Clinical Study Protocol

An Open-Label, Long-Term Safety Study Including a Double-Blind, Placebo-Controlled, Randomized Withdrawal Period of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents

Study Number TV50717-CNS-30047

NCT03567291

Protocol Approval Date: 22 May 2019

Clinical Study Protocol with Amendment 04

Study Number TV50717-CNS-30047

An Open-Label, Long-Term Safety Study Including a Double-Blind, Placebo-Controlled, Randomized Withdrawal Period of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents

Phase 3

IND number: 127692; NDA number: NA; EudraCT number: 2016-000630-22

Original Protocol Approval Date: 26 February 2016

Protocol Amendment 04 Approval Date: 22 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 Conference for Harmonisation (ICH); United States (US) Code of Federal Regulations (CFR), and European Union (EU) Directives (as applicable in the region of the study); national country regulations; 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-30047 (original protocol dated 26 February 2016) has been amended and reissued as follows:

Amendment 04	22 May 2019 100 patients randomized/enrolled to date
Amendment 03	01 February 2018 No patients randomized/enrolled to date
Amendment 02	15 November 2017 No patients randomized/enrolled to date
Amendment 01	22 June 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 17.

INVESTIGATOR AGREEMENT

Original Protocol Dated 26 February 2016

Amendment 04 Dated 22 May 2019

IND number: 127692; EudraCT number: 2016-000630-22

Article 45 or 46 of 1901/2006 does not apply

An Open-Label, Long-Term Safety Study Including a Double-Blind, Placebo-Controlled, Randomized Withdrawal Period of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol with Amendment 04 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]	22 May 2019

COORDINATING INVESTIGATOR AGREEMENT

Original Protocol Dated 26 February 2016

Amendment 04 Dated 22 May 2019

IND number: 127692; EudraCT number: 2016-000630-22

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]	05/23/2019

COORDINATING INVESTIGATOR AGREEMENT

Original Protocol Dated 26 February 2016

Amendment 04 Dated 22 May 2019

IND number: 127692; EudraCT number: 2016-000630-22

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]	5/23/19

CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS

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, LLC)

Contract Research Organization; Safety and Efficacy Data Analysis
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 PERSONNEL CONTACT INFORMATION

Sponsor's Authorized Representative:

[redacted] Teva Branded Pharmaceutical Products R&D, Inc.
Email: [redacted]

Legal Representative of the Sponsor in the EU

Syneos Health Netherlands B.V.

For medical issues, contact the physician listed below:

[redacted]
USA
Office: [redacted]
Mobile: [redacted]
Email: [redacted]

[redacted]
Mobile: [redacted]
Email: [redacted]

[redacted]
Syneos Health, LLC
Av. del Libertador 7270 9th Floor
Ciudad de Buenos Aires, Argentina
Office: [redacted]
Mobile: [redacted]

Fax: [redacted]
Email: [redacted]

[redacted]
Office: [redacted]
Mobile: [redacted]
E-mail: [redacted]

For protocol issues, contact the study leader listed below:

[redacted].
Tel: [redacted]
Email: [redacted]

[redacted]
Tel: [redacted]
Email: [redacted]

For operational issues, contact the Head of Operations listed below:

[redacted]
Tel: [redacted]
Email: [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.

CLINICAL STUDY PROTOCOL SYNOPSIS

Study TV50717-CNS-30047

Title of Study: An Open-Label, Long-Term Safety Study Including a Double-Blind, Placebo-Controlled, Randomized Withdrawal Period of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents

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 **New Drug Application (NDA) Number:** Not available **EudraCT Number:** 2016-000630-22

Name of Active Ingredient: Deutetrabenazine

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

Type of the Study: Safety (Phase 3)

Number of Investigational Centers Planned: Approximately 120

Countries Planned: Global (per Study SD-809-C-17, Study TV50717-CNS-30046, and Study TV50717-CNS-30060)

Planned Study Period: May 2018 to January 2021 with a duration of approximately 32 months

Number of Patients Planned: Up to approximately 227 patients are planned to be enrolled (approximately 1 patient is estimated to enroll from the Phase 1b Study SD-809-C-17, up to approximately 99 patients are estimated to enroll from the Phase 2/3 Study TV50717-CNS-30046, and up to approximately 127 patients are estimated to enroll from the Phase 3 Study TV50717-CNS-30060).

Study Population: Male and female patients with tics associated with Tourette syndrome (TS) who have previously completed participation in Study SD-809-C-17, Study TV50717-CNS-30046, or Study TV50717-CNS-30060.

Primary Objective: The primary objective of this study is to evaluate the safety and tolerability of long-term therapy with TEV-50717.

Secondary Objectives: The secondary objectives of this study are as follows:

- to evaluate the efficacy of long-term therapy with TEV-50717 in reducing the severity of TS tics
- to confirm long-term maintenance of effect by means of a double-blind, placebo-controlled, randomized drug withdrawal period after 28 weeks of open-label treatment

Study Endpoints:

Safety Endpoints:

The following safety endpoints will be assessed in Part A (Day 1, Titration, and Maintenance):

- incidence of adverse events
- observed values and changes from day 1 in vital signs
- observed values and changes from day 1 in the Children's Depression Inventory, Second Edition, Parent and Self-Report Profiles (CDI-2)
- observed values in the Children's Columbia-Suicide Severity Rating Scale (C-SSRS)
- observed values in electrocardiogram (ECG) parameters and shifts from parent study baseline (for patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or from day 1 (for patient[s] rolling over from Study SD-809-C-17) for clinically significant abnormal findings
- observed values and changes from day 1 in clinical laboratory parameters (hematology, serum chemistry, and urinalysis)

The following safety endpoints will be assessed in Part B (Blinded, Randomized Drug Withdrawal Period and Titration Post-Drug Withdrawal):

- incidence of adverse events

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.

Efficacy Endpoints:

The following efficacy endpoints will be assessed in Part A (Day 1, Titration, and Maintenance):

- change in the Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS) from day 1 to each visit in which the scale is administered
- change in the Tourette Syndrome-Clinical Global Impression (TS-CGI) score from day 1 to each visit in which the scale is administered
- change in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) score from day 1 to each visit in which the scale is administered
- change in the Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life (C&A-GTS-QOL) activities of daily living (ADL) subscale score from day 1 to each visit in which the scale is administered

The following efficacy endpoint will be assessed in Part B (Blinded, Randomized Drug Withdrawal Period and Titration Post-Drug Withdrawal):

- change in the TTS of the YGTSS from week 28 to week 30, with the primary analyses and sensitivity testing done as described in Section 9.5.3.1

Exploratory Endpoints:

The following exploratory endpoints will be assessed in Part A (Day 1, Titration, and Maintenance):

[redacted]

General Design and Methodology:

This is an open-label, single-arm study that includes a 2-week, double-blind, placebo-controlled, randomized drug withdrawal period followed by a 3-week blinded re-titration period in which patients with tics associated with TS may be eligible to participate after successful completion of any of the parent studies (SD-809-C-17 [Phase 1b], TV50717-CNS-30046 [Phase 2/3], or TV50717-CNS-30060 [Phase 3]). Patients rolling over from Study SD-809-C-17 will need to undergo all day 1 assessments. For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, the week 13 visit (Study TV50717-CNS-30046) or the week 9 visit (Study TV50717-CNS-30060) will be the day 1 visit for Study TV50717-CNS-30047. If the patient does not wish to enroll in Study TV50717-CNS-30047 at that visit, they can enroll up to 1 week following the week 13 or week 9 visits, respectively. The end of study is defined as the date of the week 56 visit of the last participant.

Patients who have successfully completed a parent study may be eligible to enroll in this study after they complete a 1-week washout period and the final evaluation at week 13 (TV50717-CNS-30046) or week 9 (TV50717-CNS-30060) in the parent study.

Site-administered scales include the YGTSS, [redacted], Mini International Neuropsychiatric Interview For Children and Adolescents (MINI Kid, version 6.0), and the C-SSRS; and self-administered scales include the TS-PGII, [redacted], [redacted], CDI-2, and C&A-GTS-QOL. For the YGTSS, input from the caregiver/adult is required. For [redacted] TS-PGII [redacted], input from the caregiver/adult is permitted. For all other scales, for

children 13 years of age and under, interviews may be performed separately or jointly with the caregiver/adult as appropriate or as 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. It should be noted that the CDI-2 has individual parent and child questionnaires.

Informed consent/assent, depending on the child's age, as appropriate, will be obtained before any study procedures are performed. For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, informed consent/assent, as appropriate, may be obtained prior to the day 1 visit, up to 4 weeks in advance of open-label study participation. Any patient that turns 18 years of age during the course of Study TV50717-CNS-30047 will need to be re-consented as an adult.

In the study period descriptions below, "week X" refers to the end of that week, which coincides with the study visit, unless stated otherwise. Some dose changes will occur at the start of a week rather than at the end of a week and will be indicated as such.

Screening

For patients from Study SD-809-C-17:

During the screening period (up to 31 days), all screening procedures will be performed for patients rolling over from Study SD-809-C-17 as they will have been off IMP for several months at the time of enrollment into this study.

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, assessment of vital signs, laboratory testing, and 12-lead ECG, along with rating scales to assess comorbid TS symptoms and behavioral status.

At the discretion of the investigator, the screening visit may be divided into 2 visits if the visit length is deemed to be too burdensome for the patient. Patients may be rescreened 1 time if there is a change in the 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 medical monitor and/or Clinical Surveillance and Training team.) For patients from Study TV50717-CNS-30046 or Study TV50717-CNS-30060:

The screening evaluation for this open label study occurs at the end of the treatment period in the double-blind study. To reduce patient burden and not collect duplicate information, after obtaining informed consent/assent, depending on the child's age, as appropriate, relevant data collected in Study TV50717-CNS-30046 or Study TV50717-CNS-30060 will be used to provide corresponding data in this open-label study (see Table 1).

YGTSS Rater Certification: All investigators and subinvestigators 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 where this scale is administered, especially at day 1 and at weeks 28, 30, and 54/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.

Part A:

Day 1 visit (**all patients**): For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, the week 13 visit (Study TV50717-CNS-30046) or the week 9 visit (Study TV50717-CNS-30060) will be the day 1 visit for Study TV50717-CNS-30047. Patients rolling over from Study SD-809-C-17 will need to undergo all day 1 assessments. Day 1 assessments for Study TV50717-CNS-30047 that are identical to Study TV50717-CNS-30046 week 13 or Study TV50717-CNS-30060 week 9 visit assessments **do not** need to be repeated. Additionally, Study TV50717-CNS-30047 required evaluations will be completed at Study TV50717-CNS-30046 week 13 visit or Study TV50717-CNS-30060 week 9 visit (see Table 1). For all patients, the day 1 visit should occur on or as close as possible to the week 13 or week 9 visit from Study TV50717-CNS-30046 and Study TV50717-CNS-30060, respectively, but not >7 days beyond those respective visits.

For patients with clinically significant laboratory abnormalities at week 12 in Study TV50717-CNS-30046 or at week 8 in Study TV50717-CNS-30060, week 13 values (Study TV50717-CNS-30046) or week 9 values (Study TV50717-CNS-30060) will serve as day 1 laboratory values in this study.

Titration period (7 weeks): As patients from Study SD-809-C-17 will have been off IMP for several months at the time of enrollment, and since patients from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 will have discontinued IMP (TEV-50717 or placebo) for at least 1 week at completion of the parent study, all patients will undergo TEV-50717 dose titration in this study. Patients will receive 6 mg of TEV-50717 with food on the evening of day 1. Tablets should be taken with food (eg, a snack) and should not be taken on an empty stomach. The titration scheme and maximum dose will be determined by body weight and cytochrome P450 2D6 (CYP2D6) impairment status from the parent study. 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 of the parent study. Patients who are CYP2D6 impaired will have a dose cap in the open-label trial, as shown in the table below. Patients and their caregiver/adult will interact weekly with the clinical research staff, either by telephone contact or in-clinic visits from week 1 through week 7 of the titration period, in order to evaluate safety and establish a dose of TEV-50717 that optimally reduces tics and is well tolerated (optimal dose). Safety evaluations during the titration period include assessment of vital signs, monitoring for adverse events and concomitant medications, 12-lead ECGs, and rating scales for depression and suicidality.

In-person (in-clinic) study visits will be scheduled at weeks 2, 4, and 6, and telephone contacts will be scheduled for weeks 1, 3, 5, and 7 in order to assess tic severity and adverse events.

The dose of the IMP should be increased on a weekly basis until one of the following occurs:

- The investigator determines there has been a clinically meaningful reduction in tics.
- The patient experiences a protocol-defined “clinically significant” adverse event (defined as an adverse event that is related to the IMP and is either moderate or severe in intensity or meets the criteria for a serious adverse event).
- The maximum allowable dose is reached based on the patient’s weight and CYP2D6 impairment status.

If a stable dose is reached before the week 7 telephone call, the patient should continue on that dose (ie, the dose should not be increased further) for the remainder of the titration period. If a patient experiences depression, suicidal ideation or behavior, anxiety, akathisia, parkinsonism, somnolence, any other adverse event that interferes with daily activity, or adverse event that is related to IMP, the investigator will determine if a dose reduction or suspension is necessary. If the patient requires a dose reduction or suspension during a telephone contact, an unscheduled in-clinic visit should be conducted as soon as practicable thereafter.

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 the information from rating scales.

Maximum Daily Dose of IMP by Study Day and Weight Category on Day 1 for Titration at Study Initiation

	Weight category					
Study day[a]	**20 to <30 kg**		**30 to <40 kg**		**≥40 kg**	
CYP impairment status	**Not impaired**	**Impaired**	**Not impaired**	**Impaired**	**Not impaired**	**Impaired**
Day 1-7	6 mg	6 mg	6 mg	6 mg	6 mg (Days 1 and 2) 12 mg[b]	6 mg (Days 1 and 2) 12 mg[b]
Day 8-14	12 mg	12 mg	12 mg	12 mg	18 mg	18 mg
Day 15-21	18 mg	18 mg	18 mg	18 mg	24 mg	24 mg
Day 22-28	18 mg	18 mg	24 mg	24 mg	30 mg	30 mg
Day 29-35	24 mg	18 mg	30 mg	24 mg	36 mg	36 mg
Day 36-42	24 mg	18 mg	36 mg	24 mg	42 mg	36 mg
Day 43-49	30 mg	18 mg	42 mg	24 mg	48 mg	36 mg

[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 as applicable.

[b] Patients will receive 6 mg on days 1 and 2, and 12 mg starting on day 3.

CYP=cytochrome P450; IMP=investigational medicinal product.

Note: CYP impaired=patients who are receiving a strong CYP2D6 inhibitor or who are a CYP2D6 poor metabolizer. The investigator, in consultation with the patient and caregiver/adult, will determine if a dose increase is warranted to achieve optimal tic reduction.

Maintenance period: At the end of the titration period, the patient's initial dose for the maintenance period will be established. Dose adjustments of TEV-50717 (upward or downward) may be made during the maintenance period, if necessary, but not more often than every 5 days and only in increments of 6 mg. As during titration, dose adjustments should be made based on all available information.

During the maintenance period, in-person (in-clinic) study visits will be scheduled at weeks 8, 15, 34, 41, and 54 for assessments of safety and efficacy and telephone contacts will be scheduled for weeks 21 and 47 in order to assess adverse events and tic severity. The randomized drug withdrawal and re-titration period (Part B) will occur from the end of week 28 through the end of week 33, and then the Part A maintenance period will resume, along with the ability to make dose adjustments as described above. At week 54, patients will undergo a complete evaluation, including physical and neurological examination, safety laboratory testing, 12-lead ECG, CDI-2, and C-SSRS assessments, as well as the YGTSS, TS-CGI, [redacted], TS-PGII, [redacted], and C&A-GTS-QOL.

Washout and follow-up period: All patients will discontinue IMP at the week 54 visit and will return 1 week later (week 55) for evaluation of safety and tic reduction. Patients will have a follow-up telephone contact for safety evaluation 1 week after the end of the washout period (2 weeks after their last dose of IMP) (week 56).

Part B: Blinded, Randomized Drug Withdrawal Period and Titration Post-Drug Withdrawal (5 weeks): At the week 28 visit, the patients will be randomized 2:1 to their current dose of TEV-50717 or placebo in order to check for the return of symptoms. Because IMP is dispensed as enough doses for 2 weeks (current dose level and next dose level), the week 28 visit (Day 196) is considered the first day of the randomized withdrawal period, although the patient will begin taking blinded IMP the next morning on Day 197. Patients will have a follow-up telephone contact for safety evaluation 1 week after the start of the randomized drug withdrawal period. At week 30, safety and efficacy will be assessed. At the week 30 visit, patients who receive TEV-50717 during the randomized drug withdrawal period will continue at the same dose in a blinded manner from the start of week 31 to the start of week 34. Any patient who was randomized to placebo during the 2-week randomized drug withdrawal period will undergo blinded re-titration (titration post-drug withdrawal) to their previously established maintenance dose over the 3 weeks of treatment following the randomized drug withdrawal period (start of week 31 through start of week 34 [Days 211 through 232]). The titration scheme and maximum dose will be determined based on the previously established maintenance dose as tabulated below. The dose of IMP for each patient who underwent 2 weeks of placebo will be titrated back to the maintenance dose that was used by the patient up to week 28 followed by continued maintenance therapy at that dose. Patients will have a follow-up telephone contact for safety evaluation at weeks 31 and 33. All patients should be back at their maintenance dose on or before the start of week 34 and return to open-label treatment for the remainder of the study (note that, because IMP is dispensed for 2-week periods, patients will use blinded bottles through the end of week 34; however, all patients will be known to be on active treatment at the start of week 34).

Daily Dose of IMP by Previously Established Maintenance Dose and Study Week (Titration Post-Drug Withdrawal) for Patients Randomized to Placebo During the Blinded, Randomized Drug Withdrawal Period

	Daily dose (mg) at the start of week			
Previously established maintenance dose[a] (mg)	**Day 211 (start of week 31)**	**Day 218 (start of week 32)**	**Day 225 (start of week 33)**	**Day 232 (start of week 34) maintenance dose**
6	6	6	6	6
12	12	12	12	12
18	12	18	18	18
24	12	18	24	24
30	12	18	24	30
36	12	24	30	36
42	12	24	36	42
48	12	24	36	48

[a] The previously established maintenance dose is the dose administered at the end of Part A (Day 196 [end of week 28]). The blinded, randomized drug withdrawal period will occur from the start of week 29 through the end of week 30.

IMP=investigational medicinal product.

Method of Randomization and Blinding: This is an open-label study that includes a 2-week double-blind, placebo-controlled, randomized drug withdrawal period followed by a 3-week blinded re-titration period (note that, because IMP is dispensed for 2-week periods, patients will use blinded bottles for an additional 1 week [4 weeks total after the end of the blinded, randomized withdrawal period]; however, all patients will be known to be on active treatment during that week). During the blinded drug withdrawal and re-titration period, patients and investigators will remain blinded to treatment assignment. In addition, the sponsor's and development partner's clinical personnel and all vendors (with the exception of the Interactive Response Technology (IRT) vendor and the IMP packaging 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.

IMP Dose, Mode of Administration, and Administration Rate:

IMP will be administered as oral tablets at a starting dose of 6 mg once daily, to be taken in the morning (except for day 1, when it should be taken in the evening after the clinic visit). Titration schemes based on body weight are shown in the first table above ("Titration period [7 weeks]" section). The maximum daily dose is determined by body weight and CYP2D6 impairment status (see the first table above). Dose adjustments can be made during the titration period and also, if clinically indicated, during the maintenance period dosing before and after the randomized drug withdrawal and re-titration period.

During the open-label period, TEV-50717 tablets are available in the following dose strengths: 6, 9, and 12 mg. Each dose strength will have a marking of SD 6, SD 9, and SD 12 corresponding

to the dose strength and a distinct color: 6 mg – purple, 9 mg – blue, and 12 mg – beige. IMP will be supplied in 20-or 60-count tablets per dose strength per bottle.

During the randomized drug withdrawal and re-titration period, 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 20-count bottles. The placebo tablets and packaging will match those for TEV-50717.

Patients who receive TEV-50717 during the randomized drug withdrawal period will remain on their maintenance dose of blinded active IMP from the start of week 31 to the start of week 34; those assigned to placebo during the randomized drug withdrawal period will undergo blinded re-titration from the start of week 31 to the start of week 34 back to their previously established maintenance dose from the end of week 28. Note that, because IMP is dispensed for 2-week periods, patients will use blinded bottles through the end of week 34; however, all patients will be known to be on active treatment at the start of week 34.

IMP will be administered as follows:

- IMP should be swallowed whole and taken with food. Tablets should be taken with food (eg, a snack) and should not be taken on an empty stomach.
- Dosing will be based on body weight and strong CYP2D6 impairment status, as shown in the tables above.
- The starting dose is 6 mg in all patients. With the exception of the 6-mg dose (administered once daily), doses will be administered twice daily, approximately 8 to 10 hours apart during the day. 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 increases may not occur more frequently than every 5 days.
- 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 should be notified.**
- After dose adjustment, if the maintenance dose for a patient is 6 mg, the dose should be taken once a day in the morning with food.
- During the titration period, the dose of IMP should be adjusted according to the first table above (Maximum Daily Dose of IMP by Study Day and Weight Category on Day 1 for Titration at Study Initiation) to identify a dose level that optimally reduces tics and is well tolerated. A dose cap for impaired patients is prespecified by the IRT.
- After week 24, patient dose should be kept stable, if possible, until beginning Part B.
- During the randomized drug withdrawal period, the patient will continue to receive their current dose of TEV-50717 or receive matching placebo until returning to their dose of TEV-50717 at the start of week 31 (patients who receive TEV-50717 during the randomized drug withdrawal period will remain on their maintenance dose of blinded active IMP from the start of week 31 to the start of week 34; those assigned to placebo during the randomized drug withdrawal period will undergo blinded re-

titration from the start of week 31 to the start of week 34 back to their previously established maintenance dose from the end of week 28).

IMP: TEV-50717

Placebo: Placebo tablets and packaging match TEV-50717 tablets

Duration of Patient Participation: For patients rolling over from Study SD-809-C-17, this study will consist of a 4-week screening period (up to 31 days) and up to 54 weeks of treatment. All participating patients are expected to participate in this study for its entire duration, which is a minimum of 56 weeks. Patients will have a follow-up telephone contact to evaluate safety 1 week after the end of the washout period (2 weeks after their last dose of IMP). Any patient that turns 18 years of age during the course of Study TV50717-CNS-30047 will need to be re-consented as an adult. The end of study is defined as the date of the week 56 visit of the last participant.

Inclusion Criteria: Patients who have completed Study TV50717-CNS-30046 or Study TV50717-CNS-30060 have already met the criteria below.

In addition, patients who have completed Study SD-809-C-17 may be included in the study if, during screening, they meet all of the following criteria:

a. Patient is younger than 18 years of age on day 1.
b. Patient weighs at least 44 pounds (20 kg) on day 1.
c. Patient is able to swallow IMP whole.
d. Patient and caregiver/adult are willing to adhere to IMP regimen and comply with all study procedures.
e. Patient is in good general health, as indicated by medical and psychiatric history as well as physical and neurological examination.
f. 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.
g. Patient and caregiver/adult provide written informed consent/assent, depending on the child's age, as appropriate, according to local regulations.
h. 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 on day 1 or are sterile. Definitions of sterile are given in Appendix L.
i. 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 L.

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

Patients who have completed Study TV50717-CNS-30046 or Study TV50717-CNS-30060 have already been confirmed to not meet any of the criteria below.

In addition, patients who have completed Study SD-809-C-17 will not be enrolled if, during screening, they meet any of the following criteria:

a. Patient is 18 years of age or older.
b. Patient has a neurologic disorder other than TS that could obscure the evaluation of tics.
c. The patient's predominant movement disorder is stereotypy (coordinated movements that repeat continually and identically) associated with autism spectrum disorder.
d. Patient has a confirmed diagnosis of bipolar disorder, schizophrenia, or another psychotic disorder.
e. Patient has clinically significant depression at screening or day 1.
   Note: Patients receiving antidepressant therapy may be enrolled if on a stable dose for at least 6 weeks before screening.
f. 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
g. Patient has a history of a previous actual, interrupted, or aborted suicide attempt.
h. Patient has a first-degree relative who has completed suicide.
i. Patient has clinically significant obsessive-compulsive disorder (OCD) on day 1 that, in the opinion of the investigator, is the primary cause of impairment.
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 specified exclusionary windows of screening prior to dosing for washout:
   - within 3 months: depot neuroleptics, botulinum toxin, or tetrabenazine
   - within 4 weeks: cannabidiol oil or valbenazine
   - within 21 days: reserpine
   - within 14 days: neuroleptics (oral), typical and atypical antipsychotics (see Appendix A, Table 7), 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.
     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.
     Note: Use of benzodiazepines is allowed if the 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 the 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 Tourette syndrome) 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.

l. Patient has an unstable or serious medical illness at screening or day 1.
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 12-lead ECG at screening. Patient requires treatment with drugs known to prolong the QT interval (see Appendix A Table 8 for a complete list of prohibited QT-prolonging drugs).
n. Patients with a history of torsade de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure.
o. Patient has evidence of hepatic impairment, as indicated by:
   – 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 (Tbil) >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 Tbil.
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 day 1 visit.
r. Patient has a known allergy to any of the components of the IMP.
s. Patient has participated in an investigational drug or device study (with the exception of Study SD-809-C-17, Study TV50717-CNS-30046, or Study TV50717-CNS-30060) and received IMP/intervention within 30 days.
t. The 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 Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V™).
v. Patient has a positive urine drug screen test result or is unable to refrain from substance abuse throughout the study.
w. Patient has a DSM diagnosis based on the MINI Kid modules performed at screening that, in the opinion of the investigator, makes the patient unsuitable for the study (for patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, these data will be obtained from the screening visit of the parent study).

Measures and Time Points:

Safety Measures and Time Points

Part A:

- adverse events and concomitant medications: from the signing of the informed consent/assent, depending on the child's age, as appropriate, through follow-up, inclusive of all visits and telephone contacts
- physical examination: screening (only for patients who completed Study SD-809-C-17; data from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 should be used for the remaining patients) and week 54

- neurological examination: screening (only for patients who completed Study SD-809-C-17; data from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 should be used for the remaining patients) and week 54
- vital signs, height, and weight: screening (only for patients who completed Study SD-809-C-17; data from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 should be used for the remaining patients); day 1; and weeks 2, 4, 6, 8, 15, 34, 41, 54, and 55
  Note: orthostatic blood pressure (BP) and pulse on day 1 and weeks 4, 8, and 54
- MINI Kid: screening (only for patients who completed Study SD-809-C-17)
- Children's C-SSRS:
  - Baseline/screening scale: screening (only for patients who completed Study SD-809-C-17)
  - Since Last Visit (SLV) scale: day 1 (only for patients who completed Study SD-809-C-17) and weeks 2, 4, 8, 15, 34, 41, 54, and 55
- CDI-2 (Parent and Self-Report Profiles): screening and day 1 (only for patients who completed Study SD-809-C-17) and weeks 2, 4, 8, 15, 34, 41, 54, and 55
- 12-Lead ECG: screening (only for patients who completed Study SD-809-C-17); day 1; and weeks 4, 8, and 54
- clinical laboratory tests (serum chemistry, hematology, and urinalysis): screening (only for patients who completed Study SD-809-C-17; data from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 should be used for the remaining patients); day 1; and weeks 8 and 54
- pregnancy testing (β-HCG): screening (only for patients who completed Study SD-809-C-17); day 1; and weeks 4, 8, 15, 34, and 54 (serum tests at screening and week 54 and urine tests at other visits)
- drug screen: screening (only for patients who completed Study SD-809-C-17)

Part B:

- adverse events and concomitant medications: from the signing of the informed consent/assent, depending on the child's age, as appropriate, through follow-up, inclusive of all visits and telephone contacts
- physical examination: weeks 28 and 30
- vital signs, height, and weight: weeks 28, 30, and 32
  - Note: orthostatic BP and pulse at week 28
- Children's C-SSRS:
  - SLV version: weeks 28 and 30
- CDI-2 (Parent and Self-Report Profiles): weeks 28 and 30
- 12-lead ECG: week 28
- clinical laboratory tests (serum chemistry, hematology, and urinalysis): week 28
- pregnancy testing: week 28

Efficacy Measures and Time Points:

Part A and Part B:

- YGTSS: screening (only for patients who completed Study SD-809-C-17); day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060); and weeks 2, 4, 8, 15, 28, 30, 34, 41, 54, and 55
- TS-CGI: day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060) and weeks 4, 8, 15, 28, 34, 41, 54, and 55
- TS-PGII: day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060) and weeks 4, 8, 15, 28, 34, 41, 54, and 55
- C&A-GTS-QOL (ADL subscale): day 1 and weeks 6, 28, 34, and 54

Exploratory Measures and Time Points:

Part A and Part B:

[redacted]

Allowed and Prohibited Medications before and during the Study:

See Appendix A for details of allowed and disallowed medications.

Statistical Considerations:

Sample Size Rationale: This is an open-label study. The sample size for this study is not based on statistical considerations; hence, only descriptive statistics will be presented and will be analyzed by age group at baseline. Up to approximately 227 patients who also meet patient exclusion/inclusion criteria will be enrolled (approximately 1 patient is estimated to enroll from the Phase 1b Study SD-809-C-17, up to approximately 99 patients are estimated to enroll from the Phase 2/3 Study TV50717-CNS-30046, and up to approximately 127 patients are estimated to enroll from the Phase 3 Study TV50717-CNS-30060).

For the randomized drug withdrawal period, 190 patients to be included in the analysis will provide approximately 90% power to detect a difference between TEV-50717-treated and placebo-treated patients assuming a difference in YGTSS TTS of 4.5 with a standard deviation of 9 using a two-sided test for difference at a significance level of 0.05.

Planned Interim Analysis:

When approximately 100 patients have completed the 28-week clinic visit, an interim analysis, including data from day 1 and up to week 28 visit only, will be conducted to provide descriptive, long-term safety and efficacy data to be used in regulatory submissions. To maintain data integrity of Study TV50717-CNS-30047, only a limited number of personnel who do not have contact with the sites will have access to this interim data in preparation for the regulatory filing.

As no decisions regarding conduct of the study will be made based on the descriptive interim analysis, no alpha will be spent.

Analyses of Safety: 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 IMP, serious adverse events, and adverse events causing withdrawal from the study. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

Observed values and changes from day 1 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. Changes from parent study baseline (for patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or from day 1 (for patient[s] rolling over from Study SD-809-C-17) in ECG parameters will be summarized descriptively. In addition, the number and percentage of patients with on-treatment QTcF values >450, >480, or >500 msec and change from baseline (Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or day 1 (Study SD-809-C-17) >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 Children's C-SSRS and observed values and changes from day 1 in the CDI-2 (Parent and Self-Report Profiles) will be presented for all patients.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table of Abbreviations

Abbreviation	Term
21CFR	Title 21 Code of Federal Regulations
ADHD	Attention Deficit Hyperactivity Disorder
ADL	activities of daily living
α-HTBZ	alpha-dihydrotetrabenazine
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase
β-HCG	beta-human chorionic gonadotropin
β-HTBZ	beta-dihydrotetrabenazine
bid	twice daily
BP	blood pressure
CDI-2	Children's Depression Inventory, Second Edition, Parent and Self-Report Profiles
CDMS	clinical data management system
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CST	Clinical Surveillance and Training
CY-BOCS	Children's Yale-Brown Obsessive-Compulsive Scale
CYP	cytochrome P450
CYP2D6	cytochrome P450 2D6
C&A-GTS-QOL	Child and Adolescent Gilles de la Tourette Syndrome–Quality of Life
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-V™	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision
ECG	electrocardiogram
ePRO	electronic patient-reported outcome
FDA	Food and Drug Administration
GCP	Good Clinical Practice

Abbreviation	Term
GSS	Global Severity Score
HD	Huntington's disease
IA	interim analysis
IB	Investigator's Brochure
ICH	International Conference for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IMP	investigational medicinal product
IND	Investigational New Drug
IRT	Interactive Response Technology
ITT	intent-to-treat
LSO	local safety officer
MINI Kid	Mini International Neuropsychiatric Interview For Children and Adolescents (version 6.0)
mITT	Modified Intention-to-Treat
MTSS	Motor Tic Severity Score
NDA	New Drug Application
NOAEL	no-observed-adverse-effect level
OCD	obsessive-compulsive disorder
PND	postnatal day
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
RSI	reference safety information
RWITT	Randomized Withdrawal Intent-to-Treat Population
RWmITT	Randomized Withdrawal Modified Intent-to-Treat
RRWmITT	Responder Randomized Withdrawal Modified Intent-to-Treat
RWSAF	Randomized Withdrawal Safety Population
SLV	Since Last Visit
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
Tbil	total bilirubin

Abbreviation	Term
TD	tardive dyskinesia
SD-809/TEV-50717	deutetrabenazine
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
UDS	urine drug screen
ULN	upper limit of the normal range
USA	United States of America
VMAT2	vesicular monoamine transporter 2
VTSS	Vocal Tic Severity Score
WBC	white blood cell
YGTSS	Yale Global Tic Severity Scale

1. BACKGROUND INFORMATION

1.1. Introduction

Tourette syndrome (TS) is a neurodevelopmental disorder characterized by multiple motor and phonic tics and a variety of behavioral and psychiatric comorbidities (Jankovic 2001, Jankovic and Kurlan 2011). Studies have suggested that up to 7% of school children fulfill the diagnostic criteria for TS (Kurlan et al 2002). 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, clonidine), typical neuroleptics (haloperidol, pimozide, fluphenazine), or atypical neuroleptics (olanzapine, ziprasidone, 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, has developed a deuterated tetrabenazine (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's 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 (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 granted breakthrough status for treatment of TD by the Food and Drug Administration (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 on 03 April 2017.

1.2. Name and Description of Investigational Medicinal Product

TEV-50717 (deutetrabenazine) 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. During the open-label period, TEV-50717 tablets are available in the following dose strengths: 6, 9, and 12 mg. Each dose strength will have a marking of SD 6, SD 9, and SD 12 corresponding to the dose strength and a distinct color: 6 mg – purple, 9 mg – blue, and 12 mg – beige. The investigational medicinal product (IMP) will be supplied in 20- or 60-count tablets per dose strength per bottle.

A more detailed description of the product is given in Section 3.8

During the randomized drug withdrawal and re-titration period, 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 20-count bottles.

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 current Investigator's Brochure (IB), including the IB supplement for TS (if available).

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 nondeuterated forms (Scherman et al 1988). Off-target binding occurs to a similar extent with deuterated and nondeuterated 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 that 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, 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 isoenzymes or transporters nor an inducer of CYP isoenzymes.

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 estrus 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 subsequently 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 were 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 no-observed-adverse-effect level (NOAEL) 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:

- 7 completed Phase 1 studies in healthy adult volunteers
- 2 ongoing Phase 1 studies in healthy adult volunteers
- 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 study in patients with TD
- 1 ongoing Phase 3 long-term safety study in patients with TD
- 1 completed Phase 1b study in patients with TS
- 2 ongoing Phase 2/3 and Phase 3 studies in patients with TS
- 1 ongoing Phase 3 long-term safety study in patients with TS

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 volunteers. In addition, sparse pharmacokinetic sampling was included in the Phase 3 studies with HD patients where population pharmacokinetic analyses were performed to extensively evaluate the pharmacokinetics and pharmacokinetics/pharmacodynamics relationship of TEV-50717. A summary of the clinical pharmacology findings is provided in the IB.

Pharmacometric analyses of TEV-50717's active metabolites 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 TEV-50717's 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 pharmacologic activity indistinguishable from tetrabenazine, a VMAT2 inhibitor with established efficacy in treating the motor and phonic tics associated with TS. Preliminary efficacy of TEV-50717 has been evaluated in an open-label, Phase 1b pilot study in patients with troublesome motor and phonic tics associated with TS (Study SD-809-C-17). Twenty-three patients were enrolled in this study across 9 centers in the USA. Patients who completed the study received treatment with TEV-50717 for a total of 8 weeks and had a safety follow-up assessment 4 weeks after treatment. The following efficacy observations were made in this study:

- TEV-50717 was effective in reducing both motor and vocal tics from baseline to week 8 (end of treatment), demonstrating a 37.60% reduction in the Yale Global Tic Severity Scale (YGTSS) Total Tic Score (TTS) from baseline ($p<0.0001$).
- The reduction in tic severity was associated with significant improvement (from baseline to week 8) in the YGTSS Impairment score (-35.32%; $p<0.0001$), the Tourette Syndrome-Clinical Global Impression (TS-CGI) score (-1.2 points; $p<0.0001$), and in the Patient Global Impression of Change score. For example, compared to baseline, 76% of patients completing the study reported that they were "much" or "very much" improved at week 8.
- Between week 8 (end of treatment) and week 9 (1 week post-treatment), an increase in YGTSS and TS-CGI scores were observed following discontinuation of treatment with TEV-50717 at week 8, indicating a re-emergence of symptoms, thus providing further evidence of efficacy.

The safety profile of TEV-50717 has been characterized to date in healthy volunteers as well as in patients with chorea associated with HD and TD (as detailed in the IB). Study SD-809-C-17 also evaluated the safety of TEV-50717 in patients with TS. Results of the safety analyses indicate that treatment with TEV-50717 at dosages up to 36 mg daily given in 2 divided doses is generally safe and well tolerated for up to 8 weeks in patients with TS. No serious treatment-emergent adverse events (TEAEs) or severe TEAEs occurred in this study. The most frequently observed TEAEs during the entire treatment period were fatigue and headache, each reported in 4/23 (17.4%) patients, followed by irritability which was reported in 3/23 (13.0%) patients.

There were no clinically meaningful trends in mean changes from baseline for any clinical laboratory variable or any other observations related to safety.

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

Population pharmacokinetics modeling of the TEV-50717 active metabolites α-HTBZ and β-HTBZ has been performed throughout the clinical development program. Based on sequential pharmacokinetics sampling data obtained in healthy volunteers in the Phase 1 program, a structural population pharmacokinetics model was developed to guide dose selection for HD patients with chorea (Study 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 pharmacokinetics 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 B). 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 indicated that exposure to total (α+β)-HTBZ is influenced by body weight, and a reduction in dose for pediatric and adolescent patients weighing <40 kg is necessary in order to provide comparable exposure to doses up to 48 mg per day in adults, a level previously demonstrated to be safe and well tolerated in treated patients with chorea associated with HD.

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

1.4. Known and Potential Benefits and Risks to Patients

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

1.5. Selection of Investigational Medicinal Product and Doses

A detailed description of IMP administration is presented in Section 5.1.

1.5.1. Justification for Dose of Active Drug

The dose ranges to be evaluated in this study, based on body weight and CYP2D6 impairment status on day 1, were selected on the basis of the safety, preliminary efficacy, and population pharmacokinetics data generated from Study SD-809-C-17 (Table 2). In Study SD-809-C-17, TEV-50717 up to 18 mg twice daily (bid [36 mg/day]) was well tolerated and demonstrated a clinically meaningful benefit in adolescents with TS-associated tics. The dosages proposed in the present study aim to match the exposure achieved in adults receiving up to 48 mg/day (24 mg bid), a level previously demonstrated to be efficacious, safe, and well tolerated in patients with HD-associated chorea.

Similar to one of the parent studies (TV50717-CNS-30046), IMP will be titrated based on investigator, patient, and parent/guardian assessments of tic reduction and adverse events. This dosing strategy is practical in a clinical study setting and affords sufficient time between dose steps for safety and efficacy to be assessed. It is also consistent with the clinical application of tetrabenazine, another VMAT2 inhibitor with accepted efficacy in this population.

1.6. Compliance Statement

This study will be conducted in full accordance with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) 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 GCP in the conduct of clinical studies 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 IMP as described in the IB.

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.

1.7. Study Population and Justification

The population to be studied includes male and female patients who have previously completed participation in Study SD-809-C-17, Study TV50717-CNS-30046, or Study TV50717-CNS-30060. Per selection criteria in these previous studies, these patients were children and adolescents, 6 through 16 years of age, with TS with tics troublesome enough to cause distress or impairment based on the assessment of the patient, parent/guardian, and investigator.

1.8. Location and Study Duration

This study is planned to be conducted globally (per Study SD-809-C-17, Study TV50717-CNS-30046, and Study TV50717-CNS-30060) at approximately 120 centers. It is expected to start in May 2018 and conclude in January 2021, with a duration of approximately 32 months.

2. PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1. Purpose of the Study

This is an open-label Phase 3 study with a 2-week, double-blind, placebo-controlled, randomized drug withdrawal period to evaluate the safety and efficacy of TEV-50717 tablets in patients who have previously completed participation in Study SD-809-C-17, Study TV50717-CNS-30046, or Study TV50717-CNS-30060.

2.2. Study Objectives

2.2.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of long-term therapy with TEV-50717.

2.2.2. Secondary Objectives

The secondary objectives of this study are as follows:

- to evaluate the efficacy of long-term therapy with TEV-50717 in reducing the severity of TS tics
- to confirm long-term maintenance of effect by means of a double-blind, placebo-controlled, randomized drug withdrawal period after 28 weeks of open-label treatment

2.3. Study Endpoints

2.3.1. Safety Endpoints

The following safety endpoints will be assessed in Part A:

- incidence of adverse events
- observed values and changes from day 1 in vital signs
- observed values and changes from day 1 in the Children's Depression Inventory, Second Edition, Parent and Self-Report Profiles (CDI-2)
- observed values in the Children's Columbia-Suicide Severity Rating Scale (C-SSRS)
- observed values in electrocardiogram (ECG) parameters and shifts from parent study baseline (for patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or from day 1 (for patient[s] rolling over from Study SD-809-C-17) for clinically significant abnormal findings
- observed values and changes from day 1 in clinical laboratory parameters (hematology, serum chemistry, and urinalysis)

The following safety endpoint will be assessed in Part B:

- incidence of adverse events

In addition to routine monitoring of adverse events, clinical laboratory parameters, 12-lead ECGs, and safety scales, an Independent Data Monitoring Committee (IDMC) will monitor safety during the conduct of the study.

2.3.2. Efficacy Endpoints

The following efficacy endpoints will be assessed in Part A:

- change in the YGTSS TTS from day 1 to each visit in which the scale is administered
- change in the TS-CGI score from day 1 to each visit in which the scale is administered
- change in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) score from day 1 to each visit in which the scale is administered
- change in the Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life (C&A-GTS-QOL) activities of daily living (ADL) subscale score from day 1 to each visit in which the scale is administered

The following efficacy endpoint will be assessed in Part B:

- change in the TTS of the YGTSS from week 28 to week 30, with the primary analyses and sensitivity testing done as described in Section 9.5.3.1

2.3.3. Exploratory Endpoints

The following exploratory endpoints will be assessed in Part A:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]

3. STUDY DESIGN

3.1. General Design and Study Schematic Diagram

This is a 56-week, open-label, single-arm study that includes a 2-week, double-blind, placebo-controlled, randomized drug withdrawal period followed by a 3-week blinded re-titration period to evaluate the safety of TEV-50717 in children and adolescents with tics associated with TS after they have successfully completed any of the parent studies (SD-809-C-17 [Phase 1b], TV50717-CNS-30046 [Phase 2/3], or TV50717-CNS-30060 [Phase 3]). Patients rolling over from Study SD-809-C-17 will need to undergo all day 1 assessments. For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, the week 13 visit (Study TV50717-CNS-30046) or the week 9 visit (Study TV50717-CNS-30060) will be the day 1 visit for Study TV50717-CNS-30047. If the patient does not wish to enroll in Study TV50717-CNS-30047 at that visit, they can enroll up to 1 week following the week 13 or week 9 visits, respectively.

For patients rolling over from Study SD-809-C-17, this study will consist of a 4-week screening period (up to 31 days) and up to 54 weeks of treatment. All participating patients are expected to participate in this study for its entire duration, which is a minimum of 56 weeks. Patients will have a follow-up telephone contact to evaluate safety 1 week after the end of the washout period (2 weeks after their last dose of IMP). The end of study is defined as the date of the week 56 visit of the last participant.

Informed consent/assent, depending on the child's age, as appropriate, will be obtained before any study procedures are performed. For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, informed consent/assent, as appropriate, may be obtained prior to the day 1 visit, up to 4 weeks in advance of open-label study participation. Any patient that turns 18 years of age during the course of Study TV50717-CNS-30047 will need to be re-consented as an adult.

Patients who have successfully completed any of the parent studies may be eligible to enroll in the current study after they complete a 1-week washout period and the final evaluation (week 13 in Study TV50717-CNS-30046 or week 9 in Study TV50717-CNS-30060) in the parent study. To reduce patient burden, after obtaining informed consent/assent, depending on the child's age, as appropriate, some data collected in Study TV50717-CNS-30046 or Study TV50717-CNS-30060 will be used to provide corresponding day 1 data in the current open-label study (see Table 1).

All screening procedures will be performed for patients rolling over from Study SD-809-C-17, as they will have been off IMP for several months at the time of enrollment into the current study. Site-administered scales include the YGTSS, [redacted], Mini International Neuropsychiatric Interview for Children and Adolescents (MINI Kid, version 6.0), and the C-SSRS and self-administered scales include the TS-PGII, [redacted], CDI-2, and C&A-GTS-QOL. For the YGTSS, input from the caregiver/adult is required. For [redacted] the TS-PGII [redacted], input from the caregiver/adult is permitted. For all other scales, children 13 years of age and under, interviews may be performed separately or jointly with the caregiver/adult as appropriate or as 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 assessments and procedures performed during each study visit are detailed in Table 1 and Section 3.13.

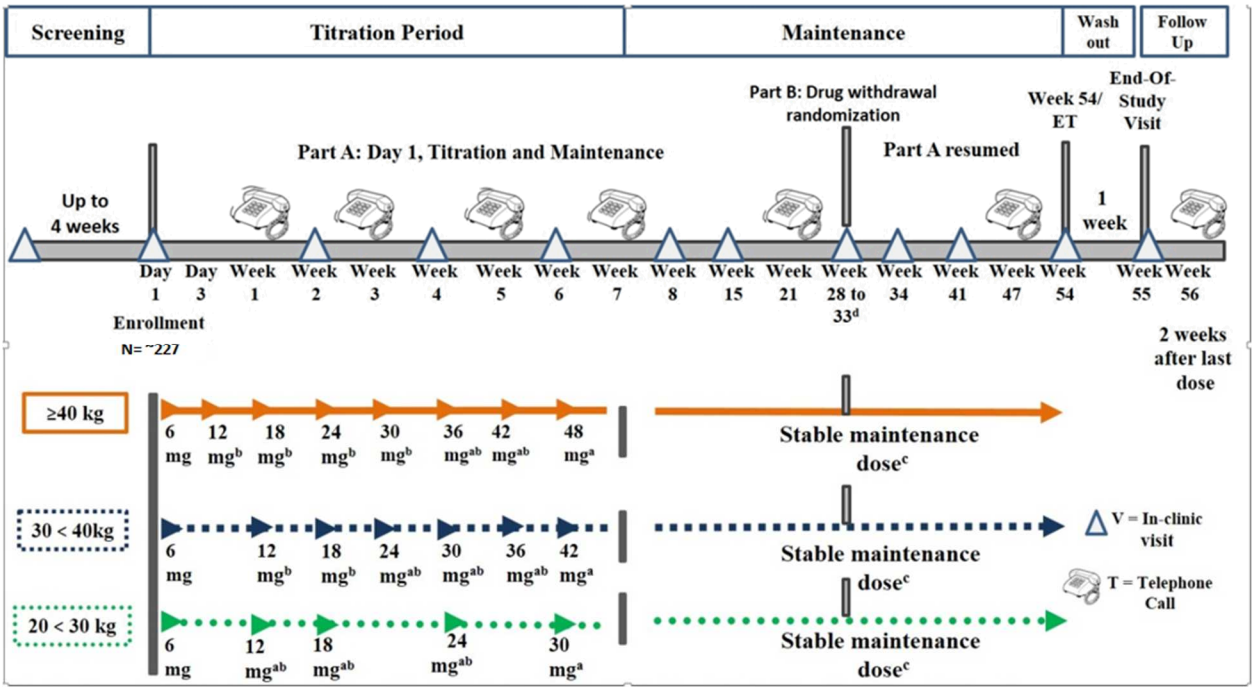
Up to approximately 227 patients are planned to be enrolled (approximately 1 patient is estimated to enroll from the Phase 1b Study SD-809-C-17, up to approximately 99 patients are estimated to enroll from the Phase 2/3 Study TV50717-CNS-30046, and up to approximately 127 patients are estimated to enroll from the Phase 3 Study TV50717-CNS-30060).

When approximately 100 patients have completed the 28-week clinic visit, an interim analysis, including data from day 1 and up to week 28 visit only, will be conducted to provide descriptive, long-term safety and efficacy data to be used in regulatory submissions. To maintain data integrity of Study TV50717-CNS-30047, only a limited number of personnel who do not have contact with the sites will have access to this interim data in preparation for the regulatory filing. As no decisions regarding conduct of the study will be made based on the descriptive interim analysis, no alpha will be spent.

Patients who complete all scheduled visits will have procedures and assessments performed at the final visit (week 54). Patients who withdraw from the study before completing the week 54 evaluation period will have the week 54 procedures and assessments performed at their final visit, and a follow-up telephone contact for safety evaluation 2 weeks after their last dose of IMP.

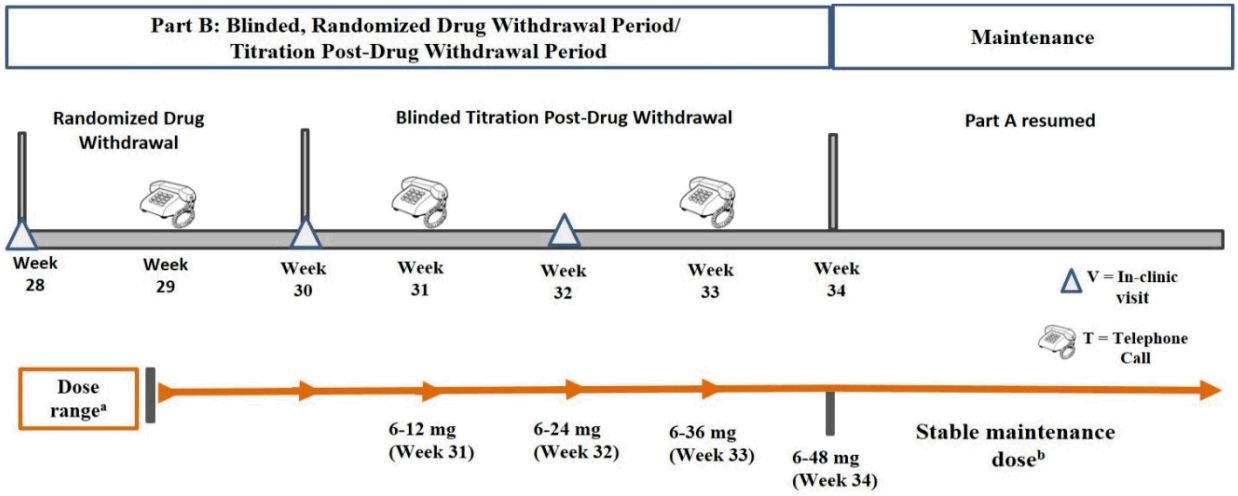
The study schematic diagram is presented in Figure 1. An additional diagram that details the blinded, randomized drug withdrawal/titration post-drug withdrawal period (Part B of the study) is presented in Figure 2.

Figure 1: Overall Study Schematic Diagram



[a] Maximum total daily dose for patients ≥40 kg is 48 mg/day (24 mg bid), 30 to <40 kg is 42 mg/day (21 mg bid), and 20 to <30 kg is 30 mg/day (15 mg bid). For those considered CYP2D6 impaired, maximum daily dose for patients ≥40 kg is 36 mg/day, 30 to <40 kg is 24 mg/day, and 20 to <30 kg is 18 mg/day (Table 2).
[b] If a stable dose is reached before the indicated time, the patient should continue taking that dose for the remainder of the titration period and throughout the maintenance therapy dosing.
[c] Dose adjustments may be made, as necessary, except for Part B.
[d] See Figure 2.
Note: Screening visit is required only for patients rolling over from Study SD-809-C-17.
bid=twice daily; CYP=cytochrome P450; ET=early termination visit.

Figure 2: Study Schematic Diagram (Part B)



[a] Ranges account for different dosing schedules for patients based on their previously established maintenance dose in Part A. Re-titration only applies to patients who were randomized to placebo during the withdrawal period.
[b] Dose adjustments may be made, as necessary.

In the study period descriptions below, "week X" refers to the end of that week, which coincides with the study visit, unless stated otherwise. Some dose changes will occur at the start of a week rather than at the end of a week and will be indicated as such.

3.1.1. Screening Period (up to 31 days)

For patients from Study SD-809-C-17:

Screening period (up to 31 days): All screening procedures will be performed for patients rolling over from Study SD-809-C-17, as they will have been off IMP for several months at the time of enrollment into this study (TV50717-CNS-30047).

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, assessment of vital signs, laboratory testing, and 12-lead ECG, along with rating scales to assess comorbid TS symptoms and behavioral status.

At the discretion of the investigator, the screening visit may be divided into 2 visits if the visit length is deemed to be too burdensome for the patient. Patients may be rescreened 1 time if there is a change in the patient's medical background, a modification of study entry criteria, or other relevant change. (Note: Details of a patient's rescreening must be approved and documented by the medical monitor and/or Clinical Surveillance and Training [CST] team.)

For patients from Study TV50717-CNS-30046 or Study TV50717-CNS-30060:

The screening evaluation for this open label study occurs at the end of the treatment period in the double-blind study. To reduce patient burden and not collect duplicate information, after obtaining informed consent/assent, depending on the child's age, as appropriate, relevant data collected in Study TV50717-CNS-30046 or Study TV50717-CNS-30060 will be used to provide corresponding data in this open-label study (see Table 1).

Part A:

3.1.2. Day 1 Visit (All Patients)

For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, the week 13 visit (Study TV50717-CNS-30046) or the week 9 visit (Study TV50717-CNS-30060) will be the day 1 visit for Study TV50717-CNS-30047. Patients rolling over from Study SD-809-C-17 will need to undergo all day 1 assessments. Day 1 assessments for Study TV50717-CNS-30047 that are identical to Study TV50717-CNS-30046 week 13 or Study TV50717-CNS-30060 week 9 assessments **do not** need to be repeated. Additionally, Study TV50717-CNS-30047 required evaluations will be completed at Study TV50717-CNS-30046 week 13 visit or Study TV50717-CNS-30060 week 9 visit (see Table 1). For all patients, the day 1 visit will occur on or as close as possible to the week 13 or week 9 visit from Study TV50717-CNS-30046 and Study TV50717-CNS-30060, respectively, but not >7 days beyond those respective visits.

For patients with clinically significant laboratory abnormalities at week 12 in Study TV50717-CNS-30046 or at week 8 in Study TV50717-CNS-30060, Study TV50717-CNS-30046 week 13 value(s) or Study TV50717-CNS-30060 week 9 value(s) will serve as day 1 laboratory values in this study. Rollover for such patients must be approved and documented by the medical monitor and may be delayed.

3.1.3. Titration Period (7 Weeks)

As patients from Study SD-809-C-17 will have been off IMP for several months at the time of enrollment, and since patients from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 will have discontinued IMP (TEV-50717 or placebo) for at least 1 week at completion of the parent study, all patients will undergo TEV-50717 dose titration in this study. Patients will receive 6 mg of TEV-50717 with food on the evening of day 1. Tablets should be taken with food (eg, a snack) and should not be taken on an empty stomach. The titration scheme and maximum dose will be determined by body weight and CYP2D6 impairment status from the parent study. 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 of the parent study. Patients who are CYP2D6 impaired will have a dose cap in the open-label study, as shown in Table 2. Patients and their caregiver/adult will interact weekly with the clinical research staff, either by telephone contact or in-clinic visits from week 1

through week 7 of the titration period, in order to evaluate safety and establish a dose of TEV-50717 that optimally reduces tics and is well tolerated (optimal dose). Safety evaluations during the titration period include assessment of vital signs, monitoring for adverse events and concomitant medications, 12-lead ECGs, and rating scales for depression and suicidality.

In-person (in-clinic) study visits will be scheduled at weeks 2, 4, and 6, and telephone contacts will be scheduled for weeks 1, 3, 5, and 7 in order to assess adverse events and tic severity.

The dose of the IMP should be increased on a weekly basis until one of the following occurs:

- The investigator determines that there has been a clinically meaningful reduction in tics.
- The patient experiences a protocol-defined "clinically significant" adverse event (defined as an adverse event that is related to IMP and is either moderate or severe in intensity or meets the criteria for a serious adverse event).
- The maximum allowable dose is reached, based on the patient's weight and use of strong CYP2D6 impairment status.

If a stable dose is reached before the week 7 telephone call, the patient should continue on that dose (ie, the dose should not be increased further) for the remainder of the titration period. If a patient experiences depression, suicidal ideation or behavior, anxiety, akathisia, parkinsonism, somnolence, any other adverse event that interferes with daily activity, or adverse event that is related to IMP, the investigator will determine if a dose reduction or suspension is necessary. If the determination is made during a telephone contact that a patient requires a dose reduction or suspension, an unscheduled in-clinic visit should be conducted as soon as practicable thereafter.

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 the information from rating scales.

3.1.4. Maintenance Period

At the end of the titration period, the patient's initial dose for the maintenance period will be established. Dose adjustments of TEV-50717 (upward or downward) may be made during the maintenance period, if necessary, but not more often than every 5 days and only in increments of 6 mg. As during titration, dose adjustments should be made based on all available information. After dose adjustment, if the maintenance dose for a patient is 6 mg, the dose should be taken once a day in the morning with food (other dose levels are taken twice daily).

During the maintenance period, in-person (in-clinic) study visits will be scheduled at weeks 8, 15, 34, 41, and 54 for assessments of safety and efficacy and telephone contacts will be scheduled for weeks 21 and 47 in order to assess adverse events and tic severity. The randomized drug withdrawal and re-titration period (Part B) will occur from the end of week 28 through the end of week 33, and then the Part A maintenance period will resume, along with the ability to make dose adjustments as described above. At week 54, patients will undergo a complete evaluation, including physical and neurological examination, safety laboratory testing, 12-lead ECG, CDI-2, and C-SSRS assessments, as well as the YGTSS, TS-CGI, [redacted] TS-PGII, [redacted], and C&A-GTS-QOL.

3.1.5. Washout Period and Follow-up

All patients will discontinue IMP at the week 54 visit and will return 1 week later (week 55) for evaluation of safety and tic reduction. Patients will have a follow-up telephone contact for safety evaluation 1 week after the end of the washout period (2 weeks after their last dose of IMP) (week 56).

See Table 1 for study procedures and assessments.

See Figure 1 and Figure 2 for study schema.

Part B:

3.1.6. Blinded, Randomized Drug Withdrawal Period and Titration Post-Drug Withdrawal Period (5 Weeks)

At the week 28 visit, the patients will be randomized 2:1 to their current dose of TEV-50717 or placebo in order to check for return of symptoms. Because IMP is dispensed as enough doses for 2 weeks (current dose level and next dose level), the week 28 visit (Day 196) is considered the first day of the randomized withdrawal period, although the patient will begin taking blinded IMP on Day 197. Patients will have a follow-up telephone contact for safety evaluation 1 week after the start of the randomized drug withdrawal period. At week 30, safety and efficacy will be assessed. At the week 30 visit, patients who receive TEV-50717 during the randomized drug withdrawal period will continue at the same dose in a blinded manner from the start of week 31 to the start of week 34. Any patient who was randomized to placebo during this 2-week period will undergo blinded re-titration. Patients will have a follow-up telephone contact for safety evaluation at weeks 31 and 33.

Titration Post-Drug Withdrawal (Weeks 31, 32, and 33)

Any patient who was randomized to placebo between the week 28 and week 30 visits will undergo re-titration to their previously established maintenance dose over the 3 weeks of treatment following the randomized drug withdrawal period (start of week 31 to the start of week 34 [Days 211 through 232]). The titration scheme and maximum dose will be determined based on the previously established maintenance dose according to Table 3. The dose of IMP for each patient who underwent 2 weeks of placebo will be titrated back to the maintenance dose that was used by the patient up to week 28 followed by continued maintenance therapy at that dose.

All patients should be back at their maintenance dose on or before the start of week 34 and return to open-label treatment for the remainder of the study (note that, because IMP is dispensed for 2-week periods, patients will use blinded bottles through the end of week 34; however, all patients will be known to be on active treatment at the start of week 34).

3.2. Justification for Study Design and Placebo-Controlled Randomized Drug Withdrawal

At the present time, effective treatment options for TS are suboptimal and limited. As a chronic condition impairing major life activities during childhood, such as occupational, social, and educational activities, TS presents an area of significant unmet medical need in the pediatric population.

Preliminary efficacy and safety data for TEV-50717 as a treatment for TS have been generated in an open-label, Phase 1b pilot study (SD-809-C-17) in patients. Results of Study SD-809-C-17 support further development of TEV-50717 as a treatment of TS.

Two parent studies, TV50717-CNS-30046 and TV50717-CNS-30060, are underway. They are randomized, double-blind, placebo-controlled studies of the efficacy and safety of TEV-50717 on the tics in patients with TS. This is an open-label, single-arm study that includes a 2-week, double-blind, placebo-controlled, randomized drug withdrawal period in which patients with TS may be eligible to participate after successful completion of any of the parent studies (SD-809-C-17 [Phase 1b], TV50717-CNS-30046 [Phase 2/3], or TV50717-CNS-30060 [Phase 3]). Patients who have successfully completed a parent study may be eligible to enroll in this study after they complete a 1-week washout period and the final evaluation in the parent study. For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, the week 13 visit (Study TV50717-CNS-30046) or the week 9 visit (Study TV50717-CNS-30060) will be the day 1 visit for Study TV50717-CNS-30047. If the patient does not wish to enroll in Study TV50717-CNS-30047 at that visit, they can enroll up to 1 week following the week 13 or week 9 visits, respectively. The end of study is defined as the date of the week 56 visit of the last participant.

Inclusion and exclusion criteria have been designed to minimize the risk to patients while maintaining a consistent level of TS symptoms to allow detection and analysis of a drug effect. Exclusion criteria were designed to exclude patients with concomitant conditions that may increase their risk to drug treatment.

The open-label study design (ie, no placebo or comparator) was selected to allow further evaluation and review long-term safety of TEV-50717 in this patient population. Patients will receive twice daily dosing for up to 54 weeks (those on the 6-mg dose will receive once-daily dosing), with an initial 7-week titration period to allow for optimal dose selection. At the week 28 visit, patients will begin a 2-week blinded, randomized drug withdrawal period. The randomized drug withdrawal period will rigorously assess the long-term maintenance of effect. Patients will be randomized to their current dose of TEV-50717 or placebo for 2 weeks. After completing the 2 weeks, patients will continue their same dose of TEV-50717 in a blinded manner or will be re-titrated (patients receiving placebo only) in a blinded manner for 3 weeks. At week 34, all patients will resume their maintenance dose. This is a classic ABA study design (ie, drug, placebo, drug) that allows for a more rigorous test of the intervention. In the traditional AB design, changes in symptoms (particularly in a long trial) could be attributed to other factors (eg, life changes, societal issues, and regression to the mean); however, an acute change demonstrated only in a placebo group among subjects that have been maintained for several months would reduce the likelihood of any other explanations for changes in symptoms.

3.3. Safety Measures and Time Points

A description of the safety measures is provided in Section 7.

Part A:

- adverse events and concomitant medications: from the signing of the informed consent/assent, depending on the child's age, as appropriate, through follow-up, inclusive of all visits and telephone contacts

- physical examination: screening (only for patients who completed Study SD-809-C-17; data from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 should be used for the remaining patients) and week 54
- neurological examination: screening (only for patients who completed Study SD-809-C-17; data from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 should be used for the remaining patients) and week 54
- vital signs, height, and weight: screening (only for patients who completed Study SD-809-C-17; data from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 should be used for the remaining patients); day 1; and weeks 2, 4, 6, 8, 15, 34, 41, 54, and 55
  - Note: orthostatic blood pressure (BP) and pulse on day 1 and weeks 4, 8, and 54
- MINI Kid: screening (only for patients who completed Study SD-809-C-17)
- Children's C-SSRS:
  - Baseline/screening scale: screening (only for patients who completed Study SD-809-C-17)
  - Since Last Visit (SLV) scale: day 1 (only for patients who completed Study SD-809-C-17) and weeks 2, 4, 8, 15, 34, 41, 54, and 55
- CDI-2 (Parent and Self-Report Profiles): screening and day 1 (ie, only for patients who completed Study SD-809-C-17) and weeks 2, 4, 8, 15, 34, 41, 54, and 55
- 12-lead ECG: screening (ie, only for patients who completed Study SD-809-C-17); day 1; and weeks 4, 8, and 54
- clinical laboratory tests (serum chemistry, hematology, and urinalysis): screening (ie, only for patients who completed Study SD-809-C-17; data from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 should be used for the remaining patients); day 1; and weeks 8 and 54
- pregnancy testing (beta-human chorionic gonadotropin [β-HCG]): screening (ie, only for patients who completed Study SD-809-C-17); day 1 and weeks 4, 8, 15, 34, and 54 (serum tests at screening and week 54 and urine tests at other visits)
- drug screen: screening (ie, only for patients who completed Study SD-809-C-17)

Part B:

- adverse events and concomitant medications: from the signing of the informed consent/assent, depending on the child's age, as appropriate, form through follow-up, inclusive of all visits and telephone contacts
- physical examination: weeks 28 and 30
- vital signs, height, and weight: weeks 28, 30, and 32
  - Note: orthostatic BP and pulse at week 28
- Children's C-SSRS:

  - SLV version: weeks 28 and 30
- CDI-2 (Parent and Self-report Profiles): weeks 28 and 30
- 12-lead ECG: week 28
- clinical laboratory tests (serum chemistry, hematology, and urinalysis): week 28
- pregnancy testing: week 28

3.4. Efficacy Measures and Time Points

A description of the efficacy measures is provided in Section 6.

