Friday, 16 October 2020

RESEARCH REPORT

CORPORATE CONNECT

Antisense Therapeutics (ANP)

And a Door Opens Wide

Share Price & Estimated Future Price

12-Month Target*	$0.305
Price	$0.14
Implied Return	118%

*Implied Return

Antisense Therapeutics' lead drug sits at the nexus of two areas of drug development that are starting to grow dramatically in importance. One relates to its mode of action and the other to the type of drug it is. Combine that with management who know the drug very well and strong results in a trial in a horrible disease afflicting children, and you have the basis for true value creation.

Introduction: Antisense Therapeutics' lead compound, ATL1102, is, essentially, a highly targeted anti-inflammatory drug and, over recent years, the role of inflammation in many diseases is becoming apparent. The indication the company is using it for is a terrible disease called Duchenne muscular dystrophy (DMD), which causes the muscles of young boys to start to waste before the age of five, ultimately leading to their death in their late teens or early 20's.

ATL1102 works by knocking down gene expression, the product of which allows the cells likely responsible for much of the muscle wasting to migrate into position to cause it. Evidence supporting the clinical trialling of ATL1102 is robust, consisting of independent basic and clinical research, as well as evidence from Antisense, which includes a peer-reviewed article on a previous clinical trial of ATL1102 in MS, as well as the results of a Phase II trial of the drug in DMD. ATL1102 was safe and all of the clinical and non-clinical data pointed towards the drug materially improving the disease.

To Market and Beyond: Antisense is aiming for marketing approval in DMD boys who can no longer walk (non-ambulant). The indication provides for all of the regulatory designations that help to get a drug to market, including rare paediatric disease designation (RPDD). RPDD could provide USD100m to the company, via the sale of a priority review voucher, right when the company is preparing to market ATL1102, if Antisense is not bought out or licences ATL1102 first. Importantly, there are no drugs for non-ambulant DMD boys and the development landscape is barren, except for ATL1102. Once on market, the revenue ATL1102 can generate is extremely large, particularly, given the three truly novel branded drugs have list prices of USD700k/year and medication use is chronic. A medicine very similar to the generics currently used to treat DMD, and approved for the indication, has a list price in excess of USD100k per year. At these prices, with approximately 20,000 DMD patients overall in the US, the addressable market for ATL1102 is substantial

Further Indications: The role of inflammation in many diseases is only now being truly understood. The obvious next indications to trial ATL1102 are the other muscular dystrophies, which add another 125k patients to ATL1102's ultimate applicable market. The molecule ATL1102 targets is also implicated in other diseases, providing opportunities beyond the muscular dystrophies and, if fleshed out, an even stronger reason for larger biopharmaceutical companies to look at Antisense.

Valuation: We have valued Antisense based on a probability weighted discounted cash flow model that assumes revenues only from the non-ambulant DMD. Other potential indications represent unaccounted for upside. **We have arrived at a 12-month price target of 30.5 cents per share, which gives the company a predicted market capitalisation of $149 million.**

Analyst: Marc Sinatra, BSc(Hons), MBA.

Company Information

ASX Ticker	ANP
Shares on Issue	489.0 million
Fully Diluted Shares on Issue	534.0 million
Market Capitalisation	$68.5 million
ASX Vol. (Shares/Day)	2.4 million

Cash Sufficiency

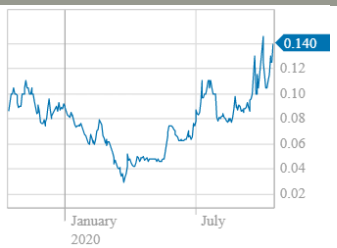
	$ Million
A) Last Appendix 4C	End June 2020
B) Cash and Equivalents at 4C	4.1
C) Burn[1]	1.4
D) Quarters Cash Remaining[2]	2.9
E) Estimated Current Q Burn[3]	0.2
F) Estimated Cash Raised Post 4C[4]	0.0
G) Estimated Current Cash[5]	**3.9**

1 Burn = Net Cash from/used In Operating Activities; **2** Quarters Cash Remaining = B/C;
3 Equals C *(# Days Since previous Q end Q4 / # Days in Current Q);
4 Equals Capital Raising(s) – Estimated Costs; **5** Equals B – E + F

Key Personnel

Mr Robert Moses	Chairman
Mr Mark Diamond	MD and CEO
Mr William Goolsbee	NED
Dr Graeme Mitchell	NED
Dr Gary Pace	NED
Dr George Tachas	Director, Drug Discovery and Patents
Nuket Desem	Director of Clinical and Regulatory Affairs

Chart



And a Door Opens Wide

Sometimes you can have a drug that hits a particular target or molecule in the human body, which has a biological effect, shifting the way the body works. The hope is that the biological effect that is created will have a beneficial effect on a disease. The whole process, though, is complex. The target you hit can be outside a cell, in the bloodstream for example, it can be on the outer surface of cells, on its cell membrane, or it can be inside a cell. Even within a cell, there are different areas where the molecule could exist. Then the molecule the drug hits must change what other molecules do. It can be as simple as removing a 'bad' molecule that causes damage or as complex as hitting a target that interacts with, and affects, a whole series of molecular pathways involving many other molecules, within, on or outside cells. Very often, our scientific understanding only covers small window of what lays ahead for a drug that has just entered the body.

The point is, you can find a target that works for one disease, but never fully understand the biology of the target, exactly why it is relevant to the disease you know it affects or how it might be useful in other diseases. It takes discovery and time to develop the level of understanding of these things to make full use of the target.

The same level of complexity can be found in applying a new technology. It might be easy to see how the technology could be generally useful, but navigating the complexity of the human body and the hurdles it creates to implementing the technology in a useful way often are not easily seen or overcome. By definition, a new technology means it has never been used before and, at best, the issues in implementing it will only be similar to those that other technologies have encountered. As with drug targets, it takes discovery and time to develop the level of understanding with a technology to make full use of it.

It can be strongly argued that ATL1102, a putative therapeutic from Antisense Therapeutics, was before its time on both of these fronts. **More importantly, it looks like research, both pure and applied, has caught up with the compound (therapeutic/drug/molecule), such that Antisense is now ready to exploit that fact.**

The way things have unfolded, the target ATL1102 hits appears to be a key molecule in inflammation, which, in turn, appears to be a major contributing factor, if not the factor, in many disease states. Many of the hurdles to its general type of technology, which knocks down expression of a gene, have also been overcome, with the first approved drugs based upon it now having received marketing approval.

It looks like the door is now wide open for Antisense to make its mark in drug development. Most importantly for investors, that means value creation can start to ramp up at incredible rates.

Introduction

Often a technology will come along or be envisioned before it is ready for application. The first therapeutic monoclonal antibody (mAb) was approved by the US Food and Drug Administration (FDA) in 1986 (Lu et al (2020) J Biomed Sci). It was called OKT3 or muromonab and was indicated for transplant patients who had become steroid resistant. It would not be for another eight years, until 1994, for the second mAb therapy, abciximab (ReoPro®, Centocor Biotech Inc), to be approved for preventing blood clots during coronary artery procedures like angioplasty. Another mAb therapy came in 1996, two more in 1997 and four in 1998. There was then a lull until 2001 and then things started back up again, but it was not until 2014, when six new mAb therapies were approved, that the record of four in 1998 was beaten. There are now 79 FDA-approved mAb therapeutics.

The next big thing after mAbs was supposed to be a range of ribonucleic acid or RNA-based drugs in the 2000s. Like mAbs, it has been a case of not quite there yet, for quite a while. However, RNA companies, like Alnylam Pharmaceuticals (NASDAQ: ALNY) and Ionis Pharmaceuticals (NASDAQ: IONS), now have FDA-approved RNA-based products. The biggest is Moderna Inc (NASDAQ: MRNA), at USD25.2 billion, who does not have a product on market yet. It is, however, one of the front runners in the race to produce a vaccine to prevent COVID-19.

This report focuses on an Australian biopharma that was listed off the back of a strategic collaboration between Circadian Technologies (formerly ASX: CIR; now Opthea, ASX: OPT)–a key player in Australia's biotechnology scene at the time–and USD6.5 billion Ionis Pharmaceuticals (then known as Isis Pharmaceuticals), which was probably the first major player in the gene knockdown/antisense space. That company is ASX-listed Antisense Therapeutics (ANP).

Antisense had the rights to several RNA-based antisense drugs, each to different targets. This report, however, will only focus on one antisense therapeutic, ATL1102, and its target, CD49, a protein that is a key part of a larger protein called very late antigen 4 or VLA-4. VLA-4 plays a major role in bringing or recruiting immune cells to inflamed areas of blood vessels and, then into the inflamed tissue beyond.

