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

Corporate Presentation

January 24, 2022

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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; Data expected in 2H-2023 (CAHmelia-203) and 2H-2024 (CAHmelia-204).**
Multiple expansion opportunities	**Phase 2 programs in pediatric classic CAH (6 to 17 years of age) and polycystic ovary syndrome (FAH-PCOS) initiated**
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 endocrine and rare disease products**

Classic CAH Overview

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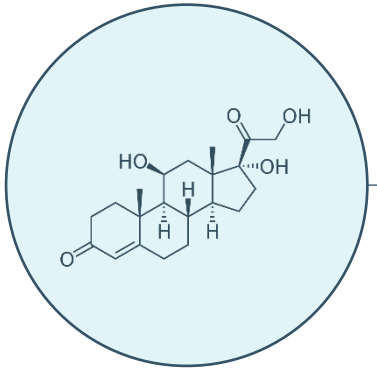
CLASSIC CAH DISEASE OVERVIEW

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

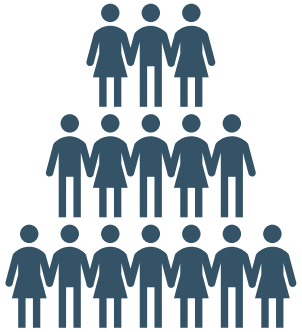


Classic CAH is an autosomal recessive disease characterized by an inability to produce cortisol, leading to a chronic imbalance of key hormones and an overprodution of adrenal androgens.

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

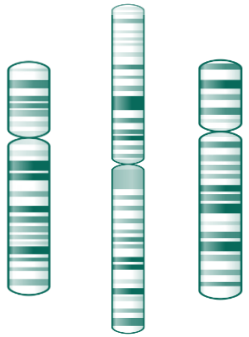


Classic 21-OHD CAH[1]

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]

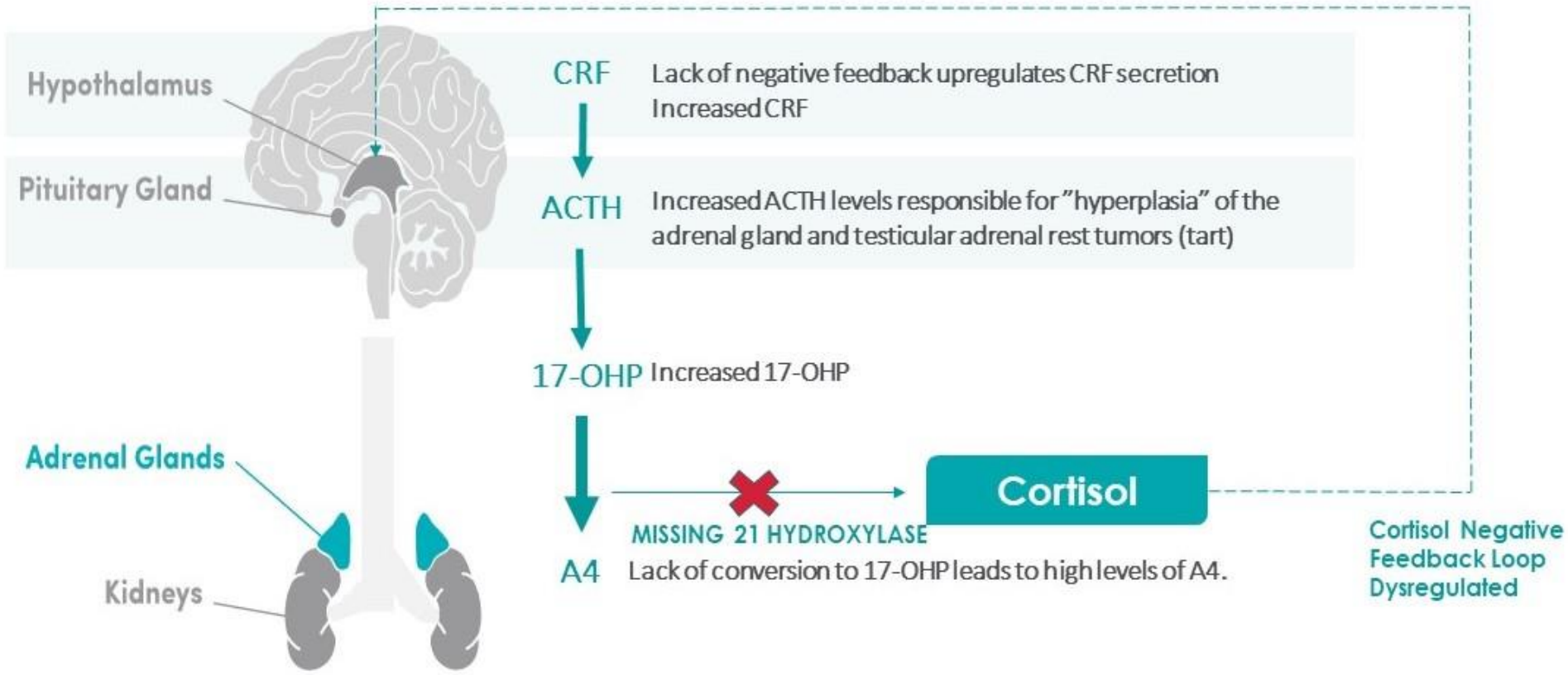
- Indicated when prior children have CAH
- Fetal hormone levels and DNA can be analyzed from amniotic fluid
- Fetal DNA analysis is also performed via chorionic villus sampling

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

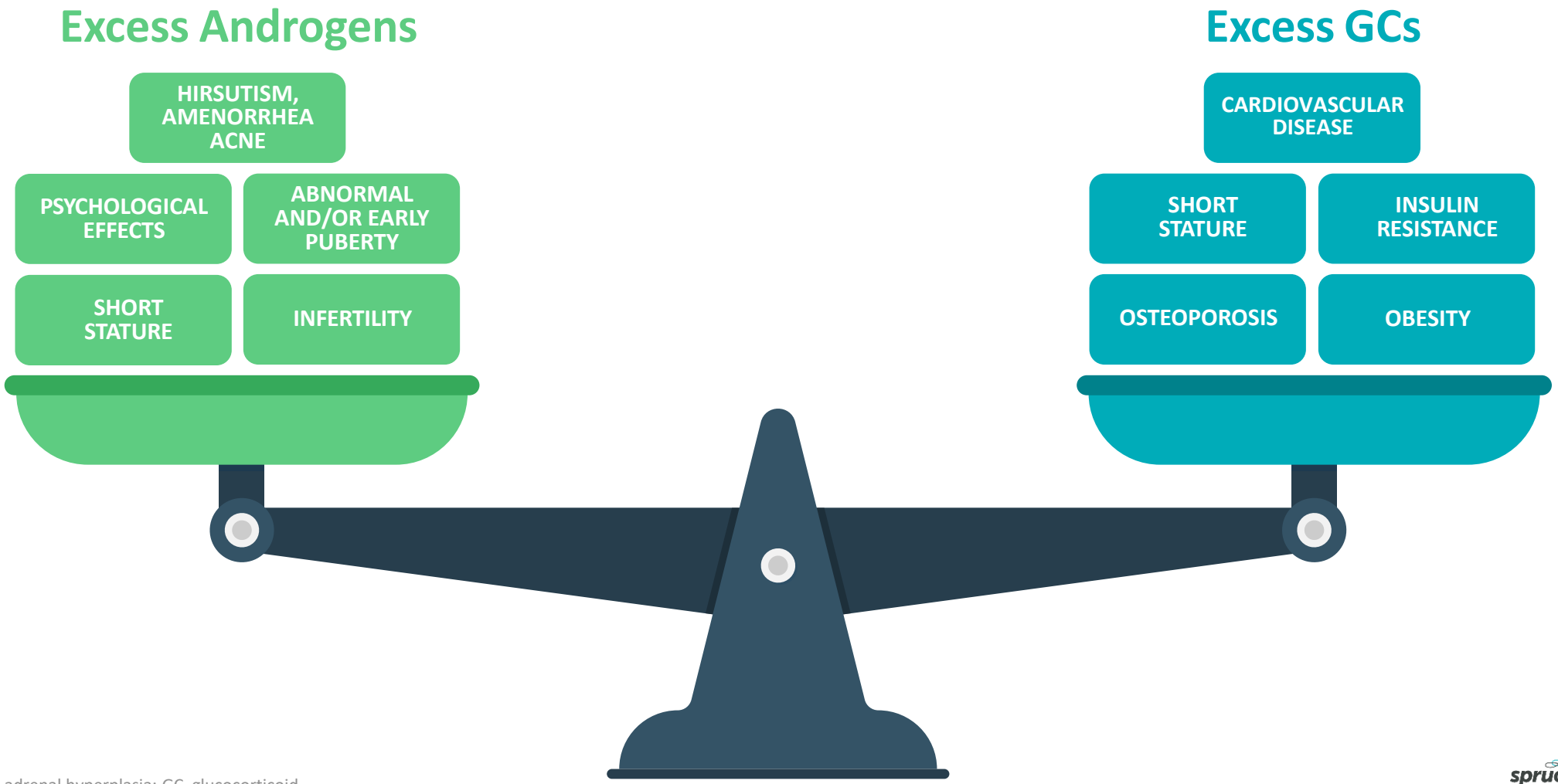
Lack of cortisol leads to overproduction of ACTH and precursor steroid molecules, resulting in excessive adrenal androgens



The dysregulation of the HPA axis in classic CAH.

