COMPOSITIONS AND METHODS FOR IMPROVED TREATMENT OF X-LINKED MYOTUBULAR MYOPATHY

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 May 24, 2022 is named "51037-057WO3_Sequence_Listing_5_24_22_ST25" and is 69,743 bytes in size.

Field of the Invention

The present invention relates to a method for the treatment of cholestatic liver dysfunction associated with current treatments of neuromuscular disorders in patients, such as human patients.

Background of the Invention

X-linked myotubular myopathy (XLMTM) is a fatal monogenic disease of skeletal muscle, resulting from loss-of-function mutations in Myotubularin 1 (MTM1). Approximately one in every 50,000 newborn boys has XLMTM, which typically displays as marked hypotonia and respiratory failure. In extremely rare cases, females can develop a severe form of XLMTM. Survival beyond the postnatal period requires intensive support, including respiratory support (i.e., mechanical ventilation) at birth in 85-90% of patients, ongoing 24-hour ventilator dependence in nearly 50% of patients, and tracheostomy in ~60% of patients. Until recently, only supportive treatment options, such as ventilator use or a feeding tube, were available. Recently, gene therapy approaches involving the delivery of MTM1 have been developed for the treatment of XLMTM. However, there is a need in the art for improved methods of administering gene therapy to patients having XLMTM.

Summary

The disclosure provides methods for treating X-linked myotubular myopathy (XLMTM) in a human patient in need thereof. In some examples, the patient is administered a therapeutically effective amount of a viral vector containing a transgene encoding myotubularin 1 (MTM1) and an anti-cholestatic agent.

In one example, the disclosure provides a method of treating XLMTM in a human patient in need thereof, the method including administering to the patient (i) a therapeutically effective amount of a transgene encoding MTM1 and (ii) an anti-cholestatic agent, wherein the anti-cholestatic agent is administered to the patient in one or more doses that commence within about six weeks (e.g., about six weeks before or about six weeks after) of administration of the transgene to the patient. In one aspect, the present disclosure refers to use of (i) a viral vector comprising a transgene encoding myotubularin 1 (MTM1) and (ii) an anti-cholestatic agent in the manufacture of a medicament for treating X-linked myotubular myopathy (XLMTM) in a human patient in need thereof, wherein the anti-cholestatic agent is to be administered to the patient in one or more doses that commence within about six weeks of administration of the viral vector to the patient.

In a second example, the disclosure provides a method of reducing stiffness and/or joint contractures in a human patient diagnosed as having XLMTM, the method comprising administering to the patient (i) a therapeutically effective amount of a viral vector comprising a transgene encoding MTM1 and (ii) an anti-cholestatic agent, wherein the anti-cholestatic agent is administered to the patient in one

or more doses that commence within about six weeks (e.g., about six weeks before or about six weeks after) of administration of the viral vector to the patient. In one aspect, the present disclosure refers to use of (i) a viral vector comprising a transgene encoding MTM1 and (ii) an anti-cholestatic agent in the manufacture of a medicament for reducing stiffness and/or joint contractures in a human patient diagnosed as having XLMTM, wherein the anti-cholestatic agent is to be administered to the patient in one or more doses that commence within about six weeks of administration of the viral vector to the patient.

In another example, the disclosure provides a method of increasing diaphragm and/or respiratory muscle progression in a human patient diagnosed as having XLMTM, the method comprising administering to the patient (i) a therapeutically effective amount of a viral vector comprising a transgene encoding MTM1 and (ii) an anti-cholestatic agent, wherein the anti-cholestatic agent is administered to the patient in one or more doses that commence within about six weeks (e.g., about six weeks before or about six weeks after) of administration of the viral vector to the patient. In one aspect, the present disclosure refers to use of (i) a viral vector comprising a transgene encoding MTM1 and (ii) an anti-cholestatic agent in the manufacture of a medicament for increasing diaphragm and/or respiratory muscle progression in a human patient diagnosed as having XLMTM, wherein the anti-cholestatic agent is to be administered to the patient in one or more doses that commence within about six weeks of administration of the viral vector to the patient.

In some examples, the anti-cholestatic agent is administered to the patient in one or more doses that commence within about five weeks (e.g., about five weeks before or about five weeks after) of administration of the transgene to the patient, optionally wherein the anti-cholestatic agent is administered to the patient in one or more doses that commence within about four weeks (e.g., about four weeks before or about four weeks after), within about three weeks (e.g., about three weeks before or about three weeks after), within about two weeks (e.g., about two weeks before or about two weeks after), or within about one week (e.g., about one week before or about one week after, about six days before or about six days after, about five days before or about five days after, about four days before or about four days after, about three days before or about three days after, about two days before or about two days after, or about one day before or about one day after) of administration of the transgene to the patient.

In some examples, the anti-cholestatic agent is administered to the patient in one or more doses that commence on the same day as administration of the transgene to the patient.

In another example, the disclosure provides a method of treating XLMTM in a human patient in need thereof and who has been previously administered an anti-cholestatic agent, the method including administering to the patient a therapeutically effective amount of a transgene encoding MTM1. In one aspect, the present disclosure refers to use of a viral vector comprising a transgene encoding MTM1 in the manufacture of a medicament for treating XLMTM in a human patient in need thereof and who has been previously administered an anti-cholestatic agent.

In another example, the disclosure provides a method of reducing stiffness and/or joint contractures in a human patient diagnosed as having XLMTM and who has been previously administered an anti-cholestatic agent, the method comprising administering to the patient a therapeutically effective amount of a viral vector comprising a transgene encoding MTM1. In one aspect, the present disclosure refers to use of a viral vector comprising a transgene encoding MTM1 in the manufacture of a medicament for reducing stiffness and/or joint contractures in a human patient diagnosed as having XLMTM and who has been previously administered an anti-cholestatic agent.

In another example, the disclosure provides a method of increasing diaphragm and/or respiratory muscle progression in a human patient diagnosed as having XLMTM and who has been previously administered an anti-cholestatic agent, the method comprising administering to the patient a therapeutically effective amount of a viral vector comprising a transgene encoding MTM1. In one aspect, the present disclosure refers to use of a viral vector comprising a transgene encoding MTM1 in the manufacture of a medicament for increasing diaphragm and/or respiratory muscle progression in a human patient diagnosed as having XLMTM and who has been previously administered an anti-cholestatic agent.

In some examples of either of the foregoing aspects, the method further includes monitoring the patient for development of cholestasis or hyperbilirubinemia.

In some examples of either of the foregoing aspects, the patient is monitored for the development of cholestasis, hyperbilirubinemia, or one or more symptoms thereof by evaluating a parameter in a blood sample obtained from the patient, wherein a finding that the parameter is above a reference level identifies the patient as having cholestasis, hyperbilirubinemia, or one or more symptoms thereof.

In some examples, the parameter includes the level of a serum bile acid in the blood sample. In some examples, the serum bile acid is cholic acid, chenodeoxycholic acid, deoxycholic acid, or ursodeoxycholic acid.

In some examples, the parameter includes one or more results of a liver function test.

In some examples of any of the foregoing aspects, the parameter includes the level of aspartate aminotransferase or alanine aminotransferase in the blood sample.

In another example, the disclosure provides a method of treating XLMTM in a human patient in need thereof, the method including: (a) administering to the patient a transgene encoding MTM1, (b) monitoring the patient for development of cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, (c) administering to the patient an anti-cholestatic agent.

