ORIGINAL ARTICLE

Phase 3 Trial of Crinecerfont in Adult Congenital Adrenal Hyperplasia

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ABSTRACT

BACKGROUND

Adrenal insufficiency in patients with classic 21-hydroxylase deficiency congenital adrenal hyperplasia (CAH) is treated with glucocorticoid replacement therapy. Control of adrenal-derived androgen excess usually requires supraphysiologic glucocorticoid dosing, which predisposes patients to glucocorticoid-related complications. Crinecerfont, an oral corticotropin-releasing factor type 1 receptor antagonist, lowered androstenedione levels in phase 2 trials involving patients with CAH.

METHODS

In this phase 3 trial, we randomly assigned adults with CAH in a 2:1 ratio to receive crinecerfont or placebo for 24 weeks. Glucocorticoid treatment was maintained at a stable level for 4 weeks to evaluate androstenedione values, followed by glucocorticoid dose reduction and optimization over 20 weeks to achieve the lowest glucocorticoid dose that maintained androstenedione control (≤120% of the baseline value or within the reference range). The primary efficacy end point was the percent change in the daily glucocorticoid dose from baseline to week 24 with maintenance of androstenedione control.

RESULTS

All 182 patients who underwent randomization (122 to the crinecerfont group and 60 to the placebo group) were included in the 24-week analysis, with imputation of missing values; 176 patients (97%) remained in the trial at week 24. The mean glucocorticoid dose at baseline was 17.6 mg per square meter of body-surface area per day of hydrocortisone equivalents; the mean androstenedione level was elevated at 620 ng per deciliter. At week 24, the change in the glucocorticoid dose (with androstenedione control) was –27.3% in the crinecerfont group and –10.3% in the placebo group (least-squares mean difference, –17.0 percentage points; P<0.001). A physiologic glucocorticoid dose (with androstenedione control) was reported in 63% of the patients in the crinecerfont group and in 18% in the placebo group (P<0.001). At week 4, androstenedione levels decreased with crinecerfont (–299 ng per deciliter) but increased with placebo (45.5 ng per deciliter) (least-squares mean difference, –345 ng per deciliter; P<0.001). Fatigue and headache were the most common adverse events in the two trial groups.

CONCLUSIONS

Among patients with CAH, the use of crinecerfont resulted in a greater decrease from baseline in the mean daily glucocorticoid dose, including a reduction to the physiologic range, than placebo following evaluation of adrenal androgen levels. (Funded by Neurocrine Biosciences; CAHtalyst ClinicalTrials.gov number, NCT04490915.)

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Congenital adrenal hyperplasia comprises several rare autosomal recessive conditions that cause disordered adrenal steroidogenesis. Pathogenic variants in the gene encoding steroid 21-hydroxylase (*CYP21A2*), an adrenal-specific enzyme required for cortisol and aldosterone production, cause approximately 95% of cases.[1-5] Patients with severe or classic congenital adrenal hyperplasia resulting from 21-hydroxylase deficiency (CAH) have insufficiencies in cortisol and frequently in aldosterone from birth.[2]

In the absence of endogenous cortisol, negative feedback on the hypothalamus and pituitary is attenuated, which increases the secretion of corticotropin-releasing factor and adrenocorticotropic hormone (ACTH) and, in turn, increases the excess production of adrenal androgens.[1-5] Excess adrenal androgens during childhood can lead to virilization, accelerated somatic growth with advanced bone age, precocious puberty, and failure to achieve predicted adult height.[5-7] During adulthood, female patients have hirsutism, acne, and irregular menses, whereas male patients have testicular adrenal rest tumors (TARTs); patients of both sexes may have hypogonadism, impaired fertility, or both.[5,6,8]

Glucocorticoids are used for cortisol replacement; however, increasing glucocorticoid doses above the physiologic range (higher than needed to treat adrenal insufficiency alone[9,10]) is the only currently available approach for androgen reduction in most patients.[1-5,11,12] Long-term supraphysiologic glucocorticoid exposure can cause multiple complications, including decreased bone density, increased fracture risk, obesity, insulin resistance, diabetes mellitus, hyperlipidemia, hypertension, and psychological disturbances.[8,13-25] One promising new strategy for reducing adrenal androgen overproduction through a glucocorticoid-independent mechanism is corticotropin-releasing factor type 1 receptor (CRF_1) antagonism to reduce ACTH secretion, thus potentially allowing for physiologic glucocorticoid administration.[26]

