3 September 2014

ATL1103 Phase II Trial - Successful Efficacy Results

- **Primary efficacy endpoint met with a statistically significant reduction of sIGF-I levels of 26% at the 400mg/week dose (P<0.0001; highly significant)**
- **36% average reduction in sIGF-I for lower body weight patients**
- **Positioned to move into Phase III stage of development**
- **Safe and well tolerated with no serious adverse events related to dosing reported**

Antisense Therapeutics Limited ("ANP" or "the Company") is pleased to report the primary efficacy results from its Phase II clinical trial of ATL1103 in patients with the potentially life threatening growth disorder, acromegaly. The Phase II trial met its primary efficacy endpoint showing a statistically significant average reduction in the serum insulin-like growth factor-I (sIGF-I) levels of 26% from baseline (P<0.0001) at week 14 (one week past the last dose) at the 400mg per week dose tested.

All patients treated with 400mg per week of ATL1103 had a reduction in sIGF-I levels from baseline at week 14. Greater reductions in sIGF-I were observed in patients who had lower body weights and thereby received a relatively higher dose per kg bodyweight (correlation of P=0.0001) with the patients who received >5.5 mg/kg per week showing a 36% average reduction in their sIGF-I levels.

The positive results achieved in this Phase II trial position ATL1103 to move into Phase III stage of development. Consequently, ANP will accelerate out-licencing activities to secure a pharmaceutical development partner for the drug's further development.

Chief Investigator for the study Dr Peter Trainer, Professor of Endocrinology, The Christie NHS Foundation Trust, UK, said; 'There are limited therapeutic options for patients with acromegaly and there is an acknowledged need for new therapies. The results achieved in this Phase II trial suggest ATL1103 with appropriate dose adjustment should be capable of achieving disease control in a significant proportion of patients with acromegaly. ATL1103's profile as a potentially efficacious and well tolerated conveniently dosed therapy strongly supports its move into Phase III stage of development."

Mark Diamond, Managing Director and CEO of Antisense Therapeutics said: "We are very pleased to have achieved this significant milestone in the late stage development of ATL1103. These results greatly enhance our partnering prospects for the drug and we expect a number of interested pharmaceutical companies to enter formal due diligence on ATL1103 in coming months."

Study Design and Detailed Results

The ATL1103 Phase II trial is a randomised, open-label, parallel group study of the safety, tolerability, pharmacokinetics and efficacy of two subcutaneous dosing regimens of ATL1103 in 26 adult acromegaly patients dosed with ATL1103 for 13 weeks (3 months) with two months of follow up. Two ATL1103 dosing regimens were tested (a) 200 mg 3 times in the first week then once weekly thereafter (200 mg/week) or (b) 200 mg 3 times in the first week then twice weekly thereafter (400 mg/week).

The primary efficacy endpoint of the 26 patient trial was the reduction of sIGF-I levels in acromegaly patients as they have significantly higher levels than healthy individuals and sIGF-I normalisation is accepted by clinical authorities as the therapeutic goal for the treatment of acromegaly.

In this study, patients on the 400mg per week dose of ATL1103 achieved an average reduction in their sIGF-I levels of 26% from baseline ($P<0.0001$) at week 14. In line with this, a 30% average reduction was achieved at week 13 (last week of dosing). All 13 patients treated with the 400mg per week dose had a reduction in their sIGF-I levels from baseline at week 14. The best reduction achieved by any patient at any time point was a 64% reduction at week 13.

Greater reductions in sIGF-I were observed in patients who had lower body weights and thereby received a relatively higher dose per kg bodyweight (mg/kg). A statistically significant correlation ($P=0.0001$) was observed between the mg/kg dose received and the level of sIGF-I reduction thereby confirming a dose response relationship on these parameters with the data showing an average reduction in sIGF-I of 36% was achieved in the five out of 13 patients who received >5.5 mg/kg per week supporting the expectation that higher dosing should result in higher sIGF-I reductions (refer Appendix 1, Figure 2).

The time-course data over the full 13 weeks of dosing at the 400 mg per week dose generally shows a progressive reduction in sIGF-I over the dosing period and maintenance of the effect well past the last dose (refer Appendix 1, Figure 1). This suggests that continued dosing of ATL1103 for longer than 13 weeks in a Phase III study could result in additional reductions in sIGF-I.

