

COMPOSITIONS AND METHODS FOR TREATING GLYCOGEN STORAGE DISORDERS

Field of the Invention

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

Sequence Listing

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on October 23, 2020 is named 51037-054WO3_Sequence_Listing_10.23.20_ST25 and is 13,144 bytes in size.

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. Gene therapy has also been investigated as a potential therapeutic paradigm for this disease. The development of gene therapies for the treatment of Pompe have been hindered by the difficulty associated with achieving expression of therapeutically effective amounts of GAA in affected tissues while suppressing toxic side effects. There remains a need for compositions and methods that achieve this balance.

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 promoter, desmin promoter, and 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 about 1×10^{13} vector genomes (vg) per kg of body weight of the subject (vg/kg) to about 3×10^{14} vg/kg (e.g., in an

amount of from about 3×10^{13} vg/kg to about 2×10^{14} vg/kg, such as in an amount of from about 4×10^{13} vg/kg to about 1×10^{14} vg/kg, such as in an amount of about 4×10^{13} vg/kg, 5×10^{13} vg/kg, 6×10^{13} vg/kg, 7×10^{13} vg/kg, 8×10^{13} vg/kg, 9×10^{13} vg/kg, or 1×10^{14} vg/kg).

The present disclosure is based, in part, on the discovery of doses of AAV vectors containing a
5 GAA transgene that effectuate a therapeutic increase in GAA expression and activity in patients suffering from Pompe disease while suppressing toxic side effects. It has presently been discovered, for example, that doses of AAV vectors containing a transgene encoding GAA ranging from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg (e.g., from about 3×10^{13} vg/kg to about 2×10^{14} vg/kg, such as a dose of about 4×10^{13} vg/kg, 5×10^{13} vg/kg, 6×10^{13} vg/kg, 7×10^{13} vg/kg, 8×10^{13} vg/kg, 9×10^{13} vg/kg, or 1×10^{14} vg/kg)
10 can engender a beneficial increase in GAA expression and activity in a patient having Pompe disease while simultaneously avoiding toxic side effects that can be associated with overexpression of GAA or administration of excessive quantities of viral vector. Using the compositions and methods of the disclosure, an AAV vector may be administered to the patient in an amount that is sufficient to enhance the patient's expression of GAA and reduce cellular accumulation of glycogen in the patient's neuronal
15 and muscle tissue, without inducing toxic side effects.

In one aspect, the disclosure provides use of an adeno-associated viral (AAV) vector comprising a transgene encoding acid alpha-glucosidase (GAA) in the manufacture of a medicament for treating Pompe disease in a human patient in need thereof, wherein the AAV vector is to be administered to the patient in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg. In a first example, the disclosure
20 features a method of treating Pompe disease in a human patient in need thereof by administering to the patient an AAV vector containing a transgene encoding acid GAA, wherein the AAV vector is administered to the patient in an amount of from about 1×10^{13} vg/kg to about 5×10^{14} vg/kg, such as in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg. For example, the AAV vector may be administered to the patient in an amount of about 1×10^{13} vg/kg, 1.1×10^{13} vg/kg, 1.2×10^{13} vg/kg, 1.3×10^{13} vg/kg, 1.4×10^{13} vg/kg, 1.5×10^{13} vg/kg, 1.6×10^{13} vg/kg, 1.7×10^{13} vg/kg, 1.8×10^{13} vg/kg, 1.9×10^{13} vg/kg, 2×10^{13} vg/kg, 2.1×10^{13} vg/kg, 2.2×10^{13} vg/kg, 2.3×10^{13} vg/kg, 2.4×10^{13} vg/kg, 2.5×10^{13} vg/kg, 2.6×10^{13} vg/kg, 2.7×10^{13} vg/kg, 2.8×10^{13} vg/kg, 2.9×10^{13} vg/kg, 3×10^{13} vg/kg, 3.1×10^{13} vg/kg, 3.2×10^{13} vg/kg, 3.3×10^{13} vg/kg, 3.4×10^{13} vg/kg, 3.5×10^{13} vg/kg, 3.6×10^{13} vg/kg, 3.7×10^{13} vg/kg, 3.8×10^{13} vg/kg, 3.9×10^{13} vg/kg, 4×10^{13} vg/kg, 4.1×10^{13} vg/kg, 4.2×10^{13} vg/kg, 4.3×10^{13} vg/kg, 4.4×10^{13} vg/kg, 4.5×10^{13} vg/kg, 4.6×10^{13} vg/kg, 4.7×10^{13} vg/kg, 4.8×10^{13} vg/kg, 4.9×10^{13} vg/kg, 5×10^{13} vg/kg, 5.1×10^{13} vg/kg, 5.2×10^{13} vg/kg, 5.3×10^{13} vg/kg, 5.4×10^{13} vg/kg, 5.5×10^{13} vg/kg, 5.6×10^{13} vg/kg, 5.7×10^{13} vg/kg, 5.8×10^{13} vg/kg, 5.9×10^{13} vg/kg, 6×10^{13} vg/kg, 6.1×10^{13} vg/kg, 6.2×10^{13} vg/kg, 6.3×10^{13} vg/kg, 6.4×10^{13} vg/kg, 6.5×10^{13} vg/kg, 6.6×10^{13} vg/kg, 6.7×10^{13} vg/kg, 6.8×10^{13} vg/kg, 6.9×10^{13} vg/kg, 7×10^{13} vg/kg, 7.1×10^{13} vg/kg, 7.2×10^{13} vg/kg, 7.3×10^{13} vg/kg, 7.4×10^{13} vg/kg, 7.5×10^{13} vg/kg, 7.6×10^{13} vg/kg, 7.7×10^{13} vg/kg, 7.8×10^{13} vg/kg, 7.9×10^{13} vg/kg, 8×10^{13} vg/kg, 8.1×10^{13} vg/kg, 8.2×10^{13} vg/kg, 8.3×10^{13} vg/kg, 8.4×10^{13} vg/kg, 8.5×10^{13} vg/kg, 8.6×10^{13} vg/kg, 8.7×10^{13} vg/kg, 8.8×10^{13} vg/kg, 8.9×10^{13} vg/kg, 9×10^{13} vg/kg, 9.1×10^{13} vg/kg, 9.2×10^{13} vg/kg, 9.3×10^{13} vg/kg, 9.4×10^{13} vg/kg, 9.5×10^{13} vg/kg, 9.6×10^{13} vg/kg, 9.7×10^{13} vg/kg, 9.8×10^{13} vg/kg, 9.9×10^{13} vg/kg, 1×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.9×10^{14} vg/kg, 2×10^{14} vg/kg, 2.1×10^{14} vg/kg, 2.2×10^{14} vg/kg, 2.3×10^{14} vg/kg, 2.4×10^{14} vg/kg, 2.5×10^{14} vg/kg, 2.6×10^{14} vg/kg, 2.7×10^{14} vg/kg, 2.8×10^{14} vg/kg, 2.9×10^{14} vg/kg, 3×10^{14} vg/kg, 3.1×10^{14} vg/kg, 3.2×10^{14} vg/kg, 3.3×10^{14} vg/kg, 3.4×10^{14} vg/kg, 3.5×10^{14} vg/kg, 3.6×10^{14} vg/kg, 3.7×10^{14} vg/kg, 3.8×10^{14} vg/kg, 3.9×10^{14} vg/kg, 4×10^{14} vg/kg, 4.1×10^{14} vg/kg, 4.2×10^{14} vg/kg, 4.3×10^{14} vg/kg, 4.4×10^{14} vg/kg, 4.5×10^{14} vg/kg, 4.6×10^{14} vg/kg, 4.7×10^{14} vg/kg, 4.8×10^{14} vg/kg, 4.9×10^{14} vg/kg, 5×10^{14} vg/kg, 5.1×10^{14} vg/kg, 5.2×10^{14} vg/kg, 5.3×10^{14} vg/kg, 5.4×10^{14} vg/kg, 5.5×10^{14} vg/kg, 5.6×10^{14} vg/kg, 5.7×10^{14} vg/kg, 5.8×10^{14} vg/kg, 5.9×10^{14} vg/kg, 6×10^{14} vg/kg, 6.1×10^{14} vg/kg, 6.2×10^{14} vg/kg, 6.3×10^{14} vg/kg, 6.4×10^{14} vg/kg, 6.5×10^{14} vg/kg, 6.6×10^{14} vg/kg, 6.7×10^{14} vg/kg, 6.8×10^{14} vg/kg, 6.9×10^{14} vg/kg, 7×10^{14} vg/kg, 7.1×10^{14} vg/kg, 7.2×10^{14} vg/kg, 7.3×10^{14} vg/kg, 7.4×10^{14} vg/kg, 7.5×10^{14} vg/kg, 7.6×10^{14} vg/kg, 7.7×10^{14} vg/kg, 7.8×10^{14} vg/kg, 7.9×10^{14} vg/kg, 8×10^{14} vg/kg, 8.1×10^{14} vg/kg, 8.2×10^{14} vg/kg, 8.3×10^{14} vg/kg, 8.4×10^{14} vg/kg, 8.5×10^{14} vg/kg, 8.6×10^{14} vg/kg, 8.7×10^{14} vg/kg, 8.8×10^{14} vg/kg, 8.9×10^{14} vg/kg, 9×10^{14} vg/kg, 9.1×10^{14} vg/kg, 9.2×10^{14} vg/kg, 9.3×10^{14} vg/kg, 9.4×10^{14} vg/kg, 9.5×10^{14} vg/kg, 9.6×10^{14} vg/kg, 9.7×10^{14} vg/kg, 9.8×10^{14} vg/kg, 9.9×10^{14} vg/kg, or 1×10^{15} vg/kg.

vg/kg, 3.7×10^{14} vg/kg, 3.8×10^{14} vg/kg, 3.9×10^{14} vg/kg, 4×10^{14} vg/kg, 4.1×10^{14} vg/kg, 4.2×10^{14} vg/kg, 4.3×10^{14} vg/kg, 4.4×10^{14} vg/kg, 4.5×10^{14} vg/kg, 4.6×10^{14} vg/kg, 4.7×10^{14} vg/kg, 4.8×10^{14} vg/kg, 4.9×10^{14} vg/kg, or 5×10^{14} vg/kg.

5 In another aspect, the disclosure provides use of an AAV vector comprising a transgene encoding GAA in the manufacture of a medicament for improving muscle function in a human patient diagnosed as having Pompe disease, wherein the AAV vector is to be administered to the patient in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg. In another example, the disclosure features a method of improving muscle function in a human patient diagnosed as having Pompe disease by administering to the patient an AAV vector containing a transgene encoding GAA, wherein the AAV
10 vector is administered to the patient in an amount of from about 1×10^{13} vg/kg to about 5×10^{14} vg/kg, such as in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg. For example, the AAV vector may be administered to the patient in an amount of about 1×10^{13} vg/kg, 1.1×10^{13} vg/kg, 1.2×10^{13} vg/kg, 1.3×10^{13} vg/kg, 1.4×10^{13} vg/kg, 1.5×10^{13} vg/kg, 1.6×10^{13} vg/kg, 1.7×10^{13} vg/kg, 1.8×10^{13} vg/kg, 1.9×10^{13} vg/kg, 2×10^{13} vg/kg, 2.1×10^{13} vg/kg, 2.2×10^{13} vg/kg, 2.3×10^{13} vg/kg, 2.4×10^{13} vg/kg, 2.5×10^{13} vg/kg, 2.6×10^{13} vg/kg, 2.7×10^{13} vg/kg, 2.8×10^{13} vg/kg, 2.9×10^{13} vg/kg, 3×10^{13} vg/kg, 3.1×10^{13} vg/kg, 3.2×10^{13} vg/kg, 3.3×10^{13} vg/kg, 3.4×10^{13} vg/kg, 3.5×10^{13} vg/kg, 3.6×10^{13} vg/kg, 3.7×10^{13} vg/kg, 3.8×10^{13} vg/kg, 3.9×10^{13} vg/kg, 4×10^{13} vg/kg, 4.1×10^{13} vg/kg, 4.2×10^{13} vg/kg, 4.3×10^{13} vg/kg, 4.4×10^{13} vg/kg, 4.5×10^{13} vg/kg, 4.6×10^{13} vg/kg, 4.7×10^{13} vg/kg, 4.8×10^{13} vg/kg, 4.9×10^{13} vg/kg, 5×10^{13} vg/kg, 5.1×10^{13} vg/kg, 5.2×10^{13} vg/kg, 5.3×10^{13} vg/kg, 5.4×10^{13} vg/kg, 5.5×10^{13} vg/kg, 5.6×10^{13} vg/kg, 5.7×10^{13} vg/kg, 5.8×10^{13} vg/kg, 5.9×10^{13} vg/kg, 6×10^{13} vg/kg, 6.1×10^{13} vg/kg, 6.2×10^{13} vg/kg, 6.3×10^{13} vg/kg, 6.4×10^{13} vg/kg, 6.5×10^{13} vg/kg, 6.6×10^{13} vg/kg, 6.7×10^{13} vg/kg, 6.8×10^{13} vg/kg, 6.9×10^{13} vg/kg, 7×10^{13} vg/kg, 7.1×10^{13} vg/kg, 7.2×10^{13} vg/kg, 7.3×10^{13} vg/kg, 7.4×10^{13} vg/kg, 7.5×10^{13} vg/kg, 7.6×10^{13} vg/kg, 7.7×10^{13} vg/kg, 7.8×10^{13} vg/kg, 7.9×10^{13} vg/kg, 8×10^{13} vg/kg, 8.1×10^{13} vg/kg, 8.2×10^{13} vg/kg, 8.3×10^{13} vg/kg, 8.4×10^{13} vg/kg, 8.5×10^{13} vg/kg, 8.6×10^{13} vg/kg, 8.7×10^{13} vg/kg, 8.8×10^{13} vg/kg, 8.9×10^{13} vg/kg, 9×10^{13} vg/kg, 9.1×10^{13} vg/kg, 9.2×10^{13} vg/kg, 9.3×10^{13} vg/kg, 9.4×10^{13} vg/kg, 9.5×10^{13} vg/kg, 9.6×10^{13} vg/kg, 9.7×10^{13} vg/kg, 9.8×10^{13} vg/kg, 9.9×10^{13} vg/kg, 1×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.9×10^{14} vg/kg, 2×10^{14} vg/kg, 2.1×10^{14} vg/kg, 2.2×10^{14} vg/kg, 2.3×10^{14} vg/kg, 2.4×10^{14} vg/kg, 2.5×10^{14} vg/kg, 2.6×10^{14} vg/kg, 2.7×10^{14} vg/kg, 2.8×10^{14} vg/kg, 2.9×10^{14} vg/kg, 3×10^{14} vg/kg, 3.1×10^{14} vg/kg, 3.2×10^{14} vg/kg, 3.3×10^{14} vg/kg, 3.4×10^{14} vg/kg, 3.5×10^{14} vg/kg, 3.6×10^{14} vg/kg, 3.7×10^{14} vg/kg, 3.8×10^{14} vg/kg, 3.9×10^{14} vg/kg, 4×10^{14} vg/kg, 4.1×10^{14} vg/kg, 4.2×10^{14} vg/kg, 4.3×10^{14} vg/kg, 4.4×10^{14} vg/kg, 4.5×10^{14} vg/kg, 4.6×10^{14} vg/kg, 4.7×10^{14} vg/kg, 4.8×10^{14} vg/kg, 4.9×10^{14} vg/kg, or 5×10^{14} vg/kg.

