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Clinical Development Program of Crinecerfont (NBI-74788)
in Classic Congenital Adrenal Hyperplasia (CAH)

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the clinical development program of crinecerfont (NBI-74788).

Crinecerfont, a novel, orally administered, non-steroidal, and selective corticotropin-releasing factor type 1 receptor (CRF1R) antagonist, is an investigational compound in clinical development for the treatment of 21-hydroxylase deficiency (21-OHD) classic CAH and is currently not approved for use by the Food and Drug Administration.

A clinical development program has been established to investigate the use of crinecerfont for the treatment of 21-OHD classic CAH[1,3,5,6]:

Clinical Trial Name	Expected Timing	Study Details
CAH2001 (NCT03525886)	Completed	• Phase 2, open-label, multiple ascending dose study of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of crinecerfont • Participants: adults (ages 18 to 50 years) with classic CAH due to 21-OHD • Results Published. Brief summary below.
CAH2008 (NCT04045145)	Estimated study completion date: Q4 2021	• Phase 2, open-label, multiple-dose study to evaluate the safety, tolerability, PK, and PD of crinecerfont • Participants: pediatric (ages 14 to 17 years) with classic CAH due to 21-OHD • Brief study summary listed below; data not available
CAH3003 CAHtalyst Study (NCT04490915)	Estimated study completion date: Q1 2024	• Phase 3 global registrational study to evaluate the efficacy, safety, and tolerability of crinecerfont vs. placebo at 24 weeks • Participants: adults (≥18 years) with classic CAH due to 21-OHD • Brief study summary listed below; data not available
CAH2006 CAHtalyst Pediatric Study (NCT04806451)	Estimated study completion date: Q2 2024	• Phase 3 global registrational study to evaluate the efficacy, safety, and tolerability of crinecerfont vs. placebo at 28 weeks • Participants: pediatric (ages 2-17 years) with classic CAH due 21-OHD • Brief study summary listed below; data not available

CAH2001: Phase 2 Study in Adults (ages 18 to 50 years) with Classic CAH

The crinecerfont Phase 2 clinical study used a sequential-cohort design to evaluate the safety, tolerability, and efficacy of four different crinecerfont dosing regimens, each dosed for 14 days in adult female and male participants (ages 18 to 50 years old) with 21-OHD classic CAH (Figure 1).[1,2] The sequential-cohort design comprised four open-label crinecerfont dosing regimens, as follows[2]:

- Cohort 1 (50 mg once daily at bedtime [QHS], n=8)
- Cohort 2 (100 mg QHS, n=7)
- Cohort 3 (100 mg once daily in the evening [QPM], n=8)
- Cohort 4 (100 mg twice daily, morning and evening [BID], n=8)

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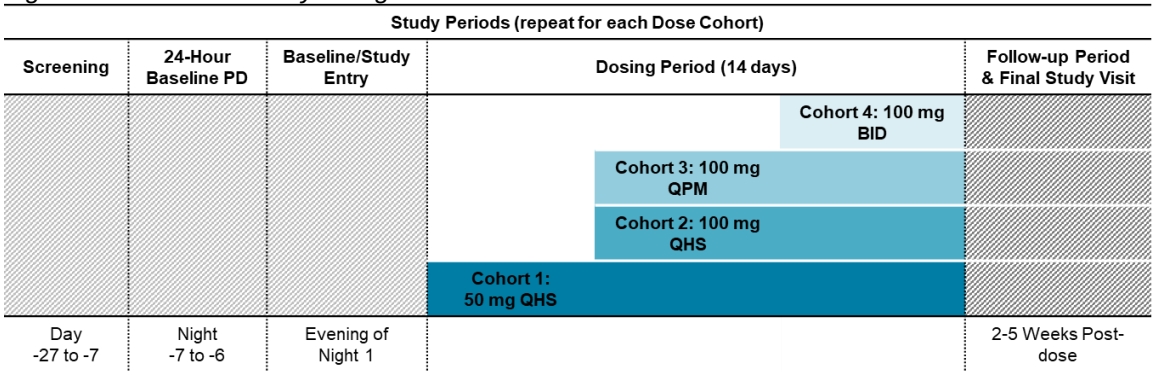
The study medication was taken with 8 oz of Ensure Plus® (Cohorts 1 and 2) or participants' regular evening (Cohort 3) or morning and evening (Cohort 4) meals. Each regimen was administered for 14 consecutive days while participants continued their normal daily glucocorticoid (GC) therapy, which was maintained stable over the 14 days.[2]

Figure 1. CAH2001: Study Design[2]:



BID=twice daily; PD, pharmacodynamic; QHS=once daily at bedtime; QPM=once daily in the evening.

Adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17OHP), androstenedione, and testosterone were measured serially over a 24-hour period at baseline and after 14 days of dosing. Key efficacy endpoints for ACTH, 17OHP, androstenedione, and testosterone concentrations were based on available values in both the morning window (timeframe between 06:00 and 10:00) and the 24-hour sampling period. Treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) and TEAEs leading to discontinuation, were assessed throughout the study. Additional safety assessments included vital signs, 12-lead electrocardiogram (ECG), clinical laboratory tests, Brief Psychiatric Rating Scale, and Columbia-Suicide Severity Rating Scale. Key inclusion criteria included a medically confirmed diagnosis of 21-OHD classic CAH; serum 17OHP ≥30.3 nmol/L (≥1000 ng/dL), serum cortisol <138 nmol/L (<5 µg/dL), and plasma ACTH ≥4.4 pmol/L (≥20 pg/mL) at screening prior to morning GC dose; and receiving a stable GC regimen for at least 30 days prior to baseline. Key exclusion criteria included dexamethasone therapy for 30 days prior to screening and throughout the study, and a known or suspected diagnosis of other forms of CAH.[2]

A total of 18 participants were enrolled in the study. Participants could enroll in more than 1 Cohort; as such, three participants enrolled in a total of three cohorts each, and seven participants enrolled in two cohorts each. Of the 18 enrolled participants (mean age 31 ± 9.3 years), 61% were female and 94% were white. At baseline, 56% of participants were receiving hydrocortisone alone, and 44% were receiving prednisone (or equivalent) with or without hydrocortisone.[2]

Median percent reductions from baseline to Day 14, based on morning window values, in plasma ACTH and serum 17OHP ranged from -53% to -66%. Dose related decreases in morning window values of serum androstenedione were observed, ranging from a 21% reduction in Cohort 1, to a 64% reduction in Cohort 4. Median percent reductions from baseline to Day 14, based on morning window values, were >60% for ACTH (-66%), 17OHP (-64%), and androstenedione (-64%) with crinecerfont 100 mg twice daily. In female participants, 73% (8/11) had ≥50% reduction in morning window testosterone levels. Male participants had median 26–65% decreases in androstenedione/testosterone ratios during the morning window.[2]

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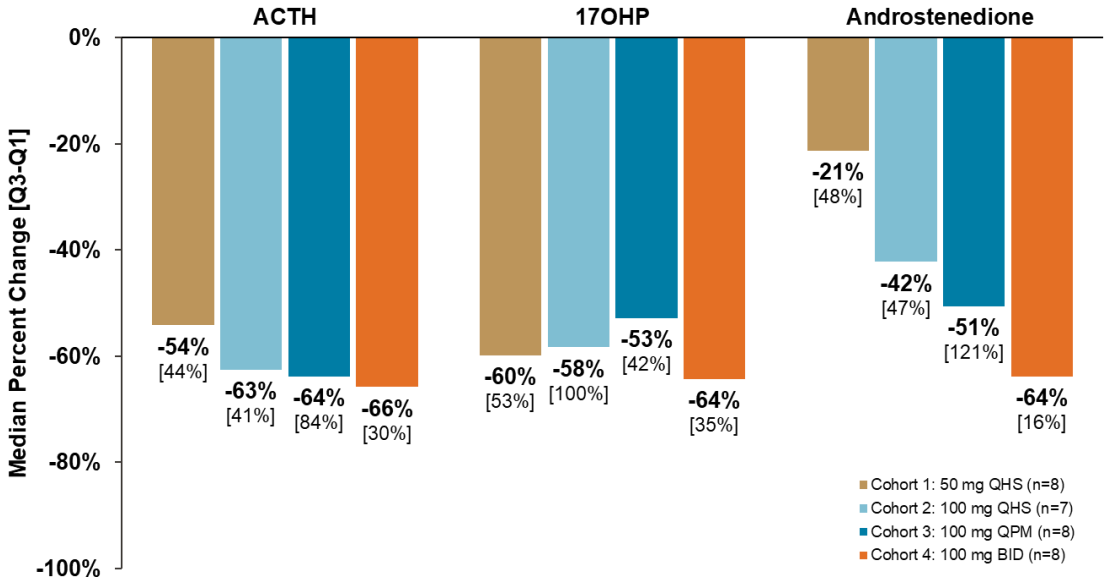
Figure 2. Median % reductions from baseline to Day 14 based on morning window values.[2]