In another example, the disclosure provides a method of treating XLMTM in a human patient in need thereof, the method including: (a) administering to the patient a viral vector including a transgene encoding MTM1 in an amount of less than about 3×10^{14} vg/kg (e.g., in an amount of less than about 3×10^{14} vg/kg, 2.9×10^{14} vg/kg, 2.8×10^{14} vg/kg, 2.7×10^{14} vg/kg, 2.6×10^{14} vg/kg, 2.5×10^{14} vg/kg, 2.4×10^{14} vg/kg, 2.3×10^{14} vg/kg, 2.2×10^{14} vg/kg, 2.1×10^{14} vg/kg, 2×10^{14} vg/kg, 1.9×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1×10^{14} vg/kg, 1×10^{14} vg/kg, 1×10^{13} vg/kg, 1×10^{12} vg/kg, 1×10^{11} vg/kg, 1×10^{10} vg/kg, 1×10^{9} vg/kg, 1×10^{8} vg/kg, or less), (b) monitoring the patient for development of cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, (c) administering to the patient an anti-cholestatic agent. In one aspect, the present disclosure refers to use of a viral vector comprising a transgene encoding MTM1 in the manufacture of a medicament for treating XLMTM in a human patient in need thereof, wherein the viral vector is to be administered to the patient in accordance with a method comprising: (a) administering to the patient the viral vector in an amount of less than about 3×10^{14} vg/kg, (b) monitoring the patient for development of cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and (c) administering to the patient an anti-cholestatic agent.

In another example, the disclosure provides a method of reducing stiffness and/or joint contractures in a human patient diagnosed as having XLMTM, the method comprising: (a) administering to the patient a viral vector comprising a transgene encoding MTM1 in an amount of less than about 3×10^{14} vg/kg (e.g., in an amount of less than about 3×10^{14} vg/kg, 2.9×10^{14} vg/kg, 2.8×10^{14} vg/kg, 2.7×10^{14} vg/kg, 2.6×10^{14} vg/kg, 2.5×10^{14} vg/kg, 2.4×10^{14} vg/kg, 2.3×10^{14} vg/kg, 2.2×10^{14} vg/kg, 2.1×10^{14} vg/kg, 2×10^{14} vg/kg, 1.9×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1×10^{14} vg/kg, 1×10^{14} vg/kg, 1×10^{13} vg/kg, 1×10^{12} vg/kg, 1×10^{11} vg/kg, 1×10^{10} vg/kg, 1×10^{9} vg/kg, 1×10^{8} vg/kg, or less), (b) monitoring the patient for development of cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, (c) administering to the patient an anti-cholestatic agent. In one aspect, the present disclosure refers to use of a viral vector comprising a transgene encoding MTM1 in the manufacture of a medicament for reducing stiffness and/or joint contractures in a human patient diagnosed as having XLMTM, wherein the viral vector is to be administered to the patient in accordance with a method comprising: (a) administering to the patient the viral vector in an amount of less than about 3×10^{14} vg/kg, (b) monitoring the patient for development of cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and (c) administering to the patient an anti-cholestatic agent.

In another example, the disclosure provides a method of increasing diaphragm and/or respiratory muscle progression in a human patient diagnosed as having XLMTM, the method comprising: a) administering to the patient a viral vector comprising a transgene encoding MTM1 in an amount of less than about 3×10^{14} vg/kg (e.g., in an amount of less than about 3×10^{14} vg/kg, 2.9×10^{14} vg/kg, 2.8×10^{14} vg/kg, 2.7×10^{14} vg/kg, 2.6×10^{14} vg/kg, 2.5×10^{14} vg/kg, 2.4×10^{14} vg/kg, 2.3×10^{14} vg/kg, 2.2×10^{14}

vg/kg, 2.1 x 10^{14} vg/kg, 2 x 10^{14} vg/kg, 1.9 x 10^{14} vg/kg, 1.8 x 10^{14} vg/kg, 1.7 x 10^{14} vg/kg, 1.6 x 10^{14} vg/kg, 1.5 x 10^{14} vg/kg, 1.4 x 10^{14} vg/kg, 1.3 x 10^{14} vg/kg, 1.2 x 10^{14} vg/kg, 1.1 x 10^{14} vg/kg, 1 x 10^{14} vg/kg, 1 x 10^{14} vg/kg, 1 x 10^{13} vg/kg, 1 x 10^{12} vg/kg, 1 x 10^{11} vg/kg, 1 x 10^{10} vg/kg, 1 x 10^{9} vg/kg, 1 x 10^{8} vg/kg, or less), (b) monitoring the patient for development of cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, (c) administering to the patient an anti-cholestatic agent. In one aspect, the present disclosure refers to use of a viral vector comprising a transgene encoding MTM1 in the manufacture of a medicament for increasing diaphragm and/or respiratory muscle progression in a human patient diagnosed as having XLMTM, wherein the viral vector is to be administered to the patient in accordance with a method comprising: (a) administering to the patient the viral vector in an amount of less than about 3 x 10^{14} vg/kg, (b) monitoring the patient for development of cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and (c) administering to the patient an anti-cholestatic agent.

In another example, the disclosure provides a method of treating XLMTM in a human patient in need thereof, the method including: (a) administering to the patient a transgene encoding MTM1, (b) determining that the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and (c) administering to the patient an anti-cholestatic agent.

In another example, the disclosure provides a method of treating XLMTM in a human patient in need thereof, the method including: (a) administering to the patient a viral vector including a transgene encoding MTM1 in an amount of less than about 3 x 10^{14} vg/kg (e.g., in an amount of less than about 3 x 10^{14} vg/kg, 2.9 x 10^{14} vg/kg, 2.8 x 10^{14} vg/kg, 2.7 x 10^{14} vg/kg, 2.6 x 10^{14} vg/kg, 2.5 x 10^{14} vg/kg, 2.4 x 10^{14} vg/kg, 2.3 x 10^{14} vg/kg, 2.2 x 10^{14} vg/kg, 2.1 x 10^{14} vg/kg, 2 x 10^{14} vg/kg, 1.9 x 10^{14} vg/kg, 1.8 x 10^{14} vg/kg, 1.7 x 10^{14} vg/kg, 1.6 x 10^{14} vg/kg, 1.5 x 10^{14} vg/kg, 1.4 x 10^{14} vg/kg, 1.3 x 10^{14} vg/kg, 1.2 x 10^{14} vg/kg, 1.1 x 10^{14} vg/kg, 1 x 10^{14} vg/kg, 1 x 10^{14} vg/kg, 1 x 10^{13} vg/kg, 1 x 10^{12} vg/kg, 1 x 10^{11} vg/kg, 1 x 10^{10} vg/kg, 1 x 10^{9} vg/kg, 1 x 10^{8} vg/kg, or less), (b) determining that the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and (c) administering to the patient an anti-cholestatic agent. In one aspect, the present disclosure refers to use of a viral vector comprising a transgene encoding MTM1 in the manufacture of a medicament for treating XLMTM in a human patient in need thereof, wherein the viral vector is to be administered to the patient in accordance with a method comprising: (a) administering to the patient the viral vector in an amount of less than about 3 x 10^{14} vg/kg, (b) determining that the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and (c) administering to the patient an anti-cholestatic agent.

