CAHtalyst™

Pediatric and **Adult** Double-Blind, Placebo-Controlled Study Results of Crinecerfont* in Congenital Adrenal Hyperplasia

Note: We refer to classic congenital adrenal hyperplasia as CAH; deviations from classic CAH are denoted by using specific terminology (i.e., non-classic CAH).

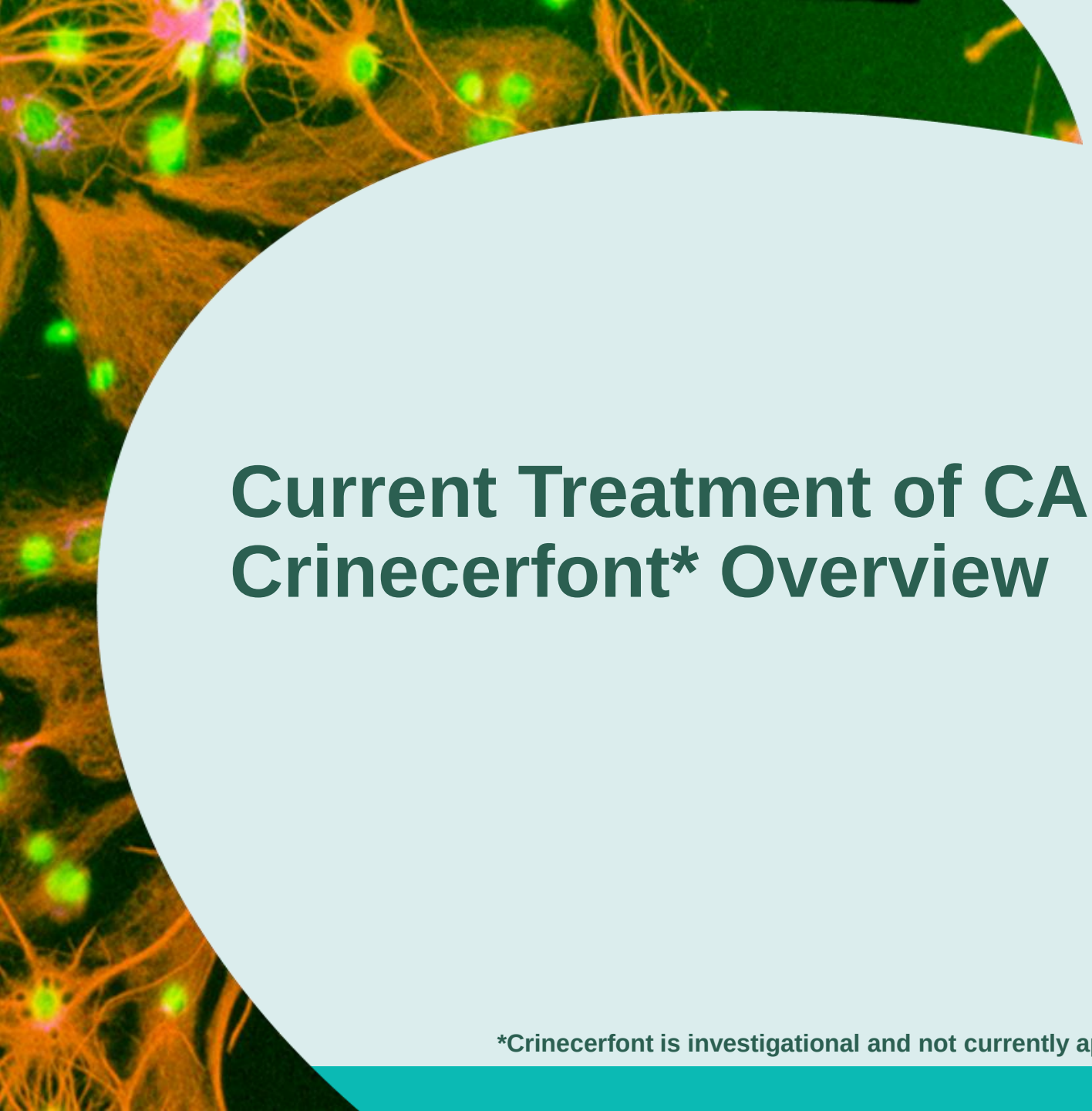
NEUROCRINE® BIOSCIENCES

***Crinecerfont is investigational and not currently approved in any country. For medical information only.**

PROACTIVE USE FOR INVESTIGATORS; REACTIVE FOR ALL OTHER USE.

Table of Contents

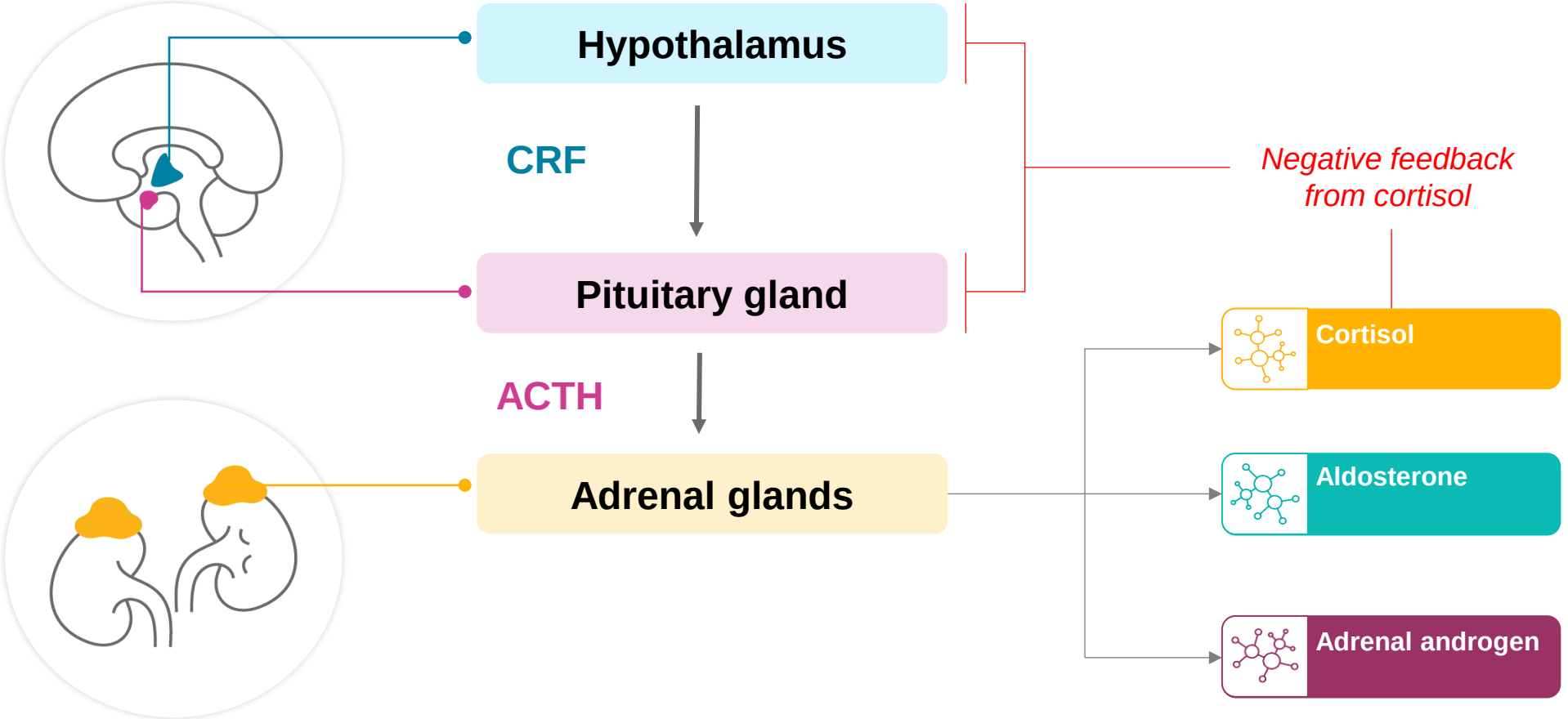
*Crinecerfont is investigational and not currently approved in any country.



Current Treatment of CAH and Crinecerfont* Overview

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

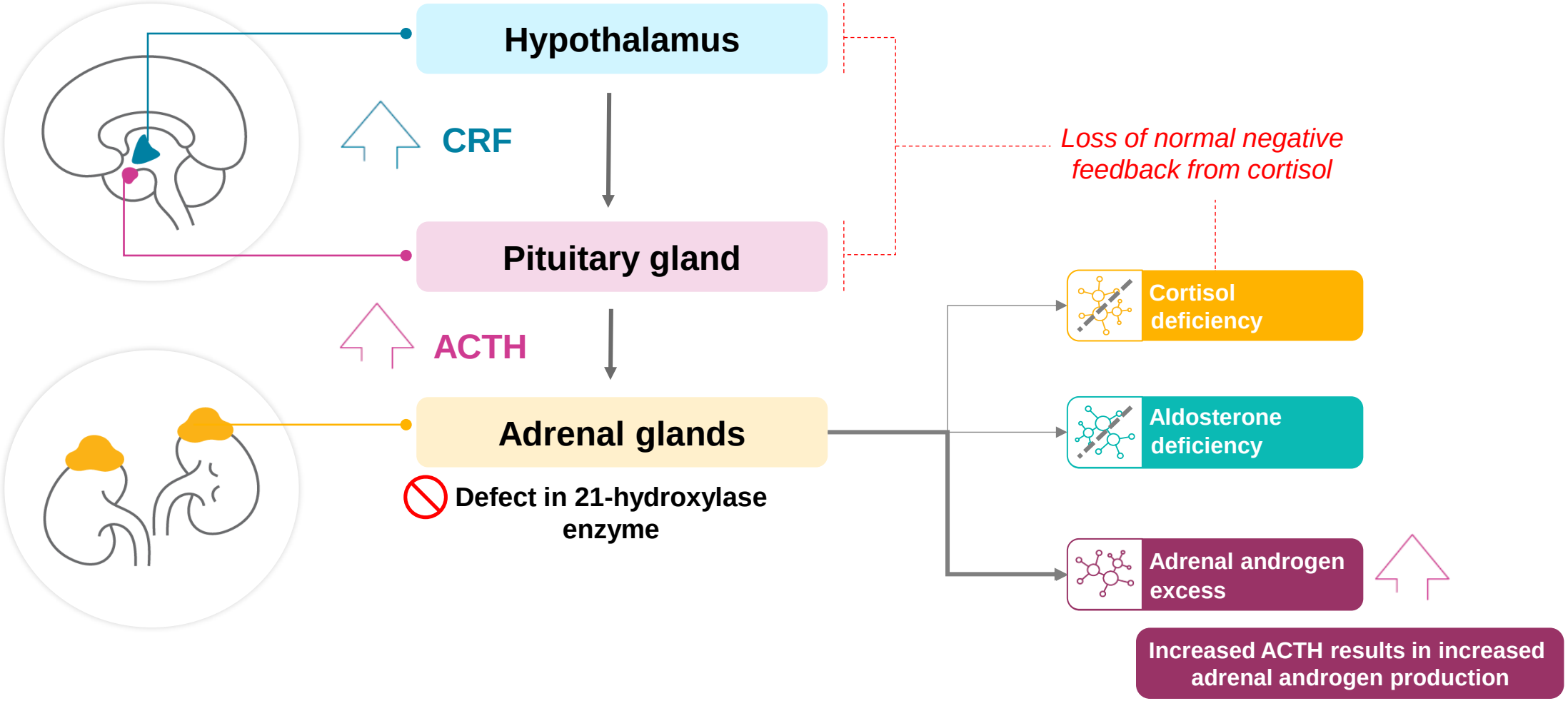
The Hypothalamic-Pituitary-Adrenal (HPA) Axis[1-3]



ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor.

1. Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088. 2. White PC, Speiser PW. *Endocr Rev.* 2000;21(3):245-291. 3. El-Maouche D, et al. *Lancet.* 2017;390(10108):2194-2210.

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



ACTH, adrenocorticotropic hormone; 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.

Current Management of CAH

GCs are used to REPLACE deficient endogenous cortisol and REDUCE excess ACTH and adrenal androgens by using *supraphysiologic* doses[1]

Complications of Excess ACTH and Adrenal Androgens[1-5]

Growth and development
- Advanced bone age
- Early puberty
- Short stature

Male health
- Testicular adrenal rest tumors
- Infertility

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

Other
- Negative psychological impact

Complications of GC Treatment at Supraphysiologic Doses[1-5]

Growth and development
- Short stature

Bone health
- Decreased bone density
- Increased fracture risk

Increased cardiovascular risk
- Hypertension

Musculoskeletal
- Muscle atrophy

Metabolic
- Weight gain
- Obesity
- Insulin resistance
- Diabetes

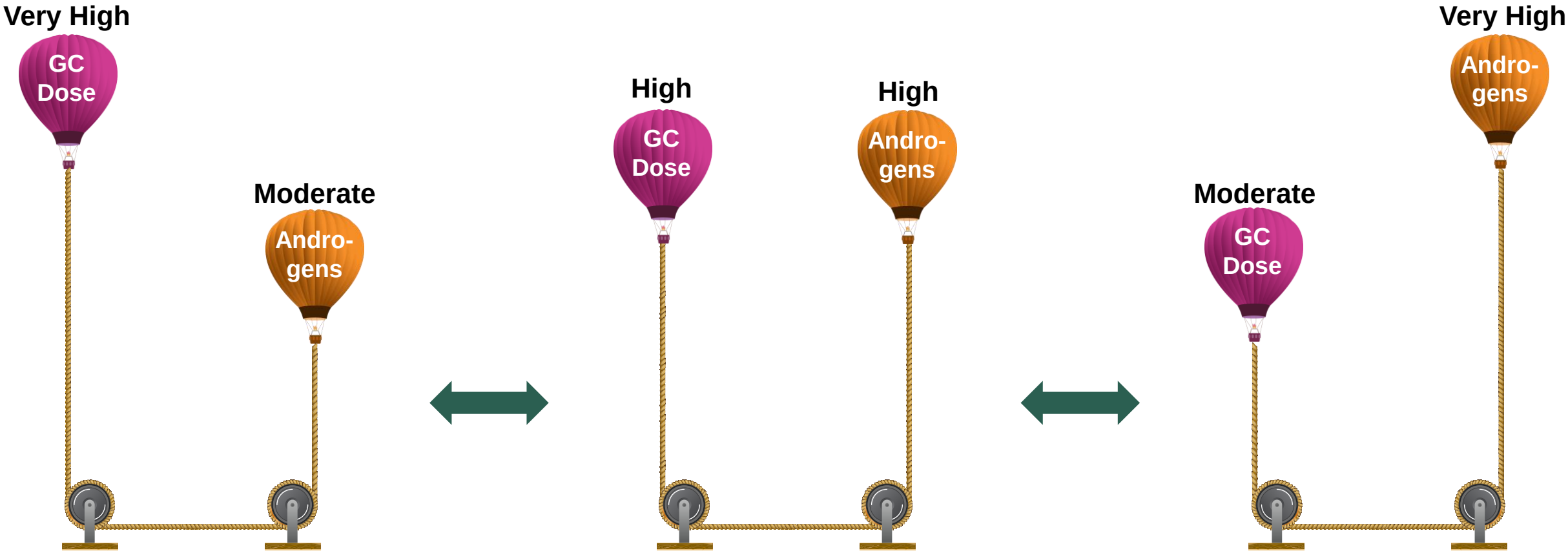
Other
- Mental health
- Cognition

Adequate adrenal androgen reduction should be balanced against the risks of chronic supraphysiologic GC exposure[2]

ACTH, adrenocorticotropic hormone; GC, glucocorticoid.

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

With Current GC Treatment Approaches, Patients With CAH Transition Between States of High GC Dose and/or Adrenal Androgen Levels

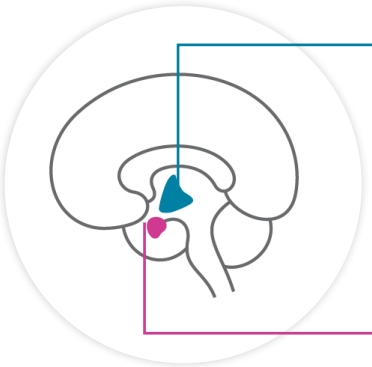


GC, glucocorticoid.

Lekarev O et al., poster presentation at ENDO; June 1-4, 2024; Boston, MA.

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

Prevents CRF from binding to the CRF type 1 receptor (CRF_1) → **Reduces ACTH and adrenal androgen levels** → **May potentially enable lower dosing of GCs**



Hypothalamus

CRF

Crinecerfont (CRF_1 antagonist)

CRF_1

Pituitary gland

ACTH

Adrenal glands

Defect in 21-hydroxylase enzyme

- **Cortisol deficiency** ← **GCs**
- **Aldosterone deficiency** ← **Mineralocorticoids**
- **Adrenal androgen excess**

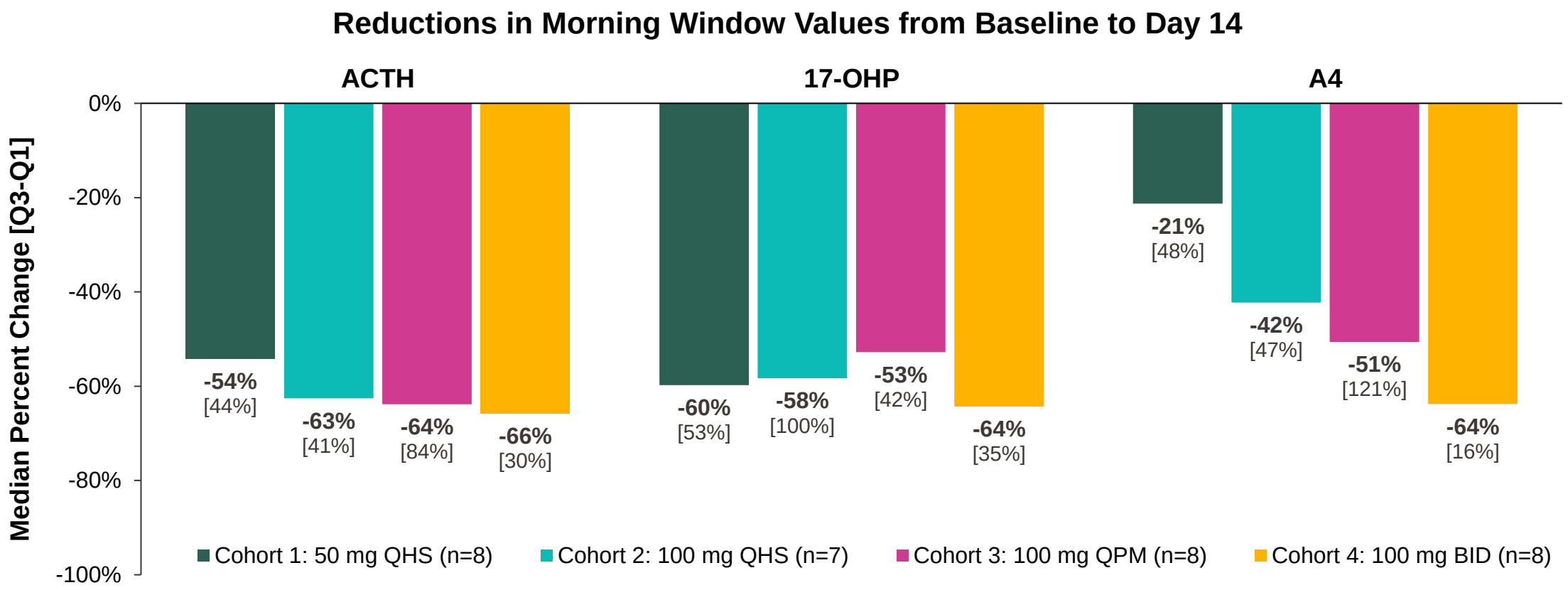
ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor; CRF_1, corticotropin-releasing factor type 1 receptor; GC, glucocorticoid.

1. Auchus RJ, et al. *J Clin Endocrinol Metab*. 2022;107(3):801-812. 2. Newfield RS, et al. *J Clin Endocrinol Metab*. 2023;108(11):2871-2878. 3. Auchus RJ, et al. *N Engl J Med*. 2024;391(6):504-514.
4. Sarafoglou K, et al. *N Engl J Med*. 2024;391(6):493-503.

