ANTISENSE THERAPEUTICS

31 August 2005

# Antisense Therapeutics to submit application to restart ATL1102 Phase IIa trial in MS patients

- Medical Advisory Board determines that "ATL1102 appears to have significant potential as a therapeutic agent in treating MS" and recommends that development should continue
- Board of Directors accept recommendation of Medical Advisory Board to continue development of ATL1102 in MS and restart the Phase IIa trial currently on hold in Germany
- Trial program has been amended to incorporate all modifications recommended by the Medical Advisory Board
- Application to restart Phase IIa trial to be submitted to Institutional Review Board and Ethics Committee of primary trial centre
- Study to commence once approval received from trial regulators

The Directors of Antisense Therapeutics have accepted and agree with the recommendation of the Medical Advisory Board (MAB) to continue the development of ATL1102 as a treatment for patients with relapsing remitting Multiple Sclerosis. Following its formal review, the advisory board recommends that the Phase IIa trial currently on hold in Germany, be restarted with additional safety monitoring of patients.

While the current market for MS drugs is large (in excess of US$4 Billion per annum) there continues to be a high demand for improved MS therapies. The Directors believe ATL1102 could have significant commercial potential should clinical investigations show the compound to be suitably safe and effective.

Background

Antisense Therapeutics established and convened the MAB after it voluntarily halted its Phase IIa trial of ATL1102 in MS patients in light of the safety issues associated with Biogen Idec and Elan Corporation's multiple sclerosis drug Tysabri®.

In the MS clinical trials of Tysabri® two patients were reported to have developed a specific type of viral infection (JC virus) leading to the rare but frequently fatal disease of the central nervous system, progressive multifocal leukoencephalopathy (PML).

While ATL1102, an antisense inhibitor, is a different drug from Tysabri®, a monoclonal antibody, and thereby works by a different mechanism, the relevance of the Tysabri® issue to Antisense Therapeutics is that ATL1102 is designed to target the same immune system protein (VLA-4) as Tysabri®.

The objective of the Medical Advisory Board, comprising relevant independent experts, was to consider the potential development paths for ATL1102 in MS, including the possible restart of the Phase IIa program.

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Medical Advisory Board – Key Recommendations

The recommendations provided by the MAB to the Board of Antisense Therapeutics Ltd are summarised below. Specific details are outlined in the attached formal recommendation document from the Advisory Board

- ATL1102 appears to have significant potential as a therapeutic agent in relapsing-remitting MS, and therefore its development should continue in earnest.
- The risk of PML developing in patients in the proposed 8-week dosing trial is considered minimal. However, to further minimize any risk potential, and to obtain a fuller understanding of the drug's safety profile with respect to its potential to cause PML, all patients enrolled into the trial should undergo regular monitoring for possible activation of the JC virus, for the entire duration of the trial. To assist in this regular monitoring process Antisense Therapeutics should establish an independent Drug Safety Monitoring Board that will assess all safety results arising from the study, including virus monitoring data.
- Patient enrollment criteria should be strictly followed for those who may have previously received immune-modulating drugs. This is to eliminate any risk of a synergistic adverse effect of drug combinations, as it would appear that the two patients who developed PML in the Tysabri® MS trial received a combination of two immune-modulating drugs.

The recommendations of the Advisory Board to address the potential safety issues related to JC viral activation and the appearance of PML reported in the Tysabri® trials have been incorporated by the Company into the clinical trial program for ATL1102 and provide the Company with increased confidence that appropriate safety measures are in place to safeguard patients in the trial.

Apart from these changes, the trial design and clinical assessment objectives remain the same for the Phase IIa trial as reported by the Company when this trial was first initiated in December 2004.

Application to be submitted to restart Phase IIa trial

An application to restart the Phase IIa trial is to be submitted to the Institutional Review Board (IRB) and Ethics Committee (EC) of the University of Essen, the primary site for the Phase IIa trial. Should the IRB and EC approve the restart of the trial, the Company will then lodge the same application with the IRB and EC's of the other 7 trial centres. The Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte: BfArM) in Germany will also be notified, who will have the authority to raise questions or issues prior to the restart of the trial.

