The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 8, 2024 VOL. 391 NO. 6

Phase 3 Trial of Crinecerfont in Pediatric Congenital Adrenal Hyperplasia

K. Sarafoglou, M.S. Kim, M. Lodish, E.I. Felner, L. Martinerie, N.J. Nokoff, M. Clemente, P.Y. Fechner, M.G. Vogiatzi, P.W. Speiser, R.J. Auchus, G.B.G. Rosales, E. Roberts, G.S. Jeha, R.H. Farber, and J.L. Chan, for the CAHtalyst Pediatric Trial Investigators*

ABSTRACT

BACKGROUND

Children with classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency require treatment with glucocorticoids, usually at supraphysiologic doses, to address cortisol insufficiency and reduce excess adrenal androgens. However, such treatment confers a predisposition to glucocorticoid-related complications. In 2-week phase 2 trials, patients with CAH who received crinecerfont, a new oral corticotropin-releasing factor type 1 receptor antagonist, had decreases in androstenedione levels.

METHODS

In this phase 3, multinational, randomized trial, we assigned pediatric participants with CAH, in a 2:1 ratio, to receive crinecerfont or placebo for 28 weeks. A stable glucocorticoid dose was maintained for 4 weeks, and the dose was then adjusted to a target of 8.0 to 10.0 mg per square meter of body-surface area per day (hydrocortisone dose equivalents), provided that the androstenedione level was controlled (≤120% of the baseline level or within the reference range). The primary efficacy end point was the change in the androstenedione level from baseline to week 4. A key secondary end point was the percent change in the glucocorticoid dose from baseline to week 28 while androstenedione control was maintained.

RESULTS

A total of 103 participants underwent randomization, of whom 69 were assigned to crinecerfont and 34 to placebo; 100 (97%) remained in the trial at 28 weeks. At baseline, the mean glucocorticoid dose was 16.4 mg per square meter per day, and the mean androstenedione level was 431 ng per deciliter (15.0 nmol/liter). At week 4, androstenedione was substantially reduced in the crinecerfont group (–197 ng per deciliter [–6.9 nmol/liter]) but increased in the placebo group (71 ng per deciliter [2.5 nmol/liter]) (least-squares mean difference [LSMD], –268 ng per deciliter [–9.3 nmol/liter]; P<0.001); the observed mean androstenedione value, obtained before the morning glucocorticoid dose, was 208 ng per deciliter (7.3 nmol/liter) in the crinecerfont group, as compared with 545 ng per deciliter (19.0 nmol/liter) in the placebo group. At week 28, the mean glucocorticoid dose had decreased (while androstenedione control was maintained) by 18.0% with crinecerfont but increased by 5.6% with placebo (LSMD, –23.5 percentage points; P<0.001). Headache, pyrexia, and vomiting were the most common adverse events.

CONCLUSIONS

In this phase 3 trial, crinecerfont was superior to placebo in reducing elevated androstenedione levels in pediatric participants with CAH and was also associated with a decrease in the glucocorticoid dose from supraphysiologic to physiologic levels while androstenedione control was maintained. (Funded by Neurocrine Biosciences; CAHtalyst Pediatric ClinicalTrials.gov number, NCT04806451.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Sarafoglou can be contacted at saraf010@umn.edu or at the University of Minnesota Medical School, 2450 Riverside Ave., Academic Office Bldg., Minneapolis, MN 55455-0349.

*The CAHtalyst Pediatric Trial Investigators are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on June 2, 2024, at NEJM.org.

N Engl J Med 2024;391:493-503.
DOI: 10.1056/NEJMoa2404655

CME

A Quick Take is available at NEJM.org

Classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a rare autosomal recessive disorder characterized by impaired synthesis of cortisol and often aldosterone.[1-5] Reduced cortisol production disrupts the dynamic equilibrium of the negative feedback inhibition of both hypothalamic corticotropin-releasing factor and pituitary corticotropin, leading to increased adrenal gland stimulation and the shunting of accumulated steroid precursors toward excess production of adrenal androgens.[1-5]

Androgen excess in childhood can result in growth acceleration, clitoromegaly, penile enlargement, early pubarche, central precocious puberty, advanced bone maturation, early growth-plate fusion, and attenuated pubertal growth that results in short stature below the target height based on midparental height.[3-12] During adolescence, androgen overproduction can lead to irregular menses and ovarian dysfunction in female patients; sustained corticotropin excess can lead to the formation of testicular adrenal rest tumors in male patients even during early childhood.[4,5,7,13-15]

Hydrocortisone, a short-acting glucocorticoid, is recommended by an Endocrine Society clinical practice guideline for growing children with CAH.[3] In order to control androgen excess, supraphysiologic doses of glucocorticoid (higher than those needed to treat adrenal insufficiency alone[16,17]) are typically required; however, exposure to glucocorticoids at even modestly supraphysiologic levels can negatively affect growth. Each increase of 1.0 mg per square meter of body-surface area per day in the dose of hydrocortisone above 9.4 mg per square meter per day is associated with a decrease of 0.37 cm in adult height.[9] Long-term glucocorticoid overexposure that begins early in life may lead to early adiposity rebound (which normally occurs at 5 to 6 years of age, when the body-mass index [BMI] starts to rise after having reached a nadir[18]), increased weight gain, hypertension, and insulin resistance, all of which can increase the risk of metabolic syndrome and cardiovascular disease in adulthood.[18-26]

In two phase 2 studies, adolescents and adults with CAH had clinically meaningful reductions in corticotropin, 17-hydroxyprogesterone (a diagnostic adrenal androgen precursor), and androstenedione (a key adrenal androgen) after 14 days of open-label treatment with crinecerfont, a new corticotropin-releasing factor type 1 receptor antagonist; substantial reductions in testosterone in female participants and in the androstenedione-to-testosterone ratio in male participants were also observed.[27,28] These results provided proof-of-concept for the potential therapeutic value of corticotropin-releasing factor type 1 receptor antagonism in CAH. Here, we report the results of CAHtalyst Pediatric, a phase 3 multinational trial evaluating the efficacy of crinecerfont in reducing androstenedione levels and ameliorating the need for supraphysiologic doses of glucocorticoids while maintaining androgen control. A companion article by Auchus et al. presents findings from a trial of crinecerfont in adults.[29]

METHODS

TRIAL DESIGN AND OVERSIGHT

The CAHtalyst Pediatric trial included a 28-week, randomized, double-blind, placebo-controlled period (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), followed by a 24-week open-label period and optional, ongoing open-label extension. We conducted the trial at 37 centers in the United States, Canada, and Europe in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines for Good Clinical Practice and relevant laws and regulations. The protocol, available at NEJM.org, was reviewed and approved by the independent ethics committee or institutional review board at each trial site and by national health authorities in each country. Written informed consent was provided by the parents or legal guardians of each participant, and participants gave assent as applicable. Safety was monitored by an independent data monitoring committee throughout the trial.

