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

# Corporate Presentation

**August 10, 2022**

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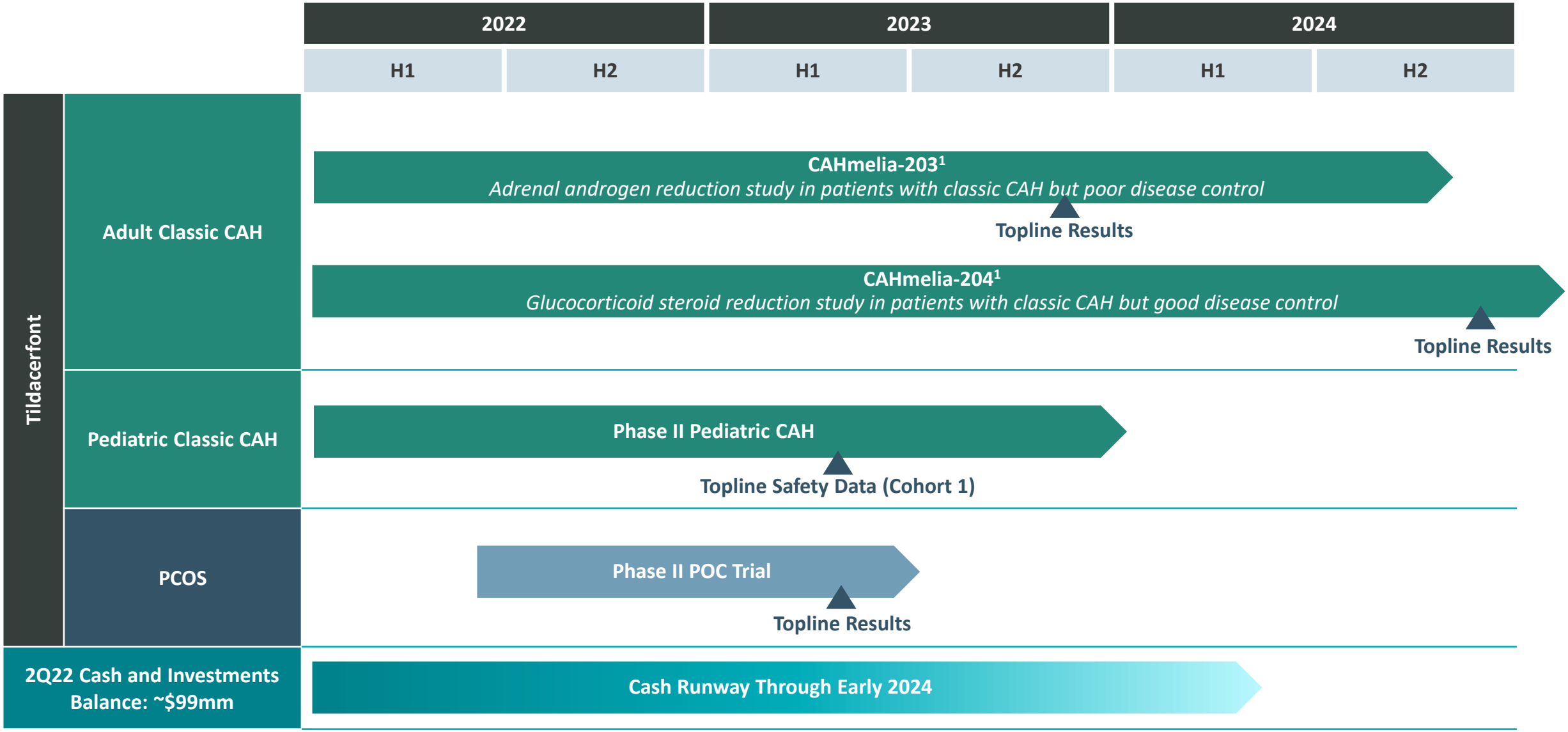
This presentation discusses a product candidate that is under clinical study and which has not yet been approved for marketing by the U.S. Food and Drug Administration. No representation is made as to the safety or effectiveness of this product candidate for the use for which it is being studied.

# SPRUCE AT-A-GLANCE

| | |
|---|---|
| **Large Orphan Market Primed for Innovation** | **~$3B+ market opportunity in CAH with high unmet need, low competitive intensity, and no new therapeutic options in ~50 years** |
| **Transformative Treatment Paradigm in CAH** | **Tildacerfont is a second generation CRF-1 receptor antagonist with clear MOA, designed to reduce disease and steroid burden** |
| **Robust Clinical Data in Adult CAH** | **Two positive Phase 2a studies demonstrating ~80% reduction in biomarkers; 235 subjects dosed across eight studies to date** |
| **Potentially Registrational Studies Ongoing** | **Data from two studies in Adult-CAH patients expected in 2H-2023 (CAHmelia-203) and 2H-2024 (CAHmelia-204)** |
| **Multiple Expansion Opportunities** | **Phase 2 programs initiated in pediatric CAH and polycystic ovary syndrome (PCOS) with data expected in 1H-2023** |
| **Strong IP Protection** | **Comprehensive IP portfolio with exclusivity to 2038 combined with Orphan Drug Designation in U.S. and E.U.** |

# TILDACERFONT PIPELINE AND CATALYSTS




Note: CAH is congenital adrenal hyperplasia, PCOS is polycystic ovary syndrome.

1. Patients in each of CAHmelia-203 and CAHmelia-204 rollover into an open-label extension following the placebo-controlled period for 58 weeks and 52 weeks, respectively. Topline data from these trials along with data from the open-label extension may form the basis for registrational filings in the United States and Europe.

# Classic CAH Overview

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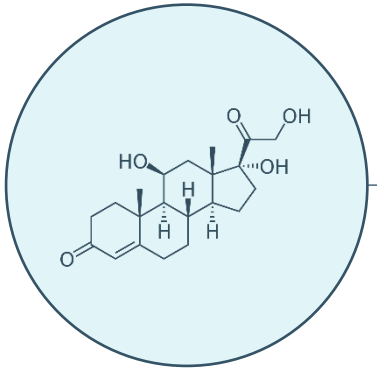
# CLASSIC CAH DISEASE OVERVIEW

## Classic CAH is a chronic and potentially life-threatening rare disease

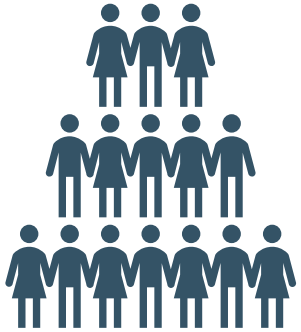



Classic CAH is an autosomal recessive disease characterized by an inability to produce cortisol, leading to a chronic imbalance of key hormones and an overproduction of adrenal androgens.

Due to the severity and high incidence of the disease, most developed countries have established newborn screening programs to test for classic CAH at birth.

We estimate the total classic CAH population to be approximately 20,000-30,000 people in the U.S., approximately 50,000 people in the EU, and at least 145,000 people in China.

# OF THE 21-OH DEFICIENT CAH SUBTYPES, CLASSIC IS MORE SEVERE

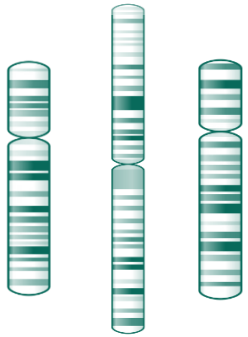


## Classic 21-OHD CAH[1]

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.

# 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]

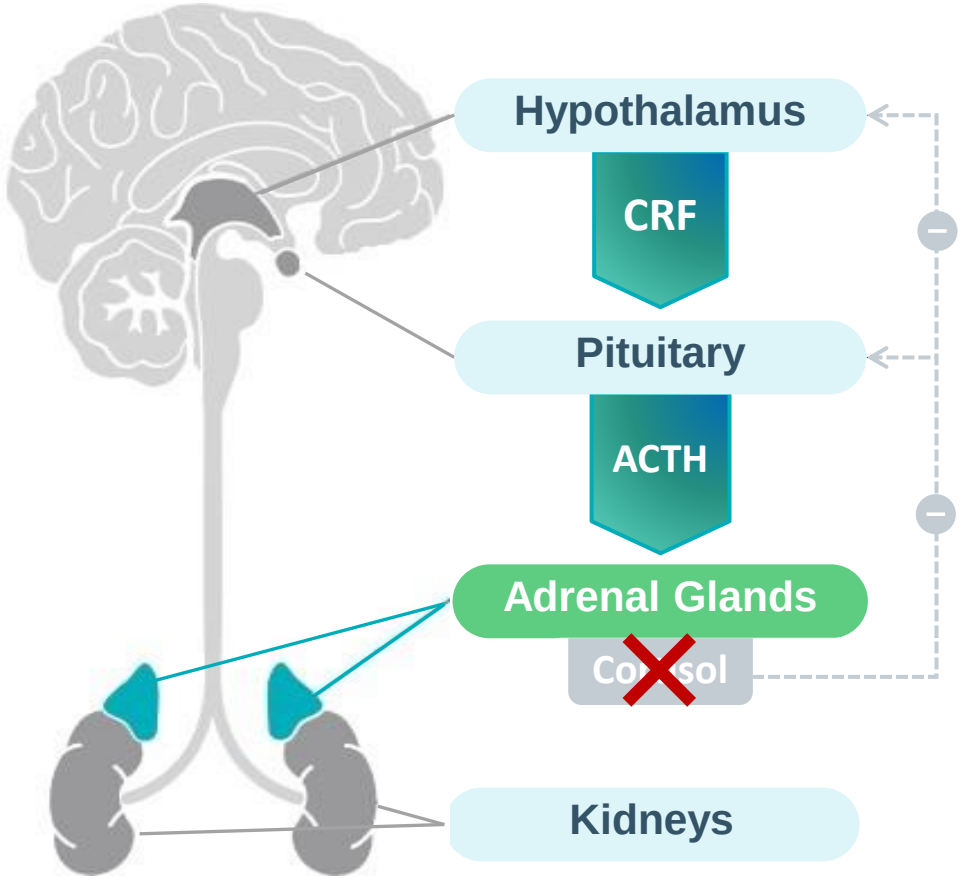
- Indicated when prior children have CAH
- Fetal hormone levels and DNA can be analyzed from amniotic fluid
- Fetal DNA analysis is also performed via chorionic villus sampling

