SAT- 435

The Treatment May Be Worse Than the Disease: The Real-World Clinical Burden of Disease and Treatment in Congenital Adrenal Hyperplasia

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Potential conflict of interest may exist. Refer to the Meeting App

Background:

- Classic congenital adrenal hyperplasia (CAH) is a group of autosomal recessive conditions that affects the production of adrenal hormones, leading to deficiencies in cortisol and aldosterone. Additionally, loss of negative feedback in the hypothalamic-pituitary-adrenal (HPA) axis leads to increased ACTH production and subsequent overproduction of adrenal androgens.
- Current treatment includes oral mineralocorticoids and glucocorticoids (GCs) for physiologic replacement. GCs are also used to suppress the HPA axis to control androgen production, but this suppression usually requires supraphysiologic GC doses.
- The health impacts of hyperandrogenemia include accelerated skeletal maturation leading to adult short stature, precocious puberty, acne, hirsutism, male pattern baldness, adrenal rest tumors, and infertility.
- There are also serious adverse events due to the long-term use of supraphysiologic doses of GCs.
- There is a paucity of research that examines the relationship between GC use and risk of comorbidities in patients with classic CAH as compared to patients without CAH.
- The aim of this study was to explore the risks associated with CAH diagnosis and treatment.

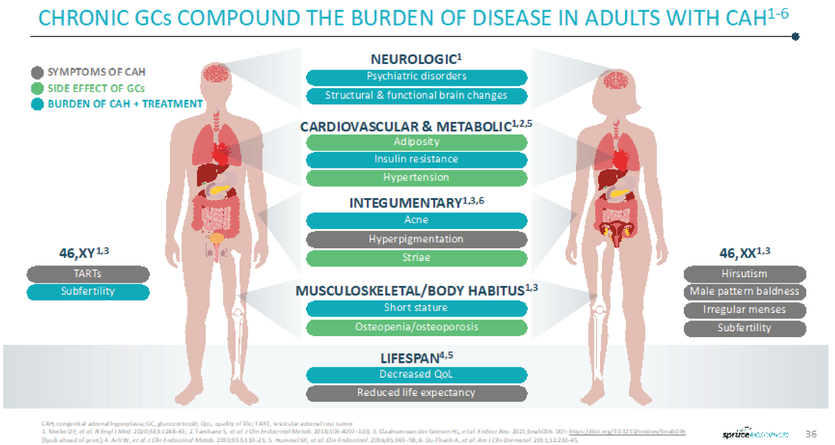
Table 1. Total number and sex study participants

Sex	CAH Cohort (N)	(%)	Non-CAH Cohort (N)	(%)
Male	677	33%	655,524	43%
Female	1,356	67%	874,584	57%
Total	2,033		1,530,108	

Methods:

- This cross-sectional study used medical administrative claims data within 2014-2021 from RWD Insights®, an all-payer claims database in the US.
- Adult patients were required to have a diagnosis of Classic CAH (ICD-9/10-CM: 255.9, E25.0, E25.9) and continuous use of oral GCs (defined as a proportion of days covered of 75% or more in any given calendar year).
- Patients were further required to receive an average daily GC dose of ≥10mg/day hydrocortisone equivalent and be free of pituitary disorders.
- Non-CAH controls were also selected based on lack of a CAH diagnosis and no GC use.
- Demographic characteristics and comorbidity rates were compared between patients with and without CAH during the study period.

Fig. 1



Results:

- A total of 1,532,141 individuals were eligible for the study (Table 1)
- A lower proportion of the CAH cohort was elderly (i.e., 65+ years; CAH cohort: 11% vs. Non-CAH cohort: 26%)(Table 2), and there were more females in the CAH cohort (67%) as compared to the non-CAH (57%).

