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A phase 1/2 clinical trial of the antisense oligonucleotide BMN 351 now actively recruiting boys with exon 51–skip-amenable Duchenne muscular dystrophy

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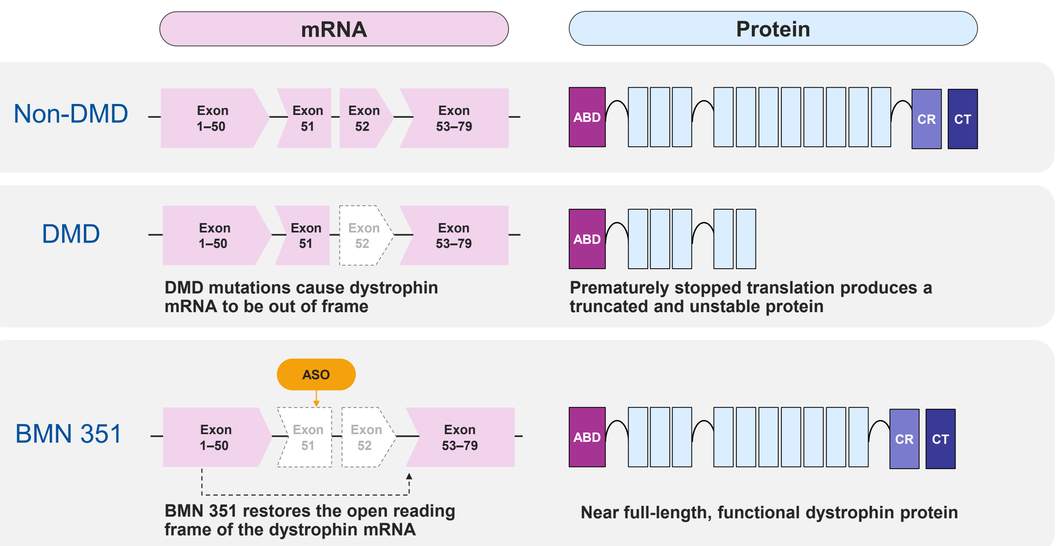
Key points

- **BMN 351 is an antisense oligonucleotide (ASO) designed to enable production of near full-length functional dystrophin in people with exon 51 skip-amenable Duchenne muscular dystrophy (DMD)**
- **BMN 351-201 is a phase 1/2 clinical trial that is actively recruiting boys with exon 51 skip-amenable DMD in Spain, the United Kingdom, the Netherlands, Italy, and Türkiye**

Introduction

- DMD is a progressive and ultimately fatal muscle-wasting disease caused by a deficiency in dystrophin, an essential protein in muscle fibers that enables motor function[1]
- Lack of functional dystrophin causes progressive skeletal muscle weakness and ultimately respiratory and cardiac failure[1]
- In some cases of DMD, frame-shift mutations introduce premature stop codons that cause the dystrophin protein to be truncated and unstable[1]
- ASOs can be used to skip over specific exons and restore the correct reading frame[2]

BMN 351 is an ASO that targets a novel, highly active splicing enhancer site to skip exon 51 and flanking introns and restore the dystrophin open reading frame in exon 51 skip–amenable DMD



ABD, actin binding domain; ASO, antisense oligonucleotide; CR, cysteine-rich domain; CT, C-terminal domain; DMD, Duchenne muscular dystrophy; mRNA, messenger RNA.

The dystrophin protein produced with BMN 351 is expected to be near full-length and to retain most of its functionality, similar to naturally occurring forms of dystrophin produced in less severe forms of muscular dystrophy

