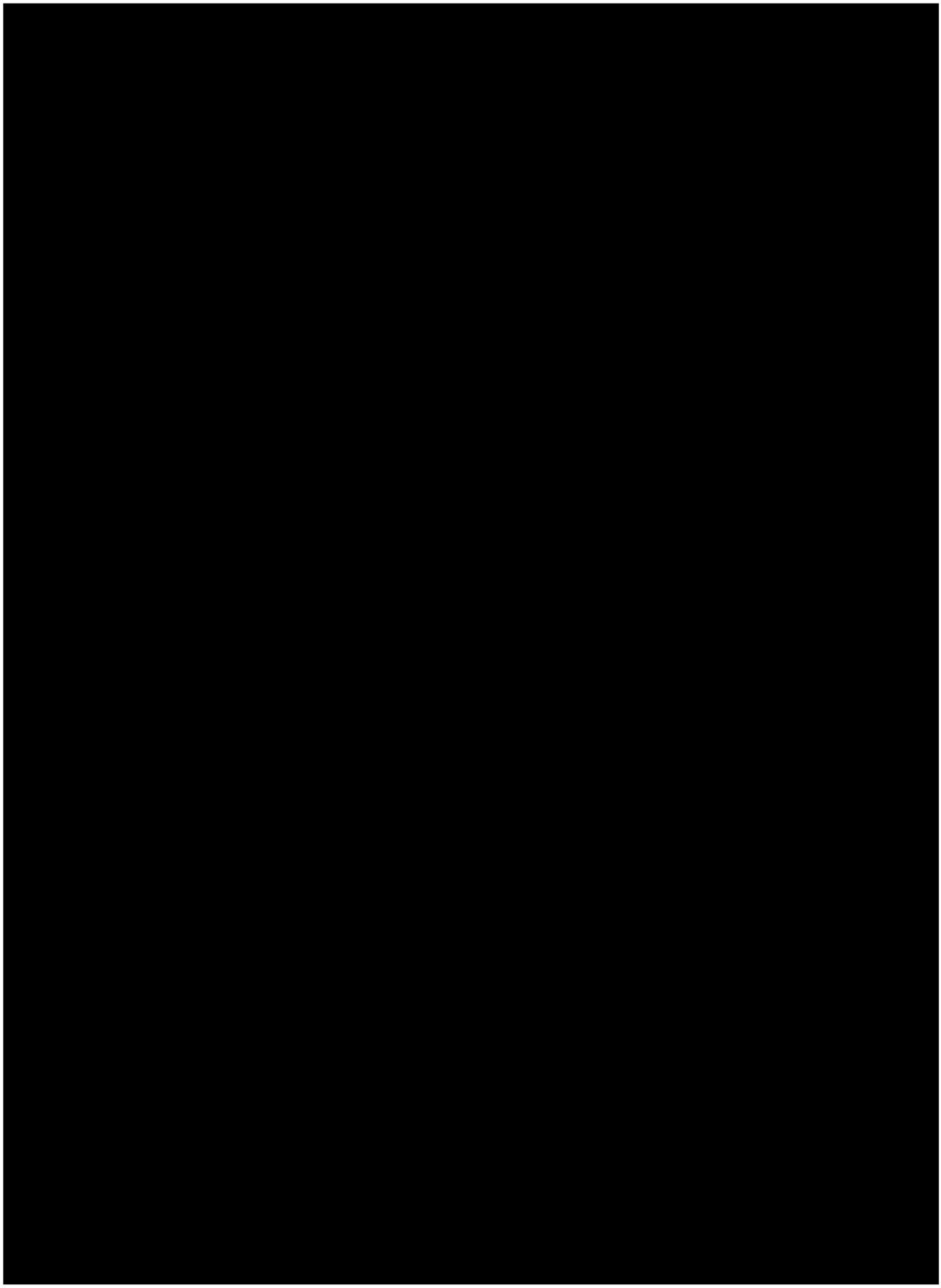

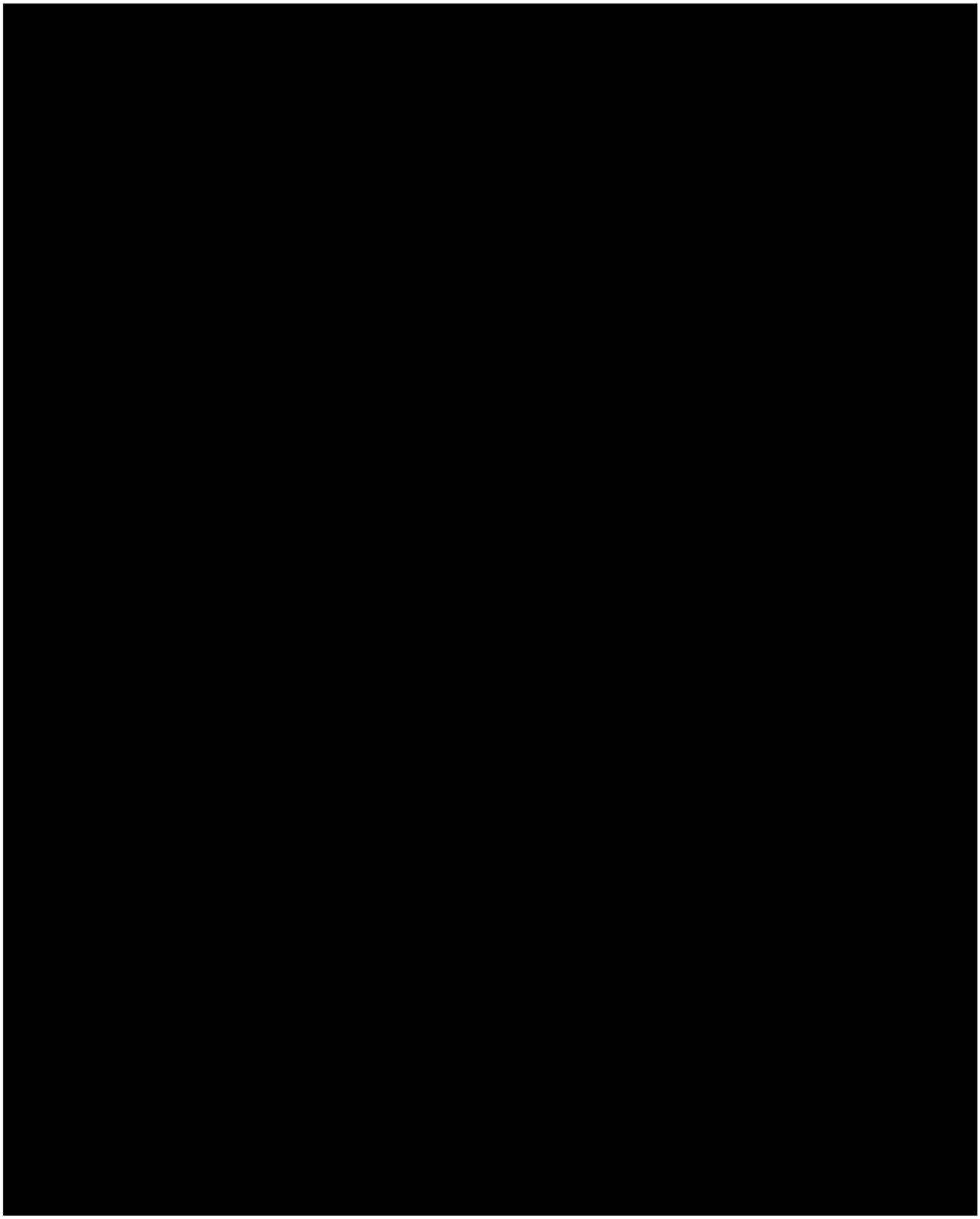

APPENDIX K. [redacted]

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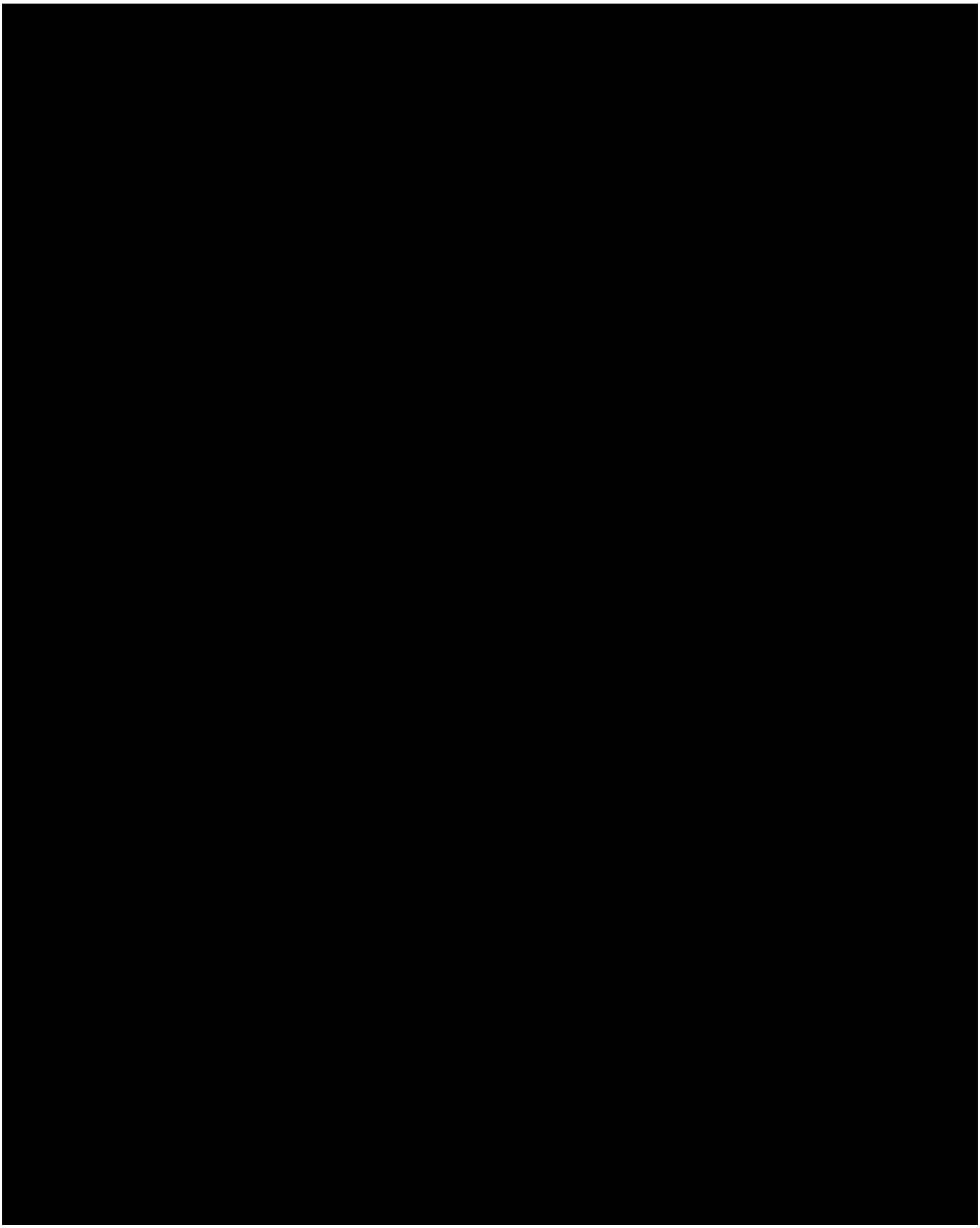

APPENDIX L. [redacted]

