Congenital Adrenal Hyperplasia (CAH) and Crinecerfont*

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

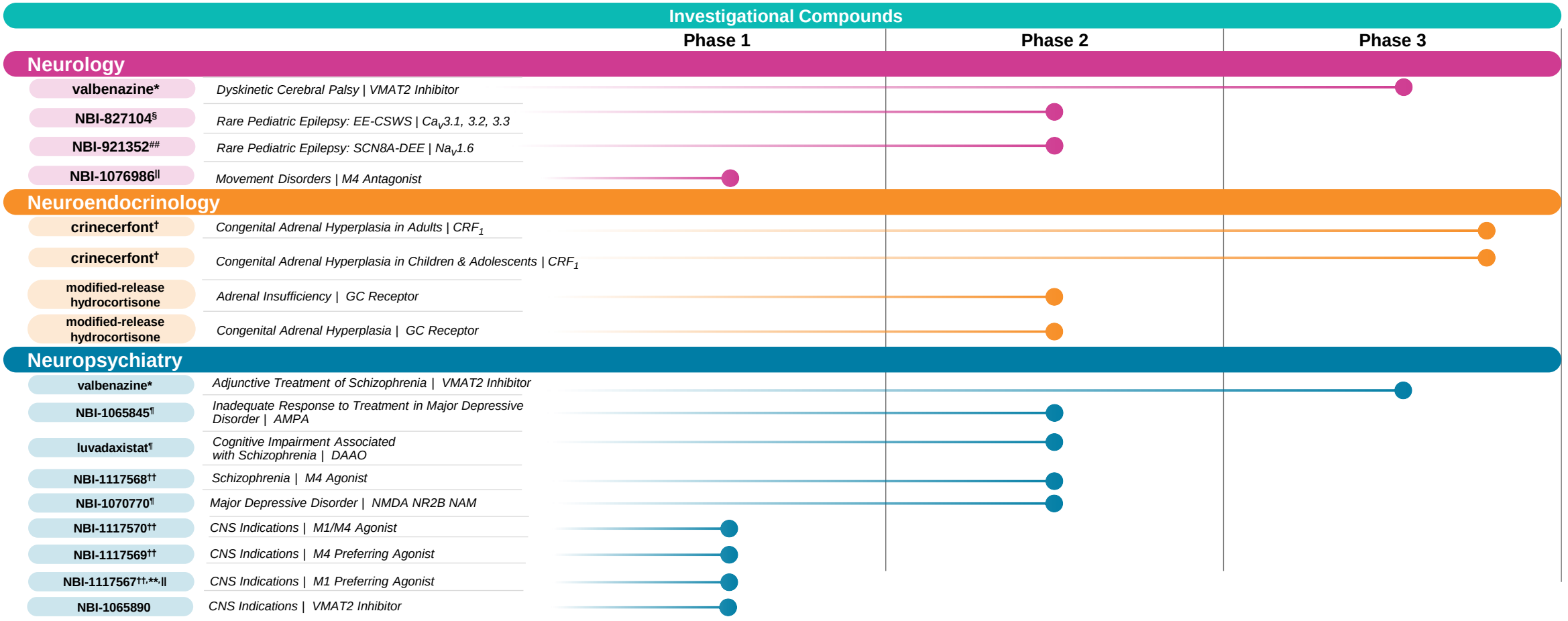
NEUROCRINE® BIOSCIENCES

Table of Contents

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

Neurocrine Pipeline

Neurocrine Clinical Pipeline[a]



Approved Products

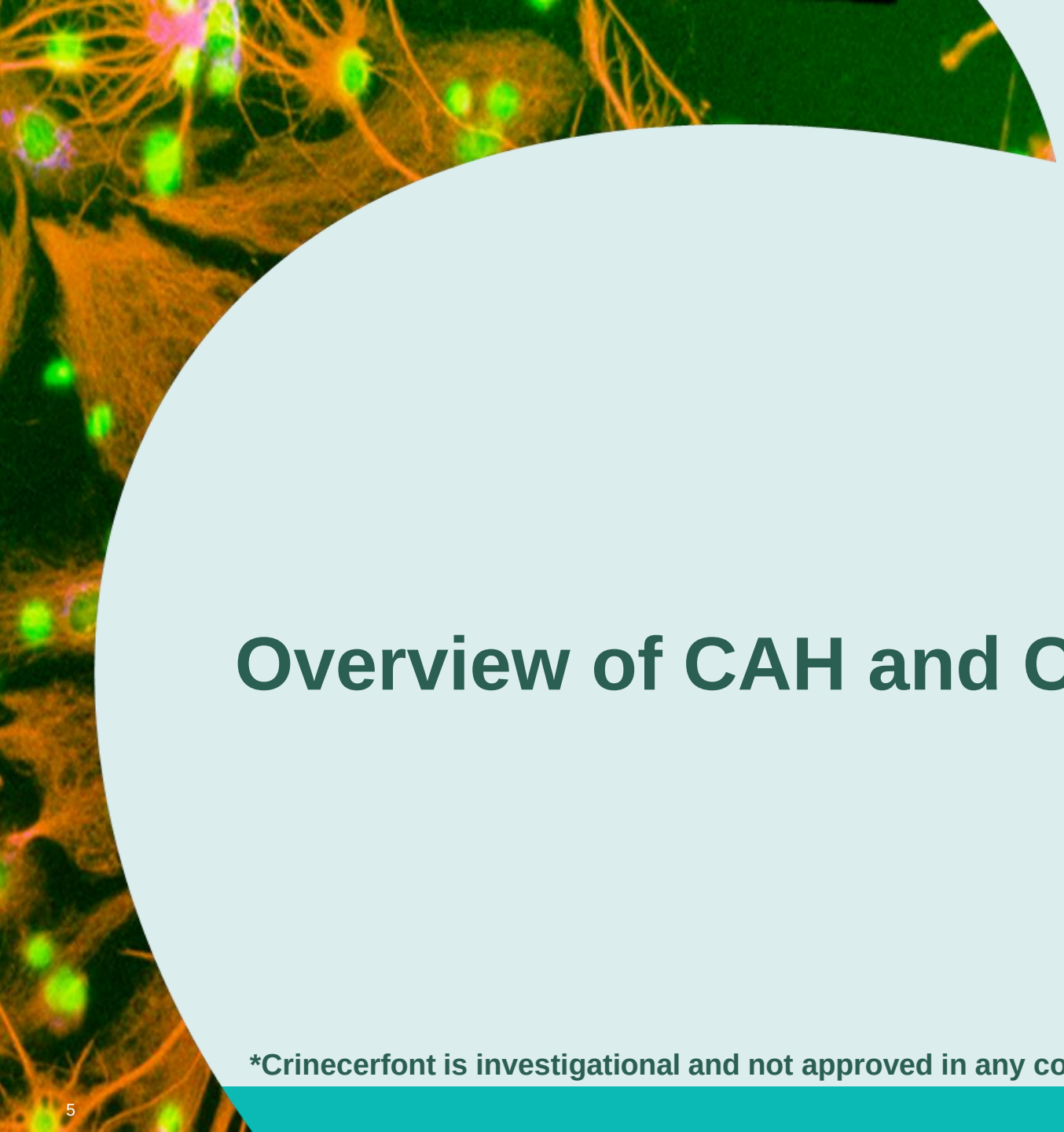
Valbenazine*
Indication: treatment of adults with tardive dyskinesia and chorea associated with Huntington's disease[1]

