A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SPR001 (Tildacerfont) in Reducing Supraphysiologic Glucocorticoid Use in Adult Subjects with Classic Congenital Adrenal Hyperplasia

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This study has been transitioned to CTIS with ID 2023-503771-13-00 check the CTIS register for the current data. The purpose of this study is to see if tildacerfont can reduce the amount of GC (e.g., hydrocortisone) you need to take and reduce the...

Ethical review	Approved WMO
Status	Pending
Health condition type	Endocrine disorders congenital
Study type	Interventional

Summary

ID

NL-OMON52645

Source
ToetsingOnline

Brief title
SPR001-204

Condition

- Endocrine disorders congenital
- Adrenal gland disorders

Synonym
Classic Congenital Adrenal Hyperplasia (CAH); 21-hydroxylase deficiency (21-OHD)

Research involving
Human

Sponsors and support

Primary sponsor: Spruce Biosciences, Inc.
Source(s) of monetary or material Support: Spruce Biosciences;Inc

Intervention

Keyword: Classic Congenital Adrenal Hyperplasia (CAH), Reducing Glucocorticoid Use, Tildacerfont

Outcome measures

Primary outcome

Primary efficacy:

To evaluate the proportion of subjects who can reduce GC use in subjects with

CAH

Safety:

To evaluate the safety of tildacerfont in subjects with CAH

Secondary outcome

Secondary efficacy:

1. To evaluate the effect of tildacerfont in reducing the median cumulative HCe

dose in subjects with CAH

2. To evaluate the effect of tildacerfont in reducing cardiovascular risk in

subjects with CAH

3. To evaluate the effect of tildacerfont in improving homeostatic model

assessment of insulin resistance (HOMA-IR) in subjects with CAH

4. To evaluate the effect of tildacerfont on body weight after 24 weeks in

subjects with CAH

5. To evaluate the effect of tildacerfont on body weight after 52 weeks of tildacerfont treatment in subjects with CAH

6. To evaluate the percentage change in GC use in subjects with CAH

Exploratory efficacy:

7. To evaluate the proportion of subjects who can reduce GC use by 8 mg HCe in subjects with CAH

8. To evaluate the effect of tildacerfont in improving quality of life (QoL) in subjects with CAH

9. To evaluate the effect of tildacerfont on waist circumference (wc) after 52 weeks of tildacerfont treatment in subjects with CAH

10. To evaluate the effect of tildacerfont in improving HOMA-IR after 52 weeks of tildacerfont treatment in subjects with CAH

11. To evaluate the effect of tildacerfont in improving bone mineral density (BMD) after 52 weeks of tildacerfont treatment in subjects with CAH

12. To evaluate the effect of tildacerfont in reducing GC use to near-physiologic levels at Week 24 in subjects with CAH

13. To evaluate the effect of tildacerfont in use to near-physiologic levels after 52 weeks of tildacerfont treatment in subjects with CAH

14. To evaluate the effect of tildacerfont in reducing GC use to near-physiologic levels in subjects with CAH

15. To evaluate the percentage change in GC use in subjects with CAH

16. To evaluate the effect of tildacerfont in reducing cardiovascular risk in

subjects with CAH and at least one cardiovascular risk factor at baseline

17. To evaluate the effect of tildacerfont in improving BMD in subjects with CAH

18. To evaluate the effect of tildacerfont in eliminating TART(s) in male CAH

subjects with TART(s) at baseline

Study description

Background summary

CAH is an inherited genetic disorder that affects the adrenal glands, a pair of walnut-sized organs above the kidneys. The disease affects the production of steroid hormones by the adrenal glands, which include *glucocorticoids* such as cortisol, which regulate the body*s response to illness or stress. People with CAH often have abnormal levels of certain adrenal sex hormones, which can have negative effects on overall health. The current standard of care for CAH is the use of glucocorticoids (GCs). These can have significant side effects and do not always work well in treating CAH. A non-steroidal treatment option that helps control adrenal hormone levels may benefit CAH patients. This study involves the use of an investigational drug, tildacerfont (SPR001). Investigational means that the study drug has not been approved for use as a prescription or over-the-counter medicine. The purpose of this study is to see if tildacerfont can reduce the amount of GC (e.g., hydrocortisone) that patients need to take and reduce the level of certain hormones in their body.

Because this is a scientific study, it is also important to collect information about patients with CAH who are not receiving tildacerfont. Therefore, tildacerfont will be compared to *placebo*, which is a medication that looks like investigational drug but does not contain any tildacerfont or any other active compound.

