ASX Announcement

24 September 2021

Statistically significant modulation in two DMD disease modifier proteins supports potential of ATL1102 in ambulant DMD and fibrotic conditions

- Statistically significant mean modulation at 24 weeks compared to baseline in Thrombospondin-1 (TSP-1) and Latent TGF-beta-binding protein 4 (LTBP4) levels, two proteins that modify the rate of loss of ambulation in DMD
- Increase at 24 weeks in plasma VCAM-1 supportive of the ATL1102 mechanism of action of reducing CD49d on the surface of cells to which soluble VCAM-1 is bound, and in CXCL16 which can promote muscle regeneration
- Positive effects on LTBP4 and TSP-1 positions ATL1102 as an exciting prospect for the treatment of both non-ambulant and ambulant patients with DMD and the treatment of other muscle and fibrotic conditions.
- New Provisional Patent application filed covering this new data and ATL1102 applications.

Antisense Therapeutics Limited [ASX:ANP | US OTC:ATHJY | FSE:AWY] today announced that the ATL1102 Phase II non-ambulant DMD patient plasma protein data was presented today at the 26th International Annual Congress of the World Muscle Society in the late breaking news poster titled "ATL1102 treatment in non-ambulant boys with DMD modulates Latent TGF-beta-binding protein 4, and thrombospondin-1, two disease genetic modifiers of ambulant DMD, and CXCL16" (see conference abstract and link to the poster below).

ATL1102 was assessed in an open label Phase II study in adolescent non-ambulant patients with DMD demonstrating highly promising trial results. Planned as part of the Phase II study, a large-scale protein analysis (known as a proteomics analysis) of retained blood plasma samples from the non-ambulant DMD patients treated with ATL1102 was undertaken to identify the proteins affected so as to provide further insight into the mode of action and biological activity of ATL1102.

At the end of the 24 week dosing period, ATL1102 treated patients demonstrated a statistically significant mean reduction in Thrombospondin-1 (-49%), and increases in LTBP4 (20.7%), soluble CXCL16 (29.9%), and VCAM-1 (18.0%) compared to baseline levels (FDR p-value <0.0005).

The ATL1102 induced positive LTBP4 increases and TSP-1 decreases in plasma indicates that ATL1102 modifies the levels of two proteins involved in modifying the rate of loss of ambulation (LoA) in DMD. LTBP4 sequesters TGF-β to keep it latent and TSP-1 activates latent TGF-β with LTBP4 and TSP-1 both involved in the fibrotic process in DMD.

- An inherited minor form of the TSP-1 gene with reduced expression of TSP-1 has been reported as being protective against loss of ambulation in DMD.
- A rare recessive inherited form of the LTBP4 gene in 12% of patients with greater levels is associated with milder DMD providing 1-2 years delayed loss of ambulation[5,6].

ATL1102 modulation of these two DMD disease modifier proteins known to impact TGF-β and the rate of loss of ambulation in DMD patients supports ATL1102's potential use in ambulant patients with DMD, and as an agent to reduce fibrosis in other human diseases.

ATL1102's effect in increasing blood levels of (i) soluble VCAM-1 (sVCAM-1), a CD49d ligand, is supportive of ATL1102's antisense mechanism of action in reducing CD49d to reduce sVCAM-1 bound to CD49d, and in reducing inflammation[7], and (ii) soluble CXCL16, a chemokine with a role in muscle regeneration[8], appears to align with the positive effects on muscle structure observed under MRI in the ATL1102 Phase II trial. These plasma proteins were increased such that they approached the median levels seen in an external control dataset of healthy adults, supporting the beneficial nature of the outcomes in ATL1102 treated DMD patients.

The protein changes observed in the plasma of the ATL1102 treated non ambulant DMD patients in the Phase II study is also consistent with the drug's positive effects on muscle function and strength reported in the ATL1102 Phase II trial.

Dr George Tachas, Antisense Therapeutics Director of Drug Discovery and Patents said, "The improvement in two genetically inherited modifiers of loss of ambulation in DMD with ATL1102 treatment over six months is to my knowledge yet to be observed with any marketed drugs or those in development for boys with DMD. TGF-β is implicated in DMD pathology and is known to stimulate fibrosis and inhibit muscle regeneration. The changes to TPS-1 and LTBP4 are positive observations as they support ATL1102 applications in DMD, and other muscle dystrophy opportunities that we have planned and are underway in our collaboration with the MCRI, and other fibrotic disease areas in need of better treatments."

Mark Diamond, Antisense Therapeutics CEO said, "These positive effects on the above proteins strengthens ATL1102's profile in the treatment of both non ambulant and ambulant DMD patients while positioning it as an exciting prospective therapeutic approach in other muscle and fibrotic conditions. We are excited about this new data and the emerging opportunities that present to expand our development of ATL1102 in DMD and other disease applications in a strategic manner."

Analysis of the plasma protein data is ongoing in order to further elucidate ATL1102's biological effects and to position the drug's development in disease settings. The Company will continue to report on any material developments from this ongoing data analysis and associated commercial opportunities.

