spruce BIOSCIENCES

Corporate Presentation

August 12, 2024

Forward Looking Statements

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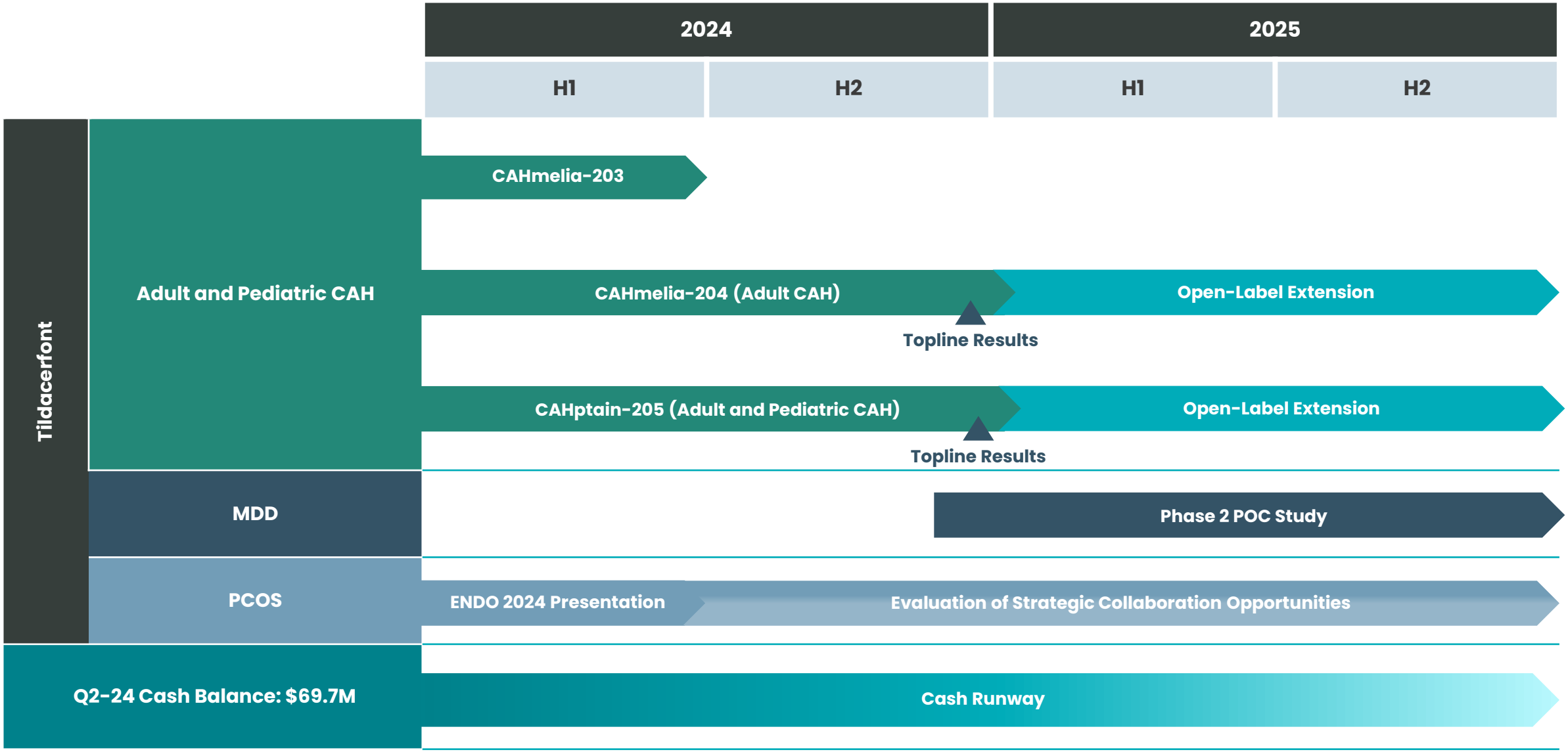
This presentation discusses a product candidate that is under clinical study and which has not yet been approved for marketing by the U.S. Food and Drug Administration. No representation is made as to the safety or effectiveness of this product candidate for the use for which it is being studied.

Spruce Bio: Transforming Care in Endocrinology and Neurology

Large Markets with High Unmet Need Primed for Innovation	**~$3B+** market in **CAH; ~$8B+** market in **PCOS,** and **~$10B+** market in **MDD**
Potentially Transformative Treatment Paradigm	Tildacerfont is an oral, **second generation CRF-1 receptor antagonist** with validated MOA and favorable safety profile
Adult and Pediatric CAH Program Ongoing	**CAHmelia-204 topline data** (Adult CAH) and **CAHptain-205 topline data** (Adult and Pediatric CAH) expected in **Q4 2024**
Strategic Collaboration to Develop Treatment for MDD	**Strategic collaboration** with HMNC Brain Health to **initiate Phase 2 study** of tildacerfont and Cortibon (CDx) for MDD **in Q4 2024**
Positive Ph2 POWER Study of Tildacerfont in PCOS	POWER study demonstrates **significant reduction in DHEAS**; evaluation of strategic collaboration opportunities underway
Strong IP Protection	Comprehensive IP portfolio with **exclusivity to 2038** combined with **Orphan Drug Designation for CAH** in U.S. and E.U.

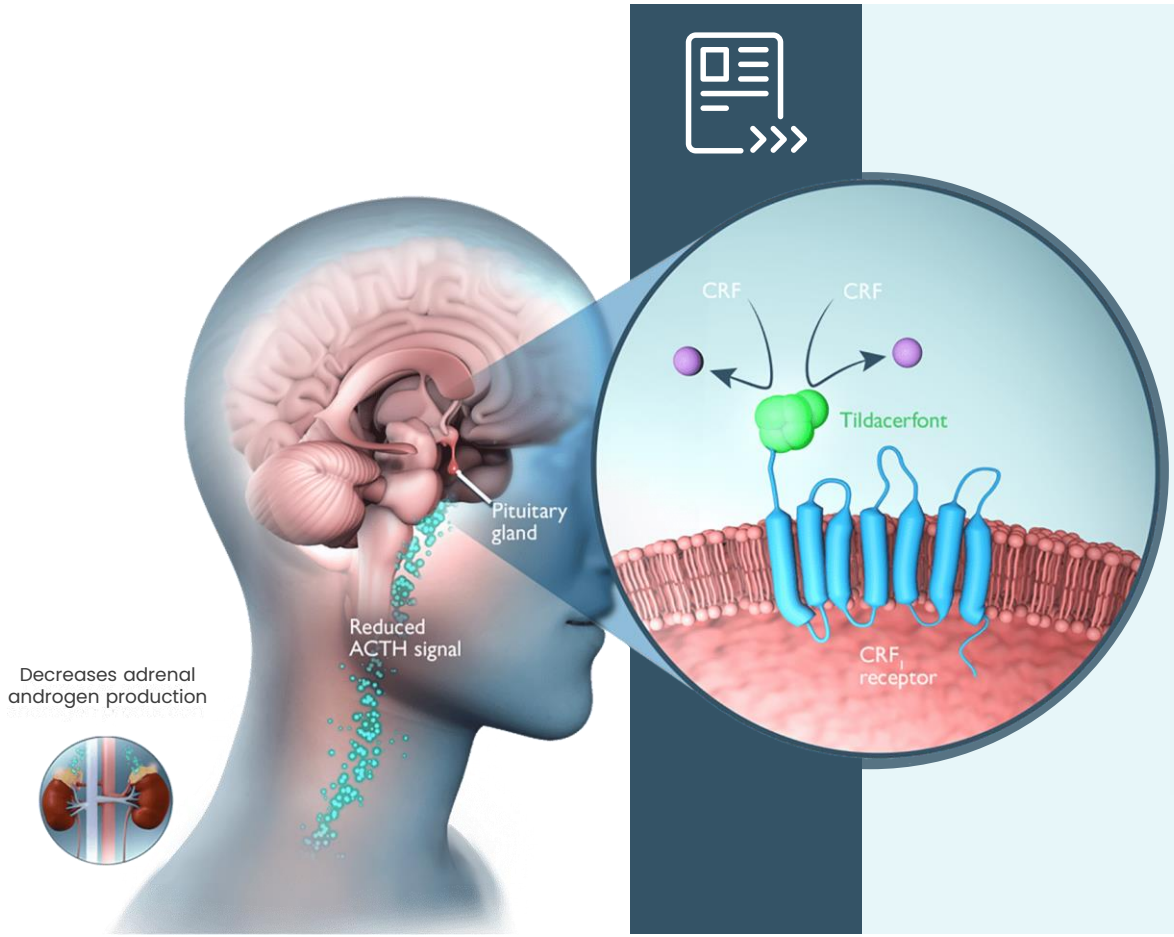
Note: CAH is congenital adrenal hyperplasia, MDD is major depressive disorder; PCOS is polycystic ovary syndrome.

