spruce BIOSCIENCES

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

Corporate Presentation

May 13, 2024

Forward Looking Statements

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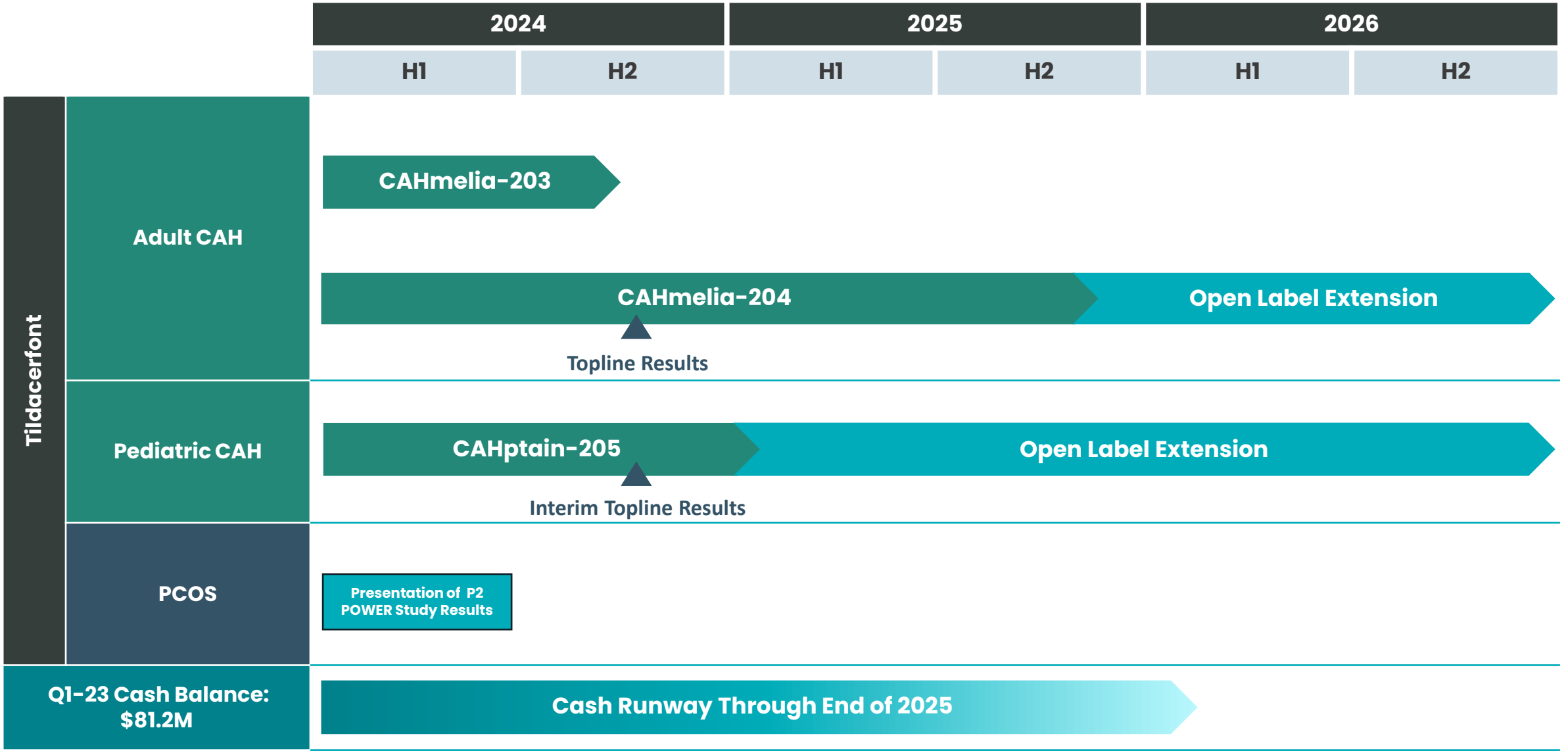
This presentation discusses a product candidate that is under clinical study and which has not yet been approved for marketing by the U.S. Food and Drug Administration. No representation is made as to the safety or effectiveness of this product candidate for the use for which it is being studied.

Spruce Bio: Transforming Care in Rare Endocrinology

Large Market Primed for Innovation	**~$3B+ orphan market in CAH** with high unmet need, low competitive intensity, and no FDA-approved treatments
Potentially Transformative Treatment Paradigm	Tildacerfont is a **once-daily, second generation CRF-1 receptor antagonist** with clear MOA
Global Phase 2b CAHmelia-204 Study in Adult CAH Ongoing	Data from CAHmelia-204 in **Adult CAH patients on supraphysiologic GCs and androgen control** expected in **Q3 2024**
Phase 2 CAHptain-205 Dose Ranging CAH Study Ongoing	**Positive topline results in CAHptain** support further dose ranging; **Interim data** from additional dose ranging anticipated in **Q3 2024**
EOP2 Meeting with FDA Planned in Early 2025	**EOP2 meeting for Adult and Pediatric CAH** anticipated in **Q1 2025**, assuming positive results from CAHmelia and CAHptain
Strong IP Protection	Comprehensive IP portfolio with **exclusivity to 2038** combined with **Orphan Drug Designation for CAH** in U.S. and E.U.

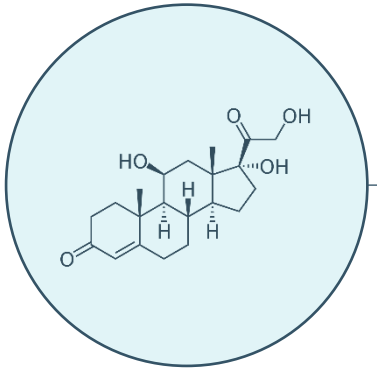
Overview of Anticipated Milestones and Cash Runway



