COMPOSITIONS AND METHODS FOR IMPROVED TREATMENT OF POMPE DISEASE

SEQUENCE LISTING

The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled 51037-066WO3_Sequence_Listing_2_2_23.xml created on February 2, 2023, which is 4.1 bytes in size. The information in electronic format of the sequence listing is incorporated herein by reference in its entirety.

Field of the Invention

The present disclosure relates to the field of gene therapy and provides compositions and methods for ameliorating genetic disorders.

Background of the Invention

Pompe disease is a lysosomal storage disorder caused by mutations in the acid alpha-glucosidase (GAA) gene, which encodes an enzyme responsible for processing lysosomal glycogen. Patients with Pompe disease exhibit clinical phenotypes across a variety of tissues, including glycogen buildup in cells, deficits in cardiac, respiratory, and skeletal muscle function, and central nervous system pathology. Some of these deficits are significantly ameliorated by enzyme replacement therapy (ERT) using recombinant human GAA (rhGAA). Clinical efficacy has been limited by the immunogenicity of hGAA ERT and the lack of uptake of rhGAA into some affected tissues. Recently, gene therapy approaches involving the delivery of GAA have been developed for the treatment of Pompe disease. However, there is a need in the art for improved methods of administering gene therapy to patients having Pompe disease.

Summary

The present disclosure provides compositions and methods that can be used for treating glycogen storage disorders, such as type II glycogen storage disorder, which is also referred to herein as Pompe disease. Using the compositions and methods of the disclosure, a patient (e.g., a mammalian patient, such as a human patient) having Pompe disease may be administered a viral vector, such as an adeno-associated viral (AAV) vector, that contains a transgene encoding acid alpha-glucosidase (GAA). The AAV vector may be, for example, a pseudotyped AAV vector, such as an AAV vector containing AAV2 inverted terminal repeats packaged within capsid proteins from AAV8 (AAV2/8) or AAV9 (AAV2/9). The transgene may, for example, be operably linked to a transcription regulatory element, such as a promoter that induces gene expression in a muscle cell and/or a neuronal cell. Exemplary promoters that may be used in conjunction with the compositions and methods of the disclosure are a muscle creatine kinase (MCK) promoter and cytomegalovirus (CMV) promoter, among others. The AAV vector may be administered to the patient in a therapeutically

effective amount, such as in an amount of from 1 x 10^{13} vector genomes (vg) per kg of body weight of the subject (vg/kg) to 3 x 10^{14} vg/kg (e.g., in an amount of from 3 x 10^{13} vg/kg to 2 x 10^{14} vg/kg, 4 x 10^{13} vg/kg to 1 x 10^{14} vg/kg, 4 x 10^{13} vg/kg, 5 x 10^{13} vg/kg, 6 x 10^{13} vg/kg, 7 x 10^{13} vg/kg, 8 x 10^{13} vg/kg, 9 x 10^{13} vg/kg, or 1 x 10^{14} vg/kg).

In one example, the disclosure provides a method of treating Pompe disease in a human patient in need thereof, the method including administering to the patient (i) a therapeutically effective amount of a viral vector including a transgene encoding GAA and (ii) an anti-transaminitis agent. In one aspect, the disclosure provides use of (i) a viral vector comprising a transgene encoding acid alpha-glucosidase (GAA) and (ii) a corticosteroid in the manufacture of a medicament for treating Pompe disease in a human patient in need thereof.

In another example, the disclosure provides a method of reducing glycogen accumulation in muscle tissue and/or in neuronal tissue in a human patient diagnosed as having Pompe disease, the method including administering to the patient (i) a therapeutically effective amount of a viral vector including a transgene encoding GAA and (ii) an anti-transaminitis agent.

In another example, the disclosure provides a method of improving pulmonary function in a human patient diagnosed as having Pompe disease (e.g., LOPD), the method including administering to the patient (i) a therapeutically effective amount of a viral vector including a transgene encoding GAA and (ii) an anti-transaminitis agent.

In another example, the disclosure provides a method of increasing GAA expression in a human patient diagnosed as having Pompe disease (e.g., LOPD), the method including administering to the patient (i) a therapeutically effective amount of a viral vector including a transgene encoding GAA and (ii) an anti-transaminitis agent.