The trial was designed by the sponsor, Neurocrine Biosciences, along with consultants that included authors not employed by the sponsor. Neurocrine Biosciences provided trial medications and monitored trial sites. Data were collected by the trial investigators or qualified trial site personnel and were analyzed by an author who represented the sponsor (see the Supplementary Appendix). The manuscript was written by two authors from academic institutions and one representative of the sponsor, with editorial

and graphics support funded by the sponsor. The decision to submit the manuscript for publication was made by the sponsor with agreement from the authors, all of whom had access to the full dataset and the analyses (on request). The sponsor and the authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

PARTICIPANTS

Eligible participants were children 2 to 17 years of age with CAH who were receiving a total glucocorticoid dose of more than 12.0 mg per square meter per day in hydrocortisone dose equivalents (with 1.0 mg of prednisone or prednisolone equivalent to 4.0 mg of hydrocortisone) that had been stable for at least 1 month and who had an androstenedione level greater than the midpoint of the reference range and a 17-hydroxyprogesterone level more than two times the upper limit of the normal range. A key exclusion criterion was the existence of any condition other than CAH for which the participant received long-term glucocorticoid therapy. Additional information is provided in section 2.1 in the Supplementary Appendix.

RANDOMIZATION AND TRIAL INTERVENTIONS

On day 1 (baseline), participants were randomly assigned, in a 2:1 ratio, to receive oral crinecerfont at a dose of 25 mg (for participants with a body weight of 10 to <20 kg), 50 mg (for those with a body weight of 20 to <55 kg), or 100 mg (for those with a body weight of ≥55 kg) or matching placebo twice daily, with morning and evening meals. Randomization was performed with the use of interactive response technology and was stratified according to Tanner stage (1 or 2 vs. 3 through 5) and sex. Participants, trial investigators, site personnel, and the sponsor were unaware of the group assignments.

Glucocorticoid doses were maintained at a stable level from baseline through week 4 (stable glucocorticoid period). From week 4 through week 28, the dose of glucocorticoid was adjusted in one to four steps to a target of 8.0 to 10.0 mg per square meter per day in hydrocortisone dose equivalents (glucocorticoid adjustment period) provided that androstenedione was controlled. Androstenedione control was specified as an androstenedione level no more than 120% of the baseline value or no higher than the upper limit of the normal range according to sex and either age (for prepubertal participants at Tanner stage 1) or pubertal status (for participants at Tanner stages 2 through 5). The target reduction at each step was approximately 1.0 to 4.0 mg per square meter per day in hydrocortisone dose equivalents and was guided by the change in the androstenedione level from the previous measurement and the availability of glucocorticoid dose strengths needed for treatment in children. Participants followed guidelines for stress dosing as needed throughout the trial. Additional details are provided in the Supplementary Appendix (section 2.2 and Tables S1 and S2).

ASSESSMENTS AND END POINTS

The primary efficacy end point was the change in the androstenedione level from baseline to week 4. The key secondary end points were the change in the serum 17-hydroxyprogesterone level from baseline to week 4 and the percent change in the daily dose of glucocorticoid from baseline to week 28 while androstenedione was controlled. Any decrease in glucocorticoid dose at week 28 was calculated as 0% change if androstenedione control was not maintained. All measurements of androgen and androgen precursors were performed at a central laboratory (Quest Diagnostics) with the use of liquid chromatography with tandem mass spectrometry.

Safety assessments included documentation of adverse events that emerged during the treatment period, vital signs, 12-lead electrocardiography, clinical laboratory testing, the Brief Psychiatric Rating Scale for Children, and the Columbia-Suicide Severity Rating Scale. All prespecified efficacy end points, post hoc analyses, and assessments of safety are described in the Supplementary Appendix (sections 3.1 through 3.6).

STATISTICAL ANALYSIS

We estimated that a sample of 81 participants (54 in the crinecerfont group and 27 in the placebo group) would provide the trial with greater than 90% power to detect an effect size of 0.83 for the primary end point, with a two-sided type I error of 0.05. Efficacy analyses included all participants who underwent randomization, according to their assigned group. Missing data for the primary and key secondary efficacy end points were imputed with the use of a regression-based multiple imputation method under

the assumption that data were missing at random. The primary and key secondary end points were tested with the use of a fixed procedure that adjusted for multiple comparisons to control the familywise type I error rate. An analysis of covariance model was used to analyze continuous end points (e.g., the primary end point), with results presented as least-squares mean changes (or percent changes) from baseline with standard errors, along with 95% confidence intervals and two-sided P values for the least-squares mean differences between treatment groups. A two-sided Cochran–Mantel–Haenszel test was used to analyze categorical end points (e.g., achievement of reduction to a physiologic glucocorticoid dose while androstenedione control was maintained), with results presented as the numbers and percentages of participants. P values for other secondary and exploratory end points are not reported. Details of statistical methods are provided in section 4.0 in the Supplementary Appendix.

Safety analyses are presented as descriptive statistics and included all participants who underwent randomization and received at least one dose of crinecerfont or placebo. No imputation of missing values, formal hypothesis testing, or designation of primary or secondary safety end points was performed.

