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

Open-label, Phase 2 Study of Crinecerfont in Adults with Classic Congenital Adrenal Hyperplasia (CAH) due to 21-hydroxylase deficiency

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding data from the Phase 2 CAHlibrate™ study (CAH2001; NCT03525886) of crinecerfont in adults with classic CAH due to 21-hydroxylase deficiency (21-OHD).

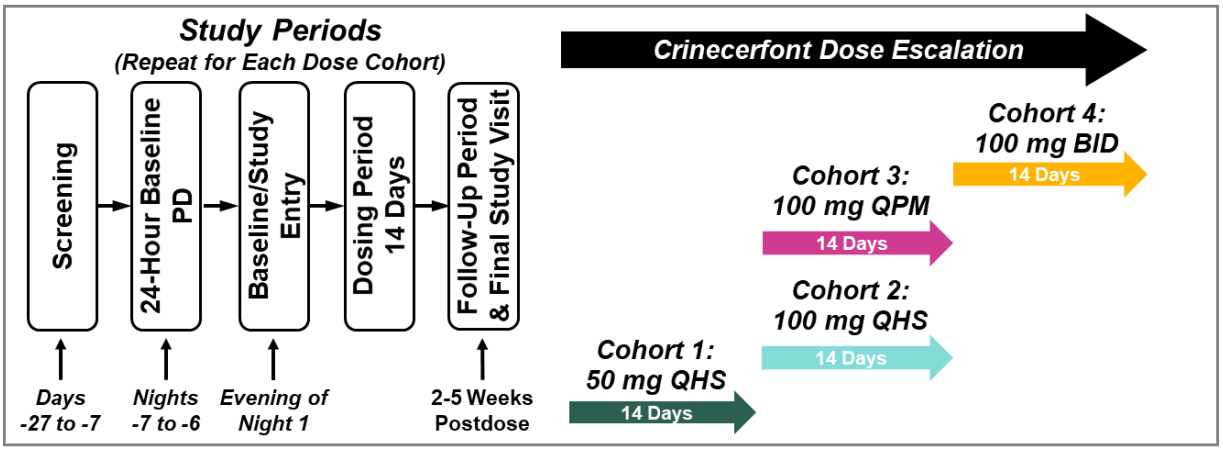
Crinecerfont is an investigational, oral, selective corticotropin-releasing factor type 1 receptor (CRF_1) antagonist being developed to help reduce and control excess adrenal androgens through a steroid-independent mechanism for the treatment of congenital adrenal hyperplasia (CAH). Crinecerfont is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

The crinecerfont Phase 2 CAHlibrate 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 (eligible ages: 18 to 50 years) 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. CAHlibrate™ 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, 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)

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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.[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. Baseline levels of adrenal androgens and precursors are included in Table 1.[1]

In all cohorts, median ACTH, 17OHP, androstenedione, testosterone (in females), and androstenedione/testosterone ratio (in males) were reduced from baseline to Day 14 whether based on samples collected during the morning window (06:00 to 10:00) or the 24-hour sampling period (**Table 1**).[1]

Table 1. Effects of crinecerfont on adrenal androgens and precursors[a,b,1]