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

Classic CAH Disease Overview

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



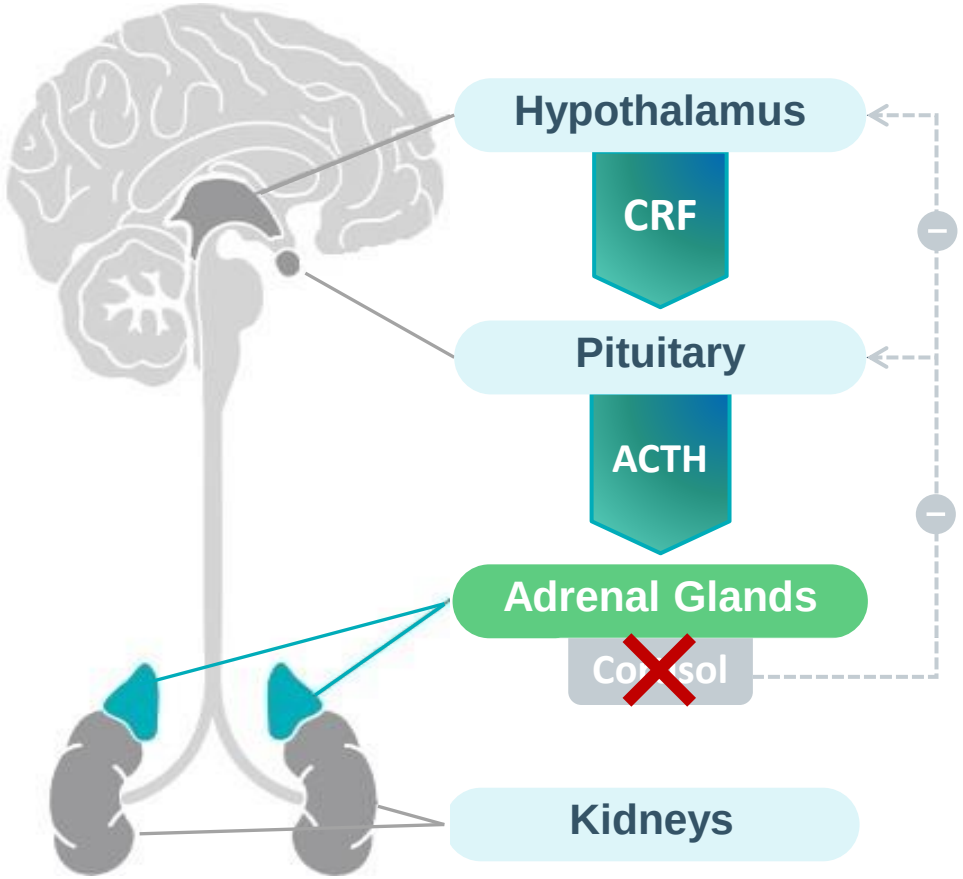
Classic CAH is an autosomal recessive disease characterized by an inability to produce cortisol, leading to a chronic imbalance of key hormones and an overproduction of adrenal androgens.

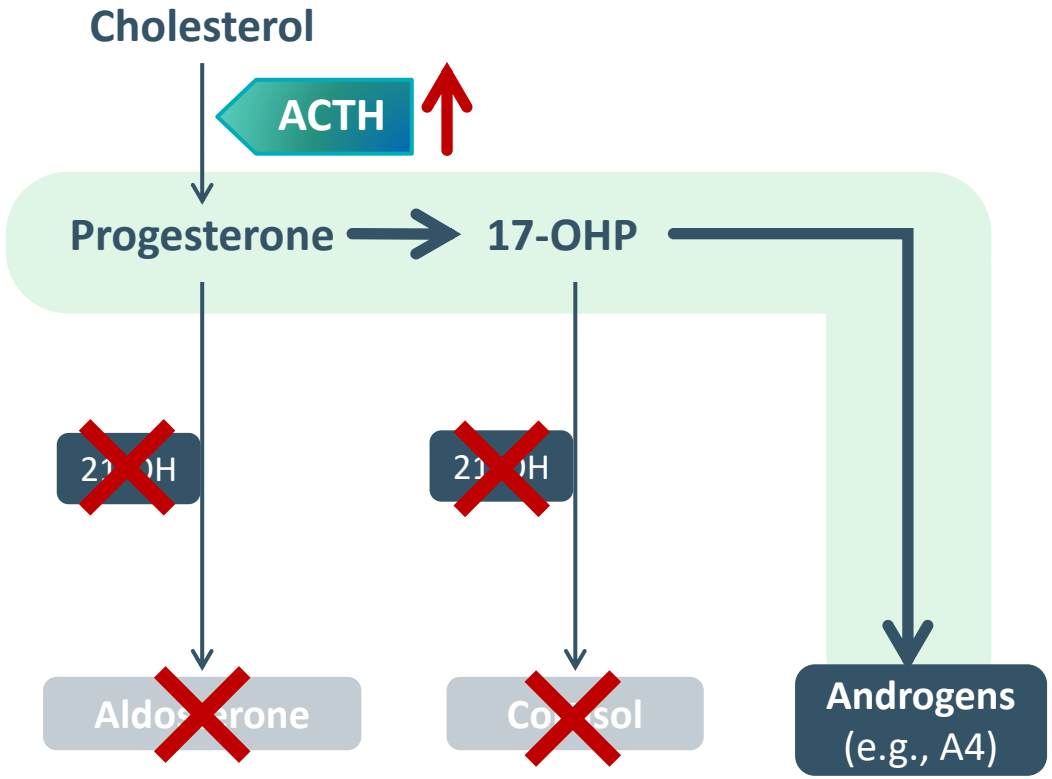
Due to the severity and high incidence of the disease, most developed countries have established newborn screening programs to test for classic CAH at birth.

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.

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 overstimulation and hyperplasia of adrenal glands
- 17-OHP is routed to the androgen pathway, resulting in excess androgens