3.4.1. Efficacy Measures and Time Points

Part A and Part B:

- YGTSS: Screening (only for patients who completed Study SD-809-C-17); day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060); and weeks 2, 4, 8, 15, 28, 30, 34, 41, 54, and 55
- TS-CGI: Day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060) and weeks 4, 8, 15, 28, 34, 41, 54, and 55
- TS-PGII: Day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060) and weeks 4, 8, 15, 28, 34, 41, 54, and 55
- C&A-GTS-QOL (ADL subscale): Day 1 and weeks 6, 28, 34, and 54

3.4.2. Exploratory Measures and Time Points

Part A and Part B:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

3.5. Randomization and Blinding

This is an open-label study that includes a 2-week, double-blind, placebo-controlled, randomized drug withdrawal period followed by a 3-week blinded re-titration period. At the start of the randomized drug withdrawal period (end of week 28), the patients will be randomized 2:1 to the

current dose or placebo in order to check for return of symptoms. During the entire 5-week period, patients randomized to TEV-50717 will stay on their established maintenance dose of blinded active IMP. Patients who receive placebo during the randomized drug withdrawal period will undergo blinded re-titration post-drug withdrawal. All patients will return to open-label dosing at week 34 (note that, because IMP is dispensed for 2-week periods, patients will use blinded bottles through the end of week 34; however, all patients will be known to be on active treatment at the start of week 34).

During the blinded drug withdrawal and re-titration period, patients and investigators will remain blinded to treatment assignment. In addition, the sponsor's and development partner's clinical personnel and all vendors (with the exception of the Interactive Response Technology [IRT] vendor and the IMP packaging 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.

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

The randomized treatment and medication allocation will be assigned to the relevant treatment groups through a qualified service provider (ie, via IRT). The 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 during the blinded drug withdrawal and re-titration period.

3.6. Maintenance of Randomization and Blinding

3.6.1. 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 (SOP).

3.6.2. Blinding and Unblinding

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. The patient's randomized treatment will be made available to the investigator(s) via the IRT system. If possible, the medical monitor should be notified of the event before breaking of the code. If this is not possible, the medical monitor should be notified immediately afterward, and the patient's randomized treatment should not be communicated to the medical monitor. Breaking of the randomization code can always be performed by the investigational center without prior approval by the medical monitor.

When a blind is broken, the patient will be withdrawn from the study, and the event will be recorded on the case report form (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 studies with blinding, 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 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.

3.7. Independent Data Monitoring Committee

An IDMC will review accumulating safety data on a regular basis to ensure the continuing safety of the study patients and to review any 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 and development partner may be present, and information is provided and discussed in a blinded manner. 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.

3.8. Investigational Medicinal Product and Placebo Used in the Study

The IMP is a matrix formulation and is designed as a gastro-erosional tablet to be administered with food 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.

During the open-label period, TEV-50717 tablets are available in the following dose strengths: 6, 9, and 12 mg. Each dose strength will have a marking of SD 6, SD 9, and SD 12 corresponding

to the dose strength and a distinct color: 6 mg – purple, 9 mg – blue, and 12 mg – beige. The IMP will be supplied in 20- or 60-count tablets per dose strength per bottle.

Each bottle will contain a sufficient supply of drug until the next specified visit/telephone contact, plus overage to account for potential delays in study visits.

A more detailed description of administration procedures is given in Section 5.1.

During the randomized drug withdrawal and re-titration periods, 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 20-count bottles.

Patients who receive TEV-50717 during the randomized drug withdrawal period will remain on their maintenance dose of blinded active IMP from the start of week 31 to the start of week 34; those assigned to placebo during the randomized drug withdrawal period will undergo blinded re-titration from the start of week 31 to the start of week 34 back to their previously established maintenance dose from the end of week 28. Note that, because IMP is dispensed for 2-week periods, patients will use blinded bottles through the end of week 34; however, all patients will be known to be on active treatment at the start of week 34.

3.9. Drug Supply and Accountability

3.9.1. Drug Storage and Security

The IMP (TEV-50717) 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 to 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.

3.9.2. Drug 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 IMP will be disposed of, as agreed with the sponsor/development partner.

3.10. Duration of Patient Participation and Justification

For patients rolling over from Study SD-809-C-17, this study will consist of a 4-week screening period (up to 31 days) and up to 54 weeks of treatment. All participating patients are expected to participate in this study for its entire duration, which is a minimum of 56 weeks (for those rolling over from Study SD-809-C-17, this can be up to 60 weeks). Patients will have a follow-up telephone contact to evaluate safety 1 week after the end of the washout period (2 weeks after their last dose of IMP).

See Section 12.4 for the definition of the end of the study.

3.11. Stopping Rules and Discontinuation Criteria

There are no formal rules for early termination of this study. During the conduct of the study, serious adverse events will be reviewed (see Section 7.1.5) as they are reported from the investigational center to identify safety concerns. The study may be terminated by the sponsor at any time.

A patient may discontinue participation in the study at any time for any reason (eg, lack of efficacy, consent withdrawn, and adverse event); every effort should be undertaken to find out the reason for discontinuation. The investigator and/or sponsor can withdraw a patient from the study at any time for any reason (eg, protocol violation or deviation as defined in Section 11.1.2, noncompliance, or adverse event).

3.12. Source Data Recorded on the Case Report Form

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

If patient data are processed from other vendors (eg, clinical laboratory, central ECG, diary data), the results will be sent to the investigational center, where they will be retained but not entered into the CRF. These data may also be sent electronically to the sponsor (or organization performing data management) for direct use with the clinical database (see Section 13.1). All clinical patient data from other vendors will be available to the investigator.

The CRFs are filed in the sponsor's central file after study completion.

3.13. Study Procedures and Assessments

Study procedures and assessments with their time points are presented in Table 1. During a visit, study procedures and assessments should be performed in the order specified in the study manual.

Detailed by-visit information is provided in the sections following the table. Detailed descriptions of each assessment are provided in Section 6 (efficacy assessments) and Section 7 (safety assessments).

Table 1: Study Procedures and Assessments

			Part A										
	Screening[a]			Titration							Maintenance		
Study week[b]	Parent study		Day 1[c]	1 (Day 7)	2 (Day 14)	3 (Day 21)	4 (Day 28)	5 (Day 35)	6 (Day 42)	7 (Day 49)	8 (Day 56)	15 (Day 105)	21 (Day 147)
	C-17	046 or 060											
Visit window (days)	**<31 days**	**<31 days**	**0**	**±3 days**									
In-clinic visit	X[d]		X		X		X		X		X	X	
Telephone contact				X		X		X		X			X
Evaluate/Adjust IMP				X[e]	X	X[e]	X	X[e]	X	X			X
Informed consent/assent	X	X[f]											
Eligibility criteria	X		X										
Medical history and psychiatric history	X	[g]											
Demographics	X	[g]											
Vital signs and weight[h]	X		X[i]		X		X[i]		X		X[i]	X	
Physical examination	X	[j]											
Neurological examination	X	[j]											
Height	X	[j]	X		X		X		X		X	X	
12-lead ECG[k]	X		X				X				X		
Chemistry/Hematology/Urinalysis	X	[j]	X[j,l]								X		
Urine drug screen	X												
CYP2D6 genotype	[m]	[m]											
β-HCG test[n]	X		X				X				X	X	
MINI Kid[o, p]	X	[g]											
CDI-2 (Parent and Self-Report)[q]	X		X[r]		X		X				X	X	
Children's C-SSRS (Baseline/Screen)[p]	X												
Children's C-SSRS (Since Last Visit) [p]			X[r]		X		X				X	X	

			Part A										
	Screening[a]			Titration							Maintenance		
Study week[b]	Parent study		Day 1[c]	1 (Day 7)	2 (Day 14)	3 (Day 21)	4 (Day 28)	5 (Day 35)	6 (Day 42)	7 (Day 49)	8 (Day 56)	15 (Day 105)	21 (Day 147)
	C-17	046 or 060											
Visit window (days)	**<31 days**	**<31 days**	**0**	**±3 days**									
YGTSS[s, t]	X		X[r]		X[u]		X				X[u]	X[u]	
TS-CGI[t]			X[r]				X				X	X	
TS-PGII[t]			X[r]				X				X	X	
[redacted][t]			X[r]				X				X	X	
[redacted]			X[r]				X				X	X	
[redacted][p]			X[r, v]						X[w]				
C&A-GTS-QOL (including VAS)[p]			X						X				
Contact IRT and dispense IMP and patient diary			X[x]		X[x]		X[x]		X[x]		X[y]	X[y]	
Collect IMP					X		X		X		X	X	
Assess IMP accountability/compliance/supply				X[z]	X	X[z]	X	X[z]	X	X[z]	X	X	X[z]
Assess adverse events	X		X[r]	X	X	X	X	X	X	X	X	X	X
Concomitant medications[aa]	X		X[r]	X	X	X	X	X	X	X	X	X	X

[a] **Full screening visit is required for patients who previously completed Study SD-809-C-17.** This visit is not required for patients who completed Study TV50717-CNS-30046 or Study TV50717-CNS-30060.

[b] Assessment to occur at the end of study week (±3 days).

[c] For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, the week 13 visit (Study TV50717-CNS-30046) or the week 9 visit (Study TV50717-CNS-30060) will be the day 1 visit for Study TV50717-CNS-30047, and patients will continue to enter dosing times in the diary through completion of Study TV50717-CNS-30047. Patients rolling over from Study SD-809-C-17 will need to undergo all day 1 assessments. Study TV50717-CNS-30047 day 1 assessments that are identical to Study TV50717-CNS-30046 week 13 or Study TV50717-CNS-30060 week 9 visit assessments do not need to be repeated.

[d] The screening visit may be conducted over 2 separate visits at the discretion of the investigator.

[e] Dose adjustment will be made by the investigator after telephone contact with the patient and caregiver/adult to evaluate tic reduction and adverse events (Table 2).

[f] For patients enrolled from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, informed consent/assent, depending on the child's age, as appropriate, may be obtained up to 4 weeks in advance.

[g] For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, these data will be obtained from the screening visit of the parent study.

[h] Weight must be measured with shoes and outerwear off. Before pulse and BP are measured, the patient must be in a supine or semi erect/seated position and resting for at least 5 minutes (the same position and arm should be used each time vital signs are measured for a given patient).

[i] Orthostatic BP and pulse will be measured after patient is in a standing position for at least 3 minutes.

[j] For patients rolling over from Study TV50717-CNS-30046, these data will be obtained from the week 12 visit of the parent study. For patients rolling over from Study TV50717-CNS-30060, these data will be obtained from the week 8 visit of the parent study.
[k] All ECGs will be performed after at least 5 minutes rest in a supine or semi-supine position.
[l] For patients with clinically significant laboratory abnormalities at week 12 in Study TV50717-CNS-30046, the week 13 value will serve as the day 1 in this study. For patients with clinically significant laboratory abnormalities at week 8 in Study TV50717-CNS-30060, the week 9 value will serve as the day 1 in this study. Rollover for such patients must be approved by the medical monitor and may be delayed.
[m] Genotype data will be obtained from the relevant parent study. For the patients rolling over from Study SD-809-C-17, these data will come from the CSR and will be communicated to the relevant investigator.
[n] For females who are postmenarchal or ≥12 years of age, a urine test will be administered on day 1 and weeks 4, 8, 15, 28, and 34. A serum test will be administered at screening, week 54, and if clinically indicated.
[o] MINI Kid modules to be used are as follows: 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] 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.
[q] Children 6 years of age at day 1 will not complete the Self-Report version; the caregiver/adult will complete the Parent version.
[r] For patients rolling over from Study TV50717-CNS-30046, these data will be obtained from the week 13 visit of the parent study. For patients rolling over from Study TV50717-CNS-30060, these data will be obtained from the week 9 visit of the parent study.
[s] Input from the caregiver/adult is required.
[t] The YGTSS, TS-CGI, TS-PGII, and [redacted] questionnaires should be performed before any blood draws or ECG assessments.
[u] 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.
[v] A complete assessment will be performed for patients who completed Study SD-809-C-17. For patients who completed Study TV50717-CNS-30046 or Study TV50717-CNS-30060, only perform the Severity Ratings of OCD symptoms (Questions 1 through 10); checklist does not need to be performed.
[w] Perform the Severity Ratings of OCD symptoms (Questions 1 through 10) only. Checklist does not need to be performed.
[x] 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. The site will determine titration (ie, starting the next dose) for the patient by telephone. See Table 2 for weight-based dosing titration.
[y] Patients will receive enough doses to cover treatment until the following in-clinic visit.
[z] The site needs to discuss the drug status during the telephone contacts to ensure the patient has adequate tablets, inform the patient if they should titrate (only during the titration period), and remind them to bring completed bottles to the next in-clinic visit.
[aa] 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 medication should be reviewed with the investigator.

ADHD=Attention Deficit Hyperactivity Disorder; β-HCG=beta-human chorionic gonadotropin; BP=blood pressure; CDI-2=Children's Depression Inventory, Second Edition, Parent and Self-Report Profiles; CSR=clinical study report; C-SSRS=Columbia-Suicide Severity Rating Scale; CY-BOCS=Children's Yale-Brown Obsessive-Compulsive Scale; 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; IMP=Investigational Medicinal Product; IRT=Interactive Response Technology; MINI Kid=Mini International Neuropsychiatric Interview For Children and Adolescents (version 6.0); TS-CGI=Tourette Syndrome-Clinical Global Impression; OCD=obsessive-compulsive disorder; TS-PGII=Tourette Syndrome-Patient Global Impression of Impact; TS-PGIS=Tourette Syndrome-Patient Global Impression of Severity; U=unscheduled visit; UA=urinalysis; VAS=visual analog scale; YGTSS=Yale Global Tic Severity Scale.

Table 1 Study Procedures and Assessments (continued)

	Part B: Blinded, randomized drug withdrawal/titration post-drug withdrawal period						Part A resumed						
	Randomized drug withdrawal		Maintenance (resumed) or titration post-drug withdrawal				Maintenance				Follow-up		U
Study week[a]	**28**[b] **(Day 196)**	**29 (Day 203)**	**30 (Day 210)**	**31 (Day 217)**	**32 (Day 224)**	**33 (Day 231)**	**34 (Day 238)**	**41 (Day 287)**	**47 (Day 329)**	**54/ET**[c] **(Day 378)**	**55 (Day 385)**	**56**[d] **(Day 392)**	
Visit window (days)	**±3 days**			**±3 days**		**±3 days**					**±3 days from week 54**		
In-clinic visit	X		X		X		X	X		X	X		X
Telephone contact		X		X		X			X			X	
Evaluate/Adjust IMP			X	X	X	X							X
Informed consent/assent													
Vital signs and weight[e]	X[f]		X		X		X	X		X[f]	X		X
Physical examination	X		X							X			X[g]
Neurological examination										X			X[g]
Height	X		X		X		X	X		X	X		X[g]
12-lead ECG[h]	X									X			X[g]
Chemistry/Hematology/Urinalysis	X									X			X[g]
Urine drug screen													X[g]
β-HCG test[i]	X						X			X			X[g]
CDI-2 (Parent and Self-Report)[j]	X		X				X	X		X	X		X[g]
Children's C-SSRS (Baseline/Screening)[k]													
Children's C-SSRS (Since Last Visit)[k]	X		X				X	X		X	X		X[g]
YGTSS[l, m]	X		X				X	X[n]		X	X[n]		

	Part B: Blinded, randomized drug withdrawal/titration post-drug withdrawal period						Part A resumed						
	Randomized drug withdrawal		Maintenance (resumed) or titration post-drug withdrawal				Maintenance				Follow-up		U
Study week[a]	**28**[b] **(Day 196)**	**29 (Day 203)**	**30 (Day 210)**	**31 (Day 217)**	**32 (Day 224)**	**33 (Day 231)**	**34 (Day 238)**	**41 (Day 287)**	**47 (Day 329)**	**54/ET**[c] **(Day 378)**	**55 (Day 385)**	**56**[d] **(Day 392)**	
Visit window (days)	**±3 days**			**±3 days**			**±3 days**				**±3 days from week 54**		
TS-CGI[m]	X						X	X		X	X		
TS-PGII[m]	X						X	X		X	X		
[redacted]	X						X	X		X	X		
[redacted]	X						X	X		X	X		
[redacted]	X						X			X	X[o]		
C&A-GTS-QOL (including VAS)[k]	X						X			X			
Contact IRT and dispense IMP and patient diary	X[p]		X[p]		X[p]		X[q]	X[q]					X[g,r]
Collect IMP	X		X		X		X	X		X			X[g]
Assess IMP accountability/compliance/supply	X	X[s]	X	X[s]	X	X	X[s]	X	X[s]	X			X[g]
Assess adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[t]	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Assessments to occur at end of study week (±3 days).

[b] At the week 28 visit, the patients will be randomized 2:1 to their current dose of TEV-50717 or placebo in order to check for return of symptoms.

[c] For patients who withdraw prematurely, an early termination visit should be conducted as soon as possible after the last dose of IMP. 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 54 visit.

[d] This visit is a telephone contact for safety evaluation.

[e] Weight must be measured with shoes and outerwear off. Before pulse and BP are measured, the patient must be in a supine or semi erect/seated position and resting for at least 5 minutes (the same position and arm should be used each time vital signs are measured for a given patient).

[f] Orthostatic BP and pulse will be measured after patient is in a standing for at least3 minutes.

[g] Assessment to be completed at investigator's discretion.

[h] All ECGs will be performed after at least 5 minutes rest in a supine or semi-supine position.

[i] For females who are postmenarchal or ≥12 years of age, a urine test will be administered on day 1 and weeks 4, 8, 15, 28, and 34. A serum test will be administered at screening, week 54, and if clinically indicated.
[j] Children 6 years of age at day 1 will not complete the Self-Report version; the caregiver/adult will complete the Parent version.
[k] 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.
[l] Input from the caregiver/adult is required.
[m] The YGTSS, TS-CGI, TS-PGIS, and TS-PGII questionnaires should be performed before any blood draws or ECG assessments.
[n] 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.
[o] Perform the Severity Ratings of OCD symptoms (Questions 1 through 10) only. Checklist does not need to be performed.
[p] IMP will be dispensed in the clinic; patients will receive doses for 2 weeks (current dose level and next dose level, when applicable [week 30 and week 32 visits]) to cover the telephone contacts. Because IMP for Part B is dispensed then, the week 28 visit (Day 196) is considered the first day of the randomized withdrawal period, although the patient will begin taking blinded IMP on Day 197. When applicable, the site will determine titration (ie, starting the next dose) for the patient by telephone. See Table 3 for dosing titration based on the patient's previously established maintenance dose at the end of Part A.
[q] Patients will receive enough doses to cover treatment until the following in-clinic visit.
[r] Contact IRT if IMP assignment or adjustment is required.
[s] The site needs to discuss the drug status during the telephone contacts to ensure the patient has adequate tablets, inform the patient if they should titrate (only during the titration period), and remind them to bring completed bottles to the next in-clinic visit.
[t] 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 medication should be reviewed with the investigator.

ADHD=Attention Deficit Hyperactivity Disorder; β-HCG=beta-human chorionic gonadotropin; BP=blood pressure; 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; IMP=Investigational Medicinal Product; IRT=Interactive Response Technology; MINI Kid=Mini International Neuropsychiatric Interview For Children and Adolescents (version 6.0); TS-CGI=Tourette Syndrome-Clinical Global Impression; OCD=obsessive-compulsive disorder; TS-PGII=Tourette Syndrome-Patient Global Impression of Impact; [redacted] U=unscheduled visit; UA=urinalysis; VAS=visual analog scale; YGTSS=Yale Global Tic Severity Scale.

3.13.1. Procedures for Screening and Enrollment (Visit 1)

Informed consent/assent, depending on the child's age, as appropriate, will be obtained before any study procedures are performed. For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, informed consent/assent, as appropriate, may be obtained prior to the day 1 visit, up to 4 weeks in advance of open-label study participation.

For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, screening data will be obtained from the parent study (see Table 1). Informed consent/assent, as appropriate, must be given before any procedures related solely to Study TV50717-CNS-30047 are performed.

For patients from Study SD-809-C-17:

All screening procedures will be performed for patients rolling over from Study SD-809-C-17, as they will have been off IMP for several months at the time of enrollment into this study (TV50717-CNS-30047). A signed and dated informed consent form 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 before any screening procedures commence, according to national laws and local IEC/IRB requirements. Parents/legally acceptable representatives will acknowledge and agree to the possible use of this information for the study by giving informed consent.

A patient who is screened but not enrolled may be rescreened 1 time if there is a change in the 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 medical monitor and/or CST team.)

The screening visit will take place not more than 31 days before the day 1 visit. The screening visit may be conducted over 2 separate visits at the discretion of the investigator. The following procedures will be performed at the screening visit for patients from Study SD-809-C-17:

- obtain written informed consent (and assent, depending on the child's age, as appropriate) before any other study-related procedures are performed
- conduct clinic visit
- review eligibility (inclusion and exclusion) criteria
- inform patients of study restrictions and compliance requirements
- review medical and psychiatric history
- review demographics information
- measure vital signs (pulse, BP, body temperature, and respiratory rate)
- perform full physical and neurological examinations (including height 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 clinical laboratory tests, including serum chemistry, hematology, and urine analyses
- perform urine drug screen (UDS)
- perform a serum pregnancy (β-HCG) test (only in females who are postmenarchal or ≥12 years of age)
- administer the following questionnaires (Note: For MINI Kid and Children's 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].)
  - CDI-2, Parent and Self-Report Profiles (Note: Children 6 years of age on day 1 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.)
- review medication history and concomitant medications
- inquire about adverse events

3.13.1.1. YGTSS Rater Certification

All investigators and subinvestigators 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 where this scale is administered, especially at day 1 and at weeks 28, 30, and 54/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.

3.13.2. Procedures Before Investigational Medicinal Product Treatment (Day 1)

For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, the week 13 visit (Study TV50717-CNS-30046) or the week 9 visit (Study TV50717-CNS-30060) will be the day 1 visit for Study TV50717-CNS-30047. Patients rolling over from Study SD-809-C-17 will need to undergo all day 1 assessments. Day 1 assessments for

Study TV50717-CNS-30047 that are identical to Study TV50717-CNS-30046 week 13 or Study TV50717-CNS-30060 week 9 visit assessments do not need to be repeated.

The following procedures will be performed at the day 1 visit, as they:

- conduct clinic visit
- review eligibility (inclusion and exclusion) criteria (required for all patients)
- measure vital signs (orthostatic pulse and BP after standing for at least 3 minutes), height, and weight
- perform 12-lead ECG (required for all patients). Note: ECG will be performed after at least 5 minutes rest in a supine or semi-supine position.
- perform clinical laboratory tests, including serum chemistry, hematology, and urine analyses
- perform a urine pregnancy (β-HCG) test (required for all 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, [redacted] and TS-PGII questionnaires should be performed before any blood draws or ECG assessments.):
  - CDI-2, Parent and Self-Report Profiles (Note: Children 6 years of age on day 1 will not complete the Self-Report version; the caregiver/adult will complete the Parent version.)
  - C-SSRS (children's SLV)
  - YGTSS; a complete assessment will be performed for patients who completed Study SD-809-C-17. For patients who completed Study TV50717-CNS-30046 or Study TV50717-CNS-30060, 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 (Input from the caregiver/adult is required).
  - TS-CGI
  - TS-PGII (Input from the caregiver/adult is permitted.)

[redacted]

[redacted]

  - C&A-GTS-QOL (including VAS) (required for all patients)
- dispense IMP (sufficient doses for 2 weeks [current dose level and next dose level] to cover the telephone contacts) and patient diary
- patients will continue to enter dosing times in the diary through completion of the study
- review concomitant medications
- inquire about adverse events

A patient who is not enrolled in the study on the basis of results of day 1 assessments (eg, because inclusion and exclusion criteria were not met or enrollment did not occur within the specified time) may be rescreened if there is a change in the patient's medical background, a modification of study inclusion and exclusion criteria, or other relevant change. (Note: Details of rescreening must be approved and documented by the medical monitor and/or CST team.)

Patients from Study SD-809-C-17 who continue to meet the inclusion and exclusion criteria will be assigned a permanent unique treatment number. This assigned number will be entered in the CRF.

3.13.3. Procedures During Investigational Medicinal Product Treatment

3.13.3.1. Titration Period (Weeks 1 to 7)

3.13.3.1.1. Telephone Contacts (Weeks 1, 3, 5, and 7)

Patients will be contacted by telephone to evaluate tic reduction and adverse events. Dose adjustment will be made by the investigator after telephone contact with the patient and caregiver/adult. The following procedures/assessments will be performed via telephone contact at weeks 1, 3, 5, and 7:

- assess IMP accountability/compliance/supply status to ensure the patient has adequate tablets, inform the patient if they should titrate, and remind them to bring used and unused IMP bottles to the next in-clinic visit
- inquire about adverse events
- review concomitant medications

If a patient experiences an adverse event that is reported during a telephone contact and is probably related to the IMP, he or she will be brought to the clinic for evaluation (see Section 3.13.5). Based on the telephone evaluation, the investigator will determine whether, with the medication already provided, the patient should titrate up, stay at that dose, or reduce the dose. If additional IMP is required, it would be ordered from the distributor and provided to the patient at an unscheduled visit.

3.13.3.1.2. In-Clinic Visits (Weeks 2, 4, and 6)

The following procedures/assessments will be performed at in-clinic visits at weeks 2, 4, and 6:

- conduct clinic visit
- evaluate and, if required, adjust IMP dose (see Section 5.1)
- measure vital signs (pulse, BP, body temperature, and respiratory rate); at week 4, orthostatic BP and pulse should be measured after the patient is in a standing position for at least 3 minutes
- measure height and weight (Note: Weight must be measured with shoes and outerwear off)
- at week 4 only, perform 12-lead ECG (Note: ECG will be performed after at least 5 minutes rest in a supine or semi-supine position)
- perform a urine pregnancy (β-HCG) test (required for all females who are postmenarchal or ≥12 years of age) at week 4
- 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, [redacted], and TS-PGII questionnaires should be performed before any blood draws or ECG assessments.):
  - CDI-2, Parent and Self-Report Profiles at weeks 2 and 4 only (Note: Children 6 years of age on day 1 will not complete the Self-Report version; the caregiver/adult will complete the Parent version.)
  - C-SSRS (children's SLV) at weeks 2 and 4 only
  - YGTSS at weeks 2 and 4 only (Note: at week 2, only perform assessment of "Severity Ratings" of the questionnaire only. Inventory portions [ie, "Motor Tic Symptom Checklist" and "Phonic Tic Symptom Checklist"] do not need to be performed. Input from the caregiver/adult is required.)
  - TS-CGI at week 4
  - TS-PGII at week 4 (Input from the caregiver/adult is permitted.)
  - [redacted]
  - [redacted]
  - [redacted] [Questions 1 through 10] only; checklist does not need to be performed.)
  - C&A-GTS-QOL (including VAS); week 6 only

- dispense IMP (sufficient doses for 2 weeks [current dose level and next dose level]) and patient diary
- collect used and unused IMP bottles
- assess drug accountability/compliance/supply
- inquire about adverse events
- review concomitant medications

3.13.3.2. Maintenance Period (Part A: Weeks 8 to 21 and Weeks 34 to 54/Early Termination) and Part B: Weeks 30 to 33

3.13.3.2.1. In-Clinic Visits (Weeks 8, 15, 30, 32, 34, 41, and 54/Early Termination Visits)

The following procedures/assessments will be performed at weeks 8, 15, 30, 32, 34, 41, and 54/ET:

- conduct clinic visit
- measure vital signs (pulse, BP, body temperature, and respiratory rate); at weeks 8 and 54, orthostatic BP and pulse should be measured after the patient is in a standing position for at least 3 minutes
- measure height and weight (Note: weight must be measured with shoes and outerwear off)
- perform full physical examination (including height) at weeks 30 and 54
- perform neurological examination at week 54
- perform 12-lead ECG (Note: ECG will be performed after at least 5 minutes rest in a supine or semi-supine position.) at weeks 8 and 54
- perform clinical laboratory tests, including serum chemistry, hematology, and urine analyses at weeks 8 and 54
- perform a urine pregnancy (β-HCG) test (required for all females who are postmenarchal or ≥12 years of age) at weeks 8, 15, and 34. A serum test will be administered at week 54.
- 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, [redacted], and TS-PGII questionnaires should be performed before any blood draws or ECG assessments.):
  - CDI-2, Parent and Self-Report Profiles at weeks 8, 15, 30, 34, 41, and 54 (Note: Children 6 years of age on day 1 will not complete the Self-Report version; the caregiver/adult will complete the Parent version.)

  - C-SSRS (children's SLV) at weeks 8, 15, 30, 34, 41, and 54
  - YGTSS at weeks 8, 15, 30, 34, 41, and 54 (at weeks 8, 15, and 41, only 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. Input from the caregiver/adult is required.)
  - TS-CGI at weeks 8, 15, 34, 41, and 54
  - TS-PGII at weeks 8, 15, 34, 41, and 54 (Input from the caregiver/adult is permitted.)
  - [redacted]
  - [redacted]
  - [redacted]
  - C&A-GTS-QOL (including VAS) at weeks 34 and 54
- dispense IMP (sufficient doses to cover treatment until the following in-clinic visit) and patient diary at weeks 8, 15, 30, 32, 34, and 41
- assess drug accountability/compliance/supply
- collect used and unused IMP bottles
- inquire about adverse events
- review concomitant medications

3.13.3.2.2. Telephone Contacts (Weeks 21, 31, 33, and 47)

Patients will be contacted by telephone to evaluate tic reduction and adverse events. The following procedures/assessments will be performed via telephone contact at weeks 21, 31, 33, and 47:

- assess IMP accountability/compliance/supply status to ensure the patient has adequate tablets and remind them to bring used and unused IMP bottles to the next in-clinic visit
- inquire about adverse events
- review concomitant medications

If a patient experiences an adverse event that is reported during a telephone contact and is probably related to the IMP, he or she will be brought to the clinic for evaluation (see Section 3.13.5). Based on the telephone evaluation, the investigator will determine whether, with the medication already provided, the patient should titrate up, stay at that dose, or reduce the dose. If additional IMP is required, it would be ordered from the distributor and provided to the patient at an unscheduled visit.

3.13.3.3. Part B: Blinded, Randomized Drug Withdrawal Period/Titration Post-Drug Withdrawal Period (Weeks 28 to 33)

3.13.3.3.1. In-Clinic Visit (Week 28)

The following procedures/assessments will be performed at week 28:

- conduct clinic visit
- measure vital signs (pulse, BP, body temperature, and respiratory rate); orthostatic BP and pulse should be measured after the patient is in a standing position for at least 3 minutes
- measure height and weight (Note: weight must be measured with shoes and outerwear off)
- perform full physical examination (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 serum chemistry, hematology, and urine analyses
- perform a urine pregnancy (β-HCG) test (required for all 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, [redacted], and TS-PGII questionnaires should be performed before any blood draws or ECG assessments.):
  - CDI-2, Parent and Self-Report Profiles (Note: Children 6 years of age on day 1 will not complete the Self-Report version; the caregiver/adult will complete the Parent version.)
  - C-SSRS (children's SLV)
  - YGTSS (only 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. 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 (including VAS)
- dispense IMP (sufficient doses to cover treatment until the following in-clinic visit) and patient diary
- assess drug accountability/compliance/supply
- collect used and unused IMP bottles
- inquire about adverse events
- review concomitant medications

3.13.3.3.2. In-clinic Visit (Weeks 30 and 32):

- conduct clinic visit
- evaluate IMP
- measure vital signs (pulse, BP, body temperature, and respiratory rate)
- measure height and weight (Note: weight must be measured with shoes and outerwear off)
- perform physical examination (week 30)
- CDI-2, Parent and Self-Report Profiles at week 30 (Note: Children 6 years of age on day 1 will not complete the Self-Report version; the caregiver/adult will complete the Parent version.)
- Children's C-SSRS (SLV version) at week 30
- YGTSS at week 30
- dispense IMP (sufficient doses to cover treatment until the following in-clinic visit) and patient diary
- collect used and unused IMP bottles
- assess IMP accountability/compliance/supply status to ensure that the patient has adequate tablets and remind them to bring used and unused IMP bottles to the next in-clinic visit
- inquire about adverse events
- review concomitant medications

3.13.3.3.3. Telephone Contacts (Weeks 29, 31, and 33)

Patients will be contacted by telephone to evaluate tic reduction and adverse events. Dose adjustment will be made by the investigator after telephone contact with the patient and caregiver/adult. The following procedures/assessments will be performed via telephone contact at weeks 29, 31, and 33:

- assess IMP accountability/compliance/supply status to ensure the patient has adequate tablets, inform the patient if they should titrate, and remind them to bring used and unused IMP bottles to the next in-clinic visit
- inquire about adverse events
- review concomitant medications

3.13.4. Procedures After Investigational Medicinal Product Treatment (Follow-Up)

3.13.4.1. In-Clinic Visit (Week 55)

The following procedures/assessments will be performed at week 55:

- conduct clinic visit
- measure vital signs (pulse, BP, body temperature, and respiratory rate)
- measure height and weight (Note: weight must be measured with shoes and outerwear off)
- administer the following questionnaires (Note: For C-SSRS, [redacted], 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, [redacted], and TS-PGII questionnaires should be performed before any blood draws or ECG assessments.):
  - CDI-2, Parent and Self-Report Profiles (Note: Children 6 years of age on day 1 will not complete the Self-Report version; the caregiver/adult will complete the Parent version.)
  - C-SSRS (children's SLV)
  - YGTSS (only 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. Input from the caregiver/adult is required.)
  - TS-CGI
  - TS-PGII (Input from the caregiver/adult is permitted.)
  - [redacted]
  - [redacted]
  - [redacted]
- inquire about adverse events
- review concomitant medications

3.13.4.2. Telephone Contact (Week 56)

The following procedures/assessments will be performed at week 56:

- inquire about adverse events
- review concomitant medications

Patients who participate in the study in compliance with the protocol for at least 54 weeks of treatment will be considered to have completed the study. See Section 12.4 for the definition of the end of study.

For patients who complete the study or withdraw prematurely, final evaluations will be performed at an end-of-treatment visit or on the last day the patient receives the IMP, or as soon as possible thereafter. Procedures for patients who withdraw prematurely from the study are described in Section 4.4. Patients should be treated with standard of care after termination of the study as appropriate.

Patients with ongoing adverse events will be monitored as described in Section 7.1.2. Otherwise, the follow-up visit will be the last study visit.

3.13.5. Unscheduled Visits

An unscheduled telephone contact may be performed at the discretion of the investigator.

An in-clinic unscheduled visit should be performed if a patient requires a dose adjustment for adverse events reported during a telephone contact. 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 (eg, adverse events, concomitant medications and treatments, and results from procedures or tests).

The following procedures/assessments will be performed at all in-clinic unscheduled visits:

- conduct clinic visit
- evaluate and, if required, adjust IMP dose (see Section 5.1)
- measure vital signs (pulse, BP, body temperature, and respiratory rate)
- measure weight (Note: weight must be measured with shoes and outerwear off)
- inquire about adverse events
- review concomitant medications

The following procedures/assessments may be performed at unscheduled visits per the investigator's discretion:

- measure height
- perform physical examination
- perform neurological examination
- 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 UDS
- perform a urine/serum pregnancy (β-HCG) test (required for all 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 on day 1 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.)
- if applicable, dispense additional IMP
- collect used and unused IMP bottles
- assess drug accountability/compliance/supply

Other procedures may also be performed at the discretion of the investigator.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow patients to be enrolled are not granted by the sponsor/development partner (see Section 11.1.2).

4.1. Patient Inclusion Criteria

Patients who have completed Study TV50717-CNS-30046 or Study TV50717-CNS-30060 have already met the criteria below.

In addition, patients who have completed Study SD-809-C-17 may be included in the study if, during screening, they meet all of the following criteria:

a. Patient is younger than 18 years of age on day 1.
b. Patient weighs at least 44 pounds (20 kg) on day 1.
c. Patient is able to swallow IMP whole.
d. Patient and caregiver/adult are willing to adhere to IMP regimen and comply with all study procedures.
e. Patient is in good general health, as indicated by medical and psychiatric history as well as physical and neurological examination.
f. 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.
g. Patient and caregiver/adult provide written informed consent/assent, depending on the child's age, as appropriate, according to local regulations.
h. Females who are postmenarchal or ≥12 years of age may be included only if they have a negative β-HCG test on day 1 or are sterile. Definitions of sterile are given in Appendix L.
i. 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 L.

4.2. Patient Exclusion Criteria

Patients who have completed Study TV50717-CNS-30046 or Study TV50717-CNS-30060 have already been confirmed to not meet any of the below criteria.

In addition, patients who have completed Study SD-809-C-17 will not be enrolled if, during screening, they meet any of the following criteria:

a. Patient is 18 years of age or older.
b. Patient has a neurologic disorder other than TS that could obscure the evaluation of tics.
c. The patient's predominant movement disorder is stereotypy (coordinated movements that repeat continually and identically) associated with autism spectrum disorder.
d. Patient has a confirmed diagnosis of bipolar disorder, schizophrenia, or another psychotic disorder.

e. Patient has clinically significant depression at screening or day 1.

   Note: Patients receiving antidepressant therapy may be enrolled if on a stable dose for at least 6 weeks before screening.

f. Patient has a history of suicidal intent or related behaviors within 2 years of screening, defined as:

   – 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

g. Patient has a history of a previous actual, interrupted, or aborted suicide attempt.
h. Patient has a first-degree relative who has completed suicide.
i. Patient has clinically significant OCD on day 1 that, in the opinion of the investigator, is the primary cause of impairment.
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 specified exclusionary windows of screening prior to dosing for washout:

   – 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 A, Table 7), 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 and dosing has been stable for at least 2 weeks before screening.

     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.

     Note: Use of benzodiazepines is allowed if the 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 the 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 Tourette syndrome) 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.

l. Patient has an unstable or serious medical illness at screening or day 1.
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 12-lead ECG at screening. Patient requires treatment with

drugs known to prolong the QT interval (see Appendix A Table 8 for a complete list of prohibited QT-prolonging drugs).

n. Patients with a history of torsade de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure.
o. Patient has evidence of hepatic impairment, as indicated by:
   - 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 (Tbil) >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 Tbil.
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 day 1 visit.
r. Patient has a known allergy to any of the components of the IMP.
s. Patient has participated in an investigational drug or device study (with the exception of Study SD-809-C-17 or Study TV50717-CNS-30046 or Study TV50717-CNS-30060) and received IMP/intervention within 30 days.
t. The patient is a pregnant or lactating female, or has 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 Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-V™).
v. Patient has a positive UDS test result or is unable to refrain from substance abuse throughout the study.
w. Patient has a DSM diagnosis based on the MINI Kid modules performed at screening that, in the opinion of the investigator, makes the patient unsuitable for the study (for patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, these data will be obtained from the screening visit of the parent study).

4.3. Justification for Key Inclusion and Exclusion Criteria

Inclusion and exclusion criteria have been designed to minimize the risk to patients while maintaining a consistent level of TS symptoms to allow detection and analysis of a drug effect. Exclusion criteria were designed to exclude patients with concomitant conditions that may increase their risk to drug treatment.

4.4. Withdrawal Criteria and Procedures

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 (ie, the parent study baseline and screening values for patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 or the day 1 and screening values from the current study for patient[s] who completed Study SD-809-C-17) to the average of the 3 post-baseline QTcF values. The IMP must be stopped for any confirmed post-day 1 QTcF value >500 msec or increase from baseline >60 msec.
g. when a blind is broken due to safety concerns (see Section 3.6.2). 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 5.4).

In addition, a patient may be withdrawn from the study as described in Sections 3.11, 3.6, 5.4, 7.1.7, and 3.13.

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 Section 3.13.3.2.1.

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 (Section 3.13.4.2).

5. TREATMENT OF PATIENTS

5.1. Investigational Medicinal Products Administered During the Study

During the open-label period, TEV-50717 tablets are available in the following dose strengths: 6, 9, and 12 mg. Patients will receive twice daily dosing for up to 54 weeks (those on the 6-mg dose will receive once-daily dosing), with an initial 7-week titration period to allow for optimal dose selection.

During the randomized drug withdrawal and re-titration period, 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 20-count bottles. The placebo tablets and packaging will match those for TEV-50717.

Patients who receive TEV-50717 during the randomized drug withdrawal period will remain on their maintenance dose of blinded active IMP from the start of week 31 to the start of week 34; those assigned to placebo during the randomized drug withdrawal period will undergo blinded re-titration from the start of week 31 to the start of week 34 back to their previously established maintenance dose from the end of week 28. Note that, because IMP is dispensed for 2-week periods, patients will use blinded bottles through the end of week 34; however, all patients will be known to be on active treatment at the start of week 34.

5.1.1. Drug Administration

IMP (see Section 3.9) will be administered as oral tablets at a starting dose of 6 mg once daily. Titration schemes based on body weight on day 1 are shown in Table 2. The maximum daily dose is determined by body weight and CYP2D6 impairment status on day 1 (see Table 2). Although dose adjustments can be made up to and including the week 7 telephone call, if a stable dose is reached before then, the patient should continue taking that dose for the remainder of the titration period. If a patient experiences depression, suicidal ideation or behavior, anxiety, akathisia, parkinsonism, somnolence, any other adverse event that interferes with daily activity, or adverse event that is related to IMP, the investigator will determine if a dose reduction or suspension is necessary. At the end of the titration period, the patient's dose will be established for the maintenance period. If a patient experiences an adverse event during the maintenance period and the investigator believes a dose reduction is warranted, the dose may be reduced. Dose adjustments of TEV-50717 (upward or downward) may be made during the maintenance period, if necessary, but not more often than every 5 days and only in increments of 6 mg.

IMP will be dispensed in the clinic. Patients should take their first dose in the evening on day 1 after their day 1 clinic visit. Patients will receive sufficient doses to last until the next visit.

IMP will be administered as follows:

- IMP should be swallowed whole and taken with food. Tablets should be 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, as shown in Table 2.

- The total daily dose, as provided in Table 2, is divided into a twice daily administration. The starting dose is 6 mg in all patients. Daily doses will be administered twice daily, approximately 8 to 10 hours apart during the day (those on the 6-mg dose will have once-daily dosing). 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 increases may not occur more frequently than once every 5 days.
- 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 should be notified**.
- After dose adjustment, if the maintenance dose for a patient is 6 mg, the dose should be taken once a day in the morning with food.
- During the titration period, the dose of the IMP should be adjusted according to Table 2 to identify a dose level that optimally reduces tics (as determined by the investigator, in consultation with the patient and caregiver/adult) and is well tolerated. A dose cap for impaired patients is prespecified by the IRT and presented in Table 2.
- After week 24, patient dose should be kept stable, if possible, until beginning Part B.
- During the randomized drug withdrawal period, the patient will continue to receive their current dose of TEV-50717 or receive matching placebo until returning to their dose of TEV-50717 at the start of week 31 (patients who receive TEV-50717 during the randomized drug withdrawal period will remain on their maintenance dose of blinded active IMP from the start of week 31 to the start of week 34; those assigned to placebo during the randomized drug withdrawal period will undergo blinded re-titration from the start of week 31 to the start of week 34 back to their previously established maintenance dose from the end of week 28). During the re-titration period, the dose of the IMP should be adjusted according to Table 3.
- Following re-titration, the dose of IMP should be kept stable, if possible, but changes can be made as described for Part A.

IMP will be packaged in bottles and provided for patients to take at home (see Section 3.8).

Table 2: Maximum Daily Dose of IMP by Study Day and Weight Category on Day 1 for Titration at Study Initiation

	Weight category					
Study day[a]	**20 to <30 kg**		**30 to <40 kg**		**≥40 kg**	
CYP impairment status	**Not impaired**	**Impaired**	**Not impaired**	**Impaired**	**Not impaired**	**Impaired**
Day 1-7	6 mg	6 mg	6 mg	6 mg	6 mg (Days 1 and 2) 12 mg[b]	6 mg (Days 1 and 2) 12 mg[b]
Day 8-14	12 mg	12 mg	12 mg	12 mg	18 mg	18 mg

Table 2: Maximum Daily Dose of IMP by Study Day and Weight Category on Day 1 for Titration at Study Initiation (Continued)

	Weight category					
Study day[a]	**20 to <30 kg**		**30 to <40 kg**		**≥40 kg**	
CYP impairment status	**Not impaired**	**Impaired**	**Not impaired**	**Impaired**	**Not impaired**	**Impaired**
Day 15-21	18 mg	18 mg	18 mg	18 mg	24 mg	24 mg
Day 22-28	18 mg	18 mg	24 mg	24 mg	30 mg	30 mg
Day 29-35	24 mg	18 mg	30 mg	24 mg	36 mg	36 mg
Day 36-42	24 mg	18 mg	36 mg	24 mg	42 mg	36 mg
Day 43-49	30 mg	18 mg	42 mg	24 mg	48 mg	36 mg

[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 as applicable.

[b] Patients will receive 6 mg on days 1 and 2, and 12 mg starting on day 3.

CYP=cytochrome P450; IMP=investigational medicinal product.

Note: CYP impaired=patients who are receiving a strong CYP2D6 inhibitor or who are a CYP2D6 poor metabolizer. The investigator, in consultation with the patient and caregiver/adult, will determine if a dose increase is warranted to achieve optimal tic reduction.

Table 3: Daily Dose of IMP by Previously Established Maintenance Dose and Study Week (Titration Post-Drug Withdrawal) for Patients Randomized to Placebo During the Blinded, Randomized Drug Withdrawal Period

	Daily dose (mg) at the start of week			
Previously established maintenance dose[a] **(mg)**	**Day 211 (start of week 31)**	**Day 218 (start of week 32)**	**Day 225 (start of week 33)**	**Day 232 (start of week 34) maintenance dose**
6	6	6	6	6
12	12	12	12	12
18	12	18	18	18
24	12	18	24	24
30	12	18	24	30
36	12	24	30	36
42	12	24	36	42
48	12	24	36	48

[a] The previously established maintenance dose is the dose administered at the end of Part A (Day 196 [end of week 28]). The blinded, randomized drug withdrawal period will occur from the start of week 29 through the end of week 30.

IMP=investigational medicinal product.

5.2. Restrictions

Medications prohibited before or during the study are described in Section 5.3.

While patients receiving strong CYP2D6 inhibitors such as paroxetine, fluoxetine, and bupropion on day 1 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 use of quinidine and terbinafine are prohibited (see Appendix A, Table 9).

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.

5.3. Prior and Concomitant Medication or Treatment

Any prior or concomitant therapy, medication, or procedure a patient receives during IMP administration and up to the end of the study period, including follow-up, will be recorded on the CRF. Generic or trade name, indication, and dosage will be recorded. In addition, only for patients who completed Study SD-809-C-17, any prior or concomitant therapy, medication, or procedure a patient has had within 3 months before IMP administration will be recorded on the CRF. The sponsor will encode all therapy and medication according to the World Health Organization drug dictionary.

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/administered, including over-the-counter medications. Any prescribed/administered medication should be reviewed with the investigator. Indication, dosage, and start and end dates should be entered on the CRF.

Medications that are allowed, provided that conditions outlined in the table are met, are shown in Appendix A, Table 6.

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. Addition of a strong CYP inhibitor is prohibited.

Prohibited antipsychotic drugs medications are listed in Appendix A, Table 7, while prohibited medications that are associated with QTc prolongation are listed in Appendix A, Table 8.

5.4. Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance. A check of IMP compliance will be performed during each visit after the initial dispensation of IMP, 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. The IEC/IRB should be notified as required by national and local regulations.

5.5. Dose Reduction and Temporary Investigational Medicinal Product Discontinuation

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. **If more than 1 dose reduction is required for an adverse event, the medical monitor must be notified.** After dose adjustment, if the maintenance dose for a patient is 6 mg, the dose should be taken once a day in the morning with food (other dose levels are taken twice daily).

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 1. Patients who withdraw from the study will proceed as described in Section 4.4.

5.6. Total Blood Volume

The total volume of blood to be collected for each patient in this study is approximately 30 to 60 mL, as detailed in Table 4.

Table 4: Blood Volumes

Type of samples	Volume per sample (mL)	Total number of samples	Total volume (mL)
Clinical laboratory (chemistry/hematology)	10	3[a] to 6[b]	**30[a] to 60[b]**

[a] For patients who completed Study TV50717-CNS-30046 or Study TV50717-CNS-30060, 30 to 40 mL will be collected.
[b] For patients who completed Study SD-809-C-17, 50 to 60 mL will be collected.
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 the YGTSS and [redacted] and self-administered efficacy scales include the [redacted] TS-PGII, [redacted] and C&A-GTS-QOL.

6.1. Efficacy and Exploratory Measures

[redacted]

6.1.1. Tourette Syndrome–Clinical Global Impression

TS-CGI is administered on day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060) and weeks 4, 8, 15, 28, 34, 41, 54, and 55. 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 H.

6.1.2. Tourette Syndrome-Patient Global Impression of Impact

The TS-PGII is administered on day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717 CNS-30060) and weeks 4, 8, 15, 28, 34, 41, 54, and 55. Input from the caregiver/adult is permitted.

The TS-PGII is a single-item questionnaire that asks the patient to assess the 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.

6.1.3. [redacted]

6.1.4. [redacted]

6.1.5. Child and Adolescent Gilles de la Tourette Syndrome-Quality of Life Scale

The C&A-GTS-QOL is administered on day 1 and weeks 6, 28, 34, and 54. Children 13 years of age and under must be interviewed in conjunction with the caregiver/adult. Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. 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 4 subscales (psychological, physical, obsessional, and cognitive) 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 K.

6.1.6. [redacted]

[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 medication, 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
- drug interactions
- events occurring during diagnostic procedures or during any washout phase 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 IMP are not considered adverse events.)

7.1.2. Recording and Reporting of Adverse Events

For recording of adverse events, 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. The follow-up period is defined as 2 weeks after the last dose of IMP.

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 (see 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:

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

For recording of serious adverse events, the study period is defined for each patient as the time period from signing 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 (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 signed the informed consent form will not be considered serious adverse events, unless there was worsening of the preexisting 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
- is 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 >3 × the upper limit of normal (ULN)
- total bilirubin increase of >2 × ULN
- absence of initial findings of cholestasis (ie, no substantial increase of 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.

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.

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 should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the local safety officer (LSO) or designee (a contract research organization 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 Global Patient Safety and Pharmacovigilance.

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 Global Patient Safety and Pharmacovigilance will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/Extensible Markup Language (XML) file to the LSO/Syneos Health 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.

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 7.3).

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 actions may be required, including:

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- modifying the existing consent 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 IMP at any time at the discretion of the investigator. If a post-day 1 QTcF value >500 msec or change from baseline (Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or day 1 (Study SD-809-C-17), as appropriate (see Section 9.7.2) >60 msec is found, the investigator should repeat the ECG assessment twice and compare the average of the 2 pre-treatment QTcF values (ie, the parent study baseline and screening values for patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 or the day 1 and screening values from the current study for patient[s] who completed Study SD-809-C-17) to the average of the 3 post-day 1 QTcF values. The IMP must be stopped for any confirmed post-day 1 QTcF value >500 msec or increase from baseline (Study TV50717-CNS-30046 or Study TV50717-CNS 30060) or day 1 (Study SD-809-C-17) >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.

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 (CPP)/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 the CDI-2.

7.2.1. Mini International Neuropsychiatric Interview for Children and Adolescents, (version 6.0)

Select MINI Kid modules are administered at screening (only for patients who completed Study SD-809-C-17). 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 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 6.0) 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 C.

7.2.2. Columbia-Suicide Severity Rating Scale

The C-SSRS children's baseline/screening version assesses past and current suicidal ideations and behaviors to determine suicide risk and is administered at screening. The C-SSRS children's SLV scale is administered on day 1 (only for patients who completed Study SD-809-C-17) and weeks 2, 4, 8, 15, 28, 30, 34, 41, 54, and 55. 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 administered through 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, patients 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 E.

7.2.3. Children's Depression Inventory, Second Edition, Parent and Self-Report Profiles

CDI-2 (Parent and Self-Report Profiles) is administered at screening and day 1 (only for patients who completed Study SD-809-C-17) and weeks 2, 4, 8, 15, 28, 30, 34, 41, 54, and 55. As the CDI-2 is designed for children 7 to 17 years of age, children 6 years of age on day 1 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 D.

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 physician identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the sponsor (LSO/Syneos Health) 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 day 1, 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 Product

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 (Section 11.1.2), or as a deviation, in the patients source documents, regardless of whether or not an adverse event occurs as a result. All instances of incorrect medication administration should be categorized on the CRF as “Non-Compliance with IMP”.

The following are types of medication errors and special situations:

2. 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.
3. 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.
4. Misuse: Situations where the IMP is intentionally and inappropriately used not in accordance with the authorized product information.
5. Abuse: Persistent or sporadic, intentional excessive use of IMP which is accompanied by harmful physical or psychological effects.

6. Off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the authorized product information.
7. Occupational exposure: Exposure to an IMP, as a result of one's professional or non-professional occupation.
8. Breastfeeding: Suspected adverse reactions that 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 values will be evaluated by the criteria described in the study laboratory manual and by the judgment 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 cessation of administration of IMP or medical treatment, or further diagnostic work-up. Abnormal laboratory tests can be repeated without approval from the medical monitor. (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).

7.5.1. Serum Chemistry, Hematology, and Urinalysis

Clinical laboratory tests (eg, serum chemistry, hematology and urinalysis) will be performed at the time points detailed in Table 1. Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are provided in Table 5.

Table 5: Clinical Laboratory Tests

Serum Chemistry	Hematology	Urinalysis
calcium phosphate sodium potassium chloride creatinine glucose magnesium blood urea nitrogen (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

7.5.2. Other Clinical Laboratory Tests

7.5.2.1. Human Chorionic Gonadotropin Tests

Human chorionic gonadotropin tests in urine or serum will be performed for all females who are postmenarchal or ≥12 years of age as detailed in Table 1 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 UDS will be performed at the time points specified in Table 1. A positive result for any of the specified drugs or their metabolites, without medical explanation, will preclude the patient from enrollment or continued participation in the study.

7.6. Vital Signs

Vital signs (BP, respiratory rate, body temperature, and pulse) will be measured at the time points detailed in Table 1. 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 and resting 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 finding, 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.

On day 1 and weeks 4, 8, 28, and 54, orthostatic BP and pulse will be measured after the patient is in a standing position for at least 3 minutes.

7.7. Electrocardiography

A 12-lead ECG will be recorded at the time points detailed in Table 1. 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-day 1 QTcF value >500 msec or change from baseline (Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or day 1 (Study SD-809-C-17), as appropriate (see Section 9.7.2)>60 msec is found, the investigator should repeat the ECG assessment twice and compare the average of the 2 pre-treatment QTcF values (ie, the parent study baseline and screening values for patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060; or the day 1 and screening values from the current study for patient[s] who completed Study SD-809-C-17) to the average of the 3 post-day 1 QTcF values. The IMP must be stopped for any confirmed post-day 1 QTcF value >500 msec or increase from baseline (Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or day 1 (Study SD-809-C-17) >60 msec.

7.8. Physical Examinations

Physical examinations, 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 1.

Weight must be measured with shoes and outerwear off.

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.

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, and detailed recommendations are provided in Section 7.2.2.

The day 1 assessment of suicidal ideation and behavior and treatment-emergent suicidal ideation and behavior will be assessed during the study using the Children's C-SSRS described in Section 7.2.2.

Depression and Suicidality as an Adverse Event

Families and caregivers of patients 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 E.

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 1. 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 Table 6. 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 A.

Prohibited medications that are associated with QTc prolongation are listed in Table 8, while prohibited antipsychotic drugs are listed in Table 7.

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 CPP/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 3.13. Procedures for recording safety data are discussed in Section 13.1, and methods of analyses are discussed in Section 9.7.2.

Information about the IDMC used for this study is provided in Section 3.7.

8. ASSESSMENT OF PHARMACOKINETICS/PHARMACODYNAMICS

Pharmacokinetic and pharmacodynamic assessments will not be performed as part of Study TV50717-CNS-30047.

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 clinical study report (CSR).

9.1. Sample Size and Power Considerations

This study is safety-oriented in nature; therefore, no formal hypothesis testing is planned for Part A. Based on the number of patients in the previous studies, up to approximately 227 patients (approximately 1 patient from the Phase 1b Study SD-809-C-17, up to approximately 99 patients from the Phase 2/3 Study TV50717-CNS-30046, and up to approximately 127 patients from the Phase 3 Study TV50717-CNS-30060) are estimated to enroll.

All patients who complete Study TV50717-CNS-30060 or Study TV50717-CNS-30046 are eligible to participate in Study TV50717-CNS-30047. As the number of patients to be randomized in parent Study TV50717-CNS-30046 has increased, the number of patients anticipated to be randomized into Study TV50717-CNS-30047 has also increased. The rationale for the increased sample size in Study TV50717-CNS-30046 is provided that protocol.

For the randomized drug withdrawal period, 190 patients to be included in the analysis will provide approximately 90% power to detect a difference between TEV-50717-treated and placebo-treated patients assuming a difference in YGTSS TTS of 4.5 with a standard deviation of 9 using a two-sided test for difference at a significance level of 0.05.

9.2. Analysis Sets

9.2.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all enrolled patients, regardless of whether or not a patient took any IMP. Enrolled subjects who are not randomized will be summarized separately as “Not randomized,” and randomized subjects will be analyzed based on their randomized treatment. A patient is considered enrolled according to the status reported in the database. All efficacy analyses will be based on the ITT analysis set.

9.2.2. Safety Analysis Set

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

The safety analysis set will be used for all safety analyses.

9.2.3. Randomized Withdrawal ITT Population

The Randomized Withdrawal ITT (RWITT) Population will include all patients enrolled in the randomized drug withdrawal period of the study.

9.2.4. Randomized Withdrawal Safety Population

The Randomized Withdrawal Safety (RWSAF) Population will include all patients enrolled in the randomized drug withdrawal period who are administered any study drug. All summaries of safety measures in the randomized withdrawal period will be summarized descriptively in the RWSAF Population.

9.2.5. Randomized Withdrawal Modified Intent-to-Treat Population

The Randomized Withdrawal Modified Intent-to-Treat (RWmITT) Population will include all patients enrolled in the randomized drug withdrawal period who receive study drug and have a YGTSS TTS at both the randomized drug withdrawal week 28 visit and the week 30 visit. Efficacy measures in the randomized drug withdrawal period will be analyzed as described in Section 9.5.3.1.

9.2.6. Responder Randomized Withdrawal Modified Intent-to-Treat Population

The Responder Randomized Withdrawal mITT (RRWmITT) Population will include all patients enrolled in the randomized drug withdrawal period who receive study drug and have a YGTSS TTS at both the week 28 visit and the week 30 visit and a ≥25% reduction in the TTS from baseline in the parent protocol to week 28. Efficacy measures in the randomized drug withdrawal period will be analyzed as described in Section 9.5.3.1.

9.3. Data Handling Conventions

For all variables, only the observed data from the patients will be used in the statistical analyses.

9.4. Study Population

The ITT analysis set (see Section 9.2.1) will be used for all open-label efficacy summaries and analyses unless otherwise noted. The safety analyses set will be used for all safety summaries. Summaries will be presented for all patients.

The RRWmITT or RWmITT analysis set (see Section 9.2.5) will be used for all randomized withdrawal efficacy summaries and analyses unless otherwise noted. The RWSAF analysis set will be used for all randomized-withdrawal safety summaries.

9.4.1. Patient Disposition

Data from patients who are enrolled, patients enrolled but not treated (and the reason), patients in the ITT, safety, and other analysis sets, patients who enter the randomized drug withdrawal period, patients who complete the randomized drug withdrawal period, 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 (day 1), including medical history, prior medications and treatments, and ECG findings, will be summarized using descriptive statistics and will be analyzed by age group. 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

No formal inferential statistics will be applied to the efficacy endpoints in Part A; however, inferential statistics will be applied to the efficacy endpoint in Part B (see Section 9.5.1).

9.5.1. Efficacy Endpoints

The following efficacy endpoints will be assessed in Part A:

- change in the TTS of the YGTSS from day 1 to each visit in which the scale is administered
- change in the Tourette Syndrome-Clinical Global Impression (TS-CGI) score from day 1 to each visit in which the scale is administered
- change in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) score from day 1 to each visit in which the scale is administered
- change in the Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life (C&A-GTS-QOL) activities of daily living (ADL) subscale score from day 1 to each visit in which the scale is administered

The following efficacy endpoint will be assessed in Part B:

- change in the TTS of the YGTSS from week 28 to week 30, with the primary analyses and sensitivity testing done as described in Section 9.5.3.1

9.5.2. Exploratory Endpoints

The following exploratory endpoints will be assessed in Part A:

9.5.3. Planned Method of Analysis

The ITT analysis set (see Section 9.2.1) will be used for all efficacy analyses in Part A. Summaries will be presented for all patients.

9.5.3.1. Efficacy Analysis for the Randomized Drug Withdrawal Period

For the randomized drug withdrawal portion of the study, an analysis of covariance model will be used as the primary analysis model with the change from randomized-withdrawal week 28 to week 30 in YGTSS TTS as the dependent variable, and treatment group, randomized-withdrawal week 28 TTS, and age group at baseline as covariates. The least squares mean of the change in TTS from week 28 to week 30 will be compared (the active treatment arm and placebo arm) using a 2-sided test at the alpha=0.05 level of significance.

The primary analysis will be in the RRWmITT population (see Section 9.2.6). In addition, sensitivity testing will be done using the same model in the RWmITT population and in a subpopulation of the RRWmITT who had a ≥35% reduction in the TTS from baseline in the parent protocol to week 28.

9.6. Multiple Comparisons and Multiplicity

This does not apply to this study.

9.7. Safety Endpoints and Analysis

Safety analyses will be performed on the safety analysis set (Section 9.2.2) for the open-label study and the RWSAF set for the randomized drug withdrawal portion.

9.7.1. Safety Endpoints

The following safety endpoints will be assessed in Part A (Day 1, Titration, and Maintenance):

- incidence of adverse events
- observed values and changes from day 1 in vital signs
- observed values and changes from day 1 in the CDI-2 (Parent and Self-Report Profiles)
- observed values in the C-SSRS
- observed values in electrocardiogram (ECG) parameters and shifts from parent study baseline (for patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or from day 1 (for patient[s] rolling over from Study SD-809-C-17) for clinically significant abnormal findings

- observed values and changes from day 1in clinical laboratory parameters (hematology, serum chemistry, and urinalysis)

The following safety endpoint will be assessed in Part B (Blinded, Randomized Drug Withdrawal Period and Titration Post-Drug Withdrawal Period):

- incidence of adverse events

In addition to routine monitoring of adverse events, clinical laboratory parameters, 12-lead ECGs, and safety scales, an IDMC will monitor safety during the conduct of the study.

9.7.2. 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 (overall and by severity), adverse events determined by the investigator to be related to IMP (ie, reasonable possibility [see Section 7.1.4] defined as related or with missing relationship) (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

Changes in laboratory and vital signs measurement data will be summarized descriptively.

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 ECG parameters will be summarized, and counts and percentages of abnormal findings will be presented. Changes from parent study baseline (for patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or from day 1 (for patient[s] rolling over from Study SD-809-C-17) in ECG parameters will be summarized descriptively. In addition, the number and percentage of patients with on-treatment QTcF values >450, >480, or >500 msec and change from baseline (Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or day 1 (Study SD-809-C-17) >30 or >60 msec will be presented.

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 for all patients.

If any patient dies during the study, a listing of deaths will be provided, and all relevant information will be discussed in the patient narrative included in the CSR.

9.8. Tolerability Variables and Analysis

Tolerability was not specifically defined.

9.9. Planned Interim Analysis

When approximately 100 patients have completed the 28-week clinic visit, an interim analysis, including data from day 1 and up to week 28 visit only, will be conducted to provide descriptive, long-term safety and efficacy data to be used in regulatory submissions. To maintain data integrity of Study TV50717-CNS-30047, only a limited number of personnel who do not have contact with the sites will have access to this interim data in preparation for the regulatory filing.

As no decisions regarding conduct of the study will be made based on the descriptive interim analysis, no alpha will be spent.

9.10. 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. DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

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. Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, drug inventory, IMP label records, diary data, protocol-required worksheets, and CRFs that are used as the source (see Section 3.12).

The investigator will maintain a confidential patient identification list that allows the unambiguous identification of each patient. All study-related documents must be kept until notification by the sponsor.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Protocol Amendments and Protocol Deviations and Violations

11.1.1. 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.

11.1.2. Protocol Violations

Any deviation from the protocol that affects, to a significant degree, (a) the safety, physical, or mental integrity of the patients of the study and/or (b) the scientific value of the study will be considered a protocol violation. Protocol violations 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 the administration of IMP; use of prohibited medications. Protocol violations will be identified and recorded by investigational center personnel in a log or as part of the CRF. All protocol violations will be reported to the responsible IEC/IRB, as required.