In some examples, the anti-transaminitis agent is administered to the patient in one or more doses that commence within 48 weeks of administration of the viral vector to the patient (e.g., 36 weeks, 24 weeks, 12 weeks, 10 weeks, 8 weeks, 6 weeks, or 4 weeks) of administration of the viral vector to the patient. In some examples, the anti-transaminitis agent is administered to the patient in one or more doses that commence within 12 weeks of administration of the viral vector to the patient (e.g., 10 weeks, 8 weeks, 6 weeks, or 4 weeks) of administration of the viral vector to the patient.

In another example, the disclosure provides a method of treating Pompe disease in a human patient in need thereof and who has been previously administered an anti-transaminitis agent, the method including administering to the patient a therapeutically effective amount of a viral vector including a transgene encoding GAA. In one aspect, the disclosure provides use of a viral vector comprising a transgene encoding GAA in the manufacture of a medicament for treating Pompe disease in a human patient in need thereof and who has been previously administered a corticosteroid.

In another example, the disclosure provides a method of reducing glycogen accumulation in muscle tissue and/or in neuronal tissue in a human patient diagnosed as having Pompe disease and who has been previously administered an anti-transaminitis agent, the method including administering to the patient a therapeutically effective amount of a viral vector including a transgene encoding GAA.

In another example, the disclosure provides a method of improving pulmonary function in a human patient diagnosed as having Pompe disease and who has been previously administered an anti-transaminitis agent, the method including administering to the patient a therapeutically effective amount of a viral vector including a transgene encoding GAA.

In another example, the disclosure provides a method of increasing GAA expression in a human patient diagnosed as having Pompe disease and who has been previously administered an anti-transaminitis agent, the method including administering to the patient a therapeutically effective amount of a viral vector including a transgene encoding GAA.

In another example, the disclosure provides a method of treating Pompe disease in a human patient in need thereof, the method including: (a) administering to the patient a viral vector including a transgene encoding GAA, (b) monitoring the patient for development of transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, (c) (i) administering to the patient an anti-transaminitis agent, (ii) re-administering an anti-transaminitis agent to the patient, wherein the patient had previously been treated with an anti-transaminitis agent upon administration of the viral vector, or (iii) increasing the dosage and/or frequency of an anti-transaminitis agent that is being provided to the patient. In one aspect, the disclosure provides use of a viral vector comprising a transgene encoding GAA in the manufacture of a medicament for treating Pompe disease in a human patient in need thereof, wherein the viral vector is to be administered to the patient in accordance with the following: (a) monitoring the patient who has been administered the viral vector in an amount of from 1 x 10^{13} vg/kg to 3 x 10^{14} vg/kg for development of transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, (b) (i) a corticosteroid is to be further administered to the patient, (ii) a corticosteroid is to be further re-administered to the patient, wherein the patient had previously been treated with a corticosteroid upon administration of the viral vector, or (iii) the dosage and/or frequency of a corticosteroid that is being provided to the patient is to be increased.

In another example, the disclosure provides a method of reducing glycogen accumulation in muscle tissue and/or in neuronal tissue in a human patient diagnosed as having Pompe disease (e.g., LOPD), the method including: (a) administering to the patient a viral vector including a transgene encoding GAA, (b) monitoring the patient for development of transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, (c) (i) administering to the patient an anti-transaminitis agent, (ii) re-administering an anti-transaminitis agent to the patient, wherein the patient had previously been treated with an anti-transaminitis agent upon administration of the viral vector, or (iii) increasing the dosage and/or frequency of an anti-transaminitis agent that is being provided to the patient.

In another example, the disclosure provides a method of improving pulmonary function in a human patient diagnosed as having Pompe disease (e.g., LOPD), the method including: (a) administering to the patient a viral vector including a transgene encoding GAA, (b) monitoring the patient for development of transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, (c) (i) administering to the patient an anti-transaminitis agent, (ii) re-administering an anti-transaminitis agent to the patient, wherein the patient had previously been treated with an anti-transaminitis agent upon administration of the viral vector, or (iii) increasing the dosage and/or frequency of an anti-transaminitis agent that is being provided to the patient.

