Extract from Bioshares –

Antisense Therapeutics (ANP: $0.039) raised a further $1.6 million last week to prepare for expanding its current Phase II trial in Duchenne muscular dystrophy in Australia into a larger European study. Two of the company's major investors, Australian Ethical Investment and Platinum Asset Management, participated in the raise.

Duchenne muscular dystrophy (DMD) is a muscle wasting disease caused by mutations in the dystrophin gene. Muscles need dystrophin to maintain their structure.

The company is currently conducting a Phase II trial in DMD in Melbourne at the Royal Children's Hospital. That trial has recruited five of a total of nine boys (as of 18 January 2019), with full patient recruitment expected to be completed by the end of this month. Patients in the study, who are between the ages of 10 - 18, will be treated with the company's antisense drug candidate ATL1102, weekly for a period of six months.

The dose being administered is 25mg/week. To date one of the patients has completed the six month treatment course and no safety issues having been uncovered. Treatment of the nine patients is expected to be completed in Q3 this year with results out by year's end. The trial is an open label study, which leaves the possibility of earlier patient data becoming available.

On completion of the study, Antisense expects to move into a larger European study, regardless of whether positive efficacy signs have been observed in the current trial.

A limitation of the current study is the low dose of 25mg/week that is being investigated. Antisense had previously conducted a Phase II study with ATL1102 in relapsing-remitting multiple sclerosis (MS) (in 77 patients) with a positive efficacy readout (a 54% reduction in new active lesions). The dose explored in those adult patients was 400mg/week (16 times higher than the current study). However, there were some safety concerns at this higher dose, including platelet reduction in around one third of subjects and elevated liver enzymes. Both were reversible when treatment stopped and were easily managed.

Modelling has found that at lower weekly doses, including 200mg, 100mg and 60mg, activity of the drug in MS should still observed but without the adverse event of platelet reduction.

This previous data in adults treated for higher doses but for a shorter period of two months, gives Antisense some optimism for activity of the drug in children at a much lower dose but for a more extended period of time (six months). Antisense drugs accumulate in the tissue and so a cumulative effect can be expected with longer treatment.

Passing the safety hurdle in the current study will allow the company to consider higher doses in the forthcoming European Phase IIb, placebo controlled study (in 2020 likely) and treated for a longer period, potentially 12 months. These aspects still remain to be
determined by the company and will be selected following discussions with the European regulator.

The Phase IIb study could also be a registration study, requiring less than 100 subjects, if positive efficacy results can be achieved. The company may have sufficient drug material to conduct the Phase IIb study in Europe (and potentially in other regions) depending on the study design.

Outcome from Current Phase Ila DMD trial
All nine patients in the current DMD study in Melbourne will be wheelchair-bound. The main assessment will be changes in upper limb function, or more specifically, whether upper limb function can be maintained over the study, or if the decline in function can be slowed compared to the rate of decline expected. The rate of expected decline in function over a period of six months is well established according to Antisense CEO, Mark Diamond. Other markers to be analysed include inflammatory biomarkers.

Another potential benefit in the DMD studies, for longer periods and at lower doses, is that the safety profile of ATL1102 will be better characterised at lower doses, allowing for the potential pursuit of moderately higher doses for the treatment of MS in adults.

Rationale for Pursuing DMD with ATL1102
The reason Antisense is investigating ATL1102 for the treatment of DMD is because of findings by others and reported in 2015 that found patients with DMD who had higher levels of CD49d (part of VLA-4) on their T-cells experienced a more rapid and severe progression of their disease than those with lower CD49d levels. By coincidence, ATL1102 works by blocking production of CD49d. In the Phase II trial in MS, lymphocyte levels were reduced by 25% (T-cells) - 50% (B-cells), with the drug having a strong anti-inflammatory effect.

Very Low Hurdle in DMD
In September 2016, US biotech Sarepta Therapeutics received a controversial approval of its drug, Exondys 51, for the treatment of DMD, or more specifically, for 13% of boys with DMD. Through bypassing parts of the mutated dystrophin gene, it allows a truncated but functional dystrophin protein to be produced.

In 2018, Sarepta generated sales of US$301 million for the drug, up from US$155 million in 2017. However, the drug did not show a clinical benefit, with the third study of the drug, in only 13 boys, achieving only 0.44% levels of dystrophin compared to healthy subjects, up from 0.16% before treatment. The first study in 12 boys showed no difference in the six minute walk test. The second study compared results to historical controls and could not be considered by the FDA.

Exondys 51 failed to gain approval in Europe last year. The company is undertaking a confirmatory study with the drug. That trial is expected to be completed in May this year. Sarepta is currently conducting a US$375 million capital raising. The company has a market capitalisation of US$9.5 billion.

Intellectual property around Exondys 51 was licensed from the University of Western Australia, based on work conducted by Professors Sue Fletcher and Steve Wilton, who are both on Antisense Therapeutics’ Scientific Advisory Board. Of interest also is that one of the company’s directors, William Goolsbee, was previously a director (and chairman) of Sarepta.

For Antisense Therapeutics, any hint of benefit in slowing down progression of this disease should have a significant impact on the stock.

IP Around ATL1102
A US patent, which is under examination (for reducing circulating leukocytes) would give protection for ATL1102 out to 2031 (plus up to a five year extension) and a Use Patent has been filed that would expire in 2039 if granted.

Acromegaly Update with ATL1103
Antisense is also seeking to progress ATL1103 for the treatment of acromegaly, a disorder that arises from excessive production of the human growth hormone that stimulates high IGF-1 levels in circulation. The result is excessive growth in organs and other parts of the body including the hands and face.

