Congenital Adrenal Hyperplasia Clinical Program Overview

NEUROCRINE® BIOSCIENCES

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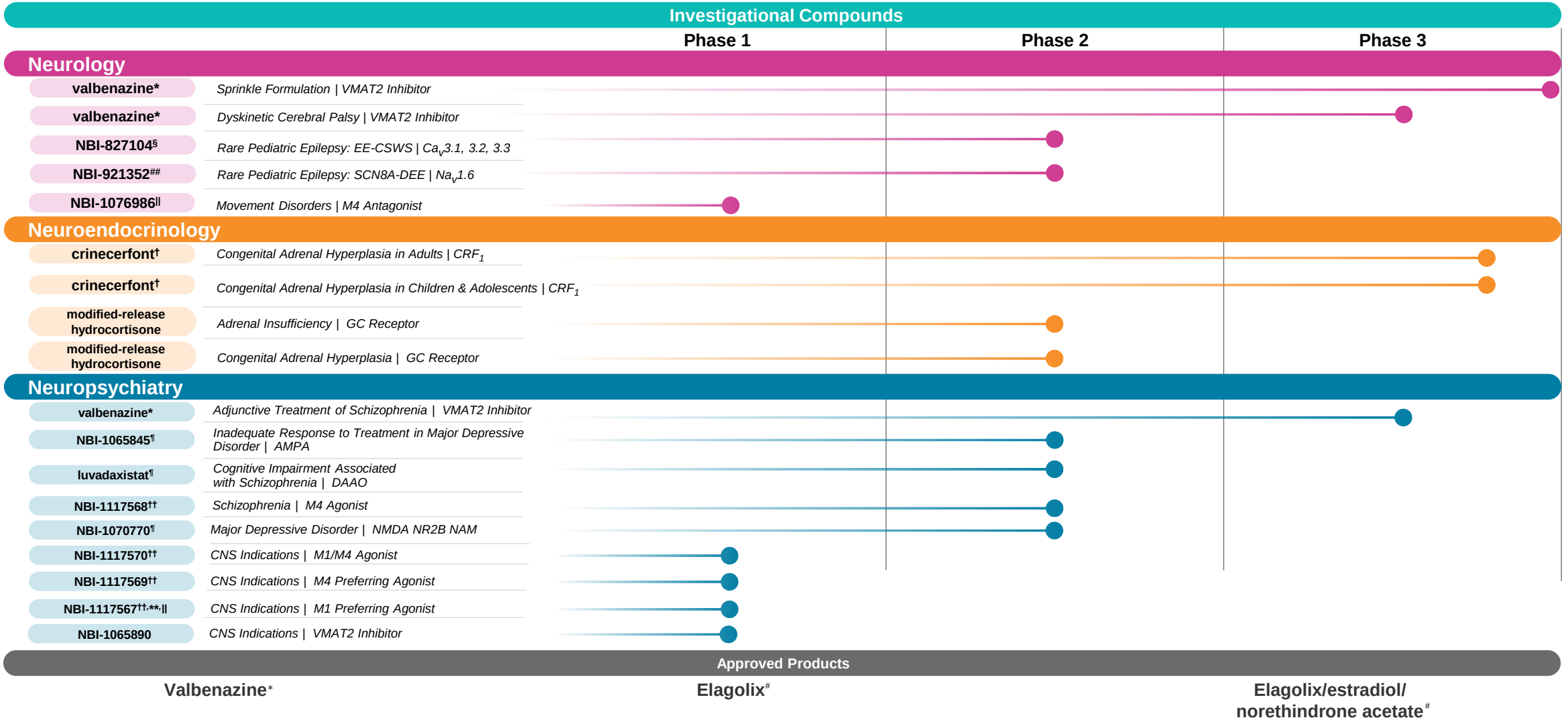
***Crinecerfont is investigational and not approved in any country.**

Neurocrine Pipeline

Neurocrine Clinical Pipeline[a]



EE-CSWS = Epileptic Encephalopathy with Continuous Spike-and-Wave During Sleep; SCN8A-DEE = SCN8A Developmental and Epileptic Encephalopathy Syndrome.
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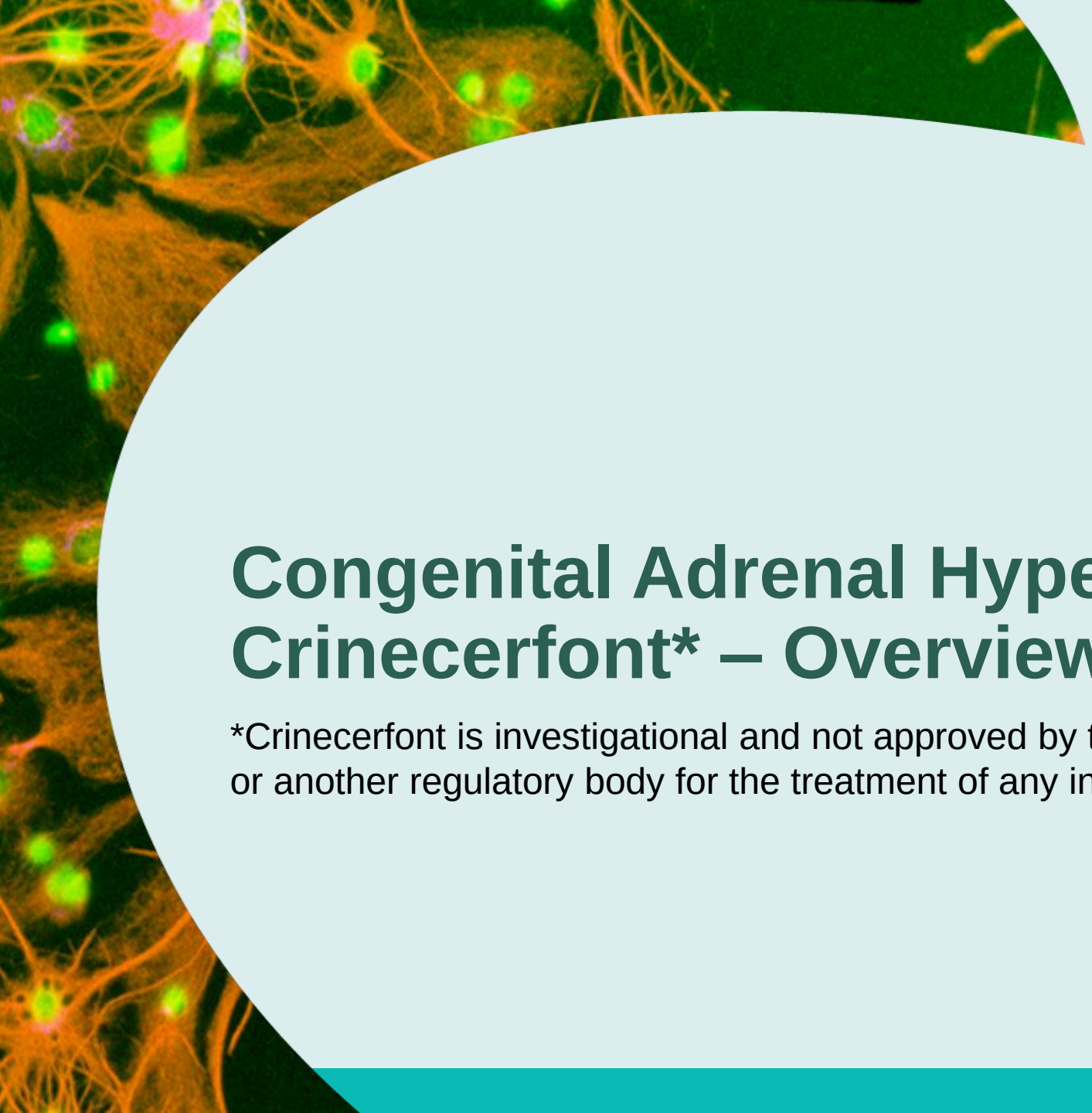
[a]as of March 2024



Congenital Adrenal Hyperplasia and Crinecerfont* – Overview

*Crinecerfont is investigational and not approved by the US Food and Drug Administration (FDA) or another regulatory body for the treatment of any indication

Classic Congenital Adrenal Hyperplasia (CAH)

Rare genetic condition affecting ~1:15,000 live births worldwide[1,2]

Dynamic condition of adrenal insufficiency & adrenal androgen excess[1]

Complex symptoms affect multiple organ systems[1,3]

- Salt-wasting adrenal crisis, virilization in females, abnormalities in growth leading to short stature, early puberty, infertility

Supraphysiological doses of glucocorticoids are often needed for adrenal androgen reduction[4]

Patients may experience complications due to chronic supraphysiological doses of glucocorticoids[5,6]

1. Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088. 2. Pang S, et al. *Screening*.1993;2:105-139. 3. Merke DP et al. *N Eng J Med*. 2020;383(13):1248-1261. 4. Mallappa A, et al. *Nat Rev Endocrinol*. 2022;18(6):337-352. 5. Finkielstain GP, et al. *J Clin Endocrinol Metab*. 2012;97(12):4429-4438. 6. Arlt W, et al. *J Clin Endocrinol Metab*. 2010;95(11):5110-5121.

Congenital Adrenal Hyperplasia

CONGENITAL

Present at Birth

ADRENAL

Glands synthesize and secrete multiple hormones

HYPERPLASIA

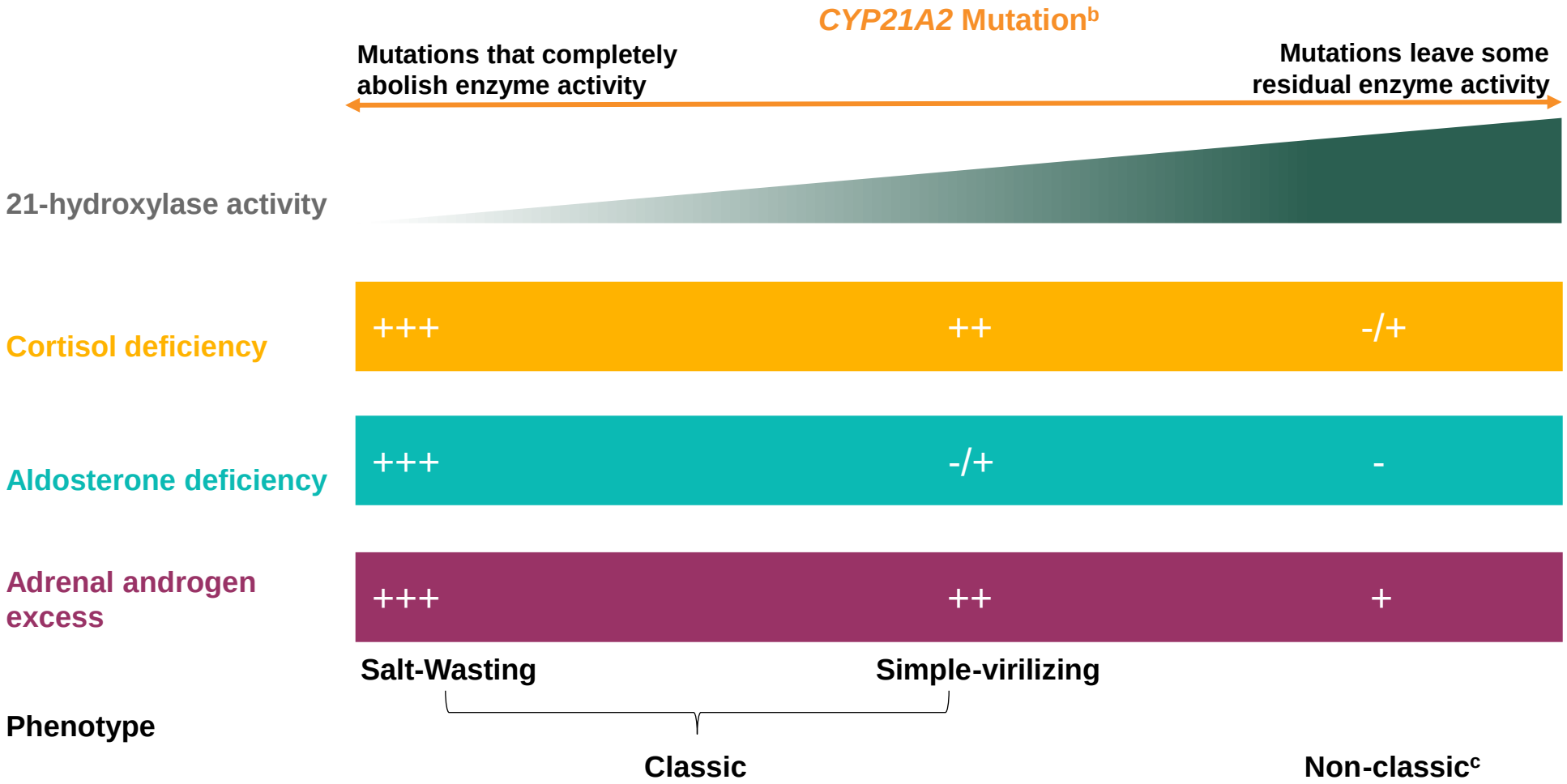
Organ enlargement, increase in cell number

- Rare autosomal recessive condition[1]
- Deficiency in cortisol and often aldosterone[1]
- Excessive production of ACTH, steroid precursors, and adrenal androgens[1]
- GC treatment at supraphysiological doses often needed for androgen reduction[2]

ACTH, adrenocorticotropic hormone, GC, Glucocorticoid.

1. Speiser PW, et al. *J Clin Endocrinol Metab.* 2018;103(11):4043-4088. 2. Mallappa A, et al. *Nat Rev Endocrinol*. 2022;18(6):337-352.

CAH Disease Spectrum Due to 21-hydroxylase Deficiency[a]



[a]This schematic is a general summary and is not meant to represent all 21-OHD CAH patients. Distinctions between CAH phenotypes are a continuum, and not absolute.
[b]Mutations of the gene CYP21A2 cause 21-hydroxylase deficiency.
[C]Estimated prevalence of non-classic CAH: ~1:200 to 1:2,000.[1,2]
CAH, Congenital adrenal hyperplasia.
Figure adapted from Auer MK, et al. 2023.

1. Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088. 2. Auer MK, et al. *Lancet*. 2023;401(10372):227-244.