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

Crinecerfont* Proof of Concept: CAHlibrate Study

Median percent changes from baseline in adrenal androgens and precursors



Crinecerfont treatment for 14 days lowered ACTH, 17-OHP, and A4 in adults with CAH

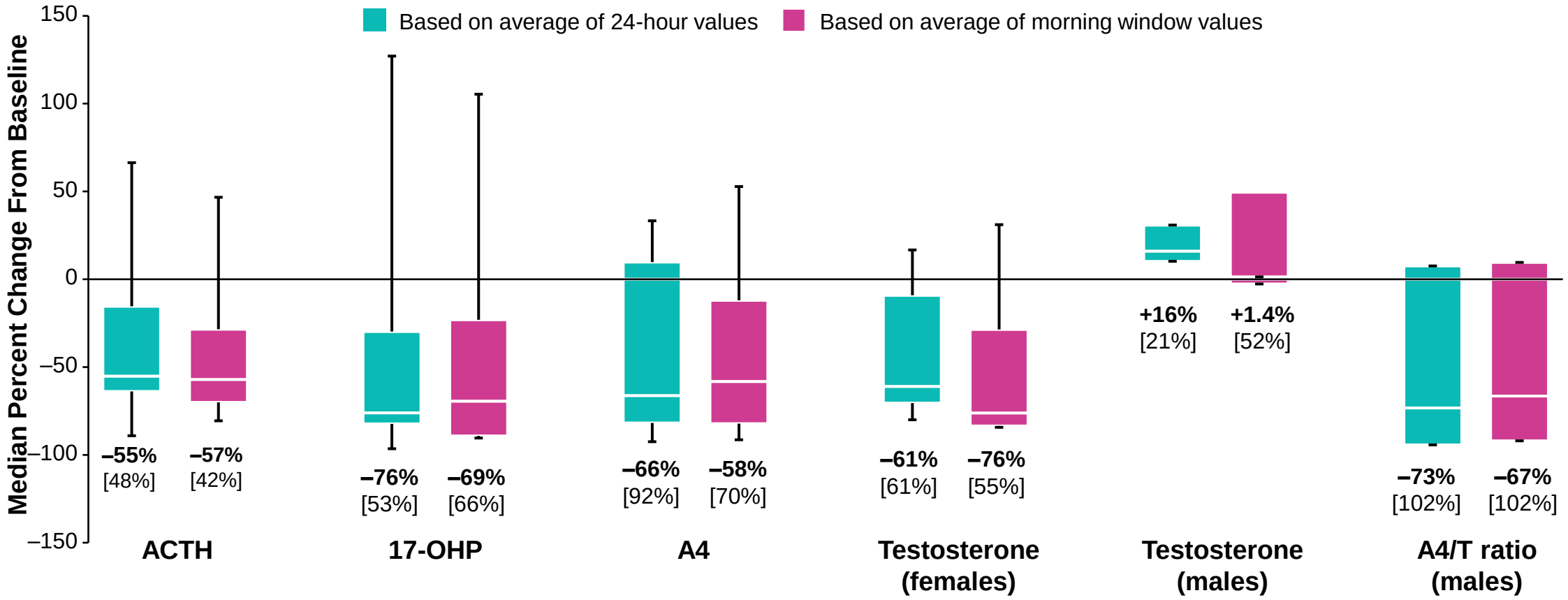
Median percent reductions from baseline to day 14 based on morning window values. Based on each participant's values from the morning window time points (06:00, 08:00, 10:00). The IQRs (absolute value of Q3-Q1) for median percent reductions are shown in brackets.
17-OHP, 17-hydroxyprogesterone; A4, androstenedione;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

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

CAHlibrate Study Design

Crinecerfont* Proof of Concept: CAHlibrate Pediatric Study in Adolescents

Median percent changes from baseline in adrenal androgens and precursors with crinecerfont 50 mg BID[a]

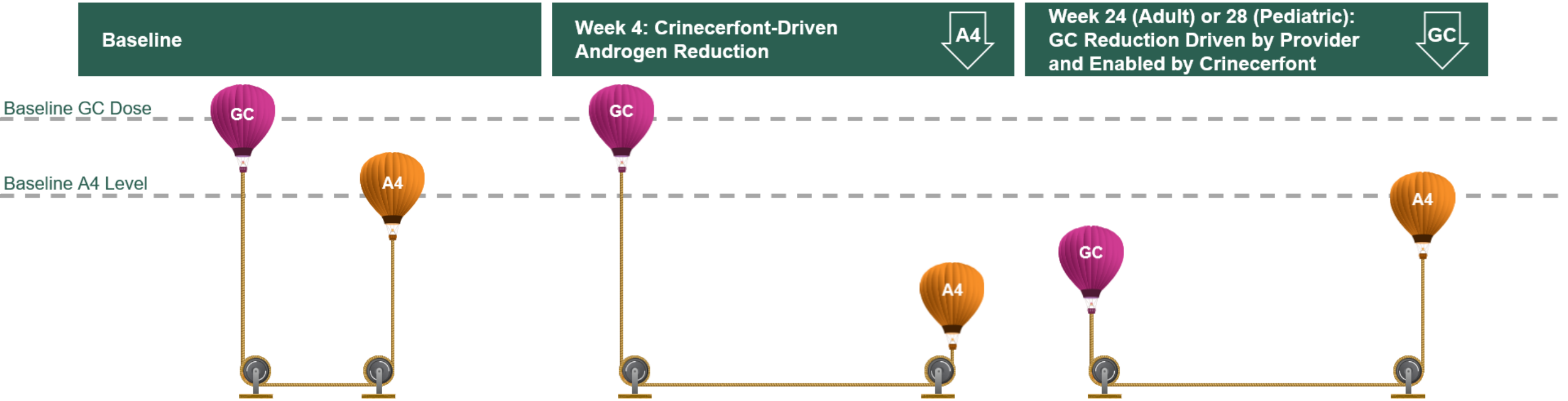


≥50% Median reductions in ACTH, 17-OHP, A4, testosterone (females), and A4/T ratio (males)

17-OHP, 17-hydroxyprogesterone; A4, androstenedione; A4/T, androstenedione-to-testosterone; ACTH, adrenocorticotropic hormone; IQR; interquartile range.
[a]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 below the bars represent median [IQR] values, except for the testosterone and A4/T ratio in males, where data represent median [minimum and maximum] values (n=3).
Newfield RS, et al. *J Clin Endocrinol Metab*. 2023:dgad270.

CAHlibrate Pediatric Study Design

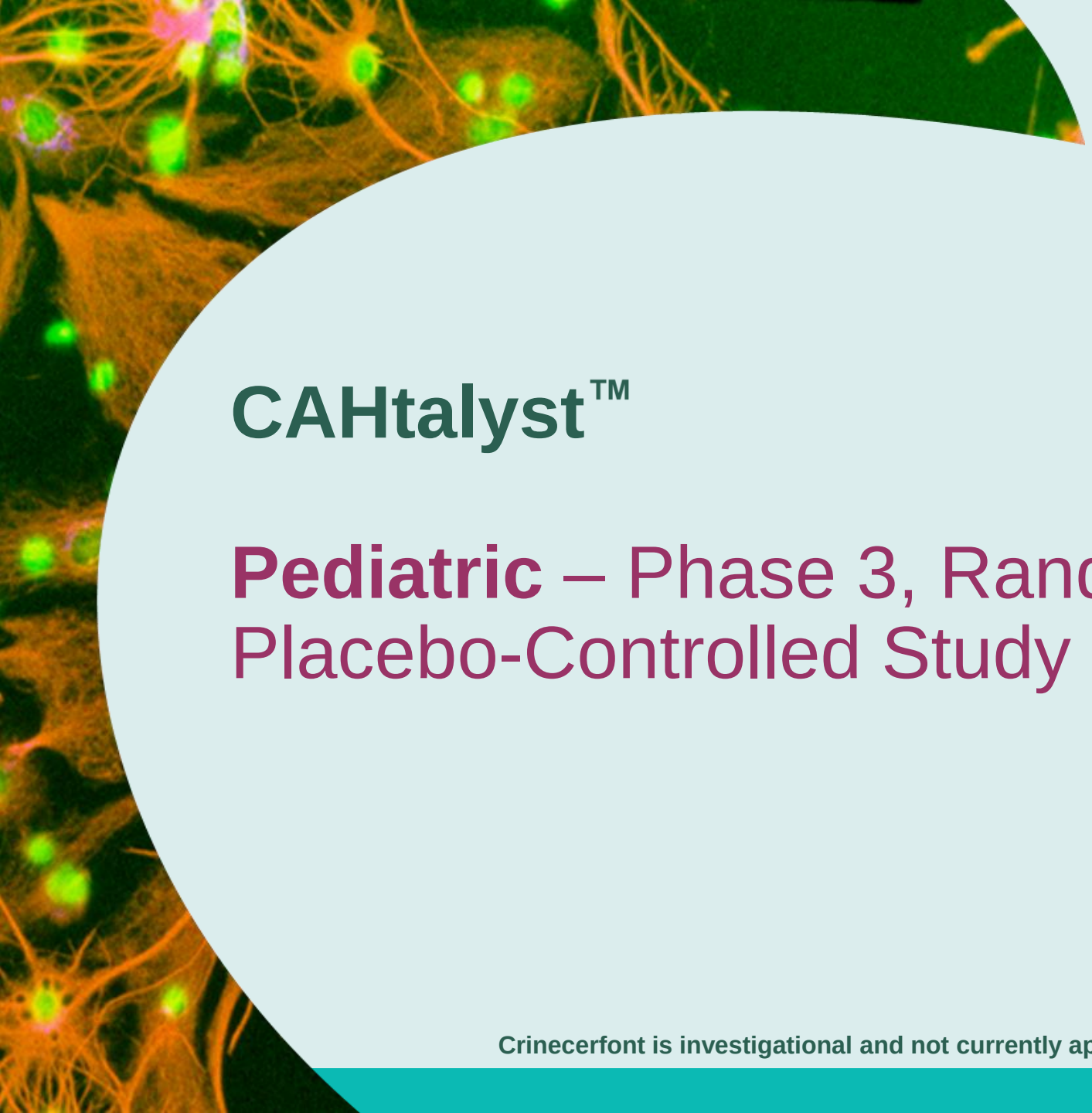
Crinecerfont* Phase 3 Studies: Hypotheses



Hypothesis 1:
While holding GC dose stable, **crinecerfont can reduce A4**

Hypothesis 2:
Crinecerfont allows for GC reduction ***while maintaining A4 levels[a]***

A4, androstenedione; GC, glucocorticoid; ULN, upper limit of normal.
[a]A4 maintenance was defined as ≤120% of baseline or ≤ULN according to sex and age.
Auchus RJ, et al. Presented at: The Endocrine Society's Annual Meeting; June 1-4, 2024; Boston, MA.

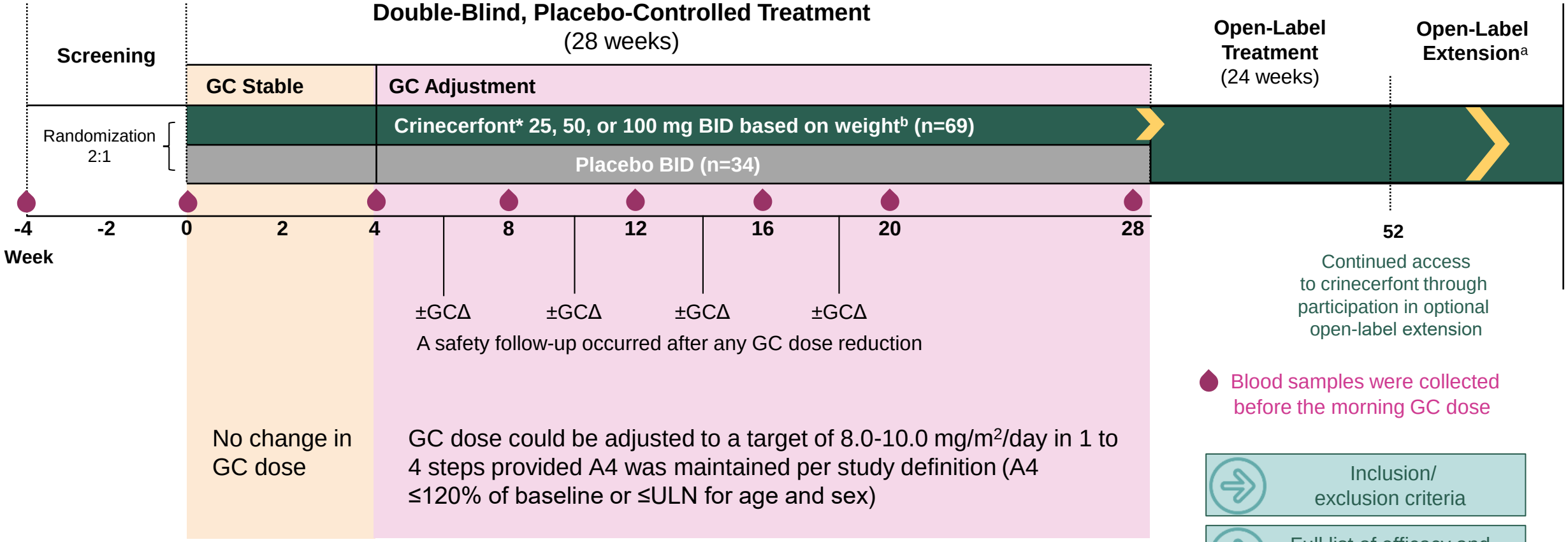


CAHtalyst™

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

Crinecerfont is investigational and not currently approved in any country.

CAHtalyst Pediatric Study Design



- Inclusion/ exclusion criteria
- Full list of efficacy and safety endpoints
- Participant flow chart

A4, androstenedione; BID, twice daily; GC, glucocorticoid; ULN, upper limit of normal.
[a]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.
[B]25 mg for participants with a body weight of 10 to <20 kg, 50 mg for those with a body weight of 20 to <55 kg, or 100 mg for those with a body weight of ≥55 kg.
Sarafoglou K, et al. *N Engl J Med*. 2024;391(6):493-503.

Demographics and Baseline Characteristics

	Placebo (n=34)	Crinecerfont* (n=69)	All Participants (n=103)
Demographics			
Age, mean (SD), years	12.1 (3.7)	12.0 (3.4)	12.1 (3.5)
Median	12.2	12.6	12.6
(min, max)	(4.6, 17.8)	(5.3, 17.8)	(4.6, 17.8)
12-17 years, n (%)	18 (52.9)	38 (55.1)	56 (54.4)
Male, n (%)	18 (52.9)	35 (50.7)	53 (51.5)
Race, n (%)[a]			
White	23 (67.6)	42 (60.9)	65 (63.1)
Asian	2 (5.9)	7 (10.1)	9 (8.7)
Black or African American	0	3 (4.3)	3 (2.9)
Ethnicity, n (%)[b]			
Hispanic or Latino	3 (8.8)	8 (11.6)	11 (10.7)
Not Hispanic or Latino	25 (73.5)	52 (75.4)	77 (74.8)
Geographic region, n (%)			
United States	14 (41.2)	44 (63.8)	58 (56.3)
Rest of the world[c]	20 (58.8)	25 (36.2)	45 (43.7)

SD, standard deviation.
[a]Race not reported for 15 participants. Additional categories were as follows: Native American or Alaska Native (n=1, crinecerfont arm), Native Hawaiian or Pacific Islander (n=1, crinecerfont arm), Other (n=5 [not specified]), or multiple (n=4).
[b]Ethnicity not collected for 15 participants.
[c]Includes Canada and Europe.
Sarafoglou K, et al. Supplementary Appendix. *N Engl J Med*. 2024;391(6):493-503.

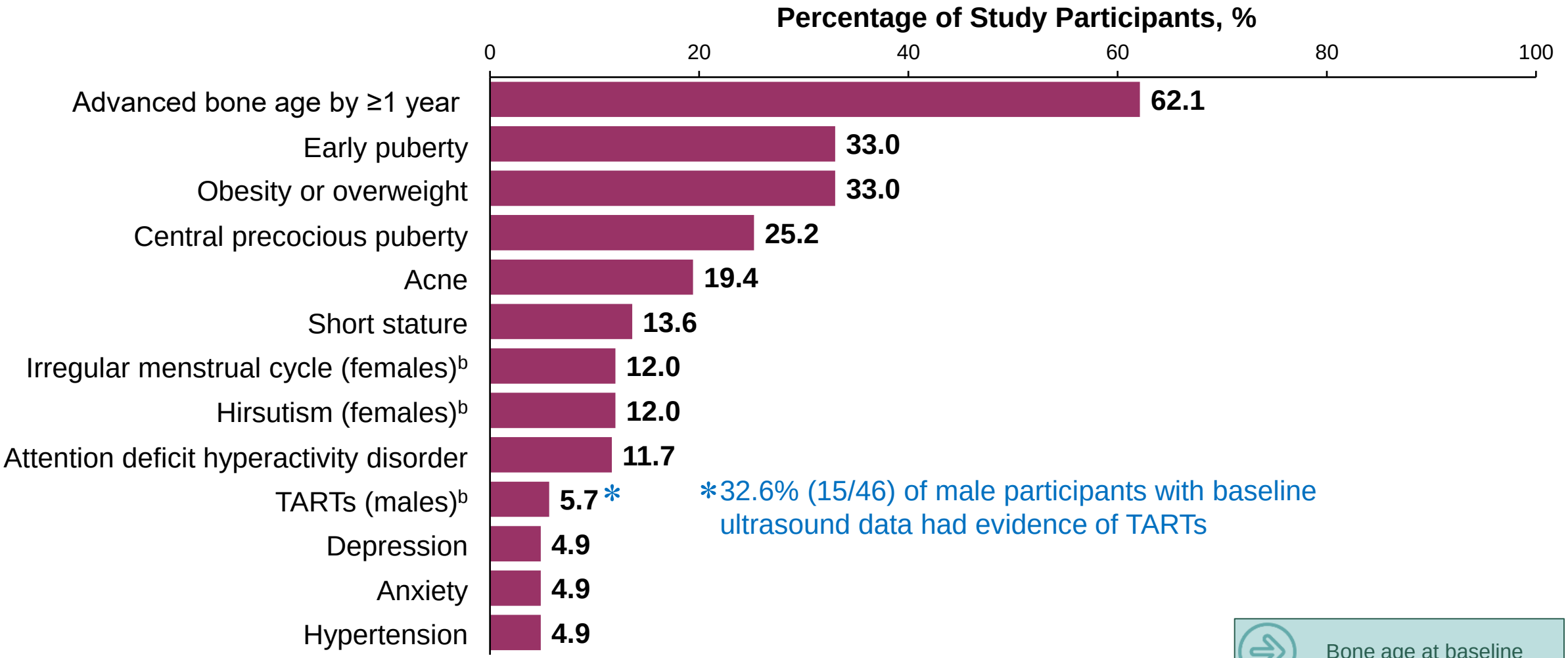
*Crinecerfont is investigational and not currently approved in any country.

Demographics and Baseline Characteristics (cont'd)

	Placebo (n=34)	Crinecerfont* (n=69)	All Participants (n=103)
Height SDS, mean (SD)[a]	0.4 (1.2)	0.3 (1.4)	0.3 (1.3)
BMI SDS, mean (SD)[a]	1.1 (1.0)	1.2 (0.9)	1.2 (0.9)
BMI ≥ 85th percentile, n (%)	20 (58.8)	40 (58.0)	60 (58.3)
In growing participants, n[b]	16	39	55
Height SDS, adjusted for BA, mean (SD)[a]	-0.9 (1.3)	-0.5 (1.0)	-0.6 (1.1)
BA:CA, mean (SD)	1.2 (0.3)	1.1 (0.2)	1.1 (0.2)
BA SDS, mean (SD)[c]	2.6 (2.5)	1.8 (2.0)	2.0 (2.2)
Tanner stage (breast or testicular), n (%)			
Stage 1	12 (35.3)	18 (26.1)	30 (29.1)
Stage 2	2 (5.9)	10 (14.5)	12 (11.7)
Stage 3	5 (14.7)	8 (11.6)	13 (12.6)
Stage 4	4 (11.8)	15 (21.7)	19 (18.4)
Stage 5	11 (32.4)	18 (26.1)	29 (28.2)
Age at menarche in female participants, mean (SD), years[d]	13.0 (2.9)	11.6 (1.8)	11.9 (2.1)
TARTS in male participants, n (%)[e]	5 (33.3)	10 (32.3)	15 (32.6)
A4, mean (SD), ng/dL[f]	483 (456)	405 (464)	431 (461)
17-OHP, mean (SD), ng/dL[f]	9026 (5563)	8513 (7431)	8682 (6847)

17-OHP, 17-hydroxyprogesterone; A4, androstenedione; BA, bone age; BA:CA bone age–to–chronologic age; BMI, body mass index; SD, standard deviation; SDS, standard deviation score.
[a]Height and BMI SDS calculated using the Centers for Disease Control and Prevention growth charts.
[b]In participants not at adult height (i.e., bone age <14 years in female or <16 years in male participants) and not on GnRH agonist therapy, growth hormone therapy, or aromatase inhibitors at study entry.
[c]Bone age SDS calculated using the *Radiographic Atlas of Skeletal Development of the Hand and Wrist – Second Edition* [Greulich 1959].
[d]In 16 female participants (12 crinecerfont, 4 placebo) who had undergone menarche and were not on hormonal contraceptives.
[e]In 46 male participants (31 crinecerfont, 15 placebo) who had available testicular ultrasound assessments at baseline.
[f]Analyzed using blood samples collected before the morning GC dose.
Sarafoglou K, et al. Supplementary Appendix. *N Engl J Med*. 2024;391(6):493-503.

