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Phase 3 Trial of Crinecerfont in Adult Congenital Adrenal Hyperplasia

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Disclosures

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

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Abstract

Background: Adrenal insufficiency in patients with classic 21-hydroxylase deficiency congenital adrenal hyperplasia (CAH) mandates glucocorticoid replacement therapy. Control of adrenal-derived androgen excess usually requires supraphysiological glucocorticoid doses, predisposing patients to glucocorticoid-related complications. Crinecerfont, an oral corticotropin-releasing factor type 1 receptor antagonist, lowered androstenedione in phase 2 trials for CAH.

Methods: In this phase 3 trial, adults with CAH were randomized (2:1) to crinecerfont or placebo for 24 weeks. Glucocorticoid treatment was maintained stable for 4 weeks to evaluate androstenedione reduction, followed by glucocorticoid dose reduction and optimization over 20 weeks to achieve the lowest glucocorticoid dose that maintained androstenedione control (≤120% baseline or within reference range). Primary efficacy end point was percent change in daily glucocorticoid dose from baseline to week 24 while maintaining androstenedione control.

Results: Of 182 randomized participants (122 crinecerfont, 60 placebo), 176 (96.7%) reached 24 weeks. Baseline mean glucocorticoid dose was 17.6 mg/m^2/day (hydrocortisone equivalents); mean androstenedione levels were elevated (620 ng/dL). At week 24, glucocorticoid dose reduction (with androstenedione control) was −27.3% for the crinecerfont group versus −10.3% (placebo) (least-squares mean difference [LSMD]: −17.0%; P<0.001) (primary end point); 62.7% versus 17.5% achieved physiological glucocorticoid dose (P<0.001). At week 4, androstenedione levels decreased with crinecerfont (−299 ng/dL) but increased with placebo (+45.5 ng/dL) (LSMD: −345 ng/dL; P<0.001). Fatigue and headache were the most common adverse events in both treatment groups.

Conclusions: In this trial, crinecerfont permitted reduction of supraphysiological glucocorticoid doses, including to physiological range, following evaluation of adrenal androgen levels in patients with CAH.

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

In the absence of endogenous cortisol, negative feedback on the hypothalamus and pituitary is attenuated, which increases corticotropin-releasing factor (CRF) and adrenocorticotropic hormone (ACTH) secretion and, in turn, 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 experience hirsutism, acne, and irregular menses, while male patients develop testicular adrenal rest tumors (TARTs); persons of both sexes may have hypogonadism and/or impaired fertility.[5,6,8]

Glucocorticoids (GCs) are used for cortisol replacement; however, increasing GC doses above the physiological 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] Chronic supraphysiological GC exposure can cause multiple complications, such as 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 GC-independent mechanism is CRF type 1 receptor (CRF_1) antagonism to reduce ACTH secretion, thus potentially allowing for physiological GC dosing.[26]

Crinecerfont is a novel orally administered CRF_1 antagonist that reduced key hormone biomarkers in phase 2 studies in adults (NCT03525886[27]) and adolescents (NCT04045145[28]) with CAH. Meaningful reductions in ACTH, 17-hydroxyprogesterone (17OHP) (diagnostic adrenal androgen precursor), and androstenedione (key adrenal androgen) were observed after 14-day open-label treatment, providing proof-of-concept that CRF_1 receptor antagonism has therapeutic value in CAH. Moreover, elevated testosterone in female participants and androstenedione-to-testosterone ratio in male participants decreased substantially.[27,28] Here, we report the results of CAHtalyst (NCT04490915), a phase 3 multinational trial in adults with CAH evaluating the efficacy of crinecerfont to improve androgen control and potentially enable GC dose reduction to a physiological range. A companion paper concerning crinecerfont in children and adolescents (age 2–17 years) accompanies this paper (NCT04806451).[29]

METHODS

Trial Design and Oversight

Our study included a 24-week, randomized, double-blind, placebo-controlled period (see study design in the Supplementary Appendix, Fig. S1), reported herein, followed by a

