HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FAYUVI safely and effectively. See full prescribing information for FAYUVI.

FAYUVI™ (rebisufligene etisparvovec-hopf) suspension for intravenous infusion
Initial U.S. Approval: 2026

----------INDICATIONS AND USAGE----------
FAYUVI is an adeno-associated virus (AAV) vector-based gene therapy indicated for the treatment of neurologic manifestations of mucopolysaccharidosis type IIIA (MPS IIIA, Sanfilippo syndrome type A) in pediatric patients with preserved neurodevelopmental function.

----------DOSAGE AND ADMINISTRATION----------
For single-dose intravenous infusion only.
- Review baseline liver function tests and assess platelet counts, prothrombin time, and activated partial thromboplastin time prior to FAYUVI infusion. (2.1)
- The recommended dose of FAYUVI is 3.0×10^{13} vector genomes (vg) per kg body weight. (2.1)
- Starting 1 day prior to infusion, administer corticosteroids for a minimum of 8 weeks. (2.1)
- Administer FAYUVI as a slow intravenous infusion over approximately 1 hour. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
- FAYUVI is a suspension for intravenous infusion with a concentration of 1.0×10^{13} vg/mL. Each vial contains 2 mL of extractable volume. (3)
- FAYUVI is provided in a kit containing 5 to 105 single-dose vials, with each kit constituting a dosage unit based on the patient's body weight. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Hepatotoxicity: Monitor liver enzymes and total bilirubin levels until 2 weeks after the corticosteroid taper is complete and as clinically indicated. Continue to monitor patients who develop liver enzyme elevations until liver enzymes return to baseline. (2.3, 5.1)
- Thrombocytopenia: Monitor platelet counts weekly for the first 4 weeks, then monthly for 6 months following infusion (2.3, 5.2)
- Thrombotic Microangiopathy (TMA): If signs and symptoms occur, promptly undertake further diagnostic evaluation for hemolytic anemia and renal dysfunction. (5.3)
- Hypersensitivity and Infusion Reactions: Monitor during and after infusion. If symptoms occur, pause the infusion. If appropriate, restart at a slower rate after the infusion reaction has resolved. (5.4)
- Risk of Malignancy: In the event that a malignancy occurs, contact Ultragenyx Pharmaceutical Inc. at 1-888-756-8657. (5.5)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥5%): liver enzyme increased, vomiting, pyrexia, white cell count decreased, decreased appetite, platelet count decreased, nausea, amylase increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ultragenyx Pharmaceutical Inc. at 1-888-756-8657 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
A patient's vaccination schedule may need to be adjusted to accommodate corticosteroid administration prior to and following FAYUVI infusion. (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 09/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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.

2 DOSAGE AND ADMINISTRATION

2.1 Dose

For single-dose intravenous infusion only.

The recommended dose of FAYUVI is 3.0×10^{13} vector genomes per kilogram (vg/kg) body weight, administered as a single intravenous infusion.

Table 1: Recommended Dosing

Patient weight range (kg)	Dose volume[a] (mL)	Number of vials
2.5 to 3.0	10	5
3.1 to 4.0	12	6
4.1 to 5.0	16	8
5.1 to 6.0	18	9
6.1 to 7.0	22	11
7.1 to 8.0	24	12
8.1 to 9.0	28	14
9.1 to 10.0	30	15
10.1 to 12.0	36	18
12.1 to 14.0	42	21
14.1 to 16.0	48	24
16.1 to 18.0	54	27
18.1 to 20.0	60	30
20.1 to 22.0	66	33
22.1 to 24.0	72	36
24.1 to 26.0	78	39
26.1 to 28.0	84	42
28.1 to 30.0	90	45
30.1 to 32.0	96	48
32.1 to 34.0	102	51
34.1 to 36.0	108	54
36.1 to 38.0	114	57
38.1 to 40.0	120	60

Patient weight range (kg)	Dose volume[a] (mL)	Number of vials
40.1 to 42.0	126	63
42.1 to 46.0	138	69
46.1 to 50.0	150	75
50.1to 54.0	162	81
54.1 to 58.0	174	87
58.1 to 62.0	186	93
62.1 to 66.0	198	99
66.1 to 70.0[b]	210	105

[a] Dose volume is calculated using the upper limit of the patient weight range, rounded up to the nearest 2 mL.

