Clinical Study Protocol

NCT Number: NCT04085172

Title: A Phase 4, Multicenter, 2-part Study Composed of a Randomized, Double-blind, Parallel-group, Placebo-controlled, Active-comparator, Dose-optimization Evaluation Followed by a 1-Year Open-label Evaluation to Assess the Safety and Efficacy of Guanfacine Hydrochloride Prolonged-release (SPD503) in Children and Adolescents Aged 6 to 17 Years With Attention-deficit/Hyperactivity Disorder

Study Number: SPD503-401

Document Version and Date: Protocol Amendment 8.0, 12 Apr 2024

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

CONFIDENTIAL

PROTOCOL: SPD503-401

TITLE:	A Phase 4, Multicenter, 2-part Study Composed of a Randomized, Double-blind, Parallel-group, Placebo-controlled, Active-comparator, Dose-optimization Evaluation followed by a 1-Year Open-label Evaluation to Assess the Safety and Efficacy of Guanfacine Hydrochloride Prolonged-release (SPD503) in Children and Adolescents aged 6 to 17 Years with Attention-deficit/Hyperactivity Disorder
DRUG:	TAK-503 (SPD503)
IND No:	63,551
EUDRACT Number:	2018-000821-29
EU CT Number (abbreviated):	2022-502630-71
SPONSOR:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington, MA 02421 USA
PRINCIPAL/ COORDINATING INVESTIGATOR:	PPD, MD Universitätsmedizin Mainz Klinik und Poliklinik für Kinder-und Jugendpsychiatrie und - psychotherapie Langenbeckstrasse 1 Geb. 406, 2. OG 55131 Mainz, Rheinland-Pfalz Germany
PROTOCOL HISTORY:	Protocol Amendment 8.0: 12 April 2024 Protocol Amendment 7.0: 02 Feb 2024 Protocol Amendment 6.0: 10 May 2023 Protocol Amendment 5.0: 08 Jun 2021 Protocol Amendment 4.0: 08 Jun 2020 Protocol Amendment 3.0: 09 Sep 2019 Protocol Amendment 2.1: 11 Jul 2019 Protocol Amendment 2: 28 May 2019 Protocol Amendment 1.1: 10 Apr 2019 Protocol Amendment 1: 02 May 2018 Original Protocol: 08 Feb 2018; Endorsed by PRAC: 14 Sep 2017

Confidentiality Statement

PROTOCOL SIGNATURE PAGE

Sponsor's Approval

Signature: DocuSigned by: PPD	**Date:**
PPD, MD, M	
Signature:	**Date:**
PPD, E	

Investigator's Acknowl

I have read this protocol for Study SPD503-401.

Title: A Phase 4, Multicenter, 2-part Study Composed of a Randomized, Double-blind, Parallel-group, Placebo-controlled, Active-comparator, Dose-optimization Evaluation followed by a 1-Year Open-label Evaluation to Assess the Safety and Efficacy of Guanfacine Hydrochloride Prolonged-release (SPD503) in Children and Adolescents aged 6 to 17 Years with Attention-deficit/Hyperactivity Disorder.

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)

Signature: _____ **Date:** _____

SUMMARY OF CHANGES

The primary reasons for this amendment are:

- Correct a typographical error of the inclusion of the CGI-I and CGI-S assessments at the dose-tapering visits in Part A
- Align the protocol with the current Clinical Trial Regulation EU No 536/2014 requirements
- Align the protocol with the current Takeda safety reporting procedures

In addition, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Summary of Change(s) Since Last Version of Approved Protocol (Amendment 7.0, dated 02 Feb 2024)		
Amendment Number: **8.0**	**Amendment Date:** **12 April 2024**	**Global/Country/Site** **Global**
Added the EUDRACT Number for sites in the UK		Title page; Study Synopsis
Replaced the EU Trial No with the EU CT Number (abbreviated)		Title page; Study Synopsis
Added a high-level assessment of the benefit-risk profile of TAK-503 in pediatric patients		Study Synopsis
Clarified that the double-blind safety set will be used for safety analysis in Study Part A except for CANTAB domains.		Study Synopsis; Section 9.7
Clarified that time adjusted event rates will only be in the overall summary tables		Study Synopsis; Section 9.8.1
Removed the CGI-I and CGI-S assessments from the dose-taper visits in Part A (typographical error)		Study Schedules
Clarified that subjects who discontinue during Part A do not need to complete Visit 11A in addition to the ET visit		Study Schedules; Section 4.5
Updated the form names for reporting pregnancy; abuse, misuse, overdose, and medication errors; and SAEs		Emergency Contact Information; Section 8.1.6; Section 8.2.1
Removed a typographical error regarding ET visits for subjects who do not roll over into Study Part B		Section 3.1
Added clarification that all IMP will be labeled as per local regulation		Section 6.2.3
Clarified safety reporting procedures for SUSARs to Eudravigilance (per EU CTR requirements)		Section 8.2.7
Removed details on reporting early termination assessments to align with the current statistical analysis plan		Section 9.8
Clarified the investigator responsibilities for providing access to authorities (including those from a third country) to source data		Section 10.2.3
Provided the procedures for a serious breach of protocol for EU clinical trial regulation		Section 10.3.3

See Appendix 9 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the "Safety Report Form" within 24 hours of awareness to the sponsor's Global Drug Safety Department. Applicable fax numbers and e-mail address can be found on the fax cover sheet (sent under a separate cover).

Fax: 1-484-595-8155

Email: GPSE@takeda.com

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or non-medical complaints to the sponsor within 24 hours. If requested, defective product(s) will be returned to the sponsor for inspection and analysis.

A product quality complaint includes any instances where there is an allegation or report relating to sponsor-licensed or investigational products, received in writing, electronically, or orally, which indicates an impact to a product's strength, identity, safety, purity, or quality, or which suggests that a product did not meet the criteria defined in the regulatory applications, licenses, or marketing authorizations for the product. Examples of investigational product quality complaints include, but are not limited to, the following:

Unit issues	• Capsule fill empty or overage • Bottle/vial fill shortage or overage • Capsule/tablet damaged/broken • Syringe/vial cracked/broken	• Syringe leakage • Missing components • Product discoloration • Device malfunction
Labeling	• Label missing • Leaflet or Instructions For Use (IFU) missing • Label illegible	• Incomplete, inaccurate, or misleading labeling • Lot number or serial number missing
Packaging	• Damaged packaging (eg, secondary, primary, bag/pouch) • Tampered seals • Inadequate or faulty closure	• Missing components within package
Foreign material	• Contaminated product • Particulate in bottle/vial • Particulate in packaging	

Please report the product quality complaint using the "Product Complaint Data Collection Form" via the email address:

pqc@takeda.com

For instructions on reporting AEs related to product complaints, see Section 8.2.

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ABBREVIATIONS

Abbreviation	Definition
ADHD	attention-deficit/hyperactivity disorder
ADHD-RS-5	ADHD-Rating Scale-5
AE	adverse event
AMOME	abuse, misuse, overdose, or medication error
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
BPRS-C-21	Brief Psychiatric Rating Scale for Children
BRI	Behavioral Regulation Index (subscale of the BRIEF scale)
BRIEF	Behavior Rating Inventory of Executive Function
C3PS	Conners 3 Parent Short Form
CANTAB	Cambridge Neuropsychological Test Automated Battery
CDC	Centers for Disease Control
CGI-I	Clinical Global Impression–Improvement
CGI-S	Clinical Global Impression–Severity
CHIP-CE:PRF	Child Health and Illness Profile – Child Edition: Parent Report Form
CI	confidence interval
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CTR	Clinical Trial Regulation
CTRS-R	Conners' Teaching Rating Scale - Revised
CYP	cytochrome P450
DMS	Delayed Matching to Sample (CANTAB task)
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DTP	direct-to-patient
(e)consent	electronic consent
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EF	executive function
EMA	European Medicines Agency
ET	early termination
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration

Abbreviation	Definition
FOCP	females of childbearing potential
GCP	Good Clinical Practice
GEC	Global Executive Composite (subscale of the BRIEF scale)
HR	heart rate
IB	investigator's brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	interactive response technology
K-SADS-PL	Kiddie-Schedule for Affective Disorders-Present and Lifetime Version
LAR	legally authorized representative
LS	least squares
MDMA	methylenedioxy-methamphetamine
MedID	medication identification
MI	Metacognition Index (subscale of the BRIEF scale)
MMRM	mixed-effects model for repeated measures
OCD	obsessive compulsive disorder
PASS	postapproval safety study
PDSS	Pediatric Daytime Sleepiness Scale
PPS	per-protocol set
PSMQ	Prior Stimulant Medication Questionnaire
PTSD	post-traumatic stress disorder
QD	once daily
RTI	Reaction Time/5-Choice Reaction Time (CANTAB task)
RVP	Rapid Visual Information Processing (CANTAB task)
SAE	serious adverse event
SAP	statistical analysis plan
SARI	serotonin antagonist and reuptake inhibitor
SmPC	Summary of Product Characteristics
SNRI	selective norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SST	Stop Signal Task (CANTAB task)
SWM	Spatial Working Memory (CANTAB task)
TEAE	treatment-emergent adverse event
UKU	Udvalg for Kliniske Undersøgelser
WFIRS-P	Weiss Functional Impairment Rating Scale – Parent

STUDY SYNOPSIS

Protocol number: SPD503-401	**Drug**: TAK-503 (SPD503) (guanfacine hydrochloride extended-/prolonged-release)
EUDRACT Number: 2018-000821-29 **EU CT Number (abbreviated)**: 2022-502630-71	
Title of the study: A Phase 4, Multicenter, 2-part Study Composed of a Randomized, Double-blind, Parallel-group, Placebo-controlled, Active-comparator, Dose-optimization Evaluation followed by a 1-Year Open-label Evaluation to Assess the Safety and Efficacy of Guanfacine Hydrochloride Prolonged-release (SPD503) in Children and Adolescents aged 6 to 17 Years with Attention-deficit/Hyperactivity Disorder	
Number of subjects (total and for each treatment arm): Approximately 288 children and adolescents aged 6 to 17 years inclusive diagnosed with attention-deficit/hyperactivity disorder (ADHD) by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) will be enrolled in Study Part A (96 subjects per treatment arm). Approximately 25% of all subjects will be aged 13 to 17 years. Approximately 25% of all subjects will be female. Once 120 subjects have entered into Study Part B, only subjects in the placebo arm in Study Part A will enter Study Part B, to assure that all placebo arm subjects have the opportunity to enter into the 1-year TAK-503 open-label treatment arm.	
Investigators: Multicenter study	
Sites and Region: Approximately 55 sites in Europe and the United States	
Study period: 2019 to 2027	**Clinical phase**: 4

Objectives

Primary objective: To evaluate the comparative long-term safety of TAK-503 (formerly known as SPD503) treatment in children and adolescents aged 6 to 17 years diagnosed with ADHD for whom stimulants are not suitable, not tolerated, or shown to be ineffective:

- To evaluate TAK-503 compared with atomoxetine after 12 months of once daily (QD) treatment on psychomotor speed and attention as measured by the Cambridge automated neuropsychological test battery (CANTAB) reaction time (RTI) task, using the mixed-effects model for repeated measures (MMRM). The effect of TAK-503 on cognition will be assessed and interpreted on the totality of the data.

Secondary objectives:

Secondary safety objectives

- Cognitive domain, sustained attention as measured by CANTAB Rapid Visual Information Processing (RVP) task
- Cognitive domain, Spatial Working Memory (SWM), a component of executive function (EF), as measured by the CANTAB SWM task between errors
- Cognitive domain, response control/inhibition as measured by the CANTAB Stop Signal Task (SST)
- Cognition domain, recognition memory as measured by the CANTAB Delayed Matching to Sample (DMS) task
- Sexual maturation as measured by Tanner stage
- Growth as measured by weight, height, and body mass index (BMI)
- Incidence of treatment-emergent adverse events (TEAE)
- Vital sign and electrocardiogram (ECG) results
- Psychiatric symptoms as measured by the Brief Psychiatric Rating Scale for Children (BPRS-C) total score and factors for Depression, Anxiety, Psychomotor Excitation, Behavior Problems, Withdrawal, Thinking Disturbance, and Organicity
- Suicidal ideation/behavior as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS)
- Asthenia/Lassitude/Increased Fatigability, Sleepiness/Sedation, Increased Duration of Sleep, and Orthostatic Dizziness based on the ratings of specific Udvalg for Kliniske Undersøgelser (UKU) scale items
- Sedative effects as measured by subject ratings on the Pediatric Daytime Sleepiness Scale (PDSS)

Secondary efficacy objectives

- Attention-deficit/hyperactivity disorder symptoms as measured by the investigator-administered ADHD-Rating Scale-5 (ADHD-RS-5) total score and hyperactivity/impulsivity and inattention subscale scores
- Global clinical measurement of ADHD improvement as measured by Clinical Global Impression-Improvement (CGI-I) using the Clinical Global Impression–Severity (CGI-S) to establish baseline
- Function as measured by the Child Health and Illness Profile – Child Edition: Parent Report Form (CHIP-CE:PRF) domains of satisfaction, comfort, resilience, risk avoidance, and achievement. The effect of TAK-503 on all subdomains will be summarized, including the subdomain satisfaction with self, using parental ratings of the child's self-esteem.
- Assessment of behavioral, social, and academic issues with the Conners 3 Parent Short Form (C3PS) Total Score and the Learning Problems and Executive Functioning subscale scores.

Rationale: Study SPD503-401 has been designed to evaluate the long-term safety and efficacy of TAK-503 with a specific focus on neurocognition, growth, and sexual maturation. In Study Part A, an atomoxetine arm has been included as an active comparator and a placebo treatment arm as a control for assay sensitivity.

Benefits and Risks: Overall, the clinical development program has demonstrated a favorable benefit-risk profile of TAK-503 in treatment of ADHD in children and adolescents. The efficacy of TAK-503 for the treatment of ADHD compared to placebo has been rigorously demonstrated with several well controlled studies. Post-marketing reports have continued to indicate that TAK-503 is generally safe and well tolerated in the majority of subjects, and the incidence and nature of the adverse events remains in accordance with the current reference safety information for the product and the known clinical characteristics of the treated patient population.

Investigational product, dose, and mode of administration

Study Part A: Double-blind Evaluation

The investigational medicinal products (IMPs) include TAK-503, atomoxetine, and placebo. The IMPs will be administered using a double-blinded double-dummy design. Dosing of IMP will be flexibly optimized to maximize potential benefits while minimizing risk of TEAEs.

Eligible subjects will be randomized at baseline (Day 0/Visit 2A) in a 1:1:1 ratio among TAK-503, atomoxetine, and placebo treatment arms. Allocation to treatment arm will be stratified by sex (male or female) and age subgroup (6-12 years or 13-17 years) to facilitate between-treatment balance within each stratum.

Subjects randomized to the TAK-503 treatment arm will receive TAK-503 tablet(s) and atomoxetine-matched placebo capsule(s). Subjects randomized to the atomoxetine treatment arm will receive TAK-503-matched placebo tablet(s) and atomoxetine capsule(s). Subjects randomized to the placebo treatment arm will receive TAK-503-matched placebo tablet(s) and atomoxetine-matched placebo capsule(s).

TAK-503, an extended-/prolonged-release tablet formulation of guanfacine hydrochloride, is designed for QD oral administration. TAK-503 will be provided by the sponsor in 1-, 2-, 3-, and 4-mg strength tablets.

Atomoxetine hydrochloride, the marketed comparator product, is designed for QD administration. The sponsor will provide 10-, 18-, 25-, 40-, and 60-mg strength atomoxetine capsules.

The sponsor will provide TAK-503-matched placebo tablets and atomoxetine-matched placebo capsules.

Study Part B: Open-label Evaluation

TAK-503 will be the only IMP administered in Study Part B. The dose-optimization schedule and dose levels of TAK-503 in Study Part B will be identical to those in Study Part A.

Methodology

Study SPD503-401 is a phase 4, multicenter, dose-optimization postapproval safety study (PASS) and will be conducted in 2 parts: Study Part A and Study Part B. Study Part A will be a randomized, double-blinded, parallel-group, placebo- and active comparator-controlled, 3-treatment arm safety and efficacy evaluation of TAK-503. Pediatric subjects with ADHD will be randomized in a 1:1:1 ratio among TAK-503, atomoxetine, and placebo treatment arms for 18 weeks of double-blinded treatment and evaluation. At the end of the 18 weeks (Week

18A/Visit 11A), all subjects will roll over to Study Part B directly for an additional 52 weeks of open-label TAK-503 treatment.

Once 120 subjects have entered into Study Part B, only subjects in the placebo arm in Study Part A will enter Study Part B, to assure that all placebo arm subjects have the opportunity to enter into the 1-year TAK-503 open-label treatment arm.

Study Part A will consist of the following 5 periods elapsing up to 23 weeks:

1. Screening/washout: Day -35A to Day -3A (up to 5 weeks).
2. Dose-optimization period: IMP will be dose-optimized from Week 0A through Week 4A for children aged 6 to 12 years and through Week 7A for adolescents aged 13 to 17 years.
3. Dose-maintenance period: Subjects will continue with QD dosing from Week 5A for children and Week 8A for adolescents through Week 18A.
4. Dose-taper period: Scheduled 3-week fixed-dose taper of IMP. All subjects randomized in the TAK-503 or atomoxetine treatment arms will undergo a scheduled 3-week dose taper to ensure proper downward dose titration of TAK-503 at the end of the dose-maintenance period or ET.
5. Follow-up period: Follow-up visit 1 week after the last IMP tapered dose
    - Subjects randomized to TAK-503 or atomoxetine treatment arms will participate in a follow-up visit and begin rescreening/washout procedures for Study Part B.

Placebo subjects can skip the follow-up visit after completion of Study Part A assessments at Visit 11A (Week 18A), and proceed immediately to baseline visit assessments for Study Part B.

Before enrollment in Study Part A, subjects will be screened based on inclusion/exclusion criteria to establish eligibility for study participation. Subjects who meet eligibility requirements will undergo a medication washout period, if applicable.

In Study Part A, subjects with a baseline ADHD-RS-5 total score ≥28 and CGI-S score of ≥4 will be eligible for enrollment. During the dose-optimization period, clinic visits will be scheduled once every 7 days to assess IMP safety and tolerability and to allow investigators to titrate IMP to an optimal dose that maximizes potential benefits while minimizing risk of TEAEs. If necessary, the investigator will be allowed to lower the subject's dose once during the dose optimization period in Study Parts A and B.

Subjects randomized to TAK-503 will begin dosing at 1 mg, which will be dose-titrated upward in weekly 1-mg increments until an optimal dose is reached. Children aged 6 to 12 years will not be permitted to titrate to a daily dose >4 mg QD and adolescents aged 13 to 17 years will not be permitted to titrate to a dose greater than the maximum allowed dose QD as presented in the following baseline weight groups:

Baseline weight	Maximum TAK-503 dose QD
25.0 to 41.4 kg	4 mg
41.5 to 49.4 kg	5 mg
49.5 to 58.4 kg	6 mg
≥58.5 kg	7 mg

Subjects optimized to a TAK-503 daily dose between 1 and 4 mg will take 1 TAK-503 tablet QD (or TAK-503-matched placebo tablet). Subjects optimized to a TAK-503 daily dose between 5 and 7 mg will take 2 TAK-503 tablets QD (or 2 TAK-503-matched placebo tablets).

Subjects randomized to the atomoxetine treatment arm who weigh <70 kg at baseline will begin dosing with approximately 0.5 mg/kg atomoxetine QD. If well-tolerated after 1 week minimum, this dose may be increased to the target dose of 1.2 mg/kg QD. The total daily dose will not exceed 1.4 mg/kg QD. With limited dosage forms, this upper limit is necessary to achieve appropriate weight-based dosing. Permitted doses of atomoxetine for subjects who weigh <70 kg at baseline are 10, 18, 25, 40, 60, and 80 mg QD and depend on subject's baseline weight (Visit 2A).

Subjects randomized to the atomoxetine treatment arm who weigh ≥70 kg at baseline will begin dosing with 40 mg atomoxetine QD. If well-tolerated after 1 week minimum, this dose may be increased to 80 mg QD. After a 1-week

minimum, if the 80 mg daily dose is well-tolerated, then the dose may be increased to 100 mg QD. The total dose in children and adolescents who weigh ≥70 kg at baseline will not be permitted to exceed 100 mg QD.

Subjects optimized to an atomoxetine daily dose greater than 60 mg QD will take 2 atomoxetine or atomoxetine-matched placebo capsules QD. Subjects optimized to a daily dose ≤60 mg will take 1 atomoxetine or atomoxetine-matched placebo capsule QD.

Subjects will continue daily treatment with the optimal IMP dose during the dose-maintenance period. The investigator will not be permitted to adjust the IMP dose during the dose-maintenance period of Study Part A. The dose-maintenance period will be followed by a 3-week dose-taper period.

After the last IMP tapered dose, subjects will return to the site for a follow-up visit. The follow-up visit will serve as the Study Part B screening visit for subjects randomized to the TAK-503 and atomoxetine treatment arms.
Study Part B will consist of 5 periods:

1. Screening/washout: Day -35B to Day -3B (up to 5 weeks)
2. Dose-optimization period: TAK-503 will be dose-optimized from Week 0B through Week 4B for children aged 6 to 12 years and through Week 7B for adolescents aged 13 to 17 years.
3. Dose-maintenance period: Dose-optimized TAK-503 will be administered QD from Week 5B for children and from Week 8B for adolescents through Week 49B for both age groups.
4. Dose-taper period: Scheduled 3-week dose-taper of TAK-503 through Weeks 50B, 51B, and 52B
5. Follow-up period: Last dose of TAK-503 to the follow-up visit at Week 53B

During the follow-up visit in Study Part A, subjects will undergo a partial rescreening of study criteria to confirm eligibility for continued participation in Study Part B. Subjects who complete Study Part A and roll over into Study Part B should do so without a gap except for washout. Subjects (except those randomized to placebo) must undergo a washout period of ≥30 days between the last IMP dose in Study Part A and the first dose of TAK-503 in Study Part B. Eligibility for Study Part B will be confirmed at the baseline visit (Visit 2B).

During the dose-optimization period of Study Part B, clinic visits will be scheduled once every 7 days to assess safety and tolerability and to allow investigators to titrate subjects to an optimal TAK-503 dose based on clinical judgment of tolerability and efficacy using the totality of all available clinical and safety data. All subjects will begin with 1 mg TAK-503 QD and dose-titrated upward in 1-mg increments weekly until an optimal dose is reached. Children aged 6 to 12 years will not be permitted to titrate to a daily dose greater than 4 mg and adolescents aged ≥13 years will not be permitted to titrate to a daily dose above the maximum allowed dose per baseline weight group.

Following titration to an optimal dose of TAK-503, subjects will continue with TAK-503 administration through the dose-maintenance period (ie, Week 49B). Visits to the site will occur at intervals of 13 weeks. During the dose-maintenance period, the investigator may make further dose adjustments as needed based upon TEAEs and clinical judgment of tolerability and efficacy. These dose adjustments can be to a higher dose, based on the subject's current age and weight. Children who turn 13 years or older during the dose-maintenance period may be permitted to increase the daily dose higher than 4 mg based on weight at the Study Part B baseline. The dose can be adjusted in 1 mg increments (increased or decreased) at any scheduled or unscheduled visit (not more frequently than every 3 days) during the study if deemed appropriate by the investigator.

All subjects randomized to either the TAK-503 or atomoxetine treatment arm will undergo a scheduled 3-week dose taper to ensure proper downward dose titration of TAK-503 at the end of the dose-maintenance period or ET in both Study Parts A and B, as applicable.

Each subject's last visit will be 7 (+2) days after the last TAK-503 dose in Study Part B, to measure blood pressure and heart rate, and to follow up on concomitant medications and safety assessments, including TEAEs, which may have been ongoing at the previous visit. Treatment-emergent adverse events reported up to the time of the follow-up visit will be documented and appropriate follow-up will continue until all safety concerns are resolved as judged by the investigator.

Inclusion and exclusion criteria (Study Part A – see full protocol for Study Part B eligibility criteria)
Inclusion Criteria

1. Subject is a male or female aged 6 to 17 years inclusive at the time of consent/assent.
2. Subject must meet DSM-5 criteria for a primary diagnosis of ADHD based on a detailed psychiatric evaluation using the Kiddie-Schedule for Affective Disorders-Present and Lifetime Version (K-SADS-PL) by a trained child and adolescent psychiatrist at screening (Visit 1A).

3. Subject for whom prior stimulant therapy is not suitable, not tolerated, or shown to be ineffective as determined by investigator clinical assessment and review of the Prior Stimulant Medication Questionnaire (PSMQ) administered during screening (Visit 1A).
4. Subject has an ADHD-RS-5 total score ≥28 at baseline (Visit 2A).
5. Subject has a baseline (Visit 2A) CGI-S score ≥4.
6. Subject who is a female of childbearing potential (FOCP) and postmenarchal must have a negative serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at screening (Visit 1A) and a negative urine pregnancy test at baseline (Visit 2A), be nonlactating, and agree to comply with any applicable contraceptive requirements described in the protocol. Female of childbearing potential is defined as any female subject who is at least aged 9 years or younger than 9 years and postmenarchal.
7. Subject's parent or legally authorized representative (LAR) must provide signature of informed consent. Documentation of assent (if applicable) must be provided by the subject indicating that the subject is aware of the investigational nature of the study and the required procedures and restrictions in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guideline E6[R2] and applicable regulations, before completing any study-related procedures.
8. Subject and parent/LAR are willing and able to comply with all the testing and requirements defined in this protocol, including oversight of morning dosing. Specifically, the parent/LAR must be available for the duration of the study to administer the IMP dose each morning when the subject awakens.
9. Subject has supine and standing blood pressure (BP) measurements less than the 95th percentile for age, sex, and height at both screening (Visit 1A) and baseline (Visit 2A).
10. Subject is functioning at an age-appropriate level intellectually, as judged by the investigator.
11. Subject is able to swallow intact tablets and capsules.

Exclusion Criteria

1. Subject has a current, controlled (requiring medication or therapy) or uncontrolled, comorbid psychiatric disorder (except oppositional defiant disorder), including but not limited to any of the following comorbid Axis I and Axis II disorders (the K-SADS-PL should be reviewed to confirm diagnosis, if necessary):
    a. Posttraumatic stress disorder (PTSD)
    b. Bipolar illness, psychosis, or family history in either biological parent
    c. Pervasive developmental disorder
    d. Obsessive-compulsive disorder (OCD)
    e. Psychosis/schizophrenia
    f. Serious tic disorder or a family history of Tourette's disorder
2. Subject is currently considered to be a suicide risk by the investigator; has made a previous suicide attempt; has a history of, or currently demonstrating, active suicidal ideation.
3. Subject has a substance abuse disorder as defined by DSM-5 criteria or has been suspected of a substance abuse or dependence disorder (except nicotine) within the past 6 months.
4. Subject has a clinically important abnormality on the urine drug and alcohol screen (except for the subject's current ADHD stimulant, if applicable) at screening (Visit 1A).
5. Subject has been physically, sexually, and/or emotionally abused.
6. Subject has any other disorder that as judged by the investigator could contraindicate TAK-503 or confound the results of the safety and efficacy assessments.
7. Subject has any condition or illness including any clinically significant abnormal laboratory value at screening (Visit 1A) or, if the laboratory test was repeated, at baseline (Visit 2A) that, as judged by the investigator, would be an inappropriate risk to the subject and/or could confound the interpretation of study results.
8. Subject has current abnormal thyroid function, defined as abnormal thyroid-stimulating hormone and thyroxine at screening (Visit 1A). Treatment with a stable dose of thyroid medication for ≥3 months before screening will be permitted.
9. Subject has a known history or presence of malignancy (except nonmelanoma skin cancer), pregnancy, and/or a developmental delay or abnormality associated with growth or sexual maturation delays that are not related to ADHD.
10. Children aged 6 to 12 years with a body weight <25.0 kg or adolescents aged ≥13 years with a body weight <34.0 kg at screening (Visit 1A) or baseline (Visit 2A).

11. Subject is significantly overweight based on the Centers for Disease Control (CDC) BMI-for-age sex-specific charts at screening (Visit 1A) or baseline (Visit 2A). For this study, significantly overweight will be defined as a BMI that is greater than the 95th percentile.
12. Subject has a known history or presence of: structural cardiac abnormalities, serious heart rhythm abnormalities, syncope, cardiac conduction problems (eg, clinically significant heart block or QT interval prolongation), bradycardia, or exercise-related cardiac events including syncope and presyncope.
13. Subject has clinically significant ECG findings, as judged by the investigator, at baseline (Visit 2A).
14. Subject has orthostatic hypotension* or a known history of hypertension. *(*Orthostatic hypotension is defined as a sustained reduction of systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of 10 mm Hg within 3 minutes of standing from supine.)*
15. Subject has a known family history of sudden cardiac death or ventricular arrhythmia.
16. Subject is currently using any medication that violates protocol-specified washout criteria at baseline (Visit 2A), including any ADHD medication or other prohibited medications such as herbal supplements, medications that affect BP or heart rate (HR) or medications that have central nervous system (CNS) effects or affect cognitive performance, such as sedating antihistamines and decongestant sympathomimetics (inhaled bronchodilators are permitted) or a history of chronic use of sedating medications (ie, antihistamines).
17. Subject has a medical condition except ADHD that requires treatment with any medication that affects the CNS.
18. Subject is female and pregnant or currently lactating.
19. Subject has taken another investigational product or participated in a clinical study within 30 days before screening (Visit 1A).
20. Subject does not tolerate or has a known or suspected allergy, hypersensitivity, or clinically significant intolerance to guanfacine hydrochloride, atomoxetine, or any TAK-503 or atomoxetine drug product component.
21. Subject has a history of a seizure disorder (except for a single childhood febrile seizure episode that occurred before the age of 3 years).
22. Subject is well-controlled on his/her current ADHD medication with acceptable tolerability, and the parent/treating physician does not object to the current medication.
23. Subject has ALT >2 x upper limit of normal (ULN) or AST >2 x ULN or bilirubin >1.5 x ULN at screening.

Maximum duration of subject involvement in the study (per Amendment 7)

Study Part A

- Planned duration of screening and washout: Up to 35 days
- Planned duration of the dose-optimization period: 4 weeks (children), 7 weeks (adolescents)
- Planned duration of the dose-maintenance period: 14 weeks (children), 11 weeks (adolescents)
- Planned duration of the dose-taper period: 3 weeks
- Planned duration of the follow-up period: 7 (+2) days

Study Part B

- Planned duration of washout: Up to 35 days
- Planned duration of the dose-optimization period: 4 weeks (children), 7 weeks (adolescents)
- Planned duration of the dose-maintenance period: 45 weeks (children), 42 weeks (adolescents)
- Planned duration of the dose-taper period: 3 weeks
- Planned duration of the follow-up period: 7 (+2) days

Endpoints and statistical analysis

Study Analysis Population Sets

The randomized set will be defined as all randomized subjects in Study Part A. Any subject who is not randomized will be considered a screen failure.

The double-blind safety set will be defined as all randomized subjects in Study Part A who receive ≥1 IMP dose. The double-blind safety set will be used for safety analysis (except for CANTAB domains) for Study Part A.

The open-label safety set will be defined as all subjects who receive ≥1 dose of TAK-503 in Study Part B. All safety and efficacy presentations for Study Part B will be based on the open-label safety set.

