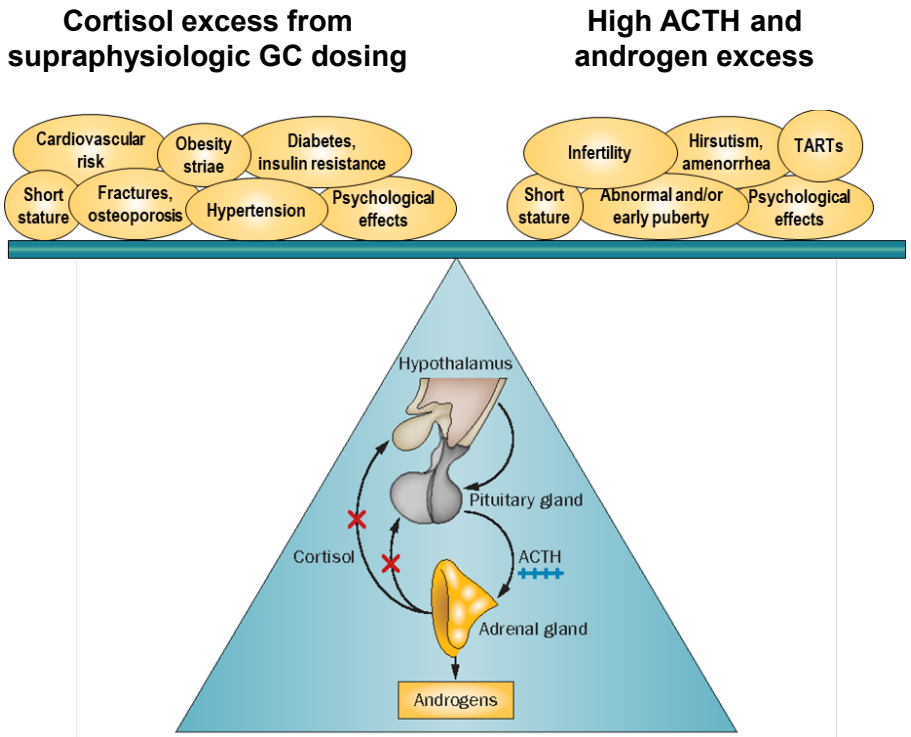
MED-MSL-CAH-US-0010_v1

Crinecerfont (NBI-74788), a Novel CRF_1 Receptor Antagonist, Lowers Adrenal Androgens and Precursors in Adolescents with Classic Congenital Adrenal Hyperplasia

NEUROCRINE® BIOSCIENCES

Classic Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency

- Classic CAH due to 21OHD results in[1]:
  - Impaired synthesis of cortisol and (often) aldosterone
  - Excess adrenal androgen production
- Treatment must balance consequences of supraphysiologic glucocorticoid doses and the consequences of high adrenocorticotropic hormone (ACTH) and androgen excess[1]



