

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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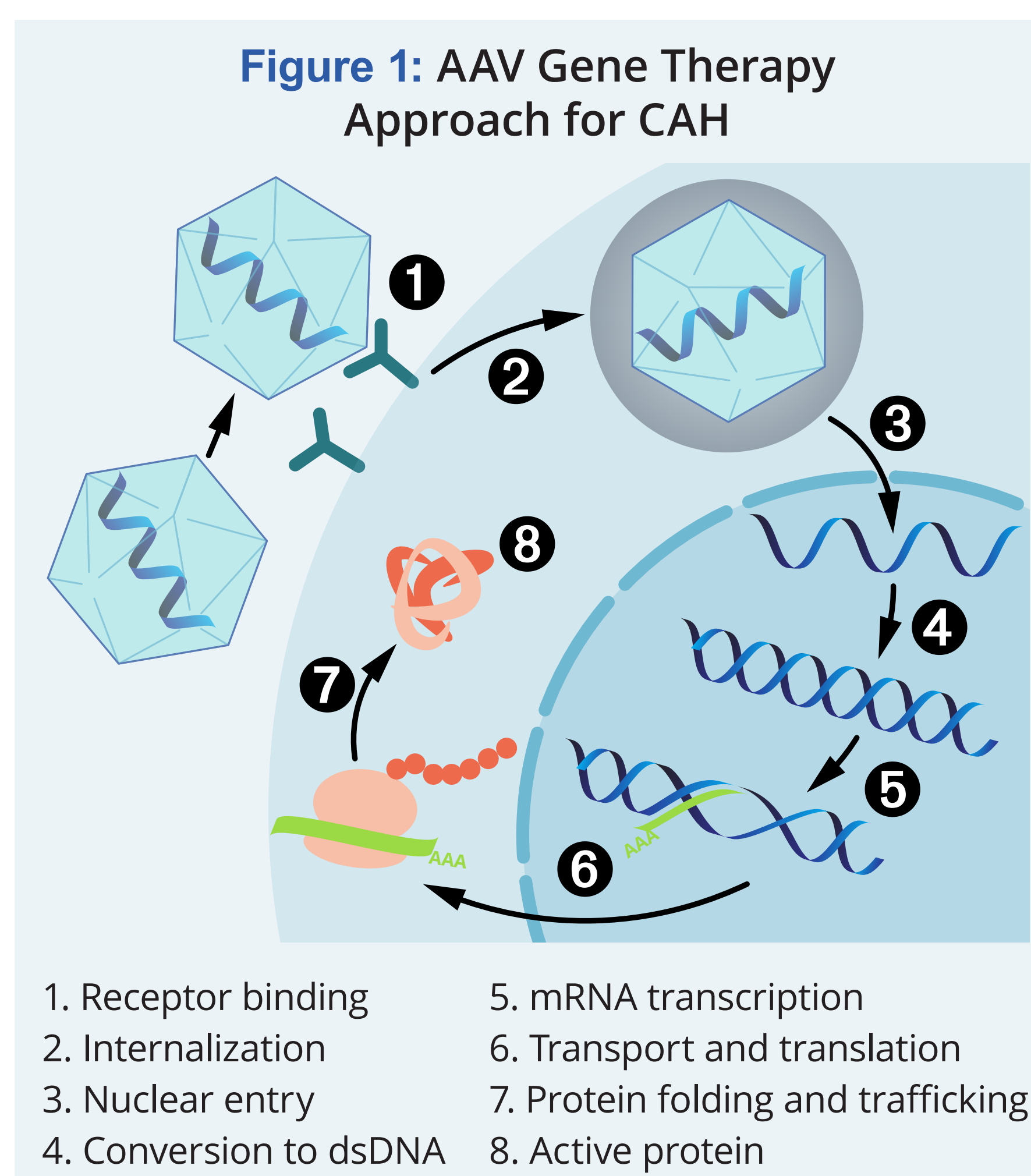
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DISEASE BACKGROUND