At the 200 mg per week dose, no reduction in average sIGF-I levels was observed at week 14, although there were sIGF-I reductions noted in individual patients (four out of 13 patients had sIGF-I reductions > 20%). Best achieved at the 200mg dose by any patient at any time point was a 46% reduction at week 13. The lower 200mg dose may nonetheless be therapeutically effective for some patients, particularly with the view to a longer dosing period.

Patients in this study had average baseline levels of IGF-I that were 2.6 times the upper limit of normal (ULN) which appear high compared to other acromegaly studies. sIGF-I levels were normalised (brought below ULN) at any point in the study in two of 13 patients dosed at 400mg per week and in one out of 13 on the 200mg per week dose. Four patients at the 400mg per week dose had reductions of their sIGF-I to below the minimum entry criterion of 1.3 times the ULN suggesting therapeutic benefit in these patients. Reduction of sIGF-I to within the normal range in a significant proportion of patients is the goal in longer term (6-12 month) Phase III registration trials for acromegaly treatments.

The monitoring of patients post dosing in the trial continues with the last patient visit scheduled for the end of September. Data base lock is expected in October with final assessment of the safety data to occur in November 2014. The safety review undertaken to date confirms that there were no patient withdrawals or reports of any serious adverse events related to dosing with ATL1103 and that ATL1103 has been assessed as generally well tolerated. The most common adverse event was injection site reactions which were predominantly mild and typically resolved within days. There have been "no flu-like" symptoms, no abnormalities in renal function, and no clinically meaningful changes in other laboratory values reported as adverse events. Liver enzyme elevations were noted as adverse events in two patients but are not being regarded as clinically meaningful in these instances. The positive safety profile demonstrated to date suggests the drug may be tolerated at higher dose levels than 400 mg per week.

Preparation for Phase III Development

As previously reported, The Company plans to conduct a small study at a higher dose than 400 mg per week for potential use in a Phase III clinical trial.

Preparatory work for a Phase III clinical trial of 6 -12 months of treatment includes manufacture and formulation of drug product and further animal toxicology studies which ANP plans to undertake with a future development partner.

The outcomes from the Phase II study are to be presented at the 7th International Congress of the GRS and IGF-I Society in Singapore, 15 – 18 October 2014 by the Chief Investigator for the study, Professor Trainer.

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ATL1103 Phase II trial is a randomised, open-label, parallel group study of the safety, tolerability, pharmacokinetics and efficacy of two subcutaneous dosing regimens of ATL1103 in 26 adult patients with acromegaly dosed with ATL1103 for 13 weeks (3 months) with two months of follow up. Two ATL1103 dosing regimens were tested (a) 200 mg 3 times in the first week then once weekly thereafter (200 mg/week) or (b) 200 mg 3 times in the first week then twice weekly thereafter (400 mg/week). The primary endpoints or main purposes of the trial as listed on the trial protocol are (i) to evaluate the safety and tolerability of ATL1103 in patients with acromegaly, and (ii) to evaluate the single dose and multiple dose pharmacokinetic profiles of ATL1103 via the subcutaneous route in patients with acromegaly. Another important endpoint that is also on the trial protocol is the evaluation of ATL1103's effect on serum insulin like growth factor I (IGF-I) levels in patients. This efficacy endpoint is the average percentage reduction in serum IGF-I levels at one week past the end of treatment compared to baseline levels for each of the two dosing regimens used in the Phase II study.

ATL1103 is a second generation antisense drug designed to block growth hormone receptor (GHr) expression thereby reducing levels of the hormone insulin-like growth factor-I (IGF-I) in the blood and is a potential treatment for diseases associated with excessive growth hormone and IGF-I action. These diseases include acromegaly, an abnormal growth disorder of organs, face, hands and feet, diabetic retinopathy, a common disease of the eye and a major cause of blindness, diabetic nephropathy, a common disease of the kidney and major cause of kidney failure, and some forms of cancer. Acromegalic patients are known to have significantly higher blood IGF-I levels than healthy individuals. Reduction of these levels to normal is accepted by clinical authorities as the primary marker of an effective drug treatment for the disease. GHr is a clinically validated target in the treatment of acromegaly. In the case of diabetic retinopathy, published clinical studies have shown that treatments producing a reduction in IGF-I levels retarded the progression of the disease and improve vision in patients. Scientific papers have been published on the suppression of blood IGF-I levels in mice (Tachas et al., 2006, J Endocrinol 189, 147-54) and inhibition of retinopathy in a mouse retinopathy model (Wilkinson-Berka et al., 2007, Molecular Vision 13, 1529-38;) using an antisense drug to the GHr. ANP have also reported that ATL1103 suppressed circulating levels of IGF-I in primates. In a Phase I study in normal volunteers, ATL1103 was assessed as being safe and well tolerated, while also demonstrating a preliminary indication of drug activity including suppression of IGF-I and the target GHR (growth hormone binding protein) levels. ATL1103 commercialisation is covered by patents to at least 2024, with the potential for extensions up to 2029 in some countries and 2030 in the US.