Medical Conditions of Interest Related to the CAH Population[a]



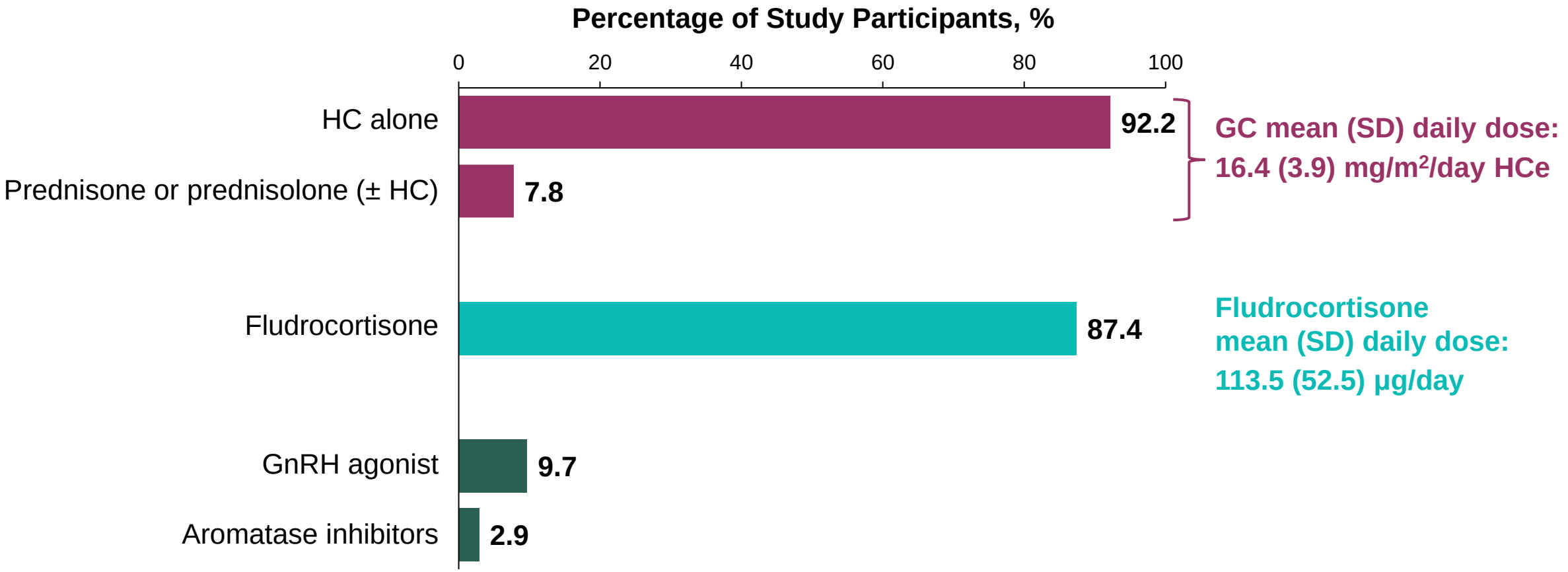
*32.6% (15/46) of male participants with baseline ultrasound data had evidence of TARTs

Bone age at baseline

TART, testicular adrenal rest tumor.
[a]As reported for ≥5 total participants in the randomized population (N=103).
[b]Percentage based on reporting for female (n=50) or male (n=53) participants.
Sarafoglou K, et al. Presented at: Pediatric Endocrine Society (PES) Annual Meeting; May 2-5, 2024; Chicago, IL.

CAHtalyst Pediatric Study

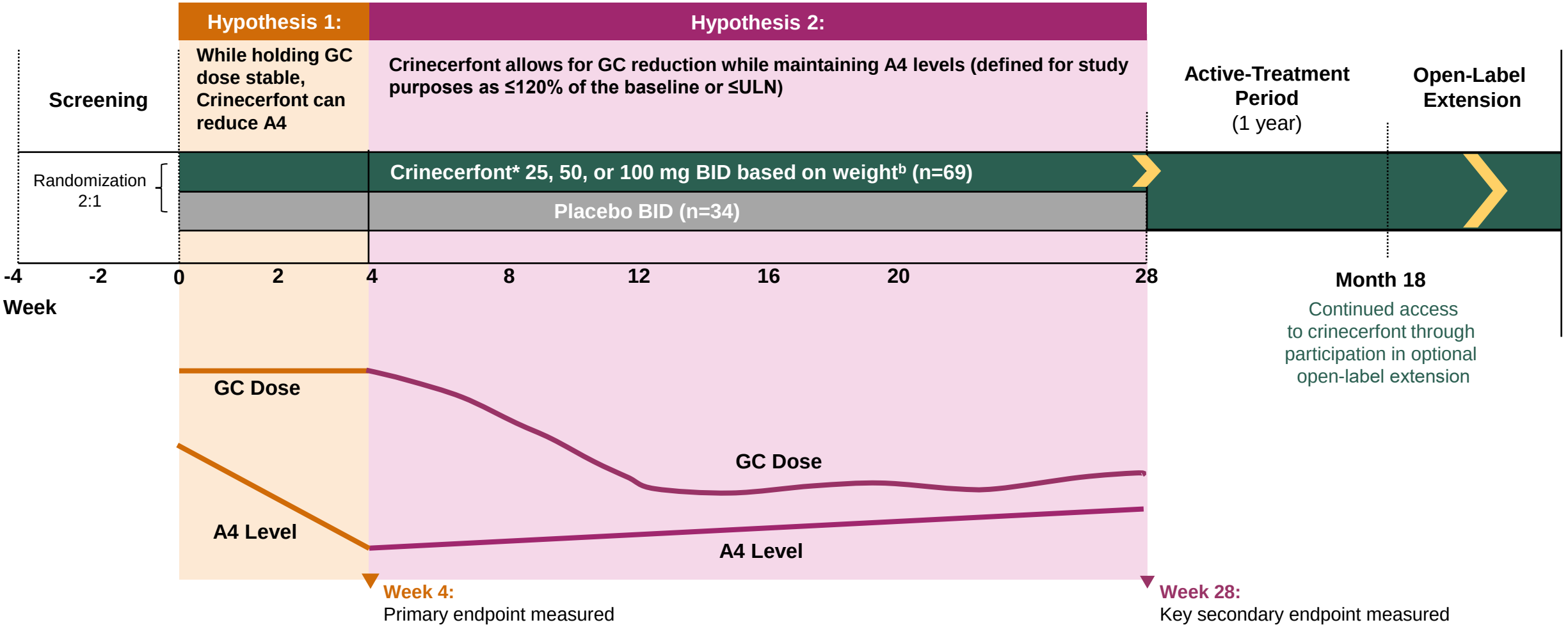
Glucocorticoids and other CAH treatments at baseline



GC, glucocorticoid; GnRH, gonadotropin-releasing hormone; HC, hydrocortisone; HCe, hydrocortisone equivalents; SD, standard deviation.

Sarafoglou K, et al. Presented at: Pediatric Endocrine Society (PES) Annual Meeting; May 2-5, 2024; Chicago, IL.

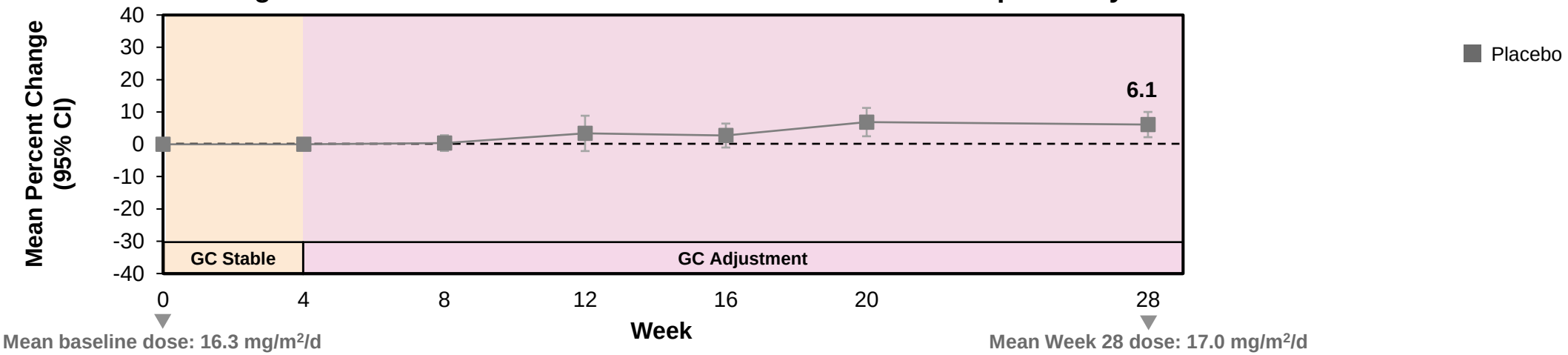
CAHtalyst Pediatric Study Design (cont'd)



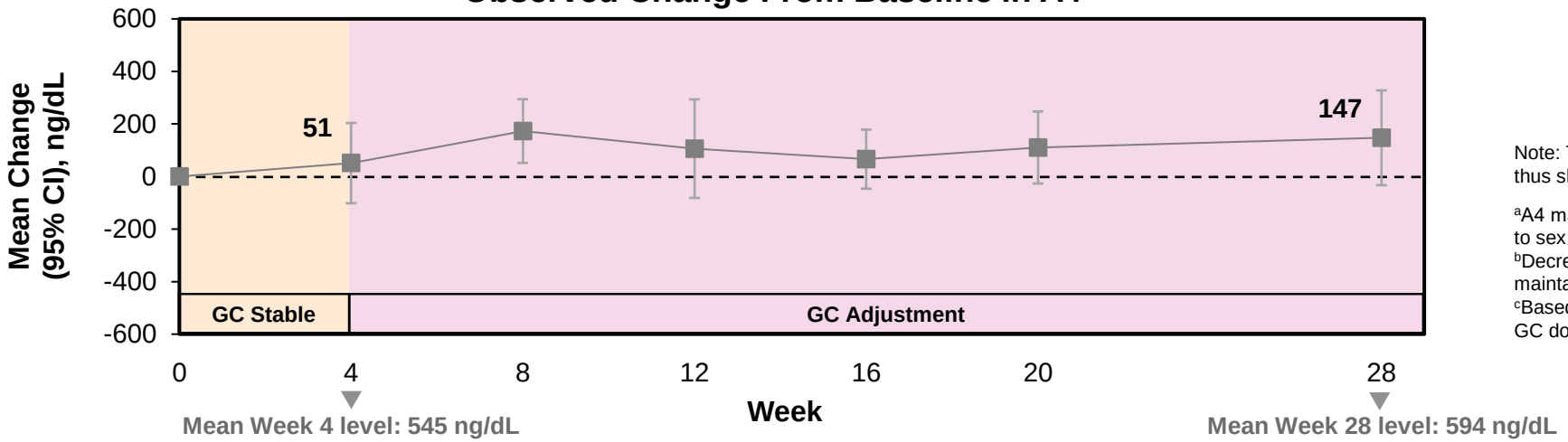
Note: Trend lines shown above for GC and A4 levels are for illustrative purposes only.
A4, androstenedione; GC, glucocorticoid; OLE, open-label extension; ULN: upper limit of normal.
[a]Duration of participation in the study is approximately 14 months for the core study and will be a variable amount of time per participant for the open-label extension.
[b]25 mg for participants with a body weight of 10 to <20 kg, 50 mg for those with a body weight of 20 to <55 kg, or 100 mg for those with a body weight of ≥55 kg.
Sarafoglou K, et al. *N Engl J Med*. 2024;391(6):493-503.

CAH Current Treatment as Depicted by Placebo Group: GC Dose Remained Stable in an Effort to Maintain A4 Levels[a]

Observed Change From Baseline in GC Dose[b] While A4 Was Maintained per Study Definition



Observed Change From Baseline in A4[c]



Note: The widths of the CIs have not been adjusted for multiplicity and thus should not be used to determine treatment effect.

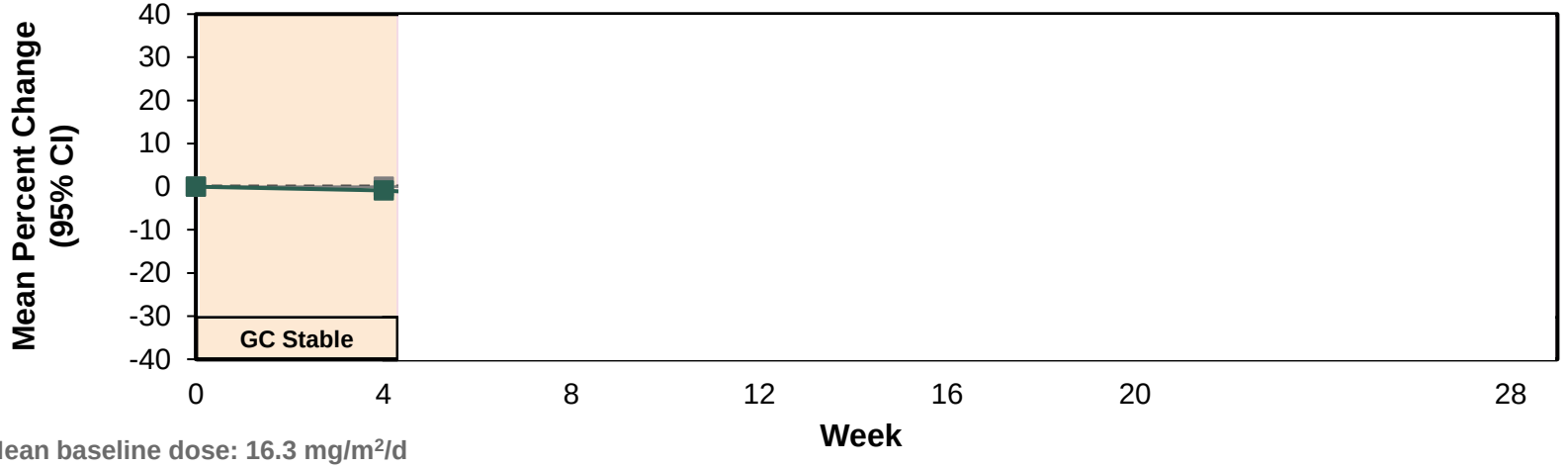
[a]A4 maintenance was defined as ≤120% of baseline or ≤ULN according to sex and age.
[b]Decreases in GC dose were set to 0 in participants who did not maintain androgen levels.
[c]Based on samples collected before participants received their morning GC doses.

A4, androstenedione; CI, confidence interval; GC, glucocorticoid; ULN, upper limit of normal.

Sarafoglou K, et al. *N Engl J Med*. 2024;391(6):493-503.

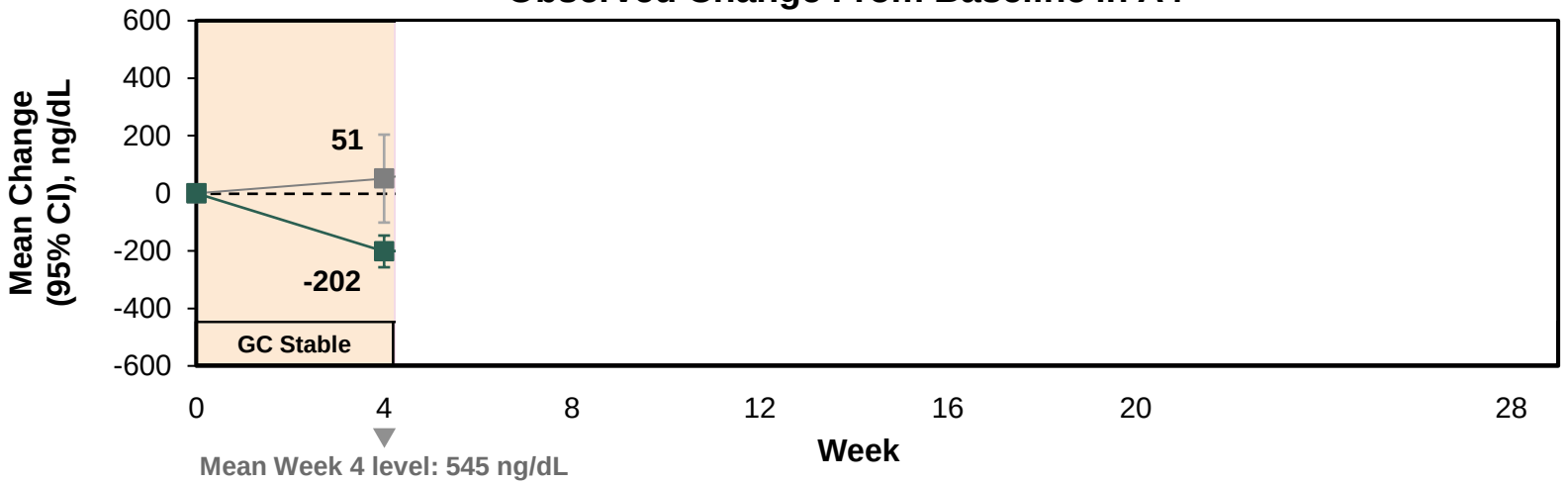
Hypothesis 1: While Holding GC Dose Stable, Crinecerfont* Can Reduce A4 At Week 4

Observed Change From Baseline in GC Dose[a] While A4 Was Maintained per Study Definition[b]



Mean baseline dose: 16.3 mg/m²/d
Mean baseline dose: 16.5 mg/m²/d

Observed Change From Baseline in A4[c]



Mean Week 4 level: 545 ng/dL
Mean Week 4 level: 208 ng/dL

Primary Endpoint Met:
A4 levels decreased with crinecerfont (−197 ng/dL) but increased with placebo (71 ng/dL) (LSMD, −268 ng/dL; *P*<0.001) during the 4-week GC stable period

Note: The widths of the CIs have not been adjusted for multiplicity and thus should not be used to determine treatment effect.

[a]Decreases in GC dose were set to 0 in participants who did not maintain androgen levels.
[b]A4 maintenance was defined as ≤120% of baseline or ≤ULN according to sex and age.
[c]Based on samples collected before participants received their morning GC doses.

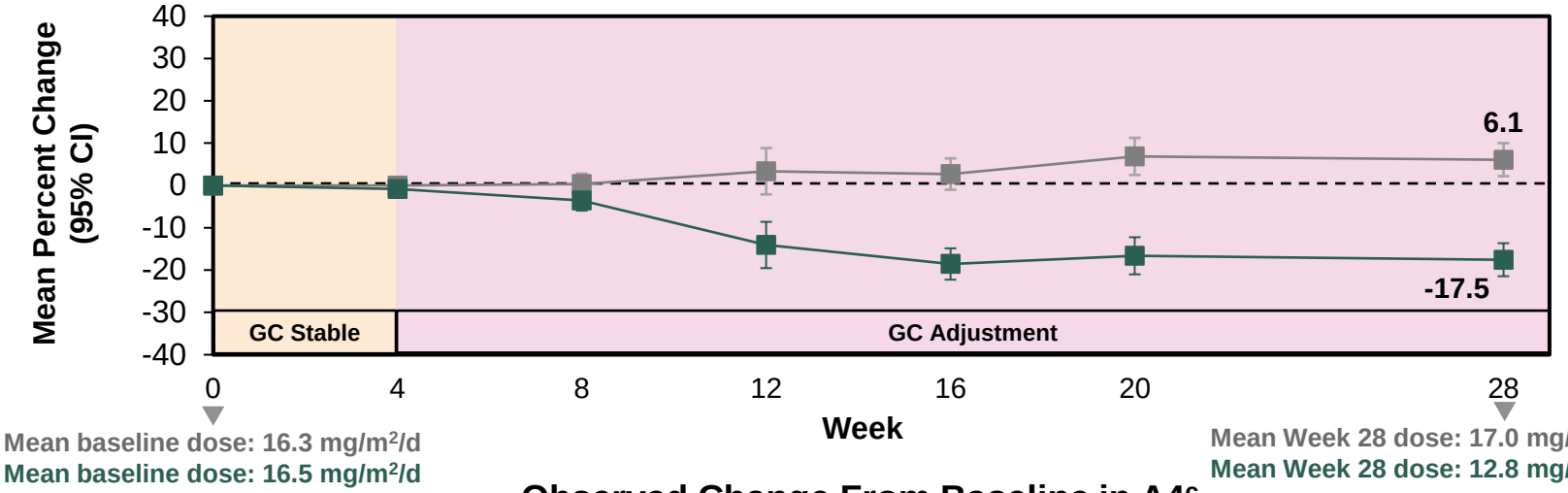
17-OHP, 17-hydroxyprogesterone; A4, androstenedione; CI, confidence interval; GC, glucocorticoid; LSMD, least-squares mean difference; ULN, upper limit of normal.

Sarafoglou K, et al. *N Engl J Med*. 2024;391(6):493-503.

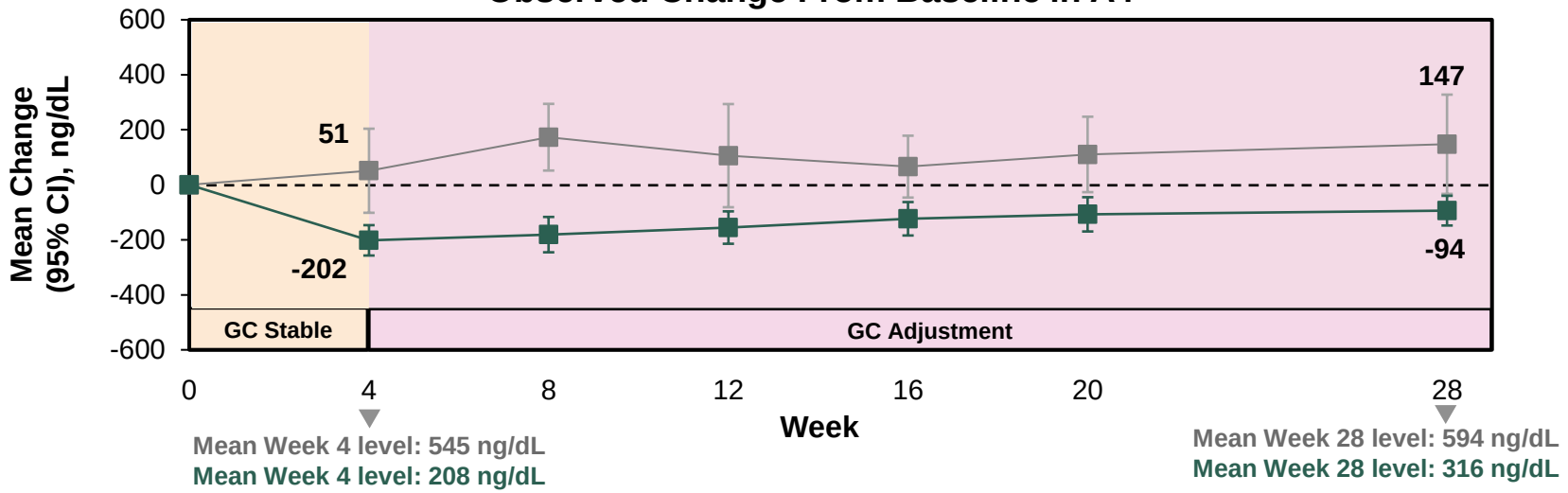
17-OHP levels at Week 4

Hypothesis 2: Crinecerfont* Allows For GC Reduction While Maintaining A4 Levels[a] at Week 28

Observed Change From Baseline in GC Dose[b] While A4 Was Maintained per Study Definition



Observed Change From Baseline in A4[c]



Placebo Crinecerfont

Key Secondary Endpoint Met: GC dose reduction while maintaining A4 levels was significantly greater in the crinecerfont group than in the placebo group at Week 28 (−18.0% vs. 5.6%; LSMD, −23.5 percentage points; *P*<0.001)

Note: The widths of the CIs have not been adjusted for multiplicity and thus should not be used to determine treatment effect.

