

mutations (~25%) in the 2.24 Mb dystrophin gene, resulting in the absence of functional dystrophin. BMD is also caused by mutations in the dystrophin gene, but these maintain the open reading frame, yield semi-functional dystrophin proteins, and result in a typically much milder phenotype and longer lifespan.

[0006] To date, four AONs have been approved for treatment of DMD: eteplirsen, golodirsen, casimersen and viltolarsen. However, these drugs possess limited efficacy and are each approved for treating only a small percentage of DMD patients.

[0007] Thus, there is a continuing need for methods of treating DMD.

SUMMARY

[0008] Provided herein are methods of treating or delaying the onset of DMD by administering a modified oligonucleotide to a subject having DMD. In one example, the modified oligonucleotide is an antisense oligonucleotide (AON). In one aspect, the disclosure refers to the use of AON1 in the manufacture of a medicament for the treatment of DMD or delaying the onset of DMD in a subject, wherein AON1 is to be administered to the subject at a dose of 0.4 mg/kg, 0.6 mg/kg, 0.8 mg/kg, 1.5 mg/kg, 3 mg/kg, 6 mg/kg, 9 mg/kg, 12 mg/kg or 18 mg/kg, wherein the AON1 is to be administered QW.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] **FIG. 1** shows the plasma concentration of AON1 over time.

[0010] **FIG. 2** shows the AON1 concentration in heart, quadriceps, liver, diaphragm, gastrocnemius and kidney tissue.

[0011] **FIG. 3** shows that AON1 achieved sustained dose dependent exon 51 skipping in muscle tissue (quadriceps, gastrocnemius, heart and diaphragm) with 25 weeks of treatment.

[0012] **FIG. 4** shows dystrophin wt% in heart and quadriceps and shows Overall Gait Score for mice treated with AON1.

[0013] **FIG. 5** shows that AON1 treatment attenuates hDMD del52(+/+) model-associated muscle pathology and sustains pharmacological effect for 12 weeks post-25 week dosing.

[0014] **FIG. 6** shows that AON1 treatment attenuates hDMD del52(+/+) model-associated cardiac pathology and sustains pharmacological effect for 12 weeks.

[0015] **FIG. 7** shows dystrophin expression in heart and quadriceps of hDMDΔ52/mdx mice treated with the AON1 having the TEG linked to the oligonucleotide by a thiophosphate group (AON1 PS, 9.4, 18.7 or 37.5 mg/kg) at 14 (solid circles) or 28 days (open circles) post-dosing QW, Q2W or Q4W.

[0016] **FIG. 8** shows % exon 51 skipping in heart of hDMDΔ52/mdx mice treated with AON1 PS (9.4, 18.7 or 37.5 mg/kg) at 14 (solid circles) or 28 days (open circles) post-dosing QW, Q2W or Q4W.