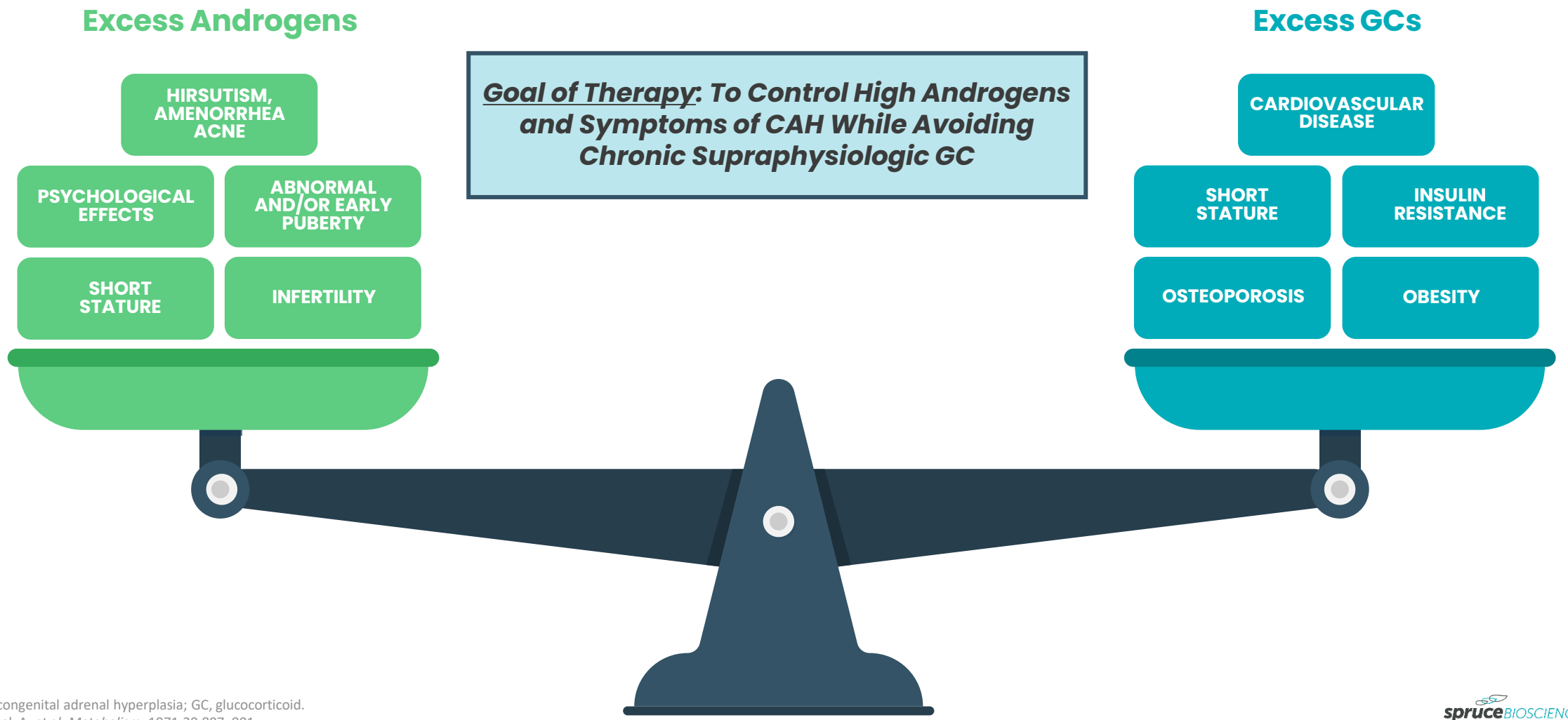


17-OHP, 17-hydroxyprogesterone; 21-OH, 21-hydroxylase; 21-OHD, 21-hydroxylase deficient; ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; CRF, corticotropin releasing factor; HPA, hypothalamic-pituitary-adrenal.

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

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 elevated adrenal androgens** which result in **comorbidities linked to excessive chronic GC use**



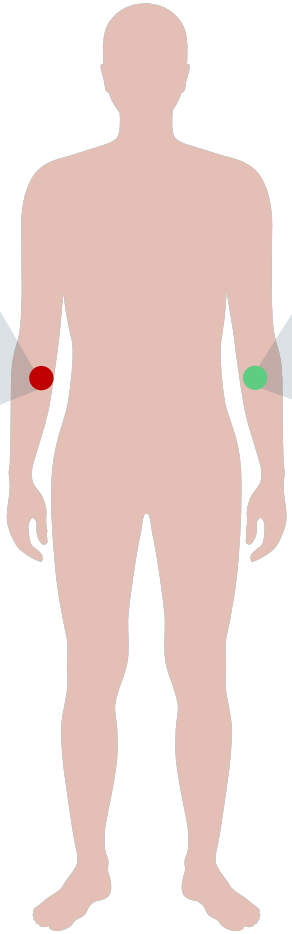
CAH, congenital adrenal hyperplasia; GC, glucocorticoid.
1. Hayek A, *et al. Metabolism*. 1971;20:897–901.

Unmet Need and Treatment Goals Vary By Disease Status

Management of classic CAH requires a balance between **adrenal androgen suppression** and **GC replacement**[1,2]

