A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Crinecerfont (NBI-74788) in Adult Subjects with Classic Congenital Adrenal Hyperplasia, Followed by Open-Label Treatment (CAHTALYST)

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Adrenal gland disorders
Study type	Interventional

Summary

ID

NL-OMON52563

Source
ToetsingOnline

Brief title
A study of safety and efficacy of NBI-74788 in CAH

Condition

- Adrenal gland disorders

Synonym
Classic Congenital Adrenal Hyperplasia, inherited adrenal gland disorder

Research involving

Human

Sponsors and support

Primary sponsor: Neurocrine Biosciences, Inc.
Source(s) of monetary or material Support: funded by the Sponsor of the study;Neurocrine Biosciences;Inc.

Intervention

Keyword: Classic Congenital Adrenal Hyperplasia, Double Blind, Placebo Controlled

Outcome measures

Primary outcome

Primary endpoint: Percent change from baseline in glucocorticoid daily dose (in

hydrocortisone equivalents adjusted for BSA [mg/m2/day]) at Week 24

Secondary outcome

- Change from baseline in serum androstenedione at Week 4

- Achievement of a reduction in glucocorticoid daily dose to physiologic levels

Week 24

- Changes from baseline in HOMA-IR, weight, and fat mass at Week 24.

Study description

Background summary

Classic congenital adrenal hyperplasia (C-CAH) is a rare genetic disorder that affects the adrenal glands. The condition results in an enzyme deficiency (in our patient population 21-hydroxylase enzyme deficiency) altering the production of adrenal steroids and because of this the adrenal glands have little to no cortisol biosynthesis (hormone which regulates body*s response to illness or stress) resulting in a potentially life-threatening condition.
If left untreated, C-CAH can result in salt wasting, dehydration and eventually death due to lack of mineralocorticoids (such as aldosterone) which regulate sodium and potassium level. Even with cortisol replacement, persistent elevation of adrenocorticotropic hormone (ACTH) from the pituitary gland

results in excessive androgen levels (such as testosterone) leading to virilization and menstrual irregularities in females. Both males and females may also experience precocious puberty, short stature, hirsutism, acne and fertility problems.
Corticosteroids are the current standard of care for C-CAH. They are used to both correct the endogenous cortisol deficiency and reduce the excessive ACTH levels and androgen excess. However, the dose and long-term duration of steroid use required to suppress ACTH is well above the normal physiological level of cortisol that often results in bone loss, growth impairment, metabolic syndrome, and Cushing*s syndrome as common and serious side effects.
Crinecerfont (NBI-74788) is a proprietary, potent, selective, orally-active, non-peptide corticotropin-releasing factor type 1 (CRF1) receptor antagonist that works by blocking corticotropin-releasing factor receptors in the pituitary gland that leads to decrease of the ACTH release, which in turn decreases the production of adrenal steroids, including androgens, and potentially the symptoms associated with C-CAH. Blockade of CRF1 receptors has been shown to decrease the release of ACTH in both animals and humans.
As research suggests that lowering ACTH levels could reduce the amount of corticosteroid treatment necessary for CCAH patients, the novel CRF1 receptor antagonist, Crinecerfont, may provide an important therapeutic approach while enabling using of lower, more physiological doses of corticosteroids to treat patients with C-CAH.

Study objective

The purpose of this study is to see if Crinecerfont is effective in reducing daily glucocorticoid dosage while maintaining adrenal androgen control.
The purpose of the study is also to see if Crinecerfont is effective in reducing adrenal steroid levels following an initial 4-week treatment period.
Additionally, the purpose of the trial is also to assess the safety and tolerability of Crinecerfont.

Study design

This is a Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of Crinecerfont versus placebo administered twice daily (bid) with breakfast and the evening meal (doses separated by approximately 12 hours) for 24 weeks in approximately 165 adult subjects with classic CAH due to 21-hydroxylase deficiency.

Intervention

Eligible subjects will be randomly assigned in a 2:1 ratio (active:placebo) to 2 treatment groups, Crinecerfont 100 mg bid or placebo. After the 24-week randomized treatment period, there will be a 6-month, open-label treatment period, during which all subjects will receive Crinecerfont 100 mg bid. At

Month 12, subjects who have not reduced their glucocorticoid dose to <=11 mg/m2/day will be re-randomized (2:1) to receive 100 mg every morning (qAM) and 200 mg every evening (qPM) or to continue 100 mg bid, in a blinded fashion. Subjects who have reduced their glucocorticoid dose to <=11 mg/m2/day will continue to receive 100 mg bid in an open label fashion.
At Month 18, subjects will review applicable portions of the informed consent form and confirm whether they will participatein the optional open-label extension (OLE) treatment period for continued access to crinecerfont.
Starting at Month 18, all subjects who are continuing in the OLE will initially receive crinecerfont 100 mg bid. Ifthe subject has inadequate disease control despite receiving glucocorticoid treatment at their target dose (in the opinion of the investigator), the crinecerfont dose may be increased to 100 mg qAM and 200mgqPM. After the Month 24 visit, an alternative dosing regimen of once daily 200 mg qPM can be considered per the investigator.

Study burden and risks

Risks of crinecerfont (study drug)
The most commonly reported side effects in participants who have received crinecerfont were:
• Headache
• Nausea
• Diarrhea
• Constipation
• Dizziness
• Postural dizziness (dizziness upon standing up)
• Dry mouth
• Somnolence (drowsiness)
• Fatigue
• Blood creatine kinase increase (may indicate muscle injury)
• Neutropenia (decreased white blood cells)
• Contact dermatitis (skin rash)
Risk mitigation: Because of possible side effects such as fatigue, drowsiness, and dizziness that have been reported from previous studies, participants should not drive or operate heavy machinery after taking the study drug.

