(P) 877-641-3461
(F) 913-451-6409
6027 Edgewood Bend Ct San Diego, CA 92130
http://www.neurocrinemedical.com/

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

Thank you for contacting Neurocrine Biosciences with your unsolicited medical information request regarding the Phase 3 CAHtalyst study (CAH3003; ClinicalTrials.gov Identifier: NCT04490915), that investigated crinecerfont in adult 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]

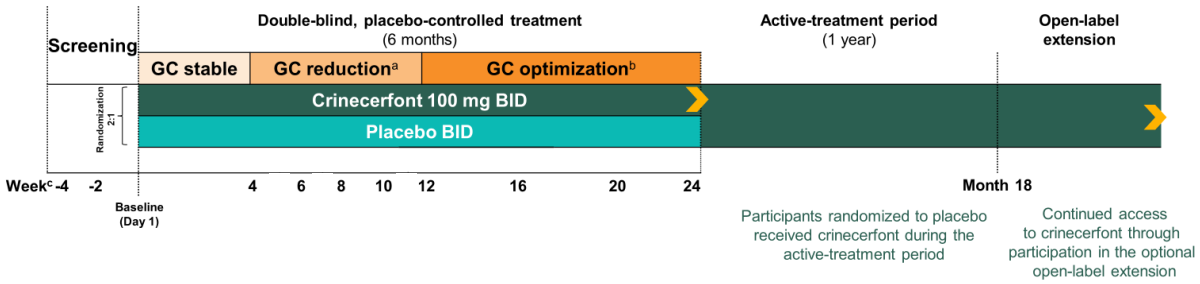
CAHtalyst™: Phase 3 Study in Adult Participants With CAH

Study Design and Methods

The CAHtalyst study was a Phase 3, multinational, registrational trial that evaluated the safety, efficacy, and tolerability of crinecerfont in adults (ages: ≥18 years of age) with CAH. The study enrolled 182 female and male participants with CAH and consisted of a 24-week randomized, double-blind, placebo-controlled period followed by a 1-year active-treatment period 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 (100 mg) 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 12 (GC-reduction period), GC doses were decreased (in ≤4 steps according to a schedule that was based on the starting dose and dosage-strength availability) to a target dose of 8 to 10 mg/m^2/day in hydrocortisone dose equivalents (HCe). From Weeks 12 to 24 (GC-optimization period), GC doses were adjusted with the goal of achieving the lowest dose by Week 24 while maintaining androstenedione (A4) control per study definition (defined as a level that was ≤120% of the baseline value or ≤ upper limit of normal [ULN] range for age and sex).[3]

Figure 1. CAH3003: Study Design[3]



BID, twice daily; GC, glucocorticoid, HCe, hydrocortisone dose equivalents.
[a]GC dosing was reduced in ≤4 steps to reach a target dose of 8 to 10 mg/m^2/day HCe by Week 12. A safety follow-up was conducted by telephone within 1 week after each GC dose reduction.
[b]GC doses were adjusted as necessary to reach the lowest dose needed to achieve androgen control per study definition.
[c]Blood samples were collected at ~2 to 3 hours after the morning GC dose (post-GC) at Week -4, Week -2, baseline, Week 2, Week 4, Week 6, Week 9, Week 12, Week 16, Week 20, and Week 24; and before the morning GC dose (pre-GC) at baseline, Week 4, and Week 24.

Key inclusion criteria were as follows: male or female participants ≥18 years of age, medically confirmed 21-hydroxylase deficiency (21-OHD), stable GC regimen of >13 mg/m^2/day HCe (conversion factors for HCe were as follows: methylprednisolone, prednisolone, and prednisone: 4×; dexamethasone: 60× for ≥1 month), and a stable fludrocortisone regimen, if necessary, for ≥1 month. Key exclusion criteria included

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known or suspected diagnosis of other forms of CAH; prior or current medical conditions other than 21-OHD that requires systemic GC therapy; evidence of GC overtreatment during screening (pre-GC morning 17-OHP < ULN, post-GC morning 17-OHP < lower limit of normal [LLN] or morning A4 < LLN based on normal ranges for sex and age)[5]; increased risk of adrenal crisis; and clinically significant unstable medical condition, chronic disease, or malignancy.[3]

Efficacy

The primary efficacy endpoint was the percent change from baseline in GC daily dose (mg/m^2/day in HCe, adjusted for body surface area) at Week 24 while A4 was controlled per study definition (at ≤120% of baseline or ≤ULN for age and sex). Select key secondary endpoints included change from baseline in serum A4 at Week 4 and achievement of a reduction in GC daily dose to physiologic levels (≤11 mg/m^2/day) at Week 24 while A4 was controlled per study definition. A select secondary endpoint included change from baseline in 17-OHP at Week 4 (**Table 1**).