Crinecerfont is an orally administered CRF_1 antagonist that reduced key hormone biomarkers in phase 2 studies involving adults[27] and adolescents[28] with CAH. Meaningful reductions in ACTH, 17-hydroxyprogesterone (diagnostic adrenal androgen precursor), and androstenedione (key adrenal androgen) were observed after 14-day open-label treatment, providing proof of concept that CRF_1 antagonism has therapeutic value in CAH. Moreover, elevated testosterone levels in female patients and androstenedione-to-testosterone ratios in male patients decreased substantially.[27,28]

Here, we report the results of the phase 3 CAHtalyst trial involving adults with CAH to evaluate the efficacy of crinecerfont to improve androgen control and potentially enable a reduction in the glucocorticoid dose to a physiologic range. A companion article by Sarafoglou et al.[29] presents findings from a trial of crinecerfont in children and adolescents.

A Quick Take is available at NEJM.org

Methods

Trial Design and Oversight

The CAHtalyst trial included a 24-week, randomized, double-blind, placebo-controlled period, which is described here, followed by a 12-month active-treatment period and optional, ongoing open-label extension (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial was performed at 54 centers in the United States, Canada, Europe, and Israel and was conducted in compliance with the Good Clinical Practice guidelines of the International Council for Harmonisation and according to 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. All the patients provided written informed consent. An independent data and safety monitoring committee reviewed the data throughout the trial and also reviewed the results of a planned interim analysis.

The trial was designed by the sponsor, Neurocrine Biosciences, and an advisory board that included four coauthors who were not employed by the sponsor. The sponsor provided the crinecerfont and placebo used in the trial and monitored the trial sites. Data were collected by the trial investigators or other qualified site personnel and were analyzed by the sponsor; representatives of the sponsor provided editorial and graphics support to the authors. The decision to submit the manuscript for publication was made by the sponsor with agreement from the authors, who all had access to the full data set and

analyses. The sponsor and authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PATIENTS

Adults (≥18 years of age) with CAH were eligible to participate in the trial if they were receiving a daily glucocorticoid dose of more than 13 mg per square meter of body-surface area of a hydrocortisone equivalent (equivalency factor, 4 times for methylprednisolone, prednisolone, and prednisone and 60 times for dexamethasone), with receipt of a stable dose for at least 1 month. Key exclusion criteria were any condition other than CAH that required long-term glucocorticoid therapy or evidence of glucocorticoid overtreatment on the basis of screening levels of 17-hydroxyprogesterone or androstenedione below normal. Additional details regarding inclusion and exclusion criteria are provided in the Supplementary Appendix.

RANDOMIZATION AND TRIAL INTERVENTIONS

On day 1 (baseline), patients were randomly assigned in a 2:1 ratio to receive crinecerfont (at a dose of 100 mg) or placebo twice daily with morning and evening meals. Randomization, which was performed by interactive-response technology, was stratified according to the baseline glucocorticoid dose (<20 or ≥20 mg per square meter per day of a hydrocortisone equivalent), glucocorticoid type, and sex.

Glucocorticoid regimens were maintained from baseline to week 4 (stable period). From week 4 through week 12 (reduction period), glucocorticoid doses were decreased (in four steps or fewer according to a schedule that was based on the starting dose and dose strength availability) to a target dose of 8 to 10 mg per square meter per day of a hydrocortisone equivalent; exceptions in dose changes were made in cases of clinical concern regarding adrenal insufficiency or hyperandrogenism. Guidance was provided to decrease the dose of the most nonphysiologic type of glucocorticoid (e.g., dexamethasone) and the nonphysiologic timing (e.g., bedtime) of administration. From weeks 12 to 24 (optimization period), glucocorticoid doses were adjusted with the goal of achieving the lowest dose by week 24 while maintaining androstenedione control, which was defined as a level that was below or equal to either 120% of the baseline level or the upper limit of the normal range (ULN). Throughout the trial, the patients followed guidelines for stress dosing (e.g., during times of illness or injury) as needed (Table S1) and were advised to return to their maintenance dose for at least 3 days before blood-sample collection for hormone evaluations. Methodologic details (including hormone reference ranges [Table S2]) are provided in the Supplementary Appendix.

