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Investment memorandum

11 Jun 2026

First-generation therapy forecast:

Delta-sarcoglycan-related limb-girdle muscular dystrophy R6

Categories: rare cardiac diseases, rare genetic diseases, rare neurological diseases +1

Gene therapies

Forecast for the first gene therapies based drug for the disease.

Disease landscape:

Orphan designations: **0**

Approved drugs: **0**

De-risked by AI:

Top 3.6%
of research

Highest probability of becoming an approved therapy from the research stage.

Disease overview

AI-generated summary. Verify critical details against original sources.

Delta-sarcoglycan-related limb-girdle muscular dystrophy R6

Synonyms: Autosomal recessive limb-girdle muscular dystrophy type 2F, Delta-sarcoglycan-related LGMD R6, Delta-sarcoglycanopathy, LGMD due to delta-sarcoglycan deficiency, LGMD type 2F, LGMD2F, Limb-girdle muscular dystrophy due to delta-sarcoglycan deficiency, Limb-girdle muscular dystrophy type 2F.

Delta-sarcoglycan-related limb-girdle muscular dystrophy R6 (LGMDR6) is an ultra-rare autosomal recessive disorder caused by SGCD mutations, leading to progressive weakness of proximal limb-girdle muscles, cardiomyopathy, and respiratory impairment. Onset typically occurs in childhood, with elevated CK levels, calf hypertrophy, and preserved neurodevelopment. Disease progression often results in loss of ambulation by early adolescence, with cardiac and respiratory complications significantly impacting morbidity and mortality [1] [4] [10].

Population

- Prevalence: 1-9 per 1,000,000, with higher incidence in consanguineous populations [1] [4] [7].
- Inheritance: Autosomal recessive; 87% of cases involve parental consanguinity [4] [10].

Current Therapeutic Strategies

- **Supportive care**: Physiotherapy for contractures, non-invasive ventilation for respiratory insufficiency, and cardiac monitoring/treatment (β-blockers, ACE inhibitors) [3] [4].
- **Gene therapy**: Preclinical studies show δ-sarcoglycan replacement improves cardiac/skeletal muscle function in animal models; Phase I human trials remain investigational [2] [5] [11].
- **Clinical trials**: Focused on sarcoglycan complex restoration and DGC stabilization, though no disease-modifying therapies exist [6] [13].

Burden of the Disease

- Rapid progression: 60% require wheelchairs by age 12, with frequent hospitalizations for cardiac/respiratory crises [4] [10].
- Multisystem morbidity: 21.7% develop cardiomyopathy; 17.4% require permanent ventilatory support [4] [12].
- Mortality: Premature death from respiratory failure or dilated cardiomyopathy despite interventions [1] [6].

Literature overview

Most influential articles for LLM-classifier prediction.

15.1% influence 28 Jul 2021

Sarcoglycanopathies: an update

Open article

Mariz Vainzof 718 Lucas Santos Souza 27 Juliana Gurgel-Giannetti 109 Mayana Zatz 1073

Sarcoglycanopathies are the most severe forms of autosomal recessive limb-girdle muscular dystrophies (LGMDs), constituting about 10-25% of LGMDs. The clinical phenotype is variable, but onset is usually in the first decade of life. Patients present muscle hypertrophy, elevated CK, variable muscle weaknesses, and progressive loss of ambulation. Four subtypes are known: LGMDR3, LGMDR4, LGMDR5 and LGMDR6, caused, respectively, by mutations in the SGCA, SGCB,SGCG and SGCD genes. Their four coded proteins, α-SG, β-SG, λ-SG and δ-SG are part of the dystrophin-glycoprotein complex (DGC) present in muscle sarcolemma, which acts as a linker between the cytoskeleton of the muscle fiber and the extracellular matrix, providing mechanical support to the sarcolemma during myofiber contraction. Many different mutations have already been identified in all the sarcoglycan genes, with a predominance of some mutations in different populations. The diagnosis is currently based on the molecular screening for these mutations. Therapeutic approaches include the strategy of gene replacement mediated by a vector derived from adeno-associated virus (AAV). Pre-clinical studies have shown detectable levels of SG proteins in the muscle, and some improvement in the phenotype, in animal models. Therapeutic trials in humans are ongoing.

