Tuesday, 28 December 2021

RESEARCH REPORT

CORPORATE CONNECT

Antisense Therapeutics (ANP)

Comprehensive Research Report

Share Price & Estimated Future Price

12-Month Target*	$0.55
Price	$0.20
Implied Return	175%

*Implied Return

Since ATL1102 returned impressive results in a phase II trial in non-ambulant Duchenne muscular dystrophy (naDMD) patients, Antisense Therapeutics (Antisense) has been perfecting its regulatory strategy for the compound. The next naDMD trial, if positive, will be central to a Marketing Authorisation Application (MAA) to the European Medicines Agency (EMA) for naDMD patients. Antisense's US strategy provides several options and leverages its European Union (EU) activities leading to a New Drug Application to the US Food and Drug Administration (FDA) for naDMD. Now, it comes down to execution.

EMA Agreement: Antisense and the EMA have agreed on a Paediatric Investigation Plan, which makes it clear to Antisense what its MAA for naDMD must contain. Further, it covers the ambulant DMD indication, as well, if Antisense decides to go that way. **Such interaction and clarity with the EMA only be of benefits Antisense.**

Antisense aims to start its gold-standard design EU pivotal trial mid-next 2021. The trial is a multicentre, double-blind, randomised, controlled, trial in 114 naDMD patients, randomised 1:1:1 to three cohorts – 25mg/week ATL1102, 50mg/week ATL1102 and placebo. The primary endpoint is Performance of Upper Limb Score 2.0 at 52 weeks. There are several quantitative secondary endpoints. Endpoint data collection is expected to complete in Q3 CY24, with MAA submission in Q1 CY25. EMA review is 210 days, plus clock stops. **Inclusion of the 50mg/day cohort was a pleasing surprise because it allows for a dose effect and may outperform 25mg/week.**

For the US, Antisense may amend the EU protocol to include US sites or, even, seek accelerated approval from the FDA based on the EU trial data. The company must run a 9-month monkey study to satisfy FDA regulations, **but the monkey study and naDMD trial can overlap 6-months.**

DMD patients lack a protein called dystrophin and experts believe combination therapy is the diseases future, due to the immune response-mediated muscle damage a lack of dystrophin causes. Corticosteroids are the only treatment shown to be efficacious in DMD, even among approved therapies. **Exon-skipping drugs, gene therapies, etc do not provide patients with full dystrophin expression or a fully functional dystrophin protein and, at best, will result in a less severe disease on average**.

ATL1102 targets a protein on a set of immune cells strongly implicated in DMD pathogenesis. The same protein is the target of drugs approved drugs for multiple sclerosis and Crohn's disease, providing broad support for Antisense's approach. CSs do not affect the cells ATL1102 targets and the phase II DMD trial indicates the therapies should combine well. **ATL1102's target is upstream to many deleterious aspects of DMD and its use may improve many of them and place it ahead of other drugs in development for DMD**.

Antisense has added two new, highly experienced directors in Drs Gittleson and Price, who both have wide-ranging expertise, but, particularly, in rare diseases and Duchenne's. Antisense has an impressive array of highly skilled and experienced people right across the areas they are required.

Valuation: Based on recent progress and adjustments to our model, we are nudging our **12-month price target up to 55 cents/share**.

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

Company Information

ASX Ticker	ANP
Shares on Issue	658 million
Fully Diluted Shares on Issue	713 million
Market Capitalisation	121.7 million
ASX Vol. (Shares/Day)*	2.1 million

* Shares per Day for the Last 20 Trading Days. **A** Includes 31.5 million Shares to be Issued through Recent Rights Announcement.

Cash Sufficiency

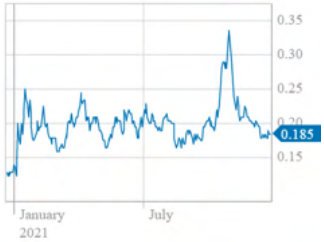
	$ Million
A) Last Appendix 4C	End September 2001
B) Cash and Equivalents at 4C	4.7
C) Burn[1]	1.3
D) Quarters Cash Remaining[2]	18.0
E) Estimated Current Q Burn[3]	0.3
F) Estimated Cash Raised Post 4C[4]	20.0
G) Estimated Current Cash[5]	**23.2**
H) Significant Estimated New Commitment(s)[6]	

1 Burn = Net Cash from/used In Operating Activities; **2** Quarters Cash Remaining =(B+F)/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
6 Equals estimated maximum new significant commitments that the company has, or is likely to, become contractually or ethically committed to.

Key Personnel

Dr Charmaine Gittleson	Chairperson
Mr Mark Diamond	Managing Director & CEP
Dr Gary Pace	Non-Executive Director
Dr Gil Price	Non-Executive Director
Dr George Tachas	Director, Drug Discovery & Patents
Nuket Desem	Director, Clinical & Regulatory Affairs

Chart



Introduction

In 2015, Pinto-Mariz published a journal article that was to prove prescient to Antisense Therapeutics (Pinto-Mariz et al (2015) Skelet Muscle). The paper tied Antisense's putative therapeutic ATL1102 to a target marker on certain blood cells of patients with Duchenne muscular dystrophy (DMD). In particular, it tied ATL1102 most closely to those DMD patients whose disease was progressing the fastest. Earlier additional studies that had been done in animal models of DMD (Barthelemy et al (2014) Dis Model Mech), as well as later studies with cells from DMD patients (Savino et al (2018) Methods Mol Biol), strongly support the cell surface protein VLA-4 (α4β1 integrin) as an excellent therapeutic target in DMD. Since ATL1102 was designed and shown, in a previous clinical trial in a different disease setting, to block the production of one of two sub-units of VLA-4, called CD49d (or α4 integrin, CD stands for Cluster Differentiation Factor), ATL1102 appeared to be just the therapeutic to aim at that target (Myers et al (2005) Neuroimmunol; Limroth et al (2014) Neurology).

Since then, Antisense has conducted a phase II trial in non-ambulant (unable to walk) DMD patients. After positive results, Antisense has spent most of the last year carefully preparing for what is highly likely to be a pivotal (phase III) clinical trial of ATL1102 in DMD patients.

With rare diseases such as DMD, regulators often only require a single pivotal trial, rather than the usual two large phase III trials, before they will consider approving the drug for patient use. The classification of clinical trials is, to a certain extent, more of an art than a science. Antisense refers to the next trial it will be running as a phase IIb/III trial, others might have classified it as a phase III trial. Since the next trial Antisense will run with ATL1102 aims to provide the clinical data required for a Marketing Authorisation Application (MAA) to the European Medicines Agency (EMA), if it returns positive results, we will use the term "pivotal trial" to make it clear that the intended next step after the trial is an MAA.

ATL1102 is not the only compound Antisense has the rights to, but it is where the vast majority of the interest is in the company at present. As such, this report will focus on, and be a deep dive into, ATL1102 and its development for DMD.

Duchenne Muscular Dystrophy

DMD is a particularly nasty disease. For those wishing to learn more about it, a recent review has been published: Duan et al (2021) Nat Rev Dis Primers. Much of what follows in describing the disease has been taken from that review.

DMD is a progressive muscle-wasting disease, with early symptoms beginning to show themselves around the age of two to three and continues throughout the patient's life. Often DMD patients are wheelchair-bound somewhere between 10 and 12 years of age. At approximately 20 years of age, they often start to require mechanical support to breathe. As our understanding of DMD has improved, so has the general medical care of DMD patients. This has led to improvements in their life expectancy. A study in France found that the median life expectancy of DMD patients born before 1970 was 25.8 years, while for those born after 1970, it was 41.0 years (Kieny et al (2013) Ann Phys Rehabil Med). With the exception of the consistent and improved use of the corticosteroids prednisone and deflazacort off-label and the registered use of deflazacort since 2017 in the US for the disease, these improvements in life expectancy appear to have been solely the result of better medical management. DMD causes the muscles that allow the patients to breathe, such as the diaphragm, to deteriorate. The same is true of the heart muscle. As a result, DMD patients generally die of respiratory or heart failure. The improvement in the median life expectancy of DMD patients, in fact, appears to be due to better respiratory and, in particular, cardiac management, although, ultimately, these are still the leading causes of death in DMD patients (Carter et al (2018) Clin Chest Med).

Dystrophin is a Key Protein

DMD is the result of a mutation (change in the DNA sequence) in the gene that encodes a protein called dystrophin. The gene is on the X chromosome and because males have only one X chromosome, they bear the burden of the disease. Females have two X chromosomes and, although they may carry one mutated dystrophin gene on one of their X chromosomes, the other X chromosome almost always carries a wildtype or normal copy of the dystrophin gene. This provides females with protection from the disease. While estimates tend to vary a bit, the incidence of DMD is about 1 in 5,000 to 6,000 live male births. Less than 1 female in every 1 million live births is thought to have the disease, although DMD in females is so rare conducting a study to quantify the number of females born with it is just too difficult.

Mutations do occur in the DMD gene, which result in a poorly functioning form of dystrophin, rather than no dystrophin or no functioning dystrophin. This leads to a disease termed Becker muscular dystrophy (BMD). The incidence of BMD is about 1 in 12,500 live male births. Overall, it is better to have poorly functioning dystrophin, than no functioning dystrophin at all and, as such, BMD patients fair better than DMD patients. The onset of the disease is later in life and it progresses more slowly than DMD. Still, BMD patients, generally, only live until the fifth or sixth decade of life (Ho et al).

The easiest way to look at the two diseases is that while the dystrophin gene from a BMD patient ultimately produces a protein that does not look quite right, the protein is still capable of carrying out its key function. In DMD patients, the mutation that has occurred has essentially rendered the dystrophin protein non-functional or absent. Either way, it leads to the same outcome, a patient that lacks even partially functioning dystrophin.

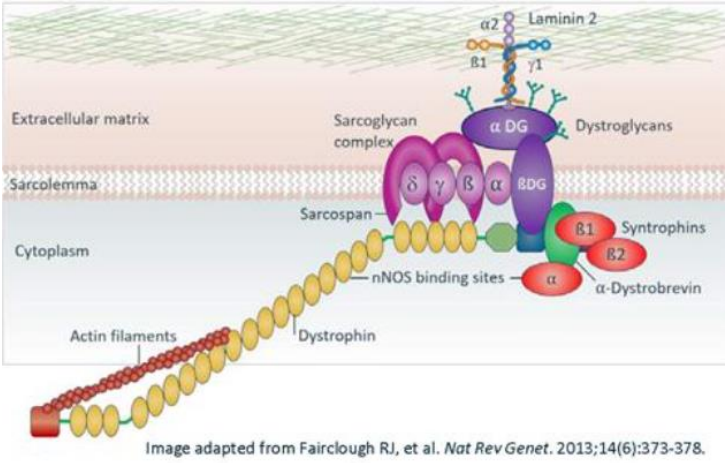
A point that we need to make early on is that there is considerable variation among BMD patients in the nature of their disease, ranging from few symptoms with little, if any, impact on life expectancy to an almost DMD-like pathogenesis (Hoffman (2020) Handb Exp Pharmacol). Importantly, the nature and severity of BMD are, at best, poorly explained by the nature of the mutation and where it occurs in the dystrophin gene. **Differences between BMD patients in genes other than the dystrophin appear to play a very significant role in the clinical severity and progression of BMD**. This will become important later, when we consider the different therapeutics that are in development of DMD.

The Role of Dystrophin

The following is based on our general knowledge of how myocytes (muscle) cells function and integrate to create a muscle, and the following review outlining dystrophin's role within the myocyte: Gawor et al (2018) Ann N Y Acad Sci

To understand the therapeutic approaches that are being developed in an attempt to treat DMD, we need to understand the role of dystrophin in healthy individuals and how the absence of functional dystrophin affects the body.

Figure 1. Dystrophin and the Dystrophin Associated Complex.



At the sarcolemma (the cell membrane of a muscle cell), dystrophin complexes with a range of other proteins to form a dystrophin-associated protein complex (DAPC). Ultimately, this complex reaches through the myocyte's (muscle cell's) cell membrane and anchors itself to components of the extracellular matrix (ECM), so the dystrophin protein is indirectly, but ultimately, anchored to the ECM as well.

The ECM is a three-dimensional framework of proteins consisting of a range of molecules and, in particular collagen. It runs between and around the myocytes and helps to give the muscle structure at the next level, that of the muscle fibre.

Long thin filaments of a protein called actin overlap and are bound to one another within the myocyte. They run longitudinally throughout the myocyte and, among other things, give the myocyte structure. These filaments are anchored to the free end of the dystrophin protein and, so, ultimately to the DAPC. These anchoring points occur at both ends of the myocyte, such that the network of filaments is anchored via a dystrophin and a DAPC to the ECM at two points opposite to one another. Figure 1 provides a one-sided illustration of how the various molecules aggregate and connect to the ECM.

Muscle contraction is the result of a chemical reaction within the myocyte that causes the filaments of actin to increase the degree to which they overlap one another, shortening the network or overall length of the overlapping filaments. Since the filaments run longitudinally through the myocyte and are attached ultimately to the ECM and both ends of the myocyte, the increased overlap of the actin filaments creates a force that is transferred through to the ECM. The increasing overlap of the actin filaments within each myocyte is coordinated with the other, such that the increasing overlap of many filaments across many myocytes becomes a contraction at the level of the entire muscle.

With more than 11 proteins forming the DAPC, this is an extremely simplified version of what occurs. Each of the proteins in the DAPC serves a function or functions. Dystrophin's function is not simply as a scaffolding protein, which anchors the filaments to the rest of the DAPC. It also plays a role in a whole range of signals that result in numerous proteins, like the actin filaments, being orientated correctly inside the myocyte. Moreover, dystrophin plays a role in the functioning of sarcolemmal proteins. For example,

sodium, potassium, calcium and water channels, which regulate the flow of those ions along with water, in the sarcolemma do not function properly in the absence of dystrophin.

The fact that dystrophin fulfils many roles in a myocyte is made clear by the differences in myocyte behaviour between those with functional dystrophin and those without. While it is not a great predictor of the clinical severity or disease progression, when the function of dystrophin is impaired, as in boys with BMD, there is some correlation between the symptoms patients' experience and the functional portions of the dystrophin protein that have been altered or are missing due to the mutation that they carry in the gene. Interestingly, the cardiac issues of DMD patients and BDM patients are often considered to be similar or even more severe in BDM patients (Chiang et al (2016) Am J Cardiol). In certain instances, altered dystrophin may not result in the same wide-ranging myocellular effects as the absence of it, but depending on the alteration, its presence may have a more severe detrimental effect on a specific aspect of myocellular functioning. The finding that the cardiac issues seen in DMD and BMD are similar, if not more severe in BMD on occasions indicates that in the heart, the domains within the dystrophin protein just as important than the two ends, which perform dystrophin's anchoring role.