The full analysis set (FAS) will be defined as all subjects in the double-blind safety set with ≥1 postbaseline CANTAB assessment.

The per-protocol set (PPS) will be defined as all subjects in the FAS who complete the study and were deemed protocol-compliant. To be protocol-compliant, no significant protocol deviations occurred during the study that could affect the assessment of the primary safety endpoint, the CANTAB RTI task.

Study Endpoints

The primary safety endpoint will be the change from baseline in the CANTAB RTI task.

Secondary safety endpoints will include the following:

- CANTAB tasks: RVP, SWM between errors, DMS, and SST
- Tanner stage, weight, height, BMI
- Vital signs (BP and pulse) and ECG results
- BPRS-C total score and scales for Depression, Anxiety, Psychomotor Excitation, Behavior Problems, Withdrawal, Thinking Disturbance, and Organicity
- C-SSRS
- Specified UKU side effect rating scale items: Asthenia/Lassitude/Increased Fatigability, Sleepiness/Sedation, Increased Duration of Sleep, and Orthostatic Dizziness
- PDSS

Primary efficacy endpoint: Not applicable for this PASS.

Secondary efficacy endpoints will include the following:

- ADHD-RS-5 total score and subscale scores for hyperactivity/impulsivity and inattention domains
- CGI-I
- CHIP-CE:PRF
- C3PS Total Score and scores for Learning Problems and Executive Functioning subscales

Study Analyses

The analyses of the safety CANTAB domains for Study Part A will be based on the FAS and PPS. The analyses of efficacy endpoints will be based on the FAS only. Other safety analyses for Study Part A will be based on the safety set; the safety and efficacy analysis for Study Part B will be based on the open-label safety set.

Study Part A: Double-blinded Evaluation

The primary safety endpoint will be the change from baseline in the CANTAB RTI task. The endpoint will be analyzed over the FAS and PPS with a MMRM with treatment arm, visit, sex (male or female), age group (6 to 12 years or 13 to 17 years), region (Europe or US) and the interaction of treatment with visit as factors, the corresponding baseline value as a covariate, and the interaction between baseline value and visit adjusted in the model. The analysis will be done for subjects who complete 18 weeks (Week 18A) and for subjects (TAK-503 and atomoxetine treatment arms only) who complete Study Part A Week 49A. The least squares (LS) mean difference for each treatment arm will be calculated with the 95% confidence interval (CI) reported.

As suggested by European Medicines Agency (EMA), using data up to 18 weeks, the superiority to placebo comparisons including TAK-503 and atomoxetine, separately, will be performed using MMRM as specified for the primary endpoint. Statistical tests will be conducted at the nominal 2-sided 0.05 level without adjustment for multiplicity. If TAK-503 is superior to placebo, then a negative impact on cognition can be excluded. If atomoxetine is superior to placebo, then assay sensitivity has been demonstrated.

Results for the TAK-503 and atomoxetine comparison at Week 49A (Visit 14A), which were collected for patients who were enrolled prior to the implementation of Protocol Amendment 7, will be evaluated in a descriptive fashion, without the performance of inferential hypothesis testing.

Similarly, the other secondary CANTAB safety endpoints will be analyzed in the same manner as the primary CANTAB safety endpoint. CANTAB results for all parameters will be evaluated together for totality of the CANTAB data.

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by treatment arm across system organ class and preferred term. Treatment-emergent AEs leading to withdrawal from study and serious adverse event will be summarized similarly. To account for differences in expected exposure durations between placebo and active arms, time adjusted event rates (per 100 years) will be presented in the overall summary tables, as well.

Other safety data will be summarized descriptively by study period, with details provided in the statistical analysis plan.

The efficacy measurement of ADHD-RS-5 will be assessed based on the FAS using the MMRM as the primary safety endpoint. The CGI-I will be summarized.

Study Part B: Open-label Evaluation

Safety data for Study Part B will be summarized descriptively. Z-scores for CANTAB measures will be calculated using age- and gender-specific normative data if available. Both observed values and z-scores will be summarized descriptively.

Efficacy and other endpoints will be summarized by time point.

Sample Size Calculation and Power Considerations

In this safety study, a descriptive analysis of TAK-503 and atomoxetine will be performed after 12 months of double-blinded treatment using results from the CANTAB RTI task. The effect of TAK-503 on cognition will be assessed and interpreted on the totality of the data.

The sample size was estimated using the assumed difference of 0 msec with a noninferiority margin of 30 msec and a common standard deviation of 63.4 for the comparison between TAK-503 and atomoxetine at Week 49A on the RTI in Study Part A. The assumed common standard deviation on RTI is based on a prior study SPD503-206: a randomized, double-blinded, placebo-controlled efficacy study of TAK-503 in children and adolescents with ADHD. The assumed margin of 30 msec is close to the value (29.3 msec) of change from baseline in reported results from an adolescent study with atomoxetine. The assumed margin was used for sample size only and will not be applied in the noninferiority evaluation.

A total of 216 subjects, 72 subjects per arm, will be required to provide 80% power for a 2-sided 95% CI. Expecting a nonevaluable rate of 25%, including postrandomization dropout, during the double-blinded period, the randomization target has been set to 288 subjects total or 96 subjects per treatment arm.

As of Amendment 7, TAK-503 and atomoxetine will be evaluated after 12 months of double-blinded treatment using results from the CANTAB RTI task via the MMRM; however, inferential hypothesis testing via the non-inferiority framework at the Week 49A timepoint will no longer be performed due to challenges with retaining an evaluable sample size that would allow for sufficient power for this comparison. Superiority to placebo comparisons of TAK-503 and atomoxetine at the 18-week timepoint, separately, will still be performed, as in the original protocol.

The number of subjects projected to participate in Study Part B is 120, which will be sufficient to have at least 90% power to obtain a 95% confidence interval for the change from baseline RTI value that excludes the value 0, given the assumed response values for TAK-503 based on Study SPD503-206 (mean=20.7, SD=63.11).

STUDY SCHEDULES

Table 1 Study Part A – Double-blinded Evaluation: TAK-503, Atomoxetine, and Placebo through Week 18A

Visit[a]	Screening Washout[b] Baseline		Dose-optimization/Dose-maintenance							Dose-maintenance[t]				Dose-taper	Follow-up[s]
	SCN V1A	BL V2A	V3A	V4A	V5A	V6A	V7A[c]	V8A[c]	V9A[c]	V10A	IMP[d]	V11A[e]	ET[x]	V15A[y] V16A[y] V17A[y]	V18A[y]
Time of Visit(s) Children aged 6-12 years	D-35A to D-3A	D0A	W1A	W2A	W3A	W4A	Children begin the dose-maintenance period during W5A			W10A	W14A	W18A			
Adolescents aged 13-17 years							W5A	W6A	W7A						
Informed consent/assent	✓														
Inclusion/exclusion criteria	✓	✓													
K-SADS-PL Psychiatric evaluation	✓														
Medical and medication history	✓														
PSMQ	✓														
Demographics	✓														
Randomization		✓													
IMP distributed		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Investigator dose assessment			✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		
Subject continuation assessment			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
IMP returned/ compliance assessed			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Safety															
Physical examination	✓	✓[f]										✓	✓		
Urine drug/alcohol screen	✓	✓[g]													
Clinical laboratory tests[h]	✓	✓[f]				✓			✓			✓	✓		
12-lead ECG	✓	✓[i]				✓			✓			✓	✓		
Vital signs[j]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	
Height[k] and BMI[l]	✓	✓								✓		✓	✓		

Table 1 Study Part A – Double-blinded Evaluation: TAK-503, Atomoxetine, and Placebo through Week 18A

Visit[a]	Screening Washout[b] Baseline		Dose-optimization/Dose-maintenance							Dose-maintenance[t]				Dose-taper	Follow-up[s]
	SCN V1A	BL V2A	V3A	V4A	V5A	V6A	V7A[c]	V8A[c]	V9A[c]	V10A	IMP[d]	V11A[e]	ET[x]	V15A[y] V16A[y] V17A[y]	V18A[y]
Time of Visit(s) Children aged 6-12 years	D-35A to D-3A	D0A	W1A	W2A	W3A	W4A	Children begin the dose-maintenance period during W5A			W10A	W14A	W18A			
Adolescents aged 13-17 years							W5A	W6A	W7A						
Weight[k]	✓	✓								✓		✓	✓		
Serum pregnancy test	✓														
Urine pregnancy test[m]		✓			✓			✓		✓		✓	✓		✓
CANTAB[n]	✓	✓								✓		✓	✓		
Tanner staging[u] (self-assessment)		✓								✓		✓	✓		
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
AEs	✓	✓	Continuous monitoring												✓[o]
Safety Questionnaires															
• UKU items[p, q]		✓								✓		✓	✓	✓	
• C-SSRS[p, r]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	
• BPRS-C[p]		✓								✓		✓	✓		
• PDSS		✓								✓		✓	✓		
Efficacy															
CGI-S[p]		✓													
CGI-I[p]			✓							✓		✓	✓		
ADHD-RS-5[p]		✓	✓							✓		✓	✓		
CHIP-CE:PRF[p]		✓								✓		✓	✓		
APRS[v]		✓								✓		✓	✓		
C3PS[w]		✓								✓		✓	✓		

ADHD=attention-deficit/hyperactivity disorder; ADHD-RS-5=ADHD-Rating Scale-5 for Children and Adolescents; AE=adverse event; APRS=Academic Performance Rating Scale; BL=baseline; BMI=body mass index; BPRS-C=Brief Psychiatric Rating Scale for Children; CANTAB=Cambridge automated neuropsychological test battery; CGI-I=Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions–Severity; CHIP-CE: PRF=Child Health and Illness Profile – Child Edition: Parent Report

Table 1 Study Part A – Double-blinded Evaluation: TAK-503, Atomoxetine, and Placebo through Week 18A

Visit[a]	Screening Washout[b] Baseline		Dose-optimization/Dose-maintenance							Dose-maintenance[t]				Dose-taper	Follow-up[s]
	SCN V1A	BL V2A	V3A	V4A	V5A	V6A	V7A[c]	V8A[c]	V9A[c]	V10A	IMP[d]	V11A[e]	ET[x]	V15A[y] V16A[y] V17A[y]	V18A[y]
Time of Visit(s)	D-35A to D-3A	D0A	W1A	W2A	W3A	W4A	Children begin the dose-maintenance period during W5A			W10A	W14A	W18A			
Children aged 6-12 years							W5A	W6A	W7A						
Adolescents aged 13-17 years															

Form; C3PS=Conners 3 Parent Short Form; ECG=electrocardiogram; ET=early termination; IMP=investigational medicinal product; K-SADS-PL=Kiddie-SADS-Present and Lifetime Version; PDSS=Pediatric Daytime Sleepiness Scale; PSMQ=Prior Stimulant Medicine Questionnaire; SCN=screening; TEAE=treatment-emergent adverse event; UKU=Udvalg for Kliniske Undersøgelser; V=visit; W=week

a. Based on baseline (V2A), the windows for clinic visits will be ±2 days during the dose-optimization period and ±7 days during the dose-maintenance period. The windows for clinic visits will be ±2 days during the dose-taper period and +2 days for the safety follow-up visit. Note that for children (6-12 years) at W5A, W6A and W7A, the visit window remains ±2 days.

b. Eligible subjects will be contacted by a member of the site staff and provided with instructions for discontinuing any protocol prohibited medications, reviewing inclusion/exclusion criteria, reviewing concomitant medications, and recording of any pretreatment AEs. The washout call will be made between Day-35A and Day-7A and completed before the baseline visit, after the screening clinical laboratory test and ECG reading results are available.

c. The IMP distributed to children (6-12 years) at V6A (W4A) will include a 6-week supply; while IMP distributed to adolescents (13-17 years) will follow the distribution schedule for the dose-optimization period. Visits 7A, 8A and 9A are mandatory for all study participants irrespective of their age. These visits shall occur every 7 days +/- 2 days in order to assess subject's safety and tolerability to IMP. No dose adjustments shall be made for children while for adolescent subjects, if needed, dose can be adjusted following protocol requirements. All assessments planned for these visits have to be completed. IMP supplies will be dispensed through the IWRS only for a 1-week period, for both age groups for Visits 7A and 8A, and for a 3-week period at Visit 9A.

d. The IMP distribution/return visits may be attended by only the parent/legally authorized representative without the presence of the subject for the sole purpose of IMP distribution/return and reconciliation. Also, see Section 6.2 regarding direct-to-patient shipment of IMP.

e. Subjects will complete ET visit procedures before rolling over to Study Part B. Once 120 subjects have entered into Study Part B, only subjects in the placebo arm in Study Part A will enter Study Part B, to assure that all placebo arm subjects have the opportunity to enter into the 1-year TAK-503 open-label treatment arm.

f. If more than 35 days elapsed between the date of obtaining informed consent and the baseline visit, then the clinical laboratory tests will be repeated, and an abbreviated physical examination will be conducted. An abbreviated physical examination will include a review of general appearance and respiratory and cardiovascular systems. The results of the clinical laboratory tests and physical examination must be reviewed by the investigator before enrolling the eligible subject in the study. In these cases, the screening period can be extended beyond the initial 35 days for an additional 3 weeks and the guidance in footnote f followed.

g. The urine drug/alcohol screen will be required only if the baseline visit occurred >35 days after the screening visit and the subject underwent a medication washout.

h. Clinical laboratory tests include hematology, biochemistry, and urinalysis.

i. To ensure proper baseline values are established, ECGs measurements will be recorded in triplicate at baseline with approximately 5 minutes between each measurement.

j. Vital signs include oral or tympanic temperature, respiratory rate, supine and standing blood pressure, and pulse.

k. Height and weight will be measured without shoes.

l. BMI will be calculated by the site (to determine subject eligibility) and also programmatically by the sponsor or sponsor's designee (for the study database).

m. Additional urine pregnancy tests may be scheduled or conducted "as needed" based on the judgment of the investigator for females of childbearing potential (FOCP).

n. The CANTAB will include the following tasks: Stop Signal Task (SST), Delayed Matching to Sample (DMS), Spatial Working Memory (SWM), Reaction Time (RTI), and Rapid Visual Information Processing (RVP).

o. AEs and SAEs will be captured up to 7 (+2) days after the last IMP dose.

Table 1 Study Part A – Double-blinded Evaluation: TAK-503, Atomoxetine, and Placebo through Week 18A

Visit[a]	Screening Washout[b] Baseline		Dose-optimization/Dose-maintenance							Dose-maintenance[t]				Dose-taper	Follow-up[s]
	SCN V1A	BL V2A	V3A	V4A	V5A	V6A	V7A[c]	V8A[c]	V9A[c]	V10A	IMP[d]	V11A[e]	ET[x]	V15A[y] V16A[y] V17A[y]	V18A[y]
Time of Visit(s) Children aged 6-12 years	D-35A to D-3A	D0A	W1A	W2A	W3A	W4A	Children begin the dose-maintenance period during W5A			W10A	W14A	W18A			
Adolescents aged 13-17 years							W5A	W6A	W7A						

p. Whenever possible, the same person should consistently administer the same questionnaire throughout the study.
q. Only the following UKU items relevant to the established safety profile of TAK-503 will be queried: Increased Duration of Sleep, Asthenia /Lassitude /Increased Fatigability, Sleepiness/Sedation, and Orthostatic Dizziness.
r. The baseline version of C-SSRS will be completed at the screening visit. The "Since last visit" version will be completed at all subsequent visits.
s. Placebo subjects can skip the follow-up visit after completion of Study Part A assessments at Visit 11A (Week 18A), and proceed immediately to baseline visit assessments for Study Part B.
t. During dose maintenance, subjects may have up to 2 consecutive remote visits. It is up to the principal investigator to allow for remote visits (see Section 7.3).
u. Self-assessment in this study is defined as subjects or parents indicating which drawing of the scale corresponds to the subject's sexual maturation stage at the time of the specific visit. For this purpose, site staff (the principal investigator or a designee) reads the guidance and the text corresponding to each drawing and asks the subject or parent to choose the applicable drawing (see Appendix 7). The response from the subject or the parent will be documented in the Tanner Staging Form by the site staff.
v. Subjects enrolled under Amendment 4 and earlier who have a baseline APRS evaluation will continue with APRS evaluations.
w. Subjects enrolled under Amendment 5 will be evaluated with the C3PS.
x. For subjects who enrolled prior to Protocol Amendment 7, and who are beyond Visit 11A (Week 18A), their next visit will be the ET visit.
y. Visits 12A, 13A, 14A, and IMP were removed in Protocol Amendment 7. The numbering of the remaining visits (15A, 16A, 17A, 18A) did not change for operational reasons.

Table 2 Study Part B – Open-label Evaluation of TAK-503

	Screening Washout[b, c] Baseline		Dose-optimization/Dose-maintenance							Dose-maintenance				Dose-taper	Follow-up
Visit[a]	SCN[b,c] V1B	BL[d] V2B	V3B	V4B	V5B	V6B	V7B[e]	V8B[e]	V9B[e]	V10B	V11B	V12B	V13B /ET	V14B V15B V16B	V17B
Time of Visit(s) Children aged 6-12 years	D-35B to D-3B	D0B	W1B	W2B	W3B	W4B	Children begin the dose-maintenance period during W5B			W10B	W23B	W36B	W49B	W50B W51B W52B	W53B
Adolescents aged 13-17 years							W5B	W6B	W7B						
Inclusion/exclusion criteria check	✓	✓													
Investigator assessment of TAK-503 dose			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Subject continuation assessment			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Distribution of TAK-503		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
TAK-503 returned/ compliance check			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Safety															
Physical examination	✓	✓[f]											✓		
Clinical laboratory tests[g]	✓[c]	✓[f]											✓		
12-lead ECG		✓[h]											✓		
Vital signs[i]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Height[j] and BMI[k]	✓	✓								✓	✓	✓	✓		
Weight[j]	✓	✓								✓	✓	✓	✓		
Serum pregnancy test	✓														

Table 2 Study Part B – Open-label Evaluation of TAK-503

	Screening Washout[b, c] Baseline		Dose-optimization/Dose-maintenance							Dose-maintenance				Dose-taper	Follow-up
Visit[a]	SCN[b,c] V1B	BL[d] V2B	V3B	V4B	V5B	V6B	V7B[e]	V8B[e]	V9B[e]	V10B	V11B	V12B	V13B /ET	V14B V15B V16B	V17B
Time of Visit(s) Children aged 6-12 years	D-35B to D-3B	D0B	W1B	W2B	W3B	W4B	Children begin the dose-maintenance period during W5B			W10B	W23B	W36B	W49B	W50B W51B W52B	W53B
Adolescents aged 13-17 years							W5B	W6B	W7B						
Urine pregnancy test[l]		✓			✓			✓		✓	✓	✓	✓		✓
CANTAB[m]		✓								✓			✓		
Tanner staging[q] (self-assessment)		✓								✓			✓		
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
AEs	✓	✓	**Continuous monitoring**												✓[n]
Safety Questionnaires															
• UKU items[o p]		✓								✓	✓	✓	✓	✓	
• C-SSRS[o]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
• BPRS-C[o]		✓								✓	✓	✓	✓		
• PDSS		✓								✓	✓	✓	✓		
Efficacy															
CGI-S[o]		✓													
CGI-I[o]										✓	✓	✓	✓		
ADHD-RS-5[o]		✓								✓	✓	✓	✓		
CHIP-CE:PRF[o]		✓								✓	✓	✓	✓		
APRS[r]		✓								✓	✓	✓	✓		
C3PS[s]		✓								✓	✓	✓	✓		

Table 2 Study Part B – Open-label Evaluation of TAK-503

	Screening Washout[b, c] Baseline		Dose-optimization/Dose-maintenance							Dose-maintenance				Dose-taper	Follow-up
Visit[a]	SCN[b,c] V1B	BL[d] V2B	V3B	V4B	V5B	V6B	V7B[e]	V8B[e]	V9B[e]	V10B	V11B	V12B	V13B /ET	V14B V15B V16B	V17B
Time of Visit(s) Children aged 6-12 years	D-35B to D-3B	D0B	W1B	W2B	W3B	W4B	Children begin the dose-maintenance period during W5B			W10B	W23B	W36B	W49B	W50B W51B W52B	W53B
Adolescents aged 13-17 years							W5B	W6B	W7B						

ADHD=attention-deficit/hyperactivity disorder; ADHD-RS-5=ADHD-Rating Scale-5 for Children and Adolescents; AE=adverse event; APRS=Academic Performance Rating Scale; BL=baseline; BMI=body mass index; BPRS-C=Brief Psychiatric Rating Scale for Children; CANTAB=Cambridge automated neuropsychological test battery; CGI-I=Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions–Severity; CHIP-CE: PRF=Child Health and Illness Profile – Child Edition: Parent Report Form; C3PS=Conners 3 Parent Short Form; ECG=electrocardiogram; ET=early termination; K-SADS-PL=Kiddie-SADS-Present and Lifetime Version; PDSS=Pediatric Daytime Sleepiness Scale; PSMQ=Prior Stimulant Medicine Questionnaire; SCN=screening; TEAE=treatment-emergent adverse event; UKU=Udvalg for Kliniske Undersøgelser; V=visit; W=week

a. Based on baseline (V2B), the windows for clinic visits will be ±2 days during the dose-optimization period and ±7 days during the dose-maintenance period. The windows for clinic visits will be ±2 days during the dose-taper period and +2 days for the safety follow-up visit. Note that for children (6-12 years) at W5B, W6B and W7B, the visit window remains ±2 days.

b. Eligible subjects will be contacted by a member of the site staff and provided with instructions for discontinuing any protocol prohibited medications, reviewing inclusion/exclusion criteria, reviewing concomitant medications, and recording of any pretreatment AEs. The washout call will be placed between Day-35B to Day-7B and completed after the screening clinical laboratory test and ECG reading results are available and before the baseline visit.

c. Subjects randomized to placebo who roll over from Study Part A can proceed immediately to baseline visit assessments for Study Part B if subject entered Part B within 35 days of Part A completion; clinical laboratory tests are not required for these subjects.

d. If more than 45 days elapse between the Study Part A follow-up visit and the Study Part B baseline visit, the subject will be discontinued from the study. A site staff member will phone eligible subjects between Day -35 and Day -7 to provide instructions for discontinuing protocol prohibited medications. The call must be completed after the screening visit once clinical laboratory test results and ECG readings are available and before the baseline visit.

e. The TAK-503 distributed to children (6-12 years) during V6B (W4B) will include a 6-week supply. The TAK-503 distributed to adolescents (13-17 years) will follow the distribution schedule for the dose-optimization period. Visits 7B, 8B and 9B are mandatory for all study participants irrespective of their age. These visits shall occur every 7 days +/- 2 days in order to assess subject's safety and tolerability to IMP. No dose adjustments shall be made for children while for adolescent subjects, if needed, dose

Table 2 Study Part B – Open-label Evaluation of TAK-503

	Screening Washout[b, c] Baseline		Dose-optimization/Dose-maintenance							Dose-maintenance				Dose-taper	Follow-up
Visit[a]	SCN[b,c] V1B	BL[d] V2B	V3B	V4B	V5B	V6B	V7B[e]	V8B[e]	V9B[e]	V10B	V11B	V12B	V13B /ET	V14B V15B V16B	V17B
Time of Visit(s) Children aged 6-12 years	D-35B to D-3B	D0B	W1B	W2B	W3B	W4B	Children begin the dose-maintenance period during W5B			W10B	W23B	W36B	W49B	W50B W51B W52B	W53B
Adolescents aged 13-17 years							W5B	W6B	W7B						

can be adjusted following protocol requirements. All assessments planned for these visits have to be completed. IMP supplies will be dispensed through the IWRS only, for a 1-week period for both age groups for Visits 7B and 8B, and for a 3-week period at Visit 9B.

f. If more than 35 days elapsed between the Study Part A follow-up visit and the Study Part B baseline visit then the clinical laboratory tests will be repeated and an abbreviated physical examination will be conducted. An abbreviated physical examination will include a review of general appearance and respiratory and cardiovascular systems. The results of the clinical laboratory tests and physical examination must be reviewed by the investigator before subject enrollment. In these cases, the screening period can be extended beyond the initial 35 days for an additional 3 weeks and the guidance in footnote f followed.

g. Clinical laboratory tests include hematology, biochemistry, and urinalysis.

h. To ensure proper baseline values are established, ECGs measurements will be recorded in triplicate at baseline with approximately 5 minutes between each measurement.

i. Vital signs include oral or tympanic temperature, respiratory rate, supine and standing blood pressure, and pulse.

j. Height and weight will be measured without shoes.

k. BMI will be calculated by the site (to determine subject eligibility) and also programmatically by the sponsor or sponsor's designee (for the study database).

l. Additional urine pregnancy tests may be scheduled or conducted "as needed" based on the judgment of the investigator for females of childbearing potential (FOCP).

m. The CANTAB will include the following tasks: Stop Signal Task (SST), Delayed Matching to Sample (DMS), Spatial Working Memory (SWM), Reaction Time (RTI), and Rapid Visual Information Processing (RVP).

n. AEs and SAEs will be recorded up to 7 (+2) days after the last dose of TAK-503.

o. Whenever possible, the same person should consistently administer the same questionnaire throughout the study.

p. Only the following UKU items relevant to the established safety profile of TAK-503 will be queried: Increased Duration of Sleep, Asthenia /Lassitude /Increased Fatigability, Sleepiness/Sedation, and Orthostatic Dizziness.

q. Self-assessment in this study is defined as subjects or parents indicating which drawing of the scale corresponds to the subject's sexual maturation stage at the time of the specific visit. For this purpose, site staff (the principal investigator or a designee) reads the guidance and the text corresponding to each drawing and asks the subject or parent to choose the applicable drawing (see Appendix 7). The response from the subject or the parent will be documented in the Tanner Staging Form by the site staff.

r. Subjects enrolled under Amendment 4 and earlier who have a baseline APRS evaluation (for Study Part A) will continue with APRS evaluations.

s. Subjects enrolled under Amendment 5 will be evaluated with the C3PS.

1. BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous neurobehavioral disorder and the essential feature of ADHD, as described in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), is a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development. The following clinical symptoms must also be present: some hyperactive-impulsive or inattentive symptoms that cause impairment must have been present before age 12 years, impairment must be present in a least 2 settings (eg, school and home), and there must be clear evidence of interference with developmentally appropriate social, academic, or occupational functioning. Core symptoms of ADHD in preschool children (aged 3 to 5 years) are similar to those observed in school-age children (aged 6 to 12 years) and include the following: difficulty in sustaining attention, excessive motor activity, low frustration tolerance, and impulsivity. Children with ADHD have trouble completing tasks that require executive function (EF) skills (Willcutt et al. 2005). As these children mature into adolescents, the ADHD symptoms associated with hyperactivity may begin to mitigate, but a higher risk remains for defiance, aggression, and antisocial behaviors as well as substance dependence (Barkley et al. 1991; Elkins et al. 2007).

The exact etiology of ADHD is unknown. Neurotransmitter deficits (Arnsten and Pliszka 2011), genetics (Arnsten 2006; Brown 2003), environment (Kahn et al. 2003), and perinatal complications (Bhutta et al. 2002) may all be contributing factors. Medications effective at reducing ADHD symptoms act by raising the levels of neurotransmitters like norepinephrine, dopamine and/or precursors at the synapse by either facilitating neurotransmitter release, decreasing neurotransmitter reuptake, or binding to and activating the postsynaptic receptor (Kratochvil et al. 2001; Wang et al. 2007).

Psychostimulant medications such as methylphenidate and amphetamine have been used to treat behavior problems in children since 1937 (Wilens and Biederman 1992), including ADHD and its diagnostic precursors. Medication management was superior to behavioral treatment and to routine community care that included medication for the immediate to long-term (eg, 14 months) treatment of children and adolescents with ADHD (The MTA Cooperative Group 1999).

Despite the effectiveness of psychostimulants, several potential confounders to treatment can arise in some individuals, including intolerable side effects; possible exacerbation of common comorbid conditions, such as anorexia, tics, and insomnia; concern about abuse potential; and lack of efficacy (Olfson 2004). Nonstimulant medications are an alternative option for treating individuals with ADHD who may not be candidates for stimulant treatment or who prefer nonstimulant pharmacotherapy. TAK-503 (formerly known as SPD503) is a nonstimulant medication and the only pharmacotherapeutic agent approved for ADHD that is an α_{2A}-adrenergic receptor agonist.

1.2 Product Background and Clinical Information

TAK-503 (extended-/prolonged-release guanfacine hydrochloride) is a nonstimulant medication with a novel mechanism of action.

TAK-503 is indicated for the treatment of children and adolescents with ADHD. Guanfacine is believed to exert its effect on ADHD symptoms by modulating the signaling in the prefrontal cortex and basal ganglia through direct modification of synaptic noradrenalin transmission at the α_2-adrenergic receptors (Intuniv 2015).

In this phase 4 postapproval safety study (PASS), the long-term safety of TAK-503 on selected domains of cognition will be evaluated in children and adolescents with ADHD for whom stimulants are not suitable, not tolerable, or shown to be ineffective.

Results of tests and scales implemented in previous studies have shown that guanfacine does not have a deleterious effect on impact on cognitive performance. In one of the first double-blinded, placebo-controlled study of guanfacine in children with ADHD and a tic disorder, significant improvement was observed with guanfacine treatment on a Continuous Performance Task, a computer-administered and -scored measure of sustained visual attention and motor response inhibition (Scahill et al. 2001). Commission errors decreased by 22% and omission errors by 17% in the guanfacine group, compared with increases of 29% in commission errors and of 31% in omission errors in the placebo group. In the phase 2, randomized, double-blinded, placebo-controlled, dose-optimization study SPD503-206, doses of TAK-503 that resulted in significant improvement in ADHD symptoms did not impair subject ability to perform cognitive tasks (Kollins et al. 2011). Despite mild to moderate sedative events, which occurred early and resolved over the treatment period, no worsening was observed on measures of psychomotor functioning and alertness with guanfacine compared to placebo as tested using the Reaction Time (RTI) task of the Cambridge automated neuropsychological test battery (CANTAB). Furthermore, selected doses of TAK-503 did not elicit sedation that resulted in adverse effects on cognitive performance (Kollins et al. 2011).

Meaningful improvement in classroom behavior in subjects treated with TAK-503 was demonstrated in the phase 3, randomized, double-blinded, placebo-controlled, fixed-dose clinical study SPD503-301. Of the 345 subjects enrolled and randomized, 215 subjects completed the study: 53 subjects in the placebo treatment arm and 58, 55, and 49 subjects in the 2, 3, and 4 mg dose groups of the TAK-503 treatment arm, respectively. Approximately 4 hours, and again 8 hours, after subjects were administered study medication, teachers completed the Conners' Teaching Rating Scale – Revised (CTRS-R) as an independent assessment of classroom behavior. No worsening in classroom behavior, a proximal indirect measure of adverse effects on overall cognitive function, was observed by teachers among students administered TAK-503. The least squares (LS) mean placebo-adjusted changes in the afternoon total score 8 hours after dosing were significantly improved in all TAK-503 dose groups, as follows:

- 2 mg TAK-503 dose group improved by 10.90 points ($p=0.0001$)
- 3 mg TAK-503 dose group improved by 13.84 points ($p<0.0001$)
- 4 mg TAK-503 dose group improved by 15.25 points ($p<0.0001$)

In the phase 3, randomized, double-blinded, placebo-controlled, dose-optimization clinical study SPD503-312 in adolescents aged 13 to 17 years with ADHD, no worsening was reported in EF behaviors in the 157 subjects randomized to TAK-503 treatment according to the parent-reported Behavior Rating Inventory of Executive Function (BRIEF).