Overview of Anticipated Milestones and Cash Runway



Note: CAH is congenital adrenal hyperplasia, MDD is major depressive disorder; PCOS is polycystic ovary syndrome.

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].

Adult and Pediatric Congenital Adrenal Hyperplasia (CAH)

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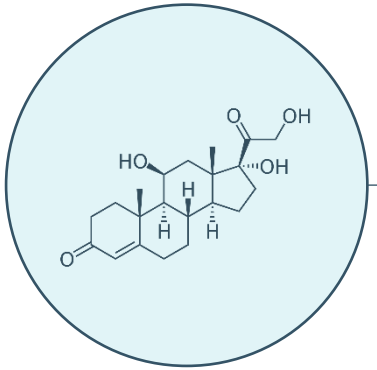
Classic CAH Disease Overview

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



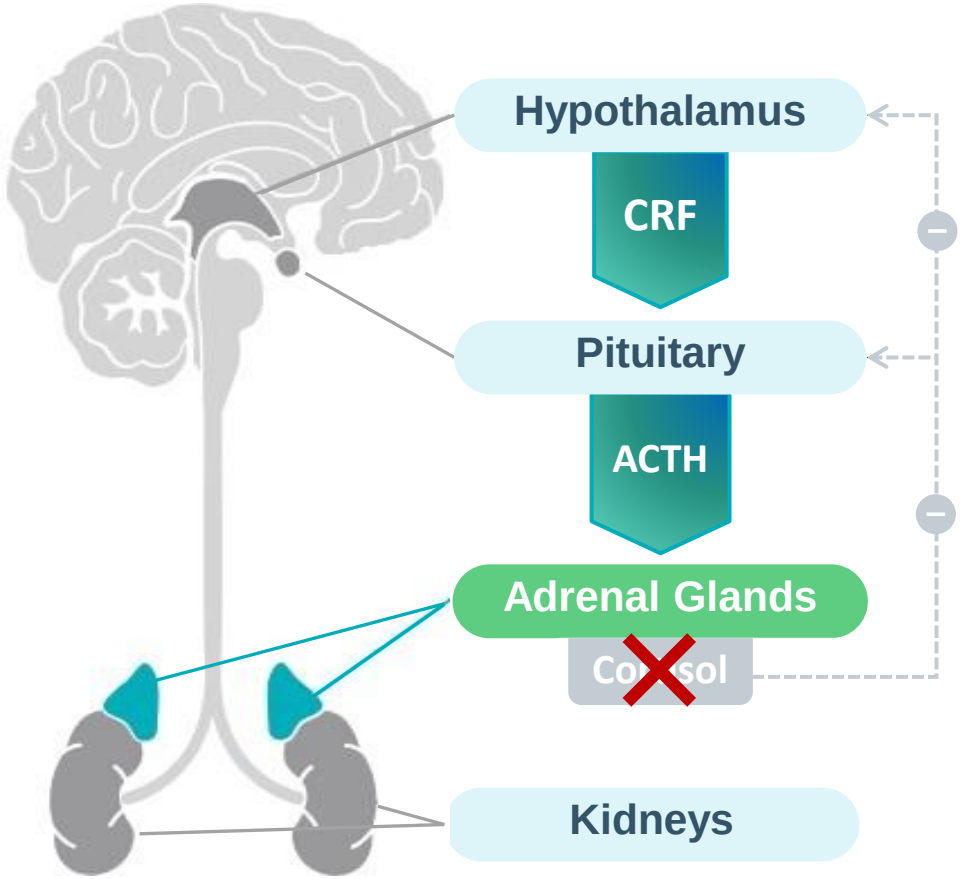
Classic CAH is an autosomal recessive disease characterized by an inability to produce cortisol, leading to a chronic imbalance of key hormones and an overproduction of adrenal androgens.

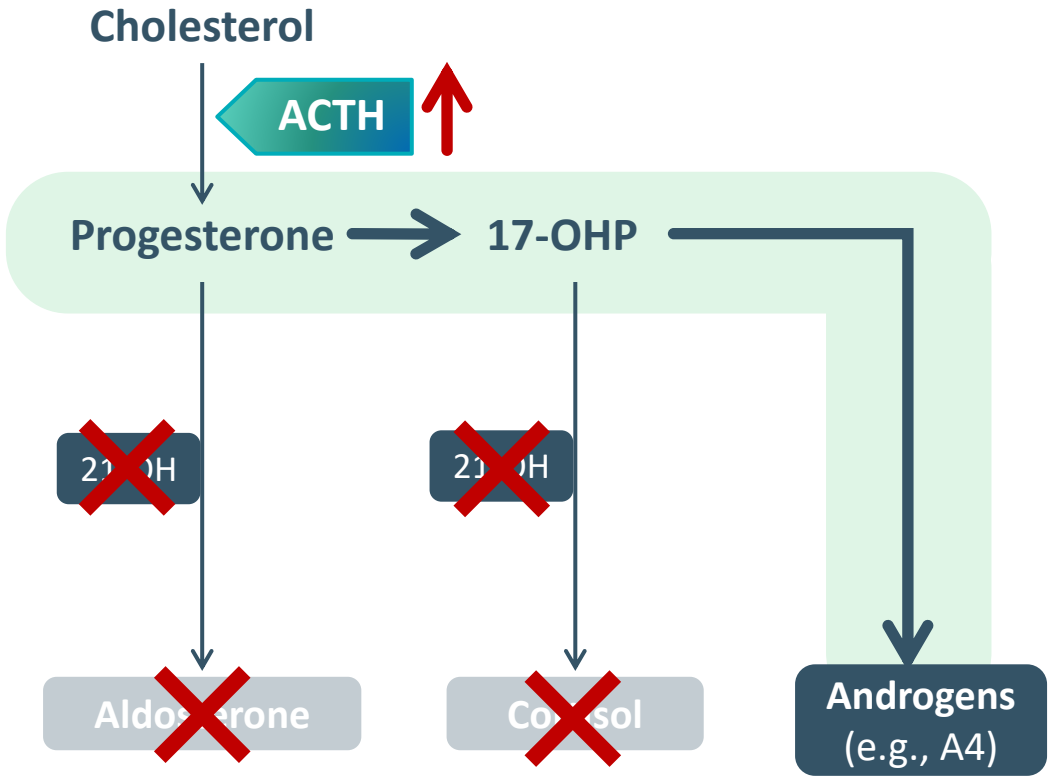
Due to the severity and high incidence of the disease, most developed countries have established newborn screening programs to test for classic CAH at birth.

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

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.

Classic CAH Presents in Infancy and Early Childhood

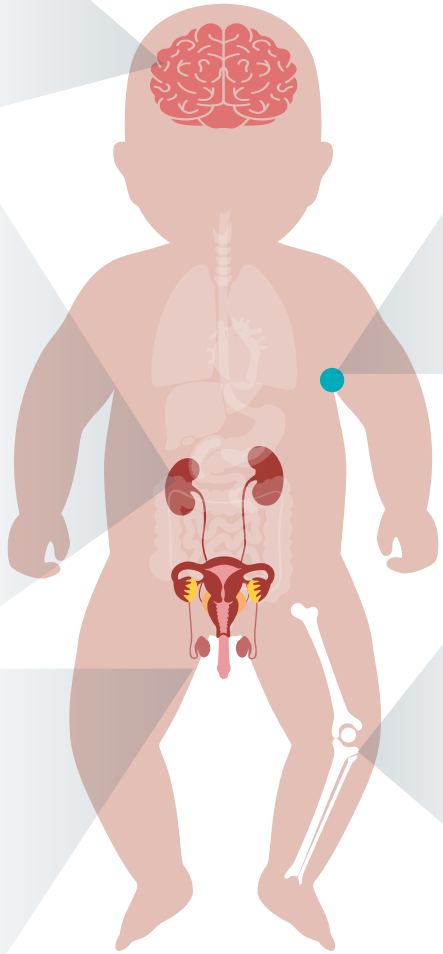
BEHAVIORAL
Increased prevalence of ADHD[4]

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]

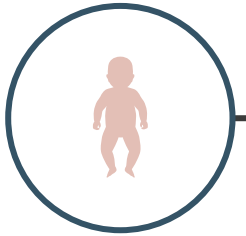
- Early growth acceleration
- Advanced bone age
- Premature epiphyseal closure

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

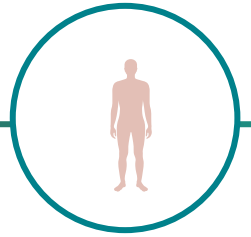


Goal of therapy:
Maximize androgen suppression for normal growth and pubertal development

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

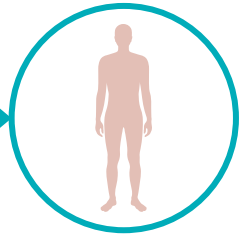


Goal of therapy:
Maintain adequate androgen suppression
despite rapid HC metabolism in puberty

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.