The Absence of Dystrophin has Many Varied Effects

The absence of dystrophin leads to a wide range of effects and leads to wholesale myocyte dysfunction, as demonstrated in the bullet points that follow and summarise the various things occurring in the myocytes of DMD patients that should not be occuring. The following is largely based on Reid & Alexander (2021) Life (Basel), Thomas G (2013) Front Physiol and Duan et al (2021) Nat Rev Dis Primers. In the dystrophin deficient myocyte:

- Sarcolemmal weakening occurs due to the lack of dystrophin, severely hampering the integrity of the connection between the myocyte and the extracellular matrix and, consequently, between the myocytes within the muscle.
- The lack of dystrophin disrupts the DAPC, which results in the absence, down-regulation or mis-localisation of various dystrophin-associated proteins.
- In normal myocytes, neuronal nitric oxide synthase-μ (nNOSμ) is recruited to the sarcolemma by dystrophin and another DAPC protein. It functions to ensure contracting muscles get the blood flow they need by producing nitric oxide (NO). NO acts as a paracrine-signalling factor to local blood vessels in the exercising muscle, counter-acting neuronal signals telling the vessels to constrict. In the absence of dystrophin, nNOSμ localises in the cytoplasm of the myocyte. In DMD patients when muscle is used, blood vessels deny the myocyte oxygen as a result of functional ischaemia (lack of sufficient blood flow).
- Increased free radical damage occurs in DMD myocytes due to the increased activity NADPH oxidase 2 (NOX2), which is also a major source of radicals in normal muscles. Activated mis-localised nNOSμ is thought to further increase the level of free radicals, along with those produced by an influx of immune cells and dysfunctioning mitochondria.
- Glutathione, the most important and abundant antioxidant in myocytes, is significantly reduced in DMD myocytes and, consequently, the myocytes' ability to cope with oxidative stress is also reduced.
- Calcium overloading occurs in dystrophic muscles and appears to be a consequence of the lack of dystrophin, as the channels and enzymes that regulate calcium movement in and out of myocytes are DAPC associated. This calcium overloading induces mitochondrial dysfunction and directly contributes to myocyte death by triggering various degradative cellular pathways.
- The calcium overloading and increased level of free radicals, among other things, activate a protein called NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), which is a master regulator of inflammatory responses and results in the production of numerous pro-inflammatory molecules. Some of these proteins have activities within the myocyte, but many are excreted by the myocyte where the result in proinflammatory responses from other myocytes and, importantly, the immune system,
- Muscle wasting occurs in DMD patients due to the failure of satellite cells to divide and regenerate. Their division is DAPC dependent, however, matrix restructuring, epigenetic changes and chronic inflammation also appear linked to regenerative failure. Regenerative failure ultimately leads to fibrosis and the deposit of fat.
- Mitophagy (where cells remove and turn over damaged internal components) and programmed cell death are strongly inhibited in DMD myocytes due to the activation of a protein called Akt, which appears to be related to the high levels of free radicals in DMD myocytes. Consequently, rather than turning over damaged internal components or undergoing an orderly death, damaged DMD myocytes degenerate. This further activates system which detects and interprets certain molecules not normally found outside of myocytes/cells as signals that cellular/tissue damage has occurred. As such, certain immune cells move in to clean up the dead, dying and abnormal cells. In young DMD patients, regeneration of dead myocytes does occur, however
- Eventually, a chronic state of inflammation develops, when the clearance of dead and damaged cells is never sufficiently completed for the switch to an anti-inflammatory, healing, state to occur and the deposition of fibrous material and fat replaces myocytes. This starts to happens at around eight years of age in DMD patients.

This is a highly complex activity should not be taken as a straight forward linear affair. Disease processes overlap one another as the muscle wasting worsens and more fibrotic and fatty tissue is deposited. Over time, more muscle wastes and is further replaced by tissue unable to do the job once done by the muscle. Eventually, the DMD patient succumbs to either respiratory or heart failure.

The fact that dystrophin associates with so many different proteins provides for the under-lying rationale for the observation of the wide range of variability associated with BMD that is not explained by the position or nature of the mutation in the DMD gene. There can be a reasonably wide number of alleles that a person can have at the site for any one gene. An allele is a particular DNA sequence that varying levels of the population will carry. Each allele, generally codes for a protein that, generally, does the same job, but the protein product of the alleles vary in their amino acid sequence. The variation in amino acid sequence can lead to functional differences between the proteins produced by two different alleles of the same gene. Since there are more than 11 proteins alone in the DAPC and that these are not the only proteins dystrophin interacts, the specific alleles that each BDM patient carries for a number of genes could all react differently to the specific mutation in the dystrophin gene the BMD patient carries. The key role of the DAPC and the high degree of potential for a mutated dystrophin gene to interact aberrantly with, at least, some of the different proteins produced by different alleles for, at least, some genes, seems likely to be responsible for the wide variation seen in BMD patients.

Even in this simplified version of DMD pathogenesis, a number of targets can be seen for therapeutic intervention. The use of antioxidants has already been tried and, to date, has not produced compelling clinical results. Another possibility is impeding immune cell over-infiltration into the muscle and/or to change the pro-inflammatory/anti-inflammatory balance in an effort to keep a chronic state of inflammation from developing. CSs have been the mainstay and the only efficacious therapeutic for DMD for decades. They are a blunt force way of reducing the inflammation in the skeletal muscles of DMD patients. ATL1102 also works to keep immune cells from entering the muscle, although it works on a different, more specific, population of immune cells. Then there are the cells and signalling molecules responsible for the deposition fibrous substances and fatty tissue, which represent an opportunity for intervention. Intramyocellularly, there are plenty of potential targets, as well, since ameliorating the level of dysfunction within the myocytes would likely slow the progression of downstream events. The list would just keep going if we had done more than skim what is known about the pathogenesis of DMD.

The level of dysfunction at a myocellular and macro-myocellular level in DMD indicates it will be extremely hard, if not impossible, to find a single target, short of replacing the mutated dystrophin gene with a fully functional one, capable of stopping the vast majority of disease processes occurring in DMD. To give DMD patients a life that comes close to resembling that of a healthy person is going to require several innovative drugs.

Why Shouldn't we Just Focus on Gene Editing?

One of the issues a complicated disease like DMD creates is that your mind tends to follow the path of least resistance when thinking about new therapies. **That is, what these patients need is fully functioning dystrophin. This leads you to start to think about gene editing**. Correcting DMD a patient's dystrophin gene would make them healthy and leave the rest of the genome (a collective term for all genes and the chromosomes that contain those genes) untouched, such that no unwanted mutations would be introduced to patients, and they would be free from medications for the rest of their lives.

If that is the case, why are we bothering with the other various and varied approaches in clinical trials to treat DMD, as described in Sheikh & Yokota (2021) Expert Opin Investig Drugs? Surely, a company like Pfizer, which currently has a gene therapy in clinical trials for DMD, can see where this is all going. **While gene editing would be the best therapy for DMD patients, the scientific and medical communities do not have the tools or knowledge to create one, yet**. **Moreover, as the old saying goes, "you don't know what you don't know" and unanticipated outcomes mean that only between 5% and 10% of new drugs that start clinical trials make it to market (Wouters et al (2020) JAMA)**. The biggest single reason a drug is abandoned in development is that something unforeseen occurs. These unforeseen events occur because some aspect of the drug, the disease or just the relevant general biology was not understood well enough. A major part of the reason for that is a high degree of understanding/knowledge is not the major factor in the mix that determines whether a company is willing to attempt developing a drug to treat a disease. The point at which a company is willing to say go, is the point at which pay-off justifies the risk. Pfizer knows all of these things, and it also knows that a gene editing therapy may be 20, 30, 40 or even 100 years away. As a result, they decided to and will continue to develop their gene therapy up until the pay-off does not justify the risk in their minds.

There are many things we do not know about gene therapies. **While some have been approved by the FDA, they all fall into one of two groups**. With one group, the gene therapy is conducted on cells that have been removed from the patient. They are then infused back into the patient. These products include the chimeric antigen receptor T-cell therapies (CAR-T), Kymriah (tisagenlecleucel, Novartis Pharmaceutical Corporation) and Tecartus (brexucabtagene autoleucel, Kite Pharma). With the other group of approved gene therapies, the therapy only needs to find its way into cells that occupy a fairly small and, generally, confined area of the body. For example, Imlygic (talimogene laherparepvec, Amgen), an oncolytic virus, is injected directly into a melanoma (skin cancer) tumour and only needs to infect nearby tumour cells. Luxtarna (voretigene neparvovec-rzyl, Spark Therapeutics) is used to treat retinal dystrophy. It is injected directly into the back of the eye and the gene product it delivers only needs to find its way into certain cells that are at the back of the eye.

The adequate delivery of a gene therapy for DMD is much more difficult and faces many more biological hurdles than faced by those gene therapies that have been approved. A gene therapy for DMD needs to find its way, after infusion into the patient's blood stream, all throughout the patient's body. It needs to find its way to the heart, which is relatively easy, but it also needs to find its way out of the blood stream, through various barriers, and then diffuse throughout each skeletal muscle, such that the therapeutic gene can find its way into enough myocytes to provide a clinical benefit to the patient. Some DMD patients, at least, suffer from cognitive impairment, such that if a gene therapy is really to do the job correctly, it also needs to find its way across the blood brain barrier, diffuse throughout the brain and into the neurons of the brain. CAR-T therapies have only been approved for haematological tumours, so the blood stream is really right where they need to be. Another issue DMD gene therapies face is that, while animal testing may indicate that the dystrophin is being made by cells and that it has enough functoriality, you cannot be 100% certain that it will do the same in humans until you actually put it into patients.

There is one point about gene therapies that needs to be made up front and it is one that most people don't understand. **Current gene therapies do not aim to cure the disease**. The dystrophin gene is the largest known gene in humans and it will not fit into the best currently available viral delivery vector, adeno-associated virus 9 (AAV9). The solution the pharmaceutical companies have come up with to deal with the issue is to use AAV9 to deliver cut down versions of dystrophin, often termed micro-dystrophin. While they obviously try to retain as much of the function of the full dystrophin protein as they can, but, as we said earlier, the nature and location of a mutation in the dystrophin gene is only a poor-predictor of the severity and progression BMD. That makes it very difficult to know whish parts of the dystrophin gene you need to keep and which parts you can discard in order to create a micro-dystrophin gene that will fit in an AAV9 vector. Since we know that an unusually large amount of the clinical severity and progression of BDM appears tied to other genes the patients' possess, we can predict with a reasonable amount of certainty that the absolute best outcome a gene therapy is likely to produce is one where a DMD patient starts to present as a BMD patient, with a high degree of variability in the level of clinical benefit each patient sees.

Pfizer discovered recently that developing a gene therapy for DMD is not going to be a walk in the park when it had a safety issue in its phase IIII gene therapy trial. Three patients developed serious side effects involving serious muscle weakness and two of the three developed myocarditis or inflammation of the heart. While Pfizer has not stopped the trial, they have had to exclude about 15% of patients who have certain DMD mutations from it (Pfizer's Letter to DMD Advocacy Group Regarding Gene Therapy Trial Safety Issues). Moreover, while Pfizer's phase III trial is enrolling patients, the FDA is yet to approve the company's Investigational New Drug (IND). The agency is not convinced that Pfizer's potency assay allows the company to determine how much active pharmaceutical ingredient (API) is in each dose a patient receives (Pfizer Press Release, 6 May 2021). Giving a patient too much active drug product increases safety risk, while too little means they will have gone through the trial and never had a chance to benefit in the first place. While Pfizer must certainly know this, they are not saying it out loud.

Sadly and very recently, a patient in Pfizer's phase Ib trial of its DMD gene therapy died according to a letter received by the Parent Project Muscular Dystrophy (The Pfizer DMD gene therapy team letter 20 December 2021; NCT03362502). Whether the death was linked to the gene therapy or not is still being investigated by Pfizer and the physicians at the clinical trial site where the patient was enrolled. The circumstances surrounding the death have not yet been made public. It is believed that the patient who passed away was non-ambulant (Fierce Biotech, News Report, 21 December 2021). If the death was linked to Pfizer's gene therapy, it will be important to understand whether the death was the result of side effects already seen in the trial or whether it was the result of previously unseen issues. Regardless, if the death is linked to the therapy Pfizer and the regulators will have some very tough decisions to make. The FDA has already placed a full clinical hold on Pfizer's IND for the therapy and Pfizer will not be allowed to open any clinical trial sites in the US until that hold is lifted. **An additional issue with gene therapies is that once they have been administered, they cannot be removed, unlike conventional drugs which will simply be eliminated by the body over time (generally, pretty quickly, once therapy is stopped, as is the case with ATL1102)**.

Sarepta Therapeutics and Solid Biosciences, the two other companies trialling gene therapies for DMD are having their own problems.

In January 2021, Sarepta announced the results of Part 1 of its phase II gene therapy trial, SRP-9001-102 (NCT03769116). The trial is a quadruple-blind, randomised, placebo-controlled, crossover trial in 41 DMD patients aged four to seven years (Sarepta Therapeutics, Press Release, 7 January 2021). The trial has three parts. In the first part, 20 patients were dosed with the gene therapy and 21 given placebo, with the key primary endpoint of the North Star Ambulatory Assessment (NSAA) for Parts 1 and 2 as measured at 48 weeks after the start of each part. The NSAA is a 17-item rating scale that is used to measure functional motor assessment in ambulant DMD patients and it is an accepted primary endpoint for DMD trials in ambulant children. It uses an ordinal scale with a maximum score of 34 points indicating fully independent function. Part 3 of the study is an open-label follow-up period. **After the first 48 weeks, the patients given the micro-dystrophin gene therapy failed to show a significant improvement over placebo (p=0.37).** NSAA scores increased in the treatment group by 1.7 points relative to baseline, while the control group increased 0.9 points. At 12 weeks post treatment, test group patients had micro-dystrophin levels equivalent to 28.1% of the dystrophin levels seen in healthy children of the same age. Sarepta said that heathier six- and seven-year-old children were randomised to the placebo arm and that this likely explained the trial's failure to show a significant difference over placebo. While they might say that, a p-value=0.37 is not really even a trend toward greater independence in treated patients. In Part 2 of the trial, the 21 patients who received the placebo in Part 1 of the study will receive SRP-9001 (the gene therapy), while those who received the gene therapy in Part 1 will receive the placebo in Part 2. The two groups will then be compared by the NSAA, again, at 48

weeks. Despite the results of Part 1, Sarepta commenced a phase III trial of SRP-9001 in ambulant DMD patients in early October 2021 (Sarepta Therapeutics, Press Release, 4 October 2021).