In another example, the disclosure provides a method of increasing GAA expression in a human patient diagnosed as having Pompe disease (e.g., LOPD), the method including: (a) administering to the patient a viral vector including a transgene encoding GAA, (b) monitoring the patient for development of transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, (c) (i) administering to the patient an anti-transaminitis agent, (ii) re-administering an anti-transaminitis agent to the patient, wherein the patient had previously been treated with an anti-transaminitis agent

upon administration of the viral vector, or (iii) increasing the dosage and/or frequency of an anti-transaminitis agent that is being provided to the patient.

In another example, the disclosure provides a method of treating Pompe disease in a human patient in need thereof, the method including: (a) administering to the patient a viral vector including a transgene encoding GAA, (b) determining that the patient exhibits transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, and (c) (i) administering to the patient an anti-transaminitis agent, (ii) re-administering an anti-transaminitis agent to the patient, wherein the patient had previously been treated with an anti-transaminitis agent upon administration of the viral vector, or (iii) increasing the dosage and/or frequency of an anti-transaminitis agent that is being provided to the patient. In one aspect, the disclosure provides use of a viral vector comprising a transgene encoding GAA in the manufacture of a medicament for treating Pompe disease in a human patient in need thereof, wherein the viral vector is to be administered to the patient in accordance with the following: (a) determining that the patient who has been administered the viral vector in an amount of from 1 x 10^{13} vg/kg to 3 x 10^{14} vg/kg exhibits transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, and (b) (i) a corticosteroid is to be further administered to the patient, (ii) a corticosteroid is to be further re-administered to the patient, wherein the patient had previously been treated with a corticosteroid upon administration of the viral vector, or (iii) the dosage and/or frequency of a corticosteroid that is being provided to the patient is to be increased.

In another example, the disclosure provides a method of reducing glycogen accumulation in muscle tissue and/or in neuronal tissue in a human patient diagnosed as having Pompe disease (e.g., LOPD), the method including: (a) administering to the patient a viral vector including a transgene encoding GAA, (b) determining that the patient exhibits transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, and (c) (i) administering to the patient an anti-transaminitis agent, (ii) re-administering an anti-transaminitis agent to the patient, wherein the patient had previously been treated with an anti-transaminitis agent upon administration of the viral vector, or (iii) increasing the dosage and/or frequency of an anti-transaminitis agent that is being provided to the patient.

In another example, the disclosure provides a method of improving pulmonary function in a human patient diagnosed as having Pompe disease (e.g., LOPD), the method including: (a) administering to the patient a viral vector including a transgene encoding GAA, (b) determining that the patient exhibits transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, and (c) (i) administering to the patient an anti-transaminitis agent, (ii) re-administering an anti-transaminitis agent to the patient, wherein the patient had previously been treated with an anti-transaminitis agent upon administration of the viral vector, or (iii) increasing the dosage and/or frequency of an anti-transaminitis agent that is being provided to the patient.

In another example, the disclosure provides a method of increasing GAA expression in a human patient diagnosed as having Pompe disease (e.g., LOPD), the method including: (a) administering to the patient a viral vector including a transgene encoding GAA, (b) determining that the patient exhibits transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, and (c) (i) administering to the patient an anti-transaminitis agent, (ii) re-administering an anti-transaminitis agent to the patient, wherein the patient had previously been treated with an anti-transaminitis agent upon administration of the viral vector, or (iii) increasing the dosage and/or frequency of an anti-transaminitis agent that is being provided to the patient.

In another example, the disclosure provides a method of treating Pompe disease in a human patient in need thereof that is one year old or older (e.g., 2 years old or older, 3 years old or older, 4 years old or older, 5 years old or older, 6 years old or older, 7 years old or older, 8 years old or older, 9 years old or older, 10 years old or older, 15 years old or older, 20 years old or older, 30 years old or

older, or 40 month old or older), the method including: (a) administering to the patient a therapeutically effective amount of a viral vector including a transgene encoding GAA, (b) monitoring the patient for development of transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, (c) (i) administering to the patient an anti-transaminitis agent, (ii) re-administering an anti-transaminitis agent to the patient, wherein the patient had previously been treated with an anti-transaminitis agent upon administration of the viral vector, or (iii) increasing the dosage and/or frequency of an anti-transaminitis agent that is being provided to the patient.