RESULTS

PARTICIPANTS

Of 103 participants who underwent randomization, 100 (97%) remained in the trial at 28 weeks: 69 in the crinecerfont group (including 3 who withdrew from the trial at week 28 but had evaluable data for key end points) and 31 in the placebo group (Fig. 1). The demographics and baseline characteristics of the participants were well balanced between the groups (Table 1 and Tables S3 and S4). Key disease- and glucocorticoid-related characteristics in the overall population included obesity (58% [60 participants]), with a BMI at or above the 85th percentile, according to growth charts from the Centers for Disease Control and Prevention; elevated levels of androstenedione (431 ng per deciliter [15.0 nmol per liter]) and 17-hydroxyprogesterone (8682 ng per deciliter [263 nmol per liter]) despite treatment with supraphysiologic glucocorticoid doses (mean, 16.4 mg per square meter per day in hydrocortisone dose equivalents); and advanced bone age (Fig. S2).

Coexisting conditions reported in more than 10% of participants were advanced bone age, early puberty, obesity or overweight, central precocious puberty, acne, short stature, attention deficit disorder, and irregular menses and hirsutism in female participants (Table S5). Testicular adrenal rest tumors were reported in 6% of the male participants (3 of 53) but were identified in 33% (15 of 46) who underwent baseline ultrasonography.

EFFICACY

In the stable glucocorticoid period, the crinecerfont group had a substantial least-squares mean decrease in the androstenedione level from baseline to week 4 (–197 ng per deciliter [–6.9 nmol per liter]), as compared with an increase in the placebo group (71 ng per deciliter [2.5 nmol per liter]) (least-squares mean difference, –268 ng per deciliter [–9.3 nmol per liter]; P<0.001) (Fig. 2A and Table 2). Observed mean androstenedione values at week 4 (before the morning glucocorticoid dose) were 208 ng per deciliter (7.3 nmol per liter) in the crinecerfont group and 545 ng per deciliter (19.0 nmol per liter) in the placebo group (Table S6). Similarly, 17-hydroxyprogesterone decreased substantially from baseline to week 4 in the crinecerfont group and increased slightly in the placebo group (least-squares mean difference, –6421 ng per deciliter [–195 nmol per liter]; P<0.001) (Fig. 2B and Table 2). Observed mean 17-hydroxyprogesterone values at week 4 were 2772 ng per deciliter (84.0 nmol per liter) in the crinecerfont group and 9418 ng per deciliter (285 nmol per liter) in the placebo group. At week 28, after adjustments in the glucocorticoid dose, the mean androstenedione level remained below baseline in the crinecerfont group but was above baseline in the placebo group (Fig. 2A).

Among participants assigned to receive crinecerfont, the glucocorticoid dose was reduced from baseline to week 28 while control of the androstenedione level was maintained, whereas the dose in the placebo group was increased (least-squares mean percent change from baseline, –18.0% vs. 5.6%; least-squares mean difference, –23.5 percentage points; P<0.001) (Fig. 2C and Table 2). Observed mean glucocorticoid doses at week 28 were 12.8 mg per square meter per day in the crinecerfont group and 17.0 mg per square meter per day in the placebo group.

Among crinecerfont-treated participants, 30% (20 of 67) achieved a physiologic glucocorticoid dose (≤11.0 mg per square meter per day in hydrocortisone dose equivalents) at week 28 with maintenance of androstenedione control, as compared with no participants in the placebo group (Fig. 2D). In post hoc analyses, crinecerfont-treated participants who did not reach a physiologic glucocorticoid dose had a mean change from baseline of –2.3 mg per square meter per day, which is a decrease of 11.5% in the glucocorticoid dose. Moreover, 57% of participants (38 of 67) in the crinecerfont group, as compared with 3% (1 of 31) in the placebo group, had either a reduction in glucocorticoid dose to physiologic levels or a decrease of more than 2.5 mg per square meter per day in the glucocorticoid dose at week 28 (with androstenedione control).

BMI standard deviation scores decreased in the crinecerfont group and increased in the placebo group at week 28, despite the relatively short duration of reduced glucocorticoid dosing. There was also evidence of improved insulin resistance in participants who received crinecerfont on the basis of the homeostasis model assessment of insulin resistance, as well as a reduction in hirsutism (assessed with the use of a visual analogue scale) among female participants and improvement in the androstenedione-to-testosterone ratio among male participants. Table S7 lists other secondary and selected exploratory end points.

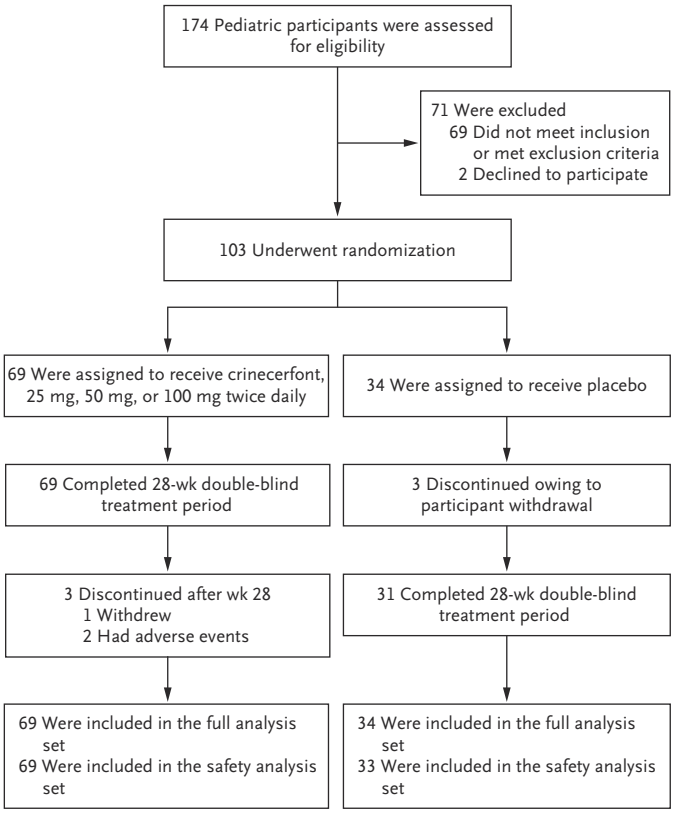

Figure 1. Screening and Randomization.