Solid Biosciences putative DMD gene therapy, SGT-001, was put on clinical hold in 2018 after one of the first three patients to receive the therapy in an eight patient phase I/II study (NCT03368742) showed signs of liver damage, while others experienced a decline in platelet counts and other side effects (Solid Biosciences, Press Release, March 14, 2018). The FDA lifted its clinical hold on SGT-001 in October 2020 (Solid Biosciences, Press Release, October 2020) and the company has dosed a further three patients since then without incident. It appears from Solid's statement that the safety issues which led to the clinical hold were tied to the company's manufacturing process for SGT-001, with there being a large number of empty viral capsids in the first doses given. Empty viral capsids don't carry the gene therapy, but they do increase the chances of safety issues. Solid has also reduced the dose patients will be given in consultation with the FDA and amended the clinical trial protocol to include the use of a complement inhibitor. Complement is a biochemical cascade that certain immune cells and immune-related molecules can activate toward a target cell. It ultimately leads to irreparable holes in the target cell's membrane causing it to die. Human cells infected by a virus can become a target against which complement is activated and, consequently, it is an adverse event the use of an AAV9 viral vector could cause.

Given each of the gene therapies in development has already had a major stumble, it seems likely that more are to come. Possibly more worrying for the companies than the safety issues is the 28.1% expression level of micro-dystrophin relative to the expression levels of dystrophin seen in healthy children. **Since micro-dystrophin is not the equivalent of the full dystrophin molecule, it is misleading to say that patients have 28.1% of the levels of dystrophin seen in healthy individuals because the form of micro-dystrophin they have received, and are expressing, does not have 28.1% of the activity of the full dystrophin gene of that of a healthy person**. However, even the term activity here is a poor one because the form of micro-dystrophin the patients have been given may be totally sufficient for the protein to carry out some functions of the full length DMD protein, but totally insufficient to carry out others. Whatever the case, looking at the level of micro-dystrophin expression as being equivalent to 28.1% of the expression of full-length dystrophin in a healthy individual overstates the reality of the situation, quite possibly considerably.

There are CEOs whose real advantage is that they can make the most implausible science sound like it is a certainty to work. When you scratch the surface, that initial certainty becomes less likely until you realise you would be better off taking your money to the casino than investing in the company. It is the complexity of DMD pathogenesis and the relative simplicity that a gene editing or gene therapy solution offers that has the same effect as the CEO who is a good story. But, once you start to think things through step-by-step, it becomes very apparent that the relative simplicity of a gene editing or gene therapy treatment is simply a mirage.

The Consensus Future of DMD Therapeutics

Since gene therapies represent more of an incremental improvement, if they work, rather than a transformative one in the treatment of DMD, they will almost certainly be used in combination with and on top of CSs. The same is true with the therapeutics in development for DMD, which are likely to show highly variable efficacy among recipients of them. Scientific and medical expert thought on these issues has developed into a consensus that, whether gene therapies are successful or not, the future treatment of DMD will involve several therapeutics, not just one (Cordova et al (2018) Front Genet; Hoffman (2020) Handb Exp Pharmacol). The need will also almost certainly exist for personalised treatment, since the variable manifestation of BMD indicates new therapeutics for DMD will likely have variable efficacy, as well, given the same modifier proteins exist in DMD patients. Those modifier proteins are just quiet in DMD, because the absence of functional dystrophin means there is nothing there to bring the effect of the modifier proteins to the fore. This remains true even if gene editing therapeutics are developed surprisingly fast because the first iteration of those therapies will also, at best, provide those born with DMD with a BMD-type disease (Himic & Davies (2021) Eur J Hum Genet). Even at the highest, least specific, level, current crude gene editing tools are lacking in their theoretical ability to edit DMD dystrophin genes in a manner that would see the patient end up with a dystrophin gene equivalent to that in healthy individuals. There are ideas and a few experiments aimed at changing that, but if gene editing is at the embryonic stage, gene editing that restores a gene back to a natural state is a zygote.

For the sake of clarity, it takes an average of 12-years from the commencement of formal preclinical testing to the point which a drug receives its first major marketing approval (either EMA or FDA) (Van Norman (2016) JACC Basic Transl Sci). Determining an average discovery period, including lead selection, is impossible due to the lack of available information and the difficulty in ascertaining such information. If it were possible to come up with a number it would be highly variable based on the nature of the process and, likely, be many years on average, at least, based on our 25 plus years of following the industry.

The overall reason multiple therapies will be required to treat DMD is that no one therapy is likely to maximise clinical outcomes (Hoffman (2020) Handb Exp Pharmacol). One group has even proposed that combinations therapies are likely to be needed simply to get the gene into the required number of myocytes or better (Cordova et al (2018) Front Genet).

Future DMD patient therapy will involve multiple therapies varying by individual patient. How long into the future that will hold is anyone's guess, but nobody has ever referred to drug development as the equivalent of the 100-metre sprint or a 10,000-metre race. At best, it is a marathon, at worst, it is an ultra-marathon, at its absolute worst, it is an ultra-marathon where a finishing line never materialises.

Integrins, Duchenne Muscular Dystrophy and ATL1102

VLA-4 is a cell adhesion molecule and it functions to allow white blood cells expressing it to on their surfaces to adhere to cells expressing Vascular Cell Adhesion Protein-1 (VCAM-1 or CD106) and components of the ECM called fibronectin and osteopontin. Osteopontin is a cytokine that is found to be expressed in high levels where there is tissue damage. It plays important roles in tissue repair and regeneration and regulation of the inflammatory response (Bello & Pegoraro (2019) J Clin Med). Similarly, fibronectin has a wide range of roles cell adhesion, growth, migration, and differentiation (Dalton & Lemmon (2021) Cells) White blood cells need to express VLA-4 in order to leave blood vessels and enter into the tissues of a human. VLA-4, however, does not help the white cells do that unless the endothelial cells (the cells that line blood vessels) are expressing VCAM-1. If the endothelial cells are expressing VCAM-1 and the white cell has received an appropriate activating signal, VLA-4 will bind VCAM-1 and in a well-defined process termed diapedesis, the white cell moves out of the blood vessel and into the tissues. Once in the tissues, VLA-4 on the surface of lymphocytes interacts with fibronectin and osteopontin in the ECM, in response to which the lymphocytes release cytokines and/or respond to appropriate chemokines (chemotactic factors which particular cells will follow in order to arrive where they are needed).

VLA-4 expression is not limited to leukocytes (white blood cells in the tissues), but it is also expressed by white blood cells in the blood stream (Limroth et al (2014) Neurology). Studies relevant to targeting VLA-4, show a marked decrease in immune cells and pre-immune cells in the blood, such that the population of white blood cells and their pre-cursors available to migrate into the muscle tissue of DMD patients is highly likely markedly reduced by ATL02, as well (Mellergård (2012) Linköping University Medical Dissertations No. 1332 and references therein).

In 2015, Pinto-Mariz et al (2015) Skelet Muscle published a highly convincing paper on a clinical trial that looked at the expression of a wide range of potential markers of DMD progression in 75 DMD patients, split into three cohorts, based on their ability to walk, relative to a group of age and sex-matched healthy volunteers. CD449d was the only maker which correlated with the progression of the disease. This study was undertaken as result of a smaller study (n=10) published in 2010 that indicated to the group that CD49d expression was much higher on two sub-groups of key immune cells known as CD4+ and CD8+ T-cells in DMD patients compared to controls (Pinto-Mariz (2010) Neuroimmunol). The group found that CD49d expression was higher on subgroups of CD4+ and CD8+ T-cells in the blood stream and the muscular infiltrates of the DMD patients. These subgroups of cells are denoted as CD4+ CD49d^{hi} (or CD4+ CD19d++) and CD8+ CD49d^{hi} (or CD8 CD19d++). Importantly, an antibody directed at CD49d was able to block the migration of the CD49d^{hi} CD4+ and CD8+ T-cells in a cell migration assay (test) and an adhesion assay using cells collected from the DMD patients. This provided compelling evidence that the high expression of CD49d on these cells was implicated in the pathogenesis of DMD. In fact, **the biology of CD4+ CD49d^{hi} and CD8+ CD49d^{hi} cells suggests they are integral to the pathogenesis of DMD and their levels in the blood and tissues of DMD patients was shown to be correlated with (Pinto-Mariz et al (2015) Skelet Muscle) and appear to determine the speed with which a patient's DMD progress**.

These findings also fit with previous studies of the autoimmune disease multiple sclerosis (MS), which also found CD4+ CD49d^{hi} and CD8+ CD49d^{hi} cells to be central to the pathogenesis of the disease (Sheremata et al (2005) CNS Drugs). The only difference was that VLA-4 and its CD49d subunit allowed CD4+ CD49d+ and CD8+ CD49d+ T-cells to migrate through the blood-brain barrier and into the brain and central nervous system in MS, while VLA-4 enables those same T-cells to pass through the walls of the blood vessels and into the musculature cells in DMD. The precise role of CD49d+ & CD49d^{hl} CD4+ & CD8+ T-cells in the pathogenesis of DMD is not completely understood. However, the levels of CD49+ & CD49d^{h} CD4+ and CD8+ appear to be unaffected by the use of CSs (Pinto-Mariz et al (2015) Skelet Muscle; Luján et al (1998) Mult Scler; Hughes et al (1996) Am J Physiol), C8+ T-cells (also referred to cytotoxic T-cells) are effector cells that can dispatch of other cells in several ways and both CD4+ and CD8+ T-cells are key cells in several autoimmune diseases. The latter two points are important because they fit with the pathogenesis of MS. It is very possible and plausible CD49d+ & CD49d^{hl} CD4+ & CD8+ T-cells are central to the damage the immune system does to skeletal muscles in DMD patients and responsible for the eventual development of chronic inflammation in the skeletal muscles of DMD patients. **This would be very similar to the MS story. It would also be similar to the story that played out in Crohn's disease, an autoimmune disease of the gut, with α4β7, a gut-specific homing integrin (reviewed in Kempster and Kaser (2014) Gut), integral to the migration of CD4+ and CD8+ cells to the areas of inflammation in the gut characteristic of the disease (Thomas et al (2012) Inflammopharmacology)**. One can imagine several ways in which the ongoing damage to myocytes as a result of muscle contraction could lead to the development of self-reactive T-cells.

All of the findings suggested CD49d was an excellent therapeutic target for treating DMD and, as we stated in the introduction, ATL1102 was designed and had been shown in the clinic to effectively target CD49d. Essentially, the scientific rationale for developing ATL1102 for DMD had become very strong. Importantly, these findings also provided an indication small enough for Antisense to develop ATL1102 on its own and it provided Antisense an indication where the risk-benefit profile of the disease strongly favoured ATL1102.

CD49d as a Therapeutic Target, Controversy and Dealing Appropriately With The Regulator

A drug called natalizumab (Tysabri®, Biogen) that targeted CD49d and had been approved for the treatment of relapsing remitting MS (RRMS, the earliest stage of MS) by the US FDA in November 2004 prior to completion of phase III trials because the interim results from the trial were so strong. **Three months after FDA approval, however, the co-developers of natalizumab, Elan Corporation and Biogen, voluntarily halted trials of natalizumab and took the drug off of the market in February 2005**. The reason was two patients had developed progressive multifocal leukoencephalopathy (PML). A third patient who developed PML was identified through a retrospective review of the clinical trial data the companies were collecting as part of natalizumab's trials in Crohn's disease. PML is a potentially lethal disease that delaminates the myelin sheath found around parts of the nerves in the brain and it is caused by a virus known as the John Cunningham (JC) virus. The FDA quickly placed all α4 integrin inhibitors on clinical hold. **When no more cases of PML were found in a review of the MS clinical trial data and data from patients who had been receiving natalizumab commercially for MS, the FDA quickly re-authorised the drug in June 2005**. The EMA approved the drug in June 2006 for RMMS. In January 2008, natalizumab received from the FDA for use in patients with moderate to severe Crohn's disease (J Clin Invest, News Report, The Comeback Kid: Tysabri Now Approved for Crohn's Disease).

The problem with potential safety issues is that it is very hard to show that a drug does not cause the issue or that the issue is not relevant in a risk-benefit context, simply because of the nature of safety issues and the realities of statistics. While the acceptable risk-benefit profile of natalizumab was strongly indicated by the FDA's quick re-authorisation of the drug in 2005, the issue did become pervasive and has remained somewhat so ever since. However, the issue was put to bed by a paper published in 2020, reporting on 10-years of data collected from the Tysabri Observational Program (TOP). TOP is an ongoing, open-label, multinational, multicentre prospective observational study of patients with RRMS prescribed natalizumab in real-world practice settings (Butzkueven at al (2020) Neurol Neurosurg Psychiatry; NCT00493298). TOP was established to answer the safety questions that arose around natalizumab in 2005. The 2020 report on TOP is based on data collected from 6,148 patients. **The authors concluded that with natalizumab "the incidence of opportunistic infections remained low over time, and such infections tended to occur within the first few years of treatment". The authors went on to state, "the results demonstrate excellent long-term safety and substantial disease control"**. To have 10 years of safety data is extremely rare and this study has demonstrated both the safety of natalizumab in a risk-benefit context and in a standard safety context.

Teva Pharmaceuticals licensed ATL1102 from Antisense in February 2008 for RRMS, demonstrating that they did not believe ATL1102's targeting of CD49d constituted a safety risk. The reasons for this according to Antisense were that despite sharing the same target as natalizumab, the overall MOA of the two drugs is quite different, as is relatively easy to imagine given natalizumab is a large molecule which acts on the outside of cells, while ATL1102 is smaller and acts inside of them. For example, tissue penetration by natalizumab would certainly be substantially less than ATL1102, giving rise to differences in the areas of the body where the two molecules are active. Secondly, ATL1102 does not influence the pathway through which latent JC virus is thought to be reactivated. All but one of the serious treatment emergent adverse events (TEAEs) associated with the drug in its phase II MS trial (n=74) was a relapse of MS, something that is to be expected in such a trial (Limroth et al (2014) Neurology). The remaining serious TEAE was a case of grade 2 thrombocytopaenia (low platelet count; measured on a scale of 0 to 5, where 0 is normal and 5 is death) in the ATL1102 treatment group.

The dosage of ATL1102 used in Antisense's phase II DMD trial was 25mg/week delivered by sub-cutaneous injection, while the company's upcoming European trial will use dosages of 25mg/week and 50mg/week. **These dosages are 1/16 and 1/8 of those used in the phase IIa MS trial, respectively, in which patients received 2 x 200mg/week subcutaneous injections, with one injection on day 4 and the other on day 7 of each week**. It is unusual for a company to trial a drug at a higher dose in a pivotal trial than was used in previous studies of the drug in a particular indication. However, the EMA has signed off on it after reviewing the entirety of ATL1102's safety data.

Additionally, the safety of ATL1102 has been assessed for 24 weeks in a non-human primate (NHP) study at 1.5mg/kg/week and 3mg/kg/week. At those doses, the drug was found to be safe and well tolerated. The doses used in the NHP study were substantially lower than those used in the MS study. **In the upcoming pivotal trial of ATL1102 in non-ambulant DMD patients, entry into the study is restricted to patients who weigh more the 25kg and, while it is possible that a couple of patients could fall below that weight during the trial it is unlikely, given the patients will be between 10-years and 18 years-old and many will still be growing**. Therefore, the highest dose any patient is likely to see is 2mg/kg/week or, perhaps a little higher, if any patient falls below 25kg. A patients would need to fall to 16.6kg and be in the 50mg dose cohort to see a dose higher than the 3mg/kg/week tested in the NHP study. More likely than not, fall in weight of this magnitude would indicate that there was something seriously wrong with patient and the protocol for the study would almost certainly prevent them from being dosed.

