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Focused on developing and commercializing novel therapies for rare endocrine disorders with significant unmet medical need

Virtual Research and Development Day

Tildacerfont for Adult and Pediatric Classic CAH

August 25, 2021

FORWARD-LOOKING STATEMENTS

This presentation contains forward-looking statements about Spruce Biosciences, Inc. ("we," "Spruce" or the "Company"). All statements other than statements of historical facts contained in this presentation are forward-looking statements, including statements about our strategy, our expectations regarding the timing and achievement of our product candidate's development activities and ongoing and planned clinical trials, and plans and expectations for future operations. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including, but not limited to: the effects of the evolving and ongoing COVID-19 pandemic; our limited operating history; net losses; our expectation that we will incur net losses for the foreseeable future, and that we may never be profitable; our need for additional funding and related risks for our business, product development programs and future commercialization activities; the timing and success of clinical trials we conduct; the ability to obtain and maintain regulatory approval of our product candidate; the ability to commercialize our product candidate; our ability to compete in the marketplace; risks regarding our license agreement; our ability to obtain and maintain intellectual property protection for our product candidate; and our ability to manage our growth. We operate in a very competitive and rapidly changing environment. New risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. In light of these risks, uncertainties and assumptions, the forward-looking events and circumstances discussed in this presentation may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements. Except as required by law, neither we nor any other person assumes responsibility for the accuracy and completeness of the forward-looking statements. We undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation to conform these statements to actual results or to changes in our expectations.

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This presentation discusses a product candidate that is under clinical study and which has not yet been approved for marketing by the U.S. Food and Drug Administration. No representation is made as to the safety or effectiveness of this product candidate for the use for which it is being studied.

AGENDA

- Classic CAH Overview
- Management of CAH
- About Tildacerfont
- Phase 2 Adult Classic CAH Development Program
- Late-stage Adult Classic CAH Development Program
- KOL Panel Discussion
- Pediatric Classic CAH Overview
- Phase 2 Pediatric Classic CAH Development Program

TODAY'S SPEAKERS

Rosh Dias, MD, MRCP
Chief Medical Officer
Spruce Biosciences

Paul Thornton, MD
Medical Director, Endocrine and Diabetes Program
Cook Children's Hospital

Rich Auchus, MD, PhD
Professor of Internal Medicine and Pharmacology
University of Michigan

Richard King
Chief Executive Officer
Spruce Biosciences

Chris Barnes, PhD
VP, Biometrics and Project Leadership
Spruce Biosciences

SPRUCE AT-A-GLANCE

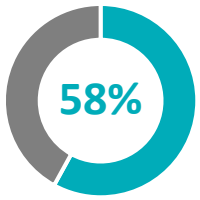
Tildacerfont poised to transform treatment paradigm in classic CAH	**Two late-stage clinical studies initiated; Data expected in 2022. NDA filing in adult classic CAH targeted for 2023**
Multiple expansion opportunities	**Initiation of Phase 2 programs in pediatric classic CAH and polycystic ovary syndrome (PCOS) in 2H 2021**
Significant commercial opportunity	**~$3B+ worldwide market opportunity in classic CAH**
Strong IP protection	**Comprehensive IP portfolio based on issued patents provides exclusivity to 2038 in U.S. combined with Orphan Drug Designation in U.S. and Europe**
Highly experienced leadership team	**Management has contributed to development and commercial launch of 40 products, including within endocrine and rare disease space**

PATIENT VIEWS ON MANAGEMENT OF ADULT CAH

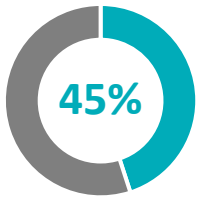
The vast majority of patients (>90%) report GCs are **effective in controlling CAH,** but…

Side-effects are common

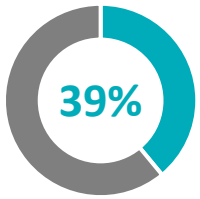
Weight gain



Fatigue

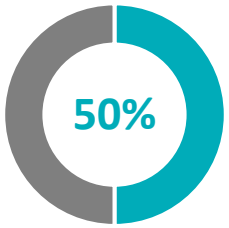


Mood swings

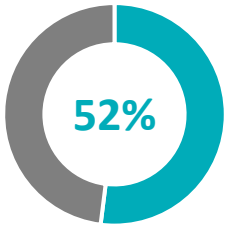


Depression

Patients do not feel sufficiently informed

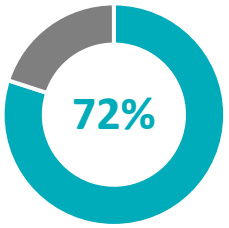


of patients either have not or are unsure whether they have discussed the **long-term risks of GCs** with their HCP



of patients felt they did not have access to enough information to make an **informed choice about GC treatment**

Patients are looking for change



of patients are willing to **change their current regimen** if they could lower their dose of steroid

"**The less steroids I have to take, the better**"

"I would like to do everything I can to keep my body healthy in the long term and **reducing steroids is a part of that**"

Based on survey of 59 patients.
CAH, congenital adrenal hyperplasia; GC, glucocorticoid; HCP, healthcare professional.
Spruce Biosciences. Data on file.

Classic CAH Overview

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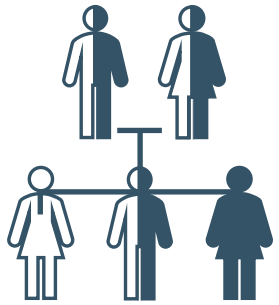
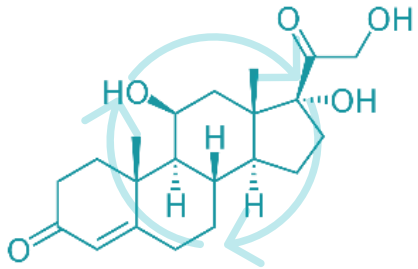
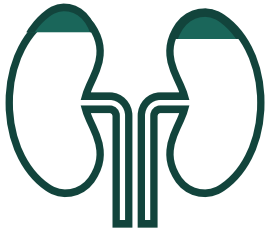
CAH IS A CHRONIC GENETIC DISEASE



Congenital adrenal hyperplasia encompasses a group of rare **autosomal recessive disorders** of the adrenal cortex



Genetic mutations cause deficiency in one or more key enzymes involved in adrenal steroidogenesis (**cortisol synthesis**)



Clinical features are linked to **cortisol deficiency** and **androgen excess**

CAH, congenital adrenal hyperplasia.
Claahsen-van der Grinten H, *et al. Endocr Rev.* 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print].

CYP21A2 MUTATION IS THE MOST COMMON CAUSE OF CAH

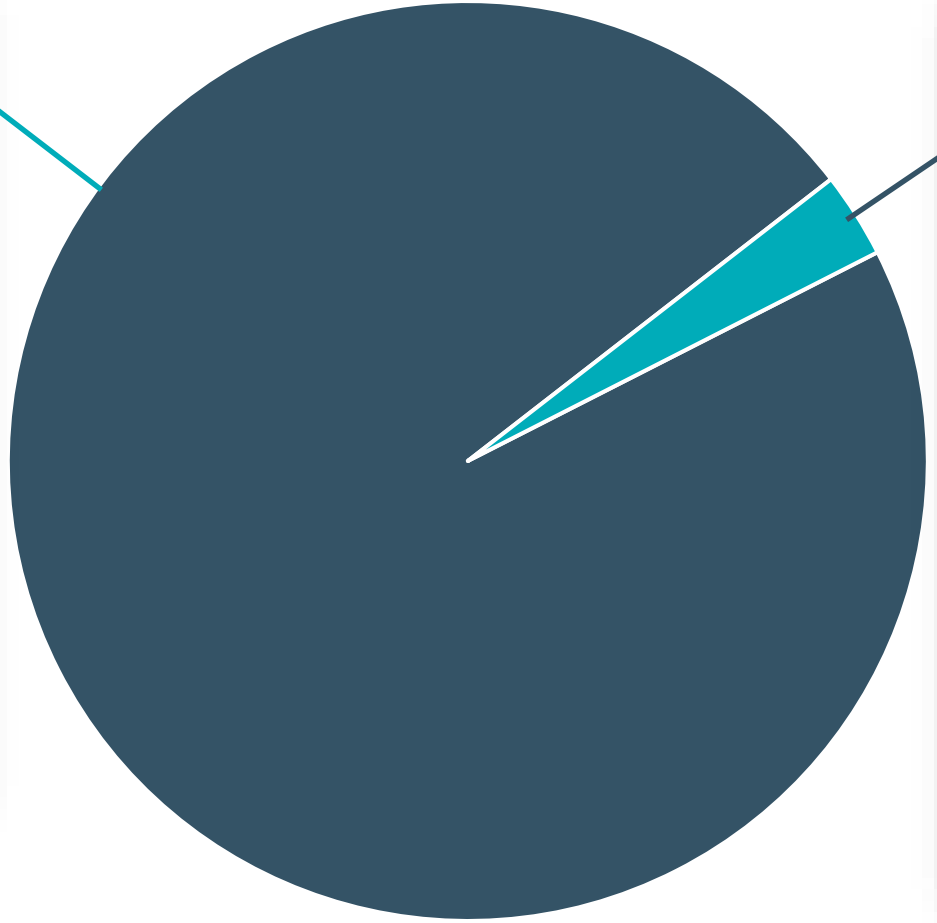
Mutations Involved in CAH

***CYP21A2* mutation**
>90%

CAUSES 21-OH DEFICIENT CAH

6p21.3

21-hydroxylase is an enzyme required for production of **aldosterone** & **cortisol**



Less common mutations
< 10%

Mutation	Enzyme/Protein Deficiency
CYP11B1	11β-hydroxylase
CYP17A1	17α-hydroxylase
POR	*CYP450 oxidoreductase*
HSD3B2	3β-hydroxysteroid dehydrogenase
StAR	Steroidogenic acute regulatory protein

21-OH, 21-hydroxylase; CAH, congenital adrenal hyperplasia; CYP, cytochrome.
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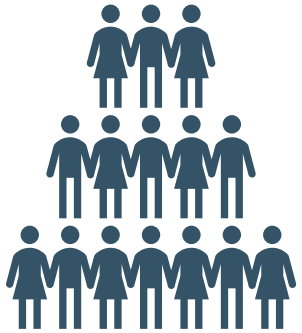
OF THE 21-OH DEFICIENT CAH SUBTYPES, CLASSIC IS MORE SEVERE

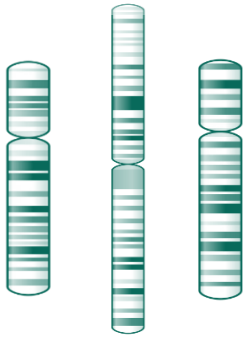


Classic 21-OHD CAH[1]

More severe, life-threatening
1:18,000-10,000 births
worldwide

Non-classic 21-OHD CAH[2]

Less severe, not life-threatening
1:500-1:100 births
worldwide



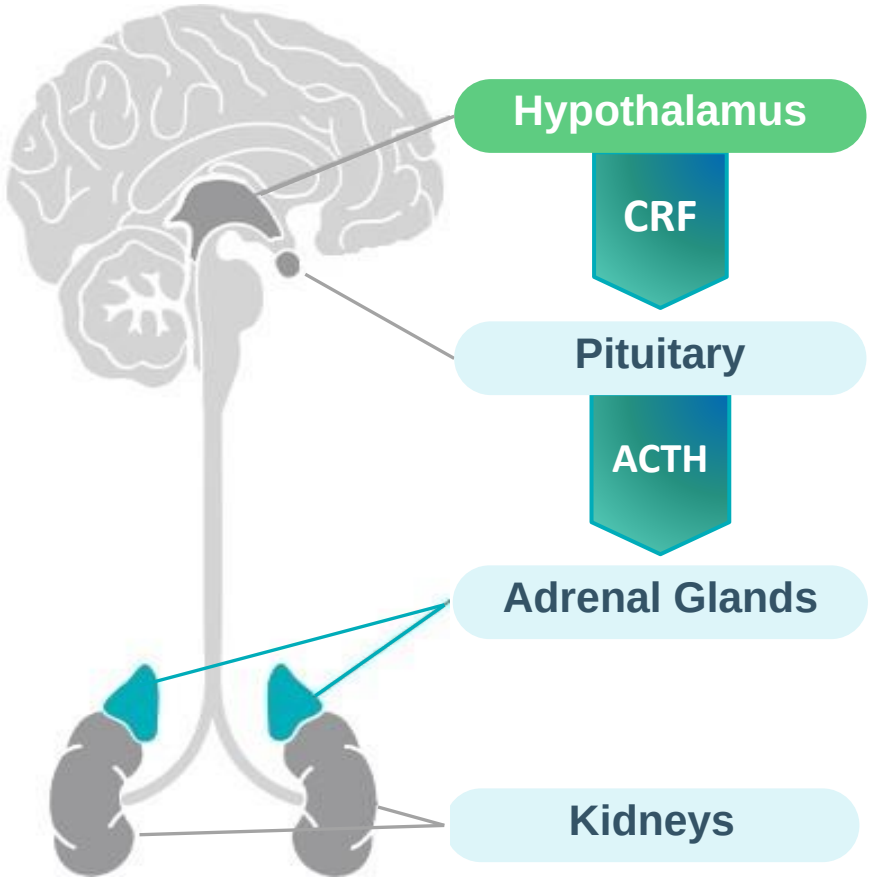
Other forms of CAH[1]

CYP11B1 1:100,000
CYP17A1, HSD3B2, POR, STAR very rare

21-OH, 21-hydroxylase; 21-OHD, 21-hydroxylase deficient; CAH, congenital adrenal hyperplasia; CYP, cytochrome.
1. White, P, et al. Endocr Rev. 2000;21:245-91.; 2. Livadas S, et al. Front Endocrinol. 2019;10:1-11; 3.

HPA AXIS FUNCTIONS AS A NEGATIVE FEEDBACK LOOP

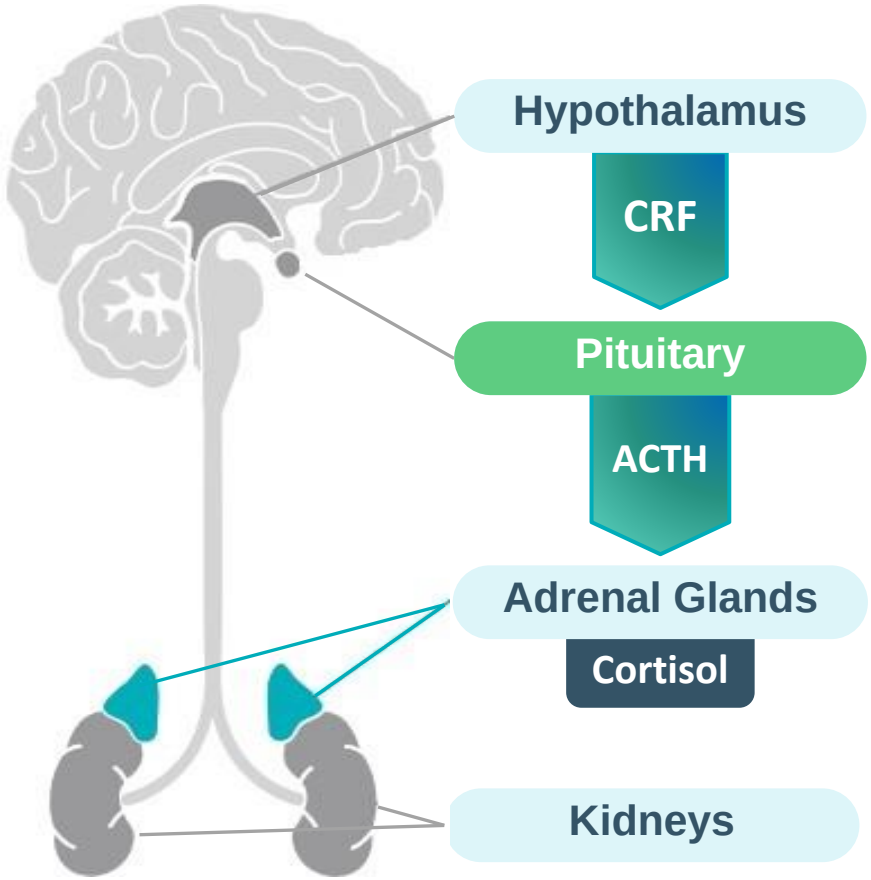
CRF from the hypothalamus stimulates the pituitary to produce ACTH

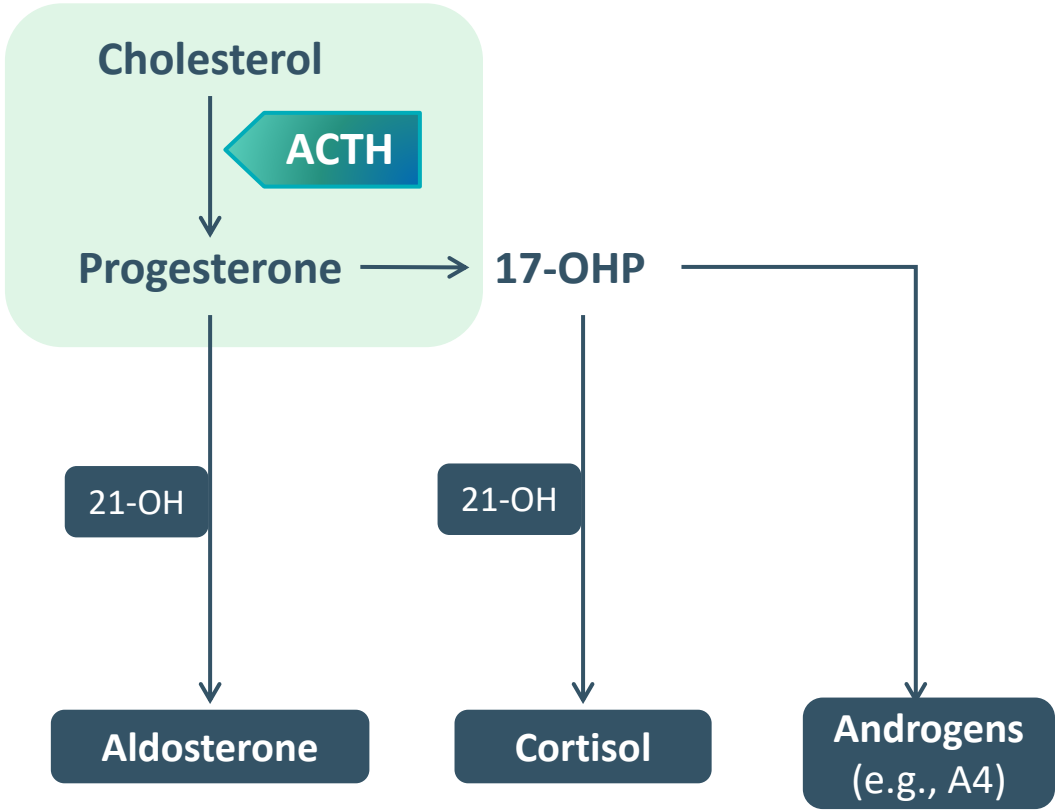


ACTH, adrenocorticotropic hormone; CRF, corticotropin releasing factor; HPA, hypothalamic-pituitary-adrenal.
Engels M, *et al. Endocr Rev.* 2019;40:973-87.

