Clinical Study Protocol

A Randomized, Double-blind, Placebo-controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents

Study Number TV50717-CNS-30046

NCT03452943

Protocol Approval Date: 25 March 2019

Clinical Study Protocol with Amendment 05

Study Number TV50717-CNS-30046

A Randomized, Double-blind, Placebo-controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents

Phase 2/3

IND number: 127692; NDA number: NA; EudraCT number: 2016-000622-19

Original Protocol Approval Date: 26 February 2016

Protocol Amendment 05 Approval Date: 25 March 2019

Sponsor

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

Teva's Development Partner

Nuvelution TS Pharma, Inc.
101 Main Street, 12th Floor
Cambridge, Massachusetts 02142
United States of America

Confidentiality Statement

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

This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Branded Pharmaceutical Products R&D and/or its affiliates and Nuvelution TS Pharma, INC. 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-30046 (original protocol dated 26 February 2016) has been amended and reissued as follows:

Amendment 05	25 March 2019 86 patients randomized/enrolled to date
Amendment 04	13 September 2018 35 patients randomized/enrolled to date
Amendment 03	06 November 2017 No patients randomized/enrolled to date
Amendment 02	03 October 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 05 Dated 25 March 2019

IND number: 127692; EudraCT number: 2016-000622-19

Article 45 or 46 of 1901/2006 does not apply

A Randomized, Double-blind, Placebo-controlled Study 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 05 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]	Mar 25 2019

COORDINATING INVESTIGATOR AGREEMENT

Original Protocol Dated 26 February 2016

Amendment 05 Dated 25 March 2019

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

Article 45 or 46 of 1901/2006 does not apply

A Randomized, Double-blind, Placebo-controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents

I have read the protocol with amendment 05 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 and 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 patient information, IMPs shipment and return forms, and other information collected during the study, in accordance with my responsibilities under the function of the coordinating investigator and in accordance with national and local GCP regulations as well as all other national and international laws and regulations. In addition I will assume the responsibility of the coordinating investigator according to a separate contract.

Coordinating Investigator [redacted]

Title: [redacted]

Address of Investigational Center: [redacted]

Tel: [redacted]

Coordinating Investigator	Signature	Date
[redacted]	[redacted]	03/25/2019

COORDINATING INVESTIGATOR AGREEMENT

Original Protocol Dated 26 February 2016

Amendment 05 Dated 25 March 2019

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

Article 45 or 46 of 1901/2006 does not apply

A Randomized, Double-blind, Placebo-controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents

I have read the protocol with amendment 05 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 and 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 patient information, IMPs shipment and return forms, and other information collected during the study, in accordance with my responsibilities under the function of the coordinating investigator and in accordance with national and local GCP regulations as well as all other national and international laws and regulations. In addition I will assume the responsibility of the coordinating investigator according to a separate contract.

Coordinating Investigator [redacted]

Title: [redacted]

Address of Investigational Center: [redacted]

Tel: [redacted]

Coordinating Investigator	Signature	Date
[redacted]	[redacted]	3/25/19

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)

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.

Legal Representative of the Sponsor in the EU

[redacted]

For medical issues, contact the physician listed below:

[redacted]

For protocol issues, contact the study leaders listed below:

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

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-30046

Title of Study: A Randomized, Double-blind, Placebo-controlled Study 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., 101 Main Street, 12th Floor, Cambridge, Massachusetts 02142, United States of America

Investigational New Drug (IND) Number: 127692 **New Drug Application (NDA) Number:** Not available
EudraCT Number: 2016-000622-19

Name of Active Ingredient: Deutetrabenazine

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

Type of the Study: Efficacy and Safety **(**Phase 2/3)

Number of Investigational Centers Planned: Approximately 50

Countries Planned: North America, Russia, and Europe

Planned Study Period: Planned start in January 2018 with a duration of approximately 15 months

Number of Patients Planned: Approximately 116 (58 per treatment arm; TEV-50717 versus placebo randomized in a 1:1 ratio stratified by age at baseline [6 to 11 years, 12 to 16 years])

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

Primary Objective: The primary objective of this study is to evaluate the efficacy of TEV-50717 to reduce motor and phonic tics associated with TS.

Secondary Objectives: The secondary objective of the study is to evaluate the safety and tolerability of titration and maintenance therapy with TEV-50717.

Study Endpoints:

Primary Efficacy Endpoint:

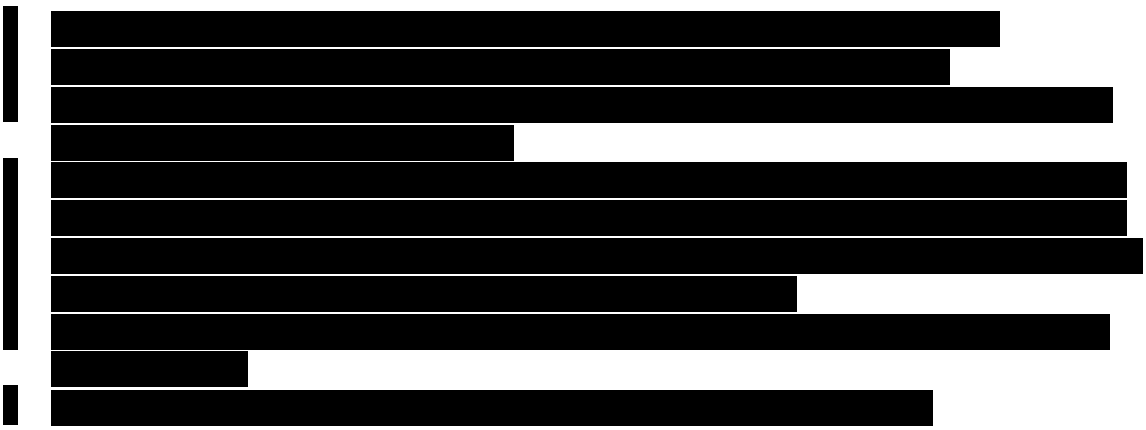
- Change in the Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS) from baseline to week 12

Key Secondary Efficacy Endpoints:

1. Change in the Tourette Syndrome-Clinical Global Impression (TS-CGI) score from baseline to week 12
2. Change in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) score from baseline to week 12
3. 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 baseline to week 12

Exploratory Endpoints:

[redacted]



Safety Endpoints:

- Incidence of adverse events
- Observed values and changes from baseline in vital signs
- Observed values and change from baseline in the Children's Depression Inventory, Second Edition (CDI-2), Parent and Self-report Profiles
- Observed values in the Children's Columbia-Suicide Severity Rating Scale (C-SSRS)
- Observed values in electrocardiogram (ECG) parameters and shifts from screening for clinically significant abnormal findings
- Observed values and changes from screening in clinical laboratory parameters (hematology, chemistry, and urinalysis)

Pharmacokinetic Endpoint:

- The pharmacokinetics of the alpha-dihydrotetrabenazine (α-HTBZ) and beta-dihydrotetrabenazine (β-HTBZ) metabolites of TEV-50717, and other metabolites (as needed), will be explored based on sparse sampling at week 12.

General Design and Methodology:

This is a Phase 2/3, randomized, double-blind, placebo-controlled, parallel group study in which patients with tics associated with TS will be invited to participate. Patients who qualify for the study will be centrally randomized in a 1:1 ratio (stratified by age at baseline [6 to 11 years, 12 to 16 years]) to receive either TEV-50717 or placebo. Throughout the study, patients will interact regularly with investigative site personnel, in clinic and by telephone, for the evaluation of safety, tic severity, and behavioral status (in clinic only). The target dose for each patient receiving TEV-50717 will be based on body weight and cytochrome P450 2D6 (CYP2D6) impairment status at baseline. Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor or are a CYP2D6 poor metabolizer based on blinded assessment of CYP2D6 genotype at baseline. CYP2D6 status will be used by Interactive Response Technology (IRT) for randomization into the study. The dose of IMP for each patient will be titrated to an optimal level followed by maintenance therapy at that dose. Investigators will be blinded to CYP status, with a dose cap for poor metabolizers prespecified by the IRT. The overall treatment period will be 12 weeks in duration, including a titration period of 7 weeks, a maintenance period of 5 weeks, followed by a washout period of 1 week [redacted]. For the YGTSS, input from the caregiver/adult is required. For both the TS-PGII and [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 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.

Patients who complete the study may be eligible to begin participation in an open-label safety extension study TV50717-CNS-30047 after the end of the washout period. At the week 13 visit, patients may choose to enter Study TV50717-CNS-30047 (on that day), or they will have an additional week to make a decision and return for day 1. Patients not participating in Study TV50717-CNS-30047 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).

Screening period (up to 31 days): After informed consent/assent, depending on the child's age, as appropriate, is obtained, patients who are stable from a medical and psychiatric standpoint will undergo a screening evaluation, including medical history, physical and neurological examination, laboratory testing, and 12-lead ECG, along with rating scales to assess severity, frequency, and impairment of tics and comorbid TS symptoms and behavioral status.

At the discretion of the investigator, the screening visit may be divided into 2 visits if the visit length is felt to be too burdensome for the patient. If the screening visit is divided into 2 visits, the blood sample should be obtained during the first of the 2 visits. Patients who have received comprehensive behavioral intervention for tics (CBIT) for TS or cognitive behavioral therapy (CBT) for obsessive-compulsive disorder (OCD) may participate in this study as long as therapy was completed at least 4 weeks prior to screening. Patients will return to the clinic on day 1 for baseline procedures and to re-confirm eligibility. Patients may be rescreened 1 time if there is a change in the status of the patient regarding eligibility for the study. (Note: Details of rescreening must be approved and documented by the medical monitor and/or Clinical Surveillance and Training [CST] team.)

YGTSS Rater Certification: All investigators and 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, especially at the baseline and week 12/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.

Titration period (7 weeks): Patients who remain eligible for participation in the study will be randomized at the baseline visit (day 1), and that evening (ie, after the study visit) will receive 6 mg of blinded IMP with food. 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 at baseline, as shown in the tables below. Patients and their caregiver/adult will interact weekly with the clinical research staff, either by telephone contact or clinic visit from week 1 through week 7 of the titration period, in order to evaluate safety and establish a dose of IMP that optimally reduces tics and is well tolerated (optimal dose). Safety evaluations during titration 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 criteria is met:

- 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 study medication 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 at baseline.

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 on that dose (ie, the dose should not be increased further) for the remainder of the titration period and throughout maintenance dosing, unless there is a change in symptoms during the titration period. If a patient experiences a "clinically significant" adverse event attributable to the IMP, the investigator will determine if a dose reduction or suspension is necessary. 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 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. At the end of the titration period, the patient's dose will be established for the maintenance period.

Maintenance period (5 weeks): Patients will continue to receive their maintenance dose over the next 5 weeks, although dose reductions for adverse events are allowed. Patients will return to the clinic at weeks 9 and 12 for assessments of safety and efficacy. At week 12, patients will undergo a complete evaluation, including physical and neurological examination, safety laboratory testing, and 12-lead ECG, CDI-2, and C-SSRS assessments, as well as the YGTSS, TS-CGI, TS-PGII, [redacted], [redacted], [redacted] and C&A-GTS-QOL. In addition, patients will undergo pharmacokinetic sampling at week 12.

Washout period and follow-up: All patients will discontinue IMP at the week 12 visit and will return 1 week later for evaluation of safety and tic reduction (week 13). Patients who complete the study may be eligible to begin participation in the open-label safety extension study, TV50717-CNS-30047, at that time. For this study, the follow-up period is defined as 1 week of washout for patients who will participate in the open-label safety extension study TV50717-CNS-30047 and 2 weeks after the last dose of IMP (1 week after the end of the washout period) for patients who will not roll over into the open-label safety extension study TV50717-CNS-30047. At the week 13 visit, patients may choose to enter Study TV50717-CNS-30047 (on that day), or they will have an additional week to make a decision and return for day 1. Patients not participating in Study TV50717-CNS-30047 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 14]).

Prohibited drugs will remain the same during the washout period for patients who will participate in the open-label extension study TV50717-CNS-30047.

Patients who will not participate in the extension study (Study TV50717-CNS-30047) may begin/resume tic therapy medication after the first week of the washout period.

Method of Blinding and Randomization:

Patients will be randomly assigned to receive treatment with TEV-50717 or matching placebo in a 1:1 ratio using an IRT. Patients will be stratified by age at baseline (6 to 11 years, 12 to 16 years). Patients and investigators will remain blinded to treatment assignment during the study. In addition, the sponsor's clinical personnel and all vendors (with the exception of the IRT vendor and the bioanalytical sample analysis vendor) involved in the study will be blinded to the IMP identity until the database has been locked for analysis and the treatment assignments are revealed. After unblinding of this study, the study site may remain blinded to patient treatment assignments until completion of the safety extension study TV50717-CNS-30047.

IMP Dose, Mode of Administration, and Administration Rate:

IMP will be administered as oral tablets at a starting dose of 6 mg. Titration schemes based on body weight at baseline are shown in the tables below. The maximum daily dose is determined by body weight and CYP2D6 impairment status at baseline (see the table below). 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 in warranted, the dose may be reduced.

TEV-50717 tablets are available in the following dose strengths: 6, 9, 12, 15, and 18 mg, all of which are identical in size, shape, and color (white). The IMP will be supplied in 40-count blister packs. The placebo tablets and packaging will match those for TEV-50717.

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 at the baseline visit, as shown in the tables below.
- 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. 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 must be notified.**
- During the titration period, the dose of IMP should be adjusted weekly according to the table below to identify a dose level that optimally reduces tics and is well tolerated. Investigators will be blinded to CYP status, with a dose cap for poor metabolizers prespecified by the IRT.

Maximum Daily Dose of IMP by Study Day and Weight Category at Baseline

	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 (ie, Days 8, 15, 22, 29, 36, and 43), as applicable.
[b] Patients will receive 6 mg on days 1 and 2, and 12 mg starting on day 3.

bid=twice a day; 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.

IMP: TEV-50717

Reference Therapy: Placebo

Duration of Patient Participation: This study will consist of up to a 31-day screening period, a 12-week double-blind treatment period, and a 1-week washout period. Patients who complete the study may be eligible to begin participation in an open-label safety extension study TV50717-CNS-30047 after the end of the washout period. Patients not participating in Study TV50717-CNS-30047 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 14 weeks.

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

a. Patient is 6 to 16 years of age, inclusive, at baseline.

b. Patient weighs at least 44 pounds (20 kg) at baseline.

c. Patient meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-V™) diagnostic criteria for TS and, in the opinion of the investigator, patient, and caregiver/adult, the patient's active tics are causing distress or impairment.

d. Patient has a TTS of 20 or higher on the YGTSS at screening and baseline.

e. Patient is able to swallow study medication whole.

f. Patient and caregiver/adult are willing to adhere to the medication regimen and to comply with all study procedures.

g. Patient is in good general health, as indicated by medical and psychiatric history as well as physical and neurological examination.

h. In the investigator's opinion, the patient and caregiver/adult have the ability to understand the nature of the study and its procedures, and the patient is expected to complete the study as designed.

i. Patient and caregiver/adult provide written informed consent/assent, depending on the child's age, as appropriate, according to local regulations.

j. Females who are postmenarchal or ≥12 years of age may be included only if they have a negative beta-human chorionic gonadotropin (β-HCG) test at baseline or are sterile. Definitions of sterile are given in Appendix L.

k. Females who are postmenarchal or ≥12 years of age whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study (ie, starting at screening) and for 30 days or 5 half-lives, whichever is longer after last dose of IMP. Further details are included in Appendix L.

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

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

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

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

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

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

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

   - previous intent to act on suicidal ideation with a specific plan, irrespective of level of ambivalence, at the time of suicidal thought
   - previous suicidal preparatory acts or behavior

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

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

h. Patient has clinically significant OCD at baseline that, in the opinion of the investigator, is the primary cause of impairment.

i. Patient has received CBIT for TS or CBT for OCD within 4 weeks of screening.

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

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

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

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

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

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

   - Note: Use of guanfacine or clonidine is allowed regardless of indication (ie, if prescribed for tics or 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. If discontinuation of either medication is anticipated due to ineffectiveness, poor tolerability, or patient/caregiver preference, discontinuation should occur 4 or more weeks prior to the screening visit.

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

l. Patient has an unstable or serious medical illness at screening or baseline

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 >480msec (with right bundle branch block) on 12-lead ECG at screening, OR requires treatment with drugs known to prolong the QT interval (see Appendix A, Table 6 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 baseline 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 and received IMP/intervention within 30 days or 5 drug half-lives of baseline, whichever is longer.

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 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 Inventory modules performed at screening that, in the opinion of the investigator, makes the patient unsuitable for the study.

Measures and Time Points:

Primary Efficacy Measures and Time Points: YGTSS (to calculate TTS): Screening; baseline; and weeks 2, 4, 6, 9, 12, and 13

Key Secondary Efficacy Measures and Time Points:

1. TS-CGI: baseline and weeks 2, 4, 6, 9, 12, and 13
2. TS-PGII: baseline and weeks 2, 4, 6, 9, 12, and 13
3. C&A-GTS-QOL ADL subscale: baseline, week 6, and week 12

Exploratory Measures and Time Points:

[redacted]

Safety Measures and Time Points:

- 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 and week 12
- neurological examination: screening and week 12
- vital signs: screening; baseline; and weeks 2, 4, 6, 9, 12, and 13
  Note: orthostatic blood pressure and pulse at baseline and weeks 4 and 12
- MINI Kid: screening
- Children's C-SSRS
  - Baseline/screening scale: screening
  - Since Last Visit scale: baseline and weeks 2, 4, 6, 9, 12, and 13
- CDI-2 (Parent and Self-Report versions): screening; baseline; and weeks 2, 4, 6, 9, 12, and 13
- 12-lead ECG: screening; baseline; and weeks 4, 6, and 12
- clinical laboratory tests (serum chemistry, hematology, and urinalysis): screening and week 12
- pregnancy testing: screening, baseline, and weeks 4 and 12
- drug screen: Screening and week 12

Pharmacokinetic Measures and Time Points:

Blood samples will be obtained for the measurement of plasma concentrations of TEV-50717 (deutetrabenazine), α-HTBZ, β-HTBZ, and other metabolites, as needed. Blood sampling for pharmacokinetic analysis will be performed at the week 12 visit. Two samples will be collected. The first sample will be collected upon arrival at the clinic. The second sample will be collected 2 to 3 hours after the first pharmacokinetic sample collection. The time between samples should be maximized in order to provide the most useful information. Patients with early morning visits (ie, within 2 hours of their scheduled AM dosing) should take their dose in the clinic after the first pharmacokinetic sample is collected.

Patients will be provided with a diary to provide critical information on dosing before the week 12 visit. The date and time of the last dose of study medication before the week 12 visit should be recorded in the diary by the patient or caregiver/adult. The site will document the date and time of the sample collection. Prior to the clinic visit on week 12, patients will be reminded to record the start time of their last meal and the time of their last dose in their diary

Plasma samples for both α-HTBZ and β-HTBZ metabolites will be pooled with previous data and incorporated into a population pharmacokinetic analysis. The population pharmacokinetic analysis will result in a final structural model that best describes the data. A covariate assessment will evaluate the relationship between potential covariates (ie, body weight, age, height, etc) and concentrations of α-HTBZ and β-HTBZ metabolites. The final population pharmacokinetic analysis will be included in a separate report. Exposure-response (eg, pharmacodynamic [PD] and/or safety endpoints) may be assessed if the appropriate data are available.

At the screening visit, a blood sample (3 mL) will be obtained for analysis of CYP2D6 genotype. The patient's genotype for CYP2D6 will remain blinded during the conduct of the study.

Allowed and Disallowed Medications Before and During the Study:

See Appendix A for details of allowed and disallowed medications.

Statistical Considerations:

Sample Size Rationale: It is estimated that approximately 58 patients per arm will enable a power of at least 90% to detect a beneficial standardized effect of 63% or more when the TEV-50717 arm is compared to placebo (difference of 6.0 in the change from baseline to week 12 in TTS, assuming a standard deviation of 9.5 in each arm) in a 2-sided type I error rate of 5% after accounting for potential dropouts.

[redacted]

Analysis of Primary Endpoint: The primary efficacy endpoint for this study is the change in the TTS of the YGTSS from baseline to week 12. The primary analysis will be a mixed-model repeated-measures model with the change in the TTS as the dependent variable. The model will include fixed effects for treatment group, week (5 levels: Weeks 2, 4, 6, 9, and 12), and the treatment group by week interaction. The baseline TTS, region, and age group at baseline will be included as covariates. The unstructured covariance matrix for repeated observations within patients will be used. The least squares means of the change in TTS from baseline at week 12 will be compared (the active treatment arm and the placebo arm) using a 2-sided test at the alpha=0.05 level of significance.

In addition, actual values and changes in the TTS from baseline to each visit will be summarized using descriptive statistics.

Analysis of Key Secondary Endpoints: A hierarchical (fixed-sequence) testing approach will be used for the analysis of the primary and key secondary endpoints to maintain the experiment-wise type I error rate of 5%. If an endpoint is not statistically significant, confirmatory hypothesis testing will not be carried out on the remaining hypotheses, and remaining hypotheses will be considered exploratory rather than confirmatory. The change in the TS-CGI (1) and C&A-GTS-QOL ADL subscale (3) scores from baseline to week 12 will be summarized and analyzed in the same fashion as the primary analysis, with the exception that the baseline value of the given endpoint will be included as the covariate. TS-PGII (2) will be analyzed using a Cochran-Mantel-Haenszel row mean score test with a modified ridit score that controls for age group.

Exploratory Analyses:

[redacted]

[redacted]

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

Analysis of Pharmacokinetic Endpoint: Samples collected for pharmacokinetic analysis will be quantified for α-HTBZ and β-HTBZ active metabolites and will be analyzed using population pharmacokinetic techniques. Analysis methods will be detailed in a separate population pharmacokinetic analysis plan. Exploratory pharmacokinetic/PD analysis may be performed on PD/safety endpoints.

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

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

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

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

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table of Abbreviations

Abbreviation or Specialist Term	Explanation
21CFR	Title 21 Code of Federal Regulations
ADHD	Attention Deficit Hyperactivity Disorder
α-HTBZ	alpha-dihydrotetrabenazine
ADL	activities of daily living
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase (SGOT)
AUC	area under the curve
β-HCG	beta-human chorionic gonadotropin
β-HTBZ	beta-dihydrotetrabenazine
bid	twice a day
BL	baseline visit
BP	blood pressure
BUN	blood urea nitrogen
CBIT	comprehensive behavioral intervention for tics
CBT	cognitive behavioral therapy
CDI-2	Children's Depression Inventory, Second Edition
CDMS	clinical data management system
CNS	central nervous system
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CST	Clinical Surveillance and Training
[redacted]	[redacted]
CYP	cytochrome P450
CYP2D6	cytochrome P450 2D6
DSM-V™	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

Abbreviation or Specialist Term	Explanation
ECG	electrocardiogram
ePRO	electronic patient-reported outcome
ET	early termination visit
FDA	Food and Drug Administration [United States]
GCP	Good Clinical Practice
GPSP	Global Patient Safety and Pharmacovigilance
[redacted]	[redacted]
C&A-GTS-QOL	Child and Adolescent Gilles de la Tourette Syndrome–Quality of Life
HD	Huntington disease
IB	Investigator's Brochure
ICH	International Council for Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IDMC	Independent Data Monitoring Committee
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IMP	investigational medicinal product
IND	Investigational New Drug [Application]
IRT	Interactive Response Technology
ITT	intent-to-treat
LDH	lactate dehydrogenase
LSO	local safety officer
MA	Marketing Authorization
MAOI	monoamine oxidase inhibitor
MINI Kid	Mini International Neuropsychiatric Interview For Children and Adolescents (version 6.0)
mITT	Modified Intent-to-Treat
[redacted]	[redacted]
NA	not available
NDA	New Drug Application
NOAEL	no-observed-adverse-effect level
OCD	obsessive-compulsive disorder
PD	pharmacodynamic
PGx	pharmacogenetics

Abbreviation or Specialist Term	**Explanation**
PND	postnatal day
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
SD-809/TEV-50717	deutetrabenazine
SLV	Since Last Visit
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
Tbil	total bilirubin
TD	tardive dyskinesia
TEAE	treatment-emergent adverse event
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
U	unscheduled visit
UDS	urine drug screen
ULN	upper limit of the normal range
USA	United States of America
VAS	visual analog scale
VMAT2	vesicular monoamine transporter 2
[redacted]	[redacted]
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 that frequently co-occurs with a variety of behavioral and psychiatric problems (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, developed deutetrabenazine (referred to

as TEV-50717, previously SD-809) that is eliminated more slowly than tetrabenazine. TEV-50717 has been shown to reduce plasma fluctuation and dosing frequency and thus can improve overall tolerability as compared to that of tetrabenazine. Data in patients receiving TEV-50717 for the treatment of chorea associated with Huntington disease (HD) demonstrate a favorable safety profile with low rates of neuropsychiatric adverse events. In TS patients with troublesome motor and phonic tics, preliminary efficacy and safety data for TEV-50717 have been generated in an open-label, Phase 1b pilot study (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 and for the treatment of chorea associated with TD on 30 August 2017.

1.2. Name and Description of IMP

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. TEV-50717 is provided for this study as 6-mg, 9-mg, 12-mg, 15-mg, and 18-mg oral tablets, all of which are identical in size, shape, and color (white). The investigational medicinal product (IMP) will be supplied in 40-count blister packs.

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

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).

1.3.1. Nonclinical Studies

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

1.3.1.1. Nonclinical Pharmacology

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

1.3.1.2. Nonclinical Pharmacokinetics and Drug Metabolism

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

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

1.3.1.3. Toxicology

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

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

Juvenile Toxicology: The effects of TEV-50717 on juvenile development was assessed in male and female rats with oral dosing from weaning (postnatal day [PND] 21) to PND 71, similar to human dosing from Year 2 through early adolescence and overlapping with TEV-50717 oral dosing in a general adult toxicology study. The effects of M1 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 NOAEL (no-observed-adverse-effect level) for toxicities in juvenile rats is lower than that in adults; however, the total (α+β)-HTBZ exposure multiples or safety margins comparing rat to humans at the adult and juvenile age categories are similar. The potential for increased sensitivity to the effects of TEV-50717 in pediatric patients is mitigated by 2 factors. First, the effects of TEV-50717 on behavior and weight gain recovered with cessation of test article administration in the juvenile rat toxicology study. Second, the clinical significance of tremors and reduced body weight gain in rats dosed with TEV-50717 are unclear because these findings were not adverse events of note in adults or adolescent patients. While hypoactivity in rats has the potential to relate to clinical observations of somnolence, this adverse effect is controlled with dose reduction. In clinical comparison, the adverse event profile of tetrabenazine in adult patients is qualitatively similar to patients from approximately 22 months to 18 years of age (Jain et al 2006, Kenney et al 2007, Porta et al 2008).

1.3.2. Clinical Studies

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

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

Further details may be found in the IB.

1.3.2.1. Clinical Pharmacology Studies

Seven Phase 1 clinical pharmacology studies were conducted in healthy adult subjects. In addition, sparse pharmacokinetic sampling was included in the Phase 3 studies with HD 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 the active metabolites of TEV-50717 based on the Phase 1 clinical pharmacology in healthy adult subjects were performed to support dose selection and pharmacokinetic characterization in a pediatric population. Subsequently, a further pharmacometric analysis of active metabolites following administration of TEV-50717 to adolescent TS patients with tics (Study SD-809-C-17) was recently completed. The results of these analyses are described in Section 1.3.2.3.

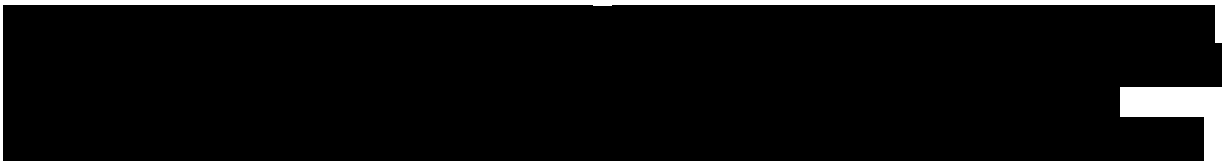
1.3.2.2. Clinical Safety and Efficacy Studies

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

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

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

Employing the structural model defined in Study SD-809-CLN-077, sequential and sparse pharmacokinetic sampling data obtained from Study SD-809-C-17 were combined with the Phase 1 data employed in Study SD-809-CLN-077 to estimate the exposure total of (α+β)-HTBZ in adolescent patients (age 12 to 18 years) with TS and to simulate exposure in adolescent and pediatric patients (age 6 to 11 years) with and without concomitant use of a strong CYP2D6 inhibitor across a range of doses (Appendix 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 provides the basis for the dosing recommendations in Section 5.1.

1.4. Known and Potential Risks and Benefits to Human 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 Drugs and Dosages

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

1.5.1. Justification for Dosage of Active Drug

The dose ranges to be evaluated in this study, based on body weight and CYP2D6 impairment status at baseline, were selected on the basis of the safety, preliminary efficacy, and population pharmacokinetic data generated from Study SD-809-C-17 (Table 2). In this study, TEV-50717 up to 18 mg twice daily (36 mg/day) was well tolerated and demonstrated 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 twice daily), a level previously demonstrated to be efficacious, safe, and well tolerated in patients with HD-associated chorea.

IMP will be titrated on a weekly basis for 7 weeks, based on investigator, patient, and parent/guardian assessments of tic reduction and adverse events. This dosing strategy is practical in a clinical setting and affords sufficient time between dose steps for efficacy and safety to be assessed. It is also consistent with the clinical application of tetrabenazine, another VMAT2 inhibitor with accepted efficacy in this population. A 5-week maintenance period is sufficient for stable treatment to allow evaluation of safety and efficacy at the target dose.

1.5.2. Justification for Use of Placebo

As TS is not a progressive neurological disorder, and available treatments are for symptomatic control, the use of placebo is justified in a short-term study where safety is carefully monitored.

Moreover, a placebo control is ideal for characterizing the efficacy and safety of an experimental agent in a new study population.

1.6. Compliance Statement

This study will be conducted in full accordance with the International Council for 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 children and adolescents, 6 through 16 years of age, with TS. Per selection criteria, the participants' tics need to be troublesome and cause distress or impairment based on the assessment of the patient, parent/guardian, and investigator. Based on these criteria, this is a study population in need of treatment.

1.8. Location and Study Duration

This study is planned to be conducted in North America, Russia, and Europe, at approximately 50 centers. It is expected to start in January 2018 and have a duration of approximately 15 months. Additional centers will be added, if needed. Expected duration of the study may also be extended dependent on enrollment and other factors.

2. PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1. Purpose of the Study

This is a Phase 2/3 study to evaluate the efficacy and safety of deutetrabenazine (TEV-50717) tablets for the reduction of motor and phonic tics associated with TS in children and adolescents 6 through 16 years of age.

2.2. Study Objectives

2.2.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of TEV-50717 to reduce motor and phonic tics associated with TS.

2.2.2. Secondary Objective

The secondary objective of the study is to evaluate the safety and tolerability of titration and maintenance therapy with TEV-50717.

2.3. Study Endpoints

2.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change in the TTS of the YGTSS from baseline to week 12.

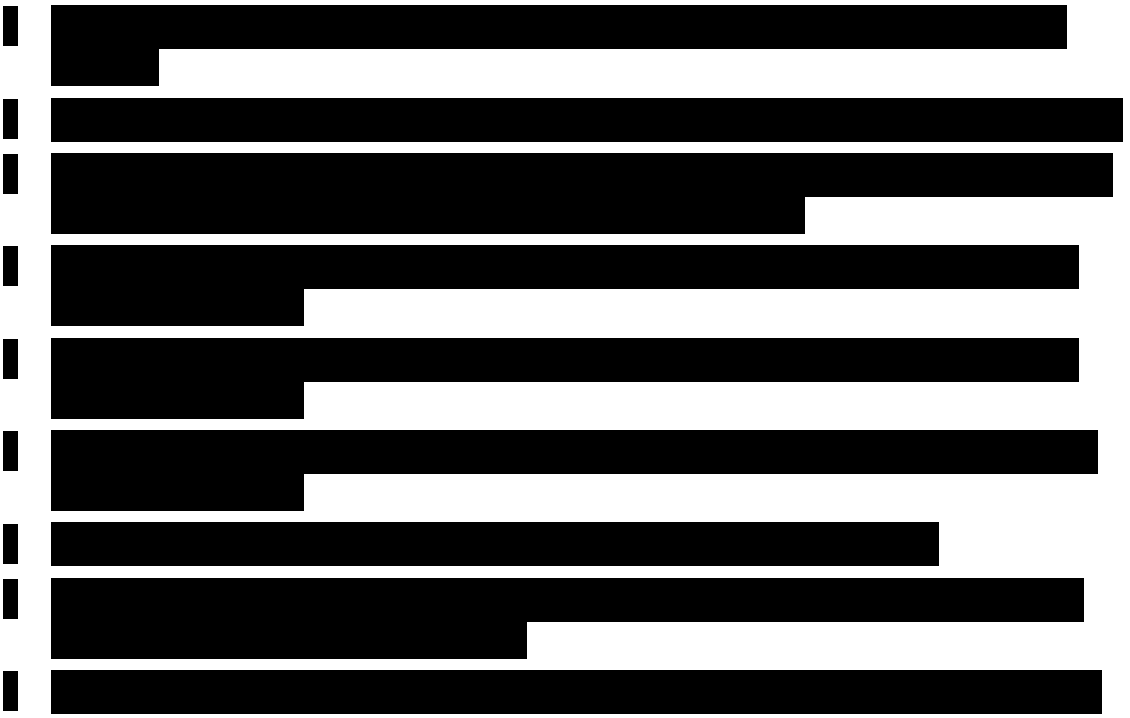
2.3.2. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are as follows:

1. Change in the TS-CGI score from baseline to week 12
2. Change in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) score from baseline to week 12
3. 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 baseline to week 12

2.3.3. Exploratory Endpoints

Exploratory endpoints are as follows:



2.3.4. Safety Endpoints

The safety endpoints for this study are as follows:

- incidence of adverse events
- observed values and changes from baseline in vital signs
- observed values and change from baseline in the Children's Depression Inventory, Second Edition (CDI-2), Parent and Self-report Profiles
- observed values in the Children's Columbia-Suicide Severity Rating Scale (C-SSRS)
- observed values in electrocardiogram (ECG) parameters and shifts from screening for clinically significant abnormal findings
- observed values and changes from screening in clinical laboratory parameters (hematology, chemistry, and urinalysis)

2.3.5. Pharmacokinetic Endpoint

The pharmacokinetics of the α- and β-HTBZ metabolites of TEV-50717, and other metabolites (as needed), will be explored based on sparse sampling at week 12.

3. STUDY DESIGN

3.1. General Design and Study Schema

3.1.1. Overall Design and Screening Period

This is a Phase 2/3, randomized, double-blind, placebo-controlled, parallel group study in which patients with tics associated with TS will be invited to participate. Patients who qualify for the study will be centrally randomized in a 1:1 ratio (stratified by age at baseline [6 to 11 years, 12 to 16 years]) to receive either TEV-50717 or placebo. Throughout the study, patients will interact regularly with investigative site personnel, in clinic and by telephone, for the evaluation of safety, tic severity, and behavioral status (in clinic only). The target dose for each patient receiving TEV-50717 will be based on body weight and CYP2D6 impairment status at baseline. Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor or are a CYP2D6 poor metabolizer based on blinded assessment of CYP2D6 genotype at baseline. CYP2D6 status will be used by Interactive Response Technology (IRT) for randomization into the study. The dose of IMP for each patient will be titrated to an optimal level followed by maintenance therapy at that dose. Investigators will be blinded to CYP status, with a dose cap for poor metabolizers prespecified by the IRT (Table 2). The overall treatment period will be 12 weeks in duration, including a titration period of 7 weeks, a maintenance period of 5 weeks, followed by a washout period of 1 week. [redacted] For the YGTSS, input from the caregiver/adult is required. For both the TS-PGII and [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 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.

Patients who complete the study may be eligible to begin participation in an open-label safety extension study (TV50717-CNS-30047) after the end of the washout period. At the week 13 visit, patients may choose to enter Study TV50717-CNS-30047 (on that day), or they will have an additional week to make a decision and return for day 1. Patients not participating in Study TV50717-CNS-30047 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).

3.1.2. Screening Period

The screening period in this study is up to 31 days. After informed consent/assent, depending on the child's age, as appropriate, is obtained, patients who are stable from a medical and psychiatric standpoint will undergo a screening evaluation, including medical history, physical and neurological examination, laboratory testing, and 12-lead ECG, along with rating scales to assess severity, frequency, and impairment of tics and comorbid TS symptoms and behavioral status.

At the discretion of the investigator, the screening visit may be divided into 2 visits if the visit length is felt to be too burdensome for the patient. If the screening visit is divided into 2 visits, the blood sample should be obtained during the first of the 2 visits. Patients who have received comprehensive behavioral intervention for tics (CBIT) for TS or cognitive behavioral therapy (CBT) for obsessive-compulsive disorder (OCD) may participate in this study as long as therapy was completed at least 4 weeks prior to screening. Patients will return to the clinic on day 1 to perform baseline procedures and to reconfirm eligibility. Patients may be rescreened 1 time if there is a change in the status of the patient regarding eligibility for the study. (Note: Details of rescreening must be approved and documented by the medical monitor and/or Clinical Surveillance and Training [CST] team.)

3.1.3. Titration Period

During the titration period (7 weeks), patients who remain eligible for participation in the study will be randomized in a 1:1 ratio stratified by age (6 to 11 years, 12 to 16 years) at the baseline visit (day 1), and that evening (ie, after the study visit) will receive 6 mg of blinded IMP with food. 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 at baseline, as shown in Table 2. Patients and their caregiver/adult will interact weekly with the clinical research staff, either by telephone contact or clinic visit from week 1 through week 7 of the titration period, in order to evaluate safety and establish a dose of IMP that optimally reduces tics and is well tolerated (optimal dose). Safety evaluations during titration 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 criteria is met:

- The investigator determines that 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 study medication 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 at baseline.

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 on that dose (ie, the dose should not be increased further) for the remainder of the titration period and throughout maintenance dosing, unless there is a change in symptoms during the titration period. If a patient experiences a “clinically significant” adverse event attributable to the IMP, the investigator will determine if a dose reduction or suspension is necessary. 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 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. At the end of the titration period, the patient's dose will be established for the maintenance period.

3.1.4. Maintenance Period

During the maintenance period (5 weeks), patients will continue to receive their maintenance dose, although dose reductions for adverse events are allowed. Patients will return to the clinic at weeks 9 and 12 for assessments of safety and efficacy. At week 12, 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-PGII, [redacted], [redacted], and C&A-GTS-QOL.

In addition, patients will undergo pharmacokinetic sampling at week 12.

3.1.5. Washout Period and Follow-up

All patients will discontinue IMP at the week 12 visit and will return 1 week later for evaluation of safety and tic reduction (week 13). Patients who complete the study may be eligible to begin participation in the open-label safety extension study TV50717-CNS-30047. For this study, the follow-up period is defined as 1 week of washout for patients who will participate in the open-label safety extension study TV50717-CNS-30047 and 2 weeks after the last dose of IMP (1 week after the end of the washout period) for patients who will not roll over into the open-label safety extension study TV50717-CNS-30047. At the week 13 visit, patients may choose to enter Study TV50717-CNS-30047 (on that day), or they will have an additional week to make a decision and return for day 1. Patients not participating in Study TV50717-CNS-30047 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).

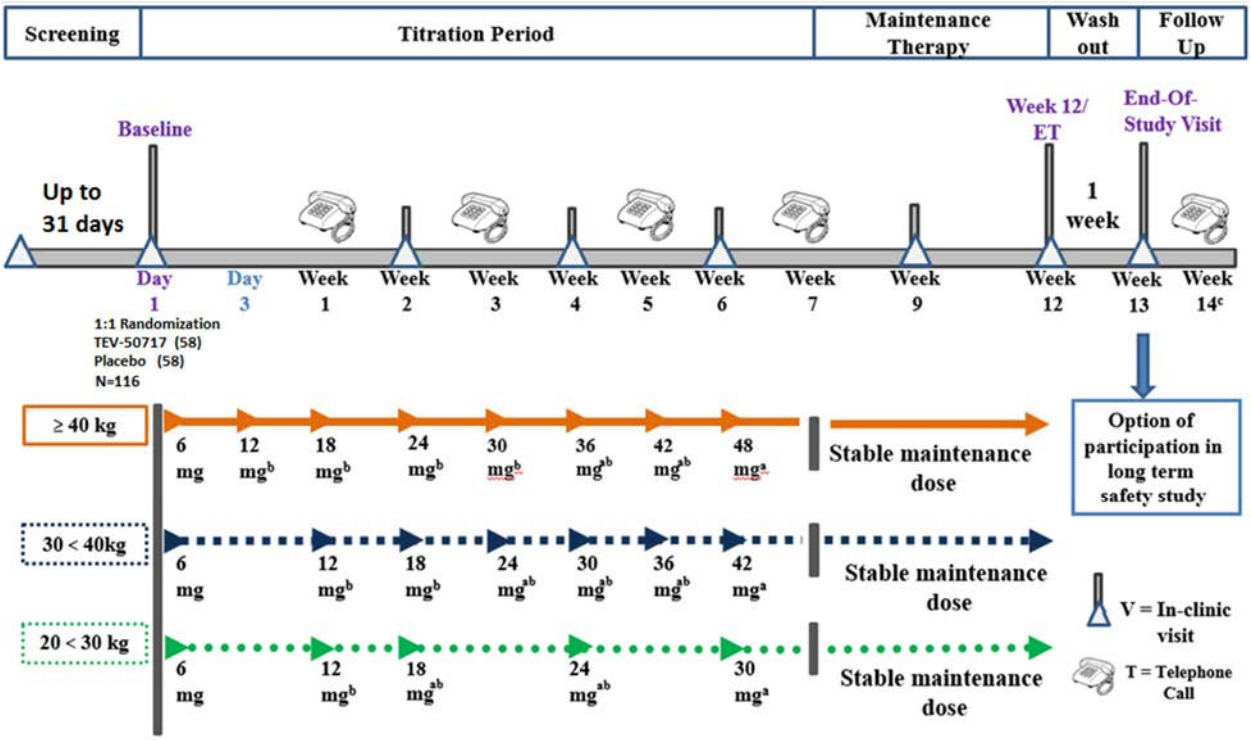
Prohibited drugs will remain the same during the washout period for patients who will participate in the open-label extension study TV50717-CNS-30047.

Patients who will not participate in the extension study (Study TV50717-CNS-30047) may begin/resume tic therapy medication after the first week of the washout period.

See Table 1 for study procedures and assessments.

See Figure 1 for study schema.

Figure 1: Overall Study Schema



[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] This is a telephone contact for safety evaluation, required only for patients who will not roll over into the open-label safety extension study TV50717-CNS-30047.
bid=twice a day; CYP=cytochrome P450; ET=early termination visit.

3.2. Justification for Study Design

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 (Study SD-809-C-17). Results of Study SD-809-C-17 supported further development of TEV-50717 as a treatment of TS.

Consequently, the standard placebo-controlled, double-blind study design (TEV-50717 versus placebo in a 1:1 ratio) was chosen for the next study (ie, this Phase 2/3 study) to determine whether IMP treatment results in a statistically significant effect on tics in patients with TS.

The justification for the choice of the comparator (placebo) is provided in Section 1.5.2, the choice of dosage is discussed in Section 1.5.1, while the justifications for the choice of the population and the inclusion and exclusion criteria for the study are provided in Section 1.7 and Section 4.3, respectively.

3.3. Primary and Secondary Efficacy Measures and Time Points

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

3.3.1. Primary Efficacy Measure and Time Points

YGTSS (to calculate TTS): Screening; baseline; and weeks 2, 4, 6, 9, 12, and 13.

