

## Deliverable D.4.2.

# Towards a cure for Charcot-Marie-Tooth: a critical overview on new therapeutic approaches with patients as partners

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## 1. Charcot-Marie-Tooth disease: clinical and biological framework

Charcot-Marie-Tooth disease (CMT) comprises a heterogeneous group of inherited peripheral neuropathies affecting approximately 1 in 2,500 individuals worldwide. Clinically, CMT is characterized by slowly progressive distal muscle weakness and atrophy, sensory loss, reduced reflexes, and characteristic foot deformities. Based on neurophysiological criteria, CMT is classified into demyelinating (CMT1/CMT4), axonal (CMT2), and intermediate forms (Skre, 1974; Pareyson et al., 2017).

At the cellular level, demyelinating forms primarily involve defects in Schwann cell myelin formation and maintenance, whereas axonal forms are characterized by primary axonal degeneration. Despite these differences, disease progression across CMT subtypes ultimately converges on axonal dysfunction and loss, which closely correlates with clinical disability (Sahenk et al., 2008).

Although more than 130 causative genes have been identified, current clinical management remains largely symptomatic. Nevertheless, advances in molecular genetics, disease modeling, and therapeutic delivery have enabled the development of targeted therapeutic strategies that are now entering translational and early clinical phases. A recent account has been given in Session 3 of the Conference on „[Therapeutic approaches on CMT neuropathies](#)“ by Kleopas Kleopa, and promising examples of specific research projects in the field can be found in the [Youtube-playlist](#) of selected talks and presentations given at the Conference.

## 2. Therapeutic strategies under development

### 1.2.1 Gene-based approaches

Gene-based therapies aim to address the primary genetic cause of CMT by restoring gene function, modulating gene dosage, or selectively silencing pathogenic alleles using viral vectors, antisense oligonucleotides (ASOs), small interfering RNA (siRNA), or genome-editing approaches.

In demyelinating CMT, particularly CMT1A caused by PMP22 duplication, several strategies aim to reduce toxic PMP22 overexpression. These include AAV-mediated RNA interference

(Gautier et al., 2015; Stavrou et al., 2022), systemically delivered ASOs (Zhao et al., 2018), chemically modified siRNA formulations (Boutary et al., 2020), and CRISPR/Cas9-based transcriptional repression strategies (Lee et al., 2020). Loss-of-function demyelinating neuropathies such as CMT1X or CMT4C are being addressed by Schwann-cell-targeted AAV-mediated gene replacement, restoring myelination and nerve function in preclinical models (Kagiava et al., 2016; Kagiava et al., 2021; Georgiou et al., 2023).

In axonal CMT, gene-based approaches include intrathecal AAV-mediated gene replacement for giant axonal neuropathy (El Mallakh et al., 2017; Bharucha-Goebel et al., 2024), allele-specific RNA interference for GARS-related CMT2D (Morelli et al., 2019), and early gene replacement in FIG4-related CMT4J (Winborn et al., 2018). In addition, intramuscular AAV-mediated delivery of neurotrophin-3 (NT3) provides a broadly applicable strategy supporting Schwann cell-axon interactions across multiple CMT subtypes (Sahenk et al., 2014).

More information on the genetic CMT therapy development is presented at the webinar given by Kleopas Kleopa in a series set up jointly by EAN, the ERN EURO NMD and ECRA in January 2026: "[Current Progress in Charcot-Marie-Tooth disease \(CMT\) Treatments](#)".

## 2.2.2 Pharmacological approaches

Pharmacological strategies primarily target downstream pathogenic mechanisms shared across multiple CMT forms and may complement gene-based interventions or serve as earlier therapeutic options.

In demyelinating CMT, approaches focus on PMP22 modulation, restoration of proteostasis, Schwann cell differentiation, unfolded protein response (UPR) activation, and inflammation. The most advanced example is PXT3003, an oral combination therapy designed to downregulate PMP22 expression, which has shown modest but measurable functional benefit in Phase III trials (Attarian et al., 2014; Attarian et al., 2021). Additional strategies include UPR and proteostasis modulation using IFB-088/Sephin1 (D'Antonio et al., 2013; Das et al., 2015), and proteasome activation via cGMP signaling using sildenafil (VerPlank et al., 2022).

In axonal CMT, therapeutic strategies aim to prevent axonal degeneration and restore axonal transport and mitochondrial dynamics. Inhibition of SARM1, a central executor of axon degeneration, is strongly protective in CMT2A models (Osterloh et al., 2012; Gerdtts et al., 2015; Sato-Yamada et al., 2022). HDAC6 inhibition restores microtubule acetylation and axonal transport in several axonal CMT models (d'Ydewalle et al., 2011). Metabolic correction in SORD-related neuropathies using aldose reductase inhibitors represents a further targeted approach (Cortese et al., 2020).

