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

Corporate Presentation

September 15, 2021

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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

Tildacerfont poised to transform treatment paradigm in classic CAH	**Two late-stage clinical studies initiated; Enriched patient populations across two studies designed to observe clinically meaningful outcomes**
Multiple expansion opportunities	**Initiation of Phase 2 programs in pediatric classic CAH (6 to 17 years of age) and polycystic ovary syndrome (FAH-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**

Classic CAH Overview

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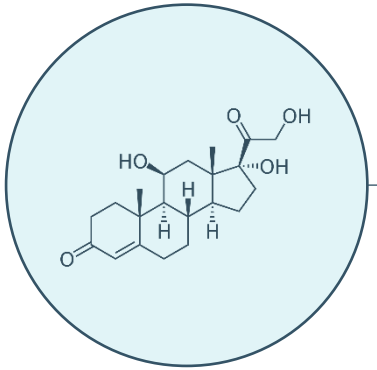
CLASSIC CAH DISEASE OVERVIEW

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

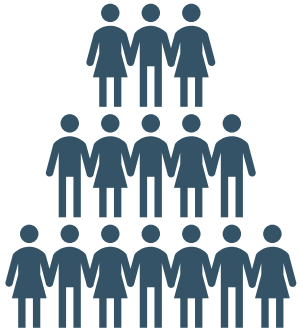


Classic CAH is an autosomal recessive disease characterized by an inability to produce cortisol, leading to a chronic imbalance of key hormones and an overprodution of adrenal androgens.

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., 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

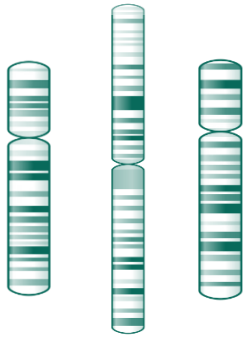


Classic 21-OHD CAH[1]

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]

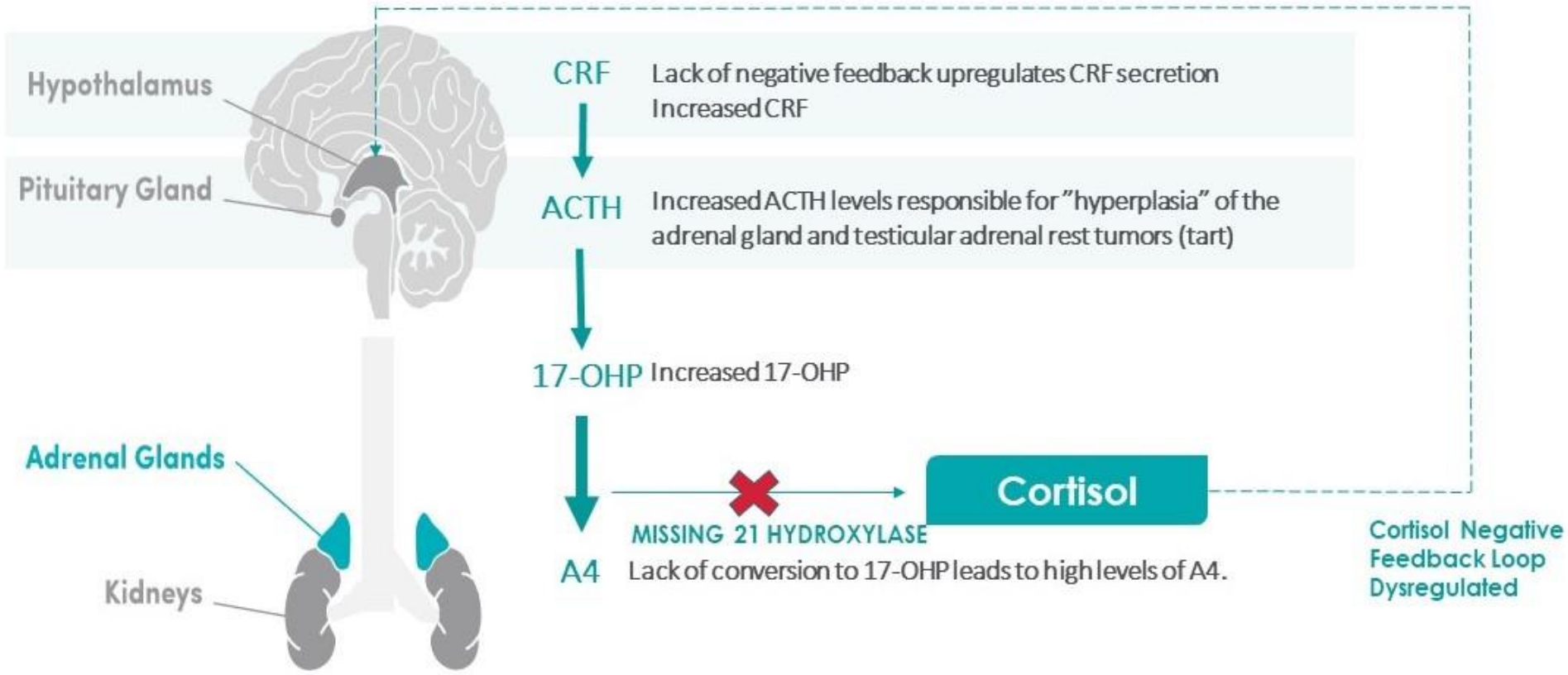
- Indicated when prior children have CAH
- Fetal hormone levels and DNA can be analyzed from amniotic fluid
- Fetal DNA analysis is also performed via chorionic villus sampling

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

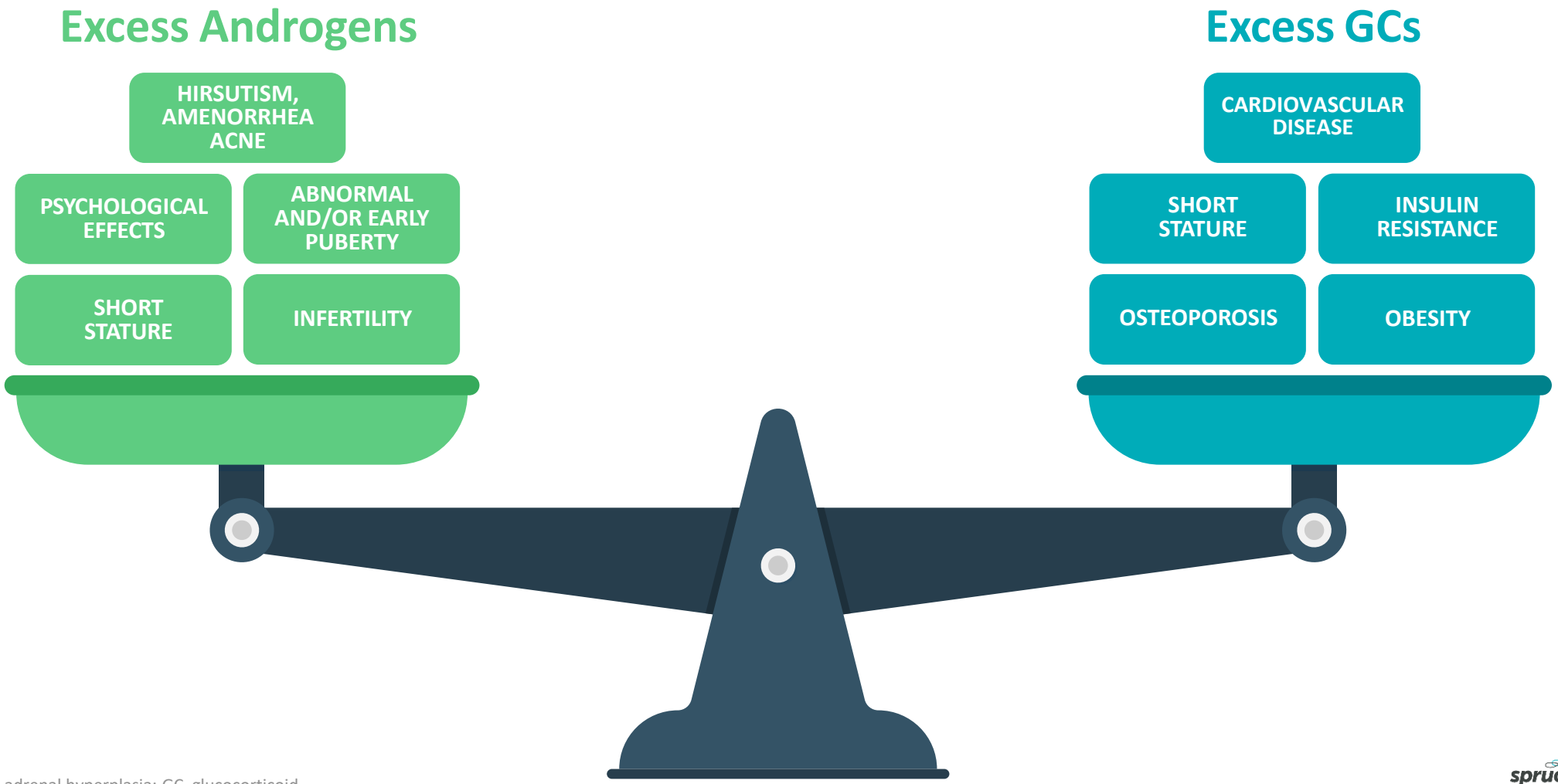
Lack of cortisol leads to overproduction of ACTH and precursor steroid molecules, resulting in excessive adrenal androgens



The dysregulation of the HPA axis in classic CAH.

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.