Clinical Characteristics of CAH[1]

Infancy

- Salt-wasting adrenal crisis (poor feeding, weight loss, dehydration)
- **Females:** atypical genitalia

Childhood

- Increased growth velocity
- Advanced bone age
- Premature growth plate closure
- Early puberty
- **Females:** clitoromegaly

Adolescence and adulthood

- Short stature
- Infertility or subfertility
- Hirsutism, acne
- Adrenal myelolipomas
- **Females:** menstrual irregularities
- **Males:** testicular adrenal rest tumors (TARTs)

Patients with classic CAH are **at risk for potentially fatal adrenal crises**, often triggered by infections, throughout their lives[2]

1. Merke DP, et al. *N Engl J Med*. 2020;383(13):1248-1261. 2. Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088.

Current Management of CAH

Adequate androgen reduction should be balanced against the risks of chronic supraphysiological GC exposure[1]

Excess ACTH and adrenal androgens[2-6]

Abnormal growth and development
- Advanced bone age
- Early puberty
- Short stature

Male health problems
- Testicular adrenal rest tumors
- Infertility

Female health problems
- Acne
- Hirsutism
- Oligomenorrhea
- Amenorrhea
- Infertility

Other problems
- Psychological impact

Standard GC treatment at
PHYSIOLOGICAL DOSES
may not always control excess androgen levels

Supraphysiological doses of GCs[2-6]

Abnormal growth and development
- Short stature

Bone health problems
- Decreased bone density
- Increased fracture risk

Increased cardiovascular risk
- Hypertension

Metabolic issues
- Weight gain
- Obesity
- Insulin resistance
- Diabetes

Other problems
- Muscle weakness
- Psychological impact

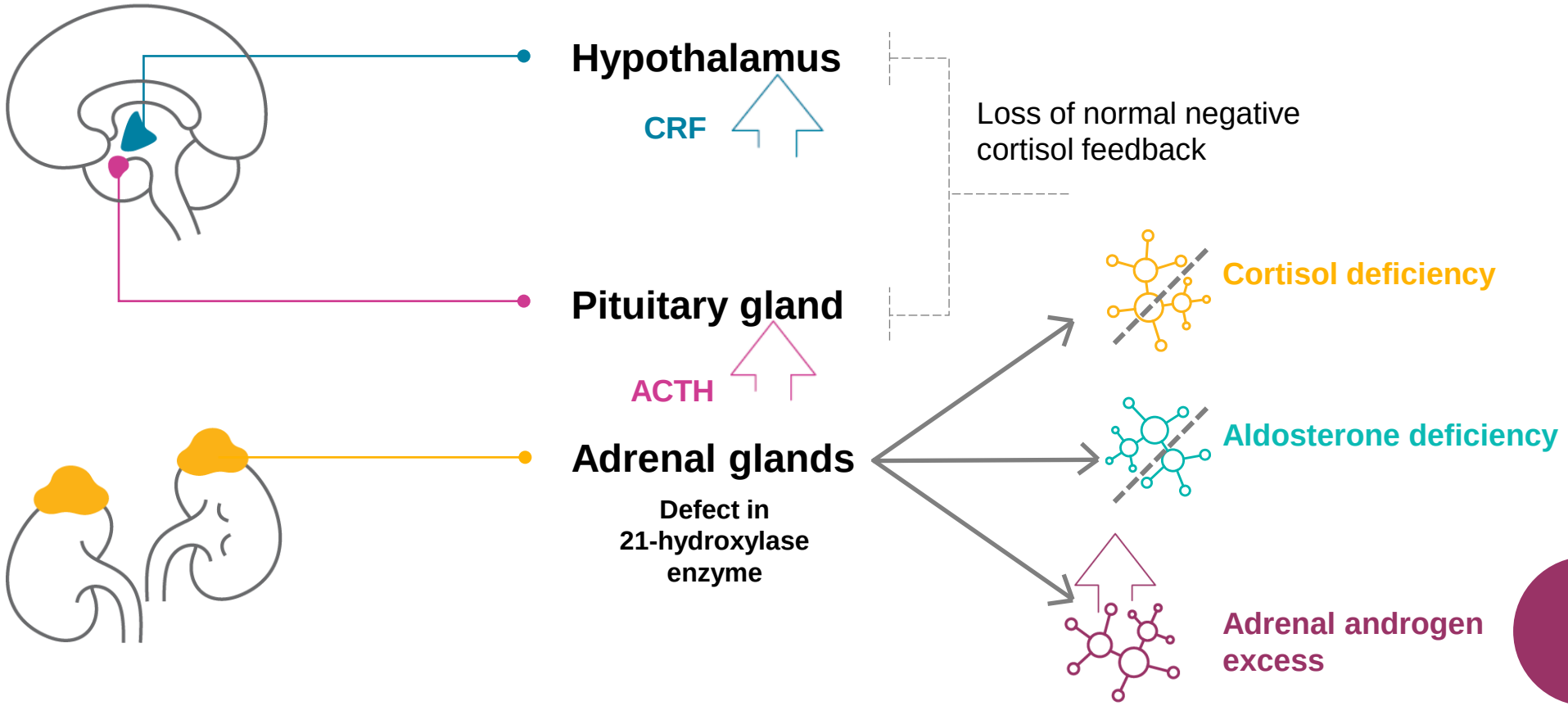
Standard GC treatment at
SUPRAPHYSIOLOGICAL DOSES
for androgen reduction has been associated with complications

Supraphysiological doses of GCs are often needed for adrenal androgen reduction[2]

ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; GC, glucocorticoid.

1. Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088. 2. Mallappa A, Merke DP. *Nat Rev Endocrinol.* 2022;18(6):337-352. 3. Finkielstain GP, et al. *J Clin Endocrinol Metab*. 2012;97(12):4429-4438. 4. Arlt W, et al. *J Clin Endocrinol Metab*. 2010;95(11):5110-5121. 5. Merke DP, Auchus RJ. *N Engl J Med*. 2020;383(13):1248-1261. 6. Han TS, et al. *Nat Rev Endocrinol*. 2014;10(2):115-124.

CAH Pathophysiology: Cortisol Deficiency Drives Adrenal Androgen Excess[1,2]

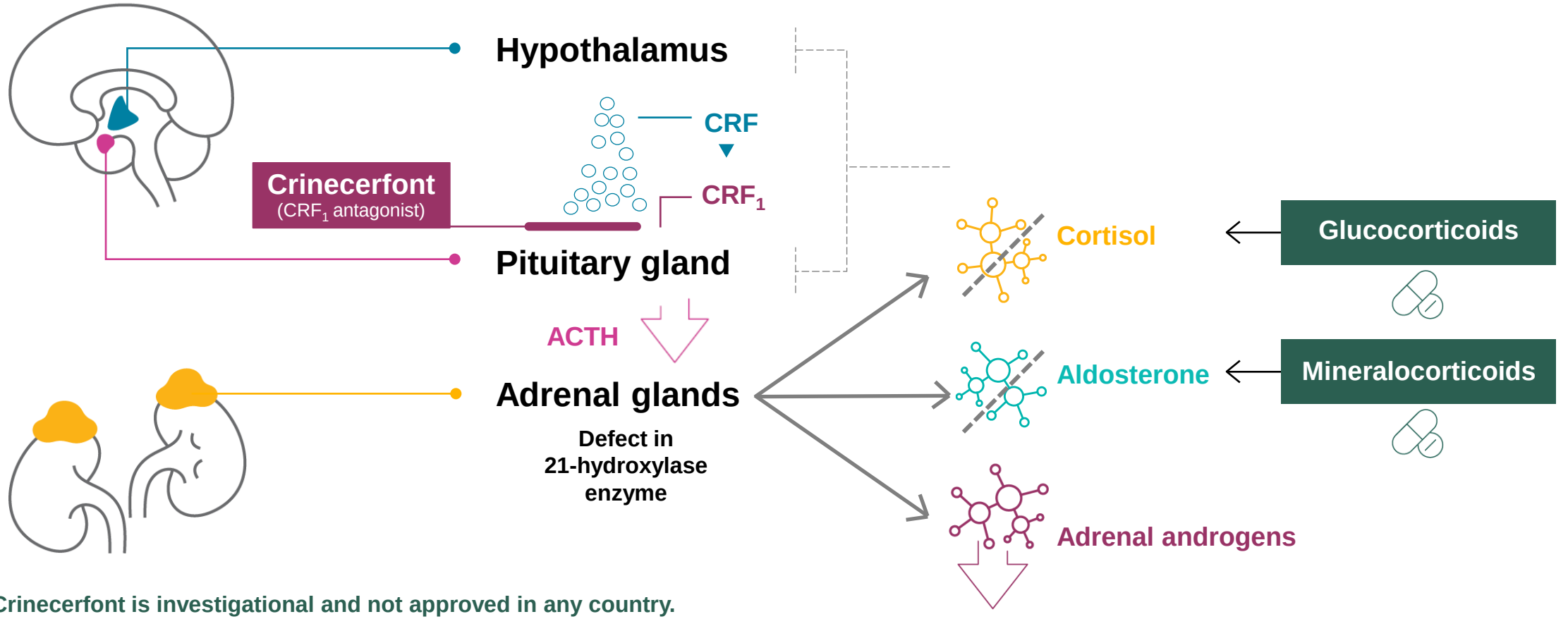


ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; CRF, corticotropin-releasing factor.

1. Merke DP, et al. *N Engl J Med*. 2020;383(13):1248-1261. 2. Claahsen-van der Grinten HL, et al. *Endocr Rev*. 2022;43(1):91-159.

Our Investigational Treatment Crinecerfont* May Offer a New Approach for Treating CAH[1-4]

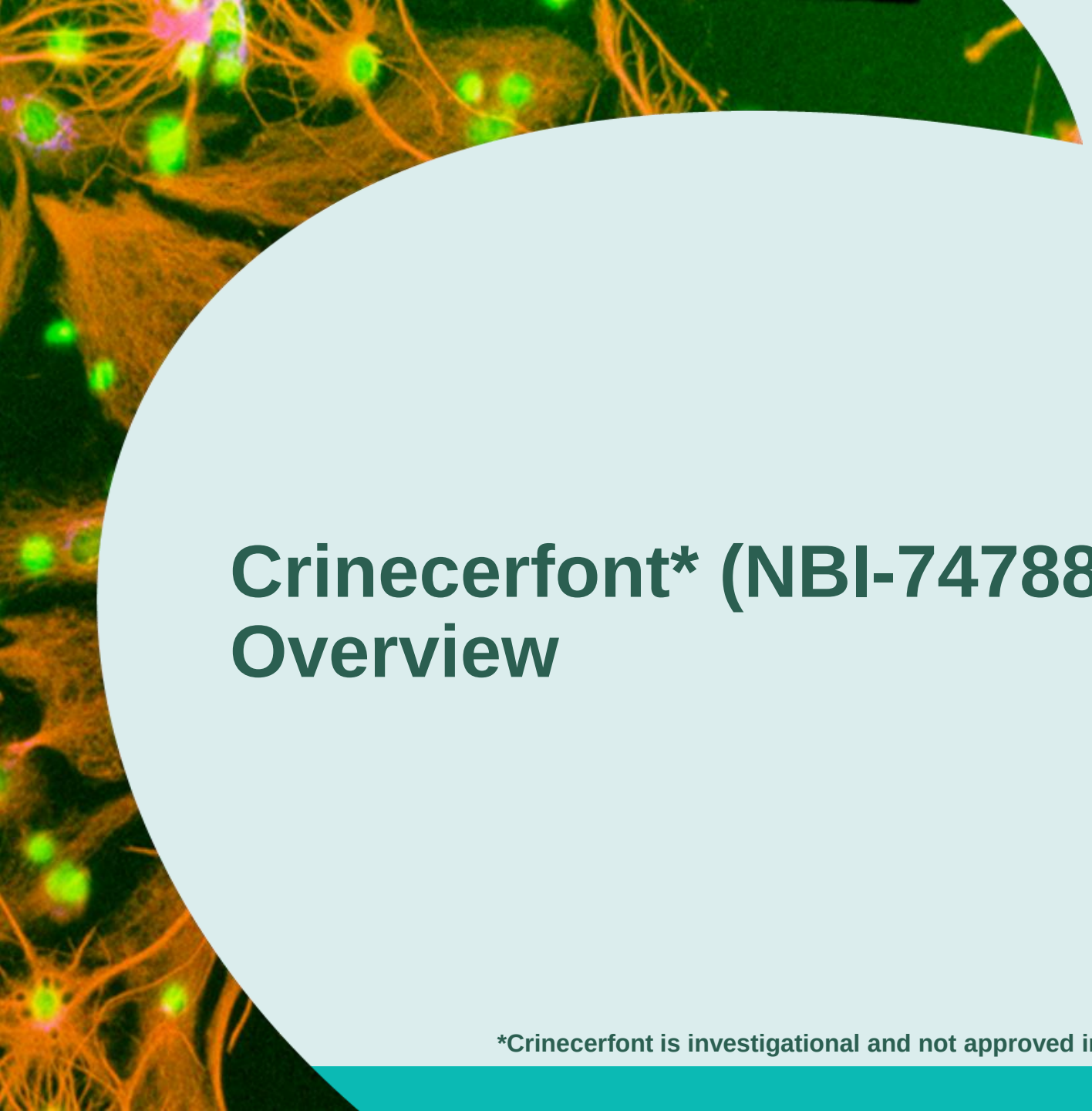
Thought to prevent CRF from binding to the CRF type 1 receptor (CRF_1) → **Could potentially decrease ACTH and adrenal androgen levels** → **May potentially enable lower dosing of glucocorticoids**



***Crinecerfont is investigational and not approved in any country.**

ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; CRF, corticotropin-releasing factor; CRF_1, corticotropin-releasing factor type 1 receptor.

1. Auchus RJ, et al. *J Clin Endocrinol Metab.* 2022;107(3):801-812. 2. Newfield RS, et al. *J Clin Endocrinol Metab.* 2023; dgad270. 3. Neurocrine.com. (2023). [Press release]. Retrieved from: https://neurocrine.gcs-web.com/news-releases/news-release-details/neurocrine-biosciences-announces-positive-top-line-data-phase-3. Accessed September 12, 2023. 4. Neurocrine.com. (2023). [Press release]. Retrieved from: https://neurocrine.gcs-web.com/news-releases/news-release-details/neurocrine-biosciences-announces-phase-3-pediatric-study-results. Accessed October 5, 2023.



Crinecerfont* (NBI-74788) Clinical Trials – Overview

*Crinecerfont is investigational and not approved in any country.

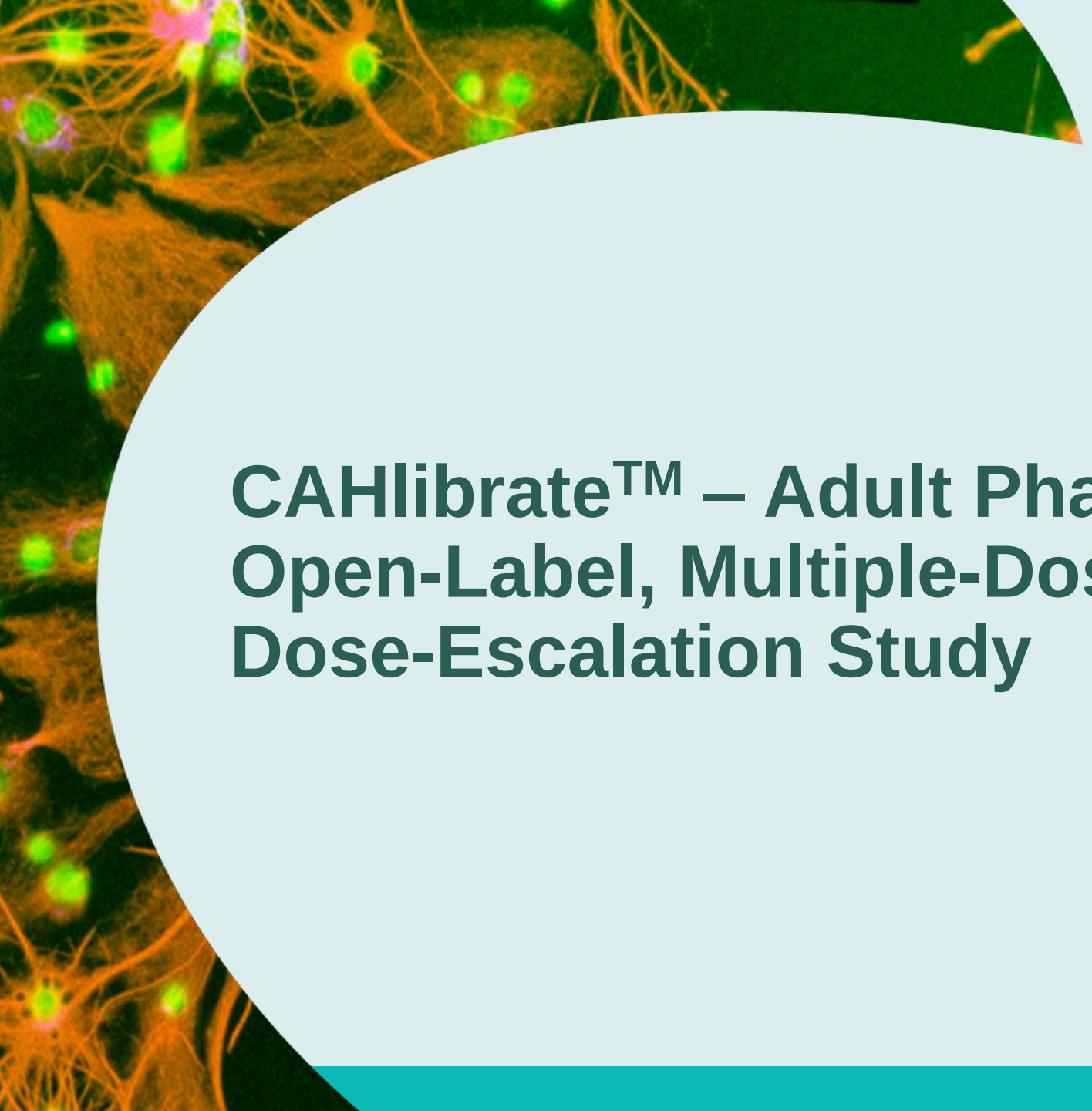
Crinecerfont* Clinical Trials Overview

Clinical Development in Classic CAH Participants

- Study Completed
  - CAHlibrate™ Study (NCT03525886)[1]
    - Phase 2, open-label, multiple-dose, dose-escalation study
    - Adult female and male participants (eligible ages: 18-50 years)
    - Results published in the *Journal of Clinical Endocrinology & Metabolism*
  - CAHlibrate™ Pediatric Study (NCT04045145)[2]
    - Phase 2, open-label, multiple-dose, dose-escalation study
    - Adolescent female and male participants (eligible ages: 14-17 years)
    - Results published in the *Journal of Clinical Endocrinology & Metabolism*
- Enrollment Completed
  - CAHtalyst™ Study (NCT04490915)[3]
    - Phase 3, randomized, double-blind, placebo-controlled 6-month study followed by a 12-month open-label treatment period
    - Adult female and male participants (eligible ages: ≥18 years)
  - CAHtalyst™ Pediatric Study (NCT04806451)[4]
    - Phase 3, randomized, double-blind, placebo-controlled 28-week study followed by a 24-week open-label treatment period
    - Pediatric and adolescent female and male participants (eligible ages: 2-17 years)

***Crinecerfont is investigational and not approved in any country.**

1. ClinicalTrials.gov Identifier: NCT03525886. Accessed June 22, 2023. https://clinicaltrials.gov/study/NCT03525886.
2. ClinicalTrials.gov Identifier: NCT04045145. Accessed June 22, 2023. https://clinicaltrials.gov/study/NCT04045145.
3. ClinicalTrials.gov Identifier: NCT04490915. Accessed March 27, 2023. https://clinicaltrials.gov/study/NCT04490915.
4. ClinicalTrials.gov Identifier: NCT04806451. Accessed March 17, 2023. https://clinicaltrials.gov/study/NCT04806451.