Severe Hyperandrogenemia

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



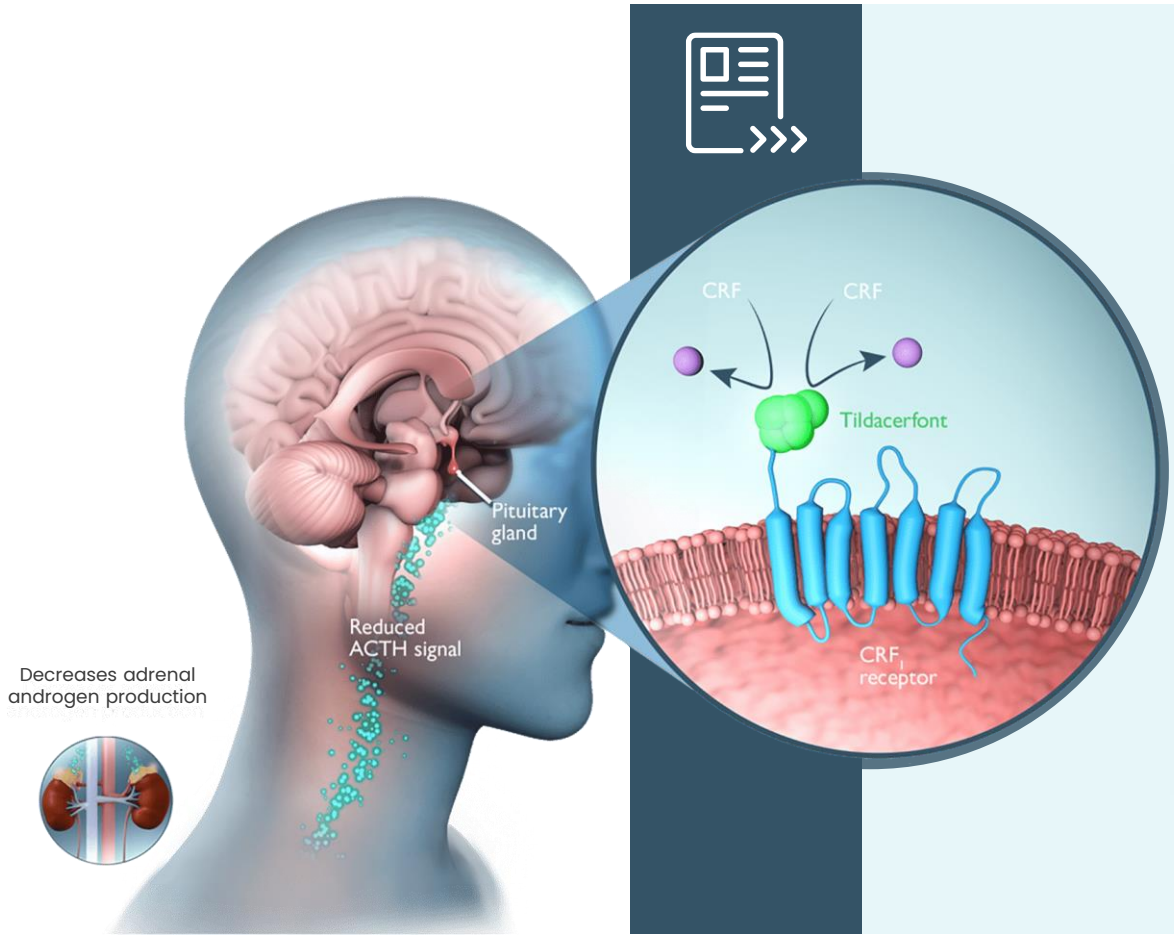
Supraphysiologic GCs

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

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.

Tildacerfont is a Second-Generation 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].

P2a Study 202: Baseline Demographics

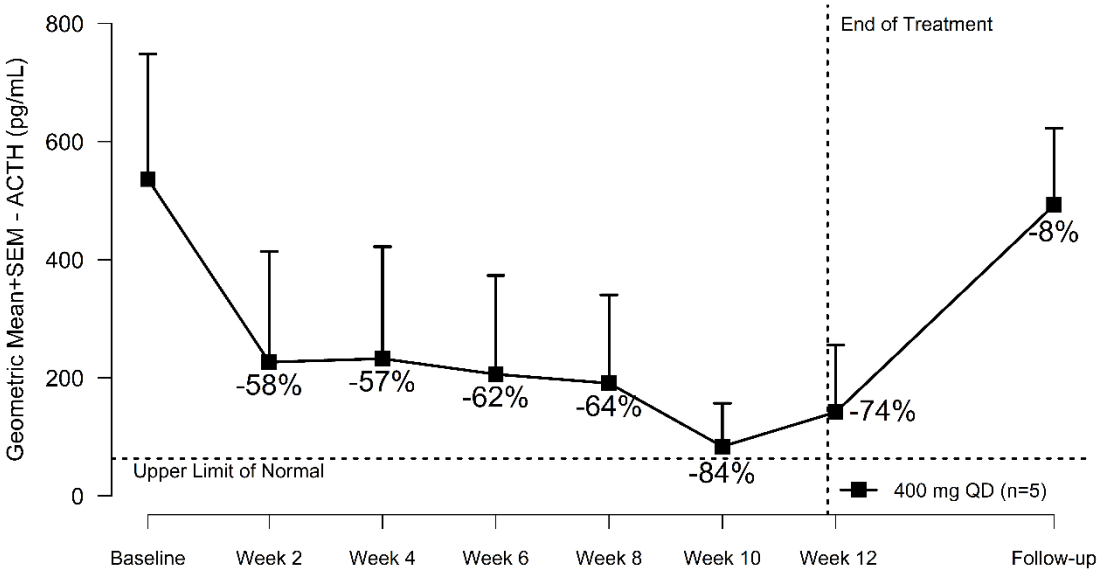
	Patients with A4 < 2x ULN (N=3)	Patients with A4 > 2x ULN (N=5)
Demographics		
Age (yrs), mean (SD)	48.0 (17.69)	42.4 (15.63)
Sex, Female, n (%)	3 (100%)	2 (40%)
Race, White n (%)	3 (100%)	4 (80%)
BMI (kg/m2), mean (SD)	35.5 (6.10)	27.8 (5.56)
Baseline Glucocorticoid dose		
Dose (mg) in Hydrocortisone equivalents	36.7 (11.6)	24.5 (11.5)
Baseline hormones		
ACTH (ng/mL), geometric mean (CV%)	12.2 (584.1%)	536.6 (108.5%)
17-OHP (ng/dL), geometric mean (CV%)	314.1 (1068.6%)	15323.3 (46.9%)
A4 (pg/dL), geometric mean (CV%)	28.8 (216.1%)	1001.1 (48.4%)

Subjects on dexamethasone (n=3), metabolized through CYP3A4, excluded from baseline and efficacy summaries due to observed increased in exposures but included in safety summary

P2a Study 202: Robust Reduction in Disease Biomarkers

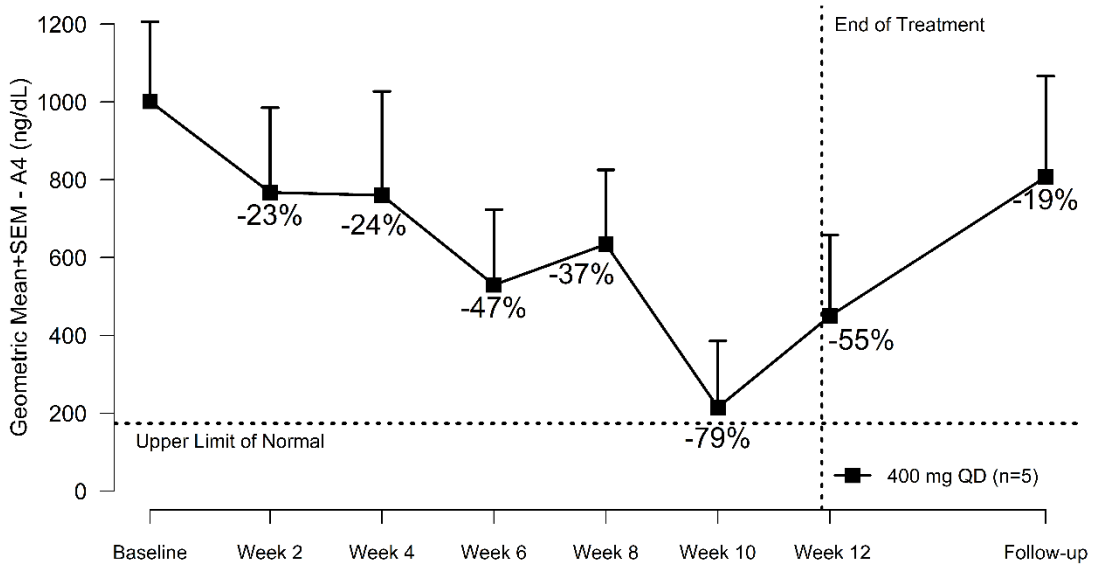
- Maximum reduction in **adrenocorticotropic hormone (ACTH) and androstenedione (A4) of 84% and 79**%, respectively, in patients with highly elevated androstenedione (A4) levels at baseline.