Acromegaly is a serious chronic life threatening disease triggered by excess secretion of growth hormone (GH) by benign pituitary tumours. Oversupply of GH over stimulates liver, fat and kidney cells, through their GH receptors, to produce excess levels of (IGF-I) in the blood manifesting in abnormal growth of the face, hands and feet, and enlargement of body organs including liver, kidney and heart. The primary treatments for acromegaly are to surgically remove the pituitary gland and/or drug therapy to normalize GH and serum IGF-I levels. In North America and Europe there are approximately 85,000 acromegaly patients with about half requiring drug therapy. Cost of drug therapy ranges from approximatelyA$30,000/annum to over A$60,000/annum depending on the treatment.

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. ANP has 4 products in its development pipeline that it has in-licensed from Isis Pharmaceuticals Inc. (NASDAQ:ISIS), world leaders in antisense drug development and commercialisation - ATL1102 (injection) which has successfully completed a Phase II efficacy and safety trial, significantly reducing the number of brain lesions in patients with multiple sclerosis, ATL1103 a second-generation antisense drug designed to block GHr production and thereby lower blood IGF-I levels and is in clinical development as a potential treatment for growth and other GH-IGF-I disorders, ATL1102 (inhaled) which is at the pre-clinical research stage as a potential treatment for asthma and ATL1101 a second-generation antisense drug at the pre-clinical stage being investigated as a potential treatment for cancer.

Appendix 1: Summary of ATL1103 Phase 2 clinical trial to end of August 2014

Title	A Phase II Randomised, Open-Label, Parallel Group Study of the Safety, Tolerability, Pharmacokinetics and Efficacy of Two Subcutaneous Dosing Regimens of ATL1103 in Adult Patients with Acromegaly.
Trial description	Phase 2 trial of subcutaneous administration of ATL1103 in acromegaly patients
Chief Investigator	Professor Peter Trainer BSc MD FRCP Christie Hospital, Manchester, United Kingdom
Study Period:	2012 - 2014
Methodology:	Multicentre, open-label, randomised, controlled, parallel group comparison.
Sites	13 trial sites in United Kingdom, France, Spain and Australia
Study Objectives	Primary objectives: • To evaluate the safety and tolerability of ATL1103 in patients with acromegaly. • To evaluate the single dose and multiple dose pharmacokinetic profiles of ATL1103 via the subcutaneous route in patients with acromegaly. Secondary objectives: • To evaluate the effect of two dosing regimens of ATL1103 on serum sIGF-I levels in patients with acromegaly (primary efficacy endpoint is the percentage change in IGF-I one week past the last dose (i.e. at week 14) • To explore the effects of ATL1103 on the following parameters in patients with acromegaly: o GH, GHBP o IGFBP-3, ALS, IGF-II o Ring size assessment o Signs and Symptoms Scale o Acromegaly Quality-of-Life questionnaire
Main selection criteria; number of subjects	• 26 acromegaly patients • Males and Females 18 – 80 years of age • Acromegaly due to pituitary adenoma identified by magnetic Resonance Imaging (MRI) • sIGF-I level at screening of >1.3 ng/mL • Nadir Growth Hormone (GH) >1 ng/mL for 2h after oral glucose load • Treatment naïve, or completed a period of washout from previous acromegaly treatment
Test Drug, Dose and Mode of administration	Subcutaneous administration of ATL1103 in the following regimens: Regimen 1 : 200 mg ATL1103 three times in the first week, then weekly for the next 12 weeks Regimen 2: 200 mg ATL1103 three times in the first week, then *twice* weekly for the next 12 weeks
Duration on study	28 day screening, 13 week dosing period, 8 week follow up period (total approx. 25 weeks on study)
Criteria for assessment	Safety and tolerability: Physical examinations, vital signs, adverse event monitoring and ECGs. Blood sampling for clinical safety (haematology, biochemistry), coagulation (PT, APTT and TT), urinalysis, complement assessments (Bb) and MRI of tumour size Pharmacokinetic: Blood sampling for plasma ATL1103 levels at various time points over the dosing and follow up periods Pharmacodynamic/Efficacy: sIGF-I: Serum samples collected at each clinic visit. Serum levels of GH; GHBP ALS, IGF-II, IGFBP-3 Ring size assessment; Acromegaly Quality of Life Questionnaire; Acromegaly Signs & Symptoms Questionnaire
Status at end of August 2014	26 patients randomised; all completed dosing; 2 in follow up Last patient follow up visit scheduled September 2014
Patient demographics	Regimen 1: 13 patients (5 males, 8 females) Regimen 2: 13 patients (7 males, 6 females) Mean age 50.3 y (range: 26 to 80 y)
Subject withdrawals	One patient from Regimen 1 withdrew from the study at the end of the dosing phase No subject withdrew or was withdrawn for safety reasons related to treatment with ATL1103.
Outcomes	**Primary efficacy endpoint outcome** The effect of ATL1103 on serum sIGF-I levels at week 14 is summarized in **Table 1** (intent to treat) and **Table 2** (per protocol). The time course for the mean percentage IGF-I change from baseline for patients treated with Regimen 2, is plotted in **Figure 1**.