[b] Patients weighing > 70 kg will be dosed at the 70 kg weight.

Prior to FAYUVI Infusion:

- Due to the concern for potential hepatotoxicity, assess liver function [alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total bilirubin] and liver-related medical history *[see Warnings and Precautions (5.1)]*.
- Due to the concern for potential thrombocytopenia, assess platelet counts, prothrombin time (PT), and activated partial thromboplastin time (aPTT).
- Evaluate patients for conditions that may increase the risks associated with corticosteroid therapy. Delay treatment until clinically significant infections are adequately controlled.
- Perform testing for the presence of anti-AAV9 antibodies. FAYUVI administration is not recommended for patients with elevated anti-AAV9 total binding antibody titers (≥ 1:100) *[see Clinical Pharmacology (12.6)].* An FDA-authorized test for the detection of anti-AAV9 total binding antibodies is not currently available. For information regarding anti-AAV9 testing, contact Ultragenyx Pharmaceutical Inc. at 1-888-756-8657. Currently available tests may vary in accuracy and design.
- Starting 1 day prior to FAYUVI infusion, administer oral corticosteroids (prednisone or prednisolone) as recommended in Table 2.

Table 2: Recommended Corticosteroid Regimen Starting 1 Day Prior to FAYUVI Administration

	Corticosteroid (prednisone or prednisolone) Dosage
Starting dose	1.0 mg/kg/day for 8 weeks
Tapering	Taper slowly for a minimum of 4 weeks. Refer to Management of Corticosteroid Regimen.

Management of Corticosteroid Regimen

- Monitor ALT, AST, GGT, and total bilirubin levels closely during corticosteroid therapy *[see Dosage and Administration (2.3)]*. If liver enzymes are rising or remain elevated above baseline, the corticosteroid dose may be increased or prolonged. Taper corticosteroids after 8 weeks if liver enzymes are at or below baseline. If elevated liver enzymes persist despite the use of corticosteroids, promptly consult a pediatric gastroenterologist or hepatologist and/or immunologist to discuss additional immunosuppression.
- Monitor for and manage adverse reactions secondary to corticosteroid use. Refer to the corticosteroid prescribing information for risks and required precautions.

2.2 Preparation

Required Equipment and Materials

- Flow rate-controlled syringe pump (prepare the syringe pump prior to administration).
- 20 mL or 50 mL polypropylene syringes for FAYUVI administration (prepare syringes prior to administration)
    - The number and size of syringes will depend on the patient's dose volume.
- 21-gauge stainless steel needles.
- 0.2 micrometer (µm) in-line infusion filter with maximum operating pressure adequate for the syringe pump or pump settings.
- Sterile syringe of Lactated Ringer's solution, Hartmann's solution, or 0.9% sodium chloride injection for flushing the infusion line.

General Precautions

- Prepare FAYUVI using aseptic technique. Wear gloves and safety glasses during preparation and administration.
- Keep vials away from direct sunlight and in carton packaging prior to use.
- Treat spills of FAYUVI with a virucidal agent with proven activity against non-enveloped viruses and blot using absorbent materials.
- Dispose of unused medicinal product and materials that may have come in contact with FAYUVI in accordance with the local biosafety guidelines.

Thaw and Inspect

1. Verify the required dose of FAYUVI based on patient's body weight, and confirm the kit contains a sufficient number of vials to prepare FAYUVI infusion for the patient.
2. Do not thaw or puncture vials until immediately prior to use. If the patient is not expected to be ready for same-day administration, store FAYUVI in a manner consistent with *How Supplied/Storage and Handling (16)*.
3. Remove vials from the original packaging. Inspect vials for damage to the vial or cap. Do not use if damaged.
4. Allow vials to thaw at room temperature 20°C – 25°C (68°F – 77°F) for a minimum of 30 minutes until there is no visible ice. Do not use a water bath or external heat sources. Do not shake the vials to avoid foaming. Do not thaw overnight.
5. Visually inspect the thawed vials. FAYUVI is a clear to translucent, colorless liquid that may contain small white to off-white particles. Do not use the vial if the solution is discolored or contains matter other than small white to off-white particles.