Elagolix#
Indication: management of moderate to severe pain associated with endometriosis[2]

Elagolix/estradiol/norethindrone acetate#
Indication: management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women[3]

EE-CSWS = Epileptic Encephalopathy with Continuous Spike-and-Wave During Sleep; SCN8A-DEE = SCN8A Developmental and Epileptic Encephalopathy Syndrome.
Neurocrine Biosciences has global rights unless otherwise noted. Neurocrine Biosciences shares profits and losses on NBI-1065845 with Takeda Pharmaceutical Company Limited.
*Mitsubishi Tanabe Pharma Corporation has commercialization rights in Japan and other select Asian markets; †Licensed from Sanofi; §Licensed from Idorsia Ltd; ##Licensed from Xenon Pharmaceuticals, Inc; ¶Licensed from Takeda Pharmaceutical Company Limited; †† Licensed from Sosei Heptares;**Sosei Heptares has retained rights in Japan; Neurocrine Biosciences may opt-in to a 50:50 cost and revenue share upon certain development events; ‖Phase 1 initiating; #AbbVie has global commercialization rights.
1. INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego, CA. 2. ORLISSA™ (elagolix). Package insert. Abbvie, Inc. North Chicago, IL. 3. ORIAHN® (elagolix/estradiol/norethindrone acetate). Package insert. Abbvie, Inc. North Chicago, IL.

[a]as of May 2024



Overview of CAH and Crinecerfont*

*Crinecerfont is investigational and not approved in any country.

Classic CAH

Rare genetic condition with deficiency of 21-hydroxylase[1,a,b]

Resulting in[1]:

- Deficient cortisol and often aldosterone
- Excessive production of ACTH, steroid precursors, and adrenal androgens

Incidence:

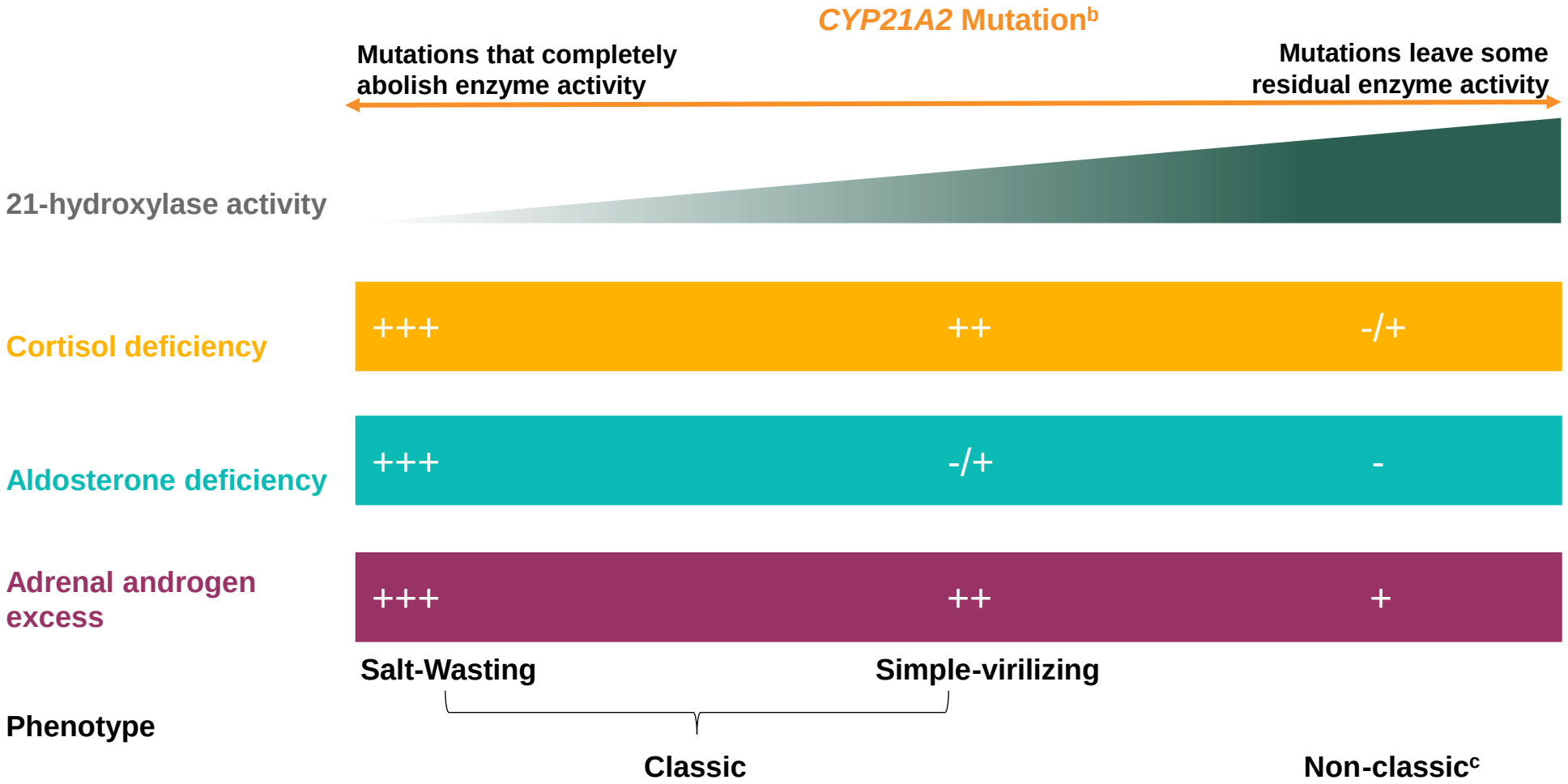
~1:15,000 live births worldwide[1,2]

Complex symptoms affect **multiple organ systems**[1,3]

[a]There are other rare forms of CAH.[4]
[b]21-hydroxylase is an enzyme involved in adrenal hormone steroidogenesis.
ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; TART, testicular adrenal rest tumor.