Based on the average value from the morning window timepoints (06:00, 08:00, and 10:00); 17OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotropic hormone; BID, twice daily; QHS, once daily at bedtime; Q3-Q1, interquartile range; QPM, once daily in the evening.

The majority of TEAEs were mild or unrelated to study drug, with no deaths, severe TEAEs, or discontinuations due to TEAEs. The most common TEAEs (reported in ≥2 subjects overall) were headache, upper respiratory tract infection, fatigue, contusion (bruising), insomnia, nasopharyngitis, pyrexia, and nausea. One serious TEAE of cholelithiasis, occurring 34 days after the last dose of study drug, was assessed as unlikely related to the study drug by the investigator. There were no safety concerns with respect to routine clinical laboratory values, vital signs, ECGs, or neuropsychiatric assessments. [2]

For more information please refer to the article published in *J Clin Endocrinol Metab.*
https://academic.oup.com/jcem/advance-article/doi/10.1210/clinem/dgab749/6398210

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

The crinecerfont Phase 2 clinical study (NCT04045145) is an open-label, multiple-dose study of the safety, tolerability, PK, and PD of crinecerfont in approximately 12 female and male participants ages 14 to 17 years with classic CAH due to 21-OHD. Pharmacokinetics, 17-OHP and other biomarkers will be measured at baseline and after 14 days of treatment with crinecerfont. Safety and tolerability of crinecerfont will be assessed (Figure 3). Key inclusion criteria include a medically confirmed diagnosis of 21-OHD classic CAH and stable glucocorticoid doses prior to study start. Key exclusion criteria include 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 glucocorticoids.[3,4] Data for this ongoing study is not available at this time.

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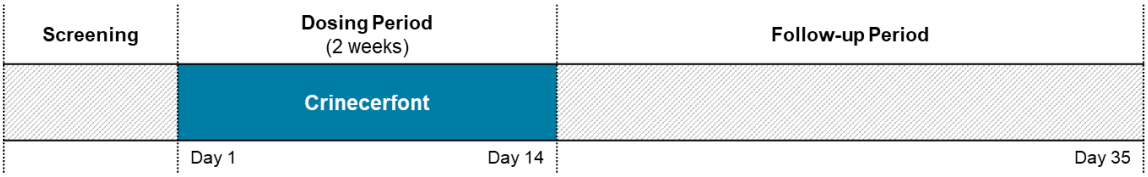
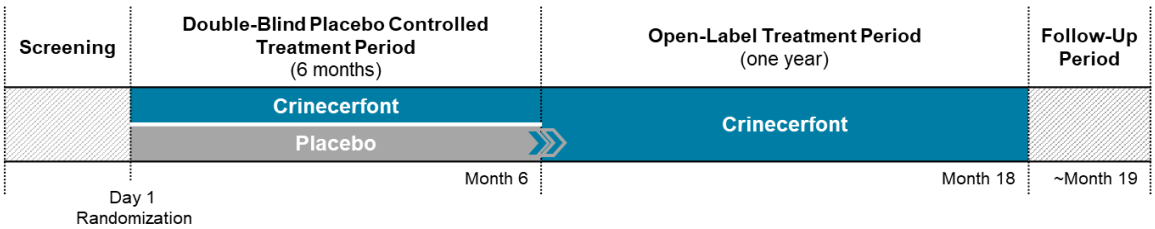
Figure 3. CAH 2008: Study Design[3,4]:



