

Summary Basis for Regulatory Action

Date:	September 17, 2026
From:	Susan Butler, PhD,
BLA STN:	BLA 125845/0
Applicant:	Ultragenyx Pharmaceutical Inc.
Submission Receipt Date:	Original Submission: December 18, 2024 Resubmission Date: March 20, 2026
PDUFA Action Due Date:	September 19, 2026
Proper Name:	rebisufligene etisparvovec-hopf
Proprietary Name:	FAYUVI
Indication:	Treatment of neurologic manifestations of mucopolysaccharidosis type IIIA (MPS IIIA, Sanfilippo syndrome type A) in pediatric patients with preserved neurodevelopmental function.

* PDUFA=Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of this product.

Rosa Sherafat, MD

**Acting Director, Office of Clinical Evaluation, Office of Therapeutic Products,
Center for Biologics Evaluation and Research**

Discipline Reviews	Reviewer / Consultant - Office/Division
Regulatory Project Management ORMRR RPM	Rommel Maglalang, CBER/OTP/ORMRR/DRMRR
CMC - CMC Product (Product Office and OCBQ/DBSQC) - Facilities review (OCBQ/DMPQ) - Establishment Inspection Report (OCBQ/DMPQ and Product Office) - QC, Test Methods, Product Quality (OCBQ/DBSQC)	- Susan Butler, PhD, CBER/OTP/OGT/DGT1 - Jacob Bitterman, PhD, CBER/OTP/OGT/DGT1 - Timothy Kamaldinov, PhD, CBER/OTP/OGT/DGT2 - Jana Highsmith, CBER/OCBQ/DMPQ - Antonia Panthiruvellil, CBER/OCBQ/DMPQ - Kula Jha, PhD, CBER/OCBQ/DMPQ - Massoud Motamed, PhD, CBER/OCBQ/DMPQ - Holly Brevig, PhD, CBER/OCBQ/DMPQ - George Kastanis, MS, CBER/OTP/OCBQ/DBSQC - Esmeralda Alvarado, PhD CBER/OTP/OCBQ/DBSQC - Salil Ghosh, PhD, CBER/OTP/OCBQ/DBSQC - Hyesuk Kong, PhD, CBER/OTP/OCBQ/DBSQC
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Other Review(s) not captured above categories, for example: • CMC/OPPT • CDRH/OHTVII (device consult)	• Andrey Sarafanov, PhD, CBER/OTP/OPPT • Megan Martino, CDRH/OHTVII/DIHD • Takeesha Taylor-Bell, CDRH/OHTVII/DIHD

Table of Contents

1. Introduction	4
2. Background	5
3. Chemistry Manufacturing and Controls (CMC) Evaluation	6
a. Product Quality	7
b. Testing Specifications.....	7
c. CBER Lot Release	9
d. Facilities Review / Inspection	9
e. Container/Closure System.....	10
f. Environmental Assessment.....	11
4. Nonclinical Pharmacology/Toxicology Evaluation.....	11
5. Clinical Pharmacology Evaluation.....	12
6. Clinical and Statistical Evaluation	13
a. Clinical Program.....	13
b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance	15
c. 15	
Pediatrics	15
d. Other Special Populations.....	15
7. Safety and Pharmacovigilance Evaluation.....	15
8. Labeling	17
9. Advisory Committee Meeting	17
10. Other Relevant Regulatory Issues	17
11. Recommendations and Benefit/Risk Assessment	18
a. Recommended Regulatory Action	18
b. Benefit-Risk Assessment.....	18

c. Recommendation for Post-marketing Activities	20
12. References	21

1. Introduction

Ultragenyx Pharmaceutical Inc. (hereafter referred to as the Applicant) submitted Biologics License Application (BLA)125845 for licensure of rebisufligene etisparvovec-hopf, with the proprietary name FAYUVI. FAYUVI is indicated for the treatment of neurologic manifestations of mucopolysaccharidosis type IIIA (MPS IIIA, Sanfilippo syndrome type A) in pediatric patients with preserved neurodevelopmental function. This document summarizes the regulatory basis for traditional approval of FAYUVI in this patient population.

Rebisufligene etisparvovec-hopf (FAYUVI) is a non-replicating adeno-associated virus serotype 9 (AAV9)-based gene therapy designed to deliver a functional copy of the *SGSH* gene to cells of the central nervous system (CNS). A one-time intravenous (IV) infusion of FAYUVI results in production of sulfamidase, the deficient enzyme in MPS IIIA, with subsequent breakdown of heparan sulfate (HS) within lysosomes in the CNS.

The Applicant has provided substantial evidence of effectiveness based on a single adequate and well-controlled clinical investigation (Study ABT-001) with confirmatory evidence to support approval of FAYUVI. Study ABT-001 was an open-label, single-arm trial that enrolled 28 pediatric patients with MPS IIIA (rapid progressors; RP), 22 of whom were treated with the intended commercial dose of 3×10^{13} vector genomes (vg)/kg. Most patients enrolled in Study ABT-001 were in early stages of MPS IIIA prior to the onset of developmental regression; 17 of 22 patients formed the Applicant-defined Modified Intention-to-Treat (mITT) Analysis Set, which is the primary efficacy analysis population. Data was also submitted for the 5 remaining patients outside the mITT Analysis Set, as well as for 5 additional pediatric patients with middle- or advanced-stage MPS IIIA who were treated with the intended commercial dose in a separate open-label, single-arm trial (Study ABT-003). Both ABT-001 and ABT-003 were designed to be 24 months in duration, but ABT-003 was prematurely terminated prior to transfer to Ultragenyx Pharmaceutical from a different sponsor. All patients treated with FAYUVI in Studies ABT-001 or ABT-003 were offered enrollment into an ongoing observational long-term follow-up study, LTFU-ABO-102, to provide a minimum of 5 years of post-treatment follow-up. Longitudinal neurocognitive data in untreated MPS IIIA patients from two external natural history (NH) studies (Shapiro et al. 2016; Wijburg et al. 2022) were used by the Applicant as the control group in the primary efficacy analysis of neurodevelopmental outcomes.