Table 2. Age demographics for CAH and Non-CAH cohorts

Age	CAH Cohort (N)	(%)	Non-CAH Cohort (N)	(%)
18 to 25 years	369	18%	181,725	12%
26 to 35 years	472	23%	235,775	15%
36 to 45 years	376	18%	212,908	14%
46 to 54 years	308	15%	224,851	15%
55 to 64 years	286	14%	281,087	18%
65 to 74 years	166	8%	230,240	15%
75+ years	56	3%	163,522	11%

Results (cont.):

- After propensity score matching (PSM) on demographic characteristics, there were 2,019 and 8,076 patients in the CAH and non-CAH cohort, respectively, and patient characteristics were balanced.
- There were higher rates of comorbidities in the CAH cohort.
- Some notable differences include GC-related comorbidities such as:
  - Osteoporosis/necrosis and fractures
  - Metabolic disorders, obesity, and type 2 diabetes
  - Cardiovascular disorders
  - CAH related comorbidities:
    - Hirsutism
    - Testicular hypofunction

Table 3. Comorbidities with increased risk ratio in the CAH Cohort

Comorbidities	Rate Ratio	95% CI	P-value
Osteoporosis/Osteonecrosis	3.48	3.36, 3.60	<0.0001
Fractures	2.14	1.90, 2.39	<0.0001
Metabolic disorders	2.20	2.08, 2.33	<0.0001
Obesity	1.35	1.26, 1.44	<0.0001
Type 2 Diabetes	1.27	1.18, 1.36	<0.0001
Cardiovascular disorders	1.24	1.16, 1.33	<0.0001
Hirsutism	11.70	11.34, 12.06	<0.0001
Testicular hypofunction	5.48	5.24, 5.71	<0.0001

Conclusions:

- This study suggests the association of multiple comorbidities with CAH, highlighting the burden of both the disease and treatment.
- A new treatment paradigm that uses novel, non-steroidal modalities to address androgen control as a clinical goal distinct from physiologic GC replacement could ameliorate the systemic risks associated with hyperandrogenemia and chronic overexposure to GCs.

SAT-436

Impact of Geography and Insurance on Healthcare Utilization Preferences of Individuals with Congenital Adrenal Hyperplasia

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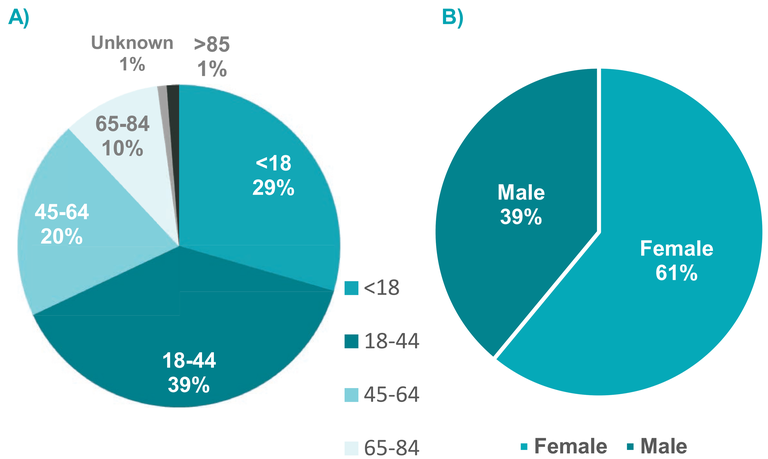
Potential conflict of interest may exist. Refer to the Meeting App

Background:

- Relative to the general population, patients with classic congenital adrenal hyperplasia (CAH) have increased risks for morbidity and mortality which require specialized management across the life span[1].
- Several studies in Europe have reported that nearly 50% of individuals with classic CAH either do not complete the transition from pediatric to adult endocrinology care or are lost to follow-up once seen by an adult endocrinologist[2,3].
- Endocrine care, particularly as part of multi-disciplinary teams, can help mitigate risks of developing adrenal crises as well as the impact of glucocorticoid (GC) underexposure or overexposure[4].
- Impact of GC underexposure[5]:
  - Hyperandrogenism
  - Adrenal insufficiency
- Implications of GC overexposure[5]:
  - Increased cardiometabolic risk associated with insulin resistance and excessive weight gain
  - Fertility issues associated with irregular menses and testicular adrenal rest tumors
  - Diminished quality of life
  - Increased mental health issues including anxiety, depression, and sleep disturbance
  - Increased fracture risk associated with decreased bone mineral density

Figure 1: CAH study population by age (A) and sex (B)



