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Phase 2, Open-label Study of Crinecerfont in Adolescent Participants with Classic Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency

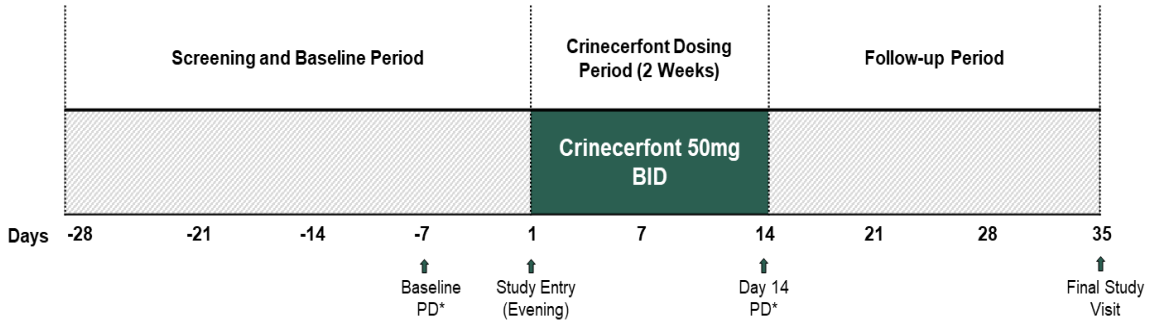
Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the Phase 2 CAH2008 study (NCT04045145) of crinecerfont in adolescents with classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD).

Crinecerfont, an oral, nonsteroidal, selective corticotropin-releasing factor type 1 receptor (CRF_1) antagonist, is an investigational compound in clinical development for the treatment of classic CAH due to 21-OHD and is currently not approved by the US Food and Drug Administration (FDA) or another regulatory body for the treatment of any indication.[1,2]

CAH2008: Phase 2 Study in Adolescent Participants (eligible ages: 14 to 17 years) with Classic CAH

The crinecerfont Phase 2 clinical study (NCT04045145) was a 14-day, open-label study of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of crinecerfont in eight adolescents 14 to 16 years of age (three males, five females) with classic CAH due to 21-OHD. Participants received crinecerfont 50 mg, orally, twice daily (BID) in the morning and evening with meals for 14 days (**Figure 1**).[2,3]

Figure 1. CAH 2008: Study Design[2,3]:

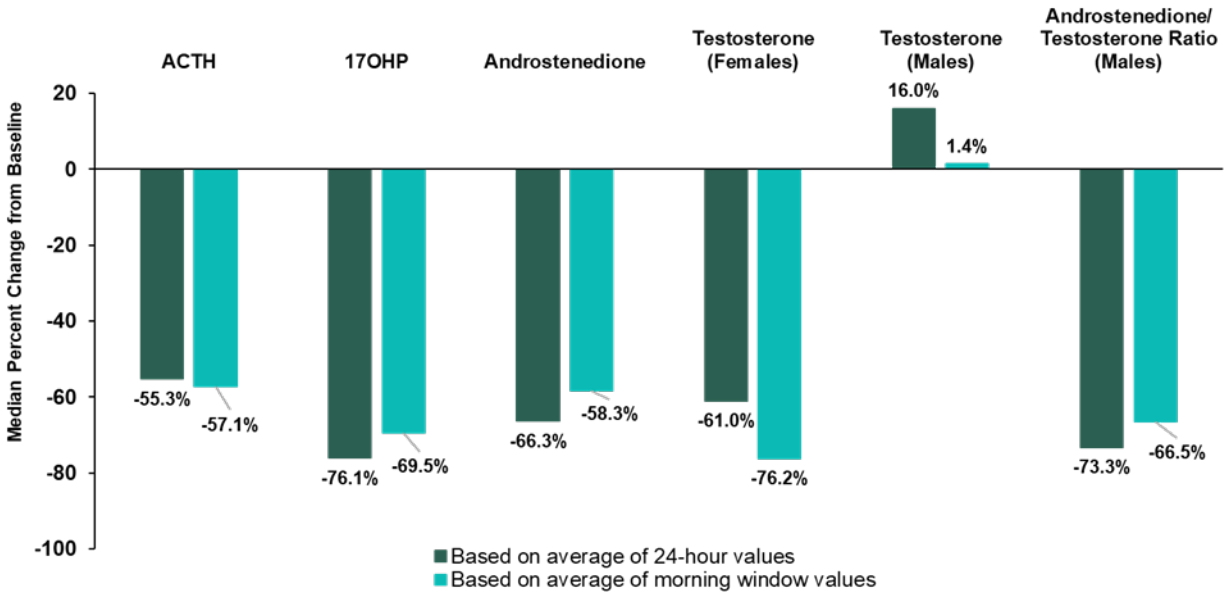


BID, twice daily; PD, pharmacodynamic.

