Nya diagnostiska och terapeutiska möjligheter vid congenital adrenal hyperplasi (CAH)

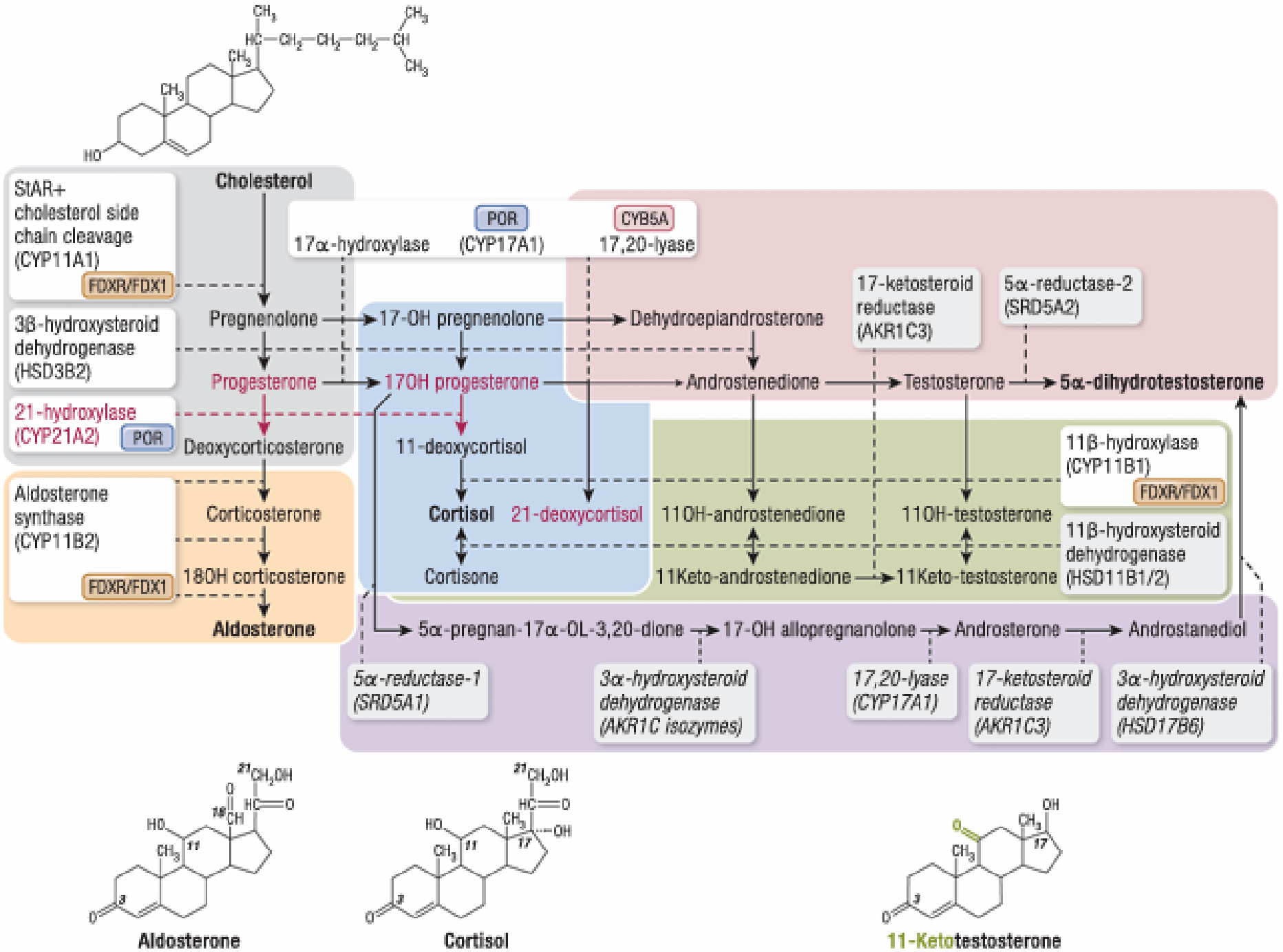
Associate Professor Henrik Falhammar; MD, PhD, FRACP

Karolinska University Hospital and Karolinska Institutet

Stockholm, Sweden

Disclosures

- Consultation fees and/or PI for studies from
  - Neurocrine Biosciences, Inc.
  - Spruce Biosciences, Inc.
  - H. Lundbeck A/S
  - Crinetics Pharmaceuticals, Inc
  - Frost Pharma AB



Claahsen - van der Grinten et al. Endocrine Reviews 2022

New diagnostics in CAH

Alternative Steroid Biomarkers

- The usual markers we measure in CAH are 17OHP (diurnal curves preferred), A4, Testosterone and sometimes DHEAS, LH and FSH (LH and FSH are not steroid biomarkers)
- 11-oxyandrogens are ”new” steroid biomarkers
  - 11β-hyroxyandrostenedione (11OHA4)
  - 11-ketotestosterone (11KT)
  - In patients with 21OHD, except for well-controlled postpubertal males, the major circulating androgen is 11KT, not T

Claahsen - van der Grinten et al. Endocrine Reviews 2022 and Sarafoglou et al. JCEM 2025

11-oxyandrogens in CAH

- Limited data suggest that 11OHA4 may help diagnose NC 21OHD without ACTH-stimulation, especially when combined with other steroid biomarkers in women[1]
- In children with 21OHD, 11KT was higher with poor vs good disease control and often matched clinical assessment when 17OHP and A4 were discordant[2]
- In men with TART, 11OHT showed the largest spermatic-to-peripheral gradient of all steroids, indicating direct production by TART cells. 11OHT also seemed rapidly converted to 11KT and/or 11OHA4, as peripheral 11OHT was not higher than in men without TART[3]

1. Mallappa et al Nat Rev Endo 2022. 2. Jha et al JES 2021, 3. Schroder et al. JCEM 2022

Diurnal curves of steroids

- Diurnal curves can be done on dried blood spots/special containers (Sweden, Norway, Australia), saliva (Netherlands) and plasma/serum (as inpatient).
- 17OHP is the most common one but 11-oxyandrogens can be done if available
- Portable microdialysis device (U-RHYTHM) has been used for cortisol curves

Hydrokortison dos/kroppsyta

Analyt	Resultat	Enhet
Längd	162	cm
Vikt	91	kg
Hydrokortisondos	—	mg
Dos/kroppsyta	Kan ej beräknas	mg/m2

B-17-OH-progesteron (¤)

Datum och tid	Resultat (nmol/L)	Kommentar
2026-02-13 06:30	320	
2026-02-13 14:00	33	
2026-02-13 19:00	48	
2026-02-14 01:00	9	
2026-02-14 06:00	260	

Hydrokortison dos/kroppsyta

Analyt	Resultat	Enhet
Längd	—	cm
Vikt	—	kg
Hydrokortisondos	25,0	mg
Dos/kroppsyta	Kan ej beräknas	mg/m2

B-17-OH-progesteron (¤)

Datum och tid	Resultat (nmol/L)	Kommentar
2026-02-25 06:05	260	
2026-02-25 14:04	140	
2026-02-25 19:10	20	
2026-02-26 01:05	8	
2026-02-26 06:00	260	

Hydrokortison dos/kroppsyta

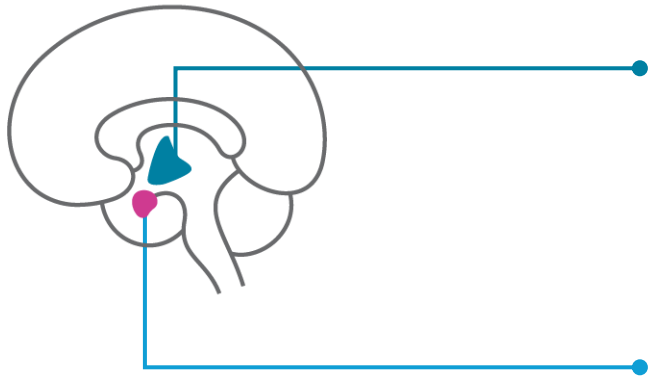
Analyt	Resultat	Enhet
Längd	178	cm
Vikt	96	kg
Hydrokortisondos	—	mg
Dos/kroppsyta	Kan ej beräknas	mg/m2

B-17-OH-progesteron (¤)

Datum och tid	Resultat (nmol/L)	Kommentar
2026-03-09 06:15	3	
2026-03-09 14:00	<3	
2026-03-09 19:00	<3	
2026-03-10 01:00	<3	
2026-03-10 06:00	<3	

New Therapies in CAH

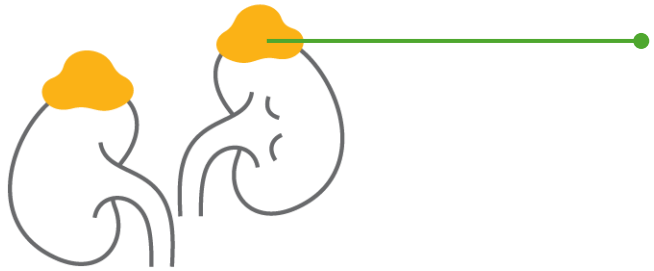
CAH Pathophysiology: Cortisol Deficiency Drives Adrenal Androgen Excess[1,2]



Hypothalamus

CRF

Loss of normal negative cortisol feedback



Pituitary gland

ACTH

Adrenal glands

Defect in 21-hydroxylase enzyme

Cortisol deficiency

Aldosterone deficiency

Adrenal androgen excess

Increased ACTH results in increased adrenal androgen production

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.

