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Pharmacokinetics and safety of afamelanotide in adolescent and adult erythropoietic protoporphyria (EPP)

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EADV CUV052 Abstract (oral presentation)

Introduction & Objectives:

Erythropoietic protoporphyria (EPP) is an ultra-rare inherited disorder of haem metabolism, where systemic accumulation of the highly photoreactive haem precursor protoporphyrin IX (PPIX) causes debilitating phototoxicity following brief exposure to visible light (within minutes). Symptoms are present from early childhood, resulting in conditioned behaviour that has a severe impact on patient quality of life.

Afamelanotide is a synthetic analogue of naturally occurring α-melanocyte stimulating hormone (α-MSH) and the only approved treatment for EPP. Afamelanotide binds and activates MC1R on epidermal melanocytes, resulting in epidermal eumelanogenesis which, due to eumelanin filtering and absorbing light, prevents PPIX photoactivation and phototoxicity in EPP. Moreover, eumelanogenesis exerts antioxidant properties within cells, thereby neutralizing the inflammatory effects of free radicals which are generated following PPIX photoactivation.

Currently, afamelanotide is licensed for adults only, leaving a significant unmet need for treatment of paediatric EPP, with only a small number of adolescent patients treated off-label. CUV052 was the first interventional study to assess afamelanotide in the adolescent EPP population (12-17 years).

Materials & Methods:

Eligible participants were patients with EPP aged 12-70 inclusive and a weight greater than 50 kg. Participants received one 16mg afamelanotide implant (SCENESSE®) and had plasma PK samples taken at regular timepoints. The primary objective was to determine and compare the pharmacokinetic (PK) profiles of afamelanotide in adolescents and adult EPP patients. Primary endpoints were area under the plasma-concentration time curve (AUC0-t) and maximum plasma concentration (Cmax); secondary endpoints included area under the curve extrapolated to infinity (AUC0-∞), time at Cmax (tmax) and apparent half-life (t1/2).

Results:

In total, 28 participants (14 adolescents 8F:6M, 13-17 years) and 14 adults (4F:10M, age 18-55 years) consented and were enrolled. PK analyses showed that afamelanotide exposure was higher in EPP adolescents compared to adults, although at levels consistent with historical data from healthy volunteer studies. Afamelanotide was eliminated at a similar rate in adults and adolescents, as evidenced by similar terminal rate constants and plasma concentration half-lives.

Safety analyses showed afamelanotide was well tolerated by all study participants. Of the 28 TEAEs reported in adolescents, only 8/28 (28.6%) were assessed as related to afamelanotide. By comparison, 25 TEAEs were reported in adults, of which 14/25 (56%) were assessed as related. All related treatment-emergent adverse events (TEAEs) were mild in severity and resolved during the study, with no serious related TEAEs reported.

Conclusion:

In conclusion, PK profiles for afamelanotide were higher in adolescents versus adults and consistent with previous data. Afamelanotide was well tolerated in both adolescents and adults. Data from this study adds to the safety and efficacy profile for afamelanotide in the adolescent population.

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