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 Engl J Med*. 2020;383(13):1248-1261. 4. White PC, et al. *Endocr Rev*. 2000;21(3):245-291.

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

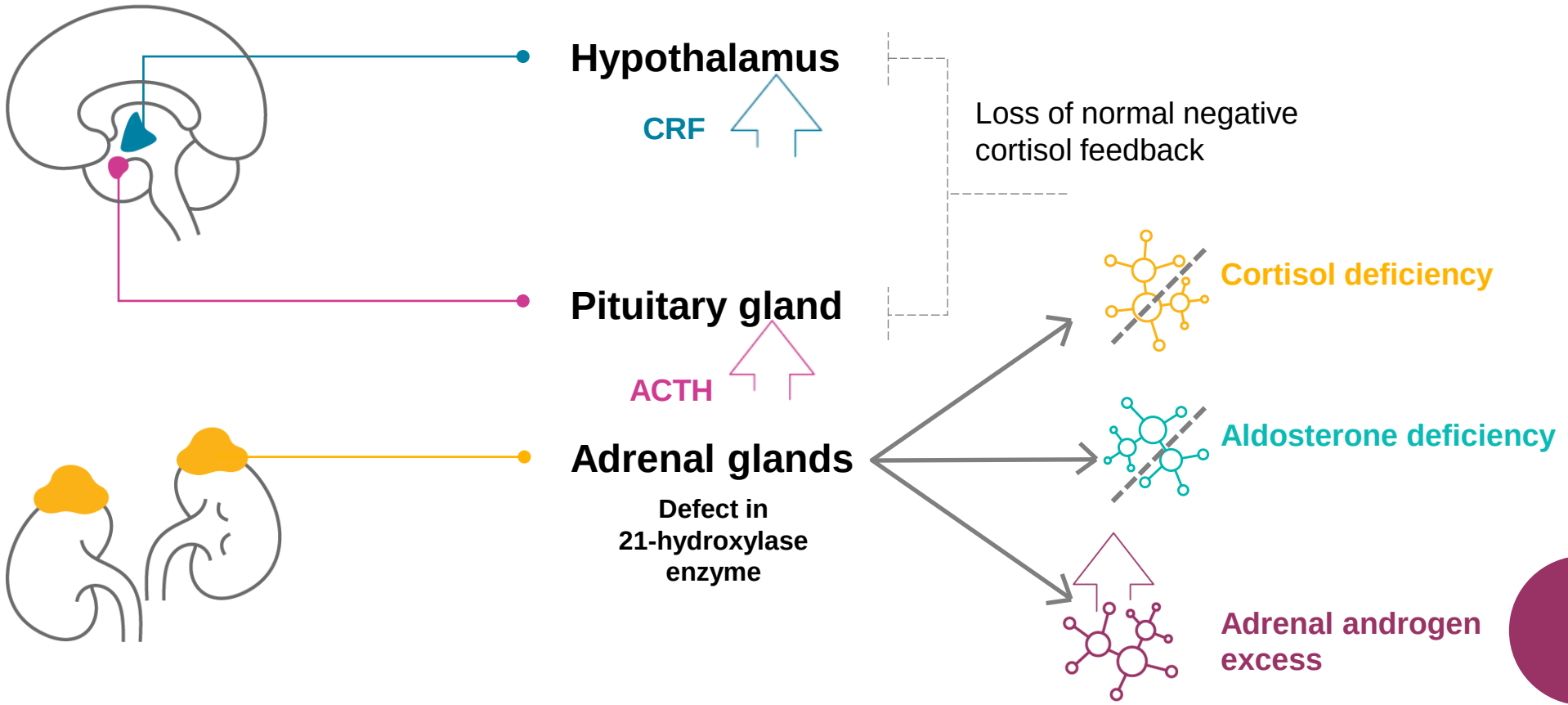
Standard GC treatment at
SUPRAPHYSIOLOGICAL DOSES
for androgen reduction has been associated with complications

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]

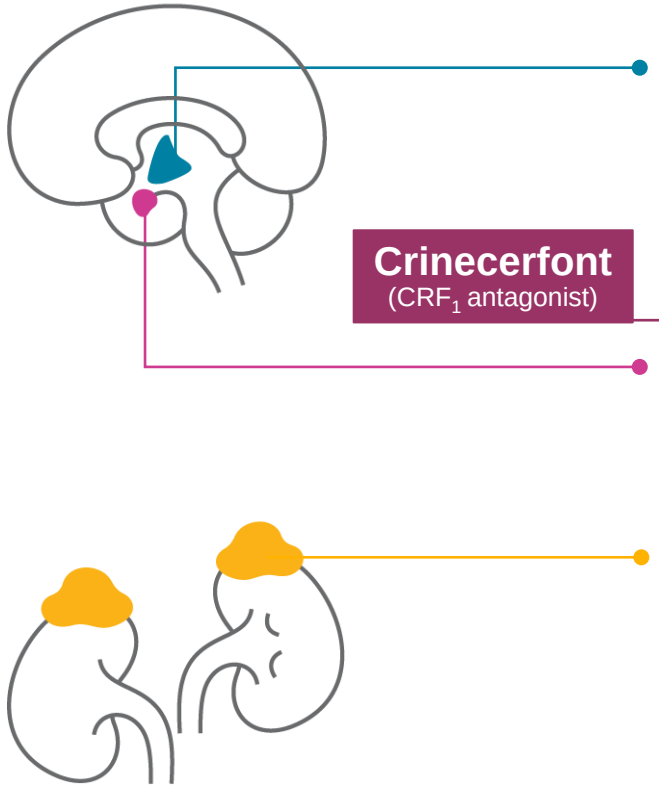


ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; CRF, corticotropin-releasing factor.