Results from the Phase II study were reported in 2014. That trial treated 26 patients for 13 weeks at two doses; one at 200mg per week (one injection) and one at 400mg/week (two injections). The drug was well tolerated, with two patients experiencing raised liver enzymes (a common side effect with antisense drugs) and mild-moderate injection site reactions in most patients, which is another side effect of antisense drugs. This was better managed in the three higher dose patients (see below) through icing of the skin and use of microneedles. Worth noting is that all of the 13 patients in the 400mg dose group completed full treatment with only one patient in the lower dose group not completing treatment.

The results showed that an average 30% reduction in IGF-1 levels in the blood was achieved at the end of dosing at 13 weeks, and was higher in patients with a lower body weight (36% reduction at 14 weeks), indicating that a higher dose could be more effective. The highest reduction achieved in any single patient was a 64% drop in IGF-1 levels.

Higher Dose Trial in Three Patients
The company subsequently conducted a higher dose trial in three patients with acromegaly. It found that the average reduction in IGF-1 levels was 27% at week 13, slightly less than the lower dose, although two of the patients achieved a normalisation in their IGF-1 levels. In one of those patients, normalisation was achieved when the drug given for an additional period of 12 weeks, although dose had to be reduced due to a decrease in platelet levels in the blood. That patient had not previously been able to control his/her disease with other medications.

Commercialisation Path for ATL1103
Antisense has been approached by myTomorrows to make ATL1103 available to patients with acromegaly through a special access program, but on a commercial basis. Presumably ATL1103

Continued over
will be offered to those patients with acromegaly who are poorly served by existing medications, these being Octreotide, as a first line therapy, and Somavert as a second line treatment (at a cost of around $80,000 a year).

ATL1103 is being positioned as an alternative for a second line therapy with Somavert. In a post-marketing study with Somavert in 710 patients followed for up to five years, IGF-1 levels were normalised in 67.5% of patients. However, there were adverse events in around half of the patients (345) and serious adverse events in 19% (133) of patients. Somavert is expensive and also has a high demand on patients, requiring daily injections (compared to twice a week with ATL1103).

Antisense has sufficient ATL1103 material for the treatment of 10 patients with acromegaly for one year under the special access program (at a dose of 400mg/week), and may manufacture more product is there is sufficient demand. Whilst the product is approved for use in clinical trials, use under the special access program requires additional product data and documentation to be provided, which is currently underway.

Under the special access program, Antisense will generate real world data on the demand and utility for ATL1103 for the treatment of acromegaly. A larger Phase II/III trial would need to be undertaken by a partner, to look at longer dosing – greater than three months – and potentially higher doses. In the Phase II study it was found that IGF-1 levels were continuing to decline at the last dose, with a steady state treatment effect expected to take up to five months, given the long half-life of the drug in the tissue of more than four weeks.

**Market Size for ATL1103 in Acromegaly**
The initial application for ATL1103 would be as a second line therapy for those patients not well served by the drug Somavert, which is around one third of patients on second line drug therapy. Somavert is generating annual sales of around US$280 million, which presents a market opportunity to Antisense for those patients not well served with current drug treatments of around US$140 million a year.

**Summary**
Antisense Therapeutics is capitalised at $16 million. The main focus for the company at this point is ATL1102 for the treatment of DMD, for which there exists a very low therapeutic hurdle, and for which drug pricing is very high. A serendipitous discovery that the disease is impacted by CD49d expression on T-cells which ATL1102 has been shown to inhibit has opened a new and potentially valuable commercial path for the company.

The company has also substantially improved the quality of its register through the introduction of two large investment funds.

At the end of last year the company had $2.9 million in funds, plus an additional $1.6 million that has recently been raised. An R&D tax incentive refund is expected. The company also has options due to expire in December this year (exercise price of $0.08) which could bring in $5.5 million in funds if exercised.

**Bioshares recommendation: Speculative Buy Class B**

(This extract contains minor factual corrections to the original article.)
How Bioshares Rates Stocks

For the purpose of valuation, Bioshares divides biotech stocks into two categories. The first group are stocks with existing positive cash flows or close to producing positive cash flows. The second group are stocks without near term positive cash flows, history of losses, or at early stages of commercialisation. In this second group, which are essentially speculative propositions, Bioshares grades them according to relative risk within that group, to better reflect the very large spread of risk within those stocks. For both groups, the rating “Take Some Profits” means that investors may re-weight their holding by selling between 25%-75% of a stock.

**Group A**

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<th>Stocks with existing positive cash flows or close to producing positive cash flows.</th>
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<tr>
<td><strong>Buy</strong></td>
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<td><strong>Accumulate</strong></td>
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<td><strong>Hold</strong></td>
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<td><strong>Lighten</strong></td>
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<td><strong>Sell</strong></td>
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<td>(CMP–Current Market Price)</td>
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**Group B**

Stocks without near term positive cash flows, history of losses, or at early stages commercialisation.

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<tr>
<th>Speculative Buy – Class A</th>
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<td>These stocks will have more than one technology, product or investment in development, with perhaps those same technologies offering multiple opportunities. These features, coupled to the presence of alliances, partnerships and scientific advisory boards, indicate the stock is relative less risky than other biotech stocks.</td>
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<th>Speculative Buy – Class B</th>
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<td>These stocks may have more than one product or opportunity, and may even be close to market. However, they are likely to be lacking in several key areas. For example, their cash position is weak, or management or board may need strengthening.</td>
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<th>Speculative Hold – Class A or B or C</th>
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<td>These stocks generally have one product in development and lack many external validation features.</td>
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