Tildacerfont

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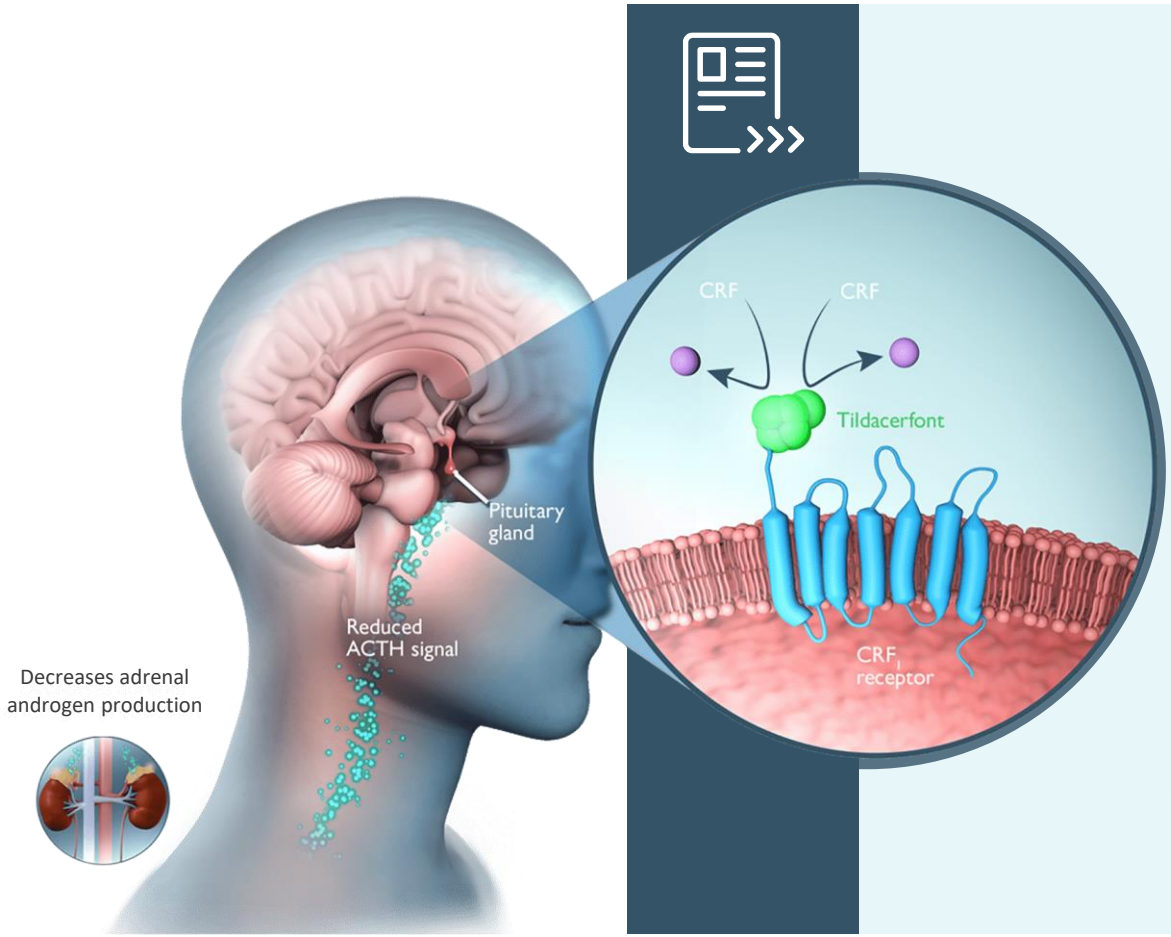
TILDACERFONT IS A NOVEL CRF_1 RECEPTOR ANTAGONIST



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.

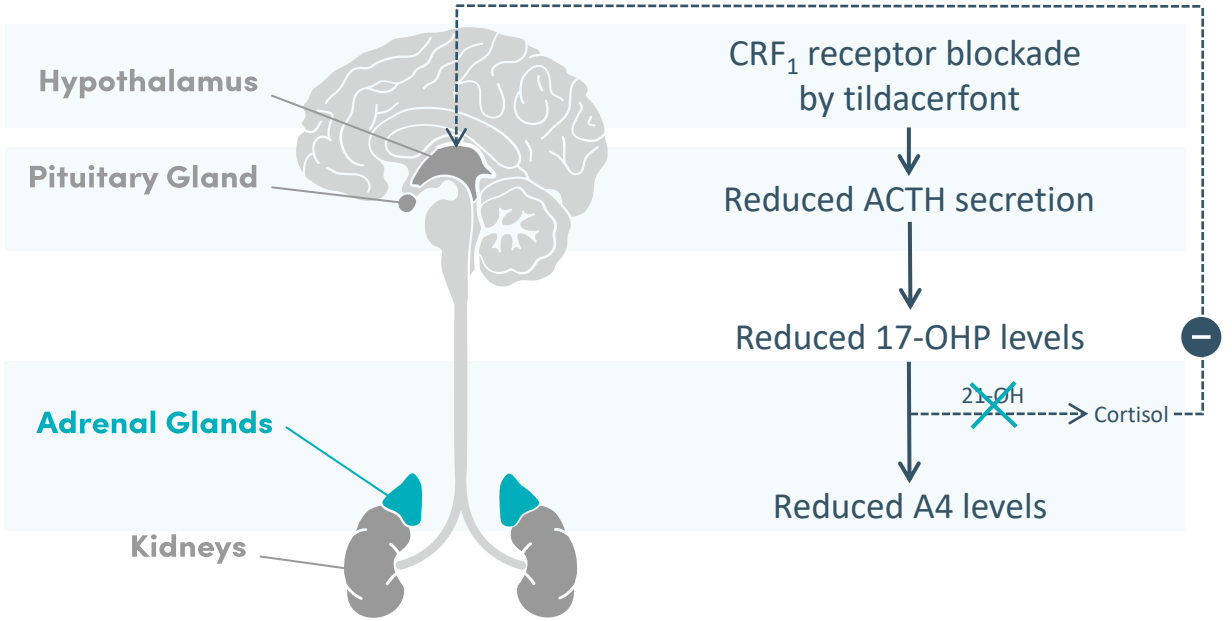
1. Sarafoglou K, *et al. J Clin Endocrinol Metab.* 2021:dgab438. DOI: https://doi.org/10.1210/clinem/dgab438 [Epub ahead of print].

TILDACERFONT 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.

Adult Classic CAH
Clinical Development Program

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KEY FINDINGS FROM PHASE 1 AND 2 STUDIES: SUMMARY

Two distinct patient populations:[1]

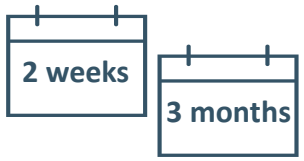
Poor disease control

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]

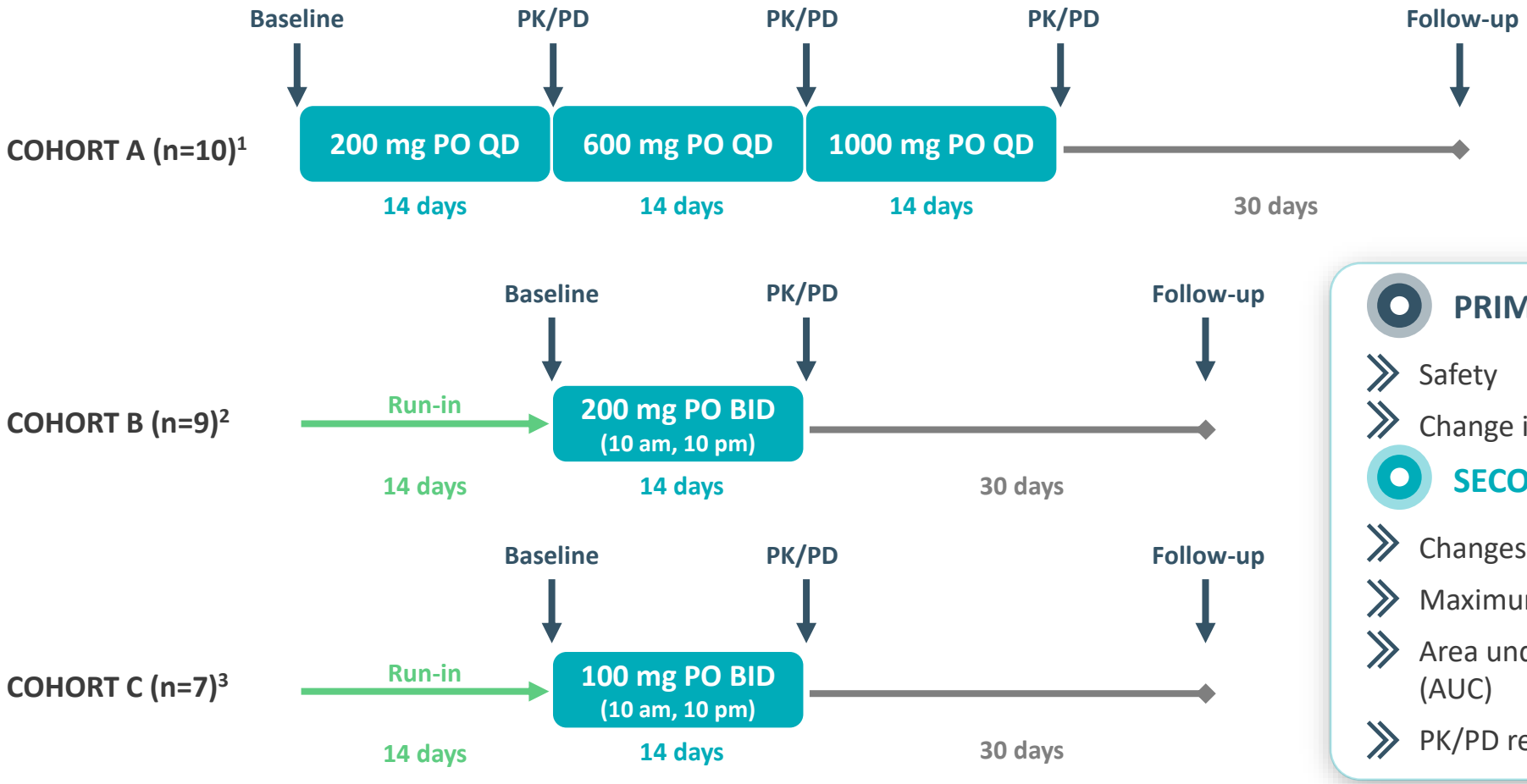
No drug-related SAEs reported to date[1,2]