Teva Hands ATL1102 Back to Antisense

While Teva was in control of ATL1102, it conducted a long-term NHP toxicology study, which encountered a widespread issue. We believe the issue was vasculitis (inflammation of the blood vessels) and that it occurred at dose all levels tested. The development of vasculitis in NHPs treated with antisense oligonucleotides (ASOs; the general term for the class of Antisense's drug) is not surprising, since it, along with glomerulonephritis, are considered the number one challenge in the toxicological testing of ASOs largely and because NHPs are thought to be particularly prone to ASO-induced vasculitis (Frazier (2015) Toxicol Pathol). **However,**

Vasculitis has not been an issue in human ASO trials and it may be an NHP specific effect. However, it is considered a pro-inflammatory effect and other pro-inflammatory effects, although, pro-inflammatory effects due to ASOs have been noted in humans, such as flu-like symptoms and injection-site reactions. The occurrence of these lesser TEAEs keeps vasculitis on the table as a potential issue in human trials.

Unfortunately, the issue with the NHP study meant that it would need to be repeated and the program delayed. Teva had other irons in the fire for MS and, all things considered they felt they were in a position where a tough decision needed to be made. Consequently, they handed ATL1102 back to Antisense.

We do not know enough about is the doses used in Teva's long-term NHP toxicology study or how the dose of 2 x 200mg/week of ATL1102 was derived for the MS study to make an informed comment specifically on those events, however, we do have enough information to assess the situation and where things stand at the moment.

The FDA guides industry to base their starting dose in human trials on the highest dose at which no adverse effects were in the most sensitive animal species (the so-called NOAEL or no-observed-adverse-effect level) less a safety factor, where the default factor is 10 (FDAs Clinical Investigator Course, Safety Considerations in Phase 1, Accessed 191221). In a lot of ways, the agency expects logic to guide you toward the most sensitive species for the determination of NOAEL. The agency then expects logic to guide to an appropriate risk factor starting 10.

What we do know, however, is that:

- ATL1102 has had a fair amount of toxicology testing and a reasonable amount of clinical trialling, such that the safety factor that would have been used to determine the initial dose for a first-in-human trial, can be reduced,
- In a repeat NHP study conducted by Antisense doses of 1.5mg/kg/week and 3mg/kg/week were well tolerated. Moreover, signals of efficacy have been seen at 25mg/week in DMD patients,
- The EMA has reviewed the safety data collected on ATL1102 and agreed to the inclusion of a higher dose than has previously been used in DMD patients,
- Good signals of efficacy were see in the first phase II trial of ATL1102 at 25mg/week, such that the company and investors can be reasonably comfortable, particularly with the inclusion of the 50mg/week arm in the pivotal study, that the doses of ATL1102 in that trial are within a clinically relevant range.

The FDA is Playing Fair

The FDA denied an application for Fast Track Designation (FTD) which the Antisense had submitted to the agency. FTD is designed to speed. the development of drugs to treat serious or life-threatening diseases. **There is no question that ATL1102 with non-ambulant DMD is worthy of the designation**. Unfortunately, though, a past that Antisense played no direct role in came back to haunt them. When Antisense moved to conduct a 6-month phase IIb study at a dose of 25mg/weekly in MS in 2017, they did persuade the FDA to lift the full clinical hold to allow it (FDA never lifted the March 2005 clinical hold it placed on all α4 integrin inhibitors, leaving companies with them to negotiate with the FDA on a case-by-case basis). The FDA, however, left a partial clinical hold ATL1102, which limited Antisense to ATL1102 to studies of no longer than 6-months in duration at a dose no higher than 25mg/week. Since Antisense's development plan for DMD contained in the FTD application sought a 52-week study in DMD and, presumably, incorporated a 50mg/week dose arm of ATL1102 dose, as its paediatric investigation plan for the EMA did, the FDA took the view that Antisense could not meet its development plan at that time. Being able to do so is a requirement for the grant of FTD.

Underlying that partial clinical was the fact that the FDA's guidance is that a company needs a 9-month non-rodent toxicology study to support a multidose study of an investigational drug greater than 6-months duration in humans (FDA Guidance for Industry, Studies for the Conduct of Human Clinical Trials, 2010). This is something Antisense has never done before to our knowledge, and at the next meeting Antisense had with the agency, they advised Antisense of the need for a 9-month toxicology study. **The FDA did concede some ground in that they would allow Antisense to start a US pivotal study, as long as the animal toxicology study was completed before any patients had been dosed for longer than 6-months. Obviously, this could save Antisense some time**. So, it is not the distant past that is influencing the FDA here nor are they making demands due to some perceived safety risk. They are simply making Antisense telling Antisense what the guidelines say and the FDA has very little choice but to stick to their guidelines. In the past, when the FDA has granted any company an exemption from a rule, a line of pharmaceutical companies two blocks long forms in less than 5-minutes. All of whom want the same exemption. Once Antisense delivers the study report on new NHP toxicology study and the pivotal study trial protocol to the agency and they have reviewed the documents, the partial hold should be lifted, FTD granted and the company in a position to run the US study in non-ambulant DMD patients that it wants to run.

Intelligently and to that end, just recently, Antisense sent the agency a protocol for a 9-month NHP toxicology study for the FDA to review. The protocol was developed with the help of John C. Kapeghian, Ph.D. DABT of Preclinical Safety Associates, LLC. Dr Kapeghian has been Antisense's toxicology consultant for well over a decade and, like everybody else involved in the ATL1102 program in terms of their area of speciality, he has developed deep understanding of the compounds toxicology. We believe the FDA will be satisfied with the NHP protocol Antisense has delivered to them, although, as with just about every aspect of a drug development program, the FDA may have some minor suggestions.

The overall take home point from this section whole section, from natalizumab's early PML issues through to Antisense being denied FTD by the FDA is really just one thing, these events, when examined closely, to do not provide a negative signal or raise potential red flags about ATL1102. Antisense simply appears to have had bad luck and that happens sometimes.

The Mechanism of Action of ATL1102

ATL1102 has a unique MOA, compared to other drugs and, certainly, in the area of DMD drug development. It works by entering the CD4+ CD49d+, CD8+ CD49d+, CD4+ CD49d^{hi} and CD8+ CD49d^{hi} cells and binding a temporary molecule copied from the gene containing the code for CD49d. Normally, this molecule would translated into a protein. However, when it is bound to ATL1102 it creates what human cells view as a generally undesirable molecule. An enzyme in our cells called ribonuclease H1 (RNAse H1) recognises these types of 'undesirable' molecules and degrades them. As such, ATL1102 prevents the CD49d protein from being made. Without CD49d, functional VLA-4 cannot be made, so there is nothing on these cells to create the required interaction with VCAM-1 needed to migrate out of the blood stream and into the tissues where they cause disease. ATL-1102 also appears extremely likely to be active in the blood stream and the lymphoid tissues, where it would act to decrease the pool of cells available to migrate into the tissues of DMD patients.

An extensive review of antisense technology can be found here: Crooke et al (2021) J Biol Chem.

The following provides an explanation of the technology as it applies to ATL1102 and CD49d.

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 protein will eventually be made from 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 is termed the 'antisense' strand. Together, the two strands are said to be complementary to one another. ATL1102 and the antisense drugs of today are chemically different to the nucleic acids found in our body, but the general principal remains the same, with the antisense drug being the exact opposite and complementary to the target gene.

ATL1102 has been designed to be the antisense strand of the mRNA that is produced by the body from the CD49d gene. mRNA is the term for strands of RNA that will eventually be read by to build a protein. In the absence of ATL1102, the mRNA for CD49d would be translated by the cell's ribosomes into the protein CD49d. Ribosomes are, effectively, protein builders, reading off the plan of the mRNA produced from the DNA gene. 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 mRNA and the complete CD49d protein is made. The process is generalised and applicable to the way all proteins are made.

It was discovered in the 1990s that cells have an enzyme, called RNAse H1, which does not like to see mRNA in a double-stranded form (Crooke (1998) Antisense Nucleic Acid Drug Dev). The reason is that through evolution, these types of molecules have come to be recognised by mammalian cells as viral in origin. If RNAse H1 comes into contact with mRNA in a double-stranded form, it breaks it down as a defence against the virus. 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 complementary in structure to each other. Similarly, complementary strands of DNA and RNA can bind to each other.

Scientists worked out that they could exploit this situation. Single strands of nucleic acids could be designed in the laboratory that are complementary to particular molecules of mRNA in a cell. By allowing the designed molecule to enter the cell, it binds the complementary strand of mRNA. RNAse H1 detects the double-stranded nucleic acid molecule and moves in and degrades it. Since the mRNA never reaches the ribosomes, the protein the strand of mRNA encoded is never produced. Effectively, the gene is silenced.

The differences in the ways that antisense and antibody drugs work can make a difference to how well one or the other works in treating a disease, due to the general pharmacokinetic and pharmacodynamic properties of the two types of drugs. An antisense drug stops the whole protein being made, while an antibody binds to only a small portion of the target protein. Most likely, the nature of the disease will determine which type of drug is likely to work best. Certainly, there are arguments that had ATL1102 been developed for RRMS, it would have worked better than natalizumab and that the initial severe adverse events with natalizumab that caused problems for that drug may never have been an issue. Unfortunately, an in-depth discussion of the differences between the two classes of drug and which class may work better for certain diseases is beyond the scope of this report.

ATL1102: Early Signs of Activity

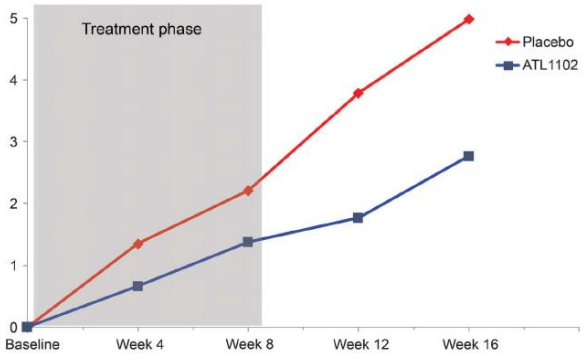
ATL1102 has been shown to be biologically and clinically active. Antisense demonstrated this in its phase IIa clinical trial in patients with RRMS (Limroth et al (2014) Neurology). The study was a multicentre, randomised, double blind, placebo-controlled, trial, such that it had all the components of a gold-standard clinical study. Seventy-four patients were recruited into the study, representing the intention-to-treat (ITT) study population, with 72 patients completing the study, representing the per protocol population (PP).

At times, it can be important to know whether the data you are looking at is based on the ITT population or a PP population. The reason the FDA and other regulators will only give weight to the ITT population is that 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 and they can be informative. For example, a high dropout rate may cause a drug to fail a trial. If the reason for that dropout rate can be ascertained and fixed or ameliorated, the development of a drug that might otherwise be abandoned, can be turned into a success. A quality company, however, will always release the ITT results if they release the PP results. A company that releases only the PP results from a trial is usually trying to hide something. In this trial, there is only a two-patient difference between the two populations, such that it is likely it would not make much difference which population you looked at. As stated earlier, MS is a progressive autoimmune disease where the immune system attacks the nerves in the brain. These attacks create lesions in the brain and cause problems with movement and other aspects of normal human functioning. These lesions are visible by magnetic resonance imaging (MRI) and the primary endpoint for this, and most other MS trials, is to reduce the cumulative number of new active lesions (either new or enhancing lesions).

The main results of the trial are given in figure 2 (Limmroth et al (2014) Neurology). The primary endpoint of the trial was met, with ATL1102 significantly reducing the cumulative number of new active lesions by 54.4% at eight weeks. ATL1102 also significantly reduced the number of new lesions by 67.9%. These results were highly comparable to those obtained with natalizumab over a 12-week period (Tubridy et al (1999) Neurology).

The results from this trial were unequivocally positive.

Figure 2. Cumulative New Active MS Lesions in the Phase II Trial of ATL1102 in MS.



Limmroth et al (2014) Neurology

As mentioned, Teva Pharmaceuticals did licence ATL1102 from Antisense for RRMS in late 2008 and if Teva, was not a generics company, but an innovator company, it may well have done a better job with the compound and studied it at lower doses in the long term NHP toxicology that went poorly, rather than the higher doses it went for.

Clinical Development of ATL1102 for DMD

Antisense has chosen to target non-ambulant DMD patients as its first indication for the re-development of ATL1102. This appears to be a shrewd move for several reasons:

- Only one other company appears to be truly focused on developing a therapeutic for this indication and ATL1102 should work synergistically with it.
- This is the DMD population in which the clinical need is the greatest,
- The risk-benefit profile for a therapeutic for this population is unlikely to be burdensome,
- It is a population for which Antisense could choose to market ATL1102 itself, at least, in Europe or the US.
- CSs, the only therapy for DMD patients for which there is a large body of evidence supporting their use, have no effect on the number of CD49 + or CD49d^{hi} T-cells in DMD patients.
- A relatively small single pivotal trial is likely to be sufficient for marketing applications to be submitted to the major regulatory agencies.
- The number of non-ambulant DMD patients is greater than the number of ambulant ones,

- There is nothing stopping Antisense from commencing a pivotal trial in ambulant DMD patients if it chooses to do so and with a trial already being run, or having been run, in non-ambulant patients, much of the clinical infrastructure will already be in place, making it a much easier proposition than starting a de novo trial.

Antisense's First Trial in DMD Patients

Antisense's first trial of ATL1102 in DMD was a single arm, open-label trial in nine non-ambulatory patients receiving 25mg of ATL1102 by subcutaneous injection, weekly, for 24 weeks. This is a fairly typical trial design for a therapeutic being studied in a rare disease for the first time. In fact, the vast majority of all clinical trials are single arm. A non-ambulatory DMD patient was defined as one who could walk no more than 75 metres in the six-minute walk test. Most of the research and clinical trials in DMD have been focused on patients who are ambulatory, so endpoints, particularly the primary one, are a matter for discussion with the regulators.

The primary endpoint of the study was to assess the safety and tolerability of ATL1102 in non-ambulatory DMD patients. Whenever a therapeutic is studied in a new indication, the primary endpoint of that study will be the safety and tolerability of the treatment in that population. The reason is that if a therapeutic is not safe or tolerable, it almost certainly won't prove efficacious, and exposing a large number of patients to any new therapeutic is unethical. Furthermore, while a therapeutic may work in one disease, that does not mean it will work in a similar disease or, necessarily, be safe and tolerable in that similar disease.

