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Rebisufligene etisparvovec: The first AAV9-mediated *SGSH* gene therapy approved for the treatment of mucopolysaccharidosis type IIIA (MPS IIIA)

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SUMMARY: Mucopolysaccharidosis type IIIA (MPS IIIA; Sanfilippo syndrome type A) is a rare lysosomal storage disorder caused by biallelic *SGSH* pathogenic variants that results in heparan sulfate accumulation and progressive neurodegeneration. Previously, treatment was limited to supportive care. In September 2026, the US Food and Drug Administration approved rebisufligene etisparvovec-hopf (FAYUVI), an adeno-associated virus serotype 9–mediated *SGSH* gene-addition therapy, for neurological manifestations in pediatric patients with preserved neurodevelopmental function. Evidence was primarily derived from the open-label Transpher A study, which compared 17 early-treated patients with 27 external natural history controls. Between 24 and 60 months of age, the model-estimated difference in the change in Bayley-III cognitive raw score was 23.5 points (95% confidence interval, 17.2–29.9), favoring treatment. Heparan sulfate levels in cerebrospinal fluid decreased by a mean of 57.1% at 24 months. Among patients receiving the recommended dose, elevated liver enzymes (85%) and vomiting (67%) were common; serious adverse events occurred in 18 of 33 patients across all dose levels. The approval of rebisufligene etisparvovec represents a landmark advance in the treatment of MPS IIIA, establishing the first disease-modifying gene therapy for this disorder and demonstrating the therapeutic potential of early intervention. Ongoing follow-up and postmarketing surveillance need to be conducted to establish the therapy's long-term efficacy, durability, and safety.

Keywords: mucopolysaccharidosis, Sanfilippo syndrome, rebisufligene etisparvovec, gene therapy, heparan sulfate

Mucopolysaccharidosis type IIIA (MPS IIIA), also known as Sanfilippo syndrome type A, is an autosomal recessive lysosomal storage disorder. Biallelic pathogenic variants in the *SGSH* gene result in a deficiency of N-sulfoglucosamine sulfohydrolase (sulfamidase), impairing the degradation of heparan sulfate (HS) and leading to its accumulation in tissues and progressive neurodegeneration (*1*). Affected individuals gradually lose cognitive, language, and motor abilities and develop behavioral disturbances, sleep disorders, and swallowing difficulties. As the disease progresses, patients often become dependent on comprehensive care, placing a substantial long-term burden on their families. Premature death may occur due to neurologic disease-related complications (*1,2*).

A global systematic review and meta-analysis estimated the pooled birth prevalence of MPS IIIA to be approximately 0.52 per 100,000 live births (95% confidence interval [CI], 0.33–0.72), although estimates vary across regions because of differences in diagnostic capabilities and epidemiological methods (*3*). In children with rapidly progressive disease, cognitive development typically reaches a plateau at approximately 30 months of age, followed by marked regression at 40-50 months, suggesting that the window for effective intervention occurs early in life (*1*). Currently, the management of MPS IIIA relies primarily on supportive and symptomatic care, while established treatments capable of modifying disease progression have historically been lacking. There is therefore an urgent need for disease-modifying therapies that can be administered before the onset of cognitive decline.

On September 17, 2026, the US Food and Drug Administration (FDA) approved rebisufligene etisparvovec (FAYUVI; formerly UX111/ABO-102), developed by Ultragenyx, for the treatment of neurological manifestations of MPS IIIA in pediatric patients with preserved neurodevelopmental function, making it the first FDA-approved treatment for this disease (*4*). Rebisufligene etisparvovec uses an adeno-associated virus serotype 9 (AAV9) vector to deliver a functional SGSH expression cassette, thereby restoring SGSH enzymatic activity and promoting the lysosomal degradation of heparan sulfate (*5*). This gene replacement strategy provides a functional copy of the gene without correcting the underlying pathogenic variants. The recommended dose is a single intravenous

infusion of 3.0×10^{13} vector genomes/kg (*5*). The principal advantages of this approach are its ability to address the underlying enzymatic deficiency and its single-dose administration, potentially eliminating the need for repeated delivery of therapeutic agents to the central nervous system. Rebisufligene etisparvovec therefore represents a disease-modifying treatment option for a defined population of pediatric patients, and its efficacy cannot yet be extrapolated to patients in all stages of MPS IIIA.

