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 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]

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

Crinecerfont	**CAH2001**	CAH2008	CAH3003	CAH2006

CAH2001: CAHlibrate™ Study (NCT03525886)[5]

Completed

Phase 2, open-label, multiple ascending dose study of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of crinecerfont

Phase 2

Adults (eligible ages: 18 to 50 years) with classic CAH due to 21-OHD

Published results

Summary

21-ODH=21-hydroxylase deficiency

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.

(p) 877-641-3461
(f) 913-451-6409

12780 El Camino Real, San Diego, CA 92130
www.neurocrinemedical.com

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

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

Crinecerfont	CAH2001	**CAH2008**	CAH3003	CAH2006

CAH2008: CAHlibrate™ Pediatric Study (NCT04045145)[6]

Completed

Phase 2, open-label study to evaluate the safety, tolerability, PK, and PD of crinecerfont

Phase 2

Adolescents (eligible ages: 14 to 17 years) with classic CAH due to 21-OHD

Published results

Summary

21-ODH=21-hydroxylase deficiency

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(f) 913-451-6409

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

Crinecerfont	CAH2001	CAH2008	**CAH3003**	CAH2006

CAH3003: CAHtalyst™ Study (NCT04490915)[7]

Enrollment completed

Phase 3 global registrational study to evaluate the efficacy, safety, and tolerability of crinecerfont vs. placebo at 24 weeks

Estimated study completion: **Q3 2027**

Phase 3

Adults (eligible ages: ≥18 years) with classic CAH due to 21-OHD

Top-line data released

Summary

21-ODH=21-hydroxylase deficiency

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(f) 913-451-6409

12780 El Camino Real, San Diego, CA 92130
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Clinical Development Program of Crinecerfont (NBI-74788) in Classic Congenital Adrenal Hyperplasia (CAH)

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

Crinecerfont	CAH2001	CAH2008	CAH3003	**CAH2006**

CAH2006:
CAHtalyst™ Pediatric Study (NCT04806451)[8]

Enrollment completed

Phase 3 global registrational study to evaluate the efficacy, safety, and tolerability of crinecerfont vs. placebo at 28 weeks

Estimated study completion: **Q3 2027**

Phase 3

Pediatric participants (eligible ages: 2-17 years) with classic CAH due to 21-OHD

Top-line data released

Summary

21-ODH=21-hydroxylase deficiency

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(p) 877-641-3461
(f) 913-451-6409

12780 El Camino Real, San Diego, CA 92130
www.neurocrinemedical.com

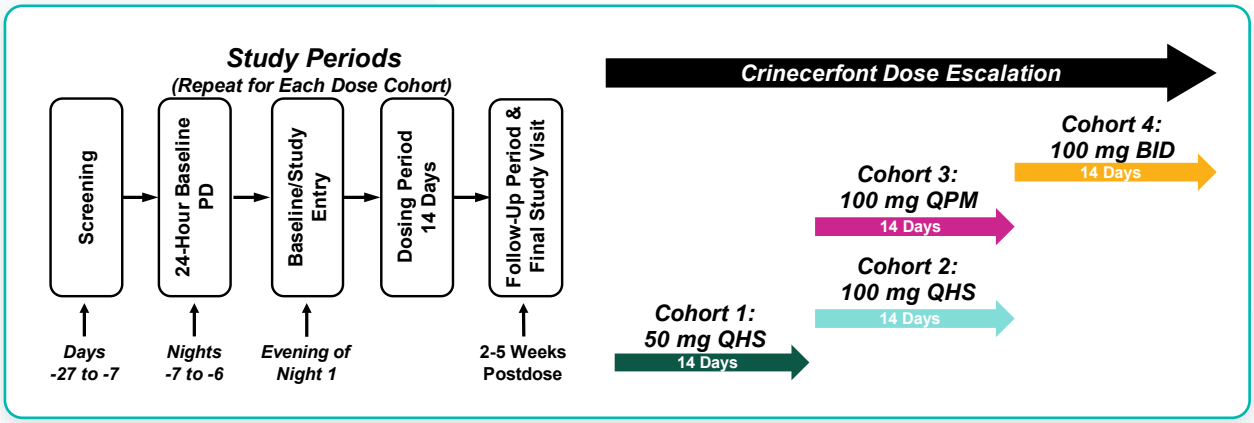
CAH2001 (CAHlibrate™ Study): Phase 2 Study in Adults (eligible ages: 18 to 50 years) with Classic CAH