Extraction into Syringes

6. Once thawed, withdraw FAYUVI from the vials into polypropylene syringes using 21-gauge stainless steel needles.
7. Multiple syringes may be needed. Prepare all syringes prior to administering FAYUVI. The contents of multiple vials may be combined into a single syringe.

Addition of In-line Filter and Priming the Infusion System

8. Insert a 0.2 micrometer (µm) in-line filter between the syringe with FAYUVI and tubing.
9. Prime tubing and filter with FAYUVI.
10. Maintain syringes at room temperature prior to and during administration. FAYUVI is stable for up to 24 hours at room temperature 20°C – 25°C (68°F – 77°F).

2.3 Administration

1. Administer FAYUVI in a setting where personnel and equipment are immediately available to treat severe infusion and hypersensitivity reactions *[see Warnings and Precautions (5.4)]*.
    - Insertion of a second intravenous catheter is recommended to treat infusion reactions.
2. Administer FAYUVI as a single-dose slow infusion over approximately 1 hour, through a peripheral vein using an intravenous catheter with a 0.2 micrometer (µm) in-line filter and a syringe pump.
    - *Do not* administer FAYUVI as an intravenous push or bolus.
    - *Do not* infuse FAYUVI in the same intravenous line with any other products.
    - *Do not* use a central line or port.
3. In the event of a severe infusion or hypersensitivity reaction, pause the infusion, and administer supportive care and medical treatment as appropriate. If the infusion is paused, the infusion may be restarted at a slower rate after symptoms are resolved, at the discretion of the treating healthcare provider *[see Warnings and Precautions (5.4)].*
4. To ensure the patient receives the complete dose, after the content of the last FAYUVI-containing syringe is infused, infuse Lactated Ringer's solution, Hartmann's solution, or 0.9% sodium chloride injection at the same rate that was used for the last part of the infusion to clear FAYUVI from the tubing.

Monitoring Post-Infusion

Conduct the following tests after FAYUVI administration *[see Warnings and Precautions (5.1, 5.2)]*:

- ALT, AST, GGT, and total bilirubin levels once weekly during the first 2 weeks, then every 2 weeks until 2 weeks after the corticosteroid taper is complete and as clinically indicated. Continue to monitor liver function in all patients who develop elevated liver enzymes until levels return to baseline.
- Platelet counts weekly for the first 4 weeks, then monthly for 6 months following infusion. Continue monitoring as clinically indicated.

3 DOSAGE FORMS AND STRENGTHS

FAYUVI is supplied as a clear to translucent, colorless, sterile suspension for intravenous infusion at a concentration of 1.0×10^{13} vector genomes/mL (vg/mL) solution. Each vial of FAYUVI contains 2 mL of extractable volume.

FAYUVI is provided in a kit containing 5 to 105 single-dose vials, with each kit constituting a dosage unit based on the patient's body weight *[see How Supplied/Storage and Handling (16.1)]*.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Elevated liver enzymes (ALT, AST, and GGT) were observed in clinical studies of FAYUVI *[see Adverse Reactions (6.1)]*.

Prior to FAYUVI infusion, assess liver function by clinical examination and laboratory testing (ALT, AST, GGT and total bilirubin) and evaluate liver-related medical history. Administer corticosteroids to

all patients before and after FAYUVI infusion. If abnormalities are observed, adjust the corticosteroid treatment regimen, including increasing the dose and/or prolonging the corticosteroid taper period *[see Dosage and Administration (2.1)]*.

Closely monitor ALT, AST, GGT and total bilirubin levels after FAYUVI administration until 2 weeks after the corticosteroid taper is complete and as clinically indicated. Continue to monitor liver function in all patients who develop elevated liver enzymes until levels return to baseline *[see Dosage and Administration (2.3)]*.

5.2 Thrombocytopenia

Decreased platelet counts were observed in clinical studies of FAYUVI [*see Adverse Reactions (6.1)*].