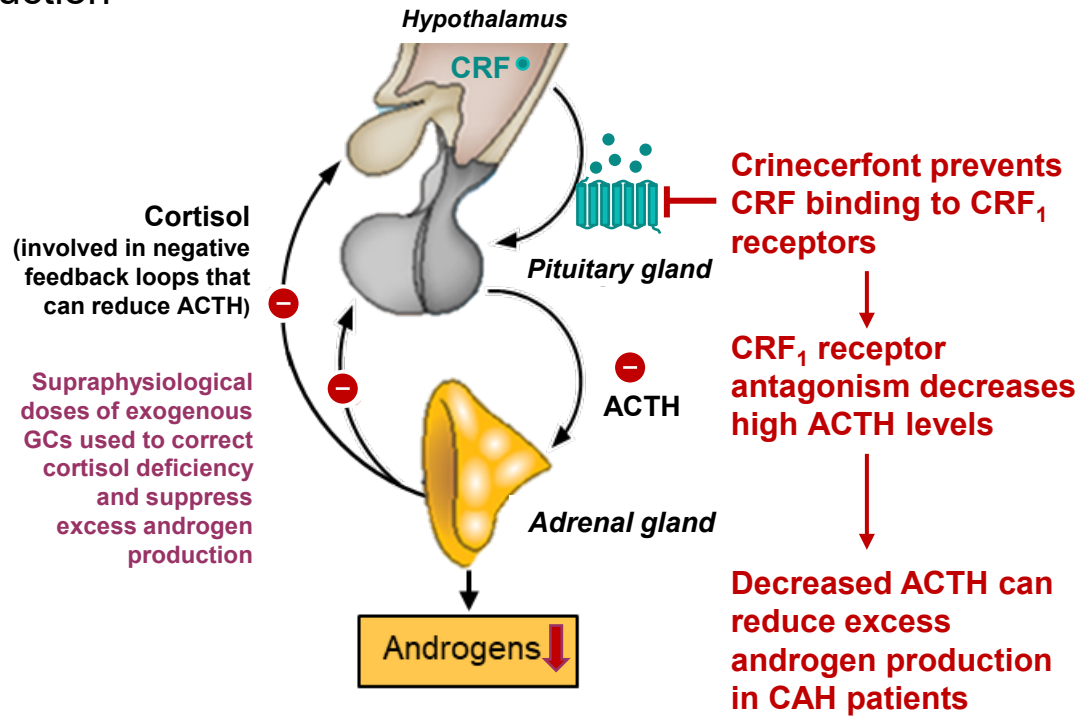
ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia.

1. Mallappa A and Merke DP. *Nat Rev Endocrinol.* 2022;43(1):91-159.

Figure Adapted from: Han TS et al. *Nat Rev Endocrinol*. 2014;10(2):115-24.

Crinecerfont*: A Novel CRF_1 Receptor Antagonist

- Crinecerfont is an orally administered, nonsteroidal, selective CRF_1 receptor antagonist[1,2]
- CRF_1 receptor antagonism in classic CAH could inhibit ACTH release & reduce excess androgen production[1,2]



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

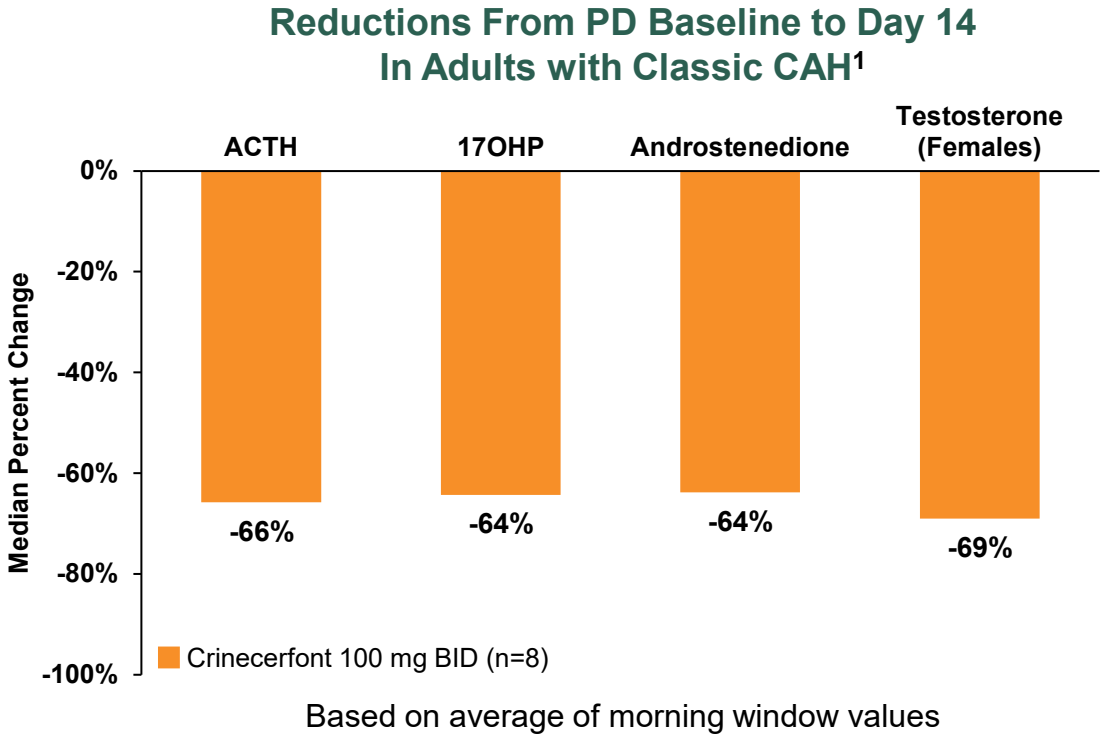
ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; CRF_1, corticotropin-releasing factor type 1.