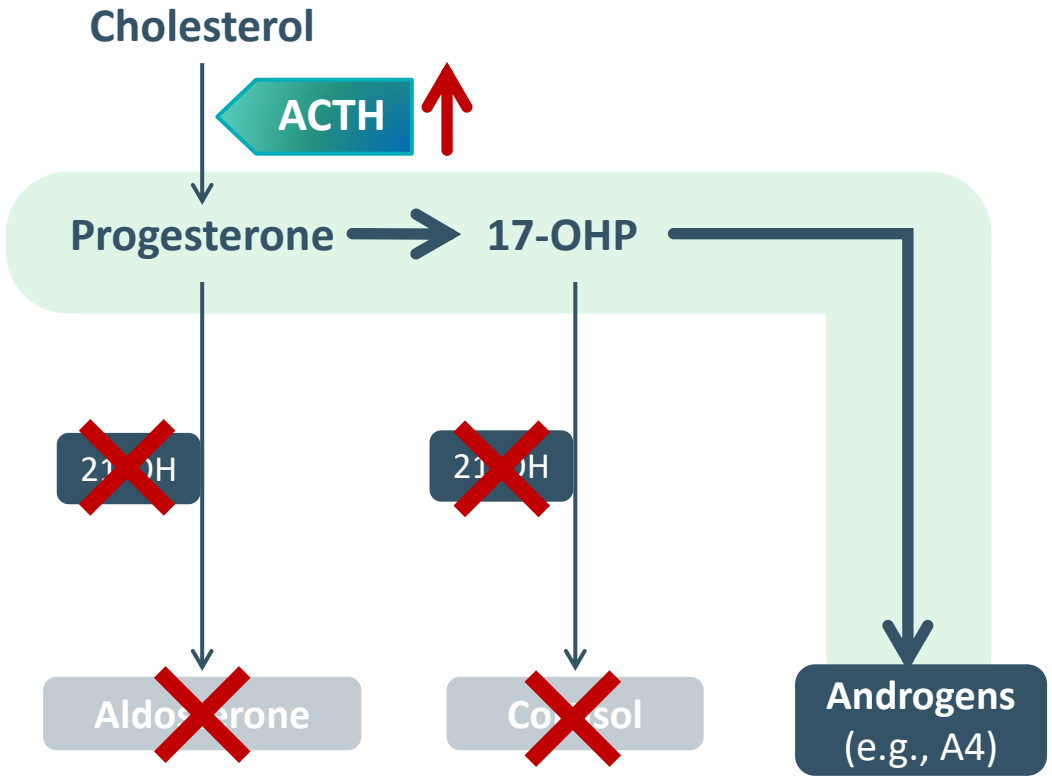
17-OHP, 17-hydroxyprogesterone; 21-OHD, 21-hydroxylase deficient; ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia.

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.

# HPA AXIS FUNCTION IN CLASSIC CAH PATIENTS

- Deficiency in 21-OH results in lack of cortisol & aldosterone production
- Lack of cortisol upregulates CRF & ACTH leading to hyperplasia of the adrenal glands
- 17-OHP is routed to the androgen pathway, resulting in excess androgens

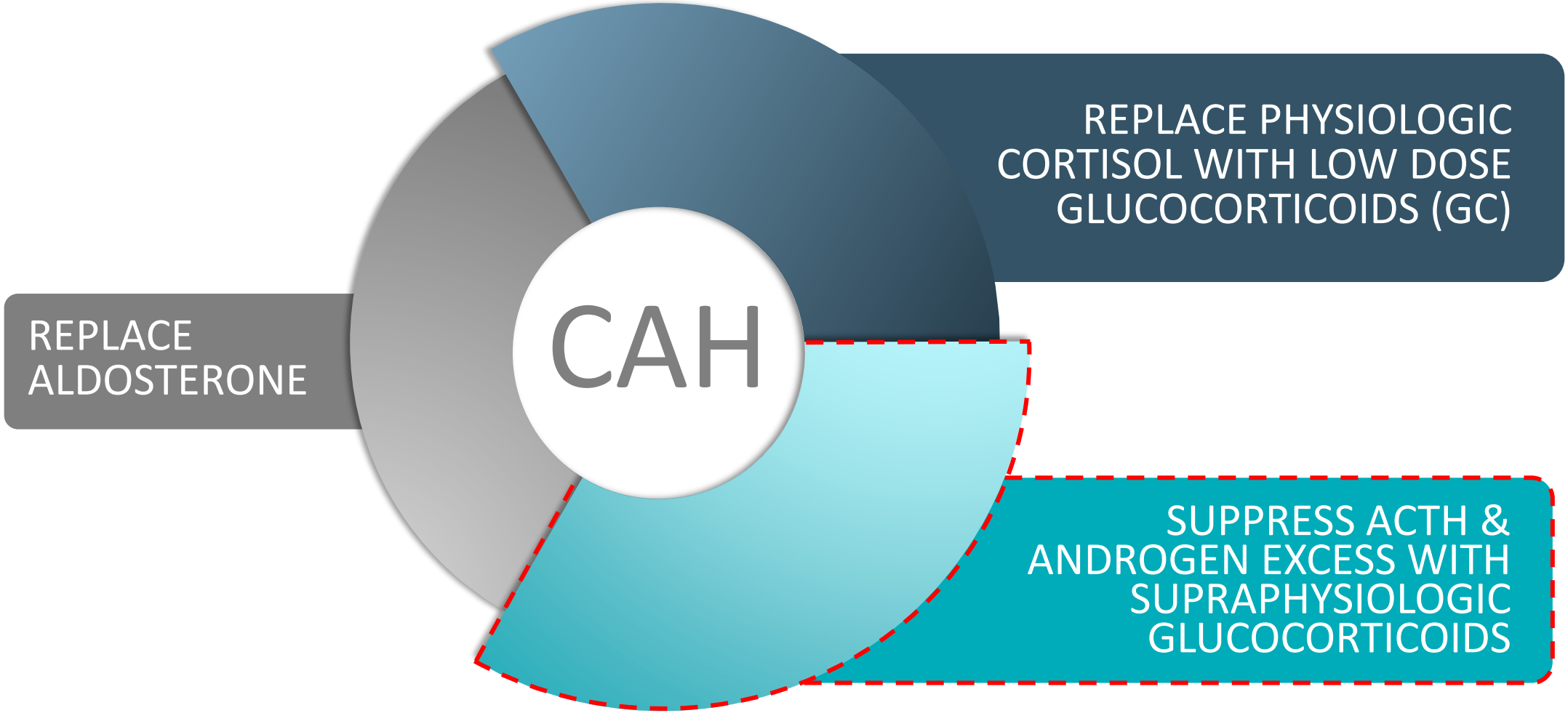



17-OHP, 17-hydroxyprogesterone; 21-OH, 21-hydroxylase; 21-OHD, 21-hydroxylase deficient; ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; CRF, corticotropin releasing factor; HPA, hypothalamic-pituitary-adrenal.

Engels M, *et al. Endocr Rev.* 2019;40:973-87.

# MANAGEMENT OF CLASSIC CAH REQUIRES A THREE-PRONGED APPROACH BUT UNMET NEED REMAINS




ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia.

# NOVEL THERAPIES ARE NEEDED IN CLASSIC CAH

Glucocorticoids have been the SoC since the 1950s[1] **but contribute to the burden of disease. Supraphysiologic doses** are required to **control high adrenal androgens which** result in **comorbidities linked to excessive chronic GC use. Therefore, novel therapies are needed**

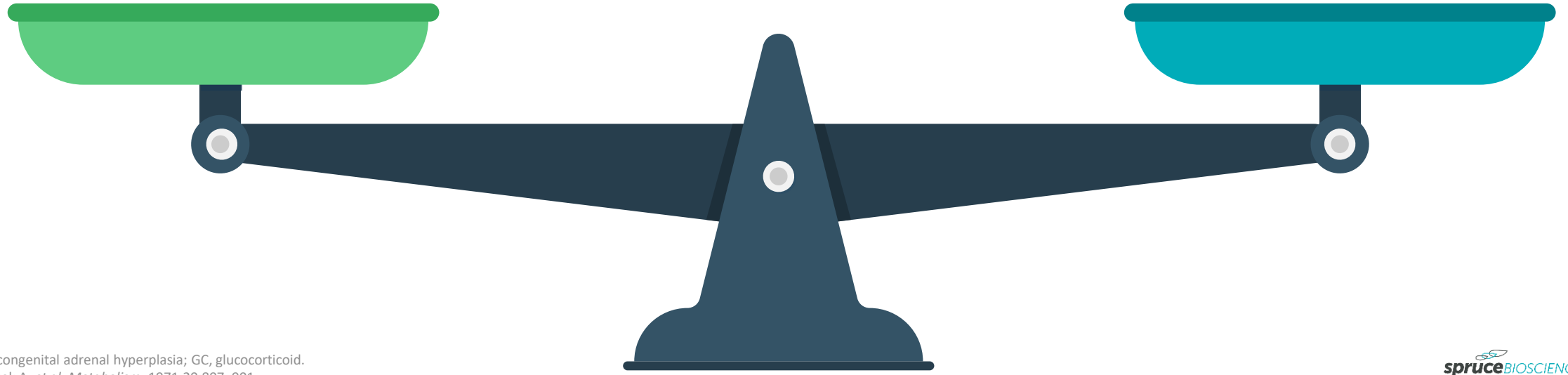
## Excess Androgens

- HIRSUTISM, AMENORRHEA ACNE
- PSYCHOLOGICAL EFFECTS
- ABNORMAL AND/OR EARLY PUBERTY
- SHORT STATURE
- INFERTILITY

***Goal of Therapy*: To Control High Androgens and Symptoms of CAH While Avoiding Chronic Supraphysiologic GC**

## Excess GCs

- CARDIOVASCULAR DISEASE
- SHORT STATURE
- INSULIN RESISTANCE
- OSTEOPOROSIS
- OBESITY



CAH, congenital adrenal hyperplasia; GC, glucocorticoid.