When a protocol violation is reported, the sponsor will determine whether to discontinue 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.

11.2. 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. Additional information will be

made available during the study when new personnel members become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

11.3. 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 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 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 will contact the investigator and visit the investigational center at regular intervals throughout the study. The study monitor will be permitted to check and verify the various records (CRFs and other pertinent source data records, including specific electronic source document [see Section 3.12]) relating to the study to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded. If electronic CRFs are used for the study, the study monitor will indicate verification by electronically applying source document verification flags to the CRF and will ensure that all required electronic signatures are being implemented accordingly.

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 in the course of these monitoring visits or provided in follow-up written communication.

11.4. Clinical Product Complaints

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical drug 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 clinical.productcomplaints@tevapharm.com 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 a drug product, all relevant samples (eg, the remainder of the patient's drug supply) should be sent back to the sponsor for investigative testing whenever possible.

11.4.1. Product Complaint Information Needed from the Investigational Center

In the event that the product complaint form cannot be completed, the investigator will obtain 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, bottle, 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.

11.4.2. Handling of Investigational Medicinal Product at the Investigational Center

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.

11.4.3. 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).

11.4.4. 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.

11.5. 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 Clinical 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.

12. ETHICS

Details of compliance with regulatory requirements and applicable laws are provided in Section 1.6.

12.1. 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 parent/legally acceptable representative and the patient. The patient and 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 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; according to national and local 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/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 (and 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. Any patient that turns 18 years of age during the course of Study TV50717-CNS-30047 will need to be re-consented as an adult.

For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, informed consent/assent, as appropriate, may be obtained prior to the day 1 visit, up to 4 weeks in advance of open-label study participation.

12.2. Competent Authorities and Independent Ethics Committees/Institutional Review Boards

Before this study starts, the protocol will be submitted to the national and local competent authority and to each IEC/IRB for review. As required, the study will not start at a given investigational center before the IEC/IRB and competent authority (where applicable) for the investigational center give written approval or a favorable opinion.

12.3. 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, or competent authorities. Personal medical information will always be treated as confidential.

12.4. Declaration of the End of Clinical Study

The end of study is defined as the date of the week 56 visit of the last participant.

For investigational centers located in the European Union, a declaration of the end of the clinical study will be made according to the procedures outlined in Directive 2001/20/EC, Article 10(c); for other countries, national and local regulations will be followed.

12.5. Registration of the Clinical Study

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

13. DATA HANDLING, DATA QUALITY CONTROL, AND RECORD KEEPING

13.1. 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. The CDMS will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study before it is used to capture data from this study. Before using the CDMS, 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. Data will be verified by the study monitor using the data source, and reviewed for consistency by Data Management using both automated logical checks and manual review. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central ECG center, diary data, electronic patient-reported outcome [ePRO] Tablet), the results will be sent to the investigational center, where they will be retained but not entered in the CRF, unless otherwise specified in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management) for direct entry in the clinical database. Laboratory test results will not be entered in the CRF unless otherwise specified in the protocol. All data from other sources will be available to the investigators.

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.

13.2. 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.

13.3. Archiving of Case Report Forms and Source Documents

13.3.1. Sponsor Responsibilities

The sponsor will have final responsibility for the processing and quality control of the data. Data management oversight will be carried out as described in the sponsor's SOPs for clinical studies.

Day to day data management tasks for this study are delegated to a contract organization, and these functions may be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management activities. The original CRFs will be archived by the sponsor. Investigational center-specific CRFs will be provided to the respective investigational centers for archiving.

13.3.2. 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
- CRFs for each patient on a per-visit basis
- data from other sources (eg, central laboratory, bioanalytical laboratory, central image center, diary)
- safety reports
- financial disclosure reports/forms
- reports of receipt, use, and disposition of the IMP
- 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 Syneos Health 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.

14. 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.

This clinical study is 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 inter alia, 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 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.

15. REPORTING AND PUBLICATION OF RESULTS

The sponsor is responsible for ensuring that the public has access to the appropriate information about the study by conforming to national, local, and regional requirements and regulations for registration and posting of results.

The sponsor is responsible for the preparation of a CSR, in cooperation with the coordinating investigator. The final report is signed by the sponsor and, if applicable, by the coordinating investigator.

When the sponsor generates reports from the data collected in this study for presentation to competent authorities, drafts may be circulated to the principal investigator for comments and suggestions. An endorsement of the final report will be sought from the principal investigator.

All unpublished information given to the investigator by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor. The primary publication from this study will report the results of the study in accordance with the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (www.ICMJE.org). Publication of the results will occur in a timely manner according to applicable regulations. Authorship will be based on meeting all the following 4 criteria:

- substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
- drafting the work or revising it critically for important intellectual content
- final approval of the version to be published
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

The publications committee established by the sponsor will oversee this process. Additional publications may follow. Policies regarding the publication of the study results are defined in the financial agreement.

No patent applications based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.

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17. SUMMARY OF CHANGES TO PROTOCOL

17.1. Amendment 01 Dated 22 June 2017

The primary reason for this amendment is to change aspects of the conduct, include concomitant medications, titration instructions, number of patients randomized, 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		
Study drug	Investigational Medicinal Product (IMP)	"Study drug" to "IMP" for consistency throughout the document.
TITLE PAGE		
Not applicable	Teva's Development Partner Nuvelution Pharma, Inc. 601 Gateway Boulevard Suite 1270 South San Francisco, California 94080 United States of America	Title page was updated to add Teva's Development Partner Nuvelution Pharma, Inc.
CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS		
Electronic Data Capture Medidata RAVE (through ~~PRA International~~INC Research) **Contract Research Organization; Safety and Efficacy Data Analysis** ~~PRA International~~ ~~4130 ParkLake Avenue, Suite 400~~ ~~Raleigh, NC 27612~~ ~~USA~~ INC Research 3201 Beechleaf Court Suite 600 Raleigh, NC 27604-1547 USA	**Electronic Data Capture** Medidata RAVE (through INC Research) **Contract Research Organization; Safety and Efficacy Data Analysis** INC Research 3201 Beechleaf Court Suite 600 Raleigh, NC 27604-1547 USA **Integrated Response**	The administrative changes made to this section were completed for accuracy of laboratories, other departments, and institutions.

Integrated Response Technology ~~Y-Prime~~ ~~263 Great Valley Parkway~~ ~~Malvern, PA 19355~~ ~~USA~~ Bracket Global, LLC 575 East Swedesford Road, Suite 200 Wayne, PA 19087 USA **ePRO, eCOA, and Scales Training** Bracket Global, LLC 575 East Swedesford Road, Suite 200 Wayne, PA 19087 USA **Bioanalytical Pharmacokinetics Evaluation Data Analysis** Information will be included in the Trial Master File.	**Technology** Bracket Global, LLC 575 East Swedesford Road, Suite 200 Wayne, PA 19087 USA **ePRO, eCOA, and Scales Training** Bracket Global, LLC 575 East Swedesford Road, Suite 200 Wayne, PA 19087 USA **Bioanalytical Pharmacokinetics Evaluation Data Analysis** Information will be included in the Trial Master File.	
CLINICAL STUDY PERSONNEL CONTACT INFORMATION		
[redacted] [redacted] ~~Tel:~~ [redacted] ~~Email:~~ [redacted] [redacted] Medical Director, Medical Affairs INC Research 3201 Beechleaf Court Suite 600 Raleigh, NC 27604 USA Office: [redacted] Mobile: [redacted] Email: [redacted] **For operational issues, contact the operational lead listed below:** [redacted], ~~Teva Branded Pharmaceutical Products R&D, Inc.~~ ~~Tel: +~~ [redacted] ~~Fax:~~ [redacted] ~~Cell:~~ [redacted] ~~Email: S~~ [redacted] [redacted], Nuvelution Pharma	[redacted] Medical Director, Medical Affairs INC Research 3201 Beechleaf Court Suite 600 Raleigh, NC 27604 USA Office: [redacted] Mobile: [redacted] **For operational issues, contact the operational lead listed below:** [redacted] Nuvelution Pharma Tel: [redacted] Email: [redacted]	These changes were made to update the clinical study personnel.

Tel: +[redacted] Email: [redacted] **For protocol issues, contact the study leader listed below:** [redacted] ~~Teva Branded Pharmaceutical Products R&D, Inc.~~ ~~Tel: +[redacted]~~ ~~Fax: +[redacted]~~ ~~Cell: +1 202 494 6059~~ ~~Email:~~ [redacted] [redacted], Nuvelution Pharma Tel: +[redacted] Email: [redacted] [redacted] Nuvelution Pharma Tel: +[redacted] Email: [redacted]	**For protocol issues, contact the study leader listed below:** [redacted] Nuvelution Pharma Tel: +[redacted] Email: [redacted] [redacted] Nuvelution Pharma Tel: +[redacted] Email: [redacted]	
1.1. Introduction		
Not applicable	TEV-50717 was granted breakthrough status for treatment of TD by the Food and Drug Administration (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 on 03 April 2017.	Addition based on recent granting of breakthrough status of TEV-50717 for the treatment of TD by the FDA
1.2. Name and Description of Investigational Medicinal Product (Other Sections that apply to this change: 3.7., 5.1.)		
TEV-50717 tablets are available in the following dose strengths: 6, 9, and 12, ~~15, and 18 mg~~. Each dose strength will have a marking of SD 6, SD 9, and SD 12, ~~SD 15, and SD 18~~ corresponding to the dose strength and a distinct color: 6 mg – purple, 9 mg – blue, and 12 mg – beige~~, 15 mg – white, and 18 mg – yellow~~. Study drug will be supplied in	TEV-50717 tablets are available in the following dose strengths: 6, 9, and 12 mg. Each dose strength will have a marking of SD 6, SD 9, and SD 12 corresponding to the dose strength, and a distinct color: 6 mg – purple, 9 mg – blue, and 12 mg – beige. Study drug will be	This change reflects the correct dosages and strengths of IMP available for the study.

20- or ~~7~~60-count tablets per dose strength per bottle.	supplied in 20- or 60-count tablets per dose strength per bottle	
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 subsequently 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 ~~are~~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 were 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 embyros from matings during recovery from	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 subsequently 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	This section was updated to include results from oral administration of metabolite M1 to pregnant rats

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).	through early adolescence and overlapping with TEV-50717 oral dosing in a general adult toxicology study. The effects of M1 were 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)	
1.3.2. Clinical Studies		
The clinical development plan for TEV-50717 to date includes: • 6 completed Phase 1 studies in healthy adult volunteers • 1 completed Phase 3 pivotal study for the treatment of chorea associated with HD • 1 ongoing Phase 3 long-term safety study in patients with HD • ~~1~~2 completed Phase 2/3 and Phase 3studies in patients with TD • ~~3~~1 ongoing Phase 3 long-term safety studies in patients with TD • 1 completed Phase 1b study in patients	The clinical development plan for TEV-50717 to date includes: • 6 completed Phase 1 studies in healthy adult volunteers • 1 completed Phase 3 pivotal study for the treatment of chorea associated with HD • 1 ongoing Phase 3 long-term safety study in patients with HD • 2 completed Phase 2/3 and Phase 3 studies in patients with TD • 1 ongoing Phase 3 long-term	The status and details of clinical studies were updated to the current status of study information.

with TS • ~~1 planned Phase 2/3 study in patients with TS~~	safety studies in patients with TD • 1 completed Phase 1b study in patients with TS	
1.3.2.1. Clinical Pharmacology Studies		
~~Six~~Five Phase 1 clinical pharmacology studies were conducted in healthy adult volunteers. In addition, sparse pharmacokinetic sampling was included in the Phase 3 studies with HD patients where population pharmacokinetic analyses were performed to extensively evaluate the ~~pharmacological profile~~ pharmacokinetics and pharmacokinetics/pharmacodynamics relationship of TEV-50717. A summary of the clinical pharmacology findings is provided in the IB.	Five Phase 1 clinical pharmacology studies were conducted in healthy adult volunteers. In addition, sparse pharmacokinetic sampling was included in the Phase 3 studies with HD patients where population pharmacokinetic analyses were performed to extensively evaluate the pharmacokinetics and pharmacokinetics/pharmacodynamics relationship of TEV-50717. A summary of the clinical pharmacology findings is provided in the IB.	The details of clinical pharmacology studies was updated to reflect accuracy of clinical pharmacology study information.
1.4. Known and Potential Benefits and Risks to Patients (Other sections affected by this change: 1.4.1., 1.4.1.2., 1.4.2.)		
1.4. Known and Potential Benefits and Risks to Patients Additional information regarding benefits and risks to patients may be found in the current IB and in the United States prescribing information for AUSTEDO™ (deutetrabenazine). ~~1.4.1.1.Benefits of TEV50717~~ ~~Although the efficacy of TEV-50717 in patients with TS has not yet been definitively established, preliminary efficacy data from Study SD-809-C-17 indicates a clinically meaningful reduction in motor and phonic tics observed by patients, parents, and treating clinicians. Furthermore, TEV-50717 has the same mechanism of action and indistinguishable pharmacology as tetrabenazine, an agent that is generally accepted among movement disorder experts to provide clinical benefit in this patient population (Jankovic and Kurlan 2011). Based on the nonclinical data discussed above and similar efficacy observed for tetrabenazine and TEV-50717 in studies of other indications~~	**1.4. Known and Potential Benefits and Risks to Patients** Additional information regarding benefits and risks to patients may be found in the current IB and in the United States prescribing information for AUSTEDO™ (deutetrabenazine).	The section was modified to reflect accurate and consistent information regarding known and potential benefits and risks to patients.

~~(see IB), TEV-50717 has the potential to offer effective treatment in children and adolescents with TS.~~ **~~1.4.1.2. Potential Risks of TEV-50717~~** ~~The following information is based on clinical trial experience with TEV-50717 and the United States prescribing information for Xenazine (tetrabenazine):~~ • ~~TEV-50717 is contraindicated in patients who are actively suicidal, or in patients with untreated or inadequately treated depression.~~ • ~~TEV-50717 is contraindicated in patients with impaired hepatic function.~~ • ~~TEV-50717 is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). TEV-50717 should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI.~~ • ~~TEV-50717 is contraindicated in patients taking reserpine. At least 21 days should elapse after stopping reserpine before starting TEV-50717.~~ ~~Additional information regarding each potential issue may be found in the current IB.~~ **~~1.4.2. Overall Risk and Benefit Assessment for This Study~~** ~~There is a significant need to identify new treatments for TS that do not antagonize dopamine receptors, as these latter agents pose serious risks such as metabolic syndrome and TD, a movement disorder that is often irreversible. The results from Study SD-809-C-17 demonstrated meaningful efficacy in the context of good tolerability and no signal on safety scales, vital signs, laboratory parameters, or 12-lead electrocardiograms (ECGs). These findings are consistent with results in other study populations, such as HD, where the rates for TEV-50717 and placebo were similar for overall adverse events, neurologic and psychiatric adverse events, as well as dose reduction or dose suspension for adverse events (see IB for details).~~		
1.8. Location and Study Duration		

This study is planned to be conducted in ~~the USA, Canada, Denmark, Spain, Germany, and Russia~~ North America and Europe ~~at approximately 40~~100 centers. It is expected to start in ~~June 2016~~ January 2018 and conclude in ~~October 2018~~ June 2020 and have a duration of approximately ~~28~~ 30 months.	This study is planned to be conducted in North America and Europe at approximately 100 centers. It is expected to start in January 2018 and conclude in June 2020 and have a duration of approximately 30 months.	The study duration was updated to reflect accurate timing and duration of the planned study period.
2.3.3. Exploratory Endpoints (Other sections affected by this change: 3.4.2., 9.5.2.)		
[redacted]	[redacted]	[redacted]
3.1. General Design and Study Schematic Diagram (Other sections affected by this change: 9.1.)		
This is a 56-week, open-label, single-arm study to evaluate the safety of TEV-50717 in children and adolescents with tics associated with TS after they have successfully completed ~~either~~any of the parent ~~study~~ ~~(Study~~ studies (SD-809-C-17 [Phase 1b~~]~~ ~~or Study~~], TV50717-CNS-30046 [Phase 2/3], or TV50717-CNS-30060 [Phase 3]). Informed consent/assent and/or co-consent for patients 14 years of age and older, as appropriate, will be obtained before any study procedures are performed. Patients may have informed consent/assent and/or co-consent for patients 14 years of age and older, as appropriate, obtained prior to the baseline visit, up to 4 weeks in advance of open-label participation. Patients who have successfully completed ~~either parent study~~ any of the parent studies may be eligible to enroll in the current study after they complete a 1-week washout period and the final evaluation in the parent study. To reduce patient burden, after obtaining informed consent/assent and/or co-consent for patients 14 years of age and older, as appropriate, some data collected in Study TV50717-CNS-30046 or Study TV50717-CNS-30060 will be used to provide corresponding baseline data in the	This is a 56-week, open-label, single-arm study to evaluate the safety of TEV-50717 in children and adolescents with tics associated with TS after they have successfully completed any of the parent studies (SD-809-C-17 [Phase 1b], TV50717-CNS-30046 [Phase 2/3], or TV50717-CNS-30060 [Phase 3]). Informed consent/assent and/or co-consent for patients 14 years of age and older, as appropriate, will be obtained before any study procedures are performed. Patients may have informed consent/assent and/or co-consent for patients 14 years of age and older, as appropriate, obtained prior to the baseline visit, up to 4 weeks in advance of open-label participation. Patients who have successfully completed any of the parent studies may be eligible to enroll in the current study after they complete a 1-week washout period and the final evaluation in the parent study. To reduce patient burden, after obtaining	The general design, sample size, and power calculations were updated to include Study TV5017-CNS-30060 calculations. Study TV50717-CNS-30060 was added globally throughout the document as a parent study for patients to enroll from into Study TV50717-CNS-30047.

current open-label study (see Table 1). Up to ~~110~~260 patients are planned to be enrolled (up to 10 patients are estimated to enroll from the Phase 1b Study SD-809-C-17, ~~and~~ up to ~~90~~100 patients are estimated to enroll from Phase 2/3 Study TV50717-CNS-30046, and up to 150 patients are estimated to enroll from the Phase 3 Study TV50717-CNS-30060).	informed consent/assent and/or co-consent for patients 14 years of age and older, as appropriate, some data collected in Study TV50717-CNS-30046 or Study TV50717-CNS-30060 will be used to provide corresponding baseline data in the current open-label study (see Table 1). Up to 260 patients are planned to be enrolled (up to 10 patients are estimated to enroll from the Phase 1b Study SD-809-C-17, up to 100 patients are estimated to enroll from Phase 2/3 Study TV50717-CNS-30046, and up to 150 patients are estimated to enroll from the Phase 3 Study TV50717-CNS-30060).	
3.1.1 Screening Period (up to 4 Weeks; Minimum of 3 Days) (Other sections affected by this change: 3.12, 3.12.1, 4.1, 12.1)		
After informed consent (and written assent and/or co-consent for patients 14 years of age and older, 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.	After informed consent (and written assent and/or co-consent for patients 14 years of age and older, 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, assessment of vital signs, laboratory testing, and 12-lead ECG, along with rating scales to assess comorbid TS symptoms and behavioral status.	An option was added for co-consent for patients 14 years of age and older, as appropriate.
3.1.1 Screening Period (up to 4 Weeks; Minimum of 3 Days)		
For patients from Study TV50717 CNS-30046 or Study TV50717-CNS-30060:	For patients from Study TV50717 CNS-30046 or Study TV50717-CNS-30060:	Study TV50717-CNS-30060 was added globally as a parent study throughout the document for patients to enroll from into Study TV50717-CNS-30047.

3.1.2. Baseline Visit (All Patients) (Other section affected by this change: 3.12.2.)		
Baseline visit (all patients): For patients ~~enrolled in~~rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, ~~the baseline visit of this study will occur simultaneously with~~the week 13 visit (Study TV50717-CNS-30046) or week 9 visit (Study TV50717-CNS-30060) will be the baseline visit for Study TV50717-CNS-30047. Patients rolling over from Study SD-809-C-17 will need to undergo all baseline assessments. Baseline assessments for Study TV50717-CNS-30047 ~~that are also specified for the baseline visit of~~that are identical to Study TV50717-CNS-30046 week 13 or Study TV50717-CNS-30060 week 9 visit assessments do not need to be repeated. ~~In addition to assessments~~Additionally, Study TV50717-CNS-30047 required evaluations will be completed at Study TV50717-CNS-30046 week 13 visit~~, evaluations required as part of the current study will be completed on the same day as the week13~~ or Study TV50717-CNS-30060 week 9 visit (see Table 1). For all patients, the baseline visit will occur on the same day as the scheduled first dose of the ~~study drug~~IMP (day 1). If washout period is >7 days, the medical monitor must be consulted for which entry tests that require repeating. For patients with clinically significant laboratory abnormalities at week 12 in Study TV50717-CNS-30046~~, the~~ or at week 8 in Study TV50717-CNS-30060, Study TV50717 CNS-30046 week 13 value(s) or Study TV50717-CNS-30060 week 9 value(s) will serve as baseline laboratory values in this study. Rollover for such patients must be approved by the medical monitor and may be delayed.	Baseline visit (all patients): For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, the week 13 visit (Study TV50717-CNS-30046) or the week 9 visit (Study TV50717-CNS-30060) will be the baseline visit for Study TV50717-CNS-30047. Patients rolling over from Study SD-809-C-17 will need to undergo all baseline assessments. Baseline assessments for Study TV50717-CNS-30047 that are identical to Study TV50717-CNS-30046 week 13 or Study TV50717-CNS-30060 week 9 assessments do not need to be repeated. Additionally, Study TV50717-CNS-30047 required evaluations will be completed at Study TV50717-CNS-30046 week 13 visit or Study TV50717-CNS-30060 week 9 visit (see Table 1). For all patients, the baseline visit will occur on the same day as the scheduled first dose of the IMP (day 1). If washout period is >7 days, the medical monitor must be consulted for which entry tests that require repeating. For patients with clinically significant laboratory abnormalities at week 12 in Study TV50717 CNS-30046 or at week 8 in Study TV50717-CNS-30060, Study TV50717 CNS-30046 week 13 value(s) or Study TV50717-CNS-30060 week 9 value(s) will serve as baseline laboratory values in this study. Rollover for such patients must be approved by the medical monitor and may be delayed.	The baseline visit assessment design has been updated to include handling and results from previous study assessment.
3.1.3. Titration Period (Other section affected by this change: 5.1.)		
Patients will receive 6 mg of TEV-50717 with food on the evening of day 1. Tablets should	Patients will receive 6 mg of TEV-50717 with food on the	A statement was added to further

be taken with food (eg, a snack) and should not be taken on an empty stomach.	evening of day 1. Tablets should be taken with food (eg, a snack) and should not be taken on an empty stomach.	clarify that the IMP should be taken with a snack and not on an empty stomach.
3.1.3. Titration Period		
In-person (in-clinic) study visits will be scheduled at weeks 2, 4, and 6, and telephone contacts will be scheduled for weeks 1, 3, 5, and 7 in order to assess tic severity and adverse events. The dose of the ~~study drug~~IMP should be increased on a weekly basis until one of the following ~~criteria is met~~occurs: ~~there is optimal reduction of tics, as determined by the investigator, in consultation with the patient and caregiver/adult.~~The investigator determines there has been a clinically meaningful reduction in tics, as indicated by a sustained reduction in the TS-CGI The patient experiences a protocol-defined "clinically significant" adverse event (defined as an adverse event that is related to ~~medication drug~~IMP and is either moderate or severe in intensity or meets the criteria for a serious adverse event) The maximum allowable dose is reached, based on the patient's weight and use of strong CYP2D6 inhibitors	In-person (in-clinic) study visits will be scheduled at weeks 2, 4, and 6, and telephone contacts will be scheduled for weeks 1, 3, 5, and 7 in order to assess tic severity and adverse events. The dose of the IMP should be increased on a weekly basis until one of the following occurs: The investigator determines there has been a clinically meaningful reduction in tics, as indicated by a sustained reduction in the TS-CGI The patient experiences a protocol-defined "clinically significant" adverse event (defined as an adverse event that is related to IMP and is either moderate or severe in intensity or meets the criteria for a serious adverse event) The maximum allowable dose is reached, based on the patient's weight and use of strong CYP2D6 inhibitors	The titration instructions were modified to provide more objective guidance to investigators, who are now directed to increase the dose until there is a sustained reduction in the TS-CGI.
3.4.1. Efficacy Measures and Time Points (Other sections affected by this change: Sections 6.1., 6.1.1., 6.1.2.)		
• YGTSS (to calculate TTS): Screening (only for patients who completed Study SD-809-C-17**);** baseline (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060); and weeks 2, 4, 6, 8, 15, 28, 41, 54, and 55 • TS-CGI: Baseline ~~(only for patients who completed Study SD-809-C-17)~~ (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060) and weeks 2, 4, 6, 8, 15, 28, 41,	• YGTSS (to calculate TTS): Screening (only for patients who completed Study SD-809-C-17**);** baseline (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060); and weeks 2, 4, 6, 8, 15, 28, 41, 54, and 55 • TS-CGI: Baseline (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from	This section was updated to identify baseline data from parent studies, which will be utilized in this open-label study.

54, and 55 • TS-PGIS: Baseline (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060) and weeks 2, 4, 6, 8, 15, 28, 41, 54, and 55	Study TV50717-CNS-30060) and weeks 2, 4, 6, 8, 15, 28, 41, 54, and 55 • TS-PGIS: Baseline (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060) and weeks 2, 4, 6, 8, 15, 28, 41, 54, and 55	
3.7. Drugs Used in the Study		
The IMP is a matrix formulation and is designed as a gastro-erosional tablet to be administered with food and should not be taken on an empty stomach.	The IMP is a matrix formulation and is designed as a gastro-erosional tablet to be administered with food and should not be taken on an empty stomach.	A statement was added to further clarify that the IMP should not be taken on an empty stomach.
3.12. Study Procedures and Assessments		
Study procedures and assessments with their timinge points are summarized presented in Table 1. During a visit, study procedures and assessments should be performed in the order specified in the study manual.	Study procedures and assessments with their time points are presented in Table 1. During a visit, study procedures and assessments should be performed in the order specified in the study manual.	The section was modified to provide guidance that the order of procedures will be determined in a study manual.
3.12.1 Procedures for Screening and Enrollment (Visit 1)		
~~After informed consent is obtained, patients rolling over from Study SD-809-C-17 who are screened will be assigned an 8-digit permanent identification number such that all patients from each investigational center are given consecutive identification numbers in successive order of inclusion. The first 2 digits of the screening number will be the number assigned to the country where the investigational center is located, the next 3 digits will be the assigned number of the investigational center, and the last 3 digits will be assigned at the investigational center (eg, if the number assigned to the country is 01, the third patient screened at fifth investigational center would be given the number of 01005003).~~		This paragraph was deleted to remove the detailed specificity for patient ID assignment.
3.12.1 Procedures for Screening and Enrollment (Visit 1)		
• administer the following questionnaires (Note: For MINI Kid and C-SSRS,	• administer the following questionnaires (Note: For	Specific instruction was provided for

children 13 years of age and under must be interviewed in conjunction with the caregiver/adult. 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 and C-SSRS, children 13 years of age and under must be interviewed in conjunction with the caregiver/adult. 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.):	the YGTSS assessment to be performed before any blood draws or ECG.
3.12.1.1. YGTSS Rater Certification		
3.12.1.1. 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 54/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.	**3.12.1.1. 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 54/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.	This section was added for instruction related to protocol specific YGTSS rater certification.
3.12.2. Procedures before Investigational Medicinal Product Treatment (Baseline) (Other sections affected by this change: 3.12.3.1.2., 3.12.3.2.1., 3.12.4.1)		

• administer the following questionnaires (Note: For C-SSRS, Tic-free Interval, CY-BOCS, and GTS-QOL, children 13 years of age and under must be interviewed in conjunction with the caregiver/adult. 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, and TS-PGIS questionnaires should be performed before any blood draws or ECG assessments.):	• administer the following questionnaires (Note: For C-SSRS, Tic-free Interval, CY-BOCS, and GTS-QOL, children 13 years of age and under must be interviewed in conjunction with the caregiver/adult. 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, and TS-PGIS questionnaires should be performed before any blood draws or ECG assessments.):	Specific instruction was provided for the YGTSS, TS-CGI, and TS-PGIS assessments to be performed before any blood draws or ECG.
4.1. Patient Inclusion Criteria		
h. ~~Women/girls of childbearing potential (not surgically sterile [at least 3 months] or congenitally sterile) whose male partners are of childbearing potential must use contraception for the duration of the study and for 30 days after discontinuation of study drug. Acceptable methods of contraception are those with a failure rate of less than 1% per year (eg, intrauterine device inert, copper or levonorgestrel; combined [estrogen and progestogen] hormonal contraceptive [oral, implanted, transdermal]; progesterone only [implanted, oral and injected]; and intrauterine hormone releasing system); and sole partner vasectomy (medically assessed for surgical success). Examples of surgical sterility are documented: Bi-tubal ligation, hysterectomy, bilateral salpingo oophorectomy, bilateral oophorectomy, and hysterectomy with bilateral salpingo oophorectomy. These methods need to be initiated at least 3 months prior to study drug administration.~~ Females may be included only if they have a negative β-human chorionic gonadotropin test at baseline or are sterile. Definitions of sterile are given in Appendix L. i. Females of childbearing potential whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth	h. Females may be included only if they have a negative β-human chorionic gonadotropin test at baseline or are sterile. Definitions of sterile are given in Appendix L. i. Females of childbearing potential 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 drug half lives, whichever is longer after last dose of IMP. Further details are included in Appendix L.	The inclusion criteria for females was updated to include additional inclusion criteria related to β HCG test and the requirement to use highly effective birth control methods.

control methods for the duration of the study (ie, starting at screening) and for 30 days or 5 drug half lives, whichever is longer after last dose of IMP. Further details are included in Appendix L.		
4.2. Patient Exclusion Criteria		
m. Patient ~~requires treatment with drugs known to prolong the QT interval (see Appendix A, Table 7) for a complete list of prohibited QT-prolonging drugs).~~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 12-lead ECG at screening. ~~m.~~n. ~~Patient has a QTcF interval value >440 msec on 12-lead ECG at screening.~~Patients with a history of torsade de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure.	m. Patient has a QT interval corrected for heart rate using Frederica's formula (QTcF) interval value >450 msec (males) or >460 msec (females) or >480 msec (with right bundle branch block) on 12-lead ECG at screening. n. Patients with a history of torsade de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure.	The exclusion criteria was modified to further define criteria for QTc and add additional exclusion criteria related to specific cardiac conditions.
4.2 Patient Exclusion Criteria		
t. Patient is a pregnant or ~~breastfeeding~~ or lactating female, or plans to become pregnant during the study	t. The patient is a pregnant or lactating female, or plans to become pregnant during the study.	The exclusion criteria for females was updated to include additional exclusion criteria.
4.4. Withdrawal Criteria and Procedures (Other sections affected by this change: 7.1.7., 7.7.)		
In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each patient is free to withdraw from the ~~study drug~~IMP at any time. The investigator also has the right to withdraw a patient from the ~~study drug~~IMP in the event of intercurrent illness, adverse events, pregnancy (see Section 7.3), or other reasons concerning the health or well-being of the patient, or in the event of lack of cooperation. 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	In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each patient is free to withdraw from the IMP at any time. The investigator also has the right to withdraw a patient from the IMP in the event of intercurrent illness, adverse events, pregnancy (see Section 7.3), or other reasons concerning the health or well-being of the patient, or in the event of lack of cooperation. 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	The additional text regarding ECG assessments and QTc limit was included to identify QTc changes that will require IMP suspension.

>60 msec. In addition, a patient may be withdrawn from the ~~study drug~~IMP as described in Sections 3.10, 3.12.3.2.2, 5.4, and 7.1.7.	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. In addition, a patient may be withdrawn from the IMP as described in Sections 3.10, 3.12.3.2.2, 5.4, and7.1.7.	
5.1. Drugs Administered During the Study		
Not applicable	Added header "Daily dose (mg) at the start of visit/week"	The table header was updated in the synopsis to clarify table contents.
5.1. Drugs Administered During the Study		

	~~Weight category~~ Daily dose (mg) at the start of visit/week		
Study week[a]	**20 to <30 kg (44 to <66 lbs)**	**30 to <40 kg 66 to <88 lbs)**	**≥40 kg (≥88 lbs)**
~~Week 1~~ Baseline	mg	6 mg	6 mg (Days 1 and 2) 12 mg[b]
Week ~~2~~ 1	12 mg	12 mg	18 mg
Week ~~3~~ 2	18 mg	18 mg	24 mg
Week ~~4~~3	18 mg[c]	24 mg[c]	30 mg
Week ~~5~~4	24 mg[c]	30 mg[c]	36 mg[c]
Week ~~6~~ 5	24 mg[c]	36 mg[c]	42 mg[c]
Week ~~7~~ 6	30 mg[c]	42 mg[c]	48 mg[c]

	Daily dose (mg) at the start of visit/week		
Study week[a]	**20 to <30 kg (44 to <66 lbs)**	**30 to <40 kg (66 to <88 lbs)**	**≥40 kg (≥88 lbs)**
Baseline	6 mg	6 mg	6 mg (Days 1 and 2) 12 mg[b]
Week 1	12 mg	12 mg	18 mg
Week 2	18 mg	18 mg	24 mg
Week 3	18 mg[c]	24 mg[c]	30 mg
Week 4	24 mg[c]	30 mg[c]	36 mg[c]
Week 5	24 mg[c]	36 mg[c]	42 mg[c]
Week 6	30 mg[c]	42 mg[c]	48 mg[c]

The table was updated with weight details and clarifications regarding how study weeks are defined with the visit occurring at the beginning of the week.

5.3. Prior and Concomitant Medication or Treatment (Other sections affected by this change: 7.10.)

Any prior or concomitant therapy, medication, or procedure a patient has had within 3 months before ~~study drug~~IMP administration and up to the end of the study period, including follow-up, will be recorded on the CRF. Generic or trade name, indication, and dosage will be recorded. The sponsor will encode all therapy and medication according to the World Health Organization drug dictionary. At each clinic visit after the screening visit, the investigator will ask patients whether they	Any prior or concomitant therapy, medication, or procedure a patient has had within 3 months before IMP administration and up to the end of the study period, including follow-up, will be recorded on the CRF. Generic or trade name, indication, and dosage will be recorded. The sponsor will encode all therapy and medication according to the World Health Organization drug dictionary.	This additional instruction will allow the investigator to monitor new concomitant medications, thus enhancing patient safety.

have taken any medications (other than ~~study drug~~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.	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.	
6.1. Efficacy and Exploratory Measures		
• [redacted]	• [redacted]	[redacted] .
7.5. Clinical Laboratory Tests		
The clinical significance of the lab values will be evaluated by the criteria described in the study lab manual and by the judgment of the investigator.	The clinical significance of the lab values will be evaluated by the criteria described in the study lab manual and by the judgment of the investigator.	This sentence was included to provide further guidance regarding clinical significance of laboratory values and investigator judgement.
7.7. Electrocardiography		
A 12-lead ECG will be recorded at the time points detailed in Table 1. 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	A 12-lead ECG will be recorded at the time points detailed in Table 1. 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.	This section was updated to specify ECG clinical significance correlating with adverse event determination.

<table>
<tr><td>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 ~~12-Lead ECGs will be interpreted by a cardiologist at a central diagnostic center. Heart rate and ECG intervals (PR, QRS, QT, and QTcF) and clinical interpretation will be assessed by the central cardiologist, recorded~~, and monitored as described in Section 7.1.2.</td><td>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.</td><td></td></tr>
<tr><td colspan="3">9.4.2. Demographic and Baseline Characteristics</td></tr>
<tr><td>Patient demographic and baseline characteristics, including medical history, prior medications and treatments, and ECG findings, will be summarized using descriptive statistics and will be analyzed by age group.</td><td>Patient demographic and baseline characteristics, including medical history, prior medications and treatments, and ECG findings, will be summarized using descriptive statistics and will be analyzed by age group.</td><td>This section was updated to add that data will be analyzed by age group.</td></tr>
<tr><td colspan="3">11.1.2. Protocol Violations</td></tr>
<tr><td>Protocol violations will be identified and recorded by investigational center personnel in a log or as part of the CRF.</td><td>Protocol violations will be identified and recorded by investigational center personnel in a log or as part of the CRF.</td><td>The documentation mechanism for recording protocol violations was updated to include a log.</td></tr>
<tr><td colspan="3">APPRENDIX A ALLOWED AND DISALLOWED MEDICATIONS</td></tr>
<tr><td>~~Prohibited QTc-Prolonging Drugs~~
<table><tr><th>~~Generic~~</th><th>~~Class/clinical use~~</th><th>~~Note~~</th></tr><tr><td>~~Azithromycin~~</td><td>~~Antibiotic/bacterial infection~~</td><td>~~-~~</td></tr><tr><td>~~Chloroquine / Mefloquine~~</td><td>~~Anti-malarial/malaria infection~~</td><td>~~-~~</td></tr><tr><td>~~Clarithromycin[a]~~</td><td>~~Antibiotic/bacterial infection~~</td><td>~~-~~</td></tr><tr><td>~~Domperidone~~</td><td>~~Anti-nausea/nausea~~</td><td>~~Not available in~~</td></tr></table></td><td>Not applicable</td><td>The restriction on the use of concomitant medications that are commonly used within the pediatric population and that prolong the QT interval (eg, antibiotics) was removed. Antipsychotic medications remain prohibited owing to their ability to</td></tr>
</table>

		~~USA~~		confound the efficacy and safety of TEV-50717. These changes were made based on the cardiodynamic data from the thorough QT study, the PK-PD modeling of maximal steady exposure in studies with HD and TD, and with observed data from the TD program in which QT interval prolonging drugs were safely administered in conjunction with TEV-50717.
~~Droperidol~~	~~Sedative; anti-nausea/anesthesia adjunct, nausea~~	-		
~~Erythromycin~~	~~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 Systemic use only. Topical use is allowed.~~
~~USA=United States of America.~~

APPENDIX I TOURETTE SYNDROME-PATIENT GLOBAL IMPRESSION OF SEVERITY

~~Choose the statement that best describes your tics over the past week:~~		Not applicable	The "first table" in the appendix was deleted. The PGIS questionnaire remains in Appendix I.
~~1~~	~~None. I have had no tics at all.~~		
~~2~~	~~Mild. My tics are rarely noticed by others, they are not distressing, and they do not interfere with my daily life.~~		
~~3~~	~~Moderate. My tics are sometimes noticed by others and occasionally bring me unwanted attention. They can be distressing or interfere with my daily life.~~		
~~4~~	~~Marked. My tics are frequently noticed by others. They cause me substantial distress and interfere with my daily life.~~		
~~5~~	~~Severe. My tics are almost always noticed by others and can cause pain, injury, or severe distress. They prevent me from doing most of my daily activities.~~		

APPENDIX L BIRTH CONTROL METHODS AND PREGNANCY TESTING		
Not applicable	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) 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) before the first dose of IMP. • Intrauterine device (IUD) and intrauterine hormone-releasing system (IUS) need to be in place at least 2 months before screening. • Bilateral tubal occlusion • Vasectomized partner provided he is the sole sexual partner and has received medical assessment of the surgical process. • Sexual abstinence is only considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be	The Appendix for acceptable contraceptive methods for females was included and has been altered to include abstinence in the definition of highly effective birth control.

	evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. • Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception (according to Medicines and Healthcare Products Regulatory Agency, MHRA).	

17.2. Amendment 02 Dated 15 November 2017

The primary reason for this amendment is to incorporate a randomized drug withdrawal period, include and define CYP2D6 impairment status, reorder the statistical testing methodology (ie, the inclusion of the TS-PGII assessment after TS-CGI and before the C&A-GTS-QOL ADL subscale), and include prohibited medications that are associated with QTc prolongation.

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.

Protocol Amendment 01 text with changes shown	**New wording**	**Reason/Justification for change**
Global		
An Open-Label, Long-Term Safety Study Including a Double-Blind, Placebo-Controlled, Randomized Withdrawal Period of TEV-50717 (deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents	An Open-Label, Long-Term Safety Study Including a Double-Blind, Placebo-Controlled, Randomized Withdrawal Period of TEV-50717 (deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents	Updated to reflect randomized drug withdrawal period
Reference Treatment: Not applicable	Placebo IMP: Placebo tablets and packaging match TEV-50717 tablets	Added placebo to IMP
Child and Adolescent Gilles de la Tourette Syndrome - Quality of Life (C&A-GTS-QOL)	Child and Adolescent Gilles de la Tourette Syndrome - Quality of Life (C&A-GTS-QOL)	Updated Gilles de la Tourette Syndrome - Quality of Life (GTS-QOL) to Child and Adolescent Gilles de la Tourette Syndrome - Quality of Life (C&A-GTS-QOL)
Site-administered scales include the YGTSS, CY-	Site-administered scales include the YGTSS, CY-BOCS, Mini	Added TS-PGII

Protocol Amendment 01 text with changes shown	**New wording**	**Reason/Justification for change**
BOCS, Mini International Neuropsychiatric Interview For Children and Adolescents (MINI Kid), and the C-SSRS and self-administered scales include the TS-PGIS, TS-PGII, Tic-free Interval, CDI-2, and C&A-GTS-QOL.	International Neuropsychiatric Interview For Children and Adolescents (MINI Kid), and the C-SSRS and self-administered scales include the TS-PGIS, TS-PGII, Tic-free Interval, CDI-2, and C&A-GTS-QOL.	
~~baseline~~ day 1	day 1	To provide greater protocol clarity and timing of assessments and procedures, references to "baseline" of study 30047 were removed and replaced by "day 1".
Not applicable	Created Part A (screening, titration, maintenance) and Part B (randomized drug withdrawal, re-titration, maintenance)	Added Part B Double-blind placebo controlled randomized drug withdrawal
TS-PGII (Note: Input from the caregiver/adult is ~~required~~ permitted.) TS-PGIS (Note: Input from the caregiver/adult is ~~required~~ permitted.)	TS-PGII (Note: Input from the caregiver/adult is permitted.) TS-PGIS (Note: Input from the caregiver/adult is permitted.)	Changed to indicate that TS-PGII and TS-PGIS input from caregiver/adult is permitted
females ~~of childbearing potential~~ who are postmenarchal or ≥12 years of age	females who are postmenarchal or ≥12 years of age	The definition of women of childbearing potential has been updated

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
		throughout the protocol
TITLE PAGE		
Teva's Development Partner Nuvelution TS Pharma, Inc. 601 Gateway Boulevard Suite 1270 South San Francisco, California 94080 United States of America	Teva's Development Partner Nuvelution TS Pharma, Inc. 601 Gateway Boulevard Suite 1270 South San Francisco, California 94080 United States of America	Title page was changed to update Teva's Development Partner to Nuvelution TS Pharma, Inc.
Clinical Laboratory and Other Departments and Institutions		
Central Institutional Review Board ~~Quorum Review IRB~~ ~~1501 Fourth Avenue, Suite 800~~ ~~Seattle, WA 98101~~ Copernicus Group IRB 1 Triangle Drive Durham, NC 27709 USA **Central Electrocardiogram Evaluation** ~~Biomedical Systems~~ ~~77 Progress Parkway~~ ~~St. Louis, MO 63043~~ ~~USA~~ ERT 1818 Market Street 10th Floor Philadelphia, PA 19103 USA	**Central Institutional Review Board** Copernicus Group IRB 1 Triangle Drive Durham, NC 27709 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	Update Institutional Review Board to Copernicus Group IRB. Change in client vendors

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
Integrated Response Technology ~~Bracket Global, LLC~~ ~~575 East Swedesford Road, Suite 200~~ ~~Wayne, PA 19087~~ ~~USA~~ Endpoint 55 Francisco Street, Suite 200 San Francisco, CA 94133 USA	USA	
Clinical Study Personnel Contact Information		
For operational issues, contact the operational lead listed below: [redacted] [redacted] Nuvelution TS Pharma, INC Tel: [redacted] Email: [redacted] [redacted] **For protocol issues, contact the study leader listed below:** [redacted] Nuvelution TS Pharma, INC. Tel: [redacted] Email: [redacted] [redacted] [redacted] ~~Nuvelution Pharma~~ ~~Tel: +~~ [redacted]	**For operational issues, contact the operational lead listed below:** [redacted] Nuvelution TS Pharma, INC. Tel: [redacted] Email: [redacted] **For protocol issues, contact the study leader listed below:** [redacted] Nuvelution TS Pharma, INC. Tel: [redacted] Email: [redacted] [redacted] [redacted] Nuvelution TS Pharma, INC Tel: + [redacted] Email: [redacted]	Change in Nuvelution study personnel

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
~~Email:~~ [redacted] [redacted] Nuvelution TS Pharma, INC Tel: [redacted] Email: [redacted]		
1.2 Name and Description of Investigational Medicinal Product		
During the randomized drug withdrawal, 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 20-count bottles.	During the randomized drug withdrawal, 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 20-count bottles.	Added last paragraph to describe IMP at randomized drug withdrawal
1.5.1 Justification for Dose of Active Drug		
The dose ranges to be evaluated in this study, based on body weight and ~~the use of strong~~ CYP2D6 ~~inhibitors at baseline,~~ impairment status on day 1, were selected on the basis of the safety, preliminary efficacy, and population pharmacokinetics data generated from Study SD-809-C-17 (Table 2).	The dose ranges to be evaluated in this study, based on body weight and CYP2D6 impairment status on day 1, were selected on the basis of the safety, preliminary efficacy, and population pharmacokinetics data generated from Study SD-809-C-17 (Table 2).	Updated dose ranges to be based on "body weight and CYP2D6 impairment status"
1.8 Location and Study Duration		
This study is planned to be conducted in North America, Latin America, Russia, Ukraine, South Korea, Turkey, and Europe at approximately 100 centers.	This study is planned to be conducted in North America, Latin America, Russia, Ukraine, South Korea, Turkey, and Europe at approximately 100 centers.	Added Latin America, Russia, Ukraine, South Korea, and Turkey to study location list
2.1 Purpose of the Study		
This is an open-label, Phase 3 study with a 2-week, double-blind, placebo-controlled, randomized drug withdrawal period to evaluate the safety and efficacy of	This is an open-label, Phase 3 study with a 2-week, double-blind, placebo-controlled, randomized drug withdrawal period to evaluate the safety and efficacy of TEV 50717 tablets in patients	Updated to more clearly specify the inclusion of the 2-

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
TEV 50717 tablets in patients who have previously completed participation in Study SD-809 C-17, Study TV50717 CNS-30046, or Study TV50717-CNS-30060.	who have previously completed participation in Study SD-809 C-17, Study TV50717 CNS-30046, or Study TV50717-CNS-30060.	week, double-blind, placebo-controlled, randomized drug withdrawal period
2.2.2 Secondary Objectives		
The secondary objectives of ~~the~~this study ~~is~~ are as follows: to evaluate the efficacy of long-term therapy ~~of~~ with TEV-50717 in reducing the severity of TS tics to confirm long-term maintenance of effect by means of a double-blind, placebo-controlled, randomized drug withdrawal period after 28 weeks of open-label treatment	The secondary objectives of this study are as follows: to evaluate the efficacy of long-term therapy with TEV-50717 in reducing the severity of TS tics to confirm long-term maintenance of effect by means of a double-blind, placebo-controlled randomized withdrawal period after 28 weeks of open-label treatment	Added objective for randomized drug withdrawal
2.3.1 Safety Endpoints		
The following safety endpoints will be assessed in Part A:	The following safety endpoints will be assessed in Part A: The following safety endpoints will be assessed in Part B: incidence of adverse events	Added endpoints for Part B
2.3.2 Efficacy Endpoints		
The following efficacy endpoints will be assessed in Part A: Change in the YGTSS TTS from ~~baseline~~ day 1 to each visit in which the scale is administered Change in the TS-CGI score from ~~baseline~~ day 1 to each visit in which the scale is administered Change in the Tourette Syndrome-Patient Global Impression of ~~Severity~~ Impact (~~TS-PGIS~~PGII) score from ~~baseline~~ day 1 to each visit in which the scale is	The following efficacy endpoints will be assessed in Part A: change in the YGTSS TTS from day 1 to each visit in which the scale is administered change in the TS-CGI score from day 1 to each visit in which the scale is administered change in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) score from day 1 to each visit in which the scale is administered change in the Child and Adolescent Gilles de la Tourette	Added Part B endpoints Added TS-PGII to efficacy endpoints;

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
administered Change in the Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life (C&A-GTS QOL) ~~physical/~~activities of daily living (ADL) subscale score from ~~baseline~~ day 1 to each visit in which the scale is administered The following efficacy endpoints will be assessed in Part B: change in the TTS of the YGTSS from week 28 to week 30	Syndrome – Quality of Life (C&A-GTS-QOL) activities of daily living (ADL) subscale score from day 1 to each visit in which the scale is administered The following efficacy endpoints will be assessed in Part B: change in the TTS of the YGTSS from week 28 to week 30	
2.3.3 Exploratory Endpoints		
The following exploratory endpoints will be assessed in Part A: • [redacted]	• [redacted]	[redacted]

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
[redacted]	[redacted]	
3.1 General Design and Study Schematic Diagram		
This is a 56-week, open-label, single-arm study that included a 2-week, double-blind, placebo-controlled, randomized drug withdrawal period to evaluate the safety of TEV-50717 in children and adolescents with tics associated with TS after they have successfully completed any of the parent studies (SD-809-C-17 [Phase 1b], TV50717-CNS-30046 [Phase 2/3], or TV50717-CNS-30060 [Phase 3]). Patients rolling over from Study SD-809-C-17 will need to undergo all day 1 assessments. For patients rolling over from Study TV50717-CNS-30046 or Study TV50717 CNS-30060, the week 13 visit (Study TV50717-CNS-30046) or the week 9 visit (Study TV50717-CNS-30060) will be the day 1 visit for Study TV50717-CNS-30047. If the patient does not wish to enroll in Study TV50717-CNS-30047 at that visit, they can enroll up to 1 week	This is a 56-week, open-label, single-arm study that included a 2-week, double-blind, placebo-controlled, randomized drug withdrawal period to evaluate the safety of TEV-50717 in children and adolescents with tics associated with TS after they have successfully completed any of the parent studies (SD-809-C-17 [Phase 1b], TV50717-CNS-30046 [Phase 2/3], or TV50717-CNS-30060 [Phase 3]). Patients rolling over from Study SD-809-C-17 will need to undergo all day 1 assessments. For patients rolling over from Study TV50717-CNS-30046 or Study TV50717 CNS-30060, the week 13 visit (Study TV50717-CNS-30046) or the week 9 visit (Study TV50717-CNS-30060) will be the day 1 visit for Study TV50717-CNS-30047. If the patient does not wish to enroll in Study TV50717-CNS-30047 at that visit, they can enroll up to 1 week following the week 13 or week 9 visits, respectively. For patients rolling over from Study SD-809-C-17, this study will	Update study design; include time allowed for patients to enroll in study; include re-consent text. Updated assessment scale instructions. Added text to cross-reference Figure 2; the additional diagram that details the blinded, randomized drug

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
following the week 13 or week 9 visits, respectively. For patients rolling over from Study SD-809-C-17, this study will consist of up to a 4-week screening period, ~~a 54-week, open-label treatment period (including 7~~ (up to 31 days) and up to 52 weeks of ~~titration and 47 weeks of maintenance), and a 1-week washout period~~ treatment. Patients will have a follow-up telephone contact to evaluate safety 1 week after the end of the washout period (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 56 weeks. The end of study is defined as the date of the week 56 visit of the last participant. Informed consent/assent and/or co-consent for patients 14 years of age and older, as appropriate, will be obtained before any study procedures are performed. Patients may have informed consent/assent and/or co-consent for patients 14 years of age and older, as appropriate, obtained prior to the ~~baseline~~ day 1 visit, up to 4 weeks in advance of open-label participation. Any patient that turns 18 years of age during the course of Study TV50717-CNS-30047 will need to be re-consented as an adult. Patients who have successfully completed any of the parent studies may be eligible to enroll in the current study after they complete a 1-week washout period and the final evaluation (week 13 in TV50818-CNS-30046 or week 9 in TV50717-CNS-30060) in the parent study. To reduce patient burden, after obtaining informed consent/assent and/or co-consent for patients 14 years of age and older, as appropriate, some data collected in Study TV50717-CNS-30046 or Study TV50717-CNS-30060 will be used to provide corresponding	consist of up to a 4-week screening period (up to 31 days) and up to 52 weeks of treatment. Patients will have a follow-up telephone contact to evaluate safety 1 week after the end of the washout period (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 56 weeks. The end of study is defined as the date of the week 56 visit of the last participant. Informed consent/assent and/or co-consent for patients 14 years of age and older, as appropriate, will be obtained before any study procedures are performed. Patients may have informed consent/assent and/or co-consent for patients 14 years of age and older, as appropriate, obtained prior to the day 1 visit, up to 4 weeks in advance of open-label participation. Any patient that turns 18 years of age during the course of Study TV50717-CNS-30047 will need to be re-consented as an adult. Patients who have successfully completed any of the parent studies may be eligible to enroll in the current study after they complete a 1-week washout period and the final evaluation (week 13 in TV50818-CNS-30046 or week 9 in TV50717-CNS-30060) in the parent study. To reduce patient burden, after obtaining informed consent/assent and/or co-consent for patients 14 years of age and older, as appropriate, some data collected in Study TV50717-CNS-30046 or Study TV50717-CNS-30060 will be used to provide corresponding day 1 data in the current open-label study (see Table 1). All screening procedures will be performed for patients rolling over from Study SD 809 C 17, as they will have been off IMP for several months at the time of enrollment into the current study. Site-administered scales include the YGTSS, CY-BOCS, Mini International Neuropsychiatric Interview for Children and Adolescents (MINI Kid), and the C-SSRS and self-administered scales include the TS-PGII, TS-PGIS, Tic-free Interval, CDI-2, and C&A-GTS- QOL. For the YGTSS, input from the	withdrawal/titration period (Part B of the study)

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
~~baseline~~ day 1 data in the current open-label study (see Table 1). All screening procedures will be performed for patients rolling over from Study SD 809 C 17, as they will have been off IMP for several months at the time of enrollment into the current study. Site-administered scales include the YGTSS, CY-BOCS, Mini International Neuropsychiatric Interview for Children and Adolescents (MINI Kid), and the C-SSRS and self-administered scales include the TS-PGII, TS-PGIS, Tic-free Interval, CDI-2, and C&A-GTS- QOL. For the YGTSS, input from the caregiver/adult is required. For both the TS-PGII and TS -PGIS, input from the caregiver/adult is ~~required. For the Tic-free Interval, C SSRS, and CY-BOCS~~ permitted. For all other scales, children 13 years of age and under ~~must~~, interviews may be ~~interviewed in conjunction~~ performed separately or jointly with the caregiver/adult as appropriate or as defined by the scale. The study schematic diagram is presented in Figure 1. An additional diagram that details the blinded, randomized drug withdrawal/titration period (Part B of the study) is presented in Figure 2.	caregiver/adult is required. For both the TS-PGII and TS -PGIS, input from the caregiver/adult is permitted. For all other scales, children 13 years of age and under, interviews may be performed separately or jointly with the caregiver/adult as appropriate or as defined by the scale. The study schematic diagram is presented in Figure 1. An additional diagram that details the blinded, randomized drug withdrawal/titration period (Part B of the study) is presented in Figure 2.	
Figure 1 and Figure 2		
Not applicable	[Figure 1 was updated for consistency with changes made to the table of procedures] [Figure 2 was created and inserted to more clearly indicate the processes for Part B]	Updated study schematic Figure 1 and Figure 2 for consistency with protocol edits and to include drug withdrawal re-randomization

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
		period, respectively
Section 3.1.1 Screening Period (up to 31 Days)		
Screening period (up to ~~4 weeks; minimum of 3~~31 days): All screening procedures will be performed for patients rolling over from Study SD 809 C 17, as they will have been off IMP for several months at the time of enrollment into this study (TV50717 CNS-30047). At the discretion of the investigator, the screening visit may be divided into 2 visits if the visit length is deemed to be too burdensome for the patient. Patients may be rescreened ~~at~~1 time if there is a change in ~~the discretion of the~~ patient's medical ~~monitor~~ background, a modification of study entry criteria, or other relevant change (Note: Details of a patient's rescreening must be approved).	Screening period (up to 31 days): All screening procedures will be performed for patients rolling over from Study SD 809 C 17, as they will have been off IMP for several months at the time of enrollment into this study (TV50717 CNS-30047). At the discretion of the investigator, the screening visit may be divided into 2 visits if the visit length is deemed to be too burdensome for the patient. Patients may be rescreened 1 time if there is a change in the patient's medical background, a modification of study entry criteria, or other relevant change (Note: Details of a patient's rescreening must be approved).	Change screening period from up to 4 weeks to up to 31 days. Updated screening visit details
3.1.2 Day 1 Visit (All Patients)		
For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, the week 13 visit (Study TV50717-CNS-30046) or the week 9 visit (Study TV50717-CNS-30060) will be the ~~baseline~~ day 1 visit for Study TV50717-CNS-30047. Patients rolling over from Study SD-809-C-17 will need to undergo all ~~baseline~~ day 1 assessments.~~Baseline~~ Day 1 assessments for Study TV50717-CNS-30047 that are identical to Study TV50717-CNS-30046 week 13 or Study TV50717-CNS-30060 week 9 assessments do not need to be repeated. Additionally, Study TV50717-CNS-30047 required evaluations will be completed at Study TV50717-CNS-30046 week 13 visit or Study TV50717-CNS-30060 week 9 visit (see Table 1).	For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, the week 13 visit (Study TV50717-CNS-30046) or the week 9 visit (Study TV50717-CNS-30060) will be the day 1 visit for Study TV50717-CNS-30047. Patients rolling over from Study SD-809-C-17 will need to undergo all day 1 assessments. Day 1 assessments for Study TV50717-CNS-30047 that are identical to Study TV50717-CNS-30046 week 13 or Study TV50717-CNS-30060 week 9 assessments do not need to be repeated. Additionally, Study TV50717-CNS-30047 required evaluations will be completed at Study TV50717-CNS-30046 week 13 visit or Study TV50717-CNS-30060 week 9 visit (see Table 1). For all patients, the day 1 visit will occur on or as close as possible to the week 13 or week 9 visit from Study TV50717-CNS-30046 and Study TV50717-CNS-30060, respectively, but	Updated day 1 visits

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
For all patients, the ~~baseline~~ day 1 visit will occur on or as close as possible to the ~~same day as the scheduled first dose of the IMP (day 1). If washout period is~~ week 13 or week 9 visit from Study TV50717-CNS-30046 and Study TV50717-CNS-30060, respectively, but not >7 days, ~~the medical monitor must be consulted for which entry tests that require repeating~~ beyond those respective visits.	not >7 days, beyond those respective visits.	
3.1.3 Titration Period		
As patients from Study SD-809-C-17 will have been off study drug for several months at the time of enrollment, and since patients from Study TV50717-CNS-30046 will have discontinued study drug (TEV-50717 or placebo) for at least 1 week at completion of the parent study, all patients will undergo TEV-50717 dose titration in this study. Patients will receive 6 mg of TEV-50717 with food on the evening of day 1. The titration scheme and maximum dose will be determined by body weight and ~~use of strong cytochrome P450 2D6 (CYP2D6) inhibitors, as shown in~~ CYP2D6 impairment status from the parent study. 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 of the parent study. Patients who are CYP2D6 impaired will have a dose cap in the open label study, as shown in Table 2 ~~and Table 3, respectively~~.	As patients from Study SD-809-C-17 will have been off IMP for several months at the time of enrollment, and since patients from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 will have discontinued IMP (TEV-50717 or placebo) for at least 1 week at completion of the parent study, all patients will undergo TEV-50717 dose titration in this study. Patients will receive 6 mg of TEV-50717 with food on the evening of day 1. Tablets should be taken with food (eg, a snack) and should not be taken on an empty stomach. The titration scheme and maximum dose will be determined by body weight and CYP2D6 impairment status from the parent study. 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 of the parent study. Investigators will be unblinded to CYP2D6 metabolizer by a dose cap for CYP2D6 impairment status, as shown in Table 2.	Update titration period to include and define CYP2D6 impairment status in titration scheme and dosing
3.1.4 Maintenance Period		
At the end of the titration period, the patient's initial dose for the maintenance period will be established. Dose adjustments of TEV 50717 (upward or	At the end of the titration period, the patient's initial dose for the maintenance period will be established. Dose adjustments of TEV 50717 (upward or downward) may be made during the	Updated the maintenance

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
downward) may be made during the maintenance period, if necessary, but not more often than every 5 days and only in increments of 6 mg. ~~Dose~~ As during titration, 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, the patient's weight, and information from the rating scales~~. During the maintenance period, in-person (in-clinic) study visits will be scheduled at weeks 8, 15, ~~28~~ 34, 41, and 54 for assessments of safety and efficacy and telephone contacts will be scheduled for weeks 21~~, 34,~~ and 47 in order to assess adverse events and tic severity. At week 54, patients will undergo a complete evaluation, including physical and neurological examination, safety laboratory testing, 12-lead ECG, CDI-2, and C SSRS assessments, as well as the YGTSS, TS-CGI, TS-PGIS, TS-PGII, Tic free Interval, CY-BOCS, and C&A-GTS- QOL.	maintenance period, if necessary, but not more often than every 5 days and only in increments of 6 mg. As during titration, dose adjustments should be made based on all available information. During the maintenance period, in-person (in-clinic) study visits will be scheduled at weeks 8, 15, 34, 41, and 54 for assessments of safety and efficacy and telephone contacts will be scheduled for weeks 21 and 47 in order to assess adverse events and tic severity. At week 54, patients will undergo a complete evaluation, including physical and neurological examination, safety laboratory testing, 12-lead ECG, CDI-2, and C SSRS assessments, as well as the YGTSS, TS-CGI, TS-PGIS, TS-PGII, Tic free Interval, CY-BOCS, and C&A-GTS- QOL	period statement
3.1.5 Washout Period and Follow-up		
See Figure 1 and Figure 2 for study schema	See Figure 1 and Figure 2 for study schema	Added Figure 2 as reference
3.1.6. Part B: Blinded, Randomized Drug Withdrawal Period and Titration Post-Drug Withdrawal Period		
Not applicable	At week 28, the patients will be randomized 2:1 to their current dose of TEV-50717 or placebo in order to check for return of symptoms. Patients will have a follow-up telephone contact for safety evaluation 1 week after the start of the randomized drug withdrawal period. At week 30, safety and efficacy will be assessed. At the week 30 visit, patients who receive TEV-50717 during the randomized drug withdrawal period will continue at the	Added section and statements for randomized drug withdrawal period and re-titration

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
	same dose. Any patient who was randomized to placebo during this 2-week period will begin re titration. Patients will have a follow-up telephone contact for safety evaluation at weeks 31 and 33. All patients should be back at their maintenance dose on or before week 34 and return to open-label treatment for the remainder of the study.	
3.1.7. Titration Post-Drug Withdrawal (Weeks 31, 32, and 33)		
Not applicable	Any patient who was randomized to placebo during weeks 28 to 30 will undergo re-titration to their target dose over the 3 weeks of treatment following the randomized drug withdrawal period. The titration scheme and maximum dose will be determined by body weight and CYP2D6 impairment status. The dose of IMP for each patient who underwent 2 weeks of placebo will be titrated back to the maintenance dose that was used by the patient up to week 28 followed by continued maintenance therapy at that dose.	Added section and statements for the titration post-withdrawal (Weeks 31 to 33)
3.2. Justification for Study Design		
This is an open-label, single-arm study that includes a 2-week, double-blind, placebo-controlled, randomized drug withdrawal period in which patients with TS may be eligible to participate after successful completion of any of the parent studies (SD-809-C-17 [Phase 1b], TV50717-CNS-30046 [Phase 2/3], or TV50717-CNS-30060 [Phase 3]). Patients who have successfully completed a parent study may be eligible to enroll in this study after they complete a 1-week washout period and the final evaluation in the parent study. For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, the week 13 visit (Study TV50717-CNS-30046) or the week 9 visit (Study TV50717-CNS-30060) will be the day 1 visit for Study TV50717-CNS-30047. If the patient does not wish to enroll in Study TV50717-CNS-30047 at that	This is an open-label, single-arm study that includes a 2-week, double-blind, placebo-controlled, randomized drug withdrawal period in which patients with TS may be eligible to participate after successful completion of any of the parent studies (SD-809-C-17 [Phase 1b], TV50717-CNS-30046 [Phase 2/3], or TV50717-CNS-30060 [Phase 3]). Patients who have successfully completed a parent study may be eligible to enroll in this study after they complete a 1-week washout period and the final evaluation in the parent study. For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, the week 13 visit (Study TV50717-CNS-30046) or the week 9 visit (Study TV50717-CNS-30060) will be the day 1 visit for Study TV50717-CNS-30047. If the patient does not wish to enroll in Study TV50717-CNS-30047 at that visit, they can enroll up to 1 week following the week 13 or week 9 visits, respectively. The end of study is defined as the date of the week 56 visit of the last	Updates made to clarify study design and guidance to the investigators