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]

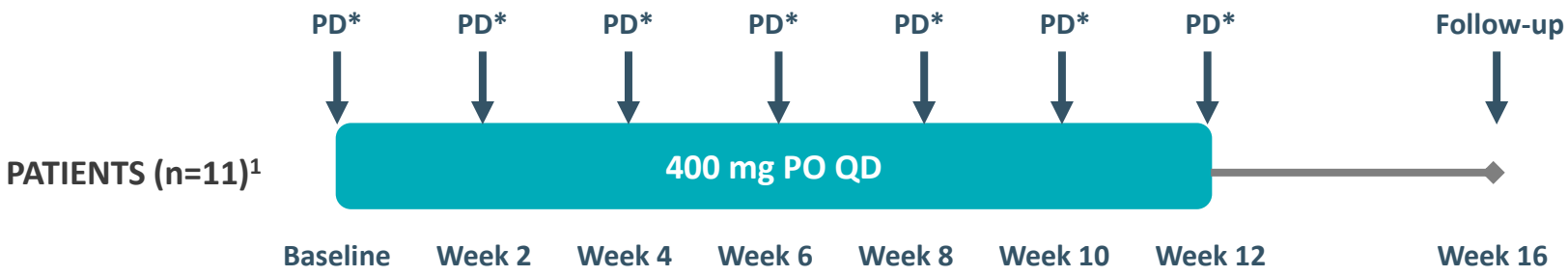
- Changes in PD markers
- Maximum plasma concentration (C_{max})
- Area under the concentration-time curve (AUC)
- PK/PD relationships

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, multicenter, open-label study[1]



PRIMARY ENDPOINT[2]

- Safety and tolerability

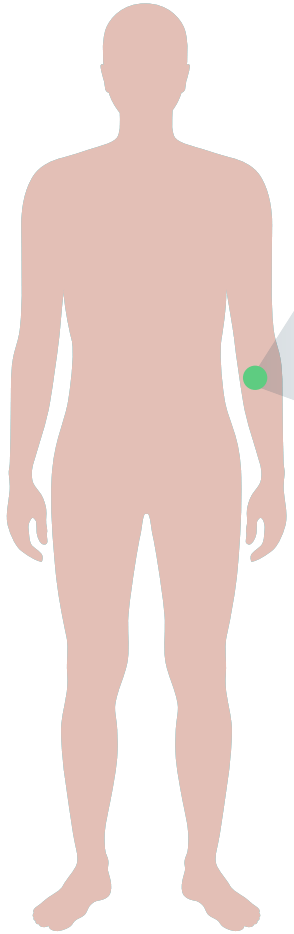
SECONDARY ENDPOINTS[2]

- 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).

UNMET MEDICAL NEEDS ACCORDING TO DISEASE STATUS

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



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.

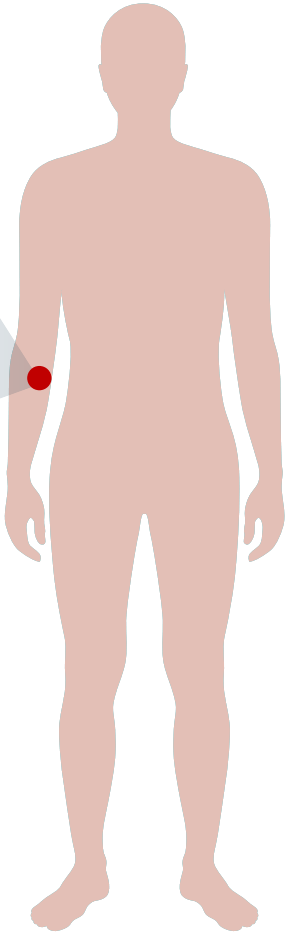
1. Claahsen-van der Grinten H, *et al. Endocr Rev.* 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print]; 2. Speiser P, *et al. J Clin Endocrinol Metab.* 2018;103:4043-88.

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



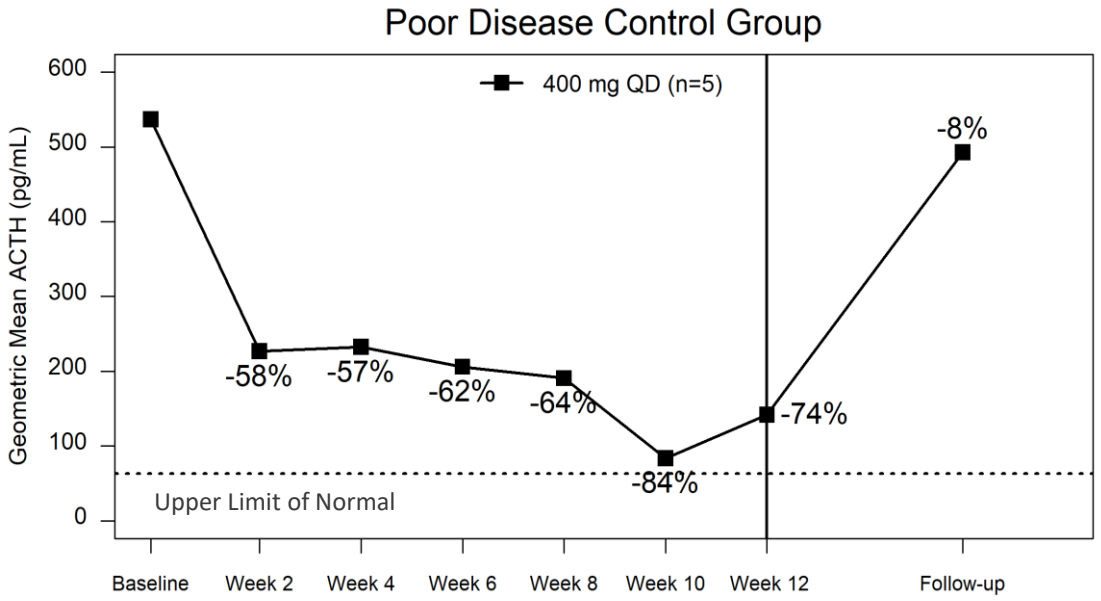
CAH, congenital adrenal hyperplasia; GC, glucocorticoid.

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 IN POORLY CONTROLLED DISEASE

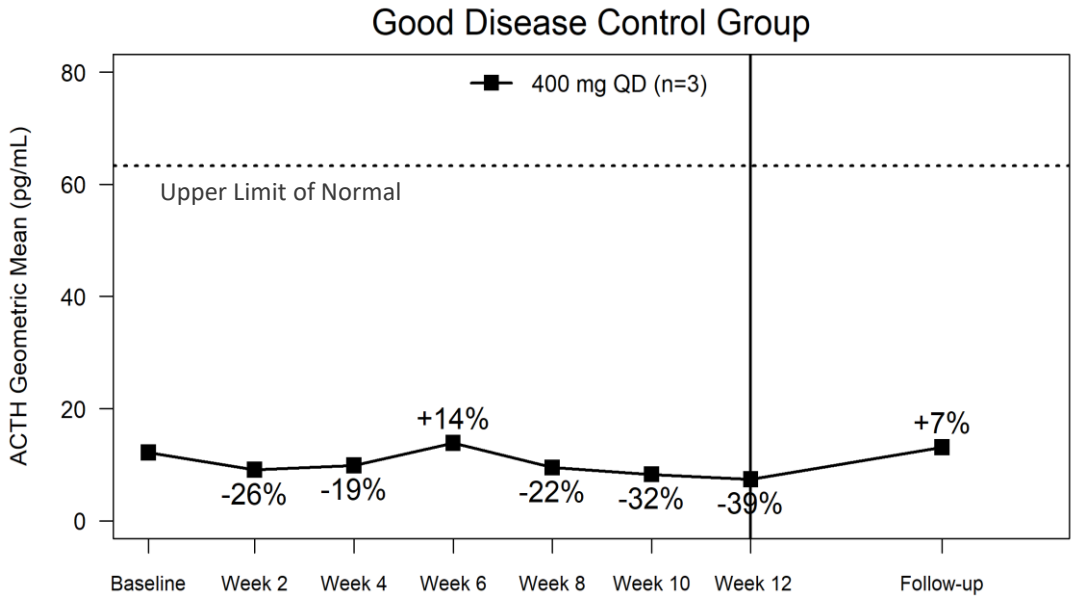
In the poor disease control group, a robust initial drop in ACTH was seen at week 2, followed by further reduction over 12 weeks; there was a maximum reduction in ACTH of **84%** at week 10 of the study in the poor disease control group

POOR DISEASE CONTROL



- Normalization of ACTH achieved in 60% of patients*

GOOD DISEASE CONTROL



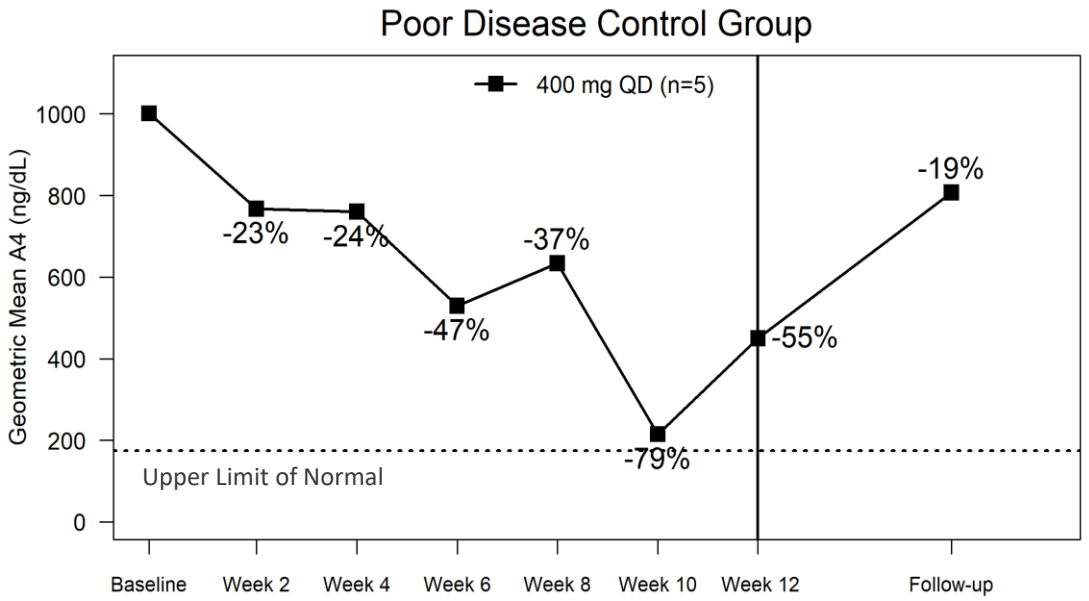
- No excessive suppression of adrenal function