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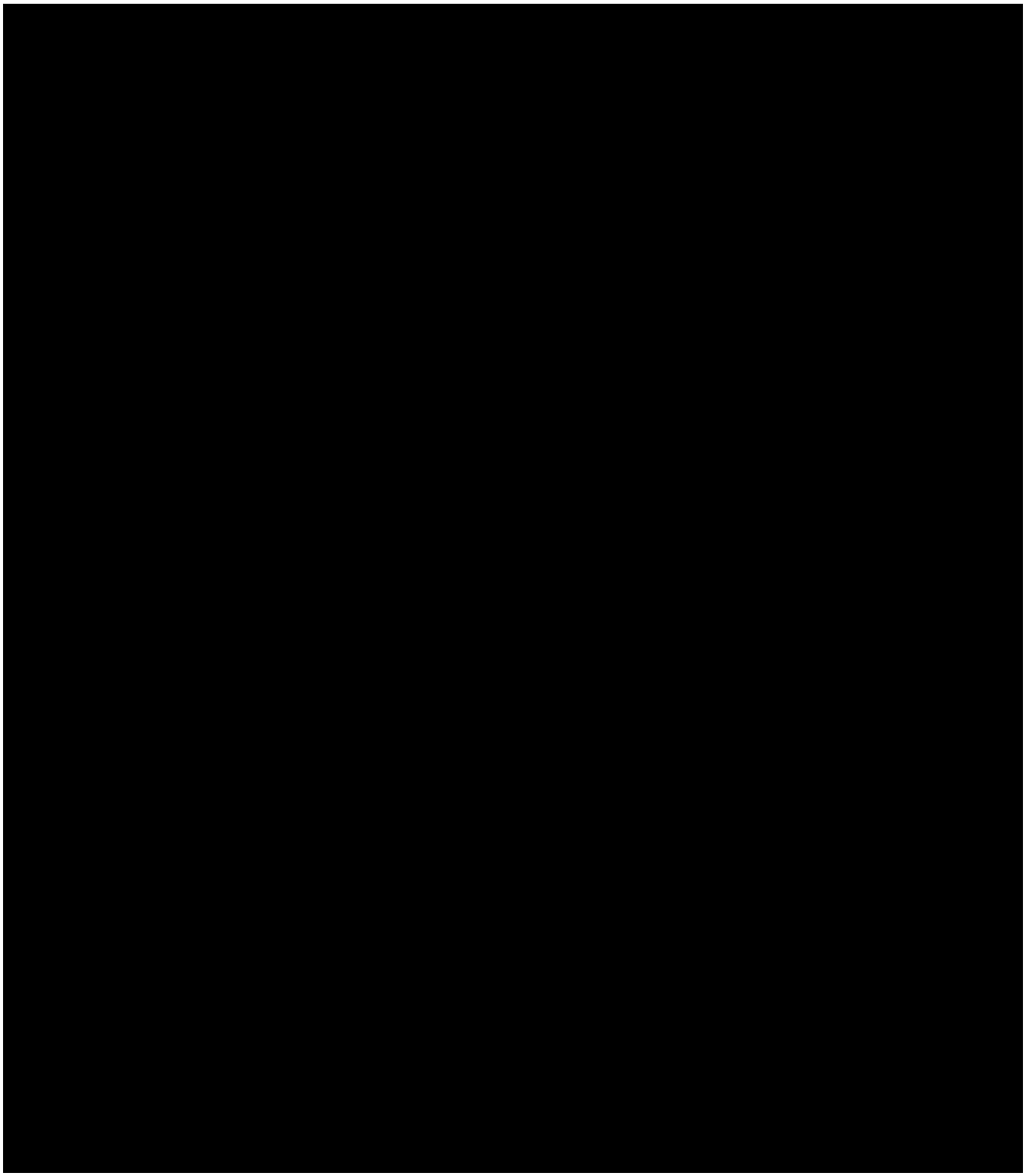

Procedure:

Name **Date**

[redacted]

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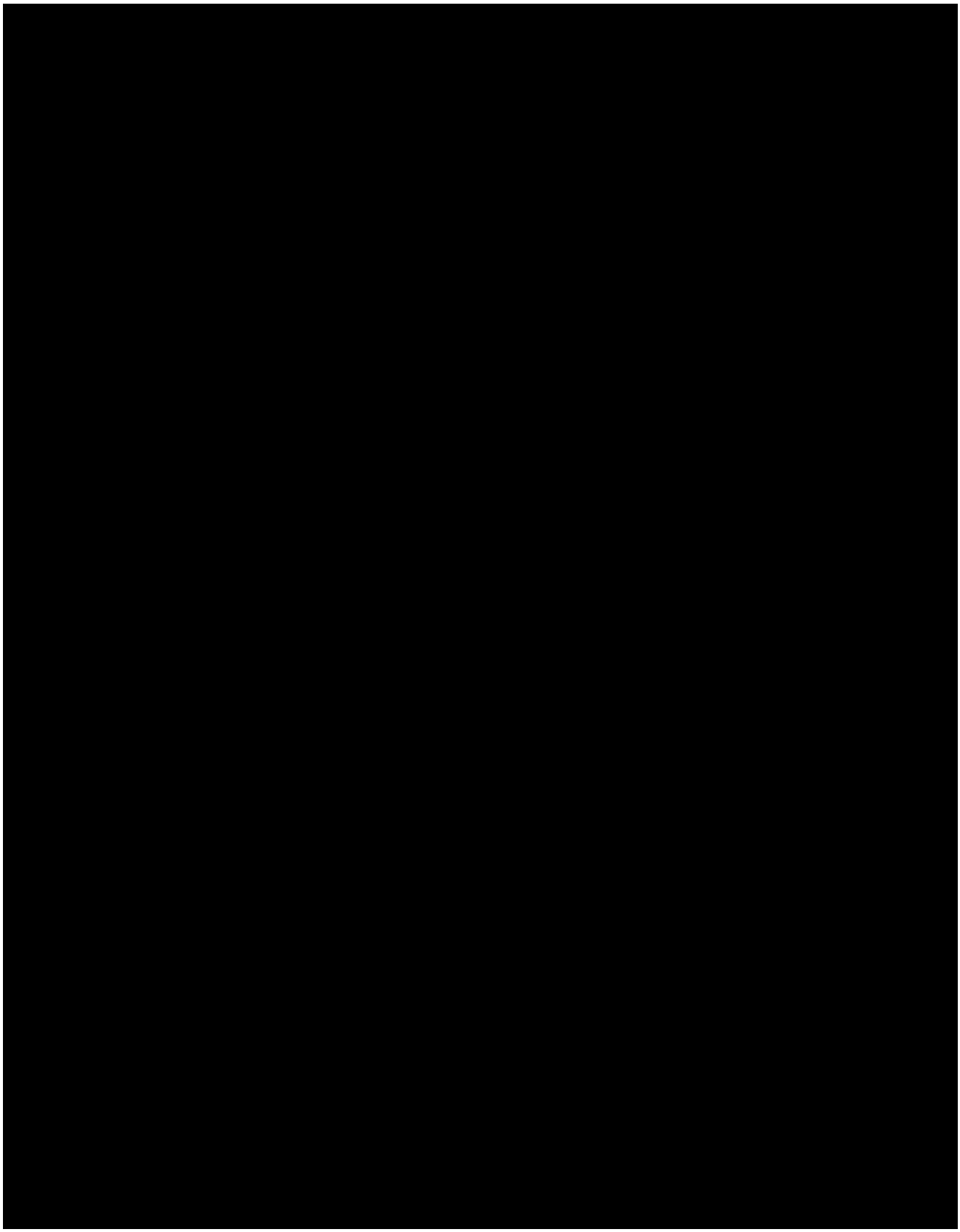

