Taylor & Francis
Taylor & Francis Group

Expert Opinion on Biological Therapy

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iebt20

X-linked myotubular myopathy: an untreated treatable disease

Cristina Martin & Laurent Servais

To cite this article: Cristina Martin & Laurent Servais (2025) X-linked myotubular myopathy: an untreated treatable disease, Expert Opinion on Biological Therapy, 25:4, 379-394, DOI: 10.1080/14712598.2025.2473430

To link to this article: https://doi.org/10.1080/14712598.2025.2473430

Published online: 06 Mar 2025.

EXPERT OPINION ON BIOLOGICAL THERAPY
2025, VOL. 25, NO. 4, 379–394
https://doi.org/10.1080/14712598.2025.2473430

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

X-linked myotubular myopathy: an untreated treatable disease

Cristina Martin[a] and Laurent Servais[a,b]

[a]Department of Paediatrics, MDUK Oxford Neuromuscular Centre & NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK; [b]Department of Pediatrics, Neuromuscular Reference Center, University and University Hospital of Liège, Liège, Belgium

ABSTRACT

Introduction: X-linked myotubular myopathy (XLMTM) is a life-threatening congenital disorder characterized by severe respiratory and motor impairment. This disease presents significant therapeutic challenges, with various strategies being explored to address its underlying pathology. Among these approaches, gene replacement therapy has demonstrated substantial functional improvements in clinical trials. However, safety issues emerged across different therapeutic approaches, highlighting the need for further research.

Areas covered: This review provides a comprehensive analysis of the data gathered from natural history studies, preclinical models and clinical trials, with a particular focus on gene replacement therapy for XLMTM. The different therapeutic strategies are addressed, including their outcomes and associated safety concerns.

Expert opinion: Despite the encouraging potential of gene therapy for XLMTM, the occurrence of safety challenges emphasizes the urgent need for a more comprehensive understanding of the disease's complex phenotype. Enhancing preclinical models to more accurately mimic the full spectrum of disease manifestations will be crucial for optimizing therapeutic strategies and reducing risks in future clinical applications.

ARTICLE HISTORY
Received 31 October 2024
Accepted 25 February 2025

KEYWORDS
X-linked myotubular myopathy; centronuclear myopathy; myotubularin; gene therapy; adeno-associated viral vectors; neuromuscular junction; congenital myopathy

1. Introduction

X-linked myotubular myopathy (XLMTM, OMIM 310,400) is a devastating congenital disease. This childhood neuromuscular disorder presents an incidence of approximately 1:50,000 in males [1,2]. Severe XLMTM has a poor prognosis as it presents a high death rate, mostly because of respiratory failure [3–5].

In the most severe and frequent clinical presentation, XLMTM male living patients exhibit severe global hypotonia, hyporeflexia or areflexia and respiratory insufficiency leading to early death [6–8]. Patients surviving the neonatal period present with a delay in motor milestones and most of the patients do not achieve independent ambulation [3,9]. In addition, patients eventually exhibit motor regression- progression of respiratory insufficiency, and early death is frequent. Additionally, recent studies have frequently identified liver dysfunction in patients, which is linked to intrahepatic cholestasis [10–13].

Although most of the heterozygous females are asymptomatic, manifesting carriers may experience myalgia, muscle weakness and rarely respiratory failure [14–18].

Different phenotypes of XLMTM have been classified into severe, moderate and mild based on the delay in motor milestones, need for respiratory support, and achievement of independent ambulation [7,19]. Moderate and mild forms have been identified as progressive conditions with loss of acquired milestones and a decline in motor scales [9]. Nevertheless, since the publication of this classification, other milder phenotypes have been identified [20].

XLMTM is caused by mutations in the *myotubularin (MTM1)* gene [6,21]. This gene codes for a lipid phosphatase, which dephosphorylates phosphatidylinositol-3-phosphate (PtdIns3P) and phosphatidylinositol 3,5-bisphosphate (PtdIns(3,5)P2) [22,23]. It is ubiquitously expressed throughout the body and is involved in vacuole formation and transport, desmin assembly and architecture, mitochondrial morphology and positioning, and cytoskeletal organization [23–27].

The lack of functional myotubularin disrupts triad structure, leading to defective excitation-contraction coupling and impaired neuromuscular junction (NMJ) structure and function. This deficiency also results in centrally located cell nuclei, organelle disorganization, pale peripheral halos detectable with oxidative staining and perinuclear vacuole-like areas [28–32]. Additionally, loss of myotubularin triggers dysregulation of the ubiquitin-proteasome system, AKT/mTOR signaling and apoptotic pathways [27,33–36].

Several re-positioned medications are used off-label, such as pyridostigmine and salbutamol [29,31,37–40] but their efficacy has never been formally demonstrated.

Currently, no disease-modifying treatments have been approved for XLMTM. Although gene therapy has been demonstrated to be transformative for patients with XLMTM [41], clinical development is currently on hold for Sudden Unexpected Serious Adverse Reactions (SUSAR) that led to death in four patients [42]. Oligo-antisense development (NCT04033159) and tamoxifen (NCT04915846) have also recently been stopped for safety reasons during clinical trials [43,44].

CONTACT Laurent Servais laurent.servais@paediatrics.ox.ac.uk Department of Paediatrics, MDUK Oxford Neuromuscular Centre & NIHR Oxford Biomedical Research Centre, University of Oxford, John Radcliffe Hospital- Children Hospital, Academic Level 2, Headley Way, Headington, Oxford OX3 9DU, UK

Article highlights

- X-linked myotubular myopathy (XLMTM) is a severe congenital disorder characterized by high mortality and severe motor and respiratory dysfunction.
- Gene therapy has shown transformative potential for XLMTM, with clinical trials demonstrating marked improvements in motor function and respiratory outcomes.
- Serious safety concerns have emerged in a gene therapy trial, prompting the FDA to halt the clinical studiy.
- Additional therapeutic strategies, such as the use of estrogen modulators and antisense oligonucleotides, have also faced clinical holds due to safety issues.
- Existing preclinical models do not fully capture the disease's complexity, lacking several clinical features that are present in patients.
- A deeper understanding of the complex phenotype associated with XLMTM is crucial to advance therapeutic development and improve patient outcomes.

The improvement of neuromuscular and respiratory functions in patients following gene therapy illustrates the possibility to treat XLMTM and to significantly ameliorate the conditions of patients [42]. This review aims to analyze the different treatment options, the reasonable expectations they may generate, the safety limitations and the ethical issues related to the benefit/risk ratio.

2. Natural history studies

Natural History Studies have consistently demonstrated the severity of XLMTM across all age ranges (Table 1). Retrospective studies, such as RECENSUS (NCT02231697) have captured data on the patients deceased during the neonatal period, thereby illustrating the high mortality rate associated with the congenital form, which was reported at 64% for patients under 5 years of age [45]. On the other hand, two prospective studies, INCEPTUS (NCT02704273) and NatHis-MTM (NCT02057705), monitored young patients with respiratory dysfunction [12] and the entire spectrum of patients [9], respectively.

INCEPTUS was initiated in 2016 to collect longitudinal data on XLMTM and to serve as a run-in study before the ASPIRO gene therapy phase I trial (NCT03199469). This study was focused on a young and severely affected population, all under four years old and dependent on mechanical ventilatory support. Given the inclusion criteria participants exhibited low respiratory capacity, severely limited motor functions and inability to ambulate, and three of them succumbed to serious adverse events related to cardiopulmonary failure, aspiration pneumonia and hepatic hemorrhage. It should be noted that nearly a quarter of the patients exhibited hepatic disease and half of them received treatment for cholestatic and other hepatic conditions [12].

NatHis-MTM enrolled a broader range of patients who had survived beyond the neonatal period, providing a comprehensive perspective on the progression of the disease. The most significant finding, observed over a 1-year period, was the progressive decline in motor function. However, other analyzed outcomes, such as pulmonary capacity, remained stable within a 1-year timeframe [9].

3. Animal models

3.1. Murine models

The *MTM1* knockout (KO), *MTM1*$^{-/y}$ mouse, also referred to as *MTM1*δ4 mouse, represents the first animal model developed for XLMTM, created through a large deletion in exon 4 [46]. *MTM1* KO mice are the most extensively utilized models in preclinical studies due to their availability and ability to replicate most of the key features of XLMTM.

Since then, additional engineered murine models have been generated: (1) condition tissue-specific *MTM1*$^{-/y}$ mice, in which the MTM1 deficiency is limited to skeletal muscle utilizing a muscle-specific desmin promoter [35]; (2) *MTM1*$^{R69C/y}$ mice, which reproduce the mild XLMTM phenotype by knocking in the c.205C>T mutation, resulting in exon 4 skipping [47]; (3) *MTM1*$^{gt/y}$ mice, developed through gene trapping in intron 1, leading to a truncated, nonfunctional version of MTM1 and exhibiting similar muscle pathology compared to that observed in *MTM1*$^{-/y}$ mice [36]; (4) *MTM1*$^{\Delta 5/y}$ and *MTM1*$^{\Delta 7/y}$ mice, generated by deletions of 5 and 7 base pairs, respectively, within the *MTM1* gene, display similar features than *MTM1*$^{-/y}$ mice [48].

3.2. Zebrafish models

A zebrafish knockdown model was developed using morpholino antisense to reduce MTM1 expression. This knockdown model exhibits impaired skeletal muscle function and recapitulates the clinical manifestations observed in patients living with XLMTM [29,49]. However, it is important to note that MTM1 deficiency in this model does not impact autophagy [50].

Additionally, a homozygous zebrafish MTM1 mutant line (*MTM1*$^{\Delta 8/\Delta 8}$) was generated using zinc finger nucleases, leading to an early stop mutation as a result of an 8 base pairs deletion in exon 5 [51].

3.3. Canine models

Naturally occurring missense variants in the *MTM1* gene have been identified in dogs: the p.N155K mutation was found in Labrador Retrievers [52] and the pQ384P mutation was discovered in Rottweilers [53]. Both mutations result in a dramatic reduction in MTM1 levels.

These affected dogs present similar features to those observed in murine models and effectively reproduce the phenotype associated with human XLMTM [52–55]. Nevertheless, it should be emphasized that canine carriers do not exhibit any pathological features [56].

4. Potential therapeutic targets

The different therapeutic targets and the corresponding preclinical and clinical data are summarized in. Table 2

4.1. Myotubularin

More than 250 pathogenic variants have been described for the *MTM1* gene [6,20,57–59]. In order to target the underlying

Table 1. XLMTM natural history studies.

