# 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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## 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 *PCCA*-related PA with AAV-driven *PCCA* transgene and protein expression | Treatment of *PCCA*-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 PCCA | Pediatric and adult patients, unrestricted in age, with PA resulting from a deficiency of PCCA |
| **Mechanism of Action** | Gene replacement therapy intended to replace mutated *PCCA* transgene | Gene replacement therapy intended to replace mutated *PCCA* 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<br>Change in surrogate endpoints (metabolite levels)<br>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<br>Devoid of systemic infusion reactions | Devoid of serious adverse events<br>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 *cblB*-related methylmalonic acidemia (MMAB) with AAV-driven *MMAB* transgene and protein expression | Treatment of *cblB*-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 *MMAB* transgene | Gene replacement therapy intended to replace mutated *MMAB* 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 |
| **Regimen** | Single-dose IV infusion | Single-dose IV infusion |
| **Efficacy** | Stabilization of disease progression<br>Change in surrogate endpoints (metabolite levels)<br>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<br>Devoid of systemic infusion reaction | Devoid of serious adverse events<br>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<br>Change in surrogate endpoints (motor function measures)<br>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<br>Devoid of systemic infusion reaction | Devoid of serious adverse events<br>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 *DOK7*-related CMS (CMS10 caused by DOK7 deficiency) with AAV-driven *DOK7* transgene and protein expression | Treatment of *DOK7*-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 *DOK7*-CMS resulting from a deficiency of DOK7 | Pediatric and adult patients, unrestricted in age, with *DOK7*-CMS resulting from a deficiency of DOK7 |
| **Mechanism of Action** | Gene replacement therapy intended to replace mutated *DOK7* transgene | Gene replacement therapy intended to replace mutated *DOK7* 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<br>Change in surrogate endpoints (motor function measures)<br>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<br>Devoid of systemic infusion reaction | Devoid of serious adverse events<br>Devoid of systemic infusion reaction |