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**



Hypothalamus

CRF

CRF_1

Crinecerfont (CRF_1 antagonist)

Pituitary gland

ACTH

Adrenal glands

Defect in 21-hydroxylase enzyme

Cortisol ← **Glucocorticoids**

Aldosterone ← **Mineralocorticoids**

Adrenal androgens

***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.

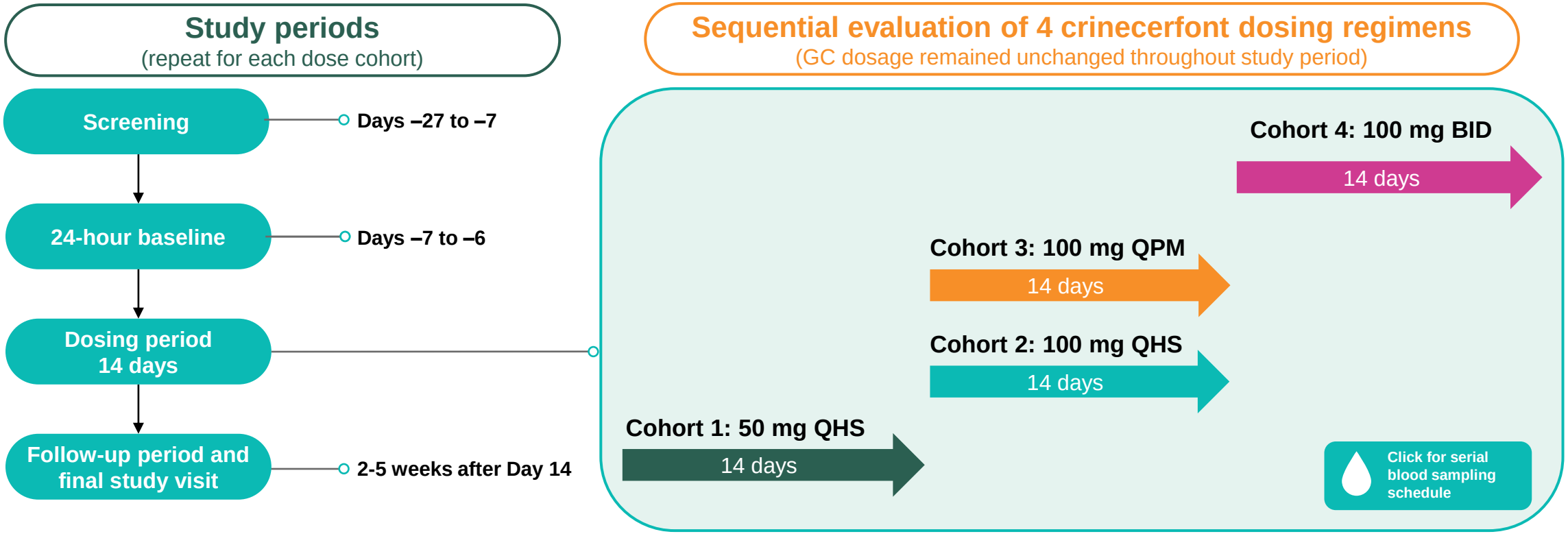
CAHlibrate™ Study: Phase 2, Open-label, Multiple-dose, Dose-escalation Study in Adult Patients With CAH

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

CAHlibrate Study: A Phase 2, Open-label, Multiple-dose, Dose-escalation Study of Crinecerfont* in Adults With Classic CAH[1,2]

Study design

- 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

CAHlibrate Study: Eligibility 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.

CAHlibrate Study: 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.

CAHlibrate Study: Effects of Crinecerfont* on Adrenal Androgens and Precursors[1,a]

	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		
Median (IQR)	Morning window[b]	24-hour period[c]	Morning window[b]	24-hour period[c]	Morning window[b]	24-hour period[c]	Morning window[b]	24-hour period[c]	Normal ranges
ACTH, pmol/L									
At baseline	33 (103)	20 (69)	43 (83)	16 (21)	98 (104)	28 (26)	68 (86)	22 (25)	**All adults:** 2.2-13.2 pmol/L
Change from baseline to Day 14	–24 (48)	–7.6 (48)	–34 (42)	–9.2 (16)	–85 (101)	–18 (29)	–45 (57)	–5.8 (15)	
17-OHP, nmol/L									**Adult men:** <6.7 nmol/L **Follicular women:** <2.4 nmol/L **Luteal women:** <8.6 nmol/L **Postmenopausal women:** <1.5 nmol/L
At baseline	162 (77)	69 (89)	299 (452)	114 (260)	197 (292)	89 (150)	327 (425)	103 (175)	
Change from baseline to Day 14	–81 (43)	–20 (43)	–135 (281)	–38 (104)	–102 (208)	–59 (94)	–171 (330)	–41 (74)	
A4, nmol/L									**Adult men:** 2.3-7.3 nmol/L **Adult women:** 2.8-8.4 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)	
Change from baseline 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)	

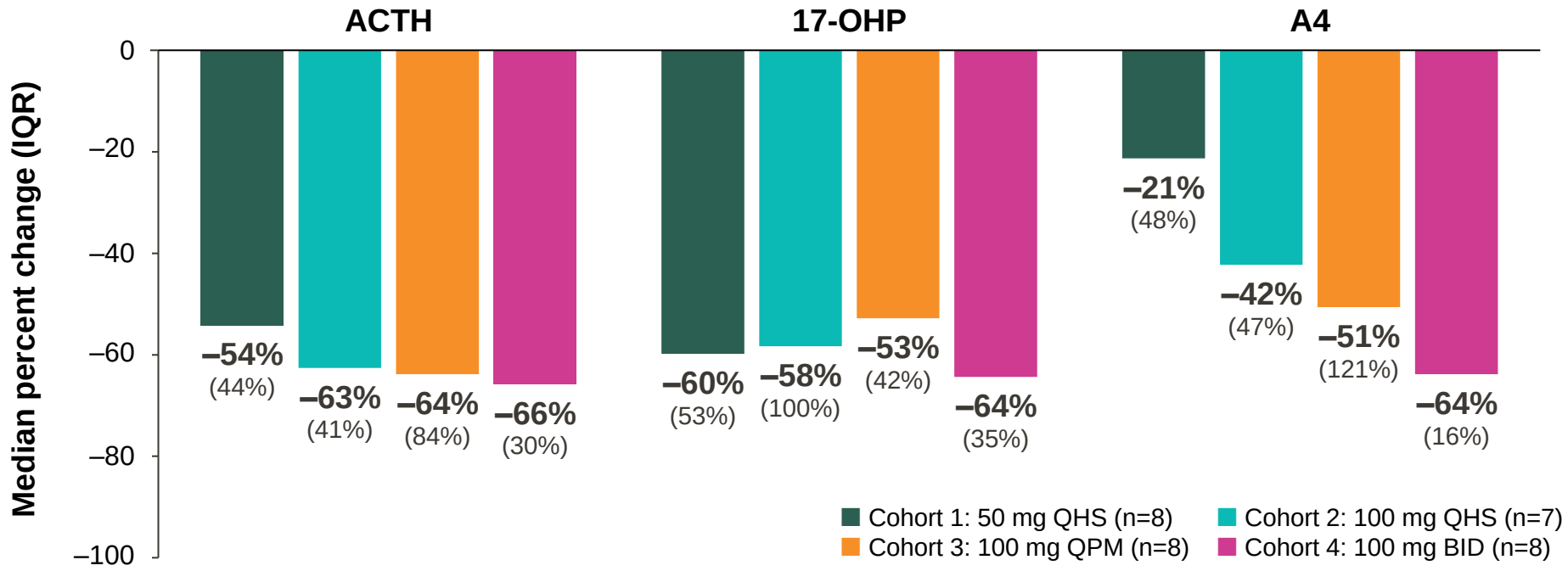
***Crinecerfont is investigational and not approved in any country.**

[a]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.
[b]Based on values from the morning window time points (06:00, 08:00, 10:00).
[c]Based on values from all time points in serial blood sampling period: Cohorts 1 and 2 (from 23:00-22:00 [following day]); Cohorts 3 and 4 (from 20:00-22:00 [following day]).
17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; BID, twice daily; GC, glucocorticoid; IQR, interquartile range (Q3-Q1); 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.

