ASX Announcement

1 February 2023

Positive outcomes in DMD combination therapy animal study

- Statistically significant effects on muscle function endpoints with ASO to CD49d in combination with dystrophin restoration drug
- Results support the potential for ATL1102 use in combination with dystrophin restoration drugs to show benefit over the use of a dystrophin restoration agent alone
- Patent application has been filed to protect the use of the combination treatment
- Further investigation is ongoing with the assessment of muscle dystrophin levels and other cellular markers with results anticipated Q1'CY23

Antisense Therapeutics Limited [ASX:ANP | US OTC:ATHJY | FSE:AWY], is pleased to report initial positive muscle functional data from a DMD *mdx* animal study assessing the use of the combination of antisense (ASO) to CD49d with a dystrophin exon skipping restoration drug. The use of the combination improved the specific maximum force of the extensor digitorum longus (EDL) muscle, a lower leg muscle, and the eccentric muscle force remaining following induced damage to the EDL. This functional data supports the potential use of ATL1102 in combination with dystrophin restoration drugs to improve therapeutic outcomes in patients with DMD.

Under the collaborative research agreement with the Murdoch Children's Research Institute's (MCRI), six groups of DMD mdx mice (n=8 per group) were treated for 6 weeks with antisense oligonucleotide to CD49d (mouse equivalent of ATL1102), or control oligonucleotide mismatch or saline treatments, or the morpholino exon skipping dystrophin restoration drug alone and in combination. The muscle physiology of the EDL was assessed for force parameters including specific maximum force and the force drop following 1 to 10 eccentric (lengthening) contraction each involving induced muscle damage by the stretching of the muscle by 10%. The EDL is 1 of 4 muscles in the front of the lower leg whose function is to invert the foot at the ankle. Another of these muscles is the tibialis anterior (TA) on which the ASO to CD49d has previously reported a benefit in reducing eccentric muscle damage in *mdx* mice[1].

The ASO to CD49d and morpholino exon skipping combination improved the specific maximum force (the maximum force corrected for size/mass and cross-sectional area of the EDL muscle) and both the eccentric muscle force remaining after a single and 10 repeated lengthening contractions with statistically significant effects compared to saline control (see Figures 1 to 3). This combination after the 10 repeated lengthening contractions, also **showed a significant effect (P<0.001) compared to the exon skipping drug used alone** and the exon skipping drug used together with the control oligo (Figure 3a and 3b). In addition, the ASO to CD49d showed a significant effect vs the saline and its control oligo. The morpholino exon skipping drug showed a significant effect compared to the saline control (Figure 3a and 3b).

Dr Peter Houweling, Team Leader of the MCRI Muscle Research group said "These early pre-clinical findings suggest that a combination therapy using an established dystrophin restorative ASO and CD49d result in improved functional outputs in the *mdx* mouse model of Duchenne muscular dystrophy. These effects appear to be beneficial beyond the individual monotherapy and we look forward to continuing our investigations into the biological mechanisms that may be at play".

Dr George Tachas, Director of Drug Discovery and Patents at Antisense Therapeutics said "The encouraging effects observed in our study of the combination treatment on the EDL muscle function suggest the potential for the combination treatment to show benefit beyond monotherapy is on the right track. The study design and functional endpoints assessed have featured in many *mdx* mouse

studies published in the scientific literature, and as such supports the validity of our study and its outcomes".

A provisional patent application titled "Combination Compositions and Methods for Treatment of Muscular Dystrophy" is to be filed today to cover the use of the ASO to CD49d and the morpholino exon skipping drug combination to seek protection of the combination of ATL1102 with the dystrophin restoration/ exon skipping drugs to 2044, well beyond the patent life of the registered dystrophin restoration drugs. Notably the dystrophin restoration drugs have yet to demonstrate in controlled clinical studies a slowing of the loss of ambulation beyond use of corticosteroids, highlighting the clinical need for a more efficacious therapeutic approach.