1. Auchus RJ et al. *J Clin Endocrinol Metab.* 2022;107(3):801-812. 2. Newfield RS, et al. Oral presentation at the ENDO; June 11-14, 2022; Atlanta, GA.

Figure Adapted from: Han TS et al. *Nat Rev Endocrinol*. 2014;10(2):115-24.

Crinecerfont*: A Novel CRF_1 Receptor Antagonist

- In a phase 2 study of crinecerfont, adults with classic CAH experienced clinically meaningful reductions in ACTH, 17OHP, androstenedione, and (female) testosterone levels[1]

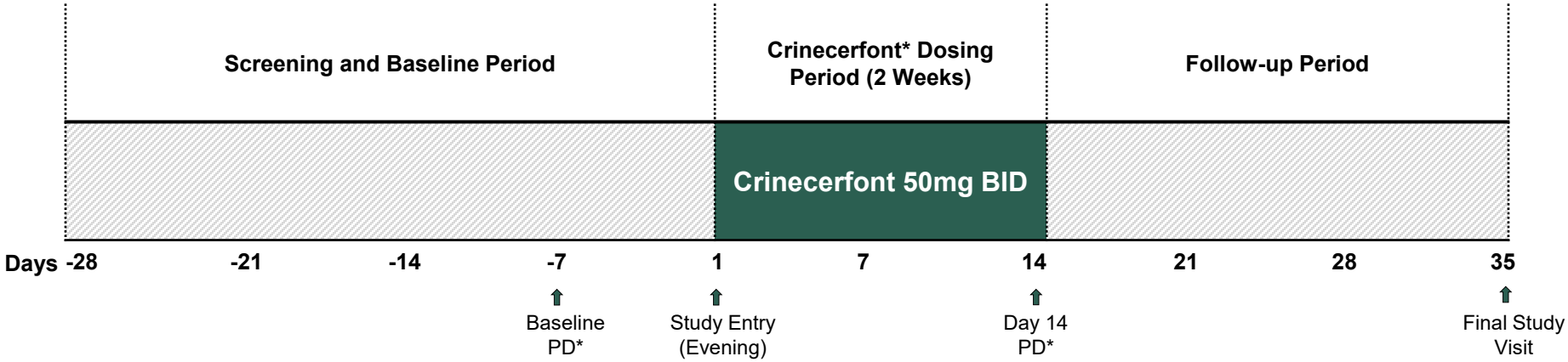


***Crinecerfont is investigational and not approved for use in any country for any indication.**

17OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotropic hormone; BID, twice daily; CAH, congenital adrenal hyperplasia; CRF_1, corticotropin-releasing factor type 1; PD, pharmacodynamic.

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

Study of Crinecerfont* in Adolescents with Classic CAH



Study Details (CAH2008 - NCT04045145)	
Study overview	Phase 2, open-label study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of crinecerfont in adolescents (eligible ages: 14 to 17 years) with classic CAH due to 21-OHD
Treatment	Crinecerfont 50 mg twice daily (BID), taken orally in the morning and evening with meals for 14 days
Primary endpoint	Number of participants with adverse events following dosing of crinecerfont
Pharmacodynamic assessment	24-hour serial sampling at baseline and Day 14 for ACTH, 17OHP, androstenedione, and testosterone – The primary pharmacodynamic assessment was based on the morning window (average of 2 samples collected at 07:00 and 10:00)
Expected timing	Completed

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

17OHP, 17-hydroxyprogesterone; 21-OHD, 21-hydroxylase deficiency; ACTH, adrenocorticotropic hormone; BID, twice daily; GC, glucocorticoid; PD, pharmacodynamic.

