30 October 2017

ATL1102 'Black Hole' MS data presented at the 7th Joint ECTRIMS-ACTRIMS Meeting

As advised on 30th August 2017, Antisense Therapeutics Ltd (ASX:ANP) reports today that the data showing ATL1102 significantly reduces the number of active multiple sclerosis (MS) brain lesions that convert to 'Black Holes' [areas of nerve fiber loss or permanent brain tissue damage] was presented by Dr Frederik Barkhof, Professor of Neuroradiology, Department of Radiology and Nuclear Medicine, VU University Medical Centre, Amsterdam, at the 7th Joint ECTRIMS-ACTRIMS Meeting in Paris, France on 27 October 2017. The Joint ECTRIMS-ACTRIMS Meeting is the world's largest international conference devoted to basic and clinical research in MS.

The poster presented entitled "ATL1102 treatment reduces conversion of active multiple sclerosis lesions into persistent black holes" follows this announcement. The abstract for the poster was also published in the *Multiple Sclerosis Journal Online* on the congress website. Click here to access abstract.

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ECTRIMS – European Committee For Treatment And Research In Multiple Sclerosis
ACTRIMS – American Committee For Treatment And Research In Multiple Sclerosis

Antisense Therapeutics Limited (ASX: ANP) is an Australian publicly listed biopharmaceutical drug discovery and development company. Its mission is to create, develop and commercialise second generation antisense pharmaceuticals for large unmet markets. The products in ANP's development pipeline are in-licensed from Ionis Pharmaceuticals Inc., world leaders in antisense drug development and commercialisation. ATL1102 (injection) has successfully completed a Phase II efficacy and safety trial, significantly reducing the number of brain lesions in patients with relapsing-remitting multiple sclerosis (RRMS). ATL1103 drug designed to block GHr production successfully reduced blood IGF-I levels in Phase II clinical trials in patients with the growth disorder acromegaly.

About Multiple Sclerosis (**MS**) MS is a life-long, chronic disease that progressively destroys the central nervous system (CNS). It affects approximately 400,000 people in North America and more than 2 million worldwide. It is a disease that affects more women than men, with onset typically occurring between 20 and 40 years of age. Symptoms of MS may include vision problems, loss of balance, numbness, difficulty walking and paralysis. In Australia MS affects over 20,000 people. **Relapsing-Remitting MS (RR-MS):** People with this type of MS experience clearly defined attacks of worsening neurologic function. These attacks—which are called relapse or exacerbations —are followed by partial or complete recovery periods (remissions), during which no disease progression occurs. Approximately 85% of people are initially diagnosed with relapsing-remitting MS. **Secondary-Progressive MS** (**SP-MS)** occurs when after an initial period of relapsing-remitting MS, many people develop a secondary-progressive disease course in which the disease worsens more steadily, with or without occasional flare-ups, minor recoveries (remissions), or plateaus. Before the disease-modifying medications became available, approximately 50% of people with relapsing-remitting MS developed this form of the disease within 10 years. The market for drugs treating RR-MS has been valued at more than USD$20 billion. There are limited treatment options for SP-MS patients. The market potential for SP-MS treatments has been estimated at US$7billion.

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 RR-MS patients. 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 treatment reduces conversion of active multiple sclerosis lesions into persistent black holes

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Introduction

ATL1102 is an antisense drug to the RNA for human CD49d, the alpha subunit of VLA-4.

A Phase II study of ATL1102 dosed for 8 weeks in relapsing remitting multiple sclerosis (MS) patients met its primary endpoint in reducing the cumulative number of new active MS lesions by 54% vs placebo at week 12 (P=0.01)[1].

Notably, ATL1102 treated patients had 90 % fewer new enhancing lesions than those receiving placebo at week 12 (P < 0.005) (Figure 1).

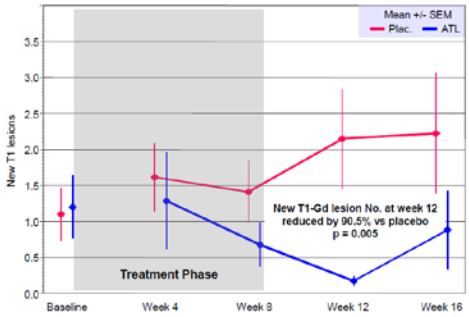

Fig 1. Reduction in the cumulative number of T1-GdE lesions at weeks 4, 8,12 and 16 following administration of ATL1102 (3 x 200mg in week 1 followed by 2 x 200mg per week for 7 weeks)

Results

There was a significant reduction in the proportion of active lesions at week 8 and 12 converting to BH at week 16 in ATL1102 treated patients (13.2%) compared to patients on placebo (27.6%).

The odds of converting to a BH in the placebo arm were 2.51 times the odds of converting in the treatment arm (95% Wald Confidence Interval: (1.054, 5.959), p= 0.0376).

Analysis Black Hole Evolution	Characteristics	Placebo (arm1)	ATL1102 (arm2)
Origin active lesions week 8–12 combined	N= number of patients	23	17
	Active lesions, mean (SD	7.1 (7.9)	3.1 (3.4)
	Active lesions, median (range)	4 (1-33)	2 (1-13)
	%BH Conversions[1],	45/163=27.6%	7/53=13.3%
	Overall Ratio[2], mean (SD)	23.6 (32.0)	19.2 (38.8)
Treatment Arm Comparison	P-value = 0.0376 Odds Ratio: Arm 1 v Arm 2 : 2.506, 95% CI, (1.054, 5.959) There is a significant difference between Placebo and ATL1102		
Notes:	(i) %BH Conversion is the sum of converted/sum of active in each arm, no standard deviations are derived for this measure. (ii) Overall Ratio = The average of individual Converted lesions/Active lesions in each arm.		

Table 1. Results of Logistic Regression Analysis of active lesions at Weeks 8-12 converting to BH at week 16

Objective

A post-hoc analysis of the magnetic resonance imaging data was conducted to measure the effect of ATL1102 on the conversion of remaining new active lesions to T1 black holes (BH), a marker of axonal loss and permanent tissue damage.

Conclusions

The positive effect of ATL1102 on reducing BH evolution suggests that along with its action in reducing the number of new inflammatory brain lesions, ATL1102 may also be neuroprotective by reducing damage to axons in residual new lesions.

Methods

In the Phase II study, new active lesions were defined as either gadolinium-enhancing or new non-enhancing T2 or enlarged non-enhancing T2 lesions.

Evolution of active lesions into BH or T1 iso-intensity was determined by a blinded observer[2]. Data were analysed with a logistic regression of treatment groups with a binomial error distribution as required[3].

References

1. Limmroth, V. et al CD49d antisense drug ATL1102 reduces disease activity in patients with relapsing-remitting MS. Neurology 2014:11:83 (20) 1780-1788.

2. Barkhof F et al. Ibudilast in relapsing-remitting multiple sclerosis: a neuroprotectant? Neurology 2010: 74: 1033-1040.

3. Zivadinov et al Effect of glatiramer acetate three-times weekly on the evolution of new, active, multiple sclerosis lesions into T1-hypintense "black holes": a post hoc magnetic resonance imaging analysis. Neurology 2015: 262:648–653

Disclosures: VU Medical Centre, Amsterdam, the Netherlands, has received compensation for the MRI analysis.
CPR Pharma Services Pty Ltd Thebarton, Adelaide, SA, Australia has received compensation for the statistical analysis.
G. Tachas holds an equity interest in the sponsor (Antisense Therapeutics Ltd, Melbourne. Victoria, Australia).

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