## 3. Biomarkers and outcome measures

The slow clinical progression of CMT presents a major challenge for clinical trials and underscores the need for sensitive and treatment-responsive biomarkers. Established clinical scales such as the CMT Neuropathy Score (CMTNS) and CMT Examination Score (CMTES) remain fundamental for assessing disability but often lack sensitivity over short observation periods (see also D.5.1. and D.5.2.).

Blood-based biomarkers such as neurofilament light chain reflect axonal injury and are elevated in CMT, although correlations with disease progression in humans remain limited. Schwann cell-derived proteins, including periaxin, have emerged as promising biomarkers of disease severity in demyelinating CMT. In parallel, quantitative muscle MRI has proven to be a highly sensitive tool for detecting disease progression over 12-month intervals.

## 4. Translational challenges and patient partnership

Despite substantial therapeutic progress, translation of CMT therapies remains limited by incomplete genetic diagnosis in a subset of patients, the need for early intervention prior to irreversible axonal loss, challenges in outcome measurement, and difficulties in delivering advanced therapies to peripheral nerves. These barriers are amplified by the rarity and heterogeneity of the disease.

In this context, the active involvement of patients as partners is particularly important (see D.6.2.). Patients contribute unique insights into disease burden, symptom variability, and outcomes that are meaningful in daily life, informing trial design and endpoint selection. Their engagement facilitates recruitment, long-term follow-up, and natural history studies, which are essential for biomarker validation and therapeutic assessment. Embedding patient partnership across the research continuum ultimately strengthens the translational relevance and societal impact of CMT research.

## 5. Overview: planned and ongoing clinical trials

EU4Health Program

Milestone no. 13: List of running and planned clinical trials

### Literature

Overview preclinical research and ongoing clinical trials

<https://cmtrf.org/research/cmt-research-pipeline/>

Review: Charcot-Marie-Tooth disease: a review of clinical developments and its management - What's new in 2025?

<https://www.tandfonline.com/doi/epdf/10.1080/14737175.2025.2470980?needAccess=true>

### List of ongoing clinical trials and literature references

#### 1. Applied Therapeutics

##### a. INSPIRE Trial, NCT05397665

Govorestat

Aldose reductase inhibitor

People with SORD deficiency (CMT-SORD)

Phase II/III

<https://www.appliedtherapeutics.com/pipeline/govorestat/>

Cortese et al. Genotype and phenotype spectrum of Charcot-Marie-Tooth disease due to mutations in SORD. 2025. BRAIN <https://academic.oup.com/brain/advance-article/doi/10.1093/brain/awaf021/8010720>

#### 2. UCL Queen Square centre for neuromuscular disorders

##### SENSE trial, NCT06113055

HSN1 (Hereditary Sensory Neuropathy)

SPTLC1 or SPTLC2 mutations

L-Serine (amino acid therapy)

Phase II

<https://cmtausa.org/research-projects/hereditary-sensory-neuropathy-serine-trial-sense-trial/>

Garofalo et al. Oral L-serine supplementation reduces production of neurotoxic deoxysphingolipids in mice and humans with hereditary sensory autonomic neuropathy type 1. 2011. Journal of Clinical Investigation <https://pubmed.ncbi.nlm.nih.gov/22045570/>