12-month active-treatment period and optional, ongoing open-label extension. The study was performed at 54 centers in the United States, Canada, Europe, and Israel and conducted in compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines and according to relevant laws and regulations. The protocol was reviewed and approved by Independent Ethics Committees or Institutional Review Boards at each study site and by national health authorities for each country. All participants provided written informed consent. An independent data monitoring committee (DMC) monitored safety 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 coauthors (RJA, HF, DPM, NR) not employed by the Sponsor. Neurocrine provided study medication and monitored trial sites. Data were collected by the study investigators (Supplementary Appendix 1.0) or other qualified study site personnel and were analyzed by Neurocrine (JS). Authors (RJA, KS, JLC, JS) drafted the manuscript with editorial and graphics support funded by the Sponsor. The decision to publish was made by the Sponsor with agreement from the authors, all of whom had access to the full dataset and analyses (upon request). The Sponsor and authors vouch for the accuracy and completeness of the data and affirm the fidelity of the trial to the protocol (available at NEJM.org).

Participants

Eligible participants were male or female age ≥18 years with CAH receiving a GC dose >13 mg/m^2/day hydrocortisone equivalents (HCe; equivalency factor 4x for [me]prednis[ol]one, 60x for dexamethasone), stable ≥1 month. Key exclusion criteria included any condition requiring chronic GC therapy other than CAH or evidence of GC overtreatment based on screening 17OHP or androstenedione levels below normal. Additional information is provided in Supplementary Appendix 2.1.

Randomization and Trial Interventions

On Day 1 (baseline), participants were randomized (2:1) to crinecerfont 100 mg or placebo twice daily with morning and evening meals. Randomization by interactive response technology was stratified by GC dose (<20 or ≥20 mg/m^2/day HCe), GC type, and sex (Supplementary Appendix 2.2).

GC regimens were maintained from baseline to week 4 (GC stable period). From week 4 through week 12 (GC reduction period), GC doses were decreased (in 4 steps or fewer using a schedule based on starting dose and dose strength availability) to a target dose of 8–10 mg/m^2/day HCe, except for clinical concern of adrenal insufficiency or hyperandrogenism. Guidance was provided to decrease first the most non-physiological type (e.g., dexamethasone) and timing (bedtime). From weeks 12 to 24 (GC optimization period), GC doses were adjusted with the goal of achieving the lowest GC dose by week 24 while maintaining androstenedione control, defined as ≤120% of baseline or ≤ upper limit of normal (ULN). Throughout the study, participants followed stress-dosing guidelines (Table S1) as needed and were to return to their maintenance dose for ≥3 days prior to blood

sample collection for hormone evaluations. Methodological details are in the Supplementary Appendix 2.2, including hormone reference ranges (Table S2).

Assessments and End Points

The primary efficacy end point was the percent change from baseline at week 24 in GC daily dose while maintaining androstenedione control, where any decrease in GC dose was set to zero if androstenedione control was not maintained at week 24. Key secondary end points were as follows: change from baseline at week 4 in serum androstenedione, obtained prior to the morning glucocorticoid dose; achievement of a physiological GC dose at week 24, defined as ≤11 mg/m^2/day HCe, based on the 95th percentile for cortisol production in healthy persons[30,31] (participants were considered not to have achieved this end point if androstenedione control was not maintained); changes from baseline at week 24 in homeostatic model assessment for insulin resistance (HOMA-IR; in participants not taking insulin) and percent total fat mass; and percent change from baseline at 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 treatment-emergent adverse events (TEAEs), vital signs, 12-lead electrocardiograms, clinical laboratory tests, Brief Psychiatric Rating Scale, and Columbia-Suicide Severity Rating Scale. The Supplementary Appendix describes all efficacy end points (3.1–3.4) and safety assessments (3.5).

Statistical Analyses

A sample of 165 participants (110 crinecerfont, 55 placebo) was estimated to provide >90% power to detect an effect size as small as 0.55 for the primary end point with 2-sided type 1 error of 0.05.