THE CHALLENGE 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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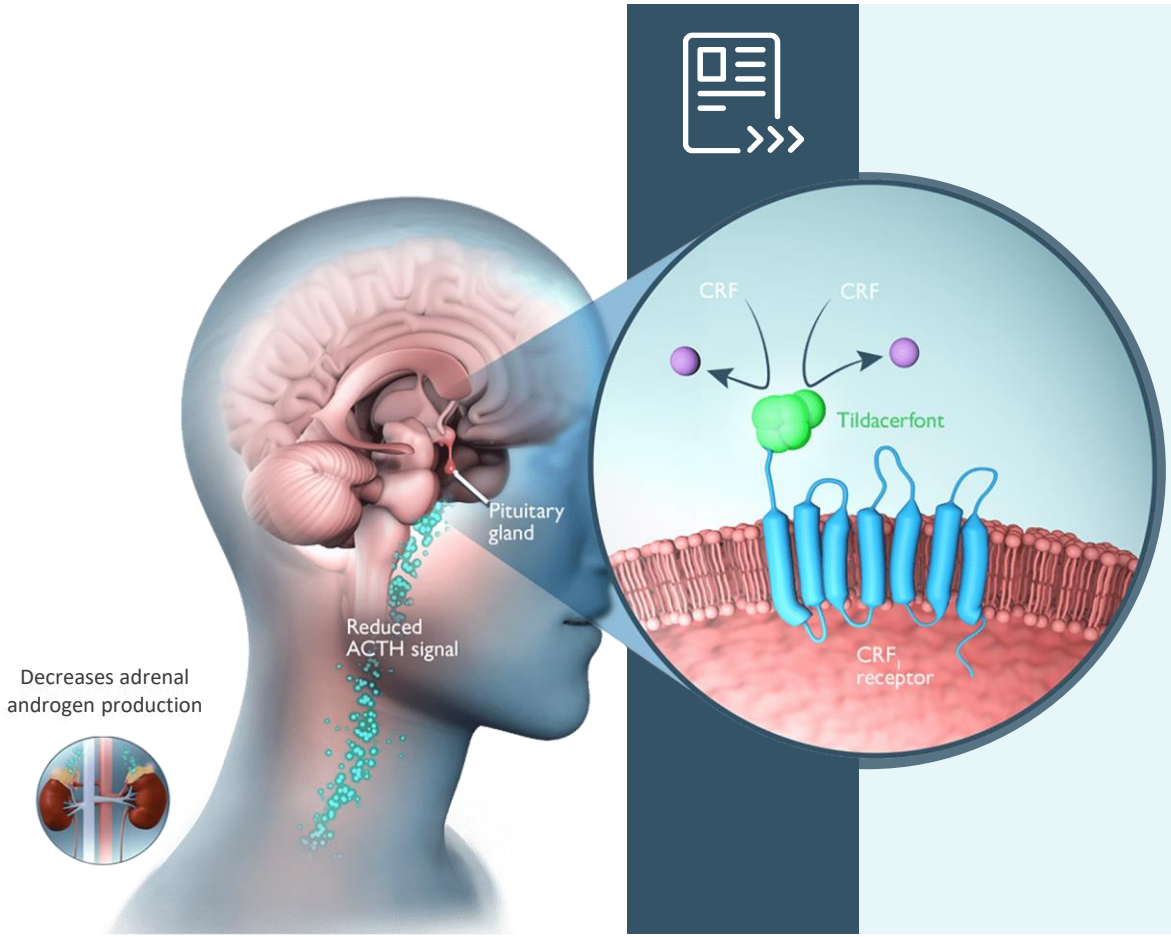
TILDACERFONT IS A NOVEL CRF_1 RECEPTOR ANTAGONIST



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.

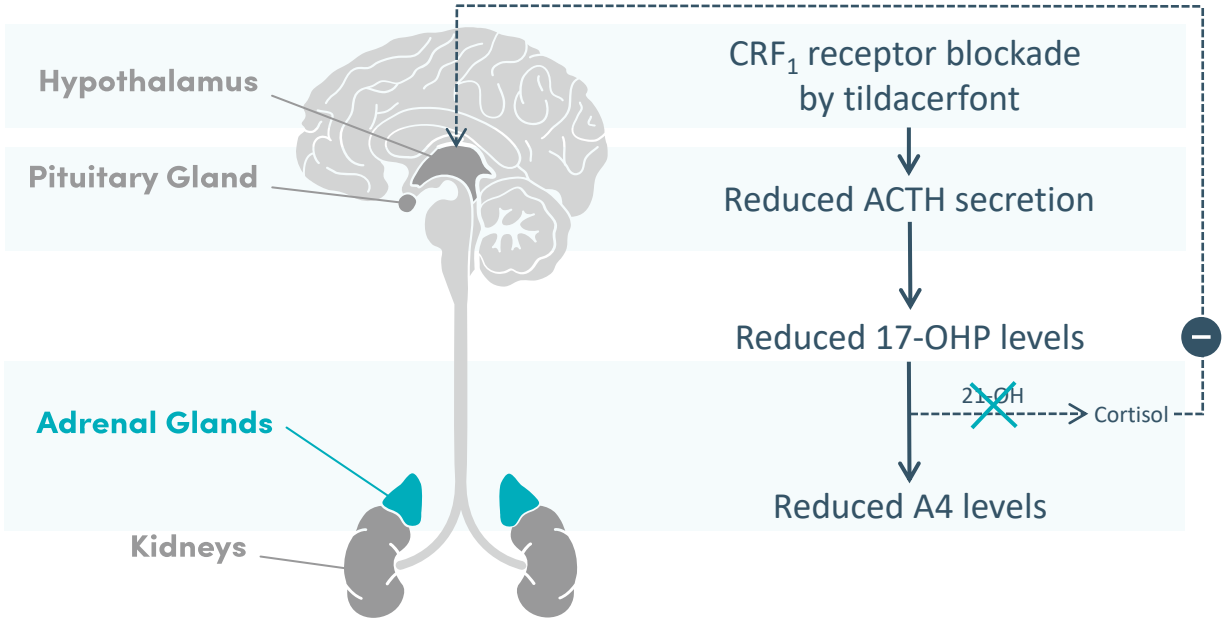
1. Sarafoglou K, *et al. J Clin Endocrinol Metab.* 2021:dgab438. DOI: https://doi.org/10.1210/clinem/dgab438 [Epub ahead of print].

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]

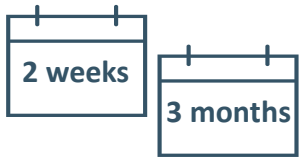
Poor disease control

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]

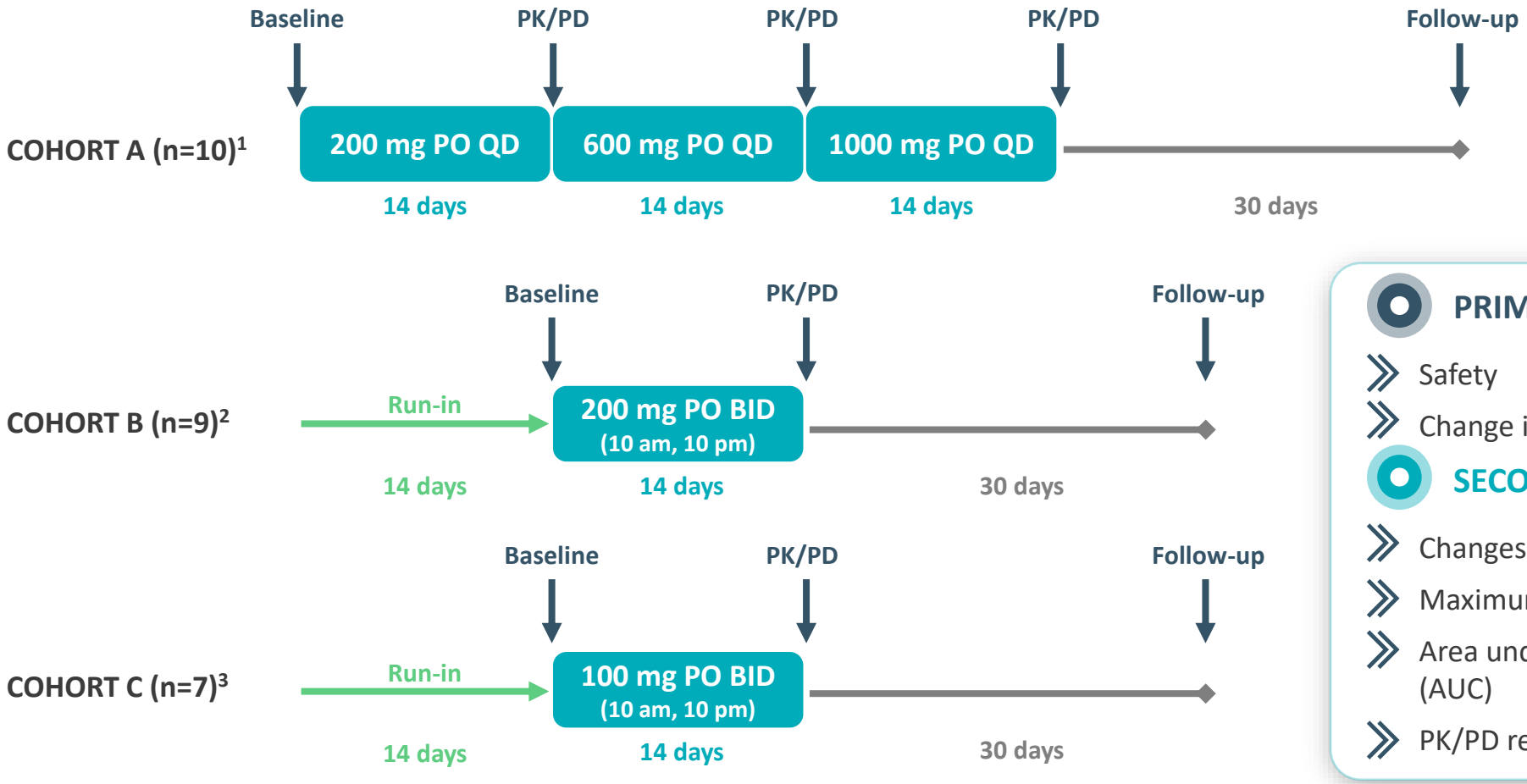
Most common adverse events: headache and upper respiratory tract infection (mild)

