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Phase 3 Study of Crinecerfont in Pediatrics with Congenital Adrenal Hyperplasia (CAHtalyst™ Pediatric)

Thank you for contacting Neurocrine Biosciences with your unsolicited medical information request regarding the Phase 3 CAHtalyst Pediatric study (CAH2006; ClinicalTrials.gov Identifier: NCT04806451), that investigated crinecerfont in pediatric participants with classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency.

Crinecerfont is an investigational, oral, selective corticotropin-releasing factor type 1 receptor antagonist being developed to reduce and control excess adrenocorticotropic hormone (ACTH) and adrenal androgens through a glucocorticoid (GC)-independent mechanism for the treatment of CAH and is currently not approved by the US Food and Drug Administration or another regulatory body for the treatment of any indication.[1-4]

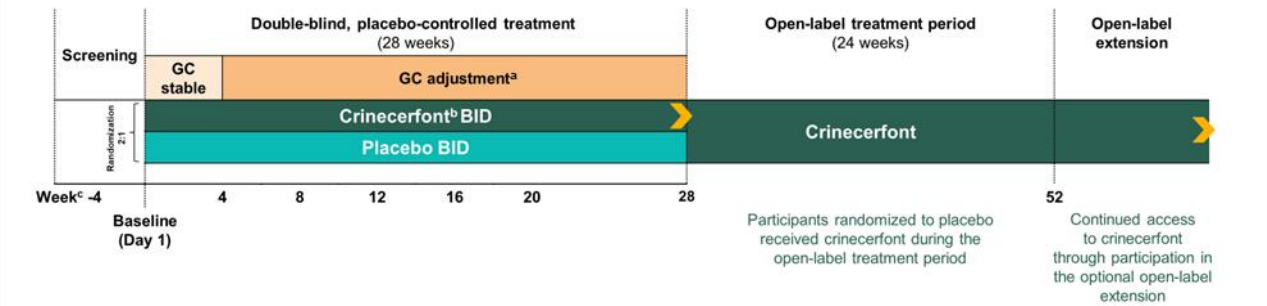
CAHtalyst™ Pediatric: Phase 3 Study in Pediatric Participants With CAH

Study Design and Methods

The CAHtalyst Pediatric study was a Phase 3, multinational, registrational trial that evaluated the safety, efficacy, and tolerability of crinecerfont in children and adolescents (ages: 4-17 years of age) with CAH. The study enrolled 103 female and male participants with CAH and consisted of a 28-week randomized, double-blind, placebo-controlled period followed by 24 weeks of open-label treatment with crinecerfont. At the end of the study, participants have the opportunity to continue to receive crinecerfont in an open-label extension.[3]

Participants were randomly assigned in a 2:1 ratio to receive oral crinecerfont (25 mg [for body weight 10 kg to <20 kg], 50 mg [20 kg to <55 kg], or 100 mg [≥55 kg]) or matching placebo twice daily with morning and evening meals (**Figure 1**). GC regimens were stably maintained from baseline through Week 4 (GC-stable period). From Week 4 through Week 28, GC doses were adjusted in 1 to 4 steps to a target dose of 8 to 10 mg/m^2/day in hydrocortisone dose equivalents (HCe; GC-adjustment period) provided that androstenedione (A4) was controlled per study definition (defined as ≤120% of the baseline value or ≤ upper limit of normal [ULN] according to sex and either age for prepubertal [Tanner stage 1] or pubertal [Tanner stages 2-5] status). The target reduction at each step was approximately 1 to 4 mg/m^2/day in HCe, which was guided by A4 change from the previous measurement and the availability of GC-dosage strengths.[3]

Figure 1. CAH2006: Study Design[3]



BID, twice daily; GC, glucocorticoid.
[a]GC dosing was adjusted in ≤4 steps, with a safety follow-up telephone call after each reduction in GC dose.
[b]25, 50, or 100 mg based on weight.
[c]Blood samples were collected before the morning GC dose (pre-GC) at Week -4, baseline, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 28.

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Key inclusion criteria were as follows: male or female participants 2 to 17 years of age with CAH, treatment with a GC dose >12 mg/m^2/day in HCe (4× equivalency factor for prednisolone or prednisone) for ≥1 month, A4 greater than the midpoint of the reference range, and 17-hydroxyprogesterone (17-OHP) >2× the ULN based on sex and either prepubertal (Tanner stage 1) or pubertal (Tanner stages 2-5) status. The key exclusion criterion was having any condition other than CAH that requires chronic GC therapy.[3]

Efficacy

The primary efficacy endpoint was the change from baseline in serum A4 at Week 4. Key secondary endpoints included the change from baseline in serum 17-OHP at Week 4 and the percent change from baseline in GC daily dose (mg/m^2/day in HCe; adjusted for body surface area [BSA]) at Week 28 while A4 was controlled per study definition. A select secondary endpoint included achievement of a reduction in GC daily dose to physiologic levels (≤11 mg/m^2/day HCe; adjusted for BSA) at Week 28 while serum A4 was controlled per study definition (**Table 1**).