*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 A4 IN POORLY CONTROLLED DISEASE

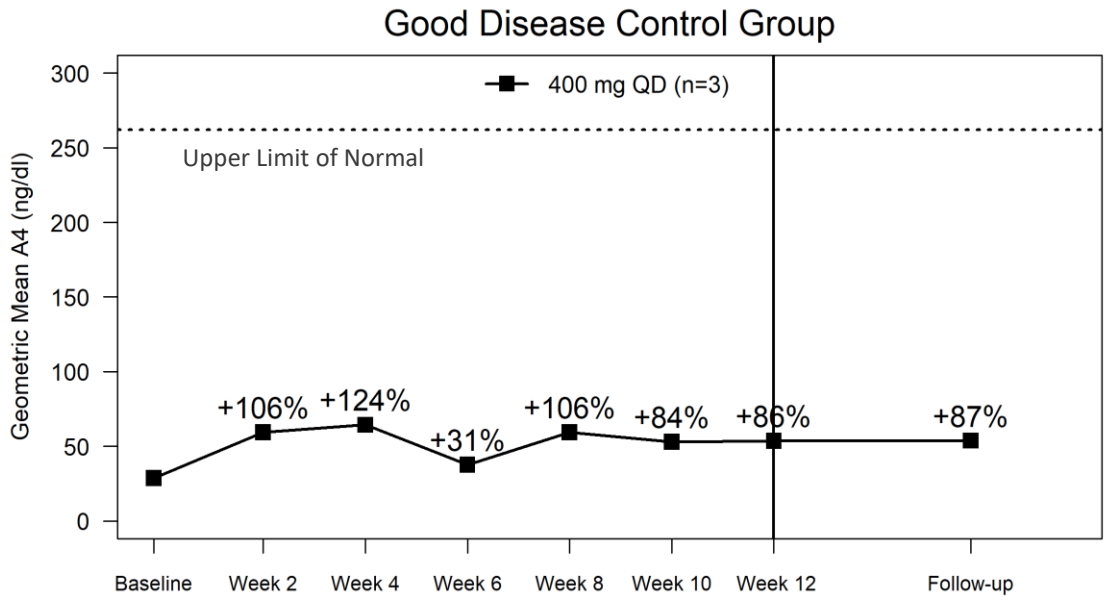
In poor disease control group, an initial drop in A4 was seen at week 2, followed by further reduction over 12 weeks; there was a maximum reduction in A4 of **79% at week 10** of study in the poor disease control group

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].

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

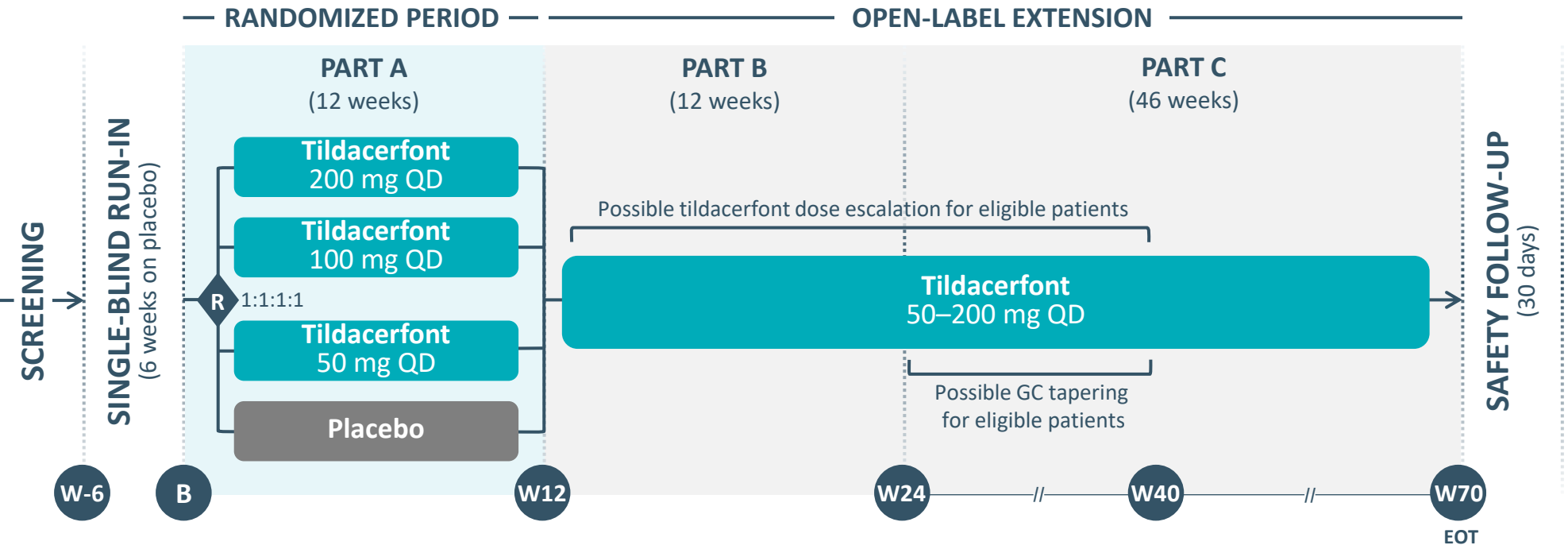
Key eligibility criteria

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 change from baseline to Week 12 in 17-OHP and ACTH
- Proportion of patients achieving the following at Week 12: A4 ≤ULN, 17-OHP ≤4 × ULN, ACTH ≤ULN
- Absolute change from baseline to Week 12 in A4, 17-OHP, and ACTH
- Adverse events and serious adverse events

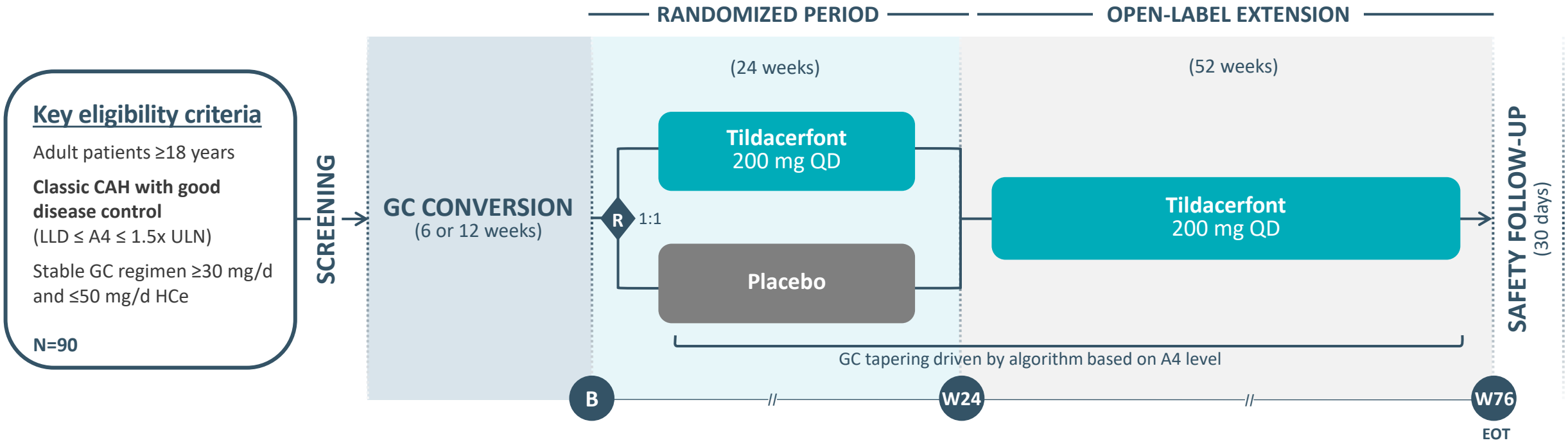
KEY EXPLORATORY ENDPOINTS

- Percentage change from baseline to Week 70 in A4, 17-OHP, and ACTH
- Proportion of patients achieving the following at Week 70: A4 ≤ULN, 17-OHP ≤4 × ULN, ACTH ≤ULN
- Absolute change from baseline to Week 70 in A4, 17-OHP, and ACTH
- Change from baseline to Week 12/Week 70 in QoL, clinical CAH symptoms, 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 (baseline to Week 24; Week 24 to Week 76; baseline to Week 76)
- Change from baseline to Week 24/Week 76 in A4, 17-OHP, and ACTH
- Change from baseline to Week 24/Week 76 in QoL, clinical CAH symptoms, markers of bone turnover, metabolic parameters (glucose, lipids, blood pressure, BMI, 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.

