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PEGTIBATINASE, AN INVESTIGATIONAL ENZYME REPLACEMENT THERAPY FOR THE TREATMENT OF CLASSICAL HOMOCYSTINURIA: INITIAL RESULTS FROM THE PHASE 1/2 COMPOSE STUDY

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Cystathionine beta synthase (CBS)-deficient homocystinuria (HCU), also known as classical HCU, is a rare autosomal recessive disorder caused by pathogenic variants in the *CBS* gene. CBS is a critical enzyme required for the processing of homocysteine (Hcy), a key intermediate in the metabolism of methionine through the transsulfuration pathway. CBS deficiency causes toxic accumulation of Hcy, which results in the clinical manifestations of HCU. These primarily affect cardiovascular, skeletal, neurologic, and ocular organ systems, with thromboembolism being the major cause of early mortality. The current standard-of-care for HCU includes a methionine-restricted diet, vitamin B_6, and betaine. Despite these treatments, many patients with HCU are unable to sufficiently reduce their Hcy levels and ultimately develop the clinical manifestations associated with HCU. Thus, there exists a significant unmet medical need for novel disease-modifying treatments for HCU.

Pegtibatinase is an engineered pegylated form of human CBS that is currently being studied as the first-in-class investigational enzyme replacement therapy for HCU. COMPOSE (NCT 03406611) is a double-blind, randomized, placebo-controlled, Phase 1/2 dose escalation study with 4 subjects per cohort, randomized at 3:1 for active drug versus placebo. Study objectives include assessment of safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of pegtibatinase given subcutaneously once or twice weekly. Key eligibility criteria were confirmed diagnosis of HCU with total plasma Hcy level ≥80 micromoles/L and age 12-65 years. The study began in 2019 and 19 subjects have been enrolled across five dose cohorts at the following doses: 0.33mg/kg weekly, 0.66mg/kg weekly, 1.0mg/kg weekly, 1.0mg/kg twice weekly, and 1.5mg/kg twice weekly. After each dose cohort completed the first 6 weeks of treatment, an independent data monitoring committee reviewed the unblinded safety data prior to enrollment of the next higher dose cohort. A planned unblinded analysis was conducted after the last subject in Cohort 5 completed 12 weeks of double-blind treatment. Results of the COMPOSE study, including incidence of adverse events, immunogenicity, and treatment effect of pegtibatinase on total plasma Hcy, along with other related metabolites will be presented.