END POINTS

The primary efficacy end point was the percent change from baseline to week 24 in the daily dose of glucocorticoid while maintaining androstenedione control. Any decrease from baseline in the glucocorticoid dose was set to zero if androstenedione control had not been maintained at week 24. Key secondary end points were the change from baseline to week 4 in the serum androstenedione level, obtained before the morning glucocorticoid dose; report of a physiologic glucocorticoid dose at week 24, which was defined as a hydrocortisone equivalent of 11 mg per square meter per day or less according to the 95th percentile of cortisol production in healthy persons,[30,31] with maintenance of androstenedione control; changes from baseline to week 24 in a homeostasis model assessment of insulin resistance (in patients not taking insulin) and percent total fat mass; and percent change from baseline to week 24 in body weight. All androgens and androgen precursors were measured at a central laboratory (Quest Diagnostics) by liquid chromatography with tandem mass spectrometry.

Safety assessments included adverse events, vital signs, 12-lead electrocardiograms, clinical laboratory tests, and scores on the Brief Psychiatric Rating Scale and Columbia–Suicide Severity Rating Scale. Details regarding all efficacy end points and safety assessments are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We determined that the enrollment of 165 patients would provide the trial with more than 90% power to detect a treatment effect size as small as 0.55 for the primary end point with a two-sided type I error of 0.05. Efficacy analyses were performed on data obtained from all the patients who had undergone randomization, according to their trial-group assignments. Missing data for the primary and key secondary efficacy

end points were imputed with the use of a regression-based multiple imputation method, which assumed that data were missing at random. We tested the primary and key secondary end points using a procedure that adjusted for multiple comparisons to control the family-wise type I error rate (Fig. S2).

An analysis-of-covariance model was used to evaluate continuous end points (e.g., primary end point), with results presented as the least-squares mean percent change from baseline with standard error of the mean, along with 95% confidence intervals and two-sided P values for the least-squares mean difference between the trial groups. We used a two-sided Cochran–Mantel–Haenszel test to analyze categorical end points (e.g., reduction to a physiologic glucocorticoid dose with androstenedione control), with results presented as the number and percentage of patients and the P value for test of association. Details regarding the statistical methods are provided in the Supplementary Appendix.

After approximately half the patients had completed week 24, we performed a planned interim analysis with respect to the primary end point, including a sample-size reestimation and futility assessment, which was unblinded only to the data and safety monitoring committee. The data and safety monitoring committee recommended continuing the trial as planned.

Safety analyses, which involved all the patients who had undergone randomization and received at least one dose of crinecerfont or placebo, were performed with descriptive statistics. No imputation of missing values, formal hypothesis testing, or designation of primary or secondary safety end points was performed.

RESULTS

PATIENTS

Of the 182 patients who underwent randomization, more than 95% completed the trial (117 of 122 patients in the crinecerfont group and 57 of 60 patients in the placebo group) (Fig. S3). The demographic and clinical characteristics of the patients were well balanced in the two groups (Table 1 and Tables S3 and S4). At baseline, the mean glucocorticoid dose was 17.6 mg per square meter per day of a hydrocortisone equivalent. The mean androstenedione level was elevated at 620 ng per deciliter (two to three times the ULN), which indicated elevated adrenal androgen levels despite supraphysiologic glucocorticoid administration.

Common coexisting illnesses (which were reported by ≥10% of the patients who had undergone randomization) were irregular menses, acne, and hirsutism in women and anxiety, osteopenia, depression, hypertension, and hyperlipidemia in both men and women (Table S5). Notably, 44 men (48%) reported having received a diagnosis of TARTs, but 53 (66%) had ultrasonographic evidence of this condition at baseline (Table 1).

EFFICACY

The primary and key secondary end points are shown in Table 2; exploratory bone-marker end points (serum bone-specific alkaline phosphatase, C-terminal telopeptide, and osteocalcin, along with urine N-terminal telopeptide) are shown in Table S6. After the 4-week glucocorticoid-stable period, the mean percent reduction in the glucocorticoid dose was greater with crinecerfont than with placebo at all time points and was maintained from weeks 12 to 24 with crinecerfont but increased toward baseline with placebo (Fig. 1A).