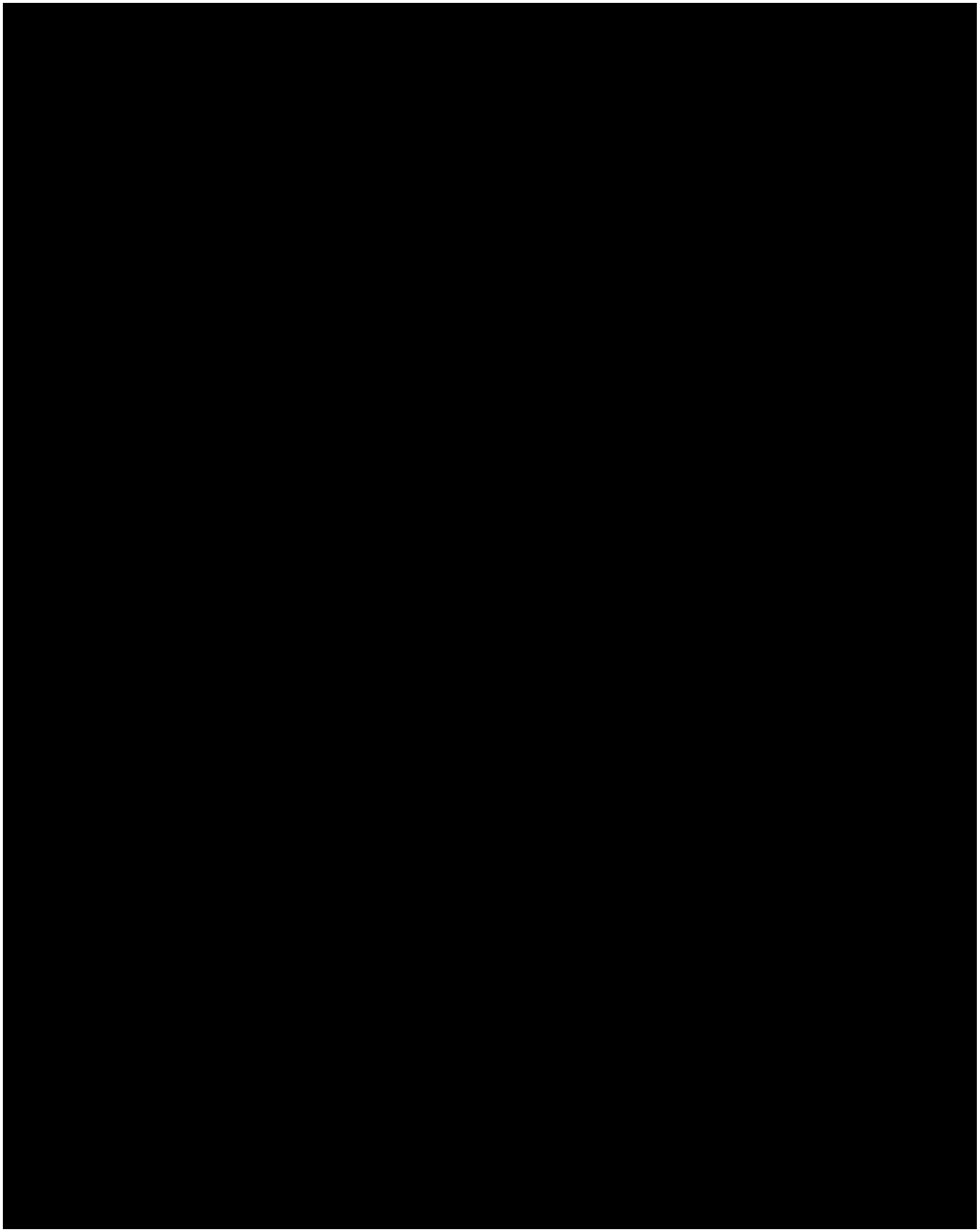

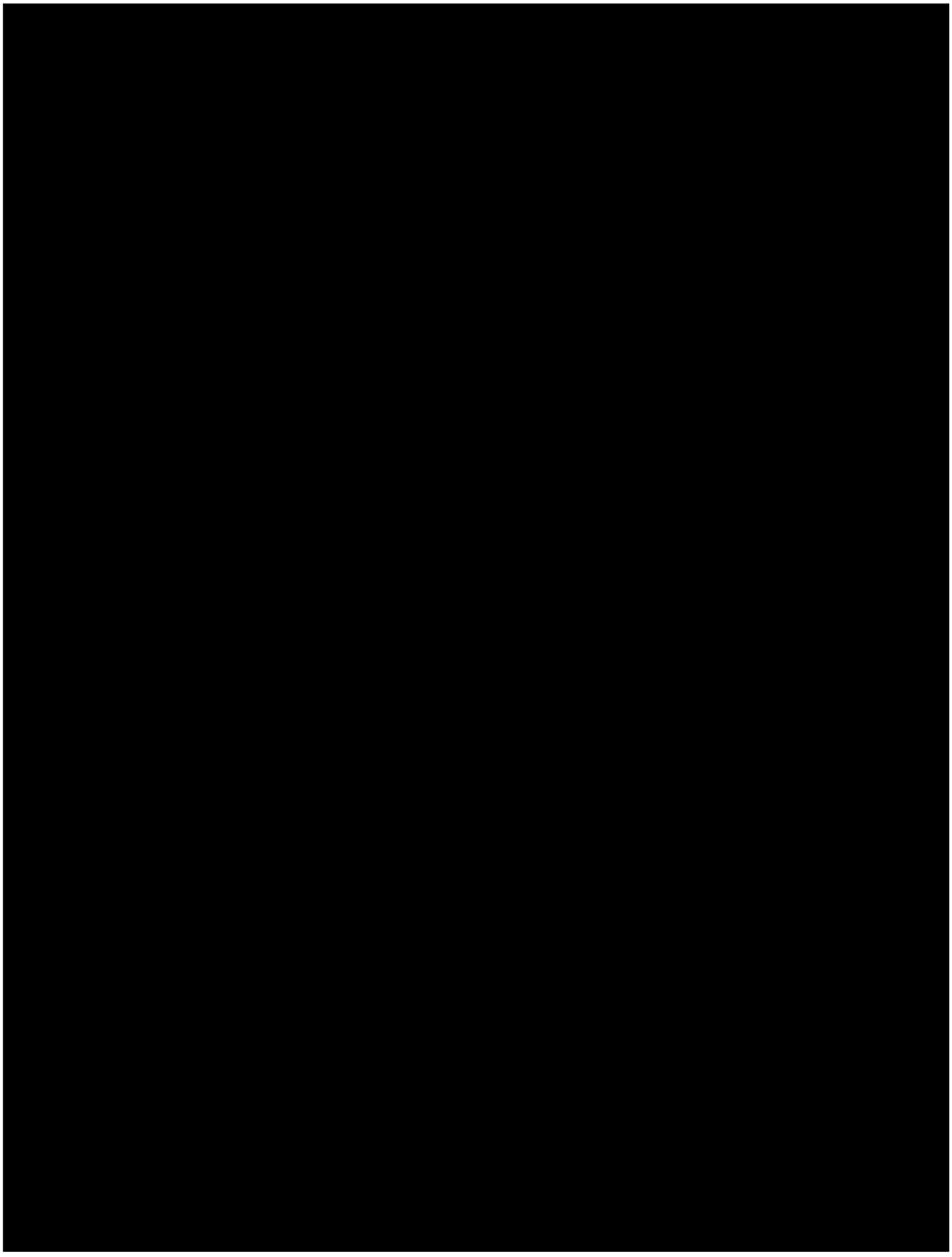

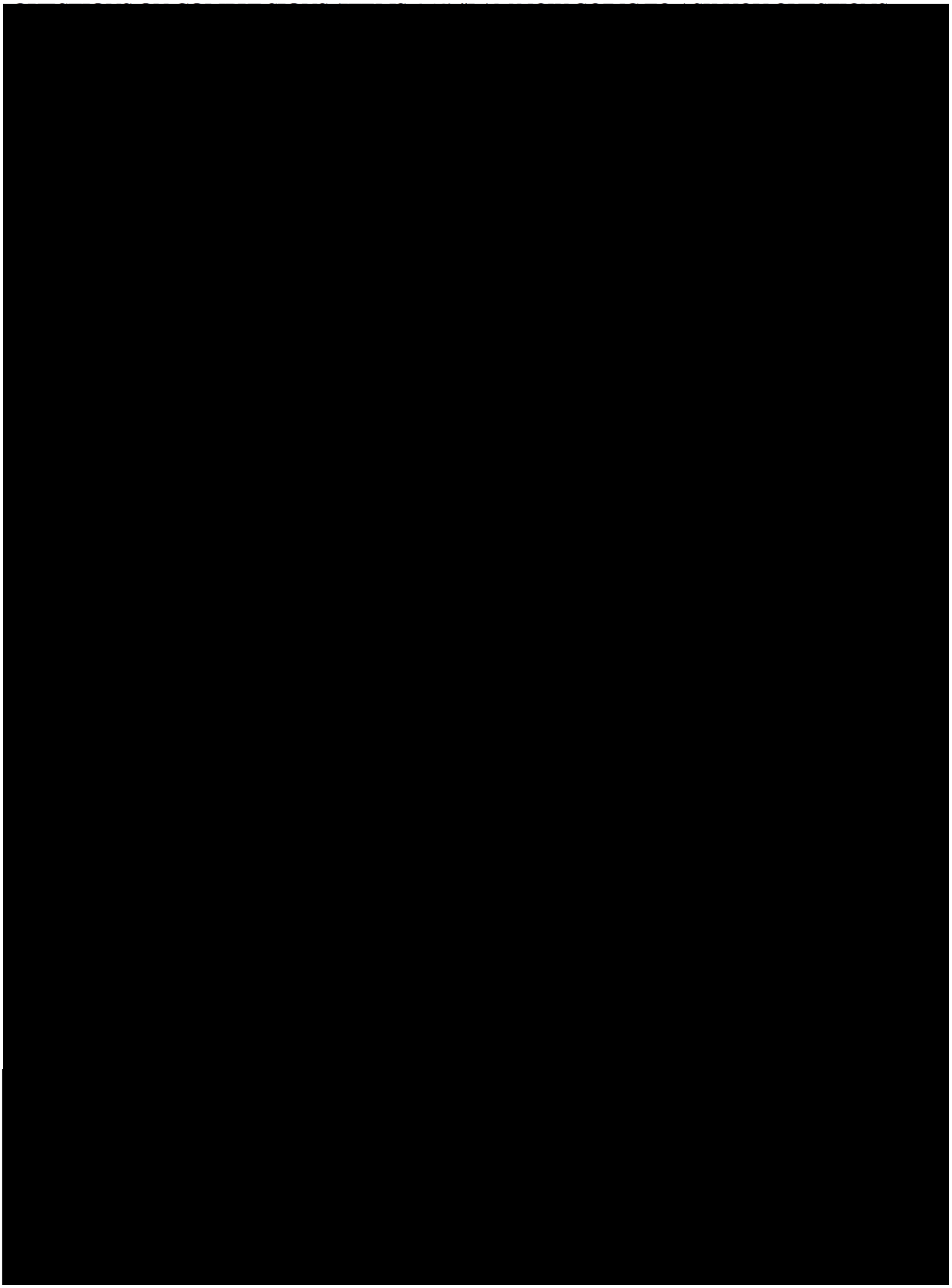

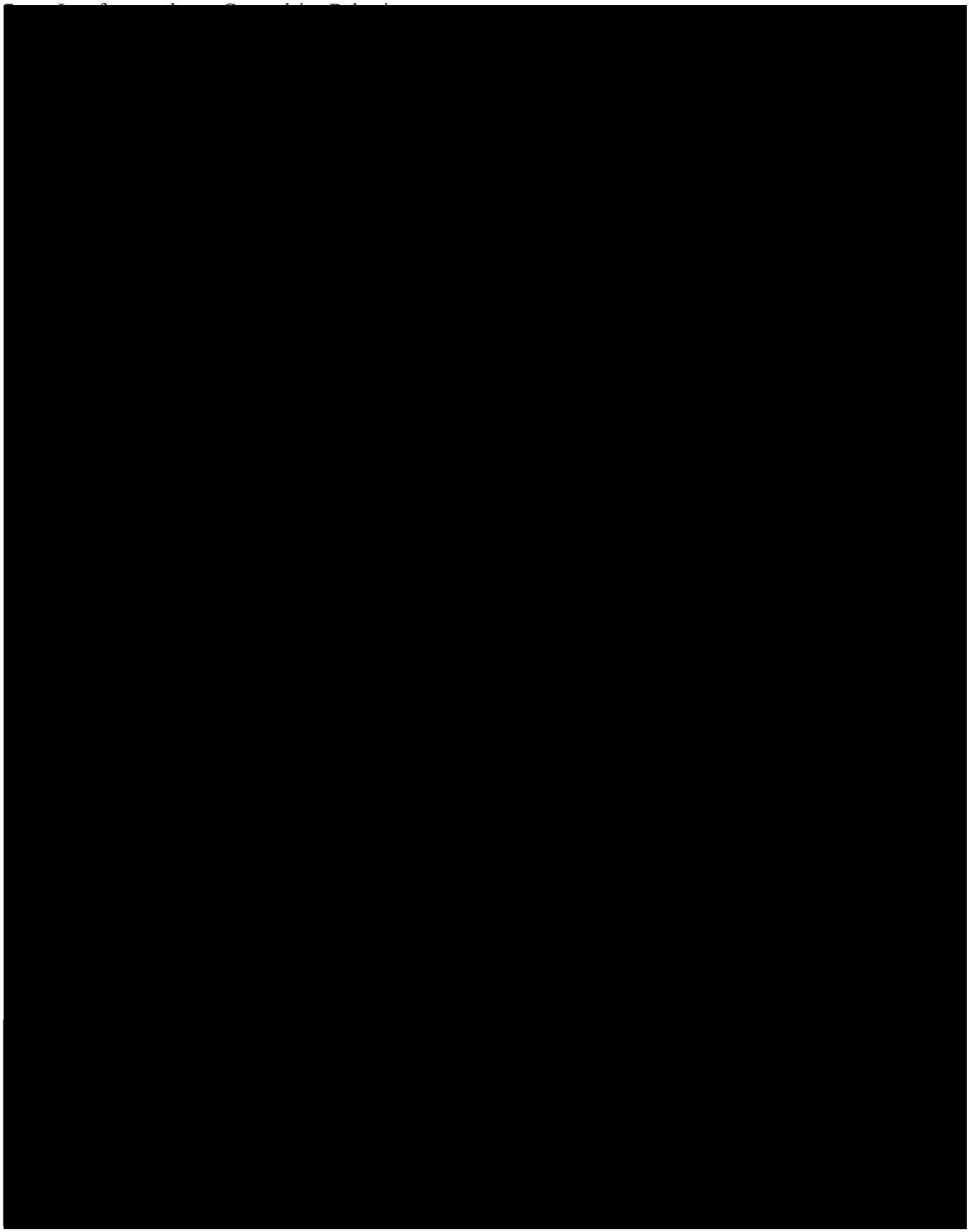

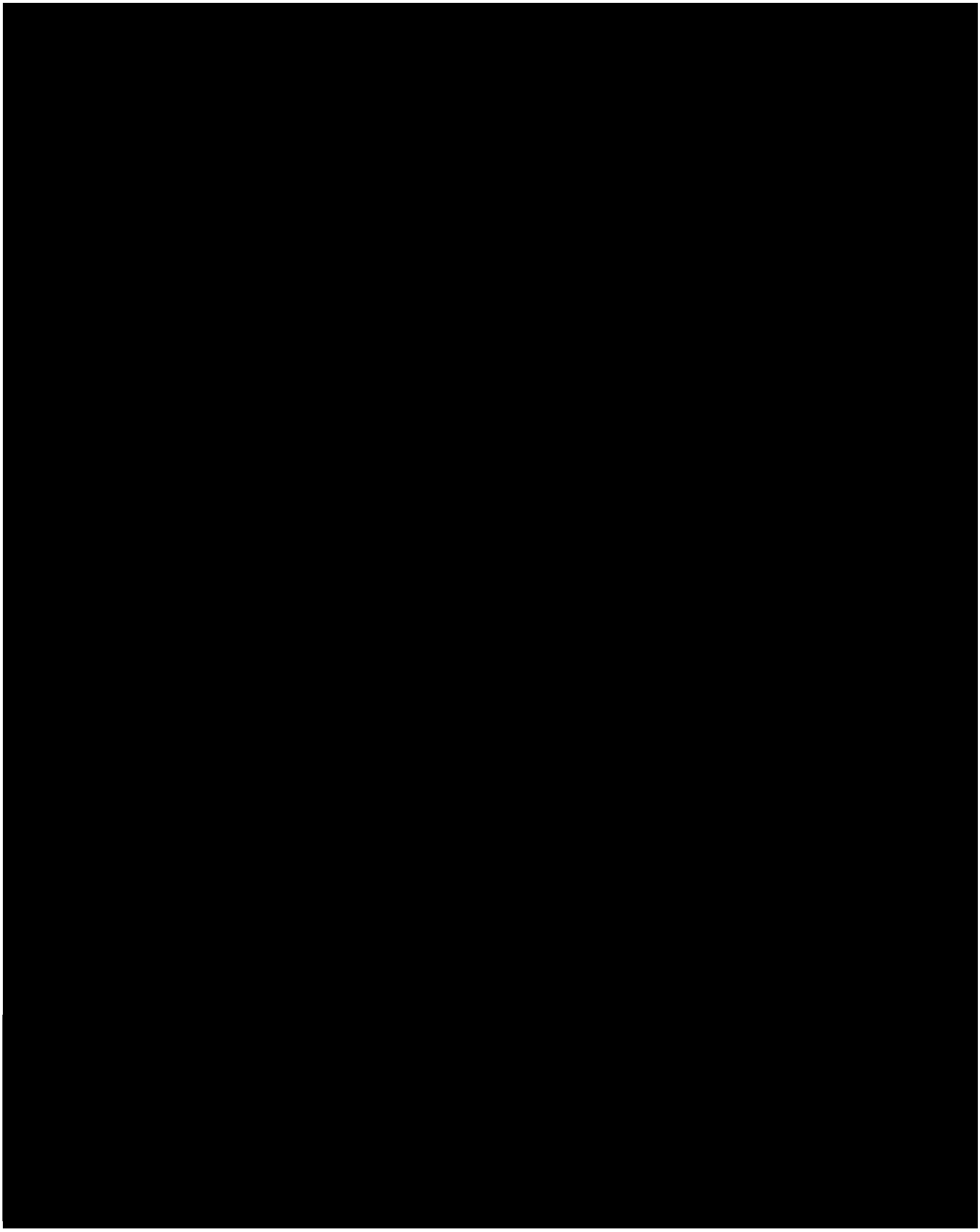