35 In yet another aspect, the disclosure provides use of an AAV vector comprising a transgene encoding GAA in the manufacture of a medicament for reducing glycogen accumulation in a human patient diagnosed as having Pompe disease, wherein the AAV vector is to be administered to the patient in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg. In a further example, the disclosure features a method of reducing glycogen accumulation in a human patient diagnosed as having Pompe
40 disease by administering to the patient an AAV vector containing a transgene encoding GAA, wherein the AAV vector is administered to the patient in an amount of from about 1×10^{13} vg/kg to about 5×10^{14} vg/kg, such as in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg. For example, the AAV vector may be administered to the patient in an amount of about 1×10^{13} vg/kg, 1.1×10^{13} vg/kg, 1.2×10^{13} vg/kg, 1.3×10^{13} vg/kg, 1.4×10^{13} vg/kg, 1.5×10^{13} vg/kg, 1.6×10^{13} vg/kg, 1.7×10^{13} vg/kg, 1.8×10^{13} vg/kg, 1.9×10^{13} vg/kg, 2×10^{13} vg/kg, 2.1×10^{13} vg/kg, 2.2×10^{13} vg/kg, 2.3×10^{13} vg/kg, 2.4×10^{13} vg/kg, 2.5×10^{13} vg/kg, 2.6×10^{13} vg/kg, 2.7×10^{13} vg/kg, 2.8×10^{13} vg/kg, 2.9×10^{13} vg/kg, 3×10^{13} vg/kg, 3.1×10^{13} vg/kg, 3.2×10^{13} vg/kg, 3.3×10^{13} vg/kg, 3.4×10^{13} vg/kg, 3.5×10^{13} vg/kg, 3.6×10^{13} vg/kg, 3.7×10^{13} vg/kg, 3.8×10^{13} vg/kg, 3.9×10^{13} vg/kg, 4×10^{13} vg/kg, 4.1×10^{13} vg/kg, 4.2×10^{13} vg/kg, 4.3×10^{13} vg/kg, 4.4×10^{13} vg/kg, 4.5×10^{13} vg/kg, 4.6×10^{13} vg/kg, 4.7×10^{13} vg/kg, 4.8×10^{13} vg/kg, 4.9×10^{13} vg/kg, or 5×10^{13} vg/kg.

vg/kg, 3.4×10^{13} vg/kg, 3.5×10^{13} vg/kg, 3.6×10^{13} vg/kg, 3.7×10^{13} vg/kg, 3.8×10^{13} vg/kg, 3.9×10^{13} vg/kg, 4×10^{13} vg/kg, 4.1×10^{13} vg/kg, 4.2×10^{13} vg/kg, 4.3×10^{13} vg/kg, 4.4×10^{13} vg/kg, 4.5×10^{13} vg/kg, 4.6×10^{13} vg/kg, 4.7×10^{13} vg/kg, 4.8×10^{13} vg/kg, 4.9×10^{13} vg/kg, 5×10^{13} vg/kg, 5.1×10^{13} vg/kg, 5.2×10^{13} vg/kg, 5.3×10^{13} vg/kg, 5.4×10^{13} vg/kg, 5.5×10^{13} vg/kg, 5.6×10^{13} vg/kg, 5.7×10^{13} vg/kg, 5.8×10^{13} vg/kg, 5.9×10^{13} vg/kg, 6×10^{13} vg/kg, 6.1×10^{13} vg/kg, 6.2×10^{13} vg/kg, 6.3×10^{13} vg/kg, 6.4×10^{13} vg/kg, 6.5×10^{13} vg/kg, 6.6×10^{13} vg/kg, 6.7×10^{13} vg/kg, 6.8×10^{13} vg/kg, 6.9×10^{13} vg/kg, 7×10^{13} vg/kg, 7.1×10^{13} vg/kg, 7.2×10^{13} vg/kg, 7.3×10^{13} vg/kg, 7.4×10^{13} vg/kg, 7.5×10^{13} vg/kg, 7.6×10^{13} vg/kg, 7.7×10^{13} vg/kg, 7.8×10^{13} vg/kg, 7.9×10^{13} vg/kg, 8×10^{13} vg/kg, 8.1×10^{13} vg/kg, 8.2×10^{13} vg/kg, 8.3×10^{13} vg/kg, 8.4×10^{13} vg/kg, 8.5×10^{13} vg/kg, 8.6×10^{13} vg/kg, 8.7×10^{13} vg/kg, 8.8×10^{13} vg/kg, 8.9×10^{13} vg/kg, 9×10^{13} vg/kg, 9.1×10^{13} vg/kg, 9.2×10^{13} vg/kg, 9.3×10^{13} vg/kg, 9.4×10^{13} vg/kg, 9.5×10^{13} vg/kg, 9.6×10^{13} vg/kg, 9.7×10^{13} vg/kg, 9.8×10^{13} vg/kg, 9.9×10^{13} vg/kg, 1×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.9×10^{14} vg/kg, 2×10^{14} vg/kg, 2.1×10^{14} vg/kg, 2.2×10^{14} vg/kg, 2.3×10^{14} vg/kg, 2.4×10^{14} vg/kg, 2.5×10^{14} vg/kg, 2.6×10^{14} vg/kg, 2.7×10^{14} vg/kg, 2.8×10^{14} vg/kg, 2.9×10^{14} vg/kg, 3×10^{14} vg/kg, 3.1×10^{14} vg/kg, 3.2×10^{14} vg/kg, 3.3×10^{14} vg/kg, 3.4×10^{14} vg/kg, 3.5×10^{14} vg/kg, 3.6×10^{14} vg/kg, 3.7×10^{14} vg/kg, 3.8×10^{14} vg/kg, 3.9×10^{14} vg/kg, 4×10^{14} vg/kg, 4.1×10^{14} vg/kg, 4.2×10^{14} vg/kg, 4.3×10^{14} vg/kg, 4.4×10^{14} vg/kg, 4.5×10^{14} vg/kg, 4.6×10^{14} vg/kg, 4.7×10^{14} vg/kg, 4.8×10^{14} vg/kg, 4.9×10^{14} vg/kg, or 5×10^{14} vg/kg. In some examples of this aspect, administration of the AAV vector to the patient reduces glycogen accumulation in muscle tissue (e.g., in cardiac and/or skeletal muscle tissue) and/or in neuronal tissue.

In one aspect, the disclosure provides use of an AAV vector comprising a transgene encoding GAA in the manufacture of a medicament for improving pulmonary function in a human patient diagnosed as having Pompe disease, wherein the AAV vector is to be administered to the patient in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg. In another example, the disclosure features a method of improving pulmonary function in a human patient diagnosed as having Pompe disease by administering to the patient an AAV vector containing a transgene encoding GAA, wherein the AAV vector is administered to the patient in an amount of from about 1×10^{13} vg/kg to about 5×10^{14} vg/kg, such as in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg. For example, the AAV vector may be administered to the patient in an amount of about 1×10^{13} vg/kg, 1.1×10^{13} vg/kg, 1.2×10^{13} vg/kg, 1.3×10^{13} vg/kg, 1.4×10^{13} vg/kg, 1.5×10^{13} vg/kg, 1.6×10^{13} vg/kg, 1.7×10^{13} vg/kg, 1.8×10^{13} vg/kg, 1.9×10^{13} vg/kg, 2×10^{13} vg/kg, 2.1×10^{13} vg/kg, 2.2×10^{13} vg/kg, 2.3×10^{13} vg/kg, 2.4×10^{13} vg/kg, 2.5×10^{13} vg/kg, 2.6×10^{13} vg/kg, 2.7×10^{13} vg/kg, 2.8×10^{13} vg/kg, 2.9×10^{13} vg/kg, 3×10^{13} vg/kg, 3.1×10^{13} vg/kg, 3.2×10^{13} vg/kg, 3.3×10^{13} vg/kg, 3.4×10^{13} vg/kg, 3.5×10^{13} vg/kg, 3.6×10^{13} vg/kg, 3.7×10^{13} vg/kg, 3.8×10^{13} vg/kg, 3.9×10^{13} vg/kg, 4×10^{13} vg/kg, 4.1×10^{13} vg/kg, 4.2×10^{13} vg/kg, 4.3×10^{13} vg/kg, 4.4×10^{13} vg/kg, 4.5×10^{13} vg/kg, 4.6×10^{13} vg/kg, 4.7×10^{13} vg/kg, 4.8×10^{13} vg/kg, 4.9×10^{13} vg/kg, 5×10^{13} vg/kg, 5.1×10^{13} vg/kg, 5.2×10^{13} vg/kg, 5.3×10^{13} vg/kg, 5.4×10^{13} vg/kg, 5.5×10^{13} vg/kg, 5.6×10^{13} vg/kg, 5.7×10^{13} vg/kg, 5.8×10^{13} vg/kg, 5.9×10^{13} vg/kg, 6×10^{13} vg/kg, 6.1×10^{13} vg/kg, 6.2×10^{13} vg/kg, 6.3×10^{13} vg/kg, 6.4×10^{13} vg/kg, 6.5×10^{13} vg/kg, 6.6×10^{13} vg/kg, 6.7×10^{13} vg/kg, 6.8×10^{13} vg/kg, 6.9×10^{13} vg/kg, 7×10^{13} vg/kg, 7.1×10^{13} vg/kg, 7.2×10^{13} vg/kg, 7.3×10^{13} vg/kg, 7.4×10^{13} vg/kg, 7.5×10^{13} vg/kg, 7.6×10^{13} vg/kg, 7.7×10^{13} vg/kg, 7.8×10^{13} vg/kg, 7.9×10^{13} vg/kg, 8×10^{13} vg/kg, 8.1×10^{13} vg/kg, 8.2×10^{13} vg/kg, 8.3×10^{13} vg/kg, 8.4×10^{13} vg/kg, 8.5×10^{13} vg/kg, 8.6×10^{13} vg/kg, 8.7×10^{13} vg/kg, 8.8×10^{13} vg/kg, 8.9×10^{13} vg/kg, 9×10^{13} vg/kg, 9.1×10^{13} vg/kg, 9.2×10^{13} vg/kg, 9.3×10^{13} vg/kg, 9.4×10^{13} vg/kg.

vg/kg, 9.5×10^{13} vg/kg, 9.6×10^{13} vg/kg, 9.7×10^{13} vg/kg, 9.8×10^{13} vg/kg, 9.9×10^{13} vg/kg, 1×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.9×10^{14} vg/kg, 2×10^{14} vg/kg, 2.1×10^{14} vg/kg, 2.2×10^{14} vg/kg, 2.3×10^{14} vg/kg, 2.4×10^{14} vg/kg, 2.5×10^{14} vg/kg, 2.6×10^{14} vg/kg, 2.7×10^{14} vg/kg, 2.8×10^{14} vg/kg, 2.9×10^{14} vg/kg, 3×10^{14} vg/kg, 3.1×10^{14} vg/kg, 3.2×10^{14} vg/kg, 3.3×10^{14} vg/kg, 3.4×10^{14} vg/kg, 3.5×10^{14} vg/kg, 3.6×10^{14} vg/kg, 3.7×10^{14} vg/kg, 3.8×10^{14} vg/kg, 3.9×10^{14} vg/kg, 4×10^{14} vg/kg, 4.1×10^{14} vg/kg, 4.2×10^{14} vg/kg, 4.3×10^{14} vg/kg, 4.4×10^{14} vg/kg, 4.5×10^{14} vg/kg, 4.6×10^{14} vg/kg, 4.7×10^{14} vg/kg, 4.8×10^{14} vg/kg, 4.9×10^{14} vg/kg, or 5×10^{14} vg/kg.

In another aspect, the present disclosure provides use of an AAV vector comprising a transgene encoding GAA in the manufacture of a medicament for increasing GAA expression in a human patient diagnosed as having Pompe disease, wherein the AAV vector is to be administered to the patient in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg. In another example, the disclosure features a method of increasing GAA expression in a human patient diagnosed as having Pompe disease by administering to the patient an AAV vector containing a transgene encoding GAA, wherein the AAV vector is administered to the patient in an amount of from about 1×10^{13} vg/kg to about 5×10^{14} vg/kg, such as in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg. For example, the AAV vector may be administered to the patient in an amount of about 1×10^{13} vg/kg, 1.1×10^{13} vg/kg, 1.2×10^{13} vg/kg, 1.3×10^{13} vg/kg, 1.4×10^{13} vg/kg, 1.5×10^{13} vg/kg, 1.6×10^{13} vg/kg, 1.7×10^{13} vg/kg, 1.8×10^{13} vg/kg, 1.9×10^{13} vg/kg, 2×10^{13} vg/kg, 2.1×10^{13} vg/kg, 2.2×10^{13} vg/kg, 2.3×10^{13} vg/kg, 2.4×10^{13} vg/kg, 2.5×10^{13} vg/kg, 2.6×10^{13} vg/kg, 2.7×10^{13} vg/kg, 2.8×10^{13} vg/kg, 2.9×10^{13} vg/kg, 3×10^{13} vg/kg, 3.1×10^{13} vg/kg, 3.2×10^{13} vg/kg, 3.3×10^{13} vg/kg, 3.4×10^{13} vg/kg, 3.5×10^{13} vg/kg, 3.6×10^{13} vg/kg, 3.7×10^{13} vg/kg, 3.8×10^{13} vg/kg, 3.9×10^{13} vg/kg, 4×10^{13} vg/kg, 4.1×10^{13} vg/kg, 4.2×10^{13} vg/kg, 4.3×10^{13} vg/kg, 4.4×10^{13} vg/kg, 4.5×10^{13} vg/kg, 4.6×10^{13} vg/kg, 4.7×10^{13} vg/kg, 4.8×10^{13} vg/kg, 4.9×10^{13} vg/kg, 5×10^{13} vg/kg, 5.1×10^{13} vg/kg, 5.2×10^{13} vg/kg, 5.3×10^{13} vg/kg, 5.4×10^{13} vg/kg, 5.5×10^{13} vg/kg, 5.6×10^{13} vg/kg, 5.7×10^{13} vg/kg, 5.8×10^{13} vg/kg, 5.9×10^{13} vg/kg, 6×10^{13} vg/kg, 6.1×10^{13} vg/kg, 6.2×10^{13} vg/kg, 6.3×10^{13} vg/kg, 6.4×10^{13} vg/kg, 6.5×10^{13} vg/kg, 6.6×10^{13} vg/kg, 6.7×10^{13} vg/kg, 6.8×10^{13} vg/kg, 6.9×10^{13} vg/kg, 7×10^{13} vg/kg, 7.1×10^{13} vg/kg, 7.2×10^{13} vg/kg, 7.3×10^{13} vg/kg, 7.4×10^{13} vg/kg, 7.5×10^{13} vg/kg, 7.6×10^{13} vg/kg, 7.7×10^{13} vg/kg, 7.8×10^{13} vg/kg, 7.9×10^{13} vg/kg, 8×10^{13} vg/kg, 8.1×10^{13} vg/kg, 8.2×10^{13} vg/kg, 8.3×10^{13} vg/kg, 8.4×10^{13} vg/kg, 8.5×10^{13} vg/kg, 8.6×10^{13} vg/kg, 8.7×10^{13} vg/kg, 8.8×10^{13} vg/kg, 8.9×10^{13} vg/kg, 9×10^{13} vg/kg, 9.1×10^{13} vg/kg, 9.2×10^{13} vg/kg, 9.3×10^{13} vg/kg, 9.4×10^{13} vg/kg, 9.5×10^{13} vg/kg, 9.6×10^{13} vg/kg, 9.7×10^{13} vg/kg, 9.8×10^{13} vg/kg, 9.9×10^{13} vg/kg, 1×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.9×10^{14} vg/kg, 2×10^{14} vg/kg, 2.1×10^{14} vg/kg, 2.2×10^{14} vg/kg, 2.3×10^{14} vg/kg, 2.4×10^{14} vg/kg, 2.5×10^{14} vg/kg, 2.6×10^{14} vg/kg, 2.7×10^{14} vg/kg, 2.8×10^{14} vg/kg, 2.9×10^{14} vg/kg, 3×10^{14} vg/kg, 3.1×10^{14} vg/kg, 3.2×10^{14} vg/kg, 3.3×10^{14} vg/kg, 3.4×10^{14} vg/kg, 3.5×10^{14} vg/kg, 3.6×10^{14} vg/kg, 3.7×10^{14} vg/kg, 3.8×10^{14} vg/kg, 3.9×10^{14} vg/kg, 4×10^{14} vg/kg, 4.1×10^{14} vg/kg, 4.2×10^{14} vg/kg, 4.3×10^{14} vg/kg, 4.4×10^{14} vg/kg, 4.5×10^{14} vg/kg, 4.6×10^{14} vg/kg, 4.7×10^{14} vg/kg, 4.8×10^{14} vg/kg, 4.9×10^{14} vg/kg, or 5×10^{14} vg/kg.