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).[1,5] The sequential-cohort design comprised four open-label crinecerfont dosing regimens, as follows[1]:

- 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[1,5]:



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

Adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17OHP), androstenedione (A4), and testosterone were measured serially over a 24-hour period at baseline and after 14 days of dosing. Key efficacy endpoints for ACTH, 17OHP, A4, 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]

For more information, please refer to the article published in **J Clin Endocrinol Metab**

(p) 877-641-3461
(f) 913-451-6409
12780 El Camino Real, San Diego, CA 92130
www.neurocrinemedical.com

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

CAH2001: Study Design | **CAH2001: Study Results**

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 A4 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 A4 (-64%) with crinecerfont 100 mg BID (Figure 2). In female participants, 73% (8/11) had ≥50% reduction in morning window testosterone levels. Male participants had median 26–65% decreases in A4/testosterone ratios during the morning window.[1]

Summary
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CAH2006
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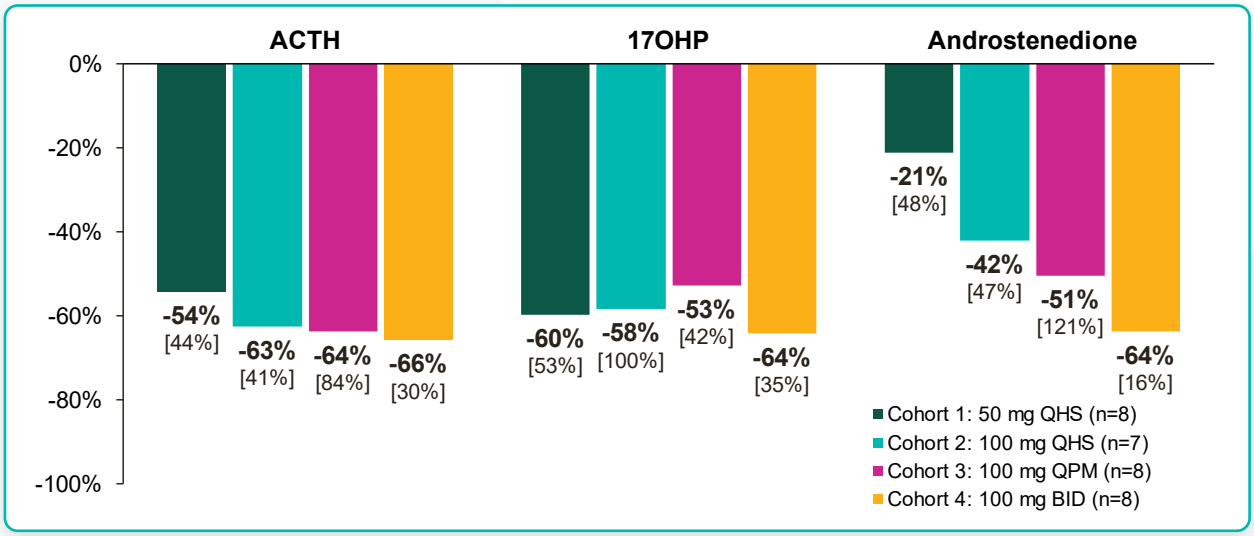
Figure 2. Median % reductions from baseline to Day 14 based on morning window values[1]:



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 participants 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**