HPA AXIS FUNCTIONS AS A NEGATIVE FEEDBACK LOOP

ACTH from the pituitary stimulates steroid hormone biosynthesis within the adrenal glands





17-OHP, 17-hydroxyprogesterone; 21-OH, 21-hydroxylase; A4, androstenedione; ACTH, adrenocorticotropic hormone; CRF, corticotropin releasing factor; HPA, hypothalamic-pituitary-adrenal.

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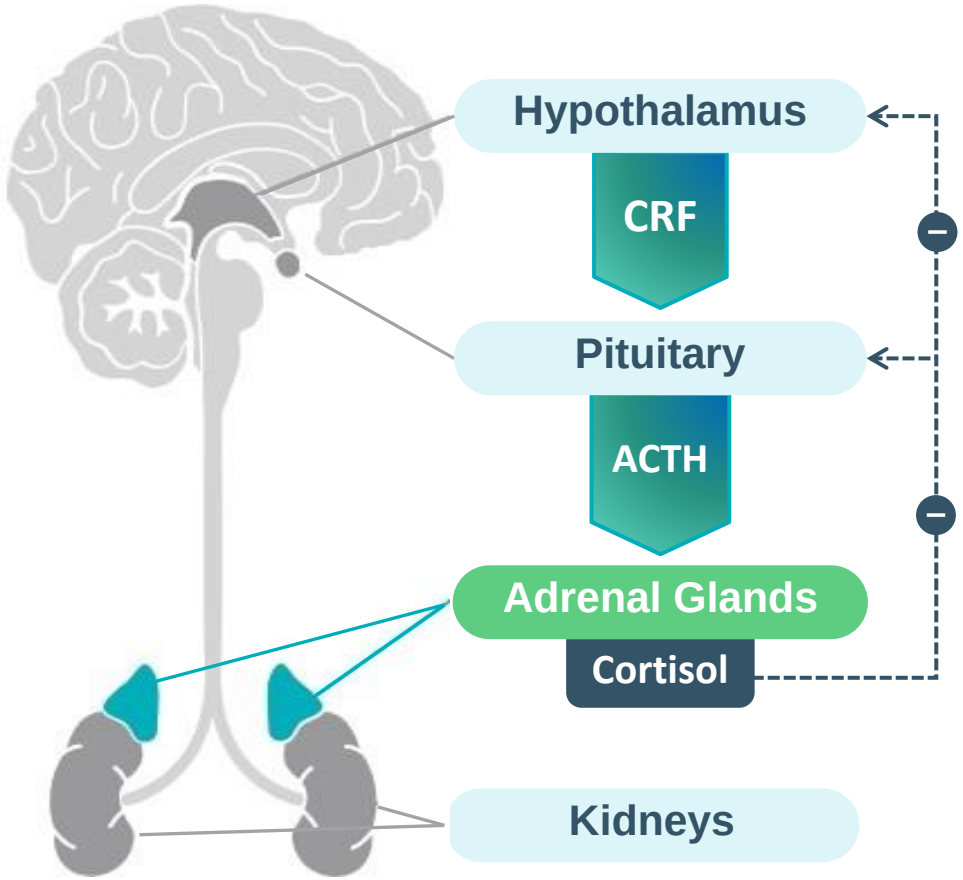
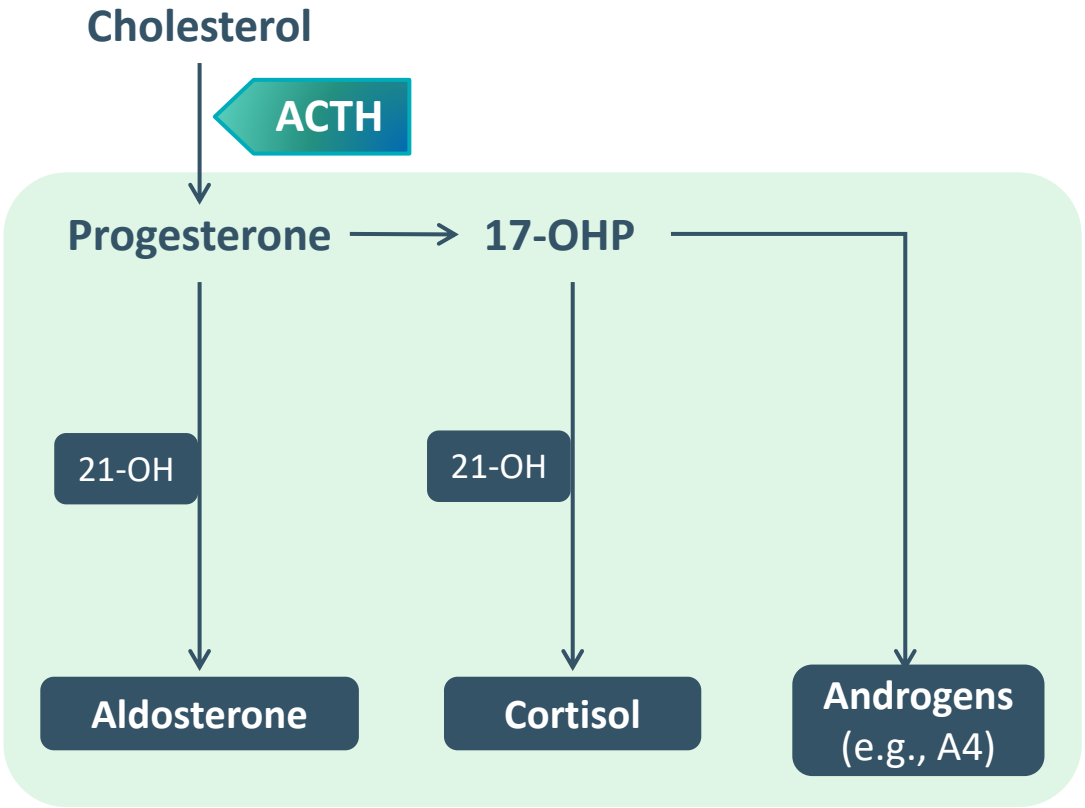
HPA AXIS FUNCTIONS AS A NEGATIVE FEEDBACK LOOP

The adrenal glands produce aldosterone, cortisol, and androgens; cortisol then supplies feedback to the hypothalamus and pituitary to slow ACTH production





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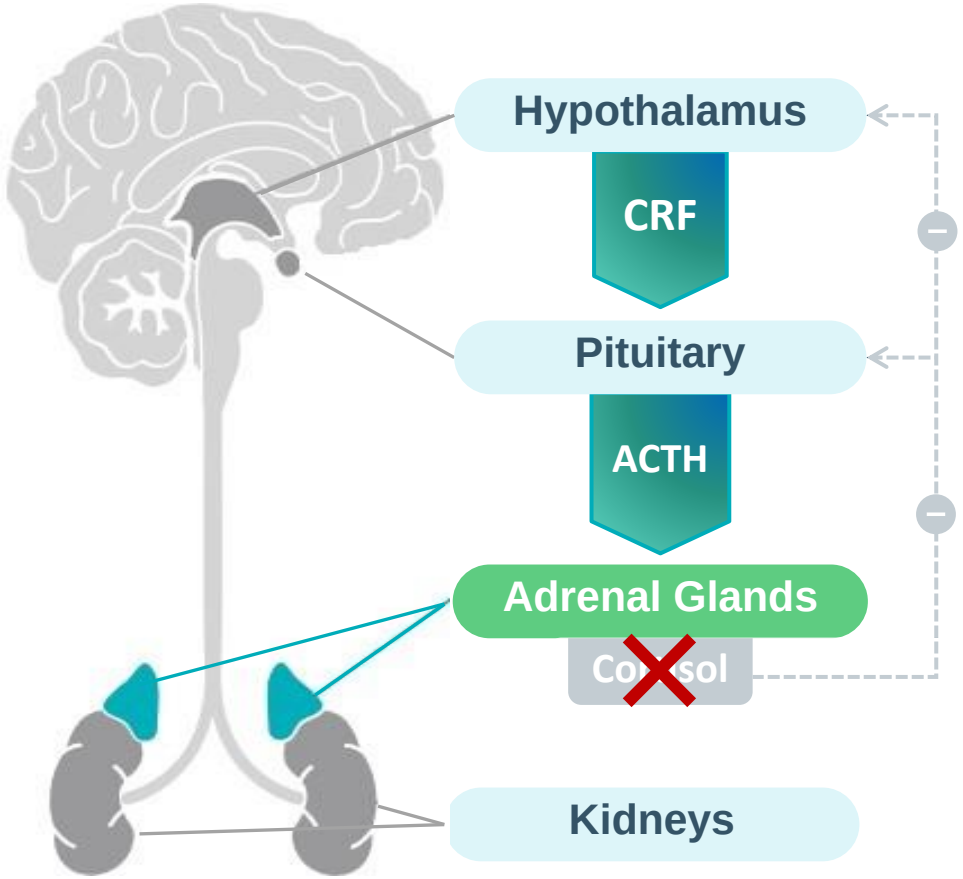
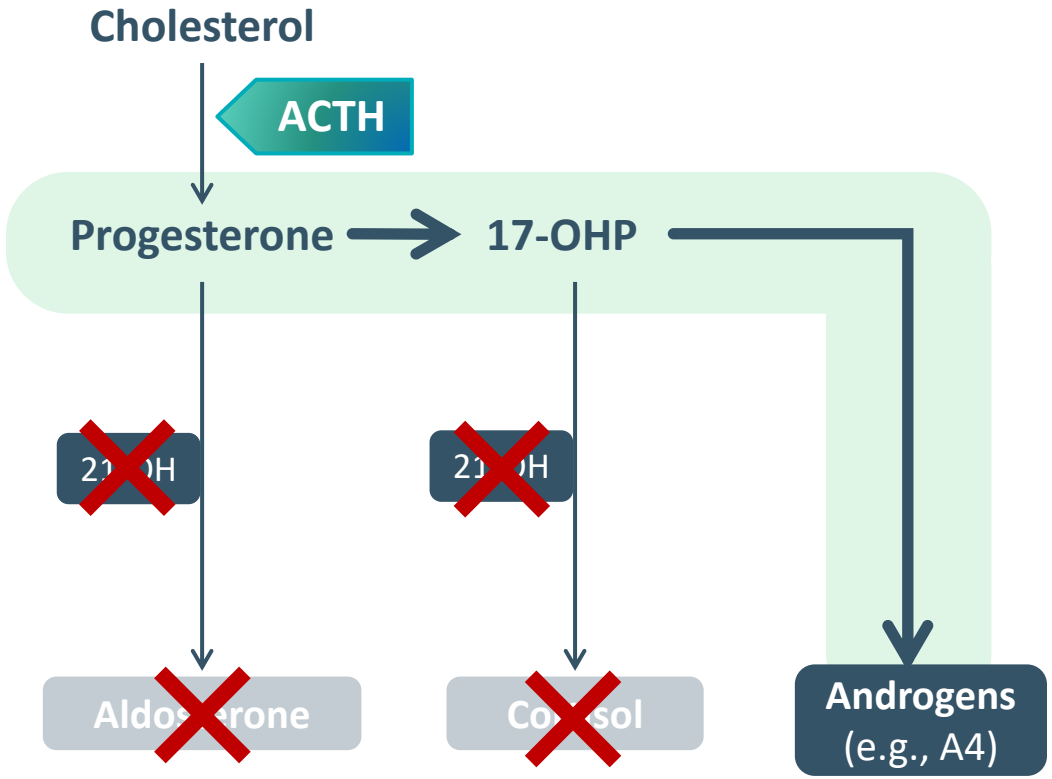
21-OHD CAH: LOSS OF NEGATIVE FEEDBACK

- Deficiency in 21-OH prevents cortisol production, & reduces or prevents aldosterone production
- Lack of cortisol upregulates CRF & ACTH, which leads to overstimulation & hyperplasia of the adrenal glands
- 17-OHP is routed to the androgen pathway, resulting in excess androgens





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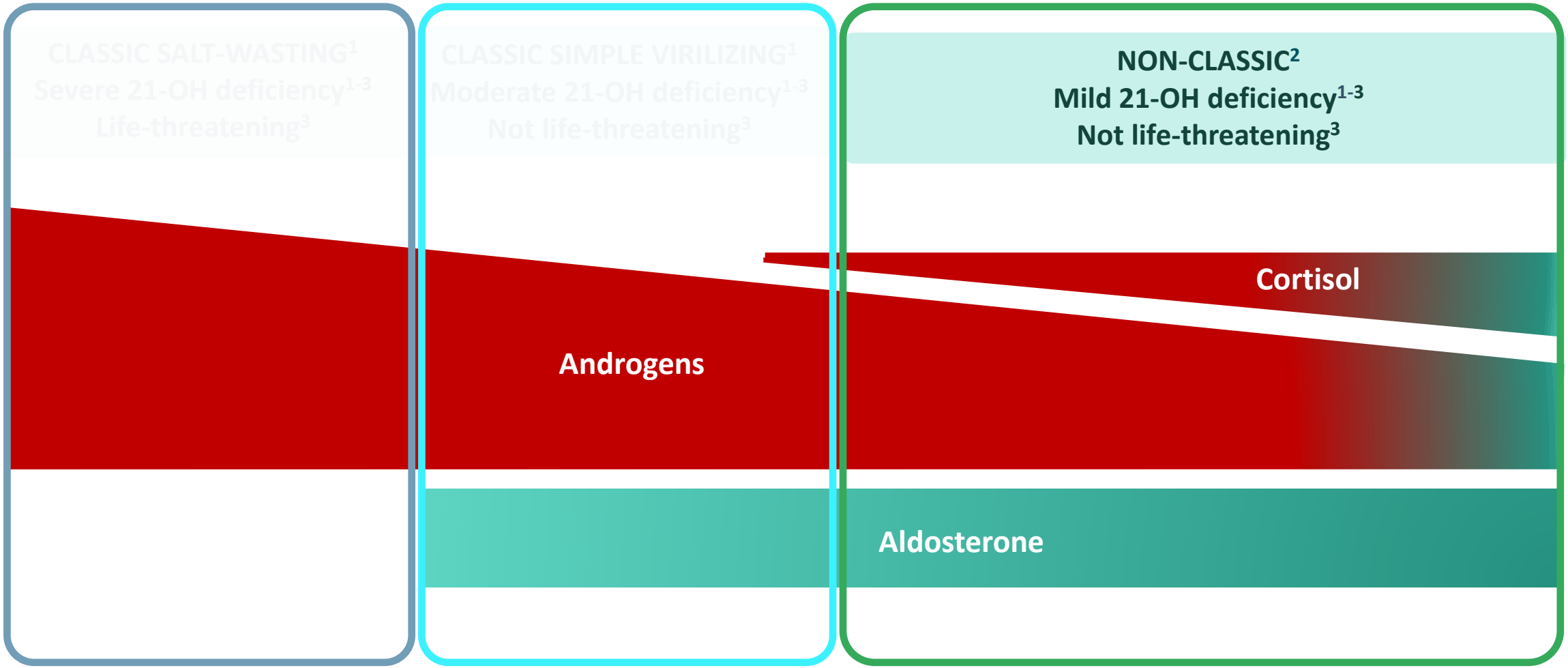
21-OHD CAH IS CLASSIFIED BY DEGREE OF HORMONE IMBALANCE[1-3]



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1. Claahsen-van der Grinten H, *et al. Endocr Rev.* 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print]; 2. Nordenstrom A, *et al. Eur J Endocrinol*. 2019;180:R127-45; 3. What are the symptoms of CAH? NIH NICHD website. Updated May 17, 2021. Accessed July 3, 2021. https://www.nichd.nih.gov/health/topics/cah/conditioninfo/symptoms.