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

# Tildacerfont

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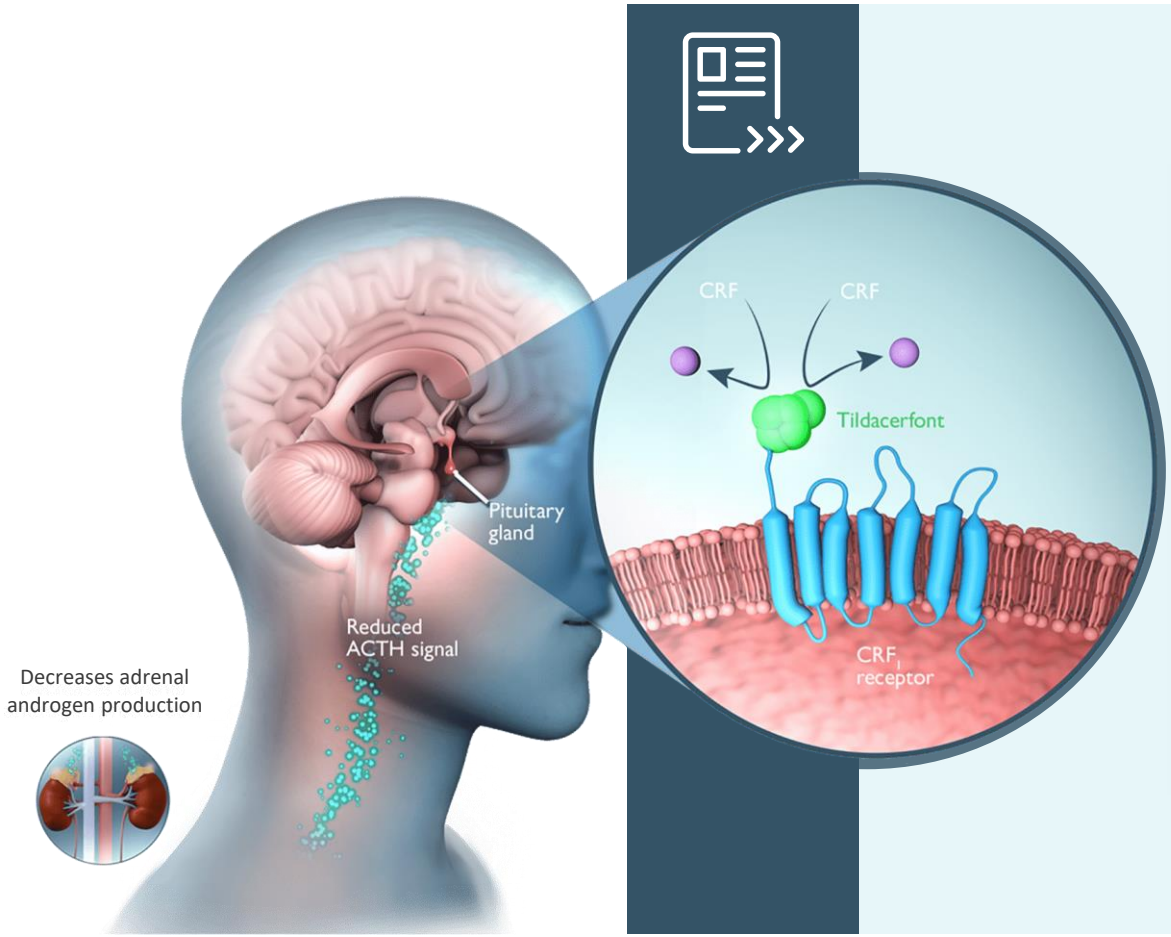
# TILDACERFONT IS A NOVEL $CRF_1$ RECEPTOR ANTAGONIST




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.

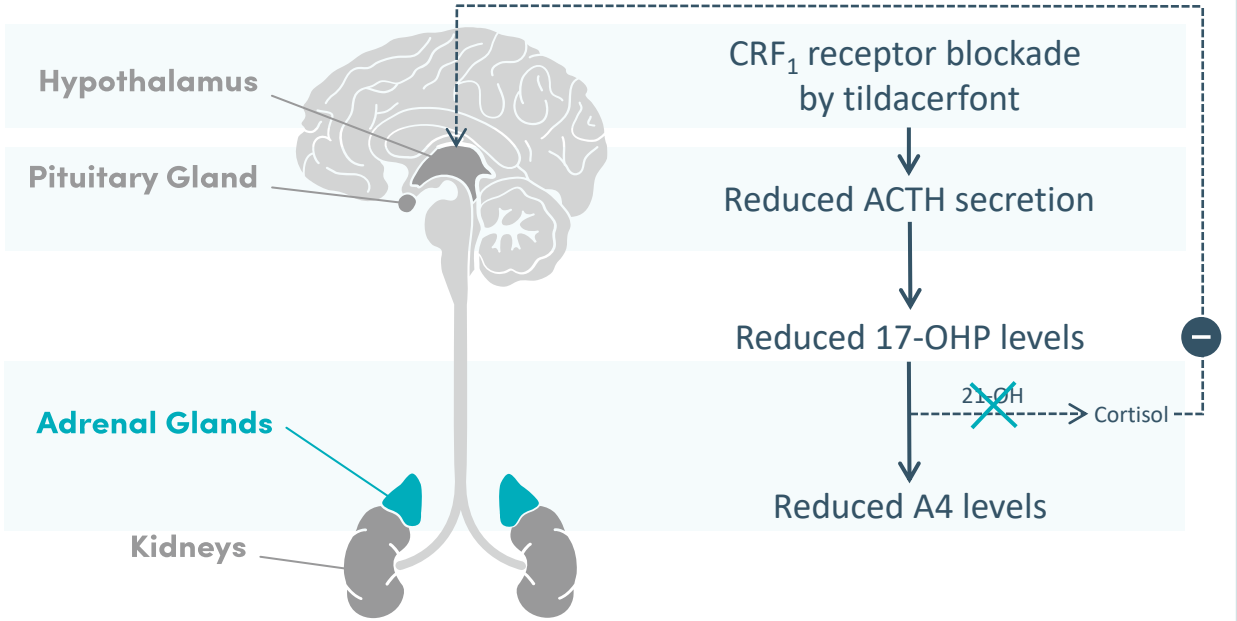
1. Sarafoglou K, *et al. J Clin Endocrinol Metab.* 2021:dgab438. DOI: https://doi.org/10.1210/clinem/dgab438 [Epub ahead of print].

# TILDACERFONT 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.

# Adult Classic CAH
# Clinical Development Program

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# KEY FINDINGS FROM PHASE 1 AND 2 STUDIES: SUMMARY

**Two distinct patient populations:**[1]

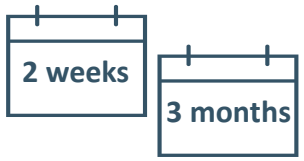
**Poor disease control**

**Good disease control**

**These form the basis of the late-stage clinical program**

## Efficacy

**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]

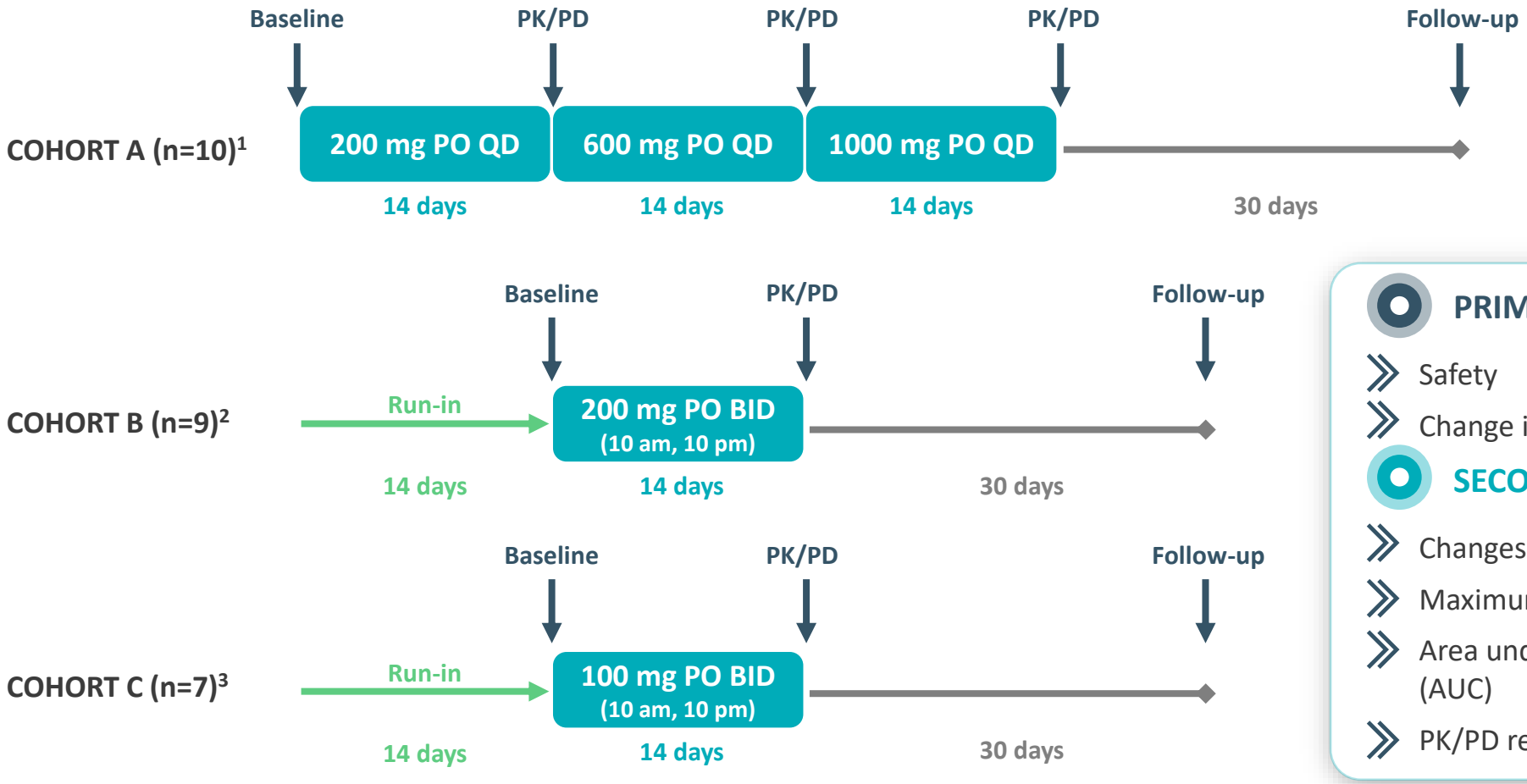
Most common adverse events: headache and upper respiratory tract infection (mild)