Of 174 children and adolescents who were screened, 103 met the eligibility criteria and were randomly assigned, in a 2:1 ratio, to receive crinecerfont or placebo. Participants could be excluded for multiple reasons, the most common of which were an androstenedione level below the midpoint of the normal range on the basis of sex, age, and Tanner stage (38 participants); treatment with glucocorticoids at a dose below supraphysiologic levels (11 participants); and treatment with fludrocortisone at a dose that had not been stable for at least 1 month before screening, lack of adequate mineralocorticoid control at screening as indicated by upright plasma renin activity as described in the Supplementary Appendix, or both (10 participants). With inclusion of 3 participants in the crinecerfont group who withdrew from the trial after completing the week 28 trial visit but had evaluable data for key end points, more than 95% of participants completed the 28-week double-blind placebo-controlled period. Two participants in the crinecerfont group discontinued treatment owing to adverse events: one with body aches, upper abdominal pain, and nausea, considered by a local trial investigator to be unrelated to treatment, and one with nausea, dizziness, retching, and motion sickness, considered to be possibly related to treatment. One participant in the placebo group who did not receive the assigned placebo was excluded from safety analyses.

SAFETY

The percentage of participants who had adverse events that emerged during the treatment period was similar in the two groups (84% with crinecerfont and 82% with placebo), and most adverse events were mild to moderate in severity (Table 3). Two crinecerfont-treated participants had adverse events that led to discontinuation of the trial regimen and withdrawal from the trial: one participant had body aches, upper abdominal pain, and nausea (which were considered by the local trial investigator to be unrelated to the treatment), and one had nausea, dizziness, retching, and motion sickness (which were considered to be possibly related to the treatment). Five participants (4 of 33 [12%] in the placebo group and 1 of 69 [1%] in the crinecerfont group) had serious adverse events that emerged during the treatment period, none of which were considered to be related to the trial regimen or led to discontinuation of the trial regimen; all participants recovered or had resolution of symptoms. No deaths occurred.

No adrenal crises were reported during the

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	All Participants (N=103)	Crinecerfont (N=69)	Placebo (N=34)
Age — yr	12.1±3.5	12.0±3.4	12.1±3.7
Male sex — no. (%)	53 (51)	35 (51)	18 (53)
Race or ethnic group — no. (%)†			
White	65 (63)	42 (61)	23 (68)
Asian	9 (9)	7 (10)	2 (6)
Black	3 (3)	3 (4)	0
Other	11 (11)	8 (12)	3 (9)
Not reported	15 (15)	9 (13)	6 (18)
Glucocorticoid use			
Total dose — mg/m²/day‡	16.4±3.9	16.5±4.2	16.3±3.4
Hydrocortisone alone — no. (%)	95 (92)	63 (91)	32 (94)
Fludrocortisone use — no. (%)	90 (87)	59 (86)	31 (91)
Standard deviation score§			
Height	0.3±1.3	0.3±1.4	0.4±1.2
Weight	1.2±1.0	1.2±1.0	1.2±1.0
BMI	1.2±0.9	1.2±0.9	1.1±1.0
BMI ≥85th percentile — no. (%)	60 (58)	40 (58)	20 (59)
Tanner stage: breast or testicular — no. (%)¶			
1	30 (29)	18 (26)	12 (35)
2	12 (12)	10 (14)	2 (6)
3	13 (13)	8 (12)	5 (15)
4	19 (18)	15 (22)	4 (12)
5	29 (28)	18 (26)	11 (32)
Androstenedione — ng/dl‖	431±461	405±464	483±456
17-Hydroxyprogesterone — ng/dl‖	8682±6847	8513±7431	9026±5563
Testosterone — ng/dl‖**			
In female participants	73±67	67±60	88±81
In male participants at Tanner stages 1–2	51±63	60±74	33±32
In male participants at Tanner stages 3–5	404±205	408±212	396±204
Androstenedione-to-testosterone ratio††			
In male participants at Tanner stage 2	3.6±2.2	3.4±2.3	5.1
In male participants at Tanner stages 3–5	3.4±8.7	4.1±10.6	2.0±1.0
Testicular adrenal rest tumors present — no. of participants/total no.(%)‡‡	15/46 (33)	10/31 (32)	5/15 (33)

* Plus–minus values are means ±SD. Data are shown for all participants who underwent randomization.
† Race or ethnic group was reported by participants or their parents or legal guardians. The category "other" includes participants whose ethnic group was reported as American Indian or Alaska Native (1 participant), Native Hawaiian or Pacific Islander (1 participant), other (not specified; 5 participants), or multiple (4 participants).
‡ The total dose of glucocorticoid is reported in hydrocortisone dose equivalents.
§ Height, weight, and body-mass index (BMI) standard deviation scores were calculated with the use of growth charts from the Centers for Disease Control and Prevention.
¶ Tanner stages range from 1 to 5, and higher stages indicate more advanced pubertal development.
‖ Normal ranges and factors for conversion from conventional units to standard international units are listed in Table S2.
** Data from hormone or hormone precursor assessments at baseline were missing for the following variables: corticotropin (1 participant in the crinecerfont group and 1 in the placebo group), testosterone (1 female participant in the placebo group), and testosterone in male participants at Tanner stages 3 through 5 (1 participant in the crinecerfont group and 1 in the placebo group).
†† The androstenedione-to-testosterone ratio at baseline in male participants at Tanner stages 3 through 5 was not available for 1 participant in the crinecerfont group and 1 in the placebo group. The value shown for male participants at Tanner stage 2 in the placebo group is not expressed as a mean ±SD because it is from a single participant. This variable was not assessed for participants at Tanner stage 1 (prepubertal).
‡‡ Total numbers are the numbers of male participants who underwent ultrasonography at baseline.