Compared to placebo-treated peers, clinically significant improvements were observed in subjects treated with TAK-503 on the following parameters:

- Improvements observed at Week 7 on the following BRIEF indices:
  - Global Executive Composite (GEC) scale ($p<0.001$)
  - Behavioral Regulation Index (BRI) ($p=0.001$)
  - Metacognition Index (MI) ($p <0.001$)
- Improvements observed at Week 9 on the following BRIEF indices:
  - GEC ($p=0.016$)
  - MI ($p=0.004$)

Although trends for improvements were observed for all 3 indices at Week 13 in TAK-503-treated subjects compared to placebo-treated subjects, the changes from baseline t-scores were not statistically significant between the 2 treatment arms. The t-score LS mean differences for these indices were -2.3 for GEC, -0.9 for BRI, and -2.7 for MI.

In the phase 3, randomized, double-blinded, placebo-controlled, dose-optimization study SPD503-316 in 337 children and adolescents aged 6 to 17 years with ADHD that included an active-reference arm, a statistically significant and clinically meaningful improvement was shown relative to placebo on the learning and school domain of the Weiss Functional Impairment Rating Scale-Parent (WFIRS-P). The treatment effect size (95% confidence interval [CI]; p-value) at Week 10 for children and Week 13 for adolescents relative to placebo for the TAK-503 group was 0.42 (0.15, 0.70; 0.003). In the phase 3, randomized-withdrawal, double-blinded, placebo-controlled, dose-optimization, longer-term maintenance of efficacy study SPD503-315, a nominally significant improvement was measured compared to placebo in the TAK-503 group at Week 39 in the WFIRS-P learning and school domain ($p=0.032$).

Due to the group heterogeneity of individuals diagnosed with ADHD, describing any cognitive deficits in general terms is difficult. Correlated variables of intelligence, academic achievement, and symptoms of comorbid disorders makes it difficult to ensure that the neuropsychological impairments associated with ADHD cannot be explained by group differences in these variables (Lahey et al. 1998a; Lahey et al. 1998b). No approved medications are available for the treatment of cognitive dysfunction in individuals with ADHD. Furthermore, the efficacy and safety of other approved ADHD medications on proposed cognitive domains (ie, to worsen or improve) have not been established in the proposed study population from which information on treatment with guanfacine will be derived; namely, subjects for whom stimulants are not suitable, not tolerated, or shown to be ineffective, as described in the European Summary of Product Characteristics (SmPC). The established safety profile for particular approved medications could influence neurocognitive function, rendering interpretation of differences across treatment arms difficult.

Also, comparisons with approved medications would be compromised because TAK-503 is indicated for second line therapy whereas the comparison could be indicated for first line therapy. Other confounders of ADHD medication effects on cognitive domains include dose, duration of follow-up, and composition of ADHD subtypes in the study subjects (predominantly inattentive symptoms or predominantly hyperactive/impulsive symptoms) and comorbid psychiatric disorders.

1.2.1 Anticipated Benefits and Risks

Overall, the clinical development program has demonstrated a favorable benefit-risk profile of TAK-503 in treatment of ADHD in children and adolescents. Guanfacine was approved in the EU in September 2015 for the treatment of ADHD in children and adolescents 6 to 17 years old for whom stimulants are not suitable, not tolerated, or have been shown to be ineffective; it must be used as a part of a comprehensive ADHD treatment program, typically including psychological, educational, and social measures. Guanfacine is also approved in: US, Canada, Japan, Australia, and Switzerland.

The total cumulative worldwide exposure as of Jun 2018 was estimated to be 1,119,675 person-years of treatment cumulatively since launch. Post-marketing reports have continued to indicate that TAK-503 is generally safe and well tolerated in the majority of subjects, and the incidence and nature of the adverse events remains in accordance with the current reference safety information for the product and the known clinical characteristics of the treated patient population.

The efficacy of TAK-503 for the treatment of ADHD compared to placebo has been rigorously demonstrated on the primary efficacy measure for all well controlled studies designed to provide substantial evidence of efficacy. In studies enrolling children and adolescents, TAK-503 was associated with a statistically significant, clinically meaningful improvement in ADHD symptoms compared to placebo, as demonstrated using a variety of study designs, a variety of validated assessments, and with data provided by investigators, parents, teachers, trained raters, and self-reports. Improvement in ADHD symptoms by TAK-503 compared with placebo is associated with improvement in functional measures in clinical trials. TAK-503 is effective among inattentive ADHD subtype compared with placebo as demonstrated by improvement in ADHD-RS-IV subscale change in the TAK-503 fixed dose studies. The therapeutic benefit of TAK-503 in pediatric subjects (6-17 years) with ADHD was demonstrated for flexible dose optimization of TAK-503 (1-7 mg). Treatment effects were generally similar between children and adolescents, males and females, and between whites and non-whites. Statistically significant improvements were demonstrated with either morning or evening dosing compared to placebo, and in a comparative study including STRATTERA (atomoxetine) the respective treatment effect sizes for the efficacy parameter were generally greater for TAK-503. Maintenance of efficacy for subjects treated with TAK-503 has been demonstrated with lower treatment failure rates compared to placebo.

To date, 20 phase 2 and 3 studies have been completed with TAK-503 in children and adolescents with ADHD. In these studies, TAK-503 at doses of 1-7 mg has been demonstrated safe and well tolerated in children (up to 4 mg) and adolescents (up to 7 mg) in the short-term fixed-dose, flexible-dose and long-term studies.

The most frequently reported treatment emergent adverse events (TEAEs) among subjects treated with TAK-503 were somnolence, headache, fatigue, sedation, and upper abdominal pain. Most TEAEs were mild or moderate in severity and the frequency of serious adverse events (SAEs) was low. In the short-term monotherapy study pool (SPD503-301 and SPD503-304), discontinuations due to AEs were more common for TAK-503 overall (11.9%) than for placebo (4.0%). The most frequent AEs that led to discontinuation of TAK-503 treatment were somnolence (3.7%), sedation (2.1%), and fatigue (1.6%). In the long-term study pool (SPD503-303 and SPD503-305), 17.5% of subjects discontinued due to AEs over 2 years. The most frequent AEs that led to discontinuation of TAK-503 treatment in the long term studies were somnolence (3.4%) and weight increased (1.8%). Sedative events including somnolence, sedation, fatigue, lethargy, asthenia and hypersomnia were commonly reported in clinical studies in children and adolescents with ADHD. In company-sponsored randomized double-blind Phase 2-3 clinical studies, the incidences of sedative events in the TAK-503 group were 31.7%, 8.4%, and 0.2% for somnolence, sedation, and hypersomnia, respectively. The vast majority of these events were mild or moderate and did not prompt or require discontinuation of TAK-503. None of the events were serious. Also, in the adjunctive therapy study SPD503-313, TAK-503 plus psychostimulant was well tolerated in general. No new safety signals emerged following the administration of TAK-503 in adjunct with psychostimulants (amphetamine or methylphenidate) compared with TAK-503 administered alone.

Psychiatric TEAEs occurred with very low frequencies in both the TAK-503 and placebo groups. The events that did occur are expected in ADHD or are commonly occurring co-morbidities.

No deaths have occurred in the TAK-503 clinical development program.

See the latest version of the TAK-503 investigator's brochure (IB) for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy, and safety of TAK-503.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

Study SPD503-401 has been designed to evaluate the long-term safety and efficacy of TAK-503, with a specific focus on neurocognition, growth, and sexual maturation. In Study Part A, an atomoxetine arm has been included as an active comparator and a placebo treatment arm as a control for assay sensitivity.

2.2 Study Objectives

2.2.1 Primary Objectives

The primary safety objective of this study is to evaluate the comparative long-term safety of TAK-503 treatment in children and adolescents aged 6 to 17 years diagnosed with ADHD for whom stimulants are not suitable, not tolerated, or shown to be ineffective:

- To evaluate TAK-503 compared with atomoxetine after 12 months of once daily (QD) treatment on psychomotor speed and attention as measured by the Cambridge automated neuropsychological test battery (CANTAB) reaction time (RTI) task, using the mixed-effects model for repeated measures (MMRM). The effect of TAK-503 on cognition will be assessed and interpreted on the totality of the data.

A primary efficacy objective is not applicable for this PASS.

2.2.2 Secondary Objectives

Secondary safety objectives

- Cognitive domain, sustained attention as measured by CANTAB Rapid Visual Information Processing (RVP) task
- Cognitive domain, Spatial Working Memory (SWM), a component of EF, as measured by the CANTAB SWM task between errors
- Cognitive domain, response control/inhibition as measured by the CANTAB Stop Signal Task (SST)
- Cognition domain, recognition memory as measured by the CANTAB Delayed Matching to Sample (DMS) task
- Sexual maturation as measured by Tanner stage
- Growth as measured by weight, height, and body mass index (BMI)
- Incidence of treatment-emergent adverse events (TEAEs)
- Vital sign and electrocardiogram (ECG) results
- Psychiatric symptoms as measured by the Brief Psychiatric Rating Scale for Children (BPRS-C) total score and factors for Depression, Anxiety, Psychomotor Excitation, Behavior Problems, Withdrawal, Thinking Disturbance, and Organicity

- Suicidal ideation/behavior as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS)
- Asthenia/Lassitude/Increased Fatigability, Sleepiness/Sedation, Increased Duration of Sleep, and Orthostatic Dizziness based on the ratings of specific Udvalg for Kliniske Undersøgelser (UKU) scale items
- Sedative effects as measured by subject ratings on the Pediatric Daytime Sleepiness Scale (PDSS)

Secondary efficacy objectives

- Attention-deficit/hyperactivity disorder symptoms as measured by the investigator-administered ADHD-Rating Scale-5 (ADHD-RS-5) total score and hyperactivity/impulsivity and inattention subscale scores
- Global clinical measurement of ADHD improvement as measured by Clinical Global Impression-Improvement (CGI-I) using the Clinical Global Impression-Severity (CGI-S) to establish baseline
- Function as measured by the Child Health and Illness Profile – Child Edition: Parent Report Form (CHIP-CE:PRF) domains of satisfaction, comfort, resilience, risk avoidance, and achievement. The effect of TAK-503 on all subdomains will be summarized, including the subdomain satisfaction with self, using parental ratings of the child's self-esteem.
- Assessment of behavioral, social, and academic issues with the Conners 3 Parent Short Form (C3PS) Total Score and the Learning Problems and Executive Functioning subscale scores.

3. STUDY DESIGN

3.1 Study Design and Flow Chart

Study SPD503-401 is a phase 4, multicenter, dose-optimization PASS and will be conducted in 2 parts: Study Parts A and B. Study Part A will be a randomized, double-blinded, parallel-group, placebo- and active comparator-controlled, 3-treatment arm safety and efficacy evaluation of TAK-503. Pediatric subjects with ADHD will be randomized 1:1:1 among TAK-503, atomoxetine, and placebo treatment arms for 18 weeks of double-blinded treatment and evaluation. At the end of the 18 weeks (Week 18A/Visit 11A), all subjects will roll over to Study Part B directly for an additional 52 weeks of open-label TAK-503 treatment. Once 120 subjects have entered into Study Part B, only subjects in the placebo arm in Study Part A will enter Study Part B, to assure that all placebo arm subjects have the opportunity to enter into the 1-year TAK-503 open-label treatment arm.

Study Part A will consist of the following 5 periods elapsing up to 23 weeks:

1. Screening/washout: Day -35A to Day -3A (up to 5 weeks).
2. Dose-optimization period: Investigational medicinal product (IMP) will be dose-optimized from Week 0A through Week 4A for children aged 6 to 12 years and through Week 7A for adolescents aged 13 to 17 years.
3. Dose-maintenance period: Subjects will continue with QD dosing from Week 5A for children and Week 8A for adolescents through Week 18A.
4. Dose-taper period: Scheduled 3-week fixed-dose taper of IMP. All subjects randomized in the TAK-503 or atomoxetine treatment arms will undergo a scheduled 3-week dose taper to ensure proper downward dose titration of TAK-503 at the end of the dose-maintenance period or at ET.
5. Follow-up period: Follow-up visit 1 week after the last IMP tapered dose
    - Subjects randomized to TAK-503 or atomoxetine treatment arms will participate in a follow-up visit and begin rescreening/washout procedures for Study Part B.

Placebo subjects can skip the follow-up visit after completion of Study Part A assessments at Visit 11A (Week 18A) and proceed immediately to baseline visit assessments for Study Part B.

Before enrollment in Study Part A, subjects will be screened based on inclusion/exclusion criteria to establish eligibility for study participation. Approximately 25% of all subjects will be aged 13 to 17 years. Approximately 25% of all subjects will be female. Subjects who meet eligibility requirements will undergo a medication washout period, if applicable, according to the schedule presented in Table 3. In Study Part B, subjects randomized to active IMP in Study Part A must undergo a washout period of ≥30 days between the last IMP tapered dose in Study Part A and the first TAK-503 dose in Study Part B.

In Study Part A, subjects with a baseline ADHD-RS-5 total score ≥28 and CGI-S score of ≥4 will be eligible for enrollment. During the dose-optimization period, clinic visits will be scheduled every 7 days to assess IMP safety and tolerability and to allow investigators to titrate

the IMP to an optimal dose that maximizes potential benefits while minimizing risk of TEAEs. If necessary, the investigator will be allowed to lower the subject's dose once during the dose optimization period in Study Parts A and B.

Subjects randomized to TAK-503 will begin dosing at 1 mg and dose-titrated upward in weekly 1-mg increments until an optimal dose is reached. Children aged 6 to 12 years will not be permitted to titrate to a daily dose >4 mg QD and adolescents aged 13 to 17 years will not be permitted to titrate to greater than the maximum allowed daily dose per baseline weight group presented in Table 4. The dose-optimization schedule for TAK-503 can be found in Table 4.

Subjects optimized to a TAK-503 daily dose between 1 and 4 mg will take 1 TAK-503 tablet QD (or TAK-503-matched placebo tablet). Subjects optimized to a TAK-503 daily dose between 5 and 7 mg will take 2 TAK-503 tablets QD (or 2 TAK-503-matched placebo tablets).

Subjects randomized to the atomoxetine treatment arm weighing <70 kg at baseline will begin daily dosing at approximately 0.5 mg/kg QD. If well-tolerated after 1 week minimum, this dose may be increased to the target daily dose of 1.2 mg/kg QD. The total daily dose will not exceed 1.4 mg/kg QD. With limited dosage forms, this upper limit is necessary to achieve appropriate weight-based doses. Permitted daily doses of atomoxetine for subjects weighing <70 kg at baseline are 10, 18, 25, 40, 60, and 80 mg QD depending on subject's baseline weight (Visit 2A).

Subjects randomized to the atomoxetine treatment arm weighing ≥70 kg at baseline will begin daily dosing at 40 mg atomoxetine QD. If well-tolerated after 1 week minimum, this daily dose may be increased to 80 mg QD. After a 1-week minimum, if the 80 mg daily dose is well-tolerated, then the daily dose may be increased to 100 mg QD. The total daily dose in children and adolescents ≥70 kg will not be permitted to exceed 100 mg QD.

Subjects optimized to an atomoxetine daily dose greater than 60 mg QD will take 2 atomoxetine or atomoxetine-matched placebo capsules QD. Subjects optimized to a daily dose ≤60 mg will take 1 atomoxetine or atomoxetine-matched placebo capsule QD. The dose-optimization schedule for atomoxetine can be found in Table 5.

Subjects will continue daily treatment with the optimal IMP dose during the dose-maintenance period, during which time the investigator will not be permitted to adjust the IMP dose in Study Part A. For subjects randomized to active IMP, the dose-maintenance period will be followed by a 3-week dose-taper period.

After the last IMP tapered dose, subjects will return to the site for a follow-up visit. The follow up visit will serve as the Study Part B screening assessments for subjects randomized to the TAK-503 and atomoxetine treatment arms.

Study Part B will consist of 5 periods:

1. Screening/washout: Day -35B to Day -3B (up to 5 weeks)
2. Dose-optimization period: TAK-503 will be dose-optimized from Week 0B through Week 4B for children aged 6 to 12 years and through Week 7B for adolescents aged 13 to 17 years.

3. Dose-maintenance period: Dose-optimized TAK-503 will be administered QD from Week 5B for children and from Week 8B for adolescents through Week 49B for both age groups.
4. Dose-taper period: Scheduled 3-week downward-titration of TAK-503 dose through Weeks 50B, 51B, and 52B
5. Follow-up period: Last dose of TAK-503 to the follow-up visit at Week 53B

During the Study Part A follow-up visit, subjects will undergo a partial rescreening of study criteria to confirm eligibility for continued participation in Study Part B. Subjects who complete Study Part A should roll over into Study Part B without a gap except for washout. Subjects (except those randomized to placebo) must undergo a washout period of ≥30 days between the last IMP tapered dose in Study Part A and the first dose of TAK-503 in Study Part B. Eligibility to continue in Study Part B will be confirmed at Visit 2B, Study Part B baseline. Once 120 subjects have entered into Study Part B, only subjects in the placebo arm in Study Part A will enter Study Part B, to assure that all placebo arm subjects have the opportunity to enter into the 1-year TAK-503 open-label treatment arm.

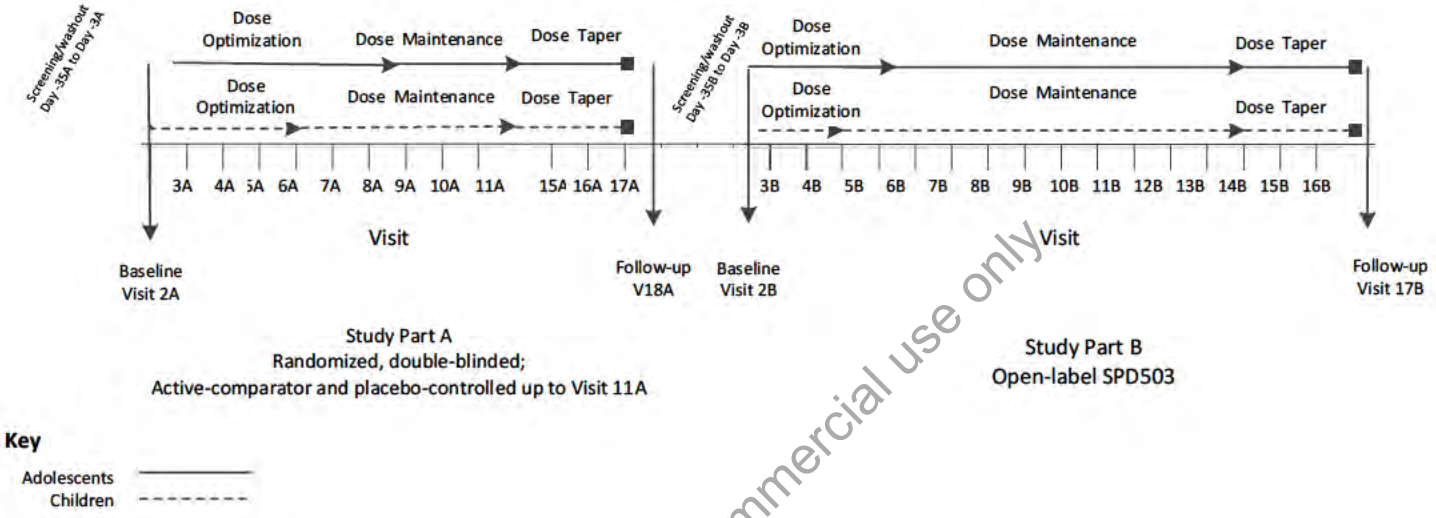
During the dose-optimization period, clinic visits will be scheduled once every 7 days to assess safety and tolerability and to allow investigators to titrate subjects to an optimal TAK-503 dose based on clinical judgment of tolerability and efficacy using the totality of the available clinical and safety data. All subjects will begin with 1 mg TAK-503 QD and dose-titrated upward in 1 mg increments weekly until an optimal dose is reached. Children aged 6 to 12 years will not be permitted to titrate to a daily dose greater than 4 mg and adolescents aged ≥13 years will not be permitted to titrate to a daily dose above the maximum allowed dose per baseline weight group.

Following titration to an optimal dose of TAK-503, subjects will continue with TAK-503 administration through the dose-maintenance period (ie, Week 49B). Visits to the site will occur at intervals of 13 weeks. During the dose-maintenance period, the investigator may make further dose adjustments as needed based upon TEAEs and clinical judgment of tolerability and efficacy. These dose adjustments can be to a higher dose, based on the subject's current age and weight. Children who turn 13 years or older during the dose-maintenance period may be permitted to increase the daily dose higher than 4 mg based on weight at the Study Part B baseline. The dose can be adjusted in 1 mg increments (increased or decreased) at any scheduled or unscheduled visit during the study if deemed appropriate by the investigator.

All subjects who receive active treatment (blinded TAK-503 or atomoxetine in Part A or unblinded TAK-503 in Part B) will undergo a scheduled 3-week dose taper to ensure proper downward dose titration of TAK-503 at the end of the dose-maintenance period or ET in both Study Parts A and B, as applicable.

Each subject's last visit will be 7 (+2) days after the last TAK-503 dose in Study Part B, to measure blood pressure and heart rate, and to follow up on concomitant medications and safety assessments, including TEAEs, which may have been ongoing at the previous visit. Treatment-emergent adverse events reported up to the time of the follow-up visit will be documented and appropriate follow-up will continue until all safety concerns are resolved as judged by the investigator.

Figure 1 Study Design Flow Chart



Note: SPD503 is now known as TAK-503.

3.2 Duration and Study Completion Definitions

For subjects enrolled under Protocol Amendment 7, an individual subject's maximum duration of participation, including washout periods, is expected to be approximately 97 weeks (Study Part A + Study Part B). For subjects enrolled under prior versions of the protocol, an individual subject's maximum duration of participation, including washout periods, is expected to be approximately 128 weeks (Study Part A + Study Part B). The study will be completed in approximately 9 years.

The study completion date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the follow-up visit or contact, whichever is later. The study completion date will be used to ascertain timing for study results posting and reporting.

3.3 Sites and Regions

This study will be conducted at approximately 55 sites in Europe and the United States.

4. STUDY POPULATION

Approximately 288 children and adolescents aged 6 to 17 years inclusive diagnosed with ADHD by the DSM-5 will be enrolled in Study Part A (96 subjects per treatment arm). Approximately 25% of all subjects will be aged 13 to 17 years. Approximately 25% of all subjects will be female. Once 120 subjects have entered into Study Part B, only subjects in the placebo arm in Study Part A will enter Study Part B, to assure that all placebo arm subjects have the opportunity to enter into the 1-year TAK-503 open-label treatment arm.

Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed. See Section 10.3.1 for further consenting instructions.

4.1 Study Part A Inclusion/Exclusion Criteria

4.1.1 Study Part A Inclusion Criteria

The subject will not be considered eligible to enroll in study SPD503-401 without meeting all of the following inclusion criteria:

1. Subject is a male or female aged 6 to 17 years inclusive at the time of consent/assent.
2. Subject must meet the DSM-5 criteria for a primary diagnosis of ADHD based on a detailed psychiatric evaluation using the Kiddie-Schedule for Affective Disorders-Present and Lifetime Version (K-SADS-PL) by a trained child and adolescent psychiatrist at screening (Visit 1A).
3. Subject for whom prior stimulant therapy is not suitable, not tolerated, or shown to be ineffective as determined by investigator clinical assessment and review of the Prior Stimulant Medication Questionnaire (PSMQ) administered during screening (Visit 1A).
4. Subject has an ADHD-RS-5 total score ≥28 at baseline (Visit 2A).
5. Subject has a baseline (Visit 2A) CGI-S score ≥4.
6. Subject who is a female of childbearing potential (FOCP) and postmenarchal must have a negative serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at screening (Visit 1A) and a negative urine pregnancy test at baseline (Visit 2A), be nonlactating, and agree to comply with any applicable contraceptive requirements described in the protocol (See Section 4.4). Female of childbearing potential is defined as any female subject who is at least aged 9 years or younger than 9 years and postmenarchal.
7. Subject's parent or legally authorized representative (LAR) must provide signature of informed consent. Documentation of assent (if applicable) must be provided by the subject indicating that the subject is aware of the investigational nature of the study and the required procedures and restrictions in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guideline E6[R2] and applicable regulations, before completing any study-related procedures.

8. Subject and parent/LAR are willing and able to comply with all the testing and requirements defined in this protocol, including oversight of morning dosing. Specifically, the parent/LAR must be available for the duration of the study to administer the IMP dose each morning when the subject awakens.
9. Subject has supine and standing blood pressure (BP) measurements less than the 95th percentile for age, sex, and height at both screening (Visit 1A) and baseline (Visit 2A).
10. Subject is functioning at an age-appropriate level intellectually, as judged by the investigator.
11. Subject is able to swallow intact tablets and capsules.

4.1.2 Study Part A Exclusion Criteria

The subject will be excluded from the study if any of the following exclusion criteria are met:

1. Subject has a current, controlled (requiring medication or therapy) or uncontrolled, comorbid psychiatric disorder (except oppositional defiant disorder), including but not limited to any of the following comorbid Axis I and Axis II disorders (the K-SADS-PL should be reviewed to confirm diagnosis, if necessary):
    a. Post-traumatic stress disorder (PTSD)
    b. Bipolar illness, psychosis, or family history in either biological parent
    c. Pervasive developmental disorder
    d. Obsessive-compulsive disorder (OCD)
    e. Psychosis/schizophrenia
    f. Serious tic disorder or a family history of Tourette's disorder
2. Subject is currently considered to be a suicide risk by the investigator; has made a previous suicide attempt; has a history of, or currently demonstrating, active suicidal ideation.
3. Subject has a substance abuse disorder as defined by DSM-5 criteria or has been suspected of a substance abuse or dependence disorder (except nicotine) within the past 6 months.
4. Subject has a clinically important abnormality on the urine drug and alcohol screen (except for the subject's current ADHD stimulant, if applicable) at screening (Visit 1A).
5. Subject has been physically, sexually, and/or emotionally abused.
6. Subject has any other disorder that, as judged by the investigator, could contraindicate TAK-503 or confound the results of the safety and efficacy assessments.
7. Subject has any condition or illness including any clinically significant abnormal laboratory value at screening (Visit 1A) or, if the laboratory test was repeated, at baseline (Visit 2A) that, as judged by the investigator, would be an inappropriate risk to the subject and/or could confound the interpretation of study results.
8. Subject has current abnormal thyroid function, defined as abnormal thyroid-stimulating hormone and thyroxine at screening (Visit 1A). Treatment with a stable dose of thyroid medication for ≥3 months before screening will be permitted.

9. Subject has a known history or presence of: malignancy (except nonmelanoma skin cancer), pregnancy, and/or a developmental delay or abnormality associated with growth or sexual maturation delays that are not related to ADHD.
10. Children aged 6 to 12 years with a body weight <25.0 kg or adolescents aged ≥13 years with a body weight <34.0 kg at screening (Visit 1A) or baseline (Visit 2A).
11. Subject is significantly overweight based on the Centers for Disease Control (CDC) BMI-for-age sex-specific charts at screening (Visit 1A) or baseline (Visit 2A). For this study, significantly overweight will be defined as a BMI that is greater than the 95th percentile.
12. Subject has a known history or presence of: structural cardiac abnormalities, serious heart rhythm abnormalities, syncope, cardiac conduction problems (eg, clinically significant heart block or QT interval prolongation), bradycardia, or exercise-related cardiac events including syncope and presyncope.
13. Subject has clinically significant ECG findings, as judged by the investigator, at baseline (Visit 2A).
14. Subject has orthostatic hypotension* or a known history of hypertension. *(*Orthostatic hypotension is defined as a sustained reduction of systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of 10 mm Hg within 3 minutes of standing from supine.*)
15. Subject has a known family history of sudden cardiac death or ventricular arrhythmia.
16. Subject is currently using any medication that violates protocol-specified washout criteria at baseline visit (Visit 2A), including any ADHD medication or other prohibited medications such as herbal supplements, medications that affect BP or heart rate (HR) or medications that have central nervous system (CNS) effects or affect cognitive performance, such as sedating antihistamines and decongestant sympathomimetics (inhaled bronchodilators are permitted) or a history of chronic use of sedating medications (ie, antihistamines).
17. Subject has a medical condition except ADHD that requires treatment with any medication that affects the CNS.
18. Subject is female and pregnant or currently lactating.
19. Subject has taken another investigational product or participated in a clinical study within 30 days before screening (Visit 1A).
20. Subject does not tolerate or has a known or suspected allergy, hypersensitivity, or clinically significant intolerance to guanfacine hydrochloride, atomoxetine, or any TAK-503 or atomoxetine drug product component.
21. Subject has a history of a seizure disorder (except for a single childhood febrile seizure episode that occurred before the age of 3 years).
22. Subject is well-controlled on his/her current ADHD medication with acceptable tolerability, and the parent/treating physician does not object to the current medication.
23. Subject has ALT >2 x upper limit of normal (ULN) or AST >2 x ULN or bilirubin >1.5 x ULN at screening.

4.2 Study Part B Inclusion/Exclusion Criteria

4.2.1 Study Part B Inclusion Criteria

The subject will not be considered eligible to enroll in Study Part B without meeting all of the following inclusion criteria:

1. Female subjects of child-bearing potential must have a negative serum β-hCG pregnancy test if a screening visit is conducted and/or a negative urine pregnancy test at baseline and agree to comply with any applicable contraceptive requirements of the protocol. An FOCP is defined as any female subject who is at least aged 9 years or younger than 9 years and postmenarchal.
2. Subject has a supine and standing BP measurement less than the 95th percentile for age, sex, and height.

4.2.2 Study Part B Exclusion Criteria

Subjects will be excluded from Study Part B if any of the following exclusion criteria are met:

1. Subject failed screening, voluntarily withdrew, or was discontinued from Study Part A for protocol nonadherence, subject noncompliance, or TEAE or SAE.
2. Subject had any clinically significant TEAE during Study Part A that, as judged by the investigator, would preclude exposure to TAK-503.
3. Subject has a history of alcohol or other substance abuse or dependence, as defined by DSM-5 (with the exception of nicotine) within the last 6 months.
4. Subject currently uses any of the prohibited medication or other medications, including herbal supplements, that affect BP or HR or that have CNS effects or affect cognitive performance, such as sedating antihistamines and decongestant sympathomimetics (inhaled bronchodilators are permitted) or a history of chronic use of sedating medications (ie, antihistamines) in violation of the protocol-specified washout criteria at baseline.
5. Subject has a known or suspected allergy, hypersensitivity, or clinically significant intolerance to guanfacine hydrochloride, or any components found in TAK-503.
6. Subject has taken any IMP except placebo in Study Part A within the 30 days before baseline of Study Part B (Visit 2B).
7. Subject is significantly overweight based on the CDC BMI-for-age sex-specific charts at screening. Significantly overweight is defined as a BMI >95th percentile.
8. Subject is a child aged 6 to 12 years with a body weight of <25.0 kg or an adolescent aged ≥13 years with a body weight of <34.0 kg at screening (Visit 1B)
9. Subject has any condition or illness including clinically significant abnormal laboratory values at screening which as judged by the investigator would represent an inappropriate risk to the subject and/or confound the interpretation of study results.