1. ClinicalTrials.gov. Safety, tolerability, pharmacokinetics, and pharmacodynamics of NBI-74788 in pediatric subjects with congenital adrenal hyperplasia. Accessed June 6, 2022. https://clinicaltrials.gov/ct2/show/NCT04045145. NLM identifier: NCT04045145. 2. Newfield RS, et al. Oral presentation at the ENDO; June 11-14, 2022; Atlanta, GA.

Key Eligibility Criteria

Key Inclusion Criteria

- Female and male participants, 14 to 17 years of age
- Be in good general health
- Have a medically confirmed diagnosis of classic 21-hydroxylase deficiency CAH
- Be on a stable regimen of steroidal treatment for CAH that is expected to remain stable throughout the study
- 17OHP ≥800 ng/dL, cortisol <5 µg/dL, and ACTH ≥20 pg/mL prior to morning GC dose
- Participants of childbearing potential must agree to use hormonal or 2 forms of nonhormonal contraception consistently from screening until the final study visit
- Participants of childbearing potential must have a negative pregnancy test at screening and baseline
- Negative urine drug test (for illegal drugs) and alcohol breath test at screening and baseline

Key Exclusion Criteria

- Have a clinically significant unstable medical condition or chronic disease, or malignancy
- Had a medically significant illness within 30 days of screening
- Have a known or suspected differential diagnosis of any of the other known forms of classic CAH
- Have a medical history that includes bilateral adrenalectomy, hypopituitarism, or other condition requiring daily therapy with orally administered glucocorticoids
- Known history of long QT syndrome or tachyarrhythmia
- Have hypersensitivity to any corticotropin-releasing hormone antagonists
- Have an active bleeding disorder

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

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

1. ClinicalTrials.gov. Safety, tolerability, pharmacokinetics, and pharmacodynamics of NBI-74788 in pediatric subjects with congenital adrenal hyperplasia. Accessed June 6, 2022. https://clinicaltrials.gov/ct2/show/NCT04045145. NLM identifier: NCT04045145. 2. Newfield RS, et al. Oral presentation at the ENDO; June 11-14, 2022; Atlanta, GA.

Study Population

	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]	3.2 (2.5, 4.7)
Body mass index, kg/m^2	25 (19, 38)
Z-score[c]	1.2 (-0.2, 2.6)
No. 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)
Glucocorticoid Treatment	
Hydrocortisone (HC) alone, n (%)	6 (75.0)
Prednisone alone, n (%)	2 (25.0)
GC dose (HC equivalent[d]), mg/m^2/day, median (min, max)	16.2 (11.9, 18.5)
Androgens, ACTH, and Precursors at Baseline, Median (IQR)[e]	
ACTH, pg/mL	226.2 (377.3)
17-hydroxyprogesterone, ng/dL	7703.7 (7123.5)
Androstenedione, 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 for use in any country for any indication.**