[a]A4 maintenance was defined as ≤120% of baseline or ≤ULN according to sex and age.
[b]Decreases in GC dose were set to 0 in participants who did not maintain androgen levels.
[c]Based on samples collected before participants received their morning GC doses.

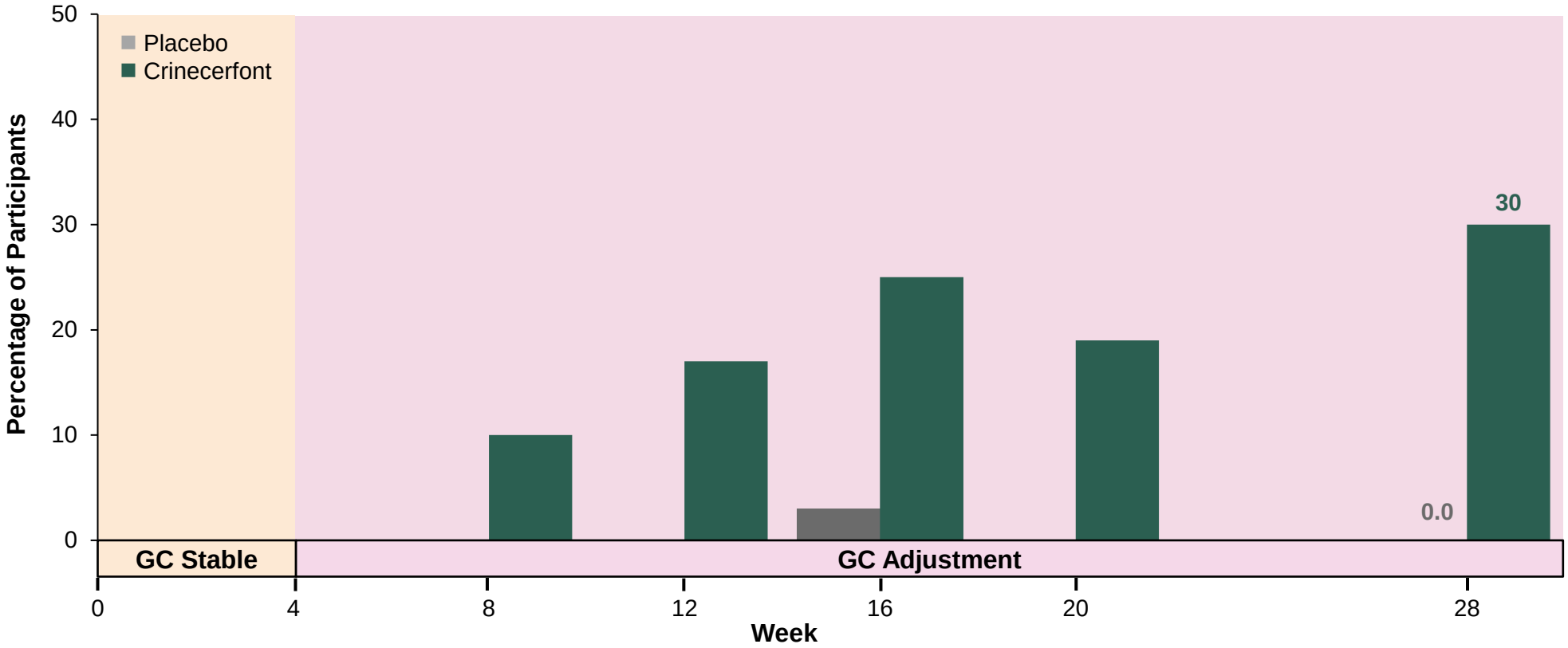
17-OHP, 17-hydroxyprogesterone; A4, androstenedione; CI, confidence interval; GC, glucocorticoid; LSMD, least-squares mean difference; ULN, upper limit of normal.

Sarafoglou K, et al. *N Engl J Med*. 2024;391(6):493-503.

17-OHP Levels at Week 28

Hypothesis 2: Crinecerfont* Allows for GC Reduction While Maintaining A4 Levels[a] at Week 28 (cont'd)

Achievement of Physiologic GC Dose (≤11 mg/m^2/day)[b] While A4 Levels Were Maintained[1,a]



Secondary Endpoint Met: Among crinecerfont-treated participants, 30% achieved a physiologic GC dose (≤11.0 mg/m^2/day) in HCe at Week 28 while maintaining A4 levels, as compared with 0% in the placebo group

A4, androstenedione; GC, glucocorticoid; HCe, hydrocortisone dose equivalents; ULN, upper limit of normal.
[a]A4 maintenance was defined as ≤120% of baseline or ≤ULN according to sex and age.
[b]A physiologic GC dose was defined as ≤11 mg/m^2/day in HCe, according to the 95th percentile of cortisol production in healthy persons.[2,3]
1. Sarafoglou K, et al. *N Engl J Med*. 2024;391(6):493-503. 2. Purnell JQ, et al. *J Clin Endocrinol Metab*. 2004;89(1):281-287. 3. Linder BL, et al. *J Pediatr*. 1990;117(6):892-896.

Additional Secondary and Exploratory Endpoints at Week 28

	Crinecerfont*		Placebo		LSM Difference (95% CI)
	n	LSM CFB (SEM)	n	LSM CFB (SEM)	
Secondary endpoints (at Week 28)[a]					
BMI SDS[b]	68	-0.09 (0.04)	31	0.04 (0.06)	-0.13 (-0.27, 0.00)
BA:CA ratio in growing participants[c]	34	-0.009 (0.007)	14	-0.006 (0.010)	-0.003 (-0.027, 0.022)
Exploratory endpoints (at Week 28)[a]					
In growing participants[c]					
• Height SDS[b]	38	0.43 (0.03)	16	0.46 (0.05)	-0.02 (-0.14, 0.10)
• Bone age SDS[d]	34	0.70 (0.09)	14	0.75 (0.15)	-0.05 (-0.39, 0.29)
• Height SDS, adjusted for BA[b]	33	-0.02 (0.06)	14	0.04 (0.09)	-0.06 (-0.28, 0.16)
HOMA-IR	64	-0.63 (0.25)	29	0.27 (0.37)	-0.90 (-1.78, -0.01)
Hirsutism VAS (female participants), mm	33	-7.0 (2.2)	14	2.3 (3.4)	-9.3 (-17.4, -1.2)
Reduction of A4/T ratio from ≥0.5 at baseline to <0.5 at week 28 (male participants), n (%)	21	8 (38.1)	9	0 (0.0)	Not applicable

17-OHP, 17-hydroxyprogesterone; A4, androstenedione; A4/T, androstenedione-to-testosterone; BA, bone age; BA:CA bone age-to-chronological age; BMI, body mass index; CFB, change from baseline; CI, confidence interval; HOMA-IR, homeostatic model assessment for insulin resistance; LSM, least-squares mean; SDS, standard deviation score; SEM, standard error of the mean; VAS, visual analog scale.

[a]Endpoints are presented as LSM CFB at week 28 with SEM, unless indicated otherwise. Where applicable, the LSM difference between treatment groups (crinecerfont – placebo) is noted, along with the 95% CI. P-values for secondary and exploratory endpoints were considered nominal and are not shown. 95% CIs for these endpoints were not adjusted for multiplicity, and the intervals may not be used in place of hypothesis testing. | [b]Weight, height, and BMI SDS were calculated based on Center for Disease Control and Prevention growth charts| [c]Participants who were not at adult height (i.e., bone age <14 years in female participants or <16 years in male participants) and not taking gonadotropin-releasing hormone agonist therapy, growth hormone therapy, or aromatase inhibitors at study entry. | [d]Bone age SDS was calculated using the Radiographic Atlas of Skeletal Development of the Hand and Wrist - Second Edition [Greulich 1959].

Sarafoglou K, et al. Supplementary Appendix. *N Engl J Med*. 2024;391(6):493-503.

Summary of Adverse Events

Crinecerfont* was generally well tolerated with few serious TEAEs or discontinuations due to TEAEs

Adverse Event	Crinecerfont (n = 69)	Placebo (n = 33)
	n (%)	
Any adverse event	58 (84)	27 (82)
Any serious adverse event[a]	1 (1)	4 (12)
Any adverse event leading to discontinuation of trial regimen[b]	2 (3)	0
Any adverse event leading to withdrawal from trial[b]	2 (3)	0
Any adverse event resulting in death	0	0
Severity of adverse event[c]		
• Mild	37 (54)	13 (39)
• Moderate	20 (29)	12 (36)
• Severe	1 (1)	2 (6)

TEAEs, treatment emergent adverse events.
[a]Serious adverse events included pyrexia (1 participant in the crinecerfont group) and vomiting and pharyngitis, gastroenteritis norovirus and gastroenteritis, gastroenteritis, and vomiting and chest pain (1 each in the placebo group). All serious adverse events were considered by the investigator to be unlikely or unrelated to the trial regimen. | [b]In the crinecerfont group, 2 participants discontinued treatment and withdrew from the trial: 1 had body aches, upper abdominal pain, and nausea (considered to be unrelated to the treatment), and 1 had nausea, dizziness, retching, and motion sickness (considered to be possibly related to the treatment). | [c]The maximum level of severity, as judged by the trial investigator, is shown.
Sarafoglou K, et al. *N Engl J Med*. 2024;391(6):493-503.

Common Adverse Events

Adverse events reported in at least 4 participants (>5%) receiving crinecerfont*

Adverse Event	Crinecerfont (n = 69)	Placebo (n = 33)
	n (%)	
Headache	17 (25)	2 (6)
Pyrexia	16 (23)	8 (24)
Vomiting	10 (14)	10 (30)
Upper respiratory tract infection	8 (12)	0
Nasopharyngitis	7 (10)	6 (18)
Influenza	6 (9)	2 (6)
Abdominal pain	5 (7)	0
Coronavirus infection	5 (7)	3 (9)
Fatigue	5 (7)	0
Nasal congestion	5 (7)	1 (3)
Cough	4 (6)	2 (6)
Dizziness	4 (6)	3 (9)
Nausea	4 (6)	2 (6)
Streptococcal pharyngitis	4 (6)	0
Viral infection	4 (6)	1 (3)

Sarafoglou K, et al. *N Engl J Med*. 2024;391(6):493-503.

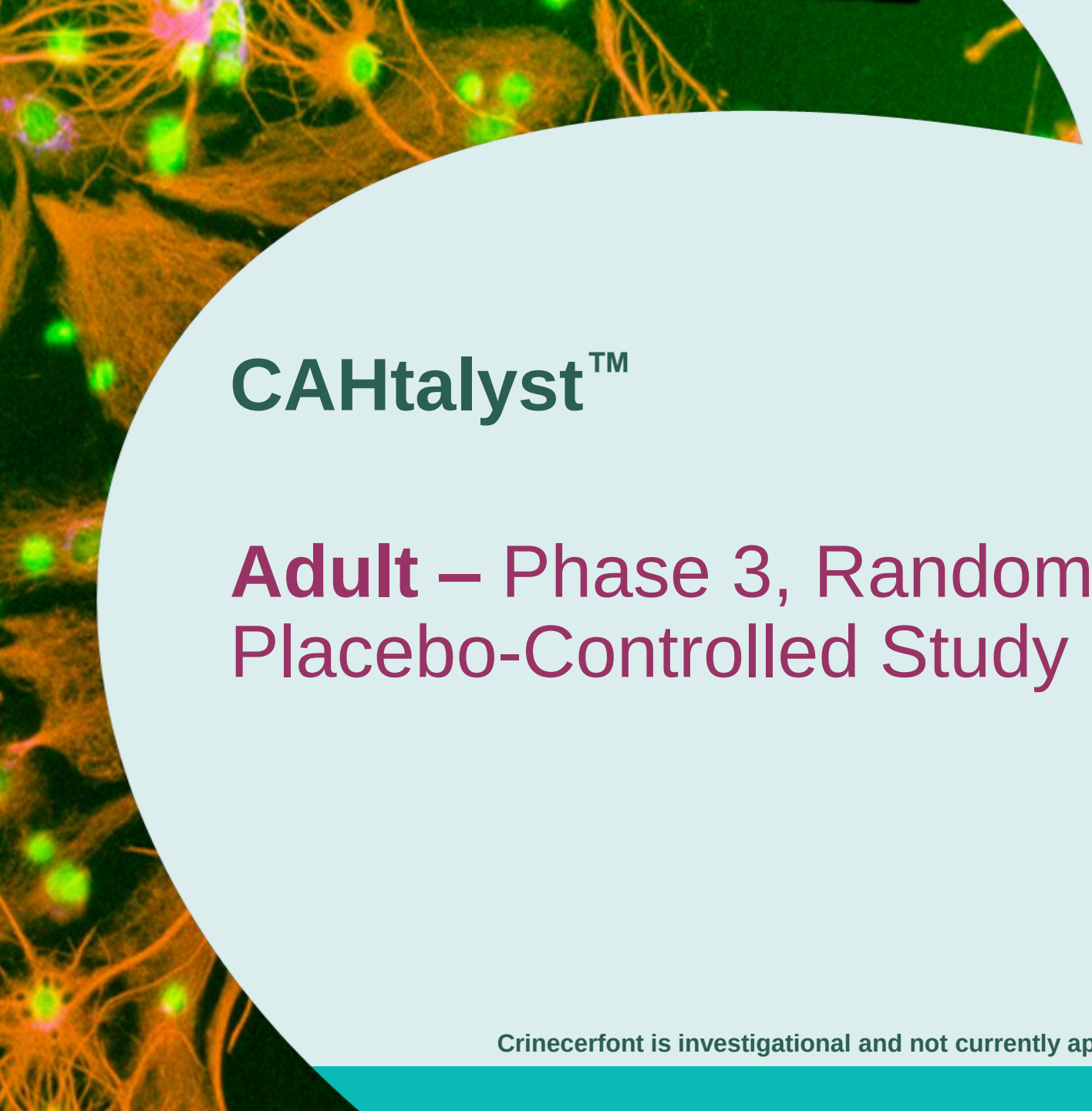
***Crinecerfont is investigational and not currently approved in any country.**

CAHtalyst Pediatric Study Summary

- CAHtalyst Pediatric was a 28-week Phase 3, randomized, DBPC study to evaluate the safety, efficacy, and tolerability of crinecerfont* for pediatric (eligible ages: 2-17) participants with CAH
- At Week 4, the A4 level was reduced in the crinecerfont group (-197 ng/dL) but increased in the placebo group (71 ng/dL) (LSMD, -268 ng/dL, *P*<0.001)
- At Week 28, the mean GC dose had decreased (with maintenance of A4 levels per study definition) by 18.0% with crinecerfont, but increased by 5.6% with placebo (LSMD -23.5, *P*<0.001)
- Among crinecerfont-treated participants, 30% achieved a physiologic GC dose (defined as ≤11 mg/m^2/day HCe) with maintenance of A4 levels per study definition at Week 28, compared to 0% in the placebo group
- Crinecerfont was generally well tolerated, with few SAEs or discontinuations due to TEAEs
- Headache, pyrexia, and vomiting were the most common adverse events in the 2 study groups

17-OHP, 17-hydroxyprogesterone; A4, androstenedione; DBPC, double-blind, placebo-controlled; GC, glucocorticoid; HCe, hydrocortisone equivalents; LSMD, least-squares mean difference; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Sarafoglou K, et al. *N Engl J Med*. 2024;391(6):493-503.

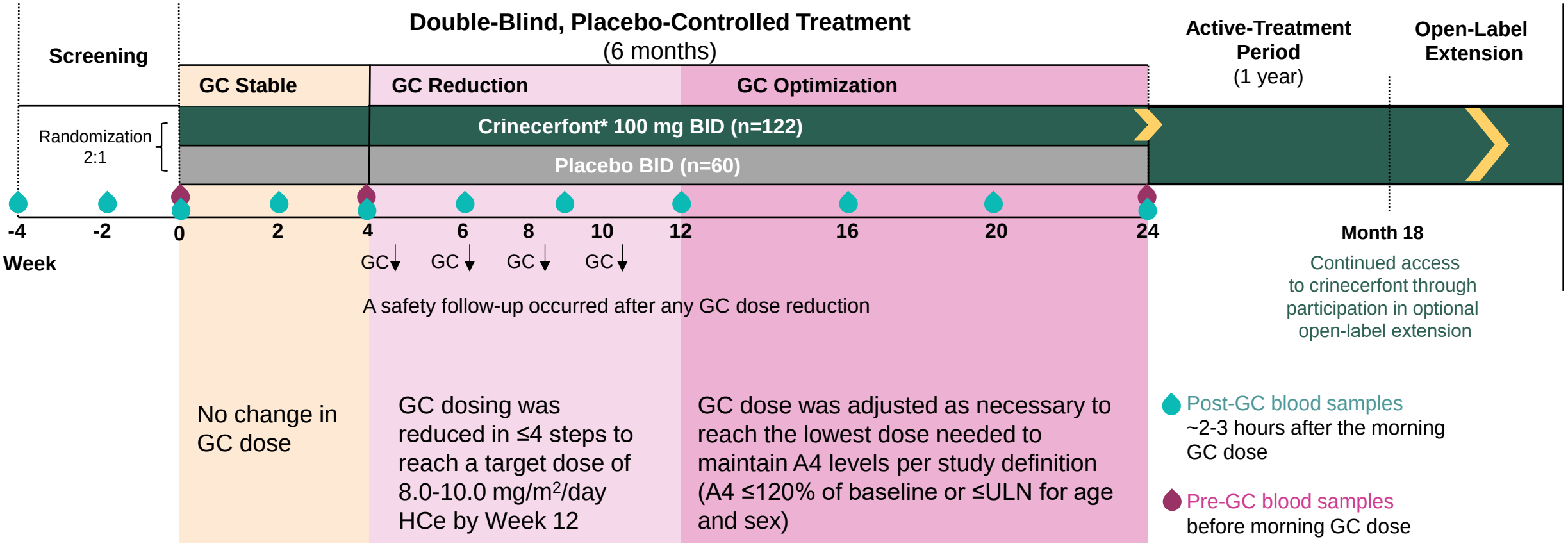


CAHtalyst™

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

Crinecerfont is investigational and not currently approved in any country.

CAHtalyst Study: Study Design



Inclusion/ exclusion criteria

Full list of efficacy and safety endpoints

Participant flow chart

A4, androstenedione; BID, twice daily; GC, glucocorticoid; ULN, upper limit of normal; HCe, hydrocortisone equivalents.

1. Auchus RJ, et al. *N Engl J Med*. 2024;391(6):504-514. 2. Auchus RJ, et al. Supplementary Appendix. *N Engl J Med*. 2024;391(6):504-514.

Demographics and Baseline Characteristics

	Placebo (n=60)	Crinecerfont* (n=122)	All Participants (n=182)
Demographics			
Age, mean (SD), years	29.8 (10.2)	31.3 (9.8)	30.8 (9.9)
Male, n (%)	31 (51.7)	61 (50.0)	92 (50.5)
Race, n (%)[a]			
White	57 (95.0)	107 (87.7)	164 (90.1)
Asian	0	5 (4.1)	5 (2.7)
Black or African American	0	2 (1.6)	2 (1.1)
Ethnicity, n (%)			
Hispanic or Latino	8 (13.3)	6 (4.9)	14 (7.7)
Not Hispanic or Latino	52 (86.7)	116 (95.1)	168 (92.3)
Geographic region, n (%)			
United States	21 (35.0)	48 (39.3)	69 (37.9)
Rest of the world[b]	39 (65.0)	74 (60.7)	113 (62.1)

SD, standard deviation.
[a]Race not reported for 5 participants. Additional categories were as follows: Native American or Alaskan Native (n=1, crinecerfont arm), Other (n=3 [not specified]), or multiple (n=2).
[b]Includes Canada, Europe, and Israel.
Auchus RJ, et al. *N Engl J Med*. 2024;391(6):504-514.

