Initial Lessons from a Pre-screening Protocol to Identify Participants with Classic CAH Potentially Eligible for Gene Therapy Treatment with BBP-631, an Adeno-Associated Virus (AAV) Serotype 5-Based Recombinant Vector Encoding the Human *CYP21A2* Gene

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DISEASE BACKGROUND

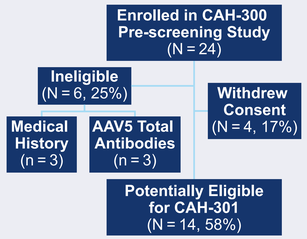
- Congenital Adrenal Hyperplasia (CAH) is a rare genetic disorder with an estimated prevalence in the US and Europe of approximately 1:15,000 live births[1]
- The most common type of CAH is due to 21-OHD caused by pathogenic variants in the *CYP21A2* gene
- Disease- and treatment-related comorbidities include life-threatening adrenal crises, impaired growth and development during childhood, adult short stature, female virilization, subfertility in both sexes, obesity and cardiovascular disease risk factors, and decreased bone mineral density[2-5]
- The all-cause mortality rate in classic (severe) CAH has been reported as > 5 times that of controls, adjusted for age and sex[6]
- Classic (severe) CAH requires lifetime GC ± MC replacement

STUDY BACKGROUND

- Gene therapy with BBP-631 is intended to restore adrenocortical cell function with the potential to provide an endogenous physiologic pathway for GC and MC synthesis
- The CAH-300 Pre-screening Study (NCT05101902) was designed in partnership with the CAH patient community and is part of a continuum for treatment of study participants with classic CAH, including the investigational gene therapy trial (CAH-301, NCT04783181) with long-term follow-up for a total of 5 years
- To help facilitate enrollment in the orphan disease population with classic CAH, the CAH-300 Pre-screening Study is being used as one of several tools to identify, monitor, and confirm the potential eligibility of study participants with CAH for enrollment in the investigational gene therapy trial
- In addition to being identified via the CAH-300 study, potentially eligible participants for treatment may be identified and prescreened directly by investigators within the CAH-301 study

PRELIMINARY RESULTS[a]

- Pre-screening Study participants have been drawn from all regions of the US, with enrollment not dependent on proximity to an academic medical center



Demographics	Enrolled Participants (N = 24)	Potentially Eligible Participants (N = 14)
Sex	**n (%), mean age**	**n (%), mean age**
Male	10 (41.7), 35.8 yr	6 (42.8), 38.3 yr
Female	14 (58.3), 38.7 yr	8 (57.1), 39.1 yr
CAH Type	**n (%)**	**n (%)**
Salt-Wasting	16 (66.7)	14 (100)
Simple-Virilizing	2 (8.3)	0 (0.0)
Not Available	6 (25.0)[b]	0 (0.0)

[a]Data as of 12 May 2022; [b]Ineligible (n = 6)

- Morning cortisol levels measured by LC-MS/MS and IA are consistent with classic CAH and suggest that meaningful increases in endogenous cortisol production will be detectable (in both SW and SV phenotypes) after administration of BBP-631 in the investigational gene therapy trial

HPA Axis Hormone Levels in Participants Pre-screened in Study CAH-300

Hormone (Test Method)	Mean Values[c]	Reference Range
Cortisol (LC-MS/MS)[a]	1.0 µg/dL	5 - 25 (morning)
Cortisol (IA)[a,b]	1.8 µg/dL	7 - 25 (morning)
ACTH	303.2 pg/mL	7.2 - 63
17-OHP	6145.0 ng/dL	Male: < 220; Female: < 285
A4	303.0 ng/dL	Male: 40 - 150; Female: 30 - 200

[a]For calculation of means, cortisol levels BLD were set to assay LLD: n = 2, cortisol (LC-MS/MS, 0.2 µg/dL); n = 6, cortisol (IA, 1.0 µg/dL)
[b]Based on participants with available values (n = 12); [c]Based on participants with available values (n = 13)

Abbreviations: A4=androstenedione; AAV=adeno-associated virus; ACTH=adrenocorticotropic hormone; BLD=below the limit of detection; CAH=congenital adrenal hyperplasia; COVID=coronavirus disease-2019; ECG=electrocardiogram; ELISA=enzyme-linked immunosorbent assay; GC=glucocorticoid; HPA=hypothalamic-pituitary-adrenal; IA=immunoassay; LC-MS/MS=liquid chromatography with tandem mass spectrometry; LLD=lower limit of detection; MC=mineralocorticoid; OH=hydroxylase; OHD=hydroxylase deficiency; OHP=hydroxyprogesterone; PE=physical exam; SV=simple-virilizing; SW=salt-wasting; US=United States; yr=year.

References: **1)** van der Kamp, *Eur J Endocrinol*, 2004. **2)** Bonfig, *Curr Opin Endocrinol Diabetes Obes*, 2017. **3)** Falhammar, *J Clin Endocrinol Metab*, 2014. **4)** Merke, *N Engl J Med*, 2020. **5)** Reisch, *Exp Clin Endocrinol Diabetes*, 2019. **6)** Jenkins-Jones, *Eur J Endocrinol*, 2018.