10. Subject is currently considered a suicide risk as judged by the investigator, has previously made a suicide attempt, has a history of, or is currently demonstrating active suicidal ideation. Subjects with intermittent passive suicidal ideation are not necessarily excluded based on the assessment of the investigator.
11. Subject has clinically significant ECG findings, as judged by the investigator, at baseline (Visit 2B).
12. Subject has a known history or presence of structural cardiac abnormalities, serious heart rhythm abnormalities, syncope, cardiac conduction problems (eg, clinically significant heart block), exercise-related cardiac events including syncope and presyncope, or clinically significant bradycardia.
13. Subject has orthostatic hypotension or a known history of hypertension. *(*Orthostatic hypotension is defined as a sustained reduction of systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of 10 mm Hg within 3 minutes of standing from supine.)*
14. Subject has a history of a seizure disorder (except for a single childhood febrile seizure episode that occurred before the age of 3 years) or the presence of a serious tic disorder including Tourette's syndrome.
15. Subject has a medical condition except ADHD, which requires treatment with any medication that affects the CNS.
16. Subject has ALT >2 x ULN or AST >2 x ULN or bilirubin >1.5 x ULN at screening.

4.3 Restrictions

1. Subjects should abstain from substance abuse during the study.
2. Subjects should abstain from the consumption of grapefruit or grapefruit juice during the study.
3. Subjects should not drive or operate heavy equipment until they know how the IMP affects them (ie, suspend driving and operation of heavy equipment until the subject is on a stable, well-tolerated dose for a minimum of 1 week).
4. Tablets and capsules should not be crushed, chewed, or broken before swallowing.
5. Subjects should avoid becoming dehydrated or overheated.

4.4 Reproductive Potential

4.4.1 Female Contraception

Sexually active FOCP should be using an acceptable form of contraception. Females of childbearing potential must be advised to use acceptable contraceptives throughout the study period and for 30 days following the last IMP dose. Hormonal contraceptives, if used, should be administered according to the package insert. Females of childbearing potential who are not currently sexually active must agree to use acceptable contraception if becoming sexually active during the study and continue use for 30 days following the last IMP dose. Acceptable contraceptive methods are defined below.

Female children and adolescent subjects should be either:

- Premenarchal and either Tanner stage 1 or younger than aged 9 years, or
- Females of childbearing potential must have a negative urine and/or serum β-hCG pregnancy test at screening (Study Parts A and B) and before randomization in Study Part A. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

The following methods of contraception are sufficient:

- Intrauterine devices plus condoms
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring) stabilized for ≥30 days before screening, plus condoms. Note: Any subject who becomes sexually active during the study should use one of the other acceptable methods indicated above in addition to hormonal contraceptive until it has been stabilized for 30 days.

4.4.2 Male Contraception

Male subjects will either abstain from sex or use condoms.

4.5 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from IMP with the medical monitor when possible.

If IMP is discontinued, regardless of the reason, the final evaluations listed for the following visits will be performed as completely as possible:

- Study Part A: ET; Visit 15A, Visit 16A, and Visit 17A (dose-taper visits)
- Study Part B: Visit 13B/ET at Week 49B; Visit 14B at Week 50B, Visit 15B at Week 51B, and Visit 16B at Week 52B (dose-taper visits)

If the subject discontinues IMP and will not undergo the dose-taper as stated in the protocol, the medical monitor must be contacted immediately.

Whenever possible, all discontinued subjects (including those who were randomized to placebo) should also undergo the protocol-specified followup. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for termination, date of stopping IMP, and total amount of IMP taken must be recorded in the electronic case report form (eCRF) and source documents.

Subjects who discontinue/withdraw from the study will not be replaced.

4.5.1 Reasons for Discontinuation/Withdrawal

The reason for discontinuation/withdrawal must be recorded in the subject's medical record and on the eCRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the eCRF.

If a TEAE is a reason for discontinuation, then the event must be recorded as the reason for discontinuation on the eCRF. If the decision is made to withdraw the subject due to lack of response, the reason for discontinuation should be recorded as lack of efficacy (as per eCRF completion guidelines). If the decision is made to withdraw the subject due to intolerability, the reason for discontinuation should be recorded as a TEAE.

Reasons for discontinuation/withdrawal include but are not limited to:

- TEAE
- Protocol significant deviation
- Withdrawal by subject
- Lost to follow-up
- Lack of efficacy
- Other (the reason must be specified on the eCRF), including, but not limited to:
    - Pregnancy
    - Hypertension
    - ALT >2 x ULN or AST >2 x ULN or bilirubin >1.5 x ULN

If a subject chooses to withdraw from study participation due to personal concerns related to a dire, exceptional situation such as the COVID-19 pandemic (other than a COVID-19-related AE), this requires documentation as the reason for subject withdrawal in the eCRF.

4.5.2 Subjects "Lost to Follow-up" Before the Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point before the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that the subject return to the site for final safety evaluations and to return any unused IMP.

5. PRIOR AND CONCOMITANT TREATMENT

All nonstudy treatment, including but not limited to herbal treatments, vitamins, behavioral treatment, and nonpharmacological treatment, such as psychotherapy, received within 30 days before screening (Visit 1A/1B) (or pharmacokinetic equivalent of 5 half-lives, whichever is longer) and through the final study contact (including protocol-defined follow-up period) must be recorded on the appropriate eCRF field.

5.1 Prior Treatment

Prior treatment includes both pharmacologic and nonpharmacologic interventions received within 30 days (or pharmacokinetic equivalent of 5 half-lives, whichever is longer) of screening and any treatments received between screening and baseline.

Prior treatment information will be recorded on the appropriate eCRF page and in the subject's medical record. For all prior pharmacologic interventions, the drug name, indication, and dates of use will be recorded.

Prior ADHD medication: The subject's lifetime psychoactive medication history will also be documented at screening. Entries for all prior psychoactive medications will include the drug name, indication, and dates of use.

Prior ADHD nonpharmacological interventions: The subject's lifetime nonpharmacological interventions (eg, behavioral therapy) for ADHD will also be documented during screening (Visit 1A: Day -35 to Day -3) and baseline (Visit 2B). Entries for all of nonpharmacological interventions for ADHD will include type(s) and dates of occurrence.

5.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first IMP dose and the end of the follow-up period, inclusive. Concomitant treatment information must be recorded in the appropriate eCRF field.

If a FOCP uses hormonal contraception as her acceptable method of birth-control, the minimum time period for use of the hormonal contraception is 30 days before baseline to ensure effectiveness in preventing pregnancy.

5.2.1 Permitted Treatment

Medications and therapies that will be allowed during the study include the following:

- Stable doses of inhaled bronchodilator inhaler (oral corticosteroids, β2-agonists [Part A only], and theophylline will be prohibited)
- Antibiotics and over-the-counter medications that do not affect BP, HR, or the CNS and are considered necessary for the subject's welfare are allowable at the discretion of the investigator (medications that are known cytochrome P450 (CYP) 3A4 inhibitors will not be allowed [eg, macrolide or quinolone antibiotics])

- Nonsedating antihistamines such as fexofenadine, loratadine, and cetirizine hydrochloride
- Over-the-counter nonstimulant cold remedies
- Continued participation in behavioral therapy, provided that the subject has been receiving the therapy for at least 1 month at the time of baseline. The behavioral therapy must remain stable throughout the study and any changes planned to the behavioral therapy must be discussed with the medical monitor.

The administration of all medications, including those listed above, must be recorded in the appropriate section of the source documents and eCRF.

5.2.2 Prohibited Treatment

The concomitant use of drugs listed below may interfere with the assessment of efficacy, safety, or tolerability of the IMP and will not be allowed throughout the study. A washout schedule for prohibited medications is presented in Table 3.

- All investigational medications other than the IMP
- Any other formulations or sources of guanfacine that are not the IMP
- All anti-hypertensive medication
- Appetite suppressants
- Cough/cold preparations that contain amphetamine or pemoline, or that contain adrenergic or noradrenergic agonists such as pseudoephedrine or phenylephrine
- Tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), antipsychotics, neuroleptics, anxiolytics, benzodiazepines or benzodiazepine derivatives, and psychostimulants (including sympathomimetics)
- Modafinil, quinidine, and pemoline
- α2-adrenergic agonists (eg, clonidine)
- Anticonvulsant medications, sedatives, sedative hypnotics such as zopiclone, sedating antihistamines (as a single preparation or in combination), and melatonin
- Any medication or herbal preparations that affects the CNS, cognitive performance, and/or BP or HR (such as, but not limited to, certain quinolone antibiotics)
- Medications that are contraindicated for concomitant use with TAK-503 use (Section 5.2.2.1)
- Medications that are contraindicated for concomitant use with atomoxetine (Section 5.2.2.2)

5.2.2.1 Medications Prohibited Based on TAK-503 Use (Study Parts A and B)

Medications known to be CYP3A4/5 inducers or inhibitors may interact with TAK-503. Examples of CYP3A4/5 inhibitors and inducers are provided in Appendix 8. Any new use of CYP3A4/5 inhibitors or inducers after baseline is prohibited; however, if use is planned for the duration of the study and a stable dose has been established for ≥14 days before baseline, then the treatment may be given concomitantly throughout the study, with no planned changes in use.

Drugs that prolong the QT interval (eg, neuroleptics, class IA and III anti-arrhythmics, moxifloxacin, erythromycin, methadone, mefloquine, tricyclic antidepressants, lithium, and cisapride) will be prohibited.

5.2.2.2 Medications Prohibited Based on Atomoxetine Use (Study Part A only)

Medications known to be CYP2D6 inhibitors (eg, bupropion, cinacalcet, fluoxetine, paroxetine, quinidine, duloxetine, sertraline, and terbinafine) may interact with atomoxetine and will be prohibited during Study Part A.

Other prohibited medications include the following:

- Medications that that lower seizure threshold, such as antidepressants, neuroleptics, mefloquine, bupropion, or tramadol
- Medications that affect noradrenaline, such as imipramine, venlafaxine, mirtazapine, pseudoephedrine, or phenylephrine
- Pressor agents
- β2-agonists

5.2.2.3 Washout Schedule for Prohibited Medications

The washout period for some of the prohibited medications is provided in Table 3. At a minimum, the washout period for all prohibited medications must be at least 5 times the half-life of the medication. Instruction to washout a medication can be given to a subject only after informed consent/assent has been obtained.

Table 3 Common Excluded Treatments and Associated Washout Period

	Minimum Number of Days Before Baseline		
Treatment	**7**	**14**	**30**
Antihypertensives	X		
Antihistamines	X		
Psychostimulants	X		
Amphetamines and amphetamine-like agents	X		
Cough/cold preparations containing stimulants/sympathomimetic agents	X		
Melatonin	X		
Grapefruit/grapefruit juice	X		
Monoamine oxidase inhibitors		X	
Anxiolytics			X
Antidepressants, including SSRIs and SARIs			X
Antipsychotics			X
SNRIs			X
Sedatives			X
α2-adrenergic agonists			X
CYP3A/4 inhibitors and inducers			X
CYP2D6 inhibitors			X
Investigational compounds			X

CYP=cytochrome P450; SARI=serotonin antagonist and reuptake inhibitor; SNRI=selective norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor

6. INVESTIGATIONAL MEDICINAL PRODUCT(S)

6.1 Identity of Investigational Medicinal Product(s)

In Study Part A, the IMPs are TAK-503, atomoxetine, and placebo. Placebo will be TAK-503 matched placebo tablets and atomoxetine-matched placebo over-encapsulated capsules.

TAK-503, an extended-/prolonged-release tablet formulation of guanfacine hydrochloride is designed for QD oral administration. TAK-503 will be provided by the sponsor in 1-, 2-, 3-, and 4-mg strength tablets with the following visual features:

- 1-mg tablet is round and white
- 2-mg tablet is oblong and white
- 3-mg tablet is round and green
- 4-mg tablet is oblong and green

Subjects will take 1 TAK-503 tablet or 1 TAK-503-matched placebo tablet if dose-optimized to 1 to 4 mg QD or 2 TAK-503 tablets or 2 TAK-503-matched placebo tablets if dose-optimized to 5 to 7 mg QD.

Atomoxetine hydrochloride, the marketed comparator product, is designed for QD administration. The sponsor will provide 10-, 18-, 25-, 40-, and 60 mg-strength atomoxetine capsules. Subjects randomized to the atomoxetine treatment arm will take 1 atomoxetine capsule or 1 atomoxetine-matched placebo capsule if dose-optimized to ≤60 mg QD or 2 atomoxetine capsules or 2 atomoxetine-matched placebo capsules if dose-optimized to >60 mg QD.

The sponsor will provide TAK-503-matched placebo tablets and atomoxetine-matched placebo capsules.

TAK-503 will be the only IMP administered in Study Part B.

Additional information for TAK-503 is provided in the Intuniv IB and the Intuniv SmPC.

Additional information for atomoxetine hydrochloride is provided in the atomoxetine hydrochloride SmPC.

6.1.1 Blinding of the Treatment Assignment (Study Part A only)

This is 2-part study in which Study Part A is a double-blinded, double-dummy, placebo-controlled study with an active reference arm. Actual treatment given to individual subjects will be determined by the randomization schedule. Treatment assignments of individual subjects will be assigned automatically using the interactive response technology (IRT).

Eligible subjects will be randomized at baseline (Day 0/Visit 2A) in a 1:1:1 ratio among TAK-503, atomoxetine, and placebo treatment arms. Subjects randomized to the TAK-503 treatment arm will receive TAK-503 tablet(s) and atomoxetine-matched placebo capsule(s). Subjects randomized to the atomoxetine treatment arm will receive TAK-503-matched placebo tablet(s) and atomoxetine capsule(s). Subjects randomized to the placebo treatment arm will receive TAK-503-matched placebo tablet(s) and atomoxetine-matched placebo capsule(s).

Placebo will include TAK-503-matched placebo tablet and atomoxetine-matched placebo capsule. TAK-503-matched placebo will be provided in 1-, 2-, 3-, and 4-mg TAK-503 dummy strength tablets to protect the blind between TAK-503 tablets and TAK-503-matched placebo tablets. Atomoxetine capsules and atomoxetine-matched placebo capsules will be over-encapsulated to protect the blind between atomoxetine and atomoxetine-matched placebo capsules.

Study Part B will be open-label TAK-503.

6.2 Administration of the Investigational Medicinal Product(s)

6.2.1 Interactive Response Technology for Investigational Medicinal Product Management

An IRT system will be used in this study to manage the tracking and confirmation of shipment, supply, inventory, ordering, IMP expiration, site assignments, subject randomization, IMP returns, unblinding of active treatment versus placebo at Week 18A, and emergency unblinding of IMP (TAK-503 or atomoxetine).

The IRT provider will supply a user manual of the IRT to each site.

If a subject is unable to reach a site to be dispensed IMP due to unavoidable dire circumstances (eg, a widespread disease outbreak such as the COVID-19 pandemic or natural disaster), alternative study drug delivery to trial participants may be necessary. Drug may be shipped directly to participants' residences by a contracted logistics provider or distributor (direct-to-patient [DTP] shipment) in compliance with national, state, and local laws or temporary national emergency measures and the sponsor's processes. Such exceptional instances should be duly justified and documented in the study records.

6.2.2 Allocation of Subjects to Treatment Arm

Allocation to treatment arm will be stratified by sex (male or female) and age subgroup (6 to 12 years or 13 to 17 years) to facilitate between-treatment balance within each stratum.

The IMP packaging identification numbers, separate from randomization numbers/unique identifiers, may also be assigned to subjects for specific treatment assignment as dictated by the study. In these cases, the same IMP packing identification number may not be assigned to more than 1 subject.

Subject numbers will be assigned to subjects as they consent to participate in the study using an IRT. A unique 3-digit number will be assigned to each site and a 4-digit number will be assigned

in an ordinal series for each subject in order of presentation. The full subject number will be a combination of site and presentation number. For example, the third subject consenting to study participation at Site 002 will be assigned the following number: 002-0003.

Once a unique subject number has been assigned, then that number will not be used again even if, for example, a subject withdraws from the study. If the unique subject number is allocated incorrectly, the clinical research associate (CRA)/study monitor must be notified as soon as the error is discovered.

6.2.3 Dosing Periods

During Study Part A, the IMP will be dosed in a double-dummy design. Subjects randomized to TAK-503 will receive TAK-503 tablet(s) and atomoxetine-matched placebo capsule(s). Subjects randomized to atomoxetine will receive atomoxetine capsule(s) and TAK-503-matched placebo tablet(s).

Subjects randomized to placebo will receive TAK-503-matched placebo tablet(s) and atomoxetine-matched placebo capsule(s). Double-blinded treatment will be for up to 18 weeks, plus the dose-taper period (except for subjects on placebo).

All subjects in this study will be instructed to take assigned medication QD in the morning orally and consistently with respect to time of eating and type of food eaten. Administering the IMP with a high-fat meal should be avoided. Subjects should not drive or operate heavy equipment until the effects of IMP are known (ie, suspend driving and operation of heavy equipment until the subject is on a stable and well-tolerated dose for a minimum of 1 week).

6.2.3.1 Dose-optimization Period

Investigational medicinal product dosing will be flexibly optimized to maximize the potential benefits while minimizing risk of TEAEs. The investigator will consider the efficacy, safety, and tolerability profile when determining the optimal dose for an individual subject.

In Study Part A, subjects who achieve at least a 30% reduction in ADHD-RS-5 total score from baseline (Day 0A) and a CGI-I of 1 or 2 at a given tolerated dose will be considered to be at an optimal IMP dose. Subjects who do not achieve this amount of reduction at a given tolerated dose may be titrated to a higher dose at the investigator's discretion. Also, if a ≥30% reduction in ADHD-RS-5 total score from baseline is reached and the dose is well tolerated, then the IMP dosage strength may be increased if the investigator believes the subject could potentially receive further symptom reduction with a higher dose, not to exceed the maximum dose as shown in Table 4 and Table 5.

The dose-optimization schedule and dose levels of TAK-503 in Study Part B will be identical to those in Study Part A. Dose-optimization of TAK-503 will be guided by investigator judgment based on emerging TEAEs and clinical assessments of tolerability and efficacy by reviewing TEAE incidence(s) and changes in CGI-I and ADHD-RS-5 scores.

If necessary, the investigator will be permitted to reduce the subject's dose once during the dose-optimization periods of Study Parts A and B, respectively.

TAK-503 Dose-optimization (Study Parts A and B)

All subjects will undergo dose-optimization during Study Parts A and B. Regardless of study part, dose-optimization will occur during the first 4 weeks for children aged 6 to 12 years and the first 7 weeks for adolescents aged 13 to 17 years.

Subjects randomized to TAK-503 will begin dosing at 1 mg QD and dose-titrated upward in weekly 1-mg increments until an optimal dose is reached. Children aged 6 to 12 years will not be permitted to titrate to a dose greater than 4 mg QD and adolescents aged 13 to 17 years will not be permitted to titrate to greater than the maximum allowed QD dose per the baseline weight group as shown in Table 4.

Table 4 Dose-optimization Schedule for TAK-503: Study Parts A and B

	Study Week						
Subject Baseline Weight	**1A/B**	**2A/B**	**3A/B**	**4A/B**	**5A/B**	**6A/B**	**7A/B**
Children aged 6 to 12 years							
≥25.0 kg (4 mg QD max dose)	1 mg	2 mg	3 mg	4 mg	Enter dose-maintenance period at optimized dose ≤4 mg		
Adolescents aged 13 to 17 years							
34.0 to 41.4 kg (4 mg QD max dose)	1 mg	2 mg	3 mg	4 mg	optimized dose ≤4 mg	optimized dose ≤4 mg	optimized dose ≤4 mg
41.5 to 49.4 kg (5 mg QD max dose)	1 mg	2 mg	3 mg	4 mg	5 mg	optimized dose ≤5 mg	optimized dose ≤5 mg
49.5 to 58.4 kg (6 mg QD max dose)	1 mg	2 mg	3 mg	4 mg	5 mg	6 mg	optimized dose ≤6 mg
≥58.5 kg (7 mg QD max dose)	1 mg	2 mg	3 mg	4 mg	5 mg	6 mg	7 mg

Max=maximum; QD=once daily

Atomoxetine Dose-optimization (Study Part A only)

The dose of atomoxetine will be optimized in Part A, since Part B will entail open-label treatment with TAK-503.

Subjects who weigh <70 kg at baseline and randomized to the atomoxetine treatment arm will begin dosing at approximately 0.5 mg/kg QD. If well-tolerated after 1 week minimum, this dose may be increased to the target dose of 1.2 mg/kg QD. The dose-optimization schedule for atomoxetine is provided in Table 5. The total atomoxetine dose will not exceed 1.4 mg/kg QD. With limited dosage forms, this upper limit is necessary to achieve appropriate weight-based doses. Permitted doses of atomoxetine for subjects weighing <70 kg at baseline are 10, 18, 25, 40, 60, and 80 mg QD, depending on the subject's baseline weight (Visit 2A).

Atomoxetine dosing in children and adolescents who weigh ≥70 kg at baseline will begin at 40 mg QD. If well-tolerated after a minimum of 1 week, then this dose may be increased to 80 mg QD. After a 1-week minimum, if the daily dose at 80 mg is well tolerated, then the dose

may be increased to 100 mg QD. The total dose in children and adolescents who weigh ≥70 kg at baseline (Visit 2A) will not exceed 100 mg QD. Subjects optimized to a dose greater than 60 mg QD will take 2 atomoxetine or atomoxetine-matched placebo capsules QD. Subjects optimized to a daily dose ≤60 mg QD will take 1 atomoxetine or atomoxetine-matched placebo capsule QD.

Table 5 Dose-optimization Schedule for Atomoxetine: Study Part A

	Weight Range (kg)	First dose 0.5 mg/kg	First dose increase 1.2 mg/kg	Second dose increase
Subjects <70 kg at Baseline	25.0-29.9	10 mg	25 mg	Not Applicable
	30.0-44.5	18 mg	40 mg	Not Applicable
	44.6-64.5	25 mg	60 mg	Not Applicable
	64.6-69.9	40 mg	80 mg	Not Applicable
Subjects ≥70 kg at Baseline	≥70	40 mg	80 mg	100 mg

6.2.3.2 Dose-maintenance Period

In Study Part A, following titration to an optimal dose, all subjects randomized will continue taking morning doses through Week 18A. The investigator will not adjust the IMP dose during the dose-maintenance period of Study Part A.

Subjects in Study Part B will continue to take morning doses of open-label optimized TAK-503 through Week 49B. The investigator may make further dose adjustments as needed based upon TEAEs and clinical judgment of tolerability and efficacy. These dose adjustments can be to a higher dose, based on the subject's current age and weight. The daily dose, based on the Study Part B baseline weight, may be increased to >4 mg in subjects who turn 13 years or older during the dose-maintenance period. The dose can be increased or decreased by 1-mg increments at any scheduled or unscheduled visit during the study if deemed appropriate by the investigator.

6.2.3.3 Dose-taper Period

All subjects randomized in active treatment arms will undergo a scheduled 3-week dose taper to ensure proper downward dose titration of TAK-503 at the end of the dose-maintenance period or at ET in both Study Parts A and B, as applicable. Subjects will be dispensed a tapering dose based on the last maintenance of dose of TAK-503 as presented in Table 6. Subjects will return IMP upon return to the study site for the third dose-tapering visit.

Table 6 Dose-taper Schedule for TAK-503 in Study Parts A and B

Last TAK-503 Maintenance Dose	Visit 15A and Visit 14B		Visit 16A and Visit 15B		Visit 17A and Visit 16B	
	Days 1 to 4[a]	Days 5 to 7[a]	Days 8 to 11[a]	Days 12 to 14[a]	Days 15 to 18[a]	Days 19 to 21[a]
1 mg	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg
2 mg	2 mg	2 mg	2 mg	1 mg	1 mg	1 mg
3 mg	2 mg	2 mg	2 mg	1 mg	1 mg	1 mg
4 mg	3 mg	3 mg	2 mg	2 mg	1 mg	1 mg
5 mg	4 mg	4 mg	3 mg	3 mg	2 mg	1 mg
6 mg	5 mg	4 mg	3 mg	3 mg	2 mg	1 mg
7 mg	6 mg	5 mg	4 mg	3 mg	2 mg	1 mg

[a] Days 1 through 21 of the 3-week dose-taper. During Study Parts A and B, days 1 to 21 refer to weeks 50, 51, and 52. Week 50 corresponds to Visit 15A in Study Part A and Visit 14B in Study Part B. Week 51 corresponds to Visit 16A in Study Part A and Visit 15B in Study Part B. Week 52 corresponds to Visit 17A in Study Part A and Visit 16B in Study Part B.

Dose-tapering will not be required for subjects randomized to the placebo treatment arm.

6.2.4 Unblinding of the Treatment Assignment

In this study, blinding to treatment assignment (TAK-503, atomoxetine, placebo) is used to avoid bias in Part A, in which the comparator arms (atomoxetine, placebo) have been included as controls for assay sensitivity.

Part A (blinded, placebo-controlled): The treatment assignment (TAK-503, atomoxetine, placebo) must not be broken for subjects during their participation in Part A of the study, except in emergency situations when the identification of the IMP is required for further treatment of the subject. If IMP unblinding is required, the treatment assignment should be broken using the IRT system. The investigator should contact the medical monitor before unblinding if feasible and by all means as soon as possible after IMP unblinding.

Transition from Part A to Part B: In Part A, Week 18A, the IRT system will notify the site to transfer subjects to Part B of the study.

Part B (open-label): Upon entry into Part B of the study, all subjects will receive open-label TAK-503. However, subjects who received active treatment in Part A must remain blinded regarding which drug they received in Part A, in order to avoid influencing data queries related to these subjects' data in Part A.

If the treatment assignment is broken for any reason, then the date, the signature of the person who broke the code and the reason for breaking the code will be recorded using the source documents. Upon study-blind breaking, the subject will be withdrawn from the study but will be followed-up for safety purposes. Any code-breaks that occur must be reported to the contract research organization (CRO) and sponsor. After subject's blinding is broken, the code-break information will be held by the pharmacist/designated person at the site and by the CRO's medical monitor for the study or designee.

6.2.5 Labeling, Packaging, Storage, Handling, and Accountability

6.2.5.1 Labeling

A computer-generated booklet label containing study information will be affixed to the primary container of the IMP.

All IMP will be labeled at a minimum with protocol number, medication identification (MedID) number, dosage form (including product name and quantity in pack), directions for use, storage conditions, expiration date (if applicable), batch number and/or packaging reference, the statements "For clinical trial use only", and/or "CAUTION: New Drug - Limited by Federal (or United States) Law to Investigational Use", and "Keep out of reach of children", and the sponsor's name and address as per local regulation.

Any additional labeling requirements for participating countries will also be included on the label. Space will be allocated on the label so that the site representative can record the unique subject identifier.

Additional labels may, on a case-by-case basis, be applied to the IMP to satisfy local or institutional requirements, but must not do the following:

- Contradict the clinical trial label
- Obscure the clinical trial label
- Identify the name of the subject

Additional labels may not be added without the sponsor's prior full agreement.

6.2.5.2 Packaging

The sponsor will provide all TAK-503 in 1-, 2-, 3-, and 4-mg strength tablets and TAK-503-matched placebo tablets.

The sponsor will provide atomoxetine in 10-, 18-, 25-, 40-, and 60-mg over-encapsulated capsules and atomoxetine-matched placebo capsule, which will also be over-encapsulated.

Primary packaging for all IMP will be in 9-count, child-resistant bottles.

Changes to sponsor-supplied packaging before dosing may not occur without full agreement by the sponsor obtained in advance.

6.2.5.3 Storage

The investigator will have overall responsibility for ensuring that IMP is stored in a secure and limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. The IMP will be distributed by the pharmacy or a nominated member of the study team who will enter the unique subject identifier on the IMP bottle/carton labels as they are distributed.

All IMP must be stored according to labeled storage conditions. Temperature monitoring will be required at the storage location to ensure that the IMP is maintained within an established temperature range. The investigator will be responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified minimum/maximum thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established temperature range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the IMP and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate by the sponsor for subject use.

The sponsor should be notified immediately if any changes are made to the storage area of the IMP that could affect the integrity of the products (eg, fumigation of a storage room).

6.2.5.4 Special Handling

No IMP stock or returned inventory from a company-sponsored trial may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. When authorized, all applicable local, state, and national laws must be adhered to for the transfer.

All documentation of delivery/drug receipts should be maintained by the site. If used, shipment return forms must be signed before shipment from the site. Validated electronic return systems (ie, IRT) will not require a shipment form. Returned IMP must be packed in a tamper-evident manner to ensure product integrity. Shipment of all returned IMP must comply with local, state, and national laws.

6.2.6 Drug Accountability

Investigators will be provided with sufficient amounts of the IMP to execute this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the IMP and document shipment content and condition. Accurate records of all IMP dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing IMP. If permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who has been adequately trained on the contents of the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will dispense the IMP only to subjects enrolled in this study and will follow the procedures set out in the study protocol. Each subject will be given only the IMP

carrying his or her treatment assignment. All dispensed IMP will be documented on the eCRF and/or other IMP record. The investigator will be responsible for ensuring the retrieval of all study supplies from subjects.

No IMP stock or returned inventory from a company-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, then all applicable local, state, and national laws must be followed.

In Study Part A, the sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records, provided that the study-blind is not compromised.

At the end of the study or as instructed by the sponsor, all unused stock, subject-returned IMP, and empty/used IMP packaging will be sent to a nominated contractor on behalf of the sponsor. The IMP returned to the sponsor's designated contractors must be counted and verified by clinical site personnel and the sponsor (or designated CRO). All certificates of delivery/drug receipts should be signed by the site representative to confirm contents of shipment.
For unused supplies in which the original supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken; the labeled amount will be documented in lieu of counting. If used, shipment return forms must be signed before shipment from the site. Validated electronic return systems (ie, IRT) will not require a shipment form. Returned IMP(s) must be packed in a tamper-evident manner to ensure product integrity. The sponsor will be contacted to authorize the return of an IMP before shipment. The shipment of all returned IMP must comply with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile IMP delivered with those used and returned. All IMP(s) must be accounted for and any discrepancies will be investigated and documented to the sponsor's satisfaction.

6.3 Subject Compliance

Subjects must be instructed to bring any unused IMP and empty/used IMP packaging to every visit. Drug accountability must be assessed at the container/packaging level for unused IMP that is contained within the original tamper-evident sealed container (eg, bottles, trays, vials) or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form.

7. STUDY PROCEDURES

7.1 Study Schedule

The timing of study procedures is provided in the Study Schedules.

All subject discontinuations and alternative approaches to study procedures (ie, procedures not conducted per the Study Schedules) due to unavoidable dire circumstances (eg, a widespread disease outbreak such as the COVID-19 pandemic or natural disaster) must be documented in study records.

7.1.1 Screening

Before performing any study-related procedures, the investigator or designee must obtain written informed consent from the subject's parent/LAR (see Section 10.3.1). Documentation of assent (as per local requirements) must indicate that the parent/LAR and the subject are aware of the investigational nature of the study and the required procedures and restrictions associated with participating in the study. Subjects must be reconsented if they reach the age of legal responsibility during the study, based on applicable local and national laws.

A diagnosis of ADHD based on a psychiatric interview and mental status examination using the K-SADS-PL will be performed at screening (Visit 1A) by a trained child and adolescent psychiatrist, who is experienced with the scale and qualified to establish the aforementioned diagnoses. Any exception will require the approval of the sponsor or designee. Documentation of study training should be maintained in the site's files.