In another example, the disclosure provides a method of reducing stiffness and/or joint contractures in a human patient diagnosed as having XLMTM, the method comprising: (a) administering to the patient a viral vector comprising a transgene encoding MTM1 in an amount of less than about 3 x 10^{14} vg/kg (e.g., in an amount of less than about 3 x 10^{14} vg/kg, 2.9 x 10^{14} vg/kg, 2.8 x 10^{14} vg/kg, 2.7 x 10^{14} vg/kg, 2.6 x 10^{14} vg/kg, 2.5 x 10^{14} vg/kg, 2.4 x 10^{14} vg/kg, 2.3 x 10^{14} vg/kg, 2.2 x 10^{14} vg/kg, 2.1 x 10^{14} vg/kg, 2 x 10^{14} vg/kg, 1.9 x 10^{14} vg/kg, 1.8 x 10^{14} vg/kg, 1.7 x 10^{14} vg/kg, 1.6 x 10^{14} vg/kg, 1.5 x 10^{14} vg/kg, 1.4 x 10^{14} vg/kg, 1.3 x 10^{14} vg/kg, 1.2 x 10^{14} vg/kg, 1.1 x 10^{14} vg/kg, 1 x 10^{14} vg/kg, 1 x 10^{14} vg/kg, 1 x 10^{13} vg/kg, 1 x 10^{12} vg/kg, 1 x 10^{11} vg/kg, 1 x 10^{10} vg/kg, 1 x 10^{9} vg/kg, 1 x 10^{8} vg/kg, or less), (b) determining that the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and (c) administering to the patient an anti-cholestatic agent. In one aspect, the present disclosure refers to use of a viral vector comprising a transgene encoding MTM1 in the manufacture of a medicament for reducing stiffness and/or joint contractures in a human patient diagnosed as having XLMTM, wherein the viral vector is to be administered to the patient in accordance with a method comprising: (a) administering to the patient the viral vector in an amount of less than about 3 x 10^{14} vg/kg, (b) determining that the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and (c) administering to the patient an anti-cholestatic agent.

In another example, the disclosure provides a method of increasing diaphragm and/or respiratory muscle progression in a human patient diagnosed as having XLMTM, the method comprising: (a) administering to the patient a viral vector comprising a transgene encoding MTM1 in an amount of less than about 3 x 10^{14} vg/kg (e.g., in an amount of less than about 3 x 10^{14} vg/kg, 2.9 x 10^{14} vg/kg, 2.8 x 10^{14} vg/kg, 2.7 x 10^{14} vg/kg, 2.6 x 10^{14} vg/kg, 2.5 x 10^{14} vg/kg, 2.4 x 10^{14} vg/kg, 2.3 x 10^{14} vg/kg, 2.2 x 10^{14} vg/kg, 2.1 x 10^{14} vg/kg, 2 x 10^{14} vg/kg, 1.9 x 10^{14} vg/kg, 1.8 x 10^{14} vg/kg, 1.7 x 10^{14} vg/kg, 1.6 x 10^{14} vg/kg, 1.5 x 10^{14} vg/kg, 1.4 x 10^{14} vg/kg, 1.3 x 10^{14} vg/kg, 1.2 x 10^{14} vg/kg, 1.1 x 10^{14} vg/kg, 1 x 10^{14} vg/kg, 1 x 10^{14} vg/kg, 1 x 10^{13} vg/kg, 1 x 10^{12} vg/kg, 1 x 10^{11} vg/kg, 1 x 10^{10} vg/kg, 1 x 10^{9}

vg/kg, 1 x 10^8 vg/kg, or less), (b) determining that the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and (c) administering to the patient an anti-cholestatic agent. In one aspect, the present disclosure refers to use of a viral vector comprising a transgene encoding MTM1 in the manufacture of a medicament for increasing diaphragm and/or respiratory muscle progression in a human patient diagnosed as having XLMTM, wherein the viral vector is to be administered to the patient in accordance with a method comprising: (a) administering to the patient the viral vector in an amount of less than about 3 x 10^{14} vg/kg, (b) determining that the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and (c) administering to the patient an anti-cholestatic agent.

In another example, the disclosure provides a method of treating XLMTM in a human patient in need thereof that is five years old or younger (e.g., 5 years old or younger, 4 years old or younger, 3 years old or younger, 2 years old or younger, 1 year old or younger, 12 months old or younger, 11 months old or younger, 10 months old or younger, 9 months old or younger, 8 months old or younger, 7 months old or younger, 6 months old or younger, 5 months old or younger, 4 months old or younger, 3 months old or younger, 2 months old or younger, or 1 month old or younger), the method including: (a) administering to the patient a therapeutically effective amount of a transgene encoding MTM1, (b) monitoring the patient for development of cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, (c) administering to the patient an anti-cholestatic agent. In one aspect, the present disclosure refers to use of a viral vector comprising a transgene encoding MTM1 in the manufacture of a medicament for treating XLMTM in a human patient in need thereof that is five years old or younger, wherein the viral vector is to be administered to the patient in accordance with a method comprising: (a) administering to the patient a therapeutically effective amount of the viral vector, (b) monitoring the patient for development of cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and (c) administering to the patient an anti-cholestatic agent.

In another example, the disclosure provides a method of reducing stiffness and/or joint contractures in a human patient diagnosed as having XLMTM, the method comprising: (a) administering to the patient a therapeutically effective amount of a viral vector comprising a transgene encoding MTM1, (b) monitoring the patient for development of cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, (c) administering to the patient an anti-cholestatic agent. In one aspect, the present disclosure refers to use of a viral vector comprising a transgene encoding MTM1 in the manufacture of a medicament for reducing stiffness and/or joint contractures in a human patient diagnosed as having XLMTM, wherein the viral vector is to be administered to the patient in accordance with a method comprising: (a) administering to the patient a therapeutically effective amount of the viral vector, (b) monitoring the patient for development of cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and (c) administering to the patient an anti-cholestatic agent.

In another example, the disclosure provides a method of increasing diaphragm and/or respiratory muscle progression in a human patient diagnosed as having XLMTM, the method comprising: (a) administering to the patient a therapeutically effective amount of a viral vector comprising a transgene encoding MTM1, (b) monitoring the patient for development of cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, (c) administering to the patient an anti-cholestatic agent. In one aspect, the present disclosure refers to use of a viral vector comprising a transgene encoding MTM1 in the manufacture of a medicament for increasing diaphragm and/or respiratory muscle progression in a human patient diagnosed as having XLMTM, wherein the viral vector is to be administered to the patient in accordance with a method comprising: (a) administering to the patient a therapeutically effective amount of the viral vector, (b) monitoring the patient for development of cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and, if the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and (c) administering to the patient an anti-cholestatic agent.

In another example, the disclosure provides a method of treating XLMTM in a human patient in need thereof that is five years old or younger (e.g., 5 years old or younger, 4 years old or younger, 3 years old or younger, 2 years old or younger, 1 year old or younger, 12 months old or younger, 11 months old or younger, 10 months old or younger, 9 months old or younger, 8 months old or younger, 7 months old or younger, 6 months old or younger, 5 months old or younger, 4 months old or younger, 3 months old or younger, 2 months old or younger, or 1 month old or younger), the method including: (a) administering to the patient a therapeutically effective amount of a transgene encoding MTM1, (b) determining that the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and (c) administering to the patient an anti-cholestatic agent. In one aspect, the present disclosure refers to use of a viral vector comprising a transgene encoding MTM1 in the manufacture of a medicament for treating XLMTM in a human patient in need thereof that is five years old or younger, wherein the viral vector is to be administered to the patient in accordance with a method comprising: (a) administering to the patient a therapeutically effective amount of the viral vector, (b) determining that the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and (c) administering to the patient an anti-cholestatic agent.