Study	Trial ID	Study Type	Participants	Age	Countries	Completion dates	Duration	Primary objective	Key Results	Conclusions	References
MTMES	NCT01840657	Prospective and cross-sectional, non-interventional study	33 males	1 day to 42.3 years	North America	Apr 2013-Oct 2015	12 months	To collect clinical and non-clinical data on XLMTM patients.	88% of patients were non-ambulant. 81% required invasive respiratory support. 82% had a gastrostomy, 76% tracheostomy and 43% had learning disabilities. Average age of death: 6 years, 10 months. 24% mortality rate, with 83% of deaths attributed to respiratory complications.	XLMTM patients experience significant morbidities and require extensive mechanical interventions.	[3]
NatHis-MTM	NCT02057705	Prospective, multicenter, longitudinal study	45 males	3.5 months to 56.8 years	North America and Europe	Feb 2014-Jun 2017	36 months	To quantify disease burden and identify optimal outcome measures	29% had a mild phenotype, 16% intermediate, and 55% severe. 71% were not ambulant by 2 years of age. 82% needed respiratory support in the first year of life. 60% had scoliosis, 60% required gastrostomy, and 82% used feeding tubes. 25% had neutralizing antibodies, with 2 patients showing high inhibitory levels.	Progression of motor dysfunction within a 1-year period.	[9]
RECENSUS	NCT02231697	Retrospective, non-interventional, multicenter medical chart review	145 males, 126 with ventilatory support	Data not available	North America, South America, Europe and Australia	Sep 2014 - Dec 2019	Not applicable	To characterize disease manifestations and record medical management practices	Nearly 90% required respiratory support at birth. 48% ventilator dependency. 72% of patients had a tracheostomy by age 2, and 94% required gastrostomy. Average of 3.7 surgeries during the first year of life. 47% mortality among 126 patients on ventilatory support (59% in patients ≤5 years old). Respiratory failure was the most common cause of death (67%).	High mortality, predominantly due to respiratory failure, especially in the neonatal period.	[5,45]

(*Continued*)

Table 1. (Continued).

Study	Trial ID	Study Type	Participants	Age	Countries	Completion dates	Duration	Primary objective	Key Results	Conclusions	References
INCEPTUS	NCT02704273	Prospective, multicenter, non-interventional clinical assessment	34 males with ventilatory support	6 months to 32.9 years	North America and Europe	Jul 2016 - Sep 2019	32.9 months	To assess neuromuscular and respiratory outcomes through a longitudinal study	80% required permanent invasive ventilation; 20% used noninvasive ventilation. 97% had a gastrostomy and 80% tracheostomy. CHOP INTEND score ranged from 19 to 52 (mean: 35.1). 91% showed signs of hepatobiliary disease. 3 deaths (due to aspiration pneumonia, cardiopulmonary failure, and hepatic hemorrhage). 61 serious events, with 52 related to respiratory complications.	High mortality and frequent medical complications, with minimal motor improvement and a high prevalence of hepatobiliary disease over a 1-year period.	[12]

cause of the disease, *MTM1* replacement strategies have been developed, such as gene therapy [24,60–63] and enzyme replacement therapy [64], and have shown a dramatic efficacy on small and large animal models.

4.2. Myotubularin-related protein 2

Myotubularin-related protein 2 (MTMR2) belongs to the myotubularin-related proteins family and plays a key role in regulating cellular membrane trafficking [65]. It exhibits high expression levels in motor and sensory neurons [66]. Mutations in the *MTMR2* gene cause Charcot-Marie-Tooth disease, characterized by chronic degenerative neuropathy [67]. Similarly to MTM1, MTMR2 exhibits lipid phosphatase activity on PtdIns3P and PtdIns(3,5)P2 [23,68,69]. Consequently, this protein has been identified as a therapeutic target for XLMTM disease [70,71]. This strategy could represent an alternative or complementary approach to traditional gene replacement therapy

4.3. Dynamin 2

This ubiquitous enzyme, coded by the *DNM2* gene, presents GTPase activity and is involved in vesicular trafficking regulation, autophagy and cytoskeletal dynamics [72–75]. Mutations in this gene are associated with another form of centronuclear myopathy (CNM) [76]. Interestingly, patients living with XLMTM and *MTM1*-deficient mice model muscle biopsies show elevated levels of dynamin 2 (DNM2), suggesting that MTM1 and DNM2 share a common molecular pathway, i.e. a gain of function of DNM2 that is normally under MTM1 control [77,78]. Indeed, reducing DNM2 expression has been shown to rescue the XLMTM phenotype in mice [77].

4.4. Myostatin

This protein, which belongs to the transforming growth factor-beta family, is expressed by myocytes and plays a crucial role in muscle differentiation and growth [79]. Decreased levels of this protein have been associated with muscle hypertrophy [80]. Therefore, it has been hypothesized that inhibiting myostatin could be a potential therapeutic approach in a broad range of muscle wasting conditions, with only limited efficacy so far in Spinal Muscular Atrophy (SMA). Nevertheless, the myostatin signaling pathway is disrupted due to MTM1 deficiency, resulting in reduced levels of this protein in XLMTM. It has been hypothesized that this reduction is triggered as a countermeasure against muscular hypotrophy [81,82]. Consequently, the concentration of circulating myostatin may serve as a biomarker for assessing disease progression and treatment efficacy, considering the age, gender, and disease severity of patients [82].

4.5. NMJ dysfunction

It has been shown that abnormalities at the NMJ are one of the factors contributing to the pathogenesis of XLMTM disease, leading to dysregulated Ca^{2+} homeostasis which causes defective excitation-contraction coupling [31]. In the case of

acetylcholinesterase inhibitors, their mechanism of action facilitates longer persistence and therefore higher concentrations of acetylcholine molecules at the NMJ, thereby counteracting the effects of non-depolarizing neuromuscular blocking agents [83–85]. β-adrenergic agonists have been shown to improve structural defects and increase the NMJ area, however, the mechanism of action is not yet fully understood [86–88].

4.6. PI3KC2β kinase

This kinase is a member of the PI3-kinases family of proteins, which generates 3-phosphorylated phosphatidylinositol [89]. Within this family, class II PI3-kinases (PI3K) produce PtdIns3P and PtdIns(3,4)P2. PI3KC2β kinase, a class II PI3-kinase, is involved in endosomal trafficking and mTORC1 pathway [90,91]. Elevated levels of PtdIns(3,5)P2 have been detected in mice due to mutations in the MTM1 protein, leading to disrupted Ca^{2+} homeostasis [28,92].

4.7. Histone deacetylases

These enzymes are essential for crucial cellular processes, including transcription, cell cycle, signal transduction, chromatin remodeling and gene expression regulation [93]. The modulation of gene expression is mediated through the acetylation and deacetylation of transcription factors [94]. A significant upregulation of histone deacetylase-4, expressed in skeletal muscles, was detected in mature muscles from patients living with XLMTM. It has been hypothesized that this over-activation may impact the expression of muscle-specific transcripts, adversely affect the triad structure and induce pathogenic features resembling those of fetal muscle [95].

4.8. Amphiphysin 2

This protein is coded by the gene bridging integrator 1 (*BIN1*) and is involved in membrane curvature and remodeling, endocytosis, excitation-contraction coupling and nuclear positioning [96–99]. Mutations in *BIN1*, analogous to those in the *MTM1* gene, cause central nuclear myopathy [100]. MTM1 binds to and regulates amphiphysin 2, playing a critical role in the modulation of transverse tubule maturation [101,102]. Disruption of this interaction can result in muscular dysfunction, suggesting that overexpression of amphiphysin 2 may compensate for the loss of MTM1 in murine models [103].

4.9. mTORC1

The mechanistic target of rapamycin (mTOR) is a member of the phosphatidylinositol kinase-related kinases family. It forms the catalytic subunit of two distinct complexes: mTORC1, which regulates cell growth and metabolism, and mTORC2, involved in cell proliferation and survival [104]. mTORC1 signaling is overactivated in *MTM1* KO mice, leading to the inhibition of autophagy in skeletal muscle, which subsequently impairs the removal of protein aggregates and damaged mitochondria [36].

5. Pre-clinical and clinical data

5.1. Gene therapy

Gene replacement strategies have shown dramatic efficacy on small and large animal models [24,60–63].

Recombinant adeno-associated viruses (rAAV) have emerged as a powerful tool for gene replacement therapy in monogenic neuromuscular diseases. Over the past several years, major clinical breakthroughs have been achieved in both small and large animal models after a single administration of rAAV.

Nevertheless, several critical factors must be addressed in preclinical studies, including the definition of a safe dose-response ratio, the feasibility of wide dose scalation and the effectiveness of the therapy in older patients. It has been reported that over 5% of potentially eligible patients living with XLMTM present neutralizing antibodies against AAV8 [9].

5.1.1. MTM1 replacement strategies

MTM1 gene is a good candidate for rAAV-mediated gene therapy, as its coding sequencing can be effectively packaged without requiring sequence optimization. Gene editing is much more challenging considering the diversity of mutation and their different position in the gene [9].

An early study utilized rAAV1-CMV-MTM1 for intramuscular injection in *MTM1* KO mice to deliver *MTM1* complementary DNA (cDNA). This approach resulted in successful phenotypic correction, evidenced by increased muscle and myofiber volume, enhanced contractile force, and the centralization of nuclei within muscle cells. However, long-term effects or immune responses were not evaluated. Remarkably, alterations in membrane homeostasis, leading to the formation of packed membrane structures near the sarcolemma, were observed in the KO mice compared to wild-type mice receiving the same doses [24]. Similar outcomes were reported in a subsequent study employing rAAV8-pDesmin-MTM1, which demonstrated long-term correction of skeletal muscle pathology for up to one year in *MTM1* KO mice following systemic administration [60].

In *MTM1* KO mice, no systemic toxicity was identified, although focal inflammatory infiltrates and fibrotic lesions were reported in the hearts of the group treated with the highest dose [24,60].

Further studies in canine models harboring p.N155K mutation showed amelioration in gait and motor, neurological, and respiratory functions for up to 4 years after treatment with rAAV8-pDesmin-MTM1 via isolated limb perfusion and intravenous administration [60,61,63,105]. These therapeutic effects were dose-dependent and a homogeneous biodistribution of the vector was observed throughout the body. It should be noted that XLMTM dogs did not develop humoral or cellular immune responses and no off-target effects were detected [61].

Additionally, no acute or chronic toxicity was observed in dogs, with liver enzyme levels and cardiac tissue appearing entirely normal [60].

ASPIRO (NCT03199469) was the first gene therapy clinical trial for XLMTM utilizing a potential disease-modifying

Table 2. Preclinical and clinical approaches for XLMTM.