3.3.2. Key Secondary Efficacy Measures and Time Points

1. TS-CGI: baseline and weeks 2, 4, 6, 9, 12, and 13
2. TS-PGII: baseline and weeks 2, 4, 6, 9, 12, and 13
3. C&A-GTS-QOL ADL subscale: baseline, week 6, and week 12

3.3.3. Exploratory Measures and Time Points

[redacted]

3.4. Safety Measures and Time Points

- 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 and week 12
- neurological examination: screening and week 12
- vital signs: screening; baseline; and weeks 2, 4, 6, 9, 12, and 13
  Note: orthostatic blood pressure (BP) and pulse at baseline and weeks 4 and 12
- MINI Kid: screening

- Children's C-SSRS
  - Baseline/screening scale: screening
  - Since Last Visit [SLV] scale: baseline and weeks 2, 4, 6, 9, 12, and 13
- CDI-2 (Parent and Self-Report versions): screening; baseline; and weeks 2, 4, 6, 9, 12, and 13
- 12-lead ECG: screening; baseline; and weeks 4, 6, and 12
- clinical laboratory tests (serum chemistry, hematology, and urinalysis): screening and week 12
- pregnancy testing: screening, baseline, and weeks 4 and 12
- drug screen: screening and week 12

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

3.5. Pharmacokinetic Measures and Time Points

Blood samples will be obtained for the measurement of plasma concentrations of TEV-50717 (deutetrabenazine), α-HTBZ, β-HTBZ, and other metabolites, as needed. Blood sampling for pharmacokinetic analysis will be performed at the week 12 visit. Two samples will be collected. The first sample will be collected upon arrival at the clinic. The second sample will be collected 2 to 3 hours after the first pharmacokinetic sample collection. The time between samples should be maximized in order to provide the most useful information.

A description of the pharmacokinetic measures is provided in Section 8.

3.6. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. Patients will be randomly assigned to receive treatment with TEV-50717 or matching placebo in a 1:1 ratio stratified by age at baseline (6 to 11 years, 12 to 16 years). Patients and investigators will remain blinded to treatment assignment during the study.

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

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

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

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

3.7. Maintenance of Randomization and Blinding

3.7.1. Randomization

Patient randomization codes will be maintained in a secure location within Syneos Health, Biometrics. At the time of analysis, when treatment codes are needed, the Syneos Health statistician assigned to the study will make a request to unblind and will receive the unblinded codes.

3.7.2. Blinding/Unblinding

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

For information about personnel who may be aware of treatment assignments, see Section 3.6. These individuals will not be involved in conduct of any study procedures or assessment of any adverse events.

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

When a blind is broken, the patient will be withdrawn from the study, and the event will be recorded onto 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. Treatment assignment should not be recorded in any study documents or source document.

In blinded studies, for adverse events that are defined as: suspected unexpected serious adverse reactions (SUSARs) (ie, reasonable possibility; see Section 7.1.4), Global Patient Safety and Pharmacovigilance (GPSP) may independently request that the treatment code be revealed (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, analysis, and reporting of the data.

3.7.3. 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 review of 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 may be present, and information is provided and discussed in a blinded fashion. During closed sessions, the only participants are members of the IDMC and the designated unblinded statistician (if approved to be present).

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

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

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

3.8. Drugs Used in the Study

3.8.1. IMP

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. TEV-50717 tablets are available in the following strengths: 6, 9, 12, 15, and 18 mg, all of which are identical in size, shape, and color (white). The IMP will be supplied in 40-count blister packs. The placebo tablets and packaging will match those for TEV-50717. Each blister pack (40-count tablets per dose strength per blister pack) will contain a sufficient supply of drug until the next specified visit/telephone contact, plus overage to account for potential delays in study visits.

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

3.8.2. Placebo

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

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

3.9. Drug Supply and Accountability

3.9.1. Drug Storage and Security

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

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

This study will consist of up to a 31-day screening period, a 12-week double-blind treatment period, and a 1-week washout period. Patients who complete the study may be eligible to begin participation in an open-label safety extension study TV50717-CNS-30047 after the end of the washout period. Patients not participating in Study TV50717-CNS-30047 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 14 weeks. 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). 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).

Please see Section 4.4 for the withdrawal criteria and procedures.

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

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), Section 7 (safety assessments), and Section 8 (pharmacokinetic and other assessments).

Table 1: Study Procedures and Assessments

	Screening	BL[a]	Titration							Maintenance		Follow-up		U
Study week[b]	**Up to 31 days**	**Day 1[c]**	**1 (Day 7)**	**2 (Day 14)**	**3 (Day 21)**	**4 (Day 28)**	**5 (Day 35)**	**6 (Day 42)**	**7 (Day 49)**	**9 (Day 63)**	**12/ET[d] (Day 84)**	**13 (Day 91**	**14[e] (Day 98)**	
Visit window (days)		**0 days**	**±3 days**									**±3 days from Week 12**		
In-clinic visit	X[f]	X		X		X		X		X	X	X		X
Telephone contact			X		X		X		X				X	
Evaluate/Adjust IMP			X[g]	X	X[g]	X	X[g]	X	X					X
Informed consent/assent	X													
Eligibility criteria	X	X												
Medical history and psychiatric history	X													
Demographics	X													
Vital signs and weight[h]	X	X[i]		X		X[i]		X		X	X[i]	X		X
Physical examination	X										X			X[j]
Neurological examination	X										X			X[j]
Height	X										X			X[j]
12-lead ECG[k]	X	X				X		X			X			X[j]
Pharmacokinetic blood sampling											X[l]			
Chemistry/Hematology/Urinalysis	X										X	X[m]		X[j]
Urine drug screen	X										X			
Randomization		X												
CYP2D6 genotype[n]	X													
β-HCG test[o]	X	X				X					X			X[j]

Table 1: Study Procedures and Assessments (Continued)

	Screening	BL[a]	Titration							Maintenance		Follow-up		U
Study week[b]	**Up to 31 days**	**Day 1[c]**	**1 (Day 7)**	**2 (Day 14)**	**3 (Day 21)**	**4 (Day 28)**	**5 (Day 35)**	**6 (Day 42)**	**7 (Day 49)**	**9 (Day 63)**	**12/ET[d] (Day 84)**	**13 (Day 91**	**14[e] (Day 98)**	
Visit window (days)		**0 days**	**±3 days**									**±3 days from Week 12**		
MINI Kid[p,q]	X													
CDI-2 (Parent and Self-report)[r]	X	X		X		X		X		X	X	X		X[j]
C-SSRS (Children's Baseline/Screen)[q]	X													
C-SSRS (Children's Since Last Visit)[q]		X		X		X		X		X	X	X		X[j]
YGTSS[s,t]	X	X		X[u]		X		X[u]		X[u]	X	X[u]		
TS-CGI[t]		X		X		X		X		X	X	X		
TS-PGII[t]		X		X		X		X		X	X	X		
[redacted][t]		X		X		X		X		X	X	X		
[redacted]		X		X		X		X		X	X	X		
[redacted]		X						X[v]			X	X[v]		
C&A-GTS-QOL[q]		X						X			X			
Dispense IMP[w]		X[x]		X[x]		X[x]		X[y]		X[y]				X[j]
Collect IMP				X		X		X		X	X			X[j]
Assess IMP accountability/compliance/supply			X[z]	X	X[z]	X	X[z]	X	X[z]	X	X			X[j]
Assess adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[aa]	X	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]

[a] The baseline visit will occur on the same day as the scheduled first dose of the IMP (day 1).

[b] Assessment to occur at the end of the study week.
[c] Patients will be provided with a diary to record critical information on dosing. The date and time of the last dose of study medication before the week 12 visit should be recorded in the diary by the patient or caregiver/adult. The site will document the date and time of the sample collection. Prior to the clinic visit on week 12, patients will be reminded to record the start time of their last meal and the time of their last dose in their diary.
[d] 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 14 (Section 3.13.4.2).
[e] This visit is a telephone contact for safety evaluation, required only for patients who will not roll over into the open-label safety extension study TV50717-CNS-30047.
[f] The screening visit may be conducted over 2 separate visits at the discretion of the investigator.
[g] Dose adjustment will be made by the investigator after telephone contact with the patient and caregiver/adult to evaluate tic reduction and adverse events.
[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] Assessment to be completed at investigator's discretion.
[k] All ECGs will be performed after at least 5 minutes rest in a supine or semi-supine position.
[l] Two samples will be collected. The first sample will be collected upon arrival at the clinic. The second sample will be collected 2 to 3 hours after the first pharmacokinetic sample collection. Patients with early morning visits (ie, within 2 hours of their scheduled AM dosing) should take their IMP dose in clinic after the first pharmacokinetic sample is collected.
[m] Patients with clinically significant laboratory abnormalities at week 12 will have those laboratory evaluations repeated at the week 13 visit.
[n] The patient's genotype for CYP2D6 will be blinded during the conduct of the study.
[o] For females who are postmenarchal or ≥12 years of age, a urine test will be administered at baseline and week 4, while a serum test will be administered at screening and week 12, and if clinically indicated.
p MINI Kid, (Children and Adolescents) modules to be used are: Major Depressive Episode (Module A), (Hypo) Manic Episode (Module D), OCD (Module J), Alcohol Dependence/Abuse (Module L), Substance Dependence/Abuse (Non-alcohol; Module M), ADHD (Module O), Conduct Disorder (Module P), and Psychotic Disorders and Mood Disorders with Psychotic Features (Module R).
[q] For children 13 years of age and under, interviews may be performed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information.
[r] Children 6 years of age at baseline will not complete the Self-report version; the caregiver/adult will complete the Parent version.
[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] Perform the Severity Ratings of OCD symptoms (Questions 1 through 10) only. Checklist does not need to be performed.
[w] Contact IRT and dispense IMP and patient diary.
[x] IMP 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 baseline weight-based dosing titration.

[y] Patients will receive doses for 3 weeks of treatment.

[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, and remind them to bring used and unused IMP blister packs 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, 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; BL=baseline visit; 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; OCD=obsessive-compulsive disorder; TS-CGI=Tourette Syndrome-Clinical Global Impression; TS-PGII=Tourette Syndrome-Patient Global Impression of Impact; [redacted]; U=unscheduled visit; YGTSS=Yale Global Tic Severity Scale.

3.13.1. Procedures for Screening and Enrollment

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 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 status of the patient regarding eligibility for the study. (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 baseline visit. The screening visit may be conducted over 2 separate visits at the discretion of the investigator. The following procedures will be performed at screening:

- obtain written informed consent/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 chemical, hematological, and urine analyses
- obtain a blood sample (3 mL) for analysis of CYP2D6 genotype
- perform urine drug screen (UDS)
- perform a serum pregnancy (beta-human chorionic gonadotropin [β-HCG]) test (only in females who are postmenarchal or ≥12 years of age)
- administer the following questionnaires (Note: For MINI 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.):

- MINI Kid (Note: The following modules will be used: 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], 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 (Note: Children 6 years of age at baseline will not complete the Self-report version; the caregiver/adult will complete the Parent version.)
- C-SSRS (children's baseline/screening)
- YGTSS (Input from the caregiver/adult is required.)

- 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, especially at the baseline and week 12/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 IMP Treatment (Baseline/Day 1)

Patients who meet the inclusion/exclusion criteria at screening will continue to the baseline visit, when baseline evaluations will be conducted.

The following procedures will be performed at baseline:

- conduct clinic visit
- review eligibility (inclusion and exclusion) criteria
- measure vital signs (orthostatic pulse and BP [after standing for at least 3 minutes], body temperature, and respiratory rate)
- measure 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 urine pregnancy (β-HCG) test (only in females who are postmenarchal or ≥12 years of age)
- randomization with stratification by age at baseline (6 to 11 years, 12 to 16 years)

- administer the following questionnaires (Note: For C-SSRS, [redacted] and C&A-GTS-QOL, children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information. The YGTSS, TS-CGI, TS-PGII, and [redacted] questionnaires should be performed before any blood draws or ECG assessments.):
  - CDI-2, Parent and Self-report (Note: Children 6 years of age at baseline will not complete the Self-report version; the caregiver/adult will complete the Parent version.)
  - C-SSRS (children's SLV)
  - YGTSS (Input from the caregiver/adult is required.)
  - TS-CGI
  - TS-PGII (Input from the caregiver/adult is permitted.)
  - [redacted]
  - [redacted]
  - [redacted]
  - C&A-GTS-QOL
- dispense IMP (patients will receive doses for 2 weeks [current dose level and next dose level] to cover the telephone contacts) and patient diary
- provide patients with a diary to record critical information on dosing
- review concomitant medications
- inquire about adverse events

A patient who is not enrolled in the study on the basis of results of baseline assessments (eg, because inclusion and exclusion criteria were not met or enrollment did not occur within the specified time) may be screened again 1 more 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.)

Patients will be assigned a permanent unique number at screening (see Section 3.13.1). Patients who continue to meet the inclusion/exclusion criteria at baseline will be randomized to a treatment (active or placebo) using an IRT, and the appropriate IMP will be dispensed.

3.13.3. Procedures During IMP Treatment

3.13.3.1. Titration Period (Baseline/ Day 1 Through 7)

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

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 blister packs 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 continue titration 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. Clinic Visits (Weeks 2, 4, and 6)

The following procedures/assessments will be performed at in-person 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 only, orthostatic BP and pulse should be measured after the patient is in standing position for at least 3 minutes
- measure weight (Note: Weight must be measured with shoes and outerwear off)
- perform 12-lead ECG (weeks 4 and 6 only [Note: ECG will be performed after at least 5 minutes rest in a supine or semi-supine position.])
- perform urine pregnancy (β-HCG) test at week 4 (only in females who are postmenarchal or ≥12 years of age)
- administer the following questionnaires (Note: For C-SSRS, [redacted], and C&A-GTS-QOL, children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information. The YGTSS, TS-CGI, TS-PGII, and [redacted] questionnaires should be performed before any blood draws or ECG assessments.):

  - CDI-2, Parent and Self-report (Note: Children 6 years of age at baseline will not complete the Self-report version; the caregiver/adult will complete the Parent version.)
  - C-SSRS (children's SLV)
  - YGTSS (Note: At weeks 2 and 6, 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 caregiver/adult is required.)
  - TS-CGI
  - TS-PGII (Input from the caregiver/adult is permitted.)
  - [redacted]
  - [redacted]
  - [redacted]
  - C&A-GTS-QOL (week 6 only)
- dispense IMP (patients will receive doses for 2 weeks at week 2 and week 4 visits [current dose level and next dose level] and for 3 weeks at week 6 visit to cover the telephone contacts) and patient diary
- assess drug accountability and compliance
- collect used and unused IMP blister packs
- inquire about adverse events
- review concomitant medications

3.13.3.2. Maintenance Period

3.13.3.2.1. Week 9

The following procedures/assessments will be performed at the in-person clinic visit during the maintenance period of the study at week 9:

- conduct clinic visit
- 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 and [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, TS-PGII, and [redacted] questionnaires should be performed before any blood draws or ECG assessments.):

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

- dispense IMP (patients will receive doses for 3 weeks) and patient diary
- assess drug accountability and compliance
- collect used and unused IMP blister packs
- inquire about adverse events
- review concomitant medications

3.13.3.2.2. Week 12/Early Termination

Dosing requirements for the week 12 visit must be followed to ensure appropriate pharmacokinetic sample collection. Patients with early morning visits (ie, within 2 hours of their scheduled AM dosing) should take their dose in clinic after the first pharmacokinetic sample is collected. The date and time of the last dose of study medication before the week 12 visit should be recorded in the diary by the patient or caregiver/adult. The site will document the date and time of the sample collection. Prior to the clinic visit on week 12, patients will be reminded to record the start time of their last meal and the time of their last dose in their diary. The following procedures/assessments will be performed at the in-person clinic visit at week 12/early termination:

- conduct clinic visit
- if a patient is withdrawn due to an adverse event, a blood sample for IMP measurement should be taken, if possible. **For week 12 visit only:** Collect 2 blood samples (5 mL each) for pharmacokinetic analysis (initial and 2 to 3 hours thereafter as specified in Table 1)
- measure vital signs (orthostatic pulse and BP [after standing for at least 3 minutes], 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 chemical, hematological, and urine analyses
- perform UDS
- perform serum pregnancy (β-HCG) test (only in females who are postmenarchal or ≥12 years of age)
- administer the following questionnaires (Note: For C-SSRS, [redacted] and C&A-GTS-QOL, children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information. The YGTSS, TS-CGI, TS-PGII, and [redacted] questionnaires should be performed before any blood draws or ECG assessments.):
  - CDI-2, Parent and Self-report (Note: Children 6 years of age at baseline will not complete the Self-report version; the caregiver/adult will complete the Parent version.)
  - C-SSRS (children's SLV)
  - YGTSS (Input from the caregiver/adult is required.)
  - TS-CGI
  - TS-PGII (Input from the caregiver/adult is permitted.)
  - [redacted]
  - [redacted]
  - [redacted]
  - C&A-GTS-QOL
- assess drug accountability and compliance
- collect used and unused IMP blister packs
- inquire about adverse events
- review concomitant medications

3.13.4. Procedures After IMP Treatment

Patients who participate in the study in compliance with the protocol for at least 12 weeks of double-blind treatment will be considered to have completed the study. See Section 12.4 for the definition of the end of the study.

All patients will discontinue IMP at the week 12 visit and will return 1 week later for evaluation of safety and tic reduction (week 13 visit; see Section 3.13.4.1). Patients who complete the study may be eligible to begin participation in an open-label safety extension study TV50717-CNS-30047. Patients not participating in Study TV50717-CNS-30047 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 14 visit]; see Section 3.13.4.2).

For patients who withdraw prematurely an early termination visit (see Section 3.13.3.2.2 for applicable procedures) 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 14 (Section 3.13.4.2). Additional details for patients who withdraw prematurely from the study are described in Section 4.4.

As appropriate, patients should be treated with standard of care following termination of the study.

Data from any efficacy evaluations performed after the specified time will not be collected on the CRF; in the event, however, that such data are collected, these data will not be analyzed. Patients with ongoing adverse events or clinically significant abnormal laboratory test results (as interpreted by the investigator) will be monitored as described in Section 4.4 and Section 7.1.2.

3.13.4.1. Week 13

The following procedures/assessments will be performed at the in-person clinic visit at week 13:

- conduct clinic visit
- measure vital signs (pulse, BP, body temperature, and respiratory rate)
- measure weight (Note: weight must be measured with shoes and outerwear off)
- for patients with clinically significant laboratory abnormalities at week 12, repeat those laboratory evaluations at this visit
- administer the following questionnaires (The YGTSS, TS-CGI, TS-PGII, and [redacted] questionnaires should be performed before any blood draws or ECG assessments.):
  - CDI-2, Parent and Self-report (Note: Children 6 years of age at baseline will not complete the Self-report version; the caregiver/adult will complete the Parent version.)
  - C-SSRS (children's SLV; Note: Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information.)
  - YGTSS (Note: 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] (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.)
- [redacted] (Note: Perform the Severity Ratings of OCD symptoms [Questions 1 through 10] only. Checklist assessments do not need to be performed. 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.)

- inquire about adverse events
- review concomitant medications

3.13.4.2. Week 14

For patients not rolling over into open-label safety extension study, following procedures/assessments will be performed via **telephone contact** at week 14:

- inquire about adverse events
- review concomitant medications

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 as deemed necessary by the investigator or at the request of the patient or caregiver/adult. 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 in-clinic unscheduled visits:

- conduct clinic visit
- evaluate and/or 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 a urine/serum pregnancy (β-HCG) test (only in females who are postmenarchal or ≥12 years of age)
- administer the following questionnaires:
  - CDI-2, Parent and Self-report (Note: Children 6 years of age at baseline will not complete the Self-report version; the caregiver/adult will complete the Parent version.)
  - C-SSRS (children's SLV; Note: Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information.)
- dispense additional IMP and patient diary, if applicable
- collect used and unused IMP blister packs
- 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 sponsor or Syneos Health (see Section 11.1.2).

4.1. Patient Inclusion Criteria

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

a. Patient is 6 to 16 years of age, inclusive, at baseline.

b. Patient weighs at least 44 pounds (20 kg) at baseline.

c. Patient meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V™) diagnostic criteria for TS and, in the opinion of the investigator, patient, and caregiver/adult, the patient's active tics are causing distress or impairment.

d. Patient has a TTS of 20 or higher on the YGTSS at screening and baseline.

e. Patient is able to swallow study medication whole.

f. Patient and caregiver/adult are willing to adhere to the medication regimen and to comply with all study procedures.

g. Patient is in good general health, as indicated by medical and psychiatric history as well as physical and neurological examination.

h. In the investigator's opinion, the patient and caregiver/adult have the ability to understand the nature of the study and its procedures, and the patient is expected to complete the study as designed.

i. Patient and caregiver/adult provide written informed consent/assent, depending on the child's age, as appropriate, according to local regulations.

j. Females who are postmenarchal or ≥12 years of age may be included only if they have a negative β-HCG test at baseline or are sterile. Definitions of sterile are given in Appendix L.

k. Females who are postmenarchal or ≥12 years of age whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study (ie, starting at screening) and for 30 days or 5 half-lives, whichever is longer after the last dose of IMP. Further details are included in Appendix L.

4.2. Patient Exclusion Criteria

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

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

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

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

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

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

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

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

   – previous suicidal preparatory acts or behavior

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

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

h. Patient has clinically significant OCD at baseline that, in the opinion of the investigator, is the primary cause of impairment.

i. Patient has received CBIT for TS or CBT for OCD within 4 weeks of screening.

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

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

   – within 4 weeks: cannabidiol oil and valbenazine

   – within 21 days: Reserpine

   – within 14 days: Neuroleptics (oral), typical and atypical antipsychotics (see Appendix A), 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 and no changes to dose or frequency are anticipated during the course of the study.

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

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

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

   – Note: Use of guanfacine or clonidine is allowed regardless of indication (ie, if prescribed for tics or 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. If discontinuation of either medication is anticipated due to ineffectiveness, poor tolerability, or patient/caregiver preference, discontinuation should occur 4 or more weeks prior to the screening visit.

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

l. Patient has an unstable or serious medical illness at screening or baseline

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 >480msec (with right bundle branch block) on 12-lead ECG at screening, OR requires treatment with drugs known to prolong the QT interval (see Appendix A, Table 6 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 MAOI within 14 days of the baseline 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 and received IMP/intervention within 30 days or 5 drug half-lives of baseline, whichever is longer.

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 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.

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 (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 Sections 4.3 and 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 3.7.2). 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 3.7, 3.11, 3.13.4, 5.4, and 7.1.7.

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 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 3.13.3.2.2.

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).

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

5. TREATMENT OF PATIENTS

5.1. Drugs Administered During the Study

IMP (see Section 3.8) will be administered as oral tablets at a starting dose of 6 mg. Titration schemes based on body weight at baseline are shown in Table 2. The maximum daily dose is determined by body weight and CYP2D6 impairment status at baseline. 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.

IMP will be dispensed in the clinic. Patients will receive doses for 2 weeks at baseline, week 2, and week 4 visits (current dose level and next dose level) to cover the telephone contacts. At week 6 and week 9 visits, patients will receive doses for 3 weeks.

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 at the baseline visit, as shown in Table 2.
- 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. 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 must be notified**.
- During the titration period, the dose of the IMP will be adjusted weekly according to Table 2 to identify a dose level that optimally reduces tics and is well tolerated. Investigators will be blinded to CYP status, with a dose cap for poor metabolizers prespecified by the IRT.

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

Table 2: Maximum Daily Dose of IMP by Study Day and Weight Category at Baseline

	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 (ie, Days 8, 15, 22, 29, 36, and 43), as applicable.
[b] Patients will receive 6 mg on days 1 and 2, and 12 mg starting on day 3.
bid=twice a day; CYP=cytochrome P450; IMP=investigational medicinal product.
Note: CYP impaired patients are those 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.

5.2. Restrictions

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

While patients receiving strong CYP2D6 inhibitors such as paroxetine, fluoxetine, and bupropion at baseline may be enrolled into this study, the addition or removal of strong CYP2D6 inhibitors during treatment is discouraged as this would have an effect on exposure to active circulating drug. If the addition or removal of a strong CYP2D6 inhibitor is required from a clinical perspective, the medical monitor should be contacted so an appropriate change in IMP can be made. The use of quinidine and terbinafine are prohibited (see Appendix A, Table 8).

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 Therapy or Medication

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.

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.

Medications that are allowed, provided that conditions outlined in the table are met, are shown in Appendix A, Table 5.

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 medications that are associated with QTc prolongation are listed in Appendix A, Table 6, while prohibited antipsychotic drugs are listed in Appendix A, Table 7.

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 IMP 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.**

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 significant, the laboratory test should be repeated at least once. If the abnormality in the repeated laboratory test is consistent with the prior laboratory test, the IMP must be suspended. 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 35 mL, as detailed in Table 3.

Table 3: Blood Volumes

Type of samples	Volume per sample	Total number of samples	Total volume
Clinical laboratory (chemistry/hematology)	10 mL	2	20 mL
Pharmacokinetic	5 mL	1 time point (week 12) × 2 samples	10 mL
CYP2D6 genotyping	3 mL	1	3 mL
Optional pharmacogenetic sample	2 mL	1	2 mL
Total			**35 mL**

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

6. ASSESSMENT OF EFFICACY

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

6.1. Primary Efficacy Measure and Justification

The primary efficacy measure is the TTS of the YGTSS.

The YGTSS is administered at screening; baseline; and weeks 2, 4, 6, 9, 12, and 13:

- Complete assessment (Checklist and Severity Ratings) at screening, baseline, and weeks 4 and 12
- Severity Ratings assessment only at weeks 2, 6, 9, and 13
- Input from caregiver/adult is required for all patients irrespective of age.

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

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

A reference sample is provided in Appendix G.

6.2. Key Secondary Efficacy and Exploratory Measures

6.2.1. Tourette Syndrome–Clinical Global Impression

The TS-CGI is administered at baseline and at weeks 2, 4, 6, 9, 12, and 13. 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.

6.2.2. Tourette Syndrome-Patient Global Impression of Impact

The TS-PGII is administered at baseline and weeks 2, 4, 6, 9, 12, and 13. 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.

6.2.3. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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

The C&A-GTS-QOL is administered at baseline, week 6, and week 12. Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information.

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

A reference sample is provided in Appendix K.

6.2.5. [redacted]

[redacted]

6.2.6. [redacted]

[redacted]

[redacted]

[redacted]

6.2.7. [redacted]

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel by evaluating the following: 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 (Note: A condition recorded as pre-existing that is intermittently symptomatic [eg, headache] and that occurs during this study should be recorded as an adverse event.)
- drug interactions
- events occurring during diagnostic procedures or during the 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 study treatment are not considered adverse events.)

7.1.2. Recording and Reporting 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. For this study, the follow-up period for recording of adverse events is defined as 1 week of washout for patients who will participate in the open-label safety extension study TV50717-CNS-30047 and 2 weeks after the last dose of IMP for patients who will not roll over into Study TV50717-CNS-30047.

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; 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 IMP

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

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

For recording of serious adverse events, the study period is defined for each patient as the time period from signature of the informed consent/assent form to the end of the follow-up period, as defined in Section 7.1.2. If the investigator becomes aware of serious adverse events occurring in a patient after the end of the follow-up period, the serious adverse events should be reported to the sponsor 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 a life-threatening adverse event (ie, the patient was at risk of death at the time of the event); it does not refer to an event which hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event.

  Hospitalizations scheduled before the patient 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
- 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 alkaline phosphatase [ALP])

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

7.1.5.2. Expectedness

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

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

The sponsor's GPSP 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 of that patient has ended should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the 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 GPSP.

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

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

Additional information includes:

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

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

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

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

For all countries, the sponsor's GPSP will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/Extensible Markup Language (XML) file to the LSO/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.

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

Note: Although pregnancy is not a serious adverse event, the process for reporting a pregnancy is the same as that for reporting a serious adverse event, but using the pregnancy form (see Section 7.3).

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 regulatory authorities (and IEC/IRB, as appropriate), other action may be required, including the following:

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- modifying the existing consent form and informing current study participants of new findings

- modifying listings of expected toxicities to include adverse events newly identified as related to TEV-50717

7.1.6. Protocol-Defined Adverse Events of Special Interest

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

7.1.7. Withdrawal Due to an Adverse Event

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

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

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

7.1.8. Protocol Deviations Because of an Adverse Event

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

7.2. Psychometric Rating Scales

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

7.2.1. Mini International Neuropsychiatric Interview for Children and Adolescents

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

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

A reference sample is provided in Appendix C.

7.2.2. Columbia-Suicide Severity Rating Scale

The C-SSRS children's baseline/screening scale assesses past and current suicidal ideation and behaviors to determine suicide risk and is administered at screening. The C-SSRS children's SLV scale is administered at baseline and at weeks 2, 4, 6, 9, 12, and 13. Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information. The C-SSRS is an interview by trained study personnel.

Suicidal ideation

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

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

Suicidal behavior

- Actual attempt:

  If patients report any suicidal behavior that is an actual attempt as assessed in the C-SSRS, they will be evaluated immediately by the study investigator, referred for psychiatric evaluation, and terminated from the study.

- Interrupted attempt, aborted attempt, or Preparatory Acts or Behavior:

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

A reference sample is provided in Appendix E.

7.2.3. Children's Depression Inventory, Second Edition

The CDI-2 (parent and self-report profiles) is administered at screening, baseline, and weeks 2, 4, 6, 9, 12, and 13. As the CDI-2 is designed for children 7 to 17 years of age, children 6 years of age at baseline will not complete the Self-report version; the caregiver/adult will complete the Parent version.

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

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

A reference sample is provided in Appendix 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 individual 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 baseline, provided no IMP was given. All female patients who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous, elective, or voluntary abortion). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after withdrawal from the study will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy in the female patients 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:

1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.
2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied. Any dose of IMP (whether the test IMP or placebo), whether taken intentionally or unintentionally in excess of the dose 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 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 laboratory manual and by the judgement of the investigator. A laboratory test result that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event, and monitored as described in Section 7.1.2. An event may include a laboratory or diagnostic test abnormality (once confirmed by repeated testing) that results in the withdrawal of the patient from the study, the temporary or permanent cessation 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, 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 4.

Table 4: Clinical Laboratory Tests

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

7.5.2. Other Clinical Laboratory Tests

7.5.2.1. Human Chorionic Gonadotrophin Test

Human chorionic gonadotrophin 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 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.

7.5.3. Cytochrome P450 2D6 Genotyping

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

This assessment potentially includes the association analysis of the variation in CYP2D6 gene with clinical treatment responses to the IMP (eg, efficacy, pharmacokinetics, tolerability, and safety features or disease susceptibility and severity features). See Section 8.3.1 for further details.

7.6. Vital Signs

Vital signs (pulse, BP, body temperature, and respiratory rate) 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 pulse and BP are measured, the patient must rest in a supine or semi-erect/seated position for at least 5 minutes. (The same position and arm should be used each time vital signs are measured for a given patient). At baseline, week 4, and week 12, orthostatic BP and pulse will be measured after the patient is in a standing position for at least 3 minutes.

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.

7.7. Electrocardiography

A 12-lead ECG will be conducted 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-baseline QTcF value >500 msec or change from baseline >60 msec is found, the investigator should repeat the ECG assessment twice and compare the average of the 2 pre-treatment QTcF values (baseline and screening) to the average of the 3 post-baseline QTcF values. The IMP must be stopped for any confirmed post-baseline QTcF value >500 msec or increase from baseline >60 msec.

7.8. Physical Examinations

Physical examination, including height and weight, general appearance, skin, head, eyes, ears, nose, throat, neck, lymph nodes, cardiovascular, respiratory, musculoskeletal, abdominal, and extremities will be performed at the time points detailed in Table 1.

Weight must be measured with shoes and outerwear off.

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

7.9. Assessment of Suicidality

TEV-50717 is considered to be 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.

Baseline 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.

Depression and Suicidality as an Adverse Event

Families and caregivers of subjects in Study 30046 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 Therapy or Medication

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

Medications that are allowed, provided that conditions outlined in the table are met, are shown in Appendix A, Table 5. The tables of 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. Prohibited medications that are associated with QTc prolongation are listed in Appendix A, Table 6, while prohibited antipsychotic drugs are listed in Appendix A, Table 7.

7.12. Methods and Timing of Assessing, Recording, and Analyzing Safety Data

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

Methods and timing 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 3.7.3.

8. ASSESSMENT OF PHARMACOKINETICS AND SCREENING ASSESSMENTS

8.1. Pharmacokinetic Assessment

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

Blood sampling for pharmacokinetic analysis will be performed at the week 12 visit. Two samples will be collected. The first sample will be collected upon arrival at the clinic. The second sample will be collected 2 to 3 hours after the first pharmacokinetic sample collection. The time between samples should be maximized in order to provide the most useful information. Patients with early morning visits (ie, within 2 hours of their scheduled AM dosing) should take their dose in the clinic after the first pharmacokinetic sample is collected.

Patients will be provided with a diary to provide critical information on dosing before the week 12 visit. The date and time of the last dose of study medication before the week 12 visit should be recorded in the diary by the patient or caregiver/adult. The site will document the date and time of the sample collection. Prior to the clinic visit at week 12, patients will be reminded to record the start time of their last meal and the time of their last dose in their diary.

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

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

8.2. Pharmacodynamics Assessment

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

8.3. Pharmacogenetics

8.3.1. CYP2D6 Genotyping/Pharmacogenetics

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

related diseases. The final list of genes to be evaluated will be determined at the time of analysis to be able to account for the most current research.

9. STATISTICS

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

9.1. Sample Size and Power Considerations

It is estimated that approximately 58 patients per arm will enable a power of at least 90% to detect a beneficial standardized effect of 63% or more when the TEV-50717 arm is compared to placebo (difference of 6.0 in the change from baseline to week 12 in TTS, assuming a standard deviation of 9.5 in each arm) in a 2-sided type I error rate of 5% after accounting for potential dropouts.

9.2. Analysis Sets

9.2.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all randomized patients. In this population, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

9.2.2. Safety Analysis Set

The safety analysis set will include all patients who receive at least 1 dose of IMP. In this population, treatment will be assigned based upon the treatment patients actually receive, regardless of the treatment to which they were randomized.

9.2.3. Modified Intent-to-Treat Analysis Set

The Modified Intent-to-Treat (mITT) analysis set will include all patients in the ITT population who receive at least 1 dose of IMP and have both a baseline and at least 1 post-baseline YGTSS assessment. In this population, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received. All primary and secondary analyses will be based on the mITT set.

9.2.4. Per-Protocol Analysis Set

The per-protocol analysis set will include patients who are compliant with study medication (80% to 105%), have a YGTSS assessment at baseline and at week 9 or week 12, who have not taken prohibited concomitant medications as indicated in exclusion criterion, and who have no

major protocol deviations that affect the validity of the efficacy measurements. The list of protocol deviations will be reviewed before unblinding and major protocol deviations that could affect the primary and secondary variables will be determined. All exclusions from the per-protocol analysis set will be reviewed in the blinded data review meeting before database lock.

9.3. Data Handling Conventions

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

9.4. Study Population

The mITT analysis set (see Section 9.2) will be used for all efficacy summaries and analyses unless otherwise noted. The safety analyses set will be used for all safety summaries. Sensitivity analyses of primary and key secondary endpoints will be conducted using the per-protocol analysis set. Summaries will be presented by treatment group and for all patients.

9.4.1. Patient Disposition

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

9.4.2. Demographic and Baseline Characteristics

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

9.5. Efficacy Analysis

9.5.1. Primary Endpoint

The primary efficacy endpoint for this study is the change in the TTS (of the YGTSS) from baseline to week 12.

9.5.2. Key Secondary Endpoints

Key secondary endpoints for this study are as follows:

1. Change in the TS-CGI score from baseline to week 12
2. Change in the TS-PGII score from baseline to week 12
3. Change in the C&A-GTS-QOL ADL subscale score from baseline to week 12

9.5.3. Exploratory Endpoints

Exploratory endpoints for this study are as follows:

9.5.4. Planned Method of Analysis

The mITT analysis set (see Section 9.2) will be used for all efficacy analyses. Summaries will be presented by treatment group.

9.5.4.1. Primary Efficacy Analysis

The primary analysis will be a mixed-model, repeated-measures with the change in the TTS as the dependent variable. The model will include fixed effects for treatment group, week (5 levels: weeks 2, 4, 6, 9, and 12), and the treatment group by week interaction. The baseline TTS, region, and age group at baseline (2 levels: 6 to 11 years, 12 to 16 years) will be included as covariates. The unstructured covariance matrix for repeated observations within patients will be used. In case that the model does not converge, the Maximum-Likelihood estimation method will be used instead of the default Restricted Maximum-Likelihood. If the model still does not converge, then a simpler covariance structure with fewer parameters will be used, according to the following order: Heterogeneous Autoregressive (1), Heterogeneous Compound Symmetry, Autoregressive (1), and Compound Symmetry. The least squares means of the change in TTS from baseline at week 12 will be compared (the active treatment arm and the placebo arm) using a 2-sided test at the alpha=0.05 level of significance.

In addition, actual values and changes in the TTS from baseline to each visit will be summarized using descriptive statistics.

9.5.4.2. Sensitivity Analysis

Sensitivity analyses for missing data, the statistical model, and the increase in sample size will be provided in the statistical analysis plan.

9.5.4.3. Key Secondary Efficacy Analyses

A hierarchical (fixed-sequence) testing approach will be used for the analysis of the primary and key secondary endpoints to maintain the experiment-wise type I error rate of 5%. If an endpoint is not statistically significant, confirmatory hypothesis testing will not be carried out on the remaining hypotheses, and remaining hypotheses will be considered exploratory rather than confirmatory. The change in the TS-CGI (1) and C&A-GTS-QOL ADL subscale (3) scores from baseline to week 12 will be summarized and analyzed in the same fashion as the primary analysis, with the exception that the baseline value of the given endpoint will be included as the covariate. TS-PGII (2) will be analyzed using a Cochran-Mantel-Haenszel row mean score test with a modified ridit scoring that controls for age group.

9.5.4.4. Exploratory Analyses

[redacted]

[redacted]

9.6. Multiple Comparisons and Multiplicity

The hierarchical testing method will be used to maintain the experiment-wise type I error of 5% level for the primary and key secondary analyses. The primary efficacy endpoint will first be tested at the 5% type I error level. If the p-value of the primary analysis is ≤0.05, the secondary hypotheses will be tested in the order listed for the secondary endpoints (Section 9.5.2) until either an analysis produces a p-value >0.05 or all analyses result in a p-value ≤0.05.

9.7. Safety Endpoints and Analysis

Safety analyses will be performed on the safety analysis set.

9.7.1. Safety Endpoints

Safety endpoints for this study are as follows:

- incidence of adverse events
- observed values and changes from baseline in vital signs
- observed values and change from baseline in the CDI-2 (Parent and Self-report versions)
- observed values in the C-SSRS
- observed values in ECG parameters and shifts from screening for clinically significant abnormal findings
- observed values and changes from screening in clinical laboratory parameters (hematology, chemistry, and urinalysis)

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, adverse events determined by the investigator to be related to study treatment, serious adverse events, and adverse events causing withdrawal from the study. Summaries will be presented by treatment group and for all patients. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

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

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

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

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

9.8. Pharmacokinetic Analysis

The pharmacokinetic endpoint is listed in Section 2.3.5. Samples collected for pharmacokinetic analysis will be quantified for α-HTBZ and β-HTBZ of TEV-50717, and other metabolites (as needed), will be analyzed using population pharmacokinetic techniques. Analysis methods will be detailed in a separate population pharmacokinetic analysis plan. Exploratory pharmacokinetic/PD analysis may be performed on PD/safety endpoints.

9.9. Planned Interim Analysis

No interim analysis is planned for this study.

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 clinical study report, 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 IMP administration; 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 Standard Operating Procedures (SOPs), the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the sponsor and the investigator. The main responsibilities of the study monitor 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 [redacted] within 48 hours of becoming aware of the issue.

For complaints involving a device or other retrievable item, it is required that the device (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving 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
- patient number, blister pack, and kit numbers (if applicable) for double-blind 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 IMP 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.

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

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 or delegate 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.

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 transcribed to 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 14 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 or delegate will have final responsibility for the quality of the data.

Day to day data management tasks for this study are delegated to Syneos Health, 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 or delegate 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 ECG 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 clinical study report 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.

16. REFERENCES

Fuenmayor LD, Vogt M. The influence of cerebral 5-hydroxytryptamine on catalepsy induced by brain-amine depleting neuroleptics or by cholinomimetics. B J Pharmacol 1979;67(2):309-18.

Gilbert D, Jankovic J. Pharmacological treatment of Tourette syndrome. J Obsessive Compuls Rel Disord 2014;3:407–14.

Heitjan F and Little RJA. Multiple Imputation for the Fatal Accident Reporting System. Applied Statistics 1991;40:13–29.

Jain S, Greene PE, Frucht SJ. Tetrabenazine therapy of pediatric hyperkinetic movement disorders. Mov Disord 2006;21(11):1966-72.

Jankovic J. Therapeutic developments for tics and myoclonus. Mov Disord 2015;30(11):1566-73.

Jankovic J. Tardive syndromes and other drug-induced movement disorders. Clin Neuropharmacol 1995;18(3):197-214.

Jankovic J. Tourette's syndrome. N Engl J Med 2001;345(16):1184-92.

Jankovic J, Beach J. Long-term effects of tetrabenazine in hyperkinetic movement. Neurology 1997;48(2):358-62.

Jankovic J, Kurlan R. Tourette syndrome: evolving concepts. Mov Disord 2011;26(6):1149.

Kenney C, Hunter C, N M, Jankovic J. Tetrabenazine in the treatment of Tourette syndrome. J Pediatric Neurol 2007;5(1):9-13.

Kurlan R, Como PG, Miller B, Palumbo D, Deeley C, Andresen EM, et al. The behavioral spectrum of tic disorders: a community-based study. Neurology 2002;59(3):414-20.

Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, et al. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. J Am Acad Child Adolesc Psychiatry 1989;28(4):566-73.

Little RJA and Rubin DB. Statistical Analysis with Missing Data, Second Edition. New York: John Wiley & Sons 2002.

Mejia NI, Jankovic J. Tardive dyskinesia and withdrawal emergent syndrome in children. Expert Rev Neurother 2010 Jun;10(6):893-901.

Mehanna R, Hunter C, Davidson A, Jimenez-Shahed J, Jankovic J. Analysis of CYP2D6 genotype and response to tetrabenazine. Mov Disord 2013 Feb;28(2):210-5.

Paleacu D, Giladi N, Moore O, Stern A, Honigman S, Badarny S. Tetrabenazine treatment in movement disorders. Clin Neuropharmacol 2004;27(5):230-3.

Pasricha PJ, Pehlivanov N, Sugumar A, Jankovic J. Drug Insight: from disturbed motility to disordered movement—a review of the clinical benefits and medicolegal risks of metoclopramide. Nat Clin Pract Gastroenterol Hepatol 2006;3(3):138-48.

Peña MS, Yaltho TC, Jankovic J. Tardive dyskinesia and other movement disorders secondary to aripiprazole. Mov Disord 2011 Jan;26(1):147-52.

Porta M, Sassi M, Cavallazzi M, Fornari M, Brambilla A, Servello D. Tourette's syndrome and role of tetrabenazine: review and personal experience. Clin Drug Investig 2008;28(7):443.

Rubin DB. Multiple Imputation for Nonresponse in Surveys, New York: John Wiley & Sons. 1987.

Scahill L, Riddle MA, McSwiggin-Hardin M, Ort SI, King RA, Goodman WL, et al. Children's Yal-Brown Obsessive Compulsive Scale: reliability and validity. J Am Acad Child Adolesc Psychiatry 1997;36(6):844-52.

Schenker N and Taylor JMG. Partially Parametric Techniques for Multiple Imputation. Computational Statistics and Data Analysis 1996;22:425-446.

Scherman D, Gasnier B, Jaudon P, Henry JP. Hydrophobicity of the tetrabenazine-binding site of the chromaffin granule monoamine transporter. Mol Pharmacol 1988;33(1):72-7.

Shaw Z, Coffey B. Tics and Tourette syndrome. Psychiatr Clin North Am 2014 Sep;37(3):269-86.

Su M, McFarlane F, Cavanna A, et al. The English Version of the Gilles de la Tourette Syndrome–Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL). J Child Neurol 2017;32(1):76-83.