What is both interesting and exciting about ATL1102 is that it sits within two areas that are almost certain to bring about major improvements in the health and healthcare of many people. One is that it is a member of the RNA-therapeutics class, whose time is rapidly approaching, if not here. The other is that it is a member of the anti-inflammatory class of therapeutics and a fairly specific one at that.

While inflammation is a positive process that indicates the body is on the road to healing itself, when inappropriately triggered the inflammatory process can have hugely negative impacts.

For example, the virus SARS-CoV-2, which inside the body causes the disease COVID-19, would not be nearly as lethal if the immune system did not over-react to the virus' presence. Most of those who have died, and will die in this pandemic, die of a disorder called acute respiratory distress syndrome (ARDS). ARDS is the result of the immune system flooding the lungs, throwing their normal homeostatic (self-correcting) mechanisms out of kilter and rendering them incapable of absorbing enough oxygen to sustain life. In this example, acute or short-term inflammation of the lungs is the culprit.

Chronic (long term), low-grade, inflammation seems to be linked to just about everything these days. From heart failure and kidney failure, to some cancers and on to metabolic diseases, like diabetes, even aging itself is thought to be dictated by chronic inflammation, at least to a certain extent. The area is so broad, it is difficult to find a reference to cite to further your knowledge in the area. Nonetheless, Straub and Schradin (2016) Evol Med Public Health looks at the evolutionary trade-off between beneficial acute inflammation and harmful long-term inflammation.

ATL1102: The History

ATL1102 is designed to knockdown the expression of the gene that encodes the protein named CD49d. It achieves this through a cell's response to the presence of double-stranded nucleic acid molecules other than the cell's DNA. The following provides an explanation.

Our chromosomes are made up of double-stranded DNA and, when you are referring to a particular gene, the sense strand is the one that tells you what will be made out of it. The other strand, due to the way in which the strands of DNA bind, has the exact opposite structure to the sense strand and, therefore, someone called it the 'antisense' strand and the name stuck. The company's DNA is a bit different to that contained in our cells. It has been specifically designed, not to bind to another DNA strand, but to a temporary copy of CD49d that exists as an intermediate. That temporary copy performs two roles at once. Firstly, it is the means by which the plan for CD49d, contained in the DNA of the CD49d gene, is carried out to the ribosomes, where proteins are made. The copy is also the plan for the protein. Ribosomes are, effectively, the builders, reading off the plan of the copied DNA. They grab a protein building block or amino acid based on the plan and attach it to the one it picked up before. The ribosomes keep doing this until they have read all of the plans off the copy and the complete CD49d protein is made. The process described is generalised and applicable to the way all proteins are made. The copy of a gene is made out of similar molecules that DNA is, termed RNA. In keeping with the delivery theme, RNA copies of the genes of DNA are called messenger RNA or mRNA.

It was discovered in the 1990's that cells have enzymes which don't like to see mRNA bound to anything. The reason is that through evolution, this is what viruses often look like and it is a protective mechanism against them. If they do see mRNA bound to anything, they move in and cut it up. As it turns, because DNA and RNA are so similar, single-stranded RNA will bind other molecules of RNA if, like the two strands of DNA, they are 'opposite' in structure to each other. In the same way, a strand of DNA and RNA will bind to each other.

Scientists worked out pretty quickly that they could exploit the situation, where mRNA bound to anything would be cut up. Single-stranded DNA can be designed in the laboratory so that it is the opposite of a particular mRNA. In a cell, the strand that the DNA binds to is opposite to the mRNA. The enzymes move in and the DNA-RNA complex is cut up.

Gene expression is the whole process of mRNA copies being made from DNA genes, with the mRNA then going to see the ribosome afterwards to have what they encode built. What Antisense's technology does is stop the expression of certain genes because it creates these double-stranded complexes with RNA. The DNA-based drug is said to knockdown expression of the particular gene. ATL1102 specifically knocksdown the mRNA of the CD49d.

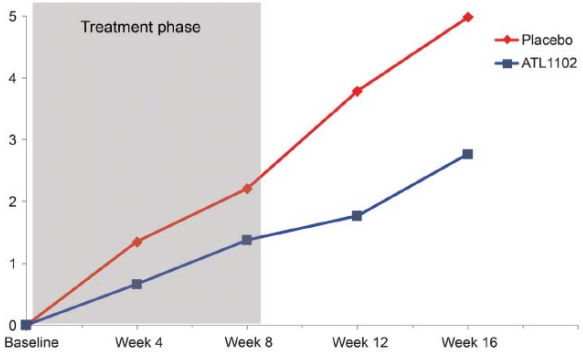
There is one contradiction that needs to be cleared up. We have put Antisense's DNA drug in the same class named for RNA-based drugs. RNA is used by most companies to knockdown gene expression and it was the original way the technology was designed. As it turns out, DNA can do the same thing and companies, like Antisense, use DNA and RNA hybrid because they feel it works better.

ATL1102: Its Early Signs of Activity

ATL1102 has been shown to be biologically and clinically active before. Antisense demonstrated this in a Phase II clinical trial in patients with relapsing-remitting multiple sclerosis (MS), the earliest clinical stage of MS. It was a multicentre, randomised, double blind, placebo-controlled study, such that it had all the components of a gold standard clinical study. Seventy-four (74) patients were recruited into the study, representing the intention-to-treat (ITT) study population. Seventy-two patients completed the study, representing the per protocol population (PP).

It is important to know whether the trial results you are looking at are based on the ITT population or a PP population. The reason is the FDA and other regulators will only give weight to the ITT population, because the results in that population better reflect what happens when the drug is on the market. However, companies developing a drug may look at the PP population to answer some questions. Unfortunately, some companies have announced results from a PP population, when the results from the ITT population have not been very good. When you see a company, be clear about what they are presenting as a positive signal. It is a little thing from which investors can often get a good idea about a company's transparency.

Figure 1.Cumulative New Active Lesions.



MS is a progressive autoimmune disease that attacks the nerves in the brain. These lesions cause problems with movement and other aspects of normal human functioning. The primary endpoint for most therapeutic studies is based on slowing the development of new lesions and that was the case in Antisense's MS trial.

Autoimmune diseases occur when a person's own immune system starts to attack a particular part of their body and the immune system is the link between MS and inflammation.

The results of that trial are given in figure 1 and come from the main scientific journal article on it. The article can be found here: Limmroth et al (2014) Neurology. These lesions can be broken down into further types of lesions, but, in terms of the primary endpoint of the study and understanding this report, this is as far as we need to go.

The results are clear. ATL1102 significantly reduces the number of lesions that develop in MS patients.

Teva Pharmaceuticals (NYSE: TEVA, Market Cap: USD10.6 billion) did licence ATL1102 from Antisense for MS in the late '00's. Unfortunately, an adverse event was observed during a long-term animal toxicology study of ATL1102. Had this event not occurred, Teva may well have continued developing ATL1102. However, the occurrence of this adverse event did raise the possibility that the long-term toxicology study would need to be repeated, which would have pushed out the eventual regulatory approval of ATL1102. It may also have raised the possibility that if the issue repeated itself, regulators would require a warning be added to ATL1102's product label. Doctors pay attention to such warnings and will preferentially use drugs without them and drugs with softer warnings. All of these factors play into the thinking of a large pharmaceutical company.

The issue that occurred in the animal study has not been seen in clinical trials of ATL1102.ATL1102 could still become a useful MS therapeutic, although it will need further MS research and, maybe, the post-market competitive landscape to break in its favour.

The history of ATL1102 and MS supports an important point. If ATL1102's target plays a significant role in a disease, ATL1102 is likely to provide a clinical benefit in that disease. Consequently, Antisense has been, and is, looking for diseases where CD49d plays an important role.

Another CD49D Dependent Disease

In 2015, the results of various experiments became a very comprehensive study of CD49d and how it was expressed in boys with DMD. The study, Pinto-Mariz (2015) Skelet Muscle, showed that the percentage immune cells CD4+CD49d^{hi} and CD8+CD49d^{hi} (CH8+ denotes cytotoxic T or T_C cells, while CD4+ denotes helper T cells or T_H cells) increased with increasing disease severity and in boys whose disease was progressing faster than others. Additionally, the group looked at the biological role of CD49d in DMD patients. They found CD4+CD49d^{hi} and CD8+CD49d^{hi} cells isolated from DMD boys migrated more quickly through blood vessel walls than those isolated from non-DMD boys. CD49d binds fibronectin molecules and fibronectin is a component of the extracellular matrix (the matrix between cells in the body). As such, the investigators looked at the ability of CD4+CD49d^{hi} and CD8+CD49d^{hi} to move through a fibronectin lattice. They found the same thing that they found in the blood vessel wall experiment, the cells from DMD migrated through the fibronectin lattice faster than those from non-DMD boys. Moreover, the cells from wheelchair bound DMD boys migrated faster than those from boys that were ambulatory.