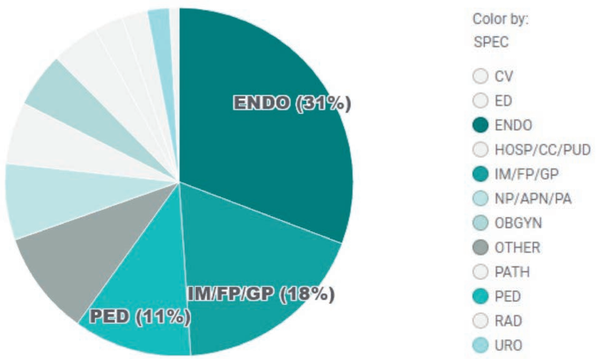
Study Objectives and Design:

- We hypothesized that utilization of endocrine and multi-disciplinary care by patients with CAH in the United States (U.S.) could be adversely affected by non-therapeutic factors associated with geographic location and difficulty obtaining commercial insurance.
- In this cross-sectional study, we utilized the Definitive Healthcare database (Nov. 2020-Nov. 2022) to gain insight into these factors in adults with CAH.

Results:

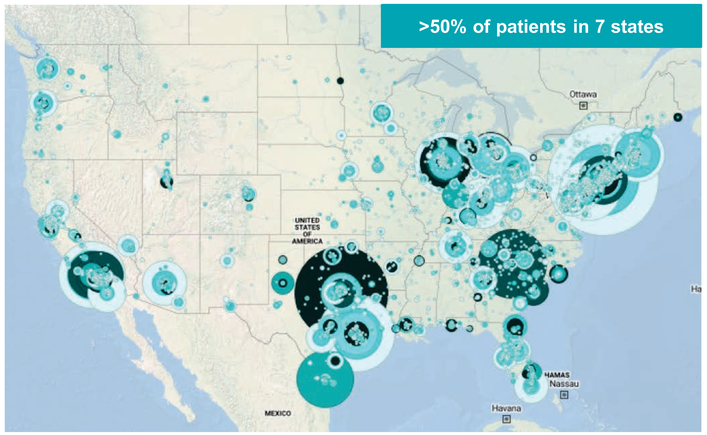
- Study population demographics for age and sex are displayed in Figure 1.
- Analysis of healthcare provider utilization revealed (Figure 2):
  - Only ~30% of U.S. adults with CAH utilized endocrinologists.
  - The remaining mostly utilized primary-care providers (PCPs: IM, FP, NP, PA, and Ob-Gyn) for medical management.
  - 54% of CAH patients receive care in practices (including endocrine) that serve only one CAH patient.
- A review of insurance coverage of U.S. adults with CAH suggests that ~70% had access to commercial insurance.

Figure 2: Healthcare provider utilization by individuals with CAH



- Analysis of geographic distribution revealed over 50% of adults with CAH resided in states with the largest populations (California, Texas, New York, Florida, Ohio, Michigan, and Illinois) where subspecialist care would presumably be most accessible.

Figure 3: Geographic distribution of individuals with CAH



*Map reflects cities in top 80% of CAH volume

Conclusions:

- In our study, only 30% of CAH adults in the U.S. received care from an endocrinologist.
- Additionally, about 50% of CAH patients are cared for by providers with only one CAH patient in their practice.
- This pattern does not appear to be due to either diverse geographical distribution or ability to obtain commercial insurance.
- The gap in expert care may adversely affect the biochemical control of CAH and contribute to associated comorbidities.
- Increased partnership between PCPs and endocrinologists, and increased awareness and education regarding specialty care among CAH patients and CAH advocacy groups, are needed to improve biochemical outcomes and thereby reduce the risk of morbidity and mortality in adults with CAH.

References:

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SUN-466

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

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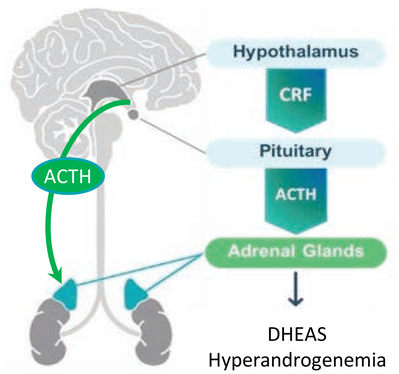
Potential conflicts of interest may exist. Refer to the Meeting App.