Further investigations are ongoing in the *mdx* mouse combination study to determine the possible mechanisms by which the combination approach is providing the observed functional benefits. Muscle RNA and protein samples have been isolated from the *mdx* mice quadricep muscle for analysis of the dystrophin levels in the muscle to determine if higher levels are seen with the use of the combination than with the dystrophin restoration agent alone. Cellular markers of inflammation and fibrosis including those observed in the ATL1102 DMD Phase II study, will also be assessed to elucidate the potential mechanisms that may be involved. Results from this analysis are anticipated before the end of the Q1'CY23.

This announcement has been authorised for release by the Board.

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[1]https://www.medrxiv.org/content/10.1101/2022.01.16.22269029v1.full.pdf

About Antisense Therapeutics Limited [ASX:ANP | US OTC:ATHJY | FSE:AWY], is an Australian publicly listed biotechnology company, developing and commercializing antisense pharmaceuticals for large unmet markets in rare diseases. The products are in-licensed from Ionis Pharmaceuticals Inc. (NASDAQ: IONS), an established leader in antisense drug development. The Company is developing ATL1102, an antisense inhibitor of the CD49d receptor, for Duchenne muscular dystrophy (DMD) patients and reported highly promising Phase II trial results. ATL1102 has also successfully completed a Phase II efficacy and safety trial, significantly reducing the number of brain lesions in patients with relapsing-remitting multiple sclerosis (RRMS). The Company has a second drug, ATL1103 designed to block GHr production that successfully reduced blood IGF-I levels in Phase II clinical trials in patients with the growth disorder acromegaly.

About ATL1102 ATL1102 is an antisense inhibitor of CD49d, a subunit of VLA-4 (Very Late Antigen-4). Antisense inhibition of VLA-4 expression has demonstrated activity in a number of animal models of inflammatory disease including the *mdx* mouse model of DMD. ATL1102 has also shown to be very effective in reducing inflammatory brain lesions in patients with MS (Limmroth, V. et al Neurology, 2014; 83(20): 1780-1788) and delivered highly promising clinical results in patients with Duchenne muscular dystrophy (DMD) a rare and fatal muscle wasting disease where inflammation in the muscle leads to fibrosis and death of muscle tissue.

About MCRI. The Murdoch Children's Research Institute (MCRI) is the largest child health research institute in Australia committed to making discoveries and developing treatments to improve child and adolescent health in Australia and around the world. They are pioneering new treatments, trialing better vaccines and improving ways of diagnosing and helping sick babies, children and adolescents. It is one of the only research institutes in Australia to offer genetic testing to find answers for families of children with previously undiagnosed conditions.

Figure 1

Specific Maximum Force EDL

(maximum force corrected for muscle size/mass and cross sectional area)