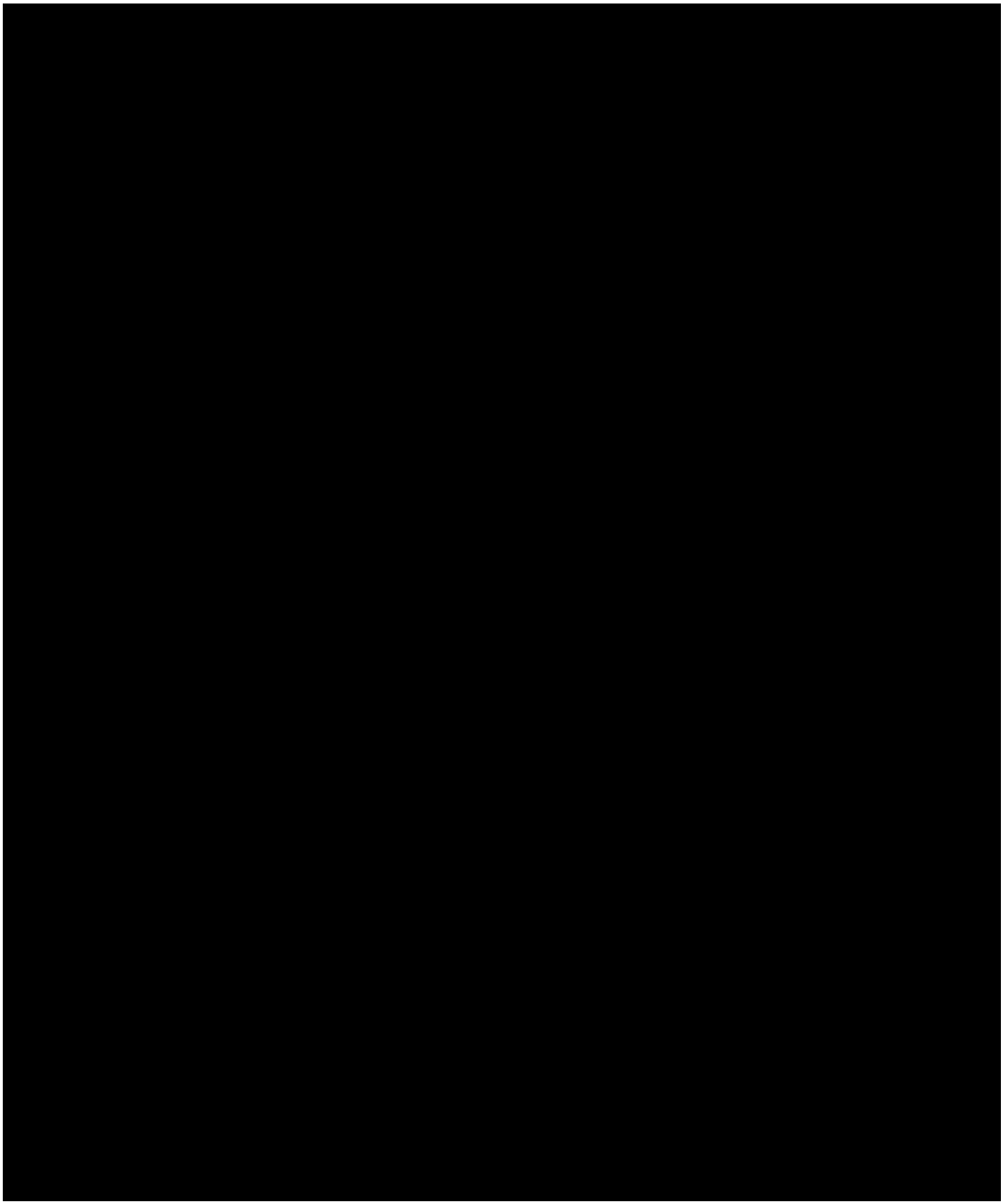

APPENDIX M. [redacted]

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October 1992 version

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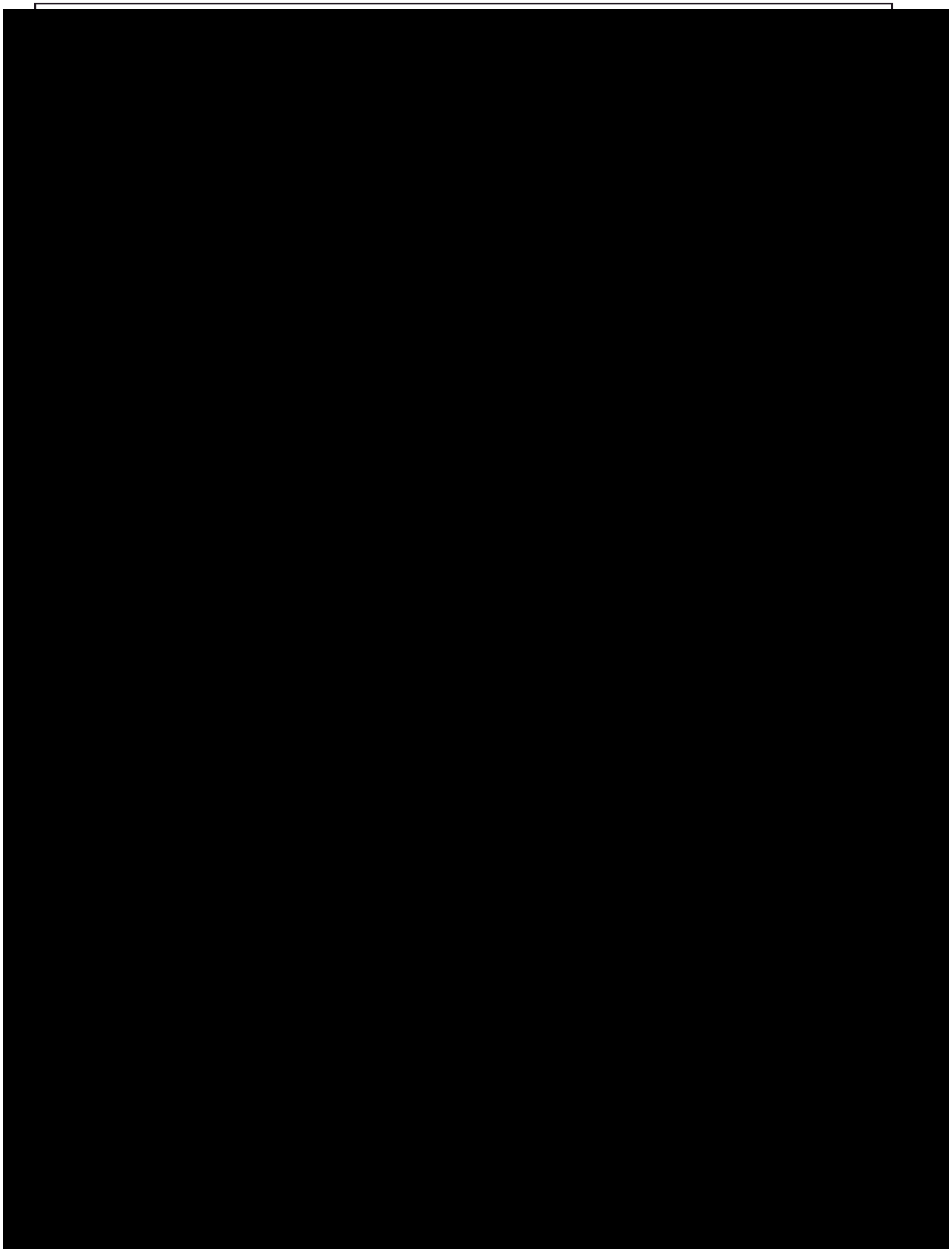

