

Target Product Profiles for PaVe-GT Candidates

Disclaimer:

1. *The Target Product Profiles (TPPs) for AAV9-hPCCA, AAV9-MMAB, AAV8-COLQ, and AAV9-DOK7 were developed during early stages of the program. The TPPs outline the minimal and ideal characteristics of the planned products and have been refined based on the FDA feedback and/or the nonclinical and clinical data obtained.*
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Table of Contents

AAV9-hPCCA TPP	2
AAV9-MMAB TPP	3
AAV8-COLQ TPP	4
AAV8-DOK7 TPP	5

List of Abbreviations

Abbreviations	Full-length Terms
AAV	Adeno-associated virus
CMS	Congenital myasthenic syndromes
COLQ	Collagen like tail subunit of asymmetric acetylcholinesterase
DOK7	Downstream of tyrosine kinase 7
IV	Intravenous
MMA	Methylmalonic acidemia
MMAB	Metabolism of cobalamin associated B
NMJ	Neuromuscular junction
PA	Propionic acidemia
PCCA	Propionyl carboxylase CoA
QoL	Quality of life

AAV9-hPCCA TPP

Product name: Adeno-associated virus 9 vector expressing a functional, human, codon-optimized propionyl carboxylase CoA transgene (AAV9-hPCCA)

Therapeutic Modality: Gene therapy

Product Target	Minimum Acceptable Result	Ideal Result
Primary Product Indication and Usage	Treatment of <i>PCCA</i> -related PA with AAV-driven <i>PCCA</i> transgene and protein expression	Treatment of <i>PCCA</i> -related PA and restoration of clinically meaningful levels of metabolic function, bypassing the need of liver transplantation
Patient Population	Pediatric and adolescent patients, aged 2–18 years, with PA resulting from a deficiency of <i>PCCA</i>	Pediatric and adult patients, unrestricted in age, with PA resulting from a deficiency of <i>PCCA</i>
Mechanism of Action	Gene replacement therapy intended to replace mutated <i>PCCA</i> transgene	Gene replacement therapy intended to replace mutated <i>PCCA</i> transgene
Dosage Form and Stability	Solution for IV infusion; stable for at least 2 years at -80° Celsius	Solution for IV infusion; long-term stability at +4° Celsius
Dosing Regimen	Single-dose IV infusion	Single-dose IV infusion
Efficacy/Endpoints	Stabilization of disease progression Change in surrogate endpoints (metabolite levels) Change in surrogate biomarker (1-13C-sodium propionate oxidative capacity)	Decreased hospitalizations and reduced need for acute care related to metabolic stability. Improved mortality and morbidity (such as prevention of cardiomyopathy, renal disease, end-organ damage, transplantation, etc.) along with subjective measures (patient and caretaker reported outcomes) of QoL
Risk/Side Effect	Devoid of serious adverse events Devoid of systemic infusion reactions	Devoid of serious adverse events Devoid of systemic infusion reactions

AAV9-MMAB TPP

Product Name: Adeno-associated virus 9 vector expressing a functional, human, codon-optimized metabolism of cobalamin associated B cDNA (AAV9-MMAB)

Therapeutic Modality: Gene therapy

Product Target	Minimum Acceptable Result	Ideal Result
Primary Product Indication and Usage	Treatment of <i>cb1/B</i> -related methylmalonic acidemia (MMAB) with AAV-driven <i>MMAB</i> transgene and protein expression	Treatment of <i>cb1/B</i> -related methylmalonic acidemia (MMAB) and restoration of clinically meaningful levels of metabolic function, bypassing the need for organ transplantation
Patient Population	Pediatric and adult patients, ≥ 2 years of age, with MMA resulting from a deficiency of MMAB	Pediatric and adult patients, unrestricted in age, with MMA resulting from a deficiency of MMAB
Mechanism of Action	Gene replacement therapy intended to replace mutated <i>MMAB</i> transgene	Gene replacement therapy intended to replace mutated <i>MMAB</i> transgene
Dosage Form and Stability	Solution for IV infusion; stable for at least 2 years at -80° Celsius	Solution for IV infusion; long-term stability at $+4^{\circ}$ Celsius
Regimen	Single-dose IV infusion	Single-dose IV infusion
Efficacy	Stabilization of disease progression Change in surrogate endpoints (metabolite levels) Change in surrogate biomarker (1-13C-sodium propionate oxidative capacity)	Decreased hospitalizations and reduced need for acute care related to metabolic stability. Improved mortality and morbidity (such as prevention of cardiomyopathy, renal disease, end-organ damage, transplantation, etc.) along with subjective measures (patient and caretaker reported outcomes) of QoL
Risk/Side Effect	Devoid of serious adverse events Devoid of systemic infusion reaction	Devoid of serious adverse events Devoid of systemic infusion reaction