The primary efficacy outcome assessed in the mITT population (primary analysis population) in Study ABT-001 (and in long-term follow-up in LTFU-ABO-102) and compared to the untreated natural history cohort was the change in neurodevelopmental function, as measured by Cognitive raw score on the Bayley Scales of Infant and Toddler Development - Third Edition (BSITD-III). Due to variability in available data collected during the developmental window of interest (24 to 60 months of age), a non-linear mixed effects model incorporating data from both treated patients and untreated NH patients was developed to estimate the treatment effect of FAYUVI. Results from the

model-based analysis demonstrated a statistically significant and clinically meaningful 23.5-point difference in the mean change in BSITD-III Cognitive Scale raw score between 24 and 60 months of age between FAYUVI-treated patients and untreated patients, favoring FAYUVI-treated patients. This treatment difference in Cognitive raw score reflects gain or maintenance of developmental skills in FAYUVI-treated patients compared to a loss of developmental skills in untreated patients within the critical window of 24-60 months of age when developmental plateau and regression are expected. The model-based analysis is supported by analyses of observed BSITD-III Cognitive raw scores, with both demonstrating a trajectory in the mITT population that clearly diverges from that expected in the NH of MPS IIIA.

Two sources of confirmatory (mechanistic) evidence independently substantiate the observed clinical effect of FAYUVI in the mITT population as follows: 1) substantial reductions in cerebrospinal fluid (CSF) HS were observed in FAYUVI-treated patients and were maintained over at least 24 months of follow up post-treatment; and 2) a nonclinical study in a murine model of MPS IIIA provides mechanistic evidence of the molecular action of FAYUVI in MPS IIIA, demonstrating expression of the *SGSH* transgene, detectable sulfamidase activity, and decreases in mean glycosaminoglycan (GAG) concentrations in the brain and somatic tissues of treated animals.

The safety population includes all patients treated with FAYUVI across all studies (N=33), of whom 27 received the intended commercial dose. The most common treatment-emergent adverse events include: liver enzyme (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma glutamyl transferase [GGT]) elevation, vomiting/nausea, pyrexia, leukopenia, thrombocytopenia, and increased amylase. The observed risks can be mitigated with prescriber and patient labeling and routine pharmacovigilance. The Applicant plans to enroll previously treated patients and those treated in the post-marketing setting in a long-term safety follow up program with the plan to follow long-term safety for 10 years after FAYUVI administration.

Overall, the observed benefits outweigh the observed risks of FAYUVI in the studied MPS IIIA pediatric population. Considering the clinical and therapeutic context of this application, and the ability to mitigate the risks through product labeling and post-marketing long-term safety follow up, as well as the agreed-upon post-marketing studies, the benefit-risk assessment of the application is favorable and supports regulatory approval via traditional approval pathway. Overall, the observed benefits outweigh the observed risks of FAYUVI in the studied MPS IIIA pediatric population. Considering the clinical and therapeutic context of this application, and the ability to mitigate the risks through product labeling and post-marketing long-term safety follow up, as well as the agreed-upon post-marketing studies, the benefit-risk assessment of the application is favorable and supports regulatory approval via traditional approval pathway. Post-Marketing Commitments include the following: validate a companion anti-AAV9 antibody diagnostic assay and update the labeling accordingly; re-evaluate release specifications after obtaining additional manufacturing experience; provide supplemental validation data for the % full capsid release assay; and submit additional stability data with product validation lots.

2. Background

MPS IIIA is a rare, autosomal recessive, lysosomal disease caused by biallelic pathogenic variants in the N-sulfoglucosamine sulfohydrolase (*SGSH*) gene encoding sulfamidase, a lysosomal enzyme responsible for the degradation of HS. Sulfamidase deficiency results in accumulation of HS in lysosomes in the brain and other organs, with subsequent progressive CNS inflammation and atrophy. MPS IIIA causes progressive neurodegeneration starting in early childhood with eventual loss of all cognitive and functional skills leading to dementia. The most common presentation is the rapidly progressive (RP) phenotype, which manifests as developmental slowing beginning around 2 years of age, followed by developmental arrest and then progressive loss of cognitive, language, and motor function beginning around 4 years of age. The median age of death is in the second decade of life due to neurologic disease-related complications (Shapiro et al. 2016). There are no FDA-approved therapies for the treatment of MPS IIIA, and thus a substantial unmet medical need exists for safe and effective therapies. Given that neuroinflammation and subsequent neurodegeneration are irreversible, it is crucial that any therapeutic intervention be administered as early in the course of the disease as possible to optimize neurologic outcomes.