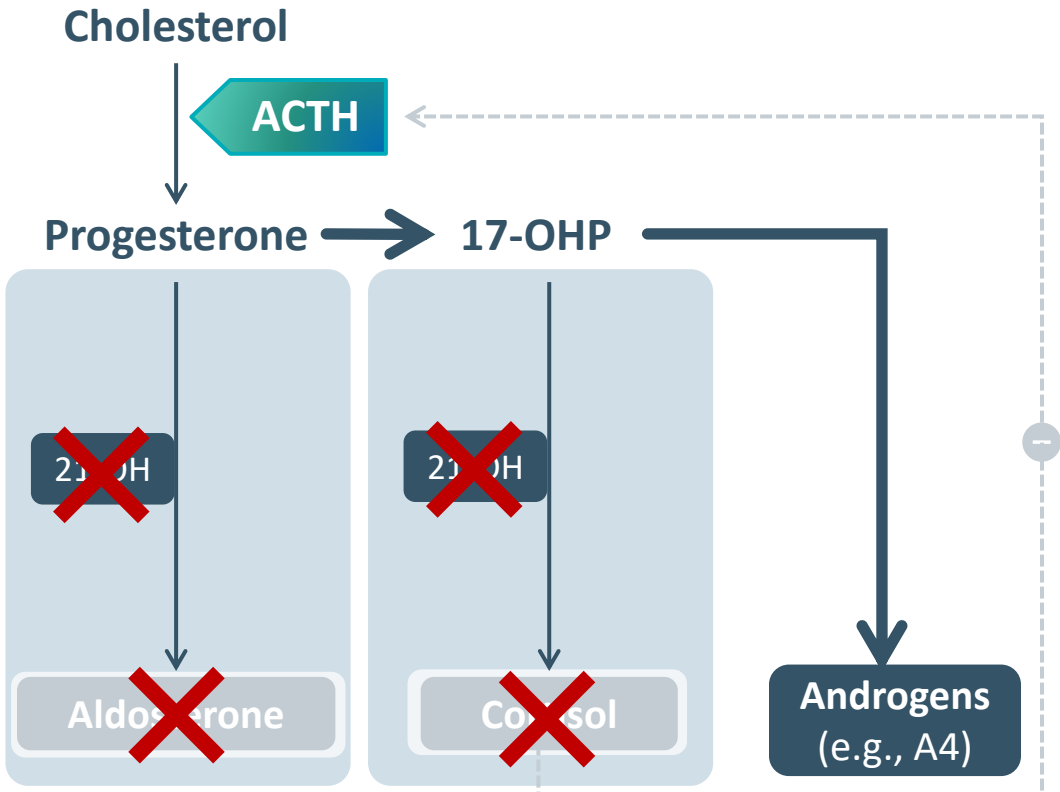
HORMONE IMBALANCES ARE CHARACTERISTIC OF 21-OHD CAH

POSSIBLE ALDOSTERONE DEFICIENCY[1]

- Causes salt-wasting CAH, with acute adrenal crisis
- Hypotension, hyponatremia, hyperkalemia, acidosis

CORTISOL DEFICIENCY[1]

- Present in both salt-wasting & simple virilizing CAH
- Impaired circadian rhythm & stress response
- Excess ACTH production in response to low cortisol



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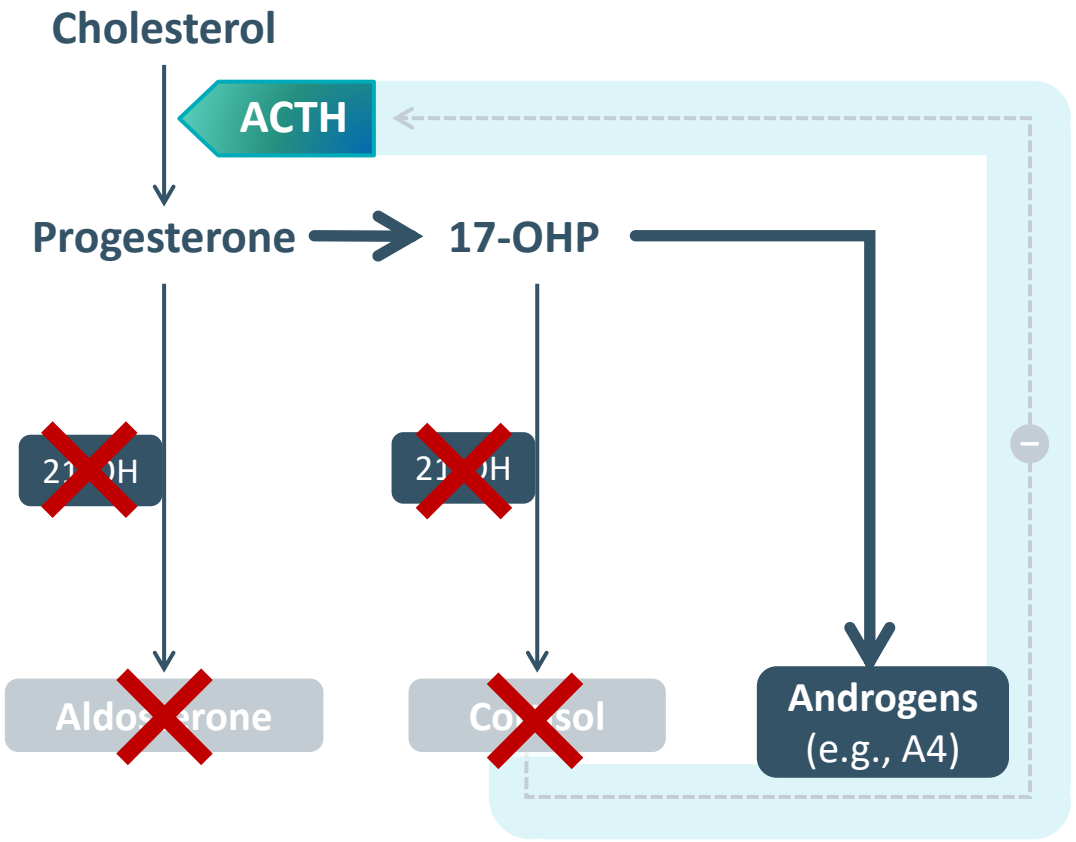
OVERPRODUCTION OF ACTH[2]

- Present in both salt-wasting & simple virilizing CAH
- Causes adrenal hyperplasia & excess androgen production
- Leads to TARTs in males



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OVERPRODUCTION OF ACTH[2]

- Present in both salt-wasting & simple virilizing CAH
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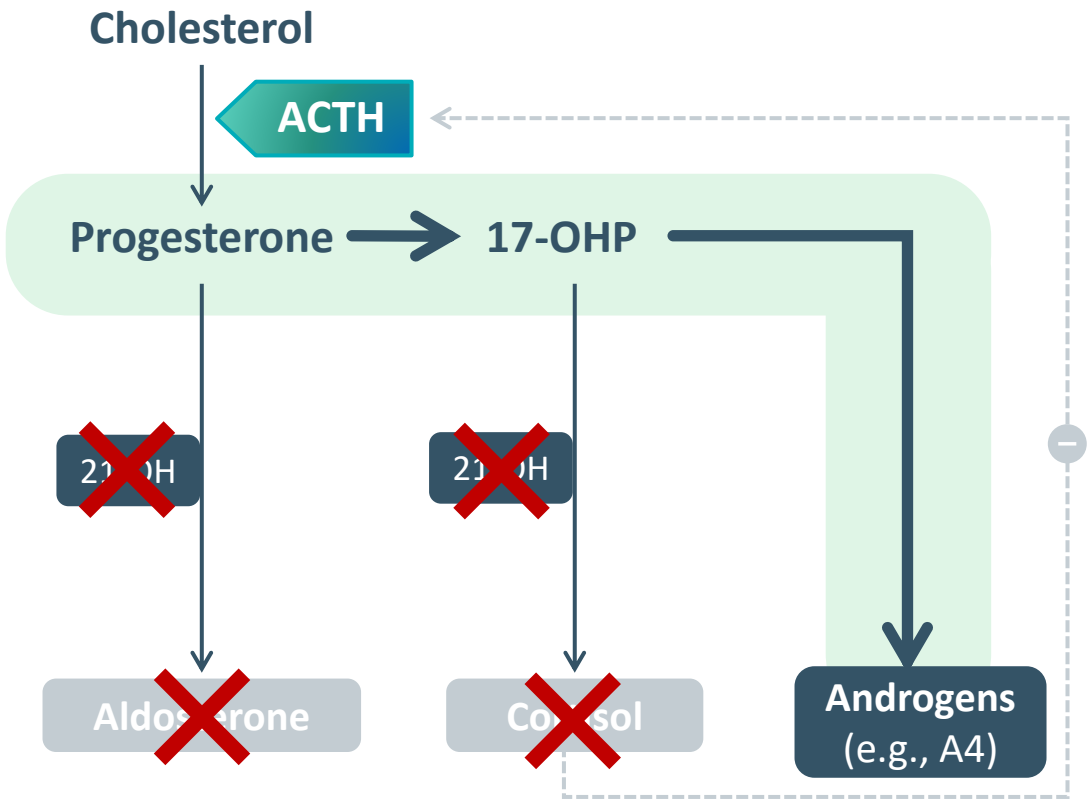
OVERPRODUCTION OF ANDROGENS[1]

- Cause of virilizing features of both SW & SV CAH
- Virilization of external genitalia in females
- Precocious puberty, irregular menses, impaired fertility
- Acne, hirsutism
- Early growth spurt, premature epiphyseal closure



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DIAGNOSIS OF 21-OHD CAH

NEWBORN SCREENING for classic CAH[1]

- Routine in over 50 countries and all 50 states, to prevent neonatal adrenal crisis
- Detects elevated 17-OHP in the blood
- Positive result requires confirmatory testing with serum 17-OHP and cortisol levels

LABORATORY TESTING for later-onset CAH[2]

- Non-classic CAH is often not detected on newborn screening
- Morning 17-OHP blood level with or without ACTH stimulation test generally diagnostic
- Genetic testing for *CYP21A2* mutations if hormone levels are non-diagnostic

PRENATAL DIAGNOSIS for carriers[1]

- Indicated when prior children have CAH
- Fetal hormone levels and DNA can be analyzed from amniotic fluid
- Fetal DNA analysis is also performed via chorionic villus sampling

17-OHP, 17-hydroxyprogesterone; 21-OHD, 21-hydroxylase deficient; ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia.

1. Claahsen-van der Grinten H, *et al. Endocr Rev.* 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print]; 2. Livadas, S, *et al. Front Endocrinol*. 2019;10:1-11.

Management of CAH

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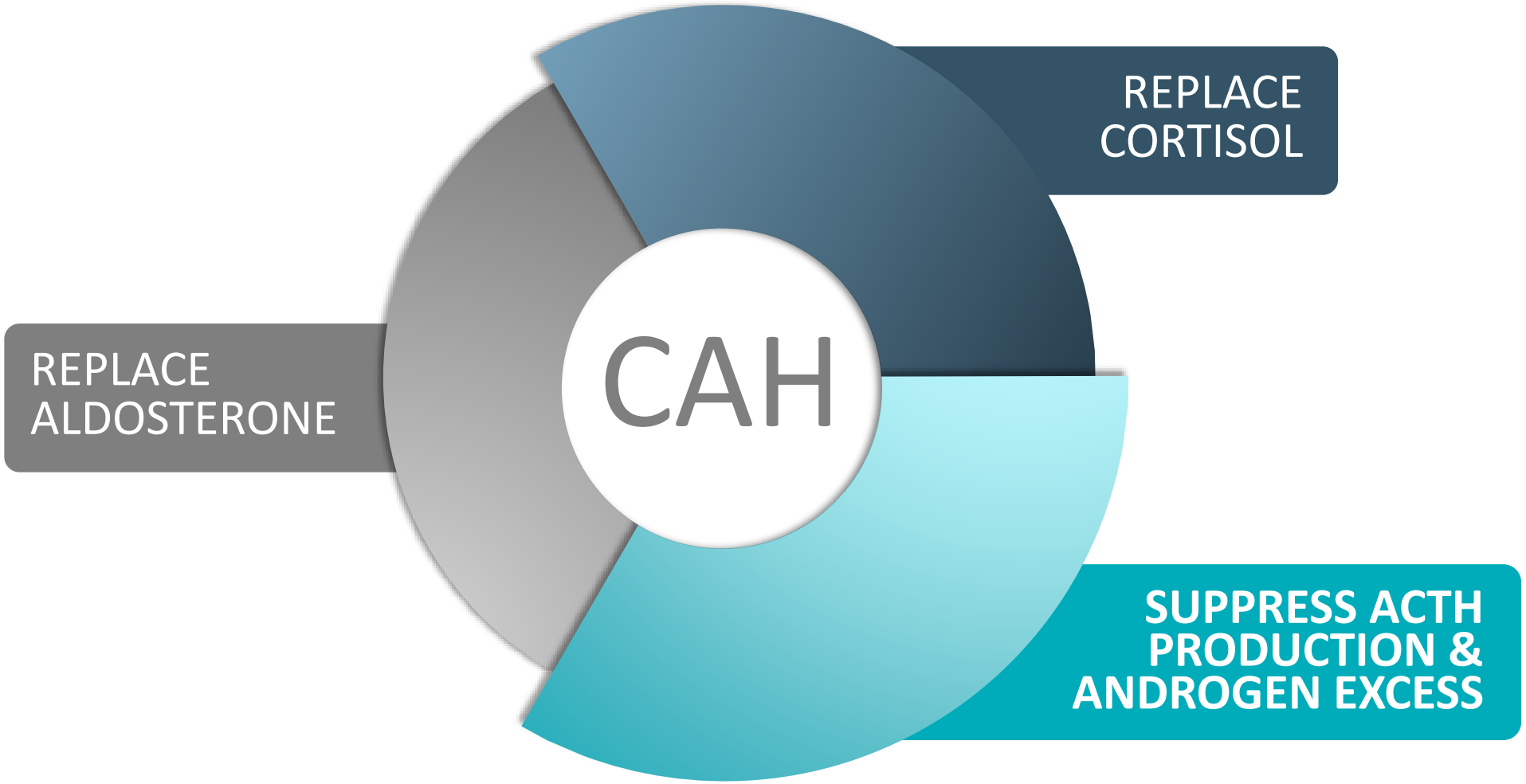
MANAGEMENT OF CLASSIC CAH IS A THREE-PRONGED APPROACH



ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia.

ALDOSTERONE IS REPLACED TO MAINTAIN FLUID & ELECTROLYTE BALANCE

Mineralocorticoids are required in infancy, but the need lessens through adolescence and adulthood[1,2]

GOALS OF THERAPY[1]

- **Maintain** acid-base balance
- **Normalize** blood pressure
- **Prevent** salt-wasting crisis
- **Maintain** euvolemia
- **Balance** electrolytes

TREATMENT GUIDELINES[2]

MINERALOCORTICOIDS
Fludrocortisone
0.05-0.2 mg/d

SODIUM CHLORIDE
1-2 g/day in infancy

CAH, congenital adrenal hyperplasia; d, day; g, gram; mg, milligram.

1. Claahsen-van der Grinten H, *et al. Endocr Rev.* 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print]; 2. Speiser P, *et al. J Clin Endocrinol Metab.* 2018;103:4043-88.

LOW DOSE HYDROCORTISONE REPLACES PHYSIOLOGIC CORTISOL

GOALS OF THERAPY[1]

- **Prevent adrenal crisis**
- **Restore circadian rhythm**
- **Simulate stress response**

TREATMENT GUIDELINES[2]

ADRENAL CRISIS
HC 200 mg/d

CIRCADIAN RHYTHM
Adult: HC 15-25 mg/d
Child: 8 mg/m^2/d

STRESS RESPONSE
HC at 2-3x maintenance dose

- Choice of GC is not limited to HC; other GCs, including prednisone and dexamethasone, may be prescribed.

CAH, congenital adrenal hyperplasia; d, day; HC, hydrocortisone; mg, milligram.

1. Claahsen-van der Grinten H, et al. Endocr Rev. 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print]; 2. Bornstein S, et al. J Clin Endocrinol Metab. 2016;101:364-89.