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]

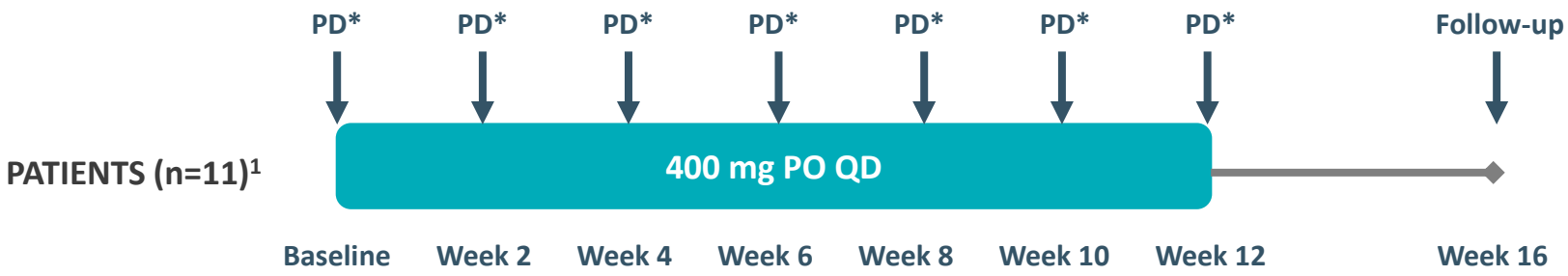
- Changes in PD markers
- Maximum plasma concentration (C_{max})
- Area under the concentration-time curve (AUC)
- PK/PD relationships

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

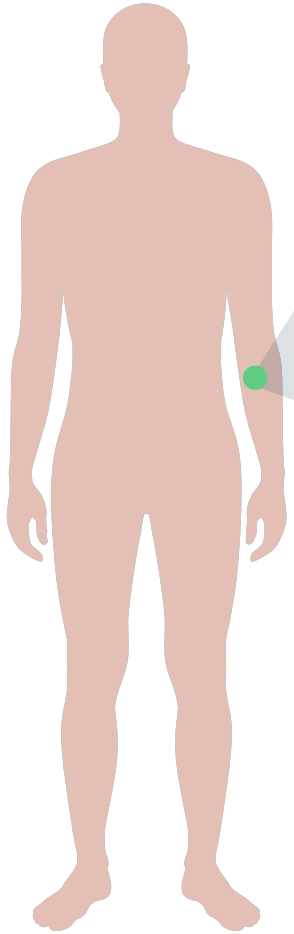
SECONDARY ENDPOINTS[2]

- 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]



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.

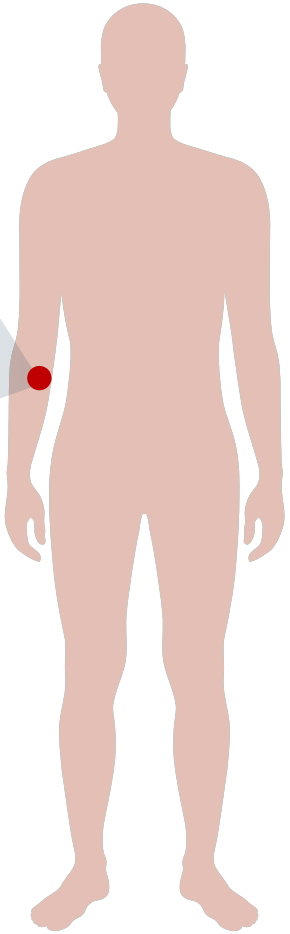
1. Claahsen-van der Grinten H, *et al. Endocr Rev.* 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print]; 2. Speiser P, *et al. J Clin Endocrinol Metab.* 2018;103:4043-88.

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



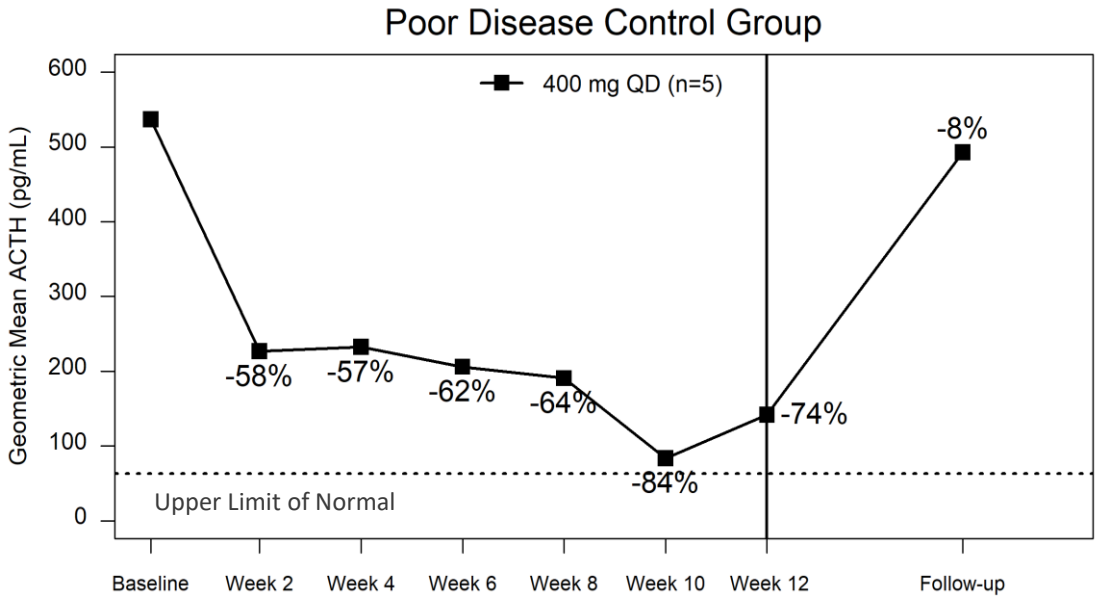
CAH, congenital adrenal hyperplasia; GC, glucocorticoid.

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

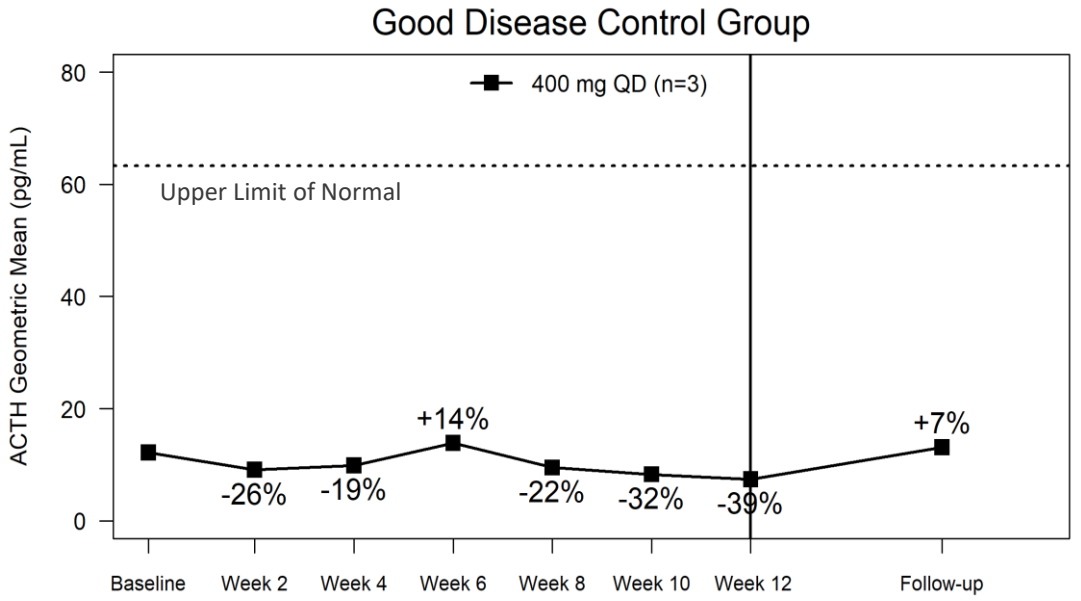
In the poor disease control group, a robust initial drop in ACTH was seen at week 2, followed by further reduction over 12 weeks; there was a maximum reduction in ACTH of **84%** at week 10 of the study in the poor disease control group