Target	Function	Strategy	Therapeutic approach	Treatment	Therapeutic effect	Current status	References
MTM1	Regulates muscle function, vacuole formation and transport, desmin assembly and architecture, mitochondrial structure and cytoskeletal organization	Replacement	Gene therapy	rAAV1-MTM1	Delivers MTM1 cDNA to muscle cells, correcting muscle pathology, improving myofiber size and contractile force.	Preclinical studies in mice.	[24]
				rAAV8-MTM1: AT132 (Resaminrigene bilparvovec)	Corrects myofiber size, improves respiratory and motor functions.	Phase 1/2/3 ASPIRO clinical trial on hold by the FDA due to SUSAR (NCT03199469).	[42,107]
			Cell therapy	Not applicable	Increases muscle mass, improves function, and regenerates NMJ.	Preclinical studies in mice.	[153]
			Enzyme replacement	3E10Fv-MTM1	Improves muscle function.	Preclinical studies in mice.	[64]
MTMR2	Regulates cellular membrane trafficking; lipid phosphatase activity on PtdIns3P and PtdIns(3,5)P2.	Overexpression	Gene therapy	rAAV9-MTMR2	Restores PtdIns3P levels, rescues muscle phenotype and extends lifespan in MTM1 KO mice.	Preclinical studies in mice.	[70,71]
BIN1	Involved in membrane curvature, endocytosis, and excitation-contraction coupling.	Overexpression	Gene therapy	rAAV8-BIN1	Extends lifespan, improves motor strength and histopathology in mouse models.	Preclinical study in mice.	[103]
DNM2	GTPase activity; regulates vesicular trafficking, autophagy, cytoskeletal dynamics.	Inhibition	ASO	DYN-101	Extends lifespan and restore muscle mass.	Phase 1/2 trials of DYN101 halted due to lack of efficacy and SUSAR (NCT04033159; NCT04743557).	[48,77,131,132]
		Inhibition	Chemical compound	Dynasore	Rescues cholestatic phenotype.	Preclinical study in zebrafish.	[13]
Myostatin	Regulates muscle differentiation and growth.	Inhibition	Protein	ActRIIB-mFC	Mild improvement in muscle function.	Preclinical studies in mice.	[81,140,141]
NMJ dysfunction	Impaired excitation-contraction coupling due to dysregulated Ca2+ homeostasis.	Restoration	Chemical compound	Pyridostigmine	Improves NMJ function, enhances muscle performance.	Preclinical studies in zebrafish and in mice, also tested in humans.	[31,37]
		Restoration	Chemical compound	Salbutamol/albuterol	Improves NMJ function, enhances muscle performance and reduce fatigue.	Phase IV trial ongoing (NCT05099107).	[39,40]
PI3KC2β kinase	Involved in endosomal trafficking and mTORC1 pathway regulation.	Inhibition	Chemical compound	Wortmannin	Improves motor function and muscle histology, mild efficacy.	Preclinical studies in mice.	[51,92]

(*Continued*)

Table 2. (Continued).

Target	Function	Strategy	Therapeutic approach	Treatment	Therapeutic effect	Current status	References
Histone deacetylase	Modulate gene expression through acetylation/ deacetylation of transcription factors.	Inhibition	Chemical compound	Valproic acid	Ameliorates phenotypic features in XLMTM mouse and zebrafish models.	Preclinical studies in zebrafish and mice.	[148]
mTORC1	Regulates cell growth, metabolism, and autophagy.	Inhibition	Chemical compound	AZD8055	Restores autophagy, increases muscle mass and improves mitochondrial function.	Preclinical study in mice.	[34,36]
Estrogen receptor	Involved in DNM2, desmin and BIN1 pathways.	Inhibition	Chemical compound	Tamoxifen	Extends lifespan, improves muscle function.	Phase 1/2 TAM4MTM trial terminated due to SUSAR (NCT04915846).	[150,151]

approach. This therapy, named Resaminrigene bilparvovec (AT132), consisted of a single intravenous administration of a non-replicating rAAV8 delivering full-length human *MTM1* complementary DNA under the control of a muscle-specific desmin promoter and enhancer. Additionally, the expression cassette was engineered to include a synthetic DNA sequence complementary to the *MTM1* coding region, along with a second intron and a polyadenylation sequence derived from the human β-globin gene. This expression cassette was flanked by inverted terminal repeats (ITRs) from the AAV2 serotype [42].

This trial was a multinational, open-label, dose-escalation, randomized study conducted in hospitals across North America and Europe, starting in June 2016. The trial enrolled 26 male patients with XLMTM, all under 5 years of age and reliant on mechanical ventilatory support. These patients had previously participated in the INCEPTUS prospective study and met the required eligibility criteria for ASPIRO. Control data for the trial were derived from 14 INCEPTUS participants who were not dosed [12,42].

The study was divided into two distinct parts. Part 1 focused on safety and dose escalation, allowing for the assessment of adverse events and tolerability at increasing dose. Following this phase, Part 2 employed a randomized delayed-treatment concurrent control design. The two different doses administered were the following: 1.3×10^{14} vector genomes (vg)/kg body weight and 3.5×10^{14} vg/kg body weight [42].

Following rAAV administration, MTM1 expression levels showed a significant increase, and remained elevated for up to 48 weeks. This outcome was accompanied by improvements in myofiber size and in organelle localization. Additionally, notable enhancements in both respiratory and motor functions were observed, with some patients achieving ventilator independence after treatment [42,106,107]. These functional gains contrast with the outcomes observed within the untreated group as well as with the results from other natural history studies, further underscoring the therapeutic potential of this approach [3,9,12].

After the completion of Part 1, the higher dose was selected for continuation into Part 2. However, after administering this dose, SUSARs led to the death of three participants. Consequently, the U.S. Food and Drug Administration (FDA), placed the trial on hold in May 2020. The deceased participants, all with a history of hepatobiliary disease, had developed severe cholestatic liver injury, which progressed to cholestatic liver failure at the time of death. In December 2020, the FDA lifted the hold, allowing the clinical trial to resume, but only with the lower dose. Enhanced hepatic monitoring was implemented, alongside the introduction of prophylactic or reactive therapies to manage chronic or recurrent cholestasis. Despite these measures, a fourth patient succumbed to the same complication after receiving the lower dose, prompting the FDA to issue a second clinical hold in September 2021, which remains in effect. Additionally, five participants, four of whom received the higher dose, exhibited non-fatal hepatobiliary adverse events, which were hypothesized to be treatment-related [42].

Hepatoxicity has also been reported in other gene therapy trials, including those for hemophilia A, hemophilia B and SMA, although, in those cases, the liver toxicity was not of cholestatic nature [108–115]. Long-term follow-up studies in hemophilia A and B gene therapy trials did not identify any evidence of liver toxicity or malignancy, suggesting that the use of corticosteroids mitigated any lasting clinical impact of elevated liver enzymes [116–119].

In addition to cholestasis, several of the adverse events reported in the treated group were also observed in the control cohort, as well as in patients from previous natural history studies, including hepatic complications and respiratory and cardiac sequelae [3,9,12]. Notably, three deaths were also reported in the control group due to these complications [42]. In the treated group, additional adverse events such as transient thrombocytopenia and elevated troponin level were documented, consistent with the side effects described for other rAAV-based gene therapy trials, particularly those targeting conditions like SMA and Duchenne Muscular Dystrophy (DMD) [120–125].

As previously noted, patients with XLMTM exhibit a distinctive form of intrahepatic cholestasis, which was underrecognized in studies conducted prior to the ASPIRO clinical trial. This condition has been identified as an inherent complication of the disease [10,126,127]. Notably, liver abnormalities were not previously detected in preclinical models; however, a recent study has demonstrated that MTM1 deficiency can lead to liver abnormalities consistent with both cholestasis and hepatic steatosis in zebrafish [13]. This discovery not only expands our understanding of the disease but also enables the evaluation of the potential impact that future treatments may have on preexisting cholestasis in this model. Nevertheless, zebrafish are not an appropriate model for rAAV infusion highlighting the need for further investigation in alternative animal models to establish a suitable approach for future preclinical gene therapy studies.

5.1.2. Myotubularin-related protein 2

rAAV9-mediated expression of *MTMR2* or its isoform, *MTMR2-S* has been shown to effectively rescue the muscular phenotype in a *MTM1* KO murine model, comparable to therapeutic approaches targeting MTM1 deficiency. Intravenous infusion of rAAV9-MTMR2 ameliorated both the structural and mechanical properties of muscle fibers, while also extending the lifespan of the mice. Furthermore, restoration of PtdIns3P levels was reported [70,71]. These findings suggest that MTMR2 may act as a compensatory mechanism, similar to those identified in limb-girdle muscular dystrophy (LGMD) type 2C or in DMD [128–130]. However, the studies were limited in duration, and further investigation is required to fully assess the long-term efficacy of this approach in animal models and in humans.

5.1.3. Amphiphysin 2

Overexpression of amphiphysin 2 in XLMTM mouse models has been demonstrated to extend lifespan generally by more than 10 months, resulting in survival rates similar to those of wildtype mice. Additionally, it ameliorates motor strength and coordination, restoring strength values to wildtype levels in 2-, 7- and 24-month-old mice. It also improves main histopathological hallmarks of XLMTMs, rescuing fiber size, nuclei position, and oxidative staining [103].

These effects were achieved through the genetic cross of humanized *BIN1* transgenic mice with *MTM1*$^{-/y}$ mouse models. A similar effect was observed following systemic administration of rAAV8-mediated *BIN1* transfer [103]. Further studies in larger animals should be conducted to assess safety and long-term BIN1 expression and before first in-human studies.

5.2. Other therapeutic approaches

5.2.1. Dynamin 2

Preclinical studies have demonstrated that reducing DNM2 expression effectively rescues skeletal muscle atrophy by increasing muscular strength and improving muscle ultrastructure. Additionally, it significantly reduces, or even eliminates, histological abnormalities in *MTM1* KO mice, including fiber hypotrophy, abnormal triad structures, mislocalized nuclei, impaired myoblast fusion, and defective myofibers maturation. Moreover, DNM2 downregulation extends lifespan, with treated mice reaching up to 2 years of age. This therapeutic effect was achieved either by crossing *MTM1* KO mice with *DNM2* heterozygous mice or by deleting miR199a-1, a conserved intragenic micro-RNA within the *DNM2* gene. These findings suggest that targeting *DNM2* downregulation may serve as a viable therapeutic strategy for patients with XLMTM [48,77].

Furthermore, similar therapeutic benefits have been observed for other CNM disorders, such as autosomal dominant CNM, through rAAV1-mediated delivery of allele-specific shRNA sequences [131].

The use of antisense oligonucleotide (ASO) to reduce DNM2 expression has been shown to extend the lifespan, restore muscle mass and force in a dose-dependent manner in *MTM1* KO mice [132]. Based on these results, a phase 1/2, multicenter, open-label, dose-confirmation trial was conducted to assess the safety and preliminary efficacy of DYN101 in patients over 16 years of age with CNM caused by mutations in *MTM1* or *DNM2* (NCT04033159). However, no clinical benefit was observed and SUSARs were reported, halting further dosing [43]. Consequently, a second planned trial following the same approach for patients ranging from 2 to 17 years of age (NCT04743557/EUCTR2020 -004,608-32-DE) was withdrawn due to outcomes of the previous trial [133].

In a separate recent study, a chemical screening identified Dynasore, a dynamin-2 inhibitor, as a potential strategy to rescue the cholestatic phenotype in the *MTM1* KO zebrafish model [13]. While this suggests a potential combination therapy with gene therapy, more research is necessary to assess its feasibility and safety.

5.2.2. Myostatin

Myostatin inhibitors have been clinically tested in other neuromuscular disorders, including facioscapulohumeral dystrophy, DMD and inclusion body myositis, with no clinical efficacy demontrated [134–138]. In SMA, efficacy has been suggested in a phase 2 trial and a phase 3 trial with the same compound has been announced being positive [139].

In the context of XLMTM, treatment with soluble activin receptor type IIB (ActRIIB-mFC) – a receptor that binds myostatin to activate the TFG-β pathway, which regulates cell cycle and myofiber size in skeletal and cardiac muscle, yielded only mild improvement in KO mice. This treatment did not significantly improve antigravity hanging performance or grip strength, nor did it rescue the abnormalities in the triad structure. Additionally, it provided only a transient histological improvement and increased median survival to just 65 days [140]. The limited effect may be due to the already significantly reduced myostatin levels inherent to XLMTM, making further suppression challenging, even when the inhibition is reversible [81,140,141].