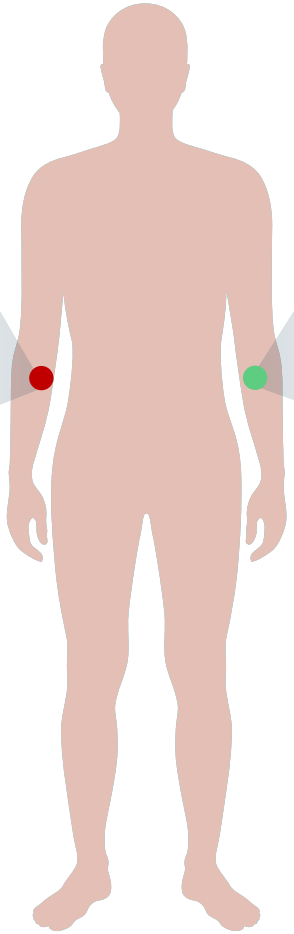
1. Claahsen-van der Grinten HL, *et al. Endocr Rev.* 2021;bnab016. DOI: https://doi.org/10.1210/endrev/bnab016 [Epub ahead of print].

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

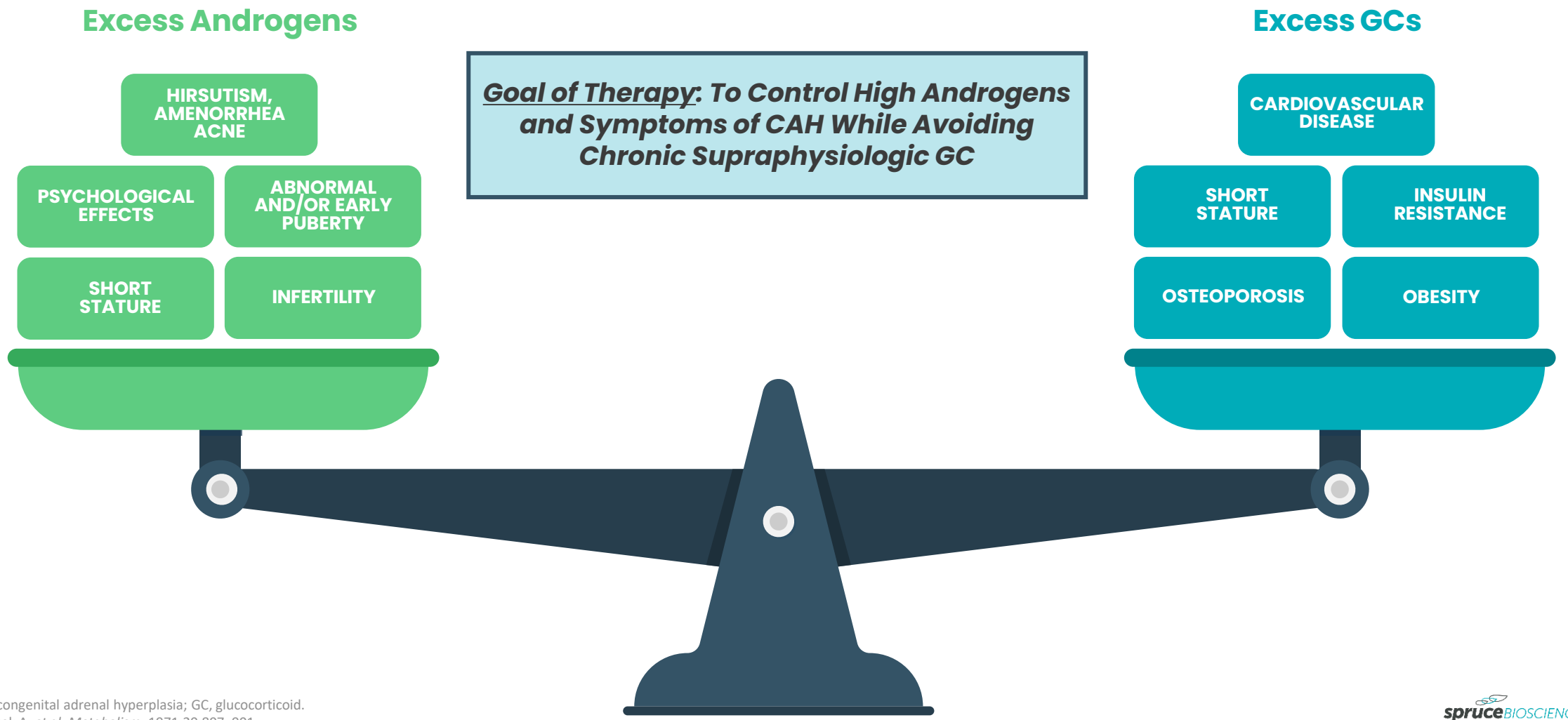
- Normal or near normal adrenal androgens
- Unmet need to **reduce GC dose** and improve related clinical outcomes
- Better adherence to GC therapy

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.

Novel Therapies are Needed in 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.

P2a Study 202 in Adult CAH: Baseline Demographics

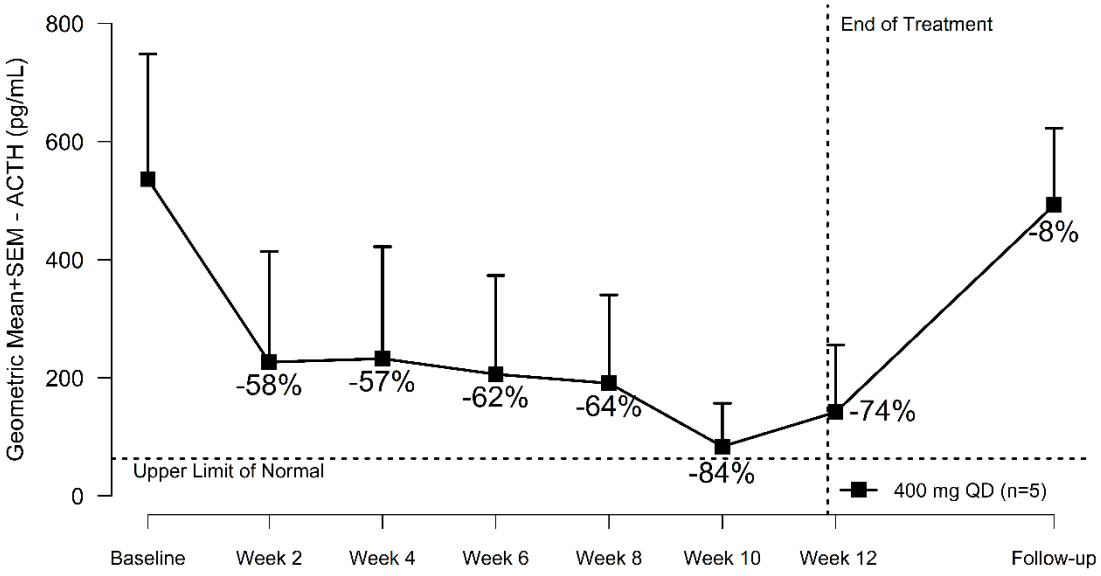
	Patients with A4 < 2x ULN (N=3)	Patients with A4 > 2x ULN (N=5)
Demographics		
Age (yrs), mean (SD)	48.0 (17.69)	42.4 (15.63)
Sex, Female, n (%)	3 (100%)	2 (40%)
Race, White n (%)	3 (100%)	4 (80%)
BMI (kg/m2), mean (SD)	35.5 (6.10)	27.8 (5.56)
Baseline Glucocorticoid dose		
Dose (mg) in Hydrocortisone 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 in Adult CAH: Robust Reduction in Adrenal Hormones