- 3. NMD Pharma®**  
**SYNAPSE-CMT, NCT06482437**  
NMD670  
ClC-1 - chloride channel modulator  
CMT1 and CMT2 patients  
Phase IIa  
<https://www.nmdpharma.com/news/nmd-pharma-initiates-phase-2-study-of-nmd670-in-patients-with-cmt-type-1-and-2>  
Skjærlund Grønnebak et al. Neuromuscular transmission deficits in patients with CMT and ClC-1 inhibition in CMT animal models. 2024. Ann Clin Transl Neurol. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/acn3.52252>
- 4. Inflectis BioScience**  
**IFB-088 (Sephin1)**  
Proteostasis modulator (inhibition dephosphorylation of eIF2α)  
CMT1A, 1B, 1E  
Phase I  
<https://inflectisbioscience.com/our-pipeline/>  
Bai et al. Treatment with IFB-088 Improves Neuropathy in CMT1A and CMT1B Mice. 2020. Mol Neurobiol. <https://link.springer.com/article/10.1007/s12035-022-02838-y>
- 5. Augustine Therapeutics**  
**AGT-100216**  
HDAC 6 inhibitor, peripherally selective  
CMT1 and CMT2 (broad potential)  
Phase I (healthy adults, CMT patients next)  
<https://www.augustinetx.com/pipeline>  
<https://www.augustinetx.com/media/augustine-therapeutics-announces-first-patient-dosed-in-phase-i-clinical-trial-evaluating-lead-candidate-agt-100216-for-the-treatment-of-charcot-marie-tooth-disease>  
Rossaert and Van Den Bosch, HDAC6 inhibitors: Translating genetic and molecular insights into a therapy for axonal CMT. 2020. Brain Research.  
<https://www.sciencedirect.com/science/article/pii/S0006899320300482?via%3Dihub>  
Benoy et al. Development of Improved HDAC6 Inhibitors as Pharmacological Therapy for Axonal Charcot-Marie-Tooth Disease. 2017. Neurotherapeutics.  
[https://www.neurotherapeuticsjournal.org/article/S1878-7479\(23\)01476-9/fulltext](https://www.neurotherapeuticsjournal.org/article/S1878-7479(23)01476-9/fulltext)  
d'Ydewalle et al. 2011 HDAC6 inhibitors reverse axonal loss in a mouse model of mutant HSPB1-induced Charcot-Marie-Tooth disease. 2011. Nature medicine. <https://www.nature.com/articles/nm.2396>
- 6. CKD Pharmaceuticals (Novartis)**  
**CKD-510**  
HDAC6 inhibitor  
CMT1 and CMT2  
Phase I
- 7. Actio Biosciences**  
**ABS-0871**  
TRPV4 ion channel inhibitor  
CMT2C (TRPV4 mutation)  
Phase I

<https://actiobiosciences.com/actio-biosciences-announces-first-participant-dosed-in-phase-1-clinical-trial-of-abs-0871-a-novel-trpv4-inhibitor-for-the-treatment-of-charcot-marie-tooth-disease-2c/>

8. **VANDA Pharmaceuticals inc.**  
**VCA-894A**  
Antisense oligonucleotide  
CMT2S (IGHMBP2 mutation) - custom for one patient  
Phase I (first dose administered June 2025)
9. **ENCell**  
**EN001**  
allogeneic Wharton's jelly mesenchymal stem cell therapy (IV infusion)  
CMT1A  
Phase I → Ib  
<https://www.encellinc.com/en/sub/rnd/pipeline.asp>  
Report on its use in Duchenne Muscular Dystrophy (phase I trial):  
<https://thejcn.com/DOIx.php?id=10.3988/jcn.2024.0299>
10. **Orthogonal Neuroscience**  
ORT247  
mAb inhibitor of EphA4 receptors  
CMT1 and CMT2
11. **Helixmith**  
**Engensis (VM202), NCT05361031**  
Phase I/IIa  
CMT1A  
Plasmid DNA expressing two isoforms of hepatocyte growth factor  
[https://www.helixmith.com/eng/s2/s2\\_1\\_1\\_5.php](https://www.helixmith.com/eng/s2/s2_1_1_5.php)  
[https://www.clinicaltrials.gov/study/NCT05361031?term=AREA%5BBasicSearch%5D\(vm202\)&rank=6](https://www.clinicaltrials.gov/study/NCT05361031?term=AREA%5BBasicSearch%5D(vm202)&rank=6)
12. **Alcyone Therapeutics**  
ACTX technology  
Gene replacement - AAV9 vector carrying the IGHMBP2 gene  
Phase I/IIa  
CMT2S  
<https://www.clinicaltrials.gov/study/NCT05152823>
13. **Pharnext S.C.A.**  
**PREMIER - NCT04762758**  
PXT3003 - baclofen, naltrexone hydrochloride [HCl], and D-sorbitol  
CMT1A  
Phase III, trial ended  
<https://clinicaltrials.gov/study/NCT04762758>  
Chumakov et al. Polytherapy with a combination of three repurposed drugs (PXT3003) down-regulates Pmp22 over-expression and improves myelination, axonal and functional parameters in models of CMT1A neuropathy. 2014. Orphanet J Rare Dis. <https://pmc.ncbi.nlm.nih.gov/articles/PMC4279797/>
14. **Novartis (DTx Pharma)**  
**DTx-1252**  
Preclinical phase → IND planned  
siRNA targeting PMP22

## Key References

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Cortese A., Zhu Y., Rebelo A.P., et al. Biallelic mutations in *sord* are a common cause of potentially treatable genetic neuropathy *Journal of Neurology, Neurosurgery and Psychiatry* 93, Aug. 6, 2022: A14-A14. DOI:10.1136/jnnp-2022-ABN.41