Design of a Phase 1/2 Open-Label, Dose-Escalation Study of the Safety and Efficacy of Gene Therapy in Adults with Classic Congenital Adrenal Hyperplasia (CAH) Due to 21-Hydroxylase Deficiency through Administration of an Adeno-Associated Virus (AAV) Serotype 5-Based Recombinant Vector Encoding the Human *CYP21A2* Gene

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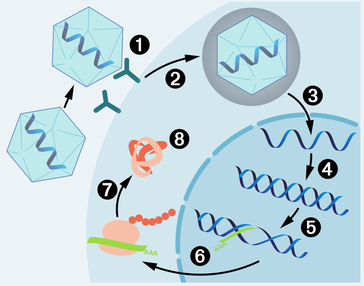
DISEASE BACKGROUND

- The most common type of CAH is due to 21-OHD caused by pathogenic variants in the *CYP21A2* gene
- Classic (severe) CAH requires lifetime GC and/or MC replacement
- 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 risk factors, and decreased bone mineral density[1-4]
- All-cause mortality rate in classic CAH patients has been reported as > 5 times that of controls, adjusted for age and sex[5]
- Gene replacement 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

GENE REPLACEMENT THERAPY

- BBP-631 is a gene therapy candidate composed of a non-replicating rAAV5 vector containing ssDNA of the human *CYP21A2* transgene
  - AAV gene therapies have been used in clinical trials in > 3000 patients across a 20-year span, suggesting that AAV-mediated gene therapy may be a well-tolerated, safe, and efficacious modality to address unmet clinical need[6-8]
- Single-dose IV infusion with BBP-631 is expected to deliver the *CYP21A2* transgene to adrenal gland cells enabling 21-OH enzyme production (Figure 1)
- *CYP21A2* gene replacement by BBP-631-mediated delivery is intended to restore physiologic endogenous cortisol and/or aldosterone biosynthesis and therefore:
  - Decrease or eliminate reliance on exogenous GC, thereby reducing sequelae of supraphysiologic GC
  - Reduce the hyperandrogenism associated with 21-OHD
  - Reduce the risk of adrenal crises
  - Reduce patient burden and non-compliance related to daily dosing of GC and/or MC

Figure 1: AAV Gene Therapy Approach for CAH



1. Receptor binding
2. Internalization
3. Nuclear entry
4. Conversion to dsDNA
5. mRNA transcription
6. Transport and translation
7. Protein folding and trafficking
8. Active protein

PROOF OF CONCEPT IN ANIMALS

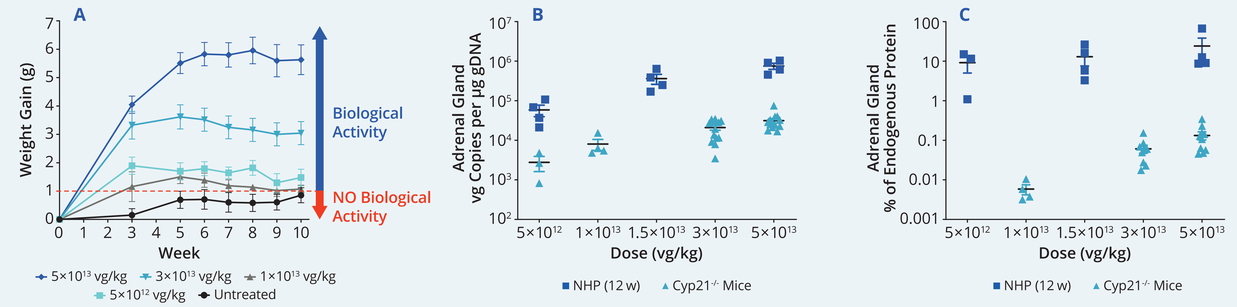
Mouse Model of CAH

- The H-2^{aw18} (Cyp21$^{-/-}$) mouse is an animal model of human CAH due to 21-OHD, which mimics a key pathophysiologic feature of CAH, ie, presenting with failure-to-thrive that leads to postnatal morbidity due to GC and MC deficiency[9-10]
- Single IV administration of a functional copy of the human *CYP21A2* gene led to early and sustained disease rescue of the Cyp21$^{-/-}$ mice (Figure 2A) accompanied by:
  - Reduction of urinary progesterone levels across 10 weeks, consistent with restoration of 21-hydroxylation of progesterone in the pathway to corticosterone, the major GC in mice
  - Reduction of renin expression in the kidney, suggesting improvement in MC function
  - Dose-dependent detection of vector genomes, human *CYP21A2* mRNA, and human 21-OH protein in the adrenal gland (Figure 2B)

Non-Human Primates

- Persistent, dose-dependent expression of human 21-OH protein was observed in adrenal glands of NHPs administered 1 dose of BBP-631 (Figure 2C)
- The amount of human 21-OH protein produced, expressed as percentage of endogenous 21-OH in NHPs, suggests the potential for clinically meaningful disease impact in patients with classic CAH

Figure 2: Identification of Biologically Active Doses in Mice and NHPs Supports the BBP-631 Starting Dose in the Phase 1/2 Clinical Study



Abbreviations: 21-OH: 21-hydroxylase; 21-OHD: 21-hydroxylase deficiency; 4W: 4 weeks; A4: androstenedione; AAV: adeno-associated virus; ACTH: adrenocorticotropic hormone; AE: adverse event; CAH: congenital adrenal hyperplasia; DNA: deoxyribonucleic acid; dsDNA: double-stranded DNA; DSMC: Data Safety Monitoring Committee; g: gram; GC: glucocorticoid; gDNA: genomic DNA; HC: hydrocortisone; HPA: hypothalamic-pituitary-adrenal; HPG: hypothalamic-pituitary-gonadal; kg: kilogram; IV: intravenous; MC: mineralocorticoid; µg: microgram; mRNA: messenger ribonucleic acid; NHP: non-human primate; PE: physical examination; rAAV5: recombinant adeno-associated virus serotype 5; ssDNA: single-stranded DNA; TART: testicular adrenal rest tumor; ULN: upper limit of normal; vg: vector genomes; VS: vital signs; w: weeks.