- 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 density¹⁻⁴
- All-cause mortality rate in classic CAH patients has been reported as > 5 times that of controls, adjusted for age and sex⁵
- 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 need⁶⁻⁸
- 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



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 therapies⁶⁻⁸

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 $> 5-10 \times$ ULN and $< 40 \times$ 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

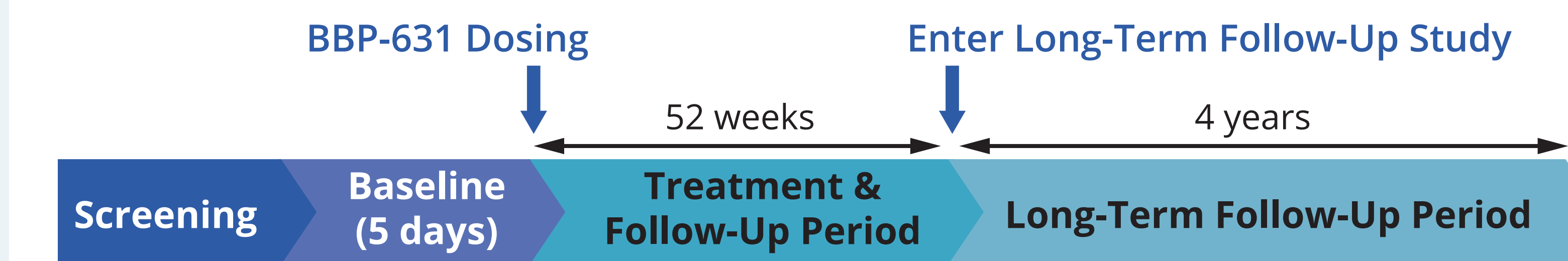
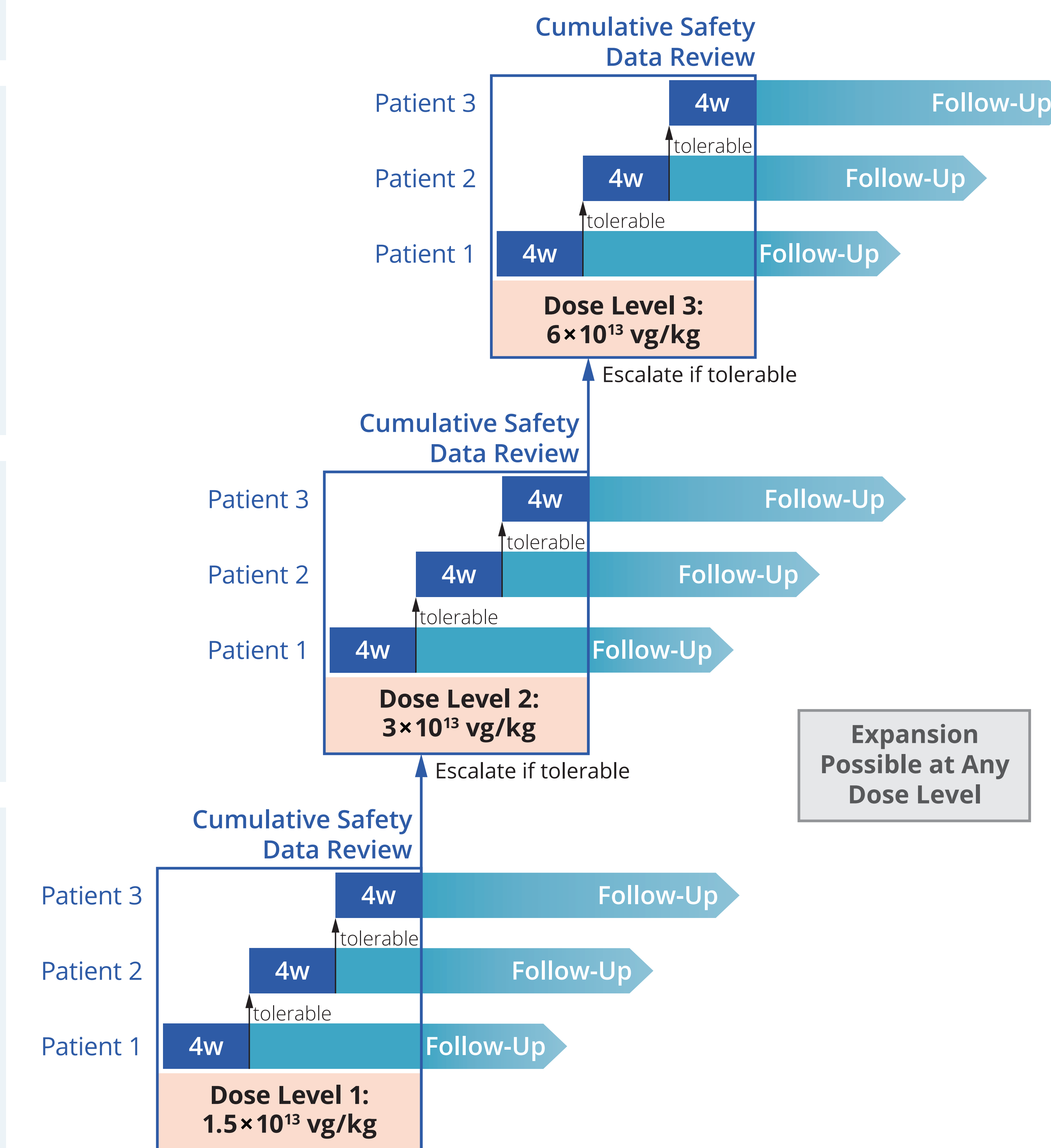