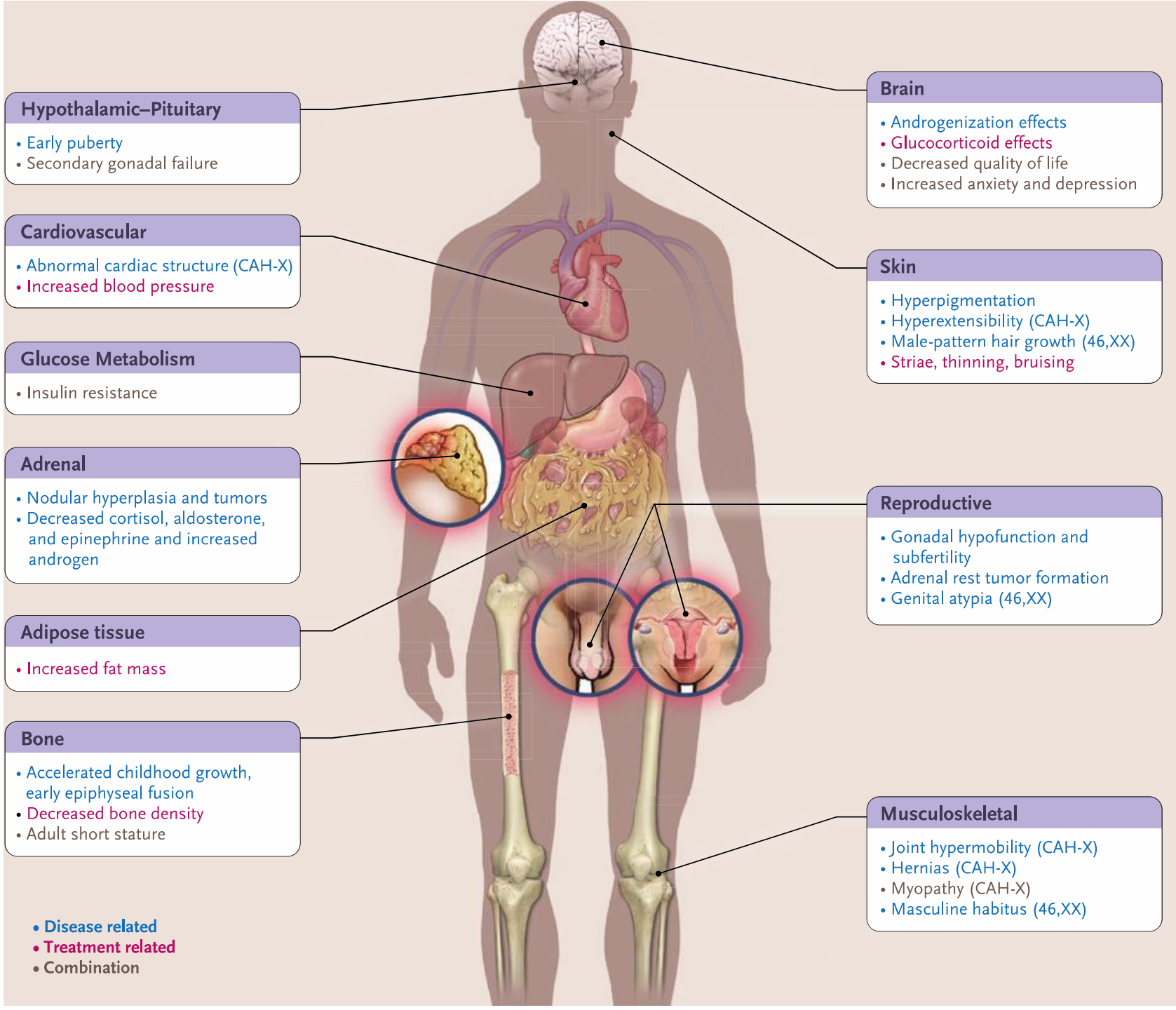
Glucocorticoid treatment in 21OHD

- Substitutes for the cortisol insufficiency
- Decreases CRF and ACTH production and secretion resulting in lower adrenal androgens
- I.e. provides for the possibility of survival and symptom control
- However, to get enough ACTH suppression supraphysiological doses of glucocorticoids are usually required

Claahsen-van der Grinten HL, et al. Endocr Rev. 2022;43(1):91-159

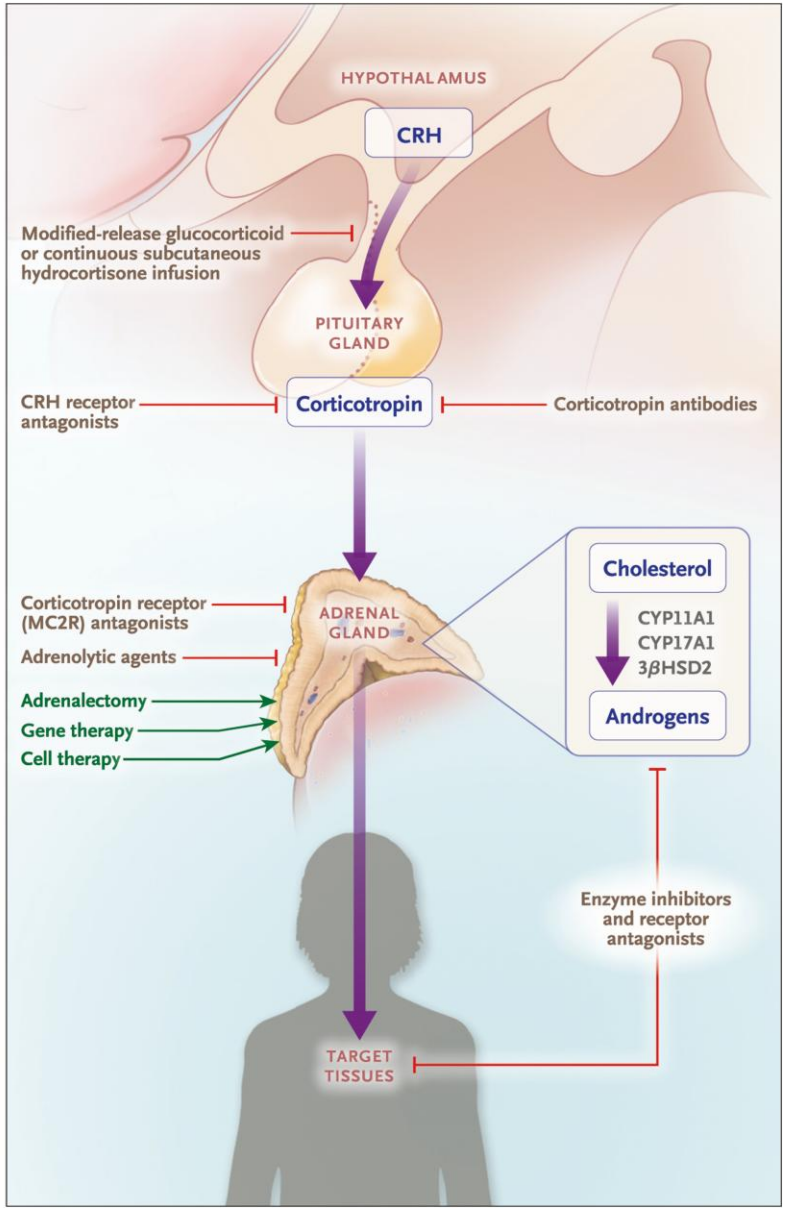
Disease- and Treatment-Related Features of 21OHD

- Supraphysiologic doses of GCs typically required for disease control, which can lead to long-term complications



- Merke DP, Auchus RJ. N Engl J Med. 2020;383:1248.

Figure 5. New therapeutic approaches target different aspects of the pathophysiology of CAH.