CAHlibrate Study: Effects of Crinecerfont* on Morning Window ACTH, 17-OHP, and A4 Levels[1,a]

Reductions in morning window values from baseline to Day 14



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

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

[a]Based on each participant's values from the morning window time points (06:00, 08:00, 10:00) on Day 14 compared to the average of their morning window values at baseline.

17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; BID, twice daily; IQR, interquartile range (Q3-Q1); 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.

CAHlibrate Study: Safety of Crinecerfont[1,*]

	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
AE summary, n (%)				
Any TEAE	7 (88)	5 (71)	5 (63)	5 (63)
Any SAE	0	1 (14)[a]	0	0
Any TEAE leading to discontinuation	0	0	0	0
Any TEAE resulting in death	0	0	0	0
TEAEs by MedDRA preferred term, n (%)				
Headache	3 (38)	1 (14)	0	1 (13)
Upper respiratory tract infection	3 (38)	0	1 (13)	0
Fatigue	1 (13)	0	1 (13)	1 (13)
Bruising	2 (25)	0	0	0
Insomnia	0	1 (14)	0	1 (13)
Nasopharyngitis	0	0	0	2 (25)
Nausea	1 (13)	1 (14)	0	0
Pyrexia	0	0	1 (13)	1 (13)

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

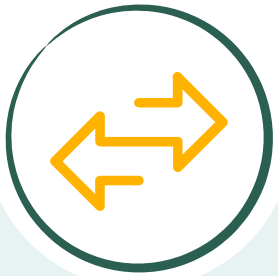
***Crinecerfont is investigational and not approved in any country.**

[a]Single event of cholelithiasis, assessed by the investigator as moderate in intensity and unrelated to treatment. The participant underwent a cholecystectomy with an intraoperative cholangiogram, followed by appropriate medical treatment. The cholelithiasis was resolved and the participant remained in the study.

AE, adverse event; BID, twice daily; ECG, electrocardiogram; MedDRA, *Medical Dictionary for Regulatory Activities*; QHS, once daily at bedtime; QPM, once daily in the evening; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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

CAHlibrate Study: 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™ Pediatric Study: Phase 2, Open-label Study in Adolescent Patients With CAH

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

CAHlibrate Pediatric Study: A Phase 2, Open-label, Study of Crinecerfont* in Adolescents With Classic CAH[1,2]

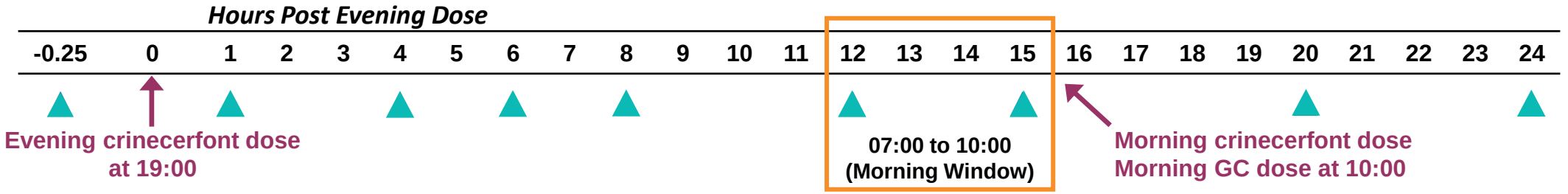
Study design

- 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.

CAHlibrate Pediatric Study: Eligibility 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.

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.

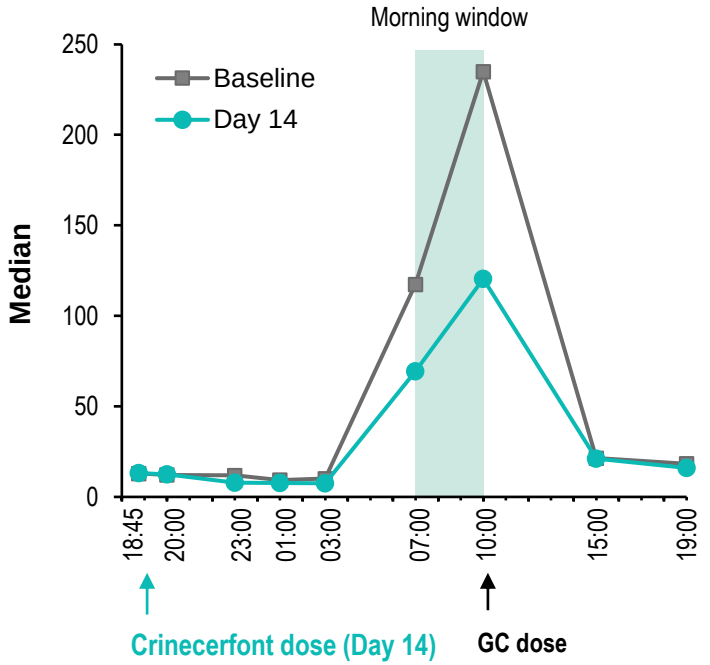
1. Newfield RS, et al. *J Clin Endocrinol Metab.* 2023:dgad270.