Prior to FAYUVI infusion, assess platelet counts. Monitor platelet counts weekly for the first 4 weeks, then monthly for 6 months following infusion. Continue monitoring as clinically indicated *[see Dosage and Administration (2.3)]*.

5.3 Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA) has been reported in association with AAV gene therapies. While there have been no cases of TMA associated with FAYUVI in clinical studies, laboratory and clinical monitoring for TMA following FAYUVI infusion is recommended.

Monitor platelet counts closely within the first 4 weeks following FAYUVI infusion *[see Warnings and Precautions (5.2)]*. Signs and symptoms of TMA may include, but are not limited to, thrombocytopenia, hemolytic anemia, easy bruising, hypertension, seizures, decreased urine output and renal dysfunction. If TMA is suspected, immediately consult a pediatric hematologist and/or nephrologist for further evaluation and management as clinically indicated.

5.4 Hypersensitivity and Infusion Reactions

Infusion reactions, including hypersensitivity reactions and anaphylaxis, may occur with infusion of FAYUVI. Symptoms may include but are not limited to hypotension, pyrexia, palpitation, nausea, vomiting, chills, or headache.

Closely monitor patients for clinical signs and symptoms of infusion reactions, including hypersensitivity reactions, and monitor vital signs during and after completion of FAYUVI infusion as clinically indicated. In the event of an infusion reaction during administration, pause the infusion and provide supportive care according to clinical practice. If the infusion is paused and continued administration is appropriate, restart at a slower rate after the infusion reaction has resolved *[see Dosage and Administration (2.3)]*.

5.5 Risk of Malignancy

Malignancy may occur following treatment with FAYUVI due to potential integration of AAV vector DNA into the genome.

In the event of a malignancy, contact Ultragenyx Pharmaceutical Inc. at 1-888-756-8657.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of FAYUVI was evaluated in 33 pediatric patients with MPS IIIA who received a single intravenous infusion of FAYUVI in 3 clinical studies: 2 open-label, single-arm studies (Study 1 and Study 3) and 1 long-term follow-up study (Study 2) which enrolled patients who participated in one of the prior studies *[see Clinical Studies (14)]*. Twenty-seven patients received the recommended dose of 3.0×10^{13} vg/kg. The mean age at the time of treatment was 38.5 months (range: 3.0 months to 9.2 years) and the mean weight was 17.1 kg (range: 3.9 to 31.2 kg). Patients treated with the recommended dose were 96% White and 4% of multiple race; 11% were Hispanic or Latino. The median duration of follow-up following FAYUVI infusion was 4.1 years (range: 7.0 months to 7.8 years).

Adverse reactions in patients who received the recommended dose of 3.0×10^{13} vg/kg of FAYUVI (N=27) in clinical studies are listed in Table 3.

Table 3: Adverse Reactions Occurring in ≥ 5% of Patients Following Treatment with FAYUVI

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

[a] Includes aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, and gamma-glutamyl transferase (GGT) increased.

[b] All adverse reactions were of Grade 1 or Grade 2 severity.

[c] 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

Hepatotoxicity
In clinical trials, 85% (23/27) of patients receiving the recommended dose of FAYUVI experienced adverse reactions associated with liver enzyme elevations (AST, ALT, and/or GGT). Most liver enzyme elevations were less than Grade 3 in severity, and none were associated with elevations of total bilirubin. A single Grade 3 ALT elevation in one patient occurred in the setting of gastroenteritis 62 days following FAYUVI infusion and resolved spontaneously within 8 days. The time to first onset was most frequently within the first 14 days and ranged from 2 days to 30.3 months following FAYUVI infusion. All liver enzyme elevations resolved within 6 days to 40.6 months of onset, except in 2 patients where slight elevations persisted.

Neutropenia
In clinical trials, 22% (6/27) of patients receiving the recommended dose of FAYUVI experienced neutropenia. One patient experienced Grade 3 neutropenia, and the remaining events were of Grade 1 or 2 severity.