AAV8-COLQ TPP

Product name: Adeno-associated virus 8 vector expressing a functional, human, codon-optimized collagen Q (COLQ) cDNA, under the control of the spc512 promoter (AAV8-COLQ)

Therapeutic Modality: Gene therapy

Product Target	Minimum Acceptable Result	Ideal Result
Primary Product Indication and Usage	Treatment of COLQ-related CMS (CMS 5 caused by COLQ deficiency) with AAV-driven COLQ transgene and protein expression	Treatment of COLQ-related CMS and restoration of clinically meaningful motor function, bypassing the need for invasive or medical supportive interventions to maintain function
Patient Population	Pediatric and adult patients, aged 2 years and above, with COLQ-CMS resulting from a deficiency of COLQ	Pediatric and adult patients, unrestricted in age, with COLQ-CMS resulting from a deficiency of COLQ
Mechanism of Action	Gene replacement therapy intended to replace mutated COLQ transgene	Gene replacement therapy intended to replace mutated COLQ transgene
Dosage Form and Stability	Solution for IV infusion; stable for at least 2 years at -80° Celsius	Solution for IV infusion; long-term stability at +4° Celsius
Dosing Regimen	Single-dose IV infusion	Single-dose IV infusion
Efficacy	Stabilization of disease progression Change in surrogate endpoints (motor function measures) Change in surrogate biomarkers (absolute and percent change in additional biomarker measures i.e., NMJ pathology)	Improved mortality and morbidity (such as prevention of respiratory insufficiency/failure requiring non-invasive or invasive ventilatory support, progressive weakness leading to deterioration in ambulation and immobility, progressive scoliosis, bulbar dysfunction causing feeding difficulty requiring enteral feeding (gastrostomy tube) along with subjective measures (patient and caretaker reported outcomes) of QoL
Risk/Side Effect	Devoid of serious adverse events Devoid of systemic infusion reaction	Devoid of serious adverse events Devoid of systemic infusion reaction

AAV8-DOK7 TPP

Product name: Adeno-associated virus 8 vector expressing a functional, human, codon-optimized downstream of tyrosine kinase 7 (DOK7) cDNA, under the control of the spc512 promoter (AAV8-DOK7)

Therapeutic Modality: Gene therapy

Product Target	Minimum Acceptable Result	Ideal Result
Primary Product Indication and Usage	Treatment of <i>DOK7</i> -related CMS (CMS10 caused by <i>DOK7</i> deficiency) with AAV-driven <i>DOK7</i> transgene and protein expression	Treatment of <i>DOK7</i> -related CMS and restoration of clinically meaningful motor function, bypassing the need for invasive or medical supportive interventions to maintain function
Patient Population	Pediatric and adult patients, aged 2 years and above, with <i>DOK7</i> -CMS resulting from a deficiency of <i>DOK7</i>	Pediatric and adult patients, unrestricted in age, with <i>DOK7</i> -CMS resulting from a deficiency of <i>DOK7</i>
Mechanism of Action	Gene replacement therapy intended to replace mutated <i>DOK7</i> transgene	Gene replacement therapy intended to replace mutated <i>DOK7</i> transgene
Dosage Form and Stability	Solution for IV infusion; stable for at least 2 years at -80° Celsius	Solution for IV infusion; long-term stability at +4° Celsius
Dosing Regimen	Single-dose IV infusion	Single-dose IV infusion
Efficacy	Stabilization of disease progression Change in surrogate endpoints (motor function measures) Change in surrogate biomarkers (absolute and percent change in additional biomarker measures i.e., NMJ pathology)	Improved mortality and morbidity (such as prevention of respiratory insufficiency/failure requiring non-invasive or invasive ventilatory support, progressive weakness leading to deterioration in ambulation and immobility, progressive scoliosis, bulbar dysfunction causing feeding difficulty requiring enteral feeding (gastrostomy tube) along with subjective measures (patient and caretaker reported outcomes) of QoL)
Risk/Side Effect	Devoid of serious adverse events Devoid of systemic infusion reaction	Devoid of serious adverse events Devoid of systemic infusion reaction