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
visit, they can enroll up to 1 week following the week 13 or week 9 visits, respectively. The end of study is defined as the date of the week 56 visit of the last participant. The open-label study design (ie, no placebo or comparator) was selected to allow further evaluation and review long-term safety of TEV-50717 in this patient population. Patients will receive twice daily dosing for up to 54 weeks, with an initial 7-week titration period to allow for optimal dose selection. At week 28, patients will begin a blinded, randomized drug withdrawal period. The randomized drug withdrawal period will rigorously assess the long-term maintenance of effect. Patients will be randomized to their current dose of TEV-50717 or placebo for 2 weeks. After completing the 2 weeks, patients will continue their same dose of TEV-50717 or be re titrated (patients receiving placebo only) for 3 weeks. At week 34, patients will resume their maintenance dose. This is a classic ABA study design (ie, drug, placebo, drug) that allows for a more rigorous test of the intervention. In the traditional AB design, changes in symptoms (particularly in a long trial) could be attributed to other factors (eg, life changes, societal issues, and regression to the mean); however, an acute change demonstrated only in a placebo group among subjects that have been maintained for several months would reduce the likelihood of any other explanations for changes in symptoms.	participant. The open-label study design (ie, no placebo or comparator) was selected to allow further evaluation and review long-term safety of TEV-50717 in this patient population. Patients will receive twice daily dosing for up to 54 weeks, with an initial 7-week titration period to allow for optimal dose selection. At week 28, patients will begin a blinded, randomized drug withdrawal period. The randomized drug withdrawal period will rigorously assess the long-term maintenance of effect. Patients will be randomized to their current dose of TEV-50717 or placebo for 2 weeks. After completing the 2 weeks, patients will continue their same dose of TEV-50717 or be re titrated (patients receiving placebo only) for 3 weeks. At week 34, patients will resume their maintenance dose. This is a classic ABA study design (ie, drug, placebo, drug) that allows for a more rigorous test of the intervention. In the traditional AB design, changes in symptoms (particularly in a long trial) could be attributed to other factors (eg, life changes, societal issues, and regression to the mean); however, an acute change demonstrated only in a placebo group among subjects that have been maintained for several months would reduce the likelihood of any other explanations for changes in symptoms.	
3.3 Safety Measures and Time Points		
Part A: Physical examination: Screening (only for patients who	Part A: Physical examination: Screening (only for patients who completed	Updates to Part A assessments

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completed Study SD-809 C-17; data from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 should be used for the remaining patients) and ~~weeks 28 and~~ week 54 Vital signs and weight: Screening (only for patients who completed Study SD-809-C 17; data from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 should be used for the remaining patients); ~~baseline~~ day 1; and weeks 2, 4, 6, 8, 15, ~~28~~ 34, 41, 54, and 55 -Note: Orthostatic blood pressure (BP) and pulse ~~at baseline;~~ on day 1 and weeks 4, ~~28~~ 8, and 54 Children's C-SSRS Since Last Visit (SLV) scale: ~~Baseline~~ Day 1 (only for patients who completed Study SD 809-C-17) and weeks 2, 4, ~~6,~~ 8, 15, ~~28~~ 34, 41, 54, and 55 • CDI-2 (Parent and Self-report versions): Screening and ~~baseline~~day 1 (ie, only for patients who completed Study SD 809 C 17) and weeks 2, 4, 6, 8, 15, ~~28~~34, 41, 54, and 55 • 12-Lead ECG: Screening (ie, only for patients who completed Study SD 809 C 17); ~~baseline~~day 1; and weeks 4, 6, ~~28~~8, and 54 • Clinical laboratory tests (serum chemistry, hematology, and urinalysis): Screening (ie, only for patients who completed Study SD 809 C 17; data from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 should be used for the remaining patients); ~~baseline~~day 1; and weeks ~~6, 28,~~8 and 54 • Pregnancy testing: Screening (ie, only for patients who completed Study SD 809 C 17); ~~baseline;~~day 1 and weeks ~~28~~4, 8, 15, 34, and 54	Study SD-809 C-17; data from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 should be used for the remaining patients) and week 54 Vital signs and weight: Screening (only for patients who completed Study SD-809-C 17; data from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 should be used for the remaining patients); day 1; and weeks 2, 4, 6, 8, 15, 34, 41, 54, and 55 -Note: Orthostatic blood pressure (BP) and pulse on day 1 and weeks 4, 8, and 54 Children's C-SSRS Since Last Visit (SLV) scale: Day 1 (only for patients who completed Study SD 809-C-17) and weeks 2, 4, 8, 15, 34, 41, 54, and 55 • CDI-2 (Parent and Self-report versions): Screening and day 1 (ie, only for patients who completed Study SD 809 C 17) and weeks 2, 4, 6, 8, 15, 34, 41, 54, and 55 • 12-Lead ECG: Screening (ie, only for patients who completed Study SD 809 C 17); day 1; and weeks 4, 6, 8, and 54 • Clinical laboratory tests (serum chemistry, hematology, and urinalysis): Screening (ie, only for patients who completed Study SD 809 C 17; data from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 should be used for the remaining patients); day 1; and weeks 8 and 54 • Pregnancy testing: Screening (ie, only for patients who completed Study SD 809 C 17); day 1 and weeks 4, 8, 15, 34, and 54	timing

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
Not applicable	Part B: Adverse events and concomitant medications: From the signing of the informed consent form through follow-up, inclusive of all visits and telephone contacts Physical examination: Weeks 28 and 30 Vital signs and weight: Weeks 28, 30, and 32 Note: Orthostatic BP and pulse at week 28 Children's C-SSRS: SLV scale: Weeks 28 and 30 CDI-2 (parent and self-report versions): Weeks 28 and 30 Pregnancy testing: Week 28	Added safety measures/assessments to be conducted for Part B
3.4.1 Efficacy Measures and Time Points		
Part A and Part B: • YGTSS (to calculate TTS): Screening (only for patients who completed Study SD 809 C 17); ~~baseline~~ day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060); and weeks 2, 4, ~~6,~~ 8, 15, 28, 30, 34, 41, 54, and 55 • ~~TS-PGIS: Baseline~~ TS-CGI: Day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060) and weeks ~~2,~~ 4, ~~6,~~ 8, 15, 28, 34, 41, 54, and 55 • TS-PGII: Day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060) and weeks 4, 8, 15, 28, 34, 41, 54, and 55 • C&A-GTS- QOL (~~physical/~~ADL subscale): ~~Baseline~~ Day 1 and weeks 6, 28, 34, and 54	Part A and Part B: • YGTSS (to calculate TTS): Screening (only for patients who completed Study SD 809 C 17); day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060); and weeks 2, 4, 8, 15, 28, 30, 34, 41, 54, and 55 • TS-CGI: Day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060) and weeks 4, 8, 15, 28, 34, 41, 54, and 55 • TS-PGII: Day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060) and weeks 4, 8, 15, 28, 34, 41, 54, and 55 • C&A-GTS- QOL (ADL subscale): Day 1 and weeks 6, 28, 34, and 54	Added efficacy measures and time points for Part A and B

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
3.4.2 Exploratory Measures and Time Points		
Part A and Part B: [redacted]	Part A and Part B: [redacted]	[redacted]
3.6 Randomization and Blinding		
~~This is a nonrandomized, open-label study with no blinding and only 1 treatment group.~~ This is an open-label study that includes a 2-week, double-blind, placebo-controlled, randomized drug withdrawal period. At the randomized drug withdrawal	This is an open-label study that includes a 2-week double-blind, placebo-controlled, randomized drug withdrawal period. At the randomized drug withdrawal period (Week 28), the patients will be randomized 2:1 to the current dose or placebo in order to check for return of symptoms. At the end of this period, patients who receive TEV-50717 during the randomized drug withdrawal	Update to randomization and blinding for randomized drug withdrawal period

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
period (week 28), the patients will be randomized 2:1 to the current dose or placebo in order to check for return of symptoms. At the end of this period, patients who receive TEV-50717 during the randomized drug withdrawal period will return to the most recent dose of TEV-50717 and patients who received placebo during the randomized drug withdrawal period will begin titration post-drug withdrawal. All patients will return to open-label dosing at week 34.	period will return to the most recent dose of TEV-50717 and patients who received placebo during the randomized drug withdrawal period will begin re-titration. All patients will return to open-label dosing at week 34.	
3.7 Drugs Used in the Study		
~~This is an uncontrolled study with no other IMP.~~ Patients who receive TEV-50717 during the randomized drug withdrawal period will remain on blinded active IMP from week 30 to week 34; those assigned to placebo during the randomized drug withdrawal period will undergo blinded re-titration from week 30 to week 34 back to their maintenance dose from week 28. 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 20-count bottles.	Patients who receive TEV-50717 during the randomized drug withdrawal period will remain on blinded active IMP from week 30 to week 34; those assigned to placebo during the randomized drug withdrawal period will undergo blinded re-titration from week 30 to week 34 back to their maintenance dose from week 28. 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 20-count bottles.	Added statement into the section to account for the randomized drug withdrawal period
3.8.2 Drug Accountability		
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 IMP will be ~~disposed of per site policy, or~~ returned to the sponsor or its designee, as agreed with the sponsor. ~~A record of IMP accountability (ie, IMP and other~~	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 IMP will be returned to the sponsor or its designee, as agreed with the sponsor.	Study drug to be returned to sponsor or designee

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
~~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 bottles of IMP will be returned to the sponsor or designee.~~		
3.9 Duration of Patient Participation and Justification		
~~This~~ For patients rolling over from Study SD-809-C-17, this study will consist of up to a 4-week screening period, ~~a 54-week, open-label~~ (up to 31 days) and up to 52 weeks of treatment ~~period, and a 1-week washout period~~. Patients will have a follow-up telephone contact to evaluate safety 1 week after the end of the washout period (2 weeks after their last dose of IMP).	For patients rolling over from Study SD-809-C-17, this study will consist of up to a 4-week screening period (up to 31 days), and up to 52 weeks of treatment. Patients will have a follow-up telephone contact to evaluate safety 1 week after the end of the washout period (2 weeks after their last dose of IMP).	Updated to more clearly indicate duration of patient participation in the study
3.11 Source Data Recorded on the Case Report Form		
If patient data are processed from other vendors (eg, clinical laboratory, central ECG, ~~electronic~~ diary data), the results will be sent to the investigational center, where they will be retained but not entered into the CRF. These data may also be sent electronically to the sponsor (or organization performing data management) for direct use with the clinical database (see Section 13.1). All clinical patient data from other vendors will be available to the investigator.	If patient data are processed from other vendors (eg, clinical laboratory, central ECG, diary data), the results will be sent to the investigational center, where they will be retained but not entered into the CRF. These data may also be sent electronically to the sponsor (or organization performing data management) for direct use with the clinical database (see Section 13.1). All clinical patient data from other vendors will be available to the investigator.	Removed "electronic"
3.12 Table 1 Study Procedures and Assessments		
Not applicable	[Table 1 was updated to add/remove assessments and to make a few adjustments as to the timing of some of the assessments. Changes were made in alignment with the changes made throughout the protocol.	Table 1 was updated to add/remove assessments and to

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
	A "second part" of the table was added to include more clear direction on the expectations of Part B and resuming of Part A thereafter. Footnotes were also adjusted as necessary]	make a few adjustments as to the timing of some of the assessments. Changes were made in alignment with the changes made throughout the protocol. The Randomized drug withdrawal period (and continuation of Part A thereafter) and respective assessments were added to the second part of the table
3.12.1 Procedures for Screening and Enrollment (Visit 1)		
• administer the following questionnaires (Note: For MINI Kid and C-SSRS, children 13 years of age and under ~~must~~may be interviewed ~~in conjunction~~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.):	• administer the following questionnaires (Note: For MINI Kid and 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.):	Updated guidance on appropriate delivery of assessments/scales
3.12.1.1 YGTSS Rater Certification		

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
All investigators and subinvestigators 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 where this scale is administered, especially at day 1 and at weeks 28, 30, and 54/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.	All investigators and subinvestigators 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 where this scale is administered, especially at day 1 and at weeks 28, 30, and 54/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.	Updated to clarify best guidance on YGTSS rater certification
3.12.2 Procedures Before Investigational Medicinal Product Treatment (Day 1)		
The following procedures will be performed at the ~~baseline~~ day 1 visit, as they: • perform a serum pregnancy (β-HCG) test (required for all females ~~of childbearing potential~~ who are postmenarchal or ≥12 years of age) • administer the following questionnaires (Note: For C-SSRS, Tic-free Interval, CY BOCS, and C&A-GTS- QOL, children 13 years of age and under ~~must~~ may be interviewed ~~in conjunction~~ 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-PGIS, and ~~TS-PGIS~~ PGII questionnaires should be performed before any blood draws or	The following procedures will be performed at the day 1 visit, as they: • perform a serum pregnancy (β-HCG) test (required for all females who are postmenarchal or ≥12 years of age) • administer the following questionnaires (Note: For C-SSRS, Tic-free Interval, CY BOCS, 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-PGIS, and PGII questionnaires should be performed before any blood draws or ECG assessments.): ----TS-PGII (Note: Input from the caregiver/adult is permitted) ----TS-PGIS (Note: Input from the caregiver/adult is	Updated guidance on appropriate delivery of assessments/scales Updated planned assessments in alignment with protocol changes

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
ECG assessments.): --TS-PGII (Note: Input from the caregiver/adult is permitted.) --TS-PGIS (Note: Input from the caregiver/adult is ~~required~~ permitted) --C&A-GTS- QOL (including VAS) (required for all patients)	permitted) ---C&A-GTS- QOL (including VAS) (required for all patients)	
3.12.3.1.2 In-Clinic Visits (Weeks 2, 4, and 6)		
• at week~~s~~ 4 ~~and 6~~ only, perform 12-lead ECG (Note: ECG will be performed after at least 5 minutes rest in a supine or semi-supine position) • perform a urine pregnancy (β-HCG) test (only in females who are postmenarchal or ≥12 years of age) at week 4 • administer the following questionnaires (Note: For C-SSRS, Tic-free Interval, CY BOCS, and C&A-GTS-QOL, children 13 years of age and under ~~must~~ may be interviewed ~~in conjunction~~ 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-PGIS, and TS-~~PGIS~~PGII questionnaires should be performed before any blood draws or ECG assessments.): ---CDI-2, Parent and Self-report at weeks 2 and 4 only (Note: Children 6 years of age at ~~baseline~~ on day 1 will not complete the self-report version; the caregiver/adult will complete the Parent version) --- C-SSRS (children's SLV) at weeks 2 and 4 only	• at week 4 only, perform 12-lead ECG (Note: ECG will be performed after at least 5 minutes rest in a supine or semi-supine position) • perform a urine pregnancy (β-HCG) test (only in females who are postmenarchal or ≥12 years of age) at week 4 • administer the following questionnaires (Note: For C-SSRS, Tic-free Interval, CY BOCS, 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-PGIS, and TS-PGII questionnaires should be performed before any blood draws or ECG assessments.): ---CDI-2, Parent and Self-report at weeks 2 and 4 only (Note: Children 6 years of age at on day 1 will not complete the self-report version; the caregiver/adult will complete the Parent version.) --- C-SSRS (children's SLV) at weeks 2 and 4 only --- YGTSS at weeks 2 and 4 only (Note: at week 2, only perform assessment of "Severity Ratings" of the questionnaire only. Inventory portions [ie, "Motor Tic Symptom Checklist" and	Updated guidance on appropriate delivery of assessments/scales Updated planned assessments in alignment with protocol changes

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
---YGTSS at weeks 2 and 4 only (Note: at weeks ~~2 and 6~~, only perform assessment of "Severity Ratings" of the questionnaire only. Inventory portions [ie, "Motor Tic Symptom Checklist" and "Phonic Tic Symptom Checklist"] do not need to be performed. Input from the caregiver/adult is required.) ---TS-CGI at week 4 ---TS-PGII at week 4 (Note: Input from the caregiver/adult is permitted) ---TS-PGIS at week 4 (Note: Input from the caregiver/adult is ~~required~~ permitted) ---Tic-free Interval at week 4 ---C&A-GTS- QOL (including VAS); week 6 only	"Phonic Tic Symptom Checklist"] do not need to be performed. Input from the caregiver/adult is required.) ---TS-CGI at week 4 ---TS-PGII at week 4 (Note: Input from the caregiver/adult is permitted) ---TS-PGIS at week 4 (Note: Input from the caregiver/adult is permitted) ---Tic-free Interval at week 4 ---C&A-GTS- QOL (including VAS); week 6 only	
3.12.3.2.1 In-Clinic Visits (Weeks 8, 15, 30, 32, 34, 41, and 54)		
The following procedures/assessments will be performed at weeks 8, 15, ~~28~~30, 32, 34, 41, and 54: • measure vital signs (pulse, BP, body temperature, and respiratory rate); at ~~weeks 28 and~~week 54, orthostatic BP and pulse should be measured after the patient is in a standing position for at least 3 minutes • measure weight (Note: weight must be measured with shoes and outerwear off) • perform full physical examination (including height) at weeks ~~28~~30 and 54 • perform neurological examination at week 54 • perform 12-lead ECG (Note: ECG will be performed after at least 5 minutes rest in a supine or semi-supine position.) at weeks ~~28~~8 and 54 • perform clinical laboratory tests, including serum chemistry, hematology, and urine analyses at weeks 8~~,~~	The following procedures/assessments will be performed at weeks 8, 15, 30, 32, 34, 41, and 54: • measure vital signs (pulse, BP, body temperature, and respiratory rate); at week 54, orthostatic BP and pulse should be measured after the patient is in a standing position for at least 3 minutes • measure weight (Note: weight must be measured with shoes and outerwear off) • perform full physical examination (including height) at weeks 30 and 54 • perform neurological examination at week 54 • perform 12-lead ECG (Note: ECG will be performed after at least 5 minutes rest in a supine or semi-supine position.) at weeks 8 and 54 • perform clinical laboratory tests, including serum chemistry, hematology, and urine analyses at weeks 8 and 54	Updated planned assessments in alignment with protocol changes Timing of study assessments and timing of procedures in Part B were added

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
~~28,~~ and 54 • perform UDS at ~~weeks 28 and~~week 54 • perform a serum pregnancy (β-HCG) test (only in females ~~of childbearing potential~~who are postmenarchal or ≥12 years of age) at weeks ~~28~~8, 15, 34, and 54 • administer the following questionnaires (Note: For C-SSRS, Tic-free Interval, CY BOCS, and C&A-GTS-QOL, children 13 years of age and under ~~must~~may be interviewed ~~in conjunction~~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. 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. ~~child, but the caregiver/adult should be encouraged to add relevant information.~~ The YGTSS, TS-CGI, TS-PGIS, and TS-PGII questionnaires should be performed before any blood draws or ECG assessments.): - CDI-2, Parent and Self-report at weeks 8, 15, 30, 34, 41, and 54 (Note: Children 6 years of age ~~at baseline~~on day 1 will not complete the self-report version; the caregiver/adult will complete the Parent version.) - C-SSRS (children's SLV) at weeks 8, 15, ~~28~~30, 34, 41, and 54 - YGTSS at weeks 8, 15, 30, 34, 41, and 54 (at weeks 8, 15, and 41, only perform assessment of "Severity Ratings" of the questionnaire; inventory	• perform UDS at week 54 • perform a serum pregnancy (β-HCG) test (only in females who are postmenarchal or ≥12 years of age) at weeks 8, 15, 34, and 54 • administer the following questionnaires (Note: For C-SSRS, Tic-free Interval, CY BOCS, 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. 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-PGIS, and TS-PGII questionnaires should be performed before any blood draws or ECG assessments.): - CDI-2, Parent and Self-report at weeks 8, 15, 30, 34, 41, and 54 (Note: Children 6 years of age on day 1 will not complete the self-report version; the caregiver/adult will complete the Parent version.) - C-SSRS (children's SLV) at weeks 8, 15, 30, 34, 41, and 54 - YGTSS at weeks 8, 15, 30, 34, 41, and 54 (at weeks 8, 15, and 41, only 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. Input from the caregiver/adult is required.) - TS-CGI at weeks 8, 15, 34, 41, and 54 - TS-PGIS at weeks 8, 15, 34, 41, and 54 (Note: Input from the caregiver/adult is permitted.) - TS-PGII at weeks 8, 15, 34, 41, and 54 (Note: Input from the caregiver/adult is permitted.)	

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
portions [ie, "Motor Tic Symptom Checklist" and "Phonic Tic Symptom Checklist"] do not need to be performed. Input from the caregiver/adult is required.) - TS-CGI at weeks 8, 15, 34, 41, and 54 - TS-PGIS at weeks 8, 15, 34, 41, and 54 (Note: Input from the caregiver/adult is permitted.) - TS-PGII at weeks 8, 15, 34, 41, and 54 (Note: Input from the caregiver/adult is ~~required~~permitted.) - Tic-free Interval assessment at weeks 8, 15, 34, 41, and 54 - CY-BOCS at weeks 34 and 54 - C&A-GTS- QOL (including VAS) at weeks ~~28~~34 and 54 • dispense IMP (sufficient doses to cover treatment until the following in-clinic visit) at weeks 8, 15, ~~28~~30, 32, 34, and 41	- Tic-free Interval assessment at weeks 8, 15, 34, 41, and 54 - CY-BOCS at weeks 34 and 54 - C&A-GTS- QOL (including VAS) at weeks 34 and 54 • dispense IMP (sufficient doses to cover treatment until the following in-clinic visit) at weeks 8, 15, 30, 32, 34, and 41	
3.12.3.3 Blinded, Randomized Drug Withdrawal Period/Titration Post-Drug Withdrawal Period (Weeks 28 to 33)		
Not applicable	[Section 3.12.3.3 was added]	Section was added to specify Part B of the study
3.12.3.3.1 In-Clinic Visit (Week 28)		
Not applicable	The following procedures/assessments will be performed at week 28: • measure vital signs (pulse, BP, body temperature, and respiratory rate)); orthostatic BP and pulse should be measured after the patient is in a standing position for at least 3 minutes • measure weight (Note: weight must be measured with shoes and outerwear off) • perform full physical examination (including height) • perform 12-lead ECG (Note: ECG will be performed after at	Addition of the section to specify assessments at week 28 during part B of the study

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
	least 5 minutes rest in a supine or semi-supine position.) • perform clinical laboratory tests, including serum chemistry, hematology, and urine analyses • up to 2 blood samples separated by 2 hours or more should be collected, if possible, for patients discontinuing for insufficient efficacy (early termination) • perform a serum pregnancy (β-HCG) test (only in females who are postmenarchal or ≥12 years of age) • administer the following questionnaires (Note: For C-SSRS, Tic-free Interval, CY-BOCS, 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-PGIS, and TS-PGII questionnaires should be performed before any blood draws or ECG assessments.): -CDI-2, Parent and Self-report versions (Note: Children 6 years of age on day 1 will not complete the self-report version; the caregiver/adult will complete the Parent version.) -C-SSRS (children's SLV) -YGTSS (only 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. Input from the caregiver/adult is required.) -TS-CGI -TS-PGII (Note: Input from the caregiver/adult is	

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
	permitted.) -TS-PGIS (Note: Input from the caregiver/adult is permitted.) -Tic-free Interval assessment -CY-BOCS -C&A-GTS QOL (including VAS) • dispense IMP (sufficient doses to cover treatment until the following in-clinic visit) • assess drug accountability/compliance/supply • collect used and unused IMP bottles • inquire about adverse events • review concomitant medications	
3.12.3.3.2 In-clinic Visit (Weeks 30 and 32)		
Not applicable	• evaluate IMP • measure vital signs (pulse, BP, body temperature, and respiratory rate) • physical examination (week 30) • CDI-2, Parent and Self-report versions at week 30 (Note: Children 6 years of age on day 1 will not complete the self-report version; the caregiver/adult will complete the Parent version.) • C-SSRS (children's SLV) at week 30 • YGTSS at week 30 • collect IMP/dispense IMP (sufficient doses to cover treatment until the following in-clinic visit) • assess IMP accountability/compliance/supply status to ensure that the patient has adequate tablets and remind them to bring used and unused IMP bottles to the next in clinic visit • inquire about adverse events	Addition of the section to specify assessments at week 30 and 32 during part B of the study

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
	• review concomitant medications	
3.12.3.3.3 Telephone Contacts (Weeks 29, 31, and 33)		
Not applicable	Patients will be contacted by telephone to evaluate tic reduction and adverse events. Dose adjustment will be made by the investigator after telephone contact with the patient and caregiver/adult. The following procedures/assessments will be performed via telephone contact at weeks 29, 31, and 33: • assess IMP accountability/compliance/supply status to ensure the patient has adequate tablets, inform the patient if they should titrate, and remind them to bring used and unused IMP bottles to the next in-clinic visit • inquire about adverse events • review concomitant medications	Addition of the section to specify expectations at weeks 29, 31, and 33 during part B of the study
3.12.4.1 In-Clinic Visit (Week 55)		
The following procedures/assessments will be performed at week 55: • measure vital signs (pulse, BP, body temperature, and respiratory rate) • measure weight (Note: weight must be measured with shoes and outerwear off) • administer the following questionnaires (Note: For C-SSRS, Tic-free Interval, and CY-BOCS, 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-PGIS, and TS-PGII questionnaires should be performed before any	The following procedures/assessments will be performed at week 55: • measure vital signs (pulse, BP, body temperature, and respiratory rate) • measure weight (Note: weight must be measured with shoes and outerwear off) • administer the following questionnaires (Note: For C-SSRS, Tic-free Interval, and CY-BOCS, 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-PGIS, and TS-PGII questionnaires should be performed before any blood draws or ECG assessments.):	Updates to the procedures after IMP treatment (Follow-up) at week 55

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
blood draws or ECG assessments.): -CDI-2, Parent and Self-report (Note: Children 6 years of age on day 1 will not complete the self-report version; the caregiver/adult will complete the Parent version.) -TS-PGII (Note: Input from the caregiver/adult is permitted.) -TS-PGIS (Note: Input from the caregiver/adult is ~~required~~permitted.)	- CDI-2, Parent and Self-report (Note: Children 6 years of age on day 1 will not complete the self-report version; the caregiver/adult will complete the Parent version.) -TS-PGII (Note: Input from the caregiver/adult is permitted.) -TS-PGIS (Note: Input from the caregiver/adult is permitted.)	
3.12.5. Unscheduled Visits		
- CDI 2, Parent and Self-report (Note: Children 6 years of age ~~at baseline~~on day 1 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 ~~must~~may be interviewed ~~in conjunction~~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.)	- CDI 2, Parent and Self-report (Note: Children 6 years of age on day 1 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.)	Updated the guidance on administration of scales during unscheduled visits
4.1 Patient Inclusion Criteria		
Patients who have completed Study TV50717-CNS-30046 or Study TV50717-CNS-30060 ~~may be enrolled in this study only if they meet~~ have already met ~~all of~~ the ~~following~~ criteria below. In addition, patients who have completed Study SD-809-C-17 may be included in the study if, during screening, they meet all of the following criteria:	Patients who have completed Study TV50717-CNS-30046 or Study TV50717-CNS-30060 have already met the criteria below. In addition, patients who have completed Study SD-809-C-17 may be included in the study if, during screening, they meet all of the following criteria: a. Patient is younger than 18 years of age on day 1 b. Patient weighs at least 44 pounds (20 kg) on day 1.	Updated age criteria at time of study and updated criteria to specify expectations that were met in parent studies during screening

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
a. ~~Patient has completed Study SD-809-C-17, Study TV50717-CNS-30046, or Study TV50717-CNS-30060~~ Patient is younger than 18 years of age on day 1. b. Patient weighs at least 44 pounds (20 kg) at ~~baseline~~ day 1. h. Females who are postmenarchal or ≥12 years of age may be included only if they have a negative β-human chorionic gonadotropin test at day 1~~baseline~~ or are sterile. Definitions of sterile are given in Appendix L. i. Females who are postmenarchal or ≥12 years of age ~~of childbearing potential~~ 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 drug half-lives, whichever is longer after last dose of IMP. Further details are included in Appendix L.	h. Females who are postmenarchal or ≥12 years of age may be included only if they have a negative β human chorionic gonadotropin test on day 1 or are sterile. Definitions of sterile are given in Appendix L. i. 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 drug half-lives, whichever is longer after last dose of IMP. Further details are included in Appendix L.	processes.
4.2 Patient Exclusion Criteria		
Patients who have completed Study TV50717-CNS-30046 or Study TV50717-CNS-30060 have already been confirmed to not ~~will not be enrolled in this study if they~~ meet any of the below ~~following~~ criteria. In addition, patients who have completed Study SD-809-C-17 will not be enrolled if, during screening, they meet any of the following criteria: a. Patient is 18 years of age or older ~~d~~e. Patient has clinically significant depression at screening or day 1~~baseline~~. ~~h~~i. Patient has clinically significant OCD at	Patients who have completed Study TV50717-CNS-30046 or Study TV50717-CNS-30060 have already been confirmed to not meet any of the below criteria. In addition, patients who have completed Study SD-809-C-17 will not be enrolled if, during screening, they meet any of the following criteria: a. Patient is 18 years of age or older e. Patient has clinically significant depression at screening or day 1. i. Patient has clinically significant OCD on day 1 that, in the opinion of the investigator, is the primary cause of impairment. m. Patient has an unstable or serious medical illness at screening	Exclusion criteria updated to account for recent safety updates/pregnancy language and to specify expectations that were met in parent studies during screening processes.

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
day 1~~baseline~~ that, in the opinion of the investigator, is the primary cause of impairment. ~~l~~m. Patient has an unstable or serious medical illness at screening or day 1~~baseline~~ ~~m~~n. Patient has a QT interval corrected for heart rate using Frederica's formula (QTcF) interval value >450 msec (males) or >460 msec (females) or >480 msec (with right bundle branch block) on 12-lead ECG at screening. Patient requires treatment with drugs known to prolong the QT interval (see Appendix A Table 8 for a complete list of prohibited QT-prolonging drugs). ~~q~~r. Patient has received a MAOI within 14 days of the day 1~~baseline~~ visit. ~~s~~t. Patient has participated in an investigational drug or device study (with the exception of Study SD 809 C 17 or Study TV50717-CNS-30046 or Study TV50717-CNS-30060) and received IMP/intervention within 30 days or 5 drug half-lives of day 1~~baseline~~, whichever is longer. ~~u~~v. Patient has a history of, or acknowledges, alcohol-related disorder ~~or substance abuse~~ in the previous 12 months, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-~~V~~5).	or day 1. n. Patient has a QT interval corrected for heart rate using Frederica's formula (QTcF) interval value >450 msec (males) or >460 msec (females) or >480 msec (with right bundle branch block) on 12-lead ECG at screening. Patient requires treatment with drugs known to prolong the QT interval (see Appendix A Table 8 for a complete list of prohibited QT-prolonging drugs). r. Patient has received a MAOI within 14 days of the day 1 visit. t. Patient has participated in an investigational drug or device study (with the exception of Study SD 809 C 17 or Study TV50717-CNS-30046 or Study TV50717-CNS-30060) and received IMP/intervention within 30 days or 5 drug half-lives of day 1, whichever is longer. v. Patient has a history of or acknowledges alcohol-related disorder in the previous 12 months, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5™).	
5.1 Drugs Administered During the Study		
During the open-label period, TEV-50717 tablets are available in the following dose strengths: 6, 9, and 12 mg. Patients will receive twice daily dosing for up to 54 weeks, with an initial 7-week titration period to allow for optimal dose selection. Patients who receive TEV-50717 during the randomized drug withdrawal period will remain on blinded active IMP from week 30 to week 34; those assigned to placebo during	During the open-label period, TEV-50717 tablets are available in the following dose strengths: 6, 9, and 12 mg. Patients will receive twice daily dosing for up to 54 weeks, with an initial 7-week titration period to allow for optimal dose selection. Patients who receive TEV-50717 during the randomized drug withdrawal period will remain on blinded active IMP from week 30 to week 34; those assigned to placebo during the randomized drug withdrawal period will undergo blinded re-titration from week 30 to week 34 back to their	Updated to include randomized drug withdrawal period

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
the randomized drug withdrawal period will undergo blinded re-titration from week 30 to week 34 back to their maintenance dose from week 28. 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 20-count bottles. The placebo tablets and packaging will match those for TEV-50717.	maintenance dose from week 28. 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 20-count bottles. The placebo tablets and packaging will match those for TEV-50717.	
• Dosing will be based on body weight and ~~strong~~ CYP2D6 ~~inhibitor use~~impairment status, as shown in Table 2 ~~and Table 3~~. • During the titration period, the dose of the IMP should be adjusted according to Table 2 to identify a dose level that optimally reduces tics (as determined by the investigator, in consultation with the patient and caregiver/adult) and is well tolerated. A dose cap for poor metabolizers will be prespecified by the Table 2. • After week 24, patient dose should be kept stable, if possible, until beginning Part B (week 28). • During the randomized drug withdrawal period, the patient will continue to receive their current dose of TEV-50717 or receive matching placebo until returning to their dose of TEV-50717 at week 30 (patients who receive TEV-50717 during the randomized drug withdrawal period will remain on blinded active IMP from week 30 to week 34; those assigned to placebo during the randomized drug withdrawal period will undergo re-titration from week 30 to week 34 back to their maintenance dose from week 28). During the re-titration period, the dose of the IMP should be adjusted according to Table 3.	• Dosing will be based on body weight and ~~strong~~ CYP2D6 impairment status, as shown in Table 2. • During the titration period, the dose of the IMP should be adjusted according to Table 2 to identify a dose level that optimally reduces tics (as determined by the investigator, in consultation with the patient and caregiver/adult) and is well tolerated. A dose cap for poor metabolizers will be prespecified by the Table 2. • After week 24, patient dose should be kept stable, if possible, until beginning Part B (week 28). • During the randomized drug withdrawal period, the patient will continue to receive their current dose of TEV-50717 or receive matching placebo until returning to their dose of TEV-50717 at week 30 (patients who receive TEV-50717 during the randomized drug withdrawal period will remain on blinded active IMP from week 30 to week 34; those assigned to placebo during the randomized drug withdrawal period will undergo re-titration from week 30 to week 34 back to their maintenance dose from week 28). During the re-titration period, the dose of the IMP should be adjusted according to Table 3. **Table 2: Maximum Daily Dose of IMP by Study Day and Weight Category on Day 1 for Titration at Study Initiation**	Updated Tables and included additional dosing instructions

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change

Table 2: Maximum Daily Dose of IMP by Study ~~Week~~Day and Weight Category on Day 1 for Titration at ~~Baseline~~Study Initiation

	~~Daily dose (mg) at the start of visit/week~~ Weight category					
~~Study week~~ Study day[a]	~~20 to <30 kg (44 to <66 lbs)~~ 20 to <30 kg		~~30 to <40 kg (66 to <88 lbs)~~ 30 to <40 kg		~~≥40 kg (≥88 lbs)~~ ≥40 kg	
CYP impairment status	Not impaired	Impaired	Not impaired	Impaired	Not impaired	Impaired
~~Baseline~~Day 1-7	6 mg	6 mg	6 mg	6 mg	6 mg (Days 1 and 2) 12 mg[b]	6 mg (Days 1 and 2) 12 mg[b]
~~Week 1~~ Day 8-14	12 mg	12 mg	12 mg	12 mg	18 mg	18 mg
~~Week 2~~ Day 15-21	18 mg	18 mg	18 mg	18 mg	24 mg	24 mg
~~Week 3~~ Day 22-28	18 mg[e]	18 mg	24 mg[e]	24 mg	30 mg	30 mg
~~Week 4~~Day 29-35	24 mg[e]	18 mg	30 mg[e]	24 mg	36 mg[e]	36 mg

	Weight category					
Study day[a]	20 to <30 kg		30 to <40 kg		≥40 kg	
CYP impairment status	Not impaired	Impaired	Not impaired	Impaired	Not impaired	Impaired
Day 1-7	6 mg	6 mg	6 mg	6 mg	6 mg (Days 1 and 2) 12 mg[b]	6 mg (Days 1 and 2) 12 mg[b]
Day 8-14	12 mg	12 mg	12 mg	12 mg	18 mg	18 mg
Day 15-21	18 mg	18 mg	18 mg	18 mg	24 mg	24 mg
Day 22-28	18 mg	18 mg	24 mg	24 mg	30 mg	30 mg
Day 29-35	24 mg	18 mg	30 mg	24 mg	36 mg	36 mg
Day 36-42	24 mg	18 mg	36 mg	24 mg	42 mg	36 mg
Day 43-49	30 mg	18 mg	42 mg	24 mg	48 mg	36 mg

[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 as applicable.

[b] Patients will receive 6 mg on days 1 and 2, and 12 mg starting on day 3.

CYP=cytochrome P450; IMP=investigational medicinal product.

Note: CYP impaired=patients who are receiving a strong CYP2D6 inhibitor or who are a CYP2D6 poor metabolizer. The investigator, in

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~~Week 5~~ Day 36-42	24 mg[e]	18 mg	36 mg[e]	24 mg	42 mg[e]	36 mg
~~Week 6~~ Day 43-49	30 mg[e]	18 mg	42 mg[e]	24 mg	48 mg[e]	36 mg

[a] Administration of a given dose will take place throughout the ~~week~~days indicated~~, with the~~ . The new dose starts the morning after the telephone contact or the morning after the clinic visit ~~occurring at the beginning of the week~~as applicable.

[b] Patients will receive 6 mg ~~once daily dose~~ on days 1 and 2, and ~~6~~ 12 mg ~~twice daily dose~~ starting on day 3.

[e] ~~For those taking strong CYP2D6 inhibitors such as paroxetine, fluoxetine, and bupropion, maximum daily dose for patients ≥40 kg is 36 mg/day, 30 to <40 kg is CYP24 mg/day, and 20 to <30 kg is 18 mg/day (see table below).~~

~~CYP2D6~~=cytochrome P450 ~~2D6~~; IMP=investigational medicinal product.

Note: CYP impaired=patients who are receiving a strong CYP2D6 inhibitor or who are a CYP2D6 poor metabolizer. The investigator, in consultation with the patient and caregiver/adult, will determine if a dose increase is warranted to achieve optimal tic reduction.

Table 3: ~~**Maximum**~~ **Daily Dose of IMP by Day 1 Body Weight Category, CYP2D6 Impairment, and Study Week (re-titration) for Patients ~~Receiving and Not Receiving CYP2D6 Inhibitors~~Randomized to Placebo During the Blinded, Randomized Drug Withdrawal Period**

New wording

consultation with the patient and caregiver/adult, will determine if a dose increase is warranted to achieve optimal tic reduction.

Table 3: Daily Dose of IMP by Day 1 Body Weight Category, CYP2D6 Impairment, and Study Week (Re-titration) for Patients Randomized to Placebo During the Blinded, Randomized Drug Withdrawal Period

Dose group Day 1 weight (kg)	Daily dose (mg) at the start of visit/week			
	Week 31	Week 32	Week 33	Week 34 maintenance dose
≥40	12	24	36	48
≥40, CYP impaired	12	18	24	30
30 to <40	12	24	30	36
30 to <40, CYP impaired	12	12	18	18
20 to <30	12	18	24	30
20 to <30, CYP impaired	12	12	12	12

CYP impaired=patients who are receiving a strong CYP2D6 inhibitor or who are a CYP2D6 poor metabolizer.
CYP=cytochrome P450; CYP2D6=cytochrome P450 2D6;

Reason/Justification for change

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change

Dose group Day 1 weight (kg)	~~Maximum daily dose~~	~~Maximum daily dose if receiving a strong CYP2D6 inhibitor~~Daily dose (mg) at the start of visit/week			
		Week 31	Week 32	Week 33	Week 34 maintenance dose
≥40		12	24	36	48
≥40, CYP impaired		12	18	24	30
~~20~~30 to <~~30 kg~~40		12	24	30 ~~mg~~	36~~1 8 mg~~
30 to <40, CYP impaired		12	12	18	18
~~30~~20 to <~~40 kg~~30		~~42 mg~~ 12	18	24 ~~mg~~	30
~~≥40 kg~~20 to <30, CYP impaired		~~48 mg~~ 12	~~36 mg~~ 12	12	12

CYP impaired=patients who are receiving a strong CYP2D6 inhibitor or who are a CYP2D6 poor metabolizer.
CYP=cytochrome P450; CYP2D6=cytochrome P450 2D6; IMP=investigational medicinal product.
~~Note: Strong CYP2D6 inhibitors include paroxetine, fluoxetine, and bupropion.~~

IMP=investigational medicinal product.

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
5.2 Restrictions		
While patients receiving strong CYP2D6 inhibitors (paroxetine, fluoxetine, and bupropion) ~~at baseline~~on day 1 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 CYP2D6 inhibitor is prohibited.	While patients receiving strong CYP2D6 inhibitors (paroxetine, fluoxetine, and bupropion) on day 1 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 CYP2D6 inhibitor is prohibited.	Updated to indicate that addition of CYP2D6 inhibitors is prohibited
5.3 Prior and Concomitant Medication or Treatment		
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. Addition of a strong CYP inhibitor is prohibited. Prohibited antipsychotic drugs medications are listed in Appendix A, Table 7, while prohibited medications that are associated with QTc prolongation are listed in Appendix A, Table 8.	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. Addition of a strong CYP inhibitor is prohibited. Prohibited antipsychotic drugs medications are listed in Appendix A, Table 7, while prohibited medications that are associated with QTc prolongation are listed in Appendix A, Table 8.	Updated to indicate that addition of CYP2D6 inhibitors is prohibited. I addition, included a reference to the table with the specific prohibited medications
6. ASSESSMENT OF EFFICACY		
Site-administered efficacy scales include the YGTSS and CY-BOCS, and self-administered efficacy scales include the TS-PGIS, TS-PGII, Tic-free Interval, and C&A-GTS-QOL.	Site-administered efficacy scales include the YGTSS and CY-BOCS, and self-administered efficacy scales include the TS-PGIS, TS-PGII, Tic-free Interval, and C&A-GTS-QOL.	Inclusion of TS-PGII as a self-administered efficacy scale
6.1 Efficacy and Exploratory Measures		
[redacted]	[redacted]	[redacted]

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
[redacted]	[redacted]	[redacted]
6.1.1 Tourette Syndrome–Clinical Global Impression		
TS-CGI is administered ~~at baseline~~on day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060) and weeks ~~2~~, 4, ~~6~~, 8, 15, 28, 34, 41, 54, and 55.	TS-CGI is administered on day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060) and weeks 4, 8, 15, 28, 34, 41, 54, and 55.	Timepoints added and removed for the TS-CGI assessment.
6.1.2. Tourette Syndrome-Patient Global Impression of Impact		
The TS-~~PGIS~~PGII is administered ~~at baseline~~on day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717 CNS-30060) and weeks ~~2,~~ 4~~, 6~~, 8, 15, 28, 34, 41, 54, and 55. Input from the parent/legal guardian is required. The TS-PGII is a single-item questionnaire that asks the patient to assess the 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.	The TS-PGII is administered on day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717 CNS-30060) and weeks 4, 8, 15, 28, 34, 41, 54, and 55. Input from the parent/legal guardian is required. The TS-PGII is a single-item questionnaire that asks the patient to assess the 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.	Description of TS-PGII included along with timepoints for the assessment

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
6.1.3. Tourette Syndrome Patient Global Impression of Severity		
The TS-PGIS is administered on day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717 CNS-30060) and weeks 4, 8, 15, 28, 34, 41, 54, and 55. Input from the caregiver/adult is ~~required~~permitted. The TS-PGIS is a single-item questionnaire that asks the patient to assess their current tics~~over the preceding week.~~	The TS-PGIS is administered on day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717 CNS-30060) and weeks 4, 8, 15, 28, 34, 41, 54, and 55. Input from the caregiver/adult is permitted. The TS-PGIS is a single-item questionnaire that asks the patient to assess their current tics.	Updated TS-PGIS assessment timepoints and details
6.1.4. Tic-Free Interval Assessment		
Tic-free Interval is assessed ~~at baseline~~on day 1 (only for patients who completed Study SD-809-C-17) and at weeks ~~2, 4, 6~~, 8, 15, 28, 34, 41, 54, and 55. Children 13 years of age and under ~~must~~may be interviewed ~~in conjunction~~separately or jointly with the caregiver/adult as appropriate or defined by the scale.	Tic-free Interval is assessed on day 1 (only for patients who completed Study SD-809-C-17) and at weeks 4, 8, 15, 28, 34, 41, 54, and 55. Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale.	Updated the guidance on administration of assessment and timepoints
6.1.5 Child and Adolescent Gilles de la Tourette Syndrome-Quality of Life Scale		
The C&A-GTS-QOL is administered ~~at baseline~~on day 1 and weeks 6, 28, 34, and 54. Children 13 years of age and under must be interviewed in conjunction with the caregiver/adult. ~~For children over~~Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult ~~involvement is strongly encouraged.~~as appropriate or defined by the scale. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information.	The C&A-GTS-QOL is administered on day 1 and weeks 6, 28, 34, and 54. Children 13 years of age and under must be interviewed in conjunction with the caregiver/adult. Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information.	Updated the guidance on administration of assessment and timepoints
6.1.6. Children's Yale-Brown Obsessive-Compulsive Scale		
Complete CY-BOCS (Checklist and Severity Ratings) is administered~~ at baseline~~on day 1 (only for patients	Complete CY-BOCS (Checklist and Severity Ratings) is administered on day 1 (only for patients who completed	Updated the guidance on

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
who completed Study SD-809-C-17) and weeks 6, 28, 34, 54, and 55. • Complete assessment (Checklist and Severity Ratings) ~~at baseline~~on day 1 (only for patients who completed Study SD-809-C-17) ~~and week 54~~ • Severity Ratings of OCD symptoms (questions 1 through 10 only) ~~at baseline~~on day 1 (only for patients who completed Study TV50717-CNS-30046 or Study TV50717-CNS-30060) and weeks 6 and 55 Children 13 years of age and under ~~must~~may be interviewed ~~in conjunction~~separately or jointly with the caregiver/adult as appropriate or defined by the scale.	Study SD-809-C-17) and weeks 6, 28, 34, 54, and 55. Complete assessment (Checklist and Severity Ratings) on day 1 (only for patients who completed Study SD-809-C-17) Severity Ratings of OCD symptoms (questions 1 through 10 only) on day 1 (only for patients who completed Study TV50717-CNS-30046 or Study TV50717-CNS-30060) and weeks 6 and 55 Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale.	administration of assessment and timepoints
(Previous version Am01) ~~Section 6.1.8 Overdose of IMP~~		
~~Any dose of IMP, whether taken intentionally or unintentionally, in excess of that prescribed during the given time period must be immediately reported to the sponsor.~~	Not applicable	This section was removed from the latest version protocol
7.1.1 Definition of an Adverse Event		
~~An adverse event is any~~Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product~~, regardless of whether it has~~and which does not necessarily have to have a causal relationship with this treatment. ~~In this study, any adverse event occurring after the clinical study patient has signed the informed consent form should be recorded and reported as 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.	Updates to adverse event definition
7.1.2 Recording and Reporting of Adverse Events		

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
	Further details are given in the Safety Monitoring Plan.	Additional reference to the Safety Monitoring Plan added.
7.1.5 Serious Adverse Event		
	For recording of serious adverse events, the study period is defined for each patient as the time period from signing of the informed consent 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.	Additional description about recording adverse events was added to the 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 ~~Reference Safety Information for expedited reporting purposes~~RSI for this study is ~~provided in Appendix A 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.	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.	The RSI for this protocol was specified
7.1.5.3.1. Investigator Responsibility		
To satisfy regulatory requirements, all serious adverse events ~~(as described in Section 7.1.5.1)~~ that occur during the study ~~period (including the protocol defined follow up period, described in Section 7.1.2)~~, regardless	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 the investigator. The event must be reported within 24 hours of when	IEC/IRB reporting requirement was removed Serious adverse

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
of judged relationship to ~~treatment with~~administration of the IMP, must be reported to the sponsor by the investigator. 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 ~~treatment~~last administration of ~~that patient has ended~~IMP should be reported to the sponsor if the investigator becomes aware of them. ~~The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations.~~ Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the ~~investigational center~~investigator within 24 hours of when it becomes known to the same address as the initial report.	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 should be reported to the sponsor if the investigator becomes aware of them. 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.	event reporting should be completed by the investigator
7.1.6. Protocol Defined Adverse Events of Special Interest		
7.1.6. Protocol Defined Adverse Events ~~for Expedited Reporting~~of Special Interest No protocol-defined adverse events ~~for expedited reporting~~of special interest were identified for this study.	7.1.6. Protocol Defined Adverse Events of Special Interest No protocol-defined adverse events of special interest were identified for this study.	Term updated from adverse events for expedited reporting to adverse events of special interest
7.2.1 Mini International Neuropsychiatric Interview for Children and Adolescents		
Select MINI Kid modules are administered at screening	Select MINI Kid modules are administered at screening (only for	Updated the

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
(only for patients who completed Study SD-809-C-17). Children 13 years of age and under ~~must~~may be interviewed ~~in conjunction~~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 ~~is~~may be interviewed separately or jointly with the ~~parent present~~caregiver/adult as appropriate or defined by the scale, and the ~~parent~~caregiver/adult is encouraged to participate when needed.	patients who completed Study SD-809-C-17). 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 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.	guidance on administration of assessment Parent was changed to caregiver/adult.

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
7.2.2 Columbia-Suicide Severity Rating Scale		
The C-SSRS children's baseline screening scale ~~collects the history~~ assesses past and current suicidal ideations and behaviors to determine suicide risk and is administered at screening. C-SSRS children's SLV scale is administered ~~at baseline~~on day 1 (only for patients who completed Study SD-809-C-17) and weeks 2, 4, ~~6,~~ 8, 15, 28, 30, 34, 41, 54, and 55. Children 13 years of age and under ~~must~~may be interviewed ~~in conjunction~~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 (Posner et al 2009) is a Food and Drug Administration (FDA) endorsed questionnaire to screen for suicidality in studies 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 ideations and behaviors to determine suicide risk and is administered at screening. C-SSRS children's SLV scale is administered on day 1 (only for patients who completed Study SD-809-C-17) and weeks 2, 4, 8, 15, 28, 30, 34, 41, 54, and 55. 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.	Updated the guidance on administration of assessment Timepoints added and removed
7.2.3 Children's Depression Inventory, Second Edition		
7.2.3 Children's Depression Inventory~~2~~, Second Edition CDI-2 (Parent and Self-report versions) is administered at screening and ~~baseline~~day 1 (only for patients who completed Study SD-809-C-17) and weeks 2, 4, ~~6,~~ 8, 15, 28, 30, 34, 41, 54, and 55. As the CDI-2 is designed for children 7 to 17 years of age, children 6 years of age ~~at baseline~~on day 1 will not complete the Self-report version; the caregiver/adult will complete the Parent version.	7.2.3 Children's Depression Inventory, Second Edition CDI-2 (Parent and Self-report versions) is administered at screening and day 1 (only for patients who completed Study SD-809-C-17) and weeks 2, 4, 8, 15, 28, 30, 34, 41, 54, and 55. As the CDI-2 is designed for children 7 to 17 years of age, children 6 years of age on day 1 will not complete the Self-report version; the caregiver/adult will complete the Parent version.	Assessment Timepoints were added and removed

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
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 physician identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the sponsor (LSO/INC Research) 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~~ The investigator is not required to report patients who are found to be pregnant ~~during~~between screening and day 1, provided no IMP was given. All female patients participating in the study ~~will discontinue treatment. All patients who~~ who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous, elective, or voluntary ~~termination~~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	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 physician identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the sponsor (LSO/INC Research) 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 day 1, provided no IMP was given. All female patients participating in the study 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	Update to pregnancy section/requirements

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
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.	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 Product		
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 IMP), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor. 3. Misuse: Situations where the ~~medicinal product~~IMP is intentionally and inappropriately used not in accordance with the authorized product information. 4. Abuse: Persistent or sporadic, intentional excessive use of ~~medicinal products~~IMP which is accompanied by harmful physical or psychological effects. 5. Off-label use: Situations where ~~a medicinal product~~an IMP is intentionally used for a medical purpose not in accordance with the authorized product information.	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 IMP), 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 that occur in infants following exposure to a medicinal product from breast	Added breastfeeding text as well as reporting info for overdose

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
6. Occupational exposure: Exposure to ~~a medicinal product~~an IMP, as a result of one's professional or non-professional occupation. 7. Breastfeeding: Suspected adverse reactions that occur in infants following exposure to a medicinal product from breast milk.	milk.	
7.5 Clinical Laboratory Tests		
The clinical significance of the ~~lab~~laboratory values will be evaluated by the criteria described in the study ~~lab~~laboratory manual and by the judgment of the investigator. A laboratory test result that is judged by the investigator as clinically significant will be recorded both on the source documentation ~~transcribed to~~ 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 cessation of ~~treatment with~~administration of IMP or medical treatment, or further diagnostic work-up. Abnormal laboratory tests can be repeated without approval from the medical monitor. (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).	The clinical significance of the laboratory values will be evaluated by the criteria described in the study laboratory manual and by the judgment 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 cessation of administration of IMP or medical treatment, or further diagnostic work-up. Abnormal laboratory tests can be repeated without approval from the medical monitor. (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).	Added note regarding abnormal laboratory or diagnostic test results at the screening visit
7.6 Vital Signs		
Before BP and pulse are measured, the patient must ~~be~~rest in a supine or semi erect/seated position and resting for at least ~~3~~5 minutes. (The same position and arm should be used each time vital signs are measured	Before BP and pulse are measured, the patient must rest in a supine or semi erect/seated position and resting for at least 5 minutes. (The same position and arm should be used each time vital signs are measured for a given patient.)	Updated directions on measuring BP and pulse Timepoints of the

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
for a given patient.) ~~At baseline~~On day 1 and weeks 4, 8, 28, and 54, orthostatic BP and pulse will be measured after the patient is in a standing position for at least 3 minutes.	On day 1 and weeks 4, 8, 28, and 54, orthostatic BP and pulse will be measured after the patient is in a standing position for at least 3 minutes.	assessments were adjusted
7.8 Physical Examinations		
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.	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.	Exception for the screening visit added
7.9. Assessment of Suicidality		
Not applicable	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. Families and caregivers of participants being treated with TEV-50717 should be instructed to monitor participants for the	Section added

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
	emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study investigator. The day 1 assessment of suicidal ideation and behavior and treatment-emergent suicidal ideation and behavior will be assessed during the study using the C-SSRS described in Section 7.2.2. A reference sample is provided in Appendix E.	
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 CPP/medical monitor according to the safety monitoring plan (eg, scheduled safety reviews for TEV 50717) as preliminary safety databases become available. ~~Safety data will additionally be evaluated periodically and ad hoc (if necessary) in the Product Safety Group~~.	All adverse events will be reviewed on a periodic basis by the CPP/medical monitor according to the safety monitoring plan (eg, scheduled safety reviews for TEV 50717) as preliminary safety databases become available.	Periodic evaluation removed.
9.1. Sample Size and Power Considerations		
Not applicable	For the randomized drug withdrawal period, enrolling at least 190 patients will provide at least 90% power to detect a difference between SD-809 and placebo-treated patients assuming a difference in YGTSS TTS of 4.5 with a standard deviation of 9 assuming a type 1 error rate of 5%.	Text added
9.2.3. Randomized Withdrawal ITT Population		
Not applicable	The Randomized Withdrawal ITT (RWITT) Population will include all subjects enrolled in the randomized drug withdrawal period of the study.	Section added
9.2.4. Randomized Withdrawal Safety Population		
Not applicable	The Randomized Withdrawal Safety (RWSAF) Population will include all subjects enrolled in the randomized drug withdrawal period who are administered any study drug. All summaries of	Section added

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
	safety measures in the randomized withdrawal period will be summarized descriptively in the RWSAF Population.	
9.2.5. Randomized Withdrawal Modified Intent-to-Treat Population		
Not applicable	The Randomized Withdrawal mITT (RWmITT) Population will include all subjects enrolled in the randomized drug withdrawal period who receive study drug and have a centrally read AIMS score at both the randomized drug withdrawal period initial visit and the week 30 visit. All efficacy measures in the randomized drug withdrawal period will be analyzed using the (RWmITT) Population.	Section added
9.4 Study Population		
The ITT analysis set (see Section ~~9.2~~9.2.1) will be used for all open-label efficacy summaries and analyses unless otherwise noted. The safety analyses set will be used for all safety summaries. Summaries will be presented for all patients. The RWmITT analysis set (see Section 9.2.5) will be used for all randomized withdrawal efficacy summaries and analyses unless otherwise noted. The RWSAF analysis set will be used for all randomized-withdrawal safety summaries.	The ITT analysis set (see Section 9.2.1) will be used for all open-label efficacy summaries and analyses unless otherwise noted. The safety analyses set will be used for all safety summaries. Summaries will be presented for all patients. The RWmITT analysis set (see Section 9.2.5) will be used for all randomized withdrawal efficacy summaries and analyses unless otherwise noted. The RWSAF analysis set will be used for all randomized-withdrawal safety summaries.	Two analysis sets, the RWmITT and the RWSAF were added
9.4.1 Patient Disposition		
Data from patients who are enrolled, patients enrolled but not treated (and the reason), patients in the ITT, safety, and other analysis sets, patients who enter the randomized drug withdrawal period, patients who complete the randomized drug withdrawal period, patients who complete the study, and patients who withdraw from the study will be summarized using descriptive statistics. Data from patients who withdraw	Data from patients who are enrolled, patients enrolled but not treated (and the reason), patients in the ITT, safety, and other analysis sets, patients who enter the randomized drug withdrawal period, patients who complete the randomized drug withdrawal period, 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	Additional populations that will be summarized by descriptive statistics were added

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
from the study will also be summarized by reason for withdrawal using descriptive statistics.	statistics.	
9.5. Efficacy Analysis		
No formal inferential statistics will be applied to the efficacy endpoints~~. Descriptive statistics will be presented.~~ in Part A; however, inferential statistics will be applied to the efficacy endpoints in Part B (see Section 9.5.1).	No formal inferential statistics will be applied to the efficacy endpoints in Part A; however, inferential statistics will be applied to the efficacy endpoints in Part B (see Section 9.5.1).	Updated the analysis methods to present strategy in both Part A and Part B
9.5.1 Efficacy Endpoints		
The following efficacy endpoints ~~are:Change~~will be assessed in Part A: • Change in the TTS of the YGTSS ~~TTS~~ from ~~baseline~~day 1 to each visit in which the scale is administered • Change in the TS-CGI score from ~~baseline~~day 1 to each visit in which the scale is administered • Change in the TS-~~PGIS~~PGII score from ~~baseline~~day 1 to each visit in which the scale is administered • Change in the C&A-GTS-QOL ~~physical/~~ADL subscale score from ~~baseline~~day 1 to each visit in which the scale is administered The following efficacy endpoint will be assessed in Part B: • Change in the TTS of the YGTSS from week 28 to week 30 (This change also applies to Section 9.5.)	The following efficacy endpoints will be assessed in Part A: • Change in the TTS of the YGTSS from day 1 to each visit in which the scale is administered • Change in the TS-CGI score from day 1 to each visit in which the scale is administered • Change in the TS-PGII score from day 1 to each visit in which the scale is administered • Change in the C&A-GTS-QOL ADL subscale score from day 1 to each visit in which the scale is administered The following efficacy endpoint will be assessed in Part B: • Change in the TTS of the YGTSS from week 28 to week 30	Efficacy endpoints were changed to be grouped by Part A or B
9.5.2 Exploratory Endpoints		

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
The <u>following</u> exploratory endpoints ~~are~~<u>will be assessed in Part A</u>:	The following exploratory endpoints will be assessed in Part A:	

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
[redacted]		
9.5.3.1 Efficacy Analysis for the Blinded, Randomized, Drug Withdrawal Study		
Not applicable	For the randomized drug withdrawal portion of the study, an analysis of covariance model will be used as the primary analysis model with the change from randomized-withdrawal week 28 to week 30 in YGTSS TTS as the dependent variable, and treatment group, randomized withdrawal week 28 TTS and age group as covariates. The least squares mean of the change in TTS from week 28 at week 30 will be compared (the active treatment arm and placebo arm) using a 2-sided test at the alpha=0.05 level of significance.	Section added
9.6 Multiple Comparisons and Multiplicity		
~~No adjustments will be made for multiplicity.~~ This does not apply to this study.	This does not apply to this study.	Adjusted text for clarity
9.7 Safety Endpoints and Analysis		
Safety analyses will be performed on the safety analysis set (Section 9.2.2) for the open-label study and the RWSAF set for the randomized drug withdrawal portion.	Safety analyses will be performed on the safety analysis set (Section 9.2.2) for the open-label study and the RWSAF set for the randomized drug withdrawal portion.	Text was added for clarity on what would be analyzed
9.7.1 Safety Endpoints		
The following safety endpoints ~~are:~~will be assessed in Part A (Day 1, Titration, and Maintenance): The following safety endpoint will be assessed in Part B (Blinded, Randomized Drug Withdrawal Period and Titration Post-Drug Withdrawal Period): • incidence of adverse events	The following safety endpoints will be assessed in Part A (Day 1, Titration, and Maintenance): The following safety endpoint will be assessed in Part B (Blinded, Randomized Drug Withdrawal Period and Titration Post-Drug Withdrawal Period): • incidence of adverse events	Safety endpoints were revised to classify Part A versus Part B assessments
9.9 Planned Interim Analysis		

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
~~Due to the open-label nature of the study, there will be no formal~~No interim ~~statistical~~ analysis is planned for this study.	No interim analysis is planned for this study.	Text revised for clarity
12.1 Informed Consent/Assent and/or Co-Consent		
A personally signed and dated informed consent form will be obtained from parent/legally acceptable representative, and a signed and dated assent and/or co-consent form for patients 14 years of age and older, 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; according to national and local 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/assent and/or co-consent forms for patients 14 years of age and older, as appropriate, and copies will be given to the patients. It will also be explained to the patients (and 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. Any patient that turns 18 years of age during the course of Study TV50717-CNS-30047 will need to be re-consented as an adult.	A personally signed and dated informed consent form will be obtained from parent/legally acceptable representative, and a signed and dated assent and/or co-consent form for patients 14 years of age and older, 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; according to national and local 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/assent and/or co-consent forms for patients 14 years of age and older, as appropriate, and copies will be given to the patients. It will also be explained to the patients (and 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. Any patient that turns 18 years of age during the course of Study TV50717-CNS-30047 will need to be re-consented as an adult.	Additional language regarding patients who turn 18 during the study was added
Appendix A Allowed and Disallowed 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 cytochrome	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 cytochrome P450 inhibitor. The addition of a strong CYP inhibitor	Add Prohibited QTc Prolonging Drugs back with comment that up

<table>
<tr><th>Protocol Amendment 01 text with changes shown</th><th>New wording</th><th>Reason/Justification for change</th></tr>
<tr><td>P450 inhibitor. The addition of a strong CYP inhibitor is prohibited.
Prohibited antipsychotic drugs are listed in Table 7. Prohibited medications that are associated with QTc prolongation are listed in Table 8.</td><td>is prohibited.
Prohibited antipsychotic drugs are listed in Table 7. Prohibited medications that are associated with QTc prolongation are listed in Table 8.

Table 8: Prohibited QTc Prolonging Drugs
<table>
<tr><th>Generic</th><th>Class/clinical use</th><th>Note</th></tr>
<tr><td>Azithromycin[a]</td><td>Antibiotic/bacterial infection</td><td></td></tr>
<tr><td>Chloroquine/Mefloquine</td><td>Anti-malarial/malaria infection</td><td></td></tr>
<tr><td>Clarithromycin[b]</td><td>Antibiotic/bacterial infection</td><td></td></tr>
<tr><td>Domperidone</td><td>Anti-nausea/nausea</td><td>Not available in USA</td></tr>
<tr><td>Droperidol</td><td>Sedative; anti-nausea/anesthesia adjunct, nausea</td><td></td></tr>
<tr><td>Erythromycin[b]</td><td>Antibiotic; gastrointestinal (GI) stimulant; GI motility</td><td></td></tr>
<tr><td>Moxifloxacin</td><td>Antibiotic/bacterial infection</td><td></td></tr>
<tr><td>Sevoflurane</td><td>Anesthetic, general/anesthesia</td><td></td></tr>
<tr><td>Probucol</td><td>Antilipemic/hypercholesterolemia</td><td>Not available in USA</td></tr>
<tr><td>Sparfloxacin</td><td>Antibiotic/bacterial infection</td><td>Not available in USA</td></tr>
</table></td><td>to 500 mg/day of Azithromycin is allowed

Table of prohibited QTc prolonging drugs added</td></tr>
</table>

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
	[a] Allowed dose of Azithromycin is up to 500 mg/day [b] Systemic use only. Topical use is allowed. GI=gastrointestinal; USA=United States of America.	
APPENDIX I. TOURETTE SYNDROME PATIENT GLOBAL IMPRESSION OF IMPACT AND SEVERITY		
Not applicable	[Appendix I was updated to include impact and severity assessments]	Updated Appendix I to present only the specific assessments that will be conducted to assess impact and severity
Appendix K Child and Adolescent Gilles De La Tourette Syndrome – Quality 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)		
Not applicable	[The previous appendix K was form for children 13 to 18 years of age was updated. An additional form was added to the appendix to account for and be used by children aged 6 to 12]	This appendix was added to show the distinct forms/assessments to be used for each of these two age categories of patients
Appendix L 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.~~	**Females of childbearing potential are defined as:** • not surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile • 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	Updated Appendix to align with edits to pregnancy language made to the body of the protocol and the observed "possible" risks

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
~~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~~ postmenarchal or ≥12 years of age ~~Description of different birth control methods~~ **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)~~ before the first dose of IMP. • Progestogen-only hormonal contraception (oral,	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. • Intrauterine device (IUD) and intrauterine hormone-releasing system (IUS) need to be in place at least 2 months before screening. • Bilateral tubal occlusion • Vasectomized partner provided he is the sole sexual partner and has received medical assessment of the surgical process. • Sexual abstinence is only considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. • Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception (according to Medicines and Healthcare Products Regulatory Agency, MHRA). **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.	