For the primary efficacy end point, the glucocorticoid dose reduction at week 24 with maintenance of androstenedione control was significantly greater with crinecerfont than with placebo (least-squares mean percent change from baseline of –27.3% vs. –10.3%; least-squares mean difference, –17.0 percentage points; P<0.001) (Table 2). These percent decreases corresponded to a daily change in the least-squares mean dose of –4.8 mg per square meter for crinecerfont and of –2.1 mg per square meter for placebo. Moreover, the percentage of patients who had a reduction to a physiologic glucocorticoid range while maintaining androstenedione control was significantly greater in the crinecerfont group than in the placebo group at week 24 (63% vs. 18%; P<0.001) (Fig. 1B). The observed mean glucocorticoid dose at week 24 was 10.7 mg per square meter in the crinecerfont group and 13.7 mg per square meter in the placebo group (Table S7).

During the initial 4-week stable period, the least-squares mean level of androstenedione decreased with crinecerfont (–299 ng per deciliter [–10.4 nmol per liter]) but increased with placebo (45.5 ng per deciliter [1.6 nmol per liter]), for a least-squares mean difference of –345 ng per

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	All Patients (N=182)	Crinecerfont (N=122)	Placebo (N=60)
Age — yr	30.8±9.9	31.3±9.8	29.8±10.2
Male sex — no. (%)	92 (51)	61 (50)	31 (52)
White race — no. (%)†	164 (90)	107 (88)	57 (95)
Glucocorticoid daily dose			
In hydrocortisone equivalents — mg/day	32.3±9.3	32.4±9.2	32.1±9.5
Adjusted for body-surface area — mg/m^2	17.6±4.9	17.5±4.5	17.9±5.5
Glucocorticoid type — no. (%)			
Hydrocortisone alone	106 (58)	71 (58)	35 (58)
Prednisone, prednisolone, or methylprednisolone, with or without hydrocortisone	53 (29)	34 (28)	19 (32)
Dexamethasone, with or without another glucocorticoid	23 (13)	17 (14)	6 (10)
Fludrocortisone — no. (%)	157 (86)	107 (88)	50 (83)
Body weight — kg	79.3±18.3	80.8±17.8	76.2±18.9
Body-mass index‡	29.8±7.0	30.1±6.9	29.0±7.1
Percent total fat mass§	35.7±9.2	36.3±9.0	34.6±9.5
Homeostasis model assessment of insulin resistance¶	3.2±2.8	3.2±2.7	3.1±3.1
Androstenedione — ng/dl‖	620±729	635±796	590±572
17-Hydroxyprogesterone — ng/dl‖	9467±8829	9314±8560	9787±9435
Testicular adrenal rest tumor — no./total no. (%) **	53/80 (66)	35/53 (66)	18/27 (67)

* Plus–minus values are means ±SD.
† Race was reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Data regarding the percent total fat mass were missing for 18 patients in the crinecerfont group and for 7 in the placebo group.
¶ Insulin resistance was measured in 172 patients (117 in the crinecerfont group and 55 in the placebo group) who did not have diabetes mellitus. The homeostasis model assessment of insulin resistance, calculated as the product of fasting glucose (measured in milligrams per deciliter) and insulin (measured in milliunits per liter) and divided by 405, is reported without units.
‖ This measure is based on samples collected before the patients had received the morning glucocorticoid dose. Normal ranges and conversion factors for conventional units to standard international units are provided in Table S2 in the Supplementary Appendix. Data were missing for 1 patient in each group regarding androstenedione and for 1 patient in the crinecerfont group and 2 patients in the placebo group regarding 17-hydroxyprogesterone.
** This category was evaluated in men who had undergone testicular ultrasound assessment at baseline.