5.2.3. NMJ modulators

Acetylcholinesterase inhibitors and β-adrenergic agonists have been extensively used in the clinic to address NMJ dysfunction, with myasthenia gravis serving as the most illustrative example [85,142]. Acetylcholinesterase inhibitors, such as pyridostigmine, have demonstrated efficacy in improving NMJ dysfunction in zebrafish and murine models of XLMTM, showing modest improvements in grip fatigue and significant enhancements in treadmill endurance in mice, as well as improved touch–evoked movement in zebrafish models [31,37].

In human cases, this treatment has led to mild improvements in muscle strength, though responses have varied considerably among patients. This therapeutic approach is not expected to interfere with other strategies, such as gene therapy [37]. Nevertheless, these results require further confirmation, as they were derived from small patient cohorts. There is no report of respiratory improvements.

An additional off-label therapeutic strategy that may hold potential for patients living with XLMTM is the use of 3,4-Diaminopyridine (3,4-DAP). This compound blocks voltage-gated potassium channels, thereby enhancing acetylcholine release and potentially improving NMJ function and muscle performance. It has shown efficacy in patients with Lambert Eaton myasthenia, in congenital myasthenia and in myasthenia gravis [143,144].

Remarkably, β2-Adrenergic receptor agonists, such as ephedrine and salbutamol/albuterol, can act as a compensatory mechanism and partially mitigate the disruption of this pathway by enhancing NMJ structure, improving muscle strength and reducing fatigue [38–40,142]. The efficacy and safety of oral salbutamol are currently being investigated in a Phase IV clinical trial for congenital myopathy (NCT05099107).

5.2.4. PI3KC2β kinase

Inhibition of PI3KC2β has been shown to counteract the elevated levels of PtdIns(3,5)P2, leading to significant improvements in motor function, extended survival and reversal of histopathological abnormalities in various animal models. These improvements were achieved by crossing *MTM1* KO mice with *PI3KC2β*-deficient mice, resulting in the normalization of PtdIns3P levels and the restoration of mTOR1C activity [51,145,146].

Although the broad-spectrum PI3K inhibitor wortmannin has demonstrated some efficacy in extending lifespan and improving muscle function and histology in *MTM1* KO mouse models [51,147], its therapeutic outcome remains limited. It has been hypothesized that a more targeted approach, using a selective PI3KC2β inhibitor, with minimal off-target effects on other PI3K isoforms, may provide a more effective therapeutic strategy [51].

5.2.5. Histone deacetylases

A recent study showed that inhibiting histone deacetylases may represent a promising therapeutic approach for XLMTM. Following a screening process, valproic acid, an anti-epileptic drug, was identified as a potential candidate. Treatment with valproic acid ameliorates several phenotypic features of XLMTM in both *MTM1* KO zebrafish and mouse models [148]. However, further studies are necessary to establish the optimal dosing and assess safety in preclinical models. Although no adverse events were observed during the study, the potential hepatotoxicity associated with valproic acid should be carefully evaluated given the liver dysfunction frequently detected in patients living with XLMTM [10–12,127,148].

This therapeutic strategy has also been explored for other muscular diseases, such as DMD, where the histone deacetylases inhibitor givinostat was recently approved by the FDA following a successful phase 3 trial [154].

5.2.6. mTORC1

The use of the ATP-competitive inhibitor AZD8055, a selective mTOR antagonist, has shown to restore autophagy through pharmacologic inhibition, thereby increasing muscle mass and improving mitochondrial function by reducing desmin accumulation in MTM1gt/y mouse models [34,36]. However, it is important to note that chronic administration of mTOR-selective antagonists can induce immunosuppression, hyperglycemia and hyperlipidemia [149]. Therefore, their potential toxicity should be carefully evaluated.

5.2.7. Estrogen modulation

Tamoxifen, an European Medical Agency (EMA- and FDA-approved drug, primarily acts through the estrogen receptor pathway and has also been shown to normalize levels of DNM2, desmin and BIN1. High dose treatment demonstrated effectiveness in extending mice lifespan, improving muscle function and enhancing both the structure and function of the triad, although it does not fully correct all pathogenic features [150,151]. This therapeutic approach has also been used in a phase 3 trial (NCT03354039) for the treatment of DMD, though no significant differences in efficacy have been observed between the treated and untreated groups [155].

It is important to highlight that some *MTM1* KO mice treated with the high dose of tamoxifen during the late stages of the disease succumbed to pulmonary hemorrhage, consistent with lung injury reported in a few treated patients [151,152]. Therefore, pulmonary complications should be closely monitored in clinical studies. Recently, a phase 1/2, randomized, double-blinded trial (TAM4MTM; NCT04915846) was

terminated due to safety issues, with further details yet to be published [43].

5.2.8. Cell therapy

Injection of syngeneic skeletal muscle-derived myoblasts was used for the treatment of XLMTM in MTM1R69C/y mouse model [153]. This approach has been also tested for the treatment of other myopathies, such as DMD, with variable results associated to cell survival, cell migration, apoptosis and delayed proliferation [156]. This transplantation led to increased muscle mass, function, and regeneration of the NMJ function. According to the observations, there were no cells that migrated out of the targeted tissue [153].

5.2.9. Enzyme replacement therapy

This strategy involves the use of the fusion protein 3E10Fv-MTM1, also known as 4s3–001, which combines the mouse monoclonal antibody 3E10Fv with the full-length MTM1 protein. This fusion protein can penetrate the cells and be expressed in the skeletal muscle. In the MTM1R69C/y mouse model, systemic administration of 3E10Fv-MTM1 led to improved muscle function. However, the study was limited in terms of time and dosage, necessitating further investigation to validate this proof of concept. Additional research is also needed to evaluate the potential immune response associated with its administration, as well as to determine the effects of 3E10Fv fragment alone [64].

6. Conclusions

Despite significant progress in identifying therapeutic targets for XLMTM, various disease-modifying treatments have encountered challenges related to efficacy or safety, reflecting the complex nature of the disorder. This underscores the critical need for a deeper understanding of the disease, not only through the refinement of clinical models but also by exploring the potential of combination therapies. Furthermore, close patient monitoring during clinical trials will be essential to enhance safety and optimize therapeutic outcomes.

7. Expert opinion

A wide array of therapeutic strategies has been developed to target different proteins and pathways implicated in XLMTM. While most of these approaches are still in the preclinical or early clinical stages, significant challenges have arisen in translating these experimental therapies into safe and effective treatments.

Among the most promising advances is the gene replacement therapy approach (AT132), delivering functional copies of *MTM1*. This approach demonstrated transformative efficacy in ameliorating the disease phenotype, reducing ventilator dependence and significantly enhancing motor function in the ASPIRO clinical trial. Some patients have even achieved milestones such as sitting, standing and walking independently, representing a substantial gain in their quality of life. This tremendous level of functional recovery in a previously non-ambulatory population underscores the therapeutic potential of gene therapy in XLMTM.

However, the death of four patients due to hepatobiliary disease led to the FDA's clinical hold on the gene therapy clinical development. These patients exhibited evidence of preexisting cholestasis, a complication previously underrecognized in patients living with XLMTM. While neuromuscular defects are well characterized, non-muscular impact should be further investigated. This also highlights the necessity for a deeper understanding of full phenotypic spectrum of XLMTM, particularly given its phenotypic complexity.

Additionally, it underscores the need for more representative models that can better capture the wide range of phenotypes observed in patients living with XLMTM. Although a zebrafish model with a cholestatic phenotype has been recently developed, it presents some limitations, such as its unsuitability for gene therapy testing. Therefore, the generation of new, more comprehensive animal models is crucial to better predict therapeutic outcomes in human patients and to further investigate the pathophysiology of the disease. More generally, this illustrates the limitation of small and even large animal models to fully predict gene therapy safety issues in humans. It must be noted that severe and sometimes lethal adverse reactions like thrombomicroangiopathy-pseudo hemolytic uremic syndrome or chronic liver toxicity that have been observed following gene therapy in SMA or in DMD were not observed in pre-clinical studies [122].

In parallel, two other therapeutic approaches have undergone clinical testing. ASO therapy targeting dynamin 2 overexpression has demonstrated preclinical success by extending lifespan and restoring muscle mass. Tamoxifen, a well-tolerated FDA-approved medication, has also been assessed and shown to improve muscle function. Although these treatments presented promising pre-clinical data, safety events have stopped their development in XLMTM.

Short and middle term safety constitute an interesting and important ethical question when it comes to a severe neuromuscular condition. In surveys performed for DMD, which has a better life and quality of life expectancy than XLMTM, it was reported that patients consider 1:10 risk of death acceptable [157]. Consequently, risks and benefits associated with clinical trials should be thoroughly assessed with the input of patients and the patients' community. In the context of XLMTM, it must be noted that four patients died following gene therapy, while in the untreated group enrolled in the natural history study INCEPTUS, 3 out of 34 patients, aged from 2.3 to 3.5 years, died from complications associated to the disease [12,42].

Beyond safety, this XLMTM rAAV-based gene therapy approach presents some limitations. The long-term durability of the clinical benefit is still unknown. Redosing, which potentially involves strong immunosuppression, is still in early stages of development.

It is important to continue investigating further alternatives and eventually, the combination of different treatments, such as gene therapy with ASOs or small molecules as there is a risk of chronic loss of efficacy for one-shot gene therapy. This necessitates first the demonstration of safety and efficacy of these approaches individually. In addition, the standard of care, including mobility

support, physical therapy and respiratory management, remains essential to prevent irreversible orthopedic, functional or respiratory complications [158]. This standard of care comes with a very significant cost estimated to be nearly $1.5 million of direct medical expenses for patients who survive beyond four years of age [159]. This underscores the potential cost/effectiveness of innovative therapies.

A reduction of these costs could be also achieved by prevention, including rapid diagnosis of patients to avoid recurrence in siblings, but also systematic screening of carriers in the general population [160]. The availability of an effective treatment could also lead to the inclusion of XLMTM in genomic newborn screening programs [161], allowing early detection and treatment of all mutations including neomutations. In conditions like SMA where effective treatments are available, newborn screening has been demonstrated to be highly cost/effective [162,163]. Recent studies on carrier screening and genomic newborn screening have demonstrated high acceptance rates [160,164].

The implementation of advanced tools, such as artificial intelligence, sensors, in-silico models and omics analyses, could also play a transformative role in deepening our understanding of the disease. These technologies could help identify new biomarkers and therapeutic targets. Additionally, other innovative clinical approaches, such as Bayesian modeling, can leverage individual patients' natural history study data to predict disease progression in the absence of treatment, and thus reducing the number of patients needed to formally demonstrate efficacy [165]. Despite their potential, these emerging approaches are still under evaluation and require further dialogue with regulatory agencies. Enhancing this understanding will not only improve patients selection but may also mitigate some safety concerns identified in the clinical trials.

Although the therapeutic landscape for XLMTM has evolved significantly, it remains crucial to prioritize a thorough evaluation of safety profiles of therapeutic approaches and deepen our understanding of the disease's full phenotypic spectrum. The generation of more robust preclinical models, the introduction of innovative tools, and the refinement and development of therapeutic strategies are essential to achieving successful outcomes in future treatments. Moreover, the promising efficacy offers a hopeful perspective for managing congenital myopathies caused by muscle disorganization, rather than muscle dystrophy. Given the severe nature of XLMTM, the gains in motor function and ventilator independence achieved so far provide substantial optimism that future therapies will further improve the quality of life for patients.