7 DRUG INTERACTIONS

Vaccinations
Prior to FAYUVI administration, consider the patient's vaccination status. Vaccines should be avoided 30 days prior to treatment with FAYUVI (and use of corticosteroids) and while on corticosteroid therapy *[see Dosage and Administration (2.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
There are no data on the use of FAYUVI in pregnant women. No animal reproductive and developmental toxicity studies have been conducted to assess whether FAYUVI can cause fetal harm when administered to a pregnant woman. Women who are pregnant or desire to become pregnant should not be treated with FAYUVI.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary
There are no data regarding the presence of FAYUVI in human milk, the effects on the breastfed infant, or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for FAYUVI and any potential adverse effects on the breastfed infant from FAYUVI or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

A negative serum pregnancy test must be confirmed before administration of FAYUVI in females of childbearing potential.

Contraception
There are insufficient exposure data to provide a recommendation on duration of contraception following treatment with FAYUVI.

Infertility
There are no data on the effects of FAYUVI on fertility. No fertility studies with FAYUVI have been conducted in animals or humans.

8.4 Pediatric Use

The safety and efficacy of FAYUVI have been established in pediatric patients with MPS IIIA. The use of FAYUVI in pediatric patients is supported by three open-label, single-arm studies (Studies 1, 2, and 3) which enrolled 33 pediatric patients with a mean age of 41.5 months (range: 3.0 months to 9.2 years) at treatment *[see Adverse Reactions (6.1), Clinical Studies (14)]*.

8.5 Geriatric Use

FAYUVI has not been studied in patients 65 years of age and older.

11 DESCRIPTION

FAYUVI™ (rebisufligene etisparvovec-hopf) is a gene therapy product. It is a non-replicating, recombinant adeno-associated serotype 9 (AAV9) based vector containing the cDNA of the R169Q variant of the human *SGSH* gene under the control of the murine small nuclear RNA promoter U1a. FAYUVI is produced in human embryonic kidney cells by recombinant DNA technology.

FAYUVI is a sterile, preservative-free, clear to translucent, colorless suspension for intravenous infusion. Each vial of FAYUVI contains an extractable volume of 2 mL of rebisufligene etisparvovec-hopf at a concentration of 1.0×10^{13} vector genomes/mL solution ([vg]/mL) and the following excipients: 0.001% poloxamer 188, 20 mM Tris base, 200 mM sodium chloride, 1 mM magnesium chloride hexahydrate, and hydrochloric acid (used to adjust the pH as required). The pH of FAYUVI is 8.0. The osmolality is 386 to 435 mOsm/kg.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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. Intravenous infusion of FAYUVI results in production of the lysosomal enzyme sulfamidase in target tissues with subsequent breakdown of heparan sulfate (HS) in lysosomes.

12.2 Pharmacodynamics

In Study 1, the mean (standard deviation [SD]) baseline cerebrospinal fluid heparan sulfate (CSF HS) concentration in the modified intention-to-treat (mITT) population (N=17) was 335.3 (156.9) nmol/L. The mean percent change from baseline (SD) in CSF HS concentration in the mITT population was

−58.5% (13.84) at Month 1 post-FAYUVI infusion, −73.6% (11.12) at Month 6, −66.7% (13.46) at Month 12, and −57.1% (22.48) at Month 24 (n=16).

CSF HS exposure represents the time-normalized area under the curve (AUC) of the percent change from baseline in CSF HS concentration. In Study 1, the mean (SD) change from baseline in CSF HS exposure 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 of at least 50%.

12.3 Pharmacokinetics

Vector Distribution and Vector Shedding

Nonclinical Data
Biodistribution of vector genome DNA was evaluated following a single intravenous administration in healthy C57BL/6 mice at dose levels of 5.0×10^{13} vg/kg and 2.0×10^{14} vg/kg. At 26 weeks post administration of 5.0×10^{13} vg/kg to adult mice, vector genome DNA was detected in all major organs analyzed, with the highest quantities detected in the liver followed by lower levels in the heart, uterus with cervix, kidney, lung, brain, lymph node, spleen, and gonads. At 90 days post administration of 2.0×10^{14} vg/kg to adolescent and neonatal mice, vector genome DNA was detected in all major organs analyzed, with the highest quantities detected in the liver and heart followed by lower levels in the lung and kidney. Human SGSH mRNA transcripts were measured in the liver and brain, with highest expression in the liver.

