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PEGylation optimization and formulation development of pegvaliase drug product in prefilled syringe of PEG phenylalanine ammonia lyase (pegvaliase) for the treatment of phenylketonuria

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Phenylketonuria (PKU) is an inherited metabolic disease caused by a deficiency of the enzyme phenylalanine hydroxylase (PAH). This results in elevated, neurotoxic levels of phenylalanine (Phe) which can affect brain function, causing severe intellectual disability, behavioral abnormalities, delayed speech and seizures. However, lowering Phe levels can improve/reverse some of these symptoms. Current management options are limited to a medical diet and treatment with sapropterin, the synthetic form of tetrahydrobiopterin (BH4), the cofactor for PAH. Only patients with residual PAH activity may benefit from sapropterin treatment. Traditional enzyme replacement therapy with recombinant PAH has many obstacles. However, treating PKU patients by enzyme substitution therapy with an alternative, exogenous Phe-metabolizing enzyme such as phenylalanine ammonia lyase (PAL) is an option for adult PKU patients. Developing PAL as a therapeutic required overcoming immunogenicity, protein expression, stability and mode of delivery challenges. After extensive evaluation of PAL enzymes from multiple species, recombinant double mutant version of *Anabaena variabilis* (rAv) PAL which improved stability by reducing aggregation was selected for PEGylation to overcome immunogenicity. An optimal PEGylation ratio was found to be critical for rAvPAL-PEG (pegvaliase) efficacy. In addition, the rAvPAL substrate, L-Phe, and product, trans-cinnamate, stabilized pegvaliase for long-term storage at 2-8°C. The optimized pegvaliase formulation has been used in several clinical studies and has successfully lowered and maintained Phe levels in PKU patients. The need to improve the dosing administration procedures and end-user convenience drove the development of pegvaliase in a Pre-Filled Syringe (PFS) packaging system for Phase III clinical trials and commercial applications. This container closure system including all the components in PFS selected for the Phase III and commercial presentation of pegvaliase drug product (DP) is compatible with pegvaliase. PFS is a suitable primary packaging system for pegvaliase DP under the recommended storage conditions of 2-8°C.

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