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LBP17

Long-term survival and cardiac efficacy of delandistrogene moxeparvovec gene therapy in the Duchenne muscular dystrophy rat model

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Objective

To evaluate the long-term survival and cardiac efficacy of delandistrogene moxeparvovec in a DMD^{MDX} rat model.

What does this study mean for the DMD community?

The totality of data from this study supports delandistrogene moxeparvovec treatment for DMD, indicating a previously undescribed role for this therapy in improving cardiac function through a rat model that closely mimics cardiac dysfunction as observed in patients with DMD.

CONCLUSIONS

- Consistent with 12- and 24-week efficacy findings, at 52 weeks, delandistrogene moxeparvovec demonstrated long-term cardiac efficacy and improved survival in the DMD^{MDX} rat model, with no evidence of cardiac toxicity or treatment-related deaths.
- Delandistrogene moxeparvovec-treated DMD^{MDX} rats exhibited statistically significant improvements across cardiac parameters to wild-type levels, improved histopathology, and reduced fibrosis compared with saline controls.
- Delandistrogene moxeparvovec micro-dystrophin expression was broadly distributed across skeletal and cardiac muscle at 52 weeks.
- Protein expression of delandistrogene moxeparvovec has been observed in cardiac tissue in NHP. Further evidence using a surrogate cassette (AAVrh74.MHCK7.eGFP) in human cardiomyocytes demonstrated robust transduction and expression. These findings suggest that micro-dystrophin expression driven by the MHCK7 promoter is likely translatable to micro-dystrophin expression in human heart cells.

BACKGROUND

- DMD is an X-linked neuromuscular disease caused by mutations in the *DMD* gene that prevent the production of functional dystrophin protein.[1,2]
- The absence of functional dystrophin protein can lead to myofiber cellular damage, degeneration, and necrosis, resulting in progressive muscle weakness and wasting and cardiomyopathy.[3,4]
- Delandistrogene moxeparvovec is an rAAV-based gene therapy, designed to compensate for missing dystrophin in DMD by delivering a transgene encoding delandistrogene moxeparvovec micro-dystrophin, an engineered dystrophin that retains key functional domains of the wild-type protein.[5–7]
- Systemic delivery of delandistrogene moxeparvovec*† in the DMD^{MDX} mouse model led to improvements in dystrophic histopathology and function of skeletal muscle, with no toxicity observed.[8] However, DMD^{MDX} mice do not develop early dilated cardiomyopathy, as seen in patients with DMD.[9]
- To evaluate long-term survival and cardiac efficacy of delandistrogene moxeparvovec, DMD^{MDX} rats present an alternative animal model of DMD, as they closely recapitulate the cardiac dysfunction observed in patients with DMD.

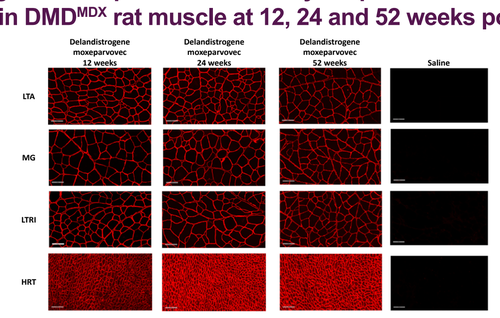
*As of August 2023, delandistrogene moxeparvovec is approved in the USA and UAE for the treatment of ambulatory pediatric patients aged 4 through 5 years with DMD with a confirmed mutation in the *DMD* gene.[10,11] †Delandistrogene moxeparvovec is contraindicated in patients with any deletion in exon 8 and/or exon 9 in the *DMD* gene.

METHODS

- We performed intravenous delivery of delandistrogene moxeparvovec in 21- to 42-day old Sprague-Dawley (DMD^{MDX}) mutated and WT rats.[12,13]
- Rats were randomized by body weight and age and received a dose of either 1.33×10^{14} vg/kg delandistrogene moxeparvovec or 0.9% sterile saline. Test operators were blinded to functional outcomes.
- Analyses of micro-dystrophin expression, vector biodistribution, and functional activity were conducted.
- Ambulation and horizontal activity were recorded via the Photobeam Activity System – Open Field.[14]
- Echocardiograms, serum troponin I levels, and histologic analyses of fibrosis were used to evaluate cardiac disease, cardiomyocyte contractility, and calcium handling.