	The relationship between the percentage IGF-I change from baseline to week 14 versus the dose of ATL1103 (expressed as mg/kg body weight/week) is shown as a scatter plot (**Figure 2**). The regression slope was calculated at -8.27 (p=0.0001). The dose response relationship was seen for the higher doses (twice weekly dosing). Assessments from the other efficacy outcomes (GH, GHBP, ALS. IGFBP-3, Ring size assessment; Acromegaly Quality of Life Questionnaire; Acromegaly Signs and Symptoms Questionnaire) have not yet been analysed. **Outcomes of the other study objectives** Full data analysis will take place once all the study data is entered into the database and the database is locked (scheduled end of Oct 2014). Safety observations to date: • ATL1103 was considered generally well tolerated at the doses used in the study • 4 serious adverse events (AE) were reported. None of them were deemed related to treatment with ATL103 • Most frequently reported adverse event was injection site reactions; mild to moderate in severity; most resolved within 1 to 4 days without the need for treatment • Other AEs that could be related to treatment include liver enzyme elevations in two patients and a transient platelet decrease in one patient. None of these reached levels that necessitated interruption to dosing. Pharmacokinetic data and MRI data is not yet available

Table 1: Percentage change in sIGF-I from baseline to week 14 (intent to treat* set)

	Regimen 1 (ITT)	Regimen 2 (ITT)
	N=13	N=13
Mean	0.22	-25.89
SD	19.64	14.35
Median	-2.00	-27.83
Range	37.2 to -34.0	-4.4 to -49.8
CI	-11 65 to 12.09	-34.56 to -17.22
p (one sample t-test); 2 sided	0.9688	<0.0001
P (Wilcoxon signed rank test)	1.0	0.0002

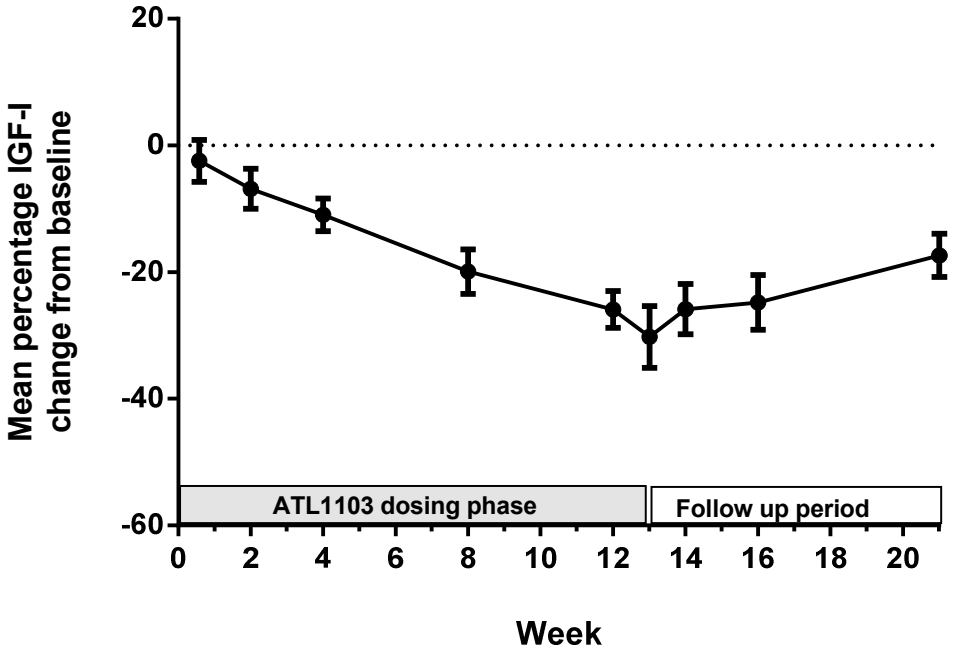
* The "intent to treat" set includes all subjects starting the trial

