

Neurocrine Biosciences Announces Publication of Primary CAHtalyst™ Pediatric Phase 3 Study Results of Crinecerfont for the Treatment of CAH in The New England Journal of Medicine

June 3, 2024

- CAHtalyst™ Pediatric Study Met Primary and Key Secondary Endpoints, with Crinecerfont Treatment Decreasing Androstenedione Levels and Enabling Glucocorticoid Dose Reduction While Maintaining Androstenedione Control
 - 30% of Crinecerfont Participants Achieved a Physiologic Glucocorticoid Dose at Week 28 while Maintaining Androgen Control versus 0% of Placebo Participants
 - Favorable Trends in Endpoints Reflecting Supraphysiologic Glucocorticoid Dosing and Androgen Excess
 - Crinecerfont was Generally Well Tolerated

SAN DIEGO, June 3, 2024 /PRNewswire/ -- [Neurocrine Biosciences, Inc.](#) (Nasdaq: NBIX) today announced that the primary study results from its CAHtalyst™ Pediatric Phase 3 study investigating crinecerfont for the treatment of congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency have been published in *The New England Journal of Medicine* [online edition](#) and will appear in a future print issue of the journal. The CAHtalyst Pediatric Phase 3 study met the primary and key secondary endpoints related to androgen reduction (during an initial glucocorticoid-stable period) and glucocorticoid (GC) dose reduction while maintaining androgen control. Favorable trends were observed with endpoints that reflect the consequences of long-term supraphysiologic glucocorticoid therapy and androgen excess. In addition to appearing in *The New England Journal of Medicine*, CAHtalyst Pediatric Phase 3 data were presented at [ENDO 2024](#) (Poster #SUN-441).

"In treating children with CAH, from the moment they are diagnosed we are challenged with finding a balance between supraphysiologic glucocorticoid dosing and the need to prevent androgen excess. Tipping the scale too far one way or the other can adversely impact growth and pubertal development," said Kyriakie Sarafoglou, M.D., Professor, Department of Pediatrics and Department of Experimental and Clinical Pharmacology, Divisions of Endocrinology and Genetics & Metabolism, at the University of Minnesota. "Based on the CAHtalyst Pediatric study results, crinecerfont represents a potential non-glucocorticoid therapeutic approach to meet this challenge. In addition to meeting primary and key secondary endpoints related to reducing elevated androstenedione and supraphysiologic glucocorticoid dosing during the 28-week study, treatment with crinecerfont also showed favorable trends in ameliorating the consequences of the current treatment paradigm, with reductions in body weight, improved insulin resistance, and reduced hirsutism in females."

Crinecerfont is an investigational, oral, selective corticotropin-releasing factor type 1 receptor (CRF₁) antagonist being developed to reduce and control excess adrenocorticotrophic hormone (ACTH) and adrenal androgens through a GC-independent mechanism for the treatment of CAH.

"The outstanding results achieved in the CAHtalyst Pediatric Phase 3 study demonstrate the ability of crinecerfont to reduce elevated androstenedione levels while also enabling reduction in supraphysiologic glucocorticoid doses to more physiologic level dosing while maintaining androgen control in pediatric participants with CAH," said Eiry W. Roberts, M.D., Chief Medical Officer at Neurocrine Biosciences. "This could potentially enable physicians to fundamentally change their approach to the important task of controlling androgens in pediatric patients with crinecerfont, without the need for long-term supraphysiologic steroid dosing, thus removing the burden that long-term excess glucocorticoid use places on development and outcome for these patients."