ACTH, adrenocorticotropic hormone; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAH, congenital ad erplasia; 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.

# 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]

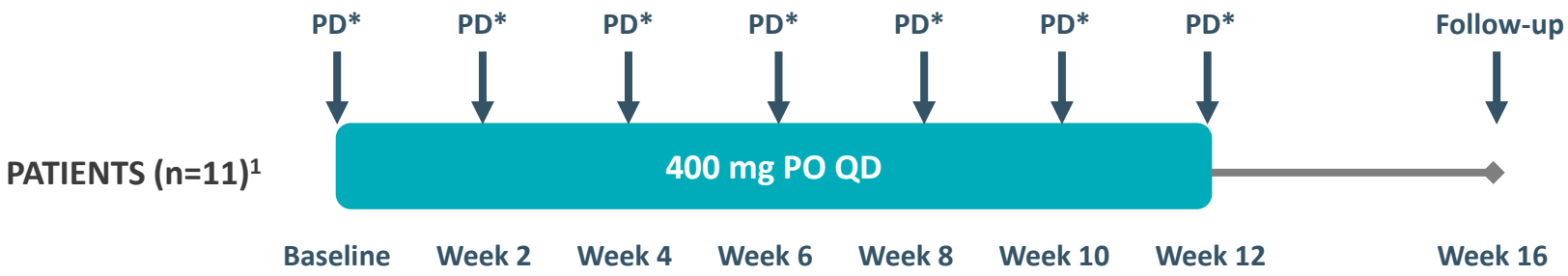
- Changes in PD markers
- Maximum plasma concentration ($C_{max}$)
- Area under the concentration-time curve (AUC)
- PK/PD relationships

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, multi-center, open-label study[1]**




**PRIMARY ENDPOINT[2]**

- Safety and tolerability

**SECONDARY ENDPOINTS[2]**

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

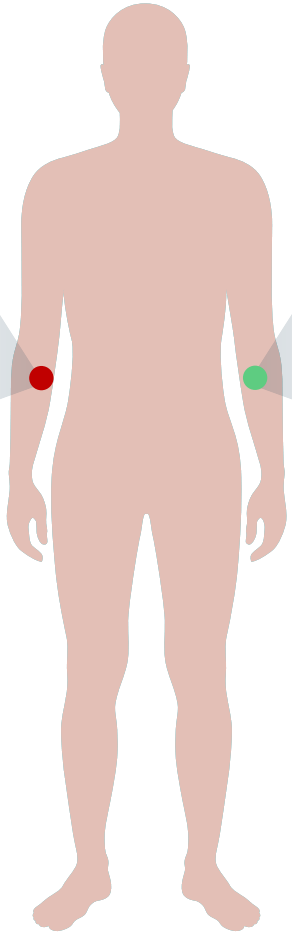
*Trial visits were conducted in the morning, at approximately 8 AM, prior to consumption of a morning GC dose at baseline (Day 1) and Weeks 2, 4, 6, 8, 10, and 12, and 30 days after the last dose.
17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; PD, pharmacodynamic 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).

# 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



## GOOD DISEASE CONTROL[1]

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

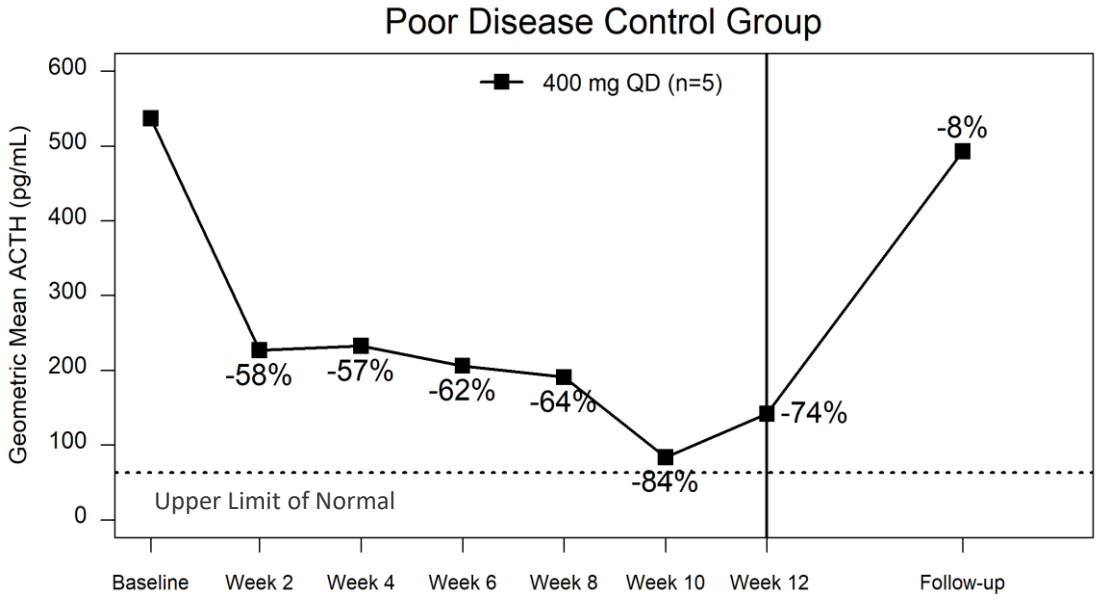
CAH, congenital adrenal hyperplasia; GC, glucocorticoid.

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.

# SPR001-202: ROBUST REDUCTION IN ACTH and A4 IN POORLY CONTROLLED DISEASE

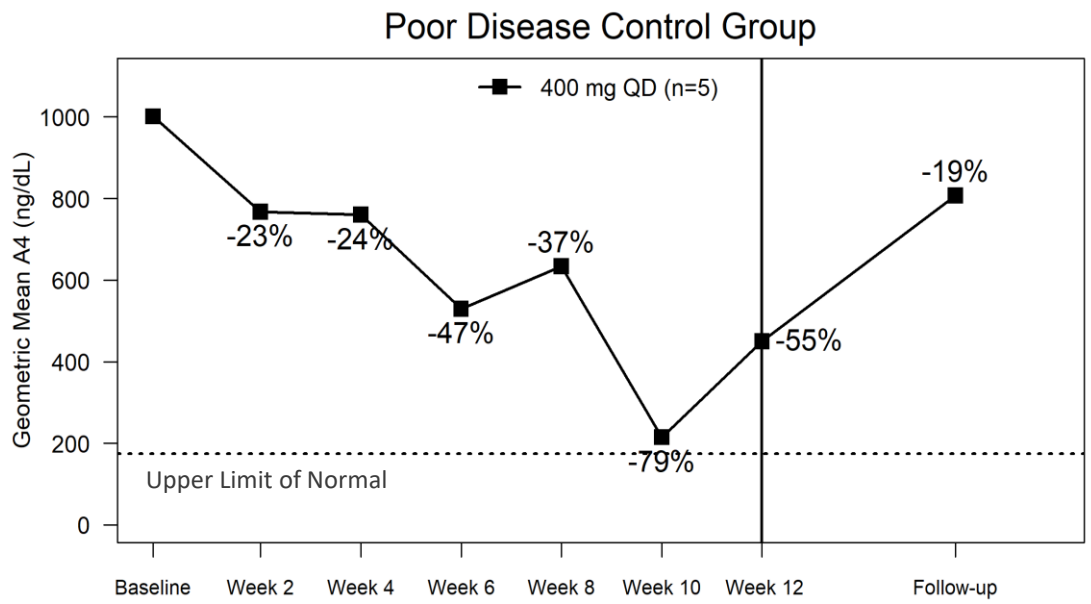
In the Poor Disease Control group, a robust initial drop in ACTH and A4 was seen at week 2, followed by further reduction over 12 weeks; there was a maximum reduction in **ACTH and A4** of **84% and 79%,** respectively, at week 10.

