A Phase 4, Multicenter, 2-part Study Composed of a 1-Year 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

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This study has been transitioned to CTIS with ID 2022-502630-71-00 check the CTIS register for the current data. Primary objective: To evaluate the comparative long-term safety of TAK-503 treatment (formerly known as SPD503) in children and...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55836

Source
ToetsingOnline

Brief title
SPD503-401

Condition

- Other condition

Synonym
Attention-deficit/hyperactivity disorder (ADHD)

Health condition

Attention-deficit/hyperactivity disorder (ADHD)

Research involving
Human

Sponsors and support

Primary sponsor: Takeda
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: Attention-deficit Hyperactivity Disorder (ADHD), Phase 4, TAK-503

Outcome measures

Primary outcome

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

task.

Secondary outcome

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

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 scores for Learning Problems and Executive Functioning

subscales

Study description

Background summary

Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous neurobehavioral disorder and the essential feature of ADHD 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.

Psychostimulant medications such as methylphenidate and amphetamine have been used to treat
behavior problems in children since 1937), including ADHD and its diagnostic precursors. 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. 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 (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 α2-adrenergic receptors.

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.

Study objective

This study has been transitioned to CTIS with ID 2022-502630-71-00 check the CTIS register for the current data.

Primary objective: To evaluate the comparative long-term safety of TAK-503 treatment (formerly known as SPD503) 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 demonstrate the noninferiority of 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, provided assay sensitivity can be demonstrated.

Study design

A Phase 4, Multicenter, 2-part Study Composed of a 1-Year Randomized, Double-blind, Parallel-group, Placebo-controlled, Active-comparator, Dose-optimization Evaluation followed by a 1-Year Open-label Evaluation

Intervention

Patients should visit the clinics and be willing to receive their study drug

comparator an/or placebo according to the dosing schema.
Furthermore their data of Medical history and demographic data will be collected They must undergo physical and vital signs examinations. An electrocardiogram will be made. Blood and urine will be collected. Patients will have to complete several questionnaires

Study burden and risks

Five key, well-controlled, short-term studies (2 pivotal fixed-dose studies and 3 pivotal dose-optimized studies) and 2 long-term studies of 1- to 2-years provide substantial evidence for the efficacy of TAK-503 for the treatment of ADHD in pediatric subjects:
•Short-term, fixed-dose Studies SPD503-301 and SPD503-304 (US children and adolescents); and Shionogi Study 1306A3122 (weight-based fixed dose (mg/kg) in Japanese children and adolescents).
•Short-term, dose-optimization Studies SPD503-312 (US adolescents); SPD503-316, which included the active control STRATTERA (European and North American children and adolescents).
•Long-term maintenance of efficacy Study SPD503-315 (European and North American children and adolescents) and Shionogi Study 1307A3131 (Japanese children and adolescents).
Other placebo-controlled Phase 3 studies also provide evidence for the efficacy of TAK-503 for the treatment of ADHD in pediatric subjects, including short-term Studies SPD503-314 in children aged 6-12 years administered morning versus evening dosing, SPD503-313 in pediatric subjects aged 6-17 coadministered with psychostimulants, and SPD503-307 in children aged 6-12 years with symptoms of oppositionality.
Supportive evidence of long-term efficacy is provided from 3 Phase 3, uncontrolled, open-labelstudies: Studies SPD503-303, SPD503-305, SPD503-318 as open-label extension studies of SPD503-301, SPD503-205/SPD503-304, and SPD503-315/SPD503-316, respectively. Further evidence of short-term efficacy is provided from 3 Phase 2 studies: Studies SPD503-202 (placebo controlled), SPD503-205 (open label), and SPD503-206 (placebo controlled).

The primary and key secondary efficacy results for the 5 key short-term and 2 long-term studies are presented graphically in Table 11 of the investigator brochure.
Additional support of efficacy was demonstrated in 7 additional studies in which subjects who were treated with TAK-503 had significant improvements in the ADHD-RS-IV compared with subjects who received placebo (Studies SPD503-206, SPD503-313, and SPD503-314) or compared with baseline (open-label Studies SPD503-205, SPD503-303, SPD503-305, and SPD503-318. The benefit/risk ratio of the proposed trial is therefore considered to be positive.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

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)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 (ICH) Good Clinical Practice (GCP) Guideline E6 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 within 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.

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/or

alcohol screen at screening.
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.
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

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	29-01-2020
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Intuniv
Generic name:	TAK-503
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Strattera
Generic name:	Atomoxetine hydrochloride
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	06-06-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-08-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-01-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-03-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-04-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-07-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-09-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-10-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-03-2021

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-10-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-12-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-04-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-09-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-10-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2022-502630-71-00
EudraCT	EUCTR2018-000821-29-NL
CCMO	NL66948.042.19