Sun S, Wang S. The Children's Depression Inventory in worldwide child development research: a reliability generalization study. J Child Fam Stud 2015;24(8):2352-63.

Waln O, Jankovic J. An update on tardive dyskinesia: from phenomenology to treatment. Tremor and other hyperkinetic movements. Tremor Other Hyperkinet Mov 2013;3.

Wijemanne S, Wu LJ, Jankovic J. Long-term efficacy and safety of fluphenazine in patients with Tourette syndrome. Mov Disord 2014 Jan;29(1):126-30.

Xenazine: Highlights of Prescribing Information. 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021894s010lbl.pdf. Accessed 27 Oct 2015.

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, concomitant mediations, titration instructions, sample size, 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
CLINICAL STUDY PERSONNEL CONTACT INFORMATION		
For medical issues, contact the physician listed below: [redacted]	For medical issues, contact the physician listed below: [redacted]	This change was made to update the medical issue contact physician.
For operational issues, contact the operational lead listed below: [redacted]	For operational issues, contact the operational lead listed below: [redacted]	This change was made to update the protocol contact physicians.

Original text with changes shown	New wording	Reason/Justification for change
[redacted] For protocol issues, contact the study leader listed below: [redacted]	[redacted]	
1.4. Known and Potential Risks and Benefits to Human Patients (Other sections affected by this change: 1.4.1.1., 1.4.1.2., 1.4.2.)		
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 (see~~	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 information regarding known and potential benefits and risks to patients.

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

Original text with changes shown	New wording	Reason/Justification for change
3.1.2 Screening Period (Other sections affected by this change: Sections 3.13, 3.13.1., 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, 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.	An option was added for co-consent for patients 14 years of age and older.
3.1.3 Titration Period (Other sections affected by this change: Section 5.1)		
Patients who remain eligible for participation in the study will be randomized at the baseline visit (day 1), and that evening (ie, after the study visit) will receive 6 mg of blinded IMP with food. Tablets should be taken with food (eg, a snack) and should not be taken on an empty stomach.	Patients who remain eligible for participation in the study will be randomized at the baseline visit (day 1), and that evening (ie, after the study visit) will receive 6 mg of blinded IMP with food. Tablets should be taken with food (eg, a snack) and should not be taken on an empty stomach.	A statement was added to further clarify that the IMP should be taken with a snack and not on an empty stomach.
3.1.3 Titration Period		
The dose of the ~~study drug~~ IMP should be increased on a weekly basis until one of the following criteria is met: • The investigator determines there has been a clinically meaningful reduction in tics, as indicated by a sustained reduction in the TS-CGI • ~~there is optimal reduction of tics, as determined by the investigator, in consultation with the patient and caregiver/adult~~	The dose of the IMP should be increased on a weekly basis until one of the following criteria is met: • The investigator determines there has been a clinically meaningful reduction in tics, as indicated by a sustained reduction in the TS-CGI	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.

Original text with changes shown	New wording	Reason/Justification for change
3.1.5. Washout Period and Follow-up		
Patients who complete the study may be eligible to begin participation in an open-label safety extension study of TEV-50717 ~~at that time~~(Study TV50717-CNS-30047). For this study, the follow-up period is defined as 1 week of washout for patients who will participate in the open-label safety extension study TV50717-CNS-30047 and 2 weeks after the last dose of IMP (1 week after the end of the washout period) for patients who will not roll over into the open-label safety extension study TV50717-CNS-30047. Patients not participating in the open-label safety extension study for TEV-50717 will have a follow-up telephone contact for safety evaluation 1 week after the end of the treatment period (2 weeks after their last dose of IMP). The end of study is defined as the date of the week 10 telephone contact with the last participant. Prohibited drugs will remain the same during the washout period for patients who will participate in the open-label extension study TV50717-CNS-30047. Patients who will not participate in the extension study (Study TV50717-CNS-30047) may begin/resume tic therapy medication after the first week of the washout period.	Patients who complete the study may be eligible to begin participation in an open-label safety extension study of TEV-50717 (Study TV50717-CNS-30047). For this study, the follow-up period is defined as 1 week of washout for patients who will participate in the open-label safety extension study TV50717-CNS-30047 and 2 weeks after the last dose of IMP (1 week after the end of the washout period) for patients who will not roll over into the open-label safety extension study TV50717-CNS-30047. Patients not participating in the open-label safety extension study for TEV-50717 will have a follow-up telephone contact for safety evaluation 1 week after the end of the treatment period (2 weeks after their last dose of IMP). The end of study is defined as the date of the week 10 telephone contact with the last participant. Prohibited drugs will remain the same during the washout period for patients who will participate in the open-label extension study TV50717-CNS-30047. Patients who will not participate in the extension study (Study TV50717-CNS-30047) may begin/resume tic therapy medication after the first week of the washout period.	The study number of the extension study was added, the washout period was clarified, and concomitant medications allowed during the washout period were clarified.
3.6 Randomization and Blinding		
In addition, the sponsor's clinical personnel and all vendors (with exception of the Interactive Response Technology [IRT] vendor and the bioanalytical sample analysis vendor) involved in the study will be blinded to the IMP identity until the database is locked for analysis and the treatment assignment revealed. After unblinding	In addition, the sponsor's clinical personnel and all vendors (with exception of the Interactive Response Technology [IRT] vendor and the bioanalytical sample analysis vendor) involved in the study will be blinded to the IMP	Statement was added about blinding until completion of the safety extension study TEV-50717-

Original text with changes shown	New wording	Reason/Justification for change
of this study, the study site may remain blinded to patient treatment assignments until completion of the safety extension study TV50717-CNS-30047**.**	identity until the database is locked for analysis and the treatment assignment revealed. After unblinding of this study, the study site may remain blinded to patient treatment assignments until completion of the safety extension study TV50717-CNS-30047.	CNS-30047.
3.8.1 IMP (Other sections affected by this change: Section 1.2)		
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. TEV-50717 tablets are available in the following strengths: 6, 9, 12, 15, and 18 mg, all of which are identical in size, shape, and color (white). IMP will be supplied in 20-count tablets per dose strength per bottle. The placebo tablets and packaging will match those for TEV-50717. Each bottle (20-count tablets per dose strength per 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.	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. TEV-50717 tablets are available in the following strengths: 6, 9, 12, 15, and 18 mg, all of which are identical in size, shape, and color (white). IMP will be supplied in 20-count tablets per dose strength per bottle. The placebo tablets and packaging will match those for TEV-50717. Each bottle (20-count tablets per dose strength per 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.	Additional details were added to the description of IMP.
3.13. Study Procedures		
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.

Original text with changes shown	New wording	Reason/Justification for change
3.13. Study Procedures (Other sections affected by this change: Sections 5.3, 7.10)		
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.	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.	This additional instruction will allow the investigator to monitor new concomitant medications, thus enhancing patient safety.
3.13.1. Procedures for Screening and Enrollment		
~~After informed consent is obtained, patients 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 designated investigator center number, and the last 3 digits will be assigned at the investigator center (eg, if the number assigned to the country is 01, the third patient screened at center 5 would be given the number of 01005003).~~		This paragraph was deleted to remove the detailed specificity for patient ID assignment.
3.13.1. Procedures for Screening and Enrollment		
• administer the following questionnaires (Note: For 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	• administer the following questionnaires (Note: For 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	Specific instruction was provided for the YGTSS assessment to be performed before any blood draws or ECG.

Original text with changes shown	New wording	Reason/Justification for change
YGTSS questionnaire should be performed before any blood draws or ECG assessments.):	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.):	
3.13.1.1. YGTSS Rater Certification		
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, especially at the baseline and week 12/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.	**3.13.1.1. 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, especially at the baseline and week 12/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.
3.13.2. Procedures before IMP Treatment (Baseline/Day 1) (Other sections affected by this change: 3.13.3.1.2., 3.13.3.2.1., 3.13.3.2.2., 3.13.4.1.)		
• administer the following questionnaires (Note: For C-SSRS, [redacted], 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 [redacted] questionnaires should be performed before any blood draws or ECG	• administer the following questionnaires (Note: For C-SSRS, [redacted] 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	Specific instruction was provided for the YGTSS, TS-CGI, and [redacted] assessments to be performed before any blood draws or ECG.

Original text with changes shown	New wording	Reason/Justification for change
assessments.):	caregiver/adult should be encouraged to add relevant information. The YGTSS, TS-CGI, and [redacted] questionnaires should be performed before any blood draws or ECG assessments.):	
4.1 Patient Inclusion Criteria		
j. Females may be included only if they have a negative β-HCG test at baseline or are sterile. Definitions of sterile given in Appendix L. **k.** 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 half-lives, whichever is longer after last dose of IMP. Further details are included in Appendix L**.**	j. Females may be included only if they have a negative β-HCG test at baseline or are sterile. Definitions of sterile given in Appendix L. k. 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 half-lives, whichever is longer after last dose of IMP. Further details are included in Appendix L.	Additional inclusion criteria for females were added to include β-HCG test and the requirement to use highly effective birth control methods.
4.2 Patient Exclusion Criteria		
m. Patient has a QT interval corrected for heart rate using Frederica's formula (QTcF) interval value >4450 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.	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 >480msec (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 were modified to define criteria for QTc.
4.2 Patient Exclusion Criteria		
~~s.~~t. The p~~P~~atient is a pregnant or lactating female, ~~breastfeeding~~ 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.	Wording of patient exclusion criteria regarding pregnancy or lactation was

<table>
<tr><th>Original text with changes shown</th><th>New wording</th><th>Reason/Justification for change</th></tr>
<tr><td></td><td></td><td>changed.</td></tr>
<tr><td colspan="3">4.4 Withdrawal Criteria and Procedures (Other sections affected by this change: 7.1.7; Section 7.5)</td></tr>
<tr><td>In accordance with the Declaration of Helsinki (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 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. <u>If a post-baseline QTcF value >500 msec or change from baseline >60 msec is found, the investigator should repeat the ECG assessment twice and compare the average of the 2 pre-treatment QTcF values (baseline and screening) to the average of the 3 post-baseline QTcF values. The IMP must be stopped for any confirmed post-baseline QTcF value >500 msec or increase from baseline >60 msec.</u></td><td>In accordance with the Declaration of Helsinki (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 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 >60 msec.</td><td>Text to identify QTc changes that will require IMP suspension was added.</td></tr>
<tr><td colspan="3">5.1. Drugs Administered During the Study</td></tr>
<tr><td>
<table>
<tr><th></th><th colspan="3"><s>Weight category</s> <u>Daily dose (mg) at the start of visit/week</u></th></tr>
<tr><th>Study week[a]</th><th>20 to <30 kg <u>(44 to <66 lbs)</u></th><th>30 to <40 kg <u>66 to <88 lbs)</u></th><th><u>≥40 kg (≥88 lbs)</u></th></tr>
<tr><td><s>Week 1</s> <u>Baseline</u></td><td>6 mg</td><td>6 mg</td><td><u>6 mg (Days 1 and 2)</u> 12 mg[b]</td></tr>
<tr><td>Week <s>2</s> <u>1</u></td><td>12 mg</td><td>12 mg</td><td>18 mg</td></tr>
<tr><td>Week <s>3</s> <u>2</u></td><td>18 mg</td><td>18 mg</td><td>24 mg</td></tr>
<tr><td>Week <s>4</s><u>3</u></td><td>18 mg[c]</td><td>24 mg[c]</td><td>30 mg</td></tr>
</table>
</td><td>
<table>
<tr><th></th><th colspan="3">Daily dose (mg) at the start of visit/week</th></tr>
<tr><th>Study week [a]</th><th>20 to <30 kg (44 to <66 lbs)</th><th>30 to <40 kg (66 to <88 lbs)</th><th>≥40 kg (≥88 lbs)</th></tr>
</table>
</td><td>The table was updated with weight details and clarifications regarding how study weeks are defined with the occurring at the beginning of the week.</td></tr>
</table>

<table>
<tr><th>Original text with changes shown</th><th>New wording</th><th>Reason/Justification for change</th></tr>
<tr><td>
<table>
<tr><td>Week ~~5~~4</td><td>24 mg[c]</td><td>30 mg[c]</td><td>36 mg[c]</td></tr>
<tr><td>Week ~~6~~ 5</td><td>24 mg[c]</td><td>36 mg[c]</td><td>42 mgc</td></tr>
<tr><td>Week ~~7~~ 6</td><td>30 mg[c]</td><td>42 mg[c]</td><td>48 mg[c]</td></tr>
</table>
</td><td>
<table>
<tr><td>Baseline</td><td>6 mg</td><td>6 mg</td><td>6 mg (Days 1 and 2)
12 mg[b]</td></tr>
<tr><td>Week 1</td><td>12 mg</td><td>12 mg</td><td>18 mg</td></tr>
<tr><td>Week 2</td><td>18 mg</td><td>18 mg</td><td>24 mg</td></tr>
<tr><td>Week 3</td><td>18 mg[c]</td><td>24 mg[c]</td><td>30 mg</td></tr>
<tr><td>Week 4</td><td>24 mg[c]</td><td>30 mg[c]</td><td>36 mg[c]</td></tr>
<tr><td>Week 5</td><td>24 mg[c]</td><td>36 mg[c]</td><td>42 mg[c]</td></tr>
<tr><td>Week 6</td><td>30 mg[c]</td><td>42 mg[c]</td><td>48 mg[c]</td></tr>
</table>
</td><td></td></tr>
<tr><td colspan="3">7.5. Clinical Laboratory Tests</td></tr>
<tr><td>The clinical significance of the lab values will be evaluated by the criteria described in the study lab manual <u>and by the judgment of the investigator</u>.</td><td>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.</td><td>This sentence included to provide further guidance regarding clinical significance of laboratory values and investigator judgement.</td></tr>
<tr><td colspan="3">7.7. Electrocardiography</td></tr>
<tr><td>A 12-lead ECG will be conducted 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. <u>A qualified physician at a central diagnostic center will be interpreting the ECG.</u>
<u>All ECG results outside of the reference ranges will be judged by the investigator as belonging to one of the following categories:</u></td><td>A 12-lead ECG will be conducted 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</td><td>Twelve-lead ECG interpretation details were updated.</td></tr>
</table>

Original text with changes shown	New wording	Reason/Justification for change
• 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~~.The 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.	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	
8.1. Pharmacokinetic Assessment		
Plasma samples for both α-HTBZ and β-HTBZ metabolites will be pooled with previous data and incorporated into a population pharmacokinetic analysis. The population pharmacokinetic analysis will result in a final structural model that best describes the data. A covariate assessment will evaluate the relationship between potential covariates (ie, body weight, age, height, etc) and concentrations of α-HTBZ and β-HTBZ metabolites. The final population pharmacokinetic analysis will be included in a separate report. ~~Blood samples (5 mL) will be collected via venipuncture for plasma concentration measurements of TEV-50717 and metabolites or other analytes.~~ ~~The dates and times of IMP administration and the date and time of each pharmacokinetic sample will be recorded on the source documentation and transcribed onto the CRF.~~	Plasma samples for both α-HTBZ and β-HTBZ metabolites will be pooled with previous data and incorporated into a population pharmacokinetic analysis. The population pharmacokinetic analysis will result in a final structural model that best describes the data. A covariate assessment will evaluate the relationship between potential covariates (ie, body weight, age, height, etc) and concentrations of α-HTBZ and β-HTBZ metabolites. The final population pharmacokinetic analysis will be included in a separate report.	Samples for pharmacokinetic assessment were updated.
9.1 Sample Size and Power Considerations		
[redacted]	[redacted]	[redacted]

Original text with changes shown	New wording	Reason/Justification for change
[redacted]	[redacted]	[redacted]
9.5.4.2 Sensitivity Analysis		
• The primary analysis at week 12 will be repeated on a complete data set using multiple imputation methodology for imputing missing data using an MNAR missing data assumption to investigate when statistical significance disappears. • ~~Using the same repeated measures model as described for the primary analysis, the groups will be compared at each of weeks 2, 4, 6, and 9.~~ • ~~An analysis of covariance (ANCOVA) model will be fit using the change from baseline to week 12 as the dependent variable, treatment group, and the baseline value as a covariate. For patients with missing data at week 12, the least favorable change from baseline to week 12 observed in either treatment group will be used as the dependent variable.~~ • ~~An ANCOVA model, as described above, will be fit. For patients with missing data at week 12, the last available change from baseline for the patients will be used as the dependent variable.~~	• The primary analysis at week 12 will be repeated on a complete data set using multiple imputation methodology for imputing missing data using an MNAR missing data assumption to investigate when statistical significance disappears.	Sensitivity analyses were simplified and made consistent with Study TV50717-CNS-30060.
9.5.4.3. Key Secondary Efficacy Analyses		
A hierarchical (fixed-sequence) testing approach will be used for the analysis of the primary and key secondary endpoints to maintain the experiment-wise type I error rate of 5%. If an endpoint is not statistically significant, confirmatory hypothesis testing will not be carried out on the remaining hypotheses,	A hierarchical (fixed-sequence) testing approach will be used for the analysis of the primary and key secondary endpoints to maintain the experiment-wise type I error rate of 5%. If an endpoint is not statistically significant, confirmatory hypothesis	The purpose of the hierarchical analysis was added.

<table>
<tr><th>Original text with changes shown</th><th>New wording</th><th>Reason/Justification for change</th></tr>
<tr><td>and remaining hypotheses will be considered exploratory rather than confirmatory. The change in the TS-CGI (1), [redacted] (2), and GTS-QOL physical/ADL subscale (3) scores from baseline to week 12 will be summarized and analyzed in the same fashion as the primary analysis, with the exception that the baseline value of the given endpoint will be included as the covariate.</td><td>testing will not be carried out on the remaining hypotheses, and remaining hypotheses will be considered exploratory rather than confirmatory. The change in the TS-CGI (1), [redacted] 2), and GTS-QOL physical/ADL subscale (3) scores from baseline to week 12 will be summarized and analyzed in the same fashion as the primary analysis, with the exception that the baseline value of the given endpoint will be included as the covariate.</td><td></td></tr>
<tr><td colspan="3">APPENDIX 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 USA~~</td></tr>
<tr><td>~~Droperidol~~</td><td>~~Sedative; anti-nausea/anesthesia adjunct, nausea~~</td><td>~~-~~</td></tr>
<tr><td>~~Erythromycin~~[a]</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~~</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 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</td></tr>
</table>

Original text with changes shown	New wording	Reason/Justification for change
~~USA~~ ~~Sparfloxacin~~ ~~Antibiotic/bacterial infection~~ ~~Not available in USA~~ ~~[a] Systemic use only. Topical use is allowed.~~ ~~USA=United States of America.~~		exposure in studies with HD and TD, and with observed data from the TD program in which QT prolonging drugs were safely administered in conjunction with TEV-50717.
APPENDIX I TOURETTE SYNDROME-PATIENT GLOBAL IMPRESSION OF SEVERITY		
Not applicable	Pictorial added	A pictorial of the recently tested PGIS questions designed for pediatric patients was inserted.
APPENDIX L BIRTH CONTROL METHODS AND PREGNANCY TESTING		
Not applicable	Birth Control Methods and Pregnancy Testing Contraception recommendations and pregnancy testing should encompass all IMPs as well as non-investigational medicinal products, eg, background therapy, and the measures to be followed should be based on the medicinal product with highest risk. Assessment of likelihood of possible interaction between IMP or concomitant medications and hormonal contraception should be conducted. Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method, eg, CYP 4A inducers. In case of suspected interaction,	Acceptable contraceptive methods for females have been altered to include abstinence in the definition of highly effective birth control.

Original text with changes shown	New wording	Reason/Justification for change
	hormonal contraceptive alone may not be sufficient. In the absence of clinical pharmacokinetic interaction study data in IMPs with demonstrated or suspected human teratogenicity/fetotoxicity, recommendation for use of hormonal contraceptives should be thoroughly justified by the sponsor. Additional contraceptive methods, including supplementary barrier methods, may be considered. Females of childbearing potential are defined as: • not surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile • not postmenopausal Description of different birth control methods Highly effective birth control methods: Highly effective birth control 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	

Original text with changes shown	New wording	Reason/Justification for change
	without suspected teratogenicity/genotoxicity) and 1 month (for IMPs potentially teratogenic/genotoxic) before the first dose of IMP. • Intrauterine device and intrauterine hormone-releasing system 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 the Medicines and Healthcare Products Regulatory Agency). 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	

Original text with changes shown	New wording	Reason/Justification for change
	either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable but not highly effective methods of birth control. Unacceptable birth control methods: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together. Male contraception: Male patients must always use a condom, except in cases of no genotoxicity; or no demonstrated or suspected human teratogenicity/fetotoxicity. 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	

Original text with changes shown	New wording	Reason/Justification for change
	human teratogenicity/genotoxicity/fetotoxicity. Conduct monthly pregnancy testing and in case the IMP has a marketing authorization, if the IMP has a demonstrated or suspected human teratogenicity/genotoxicity/fetotoxicity according to Risk Safety Information. Shorter testing intervals are to be considered depending on drug dosing schedule. 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	

Original text with changes shown	New wording	Reason/Justification for change
	study participants: Male study participants must use condoms during intercourse if their female partners are pregnant.	

17.2. Amendment 02 Dated 03 October 2017

The primary reason for this amendment is to incorporate CYP2D6 genotyping results into the IRT in order to allow for a dose cap to be applied in a blinded manner, update drug packaging to ensure blinding of CYP2D6 impairment status, reorder the statistical testing methodology (ie, the inclusion of TS-PGII assessment after TS-CGI and before the C&A-GTS-QOL ADL subscale), clarify the study day window for each visit or call, 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**
CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS		
Central Institutional Review Board ~~Quorum Review IRB~~ ~~1501 Fourth Avenue, Suite 800~~ ~~Seattle, WA 98101~~ ~~USA~~ Copernicus Group IRB 1 Triangle Drive Durham, NC 27709 USA	Copernicus Group IRB 1 Triangle Drive Durham, NC 27709 USA	Change to central IRB
CLINICAL STUDY PERSONNEL CONTACT INFORMATION		
For operational issues, contact the operational lead listed below: [redacted] For protocol issues, contact the study	For operational issues, contact the operational lead listed below: [redacted] For protocol issues, contact the study leader listed below: [redacted]	Change in Nuvelution study personnel

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
leader listed below: [redacted]	[redacted]	
1.2 Name and Description of IMP (Other sections affected by this change: 3.8.1, 3.13 [Table 1, footnote "y"], 3.13.2, 3.13.3.1.1, 3.13.3.1.2, 3.13.3.2.1, 3.13.3.2.2, 3.13.5, 5.1, 11.4.1)		
The IMP will be supplied in ~~20~~40-count ~~tablets per dose strength per bottle~~blister packs	The IMP will be supplied in 40-count blister packs	Blister pack IMP replacing bottled IMP for blinding maintenance purposes
1.5.1 Justification for Dosage of Active Drug (Other section affected by this change: 3.1.3 and 5.1)		
The dose ranges to be evaluated in this study, based on body weight and ~~the use of strong~~ CYP2D6 ~~inhibitors~~ impairment status at baseline, were selected on the basis of the safety, preliminary efficacy, and population pharmacokinetic data generated from Study SD-809-C-17 (Table 2 ~~and Table 3~~).	The dose ranges to be evaluated in this study, based on body weight and CYP2D6 impairment status at baseline, were selected on the basis of the safety, preliminary efficacy, and population pharmacokinetic data generated from Study SD-809-C-17 (Table 2).	CYP2D6 genotyping adjusted to be incorporated at screening and by CYP Impairment status
1.8 Location and Study Duration		
This study is planned to be conducted in ~~the~~ North America, Russia, and Europe, at approximately 50 centers. It is expected to start in ~~October 2017~~ January 2018 and have a duration of approximately 15 months.	This study is planned to be conducted in North America, Russia, and Europe, at approximately 50 centers. It is expected to start in January 2018 and have a duration of approximately 15 months.	Study start date pushed out to January 2018, and Russia was specified as a location to be included for this study's conduct.

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
2.3.2 Key Secondary Efficacy Endpoint (Other sections affected by this change: 3.13 [Table 1]), 9.5.2, 3.3.2		
The key secondary efficacy endpoints are as follows: 1. Change in the TS-CGI score from baseline to week 12 2. ~~Change in the [redacted] score from baseline to week 12~~ Change in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) score from baseline to week 12 3. 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 to week 12	The key secondary efficacy endpoints are as follows: 1. Change in the TS-CGI score from baseline to week 12 2. Change in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) score from baseline to week 12 3. 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 baseline to week 12	Adjusting of the Key secondary efficacy endpoint hierarchy. [redacted] was removed, and placed as an exploratory endpoint. TS-PGII was inserted as the new (2) Secondary efficacy endpoint. The child and adolescent version of the GTS-QOL scale is now being used to assess the (3) secondary efficacy endpoint.
2.3.3 Exploratory Endpoints (Other sections affected by this change: 3.3.3 and 9.5.3)		
Exploratory endpoints are as follows: [redacted]	Exploratory endpoints are as follows: [redacted]	[redacted] was moved (removed as a secondary efficacy endpoint) and is now included as an exploratory endpoint.

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
[redacted]	[redacted]	
3.1.1 Overall Design and Screening Period (Other section affected by this change: 5.1)		
Throughout the study, patients will interact regularly with investigative site personnel, in clinic and by telephone, for the evaluation of safety, tic severity, and behavioral status (in clinic only). ~~Based on this information, the~~The target dose for each patient receiving TEV-50717 will be based on body weight and CYP2D6 impairment status at baseline. Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor or are a CYP2D6 poor metabolizer based on blinded assessment of CYP2D6 genotype at baseline. CYP2D6 status will be used by Interactive Response Technology (IRT) for randomization into the study. The dose of IMP for each patient will be titrated to an optimal level followed by maintenance therapy at that dose. Investigators will be blinded to CYP status, with a dose cap for poor metabolizers prespecified by the IRT (Table 2). The overall treatment period will be 12 weeks in duration, including a titration period of 7 weeks, a maintenance period of 5 weeks, followed by a washout period of 1 week. Site- administered scales include the YGTSS, [redacted] Mini International Neuropsychiatric Interview For Children and Adolescents (MINI Kid), and the C-SSRS; and self-administered scales	Throughout the study, patients will interact regularly with investigative site personnel, in clinic and by telephone, for the evaluation of safety, tic severity, and behavioral status (in clinic only). The target dose for each patient receiving TEV-50717 will be based on body weight and CYP2D6 impairment status at baseline. Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor or are a CYP2D6 poor metabolizer based on blinded assessment of CYP2D6 genotype at baseline. CYP2D6 status will be used by Interactive Response Technology (IRT) for randomization into the study. The dose of IMP for each patient will be titrated to an optimal level followed by maintenance therapy at that dose. Investigators will be blinded to CYP status, with a dose cap for poor metabolizers prespecified by the IRT (Table 2). The overall treatment period will be 12 weeks in duration, including a titration period of 7 weeks, a maintenance period of 5 weeks, followed by a washout period of 1 week. Site- administered scales include the YGTSS, [redacted], Mini International Neuropsychiatric Interview For Children and Adolescents (MINI Kid), and the C-SSRS; and self-administered scales	CYP2D6 genotyping adjusted to be incorporated at screening and by CYP Impairment status. Text has also been updated to indicate that investigators will be blinded to CYP impairment status and how that will be addressed throughout the study. Clarification on the involvement of the adult/caregiver was provided for the scales to be used.

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
include the TS-PGII, TS PGIS, [redacted] 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~~ permitted. For all other scales, for 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 defined by the scale; for children over 13 years of age, caregiver/adult involvement is strongly encouraged.	include the TS-PGII, TS PGIS, [redacted] 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 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 defined by the scale; for children over 13 years of age, caregiver/adult involvement is strongly encouraged.	
3.1.2 Screening Period (Other sections affected by this change: 3.10, 3.13 [Table 1], 3.13.1, 3.13.2)		
The screening period in this study is up to ~~4 weeks~~ 31 days ~~(and a minimum of 3 days)~~. 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 ~~by the study monitor.~~)	The screening period in this study is up to 31 days. 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.)	The screening period was updated to more clearly indicate a maximum of 31 days, and a minimum of 3 days. Specific details on who must approve of rescreening were removed.
3.1.4 Maintenance Period (Other section affected by this change: 6)		
At week 12, 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-PGII, TS PGIS, [redacted] and C&A-GTS-QOL.	At week 12, 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-PGII, TS PGIS, [redacted] and C&A-GTS-QOL.	An adjustment was made to the scales used due to the addition of the TS-PGII assessment and child and adolescent version of the GTS-QOL.
3.9.2 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 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.	This update was made to clarify that unused IMP should be returned to the sponsor or its designee.

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
3.12 Source Data Recorded on the Case Report Form (Other sections affected by this change: 13.1 and 13.3.2)		
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.	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.	A paper diary will be used. The indication of an "electronic" diary was removed.
3.13 Study Procedures		
Table 1 was updated	Screening was updated to 31 days Study days were added in addition to the study weeks for clarification of study procedure timing. The visit window was increased throughout titration from ±1 day to ±3 days A 12-lead ECG assessment was added as a baseline assessment The TS-PGII assessment was added to the table, because it was added as a key secondary efficacy endpoint	The table of procedures was updated to provide greater clarity of study procedure timing, to include additional/clarified assessments, and to provide overall consistency to all changes made during this amendment.
3.13.1 Procedures for Screening and Enrollment (Other sections affected by this change: 3.1.1, 3.13.2, 3.13.3.1.2, 3.13.3.2.1, 3.13.3.2.2, 3.13.4.1, 3.13.5, 6.2.4, 6.2.6, 6.2.7, 7.2.1, 7.2.2)		
The screening visit will take place not more than ~~4 weeks~~ 31 days and no less than 3 days before the baseline visit. The screening visit may be conducted over 2 separate visits at the discretion of the investigator. The following procedures will be performed at screening: • obtain written informed consent/assent and/or co-consent for patients 14 years of age and older before any other study related procedures are performed • review eligibility (inclusion and exclusion) criteria • inform patients of study restrictions and compliance requirements • review medical and psychiatric history	The screening visit will take place not more than 31 days and no less than 3 days before the baseline visit. The screening visit may be conducted over 2 separate visits at the discretion of the investigator. The following procedures will be performed at screening: • obtain written informed consent/assent and/or co-consent for patients 14 years of age and older before any other study related procedures are performed • review eligibility (inclusion and exclusion) criteria • inform patients of study restrictions and compliance requirements • review medical and psychiatric history • review demographics information	The procedures to be followed (ie, the involvement of the adult/caregiver) for various scales used to assess results of patients in this study have been further clarified for children under the age of 13.

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
• 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 chemical, hematological, and urine analyses • obtain a blood sample (5 mL) for analysis of CYP2D6 genotype • perform urine drug screen (UDS) • perform a serum pregnancy (beta human chorionic gonadotropin [β-HCG]) test (only in females of childbearing potential) • 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.): - MINI Kid (Note: The following modules will be used: 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], Attention Deficit Hyperactivity Disorder [ADHD;	• 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 chemical, hematological, and urine analyses • obtain a blood sample (5 mL) for analysis of CYP2D6 genotype • perform urine drug screen (UDS) • perform a serum pregnancy (beta human chorionic gonadotropin [β-HCG]) test (only in females of childbearing potential) • 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.): - MINI Kid (Note: The following modules will be used: 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], Attention Deficit Hyperactivity Disorder [ADHD; Module O], Conduct Disorder [Module	

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
Module O], Conduct Disorder [Module P], and Psychotic Disorders and Mood Disorders with Psychotic Features [Module R]) - CDI-2, Parent and Self-report (Note: Children 6 years of age at baseline will not complete the Self-report version; the caregiver/adult will complete the Parent version.) - C-SSRS (children's baseline/screening) - YGTSS (Note: Input from the caregiver/adult is required.) • review medication history and concomitant medications • inquire about adverse events	P], and Psychotic Disorders and Mood Disorders with Psychotic Features [Module R]) - CDI-2, Parent and Self-report (Note: Children 6 years of age at baseline will not complete the Self-report version; the caregiver/adult will complete the Parent version.) - C-SSRS (children's baseline/screening) - YGTSS (Note: Input from the caregiver/adult is required.) • review medication history and concomitant medications • inquire about adverse events	
3.13.2 Procedures Before IMP Treatment (Baseline/Day 1) (Other sections affected by this change: 3.13.3.1.2, 3.13.3.2.1, 3.13.3.2.2, 3.13.4.1		
Patients who meet the inclusion/exclusion criteria at screening will continue to the baseline visit, when baseline evaluations will be conducted. The following procedures will be performed at baseline: • review eligibility (inclusion and exclusion) criteria • measure vital signs (orthostatic pulse and BP [after standing for at least 3 minutes], body temperature, and respiratory rate) • measure weight (Note: Weight must be measured with shoes and outerwear off) • <u>perform 12-lead ECG (Note: ECG will be performed after at least 5 minutes rest in a supine or semi-supine position)</u> • perform urine pregnancy (β-HCG) test (only in females of childbearing potential) • randomization with stratification by age at baseline (6 to 11 years, 12 to 16 years) • administer the following	Patients who meet the inclusion/exclusion criteria at screening will continue to the baseline visit, when baseline evaluations will be conducted. The following procedures will be performed at baseline: • review eligibility (inclusion and exclusion) criteria • measure vital signs (orthostatic pulse and BP [after standing for at least 3 minutes], body temperature, and respiratory rate) • measure 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 urine pregnancy (β-HCG) test (only in females of childbearing potential) • randomization with stratification by age at baseline (6 to 11 years, 12 to 16 years) • administer the following	The procedures to be followed at certain time points/days and the involvement of the adult/caregiver for various scales used to assess results of patients in this study have been further clarified/updated. The process of IMP randomization has also been clarified.

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
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-PGII, and [redacted] questionnaires should be performed before any blood draws or ECG assessments.): - CDI-2, Parent and Self-report (Note: Children 6 years of age at baseline will not complete the Self-report version; the caregiver/adult will complete the Parent version.) - C-SSRS (children's SLV) - YGTSS (~~Note:~~ Input from the caregiver/adult is required.) - TS-CGI - TS-PGII (Input from the caregiver/adult is permitted.) - [redacted] (~~Note:~~ Input from the caregiver/adult is ~~required~~ permitted.) - [redacted] - CY BOCS - C&A-GTS QOL • dispense IMP (patients will receive doses for 2 weeks [current dose level and next dose level] to cover the telephone contacts) • provide patients with a diary to record meal times and critical information on dosing • review concomitant medications • inquire about adverse events A patient who is not enrolled in the study on the basis of results of baseline assessments (eg, because inclusion and exclusion criteria were not met or	questionnaires (Note: For C-SSRS, [redacted] 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-PGII, and [redacted] questionnaires should be performed before any blood draws or ECG assessments.): - CDI-2, Parent and Self-report (Note: Children 6 years of age at baseline will not complete the Self-report version; the caregiver/adult will complete the Parent version.) - C-SSRS (children's SLV) - YGTSS (Input from the caregiver/adult is required.) - TS-CGI - TS-PGII (Input from the caregiver/adult is permitted.) - [redacted] (Input from the caregiver/adult is permitted.) - [redacted] - CY BOCS - C&A-GTS QOL • dispense IMP (patients will receive doses for 2 weeks [current dose level and next dose level] to cover the telephone contacts) • provide patients with a diary to record meal times and critical information on dosing • review concomitant medications • inquire about adverse events A patient who is not enrolled in the study on the basis of results of baseline assessments (eg, because inclusion and exclusion criteria were not met or	

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
enrollment did not occur within the specified time) may be screened again 1 more 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.) Patients will be assigned a permanent unique number at screening (see Section 3.13.1). Patients who continue to meet the inclusion/exclusion criteria at baseline will be ~~assigned~~ randomized to a treatment (active or placebo) ~~number (kit, bottle)~~ using an IRT, and the appropriate IMP will be dispensed.	enrollment did not occur within the specified time) may be screened again 1 more 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.) Patients will be assigned a permanent unique number at screening (see Section 3.13.1). Patients who continue to meet the inclusion/exclusion criteria at baseline will be randomized to a treatment (active or placebo) using an IRT, and the appropriate IMP will be dispensed.	
4.1 Inclusion Criteria		
j. Females of childbearing potential may be included only if they have a negative β- HCG test at baseline or are sterile. Definitions of sterile is given in Appendix L. k. Females of childbearing potential whose male partners are potentially fertile (ie, no vasectomy) or female partners of male participants 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.	j. Females of childbearing potential may be included only if they have a negative β- HCG test at baseline or are sterile. Definitions of sterile is given in Appendix L. k. Females of childbearing potential whose male partners are potentially fertile (ie, no vasectomy) or female partners of male participants 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.	Pregnancy language was updated to more clearly specify that only women of childbearing potential would undergo β-HCG test at baseline. Female partners of male participants were also included in the inclusion criteria to use effective means of birth control.
4.2 Exclusion Criteria		
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, OR requires treatment with drugs known to prolong the QT interval (see Appendix A for a complete list of prohibited QT-prolonging drugs). u. Patient has a history of or acknowledges alcohol ~~or substance abuse~~ related disorder in the previous	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, OR requires treatment with drugs known to prolong the QT interval (see Appendix A for a complete list of prohibited QT-prolonging drugs). u. Patient has a history of or acknowledges alcohol related	Exclusion criteria "m" was updated to account for the exclusion of patients who require treatment with drugs known to prolong the QT interval. Exclusion criteria "u" was updated to be more consistent with the current language in the fifth edition of the DSM.

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
12 months, as defined in the DSM-V. w. Patient has a DSM~~-V~~ diagnosis based on the MINI Kid modules performed at screening that, in the opinion of the investigator, makes the patient unsuitable for the study.	disorder in the previous 12 months, as defined in the DSM-V. 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.	Exclusion criteria "x" was updated to remove fifth edition from the DSM diagnosis criteria.
5.1 Drugs Administered During the Study		
IMP (see Section 3.8) will be administered as oral tablets at a starting dose of 6 mg ~~once daily~~. Titration schemes based on body weight at baseline are shown in Table 2. The maximum daily dose is determined by body weight a<u>nd CYP2D6 impairment status</u> at baseline ~~and any use of strong CYP2D6 inhibitors (see Table 3)~~. 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. IMP will be dispensed in the clinic. Patients will receive doses for 2 weeks at baseline, week 2, and week 4 visits (current dose level and next dose level) to cover the telephone contacts. At week 6 and week 9 visits, patients will receive doses for 3 weeks. IMP will be administered as follows: • IMP should be swallowed whole and taken with food. Tablets should be	IMP (see Section 3.8) will be administered as oral tablets at a starting dose of 6 mg. Titration schemes based on body weight at baseline are shown in Table 2. The maximum daily dose is determined by body weight and CYP2D6 impairment status at baseline. 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. IMP will be dispensed in the clinic. Patients will receive doses for 2 weeks at baseline, week 2, and week 4 visits (current dose level and next dose level) to cover the telephone contacts. At week 6 and week 9 visits, patients will receive doses for 3 weeks. 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	Updated to clarify dosing instructions and the timing of dosing for patients. Text has also been updated to indicate that investigators will be blinded to CYP impairment status.

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
taken with food (eg, a snack) and should not be taken on an empty stomach. • Dosing will be based on body weight and CYP2D6 impairment status at the baseline visit ~~and strong CYP2D6 inhibitor use~~, as shown in Table 2 ~~and Table 3~~. • 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). Subsequent~~ 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. 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.~~ • 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. • During the titration period, the dose of the IMP ~~should~~ will be adjusted weekly 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. Investigators will be blinded to CYP status, with a dose cap for poor metabolizers prespecified by the IRT. IMP will be packaged in ~~bottles~~ blister packs and provided for patients to take	stomach. • Dosing will be based on body weight and CYP2D6 impairment status at the baseline visit, as shown in Table 2. • 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. 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. • During the titration period, the dose of the IMP will be adjusted weekly according to Table 2 to identify a dose level that optimally reduces tics and is well tolerated. Investigators will be blinded to CYP status, with a dose cap for poor metabolizers prespecified by the IRT. IMP will be packaged in blister packs and provided for patients to take at home (see Section 3.8).	

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
at home (see Section 3.8). Table 2 was updated	Table 2 was updated to include CYP Impairment status. Column headers remained divided by weight, but also to include "not impaired" versus "impaired" daily doses by weight categories. Additional editorial changes were made to the table and table footnotes to more clearly specify daily dosing expectations by weight category and by CYP impairment status, and to enhance study visit clarity.	Updates wer made to account for CYP2D6 genotyping status determined at baseline, and to specify daily dosing from baseline through week 6 based on both weight category and CYP impairment.
Table 3 from version 01 was removed.	Table 3 from the previous version protocol amendment 01 was removed, as Table 2 was updated to include the additional information provided by this table.	Table 3 was removed to remove duplicate protocol detail.
5.3 Prior and Concomitant Medications		
Medications that are allowed, provided that conditions outlined in the table are met, are shown in Appendix A, ~~Table 6~~ Table 5. 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 medications that are associated with QTc prolongation are listed in Appendix A, Table 6, while prohibited antipsychotic drugs are listed in Appendix A, Table 7.	Medications that are allowed, provided that conditions outlined in the table are met, are shown in Appendix A, Table 5. 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 medications that are associated with QTc prolongation are listed in Appendix A, Table 6, while prohibited antipsychotic drugs are listed in Appendix A, Table 7.	Updates were made to clarify that the addition of strong CYP inhibitors are prohibited once a patient is enrolled. In addition, prohibited medications associated with QTc prolongation have been inserted into the protocol appendices and are referenced here.
6.2.2 Tourette Syndrome-Patient Global Impression of Impact		
The TS-PGII is administered at baseline and weeks 2, 4, 6, 9, 12, and 13. Input from the caregiver/adult is permitted.	The TS-PGII is administered at baseline and weeks 2, 4, 6, 9, 12, and 13. Input from the caregiver/adult is permitted.	The TS-PGII was included as a key secondary efficacy endpoint, so a brief

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
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 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 the scale has been included.
6.2.3 [redacted]		
[redacted]	[redacted]	[redacted]
6.2.4 Child and Adolescent Gilles de la Tourette Syndrome-Quality of Life Scale		
The C&A-GTS-QOL is administered at baseline, week 6, and week 12. 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&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	The C&A-GTS-QOL is administered at baseline, week 6, and week 12. Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information. The C&A-GTS-QOL is a 27-item questionnaire specific to TS patients that asks the patient to assess the extent to which their quality of life is impacted by their symptoms. The C&A-GTS-QOL contains 6 subscales	The child and adolescent version of the GTS-QOL is now to be used in this study. Adult/caregiver involvement has been clarified, and the scale now contains 6 subscales. The reference for this version of the scale ("C&A" version) replaced the prior reference.

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
C&A-GTS-QOL contains~~-46~~ subscales (cognitive, coprophenomena, psychological, physical, ~~obsessional~~ obsessive-compulsive, and ~~cognitive~~ ADL) and uses a 5- point Likert scale ranging from no problem to extreme problem. Patients will also be asked how satisfied they feel overall with their life at that moment by using a VAS scale between 0 and 100 (~~Cavanna et al 2008).~~Su et al 2017).	(cognitive, coprophenomena, psychological, physical, obsessive-compulsive, and ADL) and uses a 5-point Likert scale ranging from no problem to extreme problem. Patients will also be asked how satisfied they feel overall with their life at that moment by using a VAS scale between 0 and 100 (Su et al 2017).	
6.2.5 Yale Global Tic Severity Scale		
[redacted] are exploratory measures. YGTSS and its components are described in Section 6.1. Input from the caregiver/adult is required.	[redacted] are exploratory measures. YGTSS and its components are described in Section 6.1. Input from the caregiver/adult is required.	This was updated to specify that input from the caregiver/adult is required when performing the YGTSS.
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.~~ 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	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.	This was updated to include the most recent definition of an adverse event per Teva template text.