Pediatric Classic CAH Overview

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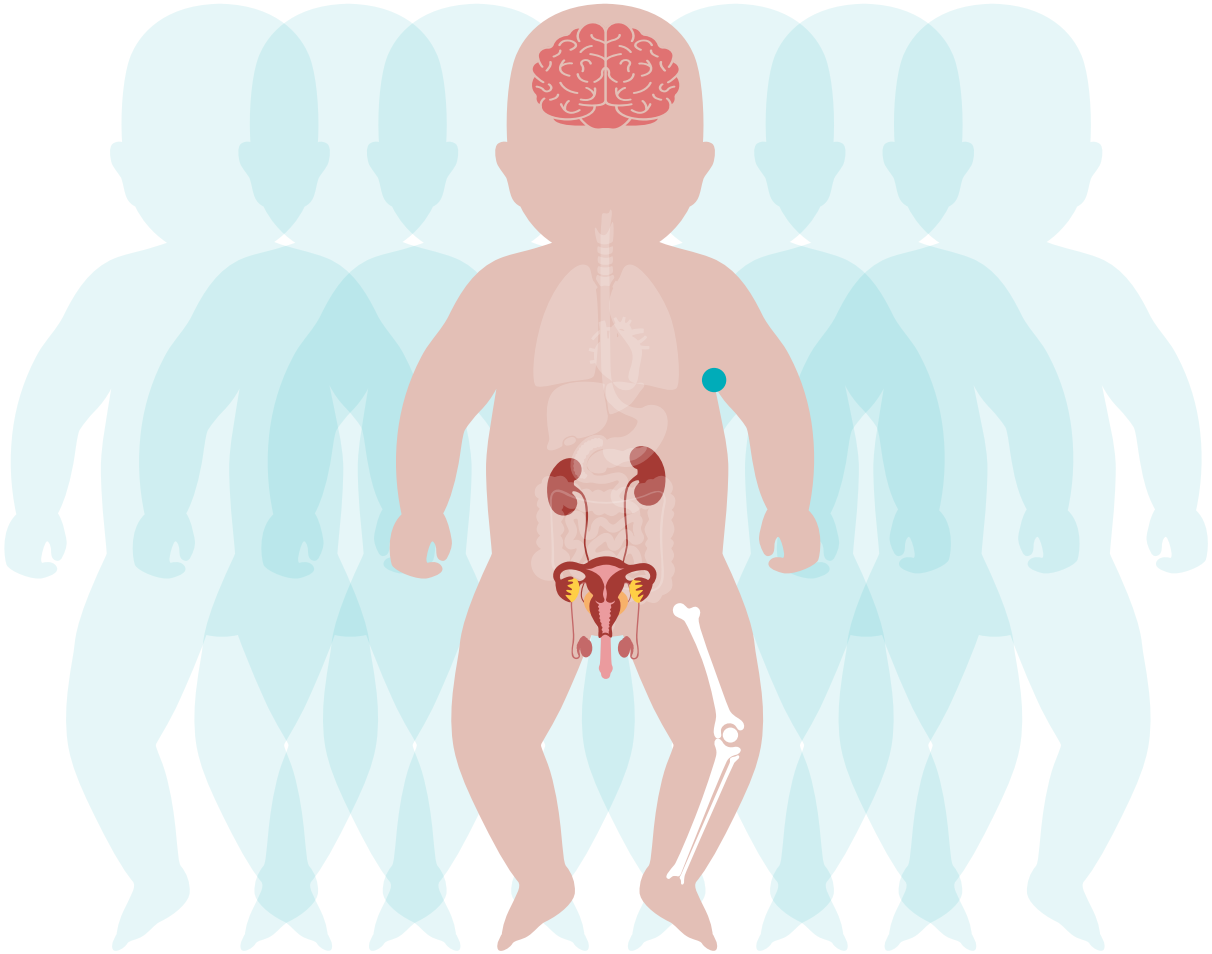
CLASSIC CAH PRESENTS IN INFANCY & EARLY CHILDHOOD



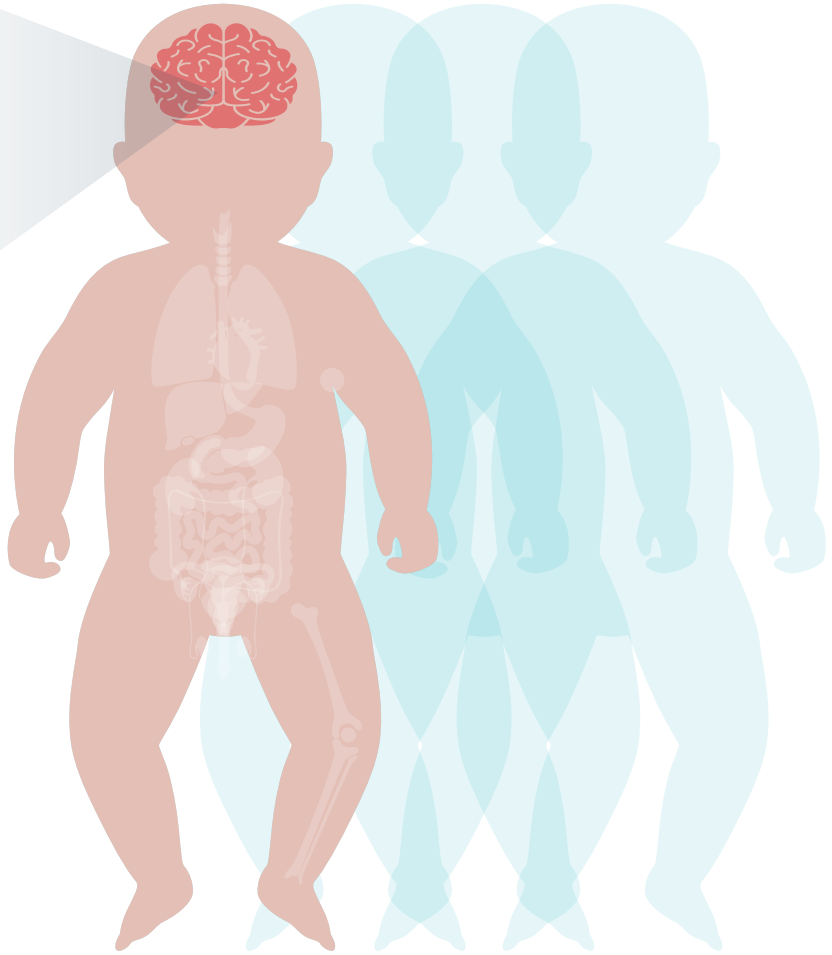
CAH, congenital adrenal hyperplasia

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]



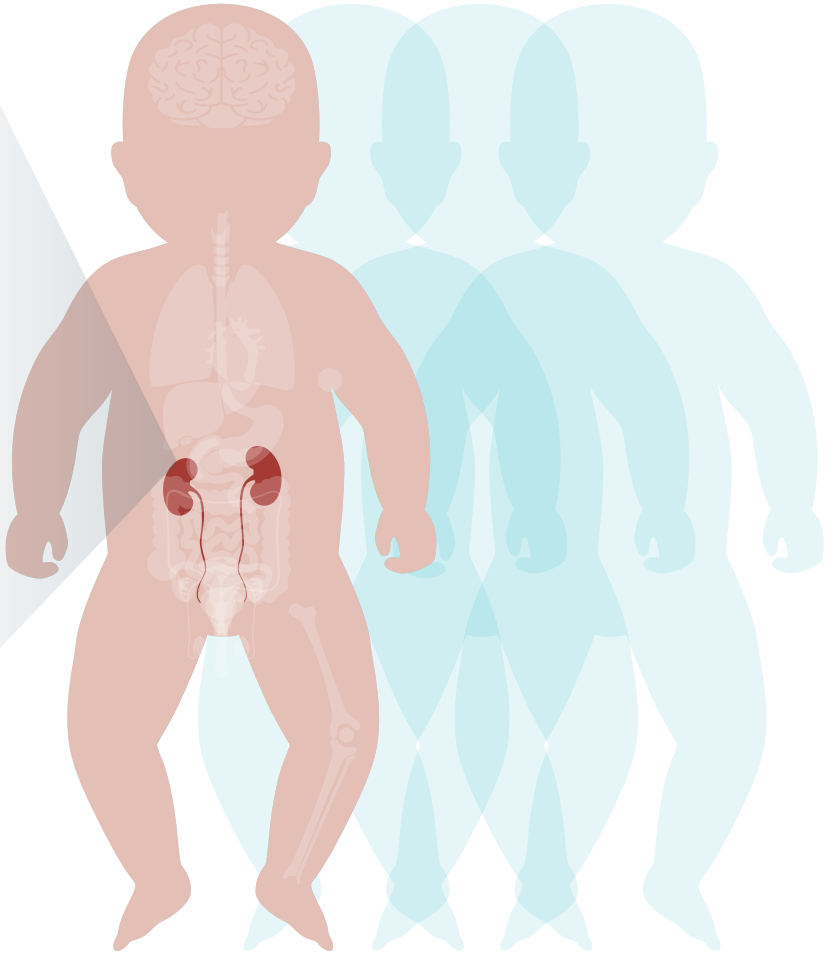
ADHD, attention deficit hyperactivity disorder; CAH, congenital adrenal hyperplasia.