Upon receipt of all relevant approvals from the trial regulators, the Company will be in a position to initiate the trial with the commencement of patient enrolment. The Company will need to formulate additional ATL1102 compound to complete the trial. Manufacture will commence once requisite regulatory approvals are in place.

The Company is hopeful that, subject to receiving these approvals, the trial may recommence before the end of the year. The Company will be in a position to provide guidance on forecast completion dates for the trial following the necessary regulatory approvals.

***About ATL1102 for MS***

ATL1102 is a second generation antisense inhibitor of CD49d, a subunit of VLA-4 (Very Late Antigen-4), and is currently in development as a treatment for MS. In inflammation, white blood cells (leukocytes) move out of the bloodstream into the inflamed tissue, for example, the CNS in MS, and the lung airways in asthma. The inhibition of VLA-4 may prevent white blood cells from entering sites of inflammation, thereby halting progression of the disease. Antisense inhibition of VLA-4 has demonstrated positive effects in a number of animal models of inflammatory disease including MS. .

***About Antisense Therapeutics Limited***
Antisense Therapeutics Limited (ASX: ANP) is an Australian publicly listed biopharmaceutical drug discovery and development company. ANP's mission is to create, develop and commercialise novel antisense pharmaceuticals for large unmet markets. Its two most advanced projects, which are both in clinical development, target Multiple Sclerosis (ATL1102), and Psoriasis (ATL1101).

ANP plans to commercialise its pipeline via licensing/collaboration agreements with major biotechnology and pharmaceutical companies.

ANP's major shareholders include Circadian Technologies Limited, Isis Pharmaceuticals Inc and Queensland Investment Corporation.

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# ATL 1102 MEDICAL ADVISORY BOARD

## Recommendations to Antisense Therapeutics Ltd

The Medical Advisory Board (MAB) for ATL 1102 was set up by Antisense Therapeutics Ltd following a decision announced on 10 March 2005 by its Board of Directors to halt the Phase IIa clinical trials being conducted in relapsing-remitting multiple sclerosis (MS) patients. These trials were being conducted in clinical trial centers in Germany. The trials were halted in light of the Biogen Idec Inc and Elan Corporation announcement that their recently registered MS product Tysabri® was being withdrawn from the market following the discovery that two patients treated with the drug for more than two years in combination with interferon beta-1a (Avonex®) had developed a rare brain disease called progressive multifocal leukoencephalopathy (PML).

Tysabri and ATL 1102 are products with different mechanisms of action. However, both serve ultimately to inhibit VLA4 binding, an important step in blocking trafficking of activated immune cells.

The remit of the MAB was to develop a set of recommendations on the most appropriate development path for the clinical testing of ATL 1102 in MS.

## Composition of the MAB

The Medical Advisory Board comprised six members, as follows:

**Professor Fred Lublin MD**, Professor of Neurology at the Mount Sinai School of Medicine, and Director of Corinne Goldsmith Dickinson Center for Multiple Sclerosis at Mount Sinai, New York, NY, served as Chairman.

**Professor Jerry Wolinsky MD**, Bartels Family Professor of Neurology, The University of Texas Health Science Center at Houston, TX.

**Professor Chris Polman MD**, Professor of Neurology at the Free University, as well as Clinical and Scientific Director of the Multiple Sclerosis Centre at the VU Medical Center in Amsterdam.

**Igor Koralnik, LLC.** Igor J. Koralnik, MD, the President of Igor J. Koralnik, LLC, is an Associate Professor of Neurology at the Harvard Medical School, Boston, MA. He is a recognized, internationally acclaimed expert in the field of Progressive Multifocal Leukoencephalopathy (PML).

**Stephen Reingold PhD**, President, Scientific and Clinical Review Associates, New York, NY. Until very recently he was Vice President, Research Programs, at the National MS Society, New York, NY

**Michael Gallatin PhD**, Scientific Consultant and formerly VP and Scientific director at ICOS Corporation, Washington. He is a leading scientist in the research area of adhesion molecule science.