Clinical Data
Biodistribution of 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 1. 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.

Pharmacokinetics in Specific/Special Populations
No dedicated pharmacokinetic studies using rebisufligene etisparvovec have been conducted in special populations.

12.6 Immunogenicity

The observed incidence of anti-AAV9 and anti-SGSH antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the

incidence of anti-AAV9 and anti-SGSH antibodies in the studies described below with the incidence of anti-AAV9 and anti-SGSH antibodies in other studies.

Anti-AAV9 antibody titers and anti-SGSH antibody titers were assessed by investigational total binding antibody enzyme-linked immunosorbent assays (ELISA) in clinical trials.

Anti-AAV9 antibodies
Baseline anti-AAV9 total antibody titers were < 1:100. The safety and efficacy of FAYUVI in patients with anti-AAV9 antibodies ≥ 1:100 have not been evaluated *[see Clinical Studies (14)]*.

All patients seroconverted to anti-AAV9 antibody positive following administration of FAYUVI. At the dose of 3.0×10^{13} vg/kg in Study 1 (N=22), individual anti-AAV9 antibody titers peaked at a mean (SD) of 15.50 (19.36) months after administration, with mean (SD) values of 2,376,590.9 (3,097,657.4) and remained stable at Month 24 onwards. Similar seroconversion rates were observed in Study 3.

Anti-SGSH antibodies
All patients had an increase in anti-SGSH antibodies in serum following administration of FAYUVI. At the dose of 3.0×10^{13} vg/kg in Study 1 (N=22), individual serum anti-SGSH antibody titers peaked at a mean (SD) of 13.88 (12.02) months after administration, with mean (SD) values of 182,552.7 (659,299.6). Individual serum anti-SGSH antibody titers varied over time.

In Study 1, 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 dose of 3.0×10^{13} vg/kg, at Month 24, mean (SD) anti-SGSH titers in the CSF was 670.7 (1850.7) (N=15) and the mean (SD) anti-SGSH titers in serum was 162,947.3 (662,526.3) (N=22). The clinical significance of CSF anti-SGSH antibodies is not clear.

In Study 3, CSF samples for anti-SGSH antibody evaluation were not collected. Anti-SGSH antibody titers in serum were below the assay limit (1:40) at Screening for all evaluated patients. All patients developed detectable anti-SGSH antibodies by Month 12 (range: Day 14 to Month 12).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been performed to evaluate the effects of FAYUVI on carcinogenesis, mutagenesis, or impairment of fertility.

13.2 Animal Toxicology and/or Pharmacology

Animal toxicology studies were conducted in healthy C57BL/6 mice at dose levels up to 2.0×10^{14} vg/kg. No adverse FAYUVI-related toxicological findings were observed.

14 CLINICAL STUDIES

The efficacy of FAYUVI was evaluated in a multi-center, open-label, single-arm, single dose, dose-escalation study (Study 1; NCT02716246) and a long-term follow-up study (Study 2; NCT04360265) in pediatric patients with mucopolysaccharidosis type IIIA (MPS IIIA; Sanfilippo syndrome type A).

The primary efficacy population includes the modified intention-to-treat (mITT) population, which included 17 patients from Study 1 who received the recommended dose of 3.0×10^{13} vg/kg and were ≤ 2 years of age at treatment, or > 2 years of age with a Cognitive Developmental Quotient (DQ) of ≥ 60 (indicating mild or moderate neurodevelopmental impairment) at treatment calculated by the Bayley Scales of Infant and Toddler Development - Third Edition (Bayley-III) or the Mullen Scales of Early Learning. Baseline anti-AAV9 total antibody titers were < 1:100 at the time of enrollment. All patients received a prophylactic regimen of corticosteroids prior to FAYUVI. Patients were observed for 24 months in Study 1 with subsequent enrollment in Study 2. Across studies, the median duration of follow-up was 4.2 years (range: 2.9 to 7.8 years), with 14 of 17 patients reaching the age of 5 years (60 months).

