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, an oral, nonsteroidal, selective corticotropin-releasing factor type 1 receptor (CRF₁) antagonist, is an investigational compound in clinical development for the treatment of classic CAH due to 21-hydroxylase deficiency (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

A clinical development program has been established to investigate the use of crinecerfont for the treatment of classic CAH:

<table>
<thead>
<tr>
<th>Clinical Trial Name</th>
<th>Expected Timing</th>
<th>Study Details</th>
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</table>
| CAH2001 (NCT03525886)³ | Completed | • Phase 2, open-label, multiple ascending dose study of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of crinecerfont  
• Participants: adults (eligible ages: 18 to 50 years) with classic CAH due to 21-OHD  
• Results Published:¹ Brief summary below. |
| CAH2008 (NCT04045145)⁴ | Completed | • Phase 2, open-label study to evaluate the safety, tolerability, PK, and PD of crinecerfont  
• Participants: adolescents (eligible ages: 14 to 17 years) with classic CAH due to 21-OHD  
• Results Published:² Brief study summary below. |
| CAH3003 CAHtalyst™ Study (NCT04490915)⁵ | 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 (eligible ages: ≥18 years) with classic CAH due to 21-OHD  
• Brief study summary listed below; data not available |
| CAH2006 CAHtalyst™ Pediatric Study (NCT04806451)⁶ | 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 (eligible ages: 2-17 years) with classic CAH due 21-OHD  
• Brief study summary listed below; data not available |

CAH2001: Phase 2 Study in Adults (eligible 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 classic CAH due to 21-OHD (Figure 1).¹,³ The sequential-cohort design comprised four open-label crinecerfont dosing regimens, as follows¹:

- 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)
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.1

**Figure 1. CAH2001: Study Design**

**Study Periods**

<table>
<thead>
<tr>
<th>Study Periods</th>
<th>(Repeat for Each Dose Cohort)</th>
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<tbody>
<tr>
<td>Screening</td>
<td>24-Hour Baseline PD</td>
</tr>
<tr>
<td></td>
<td>Baseline/Study Entry</td>
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<tr>
<td></td>
<td>Dosing Period 14 Days</td>
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<td>Follow-Up Period &amp; Final Study Visit</td>
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- **Crinecerfont Dose Escalation**
  - Cohort 1: 50 mg QHS
  - Cohort 2: 100 mg QHS
  - Cohort 3: 100 mg QPM
  - Cohort 4: 100 mg BID

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 classic CAH due to 21-OHD; 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.1

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.1

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 (Figure 2). 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.1
Figure 2. Median % reductions from baseline to Day 14 based on morning window values:\(^1\):

<table>
<thead>
<tr>
<th></th>
<th>ACTH</th>
<th>17OHP</th>
<th>Androstenedione</th>
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<tbody>
<tr>
<td>Median Percent Change [Q3-Q1]</td>
<td>-54% [44%]</td>
<td>-60% [53%]</td>
<td>-64% [35%]</td>
</tr>
<tr>
<td></td>
<td>-63% [41%]</td>
<td>-58% [42%]</td>
<td>-64% [35%]</td>
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<tr>
<td></td>
<td>-64% [84%]</td>
<td>-53% [100%]</td>
<td>-51% [121%]</td>
</tr>
<tr>
<td></td>
<td>-66% [30%]</td>
<td>-64% [100%]</td>
<td>-64% [16%]</td>
</tr>
</tbody>
</table>

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.\(^1\)

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 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, PK, and 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 3).\(^2,4\)

Figure 3. CAH 2008: Study Design\(^2,4\):

- Screening and Baseline Period
- Crinecerfont Dosing Period (2 Weeks)
- Follow-up Period

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.) ACTH, 17OHP, androstenedione (males and females), testosterone (females), and androstenedione/testosterone ratio (males) were assessed. TEAEs, including 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 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.2,4

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 4). 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 4. ≥50% Median Reductions in ACTH, 17-OHP, and Androstenedione (Males and Females), Testosterone (Females), and Androstenedione/Testosterone Ratio (Males) After 14 Days of Crinecerfont Treatment²:

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.²

CAH3003 (CAHtalyst Study): Phase 3 Study in Adults (eligible ages: ≥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 5). The primary outcome measure is the percent change from baseline in GC daily dose at Week 24, with secondary outcome measures including, but not limited to, achievement of a reduction in GC 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 classic CAH due to 21-OHD, and stable GC 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 GC therapy. At the end of the study, participants have the opportunity to continue to receive crinecerfont as part of an open-label extension. Data for this ongoing study is not available at this time.

Figure 5. CAH3003: Study Design:

For more information about the adult CAHtalyst Phase 3 study, please visit cahtalyst.cahstudies.com and ClinicalTrials.gov.

CAH2006 (CAHtalyst Pediatric Study): Phase 3 Study in Pediatric Participants (eligible 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 to 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 6). 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 GC 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 classic CAH due to 21-OHD, and stable GC 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 GC therapy. At the end of the study, participants have the opportunity to continue to receive crinecerfont as part of an open-label extension. Data for this ongoing study is not available at this time.

Figure 6. CAH2006: Study Design:
For more information about the pediatric CAHtalyst Phase 3 study, please visit [cahtalystpeds.cahstudies.com](cahtalystpeds.cahstudies.com) and [ClinicalTrials.gov](https://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:

2. 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.