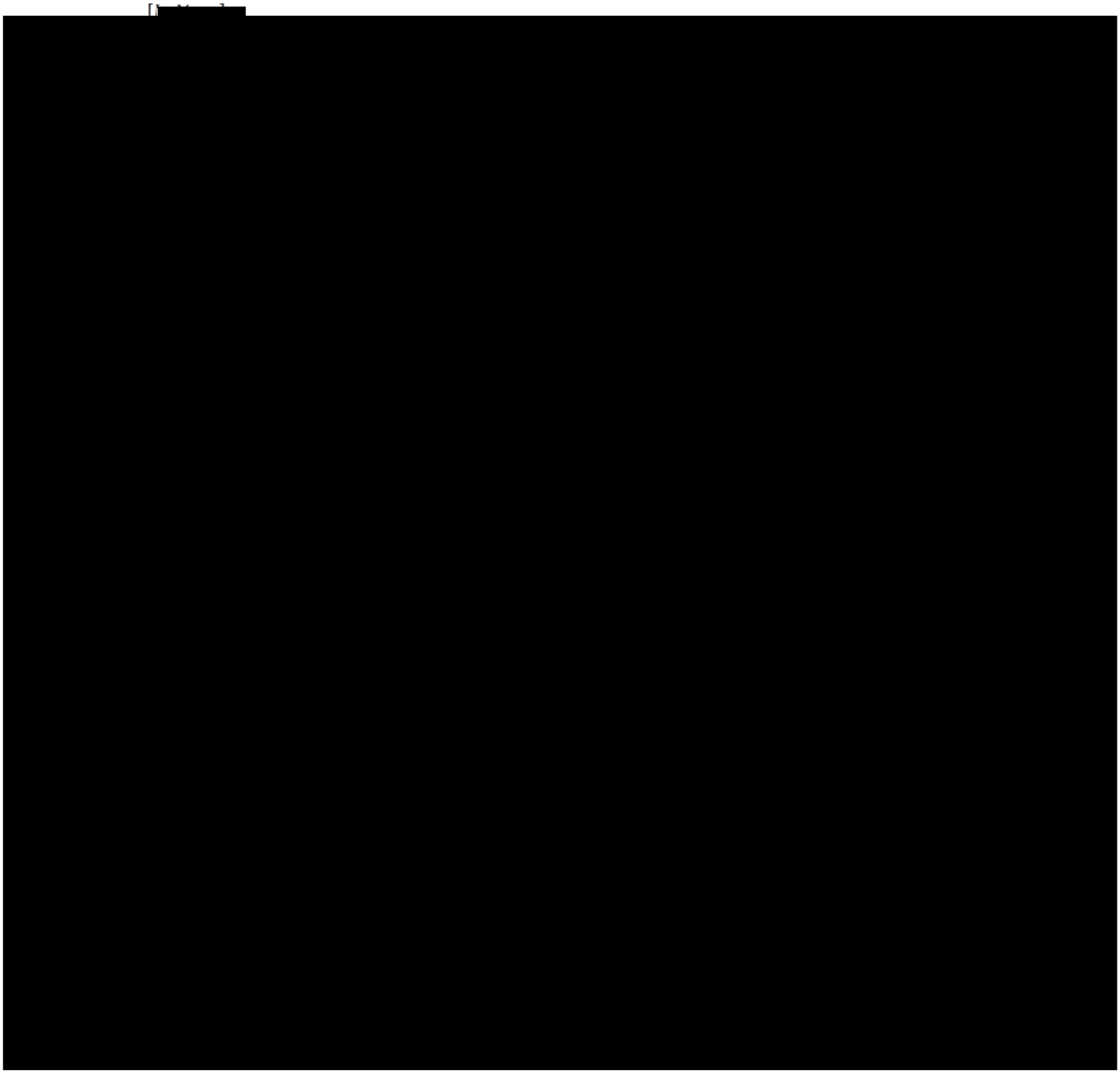

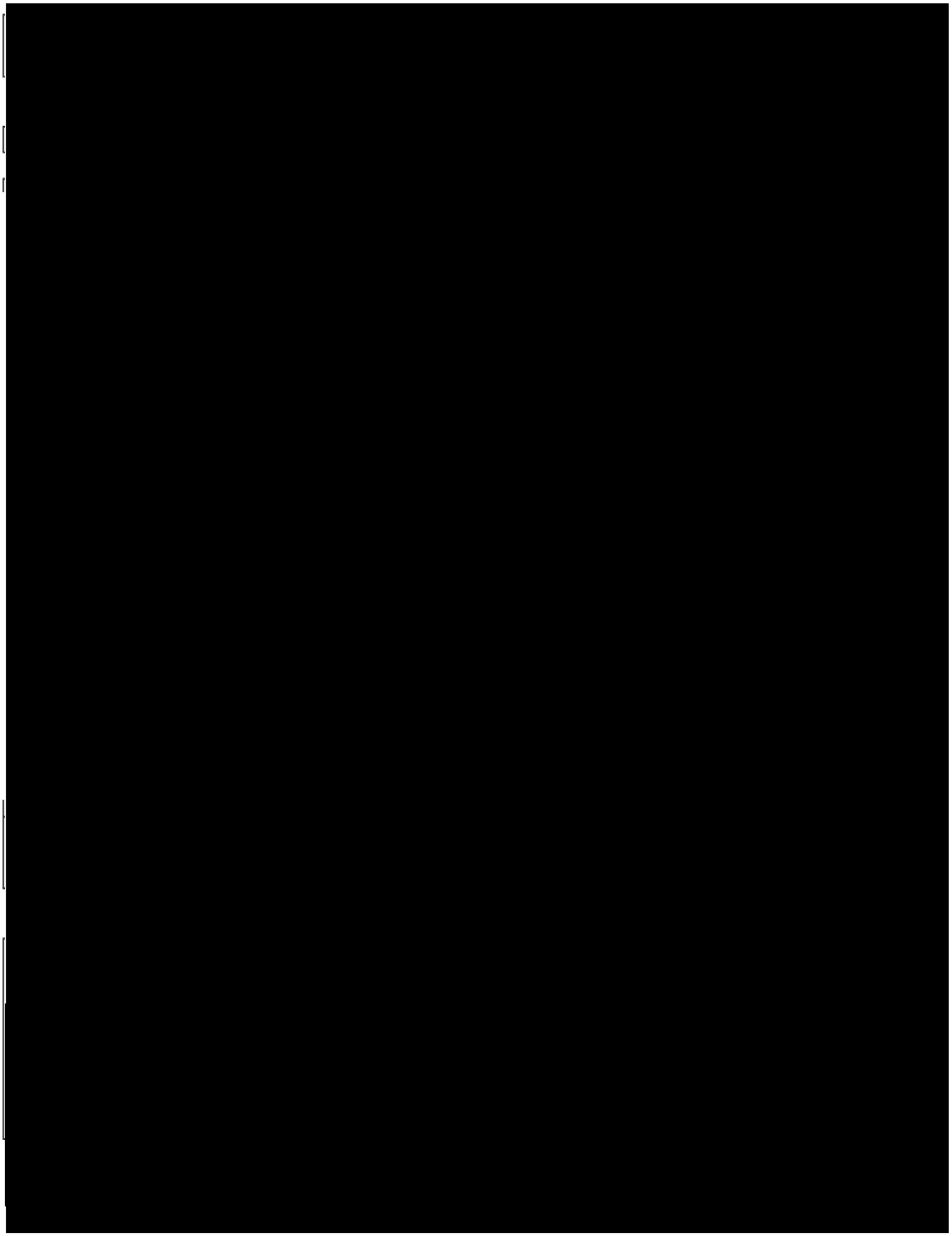

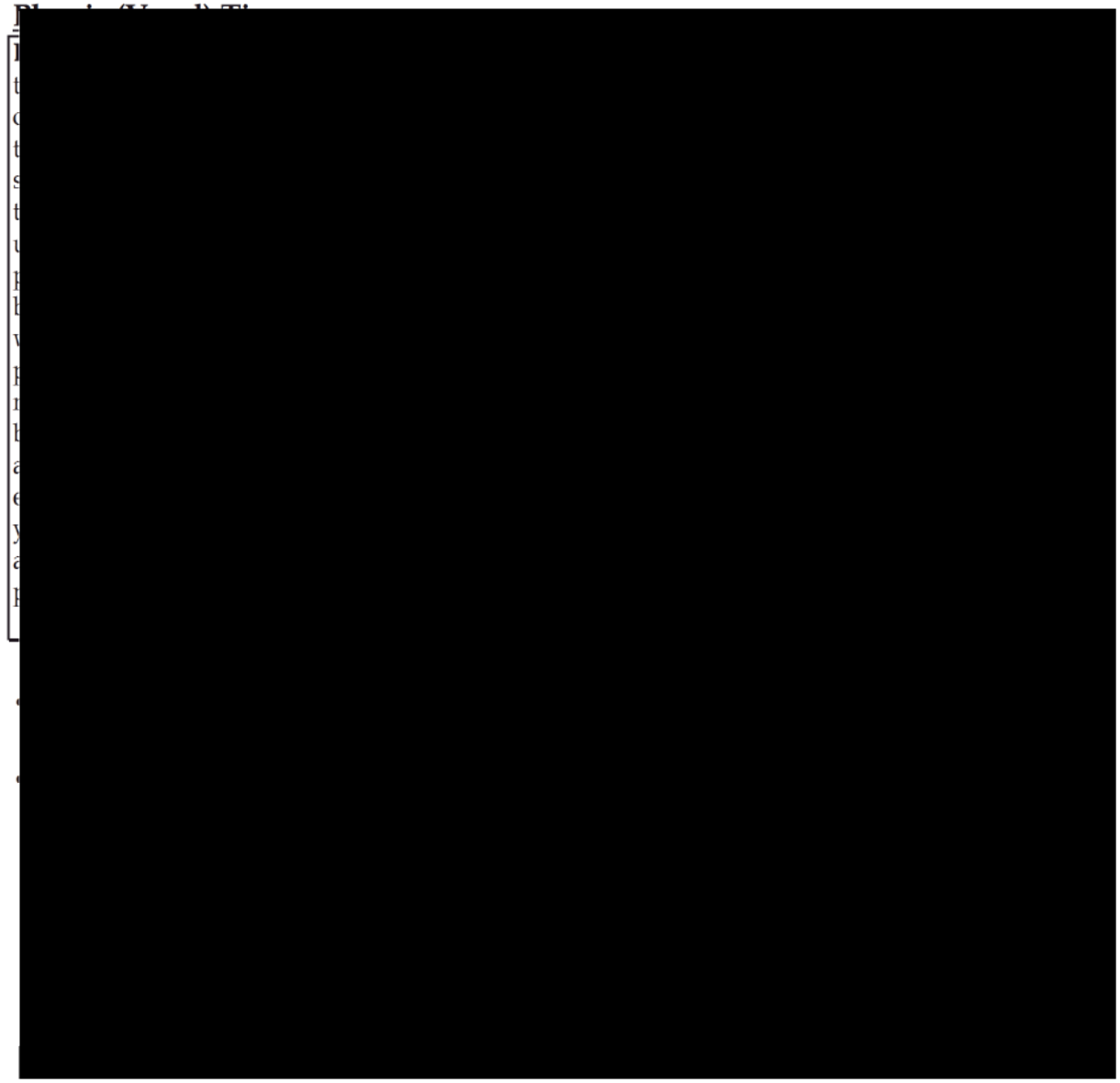

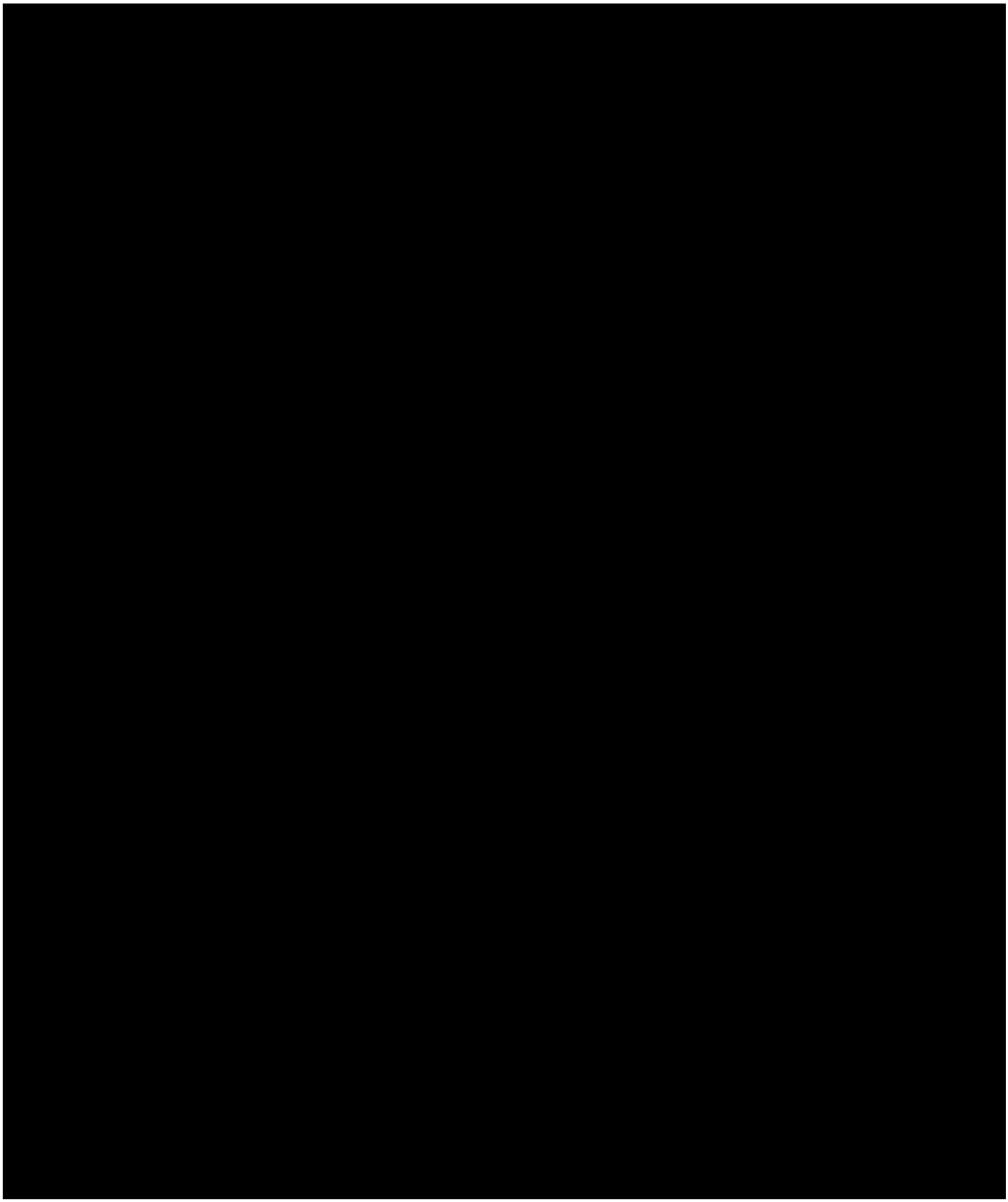

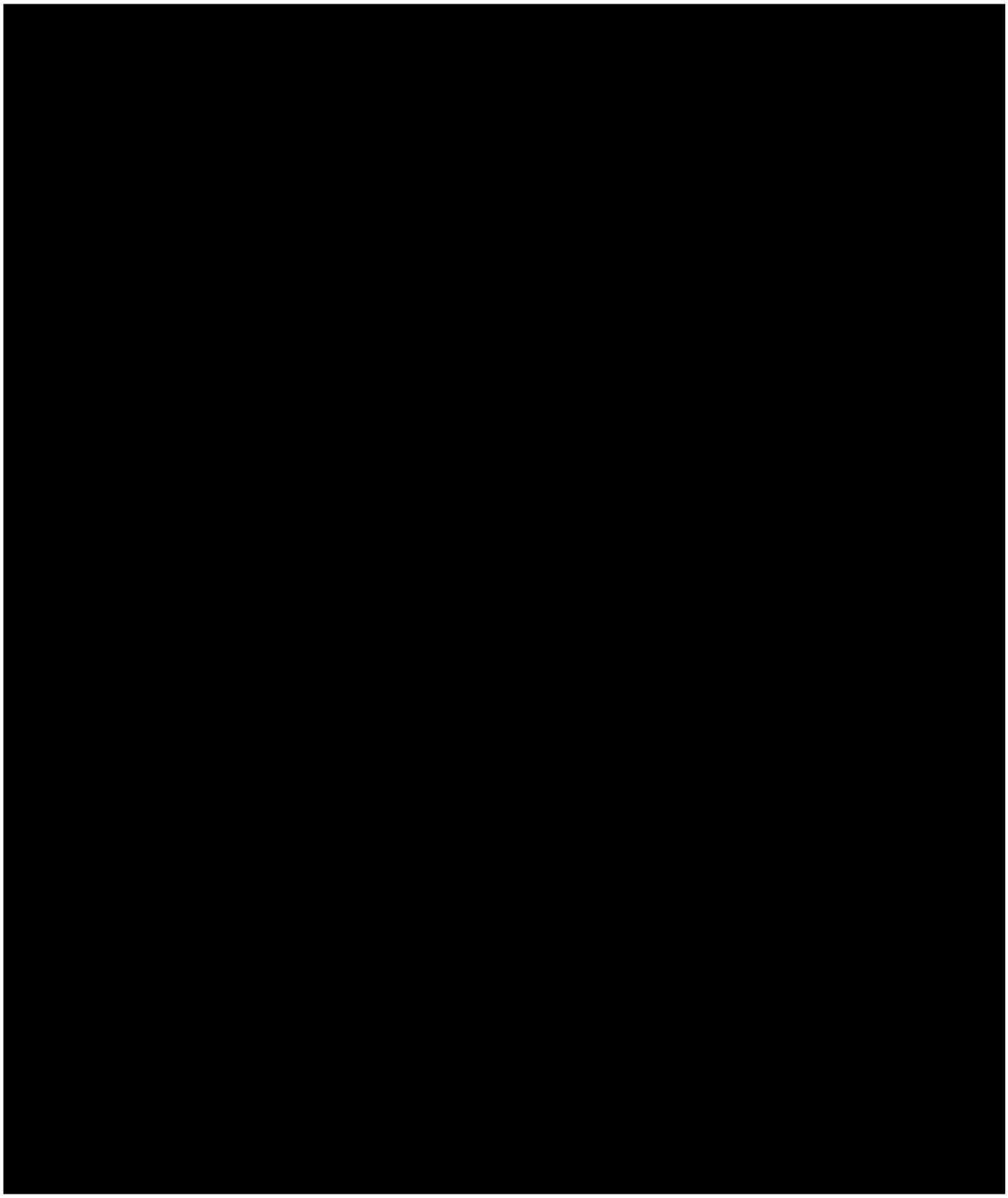