The clinical evidence supporting its approval was derived primarily from Transpher A (ABT-001; NCT02716246), a global, open-label, single-arm, dose-escalation phase I/II/III study, together with data from its long-term follow-up study (LTFU-ABO-102; NCT04360265) (*5*). A total of 28 children with rapidly progressing MPS IIIA received treatment in the main study, including 22 who received a single intravenous infusion at the recommended dose of 3×10^{13} vector genomes/kg (*6*). Of those 22 patients, 17 met the criteria for the modified intention-to-treat (mITT) population: age ≤ 2 years, or age > 2 years with a baseline cognitive developmental quotient > 60 (*5,6*). These 17 patients constituted the primary efficacy population and were compared with 27 untreated patients from external natural history studies. The primary efficacy outcome was the change in Cognitive Scale raw scores on the Bayley Scales of Infant and Toddler Development, Third Edition (BSITD-III). The percent change in the heparan sulfate level in cerebrospinal fluid (CSF) from the baseline was evaluated as a secondary endpoint. After a median follow-up of 4.2 years in the treatment group, the model-estimated changes in cognitive raw scores on the BSITD-III between chronological ages of 24 and 60 months were + 16.0 points in treated patients and − 7.6 points in natural history controls (*5*). The between-group difference was 23.5 points (95% CI, 17.2-29.9; $P < 0.0001$), suggesting that treated patients acquired or maintained cognitive skills more than would be expected from the natural course of the disease (*5*). At 24 months after treatment, heparan sulfate levels in CSF had decreased by an average of 57.1% from the baseline among 16 evaluable patients (*5*). In a pooled safety analysis, the incidence of elevated liver enzymes was 85%, that of vomiting was 67%, and that of a decreased platelet count was 19% among 27 patients receiving the recommended dose (*6*). Elevation of liver enzymes was mild or moderate (grade 1 or 2); three patients experienced grade 3 elevation, which resolved spontaneously or following corticosteroid treatment (*6*). Across all dose levels, 18 of 33 patients experienced serious adverse events, including one episode of an altered mental status considered possibly related to treatment (*6*). No deaths were reported.

As of October 19, 2026, the expansion cohort of the Transpher A study remained open for enrollment, with ongoing efforts to optimize immunomodulatory management and gain additional clinical experience (*7*). In addition, a long-term follow-up study (NCT04360265) continued to evaluate safety and cognitive outcomes (*8*). Although the available clinical data substantiate a cognitive benefit of rebisufligene etisparvovec when administered early in the disease course and they provide an initial characterization of its safety profile, the therapy's efficacy in real-world clinical practice, the durability of its therapeutic benefit, and its long-term safety remain to be established through postmarketing registries and systematic follow-up studies.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Shapiro EG, Nestrasil I, Delaney KA, Rudser K, Kovac V, Nair N, Richard CW, 3rd, Haslett P, Whitley CB. A prospective natural history study of mucopolysaccharidosis type IIIA. J Pediatr. 2016; 170:278–287 e271–274.
2. Muschol N, Giugliani R, Jones SA, Muenzer J, Smith NJC, Whitley CB, Donnell M, Drake E, Elvidge K, Melton L, O'Neill C, Group MIGD. Sanfilippo syndrome: Consensus guidelines for clinical care. Orphanet J Rare Dis. 2022; 17:391.
3. Kong W, Wu S, Zhang J, Lu C, Ding Y, Meng Y. Global epidemiology of mucopolysaccharidosis type III (Sanfilippo syndrome): An updated systematic review and meta-analysis. J Pediatr Endocrinol Metab. 2021; 34:1225–1235.
4. U.S. Food and Drug Administration. FDA Approves First Gene Therapy for Pediatric Patients with Sanfilippo Syndrome Type A. *https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-pediatric-patients-sanfilippo-syndrome-type* (accessed October 21, 2026).
5. FAYUVI™ (rebisufligene etisparvovec-hopf) suspension for intravenous infusion. *https://www.ultragenyx.com/wp-content/uploads/2026/10/FAYUVI_USPI.pdf* (accessed October 21, 2026).
6. U.S. Food and Drug Administration. Summary Basis for Regulatory Action. *https://www.fda.gov/media/195198/download?attachment=* (accessed October 22, 2026).
7. Ultragenyx Pharmaceutical Inc. Phase I/II/III gene transfer clinical trial of scAAV9.U1a.hSGSH. ClinicalTrials.gov identifier: NCT02716246. *https://clinicaltrials.gov/study/NCT02716246* (accessed October 19, 2026).
8. Ultragenyx Pharmaceutical Inc. Follow-up study of AAV-mediated gene transfer (UX111; previously known as ABO-102) for MPS type IIIA. ClinicalTrials.gov identifier: NCT04360265. *https://clinicaltrials.gov/study/NCT04360265* (accessed October 19, 2026).

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