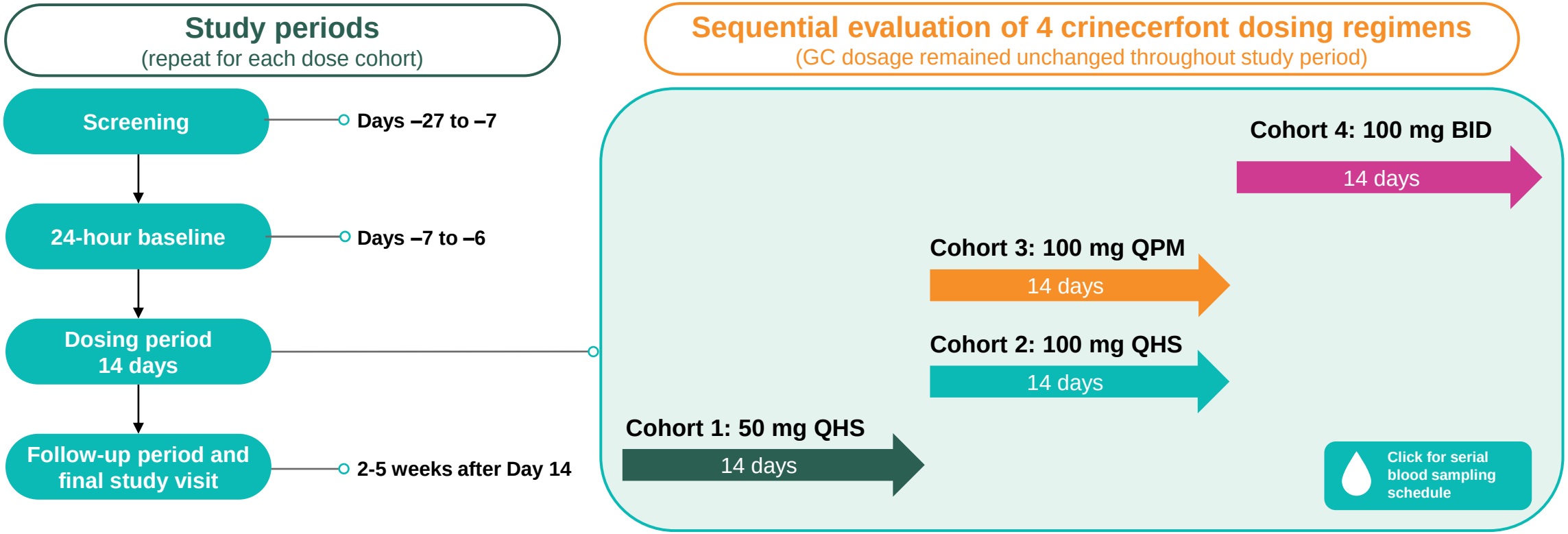
CAHlibrate™ – Adult Phase 2, Open-Label, Multiple-Dose, Dose-Escalation Study

Adult Participants (eligible ages: 18 to 50 years)

CAHlibrate Study

Study Design[1,2]

- Safety, tolerability, and efficacy of crinecerfont* in adults (eligible ages: 18-50 years) with classic CAH
- **Primary endpoint:** number of participants with AEs during the study period
- **Key efficacy endpoints:** changes from baseline to Day 14 in ACTH, 17-OHP, A4, and testosterone levels



***Crinecerfont is investigational and not approved in any country.**

17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; AE, adverse event; BID, twice daily; CAH, congenital adrenal hyperplasia; QHS, once daily at bedtime; QPM, once daily in the evening.

1. Auchus RJ, et al. *J Clin Endocrinol Metab*. 2022;107(3):801-812. 2. ClinicalTrials.gov Identifier: NCT03525886. Accessed June 22, 2023. https://clinicaltrials.gov/study/NCT03525886.

Adult Participants (eligible ages: 18 to 50 years)

CAHlibrate Study

Inclusion and Exclusion Criteria[1,2]

Key inclusion criteria

- Male or female adults aged 18 to 50 years
- Medically confirmed diagnosis of classic 21-hydroxylase deficiency CAH
- **Screening levels** prior to morning GC dose:
  - Serum 17-OHP ≥30.3 nmol/L (≥1000 ng/dL)
  - Serum cortisol <138 nmol/L (<5 µg/dL)
  - Plasma ACTH ≥4.4 pmol/L (≥20 pg/mL)
- Receiving stable GC regimen for ≥30 days prior to baseline

Key exclusion criteria

- Known or suspected diagnosis of other forms of CAH (e.g., 11β-hydroxylase deficiency)
- Prior or current medical condition requiring daily GC therapy (other than 21-OHD)
- Clinically relevant laboratory abnormality (e.g., hematologic, coagulation, renal, liver enzymes)
- QTcF interval of >450 (males) or >470 (females) ms
- Risk of suicidal or violent behavior
- Dexamethasone therapy for 30 days prior to screening and throughout the study

Crinecerfont is investigational and not approved in any country.

17-OHP, 17-hydroxyprogesterone; 21-OHD, 21-hydroxylase deficiency; ACTH, adrenocorticotropic hormone; BMI, body mass index; CAH, congenital adrenal hyperplasia; GC, glucocorticoid; QTcF, the corrected QT interval by Fridericia.

1. Auchus RJ, et al. *J Clin Endocrinol Metab*. 2022;107(3):801-812. 2. ClinicalTrials.gov Identifier: NCT03525886. Accessed June 22, 2023. https://clinicaltrials.gov/study/NCT03525886.

Adult Participants (eligible ages: 18 to 50 years)

CAHlibrate Study

Overview of Baseline Characteristics and Crinecerfont Exposure*[1]

- **18 participants** were enrolled
  - 3 participants enrolled in 3 cohorts each
  - 7 participants enrolled in 2 cohorts each
  - Median (range) time between enrollment in cohorts: 183 (49-343) days
  - 11 (61%) females; 7 (39%) males
  - Mean (SD) age: 31 (9.3) years
  - Mean (SD) BMI: 29 (4.1) kg/m^2

- At baseline, **10 participants (56%) used HC alone**, **7 participants (39%) used prednisone alone**, and **1 participant used HC and prednisone in combination**

- **Mean (SD) total daily GC dose: 26 ± 9.1 mg/day (14 ± 4.8 mg/m^2/day)** in HC equivalents[a]

Adrenal androgens, ACTH, and precursors at baseline, mean (SD)[b]		All participants (n=18)
ACTH	pg/mL pmol/L	318 (305) 70 (67)
17-OHP	ng/dL nmol/L	7789 (6040) 236 (183)
A4	ng/dL nmol/L	516 (573) 18 (20)
Testosterone (females)	ng/dL nmol/L	86 (69) 3.0 (2.4)
Testosterone (males)	ng/dL nmol/L	375 (130) 13 (4.5)

Click for detailed baseline characteristics

Click for hormone profiles

***Crinecerfont is investigational and not approved in any country.**

[a]Equivalence ratios:1 mg prednisolone, methylprednisolone, or prednisone considered equivalent to 4 mg HC. [b]Liquid dietary supplement versus usual evening meal.
17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; GC, glucocorticoid; HC, hydrocortisone; SD, standard deviation.

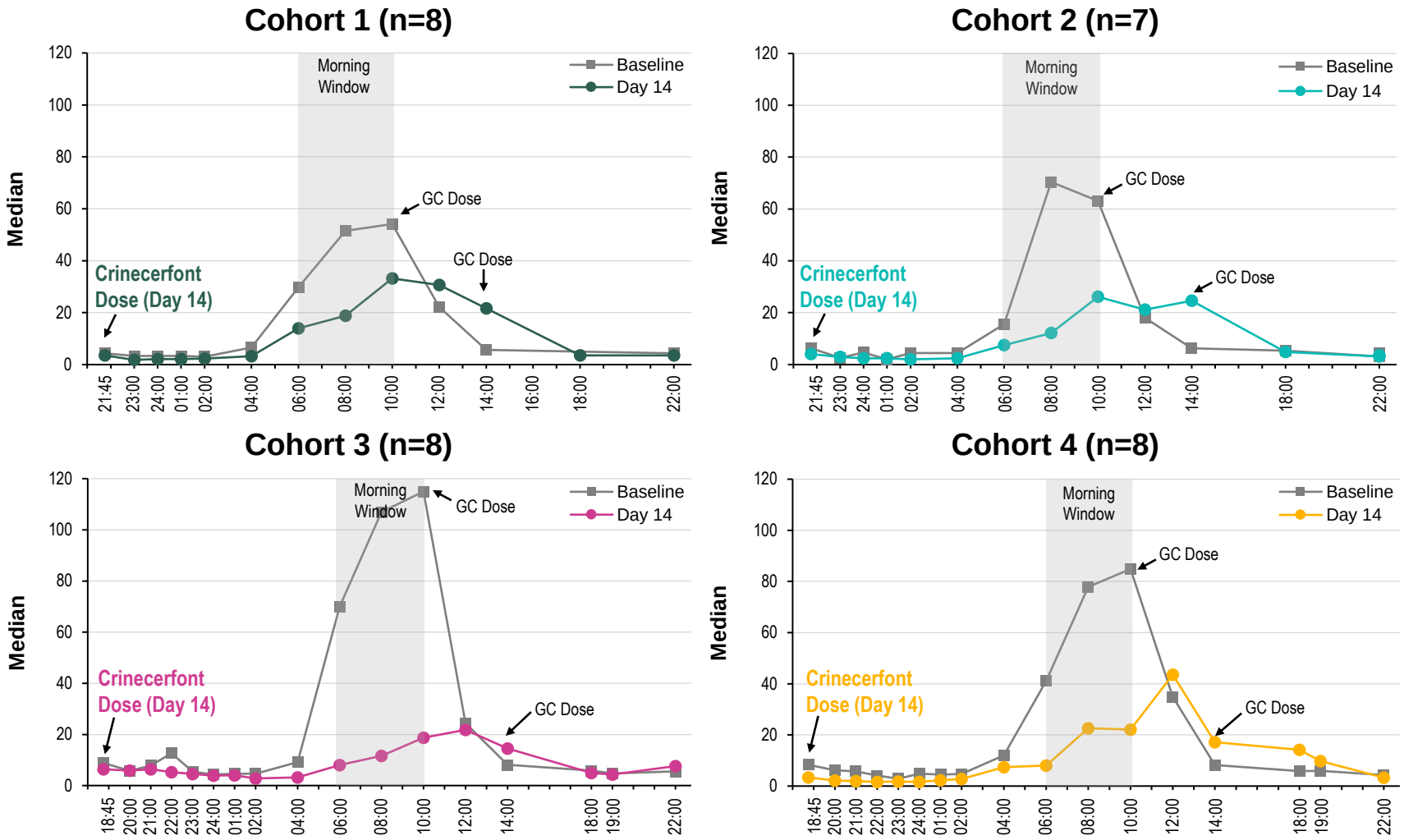
1. Auchus RJ, et al. *J Clin Endocrinol Metab*. 2022;107(3):801-812.

Adult Participants (eligible ages: 18 to 50 years)

CAHlibrate Study

Crinecerfont led to decreases in ACTH on Day 14*[1]

24-hour profiles for plasma ACTH, pmol/L



***Crinecerfont is investigational and not approved in any country.**

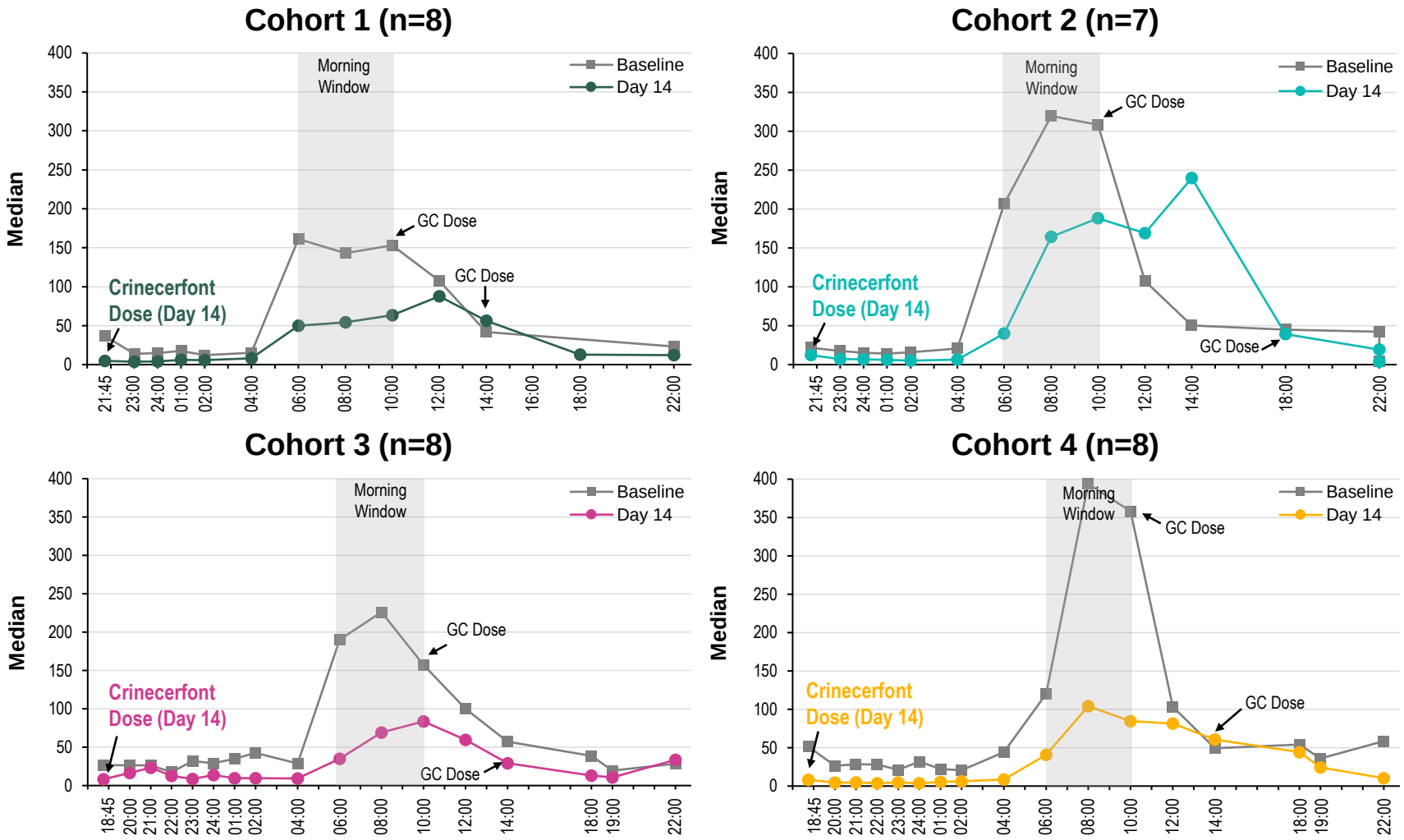
Twenty-four–hour profiles. For cohorts 1 and 2, crinecerfont dosing was at 22:00 on day 14; predose sampling was at 21:45. For cohorts 3 and 4, crinecerfont dosing was at 19:00 on day 14; predose sampling was at 18:45. ACTH, adrenocorticotropin; GC, glucocorticoid. 1. Auchus RJ, et al. *J Clin Endocrinol Metab*. 2022;107(3):801-812.