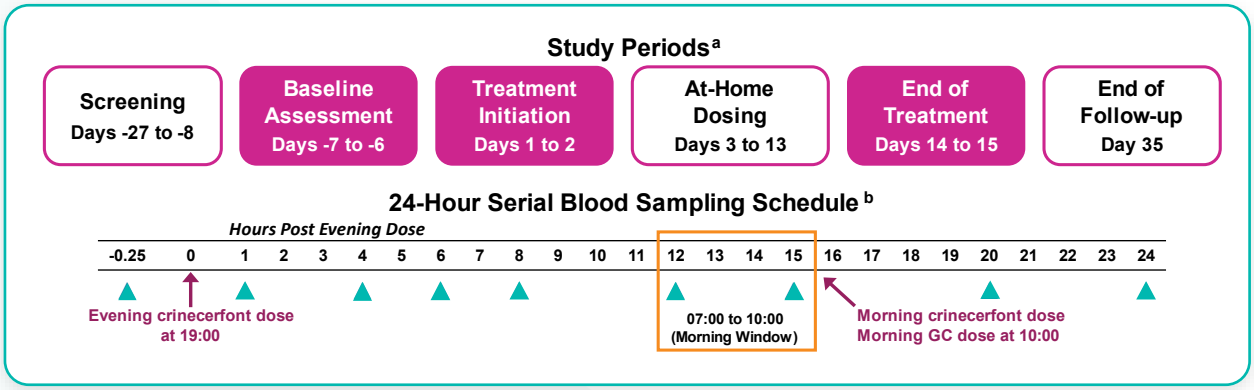
(p) 877-641-3461
(f) 913-451-6409
12780 El Camino Real, San Diego, CA 92130
www.neurocrinemedical.com

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

CAH2008: Study Design | CAH2008: Study Results

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, BID in the morning and evening with meals for 14 days (Figure 3).[2,6]

Figure 3. CAH 2008: Study Design[2,6]:



[a]Shaded boxes indicate overnight stay at study center for 24-hour serial blood sampling; [b]No crinecerfont dose was administered on Days -7/-6 (baseline visit). However, sample collection timepoints during this overnight stay were the same as Days 1/2 and 14/15 (post-baseline visits). Blue triangles indicate time points when blood samples were collected; GC, glucocorticoid.

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, A4 (males and females), testosterone (females), and A4/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.[2,6]

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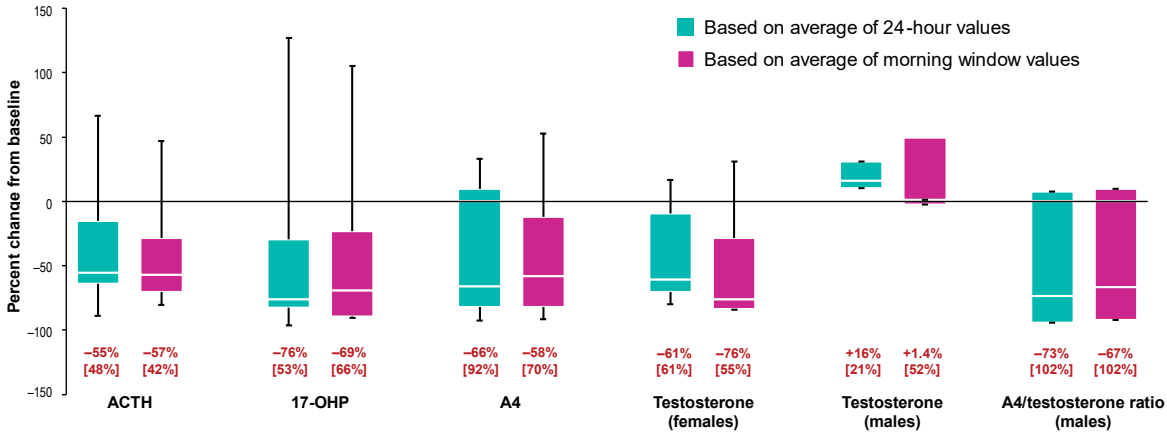
For more information, please refer to the article published in **J Clin Endocrinol Metab**