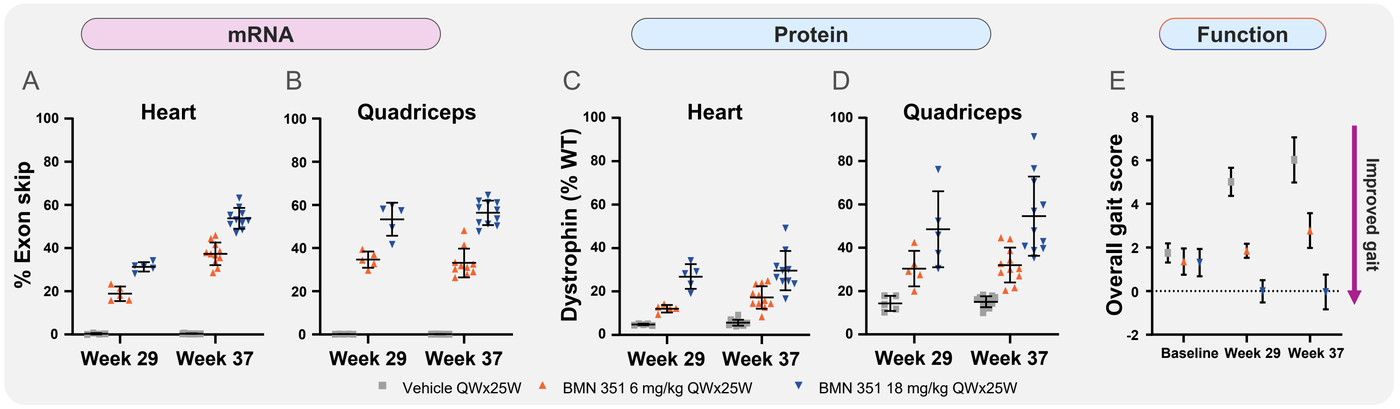
Preclinical efficacy studies

The ability of BMN 351 to skip exon 51, produce dystrophin, and prevent declines in motor function were assessed in preclinical mouse studies

hDMDdel52/*mdx* mice lack mouse dystrophin and harbor a human exon 52–deleted *DMD* transgene[3]

hDMDdel52/*mdx* mice were dosed once per week for 25 weeks with vehicle, 6 mg/kg BMN 351, or 18 mg/kg BMN 351; exon skipping, dystrophin expression, and fine motor kinematics were assessed 4 and 12 weeks after end of dosing (**Figure 1**)

Figure 1. A–B) Exon skipping, C–D) dystrophin expression, and E) fine motor kinematics over 37 weeks in hDMDdel52/*mdx* mice



mRNA, messenger RNA; QWx25W, once weekly for 25 weeks.

In the heart and quadriceps of hDMDdel52/*mdx* mice, BMN 351 induced exon skipping and dystrophin production that was associated with preservation of fine motor kinematics 4 and 12 weeks post-dosing

Toxicology

- In 13-week toxicology studies of BMN 351 in male CD1 mice and nonhuman primates (NHPs), 3 different intravenous (IV) doses of BMN 351 were generally well-tolerated. In both species, observations were broadly consistent with well-known class effects of ASO therapeutics
- BMN 351 was well-tolerated up to the highest dose in a separate study in which male mice were dosed IV with multiple dose levels for at least 26 weeks
- In a 39-week study of BMN 351 in NHPs, results were consistent with well-known ASO class effects, including complement-mediated glomerulopathy and vasculitis, thrombocytopenia, and renal and liver pathologic changes

BMN 351-201

A phase 1/2, open-label, dose escalation study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple intravenous doses of BMN 351 in people with Duchenne muscular dystrophy