HIGHER DOSES OF GC ARE REQUIRED TO SUPRESS ACTH & ANDROGENS

GOALS OF THERAPY[1]

- **Slow** skeletal maturation
- **Prevent** virilization
- **Normalize** pubertal progression
- **Preserve** reproductive function
- **Prevent** TARTs

TREATMENT GUIDELINES[2]

TARTs[1]
Supraphysiologic dexamethasone

ADULT[2]
HC 15-25 mg/d or equivalent long-acting GC

GROWING CHILD/ADOLESCENT[2]
HC 10-15 mg/m^2/d - higher doses may be needed during puberty

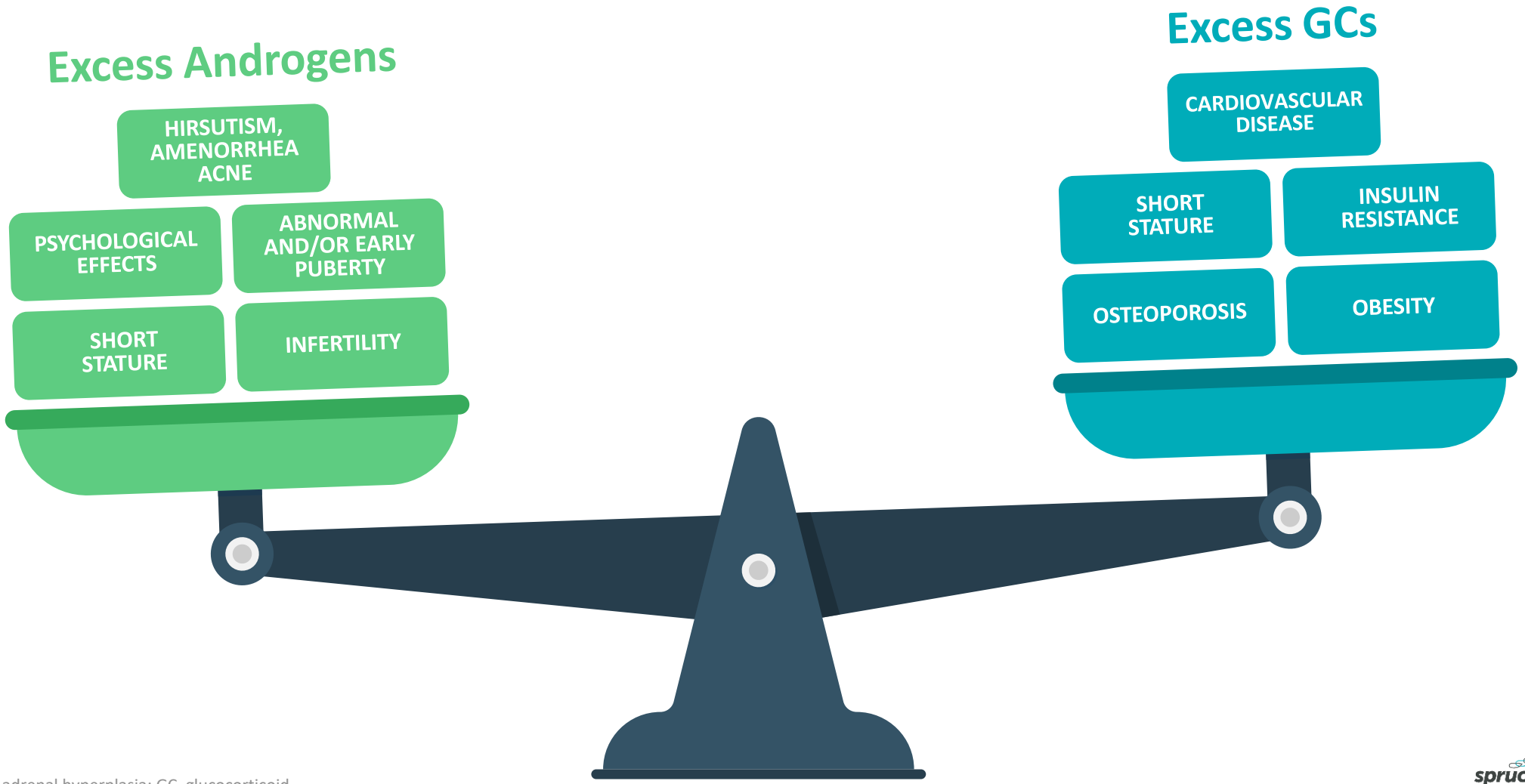
ADJUVANT THERAPY[2]
AR antagonists
OCPs

ACTH, adrenocorticotropic hormone; AR, androgen receptor; GC, glucocorticoid; HC, hydrocortisone; mg, milligram; OCP, oral contraceptive pill; TART, testicular adrenal rest tumor.

1. Claahsen-van der Grinten H, et al. Endocr Rev. 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print]; 2. Speiser P, et al. J Clin Endocrinol Metab. 2018;103:4043-88.

THIS PRESENTS A DIFFICULT CHOICE IN TREATING CLASSIC CAH

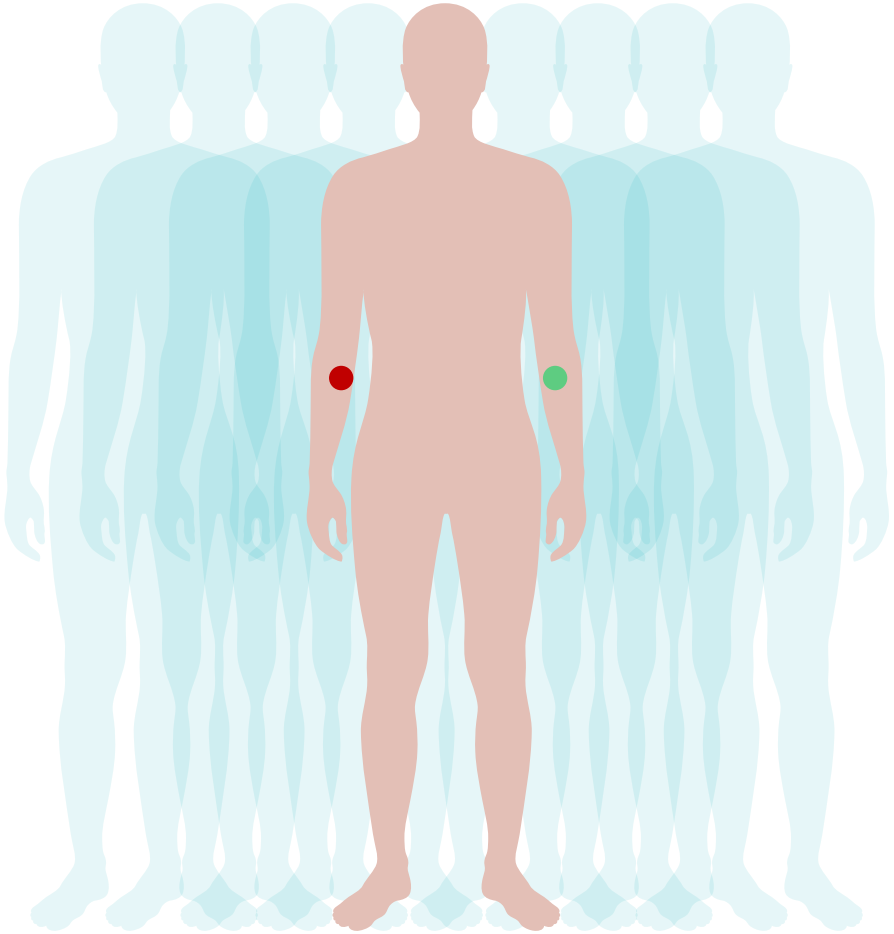
Patients and physicians must **choose between the detrimental effects** of chronically **high adrenal androgen levels** or the **harmful consequences of excessive, life-long GC use**



CAH, congenital adrenal hyperplasia; GC, glucocorticoid.

UNMET MEDICAL NEEDS ACCORDING TO DISEASE STATUS

The management of classic CAH requires a balance between
adrenal hormone suppression and **GC replacement**[1,2]



CAH, congenital adrenal hyperplasia; GC, glucocorticoid.

1. Claahsen-van der Grinten H, *et al. Endocr Rev.* 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print]; 2. Speiser P, *et al. J Clin Endocrinol Metab.* 2018;103:4043-88.

UNMET MEDICAL NEEDS ACCORDING TO DISEASE STATUS

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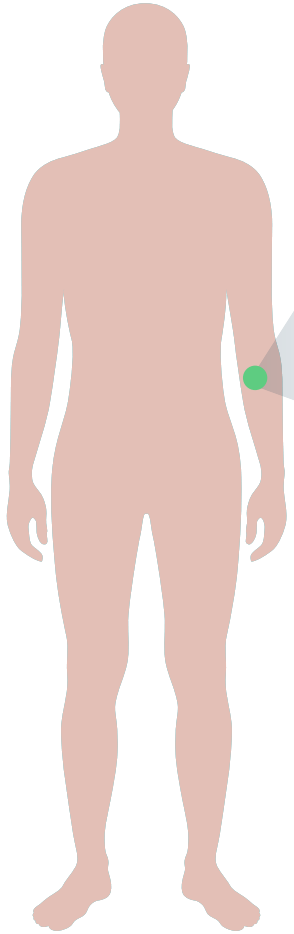


GOOD DISEASE CONTROL[1]

- Normal or near normal adrenal androgens
- Unmet need to **reduce GC dose** and improve related clinical outcomes

CAH, congenital adrenal hyperplasia; GC, glucocorticoid.

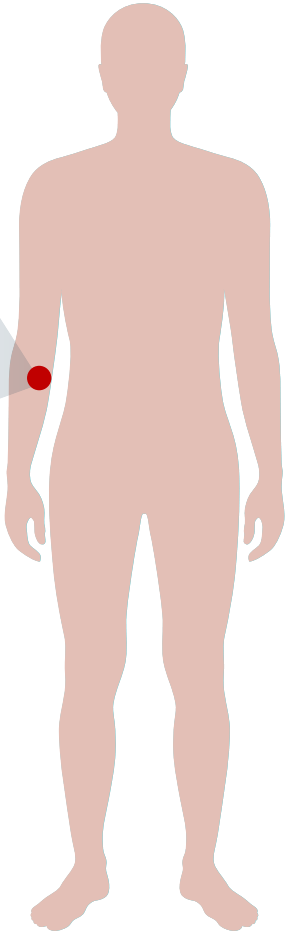
1. Claahsen-van der Grinten H, *et al. Endocr Rev.* 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print]; 2. Speiser P, *et al. J Clin Endocrinol Metab.* 2018;103:4043-88.

UNMET MEDICAL NEEDS ACCORDING TO DISEASE STATUS

The management of classic CAH requires a balance between **adrenal hormone suppression** and **GC replacement**[1,2]

POOR DISEASE CONTROL[1]

- Elevated adrenal androgens
- Unmet need to **reduce adrenal androgens** and improve related clinical outcomes



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UNMET MEDICAL NEEDS IN THE CURRENT MANAGEMENT OF CLASSIC CAH

Glucocorticoids
– the mainstay of treatment since the 1950s[1] –
contribute to the burden of disease

Novel therapies are needed
to **reduce** the need for **supraphysiologic GCs**

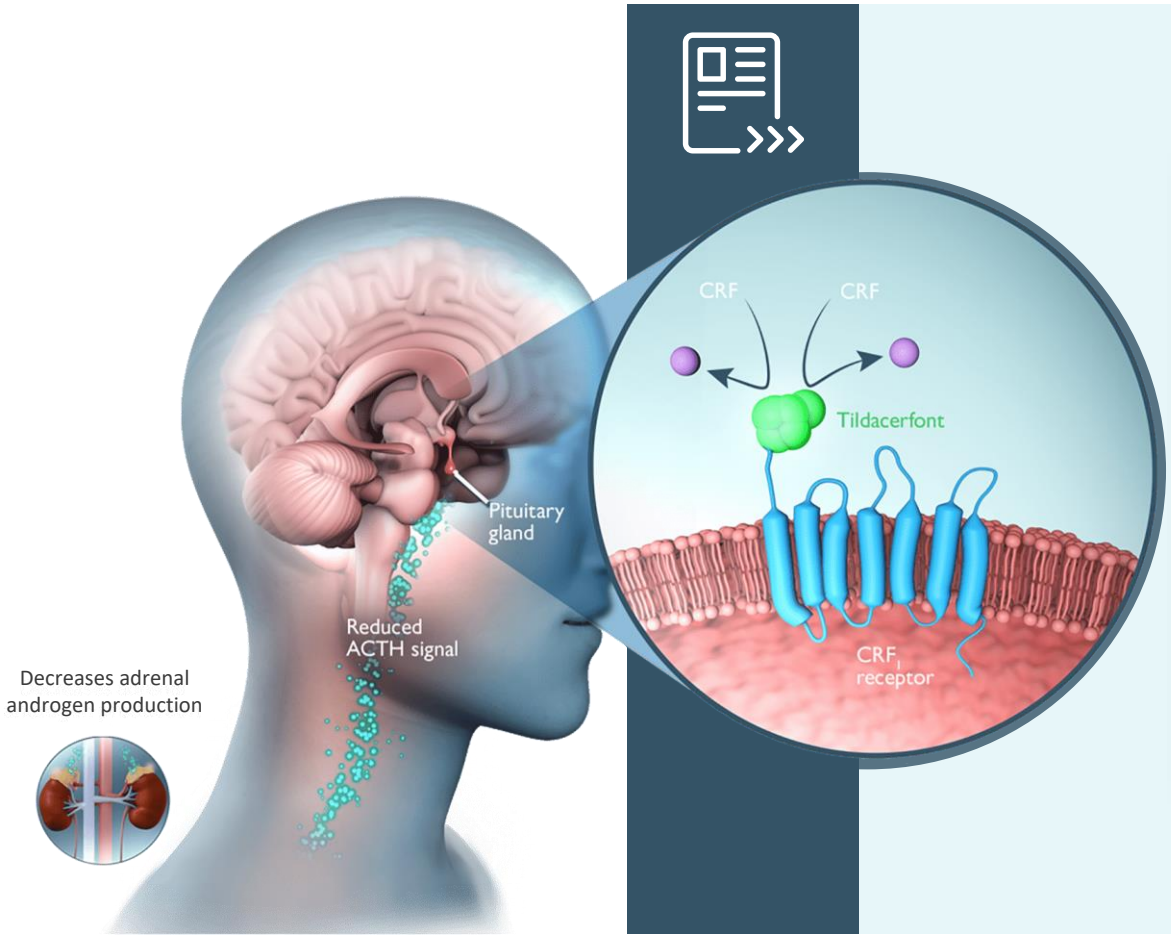
CAH, congenital adrenal hyperplasia; GC, glucocorticoid.

1. Hayek A, *et al. Metabolism*. 1971;20:897-901.

Tildacerfont

spruce BIOSCIENCES

TILDACERFONT IS A NOVEL CRF_1 RECEPTOR ANTAGONIST



Tildacerfont is an oral, second generation CRF_1 receptor antagonist[1]

Tildacerfont binds to CRF_1 receptors in the pituitary gland, blocking receptor stimulation by the hypothalamus[1]

ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor; CRF_1, corticotropin-releasing factor 1.

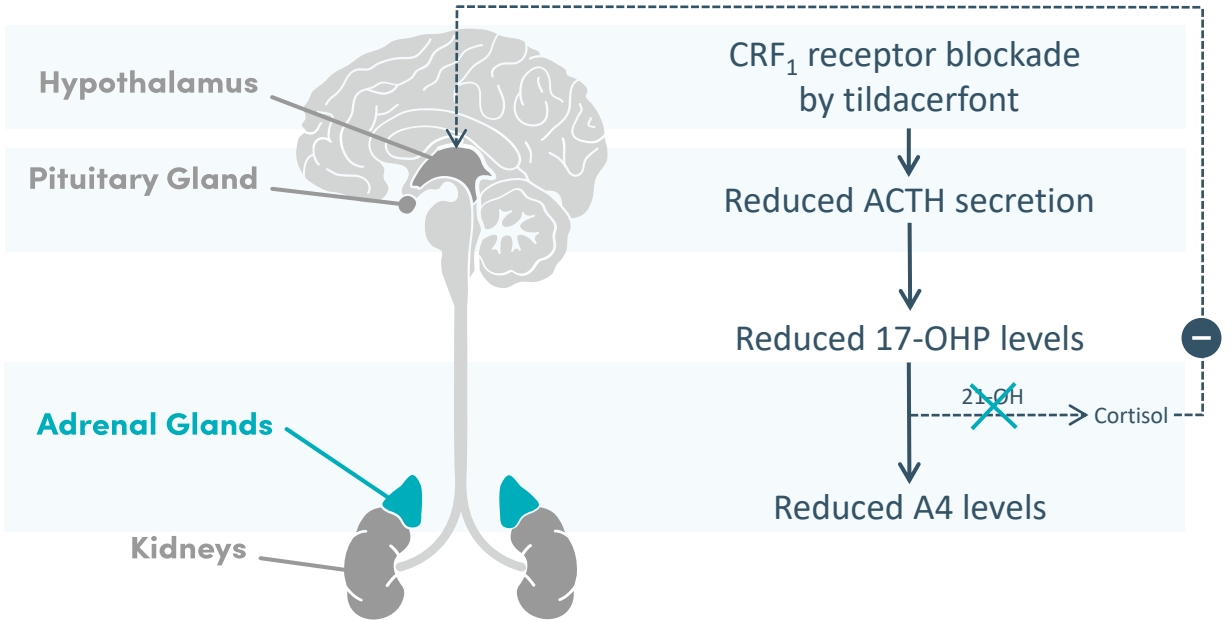
1. Sarafoglou K, *et al. J Clin Endocrinol Metab.* 2021:dgab438. DOI: https://doi.org/10.1210/clinem/dgab438 [Epub ahead of print].

TILDACERFONT IS DESIGNED TO REDUCE ADRENAL ANDROGEN PRODUCTION

Tildacerfont inhibits excessive production of **ACTH**, **17-OHP** and **adrenal androgens**[1]

By reducing excess adrenal androgens (e.g., A4), tildacerfont may improve CAH symptoms and allow **GC reduction** to near physiologic levels[1]

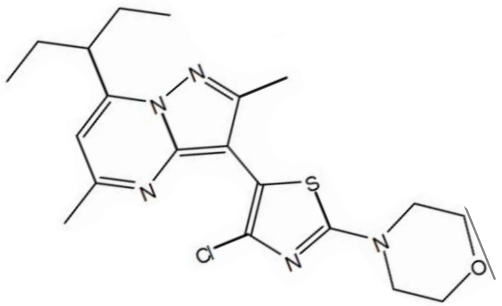
Effect of tildacerfont on HPA-axis function in CAH[1,2]



17-OHP, 17-hydroxyprogesterone; 21-OH, 21-hydroxylase, A4, androstenedione; ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; GC, glucocorticoid; CRF_1, corticotropin-releasing factor 1; HPA, hypothalamic-pituitary-adrenal.

1. Sarafoglou K, *et al. J Clin Endocrinol Metab.* 2021:dgab438. DOI: https://doi.org/10.1210/clinem/dgab438 [Epub ahead of print]; 2. Sarafoglou K, *et al. J Endocr Soc.* 2019; 3(Supplement_1):SUN-LB064.

