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Therapeutic Innovation, Clinical Trial Acceleration, and Lifestyle Interventions in Myotonic Dystrophy Type 1: A Systematic Review

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ABSTRACT

Therapeutic development in myotonic dystrophy type 1 (DM1) has accelerated in recent years, with a near doubling of clinical trials and expansion into late-stage development. The therapeutic landscape has diversified to include small molecules, oligonucleotide-based therapies, antibody–oligonucleotide conjugates, gene therapies, and microRNA-targeting strategies. Nucleic acid–based approaches have shown promising target engagement and early clinical signals, supporting their potential for disease modification. In parallel, preclinical advances and non-pharmacological interventions such as exercise and rehabilitation are broadening the therapeutic scope. Overall, DM1 research is entering a more mature phase with multiple converging therapeutic strategies.

INTRODUCTION

DM1 is an autosomal dominant disorder caused by a CTG repeat expansion in the 3'UTR of the DMPK gene. Expanded CUG-repeat transcripts form nuclear RNA foci that sequester MBNL proteins, causing widespread spliceopathy and fetal splicing program maintenance. Additional mechanisms include CELF1 upregulation, fibrosis, neurodegeneration, and microRNA dysregulation. Clinically, DM1 presents with muscle weakness, myotonia, cognitive impairment, and cardiac, gastrointestinal, and ocular involvement.

No disease-modifying therapies are currently approved. However, the field is now advancing rapidly: multiple candidates have reached late-stage trials, bringing effective therapies closer to clinical reality.

OBJECTIVE

This review aims to systematically map the accelerated DM1 therapeutic pipeline, from preclinical proof-of-concept (CRISPR, gene therapy, small molecules) to late-stage clinical trials and non-pharmacological interventions.

Table 2. Preclinical programs for DM1

Preclinical program	Type	Biological Target	Sponsor
RNA-targeted small molecules (rSM)	Small molecules	DMPK mRNA (CUG repeats)	Arrakis
LoQus23 MMR inhibitors	Small molecules	MMR (specifically MSH3)	LoQus23
EF-210 (CUG-PPR1)	AAV-PPR protein	Toxic CUG-repeat RNA	EditForce
RGT-DM1	Small molecule	MMR (specifically PMS1)	Rgenta
MDL-202	AAV-CRISPR base editing	DMPK Genomic DNA	Modalis
NoctuRNA circRNA	Circular RNA	Toxic CUG-repeat RNA/RNA secondary structures	NoctuRNA
KNA-129	ASO	Toxic CUG-repeat RNA	Kinea Bio

Abbreviations: ASO: anti-sense oligonucleotide

NEWS BOX. Strategic Inflection Points in DM1 Therapeutics
Clinical Milestones, Pipeline Evolution, M&A & Ecosystem Consolidation

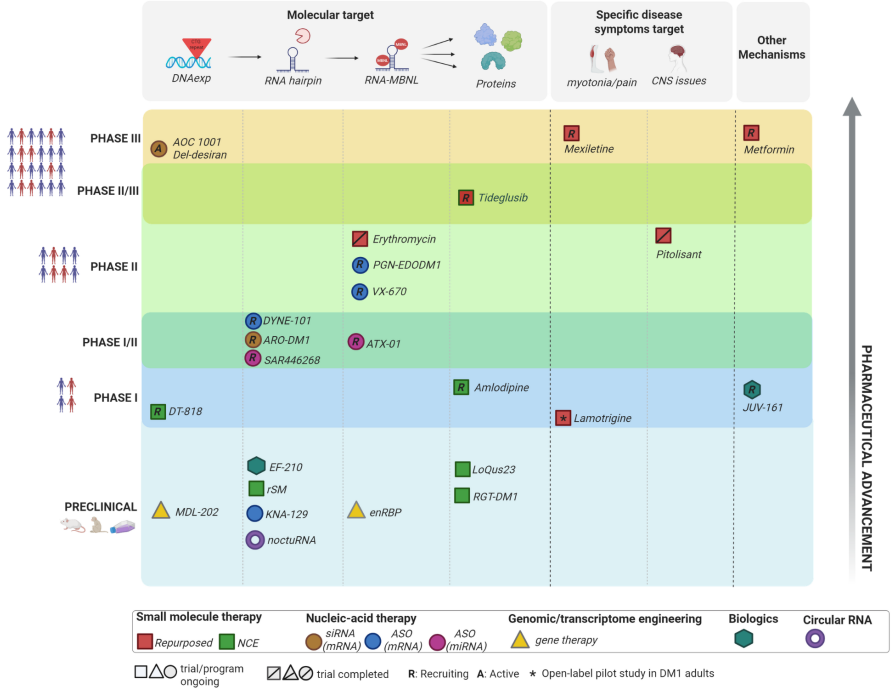
Date	Company (Asset)	Key Advance
mar 2026	Sarepta (SRP-1003)	First clinical data showing DMPK knockdown and favorable tolerability
mar 2026	Arthex (ATX-01)	FDA Fast Track designation for anti-miR-23 therapy
mar 2026	PepGen (PGN-EDODM1)	Partial clinical hold placed by FDA on Phase II FREEDOM2-DM1 MAD trial
feb 2026	Vertex (VX-670)	Dosing continues in GALILEO Phase I/II trial
Jan 2026	Juvena (JUV-161)	$33.5M funding to advance JUV-161
dec 2025	Arrakis	Preclinical proof-of-concept of oral rSM targeting CUG repeats, restoring MBNL1 and reversing myotonia in DM1 models
nov 2025	Dyne (DYNE-101)	ACHIEVE trial enrollment expected to complete in early Q2 2026
nov 2025	Design (DT-818)	Nominated for clinical development; Phase I trial planned for 2026 in Australia
sep 2025	Pepgen	~54% splicing correction reported in Phase I trial
july 2025	Sarepta & Arrowhead	Sarepta paid Arrowhead a $100M milestone payment for SRP-1003 (formerly ARO-DM1).
oct 2025	Novartis & Avidity (AOC-1001)	Novartis acquires Avidity for $12B
nov 2024	Sarepta & Arrowhead	Sarepta obtains global rights to Arrowhead's RNAi therapy ARO-DM1 (SRP-1003) in a deal up to $10B.