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];
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

ADRENAL (SALT-WASTING) CRISIS

- Risk of potentially fatal electrolyte imbalances, 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]



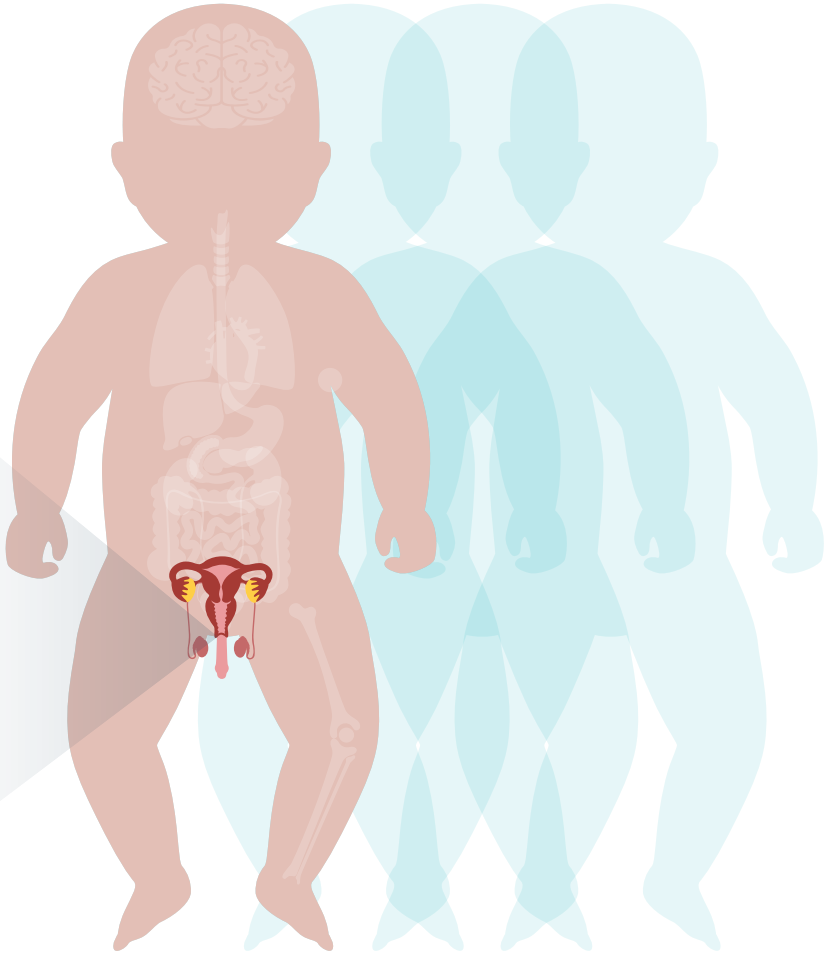
CAH, congenital adrenal hyperplasia

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

GENITOURINARY

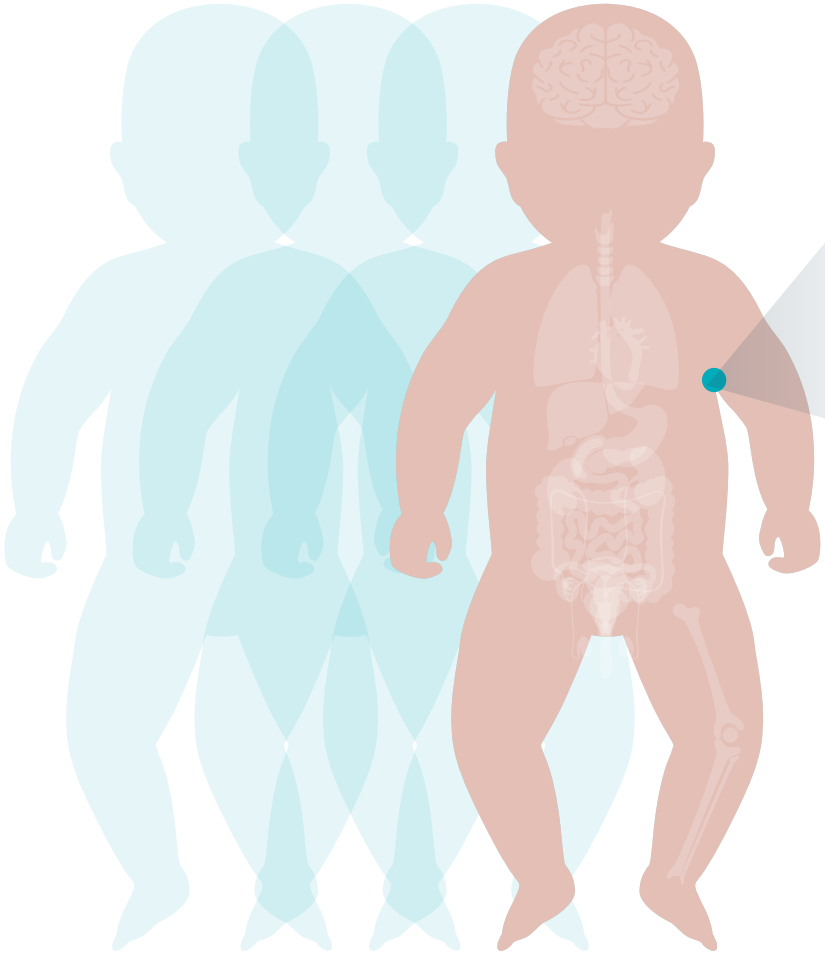
- 46,XX genital atypia/sex misassignment at birth[3]
- 46,XY TARTs may begin in childhood[5]



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



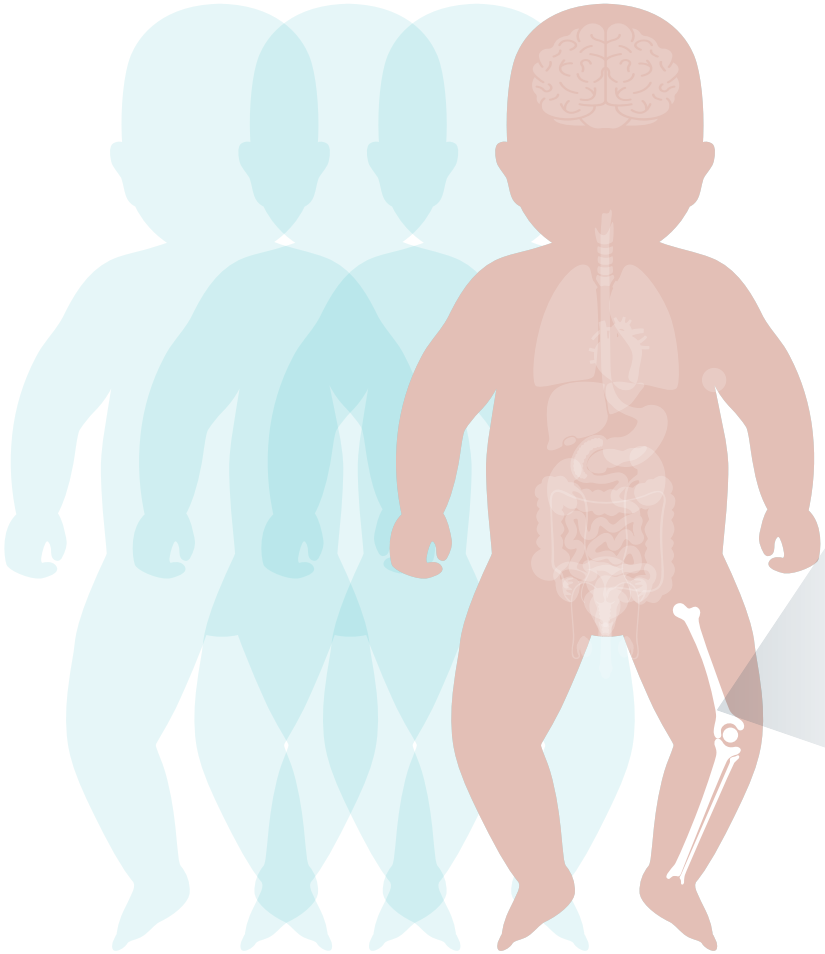
PUBARCHE[2,3]

- 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];
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



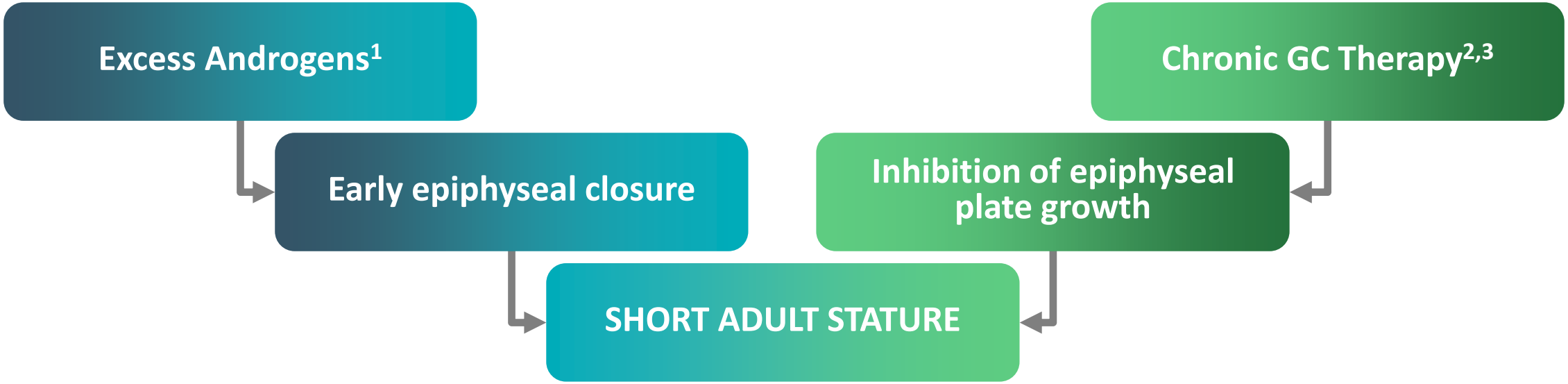
MUSCULOSKELETAL[2,3]

- 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]

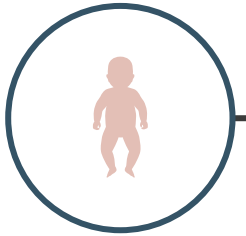
Increased risk of fractures[6]

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

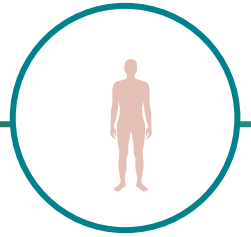


Goal of therapy:
Maximize androgen suppression
for normal growth and pubertal development

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

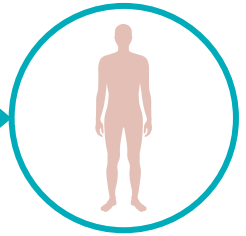


Goal of therapy:
Maintain adequate androgen suppression
despite rapid HC metabolism in puberty

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].