TILDACERFONT IS A POTENT, HIGHLY SELECTIVE CRF_1 RECEPTOR ANTAGONIST



	Tildacerfont[1,2]
Molecular formula	$C_{20}H_{26}ClN_5OS$
Molecular weight	419.98 g/mol
pKa*	0.85
LogP	4.21
Hygroscopicity (by DVS)	0.009% weight change from 5% to 95% RH
Topological PSA	83.8 Å^2
PO availability	35.8%

Tildacerfont selectivity[2]

In cell-based radioligand binding assays, tildacerfont displayed a **higher binding affinity** for the $hCRF_1$ vs. $hCRF_2$ receptor

	K_i (nM)	
Compound	**$hCRF_1$ receptor**	**$hCRF_2$ receptor**
Tildacerfont	6.16	>1000

Data are expressed as means (n=4).

Tildacerfont did not inhibit any clinically important target by >50% when tested at a concentration ~33,000-fold higher than the K_i for binding to the $hCRF_1$ receptor

Receptor binding potency[2]

In HEK293-cell membrane-based radioligand binding assays, tildacerfont exhibited **strong potency** for $hCRF_1$ receptors (K_i: 0.29 ± 0.04 nM)

Pharmacodynamic activity[2]

Tildacerfont inhibited CRF-stimulated cAMP accumulation in $hCRF_1$ receptor-expressing cells (K_b: 5.19 nM), demonstrating that tildacerfont functions as a potent $hCRF_1$ receptor antagonist

*As measured by UV.

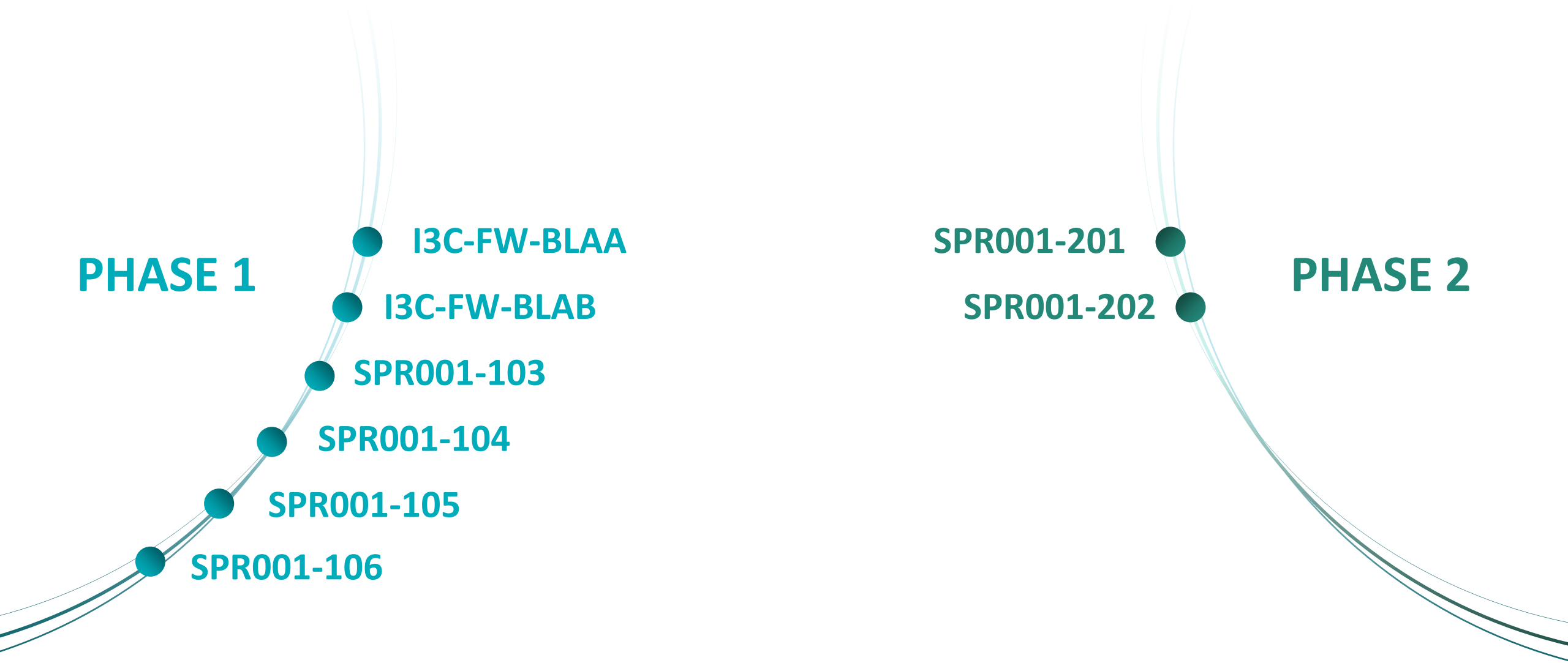
cAMP, cyclic adenosine monophosphate; CRF, corticotropin-releasing factor; DVS, dynamic vapor sorption; (h)CRF_1, (human) corticotropin-releasing factor 1; $hCRF_2$, human corticotropin-releasing factor 2; HEK, human embryonic kidney; K_b, binding constant; K_i, inhibitory constant; nM, nanomolar; pKa, acid dissociation constant; PO, oral; PSA, polar surface area; RH, relative humidity; UV, ultraviolet.

1. National Center for Biotechnology Information. PubChem Compound Summary or CID 134694266. https://pubchem.ncbi.nlm.nih.gov/compound/134694266. Accessed July 15, 2021;
2. Spruce Biosciences, Inc. Investigator's Brochure for tildacerfont (SPR001), Edition 5.0, Dated 26 March 2021.

Phase 2 Adult Classic CAH Clinical Development Program

spruce BIOSCIENCES

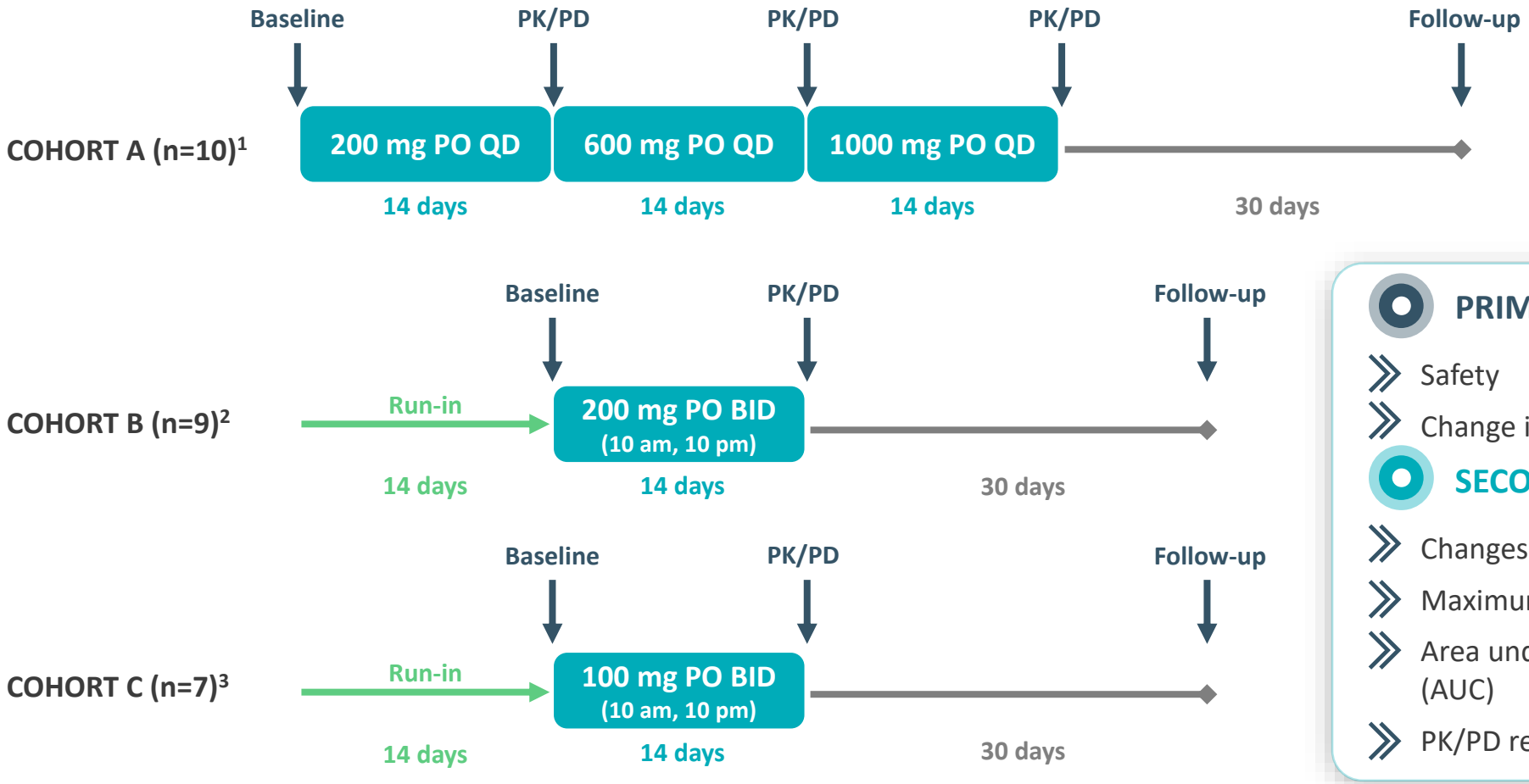
EIGHT CLINICAL STUDIES OF TILDACERFONT HAVE BEEN COMPLETED



Spruce Biosciences, Inc. Investigator's brochure for Tildacerfont (SPR001), Version 5.0, Dated 26 March 2021.

SPR001-201: CLINICAL PROOF OF CONCEPT (PHASE 2 STUDY)[1,2]

Phase 2, multicenter, open-label, multiple-dose, dose-escalation study[1]



PRIMARY ENDPOINTS[2]

- Safety
- Change in 17-OHP

SECONDARY ENDPOINTS[2]

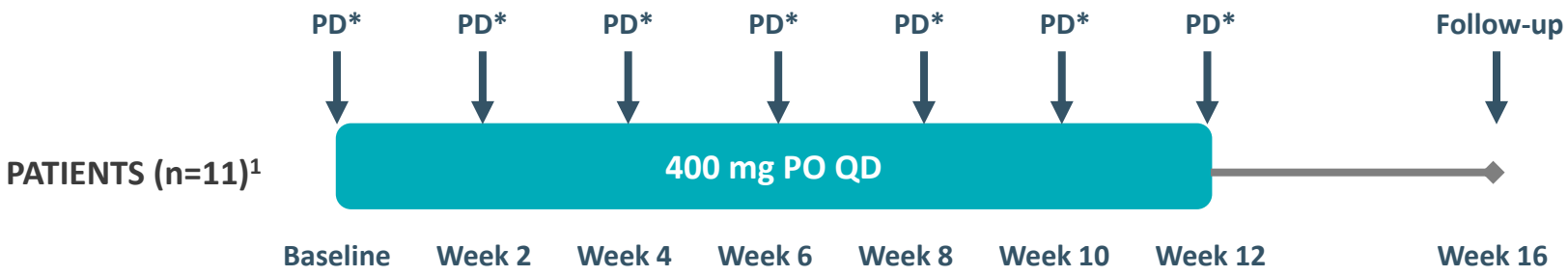
- Changes in PD markers
- Maximum plasma concentration (C_{max})
- Area under the concentration-time curve (AUC)
- PK/PD relationships

17-OHP, 17-hydroxyprogesterone; BID, twice daily; PD, pharmacodynamics; PK, pharmacokinetics; PO, oral administration; QD, once daily.

1. Sarafoglou K, et al. *J Clin Endocrinol Metab.* 2021:dgab438. DOI: https://doi.org/10.1210/clinem/dgab438 [Epub ahead of print];
2. Clinical Trial NCT03257462. Available at: https://clinicaltrials.gov/ct2/show/NCT03257462 (last accessed July 2021).

SPR001-202: TWELVE-WEEK, OPEN-LABEL PHASE 2 STUDY[1,2]

Phase 2, multicenter, open-label study[1]



PRIMARY ENDPOINT[2]

- Safety and tolerability

SECONDARY ENDPOINTS[2]

- Change from baseline in 17-OHP, ACTH, and A4

*Trial visits were conducted in the morning, at approximately 8 AM, prior to consumption of a morning GC dose at baseline (Day 1) and Weeks 2, 4, 6, 8, 10, and 12, and 30 days after the last dose.
17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; PD, pharmacodynamic profiles; PO, oral administration; QD, once daily.
1. Sarafoglou K, et al. J Clin Endocrinol Metab. 2021:dgab438. DOI: https://doi.org/10.1210/clinem/dgab438 [Epub ahead of print]; 2. Clinical Trial NCT03687242. Available at: https://clinicaltrials.gov/ct2/show/NCT03687242 (last accessed July 2021).

SPR001-202: ELIGIBILITY CRITERIA[1,2]

INCLUSION CRITERIA

Patients previously enrolled in SPR001-201:*

Successful completion of SPR001-201, with a **stable GC regimen** for **≥12 weeks** before SPR001-202 baseline[1]

Tildacerfont-naïve patients:

Meets **all inclusion criteria** for SPR001-201[1]

On a **stable GC regimen** for **≥30 days** before baseline that is expected to remain stable throughout the study[2]

EXCLUSION CRITERIA

Patients previously enrolled in SPR001-201:*

Experienced a **clinically significant AE** considered at least possibly related to tildacerfont in SPR001-201[2]

*If screening occurred >3 months after the subject's final follow-up visit for SPR001-201, 17-OHP was measured at screening and patients were screened for any clinically significant unstable medical condition, medically significant illness, or chronic disease occurring within 30 days of screening.[2]

AE, adverse event; GC, glucocorticoid.

1. Sarafoglou K, *et al. J Clin Endocrinol Metab.* 2021:dgab438. DOI: https://doi.org/10.1210/clinem/dgab438 [Epub ahead of print];
2. Clinical Trial NCT03687242. Available at: https://clinicaltrials.gov/ct2/show/NCT03687242 (last accessed July 2021).

SPR001-202: PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

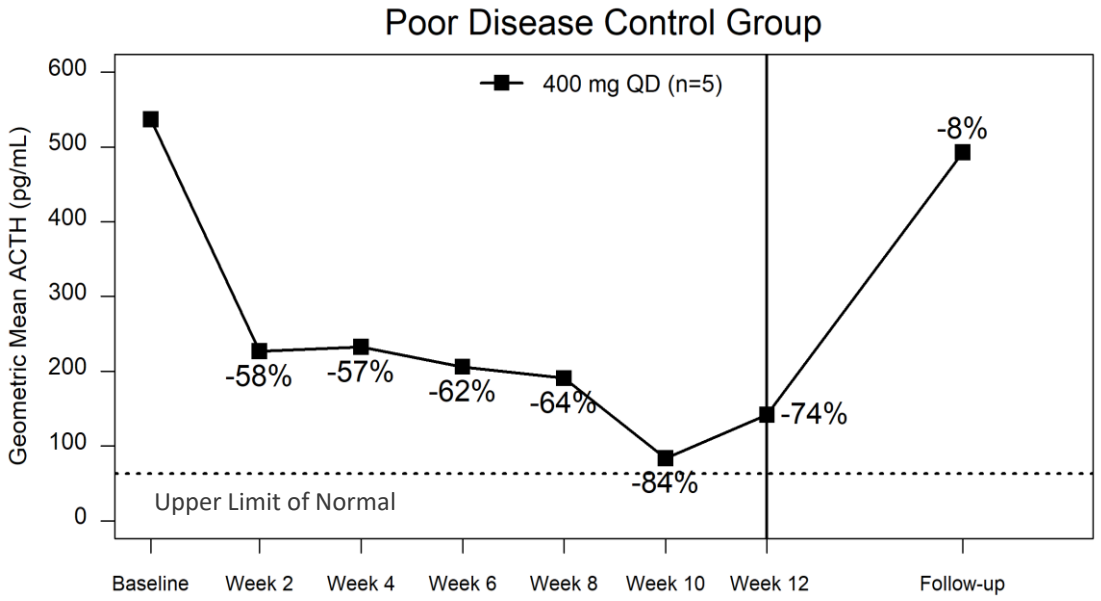
Evaluable populations*	Good Disease Control (n=3*)	Poor Disease Control (n=5*)
Demographics		
Age (yrs), mean (SD)	48 (17.7)	42 (15.6)
Female sex, n (%)	3 (100)	2 (40)
White race, n (%)	3 (100)	4 (80)
BMI ($kg/m^{2)}$, mean (SD)	35.5 (6.1)	27.8 (5.6)
Baseline glucocorticoid dose		
Mean HCe dose, mg (SD)	36.7 (11.6)	24.5 (11.5)
Glucocorticoid type		
Hydrocortisone, n (%)	0	2 (40)
Prednisolone family, n (%)	2 (67)	1 (20)
Combination‡, n (%)	1 (33)	2 (40)
Fludrocortisone use, n (%)	3 (100)	5 (100)
Baseline hormones (08:00 am)		
ACTH, pg/mL, geometric mean (CV%)	12.2 (584)	536.6 (109)
17-OHP, ng/dL, geometric mean (CV%)	314.1 (1069)	15323.3 (47)
A4, ng/dL, geometric mean (CV%)	28.8 (216)	1001.1 (48)

*Patients receiving dexamethasone (demonstrated by a post-hoc analysis to have the potential to confound efficacy assessments) were excluded from efficacy analyses but included in safety and pharmacokinetic analyses.
‡Combination therapy: combination of hydrocortisone and a member of the pred family.
17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; BMI, body-mass index; CV, coefficient of variation; HCe, hydrocortisone equivalents; SD, standard deviation.
1. Sarafoglou K, et al. *J Clin Endocrinol Metab.* 2021:dgab438. DOI: https://doi.org/10.1210/clinem/dgab438 [Epub ahead of print].