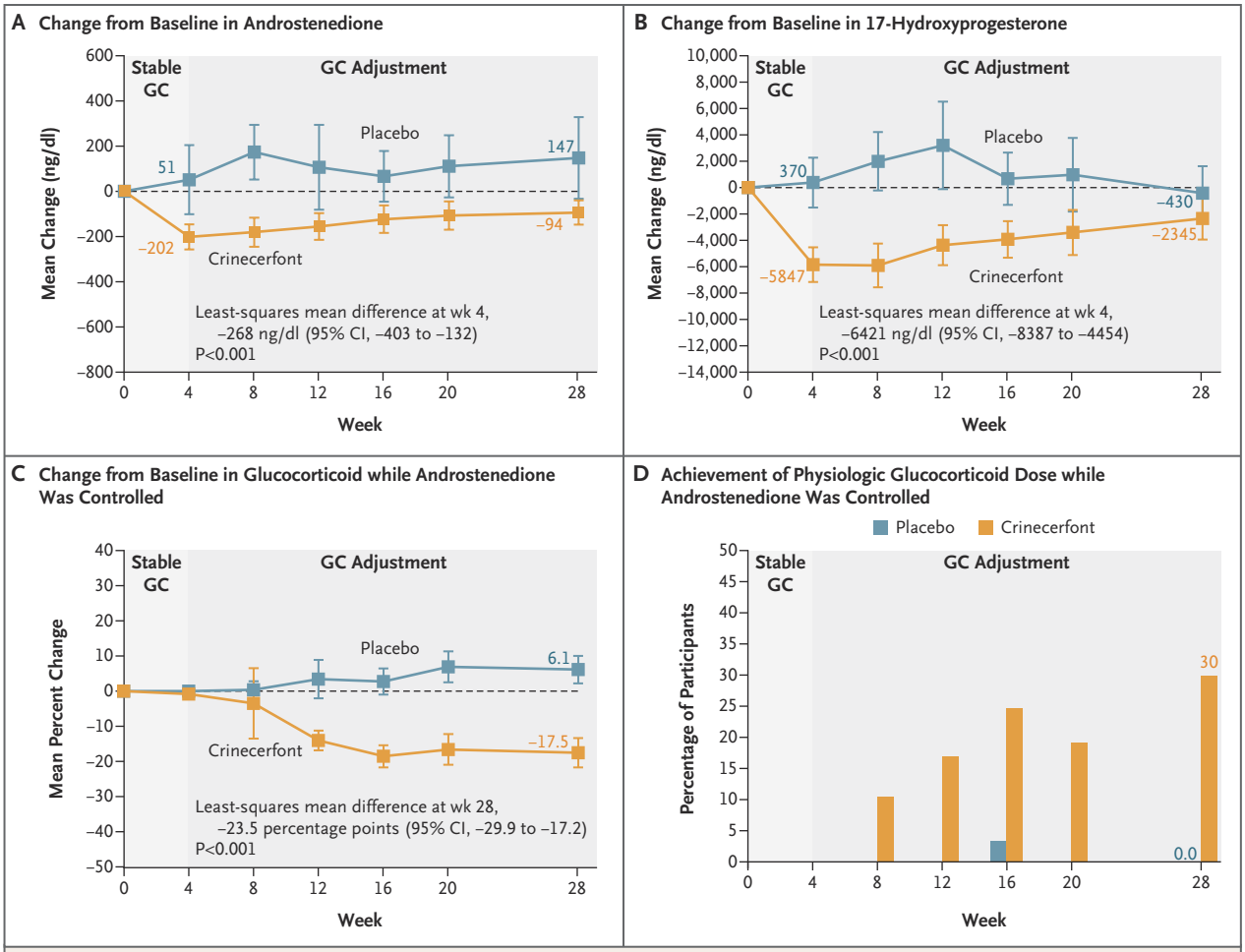

Figure 2. Efficacy End Points.

Differences between the crinecerfont and placebo groups are shown for the following end points: changes from baseline in serum androstenedione (Panel A) and 17-hydroxyprogesterone (Panel B); percent changes from baseline in glucocorticoid (GC) dose while androstenedione control was maintained (Panel C); and the percentage of participants who achieved physiologic glucocorticoid dosing while androstenedione control was maintained (Panel D). Panels A through C present mean changes for all post-baseline visits. Table 2 presents least-squares mean changes for the defined end-point visit (i.e., week 4 for androstenedione and 17-hydroxyprogesterone and week 28 for the percent change in glucocorticoid dose). Androstenedione and 17-hydroxyprogesterone values (Panels A and B) were based on samples collected before participants received their morning glucocorticoid doses. Androstenedione control (Panels C and D) was specified as an androstenedione level either no more than 120% of baseline or no higher than the upper limit of the normal range according to sex and either age (for prepubertal participants at Tanner stage 1) or pubertal status (for participants at Tanner stages 2 through 5). A physiologic glucocorticoid dose was specified as less than or equal to 11.0 mg per square meter of body-surface area per day in hydrocortisone dose equivalents. Decreases in glucocorticoid dose in participants who did not have androgen control were calculated as 0% change. I bars represent 95% confidence intervals for mean changes. The widths of these confidence intervals have not been adjusted for multiple comparisons, and the intervals may not be used in place of hypothesis testing. Least-squares mean differences with 95% confidence intervals and P values are presented for the primary and key secondary end points (Panels A through C); analyses of these end points included all participants who underwent randomization, with missing values imputed.

double-blind treatment period. Adverse events that led to stress dosing of glucocorticoid occurred in approximately half the participants in each treatment group (54% in the crinecerfont group and 52% in the placebo group); most such events involved only oral stress dosing. There were no evident safety concerns related to vital signs, clinical laboratory values, electrocardiography, or neuropsychiatric assessments with crinecerfont treatment.