Efficacy analyses were performed on all randomized participants, according to their randomized treatment assignments. Missing data for the primary and key secondary efficacy end points were imputed using a regression-based multiple imputation method, which assumes data are missing at random. The primary and key secondary end points were tested 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 least-squares (LS) mean (percent) change from baseline with standard error of the mean (SEM), along with 95% confidence interval (95% CI) and 2-sided P-value for the least-squares mean difference (LSMD) between treatment groups. A 2-sided Cochran-Mantel-Haenszel test was used to analyze categorical end points (e.g., achievement of reduction to a physiological GC dose with androstenedione control), with results presented as the number and percentage of participants and P-value for test of association. All statistical methods are in the Supplementary Appendix 4.0.

A planned interim analysis on the primary end point, including sample-size re-estimation and futility assessment (unblinded only to the DMC), was conducted when approximately

one-half of the participants completed week 24. The DMC recommended continuing the study as planned (Supplementary Appendix 4.4).

Safety analyses were performed in all randomized and dosed participants with descriptive statistics. No imputation of missing values, formal hypothesis testing, or designation of primary or secondary safety end points were performed.

RESULTS

Participants

Of 182 randomized participants, >95% completed the study (117/122 crinecerfont, 57/60 placebo) (Fig. S3). Participants' demographics and baseline characteristics were well-balanced across treatment groups (Table 1, Table S3 and S4). Baseline mean GC dose was 17.6 mg/m^2/day HCe with elevated mean androstenedione of 620 ng/dL (~2–3 times ULN), indicating elevated adrenal androgens despite supraphysiological GC dosing.

Common comorbidities (self-reported in ≥10% of the randomized population or by sex) were irregular menses, acne, and hirsutism in female participants, anxiety, osteopenia, depression, hypertension, and hyperlipidemia (Table S5). Notably, 44 (47.8%) male participants self-reported having TARTs, but 53 (66.3%) had ultrasound evidence of TARTs at baseline (Table 1).

Efficacy

Tables 2 and S6 note the primary and key secondary or secondary and exploratory bone marker end points, respectively. After the 4-week GC stable period, mean percent GC reduction was greater with crinecerfont than placebo at all timepoints and was maintained from weeks 12 to 24 with crinecerfont but increased towards baseline with placebo (Fig. 1A). For the primary efficacy end point, GC dose reduction at week 24 (while androstenedione control was maintained) was significantly greater with crinecerfont than placebo (LS mean percent change from baseline of −27.3% versus −10.3% [LSMD: −17.0%, P<0.001]) (Table 2). These percent decreases corresponded to LS mean dose changes of −4.8 and −2.1 mg/m^2/day HCe for crinecerfont and placebo, respectively. Moreover, the percentage of participants achieving reduction to a physiological GC range while maintaining androstenedione control was significantly greater in the crinecerfont group versus placebo at week 24 (62.7% vs. 17.5%; P<0.001) (Fig. 1B). Observed mean GC doses at week 24 were 10.7 and 13.7 mg/m^2/day HCe for crinecerfont and placebo, respectively (Table S7).

During the initial 4-week GC stable period, LS mean androstenedione decreased with crinecerfont (−299 ng/dL [−10.4 nmol/L]) but increased with placebo (+45.5 ng/dL [+1.6 nmol/L]) (LSMD: −345 ng/dL [−12.0 nmol/L]; P<0.001) (Fig. 1C, Table 2). Similarly, 17OHP decreased substantially from baseline to week 4 with crinecerfont but changed minimally with placebo (Fig. 1D, Table S7). At week 24, following GC reduction and optimization, mean androstenedione remained below baseline with crinecerfont (−33.0 ng/dL [−1.1 nmol/L]) but increased to above baseline with placebo (+388 ng/dL [+13.5 nmol/L]) (Fig. 1C). Androstenedione control at week 24 was achieved in 74.6% (88/118) of

crinecerfont-treated participants compared with 52.6% (30/57) with placebo. Observed mean androstenedione values at weeks 4 and 24 were 316 ng/dL (11.0 nmol/L) and 607 ng/dL (21.2 nmol/L) for crinecerfont, respectively, versus 624 ng/dL (21.8 nmol/L) and 974 ng/dL (34.0 nmol/L) for placebo, respectively (Table S7).