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
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)~~ before the first dose of IMP. • Intrauterine device (IUD) and intrauterine hormone-releasing system (IUS) need to be in place at least 2 months before screening. • Bilateral tubal occlusion • Vasectomized partner provided he is the sole sexual partner and has received medical assessment of the surgical process. • Sexual abstinence is only considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. • Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception (according to Medicines and Healthcare Products Regulatory Agency, MHRA). ~~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,~~		

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
~~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.~~ ~~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 WOCBP 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 females of childbearing potential:**~~ ~~1. 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~~		

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
~~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.~~ ~~2. 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.~~ ~~3. 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 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.~~		

17.3. Amendment 03 Dated 01 February 2018

The primary reason for this amendment is to correct and clarify the re-titration regimen in Part B.

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.

Note: In addition to the specific changes to the protocol that are listed in the table below, some minor typographical and grammatical changes were made for clarity and are not individually listed. Text that was moved but not otherwise changed is also not listed.

Original text with changes shown	**New wording**	**Reason/Justification for change**
Global		
Mini International Neuropsychiatric Interview For Children and Adolescents (MINI Kid, version 6.0)	Mini International Neuropsychiatric Interview For Children and Adolescents (MINI Kid, version 6.0)	Included MINI Kid version each time the full name (not abbreviation) was used.
DSM-5™	DSM-5™	Corrected the name of DSM-5™.
INVESTIGATOR AGREEMENT		
[redacted]	[redacted]	Updated to reflect a change in the Sponsor's Authorized Representative.
COORDINATING INVESTIGATOR AGREEMENT		
[redacted]	Title: [redacted]	Updated to provide contact information for coordinating investigator.

Original text with changes shown	New wording	Reason/Justification for change
	[redacted]	
CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS		
Central Clinical Laboratory Q2 Solutions ~~1201 S. Collegeville Road~~ 27027 Tourney Road, Suite 2E ~~Collegeville, PA 19426~~ Valencia, CA 91355 USA	Central Clinical Laboratory Q2 Solutions 27027 Tourney Road, Suite 2E Valencia, CA 91355 USA	Updated to reflect a change in the address of the central clinical laboratory.
~~Bioanalytical Pharmacokinetics Evaluation Data Analysis Information will be included in the Trial Master File.~~	Not applicable	Pharmacokinetic assessments will no longer be conducted in this study.
CLINICAL STUDY PERSONNEL CONTACT INFORMATION		
Sponsor's Authorized Representative: [redacted] VP, Therapy Area Head, Specialty R&D, Teva Branded Pharmaceutical Products R&D, Inc. [redacted] Email: [redacted]	Sponsor's Authorized Representative: [redacted] VP, Therapy Area Head, Specialty R&D, Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Email: [redacted]	Added information for the Sponsor's Authorized Representative.
Section 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 (referred to as TEV-50717, 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, has developed a deuterated tetrabenazine (referred to as TEV-50717, previously SD-809) that is eliminated more slowly than tetrabenazine.	Clarification of drug terminology.

Original text with changes shown	New wording	Reason/Justification for change
Synopsis		
Section 1.5.1 Justification for Dose of Active Drug (also affects the Synopsis)		
Similar to one of the parent studies (~~SD-809-C-17,~~ TV50717-CNS-30046~~, and TV50717-CNS-30060~~), IMP will be titrated based on investigator, patient, and parent/guardian assessments of tic reduction and adverse events.	Similar to one of the parent studies (TV50717-CNS-30046), IMP will be titrated based on investigator, patient, and parent/guardian assessments of tic reduction and adverse events.	Clarified which parent study used this approach.
Section 1.8 Location and Study Duration (also affects Synopsis)		
This study is planned to be conducted globally (per Study SD-809-C-17, Study TV50717-CNS-30046~~ in North America, Latin America, Russia, Ukraine, South Korea, Turkey,~~ and Study TV50717-CNS-30060~~Europe~~at approximately 120~~100~~ centers.	This study is planned to be conducted globally (per Study SD-809-C-17, Study TV50717-CNS-30046, and Study TV50717-CNS-30060) at approximately 120 centers.	Updated the number of sites. Updated the location of sites for flexibility to include all countries that had sites in the parent studies.
It is expected to start in ~~January~~ May 2018 and conclude in ~~June 2020~~ October 2020, with~~and have~~ a duration of approximately 30 months.	It is expected to start in May 2018 and conclude in October 2020, with a duration of approximately 30 months.	Updated the start and end dates.
Section 2.3.1 Safety Endpoints (also affects Sections 7.2.3, 9.7.1, and Synopsis)		
• observed values and changes from day 1 in the Children's Depression Inventory, Second Edition ~~(CDI-2;~~, Parent and Self-~~r~~Report Profiles~~versions~~(CDI-2) […] • observed values in electrocardiogram (ECG) parameters and shifts from ~~day 1~~ parent study baseline (for patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or from day 1 (for patient[s] rolling over from Study SD-809-C-17)for clinically significant abnormal findings […] In addition to routine monitoring of adverse events, clinical	• observed values and changes from day 1 in the Children's Depression Inventory, Second Edition, Parent and Self-Report Profiles (CDI-2) […] • observed values in electrocardiogram (ECG) parameters and shifts from parent study baseline (for patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or from day 1 (for patient[s] rolling over from Study SD-809-C-17) for clinically significant abnormal findings	Updated the definition of CDI-2 to include profile types. Clarified baseline for ECG shift analysis depending on parent study (see also changes listed for Section 4.4 below). Added IDMC (see also

Original text with changes shown	New wording	Reason/Justification for change
laboratory parameters, 12-lead ECGs, and safety scales, an Independent Data Monitoring Committee (IDMC) will monitor safety during the conduct of the study.	[…] In addition to routine monitoring of adverse events, clinical laboratory parameters, 12-lead ECGs, and safety scales, an Independent Data Monitoring Committee (IDMC) will monitor safety during the conduct of the study.	changes listed for Section 3.7 below).
Section 2.3.2 Efficacy Endpoints (also affects Section 9.5.1 and Synopsis)		
• change in the TTS of the YGTSS from week 28 to week 30, with the primary analyses and sensitivity testing done as described in Section 9.5.3.1	• change in the TTS of the YGTSS from week 28 to week 30, with the primary analyses and sensitivity testing done as described in Section 9.5.3.1	Clarification on where to find further information.
Section 2.3.3 Exploratory Endpoints (also affects Section 9.5.2. and Synopsis)		
• [redacted]	• [redacted]	[redacted]
Section 3.1 General Design and Study Schematic Diagram (also affects Section 9.1, Figure 1, and Synopsis)		
This is a 56-week, open-label, single-arm study that includes a 2-week, double-blind, placebo-controlled, randomized drug withdrawal period followed by a 3-week blinded re-titration period to evaluate the safety of TEV-50717 in children and adolescents with tics associated with TS after they have successfully completed any of the parent studies (SD-809-C-17 [Phase 1b], TV50717-CNS-30046 [Phase 2/3], or TV50717-CNS-30060 [Phase 3]). [...]	This is a 56-week, open-label, single-arm study that includes a 2-week, double-blind, placebo-controlled, randomized drug withdrawal period followed by a 3-week blinded re-titration period to evaluate the safety of TEV-50717 in children and adolescents with tics associated with TS after they have successfully completed any of the parent studies (SD-809-C-17 [Phase 1b], TV50717-CNS-30046 [Phase 2/3], or TV50717-CNS-30060 [Phase 3]). [...]	Clarified terminology and timing related to Part B.

Original text with changes shown	New wording	Reason/Justification for change
For patients rolling over from Study SD-809-C-17, this study will consist of ~~up to~~ a 4-week screening period (up to 31 days) and up to 54 weeks of treatment. [...] Patients who have successfully completed any of the parent studies may be eligible to enroll in the current study after they complete a 1-week washout period and the final evaluation (week 13 in TV50717~~818~~-CNS 30046 or week 9 in TV50717-CNS-30060) in the parent study. [...] Up to approximately 212~~260~~ patients are planned to be enrolled (~~up to 10 patients are~~ approximately 1 patient is estimated to enroll from the Phase 1b Study SD-809-C-17, up to approximately 85~~100~~ patients are estimated to enroll from the Phase 2/3 Study TV50717-CNS-30046, and up to approximately 126~~150~~ patients are estimated to enroll from the Phase 3 Study TV50717-CNS-30060). Patients who complete all scheduled visits will have procedures and assessments performed at the final visit (week 54). [...] The study schematic diagram is presented in Figure 1. An additional diagram that details the blinded, randomized drug withdrawal/titration post-drug withdrawal period (Part B of the study) is presented in Figure 2. [Figures 1 and 2 were edited to ensure consistency of terminology and clarification (in footnote c) of when dose adjustment is permissible.]	For patients rolling over from Study SD-809-C-17, this study will consist of a 4-week screening period (up to 31 days) and up to 54 weeks of treatment. [...] Patients who have successfully completed any of the parent studies may be eligible to enroll in the current study after they complete a 1-week washout period and the final evaluation (week 13 in TV50717-CNS-30046 or week 9 in TV50717-CNS 30060) in the parent study. [...] Up to approximately 212 patients are planned to be enrolled (approximately 1 patient is estimated to enroll from the Phase 1b Study SD-809-C-17, up to approximately 85 patients are estimated to enroll from the Phase 2/3 Study TV50717-CNS-30046, and up to approximately 126 patients are estimated to enroll from the Phase 3 Study TV50717-CNS-30060). Patients who complete all scheduled visits will have procedures and assessments performed at the final visit (week 54). [...] The study schematic diagram is presented in Figure 1. An additional diagram that details the blinded, randomized drug withdrawal/titration post-drug withdrawal period (Part B of the study) is presented in Figure 2. [Figures 1 and 2 were edited to ensure consistency of terminology and clarification (in	Clarification on screening period length. Corrected study identifier. Updated numbers of patients, with clarification that these numbers are estimates. Clarification.

Original text with changes shown	New wording	Reason/Justification for change
	Figure 1 footnote c) of when dose adjustment is permissible.]	
Section 3.1 General Design and Study Schematic Diagram (also affects Synopsis)		
In the study period descriptions below, "week X" refers to the end of that week, which coincides with the study visit, unless stated otherwise. Some dose changes will occur at the start of a week rather than at the end of a week and will be indicated as such.	In the study period descriptions below, "week X" refers to the end of that week, which coincides with the study visit, unless stated otherwise. Some dose changes will occur at the start of a week rather than at the end of a week and will be indicated as such.	Clarification for consistent terminology to describe Part B. Added clarification of "week" terminology to the end of the design overview.
Section 3.1.3 Titration Period (also affects the Synopsis)		
3.1.3 Titration Period (7 weeks) [...] The dose of the IMP should be increased on a weekly basis until one of the following occurs: • The investigator determines there has been a clinically meaningful reduction in tics~~, as indicated by a sustained reduction in the TS-CGI.~~	**3.1.3 Titration Period (7 weeks)** [...] The dose of the IMP should be increased on a weekly basis until one of the following occurs: • The investigator determines there has been a clinically meaningful reduction in tics.	Added detail to heading. Removed unnecessary detail.
Section 3.1.4 Maintenance Period (also affects Sections 5.1, 5.5 and Synopsis)		
As during titration, dose adjustments should be made based on all available information. After dose adjustment, if the maintenance dose for a patient is 6 mg, the dose should be taken once a day in the morning with food (other dose levels are taken twice daily). During the maintenance period, in-person (in-clinic) study visits will be scheduled at weeks 8, 15, 34, 41, and 54 for assessments of safety and efficacy and telephone contacts will be scheduled for weeks 21 and 47 in order to assess adverse events and tic severity. The randomized drug withdrawal and re-titration period	As during titration, dose adjustments should be made based on all available information. After dose adjustment, if the maintenance dose for a patient is 6 mg, the dose should be taken once a day in the morning with food (other dose levels are taken twice daily). During the maintenance period, in-person (in-clinic) study visits will be scheduled at weeks 8, 15, 34, 41, and 54 for assessments of safety and efficacy and telephone contacts will	Clarified dosing adjustment down to 6 mg. Clarified that Part B occurs in the midst of Part A rather than afterward and that dose adjustments may occur during all of Part A (both

Original text with changes shown	New wording	Reason/Justification for change
(Part B) will occur from the end of week 28 through the end of week 33, and then the Part A maintenance period will resume, along with the ability to make dose adjustments as described above.	be scheduled for weeks 21 and 47 in order to assess adverse events and tic severity. The randomized drug withdrawal and re-titration period (Part B) will occur from the end of week 28 through the end of week 33, and then the Part A maintenance period will resume, along with the ability to make dose adjustments as described above.	before and after Part B).
Section 3.1.6 Blinded, Randomized Drug Withdrawal Period and Titration Post-Drug Withdrawal Period (also affects Sections 3.5, 3.8, 5.1, and Synopsis)		
3.1.6. Blinded, Randomized Drug Withdrawal Period and Titration Post-Drug Withdrawal Period (5 weeks) At the week 28 visit, the patients will be randomized 2:1 to their current dose of TEV-50717 or placebo in order to check for return of symptoms. Because IMP is dispensed as enough doses for 2 weeks (current dose level and next dose level), the week 28 visit (Day 196) is considered the first day of the randomized withdrawal period, although the patient will begin taking blinded IMP on Day 197. […]At the week 30 visit, patients who receive TEV-50717 during the randomized drug withdrawal period will continue at the same dose in a blinded manner from the start of week 31 to the start of week 34 dose of blinded active IMP. [...]Any patient who was randomized to placebo during this 2-week period will undergo blinded ~~begin~~ re-titration. Patients will have a follow-up telephone contact for safety evaluation at weeks 31 and 33. ~~All patients should be back at their maintenance dose on or before the start of week 34 and return to open-label treatment for the remainder of the study.~~	**3.1.6. Blinded, Randomized Drug Withdrawal Period and Titration Post-Drug Withdrawal Period (5 weeks)** At the week 28 visit, the patients will be randomized 2:1 to their current dose of TEV-50717 or placebo in order to check for return of symptoms. Because IMP is dispensed as enough doses for 2 weeks (current dose level and next dose level), the week 28 visit (Day 196) is considered the first day of the randomized withdrawal period, although the patient will begin taking blinded IMP on Day 197. […] At the week 30 visit, patients who receive TEV-50717 during the randomized drug withdrawal period will continue at the same dose in a blinded manner from the start of week 31 to the start of week 34. Any patient who was randomized to placebo during this 2-week period will undergo blinded re-titration. Patients will have a follow-up telephone contact for safety evaluation at weeks 31 and 33.	Added detail to heading. Clarified terminology and timing related to the blinded, randomized drug withdrawal period and titration post-drug withdrawal period (Part B).

Original text with changes shown	New wording	Reason/Justification for change
Section 3.1.7 Titration Post-Drug Withdrawal (Weeks 31, 32, and 33) [also affects Synopsis]		
Any patient who was randomized to placebo ~~during weeks 28 to 30~~ between the week 28 and week 30 visits will undergo re-titration to their previously established maintenance ~~target~~ dose over the 3 weeks of treatment following the randomized drug withdrawal period (start of week 31 to the start of week 34 [Days 211 through 232]). The titration scheme and maximum dose will be determined based on the previously established maintenance dose according to Table 3 ~~by body weight and CYP2D6 impairment status~~. [Moved last sentence of Section 3.1.6 to this section, with the following edits: All patients should be back at their maintenance dose on or before the start of week 34 and return to open-label treatment for the remainder of the study (note that, because IMP is dispensed for 2-week periods, patients will use blinded bottles through the end of week 34; however, all patients will be known to be on active treatment at the start of week 34).	Any patient who was randomized to placebo between the week 28 and week 30 visits will undergo re-titration to their previously established maintenance dose over the 3 weeks of treatment following the randomized drug withdrawal period (start of week 31 to the start of week 34 [Days 211 through 232]). The titration scheme and maximum dose will be determined based on the previously established maintenance dose according to Table 3. All patients should be back at their maintenance dose on or before the start of week 34 and return to open-label treatment for the remainder of the study (note that, because IMP is dispensed for 2-week periods, patients will use blinded bottles through the end of week 34; however, all patients will be known to be on active treatment at the start of week 34).	Clarified additional terminology and timing related to the titration post-drug withdrawal period. (See also changes listed for Section 3.1.6.)
Section 3.2 Justification for Study Design and Placebo-Controlled Randomized Withdrawal (also affects Section 5.1)		
3.2. Justification for Study Design and Placebo-Controlled Randomized Drug Withdrawal [...] ~~A randomized, double-blind, placebo-controlled study of TEV-50717 (Study TV50717-CNS-30046 or Study TV50717-CNS-30060) has recently begun. The goal of this study is to evaluate the efficacy and safety of TEV-50717 on the tics of patients with TS in a rigorous, controlled manner.~~ Two parent studies, TV50717-CNS-30046 and TV50717-CNS-30060, are underway. They are randomized, double-blind, placebo-controlled studies of the efficacy and safety of TEV-	**3.2. Justification for Study Design and Placebo-Controlled Randomized Drug Withdrawal** [...] Two parent studies, TV50717-CNS-30046 and TV50717-CNS-30060, are underway. They are randomized, double-blind, placebo-controlled studies of the efficacy and safety of TEV-50717 on the tics in patients with TS. [...] [...]	Clarified heading. Updated descriptions of parent studies from which patients will roll over.

Original text with changes shown	New wording	Reason/Justification for change
50717 on the tics in patients with TS. [...] Patients will receive twice daily dosing for up to 54 weeks (those on the 6-mg dose will receive once daily dosing), with an initial 7-week titration period to allow for optimal dose selection. At the week 28 visit, patients will begin a 2-week blinded, randomized drug withdrawal period. The randomized drug withdrawal period will rigorously assess the long-term maintenance of effect. Patients will be randomized to their current dose of TEV-50717 or placebo for 2 weeks. After completing the 2 weeks, patients will continue their same dose of TEV-50717 in a blinded manner or will be retitrated (patients receiving placebo only) in a blinded manner for 3 weeks. At week 34, all patients will resume their maintenance dose.	Patients will receive twice daily dosing for up to 54 weeks (those on the 6-mg dose will receive once daily dosing), with an initial 7-week titration period to allow for optimal dose selection. At the week 28 visit, patients will begin a 2-week blinded, randomized drug withdrawal period. The randomized drug withdrawal period will rigorously assess the long-term maintenance of effect. Patients will be randomized to their current dose of TEV-50717 or placebo for 2 weeks. After completing the 2 weeks, patients will continue their same dose of TEV-50717 in a blinded manner or will be retitrated (patients receiving placebo only) in a blinded manner for 3 weeks. At week 34, all patients will resume their maintenance dose.	Clarified regimen for the 6 mg dose. Clarified that dosing is blinded for the 3-week re-titration period.
3.3. Safety Measures and Time Points (also affects Sections 3.13.1, 7.2.2, and Synopsis)		
Part A: […] • Children's C-SSRS: – baseline ~~Day 1~~/screening version ~~scale~~: ~~S~~screening only (ie, only for patients who completed Study SD-809-C-17) – Since Last Visit (SLV) version ~~scale~~: ~~D~~day 1 (only for patients who completed Study SD-809-C-17) and weeks 2, 4, 8, 15, 34, 41, 54, and 55 • CDI-2: ~~S~~screening and day 1 (ie, only for patients who completed Study SD-809-C-17) and weeks 2, 4, ~~6~~, 8, 15, 34, 41,	Part A: […] • Children's C-SSRS: – baseline/screening version: screening only (ie, only for patients who completed Study SD-809-C-17) – Since Last Visit (SLV) version: day 1 (only for patients who completed Study SD-809-C-17) and weeks 2, 4, 8, 15, 34, 41, 54, and 55 • CDI-2 (Parent and Self-Report versions):	Clarified pregnancy test types to be performed at different time points. Corrected C-SSRS description. Week 6 assessment was removed for CDI-2. Additional safety measures

Original text with changes shown	New wording	Reason/Justification for change
54, and 55 […] • ~~P~~pregnancy testing (beta human chorionic gonadotropin [β-HCG]): ~~S~~screening (ie, only for patients who completed Study SD-809-C-17); day 1 and weeks 4, 8, 15, 34, and 54 (serum tests at screening and week 54 and urine tests at other visits) […] Part B: […] • Children's C-SSRS: – SLV version~~scale~~: Weeks 28 and 30 • 12-lead ECG: week 28 • clinical laboratory tests (serum chemistry, hematology, and urinalysis): week 28	screening and day 1 (ie, only for patients who completed Study SD-809-C-17) and weeks 2, 4, 8, 15, 34, 41, 54, and 55 [β-human …] • ~~P~~pregnancy testing (β-HCG): screening (ie, only for patients who completed Study SD-809-C-17); day 1 and weeks 4, 8, 15, 34, and 54 (serum tests at screening and week 54 and urine tests at other visits) […] Part B: […] • Children's C-SSRS: – SLV version: Weeks 28 and 30 • 12-lead ECG: week 28 • clinical laboratory tests (serum chemistry, hematology, and urinalysis): week 28	were listed under Part B.
3.4.1. Efficacy Measures and Time Points (also affects Synopsis)		
• YGTSS ~~(to calculate TTS)~~: Screening (only for patients who completed Study SD-809-C-17); day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060); and weeks 2, 4, 8, 15, 28, 30, 34, 41, 54, and 55	• YGTSS: Screening (only for patients who completed Study SD-809-C-17); day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060); and weeks 2, 4, 8, 15, 28, 30, 34, 41, 54, and 55	Removed unnecessary detail.
3.4.2. Exploratory Measures and Time Points (also affects Synopsis)		
Part A and Part B: [redacted]	**Part A and Part B:** [redacted]	[redacted]

Original text with changes shown	New wording	Reason/Justification for change
[redacted]	[redacted]	
[section deleted] Section 3.5 Pharmacokinetic Measures (also affects Section 8 and Synopsis)		
~~**Section 3.5 Pharmacokinetic Measures**~~ ~~A blood sample for the measurement of IMP concentration should be collected, if possible, from each patient experiencing a serious adverse event or an 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.~~	Not applicable	Pharmacokinetic assessments will no longer be conducted in this study. (See also changes listed for Section 3.13.3.2.1.)
Section 3.5 Randomization and Blinding (also affects Synopsis)		
This is an <u>otherwise</u> open-label study that includes a 2-week, double-blind, placebo-controlled, randomized drug withdrawal period <u>followed by a 3-week blinded re-titration period</u>. At the <u>start of the</u> randomized drug withdrawal period (<u>end of</u> week	This is an otherwise open-label study that includes a 2-week, double-blind, placebo-controlled, randomized drug withdrawal period followed by a 3-week blinded re-titration	Clarified terminology and timing related to Part B (see also changes listed for Section 3.1.6 above).

Original text with changes shown	New wording	Reason/Justification for change
28), the patients will be randomized 2:1 to the current dose or placebo in order to check for return of symptoms. ~~At the end of this period, patients who receive TEV-50717 during the randomized drug withdrawal period will return to the most recent dose of TEV-50717 and patients who received placebo during the randomized drug withdrawal period will begin titration post-drug withdrawal.~~ During the entire 5-week period, patients randomized to TEV-50717 will stay on their established maintenance dose of blinded active IMP. Patients who receive placebo during the randomized drug withdrawal period will undergo blinded ~~re~~titration post-drug withdrawal. All patients will return to open-label dosing at week 34 (note that, because IMP is dispensed for 2-week periods, patients will use blinded bottles through the end of week 34; however, all patients will be known to be on active treatment at the start of week 34). During the blinded drug withdrawal and re-titration period, patients and investigators will remain blinded to treatment assignment. In addition, the sponsor's and development partner's clinical personnel and all vendors (with the exception of the Interactive Response Technology [IRT] vendor and the IMP packaging 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. Patients will be centrally randomly assigned to the treatment groups by means of a computer-generated randomization list. The creation of the randomization list will be under the responsibility and oversight of INC Research. The randomization treatment and medication allocation will be assigned to the relevant treatment groups through a qualified service provider (ie, via IRT). The management of the IRT system will be done by a qualified service provider under the oversight of Nuvelution TS Pharma, INC (referred to hereafter	period. At the start of the randomized drug withdrawal period (end of week 28), the patients will be randomized 2:1 to the current dose or placebo in order to check for return of symptoms. During the entire 5-week period, patients randomized to TEV-50717 will stay on their established maintenance dose of blinded active IMP. Patients who receive placebo during the randomized drug withdrawal period will undergo blinded re-titration post-drug withdrawal. All patients will return to open-label dosing at week 34 (note that, because IMP is dispensed for 2-week periods, patients will use blinded bottles through the end of week 34; however, all patients will be known to be on active treatment at the start of week 34). During the blinded drug withdrawal and re-titration period, patients and investigators will remain blinded to treatment assignment. In addition, the sponsor's and development partner's clinical personnel and all vendors (with the exception of the Interactive Response Technology [IRT] vendor and the IMP packaging 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. Patients will be centrally randomly assigned to the treatment groups by means of a computer-generated randomization list. The creation of the randomization list will be under the responsibility and oversight of INC	Added standard language related to blinding, including clarification of entities subject to blinding during the drug withdrawal and re-titration period.

Original text with changes shown	New wording	Reason/Justification for change
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 during the blinded drug withdrawal and re-titration period.	Research. The randomization treatment and medication allocation will be assigned to the relevant treatment groups through a qualified service provider (ie, via IRT). The 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 during the blinded drug withdrawal and re-titration period.	
Section 3.6 Maintenance of Randomization and Blinding		
3.6. Maintenance of Randomization and Blinding 3.6.1. 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 an unblinding request from the Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant Standard Operating Procedure (SOP). 3.6.2. Blinding and Unblinding 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	3.6. Maintenance of Randomization and Blinding 3.6.1. 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 an unblinding request from the Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant Standard Operating Procedure (SOP). 3.6.2. Blinding and Unblinding In case of a serious adverse event, pregnancy,	Added standard language related to blinding and randomization maintenance procedures.

Original text with changes shown	New wording	Reason/Justification for change
situations. The patient's randomized treatment will be made available ~~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 IRT system. ~~Randomization and Trial Supply Management, both via telephone and internet.~~ If possible, the medical monitor ~~sponsor~~ should be notified of the event before breaking of the code. If this is not possible, the medical monitor ~~sponsor~~ should be notified immediately afterward, and the patient's randomized treatment ~~IMP assignment~~ should not be communicated to the medical monitor ~~given~~. Breaking of the randomization code can always be performed by the investigational center without prior approval by the medical monitor ~~sponsor~~. When a blind is broken, the patient will be withdrawn from the study, and the event will be recorded on the case report form (CRF). 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 studies with blinding, 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 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.	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. The patient's randomized treatment will be made available to the investigator(s) via the IRT system. If possible, the medical monitor should be notified of the event before breaking of the code. If this is not possible, the medical monitor should be notified immediately afterward, and the patient's randomized treatment should not be communicated to the medical monitor. Breaking of the randomization code can always be performed by the investigational center without prior approval by the medical monitor. When a blind is broken, the patient will be withdrawn from the study, and the event will be recorded on the case report form (CRF). 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 studies with blinding, 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 may independently request that the blind code be broken (on a case-by-case basis) to comply with regulatory requirements. The report will	

Original text with changes shown	New wording	Reason/Justification for change
	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.	

Original text with changes shown	New wording	Reason/Justification for change
3.7 Independent Data Monitoring Committee (IDMC) (also affects Section 7.12)		
3.7. Independent Data Monitoring Committee (IDMC) During the conduct of this study, an IDMC will review accumulating safety data on a regular basis to ensure the continuing safety of the study patients and to review any 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 and development partner may be present, and information is provided and discussed in a blinded manner. 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 INC Research will work closely with the committee to provide the necessary data for review.	3.7. Independent Data Monitoring Committee During the conduct of this study, an IDMC will review accumulating safety data on a regular basis to ensure the continuing safety of the study patients and to review any 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 and development partner may be present, and information is provided and discussed in a blinded manner. 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	Added IDMC to the study and associated IDMC language to the protocol.

Original text with changes shown	New wording	Reason/Justification for change
The conduct and specific details regarding the IDMC sessions and requests to unblind any blinded treatment assignment are outlined in the IDMC charter.	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 INC Research 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.	
3.8 IMP and Placebo Used in the Study (also affects Sections 1.2, 5.1, and Synopsis)		
3.8 ~~Drugs~~ Investigational Medicinal Product and Placebo Used in the Study During the open-label period, TEV-50717 tablets are available in the following dose strengths: 6, 9, and 12 mg. […] During the randomized drug withdrawal and re-titration period, 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 20-count bottles. Patients who receive TEV-50717 during the randomized drug withdrawal period will remain on their maintenance dose of blinded active IMP from the start of week ~~30~~31 to the start of week 34; those assigned to placebo during the randomized drug withdrawal period will undergo blinded re-titration from the start of week ~~30~~31 to the start of week 34 back to their previously established maintenance dose from the end of week 28. Note that, because IMP is dispensed for 2 week periods, patients will use blinded bottles through the end of week 34; however, all patients will be known to be on active treatment at the start of	**3.8 Investigational Medicinal Product and Placebo Used in the Study** During the open-label period, TEV-50717 tablets are available in the following dose strengths: 6, 9, and 12 mg. […] During the randomized drug withdrawal and re titration period, 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 20-count bottles. Patients who receive TEV-50717 during the randomized drug withdrawal period will remain on their maintenance dose of blinded active IMP from the start of week 31 to the start of week 34; those assigned to placebo during the randomized drug withdrawal period will undergo blinded re-titration from the start of	Clarified which dose strengths are available during which study periods. Clarified terminology and timing related to the blinded, randomized drug withdrawal period and titration post-drug withdrawal period (Part B; see also changes listed for Section 3.1.6 above). Note that the order of 2 paragraphs was also changed (not shown).

Original text with changes shown	New wording	Reason/Justification for change
week 34.	week 31 to the start of week 34 back to their previously established maintenance dose from the end of week 28. Note that, because IMP is dispensed for 2 week periods, patients will use blinded bottles through the end of week 34; however, all patients will be known to be on active treatment at the start of week 34.	
Section 3.9.2. Drug Accountability		
Empty, partially used, and unused IMP will be disposed of ~~returned to the sponsor or its designee~~, as agreed with the sponsor/development partner.	Empty, partially used, and unused IMP will be disposed of, as agreed with the sponsor/development partner.	Clarified responsibilities related to drug disposal.
Section 3.10 Duration of Patient Participation and Justification (also affects Section 3.1 and Synopsis)		
For patients rolling over from Study SD-809-C-17, this study will consist of ~~up to~~ a 4-week screening period (up to 31 days) and up to 54~~52~~ weeks of treatment. All participating patients are expected to participate in this study for its entire duration, which is a minimum of 56 weeks (for those rolling over from Study SD-809-C-17, this can be up to 60 weeks). Patients will have a follow-up telephone contact to evaluate safety 1 week after the end of the washout period (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 56 weeks.~~ See Section 12.4 for the definition of the end of the study.	For patients rolling over from Study SD-809-C-17, this study will consist of a 4-week screening period (up to 31 days) and up to 54 weeks of treatment. All participating patients are expected to participate in this study for its entire duration, which is a minimum of 56 weeks (for those rolling over from Study SD-809-C-17, this can be up to 60 weeks). Patients will have a follow-up telephone contact to evaluate safety 1 week after the end of the washout period (2 weeks after their last dose of IMP). See Section 12.4 for the definition of the end of the study.	Corrected maximum treatment period (reflecting patients not randomized to placebo during Part B) and clarified what aspects of the duration apply to patients from all 3 parent studies.
3.13 Study Procedures and Assessments		
Not applicable	Table 1 was updated to add/remove assessments, to adjust the timing of some assessments, and to update language. All	In addition to changes made to align with the protocol text, the shading in the table

Original text with changes shown	New wording	Reason/Justification for change
	changes were made in alignment with the changes made throughout the protocol.	was corrected as needed.
3.13.1 Procedures for Screening and Enrollment (Visit 1) (also affects Sections 3.1, 3.1.1, 3.3, 4.1, 12.1, and Synopsis)		
~~Written i~~Informed consent ~~(and written~~ /assent ~~and/or co-consent for patients 14 years of~~ , depending on the child's age ~~and older~~, as appropriate~~)~~, will be obtained~~; for~~ before any study procedures are performed. For patients ~~enrolled~~ rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, informed consent/assent ~~and/or co-consent for patients 14 years of age and older~~, as appropriate, may be obtained prior to the day 1 visit, up to 4 weeks in advance of open-label study participation. For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, screening data will be obtained from the parent study (see Table 1). ~~Written~~ informed consent/ ~~(and written~~ assent ~~and/or co-consent for patients 14 years of age and older~~, as appropriate~~,)~~ must be given before any procedures related solely to Study TV50717-CNS-30047 are performed. […] A 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 for patients 14 years of age and older~~, depending on the child's age, as appropriate will be obtained from each patient before any screening procedures commence, according to national laws and local IEC/IRB requirements. […] (Note: Details of rescreening must be approved by the medical monitor.) […]	Informed consent/assent, depending on the child's age, as appropriate, will be obtained before any study procedures are performed. For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-0060, informed consent/assent, as appropriate, may be obtained prior to the day 1 visit, up to 4 weeks in advance of open-label study participation. For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, screening data will be obtained from the parent study (see Table 1). Informed consent/assent, as appropriate, must be given before any procedures related solely to Study TV50717-CNS-30047 are performed. […] A signed and dated informed consent form will be obtained from each parent/legally acceptable representative, and a signed and dated assent, depending on the child's age, as appropriate will be obtained from each patient before any screening procedures commence, according to national laws and local IEC/IRB requirements. […] (Note: Details of rescreening must be approved by the medical monitor.) […] • obtain written informed consent (and	Informed consent/assent language was updated for global alignment and applicability to all countries. Clarification and consistency edit was made regarding rescreening.

Original text with changes shown	New wording	Reason/Justification for change
• obtain written informed consent (and ~~written~~ assent, depending on the child's age ~~and/or co-consent for patients 14 years of age and older~~, as appropriate) before any other study related procedures are performed	assent, depending on the child's age, as appropriate) before any other study related procedures are performed	
Section 3.13 Study Procedures and Assessments (global for Sections 3.13.2 and 3.13.3)		
dispense IMP (sufficient doses for 2 weeks [current dose level and next dose level]) and patient diary	dispense IMP (sufficient doses for 2 weeks [current dose level and next dose level]) and patient diary	Clarified that patient diary is dispensed each time IMP is dispensed.
Section 3.13.2. Procedures Before Investigational Medicinal Product Treatment (Day 1)		
• perform clinical laboratory tests, including serum chemistry, hematology, and urine analyses ~~(required for all patients)~~	• perform clinical laboratory tests, including serum chemistry, hematology, and urine analyses	Removed unnecessary detail.
Section 3.13.3.2.1 In-Clinic Visits (Weeks 8, 15, 30, 32, 34, 41, and 54/ET) (also affects Section 4.4 and Synopsis)		
3.13.3.2.1 In-Clinic Visits (Weeks 8, 15, 30, 32, 34, 41, and 54/Early Termination Visit) The following procedures/assessments will be performed at weeks 8, 15, 30, 32, 34, 41, and 54/ET: • measure vital signs (pulse, BP, body temperature, and respiratory rate); at ~~week~~weeks 8 and 54, orthostatic BP and pulse should be measured after the patient is in a standing position for at least 3 minutes • ~~up to 2 blood samples separated by 2 hours or more should be collected, if possible, for patients discontinuing for insufficient efficacy (early termination)~~ • ~~perform UDS at week 54~~	**3.13.3.2.1 In-Clinic Visits (Weeks 8, 15, 30, 32, 34, 41, and 54/Early Termination Visit)** The following procedures/assessments will be performed at weeks 8, 15, 30, 32, 34, 41, and 54/ET: • measure vital signs (pulse, BP, body temperature, and respiratory rate); at weeks 8 and 54, orthostatic BP and pulse should be measured after the patient is in a standing position for at least 3 minutes	Clarification that ET procedures match those at week 54. Corrected timing description for orthostatic BP and pulse assessment. Removed pharmacokinetic samples (see also changes listed for Section 3.5.) Removed end of treatment drug screen assessment.

Original text with changes shown	New wording	Reason/Justification for change
Section 3.13.3.3.2. In-clinic Visit (Weeks 30 and 32):		
• ~~collect IMP/~~dispense IMP (sufficient doses to cover treatment until the following in-clinic visit) and patient diary • collect used and unused IMP bottles	• dispense IMP (sufficient doses to cover treatment until the following in-clinic visit) and patient diary • collect used and unused IMP bottles.	Clarification
Section 4.1.Patient Inclusion Criteria (also affects the Synopsis)		
i. 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 drug half lives, whichever is longer~~ after last dose of IMP. Further details are included in Appendix L.	i. 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 after last dose of IMP. Further details are included in Appendix L.	Removed unnecessary detail.
Section 4.2 Patient Exclusion Criteria		
~~l. Patient has received treatment with deep brain stimulation, transmagnetic stimulation, or transcranial direct current stimulation for reduction of ties within 4 weeks of the screening visit.~~	Not applicable	Removed criterion that is not applicable for this study population.
Section 4.4 Withdrawal Criteria and Procedures (also affects Sections 7.1.7, 7.7, 9.7.2, and Synopsis)		
If a post-day 1 QTcF value >500 msec or change from baseline (Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or day 1 (Study SD-809-C-17), as appropriate (see Section 9.7.2) >60 msec is found, the investigator should repeat the ECG assessment twice and compare the average of the 2 pre-treatment QTcF values (ie, the parent study baseline and screening values for patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 or the day 1 and screening values from the current study for patient[s] who completed Study	If a post-day 1 QTcF value >500 msec or change from baseline (Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or day 1 (Study SD-809-C-17), as appropriate (see Section 9.7.2) >60 msec is found, the investigator should repeat the ECG assessment twice and compare the average of the 2 pre-treatment QTcF values (ie, the parent study baseline and screening values for patients	Clarified baseline and pre-treatment calculations for ECG-based withdrawals depending on parent study (see also changes listed for Section 2.3.1 above).

Original text with changes shown	New wording	Reason/Justification for change
SD-809-C-17) to the average of the 3 post-day 1 QTcF values. The IMP must be stopped for any confirmed post-day 1 QTcF value >500 msec or increase from ~~day 1~~ baseline (Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or day 1 (Study SD-809-C-17) >60 msec.	rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 or the day 1 and screening values from the current study for patient[s] who completed Study SD-809-C-17) to the average of the 3 post-day 1 QTcF values. The IMP must be stopped for any confirmed post-day 1 QTcF value >500 msec or increase from baseline (Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or day 1 (Study SD-809-C-17) >60 msec.	
Section 5.1 Investigational Medicinal Products Administered During the Study (also affects the Synopsis)		
Although dose adjustments can be made up to and including the week 7 telephone call, if a stable dose is reached before then, the patient should continue taking that dose for the remainder of the titration period. ~~and throughout maintenance dosing~~. If a patient experiences a "clinically significant" adverse event that is attributed to the IMP, the investigator will determine if a dose reduction or suspension is necessary. At the end of the titration period, the patient's dose will be established for the maintenance period. If a patient experiences an adverse event during the maintenance period and the investigator believes a dose reduction is warranted, the dose may be reduced. Dose adjustments of TEV-50717 (upward or downward) may be made during the maintenance period, if necessary, but not more often than every 5 days and only in increments of 6 mg. ~~During the maintenance period, if a patient's weight shifts into a new category (see Table 2), and the investigator believes the patient is no longer at an optimal dose, the investigator may change the dose level.~~ IMP will be dispensed in the clinic. Patients should take their first dose in the evening on day 1 after their day 1 clinic visit. Patients will receive sufficient doses to last until the next visit.	Although dose adjustments can be made up to and including the week 7 telephone call, if a stable dose is reached before then, the patient should continue taking that dose for the remainder of the titration period. If a patient experiences a "clinically significant" adverse event that is attributed to the IMP, the investigator will determine if a dose reduction or suspension is necessary. At the end of the titration period, the patient's dose will be established for the maintenance period. If a patient experiences an adverse event during the maintenance period and the investigator believes a dose reduction is warranted, the dose may be reduced. Dose adjustments of TEV-50717 (upward or downward) may be made during the maintenance period, if necessary, but not more often than every 5 days and only in increments of 6 mg. IMP will be dispensed in the clinic. Patients should take their first dose in the evening on day 1 after their day 1 clinic visit. Patients will	Updated language regarding dose administration, including dose adjustments.

<table>
<tr><th>Original text with changes shown</th><th>New wording</th><th>Reason/Justification for change</th></tr>
<tr><td>[...]
• The starting dose is 6 mg in all patients. ~~This dose will be administered in the evening on days 1 and 2, followed by AM administration for the remainder of week 1 (if body weight is <40 kg).~~ Daily doses ~~of 12 mg and higher~~ will be administered ~~twice daily in 2 divided doses,~~ approximately 8 to 10 hours apart during the day (those on the 6-mg dose will have once-daily dosing). 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. ~~If patients experience insomnia while taking the initial 6-mg dose in the evening, they may switch to taking it as a morning dose on day 2.~~
[...]
• Following re-titration, the dose of IMP should be kept stable, if possible, but changes can be made as described for Part A.</td><td>receive sufficient doses to last until the next visit.
[...]
• The starting dose is 6 mg in all patients. Daily doses will be administered twice daily, approximately 8 to 10 hours apart during the day (those on the 6-mg dose will have once-daily dosing). 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.
[...]
• Following re-titration, the dose of IMP should be kept stable, if possible, but changes can be made as described for Part A.</td><td></td></tr>
<tr><td>Table 3: Daily Dose of IMP by ~~Day 1 Body Weight Category, CYP2D6 Impairment,~~Previously Established Maintenance Dose and Study Week (~~Re t~~Titration Post-Drug Withdrawal) for Patients Randomized to Placebo During the Blinded, Randomized Drug Withdrawal Period

[Formerly content was the same as for Table 2.]</td><td>Table 3: Daily Dose of IMP by Previously Established Maintenance Dose and Study Week (Titration Post-Drug Withdrawal) for Patients Randomized to Placebo During the Blinded, Randomized Drug Withdrawal Period

<table><tr><th></th><th>Daily dose (mg) at the start of week</th></tr></table></td><td>Updated title and content of Table 3 to reflect change in re-titration regimen.</td></tr>
</table>

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

Previously established maintenance dose[a] (mg)	Day 211 (start of week 31)	Day 218 (start of week 32)	Day 225 (start of week 33)	Day 232 (start of week 34) maintenance dose
6	6	6	6	6
12	12	12	12	12
18	12	18	18	18
24	12	18	24	24
30	12	18	24	30
36	12	24	30	36
42	12	24	36	42
48	12	24	36	48

[a] The previously established maintenance dose is the dose administered at the end of Part A (Day 196 [end of week 28]). The blinded, randomized drug withdrawal period will occur from the start of week 29 through the end of week 30.

IMP=investigational medicinal product.

Original text with changes shown	New wording	Reason/Justification for change
Section 5.3 Prior and Concomitant Medication or Treatment		
Any prior or concomitant therapy, medication, or procedure a patient receives during ~~has had within 3 months before~~ IMP administration and up to the end of the study period, including follow-up, will be recorded on the CRF. Generic or trade name, indication, and dosage will be recorded. In addition, only for patients who completed Study SD-809-C-17, any prior or concomitant therapy, medication, or procedure a patient has had within 3 months before IMP administration will be recorded on the CRF.	Any prior or concomitant therapy, medication, or procedure a patient receives during IMP administration and up to the end of the study period, including follow-up, will be recorded on the CRF. Generic or trade name, indication, and dosage will be recorded. In addition, only for patients who completed Study SD-809-C-17, any prior or concomitant therapy, medication, or procedure a patient has had within 3 months before IMP administration will be recorded on the CRF.	Removed duplicated prior/concomitant medication collection for patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060.
Section 5.5 Dose Reduction and Temporary Investigational Medicinal Product Discontinuation		
Suspension of study medication for up to 1 week, if warranted for patient safety, is allowed.	Suspension of study medication for up to 1 week, if warranted for patient safety, is allowed.	Clarified dose suspension criteria.
Section 5.6 Total Blood Volume		
The total volume of blood to be collected for each patient in this study is approximately 30~~20~~ to 60~~40~~ mL, as detailed in Table 4. [Table 4 footnotes] a For patients who completed Study TV50717-CNS-30046 or Study TV50717-CNS-30060, 30 to 40 mL will be collected. b For patients who completed Study SD-809-C-17, 50 to 60 mL will be collected.	The total volume of blood to be collected for each patient in this study is approximately 30 to 60 mL, as detailed in Table 4. [Table 4 footnotes] a For patients who completed Study TV50717-CNS-30046 or Study TV50717-CNS-30060, 30 to 40 mL will be collected. b For patients who completed Study SD-809-C-17, 50 to 60 mL will be collected.	Clarified how blood volume collection is dependent on parent study.
Section 6.1.2 Tourette Syndrome-Patient Global Impression of Impact		
The TS-PGII is administered on day 1 (ie, week 13 data from	The TS-PGII is administered on day 1 (ie,	Aligned to match other

Original text with changes shown	New wording	Reason/Justification for change
Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060) and weeks 4, 8, 15, 28, 34, 41, 54, and 55. Input from the caregiver/adult~~parent/legal guardian~~ is permitted~~required~~.	week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060) and weeks 4, 8, 15, 28, 34, 41, 54, and 55. Input from the caregiver/adult is permitted.	assessments.
Section 6.1.3 Tourette Syndrome Patient Global Impression of Severity		
The TS-PGIS uses a 5-point scale, ranging from no tics (1) to very severe tics (5), to assess overall response to therapy.	The TS-PGIS uses a 5-point scale, ranging from no tics (1) to very severe tics (5), to assess overall response to therapy.	Corrected scale description.
Section 7.5.2.2. Urine Drug Screen		
A UDS will be performed at the time points specified in Table 1. ~~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 specified drugs or their metabolites, without medical explanation, will preclude the patient from enrollment or continued participation in the study.	A UDS will be performed at the time points specified in Table 1. A positive result for any of the specified drugs or their metabolites, without medical explanation, will preclude the patient from enrollment or continued participation in the study.	Removed unnecessary detail.
Section 9.2.1 Intent-to-Treat Analysis Set		
The intent-to-treat (ITT) analysis set will include all enrolled patients, regardless of whether or not a patient took any IMP. Enrolled subjects who are not randomized will be summarized separately as "Not randomized," and randomized subjects will be analyzed based on their randomized treatment.	The intent-to-treat (ITT) analysis set will include all enrolled patients, regardless of whether or not a patient took any IMP. Enrolled subjects who are not randomized will be summarized separately as "Not randomized," and randomized subjects will be analyzed based on their randomized treatment.	Clarified and updated analysis presentation.
Section 9.2.5 Randomized Withdrawal Modified Intent-to-Treat Population		
The Randomized Withdrawal Modified Intent-to-Treat (~~mITT~~	The Randomized Withdrawal Modified Intent-	Corrected score from AIMS

Original text with changes shown	New wording	Reason/Justification for change
~~(~~RWmITT) Population will include all patients~~subjects~~ enrolled in the randomized drug withdrawal period who receive study drug and have a YGTSS TTS~~centrally read AIMS score~~ at both the randomized drug withdrawal (week 28)~~period initial~~ visit and the week 30 visit. ~~All e~~Efficacy measures in the randomized drug withdrawal period will be analyzed ~~using the (RWmITT)~~as described in Section 9.5.3.1.	to-Treat (RWmITT) Population will include all patients enrolled in the randomized drug withdrawal period who receive study drug and have a YGTSS TTS at both the randomized drug withdrawal (week 28) visit and the week 30 visit. Efficacy measures in the randomized drug withdrawal period will be analyzed as described in Section 9.5.3.1.	to YGTSS TTS and made editorial clarifications.
Section 9.2.6 Responder Randomized Withdrawal Modified Intent-to-Treat Population (also affects Sections 9.4 and 9.5.3.1)		
Section 9.2.6. Responder Randomized Withdrawal Modified Intent-to-Treat Population The Responder Randomized Withdrawal mITT (RRWmITT) Population will include all patients enrolled in the randomized drug withdrawal period who receive study drug and have a YGTSS TTS at both the week 28 visit and the week 30 visit and a ≥25% reduction in the TTS from baseline in the parent protocol to week 28. Efficacy measures in the randomized drug withdrawal period will be analyzed as described in Section 9.5.3.1.	Section 9.2.6. Responder Randomized Withdrawal Modified Intent-to-Treat Population The Responder Randomized Withdrawal mITT (RRWmITT) Population will include all patients enrolled in the randomized drug withdrawal period who receive study drug and have a YGTSS TTS at both the week 28 visit and the week 30 visit and a ≥25% reduction in the TTS from baseline in the parent protocol to week 28. Efficacy measures in the randomized drug withdrawal period will be analyzed as described in Section 9.5.3.1.	Added another analysis population.
Section 9.5.3.1 Efficacy Analysis for the Blinded, Randomized Drug Withdrawal Portion (also affects the Synopsis)		
Section 9.5.3.1 Efficacy Analysis for the Blinded, Randomized Drug Withdrawal Portion ~~Study~~ For the randomized drug withdrawal portion of the study […] The primary analyses will be in the RRWmITT population; in addition, sensitivity testing will be done using the same analyses on the RWmITT population and a subpopulation of the RRWmITT who had a ≥35% reduction in the TTS from baseline in the parent protocol to week 28.	**Section 9.5.3.1 Efficacy Analysis for the Blinded, Randomized Drug Withdrawal Portion** For the randomized drug withdrawal portion of the study […] The primary analyses will be in the RRWmITT population; in addition, sensitivity testing will be done using the same analyses on the RWmITT population and a	Clarified use of a primary analysis and added sensitivity analyses due to addition of another analysis population (see also changes listed for Sections 9.2.5 and 9.2.6 above).

Original text with changes shown	New wording	Reason/Justification for change
	subpopulation of the RRWmITT who had a ≥35% reduction in the TTS from baseline in the parent protocol to week 28.	

17.4. Amendment 04 Dated 22 May 2019

The primary reasons for this amendment are to address Regulatory Authority requirements; update the anticipated enrollment numbers to account for the increased sample size of Study TV50717-CNS-30046; include language on the addition of an interim analysis; 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; 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		
[redacted]	[redacted]	Update to CRO's name
Part A • vital signs, <u>height,</u> and weight: screening (only for patients who completed Study SD 809 C 17; data from Study TV50717-CNS 30046 or Study TV50717-CNS 30060 should be used for the remaining patients); day 1; and weeks 2, 4, 6, 8, 15, 34, 41, 54, and 55 Part B • vital signs, <u>height,</u> and weight: weeks 28, 30, and 32	• vital signs, height, and weight: screening (only for patients who completed Study SD 809 C 17; data from Study TV50717-CNS 30046 or Study TV50717-CNS 30060 should be used for the remaining patients); day 1; and weeks 2, 4, 6, 8, 15, 34, 41, 54, and 55 Part B • vital signs, height, and weight: weeks 28, 30, and 32	Height has been added as an assessment to be performed at every in clinic visit in Part A and Part B. The Schedule of Procedures and Assessments has been updated accordingly.
Title Page		
[redacted]	[redacted]	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 <u>Branded Pharmaceutical Products R&D, ~~Inc.~~ and Nuvelution TS Pharma, Inc., and/or its affiliates</u>. © ~~2017~~<u>2019</u> 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		
Legal Representative of the Sponsor in the EU <u>Syneos Health Netherlands B.V.</u> **For protocol issues, contact the study leader listed below:** [redacted]	**Legal Representative of the Sponsor in the EU** Syneos Health Netherlands B.V. **For protocol issues, contact the study leader listed below:** [redacted] Chief Medical Officer, Nuvelution TS Pharma, Inc.	Update to Sponsor representatives and points of contact

Original text with changes shown	New wording	Reason/Justification for change
Email:[redacted] Chief Medical Officer, Nuvelution TS Pharma, INC. Tel: +[redacted] Email: [redacted] **For medical issues, contact the physicians listed below:** [redacted]	Tel: [redacted] Email: [redacted] **For medical issues, contact the physicians listed below:** [redacted]	

Original text with changes shown	New wording	Reason/Justification for change
[redacted] ~~PhD~~	[redacted] **For operational issues, contact the Head of Operations listed below:** [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.	

Original text with changes shown	New wording	Reason/Justification for change
~~Research~~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 Clinical Laboratory** Q2 Solutions (Quest) LLC 27027 Tourney Road, Suite 2E Valencia, CA 91355 USA **Electronic Data Capture** Medidata RAVE (through~~INC Research~~Syneos Health, LLC) **Contract Research Organization; Safety and Efficacy Data Analysis** ~~INC Research~~ ~~3201 Beechleaf Court~~ ~~Suite 600~~ ~~Raleigh 27604-1547~~ Syneos Health, LLC 1030 Sync Street Morrisville, NC 27560 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, LLC) **Contract Research Organization Safety and Efficacy Data Analysis** Syneos Health, LLC 1030 Sync Street Morrisville, NC 27560 USA	

Original text with changes shown	New wording	Reason/Justification for change
1.3.1.3 Toxicology		
The no-observed-adverse-effect level (NOAEL) 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 no-observed-adverse-effect level (NOAEL) 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 (Other sections affected: Section 1.3.2.1 Clinical Pharmacology Studies)		
• ~~6~~7 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 • ~~1~~2 completed Phase 2/3 study in patients with TD • ~~1 completed Phase 3 study in patients with TD~~	• 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 completed Phase 2/3 study in patients with	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
• 1 ongoing Phase 3 long-term safety ~~studies~~study in patients with TD • 1 completed Phase 1b study in patients with TS • 2 ongoing Phase 2/3 and Phase 3 studies in patients with TS • 1 ongoing Phase 3 long-term safety study in patients with TS Further details may be found in the IB ~~(including the IB supplement for TS)~~.	TD • 1 ongoing Phase 3 long-term safety study in patients with TD • 1 completed Phase 1b study in patients with TS • 2 ongoing Phase 2/3 and Phase 3 studies in patients with TS • 1 ongoing Phase 3 long-term safety study in patients with TS Further details may be found in the IB.	
1.8 Location and Study Duration		
This study is planned to be conducted globally (per Study SD-809-C-17, Study TV50717-CNS-30046, and Study TV50717-CNS-30060) at approximately 120 centers. It is expected to start in May 2018 and conclude in ~~October 2020~~January 2021, with a duration of approximately ~~30~~ 32 months.	This study is planned to be conducted globally (per Study SD-809-C-17, Study TV50717-CNS-30046, and Study TV50717-CNS-30060) at approximately 120 centers. It is expected to start in May 2018 and conclude in January 2021, with a duration of approximately 32 months.	Updated the expected timing and duration of the study
3.1 General Design and Study Schematic Diagram (other sections effected: Section 9.9 Planned Interim Analysis and Figure 1: Overall Study Schematic Diagram)		
Up to approximately ~~212~~227 patients are planned to be enrolled (approximately 1 patient is estimated to enroll from the Phase 1b Study SD-809-C-17, up to approximately ~~85~~99 patients are estimated to enroll from the Phase 2/3 Study TV50717-CNS-30046, and up to approximately ~~126~~127 patients are estimated to enroll from the Phase 3 Study TV50717-CNS-30060). When approximately 100 patients have completed the 28-week clinic visit, an interim analysis, including data from day 1 and	Up to approximately 227 patients are planned to be enrolled (approximately 1 patient is estimated to enroll from the Phase 1b Study SD-809-C-17, up to approximately 99 patients are estimated to enroll from the Phase 2/3 Study TV50717-CNS 30046, and up to approximately 127 patients are estimated to enroll from the Phase 3 Study TV50717-CNS 30060). When approximately 100 patients have completed the 28-week clinic visit, an interim analysis, including data from day 1 and up to week 28 visit only, will be	Updated the study design to include updated enrollment numbers and to account for inclusion of an interim analysis once approximately 100 patients have completed the 28-week clinic visit

Original text with changes shown	New wording	Reason/Justification for change
up to week 28 visit only, will be conducted to provide descriptive, long-term safety and efficacy data to be used in regulatory submissions. To maintain data integrity of Study TV50717-CNS-30047, only a limited number of personnel who do not have contact with the sites will have access to this interim data in preparation for the regulatory filing. As no decisions regarding conduct of the study will be made based on the descriptive interim analysis, no alpha will be spent.	conducted to provide descriptive, long-term safety and efficacy data to be used in regulatory submissions. To maintain data integrity of Study TV50717-CNS-30047, only a limited number of personnel who do not have contact with the sites will have access to this interim data in preparation for the regulatory filing. As no decisions regarding conduct of the study will be made based on the descriptive interim analysis, no alpha will be spent.	
3.1.1 Screening Period (up to 31 days) (other sections affected: 3.13.1 Procedures for Screening and Enrollment [Visit 1] and 3.13.2 Procedures Before Investigational Medicinal Product Treatment [Day 1])		
Patients may be rescreened 1 time if there is a change in the patient's medical background, a modification of study entry criteria, or other relevant change. (Note: Details of a patient's rescreening must be approved and documented by the medical monitor~~).~~ and/or Clinical Surveillance and Training [CST] team.)	Patients may be rescreened 1 time if there is a change in the patient's medical background, a modification of study entry criteria, or other relevant change. (Note: Details of a patient's rescreening must be approved and documented by the medical monitor and/or Clinical Surveillance and Training [CST] team.)	Updated guidance language pertaining to patient rescreening
3.1.3 Titration Period (7 Weeks)		
If a patient experiences ~~a "clinically significant"~~depression, suicidal ideation or behavior, anxiety, akathisia, parkinsonism, somnolence, any other adverse event that interferes with daily activity, or adverse event that is related to ~~the~~ IMP, the investigator will determine if a dose reduction or suspension is necessary.	If a patient experiences depression, suicidal ideation or behavior, anxiety, akathisia, parkinsonism, somnolence, any other adverse event that interferes with daily activity, or adverse event that is related to IMP, the investigator will determine if a dose reduction or suspension is necessary.	Updated guidance language pertaining to dose reductions and suspensions
3.6.1 Maintenance of Randomization		
Patient randomization codes will be maintained in a secure location ~~at the service provider contracted to generate the codes.~~within Syneos Health. At the time of analysis ~~(after the end of study), after receiving an unblinding request from the Teva~~, when treatment codes are needed, the Syneos Health statistician~~,~~ assigned to the ~~service provider~~study will ~~provide the~~make a request to unblind and will receive the unblinded codes and unblinded IMP assignment according to the	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 (SOP).	Updated language on the responsibilities and maintenance of randomization Dosing information and dose reduction guidelines were clarified

Original text with changes shown	New wording	Reason/Justification for change
processes defined in the relevant Standard Operating Procedure (SOP).		
3.6.2 Blinding and Unblinding		
When a blind is broken, the patient will be withdrawn from the study, and the event will be recorded on the case report form (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.	When a blind is broken, the patient will be withdrawn from the study, and the event will be recorded on the case report form (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.	Updated guidance on how to handle the unblinding of patients by mistake
3.9.1 Drug Storage and Security		
The IMP (TEV-50717) ~~must~~should be stored protected from light, at a controlled room temperature, ~~15~~20°C to ~~30~~25°C (68°F to 77°F); however, storage between 15°C and 20°C (59°F to ~~86°F),~~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) 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 to 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 the direction for the storage temperatures and proper handling of the study drug

Original text with changes shown	New wording	Reason/Justification for change
3.13.1 Procedures for Screening and Enrollment (Visit 1) (other sections affected: 3.13.3.1.2 In-Clinic Visits [Weeks 2, 4, and 6], 3.13.3.2.1 In-Clinic Visits [Weeks 8, 15, 30, 32, 34, 41, and 54/Early Termination Visits], 3.13.3.3.1 In-Clinic Visit [Week 28], 3.13.3.3.2 In-clinic Visit [Weeks 30 and 32], 3.13.4.1 In-Clinic Visit [Week 55], and 3.13.5 Unscheduled Visits)		
• conduct clinic visit	• conduct clinic visit	This addition was made strictly for clarity. Clinic visits were already occurring at the specified visits in which this verbiage was added. This bullet was added at each week in which a clinic visit takes place.
3.13.2 Procedures Before Investigational Medicinal Product Treatment (Day 1)		
• conduct clinic visit • measure vital signs (orthostatic pulse and BP [after standing for at least 3 minutes]), height, and weight • dispense IMP (sufficient doses for 2 weeks [current dose level and next dose level]) to cover the telephone contacts) and patient diary	• conduct clinic visit • measure vital signs (orthostatic pulse and BP after standing for at least 3 minutes), height, and weight • dispense IMP (sufficient doses for 2 weeks [current dose level and next dose level] to cover the telephone contacts) and patient diary	Clinic visits were already occurring at the specified visits in which this verbiage of "conduct clinic visit" was added. This bullet was added at each week in which a clinic visit takes place. Other minor additions were included for clarity and to include height as a specific assessment at each in clinic visit.
4.1 Patient Inclusion Criteria		
i. 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 L.	i. 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 L	Updated criteria "i" to include additional duration criteria for the use of birth control methods.
4.2 Patient Exclusion Criteria (other sections affected: Appendix A Allowed and Disallowed Medications)		
k. Patient has received any of the following concomitant	k. Patient has received any of the following	Added cannabidiol oil and

Original text with changes shown	New wording	Reason/Justification for change
medications for tics within the following specified exclusionary windows of screening prior to dosing for washout: → 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 and dosing has been stable for at least 2 weeks before screening. 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. Note: Use of guanfacine or clonidine is allowed regardless of indication (ie, if prescribed for tics or Tourette syndrome) 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.	concomitant medications for tics within the following specified exclusionary windows of screening prior to dosing for washout: → 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 and dosing has been stable for at least 2 weeks before screening. 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. Note: Use of guanfacine or clonidine is allowed regardless of indication (ie, if prescribed for tics or Tourette syndrome) 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.	valbenazine as concomitant medications Included notes for various different concomitant medications and stipulations
4.4 Withdrawal Criteria and Procedures for the Patient		
The investigator also has the right to withdraw a patient from the ~~IMP in~~ study if any of the ~~event of~~ 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~~), or~~) d. other reasons concerning the health or well-being of the patient~~, or in the event of~~	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, procedures, and withdrawal criteria due to adverse event

Original text with changes shown	New wording	Reason/Justification for change
e. lack of cooperation~~. If a~~ f. post-~~day 1~~baseline QTcF value >500 msec or change from baseline ~~(Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or day 1 (Study SD-809-C-17), as appropriate (see Section **9.7.2**(~~>60 msec ~~is found, the~~ (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-~~day 1~~baseline QTcF values. The IMP must be stopped for any confirmed post-baseline QTcF value >500 msec or increase from baseline ~~(Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or day 1 (Study SD-809-C-17), as appropriate (see Section **9.7.2**(~~>60 msec. ~~In addition, a patient may be withdrawn from the IMP as described in Sections **3.11, 3.13.3.2.2, 5.4, and**~~7.1.7.~~ g. when a blind is broken due to safety concerns (see Section 3.6.2). 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 5.4). In addition, a patient may be withdrawn from the study as described in Sections 3.11, 3.6, 5.4, 7.1.7, and 3.13. ~~For patients who withdraw prematurely, an early termination visit should be conducted as soon as possible after the last dose of IMP. 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 the week 54 visit.~~ All patients who discontinue early will have a follow-up telephone contact for safety evaluation 2 weeks after their last	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 3.6.2). 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 5.4). In addition, a patient may be withdrawn from the study as described in Sections 3.11, 3.6, 5.4, 7.1.7, and 3.13. All patients who discontinue early will have a follow-up telephone contact for safety evaluation 2 weeks after their last dose of IMP (Section 3.13.4.2).	