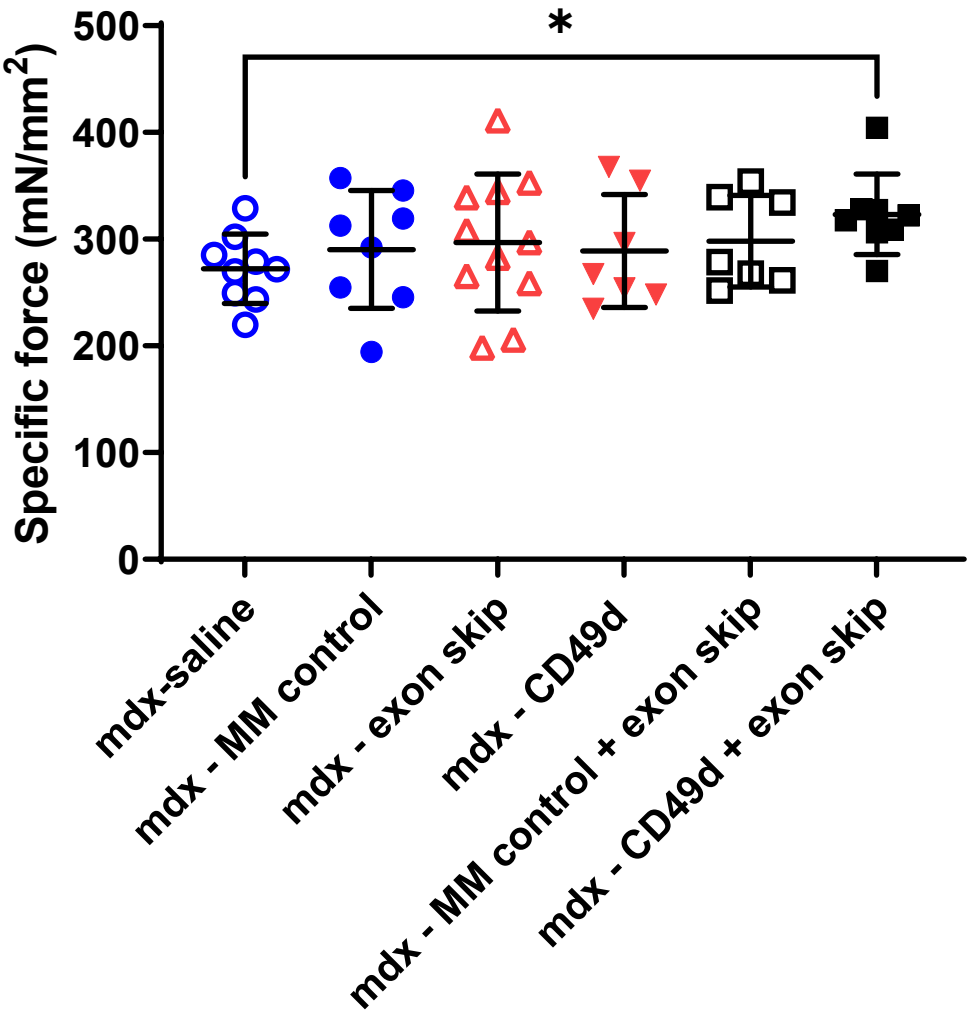


Figure 2

EDL Force Loss after the first Eccentric Contraction

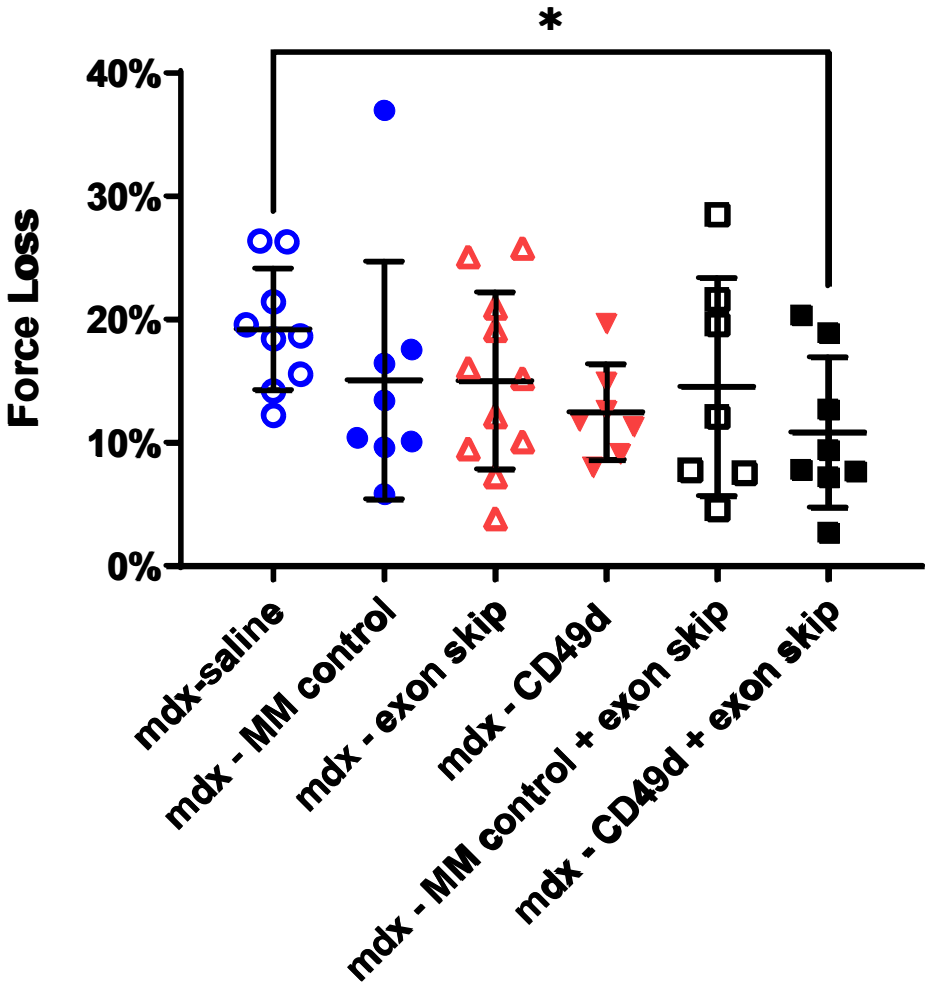