Sensitivity analyses confirmed the robustness of the primary end point and the key secondary end points of achievement of physiological GC dose at week 24 and change in serum androstenedione at week 4 (Supplementary Appendix 4.5). There were no significant differences between treatment 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 be acceptably tolerated, with similar incidences of TEAEs in both groups (Table 3). Most TEAEs were mild or moderate in intensity and resolved spontaneously, including fatigue, which was more common in the crinecerfont group. Four participants in the crinecerfont group had TEAEs leading to discontinuation, one during the randomized period. Four crinecerfont-treated participants had a serious TEAE, all assessed as unlikely related to study drug and none leading to discontinuation. No deaths occurred.

Adrenal insufficiency or acute adrenocortical insufficiency was reported for two (1.6%) crinecerfont-treated participants and one (1.7%) placebo-treated participant. TEAEs leading to GC stress dosing were reported in 41.8% of crinecerfont-treated and 44.1% of placebo-treated participants, with most cases involving only oral stress dosing. There were no safety concerns related to vital signs, clinical laboratory tests, electrocardiogram, or neuropsychiatric assessments with crinecerfont treatment.

DISCUSSION

Since the 1950s, GC therapy has been used for both cortisol replacement and adrenal androgen control in patients with CAH, yet patients with CAH suffer from a higher prevalence of osteoporosis, obesity, insulin resistance, diabetes mellitus, hyperlipidemia, and hypertension compared with controls.[2–5,23–25] Consistent with earlier cohort studies,[21,32] the mean baseline GC dose in this phase 3 study was at least 2-fold higher than the mean physiological cortisol production rate of ~7 mg/m^2/day.[30,31] Conversely, the few prospective studies that have evaluated reduction of supraphysiological glucocorticoid doses in a range relevant to CAH have demonstrated 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 GC doses to a more physiological range. This study found that crinecerfont achieved the primary efficacy end point, significantly greater GC dose reduction at week 24 while androstenedione control was maintained.

Consistent with data from the phase 2 trials,[27,28] crinecerfont markedly lowered androstenedione and 17OHP compared with placebo after the initial 4-week GC stable period. We then tested the hypothesis that the anticipated improvement in androgen control would enable reduction in GC dosing to a physiological range (≤11 mg/m^2/day HCe)

following a protocol-specified schedule, without loss of androstenedione control. The major finding of this trial is that crinecerfont therapy allowed both GC reduction to this goal and maintenance of prespecified androstenedione control in 62.7% of participants, compared with 17.5% in the placebo group. Importantly, the trial also demonstrated that supraphysiological GC doses could be safely reduced to a target physiological range without causing an increase in adrenal crises, with the observed rate (3.29 per 100 patient-years) being lower than expected in this patient population (10.2 per 100 patient-years).[35,36] Fatigue, possibly due to withdrawal symptoms precipitated by GC reduction, was more common with crinecerfont but generally resolved without treatment.

Strengths of this trial include the randomized double-blind placebo-controlled design, large sample size given the rarity of the condition, inclusion of participants across a broad range of androstenedione levels, focus on a clinically relevant end point of reduction in the GC dose while maintaining androstenedione control, a very high completion rate, and minimal missing data. The trial also had certain limitations, which included the restriction to participants who had been receiving supraphysiological GC doses, the short time frame to observe changes in clinical end points related to GC exposure, and the focus on achieving the lowest GC dose, which might have limited interpretation of end points associated with androgen excess. Similar to the prevalence of CAH in the United States and Europe (Table S8), the majority of patients in this study were White, with few Black or African American participants, potentially limiting generalizability.