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
present before study entry and do not worsen during this study will not be considered adverse events.		
7.1.5 Serious Adverse Events		
An additional blood sample for the measurement of IMP concentration should be collected, if possible, from each patient experiencing a serious adverse event 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. For recording of serious adverse events, the study period is defined for each patient as the time period from signature of the informed consent form to the end of the follow up period, as defined in Section 7.1.2. If the investigator becomes aware of serious adverse events occurring in a patient after the end of the follow up period, the serious adverse events should be reported to the sponsor following the procedures described in Section 7.1.5.3.1.	An additional 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. For recording of serious adverse events, the study period is defined for each patient as the time period from signature of the informed consent form to the end of the follow up period, as defined in Section 7.1.2. If the investigator becomes aware of serious adverse events occurring in a patient after the end of the follow up period, the serious adverse events should be reported to the sponsor following the procedures described in Section 7.1.5.3.1.	Additional text was included to define the period for recording serious adverse events occurring in patients, and to specify the actions to be taken by the investigator should they become aware of a serious adverse event after the end of the follow-up period.
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 a life threatening adverse event (ie, the patient was at ~~immediate~~ risk of death ~~from~~ at the time of the event ~~as~~); it ~~occurred);~~ does not ~~include~~ refer to an event ~~that, had it occurred in a more severe form,~~ which hypothetically might have caused death if it were more severe. • requires inpatient hospitalization or prolongation of existing	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 a life threatening adverse event (ie, the patient was at risk of death at the time of the event); it does not refer to an event which hypothetically might have caused death if it were more severe. • requires inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission or	This was updated to include the most recent definition of a serious adverse event per Teva template text.

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
hospitalization, which means that hospital inpatient admission ~~and/~~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 ~~prior to study entry~~ 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 or /incapacity (refers to a substantial disruption of one's ability to conduct normal life functions) • is a congenital anomaly/birth defect • an important medical event that may not result in death, be life threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.	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 or /incapacity (refers to a substantial disruption of one's ability to conduct normal life functions) • is a congenital anomaly/birth defect • an important medical event that may not result in death, be life threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.	
7.1.5.3.1 Investigator Responsibility		
~~The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations.~~ 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	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	Updates were made to more clearly indicate investigator responsibilities and expectations.

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
disease. 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. For all countries, the sponsor's GPSP will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/Extensible Markup Language (XML) file to the LSO/INC Research for submission to the competent authorities, IEC/IRBs, and investigators, according to regulations. The investigator ~~is responsible for ensuring~~ must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations. Blinding will be maintained for ~~the people who are involved directly in the~~ all study personnel. Therefore, in case of a SUSAR, only the LSO/INC Research will receive the unblinded report for regulatory submission; the others will receive a blinded report.	should be forwarded by the investigator within 24 hours of when it becomes known to the same address as the initial report. For all countries, the sponsor's GPSP will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/Extensible Markup Language (XML) file to the LSO/INC Research for submission to the competent authorities, IEC/IRBs, and investigators, according to regulations. The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations. Blinding will be maintained for all study personnel. Therefore, in case of a SUSAR, only the LSO/INC Research will receive the unblinded report for regulatory submission; the others will receive a blinded report.	
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.	No protocol defined adverse events of special interest were identified for this study.	This was updated to more specifically state adverse events of special interest
7.1.8 Overdose of IMP		
~~Any dose of IMP (whether the IMP or a placebo), whether taken intentionally or unintentionally, in excess of that prescribed during the given time period must be immediately reported to the sponsor. When the identification of the IMP must be known, the investigator must follow the procedures outlined in Section 3.7.~~	Not applicable	Section 7.1.8 of the previous version has been deleted.

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 and female partners of male patients participating in the study that occur during the study, or within 14 days ~~of completion~~ after the end of the study, are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the investigator must provide the sponsor (LSO/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 baseline, provided no IMP was given. All female patients or female partners of male patients participating in the study ~~will discontinue treatment. All patients~~ 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 ~~16~~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. Since this IMP has suspected human	Any female patient becoming pregnant during the study will discontinue IMP. All pregnancies of female patients participating in the study and female partners of male patients participating in the study that occur during the study, or within 14 days after the end of the study, are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the investigator must provide the sponsor (LSO/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 baseline, provided no IMP was given. All female patients or female partners of male 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. Since this IMP has suspected human teratogenicity, genotoxicity, fetotoxicity, or spermatoxicity, female partners of male patients participating	This was updated to include additional pregnancy details and guidance for the patients and study personnel (ie, when reporting of events is expected, where the information must be provided, how the pregnancy should be reported, and the investigators responsibilities).

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
teratogenicity, genotoxicity, fetotoxicity, or spermatoxicity, female partners of male patients participating in the study who become pregnant will be asked to sign an informed consent form and 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 ~~termination~~ withdrawal from the study will be reported as an adverse event or serious adverse event, as appropriate. If the pregnancy in the female patients participating in the study and/or the female partners of male patients 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.	in the study who become pregnant will be asked to sign an informed consent form and 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 ~~termination~~ withdrawal from the study will be reported as an adverse event or serious adverse event, as appropriate. If the pregnancy in the female patients participating in the study and/or the female partners of male patients 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 ~~medication~~ 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	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	Updates were made to clarify medication error could be with both the test product and IMP. Breastfeeding was added as an additional special

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
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". ~~Types~~ The following are types of medication errors and special situations: 1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer. 2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied. Any dose of IMP (whether the test IMP or placebo IMP), whether taken intentionally or unintentionally in excess of the dose 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 ~~medicinal product~~ an IMP is intentionally used for a medical purpose not in accordance with the authorized product information. 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	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: 1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer. 2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied. Any dose of IMP (whether the test IMP or placebo IMP), whether taken intentionally or unintentionally in excess of the dose 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 milk.	situation.

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
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 ~~interpreted~~ 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 laboratory manual and by the judgement of the investigator. A laboratory test result that is judged by the investigator as clinically significant will be recorded both on the source documentation~~,~~ ~~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~~ 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.)	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 laboratory manual and by the judgement of the investigator. A laboratory test result that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event, and monitored as described in Section 7.1.2. An event may include a laboratory or diagnostic test abnormality (once confirmed by repeated testing) that results in the withdrawal of the patient from the study, the temporary or permanent cessation 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.)	A note was added to clarify that abnormal test results at screening that preclude a patient from entering the study are not considered adverse events.
7.6 Vital Signs		
Vital signs (pulse, BP, body temperature, and respiratory rate) 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	Vital signs (pulse, BP, body temperature, and respiratory rate) 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	This was updated to specify that patients must rest in a supine or semi-erect position for 5 minutes before

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
to one of the following categories: • abnormal and not clinically significant • abnormal and clinically significant Before pulse and BP 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 for a given patient). At baseline, week 4, and week 12, orthostatic BP and pulse will be measured after the patient is in a standing position for at least 3 minutes. 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 ~~a~~ clinically significant will be recorded both on the source documentation~~, transcribed onto~~ and the CRF as an adverse event, and monitored as described in Section 7.1.2. ~~At baseline, week 4, and week 12, orthostatic BP and pulse will be measured after the patient is in a standing position for at least 3 minutes.~~	to one of the following categories: • abnormal and not clinically significant • abnormal and clinically significant Before pulse and BP are measured, the patient must ~~be~~ rest in a supine or semi erect/seated position for at least 5 minutes. (The same position and arm should be used each time vital signs are measured for a given patient). At baseline, week 4, and week 12, orthostatic BP and pulse will be measured after the patient is in a standing position for at least 3 minutes. 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 ~~a~~ 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.	pulse and BP are measured.
7.8 Physical Examinations		
Any physical examination finding that is judged by the investigator as a clinically significant (except at the screening visit) will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.	Any physical examination finding that is judged by the investigator as a clinically significant (except at the screening visit) will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.	This minor clarification was made.
7.9. Assessment of Suicidality		
TEV-50717 is considered to be 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.	TEV-50717 is considered to be 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.	This was updated to include a section on the assessment of suicidality.

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
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 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. Baseline 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.	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 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. Baseline 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.	
7.11 Concomitant Therapy or Medication		
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	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	This was updated to include a cross reference and statement that medications associated with QTc prolongation have been inserted into the

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
prescribed/administered medication should be reviewed with the investigator. Medications that are allowed, provided that conditions outlined in the table are met, are shown in Appendix A, Table 5. 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. Table 6. Prohibited medications that are associated with QTc prolongation are listed in Appendix A, Table 6, while prohibited antipsychotic drugs are listed in Appendix A, Table 7.	prescribed/administered medication should be reviewed with the investigator. Medications that are allowed, provided that conditions outlined in the table are met, are shown in Appendix A, Table 5. The medical monitor must be contacted if a patient is receiving (or has to begin or stop receiving during the study) a medication that is associated with QTc prolongation or that is a known strong CYP inhibitor. Prohibited medications that are associated with QTc prolongation are listed in Appendix A, Table 6, while prohibited antipsychotic drugs are listed in Appendix A, Table 7.	protocol into Appendix A.
7.12 Methods and Timing of Assessing, Recording, and Analyzing Safety Data		
All adverse events will be reviewed on a periodic basis by the clinical project physician/medical monitor according to the safety monitoring plan (eg, scheduled safety reviews for TEV-50717) as preliminary safety databases become available. Safety data will additionally be evaluated periodically and ad hoc (if necessary) in the Product Safety Group. Methods and timing 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 3.7.3.	All adverse events will be reviewed on a periodic basis by the clinical project physician/medical monitor according to the safety monitoring plan (eg, scheduled safety reviews for TEV-50717) as preliminary safety databases become available. Methods and timing 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 3.7.3.	This was updated to remove the ad hoc evaluation of safety data by the Product Safety Group.
8.2 Pharmacodynamics Assessment		
Exposure-response (eg, pharmacodynamic [PD] and/or safety endpoints) may be assessed if the appropriate data are available.	Exposure-response (eg, pharmacodynamic [PD] and/or safety endpoints) may be assessed if the appropriate data are available.	This section was added to account for possible pharmacodynamics assessment of data.

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
8.3 Pharmacogenetics		
Not applicable	Level 2 heading added to the protocol	This level 2 heading was added to streamline the genotyping portion of the protocol
8.3.1 CYP2D6 ~~Genotype~~ Genotyping/Pharmacogenetics		
At the screening visit, a blood sample (5 to 6 mL) will be obtained for analysis of CYP2D6 genotype. The patient's genotype for CYP2D6 will remain blinded during the conduct of the study. If the patient elects this option on the optional informed consent, the remaining sample will be stored for exploratory pharmacogenetics (PGx) evaluation. This PGx assessment will investigate the relationship between subjects' genetic variability and study outcomes. Candidate genes included in this assessment may be related to, or hypothesized to be related to pharmacokinetics, safety features, drug mechanism of action, Tourette syndrome, or related diseases. The final list of genes to be evaluated will be determined at the time of analysis to be able to account for the most current research.	At the screening visit, a blood sample (5 to 6 mL) will be obtained for analysis of CYP2D6 genotype. The patient's genotype for CYP2D6 will remain blinded during the conduct of the study. If the patient elects this option on the optional informed consent, the remaining sample will be stored for exploratory pharmacogenetics (PGx) evaluation. This PGx assessment will investigate the relationship between subjects' genetic variability and study outcomes. Candidate genes included in this assessment may be related to, or hypothesized to be related to pharmacokinetics, safety features, drug mechanism of action, Tourette syndrome, or related diseases. The final list of genes to be evaluated will be determined at the time of analysis to be able to account for the most current research.	This section was updated to include greater clarity on the process of CYP2D6 genotyping and the genetic samples that may be obtained from patients.
9.5.4.3 Key Secondary Efficacy Analyses		
A hierarchical (fixed-sequence) testing approach will be used for the analysis of the primary and key secondary endpoints to maintain the experiment-wise type I error rate of 5%. If an endpoint is not statistically significant, confirmatory hypothesis testing will not be carried out on the remaining hypotheses, and remaining hypotheses will be considered exploratory rather than confirmatory. The change in the TS CGI (1), ~~(2),~~ and C&A-GTS-QOL ~~physical~~/ADL subscale (3) scores from baseline to week 12 will be	A hierarchical (fixed-sequence) testing approach will be used for the analysis of the primary and key secondary endpoints to maintain the experiment-wise type I error rate of 5%. If an endpoint is not statistically significant, confirmatory hypothesis testing will not be carried out on the remaining hypotheses, and remaining hypotheses will be considered exploratory rather than confirmatory. The change in the TS CGI (1) and C&A-GTS-QOL ADL subscale (3) scores from baseline to week 12 will be summarized and	This section was updated to present the changes in the key secondary efficacy endpoints and analyses (ie, the addition of TS-PGII, the removal of TS-PGIS, and the use of the child and adolescent version of the GTS-QOL scale.)

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
summarized and analyzed in the same fashion as the primary analysis, with the exception that the baseline value of the given endpoint will be included as the covariate. TS PGII (2) will be analyzed using a Cochran-Mantel-Haenszel row mean score test with a modified ridit scoring that controls for age group.	analyzed in the same fashion as the primary analysis, with the exception that the baseline value of the given endpoint will be included as the covariate. TS PGII (2) will be analyzed using a Cochran-Mantel-Haenszel row mean score test with a modified ridit scoring that controls for age group.	
9.5.4.4 Exploratory Analyses		
[redacted]	[redacted]	This section was updated to present the changes in the exploratory endpoints and analyses [redacted]

Protocol Amendment 01 text with changes shown	New wording	Reason/Justification for change
[redacted]		
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 P450 inhibitor. Prohibited medications that are associated with QTc prolongation are listed in Table 6, while prohibited antipsychotic drugs are listed in Table 7. "Table 6: Prohibited QTc Prolonging Drugs" was added to the protocol	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. Prohibited medications that are associated with QTc prolongation are listed in Table 6, while prohibited antipsychotic drugs are listed in Table 7. "Table 6: Prohibited QTc Prolonging Drugs" was added to the protocol	Table 6: Prohibited QTc Prolonging Drugs" was added to the protocol to include additional safety precautions and exclusion criteria.
APPENDIX I. TOURETTE SYNDROME-PATIENT GLOBAL IMPRESSION OF IMPACT AND SEVERITY		
Appendix I was updated to include only PGIS and PGII assessments from the latest RTI report. Assessments of change and the parent/guardian items were removed.	Appendix I was updated to include only PGIS and PGII assessments from the latest RTI report.	Appendix I was updated to include only PGIS and PGII assessments from the latest RTI report. Assessments of change and the parent/guardian items were removed.
APPENDIX K. CHILD AND ADOLESCENT GILLES DE LA TOURETTE SYNDROME – QUALITY OF LIFE SCALE FOR PATIENTS AGED 13 TO 18 YEARS (C&A-GTS-QOL 13-18)		
The existing GTS-QOL scale was replaced by the Children and Adolescent version of the scale for patients aged 6 to 12 (C&A-GTS-QOL 6-12) and aged 13 to 18 (C&A-GTS-QOL 13-18)	The Children and Adolescent version of the scale for patients aged 6 to 12 (C&A-GTS-QOL 6-12) and aged 13 to 18 (C&A-GTS-QOL 13-18) replaced the existing GTS-QOL scale.	The existing GTS-QOL scale was replaced by the Children and Adolescent version of the scale for patients aged 6 to 12 (C&A-GTS-QOL 6-12) and aged 13 to 18 (C&A-GTS-QOL 13-18), in alignment with the adjustments made to the secondary and exploratory endpoints.

17.3. Amendment 03 Dated 06 November 2017

The primary reason for this amendment is to update dosing instructions/timing, further specify timing of enrollment into the open-label extension study TV50717-CNS-30047, update pregnancy language, and update the timing/frequency of a few assessments.

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 02 text with changes shown	**New wording**	**Reason/Justification for change**
Section 3.1.1 Overall Design and Screening Period (Other section affected by this change: 3.1.5 Washout Period and Follow-up)		
Patients who complete the study may be eligible to begin participation in an open-label safety extension study TV50717-CNS-30047 after the end of the washout period. <u>At the week 13 visit, patients may choose to enter study TV50717-CNS-30047 (on that day), or they will have an additional week to make a decision and return for day 1.</u> Patients not participating in Study TV50717-CNS-30047 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 who complete the study may be eligible to begin participation in an open-label safety extension study TV50717-CNS-30047 after the end of the washout period. At the week 13 visit, patients may choose to enter study TV50717-CNS-30047 (on that day), or they will have an additional week to make a decision and return for day 1. Patients not participating in Study TV50717-CNS-30047 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 clarify the timing of participation/enrollment into open-label study TV50717-CNS-30047
Section 3.1.5 Washout Period and Follow up (Figure 1)		
Not applicable	[Minor updates were made to Figure 1. An updated Figure 1 was inserted.]	Minor updates were made to Figure 1 to enhance the clarity of the study design and anticipated enrollment numbers
Section 3.4 Safety Measures and Time Points		
• 12-lead ECG: Screening<u>; baseline;</u> and weeks 4, 6, and 12 • Pregnancy testing: Screening, baseline, and ~~week~~<u>weeks 4 and</u> 12	• 12-lead ECG: Screening; baseline; and weeks 4, 6, and 12 • Pregnancy testing: Screening, baseline, and weeks 4 and 12	Updated to include specific assessments at additional time points

Protocol Amendment 02 text with changes shown	New wording	Reason/Justification for change
Section 3.13 Study Procedures (Table 1)		
Not applicable	[Minor updates were included in Table 1. Assessments were added/removed, and footnotes were edited/adjusted. Updates were made in alignment with assessments added/removed within the protocol. Visit windows were also adjusted]	Updates were made to the table and table footnotes in alignment with assessments added/removed within the protocol, in order to enhance protocol clarity
Section 3.13.1 Procedures for Screening and Enrollment (Other sections affected by this change: 3.13.2 and 3.13.3.2.2)		
The screening visit will take place not more than 31 days ~~and no less than 3 days~~ before the baseline visit. The screening visit may be conducted over 2 separate visits at the discretion of the investigator. The following procedures will be performed at screening: • perform a serum pregnancy (beta human chorionic gonadotropin [β-HCG]) test (only in females ~~of childbearing potential~~who are postmenarchal or ≥12 years of age)	The screening visit will take place not more than 31 days before the baseline visit. The screening visit may be conducted over 2 separate visits at the discretion of the investigator. The following procedures will be performed at screening: • perform a serum pregnancy (beta human chorionic gonadotropin [β-HCG]) test (only in females who are postmenarchal or ≥12 years of age)	Screening visit updated to be "up to 31 days" before the baseline visit, in alignment with the table of assessments Updated the definition of females of childbearing potential throughout the protocol
Section 3.13.3.1.2 Clinic Visits (Weeks 2, 4, and 6)		
Not applicable	• perform urine pregnancy (β-HCG) test at week 4 (only in females who are postmenarchal or ≥12 years of age)	Updated to add the assessment of a urine pregnancy test at week 4, per updates made to Table 1
Section 3.13.5 Unscheduled Visits		
• perform a urine/serum pregnancy (β-HCG) test (only in females who are postmenarchal or ≥12 years of age)	• perform a urine/serum pregnancy (β-HCG) test (only in females who are postmenarchal or ≥12 years of age)	Updated to include that the urine pregnancy test should only occur in "females who are postmenarchal or ≥12 years of age"
Section 4.1.Patient Inclusion Criteria		
j. Females ~~of childbearing potential~~who are postmenarchal or ≥12 years of age may be included only if they have a negative β HCG test at baseline or are sterile. Definitions of	j. Females who are postmenarchal or ≥12 years of age may be included only if they have a negative β HCG test at baseline or are sterile. Definitions	Updated the inclusion criteria to more specifically define females of childbearing potential and to adjust some of the text

Protocol Amendment 02 text with changes shown	New wording	Reason/Justification for change
sterile is given in .Appendix L k. Females who are postmenarchal or ≥12 years of age ~~childbearing potential~~ whose male partners are potentially fertile (ie, no vasectomy) ~~or female partners of male participants~~ 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	of sterile is given in Appendix L. k. Females who are postmenarchal or ≥12 years of age whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study (ie, starting at screening) and for 30 days or 5 half-lives, whichever is longer after last dose of IMP. Further details are included in .Appendix L	regarding birth-control methods
Section 5.1. Drugs Administered During the Study		
• 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~~must be notified. Table 2 was updated	• Dose reductions, if required, should be in increments of 6 mg. If more than 1 dose reduction is required for an adverse event, the medical monitor must be notified. [Table 2 was updated to remove specification of dosing "week." The timing of dosing and dosing instructions are indicated by study day.] [Footnote "a" was also updated to correct the start time of a patient's new dose.]	Updated to include more clear direction and instruction on the timing of IMP dosing during the study
Section 5.5 Dose Reduction and Temporary IMP Discontinuation		
Dose Reduction If more than 1 dose reduction is required for an adverse event, the medical monitor ~~should~~must be notified. **Dose Suspension** The patients who restart IMP treatment will follow the visit schedule as outlined in ~~the protocol.~~Table 1.	**Dose Reduction** If more than 1 dose reduction is required for an adverse event, the medical monitor must be notified. **Dose Suspension** The patients who restart IMP treatment will follow the visit schedule as outlined in Table 1.	Updated to more clearly guide study personnel on the expectations following dose reductions or suspensions
Section 7.3.Pregnancy		
All pregnancies of female patients participating in the study ~~and female partners of male patients participating~~	All pregnancies of female patients participating in the study that occur during the study, or	Updated pregnancy language.

Protocol Amendment 02 text with changes shown	New wording	Reason/Justification for change
~~in the study~~ that occur during the study, or within 14 days after the end of the study, are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the investigator must provide the sponsor (LSO/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 baseline, provided no IMP was given. All female patients ~~or female partners of male 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. ~~Since this IMP has suspected human teratogenicity, genotoxicity, fetotoxicity, or spermatoxicity, female partners of male patients participating in the study who become pregnant will be asked to sign an informed consent form and 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~~	within 14 days after the end of the study, are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the investigator must provide the sponsor (LSO/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 baseline, provided no IMP was given. All female patients who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous, elective, or voluntary abortion). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after withdrawal from the study will be reported as an adverse event or serious adverse event, as appropriate. If the pregnancy in the female patients participating in the study does not continue to term, 1 of the following actions will be taken:	

Protocol Amendment 02 text with changes shown	New wording	Reason/Justification for change
~~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 patients participating in the study ~~and/or the female partners of male patients participating in the study~~ does not continue to term, 1 of the following actions will be taken:		
Section 7.5.2.1. Human Chorionic Gonadotrophin Test		
Human chorionic gonadotrophin tests in urine or serum will be performed for all females ~~of childbearing potential~~who are postmenarchal or ≥12 years of age as detailed in Table 1, and if clinically indicated.	Human chorionic gonadotrophin 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.	Updated to more specifically define females of childbearing potential
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. 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~~	**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 **Recommendations for application of birth control methods:** • IMP (TEV-50717) with possible human teratogenicity/fetotoxicity - Highly effective method of contraception	Updated pregnancy expectations/language/risks to be consistent with changes made to the protocol

Protocol Amendment 02 text with changes shown	New wording	Reason/Justification for change
~~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~~Recommendations for application of birth control methods:** • IMP (TEV-50717) with possible human teratogenicity/fetotoxicity - Highly effective method of contraception - Contraception during treatment and until the end of relevant systemic exposure - Additional pregnancy testing to be considered; as a minimum, at the end of relevant systemic exposure - In each case of delayed menstrual period (over 1 month between menstruations), confirmation of absence of pregnancy is strongly recommended. This recommendation also applies to women of childbearing potential with infrequent or irregular menstrual cycles. **Highly effective birth control methods:** Highly effective birth control methods that can achieve a failure rate of less than 1% per year when used	- Contraception during treatment and until the end of relevant systemic exposure - Additional pregnancy testing to be considered; as a minimum, at the end of relevant systemic exposure - In each case of delayed menstrual period (over 1 month between menstruations), confirmation of absence of pregnancy is strongly recommended. This recommendation also applies to women of childbearing potential with infrequent or irregular menstrual cycles. **Highly effective birth control methods:** Highly effective birth control 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 before the first dose of IMP. **Unacceptable birth control methods:** Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea	

Protocol Amendment 02 text with changes shown	New wording	Reason/Justification for change
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. ~~**Acceptable birth control methods:**~~ ~~Acceptable birth control methods that result in a failure rate of more than 1% per year include: progestogen-only oral hormonal contraception for which the inhibition of ovulation is not the primary mode of action; male or female condom with or without spermicide; cap, diaphragm, or sponge with spermicide. The combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable but not highly effective methods of birth control.~~ **Unacceptable birth control methods:** Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.	method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together. **Pregnancy tests in females of childbearing potential:** 1. Consider additional pregnancy testing, but at least at the end of relevant systemic exposure.	

Protocol Amendment 02 text with changes shown	New wording	Reason/Justification for change
~~**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 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~~		

Protocol Amendment 02 text with changes shown	New wording	Reason/Justification for change
~~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.~~		

17.4. Amendment 04 Dated 13 September 2018

The primary reason for this amendment is to 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 and security; update/clarify patient inclusion criteria, exclusion criteria, and withdrawal criteria; provide updates on allowed and prohibited medications; include additional guidance for evaluation and handling of suicidal ideation, suicidal behavior, and depression; and to streamline birth control methods language for females of childbearing potential.

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 03 text with changes shown	**New wording**	**Reason/Justification for change**
LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS		
Central Clinical Laboratory Q2 Solutions (Quest) LLC~~1201 S. Collegeville Road~~ ~~Collegeville, PA 19426~~ 27027 Tourney Road, Suite 2E Valencia, CA 91355 USA	**Central Clinical Laboratory** Q2 Solutions (Quest) LLC 27027 Tourney Road, Suite 2E Valencia, CA 91355 USA	Administrative change.
Contract Research Organization; Safety and Efficacy Data Analysis INC Research, LLC, a Syneos health group company ("Syneos Health") 3201 Beechleaf Court Suite 600 Raleigh, NC 27604-1547 USA	**Contract Research Organization; Safety and Efficacy Data Analysis** INC Research, LLC, a Syneos health group company ("Syneos Health") 3201 Beechleaf Court Suite 600 Raleigh, NC 27604-1547 USA	Administrative change.
Central Electrocardiogram Evaluation ~~Biomedical Systems~~ ~~77 Progress Parkway~~ ~~St. Louis, MO 63043~~ ERT 1818 Market Street 10th Floor Philadelphia, PA 19103 USA **Integrated Response Technology**	**Central Electrocardiogram Evaluation** ERT 1818 Market Street 10th Floor Philadelphia, PA 19103 USA **Integrated Response Technology** Endpoint 55 Francisco Street, Suite 200	Change in central ECT and IRT vendors.

Protocol Amendment 03 text with changes shown	New wording	Reason/Justification for change
~~Bracket Global, LLC~~ ~~575 East Swedesford Road~~ Endpoint 55 Francisco Street, Suite 200 ~~Wayne, PA 19087~~ San Francisco, CA 94133 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.~~	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] **For medical issues, contact the physician listed below:** [redacted] ~~**For operational issues, contact the operational lead listed below:**~~ [redacted]	**Sponsor's Authorized Representative:** [redacted] **For medical issues, contact the physician listed below:** [redacted]	Update to the Sponsor's authorized representative. In addition, medical director/medical monitor contacts outside of North America have been included. Administrative changes carried out for clarity.

Protocol Amendment 03 text with changes shown	New wording	Reason/Justification for change
[redacted]	[redacted] **For protocol issues, contact the study leaders listed below:** [redacted]	

Protocol Amendment 03 text with changes shown	New wording	Reason/Justification for change
For protocol issues, contact the study ~~leader~~leaders listed below: [redacted] [redacted] [redacted]	[redacted] **For operational issues, contact the operational lead listed below:** [redacted]	
CLINICAL STUDY PROTOCOL SYNOPSIS		
Type of the Study ~~Phase of Clinical Development~~: Efficacy and Safety (Phase 2/3)	**Type of the Study:** Efficacy and Safety **(**Phase 2/3)	Template update.
CLINICAL STUDY PROTOCOL SYNOPSIS (Other sections affected by this change: 3.1.2 Screening Period, 3.4 Safety Measures and Time Points, 3.13.1 Procedures for Screening and Enrollment, 4.1 Patient Inclusion Criteria, 5.2 Restrictions, 7.1.2 Recording and Reporting Adverse Events, 7.1.5 Serious Adverse Events, 11.3 Study Monitoring, 12.1 Informed Consent/Assent, 13.1 Data Collection, 13.3.2 Investigator Responsibilities**)**		
After informed consent ~~(and written~~ /assent ~~and/or co-consent for patients 14 years of~~, depending on the child's age ~~and older~~, as appropriate~~)~~, is obtained	After informed consent/assent, depending on the child's age, as appropriate, is obtained	Provisions on informed consent/assent have been more clearly provided
CLINICAL STUDY PROTOCOL SYNOPSIS (Other sections affected by this change: 3.1.2 Screening Period)		

Protocol Amendment 03 text with changes shown	**New wording**	**Reason/Justification for change**
At the discretion of the investigator, the screening visit may be divided into 2 visits if the visit length is felt to be too burdensome for the patient. If the screening visit is divided into 2 visits, the blood sample should be obtained during the first of the 2 visits.	At the discretion of the investigator, the screening visit may be divided into 2 visits if the visit length is felt to be too burdensome for the patient. If the screening visit is divided into 2 visits, the blood sample should be obtained during the first of the 2 visits.	Guidance provided on the timing of obtaining blood samples in situations where the screening visit is divided into 2 visits.
CLINICAL STUDY PROTOCOL SYNOPSIS (Other sections affected by this change: 3.1.2 Screening Period, 3.13.1 Procedures for Screening and Enrollment)		
(Note: Details of rescreening must be approved.) and documented by the medical monitor and/or Clinical Surveillance and Training (CST) team.	(Note: Details of rescreening must be approved and documented by the medical monitor and/or Clinical Surveillance and Training [CST] team.)	Further elaborated on the documentation process for rescreening of patients.
CLINICAL STUDY PROTOCOL SYNOPSIS (Other sections affected by this change: 3.13.1 Procedures for Screening and Enrollment, 4.1 Patient Inclusion Criteria, 12.1 Informed Consent/Assent)		
Patient and caregiver/adult (may also include an adult other than a parent or legal representative).	Patient and caregiver/adult (may also include an adult other than a parent or legal representative).	Provisions on informed consent/assent have been more clearly provided.
CLINICAL STUDY PROTOCOL SYNOPSIS (Other sections affected by this change: 4.2 Patient Exclusion Criteria)		
Patient has received any of the following concomitant medications for tics within the specified exclusionary washout windows of screening first dose: Withinwithin 3 months: depot neuroleptics, botulinum toxin, or tetrabenazine Withinwithin 4 weeks: cannabidiol oil and Valbenazine within 21 days: reserpine	Patient has received any of the following concomitant medications for tics within the specified exclusionary washout windows of first dose: within 3 months: depot neuroleptics, botulinum toxin, or tetrabenazine within 4 weeks: cannabidiol oil and valbenazine within 21 days: reserpine	Further guidance provided on prohibited and allowed medication.

Protocol Amendment 03 text with changes shown	New wording	Reason/Justification for change
~~Within~~within 14 days: neuroleptics (oral), typical and atypical antipsychotics (see Appendix A), metoclopramide, levodopa, and dopamine agonists Note: Use of stimulant medications, including amphetamine, methylphenidate, and lisdexamfetamine, is allowed if primary use is for the treatment of ADHD, dosing has been stable for at least 2 weeks before screening, and no changes to dose or frequency are anticipated during the course of the study. Note: Use of atomoxetine is allowed if the primary use is for the treatment of ADHD, dosing has been stable for at least 4 weeks before screening, and no changes to dose or frequency are anticipated during the course of the study. Note: Use of benzodiazepines is allowed if primary use is not for tics and dosing has been stable for at least 4 weeks before screening. Note: Use of topiramate (up to 200 mg/day) is allowed if dosing has been stable for at least 4 weeks before screening. Note: Use of guanfacine or clonidine is allowed ~~if~~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. If discontinuation of either medication is anticipated due to ineffectiveness, poor tolerability, or patient/caregiver preference, discontinuation should occur 4 or more weeks prior to the screening visit.	within 14 days: neuroleptics (oral), typical and atypical antipsychotics (see Appendix A), metoclopramide, levodopa, and dopamine agonists Note: Use of stimulant medications, including amphetamine, methylphenidate, and lisdexamfetamine, is allowed if primary use is for the treatment of ADHD, dosing has been stable for at least 2 weeks before screening, and no changes to dose or frequency are anticipated during the course of the study. Note: Use of atomoxetine is allowed if the primary use is for the treatment of ADHD, dosing has been stable for at least 4 weeks before screening, and no changes to dose or frequency are anticipated during the course of the study. Note: Use of benzodiazepines is allowed if primary use is not for tics and dosing has been stable for at least 4 weeks before screening. Note: Use of topiramate (up to 200 mg/day) is allowed if dosing has been stable for at least 4 weeks before screening. Note: Use of guanfacine or clonidine is allowed regardless of indication (ie, if prescribed for tics or 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. If discontinuation of either medication is anticipated due to ineffectiveness, poor tolerability, or patient/caregiver preference, discontinuation should occur 4 or more weeks prior to the screening visit.	
CLINICAL STUDY PROTOCOL SYNOPSIS (Other sections affected by this change: 8.3.1 CYP2D6 Genotyping/Pharmacogenetics)		
At the screening visit, a blood sample (~~5 to 6~~3 mL) will be obtained for analysis of CYP2D6 genotype. The patient's genotype for CYP2D6 will remain blinded during the conduct of the study. If the patient elects ~~this option~~ for PGx evaluation on the	At the screening visit, a blood sample (3 mL) will be obtained for analysis of CYP2D6 genotype. The patient's genotype for CYP2D6 will remain blinded during the conduct of the study. If the patient elects for PGx evaluation on the optional informed	Clarification on PGx sampling and details.

Protocol Amendment 03 text with changes shown	New wording	Reason/Justification for change
optional informed consent/assent, a pharmacogenetic (PGx) ~~the remaining~~ sample (2 mL) will be obtained and stored for exploratory ~~pharmacogenetics~~ PGx evaluation.	consent/assent, a pharmacogenetic (PGx) sample (2 mL) will be obtained and stored for exploratory PGx evaluation.	
CLINICAL STUDY PROTOCOL SYNOPSIS (Other sections affected by this change: 9.5.4.1 Primary Efficacy Analysis)		
The baseline TTS, region, and age group at baseline will be included as covariates.	The baseline TTS, region, and age group at baseline will be included as covariates.	Addition of region to covariate list.
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~~deutetrabenazine (referred to as TEV-50717 ~~or~~, previously SD-809) that is eliminated more slowly than tetrabenazine. 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~~.~~ and for the treatment of chorea associated with TD on 30 August 2017.	To address the limitations of commercial tetrabenazine (Xenazine®), Auspex, a wholly owned subsidiary of Teva Pharmaceutical Products R&D, Inc, developed deutetrabenazine (referred to as TEV-50717, previously SD-809) that is eliminated more slowly than tetrabenazine. TEV-50717 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 and for the treatment of chorea associated with TD on 30 August 2017.	Alignment of drug naming and drug approval status.
Section 1.3.1.3 Toxicology		
Not applicable	The NOAEL (no-observed-adverse-effect level) for toxicities in juvenile rats is lower than that in adults; however, the total (α+β)-HTBZ exposure multiples or safety margins comparing rat to humans at the adult and juvenile age categories are similar. The potential for increased sensitivity to the effects of TEV-50717 in pediatric patients is mitigated by two factors. First, the effects of TEV-50717 on behavior and weight gain recovered with cessation of test article	Nonclinical background information addition.

Protocol Amendment 03 text with changes shown	New wording	Reason/Justification for change
	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 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).	
Section 1.3.2 Clinical Studies		
The clinical development plan for TEV 50717 to date includes: • 6 completed Phase 1 studies in healthy adult subjects • 1 completed Phase 3 pivotal study for the treatment of chorea associated with HD • 1 ~~ongoing~~ completed 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 safety study in patients with TD • 1 completed Phase 1b study in patients with TS Further details may be found in the IB.	The clinical development plan for TEV 50717 to date includes: • 6 completed Phase 1 studies in healthy adult subjects • 1 completed Phase 3 pivotal study for the treatment of chorea associated with HD • 1 completed Phase 3 long-term safety study in patients with HD • 2 completed Phase 2/3 and Phase 3 studies in patients with TD • 1 ongoing Phase 3 long-term safety study in patients with TD • 1 completed Phase 1b study in patients with TS Further details may be found in the IB.	Update to current clinical study status within the clinical development plan for TEV-50717.
Figure 1: Overall Study Schema		
[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 taking strong CYP inhibitors such as paroxetine/fluoxetine/bupropion~~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).	[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).	Clarity for CYP2D6 impaired.
Section 3.9.1 Drug Storage and Security		

Protocol Amendment 03 text with changes shown	**New wording**	**Reason/Justification for change**
The IMP (TEV-50717 and placebo) must 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 ~~to~~and 30°C (59°F to 86°F~~),~~) is acceptable if there is no alternative. The IMP should be stored in a dry, securely locked, substantially constructed cabinet or enclosure with access limited to authorized staff.	The IMP (TEV-50717 and placebo) must 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 30°C (59°F to 86°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.	Drug storage and security specification.
Section 3.9.2 Drug Accountability		
Empty, partially used, and unused IMP will be ~~returned to the sponsor or its designee~~disposed of, as agreed with the sponsor/development partner.	Empty, partially used, and unused IMP will be disposed of, as agreed with the sponsor/development partner.	Drug disposal details.
Table 1: Study Procedures and Assessments		
Informed consent/assent ~~and/or co-consent for patients 14 years of age and older~~	Informed consent/assent	Provisions on informed consent/assent have been more clearly provided
Not applicable	[w] Contact IRT and dispense IMP and patient diary.	Addition of footnote to study procedures for specification.
Table 1: Study Procedures and Assessments, footnote c (Other sections affected by this change: 3.13.2 Procedures Before IMP Treatment [Baseline/Day 1])		
Patients will be provided with a diary to record ~~meal times and~~ critical information on dosing.	Patients will be provided with a diary to record critical information on dosing.	Clarification of diary entries.
Section 3.13.1 Procedures for Screening and Enrollment		
• obtain a blood sample (~~5~~3 mL) for analysis of CYP2D6 genotype	• obtain a blood sample (3 mL) for analysis of CYP2D6 genotype	Blood sample quantity specification.

Protocol Amendment 03 text with changes shown	New wording	Reason/Justification for change
Section 3.13.2 Procedures Before IMP Treatment (Baseline/Day 1) (Other sections affected by this change: 3.13.3.1.2 Clinic Visits [Weeks 2, 4, and 6] and 3.13.3.2.1 Week 9)		
• dispense IMP (…) and patient diary	• dispense IMP (…) and patient diary	Clarification that patient diaries should also be dispensed at these visits/weeks.
Section 4.4 Withdrawal Criteria and Procedures		
The investigator also has the right to withdraw a patient from the study ~~in~~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 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~~ e. lack of cooperation~~. If a~~ f. post-baseline QTcF value >500 msec or change from baseline >60 msec ~~is found, the~~(as described in Sections 4.3 and 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	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 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 Sections 4.3 and 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.	Withdrawal criteria elaboration.

Protocol Amendment 03 text with changes shown	New wording	Reason/Justification for change
from baseline >60 msec. g. when a blind is broken due to safety concerns (see Section 3.7.2). If a patient is unblinded by mistake, they should not 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).	g. when a blind is broken due to safety concerns (see Section 3.7.2). If a patient is unblinded by mistake, they should not 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).	
Section 5.2 Restrictions		
While patients receiving strong CYP2D6 inhibitors (such as paroxetine, fluoxetine, and bupropion) at baseline may be enrolled into this study, the addition or removal of strong CYP2D6 inhibitors during treatment is discouraged as this would have an effect on exposure to active circulating drug. If the addition or removal of a strong CYP2D6 inhibitor is required from a clinical perspective, the medical monitor should be contacted so an appropriate change in IMP can be made. The use of quinidine and terbinafine are prohibited (see Appendix A, Table 8).	While patients receiving strong CYP2D6 inhibitors such as paroxetine, fluoxetine, and bupropion at baseline may be enrolled into this study, the addition or removal of strong CYP2D6 inhibitors during treatment is discouraged as this would have an effect on exposure to active circulating drug. If the addition or removal of a strong CYP2D6 inhibitor is required from a clinical perspective, the medical monitor should be contacted so an appropriate change in IMP can be made. The use of quinidine and terbinafine are prohibited (see Appendix A, Table 8).	Clarification on the use of quinidine and terbinafine as prohibited.
Section 5.5 Dose Reduction and Temporary IMP Discontinuation		
Suspension of study medication for up to 1 ~~one~~ week, if warranted for patient safety, is allowed. If the patient restarts study medication within 7 days of suspension, the full dose of TEV-50717 may be resumed without titration. **Suspensions of study medication for adverse events must be reviewed with the medical monitor before therapy is restarted**. If a subject's serum potassium or magnesium ~~falls~~were tested and found to be below the lower limit of normal, IMP must be suspended. The Medical Monitor must be contacted to	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, IMP must be suspended. The medical monitor must be contacted to determine the	Blood sampling quantity specification.

<table>
<tr><th>Protocol Amendment 03 text with changes shown</th><th>New wording</th><th>Reason/Justification for change</th></tr>
<tr><td>determine the appropriate investigation and treatment. ~~SD-809~~TEV-50717 may only be restarted once serum potassium or magnesium have normalized. ~~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.~~</td><td>appropriate investigation and treatment. TEV-50717 may only be restarted once serum potassium or magnesium have normalized.</td><td></td></tr>
<tr><td colspan="3">Table 3: Blood Volumes</td></tr>
<tr><td>
<table>
<tr><th>Type of samples</th><th>Volume per sample</th><th>Total number of samples</th><th>Total volume</th></tr>
<tr><td>Clinical laboratory (chemistry/hematology)</td><td>10 mL</td><td>2</td><td>20 mL</td></tr>
<tr><td>Pharmacokinetic</td><td>5 mL</td><td>1 time point (week 12) × 2 samples</td><td>10 mL</td></tr>
<tr><td>CYP2D6 genotyping</td><td>~~5~~3 mL</td><td>1</td><td>~~5~~3 mL</td></tr>
<tr><td><u>Optional pharmacogenetic sample</u></td><td><u>2 mL</u></td><td><u>1</u></td><td><u>2 mL</u></td></tr>
<tr><td>Total</td><td></td><td></td><td>35 mL</td></tr>
</table>
CYP2D6=cytochrome P450 2D6.
Note: beta human chorionic gonadotropin testing (in females who are postmenarchal or ≥12 years of age) is included in the clinical laboratory sample.
</td><td>
<table>
<tr><th>Type of samples</th><th>Volume per sample</th><th>Total number of samples</th><th>Total volume</th></tr>
<tr><td>Clinical laboratory (chemistry/hematology)</td><td>10 mL</td><td>2</td><td>20 mL</td></tr>
<tr><td>Pharmacokinetic</td><td>5 mL</td><td>1 time point (week 12) × samples</td><td>10 mL</td></tr>
<tr><td>CYP2D6 genotyping</td><td>3 mL</td><td>1</td><td>3 mL</td></tr>
<tr><td>Optional pharmacogenetic sample</td><td>2 mL</td><td>1</td><td>2 mL</td></tr>
<tr><td>Total</td><td></td><td></td><td>35 mL</td></tr>
</table>
CYP2D6=cytochrome P450 2D6.
Note: beta human chorionic gonadotropin testing (in females who are postmenarchal or ≥12 years of age) is included in the clinical laboratory sample.
</td><td>Blood sampling quantity specification.</td></tr>
<tr><td colspan="3">Section 7.1.5.3.1 Investigator Responsibility</td></tr>
<tr><td>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</td><td>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</td><td>Clarification on the expectation of reporting</td></tr>
</table>

Protocol Amendment 03 text with changes shown	New wording	Reason/Justification for change
~~to the sponsor~~ 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.	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.	serious adverse events.
Section 7.2.2 Columbia-Suicide Severity Rating Scale		
The C-SSRS is an interview by trained study personnel. Suicidal ideation • Patients with a positive C-SSRS suicidal ideation score on either items 1 or 2 or a change on the CDI-2 Parent or Self-Report Profiles consistent with increasing depressive symptoms must be 1) discussed with the medical monitor, 2) re-evaluated within 2 to 3 days in a clinic visit, and 3) treated according to the investigator's medical judgment. Consultation with a child and adolescent psychiatrist or licensed child/adolescent mental health provider is advised, followed by close ongoing monitoring. • If patients 1) endorse or 2) report a C-SSRS suicidal ideation level of 3, 4, or 5, subjects will be evaluated immediately by the study investigator and referred for psychiatric evaluation. The medical monitor will be immediately consulted. If it is determined by the investigator, after consultation with the medical monitor and the consulting psychiatrist, that exposure to the IMP may have contributed to this change in C-SSRS and/or increased depressive symptoms, IMP will be immediately discontinued and the patient terminated from the study. In cases where it is determined that IMP did not contribute to changes in depression or suicidality, the	The C-SSRS is an interview by trained study personnel. Suicidal ideation • Patients with a positive C-SSRS suicidal ideation score on either items 1 or 2 or a change on the CDI-2 Parent or Self-Report Profiles consistent with increasing depressive symptoms must be 1) discussed with the medical monitor, 2) re-evaluated within 2 to 3 days in a clinic visit, and 3) treated according to the investigator's medical judgment. Consultation with a child and adolescent psychiatrist or licensed child/adolescent mental health provider is advised, followed by close ongoing monitoring. • If patients 1) endorse or 2) report a C-SSRS suicidal ideation level of 3, 4, or 5, subjects will be evaluated immediately by the study investigator and referred for psychiatric evaluation. The medical monitor will be immediately consulted. If it is determined by the investigator, after consultation with the medical monitor and the consulting psychiatrist, that exposure to the IMP may have contributed to this change in C-SSRS and/or increased depressive symptoms, IMP will be immediately discontinued and the patient terminated from the study. In cases where it is determined that IMP did not contribute to changes in depression or suicidality, the	Suicide and depression details required by authorities.

