ASX Announcement

14 March 2022

**Significant modulation of two bone morphogenetic proteins supports potential of ATL1102 for improving bone density in DMD**

- Statistically significant mean increases in plasma BMP-5 and BMP-6 with a role in cartilage and bone formation
- Increases in mean plasma BMP-5 and BMP-6 to external healthy adult control levels are supportive of ATL1102's potential to promote bone regeneration and improve bone density in DMD
- New proteomics data compliments previously presented data on ATL1102's unique and highly relevant mechanism as a potential DMD treatment

Antisense Therapeutics Limited [ASX:ANP | US OTC:ATHJY | FSE:AWY] today announced that new plasma protein data from the Phase II trial of ATL1102 in Duchenne Muscular Dystrophy (DMD) was presented at the Muscular Dystrophy Association (MDA) Clinical & Scientific Conference in the poster presentation titled **"ATL1102 treatment in non-ambulant boys with DMD modulates plasma proteins with roles in TGF-beta mediated fibrosis, and cartilage and bone physiology"** (see below link to the poster presentation).

As previously reported ATL1102 was assessed in an open label Phase II study in adolescent non-ambulant patients with DMD. As part of the Phase II study, a large-scale protein analysis (known as a proteomics analysis) of retained blood plasma samples was undertaken to identify proteins affected to provide further insight into the mode of action and biological activity of ATL1102. Following on from the previously reported positive data from this proteomics analysis (refer ASX announcement 24 September 2021) the further ongoing analysis of the 7,000 plasma proteins assessed in the assay has led to the new plasma protein data reported herein.

Statistically significant mean increases in BMP-5 (46.2%) and BMP-6 (34.4%) were observed at 24 weeks compared to baseline levels (FDR p-value <0.0005). When compared to an external healthy adult proteomics dataset used as a control, the baseline BMP-5 and BMP-6 levels of patients in the Phase II study were below average with the levels of each protein increasing to near the external healthy adult control mean by the end of the 24 week ATL1102 dosing period.

BMP-5 and BMP-6, are both members of the TGF-beta superfamily of proteins and both play a role in cartilage and bone formation. ATL1102's effect in increasing blood levels of BMP-5 and BMP-6 to healthy controls suggests the potential for ATL1102 to improve bone density in DMD. Notably it has been reported that higher serum BMP-6 levels are associated with improved elbow flexion in patients with DMD, which appears to correlate with the positive effects seen on elbow function as assessed in the ATL1102 Phase II trial. BMP-5 and BMP-6 levels are reduced with use of corticosteroid (CS), and the prior administration of CS appears to have reduced baseline levels to below normal in the non-ambulant DMD boys in the Phase II trial. Patients with DMD have an increased risk of bone fractures due to bone fragility through progressive muscle weakness affecting bone strength. Prolonged corticosteroid use also reduces bone density and significantly increases risk of bone fractures (Ward et al 2018).

In addition to previously reported reduction of Thrombospondin-1 (TSP-1) and increases in Latent TGF-beta-binding protein 4 (LTBP4) levels, two proteins that modify the rate of loss of ambulation in

DMD related to blocking TGF-beta mediated fibrosis, and increase CXCL16 which can promote muscle regeneration, this new plasma BMP-5 and BMP-6 data reported today adds further compelling evidence of ATL1102's unique and highly relevant mechanism of action in its application as a potential DMD treatment.

The link to the poster presentation is located here .

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*This announcement has been authorised for release by the Board.*

**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 recently 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 asthma and MS with the MS animal data having been published in a peer reviewed scientific journal. ATL1102 was shown to be highly effective in reducing MS lesions in a Phase IIa clinical trial in patients with RR-MS. The ATL1102 Phase IIa clinical data has been published in the medical Journal ***Neurology*** (Limmroth, V. et al Neurology, 2014; 83(20): 1780-1788). ATL1102 is the only drug targeting CD49d in clinical development for DMD.

**About DMD** Duchenne Muscular Dystrophy (DMD) is an X-linked disease that affects 1 in 3600 to 6000 live male births (Bushby *et al*, 2010). DMD occurs as a result of mutations in the dystrophin gene which causes a substantial reduction in or absence of the dystrophin protein. Children with DMD have dystrophin deficient muscles and are susceptible to contraction induced injury to muscle that triggers the immune system which exacerbates muscle damage as summarized in a publication co-authored by the Director of the FDA CDER (Rosenberg et al, 2015). Ongoing deterioration in muscle strength affects lower limbs leading to impaired mobility, and also affects upper limbs, leading to further loss of function and self-care ability. The need for wheelchair use can occur in early teenage years for patients on corticosteroids with a mean age of 13, with respiratory, cardiac, cognitive dysfunction also emerging. Patients with a greater number of immune T cells expressing high levels of CD49d have more severe and progressive disease and are non-ambulant by the age of 10 despite being on corticosteroid treatment (Pinto Mariz et al, 2015). With no intervention, the mean age of life is approximately 19 years and with current treatment typically limited to only the second or third decade of life. The management of the inflammatory damage to muscle associated with DMD is currently addressed via the use of corticosteroids prednisolone and deflazacort which delay disease progression prolonging ambulation by a median 2 to 3 years (Shieh et al, 2018) and reduce loss of upper limb function as measured by performance of upper limb function (PUL) scores, (Pane et al, 2018), an objective measurement of function. Corticosteroids are, however, acknowledged as providing insufficient efficacy and are associated with significant side effects including bone loss that require monitoring, management, and treatment (Ward et al 2018). As a consequence, there is an acknowledged high need for new therapeutic approaches for the treatment of the immune mediated inflammation associated muscle damage in DMD.

*Rosenberg AS, Puig M, Nagaraju K, et al. Immune-mediated pathology in Duchenne muscular dystrophy. Sci Transl Med 2015, 7: 299rv4.*

*Bushby et al for the DMD Care Consideration Working Group/ Diagnosis and management of Duchenne muscular dystrophy, part 1 Lancet Neurol. 2010 Jan;9(1):77-93 and part 2 Lancet Neurol. 2010 Feb;9(2):177-89 .*

*Pinto-Mariz F, Carvalho LR, Araújo AQC, et al. CD49d is a disease progression biomarker and a potential target for immunotherapy in Duchenne muscular dystrophy. Skeletal Muscle 2015, 5: 45-55.*

*Shieh et al, Deflazacort versus prednisone/prednisolone for maintaining motor function and delaying loss of ambulation: A post HOC analysis from the ACT DMD trial. Muscle Nerve. 2018 Nov; 58(5): 639–645. Muscle & Nerve November 2018 639*

*Pane M, Coratti G, Brogna C, Mazzone ES, Mayhew A, Fanelli L, Mercuri E et al. (2018) Upper limb function in Duchenne muscular dystrophy: 24 month longitudinal data. PLoS ONE 13(6): e0199223. https://doi.org/10.1371/journal. pone.0199223*

*Ward L.M, Hadjiyannakis, S, McMillan, HJ, Noritz, G, and Weber, DR, Bone Health and Osteoporosis Management of the Patient With Duchenne Muscular Dystrophy. Pediatrics. 2018 October; 142(Suppl 2): S34–S42. doi:10.1542/peds.2018-0333E.*