In another example, the disclosure provides a method of reducing glycogen accumulation in muscle tissue and/or in neuronal tissue in a human patient diagnosed as having Pompe disease (e.g., LOPD), the method including: (a) administering to the patient a therapeutically effective amount of a viral vector including a transgene encoding GAA, (b) monitoring the patient for development of transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, (c) (i) administering to the patient an anti-transaminitis agent, (ii) re-administering an anti-transaminitis agent to the patient, wherein the patient had previously been treated with an anti-transaminitis agent upon administration of the viral vector, or (iii) increasing the dosage and/or frequency of an anti-transaminitis agent that is being provided to the patient.

In another example, the disclosure provides a method of improving pulmonary function in a human patient diagnosed as having Pompe disease (e.g., LOPD), the method including: (a) administering to the patient a therapeutically effective amount of a viral vector including a transgene encoding GAA, (b) monitoring the patient for development of transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, (c) (i) administering to the patient an anti-transaminitis agent, (ii) re-administering an anti-transaminitis agent to the patient, wherein the patient had previously been treated with an anti-transaminitis agent upon administration of the viral vector, or (iii) increasing the dosage and/or frequency of an anti-transaminitis agent that is being provided to the patient.

In another example, the disclosure provides a method of increasing GAA expression in a human patient diagnosed as having Pompe disease (e.g., LOPD), the method including: (a) administering to the patient a therapeutically effective amount of a viral vector including a transgene encoding GAA, (b) monitoring the patient for development of transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, (c) (i) administering to the patient an anti-transaminitis agent, (ii) re-administering an anti-transaminitis agent to the patient, wherein the patient had previously been treated with an anti-transaminitis agent upon administration of the viral vector, or (iii) increasing the dosage and/or frequency of an anti-transaminitis agent that is being provided to the patient.

In another example, the disclosure provides a method of treating Pompe disease in a human patient in need thereof that is one year old or older (e.g., 2 years old or older, 3 years old or older, 4

years old or older, 5 years old or older, 6 years old or older, 7 years old or older, 8 years old or older, 9 years old or older, 10 years old or older, 15 years old or older, 20 years old or older, 30 years old or older, or 40 month old or older), the method including: (a) administering to the patient a therapeutically effective amount of a viral vector including a transgene encoding GAA, (b) determining that the patient exhibits transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, and (c) (i) administering to the patient an anti-transaminitis agent, (ii) re-administering an anti-transaminitis agent to the patient, wherein the patient had previously been treated with an anti-transaminitis agent upon administration of the viral vector, or (iii) increasing the dosage and/or frequency of an anti-transaminitis agent that is being provided to the patient.

In another example, the disclosure provides a method of reducing glycogen accumulation in muscle tissue and/or in neuronal tissue in a human patient diagnosed as having Pompe disease that is one year old or older (e.g., 2 years old or older, 3 years old or older, 4 years old or older, 5 years old or older, 6 years old or older, 7 years old or older, 8 years old or older, 9 years old or older, 10 years old or older, 15 years old or older, 20 years old or older, 30 years old or older, or 40 month old or older), the method including: (a) administering to the patient a therapeutically effective amount of a viral vector including a transgene encoding GAA, (b) determining that the patient exhibits transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, and (c) (i) administering to the patient an anti-transaminitis agent, (ii) re-administering an anti-transaminitis agent to the patient, wherein the patient had previously been treated with an anti-transaminitis agent upon administration of the viral vector, or (iii) increasing the dosage and/or frequency of an anti-transaminitis agent that is being provided to the patient.

In another example, the disclosure provides a method of improving pulmonary function in a human patient diagnosed as having Pompe disease that is one year old or older (e.g., 2 years old or older, 3 years old or older, 4 years old or older, 5 years old or older, 6 years old or older, 7 years old or older, 8 years old or older, 9 years old or older, 10 years old or older, 15 years old or older, 20 years old or older, 30 years old or older, or 40 month old or older), the method including: (a) administering to the patient a therapeutically effective amount of a viral vector including a transgene encoding GAA, (b) determining that the patient exhibits transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, and (c) (i) administering to the patient an anti-transaminitis agent, (ii) re-administering an anti-transaminitis agent to the patient, wherein the patient had previously been treated with an anti-transaminitis agent upon administration of the viral vector, or (iii) increasing the dosage and/or frequency of an anti-transaminitis agent that is being provided to the patient.