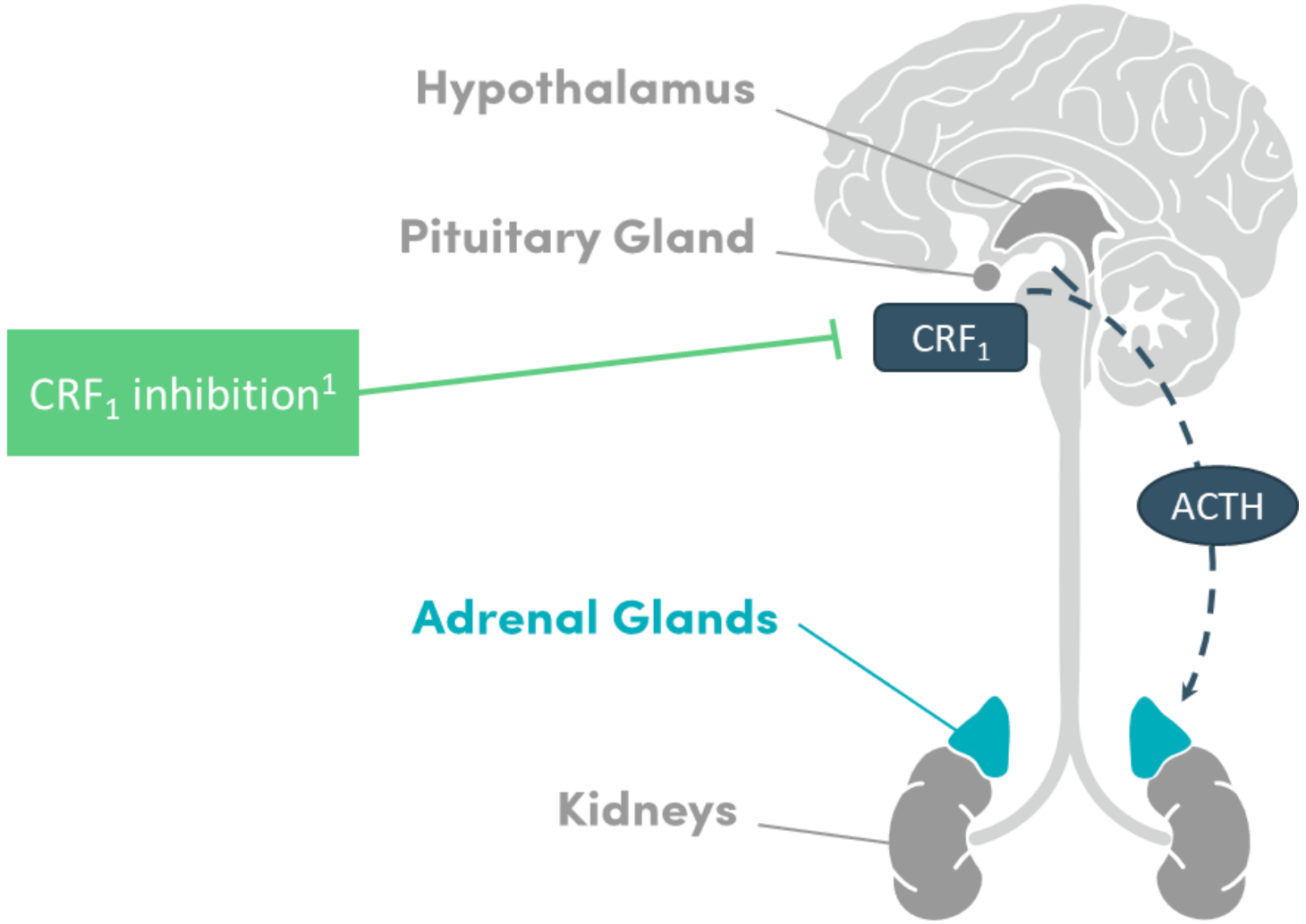


Endocr Rev, Volume 43, Issue 1, February 2022, Pages 91–159, https://doi.org/10.1210/endrev/bnab016

NON-GC TREATMENT APPROACHES ARE NEEDED TO REDUCE LONG-TERM TOXICITY

- Novel pathways under investigation may allow disease control at **physiologic** or **near-physiologic** GC doses

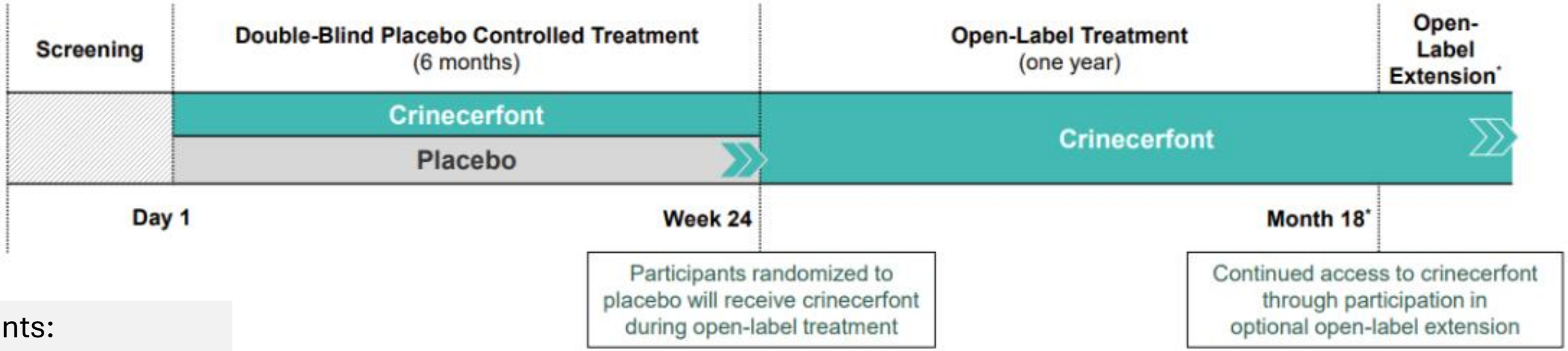
Crinecerfont
Tildacerfont



1. Sarafoglou K, et al. J Clin Endocrinol Metab 2021; 2. Fowler MA, et al. J Endocr Soc 2021;5(Suppl 1):A167;
3. Perdomini M, et al. Gene Ther 2017;24:275–81.

Crinecerfont

CAHtalyst Study Design



Patients:

- Adults (≥18 years of age) with classic CAH
- Receiving a daily GC dose of > 13 mg/m2 BSA of a HC equivalent – on stable dose for at least 1 month

Objective

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

Primary Endpoint

Percent change from baseline in glucocorticoid daily dose at Week 24 while maintaining androgen control

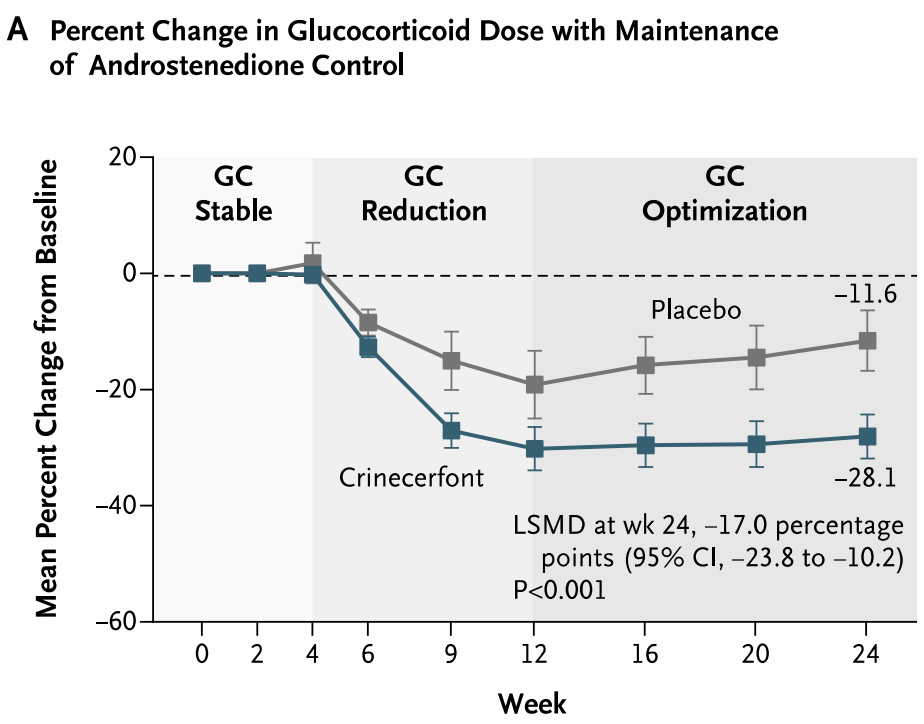
- Auchus RJ, et al. N Engl J med. 2024

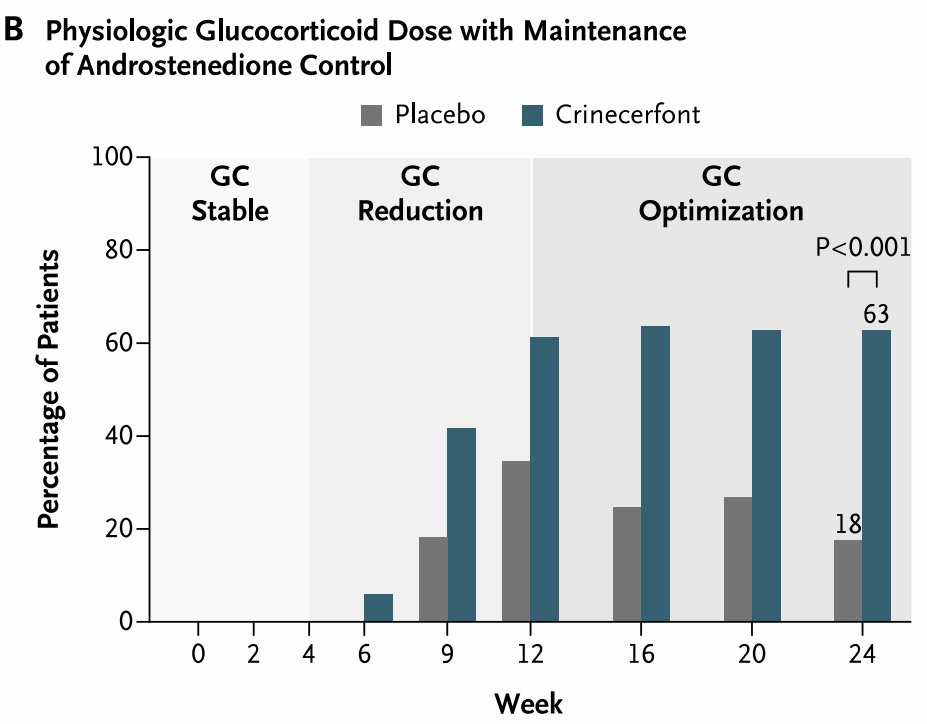
Table 1. Characteristics of the Patients at Baseline.*