In some examples of any of the above aspects of the disclosure, the AAV vector is administered to the patient in an amount of from about 2×10^{13} vg/kg to about 2×10^{14} vg/kg, such as an in amount of about 2×10^{13} vg/kg, 2.1×10^{13} vg/kg, 2.2×10^{13} vg/kg, 2.3×10^{13} vg/kg, 2.4×10^{13} vg/kg, 2.5×10^{13} vg/kg, 2.6×10^{13} vg/kg, 2.7×10^{13} vg/kg, 2.8×10^{13} vg/kg, 2.9×10^{13} vg/kg, 3×10^{13} vg/kg, $3.1 \times$

10¹³ vg/kg, 3.2 x 10¹³ vg/kg, 3.3 x 10¹³ vg/kg, 3.4 x 10¹³ vg/kg, 3.5 x 10¹³ vg/kg, 3.6 x 10¹³ vg/kg, 3.7 x 10¹³ vg/kg, 3.8 x 10¹³ vg/kg, 3.9 x 10¹³ vg/kg, 4 x 10¹³ vg/kg, 4.1 x 10¹³ vg/kg, 4.2 x 10¹³ vg/kg, 4.3 x 10¹³ vg/kg, 4.4 x 10¹³ vg/kg, 4.5 x 10¹³ vg/kg, 4.6 x 10¹³ vg/kg, 4.7 x 10¹³ vg/kg, 4.8 x 10¹³ vg/kg, 4.9 x 10¹³ vg/kg, 5 x 10¹³ vg/kg, 5.1 x 10¹³ vg/kg, 5.2 x 10¹³ vg/kg, 5.3 x 10¹³ vg/kg, 5.4 x 10¹³ vg/kg, 5.5 x 10¹³ vg/kg, 5.6 x 10¹³ vg/kg, 5.7 x 10¹³ vg/kg, 5.8 x 10¹³ vg/kg, 5.9 x 10¹³ vg/kg, 6 x 10¹³ vg/kg, 6.1 x 10¹³ vg/kg, 6.2 x 10¹³ vg/kg, 6.3 x 10¹³ vg/kg, 6.4 x 10¹³ vg/kg, 6.5 x 10¹³ vg/kg, 6.6 x 10¹³ vg/kg, 6.7 x 10¹³ vg/kg, 6.8 x 10¹³ vg/kg, 6.9 x 10¹³ vg/kg, 7 x 10¹³ vg/kg, 7.1 x 10¹³ vg/kg, 7.2 x 10¹³ vg/kg, 7.3 x 10¹³ vg/kg, 7.4 x 10¹³ vg/kg, 7.5 x 10¹³ vg/kg, 7.6 x 10¹³ vg/kg, 7.7 x 10¹³ vg/kg, 7.8 x 10¹³ vg/kg, 7.9 x 10¹³ vg/kg, 8 x 10¹³ vg/kg, 8.1 x 10¹³ vg/kg, 8.2 x 10¹³ vg/kg, 8.3 x 10¹³ vg/kg, 8.4 x 10¹³ vg/kg, 8.5 x 10¹³ vg/kg, 8.6 x 10¹³ vg/kg, 8.7 x 10¹³ vg/kg, 8.8 x 10¹³ vg/kg, 8.9 x 10¹³ vg/kg, 9 x 10¹³ vg/kg, 9.1 x 10¹³ vg/kg, 9.2 x 10¹³ vg/kg, 9.3 x 10¹³ vg/kg, 9.4 x 10¹³ vg/kg, 9.5 x 10¹³ vg/kg, 9.6 x 10¹³ vg/kg, 9.7 x 10¹³ vg/kg, 9.8 x 10¹³ vg/kg, 9.9 x 10¹³ vg/kg, 1 x 10¹⁴ vg/kg, 1.1 x 10¹⁴ vg/kg, 1.2 x 10¹⁴ vg/kg, 1.3 x 10¹⁴ vg/kg, 1.4 x 10¹⁴ vg/kg, 1.5 x 10¹⁴ vg/kg, 1.6 x 10¹⁴ vg/kg, 1.7 x 10¹⁴ vg/kg, 1.8 x 10¹⁴ vg/kg, 1.9 x 10¹⁴ vg/kg, or 2 x 10¹⁴ vg/kg. In some examples, the AAV vector is administered to the patient in an amount of from about 2 x 10¹³ vg/kg to about 7 x 10¹³ vg/kg, such as in an amount of from about 2 x 10¹³ vg/kg to about 4 x 10¹³ vg/kg (e.g., about 3 x 10¹³ vg/kg) or in an amount of from about 5 x 10¹³ vg/kg to about 7 x 10¹³ vg/kg (e.g., about 6 x 10¹³ vg/kg).

In some examples of any of the above aspects of the disclosure, the AAV vector is administered to the patient in an amount of from about 3 x 10¹³ vg/kg to about 2 x 10¹⁴ vg/kg, such as an in amount of about 3 x 10¹³ vg/kg, 3.1 x 10¹³ vg/kg, 3.2 x 10¹³ vg/kg, 3.3 x 10¹³ vg/kg, 3.4 x 10¹³ vg/kg, 3.5 x 10¹³ vg/kg, 3.6 x 10¹³ vg/kg, 3.7 x 10¹³ vg/kg, 3.8 x 10¹³ vg/kg, 3.9 x 10¹³ vg/kg, 4 x 10¹³ vg/kg, 4.1 x 10¹³ vg/kg, 4.2 x 10¹³ vg/kg, 4.3 x 10¹³ vg/kg, 4.4 x 10¹³ vg/kg, 4.5 x 10¹³ vg/kg, 4.6 x 10¹³ vg/kg, 4.7 x 10¹³ vg/kg, 4.8 x 10¹³ vg/kg, 4.9 x 10¹³ vg/kg, 5 x 10¹³ vg/kg, 5.1 x 10¹³ vg/kg, 5.2 x 10¹³ vg/kg, 5.3 x 10¹³ vg/kg, 5.4 x 10¹³ vg/kg, 5.5 x 10¹³ vg/kg, 5.6 x 10¹³ vg/kg, 5.7 x 10¹³ vg/kg, 5.8 x 10¹³ vg/kg, 5.9 x 10¹³ vg/kg, 6 x 10¹³ vg/kg, 6.1 x 10¹³ vg/kg, 6.2 x 10¹³ vg/kg, 6.3 x 10¹³ vg/kg, 6.4 x 10¹³ vg/kg, 6.5 x 10¹³ vg/kg, 6.6 x 10¹³ vg/kg, 6.7 x 10¹³ vg/kg, 6.8 x 10¹³ vg/kg, 6.9 x 10¹³ vg/kg, 7 x 10¹³ vg/kg, 7.1 x 10¹³ vg/kg, 7.2 x 10¹³ vg/kg, 7.3 x 10¹³ vg/kg, 7.4 x 10¹³ vg/kg, 7.5 x 10¹³ vg/kg, 7.6 x 10¹³ vg/kg, 7.7 x 10¹³ vg/kg, 7.8 x 10¹³ vg/kg, 7.9 x 10¹³ vg/kg, 8 x 10¹³ vg/kg, 8.1 x 10¹³ vg/kg, 8.2 x 10¹³ vg/kg, 8.3 x 10¹³ vg/kg, 8.4 x 10¹³ vg/kg, 8.5 x 10¹³ vg/kg, 8.6 x 10¹³ vg/kg, 8.7 x 10¹³ vg/kg, 8.8 x 10¹³ vg/kg, 8.9 x 10¹³ vg/kg, 9 x 10¹³ vg/kg, 9.1 x 10¹³ vg/kg, 9.2 x 10¹³ vg/kg, 9.3 x 10¹³ vg/kg, 9.4 x 10¹³ vg/kg, 9.5 x 10¹³ vg/kg, 9.6 x 10¹³ vg/kg, 9.7 x 10¹³ vg/kg, 9.8 x 10¹³ vg/kg, 9.9 x 10¹³ vg/kg, 1 x 10¹⁴ vg/kg, 1.1 x 10¹⁴ vg/kg, 1.2 x 10¹⁴ vg/kg, 1.3 x 10¹⁴ vg/kg, 1.4 x 10¹⁴ vg/kg, 1.5 x 10¹⁴ vg/kg, 1.6 x 10¹⁴ vg/kg, 1.7 x 10¹⁴ vg/kg, 1.8 x 10¹⁴ vg/kg, 1.9 x 10¹⁴ vg/kg, or 2 x 10¹⁴ vg/kg.

In some examples of any of the above aspects of the disclosure, the AAV vector is administered to the patient in an amount of from about 4 x 10¹³ vg/kg to about 2 x 10¹⁴ vg/kg, such as an in amount of about 4 x 10¹³ vg/kg, 4.1 x 10¹³ vg/kg, 4.2 x 10¹³ vg/kg, 4.3 x 10¹³ vg/kg, 4.4 x 10¹³ vg/kg, 4.5 x 10¹³ vg/kg, 4.6 x 10¹³ vg/kg, 4.7 x 10¹³ vg/kg, 4.8 x 10¹³ vg/kg, 4.9 x 10¹³ vg/kg, 5 x 10¹³ vg/kg, 5.1 x 10¹³ vg/kg, 5.2 x 10¹³ vg/kg, 5.3 x 10¹³ vg/kg, 5.4 x 10¹³ vg/kg, 5.5 x 10¹³ vg/kg, 5.6 x 10¹³ vg/kg, 5.7 x 10¹³ vg/kg, 5.8 x 10¹³ vg/kg, 5.9 x 10¹³ vg/kg, 6 x 10¹³ vg/kg, 6.1 x 10¹³ vg/kg, 6.2 x 10¹³ vg/kg, 6.3 x 10¹³

In some examples of any of the above aspects of the disclosure, the AAV vector is administered to the patient in an amount of 1.5×10^{14} vg/kg.

In some examples of any of the above aspects of the disclosure, the AAV vector is administered to the patient in an amount of 1.6×10^{14} vg/kg.

5 In some examples of any of the above aspects of the disclosure, the AAV vector is administered to the patient in an amount of 1.7×10^{14} vg/kg.

In some examples of any of the above aspects of the disclosure, the AAV vector is administered to the patient in an amount of 1.8×10^{14} vg/kg.

10 In some examples of any of the above aspects of the disclosure, the AAV vector is administered to the patient in an amount of 1.9×10^{14} vg/kg.

In some examples of any of the above aspects of the disclosure, the AAV vector is administered to the patient in an amount of 2×10^{14} vg/kg.

15 In some examples of any of the above aspects of the disclosure, the AAV vector is administered to the patient in a single dose containing the specified amount. In some examples, the AAV vector is administered to the patient in two or more doses that, together, total the specified amount. For example, the AAV vector may be administered to the patient in from two to ten doses that, together, total the specified amount (e.g., in two, three, four, five, six, seven, eight, nine, or ten doses that, together, total the specified amount). In some examples, the AAV vector is administered to the patient in two, three, or four doses that, together, total the specified amount. In some examples, the AAV vector is administered to the patient in two doses that, together, total the specified amount.

20 In some examples, the two or more doses of the AAV vector that, together, total the specified amount are separated from one another, for example, by a year or more. In some examples, the two or more doses are administered to the patient within about 12 months of one another (e.g., within about 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 25 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, or 52 weeks of one another). For example, in some examples, the two or more 30 doses are administered to the patient within from about one week to about 48 weeks of one another (e.g., within about 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 35 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, or 48 weeks of one another). In some examples, the two or more doses are administered to the patient within from about two weeks to about 44 weeks of one another (e.g., within about 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks,

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24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, or 44 weeks of one another). In some examples, the two or more doses are administered to the patient within from about three weeks to about 40 weeks of one another (e.g., within about 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, or 40 weeks of one another). In some examples, the two or more doses are administered to the patient within from about four weeks to about 36 weeks of one another (e.g., within about 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, or 36 weeks of one another). In some examples, the two or more doses are administered to the patient within from about five weeks to about 32 weeks of one another (e.g., within about 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, or 32 weeks of one another). In some examples, the two or more doses are administered to the patient within from about six weeks to about 24 weeks of one another (e.g., within about 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, or 24 weeks of one another). In some examples, the two or more doses are administered to the patient within from about 12 weeks to about 20 weeks of one another (e.g., within about 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, or 20 weeks of one another). In some examples, the two or more doses are administered to the patient within about 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, or 19 weeks of one another.

In some examples, the AAV vector is administered to the patient in two or more doses that each, individually, contain the specified amount. For example, the AAV vector may be administered to the patient in from two to ten doses that each, individually, contain the specified amount (e.g., in two, three, four, five, six, seven, eight, nine, or ten doses that each, individually, contain the specified amount). In some examples, the AAV vector is administered to the patient in two, three, or four doses that each, individually, contain the specified amount. In some examples, the AAV vector is administered to the patient in two doses that each, individually, contain the specified amount.

In some examples, the AAV vector is administered to the patient by way of intravenous, intrathecal, intracisternal, intracerebroventricular, intramuscular, intradermal, transdermal, parenteral, intranasal, subcutaneous, percutaneous, intratracheal, intraperitoneal, intraarterial, intravascular, inhalation, perfusion, lavage, and/or oral administration. For example, the AAV vector may be administered to the patient by way of intravenous, intrathecal, intracisternal, intracerebroventricular, and/or intramuscular administration. In some examples, the AAV vector is administered to the patient

by way of intravenous and/or intrathecal administration. some examples, the AAV vector is administered to the patient by way of intravenous administration.

In some examples, the AAV is an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAVrh74, AAVrh.8, or AAVrh.10 serotype. The AAV may be a pseudotyped AAV, such as an AAV2/8 or AAV2/9. In some examples, the AAV contains a recombinant capsid protein.

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. The promoter may be, for example, a muscle creatine kinase (MCK) promoter, desmin promoter, chicken beta actin promoter, cytomegalovirus (CMV) promoter, myosin light chain-2 promoter, alpha actin promoter, troponin 1 promoter, Na⁺/Ca²⁺ 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 promoter is a MCK promoter. The MCK promoter may have, for example, a nucleic acid sequence that is at least 85% identical to SEQ ID NO: 1 (e.g., a nucleic acid sequence that is 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 1). In some examples, the MCK promoter has a nucleic acid sequence that is at least 90% identical to SEQ ID NO: 1 (e.g., a nucleic acid sequence that is 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 1). In some examples, the MCK promoter has a nucleic acid sequence that is at least 95% identical to SEQ ID NO: 1 (e.g., a nucleic acid sequence that is 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 1). In some examples, the MCK promoter has a nucleic acid sequence that is at least 97% identical to SEQ ID NO: 1 (e.g., a nucleic acid sequence that is 97%, 98%, 99%, or 100% identical to SEQ ID NO: 1). In some examples, the MCK promoter has a nucleic acid sequence that is at least 98% identical to SEQ ID NO: 1 (e.g., a nucleic acid sequence that is 98%, 99%, or 100% identical to SEQ ID NO: 1). In some examples, the MCK promoter has a nucleic acid sequence that is at least 99% identical to SEQ ID NO: 1 (e.g., a nucleic acid sequence that is 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9%, or 100% identical to SEQ ID NO: 1). In some examples, the MCK promoter has a nucleic acid sequence that is 100% identical to SEQ ID NO: 1.

In some examples, the transgene encoding GAA is operably linked to an enhancer that induces expression of the transgene in a muscle and/or neuronal cell. For example, the transgene encoding GAA may be operably linked to a CMV enhancer, a myocyte enhancer factor 2 (MEF2) enhancer, or a MyoD enhancer.

In some examples, the GAA has an amino acid sequence that is at least 85% identical to SEQ ID NO: 2 (e.g., an amino acid sequence that is 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 2). In some examples, the GAA has an amino acid sequence that is at least 90% identical to SEQ ID NO: 2 (e.g., an amino acid sequence that is 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 2). In some examples, the GAA has an amino acid sequence that is at least 95% identical to SEQ ID NO: 2 (e.g., an amino acid sequence that is 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 2). In

some examples, the GAA has an amino acid sequence that is at least 97% identical to SEQ ID NO: 2 (e.g., an amino acid sequence that is 97%, 98%, 99%, or 100% identical to SEQ ID NO: 2). In some examples, the GAA has an amino acid sequence that is at least 98% identical to SEQ ID NO: 2 (e.g., an amino acid sequence that is 98%, 99%, or 100% identical to SEQ ID NO: 2). In some examples, the GAA
5 has an amino acid sequence that is at least 99% identical to SEQ ID NO: 2 (e.g., an amino acid sequence that is 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9%, or 100% identical to SEQ ID NO: 2). In some examples, the GAA has an amino acid sequence that is 100% identical to SEQ ID NO: 2. In some examples, the GAA differs from human wild-type GAA only by way of one or more conservative amino acid substitutions. In some examples, the GAA differs from human wild-type GAA by
10 way of one or more non-conservative amino acid substitutions.

