A Phase 3, Open-label, Multicentre Study to Provide Access to Guanfacine Hydrochloride Extended Release for European Subjects with Attention-deficit/Hyperactivity Disorder (ADHD) who Participated in Study SPD503-315 or SPD503-316

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cognitive and attention disorders and disturbances
Study type	Interventional

Summary

ID

NL-OMON39256

Source
ToetsingOnline

Brief title
Study to provide Access to Guanfacine Hydrochloride in Subjects with ADHD

Condition

- Cognitive and attention disorders and disturbances

Synonym
ADHD, Attention Deficit Hyperactivity Disorder

Research involving
Human

Sponsors and support

Primary sponsor: Shire
Source(s) of monetary or material Support: Shire Pharmaceutical Development;Ltd.

Intervention

Keyword: ADHD, extension study, Guanfacine Hydrochloride

Outcome measures

Primary outcome

The primary objective of this study is to provide access to SPD503 following participation in SPD503-315 or SPD503-316.

The primary outcome of this study is to evaluate the long-term safety of SPD503. The evaluation of safety will be based on the occurrence of TEAEs, specific evaluation of vital signs, electrocardiogram (ECG) and the Columbia-Suicide Severity Rating Scale (C-SSRS) results. Additionally, the effects on growth will be assessed.
The C-SSRS is a semi-structured interview that captures the occurrence, severity, and frequency of suicide related thoughts and behaviours during the assessment phase. The interview includes definitions and suggested questions to solicit the type of information needed to determine if a suicide-related thought or behaviour occurred.

The primary endpoints of this study are the long-term safety of SPD503 as follows:

* Occurrence of TEAEs

* Specific evaluation of BP and pulse

* ECG results

* C-SSRS

* Effects on growth will be assessed.

Secondary outcome

* The ADHD-Rating Scale-IV (ADHD-RS-IV) consists of 18 items designed to reflect current symptomatology of ADHD based on DSM-IV-TR criteria. The scale will be sub-divided into 2 subscales of 9 items each: hyperactivity/impulsivity and inattentiveness.

* The Clinical Global Impression (CGI) Scale permits a global evaluation of a subject*s severity of illness, and will be carried out at all visits.

The secondary efficacy endpoints of the study are listed below:

* The change from baseline in ADHD-RS-IV total score and the hyperactivity/impulsivity and inattention subscale scores at each of Visits 3 19. Baseline will be defined in 2 ways; firstly as the Baseline Visit from the antecedent study, and secondly as Visit 2 from this study.

* The CGI-S at each of Visits 2 19

Study description

Background summary

The symptoms and subsequent impairment associated with ADHD are increasingly being recognised as a lifetime disease.

While the SPD503 clinical program has studied the efficacy, safety, and tolerability of SPD503 in treating core symptoms of ADHD in children and adolescents aged 6-17 years, the majority of the controlled studies have been of short duration (up to 8 weeks). Two, 2-year, open-label studies have confirmed the safety and ongoing efficacy in this patient population. Study SPD503-318 has been designed to provide up to 2 years access to SPD503 for European subjects who participated in study SPD503-315 or SPD503-316,

Study objective

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Study design

This study is a Phase 3, multicentre, open-label study designed to provide access to SPD503. Children and adolescents (aged 6-17 years of age inclusive at time of consent in the antecedent SPD503 Studies SPD503-315 or SPD503-316) who have been diagnosed with ADHD will be enrolled and treated with SPD503 for up to 104 weeks.
The study will have 4 phases: (1) a 3-35 day Screening Phase including washout; (2) a 102-week Treatment Phase comprising a 7 week Dose Optimisation Period and a 95-week Maintenance Period; (3) a 2-week Dose taper Period; and (4) a Safety Follow-up Period including a Safety Follow-up Visit (7 [+2] days after the last dose of investigational product. Subjects will be required to visit the site a maximum of 21scheduled times during the study.
Subjects will be screened to establish eligibility for study participation. Subjects should have completed the Dose-taper and Safety Follow-up Visits of their antecedent study and will therefore be eligible for screening after a minimum of 1 week following their last dose in the antecedent study. The Screening Visit for this study can occur as early as the Dose-taper Visit for the antecedent study. Those who meet eligibility requirements will undergo medication washout, if applicable.
Subjects enrolling from SPD503-315 must have a gap in treatment of *7 days between their last dose in Study SPD503-315 and first dose in this study.
Subjects enrolling from SPD503-316 must have a gap in treatment of *30 days,