Declaration of interest

C Martin is currently an employee of Viralgen, the present work has been conducted outside of her working time and does not reflect the position or opinion of Viralgen. L Servais has conducted consultancy for Astellas, Italfarmaco, BioHaven, Scholar Rock and Roche. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosure

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

C Martin reviewed the literature. C Martin and L Servais contributed to different sections of the initial draft, and both approved the final version of the manuscript. Both authors are accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgments

The authors thank Mr Matthew Woods for language editing and Ms Mathilbin for reference management.

Funding

This paper was not funded.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Laporte J, Blondeau F, Buj-Bello A, et al. The myotubularin family: from genetic disease to phosphoinositide metabolism. Trends Genet. 2001;17(4):221–228. doi: 10.1016/s0168-9525(01)02245-4
2. Vandersmissen I, Biancalana V, Servais L, et al. An integrated modelling methodology for estimating the prevalence of centronuclear myopathy. Neuromuscul Disord. 2018;28(9):766–777. doi: 10.1016/j.nmd.2018.06.012
3. Amburgey K, Tsuchiya E, de Chastonay S, et al. A natural history study of X-linked myotubular myopathy. Neurology. 2017;89(13):1355–1364. doi: 10.1212/WNL.0000000000004415
4. Funayama K, Shimizu H, Tanaka H, et al. An autopsy case of peliosis hepatis with X-linked myotubular myopathy. Leg Med (Tokyo). 2019;38:77–82. doi: 10.1016/j.legalmed.2019.04.005
5. Graham RJ, Muntoni F, Hughes I, et al. Mortality and respiratory support in X-linked myotubular myopathy: a RECENSUS retrospective analysis. Arch Dis Child. 2020;105(4):332–338. doi: 10.1136/archdischild-2019-317910
•• **A natural history study of patients with X-linked myotubular myopathy.**
6. Herman GE, Kopacz K, Zhao W, et al. Characterization of mutations in fifty North American patients with X-linked myotubular myopathy. Hum Mutat. 2002;19(2):114–121. doi: 10.1002/humu.10033
7. McEntagart M, Parsons G, Buj-Bello A, et al. Genotype-phenotype correlations in X-linked myotubular myopathy. Neuromuscul Disord. 2002;12(10):939–946. doi: 10.1016/s0960-8966(02)00153-0
8. Dowling JJ, Lawlor MW, Das S, et al. X-Linked myotubular myopathy. GeneReviews. Seattle (WA): University of Washington; 2002 Feb 25.
9. Annoussamy M, Lilien C, Gidaro T, et al. X-linked myotubular myopathy: a prospective international natural history study. Neurology. 2019;92(16):e1852–e1867. doi: 10.1212/WNL.0000000000007319
• **A natural history study of patients with X-linked myotubular myopathy.**
10. D'Amico A, Longo A, Fattori F, et al. Hepatobiliary disease in XLMTM: a common comorbidity with potential impact on treatment strategies [published correction appears in orphanet J rare dis. 2022 Jan 17;17(1): 18. doi: 10.1186/s13023-021-02171-y].

Orphanet J Rare Dis. 2021 Oct 12;16(1):425. doi: 10.1186/s13023-021-02055-1
11. Gangfuss A, Schmitt D, Roos A, et al. Diagnosing X-linked myotubular myopathy - a German 20-year follow up experience. J Neuromuscul Dis. 2021;8(1):79–90. doi: 10.3233/JND-200539
12. Dowling JJ, Müller-Felber W, Smith BK, et al. INCEPTUS natural history, run-in study for gene replacement clinical trial in X-Linked myotubular myopathy. J Neuromuscul Dis. 2022;9(4):503–516. doi: 10.3233/JND-210781
• **A natural history study of patients with X-linked myotubular myopathy.**
13. Karolczak S, Deshwar AR, Aristegui E, et al. Loss of Mtm1 causes cholestatic liver disease in a model of X-linked myotubular myopathy. J Clin Invest. 2023 Sep 15;133(18):e166275. doi: 10.1172/JCI166275
14. Grogan PM, Tanner SM, Ørstavik KH, et al. Myopathy with skeletal asymmetry and hemidiaphragm elevation is caused by myotubularin mutations. Neurology. 2005;64(9):1638–1640. doi: 10.1212/01.WNL.0000160393.99621.D0
15. Drouet A, Ollagnon-Roman E, Streichenberger N, et al. Expression hémicorporelle d'une myopathie myotubulaire liée à l'X (XLMTM) chez deux des trois femmes conductrices d'une même famille sans cas masculin [Unilateral presentation of X-linked myotubular myopathy (XLMTM) in two out of three female carriers in a family with no affected male]. Rev Neurol (Paris). 2008;164(2):169–176. doi: 10.1016/j.neurol.2007.08.008
16. Biancalana V, Scheidecker S, Miguet M, et al. Affected female carriers of MTM1 mutations display a wide spectrum of clinical and pathological involvement: delineating diagnostic clues. Acta Neuropathol. 2017;134(6):889–904. doi: 10.1007/s00401-017-1748-0
17. Cocanougher BT, Flynn L, Yun P, et al. Adult MTM1-related myopathy carriers: classification based on deep phenotyping. Neurology. 2019;93(16):e1535–e1542. doi: 10.1212/WNL.0000000000008316
18. Takeuchi Y, Masuda T, Kimura N, et al. X-linked myotubular myopathy manifesting carrier with central and peripheral nervous system involvement. Intern Med. [cited 2024 Apr 16];63(24):3371–3375. doi: 10.2169/internalmedicine.3417-23
19. Herman GE, Finegold M, Zhao W, et al. Medical complications in long-term survivors with X-linked myotubular myopathy. J Pediatr. 1999;134(2):206–214. doi: 10.1016/s0022-3476(99)70417-8
20. Biancalana V, Caron O, Gallati S, et al. Characterisation of mutations in 77 patients with X-linked myotubular myopathy, including a family with a very mild phenotype. Hum Genet. 2003;112(2):135–142. doi: 10.1007/s00439-002-0869-1
21. Laporte J, Hu LJ, Kretz C, et al. A gene mutated in X-linked myotubular myopathy defines a new putative tyrosine phosphatase family conserved in yeast. Nat Genet. 1996;13(2):175–182. doi: 10.1038/ng0696-175
22. Nandurkar HH, Layton M, Laporte J, et al. Identification of myotubularin as the lipid phosphatase catalytic subunit associated with the 3-phosphatase adapter protein, 3-PAP. Proc Natl Acad Sci U S A. 2003;100(15):8660–8665. doi: 10.1073/pnas.1033097100
23. Tronchère H, Laporte J, Pendaries C, et al. Production of phosphatidylinositol 5-phosphate by the phosphoinositide 3-phosphatase myotubularin in mammalian cells. J Biol Chem. 2004;279(8):7304–7312. doi: 10.1074/jbc.M311071200
24. Buj-Bello A, Fougerousse F, Schwab Y, et al. Aav-mediated intramuscular delivery of myotubularin corrects the myotubular myopathy phenotype in targeted murine muscle and suggests a function in plasma membrane homeostasis. Hum Mol Genet. 2008;17(14):2132–2143. doi: 10.1093/hmg/ddn112
25. Hnia K, Tronchère H, Tomczak KK, et al. Myotubularin controls desmin intermediate filament architecture and mitochondrial dynamics in human and mouse skeletal muscle. J Clin Invest. 2011;121(1):70–85. doi: 10.1172/JCI44021
26. Ribeiro I, Yuan L, Tanentzapf G, et al. Phosphoinositide regulation of integrin trafficking required for muscle attachment and maintenance. PloS Genet. 2011 [cited 2011 Feb 10];7(2):e1001295. doi: 10.1371/journal.pgen.1001295
27. Gavriilidis C, Laredj L, Solinhac R, et al. The MTM1-UBQLN2-HSP complex mediates degradation of misfolded intermediate filaments in skeletal muscle. Nat Cell Biol. 2018;20(2):198–210. doi: 10.1038/s41556-017-0024-9
28. Al-Qusairi L, Weiss N, Toussaint A, et al. T-tubule disorganization and defective excitation-contraction coupling in muscle fibers lacking myotubularin lipid phosphatase. Proc Natl Acad Sci U S A. 2009;106(44):18763–18768. doi: 10.1073/pnas.0900705106
29. Dowling JJ, Vreede AP, Low SE, et al. Loss of myotubularin function results in T-tubule disorganization in zebrafish and human myotubular myopathy. PloS Genet. 2009;5(2):e1000372. doi: 10.1371/journal.pgen.1000372
30. Toussaint A, Cowling BS, Hnia K, et al. Defects in amphiphysin 2 (BIN1) and triads in several forms of centronuclear myopathies. Acta Neuropathol. 2011;121(2):253–266. doi: 10.1007/s00401-010-0754-2
31. Dowling JJ, Joubert R, Low SE, et al. Myotubular myopathy and the neuromuscular junction: a novel therapeutic approach from mouse models. Dis Model Mech. 2012;5(6):852–859. doi: 10.1242/dmm.009746
32. Jungbluth H, Treves S, Zorzato F, et al. Congenital myopathies: disorders of excitation-contraction coupling and muscle contraction. Nat Rev Neurol. 2018;14(3):151–167. doi: 10.1038/nrneurol.2017.191
33. Razidlo GL, Katafiasz D, Taylor GS. Myotubularin regulates Akt-dependent survival signaling via phosphatidylinositol 3-phosphate. J Biol Chem. 2011;286(22):20005–20019. doi: 10.1074/jbc.M110.197749
34. Al-Qusairi L, Prokic I, Amoasii L, et al. Lack of myotubularin (MTM1) leads to muscle hypotrophy through unbalanced regulation of the autophagy and ubiquitin-proteasome pathways. FASEB J. 2013;27(8):3384–3394. doi: 10.1096/fj.12-220947
35. Joubert R, Vignaud A, Le M, et al. Site-specific Mtm1 mutagenesis by an AAV-Cre vector reveals that myotubularin is essential in adult muscle. Hum Mol Genet. 2013;22(9):1856–1866. doi: 10.1093/hmg/ddt038
36. Fetalvero KM, Yu Y, Goetschkes M, et al. Defective autophagy and mTORC1 signaling in myotubularin null mice. Mol Cell Biol. 2013;33(1):98–110. doi: 10.1128/MCB.01075-12
37. Robb SA, Sewry CA, Dowling JJ, et al. Impaired neuromuscular transmission and response to acetylcholinesterase inhibitors in centronuclear myopathies. Neuromuscul Disord. 2011;21(6):379–386. doi: 10.1016/j.nmd.2011.02.012
38. Beeson D. Congenital myasthenic syndromes: recent advances. Curr Opin Neurol. 2016;29(5):565–571. doi: 10.1097/WCO.0000000000000370
39. Vanhaesebrouck AE, Webster R, Maxwell S, et al. β2-adrenergic receptor agonists ameliorate the adverse effect of long-term pyridostigmine on neuromuscular junction structure. Brain. 2019;142(12):3713–3727. doi: 10.1093/brain/awz322
40. Nigro E, Amburgey K, Djordjevic D, et al. P66 salbutamol therapy in a neuromuscular cohort. Neuromuscul Disord. 2023;33(1):S75. doi: 10.1016/j.nmd.2023.07.047
41. Shieh PB, Kuntz N, Smith B, et al. ASPIRO gene therapy trial in X-Linked myotubular myopathy (XLMTM): update on preliminary safety and efficacy findings up to 72 weeks post-treatment (1053). Neurology. 2020;94(15):1053. doi: 10.1212/WNL.94.15_supplement.1053
42. Shieh PB, Kuntz NL, Dowling JJ, et al. Safety and efficacy of gene replacement therapy for X-linked myotubular myopathy (ASPIRO): a multinational, open-label, dose-escalation trial. Lancet Neurol. 2023;22(12):1125–1139. doi: 10.1016/S1474-4422(23)00313-7
•• **Clinical trial conducted to study the safety and efficacy of Resaminrigene bilparvovec (AT132) for patients under 5 years of age and reliant on mechanical ventilatory support.**
43. myotubulartrust.org [Internet] Dynacure; [cited 2024 Oct 23]. Available from: https://myotubulartrust.org/wp-content/uploads/PatientCommunicationsFinalJuly.pdf
44. clinicaltrials.gov [Internet]. [cited 2024 Oct 23]. Available from: https://clinicaltrials.gov/study/NCT04915846?cond=NCT04915846&rank=1