In one aspect, the present disclosure refers to use of a viral vector comprising a transgene encoding MTM1 in the manufacture of a medicament for reducing stiffness and/or joint contractures in a human patient diagnosed as having XLMTM, wherein the viral vector is to be administered to the patient in accordance with a method comprising: (a) administering to the patient a therapeutically effective amount of the viral vector, (b) determining that the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and (c) administering to the patient an anti-cholestatic agent.

In one aspect, the present disclosure refers to use of a viral vector comprising a transgene encoding MTM1 in the manufacture of a medicament for increasing diaphragm and/or respiratory muscle progression in a human patient diagnosed as having XLMTM, wherein the viral vector is to be administered to the patient in accordance with a method comprising: (a) administering to the patient a therapeutically effective amount of the viral vector, (b) determining that the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and (c) administering to the patient an anti-cholestatic agent.

In another example, the disclosure provides a method of treating XLMTM in a human patient in need thereof that is five years old or younger (e.g., 5 years old or younger, 4 years old or younger, 3 years old or younger, 2 years old or younger, 1 year old or younger, 12 months old or younger, 11 months old or younger, 10 months old or younger, 9 months old or younger, 8 months old or younger, 7 months old or younger, 6 months old or younger, 5 months old or younger, 4 months old or younger, 3 months old

or younger, 2 months old or younger, or 1 month old or younger), the method including: (a) administering to the patient a therapeutically effective amount of a transgene encoding MTM1, (b) determining that the patient exhibits cholestasis, hyperbilirubinemia, or one or more symptoms thereof, and (c) administering to the patient an anti-cholestatic agent.

In another example, the disclosure provides a method of treating or preventing cholestasis or hyperbilirubinemia in a human patient that has XLMTM and who has been previously administered a transgene encoding MTM1, the method including administering to the patient an anti-cholestatic agent.

In another example, the disclosure provides a method of treating or preventing cholestasis or hyperbilirubinemia in a human patient that has XLMTM and who has been previously administered a viral vector including a transgene encoding MTM1 in an amount of less than about 3×10^{14} vg/kg (e.g., in an amount of less than about 3×10^{14} vg/kg, 2.9×10^{14} vg/kg, 2.8×10^{14} vg/kg, 2.7×10^{14} vg/kg, 2.6×10^{14} vg/kg, 2.5×10^{14} vg/kg, 2.4×10^{14} vg/kg, 2.3×10^{14} vg/kg, 2.2×10^{14} vg/kg, 2.1×10^{14} vg/kg, 2×10^{14} vg/kg, 1.9×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1×10^{14} vg/kg, 1×10^{14} vg/kg, 1×10^{13} vg/kg, 1×10^{12} vg/kg, 1×10^{11} vg/kg, 1×10^{10} vg/kg, 1×10^{9} vg/kg, 1×10^{8} vg/kg, or less), the method including administering to the patient an anti-cholestatic agent. In one aspect, the present disclosure refers to use of an anti-cholestatic agent in the manufacture of a medicament for treating or preventing cholestasis or hyperbilirubinemia in a human patient that has XLMTM and who has been previously administered a viral vector comprising a transgene encoding MTM1 in an amount of less than about 3×10^{14} vg/kg.

In another example, the disclosure provides a method of treating or preventing cholestasis or hyperbilirubinemia in a human patient that has XLMTM, has been previously administered a transgene encoding MTM1, and that was five years old or younger (e.g., 5 years old or younger, 4 years old or younger, 3 years old or younger, 2 years old or younger, 1 year old or younger, 12 months old or younger, 11 months old or younger, 10 months old or younger, 9 months old or younger, 8 months old or younger, 7 months old or younger, 6 months old or younger, 5 months old or younger, 4 months old or younger, 3 months old or younger, 2 months old or younger, or 1 month old or younger) at the time of administration of the transgene, the method including administering to the patient an anti-cholestatic agent. In one aspect, the present disclosure refers to use of an anti-cholestatic agent in the manufacture of a medicament for treating or preventing cholestasis or hyperbilirubinemia in a human patient that has XLMTM, has been previously administered a viral vector comprising a transgene encoding MTM1, and that was five years old or younger at the time of administration of the viral vector.

In some examples of any of the foregoing aspects, the transgene encoding MTM1 was administered to the patient by transduction with a viral vector containing a transgene encoding MTM1.

In some examples of any of the foregoing aspects, the patient is five years old or younger (e.g., 5 years old or younger, 4 years old or younger, 3 years old or younger, 2 years old or younger, 1 year old or younger, 12 months old or younger, 11 months old or younger, 10 months old or younger, 9 months old or younger, 8 months old or younger, 7 months old or younger, 6 months old or younger, 5 months old or younger, 4 months old or younger, 3 months old or younger, 2 months old or younger, or 1 month old or younger) at the time of administration of the transgene or viral vector.

In some examples of any of the foregoing aspects, the patient is four years old or younger (e.g., 4 years old or younger, 3 years old or younger, 2 years old or younger, 1 year old or younger, 12 months old or younger, 11 months old or younger, 10 months old or younger, 9 months old or younger, 8 months old or younger, 7 months old or younger, 6 months old or younger, 5 months old or younger, 4 months old or younger, 3 months old or younger, 2 months old or younger, or 1 month old or younger) at

the time of administration of the transgene or viral vector, optionally wherein the patient is three years old or younger (e.g., 3 years old or younger, 2 years old or younger, 1 year old or younger, 12 months old or younger, 11 months old or younger, 10 months old or younger, 9 months old or younger, 8 months old or younger, 7 months old or younger, 6 months old or younger, 5 months old or younger, 4 months old or younger, 3 months old or younger, 2 months old or younger, or 1 month old or younger), two years old or younger (e.g., 2 years old or younger, 1 year old or younger, 12 months old or younger, 11 months old or younger, 10 months old or younger, 9 months old or younger, 8 months old or younger, 7 months old or younger, 6 months old or younger, 5 months old or younger, 4 months old or younger, 3 months old or younger, 2 months old or younger, or 1 month old or younger), one year old or younger (e.g., 1 year old or younger, 12 months old or younger, 11 months old or younger, 10 months old or younger, 9 months old or younger, 8 months old or younger, 7 months old or younger, 6 months old or younger, 5 months old or younger, 4 months old or younger, 3 months old or younger, 2 months old or younger, or 1 month old or younger), or six months old or younger (e.g., 6 months old or younger, 5 months old or younger, 4 months old or younger, 3 months old or younger, 2 months old or younger, or 1 month old or younger).

In some examples of any of the foregoing aspects, the patient was from about 1 month old to about 5 years old (e.g., about 1 month old to about 5 years old, about 2 months old to about 5 years old, about 3 months old to about 5 years old, about 4 months old to about 5 years old, about 5 months old to about 5 years old, about 6 months old to about 5 years old, about 1 year old to about 5 years old, about 2 years old to about 5 years old, about 3 years old to about 5 years old, or about 4 years old to about 5 years old) at the time of administration of the transgene or viral vector.