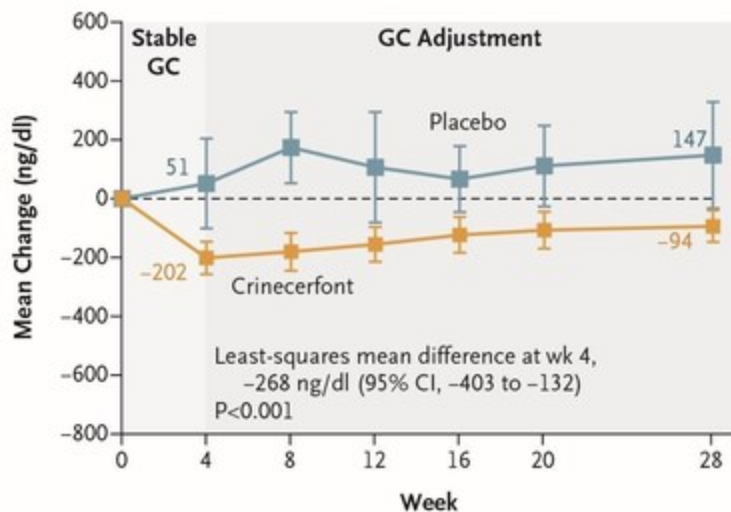
The CAHtalyst Pediatric Phase 3 global registrational study was conducted in 103 participants and designed to evaluate the safety, efficacy, and tolerability of crinecerfont in children and adolescents ages 2 to 17 years with CAH due to 21-hydroxylase deficiency. Over 95% of participants completed the 28-week double-blind, placebo-controlled treatment period of the study with minimal missing data.

The Phase 3 Pediatric study met the primary endpoint of change from baseline in androstenedione (key adrenal androgen) following the initial 4-week GC-stable period.

- Crinecerfont treatment led to a significantly greater reduction in androstenedione compared to an increase with placebo at Week 4 (least squares mean [LSM] change from baseline of -196.8 ng/dL versus +71.0 ng/dL, with least squares mean difference [LSMD] of -268 ng/dL, P < 0.001). Actual value is P < 0.0001. (Figure A)

After Week 4 and through Week 28, mean androstenedione remained below baseline in the context of reduced GC dose with crinecerfont but increased above baseline in the placebo group despite increased GC dose, highlighting the challenge of maintaining androgen control even with supraphysiologic GC doses in pediatric patients enrolled in this trial.

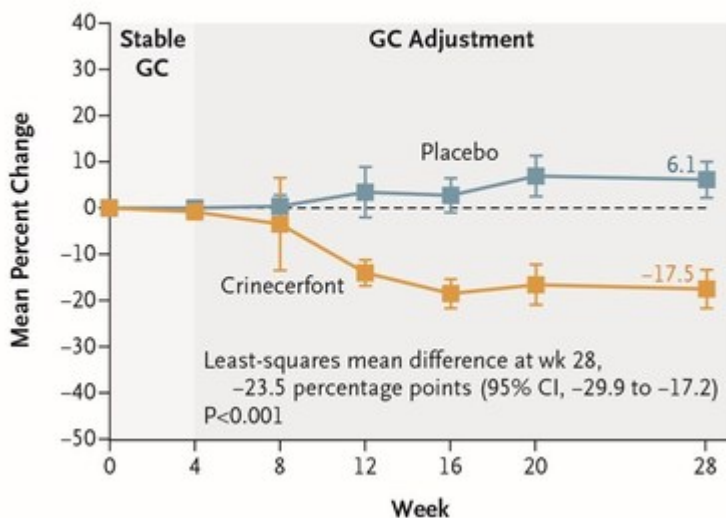
A Change from Baseline in Androstenedione



The Phase 3 Pediatric study also met the key secondary endpoint of percent change from baseline in GC dose (while maintaining androstenedione control) and the secondary endpoint of achievement of reduction to a physiologic GC dose (while maintaining androstenedione control) at Week 28:

- Crinecerfont treatment led to a significantly greater GC dose reduction at Week 28 while maintaining androstenedione control compared to placebo (LSM change from baseline of -18% versus +5.6%, with LSMD of -23.5%; $P < 0.001$). Actual value is $P < 0.0001$. (Figure C)