Click for detailed baseline characteristics

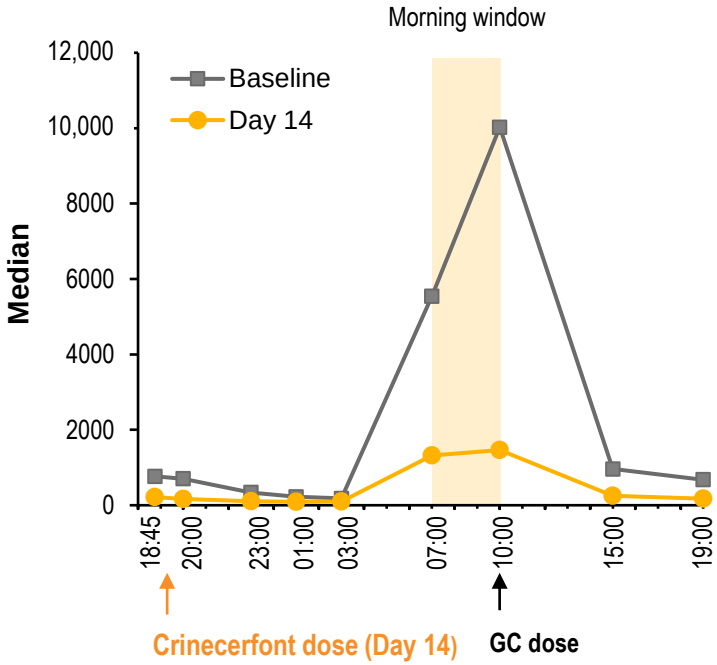
CAHlibrate Pediatric Study: Crinecerfont* Led to Clinically Meaningful Reductions in ACTH, 17-OHP, and A4, Especially During Morning Window[1]

24-hour concentration profiles

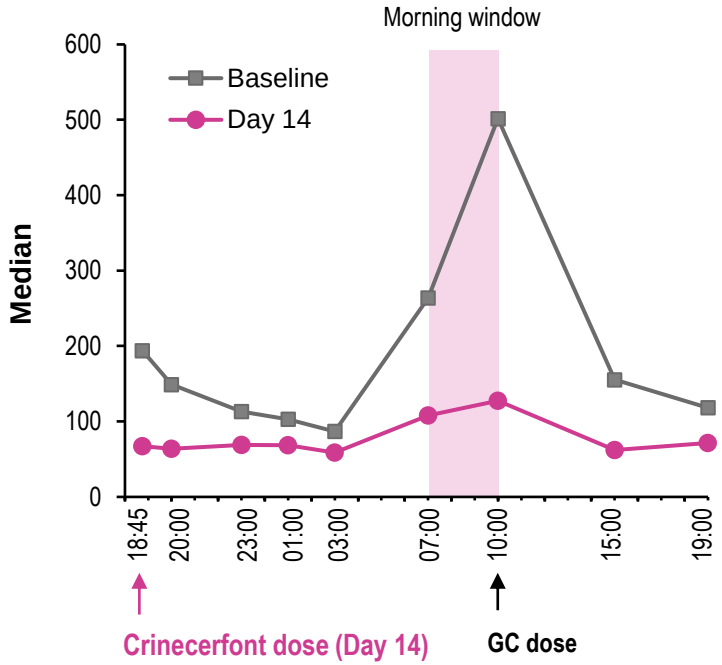
Plasma ACTH, pg/mL



Serum 17-OHP, ng/dL



Serum A4, ng/dL

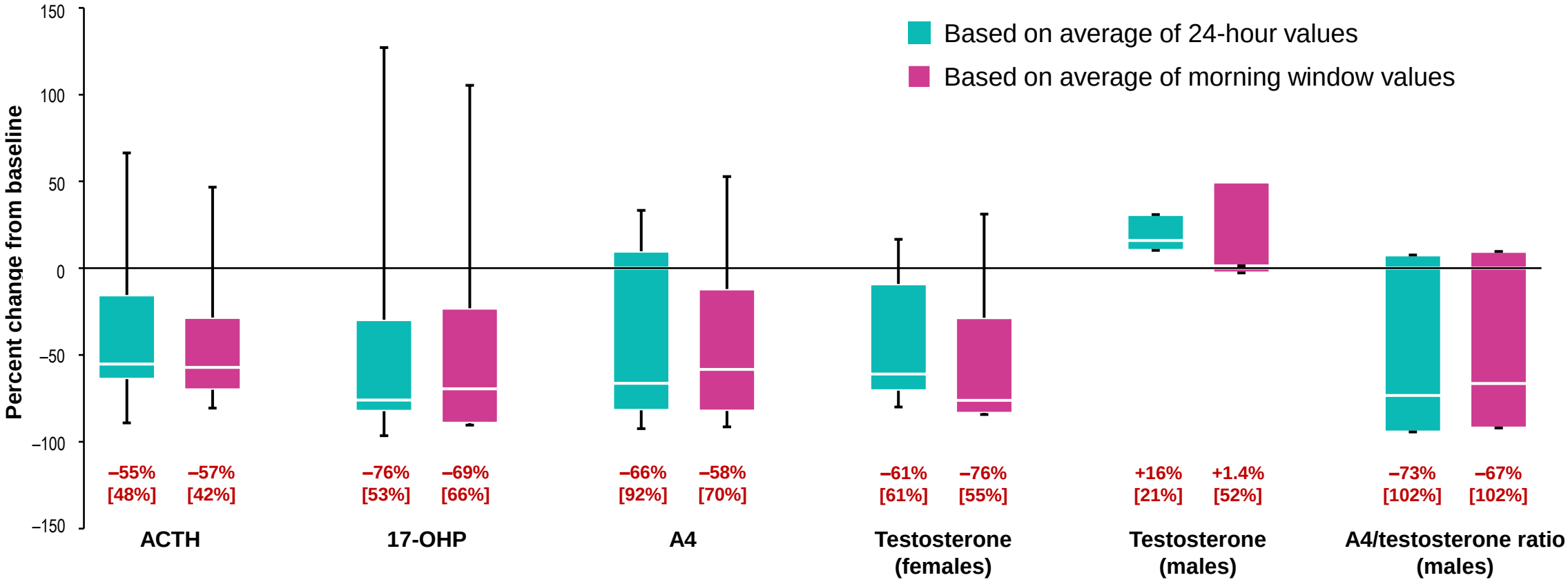


***Crinecerfont is investigational and not approved in any country.**

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

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

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.**

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).
17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; IQR; interquartile range.

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

CAHlibrate Pediatric Study: 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.

CAHlibrate Pediatric Study: 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.

CAHtalog™ Registry

CAHtalog Registry[1]

What is it?	An IRB-approved, direct-to-patient registry used to capture a **real-world sample** of patient care characteristics
What is its purpose?	Obtain information about how adults and children with CAH are managed by their health care providers in a **real-world setting**
How does it work?	Adults and children living with classic CAH will consent to have PicnicHealth collect their medical records, which will be **stripped of any personally identifiable information** and combined into a de-identified CAH database
Who supports it?	CAHtalog™ is sponsored by **Neurocrine Biosciences, Inc.,** in partnership with and supported by **CARES Foundation**, and operationalized by **PicnicHealth**

CAHtalog™
Congenital Adrenal Hyperplasia Patient & Clinical Outcomes in Real-World Practice Settings

CARES FOUNDATION
CONGENITAL ADRENAL HYPERPLASIA

PicnicHealth

CAH, congenital adrenal hyperplasia; IRB, institutional review board.