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References: 1) Bonfig, *Curr Opin Endocrinol Diabetes Obes*, 2017; 2) Falhammar, *J Clin Endocrinol Metab*, 2014; 3) Merke, *N Engl J Med*, 2020; 4) Reisch, *Exp Clin Endocrinol Diabetes*, 2019; 5) Jenkins-Jones, *Eur J Endocrinol*, 2018; 6) Miesbach, *Blood*, 2018; 7) Pasi, *N Engl J Med*, 2020; 8) Rangarajan, *N Engl J Med*, 2017; 9) Gotoh, *Endocrinology*, 1988; 10) Perdomini, *Gene Ther*, 2017.

PHASE 1/2 CLINICAL STUDY CAH-301

Study Design

- Phase 1/2, first-in-human, open-label, dose-escalation study in adults with classic CAH due to 21-OHD who will be monitored acutely and long-term for safety, tolerability, and efficacy over 5 years (Figure 3)
- Baseline (5-day period) with a detailed assessment of diurnal hormonal profile (including 17-OHP and A4), cortisol clearance, ACTH-stimulation testing, renin and aldosterone, and other exploratory hormones
- The protocol permits home assessments to minimize travel burden and mitigate patient risk

Dose Escalation Design

- Three dose levels of BBP-631 are planned for the study (Figure 4):
  - Level 1: 1.5 × 10^{13} vg/kg
  - Level 2: 3.0 × 10^{13} vg/kg
  - Level 3: 6.0 × 10^{13} vg/kg
- Study participants will receive only 1 dose of BBP-631
- DSMC will review safety data before dose escalation or dose expansion
- A tacrolimus regimen will be used to prevent or dampen potential immune responses that have been observed with other AAV-based therapies[6-8]

Patient Population (Key Eligibility Criteria)

- Adult male and non-pregnant females with classic CAH (simple virilizing or salt-wasting) due to 21-OHD
- Screening/baseline 17-OHP levels > 5-10 × ULN and < 40 × ULN
- Stable oral HC regimen as the only GC maintenance therapy
- Naïve to prior gene therapy or AAV-mediated therapy
- Negative for anti-AAV5 antibodies
- No history of adrenalectomy and has no significant liver disease

Key Safety and Efficacy Endpoints for Selection of Optimum Dose

- AEs, clinical laboratory measures (chemistry, hematology, urinalysis), VS, and PE
- Levels of endogenous cortisol (pre- and post-ACTH stimulation), 17-OHP, A4, and other hormones associated with the HPA and HPG axes
- Levels of renin and aldosterone
- Changes in HC and MC use
- Quality-of-life assessments measuring physical and physiological impacts of the hormonal imbalance

Figure 3: Study Timeline

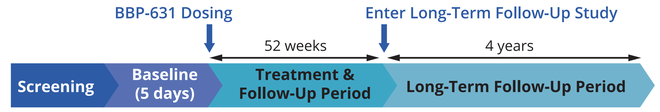
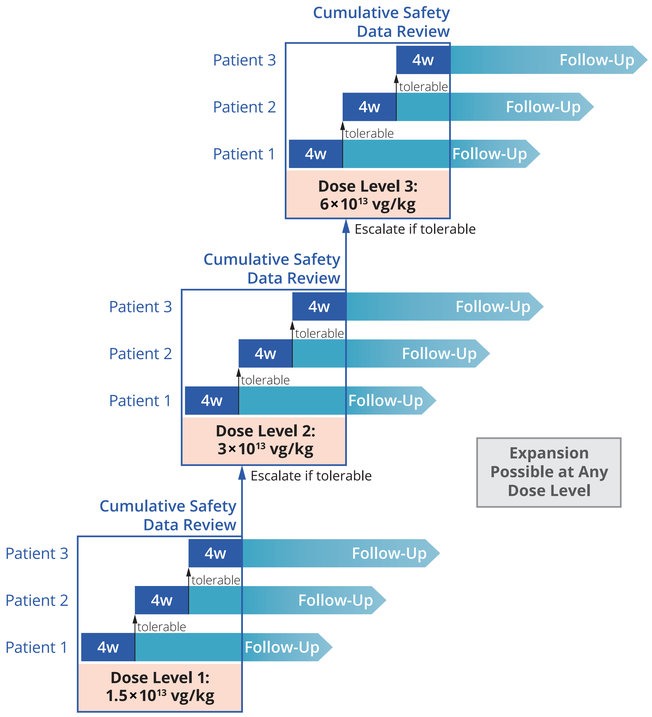


Figure 4: Dose Escalation and Expansion



SUMMARY

- Study CAH-301 is the first study to use AAV-mediated gene transfer for investigational treatment of adults with classic CAH due to 21-OHD
- Endpoints were selected to provide robust evidence of activity of BBP-631
- The potential for clinical benefit in patients with classic CAH who receive BBP-631 is supported by:
  - Successful, durable *CYP21A2* gene transfer in a mouse model
  - NHP data showing robust transgene mRNA expression and transduction in the adrenal gland, leading to sustained expression of the human 21-OH protein
  - Emerging clinical evidence of tolerability, safety, and efficacy using AAV as the modality for gene transfer
- Study CAH-301 is planned to start in 2021 and will be enrolling at multiple centers across the United States (NCT04783181)

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