The secondary endpoints of studies like these is where things begin to get interesting, because they inform the company and investors about the effects of the drug that could be related to potential efficacy. In this trial, a major secondary endpoint was whether ATL1102 had an effect on the levels of circulating CD4+ CD49d^{hi} and CD8+ CD49d^{hi} T-cells. Other secondary endpoints are measurements of upper limb strength and lung function. All of these things progressively decline in DMD patients from approximately 10 years of age, despite the use of CSs. If it looks like ATL1102 might be slowing that decline, it would be a positive result as far as the potential clinical efficacy of ATL1102 is concerned. Since this is a single-arm study and the patient numbers are small, detecting a slowing in the decline of the functional aspects of DMD patients might have proved difficult and it is one reason why the measurement of CD4+ CD49d^{hi} and CD8+ CD49d^{hi} T-cells were such an important part of the study. Since the mechanism of action (MOA) data around ATL1102 is so tight, if the drug is decreasing those populations of cells, it will likely be only a matter of trial size before a significant clinical benefit is seen. The similarities between what seems to be occurring in DMD with what occurs in RRMS and Crohn's disease increases the strength of that observation since drugs which target CD49d have been shown to be efficacious for both them and approved by the regulator. Declines in the level of CD49d^{hi} T-cells are also likely to be relatively easy to detect, since the effect of ATL1102 on the number of these cells can be compared to the level of the cells that each patient had at baseline (just prior to commencing therapy with ATL1102). In other words, each patient sort of acts like their own control.

The Results

Overall, the trial met its primary endpoint, with ATL1102 found to be safe and tolerable.

The results of functional measurements from the study, as announced by the company, are given in figures 3, 4, 5 and 6.

The Performance of Upper Limb Module, version 2.0 (PUL2.0), while officially a secondary endpoint, would be considered the main efficacy endpoint of the trial. PUL2.0 is analogous to the NSAA used in ambulatory patients, of course, is focused on capabilities non-ambulant patients still have. PUL2.0 provides a standardised scale specifically designed to assess upper limb function in DMD patients (Mayhew et al (2013) Dev Med Child Neurol). There were a range of other secondary endpoints as follows:

- The MyoGrip test, which uses a specially-designed device to measure hand grip strength via the pressure it exerts, squeezing the device in a manner in which the reader should be able to visualise.
- The MyoPinch test, a specially-designed pressure measurement device placed between the thumb and the side of the index finger, as one might hold a dinner plate with one hand. The patient pinches the measurement device and the pressure is recorded by the device.
- The MoviPlate test, another specifically-designed device, broadly assesses how well the hand and fingers are working by determining how many times a patient can tap an upper and lower target in 30 seconds.
- Forced Vital Capacity (FVC) or the maximum volume of air a patient can exhale after a maximal inhalation provides one measure of lung function,
- Peak Expiratory Flow (PEF) or the maximal rate at which a patient can expel air from their lungs after a full inhalation provides another,
- Relevant peripheral lymphocyte (or white blood cell) counts, including natural killer cells.
- Magnetic resonance imaging of the muscles to determine changes in fat and lean muscle content.

All tests were performed according to accepted practice.

PUL2.0 is the cumulative score of 0, 1 or 2 to the answers to a questionnaire that looks at three dimensions of upper limb performance. Those dimensions are the shoulder (six items), elbow (nine items) and wrist and hand (seven items). The maximum score is 42 for the healthiest patients. PUL2.0 has been shown to be more reliable than the previous version, PUL1.2, and it is sensitive enough to detect changes in a patient's CS regime (Pane et al (2015) Neuromuscul Disord). Currently, PUL2.0 represents the gold standard in assessing upper limb performance in both ambulant and non-ambulant DMD patients.

Figure 3. Clinical Data from the Phase II Trial of ATL1102 in Non-Ambulant DMD Patients.

	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)

Source: Antisense Therapeutics Limited, ASX Announcement, 21 Mat 2020

The results of some of the tests just described are normalised and presented as the percentage expected in healthy humans. This is done because the patients are still growing. As a result of DMD's progression, the MyoGrip results, for example, would be expected to decline over time (Hogrel et al (2020) J Neurol; Hogrel Interview (2020) First Author Grip Strength Study). However, younger DMD patients are putting on muscle mass faster than the disease destroys it and, hence, in young patients you expect to and do see increasing MyoGrip scores until they reach the stage where the progression of their DMD becomes the dominant determinant of their muscle mass, rather than their growth. This dynamic means that if only the raw results of tests were looked at, they would be heavily influenced by the age of the patients in the study, particularly when the number of patients is small. As such, it would be easy to erroneously interpret the raw results of the individual tests. Normalising the data helps to remove the influence of the age of the patients in the study as a variable, making the results more reliable and easier to interpret. In DMD patients, growth tends to dominate over the progression of DMD up until approximately the age of 12. After that, the progression of DMD starts to dominate.

Figure 3 provides the clinical results from the trial for PUL2.0, as well as the MyoGrip, MyoPinch and the lung tests.

The PUL2.0 scores are the highlight because PUL2.0 was the single broadest measurement of patients' upper limb function. Given the fairly consistent progressive nature of DMD and the age of participants in the study, PUL2.0 scores would be expected to decline in non-ambulant patients over time (Pane et al (2018) PLoS One). **The mean PUL2.0 score in the ATL1102-treated patients is suggestive of an approximate one-point improvement, which goes against the natural history of DMD and represents a really promising result** (Pane et al (2018) PLoS One). We have not provided the full set of MoviPlate results, however, they came out in ATL1102's favour, as well, by 1.9 points. As with the other tests that were done, the MoviPlate would have been expected to decline, as well.

Due to the size and nature of the study, a promising stabilizing result is the best that can be hoped for in any of these measurements. That is the nature of the trial. In fact, all of the results, with the exception of percentage predicted FVC, can be regarded as promising. Given the trial size, the natural variation associated with each test and the effect of chance on the results, the Antisense would have required a fair bit of luck to see all of the ATL1102 results go its way.

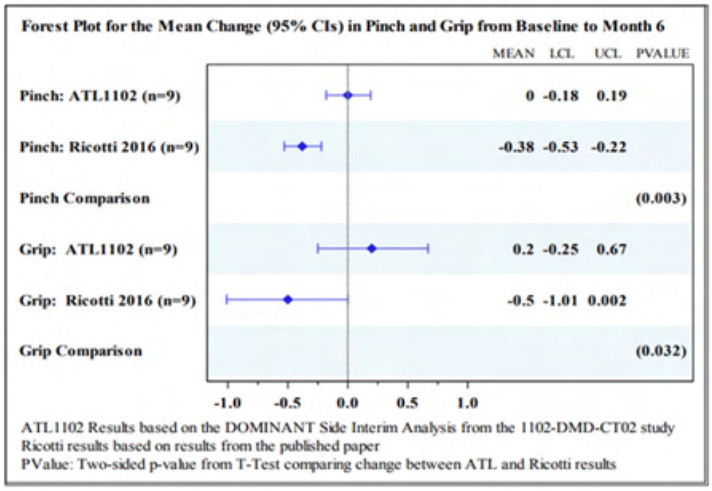
Figure 4 compares the MyoGrip and MyoPinch scores from the ATL1102 study with a historical control group derived from Ricotti (2016) PLoS One. The control group consisted of the same number of boys (n=nine) as the ATL1102 study, with eight out of nine in each group being on CSs. The statistical testing provides a measure of the difference between the results, as opposed to a strict determination of whether the results are significantly different or not due to the nature of the two groups being compared. The comparison provides some evidence that ATL1102 is slowing the progression of DMD relative to untreated non-ambulant DMD patients, but there is a proviso to that statement.

A great degree of care needs to be taken when comparing the results of a single-arm trial to an external or historical control group. There are almost an infinite number of differences that can occur in the way the data was collected between the two groups of patients that can lead to an erroneous result. We recently looked at a study where a certain number of patients were recruited into it and, if the results of that group of patients met a particular hurdle rate, a further group of patients was recruited. When the results from the two groups of patients were compared, the drug appeared to perform worse in the second group of patients than it did in the first group, even though nothing had effectively changed between the recruitment of the groups. However, that was not strictly true. The investigators who recruited patients into the trial saw how they the patients fared. Since the patients were not suffering any side effects from the study drug, the investigators gradually became more willing to enrol sicker patients into the study.

Consequently, the drug did not appear to perform as well in the second group of patients. The reality, however, was the drug did not appear to perform as well because the second group of patients was, on average, sicker than the first group. If that sort of difference can occur within the same arm of one trial, it really highlights what sort of differences can occur when the data from the two groups being compared was collected completely independently of each other and with a significant time period in between. 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. Moreover, the fact of the matter is that DMD buys always progress. Demonstrating improvements in disease progression from baseline improves the strength of the data in a disease like DMD, in particular.**

To its credit, Antisense undertook a further post-study analysis, this time comparing the PUL2.0 results obtained in its phase II trial with a cohort of age-matched patients from a natural history database of DMD patients held in Rome, Italy. This was done to create a better-quality historical control, which should provide more reliable results to compare with those from the ATL1102 study. The defining feature of this analysis was that the external control was generated by applying the inclusion/exclusion criteria of Antisense's trial to the database. **This helps to remove selection bias from the process of choosing which patients should be included in the external control group**.

Figure 4. Comparison of the MyoGrip and MyoPinch Trial Data Compared with a Historical Data Set From Ricotti (2016) PLoS One.



Source: Antisense Therapeutics Limited, ASX Announcement, 21 May 2020

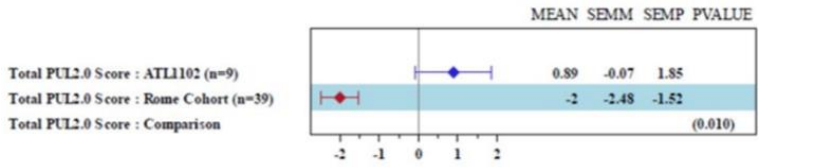
The inclusion/exclusion criteria identified 20 patients in the database that were suitable for use in an external control. The patients in this Rome cohort (RC) had a total of 39 PUL2.0 six-monthly assessments, which were compared to the nine patients and nine PUL2.0 assessments in the ATL1102 trial. The RC was slightly older than the ATL1102 cohort, at a mean age of 15.6 years and 14.9 years old, respectively. At baseline, the total PUL2.0 mean score was slightly lower in the RC compared to the ATL1102 cohort, with means of 20.2 and 24.8, respectively. The standard deviation of the mean total PUL2.0 was considerably lower in the RC than in 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 in the analysis 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 -2.00 for the RC and +0.89 for the ATL1102 cohort provides a nice hint 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 significant difference between the two groups in favour of ATL1102, with a strong p-value of 0.01. Still, caution needs to be exercised when considering these results. It is an external/historical measurement, albeit better than the previous one used. The use of multiple measurements from the same patients in the RC is also likely to have tightened the 95% confidence intervals around the mean PUL2.0 scores for this cohort. This has the effect of artificially lowering the p-value. Still, at p=0.01, the difference between the two groups was strong.

With small data sets like this, the company and investors must not put too much weight on any one analysis. The numbers are too small and can be misleading. It is important to look at the data in its totality. **Essentially, the totality of the data is pointed squarely in the right direction for ATL1102. The data also suggest that some boys in the ATL1102 trial did not decline,**

which is remarkable given the natural history of DMD. Additionally, four out of nine patients showed clinically meaningful improvements, as judged by experts in DMD.

Figure 5. Comparison of the PUL2.0 Results From the Phase II ATL1102 Study to an External Control Generated From a DMD Patient Database Using the Phase II Trial Inclusion/Exclusion Criteria.



Source: Antisense Therapeutics Limited, ASX Announcement, 2 October 2020

Peripheral Blood Lymphocyte Readings

Probably the most important data Antisense released from its phase II DMD trial was that pertaining to lymphocyte counts, particularly, those pertaining to the CD4+ CD49d+^{hi} and CD8+ CD49+ ^{hi} T-cells at baseline and at 24 weeks. The reason is that the results go directly to ATL1102's MOA. Since there were only a small number of patients in the phase II trial, interpreting the clinical data is difficult given the large variation between patients, as the number of factors determining a clinical outcome are so broad. Narrowing down on a much more specific marker of ATL1102's activity should provide more definitive results, because there should be less variation between patients across the biological system being looked at. **Understanding a drug's MOA is also extremely important because it helps to explain the clinical data and it allows you to look for other applications of the drug**.

Figure 6 shows the results pertaining to the key groups of white blood cells.

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 population 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 CD4+ CD49d+ and CD8+ CD49d+. Then the measurements pertaining to the most specific population of cells of interest are given. They are the CD4+ CD49d+^{hi} (CD49d++) and CD8+ CD49d+^{hi} (CD49d++) cells.

The relative baseline population 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+ cells, CD4+ CD49d+ cells, CD4+ CD49d+^{hi} cells, CD8+ CD49d+ cells and CD8+ CD49d+^{hi} cells. One reason this is important is that the data from Antisense's phase II DMD trial has not been published yet and, as such, hasn't been through the peer review process. As the data lines-up with Pinto-Mariz (2015) Skelet Muscle, we have a level of confidence in Antisense's results that we might otherwise not have.

The results in figure 6 are largely as expected where the biggest reductions from baseline are seen in CD49d+ and CD49d+^{hi} T-cells, be they CD3+, CD4+ or CD8+ positive cells, with statistical analyses showing either a strong trend, very strong trend or significant differences when baseline cell counts are compared to those at week 24. Over the 24-week dosing period, the number of CD3+ T-cells (mainly CD3+ CD4+ and CD3+ CD8+ T-cells) and those that express CD49d decline and CD4+ CD49d+ cells declined by more than the number of CD4+ CD49+^{hi} cells. However, 4-weeks after the cessation of dosing, the cells in those two populations rebounded and in the manner that would be expected. T-cells, which are all CD3+, are not the only lymphocytes that express CD49d T-cells are not the only lymphocytes that express CD49d. Some CD3- lymphocytes also express CD49d. **What we can with certainty is that overall, the results strongly support the view that ATL1102 is doing exactly as it would be expected to do and that is to reduce the number of CD49+ cells.** These numbers would almost certainly fall in line with expectations in a larger trial and the strong statistical trends would quickly become significant differences.

In addition to the types of cells for which counts are provided in the table, a population of another type of immune cell, called the natural killer (NK) cell, was also counted. CD3+ T-cells are part of what is termed the adaptive immune system and the cells of that system need to be activated before they will perform their immune function. NK cells, on the other hand, are part of the innate immune system and they do not require any activation to perform their function. If they see a cell or bacterium they regard as abnormal, they will take care of it straight away. NK cells are CD3+ lymphocytes and mostly CD49d+. Despite being in a different arm of the immune system, we would still expect ATL1102 to have an effect on them. Although we have not shown the data specific to NK-cells, their numbers fell significantly from baseline after dosing with ATL1102 and rebounded once treatment was stopped. **While the fall was to be expected, since it is hard to identify a feature of the NK-cell population that might cause a converse result or no change, it is still nice to see ATL1102 have an effect simply because a cell is expressing ATL1102's target. It just adds that little bit extra to the drug's MOA**.