Table 1. Drugs currently in Clinical Trials for DM1

Agent	Type	Biological target	Phase	Status	Sponsor
Metformin	SM (repurposed)	AMPK activation	III	Recruiting	AP-HP
Mexiletine	SM (repurposed)	Nav1.4	III	Recruiting	Lupin
			III	Recruiting	Lupin
AOC 1001 (del-desiran)	NAT (siRNA-Ab)	DMPK toxic CUG-expanded mRNA	III	Active	Avidity
Tideglusib	SM (repurposed)	GSK3β	II/III	Recruiting	AMO Pharma
Erythromycin (MYD-0124)	SM (repurposed)	DMPK toxic CUG-expanded mRNA	II	Completed	Nakamori Masayuki-Osaka University Hospital
PGN-EDODM1	NAT (PMO)	DMPK toxic CUG-expanded mRNA	II	Recruiting	PepGen
VX-670	NAT (PMO)	DMPK toxic CUG-expanded mRNA	I/II	Recruiting	Vertex
Pitolisant	SM (repurposed)	H3R antagonist	II	Completed (2024)	Harmony
DYNE-101 (z-basivarsen)	NAT (gapmer-Fab conjugate)	DMPK toxic CUG-expanded mRNA	I/II	Recruiting	Dyne
ARO-DM1 (SRP-1003)	NAT (siRNA)	DMPK toxic CUG-expanded mRNA	I/II	Recruiting	Arrowhead / Sarepta
SAR446268	NAT(AAV-RNAi)	DMPK toxic CUG-expanded mRNA	I/II	Recruiting	Sanofi
ATX-01	NAT (anti-miRNA)	miR-23b	I/II	Recruiting	ARTHEx
DT-818	NCE	DMPK toxic CUG-expanded mRNA	I	Recruiting	Design
Amlodipine	SM (repurposed)	Cav1.1	I	Not yet recruiting	University of Rochester
JUV-161	Recombinant fusion protein	MAPK/ERK and PI3K/AKT signalling pathways	I	Recruiting	Juvena Therapeutics
Lamotrigine*	SM (repurposed)	Nav1.4	*Open-label pilot study in DM1 adults		-

Abbreviations: AAV: adeno-associated virus; Ab: antibody; AP-HP: Assistance Publique–Hôpitaux de Paris; Fab: fragment antigen-binding; mRNA: messenger RNA; NAT: nucleic acid therapeutic; NCE: new chemical entity; PMO: phosphorodiamidate morpholino oligonucleotide; RNAi: RNA interference; siRNA: small interfering RNA; SM: Small Molecule; TfR1: transferrin

Figure 1. Therapeutic landscape and clinical/preclinical development pipelines for DM1



CONCLUSIONS & FUTURE PERSPECTIVES

DM1 therapies are advancing rapidly, but heterogeneity, lack of blood biomarkers, and CNS delivery remain key hurdles. Success requires moving beyond muscle-centric endpoints toward personalized, multisystem approaches that address aging-related decline, neuropsychiatric features, and quality of life.

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