Study objective

This study has been transitioned to CTIS with ID 2023-503771-13-00 check the CTIS register for the current data.

The purpose of this study is to see if tildacerfont can reduce the amount of GC (e.g., hydrocortisone) you need to take and reduce the level of certain hormones in your body.

Study design

This is a study with a 2-part treatment period that will evaluate the potential of tildacerfont to reduce GC burden in adult subjects with classic CAH who are have A4 <=2.5x ULN and are on supraphysiologic doses of GC therapy (>=30 mg/day and <=60 mg/day in HCe).
The first 24 weeks of the treatment period will be a randomized, double-blind, and placebo-controlled study in which subjects are randomized in a 1:1 ratio to receive either placebo or tildacerfont at 200 mg once daily (QD).
The 52-week Open-Label Period (day after Week 24 to Week 76) will provide subjects who complete the Placebo-Controlled Treatment Period with 52 weeks of open-label treatment with tildacerfont 200 mg QD. An optional Open-Label Extension Period will provide an open-label treatment with tildacerfont at 200 mg QD for up to 240 weeks.
During the 30-day Follow-up period, subjects will maintain the GC dose regimen and mineralocorticoid regimen (as applicable) established during the course of the study until the 30-day follow-up visit unless the Investigator determines that the subject*s clinical status necessitates a dosing change. After completion of the study, GC therapy will be managed at the discretion of the subject's treating physician.

Intervention

The drug product is a small-molecule CRF1 receptor antagonist and will be supplied as yellow, round, convex tablets containing 50 mg of drug substance. Placebo will be supplied as tablets that look identical to drug product but contain no drug substance.

At the beginning of the Placebo-Controlled Treatment Period, subjects will be randomized in a 1:1 ratio to receive either placebo or tildacerfont at 200 mg QD for 24 weeks. During the Open-Label Extension Period, all subjects will receive open-label tildacerfont at 200 mg QD for 52 weeks. Study drug will be taken orally between 6 PM and midnight, with an evening meal. The evening meal should contain <50% fat content. Study drug may be consumed up to 30 minutes after completing the evening meal, if necessary.

Subjects will also receive a subject-specific standardized oral 3-times-daily (TID) HC or twice-daily BID prednisolone regimen provided by the Sponsor. On the mornings of clinic visits, subjects should delay taking any morning dose of GC medication until after the 8 AM (±1 hour) laboratory assessments have been completed. On all other days during the study, subjects should take their GC medication at the usual time(s). Mineralocorticoid may be taken at any time of day, but its timing relative to laboratory assessments should be consistent throughout the study. During times of clinically significant physical stress such as intercurrent illness with fever, surgical procedures, or significant trauma, stress dosing with extra GC (in the form of HC) for prevention of adrenal crisis will be allowed according to *sick day guidelines*. Study drug will be discontinued in subjects who meet individual treatment-stopping criteria such as having clinically significant liver chemistry or QTcF values

at any time during the Treatment Period. During the Open-Label Extension Period, it may be possible to decrease the tildacerfont dose from 200 mg QD to 100 mg QD in subjects assessed by the Investigator as having ongoing issues with study drug tolerability, upon discussion with the Medical Monitor.

Study burden and risks

The Sponsor believes that the benefit-to-risk profile of this study is favorable. Given the serious nature of CAH and the limitations and risks of chronic steroid therapy, new treatment modalities are needed for patients with CAH. Given 1) the acceptable overall safety and tolerability profile of tildacerfont in healthy volunteers and subjects with CAH; 2) the ability to monitor the observed risk of LFT elevation, which is reversible and occurred at higher exposures than those expected in this study; and 3) the evidence of reductions in ACTH, 17-OHP, and A4 at multiple dose levels tested in previous Phase 2 studies, the Sponsor believes that the benefit-to-risk profile favors the continued clinical investigation of tildacerfont, including this investigation of tildacerfont*s potential to reduce GC use and of extended treatment with tildacerfont for up to 1 year in subjects with CAH. An optional Open-Label Extension Period will provide an open-label treatment with tildacerfont at 200 mg QD for up to 240 weeks.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male and female subjects >= 18 years at screening
2. Has a known childhood diagnosis of classic CAH due to 21-hydroxylase deficiency based on genetic mutation in CYP21A2 and/or documented (at any time) elevated 17-OHP and currently treated with HC, HC acetate, prednisone, prednisolone, methylprednisolone (or a combination of the aforementioned GCs)
3. Has LLD <= A4 <= 2.5x ULN at screening measured before AM GC dose
4. Has been on a stable, supraphysiologic dose of GC replacement (defined as >=30 mg/day and <=60 mg/day in HCe) for >=1 month before screening
5. For subjects with the salt-wasting form of CAH, subject has been on a stable dose of mineralocorticoid replacement for >=1 month before screening
6. Agrees to follow contraception guidelines (Section 5.2.5). Male subjects must also agree to refrain from donating sperm throughout the Treatment Period and for 90 days after the last dose of study drug.
7. Is able to understand all study procedures and risks involved and provides written informed consent indicating willingness to comply with all aspects of the protocol.