POOR DISEASE CONTROL



- Normalization of ACTH achieved in 60% of patients*

GOOD DISEASE CONTROL



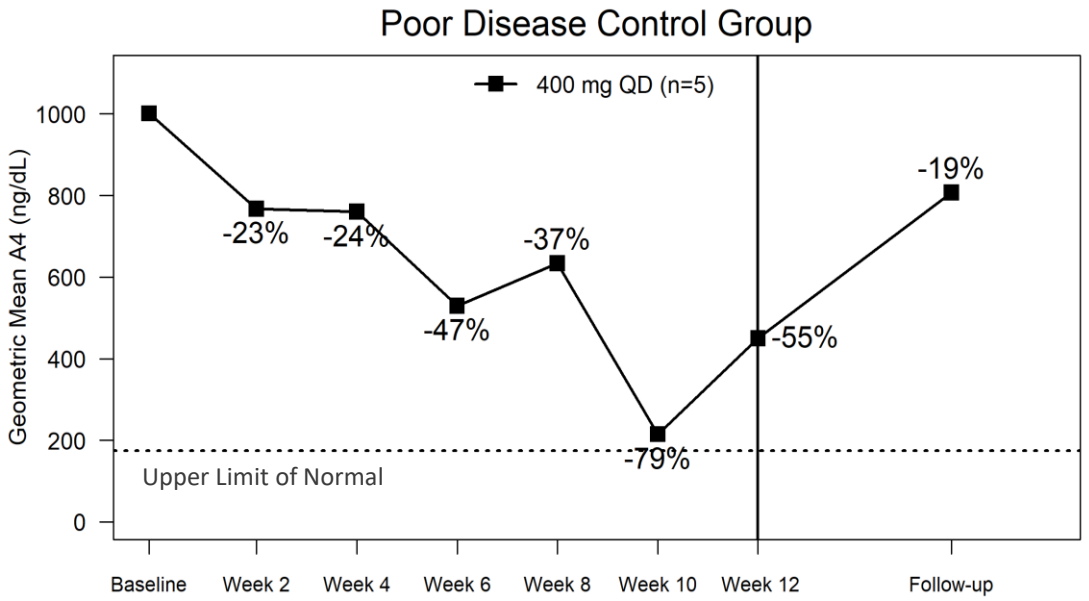
- No excessive suppression of adrenal function

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; 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

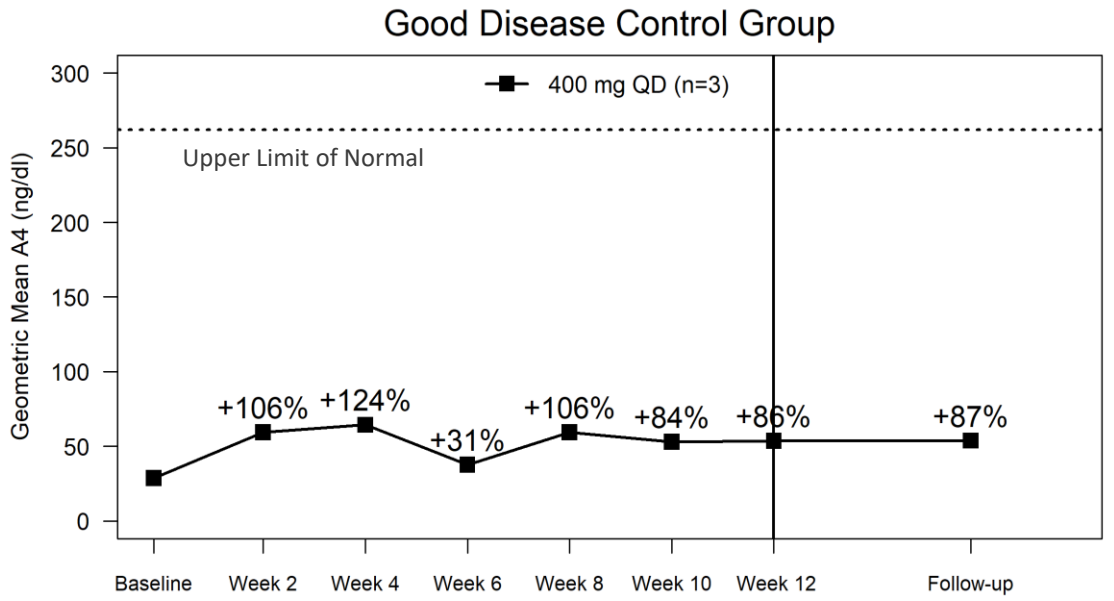
In poor disease control group, an initial drop in A4 was seen at week 2, followed by further reduction over 12 weeks; there was a maximum reduction in A4 of **79% at week 10** of study in the poor disease control group

POOR DISEASE CONTROL



- Normalization of A4 achieved in 40% of patients

GOOD DISEASE CONTROL



- No excessive suppression of adrenal function

3 patients were on dexamethasone and excluded from analysis
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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Program Update

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

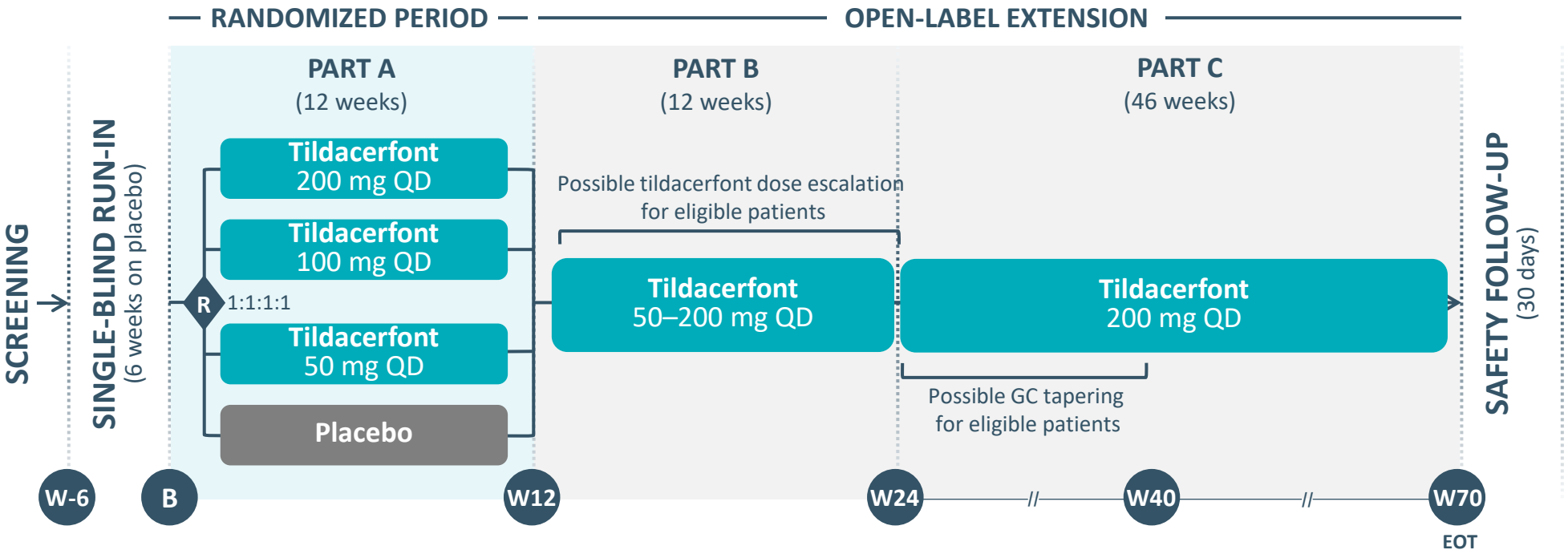
Key eligibility criteria

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



Study schema is not drawn to scale.

CAHmelia 203: UPDATES TO INCLUSION CRITERIA

Optional Pre-Screening Protocol Added

Pre-Screening Protocol **simplifies** and **streamlines** site screening activities:

- PI checks **GC dosage, contraindicated medications,** and **A4 levels,** and **informs about trial**

CAHmelia 203 CAHmelia 204

Revised A4 and ACTH criteria

Removed the ACTH inclusion criterion

Increased A4 boundaries according to **current GC dose:**

- Has **A4 >2.5x ULN** at both screening and Week 4
- Has **A4 > ULN** at both screening and Week 4 (measured before any morning GC dose) if daily **GC dose <30 mg**

Simplified GC criteria

Broadened the range of allowable prior **GC dosing:**

- Has been on a stable, supraphysiologic dose of GC replacement, defined as **>15 mg/day** and **≤60 mg/day** in HCe, for ≥1 month before screening (stress dosing still allowed)

CAHmelia 203

A4, androstenedione; ACTH, adrenocorticotropic hormone; GC, glucocorticoid; HC, hydrocortisone; HCe, hydrocortisone equivalents; ULN, upper limit of normal.