Adult Participants (eligible ages: 18 to 50 years)

CAHlibrate Study

Crinecerfont led to decreases in 17OHP on Day 14[1]*

24-hour profiles for serum 17OHP, nmol/L



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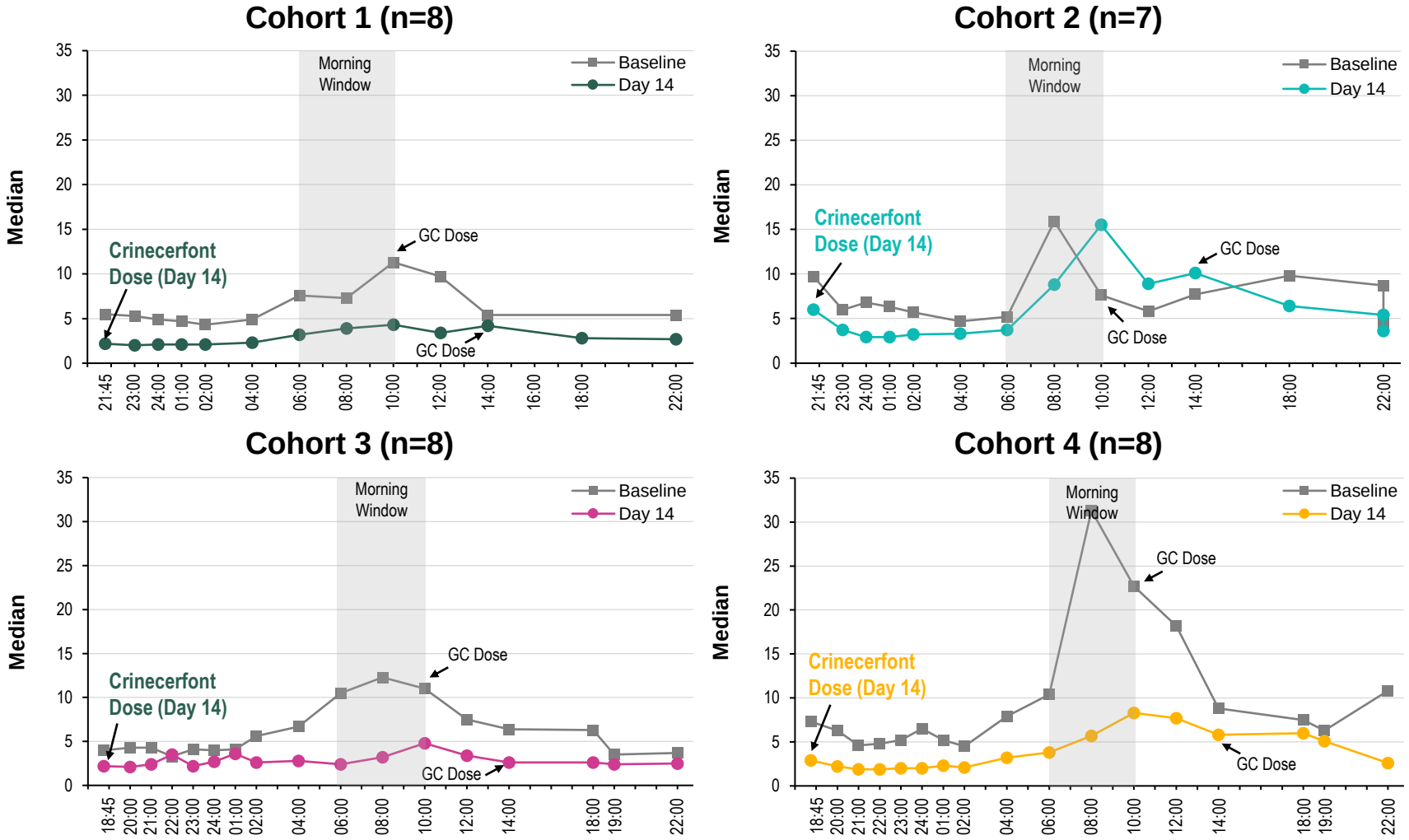
Twenty-four–hour profiles. For cohorts 1 and 2, crinecerfont dosing was at 22:00 on day 14; predose sampling was at 21:45. For cohorts 3 and 4, crinecerfont dosing was at 19:00 on day 14; predose sampling was at 18:45. 17OHP, 17-hydroxyprogesterone; GC, glucocorticoid. 1. Auchus RJ, et al. *J Clin Endocrinol Metab*. 2022;107(3):801-812.

Adult Participants (eligible ages: 18 to 50 years)

CAHlibrate Study

Crinecerfont led to decreases in A4 on Day 14[1]*

24-hour profiles for serum A4, nmol/L



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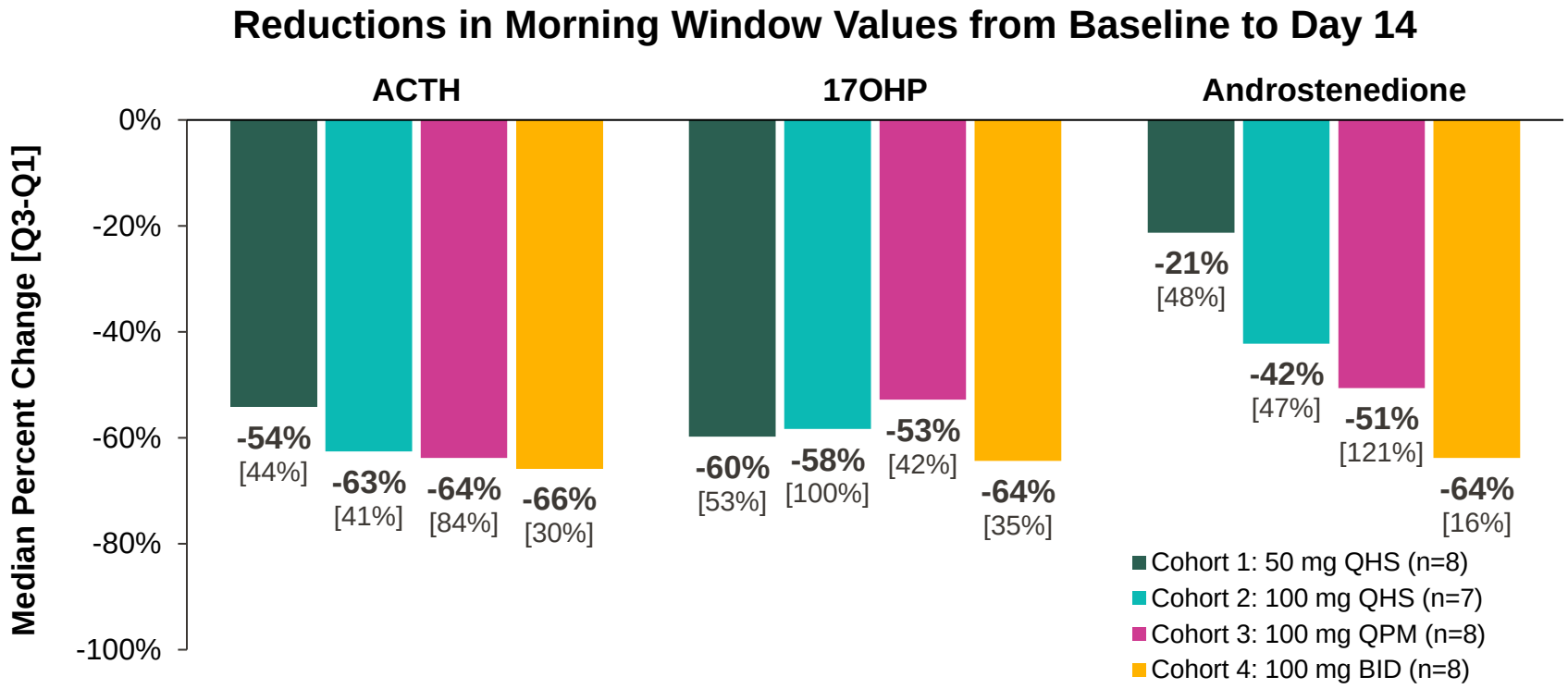
Twenty-four–hour profiles. For cohorts 1 and 2, crinecerfont dosing was at 22:00 on day 14; predose sampling was at 21:45. For cohorts 3 and 4, crinecerfont dosing was at 19:00 on day 14; predose sampling was at 18:45. A4, androstenedione; GC, glucocorticoid. 1. Auchus RJ, et al. *J Clin Endocrinol Metab*. 2022;107(3):801-812.

Adult Participants (eligible ages: 18 to 50 years)

CAHlibrate Study

Median percent changes from baseline[1]



- Across crinecerfont* dosing cohorts, median percent changes from baseline for ACTH and 17OHP ranged from -53% to -66%
- Dose-related decreases in A4 were observed

***Crinecerfont is investigational and not approved in any country.**

Median percent reductions from baseline to day 14 based on morning window values. Based on each participant's values from the morning window time points (06:00, 08:00, 10:00). The interquartile ranges (absolute value of Q3-Q1) for median percent reductions are shown in brackets.
17OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; BID, twice daily; QHS, once daily at bedtime; QPM, once daily in the evening.

1. Auchus RJ, et al. *J Clin Endocrinol Metab*. 2022;107(3):801-812.

Adult Participants (eligible ages: 18 to 50 years)

CAHlibrate Study

Safety[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 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)

- There were no safety concerns with respect to routine clinical laboratory values, vital signs, ECGs, or neuropsychiatric assessments

Crinecerfont is investigational and not approved in any country.

[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; ECG, electrocardiogram; 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.

1. Auchus RJ, et al. *J Clin Endocrinol Metab*. 2022;107(3):801-812.

Adult Participants (eligible ages: 18 to 50 years)

CAHlibrate Study

Limitations[1]

Wide range of adrenal steroid levels at baseline

Small number of participants in each crinecerfont* dosing cohort

Study was not powered to demonstrate statistical significance of a treatment effect or between-cohort differences, and data analyses were restricted to descriptive statistics

***Crinecerfont is investigational and not approved in any country.**

1. Auchus RJ, et al. *J Clin Endocrinol Metab*. 2022;107(3):801-812.

CAHlibrate™ – Post hoc Analyses

Auchus RJ, et al. Poster presentation at the ECE Congress; May 13-16, 2023; Istanbul, Turkey.

Adult Participants (eligible ages: 18 to 50 years)

CAHlibrate Study

Post hoc Analyses

- Post hoc analyses of the CAHlibrate data were conducted to assess whether baseline hormone concentrations (ACTH, 17OHP, and A4) and glucocorticoid (GC) dose correlated with **treatment response**[1]
- **Treatment Response:** Magnitude of change in ACTH, 17OHP, and A4 concentrations after 14 days of treatment with crinecerfont[1,*]
  - Hormone concentrations were assessed during the **morning window** and **24-hour period**
- **Sampling periods**[1]:
  - **Morning window:** average concentration of samples collected before the morning GC dose
    - 06:00, 08:00, and 10:00
  - **24-hour period:** average concentration over a full 24-hour sampling period
- **Post hoc Analyses:** Pearson correlation coefficients (r) were used to assess the strength and direction of the relationship between the variables[1]
  - Range: -1 (perfect negative correlation) to +1 (perfect positive correlation)
- **Safety assessments**: TEAEs, clinical laboratory tests, vital signs, physical examinations, electrocardiograms, Brief Psychiatric Rating Scale, Columbia-Suicide Severity Rating Scale[2]

***Crinecerfont is investigational and not approved in any country.**

17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone.

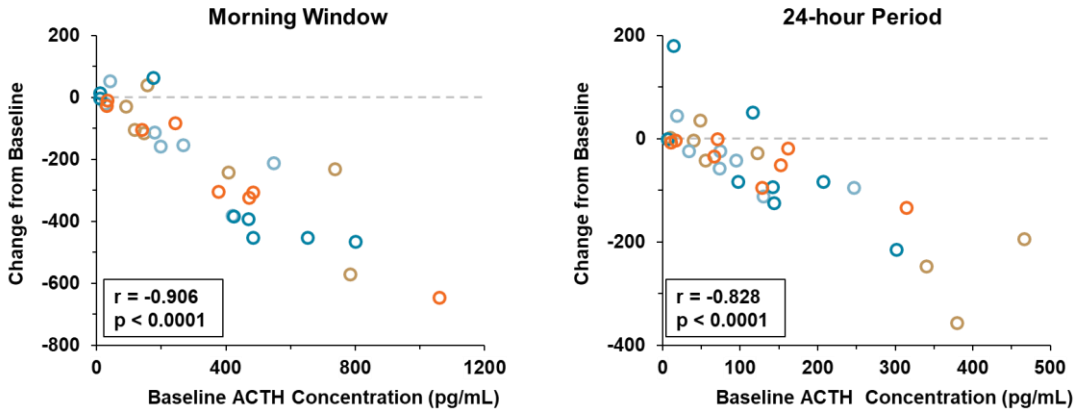
1. Auchus RJ, et al. Poster presentation at the ECE Congress; May 13-16, 2023; Istanbul, Turkey. 2. Auchus RJ, et al. *J Clin Endocrinol Metab*. 2022;107(3):801-812.

Adult Participants (eligible ages: 18 to 50 years)

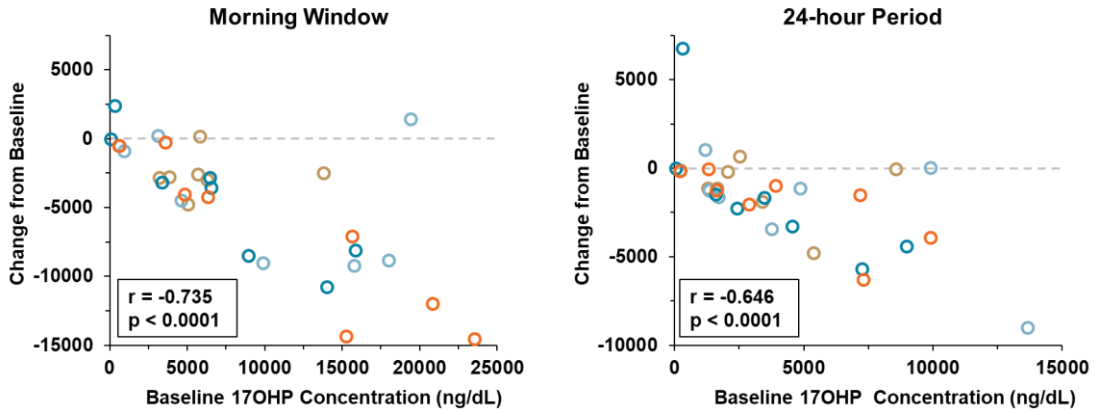
CAHlibrate Study

Post hoc Analyses[1]

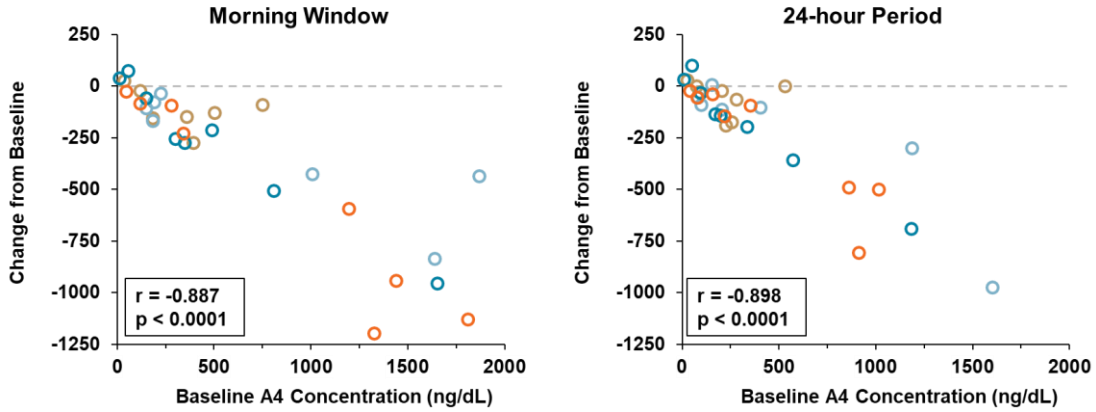
Paired Baseline ACTH Concentrations and Change from Baseline to Day 14



Paired Baseline 17OHP Concentrations and Change from Baseline to Day 14



Paired Baseline A4 Concentrations and Change from Baseline to Day 14



- Strong correlation between baseline ACTH, 17OHP, and A4 concentrations and change from baseline to Day 14 treatment with crinecerfont[1,*]

Cohort 1 Cohort 2 Cohort 3 Cohort 4

***Crinecerfont is investigational and not approved in any country.**

17OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone.