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

The crinecerfont Phase 3 clinical study (NCT04490915) is designed to evaluate the efficacy, safety, and tolerability of crinecerfont vs. placebo in approximately 165 adult male and female participants (≥18 years of age) with classic CAH due to 21-OHD. There will be a 6 month randomized, double blind, placebo-controlled period, followed by 1 year open-label treatment period with crinecerfont capsules, administered orally, twice daily (Figure 4). The primary outcome measure is the percent change from baseline in glucocorticoid daily dose at Week 24, with secondary outcome measures including, but not limited to, achievement of a reduction in glucocorticoid daily dose to physiologic levels, change from baseline in body weight, fat mass, blood pressure, glucose tolerance, and waist circumference at Week 24. Key inclusion criteria include a medically confirmed diagnosis of 21-OHD classic CAH and stable glucocorticoid doses prior to study start. Key exclusion criteria include 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.[4,5] Data for this ongoing study is not available at this time.

Figure 4. CAH3003: Study Design[4,5]:



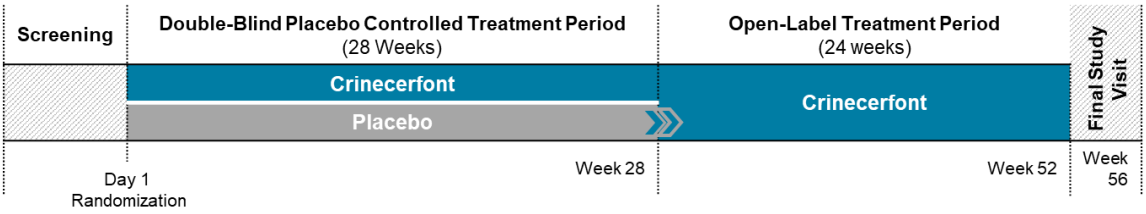
For more information on the CAHtalyst Study, please see www.CAHtalyststudy.com

CAH2006 (CAHtalyst Pediatric Study): Phase 3 Study in Pediatric Participants (ages 2-17 years) with Classic CAH

The crinecerfont Phase 3 clinical study (NCT04806451) is designed to evaluate the efficacy, safety, and tolerability of crinecerfont vs. placebo in approximately 81 pediatric male and female participants (2-17 years of age) with classic CAH due 21-OHD. There is a 28-week randomized, double blind, placebo-controlled period, followed by 24 weeks of open-label treatment with crinecerfont capsules, administered orally, twice daily (Figure 5). The primary outcome measure is the change from baseline in serum A4 at Week 4, with secondary outcome measures including, but not limited to, change from baseline in serum 17-OHP at Week 4, percent change from

baseline in glucocorticoid daily dose at Week 28, change from baseline in body mass index, bone age advancement, and salivary 17-OHP at Week 28, and change from baseline in predicted adult height at Week 52. Key inclusion criteria include a medically confirmed diagnosis of 21-OHD classic CAH and stable glucocorticoid doses prior to study start. Key exclusion criteria include 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.[4,6] Data for this ongoing study is not available at this time.

Figure 5. CAH2006: Study Design[4,6]:



For more information on the CAHtalyst Pediatric Study, please see www.CAHtalystpediatricstudy.com

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. ClincialTrials.gov. Safety, tolerability, pharmacokinetics, and pharmacodynamics of NBI-74788 in adults with congenital adrenal hyperplasia. Available from: https://clinicaltrials.gov/ct2/show/NCT03525886?term=CAH2001&draw=2&rank=1. NLM identifier: NCT03525886. Accessed May 25, 2021.
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6. ClincialTrials.gov. Global safety and efficacy registration study of crinecerfont in pediatric patients with classic congenital adrenal hyperplasia (CAHtalyst pediatric study). Available from:https://clinicaltrials.gov/ct2/show/NCT04806451?recrs=a&cond=congenital+adrenal+hyperplasia&phase=2&draw=2&rank=1. NLM identifier: NCT04806451. Accessed May 25, 2021.

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