SPR001-202: ROBUST REDUCTION IN ACTH IN POORLY CONTROLLED DISEASE

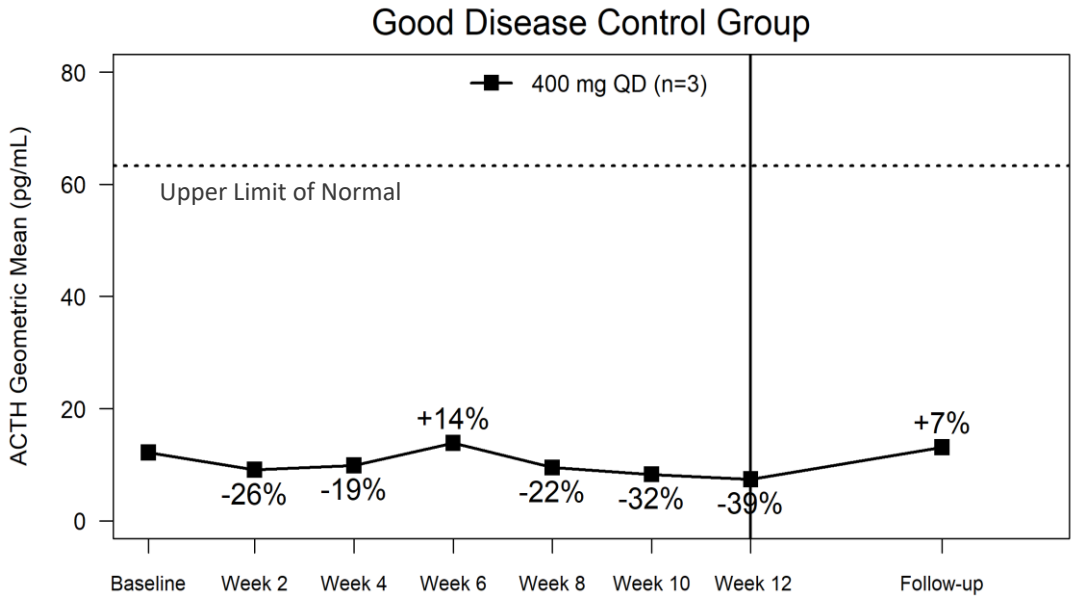
In the poor disease control group, a robust initial drop in ACTH was seen at week 2, followed by further reduction over 12 weeks; there was a maximum reduction in ACTH of **84%** at week 10 of the study in the poor disease control group

POOR DISEASE CONTROL



- Normalization of ACTH achieved in 60% of patients*

GOOD DISEASE CONTROL



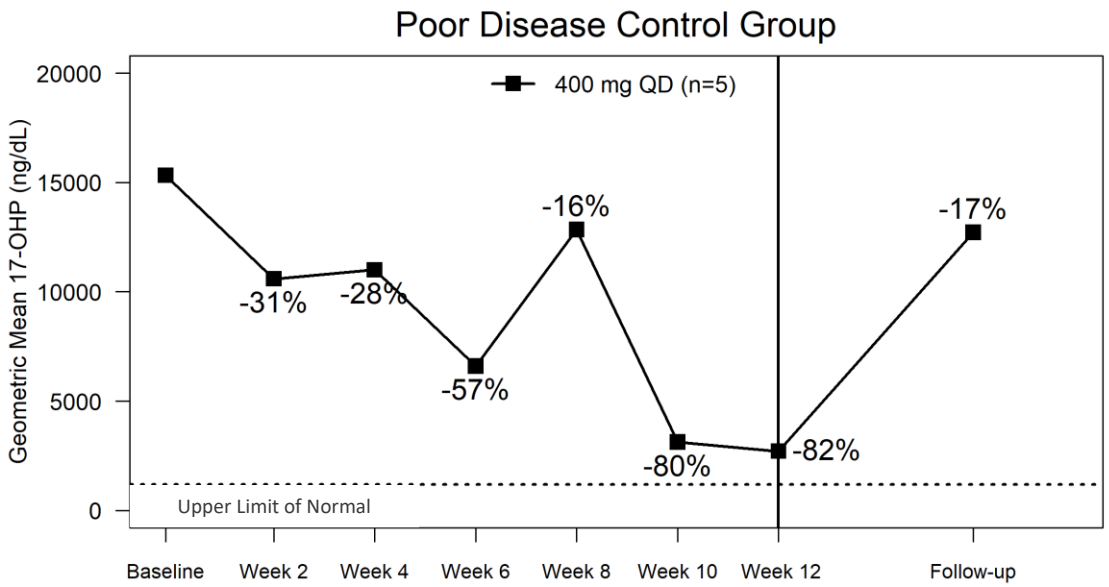
- No excessive suppression of adrenal function

*One subject at week 2 prior to discontinuation from the trial and two patient during month 3.
ACTH, adrenocorticotropic hormone; QD, once daily.
Sarafoglou K, et al. *J Clin Endocrinol Metab.* 2021:dgab438. DOI: https://doi.org/10.1210/clinem/dgab438 [Epub ahead of print].

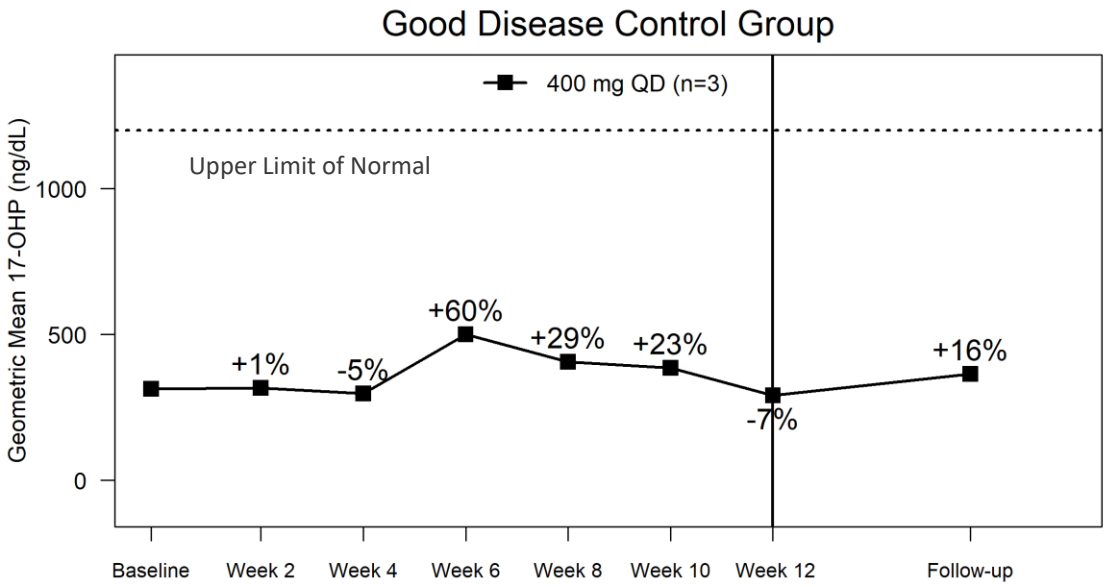
SPR001-202: SUSTAINED REDUCTION IN 17-OHP IN POORLY CONTROLLED DISEASE

In poor disease control group, an initial drop in 17-OHP was seen at week 2, followed by further reduction over 12 weeks; there was a maximum reduction in 17-OHP of **82% at week 12** of study in the poor disease control group

POOR DISEASE CONTROL



GOOD DISEASE CONTROL



- No excessive suppression of adrenal function

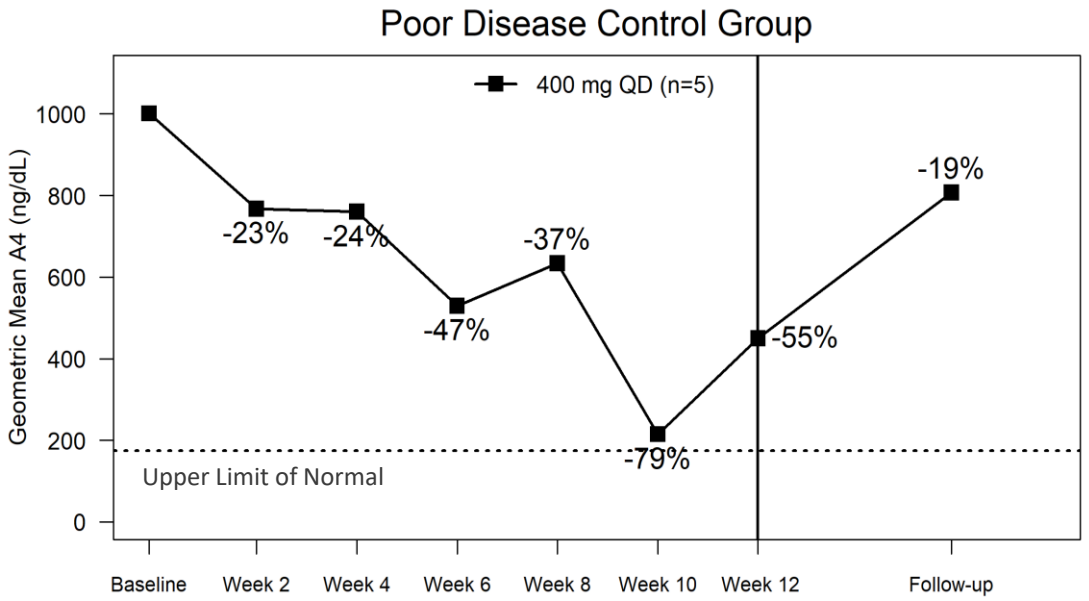
A4, androstenedione; QD, once daily.

Sarafoglou K, et al. *J Clin Endocrinol Metab.* 2021:dgab438. DOI: https://doi.org/10.1210/clinem/dgab438 [Epub ahead of print].

SPR001-202: SUSTAINED REDUCTION IN A4 IN POORLY CONTROLLED DISEASE

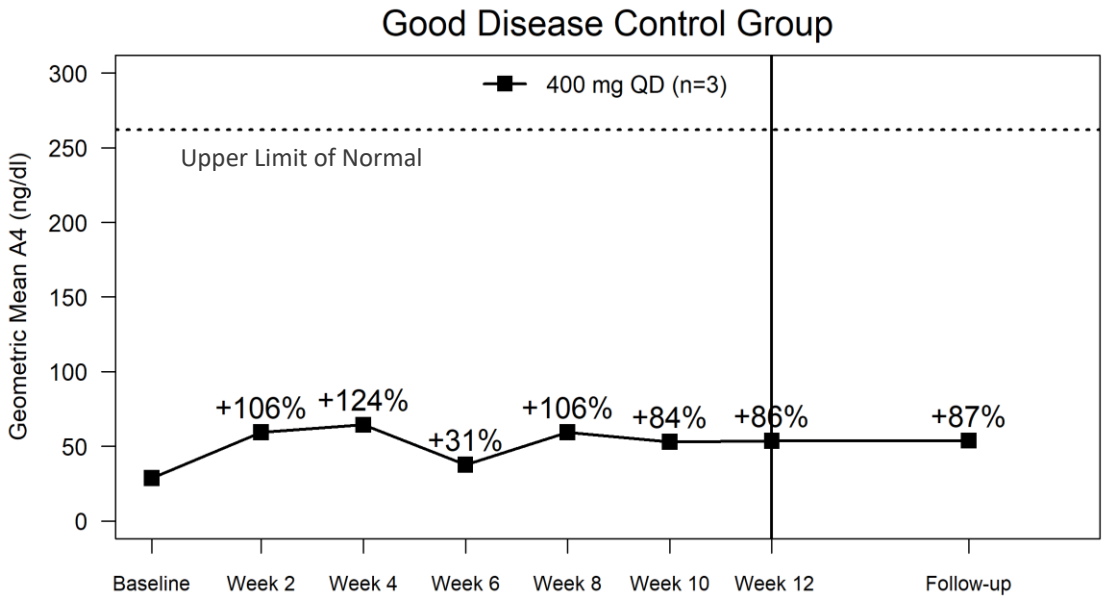
In poor disease control group, an initial drop in A4 was seen at week 2, followed by further reduction over 12 weeks; there was a maximum reduction in A4 of **79% at week 10** of study in the poor disease control group

POOR DISEASE CONTROL



- Normalization of A4 achieved in 40% of patients

GOOD DISEASE CONTROL



- No excessive suppression of adrenal function

A4, androstenedione; QD, once daily.

Sarafoglou K, et al. *J Clin Endocrinol Metab.* 2021:dgab438. DOI: https://doi.org/10.1210/clinem/dgab438 [Epub ahead of print].

SPR001-202: TREATMENT-EMERGENT ADVERSE EVENTS

Preferred Term	400 mg QD (n=11)
Participants with at least one TEAE, n (%)	**9 (81.8)**
Upper respiratory tract infection	2 (18.2)
Hypothyroidism	1 (9.1)
Abdominal pain upper	1 (9.1)
Diarrhea	1 (9.1)
Nausea	1 (9.1)
Vomiting	1 (9.1)
Dysgeusia	1 (9.1)
Glycosylated hemoglobin increased	1 (9.1)
Hepatic enzyme increased	1 (9.1)
Nasopharyngitis	1 (9.1)
Pruritus	1 (9.1)
Pruritus generalized	1 (9.1)
Acne	1 (9.1)
Lacrimation increased	1 (9.1)
Contusion	1 (9.1)
Back pain	1 (9.1)
Headache	1 (9.1)
Insomnia	1 (9.1)

- Treatment with tildacerfont 400 mg QD for up to 12 weeks was generally well-tolerated
- No new TEAEs observed with longer dosing
- **Most common SOC: gastrointestinal** (diarrhea, nausea, vomiting) in 3 patients
- **Most common AE: upper respiratory tract infection** (n=2); both unrelated
- Majority of AEs were grade 1 and considered unrelated to treatment
- Discontinuation (n=1): Grade 2 itching without rash and was also found to have grade 1 liver elevation at next visit when subject discontinued the study
- No SAEs were observed

AE, adverse event; QD, once daily; SAE, serious adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event.

KEY FINDINGS FROM PHASE 1 AND 2 STUDIES: SUMMARY

Efficacy

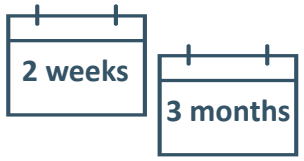
Two distinct patient populations:[1]

Poor disease control

Good disease control

These form the basis of the late-stage clinical program

Treatment with tildacerfont resulted in:[1]



Reduced adrenal androgens at **2 weeks** (Study 201) and **3 months** (Study 202) in poor disease control patients

Robust reduction in ACTH at the **lowest dose studied** (200mg QD)[1]

- No added benefit observed with higher or more frequent dosing
- Evidence of clinical outcome improvement (TART reduction)

Safety

Tildacerfont was generally well-tolerated in both:

Healthy adults[2]

People with CAH[1]

No drug-related SAEs reported to date[1,2]

Tildacerfont is metabolized primarily by CYP3A4[2]

- Coadministration of drugs that are known strong inducers or inhibitors of CYP3A4 is prohibited[1,2]

ACTH, adrenocorticotropic hormone; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAH, congenital adrenal hyperplasia; QD, once daily; SAE, serious adverse event; TART, testicular adrenal rest tumor. Liver icon by Edwin PM, Noun Project.

1. Sarafoglou K, et al. J Clin Endocrinol Metab. 2021:dgab438. DOI: https://doi.org/10.1210/clinem/dgab438 [Epub ahead of print]; 2. Barnes C, et al. J Endocr Soc 2021; 5(Suppl 1): A67.

Late-Stage Adult Classic CAH
CAHmelia Program

spruce BIOSCIENCES

CAHmelia-203: ADRENAL ANDROGEN REDUCTION STUDY

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

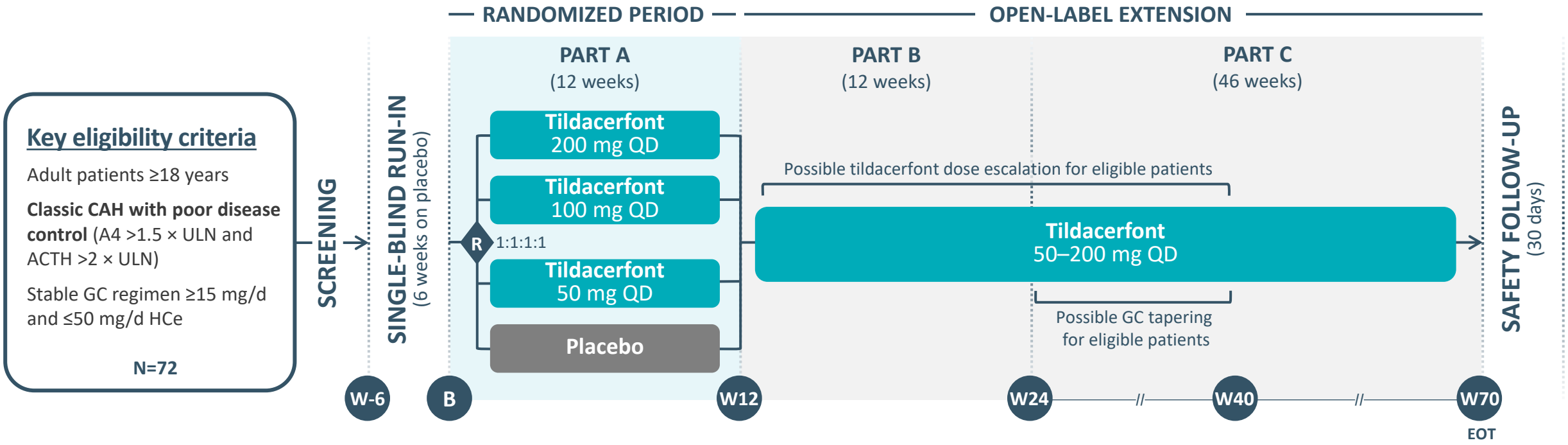
Key eligibility criteria

Adult patients ≥18 years

Classic CAH with poor disease control (A4 >1.5 × ULN and ACTH >2 × ULN)

Stable GC regimen ≥15 mg/d and ≤50 mg/d HCe

N=72



Study schema is not drawn to scale.

