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CAHtalyst™ Study:
Global Safety and Efficacy Study of Crinecerfont for the Treatment of Classic Congenital Adrenal Hyperplasia (CAH) due to 21-Hydroxylase Deficiency (21-OHD) in Adults

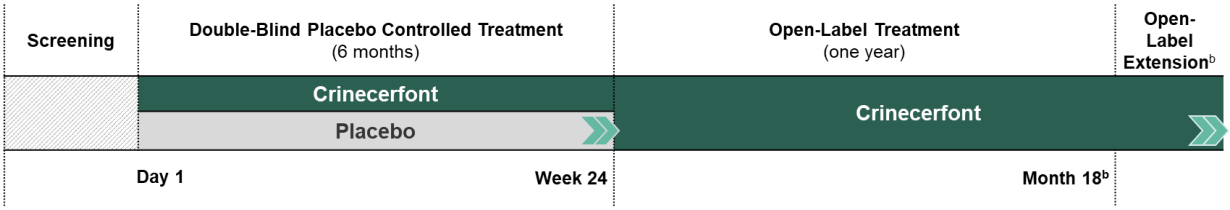
Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the CAHtalyst Study (NCT04490915), investigating the use of crinecerfont for the treatment of classic CAH due to 21-OHD in adults.

Crinecerfont is an investigational, oral, selective corticotropin-releasing factor type 1 receptor (CRF_1) antagonist being developed to help reduce and control excess adrenal androgens through a steroid-independent mechanism for the treatment of CAH. Crinecerfont is currently not approved by the US Food and Drug Administration (FDA) or another regulatory body for the treatment of any indication.[1-4]

CAH3003 (CAHtalyst™ Study): Phase 3 Study in Adults (eligible ages: ≥18 years) with Classic CAH

The crinecerfont Phase 3 CAHtalyst study was designed to evaluate the efficacy, safety, and tolerability of crinecerfont vs. placebo in 182 adult male and female participants (eligible ages: ≥18 years of age) with classic CAH due to 21-OHD. There was a 6 month randomized, double blind, placebo-controlled period, followed by a 1 year open-label treatment period with crinecerfont capsules, administered orally, twice daily (**Figure 1**). The primary outcome measure was the mean percent change from baseline in glucocorticoid daily dose (in hydrocortisone equivalents adjusted for body surface area) while maintaining androgen control at Week 24. Secondary outcome measures included, but were not limited to, a change from baseline in serum androstenedione (A4) at Week 4, the percentage of participants achieving a reduction to a physiological glucocorticoid dose while maintaining androgen control, change from baseline in body weight, fat mass, blood pressure, glucose tolerance, and waist circumference at Week 24. Key inclusion criteria included a medically confirmed diagnosis of classic CAH due to 21-OHD and stable glucocorticoid doses 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 chronic glucocorticoid therapy. At the end of the study, participants have the opportunity to continue to receive crinecerfont as part of an open-label extension.[5]

Figure 1. CAH3003: Study Design[5a]:



[a]Enrollment completed; [b]Duration of participation in the study is ~20 months for the core study and will be a variable amount of time per participant for the open-label extension.

The Phase 3 CAHtalyst study met its primary endpoint at Week 24, demonstrating that treatment with crinecerfont resulted in a statistically significant percent reduction from baseline in glucocorticoid daily dose vs. placebo while maintaining androgen control ($p<0.0001$).The study also met key secondary endpoints, with a statistically significant decrease from baseline in serum A4 at Week 4 vs. placebo ($p<0.0001$), and approximately 63% of participants on crinecerfont achieved a reduction to a physiological glucocorticoid daily dose while maintaining androgen control vs. approximately 18% on placebo at Week 24 ($p<0.0001$).[3]

During the phase 3 double-blind, placebo-controlled period of the CAHtalyst study, crinecerfont was generally well tolerated. The most common adverse events were fatigue, headache, and coronavirus infection. There were few serious adverse events, with none assessed as related to crinecerfont.[3]

For more information about the CAHtalyst study, please visit ClinicalTrials.gov.

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, Sarafoglou K, Fechner PY, et al. Crinecerfont, a CRF1 Receptor Antagonist, Lowers Adrenal Androgens in Adolescents with Congenital Adrenal Hyperplasia [published online ahead of print, 2023 May 22]. *J Clin Endocrinol Metab*. 2023; dgad270. doi:10.1210/clinem/dgad270.
3. Neurocrine.com. (2023). Neurocrine Biosciences Announces Positive Top-Line Data from Phase 3 Study of Crinecerfont in Adults for the Treatment of Congenital Adrenal Hyperplasia (CAH) [Press release]. Retrieved from: https://neurocrine.gcs-web.com/news-releases/news-release-details/neurocrine-biosciences-announces-positive-top-line-data-phase-3. Accessed September 12, 2023.
4. Neurocrine.com. (2023). Neurocrine Biosciences Announces Phase 3 Pediatric Study Results of Crinecerfont in Children and Adolescents for the Treatment of Congenital Adrenal Hyperplasia Met Primary and Key Secondary Endpoints [Press release]. Retrieved from: https://neurocrine.gcs-web.com/news-releases/news-release-details/neurocrine-biosciences-announces-phase-3-pediatric-study-results. Accessed October 5, 2023.
5. Global safety and efficacy registration study of crinecerfont for congenital adrenal hyperplasia (CAHtalyst). ClinicalTrials.gov identifier: NCT04490915. Updated August 21, 2023. Accessed September 12, 2023. https://clinicaltrials.gov/ct2/show/NCT04490915.