Table 1: Regulatory History

Regulatory Events / Milestones	Date
1. Orphan Drug designation granted	April 29, 2014
2. Rare Pediatric Disease designation granted	August 27, 2014
3. IND submission	January 28, 2016
4. Fast Track designation granted	October 24, 2016
5. Regenerative Medicine Advanced Therapy (RMAT) granted	April 19, 2018
6. Pre-BLA meeting	October 2, 2024
7. BLA 125845/0 submission	December 18, 2024
8. BLA filed	February 14, 2025
9. Mid-Cycle communication	April 9, 2025
10. Late-Cycle meeting	June 3, 2025
11. Complete Response	July 7, 2025
12. 1 st Re-submission after Complete Response	January 29, 2026
13. Incomplete Response	February 12, 2026
14. 2 nd Re-submission after Complete Response	March 20, 2026
15. Action Due Date	September 19, 2026

3. Chemistry Manufacturing and Controls (CMC) Evaluation

Based on the review of the information provided in the initial submission, resubmission, and amendments, the CMC review team concludes that the manufacturing controls for FAYUVI are acceptable for commercial manufacturing under the BLA. This includes review of the resolution of manufacturing and facility deficiencies that formed the basis of a complete response letter (CRL) issued on 07/07/2025. These CRL deficiencies included: unresolved findings from three pre-license inspections conducted by CBER, where the firms' responses to the Form FDA 483 observations were found insufficient, with corrective actions deemed not comprehensive enough to address the systemic issues identified.

a. Product Quality

Manufacturing and Quality Control Strategy

FAYUVI is produced through (b) (4)

The drug product (DP) production consists of (b) (4) DS to the final product target concentration of 1.0×10^{13} GC/mL and filling the vector product into sterile stoppered vials. Finished drug product is 100% visually inspected, packaged, and frozen (≤ -60 °C). The manufacturing process is controlled by (1) raw material and reagent qualification programs, (2) in-process monitoring and in-process control testing, (3) validation of the manufacturing process, and (4) validation of lot release tests. Following the July 2025 completion of the PPQ campaign, the manufacturing process has been successfully validated. The manufacturer accepts raw materials based on on-site verification of raw material specifications. Suppliers are qualified and audited according to established supplier qualification programs.

The risk of leachables that could originate from the product manufacturing process and the container closure system was analyzed, and the analytical studies and toxicological assessments did not raise concerns and were found sufficient to mitigate this risk.

Stability

The stability study for FAYVUI is ongoing. Leveraging data from the interim GMP Process B.1 lot, a shelf life of 24 months was granted for commercial (Process B.2) (b) (4) DP lots. A PMC regarding submission of PPQ lot 24-month stability data has been agreed to by the Applicant.

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for rebisufligene etisparvovec (b) (4) drug product were found to be adequate for their intended use.

Table 2: Release Specifications

Attribute	Test Method	Acceptance Criteria
Identity	Genome Identity by (b) (4)	(b) (4)
Content/Concentration	Genome Titer by (b) (4)	(b) (4)

Attribute	Test Method	Acceptance Criteria
	(b) (4)	(b) (4)
Potency	In Vitro Potency	
	(b) (4)	
	(b) (4)	
Purity and Impurities	(b) (4)	
	(b) (4)	
	(b) (4)	
	(b) (4)	
	(b) (4)	
	(b) (4)	
	Capsid purity by (b) (4)	
	(b) (4)	
	Full Capsid by (b) (4)	
	(b) (4)	
	(b) (4)	
Safety	Endotoxin (b) (4)	None Detected
	Bioburden	
	Mycoplasma (b) (4)	
	In vitro Adventitious Virus	
	Sterility (b) (4)	
General	Appearance (b) (4)	Liquid, colorless, clear to translucent, may contain proteinaceous

Attribute	Test Method	Acceptance Criteria
		particulates but free from foreign matter
	pH (b) (4)	(b) (4)
	Osmolality (b) (4)	386-435 mOsm/kg
	Poloxamer 188 by (b) (4)	(b) (4)
Capsid Identity	Capsid Identity by (b) (4)	(b) (4)

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan is being developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of FAYUVI are listed in the table below. The activities performed and inspectional histories are noted in the table.

Table 3: Manufacturing Facilities Table for FAYUVI (rebisufligene etisparvovec)

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
Andelyn Biosciences, Inc. Andelyn Corporate Center 1180 Arthur E Adams Drive Columbus, OH 43221 USA DS manufacture	3026042970	117573946	PLI	June 2026 PLI CBER/DMPQ VAI
Ultragenyx Pharmaceutical Inc. 170 Middlesex Turnpike Bedford, MA 01730 USA DP manufacture	3025268614	119414797	PLI	April 2026 PLI CBER/DMPQ VAI
Ultragenyx Pharmaceutical Inc. 150 Presidential Way Woburn, MA 01801 USA	3023224237	118377074	PLI	April 2026 PLI CBER/DMPQ NAI

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
DP release testing				
(b) (4) DP release testing	(b) (4)		Waiver	(b) (4) Surveillance OII NAI
(b) (4) DP primary labeling	(b) (4)		Waiver	(b) (4) Surveillance OII VAI

Acronym key: Center for Biologics Evaluation and Research (CBER); Division of Manufacturing and Product Quality (DMPQ); Drug product (DP); Drug substance (DS); Pre-license inspection (PLI); Voluntary Action Indicated (VAI); No Action Indicated (NAI); Office of Inspections and Investigations (OII); Office of Biological Products Operations (OBPO)

CBER DMPQ and OTP conducted a PLI of the Andelyn Biosciences, Inc. facility located in Columbus, OH, from June 08 – 12, 2026. A Form FDA 483, Inspectional Observations, was issued at the end of the inspection. All inspectional issues were resolved, and the inspection was classified as VAI.

CBER DMPQ and OTP conducted a PLI of the Ultragenyx Pharmaceutical Inc. facility located in Bedford, MA, from April 06 – 10, 2026, and April 13 – 14, 2026. A Form FDA 483, Inspectional Observations, was issued at the end of the inspection. All inspectional issues were resolved, and the inspection was classified as VAI.