Overall, the study overwhelmingly highlights that CD4+CD9d^{hi} and CD8+CD49d^{hi} cells are clearly involved in the progression of DMD. They also show *in vitro* that CD49d allows the cells to move through blood vessel walls and through a lattice made of fibronectin. In terms of a moving picture, CD4+CD9d^{hi} and CD8+CD49d^{hi} move out of the bloodstream and through the extracellular tissue to the sites of inflammation in DMD boys. Most importantly, from the point of view of Antisense, this study provided excellent evidence for the role of CD49d in the progression of DMD and clearly supports the hypothesis that ATL1102 can have a meaningful clinical benefit in DMD.

Duchenne Muscular Dystrophy

DMD is the result of a mutation on the X-chromosome that reduces or eliminates the production of a protein called dystrophin. There is conjecture about the various roles dystrophin plays throughout the human body, but it is clear that a key role is in skeletal muscle contraction. DMD is a recessive disease, such that only one functional copy of the dystrophin gene is required for a person to avoid the disease. Males, of course, only have one X chromosome, meaning they need to get a functional copy of the dystrophin on that one X chromosome or they will develop DMD.

In terms of natural history, the age at which boys start to show signs of DMD varies, but essentially all boys with DMD have started to show signs by the age of five. Underlying the symptoms that DMD patients display, is a gradual persistent muscle wasting, causing a decline in a sufferer's physical ability to do pretty much everything. Marking this physical decline are two key events. The first is the loss of the ability to walk. This, generally, has occurred by the age of 12. The next one varies between DMD patients, but it is the cause of their death (COD). The heart muscle and the muscles required to breathe are both affected in DMD boys. With medical improvements, heart failure has become the main COD in DMD. DMD boys also lose the ability to clear their lungs. This leads to frequent infections and it, ultimately, can lead to death. It appears to be the second leading cause of death. These two CODs appear to account for about 80% to 90% of DMD deaths. Before home ventilation was available, the COD of DMD patients was invariably the loss of the ability to breathe. The longest a patient with confirmed DMD has survived is 35 years. The vast majority, however, die in their late teens or early 20's.

Females can get DMD, but it is extremely unlikely, because they have two X chromosomes and must inherit two dysfunctional copies of the DC49d gene. Essentially, a *de novo* mutation must have occurred in the father's sperm or the father must have DMD. The latter becomes unlikely due to the physical decline DMD patients suffer. The incidence of female DMD is estimated at one in 50 million. In terms of prevalence, that number suggests that there are roughly 10 women/girls living with DMD in Australia at any one time. In fact, the occurrence in females is so rare, that even one in 50 million is likely to be only a ball park figure.

How the Absence of Dystrophin Affects Muscles and the Role of the Immune System

At a molecular level, a skeletal muscle contraction starts with two molecules, myosin and actin, each in the form of a filament in a muscle cell or myocyte. A neuronal signal to contract creates a reaction that causes the myosin and actin filaments to move in way that they become more overlapped and shorter. In isolation, this would not have an effect on the myocyte or the muscle as a whole.

A group of proteins, termed the dystrophin glycoprotein complex, is central in ensuring the integrity of the contractile myosin and actin filaments inside the myocyte and an extracellular connective tissue layer surrounding the myocyte termed the basal lamina. The basal lamina creates a network of flexible, yet strong, connective tissue that helps to maintain the structure of the muscle as a whole, while stabilizing each myocyte. Dystrophin is thought to be the key protein in the complex, sitting in the myocyte membrane and acting as a focal point for attachment to the cytoskeleton of the myocyte and the basal lamina outside of it.

Obviously, DMD boys can still contract their muscles even though they lack dystrophin. Consequently, it is clear dystrophin does not play the dominant role in passing the contractile activity within a myocyte to the basal lamina and beyond. Instead, dystrophin is thought to function to protect the myocyte and, specifically, the myocyte cell membrane from the forces created during muscle activity. Under this hypothesis, if dystrophin is removed from the equation, muscle movement causes damage to the myocyte.

The immune system is generally thought of in terms of the protection it provides from infection due to bacteria, viruses and the like, as well as the offensive activities against invaders should an infection take hold. However, it has an equally important role in the repair of damaged tissue whether it is the result of an invader or not.

There is strong evidence that immune cell invasion of the muscles of children with DMD precedes symptomatic onset of the disease. Immune cell invasion is also really the only explanation for the inflammation seen in the muscles of DMD patients throughout their lives.

The specific immune cells found within DMD muscles are capable of causing considerable damage. Normally, when a tissue is damaged, various immune cells receive signals of the damage and migrate to it. They then clear away damaged cells and debris, leaving the way clear for tissue regeneration to occur. In DMD patients, though, the damage is continual and, due to the nature of the immune system, a state of chronic inflammation occurs. To frame this in a simplistic context, the immune system ends up stuck in the destructive phase of tissue repair and is constantly clearing away damaged cells and cellular debris. The longer this goes on, the more the muscle will decline and will continue to decline until the function of certain muscles falls below that required to sustain life.

Part of the therapeutic regimen for DMD patients are corticosteroids (CS). CSs can be given topically or systemically, either through ingestion or injection. The reason they are given to DMD patients is that they decrease both the level of inflammation and the activity of the immune system. They are a fairly blunt instrument for doing so, though, with little specificity regarding the source of inflammation or nature of the immune response. Given that an appropriately active immune system is required for humans to stay healthy, the side-effects of longer-term CS therapy tend to rule out their use unless the disease is severe, like DMD.

The reason for raising the use of CSs in this report is that they have been shown to improve muscle strength and function over one year and muscle strength for up to two years (Matthews et al (2016) Cochrane Database Syst Rev). The authors of the review of CSs use in DMD patients cite a lack of studies examining CS use for longer than year as the probable reason an improvement in muscle function has not yet been shown for a period greater than a year. Based on the findings of the study conducted into DMD boys we looked at earlier (Pinto-Mariz (2015) Skelet Muscle), CSs would be expected to have this effect given the immune cells involved. In this way, the success CSs support the hypothesis that ATL1102 will have activity in DMD. One could even argue, quite strongly, that ATL1102 will have a stronger effect than CSs because it is infinitely more targeted and the long-term side effects will be considerably lower for the same reason (i.e. ATL1102 leaves much of the immune system untouched, unlike CSs, and, as a result, shouldn't display the same breadth or depth of side effects). **At the end of the day, the mechanism of action of ATL1102 is different to, and much more precise than that of CSs, which is a significant differentiating feature of the two treatments.**

ATL1102: Data Trumps Theory

Everything in this report so far suggests ATL1102 will be clinically active in DMD patients. There is a big difference between 'suggests' and 'is' and that is why regulators like the FDA won't approve a drug without direct evidence that the drug works as intended in the precise patient group it is intended for.

About the Trial

Antisense's first trial of ATL1102 was a single arm, open label, study in nine non-ambulatory patients. Overall, this is a pretty typical trial design for a therapeutic being studied in a disease for the first time. Single arm means there is no control group. The term open label means the patient, the doctor and anybody else involved in the study knows what the patient is receiving. The vast majority of single arm studies are open label. The really interesting part of this study is that it is being undertaken in non-ambulatory DMD, some might say wheelchair-bound patients, where non-ambulatory is defined as a patient who can walk no more than 75 metres in a six-minute walk test. A six-minute walk test is pretty much as it sounds. Most of the research and clinical trials in DMD have been focused on patients who are ambulatory. The reason for this seems likely to be that ambulatory patients are younger and, therefore the ability to prolong life and the quality of it, more significant. Nonetheless, the therapies developed so far will not stop them from becoming non-ambulatory, nor from seeking other treatments. In terms of therapeutic development, whether a drug is studied in ambulatory or non-ambulatory patients is likely to have significant impact on the developmental and commercial prospects of a drug.