Figure 6. 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, ASX Announcement, 21 May 2020

These results give us an extremely high level of confidence that ATL1102 is doing exactly what it is designed to do and that is to significantly reduce the number of CD4+ CD49d+^{hi} and CD8+ CD49d+^{hi} cells, as well as the number of T- cells expressing CD49d. Importantly, these numbers combined with the clinical data the trial produced provide an extremely compelling case for developing ATL1102 for DMD.

Magnetic Resonance Imaging Results

Magnetic resonance imaging (MRI) takes a range of images of the body for multiple reasons. One is that it provides better imaging of soft tissues. The investigators in Antisense's phase II DMD trial used it to look at the fat content and the amount of lean muscle they retained. The natural history of DMD suggests an increase in the fat fraction of the muscles and a concomitant decline in lean muscle mass over time. Although these images can be hard to quantify, they clearly showed a stabilisation in the average fat fraction of a muscle according to the company. **Additionally, they showed a stabilisation in lean muscle mass, if not an increase. These results square with the with the results obtained using PUL2.0 and most of the other quantitative tests performed**.

While it is hard to convey the MRI results due to the lack of quantification, these results are simply pictures. The images do require skill to read, but as long as you have two readers and a third to break ties, it is hard to introduce a lot of bias, which is important in a single-arm study. These results probably do not get as much weight as they deserve, because they are hard to convey to investors. However, when you can take a picture and physically see no change, they are meaningful.

Dr Valeria Ricotti MD, Researcher and Honorary Clinical Lecturer, Great Ormond Street Institute of Child Health, University College, London, UK probably stated it best when she said "Based on the MRI data from the study, the observed stabilisation in the percentage fat fraction with ATL1102 treatment would not be expected in the natural course of disease in DMD even under corticosteroid treatment. Furthermore, the stabilisation of fat fraction percentage combined with the observed maintenance/increase of remaining muscle area is suggestive that ATL1102's effect could preserve the contractile muscle mass."

The results from Antisense's phase II trial of ATL1102 in non-ambulant DMD patients are impressive, but so has been management's ability to get everything out of this trial that it could. In some cases, if the results from a trial raise additional questions that were not obvious when the trial was initially designed, it may be possible to go back to stored samples to collect the data of interest., although the analysis is still considered to be post hoc. However, for the most part, once a clinical trial is over, a new one will be required to answer additional questions and conducting a new clinical trial is not a trivial matter. **That Antisense**

has been able to get so much useful information out of this trial provides a strong positive signal about its ability to execute the larger, more complex and more stringent trial(s) that are to come.

This trial demonstrated that ATL1102 is safe and tolerable at a dose of 25mg weekly in non-ambulant DMD patients, with definite signals of clinical activity. Moreover, the data on changes in the lymphocyte populations go straight to the heart of ATL1102's MOA. It also provided a wealth of data to support ATL1102's MOA. Additional data collected showed good signals of clinical activity. **Most importantly, however, was that the totality of the data produced strongly pointed in ATL1102's favour. There is no question that Antisense should pursue a pivotal trial in non-ambulant DMD patients.** The next trial is the big one for β Antisense. ATL1102 will need to show that it has a clinically significant effect on DMD. Antisense needs to do all it can to ensure that ATL1102 has the best chance possible to do that.

Proteomic Analysis

In September 2021, Antisense announced the results of a large-scale analysis on how ATL1102 affected the level of proteins in The DMD patients in this trial. The study found positive changes in two modifier proteins (proteins that are not responsible for but can affect the course of disease, depending on their precise nature).

These protein changes were increases LTB4 (Latent Transforming Growth Factor β) and decreases in TSP-1 (Thrombospondin 1; also referred to as THSB1). LTB4 sequesters transforming growth factor β (TGF-β), such that it is not active, while TSP-1 activates TGF-β. Active TGF-β is an important protein in driving fibrotic processes and creating fibrotic tissue. TSP-1 activates TGF-β and, upon its activation by TSP-1, both TGF-β and LTB4 promote the fibrotic process in DMD patients.

ATL1102 also had a significant impact on the levels of CXCL16 (chemokine C-X-C motif ligand 16) and VCAM-1. CXCL16 is a chemokine to which a number of T-cell subsets and NK-cells bind and migrate in response to and also plays a role in muscle regeneration. VCAM-1, as mentioned earlier, is the ligand for VLA-4 and it allows CD4+ and CD8+ cells expressing VLA-4 to leave the blood stream. The levels of these two proteins approached those of the healthy control set and, at least, in part explain the positive phase II trial results just discussed.

The fluctuations in all four of these proteins go straight to the heart of ATL1102's MOA, such that, again, we find the argument for developing ATL1102 for DMD further strengthened. Of course, this also increases the likelihood that ATL1102 will have a significant clinical impact on DMD on patients.

ATL1102 Development: Where to From Here?

Since completing the phase II trial, Antisense has focused on developing the regulatory and clinical trial strategy to gain marketing approval for ATL1102 in non-ambulant DMD patients. **It is running a two-track program, the primary program is aimed at gaining regulatory approval for ATL1102 in the EU via the EMA, first. The second, and lagging, track aims to gain marketing approval in the United States**. The reason for the EU first focus is based largely on Antisense's pre-existing connections there, making it easier to gain expert advice in the DMD space, leverage existing relationships with key opinion leaders and help Parexel, the clinical research organisation Antisense has appointed to manage and run the EU pivotal trial, identify clinical investigators and clinical trial sites, among other things. Usually, companies try and harmonise their strategies for the EU and US to gain marketing approvals for the world's two largest markets as efficiently as they can. **At this stage, it is not clear how Antisense intends to do that, but it has provided investors with options. At one point, we will see the regulatory strategies for these two markets converge**, but, given Antisense appears to have several options, that won't happen until the company feels the time is optimum.

European Progress

Over the last year, Antisense has held a number of meetings with the EMA to clarify the requirements to gain its blessing.

As is common for rare, life-threatening diseases like DMD, Antisense expects that it will be able to gain European marketing authorisation by providing positive results from a single, well-designed, randomised controlled trial, along with being able to show the documented ability to manufacture ATL1102 to accepted clinical standards.

One of the major tasks that Antisense has been working on is its paediatric investigational plan or PIP for ATL1102. A PIP is an investigation plan for a developmental medicine for children. Its purpose is to ensure that all of the necessary data required for a medicine to be adequately assessed by the EMA is collected. A PIP also helps to ensure that children are not put through any unnecessary clinical trials or clinical assessments, as well, provided it is done early enough in a new drug's clinical trialling. A PIP must be submitted and agreed to by the EMA prior to the submission of a MAA by the sponsor company. The MAA must include the results of studies as described and agreed to in the PIP. A PIP must be submitted following the first human pharmacokinetic studies of a drug conducted in the EU and the earlier a PIP is submitted and agreed to by the EMA, the earlier the company will know the studies it needs to undertake for its medicine to gain marketing authorisation from the EMA. **Following a meeting by the Paediatric Committee of the EMA to consider Antisense's PIP for ATL1102 in mid-October, the company was notified that the committee adopted a final positive opinion on it shortly thereafter**.

PIPs are comprehensive documents. For example, Antisense's PIP describes its developmental plans for ATL1102 for non-ambulant patients with DMD and its plans for ambulant boys should it choose to head down that path. However, a PIP does not

unnecessarily lock a company into undertaking particular activities. They can be amended with the Paediatric Committee's agreement.

As mentioned, Antisense has appointed Parexel International, the highly-regarded clinical research organisation (CRO), to manage and conduct ATL1102's pivotal trial in non-ambulant boys in the EU. Appointing a highly capable CRO is a must if a company wants to have a realistic shot at gaining marketing authorisation for a new drug and extra important where an orphan disease is concerned because patients can be difficult to find at the best times. There may also be competition for patients from other trials, given development activities in the space have increased considerably. This means Antisense will need to get the right clinical investigators who see enough patients to ensure the trial recruits efficiently and between Antisense's existing contacts and those of an organisation like Parexel, they should be able to do that. Making inroads into the groups with a special interest DMD is can also be important in terms of clinical trial recruitment and, in fact, through the whole commercialisation process. A pivotal trial is also a huge undertaking. Even a comparatively small one in an orphan disease. For example, the ATL1102 pivotal trial is expected to involve more than 30 clinical trial sites. Pre-existing contacts with potential trial sites are a must so that capable sites can be quickly identified and evaluated for suitability as a participating trial site. Remember that clinical investigators and hospitals do not exist to help companies gain approval for new drugs. They are there to treat people. **A key responsibility of a CRO, and the main reason to engage a proven one, is to motivate clinical sites and ensure the trial is conducted according to the rules and regulations of various bodies, including participating hospitals and their ethics committees, the government of the country the trial site is in, the EMA and, ultimately, the European Council, as the governing body of the EU**.

Figure 7 provides an outline of the pivotal trial that Antisense has agreed to with the EMA.

The trial is a typical gold-standard design for a pivotal trial in an orphan indication. It is a multicentre, randomised, double-blind, placebo-controlled, 52-week, three-arm trial that will recruit and randomise 114 non-ambulant DMD patients, with the anticipation that 108 will complete the trial. The three arms will be a 25mg/week ATL1102 dose arm, a 50mg/week dose arm and a placebo arm, with an expectation that 38 patients will be randomised to each arm. As stated, more than 30 trial sites will be involved across approximately nine countries.

Main inclusion/exclusion criteria:

- Have DMD as confirmed by genetic testing and be unable to walk more than 10 metres unassisted.
- Aged between 10 and 18 years and weigh at least 25kg.
- Have an item A PUL2.0 score of ≥ 2.0.
- If on CS therapy, it must have been initiated six months prior to the baseline trial visit and the patient must have been on a stable dose for three months prior to that visit.

Primary endpoint: Change in PUL2.0 score compared to placebo.

Main secondary endpoints:

- Change in muscle strength as assessed by MyoGrip and MyoPinch relative to placebo.
- A responder analysis on PUL2.0 relative to placebo (important if there are patients who do and don't respond to ATL1102).
- Change in percentage predicted PEF and FVC compared to placebo.
- Quality of life assessments.
- Safety and tolerability of ATL1102.
- The pharmacokinetic profile of ATL1102.

When a patient completes the randomised portion of the trial, they will be offered a spot in an open-label extension study. This allows Antisense to collect longer-term data on ATL1102 and gives those patients who were randomised to the placebo arm a chance to receive the drug and those who did receive the drug a chance to continue on it. Such extension studies are normal practice for these sorts of indications where, if the drug is approved, patients may well be on it long term and extension study provide, at least, a little information about how patients on the drug need to be managed and what the longer term safety effects of the drug might be.

The only real surprise regarding the trial was the inclusion of a 50mg dose arm, in addition to the 25mg dose arm. Antisense had kept very quiet that they were negotiating with the EMA's Paediatric Committee about the possibility of including a higher dose. It was surprising for a few reasons, but a main one was that not even a hint of what Antisense was leaked. **This is a win for Antisense because it will give the company some idea of the dose effect of ATL1102 in DMD and provide an opportunity for the drug to perform better than it did in its phase II DMD trial**. It may also open the door for a supplementary application to the EMA, if the company feels that after ATL1102 has received marketing authorisation, it would be desirable to try an even higher doses of the drug.

The trial design Antisense is employing is a much better pivotal trial design than has been used for a lot other potential DMD therapeutics, largely because of the numerous quantitative secondary. PTC is using the six-minute walk test for their trial aimed at satisfying the EMA that their drug actually does something. The six-minute walk test measures only one parameter and the boys doing it can feel a lot of pressure to do well in it simply to make their carers happy. Consequently, it can be quite open to bias. The NSAA is largely PUL2.0 for ambulant DMD patients and vice versa, with all of the issues associated with largely

qualitative endpoints, where the questioner can bias the results. However, the inclusion of MyoGrip, MyoPinch, Moviplate, percentage PEF, percentage FVC and perhaps MRI means that, should ATL1102 get a borderline result on PUL2.0, but the secondary endpoints are pointing in its direction, it will get approved. **Should either dose of ATL1102 prove significantly superior to placebo by PUL2.0, the EMA will also have little choice but to authorise ATL1102**.

United States Progress

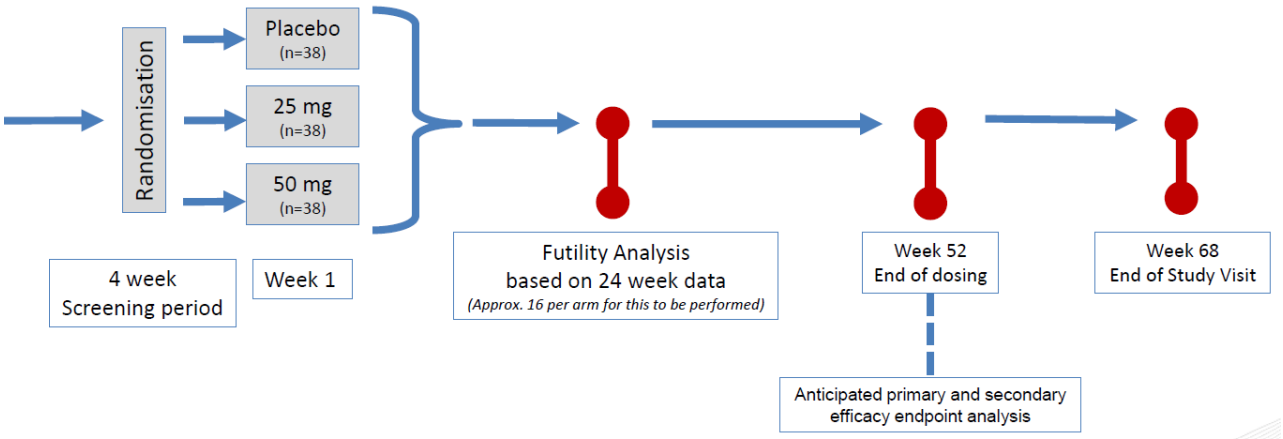
Antisense has been keeping its US plans close to its chest. This is probably a smart move since the FDA keeps tabs on the public statements a company makes and DMD has been somewhat of a flashpoint with the agency. Still, the US is the single largest pharmaceutical market in the world and it doesn't have near the same level of negotiations that have to be undertaken in the EU to market a drug. That is because, while the EMA can give a drug an approval that will allow it to be sold in any EU member state, each member state has its own healthcare system, each of which needs to be navigated to ensure that the company maximises the number of patients who are eligible for the drug and that they receive proper compensation for it.

Antisense held a Type C meeting with the US FDA on 19 April 2021. A company can request a Type A, B or C meeting with the FDA, where a Type A meeting is immediately necessary for an otherwise stalled drug development program to proceed. A Type B meeting may be requested to discuss a pre-Investigational New Drug Application, matters the company may want guidance on after a phase I or phase II trial, matters arising related to an intended phase III trial or matters pertaining to a New Drug Application (NDA) or Biological Licence Application (BLA). A Type C meeting is a meeting about anything else.