A washout period to discontinue any current psychoactive medication or current prohibited medication may be required before baseline of Study Part A and will be required before baseline of Study Part B. For Study Part A, the washout is intended to remove any medication that is prohibited in this study that the subject may have been receiving before enrollment. A subject cannot be instructed to washout any medication until after informed consent has been obtained. Schedules for medication requiring a washout are presented in Table 3.

Except for subjects randomized to the placebo treatment arm, a washout period of ≥30 days but no more than 45 days from the last dose of IMP in Study Part A will be required for Study Part B to remove blinded IMP to which the subject was randomized in Study Part A. If more than 45 days has elapsed between the follow-up visit in Study Part A and the baseline visit in Study Part B, then the subject will be discontinued from the study.

Screening assessments may take place over several days to provide enough time to complete all procedures and confirm study eligibility. If screening assessments are performed on different dates, then the screening date will be recorded as the date signed on the source documents that consent was obtained as no study procedures should precede this date.

The screening period will not be less than 3 days to allow for all screening results to be obtained and evaluated. If the screening period extends past 35 days, then certain assessments will be repeated (see Section 7.1.2).

If a subject discontinued from screening (and was thus considered a screen failure due to unavoidable dire circumstances, eg, a widespread disease outbreak such as the COVID-19 pandemic or natural disaster), but was otherwise qualified to participate in the trial, the subject may be rescreened if the sponsor medical monitor agrees. Such exceptional circumstances require documentation in the eCRF.

The procedures to be completed at screening are presented in the Study Schedules and clarified further below:

- The investigator or assigned site staff will access the IRT to register the subject and obtain the assigned unique subject identification number.
- Reporting of AEs will begin at the time informed consent is obtained.
- Prior/concomitant medications will be reported as follows:
- All lifetime psychoactive medications will be documented on the PSMQ.
- Other medications used during the 30 days before screening (Visit 1A) will be documented.
- Any abnormal physical examination finding(s) will be documented on the appropriate eCRF for medical history with enough detail to permit detection of change over time. See Section 7.2.2.1.
- Historical and current nonpharmacological interventions for ADHD will be recorded. Note: Continued participation in behavioral therapy will be permitted if the subject has been receiving the therapy for at least 1 month at the time of baseline and therapy will remain stable throughout the study. Any unplanned changes to behavioral therapy must be discussed with the medical monitor.
- Before baseline (Visit 2A), a site representative will contact the subject's parent/LAR after successful screening to provide instruction(s) for discontinuing the subject's psychoactive medication (if any) or current prohibited medication (if any). The minimum washout period for all prohibited medications is 5 times the half-life of the medication (see Table 3).

A screen failure will be defined as a subject who has given informed consent and failed to meet the inclusion criteria and/or met at least 1 of the exclusion criteria and has not been randomized. The investigator or assigned study staff will use the IRT to record any subject designated as a screen failure. Any subject designated a screen failure under normal circumstances (ie, failure not related to a widespread disease outbreak such as the COVID-19 pandemic or natural disaster) will not be rescreened. Screen failures that are related to such exceptional circumstances require documentation in the eCRF and will be allowed to rescreen.

7.1.2 Baseline

Once all screening results, including clinical laboratory tests and ECGs, have been obtained and reviewed and after the subject has completed the required washout period (if necessary), subjects will return to the site for baseline (Visit 2A and Visit 2B).

Procedures to be completed at baseline are presented in the Study Schedules with further clarification provided as follows:

- If the clinical laboratory tests to be completed for screening were not conducted within the 35 days before the baseline visits, then these tests must be repeated, and results obtained, prior to determining eligibility.
- Concomitant and psychoactive medications will be documented as follows:
- Medications used between screening and baseline
- A minimum of 3 ECG measurements, with approximately 5 minutes between each measurement, will be collected at baseline to ensure that appropriate baseline intervals are established. The eligibility of a subject will be based on ECG measurements from the central reader (normal/abnormal) and the determination of the clinical significance of any ECG finding by the central reader by the investigator, in consultation with the medical monitor, if applicable.
- A subject must have an ADHD-RS-5 total score of ≥28 and a CGI-S score ≥4 at baseline (Visit 2A) for inclusion (Study Part A only).

If the subject is eligible for the study, then the investigator or assigned site staff will access the IRT to enroll the subject and obtain a MedID number to dispense IMP to the subject. The subject will take the first IMP dose on the morning after baseline (Visit 2A and Visit 2B).

7.1.3 Treatment Periods: Dose-optimization, Dose-maintenance, and Dose-taper

For Study Parts A and B, the treatment periods comprise dose-optimization, dose-maintenance, and dose-taper. The treatment period will be double-blinded in Study Part A and open-label in Study Part B.

7.1.3.1 Dose-optimization Period

In Study Parts A and B, dose-optimization of IMP will occur from Week 1A/B through Week 4A/B for children aged 6 to 12 years and through Week 7A/B for adolescents aged 13 to 17 years. During the dose-optimization period, clinic visits will be scheduled every 7 days to assess IMP safety and tolerability and to allow investigators to titrate the IMP to an optimal dose that maximizes potential benefits while minimizing risk of TEAEs. The investigator will consider the efficacy, safety, and tolerability profile when determining the optimal dose for each subject. Subjects who achieve at least a 30% reduction in ADHD-RS-5 total score from baseline (Study Part A only) and a CGI-I of 1 or 2 at a given tolerated dose will be considered to be receiving an optimal dose. Subjects who do not achieve this level of reduction at a given tolerated dose may be titrated to a higher dose at the investigator's discretion. Also, if a ≥30% reduction in the ADHD-RS-5 total score from baseline is obtained and the dose is well-tolerated, then the IMP dosage strength may be increased if the investigator believes the subject could potentially receive further symptom reduction with a higher dose, though not to exceed the maximum dose shown in Table 4 and Table 5, as applicable.

In Study Part B, optimization of TAK-503 dosing will be guided by investigator judgment based on emerging TEAEs and clinical assessments of tolerability and efficacy by reviewing TEAE incidence(s) and changes in CGI-I and ADHD-RS-5 scores.

If necessary, the investigator will be permitted to lower the subject's dose once during the dose-optimization periods of Study Parts A and B.

Procedures to be completed during the dose-optimization periods are presented in the Study Schedules.

7.1.3.2 Dose-maintenance Period

Subjects will remain on an optimized IMP dose during the entirety of the dose-maintenance periods of Study Parts A and B.

In Study Part A, subjects randomized to TAK-503 or atomoxetine treatment arms will continue with daily dosing at the optimized IMP dose from Week 5A for children and Week 8A for adolescents. At the principal investigator's discretion, a subject may conduct up to 2 consecutive visits remotely. Note that this is not a cumulative limit on the total number of remote visits. A subject may have more than 2 remote visits throughout the entire course of the study, but cannot have 3 remote visits in a row (unless required due to unavoidable dire circumstances, eg, a widespread disease outbreak such as the COVID-19 pandemic or natural disaster). Such exceptional circumstances require documentation in the study records.

Subjects randomized to the placebo treatment arm will continue with daily dosing from Week 5A for children and Week 8A for adolescents through Week 18A and complete procedures specified for Visit 11A (Week 18A) before rolling over to Study Part B.

All subjects who complete the dose-maintenance period of Study Part A or who terminate early will undergo the procedures indicated for ET in the Study Schedules. Likewise, in Study Part B, all subjects who complete the dose-maintenance period or who terminate early will undergo the procedures indicated for Visit 13B (Week 49B) in the Study Schedules.

7.1.3.3 Dose-taper Period

After completion of the dose-maintenance period, or upon ET, subjects who received TAK-503 treatment (blinded active or placebo) in Study Part A and all subjects in Study Part B will be required to taper downward the last dose-maintenance dose over 3 weeks. The dose-taper schedule will be determined by the last maintenance dose of TAK-503 as presented in Table 6.

7.1.4 Follow-up Period

The follow-up period for this study is 7 (+2) days each for Study Part A and Study Part B (Week 53B). The procedures to be performed at the follow-up visit are presented in the Study Schedules.

If a subject refuses to return to the site for a follow-up visit, then the study site personnel will contact the subject 7 days after the subject's last IMP dose to collect information on any ongoing

or emergent TEAEs, SAEs, and concomitant medications since the last IMP dose. Appropriate follow-up should continue until all safety concerns are resolved as judged by the investigator.

All TEAEs and SAEs that are not resolved at the time of this contact will be followed until the event is closed (see Section 7.1).

7.1.5 Additional Care of Subjects After the Study

No aftercare is planned for this study; subjects will be referred to their primary care physician or psychiatrist for care after the follow-up.

7.2 Study Evaluations and Procedures

All assessments described in the following subsections will be performed by the subject, parent/LAR, or clinician as indicated in the description of the assessment. Changes must not be made to subject or parent/LAR completed scales after the visit has been completed. Care must be taken by the investigator or documented designee to explain fully the scale before the subject or parent/LAR completes the scale and responses should be reviewed by the investigator or designee during the study visit. Corrections can only be made to scales by the subject or parent/LAR during a study visit. In the event that paper forms are used and the subject/parent/LAR marks an answer in error, the entry may be corrected by drawing a single line through the error and initialing and dating the change. Assessments are to be performed according to the schedules provided in the Study Schedules.

Whenever possible, raters (including parent/LAR or caregiver, and the investigator or site designee) observing the subject's behavior should be consistent from week to week throughout the study.

7.2.1 Demographic and Other Baseline Characteristics

7.2.1.1 Demographics

The age at baseline, sex, ethnicity, and race will be recorded for each subject. Approximately 25% of all subjects will be aged 13 to 17 years. Approximately 25% of all subjects will be female.

7.2.1.2 Medical and Medication History

A complete medical history will be recorded at screening and will include a record of the subject's medication history and all clinically or medically relevant information regardless of how much time has elapsed since the date of diagnosis.

The medical and medication history should include, but will not be limited to the following:

- Ingestion of medication, including a lifetime history of psychoactive medications and recent use of any other medication received during the 30 days before screening and between screening and baseline
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, and any other diseases

- Complete psychiatric history
- Any nonpharmacological interventions for ADHD

7.2.1.3 Prior Stimulant Medicine Questionnaire

The PSMQ is a form designed to collect information on reasons for discontinuation of prior stimulant ADHD medications. This questionnaire will be administered at Study Part A screening only (Visit 1A). The PSMQ is provided in Appendix 4.

7.2.1.4 Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version

The K-SADS-PL is a semistructured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents using the criteria from the DSM-5. Probes and objective criteria are provided to rate individual symptoms. The primary diagnoses assessed with the K-SADS-PL include, but are not limited to the following:

- Major depression
- Dysthymia
- Mania
- Bipolar disorders
- Schizoaffective disorders
- Panic disorders
- Agoraphobia
- Separation anxiety disorder
- Avoidant disorder of childhood and adolescence
- Simple phobia
- Social phobia
- Overanxious disorder
- Generalized anxiety
- Obsessive compulsive disorder
- ADHD
- Conduct disorder
- Oppositional-defiant disorder

The K-SADS-PL will be administered at screening (Visit 1A) in Study Part A by a trained child and adolescent psychiatrist who is experienced with the scale and qualified to establish the aforementioned diagnoses. Any exception will require the approval of the sponsor or designee. Documentation of study training should be maintained in the site's files.

The K-SADS-PL will be administered by interviewing the subject and the subject's parent(s)/LAR(s) and achieving summary ratings, which include all sources of information (parent, child/adolescent, school, chart, and other). When administering the instrument to children, the subject's parent(s)/LAR(s) interview should be conducted first.

7.2.2 Safety Assessments

The name and address of each third-party vendor (eg, clinical laboratory) used in this study will be maintained in the investigator's and sponsor's files.

7.2.2.1 Physical Examination (Including Height and Weight)

A full physical examination will be performed by a qualified individual licensed in his/her respective country/state (eg, physician, physician assistant, or a nurse practitioner) at the visits identified in the Study Schedules.

A full physical examination will include an assessment of the following:

- General appearance
- Skin
- Head, eyes, ears, nose, and throat
- Spine/neck/thyroid
- Respiratory
- Cardiovascular
- Abdomen (including liver and kidneys)
- Musculoskeletal
- Neurological

An abbreviated physical examination will include a review of general appearance and respiratory and cardiovascular systems. The results of the clinical laboratory tests and physical examination must be reviewed by the investigator before subject enrollment.

Any abnormal physical examination findings will be documented in the subject's source documents and on the medical history eCRF with enough detail to permit detection in changes during the course of the study (eg, lower right extremity weakness +2/5 or erythematous macule 2 cm in diameter).

Any abnormalities or changes in intensity noticed upon the physical examination during the study will be documented in the subject's medical record. New or worsening physical examination findings that are considered clinically significant will be recorded as a TEAE (Section 7.1).

Height will be captured at the visits identified in the Study Schedules. A calibrated stadiometer should be used for all height measurements. Height should be measured in cm to the nearest 0.5 cm, with the subject standing without shoes on a flat surface and with chin parallel to the floor. The body should be straight but not rigid.

Weight will be captured at the visits identified in the Study Schedules. The same calibrated scale should be used for all weight measurements. Weight should be measured in kg without shoes and recorded to the nearest 0.1 kg. Bulky clothing items should be removed whenever possible to ensure that the most accurate weight is recorded.

For all visits indicated in the Study Schedules, the subject's BMI will be calculated using the following formula:

$$BMI = (\text{weight in kg} \times 10{,}000)/(\text{height in cm})^2$$

All height and weight measurements should be performed by the same site personnel (if possible) throughout the study.

7.2.2.2 Tanner Staging

The stage of puberty/sexual maturation will be evaluated for each subject according to Tanner staging (Marshall and Tanner 1969; Marshall and Tanner 1970). The Tanner stage for genitals (male, stages I-V), breasts (females, stages I-V), and pubic hair (both sexes, stages I-V) will be documented at the times specified in the Study Schedules. More information on can be found in Appendix 7.

Tanner staging will be self-assessed. Self-assessment in this study is defined as subjects or parents indicating which drawing of the scale corresponds to subject's sexual maturation stage at the time of the specific visit. For this purpose, site staff (the principal investigator or a designee) reads the guidance and the text corresponding to each drawing and asks the subject or parent to choose the applicable drawing (see Appendix 7). The response from the subject or the parent will be documented in the Tanner Staging Form by the site staff.

7.2.2.3 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if any TEAEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed consent is signed. (Please refer to Section 8, Adverse and Serious Adverse Events Assessment.)

7.2.2.4 Vital Signs

For all visits indicated in the Study Schedules, vital sign measurements will include body temperature (oral or tympanic), supine BP and pulse (after 5 minutes of rest), and standing BP and pulse (after 2 minutes of standing from supine). If the subject expresses the need to sit-down before the 2-minute time point is reached, then care must be taken to adequately support the subject while taking the standing BP measurement. Tilt tables should not be used to adjust the subject's position for the purpose of BP measurements.

Blood pressure should be determined by cuff (using the same method, the same arm, and the same position throughout the study). Any clinically significant deviations from baseline vital sign measurements in Study Parts A and B that are deemed clinically significant by the investigator will be recorded as an AE.

7.2.2.5 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the laboratory's normal procedures. Reference ranges will be supplied by the laboratory and used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance and indicating if the value(s) is/are clinically significant or not clinically significant. Abnormal clinical laboratory values that are unexpected or not explained by the subject's clinical condition may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

Biochemistry blood samples can be drawn with the subject in a fasting or non-fasting state. If fasting samples are drawn at the screening visit (Visit 1A), subsequent samples should be drawn with the subject in the same fasting status, at the visits indicated in the Study Schedules.

The following clinical laboratory assessments will be performed:

Biochemistry (approximately 7 mL blood sample)

Cholesterol	Total protein
Phosphorus	Aspartate transaminase
Sodium	Alanine transaminase
Potassium	Gamma glutamyl transferase
Bicarbonate	Uric acid
Calcium	Total bilirubin
Blood urea nitrogen (BUN)	Glucose
Creatinine	Lactate dehydrogenase
Albumin	Thyroid stimulating hormone
Magnesium	Thyroxine
Chloride	

Serum β-hCG for females of childbearing potential at screening visits only

Hematology (approximately 2 mL blood sample)	
Hemoglobin	Neutrophils
Hematocrit	Lymphocytes
Red blood cells (RBC)	Monocytes
Platelet count	Eosinophils
White blood cell (WBC) count – total and differential	Basophils
Urinalysis (approximately 10 mL urine sample)	
Specific gravity	Glucose
Blood[a]	Protein[a]
pH	Ketones
Bilirubin	

[a] If protein and/or blood are detected during urinalysis, then a microscopic examination will be conducted and the following parameters will be assessed: RBCs, WBCs, bacteria, casts

The investigator will assess any out-of-range clinical laboratory values (ie, high or low) for clinical significance on the original clinical laboratory report.

7.2.2.6 Urine Drug and Alcohol Screen

A urine drug and alcohol screen will be conducted at screening (Study Part A) by the central laboratory. Additional drug and alcohol screens may be performed at the investigator's discretion. Urine samples (approximately 10 mL) will be collected for this testing.

The following drugs/drug classes will be tested:

Cocaine	Cannabinoids
Phencyclidine	Benzodiazepines class
Barbiturates class	Opiates class
Methamphetamine	MDMA (3,4-methylenedioxy-methamphetamine; Ecstasy)
Methadone	Amphetamines
Ethanol	Oxycodone

For the subject to be eligible for the study, the results from the urine drug and alcohol screen must be negative at screening (Study Part A) (except for the subject's current ADHD psychostimulant, if applicable). The investigator and the medical monitor will evaluate the potential impact of a positive urine drug and alcohol screen result on the continued participation of the subject.

7.2.2.7 Pregnancy Test

A serum β-hCG pregnancy test will be performed on all FOCP at the screening visits (Study Parts A and B). A urine pregnancy test will be performed on all FOCP (Study Parts A and B), and at the time points indicated in the Study Schedules. Additional urine pregnancy tests may be performed at the investigator's discretion.

If at any time a subject has a positive pregnancy test result outside the study center, she should contact the study center immediately. If any subject tests positive for pregnancy at any time during the study, then the site staff should immediately contact the medical monitor/sponsor for guidance. Subjects receiving TAK-503 or TAK-503-matched placebo at a dose >3 mg QD must be tapered-off as advised by the medical monitor/sponsor. Any subject with a positive pregnancy test result will be discontinued from the study and complete the procedures indicated for the ET visits.

7.2.2.8 Electrocardiogram

A minimum of 3 ECGs will be collected at baseline with approximately 5 minutes between each measurement to ensure that appropriate baseline intervals are established. The subject will be assessed while in a quiet state (after 5 minutes of rest) in the supine position. Subject eligibility will be based on the assessment of the ECG from the central reader (normal/abnormal) and the determination of the clinical significance by the investigator, in consultation with the medical monitor if the ECG is an abnormal alert value per the central reader.

The HR, PR interval, QRS interval, and QT interval will be measured from all ECGs and the QTcB and QTcF will be calculated.

All 12-lead ECGs will be performed using the central ECG provider's equipment and sent to the central ECG provider laboratory electronically. The name and address of the central ECG laboratory will be maintained in the investigator's files at each site and in the Trial Master File. The central ECG provider will send an initial report within 72 hours and a final report, including the ECG analysis, thereafter. The site will be required to print at least 1 copy of the original ECG tracing. The original ECG(s) and the final report provided by the central ECG laboratory should be signed by the investigator and maintained at the site with source documents. The investigator will be responsible for determining the clinical significance of each ECG (after review of both the ECG and the report provided by the central ECG laboratory) and for documenting any findings in the appropriate eCRF field.

No ECG should be deleted by site personnel. All ECGs must be transmitted to the central ECG laboratory provider regardless of the quality, result, or number of ECGs taken at a respective visit.

7.2.2.9 The Columbia-Suicide Severity Rating Scale

The C-SSRS is the prospective counterpart to the Columbia Classification Algorithm for Suicide Assessment suicidality categorization system. Through a semi-structured interview format, the occurrence, severity, and frequency of suicide-related thoughts and behaviors are captured during an assessment period (Posner 2007). The interview includes definitions and suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior occurred. A maximum of 19 items will be completed as follows: 7 items are required, a potential 10 additional items will be completed upon a positive response to a required item, and 2 items completed if suicide/suicide-like behavior is observed during the interview. The C-SSRS uses dichotomous scales (ie, yes or no), Likert scales, and text or narrative to further describe thoughts or behaviors.

7.2.2.10 Suitability of the Subject to Remain in the Study

Following completion of each C-SSRS interview, the investigator or a medically qualified designee should assess whether it remains in the best interest of the subject to continue in the study and that it is safe for the subject to do so. As part of the assessment of the subject's suitability to remain in the study, the investigator should assess the subject's current potential for suicide, suicidal ideation, self-harm or harm to others. The investigator should make this assessment by conducting a clinical interview with the subject and by reviewing all other relevant sources available, including results of the C-SSRS. The investigator should also ensure that there is appropriate documentation of this suitability assessment in the subject's source notes. As part of this assessment, if appropriate, the investigator should discuss risk factors for suicide with the subject. Where a subject has suffered an accidental injury, the investigator should ensure that this was a true accidental injury, rather than an episode of self-harming or a suicide attempt.

The subject's source notes should clearly document that the assessment of continued suitability, including an assessment of the subject's current potential risk of suicide, suicidal ideation, feelings of hopelessness, drug use, self-harm, or harm to others, has taken place and should contain the decision on whether the subject is suitable to continue in the study.

The investigator should pay particular attention to a positive score for questions 4 and/or 5 on the C-SSRS or any suicidal behavior. If a subject answered 'yes' to either of these questions, they must undergo further evaluation to ensure that they are not in any way at risk. This should be discussed with the Medical Monitor, and the registering of an AE considered. The evaluation and decision should be clearly documented in the subject's source notes.

As part of routine good clinical care, subjects will be provided with 24-hour emergency contact details in case of an emergency situation where the subject feels that they are acutely at risk. In addition, subjects who are recruited into the study will be advised of the location of their closest emergency room.

7.2.2.11 Brief Psychiatric Rating Scale for Children

The BPRS-C-21 was developed to provide a concise symptom profile of psychiatric problems that can occur during childhood (Hughes et al. 2001; Hughes 2008; Overall and Pfefferbaum 1982). The 21 items of the clinician-rated BPRS-C are grouped into the following 7 scales:

- Behavioral Problems
- Depression
- Thinking Disturbance
- Psychomotor Excitation
- Withdrawal
- Anxiety
- Organicity

Each item of the 21 items is clinician-graded using the following 7-point severity Likert-scale:

- 0=not present
- 1=very mild
- 2=mild
- 3=moderate
- 4=moderately severe
- 5=severe
- 6=extremely severe

To provide accurate ratings, a licensed clinician will collect information from medical records, direct observation, school reports, and clinical interviews of parents/caregivers, other family members, and the subject. The clinician will aggregate the accumulated data to provide a blended rating of an average score over a defined time period. A licensed clinician is defined as a mental health professional (MD, PhD, or DO) who has been trained to assess children and adolescents using basic measurement principles.

7.2.2.12 Pediatric Daytime Sleepiness Scale

The PDSS is a self-reported assessment of daytime sleepiness in children (Drake et al. 2003). The PDSS questionnaire was designed to be easy to administer, score, and interpret. Sleepiness-related questions are based on previous research of situations that can be sensitive to sleep loss in this age group (eg, trouble getting out of bed in the morning, somnolence during class).

The 8 questions are scored on Likert-scale from 0 to 4 (never=0; seldom=1; sometimes=2; frequently=3; always=4). The total score on the PDSS can range from 0 (never sleepy) to 32 (always sleepy).

Subjects will complete the PDSS questionnaire at the study site at the time points indicated in the Study Schedules with assistance from the site staff if necessary.

7.2.2.13 The Udvalg for Kliniske Undersøgelser Side Effect Rating Scale

Designed for use in both clinical trials and routine clinical practice, the UKU rating scale was developed for clinicians to assess side effects of psychopharmacological medications based on patient interviews and other relevant source information (Lingjaerde et al. 1987). Adverse events occurring within the 3 days before the interview are rated and described independently of drug causality. For each item recorded, the probability of the causal relationship (or lack of it) to the medication in question is indicated in a separate column, making this scale useful for subsequent course of action.

The scale was developed initially to assess effects of antipsychotic medication and many of the subscale items, such as those related to movement disorders, are not relevant to this study. For this study, only the following items relevant to the established safety profile of TAK-503 will be queried: Asthenia /Lassitude /Increased Fatigability, Sleepiness/Sedation, Increased Duration of Sleep, and Orthostatic Dizziness.

7.2.2.14 The Cambridge Automated Neuropsychological Test Battery

The neurocognitive function effects of TAK-503 on adolescents and children diagnosed with ADHD will be evaluated using the CANTAB cognitive assessments.

Tasks selected from the CANTAB suite are presented in Table 7.

Table 7 Selected Tasks from CANTAB to Assess Neurocognition

Domain	Task
Memory	**Delayed Matching to Sample**: The DMS task tests both simultaneous matching and short-term visual memory. The subject is shown a complex visual pattern (the sample) and after a brief delay, 4 similar patterns. The subject must identify the pattern that matches the sample.
Attention	**Reaction time**: The RTI task involves elements of decision-making and attention as measured by choice accuracy (Jäkälä et al. 1999) as well as motor responses, by measuring motor and mental response speeds, and assesses movement time, reaction time, response accuracy, and impulsivity.
	Rapid Visual Information Processing: The RVP task measures the ability to sustain attention over time and is a sensitive measure of frontal-parietal function. In this task, single digits appear in a pseudo--random order at a rate of 100 digits per minute in a box at the center of the screen. Subjects are to detect a 3-digit target sequence (eg, 2-4-6) and respond by pressing a button at the bottom of the screen when the final number of the sequence appears on the screen.
Executive Function	**Spatial Working Memory**: The ability to retain spatial information and manipulate remembered items in working memory are measured with the SWM task. The task is self-ordered and assesses the individual's ability to strategize heuristically. The test is a sensitive measure of frontal lobe and executive dysfunction
	Stop Signal Task: The SST measures response inhibition. The subject must respond to an arrow stimulus by touching either of 2 choices depending on the direction the arrow points. If an audio tone is present, the subject is not to respond.

CANTAB=Cambridge Automated Neuropsychological Test Battery; DMS=Delayed Matching to Sample; RTI=Reaction Time/5-Choice Reaction Time; RVP=Rapid Visual Information Processing; SST=Stop Signal Task; SWM=Spatial Working Memory

These cognitive tasks are accepted and validated methods for assessing potentially deleterious and/or beneficial effects of psychopharmacologics in psychiatric disorders, including ADHD (Coghill et al. 2014).

7.2.3 Efficacy Assessments

Efficacy will be evaluated by performing the assessments described in the following subsections and according to the times specified in the Study Schedules.

7.2.3.1 The ADHD-Rating Scale-5

The ADHD-RS-5 (DuPaul et al. 2016) is used widely by mental health, educational, and medical practitioners in screening, diagnosis, and treatment evaluation to determine the frequency and severity of ADHD symptoms and impairments in children and adolescents.

The ADHD-RS-5 is based on the diagnostic criteria for ADHD as described in the DSM-5 and consists of 2 symptom subscales, inattention and hyperactivity-impulsivity, each with 9 items and a total scale of 18 items. Each item in the subscale is scored with a value ranging from 0 (no symptoms) to 3 (severe symptoms). The total score can range from 0 to 54.

The following 6 domains of impairment common among children and adolescents with ADHD are also assessed with the ADHD-RS-5:

- Relationships with significant others (such as family members and teachers)
- Relationships with peers
- Academic functioning
- Behavioral functioning
- Homework performance
- Self-esteem

The ADHD-RS-5 will be completed by a licensed clinician who is familiar with the scale, including physicians (MD or DO) or licensed psychologists (PhD). Any exception will require the approval of the sponsor or designee.

7.2.3.2 Clinical Global Impressions

The CGI scale (Guy 1976) will be used to evaluate the severity of mental illness over time. The CGI-S will be administered to assess the severity of mental illness at baseline. During subsequent visits, the CGI-I will be administered to assess any improvement in symptoms and to guide the clinician on dosing adjustments. The CGI-S is scored on a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill subjects). The CGI-I is also scored on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

The CGI-I and CGI-S will be completed by the investigator or delegated sub-investigator who is a licensed clinician (MD, DO, or licensed psychologist with a PhD).

7.2.3.3 Child Health and Illness Profile – Child Edition: Parent Report Form

The Parent Report Form of the Child Health and Illness Profile – Child Edition (CHIP-CE:PRF) will be administered to provide information on self–esteem and school functioning in pediatric subjects diagnosed with ADHD. As reported by a parent or caregiver, a child's functioning and well-being as well as emotional, physical, and behavioral symptoms will be captured with this generic scale that is useful for monitoring symptoms and identifying improvements. The 5 domains and 12 subdomains covered in the 76 items comprising the CHIP-CE:PRE are presented in Table 8.

Table 8 Domains and Subdomains of the CHIP – CE:PRF

Domain	Subdomain
Satisfaction: with health and self	Satisfaction with health (7 items)
	Satisfaction with self (4 items)
Comfort: physical and emotional symptoms and activity restrictions due to illness	Physical comfort (9 items)
	Emotional comfort (9 items)
	Restricted activity (4 items)
Resilience: behaviors and family involvement in activities likely to enhance health	Family involvement (8 items)
	Social problem-solving (5 items)
	Physical activity (6 items)
Risk avoidance: behaviors that if not avoided are likely to pose risks to health	Individual risk avoidance (4 items)
	Threats to achievement (10 items)
Achievement: developmentally appropriate role functioning in school and with peers	Academic performance (5 items)
	Peer relations (5 items)

CHIP-CE:PRF=Child Health and Illness Profile-Child Edition: Parent Report Form

The effect of TAK-503 on all subdomains will be summarized, including the sub-domain satisfaction with self, using parent rated self-esteem items. Parents will assess each item in a 5-point response format; higher scores indicate better health-related quality of life. The CHIP-CE is psychometrically robust over time in terms of consistency and structure (Schacht et al. 2011) and has been shown to be reliable and valid in socioeconomically and ethnically diverse populations in Spain (Rajmil et al. 2004) and the United States (Rajmil et al. 2004; Riley et al. 2004).

7.2.3.4 Conners 3 Parent Short Form

Subjects enrolled after Amendment 5 will be assessed with the C3PS (Conners 2008). This assessment is used to better understand certain behavioral, social, and academic issues in children between 6 and 18 years old. The scale aids in diagnosis by helping to delineate the child's issues as well as in what settings these issues are most troublesome. The C3PS has the following subscales: Inattention, Hyperactivity/Impulsivity, Learning Problems, Executive Functioning, Defiance/Aggression, Peer Relation and Validity Scores (Positive Impression and Negative Impression).

In addition to the Total Score, analysis of Learning Problems subscale and Executive Functioning subscale data will be conducted as an alternative approach to obtain schoolwork performance-related data following removal of the APRS as a secondary efficacy endpoint. All the items included in the Learning Problems subscale and Executive Functioning subscale either directly or indirectly evaluate performance related to schoolwork.

In the current environment and for the foreseeable future, remote schooling either in part or in full will be prevalent in many areas. Parents/LARs will have the opportunity to very closely observe the performance of their children with schoolwork. Therefore, an assessment of schoolwork performance by a parent(s)/LAR(s) will be highly appropriate to obtain schoolwork performance-related data.