While there is a formal list of primary and secondary endpoints for this study, it is probably easier to understand if stated in a different way, at least, initially. Antisense really wanted an answer to one question with two parts out of this trial. The question is, has ATL1102 shown enough promise in treating non-ambulatory DMD in terms of safety (part 1) and signals of efficacy (part 2) to justify studying it in larger, more expensive, trials? Safety is the main component of the first study of any drug in a distinct indication, where distinct indication refers to diseases and populations examined in previous studies. Signals of efficacy refers to evidence the trial uncovers that ATL1102 may 'work' in DMD patients. A trial of this nature is simply not designed to determine if ATL1102 'works' or, more correctly, is efficacious. A much larger and more expensive randomised controlled trial (RCT) is required for that. Antisense is simply taking a prudent approach to risk by doing things the way it is. The regulators, on the other hand, in allowing a trial want to know that patients are not being exposed to too much risk, particularly where safety is concerned.

The Results

The efficacy results from the study, as announced by the company are given in Figures 2 A & B (page 7) and Figure 3 (page 8).

In Figure 2A, PUL2.0 refers to the Performance of Upper Limb Module, version 2.0. It is a functional scale specifically designed for assessing upper limb function in DMD patients (Mayhew et al (2013) Dev Med Child Neurol). It looks at three domains (shoulder, mid-elbow, distal-wrist/hands) and includes measurements related to activities of daily living. Given the fairly consistent progressive nature of DMD, PUL2.0 scores would be expected to decline in untreated and CS treated patients (Pane et al (2018) PLoS One). The mean in the ATL1102 treated patients is suggestive of an approximate one-point improvement, which goes against the natural history of DMD. (Pane et al (2018) PLoS One). A solid number to reflect a clinically significant improvement in PUL2.0 could not be found. There is a way around this, which is covered further on in our Figure 3 data summary.

The MyoGrip and MyoPinch results were done according to accepted practice and taken using the dominant (dom) arm and are given in two forms. The raw results are expressed in kilograms, while a normalised value is given as percentage predicted. The reason for normalising values is that DMD patients are young and growing for the most part (Hogrel et al (2020) J Neurol; Hogrel Interview (2020) First Author Grip Strength Study). Growth and the increase in muscle mass that comes with it can compensate for the loss of grip strength due to DMD. From a time-course perspective, younger DMD patients' growth more than compensates for the theoretical loss of grip strength that would have occurred had they not been growing. After the age of approximately 12 years, muscle wasting due to DMD starts dominating physical growth and recorded grip strength starts to decline over time, with muscle wasting becoming more dominant over growth until growth ceases.

Normalising the grip strength data makes perfect sense, based on the rationale above, and, given the older age of non-ambulant DMD boys, the process of normalising the results improves the raw results. As a general rule, though, the less data is manipulated, the more regulators are likely to accept it. This is particularly so if the changes over time work against a benefit being shown by an intervention, in this case ATL1102.

The MyoGrip and MyoPinch data, again, suggest a trend toward better grip and pinch strength as a result of treatment with ATL1102. Figure 2B compares the MyoGrip and MyoPinch scores from the ATL1102 study with a historical control, with statistical testing being used to provide a measure of the difference. The historical control was drawn from Ricotti (2016) PLoS One and consisted of nine boys, eight of whom had been on CS. In the ATL1102 study, eight of the nine patients were CS.

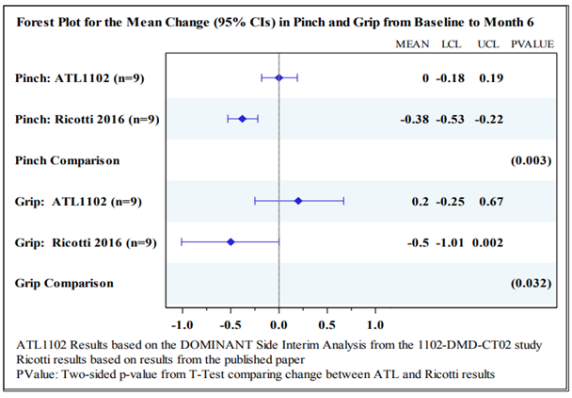
Normally, when analysing a company, it is best to conduct the analysis in chronological order to consider company events in the context of the external events of the day and to understand how the company evolves.

Figures 2 A & B. Clinical Data from the Phase II Trial of ATL1102 in Non-Ambulant DMD Patients.

A. PUL2.0, MyoGrip, MyoPinch, Respiratory Forced Vital Capacity & Peak Expiratory Flow as a Percentage of Predicted.

	Change from Baseline to Week 24						
Patient No.	PUL 2.0	MyoGrip (dom) (Kg)	MyoGrip (dom) (% Pred)	MyoPinch (dom) (Kg)	MyoPinch (dom) (% Pred)	% Predicted FVC	% Predicted PEF
01-001	+2	-0.63	-4.49	0.03	-0.62	-3.20	6.30
01-002	+2	0.22	0.49	-0.02	-0.29	-14.8	-17.3
01-003	0	0.68	1.02	-0.40	-6.59	-9.10	8.70
01-004	+2	1.09	1.01	0.37	2.99	0.80	7.20
01-006	-3	-0.27	-0.60	0.07	0.94	-6.50	6.90
01-008	+7	1.00	1.11	0.30	2.77	-7.70	-18.2
10-009	0	-0.33	-3.75	-0.22	-4.97	-9.10	-4.30
01-010	0	0.05	0.11	0.06	0.72	-0.40	9.20
01-011	-2	0.11	-1.31	-0.18	-3.63	-1.10	2.00
Mean Change (95% CI):	0.9 (-1.33, 3.11)	0.2 (-0.25, 0.67)	-0.7 (-2.33, 0.90)	0.0 (-0.18, 0.19)	-1.0 (-3.56, 1.63)	-5.68 (-9.60,-1.76)	0.06 (-8.33, 8.44)

B. Comparison of the MyoGrip & MyoPinch Trial Data Compared with a Historical Data Set.



Source: Antisense Therapeutics Limited.

By bringing two or more events separated by reasonable amounts of time, you can miss how one event may have led to another event and the signal that it provides. However, there also times where you want to compare two events to get a view of the totality of similar events. In researching this report, we looked at events in chronological order, and decided the time gap between the events we have been looking at and the one we are about to look at do not provide a signal. Consequently, it is better to see these two events together.

First, we will examine the nature of single arm trials and comparisons to external controls.

A great degree of care needs to be taken when comparing the results of a single arm trial to a control group that was not collected using the same protocol at the same time and even in the same hospital or hospitals. Biases in the data can emerge at a later date or, worse, the bias may not emerge but become apparent when a later stage trial, based on a comparison to external controls, fails. That is not to say that single arm trials are bad or that they are done by a company to avoid possible failure. **Single arm trials are almost always done because they have been shown to be the most cost-effective way to get the answers researchers need to progress the development of a drug.**

To its credit, Antisense has undertaken a further post-study analysis, this time comparing the PUL2.0 results obtained in their Phase II trial with a cohort from a natural history database of DMD patients held in Rome, Italy. The defining feature of this analysis was that the external control was generated by applying the inclusion/exclusion criteria to the database. These criteria define who can and cannot participate in a study. By doing things this way, it removes human bias from the process of selecting an external control and human bias is one of the main reasons you need to be wary of external controls.

Figure 3 provides the recent results of Antisense's analysis of ATL1102 on PUL2.0 to the external control. Previously the company compared the performance of ATL1102 on MyoGrip and MyoPinch to a published historical control (Figure 2B). The company looked at PUL2.0 on the stated basis that PUL2.0 was the generally accepted primary endpoint for pivotal or registrational studies, which is clearly reasonable. Moreover, the Rome database did not contain MyoGrip and MyoPinch scores.

The inclusion/exclusion criteria identified 20 patients for the Rome cohort (RC) on which 39 six-month assessments had been done, compared to nine patients and nine assessments for ATL1102. The RC was slightly older than the ATL1102 cohort, at a mean of 15.6-years old and 14.9-years old, respectively. The total PUL2.0 mean was slightly lower in the RC compared to the ATL1102 cohort, at a mean of 20.2 compared to 24.8, respectively. The standard deviation of the mean total PUL2.0 was lower in the RC

than the ATL1102 cohort, at 3.8 compared to 9.6. This difference likely arises due to the use of an average of 1.95 measurements from each of the 20 patients in the RC, compared to one measurement from each of the nine ATL1102 patients.

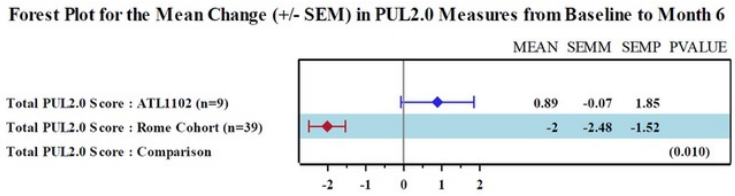
The PUL2.0 score of -2 for the RC and +0.89 for the ATL1102 cohort, suggests quite clearly that ATL1102 had a beneficial effect on the patients who were given it. Statistical testing comparing the mean PUL2.0 scores from each group indicated a difference between them in favour of ATL1102. Since the p-value was strong (p=0.01), the use of more than one measurement from the patients in the RC cohort probably has not affected the result overall, via a tighter standard deviation.