A written response to the Type C meeting was announced by Antisense on 1 June 2021. Particularly relevant points that Antisense made about the meeting were as follows:

- Antisense's phase II trial of ATL1102 in non-ambulant DMD patients was adequate to support larger studies in that patient population in the FDA's eyes.
- It would consider higher doses of ATL1102 than 25mg/week given adequate justification.
- The proposed pivotal trial design, which we assume was the same as that proposed to the EMA, appeared acceptable, including the primary endpoint and secondary endpoints assuming appropriate statistical powering (i.e., the trial was large so as to be confident in a positive result and not so large as to find statistical differences where the effect of the drug was not clinically meaningful).
- It would be a good idea for Antisense to submit its planned study protocol to the agency for review.
- It expected Antisense to conduct a nine-month NHP toxicology study of ATL1102 and Antisense has submitted that protocol to the FDA for their review just recently.
- Antisense could commence its pivotal trial while the NHP study was underway, as long as the NHP study was completed before any of the pivotal trial patients had been dosed for six months.

Figure 7. The Clinical Trial Design for Antisense Therapeutics Pivotal Trial of ATL1102 in Non-ambulatory DMD Patients.



Source: Antisense Therapeutics Limited, ASX Announcement, 1 November 2020

None of this was surprising, given the history of ATL1102, its current stage of development for non-ambulant DMD and the exceptional need for new treatments for the indication. Antisense said later that the feedback from the FDA did offer the company opportunities to streamline and harmonise its global development plans for ATL1102, although it has not said a lot about what those opportunities are. This is probably because it is still assessing them and is not yet at a point where a decision needs to be made. It did say that one possibility was to allow the FDA to assess the EU pivotal trial data, if warranted, as supportive data for

a future NDA or a possible approval. In a subtle way, that last statement says the FDA may provide ATL1102 a provisional approval if the data from the EU trial is strong enough. A provisional approval would allow Antisense (or its partner) to market ATL1102 in the US, while the company conducts a pivotal US trial. It is exactly like the accelerated approvals Sarepta received for its three drugs. Another option that Antisense has put forward is to submit the protocol approved by the EU to the FDA, amended to add US sites to the ongoing EU trial. **Both of these options are distinct possibilities that would likely considerably speed ATL1102's entry to the US market**. We also understand that a commitment to any strategy is not needed yet. How to proceed is a tricky question, each having potential benefits and risks. **The company recently recruited two new directors, discussed later, whose experience will be invaluable in choosing the best path forward**.

Antisense will continue its interactions with the FDA as it prepares and commences the EU pivotal trial. The commencement of the nine-month NHP toxicology study required by the FDA is also likely to be a key driver of the path forward in the US, as it will be dependent on continued discussions with the FDA and a current ban on the importation of NHPs from China. China is by far the largest supplier of NHPs for research purposes, exporting substantially more NHPs than the next largest suppliers, Mauritius and Israel (The Future of NonHuman Primate Resources: proceedings of the Workshop Held April 17-19, 1002 (2003) International Perspectives).

With respect to the US, Antisense appears to have the situation under control, although, obviously, some things are out of its control in terms of timing. **We don't see the variables that are out of Antisense's control as a significant risk or even affecting the company's value too much.** Clinical development of a drug always involves an unexpected hurdle or two. All a company can do is prepare and execute to the best of its ability and when the unexpected happens, formulate a plan to address the situation and, as with everything else in drug development, execute that plan to the best of its ability.

Granted Special Regulatory Classifications

Over the past year, Antisense has picked up a few special regulatory classifications that are likely to prove beneficial to the company.

ATL1102 was granted orphan drug designation (ODD) by the European Commission on the EMA's recommendation in December 2020 and by the FDA in October 2020. The designation was introduced to provide an incentive for companies to develop approved drugs to treat diseases for which the patient numbers are small. In the EU, that number is five in every 10,000 persons, while in the US it is a disease that affects less than 200,000 people. The incentives that ODD provides help the company developing the ODD in two ways. Firstly, it improves the company's chances of gaining approval for the drug. Secondly, it provides financial incentives for developing ODDs.

In the EU, medicines granted ODD are eligible to receive a range of benefits. This includes scientific advice above and beyond that usually provided, help with developing clinical trial protocols, a 75% fee reduction 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 collects 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, totalling 12 years of market exclusivity.

In the US, ODD provides the company developing the drug with assistance in developing clinical trial protocols, a potential decrease in the wait time for drug approval, tax credits of 50% of the cost of clinical trials, waived NDA fees (~approximately USD3.0 million) and market exclusivity of seven-years regardless of the drug's patent coverage.

While many investors take note of the guaranteed market exclusivities, many under-estimate the value of the extra assistance from the regulators during the development process. The regulator decides the fate of companies drug if it makes it to a marketing application. The more time a company can spend with the regulator to understand exactly what they want to see in order to grant approval is the biggest advantage of having an ODD.

Antisense's ATL1102 has also been given rare paediatric disease designation (RPDD) from the 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 NDA or BLA of its choice examined as if it had been eligible for, and granted, priority review. Under normal circumstances, the FDA should complete its review of an NDA or a BLA within 10 months. Under priority review, the process is supposed to be completed in six months. Most importantly, PRVs are transferable and smaller companies who 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 it would receive by extending its exclusivity over a product for four months. A few PRVs have been sold for huge numbers, with the highest known price paid to date being USD350 million (M. Sinatra, Data on File) and the lowest USD67.5 million. Recently, the price of PRVs has settled at approximately USD100 million. If Antisense gains 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 into the US market on its own (although we think it would be more likely to take on a partner for US marketing or co-marketing role).

Antisense recently clarified that it had relative certainty that if it gains approval for ATL1102 for non-ambulant DMD as a first indication for the drug prior 30 September 2026, it will receive a PRV. The US Government regularly passes legislation

that has a sunset date and congress needs to reauthorise the legislation before that date, otherwise it ceases to have effect. The FDA lost its ability to grant rare paediatric disease designation for 10 days after the short-term extension to the program congress granted until 11 December 2020 passed without the Senate acting on the Creating Hope Reauthorization Act, which the House passed in September 2020. The Secretary of Health and Human Services was to lose the power to grant PRVs on December 11, 2022. However, the senate passed the act on 21 December 2020 and it went to the President who signed it. **The FDA can now confer RPDD to a company's drug candidate up until 30 September 2024 and the Secretary of Health and Human Services can grant PRVs up until 30 September 2026.**

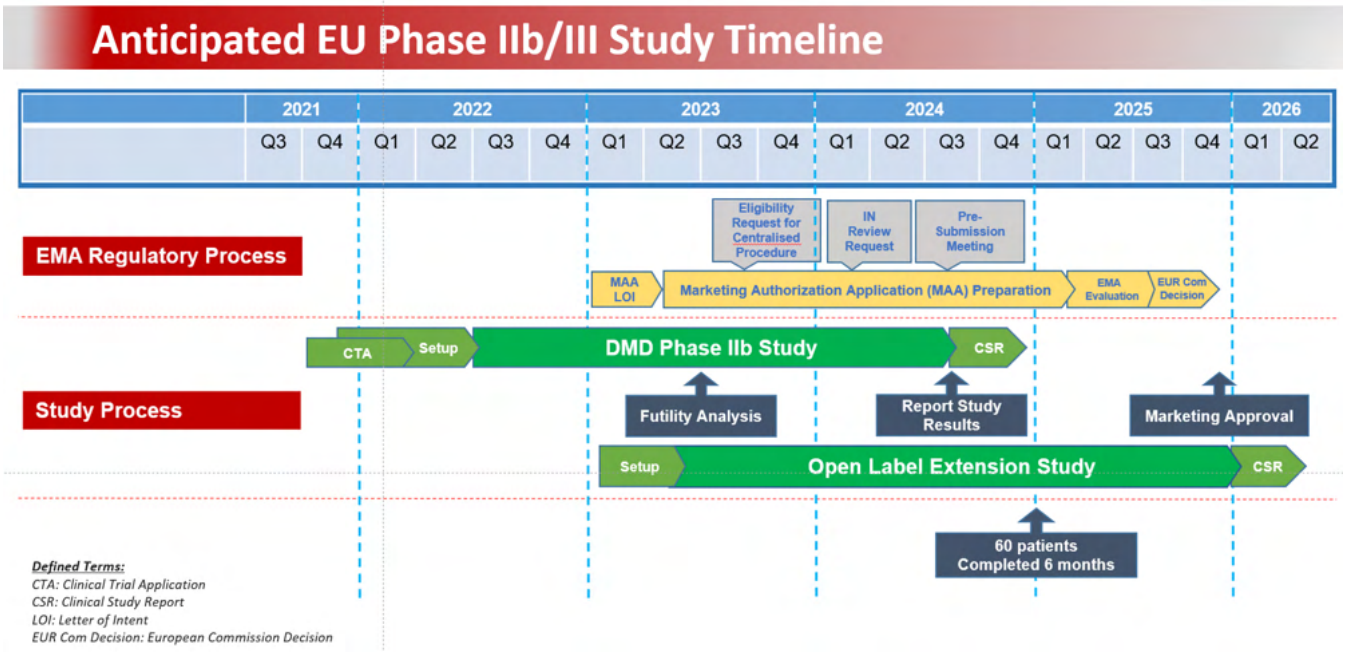
Antisense's Foreseeable Plans for Developing ATL1102

Figure 8 details Antisense's publicly-released plans for the foreseeable future.

The reasonably foreseeable future is the timeline for the European pivotal trial of ATL1102, the key dates of which follow:

- June 2022, recruitment for the EU pivotal trial is expected to commence,
- Q3 CY2024, the pivotal trial should complete,
- Q1/Q2 CY2025, Antisense intends to submit the ATL1102 MAA to the EMA, if the trial results are positive,
- Q4 2025, Antisense expects the EMA to decide on its application. The EMA is supposed to make a final decision on ATL1102 within 210 'active' days or 7.5 months. There are two periods where the clock stops, however, which can add to that 210 days.

Figure 8. The Reasonably Foreseeable Future of ATL1102's Development.



Source: Antisense Therapeutics Limited, ASX Announcement, 1 November 2020

One activity that is reasonably foreseeable, but not in figure 8, is all of the work that goes into the commercial manufacturing of a drug. Part of this process is the manufacture of the active pharmaceutical ingredient (API), and its formulation and packaging for the European pivotal trial and for potential approval. Developing a manufacturing process for a commercial drug is considerably broader and more complex than manufacturing a drug product for a single trial. The process also needs to commence early because part of gaining a marketing authorisation or new drug approval is that the company can demonstrate the ability to manufacture the drug to the appropriate standards (termed Good Manufacturing Principals). To do this, it must have a quality manual in place and all of the documents referred to in the quality manual ready to go, which includes protocols for the various manufacturing steps, quality assessments that need to be done, as well as record sheets for those quality assessments and other information that needs to be recorded, such as the date particular manufacturing steps were performed and the equipment used in each step of the production process. The manufacturing process will need to be refined and appropriate assays may need to be developed. This is a big and important job. One of the two key reasons the FDA issued Mesoblast (ASX: MSB) a Complete Response Letter (effectively, the denial of an NDA) for remestemcel-L after Mesoblast had submitted a BLA for therapy for

paediatric graft-versus-host disease was that the FDA did not feel Mesoblast (or, its contract manufacturer) could appropriately assess the therapy's potency. **History is littered with companies who had the data to support a drug's approval but were denied based on manufacturing deficiencies.**

In terms of manufacturing, Antisense is working with a contract manufacturing organisation with over 27-years of experience in oligonucleotide manufacturing and a highly regarded drug product manufacturer who formulates the ATL1102 API into a parenteral (injectable) drug product. The drug product for Antisense's upcoming pivotal trial has already been packaged, tested and released for clinical use.

Obviously, as events happen and key decisions are made, many things can be added and will be added to Antisense's reasonably foreseeable future. When plans for gaining US approval become clear, figure 8 will approximately double in size. **To add them now would be guess work and likely lead to creating false expectations among investors. For now, investors must be satisfied that particular things will happen and that declaring a timing now could cost Antisense option value later.**

Approved Therapeutics and Those in Development for DMD

CSs have been used to treat DMD patients off-label for decades, with research reports appearing in literature in the 1970s. The most recent clinical guidelines strongly recommend the use of either deflazacort (Emflaza®, PTC Therapeutics) or prednisone once a patient's motor development stops or starts to decline, usually around four to five years of age, and to continue their use throughout life (Birkrant et al (2018) Lancet Neurol). **The most recent Cochrane report (a systematic review conducted by a group dedicated to them named the Cochrane Collaboration) of the use of CSs to treat DMD concluded that there was moderate quality evidence from randomised control trials indicating that CS therapy in DMD improves muscle strength and function in the short term (12 months), and strength up to two years (Matthews et a; (2016) Cochrane Database Syst Rev). However, there was no evidence from randomised control trials that the use of CSs delayed the loss of ambulation**.

Glucocorticoid receptors (GR) are found in almost every human cell and are the target of glucocorticoids or, as we have been referring to them, CSs. In DMD, the beneficial activity of CSs is thought to be through the repression of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells). Essentially, the CS enters the cell and binds with the GR, creating a CS-GR complex. This complex binds directly to a certain segment of DNA called the glucocorticoid response element (GRE). GREs are found in the promoters of many genes (reviewed in Kourakis et al (2021) Orphanet J Rare Dis). A promoter is a non-RNA coding section of DNA that is found before the beginning of a gene and functions to regulate the expression (transcription) of the gene into mRNA. A GRE is in the promoter of the gene for NF-κB and the CS-GR complex binds to it. The effect of that is to stop or, at least, severely limit NF-κB mRNA production and, consequently, it stops the production of NF-κB protein (Hudson (2018) Nat Commun). **NF-κB is a master regulator of inflammation and when activated it, too, acts as a regulator of transcription by binding the promoters of numerous pro-inflammatory genes, working to up regulate their expression (i.e., produce more)**. GREs are also found in the promoters of other anti-inflammatory genes, such as IL10 a key anti-inflammatory cytokine which plays a central role in limiting the immune response to pathogens. The binding of the CS-GR complex to the GRE elements in promoters that regulate those anti-inflammatory genes actually increases their expression. This is what gives CSs their broad anti-inflammatory activity. Many of the molecules produced by NF-κB up-regulated genes are released by the cell and activate the immune system very broadly. In DMD muscles, NF-κB is chronically elevated (Messina et al (2011) Acta Myol). Several characteristics of DMD cells cause this chronic NF-κB activation. One is the increased levels of calcium in DMD myocytes, which have been shown to activate NF-κB-mediated inflammation (Altamirano et al (2012) J Biol Chem), while another is the elevated level of free radicals in DMD myocytes. The damage caused to DMD myocytes when muscles contract can also work to increase NF-κB activation. This damage releases particular compartmentalised molecules into areas they should not be. The molecules, such as nuclear DNA have evolved to be damage associated molecular patterns (DAMPS) and cells have what are termed pattern recognition receptors (PRRs) that recognise them. When a PRR is bound by a DAMP, the PRR sends a signal to activate NF-κB. Several other factors also play a role in the activation of NF-κB in DMD myocytes. **CSs act as a strong counter-weight to the numerous characteristics of DMD myocytes which are triggers of NF-κB activation.**

The problem with CSs is their side effects. In addition to the GREs in the promoters of anti-inflammatory genes they bind and increase the expression of, they also bind GREs found in the promoters of many other genes, such as a corticotrophin-releasing hormone (a stress response protein) and osteocalcin (which plays a role in matrix mineralisation and global metabolism), repressing the expression of these genes. These genes do not play a role in inflammation but have effects on other systems in the body and their aberrant repression/expression causes adverse effects. Additionally, CSs bind another set of receptors known as mineralocorticoids in an agonist fashion (i.e., they increase their activity) and may have a wide range of adverse effects, including hypertension (high blood pressure), fluid retention, weight gain and skin atrophy (Duan et al (2021) Nat Rev Dis Primers). The hypertension they cause is thought to be a contributor to the cardiomyopathy seen in DMD patients (Heier et al (2019) Life Sci Alliance). A review of side effects caused by CSs can be found here: (Yasir et al (2021) StatPearls [Internet]). With long-term use, some of the side effects of CSs are as follows:

- **Profound effects on bone growth/loss leading to osteoporosis and extremely high rates of bone fractures, including the vertebral fractures, as well as osteonecrosis (bone tissue death),**
- Adrenal insufficiency causing chronic fatigue, muscle weakness and abdominal pain among other symptoms,
- Growth impairment in young children,

- A higher risk of infections,
- Adverse dermatologic effects,
- Increased risk of cataracts,
- Increased risk of gastritis, gastric ulcer and gastrointestinal bleeding, and
- A range of neuropsychiatric effects, such as anxiety, sleep disturbance and motor restlessness.