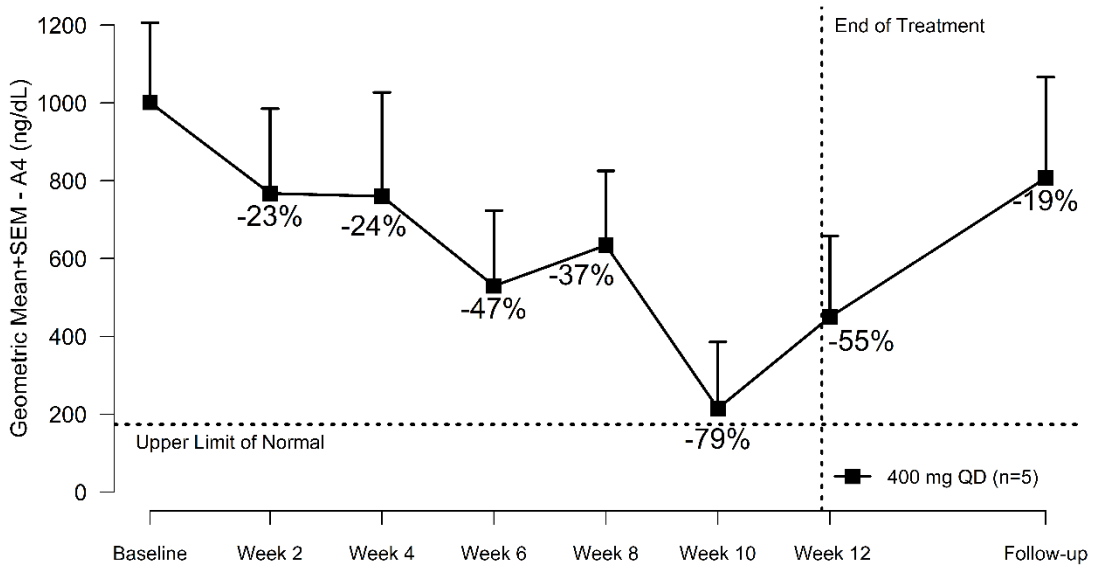
- Maximum reduction in **adrenocorticotropic hormone (ACTH) and androstenedione (A4) of 84% and 79**%, respectively, in patients with highly elevated androstenedione (A4) levels at baseline.

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

CAHmelia Baseline Characteristics

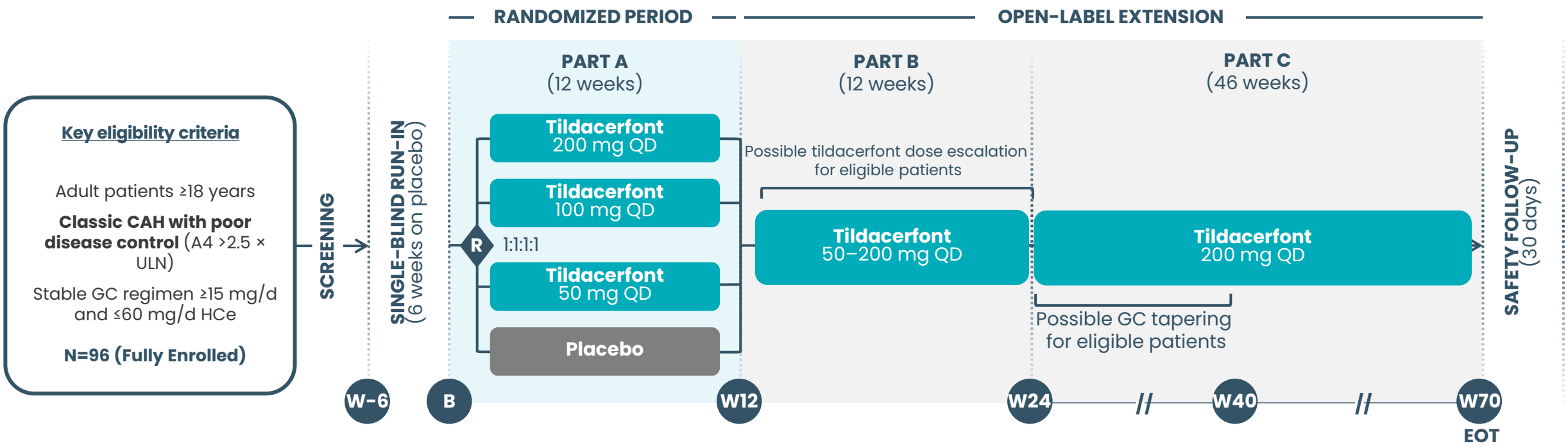
CAHmelia 203 and 204 Baseline Characteristics Highlight Two Distinct Patient Populations in Adult CAH with Differing Disease Status and Treatment Goals

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 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**



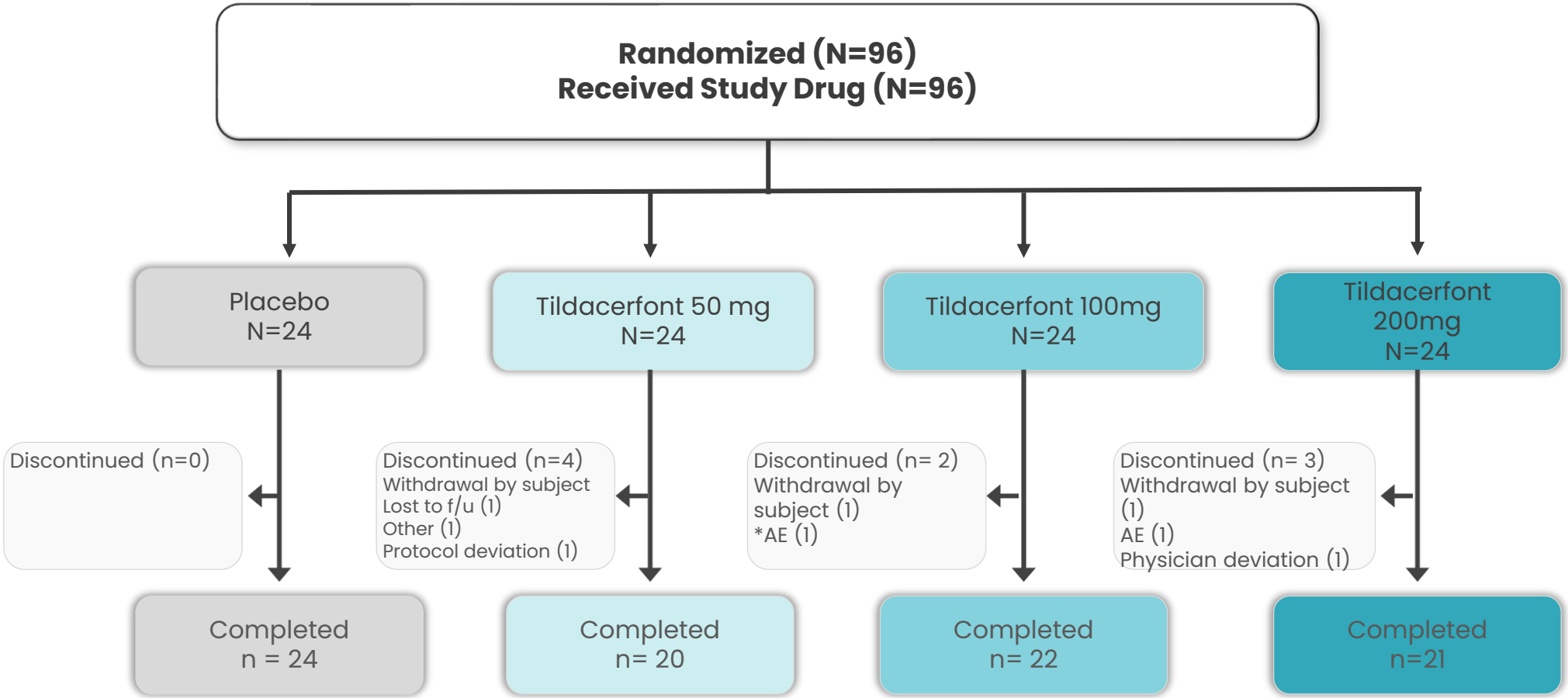
PRIMARY ENDPOINT

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

Study schema is not drawn to scale.

CAHmelia-203 Study Participant Disposition

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

Analyses of Data from CAHmelia-203

Correlation Between Tildacerfont Response and Baseline GC Dose and Drug Compliance

- **Directionally favorable reductions in ACTH** were noted in the blinded and open-label portions of the study with a **maximum mean reduction of 45%** at week 64 (n = 19).

- **Higher GC doses at baseline** were associated with **larger placebo-adjusted reductions from baseline in A4 after** the initial 12 weeks of treatment with tildacerfont.
  - **Baseline GC dose of 15mg hydrocortisone equivalents (HCe)** had a **mean placebo-adjusted *increase* from baseline in A4 of 18%**, compared to a **baseline GC dose of 55mg HCe**, which had a **mean placebo-adjusted *decrease* from baseline in A4 of 27%**.