Additional approaches to GC-sparing therapy in classic CAH include subcutaneous or modified-release hydrocortisone[37,38] and flutamide plus testolactone[39] or abiraterone acetate[40,41] with physiological 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 the protocol for our study was the reduction of GC dosing to as close to physiological as possible without loss of androgen control, rather than primarily lowering adrenal androgens. In specific cases, clinical management in adults with CAH requires intense control (e.g., for shrinking TARTs in men or achieving pregnancy in women). This study did not assess whether the GC dose required for intense control was lower with crinecerfont therapy. TART shrinkage with crinecerfont was not demonstrated in this trial, as reversal may require longer treatment; however, there was no increase in mean TART volume, despite substantial GC dose reduction with crinecerfont. In women, interpretation of menstrual regularity was limited by the small number for whom this could be evaluated, given the requirement for contraception.

Certain secondary end points that reflect consequences of chronic supraphysiological GC therapy (e.g., body weight, insulin resistance, glucose tolerance) showed modest improvements in both groups at 24 weeks. Exploratory analyses showed that bone formation and resorption markers increased in both groups, which is consistent with relief of GC-induced suppression of bone turnover; however, 24-week treatment is not long enough to conclusively assess effects on bone density.

In conclusion, crinecerfont therapy allowed substantial and clinically meaningful GC reduction to more physiological doses in adults with classic CAH and was associated with reduced adrenal androgen production.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Baseline data were presented at the annual meetings of the American Association of Clinical Endocrinology in New Orleans, Louisiana, May 9–11, 2024, and the European Congress of Endocrinology in Stockholm, Sweden, May 11–14, 2024; baseline and key efficacy and safety data were presented at the annual Endocrine Society meeting in Boston, Massachusetts, June 1–4, 2024.

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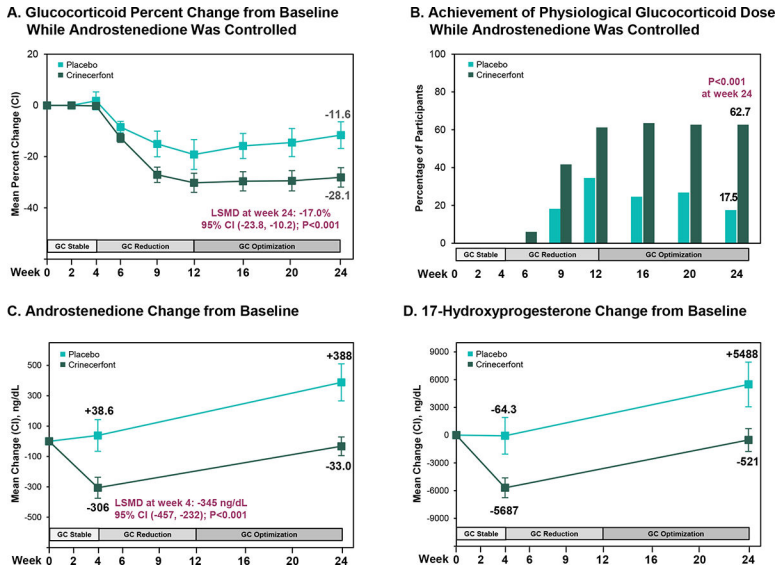

Figure 1. Efficacy Endpoints

Differences between crinecerfont and placebo are shown for the following: percent reduction in glucocorticoid (GC) dose while maintaining androstenedione (adrenal androgen) control (Panel A) and percentage of participants achieving reduction to a physiological GC range (≤11 mg/m^2/day in hydrocortisone equivalents) while maintaining androstenedione control (Panel B); changes from baseline to week 4 in serum androstenedione (Panel C) and 17-hydroxyprogesterone (17OHP) (Panel D). Change in GC dose was set to zero in participants who had a reduction in GC dose but did not achieve androgen control. Androstenedione and 17OHP values for the two 4-week end points (Panels C and D) are based on samples collected before participants received their morning GC doses. Androstenedione control was defined as equal to or less than either 120% of baseline or the upper limit of normal, based on samples collected after participants received their morning GC doses. Error bars represent 95% confidence intervals (CI) for mean changes. The widths of these CIs have not been adjusted for multiplicity, and the intervals may not be used in place of hypothesis testing. Least-squares mean differences (LSMDs) with 95% CIs and P-values are presented for the primary end point (Panel A) and first key secondary end point (Panel C); P-value for the second key secondary end point is also presented (Panel B, LSMD not applicable). Analyses for the primary and key secondary end points included all randomized participants, as missing values were imputed (Methods).