In some examples of any of the foregoing aspects, the viral vector is administered to the patient in an amount of less than about 3×10^{14} vg/kg (e.g., in an amount of less than about 3×10^{14} vg/kg, 2.9×10^{14} vg/kg, 2.8×10^{14} vg/kg, 2.7×10^{14} vg/kg, 2.6×10^{14} vg/kg, 2.5×10^{14} vg/kg, 2.4×10^{14} vg/kg, 2.3×10^{14} vg/kg, 2.2×10^{14} vg/kg, 2.1×10^{14} vg/kg, 2×10^{14} vg/kg, 1.9×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1×10^{14} vg/kg, 1×10^{14} vg/kg, 1×10^{13} vg/kg, 1×10^{12} vg/kg, 1×10^{11} vg/kg, 1×10^{10} vg/kg, 1×10^{9} vg/kg, 1×10^{8} vg/kg, or less).

In some examples of any of the foregoing aspects, the viral vector is administered to the patient in an amount of less than about 2.5×10^{14} vg/kg (e.g., in an amount of less than about 2.5×10^{14} vg/kg, 2.4×10^{14} vg/kg, 2.3×10^{14} vg/kg, 2.2×10^{14} vg/kg, 2.1×10^{14} vg/kg, 2×10^{14} vg/kg, 1.9×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1×10^{14} vg/kg, 1×10^{14} vg/kg, 1×10^{13} vg/kg, 1×10^{12} vg/kg, 1×10^{11} vg/kg, 1×10^{10} vg/kg, 1×10^{9} vg/kg, 1×10^{8} vg/kg, or less), optionally wherein the viral vector is administered to the patient in an amount of less than about 2×10^{14} vg/kg (e.g., in an amount of less than about 2×10^{14} vg/kg, 1.9×10^{14} vg/kg, 1.8×10^{14} vg/kg, 1.7×10^{14} vg/kg, 1.6×10^{14} vg/kg, 1.5×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.2×10^{14} vg/kg, 1.1×10^{14} vg/kg, 1×10^{14} vg/kg, 1×10^{14} vg/kg, 1×10^{13} vg/kg, 1×10^{12} vg/kg, 1×10^{11} vg/kg, 1×10^{10} vg/kg, 1×10^{9} vg/kg, 1×10^{8} vg/kg, or less), less than about 1.5×10^{14} vg/kg (e.g., less than about 1.5×10^{14} vg/kg, 1.4×10^{14} vg/kg, 1.3×10^{14} vg/kg, 1.2×10^{14}

vg/kg, 1.1 x 10^{14} vg/kg, 1 x 10^{14} vg/kg, 1 x 10^{14} vg/kg, 1 x 10^{13} vg/kg, 1 x 10^{12} vg/kg, 1 x 10^{11} vg/kg, 1 x 10^{10} vg/kg, 1 x 10^{9} vg/kg, 1 x 10^{8} vg/kg, or less), or less than about 1.4 x 10^{14} vg/kg (e.g., less than about 1 x 10^{14} vg/kg, 1 x 10^{14} vg/kg, 1 x 10^{13} vg/kg, 1 x 10^{12} vg/kg, 1 x 10^{11} vg/kg, 1 x 10^{10} vg/kg, 1 x 10^{9} vg/kg, 1 x 10^{8} vg/kg, or less).

In some examples of any of the foregoing aspects, the viral vector is administered to the patient in an amount of from about 3 x 10^{13} vg/kg to about 2.3 x 10^{14} vg/kg, optionally wherein the viral vector is administered to the patient in an amount of from about 8 x 10^{13} vg/kg to about 1.8 x 10^{14} vg/kg, from about 1 x 10^{14} vg/kg to about 1.6 x 10^{14} vg/kg, from about 1.1 x 10^{14} vg/kg to about 1.5 x 10^{14} vg/kg, or from about 1.2 x 10^{14} vg/kg to about 1.4 x 10^{14} vg/kg. For example, the viral vector may be administered to the patient in an amount of about 3 x 10^{13} vg/kg, 3.1 x 10^{13} vg/kg, 3.2 x 10^{13} vg/kg, 3.3 x 10^{13} vg/kg, 3.4 x 10^{13} vg/kg, 3.5 x 10^{13} vg/kg, 3.6 x 10^{13} vg/kg, 3.7 x 10^{13} vg/kg, 3.8 x 10^{13} vg/kg, 3.9 x 10^{13} vg/kg, 4 x 10^{13} vg/kg, 4.1 x 10^{13} vg/kg, 4.2 x 10^{13} vg/kg, 4.3 x 10^{13} vg/kg, 4.4 x 10^{13} vg/kg, 4.5 x 10^{13} vg/kg, 4.6 x 10^{13} vg/kg, 4.7 x 10^{13} vg/kg, 4.8 x 10^{13} vg/kg, 4.9 x 10^{13} vg/kg, 5 x 10^{13} vg/kg, 5.1 x 10^{13} vg/kg, 5.2 x 10^{13} vg/kg, 5.3 x 10^{13} vg/kg, 5.4 x 10^{13} vg/kg, 5.5 x 10^{13} vg/kg, 5.6 x 10^{13} vg/kg, 5.7 x 10^{13} vg/kg, 5.8 x 10^{13} vg/kg, 5.9 x 10^{13} vg/kg, 6 x 10^{13} vg/kg, 6.1 x 10^{13} vg/kg, 6.2 x 10^{13} vg/kg, 6.3 x 10^{13} vg/kg, 6.4 x 10^{13} vg/kg, 6.5 x 10^{13} vg/kg, 6.6 x 10^{13} vg/kg, 6.7 x 10^{13} vg/kg, 6.8 x 10^{13} vg/kg, 6.9 x 10^{13} vg/kg, 7 x 10^{13} vg/kg, 7.1 x 10^{13} vg/kg, 7.2 x 10^{13} vg/kg, 7.3 x 10^{13} vg/kg, 7.4 x 10^{13} vg/kg, 7.5 x 10^{13} vg/kg, 7.6 x 10^{13} vg/kg, 7.7 x 10^{13} vg/kg, 7.8 x 10^{13} vg/kg, 7.9 x 10^{13} vg/kg, 8 x 10^{13} vg/kg, 8.1 x 10^{13} vg/kg, 8.2 x 10^{13} vg/kg, 8.3 x 10^{13} vg/kg, 8.4 x 10^{13} vg/kg, 8.5 x 10^{13} vg/kg, 8.6 x 10^{13} vg/kg, 8.7 x 10^{13} vg/kg, 8.8 x 10^{13} vg/kg, 8.9 x 10^{13} vg/kg, 9 x 10^{13} vg/kg, 9.1 x 10^{13} vg/kg, 9.2 x 10^{13} vg/kg, 9.3 x 10^{13} vg/kg, 9.4 x 10^{13} vg/kg, 9.5 x 10^{13} vg/kg, 9.6 x 10^{13} vg/kg, 9.7 x 10^{13} vg/kg, 9.8 x 10^{13} vg/kg, 9.9 x 10^{13} vg/kg, 1 x 10^{14} vg/kg, 1.1 x 10^{14} vg/kg, 1.2 x 10^{14} vg/kg, 1.3 x 10^{14} vg/kg, 1.4 x 10^{14} vg/kg, 1.5 x 10^{14} vg/kg, 1.6 x 10^{14} vg/kg, 1.7 x 10^{14} vg/kg, 1.8 x 10^{14} vg/kg, 1.9 x 10^{14} vg/kg, 2 x 10^{14} vg/kg, 2.1 x 10^{14} vg/kg, 2.2 x 10^{14} vg/kg, or 2.3 x 10^{14} vg/kg.

In some examples of any of the foregoing aspects, the viral vector is administered to the patient in an amount of about 1.3 x 10^{14} vg/kg.

In some examples of any of the foregoing aspects, the transgene or viral vector is administered to the patient in a single dose including the amount.