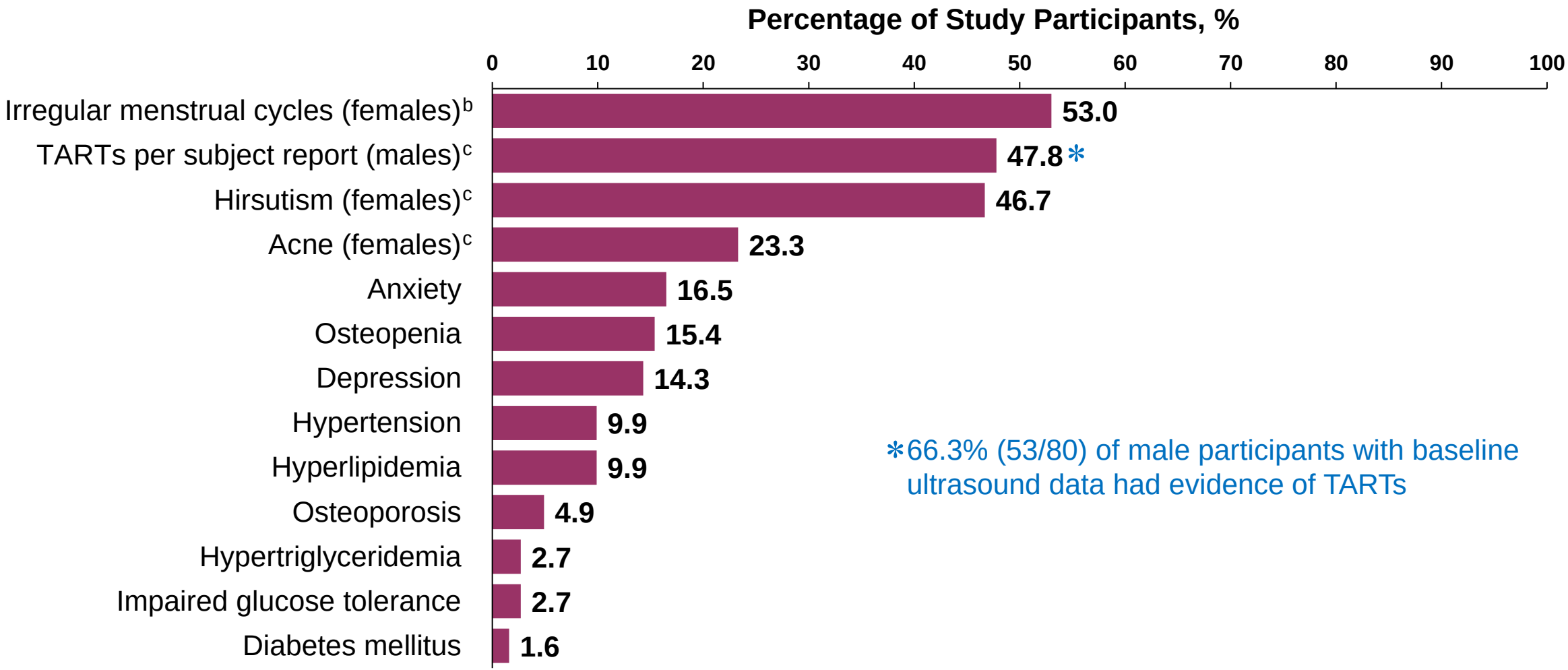
Demographics and Baseline Characteristics (cont'd)

	Placebo (n=60)	Crinecerfont* (n=122)	All Participants (n=182)
Physical exams and tests at baseline			
Body weight, mean (SD), kg	76.2 (18.9)	80.8 (17.8)	79.3 (18.3)
BMI, mean (SD), kg/m^2	29.0 (7.1)	30.1 (6.9)	29.8 (7.0)
BMI ≥30, n (%), kg/m^2	27 (45.0)	58 (47.5)	85 (46.7)
BSA, mean (SD), m^2	1.8 (0.2)	1.9 (0.2)	1.8 (0.2)
Percent total fat mass, mean (SD)[a]	34.6 (9.5)	36.3 (9.0)	35.7 (9.2)
Waist circumference, mean (SD), cm[a]	92.1 (17.2)	96.1 (14.8)	94.8 (15.7)
HOMA-IR, mean (SD)[a]	3.1 (3.1)	3.2 (2.7)	3.2 (2.8)
Plasma glucose 2 hours post 75-g glucose load, mean (SD), mg/dL[b]	96.9 (24.7)	99.5 (26.1)	98.6 (25.6)
Blood pressure, mean (SD), mmHg			
Systolic	120.3 (13.0)	124.1 (12.3)	122.8 (12.6)
Diastolic	74.4 (10.5)	77.6 (9.1)	76.5 (9.7)
TARTs in male participants, n (%)[c]	18 (66.7)	35 (66.0)	53 (66.3)
A4, ng/dL	590 (572)	635 (796)	620 (729)
17-OHP, ng/dL	9787 (9435)	9314 (8560)	9467 (8829)

17-OHP, 17-hydroxyprogesterone; A4, androstenedione; BMI, body mass index; BSA, body surface area; HOMA-IR, homeostatic model assessment for insulin resistance; SD, standard deviation; TART, testicular adrenal rest tumor.
[a]Number of participants with missing physical exams or tests: percent total fat mass (18 crinecerfont, 7 placebo); waist circumference (2 crinecerfont); HOMA-IR (4 crinecerfont, 2 placebo). Percent total fat mass corresponds to mean (SD) total fat mass in kg as follows: all participants, 28.9 (12.0); crinecerfont, 29.4 (11.3); placebo (27.8 (13.3).
[b]In 172 participants (117 crinecerfont, 55 placebo) without diabetes mellitus.
[C]in 80 male participants (53 crinecerfont, 27 placebo) with ultrasound data.
Auchus RJ, et al. Supplementary Appendix. *N Engl J Med*. 2024;391(6):504-514.

CAHtalyst Study

Medical conditions of interest related to the CAH population[a]

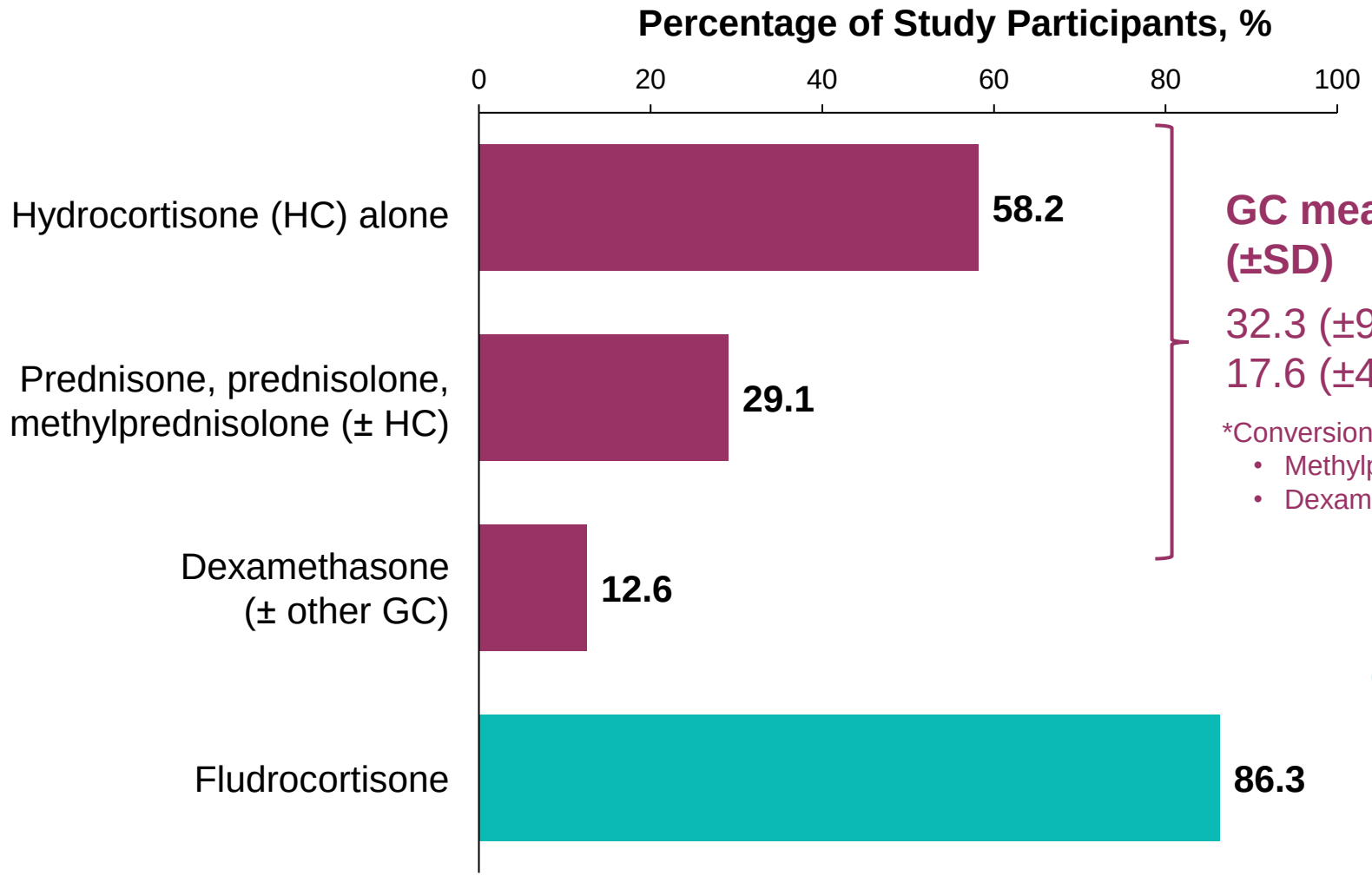


*66.3% (53/80) of male participants with baseline ultrasound data had evidence of TARTs

TART, testicular adrenal rest tumor.
[a]Self-reported by ≥3% of participants in either treatment group.
[b]In 66 female participants of childbearing potential not on hormonal or intrauterine contraception.
[c]In 90 female participants or 92 male participants.
Hamidi O, et al. Presented at: American Association of Clinical Endocrinology (AACE) Annual Meeting; May 9-11, 2024; New Orleans, LA

CAHtalyst Study

Corticosteroid use at baseline



GC mean total daily dose (±SD)

32.3 (±9.3) mg/day HCe*

17.6 (±4.9) mg/m^2/day HCe*

*Conversion factors for hydrocortisone equivalents (HCe):

- Methylprednisolone, prednisolone, and prednisone: 4x
- Dexamethasone: 60x

Fludrocortisone mean daily dose (±SD)

136.1 (±71.9) µg/day

GC, glucocorticoid; HC, hydrocortisone; HCe, hydrocortisone equivalents; SD, standard deviation; SD, standard deviation.

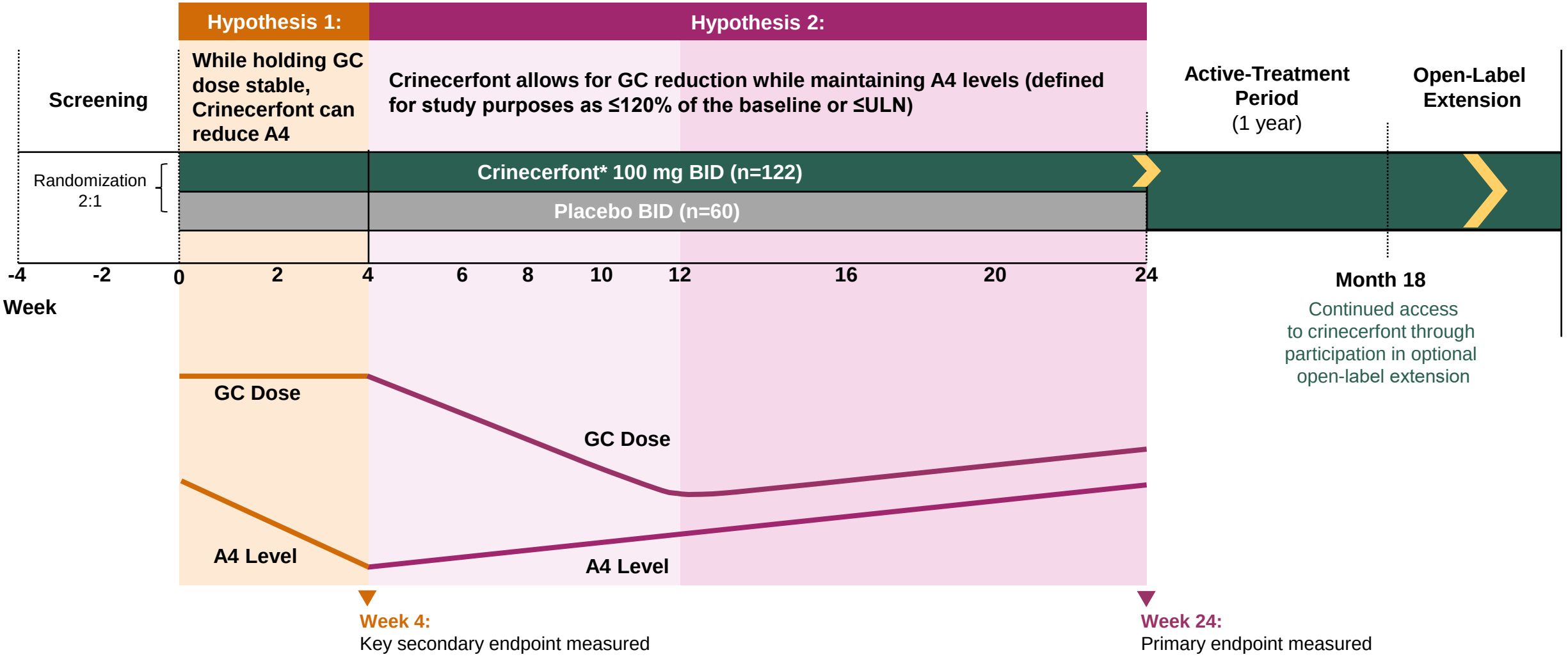
[a]Self-reported by ≥3% of participants in either treatment group.

[b]In 66 female participants of childbearing potential not on hormonal or intrauterine contraception.

[c]In 90 female participants or 92 male participants

Hamidi O, et al. Presented at: American Association of Clinical Endocrinology (AACE) Annual Meeting; May 9-11, 2024; New Orleans, LA

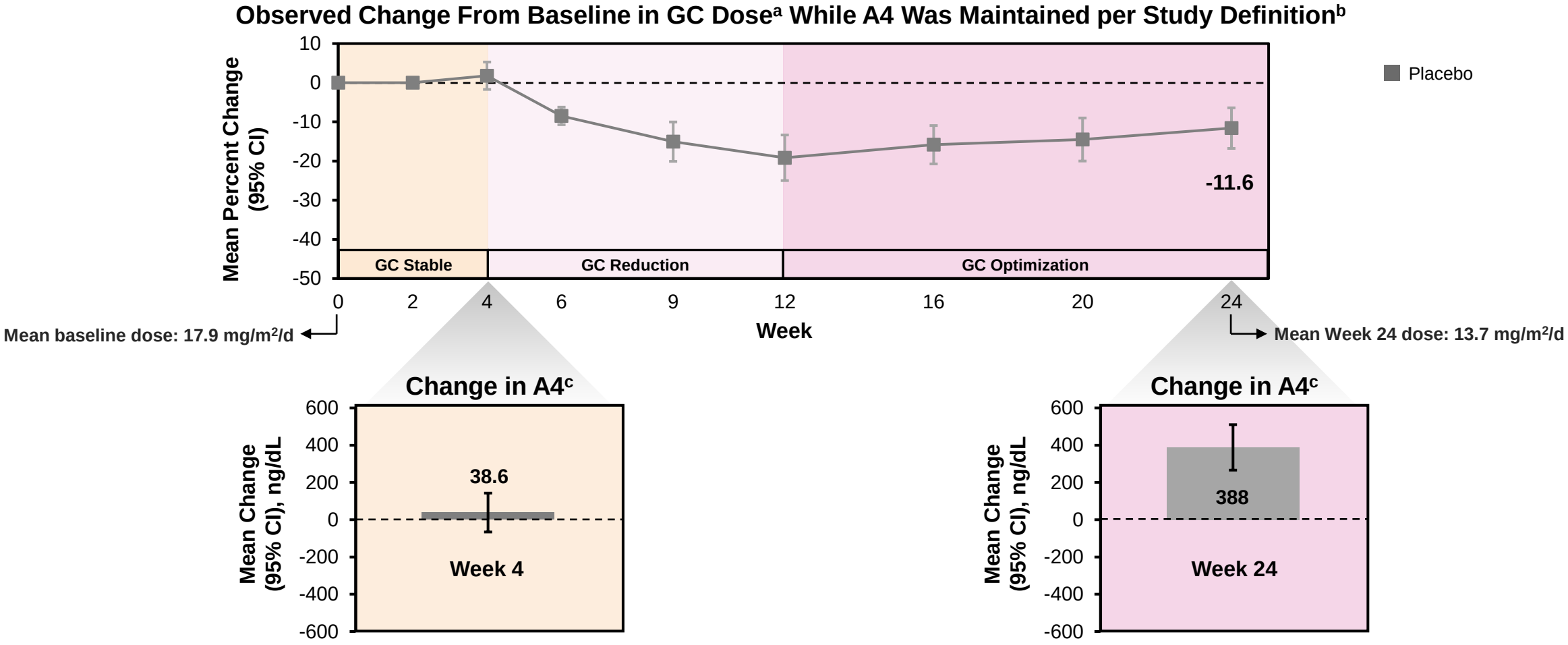
CAHtalyst Study: Study Design



Note: Trend lines shown above for GC and A4 levels are for illustrative purposes only.
A4, androstenedione; BID, twice daily; GC, glucocorticoid; ULN, upper limit of normal.

Auchus RJ, et al. *N Engl J Med*. 2024;391(6):504-514.

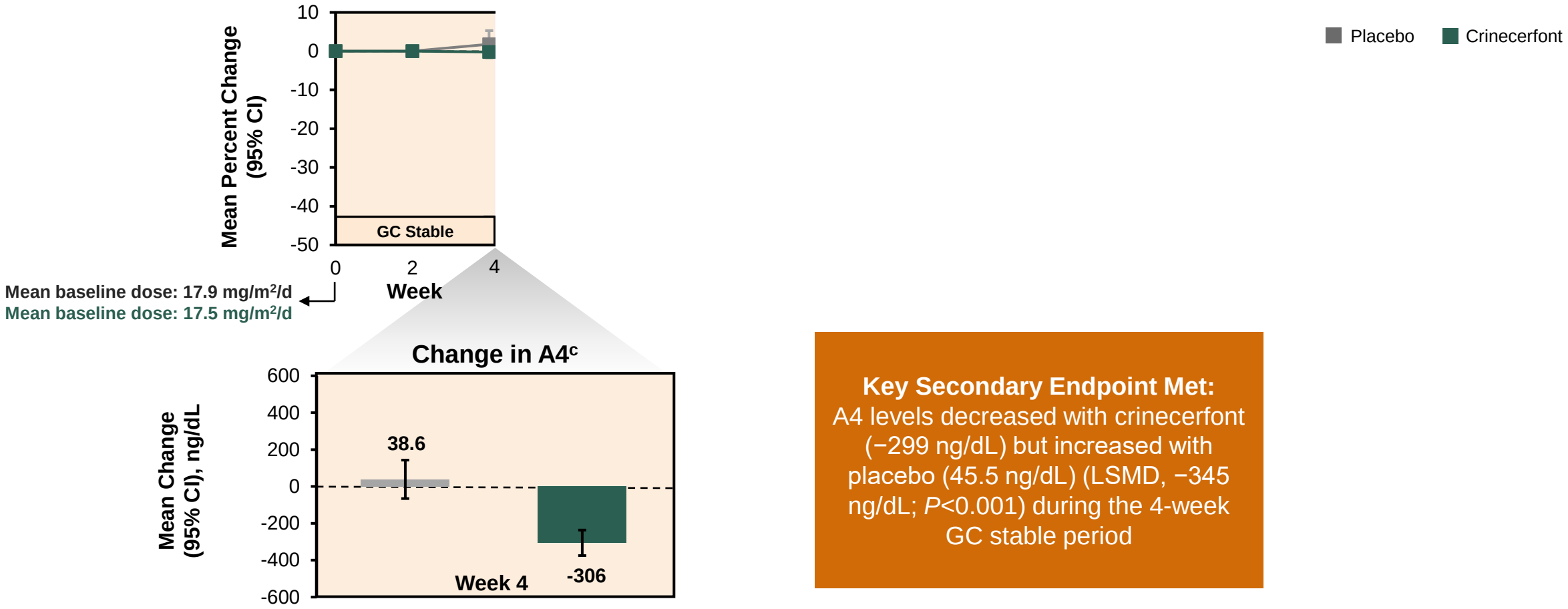
CAH Current Treatment as Depicted by Placebo Group: GC Reduction Results in Increased A4 Levels



Note: The widths of the CIs have not been adjusted for multiplicity and thus should not be used to determine treatment effect.
A4, androstenedione; CI, confidence interval; GC, glucocorticoid.
[a]Decreases in GC dose were set to 0 in participants who did not maintain androgen levels.
[b]A4 maintenance was defined as ≤120% of baseline or ≤ULN according to sex and age.
[c]Based on samples collected before participants received their morning GC doses.
Auchus RJ, et al. *N Engl J Med*. 2024;391(6):504-514.

Hypothesis 1: While Holding GC Dose Stable, Crinecerfont* Can Reduce A4 At Week 4

Observed Change From Baseline in GC Dose[a] While A4 Was Maintained per Study Definition[b]



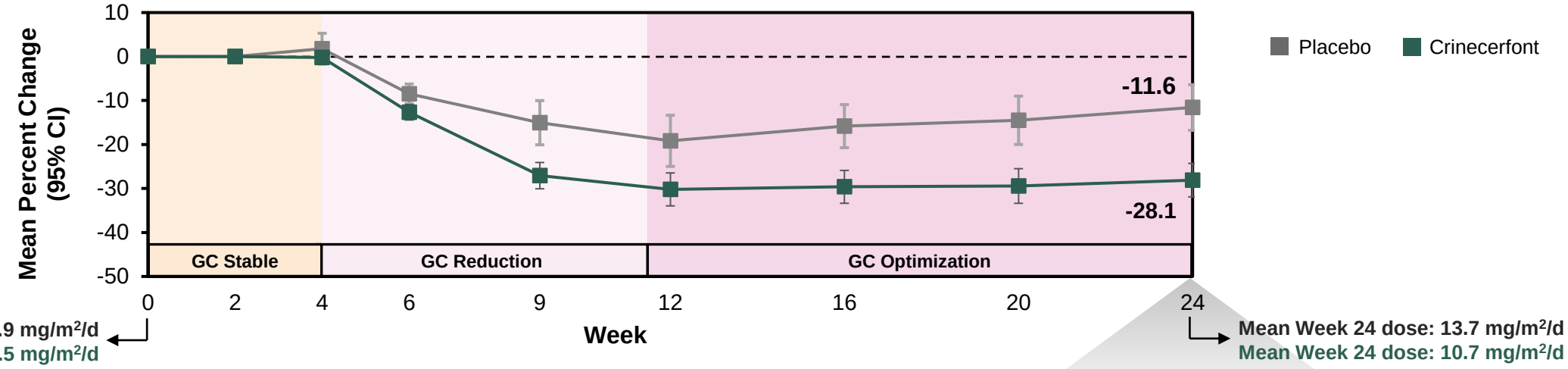
Key Secondary Endpoint Met:
A4 levels decreased with crinecerfont (−299 ng/dL) but increased with placebo (45.5 ng/dL) (LSMD, −345 ng/dL; *P*<0.001) during the 4-week GC stable period

Note: The widths of the CIs have not been adjusted for multiplicity and thus should not be used to determine treatment effect.
17-OHP, 17-hydroxyprogesterone; A4, androstenedione; CI, confidence interval; GC, glucocorticoid.
[a]Decreases in GC dose were set to 0 in participants who did not maintain androgen levels.
[b]A4 maintenance was defined as ≤120% of baseline or ≤ULN according to sex and age.
[c]Based on samples collected before participants received their morning GC doses.
Auchus RJ, et al. *N Engl J Med*. 2024;391(6):504-514.