The analyses of Conners 3 Parent Rating Scale data will be conducted for the Total Score that includes all subscales, as well as the scores for the Learning Problems and Executive Functioning subscales individually.

The CP3S will be completed by a parent/LAR who is very familiar with the subject.

7.2.4 Volume of Blood to Be Drawn from Each Subject

As shown in Table 9, approximately 54 mL of blood is expected to be withdrawn from subjects randomized in Study Parts A and B for subjects enrolled under protocol amendment 7. For subjects enrolled under prior versions of the protocol, approximately 72 mL of blood is expected to be withdrawn from subjects randomized in Study Parts A and B.

Table 9 Volume of Blood to Be Drawn from Subjects Randomized to Active IMP Treatments in Study Part A and Part B

Assessment		Sample Volume	Number of Samples in Part A	Number of Samples in Part B	Total Volume
Safety:	Biochemistry and β-hCG[a]	7 mL	4[b]	2[b]	42 mL
	Hematology	2 mL	4[b]	2[b]	12 mL
Total volume extracted from each subject		9 mL			54 mL

β-hCG=beta-human chorionic gonadotropin

[a] β-hCG will be tested only in females.

[b] An additional sample will be required if the baseline visit occurs more than 35 days after screening (applies to Study Parts A and B) or as requested by the investigator due to safety reason.

The above amount of blood quoted for each assessment is an estimate and can vary according to the instructions provided by the manufacturer or laboratory for an individual assessment.

7.3 Remote Visits and Assessments

If a subject is unable to participate in a visit on site due to unavoidable dire circumstances (eg, a widespread disease outbreak such as the COVID-19 pandemic or natural disaster), remote visits may be conducted by phone (eg, collection of AEs and monitoring), video conferencing (telehealth/telemedicine), or qualified site staff or qualified designees visiting the participant's residence. Local visits and telemedicine must comply with local, state, and national laws.

The principal investigator is expected to evaluate the impact to the safety of the study participants and site personnel for subjects to continue. In evaluating such requests, the sponsor or designee will give the highest priority to the safety and welfare of the subjects. Subjects must be willing and able to continue taking study medication and remain compliant with the protocol.

Assessments may be performed remotely when necessary. For home healthcare visits, collection of clinical laboratory samples (blood specimen collection or other diagnostic tests) may be performed by the investigator, qualified site staff, or qualified designees who can visit the trial participant's residence. Such exceptional circumstances require specifications to be documented in study records.

During the dose maintenance phase, subjects may participate in up to 2 consecutive remote visits. Note that this is not a cumulative limit on the total number of remote visits. A subject may have more than 2 remote visits throughout the course of the study, but cannot have 3 remote visits in a row (unless required due to unavoidable dire circumstances, eg, a widespread disease outbreak such as the COVID-19 pandemic or natural disaster).

The type of alternative visit must be recorded in the eCRF. Data collected with alternative methods may be handled differently in the final data analyses. This will be documented in the statistical analysis plan (SAP).

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An **AE** is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.4. This includes events occurring during the screening period of the study, regardless of whether or not IMP was administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the AE pages of the source documents and in the appropriate eCRF field. In addition to untoward AEs, unexpected benefits outside the IMP indication should also be captured on the AE eCRF field.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization is achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations will be performed so that resolution of the event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of IMP, must be recorded as new AEs (for example, if a subject has mild intermittent dyspepsia before IMP dosing, but the dyspepsia becomes severe and more frequent after first dose of IMP has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate eCRF field).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to IMP for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the IMP. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related." Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the IMP and the occurrence of the AE, then the AE should be considered "related." The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the IMP is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the IMP and the event.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the eCRF. Outcomes are as follows:

- Fatal
- Not recovered/Not resolved
- Recovered/Resolved
- Recovered/Resolved with sequelae
- Recovering/Resolving
- Unknown

8.1.4 Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

8.1.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during treatment with the IMP, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value.

When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the IMP, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment periods, there are abnormal clinical laboratory, vital sign, or ECG values that were not present at the start of study treatment, then further investigations should be performed until the value(s) return(s) to within the reference range or until a plausible explanation (eg, concomitant disease) has been found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory, vital sign, or ECG parameter is clinically significant and therefore represents an AE.

8.1.6 Pregnancy

All pregnancies are to be reported from the time that informed consent was signed until the defined follow-up period stated in Section 7.1.4.

Any report of pregnancy in a female subject or in a female partner of a male subject must be reported within 24 hours to the sponsor's Global Drug Safety Department using the "Pregnancy Report Form." A copy of the "Pregnancy Report Form" (and any applicable follow-up reports) will also be sent to the CRO/sponsor medical monitor. Any female subject who becomes pregnant during the study must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days and 1 year postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the "Safety Report Form". Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets the seriousness criteria, then it must be reported as an SAE using the "Safety Report Form" as well as the "Pregnancy Report Form." The test date of the first positive serum/urine β-hCG test or ultrasound result will determine the pregnancy onset date.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Any abuse, misuse, overdose, or medication error (AMOME) (as defined below) must be reported to the sponsor using the AMOME reporting procedure regardless if an AE/SAE resulted, as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of AMOMEs unless an SAE occurs due to the event.

The categories below are not mutually exclusive as the event can meet more than 1 category.

Abuse – Persistent or sporadic intentional intake of IMP when used for a nonmedical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society

Misuse – Intentional use of IMP at any dose that is not as directed or indicated (Note: this includes a situation where the IMP is not used as directed at the dose prescribed by the protocol.)

Overdose – Intentional or unintentional intake of an IMP dose that exceeds in children aged 6 to 12 years, the specified total daily dose of 4 mg TAK-503 and in adolescents aged 13 to 17 years exceeds the maximum allowable dose by baseline weight group as follows:

- For children weighing 25.0 kg or more, the maximum TAK-503 dose is 4 mg QD
- For adolescents weighing 34.0 to 41.4 kg, the maximum TAK-503 dose is 4 mg QD
- For adolescents weighing 41.5 to 49.4 kg, the maximum TAK-503 dose is 5 mg QD
- For adolescents weighing 49.5 to 58.4 kg, the maximum TAK-503 dose is 6 mg QD
- For adolescents weighing 58.5 to 91.0 kg, the maximum TAK-503 dose is 7 mg QD

Medication Error – An error made in prescribing, dispensing, administering, and/or using an IMP. For clinical studies, the medication errors that are reportable to the sponsor only are specified as follows:

- Cases of subjects missing IMP doses are not considered reportable as medication errors.
- Medication errors should be collected/reported for all products under investigation.
- The administration and/or use of the unassigned treatment is/are always reportable as a medication error.
- The administration and/or use of an expired IMP should be considered as a reportable medication error.

The administration of IMP that has been provided to pediatric subjects should be supervised by the parent/LAR/caregiver.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the Intuniv IB, which the sponsor has provided to all investigators under a separate cover.

The reference for safety information for the atomoxetine comparator product in this study is the atomoxetine hydrochloride SmPC, which the sponsor has provided to all investigators under a separate cover.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the sponsor's Global Drug Safety Department and the CRO/sponsor medical monitor within 24 hours of first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of AMOMEs (see Section 8.1.7) unless an SAE results.

For reporting SAEs, the investigator must complete, sign, and date the "Safety Report Form" and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or email the form to the sponsor's Global Drug Safety Department. For reporting AMOMEs, the investigator must complete, sign, and date the "Special Situation Report Form" via the same method as reporting the SAEs. A copy of the "Safety Report Form" (and any applicable follow-up reports) will also be sent to the CRO/sponsor medical monitor.

8.2.3 Serious Adverse Event Definition

An **SAE** is any untoward medical occurrence (whether considered to be related to IMP or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.4 and must be reported to the sponsor's Global Drug Safety Department and the CRO/sponsor medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the IMP and discovered by the investigator at any interval after the study has completed must be reported to the sponsor's Global Drug Safety Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the date the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another IMP action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the IMP should be recorded as "dose not changed" or "not applicable" (if the subject never received IMP). The IMP action of "withdrawn" should not be selected solely as a result of the subject's death.

8.2.7 Safety Reporting to Investigators, Institutional Review Boards or Independent Ethics Committees, and Regulatory Authorities

The sponsor will be responsible for identifying and reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the specific regulatory authority(ies), investigators, and Institutional Review Boards (IRBs) and Independent Ethics Committee (IECs) in accordance with national regulations in the countries where the study is conducted. Timelines and format of reporting SUSARs to Eudravigilance are as follows:

- SUSARs will be submitted to Eudravigilance Clinical Trial Module in E2B
- Initial Fatal/or Life-Threatening SUSARs will be reported in 7 days and all other SUSARs will be reported in 15 days.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the eCRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO's data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Data Handling Considerations

Data that may potentially unblind the treatment assignment in Part A (ie, IMP serum concentrations, treatment allocation, and IMP preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

9.4 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The SAP will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, IMP exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

Statistical issues related to the impact of the COVID-19 pandemic or other unavoidable dire circumstances will be more fully developed in the SAP. Unless otherwise specified, the primary analyses will include all subjects with usable data in the respective analysis sets, ie, FAS, PPS, and safety. Subjects identified as being impacted by the COVID-19 pandemic will be classified prior to treatment unblinding. Sensitivity analyses focused on the primary endpoint and possibly secondary efficacy endpoints, as well as other secondary CANTAB endpoints, will be performed to characterize the potential impact of the pandemic on interpretation of the data.

The SAP will be finalized before unblinding to preserve the integrity of the statistical analysis and study conclusions.

All statistical analyses, unless otherwise specified, will be performed using SAS® version 9.3 or later (SAS Institute, Cary, NC 27513).

9.5 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

No interim analysis, adaptive design, or data monitoring committee is planned for this study.

9.6 Sample Size Calculation and Power Considerations

In this safety study, a descriptive analysis of TAK-503 and atomoxetine will be performed after 12 months of double-blinded treatment using results from the CANTAB RTI task. The effect of TAK-503 on cognition will be assessed and interpreted on the totality of the data.

The sample size was estimated using the assumed difference of 0 msec with a noninferiority margin of 30 msec and a common standard deviation of 63.4 for the comparison between TAK-503 and atomoxetine at Week 49A on the RTI in Study Part A. The assumed common standard deviation on RTI is based on a prior study SPD503-206: a randomized, double-blinded, placebo-controlled efficacy study of TAK-503 in children and adolescents with ADHD. The assumed margin of 30 msec is close to the value (29.3 msec) of change from baseline in reported results from an adolescent study with atomoxetine (Shang and Gau 2012). The assumed margin was used for sample size only and will not be applied in the noninferiority evaluation.

A total of 216 subjects, 72 subjects per arm, will be required to provide 80% power for a 2-sided 95% CI. Expecting a nonevaluable rate of 25%, including postrandomization dropout, during the double-blinded period, the randomization target has been set to 288 subjects total or 96 subjects per treatment arm.

As of Amendment 7, TAK-503 and atomoxetine will be evaluated after 12 months of double-blinded treatment using results from the CANTAB RTI task via the MMRM; however, inferential hypothesis testing via the non-inferiority framework at the Week 49A timepoint will no longer be performed due to challenges with retaining an evaluable sample size that would allow for sufficient power for this comparison. Superiority to placebo comparisons of TAK-503 and atomoxetine at the 18-week timepoint, separately, will still be performed, as in the original protocol.

The number of subjects projected to participate in Study Part B is 120, which will be sufficient to have at least 90% power to obtain a 95% confidence interval for the change from baseline RTI value that excludes the value 0, given the assumed response values for TAK-503 based on Study SPD503-206 (mean=20.7, SD=63.11).

9.7 Study Analysis Set

Study analysis population sets are defined as follows:

- The randomized set will be defined as all randomized subjects in Study Part A. Any subject who is not randomized will be considered a screen failure.
- The double-blind safety set will be defined as all randomized subjects in Study Part A who receive ≥1 IMP dose. The double-blind safety set will be used for safety analysis (except for CANTAB domains) for Study Part A.
- The open-label safety set will be defined as all subjects who receive ≥1 dose of TAK-503 in Study Part B. All safety and efficacy presentations for Study Part B will be based on the open-label safety set.
- The full analysis set (FAS) will be defined as all subjects in the double-blind safety set with ≥1 postbaseline CANTAB assessments.
- The per-protocol set (PPS) will be defined as all subjects in the FAS who complete the study and were deemed protocol-compliant. To be protocol-compliant, a subject will not have had any significant protocol deviations during the study that could affect the assessment of the primary safety endpoint, the CANTAB RTI task.

9.8 Study Analyses

The analyses of the safety CANTAB domains for Study Part A will be based on the FAS and PPS. The analyses of efficacy endpoints will be based on the FAS only. Other safety analyses for Study Part A will be based on the safety set; the safety and efficacy analysis for Study Part B will be based on the open-label safety set.

The analyses for the primary safety endpoint and other secondary CANTAB endpoints will be performed using the MMRM to handle potential missing data.

If the severity is missing for an AE during treatment, then a severity of “Severe” will be assigned. If the relationship to IP is missing for an AE starting during treatment, a causality of “Related” will be assigned. The imputed values for severity and relationship will be used for AE summaries.

The APRS assessment was removed as a secondary efficacy endpoint with Protocol Amendment 5, due in large part to the COVID-19 pandemic, since many subjects enrolled prior to Amendment 5 are missing APRS data. APRS data that has been collected will be summarized descriptively (total and subscale scores) as well as presented in a listing. Unless data permits, no inferential analysis of this endpoint will be performed. Missing APRS assessments will not be a reason for exclusion from any analysis set.

In addition, these endpoints will be summarized using region (Europe vs. US) as a subgroup. As stratum size for a few countries will likely be very small, region will be used as a factor for any subgroup analysis of these endpoints. If data permit, country level subgrouping may also be investigated in a similar manner.

The SAP will provide additional description of how missing, unused, and spurious data will be addressed. The SAP will be finalized before unblinding to preserve the integrity of the statistical analysis and study conclusion.

9.8.1 Study Part A: Double-blinded Evaluation

The primary safety endpoint will be the change from baseline in the CANTAB RTI task. The endpoint will be analyzed over the FAS and PPS with a MMRM with treatment arm, visit, sex (male or female), age group (6 to 12 years or 13 to 17 years), region (Europe or US) and the interaction of treatment with visit as factors, the corresponding baseline value as a covariate, and the interaction between baseline value and visit adjusted in the model. The analysis will be done for subjects who complete 18 weeks (Week 18A) and for subjects (TAK-503 and atomoxetine treatment arms only) who complete Study Part A Week 49A. The least squares (LS) mean difference for each treatment arm will be calculated with the 95% confidence interval (CI) reported.

As suggested by European Medicines Agency (EMA), using data up to 18 weeks, the superiority to placebo comparisons including TAK-503 and atomoxetine, separately, will be performed using MMRM as specified for the primary endpoint. Statistical tests will be conducted at the nominal 2-sided 0.05 level without adjustment for multiplicity. If TAK-503 is superior to placebo, then a negative impact on cognition can be excluded. If atomoxetine is superior to placebo, then assay sensitivity has been demonstrated.

Results for the TAK-503 and atomoxetine comparison at Week 49A (Visit 14A), which were collected for patients who were enrolled prior to the implementation of Protocol Amendment 7, will be evaluated in a descriptive fashion, without the performance of inferential hypothesis testing.

Similarly, the other secondary CANTAB safety endpoints will be analyzed in the same manner as the primary CANTAB safety endpoint. CANTAB results for all parameters will be evaluated together for totality of the CANTAB data.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by treatment arm across system organ class and preferred term. Treatment-emergent AEs leading to withdrawals and SAEs will be summarized similarly. To account for differences in expected exposure durations between placebo and active arms, time adjusted event rates (per 100 years) will be presented in the overall summary tables, as well.

Other safety data will be descriptively summarized by period, with details provided in the SAP.

The efficacy measurement of ADHD-RS-5 will be assessed based on the FAS using the same analysis method (MMRM) as the primary safety endpoint. The CGI-I will be summarized.

The raw scores for each of the 5 domains, 12 subdomains, and the global score of the CHIP-CE:PRF will be summarized by treatment arm.

The C3PS Total Score and scores for the Learning Problem and Executive Functioning subscales will be derived and summarized. These scores will be assessed based on the FAS using the same analysis method (MMRM) as the primary safety endpoint.

9.8.2 Study Part B: Open-label Evaluation

Safety data for Study Part B will be descriptively summarized. Z-scores for CANTAB measures will be calculated using age- and gender-specific normative data if available. Both the values for observed and z-scores will be summarized descriptively.

Efficacy and other endpoints will be summarized by time point.

9.9 Study Endpoints

9.9.1 Safety Endpoints

- The primary safety endpoint will be the change from baseline in the CANTAB RTI task.
- Secondary safety endpoints will include the following:
    - CANTAB tasks: RVP, SWM between errors, DMS, and SST
    - Tanner stage, weight, height, BMI
    - Vital signs (BP and pulse) and ECG results, and overall safety events
    - BPRS-C total score and scales for Depression, Anxiety, Psychomotor Excitation, Behavior Problems, Withdrawal, Thinking Disturbance, and Organicity
    - C-SSRS
    - Specified UKU side effect rating scale items: Asthenia/Lassitude/Increased Fatigability, Sleepiness/Sedation, Increased Duration of Sleep, and Orthostatic Dizziness
    - PDSS

9.9.2 Efficacy Endpoints

A primary efficacy endpoint is not applicable for this PASS.

Secondary efficacy endpoints will include the following:

- ADHD-RS-5 total score and subscale scores for hyperactivity/impulsivity and inattention domains
- CGI-I, calculated from CGI-S

- CHIP-CE:PRF
- C3PS total score and subscale score for Learning Problems and Executive Functioning subscale scores (for subjects enrolled with or after Amendment 5)

Other endpoints:

- APRS (for subjects enrolled before Amendment 5 who have a baseline APRS assessment in Part A)

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study will be conducted in accordance with this protocol, the ICH Guideline for Good Clinical Practice E6 (Integrated Addendum to ICH E6[R1]: Guideline for Good Clinical Practice E6[R2] Current Step 4 version, 9 November 2016), Title 21 of the US Code of Federal Regulations (US CFR), the EU Clinical Trial Regulation (EU-CTR, 536/2014), and applicable national and local regulatory requirements. The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6[R2] (2016) and any updates, EU-CTR, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

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

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor will ensure that suitable clinical study insurance coverage is in place before the start of the study. An insurance certificate will be supplied to the investigator as necessary.

10.1.3 Public Posting of Study Information

The sponsor will be responsible for posting appropriate study information on applicable websites. Information included in clinical study registries can include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP.

This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for nonpediatric studies as per guidance. The sponsor will provide the ECs with a copy of the same summary.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

The sponsor will make an end-of-study declaration to the relevant competent authority as required by EU-CTR.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6[R2] (2016) and any updates, EU-CTR, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators will be provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator will be appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report will be documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator will be responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators will be required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all IMP, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information will be provided during all study periods, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Case report forms will be supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

All data sent to the sponsor must be endorsed by the investigator.

The CRA/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

All data sent to the sponsor must be endorsed by the investigator.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, original clinical laboratory reports, and histology and pathology reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities (including those from a third country); the IRB/EC; and auditors to inspect facilities or perform trial related monitoring and to have direct access to original source records relevant to this study, regardless of media. Additionally, investigators

must promptly notify the sponsor of any trial related regulatory agency inspections and will be expected to provide the sponsor with a copy of the inspection report.

The CRA/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays, etc.). Non-study site personnel will not disclose any personal information or personal medical information.

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US Food and Drug Administration (FDA), EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator will be required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information will be collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in IMP; any significant equity interest in the sponsor or subsidiaries as defined in Section 21 of the FDA Code of Federal Regulations 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written and/or electronic (if applicable) informed consent and assent from all study subjects prior to any study-related procedures including screening assessments. All consent and assent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study

involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities.

A copy of the informed consent and assent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

At the principal investigator's discretion, informed consent from a potential or current trial participant may be obtained remotely via electronic consent [(e)consent]. Subjects consenting via (e)consent, where this is available, will electronically sign the consent form (paper consent will be used if required by local regulations). Such exceptional instances should be duly justified and documented in the study records.

The (e)consent provides the same information as in written paper consent, but in an electronic format that may include multimedia components. It is important to note that (e)consent is not meant to replace the important discussion between the participant and site staff. As with traditional consenting, the site will continue to own the consenting process.

A copy of the informed consent document signed by the investigator (and potential witness) should be placed in the subject's trial source documents, with a notation by the investigator of how the consent was obtained (eg, telephone or video call).

Subjects must be reconsented if they reach the age of legal responsibility during the study, based on applicable local and national laws.

Within the source documents, site personnel should document instruction of and understanding by the parent/legally authorized representative/caregiver of the safe, responsible storage and administration of IMP to the study subject.

The principal investigator provides the sponsor with a copy of the consent form (and assent form where applicable) that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

The IMP and IMP supplies will not be released until the CRO has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; this can be done by the sponsor or investigator for sites within the EU, or for multicenter studies, it can be done by the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.3.3 Serious Breach of Protocol for EU Clinical Trial Regulation

The sponsor will notify the concerned EU Member States of a serious breach of EU-CTR or the applicable protocol version through the EU portal not later than 7 days after becoming aware of the breach. In this instance a "serious breach" is one likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of trial data. All parties involved in the conduct of the clinical trial must immediately report any events they encounter that might meet the definition of a serious breach. Reporting by sites will be to the contact point designated in the Site Manual; reporting by vendors will be to the contact point provided by the sponsor.

10.4 Privacy and Confidentiality

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market TAK-503; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and month and year of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

If a serious data breach affecting personal data is detected, the sponsor or its designee and the investigator (as applicable) will take appropriate corrective and preventive actions in response. These actions will be documented, and the relevant regulatory agency(ies) will be notified as appropriate. Where appropriate, the relevant individuals materially affected by the breach would also be notified; in the case of study participants, this would be done through the investigator.

Takeda applies certain measures to protect participants' personal data and prevent data breaches, detailed in a separate document (Compliance with National Requirements on Data Protection).

10.5 Study Results/Publication Policy

The sponsor will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, the sponsor adheres to external guidelines (eg, Good Publication Practices) when forming a publication steering committee, which is done for large, multicenter phase 2 to 4 and certain other studies as determined by the sponsor. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to the sponsor's products or projects must undergo appropriate technical and intellectual property review, with sponsor agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results.

Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by the sponsor, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

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Appendix 1 Table of Evaluation Scales

Instruments and scales used in protocol SPD503-401 include the following:

Scale/Assessment	Versioning/Date (if applicable)
Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition	See Appendix 2
ADHD-Rating Scale-5 for Children and Adolescents	2016
Clinical Global Impression	Severity (baseline of Study Parts A and B only)/1976
	Improvement/1976
Columbia-Suicide Severity Rating Scale	Baseline/Screening, 1/14/2009
	Since Last Visit, 1/14/2009
Brief Psychiatric Rating Scale for Children	See Appendix 3
Pediatric Daytime Sleepiness Scale	2003
Udvalg for Kliniske Undersøgelser Side Effect Rating Scale	1987
Tanner staging	See Appendix 7
Academic Performance Rating Scale[a]	1991
Child Health and Illness Profile: Child Edition: Parent Report Form	2004
Conners 3 Parent Short Form[b]	
Prior Stimulant Medication Questionnaire	

[a] For subjects enrolled under Appendix 4 and earlier who had a baseline Academic Performance Rating Scale assessment in Part A.

[b] For subjects enrolled under Appendix 5.

All scales/assessments will be sent to the site separately. Scales/assessments updated during the study will be documented in the table as applicable and the updated scale/assessment will be provided to the site.

Raw data will be stored in the archives at the CRO.

Appendix 2 DSM-5 criteria for Attention Deficit/Hyperactivity Disorder

A. Either (1) or (2):

(1) Six (or more) of the following symptoms of **inattention** have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

Inattention

a) often fails to give close attention to details or makes careless mistakes in schoolwork, work or other activities

b) often has difficulty sustaining attention in tasks or play activities

c) often does not seem to listen when spoken to directly

d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)

e) often has difficulty organizing tasks and activities

f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)

g) often loses things necessary for tasks or activities (eg, toys, school assignments, pencils, books, or tools)

h) is often easily distracted by extraneous stimuli

i) is often forgetful in daily activities

(2) Six (or more) of the following symptoms of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

Hyperactivity

1. often fidgets with hands or feet or squirms in seat
2. often leaves seat in classroom or in other situations in which remaining seated is expected
3. often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
4. often has difficulty playing or engaging in leisure activities quietly
5. is often “on the go” or often acts as if “driven by a motor”
6. often talks excessively

Impulsivity

7. often blurts out answers before questions have been completed
8. often has difficulty awaiting turn
9. often interrupts or intrudes on others (eg, butts into conversations or games)

B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.

C. Several impairments from the symptoms are present in 2 or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).

D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning

E. The symptoms do not occur exclusively during the course of Schizophrenia or another Psychotic Disorder and are not better explained by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, Personality Disorder, substance intoxication or withdrawal).

Code based on type:

314.01 Attention-Deficit/Hyperactivity Disorder, Combined Presentation: if both Criteria A1 and A2 are met for the past 6 months

314.00 Attention-Deficit/Hyperactivity Disorder, Predominately Inattentive Presentation: if Criterion A1 is met but Criterion A2 is not met for the past 6 months

314.01 Attention-Deficit/Hyperactivity Disorder, Predominately Hyperactive-Impulsive Presentation: if Criterion A2 is met but Criterion A1 is not met for the past 6 months

From the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Copyright 2013 American Psychiatric Association.

Appendix 3 Brief Psychiatric Rating Scale for Children

From Hughes (2008)

REVISED BPRS-C WITH DESCRIPTIVE ANCHORS ADDED

Component Code: _____
Local Case Number: _____
Client's Name: _____
Date Completed: _____
Completed By: _____

		Not Present	Very Mild	Mild	Moderate	Mod. Severe	Severe	Extremely Severe
		0	1	2	3	4	5	6
1.	**Uncooperativeness - negative, uncooperative, resistant, difficult to manage.** Not present: Cooperative, pleasant Mild: Occasionally refuses to comply with rules and expectations, in only one situation or setting. Moderate-severe: Persistent failure to comply with rules/expectations in more than one setting. Causes frequent impairment in functioning. Extremely Severe: Constantly refuses to comply with rules and expectations, delinquent behaviors, running away. Causes severe impairment in functioning in most situations/settings.	☐	☐	☐	☐	☐	☐	☐
2.	**Hostility - angry or suspicious affect, belligerence, accusations & verbal condemnation of others.** Not present: Cooperative, pleasant. Mild: Occasionally sarcastic, loud, guarded, quarrelsome. Causes mild dysfunction in one situation or setting. Moderate-severe: Causes frequent impairment in several situations/settings. Extremely Severe: Assaultive, destructive. Causes severe impairment in functioning in most situations/settings.	☐	☐	☐	☐	☐	☐	☐
3.	**Manipulativeness - lying, cheating, exploitive of others.** Not present: Not at all. Mild: Occasionally gets in trouble for lying, may cheat on occasions. Moderate-severe: Frequently lies/cons/manipulates people he/she knows. Causes frequent impairment in functioning in several situation/settings. Extremely Severe: Constantly relates to others in an exploitive/manipulative manner, cons strangers out of money/situations. Cause severe impairment in functioning in most situations/settings.	☐	☐	☐	☐	☐	☐	☐
4.	**Depressed Mood - sad, tearful, depressive demeanor.** Not present: Occasionally/quickly disappears. Mild: Sustained periods/excessive for event. Moderate-severe: Unhappy most of the time/no precipitant. Extremely Severe: Unhappy all of the time/psychic pain. Causes severe impairment in functioning.	☐	☐	☐	☐	☐	☐	☐
5.	**Feelings of Inferiority - lacking self-confidence, self-depreciatory, feeling of personal inadequacy.** Not present: Feels good/positive about self. Mild: Occasionally feels not as good as others/deficits in one area. Moderate-severe: Feels others are better than they are. Gives negative, bland answers, can't think of anything good about themselves. Extremely Severe: Constantly feels others are better. Feels worthless/unlovable.	☐	☐	☐	☐	☐	☐	☐
6.	**Suicidal Ideation - thoughts, threats, or attempts of suicide.** Not present: Not at all. Mild: Thought when angry. Moderate-severe: Recurrent thoughts suicide/plans. Extremely Severe: Attempted within last month/actively.	☐	☐	☐	☐	☐	☐	☐

Component Code: _____
Local Case Number: _____
Client's Name: _____
Date Completed: _____
Completed By: _____

	Not Present	Very Mild	Mild	Moderate	Mod. Severe	Severe	Extremely Severe
	0	1	2	3	4	5	6
7. Peculiar Fantasies - recurrent, odd, unusual, or autistic ideations.	☐	☐	☐	☐	☐	☐	☐
8. Delusions - ideas of reference, persecutory or grandiose delusions.	☐	☐	☐	☐	☐	☐	☐
9. Hallucinations - visual, auditory, or other hallucinatory perceptions.	☐	☐	☐	☐	☐	☐	☐
10. Hyperactivity - excessive energy expenditure, frequent changes in posture, perpetual motion.	☐	☐	☐	☐	☐	☐	☐
11. Distractibility - poor concentration, shortened attention span, reactivity to peripheral stimuli.	☐	☐	☐	☐	☐	☐	☐
12. Speech or Voice Pressure - loud, excessive, or pressured speech.	☐	☐	☐	☐	☐	☐	☐
13. Underproductive Speech - minimal, sparse inhibited verbal response pattern, or weak low voice.	☐	☐	☐	☐	☐	☐	☐

7. Peculiar Fantasies - recurrent, odd, unusual, or autistic ideations.
Not present: Not at all.
Mild: Occasionally has elaborate fantasies, imaginary companions.
Moderate-severe: Frequently has elaborate fantasies (exclude imaginary friends). Interferes occasionally with perception of reality.
Extremely Severe: Often absorbed in elaborate fantasies, has a difficult time distinguishing reality from fantasy.

8. Delusions - ideas of reference, persecutory or grandiose delusions.
Not present: No delusions or ideas of reference.
Mild: Occasionally feels strangers may be looking/talking/laughing about them.
Moderate-severe: Frequent distortion of thinking, mistrust, suspicious of others.
Extremely Severe: Mistrusts/suspicious of everyone/thing. Can't distinguish from reality.

9. Hallucinations - visual, auditory, or other hallucinatory perceptions.
Not present: No visual, auditory, sensory experiences.
Mild: Hears name called, experiences after an event, active/vivid imagination.
Moderate-severe: Definite experienced auditory (voices either command or not command?), visual (daytime, or several incidences), sensory (specific others).
Extremely Severe: Constantly experiences auditory (commanding voices), visual (images are present during interview), or other experiences or perceptions.

10. Hyperactivity - excessive energy expenditure, frequent changes in posture, perpetual motion.
Not present: Slight restlessness, fidgeting. No impact on functioning.
Mild: Occasional restlessness, fidgeting, frequent changes of posture. Noticeable, but does not cause impairment in functioning.
Moderate-severe: Excessive energy, movement, cannot stay still or seated. Causes dysfunction on numerous occasions/situations. Seeks help for behaviors.
Extremely Severe: Continuous motor excitement, cannot be stilled. Causes major interference in functioning on most occasions/situations.