deciliter (–12.0 nmol per liter; P<0.001) (Table 2 and Fig. 1C). Similarly, 17-hydroxyprogesterone levels decreased substantially from baseline to week 4 with crinecerfont but changed minimally with placebo (Fig. 1D and Table S6). At week 24, after the reduction in the glucocorticoid dose and the optimization period, the mean androstenedione level remained below baseline with crinecerfont (–33.0 ng per deciliter [–1.1 nmol per liter]) but increased to above baseline with placebo (388 ng per deciliter [13.5 nmol per liter]) (Fig. 1C). Androstenedione control at week 24 was achieved in 88 of 118 patients (75%) in the crinecerfont group and in 30 of 57 patients (53%) in the placebo group. In the crinecerfont group, the observed mean androstenedione values were 316 ng per deciliter (11.0 nmol per liter) at 4 weeks and 607 ng per deciliter (21.2 nmol per liter) at 24 weeks, as compared with 624 ng per deciliter (21.8 nmol per liter) at 4 weeks and 974 ng per deciliter (34.0 nmol per liter) at 24 weeks in the placebo group (Table S7).

Sensitivity analyses confirmed the robustness of the primary end point and the key secondary end points of the occurrence of a physiologic glucocorticoid dose at week 24 and the change in the serum androstenedione level at week 4. There were no significant differences between

Table 2. Efficacy End Points.*

End Point	Crinecerfont (N=122)	Placebo (N=60)	Difference (95% CI)	P Value
Primary end point†				
Percent change from baseline in glucocorticoid dose with control of androstenedione at 24 wk	−27.3±2.4	−10.3±3.2	−17.0 (−23.8 to −10.2)	<0.001
Key secondary end points†				
Change from baseline in serum androstenedione at 4 wk — ng/dl‡	−299±37.7	45.5±51.0	−345 (−457 to −232)	<0.001
Patients with physiologic glucocorticoid dose with androstenedione control at 24 wk — no. (%)§	74 (63)	10 (18)	NA	<0.001
Change from baseline in homeostasis model assessment of insulin resistance at 24 wk§	−0.65±0.21	−0.36±0.28	−0.29 (−0.89 to 0.32)	0.35
Percent change from baseline in body weight at 24 wk§	−1.45±0.53	−0.07±0.72	−1.38 (−2.96 to 0.20)	0.09
Change from baseline in percent total fat mass at 24 wk§¶	−0.11±0.66	−1.04±0.98	0.93 (−1.04 to 2.90)	0.35

* Plus–minus values are the least-squares mean (±SE) change from baseline. The difference in the percent change from baseline is expressed in percentage points. CI denotes confidence interval, and NA not applicable.

† For the primary and key secondary end points, values for patients with missing data were multiply imputed for statistical testing. Therefore, analyses are based on the full analysis population, which includes all the patients who underwent randomization. The numbers of patients with complete data for each end point were 118 in the crinecerfont group and 57 in the placebo group for the primary end point; 117 and 56 patients, respectively, for the androstenedione value; 118 and 57 patients, respectively, for having a physiologic glucocorticoid dose with control of androstenedione; 112 and 54 patients, respectively, for insulin resistance; 118 and 57 patients, respectively, for weight; and 93 and 43 patients, respectively, for total fat mass.

‡ The serum androstenedione level was based on samples collected before the patients had received the morning glucocorticoid dose. Normal ranges are provided in Table S2.

§ This key secondary end point was tested with the use of a Holm procedure, which resulted in between-group differences that were not significant.

¶ The percent total fat mass was calculated as the total fat mass (in grams) divided by the total body mass (in grams) times 100. The weight measure for the least-squares mean change from baseline in total fat mass was 0.1±1.0 kg in the crinecerfont group and −1.4±1.4 kg in the placebo group, for a least-squares mean difference of 1.5 kg (95% CI, −1.5 to 4.5).

the trial groups for the remaining key secondary end points (Table 2). In exploratory analyses, bone-turnover markers rose in both groups (Table S6).

SAFETY

Crinecerfont appeared to have an acceptable side-effect profile, with similar frequencies of adverse events in the two groups (Table 3). Most adverse events were mild or moderate in intensity and resolved spontaneously, including fatigue, which was more common in the crinecerfont group. Adverse events led to trial discontinuation in four patients in the crinecerfont group, one during the 24-week randomized period. Four patients in the crinecerfont group had a serious adverse event, all of which were assessed by the investigator as unlikely to be related to crinecerfont and none of which led to trial discontinuation. No deaths occurred during the trial period.