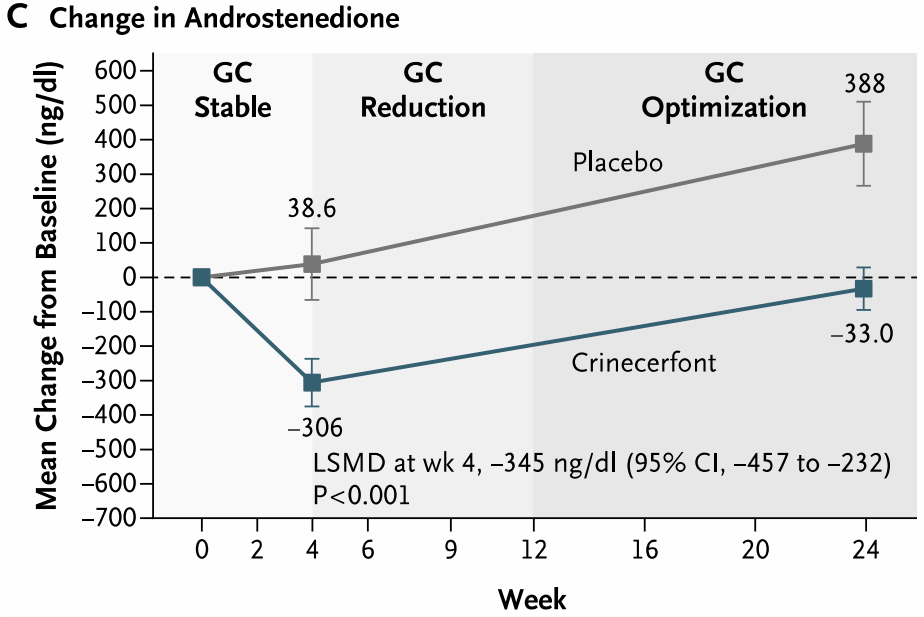
Characteristic	All Patients (N=182)	Crinecerfont (N=122)	Placebo (N=60)
Age — yr	30.8±9.9	31.3±9.8	29.8±10.2
Male sex — no. (%)	92 (51)	61 (50)	31 (52)
White race — no. (%)†	164 (90)	107 (88)	57 (95)
Glucocorticoid daily dose			
In hydrocortisone equivalents — mg/day	32.3±9.3	32.4±9.2	32.1±9.5
Adjusted for body-surface area — mg/m²	17.6±4.9	17.5±4.5	17.9±5.5
Glucocorticoid type — no. (%)			
Hydrocortisone alone	106 (58)	71 (58)	35 (58)
Prednisone, prednisolone, or methylprednisolone, with or without hydrocortisone	53 (29)	34 (28)	19 (32)
Dexamethasone, with or without another glucocorticoid	23 (13)	17 (14)	6 (10)
Fludrocortisone — no. (%)	157 (86)	107 (88)	50 (83)
Body weight — kg	79.3±18.3	80.8±17.8	76.2±18.9
Body-mass index‡	29.8±7.0	30.1±6.9	29.0±7.1
Percent total fat mass§	35.7±9.2	36.3±9.0	34.6±9.5
Homeostasis model assessment of insulin resistance¶	3.2±2.8	3.2±2.7	3.1±3.1
Androstenedione — ng/dl‖	620±729	635±796	590±572
17-Hydroxyprogesterone — ng/dl‖	9467±8829	9314±8560	9787±9435
Testicular adrenal rest tumor — no./total no. (%) **	53/80 (66)	35/53 (66)	18/27 (67)

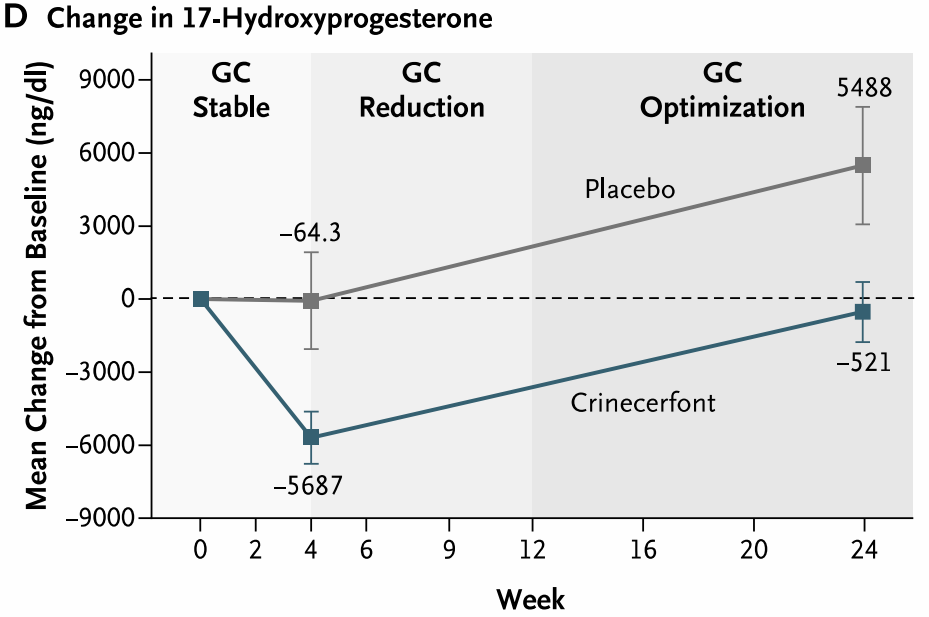
Auchus RJ, et al. N Engl J med. 2024

CAHtalyst Adult: Efficacy Endpoints









- Auchus RJ, et al. N Engl J med. 2024

CAHtalyst Adult: Safety

AE s in ≥ 5% patients taking crinecerfont

Fatigue and headache most common

Adverse Events	Crinecerfont (N = 122)	Placebo (N = 59)
	number of patients (percent)	
Any adverse event	101 (83)	48 (81)
Leading to discontinuation of crinecerfont or placebo	4 (3)*	0
Leading to trial discontinuation	4 (3)*	0
Any serious adverse event	4 (3)†	0
Severity of adverse event‡		
Mild	62 (51)	30 (51)
Moderate	36 (30)	18 (31)
Severe	3 (2)	0
Common adverse events§		
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 kinase increased	6 (5)	2 (3)
Nasopharyngitis	6 (5)	8 (14)
Vomiting	6 (5)	5 (8)

- Auchus RJ, et al. N Engl J med. 2024 June 1 [Epub ahead of print]

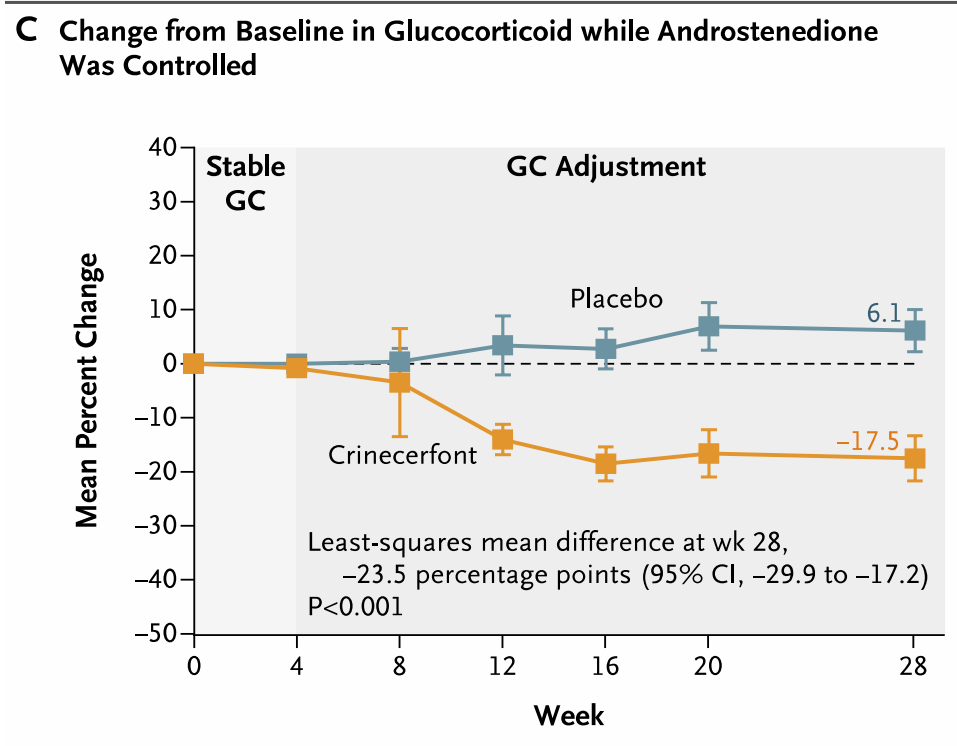
CAHtalyst Pediatric

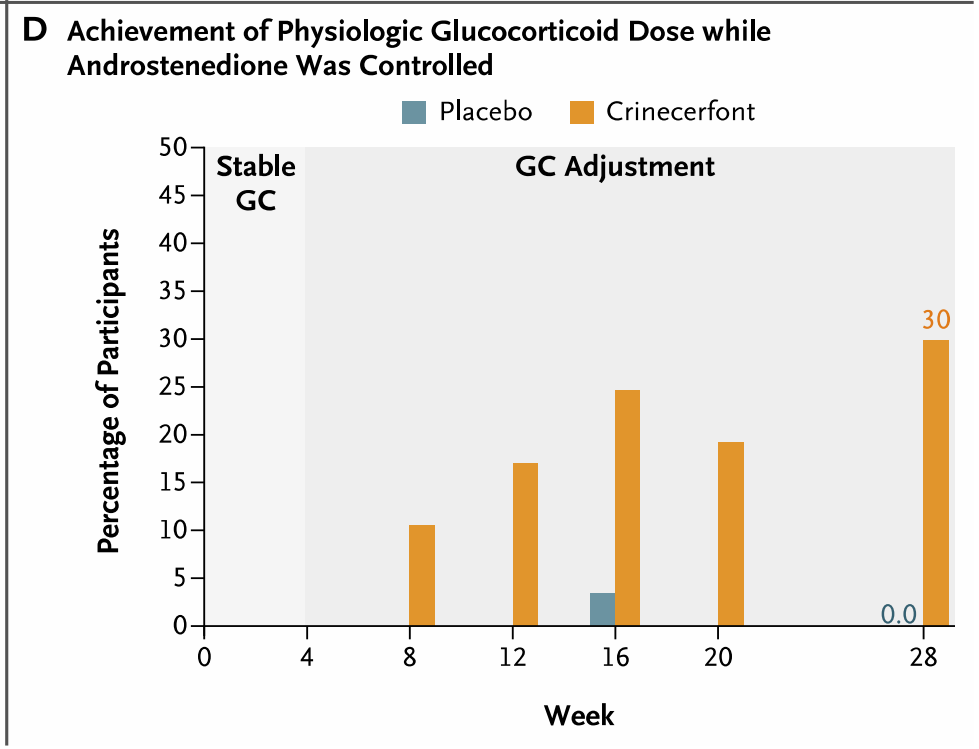
Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