CBER DMPQ and OTP conducted a PLI of the Ultragenyx Pharmaceutical Inc. facility located in Woburn, MA, from April 15 – 17, 2026. No Form FDA 483 was issued, and the inspection was classified as NAI. OII performed a surveillance inspection of the (b) (4) facility located in (b) (4), from (b) (4). No Form FDA 483 was issued, and the inspection was classified as NAI. OII performed a surveillance inspection of the (b) (4). A Form FDA 483, Inspectional Observations, was issued at the end of the inspection. All inspectional issues were resolved, and the inspection was classified as VAI.

e. Container/Closure System

The drug product is filled into (b) (4) (8 mL) clear borosilicate glass vials manufactured by (b) (4). The vials are sealed with grey chlorobutyl rubber stoppers featuring a (b) (4) coating and an (b) (4) coating, supplied by (b) (4). The closures are secured with aluminum crimp seals fitted with polypropylene flip-off caps, manufactured by (b) (4).

(b) (4) performed the container closure integrity testing at the (b) (4) facility, employing the (b) (4) analysis test method; and all acceptance criteria were met.

f. Environmental Assessment

The applicant submitted an environmental assessment (EA) pursuant to 21 CFR part 25. It was determined that approval of FAYUVI will not result in any significant environmental impact. A Finding of No Significant Impact memorandum has been prepared.

4. Nonclinical Pharmacology/Toxicology Evaluation

In vitro pharmacology studies evaluating the activity of the hSGSH protein expressed by FAYUVI demonstrated that the Arginine (R) to Glutamine (Q) substitution at position 169 (R169Q) did not negatively impact intracellular or secreted SGSH activity when expressed in SGSH knock-out cells. In vivo pharmacology studies completed to bridge FAYUVI's in vivo potency between manufacturing Process A and Process B.1 showed that manufacturing Process B.1 did not negatively impact liver SGSH activity following single intravenous (IV) administration to wild type (WT) C57Bl/6 mice. The definitive nonclinical Good Laboratory Practice (GLP) safety/biodistribution (BD) studies and all clinical trials (Nos. ABT-001, ABT-003, and LTFU-ABO-102) were conducted with FAYUVI manufactured under GMP conditions via Process A. Future clinical trials will evaluate FAYUVI manufactured using Process B.1 and the commercialized Process B.2.

The minimum effective dose level of 5.0×10^{12} vg/kg was identified in the definitive pharmacology study conducted in (b) (4) mice based on survival, brain glycosaminoglycan (GAG) concentration, Morris water maze performance, reduced brain glial fibrillary acidic protein (GFAP) (b) (4), and improved neuropathology. scAAV9.U1a.SGSH activity was directly proportional to dose level and inversely proportional to MPS IIIA phenotype severity at baseline for some assessments.

No adverse vector-related findings were observed in the 6-month Good Laboratory Practice (GLP) safety and BD study, which investigated the effect of a single intravenous administration of 5.0×10^{12} to 5.0×10^{13} vg/kg scAAV9.U1a.SGSH in WT C57Bl/6 mice. The No-Observed-Adverse-Effect-Level (NOAEL) was 5.0×10^{13} vg/kg.

The definitive 3-month GLP safety and BD study investigated the effect of a single IV administration of 5.0×10^{13} to 2.0×10^{14} vg/kg FAYUVI in WT C57BL/6 mice. Although clinical pathology findings, histopathology findings, and organ weight changes were noted, they were not adverse and resolved by Day 90. Vector immunogenicity was greater against the AAV9 capsid versus the hSGSH transgene and was proportional to vector dose level. Vector BD in brain was less than that of liver (highest) across dosed groups. There were no vector-related gross or histopathological findings identified. The NOAEL was assigned at 2.0×10^{14} vg/kg.

Developmental and reproductive toxicity (DART), genotoxicity, and carcinogenicity/tumorigenicity studies were not conducted with FAYUVI. To address these concerns, the Applicant used a weight-of-evidence approach, completing risk

assessments that integrated a literature review, FAYUVI toxicology data, and historical data from other AAV products.

5. Clinical Pharmacology Evaluation

The clinical pharmacology evaluation of FAYUVI includes review of data from two clinical studies, ABT-001 and ABT-003, and one long-term follow-up study, LTFU-ABO-102.

Pharmacokinetics/Biodistribution and Vector Shedding

The biodistribution of FAYUVI vector genome DNA in plasma and vector shedding in stool, urine, and saliva were assessed at multiple time points in 22 patients following a single intravenous administration of FAYUVI at a dose of 3.0×10^{13} vg/kg in Study ABT-001. In general, peak levels of vector genome DNA occurred within a median duration of 3 days for plasma, urine, saliva and stool after infusion. Peak vector genome DNA concentrations were highest in plasma followed by stool, saliva, and urine. After reaching the maximum in a matrix, the vector genome DNA concentration declined steadily. Clearance of vector DNA was defined as measurement of at least 2 consecutive results below the lower limit of quantification (LLOQ; 5000 vg/mL for urine, saliva, plasma and 4000 vg/mL for stool samples). Based on this definition, vector genome DNA was cleared from urine, saliva, and stool within median values of 15, 30, and 84 days post-infusion, respectively. All patients achieved clearance of vector DNA in saliva, while 96% and 82% of the patients cleared the vector DNA in urine and stool, respectively, based on available data.