Protocol Amendment 03 text with changes shown	New wording	Reason/Justification for change
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.	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.	
Section 7.5.3 Cytochrome P450 2D6 Genotyping		
One ~~5~~3-mL sample for CYP2D6 genotyping will be collected from all patients in the study at screening.	One 3-mL sample for CYP2D6 genotyping will be collected from all patients in the study at screening.	Blood sampling quantity specification.
Section 7.9 Assessment of Suicidality		
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. ~~Families and caregivers of participants being treated with TEV-50717 should be instructed to monitor participants for the~~	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. Baseline assessment of suicidal ideation and behavior and treatment-emergent suicidal ideation and behavior will be assessed	Suicide and depression details required by authorities.

Protocol Amendment 03 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.~~Baseline 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 subjects in Study 30046 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.	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 subjects in Study 30046 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.	

Protocol Amendment 03 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.		
Section 8.3.1 CYP2D6 Genotyping/Pharmacogenetics		
At the screening visit, a blood sample (~~5 to 6~~3 mL) will be obtained for analysis of CYP2D6 genotype. The patient's genotype for CYP2D6 will remain blinded during the conduct of the study. If the patient elects ~~this option~~ for PGx evaluation on the optional informed consent/assent, ~~the remaining~~ a pharmacogenetic (PGx) sample (2 mL) will be obtained and stored for exploratory ~~pharmacogenetics (PGx) evaluation~~PGx.	At the screening visit, a blood sample (3 mL) will be obtained for analysis of CYP2D6 genotype. The patient's genotype for CYP2D6 will remain blinded during the conduct of the study. If the patient elects for PGx evaluation on the optional informed consent/assent, a pharmacogenetic (PGx) sample (2 mL) will be obtained and stored for exploratory PGx.	Clarification on PGx sampling and details.
Section 9.2.1 Intent-to-Treat Analysis Set		
Not applicable	Enrolled subjects who are not randomized will be summarized separately as "Not randomized," and randomized subjects will be analyzed based on their randomized treatment.	ITT analysis population specification.
Section 9.2.4 Per-Protocol Analysis Set		
The per-protocol analysis set will include patients who are compliant with study medication (80% to 105%), have a YGTSS assessment at baseline and at week 9 or week 12, ~~and~~ who have not taken prohibited concomitant medications as indicated in exclusion criterion, and who have no major protocol deviations that affect the validity of the efficacy measurements. The list of protocol deviations will be reviewed before unblinding and major protocol deviations that could affect the primary and secondary variables will be determined. All exclusions from the per-protocol analysis set will be reviewed in the blinded data review meeting before database lock.	The per-protocol analysis set will include patients who are compliant with study medication (80% to 105%), have a YGTSS assessment at baseline and at week 9 or week 12, who have not taken prohibited concomitant medications as indicated in exclusion criterion, and who have no major protocol deviations that affect the validity of the efficacy measurements. The list of protocol deviations will be reviewed before unblinding and major protocol deviations that could affect the primary and secondary variables will be determined. All exclusions from the per-protocol analysis set will be reviewed in the blinded data review meeting before database lock.	Protocol deviation elaboration.
Section 9.5.4.1 Primary Efficacy Analysis		

Protocol Amendment 03 text with changes shown	**New wording**	**Reason/Justification for change**
The baseline TTS, region, and age group at baseline (2 levels: 6 to 11 years, 12 to 16 years) will be included as ~~a covariate~~covariates.	The baseline TTS, region, and age group at baseline (2 levels: 6 to 11 years, 12 to 16 years) will be included as covariates.	Addition of region to covariate list.
Section 9.5.4.2 Sensitivity Analysis		
~~To assess the robustness of the primary efficacy analysis, the following additional~~Sensitivity analyses ~~will include:Using the same repeated measures model as described~~ for ~~the primary analysis, the groups will be compared using the per-protocol population.~~ ~~The primary analysis at week 12 will be repeated on a complete data set using multiple imputation methodology for imputing~~ missing data ~~using an MNAR missing data assumption to investigate when~~ and the statistical ~~significance disappears.~~ ~~Data will be imputed for patients missing data at week 12 using the predictive mean matching multiple imputation method (Heitjan and Little 1991, Schenker and Taylor 1996). Under a missing not at random data assumption, patients treated with TEV-50717 who discontinue the study for any reason other than "Lost to Follow-Up" will have their missing data at week 12 imputed. Only placebo patients will be included in the imputation model, while all other patients will have data imputed from a model derived from their assigned treatment group. The imputation model will include age group at baseline, baseline TTS score, and TTS scores at all visits up to week 12 where the TTS is scheduled to be collected. The resulting complete, imputed datasets will each be analyzed using the same model as the primary analysis model, and the resulting statistics combined using methodology provided by Rubin (1987) and Little and Rubin (2002). Details on imputing missing data and combining inferences from the resultant datasets will be~~model are provided in the statistical	Sensitivity analyses for missing data and the statistical model are provided in the statistical analysis plan.	Alignment of sensitivity analysis text with SAP.

<table>
<tr><th>Protocol Amendment 03 text with changes shown</th><th>New wording</th><th>Reason/Justification for change</th></tr>
<tr><td>analysis plan.</td><td></td><td></td></tr>
<tr><td colspan="3">Section 14 FINANCING AND INSURANCE</td></tr>
<tr><td>A separate clinical study agreement, including a study budget, will be signed between each principal investigator and ~~the sponsor (or~~ INC Research~~)~~ before the IMP is delivered.</td><td>A separate clinical study agreement, including a study budget, will be signed between each principal investigator and INC Research before the IMP is delivered.</td><td>Administrative change.</td></tr>
<tr><td colspan="3">APPENDIX A. ALLOWED AND DISALLOWED MEDICATIONS</td></tr>
<tr><td>Medications that are allowed, provided that conditions outlined in the table are met, are shown in Table 9. 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.

Table 5: Allowed Medications
<table>
<tr><th>Generic/Drug class</th><th>Condition</th></tr>
<tr><td colspan="2">Stable medications allowed according to inclusion/exclusions criteria</td></tr>
<tr><td>Hormonal birth control</td><td>Must be receiving stable treatment (including dose) for at least 3 months before screening.</td></tr>
<tr><td>Antidepressants</td><td>Must be receiving stable treatment (including dose) for at least 6 weeks before screening.</td></tr>
<tr><td>Benzodiazepines</td><td>Primary use must not be for tics; dosing must have been stable QT for at least 4 weeks before screening.
Note: PRN (as needed)</td></tr>
</table></td><td>Medications that are allowed, provided that conditions outlined in the table are met, are shown in Table 9. 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.

Table 5: Allowed Medications
<table>
<tr><th>Generic/Drug class</th><th>Condition</th></tr>
<tr><td colspan="2">Stable medications allowed according to inclusion/exclusions criteria</td></tr>
<tr><td>Hormonal birth control</td><td>Must be receiving stable treatment (including dose) for at least 3 months before screening.</td></tr>
<tr><td>Antidepressants</td><td>Must be receiving stable treatment (including dose) for at least 6 weeks before screening.</td></tr>
<tr><td>Benzodiazepines</td><td>Primary use must not be for tics; dosing must have been stable QT for at least 4 weeks before screening.
Note: PRN (as needed)</td></tr>
</table></td><td>To update the list of prohibited drugs, and to clarify prior and concomitant use of guanfacine, clonidine, stimulants, and SNRIs.</td></tr>
</table>

Protocol Amendment 03 text with changes shown		New wording		Reason/Justification for change
	use is prohibited.		**use is prohibited.**	
Topiramate (up to 200 mg/day)	Must be receiving stable treatment (including dose) for at least 4 weeks before screening.	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. If discontinuation of guanfacine is anticipated due to ineffectiveness, poor tolerability, or patient/caregiver preference, discontinuation should occur 4 or more weeks prior to the screening visit.	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. If discontinuation of guanfacine is anticipated due to ineffectiveness, poor tolerability, or patient/caregiver preference, discontinuation should occur 4 or more weeks prior to the screening visit.	
Clonidine	Allowed, regardless of indication (ie, if prescribed for tics or Tourette syndrome). Must be receiving stable treatment (including dose) for at least 4 weeks before screening and no changes to dose or frequency are anticipated during the course of the study. If discontinuation of clonidine is anticipated due to ineffectiveness, poor tolerability, or patient/caregiver preference, discontinuation should occur 4 or more weeks prior to the screening visit.	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. If discontinuation of clonidine is anticipated due to ineffectiveness, poor tolerability, or patient/caregiver preference, discontinuation should occur 4 or more weeks prior to the screening visit.	

Protocol Amendment 03 text with changes shown		New wording		Reason/Justification for change
Stimulants	Include amphetamine, methylphenidate, and lisdexamfetamine. Primary use is for the treatment of ADHD; dosing must have been stable for at least 2 weeks before screening and no changes to dose or frequency are anticipated during the course of the study.	Stimulants	Include amphetamine, methylphenidate, and lisdexamfetamine. Primary use is for the treatment of ADHD; dosing must have been stable for at least 2 weeks before screening and no changes to dose or frequency are anticipated during the course of the study.	
SNRIs	Includes atomoxetine. Primary use is for the treatment of ADHD; dosing must have been stable for at least 4 weeks before screening and no changes to dose or frequency are anticipated during the course of the study.	SNRIs	Includes atomoxetine. Primary use is for the treatment of ADHD; dosing must have been stable for at least 4 weeks before screening and no changes to dose or frequency are anticipated during the course of the study.	
Additional medications allowed with preapproval from medical monitor		**Additional medications allowed with preapproval from medical monitor**		
Albuterol, levalbuterol	Asthma	Albuterol, levalbuterol	Asthma	
Guaifenesin	Cold symptoms	Guaifenesin	Cold symptoms	
Antihistamines	Allergies	Antihistamines	Allergies	
Melatonin	Insomnia	Melatonin	Insomnia	
Allowed strong CYP inhibitors[a]		**Allowed strong CYP inhibitors**[a]		
Bupropion	Antidepressant (aminoketone)	Bupropion	Antidepressant (aminoketone)	
Fluoxetine	Antidepressant (selective serotonin reuptake inhibitor)	Fluoxetine	Antidepressant (selective serotonin reuptake inhibitor)	
Paroxetine	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-		a The use of these medications will affect the maximum daily dose of IMP, as shown in Table 2. ADHD=Attention-		

<table>
<tr><th>Protocol Amendment 03 text with changes shown</th><th>New wording</th><th>Reason/Justification for change</th></tr>
<tr><td>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 6: Prohibited Antipsychotic Drugs
<table><tr><th>Typical/first generation antipsychotics</th><th>Atypical/second generation antipsychotics</th></tr><tr><td>Chlorpromazine</td><td>Aripiprazole</td></tr><tr><td>Haloperidol</td><td>Asenapine maleate</td></tr><tr><td>Loxapine</td><td>Clozapine</td></tr><tr><td>Molindone</td><td>Iloperidone</td></tr><tr><td>Perphenazine</td><td>Lurasidone</td></tr><tr><td>Pimozide</td><td>Olanzapine</td></tr><tr><td>Prochlorperazine</td><td>Olanzapine/fluoxetine</td></tr><tr><td>Thioridazine</td><td>Paliperidone</td></tr><tr><td>Thiothixene</td><td>Quetiapine</td></tr><tr><td>Trifluoperazine</td><td>Risperidone</td></tr><tr><td>Promethazine-containing compounds</td><td>Ziprasidone</td></tr><tr><td>Fluphenazine</td><td>Tiapride</td></tr></table>Note: This table does not apply in the second week of washout for patients not rolling over to the open-label extension study (Study TV50717-CNS-30047).

Table 8: 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</td></tr></table></td><td>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 6: Prohibited Antipsychotic Drugs
<table><tr><th>Typical/first generation antipsychotics</th><th>Atypical/second generation antipsychotics</th></tr><tr><td>Chlorpromazine</td><td>Aripiprazole</td></tr><tr><td>Haloperidol</td><td>Asenapine maleate</td></tr><tr><td>Loxapine</td><td>Clozapine</td></tr><tr><td>Molindone</td><td>Iloperidone</td></tr><tr><td>Perphenazine</td><td>Lurasidone</td></tr><tr><td>Pimozide</td><td>Olanzapine</td></tr><tr><td>Prochlorperazine</td><td>Olanzapine/fluoxetine</td></tr><tr><td>Thioridazine</td><td>Paliperidone</td></tr><tr><td>Thiothixene</td><td>Quetiapine</td></tr><tr><td>Trifluoperazine</td><td>Risperidone</td></tr><tr><td>Promethazine-containing compounds</td><td>Ziprasidone</td></tr><tr><td>Fluphenazine</td><td>Tiapride</td></tr></table>Note: This table does not apply in the second week of washout for patients not rolling over to the open-label extension study (Study TV50717-CNS-30047).

Table 8: 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</td></tr></table></td><td></td></tr>
</table>

Protocol Amendment 03 text with changes shown			New wording			Reason/Justification for change
		of cannabinoids			of cannabinoids	
Valbenazine	Vesicular monoamine transporter 2 inhibitor	Ingrezza off-label	Valbenazine	Vesicular monoamine transporter 2 inhibitor	Ingrezza off-label	
Quinidine	Class I antiarrhythmic agent	Strong CYP2D6 inhibitor	Quinidine	Class I antiarrhythmic agent	Strong CYP2D6 inhibitor	
Terbinafine	Antifungal medication	Weak CYP2D6 inhibitor	Terbinafine	Antifungal medication	Weak CYP2D6 inhibitor	

17.5. Amendment 05 Dated 25 March 2019

The primary reason for this amendment is to update the anticipated patient enrollment numbers and related statistical considerations, update requirements on drug storage and security, to update/clarify patient inclusion criteria and withdrawal criteria, to update administrative details with regards to clinical study personnel contact information and vendor selection, and to provide additional guidance on dose suspension.

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 04 text with changes shown	New wording	Reason/Justification for change
Global		
~~INC Research~~Syneos Health	Syneos Health	Administrative update to account for vendor name change
Title Page		
~~601 Gateway Boulevard~~ ~~Suite 1270~~ ~~South San Francisco, California 94080~~ 101 Main Street, 12th Floor Cambridge, Massachusetts 02142	101 Main Street, 12th Floor Cambridge, Massachusetts 02142	Address update
This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International ~~Conference~~Council for Harmonisation (ICH); United States (US) Code of Federal Regulations (CFR), and European Union (EU) Directives and Regulations (as applicable in the region of the study); national country ~~regulations~~legislation; and the sponsor's Standard Operating Procedures (SOPs). This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Branded Pharmaceutical Products R&D and/or its affiliates and Nuvelution TS Pharma, INC. © ~~2017~~2019 Teva Branded Pharmaceutical Products R&D, Inc. and Nuvelution TS Pharma, INC. All rights reserved.	This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Council for Harmonisation (ICH); United States (US) Code of Federal Regulations (CFR), and European Union (EU) Directives and Regulations (as applicable in the region of the study); national country legislation; and the sponsor's Standard Operating Procedures (SOPs). This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Branded Pharmaceutical Products R&D and/or its affiliates and Nuvelution TS Pharma, INC. © 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
LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS		
Contract Research Organization; Safety and Efficacy Data Analysis ~~INC Research, LLC, a Syneos health group company~~ ~~(~~Syneos Health, LLC~~)~~ ~~3201 Beechleaf Court~~	**Contract Research Organization; Safety and Efficacy Data Analysis** Syneos Health, LLC 1030 Sync Street Morrisville, NC 27560	Administrative change

Protocol Amendment 04 text with changes shown	New wording	Reason/Justification for change
~~Suite 600~~ ~~Raleigh, NC 27604-1547~~ 1030 Sync Street Morrisville, NC 27560 USA	USA	
CLINICAL STUDY PERSONNEL CONTACT INFORMATION		
Legal Representative of the Sponsor in the EU Syneos Health Netherlands B.V. **For medical issues, contact the physician listed below:** [redacted] **For protocol issues, contact the study leaders listed below:** [redacted]	**Legal Representative of the Sponsor in the EU** Syneos Health Netherlands B.V. **For medical issues, contact the physician listed below:** [redacted] **For protocol issues, contact the study leaders listed below:** [redacted]	Update to the sponsor's legal representative in the EU. Additional administrative changes have been carried out.

Protocol Amendment 04 text with changes shown	New wording	Reason/Justification for change
[redacted] **For operational issues, contact the Head of Operations~~operational lead~~ listed below:** [redacted]	[redacted] **For operational issues, contact the Head of Operations listed below:** [redacted]	
Section 1.3.2 Clinical Studies (other section affected: Section 1.3.2.1 Clinical Pharmacology Studies)		
The clinical development plan for TEV-50717 to date includes: • ~~6~~7 completed Phase 1 studies in healthy adult subjects • 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	The clinical development plan for TEV-50717 to date includes: • 7 completed Phase 1 studies in healthy adult subjects • 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	The clinical development plan for TEV-50717 has been updated to reflect the most current program information.

Protocol Amendment 04 text with changes shown	New wording	Reason/Justification for change
• 2 completed Phase 2/3 and Phase 3 studies 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	• 2 completed Phase 2/3 and Phase 3 studies 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	
Section 2.3.3 Exploratory Endpoints (other sections affected: Section 9.5.3 Exploratory Endpoints and Section 9.5.4.4 Exploratory Analyses)		
[redacted]	[redacted]	Update on and addition of the exploratory endpoints evaluating reduction
Section 3.1.2 Screening Period		
Patients may be rescreened 1 time if there is a change in the ~~patient's medical background, a modification~~status of the patient regarding eligibility for the study ~~entry criteria, or other relevant change~~.	Patients may be rescreened 1 time if there is a change in the status of the patient regarding eligibility for the study.	Provided further details about rescreening activities and process
Section 3.3.3 Exploratory Measures and Time Points		
[redacted]	[redacted]	Update on and addition of the exploratory measures and time points evaluating reduction

Protocol Amendment 04 text with changes shown	New wording	Reason/Justification for change
[redacted]	[redacted]	
Section 3.7.2 Blinding/Unblinding		
When a blind is broken, the patient will be withdrawn from the study, and the event will be recorded onto 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 onto 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.	Provided further guidance to the investigator in the situation that a patient is unblinded by mistake
Section 3.9.1 Drug Storage and Security		
The IMP (TEV-50717 and placebo) should be stored protected from light, at a controlled room temperature, 20°C to 25°C (68°F to 77°F); however, storage between 15°C and ~~30~~20°C (59°F and ~~86~~68°F) is acceptable if there is no alternative.	The IMP (TEV-50717 and placebo) should be stored protected from light, at a controlled room temperature, 20°C to 25°C (68°F to 77°F); however, storage between 15°C and 20°C (59°F and 68°F) is acceptable if there is no alternative.	Updated temperature range for storage of the IMP
Section 3.13.1 Procedures for Screening and Enrollment (other sections affected: Section 3.13.2 Procedures Before IMP Treatment (Baseline/Day 1), Section 3.13.3.1.2 Clinic Visits (Weeks 2, 4, and 6), Section 3.13.3.2.1 Week 9, Section 3.13.3.2.2 Week 12/Early Termination, Section 3.13.4.1 Week 13, and Section 3.13.5 Unscheduled Visits)		
A signed and dated informed consent form will be obtained from the parent/legally acceptable representative ~~(may also include an adult other than a parent or legal representative)~~, and a signed and dated assent, depending on the child's age, as appropriate, will be obtained from each patient before 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~~	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 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	Updated language surrounding who can be involved in the informed consent/assent process. Removed a parenthetical expression that was inserted previously Included "conduct clinic visit" strictly for clarity at each visit where patients are expected to be present at the clinic for assessment

Protocol Amendment 04 text with changes shown	New wording	Reason/Justification for change
~~medical background, a modification of study entry criteria, or other relevant change.~~status of the patient regarding eligibility for the study. The screening visit will take place not more than 31 days before the baseline visit. The screening visit may be conducted over 2 separate visits at the discretion of the investigator. The following procedures will be performed at screening: • conduct clinic visit	rescreened 1 time if there is a change in the status of the patient regarding eligibility for the study. The screening visit will take place not more than 31 days before the baseline visit. The screening visit may be conducted over 2 separate visits at the discretion of the investigator. The following procedures will be performed at screening: • conduct clinic visit	
Section 4.1. Patient Inclusion Criteria (other section affected: Section 12.1 Informed Consent/Assent)		
f. Patient and caregiver/adult ~~(may also include an adult other than a parent or legal representative)~~ are willing to adhere to the medication regimen and to comply with all study procedures. h. In the investigator's opinion, the patient and caregiver/adult ~~(may also include an adult other than a parent or legal representative)~~ have the ability to understand the nature of the study and its procedures, and the patient is expected to complete the study as designed. i. Patient and caregiver/adult ~~(may also include an adult other than a parent or legal representative)~~ provide written informed consent/assent, depending on the child's age, as appropriate, according to local regulations.	f. Patient and caregiver/adult are willing to adhere to the medication regimen and to comply with all study procedures. h. In the investigator's opinion, the patient and caregiver/adult have the ability to understand the nature of the study and its procedures, and the patient is expected to complete the study as designed. i. Patient and caregiver/adult provide written informed consent/assent, depending on the child's age, as appropriate, according to local regulations.	Updated language surrounding who can be involved in the informed consent/assent process. Removed a parenthetical expression that was inserted previously
Section 4.4 Withdrawal Criteria and Procedures (other section affected: Section 7.1.7 Withdrawal Due to an Adverse Event)		
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	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	Included clarity that patients who experience an adverse event can also be withdrawn by the sponsor. Provided further guidance to the

Protocol Amendment 04 text with changes shown	New wording	Reason/Justification for change
7.1.7) g. when a blind is broken due to safety concerns (see Section 3.7.2). If a patient is unblinded by mistake, ~~they~~the investigator should discuss with the medical monitor whether or not the patient should be withdrawn.	7.1.7) g. when a blind is broken due to safety concerns (see Section 3.7.2). If a patient is unblinded by mistake, the investigator should discuss with the medical monitor whether or not the patient should be withdrawn.	investigator in the situation that a patient is unblinded by mistake
Section 5.5 Dose Reduction and Temporary IMP Discontinuation		
Dose Suspension If a subject's serum potassium or magnesium were tested and found to be below the lower limit of normal~~, IMP must be suspended.~~ and clinically significant, the laboratory test should be repeated at least once. If the abnormality in the repeated laboratory test is consistent with the prior laboratory test, the IMP must be suspended.	**Dose Suspension** If a subject's serum potassium or magnesium were tested and found to be below the lower limit of normal and clinically significant, the laboratory test should be repeated at least once. If the abnormality in the repeated laboratory test is consistent with the prior laboratory test, the IMP must be suspended.	Updated dose suspension text to provide further guidance
Section 6.2.5 Yale Global Tic Severity Scale		
[redacted] re exploratory measures.	[redacted] are exploratory measures.	Updated to more properly capture the YGTSS measures
Section 7.11 Concomitant Therapy or Medication		
Medications that are allowed, provided that conditions outlined in the table are met, are shown in Appendix A, Table 9. The tables of allowed and prohibited medications are not comprehensive and may not include all possible concomitant medications.	Medications that are allowed, provided that conditions outlined in the table are met, are shown in Appendix A, Table 9. The tables of allowed and prohibited medications are not comprehensive and may not include all possible concomitant medications.	Updated allowed medications to clarify that the list of concomitant medications provided is not comprehensive
Section 9.1 Sample Size and Power Considerations (other section affected: Figure 1: Overall Study Schema)		
It is estimated that approximately ~~50~~58 patients per arm will enable a power of at least 90% to detect a beneficial standardized effect of ~~6.5 points~~63% or	It is estimated that approximately 58 patients per arm will enable a power of at least 90% to detect a beneficial standardized effect of 63% or more when	Recently, a Phase 2 study assessing the safety and efficacy of valbenazine in the treatment of

Protocol Amendment 04 text with changes shown	New wording	Reason/Justification for change
more when the TEV-50717 arm is compared to placebo (difference of 6.0 in the change from baseline to week 12 in TTS ~~when the TEV-50717 arm is compared to placebo~~, assuming a standard deviation of 9.5 ~~and~~ in each arm) in a 2-sided type I error rate of 5% after accounting for potential dropouts. The sample size for this study has been increased from 100 total patients (50 patients per arm) to 116 total patients (58 patients per arm). This adjustment is based solely on external data (ie, valbenazine Phase 2 study results, efficacy of TEV-50717 in the treatment of HD and TD, and ABILIFY® Phase 3 data). Data from the ongoing TEV-50717 Phase 2/3 and Phase 3 studies, TV50717-CNS-30046 and TV50717-CNS-30060, respectively, are blinded and were not used to inform the sample size calculation.	the TEV-50717 arm is compared to placebo (difference of 6.0 in the change from baseline to week 12 in TTS, assuming a standard deviation of 9.5 in each arm) in a 2-sided type I error rate of 5% after accounting for potential dropouts. The sample size for this study has been increased from 100 total patients (50 patients per arm) to 116 total patients (58 patients per arm). This adjustment is based solely on external data (ie, valbenazine Phase 2 study results, efficacy of TEV-50717 in the treatment of HD and TD, and ABILIFY® Phase 3 data). Data from the ongoing TEV-50717 Phase 2/3 and Phase 3 studies, TV50717-CNS-30046 and TV50717-CNS-30060, respectively, are blinded and were not used to inform the sample size calculation.	pediatric and adolescent TS patients (T FORCE GOLD study) failed to meet its primary efficacy objective. The details on the results from this study have not yet been made public. Based on this negative efficacy outcome, the sample size assumptions for Study TV50717-CNS-30046 were re-evaluated using data external to the ongoing TEV 50717 Phase 3 TS program. After review of the standardized effect in the TEV-50717 placebo-controlled pivotal studies in HD and TD and in collaboration with the scientific advisors to the TEV-50717 TS program (ie, Dr. Jankovic, Dr. Coffey, and Dr. Jimenez-Shahed), a treatment effect of 6.0 difference in TTS reflecting a 63% beneficial standardized effect was deemed to be a more appropriate assumption to base the sample size calculation.
Section 9.2.1 Intent-to-Treat Analysis Set		
The intent-to-treat (ITT) analysis set will include all randomized patients. In this population, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received. ~~Enrolled subjects~~	The intent-to-treat (ITT) analysis set will include all randomized patients. In this population, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.	Updated the definition of the ITT analysis set

Protocol Amendment 04 text with changes shown	New wording	Reason/Justification for change
~~who are not randomized will be summarized separately as "Not randomized," and randomized subjects will be analyzed based on their randomized treatment.~~		
Section 9.5.4.2 Sensitivity Analysis		
Sensitivity analyses for missing data~~and~~, the statistical model ~~are~~, and the increase in sample size will be provided in the statistical analysis plan.	Sensitivity analyses for missing data, the statistical model, and the increase in sample size will be provided in the statistical analysis plan.	Updated the protocol to state that sensitivity analysis will also be done for the increased sample size and further details will be provided in the statistical analysis plan

APPENDIX A. ALLOWED AND DISALLOWED MEDICATIONS

Medications that are allowed, provided that conditions outlined in the table are met, are shown in Table 5. 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 medications that are associated with QTc prolongation are listed in Table 6, while prohibited antipsychotic drugs are listed in Table 7.

Table 5: 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. If discontinuation of guanfacine is anticipated due to ineffectiveness, poor tolerability, or patient/caregiver preference, discontinuation should occur 4 or more weeks prior to the screening visit.
Clonidine	Allowed, regardless of indication (ie, if prescribed for tics or Tourette syndrome). Must be receiving stable treatment (including dose) for at least 4 weeks before screening and no changes to dose or frequency are anticipated during the course of the study. If discontinuation

Generic/Drug class	Condition
Stable medications allowed according to inclusion/exclusions criteria	
	of clonidine is anticipated due to ineffectiveness, poor tolerability, or patient/caregiver preference, discontinuation should occur 4 or more weeks prior to the screening visit.
Stimulants	Include amphetamine, methylphenidate, and lisdexamfetamine. Primary use is for the treatment of ADHD; dosing must have been stable for at least 2 weeks before screening and no changes to dose or frequency are anticipated during the course of the study.

Table 5: Allowed Medications (Continued)

Generic/Drug class	Condition
SNRIs	Includes atomoxetine. Primary use is for the treatment of ADHD; dosing must have been stable for at least 4 weeks before screening and no changes to dose or frequency are anticipated during the course of the study.
Additional medications allowed with preapproval from medical monitor	
Albuterol, levalbuterol	Asthma
Guaifenesin	Cold symptoms
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 6: 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 the USA
Droperidol	Sedative; anti-nausea/anesthesia adjunct, nausea	
Erythromycin[b]	Antibiotic; GI stimulant; GI motility	
Moxifloxacin	Antibiotic/bacterial infection	
Sevoflurane	Anesthetic, general/anesthesia	
Probucol	Antilipemic/hypercholesterolemia	Not available in the USA
Sparfloxacin	Antibiotic/bacterial infection	Not available in the USA

[a] Patients are allowed to take up 500 mg/day of azithromycin.
[b] Systemic use only. Topical use is allowed.
GI=gastrointestinal; QTc=corrected QT; USA=United States of America.

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

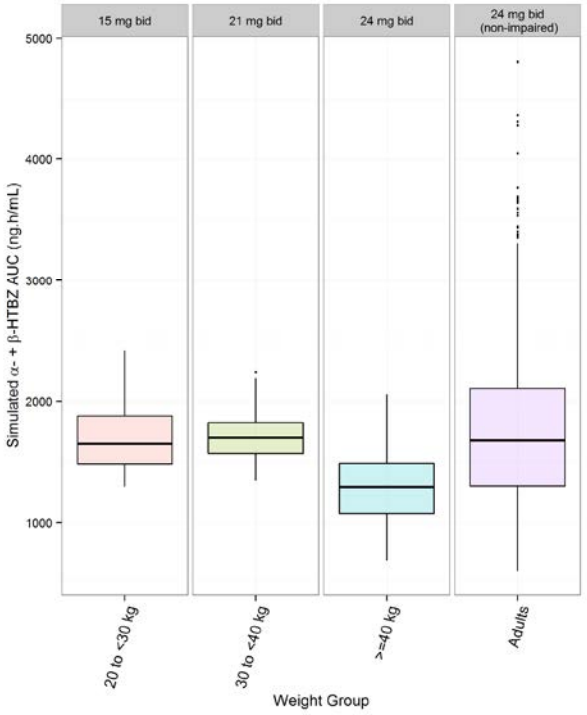
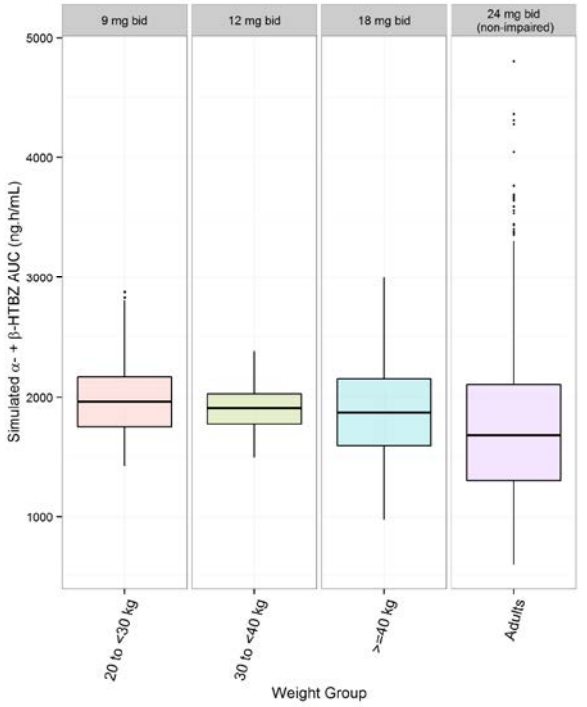
Note: This table does not apply in the second week of washout for patients not rolling over to the open-label extension study (Study TV50717-CNS-30047).

Table 8: 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 2: Distribution of AUC of Total (α+β)-HTBZ for Selected Doses Based on Weight Categories

Functional CYP2D6	Impaired CYP2D6
	

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),

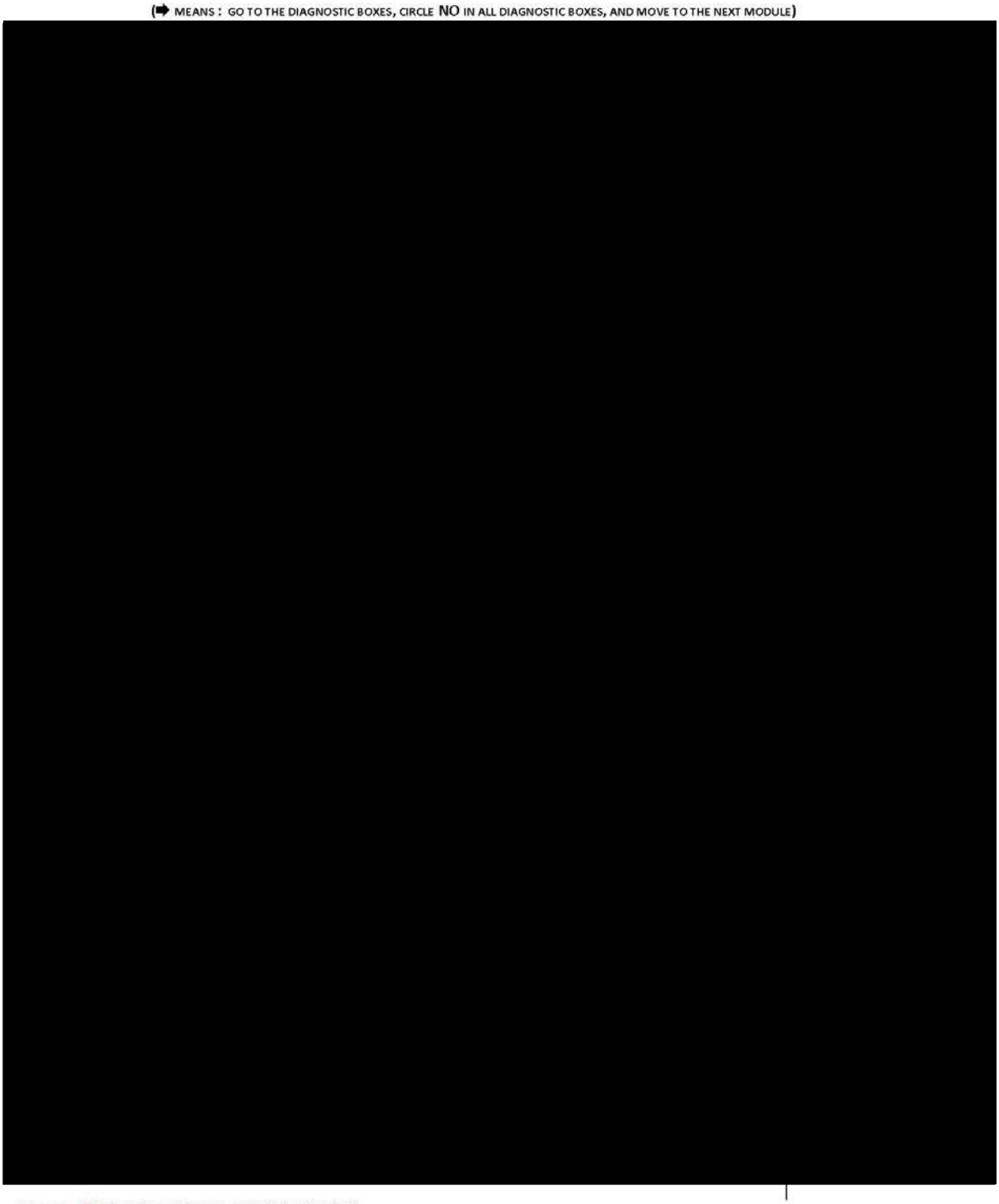
ADHD (Module O),

Conduct Disorder (Module P), and

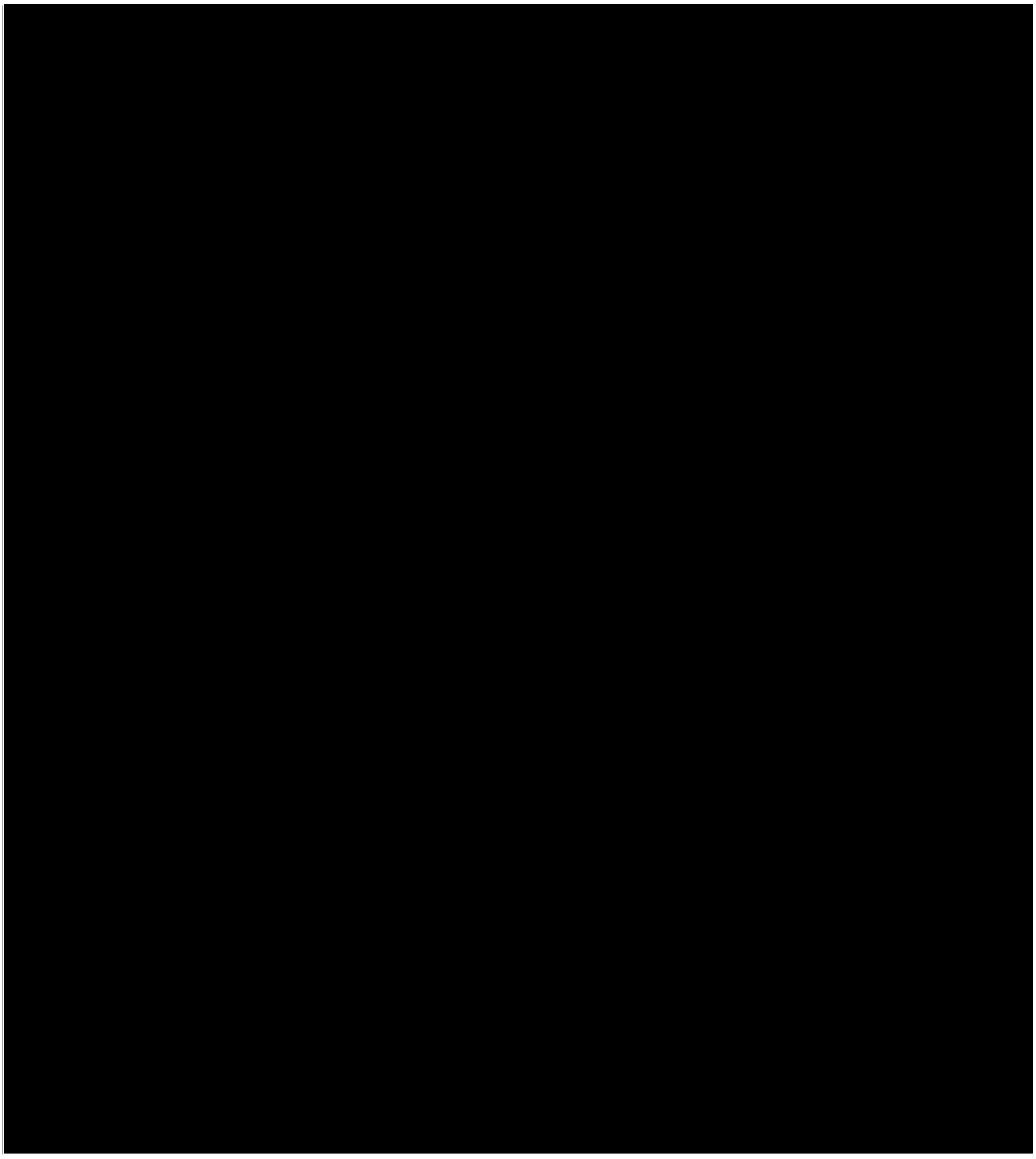
Psychotic Disorders and Mood Disorders with Psychotic Features (Module R).