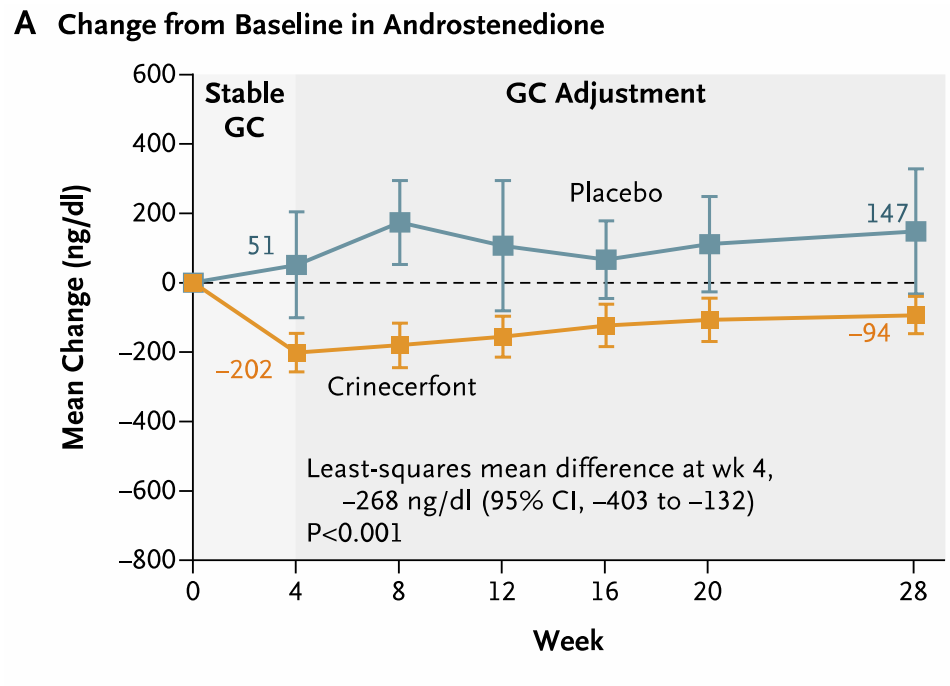
Characteristic	All Participants (N=103)	Crinecerfont (N=69)	Placebo (N=34)
Age — yr	12.1±3.5	12.0±3.4	12.1±3.7
Male sex — no. (%)	53 (51)	35 (51)	18 (53)
Race or ethnic group — no. (%)†			
White	65 (63)	42 (61)	23 (68)
Asian	9 (9)	7 (10)	2 (6)
Black	3 (3)	3 (4)	0
Other	11 (11)	8 (12)	3 (9)
Not reported	15 (15)	9 (13)	6 (18)
Glucocorticoid use			
Total dose — mg/m²/day‡	16.4±3.9	16.5±4.2	16.3±3.4
Hydrocortisone alone — no. (%)	95 (92)	63 (91)	32 (94)
Fludrocortisone use — no. (%)	90 (87)	59 (86)	31 (91)
Standard deviation score§			
Height	0.3±1.3	0.3±1.4	0.4±1.2
Weight	1.2±1.0	1.2±1.0	1.2±1.0
BMI	1.2±0.9	1.2±0.9	1.1±1.0
BMI ≥85th percentile — no. (%)	60 (58)	40 (58)	20 (59)
Tanner stage: breast or testicular — no. (%)¶			
1	30 (29)	18 (26)	12 (35)
2	12 (12)	10 (14)	2 (6)
3	13 (13)	8 (12)	5 (15)
4	19 (18)	15 (22)	4 (12)
5	29 (28)	18 (26)	11 (32)
Androstenedione — ng/dl‖	431±461	405±464	483±456
17-Hydroxyprogesterone — ng/dl‖	8682±6847	8513±7431	9026±5563
Testosterone — ng/dl‖**			
In female participants	73±67	67±60	88±81
In male participants at Tanner stages 1–2	51±63	60±74	33±32
In male participants at Tanner stages 3–5	404±205	408±212	396±204
Androstenedione-to-testosterone ratio††			
In male participants at Tanner stage 2	3.6±2.2	3.4±2.3	5.1
In male participants at Tanner stages 3–5	3.4±8.7	4.1±10.6	2.0±1.0
Testicular adrenal rest tumors present — no. of participants/total no.(%)‡‡	15/46 (33)	10/31 (32)	5/15 (33)

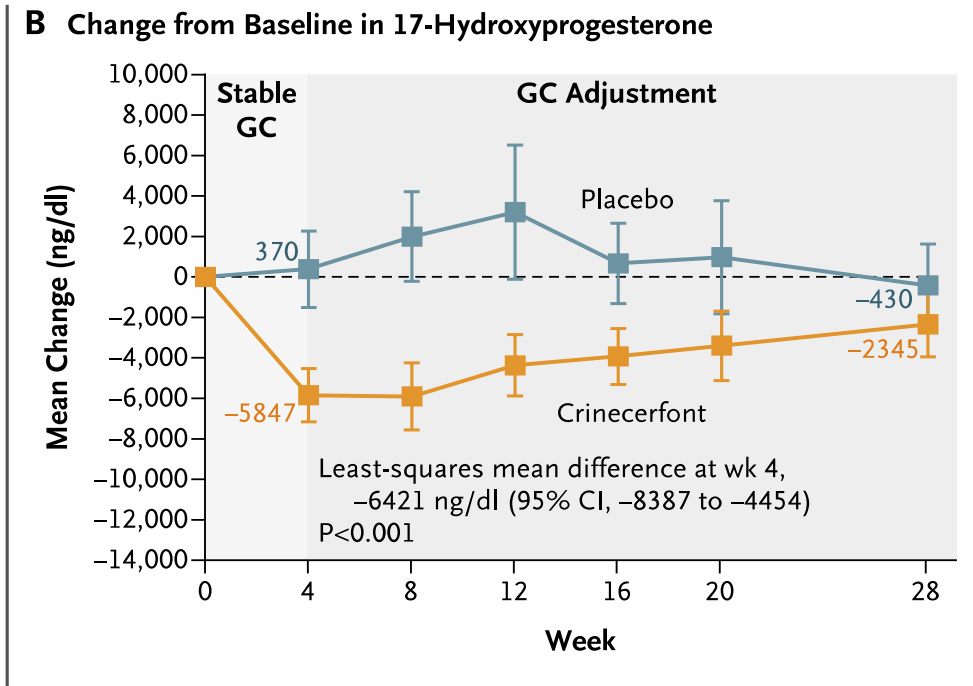
- Sarafoglou K, et al. N Engl J med. 2024

CAHtalyst Pediatric: Efficacy Endpoints









- Sarafoglou K, et al. N Engl J med. 2024

CAHtalyst Pediatric: Safety

Peds trial was largely conducted during Covid pandemic

95% of study participants completed the crinecerfont trial

AEs in > 5% patients taking crinecerfont

- Headache, pyrexia, and vomiting were most common

Adverse Event	Crinecerfont (N = 69)	Placebo (N = 33)
Common adverse events§		
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)

- Auchus RJ, et al. N Engl J med. 2024 June 1 [Epub ahead of print]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of Crinecerfont in Adult Congenital Adrenal Hyperplasia

R.J. Auchus, O. Hamidi, R. Pivonello, I. Bancos, G. Russo, S.F. Witchel, A.M. Isidori, P. Rodien, U. Srirangalingam, F.W. Kiefer, H. Falhammar, D.P. Merke, N. Reisch, K. Sarafoglou, G.B. Cutler, Jr., J. Sturgeon, E. Roberts, V.H. Lin, J.L. Chan, and R.H. Farber, for the CAHtalyst Adult Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