Pharmacodynamics

FAYUVI is an adeno-associated virus serotype 9 (AAV9) based gene therapy designed to deliver a functional copy of the human N-sulfoglucosamine sulfohydrolase (*SGSH*) gene to cells. In Study ABT-001, the mean (standard deviation [SD]) baseline cerebrospinal fluid heparan sulfate (CSF HS) level in the modified intention-to-treat (mITT) population was 335.3 (156.9) nmol/L (N=17). The mean (SD) CSF HS concentration percent change from baseline in the mITT population at Month 1 was -58.49% ([13.84], n=17), with reductions from baseline maintained at Month 6 (-73.64% [11.12], n=17), Month 12 (-66.74% [13.46], n=17), and Month 24 (-57.06% [22.48], n=16). CSF HS exposure represents the time-normalized area under the curve (AUC) of the percent change from baseline in CSF HS concentrations. In Study ABT-001, the mean (SD) CSF HS exposure change from baseline was -29.25% (6.92) at Month 1, -60.17 (9.43) at Month 6, -65.02 (9.42) at Month 12, and -63.78% (11.56) at Month 24 in the mITT population (N=17). At Month 24, 93.8% of patients (15 of 16) in the mITT population maintained a reduction in CSF HS exposure from baseline of at least 50%.

Immunogenicity

Baseline anti-AAV9 total antibody titers were < 1:100 in enrolled patients. The safety and efficacy of FAYUVI in patients with anti-AAV9 antibodies $\geq$ 1:100 have not been evaluated. All patients seroconverted to anti-AAV9 antibody positive following administration of FAYUVI. All patients had an increase in anti-SGSH antibodies in serum following administration of FAYUVI. In Study ABT-001, among patients with

available CSF samples, anti-SGSH antibodies were also detected in CSF; anti-SGSH antibody titers were generally lower in CSF than in serum. At the commercial dose of 3.0×10^{13} vg/kg, at Month 24, mean (SD) anti-SGSH titers in the CSF were 670.7 (1850.7) (N=15) and the mean (SD) anti-SGSH titers in serum were 162,947.3 (662,526.3) (N=22). The clinical significance or clinical impact of CSF anti-SGSH antibodies is unknown.

6. Clinical and Statistical Evaluation

a. Clinical Program

The FAYUVI clinical development program includes three clinical studies: two interventional studies (ABT-001 and ABT-003) and one long-term follow-up study (LTFU-ABO-102) which enrolled patients who received FAYUVI in either of the prior studies. Data from Study ABT-001 (and related data collected during LTFU-ABO-102) form the basis of traditional approval.

Study ABT-001 was a global, open-label, single-arm, 24-month study of FAYUVI in 28 pediatric patients with rapidly progressing (RP) MPS IIIA, of which 22 patients were treated at the intended commercial dose of 3×10^{13} vg/kg. Patients enrolled in ABT-001 were primarily in the early stages of MPS IIIA, prior to the onset of developmental regression; 17 of 22 patients qualified for the Applicant-defined Modified Intention-to-Treat (mITT) Analysis Set (either ≤ 2 years of age or > 2 years of age with a baseline Cognitive Developmental Quotient [DQ] > 60 at enrollment), which contributed to the primary efficacy analyses to support approval. Baseline anti-AAV9 total antibody titers were $< 1:100$ at enrollment, and all study participants received a prophylactic regimen of corticosteroids prior to a single IV infusion of FAYUVI. For the mITT Analysis Set, mean age at treatment was 21.8 (range: 3.0 to 32.9) months, 65% were male, 100% were White, 12% were Hispanic or Latino, and mean BSITD-III Cognitive Scale raw score was 47.6 (range: 3 to 69) at baseline (n=14).

The key clinical outcome assessed in Study ABT-001 (and in LTFU-ABO-102) was change in neurodevelopmental function, as measured by the BSITD-III. FAYUVI-treated patients from the mITT population (N=17) were compared to untreated patients with MPS IIIA from an external NH cohort (N=27). For the NH cohort, mean age at enrollment was 38.3 (range: 12 to 58) months, 78% were male, 48% were White and not Hispanic or Latino (race and ethnicity were not reported in 52%), and mean BSITD-III Cognitive Scale raw score was 55.1 (range: 24 to 76) at baseline. Due to variability in available data collected during the developmental window of interest (24 to 60 months of age), a non-linear mixed effects model incorporating data from both treated patients and untreated NH patients was developed to estimate the treatment effect of FAYUVI in early-stage MPS IIIA (mITT cohort). Results from the model-based analysis demonstrated a statistically significant 23.5-point difference in mean change in BSITD-III Cognitive Scale raw score between 24 and 60 months of age favoring FAYUVI-treated patients in the mITT population (see Table 4), reflecting gain or maintenance of developmental skills in the treated population versus loss of developmental skills in the untreated NH population. Results of model-based analyses were supported by analyses of observed BSITD-III Cognitive raw scores, with both demonstrating a trajectory in the mITT population that clearly diverged from that expected in the NH of disease. Across

studies, the median duration of follow-up was 4.2 (range: 2.9 to 7.8) years, with 14 of 17 mITT patients having BSITD-III Cognitive scores through 60 months of age and an additional patient reaching 59.1 months of age at the time of last assessment (data cut: Feb 27, 2026).

Table 4: Mean Change^a in BSITD-III Cognitive Raw Score from 24 to 60 Months of Age in FAYUVI (mITT) group vs Natural History Control group

	FAYUVI (N=17)	Natural History Control (N=27)	Difference
Mean (SE)	16.0 (2.4)	-7.6 (2.1)	23.5 (3.2)
95% CI	(11.2, 20.7)	(-11.8, -3.3)	(17.2, 29.9)
p value	-	-	< 0.0001

^a Least squares mean changes and p-value were based on a non-linear mixed effects model adjusted for chronological age (months), with propensity score weights based on baseline age.