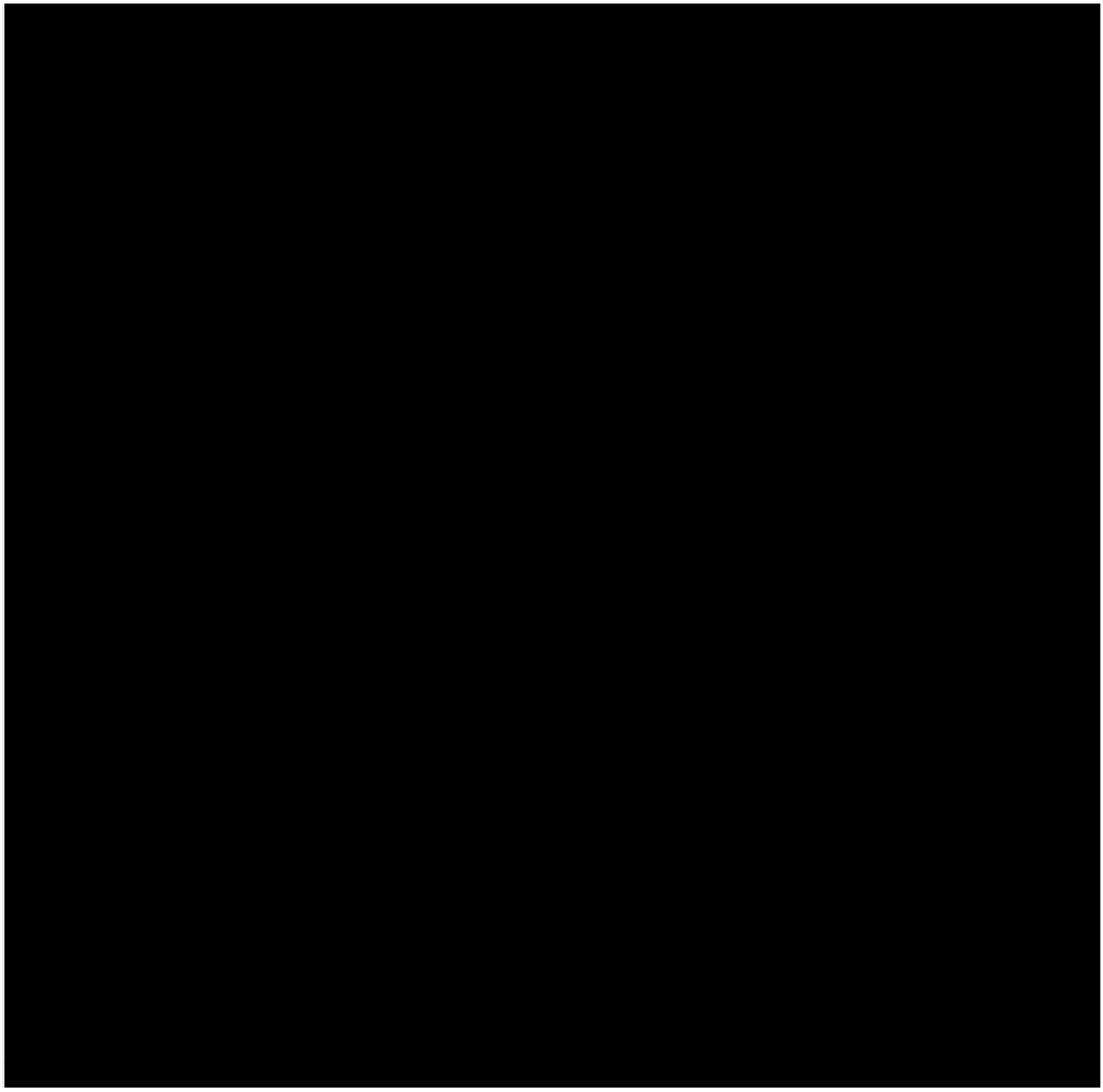
A. MAJOR DEPRESSIVE EPISODE

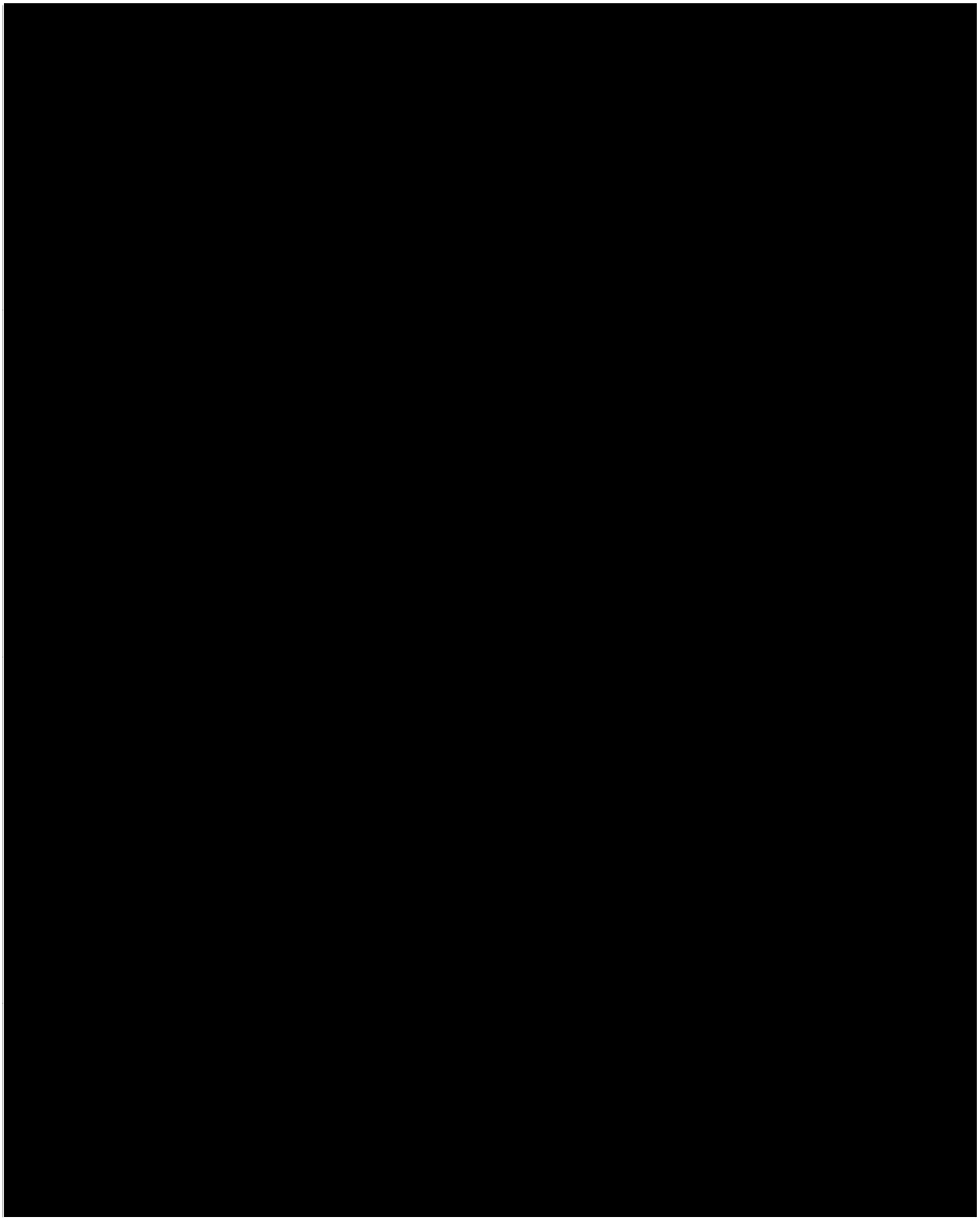
(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)



D. (HYPO) MANIC EPISODE







J. OBSESSIVE COMPULSIVE DISORDER

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

[redacted]

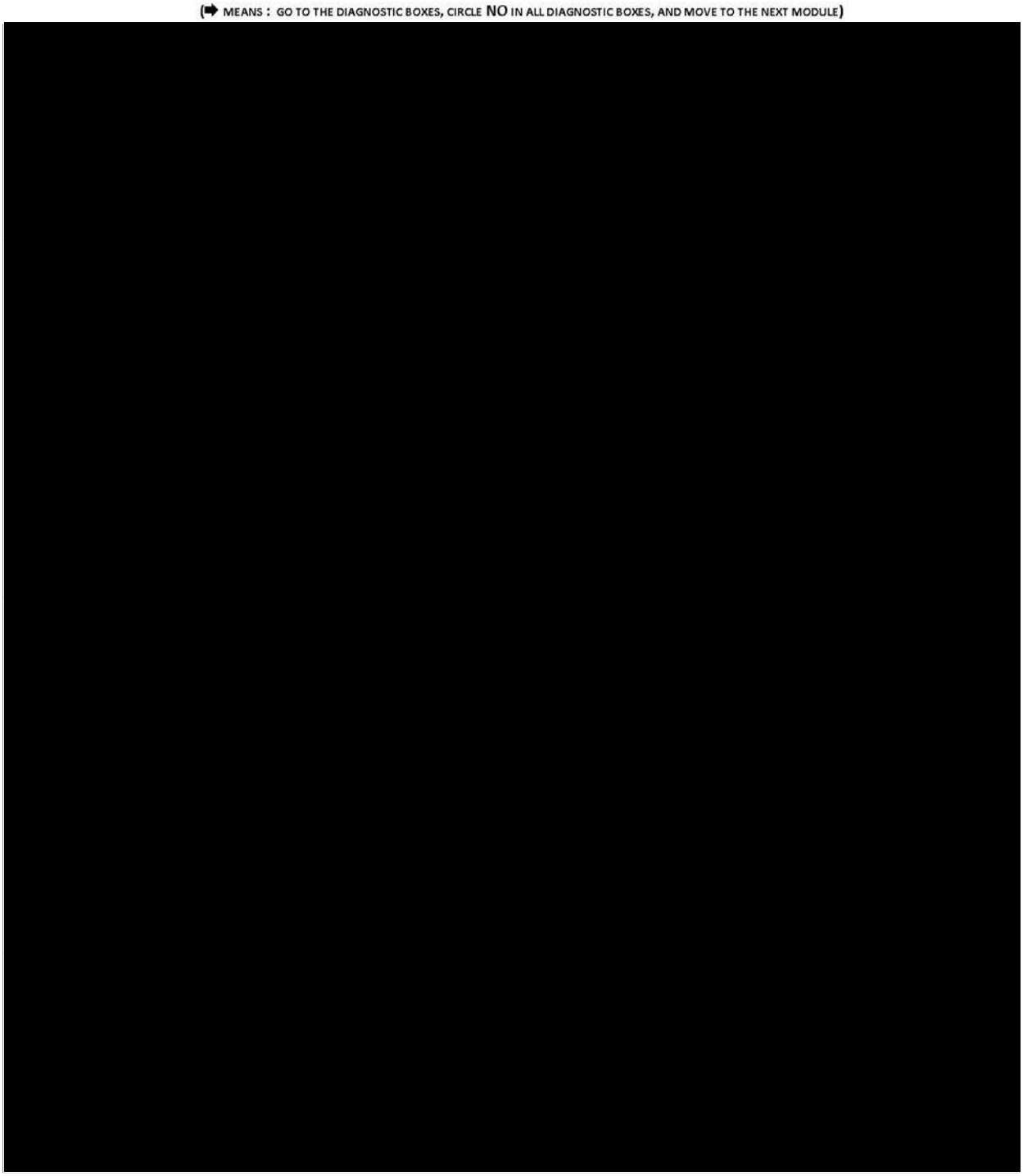
L. ALCOHOL DEPENDENCE / ABUSE

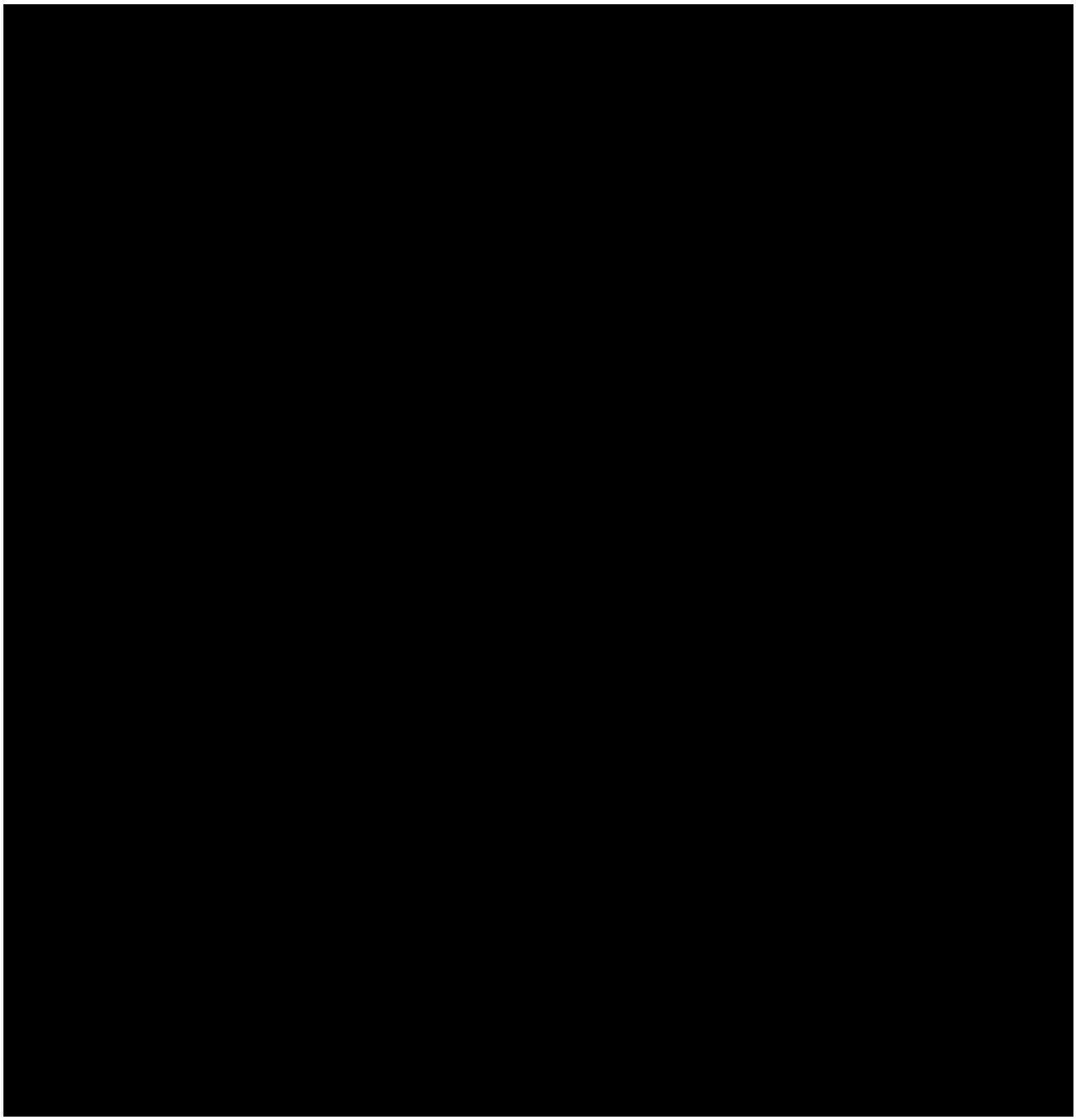
(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

[redacted]

M. SUBSTANCE DEPENDENCE / ABUSE (NON-ALCOHOL)

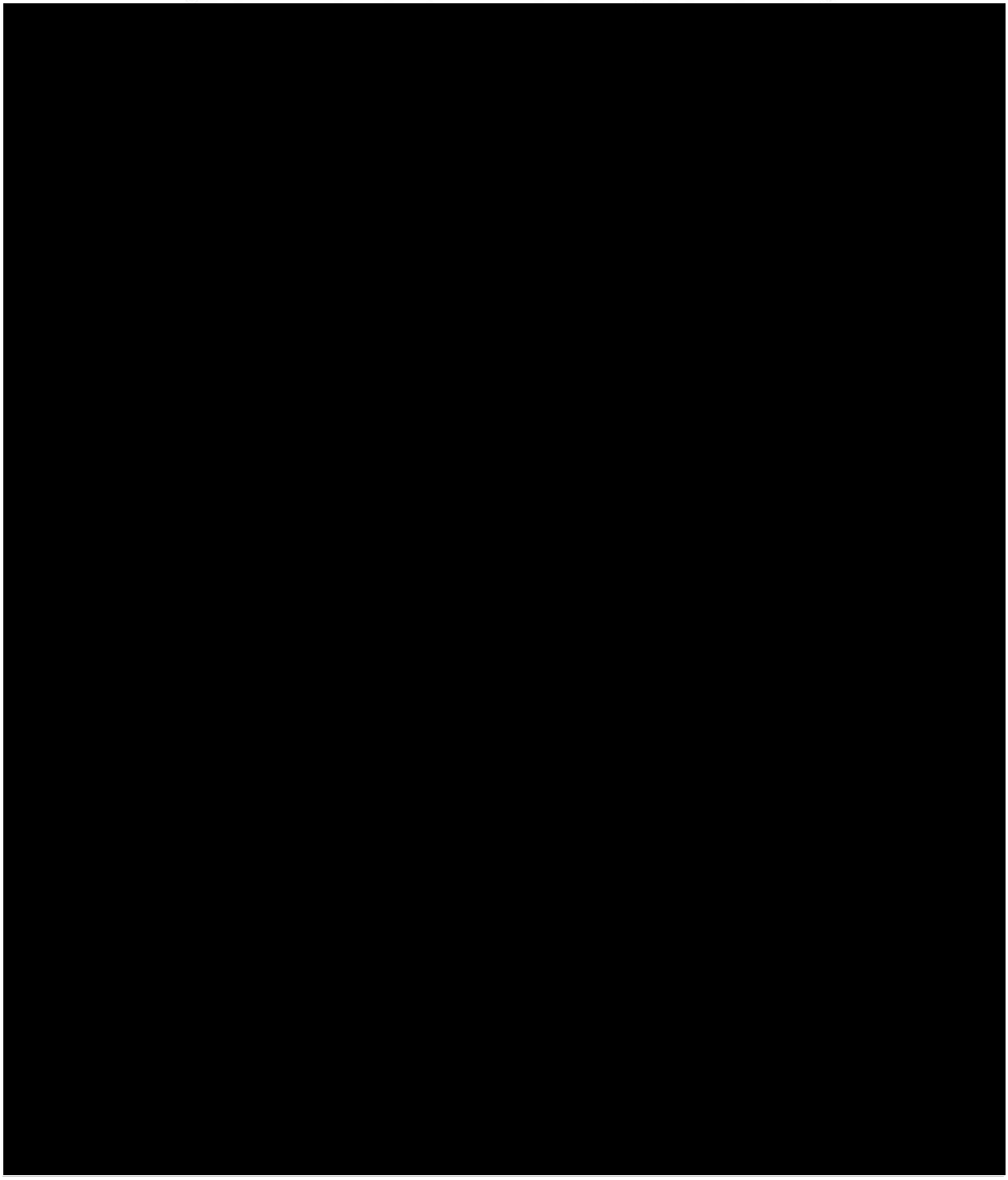
(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

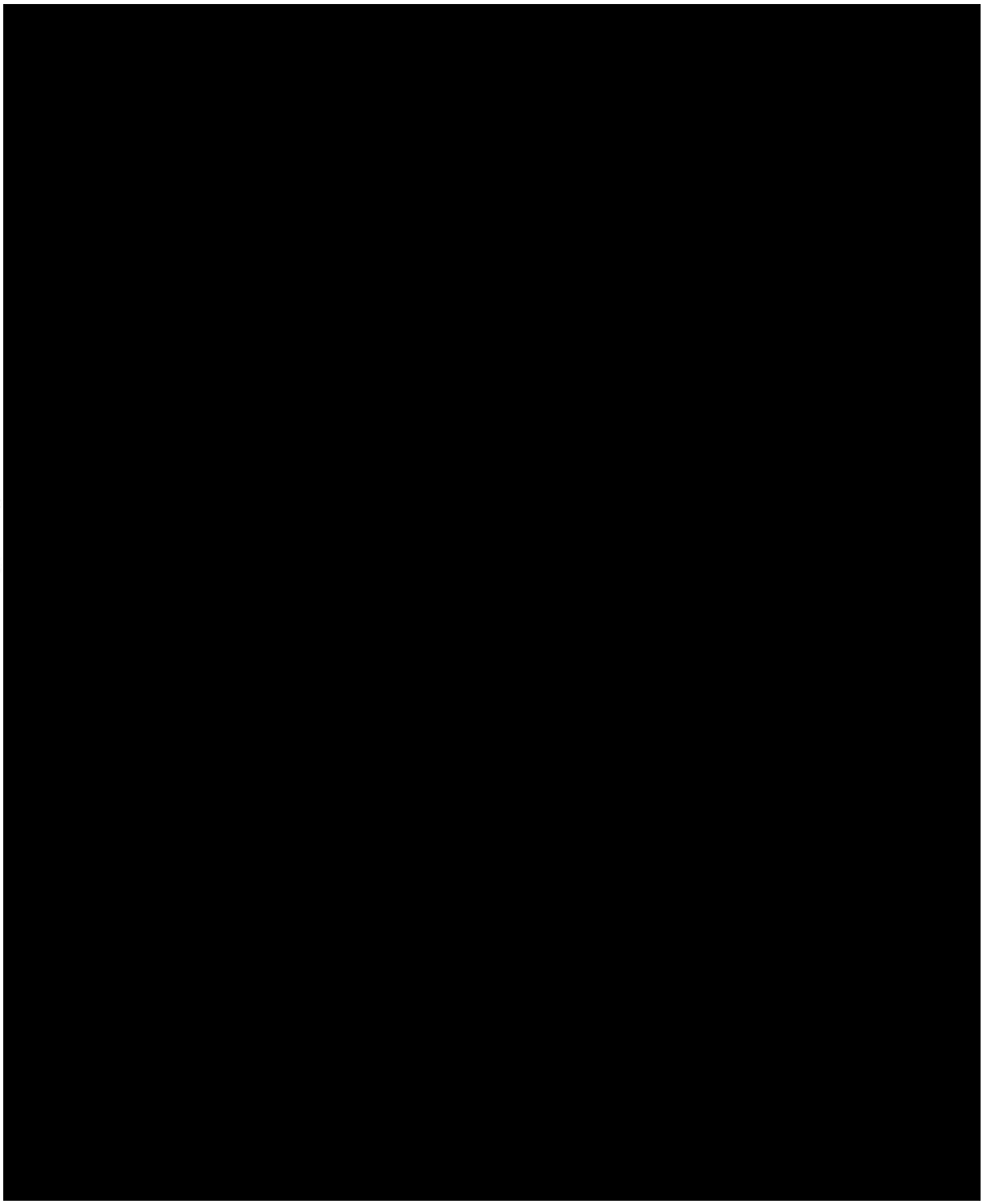




O. ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)



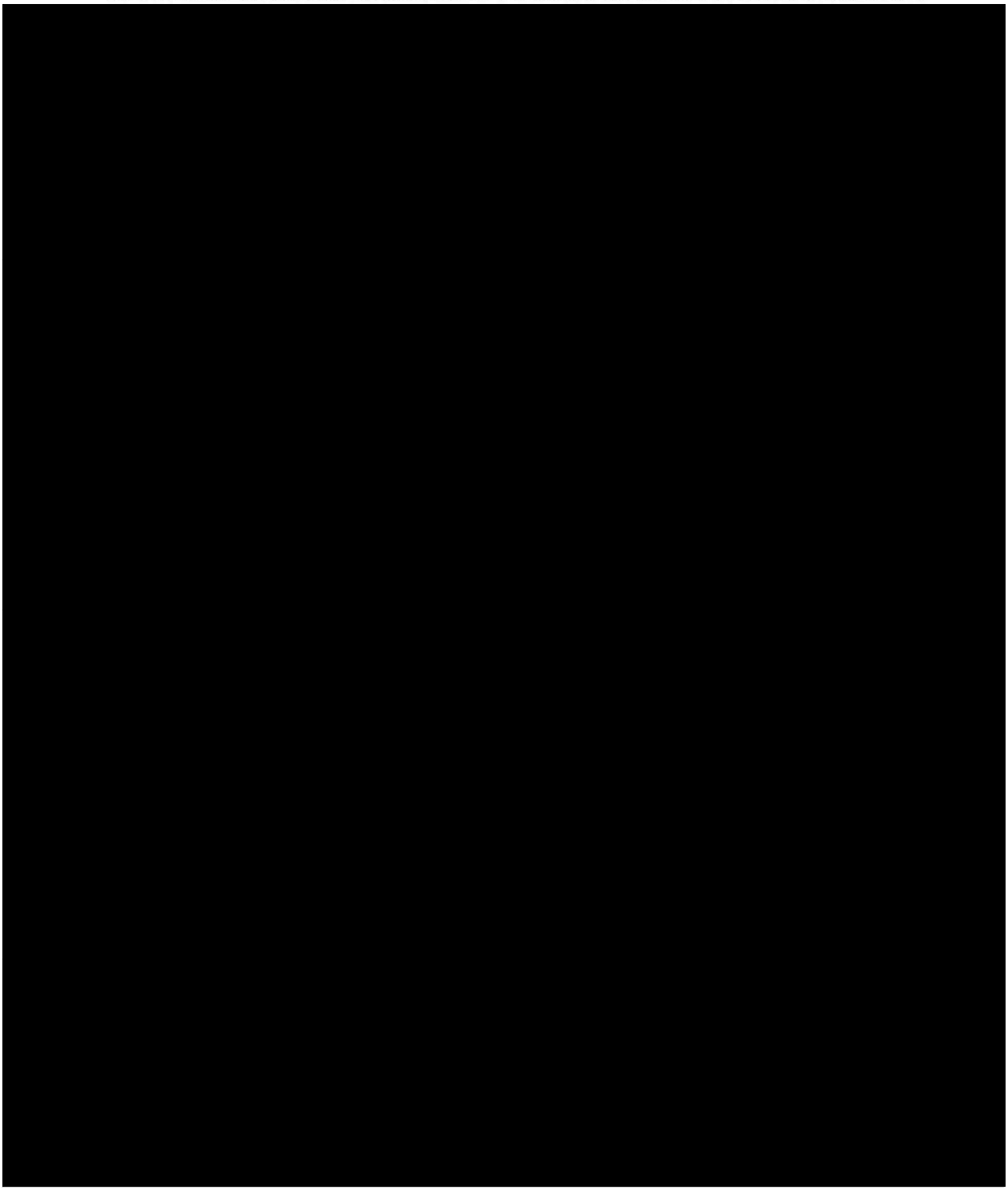


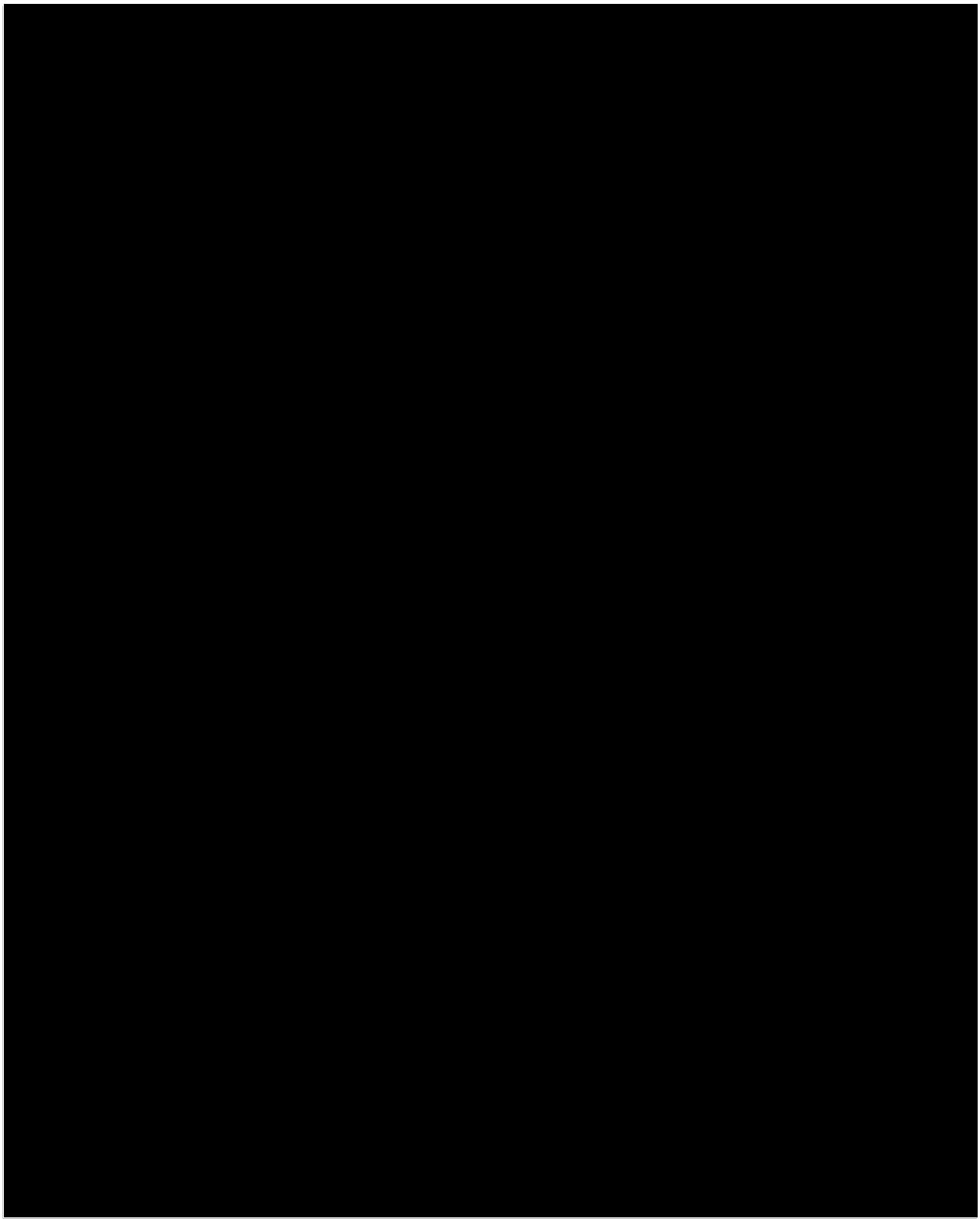
P. CONDUCT DISORDER

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

[redacted]

R. PSYCHOTIC DISORDERS AND MOOD DISORDERS WITH PSYCHOTIC FEATURES

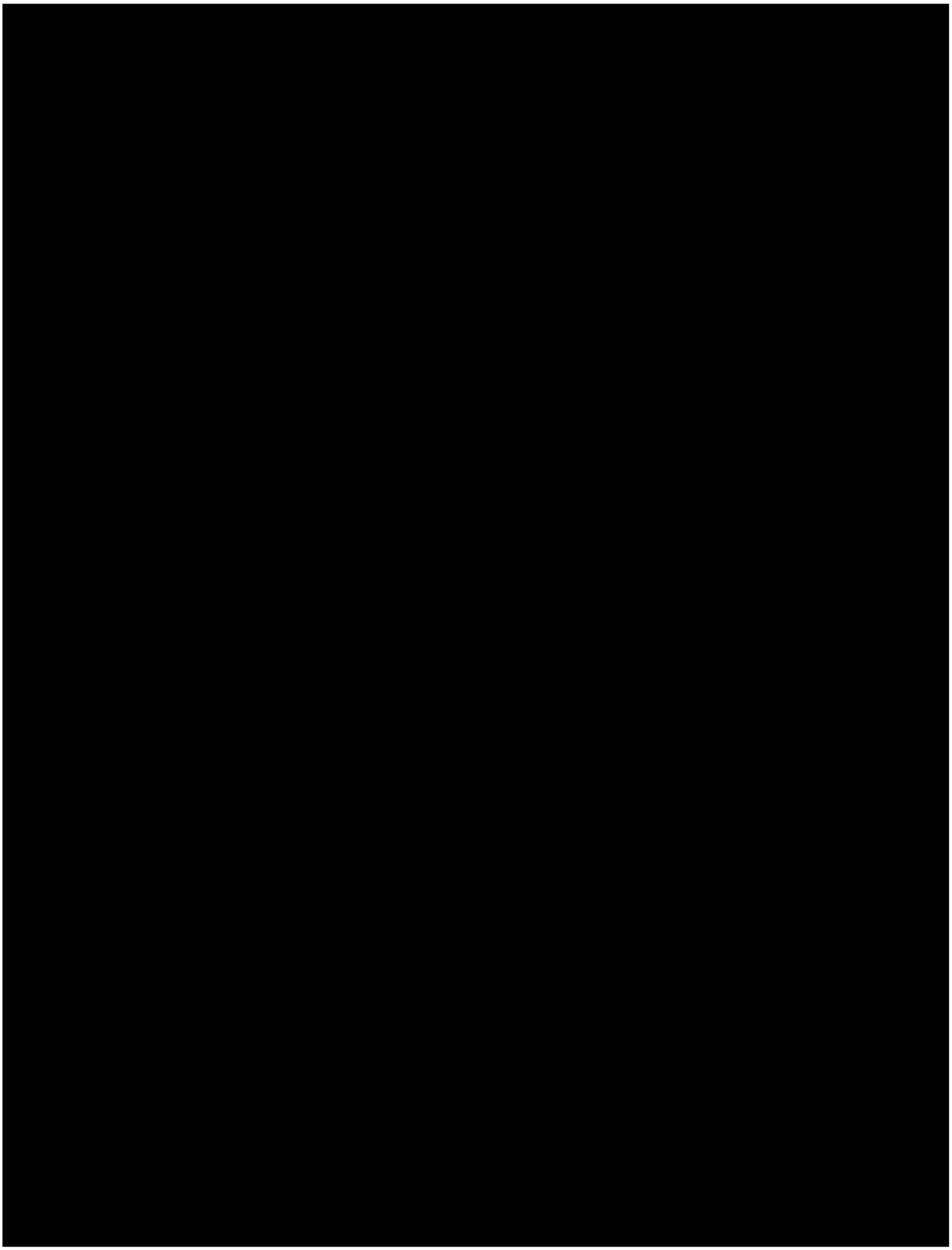


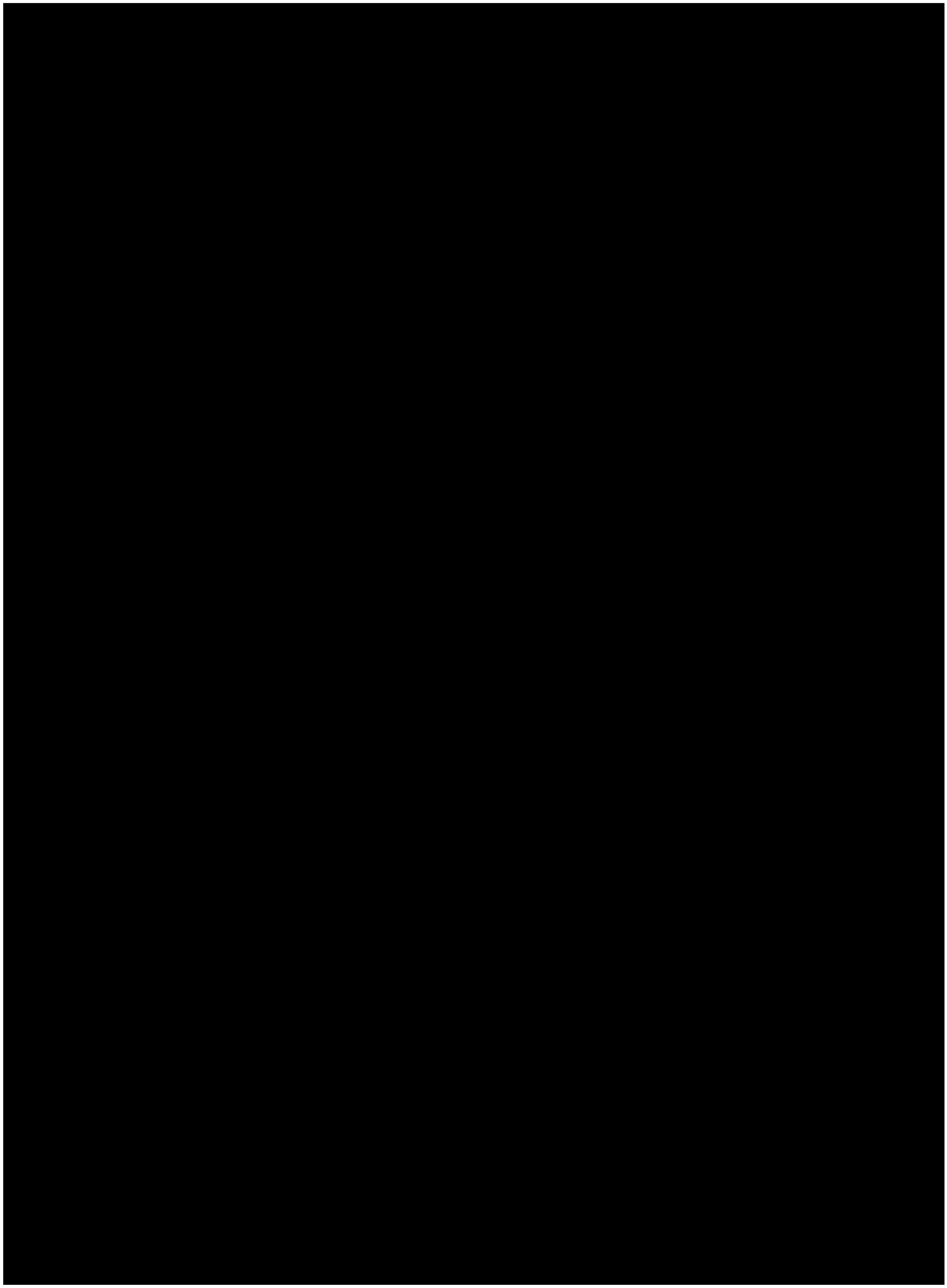


APPENDIX D. CHILDREN'S DEPRESSION INVENTORY, SECOND EDITION, PARENT AND SELF-REPORT PROFILES

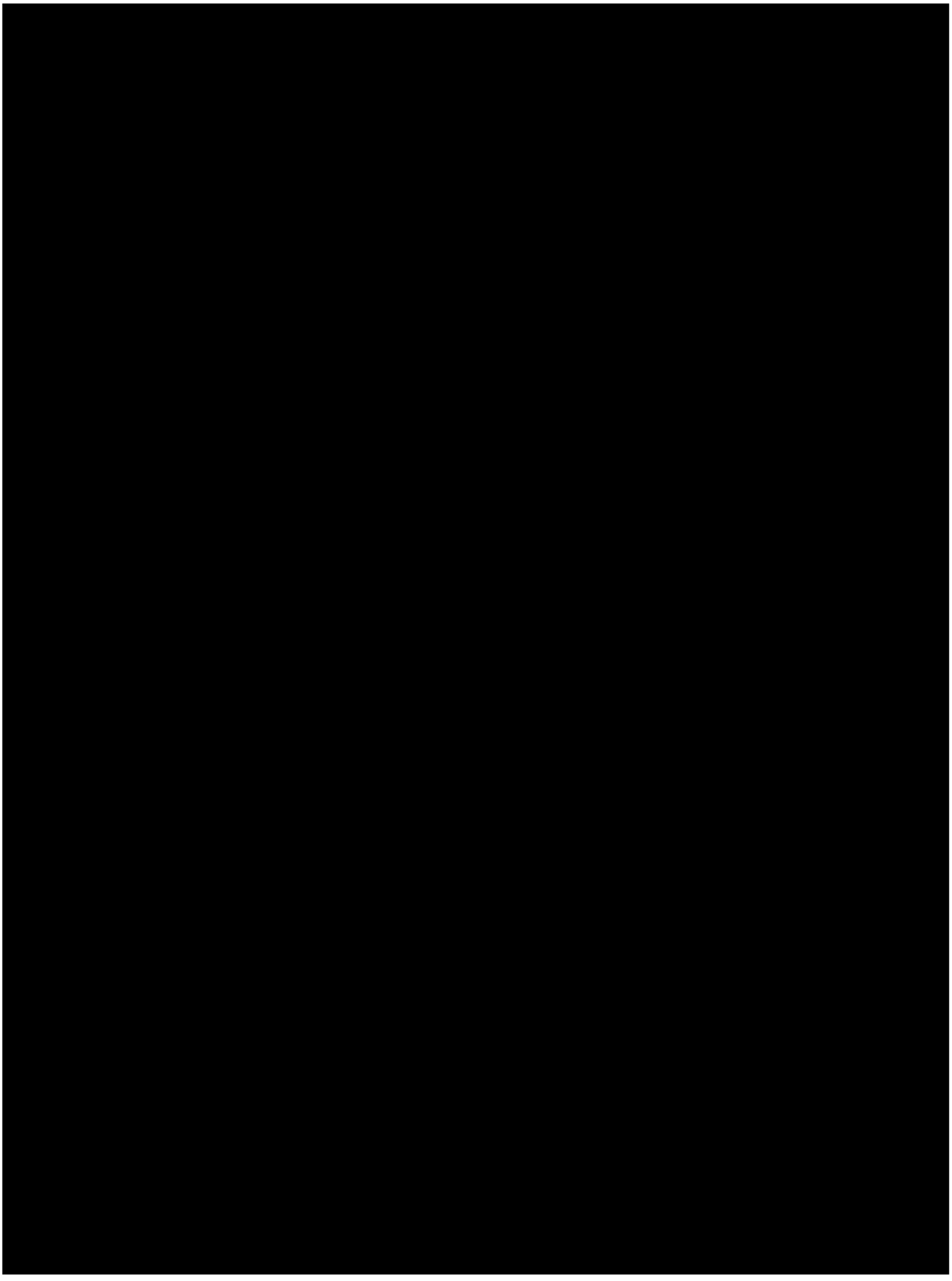
The sample provided in this appendix is for reference only.