Population characteristics are as follows: mean age at treatment 21.8 months (range: 3.0 to 32.9 months), mean weight at baseline 13.1 kg (range: 3.9 to 17.5 kg); 65% male; 100% White; and 12% Hispanic or Latino. Mean Bayley-III Cognitive raw score was 47.6 (range: 3 to 69) at baseline (n=14).

Efficacy was assessed based on the difference in mean change in Bayley-III Cognitive Scale raw score between 24 to 60 months of age (chronological age) between treated and natural history patients. The Bayley-III Cognitive subtest assesses sensorimotor development, exploration and manipulation, object relatedness, concept formation, memory, and other aspects of cognitive processing. Each item is scored 0 or 1, and scores range from 0 to 91 with higher scores indicating higher skill level. FAYUVI-treated patients from the mITT population (N=17) were compared to untreated patients with MPS IIIA from an external, natural history control (N=27).

Population characteristics for the natural history control population were as follows: mean age at enrollment 38.3 months (range: 12 to 58 months); 78% male; and 48% White and not Hispanic or Latino, with race and ethnicity not reported in 52%. Mean Bayley-III Cognitive raw score was 55.1 (range: 24 to 76) at baseline.

There was a statistically significant 23.5-point difference in the mean change in Bayley-III Cognitive raw score from 24 to 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 natural history population.

Table 4: Mean Change[a] in Bayley-III Cognitive Raw Score from 24 to 60 Months of Age (FAYUVI [mITT] and Natural History Populations)

	FAYUVI (N=17)	**Natural History (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[b]	-	-	< 0.0001

CI=confidence interval; mITT=modified intention-to-treat; SE=standard error

[a] Least squares mean changes were based on a non-linear mixed effects model adjusted for chronological age (months).

[b] p-value is based on a non-linear mixed effects model with response variable Bayley-III Cognitive raw score and with chronological age (months) as a covariate.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

FAYUVI™ is supplied as a clear to translucent, colorless, sterile suspension for intravenous infusion. FAYUVI contains 1.0×10^{13} vector genomes per mL.

FAYUVI is shipped frozen at ≤ -60°C (−76°F) in 8 mL glass vials (with 2 mL extractable volume).

FAYUVI is provided as a kit to meet the dosing requirements for each patient. Each kit contains a specified number of FAYUVI vials (NDC 69794-300-01), with a minimum of 5 vials and a maximum of 105 vials. The total number of vials in each kit corresponds to the dosing requirement for the individual patient based on the patient's weight *[see Dosage and Administration (2.1)]*.

Kit sizes and National Drug Codes (NDC) are provided in Table 5.

Table 5: FAYUVI Kits

Patient weight range (kg)	Dose volume (mL)	Number of vials	NDC Number
2.5 to 3.0	10	5	69794-301-05
3.1 to 4.0	12	6	69794-302-06
4.1 to 5.0	16	8	69794-303-08
5.1 to 6.0	18	9	69794-304-09
6.1 to 7.0	22	11	69794-305-11
7.1 to 8.0	24	12	69794-306-12
8.1 to 9.0	28	14	69794-307-14
9.1 to 10.0	30	15	69794-308-15
10.1 to 12.0	36	18	69794-309-18
12.1 to 14.0	42	21	69794-310-21
14.1 to 16.0	48	24	69794-311-24
16.1 to 18.0	54	27	69794-312-27
18.1 to 20.0	60	30	69794-313-30
20.1 to 22.0	66	33	69794-314-33
22.1 to 24.0	72	36	69794-315-36
24.1 to 26.0	78	39	69794-316-39
26.1 to 28.0	84	42	69794-317-42
28.1 to 30.0	90	45	69794-318-45
30.1 to 32.0	96	48	69794-319-48
32.1 to 34.0	102	51	69794-320-51
34.1 to 36.0	108	54	69794-321-54
36.1 to 38.0	114	57	69794-322-57
38.1 to 40.0	120	60	69794-323-60
40.1 to 42.0	126	63	69794-324-63
42.1 to 46.0	138	69	69794-325-69
46.1 to 50.0	150	75	69794-326-75
50.1 to 54.0	162	81	69794-327-81
54.1 to 58.0	174	87	69794-328-87
58.1 to 62.0	186	93	69794-329-93