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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 TART volume 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 TART volume 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

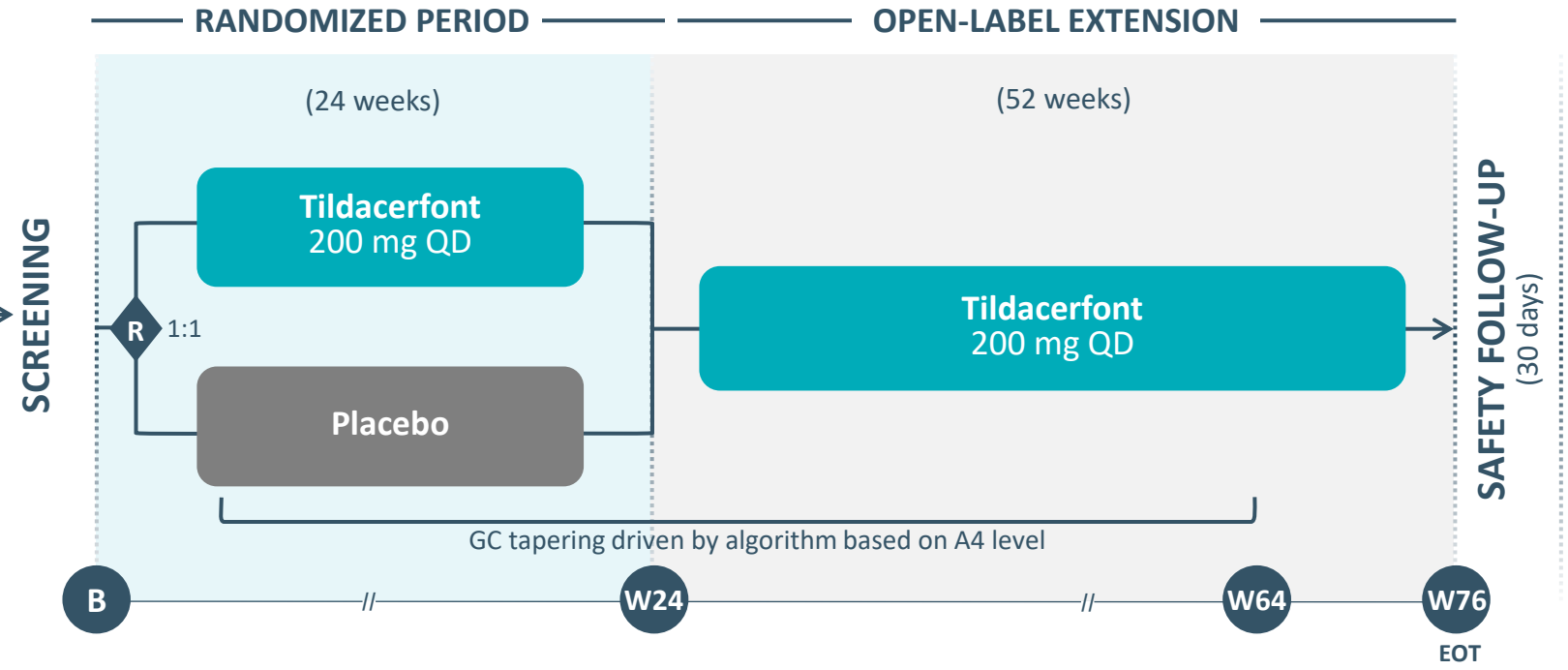
Key eligibility criteria

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



Study schema is not drawn to scale.

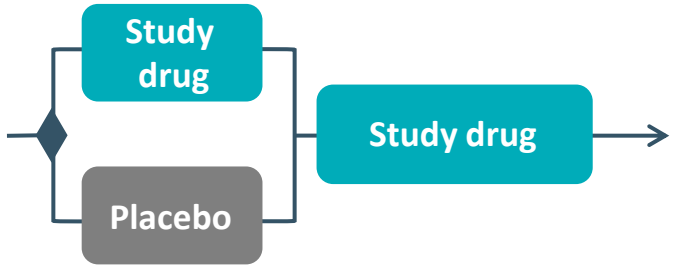
CAHmelia 204: UPDATES TO INCLUSION CRITERIA

Revised A4 Criterion

Increased range of permissible A4 levels:

Has **A4 ≤ 2.5x ULN** at screening **on existing GC regimen**

Removed GC conversion period



Participants will remain on their own medications for the trial

Simplified GC criteria

Broadened the range of allowable prior **GC dosing:**

- Has been on a stable, supraphysiologic dose of GC replacement, defined as **>30 mg/day** and **≤60 mg/day** in HCe, for ≥1 month before screening

A4, androstenedione; ACTH, adrenocorticotropic hormone; GC, glucocorticoid; HC, hydrocortisone; HCe, hydrocortisone equivalents; ULN, upper limit of normal.

CAHmelia 204: UPDATES TO PRIMARY ENDPOINT

Primary endpoint updated to **proportion of participants achieving a ≥5 mg/d dose reduction baseline in GC** dose in HCe at Week 24 with A4 < ULN

Primary endpoint a reflection of individual benefit for each subject

CAHmelia 204

A4, androstenedione; HCe, hydrocortisone equivalents; GC, glucocorticoid; ULN, upper limit of normal.

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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 weight after 52 weeks of tildacerfont treatment

KEY EXPLORATORY ENDPOINTS

- Proportion of subjects with GC dose ≤25 mg/day (HCe) with A4 ≤ ULN at Week 24 and after 52 weeks of tildacerfont treatment
- 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

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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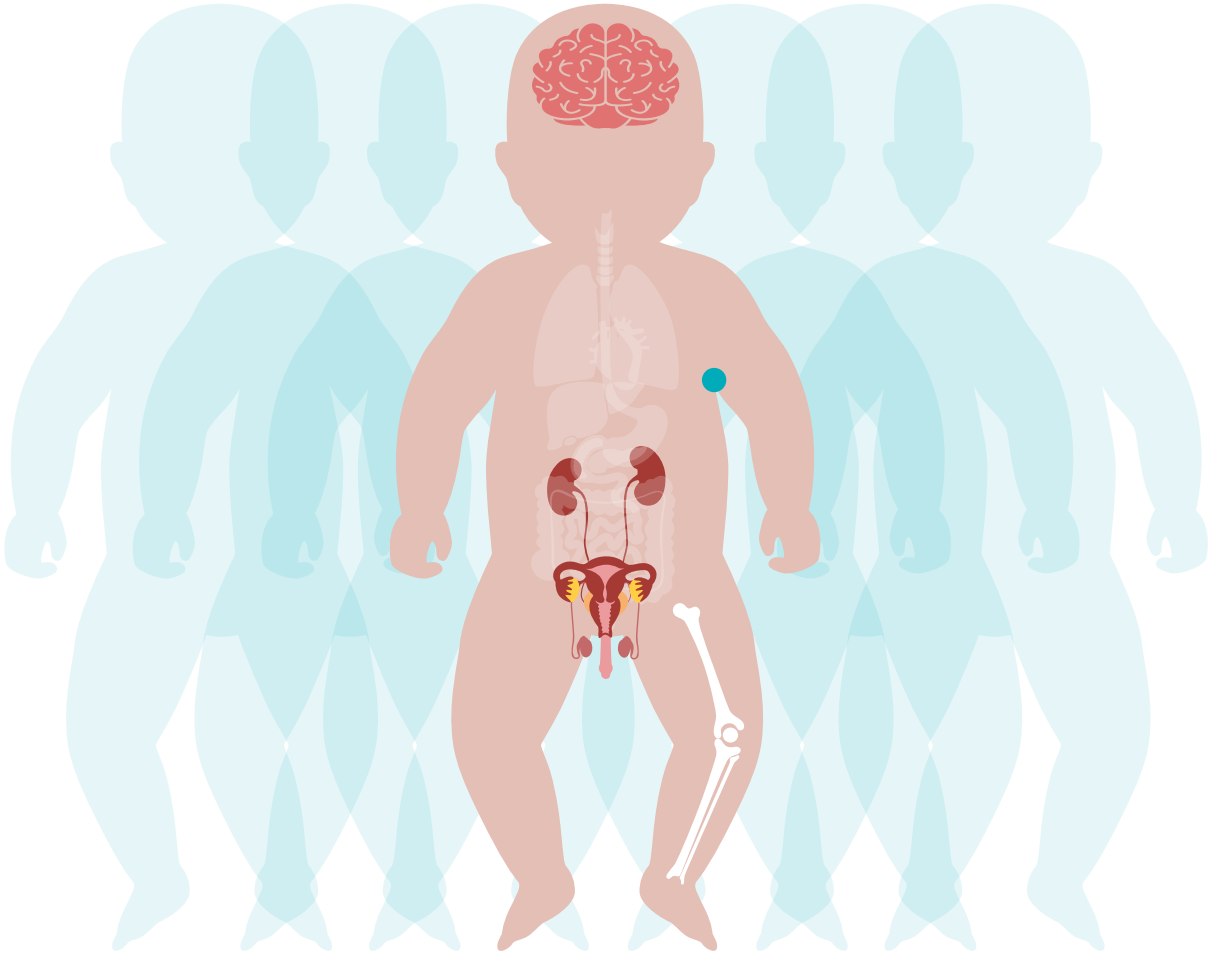
CLASSIC CAH PRESENTS IN INFANCY & EARLY CHILDHOOD