Adrenal insufficiency or acute adrenocortical insufficiency was reported in two patients (2%) in the crinecerfont group and in one patient (2%) in the placebo group. Adverse events that led to glucocorticoid stress dosing were reported in 42% of the patients in the crinecerfont group and in 44% of those in the placebo group, with most cases involving only oral stress dosing. No safety concerns regarding crinecerfont were reported with respect to vital signs, clinical laboratory tests, electrocardiographic findings, or neuropsychiatric assessments.

DISCUSSION

Since the 1950s, glucocorticoid therapy has been used for both cortisol replacement and adrenal androgen control in patients with CAH, yet patients with CAH still have a higher prevalence of osteoporosis, obesity, insulin resistance, diabetes mellitus, hyperlipidemia, and hypertension than controls.[2-5,23-25] In our phase 3 trial, the mean glucocorticoid dose at baseline was at least two times the mean physiologic cortisol production rate of approximately 7 mg per square meter per day,[30,31] a finding that was consistent with the results of earlier cohort studies.[21,32] Conversely,

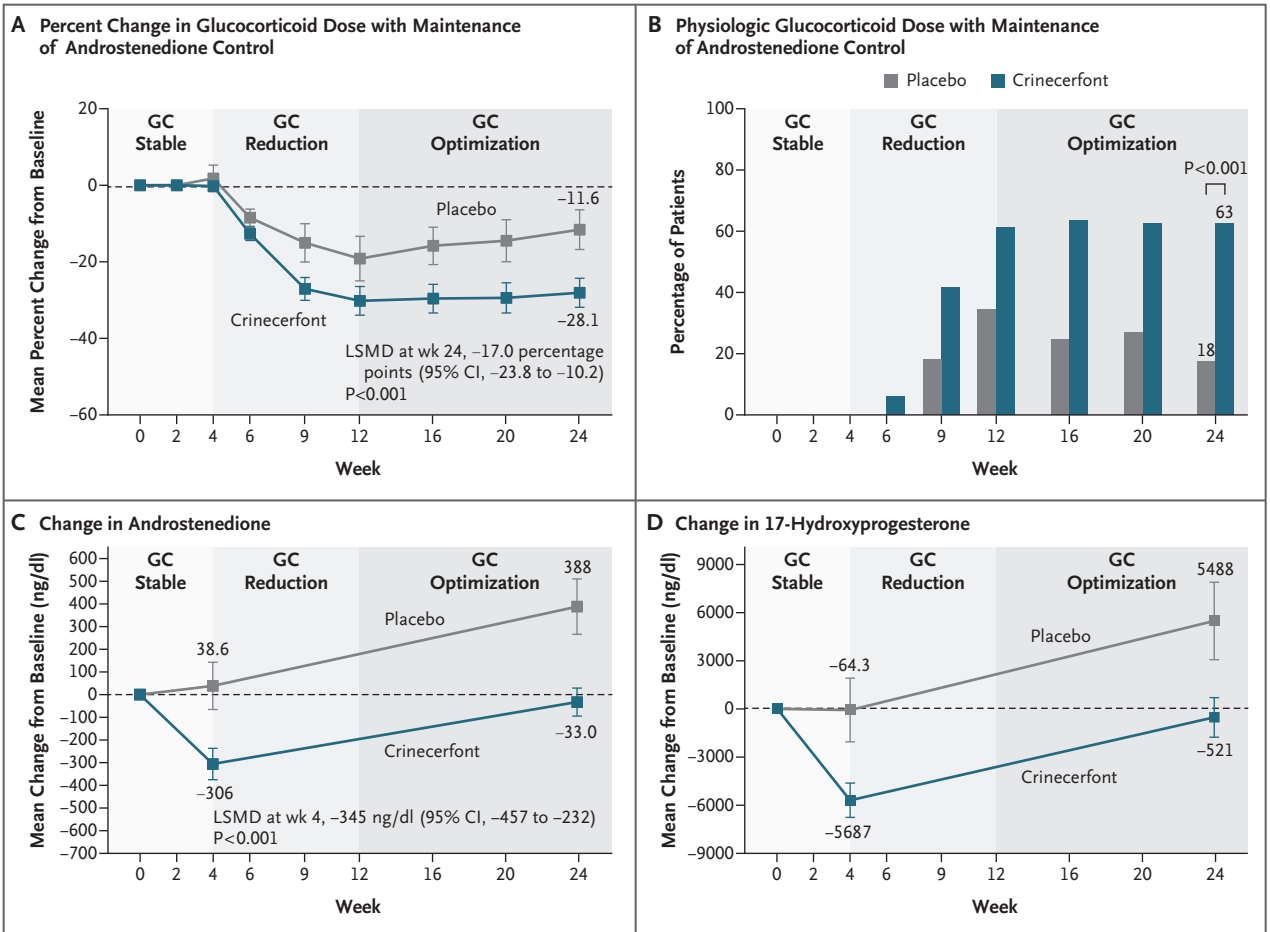

Figure 1. Efficacy End Points.

Differences between crinecerfont and placebo are shown for the percent change in the glucocorticoid (GC) dose with maintenance of androstenedione (adrenal androgen) control (Panel A), the percentage of patients who had a reduction in the glucocorticoid dose to a physiologic level (≤11 mg per square meter per day in hydrocortisone equivalents) while maintaining androstenedione control (Panel B), and changes from baseline to week 4 in the serum levels of androstenedione (Panel C) and 17-hydroxyprogesterone (Panel D). Analyses of the primary and key secondary end points included all the patients who had undergone randomization, with imputation of missing values. The change in the glucocorticoid dose was set to zero for patients who had a dose reduction without androstenedione control (which was defined as ≤120% of the baseline value or within the upper limit of the normal range) in samples collected after receipt of the morning glucocorticoid dose. Values for androstenedione and 17-hydroxyprogesterone are based on samples collected before the patients had received the morning glucocorticoid dose. The I bars represent 95% confidence intervals for mean changes. The widths of the confidence intervals have not been adjusted for multiplicity and thus should not be used to determine treatment effect. LSMD denotes least-squares mean difference.