11. Distractibility - poor concentration, shortened attention span, reactivity to peripheral stimuli.
Not present: Performance consistent with ability.
Mild: Occasionally daydreams, easily distracted. Is able to focus with prompting.
Moderate-severe: Frequently has trouble concentrating, avoids mental tasks, disruptive. Needs frequent assistance to stay focused. Causes decreased performance.
Extremely Severe: Constant, needs 1:1 assistance to stay focused.

12. Speech or Voice Pressure - loud, excessive, or pressured speech.
Not present: Not at all.
Mild: Noticeably more verbose than normal, conversation is not strained.
Moderate-severe: Very verbose or rapid, making conversation strained or difficult to maintain.
Extremely Severe: Talks rapidly, continuously and cannot be interrupted. Conversation is extremely difficult or impossible.

13. Underproductive Speech - minimal, sparse inhibited verbal response pattern, or weak low voice.
Not present: Not at all.
Mild: Occasionally conveys little information because of minimal speech, vague, sparse, low or weak voice.
Moderate-severe: Persistently the client is vague, low or weak voice, in which at least 1/4 - 1/2 of the conversation comprehension is impaired.
Extremely Severe: On numerous occasions/situations conversation is severely impaired.

Component Code: _____
Local Case Number: _____
Client's Name: _____
Date Completed: _____
Completed By: _____

	Not Present	Very Mild	Mild	Moderate	Mod. Severe	Severe	Extremely Severe
	0	1	2	3	4	5	6
14. Emotional Withdrawal – unspontaneous relations to examiner, lack of peer interaction, hypoactivity.	☐	☐	☐	☐	☐	☐	☐
Not present: Not at all.							
Mild: Occasionally is unresponsive, sometimes refuses peer interactions.							
Moderate-severe: Frequently unresponsive, lacks peer interaction, hypoactive. Interferes with relationships.							
Extremely Severe: Constantly oblivious to those around. Preoccupied facial expressions, does not respond to questions or look at interviewer.							
	0	1	2	3	4	5	6
15. Blunted Affect – deficient emotional expression, blankness, flatness of affect.	☐	☐	☐	☐	☐	☐	☐
Not present: Not at all.							
Mild: Some flattening of affect. Occasionally shows emotional response during interview (smiles, laughs, tearful).							
Moderate-severe: Considerable flattening. Frequently the client does not show emotional response (does not smile, laugh, look, cry).							
Extremely Severe: Constantly flat. The client does not show emotional response (does not smile, laugh, look, cry).							
	0	1	2	3	4	5	6
16. Tension – nervousness, fidgetiness, nervous movements of hands or feet.	☐	☐	☐	☐	☐	☐	☐
Not present: Not at all.							
Mild: Occasionally feels nervous or fidgets. Can be relaxed or reassured.							
Moderate-severe: Most days/time feels nervous/fidgety. Causes mental or physical distress.							
Extremely Severe: Pervasive and extreme nervousness, fidgeting, nervous movements of hands or feet.							
	0	1	2	3	4	5	6
17. Anxiety – clinging behavior, separation anxiety, preoccupation with anxiety topics, fears or phobias.	☐	☐	☐	☐	☐	☐	☐
Not present: Not at all.							
Mild: Occasionally worries (at least 3 times a week) about anticipated/current events, separation, fears or phobias. These worries appear excessive for situation.							
Moderate-severe: Most days/time worries about at least 2 life circumstances, or anticipated/current events.							
Extremely Severe: Pervasive and extreme worry about most everything, real or imagined.							
	0	1	2	3	4	5	6
18. Sleep Difficulties – inability to fall asleep, intermittent awakening, shortened sleep time.	☐	☐	☐	☐	☐	☐	☐
Not present: Not at all.							
Mild: Some difficulty (at least 1 hour initial, no middle or terminal insomnia).							
Moderate-severe: Definitely has difficulty (at least 2 hours initial insomnia, any middle, or terminal lasting up to half an hour). Feelings of unrestorative sleep, evidence of mild circadian reversal.							
Extremely Severe: Claims to never sleep, feels exhausted the rest of the day, or severe circadian reversal.							
	0	1	2	3	4	5	6
19. Disorientation – confusion over persons, places or things.	☐	☐	☐	☐	☐	☐	☐
Not present: Not at all.							
Mild: Occasionally appears confused or puzzled. Easily reacquainted with surroundings when prompted.							
Moderate-severe: Frequently appears puzzled, confused, baffled regarding familiar surroundings, people, or things.							
Extremely Severe: Constantly confused. Perplexed.							
	0	1	2	3	4	5	6
20. Speech Deviance – inferior level of speech development, underdeveloped vocabulary, mispronunciations.	☐	☐	☐	☐	☐	☐	☐
Not present: Not at all.							
Mild: Occasionally instances of distorted or idiosyncratic speech. Little impairment of understandability.							
Moderate-severe: Frequent instances with definite impairment in understandability.							
Extremely Severe: Constant speech distortion, almost incomprehensible.							

Component Code: _____
Local Case Number: _____
Client's Name: _____
Date Completed: _____
Completed By: _____

	Not Present	Very Mild	Mild	Moderate	Mod. Severe	Severe	Extremely Severe
	0	1	2	3	4	5	6
21. Stereotypy – rhythmic, repetitive, manneristic movements or posture.	☐	☐	☐	☐	☐	☐	☐

Not present: Not at all.
Mild: Occasionally displays rhythmic, repetitive, manneristic movements or posture.
Moderate-severe: Frequent rhythmic, repetitive, manneristic movements or posture.
Extremely Severe: Most of the time (<50%) displays rhythmic, repetitive, manneristic movement or posture.

TOTAL SCORE:_____

(add up each item – record on front page as well)

Appendix 4 Prior Stimulant Medication Questionnaire

[The following will be collected for those subjects who have taken any stimulant medications prior to this study. This form only needs to be completed for the most recent stimulant medication taken. The clinician or study coordinator will complete this questionnaire based upon an interview with the parent/caregiver at the Screening visit.]

Please record the subject's/parent's/caregiver's responses below (answers A-H).
Subjects/parents/caregivers may have multiple reasons for stopping stimulant medication. Please record all the reasons mentioned (mark all that apply in the list below)

Coordinator: Please ask the subject/parent/caregiver "why did you decide to stop taking the last stimulant medication?".

Name of most recent stimulant medication(s): _____

[ ] Because the prior medication was not effective. Coordinator: if the reason was lack of effectiveness please probe "why did you feel the stimulant was not effective?" and mark the subject/parent/caregiver response below:

[ ] Prior ADHD medication did not work (ie, did not feel the medication did anything for the subject).

[ ] The prior ADHD medication effect didn't last long enough

[ ] The prior ADHD medication wasn't optimal (the medication worked but not as well as expected) per the subject/parent/caregiver

[ ] The prior ADHD medication wasn't optimal (the medication worked but not as well as expected) per the subject's physician

[ ] Other, please explain: _____

[ ] Because the ADHD medication had side effects

[ ] Could not afford paying for the medication

[ ] Wanted to switch to another medication. Specify:

[ ] Methylphenidate hydrochloride short acting/immediate release
[ ] Methylphenidate hydrochloride long acting/prolonged release/Modified release
[ ] Dexamphetamine sulphate short acting/immediate release
[ ] Dexamphetamine sulphate long acting/prolonged release
[ ] Mixed amphetamine salts short acting/immediate release
[ ] Mixed amphetamine salts long acting/prolonged release
[ ] Atomoxetine hydrochloride
[ ] Guanfacine hydrochloride short acting/immediate release
[ ] Guanfacine hydrochloride long acting/prolonged release
[ ] Clonidine short acting/immediate release
[ ] Clonidine long acting/prolonged release
[ ] Other, please specify: _____

[ ] Wanted to stop taking a stimulant ADHD medication
[ ] Wanted to stop taking any medication for ADHD
[ ] Wanted to switch to non-pharmacological interventions to treat ADHD
[ ] Other, please specify: _____

Appendix 5 Blood Pressure for Boys by Age and Height Percentile

To determine the eligibility of a male subject for entry in the study based on the inclusion criterion (Section 4.1.1 and Section 4.2.1), firstly determine the percentile of height for the subject based on age (see Appendix 5.1). For a subject who falls between 2 percentile ranges, use the lower of the 2 ranges. Once the subject's age and height percentile are determined, use the table below to determine eligibility.

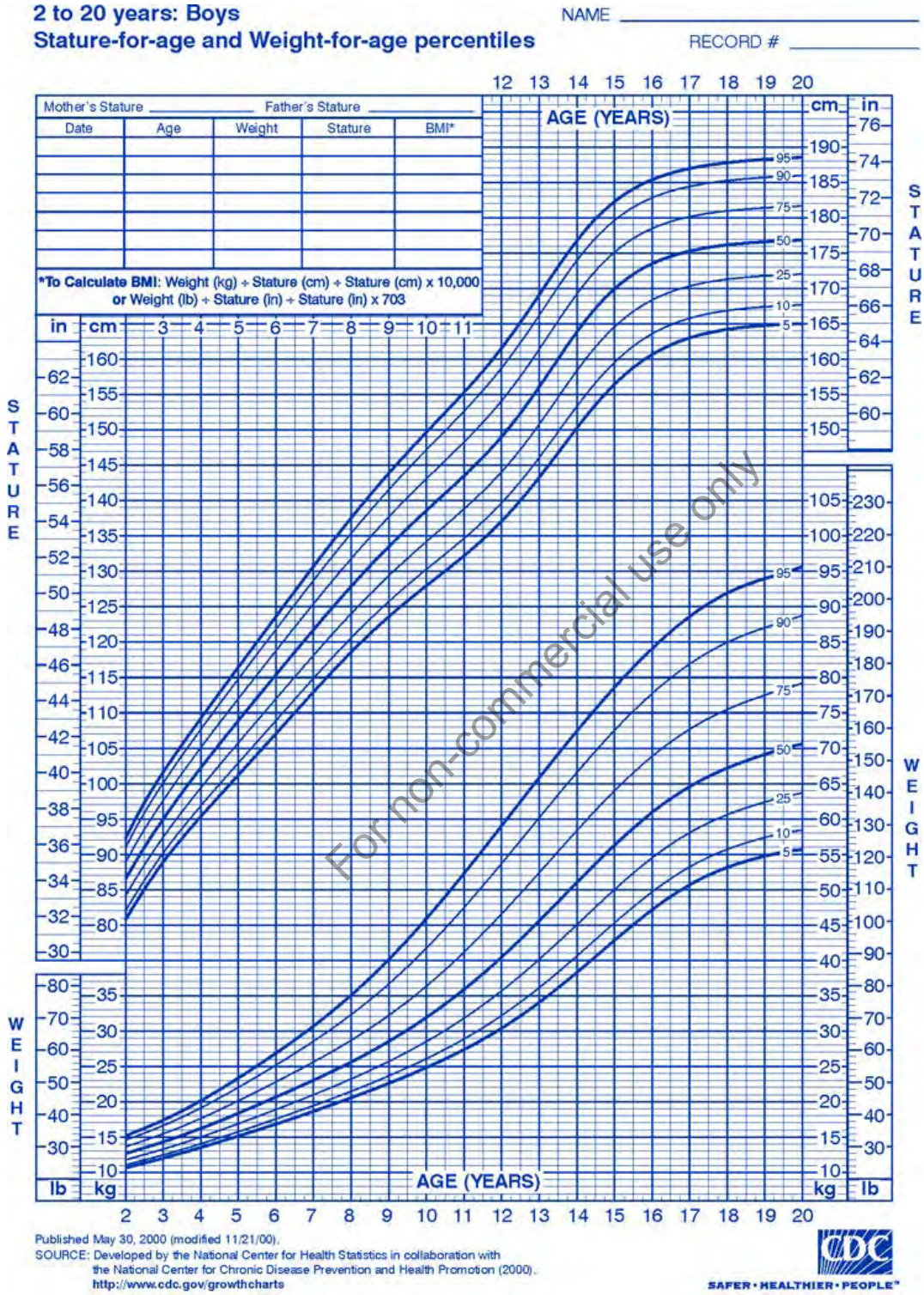
All blood pressure values provided are the 95% for age and height percentile so the subject's systolic and diastolic blood pressure readings at screening and baseline visits of Study Parts A and B must be less than the corresponding value below:

BOYS

Age (Year)	Systolic Blood Pressure (mmHg) ← Percentile of Height→							Diastolic Blood Pressure (mmHg) ← Percentile of Height→						
	5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
6	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	110	111	113	115	117	118	119	74	74	75	76	77	78	78
8	111	112	114	116	118	119	120	75	76	77	78	79	79	80
9	113	114	116	118	119	121	121	76	77	78	79	80	81	81
10	115	116	117	119	121	122	123	77	78	79	80	81	81	82
11	117	118	119	121	123	124	125	78	78	79	80	81	82	82
12	119	120	122	123	125	127	127	78	79	80	81	82	82	83
13	121	122	124	126	128	129	130	79	79	80	81	82	83	83
14	124	125	127	128	130	132	132	80	80	81	82	83	84	84
15	126	127	129	131	133	134	135	81	81	82	83	84	85	85
16	129	130	132	134	135	137	137	82	83	83	84	85	86	87
17	131	132	134	136	138	139	140	84	85	86	87	87	88	89

Source: National Heart Lung and Blood Institute; May 2004
http://www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm

Appendix 5.1 Boys' Stature-for-age and Weight-for-age Percentiles



Appendix 6 Blood Pressure for Girls by Age and Height Percentile

To determine the eligibility of a female subject for entry in the study based on the inclusion criterion (Section 4.1.1 and Section 4.2.1), firstly determine the percentile of height based on age (see Appendix 6.1). Use the lower of the 2 ranges if a subject falls between 2 percentile ranges.

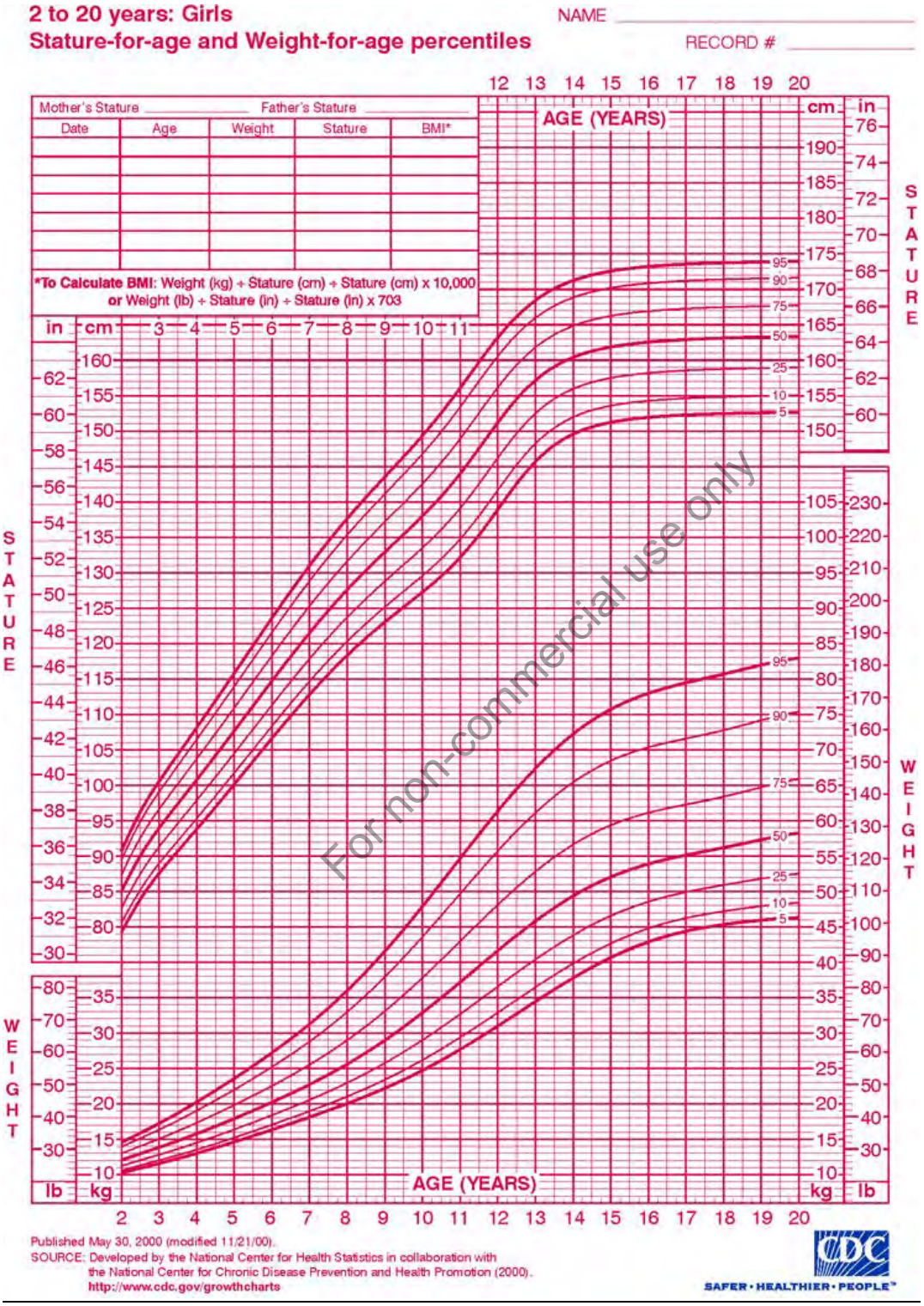
Once the subject's age and height percentile are determined, use the table provided below to determine eligibility. All blood pressure values provided are the 95% for age and height percentile and the subject's systolic and diastolic blood pressure readings at the screening and baseline visits of Study Parts A and B must be less than the corresponding value below:

Girls

Age (Year)	Systolic Blood Pressure (mmHg) ← Percentile of Height→								Diastolic Blood Pressure (mmHg) ← Percentile of Height→						
	5%	10%	25%	50%	75%	90%	95%		5%	10%	25%	50%	75%	90%	95%
6	108	109	110	111	113	114	115		72	72	73	74	74	75	76
7	110	111	112	113	115	116	116		73	74	74	75	76	76	77
8	112	112	114	115	116	118	118		75	75	75	76	77	78	78
9	114	114	115	117	118	119	120		76	76	76	77	78	79	79
10	116	116	117	119	120	121	122		77	77	77	78	79	80	80
11	118	118	119	121	122	123	124		78	78	78	79	80	81	81
12	119	120	121	123	124	125	126		79	79	79	80	81	82	82
13	121	122	123	124	126	127	128		80	80	80	81	82	83	83
14	123	123	125	126	127	129	129		81	81	81	82	83	84	84
15	124	125	126	127	129	130	131		82	82	82	83	84	85	85
16	125	126	127	128	130	131	132		82	82	83	84	85	85	86
17	125	126	127	129	130	131	132		82	83	83	84	85	85	86

Source: National Heart Lung and Blood Institute; May 2004
http://www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm

Appendix 6.1 Girls' Stature-for-age and Weight-for-age Percentiles

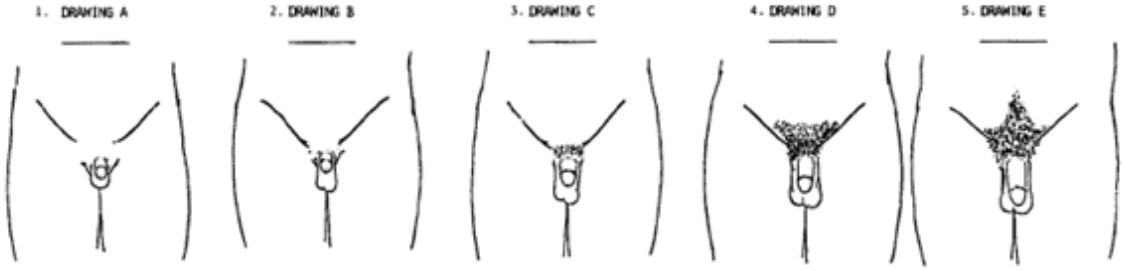


Appendix 7 Tanner Staging Self-assessment

Self-assessment in this study is defined as subjects or parents indicating which drawing of the scale corresponds to the subject's sexual maturation stage at the time of the specific visit. For this purpose, site staff (the principal investigator or a designee) reads the guidance and the text corresponding to each drawing and asks the subject or parent to choose the applicable drawing. The response from the subject or the parent will be documented in the Tanner Staging Form by the site staff.

Appendix 7.1 Tanner stage for males

THE DRAWINGS ON THIS PAGE SHOW DIFFERENT AMOUNTS OF MALE PUBIC HAIR. A BOY PASSES THROUGH EACH OF THE FIVE STAGES SHOWN BY THESE DRAWINGS. PLEASE LOOK AT EACH DRAWING AND READ THE SENTENCES UNDER THE DRAWING. THEN CHOOSE THE DRAWING CLOSEST TO YOUR STAGE OF YOUR HAIR DEVELOPMENT. MARK A 1 ON THE LINE ABOVE THAT DRAWING. THEN CHOOSE THE DRAWING THAT IS NEXT CLOSEST TO YOUR STAGE OF HAIR DEVELOPMENT AND MARK IT A 2. IN CHOOSING THE RIGHT PICTURE, LOOK ONLY AT THE PUBIC HAIR, AND NOT AT THE SIZE OF THE TESTES, SCROTUM, AND PENIS.



1. DRAWING A — THERE IS NO PUBIC HAIR AT ALL.

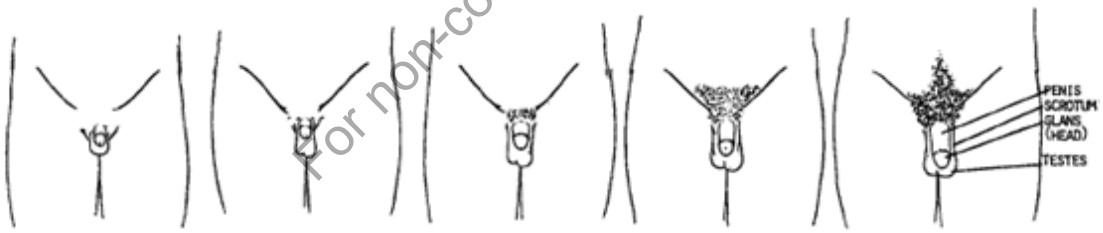
2. DRAWING B — THERE IS A LITTLE SOFT, LONG, LIGHTLY COLORED HAIR. MOST OF THE HAIR IS AT THE BASE OF THE PENIS. THIS HAIR MAY BE STRAIGHT OR A LITTLE CURLY.

3. DRAWING C — THE HAIR IS DARKER IN THIS STAGE. IT IS COARSER AND MORE CURLED. IT HAS SPREAD OUT AND THINLY COVERS A SOMEWHAT LARGER AREA.

4. DRAWING D — THE HAIR IS NOW AS DARK, CURLY, AND COARSE AS THAT OF AN ADULT MALE. HOWEVER, THE AREA THAT THE HAIR COVERS IS NOT AS LARGE AS THAT OF AN ADULT MALE. THE HAIR HAS NOT SPREAD OUT TO THE THIGHS.

5. DRAWING E — THE HAIR HAS SPREAD OUT TO THE THIGHS. THE HAIR IS NOW LIKE THAT OF AN ADULT MALE. IT COVERS THE SAME AREA AS THAT OF AN ADULT MALE.

THE DRAWINGS OF THIS PAGE SHOW DIFFERENT STAGES OF DEVELOPMENT OF THE TESTES, SCROTUM, AND PENIS. A BOY PASSES THROUGH EACH OF THE FIVE STAGES SHOWN BY THESE DRAWINGS. PLEASE LOOK AT EACH OF THE DRAWINGS AND READ THE SENTENCES UNDER THE DRAWING. THEN CHOOSE THE DRAWING CLOSEST TO YOUR STAGE OF DEVELOPMENT. MARK A "1" ON THE LINE ABOVE THAT DRAWING. THEN CHOOSE THE DRAWING THAT IS NEXT CLOSEST TO YOUR STAGE OF DEVELOPMENT AND MARK IT "2". IN CHOOSING THE RIGHT PICTURE, LOOK ONLY AT THE STAGE OF DEVELOPMENT, NOT AT PUBIC HAIR.



1. DRAWING A — THE TESTES, SCROTUM, AND PENIS ARE ABOUT THE SAME SIZE AND SHAPE AS THEY WERE WHEN YOU WERE A CHILD.

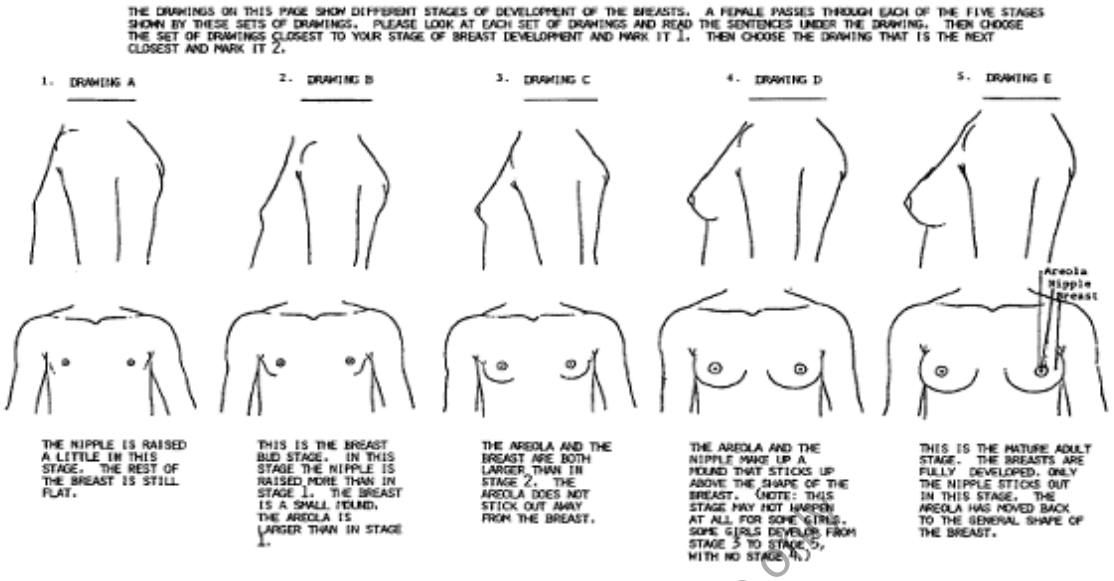
2. DRAWING B — THE TESTES AND SCROTUM HAVE GOTTEN A LITTLE LARGER. THE SKIN OF THE SCROTUM HAS CHANGED. THE SCROTUM, THE SACK HOLDING THE TESTES, HAS LOWERED A BIT. THE PENIS HAS GOTTEN ONLY A LITTLE LARGER.

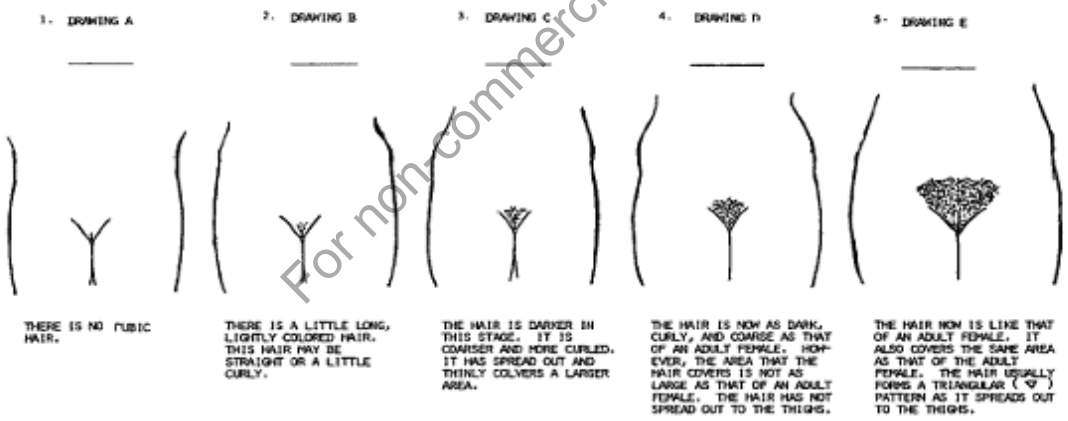
3. DRAWING C — THE PENIS HAS GROWN MAINLY IN LENGTH. THE TESTES AND SCROTUM HAVE GROWN AND DROPPED LOWER THAN IN STAGE 2.

4. DRAWING D — THE PENIS HAS GROWN EVEN LARGER. IT IS WIDER. THE GLANS (THE HEAD OF THE PENIS) IS BIGGER. THE SCROTUM IS DARKER THAN BEFORE. IT IS BIGGER BECAUSE THE TESTES HAVE GOTTEN BIGGER.