CAH-300 PRE-SCREENING STUDY DESIGN

STUDY DESIGN GOALS

The CAH-300 Pre-screening Study uses a gradient approach to assessment intensity: initial assessments are brief, and cadence and intensity increase as potential eligibility for the investigational gene therapy trial approaches. This accomplishes:

- **Reduced burden** on participants seeking enrollment in the investigational gene therapy trial
- **Improved chances** of participants ultimately being enrolled in the investigational gene therapy trial
- **Streamlined enrollment** in the investigational gene therapy trial

REDUCING PARTICIPANT BURDEN

The Pre-screening Study design is low-impact and flexible for the participant:

- Initial assessments for potential eligibility involve a 3-question online questionnaire, phone screen, informed consent, and medical record review
- Initial laboratory assessments were selected to efficiently identify ineligible participants on an objective basis for safety and to avoid unnecessary laboratory sample collection and testing:
  - *CYP21A2* genetic testing (inclusionary)
  - Immunogenicity testing for anti-21-OH and anti-viral vector antibodies
- At-home assessments and sample collection are utilized to reduce the burden of participant travel, including during the COVID-19 pandemic and surges

IMPROVING CHANCES OF ENROLLMENT IN THE INVESTIGATIONAL GENE THERAPY TRIAL

The Pre-screening Study design has 3 defined assessment periods:

Initial Pre-screening

- Genetic test results and immunogenicity testing allow for eligibility in the investigational gene therapy trial
- Additional assessments include:
  - Routine clinical laboratory assessments including pathogen screening, medical history, demographics, PE, ECG, vital signs, height, and weight
  - Hormone assessments: cortisol (by LC-MS/MS and IA), ACTH, 17-OHP, and A4

Eligibility Monitoring

- Once Initial Pre-screening is completed and a participant is determined to be potentially eligible for the investigational gene therapy trial, a subset of important assessments is performed approximately every 6 to 12 months since the last assessment:
  - Immunogenicity testing for anti-21-OH and anti-viral vector antibodies by ELISA
  - Routine clinical laboratory assessments, medical history, PE, vital signs, height, and weight
  - Hormone assessments: cortisol (by LC-MS/MS and IA), ACTH, 17-OHP, and A4

Eligibility Confirmation

- Once a treatment assignment becomes available in the investigational gene therapy trial, a potentially eligible participant may undergo a core set of assessments 25 to 30 (±3) days before transitioning to the Screening period of the gene therapy trial
- Results of some assessments may be used for Screening assessments in the investigational gene therapy trial

STREAMLINING ENROLLMENT INTO THE INVESTIGATIONAL GENE THERAPY TRIAL

- A pool of participants with known eligibility can be quickly drawn upon for enrollment, which is critical in the context of a sequentially enrolled investigational gene therapy trial
- The ability to perform at-home assessments and sample collection permits a wide geographic area to be surveyed, removing the constraint of focusing on academic centers and improving the opportunity to identify potentially eligible study participants

Flow Diagram of Study Participants in the CAH-300 Pre-screening Study

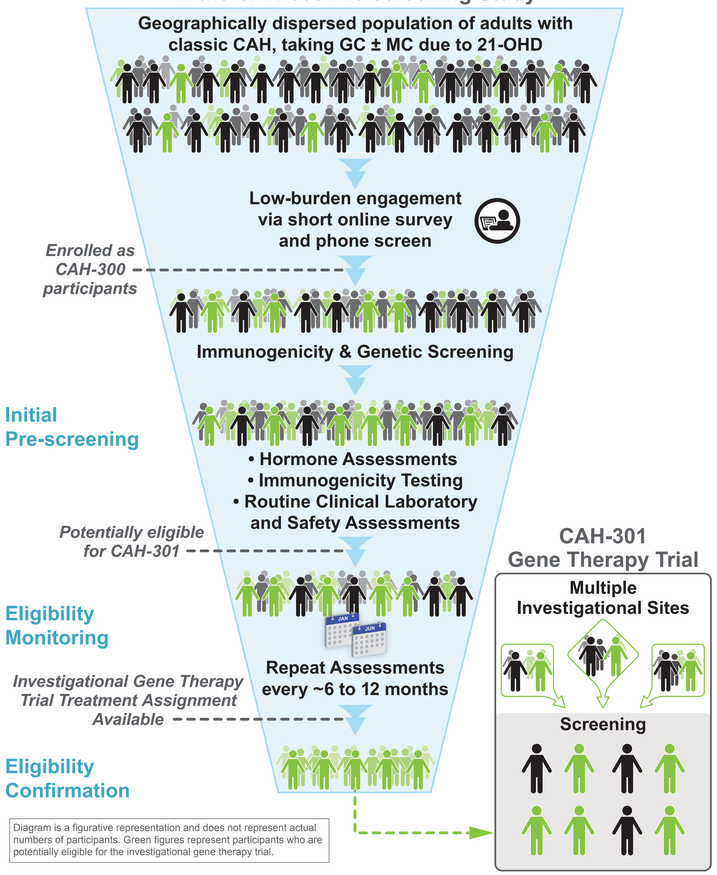


Diagram is a figurative representation and does not represent actual numbers of participants. Green figures represent participants who are potentially eligible for the investigational gene therapy trial.

CONCLUSIONS

- In addition to several other sources for identifying participants for the CAH-301 investigational gene therapy trial, the CAH-300 Pre-screening Study has enrolled 24 participants and enabled the efficient identification of multiple potentially eligible participants
- Potentially eligible participants for the CAH-301 investigational gene therapy trial have baseline profiles that will allow for detection of increased cortisol production (as well as decreased 17-OHP) after administration of gene therapy
- The design of the CAH-300 Pre-screening Study can be modified to enable identification of participants for other gene therapy studies with BBP-631, including a future pediatric study and registrational study