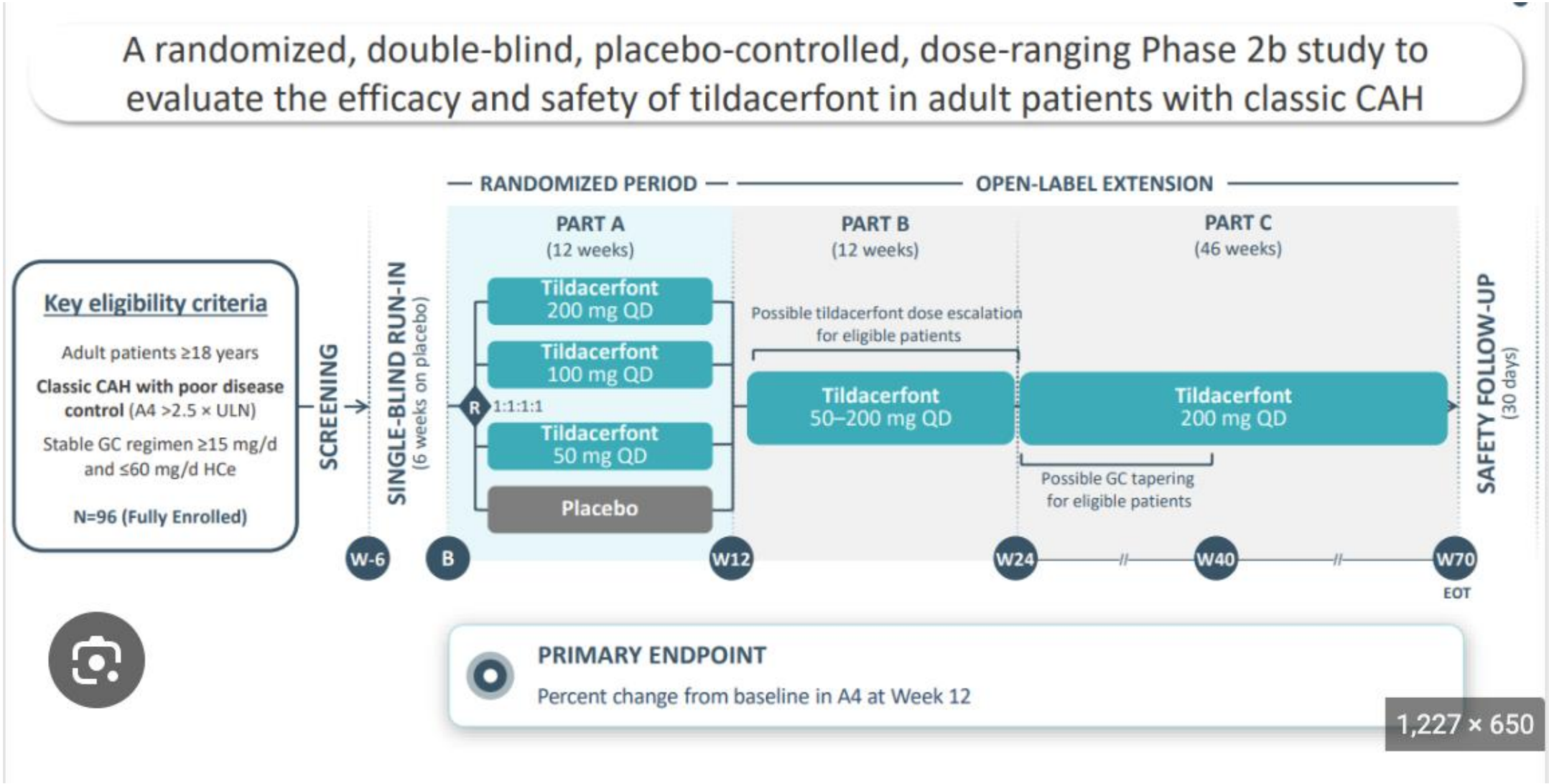
ORIGINAL ARTICLE

Phase 3 Trial of Crinecerfont in Pediatric Congenital Adrenal Hyperplasia

K. Sarafoglou, M.S. Kim, M. Lodish, E.I. Felner, L. Martinerie, N.J. Nokoff, M. Clemente, P.Y. Fechner, M.G. Vogiatzi, P.W. Speiser, R.J. Auchus, G.B.G. Rosales, E. Roberts, G.S. Jeha, R.H. Farber, and J.L. Chan, for the CAHtalyst Pediatric Trial Investigators*

Tildacerfont

CAHmelia-203: Adrenal Androgen Reduction Study



- Clinicaltrials.gov NCT04457336

CAHmelia-203: Adrenal Androgen Reduction Study

- N = 96 subjects with a mean baseline A4 concentrations of 1,151 ng/dL (39 nmol/L)
- Data highlights
  - Trial did not achieve the primary efficacy endpoint of the assessment of dose response for the change in A4 from baseline to week 12
  - 200mg QD of tildacerfont demonstrated a placebo-adjusted reduction from baseline in A4 of -2.6% at week 12 with a non-significant p-value.
  - Compliance with study medication and GC was low with approximately 50% of patients reporting 80% or greater compliance, resulting in lower-than-expected tildacerfont exposure.
  - Tildacerfont was generally safe and well tolerated at all doses with no treatment-related serious AEs. Most AEs were reported as mild to moderate.

Spruce Press release in March 2024

CAHmelia-204: GC Reduction Study

A randomized, double-blind, placebo-controlled Phase 2b study to evaluate the efficacy and safety of tildacerfont in reducing supraphysiologic GC use in adult patients with classic CAH

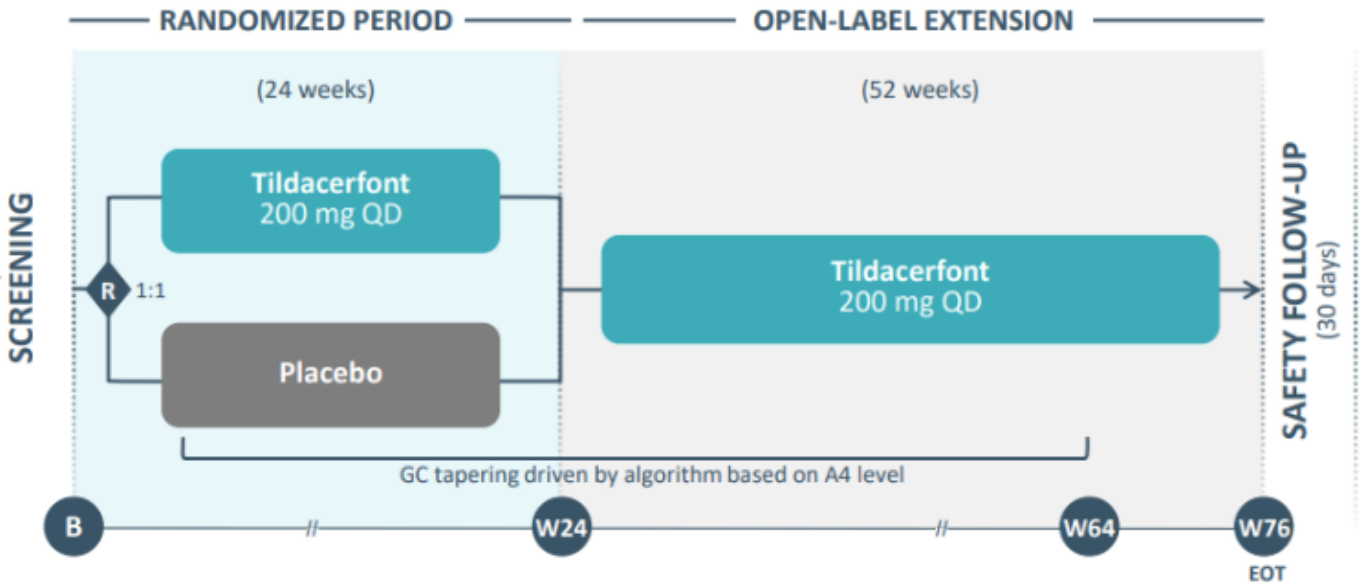
Key eligibility criteria

Adult patients ≥18 years

Classic CAH with good disease control
(LLD ≤ A4 ≤ 2.5x ULN)

Stable GC regimen ≥30 mg/d and ≤60 mg/d HCe

Projected N=98-100



PRIMARY ENDPOINT

Absolute change in daily glucocorticoid dose (HCe) from baseline at Week 24

1,241 × 639

- ClinicalTrials.gov NCT04544410.

CAHmelia-204: GC Reduction Study

- The clinical trial did not achieve the primary efficacy endpoint of the absolute change in daily GC dose from baseline at week 24.
- 200mg QD of tildacerfont demonstrated a placebo-adjusted reduction from baseline in daily GC dose of 0.7mg HCe (95% CI: -4.3 to 2.9, p=0.7).
- Approximately 98% of patients were highly compliant with study drug.
- Tildacerfont was generally safe and well tolerated with no serious adverse events (SAEs).