Table 1.

Demographics and Baseline Clinical Characteristics *

	All Participants (N=182)	Crinecerfont (N=122)	Placebo (N=60)
Age – yr	30.8±9.9	31.3±9.8	29.8±10.2
Male – no. (%)	92 (50.5)	61 (50.0)	31 (51.7)
White – no. (%)	164 (90.1)	107 (87.7)	57 (95.0)
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/day	17.6±4.9	17.5±4.5	17.9±5.5
Glucocorticoid type – no. (%)			
Hydrocortisone alone	106 (58.2)	71 (58.2)	35 (58.3)
Prednisone, prednisolone, or methylprednisolone, with or without hydrocortisone	53 (29.1)	34 (27.9)	19 (31.7)
Dexamethasone, with or without another glucocorticoid	23 (12.6)	17 (13.9)	6 (10.0)
Fludrocortisone – no. (%)	157 (86.3)	107 (87.7)	50 (83.3)
Body weight – kg	79.3± 18.3	80.8±17.8	76.2±18.9
Body mass index – kg/m^2	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
Homeostatic model assessment for 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 tumors (male participants) – no. (%)¶	53 (66.3)	35 (66.0)	18 (66.7)

* Mean values (± standard deviation) are presented for all 182 randomized participants unless indicated otherwise.

† Number of participants with missing percent total fat mass (18 crinecerfont, 7 placebo).

‡ In 172 participants (117 crinecerfont, 55 placebo) without diabetes mellitus.

§ Based on pre-morning glucocorticoid dose samples. Normal ranges and conversion factors for conventional units to standard international units are in Appendix Table S2. Number of participants with missing hormone or hormone precursor assessments at baseline: androstenedione (1 crinecerfont, 1 placebo); 17-hydroxyprogesterone (1 crinecerfont, 2 placebo).

¶ Presence of testicular adrenal rest tumors based on 80 male participants (53 crinecerfont, 27 placebo) who had available testicular ultrasound assessments at baseline.

Table 2.

Efficacy Endpoints [*]

	Crinecerfont		Placebo		Difference		
Primary end point [†]	**N**	**LSM CFB**	**N**	**LSM CFB**	**LSMD (95% CI)**	**P-value**	**2-sided Significance Level**
Percent change in glucocorticoid dose while androstenedione was controlled (week 24)	122	−27.3±2.4	60	−10.3±3.2	−17.0 (−23.8, −10.2)	<0.001	0.05
Key secondary end points [†]	N	LSM CFB	N	LSM CFB	LSMD (95% CI)	P-value	2-sided Significance Level
Serum androstenedione (week 4) – ng/dL [‡]	122	−299±37.7	60	45.5±51.0	−345 (−457, −232)	<0.001	0.02
Achieved physiological glucocorticoid dose while androstenedione was controlled (week 24) – no. (%) [§]	122	74 (62.7)	60	10 (17.5)	Not applicable	<0.001	0.03
Homeostatic model assessment for insulin resistance (week 24)	122	−0.65±0.21	60	−0.36±0.28	−0.29 (−0.89, 0.32)	¶	
Percent change in body weight (week 24)	122	−1.45±0.53	60	−0.07±0.72	−1.38 (−2.96, 0.20)	¶	
Percent total fat mass (week 24) //	122	−0.11±0.66	60	−1.04±0.98	0.93 (−1.04, 2.90)	¶	

[*] Unless noted otherwise, all end points are presented as least-squares mean (LSM) change from baseline (CFB) at week 24 with standard error of the mean (SEM), along with the least-squares mean difference (LSMD) between treatment arms and 95% confidence interval (CI) for the LSMD.