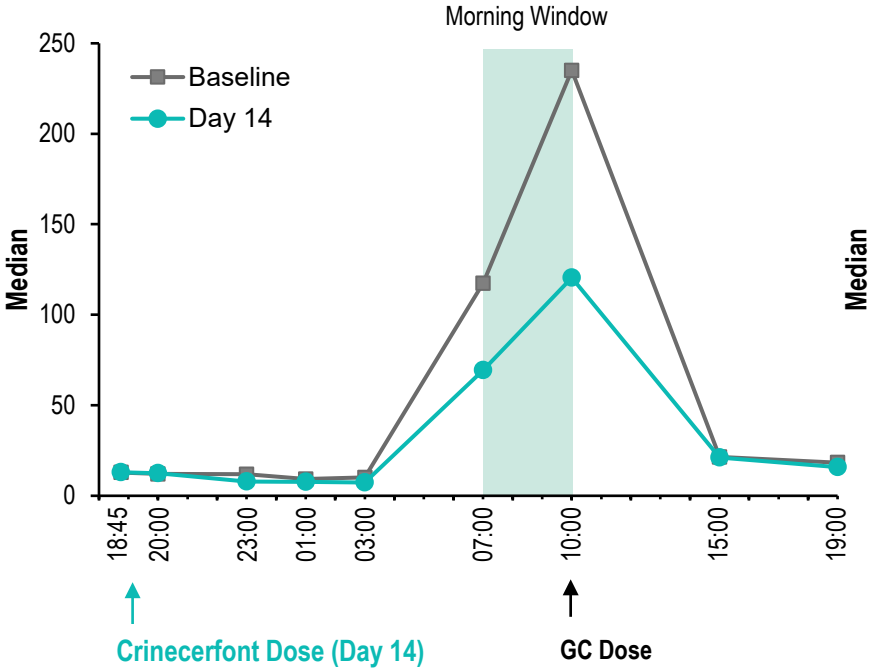
[a]Presented as median (minimum, maximum) unless indicated otherwise; [b]Includes one participant who also self-identified as Hispanic or Latino; [c]Centers for Disease Control Growth Chart used as reference, with Z-scores based on chronological age; [d]Hydrocortisone equivalents were calculated as 1 mg prednisone = 4 mg hydrocortisone. None were on dexamethasone; [e]Based on the average of morning window values (07:00, 10:00); ACTH, adrenocorticotropic hormone; GC, glucocorticoid; IQR, interquartile range.

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

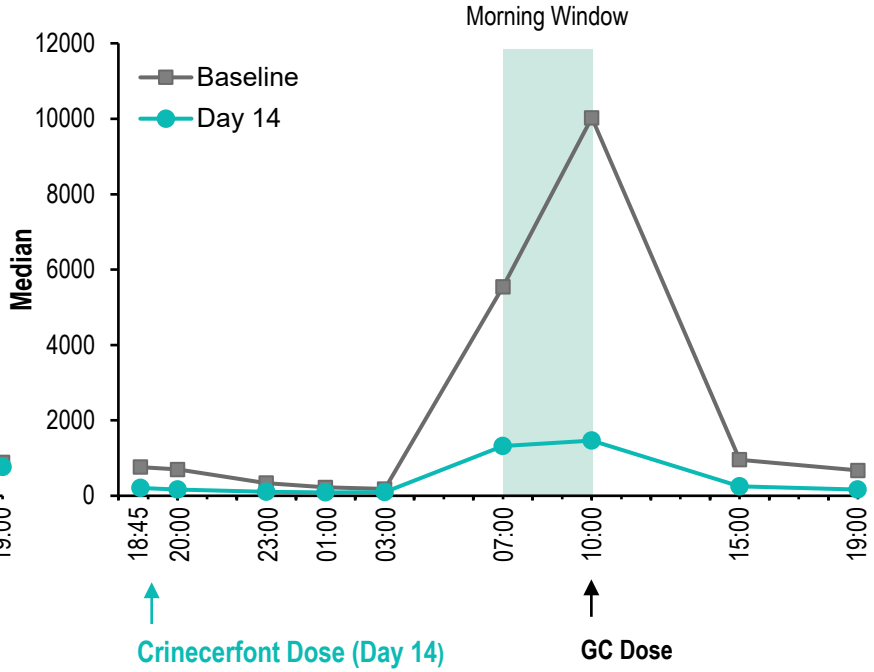
Clinically Meaningful Reductions in ACTH and 17OHP Especially During Morning Window After 14 Days of Crinecerfont* Treatment