Figure 4: Dose Escalation and Expansion



PROOF OF CONCEPT IN ANIMALS

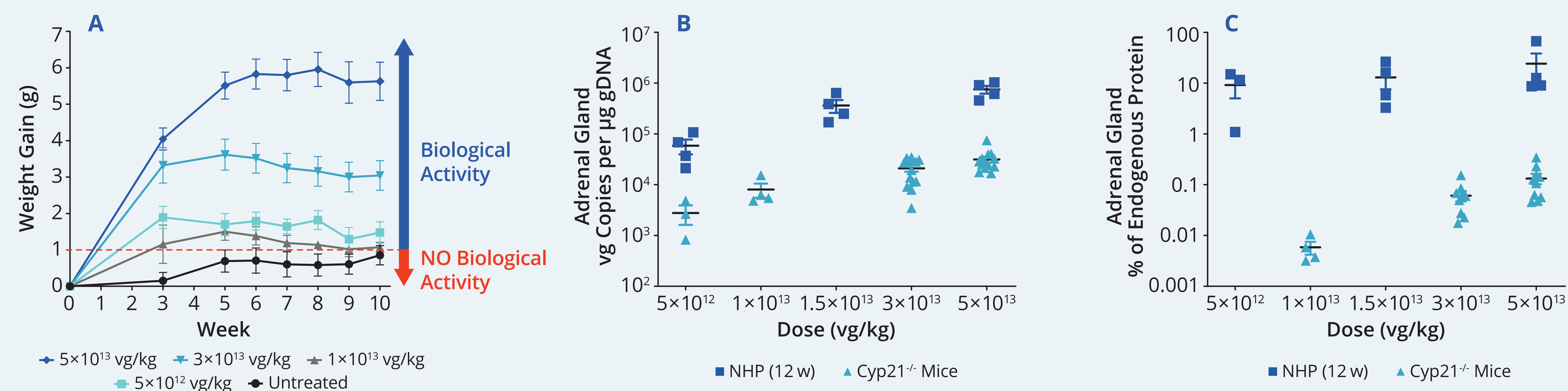
Mouse Model of CAH

- The H-2^{aw18} (*Cyp21*^{-/-}) mouse is an animal model of human CAH due to 21-OHD, which mimics a key pathophysiological feature of CAH, ie, presenting with failure-to-thrive that leads to postnatal morbidity due to GC and MC deficiency⁹⁻¹⁰
- 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



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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.

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)