Table 2. Efficacy End Points.*

End Point	Crinecerfont (N=69)	Placebo (N=34)	Least-Squares Mean Difference (95% CI)	P Value
Primary end point				
Change in serum androstenedione, baseline to wk 4 — ng/dl†	−197±39	71±56	−268 (−403 to −132)	<0.001
Key secondary end points				
Change in serum 17-hydroxyprogesterone, baseline to wk 4 — ng/dl†	−5865±572	556±818	−6421 (−8387 to −4454)	<0.001
Change in glucocorticoid dose with androstenedione control, baseline to wk 28 — %	−18.0±1.8	5.6±2.7	−23.5 (−29.9 to −17.2)‡	<0.001

* Plus–minus values are least-squares means ±SE. For the primary and key secondary end points, multiple imputation of missing data was used for statistical testing. Therefore, analyses are based on the full analysis set, which included all participants who underwent randomization. The number of participants with complete data for each end point are as follows: primary end point, 68 in the crinecerfont group and 33 in the placebo group; change in 17-hydroxyprogesterone, 68 in the crinecerfont group and 33 in the placebo group; change in glucocorticoid dose with androstenedione control, 67 in the crinecerfont group and 31 in the placebo group. CI denotes confidence interval.
† Normal ranges are listed in Table S2.
‡ The least-squares mean difference in the percent change in glucocorticoid dose between groups is expressed in percentage points.

DISCUSSION

For most patients with CAH, long-term exposure to supraphysiologic doses of glucocorticoid begins early in life. Hydrocortisone, the recommended glucocorticoid for children,[3] is usually administered in three daily doses because of its short elimination half-life, which is even shorter in children with CAH.[30,31] Consequently, most of the hydrocortisone dose is eliminated from the body within 4 to 5 hours, which results in a rebound of adrenal androgens between doses, especially in the early morning hours when corticotropin-driven adrenal androgen production increases. Thus, children are exposed to alternating periods of androgen excess and supraphysiologic glucocorticoid doses throughout the day.[6]

Finding a balance between androgen excess and exposure to supraphysiologic glucocorticoids — both of which can adversely affect growth and pubertal development — is an ongoing challenge. Participants in the present trial had suboptimal androgen control with substantially elevated mean androstenedione and 17-hydroxyprogesterone levels despite supraphysiologic glucocorticoid doses, which underscores the failure of conventional treatment to consistently control androgen excess. A high percentage of participants were already overweight or obese (58% had a BMI above the 85th percentile), with substantial bone-age advancement (especially in younger participants), and one third of male participants already had evidence of testicular adrenal rest tumors on ultrasonography.

The crinecerfont group had marked reductions in androstenedione and 17-hydroxyprogesterone levels by week 4 (while the glucocorticoid dose was stable), after which the glucocorticoid dose was reduced by 18.0% by week 28 while androstenedione control was maintained. By contrast, the androstenedione level increased from baseline to weeks 4 and 28 in the placebo group — despite a 5.6% increase in the mean glucocorticoid dose by week 28 — which highlights the limitations of current therapy. Among participants treated with crinecerfont, 30% (20 of 67) achieved glucocorticoid dose reduction to a physiologic range (≤11.0 mg per square meter per day) with androstenedione control. Of note, none of the participants achieved this end point with placebo. Post hoc analyses suggested that a majority of participants achieved either physiologic dosing or had a clinically meaningful reduction in the glucocorticoid dose with crinecerfont.

Although a key secondary trial end point was the change in the glucocorticoid dose, a priority of the protocol was to avoid exposing pediatric participants to androgen levels higher than 120% of their baseline values. Thus, glucocorticoid doses were reduced only if the criterion for androstenedione control was met at that visit, which we speculate might have limited achievement of the lowest acceptable glucocorticoid dose. Additional factors in children that may have affected the extent of glucocorticoid reduction include physiologic changes during puberty, wherein elevated sex steroids influence individual cortisol pharmacokinetics and pharmacodynamics.[31-33]

Table 3. Adverse Events.

Adverse Event	Crinecerfont (N = 69)	Placebo (N = 33)
	number (percent)	
Any adverse event	58 (84)	27 (82)
Any serious adverse event*	1 (1)	4 (12)
Any adverse event leading to discontinuation of trial regimen†	2 (3)	0
Any adverse event leading to withdrawal from trial†	2 (3)	0
Any adverse event resulting in death	0	0
Severity of adverse event‡		
Mild	37 (54)	13 (39)
Moderate	20 (29)	12 (36)
Severe	1 (1)	2 (6)
Common adverse events§		
Headache	17 (25)	2 (6)
Pyrexia	16 (23)	8 (24)
Vomiting	10 (14)	10 (30)
Upper respiratory tract infection	8 (12)	0
Nasopharyngitis	7 (10)	6 (18)
Influenza	6 (9)	2 (6)
Abdominal pain	5 (7)	0
Coronavirus infection	5 (7)	3 (9)
Fatigue	5 (7)	0
Nasal congestion	5 (7)	1 (3)
Cough	4 (6)	2 (6)
Dizziness	4 (6)	3 (9)
Nausea	4 (6)	2 (6)
Streptococcal pharyngitis	4 (6)	0
Viral infection	4 (6)	1 (3)

* Serious adverse events included pyrexia (1 participant in the crinecerfont group) and vomiting and pharyngitis, gastroenteritis norovirus and gastroenteritis, gastroenteritis, and vomiting and chest pain (1 each in the placebo group). All serious adverse events were considered by the investigator to be unlikely to be related or unrelated to the trial regimen.
† In the crinecerfont group, 2 participants discontinued treatment and withdrew from the trial: 1 had body aches, upper abdominal pain, and nausea (considered to be unrelated to the treatment), and 1 had nausea, dizziness, retching, and motion sickness (considered to be possibly related to the treatment).
‡ The maximum level of severity, as judged by the trial investigator, is shown.
§ Common adverse events were specified as those reported in at least 4 participants (>5%) receiving crinecerfont.

Despite the relatively short duration of reduced glucocorticoid exposure, changes in indicators of glucocorticoid excess (e.g., BMI standard deviation scores and insulin resistance) were discernible by the end of the double-blind period, which is consistent with the sensitivity of pediatric patients to even modest amounts of excess glucocorticoid. In addition, changes in indicators of androgen excess (e.g., hirsutism in female participants and the androstenedione-to-testosterone ratio in male participants) were observed. As might be expected in a 28-week trial, no differences in height or bone age measurements were observed between treatment groups.