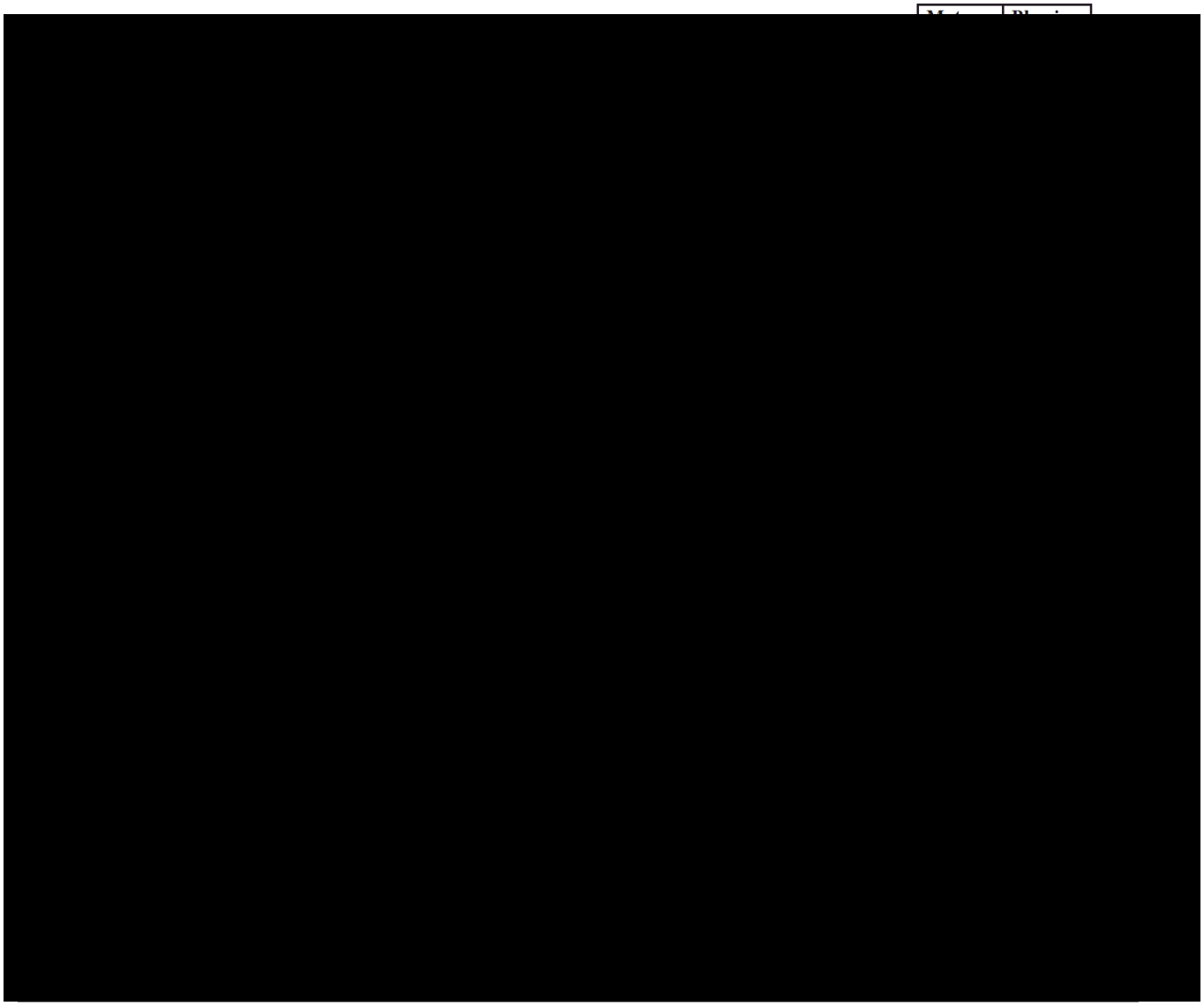

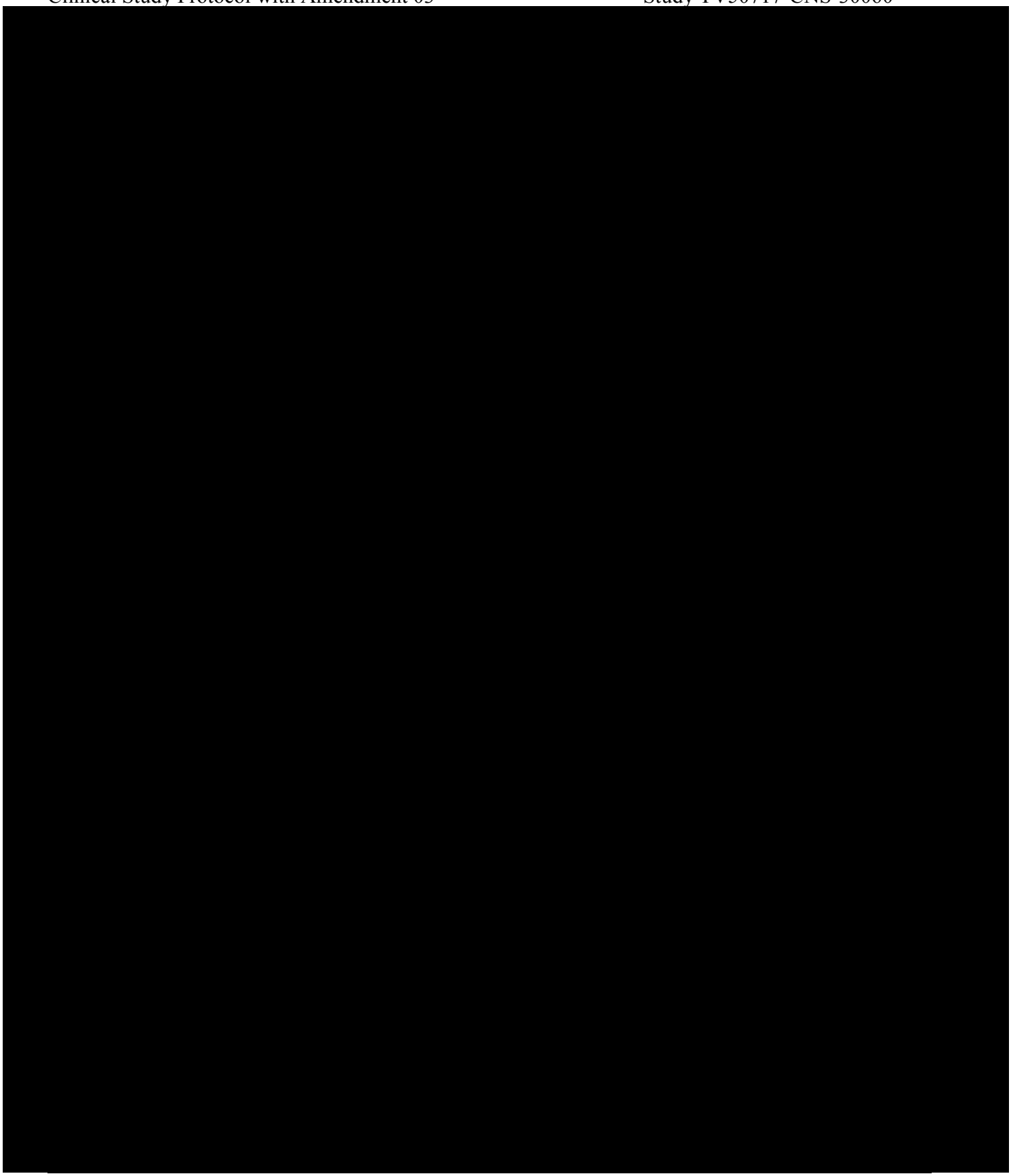

APPENDIX N. [redacted]

[redacted]

APPENDIX O. [redacted]

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APPENDIX P. [redacted]