Table 1. Summary of Efficacy Endpoints from Double-Blind, Placebo-Controlled Period [3,a]

Endpoints	Crinecerfont (n=69)	Placebo (n=34)	LSMD (95% CI)	*P* value
Primary endpoint				
LS mean change in serum A4 from baseline to Week 4,[b] ng/dL ±SEM	-197±39	71±56	-268 (-403 to -132)	<0.001
Select key secondary endpoints				
LS mean change in serum 17-OHP from baseline to Week 4,[b] ng/dL ±SEM	-5865±572	556±818	-6421 (-8387 to -4454)	<0.001
LS mean change in GC dose with A4 control per study definition from baseline to Week 28, % ±SEM	-18.0±1.8	5.6±2.7	-23.5 (-29.9 to -17.2)[c]	<0.001
Select secondary endpoint[5,d]				
Achieved physiologic GC dose with A4 control per study definition at Week 28, n (%)	20 (29.9)	0	NA	NA

17-OHP, 17-hydroxyprogesterone; A4, androstenedione; CI, confidence interval; GC, glucocorticoid; LS, least-squares; LSMD, least-squares mean difference, NA, not applicable; SEM, standard error of the mean.
[a]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 endpoint are as follows: primary endpoint, 68 in the crinecerfont group and 33 in the placebo group; change in 17-OHP, 68 in the crinecerfont group and 33 in the placebo group; change in GC dose with A4 control per study definition, 67 in the crinecerfont group and 31 in the placebo group; achieved physiologic GC dose with A4 control per study definition, 67 in the crinecerfont group and 31 in the placebo group.
[b]Normal ranges are listed in Table S2 of the CAHtalyst Pediatric Supplementary Appendix.[5]
[c]The LSMD in the percent change in GC dose between groups is expressed in percentage points.
[d]P-value for the secondary endpoint was considered nominal and is therefore not shown.

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Safety

Safety assessments included adverse events that emerged during the treatment period, vital signs, clinical laboratory tests, electrocardiography, and neuropsychiatric assessments.[3] During the treatment period, adverse events that were mainly mild to moderate in severity emerged among a similar percentage of participants from both treatment groups (with crinecerfont, 84%; with placebo, 82%; **Table 2**).

Two participants had adverse events that led to discontinuation of crinecerfont and withdrawal from the study: 1 participant had body aches, upper abdominal pain, and nausea (considered by the local study investigator to be unrelated to crinecerfont) and the other participant had nausea, dizziness, retching, and motion sickness (considered to be possibly related to crinecerfont). Five participants (1% in the crinecerfont group; 12% in the placebo group) had serious adverse events that emerged during the treatment period, but none were considered to be related to or led to the discontinuation of crinecerfont. No adrenal crises were reported, and no deaths occurred. Adverse events that lead to GC stress dosing occurred in approximately half of the participants in each treatment group. There were no safety concerns with respect to vital signs, clinical laboratory values, electrocardiography, or neuropsychiatric assessments.[3]

Table 2. Safety Summary from Double-Blind, Placebo-Controlled Period [3]

Adverse event, n (%)	Crinecerfont (N=69)	Placebo (N=33)
Any adverse event	58 (84)	27 (82)
Any serious adverse event[a]	1 (1)	4 (12)
Any adverse event leading to discontinuation of study regimen[b]	2 (3)	0
Any adverse event leading to withdrawal from the study[b]	2 (3)	0
Any adverse event resulting in death	0	0
Severity of adverse event[c]		
Mild	37 (54)	13 (39)
Moderate	20 (29)	12 (36)
Severe	1 (1)	2 (6)
Common adverse events[d]		
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)

[a]Serious adverse events included pyrexia (1 participant in the crinecerfont group) and vomiting and pharyngitis, gastroenteritis and norovirus, gastroenteritis, 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 study regimen.
[b]In the crinecerfont group, 2 participants discontinued treatment and withdrew from the study: 1 participant had body aches, upper abdominal pain, and nausea (considered to be unrelated to the treatment) and the other participant had nausea, dizziness, retching, and motion sickness (considered to be possibly related to the treatment).
[c]The maximum level of severity is shown, as judged by the investigator.
[d]Common adverse events were specified as those reported in ≥4 participants (>5%) who received crinecerfont.

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References:

1. Auchus RJ, et al. Crinecerfont lowers elevated hormone markers in adults with 21-hydroxylase deficiency congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2022;107(3):801-812.
2. Newfield RS, et al. Crinecerfont, a CRF1 receptor antagonist, lowers adrenal androgens in adolescents with congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2023;108(11):2871-2878.
3. Sarafoglou K, Kim MS, Lodish M, et al. Phase 3 Trial of Crinecerfont in Pediatric Congenital Adrenal Hyperplasia. *N Engl J Med.* 2024;391(6):493-503.
4. Auchus RJ, Hamidi O, Pivonello R, et al. Phase 3 Trial of Crinecerfont in Adult Congenital Adrenal Hyperplasia. *N Engl J Med.* 2024;391(6):504-514.
5. Sarafoglou K, et al. Phase 3 trial of crinecerfont in pediatric congenital adrenal hyperplasia. Supplementary Appendix. Secondary and Exploratory End Point Results. *N Engl J Med*. 2024;391(6):493-503.