Study population: Individuals with DMD who are amenable to exon 51 skipping

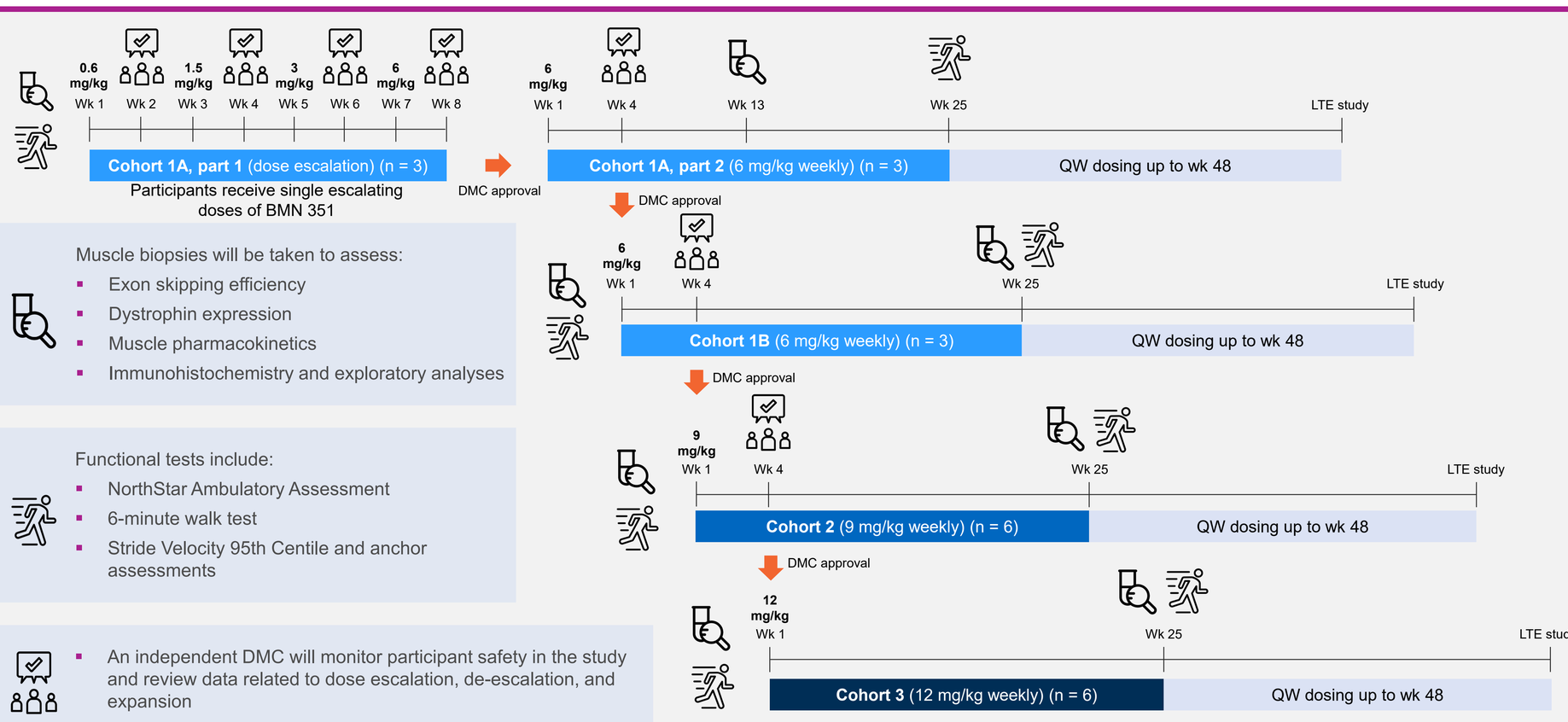
Number of participants: Up to 18

Study duration: From approximately 8 months (for the last participant enrolled) to at least 15 months

Primary objective:
To assess the safety and tolerability of BMN 351 at different dose levels in people with DMD

Secondary objective:
To evaluate the plasma and urine pharmacokinetics and muscle distribution of BMN 351

Other objectives:
Exon skipping and dystrophin expression; functional assessments



Muscle biopsies will be taken to assess:
- Exon skipping efficiency
- Dystrophin expression
- Muscle pharmacokinetics
- Immunohistochemistry and exploratory analyses

Functional tests include:
- NorthStar Ambulatory Assessment
- 6-minute walk test
- Stride Velocity 95th Centile and anchor assessments

- An independent DMC will monitor participant safety in the study and review data related to dose escalation, de-escalation, and expansion

DMC, data monitoring committee; LTE, long-term extension; QW, weekly; Wk, week.

Key eligibility criteria

- Boys age 4–10 years and ambulatory
- Clinical diagnosis of DMD resulting from a documented dystrophin mutation in the DMD gene amenable to exon 51 skipping
- On a stable dose of oral corticosteroids for at least 12 weeks prior to baseline; must remain on a consistent dose/dose regimen throughout the study (except for modifications to accommodate changes in weight)
- No current or history of liver or renal disease
- Prior treatment with an approved exon-skipping therapy is allowed, but a 12-week washout period will be required
- No prior treatment with any gene therapy for the treatment of DMD
- No known hypersensitivity to any oligonucleotide
- Previous investigational treatment must be discontinued 3 months prior to first dose

Key study features

- BMN 351 given via IV infusion every week, with the potential for at-home dosing being considered in a future protocol amendment
- Safety assessments include physical examination, vital signs, electrocardiogram, echocardiogram, and clinical laboratory tests
- Ongoing review of safety data by an Independent Data Monitoring Committee
- Two muscle biopsies are required per participant
- Opportunity for long-term extension study for continued dosing
- Participant burden minimized through home health assessments
- Education and support provided to participants and families

BMN 351-201 is currently recruiting in Spain, the United Kingdom, the Netherlands, Italy, and Türkiye

References

1. Duan D, et al. *Nat Rev Dis Primers.* 2021;7(1):13. **2.** Takeda S, et al. *J Neuromusc Dis.* 2021;8:S343-58. **3.** Veltrop M, et al. *PLoS ONE.* 2018;13(2):e0193289.

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Disclosures

All authors are current or former employees or shareholders of BioMarin Pharmaceutical Inc.

ClinicalTrials.gov

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