In some examples, the transgene encoding GAA has a nucleic acid sequence that is at least 85% identical to SEQ ID NO: 3 (e.g., a nucleic acid sequence that is 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 3). In some examples, the transgene encoding GAA has a nucleic acid sequence that is at least 90% identical to SEQ ID NO: 3
15 (e.g., a nucleic acid sequence that is 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 3). In some examples, the transgene encoding GAA has a nucleic acid sequence that is at least 95% identical to SEQ ID NO: 3 (e.g., a nucleic acid sequence that is 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 3). In some examples, the transgene encoding GAA has a nucleic acid sequence that is at least 97% identical to SEQ ID NO: 3 (e.g., a nucleic acid sequence
20 that is 97%, 98%, 99%, or 100% identical to SEQ ID NO: 3). In some examples, the transgene encoding GAA has a nucleic acid sequence that is at least 98% identical to SEQ ID NO: 3 (e.g., a nucleic acid sequence that is 98%, 99%, or 100% identical to SEQ ID NO: 3). In some examples, the transgene encoding GAA has a nucleic acid sequence that is at least 99% identical to SEQ ID NO: 3 (e.g., a nucleic acid sequence that is 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9%, or 100%
25 identical to SEQ ID NO: 3). In some examples, the transgene encoding GAA has a nucleic acid sequence that is 100% identical to SEQ ID NO: 3.

In some examples, the patient has infantile-onset Pompe disease. The patient may be, for example, from about one month to about one year of age (e.g., about one month, two months, three months, four months, five months, six months, seven months, eight months, nine months, ten months,
30 eleven months, or twelve months of age). In some examples, the patient is from about one month to about six months of age (e.g., about month, two months, three months, four months, five months, or six months of age).

In some examples, prior to administration of the AAV vector to the patient, 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.
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In some examples, the patient has late-onset Pompe disease. The patient may exhibit, for example, endogenous GAA activity of from about 1% to about 40% of the endogenous GAA activity of a human of the same gender and similar body mass index that does not have Pompe disease.

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In some examples, the patient has not previously received GAA enzyme replacement therapy. In some examples, the patient has previously received GAA enzyme replacement therapy.

In some examples, following administration of the AAV vector to the patient, the patient exhibits endogenous GAA activity of from about 50% to about 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, following administration of the AAV vector to the patient, the patient exhibits a reduction in glycogen in skeletal muscle, cardiac muscle, and/or neuronal tissue.

In one aspect, the disclosure provides use of an agent that increases GAA expression in the manufacture of a medicament for treating Pompe disease in a human patient in need thereof, wherein the agent is to be administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in a human subject of the same gender and similar body mass index as the patient upon administration to the subject of an AAV2/8 vector comprising a transgene encoding GAA in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg, wherein the transgene encoding GAA is operably linked to a MCK promoter. In another example, the disclosure features a method of treating Pompe disease in a human patient in need thereof by administering to the patient an agent that increases GAA expression. In accordance with this example, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in a human subject of the same gender and similar body mass index as the patient upon administration to the subject of an AAV2/8 vector containing a transgene encoding GAA in an amount of from about 1×10^{13} vg/kg to about 5×10^{14} vg/kg (e.g., in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg), wherein the transgene encoding GAA is operably linked to a MCK promoter. For example, the agent may be administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index upon administration to the subject of the AAV vector in an amount of about 1×10^{13} vg/kg, 1.1×10^{13} vg/kg, 1.2×10^{13} vg/kg, 1.3×10^{13} vg/kg, 1.4×10^{13} vg/kg, 1.5×10^{13} vg/kg, 1.6×10^{13} vg/kg, 1.7×10^{13} vg/kg, 1.8×10^{13} vg/kg, 1.9×10^{13} vg/kg, 2×10^{13} vg/kg, 2.1×10^{13} vg/kg, 2.2×10^{13} vg/kg, 2.3×10^{13} vg/kg, 2.4×10^{13} vg/kg, 2.5×10^{13} vg/kg, 2.6×10^{13} vg/kg, 2.7×10^{13} vg/kg, 2.8×10^{13} vg/kg, 2.9×10^{13} vg/kg, 3×10^{13} vg/kg, 3.1×10^{13} vg/kg, 3.2×10^{13} vg/kg, 3.3×10^{13} vg/kg, 3.4×10^{13} vg/kg, 3.5×10^{13} vg/kg, 3.6×10^{13} vg/kg, 3.7×10^{13} vg/kg, 3.8×10^{13} vg/kg, 3.9×10^{13} vg/kg, 4×10^{13} vg/kg, 4.1×10^{13} vg/kg, 4.2×10^{13} vg/kg, 4.3×10^{13} vg/kg, 4.4×10^{13} vg/kg, 4.5×10^{13} vg/kg, 4.6×10^{13} vg/kg, 4.7×10^{13} vg/kg, 4.8×10^{13} vg/kg, 4.9×10^{13} vg/kg, 5×10^{13} vg/kg, 5.1×10^{13} vg/kg, 5.2×10^{13} vg/kg, 5.3×10^{13} vg/kg, 5.4×10^{13} vg/kg, 5.5×10^{13} vg/kg, 5.6×10^{13} vg/kg, 5.7×10^{13} vg/kg, 5.8×10^{13} vg/kg, 5.9×10^{13} vg/kg, 6×10^{13} vg/kg, 6.1×10^{13} vg/kg, 6.2×10^{13} vg/kg, 6.3×10^{13} vg/kg, 6.4×10^{13} vg/kg, 6.5×10^{13} vg/kg, 6.6×10^{13} vg/kg, 6.7×10^{13} vg/kg, 6.8×10^{13} vg/kg, 6.9×10^{13} vg/kg, 7×10^{13} vg/kg, 7.1×10^{13} vg/kg, 7.2×10^{13} vg/kg, 7.3×10^{13} vg/kg, 7.4×10^{13} vg/kg, 7.5×10^{13} vg/kg, 7.6×10^{13} vg/kg, 7.7×10^{13} vg/kg, 7.8×10^{13} vg/kg, 7.9×10^{13} vg/kg, 8×10^{13} vg/kg, 8.1×10^{13} vg/kg, 8.2×10^{13} vg/kg, 8.3×10^{13} vg/kg, 8.4×10^{13} vg/kg, 8.5×10^{13} vg/kg, 8.6×10^{13} vg/kg, 8.7×10^{13} vg/kg, 8.8×10^{13} vg/kg, 8.9×10^{13} vg/kg, 9×10^{13} vg/kg, 9.1×10^{13} vg/kg, 9.2×10^{13} vg/kg, 9.3×10^{13} vg/kg, 9.4×10^{13} vg/kg, 9.5×10^{13} vg/kg, 9.6×10^{13} vg/kg, 9.7×10^{13} vg/kg, 9.8×10^{13} vg/kg, 9.9×10^{13} vg/kg, 1×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.9×10^{14} vg/kg, 2×10^{14} vg/kg, 2.1×10^{14} vg/kg, 2.2×10^{14} vg/kg, 2.3×10^{14} vg/kg, 2.4×10^{14} vg/kg, 2.5×10^{14} vg/kg, 2.6×10^{14} vg/kg, 2.7×10^{14} vg/kg, 2.8×10^{14} vg/kg, 2.9×10^{14} vg/kg, 3×10^{14} vg/kg, 3.1×10^{14} vg/kg, 3.2×10^{14} vg/kg, 3.3×10^{14} vg/kg, 3.4×10^{14} vg/kg, 3.5×10^{14} vg/kg, 3.6×10^{14} vg/kg, 3.7×10^{14} vg/kg, 3.8×10^{14} vg/kg, 3.9×10^{14} vg/kg, 4×10^{14} vg/kg, 4.1×10^{14} vg/kg.

vg/kg, 4.2×10^{14} vg/kg, 4.3×10^{14} vg/kg, 4.4×10^{14} vg/kg, 4.5×10^{14} vg/kg, 4.6×10^{14} vg/kg, 4.7×10^{14} vg/kg, 4.8×10^{14} vg/kg, 4.9×10^{14} vg/kg, or 5×10^{14} vg/kg.

In another aspect, the disclosure provides use of an agent that increases GAA expression in the manufacture of a medicament for improving muscle function in a human patient diagnosed as having Pompe disease, wherein the agent is to be administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in a human subject of the same gender and similar body mass index as the patient upon administration to the subject of an AAV2/8 vector comprising a transgene encoding GAA in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg, wherein the transgene encoding GAA is operably linked to a MCK promoter. In another example, the disclosure features a method of improving muscle function in a human patient diagnosed as having Pompe disease by administering to the patient an agent that increases GAA expression. In accordance with this example, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in a human subject of the same gender and similar body mass index as the patient upon administration to the subject of an AAV2/8 vector containing a transgene encoding GAA in an amount of from about 1×10^{13} vg/kg to about 5×10^{14} vg/kg (e.g., in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg), wherein the transgene encoding GAA is operably linked to a MCK promoter. For example, the agent may be administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index upon administration to the subject of the AAV vector in an amount of about 1×10^{13} vg/kg, 1.1×10^{13} vg/kg, 1.2×10^{13} vg/kg, 1.3×10^{13} vg/kg, 1.4×10^{13} vg/kg, 1.5×10^{13} vg/kg, 1.6×10^{13} vg/kg, 1.7×10^{13} vg/kg, 1.8×10^{13} vg/kg, 1.9×10^{13} vg/kg, 2×10^{13} vg/kg, 2.1×10^{13} vg/kg, 2.2×10^{13} vg/kg, 2.3×10^{13} vg/kg, 2.4×10^{13} vg/kg, 2.5×10^{13} vg/kg, 2.6×10^{13} vg/kg, 2.7×10^{13} vg/kg, 2.8×10^{13} vg/kg, 2.9×10^{13} vg/kg, 3×10^{13} vg/kg, 3.1×10^{13} vg/kg, 3.2×10^{13} vg/kg, 3.3×10^{13} vg/kg, 3.4×10^{13} vg/kg, 3.5×10^{13} vg/kg, 3.6×10^{13} vg/kg, 3.7×10^{13} vg/kg, 3.8×10^{13} vg/kg, 3.9×10^{13} vg/kg, 4×10^{13} vg/kg, 4.1×10^{13} vg/kg, 4.2×10^{13} vg/kg, 4.3×10^{13} vg/kg, 4.4×10^{13} vg/kg, 4.5×10^{13} vg/kg, 4.6×10^{13} vg/kg, 4.7×10^{13} vg/kg, 4.8×10^{13} vg/kg, 4.9×10^{13} vg/kg, 5×10^{13} vg/kg, 5.1×10^{13} vg/kg, 5.2×10^{13} vg/kg, 5.3×10^{13} vg/kg, 5.4×10^{13} vg/kg, 5.5×10^{13} vg/kg, 5.6×10^{13} vg/kg, 5.7×10^{13} vg/kg, 5.8×10^{13} vg/kg, 5.9×10^{13} vg/kg, 6×10^{13} vg/kg, 6.1×10^{13} vg/kg, 6.2×10^{13} vg/kg, 6.3×10^{13} vg/kg, 6.4×10^{13} vg/kg, 6.5×10^{13} vg/kg, 6.6×10^{13} vg/kg, 6.7×10^{13} vg/kg, 6.8×10^{13} vg/kg, 6.9×10^{13} vg/kg, 7×10^{13} vg/kg, 7.1×10^{13} vg/kg, 7.2×10^{13} vg/kg, 7.3×10^{13} vg/kg, 7.4×10^{13} vg/kg, 7.5×10^{13} vg/kg, 7.6×10^{13} vg/kg, 7.7×10^{13} vg/kg, 7.8×10^{13} vg/kg, 7.9×10^{13} vg/kg, 8×10^{13} vg/kg, 8.1×10^{13} vg/kg, 8.2×10^{13} vg/kg, 8.3×10^{13} vg/kg, 8.4×10^{13} vg/kg, 8.5×10^{13} vg/kg, 8.6×10^{13} vg/kg, 8.7×10^{13} vg/kg, 8.8×10^{13} vg/kg, 8.9×10^{13} vg/kg, 9×10^{13} vg/kg, 9.1×10^{13} vg/kg, 9.2×10^{13} vg/kg, 9.3×10^{13} vg/kg, 9.4×10^{13} vg/kg, 9.5×10^{13} vg/kg, 9.6×10^{13} vg/kg, 9.7×10^{13} vg/kg, 9.8×10^{13} vg/kg, 9.9×10^{13} vg/kg, 1×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.9×10^{14} vg/kg, 2×10^{14} vg/kg, 2.1×10^{14} vg/kg, 2.2×10^{14} vg/kg, 2.3×10^{14} vg/kg, 2.4×10^{14} vg/kg, 2.5×10^{14} vg/kg, 2.6×10^{14} vg/kg, 2.7×10^{14} vg/kg, 2.8×10^{14} vg/kg, 2.9×10^{14} vg/kg, 3×10^{14} vg/kg, 3.1×10^{14} vg/kg, 3.2×10^{14} vg/kg, 3.3×10^{14} vg/kg, 3.4×10^{14} vg/kg, 3.5×10^{14} vg/kg, 3.6×10^{14} vg/kg, 3.7×10^{14} vg/kg, 3.8×10^{14} vg/kg, 3.9×10^{14} vg/kg, 4×10^{14} vg/kg, 4.1×10^{14} vg/kg, 4.2×10^{14} vg/kg, 4.3×10^{14} vg/kg, 4.4×10^{14} vg/kg, 4.5×10^{14} vg/kg, 4.6×10^{14} vg/kg, 4.7×10^{14} vg/kg, 4.8×10^{14} vg/kg, 4.9×10^{14} vg/kg, or 5×10^{14} vg/kg.

