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Impact of Full and Empty Particle Concentration on Product Quality and *in vivo* Efficacy of HMI-102 in a Mouse Model of Phenylketonuria (PKU)

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Phenylketonuria (PKU) is an autosomal recessive disorder where a mutation occurs in the *PAH* gene on chromosome 12 that results in a deficiency of the enzyme, phenylalanine hydroxylase (PAH). Current treatment options include dietary restriction of phenylalanine (Phe) with or without augmentation of hepatic PAH activity by delivery of a cofactor necessary to metabolize Phe and/or a pegylated-derivative of the cyanobacterium enzyme phenylalanine ammonia-lyase. These therapies do not address the underlying genetic disease or restore the normal metabolic pathway and conversion of Phe to tyrosine (Tyr). Here, a gene therapy approach is described using novel AAVHSC15 vector packaging a human *PAH* cDNA, HMI-102, as a potential one-time administration treatment for PKU targeting the genetic cause of the disease. During AAV manufacturing, the vector product contains both full and empty capsids. Historically, empty capsids have been considered a process-related impurity and the impact of empty capsids *in vivo* has been debated depending on delivery method, target tissue, and clinical outcome. In this study, we examined whether varying amounts of empty capsids can influence HMI-102 biological activity and potency *in vivo* using the Pah^{enu2} murine model of PKU. The data demonstrated that a wide range of empty capsid ratios selected resulted in comparable levels of vector quality, transduction efficiency, and biological activity. Furthermore, Phe levels of dosed mice were significantly reduced and remained within the therapeutic range throughout the study duration. While a general awareness of empty capsid ratios can be used by manufacturers to find the proper balance to scale and purify the vector product long-term, the varying amounts examined did not impact the biologic activity of HMI-102 in normalizing Phe levels in a murine model of PKU.