1. Auchus RJ, et al. Poster presentation at the ECE Congress; May 13-16, 2023; Istanbul, Turkey.

Adult Participants (eligible ages: 18 to 50 years)

CAHlibrate Study

Post hoc Analyses

Correlation coefficients for baseline GC dose and change from baseline to Day 14 treatment with crinecerfont* for ACTH, 17OHP, and A4[1]:

	Morning window		24-hour period	
	Correlation coefficient, r	p-value	Correlation coefficient, r	p-value
ACTH	0.146	0.4346	0.083	0.6566
17OHP	0.115	0.5365	0.215	0.2454
A4	-0.026	0.8884	-0.022	0.9055

- No correlation found between baseline GC dose and change from baseline to Day 14 for ACTH, 17OHP, or A4[1]

- The most common TEAEs (reported in ≥2 participants in the CAHlibrate study overall) were headache, upper respiratory tract infection, fatigue, contusion (bruising), insomnia, nasopharyngitis, pyrexia, and nausea[2]
- There were no safety concerns with respect to routine clinical laboratory values, vital signs, ECGs, or neuropsychiatric assessments[2]

***Crinecerfont is investigational and not approved in any country.**

17OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; ECG, electrocardiogram ;GC, glucocorticoid; TEAE, treatment emergent adverse event.

1. Auchus RJ, et al. Poster presentation at the ECE Congress; May 13-16, 2023; Istanbul, Turkey. 2. Auchus RJ, et al. *J Clin Endocrinol Metab*. 2022;107(3):801-812.

CAHlibrate™ Pediatric – Adolescent Phase 2, Open-Label Study

Adolescent Participants (eligible ages: 14 to 17 years)

CAHlibrate Pediatric Study

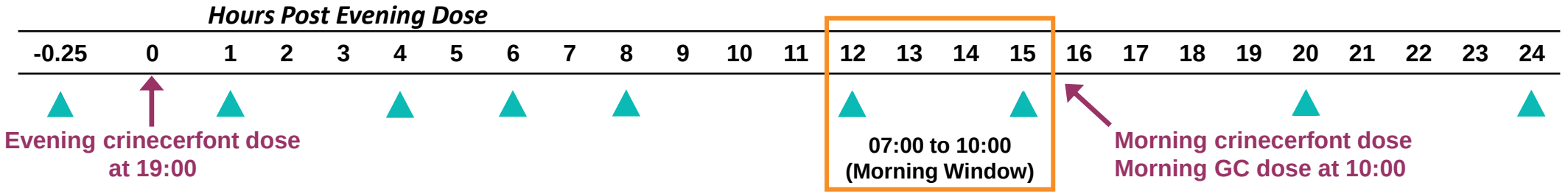
Study Design[1,2]

- Safety, tolerability, PK, and PD of crinecerfont* in adolescents (eligible ages: 14-17 years) with classic CAH
- **Primary endpoint:** number of participants with AEs following dosing of crinecerfont
- **PD assessment[a]:** 24-hour serial sampling for ACTH, 17-OHP, A4, and testosterone levels conducted at baseline and Day 14

Study Periods[a]

Screening	Baseline Assessment	Treatment Initiation	At-Home Dosing	End of Treatment	End of Follow-up
Days -27 to -8	Days -7 to -6	Days 1 to 2	Days 3 to 13	Days 14 to 15	Day 35

24-Hour Serial Blood Sampling Schedule[b]



***Crinecerfont is investigational and not approved in any country.**

[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.

A4, androstenedione; AE, adverse event; CAH, congenital adrenal hyperplasia; GC, glucocorticoid; PD, pharmacodynamic; PK, pharmacokinetic.

1. Newfield RS, et al. *J Clin Endocrinol Metab.* 2023:dgad270. 2. ClinicalTrials.gov Identifier: NCT04045145. Accessed June 22, 2023. https://clinicaltrials.gov/study/NCT04045145.

Adolescent Participants (eligible ages: 14 to 17 years)

CAHlibrate Pediatric Study

Inclusion and Exclusion Criteria[1,2]

Key inclusion criteria

- Female and male adolescents aged 14 to 17 years in good general health
- Medically confirmed diagnosis of classic CAH due to 21-OHD
- On a stable regimen of steroidal treatment for CAH that is expected to remain stable throughout the study
- **Screening levels** prior to morning GC dose:
  - 17-OHP ≥800 ng/dL
  - Cortisol <5 µg/dL
  - ACTH ≥20 pg/mL

Key exclusion criteria

- Known or suspected differential diagnosis of any of the other known forms of classic CAH
- Clinically significant unstable medical condition or chronic disease
- Clinically relevant laboratory abnormality (e.g., hematologic, coagulation, renal, liver enzymes)
- QTcF interval of >450 (males) or >470 (females) ms
- Risk of suicidal or violent behavior
- Known history of long QT syndrome or tachyarrhythmia

Crinecerfont is investigational and not approved in any country.

17-OHP, 17-hydroxyprogesterone; 21-OHD, 21-hydroxylase deficiency; ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; GC, glucocorticoid; QTcF, QT corrected for heart rate by Fridericia's cube root formula.

1. Newfield RS, et al. *J Clin Endocrinol Metab.* 2023:dgad270. 2. ClinicalTrials.gov Identifier: NCT04045145. Accessed June 22, 2023. https://clinicaltrials.gov/study/NCT04045145.

Adolescent Participants (eligible ages: 14 to 17 years)

CAHlibrate Pediatric Study

Demographic and Baseline Characteristics[1]

- **8 participants** were enrolled
  - 5 (62.5%) females; 3 (37.5%) males
  - Median (min, max) age: 15 (14, 16) years
  - Median (min, max) height: 165 (155, 175) cm
  - Median (min, max) BMI: 25 (19, 38) kg/m^2
  - 4 out of 5 female participants had reached menarche

- At baseline, **6 participants (75.0%) used HC alone** and **2 participants (25.0%) used prednisone alone**

- **Median (min, max) total daily GC dose: 16.2 (11.9, 18.5) mg/m^2/day** in HC equivalents[a]

Adrenal androgens, ACTH, and precursors at baseline, median (IQR)[b]		All participants (n=8)
ACTH	pg/mL pmol/L	226.2 (377.3) 49.8 (83.0)
17-OHP	ng/dL nmol/L	7703.7 (7123.5) 233.4 (215.8)
A4	ng/dL nmol/L	367.9 (393.3) 12.8 (13.7)
Testosterone (females)	ng/dL nmol/L	63.5 (270.0) 2.2 (9.37)
Testosterone (males)	ng/dL nmol/L	222.0 (140.0) 7.7 (4.9)

Crinecerfont is investigational and not approved in any country.

[a]HC equivalents were calculated as 1 mg prednisone = 4 mg HC. No participants were on dexamethasone.
[b]Based on the average of morning window values (07:00-10:00).
17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; BMI, body mass index; GC, glucocorticoid; HC, hydrocortisone; IQR, interquartile range.

1. Newfield RS, et al. *J Clin Endocrinol Metab.* 2023:dgad270.

Click for detailed baseline characteristics

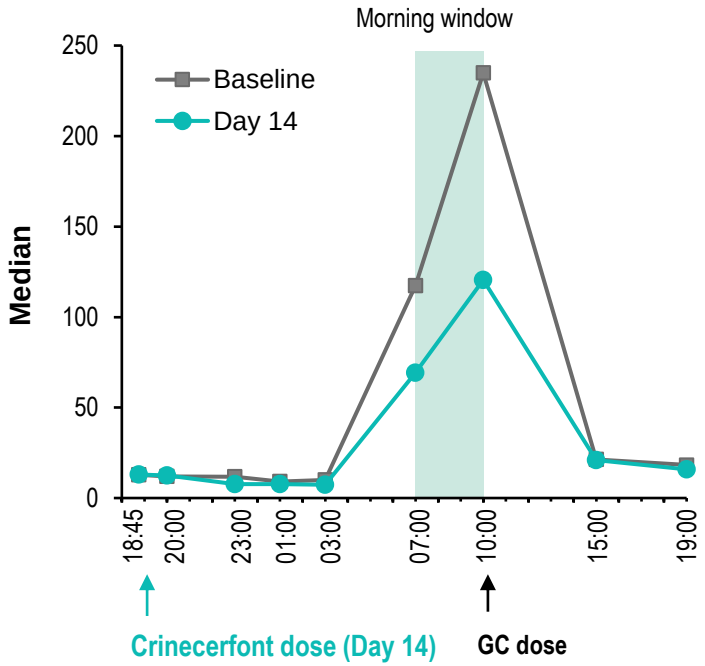
Adolescent Participants (eligible ages: 14 to 17 years)

CAHlibrate Pediatric Study

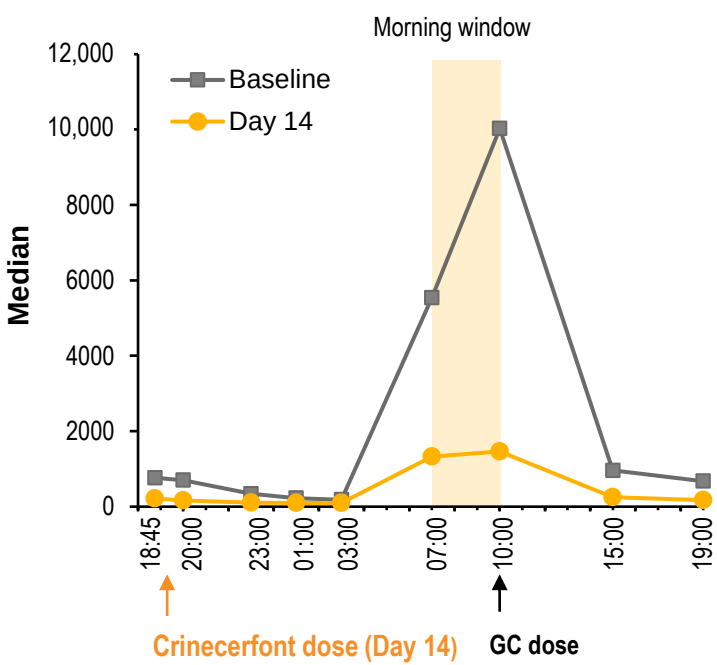
Crinecerfont Led to Clinically Meaningful Reductions in ACTH, 17-OHP, and A4, Especially During Morning Window[1]*

24-hour concentration profiles

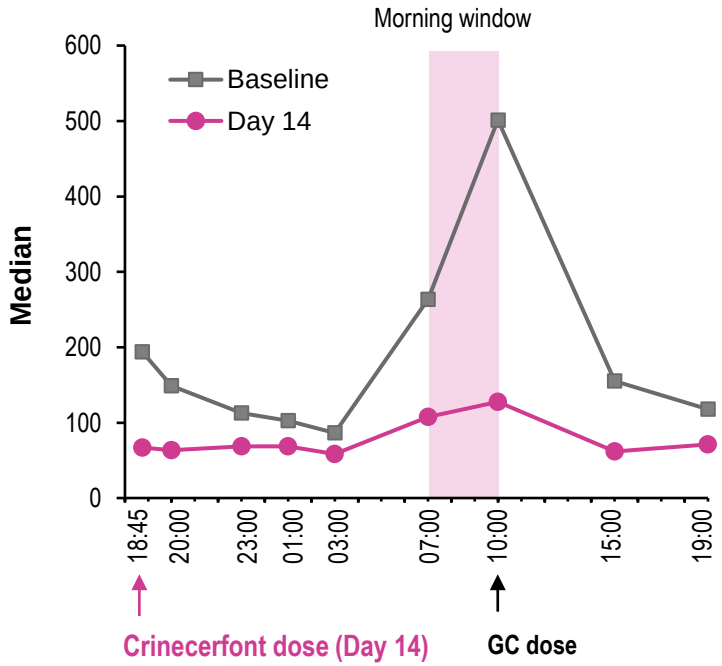
Plasma ACTH, pg/mL



Serum 17-OHP, ng/dL



Serum A4, ng/dL



***Crinecerfont is investigational and not approved in any country.**

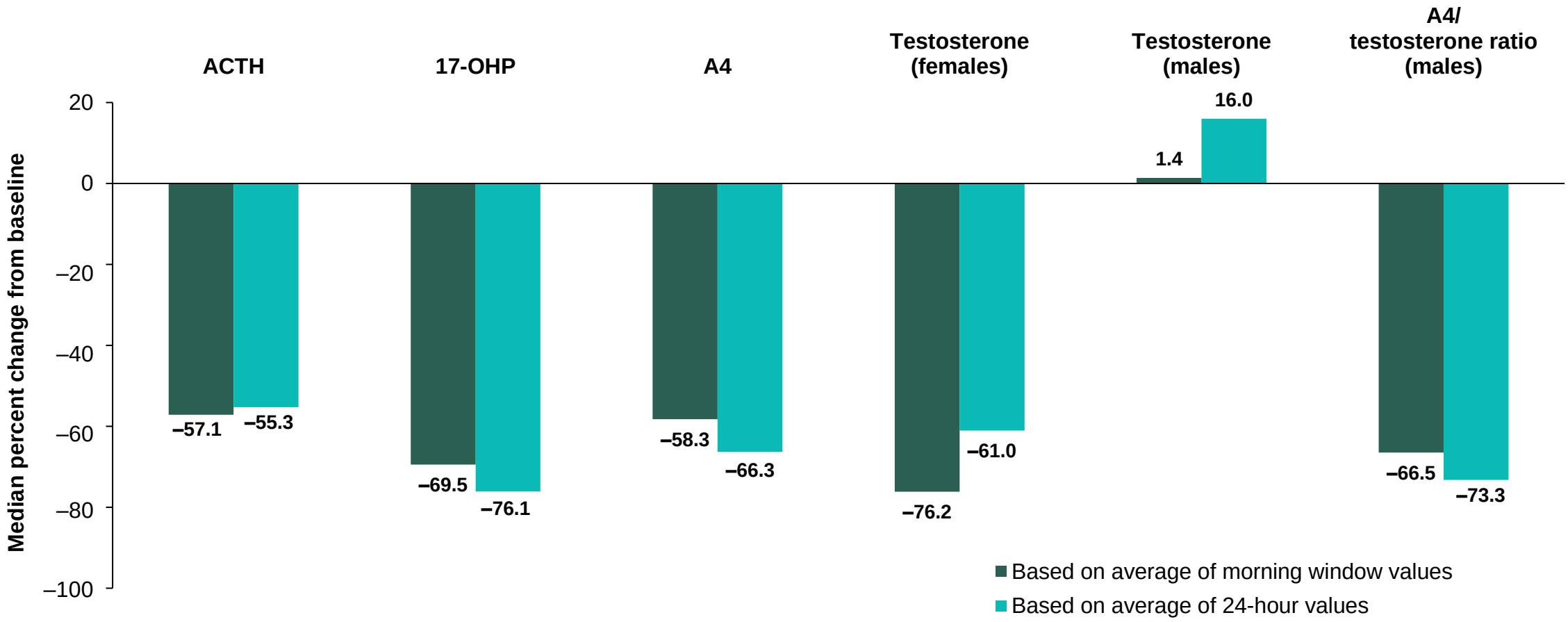
17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; GC, glucocorticoid.

1. Newfield RS, et al. *J Clin Endocrinol Metab*. 2023; dgad270.

Adolescent Participants (eligible ages: 14 to 17 years)

CAHlibrate Pediatric Study

≥50% Median Reductions in ACTH, 17-OHP, A4, Testosterone (Females), and A4/Testosterone Ratio (Males) With Crinecerfont[1,]*



***Crinecerfont is investigational and not approved in any country.**

17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone.

Newfield RS, et al. Oral presentation at: ENDO; June 11-14, 2022; Atlanta, GA.

