Baseline Characteristics of CAHptain: A Phase 2 Dose-finding Study of Tildacerfont in Children with Classic Congenital Adrenal Hyperplasia

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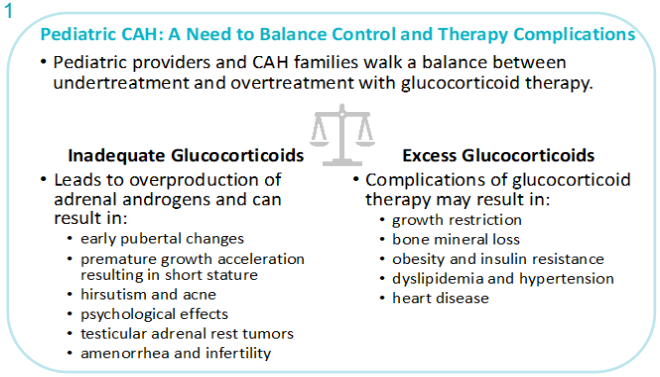
Background:

- Classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is characterized by cortisol deficiency, and sometimes mineralocorticoid deficiency accompanied by adrenal androgen overproduction
- Glucocorticoids (GC) are utilized to 1) replace endogenous cortisol, and 2) suppress androgen production
- Supraphysiologic GC doses are frequently required to suppress androgen secretion, and clinical care requires a delicate balance of GC versus androgen exposure
- Tildacerfont, a second-generation oral corticotrophin-releasing factor receptor 1 (CRFR1) antagonist, is designed to reduce ACTH and adrenal androgen production in the treatment of classic CAH
- CAHptain is an ongoing open-label phase 2 dose-finding study of tildacerfont in children and adults with classic CAH. Baseline characteristics and an overview of preliminary results are presented here

Fig. 1



Study Design:

- Children and adolescents with classic CAH were enrolled into the first three cohorts based on age and dose (Figure 2). There were no restrictions on biomarker levels for inclusion.

Primary Endpoint:

- Safety of tildacerfont

Secondary Endpoints:

- Proportion of participants with elevated baseline androstenedione (A4) who achieve a reduction in A4 at Week 4
- Proportion of participants who achieve reduction in A4 or reduction in GC dosing at Week 12
- Comparison of observed tildacerfont concentrations to those simulated in a Physiologically-Based Pharmacokinetic (PBPK) model

Fig. 2. Cohorts 1-3

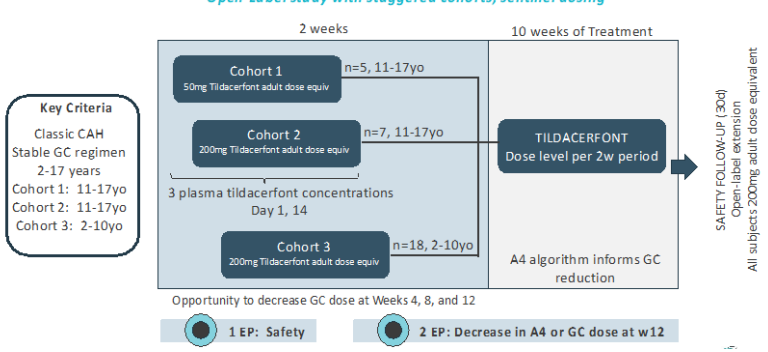


Table 1

Key Variables	Cohort 1 (n=5)	Cohort 2 (n=7)	Cohort 3 (n=18)	Total (n=30)
Age (years) mean	13.6	14.4	7.7	10.2
Sex (male; female)	0; 5	4; 3	9; 9	13; 17
BMI (kg/m^2) mean	23.1	28	20.8	22.9
BSA (m^2) mean	1.5	1.7	1.1	1.3
Daily GC dose (mg; HC equivalent mean	23.4	25.7	15.3	19.1
GC dose/BSA mean	15.1	14.8	13.3	13.9

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Results:

- Initially, 30 children were enrolled in the 12-week trial of Cohorts 1-3 (detailed below).
- Mean BMI exceeded the 85th percentile in all three cohorts.
- 24 of 30 subjects had elevated A4 at baseline (Table 2), despite supraphysiologic GC doses upon entering the study (≥11mg/m2/d).