Press release Spruce Dec 10, 2024

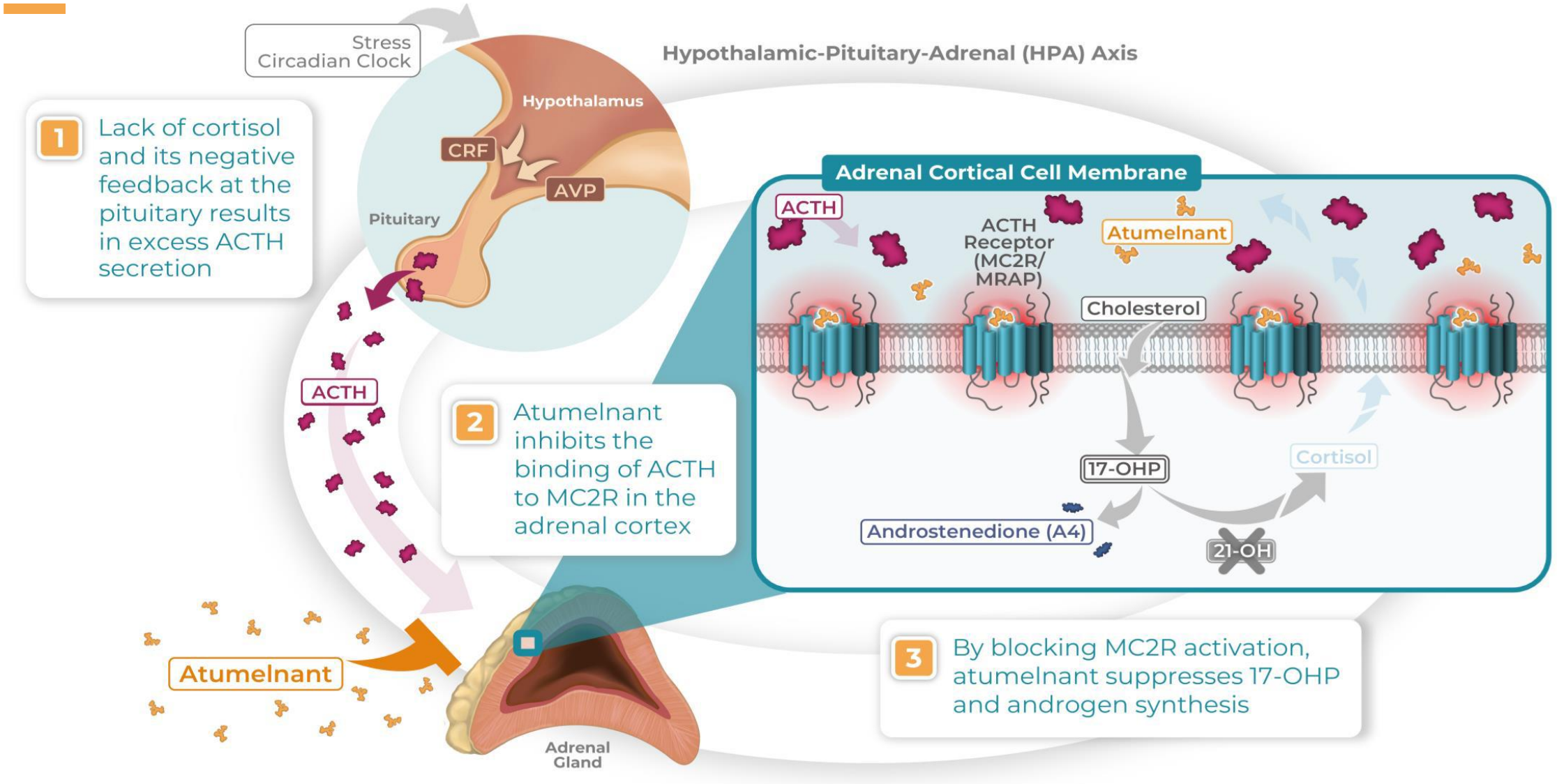
CAHptain-205: Pediatric Study

- N = 30 children (2 – 17 y/o); with a mean baseline GC dose of 14 mg/m^2/day and mean baseline A4 level of 372 ng/dL
  - Non-randomized, non-controlled study
  - Much smaller group of children; shorter duration of study
- Data highlights
  - Tildacerfont generally safe and well tolerated at all dose ranges with no treatment-related SAEs reported
  - A trend was observed of larger reductions from baseline in A4 concentrations with higher BID doses of tildacerfont.

- Clinicaltrials.gov NCT05128942, Press release Spruce Dec 10, 2024

Atumelnant

Atumelnant: Oral, Selective ACTH Antagonist



- Kim SH, et al. ACS Med Chem Lett. 2024;15:478-485.

Once Daily Oral Atumelnant (CRN04894) Induces Rapid And Profound Reductions of Androstenedione And 17-hydroxyprogesterone In Participants With Classical CAH: Initial Results From A 12-week, Phase 2, Open-label Study

TouCAHn Study

Key Eligibility Criteria

N=24

- Male or female
- Classic 21-hydroxylase deficiency
- On ≥15mg Hydrocortisone equivalent daily dose
- A4 >1.5xULN

Treatment Arms:

- 3 cohorts, each 12 weeks (N=6-12)

80 mg Once Daily (n=9)

40 mg Once Daily (n=9)

120 mg Once Daily (n=6)

Pre-trial glucocorticoid therapy (dose and regimen) maintained throughout the trial

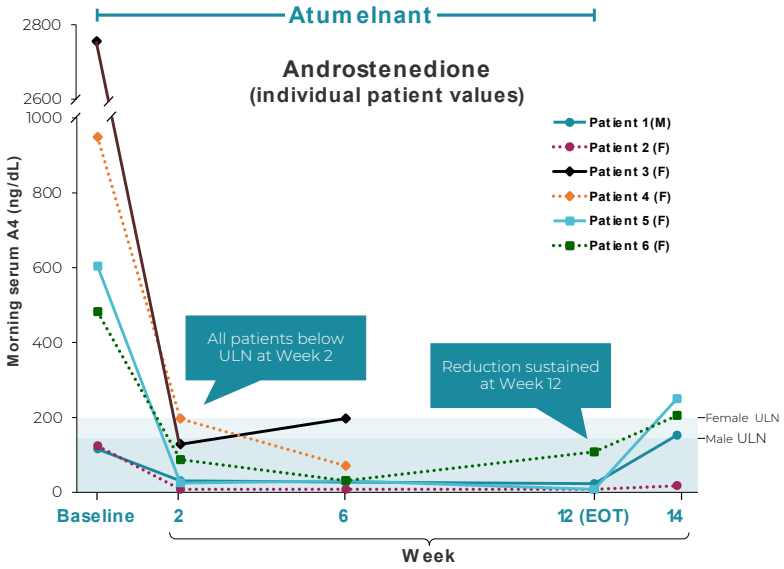
Objectives: Evaluate the Safety, Efficacy, and Pharmacokinetics of atumelnant

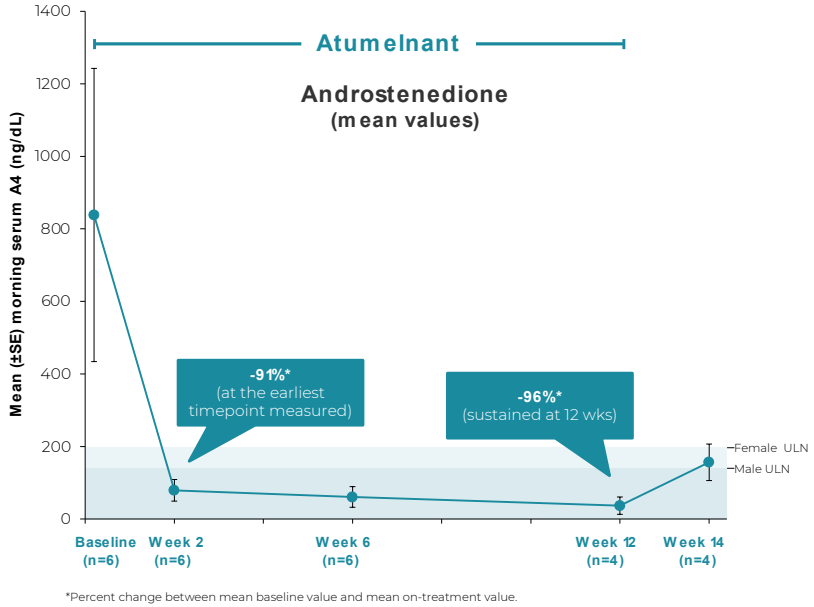
Primary Endpoint: Change from baseline in morning serum A4 at week 12
Secondary Endpoint: Change from baseline in morning serum 17-OHP at week 12
Primary Safety Assessment: Incidence of TEAEs throughout the study

- Clinicaltrials.gov NCT05907291; Auchus RJ, et al. ENDO 2024. Abstract MON-677.

TouCAHn: Efficacy Results

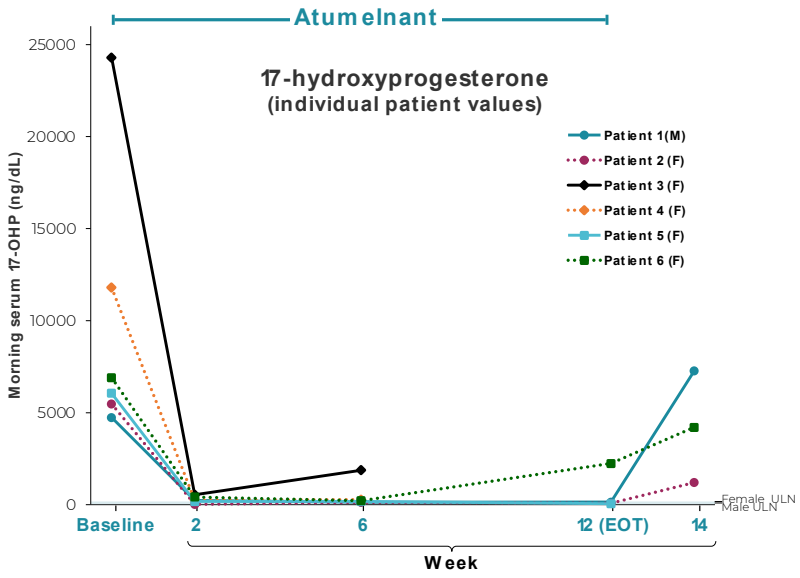
Rapid and Sustained Reduction in A4 with Atumelnant 80 mg

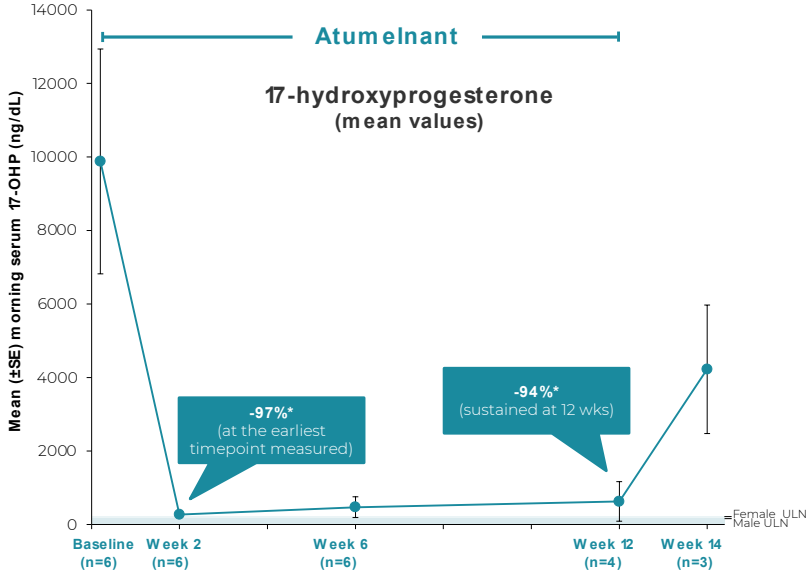




*Percent change between mean baseline value and mean on-treatment value.

