

# Investment memorandum

11 Jun 2026



## First-generation therapy forecast:

**Very long chain acyl-CoA dehydrogenase deficiency**

Categories: rare cardiac diseases, rare genetic diseases, rare inborn errors of metabolism +2

## Gene therapies

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

## Disease landscape:

 Orphan designations: 2  Approved drugs: 0



## De-risked by AI:

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



**Top 0.1%**  
of research



# Disease overview

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

## Very long chain acyl-CoA dehydrogenase deficiency

Synonyms: VLCAD deficiency, VLCADD.

**Very long-chain acyl-CoA dehydrogenase deficiency (VLCADD)** is an autosomal recessive disorder caused by mutations in the ACADVL gene, impairing mitochondrial  $\beta$ -oxidation of long-chain fatty acids. Clinical presentation varies by age: severe infantile forms feature cardiomyopathy, hypoglycemia, and liver dysfunction; childhood-onset types present with hepatic and metabolic crises; and adult myopathic forms manifest as exercise-induced rhabdomyolysis. Diagnosis involves elevated C14:1 acylcarnitines on newborn screening, genetic testing, and enzyme assays. Management prioritizes fasting avoidance, low long-chain fat diets with medium-chain triglyceride (MCT) supplementation, and emergency glucose protocols during metabolic stress <sup>1 2 7 12</sup>.

## Population

Incidence ranges from 1:30,000 to 1:120,000 globally, with higher rates in consanguineous populations (e.g., 1:3,200 in Saudi Arabia). Newborn screening programs detect most cases, though milder phenotypes may evade early diagnosis <sup>1 4 13 17</sup>.

## Current Therapeutic Strategies

- **Dietary:** Strict long-chain fat restriction, MCT supplementation, and avoidance of prolonged fasting <sup>1 8 16</sup>.
- **Emergency care:** Intravenous glucose during metabolic crises to prevent hypoglycemia and rhabdomyolysis <sup>5 19</sup>.
- **Pharmacological:** Bezafibrate (PPAR-agonist) and triheptanoin (experimental) show promise in improving  $\beta$ -oxidation and clinical outcomes <sup>3 17</sup>.

## Burden of the Disease

- High mortality risk in untreated infantile forms due to cardiac/liver complications <sup>1 7</sup>.
- Chronic morbidity includes recurrent rhabdomyolysis, cardiomyopathy, and hepatopathy <sup>6 12 19</sup>.
- Caregivers report financial strain, limited access to specialized nutrition, and psychosocial stress <sup>2 10 14</sup>.

# Literature overview

Most influential articles for LLM-classifier prediction.

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26.0% influence 1 Jan 2025

## P019: Comparison of treatment efficacy of very long chain acyl-CoA (VLCAD) deficiency with an AAV9.hVLCAD vector, synthetic VLCAD mRNA, and triheptanoin

Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency (VLCADD) is the most prevalent long chain fatty acid oxidation disorder, characterized by hypoglycemia, cardiomyopathy, and recurrent rhabdomyolysis. Previously we have reported the creation of a robust muscle specific long chain acyl-CoA dehydrogenase on a complete VLCAD deficient background (mAcadl-/-:Acadvl-/-; MDKO) mouse model exhibiting the major clinical manifestations in adolescents and adults, recurrent e rhabdomyolysis and progressive cardiomyopathy.

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Open article 

Jerry Vockley  472

Shakuntala Basu

Xuejun Zhao

Bianca Seminotti  101

Clinton Van't Land  25

Al-Walid Mohsen  99

14.0% influence 1 May 2005

## 921. Steps toward Cardiomyopathy Gene Therapy: In Vivo Expression of Human VLCAD

Cardiomyopathy (CM) is an important cause of morbidity and mortality in children. Deficiency of very-long-chain acyl-CoA dehydrogenase (VLCAD), one of four nuclear encoded mitochondrial enzymes that catalyze the initial step in the beta-oxidation of straight-chain fatty acids, often presents with CM and/or sudden death. How VLCAD deficiency causes CM is unclear, but appears to be related to the accumulation of toxic long-chain acyl-carnitine species rather than a block in energy metabolism. While dietary therapy for VLCAD deficiency has been beneficial to some, many people do not respond, and intercurrent illness with diminished oral intake, exercise, or fasting all increase demand for fatty acid

Open article 

metabolism and can trigger catastrophic events even in those on diet therapy. While VLCAD deficiency is a rare metabolic deficiency, the development of a safe and durable gene therapy for VLCAD deficiency would be the first curative gene therapy for CM.

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10.1% influence

7 Jun 2010

## Mitochondrial fatty acid oxidation disorders: pathophysiological studies in mouse models

Abstract Mouse models have been designed for a number of fatty acid oxidation defects. Studies in these mouse models have demonstrated that different pathogenetic mechanisms play a role in the pathophysiology of defects of fatty acid oxidation. Supplementation with L-carnitine does not prevent low tissue carnitine levels and induces acylcarnitine production having potentially toxic effects, as presented in very-long-chain acyl-CoA dehydrogenase (VLCAD)-deficient mice. Energy deficiency appears to be an important mechanism in the development of cardiomyopathy and skeletal myopathy in fatty acid oxidation defects and is also the underlying mechanism of cold intolerance. Hypoglycemia as one major clinical sign in all fatty acid oxidation defects occurs due to a reduced hepatic glucose output and an enhanced peripheral glucose uptake rather than to transcriptional changes that are also observed simultaneously, as presented in medium-chain acyl-CoA dehydrogenase (MCAD)-deficient mice. There are reports that an impaired fatty acid oxidation also plays a role in intrauterine life. The embryonic loss demonstrated for some enzyme defects in the mouse supports this hypothesis. However, the exact mechanisms are unknown. This observation correlates to maternal hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, as observed in pregnancies carrying a long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD)-deficient fetus. Synergistic heterozygosity has been shown in isolated patients and in mouse models to be associated with clinical phenotypes common to fatty acid oxidation disorders. Synergistic mutations may also modulate severity of the clinical phenotype and explain in part clinical heterogeneity of fatty acid oxidation defects. In summary, knowledge about the different pathogenetic mechanisms and the resulting pathophysiology allows the development of specific new therapies.