## POOR DISEASE CONTROL - ACTH




- Normalization of ACTH achieved in 60% of patients*

## POOR DISEASE CONTROL – A4



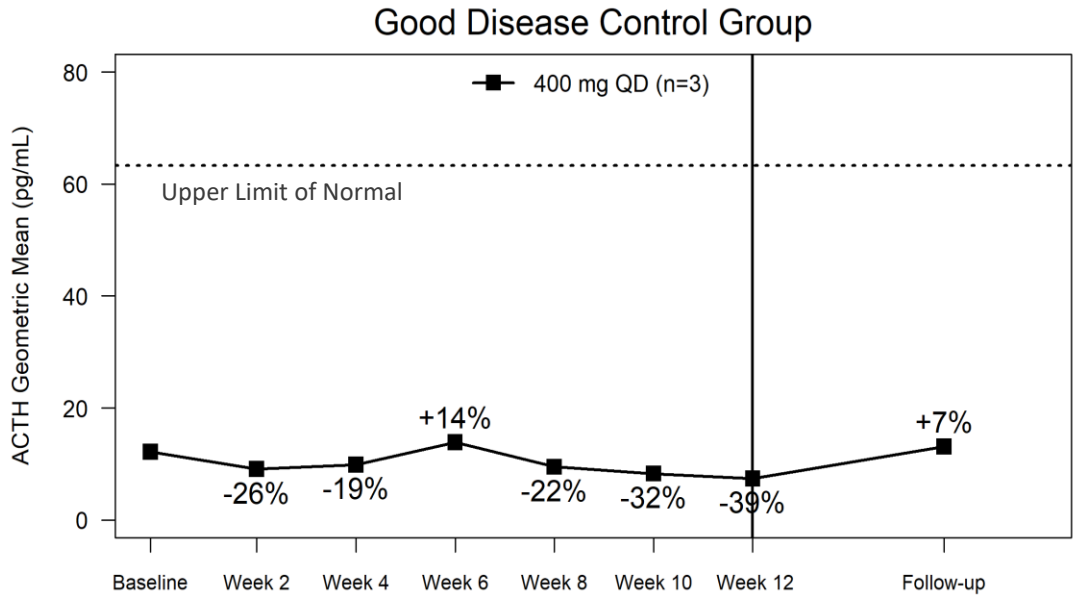

- Normalization of A4 achieved in 40% of patients

3 patients were on dexamethasone and excluded from analysis
*One subject at week 2 prior to discontinuation from the trial and two patient during month 3.
ACTH, adrenocorticotropic hormone; 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].

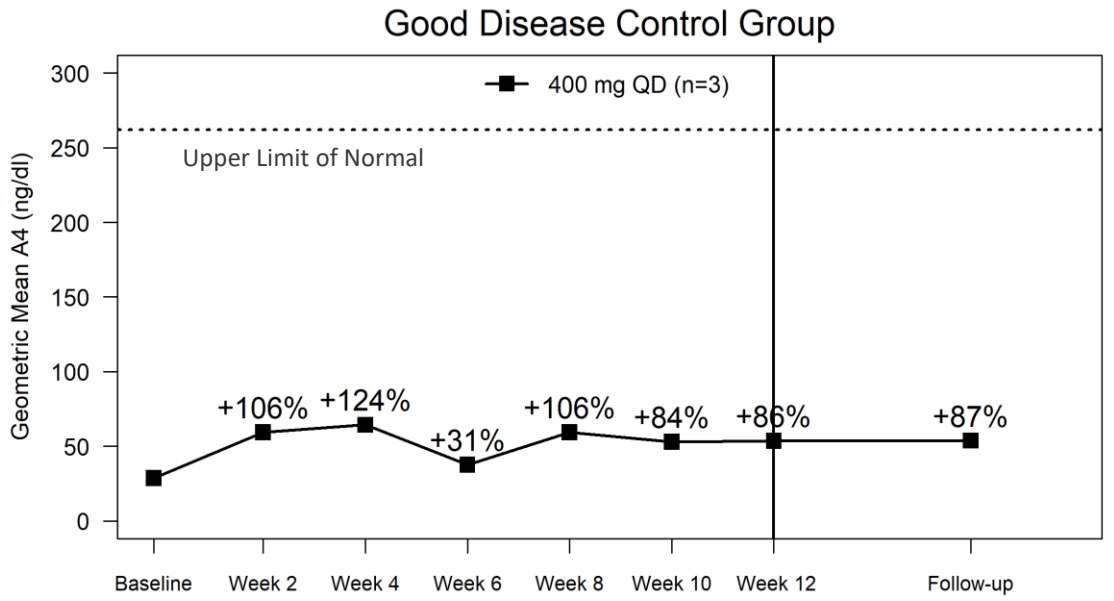
# SPR001-202: NO EXCESSIVE SUPRESSION OF ACTH and A4 IN GOOD DISEASE CONTROL

In the Good Disease Control group, no excessive suppression in ACTH and A4 was seen in the study, including no adverse events of hypoadrenalism.

## GOOD DISEASE CONTROL - ACTH




## GOOD DISEASE CONTROL – A4




3 patients were on dexamethasone and excluded from analysis
ACTH, adrenocorticotropic hormone; 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].

# CAHmelia 203·204

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# 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

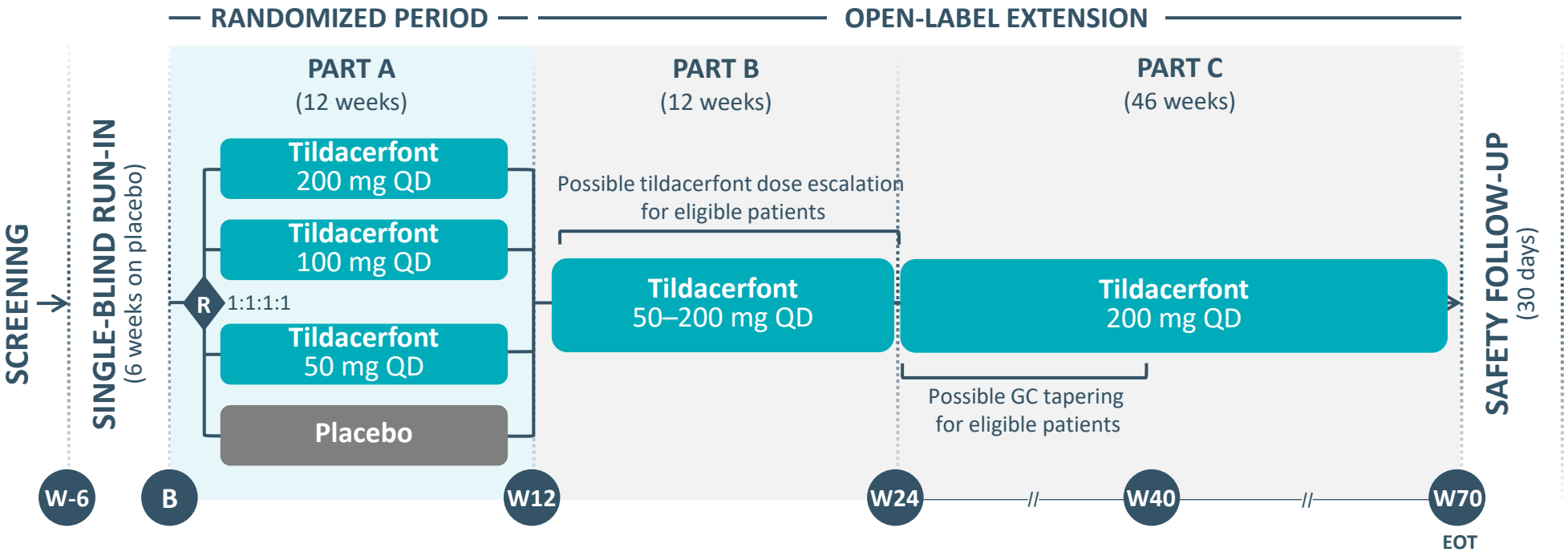
**Key eligibility criteria**

Adult patients ≥18 years

**Classic CAH with poor disease control** (A4 >2.5 × ULN)

Stable GC regimen ≥15 mg/d and ≤60 mg/d HCe

**N=72**




**PRIMARY ENDPOINT**

Percent change from baseline in A4 at Week 12

Study schema is not drawn to scale.

# CAHmelia-203: STUDY ENDPOINTS

## PRIMARY ENDPOINT

- Percent change from baseline in A4 at Week 12

## SECONDARY ENDPOINTS

- Proportion of patients who achieve A4 ≤ ULN at Week 12
- Proportion of patients who achieve 17-OHP ≤ Target at Week 12
- Change in lesion volume of TART(s) at Week 12
- Adverse events and serious adverse events

## KEY EXPLORATORY ENDPOINTS

- Change from baseline in the SF-36 total score at Weeks 12 and 70
- Change from baseline in hirsutism using the Modified Ferriman-Gallwey score at Week 70
- Change from baseline in acne using the Investigator's Global Assessment score at Week 70
- Change in lesion volume of TART(S) at Week 70
- Proportion of subjects with ≥5 mg/day (HCe) reduction with A4 ≤ ULN at Week 70

17-OHP, 17-hydroxyprogesterone; A4, androstenedione; GC, glucocorticoid; 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