This trial showed that in pediatric participants with CAH, reduction in the glucocorticoid doses to the target physiologic range could be accomplished with apparent safety. No adrenal crises were observed during the double-blind

period, and the incidence of adverse events leading to glucocorticoid stress dosing was similar in the two groups. The incidence of serious adverse events was higher in the placebo group than in the crinecerfont group (occurring in 12% vs. 1% of the participants), with few events leading to discontinuation of treatment. No safety signals or major risks were identified during the 28-week treatment period, which, in conjunction with the efficacy results, supports a favorable risk–benefit profile for crinecerfont.

Crinecerfont appears to be a potential new therapeutic option for patients with CAH, who face substantial disease burden and adverse health outcomes throughout their lives. Secondary and exploratory end points related to consequences of long-term supraphysiologic glucocorticoid therapy showed favorable trends, but longer treatment periods are needed to determine the extent of these effects. This trial had several strengths — a double-blind, randomized, placebo-controlled design; a robust sample size given the rarity of CAH; a focus on two clinically relevant end points (the primary end point of change in androgen levels and a key secondary end point of reduction in glucocorticoid dose with maintenance of androstenedione control); and a high completion rate. The present trial also had several limitations — the requirement for supraphysiologic glucocorticoid doses at trial enrollment, the lack of participants younger than 4 years of age, a short duration for observing meaningful improvement in bone age and growth-related end points, and a cautious approach toward glucocorticoid reduction to avoid an increase in androstenedione level above 120% of baseline values. The majority of participants in this trial were White, which reflects the prevalence of CAH in the United States and Europe (Table S8), and few participants were Black, which potentially limits the generalizability of the findings.

The results of this trial showed that crinecerfont therapy reduced production of excess adrenal androgens, which allowed substantial and clinically meaningful reduction of glucocorticoid doses to more physiologic levels in pediatric participants with CAH.

Baseline data were presented at the annual meetings of the Pediatric Endocrine Society in Chicago, May 2–5, 2024, and the European Congress of Endocrinology in Stockholm, May 11–14, 2024; baseline and key efficacy and safety data were presented at the annual meeting of the Endocrine Society in Boston, June 1–4, 2024.

Supported by Neurocrine Biosciences.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank Vivian H. Lin, M.D., executive medical director, and Julia Sturgeon, senior principal biostatistician, at Neurocrine Biosciences for their support during the trial; Mildred Bahn, Jennifer Kaiser, and Christina Chan at Prescott Medical Communications Group, a Citrus Health Group company (Chicago), for editorial and graphics assistance with an earlier version of the manuscript, funded by Neurocrine Biosciences; and the trial participants, their families, and the trial staff for their contributions to the CAHtalyst Pediatric trial.

APPENDIX

The authors' full names and academic degrees are as follows: Kyriakie Sarafoglou, M.D., Mimi S. Kim, M.D., Maya Lodish, M.D., Eric I. Felner, M.D., Laetitia Martinerie, M.D., Ph.D., Natalie J. Nokoff, M.D., María Clemente, M.D., Ph.D., Patricia Y. Fechner, M.D., Maria G. Vogiatzi, M.D., Phyllis W. Speiser, M.D., Richard J. Auchus, M.D., Ph.D., Gelliza B.G. Rosales, M.P.H., Eiry Roberts, M.D., George S. Jeha, M.D., Robert H. Farber, Ph.D., and Jean L. Chan, M.D.

The authors' affiliations are as follows: the University of Minnesota Medical School and College of Pharmacy, Minneapolis (K.S.); Children's Hospital Los Angeles and Keck School of Medicine of USC, Los Angeles (M.S.K.), the University of California at San Francisco, Benioff Children's Hospital, San Francisco (M.L.), and Neurocrine Biosciences, San Diego (G.B.G.R., E.R., G.S.J., R.H.F., J.L.C.) — all in California; Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta (E.I.F.); Endocrinologie Pédiatrique, Centre de Référence Maladies Endocriniennes Rares de la Croissance et du Développement, Hôpital Universitaire Robert-Debré, Groupe Hospitalo-Universitaire de l'Assistance Publique–Hôpitaux de Paris Nord, and Université Paris Cité, Faculté de Santé, UFR de Médecine, Paris, and Université Paris-Saclay, INSERM Physiologie et Physiopathologie Endocriniennes, Le Kremlin-Bicêtre — all in France (L.M.); the University of Colorado School of Medicine, Children's Hospital Colorado, Aurora (N.J.N.); Pediatric Endocrinology, Hospital Universitario Vall d'Hebrón, Barcelona (M.C.); the University of Washington School of Medicine, Seattle Children's Hospital, Seattle (P.Y.F.); the Children's Hospital of Philadelphia, Philadelphia (M.G.V.); Cohen Children's Medical Center of NY, New Hyde Park, and the Donald and Barbara Zucker School of Medicine at Hofstra–Northwell, Hempstead — both in New York (P.W.S.); and the Departments of Pharmacology and Internal Medicine, Division of Metabolism, Endocrinology and Diabetes, University of Michigan Medical School, and the Endocrinology and Metabolism Section, Medicine Services, LTC Charles S. Kettles Veterans Affairs Medical Center — both in Ann Arbor (R.J.A.).