Original text with changes shown	New wording	Reason/Justification for change
dose of IMP (Section 3.13.4.2).		
5.1.1 Drug Administration		
If a patient experiences ~~a "clinically significant"~~depression, suicidal ideation or behavior, anxiety, akathisia, parkinsonism, somnolence, any other adverse event that interferes with daily activity, or adverse event that is ~~attributed~~related to ~~the~~ IMP, the investigator will determine if a dose reduction or suspension is necessary. IMP will be administered as follows: • The total daily dose, as provided in Table 2, is divided into a twice daily administration. • … A dose cap for impaired ~~metabolizers will be~~patients is prespecified by the IRT and presented in Table 2.	If a patient experiences depression, suicidal ideation or behavior, anxiety, akathisia, parkinsonism, somnolence, any other adverse event that interferes with daily activity, or adverse event that is related to IMP, the investigator will determine if a dose reduction or suspension is necessary. IMP will be administered as follows: • The total daily dose, as provided in Table 2, is divided into a twice daily administration. • … A dose cap for impaired patients is prespecified by the IRT and presented in Table 2.	This subsection was added to provide greater clarity as to what details this section of the protocol included. Further details on determination of dose reduction or suspension were provided. Additional IMP administration information was added for clarity
5.2 Restrictions		
The ~~addition~~use of ~~a strong CYP2D6 inhibitor is~~quinidine and terbinafine are prohibited (see Appendix A, Table 9).	The use of quinidine and terbinafine are prohibited (see Appendix A, Table 9).	Medication restrictions were updated
5.5 Dose Reduction and Temporary Investigational Medicinal Product Discontinuation		
Dose Suspension **Suspensions of study medication for adverse events must be reviewed with the medical monitor before therapy is restarted**. ~~**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**~~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.	**Dose Suspension** **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.	Updated dose suspension text to provide further guidance to the investigators

Original text with changes shown	New wording	Reason/Justification for change
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 the investigator according to the instructions provided on the serious adverse event form.	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.	Updated guidance for investigator reporting of adverse events
7.2.2 Columbia-Suicide Severity Rating Scale		
The C-SSRS is administered through 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	The C-SSRS is administered through 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	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
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.	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.	
7.9 Assessment of Suicidality		

Original text with changes shown	New wording	Reason/Justification for change
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 symptoms immediately to the study investigator.~~ Depression and Suicidality as an Adverse Event Families and caregivers of patients ~~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.	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 patients 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.	Added further descriptions and guidance on depression and suicidality assessed as adverse events

Original text with changes shown	New wording	Reason/Justification for change
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.	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 (other sections affected: Appendix A: ALLOWED AND DISALLOWED MEDICATIONS		
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 A. Prohibited medications that are associated with QTc prolongation are listed in Table 8, while prohibited antipsychotic drugs are listed in 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 A. Prohibited medications that are associated with QTc prolongation are listed in Table 8, while prohibited antipsychotic drugs are listed in Table 7.	Included a few more details on the list of concomitant medications
9.1 Sample Size and Power Considerations		
This study is safety-oriented in nature; therefore, no formal hypothesis testing is planned for Part A. Based on the number of patients in the previous studies, up to approximately ~~212~~227 patients (approximately 1 patient from the Phase 1b Study SD-809-C-17, up to approximately ~~85~~ 99 patients from the Phase 2/3 Study TV50717-CNS-30046, and up to approximately ~~126~~ 127 patients from the Phase 3 Study TV50717-CNS-30060) are estimated to enroll. [redacted]	This study is safety oriented in nature; therefore, no formal hypothesis testing is planned for Part A. Based on the number of patients in the previous studies, up to approximately 227 patients (approximately 1 patient from the Phase 1b Study SD-809-C-17, up to approximately 99 patients from the Phase 2/3 Study TV50717-CNS-30046, and up to approximately 127 patients from the Phase 3 Study TV50717-CNS-30060) are estimated to enroll. All patients who complete Study TV50717-CNS-30060 or Study TV50717-CNS-30046 are eligible to participate in Study TV50717-CNS-30047. As the number of patients to be randomized in parent Study	Updated the anticipated enrollment numbers to account for the increased sample size of Study TV50717-CNS-30046

Original text with changes shown	New wording	Reason/Justification for change
[redacted] For the randomized drug withdrawal period, ~~enrolling at least~~ 190 patients to be included in the analysis will provide approximately ~~at least~~ 90% power to detect a difference between TEV-50717-treated and placebo-treated patients assuming a difference in YGTSS TTS of 4.5 with a standard deviation of 9 ~~assuming a type 1 error rate of 5%~~using a two-sided test for difference at a significance level of 0.05.	TV50717-CNS-30046 has increased, the number of patients anticipated to be randomized into Study TV50717-CNS-30047 has also increased. The rationale for the increased sample size in Study TV50717-CNS-30046 is provided that protocol. For the randomized drug withdrawal period, 190 patients to be included in the analysis will provide approximately 90% power to detect a difference between TEV-50717-treated and placebo-treated patients assuming a difference in YGTSS TTS of 4.5 with a standard deviation of 9 using a two sided test for difference at a significance level of 0.05.	
9.5.3.1 Efficacy Analysis for the ~~Blinded,~~ Randomized Drug Withdrawal ~~Portion~~Period		
For the randomized drug withdrawal portion of the study, an analysis of covariance model will be used as the primary analysis model with the change from randomized-withdrawal week 28 to week 30 in YGTSS TTS as the dependent variable, and treatment group, randomized-withdrawal week 28 TTS, and age group at baseline as covariates. The least squares mean of the change in TTS from week 28 to week 30 will be compared (the active treatment arm and placebo arm) using a 2-sided test at the alpha=0.05 level of significance. ~~In addition, actual values and changes in TTS will be summarized using descriptive statistics.~~ The primary ~~analyses~~analysis will be in the RRWmITT population~~; in~~ (see Section 9.2.6). In addition, sensitivity testing will be done using the same ~~analyses on~~model in the RWmITT population and in a subpopulation of the RRWmITT who had a ≥35% reduction in the TTS from baseline in the parent protocol to week 28.	For the randomized drug withdrawal portion of the study, an analysis of covariance model will be used as the primary analysis model with the change from randomized-withdrawal week 28 to week 30 in YGTSS TTS as the dependent variable, and treatment group, randomized-withdrawal week 28 TTS, and age group at baseline as covariates The least squares mean of the change in TTS from week 28 to week 30 will be compared (the active treatment arm and placebo arm) using a 2-sided test at the alpha=0.05 level of significance. The primary analysis will be in the RRWmITT population (see Section 9.2.6). In addition, sensitivity testing will be done using the same model in the RWmITT population and in a subpopulation of the RRWmITT who had a ≥35% reduction in the TTS from baseline in the parent protocol to week 28.	Included edits to the randomized drug withdrawal period for clarity on the planned analysis.
9.9 Planned Interim Analysis		
~~No interim analysis is planned for this study.~~	When approximately 100 patients have completed the 28-week clinic visit, an interim analysis, including	Included language on the addition of an interim analysis

<table>
<tr><th>Original text with changes shown</th><th>New wording</th><th>Reason/Justification for change</th></tr>
<tr><td>When approximately 100 patients have completed the 28-week clinic visit, an interim analysis, including data from day 1 and up to week 28 visit only, will be conducted to provide descriptive, long-term safety and efficacy data to be used in regulatory submissions. To maintain data integrity of Study TV50717-CNS-30047, only a limited number of personnel who do not have contact with the sites will have access to this interim data in preparation for the regulatory filing. As no decisions regarding conduct of the study will be made based on the descriptive interim analysis, no alpha will be spent.</td><td>data from day 1 and up to week 28 visit only, will be conducted to provide descriptive, long-term safety and efficacy data to be used in regulatory submissions. To maintain data integrity of Study TV50717-CNS-30047, only a limited number of personnel who do not have contact with the sites will have access to this interim data in preparation for the regulatory filing. As no decisions regarding conduct of the study will be made based on the descriptive interim analysis, no alpha will be spent.</td><td>once ~100 patients have completed the 28-week clinic visit.</td></tr>
<tr><td colspan="3">Appendix A ALLOWED AND DISALLOWED MEDICATIONS</td></tr>
<tr><td>Table 9: 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></td><td>Table 9: Other Prohibited Drugs
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<tr><td>Terbinafine</td><td>Antifungal medication</td><td>Weak CYP2D6 inhibitor</td></tr>
</table></td><td>The list of allowed and disallowed medications was updated to align with the updated exclusion criteria. Updated Appendix A to include a table (Table 9) for other prohibited drugs</td></tr>
</table>

APPENDIX A. ALLOWED AND DISALLOWED MEDICATIONS

Medications that are allowed, provided that conditions outlined in the table are met, are shown in Table 6. Tables for allowed and prohibited medications are not exhaustive 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 cytochrome P450 inhibitor, or if there are any questions regarding any medication not listed in the tables below.

Prohibited antipsychotic drugs are listed in Table 7. Prohibited medications that are associated with QTc prolongation are listed in Table 8.

Table 6: Allowed Medications

Generic/Drug class	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	Must be receiving stable treatment (including dose) for at least 6 weeks before screening.
Benzodiazepines	Primary use must not be for tics; dosing must have been stable QT 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	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.
Clonidine	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.
Stimulants	Including amphetamine, methylphenidate, and lisdexamfetamine. Primary use is for the treatment of ADHD; dosing must have been stable for at least 2 weeks before screening.
SNRIs	Including atomoxetine. Primary use is for the treatment of ADHD; dosing must have been stable for at least 4 weeks before screening.
Additional medications allowed with preapproval from medical monitor	
Albuterol, levalbuterol	Asthma
Guaifenesin	Cold symptoms

Table 6: Allowed Medications (Continued)

Generic/Drug class	Condition
Stable medications allowed according to inclusion/exclusions criteria	
Antihistamines	Allergies
Melatonin	Insomnia
Allowed strong CYP inhibitors[a]	
Bupropion	Antidepressant (aminoketone)
Fluoxetine	Antidepressant (selective serotonin reuptake inhibitor)
Paroxetine	Antidepressant (selective serotonin reuptake inhibitor)

[a] The use of these medications will affect the maximum daily dose of IMP, as shown in Table 2.
ADHD=attention-deficit/hyperactivity disorder; CYP=cytochrome P450; IMP=investigational medicinal product; SNRIs=serotonin-norepinephrine reuptake inhibitor.
Note: No dosing changes can be made during the study.

Table 7: Prohibited Antipsychotic Drugs

Typical/first generation antipsychotics	**Atypical/second generation antipsychotics**
Chlorpromazine	Aripiprazole
Haloperidol	Asenapine maleate
Loxapine	Clozapine
Molindone	Iloperidone
Perphenazine	Lurasidone
Pimozide	Olanzapine
Prochlorperazine	Olanzapine / fluoxetine
Thioridazine	Paliperidone
Thiothixene	Quetiapine
Trifluoperazine	Risperidone
Promethazine-containing compounds	Ziprasidone
Fluphenazine	Tiapride

Table 8: 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

Table 8: Prohibited QTc Prolonging Drugs (Continued)

Generic	Class/clinical use	Note
Droperidol	Sedative; anti-nausea/anesthesia adjunct, nausea	
Erythromycin[0]	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

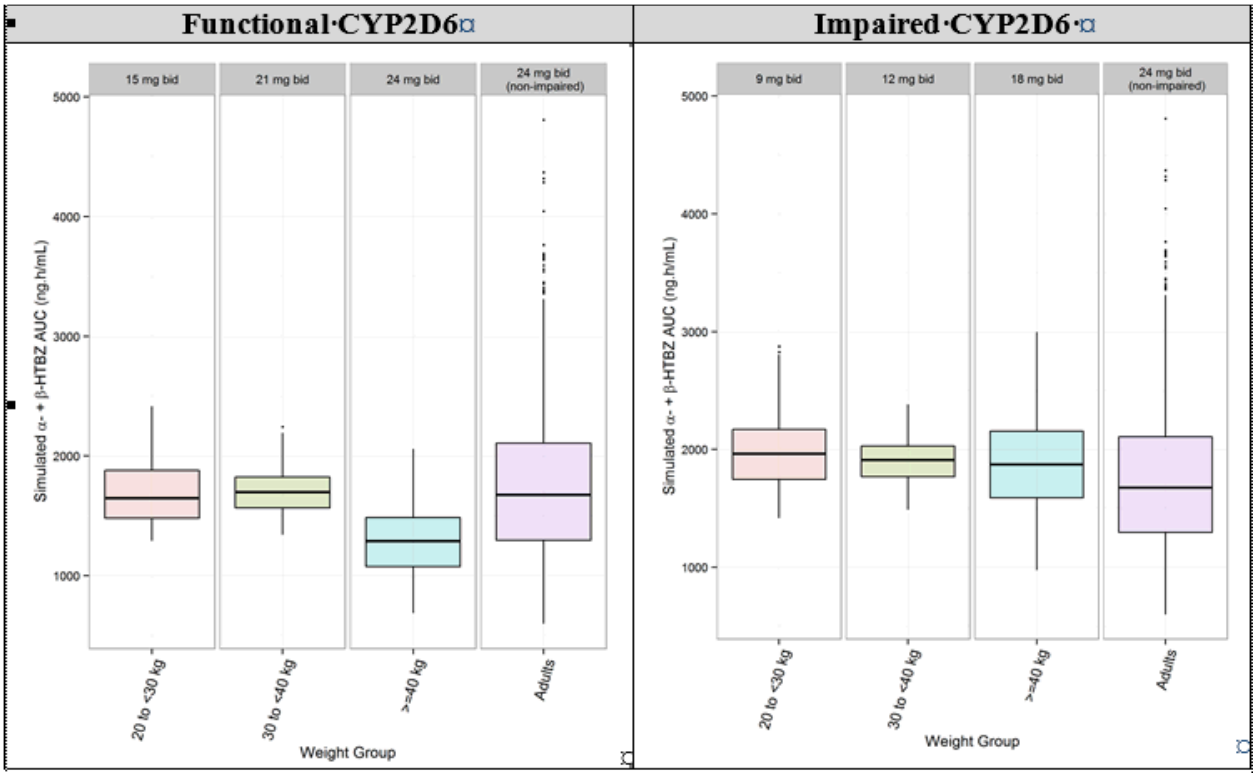
[a] Allowed dose of Azithromycin is up to 500 mg/day
[b] Systemic use only. Topical use is allowed.
GI=gastrointestinal; USA=United States of America.

Table 9: 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

APPENDIX B. DISTRIBUTION OF AUC BY WEIGHT CATEGORIES AND CYP2D6 STATUS

Figure 3: Distribution of AUC of Total (α+β)-HTBZ for Selected Doses Based on Weight Categories



AUC=area under the curve; CYP2D6=cytochrome P450 2D6; α/β-HTBZ=alpha/beta-dihydrotetrabenazine.

APPENDIX C. 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),

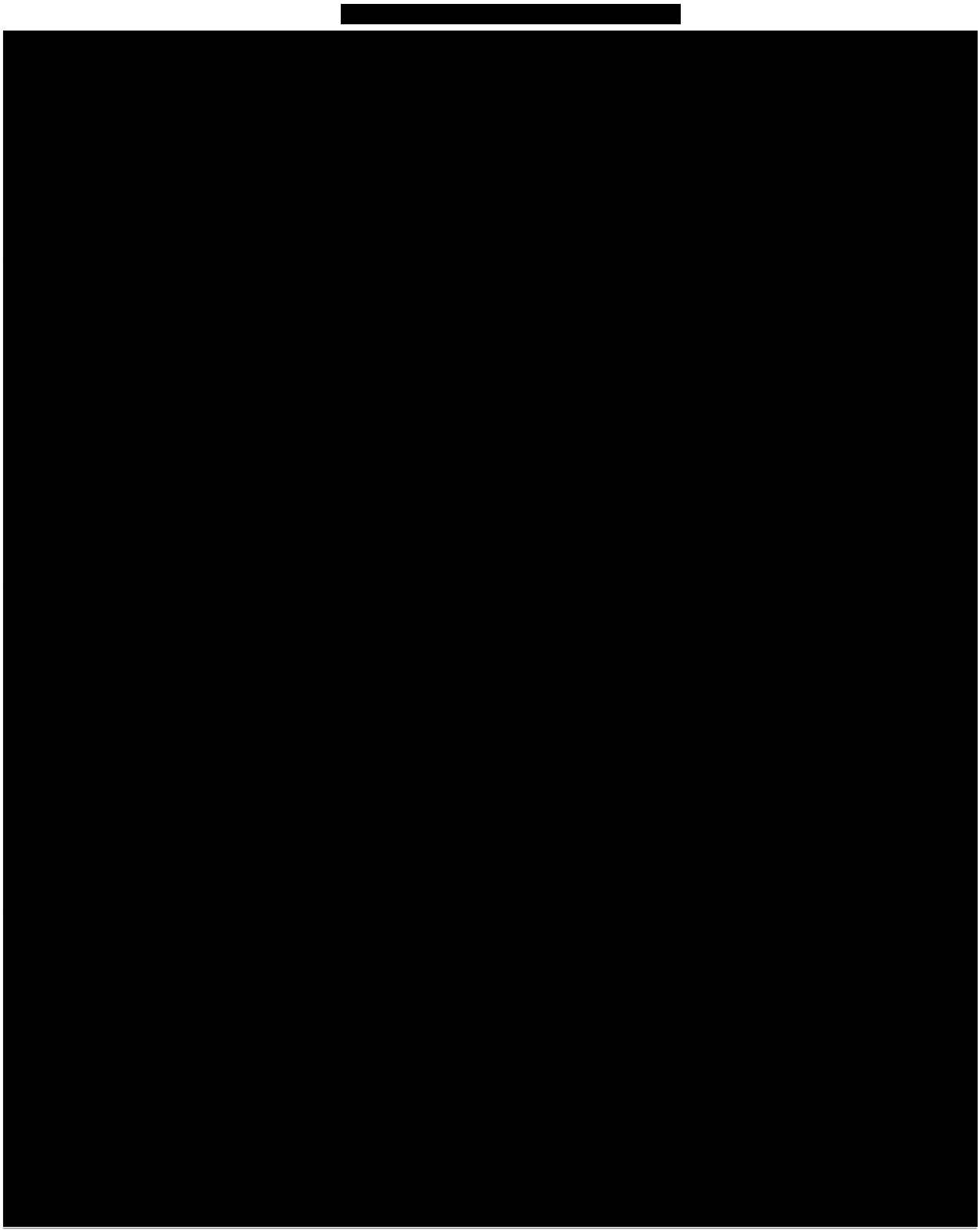
Alcohol Dependence/Abuse (Module L),

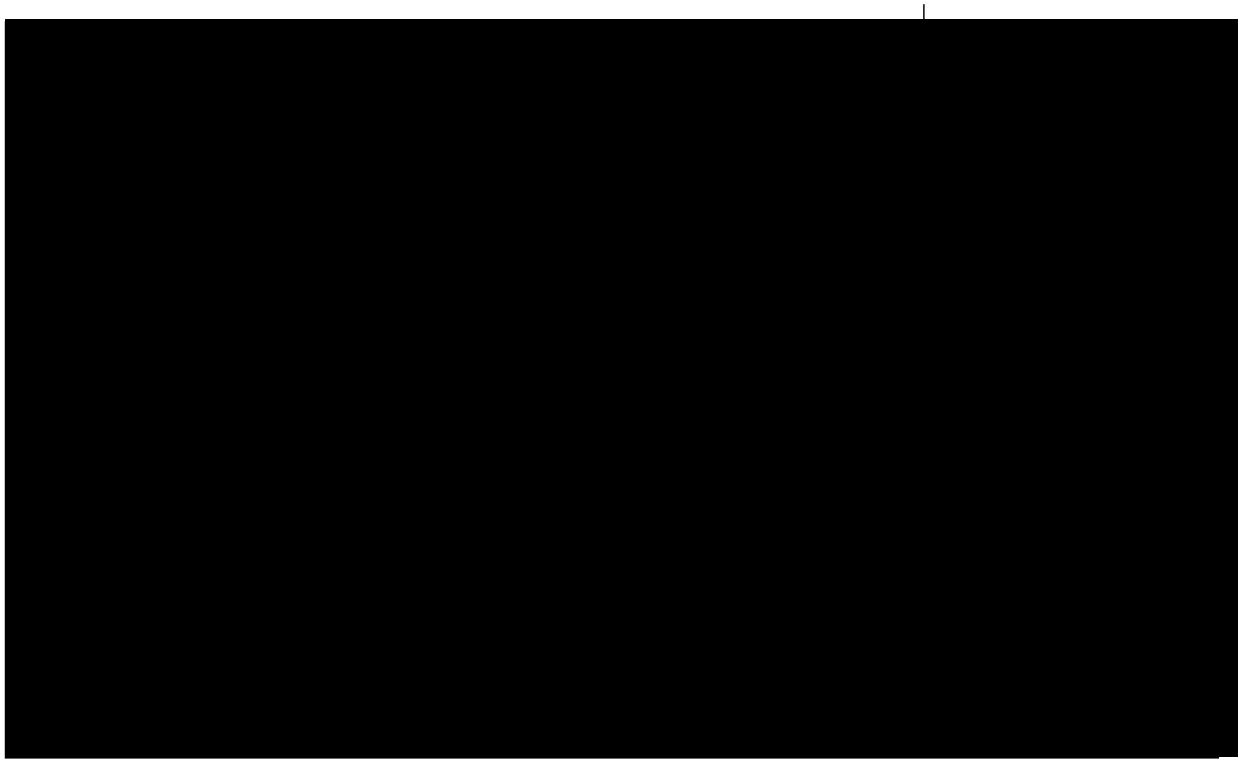
Substance Dependence/Abuse (Non-alcohol; Module M),

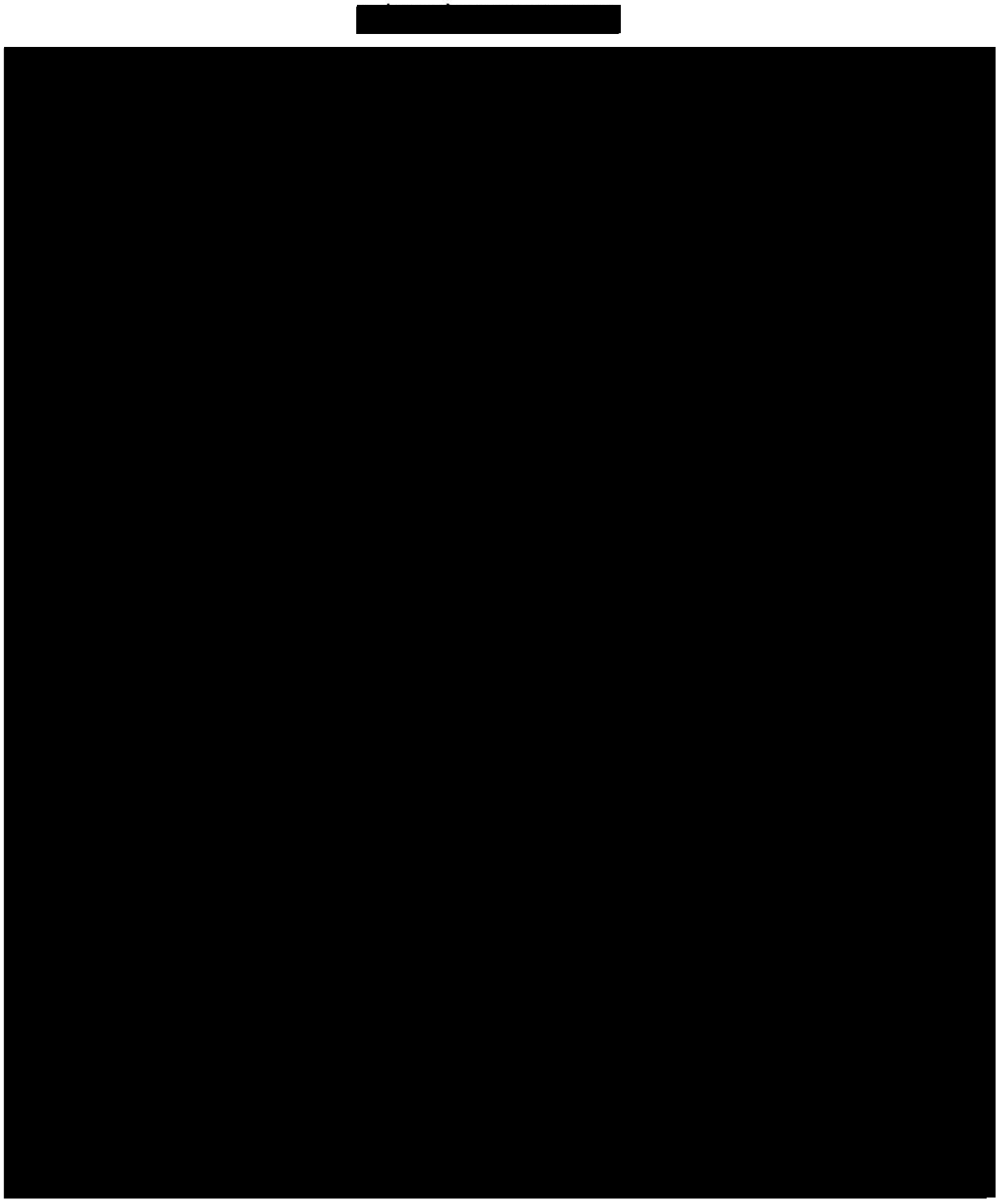
ADHD (Module O),

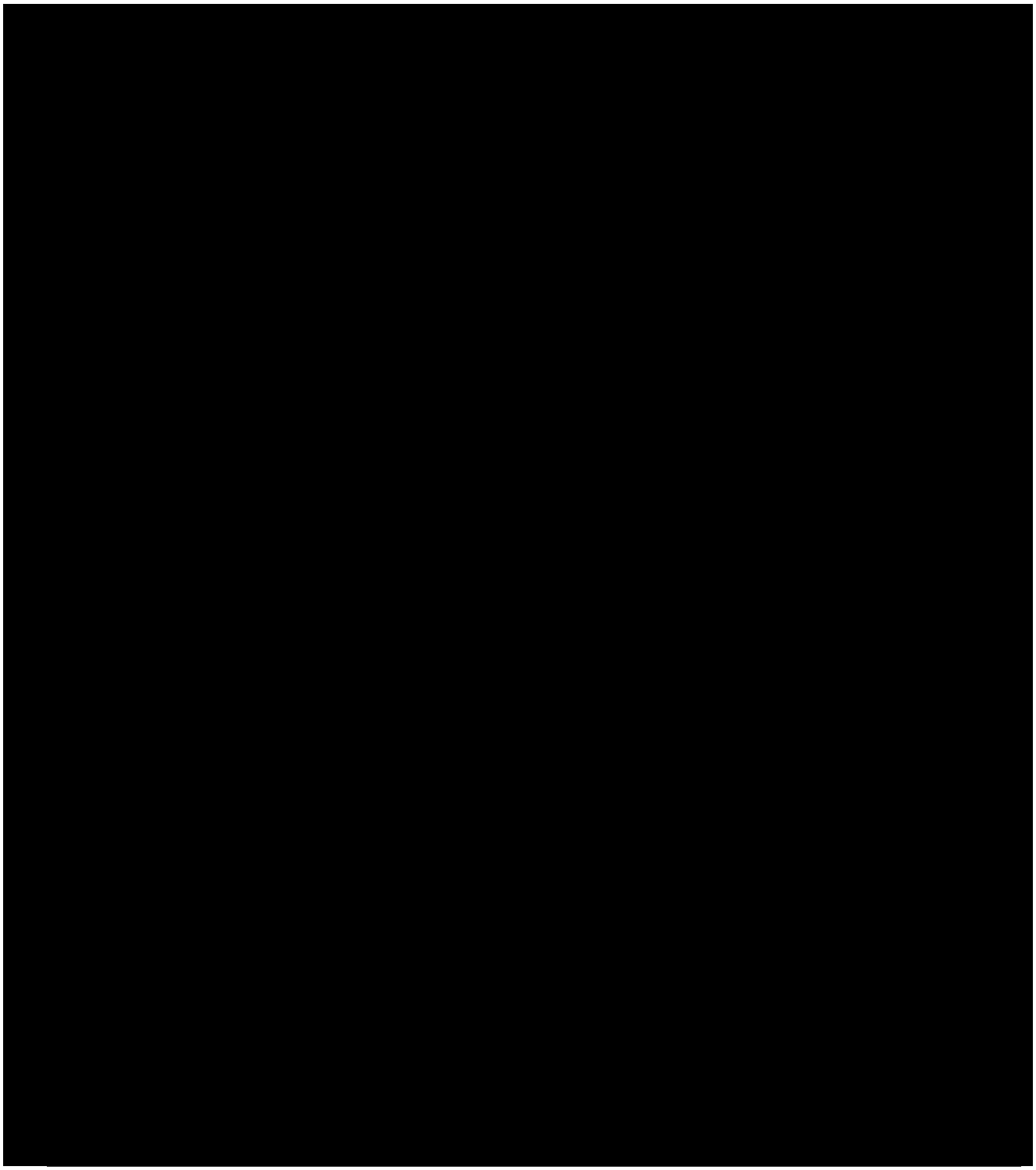
Conduct Disorder (Module P), and

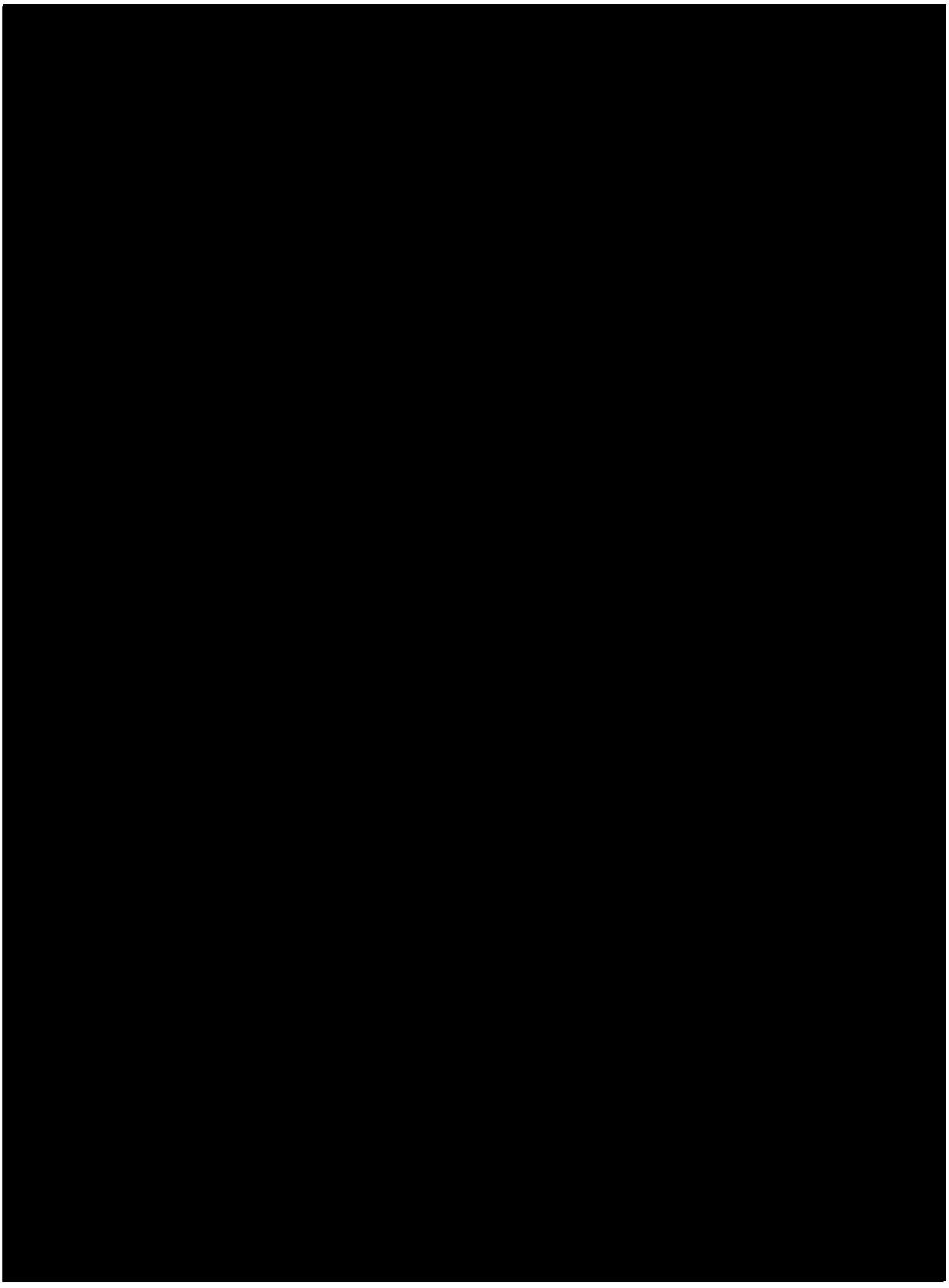
Psychotic Disorders and Mood Disorders with Psychotic Features (Module R).

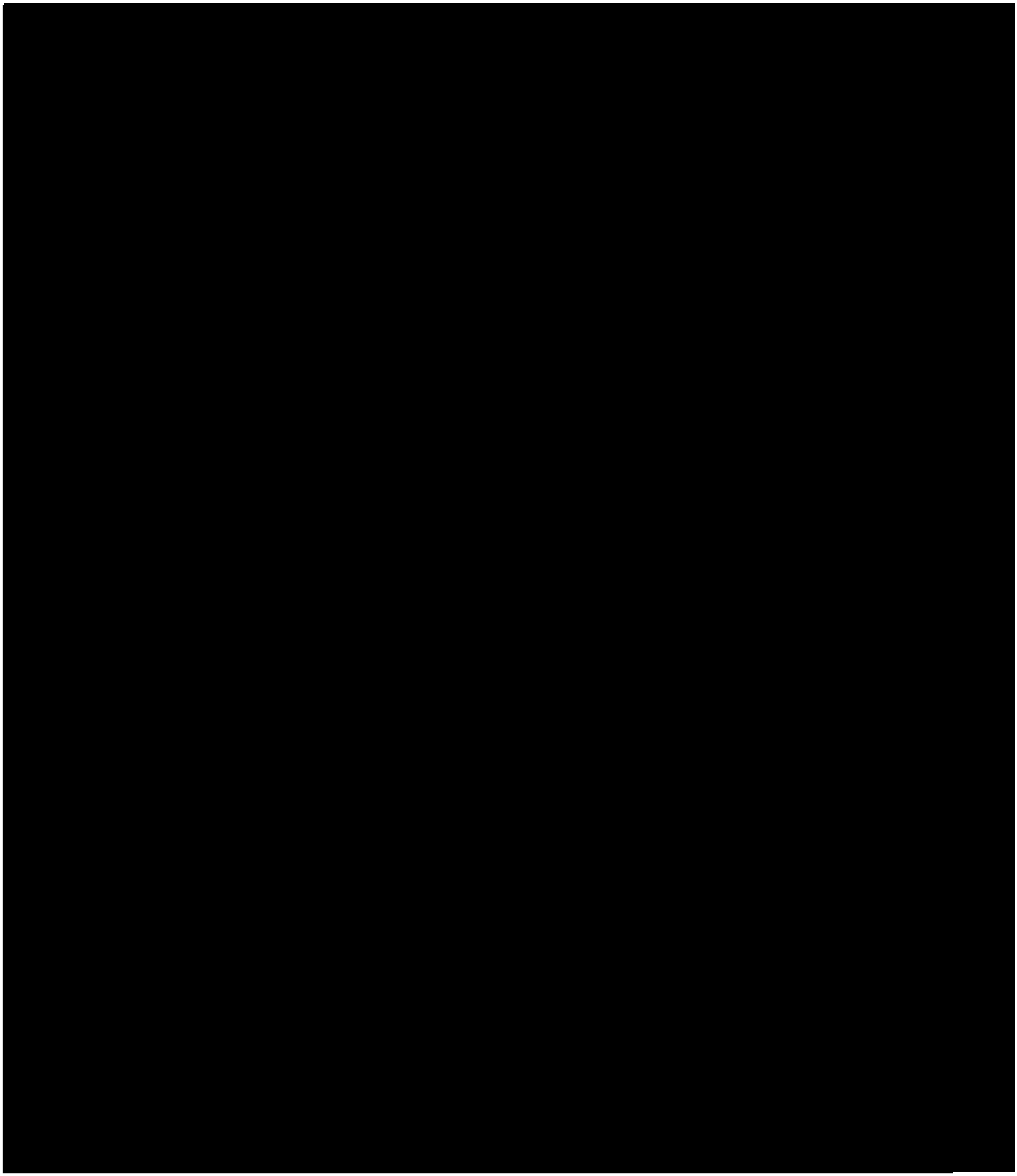


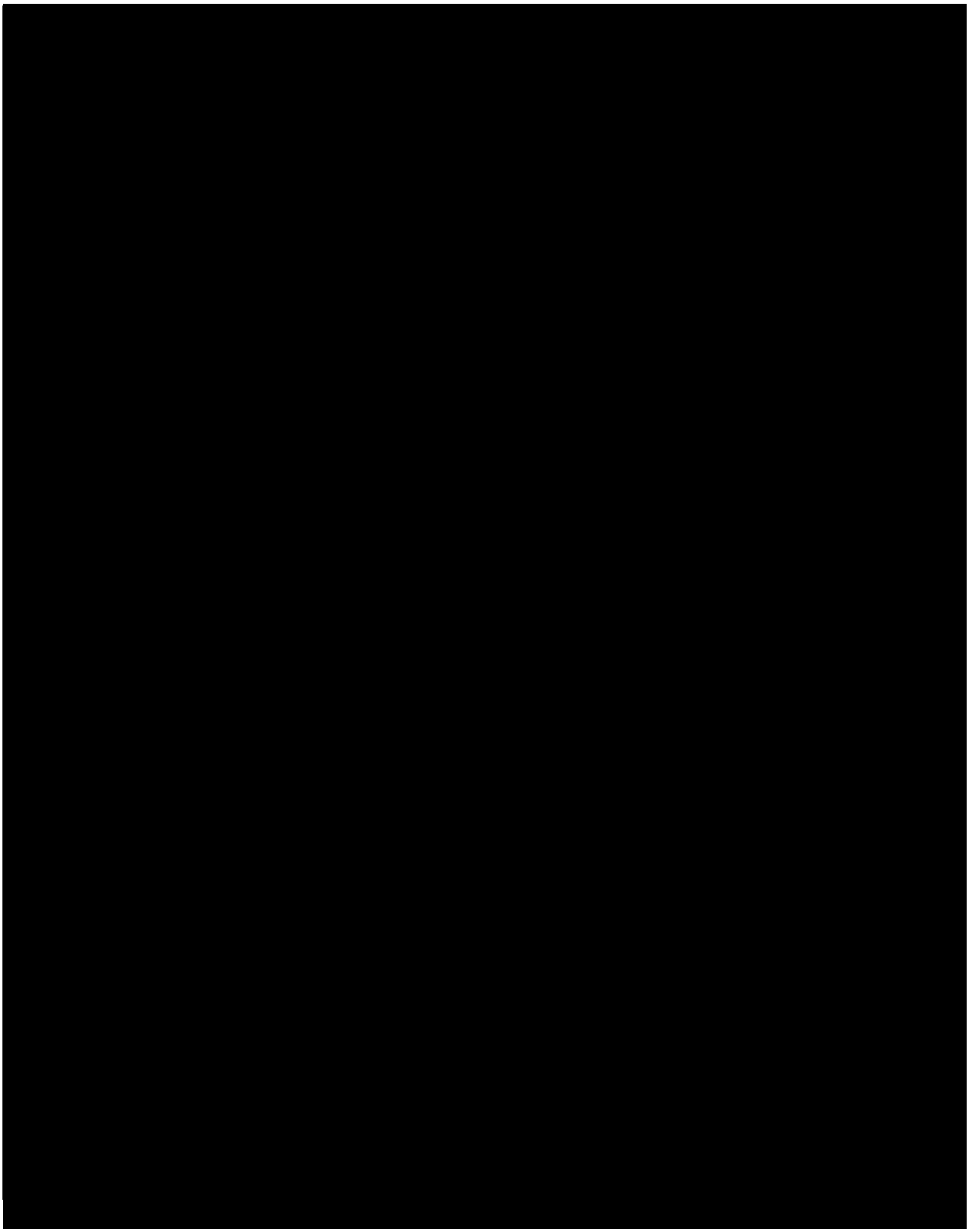


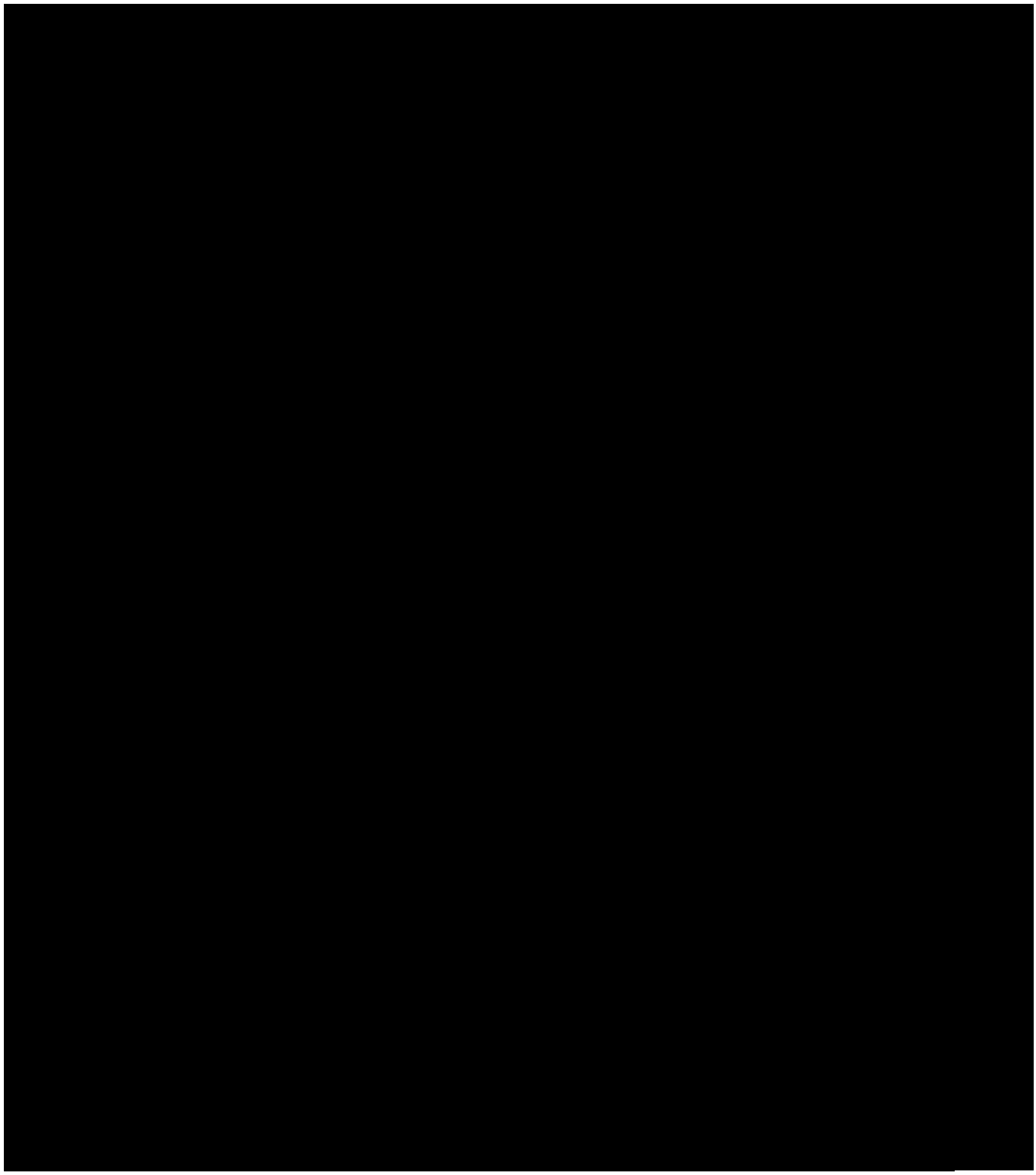


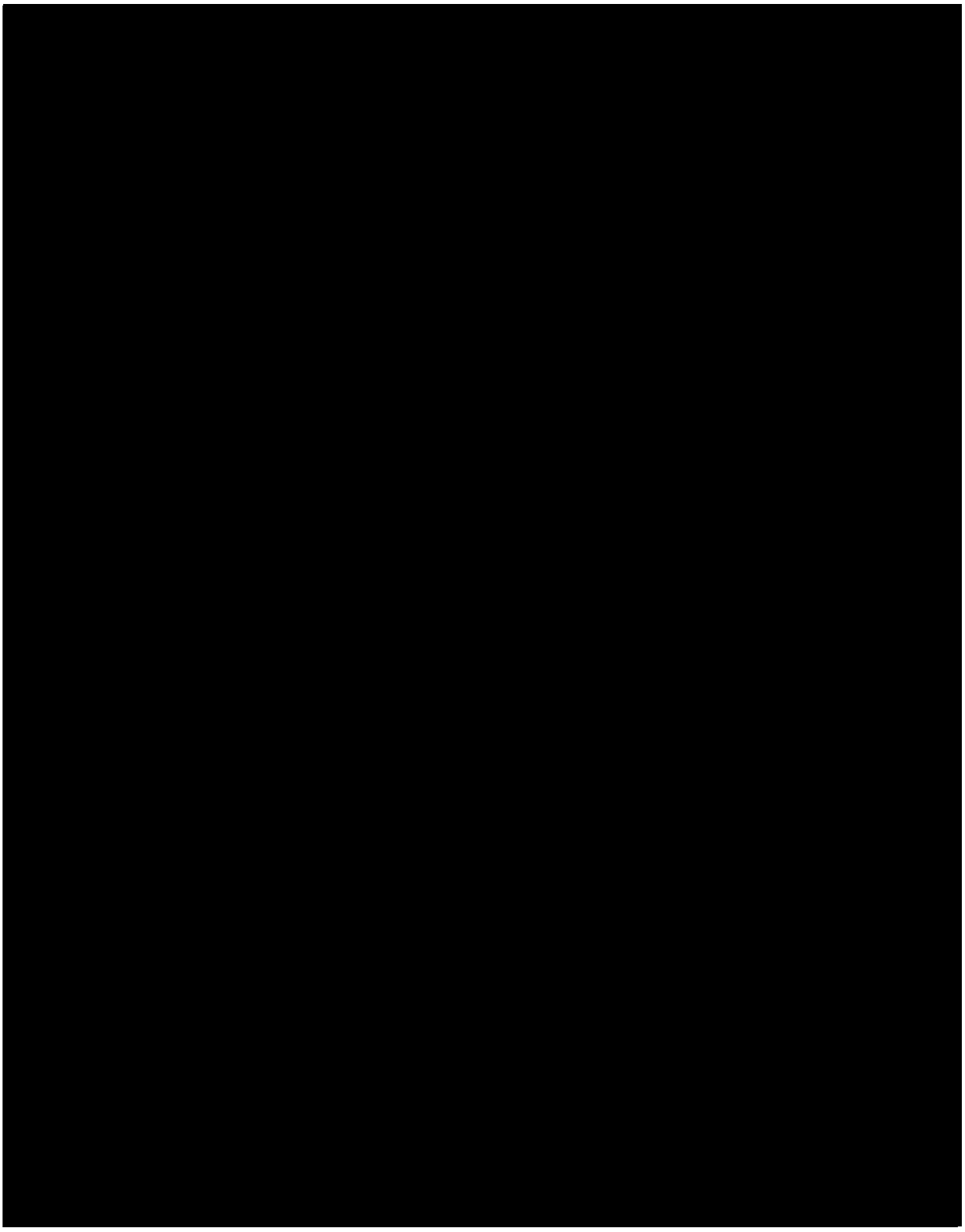


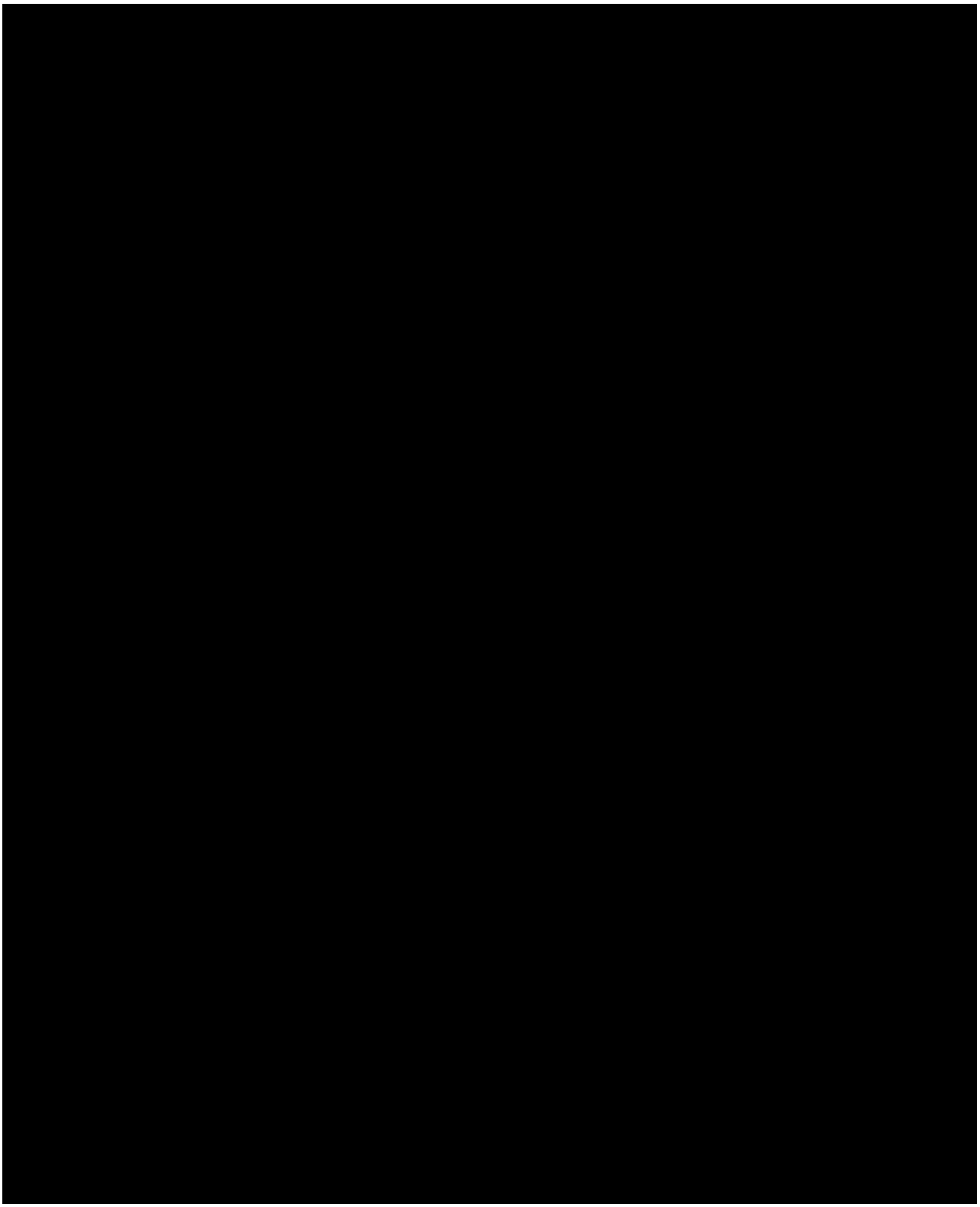


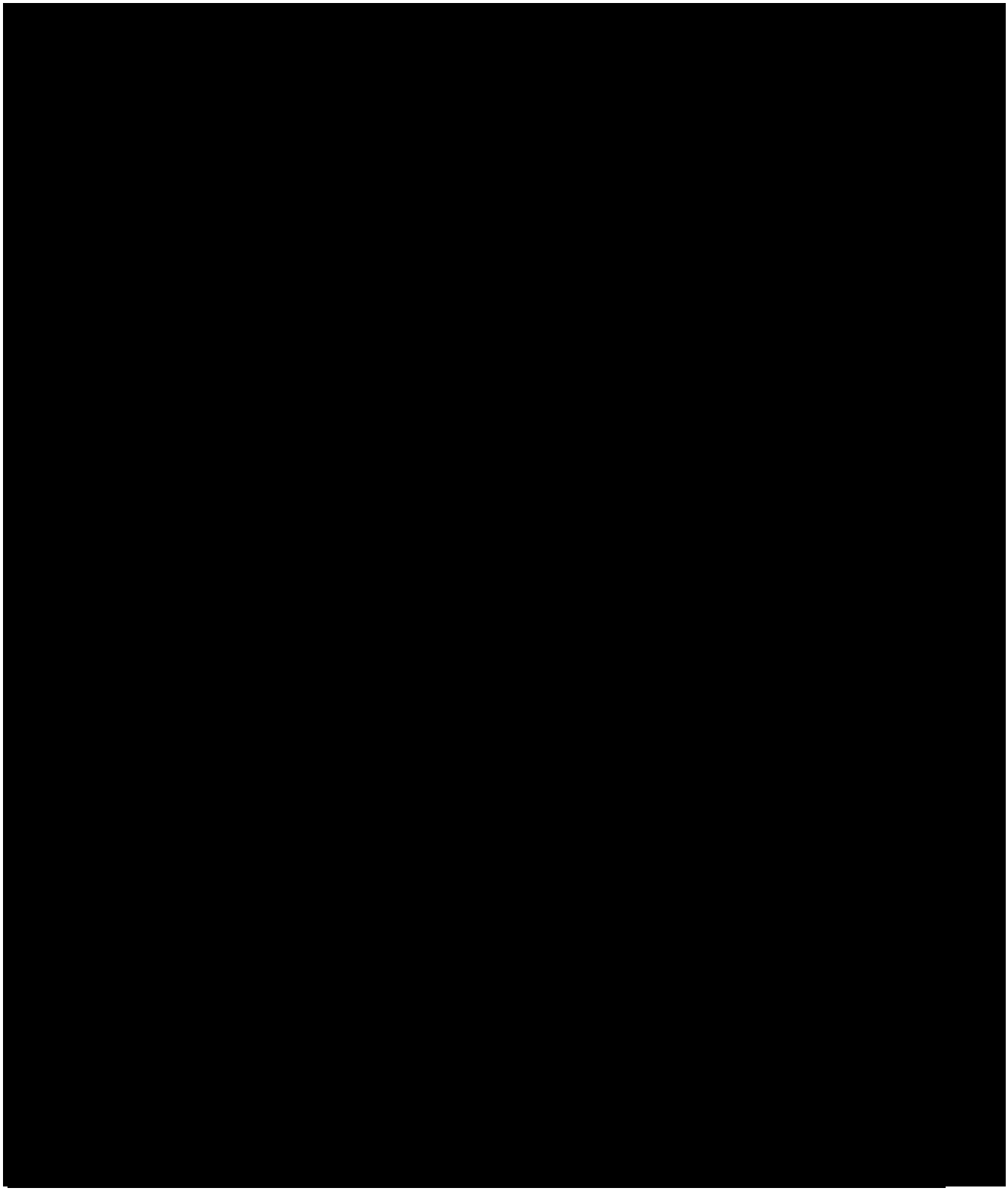


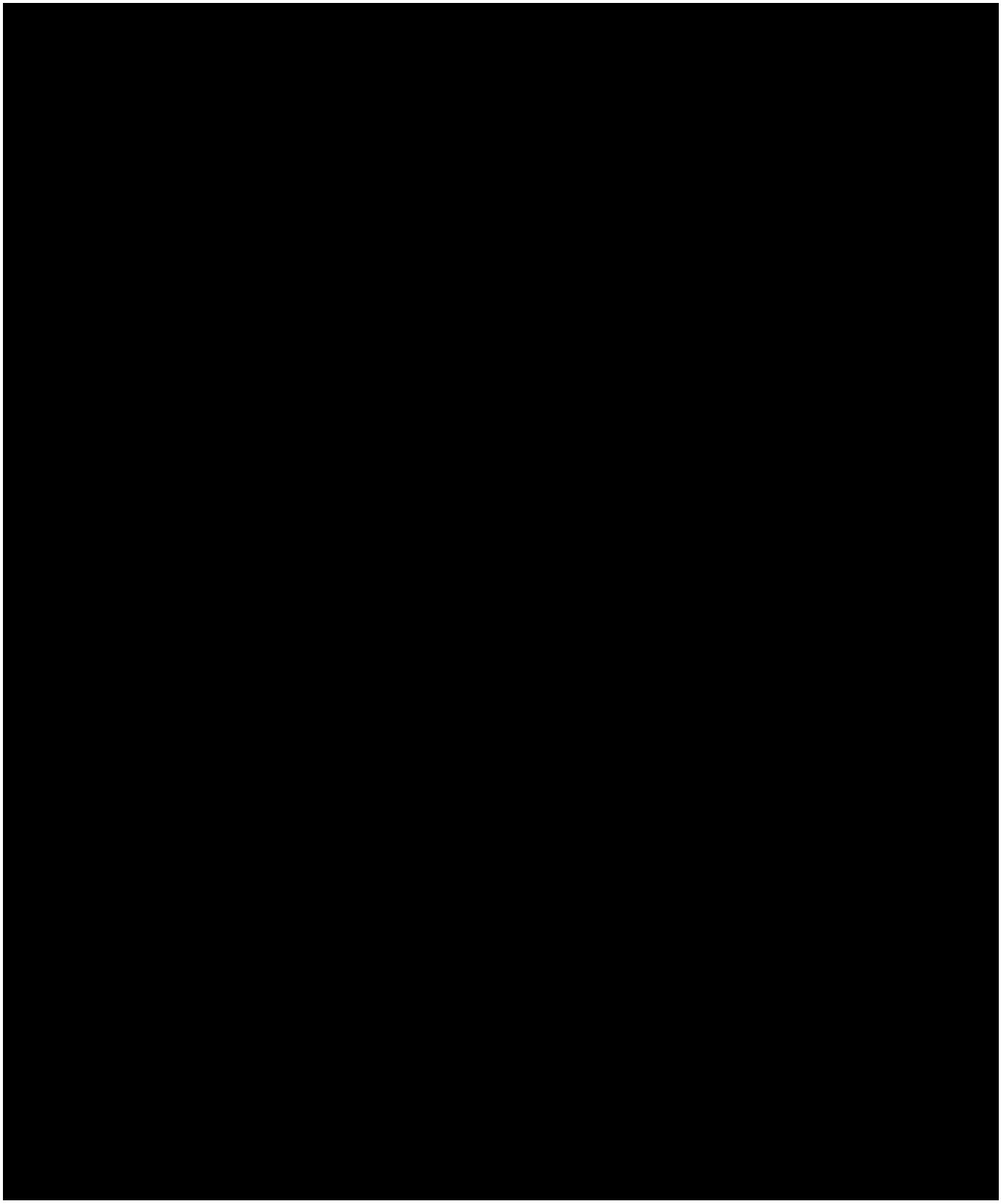












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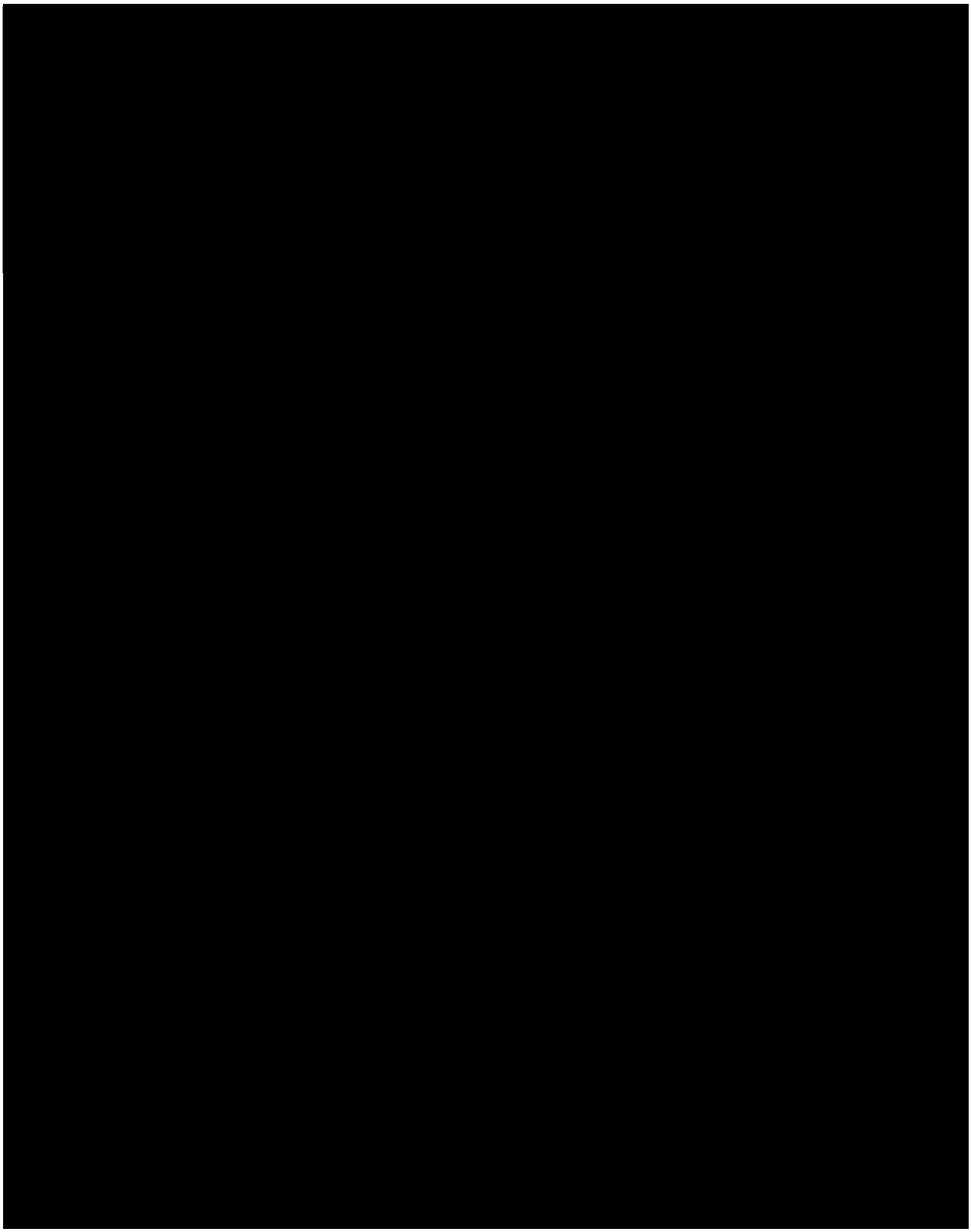
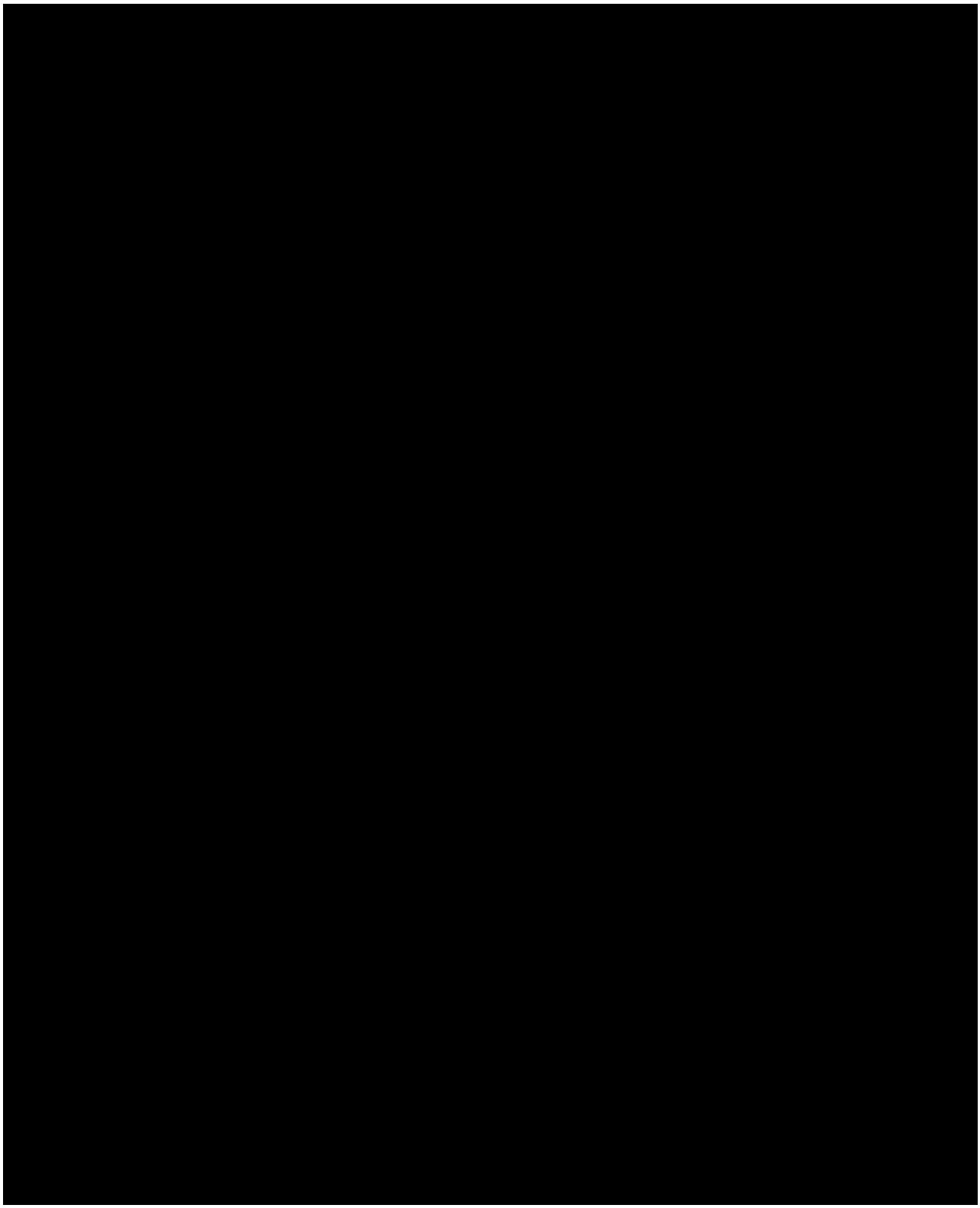
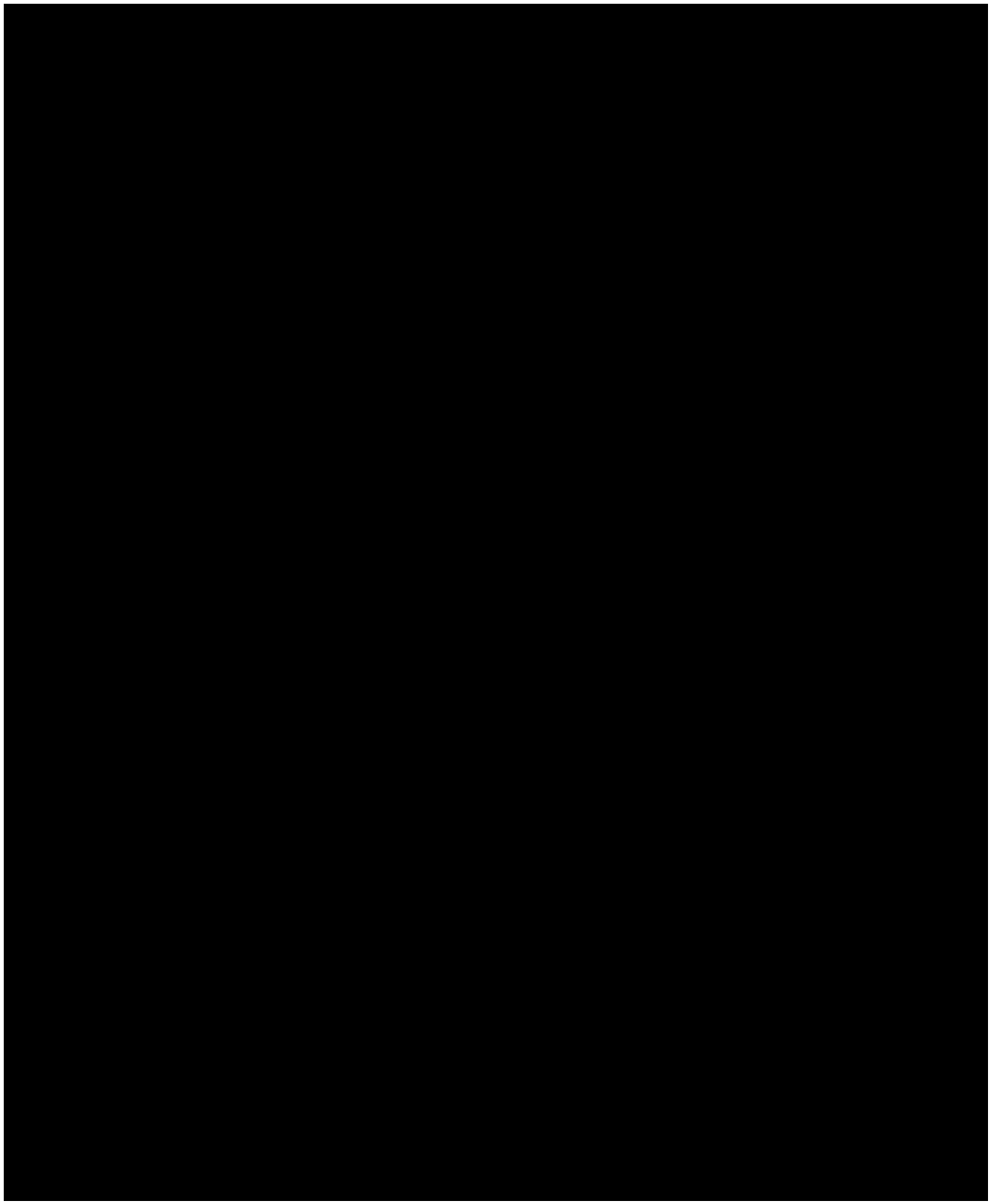