In some examples of any of the foregoing aspects, the transgene or viral vector is administered to the patient in two or more (e.g., two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, or ten or more) doses that, together, comprise the amount.

In some examples of any of the foregoing aspects, the transgene or viral vector is administered to the patient in two or more (e.g., two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, or ten or more) doses that each, individually, comprise the amount.

In some examples of any of the foregoing aspects, the two or more (e.g., two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, or ten or

more) doses are separated from one another by one year or more (e.g., one year or more, one year and six months or more, two years or more, three years or more, four years or more, or five years or more).

In some examples of any of the foregoing aspects, the two or more doses are administered to the patient within about 12 months (e.g., about 12 months, about 11 months, about 10 months, about 9 months, about 8 months, about 7 months, about 6 months, about 5 months, about 4 months, about 3 months, about 2 months, or about 1 month) of one another.

In some examples of any of the foregoing aspects, the viral vector is selected from the group consisting of adeno-associated virus (AAV), adenovirus, lentivirus, retrovirus, poxvirus, baculovirus, herpes simplex virus, vaccinia virus, and a synthetic virus.

In some examples, the viral vector is an AAV. In some examples, the AAV is an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAVrh10, or AAVrh74 serotype.

In some examples, the viral vector is a pseudotyped AAV. In some examples, the pseudotyped AAV is AAV2/8 or AAV2/9, optionally wherein the pseudotyped AAV is AAV2/8.

In some examples, the transgene encoding MTM1 is operably linked to a muscle specific promoter. In some examples, the muscle specific promotor is a desmin promoter, a muscle creatine kinase promoter, a myosin light chain promoter, a myosin heavy chain promoter, a cardiac troponin C promoter, a troponin I promoter, a myoD gene family promoter, an actin alpha promoter, an actin beta promoter, an actin gamma promoter, or a promoter within intron 1 of ocular paired like homeodomain 3. In some examples, the muscle specific promoter is a desmin promoter.

In some examples of any of the foregoing aspects, the viral vector is resamirigene bilparvovec.

In some examples of any of the foregoing aspects, the viral vector is administered to the patient by way of intravenous, intramuscular, intradermal, or subcutaneous administration.

In some examples of any of the foregoing aspects, the anti-cholestatic agent is selected from the group consisting of a bile acid, a farnesoid X receptor (FXR) ligand, a fibroblast growth factor 19 (FGF-19) mimetic, a Takeda-G-protein-receptor-5 (TGR5) agonist, a peroxisome proliferator-activated receptor (PPAR) agonist, a PPAR-alpha agonist, a PPAR-delta agonist, a dual PPAR-alpha and PPAR-delta agonist, an apical sodium-dependent bile acid transporter (ASBT) inhibitor, an immunomodulatory drug, an antifibrotic therapy, and a nicotinamide adenine dinucleotide phosphate oxidase (NOX) inhibitor.

In some examples, (i) the FXR ligand is obeticholic acid, cilofexor, tropifexor, tretinoin, or EDP-305; (ii) the FGF-19 mimetic is aldafermin; (iii) the TGR5 agonist is INT-777 or INT-767; (iv) the PPAR agonist is bezafibrate, seladelpar, or elafibrinor; (v) the PPAR-alpha agonist is fenofibrate; (vi) the PPAR-delta agonist is seladelpar; (vii) the dual PPAR-alpha and PPAR-delta agonist is elafibranor; (viii) the ASBT inhibitor is odevixibat, maralixibat, or linerixibat; (ix) the immunomodulatory drug is rituximab, abatacept, ustekinumab, infliximab, baricitinib, or FFP-104; (x) the antifibrotic therapy is a vitamin D receptor agonist or simtuzumab; and/or (xi) the NOX inhibitor is setanaxib.

In some examples, the bile acid is ursodeoxycholic acid (e.g., ursodiol), nor-ursodeoxycholic acid, or a pharmaceutically acceptable salt thereof. In some examples, the bile acid is ursodiol.

In some examples of any of the foregoing aspects, the bile acid is administered to the patient in a single dose. In some examples, the bile acid is administered to the patient in a plurality of doses.

In some examples, the bile acid is administered to the patient in an amount of from about 5 mg/kg/dose to about 20 mg/kg/dose, optionally wherein the bile acid is administered to the patient in an amount of from about 6 mg/kg/dose to about 19 mg/kg/dose, from about 7 mg/kg/dose to about 18 mg/kg/dose, from about 8mg/kg/dose to about 17 mg/kg/dose, from about 10 mg/kg/dose to about 15 mg/kg/dose, or from about 12 mg/kg/dose to about 13 mg/kg/dose. For example, the bile acid is administered to the patient in an amount of about 5 mg/kg/dose, 6 mg/kg/dose, 7 mg/kg/dose, 8 mg/kg/dose, 9 mg/kg/dose, 10 mg/kg/dose, 11 mg/kg/dose, 12 mg/kg/dose, 13 mg/kg/dose, 14 mg/kg/dose, 15 mg/kg/dose, 16 mg/kg/dose, 17 mg/kg/dose, 18 mg/kg/dose, 19 mg/kg/dose, or 20 mg/kg/dose.

In some examples, the bile acid is administered to the patient in an amount of from about 5 mg/kg/dose to about 11 mg/kg/dose, optionally wherein the bile acid is administered to the patient in an amount of from about 6 mg/kg/dose to about 10 mg/kg/dose, or from about 7 mg/kg/dose to about 9 mg/kg/dose. For example, the bile acid is administered to the patient in an amount of about 5 mg/kg/dose, 6 mg/kg/dose, 7 mg/kg/dose, 8 mg/kg/dose, 9 mg/kg/dose, 10 mg/kg/dose, or 11 mg/kg/dose.

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

In some examples, the bile acid is administered to the patient in one or more e.g., one or more, two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, or ten or more) doses per day, optionally wherein the bile acid is administered to the patient in one dose per day, in two doses per day, three doses per day, four doses per day, or five doses per day.

In some examples, the bile acid is administered to the patient in one dose per day.

In some examples, the bile acid is administered to the patient in an amount of from about 5 mg/kg/day to about 40 mg/kg/day, optionally wherein (i) the bile acid is administered to the patient in an amount of from about 6 mg/kg/day to about 39 mg/kg/day, from about 8 mg/kg/day to about 37 mg/kg/day, from about 13 mg/kg/day to about 32 mg/kg/day, or from about 20 mg/kg/day to about 25 mg/kg/day, or (ii) the bile acid is administered to the patient in an amount of from about 17 mg/kg/day to about 23 mg/kg/day, from about 18 mg/kg/day to about 22 mg/kg/day, or from about 19 mg/kg/day to about 21 mg/kg/day. For example, the bile acid is administered to the patient in an amount of about 5 mg/kg/day, 6 mg/kg/day, 7 mg/kg/day, 8 mg/kg/day, 9 mg/kg/day, 10 mg/kg/day, 11 mg/kg/day, 12 mg/kg/day, 13 mg/kg/day, 14 mg/kg/day, 15 mg/kg/day, 16 mg/kg/day, 17 mg/kg/day, 18 mg/kg/day, 19 mg/kg/day, 20 mg/kg/day, 25 mg/kg/day, 30 mg/kg/day, 35 mg/kg/day, or 40 mg/kg/day. In some examples, the bile acid is administered to the patient in an amount of 20 mg/kg/day.