ACTH



- Normalization of ACTH achieved in 60% of patients*

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; 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 Baseline Characteristics

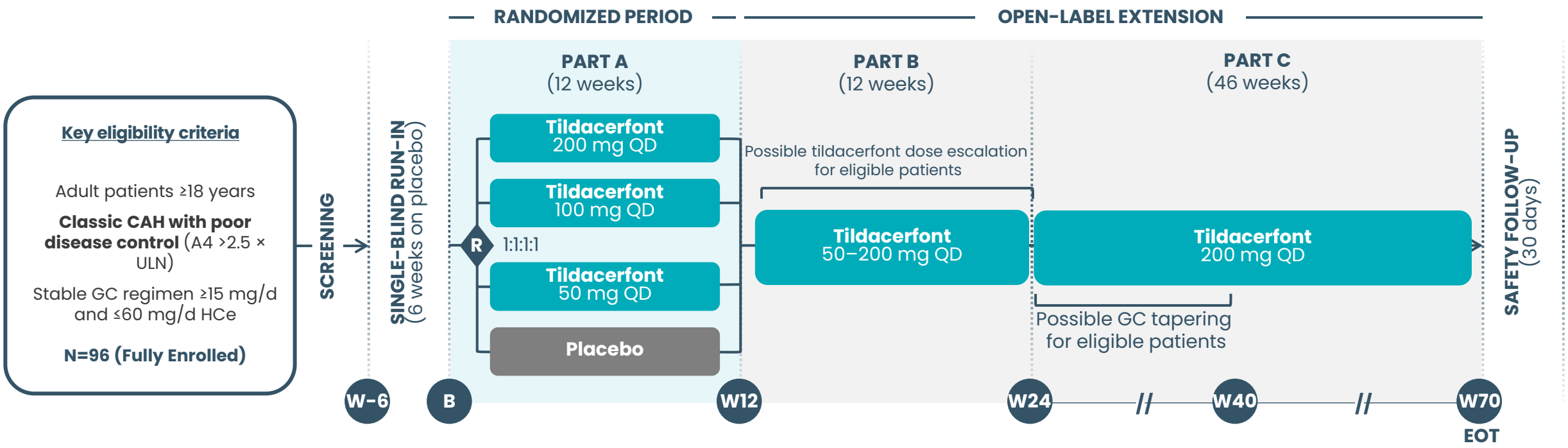
CAHmelia 203 and 204 Baseline Characteristics Highlight Two Distinct Patient Populations in Adult CAH with Differing Disease Status and Treatment Goals

Baseline Characteristics	CAHmelia-203	CAHmelia-204	Ph3 CRF_1 Study in Adult CAH
Treatment Goal	**Hyperandrogenemia Control**	**GC Reduction With Androgenic Control[3]**	**GC Reduction Without Androgenic Control[4]**
Number of Subjects	96	100	182
Male/Female	47% Male 53% Female	47% Male 53% Female	51% Male 49% Female
Average Age Age Range	32 Years Old (18 – 65 Years Old)	33 Years Old (18 – 64 Years Old)	31 Years Old (18-58 Years Old)
Average Glucocorticoid (GC) Dose[1]	27 mg/day (14 mg/m^2/day)	37 mg/day (20 mg/m^2/day)	32 mg/d (18 mg/m^2/day)
Average Androstenedione (A4) Level[2]	1,151 ng/dL (>5x ULN)	224 ng/dL (~ULN)	620 ng/dL (~3x ULN)
Average Baseline 17-Hydroxyprogesterone (17-OHP) Level[2]	16,653 ng/dL (>80x ULN)	5,675 ng/dL (>28x ULN)	Not Disclosed
Average Baseline Adrenocorticotropic (ACTH) Level[2]	435 pg/dL (>6x ULN)	168 pg/dL (>2x ULN)	Not Disclosed
Body Mass Index (BMI)	50% Obese (BMI ≥ 30 kg/m^2)	53% Obese (BMI ≥ 30 kg/m^2)	47% Obese (BMI ≥ 30 kg/m^2)

[1] In hydrocortisone equivalents (HCe) [2] Pre-GC dose. [3] A4 <ULN for age and sex. [4] A4 <120% of the subject's baseline or <ULN for age and sex.