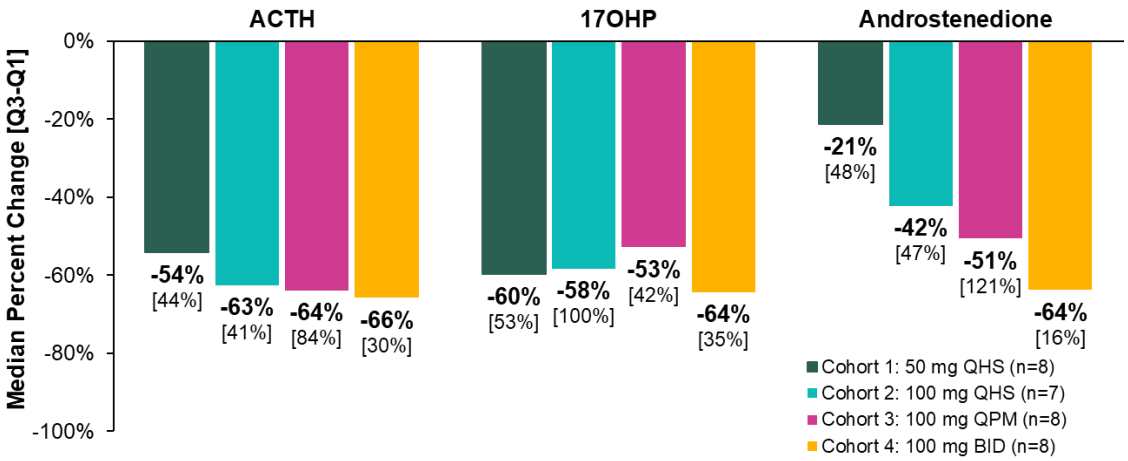
Median (IQR)	Cohort 1: 50 mg QHS (n=8)		Cohort 2: 100 mg QHS (n=7)		Cohort 3: 100 mg QPM (n=8)		Cohort 4: 100 mg BID (n=8)	
	Morning Window[c]	24-Hour Period[d]	Morning Window[c]	24-Hour Period[d]	Morning Window[c]	24-Hour Period[d]	Morning Window[c]	24-Hour Period[d]
Adrenocorticotropic hormone, pmol/L								
At baseline	33 (103)	20 (69)	43 (83)	16 (21)	98 (104)	28 (26)	68 (86)	22 (25)
CFB to Day 14	-24 (48)	-7.6 (48)	-34 (42)	-9.2 (16)	-85 (101)	-18 (29)	-45 (57)	-5.8 (15)
17-hydroxyprogesterone, nmol/L								
At baseline	162 (77)	69 (89)	299 (452)	114 (260)	197 (292)	89 (150)	327 (425)	103 (175)
CFB to Day 14	-81 (43)	-20 (43)	-135 (281)	-38 (104)	-102 (208)	-59 (94)	-171 (330)	-41 (74)
Androstenedione, nmol/L								
At baseline	9.4 (12)	7.5 (6.5)	7.8 (51)	7.2 (38)	11 (19)	6.4 (13)	27 (41)	9.9 (27)
CFB to Day 14	-3.8 (4.8)	-0.9 (4.2)	-5.8 (12)	-3.5 (8.5)	-8.1 (13)	-4.8 (9.7)	-14 (33)	-4.2 (16)
Testosterone-females, nmol/L[e]								
At baseline	1.9 (2.5)	1.4 (1.9)	2.4 (0.3)	1.9 (0.5)	3.0 (7.3)	1.9 (6.2)	2.2 (4.6)	2.0 (2.0)
CFB to Day 14	-0.4 (1.2)	-0.2 (1.0)	-1.8 (0.8)	-1.3 (0.6)	-2.6 (5.7)	-1.5 (4.9)	-1.7 (3.0)	-0.6 (1.3)
Testosterone-males, nmol/L[e]								
At baseline	12 (8.4)	8.9 (6.3)	12 (0.7)	11 (0.4)	11 (8.7)	8.9 (7.3)	12 (7.0)	9.9 (4.3)

CFB to Day 14	2.2 (7.9)	2.7 (5.8)	-0.5 (0.1)	-1.3 (1.7)	0.7 (3.0)	-0.6 (4.4)	0.9 (3.6)	0.8 (1.2)
Androstenedione/testosterone ratio-males[e]								
At baseline	0.9 (1.2)	1.0 (1.4)	5.0 (0.4)	4.3 (1.1)	0.6 (1.1)	0.5 (0.9)	3.9 (5.4)	3.2 (3.7)
CFB to Day 14	-0.3 (0.8)	-0.3 (0.8)	-1.7 (1.3)	-1.7 (1.7)	-0.5 (0.6)	-0.3 (0.6)	-3.6 (3.7)	-2.4 (2.7)