Baseline to Day 14 measurements of 24-hour and morning window (i.e., the average of the two samples collected at 7:00 a.m. and 10:00 a.m.) adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17-OHP), androstenedione (males and females), testosterone (females), and androstenedione/testosterone ratio (males) were assessed. Treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) and TEAEs leading to discontinuation, were also assessed throughout the study. Key inclusion criteria included a medically confirmed diagnosis of classic CAH due to 21-OHD; serum 17OHP ≥800 ng/dL, serum cortisol <5 µg/dL, and ACTH ≥20 pg/mL prior to the morning glucocorticoid (GC) dose; and receiving a stable GC regimen prior to study start. Key exclusion criteria included a known or suspected diagnosis of any of the other known forms of classic CAH or a history of bilateral adrenalectomy, hypopituitarism, or other condition requiring daily therapy with orally administered GCs.[2,3]

Median percent reductions from baseline to Day 14 for 24-hour measurements of ACTH, 17OHP, and androstenedione (males and females), and androstenedione/testosterone ratio (males) ranged from -55.3% to -76.1%, while morning window measurements ranged from -57.1% to -76.2% (**Figure 2**). Additionally, a greater than 50% reduction from baseline for ACTH, 17-OHP, and androstenedione (males and females), testosterone (females), and androstenedione/testosterone ratio (males) was achieved by 63%, 75%, 50%, 60% and 67% of participants, respectively.[2]

Figure 2. ≥50% Median Reductions in ACTH, 17-OHP, and Androstenedione (Males and Females), Testosterone (Females), and Androstenedione/Testosterone Ratio (Males) After 14 Days of Crinecerfont Treatment[2]:



17OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotropic hormone.

Crinecerfont was generally well tolerated, with no serious adverse events or discontinuations due to adverse events. All treatment-emergent adverse events were assessed as mild, with two adverse events (headache and dizziness) assessed as possibly related by the study investigator (**Table 1**). There were no safety concerns with respect to routine laboratory tests, vital signs, electrocardiograms, or neuropsychiatric assessments.[2]

Table 1. Treatment-emergent adverse events (TEAEs).[2]

TEAE Summary, n	All Participants (N=8)
Any TEAE	6
Any serious TEAE	0
Any TEAE leading to discontinuation	0
Any TEAE resulting in death	0
List of All Reported TEAEs, n	**All Participants (N=8)**
Headache[a]	2
Arthropod sting	1
Blepharospasm	1
Dermatitis contact	1

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Dizziness[a]	1
Frequent bowel movements	1
Gastritis	1
Myalgia	1
Nasopharyngitis	1
Pyrexia	1
Vomiting	1

[a]Mild headache and dizziness (each in 1 participant) were judged by the investigator as "possibly" related to study drug; TEAE, treatment-emergent adverse event.

This letter is provided in response to your unsolicited medical information inquiry. 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. doi:10.1210/clinem/dgab749.
2. Newfield RS, et al. Crinecerfont, a novel CRF_1 receptor antagonist, lowers adrenal androgens and precursors in adolescents with classic congenital adrenal hyperplasia. Oral presentation at the ENDO Annual Conference; June 11-14, 2022; Atlanta, GA.
3. ClinicalTrials.gov. Safety, tolerability, pharmacokinetics, and pharmacodynamics of NBI-74788 in pediatric subjects with congenital adrenal hyperplasia. Available from: https://clinicaltrials.gov/ct2/show/NCT04045145?term=neurocrine+2008&draw=2&rank=1. Accessed June 10, 2022.

Enclosures:

1. Newfield RS, et al. Crinecerfont, a novel CRF1 receptor antagonist, lowers adrenal androgens and precursors in adolescents with classic congenital adrenal hyperplasia. Oral presentation at the ENDO Annual Conference; June 11-14, 2022; Atlanta, GA.