Abbreviations: BSITD-III, Bayley Scales of Infant and Toddler Development - Third Edition; CI, confidence interval; mITT, modified intention-to-treat; SE, standard error

Data was also submitted for the 5 remaining patients treated in Study ABT-001 who were outside the mITT Analysis Set, as well as for 5 additional pediatric patients with middle- or advanced-stage neurologic disease who were treated with the intended commercial dose in Study ABT-003. Interpretation of the clinical data in these 10 patients with more advanced neurologic disease at the time of treatment (non-mITT population) was challenging due to several factors: a lack of clear and pre-defined clinically meaningful outcome measures and thresholds for success; heterogeneous baseline characteristics; very small sample size; missing assessments; lack of well-matched NH control data; and limitations to the interpretation of the non-cognitive endpoints thought to be most relevant to this sub-population. Specifically, communication subdomains of the BSITD-III were difficult to interpret due to translation of the assessment tool across multinational sites, cultural and other factors affecting language development across countries/populations, and disease-related impairments in attention, behavior, and hearing affecting the reliability of the communication assessment. As motor abilities are generally not affected until later in the disease course, longer-term follow-up is needed to assess maintenance of ambulation as an indicator of treatment effect.

Given the progressive neurodegenerative nature of MPS IIIA, the degree of clinical benefit observed following treatment likely depends on the extent of preexisting irreversible damage. In this context, patients outside the mITT cohort were noted to be older and in more advanced stages of disease, where cognitive assessments have not been found to be well-suited for measuring clinical benefit. However, analyses of non-cognitive domains in a population inclusive of non-mITT patients (all patients treated with the intended commercial dose, N=27) were difficult to interpret and not supportive of a treatment effect. Comprehensive review of available patient-level outcome data across clinical domains and assessment modalities for the non-mITT population (n=10) yielded inconclusive results with respect to efficacy in this population. While there were some patients outside the mITT population who appeared to show evidence of benefit in one or

more neurodevelopmental domains, these patients tended to be similar to the mITT population in terms of age and/or baseline cognitive scores. Available data were overall inadequate to support a broad indication across all stages of MPS IIIA, inclusive of patients in the most advanced stages of disease, characterized by significant loss of meaningful developmental skills.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

BIMO inspection assignments were issued for two clinical investigator study sites that participated in the conduct of Protocol ABT-001. The inspections did not reveal significant problems that impact the data submitted in support of this original Biologics License Application (BLA).

c. Pediatrics

FAYUVI has orphan drug designation for the treatment of mucopolysaccharidosis type IIIA (Sanfilippo syndrome type A) and is therefore exempt from Pediatric Research Equity Act (PREA) requirements.

d. Other Special Populations

N/A

7. Safety and Pharmacovigilance Evaluation

The safety review included evaluation of safety data, summaries, listings, and narratives from three clinical studies (ABT-001, ABT-003, and LTFU-ABO-102). The safety database includes 33 patients with MPS IIIA treated with FAYUVI, who had a median follow-up of 57 months (range: 7–101.7 months). Of these, 27 patients received the commercial dose in ABT-001 and ABT-003, with follow-up ranging from 7 to 93 months.

No deaths or adverse events leading to study discontinuation were reported. Overall, 54.5% (18/33) of patients experienced at least one non-fatal serious adverse event (SAE), comprising 36 total events. The most frequently affected System Organ Class (SOC) was infections and infestations (15%; 5/33), predominantly in the ABT-001 high-dose (3.0×10^{13} vg/kg) cohort. Eleven patients required hospitalization for infections, neurologic events (e.g., seizures, status epilepticus, hypophagia), or disease-related complications (e.g., obstructive sleep apnea, tonsillar hypertrophy). Twenty-nine SAEs in 16 unique patients resolved without sequelae and three patients with three unique SAEs recovered with sequelae such as inadequate oral intake, hip pain, and reflux. Three patients experienced disability including loss of ambulation, severe mixed hearing loss, cognitive disturbances, dysphagia, and abnormal gait that was attributed to disease progression. All SAEs were assessed as unrelated to the study treatment, except for one case of treatment-related mental status changes in ABT-003.

A list of adverse reaction (AR) experienced by the treated patients are described in Table 5. Liver enzyme elevations were primarily Grade 1 (85% in high-dose patients) or Grade 2 (41%), with three Grade 3 cases (ALT/AST >5x ULN) resolving spontaneously or via

corticosteroids. Other severe events included Grade 3 neutropenia (linked to immunomodulators) and two resolved, unrelated episodes of Grade 4 status epilepticus in one patient. There were no Grade 5 events. All other adverse events were Grade 1 or 2, emerged within six months post-treatment, and resolved. Overall, FAYUVI's safety profile is manageable and consistent with known AAV gene therapy class effects.

In addition to the reporting requirements in 21 CFR 600.80, the Applicant will submit adverse experience reports for cases of liver failure, thrombotic microangiopathy, and malignancy, regardless of whether they are considered as expected or unexpected, as 15-day expedited reports to the FDA Adverse Event Reporting System (FAERS) for 3 years following the date of product licensure. The applicant also plans a disease monitoring program to follow treated patients (both patients already treated in clinical studies and newly treated patients in the commercial setting) through an observational study with prospective and retrospective safety and clinical outcomes (developmental and cognitive scales) data collection over 10 years from product administration.