In another example, the disclosure provides a method of increasing GAA expression in a human patient diagnosed as having Pompe disease that is one year old or older (e.g., 2 years old or older, 3 years old or older, 4 years old or older, 5 years old or older, 6 years old or older, 7 years old or older, 8 years old or older, 9 years old or older, 10 years old or older, 15 years old or older, 20 years old or older, 30 years old or older, or 40 month old or older), the method including: (a) administering to the patient a therapeutically effective amount of a viral vector including a transgene

encoding GAA, (b) determining that the patient exhibits transaminasemia, hyperbilirubinemia, or one or more symptoms thereof, and (c) (i) administering to the patient an anti-transaminitis agent, (ii) re-administering an anti-transaminitis agent to the patient, wherein the patient had previously been treated with an anti-transaminitis agent upon administration of the viral vector, or (iii) increasing the dosage and/or frequency of an anti-transaminitis agent that is being provided to the patient.

In another example, the disclosure provides a method of treating or preventing transaminasemia or hyperbilirubinemia in a human patient that has Pompe disease and who has been previously administered a viral vector including a transgene encoding GAA in an amount of from 1×10^{13} vg/kg to 3×10^{14} vg/kg (e.g., from 1×10^{13} vg/kg to 6×10^{13} vg/kg, from 1×10^{13} vg/kg to 5×10^{13} vg/kg, from 1×10^{13} vg/kg to 4×10^{13} vg/kg, from 1×10^{13} vg/kg to 3×10^{13} vg/kg, from 2×10^{13} vg/kg to 6×10^{13} vg/kg, from 2×10^{13} vg/kg to 5×10^{13} vg/kg, or from 2×10^{13} vg/kg to 4×10^{13} vg/kg), the method including administering to the patient an anti-transaminitis agent. In one aspect, the disclosure provides use of a corticosteroid in the manufacture of a medicament for treating or preventing transaminasemia or hyperbilirubinemia in a human patient that has Pompe disease and who has been previously administered a viral vector comprising a transgene encoding GAA in an amount of from 1×10^{13} vg/kg to 3×10^{14} vg/kg.

In another example, the disclosure provides a method of treating or preventing transaminasemia or hyperbilirubinemia in a human patient that has Pompe disease (e.g., LOPD), has been previously administered a viral vector including a transgene encoding GAA, and that was one year old or older (e.g., 2 years old or older, 3 years old or older, 4 years old or older, 5 years old or older, 6 years old or older, 7 years old or older, 8 years old or older, 9 years old or older, 10 years old or older, 15 years old or older, 20 years old or older, 30 years old or older, or 40 month old or older) at the time of administration of the viral vector, the method including administering to the patient an anti-transaminitis agent. In some examples, the patient is 18 years old or older (e.g., 19 years old or older, 20 years old or older, 25 years old or older, 30 years old or older, 40 years old or older, or 50 years old or older) at the time of administration of the viral vector.

In some examples, the patient is or was one year old or older (e.g., 2 years old or older, 3 years old or older, 4 years old or older, 5 years old or older, 6 years old or older, 7 years old or older, 8 years old or older, 9 years old or older, 10 years old or older, 15 years old or older, 20 years old or older, 30 years old or older, or 40 month old or older) at the time of administration of the viral vector. In some examples, the patient is or was 18 years old or older (e.g., 19 years old or older, 20 years old or older, 25 years old or older, 30 years old or older, 40 years old or older, or 50 years old or older) at the time of administration of the viral vector.

In some examples, the patient is or was from one year old to 40 years old (e.g., 1 year old to 35 years old, 2 years old to 30 years old, 3 years old to 25 years old, 4 years old to 20 years old, or 18 years old) at the time of administration of the viral vector.