REFERENCES

1. Mallappa A, Merke DP. Management challenges and therapeutic advances in congenital adrenal hyperplasia. Nat Rev Endocrinol 2022;18:337-52.
2. El-Maouche D, Arlt W, Merke DP. Congenital adrenal hyperplasia. Lancet 2017; 390:2194-210.
3. Speiser PW, Arlt W, Auchus RJ, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2018;103:4043-88.
4. Claahsen-van der Grinten HL, Speiser PW, Ahmed SF, et al. Congenital adrenal hyperplasia — current insights in pathophysiology, diagnostics, and management. Endocr Rev 2022;43:91-159.
5. Merke DP, Auchus RJ. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. N Engl J Med 2020;383:1248-61.
6. Sarafoglou K, Merke DP, Reisch N, Claahsen-van der Grinten H, Falhammar H, Auchus RJ. Interpretation of steroid biomarkers in 21-hydroxylase deficiency and their use in disease management. J Clin Endocrinol Metab 2023;108:2154-75.
7. Turcu AF, Auchus RJ. Adrenal steroidogenesis and congenital adrenal hyperplasia. Endocrinol Metab Clin North Am 2015; 44:275-96.
8. Bomberg EM, Addo OY, Kyllo J, et al. The relation of peripubertal and pubertal growth to final adult height in children with classic congenital adrenal hyperplasia. J Pediatr 2015;166:743-50.
9. Sarafoglou K, Addo OY, Turcotte L, et al. Impact of hydrocortisone on adult height in congenital adrenal hyperplasia — the Minnesota cohort. J Pediatr 2014; 164(5):1141-1146.e1.
10. Muthusamy K, Elamin MB, Smushkin G, et al. Adult height in patients with congenital adrenal hyperplasia: a systematic review and metaanalysis. J Clin Endocrinol Metab 2010;95:4161-72.
11. Uslar T, Olmos R, Martínez-Aguayo A, Baudrand R. Clinical update on congenital adrenal hyperplasia: recommendations from a multidisciplinary adrenal program. J Clin Med 2023;12:3128.
12. New MI. Factors determining final height in congenital adrenal hyperplasia. J Pediatr Endocrinol Metab 2001;14:Suppl 2:933-7.
13. Merke DP, Poppas DP. Management of adolescents with congenital adrenal hyperplasia. Lancet Diabetes Endocrinol 2013;1:341-52.
14. Schröder MAM, Neacşu M, Adriaansen BPH, et al. Hormonal control during infancy and testicular adrenal rest tumor development in males with congenital adrenal hyperplasia: a retrospective multicenter cohort study. Eur J Endocrinol 2023; 189:460-8.
15. Mendes-Dos-Santos CT, Martins DL, Guerra-Júnior G, et al. Prevalence of testicular adrenal rest rumor and factors associated with its development in congenital adrenal hyperplasia. Horm Res Paediatr 2018; 90:161-8.
16. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2016;101:364-89.
17. Miller BS, Spencer SP, Geffner ME, et al. Emergency management of adrenal insufficiency in children: advocating for treatment options in outpatient and field settings. J Investig Med 2020;68:16-25.
18. Whitaker RC, Pepe MS, Wright JA, Seidel KD, Dietz WH. Early adiposity rebound and the risk of adult obesity. Pediatrics 1998;101:E5.
19. Torky A, Sinaii N, Jha S, et al. Cardiovascular disease risk factors and metabolic morbidity in a longitudinal study of congenital adrenal hyperplasia. J Clin Endocrinol Metab 2021;106(12):e5247-e5257.
20. Sarafoglou K, Forlenza GP, Yaw Addo O, et al. Obesity in children with congenital adrenal hyperplasia in the Minnesota cohort: importance of adjusting body mass index for height-age. Clin Endocrinol (Oxf) 2017;86:708-16.
21. Maccabee-Ryaboy N, Thomas W, Kyllo J, et al. Hypertension in children with congenital adrenal hyperplasia. Clin Endocrinol (Oxf) 2016;85:528-34.
22. Bonfig W, Roehl F-W, Riedl S, et al. Blood pressure in a large cohort of children and adolescents with classic adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. Am J Hypertens 2016;29:266-72.
23. Subbarayan A, Dattani MT, Peters CJ, Hindmarsh PC. Cardiovascular risk factors in children and adolescents with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Clin Endocrinol (Oxf) 2014;80:471-7.
24. Finkielstain GP, Kim MS, Sinaii N, et al. Clinical characteristics of a cohort of 244 patients with congenital adrenal hyperplasia. J Clin Endocrinol Metab 2012; 97:4429-38.
25. Völkl TMK, Simm D, Beier C, Dörr HG. Obesity among children and adolescents with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Pediatrics 2006;117(1):e98-e105.
26. Cornean RE, Hindmarsh PC, Brook CG. Obesity in 21-hydroxylase deficient patients. Arch Dis Child 1998;78:261-3.
27. Newfield RS, Sarafoglou K, Fechner PY, et al. Crinecerfont, a CRF_1 receptor antagonist, lowers adrenal androgens in adolescents with congenital adrenal hyperplasia. J Clin Endocrinol Metab 2023;108: 2871-8.
28. Auchus RJ, Sarafoglou K, Fechner PY, et al. Crinecerfont lowers elevated hormone markers in adults with 21-hydroxylase deficiency congenital adrenal hyperplasia. J Clin Endocrinol Metab 2022;107: 801-12.
29. Auchus RJ, Hamidi O, Pivonello R, et al. Phase 3 trial of crinecerfont in adult congenital adrenal hyperplasia. N Engl J Med 2024;391:504-14.
30. Al-Kofahi M, Ahmed MA, Jaber MM, et al. An integrated PK-PD model for cortisol and the 17-hydroxyprogesterone and androstenedione biomarkers in children with congenital adrenal hyperplasia. Br J Clin Pharmacol 2021;87:1098-110.
31. Charmandari E, Hindmarsh PC, Johnston A, Brook CG. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency: alterations in cortisol pharmacokinetics at puberty. J Clin Endocrinol Metab 2001;86: 2701-8.
32. Melin J, Parra-Guillen ZP, Michelet R, et al. Pharmacokinetic/pharmacodynamic evaluation of hydrocortisone therapy in pediatric patients with congenital adrenal hyperplasia. J Clin Endocrinol Metab 2020; 105:105.
33. Sarafoglou K, Zimmerman CL, Gonzalez-Bolanos MT, Willis BA, Brundage R. Interrelationships among cortisol, 17-hydroxyprogesterone, and androstnendione exposures in the management of children with congenital adrenal hyperplasia. J Investig Med 2015;63:35-41.