45. Beggs AH, Byrne BJ, De Chastonay S, et al. A multicenter, retrospective medical record review of X-linked myotubular myopathy: the recensus study. Muscle Nerve. 2018;57(4):550–560. doi: 10.1002/mus.26018
    - **A natural history study of patients with X-linked myotubular myopathy.**
46. Buj-Bello A, Laugel V, Messaddeq N, et al. The lipid phosphatase myotubularin is essential for skeletal muscle maintenance but not for myogenesis in mice. Proc Natl Acad Sci U S A. 2002;99 (23):15060–15065. doi: 10.1073/pnas.212498399
    - **An article detailing the development of the first animal model for X-linked myotubular myopathy, which has been extensively utilized in various preclinical research approaches.**
47. Pierson CR, Dulin-Smith AN, Durban AN, et al. Modeling the human MTM1 p.R69C mutation in murine Mtm1 results in exon 4 skipping and a less severe myotubular myopathy phenotype. Hum Mol Genet. 2012;21(4):811–825. doi: 10.1093/hmg/ddr512
48. Chen X, Gao YQ, Zheng YY, et al. The intragenic microRNA miR199A1 in the dynamin 2 gene contributes to the pathology of X-linked centronuclear myopathy. J Biol Chem. 2020;295 (26):8656–8667. doi: 10.1074/jbc.RA119.010839
49. Gupta VA, Hnia K, Smith LL, et al. Loss of catalytically inactive lipid phosphatase myotubularin-related protein 12 impairs myotubularin stability and promotes centronuclear myopathy in zebrafish. PloS Genet. 2013;9(6):e1003583. doi: 10.1371/journal.pgen.1003583
50. Dowling JJ, Low SE, Busta AS, et al. Zebrafish MTMR14 is required for excitation-contraction coupling, developmental motor function and the regulation of autophagy. Hum Mol Genet. 2010;19 (13):2668–2681. doi: 10.1093/hmg/ddq153
51. Sabha N, Volpatti JR, Gonorazky H, et al. PIK3C2B inhibition improves function and prolongs survival in myotubular myopathy animal models. J Clin Invest. 2016;126(9):3613–3625. doi: 10.1172/JCI86841
52. Beggs AH, Böhm J, Snead E, et al. MTM1 mutation associated with X-linked myotubular myopathy in Labrador Retrievers. Proc Natl Acad Sci U S A. 2010;107(33):14697–14702. doi: 10.1073/pnas.1003677107
53. Shelton GD, Rider BE, Child G, et al. X-linked myotubular myopathy in Rottweiler dogs is caused by a missense mutation in exon 11 of the MTM1 gene. Skelet Muscle. 2015 [cited 2015 Jan 27];5(1):1. doi: 10.1186/s13395-014-0025-3
54. Grange RW, Doering J, Mitchell E, et al. Muscle function in a canine model of X-linked myotubular myopathy. Muscle Nerve. 2012;46 (4):588–591. doi: 10.1002/mus.23463
55. Goddard MA, Mack DL, Czerniecki SM, et al. Muscle pathology, limb strength, walking gait, respiratory function and neurological impairment establish disease progression in the p.N155K canine model of X-linked myotubular myopathy [published correction appears in ann transl med. 2016 Jan;4(1): 23. doi: 10.3978/j.Issn.2305–5839.2015.12.44]. Ann Transl Med. 2015;3(18):262. doi: 10.3978/j.issn.2305-5839.2015.10.31
56. Lawlor MW, Beggs AH, Buj-Bello A, et al. Skeletal muscle pathology in X-Linked myotubular myopathy: review with cross-species comparisons [published correction appears in J neuropathol exp neurol. 2016 May;75(5): 479. doi: 10.1093/jnen/nlw029]. J Neuropathol Exp Neurol. 2016;75(2):102–110. doi: 10.1093/jnen/nlv020
57. Laporte J, Biancalana V, Tanner SM, et al. MTM1 mutations in X-linked myotubular myopathy. Hum Mutat. 2000;15(5):393–409. doi: 10.1002/(SICI)1098-1004(200005)15:5<393:AID-HUMU1>3.0.CO;2-R
58. Bertini E, Biancalana V, Bolino A, et al. 118th ENMC International workshop on advances in Myotubular myopathy. 26–28 September 2003, Naarden, the Netherlands. (5th workshop of the International consortium on Myotubular myopathy). Neuromuscul Disord. 2004;14 (6):387–396. doi: 10.1016/j.nmd.2004.04.002
59. Tsai TC, Horinouchi H, Noguchi S, et al. Characterization of MTM1 mutations in 31 Japanese families with myotubular myopathy, including a patient carrying 240 kb deletion in Xq28 without male hypogenitalism. Neuromuscul Disord. 2005;15(3):245–252. doi: 10.1016/j.nmd.2004.12.005
60. Childers MK, Joubert R, Poulard K, et al. Gene therapy prolongs survival and restores function in murine and canine models of myotubular myopathy. Sci Transl Med. 2014;6(220):220ra10. doi: 10.1126/scitranslmed.3007523
61. Mack DL, Poulard K, Goddard MA, et al. Systemic AAV8-mediated gene therapy drives whole-body correction of myotubular myopathy in dogs. Mol Ther. 2017;25(4):839–854. doi: 10.1016/j.ymthe.2017.02.004
62. Dupont JB, Guo J, Renaud-Gabardos E, et al. AAV-Mediated gene transfer restores a normal muscle transcriptome in a canine Model of X-Linked myotubular myopathy. Mol Ther. 2020;28(2):382–393. doi: 10.1016/j.ymthe.2019.10.018
63. Ross JA, Tasfaout H, Levy Y, et al. rAAV-related therapy fully rescues myonuclear and myofilament function in X-linked myotubular myopathy. Acta Neuropathol Commun. 2020 [cited 2020 Oct 19];8(1):167. doi: 10.1186/s40478-020-01048-8
64. Lawlor MW, Armstrong D, Viola MG, et al. Enzyme replacement therapy rescues weakness and improves muscle pathology in mice with X-linked myotubular myopathy. Hum Mol Genet. 2013;22 (8):1525–1538. doi: 10.1093/hmg/ddt003
65. Zou J, Zhang C, Marjanovic J, et al. Myotubularin-related protein (MTMR) 9 determines the enzymatic activity, substrate specificity, and role in autophagy of MTMR8. Proc Natl Acad Sci U S A. 2012;109(24):9539–9544. doi: 10.1073/pnas.1207021109
66. Quattrone A, Gambardella A, Bono F, et al. Autosomal recessive hereditary motor and sensory neuropathy with focally folded myelin sheaths: clinical, electrophysiologic, and genetic aspects of a large family. Neurology. 1996;46(5):1318–1318. doi: 10.1212/wnl.46.5.1318
67. Szigeti K, Lupski JR. Charcot-Marie-Tooth disease. Eur J Hum Genet. 2009;17(6):703–710. doi: 10.1038/ejhg.2009.31
68. Laporte J, Liaubet L, Blondeau F, et al. Functional redundancy in the myotubularin family. Biochem Biophys Res Commun. 2002;291 (2):305–312. doi: 10.1006/bbrc.2002.6445
69. Kim SA, Taylor GS, Torgersen KM, et al. Myotubularin and MTMR2, phosphatidylinositol 3-phosphatases mutated in myotubular myopathy and type 4B Charcot-Marie-Tooth disease. J Biol Chem. 2002;277(6):4526–4531. doi: 10.1074/jbc.M111087200
70. Raess MA, Cowling BS, Bertazzi DL, et al. Expression of the neuropathy-associated MTMR2 gene rescues MTM1-associated myopathy. Hum Mol Genet. 2017;26(19):3736–3748. doi: 10.1093/hmg/ddx258
71. Danièle N, Moal C, Julien L, et al. Intravenous administration of a MTMR2-encoding AAV vector ameliorates the phenotype of myotubular myopathy in mice. J Neuropathol Exp Neurol. 2018;77 (4):282–295. doi: 10.1093/jnen/nly002
72. Bitoun M, Durieux AC, Prudhon B, et al. Dynamin 2 mutations associated with human diseases impair clathrin-mediated receptor endocytosis. Hum Mutat. 2009;30(10):1419–1427. doi: 10.1002/humu.21086
73. Mooren OL, Kotova TI, Moore AJ, et al. Dynamin2 GTPase and cortactin remodel actin filaments. J Biol Chem. 2009;284 (36):23995–24005. doi: 10.1074/jbc.M109.024398
74. Søreng K, Munson MJ, Lamb CA, et al. SNX18 regulates ATG9A trafficking from recycling endosomes by recruiting dynamin-2. EMBO Rep. 2018;19(4):e44837. doi: 10.15252/embr.201744837
75. Puri C, Manni MM, Vicinanza M, et al. A DNM2 centronuclear myopathy mutation reveals a link between recycling endosome scission and autophagy. Dev Cell. 2020;53(2):154–168.e6. doi: 10.1016/j.devcel.2020.03.018
76. Bitoun M, Maugenre S, Jeannet PY, et al. Mutations in dynamin 2 cause dominant centronuclear myopathy. Nat Genet. 2005;37 (11):1207–1209. doi: 10.1038/ng1657
77. Cowling BS, Chevremont T, Prokic I, et al. Reducing dynamin 2 expression rescues X-linked centronuclear myopathy. J Clin Invest. 2014;124(3):1350–1363. doi: 10.1172/JCI71206
78. Giraud Q, Spiegelhalter C, Messaddeq N, et al. MTM1 overexpression prevents and reverts BIN1-related centronuclear myopathy. Brain. 2023;146(10):4158–4173. doi: 10.1093/brain/awad251
79. McPherron AC, Lawler AM, Lee SJ. Regulation of skeletal muscle mass in mice by a new tgf-beta superfamily member. Nature. 1997;387(6628):83–90. doi: 10.1038/387083a0