17-OHP Levels at Week 4

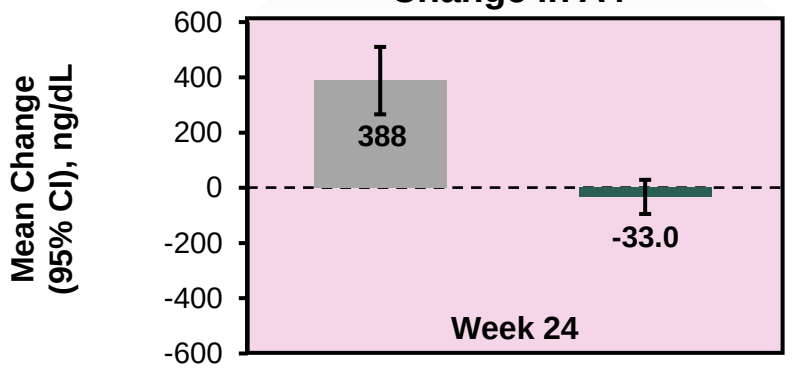
Hypothesis 2: Crincerfont* Allows for GC Reduction While Maintaining A4 Levels[a] at Week 24

Observed Change From Baseline in GC Dose[b] While A4 Was Maintained per Study Definition[a]



Primary Endpoint Met:
GC dose reduction with maintenance of A4 levels was significantly greater with crinecerfont than with placebo (LS mean % change from baseline of -27.3% vs. -10.3%; LSMD, -17.0 percentage points; *P*<0.001) at Week 24

Change in A4[c]

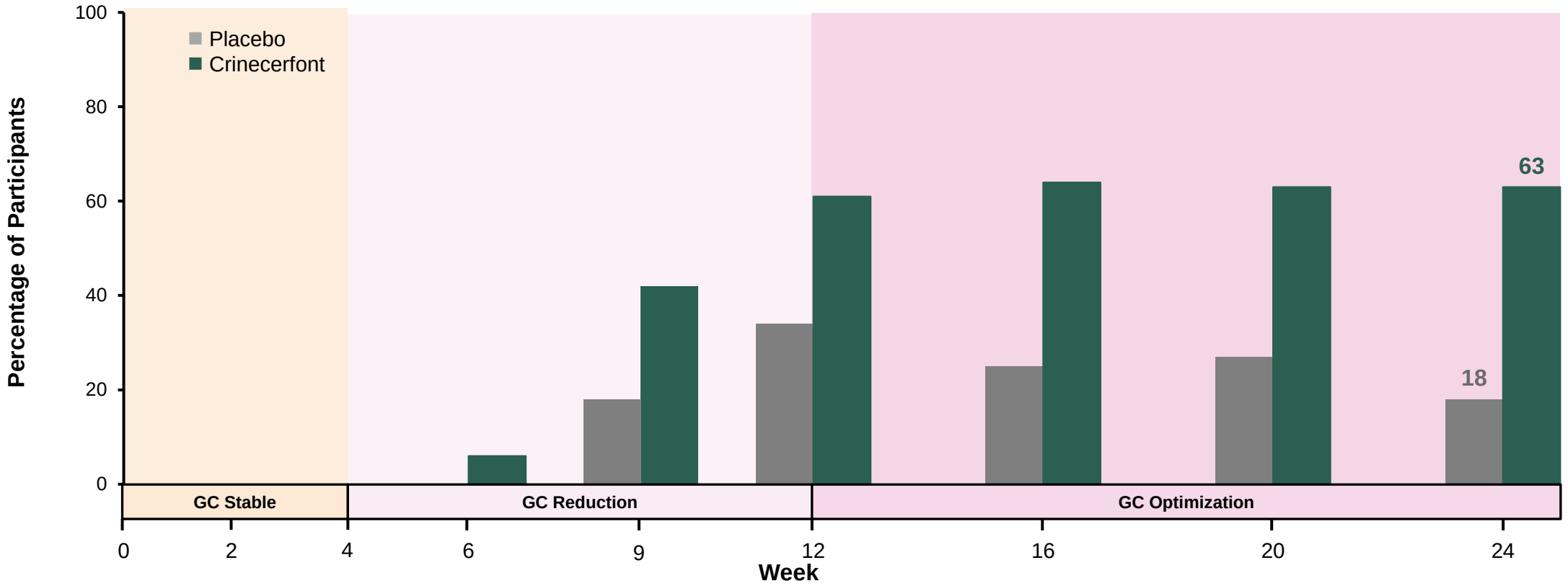


Note: The widths of the CIs have not been adjusted for multiplicity and thus should not be used to determine treatment effect.
17-OHP, 17-hydroxyprogesterone; A4, androstenedione; CI, confidence interval; GC, glucocorticoid; LSMD, least-squares mean difference; ULN, upper limit of normal.
[a]A4 maintenance was defined as ≤120% of baseline or ≤ULN according to sex and age.
[b]Decreases in GC dose were set to 0 in participants who did not maintain androgen levels.
[c]Based on samples collected before participants received their morning GC doses.
Auchus RJ, et al. *N Engl J Med*. 2024;391(6):504-514.

17-OHP Levels at Week 24

Hypothesis 2: Crinecerfont* Allows for GC Reduction While Maintaining A4 Levels[a] at Week 24 (cont'd)

Achievement of Physiologic GC Dose (≤11 mg/m^2/day)[b] While A4 Was Maintained per Study Definition[1,a]



Key Secondary Endpoint Met: The percentage of participants who had a reduction to a physiologic GC dose (≤11 mg/m^2/day) while maintaining baseline A4 levels was significantly greater in the crinecerfont group than in the placebo group at Week 24 (63% vs. 18%; P<0.001)

A4, androstenedione; GC, glucocorticoid; HCe, hydrocortisone dose equivalents; ULN, upper limit of normal.
[a]A4 maintenance was defined as ≤120% of baseline or ≤ULN according to sex and age.
[b]A physiologic GC dose was defined as ≤11 mg/m^2/day in HCe, according to the 95th percentile of cortisol production in healthy persons.[2,3]

1. Auchus RJ, et al. *N Engl J Med*. 2024;391(6):504-514. 2. Purnell JQ, et al. *J Clin Endocrinol Metab*. 2004;89(1):281-287. 3. Linder BL, et al. *J Pediatr*. 1990;117(6):892-896.

Additional Secondary and Exploratory Endpoints at Week 24

	Crinecerfont*		Placebo		LSM Difference (95% CI)
	n	LSM CFB (SEM)	n	LSM CFB (SEM)	
Secondary endpoints[a]					
Systolic blood pressure, mmHg	118	-3.1 (1.0)	57	-2.0 (1.4)	-1.1 (-4.2, 1.9)
Diastolic blood pressure, mmHg	118	-2.2 (0.8)	57	-0.9 (1.1)	-1.3 (-3.8, 1.2)
Waist circumference, cm	115	-0.2 (0.6)	57	0.4 (0.8)	-0.6 (-2.4, 1.2)
Plasma glucose 2 hours post 75 g glucose load, mg/dL	113	-0.9 (2.4)	54	-0.6 (3.2)	-0.3 (-7.2, 6.7)
Menstrual cycle regularity, n (%)[b]					
• In female participants who were regular at baseline	12	9 (75.0)	6	2 (33.3)	N/A
• In female participants who were irregular at baseline	9	7 (77.8)	4	3 (75.0)	N/A
TART volume in male participants, %[c]	29	0.1 (2.4)	15	-3.1 (3.2)	3.2 (-4.2, 10.6)
Exploratory endpoints[a]					
Serum bone-specific alkaline phosphatase, µg/L	116	1.6 (0.3)	58	1.0 (0.4)	0.6 (-0.3, 1.5)
Serum CTx, ng/L	116	110.3 (18.9)	58	22.2 (25.0)	88.1 (33.3, 142.9)
Urine NTx, nmol BCE/mmol creatinine	117	12.3 (2.6)	57	7.1 (3.5)	5.2 (-2.5, 12.9)
Serum osteocalcin, µg/L	116	8.2 (0.9)	58	3.3 (1.2)	4.9 (2.3, 7.4)

BCE, bone collagen equivalents; CFB, change from baseline; CI, confidence interval; CTx, C-terminal telopeptide; LSM, least-squares mean; NTx, N-terminal telopeptide; SEM, standard error of the mean; TART, testicular adrenal rest tumor.

[a]Endpoints are presented as LSM CFB at week 28 with SEM, unless indicated otherwise. Where applicable, the LSM difference between treatment groups (crinecerfont – placebo) is noted, along with the 95% CI. P-values for secondary and exploratory endpoints were considered nominal and are not shown. 95% CIs for these endpoints were not adjusted for multiplicity, and the intervals may not be used in place of hypothesis testing. | [b]Analyzed in female participants of childbearing potential who were not on hormonal or intrauterine contraception. Regularity at baseline was based on participant self-report. For the purposes of this analysis, a menstrual cycle was defined as 2 consecutive calendar days with any amount of flow. Regularity was defined as a menstrual cycle every 21-35 days. | [c]TART volume is expressed as the percentage of total testicular volume.

Auchus RJ, et al. Supplementary Appendix. *N Engl J Med*. 2024;391(6):504-514.

Summary of Adverse Events

Crinecerfont* was generally well tolerated with few serious TEAEs or discontinuations due to TEAEs

Adverse Event	Crinecerfont (n = 122)	Placebo (n = 59)
	n (%)	
Any adverse event	101 (83)	48 (81)
• Leading to discontinuation of crinecerfont or placebo	4 (3)[a]	0
• Leading to trial discontinuation	4 (3)[a]	0
Any serious adverse event	4 (3)[b]	0
Any adverse event resulting in death	0	0
Severity of adverse event[c]		
• Mild	62 (51)	30 (51)
• Moderate	36 (30)	18 (31)
• Severe	3 (2)	0

- In the DBPC period, **adrenal insufficiency** or **acute adrenocortical insufficiency** was reported in 2 participants (**2%**) in the **crinecerfont group** and in 1 participant (**2%**) in the **placebo group**
- AEs that led to GC **stress dosing** were reported in **42%** of participants in the **crinecerfont group** and in **44%** in the **placebo group**; most cases involved only oral stress dosing

AE, adverse event; GC, glucocorticoid; DBPC, double-blind, placebo-controlled; TEAEs, treatment emergent adverse event.
[a]These 4 adverse events that led to drug and trial discontinuation were dyspepsia, nausea, and vomiting (in 1 participant), gastric ulcer (in 1 participant), apathy and restlessness (in 1 participant), and rash (in 1 participant). All adverse events that were first identified during the 24-week randomized period and that resulted in the discontinuation of crinecerfont or placebo are presented regardless of when the discontinuation occurred. Only 1 adverse event (gastric ulcer) that was first identified during the randomized period resulted in discontinuation during that period. | [b]The 4 serious adverse events (1 in each participant) were cholecystitis, groin abscess and cellulitis, acute adrenocortical insufficiency, and presyncope. All the serious adverse events were assessed by the investigator as having an unlikely association with crinecerfont. | [c]The maximum severity was determined by the trial investigator

Auchus RJ, et al. *N Engl J Med*. 2024;391(6):504-514.

Common Adverse Events

Adverse events reported in at least 5 participants in the crinecerfont* group

Adverse Event	Crinecerfont (n = 122)	Placebo (n = 59)
	n (%)	
Fatigue	30 (25)	9 (15)
Headache	19 (16)	9 (15)
Coronavirus infection	17 (14)	5 (8)
Upper respiratory tract infection	11 (9)	7 (12)
Diarrhea	10 (8)	5 (8)
Dizziness	10 (8)	2 (3)
Nausea	10 (8)	5 (8)
Arthralgia	9 (7)	0
Back pain	7 (6)	2 (3)
Pyrexia	7 (6)	6 (10)
Blood creatine phosphokinase increased	6 (5)	2 (3)
Nasopharyngitis	6 (5)	8 (14)
Vomiting	6 (5)	5 (8)
Decreased appetite	5 (4)	1 (2)
Gastroenteritis	5 (4)	1 (2)
Influenza	5 (4)	2 (3)

Auchus RJ, et al. *N Engl J Med*. 2024;391(6):504-514.

CAHtalyst Study Summary

- CAHtalyst was a 24-week Phase 3, randomized, DBPC study to evaluate the safety, efficacy, and tolerability of crinecerfont* for adult participants with CAH
- At Week 24, the change in GC dose with maintenance of A4 levels per study definition was -27.3% in the crinecerfont group and -10.3% in the placebo group [LSMD -17.0 percentage points, *P*<0.001])
- At Week 4, A4 levels decreased with crinecerfont (-299 ng/dL) but increased with placebo (45.5 ng/dL) (LSMD -345 ng/dL, *P*<0.001)
- At Week 24, 63% of participants in the crinecerfont group achieved a physiologic GC dose (≤11 mg/m^2/day HCe) while maintaining A4 levels, compared to 18% in the placebo group (*P* <0.001)
- Crinecerfont was generally well tolerated, with few SAEs or discontinuations due to TEAEs
- Fatigue and headache were the most common adverse events in the 2 study groups

A4, androstenedione; DBPC, double-blind, placebo-controlled; GC, glucocorticoid; HCe, hydrocortisone equivalents; LSMD, least-squares mean difference; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Auchus RJ, et al. *N Engl J Med*. 2024;391(6):504-514.

Neurocrine Medical Affairs

www.neurocrinemedical.com

1-877-641-3461

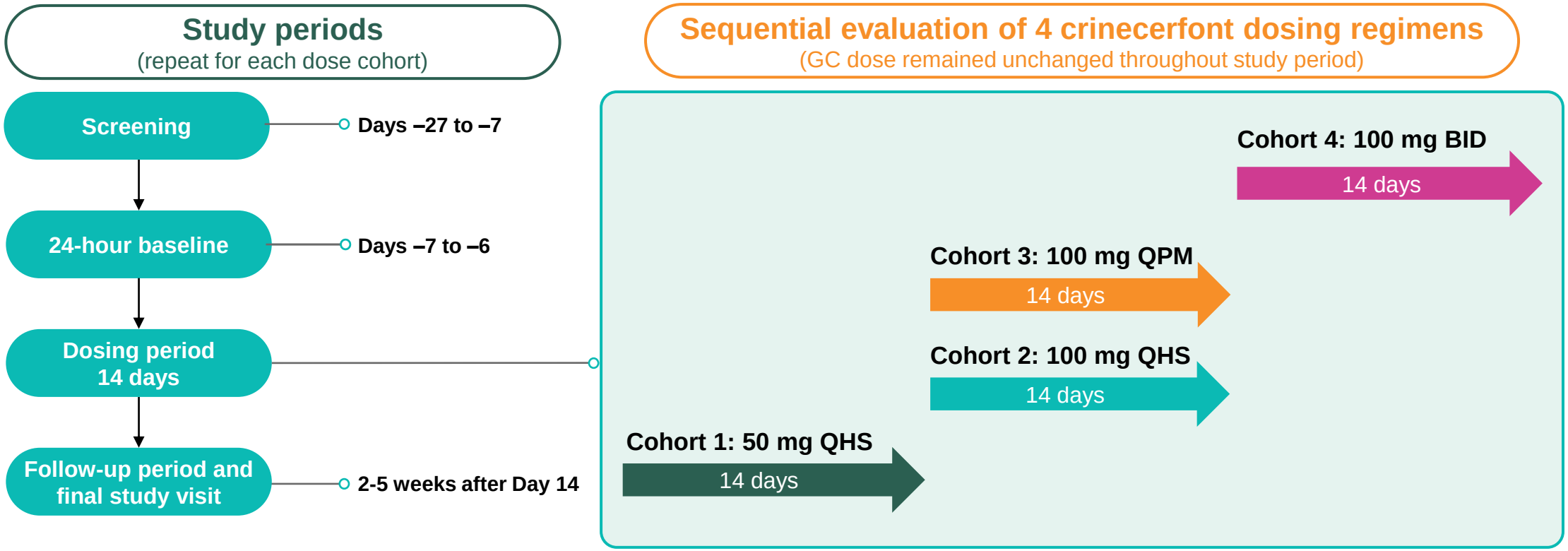
PROACTIVE USE FOR INVESTIGATORS; REACTIVE FOR ALL OTHER USE.

Appendix

CAHlibrate Study

Study design[1,2]

- Safety, tolerability, and efficacy of crinecerfont* in adults (eligible ages: 18-50 years) with 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



17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; AE, adverse event; BID, twice daily; GC, glucocorticoid; 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.

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

CAHlibrate Pediatric Study

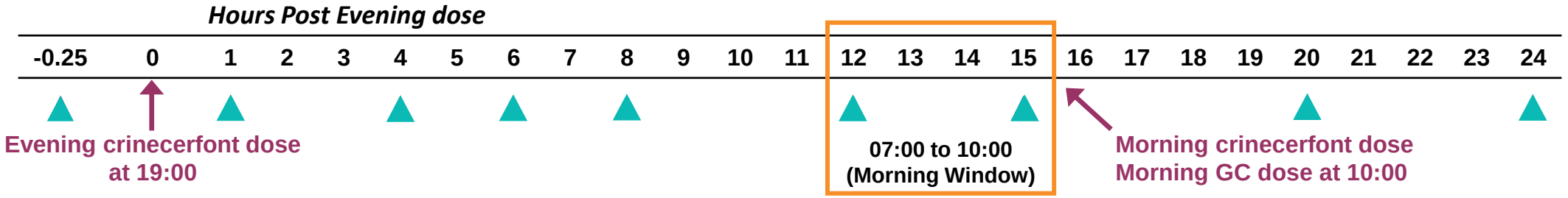
Study design[1,2]

- Safety, tolerability, PK, and PD of crinecerfont* 50 mg BID[a] in adolescents (eligible ages: 14-17 years) with CAH
- **Primary endpoint:** number of participants with AEs following dosing of crinecerfont
- **PD assessment[b]:** 24-hour serial sampling for ACTH, 17-OHP, A4, and testosterone levels conducted at baseline and Day 14

Study Periods[b]

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[c]

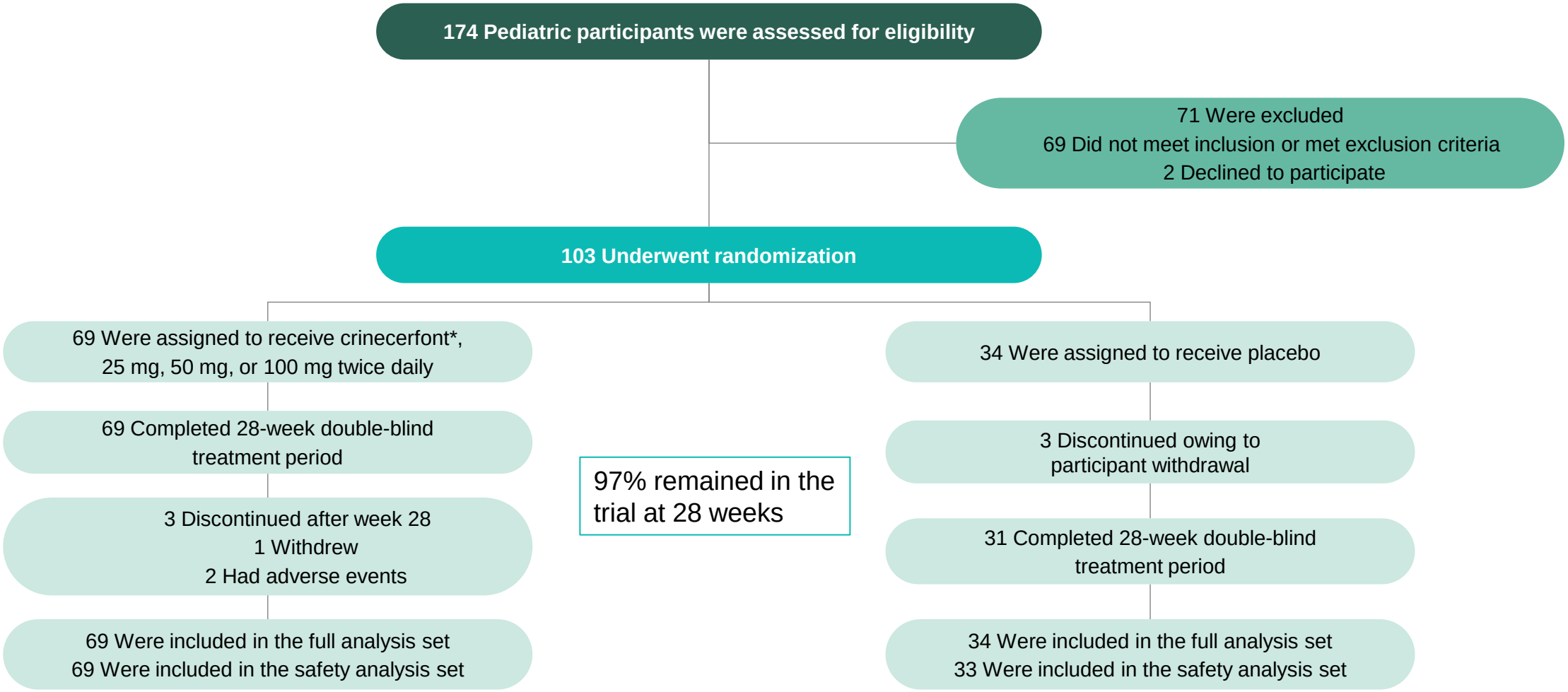


17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; AE, adverse event; BID, twice daily; GC, glucocorticoid; PD, pharmacodynamics; PK, pharmacokinetics.
[a]With morning and evening meals.
[b]Shaded boxes indicate overnight stay at study center for 24-hour serial blood sampling.
[c]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.