Table 2: Percentage change in sIGF-I from baseline to week 14 (per protocol* set)

	Regimen 1 (PP)	Regimen 2 (PP)
	N=12	N=13
Mean	-1.61	-25.89
SD	19.33	14.35
Median	-3.67	-27.83
Range	37.2 to -34.0	-4.4 to -49.8
CI	-13.89 to 10.68	-34.56 to -17.22
p (one sample t-test); 2 sided	0.7790	<0.0001
p (Wilcoxon signed rank test)	0.7334	0.0002

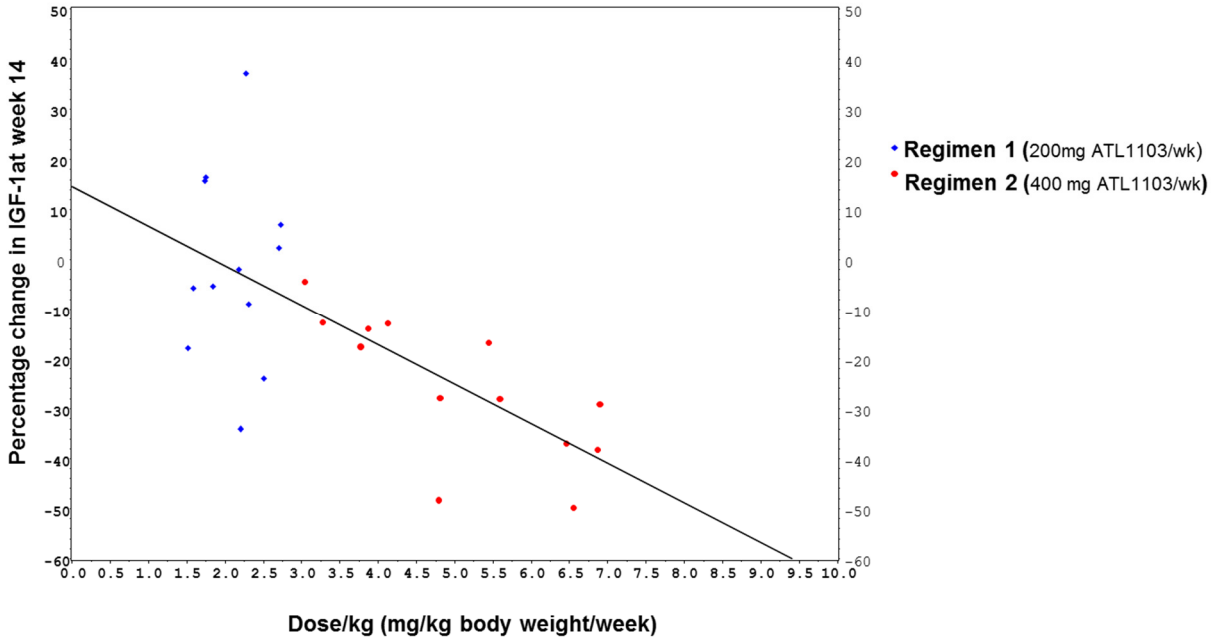
*The "per protocol" set includes the patients that completed the dosing period according to the protocol

Figure 1: Percentage change from baseline for patients on Regimen 2 (i.e. 2 x 200 mg ATL1103/week)



Mean ± SEM; ITT set; n= 13, except day 4, week 2 & week 12 (n=12) and week 21 (n=10). Note that dosing is completed at the week 13 clinic visit. Mean sIGF-I change is – 30% at week 13; and -26% at week 14.

Figure 2: Scatterplot of percentage change in sIGF-I vs ATL1103 dose/kg body weight/week



The regression slope for the dose-response correlation was calculated at -8.27 (p=0.0001).