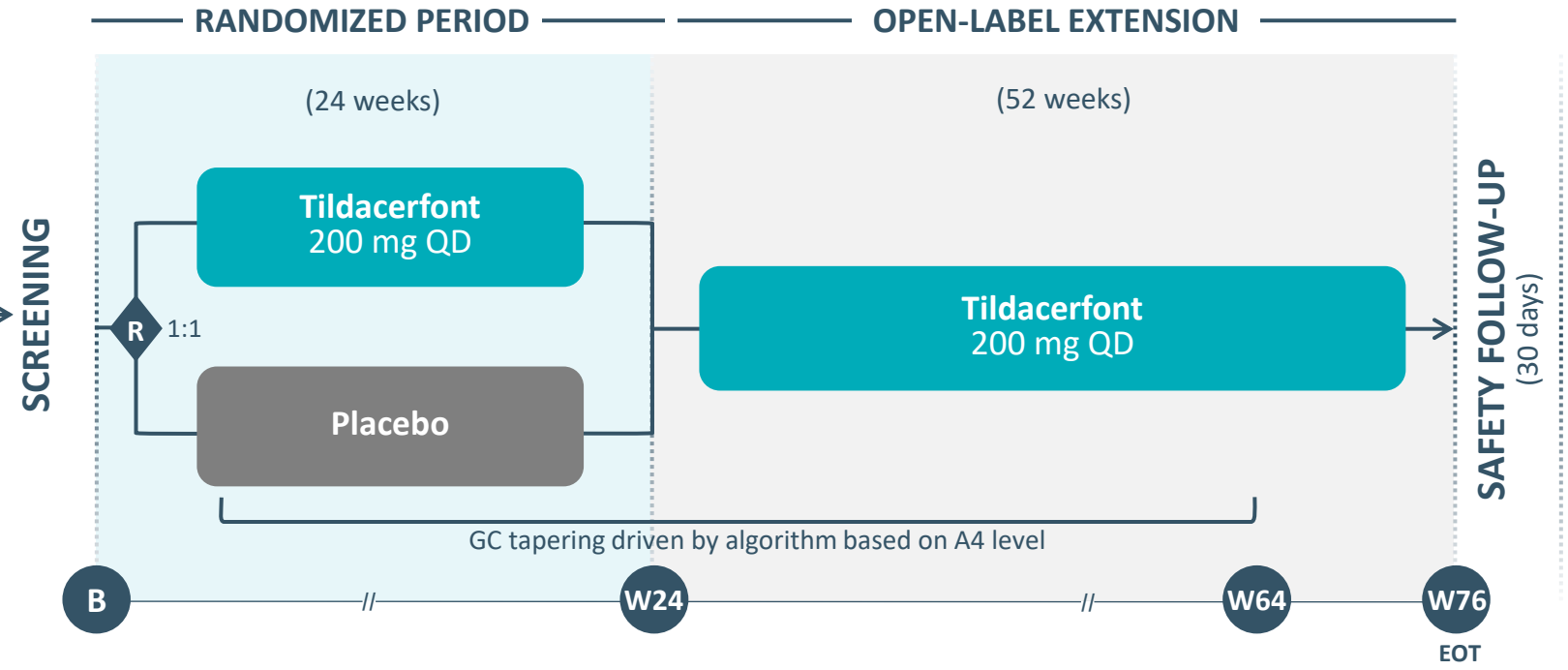
**Key eligibility criteria**

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

**N=90**




**PRIMARY ENDPOINT**

Proportion of subjects with ≥5 mg/day (HCe) reduction with A4 ≤ ULN at Week 24

Study schema is not drawn to scale.

# CAHmelia-204: STUDY ENDPOINTS

## PRIMARY ENDPOINT

- Proportion of subjects with ≥5 mg/day (HCe) reduction with A4 ≤ ULN at Week 24

## SECONDARY ENDPOINTS

- Percent change from baseline in GC dose at Week 24
- Median total cumulative GC dose (HCe) at Week 24
- Change from baseline in HOMA-IR at Week 24
- Percent change from baseline in body weight at Week 24; percent change in body weight from baseline after 52 weeks on tildacerfont treatment
- Proportion of subjects with improvement in at least one cardiovascular risk factor at Week 24

## KEY EXPLORATORY ENDPOINTS

- Proportion of subjects with ≥8 mg/day (HCe) reduction with A4 ≤ ULN at Week 24
- Change from baseline in the SF-36 total score at Week 24
- Change from baseline in HOMA-IR, weight, waist circumference, bone mineral density after 52 weeks of tildacerfont treatment
- Proportion of subjects with GC dose ≤25 mg/day (HCe) with A4 ≤ ULN at Week 24 and after 52 weeks of tildacerfont treatment

A4, androstenedione; GC, glucocorticoid; HCe, hydrocortisone equivalent(s); HOMA-IR, homeostatic model assessment of insulin resistance; ULN, upper limit of normal.

# Pediatric Classic CAH Overview

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# NOVEL THERAPIES NEEDED TO BALANCE ANDROGENS & GCs IN CHILDREN

**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.

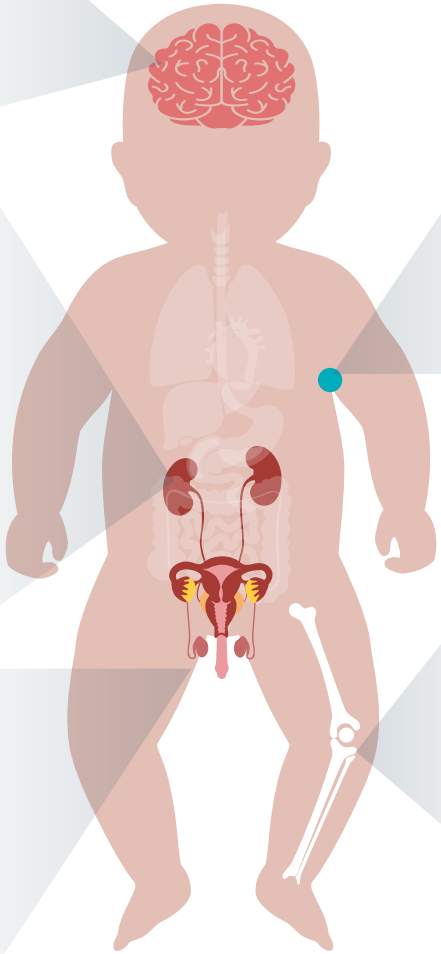
1. Claahsen-van der Grinten HL, *et al. Endocr Rev.* 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print]; 2. Pijnenburg-Kleizen KJ, *et al. J Pediatr Endocrinol Metab.* 2019;32(10):1055–63; 3. Merke DP, *et al. N Engl J Med.* 2020;383:1248–61.

# CLASSIC CAH PRESENTS IN INFANCY & EARLY CHILDHOOD

## BEHAVIORAL
Increased prevalence of ADHD[4]

## ADRENAL (SALT-WASTING) CRISIS
- Risk of potentially fatal electrolyte imbalance, acidosis, and shock begins at birth[1] ,precipitated by acute illness, often infection[2]
- Life-threatening hypoglycemia with seizures is more common in children[1,2]

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



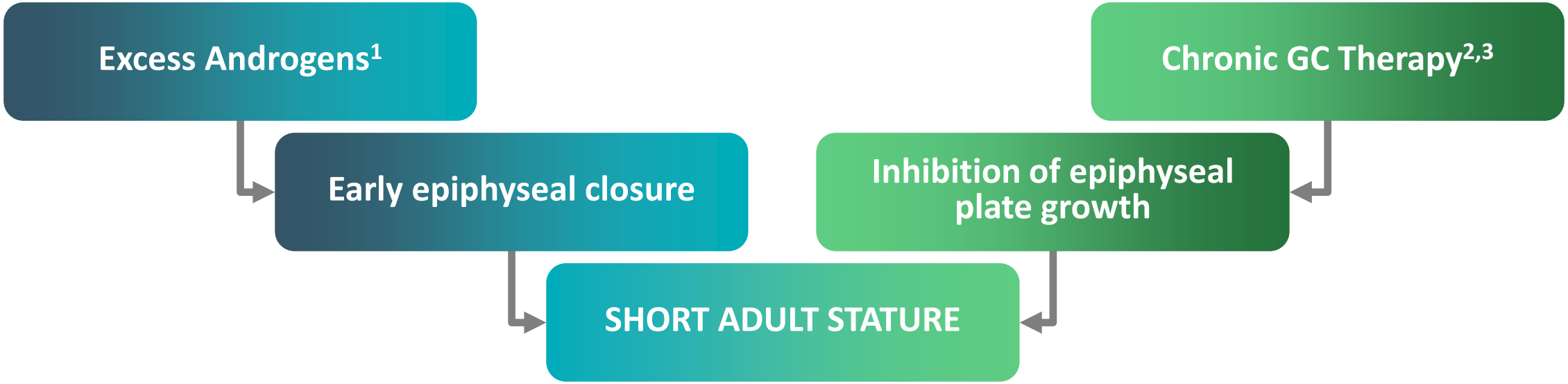
## PUBARCHE[2,3]
- Early childhood virilization
- Early onset adult body odor

## 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]

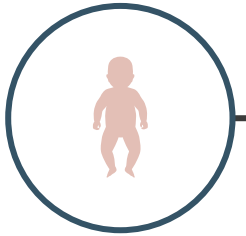
Increased risk of fractures[6]

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.