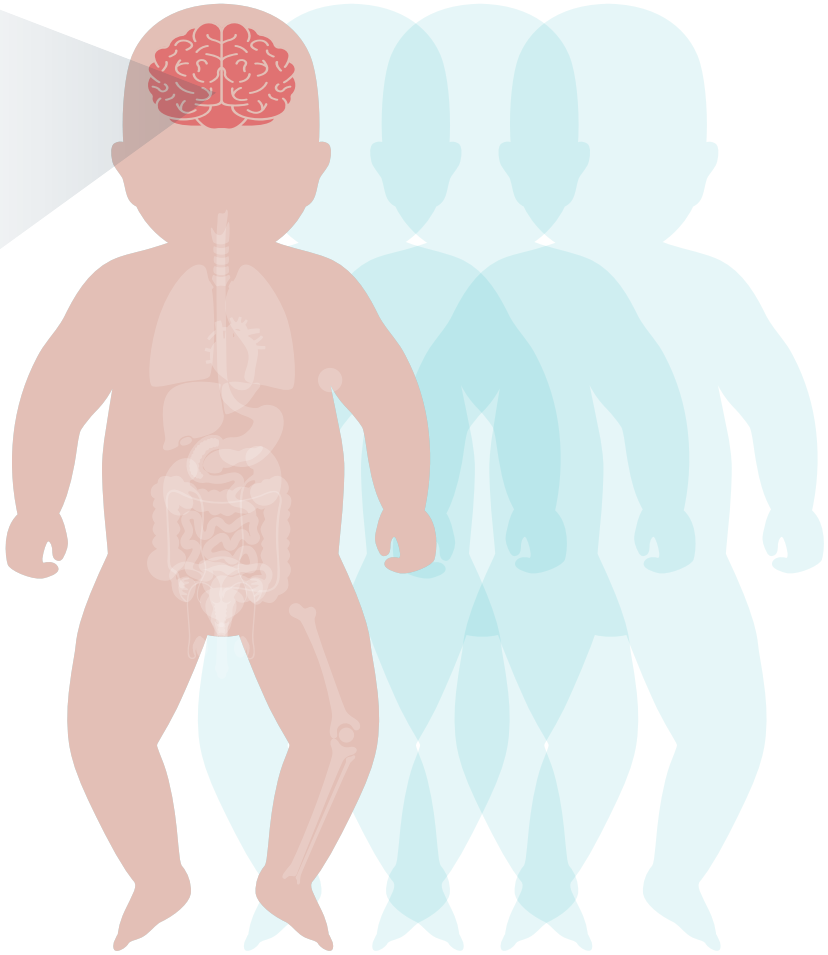
CAH, congenital adrenal hyperplasia

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]



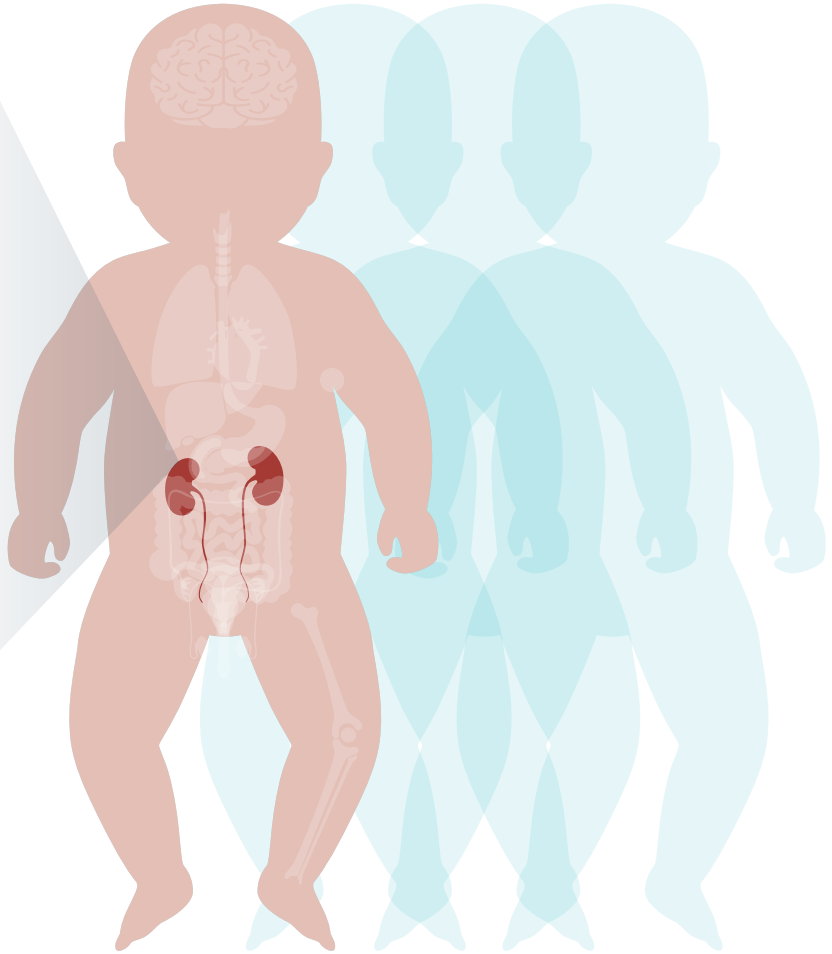
ADHD, attention deficit hyperactivity disorder; CAH, congenital adrenal hyperplasia.

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]



