Expert Consensus on Treatment Guidance for FDA-Approved and Second-Generation Exon-Skipping Therapies in Duchenne Muscular Dystrophy (DMD): a RAND/UCLA Modified Delphi Panel

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Background

- Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder caused by mutations in the DMD gene, leading to progressive muscle degeneration.[1-3]
- Current standard of care includes long-term glucocorticoid therapy and multidisciplinary supportive management.[4-6] Additionally, disease-modifying therapies, including gene therapy and exon-skipping therapies, aim to address the underlying dystrophin deficiency.[6-9]
- Newer investigational exon-skipping therapies are in development; however, their impact on long-term clinical outcomes remains uncertain. Consequently, there is a lack of clear, evidence-based guidance on treatment selection, sequencing, and long-term management.
- **We aimed to develop consensus on optimal treatment strategies for DMD, as well as the anticipated clinical value of emerging investigational exon-skipping therapies.**

Methods

- A double-blinded RAND/UCLA modified Delphi method with nine US panelists (seven pediatric neurologists and two physical therapists). The double-blinded design ensured the sponsor did not influence panelist selection and maintained the panelists' independent judgment.
- The panel reviewed and rated 88 hypothetical patient scenarios across disease stages (early/late ambulatory, early/late non-ambulatory).
- Scenarios varied by several clinical characteristics (**Table 1**).
- Panelists rated the likelihood of recommending FDA-approved therapies and the anticipated clinical value of investigational exon-skippers with Phase 1/2 data on a 1-9 scale before and after a virtual meeting.
- Disagreement was defined as ≥2 panelists rating a scenario on the extremes of the scale (1-3 and 7-9).

Table 1. Clinical characteristics

Core elements included in patient scenarios	Categories	Definitions
Likelihood of recommending	1-9 scale	The probability of advising the use of an FDA-approved therapy, either as monotherapy or in combination with other medications, for an eligible patient with DMD. This rating excludes consideration of investigational treatments or participation in clinical trials; only currently FDA-approved therapies should be considered.
Anticipated clinical value	1-9 scale	The degree of improvement in patient outcomes that an investigational exon-skipping therapy prescribed as monotherapy or in combination with other medications, is expected to provide, based on its mechanism of action, early clinical trial data, and expert judgment. This includes projected effects on disease progression, quality of life, functional outcomes, and other clinically meaningful endpoints.
Disease stage	Early ambulatory	Delayed motor milestones; Gowers' sign; difficulty running, jumping, or climbing stairs.
	Late ambulatory	Progressive loss of walking ability; frequent falls; long-distance walking fatigue; calf muscle hypertrophy.
	Early non-ambulatory	Loss of independent ambulation; begin using a wheelchair; retain good upper limb function.
	Late non-ambulatory	Loss of arm function; development of scoliosis; respiratory muscle weakness; onset of cardiac complications; often needs bilevel positive airway pressure/continuous positive airway pressure (BiPAP/CPAP).

Results

- Panelists favor standard FDA-approved therapies and combinations for early-stage patients. Disagreement persists regarding where exon-skippers fit in the treatment pathway following gene therapy, highlighting the need for further clinical evidence on additive efficacy.
- Panelists assigned higher anticipated clinical value to investigational exon-skippers and their potential use in combination with other therapies, based on early data demonstrating potential improved cardiac delivery and substantially higher dystrophin production.
- Delpacibart zotadirsen received the highest ratings for ambulatory and early non-ambulatory patients among investigational therapies, based on preliminary data. NS-089/NCNP-02 also received high ratings for early ambulatory patients.
- Disagreement decreased from 36% pre-meeting to 16% post-meeting.

Table 2. Likelihood of use of potential DMD treatments, by stage of progression

	Early ambulatory	Late ambulatory	Early non-ambulatory	Late non-ambulatory
Monotherapy				
Casimersen	High	High	High	Moderate
Eteplirsen	High	High	High	Moderate
Golodirsen[a]	Moderate	Moderate	Moderate	Moderate
Viltolarsen	High	High	High	Moderate
Givinostat	High	High	High	Moderate
Delandistrogene Moxeparvovec	High	High	n/a[d]	n/a[d]
Combination therapy				
Exon skippers, followed by gene therapy	High	Moderate	n/a[d]	n/a[d]
Exon skippers, followed by givinostat	High	High	Moderate	Moderate
Gene therapy, followed by exon skippers	Moderate	Moderate	n/a[d]	n/a[d]
Gene therapy, followed by givinostat[b]	High	High	n/a[d]	n/a[d]
Givinostat, followed by exon skippers[c]	High	High	High	Moderate
Givinostat, followed by gene therapy	High	High	n/a[d]	n/a[d]

Green = High likelihood of use Yellow = Moderate likelihood of use

[a]There was disagreement regarding the use of golodirsen in patients with DMD.
[b]There was disagreement regarding the use of gene therapy followed by givinostat in ambulatory patients with DMD. For the gene therapy and givinostat combination, it is assumed that givinostat will be temporarily held prior to gene therapy administration and then resumed in the months following gene therapy.
[c]There was disagreement regarding the use of givinostat followed by exon skippers for patients with late non-ambulatory DMD.
[d]At the time of the meeting, delandistrogene moxeparvovec was approved for use exclusively in ambulatory patients at least 4 years of age. Given the evolving regulatory landscape, this poster is limited to delandistrogene moxeparvovec's use in ambulatory patients.

Key Expert Consensus Takeaways

- Panelists viewed current FDA-approved DMD treatments as offering incremental benefit; first-generation exon-skipping therapies were considered safe but with limited benefit and high treatment burden due to weekly IV administration.
- The panel expressed optimism for significant clinical benefit from emerging next-generation exon-skipping therapies, citing early signals of greater dystrophin production and anecdotal cases of regained function.
- While early data suggest improved potency and tissue uptake in next-generation exon-skipping therapies, the functional impact and long-term durability of functional benefit remain to be established with more data and longer follow-up.
- Panelists agreed that further research should include integrating real-world evidence to refine treatment sequencing.

Table 3. Anticipated clinical value of investigational exon skippers by DMD stage

	Early ambulatory	Late ambulatory	Early non-ambulatory	Late non-ambulatory
Monotherapy				
Delpacibart zotadirsen	High	High	High	Moderate
Dyne-251	Moderate	Moderate	Moderate	Moderate
NS-089/NCNP-02	High	Moderate	Moderate	Moderate
WVE-N531	Moderate	Moderate	Moderate	Moderate
Combination therapy				
Investigational exon skippers, followed by first-generation gene therapy	High	High	n/a[d]	n/a[d]
Investigational exon skippers, followed by givinostat	High	High	High	Moderate
First-generation gene therapy, followed by investigational exon skippers	High	Moderate	n/a[d]	n/a[d]
Givinostat, followed by investigational exon skippers	High	High	High	Moderate

Green = High anticipated clinical value Yellow = Moderate anticipated clinical value

References

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