14.7% influence 2 Sep 2014

G.P.252

Open article

Roberto Maggi 285 B. Vola Massimiliano Cerletti Paola Bonetti 89

Limb girdle muscular dystrophy (LGMD) constitutes a family of rare genetic disease characterized by progressive weakness of pelvic or shoulder girdle musculature due to impairment of the dystrophin-associated protein complex (DPC) components. The sarcoglycanopathies are a common cause of LGMDs,

accounting for 3–18%, with a high percentage of severe cases. In particular, LGMD2E is a recessive autosomal disease caused by mutation in the gene, located on chromosome 4q12, encoding the beta-sarcoglycan, a major component of the DPC. Age of onset is between 2 years and the mid-teenage years. The clinical presentation includes progressive limb weakness (mainly of proximal muscles). Cardiac involvement occurs in 20% of the cases. LGMD2E is classified as a “neglected” disease by EU, underlying a substantial absence of dedicated scientific research; no specific treatments are known. Of interest, sarcoglycanopathies should be cured by gene therapy since the sarcoglycans genes are relatively short and with few exons, making them suitable for adenovirus-based therapy. Actually, a phase II clinical trial for gene therapy of alpha-sarcoglycanopathy is ongoing in USA. Another possible approach relies on autologous transplantation of stem cells, such as muscle progenitor cells. In 2013 the volunteer organization named Family Group of Beta-sarcoglycanopathy ONLUS (GFB ONLUS www.lgmd2e.org) was established to: a) contact the highest number of patients affected by LGMD and their families b) collect all data and information available on LGMD2E c) stimulate both basic and clinical research. Moreover, we would like to promote scientific research specific on LGMD2E, create collaborations with scientists to organize both informative and scientific meetings and, eventually, support researchers interested to study this disease. On April 19th 2013 the GFB ONLUS held its first scientific Meeting in Milan that allowed a fruitful confrontation amo ...

12.7% influence 9 May 2019

An AAV-SGCG Dose-Response Study in a γ-Sarcoglycanopathy Mouse Model in the Context of Mechanical Stress

Open article

David Israeli 97 Jérémie Cosette Guillaume Corre 62
Fatima Amor Jérôme Poupiot Daniel Stockholm 92
Marie Montus Bernard Gjata Isabelle Richard

Sarcoglycanopathies are rare autosomic limb girdle muscular dystrophies caused by mutations in one of the genes coding for sarcoglycans. Sarcoglycans form a complex, which is an important part of the dystrophin-associated glycoprotein complex and which protects the sarcolemma against muscle contraction-induced damage. Absence of one of the sarcoglycans on the plasma membrane reduces the stability of the whole complex and perturbs muscle fiber membrane integrity. There is currently no curative treatment for any of the sarcoglycanopathies. A first clinical trial to evaluate the safety of a recombinant AAV2/1 vector expressing γ-sarcoglycan using an intramuscular route of administration showed limited expression of the transgene and good tolerance of the approach. In this report, we undertook a dose-effect study in mice to evaluate the efficiency of an AAV2/8-expressing γ-sarcoglycan controlled by a muscle-specific promoter with a systemic mode of administration. We observed a dose-related efficiency with a nearly complete restoration of gamma sarcoglycan (SGCG) expression,

histological appearance, biomarker level, and whole-body strength at the highest dose tested. In addition, our data suggest that a high expression threshold level must be achieved for effective protection of the transduced muscle, while a suboptimal transgene expression level might be less protective in the context of mechanical stress. Sarcoglycanopathies are rare autosomic limb girdle muscular dystrophies caused by mutations in one of the genes coding for sarcoglycans. Sarcoglycans form a complex, which is an important part of the dystrophin-associated glycoprotein complex and which protects the sarcolemma against muscle contraction-induced damage. Absence of one of the sarcoglycans on the plasma membrane reduces the stability of the whole complex and perturbs muscle fiber membrane integrity. There is currently no curative treatment for any of the ...