In yet another aspect, the disclosure provides use of an agent that increases GAA expression in the manufacture of a medicament for reducing glycogen accumulation in a human patient diagnosed as having Pompe disease, wherein the agent is to be administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in a human subject of the same gender and similar body mass index as the patient upon administration to the subject of an AAV2/8 vector comprising a transgene encoding GAA in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg, wherein the transgene encoding GAA is operably linked to a MCK promoter. In another example, the disclosure features a method of reducing glycogen accumulation in a human patient diagnosed as having Pompe disease by administering to the patient an agent that increases GAA expression. In accordance with this example, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA

activity observed in a human subject of the same gender and similar body mass index as the patient upon administration to the subject of an AAV2/8 vector containing a transgene encoding GAA in an amount of from about 1×10^{13} vg/kg to about 5×10^{14} vg/kg (e.g., in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg), wherein the transgene encoding GAA is operably linked to a MCK promoter. For

5 example, the agent may be administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index upon administration to the subject of the AAV vector in an amount of about 1×10^{13} vg/kg, 1.1×10^{13} vg/kg, 1.2×10^{13} vg/kg, 1.3×10^{13} vg/kg, 1.4×10^{13} vg/kg, 1.5×10^{13} vg/kg, 1.6×10^{13} vg/kg, 1.7×10^{13} vg/kg, 1.8×10^{13} vg/kg, 1.9×10^{13} vg/kg, 2×10^{13} vg/kg, 2.1×10^{13} vg/kg, 2.2×10^{13} vg/kg, 2.3×10^{13} vg/kg, 2.4×10^{13} vg/kg, 2.5×10^{13} vg/kg, 2.6×10^{13} vg/kg, 2.7×10^{13} vg/kg, 2.8×10^{13} vg/kg, 2.9×10^{13} vg/kg, 3×10^{13} vg/kg, 3.1×10^{13} vg/kg, 3.2×10^{13} vg/kg, 3.3×10^{13} vg/kg, 3.4×10^{13} vg/kg, 3.5×10^{13} vg/kg, 3.6×10^{13} vg/kg, 3.7×10^{13} vg/kg, 3.8×10^{13} vg/kg, 3.9×10^{13} vg/kg, 4×10^{13} vg/kg, 4.1×10^{13} vg/kg, 4.2×10^{13} vg/kg, 4.3×10^{13} vg/kg, 4.4×10^{13} vg/kg, 4.5×10^{13} vg/kg, 4.6×10^{13} vg/kg, 4.7×10^{13} vg/kg, 4.8×10^{13} vg/kg, 4.9×10^{13} vg/kg, 5×10^{13} vg/kg, 5.1×10^{13} vg/kg, 5.2×10^{13} vg/kg, 5.3×10^{13} vg/kg, 5.4×10^{13} vg/kg, 5.5×10^{13} vg/kg, 5.6×10^{13} vg/kg, 5.7×10^{13} vg/kg, 5.8×10^{13} vg/kg, 5.9×10^{13} vg/kg, 6×10^{13} vg/kg, 6.1×10^{13} vg/kg, 6.2×10^{13} vg/kg, 6.3×10^{13} vg/kg, 6.4×10^{13} vg/kg, 6.5×10^{13} vg/kg, 6.6×10^{13} vg/kg, 6.7×10^{13} vg/kg, 6.8×10^{13} vg/kg, 6.9×10^{13} vg/kg, 7×10^{13} vg/kg, 7.1×10^{13} vg/kg, 7.2×10^{13} vg/kg, 7.3×10^{13} vg/kg, 7.4×10^{13} vg/kg, 7.5×10^{13} vg/kg, 7.6×10^{13} vg/kg, 7.7×10^{13} vg/kg, 7.8×10^{13} vg/kg, 7.9×10^{13} vg/kg, 8×10^{13} vg/kg, 8.1×10^{13} vg/kg, 8.2×10^{13} vg/kg, 8.3×10^{13} vg/kg, 8.4×10^{13} vg/kg, 8.5×10^{13} vg/kg, 8.6×10^{13} vg/kg, 8.7×10^{13} vg/kg, 8.8×10^{13} vg/kg, 8.9×10^{13} vg/kg, 9×10^{13} vg/kg, 9.1×10^{13} vg/kg, 9.2×10^{13} vg/kg, 9.3×10^{13} vg/kg, 9.4×10^{13} vg/kg, 9.5×10^{13} vg/kg, 9.6×10^{13} vg/kg, 9.7×10^{13} vg/kg, 9.8×10^{13} vg/kg, 9.9×10^{13} vg/kg, 1×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.9×10^{14} vg/kg, 2×10^{14} vg/kg, 2.1×10^{14} vg/kg, 2.2×10^{14} vg/kg, 2.3×10^{14} vg/kg, 2.4×10^{14} vg/kg, 2.5×10^{14} vg/kg, 2.6×10^{14} vg/kg, 2.7×10^{14} vg/kg, 2.8×10^{14} vg/kg, 2.9×10^{14} vg/kg, 3×10^{14} vg/kg, 3.1×10^{14} vg/kg, 3.2×10^{14} vg/kg, 3.3×10^{14} vg/kg, 3.4×10^{14} vg/kg, 3.5×10^{14} vg/kg, 3.6×10^{14} vg/kg, 3.7×10^{14} vg/kg, 3.8×10^{14} vg/kg, 3.9×10^{14} vg/kg, 4×10^{14} vg/kg, 4.1×10^{14} vg/kg, 4.2×10^{14} vg/kg, 4.3×10^{14} vg/kg, 4.4×10^{14} vg/kg, 4.5×10^{14} vg/kg, 4.6×10^{14} vg/kg, 4.7×10^{14} vg/kg, 4.8×10^{14} vg/kg, 4.9×10^{14} vg/kg, or 5×10^{14} vg/kg. In some examples of this aspect, administration of the agent to the patient reduces glycogen accumulation in muscle tissue (e.g., in cardiac and/or skeletal muscle tissue) and/or in neuronal tissue.

In one aspect, the disclosure provides use of an agent that increases GAA expression in the manufacture of a medicament for improving pulmonary function in a human patient diagnosed as having Pompe disease, wherein the agent is to be administered to the patient in an amount sufficient to achieve

35 a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in a human subject of the same gender and similar body mass index as the patient upon administration to the subject of an AAV2/8 vector comprising a transgene encoding GAA in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg, wherein the transgene encoding GAA is operably linked to a MCK promoter. In another example, the disclosure features a method of improving pulmonary function in a human patient

40 diagnosed as having Pompe disease by administering to the patient an agent that increases GAA expression. In accordance with this example, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in a human subject of the same gender and similar body mass index as the patient upon administration to the subject of an AAV2/8 vector containing a transgene encoding GAA in an amount of

45 from about 1×10^{13} vg/kg to about 5×10^{14} vg/kg (e.g., in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg), wherein the transgene encoding GAA is operably linked to a MCK promoter. For

example, the agent may be administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index upon administration to the subject of the AAV vector in an amount of about 1×10^{13} vg/kg, 1.1×10^{13} vg/kg, 1.2×10^{13} vg/kg, 1.3×10^{13} vg/kg, 1.4×10^{13} vg/kg, 1.5×10^{13} vg/kg, 1.6×10^{13} vg/kg, 1.7×10^{13} vg/kg, 1.8×10^{13} vg/kg, 1.9×10^{13} vg/kg, 2×10^{13} vg/kg, 2.1×10^{13} vg/kg, 2.2×10^{13} vg/kg, 2.3×10^{13} vg/kg, 2.4×10^{13} vg/kg, 2.5×10^{13} vg/kg, 2.6×10^{13} vg/kg, 2.7×10^{13} vg/kg, 2.8×10^{13} vg/kg, 2.9×10^{13} vg/kg, 3×10^{13} vg/kg, 3.1×10^{13} vg/kg, 3.2×10^{13} vg/kg, 3.3×10^{13} vg/kg, 3.4×10^{13} vg/kg, 3.5×10^{13} vg/kg, 3.6×10^{13} vg/kg, 3.7×10^{13} vg/kg, 3.8×10^{13} vg/kg, 3.9×10^{13} vg/kg, 4×10^{13} vg/kg, 4.1×10^{13} vg/kg, 4.2×10^{13} vg/kg, 4.3×10^{13} vg/kg, 4.4×10^{13} vg/kg, 4.5×10^{13} vg/kg, 4.6×10^{13} vg/kg, 4.7×10^{13} vg/kg, 4.8×10^{13} vg/kg, 4.9×10^{13} vg/kg, 5×10^{13} vg/kg, 5.1×10^{13} vg/kg, 5.2×10^{13} vg/kg, 5.3×10^{13} vg/kg, 5.4×10^{13} vg/kg, 5.5×10^{13} vg/kg, 5.6×10^{13} vg/kg, 5.7×10^{13} vg/kg, 5.8×10^{13} vg/kg, 5.9×10^{13} vg/kg, 6×10^{13} vg/kg, 6.1×10^{13} vg/kg, 6.2×10^{13} vg/kg, 6.3×10^{13} vg/kg, 6.4×10^{13} vg/kg, 6.5×10^{13} vg/kg, 6.6×10^{13} vg/kg, 6.7×10^{13} vg/kg, 6.8×10^{13} vg/kg, 6.9×10^{13} vg/kg, 7×10^{13} vg/kg, 7.1×10^{13} vg/kg, 7.2×10^{13} vg/kg, 7.3×10^{13} vg/kg, 7.4×10^{13} vg/kg, 7.5×10^{13} vg/kg, 7.6×10^{13} vg/kg, 7.7×10^{13} vg/kg, 7.8×10^{13} vg/kg, 7.9×10^{13} vg/kg, 8×10^{13} vg/kg, 8.1×10^{13} vg/kg, 8.2×10^{13} vg/kg, 8.3×10^{13} vg/kg, 8.4×10^{13} vg/kg, 8.5×10^{13} vg/kg, 8.6×10^{13} vg/kg, 8.7×10^{13} vg/kg, 8.8×10^{13} vg/kg, 8.9×10^{13} vg/kg, 9×10^{13} vg/kg, 9.1×10^{13} vg/kg, 9.2×10^{13} vg/kg, 9.3×10^{13} vg/kg, 9.4×10^{13} vg/kg, 9.5×10^{13} vg/kg, 9.6×10^{13} vg/kg, 9.7×10^{13} vg/kg, 9.8×10^{13} vg/kg, 9.9×10^{13} vg/kg, 1×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.9×10^{14} vg/kg, 2×10^{14} vg/kg, 2.1×10^{14} vg/kg, 2.2×10^{14} vg/kg, 2.3×10^{14} vg/kg, 2.4×10^{14} vg/kg, 2.5×10^{14} vg/kg, 2.6×10^{14} vg/kg, 2.7×10^{14} vg/kg, 2.8×10^{14} vg/kg, 2.9×10^{14} vg/kg, 3×10^{14} vg/kg, 3.1×10^{14} vg/kg, 3.2×10^{14} vg/kg, 3.3×10^{14} vg/kg, 3.4×10^{14} vg/kg, 3.5×10^{14} vg/kg, 3.6×10^{14} vg/kg, 3.7×10^{14} vg/kg, 3.8×10^{14} vg/kg, 3.9×10^{14} vg/kg, 4×10^{14} vg/kg, 4.1×10^{14} vg/kg, 4.2×10^{14} vg/kg, 4.3×10^{14} vg/kg, 4.4×10^{14} vg/kg, 4.5×10^{14} vg/kg, 4.6×10^{14} vg/kg, 4.7×10^{14} vg/kg, 4.8×10^{14} vg/kg, 4.9×10^{14} vg/kg, or 5×10^{14} vg/kg.

In another aspect, the disclosure provides use of an agent that increases GAA expression in the manufacture of a medicament for increasing GAA expression in a human patient diagnosed as having Pompe disease, wherein the agent is to be administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in a human subject of the same gender and similar body mass index as the patient upon administration to the subject of an AAV2/8 vector comprising a transgene encoding GAA in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg, wherein the transgene encoding GAA is operably linked to a MCK promoter. In another example, the disclosure features a method of increasing GAA expression in a human patient diagnosed as having Pompe disease by administering to the patient an agent that increases GAA expression. In accordance with this example, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in a human subject of the same gender and similar body mass index as the patient upon administration to the subject of an AAV2/8 vector containing a transgene encoding GAA in an amount of from about 1×10^{13} vg/kg to about 5×10^{14} vg/kg (e.g., in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg), wherein the transgene encoding GAA is operably linked to a MCK promoter. For example, the agent may be administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index upon administration to the subject of the AAV vector in an amount of about 1×10^{13} vg/kg, 1.1×10^{13} vg/kg, 1.2×10^{13} vg/kg, 1.3×10^{13} vg/kg, 1.4×10^{13} vg/kg, 1.5×10^{13} vg/kg, 1.6×10^{13} vg/kg, 1.7×10^{13} vg/kg, 1.8×10^{13} vg/kg, 1.9×10^{13} vg/kg, 2×10^{13} vg/kg, 2.1×10^{13} vg/kg, 2.2×10^{13} vg/kg, 2.3×10^{13} vg/kg, 2.4×10^{13} vg/kg, 2.5×10^{13} vg/kg, 2.6×10^{13} vg/kg, 2.7×10^{13}

5 vg/kg, 2.8 x 10¹³ vg/kg, 2.9 x 10¹³ vg/kg, 3 x 10¹³ vg/kg, 3.1 x 10¹³ vg/kg, 3.2 x 10¹³ vg/kg, 3.3 x 10¹³ vg/kg, 3.4 x 10¹³ vg/kg, 3.5 x 10¹³ vg/kg, 3.6 x 10¹³ vg/kg, 3.7 x 10¹³ vg/kg, 3.8 x 10¹³ vg/kg, 3.9 x 10¹³ vg/kg, 4 x 10¹³ vg/kg, 4.1 x 10¹³ vg/kg, 4.2 x 10¹³ vg/kg, 4.3 x 10¹³ vg/kg, 4.4 x 10¹³ vg/kg, 4.5 x 10¹³ vg/kg, 4.6 x 10¹³ vg/kg, 4.7 x 10¹³ vg/kg, 4.8 x 10¹³ vg/kg, 4.9 x 10¹³ vg/kg, 5 x 10¹³ vg/kg, 5.1 x 10¹³ vg/kg, 5.2 x 10¹³ vg/kg, 5.3 x 10¹³ vg/kg, 5.4 x 10¹³ vg/kg, 5.5 x 10¹³ vg/kg, 5.6 x 10¹³ vg/kg, 5.7 x 10¹³ vg/kg, 5.8 x 10¹³ vg/kg, 5.9 x 10¹³ vg/kg, 6 x 10¹³ vg/kg, 6.1 x 10¹³ vg/kg, 6.2 x 10¹³ vg/kg, 6.3 x 10¹³ vg/kg, 6.4 x 10¹³ vg/kg, 6.5 x 10¹³ vg/kg, 6.6 x 10¹³ vg/kg, 6.7 x 10¹³ vg/kg, 6.8 x 10¹³ vg/kg, 6.9 x 10¹³ vg/kg, 7 x 10¹³ vg/kg, 7.1 x 10¹³ vg/kg, 7.2 x 10¹³ vg/kg, 7.3 x 10¹³ vg/kg, 7.4 x 10¹³ vg/kg, 7.5 x 10¹³ vg/kg, 7.6 x 10¹³ vg/kg, 7.7 x 10¹³ vg/kg, 7.8 x 10¹³ vg/kg, 7.9 x 10¹³ vg/kg, 8 x 10¹³ vg/kg, 8.1 x 10¹³ vg/kg, 8.2 x 10¹³ vg/kg, 8.3 x 10¹³ vg/kg, 8.4 x 10¹³ vg/kg, 8.5 x 10¹³ vg/kg, 8.6 x 10¹³ vg/kg, 8.7 x 10¹³ vg/kg, 8.8 x 10¹³ vg/kg, 8.9 x 10¹³ vg/kg, 9 x 10¹³ vg/kg, 9.1 x 10¹³ vg/kg, 9.2 x 10¹³ vg/kg, 9.3 x 10¹³ vg/kg, 9.4 x 10¹³ vg/kg, 9.5 x 10¹³ vg/kg, 9.6 x 10¹³ vg/kg, 9.7 x 10¹³ vg/kg, 9.8 x 10¹³ vg/kg, 9.9 x 10¹³ vg/kg, 1 x 10¹⁴ vg/kg, 1.1 x 10¹⁴ vg/kg, 1.2 x 10¹⁴ vg/kg, 1.3 x 10¹⁴ vg/kg, 1.4 x 10¹⁴ vg/kg, 1.5 x 10¹⁴ vg/kg, 1.6 x 10¹⁴ vg/kg, 1.7 x 10¹⁴ vg/kg, 1.8 x 10¹⁴ vg/kg, 1.9 x 10¹⁴ vg/kg, 2 x 10¹⁴ vg/kg, 2.1 x 10¹⁴ vg/kg, 2.2 x 10¹⁴ vg/kg, 2.3 x 10¹⁴ vg/kg, 2.4 x 10¹⁴ vg/kg, 2.5 x 10¹⁴ vg/kg, 2.6 x 10¹⁴ vg/kg, 2.7 x 10¹⁴ vg/kg, 2.8 x 10¹⁴ vg/kg, 2.9 x 10¹⁴ vg/kg, 3 x 10¹⁴ vg/kg, 3.1 x 10¹⁴ vg/kg, 3.2 x 10¹⁴ vg/kg, 3.3 x 10¹⁴ vg/kg, 3.4 x 10¹⁴ vg/kg, 3.5 x 10¹⁴ vg/kg, 3.6 x 10¹⁴ vg/kg, 3.7 x 10¹⁴ vg/kg, 3.8 x 10¹⁴ vg/kg, 3.9 x 10¹⁴ vg/kg, 4 x 10¹⁴ vg/kg, 4.1 x 10¹⁴ vg/kg, 4.2 x 10¹⁴ vg/kg, 4.3 x 10¹⁴ vg/kg, 4.4 x 10¹⁴ vg/kg, 4.5 x 10¹⁴ vg/kg, 4.6 x 10¹⁴ vg/kg, 4.7 x 10¹⁴ vg/kg, 4.8 x 10¹⁴ vg/kg, 4.9 x 10¹⁴ vg/kg, or 5 x 10¹⁴ vg/kg.