Other Risks, Side Effects or Discomforts:
Participants may feel discomfort during some of the tests and may also have risks, such as:
•DXA scan: there is a very small amount of radiation exposure equivalent to about 2 days of naturally occurring background radiation.
•Blood collection: possible side effects from blood draws include discomfort, faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight possibility of infection.
•ECG: skin irritation is rare but could occur from the electrodes or gel that is used.
•Testicular ultrasound: the ultrasound itself does not cause any pain or has

any risks, but may feel uncomfortable.
•Mental health assessments: questionnaires may make a participant feel anxious or uncomfortable.
•Fasting: participants will be asked to fast at certain times during this study, this may cause discomfort.
•Glucocorticoid dose reduction: during the times when participant glucocorticoid dose is reduced, they may feel fatigue, nausea, not want to eat, experience vomiting, dizziness (especially when standing up), or worsening symptoms of high male hormones (more hair growth, worse acne, more irregular menstrual cycles).
Risk mitigation:
The participant is instructed to tell their study doctor or study staff if they have these symptoms when their glucocorticoid dose is reduced.
•Glucose tolerance test: drinking the sugary drink (within a certain time frame) may be unpleasant.

UNFORESEEN RISKS
Crinecerfont is investigational, which means that there may be side effects that are not known about the study drug when taken alone or in combination with other medications. It is not possible to know all side effects of an investigational drug, and side effects not observed in previous studies could occur. There is a chance that unknown side effects could be life-threatening.
As with any medication, there is a small but real risk of allergic reactions that can be fatal. These reactions usually start very soon after taking the study drug. They may start as skin itching and redness, difficulty breathing, swelling, and may be severe in some cases.

Risk mitigation: If a participant experiences these reactions, they are instructed to tell a study doctor or study staff immediately, or go to the nearest hospital quickly.

PREGNANCY / BIRTH CONTROL
Birth defects, including physical deformities, mental retardation, and other problems, as well as premature birth, are known risks of some drugs. Taking the study drug may involve unknown risks to a pregnant woman, an embryo, fetus (unborn baby) or nursing infant. Therefore, if a participant is pregnant, planning to become pregnant or are breastfeeding, they cannot participate in this study.
Females who can get pregnant, including women who have not been postmenopausal [no longer having menses (periods)] for at least 1 year and who have not had a hysterectomy or removal of both ovaries or both tubes, will be given a pregnancy test, and the results must be negative to qualify to participate in this study.
If a male participant*s partner becomes pregnant, there may be unknown risks to the fetus or baby.

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

• Subjects must provide written informed consent.
• Be a female or male at least 18 years of age.
• Have a medically confirmed diagnosis of classic 21-hydroxylase deficiency.
• Be on a stable, supraphysiologic glucocorticoid dose regimen (defined as >13 mg/m2/day in hydrocortisone dose equivalents) that has been stable for at least 1 month prior to screening
• If treated with fludrocortisone, dose should be stable for at least 1 month prior to screening with an upright plasma renin activity (PRA) during screening that is not greater than ULN on the subject's usual sodium intake.
• Female subjects of childbearing potential with fertile male partners must agree to use contraception consistently from screening until the final study visit or 30 days after the last dose of study drug, whichever is longer. A

subject who is not of childbearing potential must meet one of the following:
- Postmenopausal
- Permanent sterilization procedure

Exclusion criteria

• Have a known or suspected diagnosis of any of the other forms of classic CAH including 11-β-hydroxylase deficiency, 17-α-hydroxylase deficiency, 3-β-hydroxysteroid dehydrogenase deficiency, P450 sidechain cleavage deficiency, or P450 oxidoreductase deficiency.
• Have a history of bilateral adrenalectomy, hypopituitarism, or other condition requiring chronic therapy with oral, glucocorticoids, or requiring chronic therapy with inhaled glucocorticoids that based on dose and hormone profile the investigator deems would yield significant systemic exposure interfering with study endpoints.
• Have a clinically significant medical condition or chronic disease (including history of neurological, hepatic, renal, cardiovascular, gastrointestinal, significant malabsorption, hematologic, pulmonary, psychiatric, or endocrine disease [excluding CAH]) that in the opinion of the investigator would preclude the subject from participating in and completing the study or that could confound interpretation of study outcome.
• History of malignancy, unless successfully treated with curative intent and considered to be cured.
• Have a known history of clinically concerning cardiac arrhythmia (including long QT syndrome) or prolongation of screening (pretreatment) QT interval corrected for heart rate using Fridericia's correction (QTcF) of >450 msec (males) or >470 msec (females).
• Known sensitivity (ie, hypersensitivity) or allergy to any corticotropinreleasing hormone (CRH) receptor antagonist.
• Have evidence of chronic renal or liver disease Used any active investigational drug within 30 days or 5 half-lives (whichever is longer) before screening, or plans to use an investigational drug (other than the study drug) during the study.
• Females who are pregnant or lactating.

Study design

Design

Study phase:	3
Study type:	Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	25
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Crinecerfont
Generic name:	2-Thiazolamine, 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3- fluoro-4-methylphe

Ethics review

Approved WMO Date:	12-11-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-07-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-11-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-01-2022
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-02-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-05-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-08-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-11-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-12-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-01-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-02-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-06-2023
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
EudraCT	EUCTR2019-004873-17-NL
CCMO	NL74387.091.20