5. DRAWING E — THE PENIS, SCROTUM, AND TESTES ARE THE SIZE AND SHAPE OF THAT OF AN ADULT MALE.

Appendix 7.2 Tanner stage for females





Appendix 8 Examples of Clinically relevant CYP3A4 Inhibitors and Inducers

CYP3A4/5 Inhibitors	CYP3A4/5 Inducers
Macrolide Antibiotics	Carbamazepine
Clarithromycin	Barbiturates (eg, phenobarbital)
Erythromycin	Phenytoin
Troleandomycin	Rifabutin
Telithromycin	Oxcarbazepine
HIV Protease Inhibitors	Rifampin
Indinavir	St. John's Wort
Nelfinavir	Troglitazone (redrawn due to liver AE)
Ritonavir, saquinavir	**HIV Antivirals**
Calcium Channel Blockers	Efavirenz
Diltiazem	Nevirapine
Verapamil	**Other**
Miscellaneous	Glucocorticoids
Amiodarone	Modafinil
Cimetidine	Miscellaneous
Fluvoxamine	Fluconazole
Itraconazole	Aprepitant
Ketoconazole	Boceprevir
Mibefradil	Ciprofloxacin
Nefazodone	Delaviridine
Grapefruit juice or fresh grapefruit	Fluvoxamine
Gestodene	Imatinib
Mifepristone	Norfloxacin
Norfluoxetine	Telaprevir
Voriconazole	Starfruit

Flockart D. Drug Interactions. DRUG-INTERACTION TABLE (CYTOCHROME P450 SYSTEM)

Appendix 9 Protocol History

Document	Date	Global/Country/Site Specific
Protocol Amendment 8.0	12 April 2024	Global
Protocol Amendment 7.0	02 Feb 2024	Global
Protocol Amendment 6.0	10 May 2023	Global
Protocol Amendment 5.0	08 Jun 2021	Global
Protocol Amendment 4.0	08 Jun 2020	Global
Protocol Amendment 3.0	09 Sep 2019	Global
Protocol Amendment 2.1	11 Jul 2019	UK
Protocol Amendment 2	28 May 2019	Global
Protocol Amendment 1.1	10 Apr 2019	Europe
Protocol Amendment 1	02 May 2018	European Union
Original Protocol	08 Feb 2018	Global

Summary of Change(s) Since Last Version of Approved Protocol (Amendment 6.0, dated 10 May 2023)		
Amendment Number: 7.0	**Amendment Date:** 02 Feb 2024	**Global/Country/Site** Global
The study design for Part A was modified to eliminate the 18 to 49-week portion of study Part A. For subjects who enrolled prior to Amendment 7, and who are beyond Visit 11A (Week 18A), their next visit will be the ET visit.		Title page; Protocol Signature Page; Study Synopsis; Study Schedules; Section 3.1; Figure 1; Section 3.2; Section 4.5; Section 6.2.1; Section 6.2.3; Section 6.2.3.2; Section 6.2.3.3; Table 6; Section 6.2.4; Section 7.1.3.2; Section 7.1.4; Section 7.2.2.7; Section 7.2.4; Table 9
The analysis of the primary objective has been modified from an inferential test of non-inferiority to a descriptive comparison; comparison of change from baseline in CANTAB RTI task via MMRM between SPD-503 and atomoxetine will be presented, without performance of the inferential hypothesis test of non-inferiority.		Study Synopsis; Section 2.1; Section 2.2.1, Section 6.2.4; Section 9.6; Section 9.8.1
Extended the study period to 2027.		Study Synopsis
Removed analyses by country as a subgroup. These analyses will be conducted if data permit.		Section 9.8

Summary of Change(s) Since Last Version of Approved Protocol (Amendment 5.0, dated 08 Jun 2021)		
Amendment Number: 6.0	**Amendment Date:** 10 May 2023	**Global/Country/Site** Global
Replaced the EUDRACT No. with the EU Trial No.		Title page

Summary of Change(s) Since Last Version of Approved Protocol (Amendment 5.0, dated 08 Jun 2021)	
Updated the approvers on the protocol signature page.	Protocol signature page
Updated the contact information and the name of the form for serious adverse event and nonserious adverse events required by the protocol.	Emergency Contact Information; Section 8.2.2
Updated the contact information for product quality complaints.	Product Quality Complaints
Replaced references to the brand-named STRATTERA with the generic named atomoxetine.	Study Synopsis; Section 6.1; Table 5; Section 6.2.5.2; Section 8.2.1
Clarified that placebo subjects can skip the follow-up visit for Part A and proceed immediately to the baseline assessments for Part B.	Study Synopsis; Table 2; Section 3.1
Clarified that β2-agonists are only permitted in Part B.	Section 5.2.1
Updated the name of the form for pregnancy reporting. Revised text stating the form must also be sent to the CRO/sponsor medical monitor. This is done automatically by the CRO once the report is received from the investigator.	Section 8.1.6
Updated the name of the form for serious adverse event and nonserious adverse event as required by the protocol reporting. Revised text stating the form must also be sent to the CRO/sponsor medical monitor. This is done automatically by the CRO once the report is received from the investigator.	Section 8.2.2
Replaced references to the EU Clinical Trial Directive with references to the EU Clinical Trial Regulation.	Section 10; Section 10.1.1; Section 10.1.5; Section 10.2.1
Updated the data to be recorded to reflect the current practice in the study.	Section 10.4
A description of technical arrangements implemented to avoid unauthorized access, disclosure, dissemination, alteration or loss of info and personal data processed measures that will be implemented in case of data security breach has been added.	Section 10.4

Summary of Change(s) Since Last Version of Approved Protocol (Amendment 4.0, dated 08 Jun 2020)		
Amendment Number: **5.0**	**Amendment Date:** **08 Jun 2021**	**Global/Country/Site** **Global**
Removed APRS assessment as a secondary efficacy endpoint.		Study Synopsis; Study Schedules; Section 2.2.2; Section 7.2.3.4; Section 9.8.1; Section 9.9.2
Added the Conners 3 Parent Short Form as a secondary efficacy endpoint.		Study Synopsis; Study Schedules; Section 2.2.2; Section 7.2.3.4; Section 9.8.1; Section 9.9.2
Clarified handling of APRS data collected prior to Amendment 5.		Section 9.8; Section 9.9.2; Appendix 1
Adjusted projected number of sites from 45 in Europe and 20 in the United States to approximately 55 total.		Study Synopsis; Section 3.3
Described subgroup analyses to be applied to primary and secondary endpoints.		Section 9.8
Reduced the number of subjects entering Study Part B from Study Part A to 120, plus any remaining subjects randomized to placebo in Study Part A.		Study Synopsis; Section 3.1; Section 4; Section 9.6

Summary of Change(s) Since Last Version of Approved Protocol (Amendment 4.0, dated 08 Jun 2020)	
Made corrections to the wording of the primary analysis concerning how the margin for the noninferiority test is established.	Study Synopsis; Section 9.8.1
Clarified visit windows for W5A, W6A, W7A as ±2 days instead of ±7 days to ensure that subjects have sufficient investigational medicinal product (IMP) between visits.	Study Schedules
Clarified that dose-optimization period for adolescents goes through Week 7 and dose maintenance for adolescents proceeds from Week 8.	Study Synopsis; Section 3.1
Clarified self-assessment for Tanner stages.	Study Schedules; Section 7.2.2.2; Appendix 7
Provided instructions for managing study components during unavoidable dire circumstances (eg, a widespread disease outbreak such as the COVID-19 pandemic or natural disaster) and stated that such exceptional circumstances should be duly justified and documented in the study records: • direct-to-patient IMP shipments • emphasize that changes in study conduct due to unavoidable dire circumstances must be recorded • remote assessments • remote visits and home health care visits for sample collection • remote informed (e)consent	 Section 6.2.1 Section 4.5.1; Section 7.1 Section 7.1.3.2 Section 7.3 Section 10.3.1
Indicated that screen failures due solely to COVID-19 pandemic related issues can be rescreened.	Section 7.1.1
Added statement that data analysis may be adjusted to account for changes due to COVID-19 pandemic related issues.	Section 7.3; Section 9.4
Questions 14-21 in the BPRS-C-21 (see Section 7.2.2.11) were previously not included in Appendix 3. These questions have been included in Appendix 3.	Appendix 3
Renumbered Appendix 3.1 as Appendix 4, and adjusted previous Appendix 4 through Appendix 8, including adjusting references in text and Table of Contents.	Appendix 4, Appendix 5, Appendix 6, Appendix 7, Appendix 8, and Appendix 9

Summary of Change(s) Since Last Version of Approved Protocol (Amendment 3.0, dated 09 Sept 2019)		
Amendment Number: **4.0**	**Amendment Date:** **08 Jun 2020**	**Global/Country/Site** **Global**
Description of Change and Rationale		**Section(s) Affected by Change**
As part of the post-Shire integration process, the legal entity for the company has been revised form Shire to Takeda Development Center Americas, Inc.		Cover Page Headers throughout entire protocol
Modified the study number to include both the current and legacy product code.		Cover Page Headers throughout entire protocol Protocol Signature Page

Summary of Change(s) Since Last Version of Approved Protocol (Amendment 3.0, dated 09 Sept 2019)	
Corrected typo in footnote a of Table 2: Study Part B from "V2A" to "V2B."	Table 2
Removed reference to Shire and, where applicable, replaced with "sponsor."	Protocol Signature Page Product Quality Complaints Section 6.2.5.4, Section 6.2.6, Section 8.1.6, Section 8.2.2, Section8.2.4, Section 10.5
Updated description of amendments and protocol history	Appendix 8

Summary of Change(s) Since Last Version of Approved Protocol (Amendment 2.1, dated 11 July 2019)		
Amendment Number: **3.0**	**Amendment Date:** **09 Sept 2019**	**Global/Country/Site** **Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Made minor revisions to better align with text, and with Tables 1 and 2.		Figure 1
Added new exclusion criteria based on liver function test results, to align with discontinuation criterion described in Section 4.5.1.		Synopsis and Section 4.1.2 and Section 4.2.2
Text was updated to align with the schedule of assessments table regarding volume of blood to be drawn and number of visits. Table 9 in this section was also revised to clarify the number of samples required for each part of the study (Part A and Part B) as well as the total volume(s) needed.		Section 7.2.4
Due to the addition of US investigator sites, "region (non-US or US)" was added to the analysis model as a factor: "The endpoint will be analyzed over the FAS and PPS with a mixed-effects model for repeated measures (MMRM) with treatment arm, visit, sex (male or female), age group (6 to 12 years or 13 to 17 years), *region (non-US or US)*, and the interaction of treatment with visit as factors, the corresponding baseline value as a covariate, and the interaction between baseline value and visit adjusted in the model."		Synopsis and Section 9.8.1

Summary of Change(s) Since Last Version of Approved Protocol (Amendment 2.0, dated 28 May 2019)		
Amendment Number: **2.1**	**Amendment Date:** **11 July 2019**	**Global/Country/Site** **UK**
Description of Change and Rationale		**Section(s) Affected by Change**
The tapering period at the end of Parts A and B has been increased from 2 to 3 weeks to facilitate weekly titration, consistent with the SmPC, which indicates tapering in decrements of no more than 1 mg every 3 to 7 days.		Study Schedule and Other Points Throughout (including Section 6.2.3.3 and Section 7.1.3.3, and Table 6)
The final visit in Part B (V17B) has been changed to a physical visit rather than a telephone call in order to allow the measurements of heart rate and blood pressure, given the risk of elevated blood pressure during guanfacine tapering.		Study Schedule and Other Points Throughout
The schedule of activities in the study has been augmented as follows: • In order to minimize potential fetal exposure to IMP, additional urine tests for pregnancy have been added (at Visits 5A, 8A,		Table 1, Table 2

Summary of Change(s) Since Last Version of Approved Protocol (Amendment 2.0, dated 28 May 2019)		
Amendment Number: **2.1**	**Amendment Date:** **11 July 2019**	**Global/Country/Site** **UK**
Description of Change and Rationale		**Section(s) Affected by Change**
12A, 18A, 5B, 8B, and 17B) so pregnancy tests occur approximately every 4 weeks throughout the study. • Additional serum blood tests and ECGs have been added to monitor for electrolyte disturbances and arrhythmias (at Visits 6A, 9A, and 12A). • Because atomoxetine has been associated with liver injury, additional liver function tests have been added (at Visits 6A, 9A, and 12A).		
The following treatment withdrawal criteria were added: • Pregnancy, to be consistent with the statement already present in Section 8.1.6, as well as the Clinical Trial Facilitation Group Guidance (2017). • Hypertension, in accordance with the labeling for atomoxetine and guanfacine. • ALT >2 x upper limit of normal (ULN) or AST >2 x ULN or bilirubin >1.5 x ULN, to be in accordance with the SmPC of atomoxetine		Section 4.5.1
Several items in "Prohibited Treatment" have been clarified: • The IMP, guanfacine, is not prohibited unless it is a formulation or source of guanfacine other than the study's IMP. • Concomitant medications that would be contraindicated for use with either guanfacine or atomoxetine are prohibited. • The bullet describing the prohibition of anti-hypertensives has been split into several bullets to present more relevant physiological grouping of prohibited medications, and to clarify that all anti-hypertensives are prohibited. • The prohibition of α2-adrenergic agonists incorrectly stated that guanfacine, which is also an α2-adrenergic agonist, was excluded; only *other* α2-adrenergic agonists are excluded.		Section 5.2.2
Additional clarification regarding unblinding procedures has been added: 6.2.1 Interactive Response Technology for Investigational Medicinal Product Management An IRT system will be used in this study to manage the tracking and confirmation of shipment, supply, inventory, ordering, IMP expiration, site assignments, subject randomization, IMP returns, unblinding of active treatment versus placebo at Week 18A (for the purposes of determining whether subjects should continue in Part A or proceed to Part B), and emergency unblinding of IMP (SPD503 or atomoxetine). 6.2.4 Unblinding of the Treatment Assignment In this study, blinding to treatment assignment (SPD503, atomoxetine, placebo) is used to avoid bias in Part A, in which the comparator arms		Section 6.2.1, Section 6.2.4, Section 9.3

Summary of Change(s) Since Last Version of Approved Protocol (Amendment 2.0, dated 28 May 2019)		
Amendment Number: 2.1	**Amendment Date:** 11 July 2019	**Global/Country/Site** UK
Description of Change and Rationale		**Section(s) Affected by Change**
(atomoxetine, placebo) have been included as controls for assay sensitivity and noninferiority. **Part A (blinded, placebo-controlled):** The treatment assignment (SPD503, atomoxetine, placebo) must not be broken for subjects during their participation in Part A of the study, except in emergency situations when the identification of the IMP is required for further treatment of the subject. If IMP unblinding is required, the treatment assignment should be broken using the IRT system. The investigator should contact the medical monitor before unblinding if feasible and by all means as soon as possible after IMP unblinding. **Transition from Part A to Part B:** In Part A, Week 18A, the IRT system will notify the site to transfer placebo subjects to Part B of the study. Subjects receiving active treatment will remain blinded to the specific treatment (ie, SPD503 or atomoxetine) and continue in Part A until Week 53A. **Part B (open-label):** Upon entry into Part B of the study, all subjects will receive open-label SPD503. However, subjects who received active treatment in Part A must remain blinded regarding which drug they received in Part A, in order to avoid influencing data queries related to these subjects' data in Part A. If the treatment assignment is broken for any reason other than the transition from Part A to Part B, then the date, the signature of the person who broke the code and the reason for breaking the code will be recorded using the source documents. Upon study-blind breaking, the subject will be withdrawn from the study but will be followed-up for safety purposes. Any code-breaks that occur must be reported to the contract research organization (CRO) and sponsor. After subject's blinding is broken, the code-break information will be held by the pharmacist/designated person at the site and by the CRO's medical monitor for the study or designee. 9.3 Data Handling Considerations Data that may potentially unblind the treatment assignment in Part A (eg, IMP serum concentrations, treatment allocation, and IMP preparation/accountability data) will be handled with special care during the data cleaning and review process.		
Clinical laboratory assessment of bicarbonate was added to the biochemistry analysis as an essential electrolyte determination.		Section 7.2.2.5

Summary of Change(s) Since Last Version of Approved Protocol (Amendment 1.1)		
Amendment Number: **2.0**	**Amendment Date:** **28 May 2019**	**Global/Country/Site** **Europe, US**
Description of Change		**Section(s) Affected by Change**
The Sponsor's medical monitor has changed, from PPD, MD, PhD, to PPD, MD.		Protocol Signature Page
Administrative change: The name of the ICH has been updated, from "International Council on Harmonisation" to "International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use."		Protocol Signature Page Abbreviations
The section containing the emergency contact information has been updated to reflect the most current Sponsor template including the latest contact information for the Shire Global Drug Safety Department: Fax: 1-484-595-8155 Email: drugsafety@shire.com		Emergency Contact Information
The section describing the reporting of product quality complaints has been updated to include additional guidance, including the name of the reporting form, as well as examples of the kinds of product complaints that should be reported.		Product Quality Complaints
Addition of US sites to the study, with existing total of 65 sites now split between the EU (45 sites) and the US (20 sites).		Synopsis Section 3.3
Inclusion Criterion 7 mentions the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice Guideline E6, and has been updated to mention the Revision 2 (R2).		Synopsis Section 4.1.1
The requirement for follow-up visit at the end of Study Part A was modified for subjects who received placebo in Part A: • Subjects randomized to the placebo treatment arm will continue with QD dosing from Week 5A for children and Week 8A for adolescents through Week 18A. These subjects can begin baseline visit assessments for Study Part B and skip ~~at~~ the follow-up visit after completion of Study Part A assessments at Visit 11A (Week 18A). This follow up visit and assessment are not necessary for subjects who received placebo, and the open-label assessments no longer require the placebo versus treated groups to be blinded and continue to Part B. The following footnote was added to Table 1: Placebo subjects can skip the follow-up visit after completion of Study Part A assessments at Visit 11A (Week 18A), and proceed immediately to baseline visit assessments for Study Part B.		Synopsis Section 3.1 Table 1
The line "AEs/TEAEs" has been changed to "AEs" to clarify that all AEs are collected.		Table 1
The following language was clarified: "All subjects ~~randomized to~~ who receive active treatment (blinded SPD503 or atomoxetine in Part A or unblinded SPD503 in Part B) ~~either the SPD503 or atomoxetine treatment arm~~ will undergo a scheduled 2-week dose taper to ensure proper downward dose titration of SPD503 at the end of the dose-maintenance period or ET in both Study Parts A and B, as applicable.		Section 3.1

Summary of Change(s) Since Last Version of Approved Protocol (Amendment 1.1)		
Amendment Number: **2.0**	**Amendment Date:** **28 May 2019**	**Global/Country/Site** **Europe, US**
Description of Change		**Section(s) Affected by Change**
A cross reference was added to the section describing the study population, to direct the reader to additional instructions about informed consent: "See Section 10.3.1 for further consenting instructions."		Section 4
A clarification was added: Double-blinded treatment will be for up to 49 weeks (except for subjects on placebo), including the dose-taper period.		Section 6.2.3
A clarification was added to explain why atomoxetine dose-optimization only applies to Part A: **Atomoxetine Dose-optimization (Study Part A only)** The dose of atomoxetine will be optimized in Part A, since Part B will entail open-label treatment with SPD503.		Section 6.2.3.1
The description of the dose-taper period was clarified: "All subjects randomized in active ~~the SPD503 or atomoxetine~~ treatment arms will undergo a scheduled 2-week dose taper to ensure proper downward dose titration of SPD503 at the end of the dose-maintenance period or ET in both Study Parts A and B, as applicable."		Section 6.2.3.3
The section was revised for clarity as follows: The treatment assignment must not be broken for subjects during their participation in Part A of the study, except in emergency situations when the identification of the IMP is required for further treatment of the subject. If IMP unblinding is required, the treatment assignment should be broken using the IRT system. The investigator should contact the medical monitor before unblinding if feasible and by all means as soon as possible after IMP unblinding. If the treatment assignment is broken, then the date, the signature of the person who broke the code and the reason for breaking the code will be recorded using ~~the IRT and~~ the source documents. Upon study-blind breaking, the subject will be withdrawn from the study but will be followed-up for safety purposes. Any code-breaks that occur must be reported to the contract research organization (CRO) and sponsor. After subject's blinding is broken, the code-break information will be held by the pharmacist/designated person at the site and by the CRO's medical monitor for the study or designee. A provision for study unblinding during ~~in~~ Study Part A will be provided to ensure adequate treatment of the subject in case of an emergency.		Section 6.2.4
The requirement for informed consent was clarified by adding the following statement: "Subjects must be reconsented if they reach the age of legal responsibility during the study, based on applicable local and national laws."		Section 7.1.1; Section 10.3.1

Summary of Change(s) Since Last Version of Approved Protocol (Amendment 1.1)		
Amendment Number: **2.0**	**Amendment Date:** **28 May 2019**	**Global/Country/Site** **Europe, US**
Description of Change		**Section(s) Affected by Change**
Procedures at the end of the dose-maintenance period were clarified as follows: All subjects who complete the dose-maintenance period of Study Part A or who terminate early will undergo the procedures indicated for ET at Visit 14A (Week 49A) in the Study Schedules. Likewise, in Study Part B, all subjects who complete the dose-maintenance period or who terminate early will undergo the procedures indicated for Visit 13B (Week 49B) in the Study Schedules.		Section 7.1.3.2
The language was clarified as follows: "After completion of the dose-maintenance period, or upon ET, subjects ~~randomized to the~~ who received SPD503 treatment ~~arm~~ (blinded active or placebo) in Study Part A and all subjects in Study Part B will be required to taper downward the last dose-maintenance dose over 2 weeks. The dose-taper schedule will be determined by the last maintenance dose of SPD503 as presented in Table 6."		Section 7.1.3.3
The following sentence was revised for clarity: "Corrections can only be made to scales by the subject or parent/LAR during a study visit. In the event that paper forms are used and the subject/parent/LAR marks an answer in error, the entry may be corrected by drawing a single line through the error and initialing and dating the change."		Section 7.2
The urine drug and alcohol screening requirement was removed for Part B in order to maintain blinding of the specific drug assignment in treated subjects: "For the subject to be eligible for the study, the results from the urine drug and alcohol screen must be negative at screening (Study Part~~s~~ A ~~and B only~~) (except for the subject's current ADHD psychostimulant, if applicable)."		Section 7.2.2.6
The text and table name were clarified and made consistent: As shown in Table 9, approximately 45 mL of blood is expected to be withdrawn from subjects randomized to active IMP treatment arms in Study Part A for the 2-year study. Subjects randomized to placebo treatment in Study Part A will have 3 blood withdrawals as shown in Table 1 and Table 2 with approximately 27 mL of total blood.		Section 7.2.4
The table title and one column heading been reworded to clarify that it includes blood samples for both parts of the study, ie, Table 9: Volume of Blood to Be Drawn from Subjects Randomized to Active IMP Treatments in Study Part A and Part B		Table 9
Additional postpartum follow up has been added at 1 year postpartum, consistent with the most recent protocol template.		Section 8.1.6
This section was updated to include more specific and current information about the guidances being followed in this study:		Section 10 Section 10.1.1

Summary of Change(s) Since Last Version of Approved Protocol (Amendment 1.1)		
Amendment Number: **2.0**	**Amendment Date:** **28 May 2019**	**Global/Country/Site** **Europe, US**
Description of Change		**Section(s) Affected by Change**
"This study will be conducted in accordance with this protocol, the ICH Guideline for Good Clinical Practice E6 (Integrated Addendum to ICH E6[R1]: Guideline for Good Clinical Practice E6[R2] Current Step 4 version, 9 November 2016), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives (2001/20/EC; 2005/28/EC), and applicable national and local regulatory requirements. ~~This study will be conducted in accordance with current applicable regulations, ICH and any updates, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.~~"		Section 10.2.1
Administrative change: The protocol history has been updated to reflect the current amendment.		Appendix 8

Summary of Change(s) Since Last Version of Approved Protocol Amendment 1		
Amendment Number: **1.1**	**Amendment Date:** **10 Apr 2019**	**Global/Country/Site** **Europe**
Description of Change		**Section(s) Affected by Change**
Obsolete reporting information was removed from the Product Quality Complaints page: S~~PQCROW@shire.com~~ There is now a single address for reporting product complaints in all regions. Administrative changes were made in this section accordingly.		PRODUCT QUALITY COMPLAINTS
A typographical error has been corrected from "the European Union" to "Europe" in accordance with the original protocol version (16 Jun 2017): concerning the **Sites and Regions** in which the study will be conducted.		STUDY SYNOPSIS; Section 3.3 Sites and Regions, and in various locations in the text
Study Period has been updated to reflect a 2019 start date.		STUDY SYNOPSIS
Added stratification by sex (male or female) as well as by age subgroup.		STUDY SYNOPSIS; Section 6.2.2 Allocation of Subjects to Treatment Arm; Section 9.8.1 Study Part A: Double-blinded Evaluation
Inclusion criterion #2 was modified as follows, to clarify the nature of the assessment: 2. Subject must meet DSM-5 criteria for a primary diagnosis of ADHD based on a detailed psychiatric evaluation using the Kiddie-Schedule for Affective Disorders-Present and Lifetime Version (K-SADS-PL) Uby a trained child and adolescent psychiatristU at screening (Visit 1A). This change was made consistent throughout the text.		STUDY SYNOPSIS; Section 4.1.1 Study Part A Inclusion Criteria; Section 7.1.1 Screening; Section 7.2.1.4 Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version

Summary of Change(s) Since Last Version of Approved Protocol Amendment 1		
Amendment Number: **1.1**	**Amendment Date:** **10 Apr 2019**	**Global/Country/Site** **Europe**
Description of Change		**Section(s) Affected by Change**
Inclusion criterion #9 was modified as follows, to clarify the cutoff for the inclusion of subjects who do not have hypertension (with hypertension being defined as a blood pressure readings in the ≥95th percentile, adjusted for height and weight): 9. Subject has supine and standing blood pressure (BP) measurements S~~within~~ SUless than the 95th percentile for age, sex, and height at both screening (Visit 1A) and baseline (Visit 2A). This criterion was also modified in Section 4.1.1.		STUDY SYNOPSIS; Section 4.1.1 Study Part A Inclusion Criteria; Section 4.2.1 Study Part B Inclusion Criteria
In addition, Appendix 4 and Appendix 5 contain a corresponding change. The text associated with tables used to identify blood pressure values within these percentiles, has been modified as follows: "All blood pressure values provided are the 95% for age and height percentile so the subject's systolic and diastolic blood pressure readings at screening and baseline visits of Study Parts A and B must be less than S~~or equal to~~S the corresponding value below:"		Appendix 4 Blood Pressure for Boys by Age and Height Percentile
Inclusion criterion #11 was clarified as follows: 11. Subject is able to swallow intact tablets Uand capsulesU.		Appendix 5 Blood Pressure for Girls by Age and Height Percentile
Exclusion criterion was modified to include the following definition of orthostatic hypotension: U(*Orthostatic hypotension is defined as a sustained reduction of systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of 10 mm Hg within 3 minutes of standing from supine.)		STUDY SYNOPSIS; Section 4.1.1 Study Part A Inclusion Criteria
Exclusion criteria #21 and #22 were added: 21. USubject has a history of a seizure disorder (except for a single childhood febrile seizure episode that occurred before the age of 3 years) 22. USubject is well-controlled on his/her current ADHD medication with acceptable tolerability, and the parent/treating physician does not object to the current medication. Criterion #21 was added to be consistent with the exclusion criterion 14 in Part B. Criterion #22 represents standard practice as an ethical consideration and was inadvertently omitted.		STUDY SYNOPSIS (Criterion #14); Section 4.1.2 Study Part A Exclusion Criteria (Criterion #14); Section 4.2.2 Study Part B Exclusion Criteria (Criterion #13)
Removed a portion of the sentence, for clarity: "S~~Because t~~STThe effect of SPD503 on cognition will be assessed and interpreted on the totality of the dataS~~, the sample size has been estimated as a reference~~S."		STUDY SYNOPSIS; Section 4.1.2 Study Part A Exclusion Criteria
A typographical error has been corrected in the Study Schedule Table 1. Assessment forms CHIP-CE and APRS should be completed at Baseline Visit 2A (BLV2A) to establish the baseline values rather than at V3A.		STUDY SYNOPSIS; Section 9.6 Sample Size Calculation and Power Considerations
To prevent the potential for accidental unblinding, urine drug/alcohol testing will be deleted from Screening (V1B) and Baseline (V2B) visits		Study Schedule Table 1

Summary of Change(s) Since Last Version of Approved Protocol Amendment 1		
Amendment Number: **1.1**	**Amendment Date:** **10 Apr 2019**	**Global/Country/Site** **Europe**
Description of Change		**Section(s) Affected by Change**
of Study Part B. Any reference to urine drug/alcohol testing in Study Part B has been removed.		
An entirely new section, Section *1.2.1* (Anticipated Benefits and Risks) has been added as an aid to the investigator in forming an opinion about the benefits and risks to participants who are being included in the clinical trial.		Section 1.2 Product Background and Clinical Information
The restriction on the crushing of the investigational medicinal product (IMP) has been corrected, since some of the IMPs are capsules: 4. Tablets Uand capsulesU should not be crushed, chewed, or broken before swallowing.		Section 4.3 Restrictions
Clarified that subjects will be referred to their primary care physician or psychiatrist for care after the study ends.		Section 7.1.5 Additional Care of Subjects After the Study
The text in Section 8.2.7 (Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting) has been revised in order to clarify that the previous language ("related, unexpected SAEs") actually refers to "suspected, unexpected serious adverse reactions (SUSARs)."		Section 8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting
The following text has been added, regarding data handling: "The analyses for the primary safety endpoint and other secondary CANTAB endpoints will be performed using the MMRM to handle potential missing data. If the severity is missing for an AE during treatment, then a severity of "Severe" will be assigned. If the relationship to IP is missing for an AE starting during treatment, a causality of "Related" will be assigned. The imputed values for severity and relationship will be used for AE summaries. For purposes of reporting early termination assessments during the study, each early termination visit will be assigned the next nominal visit number after the last completed visit. This rule applies to the safety and efficacy variables that are analyzed and/or summarized by visit. The SAP will provide additional description of how missing, unused, and spurious data will be address. The SAP will be finalized before unblinding to preserve the integrity of the statistical analysis and study conclusion."		Section 9.8 Study Analyses
The version of the Columbia-Suicide Severity Rating Scale (C-SSRS) has been changed per the rating scale author's recommendation: Children's Baseline/Screening, 6/23/2010 Children's Since Last Visit, 6/23/2010 To: Baseline/Screening, 1/14/2009 Since Last Visit, 1/14/2009		Appendix 1
Administrative changes have been made throughout the document to reflect the current version number (v1.1) and date (10 April 2019).		Throughout
Moved Summary of Changes Since Last Version of Approved Protocol (from original protocol to Amendment 1) to appendix		Appendix 8 Protocol History

Summary of Change from Original Protocol to Protocol Amendment 1		
Amendment Number: **1**	**Amendment Date:** **02 May 2018**	**Global/Country/Site** **European Union**
Description of Change		**Section(s) Affected by Change**
Changed wording that subjects could begin baseline visit assessments (rather than screening visit assessments) for Study Part B at the follow-up visit after completion of Study Part A and deleted term "early termination (ET)"		Synopsis Methodology section and Section 3.1 Study Design and Flow Chart
Removed redundant text regarding number of tablets and capsules administered		Synopsis Investigational product, dose, and mode of administration section
Added W18A time point for collection of Tanner staging Added Subject continuation assessments at appropriate visits Deleted instruction for sampling to occur during fasted state in Footnote H		Table 1 Study Part A – Double-blinded Evaluation: SPD503, Atomoxetine, and Placebo through Week 18A; SPD503 and Atomoxetine through Week 52A
Added to Footnote C that clinical laboratory tests for subjects who received placebo in Part A would not be required at V1B and V2B if subject entered Part B within 35 days of Part A completion (V18A). Deleted urine drug/alcohol screen from V10B/W10B and V13B/ET, W49B Deleted instruction for sampling to occur during fasted state in Footnote H		Table 2 Study Part B – Open-label Evaluation of SPD503
Updated description of ADHD diagnostic criteria		Section 1.1 Indication and Current Treatment Options
Added clarification that including those who were randomized to placebo		Section 4.5 Discontinuation of Subjects
Removed bullet point regarding documentation of the most recent psychoactive stimulant on the PSMQ		Section 7.1.2 Baseline
Added instruction regarding timing of biochemistry blood sampling at screening visit (visit 1A), in relation to fasting or non-fasting state and that subsequent samples should be drawn with the subject in the same fasting status. Changed blood collection volumes for Biochemistry to 7 mL and Hematology to 2 mL Changed total blood volume to read: …approximately 45 mL of blood is expected to be withdrawn from subjects randomized to active IMP treatment arms in Study Part A for the 2-year study. Subjects randomized to placebo treatment will have 3 blood withdrawals as shown in Table 1 and Table 2 with approximately 27 mL of total blood. Updated Footnote B to: An additional sample will be required if the baseline visit occurs more than 35 days after screening (applies to Study Parts A and B) or as requested by the investigator due to safety reason.		Section 7.2.2.5 Clinical Laboratory Evaluations; Section 7.2.4 Volume of Blood to be Drawn from Each Subject; Table 9 (Volume of Blood to be Drawn from Each Subject)

Summary of Change from Original Protocol to Protocol Amendment 1		
Amendment Number: **1**	**Amendment Date:** **02 May 2018**	**Global/Country/Site** **European Union**
Description of Change		**Section(s) Affected by Change**
Updated urine drug screen testing to include methamphetamine, MDMA (Ecstasy), and oxycodone; testing for propoxyphene and methaqualone has been eliminated		Section 7.2.2.6 Urine Drug and Alcohol Screen
Added section to clarify study procedure/interpretation of C-SSRS findings at each visit		Section 7.2.2.10 Suitability of the Subject to Remain in the Study
Updated version for Columbia-Suicide Severity Rating Scales Added Prior Stimulant Medication Questionnaire to table		Appendix 1 Table of Evaluation Scales
Added Prior Stimulant Medication Questionnaire		Appendix 3.1 Prior Stimulant Medication Questionnaire