Open article 

Ute Spiekerkoetter  150

Philip A. Wood  163

10.1% influence

20 Jan 2009

## Biochemical Correction of Very Long-chain Acyl-CoA Dehydrogenase Deficiency Following Adeno-associated Virus Gene Therapy

We report the development of a gene replacement strategy for very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency. VLCAD is a mitochondrial enzyme involved in fatty acid beta-oxidation, a key step in energy production during times of fasting or stress. Deficiency of VLCAD classically presents as hepatic dysfunction, hypoglycemia, cardiomyopathy, rhabdomyolysis, and/or sudden death. While dietary therapy for VLCAD deficiency has proven beneficial in preventing some symptoms, a risk of metabolic catastrophic decompensation remains throughout life during times of increased energy demand. We designed a recombinant adeno-associated virus (AAV) expressing the human VLCAD gene (AAV8-hVLCAD). To demonstrate its in vivo activity, AAV8-hVLCAD was administered via the tail vein to VLCAD-knockout mice. A reduction in accumulated serum long-chain acylcarnitines and increased fasting tolerance judged on blood glucose concentrations were observed as of 11 days postinjections through >100 days. Western analysis of liver, skeletal muscle, and heart extracts using PEPI anti-hVLCAD antibody revealed short-term hVLCAD expression in the liver and muscle and longer-term expression in heart. This demonstrates the ability of human VLCAD to correct the biochemical phenotype of VLCAD-deficient mice.

[Open article](#) 

J. Lawrence Merritt  132

Tien Nguyen

Jan Daniels

Dietrich Matern  281

David B. Schowalter

9.9% influence

6 Mar 2012

## Long-term Correction of Very Long-chain Acyl-CoA Dehydrogenase Deficiency in Mice Using AAV9 Gene Therapy

Very long-chain acyl-coA dehydrogenase (VLCAD) is the rate-limiting step in mitochondrial fatty acid oxidation. VLCAD-deficient mice and patients clinical symptoms stem from not only an energy deficiency but also long-chain metabolite accumulations. VLCAD-deficient mice were treated systemically with 1 ×

[Open article](#) 

$10^{12}$  vector genomes of recombinant adeno-associated virus 9 (rAAV9)-VLCAD. Biochemical correction was observed in vector-treated mice beginning 2 weeks postinjection, as characterized by a significant drop in long-chain fatty acyl accumulates in whole blood after an overnight fast. Changes persisted through the termination point around 20 weeks postinjection. Magnetic resonance spectroscopy (MRS) and tandem mass spectrometry (MS/MS) revealed normalization of intramuscular lipids in treated animals. Correction was not observed in liver tissue extracts, but cardiac muscle extracts showed significant reduction of long-chain metabolites. Disease-specific phenotypes were characterized, including thermoregulation and maintenance of euglycemia after a fasting cold challenge. Internal body temperatures of untreated VLCAD<sup>-/-</sup> mice dropped below 20 °C and the mice became lethargic, requiring euthanasia. In contrast, all rAAV9-treated VLCAD<sup>-/-</sup> mice and the wild-type controls maintained body temperatures. rAAV9-treated VLCAD<sup>-/-</sup> mice maintained euglycemia, whereas untreated VLCAD<sup>-/-</sup> mice suffered hypoglycemia following a fasting cold challenge. These promising results suggest rAAV9 gene therapy as a potential treatment for VLCAD deficiency in humans.

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Allison M. Keeler 52

Thomas J. Conlon 127

Glenn A. Walter 250

Huadong Zeng 62

Scott A. Shaffer 172

Fu Dungtao

Kirsten Erger

Travis Cossette 21

Qiushi Tang

Christian Mueller 154

Terence R. Flotte 420

## Related companies

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

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Company	Lead candidate	Stage
Moderna, Inc. (Cambridge, MA, USA)	<p data-bbox="682 421 1702 506"><b>LNP-hVLCAD mRNA (synthetic human VLCAD mRNA formulated in lipid nanoparticles)</b></p> <p data-bbox="682 521 1702 714">Lipid-nanoparticle (LNP)-formulated synthetic human ACADVL (VLCAD) mRNA designed to generate functional VLCAD protein in patient cells and in vivo (liver and muscle). Reported work includes in vitro patient fibroblast and hepatocyte experiments and systemic IV dosing in <i>Acadvl</i><sup>-/-</sup> mice with biochemical and phenotypic improvement. Development stage is preclinical.</p>	<p data-bbox="1745 421 2361 464">Preclinical (in vitro and mouse model studies) <span data-bbox="2331 428 2361 464">1</span></p> <p data-bbox="1745 471 1911 506"><span data-bbox="1745 471 1783 506">2</span> <span data-bbox="1783 471 1821 506">3</span> <span data-bbox="1821 471 1860 506">4</span> <span data-bbox="1860 471 1898 506">5</span></p>

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# Drug discovery timeline

Orphan designations and approvals related to the disease.

Drug	Therapy type		Orphan designation	Approval	Sponsor
Triheptanoin	small molecules	<a href="#">EMA</a>	2015-06-19	nan	Ultragenyx Netherlands B.V.
Triheptanoin	small molecules	<a href="#">EMA</a>	2012-12-06	nan	B. Braun Melsungen AG