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.

CAHtalyst Pediatric Study

Participant flow chart



Sarafoglou K, et al. *N Engl J Med*. 2024;391(6):493-503.

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

CAHtalyst Pediatric Study

Key inclusion criteria[1]

Key Inclusion Criteria

- Written informed consent from the participant's parent(s) or legal guardian(s); written or witnessed oral assent from participant if deemed capable of providing assent in accordance with the governing IRB/IEC and according to local laws and regulations
- Female or male, 2 to 17 years of age, with a body weight of at least 10 kg
- Have a confirmed diagnosis of classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) based on standard medically accepted criteria such as elevated 17-OHP level, confirmed by CYP21A2 genotype, or diagnostic results after cosyntropin stimulation
- Chronic treatment with supraphysiologic GC regimen defined as >12 mg/m^2/day in HCe for ≥1 month prior to screening and includes any of the following orally administered GCs: hydrocortisone, prednisone, prednisolone, or methylprednisolone
  - GCs other than hydrocortisone (e.g., prednisolone and prednisone) were converted to HCe using an equivalency ration of 4 (e.g., 1 mg prednisone = 4 mg hydrocortisone)
- A4 level (prior to the morning GC dose) greater than the midpoint of the reference range, according to sex and age (Tanner stage 1) or pubertal stage (Tanner stages 2 to 5)
  - Tanner staging included an assessment of pubic hair (males and females), breast development (females), and genital development (males)
  - Testicular volume in males was assessed using a Prader orchidometer to assign a Tanner stage equivalent as follows: stage 1 (<4 mL); stage 2 (≥4 mL and <8 mL); stage 3 (≥8 mL and < 12 mL), stage 4 (≥12 mL and ≤15 mL), and stage 5 (>15 mL)[2]
- 17-OHP level (prior to morning GC dose) >2 times the ULN according to sex and age (Tanner stage 1) or pubertal stage (Tanner stages 2 to 5)
- If treated with fludrocortisone, stable dose for ≥1 month prior to screening. Regardless of fludrocortisone treatment, adequate mineralocorticoid control at screening as indicated by upright plasma renin activity (PRA) (eg <3x ULN and > lower limit of normal on participant's normal sodium intake)
- For female participants of childbearing potential, consistent use of contraception from screening until final study visit or 30 days after the last dose of study drug, whichever is longer. For female participants not of childbearing potential:
  - Postmenopausal, defined as no menses for 12 months without an alternative medical cause and confirmed by elevated follicle-stimulating hormone (FSH) consistent with a postmenopausal range
  - Permanent sterilization procedure, such as hysterectomy, bilateral salpingectomy, or bilateral oophorectomy

17-OHP, 17-hydroxyprogesterone; 21-OHD, 21-hydroxylase; A4, androstenedione; CYP21A2, steroid 21-hydroxylase or P450c21; FSH, follicle stimulating hormone; GC, glucocorticoid; HCe, hydrocortisone dose equivalents; IRB/IEC, institutional review board/ independent ethics committee; PRA, plasma renin activity; ULN, upper limit of normal.

1. Sarafoglou K, et al. Supplementary Appendix. *N Engl J Med*. 2024;391(6):493-503. 2. Nokof N, et al. *J Clin Endocrinol Metab*. 2019;104(10):4390-7.

CAHtalyst Pediatric Study

Key exclusion criteria

Key Exclusion Criteria
• Known or suspected diagnosis of any other form of classic CAH
• History of bilateral adrenalectomy, hypopituitarism, or any other condition requiring chronic therapy with oral GCs, or required chronic therapy with inhaled GCs that might interfere with study endpoints (per investigator judgement)
• Increased risk of developing adrenal crisis (per investigator judgement)
• Clinically significant medical condition or chronic disease (e.g., history of neurological, hepatic, renal, cardiovascular, gastrointestinal, significant malabsorption, hematologic, pulmonary, psychiatric, or endocrine disease [excluding CAH] that would preclude participant or completion of the study or might confound the interpretation of study outcome (per investigator judgement)
• History of malignancy, unless successfully treated with curative intent and considered to be cured
• Known history of clinically concerning cardiac arrhythmia (including long QT syndrome) or prolongation of screening (pre-treatment) QT interval, corrected for heart rate using Fridericia's correction (QTcF)
• Known sensitivity (i.e. hypersensitivity) or allergy to any corticotropin-releasing hormone (CRH) receptor antagonist
• Evidence of chronic renal or liver disease
• Clinically significant hematologic or coagulation abnormalities at screening
• Serum sodium <130 mmol/L

CRH, corticotropin-releasing hormone; GC, glucocorticoid; QTcF, QT interval, corrected for heart rate using Fridericia's correction.

Sarafoglou K, et al. Supplementary Appendix. *N Engl J Med*. 2024;391(6):493-503.

CAHtalyst Pediatric Study

Key exclusion criteria (cont'd)

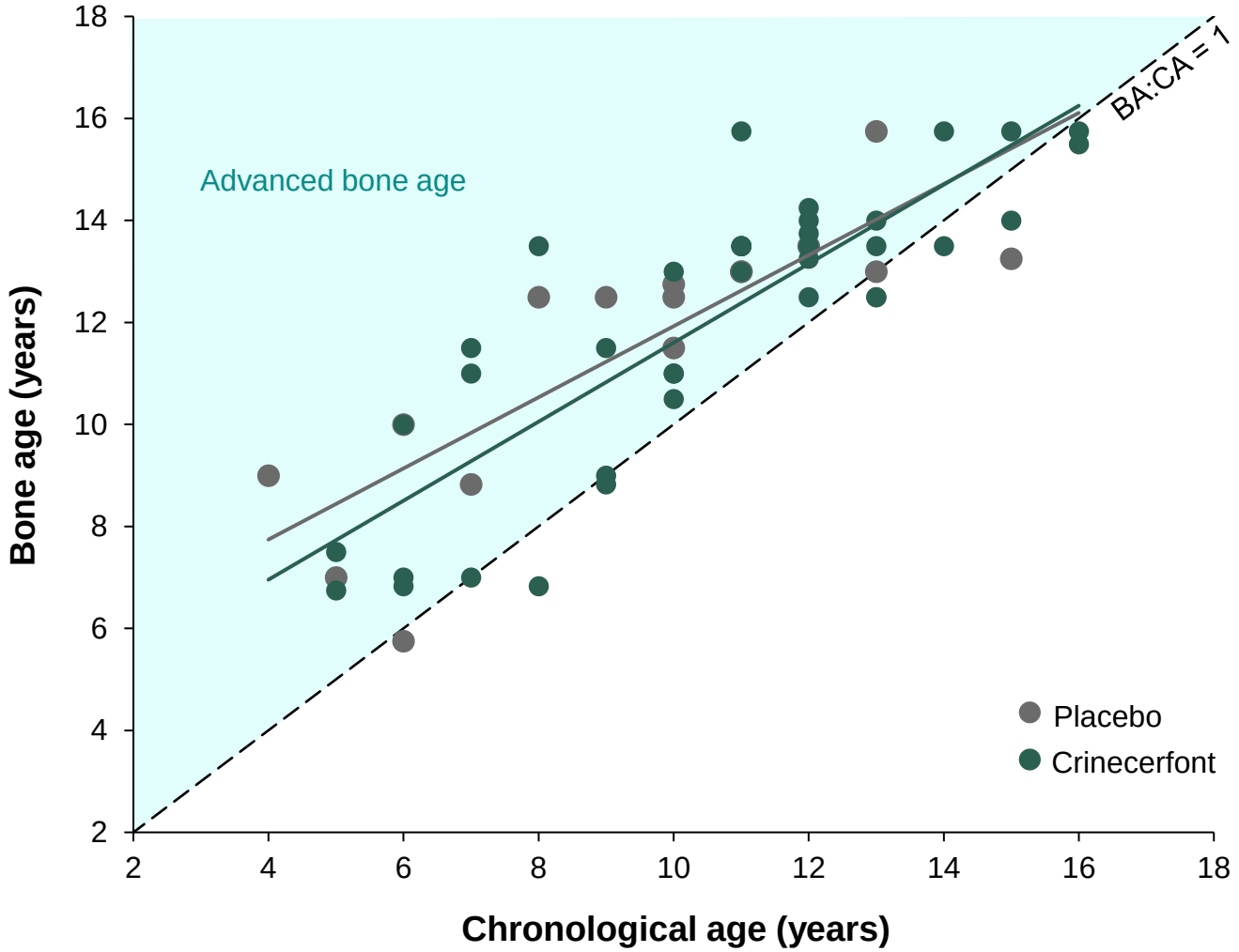
Key Exclusion Criteria (cont'd)
• Used any active investigational drug for another clinical trial within 30 days or 5 half-lives (whichever is longer) before screening, or plan to use such drug during the CAHtalyst study
• Use of any of the following excluded concomitant medications (unless discontinuation during the study was possible): – Orally administered GCs for indications other than CAH – Strong inducers of CYP3A4 or CYP2B6 except topically administered medications – Medications that affect cortisol of GC metabolism (e.g., phenytoin, mitotane, phenobarbital, strong CYP3A4 inhibitors such as ketoconazole, clarithromycin, cholestyramine, certain antivirals) except topically administered medications – Exogenous testosterone treatment
• Current dependence or abuse of any of the following: alcohol, controlled substances, non-prescribed use of prescription drugs, nicotine, or caffeine
• Significant risk of suicidal or violent behavior
• Blood loss ≥3% of total blood volume (based on 75 mL per kg body weight) or donated blood (or blood products) within 8 weeks before baseline (Day 1)
• Pregnancy or lactation (in females)
• Not capable of adhering to the protocol requirements (per investigator judgement)

CYP2B6, cytochrome P450 2B6, CYP3A4, cytochrome P450 3A4; GC, glucocorticoid.

Sarafoglou K, et al. Supplementary Appendix. *N Engl J Med*. 2024;391(6):493-503.

CAHtalyst Pediatric Study

Bone age versus chronological age at baseline[a]



Note: Significant changes in bone age or other growth-related outcomes within each treatment group were not expected in a 28-week treatment period

BA;CA, bone age-to-chronological age ratio.
[a]Data are limited to participants who had available assessments, were not at adult height (i.e., BA<14 years in female of <16 years in male participants), and who were not taking GnRH agonist therapy, growth hormone therapy, or aromatase inhibitors at study entry. Colored lines denote trendlines (not regression analyses).
Sarafoglou K, et al. Supplementary Appendix. *N Engl J Med*. 2024;391(6):493-503.

CAHtalyst Pediatric Study

Full list of endpoints

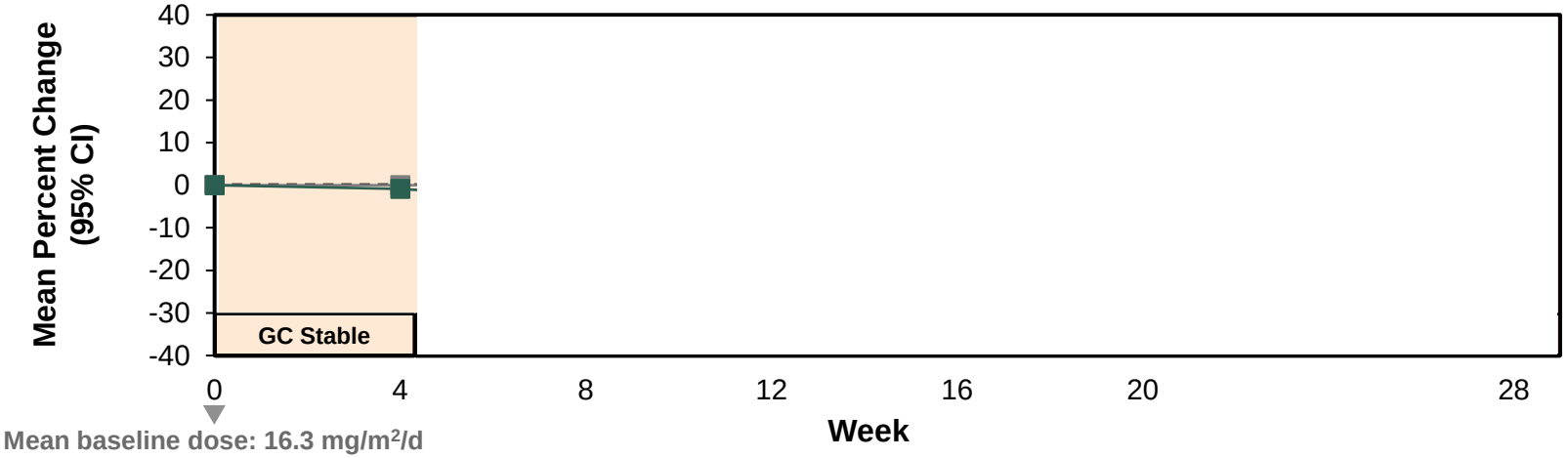
Primary Endpoint
• Change from baseline in serum A4 at Week 4
Key Secondary Endpoints
• Change from baseline in serum 17-OHP at Week 4
• Percent change from baseline in GC daily dose at Week 28 while A4 levels were maintained per study definition
Secondary Endpoints
• Achievement of a reduction in GC daily dose to physiologic levels (≤11 mg/m^2/d HCe) at Week 28 while A4 levels were maintained per study definition
• Change from baseline in BMI SDS at Week 28
• Change from baseline in mean 24-hour salivary 17-OHP at Week 28
• Change from baseline in BA:CA at Week 28 in growing participants
Select Exploratory Endpoints
• Change from baseline in height SDS at Week 28 in growing participants
• Change from baseline in HOMA-IR at Week 28
• Change from baseline in hirsutism in female participants
• Changes from baseline in serum ACTH and testosterone at Week 28
• Percentage of male participants (Tanner stage 2 to 5) who had A4/T ratio ≥0.5 at baseline and <0.5 at Week 28
Safety Assessments
• TEAEs, vital signs, 12-lead electrocardiographs, clinical laboratory tests
• Brief Psychiatric Rating Scale for Children, Columbia-Suicide Severity Rating Scale

17-OHP, 17-hydroxyprogesterone; A4, androstenedione; A4/T, androstenedione-to-testosterone ratio; BA:CA bone age–to–chronologic age; BMI, body mass index; GC, glucocorticoid; HCe, hydrocortisone equivalent; HOMA-IR: Homeostatic model assessment for insulin resistance; TEAE, treatment-emergent adverse event.

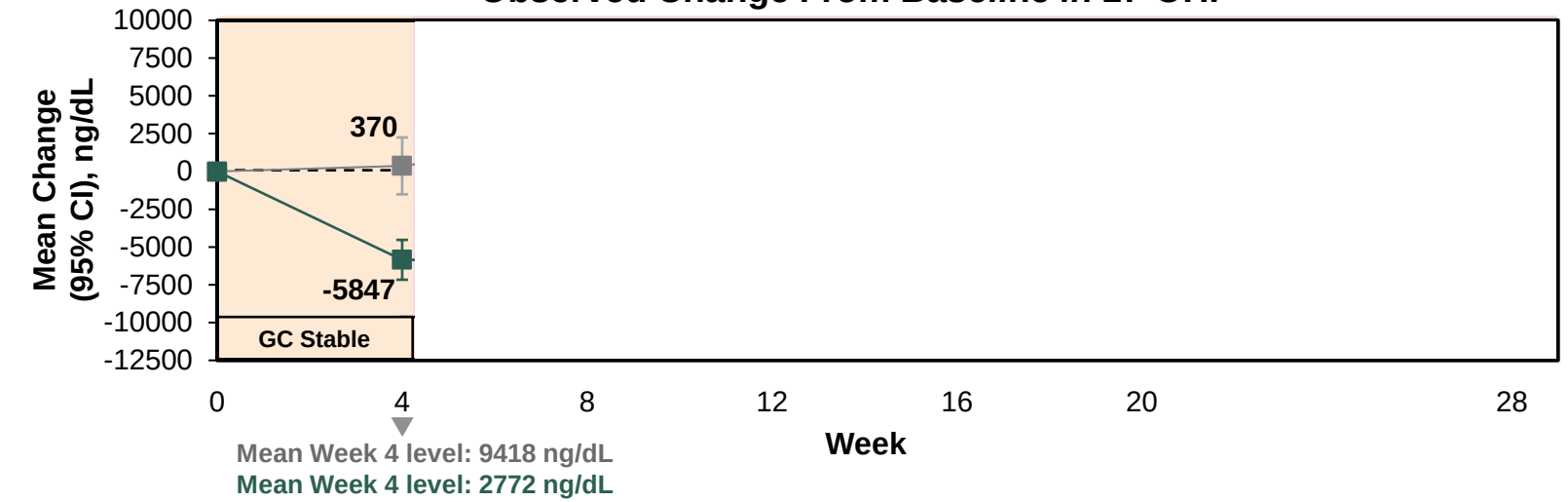
Sarafoglou K, et al. Supplementary Appendix. *N Engl J Med*. 2024;391(6):493-503.

While Holding GC Dose Stable, Crinecerfont* Can Reduce 17-OHP at Week 4

Observed Change From Baseline in GC Dose[a] While A4 Levels Were Maintained per Study Definition[b]



Observed Change From Baseline in 17-OHP[c]



Secondary Endpoint Met:
17-OHP levels decreased from baseline to Week 4 with crinecerfont and increased with placebo (LSMD, −6421 ng/dL; *P*<0.001)

Note: The widths of the CIs have not been adjusted for multiplicity and thus should not be used to determine treatment effect.

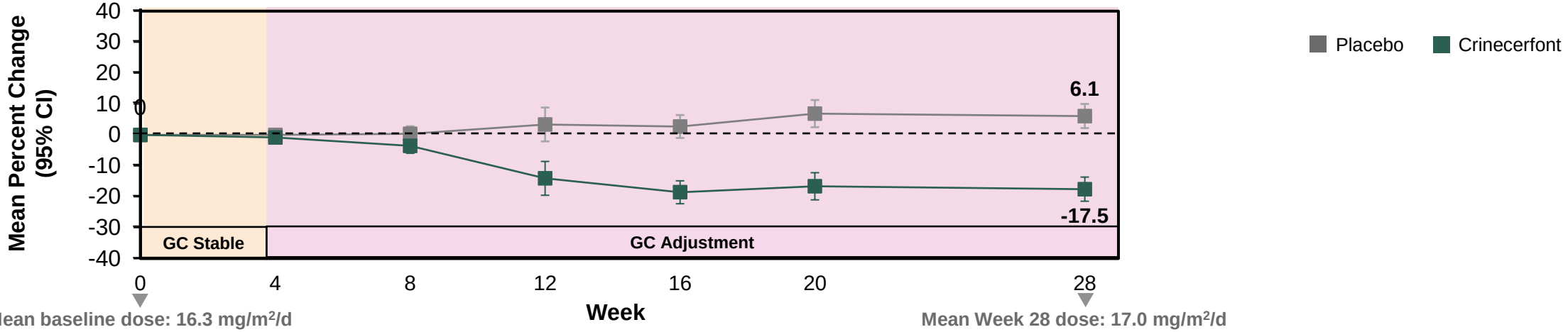
[a]Decreases in GC dose were set to 0 in participants who did not maintain androgen levels.
[b]A4 maintenance was defined as ≤120% of baseline or ≤ULN according to sex and age.
[c]Based on samples collected before participants received their morning GC doses.

17-OHP, 17-hydroxyprogesterone; A4, androstenedione; CI, confidence interval; GC, glucocorticoid; LSMD, least-squares mean difference; ULN, upper limit of normal.

Sarafoglou K, et al. *N Engl J Med*. 2024;391(6):493-503.