20 In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of from about 2 x 10¹³ vg/kg to about 2 x 10¹⁴ vg/kg, such as an in amount of about 2 x 10¹³ vg/kg, 2.1 x 10¹³
 25 vg/kg, 2.2 x 10¹³ vg/kg, 2.3 x 10¹³ vg/kg, 2.4 x 10¹³ vg/kg, 2.5 x 10¹³ vg/kg, 2.6 x 10¹³ vg/kg, 2.7 x 10¹³ vg/kg, 2.8 x 10¹³ vg/kg, 2.9 x 10¹³ vg/kg, 3 x 10¹³ vg/kg, 3.1 x 10¹³ vg/kg, 3.2 x 10¹³ vg/kg, 3.3 x 10¹³ vg/kg, 3.4 x 10¹³ vg/kg, 3.5 x 10¹³ vg/kg, 3.6 x 10¹³ vg/kg, 3.7 x 10¹³ vg/kg, 3.8 x 10¹³ vg/kg, 3.9 x 10¹³ vg/kg, 4 x 10¹³ vg/kg, 4.1 x 10¹³ vg/kg, 4.2 x 10¹³ vg/kg, 4.3 x 10¹³ vg/kg, 4.4 x 10¹³ vg/kg, 4.5 x 10¹³ vg/kg, 4.6 x 10¹³ vg/kg, 4.7 x 10¹³ vg/kg, 4.8 x 10¹³ vg/kg, 4.9 x 10¹³ vg/kg, 5 x 10¹³ vg/kg, 5.1 x 10¹³
 30 vg/kg, 5.2 x 10¹³ vg/kg, 5.3 x 10¹³ vg/kg, 5.4 x 10¹³ vg/kg, 5.5 x 10¹³ vg/kg, 5.6 x 10¹³ vg/kg, 5.7 x 10¹³ vg/kg, 5.8 x 10¹³ vg/kg, 5.9 x 10¹³ vg/kg, 6 x 10¹³ vg/kg, 6.1 x 10¹³ vg/kg, 6.2 x 10¹³ vg/kg, 6.3 x 10¹³ vg/kg, 6.4 x 10¹³ vg/kg, 6.5 x 10¹³ vg/kg, 6.6 x 10¹³ vg/kg, 6.7 x 10¹³ vg/kg, 6.8 x 10¹³ vg/kg, 6.9 x 10¹³ vg/kg, 7 x 10¹³ vg/kg, 7.1 x 10¹³ vg/kg, 7.2 x 10¹³ vg/kg, 7.3 x 10¹³ vg/kg, 7.4 x 10¹³ vg/kg, 7.5 x 10¹³ vg/kg, 7.6 x 10¹³ vg/kg, 7.7 x 10¹³ vg/kg, 7.8 x 10¹³ vg/kg, 7.9 x 10¹³ vg/kg, 8 x 10¹³ vg/kg, 8.1 x 10¹³
 35 vg/kg, 8.2 x 10¹³ vg/kg, 8.3 x 10¹³ vg/kg, 8.4 x 10¹³ vg/kg, 8.5 x 10¹³ vg/kg, 8.6 x 10¹³ vg/kg, 8.7 x 10¹³ vg/kg, 8.8 x 10¹³ vg/kg, 8.9 x 10¹³ vg/kg, 9 x 10¹³ vg/kg, 9.1 x 10¹³ vg/kg, 9.2 x 10¹³ vg/kg, 9.3 x 10¹³ vg/kg, 9.4 x 10¹³ vg/kg, 9.5 x 10¹³ vg/kg, 9.6 x 10¹³ vg/kg, 9.7 x 10¹³ vg/kg, 9.8 x 10¹³ vg/kg, 9.9 x 10¹³ vg/kg, 1 x 10¹⁴ vg/kg, 1.1 x 10¹⁴ vg/kg, 1.2 x 10¹⁴ vg/kg, 1.3 x 10¹⁴ vg/kg, 1.4 x 10¹⁴ vg/kg, 1.5 x 10¹⁴ vg/kg, 1.6 x 10¹⁴ vg/kg, 1.7 x 10¹⁴ vg/kg, 1.8 x 10¹⁴ vg/kg, 1.9 x 10¹⁴ vg/kg, or 2 x 10¹⁴ vg/kg. In some

40

examples, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of from about 2×10^{13} vg/kg to about 7×10^{13} vg/kg, such as in an amount of from about 2×10^{13} vg/kg to about 4×10^{13} vg/kg (e.g., about 3×10^{13} vg/kg) or in an amount of from about 5×10^{13} vg/kg to about 7×10^{13} vg/kg (e.g., about 6×10^{13} vg/kg).

In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of from about 3×10^{13} vg/kg to about 2×10^{14} vg/kg, such as an in amount of about 3×10^{13} vg/kg, 3.1×10^{13} vg/kg, 3.2×10^{13} vg/kg, 3.3×10^{13} vg/kg, 3.4×10^{13} vg/kg, 3.5×10^{13} vg/kg, 3.6×10^{13} vg/kg, 3.7×10^{13} vg/kg, 3.8×10^{13} vg/kg, 3.9×10^{13} vg/kg, 4×10^{13} vg/kg, 4.1×10^{13} vg/kg, 4.2×10^{13} vg/kg, 4.3×10^{13} vg/kg, 4.4×10^{13} vg/kg, 4.5×10^{13} vg/kg, 4.6×10^{13} vg/kg, 4.7×10^{13} vg/kg, 4.8×10^{13} vg/kg, 4.9×10^{13} vg/kg, 5×10^{13} vg/kg, 5.1×10^{13} vg/kg, 5.2×10^{13} vg/kg, 5.3×10^{13} vg/kg, 5.4×10^{13} vg/kg, 5.5×10^{13} vg/kg, 5.6×10^{13} vg/kg, 5.7×10^{13} vg/kg, 5.8×10^{13} vg/kg, 5.9×10^{13} vg/kg, 6×10^{13} vg/kg, 6.1×10^{13} vg/kg, 6.2×10^{13} vg/kg, 6.3×10^{13} vg/kg, 6.4×10^{13} vg/kg, 6.5×10^{13} vg/kg, 6.6×10^{13} vg/kg, 6.7×10^{13} vg/kg, 6.8×10^{13} vg/kg, 6.9×10^{13} vg/kg, 7×10^{13} vg/kg, 7.1×10^{13} vg/kg, 7.2×10^{13} vg/kg, 7.3×10^{13} vg/kg, 7.4×10^{13} vg/kg, 7.5×10^{13} vg/kg, 7.6×10^{13} vg/kg, 7.7×10^{13} vg/kg, 7.8×10^{13} vg/kg, 7.9×10^{13} vg/kg, 8×10^{13} vg/kg, 8.1×10^{13} vg/kg, 8.2×10^{13} vg/kg, 8.3×10^{13} vg/kg, 8.4×10^{13} vg/kg, 8.5×10^{13} vg/kg, 8.6×10^{13} vg/kg, 8.7×10^{13} vg/kg, 8.8×10^{13} vg/kg, 8.9×10^{13} vg/kg, 9×10^{13} vg/kg, 9.1×10^{13} vg/kg, 9.2×10^{13} vg/kg, 9.3×10^{13} vg/kg, 9.4×10^{13} vg/kg, 9.5×10^{13} vg/kg, 9.6×10^{13} vg/kg, 9.7×10^{13} vg/kg, 9.8×10^{13} vg/kg, 9.9×10^{13} vg/kg, 1×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.9×10^{14} vg/kg, or 2×10^{14} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of from about 4×10^{13} vg/kg to about 2×10^{14} vg/kg, such as an in amount of about 4×10^{13} vg/kg, 4.1×10^{13} vg/kg, 4.2×10^{13} vg/kg, 4.3×10^{13} vg/kg, 4.4×10^{13} vg/kg, 4.5×10^{13} vg/kg, 4.6×10^{13} vg/kg, 4.7×10^{13} vg/kg, 4.8×10^{13} vg/kg, 4.9×10^{13} vg/kg, 5×10^{13} vg/kg, 5.1×10^{13} vg/kg, 5.2×10^{13} vg/kg, 5.3×10^{13} vg/kg, 5.4×10^{13} vg/kg, 5.5×10^{13} vg/kg, 5.6×10^{13} vg/kg, 5.7×10^{13} vg/kg, 5.8×10^{13} vg/kg, 5.9×10^{13} vg/kg, 6×10^{13} vg/kg, 6.1×10^{13} vg/kg, 6.2×10^{13} vg/kg, 6.3×10^{13} vg/kg, 6.4×10^{13} vg/kg, 6.5×10^{13} vg/kg, 6.6×10^{13} vg/kg, 6.7×10^{13} vg/kg, 6.8×10^{13} vg/kg, 6.9×10^{13} vg/kg, 7×10^{13} vg/kg, 7.1×10^{13} vg/kg, 7.2×10^{13} vg/kg, 7.3×10^{13} vg/kg, 7.4×10^{13} vg/kg, 7.5×10^{13} vg/kg, 7.6×10^{13} vg/kg, 7.7×10^{13} vg/kg, 7.8×10^{13} vg/kg, 7.9×10^{13} vg/kg, 8×10^{13} vg/kg, 8.1×10^{13} vg/kg, 8.2×10^{13} vg/kg, 8.3×10^{13} vg/kg, 8.4×10^{13} vg/kg, 8.5×10^{13} vg/kg, 8.6×10^{13} vg/kg, 8.7×10^{13} vg/kg, 8.8×10^{13} vg/kg, 8.9×10^{13} vg/kg, 9×10^{13} vg/kg, 9.1×10^{13} vg/kg, 9.2×10^{13} vg/kg, 9.3×10^{13} vg/kg, 9.4×10^{13} vg/kg, 9.5×10^{13}

vg/kg, 9.6×10^{13} vg/kg, 9.7×10^{13} vg/kg, 9.8×10^{13} vg/kg, 9.9×10^{13} vg/kg, 1×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.9×10^{14} vg/kg, or 2×10^{14} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the agent is
5 administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of from about 5×10^{13} vg/kg to about 2×10^{14} vg/kg, such as an in amount of 5×10^{13} vg/kg, 5.1×10^{13} vg/kg, 5.2×10^{13} vg/kg, 5.3×10^{13} vg/kg, 5.4×10^{13} vg/kg, 5.5×10^{13} vg/kg, 5.6×10^{13} vg/kg, 5.7×10^{13} vg/kg, 5.8×10^{13} vg/kg, 5.9×10^{13} vg/kg, 6×10^{13} vg/kg, 6.1×10^{13} vg/kg, 6.2×10^{13} vg/kg, 6.3×10^{13} vg/kg, 6.4×10^{13} vg/kg, 6.5×10^{13} vg/kg, 6.6×10^{13} vg/kg, 6.7×10^{13} vg/kg, 6.8×10^{13} vg/kg, 6.9×10^{13} vg/kg, 7×10^{13} vg/kg, 7.1×10^{13} vg/kg, 7.2×10^{13} vg/kg, 7.3×10^{13} vg/kg, 7.4×10^{13} vg/kg, 7.5×10^{13} vg/kg, 7.6×10^{13} vg/kg, 7.7×10^{13} vg/kg, 7.8×10^{13} vg/kg, 7.9×10^{13} vg/kg, 8×10^{13} vg/kg, 8.1×10^{13} vg/kg, 8.2×10^{13} vg/kg, 8.3×10^{13} vg/kg, 8.4×10^{13} vg/kg, 8.5×10^{13} vg/kg, 8.6×10^{13} vg/kg, 8.7×10^{13} vg/kg, 8.8×10^{13} vg/kg, 8.9×10^{13} vg/kg, 9×10^{13} vg/kg, 9.1×10^{13} vg/kg, 9.2×10^{13} vg/kg, 9.3×10^{13} vg/kg, 9.4×10^{13} vg/kg, 9.5×10^{13} vg/kg, 9.6×10^{13} vg/kg, 9.7×10^{13} vg/kg, 9.8×10^{13} vg/kg, 9.9×10^{13} vg/kg, 1×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.9×10^{14} vg/kg, or 2×10^{14} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the agent is
20 administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of from about 6×10^{13} vg/kg to about 2×10^{14} vg/kg, such as an in amount of about 6×10^{13} vg/kg, 6.1×10^{13} vg/kg, 6.2×10^{13} vg/kg, 6.3×10^{13} vg/kg, 6.4×10^{13} vg/kg, 6.5×10^{13} vg/kg, 6.6×10^{13} vg/kg, 6.7×10^{13} vg/kg, 6.8×10^{13} vg/kg, 6.9×10^{13} vg/kg, 7×10^{13} vg/kg, 7.1×10^{13} vg/kg, 7.2×10^{13} vg/kg, 7.3×10^{13} vg/kg, 7.4×10^{13} vg/kg, 7.5×10^{13} vg/kg, 7.6×10^{13} vg/kg, 7.7×10^{13} vg/kg, 7.8×10^{13} vg/kg, 7.9×10^{13} vg/kg, 8×10^{13} vg/kg, 8.1×10^{13} vg/kg, 8.2×10^{13} vg/kg, 8.3×10^{13} vg/kg, 8.4×10^{13} vg/kg, 8.5×10^{13} vg/kg, 8.6×10^{13} vg/kg, 8.7×10^{13} vg/kg, 8.8×10^{13} vg/kg, 8.9×10^{13} vg/kg, 9×10^{13} vg/kg, 9.1×10^{13} vg/kg, 9.2×10^{13} vg/kg, 9.3×10^{13} vg/kg, 9.4×10^{13} vg/kg, 9.5×10^{13} vg/kg, 9.6×10^{13} vg/kg, 9.7×10^{13} vg/kg, 9.8×10^{13} vg/kg, 9.9×10^{13} vg/kg, 1×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.9×10^{14} vg/kg, or 2×10^{14} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the agent is
35 administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of from about 7×10^{13} vg/kg to about 2×10^{14} vg/kg, such as an in amount of about 7×10^{13} vg/kg, 7.1×10^{13} vg/kg, 7.2×10^{13} vg/kg, 7.3×10^{13} vg/kg, 7.4×10^{13} vg/kg, 7.5×10^{13} vg/kg, 7.6×10^{13} vg/kg, 7.7×10^{13} vg/kg, 7.8×10^{13} vg/kg, 7.9×10^{13} vg/kg, 8×10^{13} vg/kg, 8.1×10^{13} vg/kg, 8.2×10^{13} vg/kg, 8.3×10^{13}

vg/kg, 8.4×10^{13} vg/kg, 8.5×10^{13} vg/kg, 8.6×10^{13} vg/kg, 8.7×10^{13} vg/kg, 8.8×10^{13} vg/kg, 8.9×10^{13} vg/kg, 9×10^{13} vg/kg, 9.1×10^{13} vg/kg, 9.2×10^{13} vg/kg, 9.3×10^{13} vg/kg, 9.4×10^{13} vg/kg, 9.5×10^{13} vg/kg, 9.6×10^{13} vg/kg, 9.7×10^{13} vg/kg, 9.8×10^{13} vg/kg, 9.9×10^{13} vg/kg, 1×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.9×10^{14} vg/kg, or 2×10^{14} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of from about 8×10^{13} vg/kg to about 2×10^{14} vg/kg, such as an in amount of about 8×10^{13} vg/kg, 8.1×10^{13} vg/kg, 8.2×10^{13} vg/kg, 8.3×10^{13} vg/kg, 8.4×10^{13} vg/kg, 8.5×10^{13} vg/kg, 8.6×10^{13} vg/kg, 8.7×10^{13} vg/kg, 8.8×10^{13} vg/kg, 8.9×10^{13} vg/kg, 9×10^{13} vg/kg, 9.1×10^{13} vg/kg, 9.2×10^{13} vg/kg, 9.3×10^{13} vg/kg, 9.4×10^{13} vg/kg, 9.5×10^{13} vg/kg, 9.6×10^{13} vg/kg, 9.7×10^{13} vg/kg, 9.8×10^{13} vg/kg, 9.9×10^{13} vg/kg, 1×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.9×10^{14} vg/kg, or 2×10^{14} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of from about 9×10^{13} vg/kg to about 2×10^{14} vg/kg, such as an in amount of about 9×10^{13} vg/kg, 9.1×10^{13} vg/kg, 9.2×10^{13} vg/kg, 9.3×10^{13} vg/kg, 9.4×10^{13} vg/kg, 9.5×10^{13} vg/kg, 9.6×10^{13} vg/kg, 9.7×10^{13} vg/kg, 9.8×10^{13} vg/kg, 9.9×10^{13} vg/kg, 1×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.9×10^{14} vg/kg, or 2×10^{14} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of from about 1×10^{14} vg/kg to about 2×10^{14} vg/kg, such as an in amount of about 1×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.9×10^{14} vg/kg, or 2×10^{14} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of about 6×10^{13} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body

mass index as the patient upon administration to the subject of the AAV vector in an amount of about 7×10^{13} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of about 8×10^{13} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of about 9×10^{13} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of about 1×10^{14} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of about 1.1×10^{14} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of about 1.2×10^{14} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of about 1.3×10^{14} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of about 1.4×10^{14} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is

equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of about 1.5×10^{14} vg/kg.