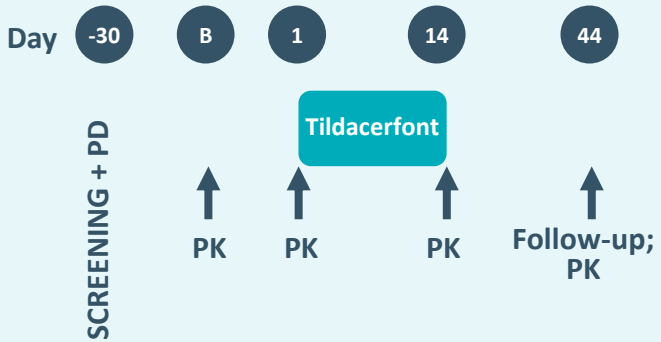
PHASE 2 STUDY IN PEDIATRIC CAH: TO BE INITIATED IN 2021

Key eligibility criteria

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

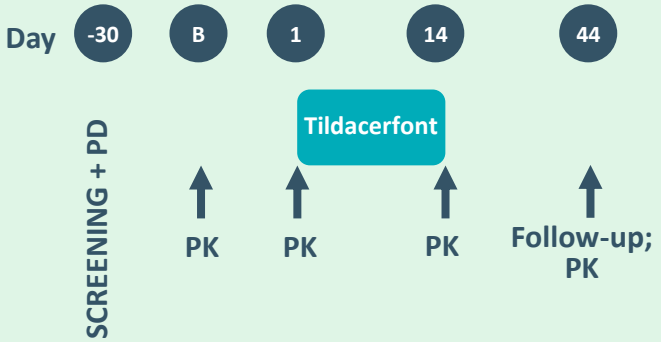
N=20

11–17 years old, 50 mg* QD
(44 days)



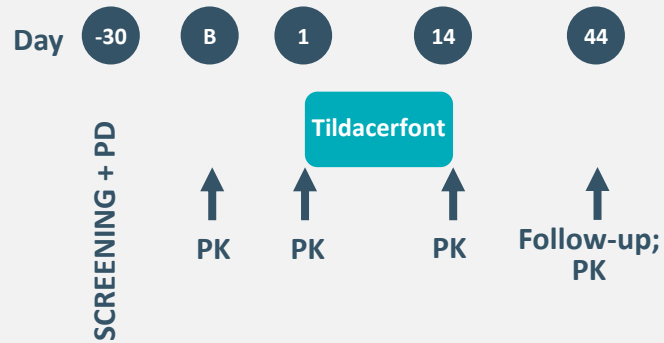
DSMB agreement to proceed

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.

Polycystic Ovary Syndrome (PCOS) Overview

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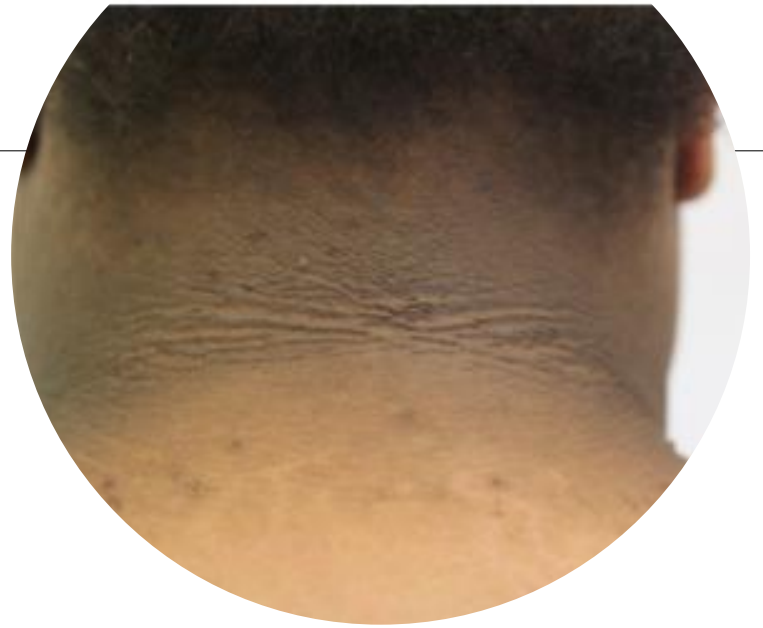
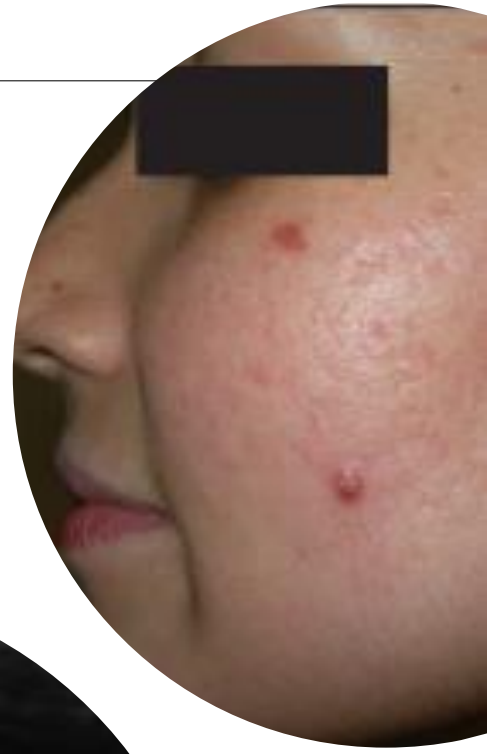
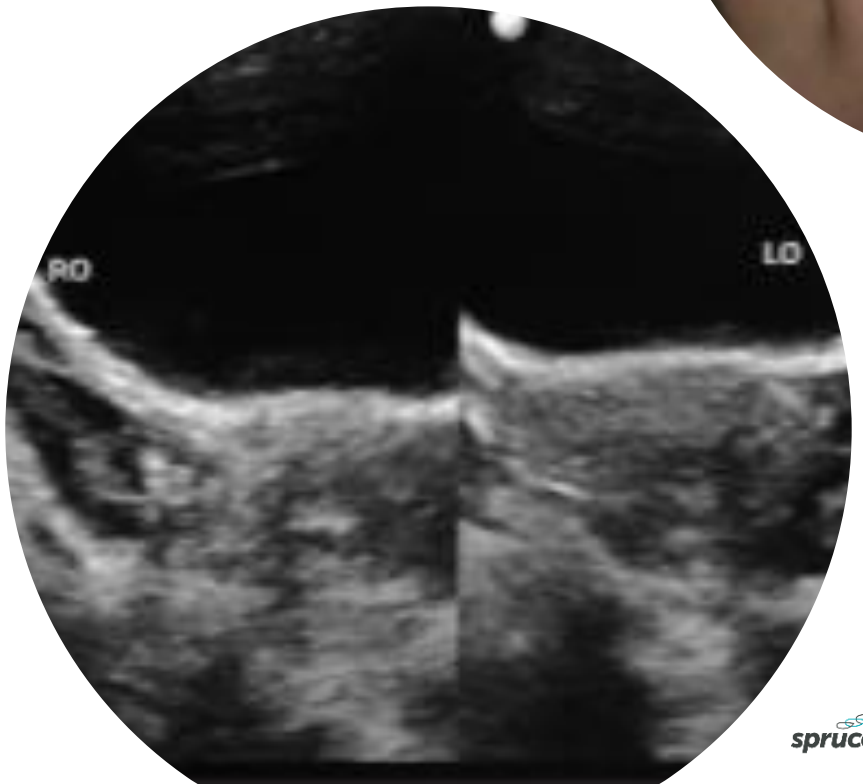
PCOS Overview

- **Polycystic ovary syndrome (PCOS) is a complex condition characterized by elevated androgen levels, menstrual irregularities, and/or small cysts on one or both ovaries.**
- **5% to 10% of females 18 to 44 years of age are affected by PCOS (~5 million women in the U.S.), making it the most common endocrine abnormality among women of reproductive age in the U.S. [1]**
- **Adolescents typically present with hirsutism, acne resistant to topical therapies, and menstrual irregularities.**
- **Adult women usually seek care for oligomenorrhea and hyperandrogenism and if applicable, fertility concerns due to ovulatory dysfunction.**
- **Providers include reproductive endocrinologists, but also endocrinologists, OBGYN, internal medicine, and dermatologists depending on clinical manifestations.**
- **Costs to the U.S. health care system for the identification and management of PCOS are approximately $4 billion per year. [2]**