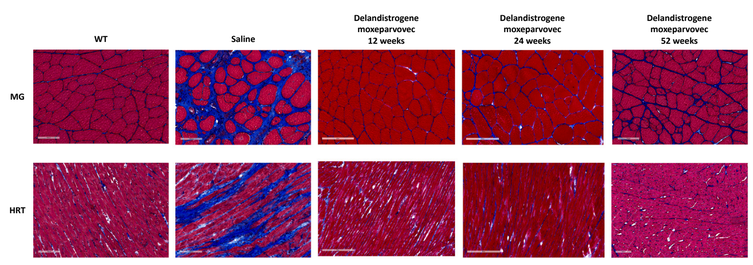
RESULTS

Delandistrogene moxeparvovec micro-dystrophin sarcolemma localization in DMD^{MDX} rat muscle at 12, 24 and 52 weeks post-dosing



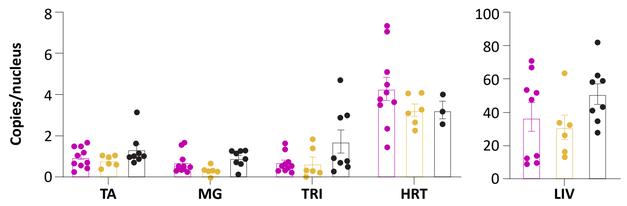
Scale bar, 100 microns. Red signal indicates micro-dystrophin.

Delandistrogene moxeparvovec-treated DMD^{MDX} rats had reduced fibrosis in skeletal and cardiac muscles versus saline control



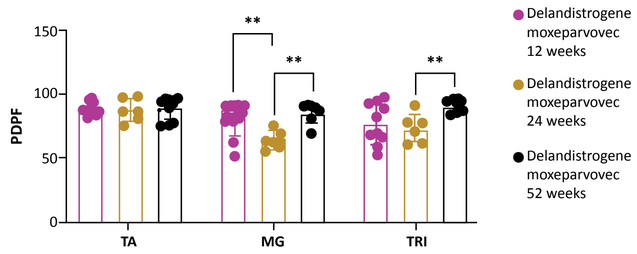
Scale bar, 100 microns. Blue staining indicates fibrosis.

The delandistrogene moxeparvovec transgene was broadly distributed across skeletal and cardiac muscle in DMD^{MDX} rats (ddPCR)



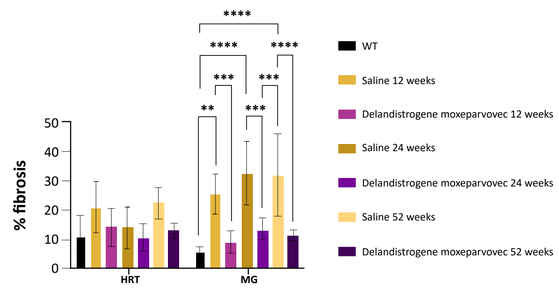
Data are represented as the mean ±SD.

Quantification of delandistrogene moxeparvovec micro-dystrophin-positive fibers



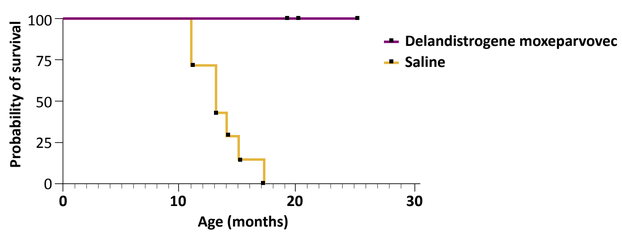
Data are represented as the mean ±SD. **P<0.01.

Quantification of fibrosis in skeletal and cardiac muscles

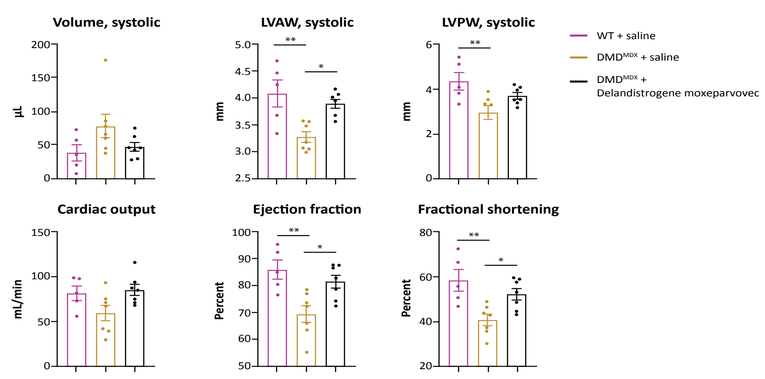


Data are represented as the mean ±SD. **P<0.01; ***P<0.001; ****P<0.0001.