Background:

- Polycystic Ovary Syndrome (PCOS) is a common lifelong endocrine disorder among women, affecting up to 5 million reproductive-aged women in the USA
- Symptoms are linked to hyperandrogenism
- Adrenal contributions to hyperandrogenemia may be due to adrenal hyper-responsiveness to adrenocorticotropic (ACTH) (Figure 1)
- There is a high unmet need, with no FDA approved therapies, and a standard of care that address symptoms only
- Tildacerfont, a second-generation oral corticotrophin-releasing factor receptor 1 (CRFR1) antagonist, may modulate ACTH release and thereby reduce adrenal androgen production
- P.O.W.E.R. was a randomized, placebo-controlled, dose-escalating trial in PCOS females with elevated dehydroepiandrosterone sulfate (DHEAS) levels at screening (>upper limit of normal [ULN]).
- DHEAS is an androgen precursor, but a biomarker of adrenal androgen production since 90% is produced in the adrenal glands.
- Study overview (Figure 2) and results from the study are presented here

Fig. 1: Adrenal Hypersensitivity to ACTH as a mechanism for hyperandrogenemia in PCOS



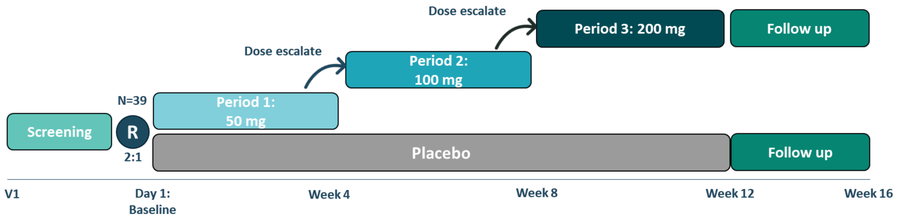
Primary Endpoint:

- Absolute change from baseline in DHEAS

Other Endpoints:

- Safety and tolerability
- Proportion of subjects with elevated baseline DHEAS who achieve ≥ 30% reduction from baseline in DHEAS
- Change from baseline in ACTH, 17-hydroxyprogesterone (17-OHP), androstenedione (A4) and testosterone (T)

Fig. 2: P.O.W.E.R. Study Design



Stratification: Screening DHEAS (≤1.2xULN, >1.2xULN)

Table 1: Summary of Demographics and Baseline Hormones; Intent to Treat Analysis Population

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/m²)	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	12 (70.6%)	7 (70.6%)	19 (70.4%)
No	5 (29.4%)	3 (29.4%)	8 (29.6%)

Results:

- P.O.W.E.R. Study enrolled N=27 women (did not meet target enrollment of N=39)
- Participant demographics and baseline hormone levels are detailed in Table 1
- Two subjects were excluded due to protocol violations of concomitant glucocorticoid (GC) use, which could confound assessment of adrenal steroid production
- Eight subjects did not meet have DHEAS > ULN (Table 1)

Safety:

- Tildacerfont was well-tolerated
  - Majority of the adverse events were mild to moderate
  - No Serious Adverse Reactions were reported
  - No evidence of adrenal insufficiency was observed

For questions: please reach out to Saba Sile, MD Spruce Biosciences
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Efficacy:

- In women with elevated baseline DHEAS, and excluding the two women with protocol violations, significant differences were observed in serum DHEAS (p=0.020) [Table 2] and serum SHBG (p=0.012) between study arms
- No effect was observed between tildacerfont and placebo for any of the other biomarkers assessed

Table 2: Change from baseline in DHEAS at Week 12; modified intent to treat (non-GC), baseline DHEAS >ULN

	Tildacerfont (N=12)	Placebo (N=7)
n	11	5
Mixed model for repeated measures		
LS Geometric Mean Ratio (% Change from Baseline)	0.876 (-12.4%)	1.057 (5.7%)
95% 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	NA
95% CI of Difference LS Mean Ratio	0.709, 0.967	NA
p-value	**0.020**	NA

Conclusions:

- The study is underpowered to test for statistical significance on the primary endpoint
- However, in women with elevated screening DHEAS, there was a significant difference in DHEAS change between study arms
- The observed increase in SHBG may reflect a beneficial change in hormonal milieu, as SHBG can bind circulating androgens
- Tildacerfont was well-tolerated with no safety signals observed
- The lowering of DHEAS, an adrenal androgen precursor, observed with 12-week exposure suggests that tildacerfont may be of therapeutic benefit for some women with PCOS
- Larger, longer duration studies should be conducted to understand the implications of the observed changes

References:

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