Figure 3

EDL Force Loss after 10 Eccentric Contractions

Figure 3A

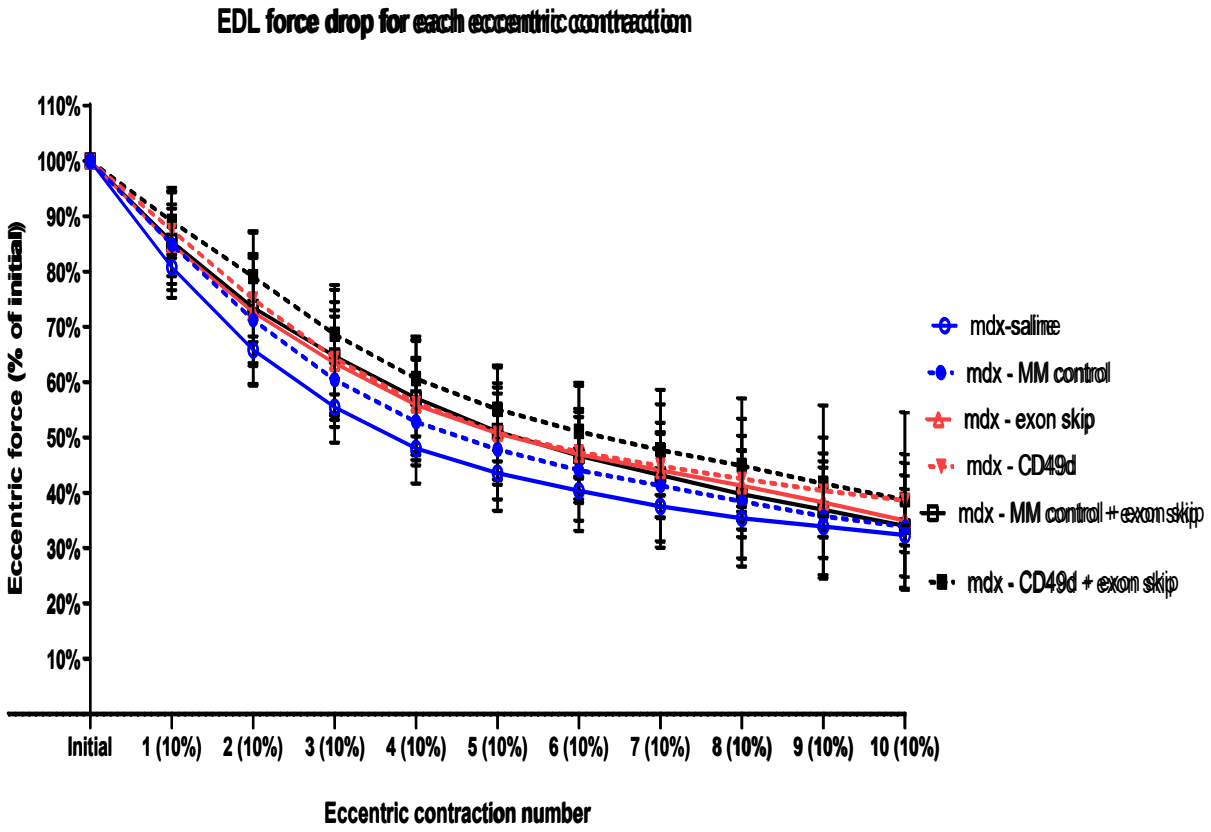