In some examples, the bile acid is administered to the patient by way of a unit dosage form including 250 mg of the bile acid. In some examples of any of the foregoing aspects, the bile acid is administered to the patient by way of a unit dosage form including 500 mg of the bile acid.

In some examples of any of the foregoing aspects, the bile is administered to the patient by way of enteral administration.

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

In some examples of any of the foregoing aspects, the patient was born at greater than or equal to 35 weeks of gestational age and is or was from term age (e.g., adjusted term age) to about 5 years old (e.g., 1 day old to about 5 years old, 2 days old to about 5 years old, 3 days old to about 5 years old, 4 days old to about 5 years old, 5 days old to about 5 years old, 6 days old to about 5 years old, 7 days old to about 5 years old, 8 days old to about 5 years old, 9 days old to about 5 years old, 10 days old to about 5 years old, 11 days old to about 5 years old, 12 days old to about 5 years old, 13 days old to about 5 years old, 14 days old to about 5 years old, 15 days old to about 5 years old, 16 days old to about 5 years old, 17 days old to about 5 years old, 18 days old to about 5 years old, 19 days old to about 5 years old, 20 days old to about 5 years old, 25 days old to about 5 years old, one month old to about 5 years old, two months old to about 5 years old, 3 months old to about 5 years old, 4 months old to about 5 years old, 5 months old to about 5 years old, 6 months old to about 5 years old, 1 year old to about 5 years old, 2 years old to about 5 years old, 3 years old to about 5 years old, and 4 years old to about 5 years old) at the time of administration of the transgene or viral vector.

In some examples of any of the foregoing aspects, the patient is male.

In some examples of any of the foregoing aspects, the patient requires mechanical ventilatory support, optionally wherein mechanical ventilatory support includes invasive mechanical ventilatory support and noninvasive mechanical ventilatory support.

In some examples of any of the foregoing aspects, upon administering the transgene or viral vector to the patient, the patient exhibits a change from baseline in hours of mechanical ventilation support over time, optionally wherein the patient exhibits the change from baseline in hours of mechanical ventilation support over time by about 24 weeks after administration of the transgene or viral vector to the patient, optionally wherein the patient displays the change from baseline in hours of mechanical ventilation support over time by about 20 weeks, 16 weeks, 12 weeks, 8 weeks, or 4 weeks after administration of the viral vector to the patient.

In some examples of any of the foregoing aspects, upon administering the transgene or viral vector to the patient, the patient achieves functionally independent sitting for at least 30 seconds, optionally wherein the patient achieves the functionally independent sitting by about 24 weeks after administration of the transgene or viral vector to the patient, optionally wherein the patient displays the functionally independent sitting for at least 30 seconds by about 20 weeks, 16 weeks, 12 weeks, 8 weeks, or 4 weeks after administration of the viral vector to the patient.

In some examples of any of the foregoing aspects, upon administering the transgene or viral vector to the patient, the patient displays a reduction in required mechanical ventilator support to about 16 hours or less per day, optionally wherein the patient displays the reduction in required mechanical ventilator support by about 24 weeks after administration of the viral vector to the patient, optionally wherein the patient displays the reduction in required mechanical ventilator support by about 20 weeks, 16 weeks, 12 weeks, 8 weeks, or 4 weeks after administration of the viral vector to the patient.

In some examples of any of the foregoing aspects, upon administering the transgene or viral vector to the patient, the patient displays a change from baseline on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), optionally wherein the patient displays the change from baseline on the CHOP INTEND by about 24 weeks after administration of the transgene or viral vector to the patient, optionally wherein the patient displays the change from baseline on the CHOP INTEND by about 20 weeks, 16 weeks, 12 weeks, 8 weeks, or 4 weeks after administration of the viral vector to the patient.

In some examples of any of the foregoing aspects, upon administering the transgene or viral vector to the patient, the patient displays a change from baseline in (MIP), optionally wherein the patient displays the change from baseline in MIP by about 24 weeks after administration of the viral vector to the patient, optionally wherein the patient displays the change from baseline in MIP by about 20 weeks, 16 weeks, 12 weeks, 8 weeks, or 4 weeks after administration of the viral vector to the patient.

In some examples of any of the foregoing aspects, upon administering the transgene or viral vector to the patient, the patient displays a change from baseline in quantitative analysis of myotubularin expression in a muscle biopsy, optionally wherein the patient displays the change from baseline in quantitative analysis of myotubularin expression in a muscle biopsy by about 24 weeks after administration of the transgene or viral vector to the patient, optionally wherein the patient displays the change from baseline in quantitative analysis of myotubularin expression in a muscle biopsy by about 20 weeks, 16 weeks, 12 weeks, 8 weeks, or 4 weeks after administration of the viral vector to the patient. In some examples, the change from baseline in quantitative analysis of myotubularin expression in a muscle biopsy persists for at least 48 weeks (e.g., 49 weeks, 50 weeks, 51 weeks, 52, weeks, 1 year, or 2 years) after administration of the viral vector to the patient.

In some examples of any of the foregoing aspects, upon administering the viral vector to the patient, the patient displays a reduction of stiffness and/or joint contractures, optionally wherein the patient displays the reduction of stiffness and/or joint contractures by about 24 weeks after administration of the viral vector to the patient, optionally wherein the patient displays the reduction of stiffness and/or joint contractures by about 20 weeks, 16 weeks, 12 weeks, 8 weeks, or 4 weeks after administration of the viral vector to the patient.

In some examples of any of the foregoing aspects, upon administering the viral vector to the patient, the patient displays diaphragm and/or respiratory muscle progression, optionally wherein the patient displays the diaphragm and/or respiratory muscle progression by about 24 weeks after administration of the viral vector to the patient, optionally wherein the patient displays the diaphragm

and/or respiratory muscle progression by about 20 weeks, 16 weeks, 12 weeks, 8 weeks, or 4 weeks after administration of the viral vector to the patient.

In some examples of any of the foregoing aspects, the patient is determined to exhibit cholestasis or one or more symptoms thereof by a finding that the patient exhibits a serum total bile acids level that is greater than 14 µmol/L (e.g., greater than 14 µmol/L, 15 µmol/L, 16 µmol/L, 17 µmol/L, 18 µmol/L, 19 µmol/L, 20 µmol/L, 21 µmol/L, 22 µmol/L, 23 µmol/L, 24 µmol/L, 25 µmol/L, 26 µmol/L, 27 µmol/L, 28 µmol/L, 29 µmol/L, 30 µmol/L, 31 µmol/L, 32 µmol/L, 33 µmol/L, 34 µmol/L, 35 µmol/L, 36 µmol/L, 37 µmol/L, 38 µmol/L, 39 µmol/L, 40 µmol/L, 41 µmol/L, 42 µmol/L, 43 µmol/L, 44 µmol/L, 45 µmol/L, 46 µmol/L, 47 µmol/L, 48 µmol/L, 49 µmol/L, 50 µmol/L, 51 µmol/L, 52 µmol/L, 53 µmol/L, 54 µmol/L, 55 µmol/L, 56 µmol/L, 57 µmol/L, 58 µmol/L, 59 µmol/L, 60 µmol/L, 61 µmol/L, 62 µmol/L, 63 µmol/L, 64 µmol/L, 65 µmol/L, 66 µmol/L, 67 µmol/L, 68 µmol/L, 69 µmol/L, 70 µmol/L, 71 µmol/L, 72 µmol/L, 73 µmol/L, 74 µmol/L, 75 µmol/L, 76 µmol/L, 77 µmol/L, 78 µmol/L, 79 µmol/L, 80 µmol/L, 81 µmol/L, 82 µmol/L, 83 µmol/L, 84 µmol/L, 85 µmol/L, 86 µmol/L, 87 µmol/L, 88 µmol/L, 89 µmol/L, 90 µmol/L, 91 µmol/L, 92 µmol/L, 93 µmol/L, 94 µmol/L, 95 µmol/L, 96 µmol/L, 97 µmol/L, 98 µmol/L, 99 µmol/L, or 100 µmol/L).