Delandistrogene moxeparvovec-treated rats still live; saline-treated rats died by 17 months

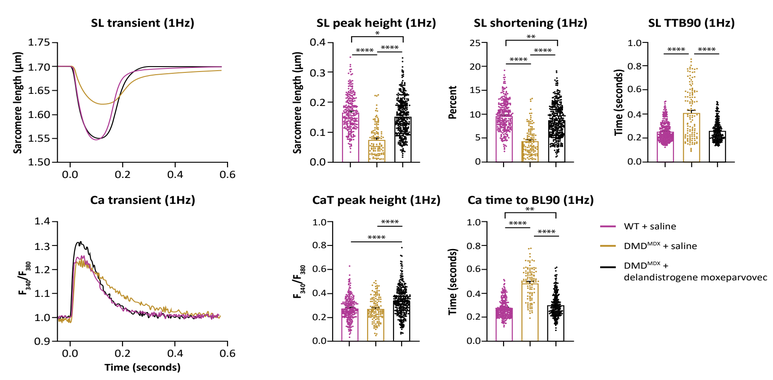


Delandistrogene moxeparvovec improved cardiac performance in DMD^{MDX} rats at 52 weeks versus saline control



Data are represented as the mean ±SD. *P<0.05; **P<0.01.

Delandistrogene moxeparvovec restored cardiomyocyte contractility and Ca^{2+} kinetics in DMD^{MDX} rats at 52 weeks



Data are represented as the mean ±SD. *P<0.05; **P<0.01; ****P<0.0001.

REFERENCES

1. Bushby K, et al. *Lancet Neurol.* 2010; 9:77–93;
2. Mendell JR, et al. *Ann Neurol.* 2013; 74:637–647;
3. Le Guiner C, et al. *Mol Ther Methods Clin Dev.* 2023; 30:30-47;
4. McNally EM. *JAMA Cardiol.* 2017; 2:199;
5. Asher DR, et al. *Expert Opin Biol Ther.* 2020; 20:263–274;
6. Zheng C and Baum BJ. *Methods Mol Biol.* 2008; 434:205–219;
7. Mendell JR, et al. *JAMA Neurol.* 2020; 77:1122–1131;
8. Potter RA, et al. *Hum Gene Ther.* 2021; 32:375–389;
9. Wasala NB, et al. *Hum Mol Genet.* 2013; 22:2634–2641;
10. US Food and Drug Administration. ELEVIDYS™ Highlights of prescribing information. https://www.fda.gov/media/169679/download. Published 2023 (Accessed September 2023);
11. UAE Ministry of Health & Prevention. https://mohap.gov.ae/en/services/registered-medicalproduct-directory (Accessed September 2023).
12. Kobayashi YM, et al. *Nature.* 2008; 456:511–515;
13. Beastrom N, et al. *Am J Pathol.* 2011; 179:2464–2474;
14. Photobeam Activity System – Open Field. San Diego Instruments; San Diego, CA, USA.

ABBREVIATIONS

AAVrh74, adeno-associated virus rhesus isolate serotype 7; BL90, baseline 90%; BW, body weight; CaT, Ca^{2+} transients; ddPCR, droplet digital polymerase chain reaction; DMD, Duchenne muscular dystrophy; F_{340}/F_{380}, peak heights of the Ca^{2+}; HRT, heart; LIV, liver; LVAW, left ventricular anterior wall; LVPW, left ventricular posterior wall; MDX, muscular dystrophy X linked; MG, medial gastrocnemius; NHP, non-human primates; PDPF, percentage dystrophin-positive fibers; rAAV, recombinant AAV; SD, standard deviation; SL, sarcomere length; TA, tibialis anterior; TRI, triceps; TTB90, time to baseline 90%; UAE, United Arab Emirates; vg, vector genome; WT, wild type.

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