Based on the positive outcomes from the protein analysis reported above, Australian Provisional Patent Application No. 2021903024 was filed 20 September 2021 with claims covering applications of ATL1102 in new potential disease settings including diabetic, respiratory and age-related diseases to support the Company's future commercial and partnering plans for ATL1102.

For further details on these new results please refer to the following conference abstract below and the link here to the poster presentation.

For more information please contact:

Antisense Therapeutics
Mark Diamond
Managing Director
+61 (0)3 9827 8999
www.antisense.com.au

Investment Enquiries
Gennadi Koutchin
XEC Partners
gkoutchin@xecpartners.com.au
1300 932 037

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).

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. The management of the inflammation associated with DMD is currently addressed via the use of corticosteroids, however they are acknowledged as providing insufficient efficacy and are associated with significant side effects. As a consequence, there is an acknowledged high need for new therapeutic approaches for the treatment of inflammation associated with 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.

References

1. Tachas G, Desem N, Button P, Coratti G, Pane E and Mercuri E., "ATL1102 treatment improves PUL2.0 in non-ambulant boys with Duchenne muscular dystrophy compared to a natural history control". 25th WMS Congress October 1 2018. POSTER 284: https://www.nmd-journal.com/article/S0960-8966(20)30478-8/fulltext Accessed
2. Desem N, Woodcock I.R, Ryan M.R, and Tachas G. ATL1102 Phase II Non ambulant DMD study (1102-DMD-CT02) The Muscular Dystrophy Association Virtual Conference 2020, POSTER https://www.antisense.com.au/wp-content/uploads/2017/11/MDA-ATL1102-DMD-Poster_V2.0.pdf
3. Desem N, Woodcock I.R, Ryan M.R, and Tachas G. "Positive results from a CD49d antisense drug ATL1102 6-month Phase II trial in non-ambulant patients with Duchenne's Muscular Dystrophy". The Muscular Dystrophy Association Virtual Conference 2020, ABSTRACT https://www.antisense.com.au/wp-content/uploads/2017/01/ASX-20_-11-June_MDA-Conference-Poster-_Final.pdf
4. Pane M, Coratti G, et al Mercuri E. Upper limb function in Duchenne Muscular dystrophy; 24 month longitudinal data 2018 One, 13(6) e0199223 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0199223
5. Bello and Pegoraro (2019) J.Clin Medicine; 8(5): 649
6. Hoffman et al (2020) Acta Myologica; 179-186
7. Rose et al (2000) Blood; 95(2) 602-9
8. Zhang et al. (2009) 175(6): 2518-2527

ATL1102 treatment in non-ambulant boys with DMD modulates Latent TGF-beta-binding protein 4, a disease genetic modifier of DMD, and CXCL16

Tachas[1] G, Mueller C[2], DeLisle[4] R.K., Woodcock[3] I, Ryan[3], M.M, and Desem[1] N.

1. Antisense Therapeutics Limited, Melbourne, Victoria, 3142, Australia. www.antisense.com.au

2. Boulder Bioconsulting, Inc., Boulder, Colorado, 80303, USA . https://boulderbioconsulting.com/

3. Murdoch Children's Research Institute, Melbourne, 3052, Australia, https://www.mcri.edu.au/

4. SomaLogic, Inc., 2945 Wilderness Pl. Boulder, Colorado 80301, USA. www.somalogic.com

ATL1102, an antisense drug to CD49d, the alpha chain of VLA-4, has been evaluated in a Phase II study in nine non-ambulant patients with Duchenne muscular dystrophy (DMD) at the Murdoch Children's Research Institute. All patients (12 to 18 years of age) were dosed with ATL1102 once weekly at 25mg s.c. for 24 weeks. Eight of the patients were on standard of care corticosteroid treatment. ATL1102 was shown to be safe, and modulated CD49d+ lymphocytes, and stabilized upper limb muscle function, strength, and fat fraction.

Post-hoc analysis of plasma from the study assessed ATL1102's effects on proteomics as measured by the Somascan® assay, a large scale, aptamer-based assay, using normalized relative fluorescence units (nRFU). Parametric mixed effect longitudinal analysis was conducted to determine the average percent change over time, p-value and Benjaminin-Hochberg false discovery rate (FDR) adjusted p-value.

At 24 weeks, statistically significant mean increases of LTBP4 (20.7%), sCXCL16 (29.9%), and sVCAM-1 (18.0%) were observed compared to baseline levels (FDR p-value <0.0005). Compared to a healthy adult control, nRFU baseline levels of the above proteins were below average, and ATL1102 modulated each to nearer the external control mean.

ATL1102 modulation of VLA-4 ligand VCAM-1 is comprehensible and indirectly CXCL16, the latter with a reported role in muscle regeneration. LTBP4, which sequesters TGF-beta, a genetic modifier of DMD involved in early loss of ambulation, interacts with fibronectin, another VLA-4 ligand. These effects have a potential role in the positive stabilization of function and strength observed in the Phase II study.