Antisense technology conforms to a novel type of biological intervention intended for therapeutic use. In order to provide expert advice on antisense technology to the MAB, **Frank Bennett PhD**, Vice President for Research at Isis Pharmaceuticals Inc, Carlsbad, CA, was co-opted as an ad-hoc member, at the invitation of the Chairman.

## Meetings of the MAB

The MAB formally met on two occasions. Mr Mark Diamond (CEO) and Dr Jega Iswaran (Development Director) from ATL were present at both meetings.

The first meeting was held at the Fink & Carney Building 6th Floor, 39 West 37th Street, New York, NY 10018, USA, on Sunday, 5 June 2005. Professor Polman and Dr Gallatin were connected to the meeting via video and audio links, respectively. Others were present in person.

The second meeting was held at the Function Room Saturn 1, Sheraton Amsterdam Airport Hotel & Conference Center, Schiphol 101, Amsterdam, The Netherlands, on Monday, 18 July 2005. Present were: Professor Lublin, Professor Polman, Professor Wolinsky, Dr Koralnik and Dr Reingold from the MAB. The meeting was also attended by Professor Volker Limmroth, of the University of Essen, Germany (Principal Investigator for the halted ATL 1102 Phase IIa clinical trial) and Professor Frederick Barkhof of the Free University of Amsterdam (MRI Investigator for the halted ATL 1102 Phase IIa clinical trial). Others present included two experts from the Contract Research Organization EPA-Europharma GmbH (Germany): Dr Uwe Hehnke (Head of Biometrics) and Mr Manfred Schlemminger (Head of Regulatory Affairs).

Discussions and analyses at these meetings, amongst others, included: aspects of antisense technology, properties of ATL 1102, adhesion molecule science & VLA-4 inhibition, differences between antisense technology & monoclonal antibody technology, multiple sclerosis disease & treatments, JC virus and PML neurology, PML cases amongst Tysabri treated patients, ATL 1102 Phase IIa study design & clinical trial protocol, adverse events risk analysis & risk minimization.

## Summary of MAB Recommendations to ATL:

This MAB has now concluded its reviews on the antisense compound ATL 1102, and unanimously recommends that:

(1) As ATL 1102 appears to have significant potential as a treatment for relapsing-remitting MS patients, its development as a therapeutic agent should continue in earnest.

(2) The risk of PML developing in patients exposed to ATL 1102 in the proposed 8-week Phase IIa dosing clinical trial is considered to be minimal. Therefore, the proposed Phase IIa clinical trial can be re-started.

(3) The following additional items of patient monitoring should be included in the trial protocol, to further minimize any risk potential that may exist for the development of PML and to help gain a better understanding of the product's safety profile.

- On-going monitoring of all patients enrolled in the trial for JC virus. Quantitative PCR testing to be done on blood samples collected at time of screening of patients for enrollment and during the trial period at weeks 0, 4, 8, 12, and 16. Urine and serum samples for JC virology/serology analysis should also be collected at these time points, but may be stored frozen until the end of study, unless otherwise needed for interim analysis during the study. Monitoring is not only included to minimize risk for study participants, but also to test efficacy and plausibility of this as screening system for future, larger studies and to give further insight regarding potential re-activation of JC virus during this type of intervention ('management' of risk rather than 'prevention').

- ATL should immediately set up an independent Drug Safety Monitoring Board (DSMB) that will be active for the full duration of the trial. The results of Quantitative PCR testing for JC activation, MRI and all other adverse events should be monitored by this Board on an on-going basis.

  Dosing should be stopped immediately if there is any indication that JC virus activation is present in any patient and appropriate clinical follow-up should be provided.

  MRI diagnostic features/guidelines should be established for distinguishing possible PML lesions from MS lesions and these guidelines should be used by the DSMB to assist with their safety monitoring .

- The restarted protocol should require strict adherence to trial inclusion criteria for patients who have undergone prior therapy for MS with immunosuppressive or immune-modulating drugs, including interferon beta. In these cases a six-month 'wash out' period must be instituted before patients are eligible for participation in the trial.

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**Professor Fred D. Lublin, MD**
As Chairman, and on behalf of the
Medical Advisory Board for ATL 1102 in MS

**Date:** 9 AUG 2011

**cc: MAB members**