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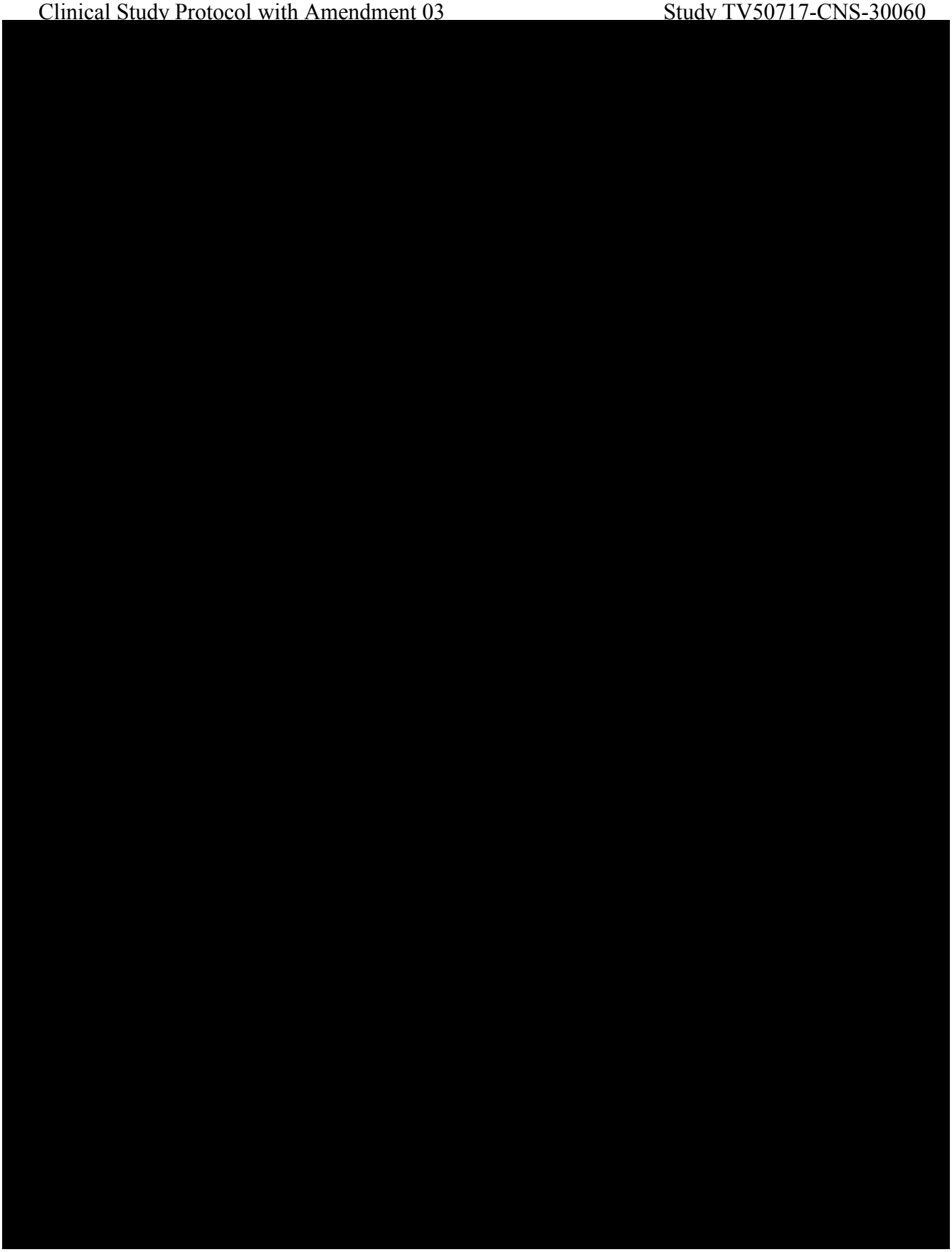
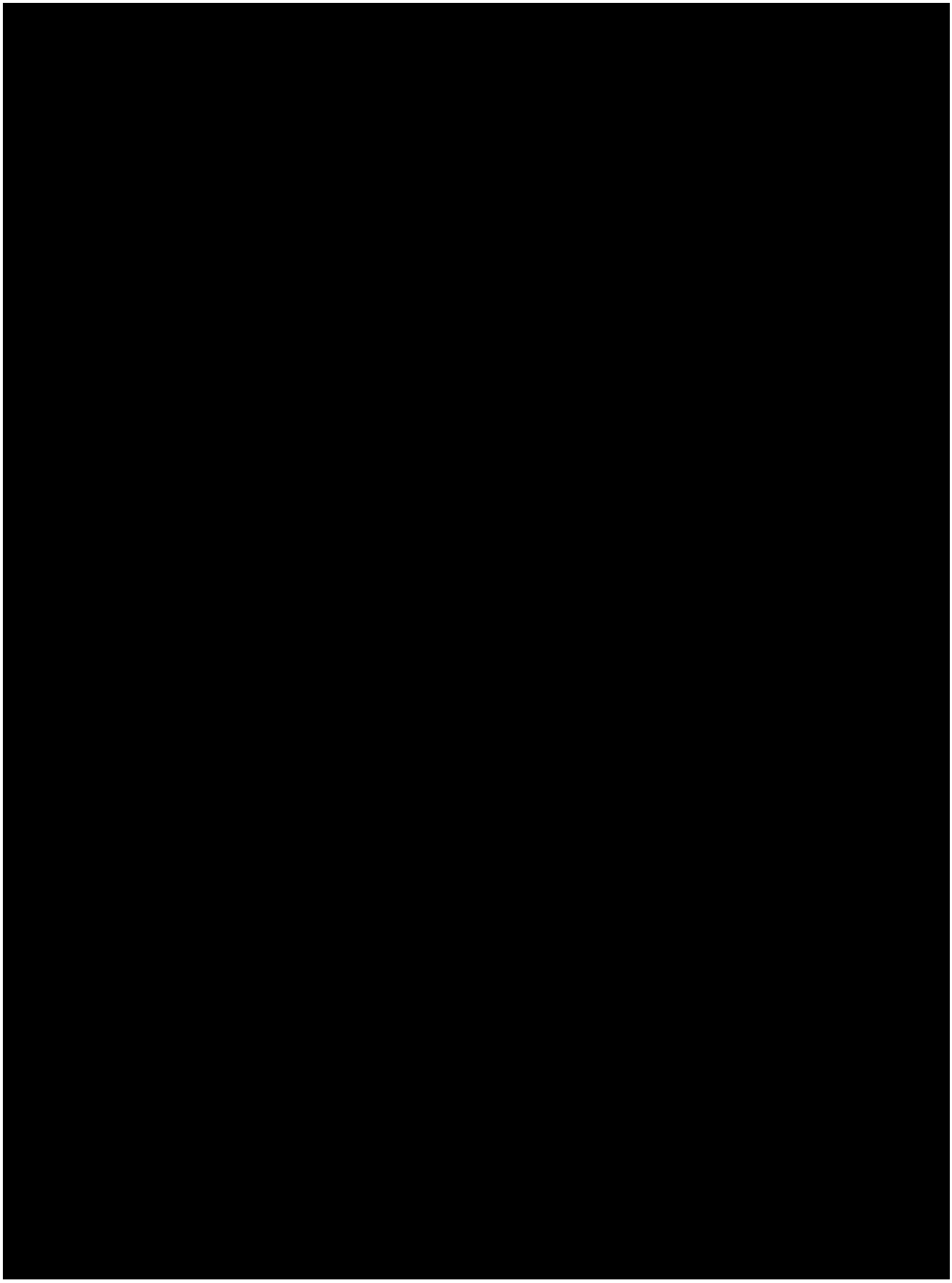
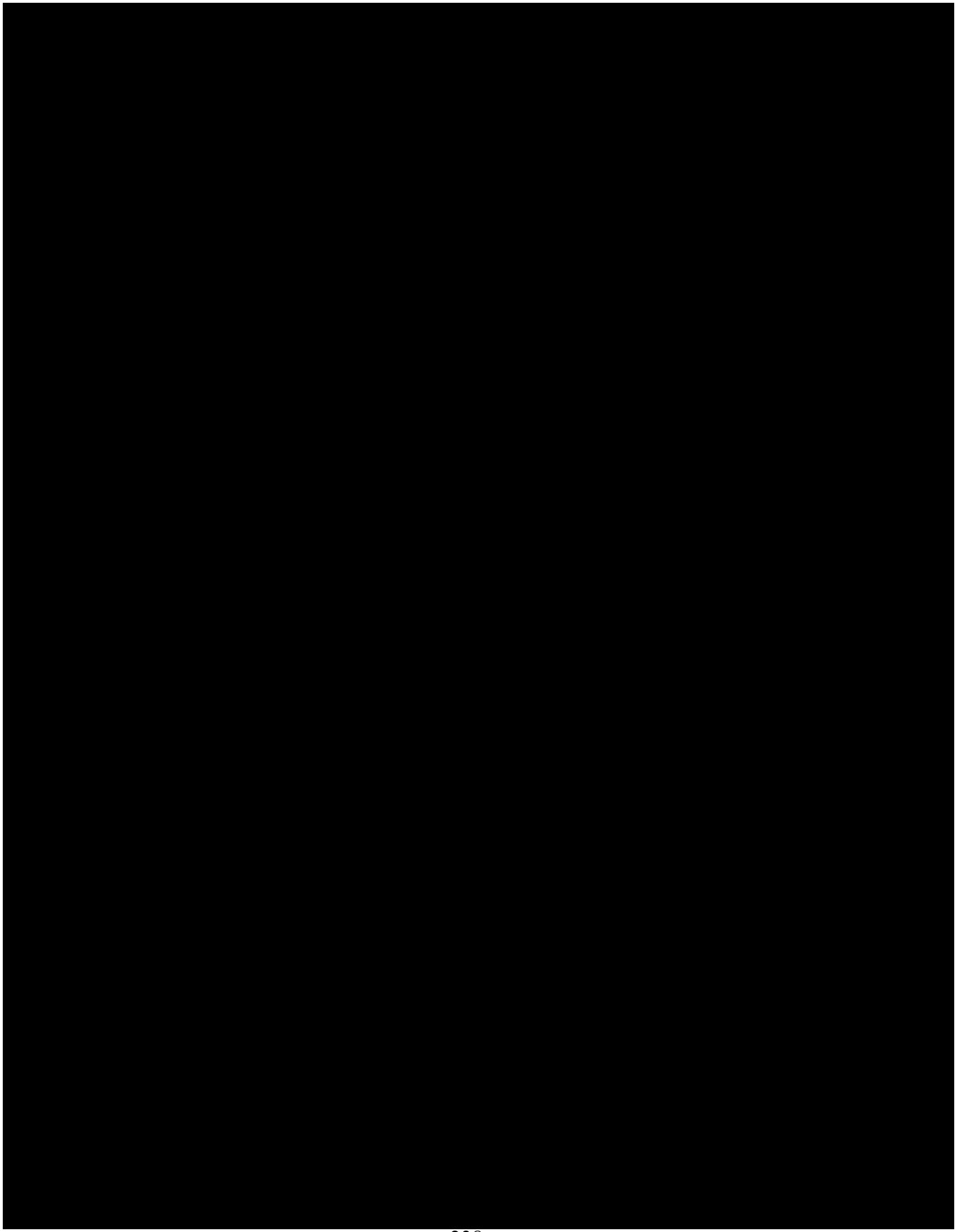
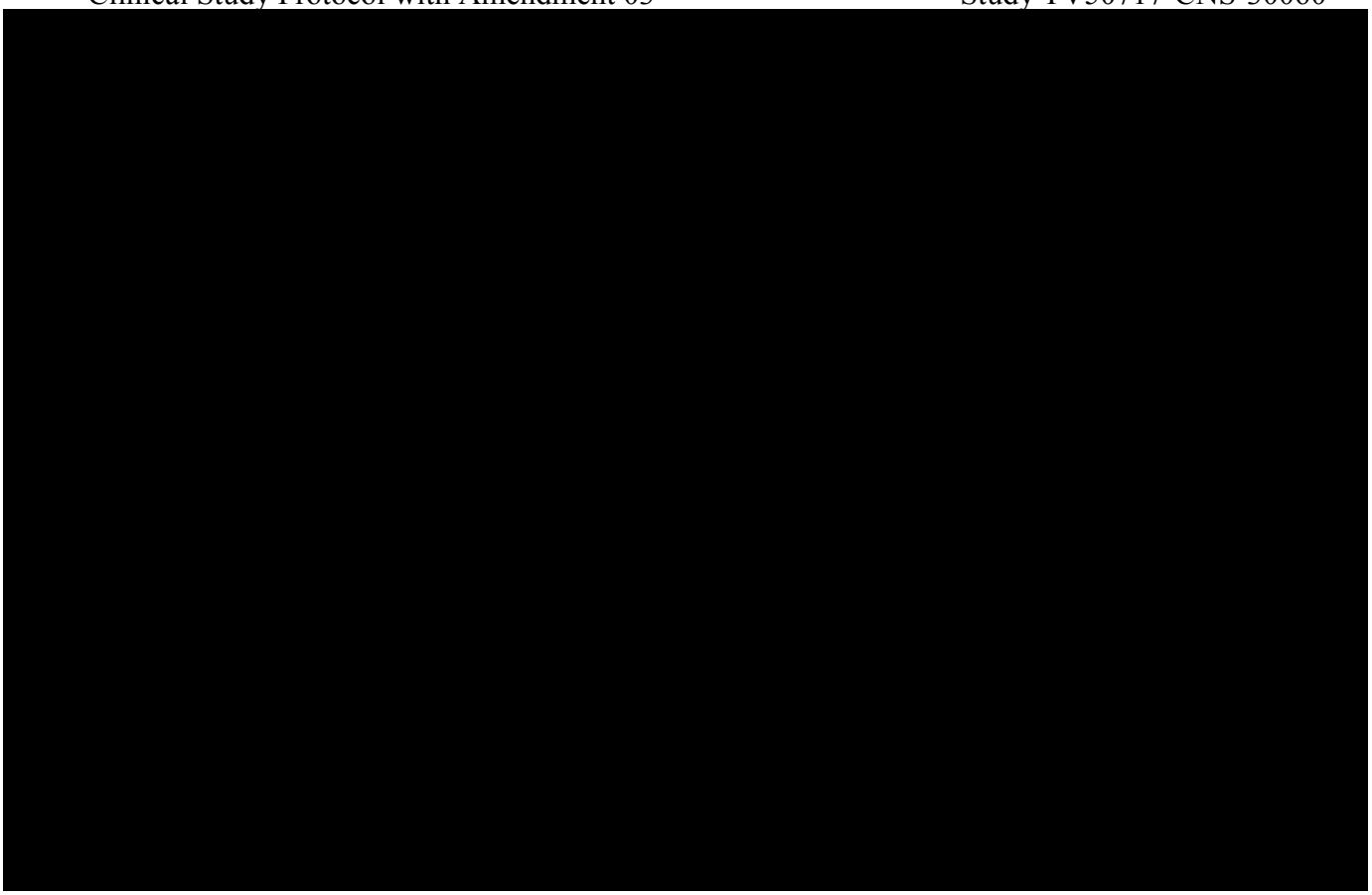
APPENDIX Q. [redacted]