1. PicnicHealth. Congenital adrenal hyperplasia (CAH) registry. Accessed June 22, 2023. https://picnichealth.com/cah.

CAHtalog: Overview[1]

CAHtalog is an IRB-approved registry designed to collect medical history information about people diagnosed with CAH retrospectively and prospectively

- CAHtalog is a direct-to-patient, decentralized registry
- Central IRB only; no site agreements or local IRCs
- People living with classic CAH can consent to having their medical records, which will be stripped of any personally identifiable information, combined into a de-identified CAH database
  - Does not require site transcription of EMR/chart data
  - Single consent by patient
  - Allows for repeated capture of patient-reported or caregiver-reported outcomes
- Retrospective and prospective data collection for an approximate total of 10 years of data per patient
- Researchers can apply to access CAHtalog data, which will be reviewed by the DGSRC, which is composed of key academic opinion leaders in the field.

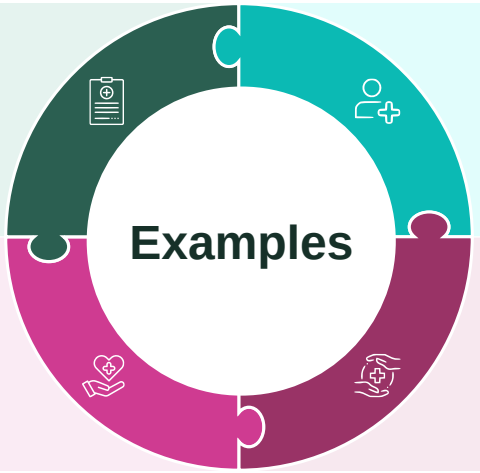
CAH, congenital adrenal hyperplasia; EMR, electronic medical record; DGSRC, Data Governance and Scientific Review Committee; IRB, institutional review board; IRC, institutional research center.

1. PicnicHealth. Congenital adrenal hyperplasia (CAH) registry. Accessed June 22, 2023. https://picnichealth.com/cah.

CAHtalog: Utility of the Registry[1]

Raise awareness and advance scientific knowledge

Improve patient care and clinical outcomes by a wide range of stakeholders



Data on disease epidemiology

Patients' characteristics

Assessment of the effectiveness and safety of therapies

Current standard of care

1. PicnicHealth. Congenital adrenal hyperplasia (CAH) registry. Accessed June 22, 2023. https://picnichealth.com/cah.

CAHtalog: Extracting Data for Research[1]

Researchers need data from actual people with CAH in order to identify patterns and fill knowledge gaps

- Medical records can provide a **real-world perspective** on how participants experience CAH (i.e., symptoms, health status, treatments)
- Once the participant's medical history is made anonymous, it will be compiled with medical history information from other people with CAH in a database to create a **resource for researchers**
- Information extracted from this registry can help the CAH community gain a better understanding of the disease, such as:
  - Natural lifetime progression of CAH
  - Real-world burden of illness
  - Current standard of clinical practice and disease management
  - Patient-reported or observer-reported outcomes and health care resource utilization
- The registry can raise awareness of CAH, which may help improve the care of future people living with CAH
- CAHtalog is an open-access registry available to all researchers[a]

CAH, congenital adrenal hyperplasia.
[a]Application accepted and reviewed though the Data Governance and Scientific Review Committee. The committee comprises key academic opinion leaders in the field.
1. PicnicHealth. Congenital adrenal hyperplasia (CAH) registry. Accessed June 22, 2023. https://picnichealth.com/cah.

CAHtalog: Enrollment[1]

- Enrollment:
  - People diagnosed with classic CAH who live in the United States are eligible to participate, including both adults and children with classic CAH
  - There is no upper or lower age cut-off for enrollment
  - Caregivers can enroll for pediatric participants
  - Sign-up takes 5 to 10 minutes through the CAHtalog website[a]
  - There is no cost associated with participation in CAHtalog
- Participant benefits:
  - Contribute to CAH research and share their unique patient journey and voice through optional PROs, without the need for in-person visits
  - Receive access to fully digitized medical records via their own PicnicHealth Timeline, which allows participants to view, download, and share their medical histories
  - Receive future updates on findings/publications
- Provider role:
  - No active work (data entry) required
- All data shared with researchers is anonymized

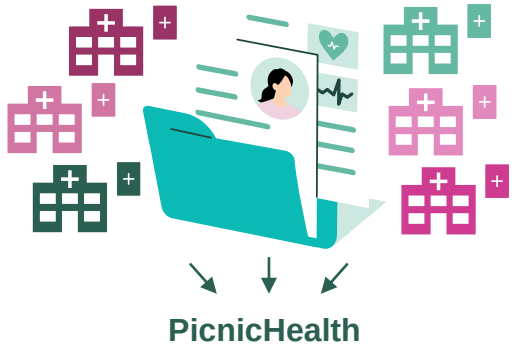
CAH, congenital adrenal hyperplasia; PRO, patient-reported outcome.
[a]Enrollment requires the last 4 digits of the patient's Social Security Number and the names of their physicians. Only 1 consent is needed by the patent or caregiver, without any additional action needed thereafter.
1. PicnicHealth. Congenital adrenal hyperplasia (CAH) registry. Accessed June 22, 2023. https://picnichealth.com/cah.

CAHtalog: Leverages Advanced NLP Technology to Collect and Analyze Medical Records From Patients Living With Classic CAH[1]

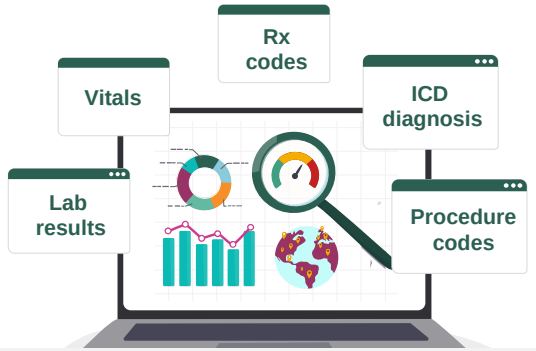
Recruited via CARES foundation and online marketing

After online consent, patients simply list every hospital and clinic they have visited in the past. No additional work is necessary

Patients have the option of participating in short bi-annual surveys (PROs)



PicnicHealth manually collects medical records from all hospitals/clinics on behalf of patients



Thousands “structured data” points per patient are automatically extracted. No pre-specification of variables is necessary.