[†] For the primary and key secondary end points, participants with missing data were multiply imputed for statistical testing. Therefore, analyses are based on the full analysis set, which includes all randomized participants. The number of participants with complete data for each end point are as follows: primary (118 crinecerfont, 57 placebo); key secondary, androstenedione (117 crinecerfont, 56 placebo), key secondary, achievement of physiological glucocorticoid dose while androstenedione was controlled (118 crinecerfont, 57 placebo); key secondary, homeostatic model for insulin resistance (112 crinecerfont, 54 placebo); key secondary, weight (118 crinecerfont, 57 placebo); key secondary, total fat mass (93 crinecerfont, 43 placebo).

[‡] Based on pre-morning glucocorticoid dose samples. Normal ranges and conversion factors for conventional units to standard international units are in Appendix Table S2.

[§] Percentages are based on observed data (118 crinecerfont, 57 placebo). However, participants with missing data were multiply imputed for statistical testing (procedure for key secondary end point).

¶ These three key secondary end points were tested using a Holm procedure, and none achieved statistical significance.

// Least-squares mean change from baseline (±standard error of the mean) in total fat mass were follows: crinecerfont, 0.1±1.0 kg; placebo, −1.4±1.4 kg. The least-squares mean difference (95% confidence interval) was +1.5 kg (−1.5, 4.5).

Abbreviations: CFB, change from baseline; CI, confidence interval; LSM, least-squares mean; LSMD, least-squares mean difference.

Table 3.

Treatment-Emergent Adverse Events (TEAEs)

	Crinecerfont (N=122)	Placebo (N=59)
TEAE summary – no. (%)		
Any TEAE	101 (82.8)	48 (81.4)
Any serious TEAE	4 (3.3)*	0
Any TEAE leading to study drug discontinuation	4 (3.3)†	0
Any TEAE leading to study discontinuation	4 (3.3)†	0
Any TEAE resulting in death	0	0
TEAE severity – no. (%)‡		
Mild	62 (50.8)	30 (50.8)
Moderate	36 (29.5)	18 (30.5)
Severe	3 (2.5)	0
Common TEAEs – no. (%)§		
Fatigue	30 (24.6)	9 (15.3)
Headache	19 (15.6)	9 (15.3)
Coronavirus infection	17 (13.9)	5 (8.5)
Upper respiratory tract infection	11 (9.0)	7 (11.9)
Diarrhea	10 (8.2)	5 (8.5)
Dizziness	10 (8.2)	2 (3.4)
Nausea	10 (8.2)	5 (8.5)
Arthralgia	9 (7.4)	0
Back pain	7 (5.7)	2 (3.4)
Pyrexia	7 (5.7)	6 (10.2)
Blood creatine phosphokinase increased	6 (4.9)	2 (3.4)
Nasopharyngitis	6 (4.9)	8 (13.6)
Vomiting	6 (4.9)	5 (8.5)
Decreased appetite	5 (4.1)	1 (1.7)
Gastroenteritis	5 (4.1)	1 (1.7)
Influenza	5 (4.1)	2 (3.4)

*Due to acute cholecystitis (n=1), groin abscess and cellulitis (n=1), acute adrenocortical insufficiency (n=1), and presyncope (n=1). All serious TEAEs were assessed by the investigator as unlikely related to study treatment.

†Due to dyspepsia, nausea and vomiting (n=1), gastric ulcer (n=1), apathy and restlessness (n=1), and rash (n=1). All adverse events that started in the double-blind period and resulted in study treatment discontinuation (regardless of when the subject discontinued study treatment) are presented. Only 1 adverse event that started in the double-blind period resulted in study treatment discontinuation during the double-blind period (gastric ulcer).

‡Maximum severity, as judged by the study investigator.

§Reported in ≥5 participants (>4%) receiving crinecerfont.

Abbreviations: TEAE, treatment-emergent adverse events.