24-Hour Concentration Profiles

Plasma ACTH, pg/mL



Serum 17OHP, ng/dL



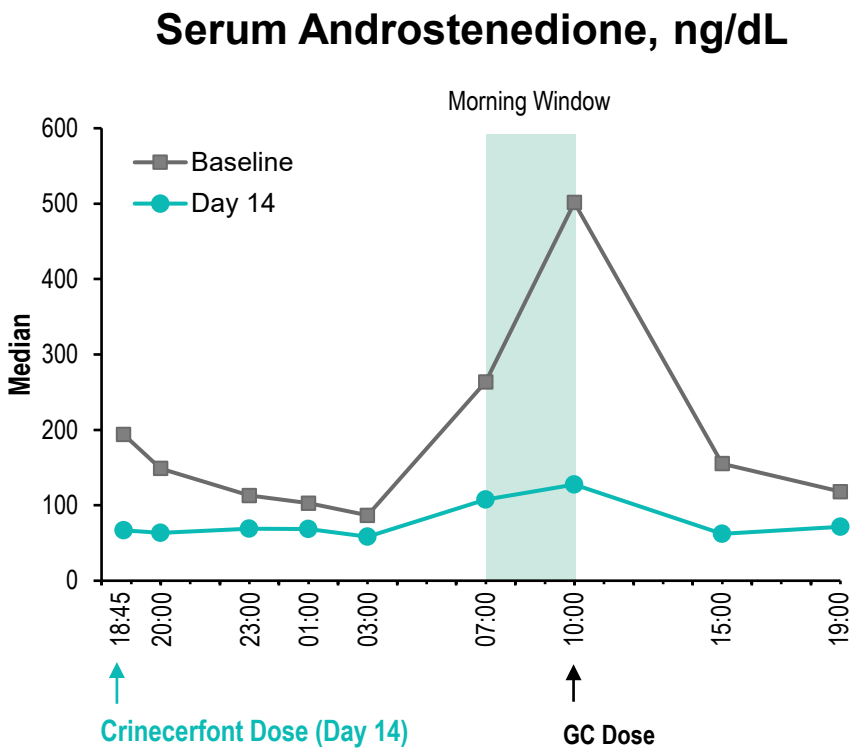
***Crinecerfont is investigational and not approved for use in any country for any indication.**

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

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

Clinically Meaningful Reductions in Androstenedione Especially During Morning Window After 14 Days of Crinecerfont* Treatment