Adolescent Participants (eligible ages: 14 to 17 years)

CAHlibrate Pediatric Study

A Majority of Participants Achieved ≥50% Reduction From Baseline in ACTH, 17OHP, A4, and (Female) Testosterone After 14 Days of Crinecerfont Treatment[1,a]*

Parameter	Participants With ≥50% Reduction From Baseline, n/N (%)
ACTH	5/8 (62.5)
17-hydroxyprogesterone	6/8 (75.0)
A4	4/8 (50.0)
Testosterone (females)	3/5 (60.0)

- 66.7% (2/3) of male participants achieved a response for A4/testosterone ratio (A4/T), defined as A4/T ≥0.5 at baseline and A4/T <0.5 at Day 14[a]

***Crinecerfont is investigational and not approved in any country.**

[a]Based on average of morning window values; 17OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone.

1. Newfield RS, et al. *J Clin Endocrinol Metab*. 2023; dgad270.

Adolescent Participants (eligible ages: 14 to 17 years)

CAHlibrate Pediatric Study: SAFETY

Crinecerfont Was Generally Well Tolerated, With No Serious TEAEs or Discontinuations Due to TEAEs[1]*

TEAE summary, n (%)	All participants (n=8)
Any TEAE	6 (75)
Any serious TEAE	0
Any TEAE leading to discontinuation	0
Any TEAE resulting in death	0

- All TEAEs were mild
- No safety concerns were identified based on routine laboratory tests, vital signs, ECGs, or neuropsychiatric assessments

All TEAEs by MedDRA preferred term, n (%)	All participants (n=8)
Headache[a]	2 (25)
Arthropod sting	1 (13)
Blepharospasm	1 (13)
Dermatitis contact	1 (13)
Dizziness[a]	1 (13)
Frequent bowel movements	1 (13)
Gastritis	1 (13)
Myalgia	1 (13)
Nasopharyngitis	1 (13)
Pyrexia	1 (13)
Vomiting	1 (13)

***Crinecerfont is investigational and not approved in any country.**

[a]Mild headache and dizziness (each in 1 participant) were judged by the investigator as "possibly" related to study drug.

ECG, electrocardiogram; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

1. Newfield RS, et al. *J Clin Endocrinol Metab.* 2023:dgad270.

Adolescent Participants (eligible ages: 14 to 17 years)

CAHlibrate Pediatric Study

Limitations[1]

Small number of participants

Short-term, open-label treatment without a placebo arm

Crinecerfont is investigational and not approved in any country.

1. Newfield RS, et al. *J Clin Endocrinol Metab*. 2023:dgad270.

CAHlibrate™ Pediatric – Post hoc Analyses

Newfield, RS, et al. Oral presentation at the ESPE Congress; September 21-23, 2023; The Hague, Netherlands.

Adolescent Participants (eligible ages: 14 to 17 years)

CAHlibrate Pediatric Study

Post hoc Analyses

- Post hoc analyses of the CAHlibrate Pediatric study data were conducted to assess whether baseline hormone concentrations (ACTH, 17OHP, and A4) and GC dose correlated with **treatment response**[1]
- **Treatment Response**: Magnitude of change in ACTH, 17OHP, and A4 concentrations after 14 days of treatment with crinecerfont[1,*]
  - Hormone concentrations were assessed during the **morning window** and **24-hour period**
- **Sampling periods**[1]:
  - **Morning window:** average concentration of samples collected at 07:00 and 10:00, before the morning GC dose (which was delayed until 10:00 on the days of sampling)
  - **24-hour period:** average concentration over a full 24-hour sampling period
- **Post hoc Analyses**: Pearson correlation coefficients (r) were used to assess the strength and direction of the relationship between the variables[1]
  - Range: -1 (perfect negative correlation) to +1 (perfect positive correlation)
- **Safety assessments**: TEAEs, clinical laboratory tests, vital signs, physical examinations, electrocardiograms, Brief Psychiatric Rating Scale for Children, Columbia-Suicide Severity Rating Scale[2]

***Crinecerfont is investigational and not approved in any country.**

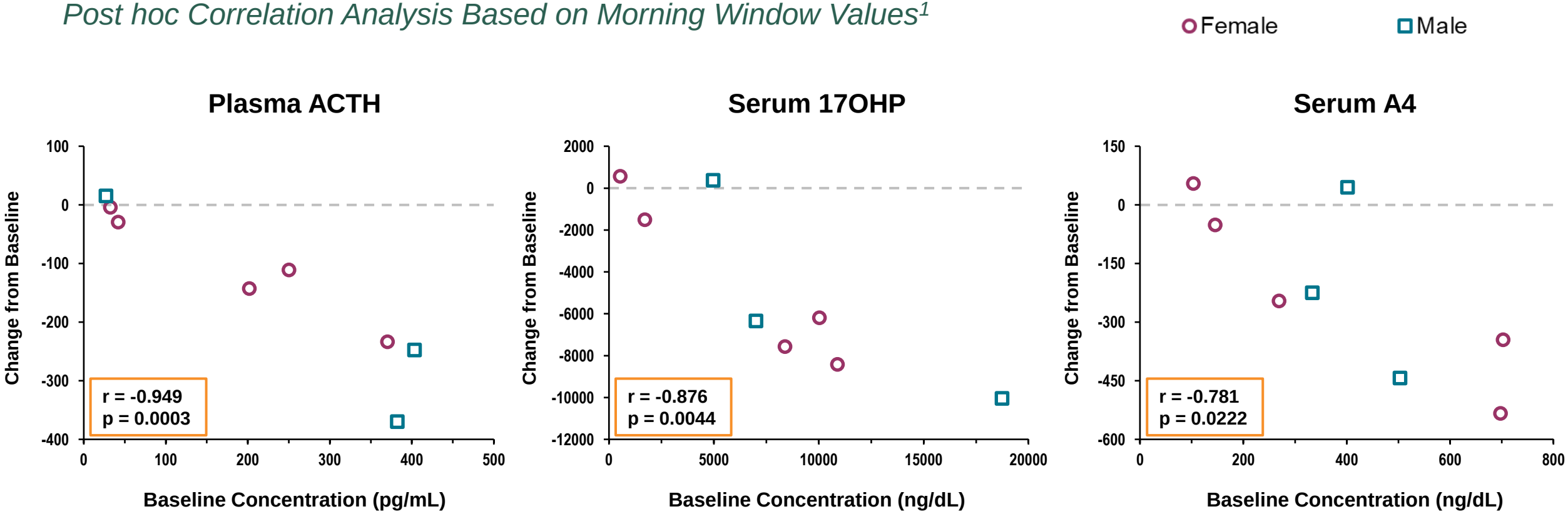
17-OHP, 17-hydroxyprogesterone; A4, androstenedione; GC, glucocorticoid; ACTH, adrenocorticotropic hormone; TEAE, treatment-emergent adverse event.

1. Newfield, RS, et al. Oral presentation at the ESPE Congress; September 21-23, 2023; The Hague, Netherlands. 2. Newfield RS, et al. *J Clin Endocrinol Metab*. 2023:dgad270.

Adolescent Participants (eligible ages: 14 to 17 years)

CAHlibrate Pediatric Study

Post hoc Correlation Analysis Based on Morning Window Values[1]



- Strong correlation between baseline ACTH, 17OHP, and A4 concentrations and change from baseline to Day 14 for morning window values and 24-hour average values of ACTH, 17OHP, and A4

Click for Post hoc correlation analysis based on 24-hour average values

Crinecerfont is investigational and not approved in any country.

17OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; GC, glucocorticoid.

1. Newfield, RS, et al. Oral presentation at the ESPE Congress; September 21-23, 2023; The Hague, Netherlands.

Adolescent Participants (eligible ages: 14 to 17 years)

CAHlibrate Pediatric Study

Post hoc Analyses

Correlation coefficients for baseline GC dose and change from baseline to Day 14 treatment with crinecerfont* for ACTH, 17OHP, and A4[1]:

	Morning window		24-hour period	
	Correlation coefficient, r	p-value	Correlation coefficient, r	p-value
ACTH	-0.057	0.8926	-0.177	0.6744
17OHP	0.007	0.9865	-0.038	0.9286
A4	-0.286	0.4919	-0.290	0.4859

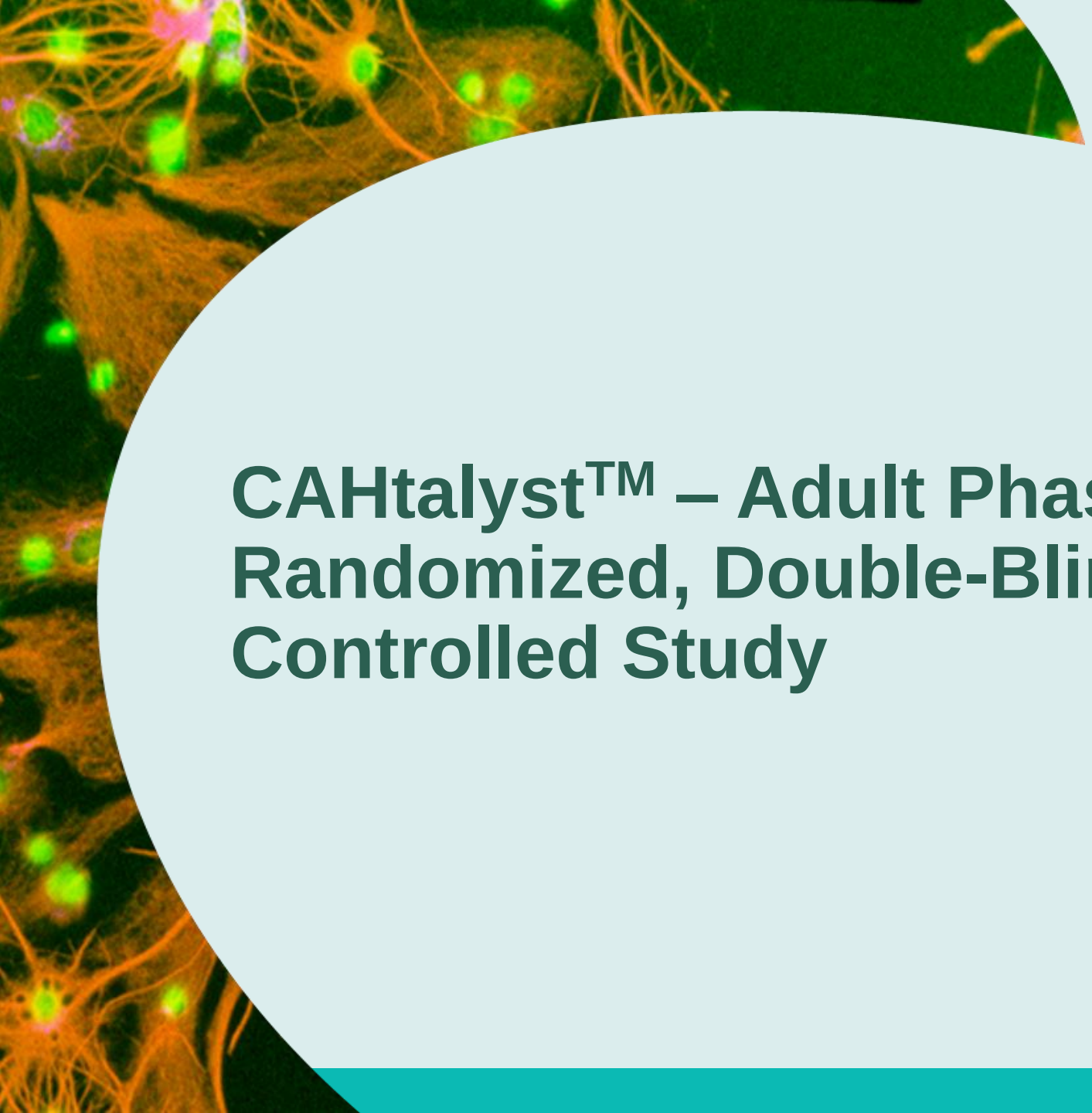
- No correlation found between baseline GC dose and change from baseline to Day 14 for ACTH, 17OHP, or A4[1]

- All treatment-emergent adverse events reported in the CAHlibrate Pediatric Study were assessed as mild, with two adverse events (headache and dizziness) assessed as possibly related by the study investigator[2]
- There were no safety concerns based on routine laboratory tests, vital signs, electrocardiograms, or neuropsychiatric assessments[2]

***Crinecerfont is investigational and not approved in any country.**

17OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; GC, glucocorticoid.

1. Newfield, RS, et al. Oral presentation at the ESPE Congress; September 21-23, 2023; The Hague, Netherlands. 2. Newfield RS, et al. *J Clin Endocrinol Metab*. 2023:dgad270.

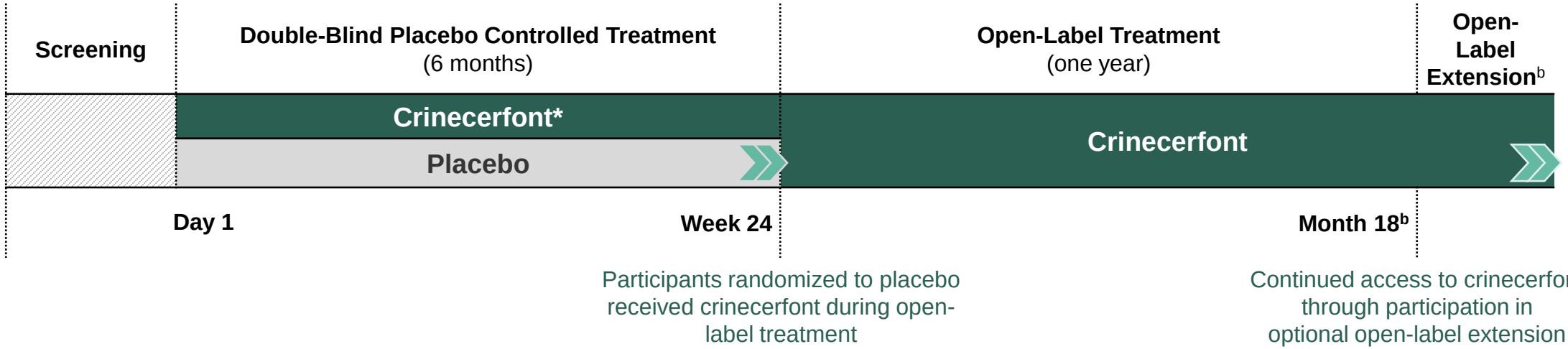


CAHtalyst™ – Adult Phase 3, Randomized, Double-Blind, Placebo-Controlled Study

Adult Participants (eligible ages: ≥18 years)

CAHtalyst Study

Study Design[1a]



Objective

Evaluate the efficacy, safety and tolerability of crinecerfont in adults with classic CAH

Primary Endpoint

Mean percent change from baseline in GC daily dose[c] at Week 24 while maintaining androgen control

***Crinecerfont is investigational and not approved in any country.**

[a]Enrollment completed; [b]The duration of participation in the study is approximately 20 months for the core study and will be a variable amount of time per participant for the open-label extension; [c]Expressed in hydrocortisone equivalents adjusted for body surface area; CAH, congenital adrenal hyperplasia; GC, glucocorticoid.

1. ClinicalTrials.gov Identifier: NCT04490915. Accessed September 12, 2023. https://clinicaltrials.gov/study/NCT04490915.

Adult Participants (eligible ages: ≥18 years)

CAHtalyst Study

Inclusion and Exclusion Criteria[1]

Key inclusion criteria

- Female and male adult participants, 18 years and older
- Have a medically confirmed diagnosis of classic 21-hydroxylase deficiency CAH
- Be on a stable regimen of steroidal treatment for CAH
- Participants of childbearing potential must agree to use hormonal or 2 forms of nonhormonal contraception or other highly effective contraception during the study

Key exclusion criteria

- Have a diagnosis of any of the other known forms of classic CAH
- Have a history of bilateral adrenalectomy, hypopituitarism, or other condition requiring chronic glucocorticoid therapy
- Have a clinically significant unstable medical condition or chronic disease other than CAH
- Have a history of cancer, unless considered to be cured
- Have a known history of clinically significant arrhythmia or abnormalities on ECG
- Have a known hypersensitivity to any corticotropin-releasing factor antagonists
- Have current substance dependence, or current substance (drug) or alcohol abuse
- Have had a blood loss ≥550 mL or donated blood or blood products within 8 weeks prior to the study

Crinecerfont is investigational and not approved in any country.

CAH, congenital adrenal hyperplasia; ECG, electrocardiogram.

1. ClinicalTrials.gov Identifier: NCT04490915. Accessed September 12, 2023. https://clinicaltrials.gov/study/NCT04490915.