between their last dose in Study SPD503-316 and first dose in this study. During the 7 week Dose Optimisation Period, visits will be scheduled every 7 days (* 2 days) to assess safety and tolerability, and to allow clinicians to titrate subjects to their optimal dose of SPD503 based on clinical judgement of tolerability and efficacy (using a review of treatment emergent adverse events (TEAEs), and changes in CGI-S and ADHD-RS-IV scores). All subjects will be started at 1mg and may be titrated in weekly increments of 1mg until an optimal dose is reached. Children aged 6 12 years will not be permitted to titrate above 4mg/day and adolescents aged 13 years and older will not be permitted to titrate above the maximum allowed daily dose per their weight group below:
* 25.0-41.4kg = maximum of 4mg/day
* 41.5-49.4kg = maximum of 5mg/day
* 49.5-58.4kg = maximum of 6mg/day
* 58.5kg and above = maximum of 7mg/day.
Following titration to an optimal dose of SPD503, subjects will continue into the Maintenance Period with daily treatment with SPD503 for the next 95 weeks with visits in intervals of 4 weeks, 12 weeks, or 14 weeks. During the Maintenance Period, the Investigator may make further dose adjustments as needed based upon TEAEs and the clinical judgement of tolerability and efficacy (using a review of TEAEs, and changes in CGI-S and ADHD RS-IV scores). These dose adjustments may be to a higher dose, based on the subject*s current age and weight. Children who turn 13 years or older during the Maintenance Period may be permitted to increase the dose above 4mg/day based on their current weight. The dose may be increased or decreased by 1mg at any scheduled or unscheduled visit during the study if deemed appropriate by the Investigator. Upon completion or early withdrawal, all subjects will undergo a 2-week Dose-taper Period to down titrate their dose.

A follow-up visit will occur for all subjects 7 (+2) days after the last dose of investigational product to follow up on safety assessments including any adverse events (AEs)/serious adverse events (SAEs) that were ongoing at the previous visit, and changes in concomitant medications. Adverse events/SAEs occurring up to the time of the follow-up visit will be captured. Appropriate follow-up should continue until all safety concerns, in the Investigator*s opinion, are resolved.

Intervention

The Sponsor will provide SPD503 (extended release guanfacine hydrochloride) in 1, 2, 3, and 4mg strength tablets. During the study, subjects will be instructed to take 1 or more tablets daily upon awakening according to their age and weight. For subjects 25.0-41.4kg the maximum dose is 4mg, 41.5-49.4kg the maximum dose is 5mg, 49.5-58.4kg the maximum dose is 6mg, 58.5kg or greater the maximum dose is 7mg. For children aged 6 12 years, the maximum dose will be 4mg, regardless of weight.

Study burden and risks

Patients will take part in the study for maximum 105 weeks (21 visits) During the study the patients will be subjected to the procedures as described under question E4. A detailed description of the patient load is included in appendix 2 of the informed consent.

Taking SPD503 may cause side effects or possible discomfort. Serious side effects, considered related to the study drug, that have been reported are seizure, low blood pressure while standing and fainting. An overview of the risks is also described in appendix 3 of the informed consent.

Contacts

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Scientific
Shire

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Elderly (65 years and older)

Inclusion criteria

For subjects enrolling from antecedent Study SPD503-315:;Subjects will be eligible if they met the response criteria for entry into Phase 2, were;randomized, and completed Phase 2 or withdrew early because the protocol-defined treatment;failure criteria was met.;For subjects enrolling from antecedent Study SPD503-316:;Children age 6-12, regardless of treatment group, must complete 10 weeks of double-blind;treatment, reach Visit 15/Final, and complete the 2-week dose taper.;Adolescents age 13 and older, regardless of treatment group, must complete 13 weeks of;double-blind treatment, reach Visit 15/Final, and complete the 2-week dose taper.;For all subjects:;1. For subjects where Study SPD503-318 was not available at the time of subject*s;final visit in the antecedent study (SPD503-315 or SPD503-316), subject may still;screen unless they are well-controlled on another ADHD medication with;acceptable tolerability and the parent/caregiver is satisfied with the current ADHD;medication.;2. Subject satisfied all entry criteria for the antecedent study (SPD503-315 or;SPD503-316).;3. Subject who is a female of child-bearing potential (FOCP), defined as >9 years of;age or <9 years of age and is post-menarchal, must have a negative serum beta;Human Chorionic Gonadotropin (*-hCG) pregnancy test at the Screening Visit;(Visit 1) and a negative urine pregnancy test at the Baseline Visit (Visit 2) and;agree to comply with any applicable contraceptive requirements of the protocol.;4. Subject*s parent or legally authorised representative (LAR) must provide signature;of informed consent, and there must be documentation of assent (if applicable) 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 Conference on Harmonisation (ICH) Good Clinical Practice (GCP);Guideline E6 and applicable regulations, before completing any study-related;procedures.;5. Subject and parent/LAR are willing, able, and likely to fully comply with all the;testing and requirements defined in this protocol, including oversight of dosing.;Specifically, the parent/LAR must be available upon awakening, to dispense the;dose of investigational product for the duration of the study.;6. Subject has a supine and standing blood pressure (BP) measurement within the;95th percentile for age, sex, and height.;7. Subject is functioning at an age-appropriate level intellectually, as deemed by the;Investigator.;8. Subject is able to swallow intact tablets.