It is also good to see a PUL2.0 external control cohort in the numbers available for investors to assess. This gives additional weight to the historical control comparison on grip, pinch and MRI, which used all nine of the patients from Ricotti (2016) PLoS One assessed at six months

Overall, Antisense has produced a large amount of data from a small study for investors to look at and more data is always a good thing, as long as it has been adequately explained, which it has.

With small data sets like this, it is important for the company and for investors not to put too much weight on any one analysis of the data. The numbers are too small and can be misleading. What is important is to look at the data in totality.

Figure 3. Comparison of the Results from the Phase II ATL1102 Study to an External Control Generated with the Phase II inclusion/Exclusion Criteria.



Source: Antisense Therapeutics Limited.

Antisense has provided data on three different measurements of upper limb function and strength, plus two external control groups for comparative purposes. What we see when we look at the data is a measure that has been used for a long time and is comprehensive, despite being of qualitative origin. Then you have two more specific measures. They are not as comprehensive, but they are quantitative. Finally, a further two historical controls, which, to a large extent, are really only putting numbers to something that is about as absolute as you will get and that is the natural history of DMD. The natural history of DMD tells us that the muscle function as determined by PUL and grip and pinch strength of untreated boys consistently declines and boys on CSs they still consistently decline.

All of the data we have seen points in the right direction for ATL1102. The data suggests that some boys, at least, do not decline. Almost by definition, that must be clinically meaningful. Additionally four out of nine patients showed clinically meaningful improvements as viewed by experts in DMD.

Peripheral Blood Lymphocyte Readings

The final collection of data from Antisense's Phase II of ATL1102 in DMD, are peripheral lymphocyte white blood cell counts. These results are shown in Figure 4 (page 9).

CD3 is a cell surface marker that largely denotes the collection of CD4+ and CD8+ cells or the broadest group of cells relevant to the populations of interest from the Pinto-Mariz (2015) Skelet Muscle study. From there, measurements of CD4+ and CD8+ cells follow, after which we get into the overall number of cells expressing CD4+ & CD49d+, and CD8+ & CD49d and then on to the specific population of cells of interest, CD4+ & CD49d+^{hi} expressors, and CD8+ and CD49d+^{hi} expressors.

The first thing we noted is that the relative populations of cells seem to align extremely well with the results from Pinto-Mariz (2015) Skelet Muscle. This is particularly true with respect to CD3+, CD49d+, as well as CD4+ & CD49d+, and CD4+ & CD49d+^{hi} cell population changes relative to the baseline, where the biggest reductions in cell numbers were seen. The number of cells in all populations also rebounded by week 28, four weeks post cessation of ATL1102 dosing to the nine DMD patients, clearly demonstrating that the observed changes were a result of ATL1102 administration.

There is some variation in the size of the change from the baseline between populations of cells, so Antisense used percentage median numbers, rather than mean numbers which make the differences clearly standout. Again, this cohort of data is only from a small number of patients. The differences observed can be expected to tighten up and fall completely in line when large cohorts of patients are studied. The relative size of each raw population of cells makes sense and provides confidence in the overall results.

Antisense has conducted various statistical analyses comparing cell populations, finding several significant differences and strong trends between the changes in these populations.

What has truly grabbed our attention, though, is not so much the individual, as the movement of all the cell populations as a whole. Again, literally every number is pointing the way it would be expected to point if ATL1102 is having the desired

effect on C49d+, CD4+ and CD8+ cells. The chances of getting an overall data set like this are intuitively infinitesimally small due to chance. These results make a scientist give a fist pump and say, "Nailed it"!

Additional Analyses

A range of additional analyses fleshed out the data. Clinical data is everything in biopharma. It is how you progress your drug to market, it is what you learn from to make your next trial better, it is what you will use to licence a program at a later date, if that is the strategy, and it is the big value add to the company. A lot of Australian investors in the space have not caught onto that, yet, fortunately. It means that truly mispriced assets can be found and you can outperform fairly easily.

The additional data to come out of the study was as follows:

Figure 4. Relevant Lymphocyte Readings per Pinto-Mariz (2015) Skelet Muscle from the Phase II Trial of ATL1102 in Non-Ambulant DMD Patients.

White blood cell type (X10^9 cells per litre)	Mean # and Change from baseline			Median % change from baseline	
	Baseline	24 weeks (end of dosing)	28 weeks	24 weeks (end of dosing)	28 weeks
Lymphocytes (mostly CD3+ T cells)	3.68	-0.28	+0.19	-4.22%	+11.81%
CD3+ T cells (mostly CD3+ CD4+ and CD3+ CD8+ T cells)	2.93	-0.18	+0.25	0.86%	+17.11%
CD3+ CD49d+ T cells (CD4+CD49d+ and CD8+CD49d+ cells)	2.44	-0.28	+0.11*	-9.78%	+9.93%
CD4+ T cells	1.57	-0.15	+0.11	-1.12%	+16.50
CD4+ CD49d+ T cells	1.20	-0.19	+0.01	-16.7%	+1.73
CD4+ CD49d++ T cells (are the high CD49d expressing CD4+ T cells)	0.24	-0.01	+0.01	-11.1%	+7.58
CD8+ T cells	1.22	-0.02	+0.14	-2.62%	+17.99
CD8+ CD49d+T cells	1.17	-0.05	+0.11	-5.79%	+13.37
CD8+ CD49d++ T cells (5 of 9 patients had these cells at baseline) (are the high CD49d expressing CD8+T cells)	-	-	-	-6.17%	+14.12

The Lymphocyte mean # of cells at week 24 (at the end of dosing) is trending significantly lower vs week 28 (p= 0.051 paired T test)
The CD3, CD4, CD8, CD4+CD49d+ and CD8+CD49d+ mean # of cells at week 24 are similarly trending lower vs week 28 (p= from 0.056 to 0.073)
*The mean # of CD3+CD49d+ T cells (=CD4+CD49d+ and CD8+CD49d+cells) at week 24 is statistically significantly lower vs week 28 (p= 0.030 paired T test)

Source: Antisense Therapeutics Limited.

A) **Natural killer or NK cells are white cells, but unlike the T-cells that we have been discussing, NK cells are a part of our innate immune system**. They are ready to go as soon as there is an issue, unlike T-cells, which need to receive a few signals before they get going. NK cells are another population of lymphocytes that are mostly CD49d+. Despite being in a different arm of the immune system, ATL1102 should have an effect on them and that is exactly what was seen, with their numbers falling significantly when the patients were given ATL1102, and rebounding once treatment was stopped.
B) **MoviPlate data was also released**. The MoviPlate itself provides a broader assessment of how fingers are working. The data collected using it from the trial, again, showed an increased finger tapping movement of 1.9 in favour of the ATL1102 arm and fits with the PUL2.0, MyoGrip and MyoPinch.
C) **The level muscle fat and quantity of lean muscle in the dominant arm moved in the expected direction**, if ATL1102 is having a beneficial effect. A worsening of the arm would, logically, see the patients use it less. Less activity and fat accumulates and lean muscle declines. The movements were small, but we would have thought a timeframe of 24 weeks would not have been long enough to detect such movements. Consequently, the data is positively surprising.

The results are impressive, but so has been management's ability to get everything out of this trial. In some cases, you can go back to specimens if there is something you want to check out. For the most part, though, once the trial is over, you cannot go back and collect more data. You have to get everything out of it then and there in most cases.

Taking a step back, these numbers are extremely convincing on their own, in the light of the Pinto-Mariz (2015) Skelet Muscle paper. Still, you need to consider them in the right context. Clinical trials are all about clinical data, not surprisingly. All of the cell surface marker data in the world will not help you if you cannot show your therapeutic improves the health of patients. When you have shown your therapeutic improves the health of patients or, at least, provided the right signals in an early stage clinical trial, as ATL1102 has done, then data, such as the marker data we have just looked at, serves the purpose of tying the clinical results back to biological results and through to the mechanism of action of a drug. Being able to say, yes, the therapeutic has a clinical effect and we know why is very persuasive. Being able to make that statement also means you are likely to predict how the therapeutic will perform in other patient populations in the same disease or in disparate diseases. Provided you can find enough applications for your therapeutic, that is exactly where you want to be and that is exactly where ATL1102 appears to be right now.