Adult Participants (eligible ages: ≥18 years)

CAHtalyst Study

Study Design and Outcome Measures[1,2]

- Phase 3 study to evaluate the efficacy, safety, and tolerability of crinecerfont* vs placebo at 24 weeks in adult participants (eligible ages: ≥18 years) with classic CAH due to 21-hydroxylase deficiency
  - 182 adult participants completed enrollment
  - 6-month randomized, double-blind, placebo-controlled period, followed by a 12-month open-label treatment period with crinecerfont
  - Crinecerfont or placebo capsule administered orally, twice daily
  - Duration of participation is approximately 20 months
  - Participants have the opportunity to continue to receive crinecerfont as part of an open-label extension
- Primary outcome measure: Mean percent change from baseline in glucocorticoid daily dose[a] while maintaining androgen control at Week 24
- Secondary outcome measures:
  - Change from baseline in serum A4 at Week 4
  - Percentage of participants achieving a reduction to a physiological glucocorticoid dose[a] while maintaining androgen control at Week 24
  - Change from baseline in homeostatic model assessment of insulin resistance index at Week 24
  - Change from baseline in body weight at Week 24
  - Change from baseline in fat mass at Week 24

***Crinecerfont is investigational and not approved in any country.**

[a]In hydrocortisone dose equivalents adjusted for body surface area; A4, androstenedione.

1. ClinicalTrials.gov Identifier: NCT04490915. Accessed September 12, 2023. https://clinicaltrials.gov/study/NCT04490915. Neurocrine.com. (2023). Neurocrine Biosciences Announces Positive Top-Line Data from Phase 3 Study of Crinecerfont in Adults for the Treatment of Congenital Adrenal Hyperplasia (CAH) [Press release]. Retrieved from: https://neurocrine.gcs-web.com/news-releases/news-release-details/neurocrine-biosciences-announces-positive-top-line-data-phase-3. Accessed September 12, 2023.

Adult Participants (eligible ages: ≥18 years)

CAHtalyst Study

Baseline characteristics from the double-blind, placebo-controlled period[1,2]

Baseline Characteristics	Participants (N = 182)
Male / Female (Proportion of total participants)	51% Male 49% Female
Average age (age ranges)	31 Years Old (18 – 58 Years Old)
Average baseline glucocorticoid dose[a]	32 mg/day (18 mg/m^2/day)
Average baseline A4 level[b]	620 ng/dL
Body Mass Index (BMI)	47% Obese (BMI ≥ 30 kg/m^2)
Percent of participants completing the 24-week placebo-controlled treatment period	>95%

Crinecerfont is investigational and not approved in any country.

[a]In hydrocortisone equivalents. [b]Pre-glucocorticoid dose. A4, androstenedione.

1. Neurocrine.com. (2023). Neurocrine Biosciences Announces Phase 3 Pediatric Study Results of Crinecerfont in Children and Adolescents for the Treatment of Congenital Adrenal Hyperplasia Met Primary and Key Secondary Endpoints [Supplemental Materials]. Retrieved from https://www.neurocrine.com//assets/2023/10/Crinecerfont-CAHtalyst-Studies-Supplemental-Materials-10.05.23_Final-2.pdf. Accessed October 5, 2023. 2. Neurocrine.com. (2023). Neurocrine Biosciences 2023 Analyst Day. [Presentation]. https://www.neurocrine.com//assets/2023/12/NBIX-Analyst-Day_120523_Static-For-Posting-on-NBIX-Website.pdf. Accessed December 5, 2023.

Adult Participants (eligible ages: ≥18 years)

CAHtalyst Study

Topline results from the double-blind, placebo-controlled period[1,2,a]

Primary Endpoint:

- Treatment with crinecerfont* resulted in a statistically significant percent reduction in daily GC dose[b] at Week 24 vs. placebo while maintaining androgen control (p-value <0.0001)

Key Secondary Endpoint: *Percent of Participants Achieving a Glucocorticoid Daily Dose[b] ≤ 11 mg/m²/day While Maintaining Androgen Control at Week 24*	
	(n=182)
Participants receiving crinecerfont	63%
Participants receiving placebo	18%
Placebo-Adjusted Difference	45%
P-value	<0.0001

***Crinecerfont is investigational and not approved in any country.**

[a]The CAHtalyst open-label study period is ongoing; [b]In hydrocortisone dose equivalents adjusted for body surface area; GC, glucocorticoid.

1. Neurocrine.com. (2023). Neurocrine Biosciences Announces Positive Top-Line Data from Phase 3 Study of Crinecerfont in Adults for the Treatment of Congenital Adrenal Hyperplasia (CAH) [Press release]. Retrieved from: https://neurocrine.gcs-web.com/news-releases/news-release-details/neurocrine-biosciences-announces-positive-top-line-data-phase-3. Accessed September 12, 2023. 2. Neurocrine.com. (2023). Neurocrine Biosciences Announces Phase 3 Pediatric Study Results of Crinecerfont in Children and Adolescents for the Treatment of Congenital Adrenal Hyperplasia Met Primary and Key Secondary Endpoints [Supplemental Materials]. Retrieved fromhttps://www.neurocrine.com//assets/2023/10/Crinecerfont-CAHtalyst-Studies-Supplemental-Materials-10.05.23_Final-2.pdf. Accessed October 5, 2023.

Adult Participants (eligible ages: ≥18 years)

CAHtalyst Study

Topline results from the double-blind, placebo-controlled period[1,2,a]

Key Secondary Endpoint:

- Treatment with crinecerfont* resulted in a statistically significant decrease in serum A4 from baseline at Week 4 vs. placebo following a GC stable period (p-value <0.0001)

Percent Change[b] in A4 at Week 4 *(Following GC stable period)*	
	(n=182)
Participants receiving crinecerfont	-45%
Participants receiving placebo	+21%
Placebo-Adjusted Difference	-66%
P-value	< 0.0001

***Crinecerfont is investigational and not approved in any country.**

[a]The CAHtalyst open-label study period is ongoing; [b]Adjusted for baseline level, treatment group, stratification factors; A4, androstenedione. GC, glucocorticoid.

1. Neurocrine.com. (2023). Neurocrine Biosciences Announces Positive Top-Line Data from Phase 3 Study of Crinecerfont in Adults for the Treatment of Congenital Adrenal Hyperplasia (CAH) [Press release]. Retrieved from: https://neurocrine.gcs-web.com/news-releases/news-release-details/neurocrine-biosciences-announces-positive-top-line-data-phase-3. Accessed September 12, 2023. 2. Neurocrine.com. (2023). Neurocrine Biosciences 2023 Analyst Day. [Presentation]. https://www.neurocrine.com//assets/2023/12/NBIX-Analyst-Day_120523_Static-For-Posting-on-NBIX-Website.pdf. Accessed December 5, 2023.

Adult Participants (eligible ages: ≥18 years)

CAHtalyst Study

Safety results from the double-blind, placebo-controlled period[1,2,a]

- Crinecerfont* was generally well tolerated in adult participants
- Few serious adverse events, none assessed as related to crinecerfont
- Most common adverse events: fatigue, headache, and coronavirus infection
- No safety concerns related to adrenal crisis

***Crinecerfont is investigational and not approved in any country.**

[a]The CAHtalyst open-label study period is ongoing.

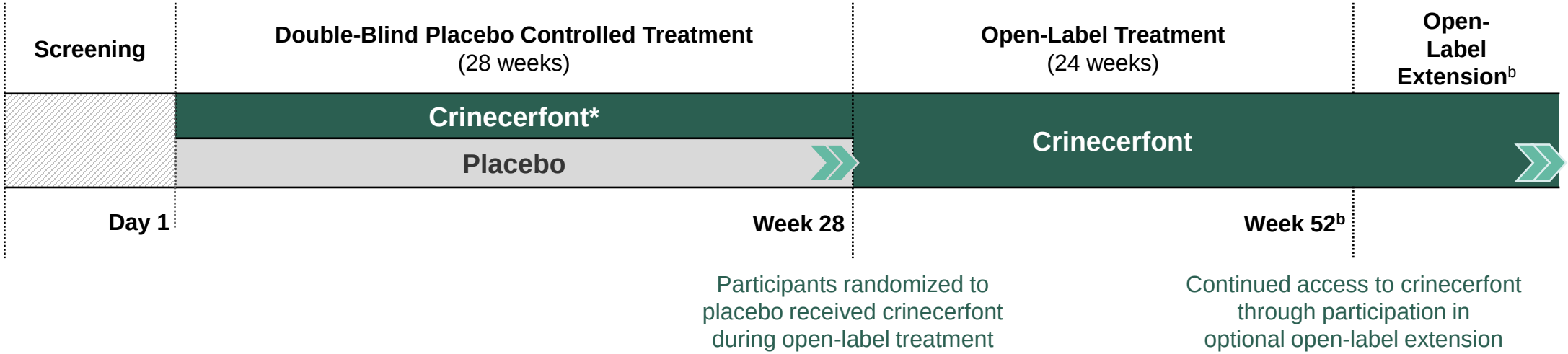
1. Neurocrine.com. (2023). Neurocrine Biosciences Announces Positive Top-Line Data from Phase 3 Study of Crinecerfont in Adults for the Treatment of Congenital Adrenal Hyperplasia (CAH) [Press release]. Retrieved from: https://neurocrine.gcs-web.com/news-releases/news-release-details/neurocrine-biosciences-announces-positive-top-line-data-phase-3. Accessed September 12, 2023. 2. Neurocrine.com. (2023). Neurocrine Biosciences Announces Phase 3 Pediatric Study Results of Crinecerfont in Children and Adolescents for the Treatment of Congenital Adrenal Hyperplasia Met Primary and Key Secondary Endpoints [Supplemental Materials]. Retrieved fromhttps://www.neurocrine.com//assets/2023/10/Crinecerfont-CAHtalyst-Studies-Supplemental-Materials-10.05.23_Final-2.pdf. Accessed October 5, 2023.

CAHtalyst™ Pediatric – Phase 3, Randomized, Double-Blind, Placebo-Controlled Study

Pediatric and adolescent participants (eligible ages: 2 to 17 years)

CAHtalyst Pediatric Study

Study Design[1a]



Objective

Evaluate the efficacy, safety and tolerability of crinecerfont in children and adolescents with classic CAH

Primary Endpoint

Change from baseline in serum androstenedione at Week 4

***Crinecerfont is investigational and not approved in any country.**

[a]Enrollment completed; [b]The duration of participation in the study is approximately 14 months for the core study and will be a variable amount of time per participant for the open-label extension; CAH, congenital adrenal hyperplasia.

1. ClinicalTrials.gov Identifier: NCT04806451. Accessed October 5, 2023. https://clinicaltrials.gov/study/NCT04806451.

Pediatric and adolescent participants (eligible ages: 2 to 17 years)

CAHtalyst Pediatric Study

Inclusion and Exclusion Criteria[1]

Key inclusion criteria

- Female and male pediatric and adolescent participants, 2 to 17 years of age
- Be willing and able to adhere to study procedures, including all requirements at the study center, and return for the follow-up visit
- Have a medically confirmed diagnosis of classic 21-hydroxylase deficiency CAH
- Be on a stable regimen of steroidal treatment for CAH
- Have elevated androgen levels
- Participants of childbearing potential must be abstinent or agree to use appropriate birth control during the study

Key exclusion criteria

- Have a diagnosis of any of the other forms of classic CAH
- Have a history of bilateral adrenalectomy, hypopituitarism, or other condition requiring chronic glucocorticoid therapy
- Have a clinically significant unstable medical condition or chronic disease other than CAH
- Have a history of cancer, unless considered to be cured
- Have a known history of clinically significant arrhythmia or abnormalities on ECG
- Have a known hypersensitivity to any corticotropin-releasing factor antagonist
- Have current substance dependence or substance (drug) or alcohol abuse
- Have had a significant blood loss or donated blood or blood products within 8 weeks prior to the study

Crinecerfont is investigational and not approved in any country.

CAH, congenital adrenal hyperplasia; ECG, electrocardiogram.

1. ClinicalTrials.gov Identifier: NCT04806451. Accessed October 5, 2023. https://clinicaltrials.gov/study/NCT04806451.

Pediatric and adolescent participants (eligible ages: 2 to 17 years)

CAHtalyst Pediatric Study

Study Design and Outcome Measures[1,2]

- Phase 3 study to evaluate the efficacy, safety, and tolerability of crinecerfont* vs placebo administered for 28 weeks in pediatric and adolescent participants (eligible ages: 2 to 17 years) with classic CAH due to 21-hydroxylase deficiency
  - 103 pediatric and adolescent participants completed enrollment
  - 28-week randomized, double-blind, placebo-controlled period, followed by 24 weeks of open-label treatment with crinecerfont
  - Crinecerfont or placebo administered orally, twice daily[a]
  - Duration of participation is approximately 14 months
  - Participants have the opportunity to continue to receive crinecerfont as part of an open-label extension
- Primary outcome measure: Change from baseline in serum A4 at Week 4
- Secondary outcome measures:
  - Change from baseline in serum 17-OHP at Week 4
  - Percent change from baseline in glucocorticoid daily dose[b] while maintaining androgen control at Week 28
  - Achievement of a reduction to a physiological GC daily dose[b] while maintaining androgen control at Week 28
  - Change from baseline in body mass index at Week 28
  - Change from baseline in salivary 17-OHP at Week 28
  - Change in bone age advancement at Week 28
  - Change from baseline in predicted adult height at Week 52

***Crinecerfont is investigational and not approved in any country.**

[a]Crinecerfont and placebo administered as solution or capsule; [b]In hydrocortisone dose equivalents adjusted for body surface area; 17-OHP, 17-hydroxyprogesterone; A4, androstenedione.

1. ClinicalTrials.gov Identifier: NCT04806451. Accessed October 5, 2023. https://clinicaltrials.gov/study/NCT04806451. 2. Neurocrine.com. (2023). Neurocrine Biosciences Announces Phase 3 Pediatric Study Results of Crinecerfont in Children and Adolescents for the Treatment of Congenital Adrenal Hyperplasia Met Primary and Key Secondary Endpoints [Press release]. Retrieved from: https://neurocrine.gcs-web.com/news-releases/news-release-details/neurocrine-biosciences-announces-phase-3-pediatric-study-results. Accessed October 5, 2023.

Pediatric and adolescent participants (eligible ages: 2 to 17 years)

CAHtalyst Pediatric Study

Baseline characteristics from the double-blind, placebo-controlled period[1,2]

Baseline Characteristics	Participants (n = 103)
Male / Female (Proportion of total participants)	52% Male 48% Female
Average age (age ranges)	12 Years Old (4 – 17 Years Old)
Average baseline glucocorticoid dose[a]	16 mg/m^2/day
Average baseline A4 level[b]	431 ng/dL
Body Mass Index (BMI)	58% ≥ 85th Percentile (Overweight or obese)
Percent of participants completing the 28-week placebo-controlled treatment period	>95%

Crinecerfont is investigational and not approved in any country.

[a]In hydrocortisone equivalents. [b]Pre-glucocorticoid dose. A4, androstenedione.

1. Neurocrine.com. (2023). Neurocrine Biosciences Announces Phase 3 Pediatric Study Results of Crinecerfont in Children and Adolescents for the Treatment of Congenital Adrenal Hyperplasia Met Primary and Key Secondary Endpoints [Supplemental Materials]. Retrieved from https://www.neurocrine.com//assets/2023/10/Crinecerfont-CAHtalyst-Studies-Supplemental-Materials-10.05.23_Final-2.pdf. Accessed October 5, 2023. 2. Neurocrine.com. (2023). Neurocrine Biosciences 2023 Analyst Day. [Presentation]. https://www.neurocrine.com//assets/2023/12/NBIX-Analyst-Day_120523_Static-For-Posting-on-NBIX-Website.pdf. Accessed December 5, 2023.

Pediatric and adolescent participants (eligible ages: 2 to 17 years)

CAHtalyst Pediatric Study

Topline results from the double-blind, placebo-controlled period[1,2,a]

Primary Endpoint:

- Treatment with crinecerfont* resulted in a statistically significant decrease in serum A4 from baseline at Week 4 vs. placebo following a GC stable period (p = 0.0002)

Percent Change[b] **in A4 at Week 4** *(Following GC stable period)*	
	(n=103)
Participants receiving crinecerfont	-54%
Participants receiving placebo	+33%
Placebo-adjusted difference	-86%
P-value	< 0.0001

Key Secondary Endpoint:

- Statistically significant decrease in serum 17-OHP from baseline at Week 4 vs. placebo (p < 0.0001)

***Crinecerfont is investigational and not approved in any country.**

[a]The CAHtalyst Pediatric open-label study period is ongoing; [b]Adjusted for baseline level, treatment group, stratification factors; 17-OHP,17-hydroxyprogesterone. A4, androstenedione. GC, glucocorticoid.