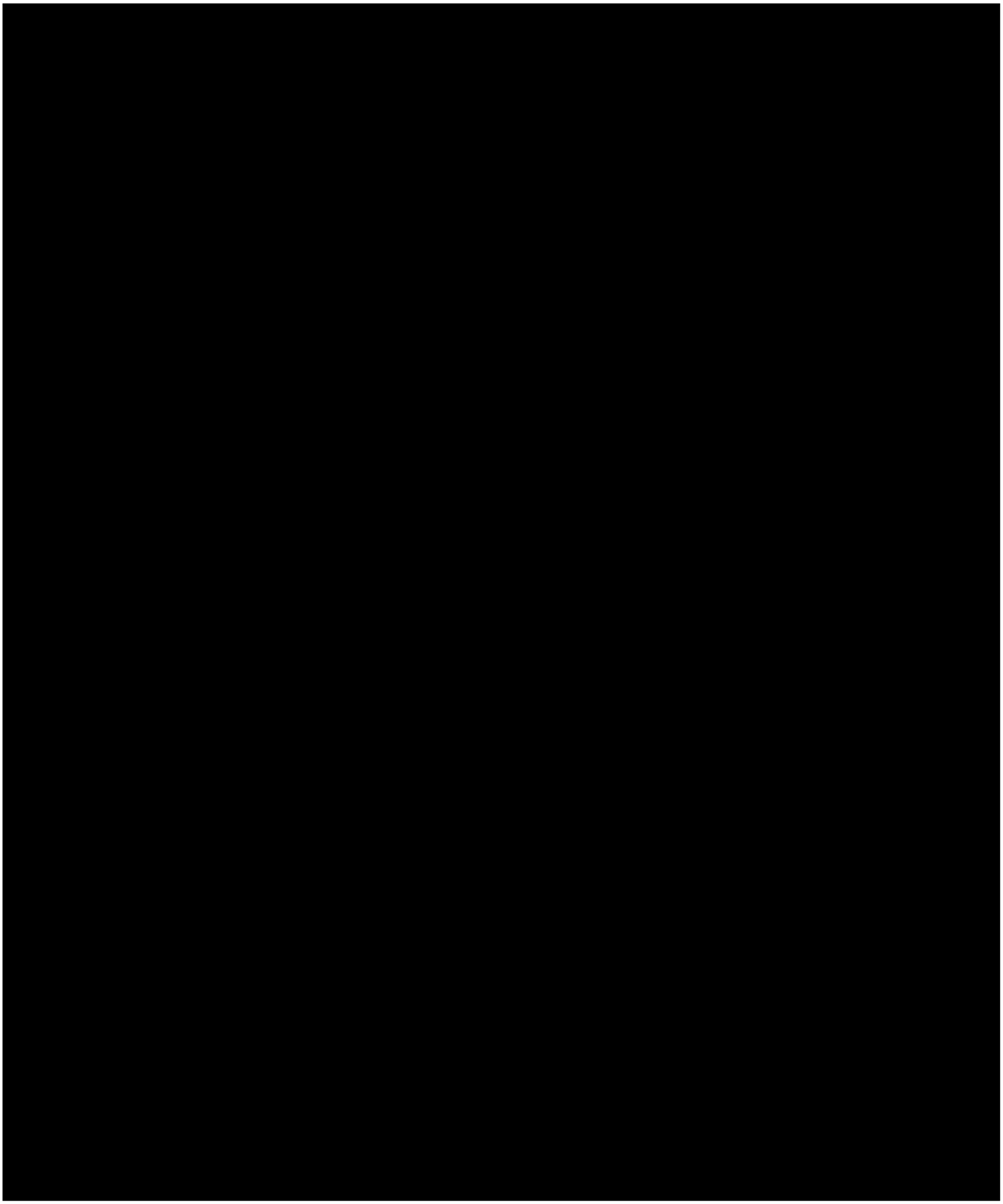


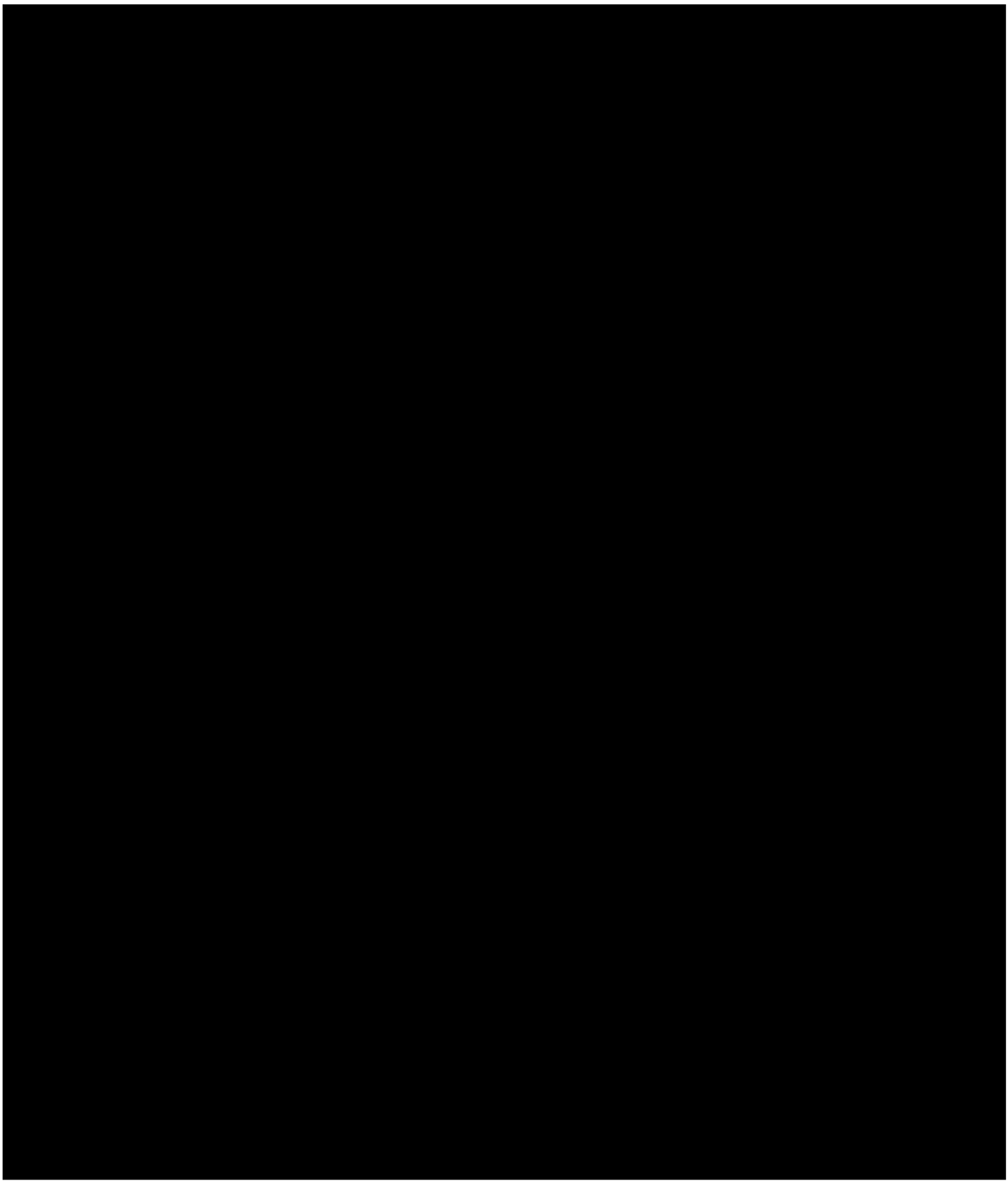


APPENDIX D. CHILDREN'S DEPRESSION INVENTORY, SECOND EDITION

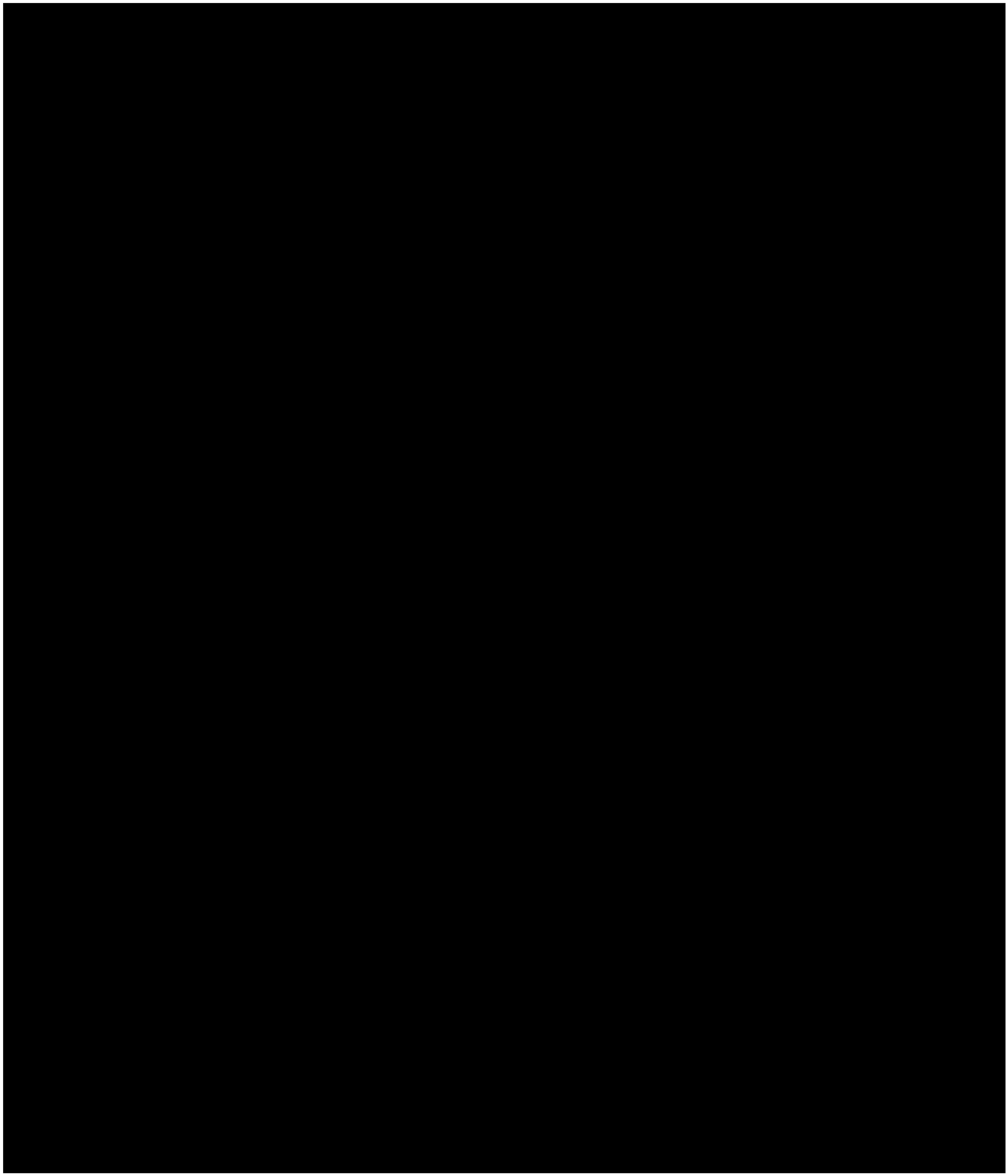
The sample provided in this appendix is for reference only.

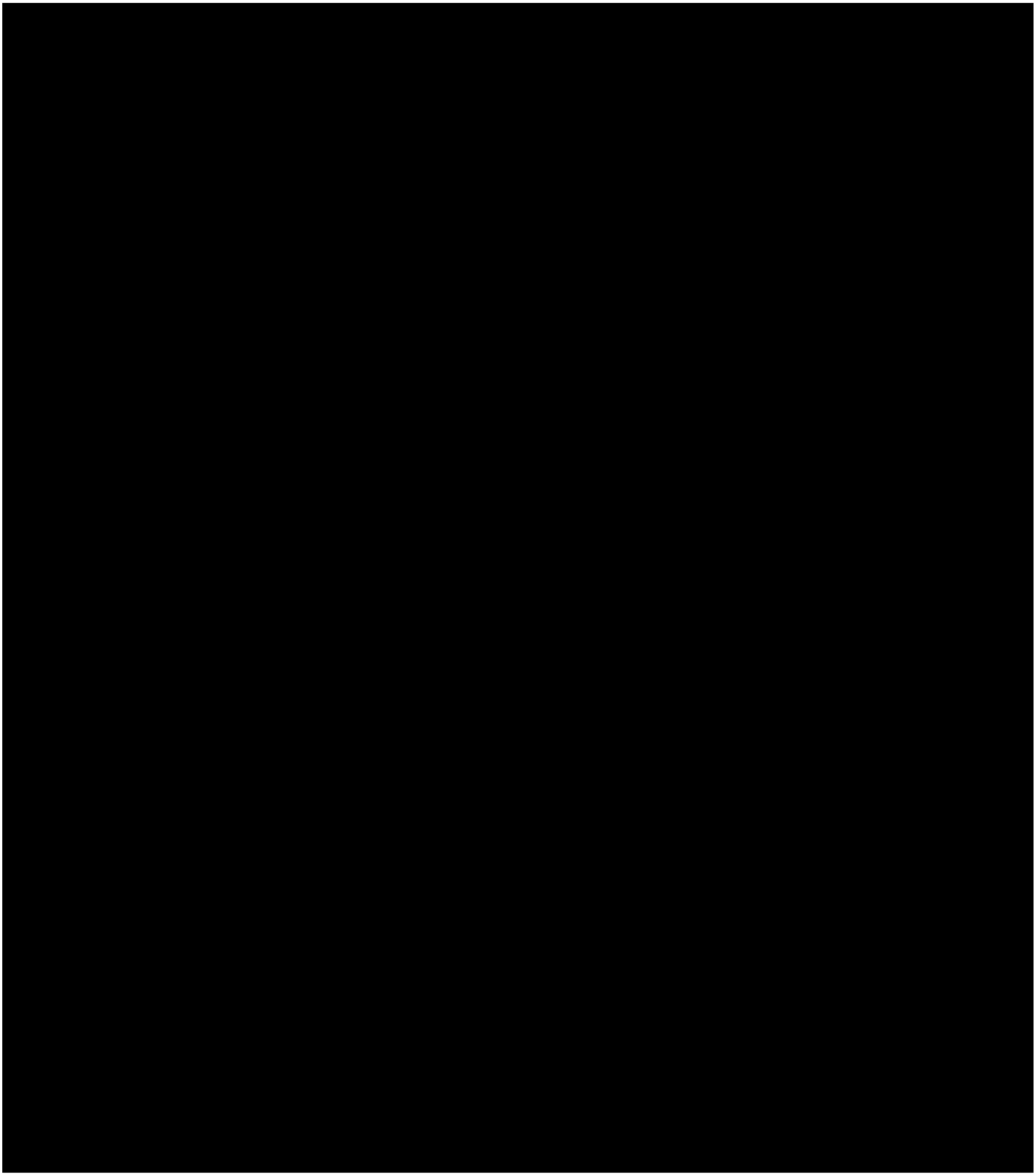
CDI-2 <u>Parent</u> Profile

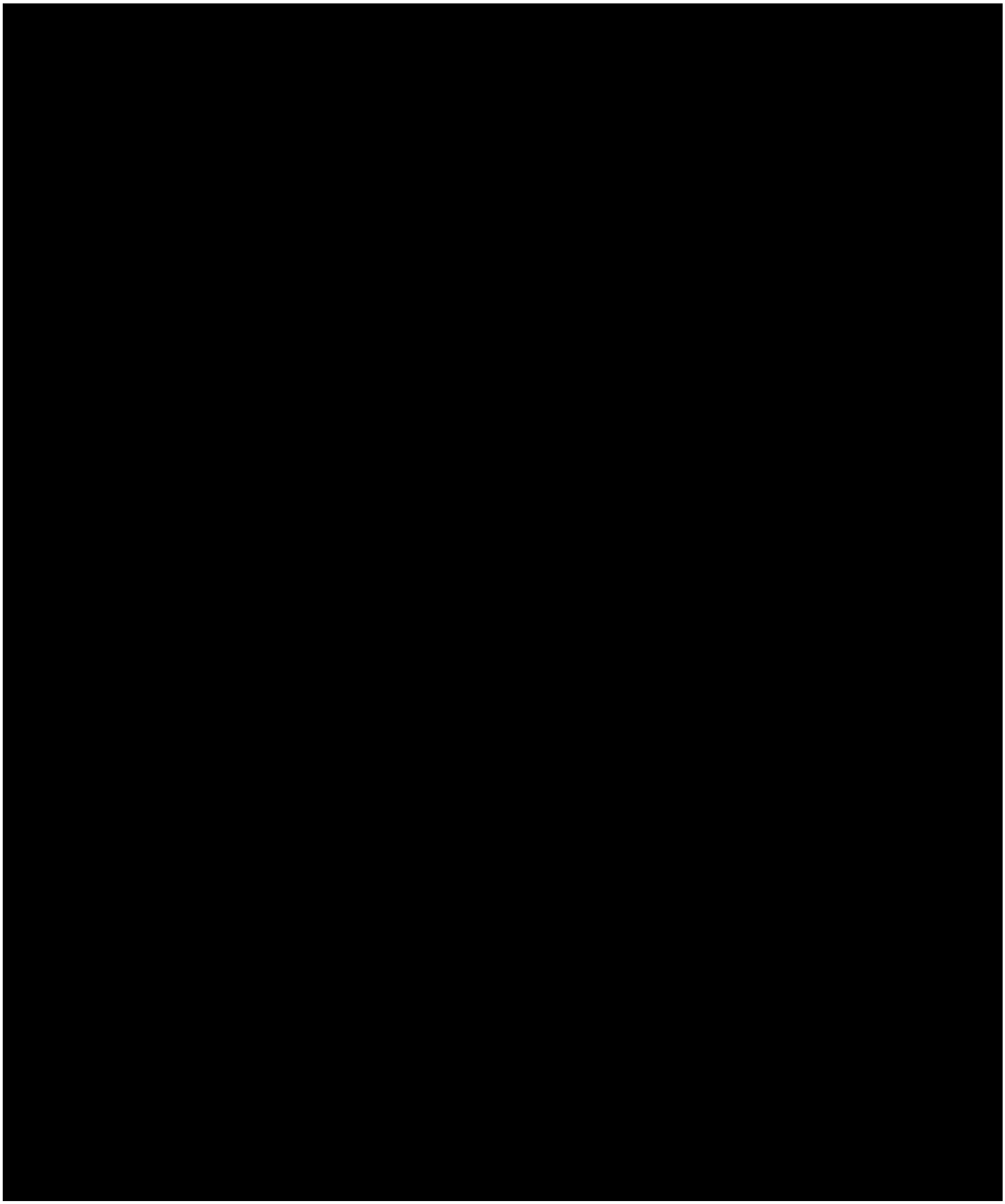


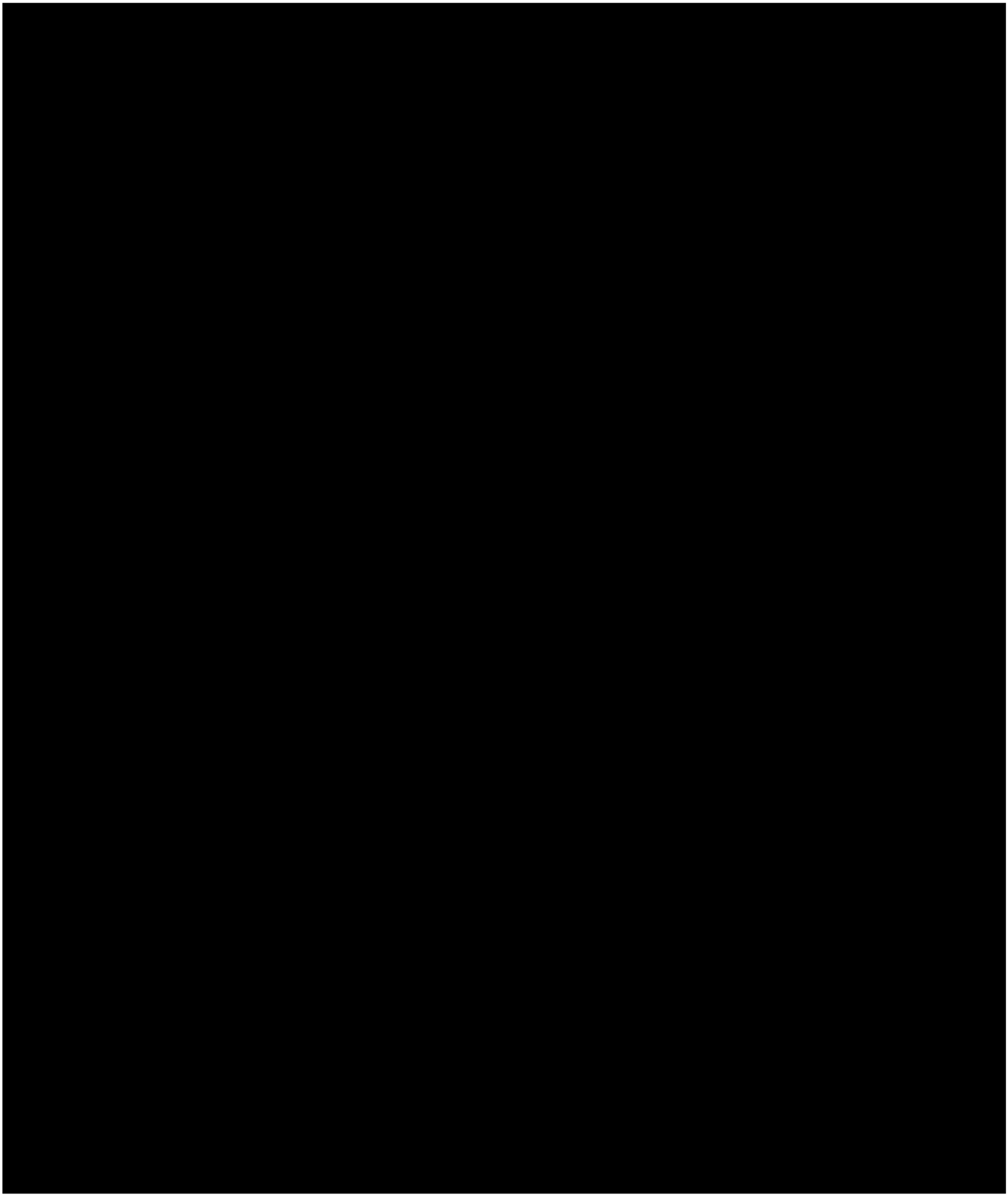


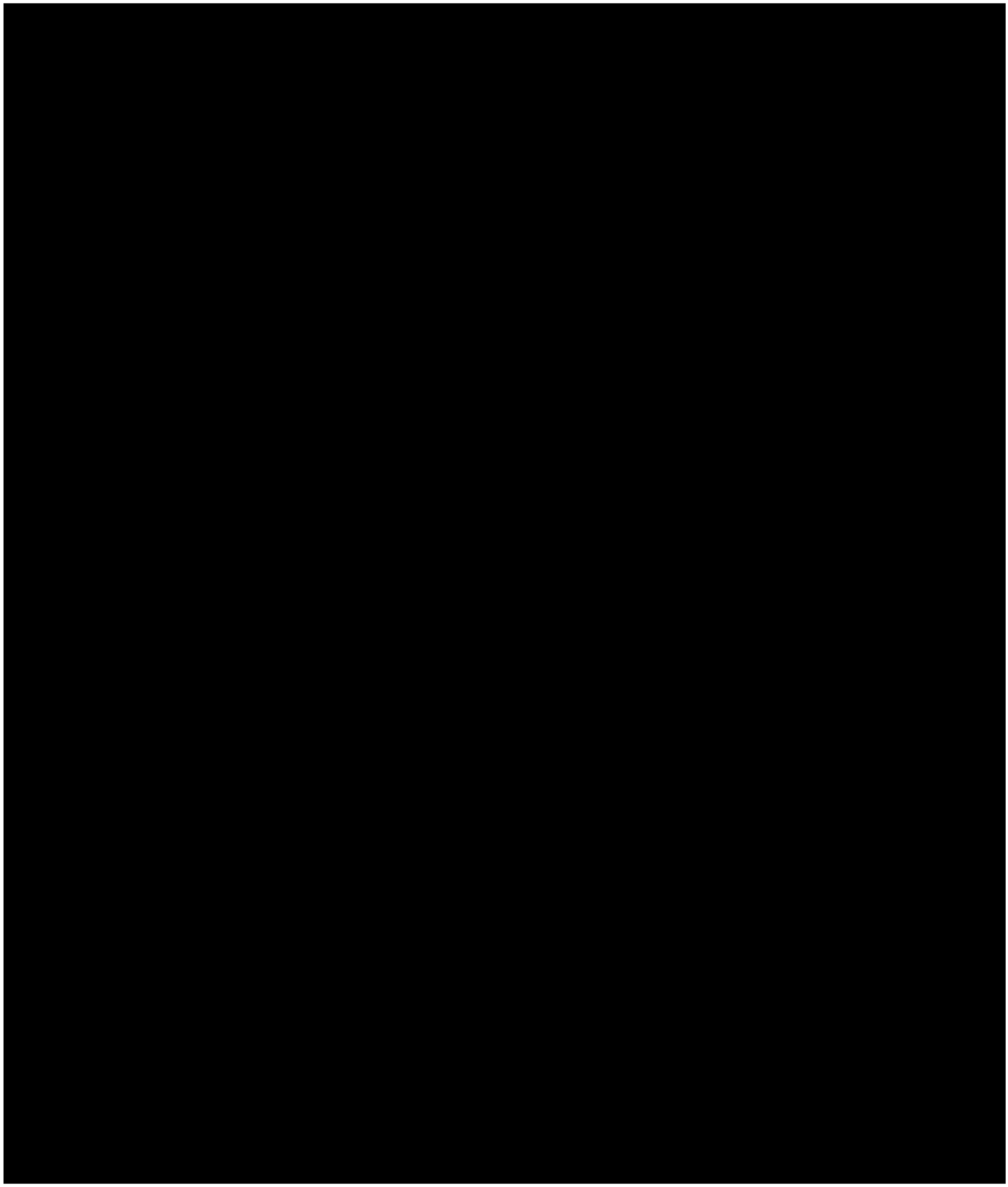
CDI-2 Self-Report











APPENDIX E. [redacted]

The sample provided in this appendix is for reference only.

Children's Baseline/Screening

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Disclaimer:

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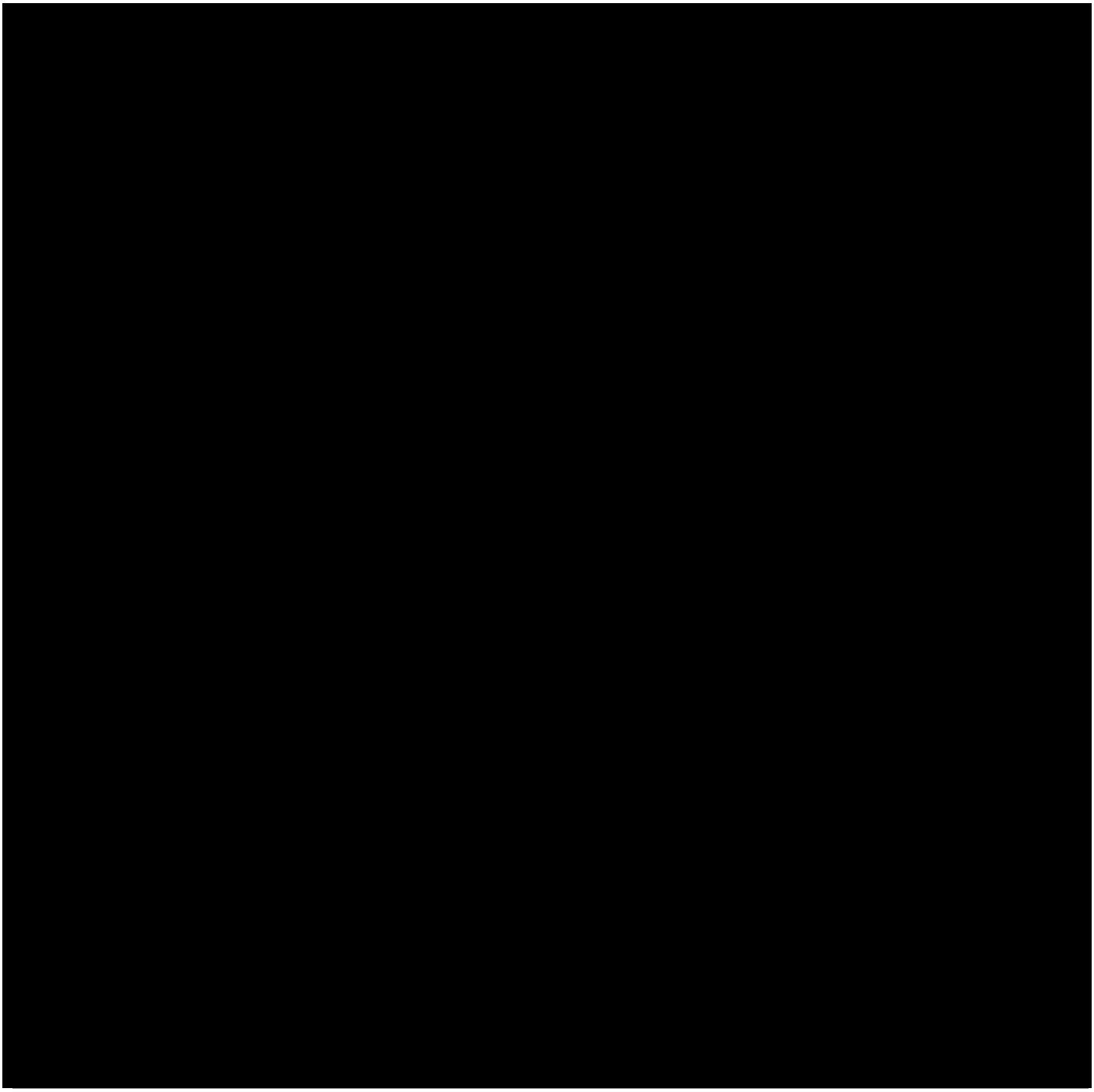

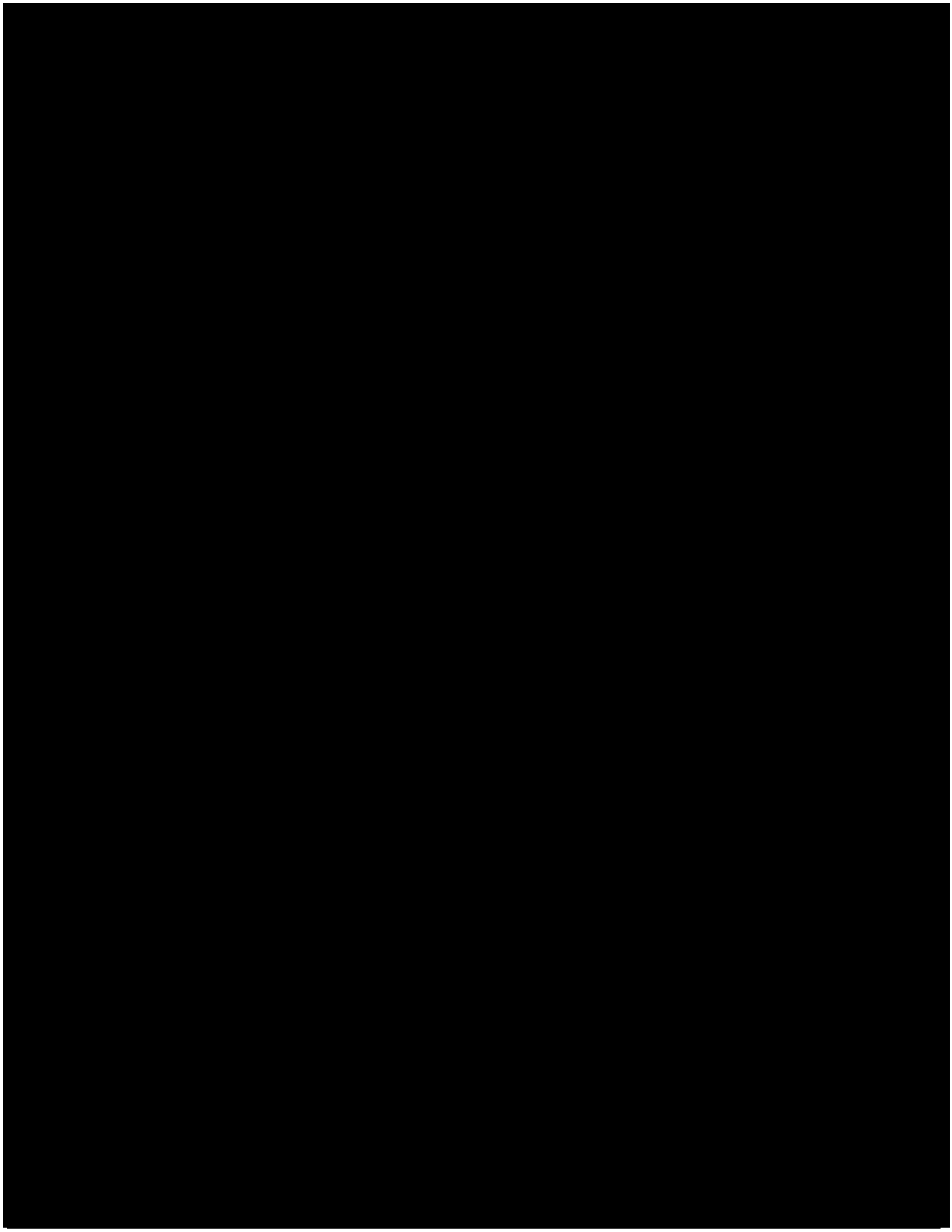

Children's Since Last Visit

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Version 6/23/10

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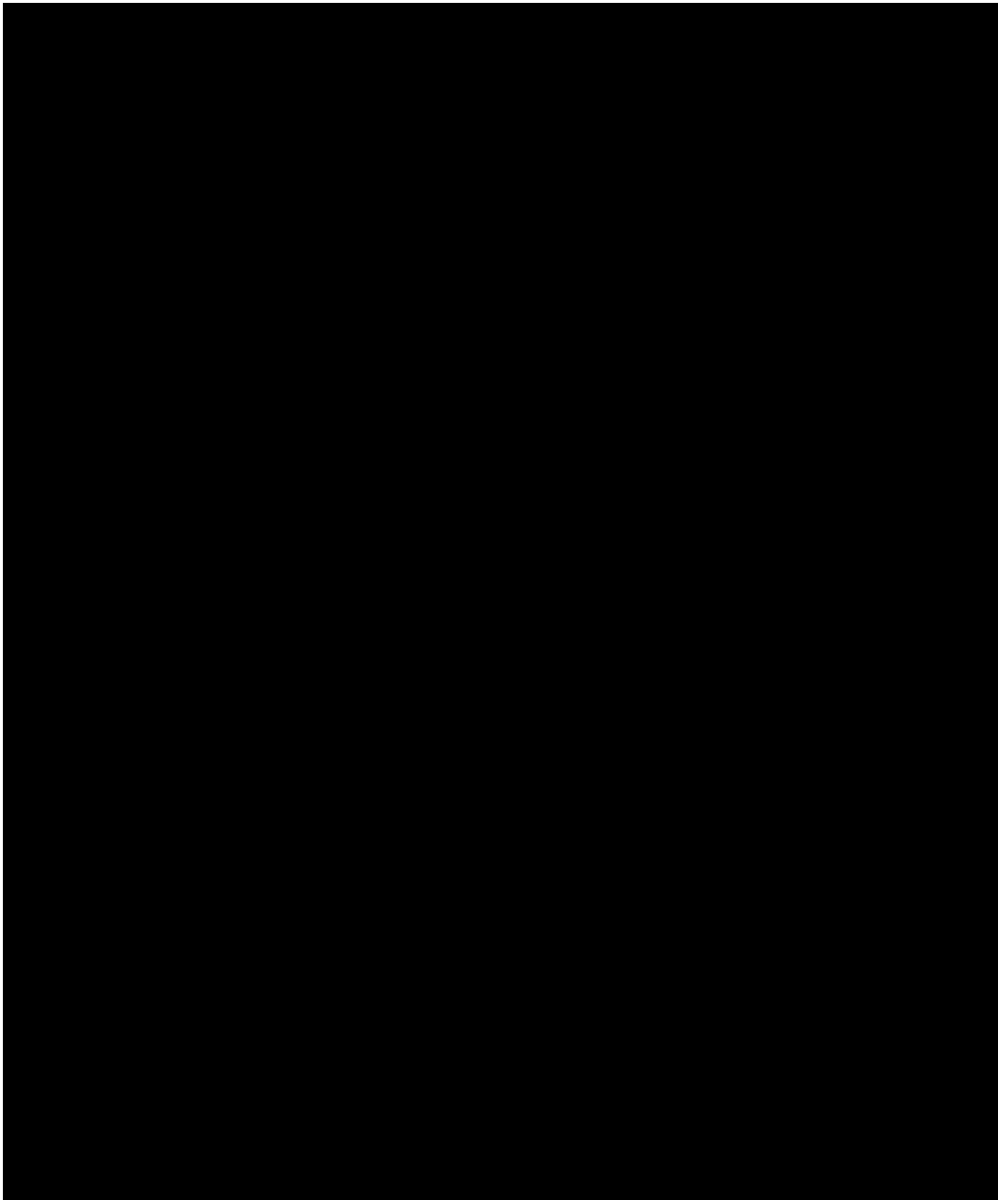

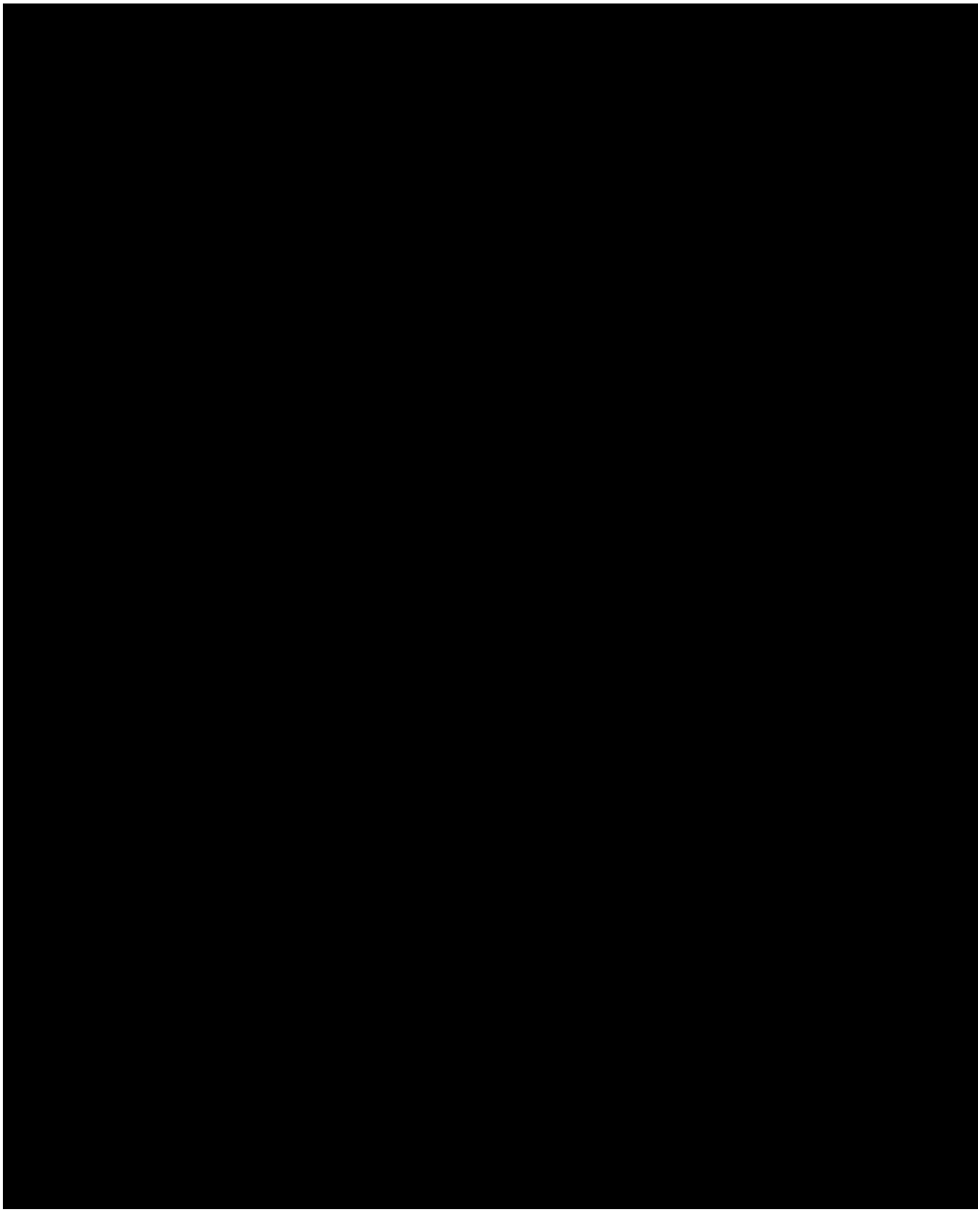

APPENDIX F. [redacted]

The sample provided in this appendix is for reference only.

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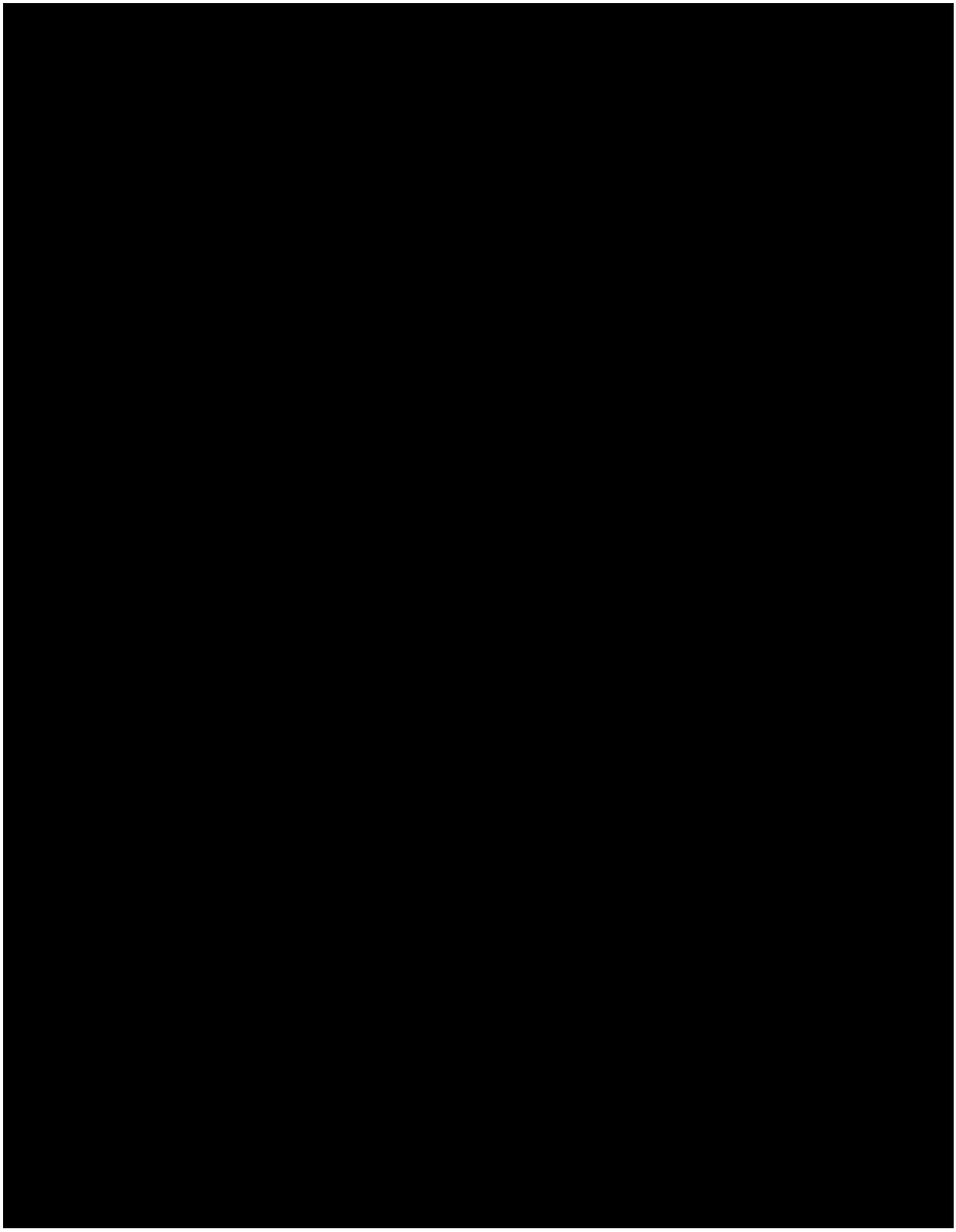