(p) 877-641-3461
(f) 913-451-6409
12780 El Camino Real, San Diego, CA 92130
www.neurocrinemedical.com

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

Median percent reductions from baseline to Day 14 for 24-hour measurements of ACTH, 17OHP, A4 (males and females), testosterone (females), and A4/testosterone ratio (males) ranged from -55% to -76%, while morning window measurements ranged from -57% to -76% (Figure 4). Additionally, a greater than 50% reduction from baseline for ACTH, 17-OHP, and A4 (males and females), testosterone (females), and A4/testosterone ratio (males) was achieved by 63%, 75%, 50%, 60% and 67% of participants, respectively.[2]

Figure 4. Median Percent Reductions from Baseline in ACTH, 17-OHP, Androstenedione (Males and Females), Testosterone (Females), and Androstenedione/Testosterone Ratio (Males) After 14 Days of Crinecerfont Treatment[2]:



Boxes represent the IQR: lower edge (25th percentile), upper edge (75th percentile), horizontal bar (median). Whiskers extend beyond the box to the minimum and maximum values. Data in red represent median [interquartile range] values, except for the testosterone and A4/testosterone ratio in males, where data in red represent median [minimum and maximum] values (n=3); 17OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotropic hormone; IQR, interquartile range.

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

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For more information, please refer to the article published in **J Clin Endocrinol Metab**

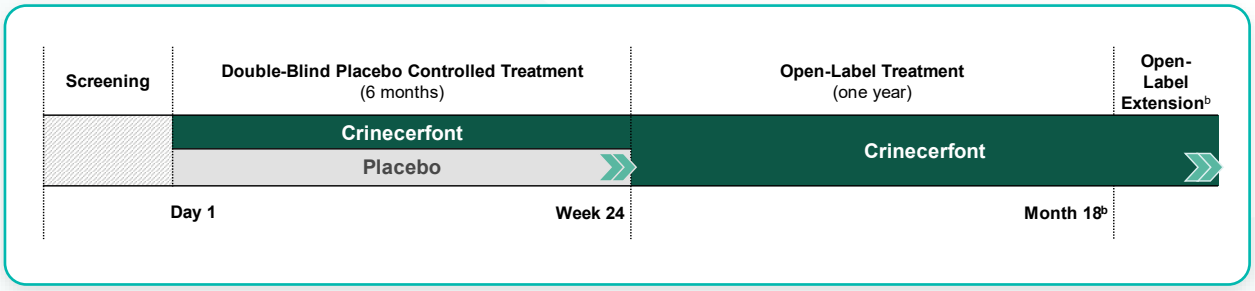
(p) 877-641-3461
(f) 913-451-6409
12780 El Camino Real, San Diego, CA 92130
www.neurocrinemedical.com

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

CAH3003: Study Design | CAH3003: Study Results

The crinecerfont Phase 3 CAHtalyst study (NCT04490915) 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, BID (Figure 5). The primary outcome measure was the mean percent change from baseline in GC 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 A4 at Week 4, the percentage of participants achieving a reduction to a physiological GC 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 GC 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 GC therapy. At the end of the study, participants have the opportunity to continue to receive crinecerfont as part of an open-label extension.[7]

Figure 5. CAH3003: Study Design[7a]:



[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.