[redacted]









APPENDIX R. PRODUCT COMPLAINTS

Clinical Product Complaints

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical IMP supplies or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc)
- defective components
- missing or extra units (eg, primary container is received at the investigational center with more or less than the designated number of units inside)
- incorrect packaging, or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor, or both
- device not working correctly or appears defective in some manner

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the product complaint form provided by Teva and emailing it to [redacted] within 48 hours of becoming aware of the issue.

For complaints involving a device or other retrievable item, it is required that the device (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving an IMP, all relevant samples (eg, the remainder of the patient's IMP supply) should be sent back to the sponsor for investigative testing whenever possible.

1. **Product Complaint Information Needed from the Investigational Center**

In the event that the product complaint form cannot be completed, the investigator will provide the following information, as available:

- investigational center number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- patient identifier (patient study number) and corresponding visit numbers, if applicable
- product name and strength for open-label studies
- patient number, blister pack, and kit numbers (if applicable) for double-blind or open-label studies
- product available for return Yes/No
- product was taken or used according to protocol Yes/No

- description or nature of complaint
- associated serious adverse event Yes/No
- clinical supplies unblinded (for blinded studies) Yes/No
- date and name of person receiving the complaint

Note: Reporting a product complaint must not be delayed even if not all the required information can be obtained immediately. Known information must be reported immediately. The sponsor will collaborate with the investigator to obtain any outstanding information.

2. **Handling of Investigational Medicinal Product(s) at the Investigational Center(s)**

The investigator is responsible for retaining the product in question in a location separate from the investigator's clinical study supplies. The sponsor may request that the investigator return the product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the IMP.

If it is determined that the investigational center must return all IMP, the sponsor will provide the information needed to handle the return.

The integrity of the randomization code and corresponding blinded clinical supplies will be maintained whenever possible. A serious adverse event or the potential for a product quality problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient.

3. **Adverse Events or Serious Adverse Events Associated with a Product Complaint**

If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 7.1.2 and Section 7.1.5.3, respectively).

4. **Documenting a Product Complaint**

The investigator will record in the source documentation a description of the product complaint, and any actions taken to resolve the complaint and to preserve the safety of the patient. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.

APPENDIX S. DATA MANAGEMENT AND RECORD KEEPING

Direct Access to Source Data and Documents

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF. Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

If data are processed from other institutions or by other means (eg, clinical laboratory or central image center) the results will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management).

The medical experts, study monitors, auditors, IEC/IRB, and inspectors from competent authority (or their agents) will be given direct access to source data and documents (eg, medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with national and local requirements.

The investigator must maintain the original records (ie, source documents) of each patient's data at all times. The investigator must maintain a confidential patient identification list that allows the unambiguous identification of each patient.

Data Collection

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21CFR Part 11 (USA) and documents of other concerned competent authorities. Before using the CDMS, it will be fully validated and all users will receive training on the system and study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel, and CRFs must be completed for each patient who provided informed consent/assent. Patient identity should not be discernible from the data provided on the CRF.

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic patient-reported outcome [ePRO] tablet), these data will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management). All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF. Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

For patients who enter a study but do not meet entry criteria, at a minimum, data for screening failure reason, demography, and adverse events from the time of informed consent/assent will be entered in the CRF.

Data Quality Control

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data quality control, will comply with international regulatory guidelines, including ICH GCP guidelines. Data management and control processes specific to this study, along with all steps and actions taken regarding data management and data quality control, will be described in a data management plan.

CRFs received will be processed and reviewed for completeness, consistency, and the presence of mandatory values. Applicable terms will be coded according to the coding conventions for this study. Logical checks will be implemented to ensure data quality and accuracy. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS. Discrepancies found will be queried.

Data corrections in the CDMS will be made using the CDMS update function. The system requires a reason for each change and keeps a complete audit trail of the data values, dates, and times of modifications, and authorized electronic approvals of the changes.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate.

Archiving of Case Report Forms and Source Documents

Sponsor Responsibilities

The original CRFs will be archived by the sponsor. Investigational center-specific CRFs will be provided to the respective investigational centers for archiving.

Investigator Responsibilities

The investigator must maintain all written and electronic records, accounts, notes, reports, and data related to the study and any additional records required to be maintained under country, state/province, or national and local laws, including, but not limited to:

- full case histories
- signed informed consent/assent forms
- patient identification lists
- case report forms for each patient on a per-visit basis
- data from other sources (eg, central laboratory, bioanalytical laboratory, central image center)
- safety reports
- financial disclosure reports/forms
- reports of receipt, use, and disposition of the IMPs
- copies of all correspondence with sponsor, the IEC/IRB, and any competent authority

The investigator will retain all records related to the study and any additional records required, as indicated by the protocol and according to applicable laws and regulations, until the CRO or sponsor notifies the institution in writing that records may be destroyed. If, after 25 years from study completion, or earlier in the case of the investigational center closing or going out of business, the investigator reasonably determines that study record retention has become unduly burdensome, and sponsor has not provided written notification of destruction, then the investigator may submit a written request to sponsor at least 60 days before any planned disposition of study records. After receipt of such request, the sponsor may make arrangements for appropriate archival or disposition, including requiring that the investigator deliver such records to the sponsor. The investigator shall notify the sponsor of any accidental loss or destruction of study records.