[a] Normal ranges are as follows: ACTH 2.2-13.2 pmol/L (10 60 pg/mL); 17OHP adult male, <6.7 nmol/L (<220 ng/dL); 17OHP follicular female <2.4 nmol/L (<80 ng/dL); 17OHP luteal female <8.6 nmol/L (<285 ng/dL); 17OHP postmenopausal female <1.5 nmol/L (<51 ng/dL); androstenedione adult male, 2.3-7.3 nmol/L (65 210 ng/dL); androstenedione adult female, 2.8-8.4 nmol/L (80-240 ng/dL); total testosterone female, 0.3-2.1 nmol/L (8-60 ng/dL); total testosterone male, 10.4-41.6 nmol/L (300-1200 ng/dL). For androstenedione/testosterone male, target ratio was <0.5.[b] Aside from GC increases found in 3 participants with a protocol deviation (received GC dosing before blood sample collection in Cohorts 1, 2, and 3 [each n=1]), no clinically meaningful changes in cortisol levels were found.[c] Based on values from the morning window timepoints (06:00, 08:00, 10:00).[d] Based on values from all timepoints in serial blood sampling period: Cohorts 1 and 2 (from 23:00 to 22:00 [following day]); Cohorts 3 and 4 (from 20:00 to 22:00 [following day]).[e] n-values for testosterone and androstenedione/testosterone were as follows: females (Cohort 1, n=4; Cohort 2, n=5; Cohort 3, n=3; Cohort 4, n=4); males (Cohort 1, n=4; Cohort 2, n=2; Cohort 3, n=5; Cohort 4, n=3).
BID=twice-daily; CFB, change from baseline; IQR=interquartile range (Q3-Q1); QHS=once-daily at bedtime; QPM=once-daily in the evening.

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.[1]

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 (**Table 2**).The most common TEAEs (reported in ≥2 subjects overall)

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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]

Table 2. Treatment-emergent adverse events (TEAEs).[1]

	Cohort 1: 50 mg QHS (n=8)	Cohort 2: 100 mg QHS (n=7)	Cohort 3: 100 mg QPM (n=8)	Cohort 4: 100 mg BID (n=8)
Adverse event summary, n (%)				
Any TEAE	7 (88)	5 (71)	5 (63)	5 (63)
Any SAE	0 (0)	1 (14)[a]	0 (0)	0 (0)
Any TEAE leading to discontinuation	0 (0)	0 (0)	0 (0)	0 (0)
Any TEAE resulting in death	0 (0)	0 (0)	0 (0)	0 (0)
TEAEs by MedDRA preferred term, n (%)				
Headache	3 (38)	1 (14)	0 (0)	1 (13)
Upper respiratory tract infection	3 (38)	0 (0)	1 (13)	0 (0)
Fatigue	1 (13)	0 (0)	1 (13)	1 (13)
Contusion	2 (25)	0 (0)	0 (0)	0 (0)
Insomnia	0 (0)	1 (14)	0 (0)	1 (13)
Nasopharyngitis	0 (0)	0 (0)	0 (0)	2 (25)
Nausea	1 (13)	1 (14)	0 (0)	0 (0)
Pyrexia	0 (0)	0 (0)	1 (13)	1 (13)

[a]Single event of cholelithiasis, assessed by the investigator as moderate in intensity and unrelated to treatment. The participant underwent a cholecystectomy with intraoperative cholangiogram, followed by appropriate medical treatment. The cholelithiasis was resolved and the participant remained in the study; BID=twice daily; MedDRA=Medical Dictionary for Regulatory Activities; QHS=once daily at bedtime; QPM=once daily in the evening; TEAE=treatment emergent adverse event; SAE=serious adverse event.

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

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:

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