CAHmelia-203: STUDY ENDPOINTS

PRIMARY ENDPOINT

- Percentage change in A4 from baseline to Week 12

SECONDARY ENDPOINTS

- Percentage and absolute change from baseline to Week 12 in 17-OHP and ACTH
- Proportion of patients achieving normalization of ACTH, 17-OHP and A4
- Adverse events and serious adverse events

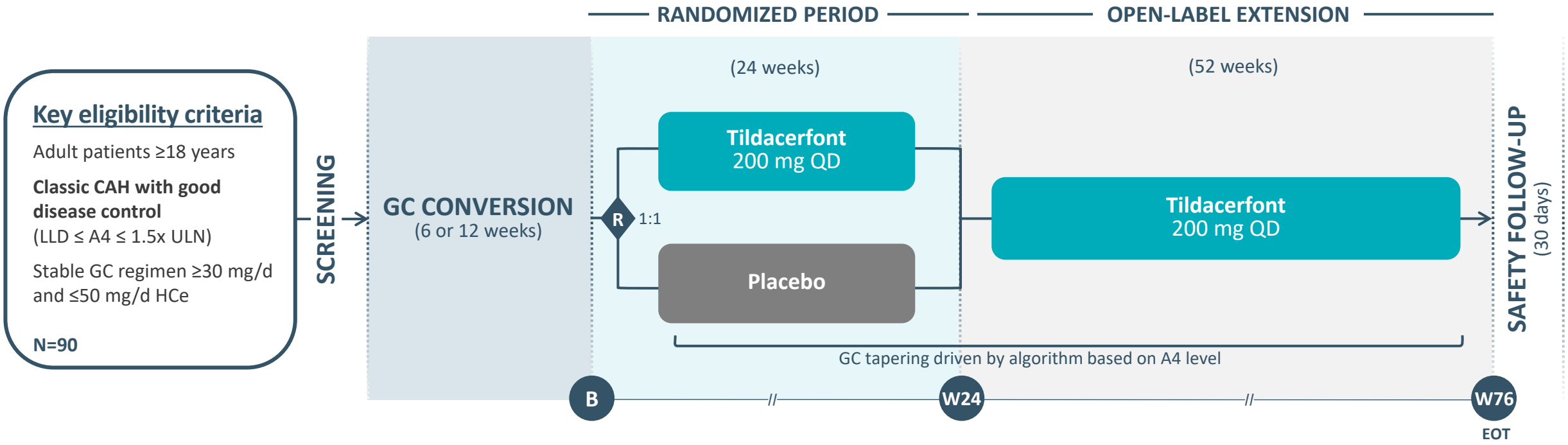
KEY EXPLORATORY ENDPOINTS

- Percentage and absolute change from baseline over full treatment period in ACTH, 17-OHP and A4
- Proportion of patients achieving the normalization of ACTH, 17-OHP and A4 at end of treatment
- Change from baseline to in QoL, clinical CAH symptoms, metabolic parameters, GC dose, TARTs in men

17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; GC, glucocorticoid; QoL, quality of life; TART, testicular adrenal rest tumor; ULN, upper limit of normal.

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



Study schema is not drawn to scale.

CAHmelia-204: STUDY ENDPOINTS

PRIMARY ENDPOINT

- Absolute change in GC dose (HCe) from baseline to Week 24

SECONDARY ENDPOINTS

- Absolute change from baseline in GC dose (HCe) in mg/m^2 at Week 24
- Median total cumulative GC dose (HCe)
- Change from baseline to Week 24 in metabolic parameters (fat mass [DXA], body weight, HOMA-IR)
- Adverse events and serious adverse events

KEY EXPLORATORY ENDPOINTS

- Proportion of patients with any reduction in GC dose
- Percentage and absolute change from baseline over full treatment period in ACTH, 17-OHP and A4
- Change from baseline in QoL, clinical CAH symptoms, metabolic parameters, body composition, bone mineral density [DXA]), and TARTs in men

SECONDARY COMPOSITE ENDPOINTS

- Absolute change from baseline in GC dose (HCe) at Week 24 in patients who maintain A4 ≤ULN
- Proportion of patients with GC dose ≤20 mg/d (HCe) at Week 24 in patients who maintain A4 ≤ULN

17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; BMI, body mass index; CAH, congenital adrenal hyperplasia; d, day; DXA, dual-energy X-ray absorptiometry; GC, glucocorticoid; HCe, hydrocortisone equivalent(s); HOMA-IR, homeostatic model assessment of insulin resistance; QoL, quality of life; TART, testicular adrenal rest tumor; ULN, upper limit of normal.

KOL Panel Discussion

spruce BIOSCIENCES

Paul Thornton, MD

Rosh Dias, MD, MRCP
Moderator

Richard Auchus, MD, PhD

TODAY'S PANELISTS

Pediatric Classic CAH Overview

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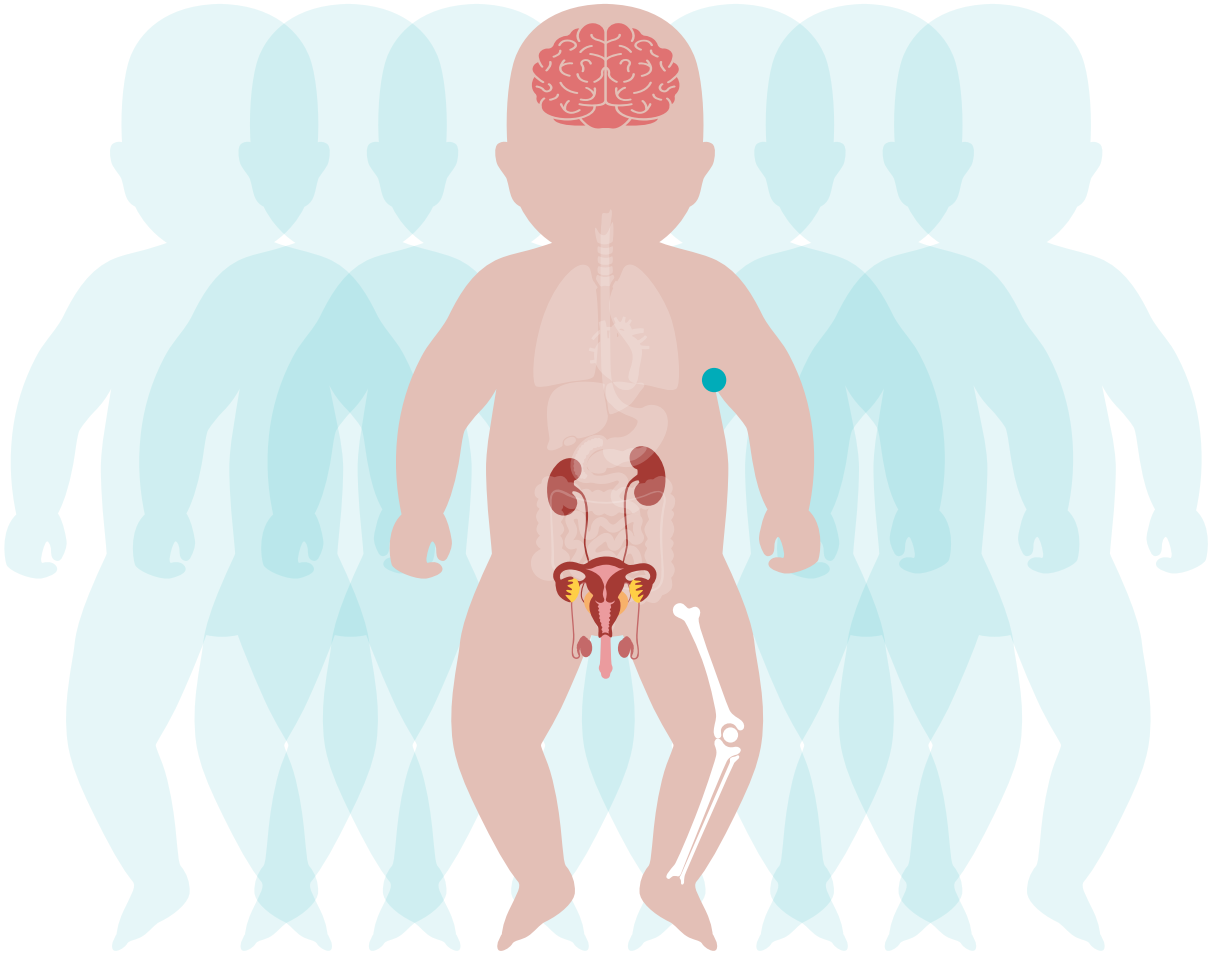
CLASSIC CAH PRESENTS IN INFANCY & EARLY CHILDHOOD



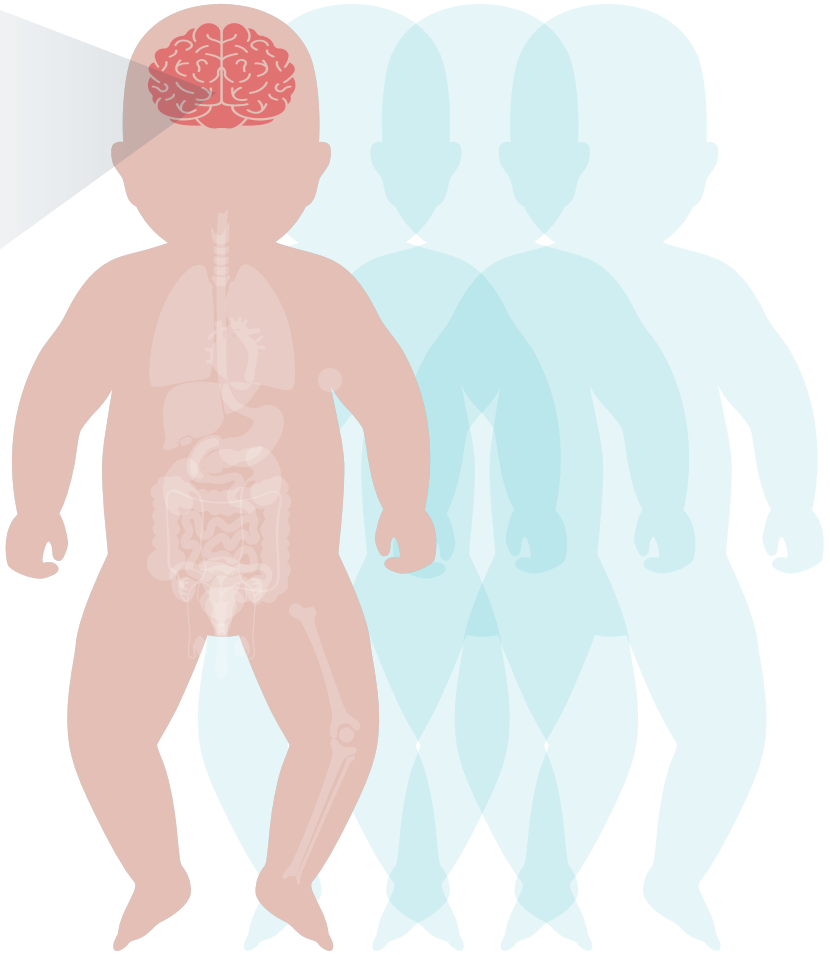
CAH, congenital adrenal hyperplasia

1. Falhammer H, *et al. J Clin Endocrinol Metab*. 2014; 99: E2715-E2721; 2. Claahsen-van der Grinten H, *et al. Endocr Rev.* 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print];
3. Merke D, *et al. N Engl J Med*. 2020;383:1248-61; 4. Mueller S, *et al. Eur J Endocrinol*. 2010;163:801-10; 5. Claahsen-van der Grinten H, *et al. Best Pract Res Clin Endocrinol Metab.* 2009;23(2):209–20.

CLASSIC CAH PRESENTS IN INFANCY & EARLY CHILDHOOD

BEHAVIORAL

Increased prevalence of ADHD[4]



ADHD, attention deficit hyperactivity disorder; CAH, congenital adrenal hyperplasia.

1. Falhammer H, *et al. J Clin Endocrinol Metab*. 2014; 99: E2715-E2721; 2. Claahsen-van der Grinten H, *et al. Endocr Rev.* 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print];
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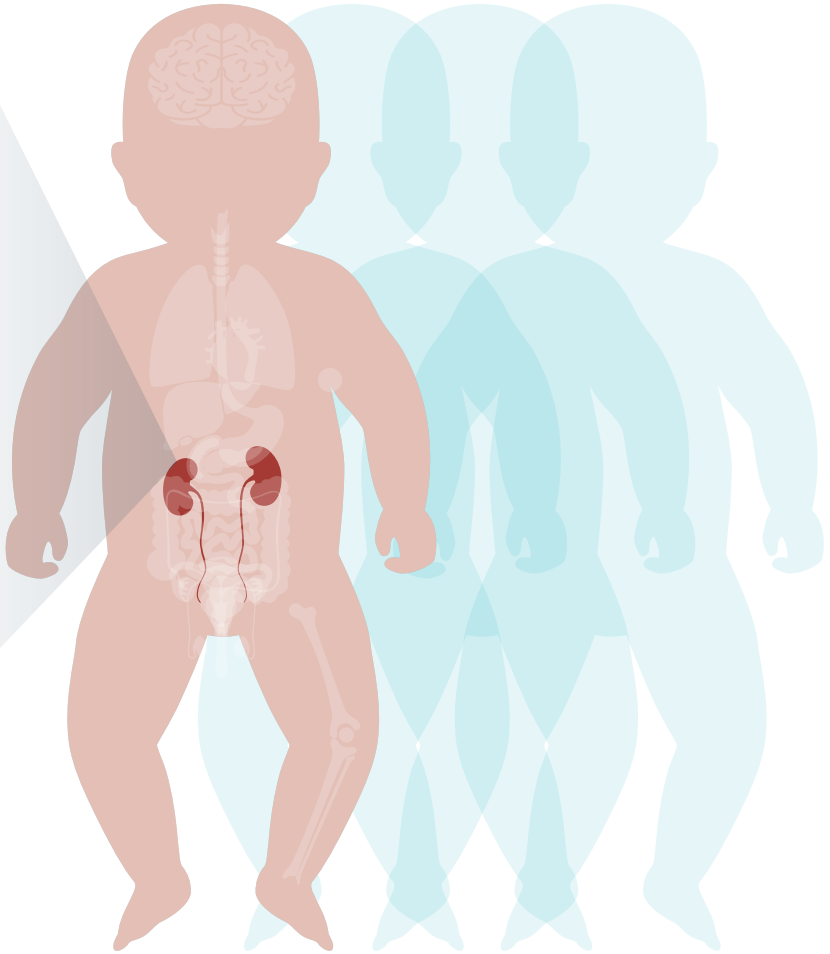
CLASSIC CAH PRESENTS IN INFANCY & EARLY CHILDHOOD

ADRENAL (SALT-WASTING) CRISIS

- Leading cause of death in CAH[1]
- Risk of potentially fatal electrolyte imbalances, acidosis, and shock begins at birth[2]
- Precipitated by acute illness, often infection[3]
- Life-threatening hypoglycemia with seizures is more common in children[2,3]



CAH, congenital adrenal hyperplasia

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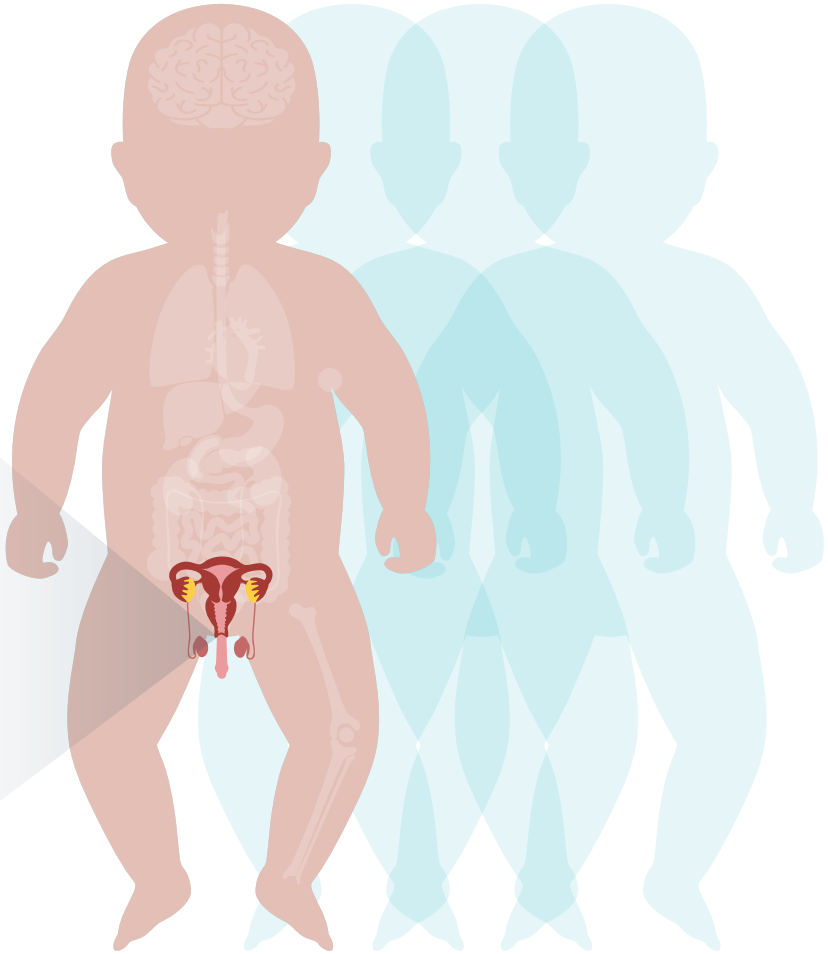
CLASSIC CAH PRESENTS IN INFANCY & EARLY CHILDHOOD