Patient weight range (kg)	Dose volume (mL)	Number of vials	NDC Number
62.1 to 66.0	198	99	69794-330-99
66.1 to 70.0	210	105	69794-331-05

16.2 Storage and Handling

- FAYUVI is shipped and stored frozen at ≤ -60°C [-76°F].
- Store upright at ≤ -60°C [-76°F].
- Store in the original carton until ready to use.
- Thawed vials should not be punctured until immediately prior to use. Once drawn from the vial and prepared in syringes, FAYUVI can be stored at room temperature (20°C – 25°C [68°F – 77°F]) for up to 24 hours, including time for infusion.
- If necessary, an intact vial (stopper not yet punctured) that has been thawed can be stored refrigerated (2°C – 8°C [36°F – 46°F]) for up to 12 days, upright and protected from light (e.g., in the original carton).
- Once thawed, *do not refreeze* FAYUVI solution vials.
- Follow local guidelines on handling of biological waste.

17 PATIENT COUNSELING INFORMATION

Discuss the following with patients and/or caregivers:

Hepatotoxicity
FAYUVI can increase certain liver enzymes. Inform patients and/or caregivers that patients will receive an oral corticosteroid medication before and after infusion with FAYUVI, and patients will undergo regular blood tests to monitor liver function. Advise patients and/or caregivers to contact their healthcare provider immediately if the patient's skin and/or whites of the eyes appear yellowish or if the patient misses a dose of corticosteroid or vomits it up *[see Warnings and Precautions (5.1)]*.

Advise patients and/or caregivers not to use any medications, herbal products, or supplements without first confirming with a healthcare professional that they are not hepatotoxic. If use of a hepatotoxic agent appears unavoidable, instruct patients or caregivers that they or their healthcare professional contact you to discuss potential alternatives.

Thrombocytopenia
FAYUVI can decrease blood platelet count and increase the risk of bruising or bleeding. Inform caregivers that thrombocytopenia has been reported to generally occur within the first 2 weeks after FAYUVI infusion. Advise patients and/or caregivers to seek medical attention if the patient experiences unexpected bruising or bleeding *[see Warnings and Precautions (5.2)]*.

Thrombotic Microangiopathy
Decreased blood platelet and red blood cell counts, acute kidney injury, and increased risk of bruising or bleeding may be indicative of TMA and have been reported in association with AAV gene therapies. Advise patients and/or caregivers to seek immediate medical attention if the patient experiences unexpected bruising or bleeding, seizures, or decreased urine output *[see Warnings and Precautions (5.3)]*.

Hypersensitivity and Infusion Reactions
Infusion reactions, including hypersensitivity reactions and anaphylaxis, may occur during and after infusion with FAYUVI. Educate patients or caregivers on possible symptoms of infusion reactions,

including hypersensitivity reactions, and advise them to immediately inform medical staff if they experience such a reaction *[see Dosage and Administration (2.3), Warnings and Precautions (5.4)]*.

Risk of Malignancy

Malignancy may occur after AAV therapies such as FAYUVI. Advise patients and/or caregivers to contact their healthcare provider and Ultragenyx Pharmaceutical Inc. (1-888-756-8657) if the patient who received FAYUVI develops a malignancy *[see Warnings and Precautions (5.5)]*.

Vaccinations

Advise patients and/or caregivers to consult with their healthcare provider to determine if adjustments to the patient's vaccination schedule are necessary prior to treatment with FAYUVI. Vaccines should be avoided 30 days prior to treatment with FAYUVI (and use of corticosteroids) and while on corticosteroid therapy *[see Drug Interactions (7)]*.

Vector Shedding

Temporary vector shedding of FAYUVI occurs primarily through bodily fluids and waste. Advise patients and/or caregivers on the proper handling of patient bodily fluids and waste; recommended procedures include sealing disposable diapers in disposable trash bags and then discarding into regular trash. Inform caregivers and family members regarding proper hand hygiene when coming into direct contact with patient bodily fluids and waste. These precautions should be followed for three months after FAYUVI infusion.

Manufactured by:
Ultragenyx Pharmaceutical Inc.
Novato, CA 94949
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