- Patients in **CAHmelia-203** enrolled with a **mean baseline daily GC dose of 27mg HCe**, compared to patients in **CAHmelia-204** who enrolled with a **mean baseline daily GC dose of 37mg HCe**.

- **Higher rates of study drug compliance** were associated with **larger placebo-adjusted reductions from baseline in A4** after 12 weeks of treatment with tildacerfont.
  - Patients with **compliance to study drug of 55%** had a **mean placebo-adjusted *increase* from baseline in A4 of 14%**, compared to patients who were **fully compliant** who had a **mean placebo-adjusted *decrease* from baseline in A4 up to 14%**.

CAHmelia-204 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

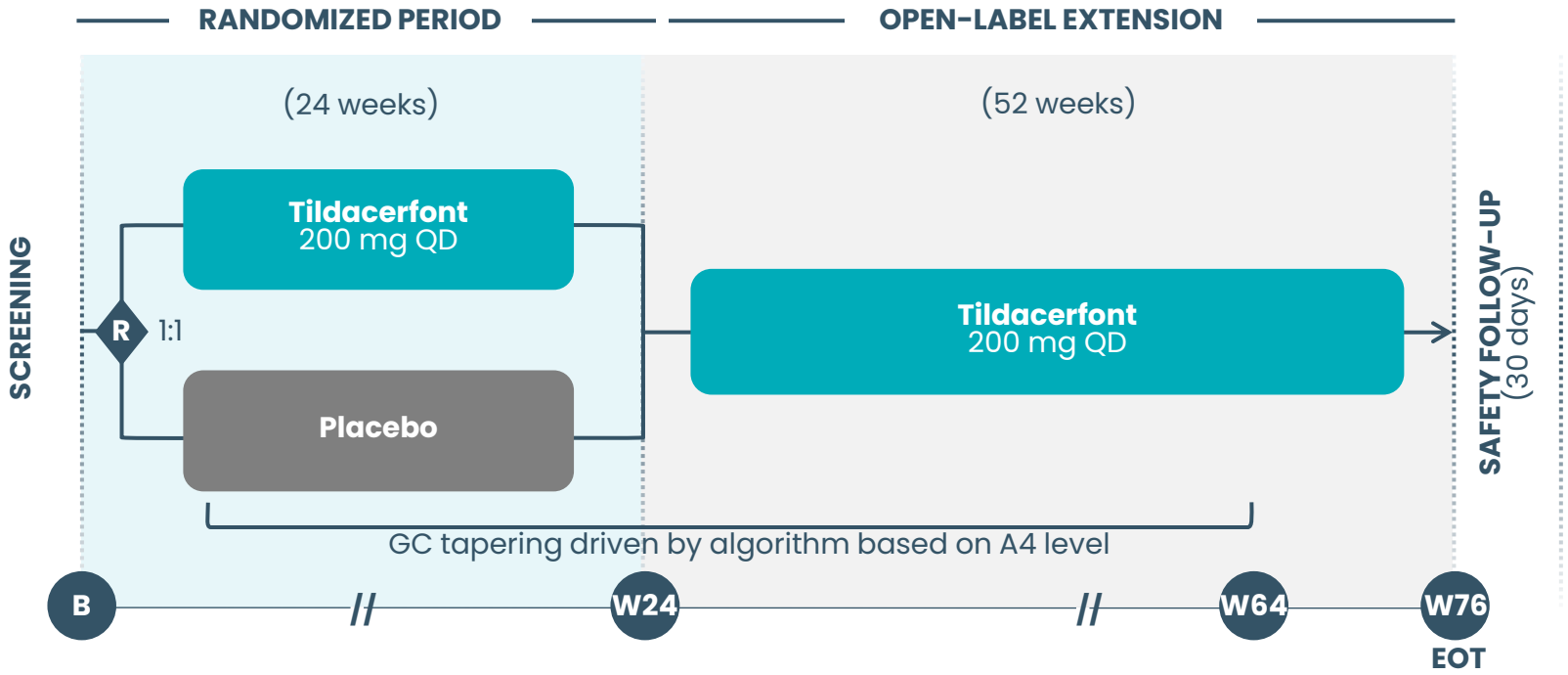
Key eligibility criteria

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=100 (Fully Enrolled)



PRIMARY ENDPOINT

Absolute change in daily glucocorticoid dose (HCe) from baseline at Week 24

Study schema is not drawn to scale.


CAHptain
205

CAHptain Study in Pediatric CAH (Cohorts 1-3)

Open-Label study with staggered cohorts, sentinel dosing

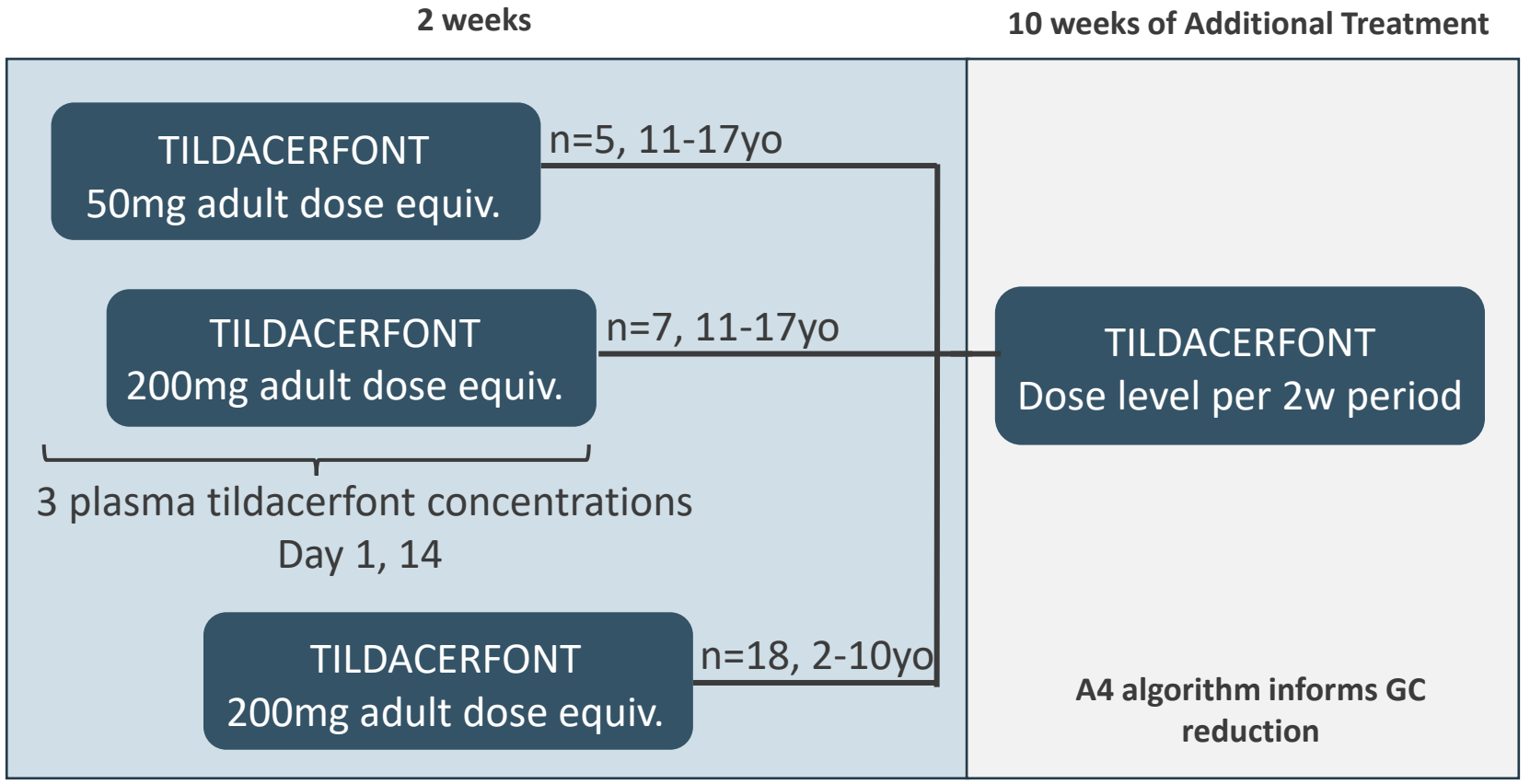
Key eligibility criteria for Cohorts 1-3

Male and female subjects aged 2 to 17 years old

Diagnosis of CAH due to 21-hydroxylase deficiency

Stable dose of GC

N=30 (Cohorts 1-3)



