ASX Announcement

30 July 2020

European Medicines Agency DMD Scientific Advice and Regulatory Process Update

- **EMA feedback reflects the prior scientific advice from the three EU national authorities on appropriateness of key trial design parameters**
- **Inclusion of 25mg dosing arm into the study given demonstrated efficacy in Phase II**
- **Company to define clinical and regulatory pathway in the US as a priority**

Antisense Therapeutics Limited [ASX:ANP | US OTC:ATHJY], (the Company) is pleased to advise that the European Medicines Agency (EMA) feedback reflects the prior scientific advice received from the three European Union national authorities on the appropriateness of the key trial design parameters of dose duration, safety monitoring plan, endpoints, and potential pivotal status for the planned Phase IIb study of ATL1102 in non-ambulant boys with Duchenne muscular dystrophy (DMD).

In light of the positive Phase II trial results, the Company is now looking to include a 25mg dosing arm into the Phase IIb trial with the view that this could be a clinically effective dose in this study. The EMA advised that further rationale be provided for the selection of the proposed higher dose levels (up to 100mg per week) and for consideration to be given to the use of intermediate doses and an increase to the sample size (to around 35 patients per arm).

The submission to EMA was made prior to the analysis of the complete Phase II trial data and confirmation of ATL1102 efficacy at 25mg per week dose. Given the efficacy demonstrated in the Phase II trial conducted at the Royal Children's Hospital in Melbourne at the 25mg per week dose and the EMA Scientific Advice guidance, the Company will consider the use of intermediate doses in the Phase IIb trial.

As previously advised the Company received independent advice from three National Agencies in Europe that was in general agreement with the nonclinical data package and proposed Phase IIb clinical trial design. Given that clinical trial approval is under National Sovereignty, the Company is encouraged that following its clinical trial application the proposed Phase IIb study could proceed in these jurisdictions.

As the next step, the EMA encouraged the Company to submit its Paediatric Investigational Plan (PIP) to the EMA Paediatric Committee (PDCO). The PIP is legally binding and addresses the entire paediatric development program (including use in patients up to and including 18 years of age). The Company is well advanced in its planning to submit the PIP. The Company will look to address EMA Scientific Advice recommendations and confirm the Phase IIb trial design through its PIP application to be submitted in Q4'20. Initial PDCO feedback is to be received ahead of submitting the Phase IIb trial application.

The Company has recently commenced activities for the manufacture of clinical trial supplies of ATL1102 for the Phase IIb trial including analytical method development and process optimisation. The Company has also made prepayments to lock in with its Contract Manufacture Organisation (CMO) the manufacture of this batch of ATL1102 and is planning to have clinical trial supplies available in line with the receipt of PDCO feedback and the approval to commence the trial, anticipated in 1H'2021.

In parallel with the planning for the Phase IIb clinical trial in Europe, the Company has been engaged in productive interactions with US based key opinion leaders, Advocacy Groups (PPMD and MDA), and expert regulatory consultants on the appropriate clinical path for ATL1102 in DMD in the US.

Given the positive Phase II trial results at the 25mg per week dose, the Company is working with its expert advisors on the clinical development and regulatory path for the US, noting that there are potential fast track or accelerated designations available to companies developing drugs for orphan indications in need of improved therapies such as in DMD.

Following the requisite strategic advice from its expert advisors the Company would then engage with the US Food and Drug Administration (FDA) to define the path forward as a priority.

Mark Diamond CEO of Antisense Therapeutics said: "With this feedback from EMA and proposed interactions with the US FDA, the Company looks forward to expanding the international clinical development of ATL1102 for DMD. The positive results achieved at the 25 mg dose and inclusion of this dose in our planning for the next stage of development has the potential to further de-risk the regulatory approval process and may provide an avenue to fast track our development plan for ATL1102 in the US".

This announcement has been authorised for release by the Board

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About Antisense Therapeutics Limited (ASX:ANP | US OTC:ATHJY) 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 ATL1102 DMD Trial The Phase II clinical trial of ATL1102 in patients with Duchenne Muscular Dystrophy was an open label six-month dosing trial of ATL1102 administered SC at 25mg per week in nine non-ambulant patients with DMD aged between 10 and 18 years. The trial was conducted at the neuromuscular centre of the Royal Children's Hospital (RCH) in Melbourne, Australia. The primary endpoints of the trial related to the safety and tolerability of ATL1102. The efficacy of ATL1102 was also assessed in terms of its effects on disease processes and progression (e.g. the upper limb strength and function of the boys). Given the exploratory nature of this first trial in boys with DMD, it was not powered to see a statistical difference on these disease progression endpoints, which would be expected in future longer-term clinical studies in a larger number of patients. However, highly encouraging positive trends across multiple parameters have been reported in this Phase II clinical trial. Further details on the trial are available here on the Australia and New Zealand Clinical Trials Registry.

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.