Table 5: Adverse Reactions Occurring in $\geq 5\%$ of Patients Following Treatment with FAYUVI

Adverse Reactions	Number of Patients (%) N=27
Liver enzyme increased ^{b,d}	23 (85%)
Vomiting ^c	18 (67%)
Abnormal behavior ^e	15 (56%)
Diarrhea	13 (48%)
Pyrexia ^c	11 (41%)
White cell count decreased ^d	8 (30%)
Cushingoid features	8 (30%)
Decreased appetite ^c	6 (22%)
Platelet count decreased ^{c,e}	5 (19%)
Anemia	5 (19%)
Constipation	4 (15%)
Nausea ^c	3 (11%)
Amylase increased ^c	3 (11%)
Alkaline phosphatase increase	3 (11%)
Seizure ^{a,f}	3 (11%)
Hepatomegaly	3 (11%)
Muscle spasticity	2 (7%)
Hypokalemia	2 (7%)
Gait disturbance	2 (7%)
Adrenal Insufficiency	2 (7%)
Pericardial effusion	1 (4%)

^a Grade 4 severity

^b 3 patients with grade 3 severity

^c Grade 1 or 2 severity

^d Includes aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, and gamma-glutamyl transferase (GGT) increased.

^e Includes abnormal behavior, affect lability, aggression, agitation, irritability, nervousness, anxiety, attention deficit hyperactivity disorder, behavior disorder, insomnia, mental status changes, and related behavioral terms.

^d Includes white blood cell count decreased, leukopenia, lymphocyte count decreased, lymphopenia, and neutropenia.

^e Includes platelet count decreased and thrombocytopenia.

^f Includes seizure, epilepsy, status epilepticus, partial seizures

8. Labeling

The Office of Review Management and Regulatory Review (ORMRR) and the Office of Gene Therapy reviewed the package and container labels on September 14, 2026, and with the agreed revisions, determined they meet regulatory/statutory requirements.

OTP ADL Team

The Office of Therapeutic Products (OTP) labeling review team, together with the relevant discipline review teams, reviewed and revised the proposed prescribing information to ensure that it meets regulatory/statutory requirements, is consistent with current labeling practice, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the product, and provides clear and concise information for the healthcare providers. With the agreed revisions, the prescribing information is acceptable.

APLB

A resubmission from Ultragenyx Pharmaceutical, Inc., was received on March 20, 2026. The proposed proprietary name, FAYUVI, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on June 18, 2026, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on July 10, 2026.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed prescribing information, package and container labels, and found them acceptable from a promotional and comprehension perspective.

9. Advisory Committee Meeting

An Advisory Committee Meeting was not held for this BLA because the review did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

In clinical trials of FAYUVI, a quantitative enzyme-linked immunosorbent assay (ELISA) for total anti-AAV9 antibodies in human serum was used to screen patients for enrollment, with eligible patients having titers <1:100. Because the safety and efficacy of FAYUVI have not been evaluated in patients with anti-AAV9 antibodies ≥1:100, the clinical review team recommended inclusion of labeling language to convey that patients should be tested for anti-AAV9 antibodies prior to treatment and that administration is not

advised if titers are $\geq 1:100$. CDRH was consulted to assist in determining whether labeling and approval would require a companion diagnostic device (anti-AAV9 antibody assay) and whether a suitable companion diagnostic exists. CDRH concluded that labeling language was consistent with a companion diagnostic being essential for the safe and effective use of the therapeutic product and that an FDA-authorized device for the intended use outlined in the labeling would be required to identify the appropriate patient population for treatment. CDRH further noted that there are currently no FDA-cleared or approved in vitro diagnostics (IVD) for the detection of anti-AAV9 antibodies in the intended patient population. Therefore, validation of an in vitro assay for detection of anti-AAV9 antibodies is necessary. Given the high unmet need for treatments for this rare and serious disease, the clinical review team advised approval of FAYUVI without contemporaneous authorization of an IVD for anti-AAV9 antibody testing. A Post-marketing Commitment has been issued to validate a companion diagnostic following approval as outlined in Section 11c.

FAYUVI received Orphan Drug, Rare Pediatric Disease, Fast Track, and Regenerative Medicine Advanced Therapy (RMAT) designations, and a Rare Pediatric Disease Priority Review Voucher will be granted upon approval.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Applicant has provided substantial evidence of effectiveness based on a single adequate and well-controlled trial with confirmatory evidence to support traditional approval of FAYUVI for the treatment of neurologic manifestations of mucopolysaccharidosis type IIIA (MPS IIIA, Sanfillipo syndrome type A) in pediatric patients with preserved neurodevelopmental function.

The recommendation for a narrowed indication is based on the limited evidence of efficacy in patients with advanced disease at the time of treatment. The clinical review team recommends that determination of preserved neurodevelopmental function as an indicator of earlier disease stage be at the discretion of the treating healthcare provider, as there is insufficient evidence to support a strict age- or score-based threshold for treatment.

While efficacy data are only available for patients with the RP phenotype, it is anticipated that patients with the slowly progressive (SP) phenotype will also derive clinical benefit if treated in an early stage of disease, prior to the loss of meaningful developmental skills. As such, the clinical review team does not recommend limiting the indication by disease phenotype.

b. Benefit-Risk Assessment

MPS IIIA is a rare and serious genetic disease with a high unmet medical need for safe and effective therapies that target the underlying cause of the disease which is predominantly neurologic. The disease involves severe and progressive neurodegeneration starting in early childhood leading to dementia in the teenage years. There are currently no FDA-approved treatments for MPS IIIA.

The clinical benefit of FAYUVI was demonstrated through robust model-based analyses showing a statistically significant and clinically meaningful difference in mean change in BSITD-III Cognitive Scale raw score from 24 to 60 months of age favoring FAYUVI-treated patients in the MITT population (early-stage MPS IIIA with preserved neurodevelopmental skills), as compared to matched untreated NH control patients. These results reflect gain or maintenance of neurodevelopmental skills in FAYUVI-treated pediatric patients compared to loss of developmental skills in untreated patients over the same chronological age window when developmental plateau and regression are expected in the disease natural history. The safety profile of FAYUVI includes the risks for liver toxicity, thrombocytopenia, leukopenia, and the general class risk of TMA and malignancy (with no cases of TMA or malignancy reported in trials). Those risks can be adequately mitigated through prescriber and patient labeling and routine post-marketing pharmacovigilance.