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

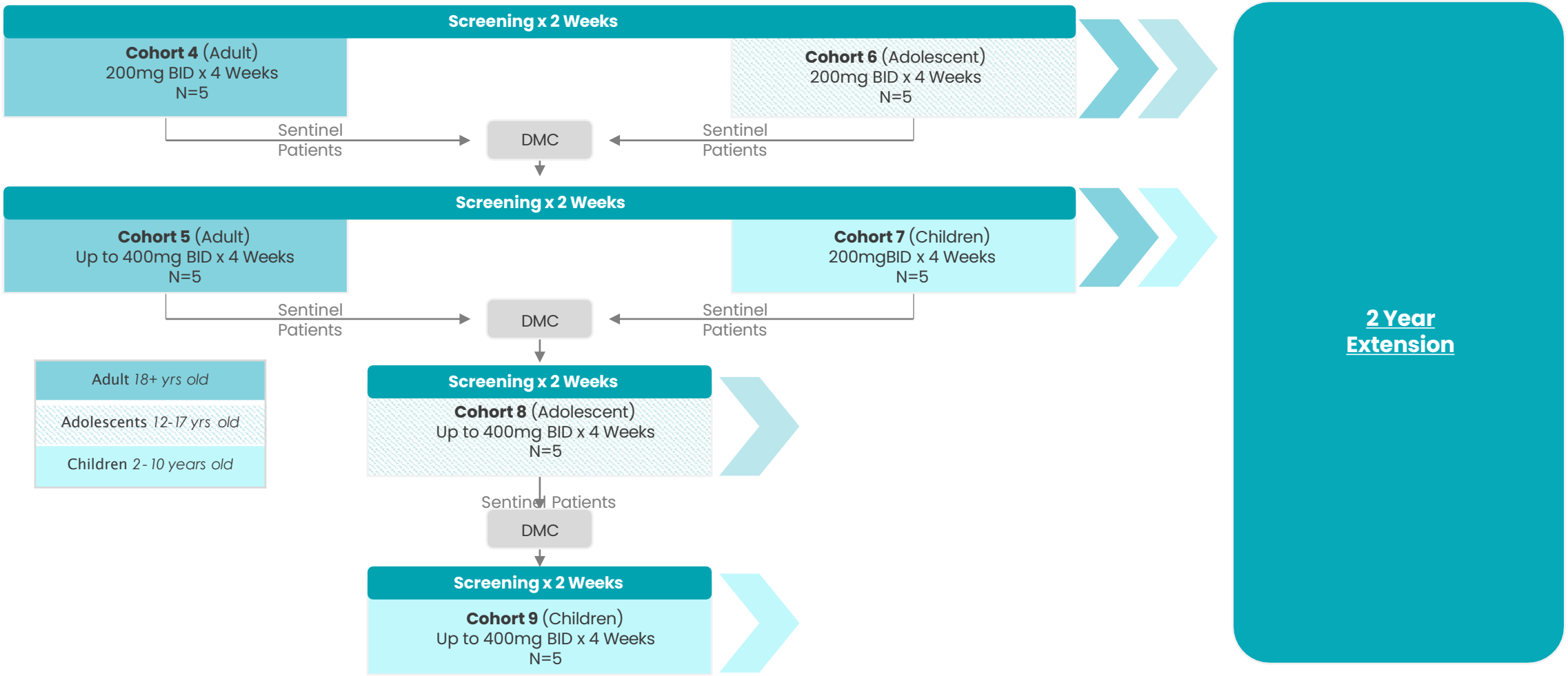
- 70% (16/23) of participants with elevated baseline A4 achieved A4 reductions at W4
- 73% (22/30) *demonstrated A4 or GC reduction after 12 weeks of treatment*

- 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

CAHptain-205 Dose Ranging Expanded into Adults and Pediatric



Polycystic Ovary Syndrome (PCOS)

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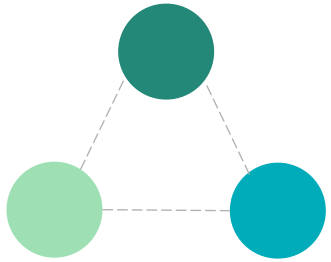
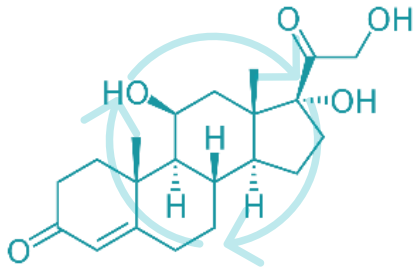
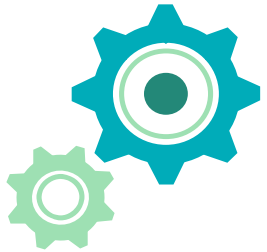
PCOS IS A COMMON, CHRONIC ENDOCRINE DISORDER



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 RISKS

INTEGUMENTARY[1,2]

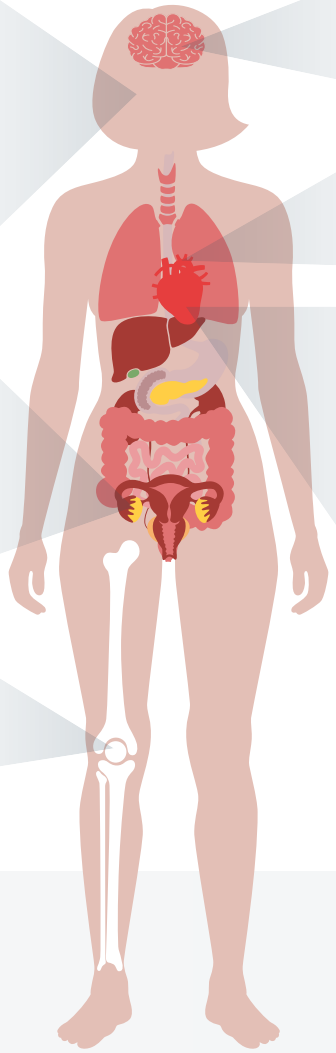
- Hirsutism
- Virilization
- Acne
- Acrochordons
- Androgenic alopecia
- Acanthosis nigricans

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

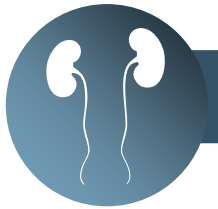
CLINICAL FEATURES OF PCOS

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.

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

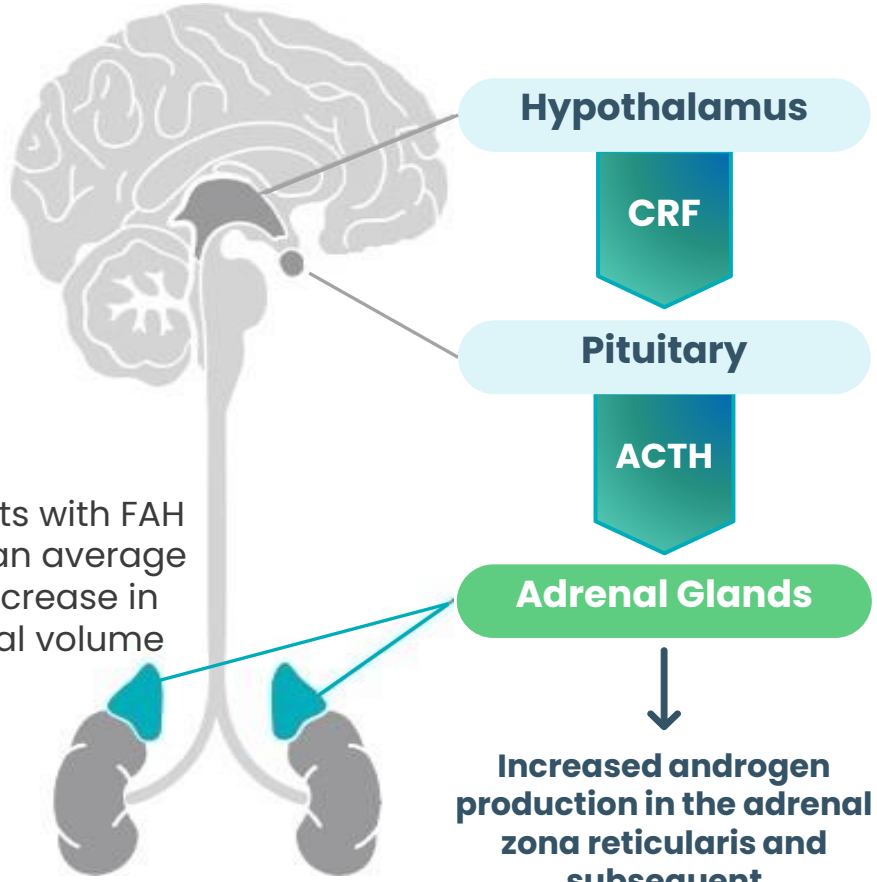
Insulin sensitization (metformin): alternative option if lifestyle changes yield insufficient results