# MANAGEMENT GOALS OF PEDIATRIC CAH VARY WITH AGE

## Early childhood to puberty

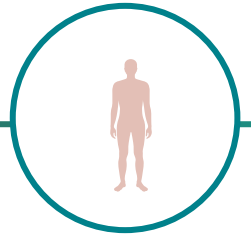


**Goal of therapy:**
Maximize androgen suppression
for normal growth and pubertal development

**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

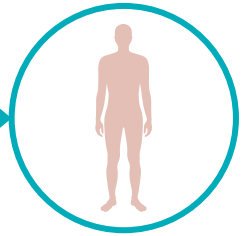


**Goal of therapy:**
Maintain adequate androgen suppression
despite rapid HC metabolism in puberty

**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.

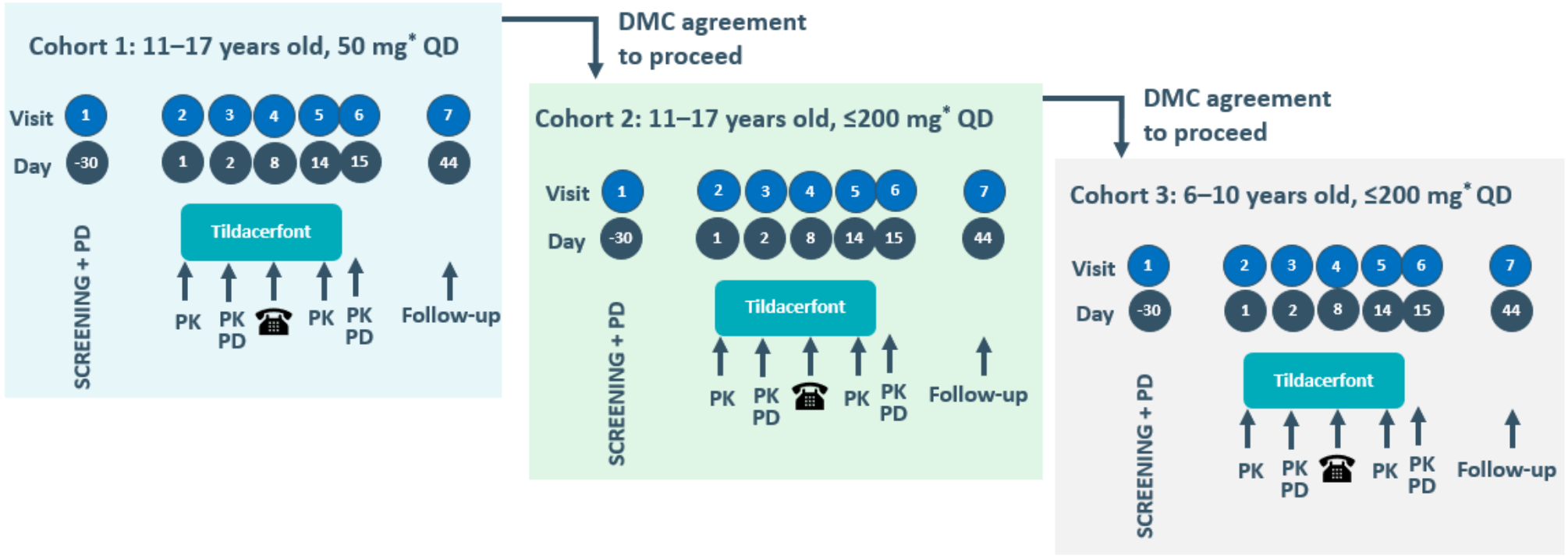
1. Claahsen-van der Grinten HL, *et al. Endocr Rev.* 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print].

# PHASE 2 STUDY IN PEDIATRIC CLASSIC CAH

## Key eligibility criteria

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

**N=20**




**PRIMARY ENDPOINT**
Safety

**SECONDARY ENDPOINT**
PK on Days 1 and 14

**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; 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.

# Polycystic Ovary Syndrome (PCOS) Overview

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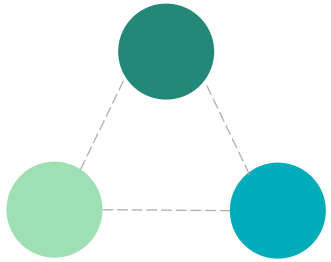
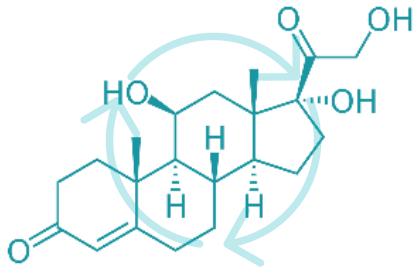
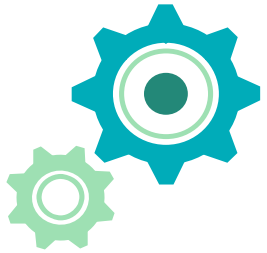
# PCOS IS A COMMON, CHRONIC ENDOCRINE DISORDER



Heterogeneous in nature: typically characterized by **hyperandrogenism, ovulatory dysfunction,** and **polycystic ovaries**[1]




Symptoms are linked to **androgen excess** and **metabolic dysfunction**[2]



Results from a complex interplay of **hereditary and environmental factors;** exact cause is not fully elucidated[3]

Affects up to **12% of reproductive aged women** in the US; the **most common cause of anovulatory female infertility**[3]

PCOS, polycystic ovary syndrome.

1. Williams T, et al. *Am Fam Physician*. 2016;94(2):106-113. 2. McCartney CR, et al. *New Engl J Med*. 2016;375:54-64. 3. Centers for Disease Control and Prevention. PCOS (polycystic ovary syndrome) and diabetes. Accessed October 15, 2021. https://www.cdc.gov/diabetes/basics/pcos.html.

# PCOS LEADS TO VARIED SYMPTOMATOLOGY AND LONG-TERM HEALTH RISKS

## INTEGUMENTARY[1,2]

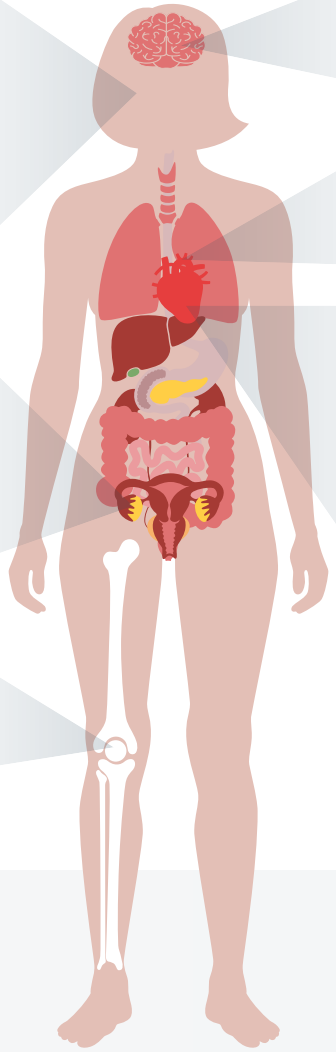
- Hirsutism
- Virilization
- Acne
- Acrochordons
- Androgenic alopecia
- Acanthosis nigricans

## REPRODUCTIVE[1,2]

- Polycystic ovaries
- Irregular menses
- Infertility
- Endometrial cancer
- Pregnancy complications

## MUSCULOSKELETAL[3]

- Reduced bone mineral density



## PSYCHIATRIC[1,2]

- Anxiety
- Depression

## RESPIRATORY[1,2]

- Obstructive sleep apnea

## CARDIOVASCULAR & METABOLIC[1,2]

- Metabolic syndrome
- Obesity
- T2DM
- CVD
- Insulin resistance
- Dyslipidemia
- Hypertension

**CLINICAL FEATURES OF PCOS**

**CONSEQUENCES OF PCOS**

CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus; PCOS, polycystic ovary syndrome.

1. McCartney CR, et al. *New Engl J Med*. 2016;375:54-64. 2. Deswal R, et al. *J Hum Reprod Sci.* 2020;13:261-271. 3. Katulski K, et al. *J Endocrinol Invest.* 2014;37:1219–1224.

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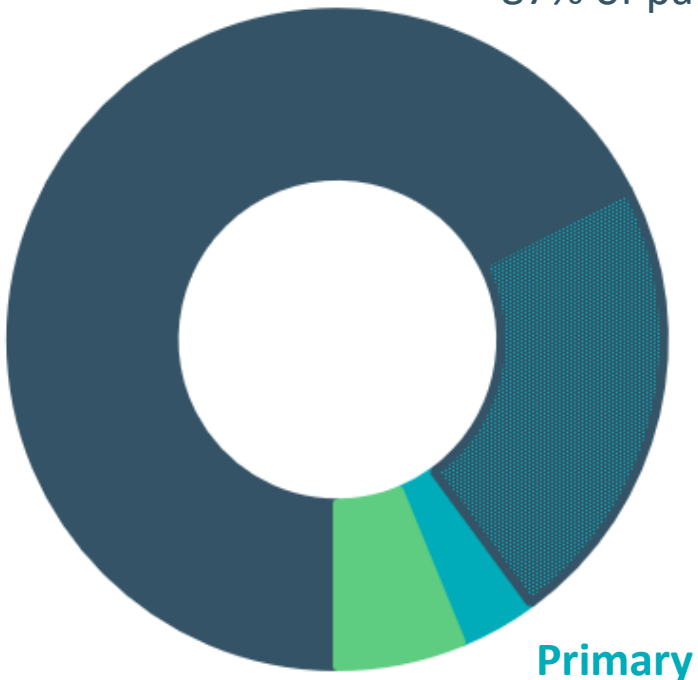
# PCOS CAN BE CLASSIFIED ACCORDING TO SOURCE OF EXCESS ANDROGENS[1]

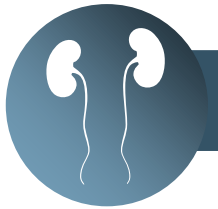



| Source of Androgen | GnRHag 17-OHP Response | DAST Testosterone Response | ACTH DHEAS Response |
|---|---|---|---|
| Primary FOH | High | High | Normal |
| **Mixed pathology** | **High** | **High** | **High** |
| **Primary FAH** | **Normal** | **Normal** | **High** |
| Other | Normal | Normal | Normal |

17-OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotropic hormone; DAST, dexamethasone androgen suppression test; DHEAS, dehydroepiandrosterone sulfate; FAH, functional adrenal hyperandrogenism; FOH, functional ovarian hyperandrogenism; GnRH, gonadotropin-releasing hormone; HPA, hypothalamic–pituitary–adrenal; HPO, hypothalamic–pituitary–ovarian; PCOS, polycystic ovary syndrome.