In some examples, the viral vector is or was administered to the patient in an amount of from 1×10^{13} vg/kg to 3×10^{14} vg/kg (e.g., from 1×10^{13} vg/kg to 6×10^{13} vg/kg, from 1×10^{13} vg/kg to 5×10^{13} vg/kg, from 1×10^{13} vg/kg to 4×10^{13} vg/kg, from 1×10^{13} vg/kg to 3×10^{13} vg/kg, from 2×10^{13} vg/kg to 6×10^{13} vg/kg, from 2×10^{13} vg/kg to 5×10^{13} vg/kg, or from 2×10^{13} vg/kg to 4×10^{13} vg/kg). In some examples, the viral vector is or was administered to the patient in an amount of from 3×10^{13} vg/kg to 6×10^{13} (e.g., from 4×10^{13} vg/kg to 5×10^{13} vg/kg).

In some examples, the viral vector is or was administered to the patient in a single dose including the amount.

In some examples, the viral vector is or was administered to the patient in two or more doses that, together, include the amount. In some examples, the viral vector is or was administered to the patient in two or more doses that each, individually, include the amount. In some examples, the two or more doses are separated from one another by one year or more. In some examples, the two or more doses are administered to the patient within 12 months of one another.

In some examples, the viral vector is selected from the group consisting of AAV, adenovirus, lentivirus, retrovirus, poxvirus, baculovirus, herpes simplex virus, vaccinia virus, and a synthetic virus. In some examples, the viral vector is an AAV. In some examples, the AAV is an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAVrh10, or AAVrh74 serotype. In some examples, the viral vector is a pseudotyped AAV. In some examples, the pseudotyped AAV is AAV2/8. In some examples, the pseudotyped AAV is AAV2/9.

In some examples, the transgene encoding GAA is operably linked to a promoter that induces expression of the transgene in a muscle and/or neuronal cell. In some examples, the promoter is a muscle MCK promoter, MCK promoter, chicken beta actin promoter, CMV promoter, myosin light chain-2 promoter, alpha actin promoter, troponin 1 promoter, Na^{+}/Ca^{2+} exchanger promoter, dystrophin promoter, alpha7 integrin promoter, brain natriuretic peptide promoter, alpha B-crystallin/small heat shock protein promoter, alpha myosin heavy chain promoter, or atrial natriuretic factor promoter.

In some examples, the GAA is operably linked to an enhancer that induces expression of the transgene in a muscle and/or neuronal cell. In some examples, the enhancer is a CMV enhancer, a MEF2 enhancer, or a MyoD enhancer.

In some examples, the viral vector is or was administered to the patient by way of intravenous, intrathecal, intracisternal, intracerebroventricular, or intramuscular administration to the patient administration.

In some examples, the anti-transaminitis agent is selected from the group consisting of a corticosteroid, a farnesoid X receptor (FXR) ligand, a fibroblast growth factor 19 (FGF-19) mimetic, a Takeda-G-protein-receptor-5 (TGR5) agonist, a peroxisome proliferator-activated receptor (PPAR) agonist, a PPAR-alpha agonist, a PPAR-delta agonist, a dual PPAR-alpha and PPAR-delta agonist, an apical sodium-dependent corticosteroid transporter (ASBT) inhibitor, an immunomodulatory drug, an antifibrotic therapy, and a nicotinamide adenine dinucleotide phosphate oxidase (NOX) inhibitor. In some examples, (i) the corticosteroid is cortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, or hydrocortisone; (ii) the bile acid is ursodeoxycholic acid or nor-ursodeoxycholic acid; (iii) the FXR ligand is obeticholic acid, cilofexor, tropifexor, tretinoin, or EDP-305; (iv) the FGF-19 mimetic is aldafermin; (v) the TGR5

agonist is INT-777 or INT-767; (vi) the PPAR agonist is bezafibrate, seladelpar, or elafibrinor; (vii) the PPAR-alpha agonist is fenofibrate; (viii) the PPAR-delta agonist is seladelpar; (ix) the dual PPAR-alpha and PPAR-delta agonist is elafibranor; (x) the ASBT inhibitor is odevixibat, maralixibat, or linerixibat; (xi) the immunomodulatory drug is rituximab, abatacept, ustekinumab, infliximab, baricitinib, or FFP-104; (xii) the antifibrotic therapy is a vitamin D receptor agonist or simtuzumab; and/or (xiii) the NOX inhibitor is setanaxib. In some examples, the corticosteroid is prednisolone.