5 In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of about 1.6×10^{14} vg/kg.

10 In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of about 1.7×10^{14} vg/kg.

15 In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of about 1.8×10^{14} vg/kg.

20 In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of about 1.9×10^{14} vg/kg.

25 In some examples of any of the preceding five aspects of the disclosure, the agent is administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in the human subject of the same gender and similar body mass index as the patient upon administration to the subject of the AAV vector in an amount of about 2×10^{14} vg/kg.

30 In some examples, the agent is administered to the patient in a single dose. In some examples, the agent is administered to the patient in two or more doses.

In some examples, the agent is administered to the patient by way of intravenous, intrathecal, intracisternal, intracerebroventricular, intramuscular, intradermal, transdermal, parenteral, intranasal, subcutaneous, percutaneous, intratracheal, intraperitoneal, intraarterial, intravascular, inhalation, perfusion, lavage, and/or oral administration.

35 In some examples, the agent contains (i) a nucleic acid molecule encoding GAA, (ii) one or more interfering RNA molecules that collectively increase expression of endogenous GAA, (iii) one or more nucleic acid molecules encoding the one or more interfering RNA molecules, (iv) a GAA protein, and/or (v) one or more small molecules that collectively increase expression of endogenous GAA. For

example, the agent may be one that contains one or more interfering RNA molecules that comprise short interfering RNA (siRNA), short hairpin RNA (shRNA), and/or micro RNA (miRNA).

In some examples, the agent contains a nucleic acid molecule encoding GAA. The nucleic acid molecule encoding GAA may be provided to the patient, for example, by administering to the patient a viral vector that contains the nucleic acid molecule. The viral vector may be, for example, an AAV, an adenovirus, a parvovirus, a coronavirus, a rhabdovirus, a paramyxovirus, a picornavirus, an alphavirus, a herpes virus, a poxvirus, or a Retroviridae family virus.

In some examples, the nucleic acid molecule encoding GAA is provided to the patient by administering to the patient an AAV containing the nucleic acid molecule. The AAV may have, for example, a serotype selected from AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, and AAVrh74. In some examples, the AAV is a pseudotyped AAV. In some examples, the pseudotyped AAV is AAV2/8. In some examples, the AAV is a pseudotyped AAV. In some examples, the pseudotyped AAV is AAV2/9. In some examples, the AAV contains a recombinant capsid protein.

In some examples, the nucleic acid molecule encoding GAA is operably linked to a promoter that induces expression of the transgene in a muscle and/or neuronal cell. The promoter may be, for example, a MCK promoter, desmin promoter, chicken beta actin promoter, CMV promoter, myosin light chain-2 promoter, alpha actin promoter, troponin 1 promoter, Na⁺/Ca²⁺ 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 promoter is a MCK promoter. The MCK promoter may have, for example, a nucleic acid sequence that is at least 85% identical to SEQ ID NO: 1 (e.g., a nucleic acid sequence that is 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 1). In some examples, the MCK promoter has a nucleic acid sequence that is at least 90% identical to SEQ ID NO: 1 (e.g., a nucleic acid sequence that is 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 1). In some examples, the MCK promoter has a nucleic acid sequence that is at least 95% identical to SEQ ID NO: 1 (e.g., a nucleic acid sequence that is 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 1). In some examples, the MCK promoter has a nucleic acid sequence that is at least 97% identical to SEQ ID NO: 1 (e.g., a nucleic acid sequence that is 97%, 98%, 99%, or 100% identical to SEQ ID NO: 1). In some examples, the MCK promoter has a nucleic acid sequence that is at least 98% identical to SEQ ID NO: 1 (e.g., a nucleic acid sequence that is 98%, 99%, or 100% identical to SEQ ID NO: 1). In some examples, the MCK promoter has a nucleic acid sequence that is at least 99% identical to SEQ ID NO: 1 (e.g., a nucleic acid sequence that is 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9%, or 100% identical to SEQ ID NO: 1). In some examples, the MCK promoter has a nucleic acid sequence that is 100% identical to SEQ ID NO: 1.

In some examples, the nucleic acid molecule encoding GAA is operably linked to an enhancer that induces expression of the transgene in a muscle and/or neuronal cell. For example, the

nucleic acid molecule encoding GAA may be operably linked to a CMV enhancer, a MEF2 enhancer, or a MyoD enhancer.

In some examples, the GAA has an amino acid sequence that is at least 85% identical to SEQ ID NO: 2 (e.g., an amino acid sequence that is 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 2). In some examples, the GAA has an amino acid sequence that is at least 90% identical to SEQ ID NO: 2 (e.g., an amino acid sequence that is 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 2). In some examples, the GAA has an amino acid sequence that is at least 95% identical to SEQ ID NO: 2 (e.g., an amino acid sequence that is 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 2). In some examples, the GAA has an amino acid sequence that is at least 97% identical to SEQ ID NO: 2 (e.g., an amino acid sequence that is 97%, 98%, 99%, or 100% identical to SEQ ID NO: 2). In some examples, the GAA has an amino acid sequence that is at least 98% identical to SEQ ID NO: 2 (e.g., an amino acid sequence that is 98%, 99%, or 100% identical to SEQ ID NO: 2). In some examples, the GAA has an amino acid sequence that is at least 99% identical to SEQ ID NO: 2 (e.g., an amino acid sequence that is 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9%, or 100% identical to SEQ ID NO: 2). In some examples, the GAA has an amino acid sequence that is 100% identical to SEQ ID NO: 2. In some examples, the GAA differs from human wild-type GAA only by way of one or more conservative amino acid substitutions. In some examples, the GAA differs from human wild-type GAA by way of one or more non-conservative amino acid substitutions.

In some examples, the nucleic acid molecule encoding GAA has a nucleic acid sequence that is at least 85% identical to SEQ ID NO: 3 (e.g., a nucleic acid sequence that is 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 3). In some examples, the nucleic acid molecule encoding GAA has a nucleic acid sequence that is at least 90% identical to SEQ ID NO: 3 (e.g., a nucleic acid sequence that is 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 3). In some examples, the nucleic acid molecule encoding GAA has a nucleic acid sequence that is at least 95% identical to SEQ ID NO: 3 (e.g., a nucleic acid sequence that is 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 3). In some examples, the nucleic acid molecule encoding GAA has a nucleic acid sequence that is at least 97% identical to SEQ ID NO: 3 (e.g., a nucleic acid sequence that is 97%, 98%, 99%, or 100% identical to SEQ ID NO: 3). In some examples, the nucleic acid molecule encoding GAA has a nucleic acid sequence that is at least 98% identical to SEQ ID NO: 3 (e.g., a nucleic acid sequence that is 98%, 99%, or 100% identical to SEQ ID NO: 3). In some examples, the nucleic acid molecule encoding GAA has a nucleic acid sequence that is at least 99% identical to SEQ ID NO: 3 (e.g., a nucleic acid sequence that is 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9%, or 100% identical to SEQ ID NO: 3). In some examples, the nucleic acid molecule encoding GAA has a nucleic acid sequence that is 100% identical to SEQ ID NO: 3.

In some examples, the patient has infantile-onset Pompe disease. The patient may be, for example, from about one month to about one year of age (e.g., about one month, two months, three months, four months, five months, six months, seven months, eight months, nine months, ten months,

eleven months, or twelve months of age). In some examples, the patient is from about one month to about six months of age (e.g., about month, two months, three months, four months, five months, or six months of age).

In some examples, prior to administration of the AAV vector to the patient, 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 has late-onset Pompe disease. The patient may exhibit, for example, endogenous GAA activity of from about 1% to about 40% 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, the patient has not previously received GAA enzyme replacement therapy. In some examples, the patient has previously received GAA enzyme replacement therapy.

In some examples, following administration of the AAV vector to the patient, the patient exhibits endogenous GAA activity of from about 50% to about 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, following administration of the AAV vector to the patient, the patient exhibits a reduction in glycogen in skeletal muscle, cardiac muscle, and/or neuronal tissue.

In one aspect, the disclosure provides a kit comprising an AAV vector comprising a transgene encoding GAA and a package insert, wherein the package insert instructs a user of the kit to administer the AAV vector to a human patient in accordance with the use disclosed herein. In one aspect, the disclosure provides a kit comprising an agent that increases GAA expression and a package insert, wherein the package insert instructs a user of the kit to administer the agent to a human patient in accordance with the use disclosed herein. In another example, the disclosure features a kit containing (i) an AAV vector containing a transgene encoding GAA, e.g., in an amount specified above, or (ii) an agent that increases GAA expression, e.g., in an amount specified above. The kit may further contain, for example, a package insert that instructs a user of the kit to administer the AAV vector or agent to a human patient in accordance with the method of any of the above examples of the disclosure.

In one aspect, the disclosure provides use of an AAV 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 medicament comprises the AAV vector in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg. In another example, the disclosure features a use of an AAV vector containing a transgene encoding GAA in the manufacture of a medicament for treating Pompe disease in a human patient in need thereof, wherein the medicament contains the AAV vector in an amount of from about 1×10^{13} vg/kg to about 5×10^{14} vg/kg (e.g., in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg). For example, the medicament may contain the AAV vector in an amount of about 1×10^{13} vg/kg, 1.1×10^{13} vg/kg, 1.2×10^{13} vg/kg, 1.3×10^{13} vg/kg, 1.4×10^{13} vg/kg, 1.5×10^{13} vg/kg, 1.6×10^{13} vg/kg, 1.7×10^{13} vg/kg, 1.8×10^{13} vg/kg, 1.9×10^{13} vg/kg, 2×10^{13} vg/kg, 2.1×10^{13} vg/kg, 2.2×10^{13} vg/kg, 2.3×10^{13} vg/kg, 2.4×10^{13} vg/kg, 2.5×10^{13} vg/kg, 2.6×10^{13} vg/kg, 2.7×10^{13} vg/kg, 2.8×10^{13} vg/kg, 2.9×10^{13} vg/kg, 3×10^{13} vg/kg, 3.1×10^{13} vg/kg, 3.2×10^{13} vg/kg, 3.3×10^{13} vg/kg, 3.4×10^{13} vg/kg, 3.5×10^{13} vg/kg, 3.6×10^{13} vg/kg, 3.7×10^{13} vg/kg, 3.8×10^{13} vg/kg, 3.9×10^{13} vg/kg, 4×10^{13} vg/kg, 4.1×10^{13} vg/kg, 4.2×10^{13} vg/kg, 4.3×10^{13} vg/kg, 4.4×10^{13} vg/kg, 4.5×10^{13} vg/kg, 4.6×10^{13} vg/kg, 4.7×10^{13} vg/kg, 4.8×10^{13} vg/kg, 4.9×10^{13} vg/kg, 5×10^{13} vg/kg, 5.1×10^{13} vg/kg, 5.2×10^{13} vg/kg, 5.3×10^{13} vg/kg, 5.4×10^{13} vg/kg, 5.5×10^{13} vg/kg, 5.6×10^{13} vg/kg, 5.7×10^{13} vg/kg, 5.8×10^{13} vg/kg, 5.9×10^{13} vg/kg, 6×10^{13} vg/kg, 6.1×10^{13} vg/kg, 6.2×10^{13} vg/kg, 6.3×10^{13} vg/kg, 6.4×10^{13} vg/kg, 6.5×10^{13} vg/kg, 6.6×10^{13} vg/kg, 6.7×10^{13} vg/kg, 6.8×10^{13} vg/kg, 6.9×10^{13} vg/kg, 7×10^{13} vg/kg, 7.1×10^{13} vg/kg, 7.2×10^{13} vg/kg, 7.3×10^{13} vg/kg, 7.4×10^{13} vg/kg, 7.5×10^{13} vg/kg, 7.6×10^{13} vg/kg, 7.7×10^{13} vg/kg, 7.8×10^{13} vg/kg, 7.9×10^{13} vg/kg, 8×10^{13} vg/kg, 8.1×10^{13} vg/kg, 8.2×10^{13} vg/kg, 8.3×10^{13} vg/kg, 8.4×10^{13} vg/kg, 8.5×10^{13} vg/kg, 8.6×10^{13} vg/kg, 8.7×10^{13} vg/kg, 8.8×10^{13} vg/kg, 8.9×10^{13}

vg/kg, 9×10^{13} vg/kg, 9.1×10^{13} vg/kg, 9.2×10^{13} vg/kg, 9.3×10^{13} vg/kg, 9.4×10^{13} vg/kg, 9.5×10^{13} vg/kg, 9.6×10^{13} vg/kg, 9.7×10^{13} vg/kg, 9.8×10^{13} vg/kg, 9.9×10^{13} vg/kg, 1×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.9×10^{14} vg/kg, 2×10^{14} vg/kg, 2.1×10^{14} vg/kg, 2.2×10^{14} vg/kg, 2.3×10^{14} vg/kg, 2.4×10^{14} vg/kg, 2.5×10^{14} vg/kg, 2.6×10^{14} vg/kg, 2.7×10^{14} vg/kg, 2.8×10^{14} vg/kg, 2.9×10^{14} vg/kg, 3×10^{14} vg/kg, 3.1×10^{14} vg/kg, 3.2×10^{14} vg/kg, 3.3×10^{14} vg/kg, 3.4×10^{14} vg/kg, 3.5×10^{14} vg/kg, 3.6×10^{14} vg/kg, 3.7×10^{14} vg/kg, 3.8×10^{14} vg/kg, 3.9×10^{14} vg/kg, 4×10^{14} vg/kg, 4.1×10^{14} vg/kg, 4.2×10^{14} vg/kg, 4.3×10^{14} vg/kg, 4.4×10^{14} vg/kg, 4.5×10^{14} vg/kg, 4.6×10^{14} vg/kg, 4.7×10^{14} vg/kg, 4.8×10^{14} vg/kg, 4.9×10^{14} vg/kg, or 5×10^{14} vg/kg.