The question Antisense needs to answer from this study was, has ATL1102 shown enough promise in treating non-ambulatory DMD in terms of safety (part 1) and signals of efficacy (part 2) to justify studying it in larger, more expensive, trials?

Overall, the answer to the question is a resounding "yes".

For part 1 of the question, we have not really looked at the safety results from the trial, yet. This is because they produced no concerns and the dose of ATL1102, at an adult equivalent dose of 25mg a day (0.4-1mg/kg/w dose 25kg-65kg patients), given as a subcutaneous injection (just under the skin) once a week for 24 weeks, is very low compared to some of the other clinical trials of ATL1102. Still, it is important to never simply "skip over" looking at safety results. For the record, ATL1102 was found to be generally safe and well tolerated. **Importantly, no serious adverse events were reported and no potential safety concerns were raised by the Data Safety Monitoring Board**. The most common adverse events reported were injection site erythema (redness due to increased blood as a result of the minor injury to the skin caused by the injection) and skin discoloration, as a result

of the injection. Erythema and skin discoloration seem to go hand-in-hand with just about every therapeutic that is delivered by piercing the skin, in our experience. As far as the key question is concerned, the safety of ATL1102 at the dosage used in the study does not provide a reason to say, "no".

The dosage of ATL1102 used in this study appears to leave a very large amount of room for Antisense to move it upwards. In the MS trial, discussed at the start of this report, a dosage of 200mg was used. This is eight times the dose used in this study. As a result, we expect Antisense to examine the safety of ATL1102 at higher doses in the next trial it conducts. If it turns out that ATL1102 is just entering its therapeutic range (i.e. the dose range in which clinical benefit is seen), the results could be exciting for non-ambulant DMD patients and Antisense investors.

Where to Next for ATL1102?

Phase IIb Study Design

Antisense has announced that it is seeking to conduct a Phase IIb of ATL1102 in non-ambulant DMD patients. These studies are where efficacy becomes a major focus, in addition to safety. Phase IIb studies are usually undertaken by a company to determine whether they should proceed to Phase III or registrational studies. Companies, occasionally, may also see a Phase IIb study as the first of the two registrational studies that are required to gain approval for therapeutics for most indications.

There are, however, indications where only a single pivotal trial ends up being required. These indications are almost always, if not always, orphan or rare diseases where there is a large unmet need. Because these diseases are rare, if regulatory agencies were to require the standard two pivotal studies, the idea has tended to be that companies would find this too onerous. They fear many rare diseases that have a high unmet need would see that need go unfulfilled.

Non-ambulatory DMD falls into the category of disease indications where only one pivotal trial is likely to be required. That is a good thing for investors and the company.

Antisense is yet to finalise its Phase IIb trial and the timeline it is on is not unusual. Companies normally want to talk to the key regulatory bodies around the world, like the US FDA and the EU's European Medicines Agency (EMA), to understand what they believe an approvable trial design would look like. In particular, they are looking for guidance on things like overall trial design, the length of the trial, trial size, the primary endpoint on which the therapeutic will be judged, etc. If possible, they will also try and harmonise the trial(s) between, at least, the EMA and FDA, so that the same pivotal study or studies can be used for each regulator. Fairly often, this can be done.

At this stage, Antisense has received initial feedback from the EMA and is engaging further. The company is gathering information and opinions on how it should proceed in the US, as well. Once it has that feedback, they can then determine the regulatory questions it would like answered by the FDA. It is important to remember the regulator is the decision maker and a speedy approval usually means complying with what the regulator asks for. Companies are not required to proceed as the regulator requests, but by not doing so, there is the risk that the regulator may not approve a therapeutic based on a trial that the company and its advisers thought would be approvable.

Based on the feedback to date from EMA, Antisense looks like it will need to perform one trial to satisfy them, provided the results are strong enough. We think that trial will look something like this. A multicentre, open label, randomised, controlled study, in non-ambulant DMD boys up to the age of 18, where non-ambulant is defined in similar fashion to Antisense's Phase II trial. To tackle the issue of dose, we believe Antisense will look to test two doses of ATL1102 in the trial. The dose of 25mg/weekly would need to be kept and Antisense will likely negotiate with the regulators on a higher dose. Recruitment will be 1:1:1 between the test (ATL1102) arm and the control arm, requiring about 105 patients in total. Antisense may work an interim analysis into the study and, if so, it may be possible to keep the better performing of the two arms and drop the other one. The primary endpoint will be PUL2.0 and each patient will spend 48 weeks in the trial. We expect the study to take 24 to 30 months to complete, but this is dependent on a number of factors within Antisense's control and can be shortened.

We expect Antisense to commence a Phase IIb clinical trial of ATL1102 in non-ambulant DMD patients in the 1H CY21, which is in line with the company's commentary.

Special Regulatory Classifications

One of the good things about developing a drug for a rare paediatric disease is that there are some helpful regulatory classifications that can be obtained. Principally, these classifications are orphan drug designation (ODD) in the US and EU, as well as rare paediatric disease classification in the US. These programs are designed to increase the development of therapeutics for rare diseases and, obviously, childhood diseases. They are also designed to help companies produce the best quality clinical trial data, the right clinical data and the highest quality applications for regulatory review and approval.

Antisense has applied for ODD designation in both the EU and the US. In the EU, medicines granted ODD are eligible to receive a range of benefits, which include scientific advice above and beyond that usually provided, including help with developing clinical trial protocols, a 75% reduction in the fees for those services and the potential conditional marketing authorisation of the drug,

which lets the company market and sell its drug in the EU, provided it complies with various requirements and endeavours to collect the data to allow it to seek full approval. Finally, orphan drugs receive 10 years of market exclusivity, which protects the company's product from competitors, regardless of the standing of patents over a drug. As a paediatric ODD, the company becomes eligible for, and will receive, an additional two years of market exclusivity on top of the initial 10 years for a total of 12 years of market exclusivity. In the US, the benefits of ODD are primarily financial and include tax credits covering 50% of the clinical trial cost, the waiving of application fees and seven years of market exclusivity.

By far, the main criteria assessed for granting of ODD is based on the incidence or prevalence of the disease in question. In the case of ATL1102, it will be those numbers for non-ambulant DMD, not the overall DMD population. By reputation, gaining ODD is considered a 'tick the box' exercise and the metrics around the number of patients with non-ambulant DMD will not be a barrier to obtaining it. Consequently, Antisense should have no problem gaining ODD for ATL11102 in either the EU or US.

Antisense's ATL1102 recently received rare paediatric disease designation (RPDD) from the US FDA. This means that if Antisense gains approval of ATL1102 for non-ambulant DMD it should receive a priority review voucher (PRV). PRVs entitle the holder to have the new drug or biologics application (NDBA) of its choice examined as if it had been eligible for, and granted, priority review. Under normal circumstances, the FDA must complete its review of an NDBA within 10 months. Under priority review the process is supposed to be completed in six months. PRVS are transferable and smaller companies that receive one almost invariably sell it to a large biopharmaceutical company. A large biopharmaceutical company will seek to purchase a PRV if it believes it can acquire one for less than the present value of net revenue minus the cost-of-goods-sold that they would receive by extending their exclusivity over a product for four months. A few PRVs have been sold for huge numbers, with the known highest price being paid to date sitting at USD350 million (M. Sinatra, Data on File). The lowest is USD67.5 million. Recently, the price of PRVs has settled at approximately USD100 million. If Antisense was to gain approval of ATL1102 for non-ambulant DMD, the proceeds from selling the PRV would go a long way to helping it establish the relatively small sales and marketing team it would need to take ATL1102 to market in the US.

Non-Ambulant DMD: Addressable Market Size and Relevant Pricing Indicators

Addressable Market Sizes

Antisense is likely to undertake its Phase IIb study of ATL1102 in Europe, based on the fact that it has approached the EMA before the FDA. Should the FDA provide guidance that Antisense can harmonise the Phase IIb trial and use it as the basis for marketing applications in both the EU and US, the trial may be altered to include US patients. The FDA usually requires at least some of the data in a marketing application to be from the US.

DMD is the largest of the muscular dystrophy class, representing around 50% of cases, according to the US National Institute of Neurological Disorders and Stroke (NINDS).

Even though the EU seems likely to be the first jurisdiction that Antisense would target ATL1102 at, should it pass a pivotal trial, we have assessed the US market as the basis for the metrics around our DCF model. The reason is it is generally easier to do. After estimating the key variables of the US market, transposing them to Europe and the rest of the world is fairly easy because there is so much data on how the US relates to those areas. Moreover, since the US represents a big part of the world market, it is important to get it right. Working off a few countries in Europe would likely lead to substantial error in the calculations.