In some examples of any of the foregoing aspects, the patient is determined to exhibit cholestasis or one or more symptoms thereof by a finding that the patient exhibits one or more parameters in a blood test that is increased or decreased relative to a reference level.

In some examples of any of the foregoing aspects, the blood test is a liver function test.

In some examples of any of the foregoing aspects, the one or more parameters includes the level of gamma-glutamyl transferase, alkaline phosphatase, aspartate aminotransferase, and/or alanine aminotransferase.

In some examples of any of the foregoing aspects, the patient is determined to exhibit hyperbilirubinemia or one or more symptoms thereof by a finding that the patient exhibits a bilirubin level that is greater than 1 mg/dL (e.g., greater than 1 mg/dL, 1.1 mg/dL, 1.2 mg/dL, 1.3 mg/dL, 1.4 mg/dL, 1.5 mg/dL, 1.6 mg/dL, 1.7 mg/dL, 1.8 mg/dL, 1.9 mg/dL, 2 mg/dL, 2.1 mg/dL, 2.2 mg/dL, 2.3 mg/dL, 2.4 mg/dL, 2.5 mg/dL, 2.6 mg/dL, 2.7 mg/dL, 2.8 mg/dL, 2.9 mg/dL, 3 mg/dL, 3.1 mg/dL, 3.2 mg/dL, 3.3. mg/dL, 3.4 mg/dL, 3.5 mg/dL, 3.6 mg/dL, 3.7 mg/dL, 3.8 mg/dL, 3.9 mg/dL, 4 mg/dL, 4.1 mg/dL, 4.2 mg/dL, 4.3 mg/dL, 4.4 mg/dL, 4.5 mg/dL, 4.6 mg/dL, 4.7 mg/dL, 4.8 mg/dL, 4.9 mg/dL, 5 mg/dL, 10 mg/dL, 15 mg/dL, 20 mg/dL, 30 mg/dL, 40 mg/dL, 50 mg/dL, 60 mg/dL, 70 mg/dL, 80 mg/dL, 90 mg/dL, or 100 mg/dL) in a bilirubin test.

In some examples of any of the foregoing aspects, upon administering the viral vector to the patient, the patient displays a bilirubin level that is greater than 1 mg/dL (e.g., greater than 1 mg/dL, 1.1 mg/dL, 1.2 mg/dL, 1.3 mg/dL, 1.4 mg/dL, 1.5 mg/dL, 1.6 mg/dL, 1.7 mg/dL, 1.8 mg/dL, 1.9 mg/dL, 2 mg/dL, 2.1 mg/dL, 2.2 mg/dL, 2.3 mg/dL, 2.4 mg/dL, 2.5 mg/dL, 2.6 mg/dL, 2.7 mg/dL, 2.8 mg/dL, 2.9 mg/dL, 3 mg/dL, 3.1 mg/dL, 3.2 mg/dL, 3.3. mg/dL, 3.4 mg/dL, 3.5 mg/dL, 3.6 mg/dL, 3.7 mg/dL, 3.8 mg/dL, 3.9 mg/dL, 4 mg/dL, 4.1 mg/dL, 4.2 mg/dL, 4.3 mg/dL, 4.4 mg/dL, 4.5 mg/dL, 4.6 mg/dL, 4.7 mg/dL, 4.8 mg/dL, 4.9 mg/dL, 5 mg/dL, 10 mg/dL, 15 mg/dL, 20 mg/dL, 30 mg/dL, 40 mg/dL, 50 mg/dL,

60 mg/dL, 70 mg/dL, 80 mg/dL, 90 mg/dL, or 100 mg/dL) in a bilirubin test by about 3 weeks after administration of the viral vector to the patient.

In some examples of any of the foregoing aspects, the bilirubin level comprises a direct bilirubin level or a total bilirubin level.

In some examples of any of the foregoing aspects, the patient is determined to exhibit cholestasis, hyperbilirubinemia, or one or more symptoms thereof by a finding that the patient exhibits a parameter in blood test that is increased relative to a reference level.

In some examples of any of the foregoing aspects, the parameter includes the level of a serum bile acid.

In some examples of any of the foregoing aspects, the serum bile acid is cholic acid, chenodeoxycholic acid, deoxycholic acid, or ursodeoxycholic acid.

In some examples of any of the foregoing aspects, the blood test is a liver function test.

In some examples of any of the foregoing aspects, the parameter includes the level of aspartate aminotransferase or alanine aminotransferase.

In one example, the disclosure provides a kit including a transgene encoding MTM1 and a package insert, wherein the package insert instructs a user of the kit to administer the transgene to a patient having XLMTM in accordance with the method of any one of the foregoing aspects.

In one example, the disclosure provides a kit including a viral vector including a transgene encoding MTM1 and a package insert, wherein the package insert instructs a user of the kit to administer the viral vector to a patient having XLMTM in accordance with the method of any one of the foregoing aspects. In one aspect, the present disclosure refers to a kit comprising a viral vector comprising a transgene encoding MTM1 and a package insert, wherein the package insert instructs a user of the kit to administer the viral vector to a patient having XLMTM in accordance with the use of any one of the foregoing aspects.

In one example, the disclosure provides a kit including an anti-cholestatic agent and a package insert, wherein the package insert instructs a user of the kit to administer the anti-cholestatic agent to a patient to treat or prevent cholestasis or hyperbilirubinemia in accordance with the method of any one of the foregoing aspects. In one aspect, the present disclosure refers to a kit comprising an anti-cholestatic agent and a package insert, wherein the package insert instructs a user of the kit to administer the anti-cholestatic agent to a patient to treat or prevent cholestasis or hyperbilirubinemia in accordance with the use of any one of the foregoing aspects.

Brief Description of the Drawings

FIG. 1. is a schematic drawing of an exemplary pseudotyped adeno-associated virus (AAV) 2/8 (AAV2/8) viral vector for the expression of the human myotubularin 1 (hMTM1) gene (e.g., resamirigene bilparvovec). From left to right, the shaded arrows and rectangles represents the nucleic acid sequences encoding a human desmin (hDes) promotor (SEQ ID NO: 3) operatively linked to a Beta-globin Intron, a hMTM1 gene (SEQ ID NO: 4), a Beta-globin poly-adenylation signal (Beta-globin_pA), and flanking AAV2 inverted terminal repeat sequences (ITR). Abbreviations: AAV2_ITR, adeno associated virus 2 inverted terminal repeat; Beta-globin_pA, human Beta-globin polyadenylation signal; hDes, human desmin promotor; hMTM1, human myotubularin complementary DNA.

FIG. 2 is a graph showing changes in total and/or direct bilirubin (fold over the upper limit of normal (ULN)) in human patients treated with 3.0×10^{14} vg/kg (3e14; light gray) or 1.0×10^{14} vg/kg (1e14; dark gray) of resamirigene bilparvovec, as described in Example 2, below. Solid rectangles define the 25th to 75th percentiles; crosses define the mean; lower whiskers define the minimum observations