1. Rosenfield RL, Ehrmann DA. *Endocrine Rev*. 2016;37:467-520. 2. Moran C, et al. *Fertil Steril*. 1999;71:671-674.

# CURRENTLY, ONLY SYMPTOMATIC TREATMENT EXISTS FOR PCOS



## HYPERANDROGENEMIA

**Hormonal contraception:** 1st line treatment for hirsutism and acne

**Antiandrogens:** typically used as an adjunct to hormonal contraception to treat hirsutism

## INFERTILITY

**Estrogen modulators (clomiphene, letrozole):** 1st line for anovulatory infertility

**Insulin sensitization (metformin):** adjuvant to prevent OHSS during IVF

## IRREGULAR MENSTRUATION

**Hormonal contraception:** 1st line treatment for menstrual irregularities

**Insulin sensitization (metformin):** alternative for women intolerant to hormonal contraception

## RISK MANAGEMENT

**Lifestyle changes:** weight loss via calorie restriction and exercise

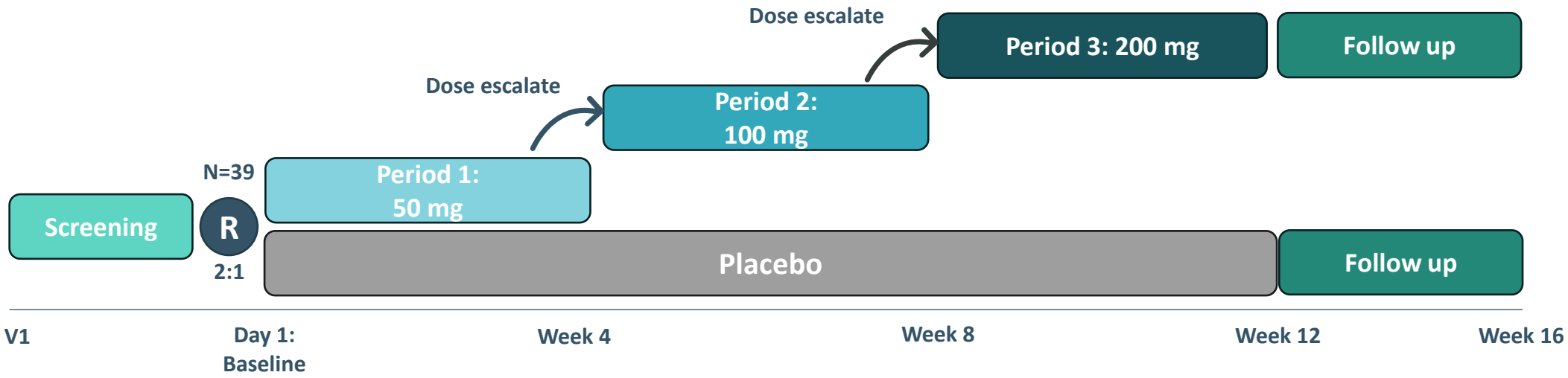
**Insulin sensitization (metformin):** alternative option if lifestyle changes yield insufficient results

IVF, in vitro fertilization; OHSS, ovarian hyperstimulation syndrome; PCOS, polycystic ovary syndrome.

Sirmans SM, Pate KA. *Clin Epidemiol.* 2014;6:1–13.

# PHASE 2 CLINICAL PROOF OF CONCEPT STUDY

## A Randomized, Placebo-Controlled, Dose Escalation Study to Evaluate the Safety and Efficacy of Tildacerfont in Adult Subjects with PCOS and Elevated Adrenal Androgens




**Key eligibility criteria**

- Females 18—40 years old with PCOS
- BMI <38 kg/m$^2$
- DHEAS > ULN

**Strata**

- DHEAS (baseline DHEAS ≤ 1.2xULN, DHEAS > 1.2xULN)

**Primary endpoint**

- Absolute change from baseline in DHEAS

**Additional endpoints**

- Safety and tolerability
- Proportion of subjects with: ≥ 30% reduction from baseline in DHEAS and DHEAS ≤ ULN
- Change from baseline in ACTH, 17OHP, T, A4, 11OHA4, 11OHT, 11KA4, and 11KT

11KA4, 11-ketoandrostenedione; 11KT, 11-ketotestosterone; 11OHA4, 11β-hydroxyandrostenedione; 11OHT, 11β-hydroxytestosterone; 17OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; BMI, body mass index; DHEAS, dehydroepiandrosterone sulfate; PCOS, polycystic ovary syndrome; T, testosterone; ULN, upper limit of normal

# Financial Highlights and Anticipated Milestones

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# COMMERCIAL OPPORTUNITY – CLASSIC CAH

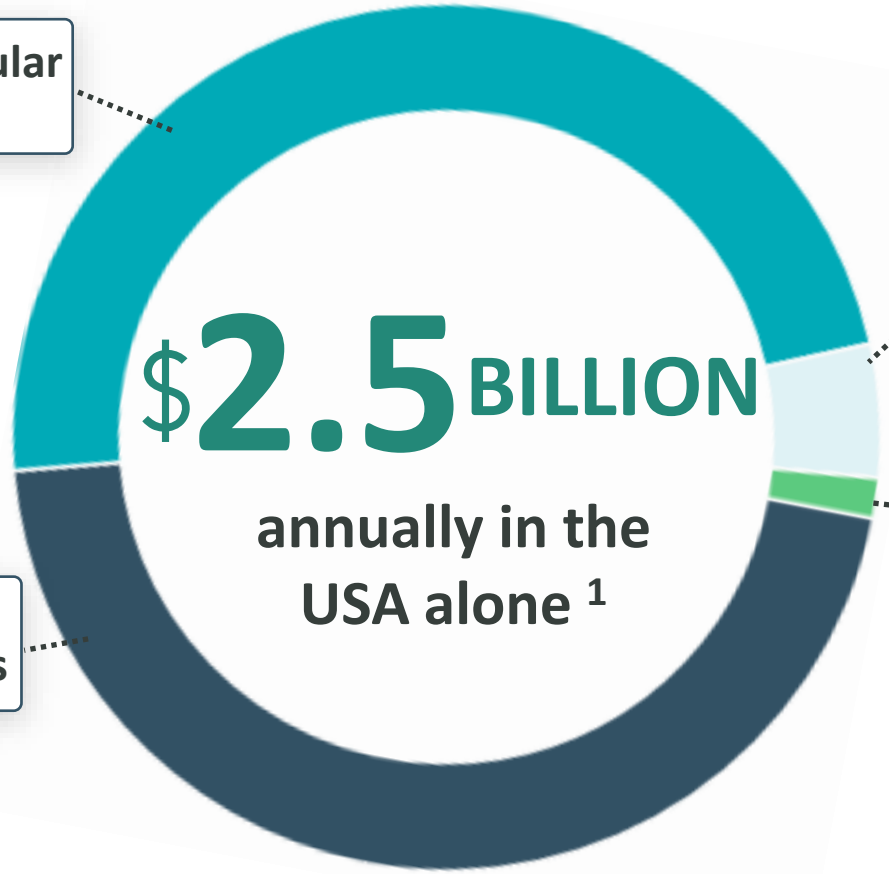
- Large rare disease, up to 80,000 patients in U.S./EU
- $3B+ global market opportunity[1]
- Orphan drug pricing anticipated
- IP: Composition of Matter (2028)[2] / Methods (2038)
- Orphan Drug Designation: U.S. (7.5 years) / EU (12 years)[3]

1. Based on industry reports
2. Absent any patent term adjustments or extensions
3. Assumes 6-month (U.S.) and 2-year (EU) extension if clinical trials are conducted in accordance with agreed-upon pediatric investigational plan

# COMMERCIAL OPPORTUNITY – PCOS

**~48%** Metabolic and vascular complications

**~5%** Pregnancy-related complications




**~46%** Reproductive endocrine morbidities

**<2%** Initial diagnostic evaluation

**Effective treatments for PCOS may mitigate serious sequelae, potentially reducing associated healthcare costs**

PCOS, polycystic ovary syndrome.

1. Riestenberg C, et al. *J Clin Endocrinol Metab*. 2021. doi: 10.1210/clinem/dgab613. Online ahead of print. Estimated market size of Primary Functional Adrenal Hyperandrogenism (FAH) and Mixed Pathology (Primary FAH and Functional Ovarian Hyperandrogenism), or 30% of the overall market.

# FINANCIAL HIGHLIGHTS

***Capital Structure and Summary Financials as of June 30, 2022***

| Capital Structure | Shares (M) |
|---|---|
| Shares Outstanding | 23.6 |
| Equity Awards Issued and Outstanding | 4.4 |
| Warrants | - |
| Fully Diluted Shares Outstanding | 28.0 |

| Financials | 000's |
|---|---|
| Cash, Cash Equivalents and Investments | $99,100 |
| Debt[1] | $5,000 |

1. Principal balance of debt owed as of June 30, 2022. Does not include discounts on debt recorded pursuant to U.S. GAAP requirements.

# KEY ANTICIPATED MILESTONES

| | |
|---|---|
| 1H2023 | Topline results from the Phase 2 POC clinical trial in PCOS |
| 1H2023 | Topline safety results from cohort 1 of the Phase 2 open-label clinical trial in pediatric classic CAH |
| 2H2023 | Topline results from CAHmelia-203 in adult classic CAH |
| 2H2024 | Topline results from CAHmelia-204 in adult classic CAH |

# INVESTMENT HIGHLIGHTS

| | |
|---|---|
| **Large Orphan Market Primed for Innovation** | **~$3B+ market opportunity in CAH with high unmet need, low competitive intensity, and no new therapeutic options in ~50 years** |
| **Transformative Treatment Paradigm in CAH** | **Tildacerfont is a second generation CRF-1 receptor antagonist with clear MOA, designed to reduce disease and steroid burden** |
| **Robust Clinical Data in Adult CAH** | **Two positive Phase 2a studies demonstrating ~80% reduction in biomarkers; 235 subjects dosed across eight studies to date** |
| **Potentially Registrational Studies Ongoing** | **Data from two studies in Adult-CAH patients expected in 2H-2023 (CAHmelia-203) and 2H-2024 (CAHmelia-204)** |
| **Multiple Expansion Opportunities** | **Phase 2 programs initiated in pediatric CAH and polycystic ovary syndrome (PCOS) with data expected in 1H-2023** |
| **Strong IP Protection** | **Comprehensive IP portfolio with exclusivity to 2038 combined with Orphan Drug Designation in U.S. and E.U.** |

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