Mean Change in 17-OHP at Week 28[1]

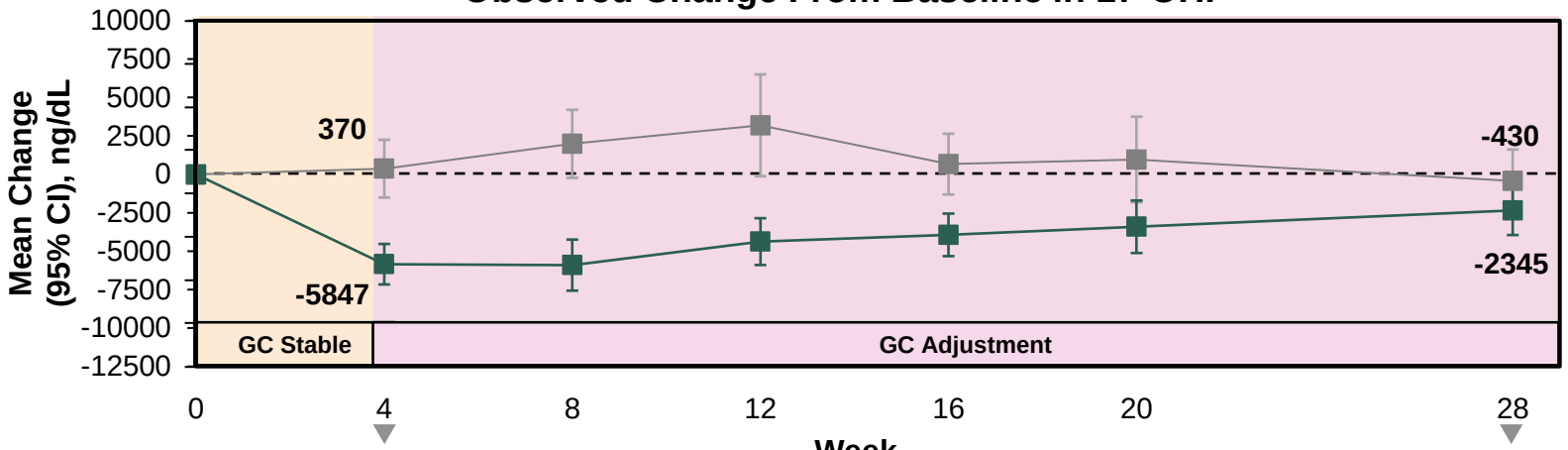
Observed Change From Baseline in GC Dose[a] While A4 Levels Were Maintained per Study Definition[b]



Mean baseline dose: 16.3 mg/m²/d
Mean baseline dose: 16.5 mg/m²/d

Mean Week 28 dose: 17.0 mg/m²/d
Mean Week 28 dose: 12.8 mg/m²/d

Observed Change From Baseline in 17-OHP[c]



Mean Week 4 level: 9418 ng/dL
Mean Week 4 level: 2772 ng/dL

Mean Week 28 level: 8289 ng/dL[2]
Mean Week 28 level: 6100 ng/dL[2]

Note: The widths of the CIs have not been adjusted for multiplicity and thus should not be used to determine treatment effect.

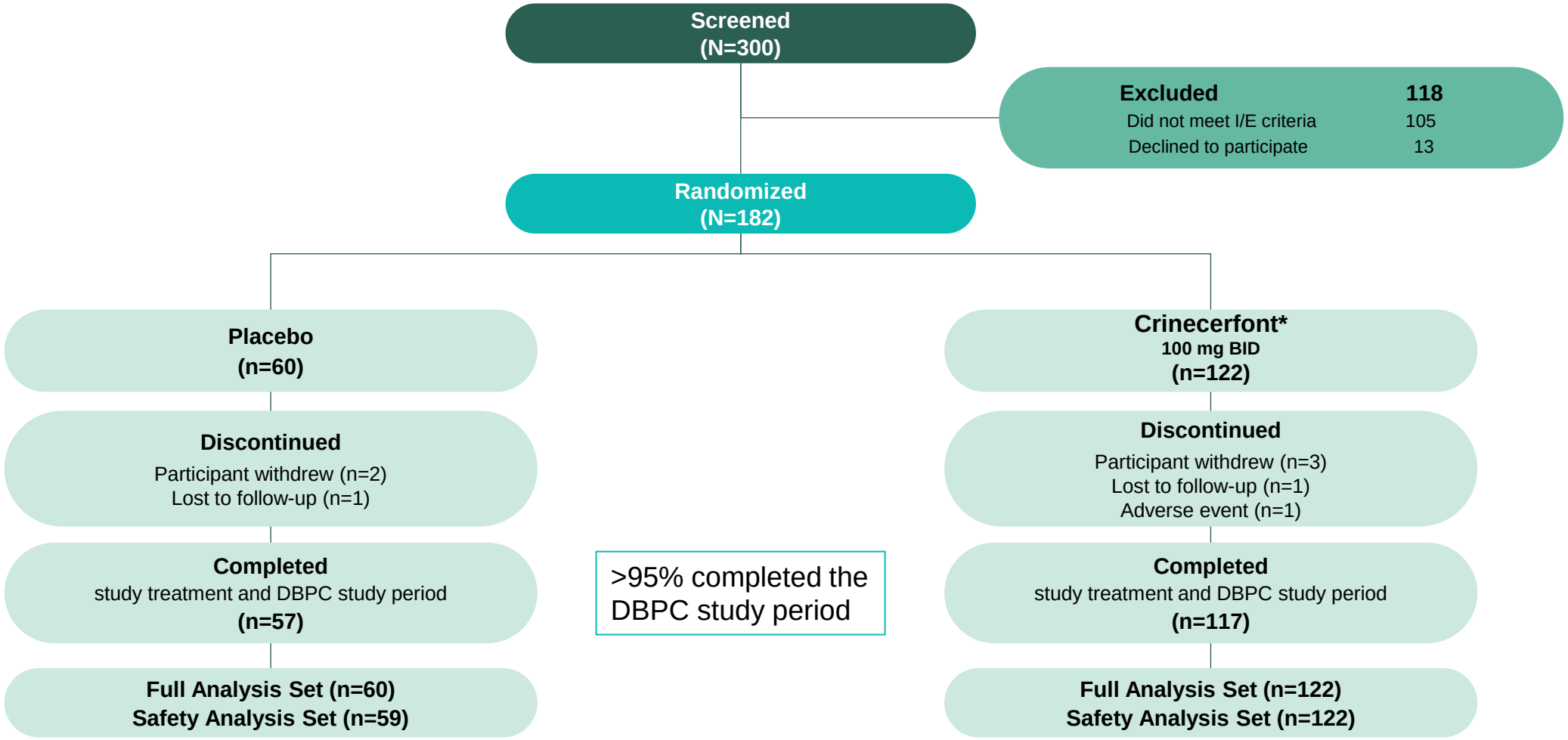
[a]Decreases in GC dose were set to 0 in participants who did not maintain androgen levels.
[b]A4 maintenance was defined as ≤120% of baseline or ≤ULN according to sex and age.
[c]Based on samples collected before participants received their morning GC doses.

17-OHP, 17-hydroxyprogesterone; A4, androstenedione; CI, confidence interval; GC, glucocorticoid; LSMD, least-squares mean difference; ULN, upper limit of normal.

1. Sarafoglou K, et al. *N Engl J Med*. 2024;391(6):493-503. 2. Sarafoglou K, et al. Supplementary Appendix. *N Engl J Med*. 2024;391(6):493-503.

CAHtalyst Study

Participant flow chart



BID, twice daily; DBPC, double-blind, placebo-controlled; E, exclusion; GC, glucocorticoid; I, inclusion.

Auchus RJ, et al. Supplementary Appendix. *N Engl J Med*. 2024;391(6):504-514.

CAHtalyst Study

Key inclusion criteria

Key Inclusion Criteria

- Provided written informed consent
- Female or male at least 18 years of age
- Have a confirmed diagnosis of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency (21-OHD) based on standard medically accepted criteria such as elevated 17-OHP level, confirmed CYP21A2 genotype, positive newborn screening with confirmatory second-tier testing, or cosyntropin stimulation
- Chronic treatment with a supraphysiologic GC regimen, defined as >13 mg/m2/day in hydrocortisone equivalents (HCe) adjusted for body surface area (BSA), that was stable for ≥1 month prior to screening and included any of the following orally administered GCs: hydrocortisone, prednisone, prednisolone, methylprednisolone, and/or dexamethasone
  - Conversion factors for HCe were as follows: methylprednisolone, prednisolone, prednisone (4x); dexamethasone (60x)
- If treated with fludrocortisone, stable dose for ≥1 month prior to screening with an upright plasma renin activity (PRA) at screening that was not greater than upper limit of normal (ULN) usual sodium intake. If PRA >ULN, systolic blood pressure >100 mmHg, without orthostatic hypotension, and with serum sodium and potassium in the normal range
  - Participants taking fludrocortisone were strongly encouraged to maintain their dose during the study. All dose changes were documented
- For female participants of childbearing potential, consistent use of contraception from screening until final study visit or 30 days after the last dose of study drug, whichever is longer. For female participants not of childbearing potential:
  - Postmenopausal, defined as no menses for 12 months without an alternative medical cause and confirmed by elevated follicle-stimulating hormone (FSH) consistent with a postmenopausal range
  - Permanent sterilization procedure, such as hysterectomy, bilateral salpingectomy, or bilateral oophorectomy

17-OHP, 17-hydroxyprogesterone; 21-OHD, 21-hydroxylase deficiency; BSA, body surface area; CYP21A2, cytochrome p450 21A2; FSH, follicle-stimulating hormone; GC, glucocorticoid; HCe, hydrocortisone equivalent; PRA, plasma renin activity; ULN: upper limit of normal.

Auchus RJ, et al. Supplementary Appendix. *N Engl J Med*. 2024;391(6):504-514.

CAHtalyst Study

Key exclusion criteria

Key Exclusion Criteria
• Known or suspected diagnosis of any other form of classic CAH
• History of bilateral adrenalectomy, hypopituitarism, or other condition requiring chronic therapy with oral GCs, or required chronic therapy with inhaled GCs that might interfere with study endpoints (per investigator judgment)
• Evidence of GC overtreatment during screening
• Increased risk of developing adrenal crisis (per investigator judgment)
• Clinically significant medical condition or chronic disease (e.g., history of neurological, hepatic, renal, cardiovascular, gastrointestinal, significant malabsorption, hematologic, pulmonary, psychiatric, or endocrine disease [excluding CAH]) that would preclude participant or completion of the study or might confound interpretation of study outcome (per investigator judgment)
• History of malignancy, unless successfully treated with curative intent and considered to be cured
• Known history of clinically concerning cardiac arrhythmia (including long QT syndrome) or prolongation of screening (pre-treatment) QT interval, corrected for heart rate using Fridericia's correction (QTcF)
• Known sensitivity (i.e., hypersensitivity) or allergy to any corticotropin-releasing hormone (CRH) receptor antagonist
• Evidence of chronic renal or liver disease

CRH, corticotropin-releasing hormone; GC, glucocorticoid; QTcF, QT interval, corrected for heart rate using Fridericia's correction.

Auchus RJ, et al. Supplementary Appendix. *N Engl J Med*. 2024;391(6):504-514.

CAHtalyst Study

Key exclusion criteria (cont'd)

Key Exclusion Criteria (cont'd)

- Clinically significant hematologic or coagulation abnormalities at screening
- Used any active investigational drug for another clinical trial within 30 days or 5 half-lives (whichever is longer) before screening, or plan to use such drug during the CAHtalyst study
- Use of any of the following excluded concomitant medications (unless discontinuation during the study was possible):
  - Orally administered GCs for indications other than CAH
  - Strong inducers of CYP3A4 or CYP2B6 except topically administered medications
  - Medications that affect cortisol or GC metabolism (e.g., phenytoin, mitotane, phenobarbital, strong CYP3A4 inhibitors such as ketoconazole, clarithromycin, cholestyramine, certain antivirals) except topically administered medications
  - Aromatase inhibitors (e.g., anastrozole, letrozole, testolactone)
- Current dependence or abuse of any of the following: alcohol, controlled substances, non-prescribed use of prescription drugs, nicotine, or caffeine
- Significant risk of suicidal or violent behavior
- Blood loss ≥550 mL or blood/plasma donation within 8 weeks before baseline (day 1)
- Pregnancy or lactation (in females)
- Not capable of adhering to the protocol requirements (per investigator judgement)

CYP3A4, Cytochrome P450 3A4; CYP2B6, Cytochrome P450 2B6; GC, glucocorticoid.

Auchus RJ, et al. Supplementary Appendix. *N Engl J Med*. 2024;391(6):504-514.

CAHtalyst Study

Full list of endpoints

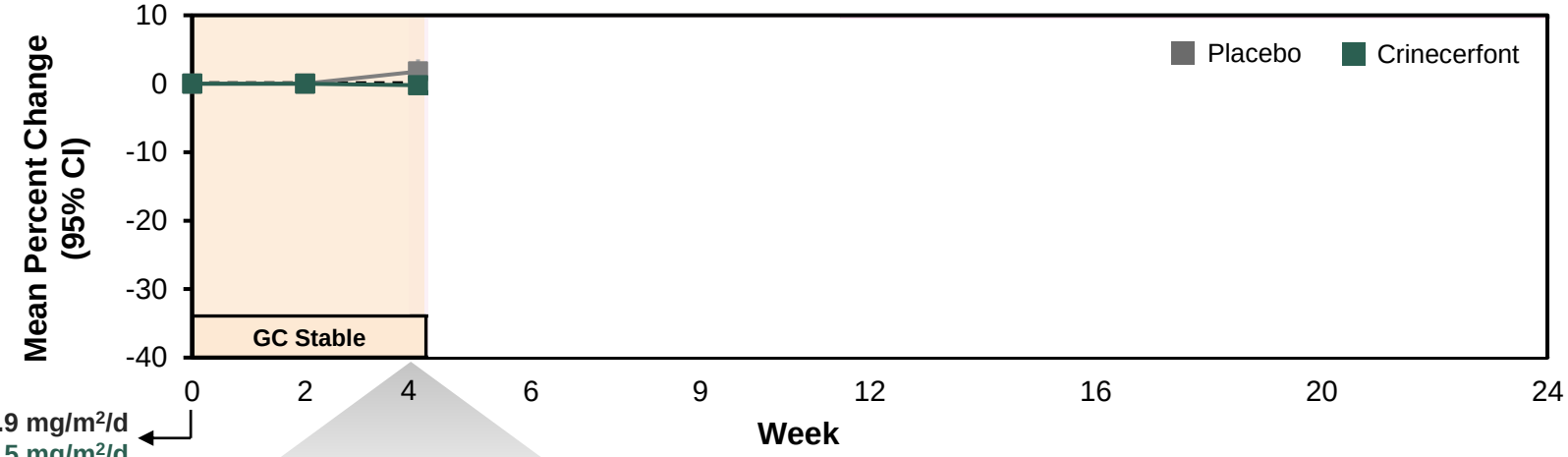
Primary Endpoint
• The percent change from baseline in GC daily dose (mg/m2/day in HCe, adjusted for BSA) at week 24 while A4 levels were maintained (at ≤120% of baseline or ≤ULN for age and sex)
Key Secondary Endpoints
• Change from baseline in serum A4 at week 4
• Achievement of a reduction in GC daily dose to physiologic levels (≤11 mg/m2/day) at week 24 while A4 levels were maintained
• Change from baseline in homeostatic model assessment of insulin resistance (HOMA-IR) at week 24 in fasting participants not on insulin
• Percent change from baseline in body weight at week 24
• Change from baseline in percent total fat mass at week 24, assessed using a whole-body scan
Secondary Endpoints
• Change from baseline in 17-OHP at week 4
• Change from baseline in blood pressure at week 24
• Change from baseline in glucose tolerance at week 24, as measured by post-GTT (glucose tolerance test) load glucose levels
• Change from baseline in waist circumference at week 24
• Change from baseline in menstrual regularity at week 24 in premenopausal female participants not using hormonal or intrauterine device contraception
• Change from baseline in testicular adrenal rest tumor (TART) volume at week 24 in male participants, expressed as a percentage of total testicular volume
Exploratory Bone Marker Endpoints
• Bone formation was assessed using changes in serum osteocalcin and bone-specific alkaline phosphatase. Serum C-terminal telopeptide (CTx) and urine N-terminal telopeptide (NTx, collected after the first morning void after an overnight fast) were used to assess bone resorption
Safety Assessments
• Treatment-Emergent Adverse Events (TEAEs)
• Vital Signs and Physical Examinations
• Electrocardiograms and Clinical Laboratory Tests
• Brief Psychiatric Rating Scale (BPRS)
• Columbia-Suicide Severity Rating Scale (C-SSRS)

17-OHP, 17-hydroxyprogesterone; A4, androstenedione; BPRS, Brief Psychiatric Rating Scale; BSA, body surface area; C-SSRS, Columbia-Suicide Severity Rating Scale; CTx, C-terminal telopeptide; GC, glucocorticoid; GTT, glucose tolerance test; HCe, hydrocortisone equivalent; HOMA-IR: Homeostatic model assessment for insulin resistance; NTx, N-terminal telopeptide; TART: Testicular adrenal rest tumor; TEAE, treatment-emergent adverse event; ULN: Upper limit of normal.

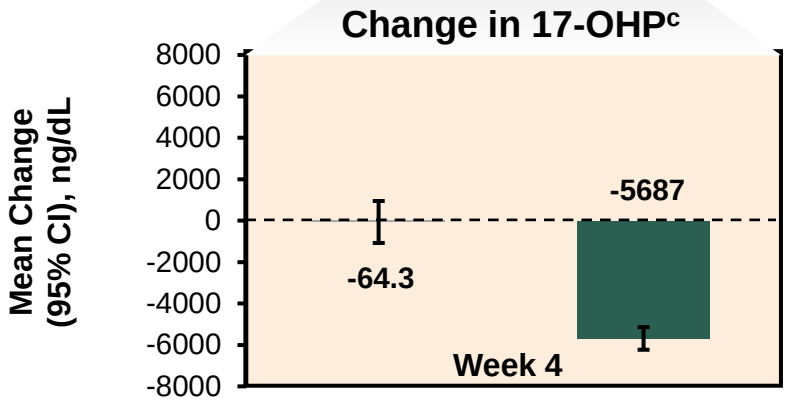
Auchus RJ, et al. Supplementary Appendix. *N Engl J Med*. 2024;391(6):504-514.

While Holding GC Dose Stable, Crinecerfont* Can Reduce 17-OHP at Week 4

Observed Change From Baseline in GC[a] While A4 Levels Were Maintained per Study Definition[b]



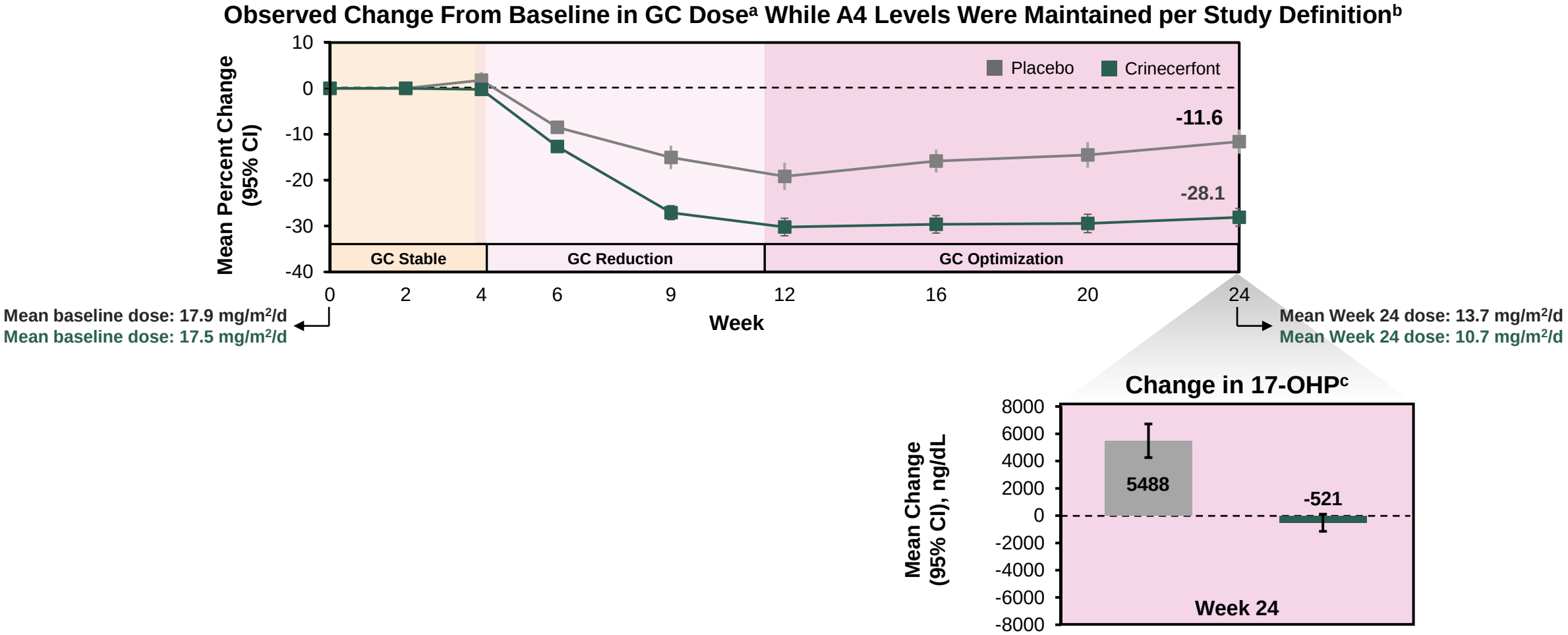
Mean baseline dose: 17.9 mg/m^2/d
Mean baseline dose: 17.5 mg/m^2/d



Secondary Endpoint Met:
17-OHP levels decreased from baseline to Week 4 with crinecerfont but increased with placebo
(LSMD: -5838 ng/dL
[95% CI: -7441, -4235])

Note: The widths of the CIs have not been adjusted for multiplicity and thus should not be used to determine treatment effect.
A4, androstenedione; CI, confidence interval; GC, glucocorticoid.
[a]Decreases in GC dose were set to 0 in participants who did not maintain androgen levels.
[b]A4 maintenance was defined as ≤120% of baseline or ≤ULN according to sex and age.
[c]Based on samples collected before participants received their morning GC doses.
Auchus RJ, et al. *N Engl J Med*. 2024;391(6):504-514.

Mean Change in 17-OHP at Week 24



Note: The widths of the CIs have not been adjusted for multiplicity and thus should not be used to determine treatment effect.
A4, androstenedione; CI, confidence interval; GC, glucocorticoid.
[a]Decreases in GC dose were set to 0 in participants who did not maintain androgen levels.
[b]A4 maintenance was defined as ≤120% of baseline or ≤ULN according to sex and age.
[c]Based on samples collected before participants received their morning GC doses.
Auchus RJ, et al. *N Engl J Med*. 2024;391(6):504-514.