1. Neurocrine.com. (2023). Neurocrine Biosciences Announces Phase 3 Pediatric Study Results of Crinecerfont in Children and Adolescents for the Treatment of Congenital Adrenal Hyperplasia Met Primary and Key Secondary Endpoints [Press release]. Retrieved from: https://neurocrine.gcs-web.com/news-releases/news-release-details/neurocrine-biosciences-announces-phase-3-pediatric-study-results. Accessed October 5, 2023. 2. Neurocrine.com. (2023). Neurocrine Biosciences 2023 Analyst Day. [Presentation]. https://www.neurocrine.com//assets/2023/12/NBIX-Analyst-Day_120523_Static-For-Posting-on-NBIX-Website.pdf. Accessed December 5, 2023.

Pediatric and adolescent participants (eligible ages: 2 to 17 years)

CAHtalyst Pediatric Study

Topline results from the double-blind, placebo-controlled period[1,2,a]

Key Secondary Endpoint:

- Treatment with crinecerfont* resulted in a statistically significant percent reduction in daily GC dose[b] at Week 28 vs. placebo while maintaining androgen control (p-value <0.0001)

Secondary Endpoint: *Percent of Participants Achieving a Glucocorticoid Daily Dose[b] ≤ 11 mg/m²/day While Maintaining Androgen Control at Week 28*	
	(n=103)
Participants receiving crinecerfont	30%
Participants receiving placebo	0%
Placebo-Adjusted Difference	30%
P-value	0.0009[c]

***Crinecerfont is investigational and not approved in any country.**

[a]The CAHtalyst Pediatric open-label study period is ongoing; [b]In hydrocortisone dose equivalents adjusted for body surface area; [c]p-value not adjusted for multiplicity; GC, glucocorticoid.

1. Neurocrine.com. (2023). Neurocrine Biosciences Announces Phase 3 Pediatric Study Results of Crinecerfont in Children and Adolescents for the Treatment of Congenital Adrenal Hyperplasia Met Primary and Key Secondary Endpoints [Press release]. Retrieved from: https://neurocrine.gcs-web.com/news-releases/news-release-details/neurocrine-biosciences-announces-phase-3-pediatric-study-results. Accessed October 5, 2023. 2. Neurocrine.com. (2023). Neurocrine Biosciences Announces Phase 3 Pediatric Study Results of Crinecerfont in Children and Adolescents for the Treatment of Congenital Adrenal Hyperplasia Met Primary and Key Secondary Endpoints [Supplemental Materials]. Retrieved fromhttps://www.neurocrine.com//assets/2023/10/Crinecerfont-CAHtalyst-Studies-Supplemental-Materials-10.05.23_Final-2.pdf. Accessed October 5, 2023.

Pediatric and adolescent participants (eligible ages: 2 to 17 years)

CAHtalyst Pediatric Study

Safety results from the double-blind, placebo-controlled period[1,2,a]

- Crinecerfont* was generally well tolerated in pediatric participants
- Few serious adverse events, none assessed as related to crinecerfont
- Most common adverse events: headache, fever, vomiting, upper respiratory tract infection, & nasopharyngitis
- No safety concerns related to adrenal crisis

***Crinecerfont is investigational and not approved in any country.**

[a]The CAHtalyst Pediatric open-label study period is ongoing.

1. Neurocrine.com. (2023). Neurocrine Biosciences Announces Phase 3 Pediatric Study Results of Crinecerfont in Children and Adolescents for the Treatment of Congenital Adrenal Hyperplasia Met Primary and Key Secondary Endpoints [Press release]. Retrieved from: https://neurocrine.gcs-web.com/news-releases/news-release-details/neurocrine-biosciences-announces-phase-3-pediatric-study-results. Accessed October 5, 2023. 2. Neurocrine.com. (2023). Neurocrine Biosciences Announces Phase 3 Pediatric Study Results of Crinecerfont in Children and Adolescents for the Treatment of Congenital Adrenal Hyperplasia Met Primary and Key Secondary Endpoints [Supplemental Materials]. Retrieved fromhttps://www.neurocrine.com//assets/2023/10/Crinecerfont-CAHtalyst-Studies-Supplemental-Materials-10.05.23_Final-2.pdf. Accessed October 5, 2023.

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Appendix

Adult Participants (eligible ages: 18 to 50 years)

CAHlibrate Study

Study Design: Serial Blood Sampling Schedule[1]

Serial blood sampling schedule: Cohorts 1 and 2

Crinecerfont* dosing:
22:00 (Days 1 and 14)

0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
▲	▲	▲	▲	▲		▲		▲		▲		▲		▲		▲				▲				▲

Hours postdose

06:00-10:00 (morning window)

Serial blood sampling schedule: Cohorts 3 and 4

Crinecerfont dosing:
19:00 (Day 14)

0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
▲	▲	▲	▲	▲	▲	▲	▲		▲		▲		▲		▲		▲		▲				▲	▲			▲

Hours postdose

06:00-10:00 (morning window)

***Crinecerfont is investigational and not approved in any country.**

Triangle denotes sample collection.

1. Auchus RJ, et al. *J Clin Endocrinol Metab*. 2022;107(3):801-812.

Adult Participants (eligible ages: 18 to 50 years)

CAHlibrate Study

Baseline Characteristics

	Cohort 1 (n=8) 50 mg QHS	Cohort 2 (n=7) 100 mg QHS	Cohort 3 (n=8) 100 mg QPM	Cohort 4 (n=8) 100 mg BID	All participants (n=18)
Demographics[1]					
Female, n (%)	4 (50)	5 (71)	3 (38)	5 (63)	11 (61)
White, n (%)[a]	7 (88)	7 (100)	7 (88)	8 (100)	17 (94)
Age, mean (SD), years	31 (9.4)	33 (9.7)	31 (10.5)	29 (8.2)	31 (9.3)
BMI, mean (SD), kg/m^2	29 (5.5)	29 (2.7)	29 (4.7)	31 (2.8)	29 (4.1)
GC treatment, n (%)[1]					
HC	3 (38)	4 (57)	4 (50)	5 (63)	10 (56)
Prednisone or equivalent	4 (50)	3 (43)	3 (38)	2 (25)	7 (39)
HC + prednisone or equivalent	1 (13)	0	1 (13)	1 (13)	1 (5.6)
Total daily GC dose, mean (SD)[1]					
HC equivalent, mg/day	25 (11.1)	26 (6.9)	26 (9.0)	26 (8.0)	26 (9.1)
HC equivalent, mg/m^2/day	14 (6.6)	14 (2.5)	14 (4.9)	13 (3.6)	14 (4.8)
Total daily GC dose, median (min, max)[2,b]					
HC equivalent, mg/day	22 (9.0, 40)	25 (16, 35)	25 (14, 40)	26 (14, 40)	25 (9.0, 40)
HC equivalent, mg/m^2/day	12 (5.9, 25)	15 (9.1, 16)	14 (9.1, 24)	13 (9.0, 20)	14 (5.9, 25)

Crinecerfont is investigational and not approved for use in any country.

[a]Included 1 participant who also self-identified as Hispanic or Latino.[b]Hydrocortisone equivalents were calculated as 1 mg prednisolone, methylprednisolone, or prednisone = 4 mg hydrocortisone.
BID, twice daily; BMI, body mass index; GC, glucocorticoid; HC, hydrocortisone; QHS, once daily at bedtime; QPM, once daily in the evening; SD, standard deviation.

1. Auchus RJ, et al. *J Clin Endocrinol Metab*. 2022;107(3):801-812. 2. Auchus RJ, et al. Poster presentation at the ECE Congress; May 13-16, 2023; Istanbul, Turkey.

Adult Participants (eligible ages: 18 to 50 years)

CAHlibrate Study

Baseline Hormone Levels

	Cohort 1 (n=8) 50 mg QHS	Cohort 2 (n=7) 100 mg QHS	Cohort 3 (n=8) 100 mg QPM	Cohort 4 (n=8) 100 mg BID	All participants (n=18)
Adrenal androgens and precursors, mean (SD)[1,a]					
ACTH, pmol/L	67 (66)	53 (42)	83 (64)	78 (74)	70 (67)
17-OHP, nmol/L	167 (116)	310 (229)	210 (177)	343 (260)	236 (183)
Males	230 (126)	533 (78)	197 (177)	428 (303)	304 (213)
Females	105 (70)	221 (207)	232 (213)	292 (253)	217 (195)
A4, nmol/L	11 (8.5)	26 (26)	17 (19)	29 (24)	18 (20)
Males	14 (10)	61 (5.7)	18 (23)	40 (27)	28 (24)
Females	7.7 (6.4)	12 (13)	14 (14)	22 (23)	14 (15)
Testosterone, nmol/L					
Males	12 (5.8)	12 (0.5)	14 (5.6)	13 (3.8)	13 (4.5)
Females	1.8 (1.5)	3.1 (1.6)	3.7 (3.7)	3.4 (3.7)	3.0 (2.4)
A4/testosterone ratio (males)	1.2 (1.0)	5.0 (0.3)	1.9 (2.8)	3.5 (2.7)	2.2 (2.1)
Adrenal androgens and precursors, median (min, max)[2,a]					
ACTH, pg/mL	151 (18, 784)	196 (27, 546)	447 (8.7, 801)	310 (31, 1059)	188 (18, 1059)
17-OHP, ng/dL	5352 (620, 13,800)	9875 (935, 19,393)	6489 (72, 15,871)	10,783 (567, 23,519)	5352 (620, 19,393)
A4, ng/dL	270 (34, 750)	223 (150, 1867)	323 (11, 1650)	769 (44, 1811)	250 (34, 1867)

Crinecerfont is investigational and not approved for use in any country.

[a]Based on values from the morning window time points (06:00, 08:00, 10:00).

Normal ranges are as follows: ACTH, 2.2 to 13.2 pmol/L (10-60 pg/mL); 17-OHP (adult men), <6.7 nmol/L (<220 ng/dL); 17-OHP (follicular women), <2.4 nmol/L (<80 ng/dL); 17-OHP (luteal women), <8.6 nmol/L (<285 ng/dL); 17-OHP (postmenopausal women), <1.5 nmol/L (<51 ng/dL); androstenedione (adult men), 2.3 to 7.3 nmol/L (65-210 ng/dL); androstenedione (adult women), 2.8 to 8.4 nmol/L (80-240 ng/dL); total testosterone (women), 0.3 to 2.1 nmol/L (8-60 ng/dL); total testosterone (men), 10.4 to 41.6 nmol/L (300-1200 ng/dL). For androstenedione/testosterone (men), the target ratio was <0.5. In Cohort 3, results for testosterone (women) are based on 4 participants who had available baseline morning window values.

17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone, BID, twice daily; QHS, once daily at bedtime; QPM, once daily in the evening; SD, standard deviation.

1. Auchus RJ, et al. *J Clin Endocrinol Metab*. 2022;107(3):801-812. 2. Auchus RJ, et al. Poster presentation at the ECE Congress; May 13-16, 2023; Istanbul, Turkey.

Adolescent Participants (eligible ages: 14 to 17 years)

CAHlibrate Pediatric Study

Demographic and Baseline Characteristics[1]

	All participants (n=8)
Participant characteristics[a]	
Female, n (%)	5 (62.5)
White, n (%)[b]	7 (87.5)
Asian, n (%)	1 (12.5)
Age, years	15 (14, 16)
Height, cm	165 (155, 175)
Z-score[c]	0.2 (–2.1, 0.8)
Weight, kg	62 (52,115)
Z-score[c]	0.7 (–0.4, 2.8)
BMI, kg/m^2	25 (19, 38)
Z-score[c]	1.2 (–0.2, 2.6)
Number of adrenal crises within past 2 years	0 (0, 1)
Age at menarche (females), years	14 (13, 14)
Menstrual cycle interval (females), days	28 (21, 56)

	All participants (n=8)
GC treatment[a]	
HC alone, n (%)	6 (75.0)
Prednisone alone, n (%)	2 (25.0)
GC dose (HC equivalent[d]), mg/m^2/day	16.2 (11.9, 18.5)
Adrenal androgens, ACTH, and precursors at baseline, median (IQR)[e]	
ACTH, pg/mL	226.2 (377.3)
17-OHP, ng/dL	7703.7 (7123.5)
A4, ng/dL	367.9 (393.3)
Testosterone (females), ng/dL	63.5 (270.0)
Testosterone (males), ng/dL	222.0 (140.0)

- One participant had an adrenal crisis in the last 2 years
- 4 of the 5 female participants had reached menarche

Crinecerfont is investigational and not approved in any country.

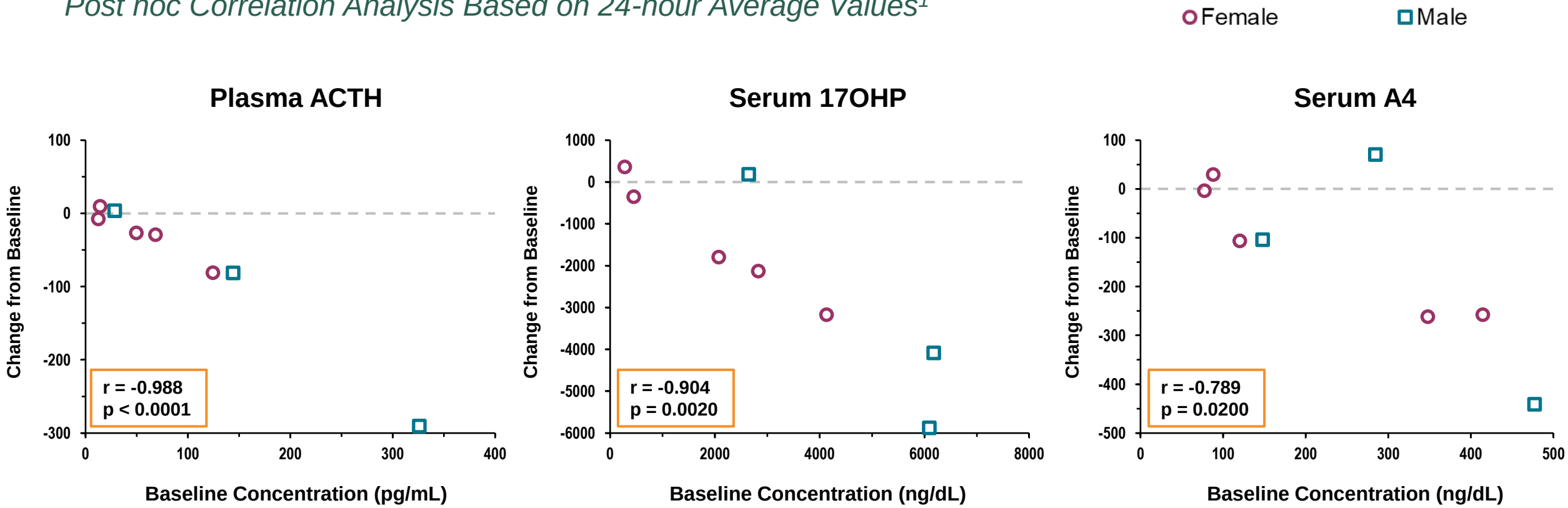
[a]Presented as median (min, max) unless indicated otherwise.
[b]Includes 1 participant who also self-identified as Hispanic or Latino.
[c]Centers for Disease Control Growth Chart used as reference, with Z-scores based on chronological age.
[d]HC equivalents were calculated as 1 mg prednisone = 4 mg HC. No participants were on dexamethasone.
[e]Based on the average of morning window values (07:00-10:00).
17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; BMI, body mass index; GC, glucocorticoid; HC, hydrocortisone; IQR, interquartile range.

1. Newfield RS, et al. *J Clin Endocrinol Metab.* 2023:dgad270.

Adolescent Participants (eligible ages: 14 to 17 years)

CAHlibrate Pediatric Study

Post hoc Correlation Analysis Based on 24-hour Average Values[1]



- Strong correlation between baseline ACTH, 17OHP, and A4 concentrations and change from baseline to Day 14 for 24-hour average values of ACTH, 17OHP, and A4

Crinecerfont is investigational and not approved in any country.

17OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; GC, glucocorticoid.

1. Newfield, RS, et al. Oral presentation at the ESPE Congress; September 21-23, 2023; The Hague, Netherlands.