24-Hour Concentration Profile

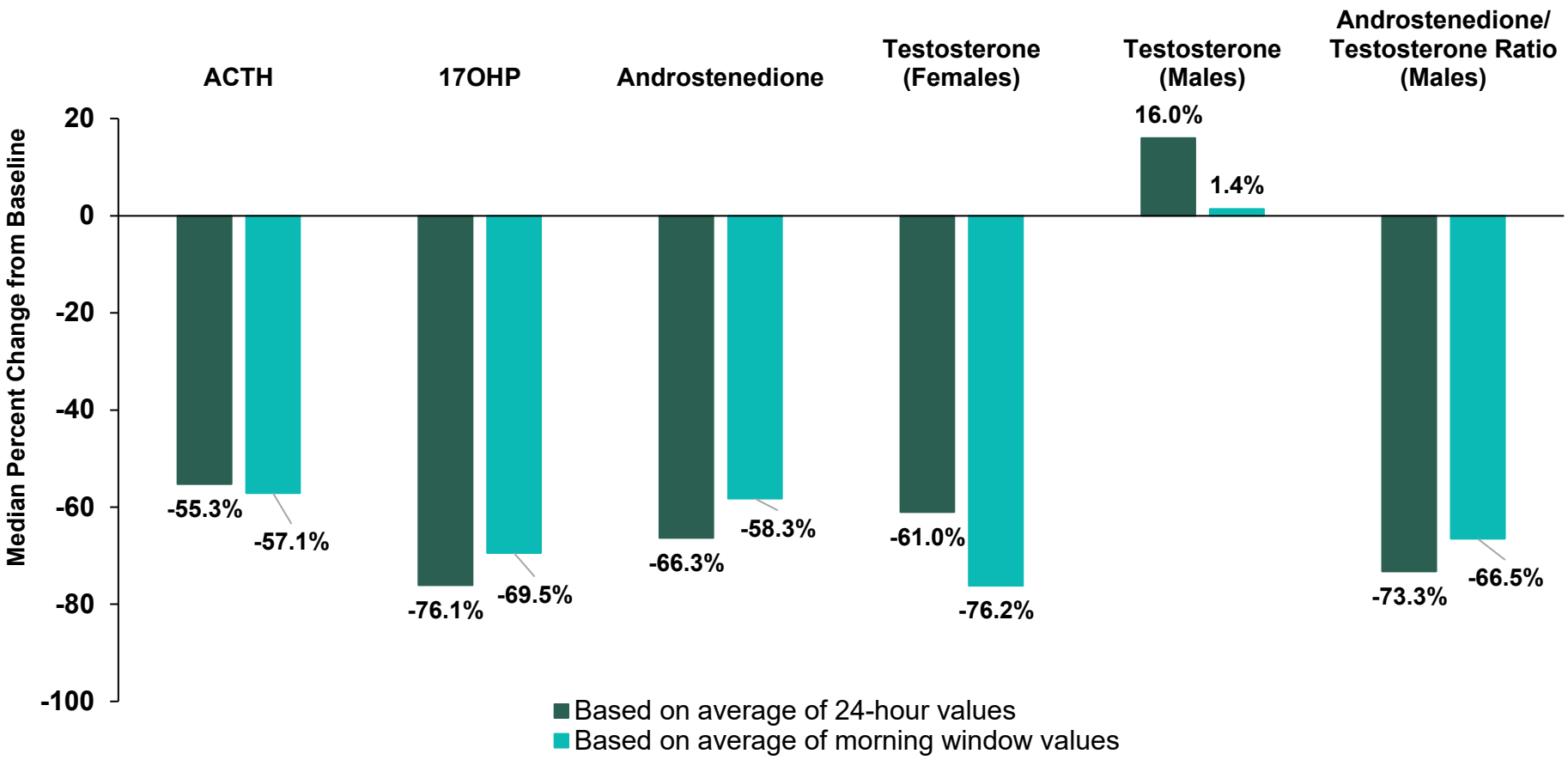


***Crinecerfont is investigational and not approved for use in any country for any indication.**

GC, glucocorticoid.

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

≥50% Median Reductions in ACTH, 17OHP, Androstenedione, Testosterone (Females), and Androstenedione/Testosterone Ratio (Males) After 14 Days of Crinecerfont* Treatment

