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Study of Intraventricular Cerliponase Alfa for CLN2 Disease

Angela Schulz, M.D., Temitayo Ajayi, M.D., Nicola Specchio, M.D., Ph. D., Emily de Los Reyes, M.D., Paul Gissen, M.B., Ch.B., Ph.D., Douglas Ballon, Ph.D., Jonathan P. Dyke, Ph.D., Heather Cahan, M.D., Peter Slasor, Sc.D., David Jacoby, M.D., Ph.D., Alfried Kohlschütter, M.D., and the CLN2 Study Group UKE members Christoph Schwering, M.D., Eva Wibbeler, M.D., Miriam Nickel, M.D.

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ABSTRACT: BACKGROUND: Recombinant human tripeptidyl peptidase 1 (cerliponase alfa) is an enzyme-replacement therapy that has been developed to treat neuronal ceroid lipofuscinosis type 2 (CLN2) disease, a rare lysosomal disorder that causes progressive dementia in children. METHODS: In a multicenter, open-label study, we evaluated the effect of intraventricular infusion of cerliponase alfa every 2 weeks in children with CLN2 disease who were between the ages of 3 and 16 years. Treatment was initiated at a dose of 30 mg, 100 mg, or 300 mg; all the patients then received the 300-mg dose for at least 96 weeks. The primary outcome was the time until a 2-point decline in the score on the motor and language domains of the CLN2 Clinical Rating Scale (which ranges from 0 to 6, with 0 representing no function and 3 representing normal function in each of the two domains), which was compared with the rate of decline in 42 historical controls. We also compared the rate of decline in the motor–language score between the two groups, using data from baseline to the last assessment with a score of more than 0, divided by the length of follow-up (in units of 48 weeks). RESULTS Twenty-four patients were enrolled, 23 of whom constituted the efficacy population. The median time until a 2-point decline in the motor–language score was not reached for treated patients and was 345 days for historical controls. The mean (• }SD) unadjusted rate of decline in the motor–language score per 48-week period was 0.27• }0.35 points in treated patients and 2.12• }0.98 points in 42 historical controls (mean difference, 1.85; P<0.001). Common adverse events included convulsions, pyrexia, vomiting, hypersensitivity reactions, and failure of the intraventricular device. In 2 patients, infections developed in the intraventricular device that was used to administer the infusion, which required antibiotic treatment and device replacement. CONCLUSIONS: Intraventricular infusion of cerliponase alfa in patients with CLN2 disease resulted in less decline in motor and language function than that in historical controls. Serious adverse events included failure of the intraventricular device and devicerelated infections. (Funded by BioMarin Pharmaceutical and others; CLN2 ClinicalTrials.gov numbers, NCT01907087 and NCT02485899.)

STATEMENT: *In an international study, scientists of the Children's Hospital, University Medical Center Hamburg-Eppendorf (UKE) have discovered the worldwide first therapeutic approach for Late Infantile Neuronal Ceroid Lipofuscinosis (CLN2) – a form of childhood dementia. This disease is characterized by seizures, language and motor function loss, blindness and early death. Intracerebroventricular enzyme replacement therapy with cerliponase alfa was shown to stop the loss of motor and language function in 80% of the patients over a period of 96 weeks so far. The synthetic enzyme is introduced into brain ventricles of the patient via a catheter every 14 days. The scientists have now published their findings in the New England Journal of Medicine.*

BACKGROUND: This work was performed at the Children's Hospital in the NCL research group for Dr. Angela Schulz. The UKE study team – listed as co-authors – consist of Dr. Angela Schulz as International Principal Investigator, Prof. emeritus Alfried Kohlschütter, who developed the clinical scoring system used for primary outcome measures and Drs. Nickel, Schwering and Wibbeler as sub-investigators. The clinical trials was sponsored by the company BioMarin, who manufactures the investigational product. The collection of the natural history data used for comparison has been funded in an FP project DEM-CHILD coordinated by Dr. Angela Schulz.