Safety:

- Tildacerfont was well-tolerated
  - All adverse events (AEs) were mild to moderate
  - There were no treatment-related serious AEs or AEs leading to study withdrawal

Efficacy:

- 70% (16/23) of study participants with elevated baseline A4 demonstrated reduced A4 after 4 weeks of treatment
- 73% (22/30*) demonstrated improved CAH control (A4 or GC reduction) after 12 weeks of treatment.
  - GC reduction required A4 normalization

Pharmacokinetics:

- Preliminary PK data suggests tildacerfont clearance is more rapid in children than adults

Table 14.2.2.2.1 06Mar24, Table 14.2.2.1.1 06Mar24, Listing 16.2.6.2.2.1
*80-1003 was excluded due to increase in GC based on W12 A4 levels

Table 2

Key Variables	Cohort 1 (n=5)	Cohort 2 (n=7)	Cohort 3 (n=18)
Baseline Androstenedione (ng/dL)	238.3	645.3	65.6
Baseline 17OHP (ng/dL)	3182	9986	3249
Baseline ACTH (pg/mL)	260	129	159

14.1.4.2.2 06Mar24

Conclusions:

- The preliminary baseline characteristics of CAHptain highlight that androgen control in children and adolescents with CAH often requires supraphysiologic GC doses
- Tildacerfont was well-tolerated with no safety signals observed in the initial 3 cohorts
- A4 reductions and GC reductions were observed in a majority of participants, although response was not consistent
  - A4 normalization was required for GC reduction
- PK data suggests a need for increased exposure via higher and/or more frequent dosing
- Further dose ranging in adults and children is ongoing in Cohorts 4-9 to inform dosing decisions for a pediatric Phase 3 trial

Baseline Characteristics of Two Randomized, Placebo-controlled Trials with Tildacerfont in Adults (CAHmelia Studies) Highlight Unmet Medical Need in Pediatric Congenital Adrenal Hyperplasia

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Background:

- Classical congenital adrenal hyperplasia (CAH) is a chronic and life-threatening genetic disorder involving cortisol (and often aldosterone) deficiency and adrenal androgen overproduction
- In addition to physiologic glucocorticoid (GC) replacement, most people living with CAH require supraphysiologic GC doses to control androgen excess
- Supraphysiologic GC commonly result in growth restriction/short stature, obesity, insulin resistance, and decreased bone mineral density
- Inadequate GC treatment results in endogenous hyperandrogenism, which can also lead to short stature due to advanced skeletal maturation and early epiphyseal closure, early puberty, and virilization
- Growth and metabolic disturbances in children with CAH lead to adult short stature and obesity, as observed in these adult CAH cohorts
- Since the introduction of glucocorticoids and fludrocortisone in the 1950s, there have been no therapeutic advances to improve pediatric CAH care and therefore clinical outcomes in adults with CAH remain suboptimal
- Tildacerfont, a second-generation oral corticotrophin-releasing factor receptor 1 (CRFR1) antagonist being studied for the treatment of classic CAH, is designed to reduce ACTH and adrenal androgen production
- By decreasing ACTH-mediated adrenal androgen production, tildacerfont may allow for improved androgen control and reduced GC requirements in childhood CAH, thereby improving adult height and decreasing risks associated with overweight and obesity in adulthood

