OBJECTIVE: MPS II is an x-linked lysosomal storage disease caused by deficiency of iduronate-2-sulfatase (I2S) leading to accumulation of glycosaminoglycans in tissues. Severe MPS II results in irreversible neurodevelopmental decline not addressed by intravenously administered enzyme replacement therapy. RGX-121, a recombinant adeno-associated virus serotype 9 capsid containing a human iduronate-2-sulfatase expression cassette (AAV9.CB7.hIDS), administered to the central nervous system (CNS) may provide a permanent source of secreted I2S, potentially correcting neurologic and systemic disease manifestations.

METHODS: In this phase 1/2, first-in-human, multicenter, open-label, dose escalation trial (NCT03566043), participants with severe MPS II ages 4 months to 5 years receive one image-guided RGX-121 injection to the CNS with follow-up for safety, tolerability, and efficacy for 104 weeks. Assessments include CSF, plasma and urine biomarkers; cognition, language, and motor neurodevelopmental scales; and liver and spleen imaging. Nine participants have been enrolled in 3 dose cohorts (1.3x10^10, 6.5x10^10, and 2.0x10^11 genome copies/gram brain mass) as of April 25, 2021.

RESULTS: As of April 25, 2021, RGX-121 was reported to be well tolerated with no drug-related serious adverse events. Time of post-administration follow-up ranged from < 8 weeks to two years. Heparan sulfate CSF levels, a biomarker of neuronopathic MPS II disease, showed consistent reductions, and interim neurodevelopmental testing demonstrated ongoing skill acquisition in multiple domains. Plasma I2S enzyme expression, total urine GAGs, and abdominal ultrasound imaging suggested emerging evidence of systemic RGX-121 efficacy.

CONCLUSIONS: RGX-121 has the potential to provide sustained CNS clinical outcomes and additional systemic effects in MPS II patients.