CAHmelia-203: P2b Study in Adult CAH with Severe Hyperandrogenemia

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



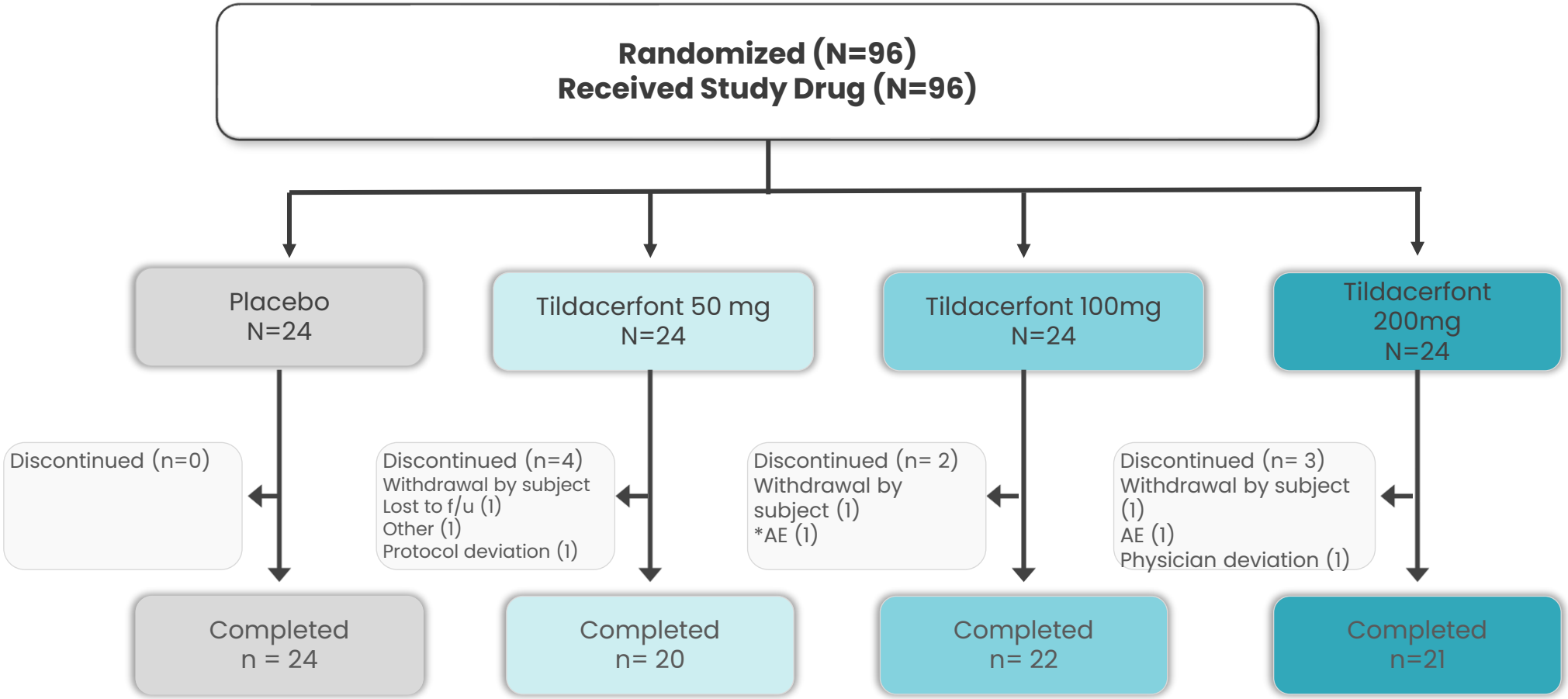
PRIMARY ENDPOINT

Assessment of dose response for the change from baseline in A4 after 12 weeks

Study schema is not drawn to scale.

CAHmelia-203 Participants Disposition in 12-Week Double Blind Period

91% of patients completed CAHmelia-203 through week 12



Source: Table 14.1.1.2.1; *AE=bilateral breast pain; depression

CAHmelia-203 Topline: No Dose Response or Reduction in A4

Data Highlights

The clinical trial did not achieve the primary efficacy endpoint of the assessment of dose response for the change in A4 from baseline to week 12.

200mg QD of tildacerfont demonstrated a placebo-adjusted reduction from baseline in A4 of -2.6% (p-value not significant) at week 12.

Compliance with study medication and GC was low with only 50% of patients reporting 80% or greater compliance.

Tildacerfont was generally safe and well tolerated at all doses with no treatment-related serious adverse events (SAEs). Most adverse events were reported as mild to moderate.

The CAHmelia-203 results underscore the complexities inherent in managing a patient group with challenges related to androgenic control and GC compliance. Based on my clinical experience, patients within this group may face difficulties adhering to any therapeutic interventions, potentially impacting treatment outcomes…" -