The following global DMD prevalence data comes from Cristafulli et al (2020) Orphanet J Rare Dis. The pooled global prevalence and birth prevalence of DMD have been reported as 7.1 (95% CI: 5.0–10.1) and 19.8 (95% CI: 16.6–23.6) per 100k males, respectively. Looking at it from an overall population prevalence, the prevalence of DMD is 2.8 (95% CI: 1.6–4.6) cases per 100k. The birth prevalence of DMD is much higher than the global prevalence because children with DMD may not survive beyond paediatric age, most likely in developing countries with low adherence to standards of care. That means that this is data is interesting from a global view, but it cannot be generalised down to the country.

In the US, the prevalence of DMD in males aged five to 24 years was estimated at 1.02 per 10k boys, ages 5 to 24 years old (Romitti (2015) Pediatrics). Interestingly, in the age groups of 5 to 9 years, 10 to 14 years and 15 to 19 years the prevalence was relatively flat, with high and low prevalences of 1.04 and 1.29 boys per 100k. In males, 20 to 24 years old, it fell sharply to 0.67 per 10k, indicating that 20 to 24 years is the age bracket where mortality really sets in. Other than Romitti, there are quite a few numbers around for incidence and prevalence of DMD. Based on a 2010 report, there were 17,951 patients with DMD in the US (McNeil et al (2010) Muscle and Nerve). The same report provides a birth incidence for DMD of 1/3,500, which is a widely used figure in the literature and on health websites. Given population growth and general improvements in healthcare, using a prevalence for the US of 20,000 in 2020 terms is reasonable.

Table 1. FDA-Approved Therapies and Their Cost to Treat a 30 Kilogram Child per Year.

Brand Name	INN[1]	Year Granted FDA Approval	Dose - 30kg Child	Form	Company	Cost (USD) Yearly
Emflaza	deflazacort	Feb, 2017	27mg/day	Tablet	PTC Therapeutics	114,817
Exondys 51	eteplirsen	Sept, 2016	900mg/week	Infusion	Sarepta Therapeutics	784,217

Viltepso	vitolarsen	Aug, 2020	240mg/week	Infusion	NS Pharma	733,333
Vyondis 53	golodirsen	Dec, 2019	900mg/week	Injection	Sarepta Therapeutics	786,193

Sources: www.drugs.com; M.Sinatra Research
1 INN = International Non-proprietary Names1

Relevant Pricing Data

Table 1. lists the four drugs that have been approved by the FDA for ambulant DMD. Deflazacort is the least interesting of them, being a corticosteroid. Not surprisingly, it is also the cheapest. That is, cheap relative to the other three Duchenne drugs in the table. If this table compared deflazacort to other corticosteroids, it would look frightfully expensive. This because most corticosteroids are off-patent and made by generics companies. This includes prednisolone, which has historically been used to treat DMD.

The three other drugs fall into a fairly new class of drugs that are called exon-skipping drugs. Their aim is to ameliorate a specific mutation that would otherwise result in the production of a non-functional protein. To do that, exon-skipping drugs have to be highly specific. A gene as large as the dystrophin gene will need several exon-skipping drugs before all of those with relevant DNA errors will have one.

Regarding Sarepta's, Exondys 51, there was a high degree of scepticism among scientists who did not believe the drug was shown to work by the clinical trials it was put through. There certainly was a very strong influence campaign run by special interest groups to try and sway the FDA's decision in favour of the drug. It is also the first time we have seen the FDA announce a product approval and not mention any of the data that supported the approval. In the end, it looks like Sarepta and the special interest groups got their way. Still, we do not even think proponents of the approval of the drug would be saying anything other than the data was pretty thin. Sarepta was still bold enough to put a price of over USD700k per year on the drug and that they got away with it is astounding. It also demonstrates that a drug can still command a high price even with very borderline data.

There is no question, however, that exon-skipping drugs represent a leading-edge technology and that they are only going to get better. In fact, the remaining two drugs on the list, Vyondis 53 and Viltepso have both been granted accelerated approval and are on the market or will be shortly. Interestingly, both of these drugs target patients who need exon 53 within the messenger RNA produced from the dystrophin gene to be skipped. Both drugs demonstrated substantial enough improvements in the amount of dystrophin within the muscles of DMD trial participants that the FDA thought it would be against the public interest to make each drug fully complete the approval process before they were allowed on the market. Each will eventually need to complete the process.

The prices of these drugs are high and do bode well for ATL1102 and Antisense. However, list prices for pharmaceuticals in the US, at least, tend to be over inflated. If you pay list price for a drug, it is like paying full price for a car or rug here. The prices are so inflated, in fact, that the larger pharmaceuticals have two lines of revenue at the top of their profit and loss statement, whereas every other industry seems to have only one. These two lines are gross revenue and net revenue. Gross revenue reflects the contracted price with the customer, net revenue reflects all of the other payments that need to be made to contract with the customer. This includes things like coupons, payments to particular companies called pharmacy benefits managers, and other payments along the way.

Unfortunately, Sarepta Therapeutics only reports one revenue line, otherwise we could see how much they had been discounting Exondys 51. Having said that, with only one product, Sarepta would know that reporting that way would give its competitors a good view and that may be the reason they do not report that way. Luckily, somebody else has done the work for us.

In 2018, a group called IQVIA put out a report that covered the gross to net discount. IQVIA is an amalgamation of Quintiles (which was a large contract research organisation in its own right - they conducted a lot of clinical trials for large biopharmaceuticals companies) and IMS Health (a huge industry information gathering and dissemination organisation reliant on many in the industry, some who supply them information and others who buy it from them). The report can be found here: Reports (2018) IQIVIA. It found that the larger biopharmaceutical companies had an average gross to net discount of 28%. That is pretty big. There have been others, though, who say it is considerably higher. The reason for the brackets earlier in the paragraph was simply to point out that IQVIA is reliant on the industry it is researching and, logically, would not put out numbers that hurt those who it is reliant on. We tend to think the discount is a bit higher than 28%, too.

Competition and the Potential for It

Antisense has chosen to study ATL1102 in non-ambulant DMD patients for three reasons.

One is competition for clinical trial patients. Interest in DMD seems to have spiked since the FDA approved Exondys 51 back in 2016 and more companies have focussed on it. DMD is also a rare disease. In situations like this, you often find that it can become harder to recruit patients. Competition for patients even occurred for COVID-19 earlier this year in China, despite there being so many about, such was the exuberant rush for companies to take advantage of the situation.

The second reason relates to gaining regulatory approval and then subsequently marketing ATL1102, and competition plays a role here, too. As could be seen earlier in the report, there are now four approved therapies for ambulant DMD and there is likely to be more. Each time a therapy manages to get past the regulator, in general, it makes it harder for the next group to have theirs approved. The reason is straightforward, the more marketed therapies there are, the less is the clinical need. In these situations, regulators can afford to raise the bar. In fact, it is in their own interests to raise it, because it reduces the likelihood of a marginal product making it on to the market and then turning around and giving the FDA a black eye, with a safety problem (Zhang et al (2019) Milbank Q). While that might sound strange, the FDA and EMA are protective of their image. The reason is, to survive, they need government funding. That can be threatened by errors that cause the population and politicians to question the job they are doing.

Having searched the major clinical trial databases (ClinicalTrials.gov, EU Clinical Trials Register) and Google News with the terms Duchenne/DMD and non-ambulant, it is apparent that the non-ambulant patient population is, by far, ATL1102's path of least resistance through the regulator and on to market. That is not to say it couldn't achieve the same feat competing with a number of others and get an approval for ambulant DMD boys. It is the fact that we have watched so many companies make life harder for themselves by wanting to play with all others and then stumbling due to it. Therapeutic development is too hard to take that approach. The market for non-ambulant boys is wide-open.

The final reason Antisense likely targeted the non-ambulant population of boys was the original finding by Pinto-Mariz (2015) Skeletal Muscle, that found higher levels of CD49d+ cells in the later stages of DMD. The rationale being that the more CD49d+ cells, the bigger the impact ATL1102 was likely to have. Certainly, the logic appears to be sound, as is the risk-mitigation strategy it implies.

Intellectual Property

To a certain large extent, ATL1102's need for intellectual property is likely to be fairly low, given the regulatory exclusivities they will enjoy as a result of having obtained ODD in each jurisdiction. ODD will earn Antisense seven years of protection from competition in the US and 12 years in the EU (10 for being an orphan drug and two for being a paediatric orphan drug). There is an avenue for extending protection in the EU by a year, but the point has really been made. Data exclusivity means someone wanting to produce a generic copy of a protected drug can do so, but they cannot rely on the branded drug's data to gain approval. Effectively, this means they must gather their own data, including clinical trial data, to support their marketing application, which would likely need to spend as much as Antisense did to get its drug on to the market. Unlike Antisense, though, they would face an incumbent in the market and immediate competition. There may be a company who has developed a copy of a drug in these circumstances, but if there is, there will not be too many of them. We certainly do not know of any.