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

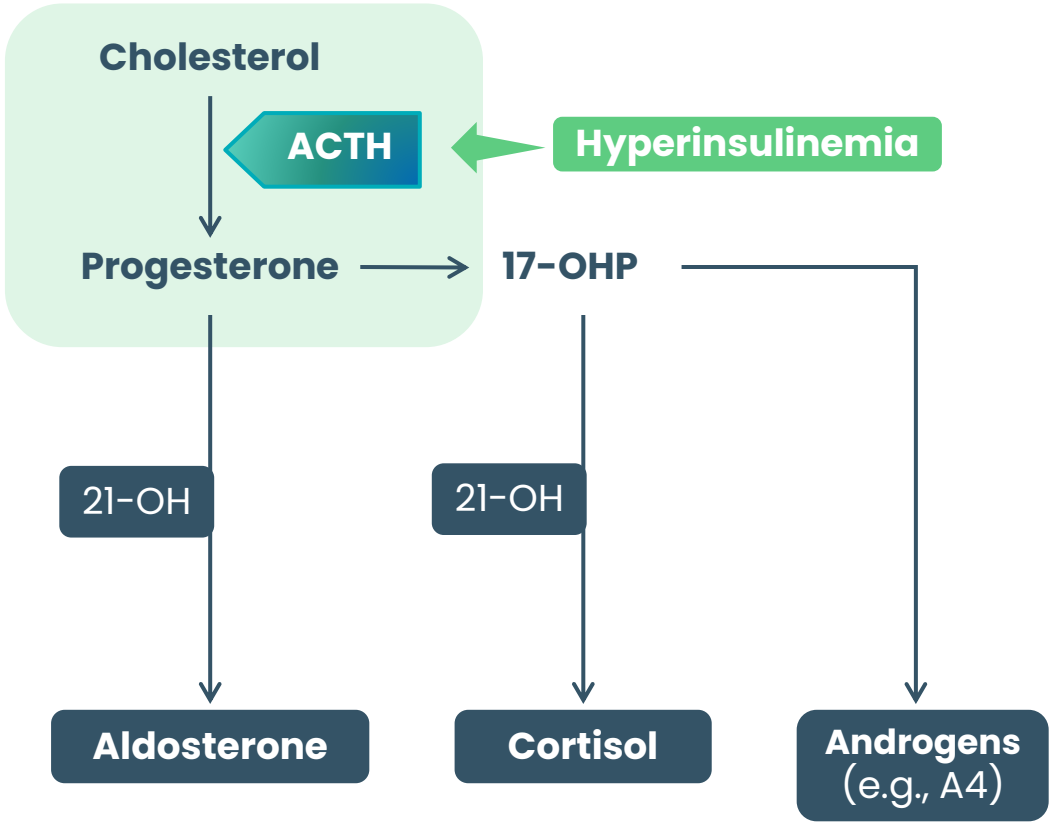
Sirmans SM, Pate KA. *Clin Epidemiol.* 2014;6:1–13.

ADRENAL HYPERSENSITIVITY TO ACTH IN PCOS

Hyperinsulinemia may potentiate corticotropin-mediated adrenal androgen production



Patients with FAH have an average 50% increase in adrenal volume



17-OHP, 17-hydroxyprogesterone; 21-OH, 21-hydroxylase; A4, androstenedione; ACTH, adrenocorticotropic hormone; CRF, corticotropin releasing factor; FAH, functional adrenal hyperandrogenism; PCOS, polycystic ovary syndrome.

Rosenfield RL, Ehrmann DA. *Endocrine Rev*. 2016;37:467-520.

P.O.W.E.R. study

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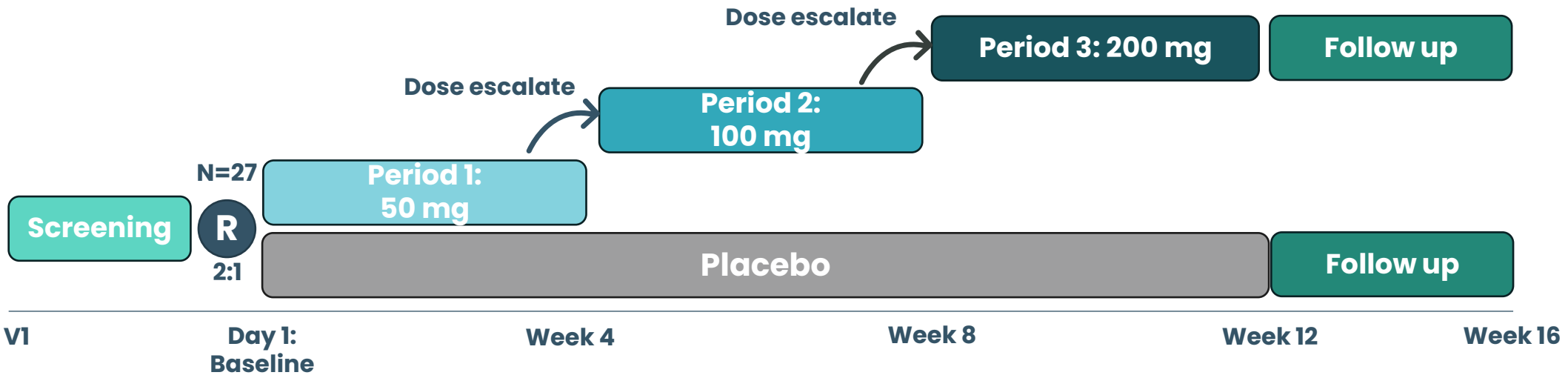
PHASE 2 CLINICAL PROOF OF CONCEPT STUDY COMPLETED

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
- DHEAS > ULN

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

Primary endpoint
- Absolute change from baseline in DHEAS

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

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

POWER Baseline Characteristics

Key Variables Mean (SD)	Tildacerfont (n = 17)	Placebo (n = 10)	Total (n = 27)
Age	28.4 (5.6)	29.3 (5.5)	28.7 (5.4)
Age at PCOS Diagnosis	22.6 (6.3)	21.6 (6.0)	22.3 (6.1)
BMI (kg/m^2)	32.1 (5.8)	32.4 (12.5)	32.2 (8.6)
DHEAS (µg/dL)	351.3 (90.5)	387.8 (107.2)	364.8 (96.7)
17-OHP (ng/dL)	83.2 (86.3)	62.1 (54.1)	75.4 (75.5)
ACTH (pg/mL)	23.9 (11.9)	22.3 (12.0)	23.3 (11.7)
A4 (ng/dL)	185.2 (75.2)	130.0 (66.0)	166.8 (75.6)
T (ng/dL)	61.0 (22.0)	61.1(27.0)	61.0 (23.4)
Screening DHEAS > ULN, N (%) Yes No	 12 (70.6%) 5 (29.4%)	 7 (70.6%) 3 (29.4%)	 19 (70.4%) 8 (29.6%)

Significant Reduction in DHEAS Versus Placebo Observed

In women with elevated baseline DHEAS, a significant reduction in DHEAS versus placebo was observed (p = 0.020).

	Tildacerfont (n = 12)[1]	Placebo (n = 7)[1]
n	11[2]	5[3]
Mixed Model of Repeated Measures		
Least Squares (LS) Geometric Mean Ratio (% Change from Baseline)	0.876 (-12.4%)	1.057 (5.7%)
95% Confidence Interval (CI) of Geometric Mean Ratio	0.802, 0.955	0.931, 1.200
95% CI of Percent Change from Baseline	-19.8%, -4.5%	-6.9%, 20.0%
Difference LS Mean Ratio [tildacerfont/placebo]	0.828	N/A
95% CI of Difference LS Mean Ratio	0.709, 0.967	N/A
p-value	0.020	N/A

1. Eight subjects (five in the tildacerfont arm and three in the placebo arm) did not meet inclusion criteria #3 requiring DHEAS to be greater than the ULN and were excluded from the analyses.
2. One subject was excluded from the analyses due to no post-baseline DHEAS assessment.
3. Two subjects were excluded from the analyses due to concomitant glucocorticoid (GC) use, which confounded assessment of adrenal steroid reduction.