C Change from Baseline in Glucocorticoid while Androstenedione Was Controlled



- Importantly, 30% of crinecerfont-treated participants achieved a physiologic GC dose (≤ 11 mg/m²/day hydrocortisone equivalents) at Week 28 while maintaining androstenedione control, compared to zero participants in the placebo group (nominal P -value = 0.0009). (Figure D)

Despite the short-term duration of this Phase 3 study, favorable trends were observed for endpoints associated with long-term suprathreshold GC therapy such as body mass index standard deviation score and insulin resistance that were encouraging considering the relatively short time frame of reduced GC dose. In addition, there was reduction in hirsutism (excessive hair growth) in female participants and improvement in the androstenedione to testosterone ratio in male participants.

Crinecerfont was generally well tolerated, with the most common adverse events being headache, fever and vomiting. There were no adrenal crises in either group. Few serious adverse events occurred, with none assessed as related to crinecerfont, and there were few discontinuations due to adverse events. No events of adrenal crisis were reported during the double-blind period, and the incidence of adverse events leading to glucocorticoid stress dosing was similar in the crinecerfont and placebo groups.

Note: P -values in the text and figures reflect the Journal's convention of calculating to two significant figures. Actual P -values to

three significant figures are also provided. Figures reflect observed means rather than the LSM and LSMD described in the text.

Figures are from *The New England Journal of Medicine*, Phase 3 Trial of Crinecerfont in Pediatric Congenital Adrenal Hyperplasia, Sarafoglou K, Kim M, Lodish M, et.al. This article was published online on June 2, 2024. Copyright © 2024 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

About Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is a rare genetic condition that results in an enzyme deficiency that alters the production of adrenal hormones which are essential for life. Approximately 95% of CAH cases are caused by a mutation that leads to deficiency of the enzyme 21-hydroxylase (21-OHD). Severe deficiency of this enzyme leads to an inability of the adrenal glands to produce cortisol and, in approximately 75% of cases, aldosterone. If left untreated, CAH can result in salt wasting, dehydration, and even death.

Glucocorticoids (GCs) are currently used not only to correct the endogenous cortisol deficiency, but doses used are higher than cortisol replacement needed (supraphysiologic) to lower the levels of adrenocorticotrophic hormone (ACTH) and adrenal androgens. However, glucocorticoid treatment at supraphysiologic doses has been associated with serious and significant complications of steroid excess, including metabolic issues such as weight gain and diabetes, cardiovascular disease, and osteoporosis. Additionally, long-term treatment with supraphysiologic GC doses may have psychological and cognitive impact, such as changes in mood and memory. Adrenal androgen excess has been associated with abnormal bone growth and development in pediatric patients, female health problems such as acne, excess hair growth and menstrual irregularities, testicular rest tumors in males, and fertility issues in both sexes.

To learn more about CAH, click [here](#).

About Crinecerfont and the CAHtalyt™ Studies

Crinecerfont is an investigational, oral, selective corticotropin-releasing factor type 1 receptor (CRF₁) antagonist being developed to reduce and control excess adrenocorticotrophic hormone (ACTH) and adrenal androgens through a glucocorticoid-independent mechanism for the treatment of congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. Antagonism of CRF₁ receptors in the pituitary has been shown to decrease ACTH levels, which in turn decreases the production of adrenal androgens and potentially the symptoms associated with CAH. Our data demonstrate that lowering adrenal androgen levels enables lower, more physiologic dosing of glucocorticoids and thus could potentially reduce the complications associated with exposure to greater than normal glucocorticoid doses in patients with CAH.

The CAHtalyt™ Pediatric and Adult Phase 3 global registrational studies are designed to evaluate the safety, efficacy, and tolerability of crinecerfont in children and adolescents, and adults respectively, with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. The primary portions of the CAHtalyt Phase 3 studies have completed and enrollment is closed, while the open-label extension treatment portions of both studies are ongoing. Data from the CAHtalyt Pediatric and CAHtalyt Adult Phase 3 studies supported two New Drug Application submissions to the U.S. Food and Drug Administration in April 2024.