Antisense has filed a method patent to cover DMD, which has the priority date of December 2018 and, which, if granted, would provide commercial protection to December 2039. In a sign of where Antisense will likely take ATL1102, it filed a method patent covering additional muscular dystrophies in May 2019. The patent estate is on page 8 of the 2020 ANP annual report, and includes a granted US patent covering ATL1102 methods of reducing circulating leukocytes to 2031 .

Key Personnel

Antisense has quite a few highly regarded names on its board of directors, who have quite a complementary skill sets, as well. One that should be highlighted for the specific expertise he brings is Mr Goolsbee. He was the chairman of the company that was to become Sarepta Therapeutics. Sarepta developed and owns the first drug to be approved for DMD by the FDA, Exondys 51. Mr Goolsbee continued on the board of Sarepta as a director until just before Exondys 51 was approved and, as a result, he brings with him very rare experience.

Mr Robert Moses

Chairman

Robert (Bob) Moses was formerly Corporate Vice President of CSL Limited. Mr. Moses draws on more than 40 years' experience in the pharmaceutical/biotechnology industry. During the period 1993-2001, Mr. Moses played a central role in CSL's development internationally. Prior to joining CSL, Mr. Moses was Managing Director of the commercial law firm Freehills, Chairman and CEO of a NASDAQ-listed medical service company, and Corporate Manager of New Business Development at ICI (now Orica). Mr. Moses is also the former Non-Executive Chairman of TGR Biosciences Pty Ltd. Mr. Moses also spent 17 years in various management roles at the multinational pharmaceutical company Eli Lilly.

Mr Mark Diamond

CEO and Managing Director

Mark Diamond has over 30 years' experience in the pharmaceutical and biotechnology industry. Before joining Antisense Therapeutics Limited as MD and CEO in 2001, Mr. Diamond was employed in the US as Director, Project Planning/Business Development at Faulding Pharmaceuticals. Prior to this he held the positions of Senior Manager, Business Development and In-licensing within Faulding's European operation based in the UK and International Business Development Manager with Faulding in Australia.

Mr William Goolsbee

Non-Executive Director

Mr. Goolsbee was founder, Chairman and Chief Executive Officer of Horizon Medical Inc. from 1987 until its acquisition by a unit of UBS Private Equity in 2002. Mr Goolsbee was a founding Director of ImmunoTherapy Corporation in 1993 and became Chairman in 1995, a position he held until overseeing the successful acquisition of ImmunoTherapy by AVI Biopharma, Inc. (now Sarepta Therapeutics) in 1998. Mr. Goolsbee served as Chairman of privately held BMG Pharma LLC, a pharmaceutical company, from 2006 through 2011, and of Metrodora Therapeutics until 2015. Mr Goolsbee was, until the end of 2016, a Director of Sarepta Therapeutics Inc.

Dr Graeme Mitchell

Non-Executive Director

Graham Mitchell, through Foursight Associates Pty Ltd, acts as joint Chief Scientist for the Victorian Government Department of Environment and Primary Industries. Dr. Mitchell is a Non-Executive Director of Avipep Pty Ltd and is a Principal of Foursight. Dr. Mitchell has held the position of Director of Research in the R&D Division of CSL Limited and, for many years, was a research scientist at The Walter & Eliza Hall Institute (WEHI). He is currently a Board Member of WEHI.

Dr Gary Pace

Non-Executive Director

Dr Pace has more than 40 years of experience in the development and commercialisation of advanced technologies in biotechnology, pharmaceuticals, medical devices and the food industries. He has long-term board level experience with both multi-billion and small cap companies. In 2003 Dr Pace was awarded a Centenary Medal by the Australian Government “for service to Australian society in research and development”, and in 2011 was awarded Director of the Year (corporate governance) by the San Diego Directors Forum. In addition, he has held visiting academic positions at the Massachusetts Institute of Technology and the University of Queensland. Dr Pace is an elected Fellow of the Australian Academy of Technological Sciences and Engineering. Dr Pace is currently a Director of Pacira Pharmaceuticals, Simavita Ltd, Antisense Therapeutics, Invitrocue and several private companies.

Dr George Tachas

Director, Drug Discovery and Patents

Dr Tachas received his Ph.D. from the University of Melbourne in 1988 and a Diploma of Intellectual Property Law in 1994. Dr Tachas’ Ph.D. studies (1984-88) were in gene transfer, cloning and characterising of genes important in immunology at the Centre for Cancer and Transplantation (now the Austin Research Institute) at the University of Melbourne.

Dr Tachas’ three years’ post-doctoral studies (1989-1991) were in the molecular and cellular biology of vascular smooth muscle cells in cardiovascular disease as Head of Molecular Biology at the Cardiovascular Research Unit of the University of Melbourne’s Anatomy Department. It was during this time that he first used antisense oligonucleotides as research tools and developed an interest in antisense as potential therapeutic agents. Dr Tachas moved to a leading Australian patent attorney firm, Griffith Hack and Co, in late 1991 where he spent three years as a biotechnology assistant and, from 1995 to 1998, was a biotechnology-patent law consultant, inter alia, to the patent firm, Callinan Lawrie. Dr Tachas is well versed in biotechnology patent prosecution, opposition, infringement and licensing, portfolio management and the use of patents as a business tool. In 1997 Dr Tachas planned to start up an antisense company. In synergy with interests of the Circadian group of companies in also setting up an antisense company, Dr Tachas was exclusive consultant first to Syngene Ltd and then to ATL (2000-2001). Since the ASX listing of ATL, Dr Tachas has directed the company’s efforts in expanding its product pipeline and managing the company’s IP portfolio.

Nuket Desem

Director of Clinical and Regulatory Affairs

Ms Desem has over 25 years’ experience in global regulatory affairs, clinical development and project management through her roles within the pharmaceutical/biotechnology industry, including senior positions in biotechnology groups. Ms Desem was previously employed at Antisense Therapeutics (2004–2010) as the Company’s Development Director where part of her responsibility was the management of ANP’s clinical trial programs. Major achievements in this role included the successful conduct and completion of the Company’s multinational Phase IIa clinical trial of ATL1102 for the treatment of Multiple Sclerosis. Nuket joins Antisense Therapeutics from Paranta Biosciences, where she held the position of Director Clinical and Regulatory Affairs. Prior to Paranta, Nuket was Senior Manager Development and Regulatory Affairs at Prana Biotechnology. Earlier, Nuket served as Vice President Clinical and Regulatory Affairs at Spinifex Pharmaceuticals and was responsible for the management of the company’s regulatory and clinical trial programs. In this role, Nuket completed multiple clinical trials including a successful multinational proof of concept study of EMA401 in patients with post-herpetic neuralgia. Spinifex was acquired by Novartis for continued development of EMA401. Previously, Nuket spent over 10 years at CSL Limited in R&D and Regulatory Affairs. Nuket holds a Bachelor of Science (Honours) from La Trobe University and a Master of Business Administration (MBA) from Monash University.

Gil Price M.D.

Consultant Medical Director

Dr. Price is a clinical physician trained in internal medicine with a long-standing focus in drug development, adverse drug reactions, drug utilization and regulation. Dr. Price is an experienced biotech executive and entrepreneur with a depth of expertise across clinical asset investment strategy, evaluation, financing and execution. Dr. Price has served on multiple boards of public, private and not-for-profit entities. From 2007 to 2016, Dr. Price was a Non-Executive Director of Sarepta Therapeutics, Inc., guiding Sarepta’s transition from US$80 million market capitalisation (2008) to a multi-billion dollar company with the first approved drug for DMD (now with sales approaching US$400m annually) .

Dr. Price is currently a Board Member of Rexahn Pharmaceuticals, Inc. (NYSE American: RNN) and consults on Compensation, Governance, and Business Development. From 2007 – 2016 Dr. Price served as a Board Member with Sarepta Therapeutics (NASDAQ: SRPT). Dr. Price has also held positions as Chief Executive Officer, Chief Medical Officer, Medical Affairs, Business Development and Clinical Development for a number of

successful pharmaceutical companies. Dr. Price holds a Bachelor of Science degree from University of Rio Grande and a Doctor of Medicine from Santiago University. He also studied Political Science and Economics at Cambridge University.

Antisense Therapeutics (ANP)

And a Door Opens Wide

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