the few prospective studies that have evaluated a reduction of supraphysiologic glucocorticoid doses in a range relevant to CAH have shown improvements in markers of cardiovascular and metabolic disease and bone health.[33,34]

Consequently, one essential need for these patients is an alternative strategy for controlling excess adrenal androgens while reducing glucocorticoid doses to a more physiologic range. In this trial, we found that the patients who received crinecerfont had a significantly greater reduction in their glucocorticoid dose at week 24 with maintenance of androstenedione control than the patients who received placebo.

Crinecerfont markedly lowered levels of androstenedione and 17-hydroxyprogesterone as compared with placebo after the initial 4-week stable-dose period, results that were consistent with data from the phase 2 trials.[27,28] We then tested the hypothesis that the anticipated im-

Table 3. Adverse Events.

Adverse Events	Crinecerfont (N=122)	Placebo (N=59)
	number of patients (percent)	
Any adverse event	101 (83)	48 (81)
Leading to discontinuation of crinecerfont or placebo	4 (3)*	0
Leading to trial discontinuation	4 (3)*	0
Any serious adverse event	4 (3)†	0
Severity of adverse event‡		
Mild	62 (51)	30 (51)
Moderate	36 (30)	18 (31)
Severe	3 (2)	0
Common adverse events§		
Fatigue	30 (25)	9 (15)
Headache	19 (16)	9 (15)
Coronavirus infection	17 (14)	5 (8)
Upper respiratory tract infection	11 (9)	7 (12)
Diarrhea	10 (8)	5 (8)
Dizziness	10 (8)	2 (3)
Nausea	10 (8)	5 (8)
Arthralgia	9 (7)	0
Back pain	7 (6)	2 (3)
Pyrexia	7 (6)	6 (10)
Blood creatine kinase increased	6 (5)	2 (3)
Nasopharyngitis	6 (5)	8 (14)
Vomiting	6 (5)	5 (8)
Decreased appetite	5 (4)	1 (2)
Gastroenteritis	5 (4)	1 (2)
Influenza	5 (4)	2 (3)

* The four adverse events that led to drug and trial discontinuation were dyspepsia, nausea, and vomiting (in 1 patient), gastric ulcer (in 1 patient), apathy and restlessness (in 1 patient), and rash (in 1 patient). All adverse events that were first identified during the 24-week randomized period and that resulted in the discontinuation of crinecerfont or placebo are presented regardless of when the discontinuation occurred. Only one adverse event (gastric ulcer) that was first identified during the randomized period resulted in discontinuation during that period.