80. Lee SJ, McPherron AC. Regulation of myostatin activity and muscle growth. Proc Natl Acad Sci U S A. 2001;98(16):9306–9311. doi: 10.1073/pnas.151270098
81. Mariot V, Joubert R, Hourdé C, et al. Downregulation of myostatin pathway in neuromuscular diseases may explain challenges of anti-myostatin therapeutic approaches. Nat Commun. 2017 [cited 2017 Nov 30];8(1):1859. doi: 10.1038/s41467-017-01486-4
82. Koch C, Buono S, Menuet A, et al. Myostatin: a circulating Biomarker correlating with disease in myotubular myopathy mice and patients. Mol ther methods Clin Dev. 2020 [cited 2020 May 4];17:1178–1189. doi: 10.1016/j.omtm.2020.04.022
83. Bom A, Hope F, Rutherford S, et al. Preclinical pharmacology of sugammadex. J Crit Care. 2009;24(1):29–35. doi: 10.1016/j.jcrc.2008.10.010
84. Caldwell JE. Clinical limitations of acetylcholinesterase antagonists. J Crit Care. 2009;24(1):21–28. doi: 10.1016/j.jcrc.2008.08.003
85. Lorenzoni PJ, Scola RH, Kay CS, et al. Salbutamol therapy in congenital myasthenic syndrome due to DOK7 mutation. J Neurol Sci. 2013;331(1–2):155–157. doi: 10.1016/j.jns.2013.05.017
86. Webster RG, Vanhaesebrouck AE, Maxwell SE, et al. Effect of salbutamol on neuromuscular junction function and structure in a mouse model of DOK7 congenital myasthenia. Hum Mol Genet. 2020;29(14):2325–2336. doi: 10.1093/hmg/ddaa116
87. McMacken G, Whittaker RG, Wake R, et al. Neuromuscular junction involvement in inherited motor neuropathies: genetic heterogeneity and effect of oral salbutamol treatment. J Neurol. 2023;270(6):3112–3119. doi: 10.1007/s00415-023-11643-z
88. Rossi L, Mota BI, Valadão PAC, et al. Influence of β_2-adrenergic selective agonist formoterol on the motor unit of a mouse model of a congenital myasthenic syndrome with complete VAChT deletion. Neuropharmacology. 2024;260:110116. doi: 10.1016/j.neuropharm.2024.110116
89. Jean S, Kiger AA. Classes of phosphoinositide 3-kinases at a glance. J Cell Sci. 2014;127(5):923–928. doi: 10.1242/jcs.093773
90. Zoncu R, Perera RM, Balkin DM, et al. A phosphoinositide switch controls the maturation and signaling properties of APPL endosomes. Cell. 2009;136(6):1110–1121. doi: 10.1016/j.cell.2009.01.032
91. Marat AL, Wallroth A, Lo WT, et al. mTORC1 activity repression by late endosomal phosphatidylinositol 3,4-bisphosphate. Science. 2017;356(6341):968–972. doi: 10.1126/science.aaf8310
92. Kutchukian C, Szentesi P, Allard B, et al. Ca2±induced sarcoplasmic reticulum Ca2+ release in myotubularin-deficient muscle fibers. Cell Calcium. 2019;80:91–100. doi: 10.1016/j.ceca.2019.04.004
93. Yang XJ, Seto E. HATs and HDACs: from structure, function and regulation to novel strategies for therapy and prevention. Oncogene. 2007;26(37):5310–5318. doi: 10.1038/sj.onc.1210599
94. Shahbazian MD, Grunstein M. Functions of site-specific histone acetylation and deacetylation. Annu Rev Biochem. 2007;76(1):75–100. doi: 10.1146/annurev.biochem.76.052705.162114
95. Bachmann C, Jungbluth H, Muntoni F, et al. Cellular, biochemical and molecular changes in muscles from patients with X-linked myotubular myopathy due to MTM1 mutations. Hum Mol Genet. 2017;26(2):320–332. doi: 10.1093/hmg/ddw388
96. Lee E, Marcucci M, Daniell L, et al. Amphiphysin 2 (Bin1) and T-tubule biogenesis in muscle. Science. 2002;297(5584):1193–1196. doi: 10.1126/science.1071362
97. Peter BJ, Kent HM, Mills IG, et al. BAR domains as sensors of membrane curvature: the amphiphysin BAR structure. Science. 2004;303(5657):495–499. doi: 10.1126/science.1092586
98. Daumke O, Roux A, Haucke V. BAR domain scaffolds in dynamin-mediated membrane fission. Cell. 2014;156(5):882–892. doi: 10.1016/j.cell.2014.02.017
99. D'Alessandro M, Hnia K, Gache V, et al. Amphiphysin 2 orchestrates nucleus positioning and shape by linking the nuclear envelope to the actin and Microtubule Cytoskeleton. Dev Cell. 2015;35(2):186–198. doi: 10.1016/j.devcel.2015.09.018
100. Nicot AS, Toussaint A, Tosch V, et al. Mutations in amphiphysin 2 (BIN1) disrupt interaction with dynamin 2 and cause autosomal recessive centronuclear myopathy. Nat Genet. 2007;39(9):1134–1139. doi: 10.1038/ng2086
101. Royer B, Hnia K, Gavriilidis C, et al. The myotubularin–amphiphysin 2 complex in membrane tubulation and centronuclear myopathies. EMBO Rep. 2013;14(10):907–915. doi: 10.1038/embor.2013.119
102. Perdreau-Dahl H, Lipsett DB, Frisk M, et al. BIN1, Myotubularin, and Dynamin-2 coordinate T-Tubule growth in Cardiomyocytes. Circ Res. 2023;132(11):e188–e205. doi: 10.1161/CIRCRESAHA.122.321732
103. Lionello VM, Nicot AS, Sartori M, et al. Amphiphysin 2 modulation rescues myotubular myopathy and prevents focal adhesion defects in mice. Sci Transl Med. 2019;11(484):eaav1866. doi: 10.1126/scitranslmed.aav1866
104. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease [published correction appears in cell 2017 Apr 6;169(2):361–371. doi: 10.1016/j.Cell.2017.03.035]. Cell. 2017;168(6):960–976. doi: 10.1016/j.cell.2017.02.004
105. Elverman M, Goddard MA, Mack D, et al. Long-term effects of systemic gene therapy in a canine model of myotubular myopathy. Muscle Nerve. 2017;56(5):943–953. doi: 10.1002/mus.25658
106. Andreoletti G, Romano O, Chou HJ, et al. High-throughput transcriptome analyses from ASPIRO, a phase 1/2/3 study of gene replacement therapy for X-linked myotubular myopathy. Am J Hum Genet. 2023;110(10):1648–1660. doi: 10.1016/j.ajhg.2023.08.008
107. Lawlor MW, Schoser B, Margeta M, et al. Effects of gene replacement therapy with resamirigene bilparvovec (AT132) on skeletal muscle pathology in X-linked myotubular myopathy: results from a substudy of the ASPIRO open-label clinical trial. EBioMedicine. 2024;99:104894. doi: 10.1016/j.ebiom.2023.104894
108. George LA, Sullivan SK, Giermasz A, et al. Hemophilia B gene therapy with a high-specific-activity factor IX variant. N Engl J Med. 2017;377(23):2215–2227. doi: 10.1056/NEJMoa1708538
109. Miesbach W, Meijer K, Coppens M, et al. Gene therapy with adeno-associated virus vector 5-human factor IX in adults with hemophilia B. Blood. 2018;131(9):1022–1031. doi: 10.1182/blood-2017-09-804419
110. Chand D, Mohr F, McMillan H, et al. Hepatotoxicity following administration of onasemnogene abeparvovec (AVXS-101) for the treatment of spinal muscular atrophy. J Hepatol. 2021;74(3):560–566. doi: 10.1016/j.jhep.2020.11.001
111. George LA, Monahan PE, Eyster ME, et al. Multiyear factor VIII expression after AAV gene transfer for hemophilia a. N Engl J Med. 2021;385(21):1961–1973. doi: 10.1056/NEJMoa2104205
112. Konkle BA, Walsh CE, Escobar MA, et al. BAX 335 hemophilia B gene therapy clinical trial results: potential impact of CpG sequences on gene expression. Blood. 2021;137(6):763–774. doi: 10.1182/blood.2019004625
113. Giermasz A, Visweshwar N, Harrington TJ, et al. Updated results of the Alta study, a phase 1/2 study of Giroctocogene Fitelparvovec (PF-07055480/SB-525) gene therapy in adults with severe hemophilia A. Blood. 2022;140(1):7776–7777. doi: 10.1182/blood-2022-159421
114. Ozelo MC, Mahlangu J, Pasi KJ, et al. Valoctocogene roxaparvovec gene therapy for hemophilia a. N Engl J Med. 2022;386(11):1013–1025. doi: 10.1056/NEJMoa2113708
115. Xue F, Li H, Wu X, et al. Safety and activity of an engineered, liver-tropic adeno-associated virus vector expressing a hyperactive Padua factor IX administered with prophylactic glucocorticoids in patients with haemophilia B: a single-centre, single-arm, phase 1, pilot trial. Lancet Haematol. 2022;9(7):e504–e513. doi: 10.1016/S2352-3026(22)00113-2
116. Nathwani AC, Reiss U, Tuddenham E, et al. Adeno-associated mediated gene transfer for hemophilia B: 8 year follow up and impact of removing "empty viral particles" on safety and efficacy of gene transfer. Blood. 2018;132(1):491. doi: 10.1182/blood-2018-99-118334
117. Pasi KJ, Rangarajan S, Mitchell N, et al. Multiyear follow-up of AAV5-hFVIII-sq gene therapy for hemophilia a. N Engl J Med. 2020;382(1):29–40. doi: 10.1056/NEJMoa1908490
118. Fong S, Yates B, Sihn CR, et al. Interindividual variability in transgene mRNA and protein production following adeno-associated virus gene therapy for hemophilia a. Nat Med. 2022;28(4):789–797. doi: 10.1038/s41591-022-01751-0