Increase in SHBG Versus Placebo Observed

In study participants, an increase in Sex Hormone Binding Globulin (SHBG) versus placebo was observed (p = 0.012), which may lower levels of free, bioactive sex hormones.

	Tildacerfont (n = 17)	Placebo (n = 10)
n	16[1]	9[1]
Mixed Model of Repeated Measures		
Least Squares (LS) Geometric Mean Ratio (% Change from Baseline)	1.329 (32.9%)	0.919 (-8.1%)
95% Confidence Interval (CI) of Geometric Mean Ratio	1.124, 1.571	0.735, 1.148
95% CI of Percent Change from Baseline	12.4%, 57.1%	-26.5%, 14.8%
Difference LS Mean Ratio [tildacerfont/placebo]	1.446	N/A
95% CI of Difference LS Mean Ratio	1.093, 1.913	N/A
p-value	0.012	N/A

1. Two subjects (one in the tildacerfont arm and one in placebo arm) did not have a week 12 SHBG assessment completed.

Major Depressive Disorder (MDD)

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Strategic Collaboration with HMNC to Develop Treatment for MDD

Collaboration	Pairs Spruce's **Tildacerfont** with **Cortibon** to treat MDD patients **responsive to CRF_1 receptor antagonism**
Tildacerfont	Tildacerfont may **mediate endocrine, behavioral, and autonomic responses to stress**, which may produce antidepressant action
Cortibon (CDx)	**Genetic selection tool** developed at the Max Planck Institute utilizing samples from P2 study of CRF_1 receptor antagonist in MDD
Phase 2 Proof of Concept (POC) Study	HMNC to initiate and fund **Phase 2 POC study** of tildacerfont and Cortibon for MDD in **Q4 2024**
License Option	**Option by Spruce** to **in-license exclusive worldwide rights to Cortibon** following Phase 2 POC Study
Economics	Pursuant to license terms, **HMNC** entitled to **milestone payments and royalties on net sales** of tildacerfont in MDD

Treatment Options in MDD Demonstrate Suboptimal Efficacy

MDD biology and pathogenesis[1]

Genetic environmental psychological and biological factors cause MDD

- I. HPA axis dysfunction hypothesis
- II. Monoamine hypothesis
- III. Inflammatory hypothesis
- IV. Genetic and Epigenetic anomaly hypothesis
- V. Structural and functional brain remodeling hypothesis
- VI. Social psychological hypothesis

HMNC focus

Pharmacotherapy is one of complementary treatment options, but shows suboptimal efficacy

Pharmaco-therapy

+

Psycho-therapy

Brain stimulation

Lifestyle change

Antidepressants cover a broad spectrum of **mechanisms of action**...

- ✓ Selective serotonin reuptake inhibitors
- ✓ Serotonin noradrenalin reuptake inhibitors
- ✓ Noradrenalin and dopamine reuptake inhibitors
- ✓ Noradrenalin and specific serotonergic antidepressants
- ✓ Melatonergic agonist
- ✓ Tricyclic antidepressants
- ✓ Second generation antipsychotics
- ✓ Monoamine oxidase inhibitors
- ✓ NMDA receptor modulator

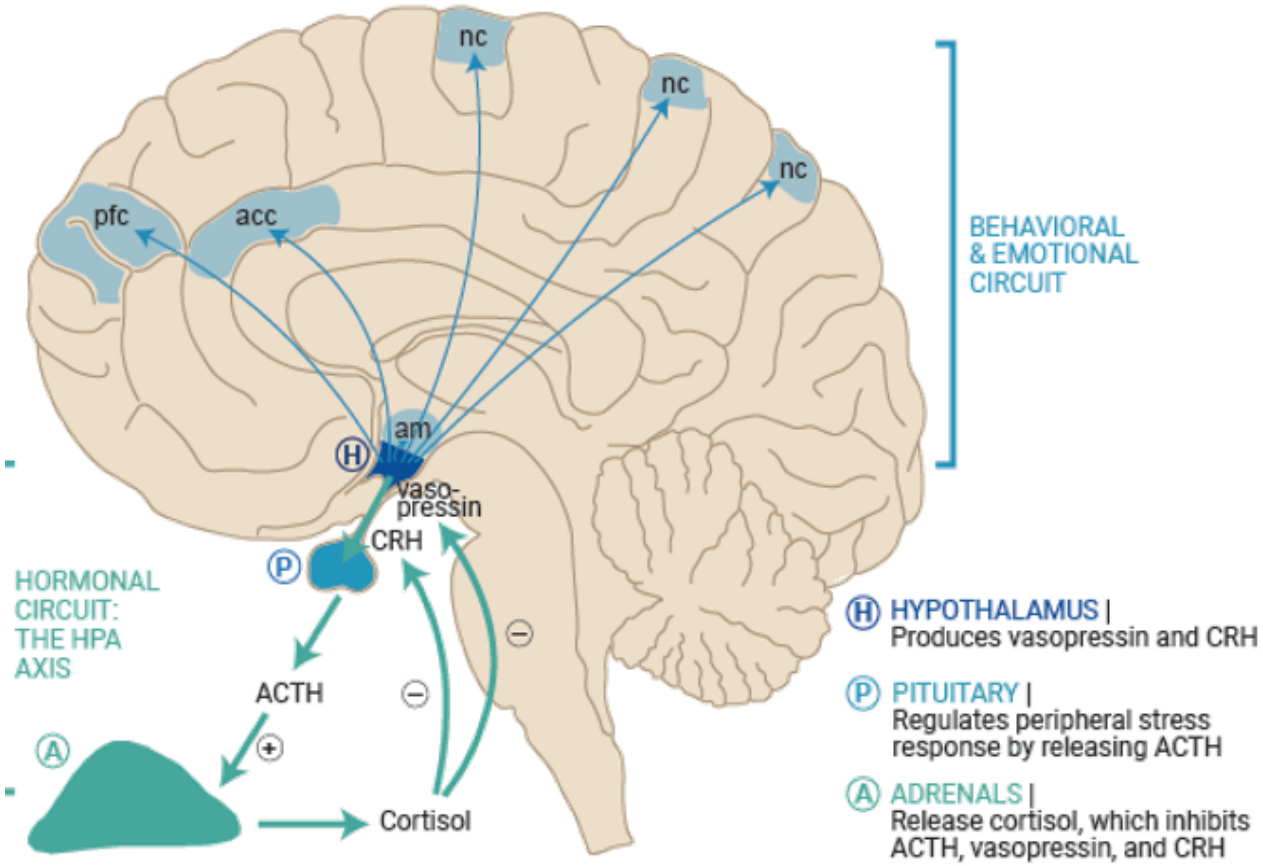
...but out of **100** **patients**...

...**72** **fail to achieve remission** after first line of antidepressant treatment...

...and **34** fail to remit even **after multiple lines of treatment**[2]

[1]Cui, Lulu, et al. (2024) [2]Rush et al (2009)

Substantial Subset of MDD Patients Possess HPA-Axis Disturbance



Background

- A substantial subset (~30-50%) of all patients with MDD have a disturbance in vasopressin and/or CRH signaling, both key stress response regulators

Breakthrough

- Our CDxes have the potential to identify especially those patients, with high specificity and sensitivity
- Our pipeline antidepressants targeting the stress axis, e.g., HMNC's nelivaptan and Spruce's CRHR1 antagonist tildacerfont are expected to be highly efficacious in CDx-positive patients

CRHR1 Antagonists – Why were they shelved?

- Developmental programs that target the HPA axis were conducted in non-selected patient populations and therefore, did not show significant efficacy

"We reviewed a range of issues that may explain why CRHR1 antagonists have been challenging to translate from bench to bedside. These include potential specificity limitations of preclinical models and the fact that CRHR1 antagonists produced therapeutic-like results only under specific conditions, unlike some clinically effective compounds that act more generally." Reference: Spierling, Zorrilla (2017)

Note: Plus sign indicates stimulation, minus sign indicates Inhibition, light blue-shaded brain areas contain CRHR1R and/or V1BR; acc, anterior cingulate cortex; ACTH, corticotropin; am, amygdala; CRH, corticotropin-releasing hormone; pfc, prefrontal cortex; nc, neocortex.

Financial Highlights

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Financial Highlights

Capital Structure and Summary Financials as of June 30, 2024

Capital Structure	Shares (M)
Shares Outstanding	41.3
Equity Awards Issued and Outstanding	7.9
Common Stock Warrants	12.7
Fully Diluted Shares Outstanding	61.9

Financials	000's
Cash & Cash Equivalents	$69,683
Debt[1]	$2,568

1. Term loan, gross balance as of June 30, 2024.

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