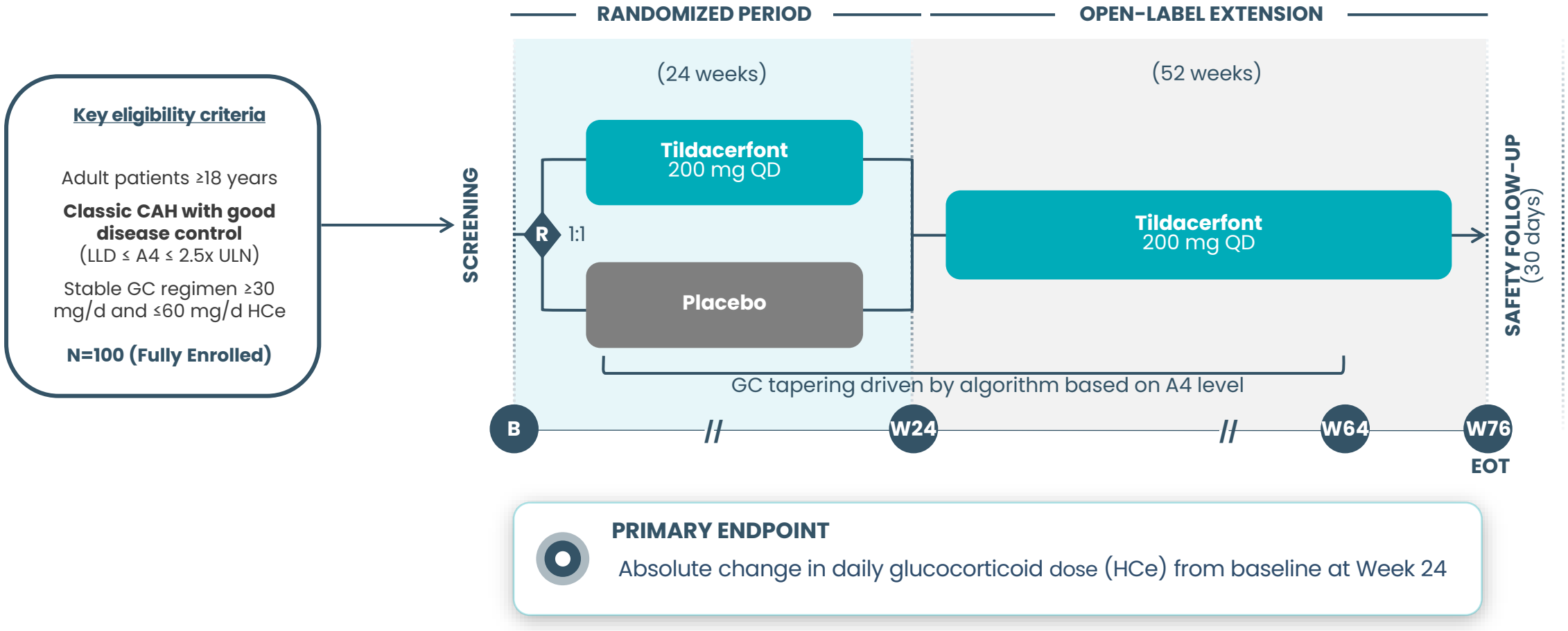
Irina Bancos, MD

Mayo Clinic

203 Investigator | CAH KOL

CAHmelia-204: P2b Study in Adult CAH with Androgenic Control

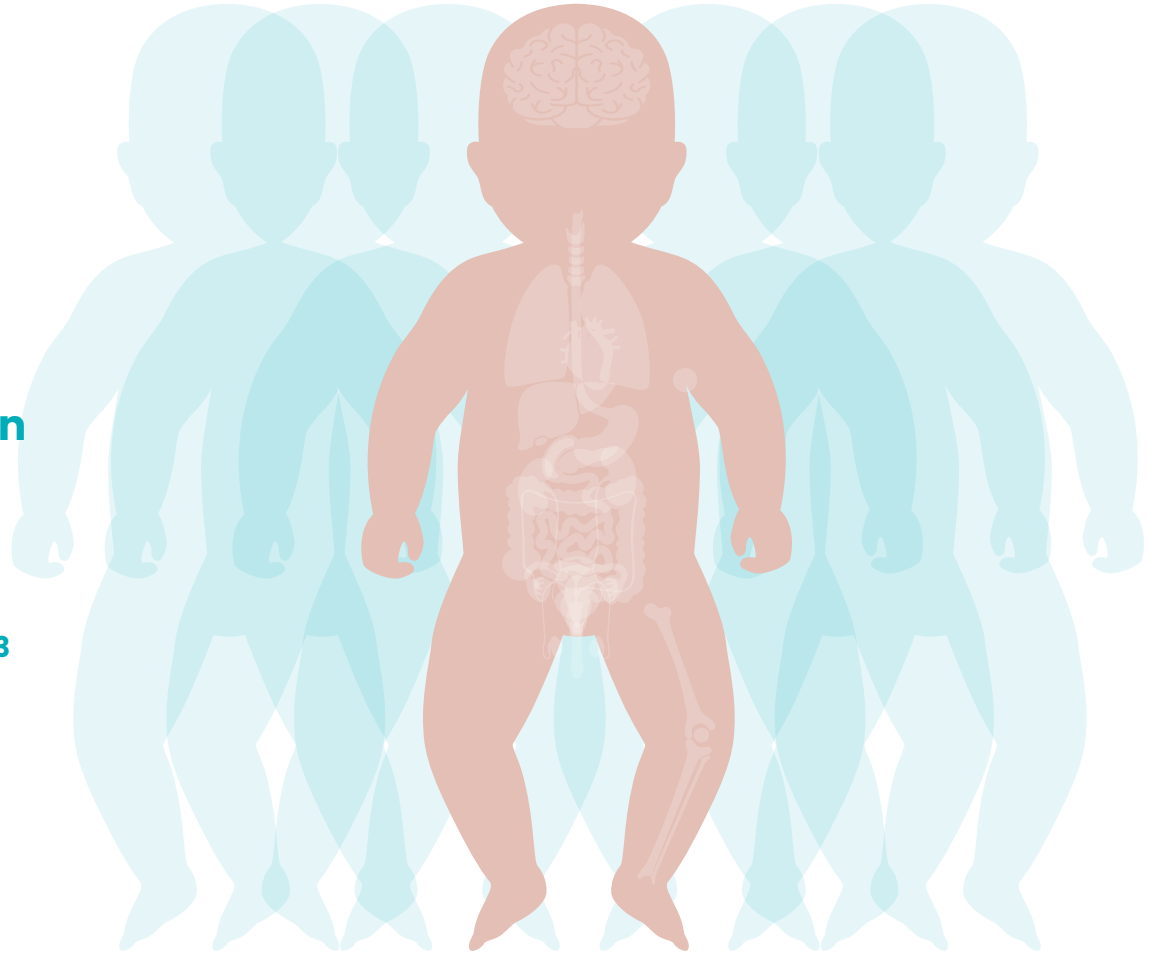
A randomized, double-blind, placebo-controlled Phase 2b study to evaluate the efficacy and safety of tildacerfont in reducing supraphysiologic GC use in adult patients with classic CAH



Study schema is not drawn to scale.

Novel Therapies Needed to Balance Androgen and 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 and Early Childhood

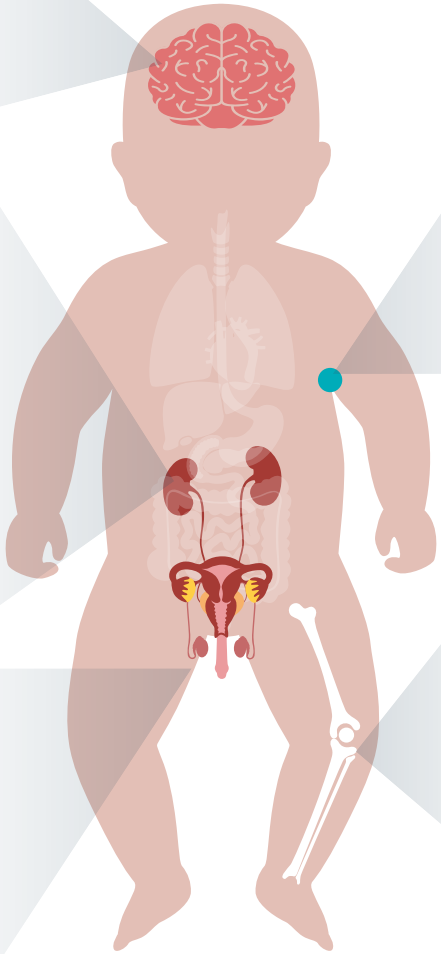
BEHAVIORAL
Increased prevalence of ADHD[4]

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]

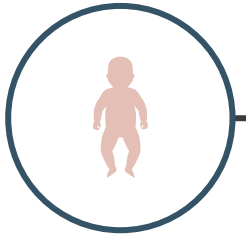
- Early growth acceleration
- Advanced bone age
- Premature epiphyseal closure

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.

Management Goals of CAH Vary by Age

Early childhood to puberty

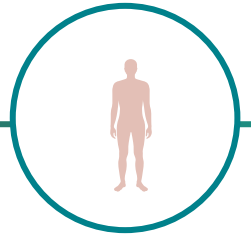


Goal of therapy:
Maximize androgen suppression for normal growth and pubertal development

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

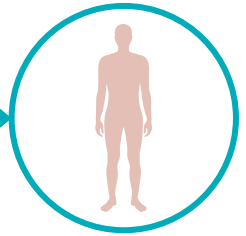


Goal of therapy:
Maintain adequate androgen suppression
despite rapid HC metabolism in puberty

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].