Exclusion criteria

1. Subject has any current, controlled (requiring a prohibited medication or behavioural;modification program) or uncontrolled, co-morbid psychiatric diagnosis [except;oppositional defiant disorder (ODD)], including any severe comorbid Axis II disorders;or severe Axis I disorders such as post traumatic stress disorder (PTSD), bipolar;illness, psychosis, pervasive developmental disorder, obsessive-compulsive disorder;(OCD), substance abuse disorder, or other symptomatic manifestations or lifetime;history of bipolar illness, psychosis or conduct disorder that, in the opinion of the;Investigator, contraindicate treatment with SPD503 or confound efficacy or safety;assessments. Review the Kiddie Schedule for Affective Disorders and Schizophrenia *;Present and Lifetime version (K-SADS-PL) from the antecedent study to confirm;diagnosis, if

necessary.;2. Subject who early terminated from Study SPD503-315 or Study SPD503-316 for;protocol non-adherence, subject non-compliance, an adverse event (AE), serious;adverse event (SAE), or withdrawal by subject.;3. Subject experienced any clinically significant AE in a prior SPD503 study (SPD503-;315 or SPD503-316) that, in the opinion of the Investigator, would preclude exposure;to SPD503.;4. Clinically important abnormality on urine drug and/or alcohol screen at the Screening;Visit (Visit 1).;5. Subject has taken any investigational medicinal product as follows: last dose of;investigational product in Study SPD503-315 within 7 days prior to the Baseline Visit;(Visit 2); investigational product in Study SPD503-316 within 30 days prior to the;Baseline Visit (Visit 2); any other investigational product within 30 days prior to the;Baseline Visit (Visit 2) or any other ADHD medication within 30 days prior to;Baseline Visit (Visit 2).;6. Subject is significantly overweight based on Center for Disease Control and;Prevention Body Mass Index (BMI)-for-age sex-specific charts at the Screening Visit;(Visit 1). Significantly overweight is defined as a BMI >95th percentile.;7. Children aged 6 to 12 years with a body weight of less than 25.0kg or adolescents;aged 13 years and older with a body weight of less than 34.0kg at the Screening Visit;(Visit 1).;8. Subject has any condition or illness including clinically significant abnormal;laboratory values at the Screening Visit (Visit 1) which, in the opinion of the;Investigator, represents an inappropriate risk to the subject and/or could confound the;interpretation of the study.;9. Subject is currently considered a suicide risk in the opinion of the Investigator, has;previously made a suicide attempt, or has a prior 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.;10. Subject has clinically significant ECG findings, as judged by the Investigator with;consideration of the central ECG laboratory*s interpretation, at the Baseline Visit;(Visit 2).;11. Subject has a known or suspected allergy, hypersensitivity, or clinically significant;intolerance to guanfacine hydrochloride, or any components found in SPD503.;12. Subject has a history of alcohol or other substance abuse or dependence, as defined by;DSM-IV-TR (with the exception of nicotine) within the last 6 months.;13. Subject has a history of a seizure disorder (other than a single childhood febrile;seizure occurring before the age of 3 years) or the presence of a serious tic disorder;including Tourette*s syndrome.;14. Subject has a known history or presence of structural cardiac abnormalities, serious;heart rhythm abnormalities, syncope, cardiac conduction problems (e.g., clinically;significant heart block), exercise-related cardiac events including syncope and pre;syncope, or clinically significant bradycardia.;15. Subject with orthostatic hypotension or a known history of controlled or uncontrolled;hypertension.;16. Current use of any prohibited medication or other medications, including herbal;supplements, that affect BP or heart rate 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 [i.e., antihistamines]) in violation of the protocol specified washout;criteria at the Baseline Visit (Visit 2).;17. Subject has a medical condition, other than ADHD, that requires treatment with;medications that have central nervous system effects and/or affect performance.;18. Subject is female and is pregnant or currently lactating.;19. Subject failed screening or was previously enrolled in this study.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-08-2012
Enrollment:	21
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	SPD503 (Guanfacine hydrochloride)
Generic name:	NVT

Ethics review

Approved WMO

Date:	16-03-2012
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	25-07-2012
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	14-09-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-10-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	27-11-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-12-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-01-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-02-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-03-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	25-03-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

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
EudraCT	EUCTR2011-004668-31-NL
CCMO	NL39448.068.12