7.5% influence 7 Feb 2012

Enhancing Muscle Membrane Repair by Gene Delivery of MG53 Ameliorates Muscular Dystrophy and Heart Failure in δ-Sarcoglycan-deficient Hamsters

Open article

Bo He 119 Ruhang Tang 94 Noah Weisleder 202 Bin Xiao 278 Zhenhua Yuan 64 Chuanxi Cai 76 Hua Zhu 374 Peihui Lin Chunping Qiao Jianbin Li 186 Christina Mayer Juan Li 373 Jianjie Ma 318 Xiao Xiao 127

Muscular dystrophies (MDs) are caused by genetic mutations in over 30 different genes, many of which encode for proteins essential for the integrity of muscle cell structure and membrane. Their deficiencies cause the muscle vulnerable to mechanical and biochemical damages, leading to membrane leakage, dystrophic pathology, and eventual loss of muscle cells. Recent studies report that MG53, a muscle-specific TRIM-family protein, plays an essential role in sarcolemmal membrane repair. Here, we show that systemic delivery and muscle-specific overexpression of human MG53 gene by recombinant adeno-associated virus (AAV) vectors enhanced membrane repair, ameliorated pathology, and improved muscle and heart functions in δ-sarcoglycan (δ-SG)-deficient TO-2 hamsters, an animal model of MD and congestive heart failure. In addition, MG53 overexpression increased dysferlin level and facilitated its trafficking to muscle membrane through participation of caveolin-3. MG53 also protected muscle cells by activating cell survival kinases, such as Akt, extracellular signal-regulated kinases (ERK1/2), and glycogen synthase kinase-3β (GSK-3β) and inhibiting proapoptotic protein Bax. Our results suggest that enhancing the muscle membrane repair machinery could be a novel therapeutic approach for MD and cardiomyopathy, as demonstrated here in the limb girdle MD (LGMD) 2F model.

7.2% influence 30 Oct 2010

Delta-Sarcoglycan Gene Therapy Halts Progression of Cardiac Dysfunction, Improves Respiratory Failure, and Prolongs Life in Myopathic Hamsters

Background— The BIO14.6 hamster provides a useful model of hereditary cardiomyopathies and muscular dystrophy. Previous δ-sarcoglycan (δSG) gene therapy (GT) studies were limited to neonatal and young adult animals and prevented the development of cardiac and skeletal muscle dysfunction. GT of a pseudophosphorylated mutant of phospholamban (S16EPLN) moderately alleviated the progression of cardiomyopathy. Methods and Results— We treated 4-month-old BIO14.6 hamsters with established cardiac and skeletal muscle diseases intravenously with a serotype-9 adeno–associated viral vector carrying δSG alone or in combination with S16EPLN. Before treatment at age 14 weeks, the left ventricular fractional shortening by echocardiography was 31.3% versus 45.8% in normal hamsters. In a randomized trial, GT halted progression of left ventricular dilation and left ventricular dysfunction. Also, respiratory function improved. Addition of S16EPLN had no significant additional effects. δSG-GT prevented severe degeneration of the transverse tubular system in cardiomyocytes (electron tomography) and restored distribution of dystrophin and caveolin-3. All placebo-treated hamsters, except animals removed for the hemodynamic study, died with heart failure between 34 and 67 weeks of age. In the GT group, signs of cardiac and respiratory failure did not develop, and animals lived for 92 weeks or longer, an age comparable to that reported in normal hamsters. Conclusion— GT was highly effective in BIO14.6 hamsters even when given in late-stage disease, a finding that may carry implications for the future treatment of hereditary cardiac and muscle diseases in humans.

Related companies

AI-generated summary of companies related to the forecast. Verify critical details against original sources.

Company	Lead candidate	Stage
—	—	—

Drug discovery timeline

Orphan designations and approvals related to the disease.