CAHptain
205

P2 CAHptain Study in Pediatric CAH (Cohorts 1-3)

Open-Label study with staggered cohorts, sentinel dosing

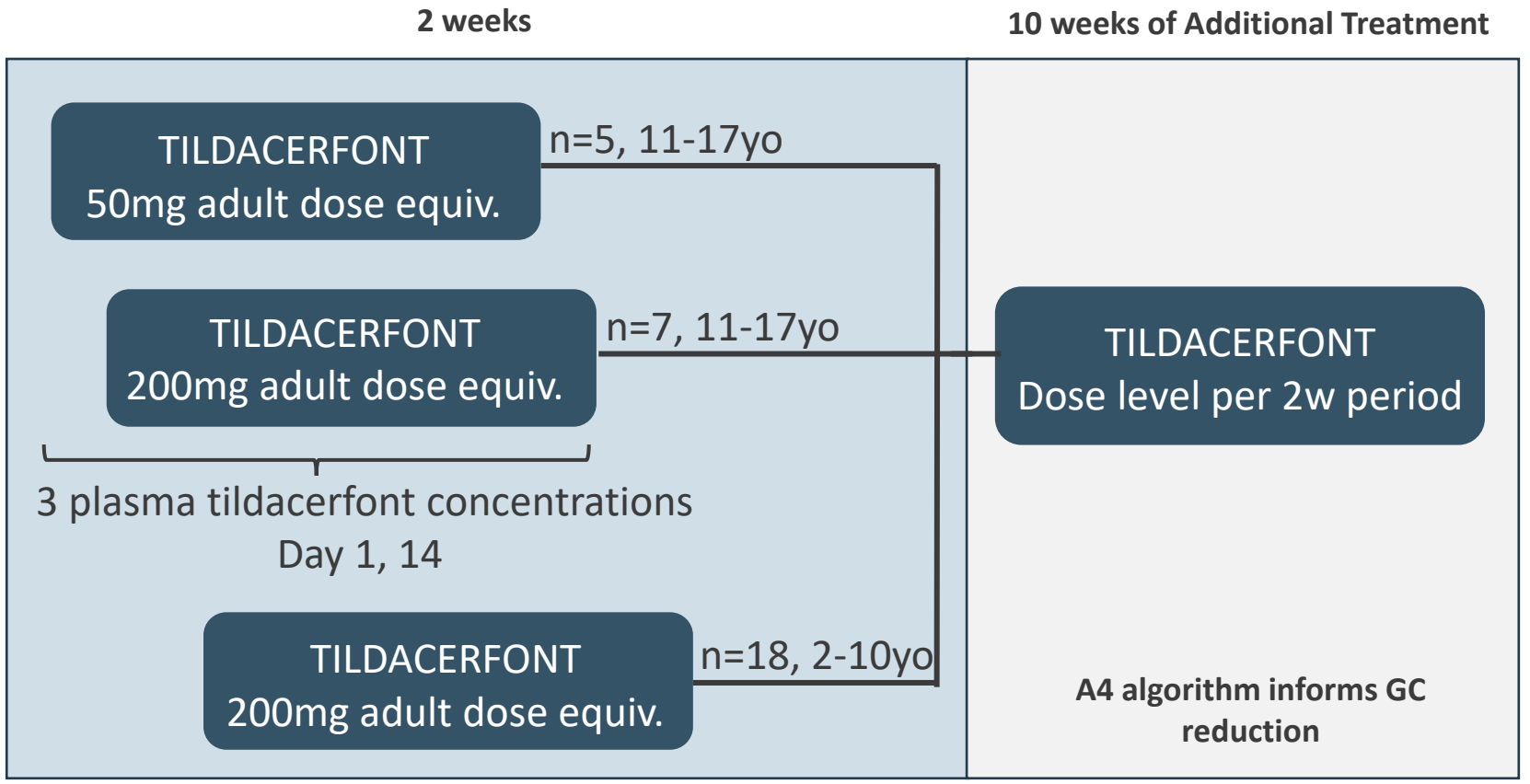
Key eligibility criteria

Male and female subjects aged 2 to 17 years old

Diagnosis of CAH due to 21-hydroxylase deficiency

Stable dose of GC

N=30 (Fully Enrolled)



Opportunity to decrease GC dose at Weeks 4, 8, and 12

1 EP: Safety

2 EP: Decrease in A4 or GC dose at w12
Decrease in A4 at w4*

* In participants with elevated baseline A4. GC doses were not changed during first 4 weeks.

CAHptain-205 Topline: Safe and Well-Tolerated in Children

Pharmacodynamic responses were observed despite lower-than-projected exposures

Data Highlights

Tildacerfont is well-tolerated in children

- All AEs were mild to moderate
- No treatment-related SAEs or AEs leading to study withdrawal

Pediatric doses were determined based on modelling

- Conservative dosing assumptions were employed to ensure patient safety
- Model overestimated exposure in children
- Tildacerfont exposure was lower than expected
  - Adult equivalent doses did not provide the same exposure in children

Target engagement was observed and led to improved CAH control despite suboptimal exposure

- 70% (16/23) of participants with elevated baseline A4 achieved A4 reductions at W4
- 73% (22/30) *demonstrated A4 or GC reduction after 12 weeks of treatment*

- No clear dose response observed- attributed to variable exposures

"These data are encouraging and suggest that tildacerfont at the right dose may enable clinically meaningful reduction of A4 and GC levels in children and adolescents,....I am excited for next stage in identifying the optimal pediatric dose that may improve long-term clinical outcomes, such as short stature and obesity, which are related to both androgen excess and exposure to chronic supraphysiologic GC doses."

Paul Thornton, M.B.B.S., Principal Investigator and Medical Director of a CAH Center of Excellence

Financial Highlights

Capital Structure and Summary Financials as of March 31, 2024

Capital Structure	Shares (M)
Shares Outstanding	41.2
Equity Awards Issued and Outstanding	7.9
Common Stock Warrants	12.7
Fully Diluted Shares Outstanding	61.8

Financials	000's
Cash & Cash Equivalents	$81,154
Debt[1]	$2,974

1. Term loan, gross balance as of March 31, 2024.

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