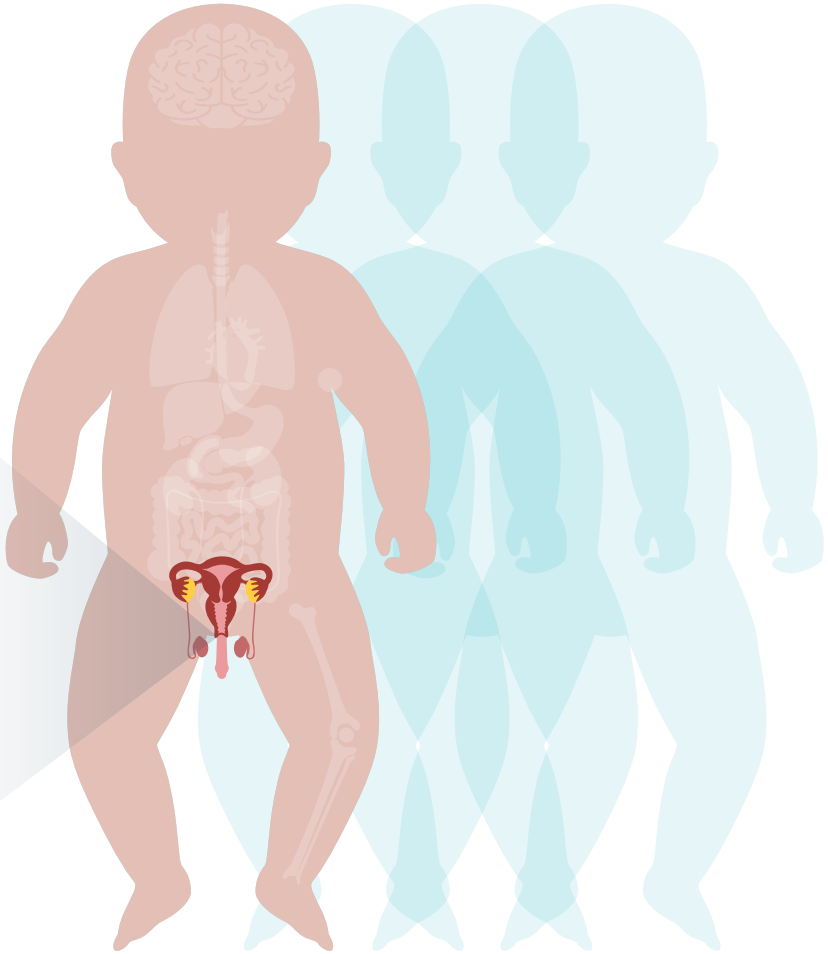
CAH, congenital adrenal hyperplasia

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

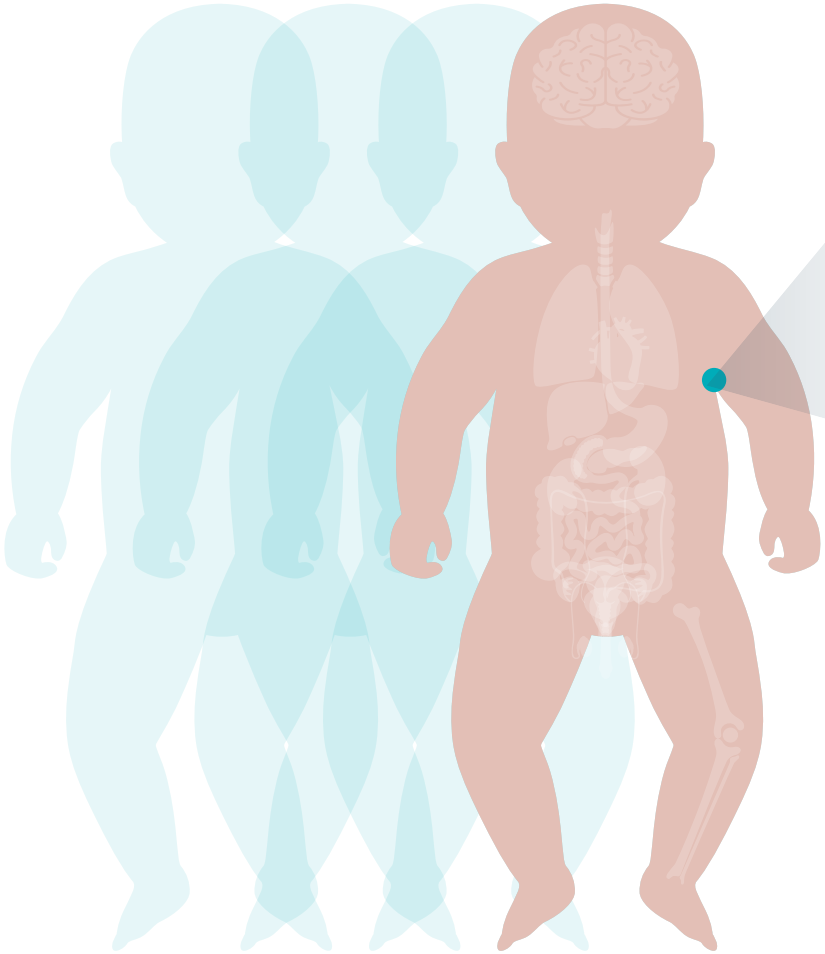
- 46,XX genital atypia/sex misassignment at birth[3]
- 46,XY TARTs may begin in childhood[5]



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



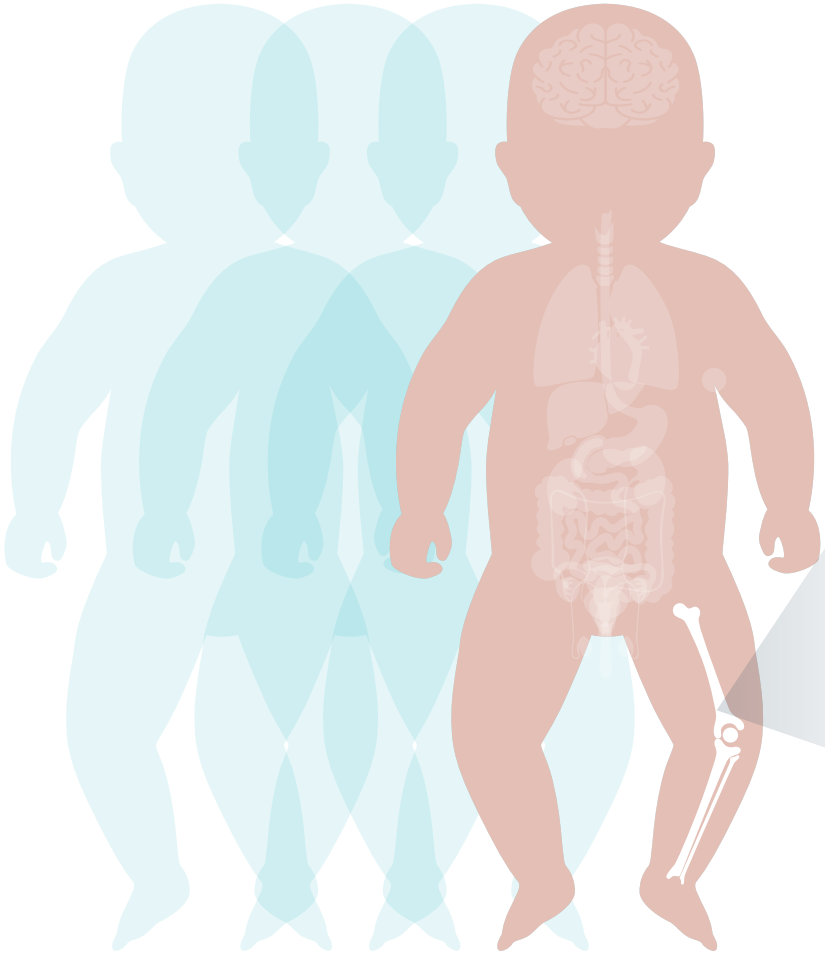
PUBARCHE[2,3]

- 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



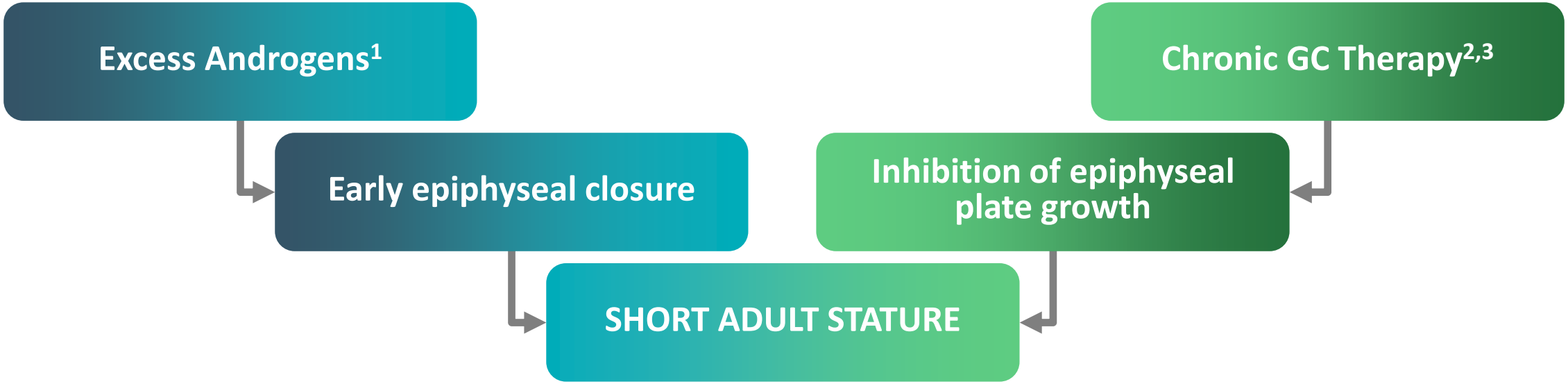
MUSCULOSKELETAL[2,3]

- 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]

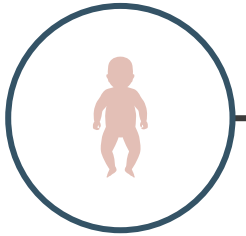
Increased risk of fractures[6]

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

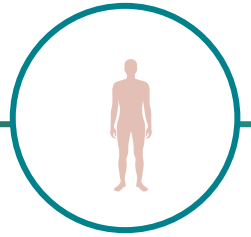


Goal of therapy:
Maximize androgen suppression
for normal growth and pubertal development

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

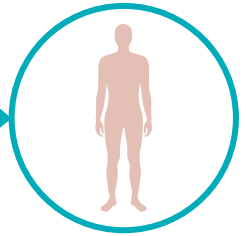


Goal of therapy:
Maintain adequate androgen suppression
despite rapid HC metabolism in puberty

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].

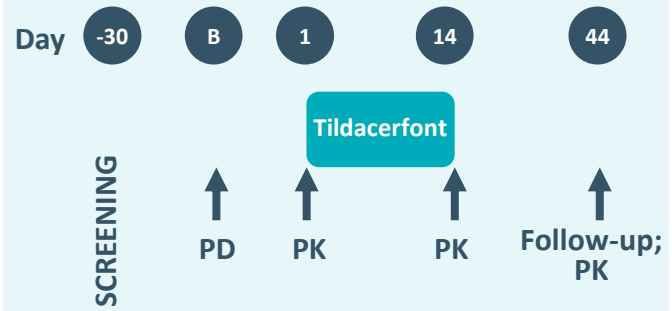
PHASE 2 STUDY IN PEDIATRIC CLASSIC CAH

Key eligibility criteria

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

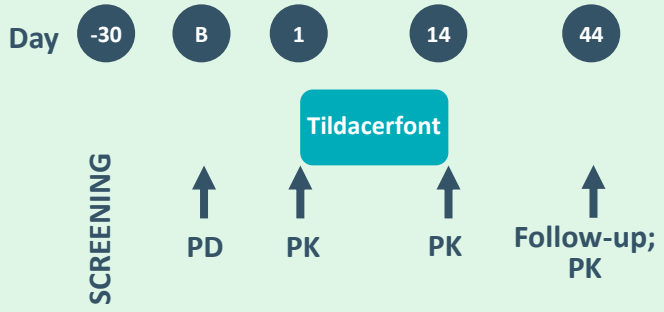
N=20

11–17 years old, 50 mg* QD
(44 days)