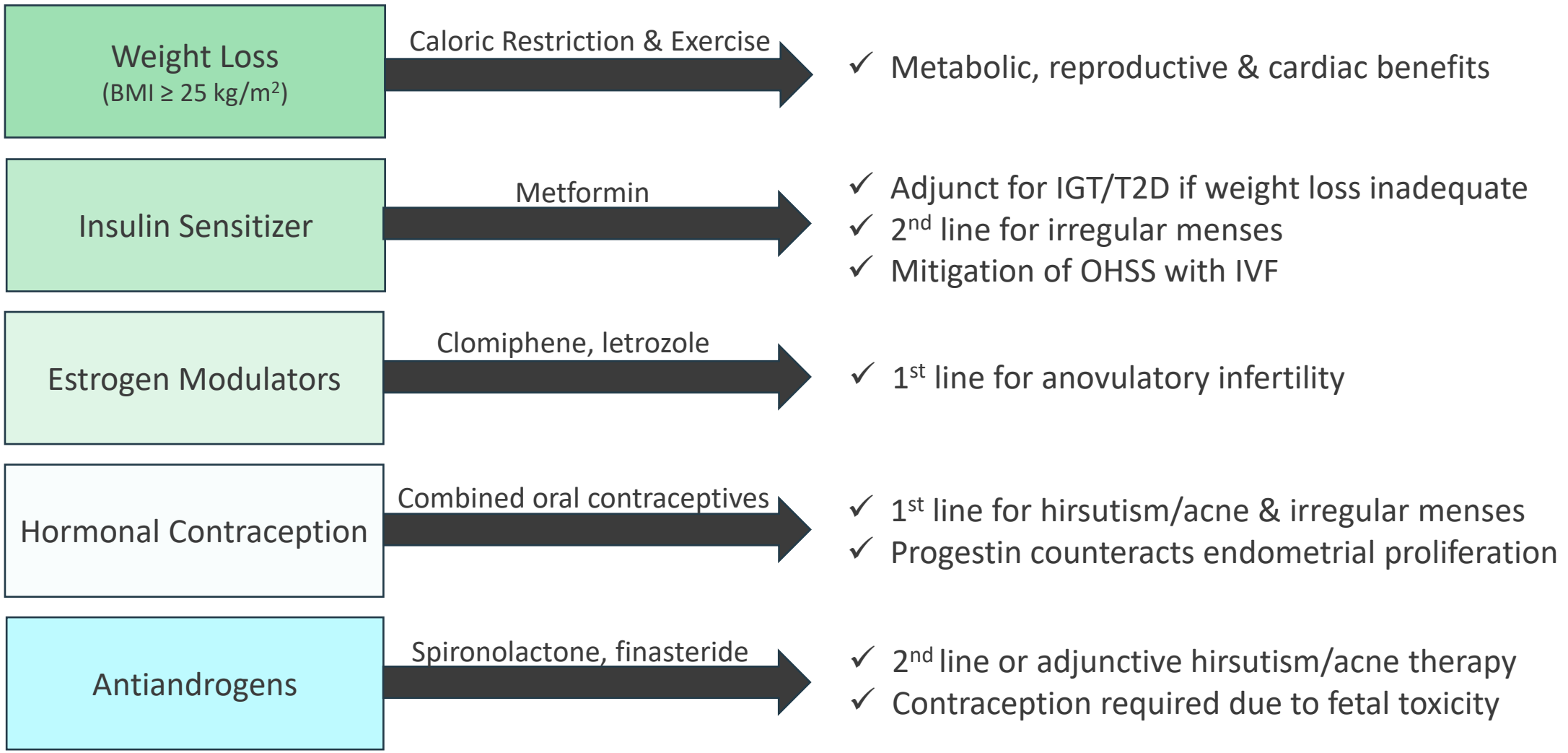






1. National Institutes of Health Department of Health and Human Services. *Beyond Infertility: Polycystic Ovary Syndrome (PCOS)* NIH Pub. No. 08-5863, April 2008
2. ACOG Practice Bulletin No. 108: Polycystic ovary syndrome. *Obstet Gynecol. 2009 Oct; 114(4):936.*

Treatment

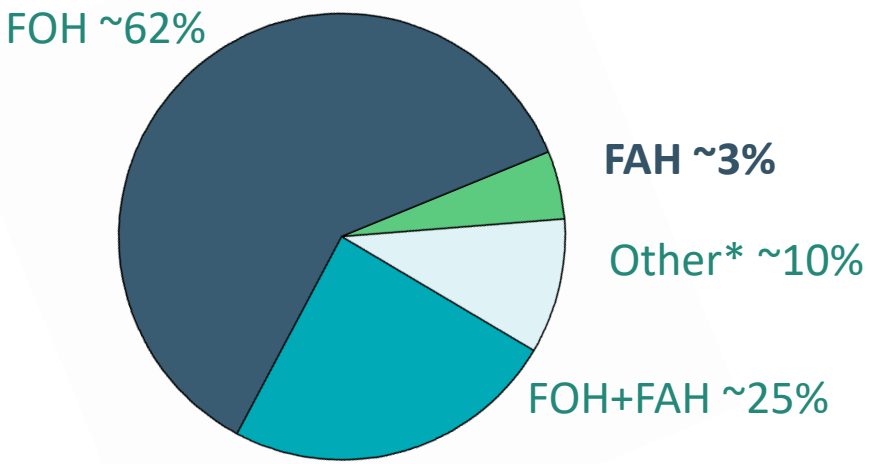

Weight Loss
(BMI ≥ 25 kg/m²)
Caloric Restriction & Exercise
✓ Metabolic, reproductive & cardiac benefits
Insulin Sensitizer
Metformin
✓ Adjunct for IGT/T2D if weight loss inadequate
✓ 2nd line for irregular menses
✓ Mitigation of OHSS with IVF
Estrogen Modulators
Clomiphene, letrozole
✓ 1st line for anovulatory infertility
Hormonal Contraception
Combined oral contraceptives
✓ 1st line for hirsutism/acne & irregular menses
✓ Progestin counteracts endometrial proliferation
Antiandrogens
Spironolactone, finasteride
✓ 2nd line or adjunctive hirsutism/acne therapy
✓ Contraception required due to fetal toxicity

Elucidating Androgen Source

- **Functional ovarian hyperandrogenism (FOH)** is detected by stimulating the hypothalamic pituitary ovarian (HPO) axis, thus a GnRH agonist is administered to detect an exaggerated 17-OHP level (>132 ng/dl is considered diagnostic)

- **Functional adrenal hyperandrogenism (FAH)** is detected by stimulating the hypothalamic pituitary adrenal (HPA) axis, thus ACTH stimulation testing is performed to detect an exaggerated DHEA level (>1136 ng/dl is considered diagnostic)

PCOS by Androgen Source



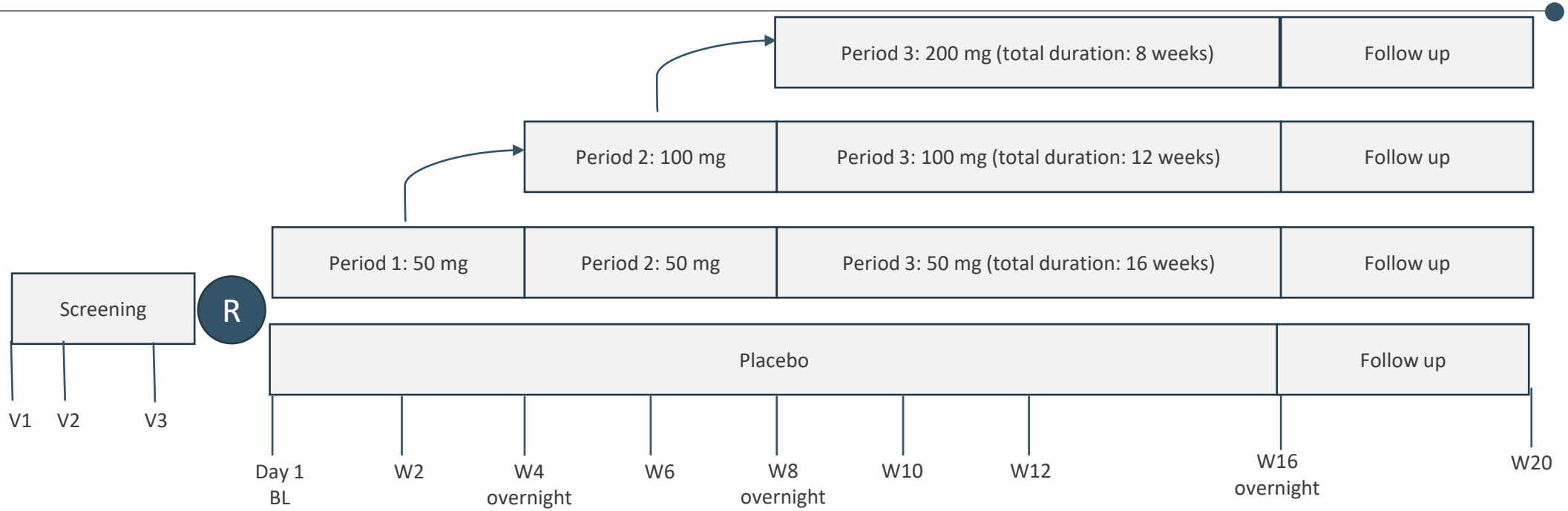
* Other comprised of obesity / idiopathic source

Rosenfield (2011) study comprised n=40 PCOS patients

Subtype	GnRHag 17-OHP Response	DAST Testosterone Response	ACTH DHEA Response
FOH	High	High	Normal
FOH + FAH	High	High	High
FAH	**Normal**	**Normal**	**High**
Other	Normal	Normal	Normal

GnRHag: low-dose, short-acting GnRH agonist
DAST: low dose dexamethasone suppression test
ACTH test: low dose cosyntropin test
17-OHP: 17-hydroxyprogesterone; DHEA: dehydroepiandrosterone

Phase 2 POC Study: Blinded Intrasubject Dose Titration to Effect



Design	Randomized, Double Blind, Placebo-controlled, Intra-subject dose-escalation
Sample size	40 subjects; 20 per treatment group; 1:1 randomization Strata: DHEAS (baseline DHEAS ≤ 1.2 x ULN, DHEAS > 1.2x ULN) and by source of androgen excess (FAH, FAH+FOH)
Key Eligibility Criteria	Adult PCOS 18-30 yrs, BMI <38 kg/m$^{2;}$ DHEAS > ULN at all screening visit No use of COC
Endpoints	1^{o} Endpoint: Safety / Tolerability of escalating doses Additional Endpoints: - Reduction of DHEAS Baseline change > 30%, DHEAS < ULN - ACTH, 17OHP, T, A4, 11OHA4, 11OHT, 11KA4, 11KT: baseline change - Ovulation + metabolic parameters

Commercial Opportunity and Milestones

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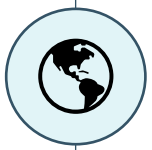
COMMERCIAL OPPORTUNITY – CLASSIC CAH

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 (2027)[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

FINANCIAL HIGHLIGHTS

Capital Structure and Summary Financials as of June 30, 2021

Capital Structure	Shares
Shares Outstanding	23,370,070
Options Issued and Outstanding	2,612,963
Warrants	-
Fully Diluted Shares Outstanding	25,983,033

Financials	000's
Cash and Investments	$139,000
Debt[1]	$5,000

1. Principal balance of debt owed as of June 30, 2021. Does not include discounts on debt recorded pursuant to U.S. GAAP requirements.

KEY ANTICIPATED MILESTONES

2H2021	Initiate Phase 2 proof-of-concept (POC) 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*

* Clinical data milestones subject to change based on continued assessment of study progress

INVESTMENT HIGHLIGHTS

Tildacerfont poised to transform treatment paradigm in classic CAH	**Two late-stage clinical studies initiated; Enriched patient populations across two studies designed to observe clinically meaningful outcomes**
Multiple expansion opportunities	**Initiation of Phase 2 programs in pediatric classic CAH (6 to 17 years of age) and polycystic ovary syndrome (FAH-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**

spruce BIOSCIENCES

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