In another aspect, the disclosure provides use of an AAV vector comprising a transgene encoding GAA in the manufacture of a medicament for improving muscle function in a human patient diagnosed as having Pompe disease, wherein the medicament comprises the AAV vector in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg. In another example, the disclosure features a use of an AAV vector containing a transgene encoding GAA in the manufacture of a medicament for improving muscle function in a human patient diagnosed as having Pompe disease, wherein the medicament contains the AAV vector in an amount of from about 1×10^{13} vg/kg to about 5×10^{14} vg/kg (e.g., in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg). For example, the medicament may contain the AAV vector in an amount of about 1×10^{13} vg/kg, 1.1×10^{13} vg/kg, 1.2×10^{13} vg/kg, 1.3×10^{13} vg/kg, 1.4×10^{13} vg/kg, 1.5×10^{13} vg/kg, 1.6×10^{13} vg/kg, 1.7×10^{13} vg/kg, 1.8×10^{13} vg/kg, 1.9×10^{13} vg/kg, 2×10^{13} vg/kg, 2.1×10^{13} vg/kg, 2.2×10^{13} vg/kg, 2.3×10^{13} vg/kg, 2.4×10^{13} vg/kg, 2.5×10^{13} vg/kg, 2.6×10^{13} vg/kg, 2.7×10^{13} vg/kg, 2.8×10^{13} vg/kg, 2.9×10^{13} vg/kg, 3×10^{13} vg/kg, 3.1×10^{13} vg/kg, 3.2×10^{13} vg/kg, 3.3×10^{13} vg/kg, 3.4×10^{13} vg/kg, 3.5×10^{13} vg/kg, 3.6×10^{13} vg/kg, 3.7×10^{13} vg/kg, 3.8×10^{13} vg/kg, 3.9×10^{13} vg/kg, 4×10^{13} vg/kg, 4.1×10^{13} vg/kg, 4.2×10^{13} vg/kg, 4.3×10^{13} vg/kg, 4.4×10^{13} vg/kg, 4.5×10^{13} vg/kg, 4.6×10^{13} vg/kg, 4.7×10^{13} vg/kg, 4.8×10^{13} vg/kg, 4.9×10^{13} vg/kg, 5×10^{13} vg/kg, 5.1×10^{13} vg/kg, 5.2×10^{13} vg/kg, 5.3×10^{13} vg/kg, 5.4×10^{13} vg/kg, 5.5×10^{13} vg/kg, 5.6×10^{13} vg/kg, 5.7×10^{13} vg/kg, 5.8×10^{13} vg/kg, 5.9×10^{13} vg/kg, 6×10^{13} vg/kg, 6.1×10^{13} vg/kg, 6.2×10^{13} vg/kg, 6.3×10^{13} vg/kg, 6.4×10^{13} vg/kg, 6.5×10^{13} vg/kg, 6.6×10^{13} vg/kg, 6.7×10^{13} vg/kg, 6.8×10^{13} vg/kg, 6.9×10^{13} vg/kg, 7×10^{13} vg/kg, 7.1×10^{13} vg/kg, 7.2×10^{13} vg/kg, 7.3×10^{13} vg/kg, 7.4×10^{13} vg/kg, 7.5×10^{13} vg/kg, 7.6×10^{13} vg/kg, 7.7×10^{13} vg/kg, 7.8×10^{13} vg/kg, 7.9×10^{13} vg/kg, 8×10^{13} vg/kg, 8.1×10^{13} vg/kg, 8.2×10^{13} vg/kg, 8.3×10^{13} vg/kg, 8.4×10^{13} vg/kg, 8.5×10^{13} vg/kg, 8.6×10^{13} vg/kg, 8.7×10^{13} vg/kg, 8.8×10^{13} vg/kg, 8.9×10^{13} vg/kg, 9×10^{13} vg/kg, 9.1×10^{13} vg/kg, 9.2×10^{13} vg/kg, 9.3×10^{13} vg/kg, 9.4×10^{13} vg/kg, 9.5×10^{13} vg/kg, 9.6×10^{13} vg/kg, 9.7×10^{13} vg/kg, 9.8×10^{13} vg/kg, 9.9×10^{13} vg/kg, 1×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.9×10^{14} vg/kg, 2×10^{14} vg/kg, 2.1×10^{14} vg/kg, 2.2×10^{14} vg/kg, 2.3×10^{14} vg/kg, 2.4×10^{14} vg/kg, 2.5×10^{14} vg/kg, 2.6×10^{14} vg/kg, 2.7×10^{14} vg/kg, 2.8×10^{14} vg/kg, 2.9×10^{14} vg/kg, 3×10^{14} vg/kg, 3.1×10^{14} vg/kg, 3.2×10^{14} vg/kg, 3.3×10^{14} vg/kg, 3.4×10^{14} vg/kg, 3.5×10^{14} vg/kg, 3.6×10^{14} vg/kg, 3.7×10^{14} vg/kg, 3.8×10^{14} vg/kg, 3.9×10^{14} vg/kg, 4×10^{14} vg/kg, 4.1×10^{14} vg/kg, 4.2×10^{14} vg/kg, 4.3×10^{14} vg/kg, 4.4×10^{14} vg/kg, 4.5×10^{14} vg/kg, 4.6×10^{14} vg/kg, 4.7×10^{14} vg/kg, 4.8×10^{14} vg/kg, 4.9×10^{14} vg/kg, or 5×10^{14} vg/kg.

In another aspect, the disclosure provides use of an AAV vector comprising a transgene encoding GAA in the manufacture of a medicament for reducing glycogen accumulation in a human patient diagnosed as having Pompe disease, wherein the medicament comprises the AAV vector in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg. In another example, the disclosure features a use of an AAV vector containing a transgene encoding GAA in the manufacture of a medicament for reducing glycogen accumulation (e.g., in muscle and/or neuronal tissue) in a human patient diagnosed as having Pompe disease, wherein the

In some examples of any of the preceding five aspects of the disclosure, the medicament contains the AAV vector in an amount of about 1.2×10^{14} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the medicament contains the AAV vector in an amount of about 1.3×10^{14} vg/kg.

5 In some examples of any of the preceding five aspects of the disclosure, the medicament contains the AAV vector in an amount of about 1.4×10^{14} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the medicament contains the AAV vector in an amount of about 1.5×10^{14} vg/kg.

10 In some examples of any of the preceding five aspects of the disclosure, the medicament contains the AAV vector in an amount of about 1.6×10^{14} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the medicament contains the AAV vector in an amount of about 1.7×10^{14} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the medicament contains the AAV vector in an amount of about 1.8×10^{14} vg/kg.

15 In some examples of any of the preceding five aspects of the disclosure, the medicament contains the AAV vector in an amount of about 1.9×10^{14} vg/kg.

In some examples of any of the preceding five aspects of the disclosure, the medicament contains the AAV vector in an amount of about 2×10^{14} vg/kg.

20 In some examples, the AAV vector is formulated for administration to the patient in a single dose containing the amount. In some examples, the AAV vector is formulated for administration to the patient in two or more doses that, together, total the specified amount (e.g., in two, three, four, five, six, seven, eight, nine, or ten doses that, together, total the specified amount). In some examples, the AAV vector is formulated for administration to the patient in two or more doses that each, individually, contain the specified amount (e.g., in two, three, four, five, six, seven, eight, nine, or ten doses that each, individually, contain the specified amount).

25 In some examples, the AAV vector is formulated for intravenous, intrathecal, intracisternal, intracerebroventricular, intramuscular, intradermal, transdermal, parenteral, intranasal, subcutaneous, percutaneous, intratracheal, intraperitoneal, intraarterial, intravascular, inhalation, perfusion, lavage, and/or oral administration to the patient. For example, the AAV vector may be formulated for intravenous, intrathecal, intracisternal, intracerebroventricular, and/or intramuscular administration to the patient. In some examples, the AAV vector is formulated for intravenous and/or intrathecal administration to the patient. The AAV vector may be, for example, formulated for intravenous administration to the patient.

30 In some examples, the AAV is an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAVrh74, AAVrh.8, or AAVrh.10 serotype. In some examples, the AAV is a pseudotyped AAV, such as an AAV2/8 or AAV2/9. In some examples, the AAV contains a recombinant capsid protein.

35 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. The promoter may be, for example, a MCK promoter, desmin promoter, chicken beta actin promoter, CMV promoter, myosin light chain-2 promoter,

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alpha actin promoter, troponin 1 promoter, Na⁺/Ca²⁺ 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.

5 In some examples, the promoter is a MCK promoter. The MCK promoter may have, for example, a nucleic acid sequence that is at least 85% identical to SEQ ID NO: 1 (e.g., a nucleic acid sequence that is 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 1). In some examples, the MCK promoter has a nucleic acid sequence that is at least 90% identical to SEQ ID NO: 1 (e.g., a nucleic acid sequence that is 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 1). In some examples, the MCK promoter has a nucleic acid sequence that is at least 95% identical to SEQ ID NO: 1 (e.g., a nucleic acid sequence that is 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 1). In some examples, the MCK promoter has a nucleic acid sequence that is at least 97% identical to SEQ ID NO: 1 (e.g., a nucleic acid sequence that is 97%, 98%, 99%, or 100% identical to SEQ ID NO: 1). In some examples, the MCK promoter has a nucleic acid sequence that is at least 98% identical to SEQ ID NO: 1 (e.g., a nucleic acid sequence that is 98%, 99%, or 100% identical to SEQ ID NO: 1). In some examples, the MCK promoter has a nucleic acid sequence that is at least 99% identical to SEQ ID NO: 1 (e.g., a nucleic acid sequence that is 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9%, or 100% identical to SEQ ID NO: 1). In some examples, the MCK promoter has a nucleic acid sequence that is 100% identical to SEQ ID NO: 1.

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

In some examples, the GAA has an amino acid sequence that is at least 85% identical to SEQ ID NO: 2 (e.g., an amino acid sequence that is 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 2). In some examples, the GAA has an amino acid sequence that is at least 90% identical to SEQ ID NO: 2 (e.g., an amino acid sequence that is 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 2). In some examples, the GAA has an amino acid sequence that is at least 95% identical to SEQ ID NO: 2 (e.g., an amino acid sequence that is 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 2). In some examples, the GAA has an amino acid sequence that is at least 97% identical to SEQ ID NO: 2 (e.g., an amino acid sequence that is 97%, 98%, 99%, or 100% identical to SEQ ID NO: 2). In some examples, the GAA has an amino acid sequence that is at least 98% identical to SEQ ID NO: 2 (e.g., an amino acid sequence that is 98%, 99%, or 100% identical to SEQ ID NO: 2). In some examples, the GAA has an amino acid sequence that is at least 99% identical to SEQ ID NO: 2 (e.g., an amino acid sequence that is 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9%, or 100% identical to SEQ ID NO: 2). In some examples, the GAA has an amino acid sequence that is 100% identical to SEQ ID NO: 2. In some examples, the GAA differs from human wild-type GAA only by way of one or more conservative amino acid substitutions. In some examples, the GAA differs from human wild-type GAA by way of one or more non-conservative amino acid substitutions.

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In some examples, the transgene encoding GAA has a nucleic acid sequence that is at least 85% identical to SEQ ID NO: 3 (e.g., a nucleic acid sequence that is 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 3). In some examples, the transgene encoding GAA has a nucleic acid sequence that is at least 90% identical to SEQ ID NO: 3 (e.g., a nucleic acid sequence that is 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 3). In some examples, the transgene encoding GAA has a nucleic acid sequence that is at least 95% identical to SEQ ID NO: 3 (e.g., a nucleic acid sequence that is 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 3). In some examples, the transgene encoding GAA has a nucleic acid sequence that is at least 97% identical to SEQ ID NO: 3 (e.g., a nucleic acid sequence that is 97%, 98%, 99%, or 100% identical to SEQ ID NO: 3). In some examples, the transgene encoding GAA has a nucleic acid sequence that is at least 98% identical to SEQ ID NO: 3 (e.g., a nucleic acid sequence that is 98%, 99%, or 100% identical to SEQ ID NO: 3). In some examples, the transgene encoding GAA has a nucleic acid sequence that is at least 99% identical to SEQ ID NO: 3 (e.g., a nucleic acid sequence that is 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9%, or 100% identical to SEQ ID NO: 3). In some examples, the transgene encoding GAA has a nucleic acid sequence that is 100% identical to SEQ ID NO: 3.

In some examples, the patient has infantile-onset Pompe disease. The patient may be, for example, from about one month to about one year of age (e.g., about one month, two months, three months, four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, or twelve months of age). In some examples, the patient is from about one month to about six months of age (e.g., about month, two months, three months, four months, five months, or six months of age).

In some examples, prior to administration of the AAV vector to the patient, 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 has late-onset Pompe disease. The patient may exhibit, for example, endogenous GAA activity of from about 1% to about 40% 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, the patient has not previously received GAA enzyme replacement therapy. In some examples, the patient has previously received GAA enzyme replacement therapy.

In some examples, following administration of the AAV vector to the patient, the patient exhibits endogenous GAA activity of from about 50% to about 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, following administration of the AAV vector to the patient, the patient exhibits a reduction in glycogen in skeletal muscle, cardiac muscle, and/or neuronal tissue.

Brief Description of the Drawings

FIGS. 1A and 1B are graphs showing changes in acid alpha-glucosidase (GAA) protein expression and enzymatic activity levels, respectively, in muscles of mice treated with an AAV2/8 vector

Claims

1. Use of an adeno-associated viral (AAV) vector comprising a transgene encoding acid alpha-glucosidase (GAA) in the manufacture of a medicament for treating Pompe disease in a human patient in need thereof, wherein the AAV vector is to be administered to the patient in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg.
2. Use of an AAV vector comprising a transgene encoding GAA in the manufacture of a medicament for improving muscle function in a human patient diagnosed as having Pompe disease, wherein the AAV vector is to be administered to the patient in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg.
3. Use of an AAV vector comprising a transgene encoding GAA in the manufacture of a medicament for reducing glycogen accumulation in a human patient diagnosed as having Pompe disease, wherein the AAV vector is to be administered to the patient in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg.
4. Use of an AAV vector comprising a transgene encoding GAA in the manufacture of a medicament for improving pulmonary function in a human patient diagnosed as having Pompe disease, wherein the AAV vector is to be administered to the patient in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg.
5. Use of an AAV vector comprising a transgene encoding GAA in the manufacture of a medicament for increasing GAA expression in a human patient diagnosed as having Pompe disease, wherein the AAV vector is to be administered to the patient in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg.
6. Use of an agent that increases GAA expression in the manufacture of a medicament for treating Pompe disease in a human patient in need thereof, wherein the agent is to be administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in a human subject of the same gender and similar body mass index as the patient upon administration to the subject of an AAV2/8 vector comprising a transgene encoding GAA in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg, wherein the transgene encoding GAA is operably linked to a MCK promoter.
7. Use of an agent that increases GAA expression in the manufacture of a medicament for improving muscle function in a human patient diagnosed as having Pompe disease, wherein the agent is to be administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in a human subject of the same gender and similar body mass index as the patient upon administration to the subject of an AAV2/8 vector comprising a transgene encoding GAA in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg, wherein the transgene encoding GAA is operably linked to a MCK promoter.
8. Use of an agent that increases GAA expression in the manufacture of a medicament for reducing glycogen accumulation in a human patient diagnosed as having Pompe disease, wherein the

agent is to be administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in a human subject of the same gender and similar body mass index as the patient upon administration to the subject of an AAV2/8 vector comprising a transgene encoding GAA in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg, wherein the transgene encoding GAA is operably linked to a MCK promoter.

9. Use of an agent that increases GAA expression in the manufacture of a medicament for improving pulmonary function in a human patient diagnosed as having Pompe disease, wherein the agent is to be administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in a human subject of the same gender and similar body mass index as the patient upon administration to the subject of an AAV2/8 vector comprising a transgene encoding GAA in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg, wherein the transgene encoding GAA is operably linked to a MCK promoter.

10. Use of an agent that increases GAA expression in the manufacture of a medicament for increasing GAA expression in a human patient diagnosed as having Pompe disease, wherein the agent is to be administered to the patient in an amount sufficient to achieve a level of GAA activity in the patient that is equivalent to a level of GAA activity observed in a human subject of the same gender and similar body mass index as the patient upon administration to the subject of an AAV2/8 vector comprising a transgene encoding GAA in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg, wherein the transgene encoding GAA is operably linked to a MCK promoter.

11. A kit comprising an AAV vector comprising a transgene encoding GAA and a package insert, wherein the package insert instructs a user of the kit to administer the AAV vector a human patient in accordance with the use of any one of claims 1-5.

12. A kit comprising an agent that increases GAA expression and a package insert, wherein the package insert instructs a user of the kit to administer the agent to a human patient in accordance with the use of any one of claims 6-10.

13. Use of an AAV 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 medicament comprises the AAV vector in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg.

14. Use of an AAV vector comprising a transgene encoding GAA in the manufacture of a medicament for improving muscle function in a human patient diagnosed as having Pompe disease, wherein the medicament comprises the AAV vector in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg.

15. Use of an AAV vector comprising a transgene encoding GAA in the manufacture of a medicament for reducing glycogen accumulation in a human patient diagnosed as having Pompe

disease, wherein the medicament comprises the AAV vector in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg.

16. Use of an AAV vector comprising a transgene encoding GAA in the manufacture of a medicament for improving pulmonary function in a human patient diagnosed as having Pompe disease, wherein the medicament comprises the AAV vector in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg.

17. Use of an AAV vector comprising a transgene encoding GAA in the manufacture of a medicament for increasing GAA expression in a human patient diagnosed as having Pompe disease, wherein the medicament comprises the AAV vector in an amount of from about 1×10^{13} vg/kg to about 3×10^{14} vg/kg.