Exclusion criteria

1. Has a known or suspected diagnosis of any other known form of classic CAH (not due to 21-hydroxylase deficiency)
2. Has a history that includes bilateral adrenalectomy or hypopituitarism
3. Has a history of allergy or hypersensitivity to tildacerfont, any of its excipients, or any other CRF1 receptor antagonist
4. Shows clinical signs or symptoms of adrenal insufficiency
5. Has had a clinically significant unstable medical condition, medically significant illness, or chronic disease occurring within 30 days of screening, including but not limited to:
a. An ongoing malignancy or <3 years of remission history from any malignancy, other than successfully treated localized skin cancer
b. Estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73 m2
c. Current or history of liver disease (with the exception of Gilbert*s syndrome).
d. History of alcohol or substance abuse within the last year, or any significant history of alcohol or substance abuse that would likely prevent the

subject from reliably participating in the study, based on the opinion of the Investigator
e. Active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) at screening
f. Subjects who plan to undergo bariatric surgery during the study are excluded.
g. Any other condition that would impact subject safety or confound interpretation of study results
6. Psychiatric conditions, including but not limited to bipolar disorder, schizophrenia, or schizoaffective disorders that are not effectively controlled on medication and may have an adverse impact on study compliance. Symptoms including hallucinations, delusions, and psychosis are exclusionary. Additionally:
a. Increased risk of suicide based on the Investigator*s judgment or the results of the Columbia-Suicide Severity Rating Scale (C-SSRS) conducted at screening and baseline (eg, C-SSRS Type 3, 4, or 5 ideation within the past 6 months or any suicidal behavior within the past 12 months)
b. Hospital Anxiety and Depression Scale (HADS) score >12 for either depression or anxiety at screening or baseline
7. Has clinically significant abnormal electrocardiogram (ECG) or clinical laboratory results. Abnormal results that must be reviewed and discussed with the Medical Monitor to determine eligibility for this study include but are not limited to:
a. Any clinically meaningful abnormal ECG results, including Fridericia-corrected QT interval (QTcF) >450 milliseconds (ms) for male participants or >470 ms for female participants
b. Alanine aminotransferase (ALT) >2x ULN
c. Total bilirubin >1.5x ULN
d. Total bile acids >5x ULN
8. Routinely works overnight shifts
9. Subjects with travel plans/work schedules that result in significant and frequent changes in time zones (>2 hours) will require Medical Monitor approval for enrollment.
10. Females who are pregnant or nursing
11. Use of any other investigational drug from 30 days or 5 half-lives (whichever is longer) before screening to the end of the study
12. Use of the following drugs from 30 days or 5 half-lives (whichever is longer) before the start of the Treatment Period to the end of the study:
a. Rosiglitazone, aromatase inhibitors, testosterone, growth hormones, or any other medication or supplement that could impact subject safety or confound interpretation of study results
b. The drugs listed in Section 13.1, which are:
i. Moderate to strong inhibitors and/or inducers of cytochrome P450 3A4 (CYP3A4)
ii. Sensitive substrates or narrow-therapeutic-range substrates of CYP3A4 (except hormonal contraception containing <=35 µg ethinyl estradiol)
iii. Sensitive substrates or narrow-therapeutic-range substrates of breast

cancer resistance protein (BCRP) (except those that can be administered QD in the morning, separated by approximately 10 hours from evening administration of study drug)
13. Donation or receipt of blood from 90 days before screening to the end of the study; donation or receipt of platelets, white blood cells, or plasma from 30 days before screening to the end of the study

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	22-02-2021
Enrollment:	1
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	SPR001
Generic name:	tildacerfont

Ethics review

Approved WMO

Date:	16-09-2020

Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-12-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-03-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-03-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-05-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-06-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-07-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-07-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-09-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-09-2021

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-10-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-12-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-06-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-07-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-01-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	CTIS2023-503771-13-00
EudraCT	EUCTR2019-004765-40-NL
CCMO	NL72896.091.20