For more information about the adult CAHtalyst Phase 3 study, please visit **ClinicalTrials.gov**

(p) 877-641-3461
(f) 913-451-6409
12780 El Camino Real, San Diego, CA 92130
www.neurocrinemedical.com

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

CAH3003: Study Design | **CAH3003: Study Results**

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 GC 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 SAEs, with none assessed as related to crinecerfont.[3]

For more information about the adult CAHtalyst Phase 3 study, please visit **ClinicalTrials.gov**

(p) 877-641-3461
(f) 913-451-6409

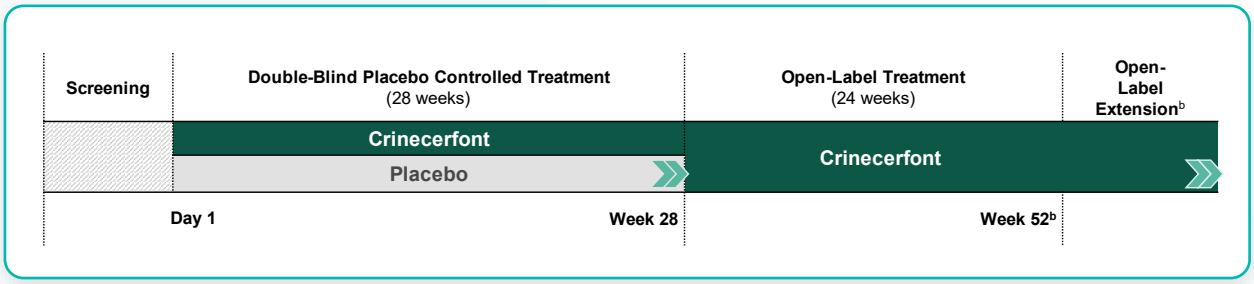
12780 El Camino Real, San Diego, CA 92130
www.neurocrinemedical.com

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

CAH2006: Study Design | CAH2006: Study Results

The crinecerfont Phase 3 CAHtalyst Pediatric study (NCT04806451) was designed to evaluate the efficacy, safety, and tolerability of crinecerfont vs. placebo in 103 pediatric male and female participants (eligible ages: 2-17 years of age) with classic CAH due to 21-OHD. There was a 28-week randomized, double blind, placebo-controlled period, followed by 24 weeks of open-label treatment with crinecerfont capsules, administered orally, BID (Figure 6). The primary outcome measure was 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 (in hydrocortisone dose equivalents adjusted for body surface area), while maintaining androgen control, 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 included a medically confirmed diagnosis of classic CAH due to 21-OHD, and stable GC 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 GC therapy. At the end of the study, participants have the opportunity to continue to receive crinecerfont as part of an open-label extension.[8]

Figure 6. CAH2006: Study Design[8a]:



[a]Enrollment completed; [b]Duration of participation in the study is ~14 months for the core study and will be a variable amount of time per participant for the open-label extension.

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For more information about the CAHtalyst Pediatric Phase 3 study, please visit **ClinicalTrials.gov**

(p) 877-641-3461
(f) 913-451-6409
12780 El Camino Real, San Diego, CA 92130
www.neurocrinemedical.com

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

CAH2006: Study Design | **CAH2006: Study Results**

The Phase 3 CAHtalyst Pediatric study met its primary endpoint, demonstrating that treatment with crinecerfont resulted in a statistically significant decrease from baseline in serum A4 at Week 4 vs. placebo, following a GC stable period (p=0.0002). The study also met key secondary endpoints, with a statistically significant percent reduction from baseline in GC daily dose vs. placebo while maintaining androgen control at Week 28 (p<0.0001), and a statistically significant decrease from baseline in serum 17-OHP at Week 4 vs. placebo (p<0.0001). Approximately 30% of participants receiving crinecerfont achieved a reduction to a physiological GC daily dose while maintaining androgen control compared to 0% of participants receiving placebo at Week 28 (p=0.0009, p-value not adjusted for multiplicity).[4]

During the phase 3 double-blind, placebo-controlled period of the CAHtalyst Pediatric study, crinecerfont was generally well tolerated. The most common adverse events were headache, fever, vomiting, upper respiratory tract infection, and nasopharyngitis. There were few SAEs, with none assessed as related to crinecerfont.[4]

For more information about the CAHtalyst Pediatric Phase 3 study, please visit **ClinicalTrials.gov**

(p) 877-641-3461
(f) 913-451-6409
12780 El Camino Real, San Diego, CA 92130
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