119. George LA, Ragni MV, Rasko JEJ, et al. Long-term follow-up of the first in human intravascular delivery of AAV for gene transfer: AAV2-hFIX16 for severe hemophilia B. Mol Ther. 2020;28 (9):2073–2082. doi: 10.1016/j.ymthe.2020.06.001
120. Friese J, Geitmann S, Holzwarth D, et al. Safety monitoring of gene therapy for spinal muscular atrophy with onasemnogene abeparvovec -A single centre experience. J Neuromuscul Dis. 2021;8 (2):209–216. doi: 10.3233/JND-200593
121. Day JW, Finkel RS, Chiriboga CA, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial. Lancet Neurol. 2021;20 (4):284–293. doi: 10.1016/S1474-4422(21)00001-6
122. Horton RH, Saade D, Markati T, et al. A systematic review of adeno-associated virus gene therapies in neurology: the need for consistent safety monitoring of a promising treatment. J Neurol Neurosurg Psychiatry. 2022;93(12):1276–1288. doi: 10.1136/jnnp-2022-329431
123. Guillou J, de Pellegars A, Porcheret F, et al. Fatal thrombotic microangiopathy case following adeno-associated viral SMN gene therapy. Blood Adv. 2022;6(14):4266–4270. doi: 10.1182/bloodadvances.2021006419
124. Deng J, Zhang J, Shi K, et al. Drug development progress in Duchenne muscular dystrophy. Front Pharmacol. 2022 Jul 22;13:950651. doi: 10.3389/fphar.2022.950651
125. Lek A, Wong B, Keeler A, et al. Death after high-dose rAAV9 gene therapy in a patient with Duchenne's muscular dystrophy. N Engl J Med. 2023;389(13):1203–1210. doi: 10.1056/NEJMoa2307798
126. Neese JM, Yum S, Matesanz S, et al. Intracranial hemorrhage secondary to vitamin K deficiency in X-linked myotubular myopathy. Neuromuscul Disord. 2021;31(7):651–655. doi: 10.1016/j.nmd.2021.04.009
127. Molera C, Sarishvili T, Nascimento A, et al. Intrahepatic Cholestasis is a clinically significant feature associated with natural history of X-Linked myotubular myopathy (XLMTM): a case series and biopsy report. J Neuromuscul Dis. 2022;9(1):73–82. doi: 10.3233/JND-210712
128. Imamura M, Mochizuki Y, Engvall E, et al. Epsilon-sarcoglycan compensates for lack of alpha-sarcoglycan in a mouse model of limb-girdle muscular dystrophy. Hum Mol Genet. 2005;14 (6):775–783. doi: 10.1093/hmg/ddi072
129. Guiraud S, Aartsma-Rus A, Vieira NM, et al. The pathogenesis and therapy of muscular dystrophies. Annu Rev Genom Hum Genet. 2015;16(1):281–308. doi: 10.1146/annurev-genom-090314-025003
130. Ricotti V, Spinty S, Roper H, et al. Safety, tolerability, and pharmacokinetics of SMT C1100, a 2-Arylbenzoxazole Utrophin modulator, following single- and multiple-dose administration to pediatric patients with Duchenne muscular dystrophy. PLoS One. 2016 Apr 7;11(4):e0152840. doi: 10.1371/journal.pone.0152840
131. Trochet D, Prudhon B, Beuvin M, et al. Allele-specific silencing therapy for dynamin 2-related dominant centronuclear myopathy. EMBO Mol Med. 2018;10(2):239–253. doi: 10.15252/emmm.201707988
132. Tasfaout H, Buono S, Guo S, et al. Antisense oligonucleotide-mediated Dnm2 knockdown prevents and reverts myotubular myopathy in mice. Nat Commun. 2017 Jun 7;8:15661. doi: 10.1038/ncomms15661
133. clinicaltrials.gov [Internet]. [cited 2024 Oct 23]. Available from: https://clinicaltrials.gov/study/NCT04743557?cond=NCT04743557&rank=1
134. Wagner KR, Fleckenstein JL, Amato AA, et al. A phase I/IItrial of MYO-029 in adult subjects with muscular dystrophy. Ann Neurol. 2008;63(5):561–571. doi: 10.1002/ana.21338
135. Wagner KR, Abdel-Hamid HZ, Mah JK, et al. Randomized phase 2 trial and open-label extension of domagrozumab in Duchenne muscular dystrophy [published correction appears in Neuromuscul Disord. 2021 Feb;31(2): 167–168. doi: 10.1016/j.Nmd.2021.01.001]. Neuromuscul Disord. 2020;30(6):492–502. doi: 10.1016/j.nmd.2020.05.002
136. Sivakumar K, Cochrane TI, Sloth B, et al. Long-term safety and tolerability of bimagrumab (BYM338) in sporadic inclusion body myositis. Neurology. 2020;95(14):e1971–e1978. doi: 10.1212/WNL.0000000000010417
137. Statland JM, Campbell C, Desai U, et al. Randomized phase 2 study of ACE-083, a muscle-promoting agent, in facioscapulohumeral muscular dystrophy. Muscle Nerve. 2022;66(1):50–62. doi: 10.1002/mus.27558
138. Muntoni F, Byrne BJ, McMillan HJ, et al. The clinical development of Taldefgrobep Alfa: an Anti-Myostatin Adnectin for the treatment of Duchenne muscular dystrophy. Neurol Ther. 2024;13(1):183–219. doi: 10.1007/s40120-023-00570-w
139. Crawford TO, Darras BT, Day JW, et al. Safety and efficacy of apitegromab in patients with spinal muscular atrophy types 2 and 3: the phase 2 TOPAZ study [published correction appears in neurology. 2024 Jul 9;103(1): e209519. doi: 10.1212/WNL.0000000000209519]. Neurology. 2024;102(5):e209151. doi: 10.1212/WNL.0000000000209151
140. Lawlor MW, Read BP, Edelstein R, et al. Inhibition of activin receptor type IIB increases strength and lifespan in myotubularin-deficient mice [published correction appears in Am J Pathol. 2011 Mar;178(3): 1406]. Am J Pathol. 2011;178(2):784–793. doi: 10.1016/j.ajpath.2010.10.035
141. Lawlor MW, Viola MG, Meng H, et al. Differential muscle hypertrophy is associated with satellite cell numbers and Akt pathway activation following activin type IIB receptor inhibition in Mtm1 p.R69C mice. Am J Pathol. 2014;184(6):1831–1842. doi: 10.1016/j.ajpath.2014.03.003
142. Messina S, Hartley L, Main M, et al. Pilot trial of salbutamol in central core and multi-minicore diseases. Neuropediatrics. 2004;35 (5):262–266. doi: 10.1055/s-2004-821173
143. Sanders DB, Juel VC, Harati Y, et al. 3,4-diaminopyridine base effectively treats the weakness of Lambert-Eaton myasthenia. Muscle Nerve. 2018;57(4):561–568. doi: 10.1002/mus.26052
144. Bonanno S, Pasanisi MB, Frangiamore R, et al. Amifampridine phosphate in the treatment of muscle-specific kinase myasthenia gravis: a phase IIb, randomized, double-blind, placebo-controlled, double crossover study. SAGE Open Med. 2018 Dec 17;6:2050312118819013. doi: 10.1177/2050312118819013
145. Massana-Muñoz X, Goret M, Nattarayan V, et al. Inactivating the lipid kinase activity of PI3KC2β is sufficient to rescue myotubular myopathy in mice. JCI Insight. 2023 May 8;8(9):e151933. doi: 10.1172/jci.insight.151933
146. Goret M, Laporte J. Une cible thérapeutique contre la myopathie myotubulaire - La kinase PI3KC2β [The PI3KC2β kinase as a therapeutic target for myotubular myopathy]. Med Sci (Paris). 2024;40(2):133–136. doi: 10.1051/medsci/2023208
147. Kutchukian C, Lo Scrudato M, Tourneur Y, et al. Phosphatidylinositol 3-kinase inhibition restores Ca2+ release defects and prolongs survival in myotubularin-deficient mice. Proc Natl Acad Sci U S A. 2016;113(50):14432–14437. doi: 10.1073/pnas.1604099113
148. Volpatti JR, Ghahramani-Seno MM, Mansat M, et al. X-linked myotubular myopathy is associated with epigenetic alterations and is ameliorated by HDAC inhibition. Acta Neuropathol. 2022;144 (3):537–563. doi: 10.1007/s00401-022-02468-7
149. Mannick JB, Lamming DW. Targeting the biology of aging with mTOR inhibitors. Nat Aging. 2023;3(6):642–660. doi: 10.1038/s43587-023-00416-y
150. Gayi E, Neff LA, Massana Muñoz X, et al. Tamoxifen prolongs survival and alleviates symptoms in mice with fatal X-linked myotubular myopathy. Nat Commun. 2018 [cited 2018 Nov 19];9 (1):4848. doi: 10.1038/s41467-018-07058-4
151. Maani N, Sabha N, Rezai K, et al. Tamoxifen therapy in a murine model of myotubular myopathy. Nat Commun. 2018 [cited 2018 Nov 19];9(1):4849. doi: 10.1038/s41467-018-07057-5
152. Etori S, Nakano R, Kamada H, et al. Tamoxifen-induced lung injury. Intern Med. 2017;56(21):2903–2906. doi: 10.2169/internalmedicine.8649-16
153. Lim HJ, Joo S, Oh SH, et al. Syngeneic myoblast transplantation improves muscle function in a murine Model of X-Linked myotubular myopathy. Cell Transplant. 2015;24(9):1887–1900. doi: 10.3727/096368914X683494
154. Mercuri E, Vilchez JJ, Boespflug-Tanguy O, et al. Safety and efficacy of givinostat in boys with Duchenne muscular dystrophy (EPIDYS):

a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial [published correction appears in lancet neurol. 2024 Jun;23(6): e10. doi: 10.1016/S1474–4422(24)00172–8] [published correction appears in lancet neurol. 2024 Aug;23(8): e12. doi: 10.1016/S1474–4422(24)00257–6]. Lancet Neurol. 2024;23(4):393–403. doi: 10.1016/S1474-4422(24)00036-X

155. Henzi BC, Schmidt S, Nagy S, et al. Safety and efficacy of tamoxifen in boys with Duchenne muscular dystrophy (TAMDMD): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2023;22(10):890–899. doi: 10.1016/S1474-4422(23)00285-5
156. Skuk D, Tremblay JP. Intramuscular cell transplantation as a potential treatment of myopathies: clinical and preclinical relevant data. Expert Opin Biol Ther. 2011;11(3):359–374. doi: 10.1517/14712598.2011.548800
157. Servais L, Horton R, Saade D, et al. Management of safety issues arising following AAV gene therapy. 261st ENMC international Workshop; 2022 Jun 17–19, Hoofddorp, the Netherlands. Neuromuscul Disord. 2023;33(11):884–896. doi: 10.1016/j.nmd.2023.09.008
158. Wang CH, Dowling JJ, North K, et al. Consensus statement on standard of care for congenital myopathies. J Child Neurol. 2012;27(3):363–382. doi: 10.1177/0883073812436605
159. Sacks NC, Healey BE, Cyr PL, et al. Costs and health resource use in patients with X-linked myotubular myopathy: insights from US commercial claims. J Manag Care Spec Pharm. 2021;27(8):1019–1026. doi: 10.18553/jmcp.2021.20501
160. Kirk EP, Delatycki MB, Archibald AD, et al. Nationwide, couple-based genetic carrier screening. N Engl J Med. 2024;391(20):1877–1889. doi: 10.1056/NEJMoa2314768
161. Boemer F, Hovhannesyan K, Piazzon F, et al. Population-based, first-tier genomic newborn screening in the maternity ward. Nat Med. 2025 Jan 28. doi: 10.1038/s41591-024-03465-x
162. Dangouloff T, Thokala P, Stevenson MD, et al. Cost-effectiveness of spinal muscular atrophy newborn screening based on real-world data in Belgium. Neuromuscul Disord. 2024;34:61–67. doi: 10.1016/j.nmd.2023.11.013
163. Dangouloff T, Hiligsmann M, Deconinck N, et al. Financial cost and quality of life of patients with spinal muscular atrophy identified by symptoms or newborn screening. Develop Med Child Neuro. 2023;65(1):67–77. doi: 10.1111/dmcn.15286
164. Dangouloff T, Hovhannesyan K, Mashhadizadeh D, et al. Feasibility and acceptability of a newborn screening program using targeted next-generation sequencing in One Maternity Hospital in Southern Belgium. Children. 2024;11:926. doi: 10.3390/children11080926
165. Fouarge E, Monseur A, Boulanger B, et al. Hierarchical Bayesian modelling of disease progression to inform clinical trial design in centronuclear myopathy. Orphanet J Rare Dis. 2021;16(1):3. doi: 10.1186/s13023-020-01663-7