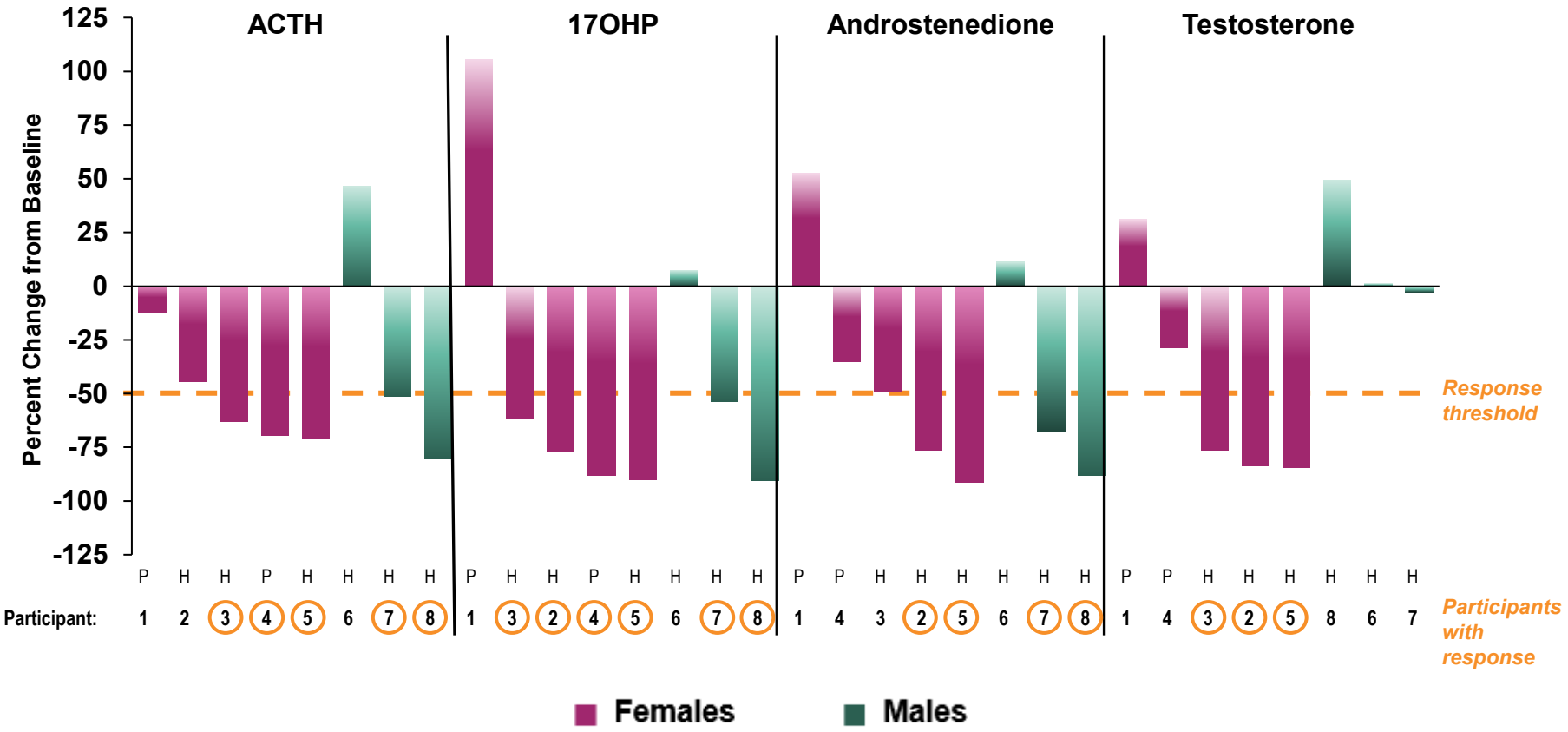


***Crinecerfont is investigational and not approved for use in any country for any indication.**

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

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

Crinecerfont* Treatment Led to Decreases in ACTH, 17OHP, Androstenedione, and (Female) Testosterone Levels in the Majority of Participants[a]



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

[a]Based on average of morning window values; 17OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotropic hormone; H, hydrocortisone; P, prednisone.

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

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

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

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

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

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

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

Crinecerfont* Was Generally Well Tolerated With No Serious TEAEs or Discontinuations Due to Safety Profile

TEAE Summary, n	All Participants (N=8)
Any TEAE	6
Any serious TEAE	0
Any TEAE leading to discontinuation	0
Any TEAE resulting in death	0

- All treatment-emergent adverse events (TEAEs) were mild
- No safety concerns based on routine laboratory tests, vital signs, electrocardiograms, or neuropsychiatric assessments

List of All Reported TEAEs, n	All Participants (N=8)
Headache[a]	2
Arthropod sting	1
Blepharospasm	1
Dermatitis contact	1
Dizziness[a]	1
Frequent bowel movements	1
Gastritis	1
Myalgia	1
Nasopharyngitis	1
Pyrexia	1
Vomiting	1

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

[a]Mild headache and dizziness (each in 1 participant) were judged by the investigator as "possibly" related to study drug; TEAE, treatment-emergent adverse event.

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

Summary

- In adolescents with classic CAH, clinically meaningful median reductions (57-76%) in morning levels of adrenal androgens and androgen precursors were observed after 14 days of crinecerfont* treatment[1]
  - These data were consistent with results from a prior study of crinecerfont in adults with classic CAH[2]
- Further studies are warranted to evaluate the potential of longer-term crinecerfont therapy to:
  - Afford sustained reduction in all adrenal-derived androgens
  - Allow for lower, more physiologic glucocorticoid dosing
  - Improve clinical outcomes (weight, metabolic risk, growth/development, fertility, etc.)

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

CAH, congenital adrenal hyperplasia.

1. Newfield RS, et al. Oral presentation at the ENDO; June 11-14, 2022; Atlanta, GA. 2. Auchus RJ et al. *J Clin Endocrinol Metab*. 2022;107(3):801-812.