† The four serious adverse events (one in each patient) were cholecystitis, groin abscess and cellulitis, acute adrenocortical insufficiency, and presyncope. All the serious adverse events were assessed by the investigator as having an unlikely association with crinecerfont. No patients died during the trial.

‡ The maximum severity was determined by the trial investigator.

§ Listed in this category are adverse events that were reported in at least 5 patients in the crinecerfont group.

provement in androgen control would enable a reduction in the daily glucocorticoid dose to a physiologic range (≤11 mg per square meter) following a protocol-specified schedule, without loss of androstenedione control. The major finding of this trial is that crinecerfont therapy allowed both a reduction in the glucocorticoid dose to this target and maintenance of prespecified androstenedione control in 63% of the patients, as compared with 18% of those in the placebo group. The trial also showed that supraphysiologic glucocorticoid doses could be safely reduced to a target physiologic range without causing an increase in adrenal crises, with a lower observed rate (3.3 per 100 patient-years) than expected in this patient population (10.2 per 100

patient-years).[35,36] Fatigue, which was possibly due to a reduction in the glucocorticoid dose, was more common with crinecerfont than with placebo but generally resolved without treatment.

Strengths of this trial include the randomized, double-blind, placebo-controlled design, along with a relatively large sample size, given the rarity of CAH. In addition, patients with a broad range of androstenedione levels were enrolled, and the trial focused on a clinically relevant end point of reduction in the glucocorticoid dose while maintaining androstenedione control and had a very high completion rate with minimal missing data.

The trial also had certain limitations, which included its restriction to patients who had been receiving supraphysiologic glucocorticoid doses, the short time frame to observe changes in clinical end points related to glucocorticoid exposure, and the focus on achieving the lowest glucocorticoid dose, which might have limited interpretation of end points associated with androgen excess. Moreover, the majority of patients were White, with few Black enrollees, a distribution that is similar to the prevalence of CAH in the United States and Europe (Table S8) but that potentially limits the generalizability of the results.

Additional approaches to glucocorticoid-sparing therapy in classic CAH include the use of subcutaneous or modified-release hydrocortisone[37,38] and flutamide plus testolactone[39] or abiraterone acetate[40,41] with physiologic hydrocortisone. Trials of the CRF_1 antagonist tildacerfont,[42] gene therapy with BBP-631, and other agents targeting various levels of the hypothalamic–pituitary–adrenal axis are ongoing.[5]

The priority in our trial was a reduction in the glucocorticoid dose to a level that was as close to physiologic as possible without loss of androgen control, rather than primarily lowering adrenal androgen levels. In specific cases, the clinical treatment of adults with CAH requires intense control (e.g., for shrinking TARTs in men or achieving pregnancy in women). This trial did not assess whether the glucocorticoid dose that was required for intense control was lower with crinecerfont therapy. The receipt of crinecerfont was not associated with TART shrinkage, but reversal may require longer treatment. However, there was no increase in the mean TART volume, despite a substantial reduction in the glucocorticoid dose with crinecerfont. In women, interpretation of menstrual regularity was limited by the small number in whom this factor could be evaluated, given the requirement for contraception.

No significant between-group differences were observed in certain secondary end points that reflect the consequences of long-term supraphysiologic glucocorticoid therapy (e.g., body weight, insulin resistance, and glucose tolerance). Exploratory analyses showed that bone formation and resorption markers increased in both groups, which is consistent with relief of glucocorticoid-induced suppression of bone turnover; however, 24-week treatment is not long enough to conclusively assess the effects on bone density.

In this trial, crinecerfont therapy allowed for a substantial and clinically meaningful reduction in glucocorticoid administration to more physiologic doses in adults with classic CAH and was associated with reduced adrenal androgen production.

The views expressed are those of the authors and not necessarily those of the National Institute for Health and Care Research (NIHR) or the Department of Health and Social Care of the NIHR.

Baseline data were presented at the annual meetings of the American Association of Clinical Endocrinology in New Orleans, May 9–11, 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 Endocrine Society meeting in Boston, June 1–4, 2024.

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APPENDIX

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