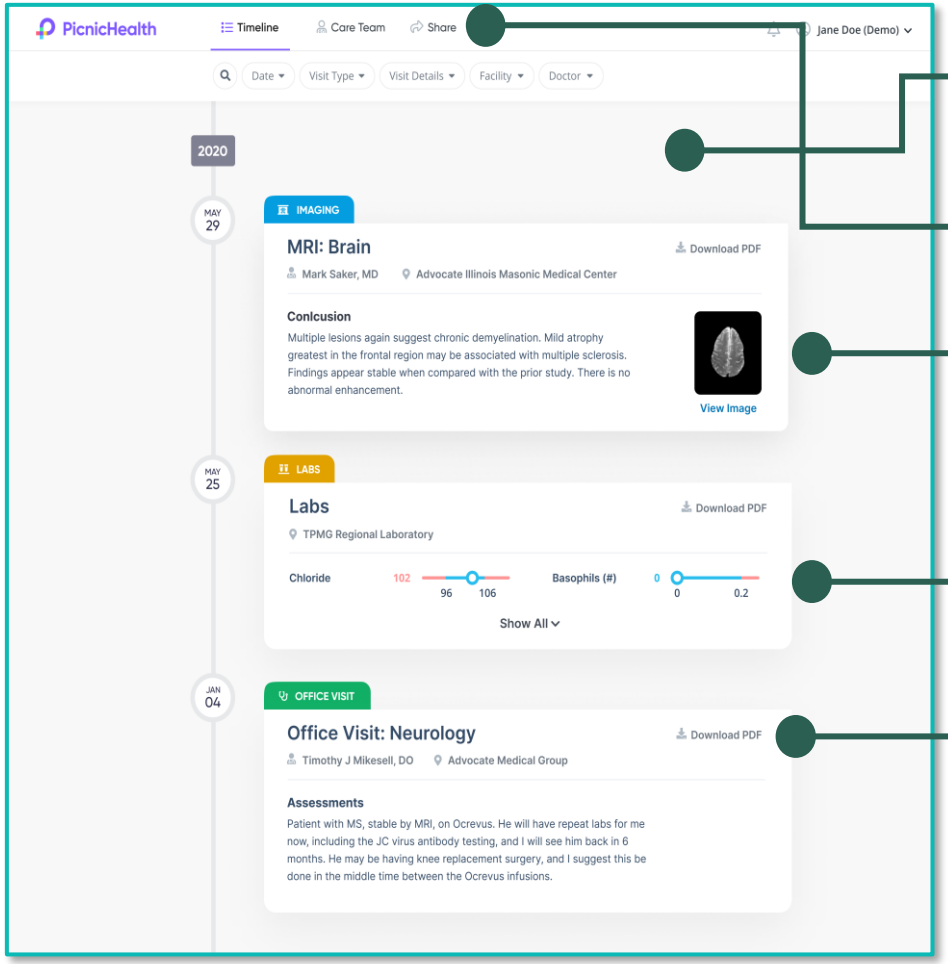
Key questions from “Physician Notes” are extracted with NLP algorithms and verified by 2 reviewers

CAH, congenital adrenal hyperplasia; ICD, *International Classification of Diseases*; NLP, natural language processing; PRO, patient-reported outcome; Rx, prescription.

1. PicnicHealth. Congenital adrenal hyperplasia (CAH) registry. Accessed June 22, 2023. https://picnichealth.com/cah.

CAHtalog: The PicnicHealth Timeline[1]

Each participant who signs up will receive their own PicnicHealth Timeline to view, manage, and share their longitudinal health histories



Access all medical records in 1 place

Share records with family and physicians

View images

Track all labs longitudinally

Download original source records

This example of a PicnicHealth Timeline is for demonstration purposes only.

FDA, US Food and Drug Administration.

1. PicnicHealth. Demo PicnicHealth Timeline. Accessed June 22, 2023. https://demo.picnichealth.com.

Neurocrine Medical Affairs

www.neurocrinemedical.com

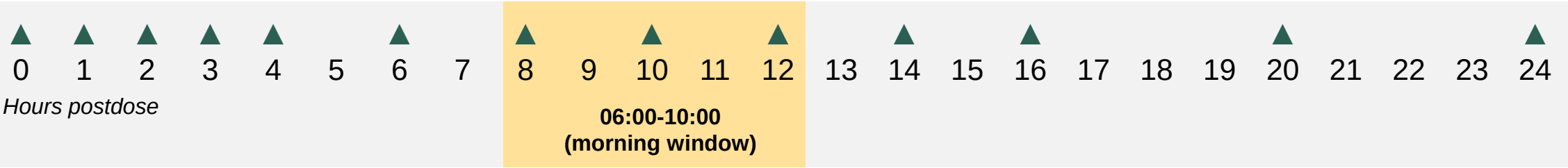
1-877-641-3461

Appendix

CAHlibrate Study: Serial Blood Sampling Schedule[1]

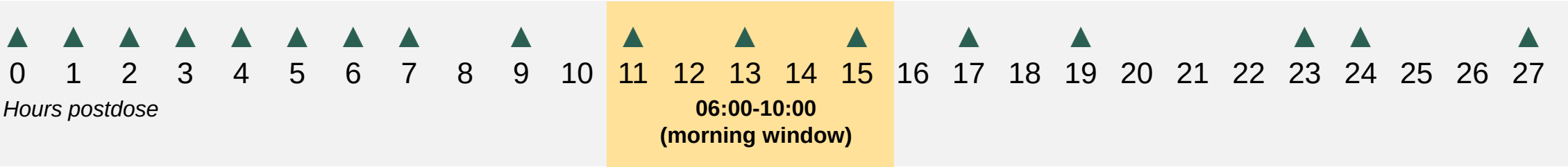
Serial blood sampling schedule: Cohorts 1 and 2

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



Serial blood sampling schedule: Cohorts 3 and 4

Crinecerfont dosing:
19:00 (Day 14)



***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.

CAHlibrate Study: Baseline Characteristics, Demographics, GC Treatment, and Total Daily GC Dose[1]

	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					
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 (%)					
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)					
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)

Crinecerfont is investigational and not approved in any country.

[a]Included 1 participant who also self-identified as Hispanic or Latino.

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.

CAHlibrate Study: Baseline Hormone Levels[1]

	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)[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)

Crinecerfont is investigational and not approved 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); A4 (adult men), 2.3 to 7.3 nmol/L (65-210 ng/dL); A4 (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 A4/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

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.