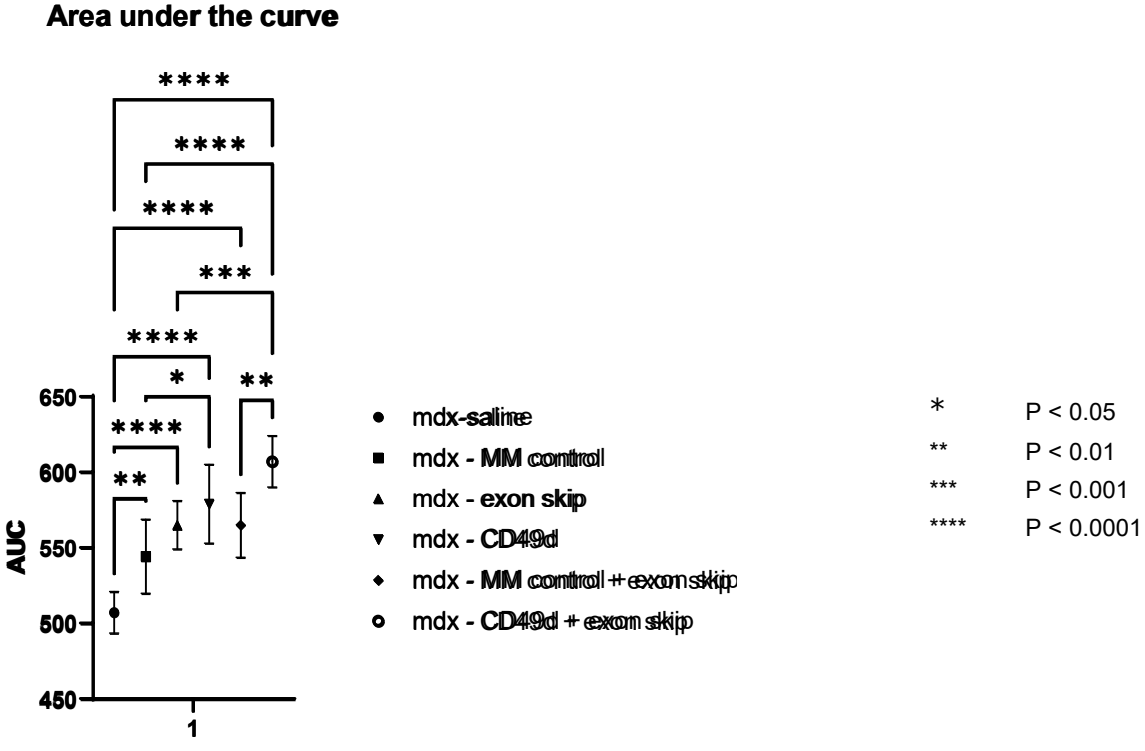


Figure 3B



The statistical analysis was conducted as a one-way analysis of variance (ANOVA)