Rapid and Sustained Reduction in 17-OHP with Atumelnant 80 mg





*Percent change between mean baseline value and mean on-treatment value.

Safety

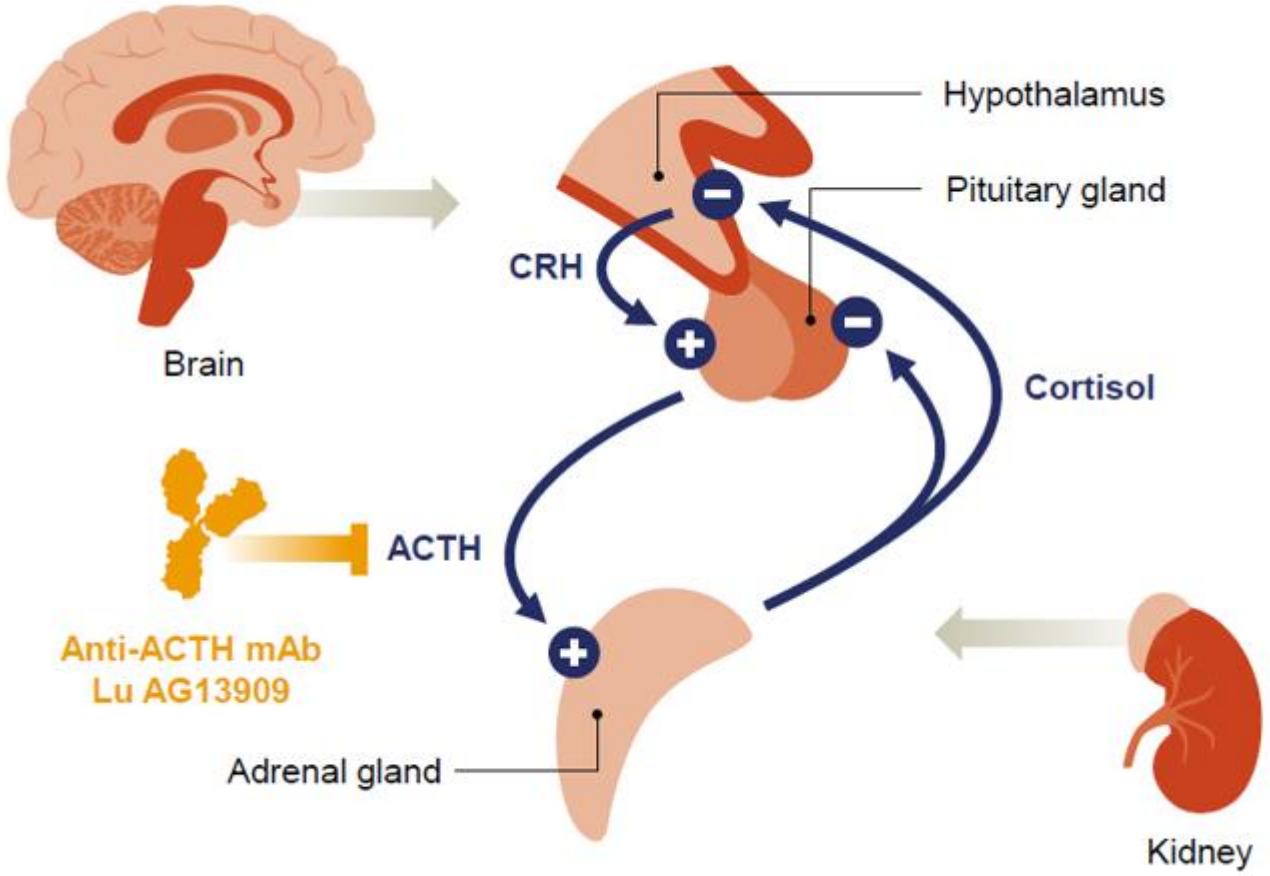
- Generally well-tolerated
- No serious or treatment-related AEs
- Most common AEs were fatigue, headache and URTI

Phase 3 RCT hopefully commence late 2025/early 2026

- Auchus RJ, et al. ENDO 2024. Abstract MON-677.

Lu AG13909

Lu AG13909 is a first in class anti-ACTH monoclonal antibody (mAb) developed by H. Lundbeck A/S



MODE OF ACTION

- Lu AG13909 is a humanized anti-ACTH mAb of the immunoglobulin G1 (IgG1) subclass
- Lu AG13909 recognizes ACTH with high affinity and specificity, preventing ACTH-induced melanocortin 2 receptor signalling

ACTH: adrenocorticotropic hormone; CRH: corticotropin releasing hormone; mAb: Monoclonal antibody

2 clinical trials with Lu AG13909 ongoing at European sites

Phase I trial in classic congenital adrenal hyperplasia (CAH)[1]

- A multi-site, open-label trial
- The main goals are to learn about the safety and tolerability of Lu AG13909, the pharmacokinetic parameters of Lu AG13909 (how the drug is absorbed, distributed, and processed by the body) and the effect on adrenal androgens
- Included 11 adult (18-70 years) individuals with classic CAH with increased androgen concentrations
- Each participant receives multiple intravenous doses of Lu AG13909
- The drug was well tolerated. Morning 17OHP and A4 concentrations were reduced at 24h after infusion by 90.5-98.7% and 66.3-89.3%, respectively, across all dose levels

Phase II trial A multi-site, open-label trial

- Just started recruiting patients

1: Clinicaltrials.gov ID: NCT05669950 Study Details | Study of Lu AG13909 in Participants With Congenital Adrenal Hyperplasia | ClinicalTrials.gov
and ENDO 2025

Gene Therapy

Phase 1/2 Trial of Investigational Gene Therapy for Congenital Adrenal Hyperplasia (CAH)

A Phase 1/2, First-in-Human, Open-Label, Dose-Escalation Study of the Safety and Efficacy of Gene Therapy for CAH through Administration of an Adeno-Associated Virus (AAV) Serotype 5-Based Recombinant Vector Encoding the Human *CYP21A2* Gene

- IV administration of AAV5 carrying the wild-type coding sequence of the CYP21A2 gene (named BBP-631)

- Patient population
  - Adult male and non-pregnant females with classic CAH due to 21-OHD
  - Screening/baseline 17-OHP levels > 5-10 × ULN and < 40 × ULN (upper limit of normal)
  - Stable oral hydrocortisone regimen as the only glucocorticoid maintenance therapy
  - Naïve to prior gene therapy or AAV-mediated therapy

- Primary outcome measures
  - Number of participants with Treatment-emergent Adverse Events that Led to Study Discontinuation
  - To select the optimum dose or dose range of BBP 631 for future studies

- Secondary outcomes measures
  - Change from Baseline in 17-OHP (hydroxyprogesterone) levels
  - Change from Baseline in endogenous cortisol levels
  - Change from Baseline in androstenedione (A4) levels

ClinicalTrials.gov. NCT04783181

Phase 1/2 Trial of Investigational Gene Therapy for Congenital Adrenal Hyperplasia (CAH)

- Increase in endogenous cortisol production achieved in all patients in higher dose cohorts of BBP-631, a result seen for the first time ever in patients with CAH
- The gene therapy was well tolerated with no treatment-related serious adverse events (SAEs) reported
- “Given that the results of the trial did not meet the threshold to warrant additional capital investment at this time, BridgeBio will be reducing the gene therapy budget more than $50M, consistent with our capital allocation principles, and reserving gene therapy for priority targets that we cannot treat any other way,”

Press release bridgebio Sept 9 2024

Future

- The future is very promising
- Hydrocortisone modified release EMEA approved but not reimbursed in many EU countries
- Crinecerfont FDA approved
- Tildacerfont. Development put on hold
- Atumelnant will start recruiting to Phase 3 trial 2025
- Lu AG13909 has started recruiting to Phase 2 2025

- Additional research is required to determine if these positive results translates into favourable long-term outcomes

Questions?


WORLD'S BEST HOSPITALS 2023
Newsweek
POWERED BY statista
KAROLINSKA UNIVERSITY HOSPITAL
KAROLINSKA UNIVERSITY HOSPITAL
NO. 6 GLOBALLY & NO. 1 IN EUROPE
RANKED 1 IN NORDICS
Karolinska Institutet
henrik.falhammar@ki.se