GENITOURINARY

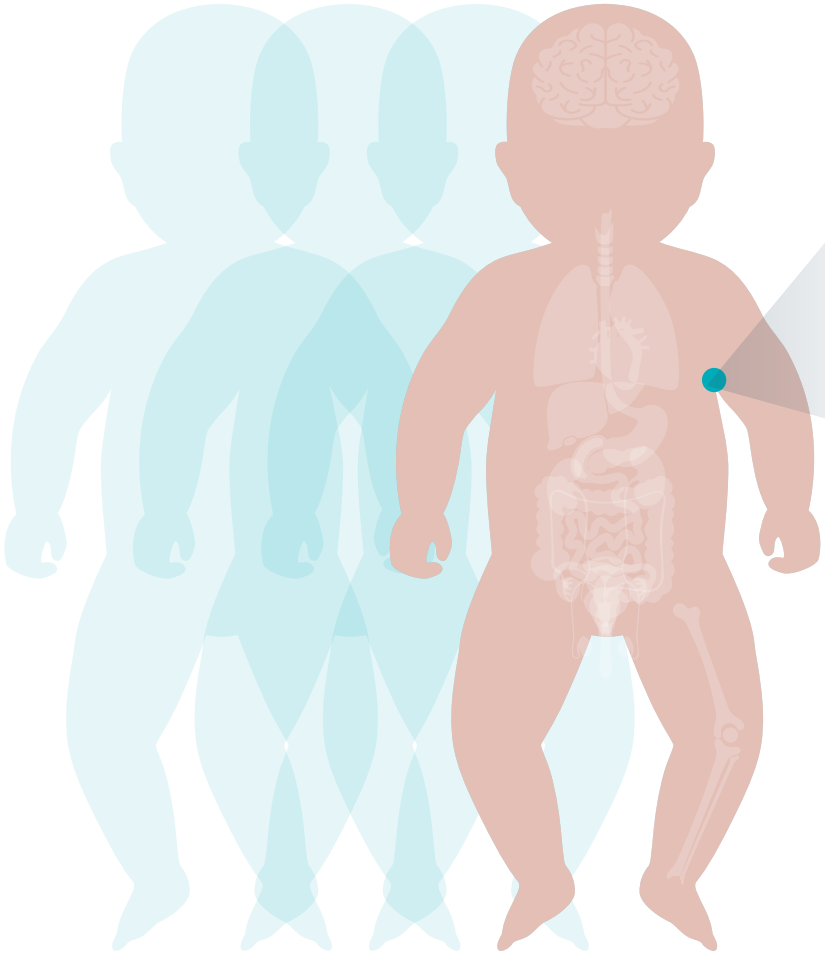
- 46,XX genital atypia/sex misassignment at birth[3]
- 46,XY TARTs may begin in childhood[5]



CAH, congenital adrenal hyperplasia; TARTs, testicular adrenal rest tumors.

1. Falhammer H, *et al. J Clin Endocrinol Metab*. 2014; 99: E2715-E2721; 2. Claahsen-van der Grinten H, *et al. Endocr Rev.* 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print]; 3. Merke D, *et al. N Engl J Med*. 2020;383:1248-61; 4. Mueller S, *et al. Eur J Endocrinol*. 2010;163:801-10; 5. Claahsen-van der Grinten H, *et al. Best Pract Res Clin Endocrinol Metab.* 2009;23(2):209–20.

CLASSIC CAH PRESENTS IN INFANCY & EARLY CHILDHOOD



PUBARCHE[2,3]

- Early childhood virilization
- Early onset adult body odor

CAH, congenital adrenal hyperplasia.

1. Falhammer H, *et al. J Clin Endocrinol Metab*. 2014; 99: E2715-E2721; 2. Claahsen-van der Grinten H, *et al. Endocr Rev.* 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print];
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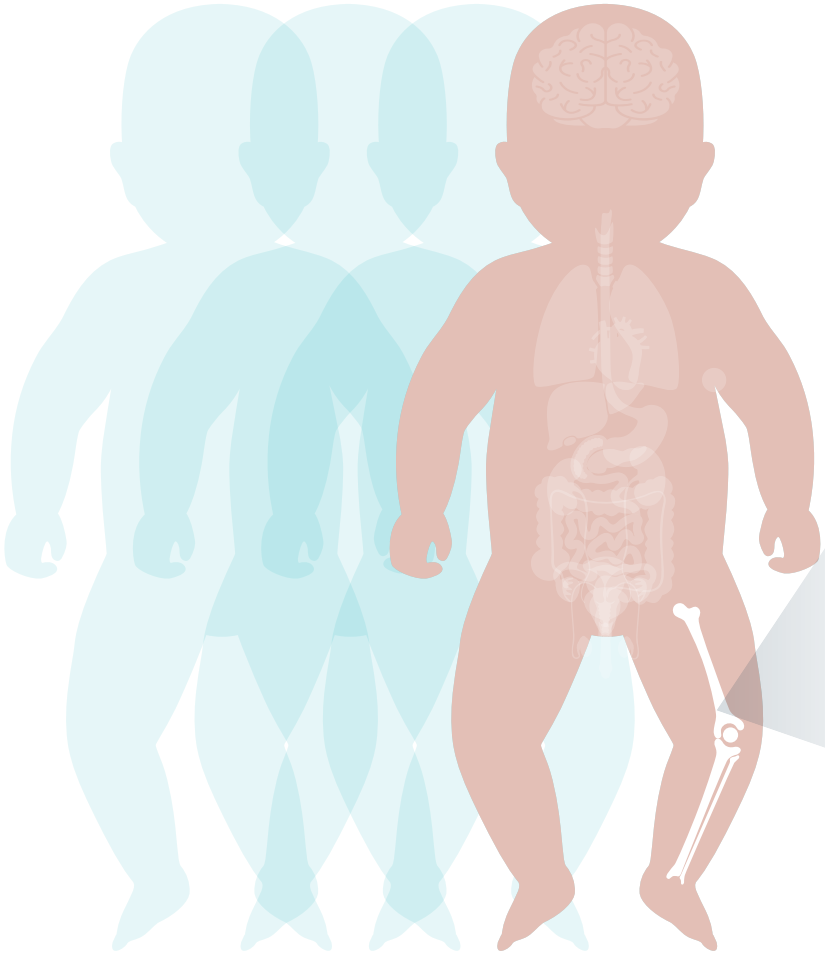


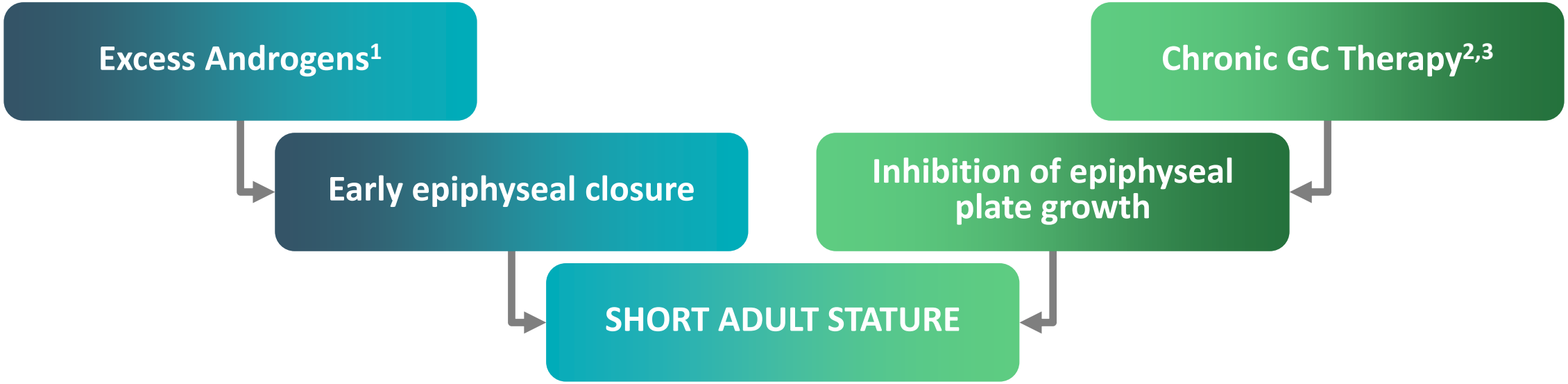
MUSCULOSKELETAL[2,3]

- Early growth acceleration
- Advanced bone age
- Premature epiphyseal closure

CAH, congenital adrenal hyperplasia.

1. Falhammer H, *et al. J Clin Endocrinol Metab*. 2014; 99: E2715-E2721; 2. Claahsen-van der Grinten H, *et al. Endocr Rev.* 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print];
3. Merke D, *et al. N Engl J Med*. 2020;383:1248-61; 4. Mueller S, *et al. Eur J Endocrinol*. 2010;163:801-10; 5. Claahsen-van der Grinten H, *et al. Best Pract Res Clin Endocrinol Metab.* 2009;23(2):209–20.

SHORT STATURE IN CAH IS CAUSED BY ANDROGENS AND GCs



OTHER EFFECTS OF GCs ON HABITUS & MUSCULOSKELETAL SYSTEM

Cushingoid appearance[3]

Decreased bone mineral density & osteoporosis[3-5]

Increased risk of fractures[6]

CAH, congenital adrenal hyperplasia; GC, glucocorticoid.

1. Merke D, *et al. N Engl J Med*. 2020;383:1248-61; 2. Lui J. *Endocr Dev.* 2011;20:187-93; 3. Claahsen-van der Grinten H, *et al. Endocr Rev.* 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print];
4. Chakhtoura Z, *et al. Eur J Endocrinol*. 2008;158:879-87; 5. Falhammer H, *et al. J Clin Endocrinol Metab*. 2007;92:4643-9; 6. Hummel S, *et al. Clin Endocrinol*. 2016;0:1-8.

UNMET NEEDS IN PEDIATRIC CAH: STRATEGIES TO BALANCE ANDROGENS & GC DOSE

Balance between androgen levels and GC excess
is critical to avoid
irreversible impacts on childhood development[1–3]

Novel therapies are needed
to **reduce** the need for **supraphysiologic GCs**

CAH, congenital adrenal hyperplasia; GC, glucocorticoid.

1. Claahsen-van der Grinten HL, *et al. Endocr Rev.* 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print]; 2. Pijnenburg-Kleizen KJ, *et al. J Pediatr Endocrinol Metab.* 2019;32(10):1055–63; 3. Merke DP, *et al. N Engl J Med*. 2020;383:1248–61.

Phase 2 Pediatric Classic CAH Development Program

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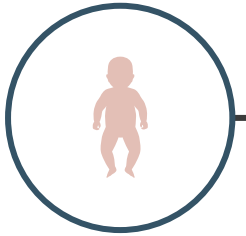
MANAGEMENT GOALS OF PEDIATRIC CAH VARY WITH AGE

Early childhood to puberty

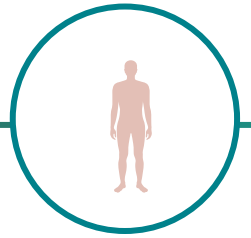


Goal of therapy:
Maximize androgen suppression
for normal growth and pubertal development

Challenges:
GC overdose may cause
iatrogenic Cushing syndrome

Strategies to achieve balance:
Use only short-acting GCs
Avoid attempts to normalize 17-OHP levels

Puberty

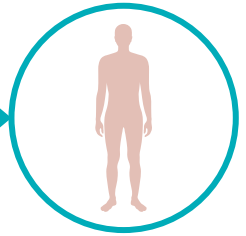


Goal of therapy:
Maintain adequate androgen suppression
despite rapid HC metabolism in puberty

Challenges:
Higher GC doses are associated
with shorter adult height

Strategies to achieve balance:
Use GC doses >17 mg/m^2/d with care
Prioritize height over normalizing hormone levels

Post puberty to early adulthood



Goal of therapy:
Prevent morbidity & mortality from adrenal crisis,
preserve fertility

Challenges:
MC requirements vary through adolescence
Medical needs vary by sex and gender

Strategies to achieve balance:
Continue GC & MC at transition to adulthood
Refer to multidisciplinary transition clinics

17-OHP, 17-hydroxyprogesterone; CAH, congenital adrenal hyperplasia; d, day; GC, glucocorticoid; HC, hydrocortisone; MC, mineralocorticoid.

1. Claahsen-van der Grinten HL, *et al. Endocr Rev.* 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print].

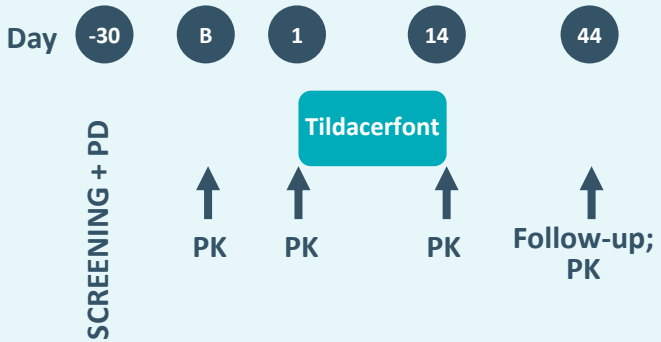
PHASE 2 STUDY IN PEDIATRIC CAH: TO BE INITIATED IN 2021

Key eligibility criteria

- Pediatric patients (male and female) aged 6–17 years at Screening
- **Classic CAH**
- 17-OHP >400ng/dl at Screening

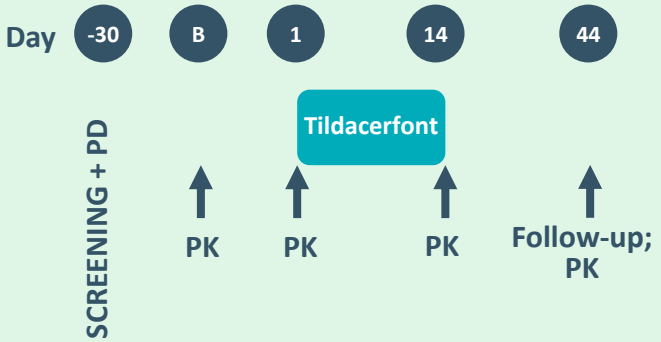
N=20

11–17 years old, 50 mg* QD
(44 days)



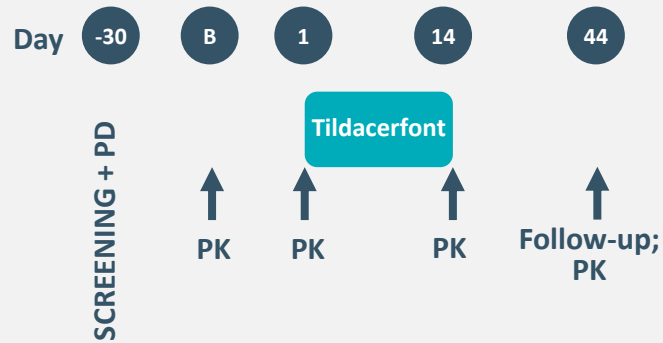
DSMB agreement to proceed

11–17 years old, ≤200 mg* QD
(44 days)



DSMB agreement to proceed

6–10 years old, ≤200 mg* QD
(44 days)



PRIMARY ENDPOINT
Safety

SECONDARY ENDPOINT
PK on Day 14 (of protocol)

OTHER ENDPOINTS
Change in PD biomarkers (ACTH, 17-OHP, A4)

Study schema is not drawn to scale.
*Weight-based dosing at adult/effective dose equivalents.
17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; B, baseline; CAH, congenital adrenal hyperplasia; DSMB, Data Safety and Monitoring Board; GC, glucocorticoid; HCe, hydrocortisone equivalent(s); PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily.
Spruce Biosciences. Data on file.

Concluding Remarks

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KEY ANTICIPATED MILESTONES

2H2021	Initiate Phase 2 proof-of-concept trial in PCOS
2H2021	Initiate Phase 2 trial in pediatric classic CAH
1H2022	Topline results in adult classic CAH (CAHmelia-203)
2H2022	Topline results in adult classic CAH (CAHmelia-204)
1H2023	Phase 2 results in pediatric classic CAH and PCOS

INVESTMENT HIGHLIGHTS

Tildacerfont poised to transform treatment paradigm in classic CAH	**Two late-stage clinical studies initiated; Data expected in 2022. NDA filing in adult classic CAH targeted for 2023**
Multiple expansion opportunities	**Initiation of Phase 2 programs in pediatric classic CAH and polycystic ovary syndrome (PCOS) in 2H 2021**
Significant commercial opportunity	**~$3B+ worldwide market opportunity in classic CAH**
Strong IP protection	**Comprehensive IP portfolio based on issued patents provides exclusivity to 2038 in U.S. combined with Orphan Drug Designation in U.S. and Europe**
Highly experienced leadership team	**Management has contributed to development and commercial launch of 40 products, including within endocrine and rare disease space**

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Focused on developing and commercializing novel therapies for rare endocrine disorders with significant unmet medical need