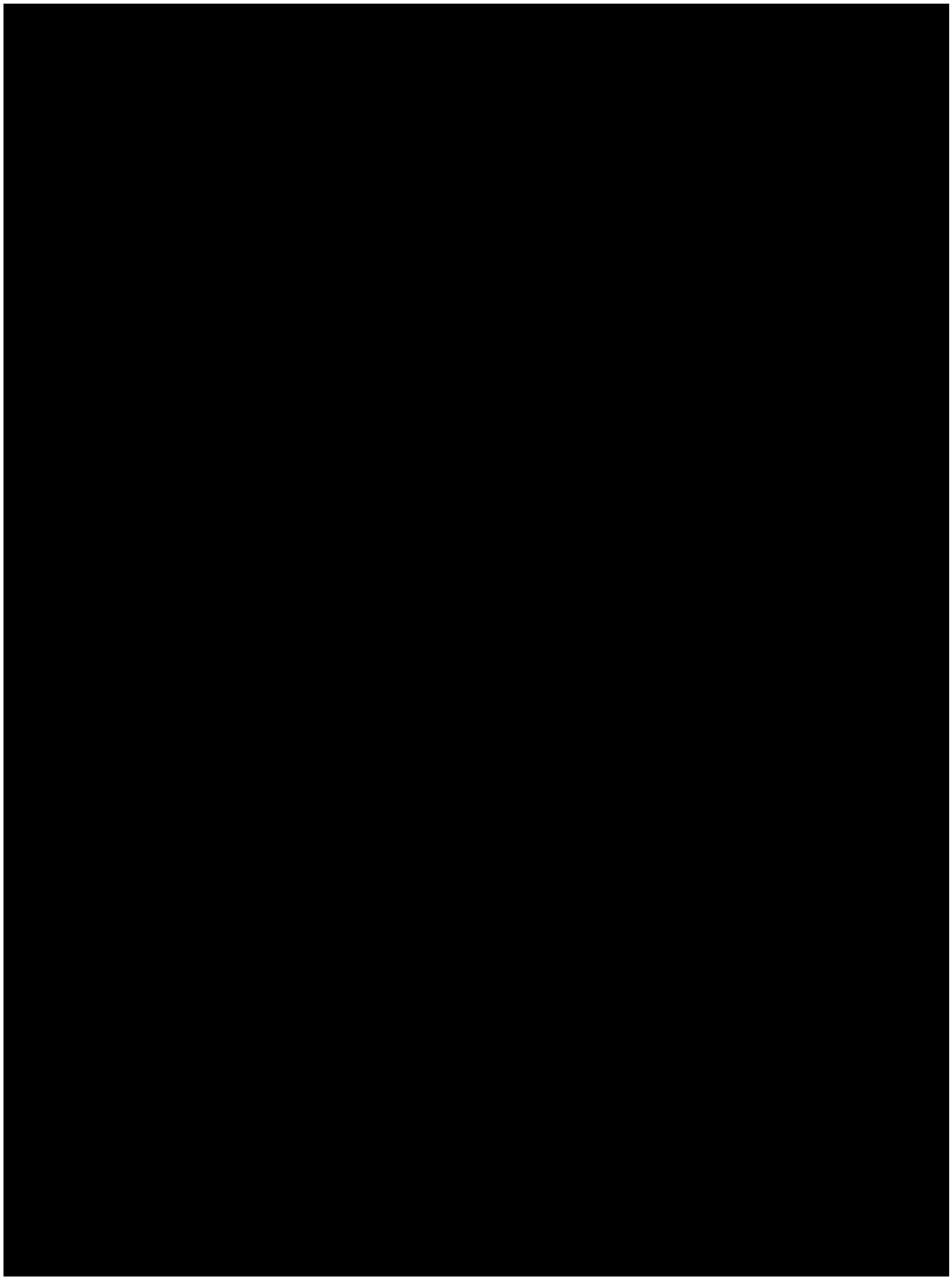
CDI-2 Parent Profile

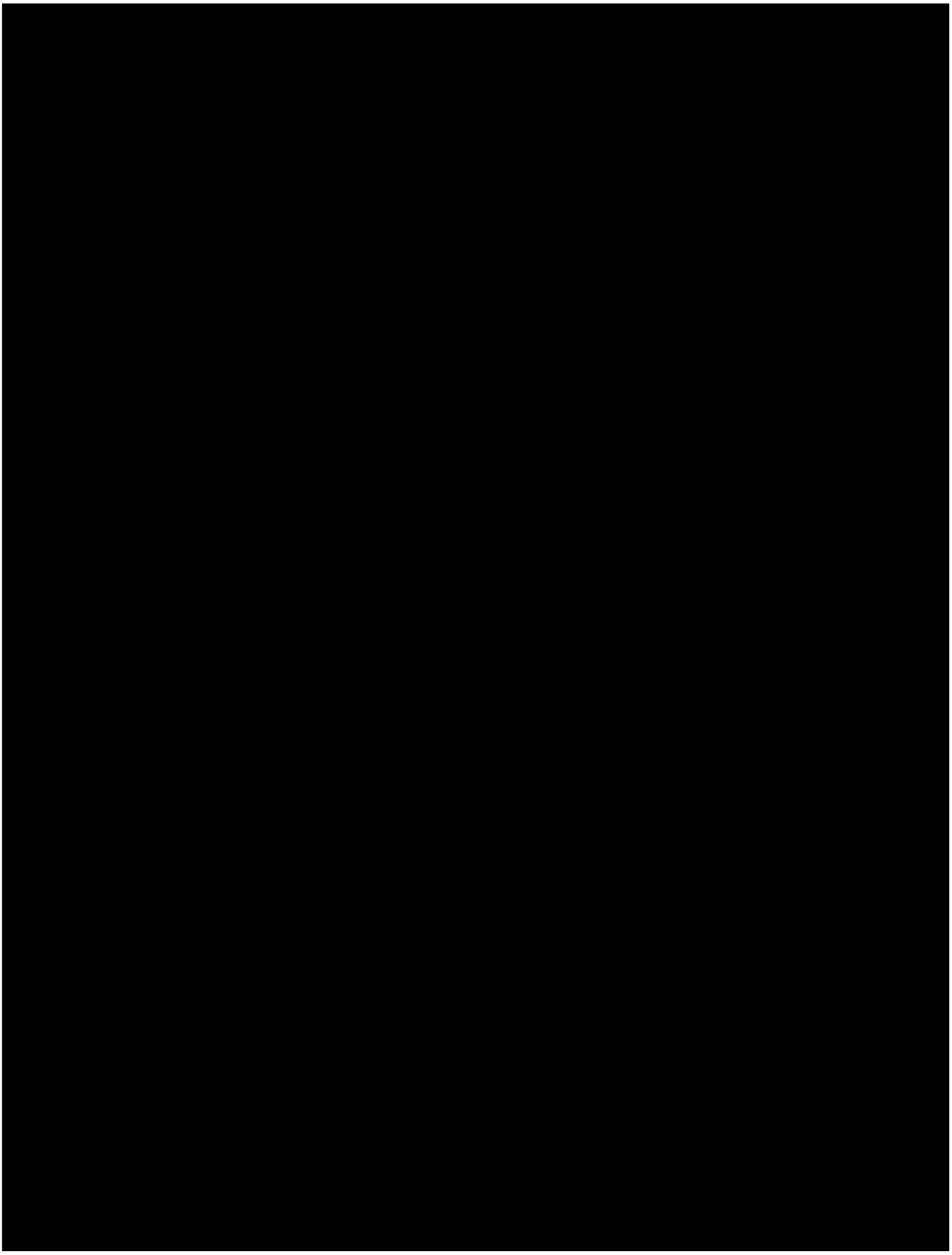


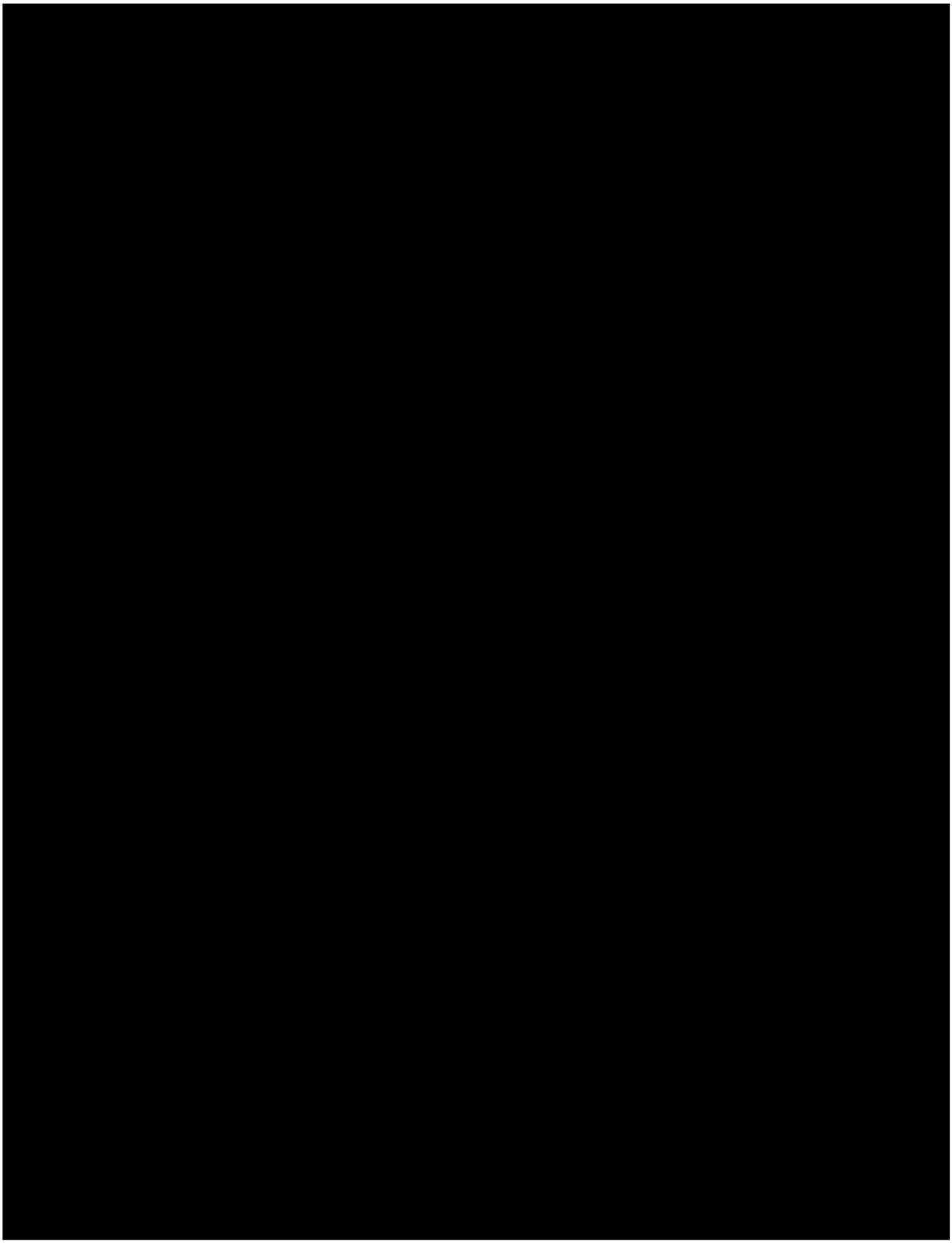


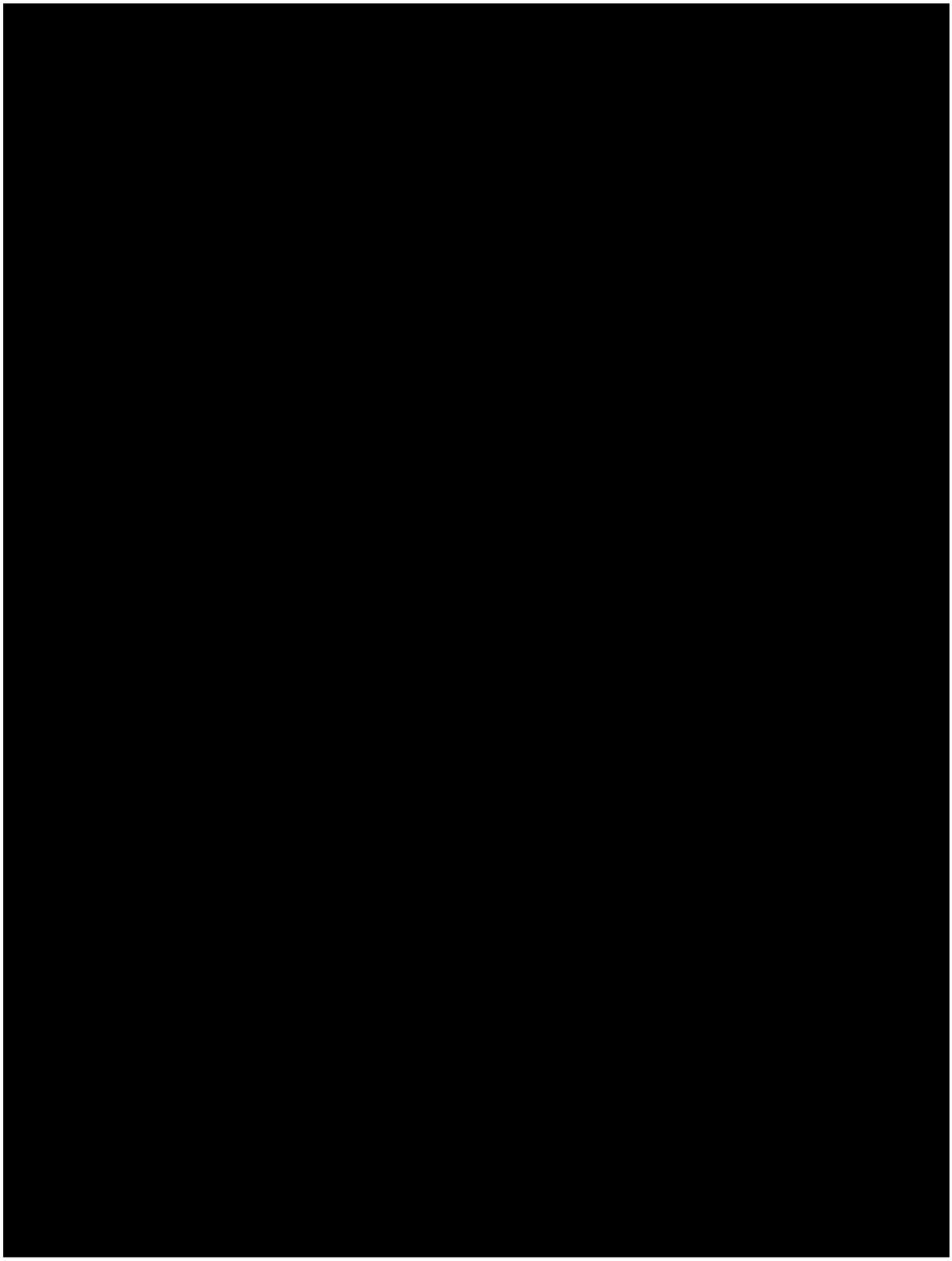
CDI-2 Self-Report











APPENDIX E. CHILDREN'S COLUMBIA-SUICIDE SEVERITY RATING SCALE

The sample provided in this appendix is for reference only.

Children's Baseline/Screening

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Baseline/Screening

Version 6/23/10

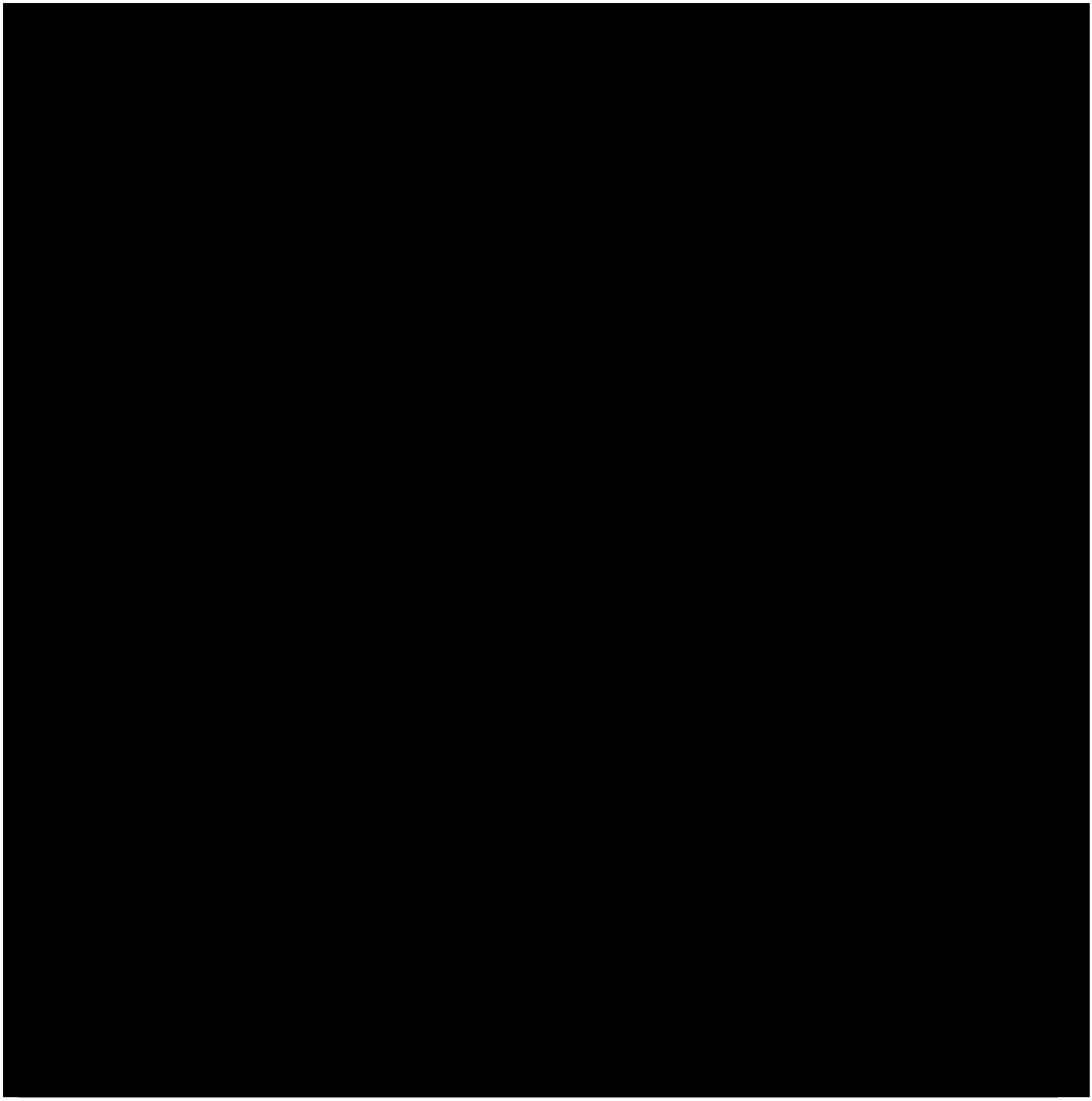
Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

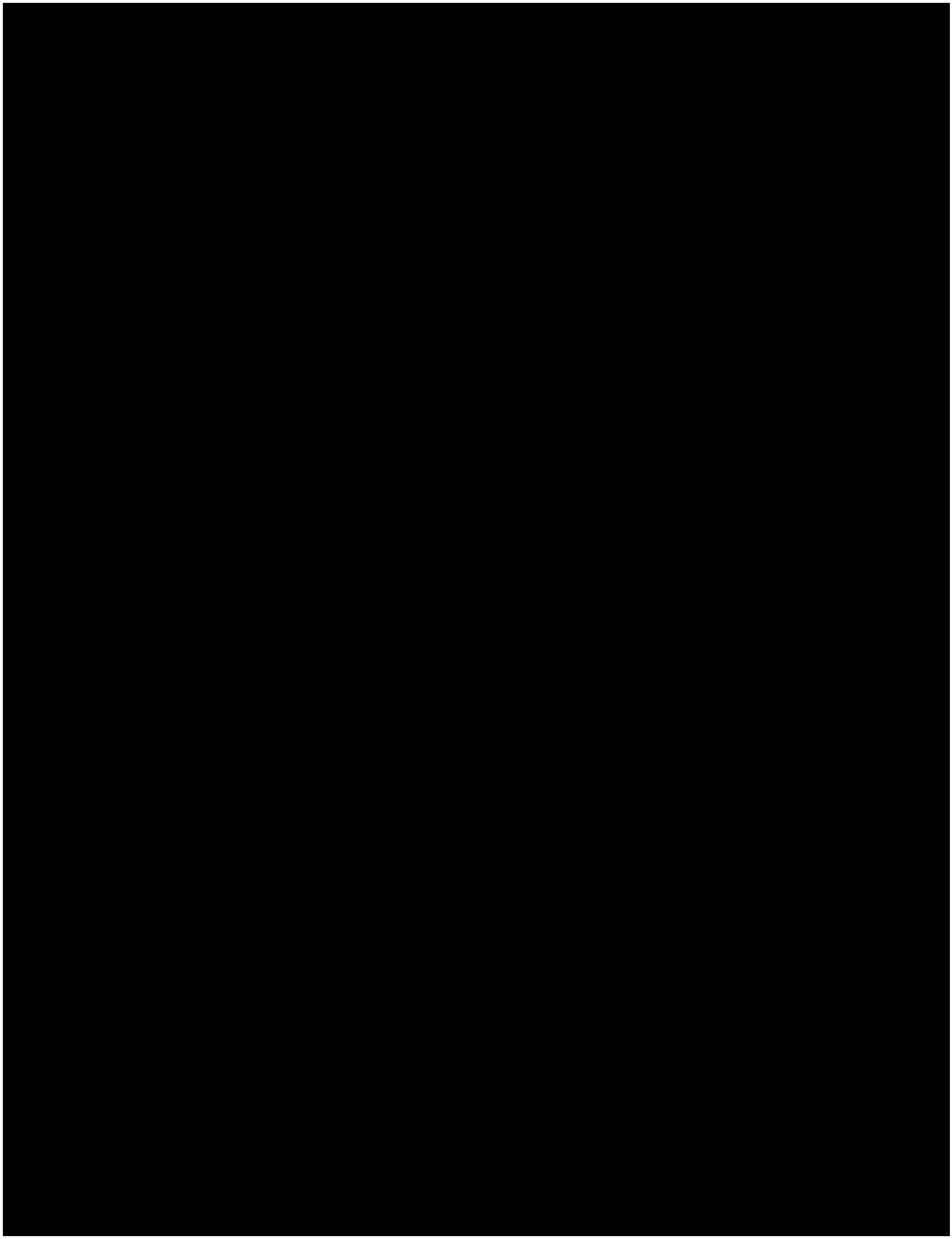
This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu



 C-SSRS—Children's Baseline/Screening (Version 6/23/10) Page 1 of 2



Children's Since Last Visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Since Last Visit

Version 6/23/10

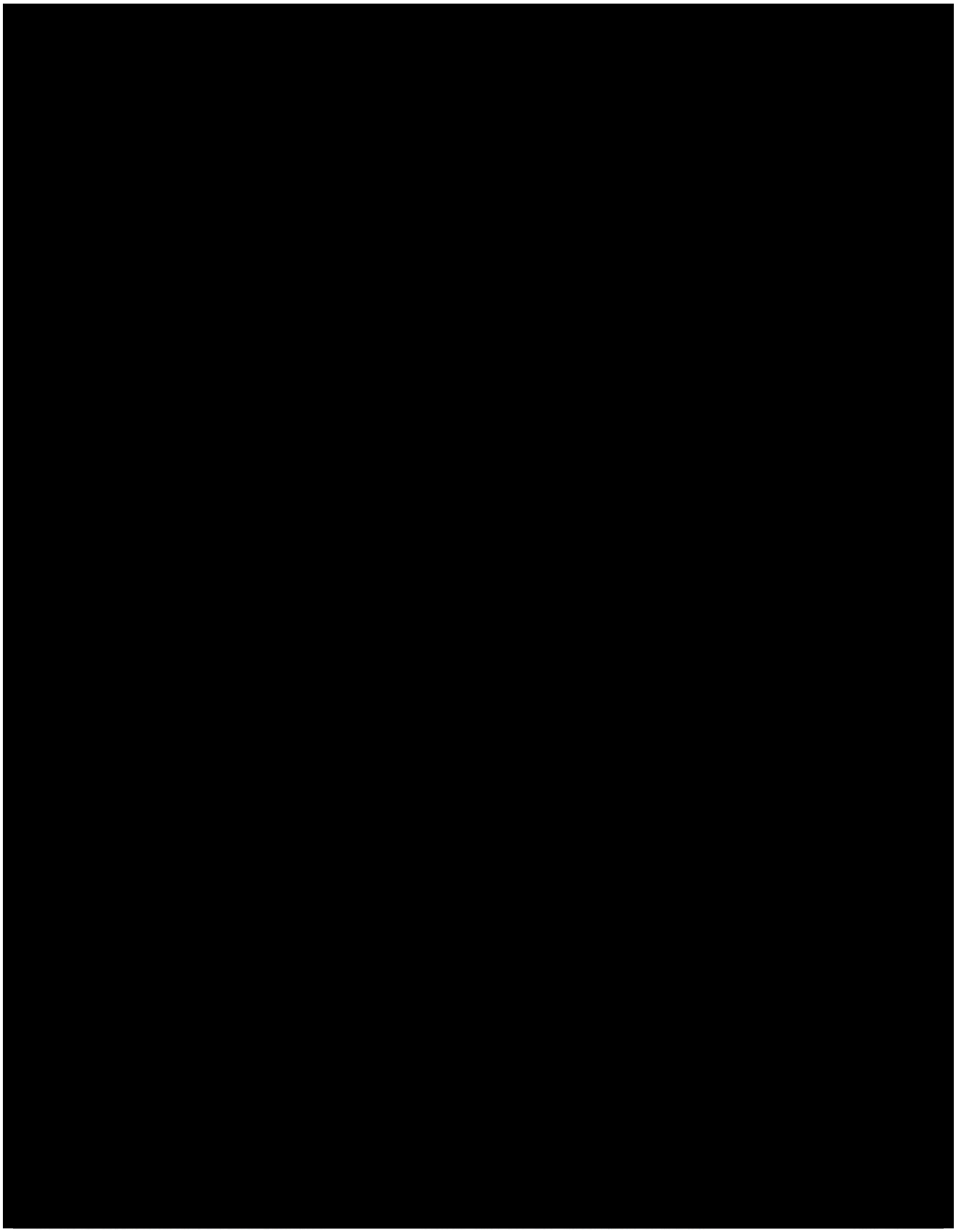
Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu



APPENDIX F. CHILDREN'S YALE-BROWN OBSESSIVE-COMPULSIVE SCALE

The sample provided in this appendix is for reference only.

Original: 10/1/86
First Revision: 3/1/90
Second Revision: 5/1/91
Third Revision: 5/1/93
Fourth Revision: 6/17/99
Fifth Revision: 12/07/07
Sixth Revision 8/20/08

CHILDREN'S
YALE-BROWN
OBSESSIVE COMPULSIVE SCALE
(CY-BOCS)

DEVELOPED BY

WAYNE K. GOODMAN, M.D.[1]
LAWRENCE SCAHILL, MSN, PhD[2]
LAWRENCE H. PRICE, M.D.[3]
STEVEN A. RASMUSSEN, M.D.[3]
MARK A. RIDDLE, M.D.[4]
JUDITH L. RAPOPORT, M.D.[5]

NATIONAL INSTITUTE OF MENTAL HEALTH[1]

THE CHILD STUDY CENTER[2]
YALE UNIVERSITY SCHOOL OF MEDICINE

DEPARTMENT OF PSYCHIATRY[3]
BROWN UNIVERSITY SCHOOL OF MEDICINE

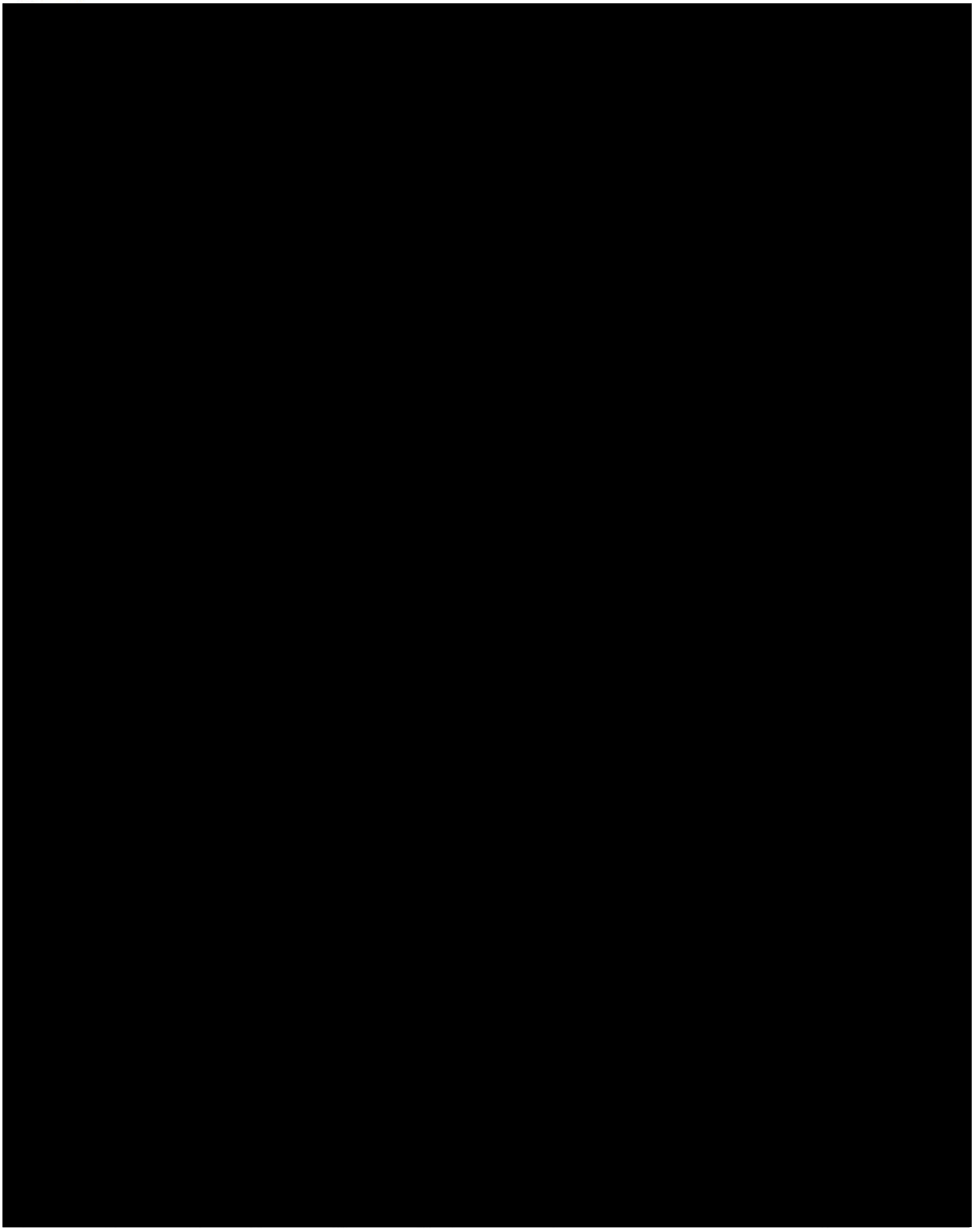
CHILD PSYCHIATRY DIVISION[4]
JOHNS HOPKINS SCHOOL OF MEDICINE
and

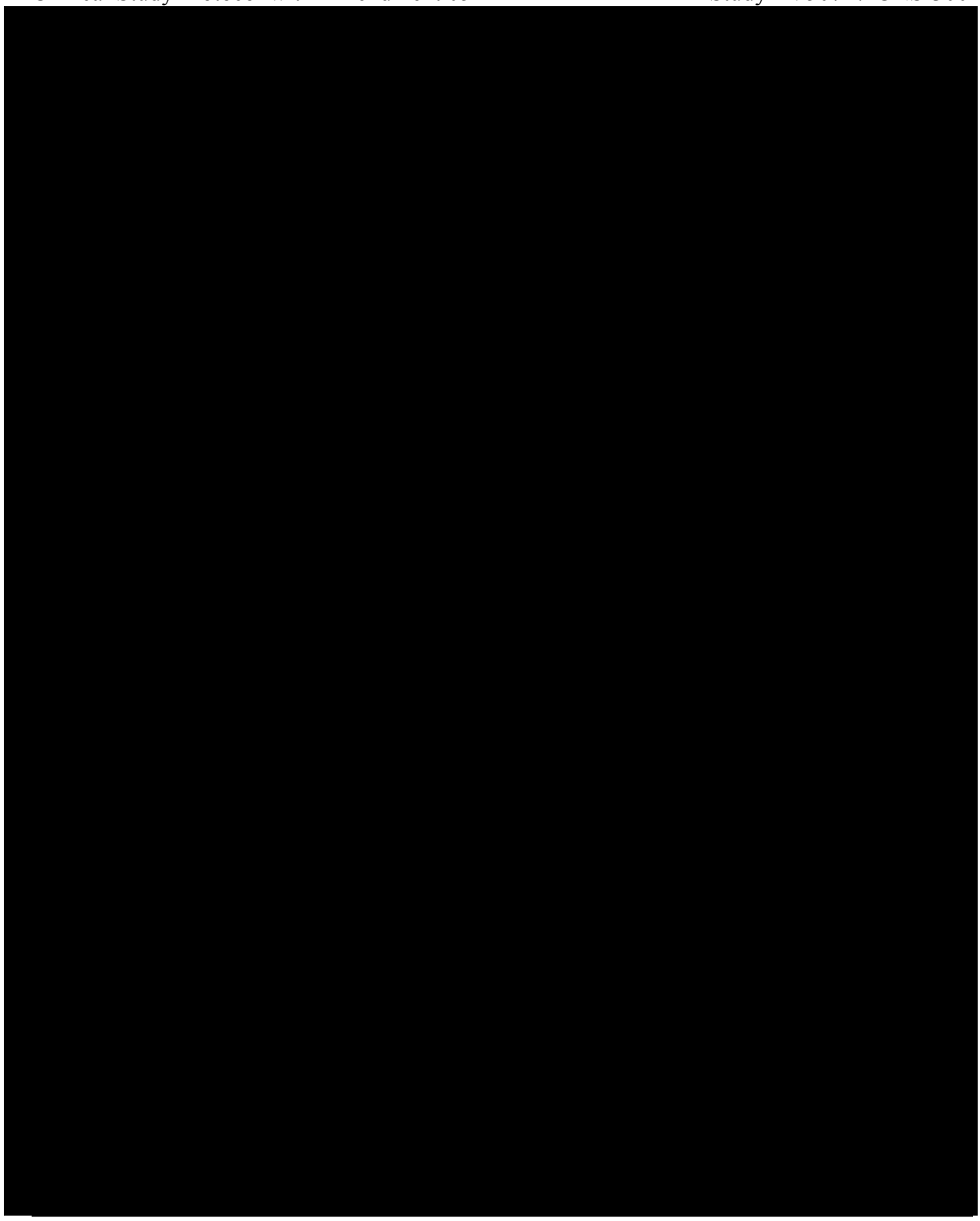
CHILD PSYCHIATRY BRANCH[5]
NATIONAL INSTITUTE OF MENTAL HEALTH

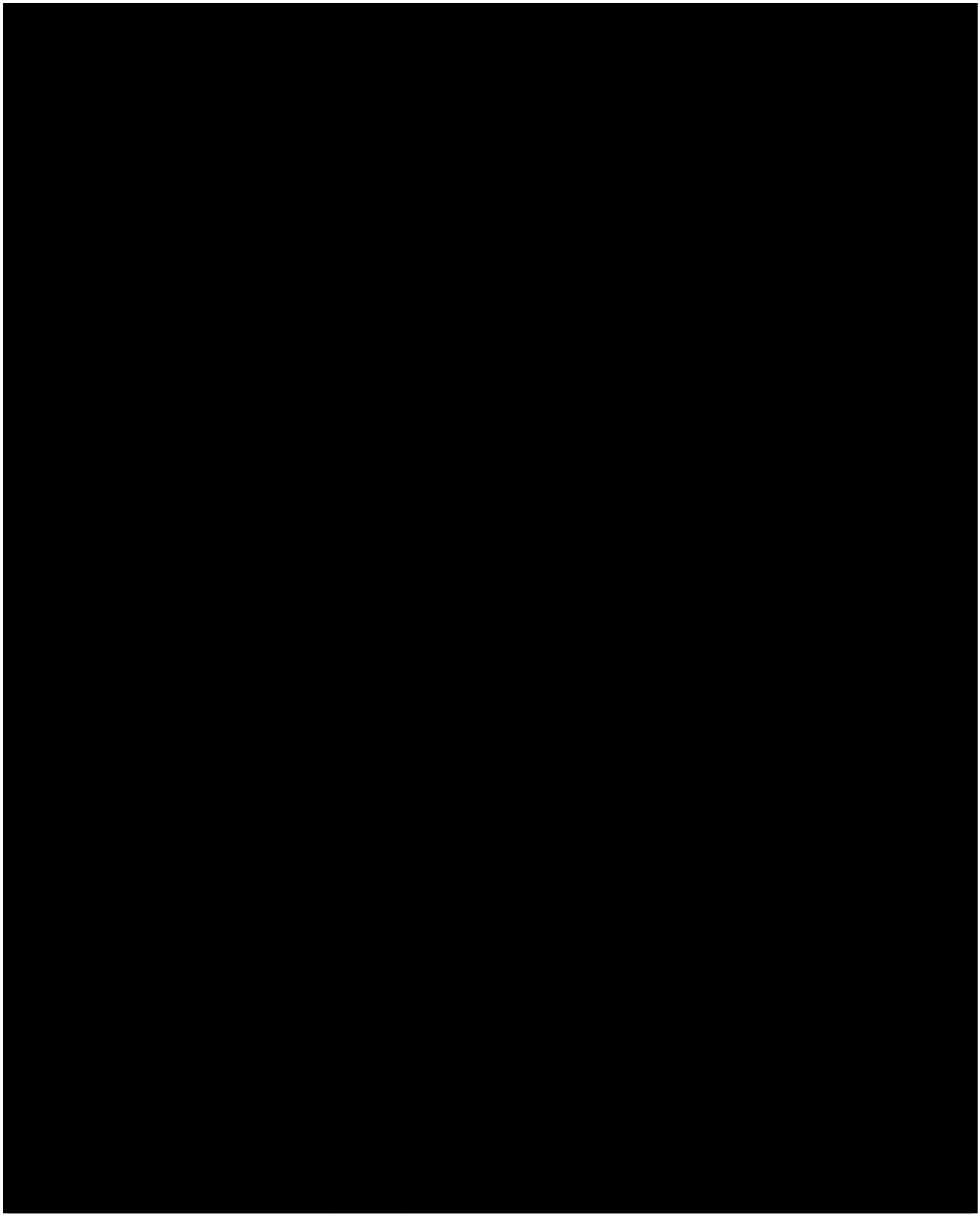
Investigators interested in using this rating scale should contact Lawrence Scahill, M.S.N., Ph.D., at the Yale Child Study Center, P.O. Box 207900, New Haven, CT 06520 or Wayne Goodman, M.D., at the National Institute of Mental Health, Bethesda, MD.

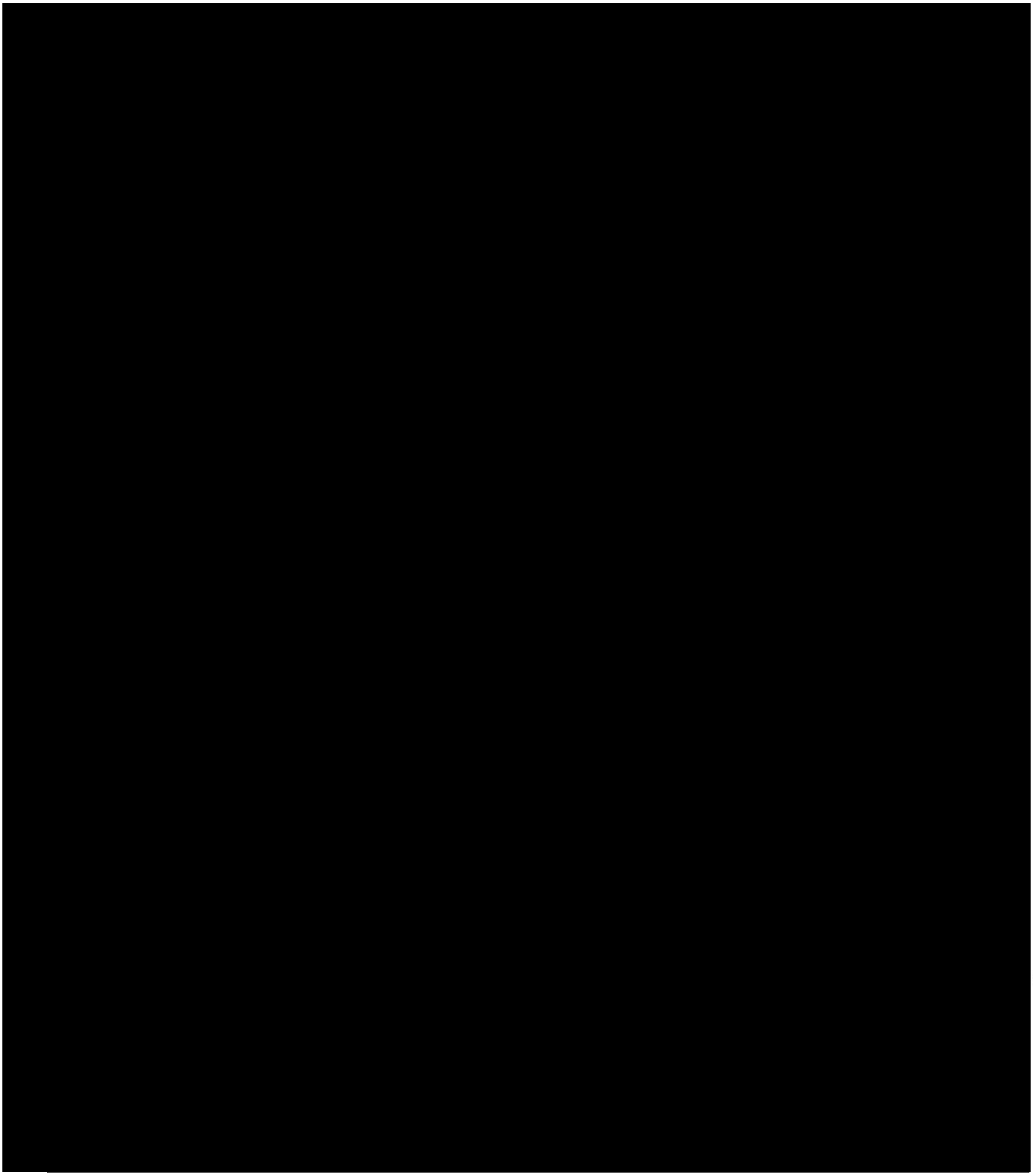
Scahill, L., Riddle, M.A., McSwiggin-Hardin, M., Ort, S.I., King, R.A., Goodman, W.K., Cicchetti, D. & Leckman, J.F. (1997). Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. *J Am Acad Child Adolesc Psychiatry*, 36(6):844-852.