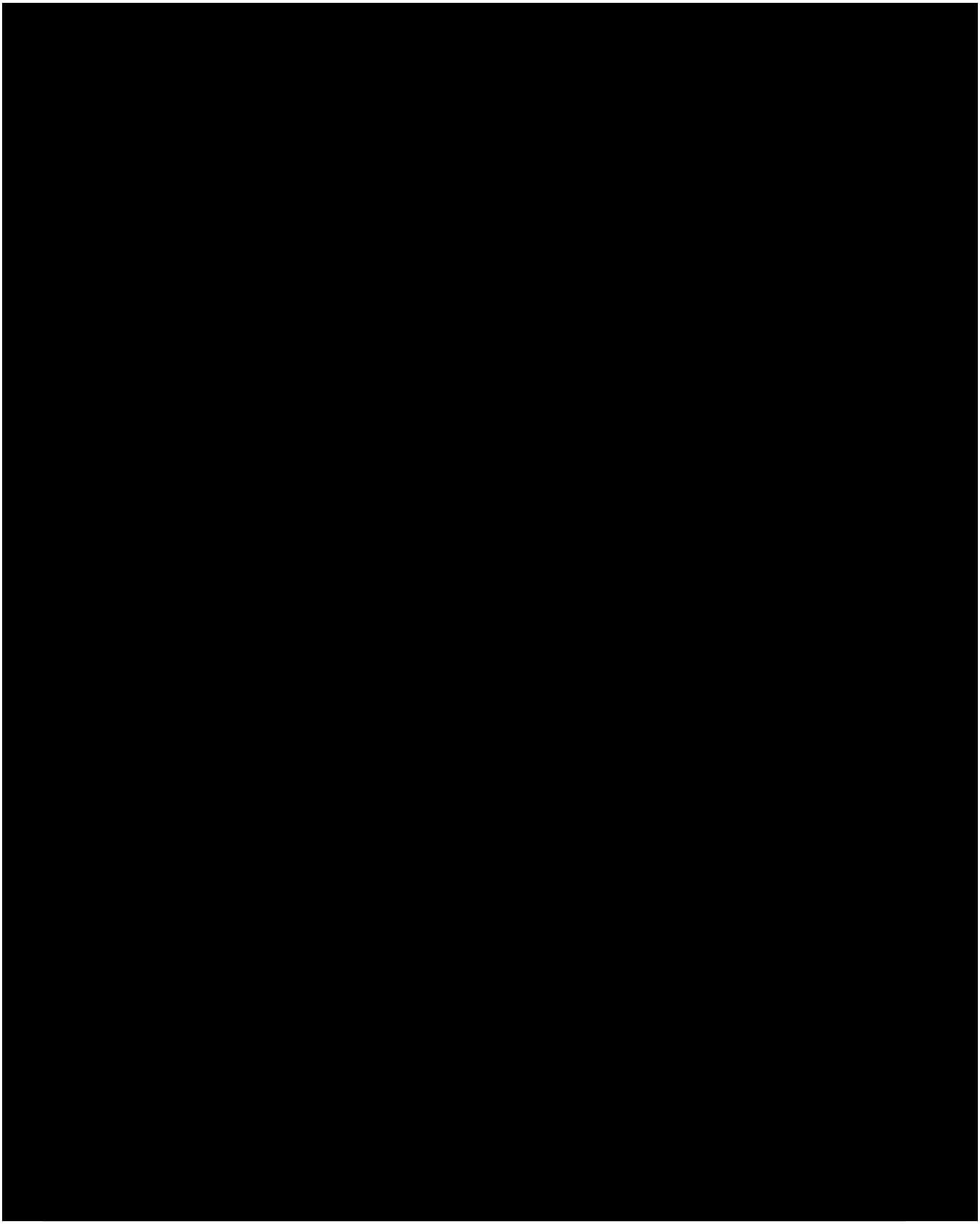

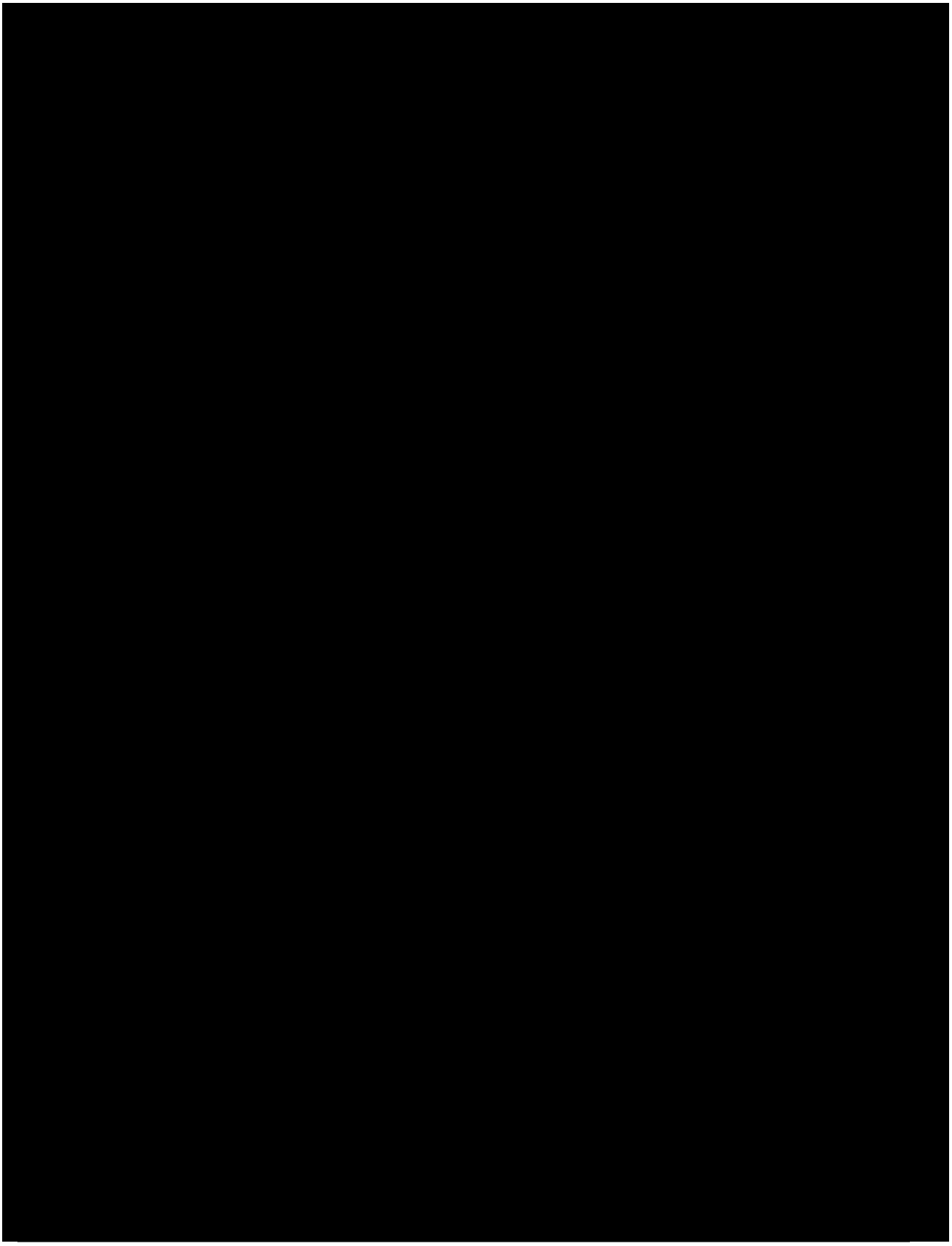

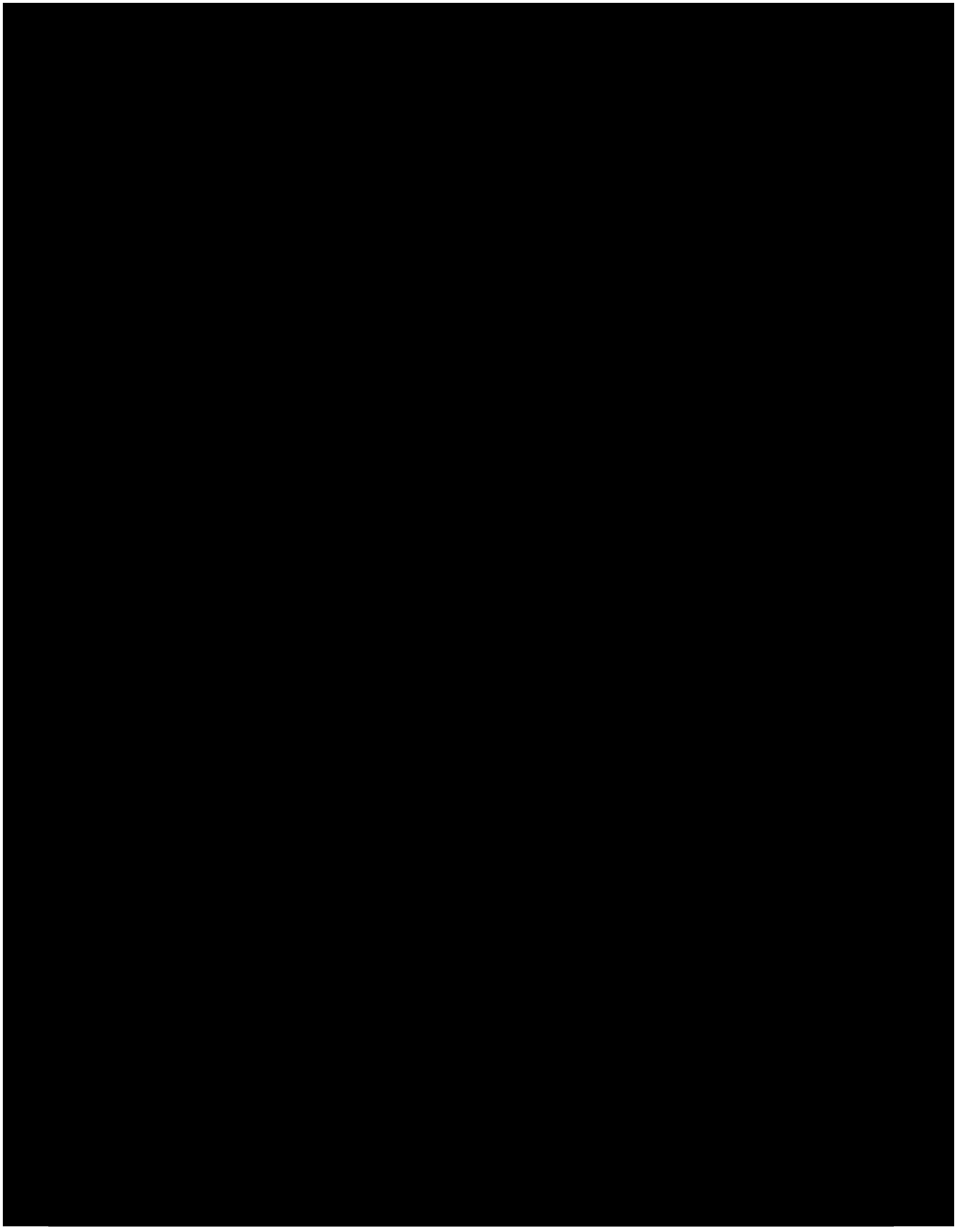

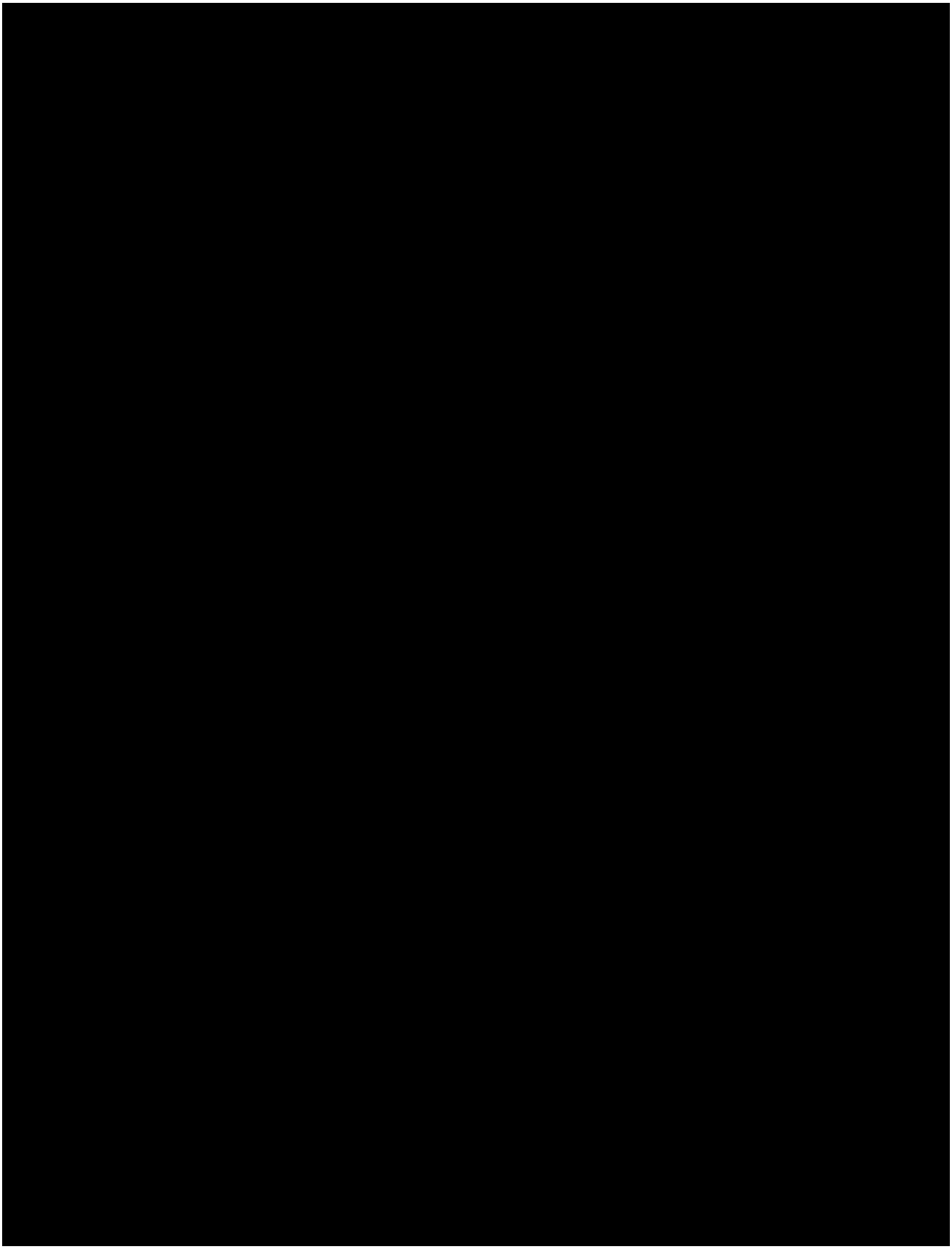

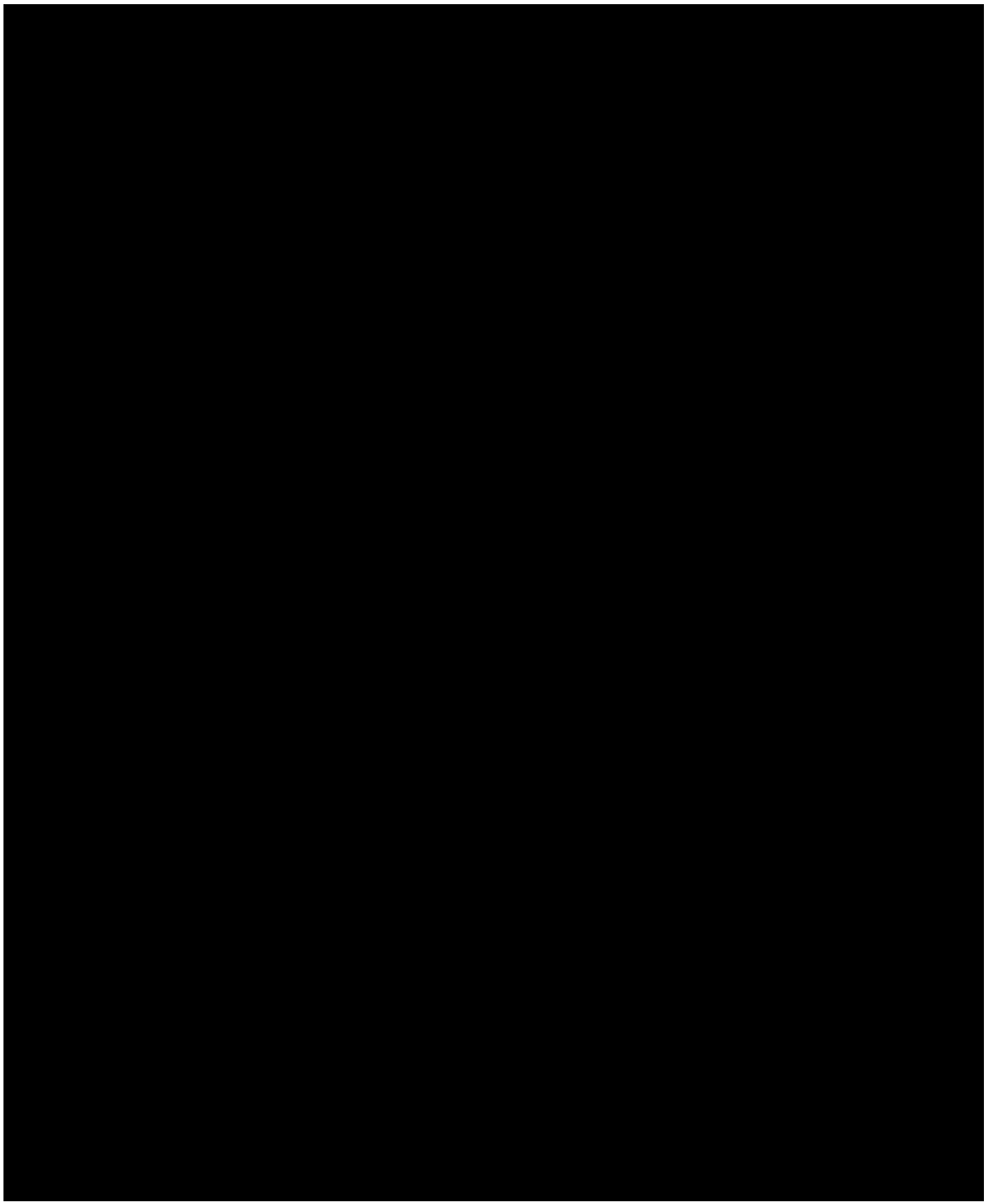

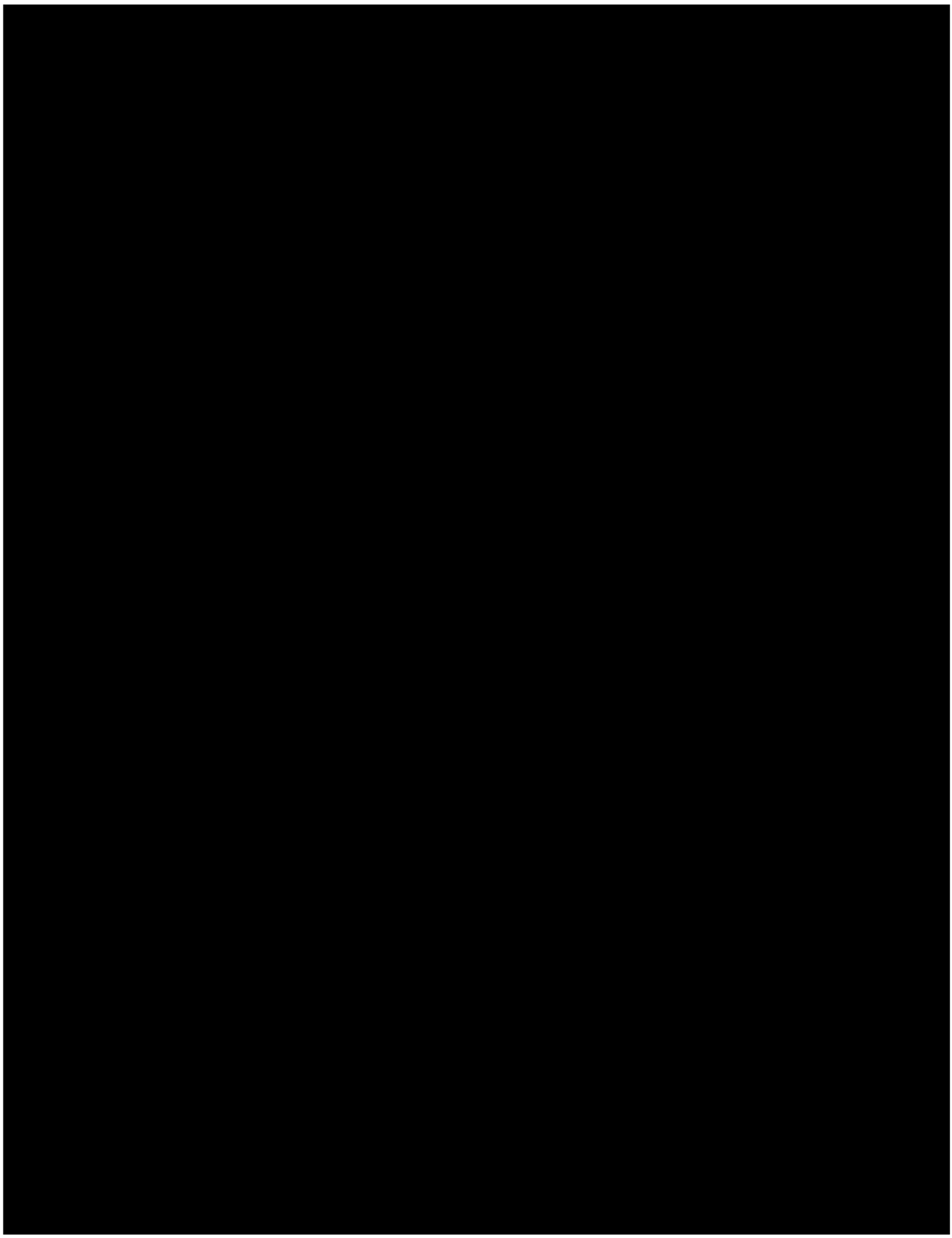

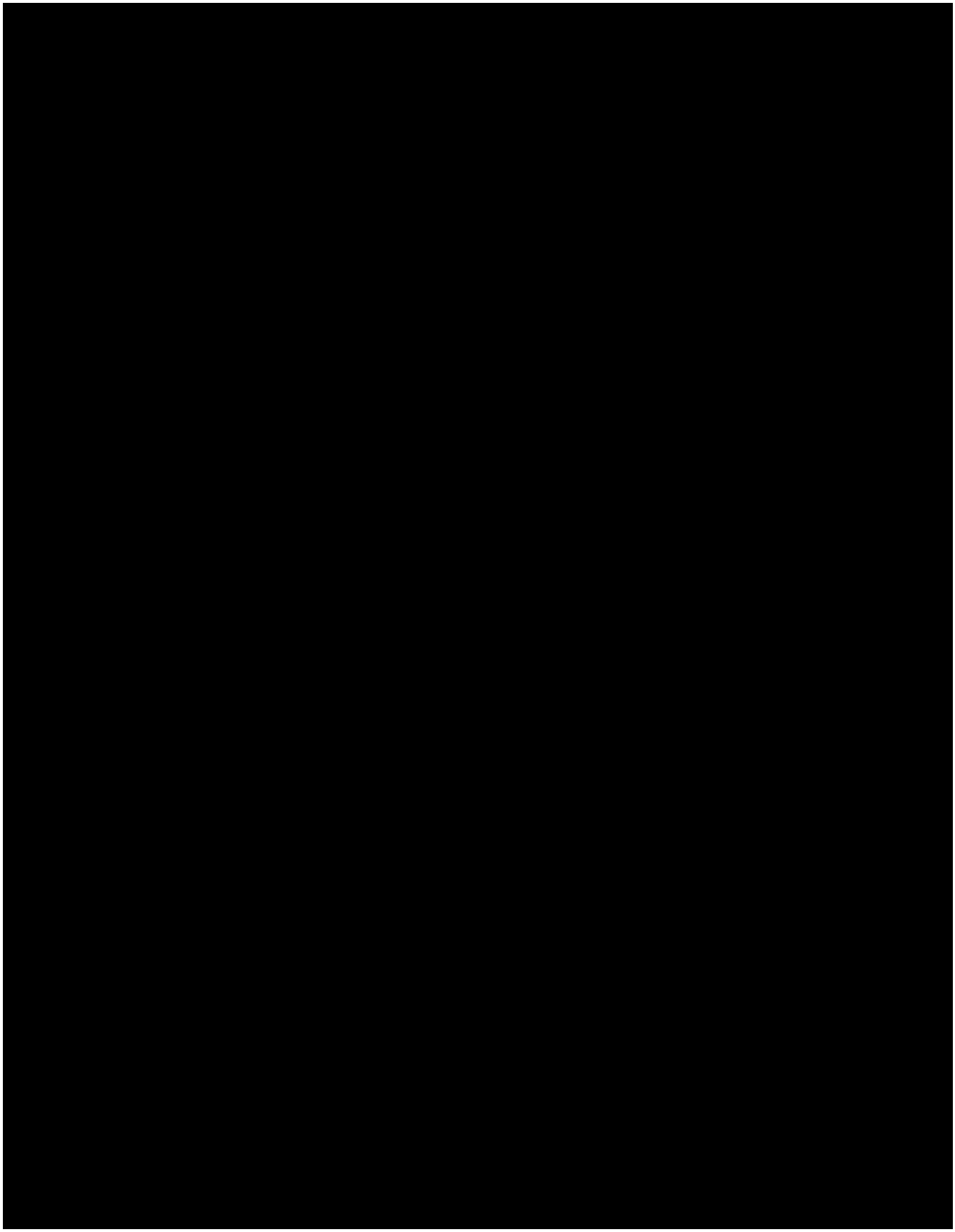

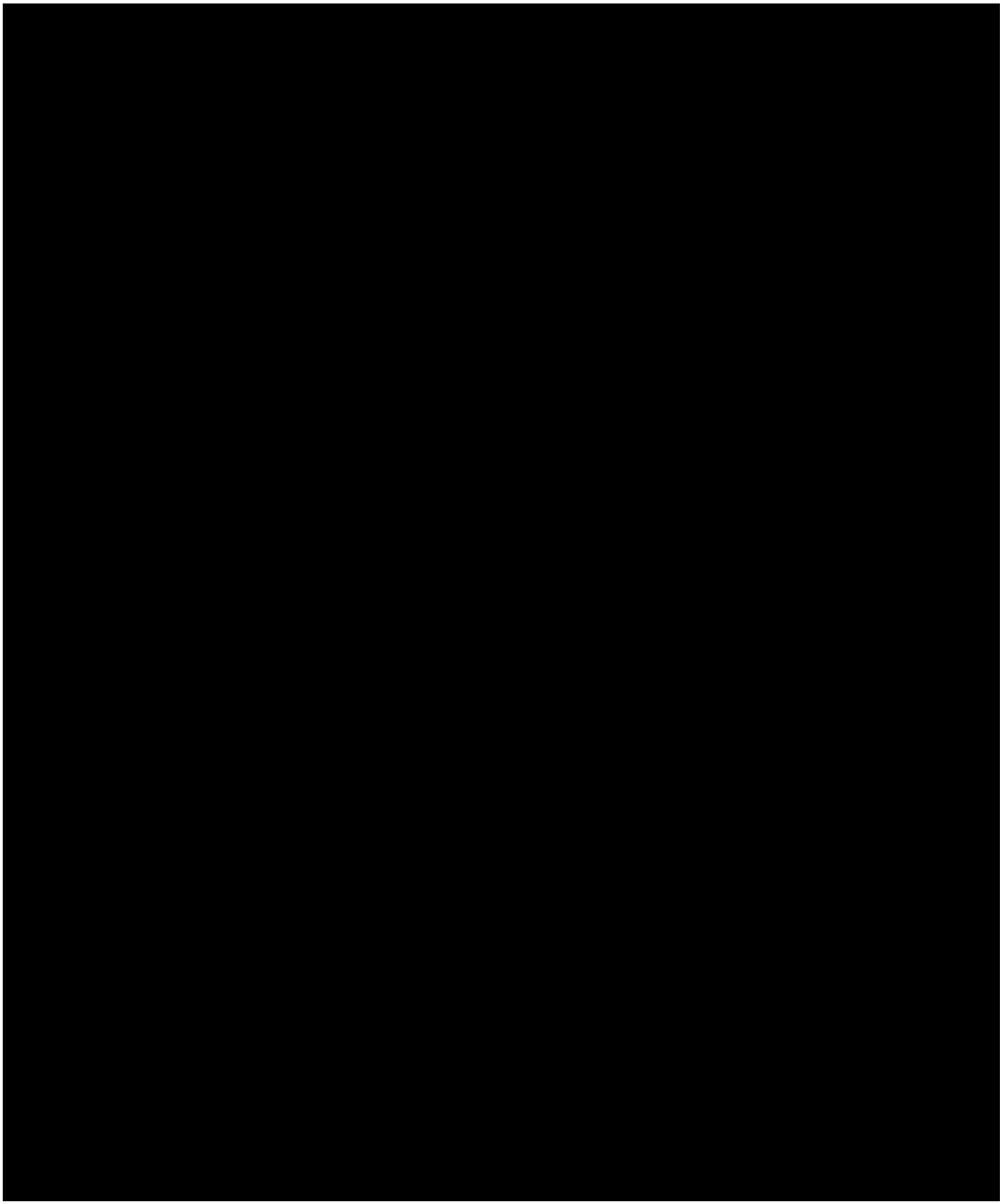

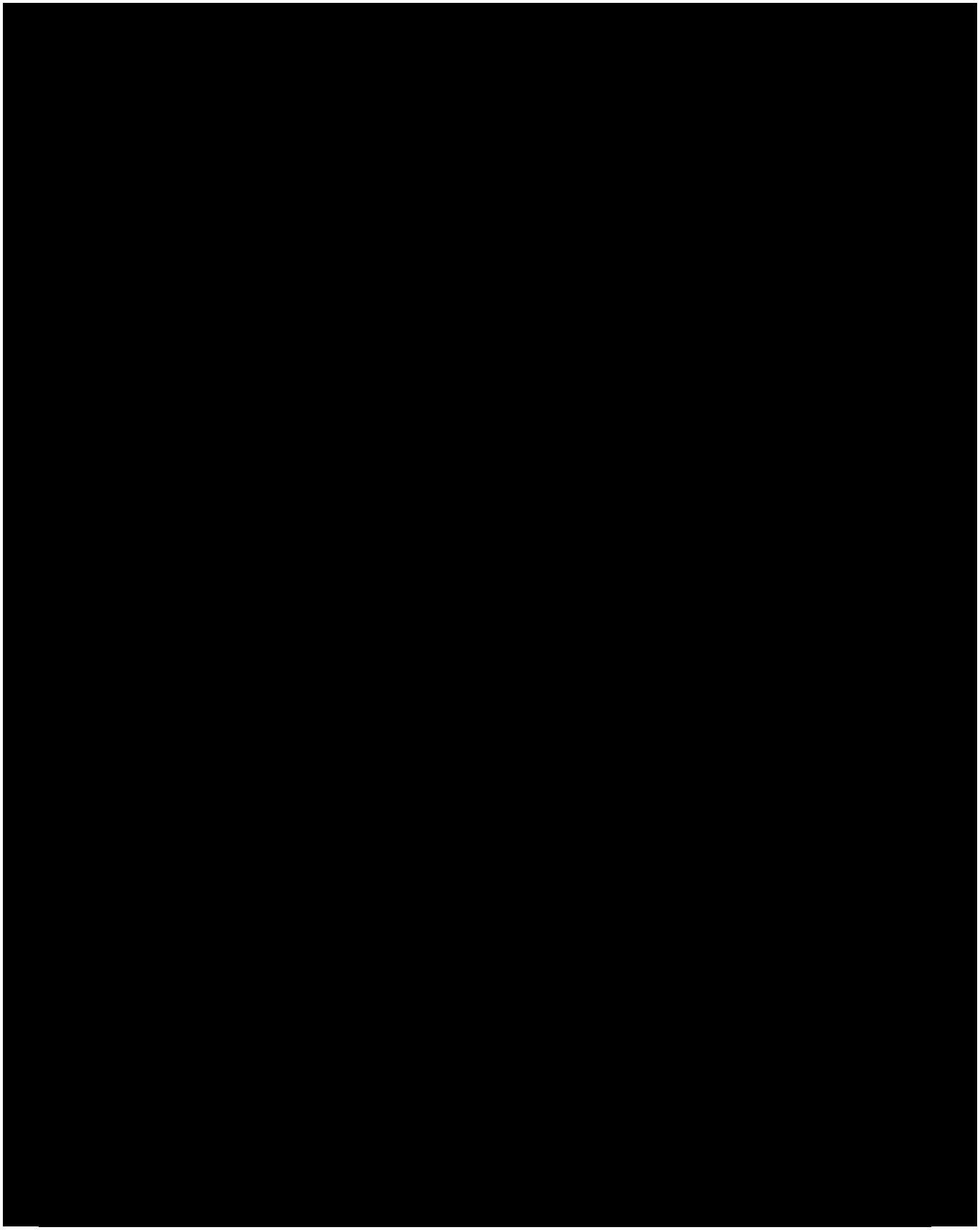

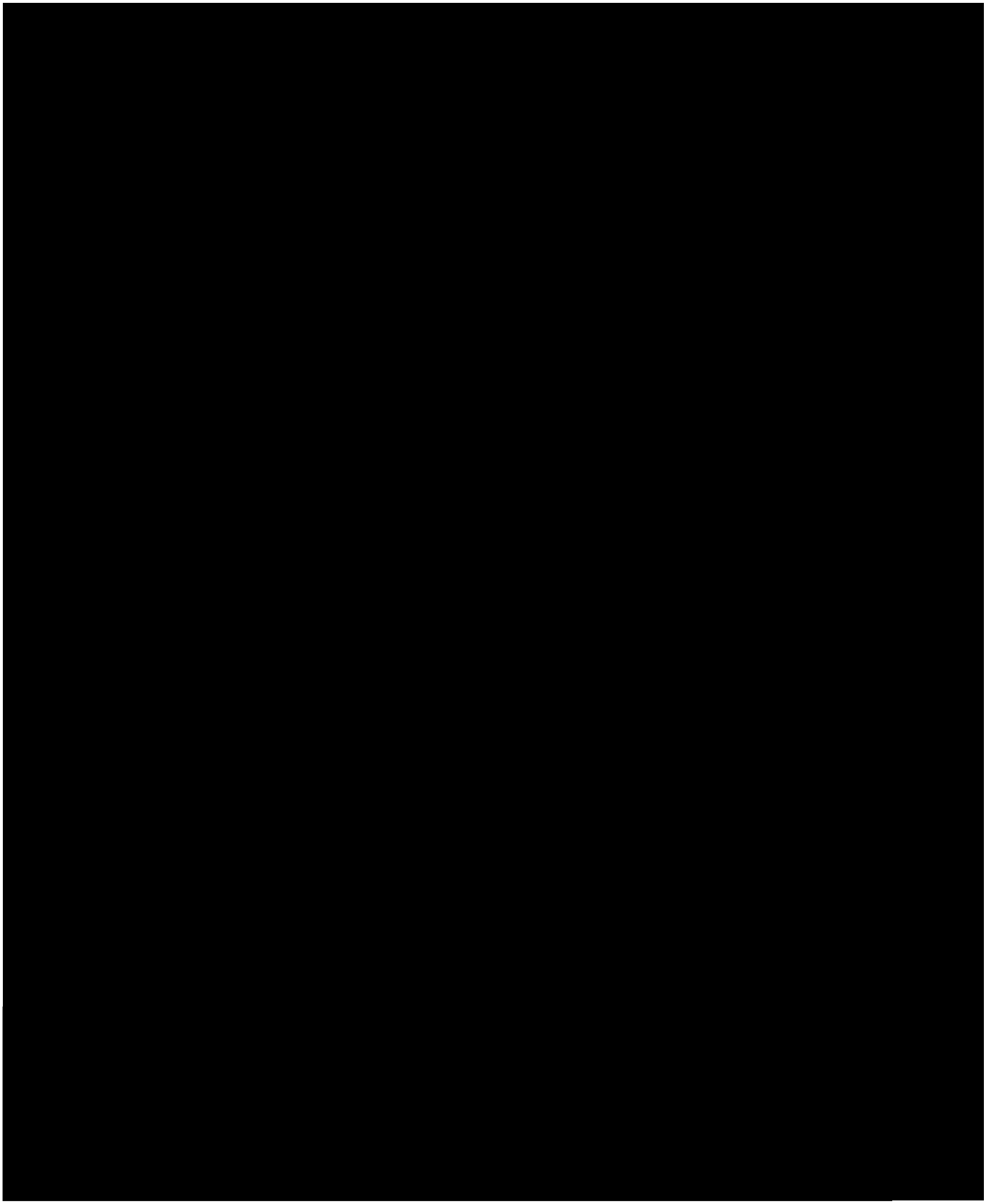

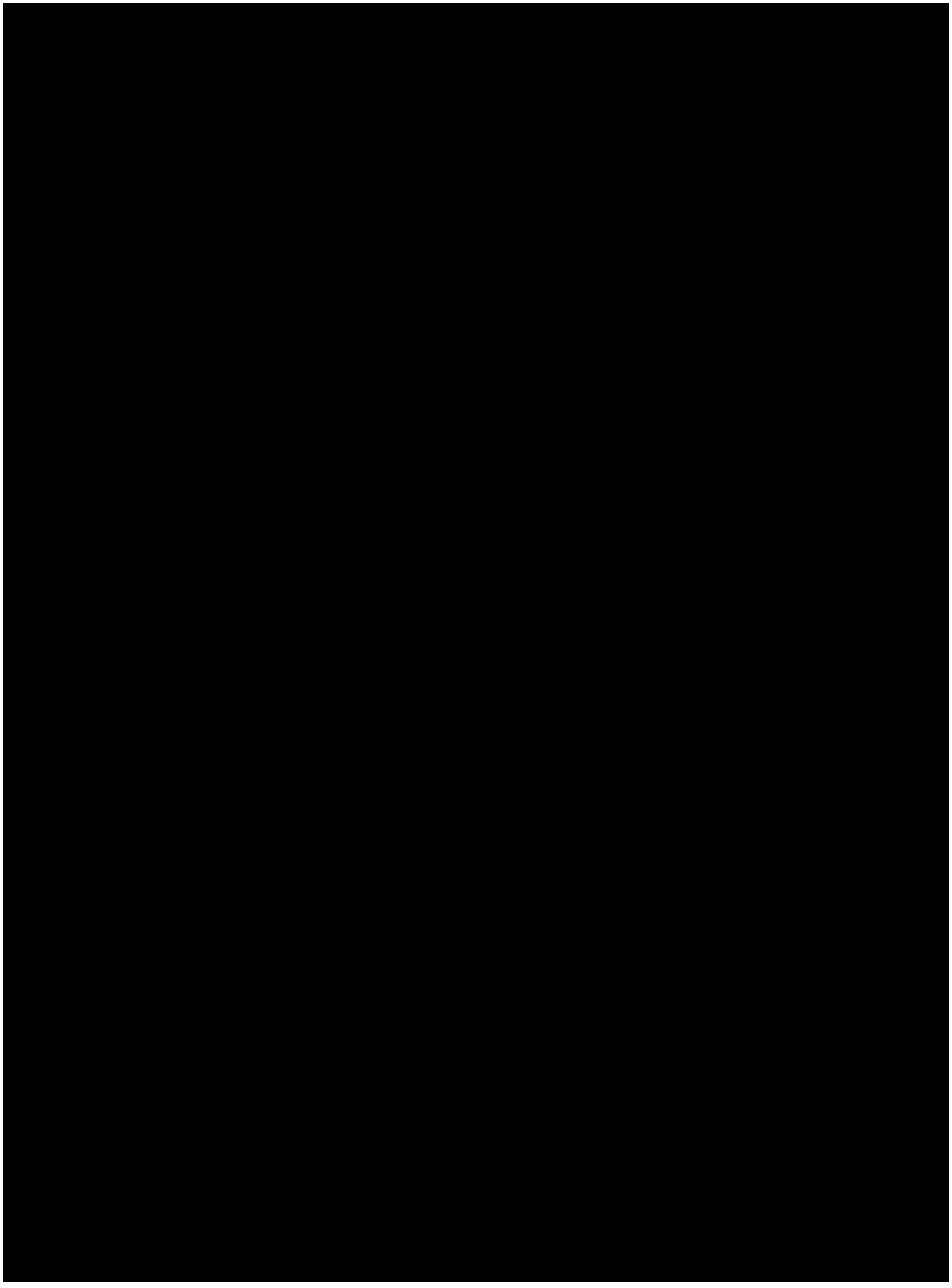

APPENDIX G. [redacted]

The sample provided in this appendix is for reference only.

ID #:

[redacted]

October 1992 version

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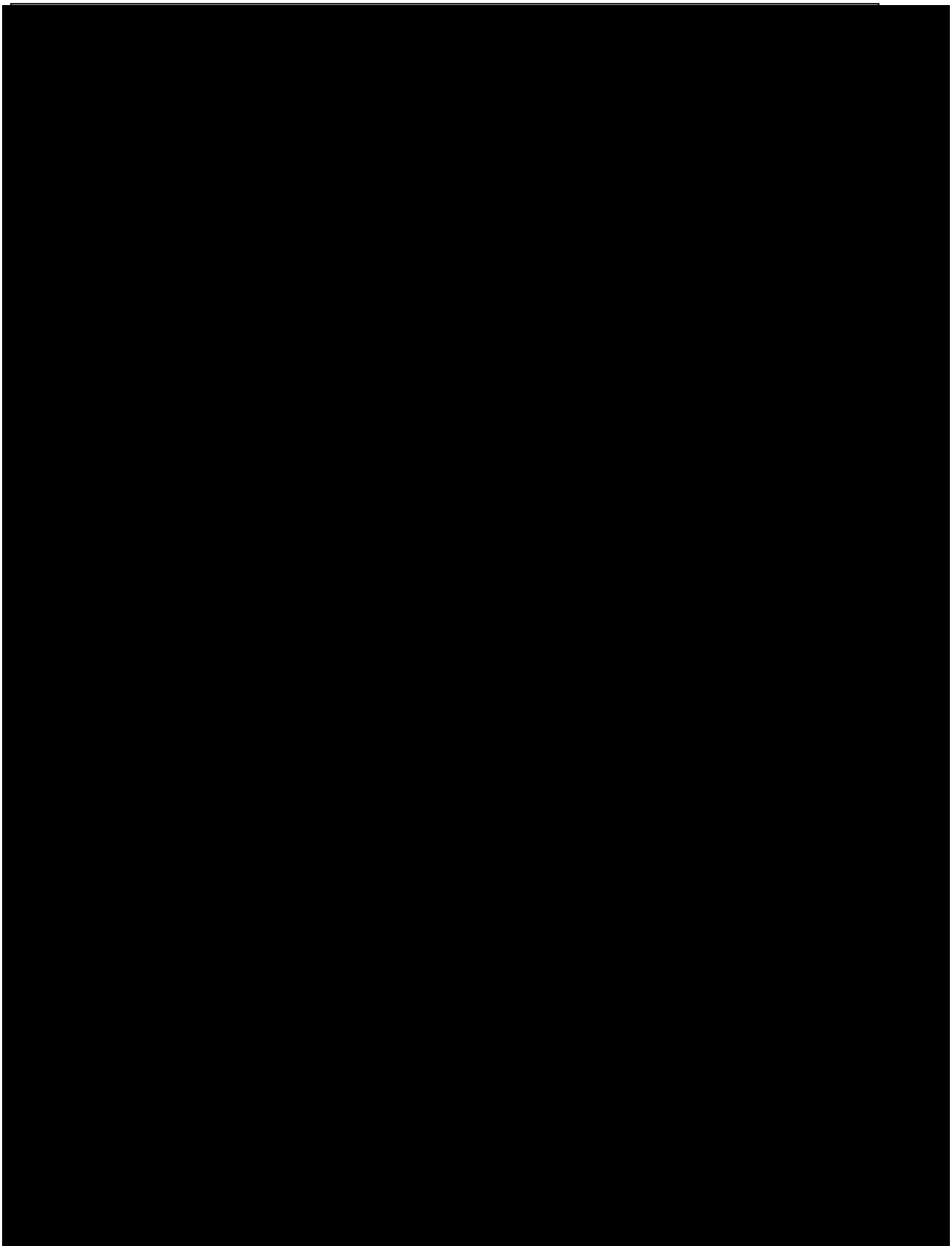

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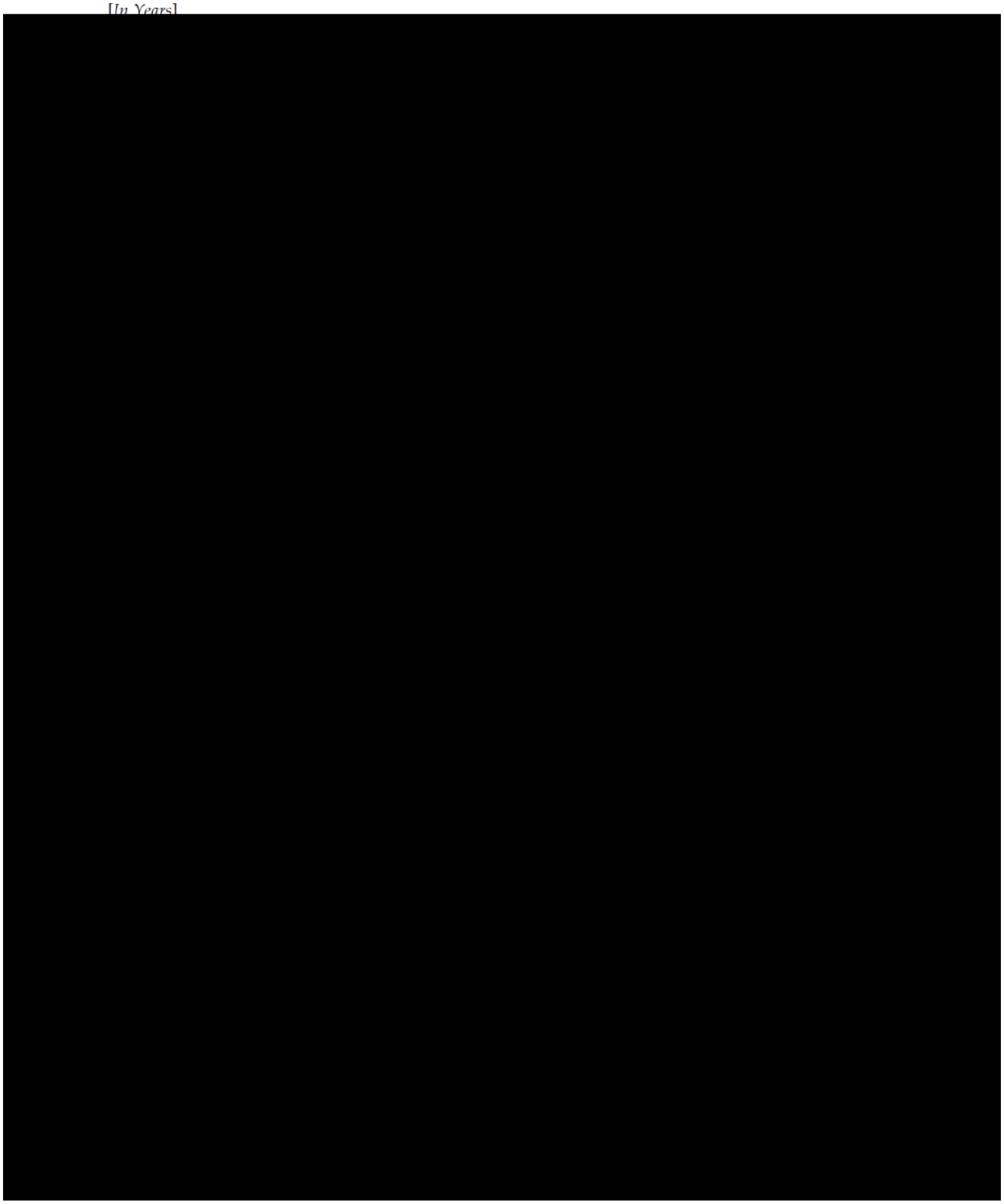

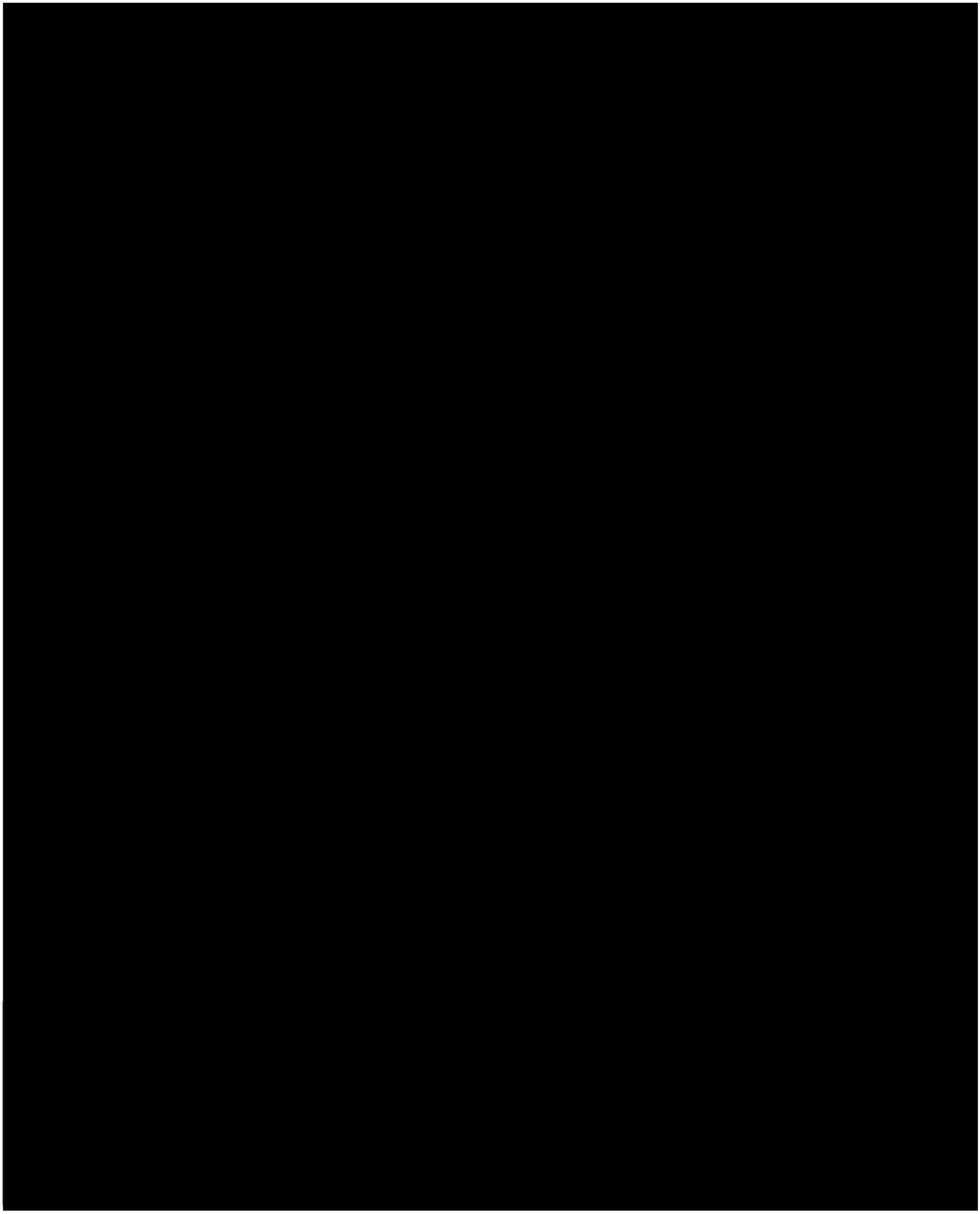

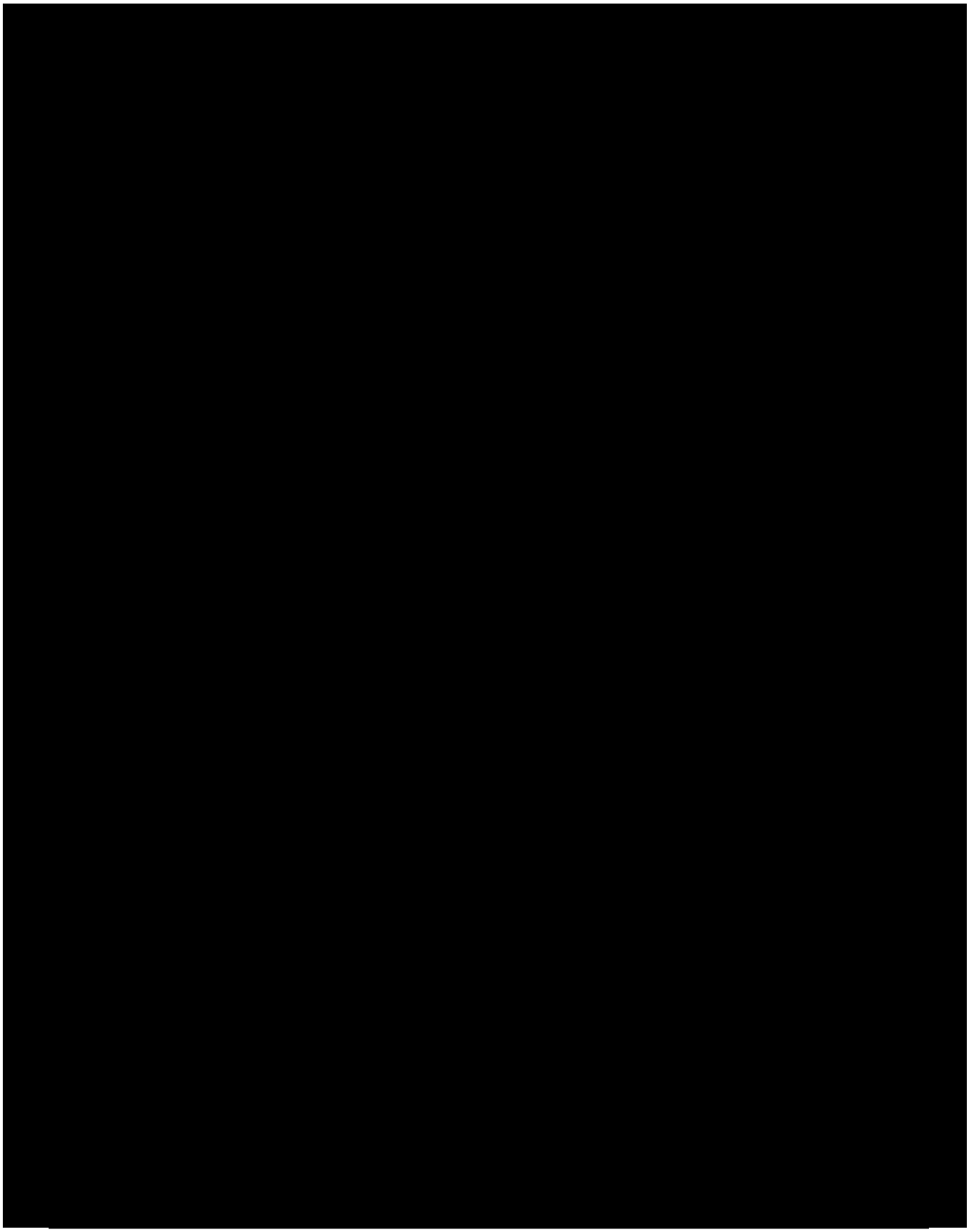

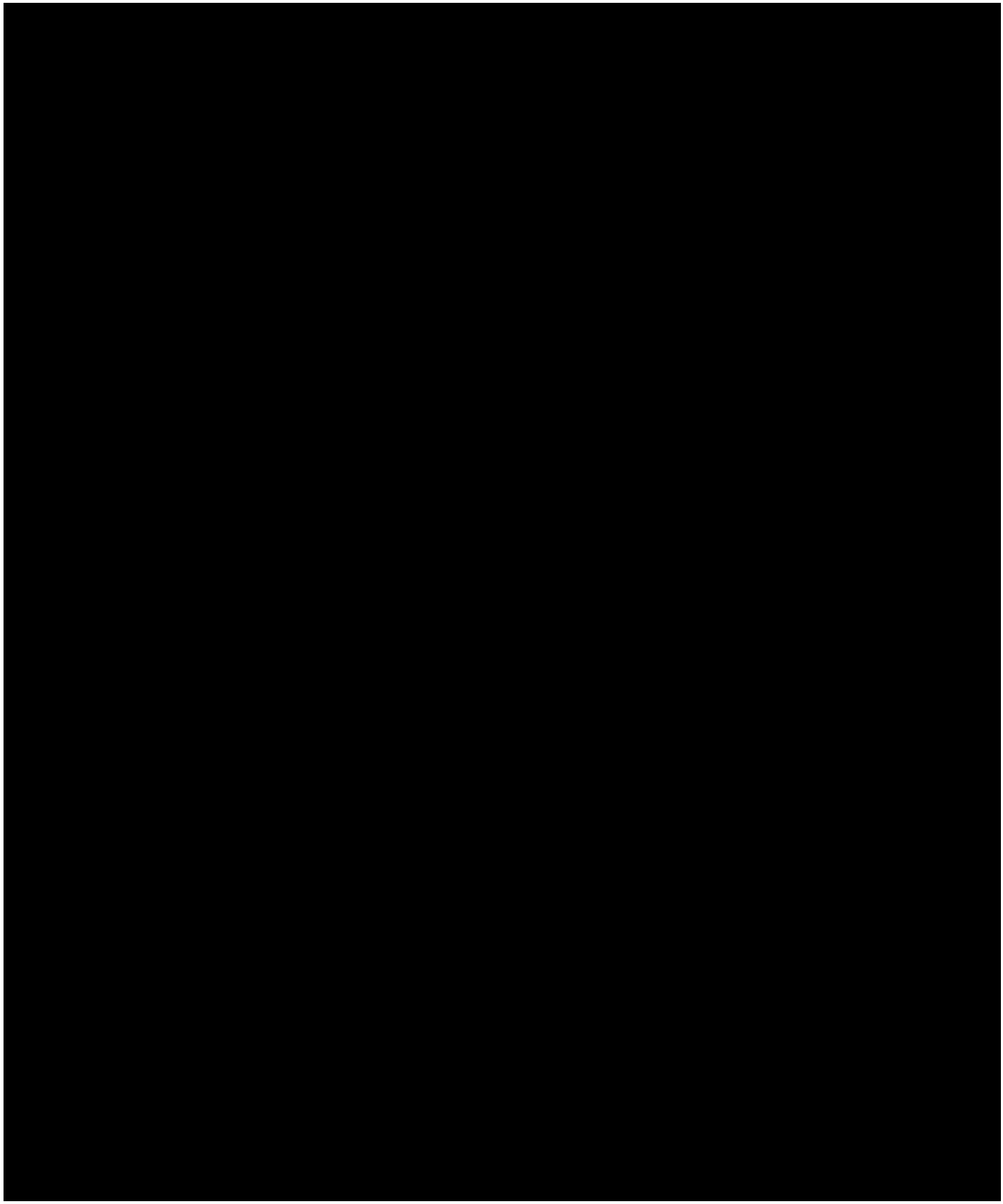

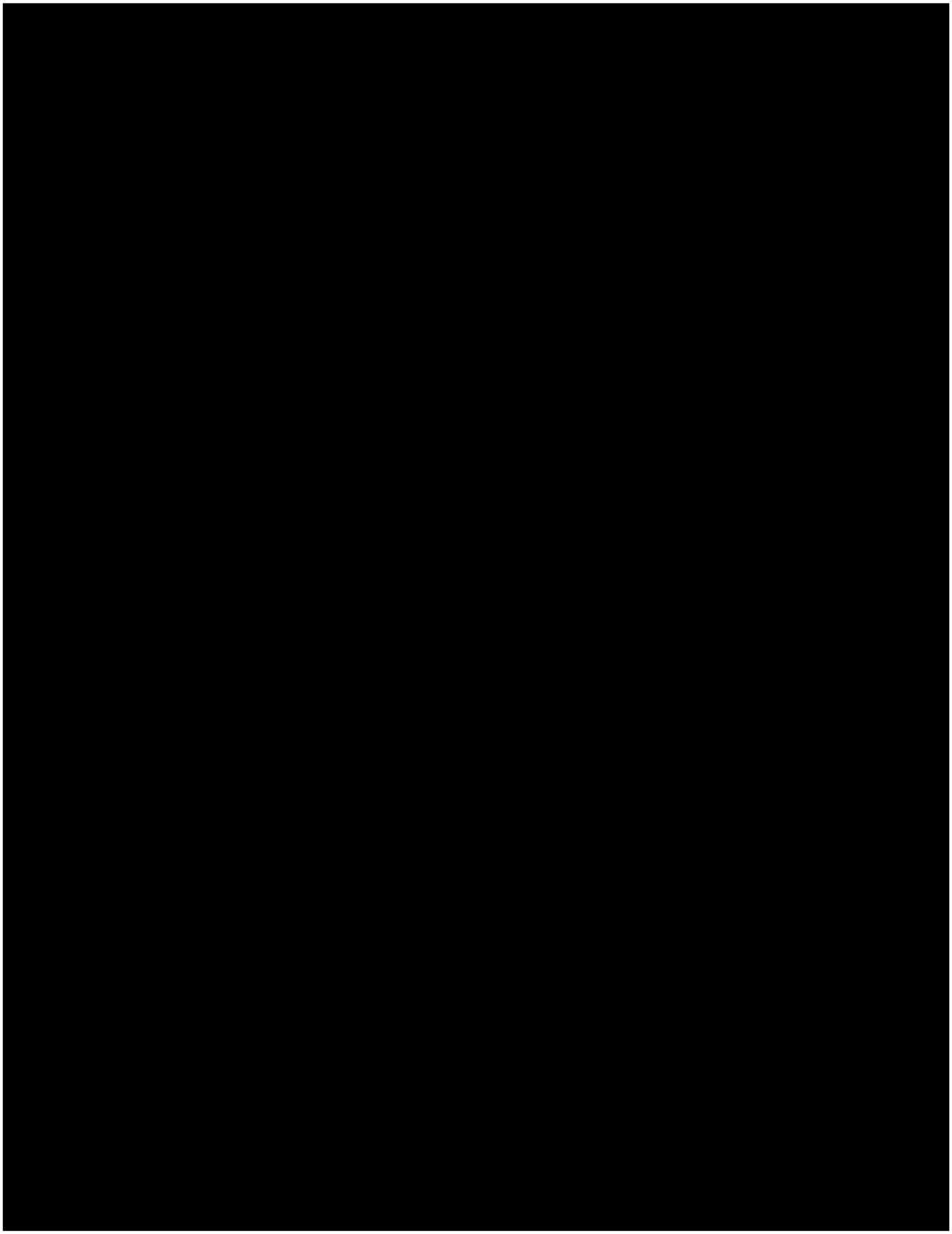

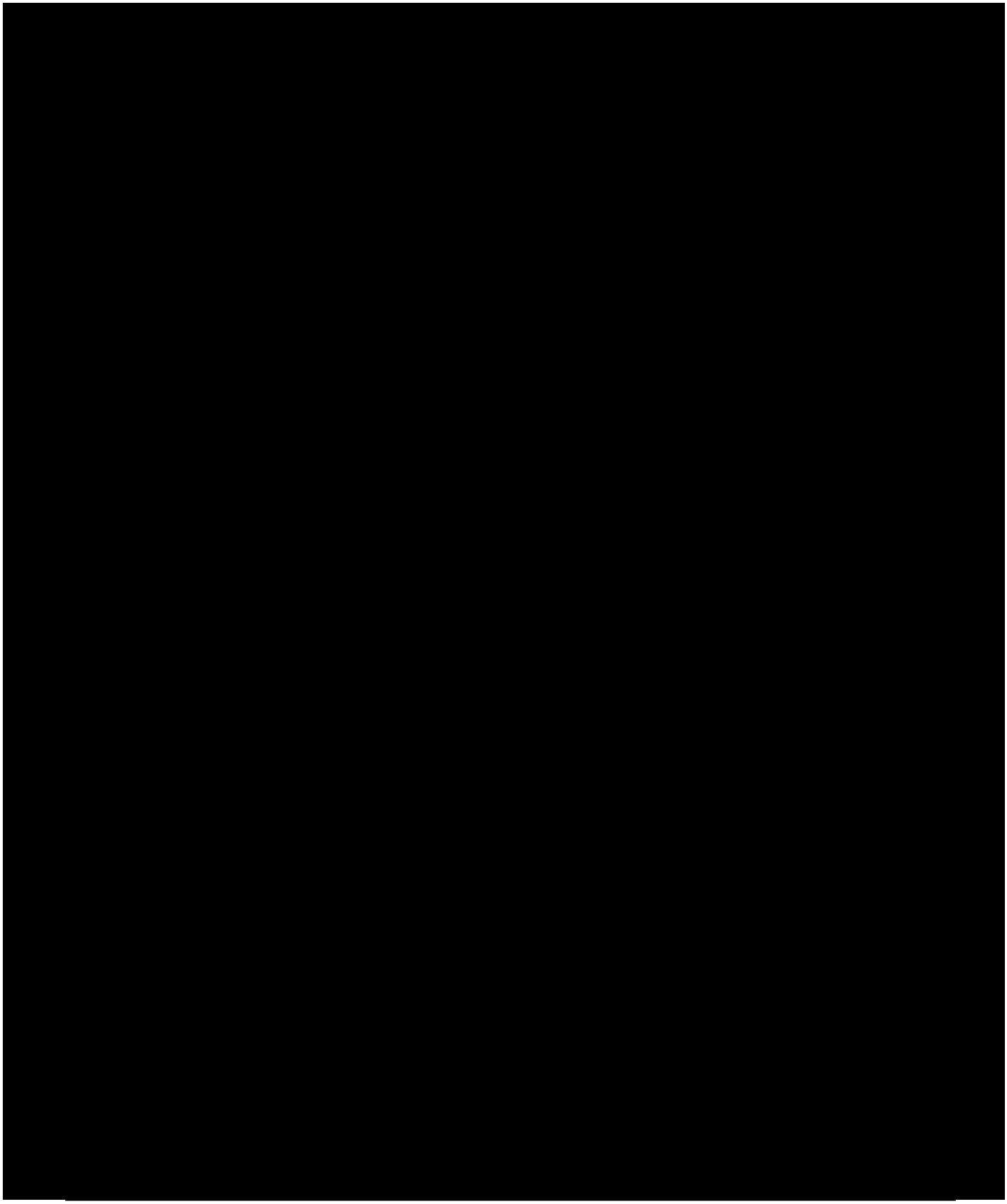

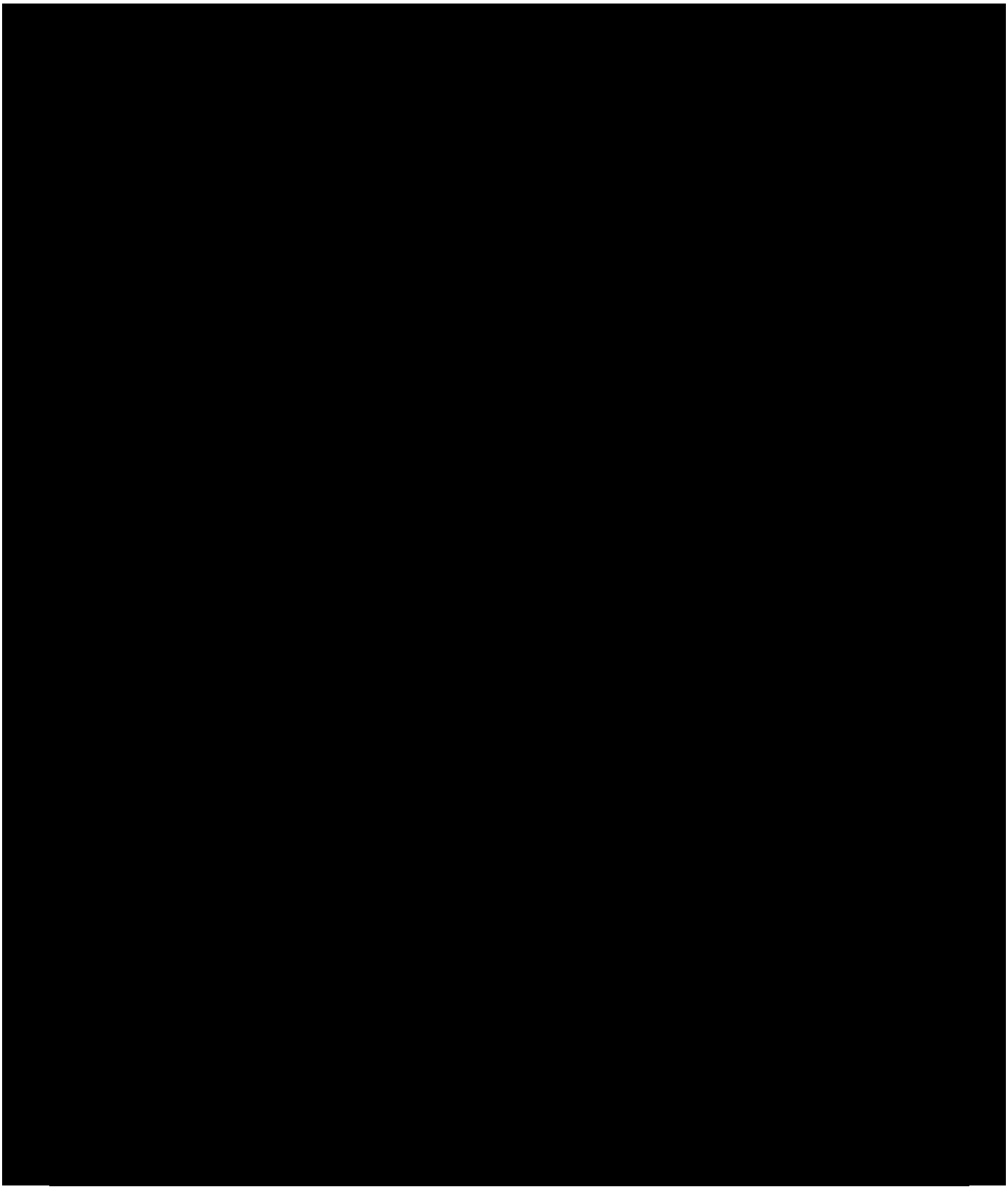

APPENDIX H. [redacted]

The sample provided in this appendix is for reference only.

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[redacted]	[redacted]
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APPENDIX I. [redacted]

[redacted]

APPENDIX J. [redacted]

The sample provided in this appendix is for reference only.

[redacted]

APPENDIX K. [redacted]

The sample provided in this appendix is for reference only.

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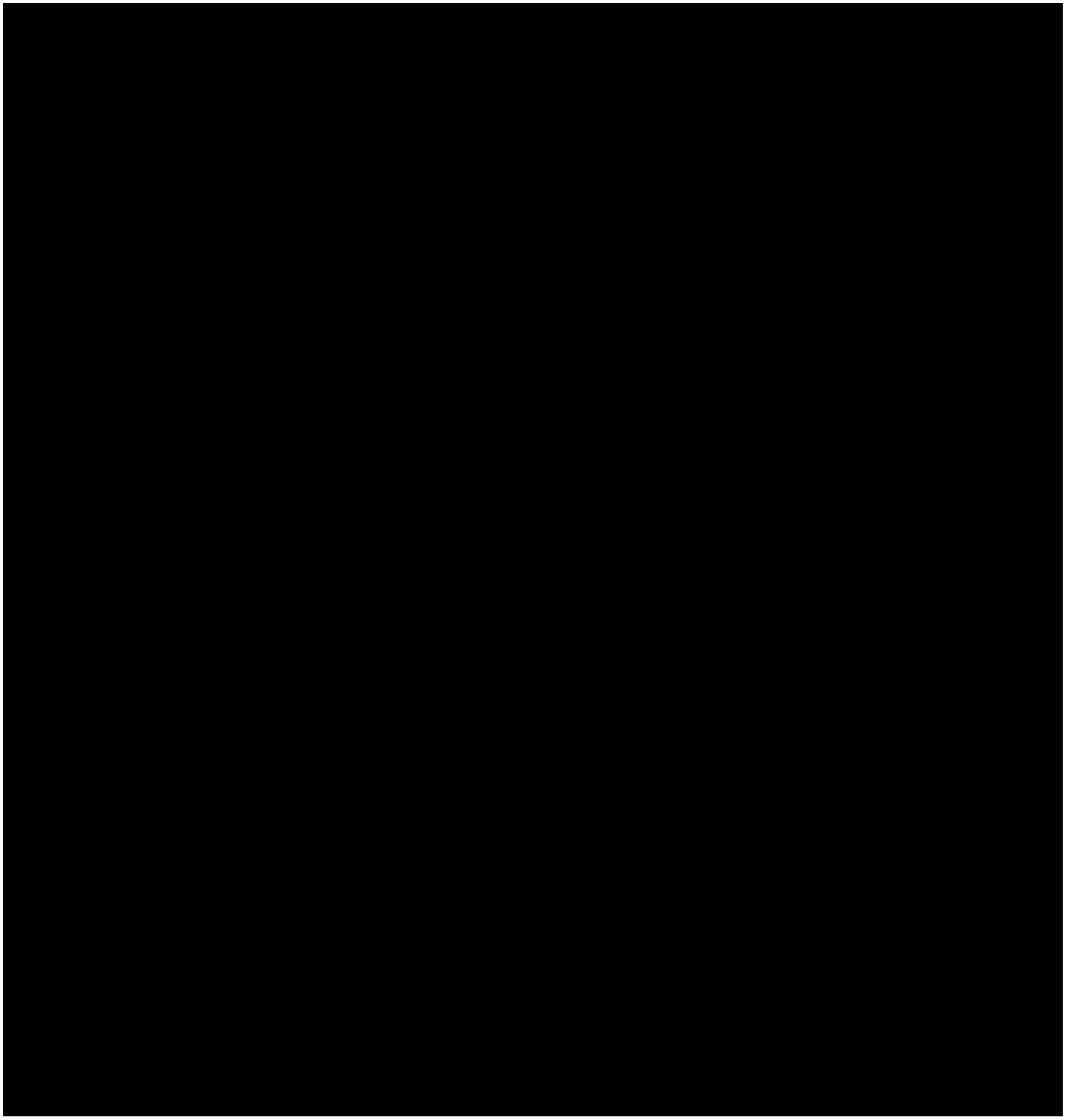

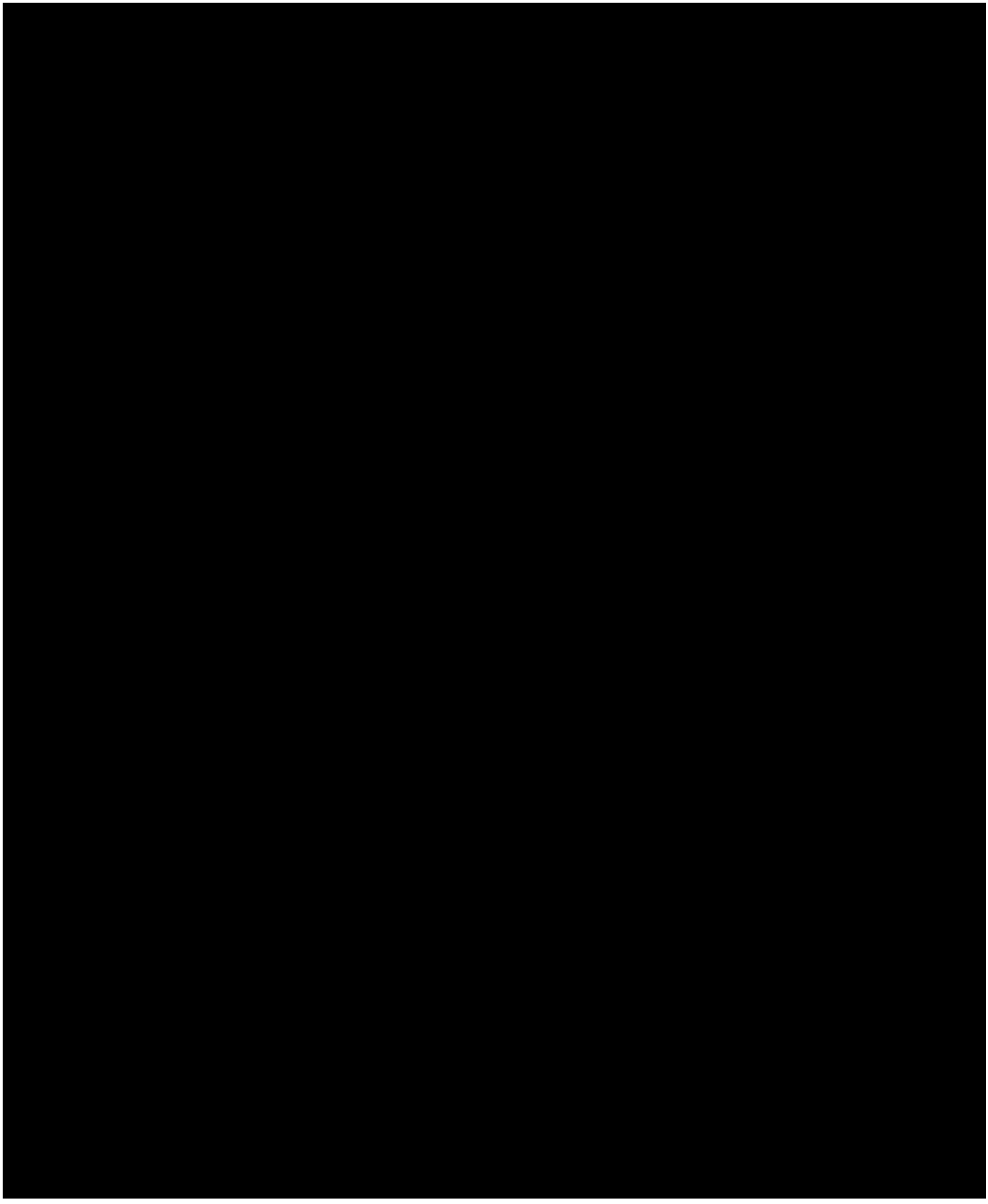

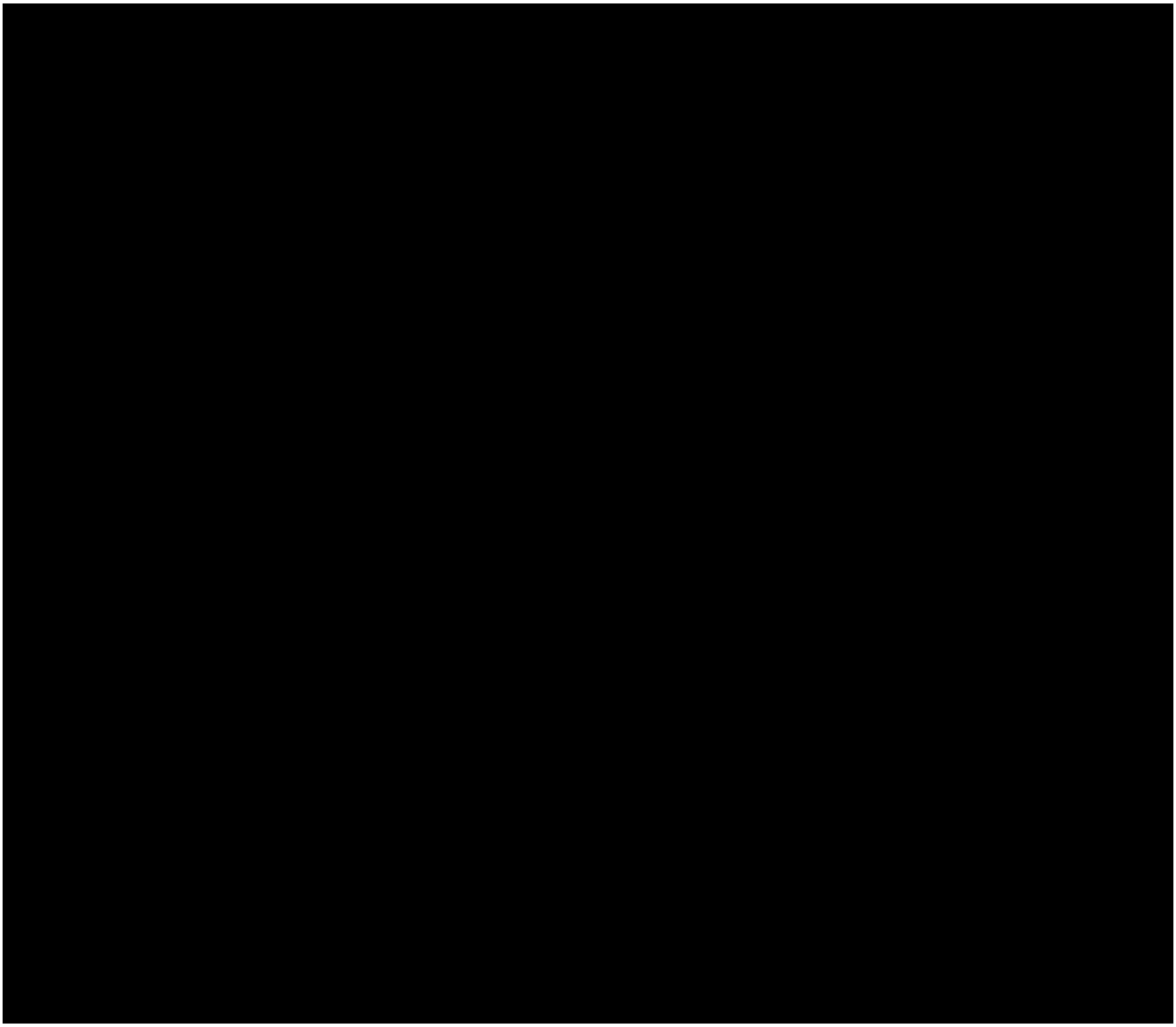

APPENDIX L. FEMALES OF CHILDBEARING POTENTIAL AND BIRTH CONTROL METHODS

Females of childbearing potential are defined as:

- not surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile
- 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.
- Intrauterine device (IUD) and intrauterine hormone-releasing system (IUS) need to be in place at least 2 months before screening.
- Bilateral tubal occlusion
- Vasectomized partner provided he is the sole sexual partner and has received medical assessment of the surgical process.
- Sexual abstinence is **only** considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.
- Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are **not** acceptable methods of contraception (according to Medicines and Healthcare Products Regulatory Agency, MHRA).

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.