In some examples, the corticosteroid is administered to the patient in a single dose.

In some examples, the corticosteroid is administered to the patient in a plurality of doses.

In some examples, the corticosteroid is administered to the patient in an amount of from 0.1 mg/kg/dose to 2 mg/kg/dose (e.g., 0.2 mg/kg/dose to 1.9 mg/kg/dose, 0.3 mg/kg/dose to 1.8 mg/kg/dose, 0.4 mg/kg/dose to 1.7 mg/kg/dose, 0.5 mg/kg/dose to 1.6 mg/kg/dose, 1 mg/kg/dose to 1.5 mg/kg/dose). In some examples the corticosteroid is administered to the patient in an amount of 0.5 mg/kg/dose. In some examples the corticosteroid is administered to the patient in an amount of 1 mg/kg/dose. In some examples the corticosteroid is administered to the patient in an amount of 2 mg/kg/dose.

In some examples, the corticosteroid is administered to the patient in an amount of from 1 mg to 120 mg (e.g., 2 mg to 119 mg, 3 mg to 118 mg, 4 mg to 117 mg, 5 mg to 116 mg, 10 mg to 115 mg, 20 mg to 110 mg, 30 mg to 100 mg, 40 mg to 90 mg, 50 mg to 80 mg, or 60 mg to 70 mg). In some examples, the corticosteroid is administered to the patient in an amount of 30 mg. In some examples, the corticosteroid is administered to the patient in an amount of 60 mg. In some examples, the corticosteroid is administered to the patient in an amount of 120 mg.

In some examples, the corticosteroid is administered to the patient in one or more (e.g., one or more, two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, or ten or more) doses per day, week, or month. In some examples, the corticosteroid is administered to the patient in one or more (e.g., one or more, two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, or ten or more) doses per day, (e.g., one dose per day, in two doses per day, three doses per day, four doses per day, or five doses per day). In some examples, the corticosteroid is administered to the patient in one dose per day.

In some examples, the corticosteroid is administered to the patient in an amount of from 1 mg/day to 120 mg/day (e.g., 2 mg/day to 119 mg/day, 3 mg/day to 118 mg/day, 4 mg/day to 117 mg/day, 5 mg/day to 116 mg/day, 10 mg/day to 115 mg/day, 20 mg/day to 110 mg/day, 30 mg/day to 100 mg/day, 40 mg/day to 90 mg/day, 50 mg/day to 80 mg/day, or 60 mg/day to 70 mg/day). In some examples, the corticosteroid is administered to the patient in an amount of 30 mg/day. In some examples, the corticosteroid is administered to the patient in an

amount of 60 mg/day. In some examples, the corticosteroid is administered to the patient in an amount of 120 mg/day.

In some examples, the corticosteroid is administered to the patient by way of a unit dosage form including 5 mg of the corticosteroid.

In some examples, the corticosteroid is administered to the patient by way of a unit dosage form including 10 mg of the corticosteroid.

In some examples, the corticosteroid is administered to the patient by way of a unit dosage form including 15 mg of the corticosteroid.

In some examples, the corticosteroid is administered to the patient by way of a unit dosage form including 30 mg of the corticosteroid.

In some examples, the corticosteroid is administered to the patient by way of oral administration.

In some examples, the patient does not have a history of transaminasemia or hyperbilirubinemia. In some examples, the patient does not have a history of any underlying liver disease.

In some examples, the patient exhibits a symptom selected from feeding difficulties, failure to thrive, hypotonia, progressive weakness, respiratory distress, severe enlargement of the tongue, and thickening of the heart muscle.

In some examples, the patient is undergoing GAA enzyme replacement therapy.

In some examples, upon administering the viral vector to the patient, the patient exhibits endogenous GAA activity of from 50% to 200% of the endogenous GAA activity of a human of the same gender and similar body mass index that does not have Pompe disease.