Figure 1. Mechanism of Tildacerfont Reduction of Adrenal Androgens

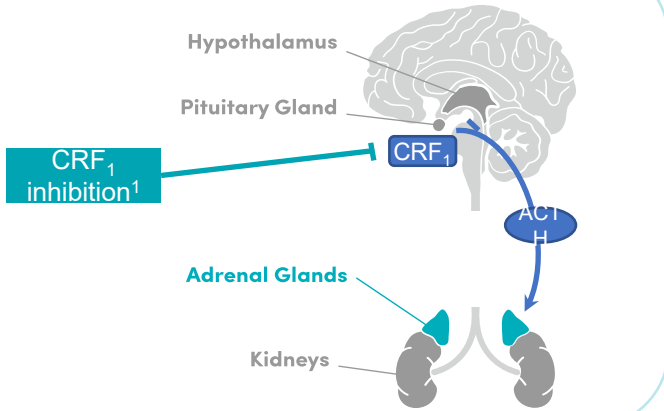
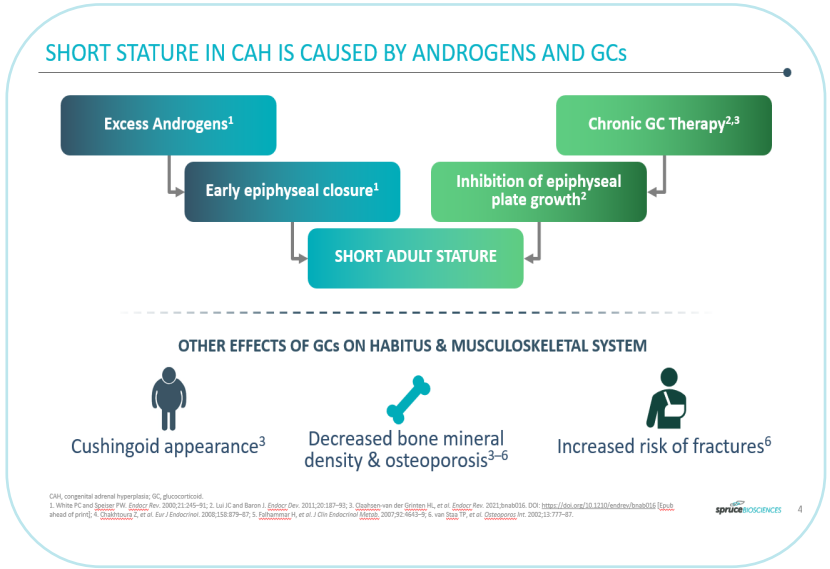


Figure 2



Methods:

- CAHmelia studies (SPR001-203 and SPR001-204) are global trials in adults with classic CAH, with the largest proportion of participants in the US
  - SPR001-203 has concluded. SPR001-204 is ongoing
- Baseline height and weight were divided by sex, and BMI was categorized and compared to national and global averages for adults.

Results:

- 96 participants enrolled in SPR001-203 and 100 participants enrolled in SPR001-204
  - **Weight:**
    - Rates of overweight and obesity were higher in both studies compared to national averages.
      - Globally, adult rates are 43% for overweight and 16% for obesity (WHO-2022)[1]. US National rates of obesity 41.9% in adults (NHANES 2021)[2]
  - **Height:**
    - Mean heights in both cohorts were approximately one standard deviation lower than the US average
      - US average: 161cm for females and 175cm for males[3]

Table 1

Mean (SD)	SPR001-203 N=96	SPR001-204 N=100
Age (years)	32	33
Sex (male; female)	45; 51	47; 53
Male height (cm)	170.2±8.0	166.04±10.2
Male Z-score vs US average	-0.93	-1.51
Female height (cm)	156.7±5.1	159.3±4.9
Female Z-score vs US average	-1.02	-0.62
Male weight (kg)	86.6±19.2	88.8±20.8
Female weight (kg)	84.8±17.1	84.0±23.5
BMI (kg/m^2, SD)	30.98 (7.332)	31.5 (8.06)
- Overweight (BMI ≥25 - <30)	28.1%	25.0%
- Obese Class I (BMI ≥30 - <35)	26.0%	27.0%
- Obese Class II/III (BMI ≥ 35)	24.0%	26.0%
BSA (m^2)	1.94	1.90

203: Table 14.1.3.2, 06Mar24, 204: Table 6.0.0.0, 20Mar24

Conclusions:

- In these adult CAH cohorts, differences in height and weight relative to national and global averages suggest that the current treatment paradigm in pediatric CAH is inadequate to address the goal of optimization of height and weight, which requires maintaining a balance between hyperandrogenemia and GC overexposure throughout childhood
- New therapies to better control androgen levels while decreasing GC burden are essential to reduce long-term consequences of childhood CAH, improving adult height and reducing BMI in young adults
- CRF1 antagonism with tildacerfont may improve the ability to manage androgen and GC exposure in childhood, leading to better outcomes for adults living with CAH

References:

1. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
2. National Health and Nutrition Examination Survey 2017–March 2020 Prepandemic Data Files Development of Files and Prevalence Estimates for Selected Health Outcomes. Stierman, B., et al. National Center for Health Statistics (U.S.). June 2021
3. Fryar, CD et al. Anthropometric reference data for children and adults: United States, 2015-2018. National Center for Health Statistics. Vital Health Stat 3(46). 2021