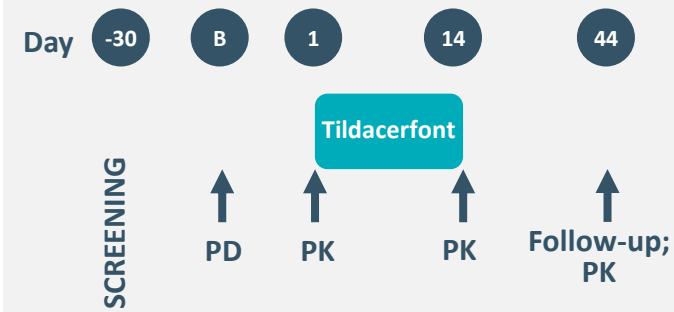
DSMB agreement to proceed

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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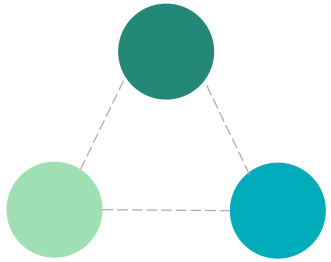
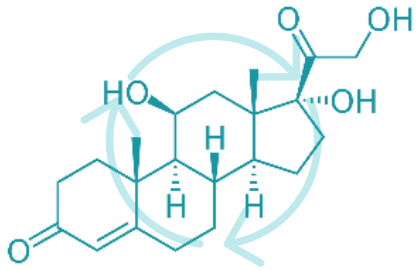
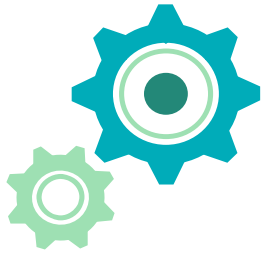
PCOS IS A COMMON, CHRONIC ENDOCRINE DISORDER



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]

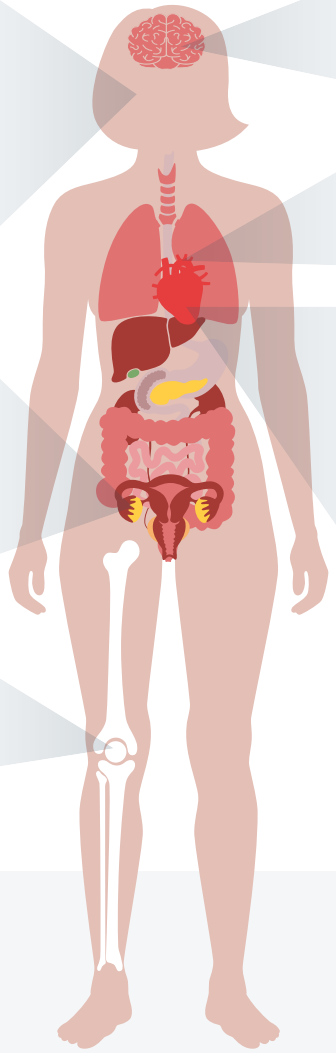
- Hirsutism
- Virilization
- Acne
- Acrochordons
- Androgenic alopecia
- Acanthosis nigricans

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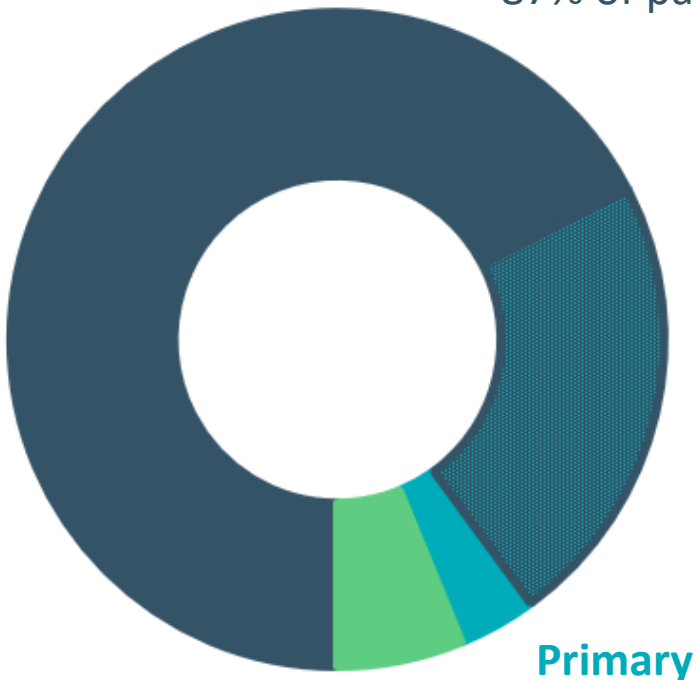
PCOS CAN BE CLASSIFIED ACCORDING TO SOURCE OF EXCESS ANDROGENS[1]

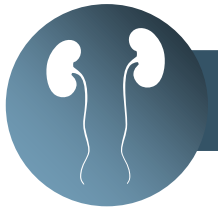


Source of Androgen	GnRHag 17-OHP Response	DAST Testosterone Response	ACTH DHEAS Response
Primary FOH	High	High	Normal
Mixed pathology	**High**	**High**	**High**
Primary FAH	**Normal**	**Normal**	**High**
Other	Normal	Normal	Normal

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

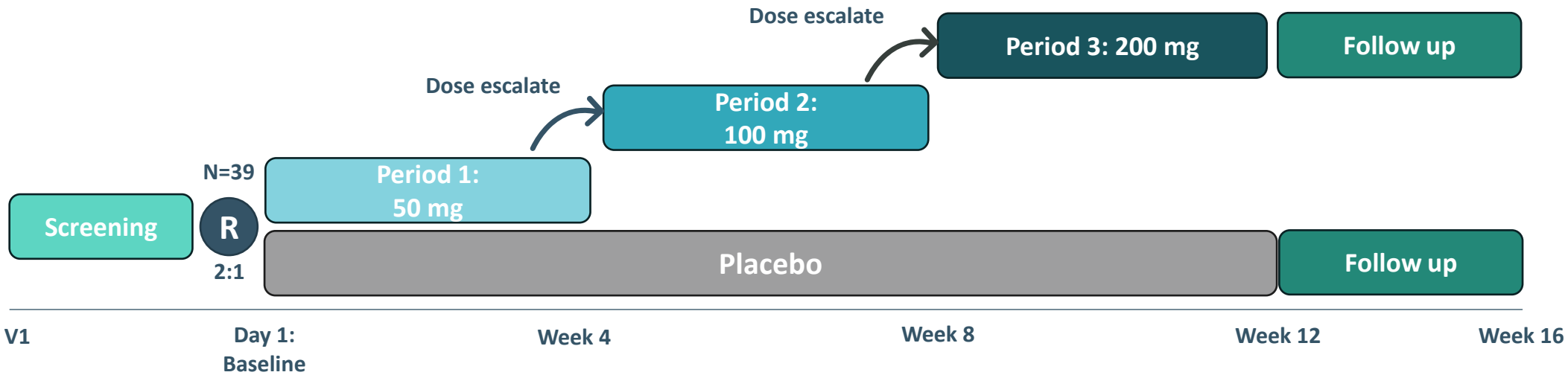
Insulin sensitization (metformin): alternative option if lifestyle changes yield insufficient results

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 reduction in DHEAS

Additional endpoints

- Safety and tolerability
- Reduction of DHEAS (baseline change > 30%; 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 Commercial Opportunity

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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

Preliminary Capital Structure and Summary Financials as of December 31, 2021

Capital Structure	Shares (M)
Shares Outstanding [1]	23.5
Equity Awards Issued and Outstanding [1]	2.7
Warrants	-
Fully Diluted Shares Outstanding [1]	26.2

Financials	000's
Cash, Cash Equivalents and Investments [1]	~$121,400
Debt[1] [2]	$5,000

1. This amount is unaudited and preliminary and is subject to completion of financial closing procedures. As a result, this amount may differ materially from the amount that will be reflected in the Company's financial statements as of and for the quarter ended December 31, 2021.
2. Principal balance of debt owed as of December 31, 2021. Does not include discounts on debt recorded pursuant to U.S. GAAP requirements.

KEY ANTICIPATED MILESTONES

2022	**Completion of enrollment in the Phase 2 POC PCOS trial**
1H2023	**Phase 2 results from the Phase 2 PCOS trial**
2H2023	**Topline results in adult classic CAH (CAHmelia-203)**
2H2024	**Topline results in adult classic CAH (CAHmelia-204)**

INVESTMENT HIGHLIGHTS

Tildacerfont poised to transform treatment paradigm in classic CAH	**Two late-stage clinical studies initiated; Data expected in 2H-2023 (CAHmelia-203) and 2H-2024 (CAHmelia-204).**
Multiple expansion opportunities	**Phase 2 programs in pediatric classic CAH (6 to 17 years of age) and polycystic ovary syndrome (FAH-PCOS) initiated**
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 endocrine and rare disease products**

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