In some examples, upon administering the viral vector to the patient, the patient exhibits a reduction in glycogen in skeletal muscle, cardiac muscle, and/or neuronal tissue.

In some examples, the method further including monitoring the patient for development of transaminasemia, hyperbilirubinemia, or one or more symptoms thereof. In some examples, the patient is monitored for the development of transaminasemia, hyperbilirubinemia, or one or more symptoms thereof by evaluating a parameter in a blood sample obtained from the patient, wherein a finding that the parameter is above a reference level identifies the patient as having transaminasemia, hyperbilirubinemia, or one or more symptoms thereof. In some examples, the parameter includes the level of aspartate aminotransferase, alanine aminotransferase and/or bilirubin in the blood sample.

In some examples, the patient is determined to exhibit transaminasemia or one or more symptoms thereof by a finding that the patient exhibits one or more transaminases in a liver function test that is increased relative to a reference level. In some

examples, the one or more transaminases includes the level of aspartate aminotransferase and/or alanine aminotransferase.

In some examples, the patient is determined to exhibit transaminasemia or one or more symptoms thereof by a finding that the patient exhibits an alanine transaminase level that is greater than 50 U/L (e.g., 55 U/L, 60 U/L, 65 U/L, 70 U/L, 75 U/L, 80 U/L, 85 U/L, 90 U/L, 100 U/L, 110 U/L, 120 U/L, 130 U/L, 140 U/L, 150 U/L, 200 U/L, 300 U/L, 400 U/L, and 500 U/L) in a liver function test.

In some examples, upon administering the viral vector to the patient, the patient displays an aspartate aminotransferase level that is greater than 50 U/L (e.g., 55 U/L, 60 U/L, 65 U/L, 70 U/L, 75 U/L, 80 U/L, 85 U/L, 90 U/L, 100 U/L, 110 U/L, 120 U/L, 130 U/L, 140 U/L, 150 U/L, 200 U/L, 300 U/L, 400 U/L, and 500 U/L) in a liver function test.

In some examples, the Pompe disease is late-onset Pompe disease (LOPD).

In another example, the disclosure provides a kit including a viral vector including a transgene encoding GAA and a package insert, wherein the package insert instructs a user of the kit to administer the viral vector to a patient having Pompe disease in accordance with the method of any one of the foregoing examples. In one aspect, the disclosure provides a kit comprising a viral vector comprising a transgene encoding GAA and a package insert, wherein the package insert instructs a user of the kit to administer the viral vector to a patient having Pompe disease in accordance with the use as disclosed herein.

In another example, the disclosure provides a kit including an anti-transaminitis agent and a package insert, wherein the package insert instructs a user of the kit to administer the anti-transaminitis agent to a patient to treat or prevent transaminasemia or hyperbilirubinemia in accordance with the method of any one of any one of the foregoing examples. In one aspect, the disclosure provides a kit comprising a corticosteroid and a package insert, wherein the package insert instructs a user of the kit to administer the corticosteroid to a patient to treat or prevent transaminasemia or hyperbilirubinemia in accordance with the use as disclosed herein.

Brief Description of the Drawings

The application file contains at least one drawing executed in color. Copies of this patent or patent application with color drawings will be provided by the Office upon request and payment of the necessary fee.

FIG. 1 is a schematic depicting the experimental outline of clinical trial FORTIS (NCT04174105), which is an ongoing multicenter, open-label, ascending dose Phase I/II first-in-human clinical trial to determine if an AAV vector encoding GAA, described herein, is safe and tolerable in adult subjects with Pompe disease. Subjects enrolled in FORTIS receive a one-time peripheral intravenous infusion of the vector described herein, followed by one year of frequent monitoring of clinical and biochemical endpoints including GAA activity and protein level in muscle and four years of long-term safety monitoring.

FIG. 2 is a set of graphs showing change in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin (TBil) levels in individual subjects 2001 (“01”), 2002 (“02”), 2003 (“03”), and 2009 (“09”) over time relative to their treatment with a corticosteroid, prednisolone, as well as an AAV2/8 vector containing an acid alpha-glucosidase (GAA) transgene operably linked to a muscle creatine kinase (MCK) promoter. Abbreviations: L, liter; U/L, units per liter; ULM, upper limit