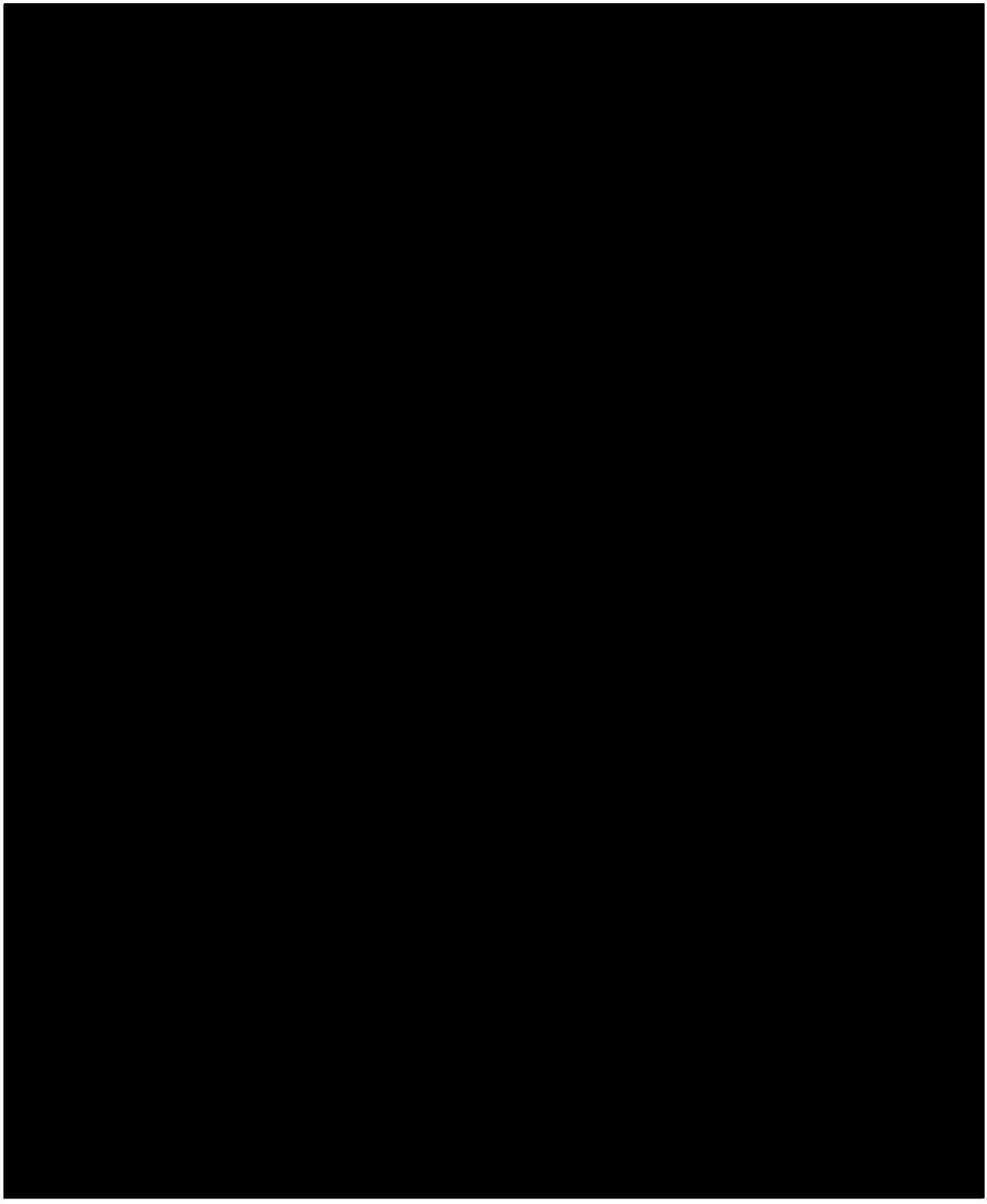
GENERAL INSTRUCTIONS

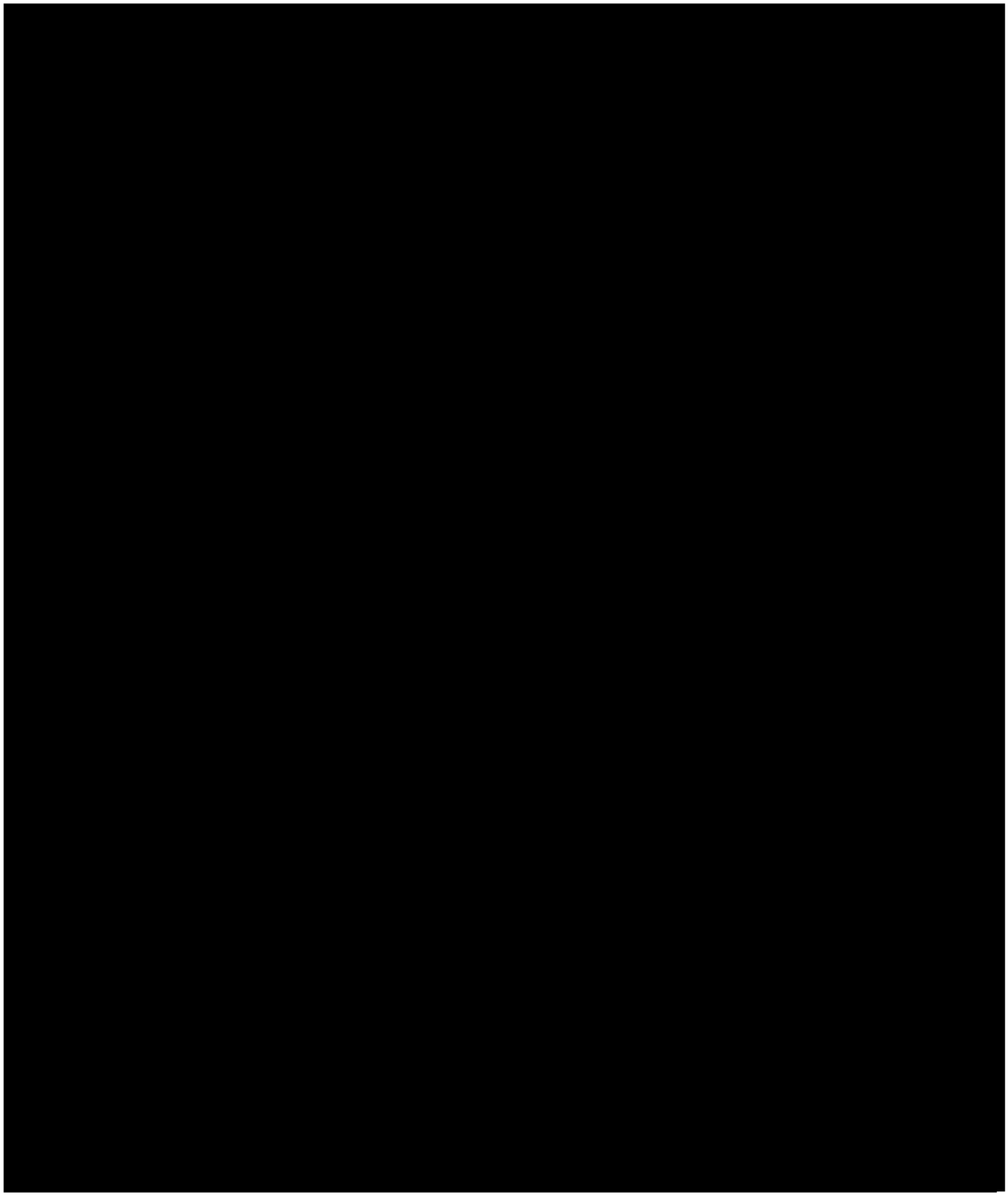


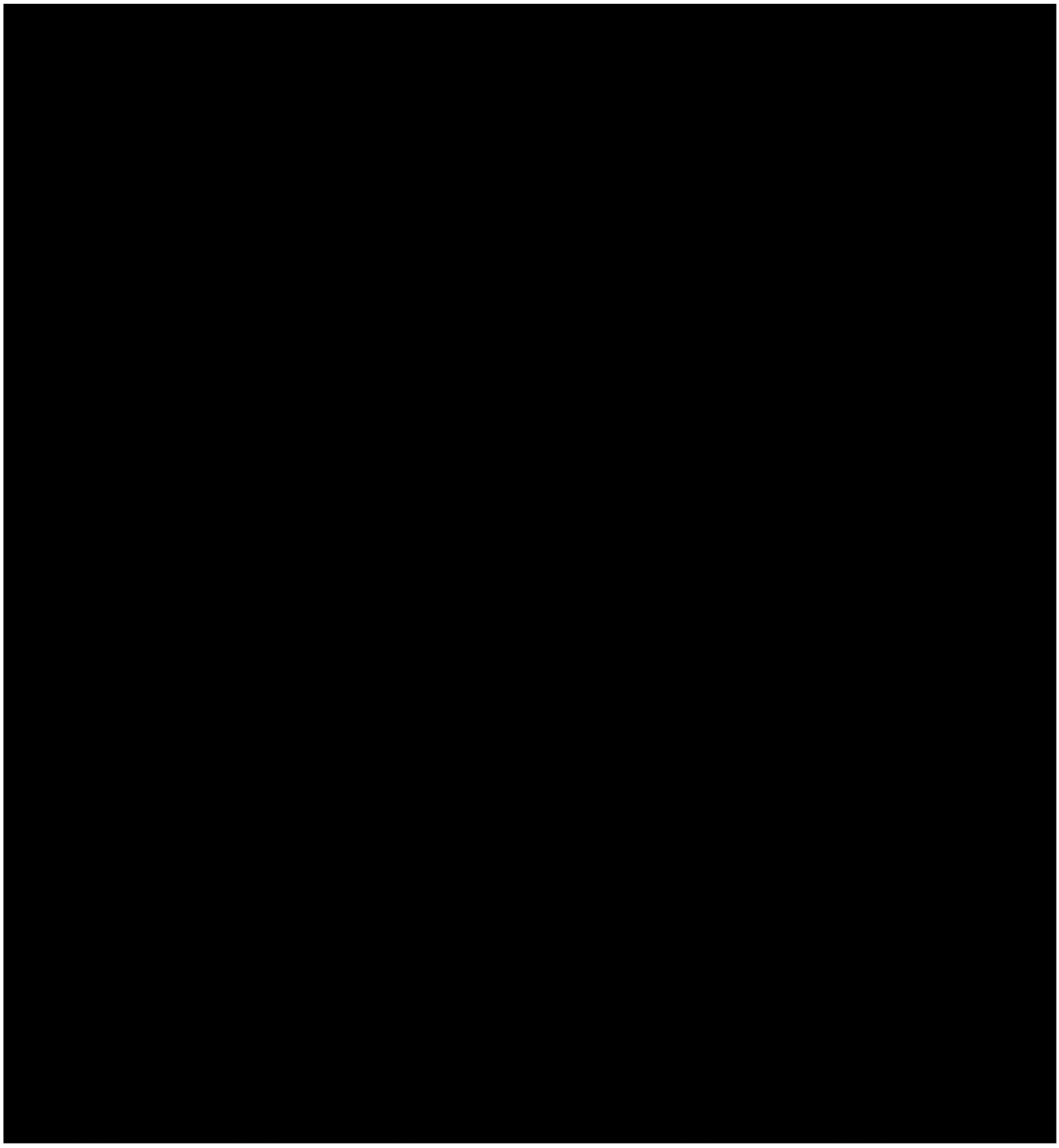


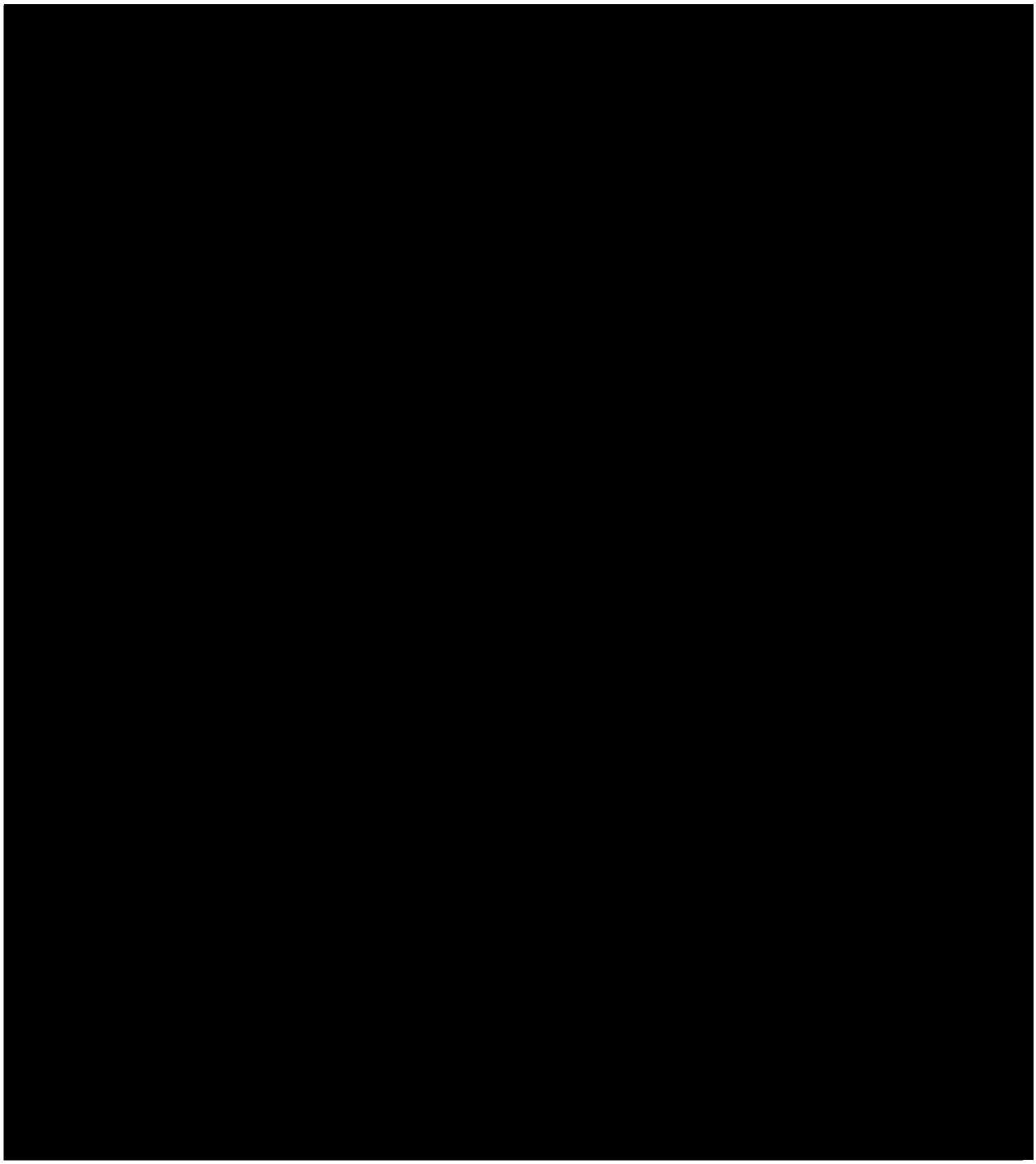


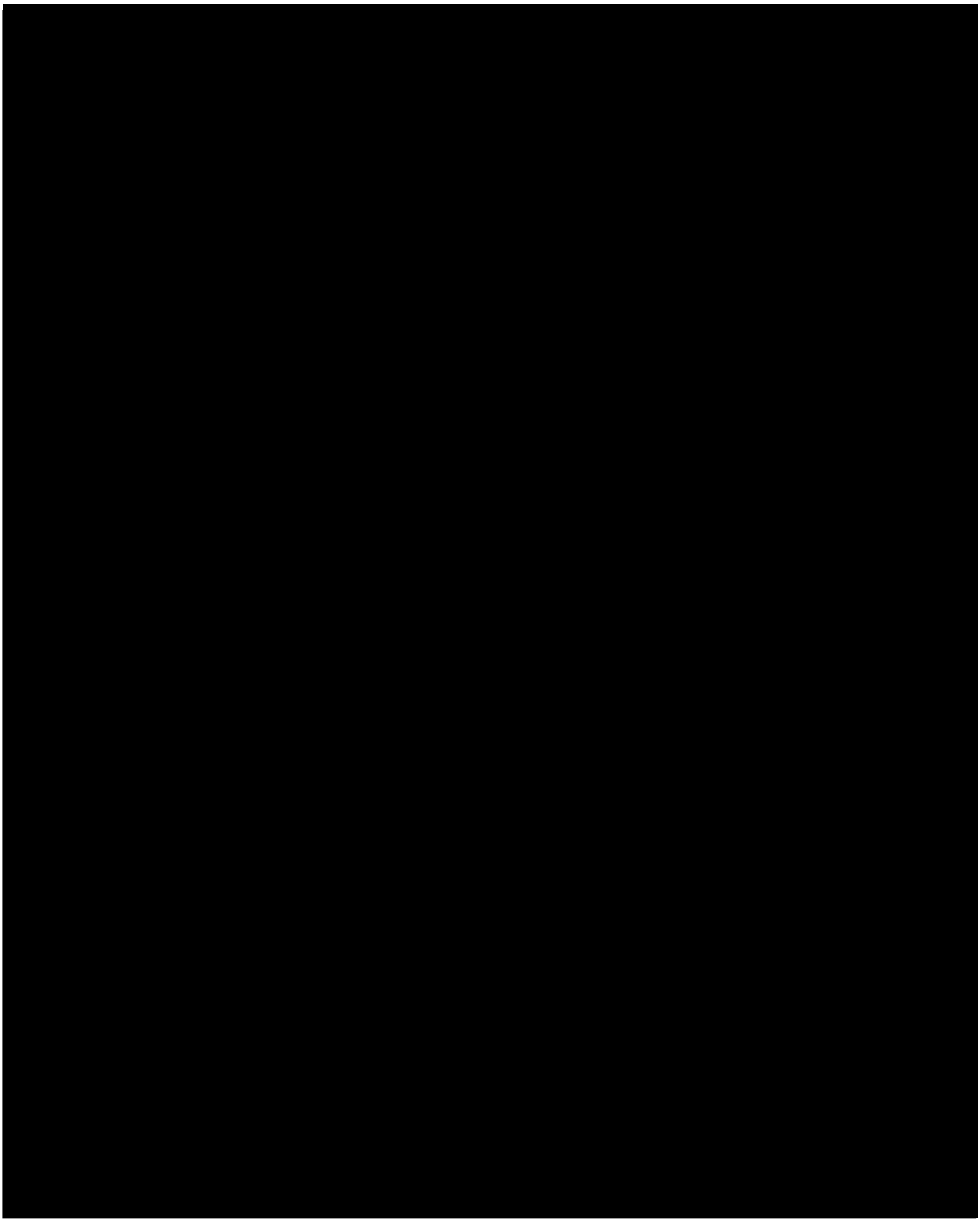












APPENDIX G. YALE GLOBAL TIC SEVERITY SCALE

The sample provided in this appendix is for reference only.

ID #:

Y G T S S

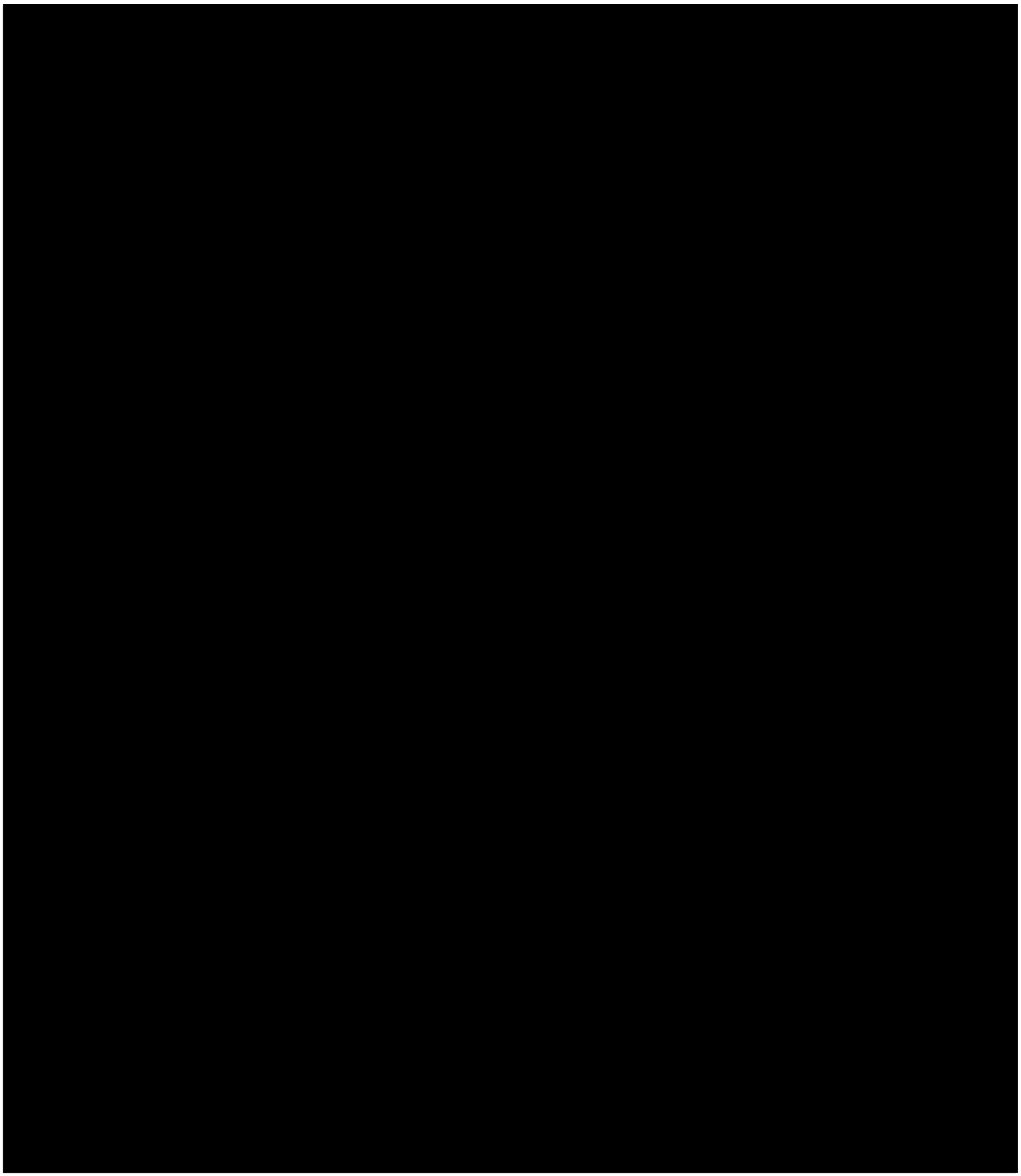
Yale Global Tic Severity Scale

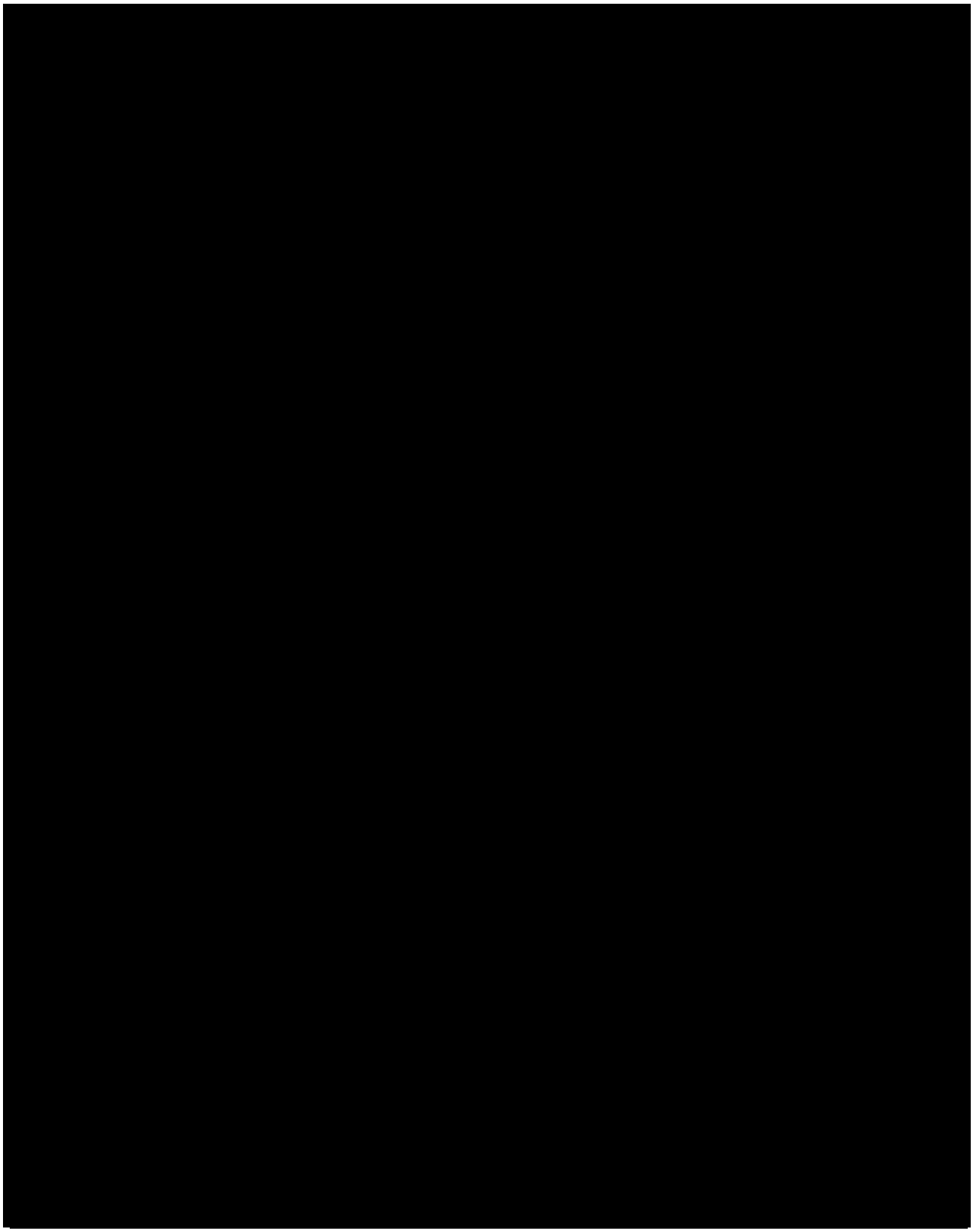
Yale Child Study Center

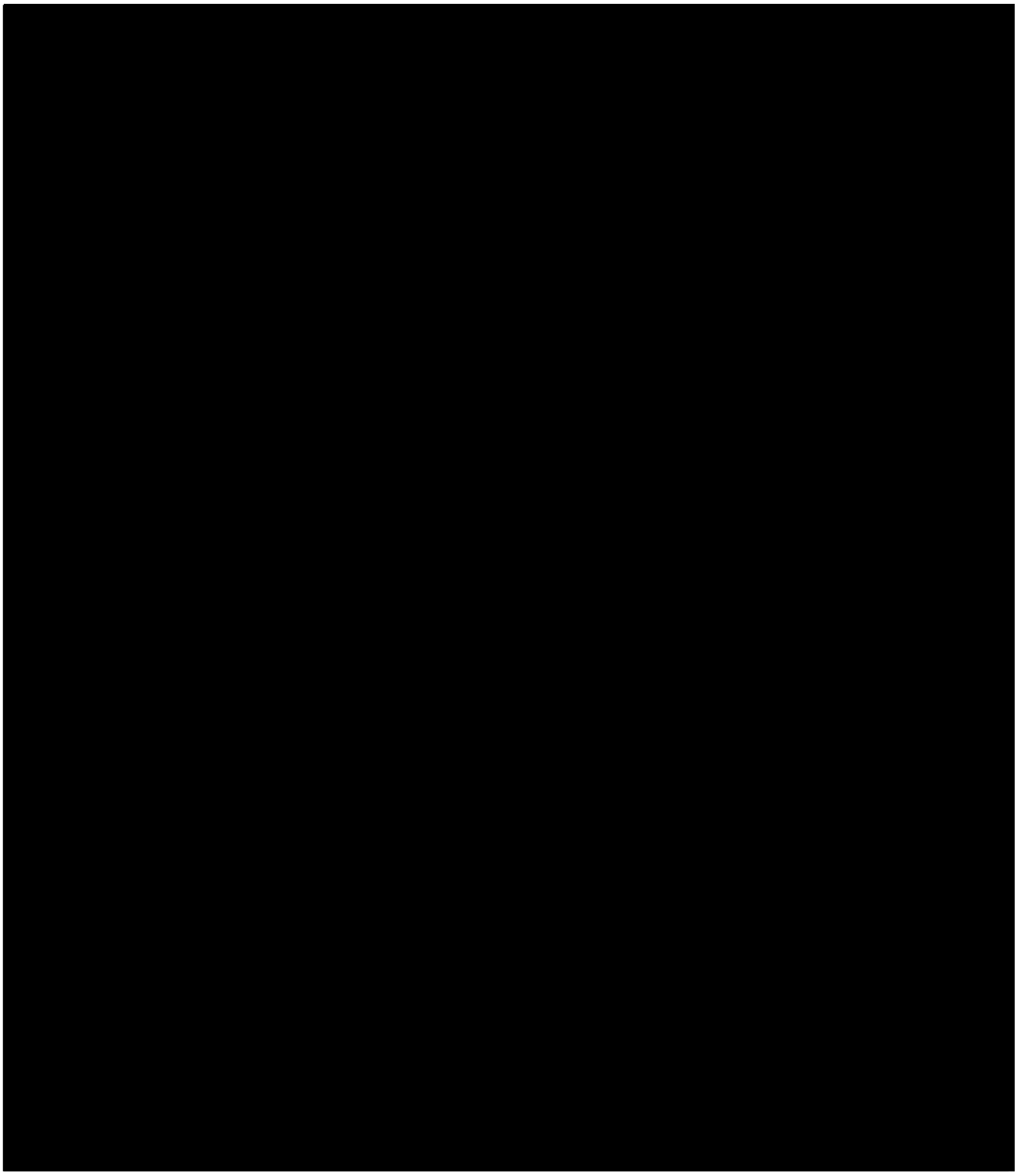
October 1992 version

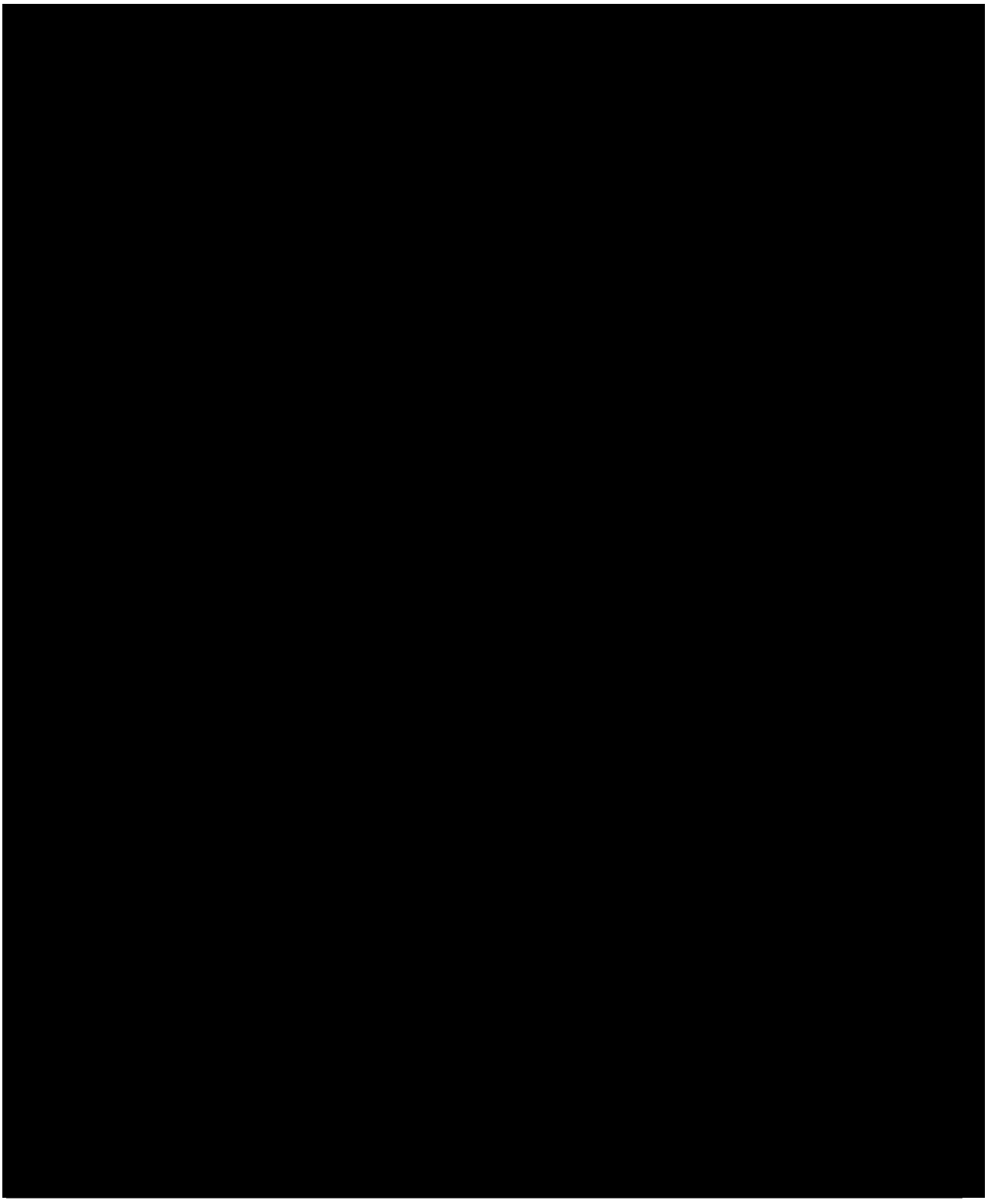
1

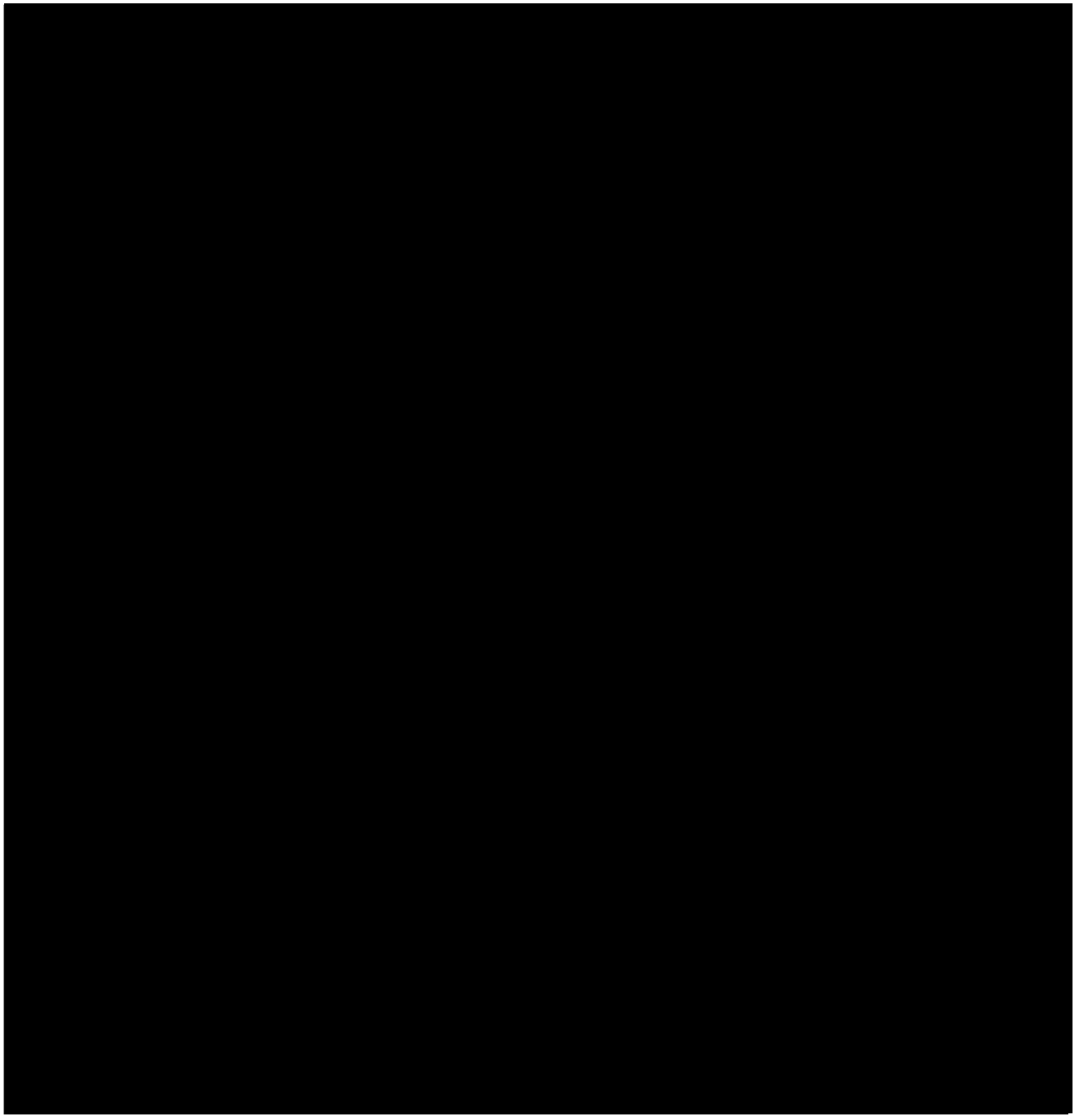
NAME:	TODAY'S DATE : / /
RATER:	











APPENDIX H. [redacted]

The sample provided in this appendix is for reference only.

[redacted]

APPENDIX I. [redacted]

The sample provided in this appendix is for reference only.

[redacted]

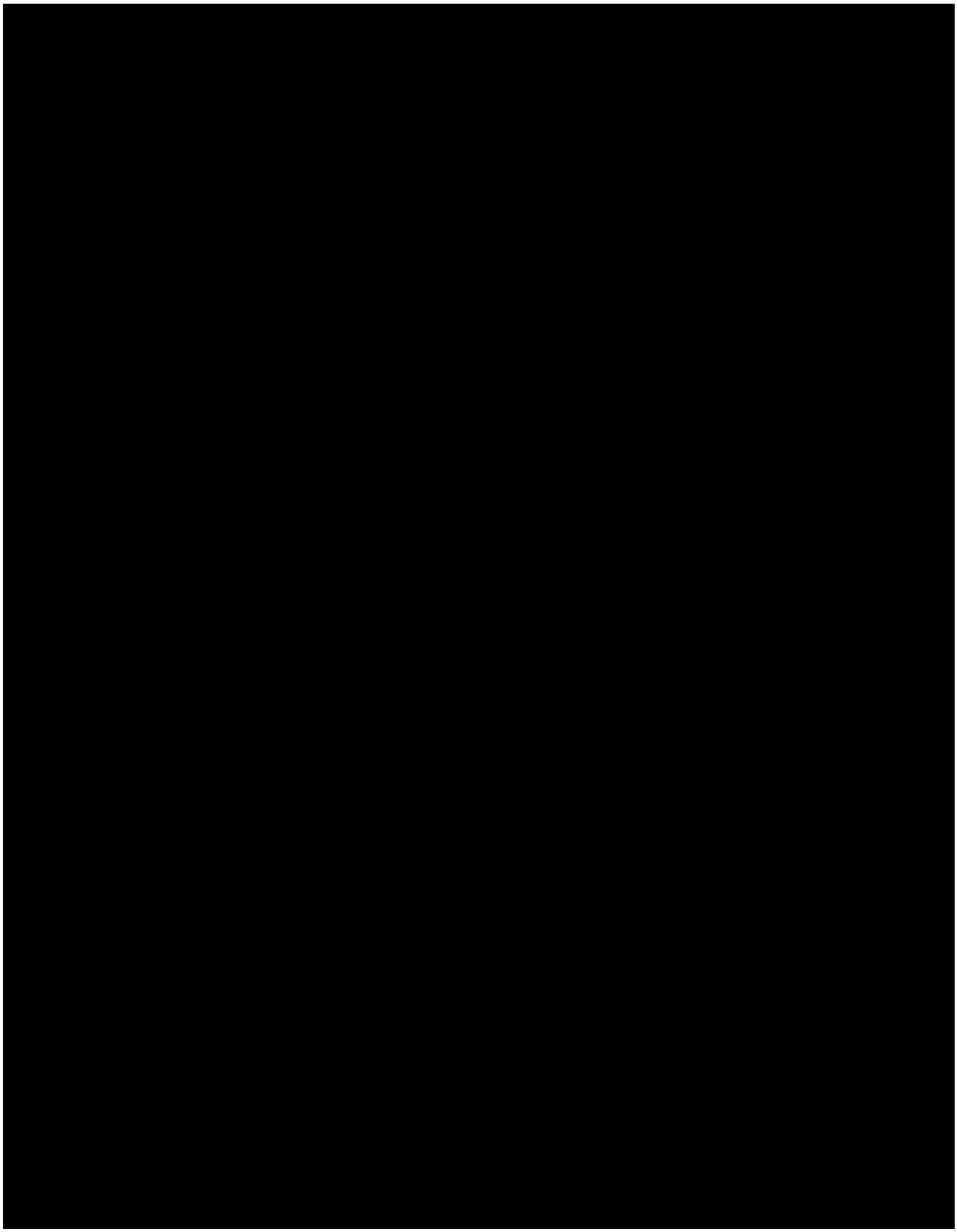
APPENDIX J. [redacted]

The sample provided in this appendix is for reference only.

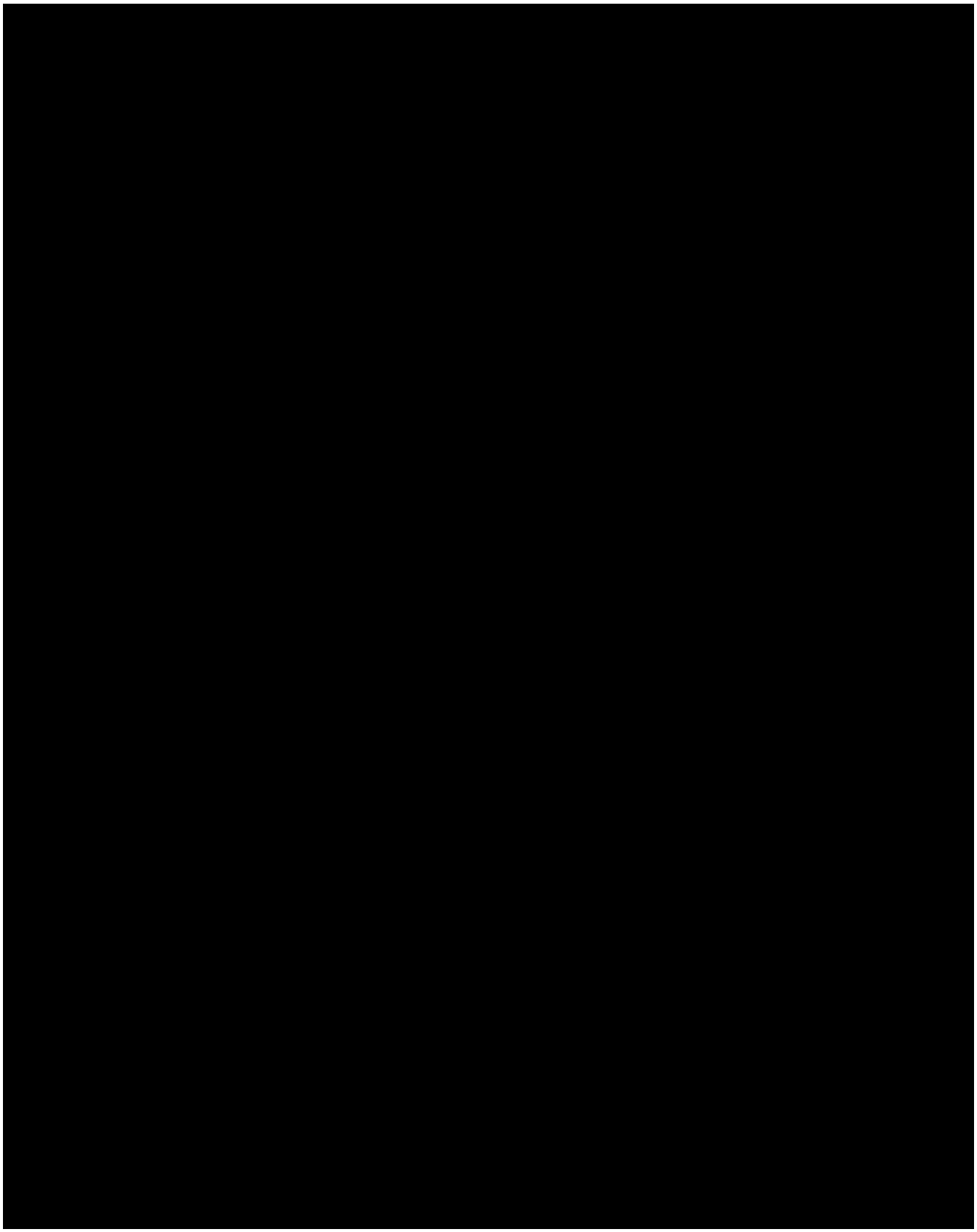
APPENDIX K. [redacted]

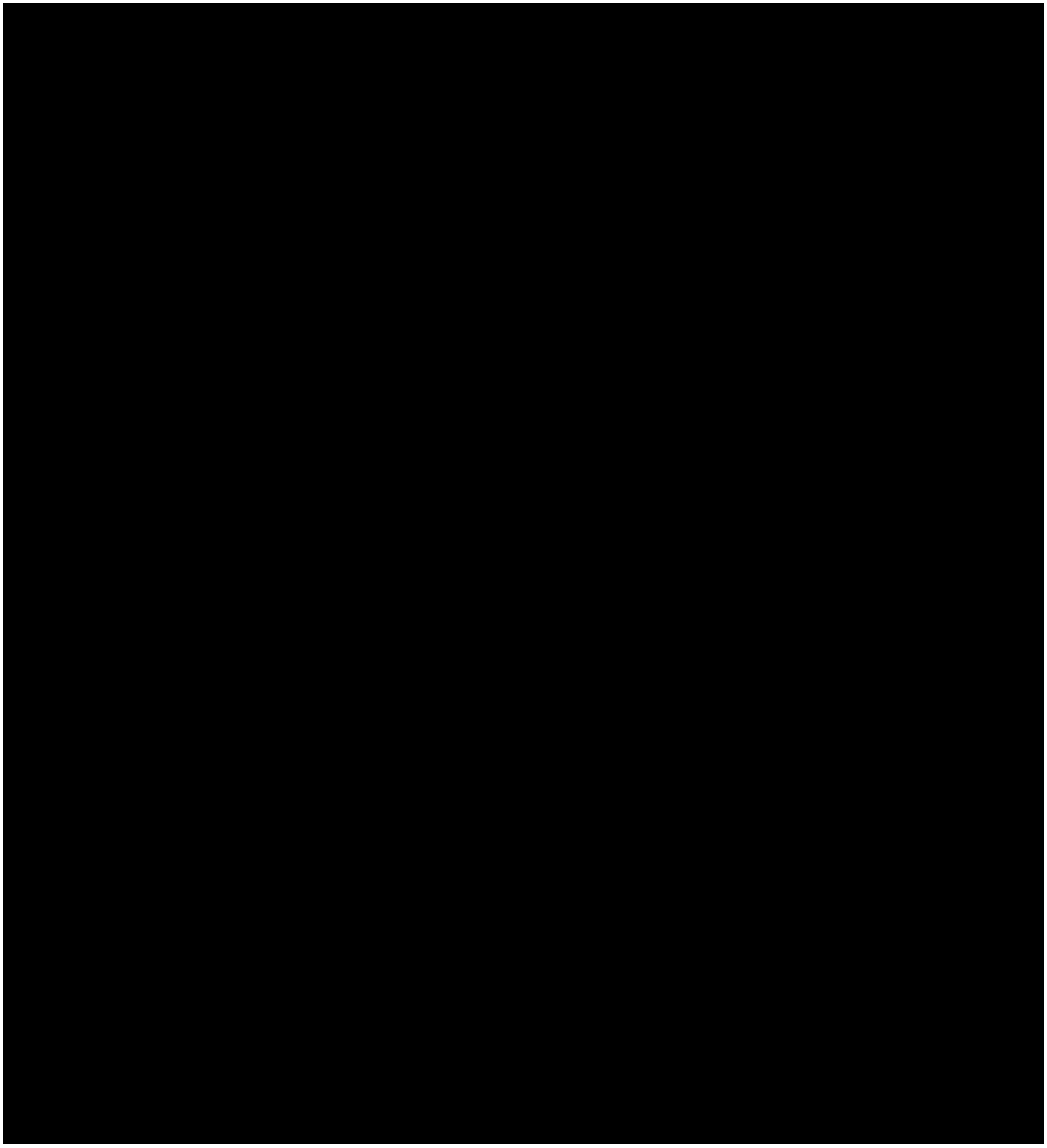
The sample provided in this appendix is for reference only.

[redacted]



Quality of life scale for patients aged 13 to 18 years (C&A-GTS-QOL 13-18)





APPENDIX L. [redacted]

[redacted]