To learn more about crinecerfont and the CAHtalyt studies, click [here](#).

About Neurocrine Biosciences, Inc.

Neurocrine Biosciences is a leading neuroscience-focused, biopharmaceutical company with a simple purpose: to relieve suffering for people with great needs, but few options. We are dedicated to discovering and developing life-changing treatments for patients with under-addressed neurological, neuroendocrine and neuropsychiatric disorders. The company's diverse portfolio includes FDA-approved treatments for tardive dyskinesia, chorea associated with Huntington's disease, endometriosis* and uterine fibroids*, as well as a robust pipeline including multiple compounds in mid- to late-phase clinical development across our core therapeutic areas. For three decades, we have applied our unique insight into neuroscience and the interconnections between brain and body systems to treat complex conditions. We relentlessly pursue medicines to ease the burden of debilitating diseases and disorders, because you deserve brave science. For more information, visit [neurocrine.com](https://www.neurocrine.com), and follow the company on [LinkedIn](#), [X \(formerly Twitter\)](#), and [Facebook](#).

(*in collaboration with AbbVie)

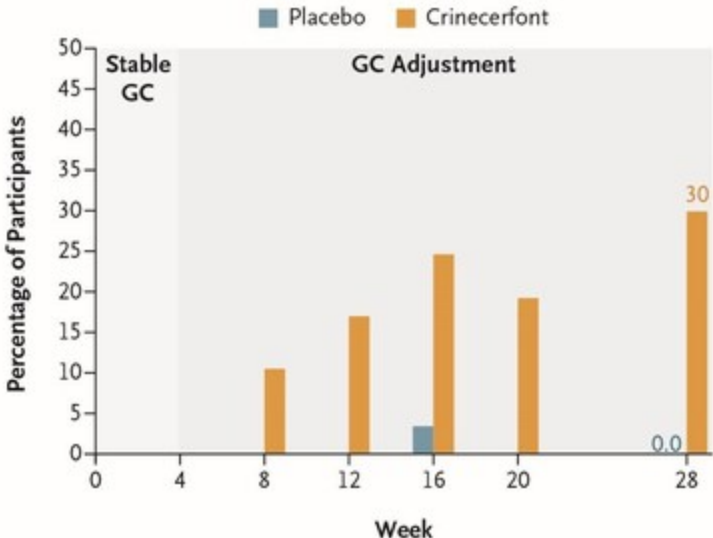
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Forward-Looking Statements

In addition to historical facts, this press release contains forward-looking statements that involve a number of risks and uncertainties. These statements include, but are not limited to, statements regarding the potential benefits to be derived from crinecerfont. Among the factors that could cause actual results to differ materially from those indicated in the forward-looking statements include: the crinecerfont NDAs may not be accepted for filing by the FDA or may not obtain regulatory approval or such approval may be delayed; additional regulatory submissions may not occur or be submitted in a timely manner; the FDA may make adverse decisions regarding crinecerfont; crinecerfont may not be found to be safe and/or effective or may not prove to be beneficial to patients; development activities for crinecerfont may not be completed on time or at all; clinical development activities may be delayed for regulatory or other reasons, may not be successful or replicate previous and/or interim clinical trial results, or may not be predictive of real-world results or of results in subsequent clinical trials; competitive products and technological changes that may limit demand for our products; uncertainties relating to patent protection and intellectual property rights of third parties; our dependence on third parties for development and manufacturing activities related to crinecerfont, and our ability to

manage these third parties; our future financial and operating performance; risks and uncertainties associated with the commercialization of our products; and other risks described in the Company's periodic reports filed with the Securities and Exchange Commission, including without limitation the Company's quarterly report on Form 10-Q for the quarter ended March 31, 2024. Neurocrine Biosciences disclaims any obligation to update the statements contained in this press release after the date hereof.

D Achievement of Physiologic Glucocorticoid Dose while Androstenedione Was Controlled



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