In this clinical and therapeutic context, the following review issues and remaining uncertainties were considered acceptable for approval given the rarity and seriousness of MPS IIIA and the high unmet medical need:

1. Acceptance of the commercial lot release acceptance criteria based on data from a limited number of lots manufactured with the commercial manufacturing process. Regulatory discretion was exercised with review of available data to ensure adequate assurance of product safety and efficacy. Additionally, the Applicant has committed to re-assess lot release acceptance criteria for selected attributes based on post-approval manufacturing experience. This approach aligns with FDA's May 2026 guidance for industry "Chemistry, Manufacturing, and Controls Flexibilities for Developing Human Cellular and Gene Therapy Products for a Biologics License Application".
2. Acceptance of a drug substance and drug product shelf life longer than the time supported by the real-time stability data for lots manufactured using the commercial process and using the commercial container closure. The shelf life was extrapolated beyond real-time stability data due to relevant supportive stability data from clinical lots using an earlier, but representative, manufacturing process. This approach aligns with FDA's draft Q1 guidance "Stability Testing of Drug Substances and Drug Products" dated June 2025.
3. Acceptance of a single adequate and well-controlled clinical trial plus confirmatory evidence in a small number of pediatric patients (N=17) and use of an external control group derived from NH studies to provide evidence of effectiveness
4. Acceptance of a small safety database (N=33) to inform the safety assessment and post-marketing risk mitigation strategies.
5. Extrapolation of safety and effectiveness to patients across the entire pediatric age range, to those with the slowly progressive (SP) clinical phenotype, and to those with neurologic disease at more advanced stages than the primary efficacy population based on a comprehensive understanding of the molecular and therapeutic basis of the disease and the product's mechanism of action.

6. Allowing product approval without contemporaneous authorization of an *in vitro* companion diagnostic device to detect anti-AAV9 antibodies to determine treatment eligibility, with a post-marketing commitment (PMC) to validate a companion anti-AAV9 antibody diagnostic assay and update the labeling accordingly.

The totality of evidence supports a favorable benefit-risk assessment for the mITT population studied in the Applicant's clinical development program (i.e., early-stage MPS IIIA). Currently available clinical outcome data for patients with more advanced disease at the time of treatment are inadequate to support a clear treatment benefit in this advanced stage of disease. Additional, more interpretable, clinical outcome data for patients who are in more advanced stages of disease at the time of treatment are likely needed to support approval for this subpopulation.

c. Recommendation for Post-marketing Activities

The observed safety profile for FAYUVI is consistent with the known class effects of AAV gene therapy products, making the risks manageable through product labeling and the proposed pharmacovigilance plan. There were no safety signals that necessitate a REMS or required post-marketing study designed to evaluate a particular safety issue.

In addition to the proposed pharmacovigilance, the applicant will conduct an international observational study (MPS IIIA Disease Monitoring Plan or Protocol number UX111-CL401) that plans to enroll pediatric patients who have completed FAYUVI clinical trials as well as newly treated patients in the post-marketing setting. The study will follow patients for at least 10 years after FAYUVI administration and will focus on long-term safety and effectiveness in the real-world post-marketing setting.

The following Post-marketing Commitments were agreed upon by Ultragenyx Pharmaceutical Inc:

1. Conduct adequate analytical and clinical validation studies to support revisions to the labeling of FAYUVI to specify the use of an FDA-authorized *in vitro* companion diagnostic device to accurately and reliably identify patients who do not have anti-AAV9 Antibodies $\geq 1:100$ and for whom FAYUVI is indicated.

The final study report should be accompanied by a revised labeling Prior Approval Supplement incorporating the authorized companion diagnostic device information.

Study Completion: December 31, 2028
Final Report Submission: June 30, 2029

2. Ultragenyx commits to re-evaluating the acceptance criteria for the (b) (4) QC release tests performed on the drug substance and drug product. Ultragenyx will submit the test results and, if applicable, revise the acceptance limits and justifications. The study report should be submitted within 60 days after the 15th commercial lot is released under the US license as a Postmarketing Study Commitment

Final Report Submission: July 31, 2028

3. Ultragenyx commits to providing supplemental validation data for the (b) (4) analytical method used to determine (b) (4). This data is intended to (b) (4) while maintaining acceptable levels of precision, accuracy and linearity and submitted as a Postmarketing Commitment

Final Report Submission: September 30, 2027

4. Ultragenyx commits to submit the 24-month stability data for PPQ1 and PPQ2 DP lots as soon as the data is available. This commitment is independent of any post-approval shelf-life extension requests, which must be submitted as a separate post-approval supplement (PAS), as a Postmarketing Commitment

Final Report Submission: February 28, 2027

12. References

Shapiro, EG, I Nestrail, KA Delaney, K Rudser, V Kovac, N Nair, CW Richard, 3rd, P Haslett, and CB Whitley, 2016, A Prospective Natural History Study of Mucopolysaccharidosis Type IIIA, J Pediatr, 170:278-287.e271-274.

Wijburg, FA, K Aiach, A Chakrapani, JB Eisengart, R Giugliani, B Héron, N Muschol, C O'Neill, S Olivier, and S Parker, 2022, An observational, prospective, multicenter, natural history study of patients with mucopolysaccharidosis type IIIA, Mol Genet Metab, 135(2):133-142.