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

Endpoints	Crinecerfont (N = 122)	Placebo (N = 60)	LSMD (95% CI)	*P* value
Primary endpoint				
LS mean change from baseline in GC dose with A4 control per study definition at Week 24, % ±SEM	-27.3±2.4	-10.3±3.2	-17.0 (-23.8 to -10.2)	<0.001
Select key secondary endpoints				
LS mean change from baseline in serum A4 at Week 4,[b] ng/dL ±SEM	-299±37.7	45.5±51.0	-345 (-457 to -232)	<0.001
Participants with physiologic GC dose with A4 control per study definition at Week 24,[c] n (%)	74 (63)	10 (18)	NA	<0.001
Select secondary endpoint[6,d]				
LS mean change from baseline in 17-OHP at Week 4,[b] ng/dL ±SEM	-5594 ± 533	-156 ± 725	-5838 (-7441 to –4235)	NA

17-OHP, 17-hydroxyprogesterone; A4, androstenedione; CI, confidence internal; GC, glucocorticoid; LS, least-squares; LSMD, least-squares mean difference; NA, not applicable; SEM, standard error of the mean.
[a]Endpoint values for participants with missing data used multiple imputation for statistical testing. Therefore, analyses are based on the full analysis population, which included all participants who underwent randomization. The number of participants with complete data for each endpoint was 118 in the crinecerfont group and 57 in the placebo group for the primary endpoint; 117 and 56 participants, respectively, for both A4 and 17-OHP; and 118 and 57 participants, respectively, for having a physiologic GC dose with control of A4 per study definition.
[b]Based on pre-GC morning dose samples. Normal ranges are provided in Table S2 of the CAHtalyst Supplementary Appendix.[6]
[c]This key secondary endpoint was tested with the use of a Holm procedure, which resulted in between-group differences that were not significant.
[d]*P*-value for the secondary end point was considered nominal and is therefore not shown. 95% CIs for this end point were not adjusted for multiplicity, and the intervals may not be used in place of hypothesis testing.

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(P) 877-641-3461
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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] Crinecerfont appeared to have an acceptable side-effect profile, with a similar frequency of adverse events in the crinecerfont and placebo groups (**Table 2**).

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 4 participants to discontinue crinecerfont treatment; 1 participant discontinued during the 24-week randomized period. Four participants in the crinecerfont group had a serious adverse event that was assessed by the investigator as unlikely to be related to crinecerfont and none of which led to study discontinuation. No deaths occurred during the study period.

Adrenal insufficiency or acute adrenocortical insufficiency was reported in 2 participants in the crinecerfont group and in 1 participant in the placebo group. Adverse events that led to GC stress dosing occurred in 42% of participants in the crinecerfont group and in 44% of participants in the placebo group, with most cases only involving oral stress dosing. No safety concerns regarding crinecerfont were reported with respect to vital signs, clinical laboratory tests, electrocardiographic findings, or neuropsychiatric assessments.[3]

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

Adverse event, n (%)	Crinecerfont (N=122)	Placebo (N=59)
Any adverse event	101 (83)	48 (81)
Leading to discontinuation of crinecerfont or placebo	4 (3)[a]	0
Leading to study discontinuation	4 (3)[a]	0
Any serious adverse event	4 (3)[b]	0
Severity of adverse event[c]		
Mild	62 (51)	30 (51)
Moderate	36 (30)	18 (31)
Severe	3 (2)	0
Common adverse events[d]		
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)

[a]The 4 adverse events that led to drug and study discontinuation were dyspepsia, nausea, and vomiting (in 1 participant); gastric ulcer (in 1 participant); apathy and restlessness (in 1 participant); and rash (in 1 participant). 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 1 adverse event (gastric ulcer) that was first identified during the randomization period resulted in discontinuation during that period.
[b]The 4 serious adverse events (1 in each participant) 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 participants died during the study.
[c]The maximum level of severity is shown, as judged by the investigator.
[d]Listed in this category are adverse events that were reported in ≥5 participants in the crinecerfont group.

This letter is provided in response to your unsolicited medical information request. Please feel free to contact Neurocrine Medical Information at 877-641-3461 or medinfo@neurocrine.com if you would like to request additional information.

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.
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3. 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.
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6. Auchus RJ, et al. Phase 3 trial of crinecerfont in adult congenital adrenal hyperplasia. Supplementary Appendix. Secondary and Exploratory End Point Results. *N Engl J Med*. 2024;391(6):493-503.