In terms of the use of CSs in the treatment of DMD, Matthews et al (2016) Cochrane Database Syst Rev found that the short-term side-effects were significantly more common than with placebo, but not clinically severe. However, they were unable to assess the long-term side effects due to a lack of appropriate studies. That leaves you to take the word of experts like Hoffman (2020) Handb Exp Pharmacol regarding the severity of the long-term side effects. It was from his review that we took the word 'profound' when describing the effect CSs has on bone, which he believes is the biggest side-effect.

While CSs suppress the immune system through NF-κB, the results from Pinto-Mariz (2015) Skeletal Muscle indicate that CSs do not have an effect on the frequency of CD4+ CD49d^{hi} and CD8+ CD49d^{hi} T-cells, leading to the conclusion that a separate pathway is involved in creating/activating the immune cells that appear to be central to DMD pathogenesis.

While there appears no question that CSs are beneficial in treating DMD, additional and better therapies are needed. Up until July 2014, no drugs had ever been approved by a major regulatory agency for treatment of DMD. However, over two years, the EMA granted a conditional approval to ataluren (Translarna, PTC Therapeutics) and, in an extraordinarily controversial decision in 2016, the FDA handed an accelerated approval to eteplirsen (Exondys 51®, Sarepta Therapeutics). Neither can claim to be great drugs and it is entirely possible that neither work at all. The FDA gave PTC a CRL for ataluren, which it appealed, but the CRL was upheld, while the EMA knocked back eteplirsen and maintained that decision when the company with the European rights to that drug appealed the EMA's original decision. **However, it can be argued that the conditional approval of ataluren and the accelerated approval of eteplirsen has stimulated significant drug development activity in the DMD space, some of which looks likely to produce quite efficacious drugs**.

DMD Drugs with Regulatory Approval

Figure 9 lists drugs approved by the FDA or EMA for DMD and their particulars.

Four of the six drugs work by a novel MOA called exon skipping. A review of the technology can be found here: Echevarria et al (2018) Hum Mol Genet.

Exon skipping came about as a result of two observations. The first was that many of the mutations that caused DMD tended to be clustered in particular regions, such as exons 3 to 9 and exons 45 to 55, with the latter containing more than the former (Aasrtsma et al (2009) Hum Mutat). The second observation was that even if parts of the DMD gene were removed, the dystrophin protein that was produced retained some function, at least, enough to turn DMD into a BDM-like disease. A gene is composed of introns and exons and before the mRNA produced from a gene is read by the ribosomes to produce a protein, the introns are removed from the mRNA. It was then postulated that if you could interfere with the splice site adjacent of the intron adjacent to the exon that was a hotspot for DMD mutations, you could effectively remove the exon from the mRNA transcript as if it were an intron. The catastrophic mutation would then be removed from the mRNA and the ribosomes would be able to transcribe a shortened dystrophin protein. **Clearly, that protein would not be equivalent to the normal dystrophin protein, but it would probably be able to perform enough of the normal dystrophin's roles to be of clinical benefit to the patient**. Interestingly, these small molecules are antisense oligonucleotides, although not exactly the same as ATL1102.

Figure 9. FDA-Approved Therapies for DMD and Their Particulars.

Brand Name	INN[1]	Year Granted FDA/EMA Approval	Dose - 30kg Child	Form	Company	Mechanism of Action
Exondys 51	eteplirsen	Sept, 2016	900mg/week	Infusion	Sarepta Therapeutics	Skipping Exon 51
Emflaza	deflazacort	Feb, 2017	27mg/day	Tablet	PTC Therapeutics	Corticosteroid
Vyondis 53	golodirsen	Dec, 2019	900mg/week	Injection	Sarepta Therapeutics	Skipping Exon 53
Viltepso	vitolarsen	Aug, 2020	240mg/week	Infusion	NS Pharma	Skipping Exon 45
Amondys 45	casimersen	April, 2021	30mg/kg/week	Infusion	Sarepta Therapeutics	Skipping Exon 45
Translarna	ataluren	July 1014	3 x Daily; 10, 10, 20mg/kg	Oral in food/liquid	PTC Therapeutics	Stop Codon Read Through

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

There are two main issues with exon-skipping drugs. **The first is we don't know how well they work**. Eteplirsen, golodirsen, vitolarsen and casimersen were all granted accelerated approvals based on observed increases in dystrophin levels (Syed Y (2016) Drugs; Heo Y (2020) Drugs; Dhillon S (2020) Drugs; Shirley M (2021) Drugs), not on the improvement in a clinical outcome, as is

normally the case. Moreover, we are not talking huge increases in the levels of dystrophin found after taking the drugs. **Eteplirsen increased dystrophin levels to 0.44% of that found in healthy subjects (not 44%, 0.44%). In two trials, golodirsen increased dystrophin levels to 0.92% and 0.88% of normal levels. Viltolarsen performed the best, producing dystrophin levels of 4.81% of that in healthy individuals and, finally, casimersen increased dystrophin levels from 0.93% to 1.74% of normal levels.** Intuitively, none of these increases in dystrophin levels seems big enough to have much, if any, clinical impact on DMD. With eteplirsen, at least, about half of the insurers in the US agree with us and have chosen not to cover the cost of the drug (Hoffman (2020) Handb Exp Pharmacol). Additionally, as with the gene therapies attempting to provide patients with micro-dystrophin, the dystrophin exon-skipping drugs do not lead to the production of normal dystrophin protein because it is missing sections of the gene. There is probably more function left in the dystrophin protein produced through exon-skipping drugs, than in micro-dystrophin, but that is largely of academic concern when expression levels are so low.

The other problem with exon-skipping drugs is that currently approved drugs are capable of treating approximately 30% of DMD patients, while approximately 80% of DMD patients have mutations that could be applicable to an exon-skipping drug if one were available for each/most of the exons (Aasrtsma et al (2009) Hum Mutat). Eteplirsen is applicable to the largest single group of DMD patients for a single exon-skipping drug at 14% of the population (Bladen et al (2015) Hum Mutat). **For the other drugs, the applicable population gets smaller and smaller and smaller. It may be possible to develop exon-skipping drugs amenable to 80% of DMD, but you need a lot of different drugs to get there considering the DMD gene contains 79 exons**. Moreover, it is hard enough to recruit patients for rare disease studies, but when you start talking about running trials in groups of patients that make up less than 10% of the population of a rare disease, the task becomes a lot harder. When you get to less than 5% of DMD patients, it would probably be close to impossible.

Ataluren (reviewed in Michorowska (2021) Pharmaceuticals) is the only drug approved in the European Union for DMD, having received conditional approval from the EMA in July 2014 (EMA, Translarna (ataluren) Overview), 2018).

Ataluren has a unique MOA amongst DMD drugs in that **it is a stop codon read through drug**. The mRNA molecules that a ribosome uses as the plans to build protein/polypeptides out of will contain one of three different stop codons which signal to the ribosome that the protein is complete and that it should stop adding amino acids to it and let it go. About 12% of DMD patients have what are termed premature stop codon mutations (PTCs, also called nonsense mutations) (Kellermayer (2006) Eur J Med Genet) and are the result a codon for an amino acid mutating into one of the three different stop codons. Interestingly, these PTCs are not, generally, treated by the cell's protein production machinery, including the ribosomes, as normal stop codons. Particular cellular machinery recognises PTCs in mRNA molecules and subjects it to a process termed nonsense mediated decay (NMD). This machinery appears to have evolved to stop the production of truncated proteins, which could disrupt normal cellular function by have a dominant, rather than recessive effect. The recognition of this phenomena creates/created the opportunity for therapeutic intervention and stop codon read through drugs have been the result. Although ataluren's MOA is not fully understood, it appears to work something like this (Siddiquio & Sonenberg (2016) PNAS). Ataluren blocks the NMD process, allowing the PTC containing mRNA molecules being read by the ribosome to continue being read by the ribosome. Since all of the right signals are not present around the PTC to result in the ribosome terminating translation, the ribosome continues to add amino acids to the protein they are making from the PTC containing mRNA. When the ribosome encounters PTC, rather than terminating translation, the ribosome tends to add an amino acid that corresponds to a codon similar to the particular PTC. Consequently, the dystrophin made by this process varies a fair with respect to one amino acid. Since the substitution of one amino acid for the correct one in the dystrophin protein generally leaves it with, at least, partial function, the therapy should be able to turn DMD into a BMD type disease, or, at least, that is the theory.

PTC conducted two, placebo-controlled, phase III trials with ataluren, both of which employed the 6-minute walk test as the primary endpoint. In the first trial (n=114), patients who received ataluren walked an average of ~30 metres further than placebo patients and in the second trial (N=228), patients who received Translarna walked ~15m metres further than those who received placebo. **Both differences, however, were not significant**. After a protracted review by the EMA, the EMA eventually gave the drug a conditional marketing authorisation based on an agreement with the company that it would conduct a further pivotal trial to demonstrate the efficacy of the drug. The conditional approval of ataluren is reviewed each year by the CHMP, unless, of course, the drug ever obtains full marketing authorisation. In 2018, the CHMP extended the indications for use of ataluren to patients aged 2 to 4-years inclusive (EMA, CHMP extension of indication variation assessment report, 2018). In 2020, the CHMP by voted by majority to drop the line "efficacy has not been demonstrated in non-ambulatory patients" from the Summary of Product characteristics (SmPC) for ataluren. In doing so, healthcare officials can now use their own judgement whether or not to prescribe ataluren to patients who have lost ambulation (PR Newswire, News Report, 29 June 2020). In 2017, PTC Therapeutics discontinued the development of ataluren in cystic fibrosis patients carrying at least one cystic fibrosis transmembrane conductance regulator gene with a nonsense mutation (PTC Therapeutics, Press Release, March 2017). Unlike exon-skipping drugs, stop codon read through drugs are not supposed to be gene specific in theory and that is what PTC studied ataluren in cystic fibrosis.

Deflazacort (Emflaza®, PTC Therapeutics) is the other drug that the FDA has approved for DMD. Deflazacort was actually first patented in 1965 and it has been used to treat DMD patients for decades outside of the US, but it had never been approved in the US for any disease. This enabled Marathon Pharmaceuticals to grab a very old drug, run some small clinical trials with it, gain FDA approval for it and receive 7-years of market exclusivity because Marathon had successfully applied to have deflazacort designated an orphan drug it had just been approved for an orphan indication. Oh, yeah. Then they started charging American's USD89,000 a

year for a drug that was available outside the US for about USD3,000 per year. Subsequently, PTC Therapeutics bought the drug from Marathon and, of course, they increased the price of the drug to over USD100,000 per year. Deflazacort does generate reasonable revenues, but like eteplirsen, many insurers have chosen not to cover the cost either (Hoffman (2020) Handb Exp Pharmacol), particularly since generic prednisone appears to have a better safety profile for DMD than deflazacort (Bello et al (2015) Neurology).

Previous DMD Therapeutic Development – Some Distasteful Aspects

Drug development activity in the DMD space has highlighted some distasteful aspects of the drug development industry. Having said that, while the finger is often pointed at the pharmaceutical companies as the problem, the fact of the matter is that the boards of these companies are simply doing what they are supposed to do. That is to maximise long-term shareholder value. Rather than pointing our fingers at the companies who use the practices, what really needs to happen is for governments to legislate the practices out of existence.

Companies that receive accelerated approval for a drug are supposed to undertake appropriate trials while the drug is on the market to demonstrate a significant effect on a relevant clinical parameter. Not surprisingly, 8-years after PTC Therapeutics received an approval for ataluren and 6-years after eteplirsen was granted an accelerated approval for ataluren, neither has managed to complete the required pivotal trial demonstrating the efficacy of their drugs. This is not a story that is unique to those two companies. The same strategy has been used by many companies before them. The companies and the regulators know that once you have approved a therapy for patients desperate for one, you cannot take it away, no matter how long the company delays completing the required trial or even if data comes to light demonstrating the drug has absolutely no efficacy. The reason the regulators cannot enforce the agreement the companies made with them is actually quite simple. There is only one group of people the regulators actually fear and it is for totality self-serving reasons. If they were to take one of the DMD drugs off the market, the patients, those close to them and the advocacy groups would start hounding the politicians who represent them relentlessly about it. That would include planting stories in the media about how the big bad regulator had taken the only treatment available for this horrible disease away from patients. Since the only thing politicians fear is defeat at the next election, they, obviously, would not be happy with this state of affairs. However, they are the bodies that provide the regulators with funding, which, in turn, is why the government is the only group regulators fear. The government controls the destiny and the funding of the regulator. For the companies who are making considerable amounts of money from drugs supported by only dubious data, it is the perfect storm.

The granting of Marathon Therapeutics 7-years of market exclusivity for deflazacort, a very old drug, falls into the somewhat distasteful category. Obviously, Marathon's and commercialisation of deflazacort for DMD was not a great scientific leap forward and involved zero innovation. It didn't even really provide US DMD patients with an improved new therapy, since prednisone is considered to be better than deflazacort. All it really did was enable Marathon to jack the price to ridiculous levels, which PTC decided were not high enough, so they bought the drug from Marathon. On the other hand, though, by conducting trials that passed regulatory muster, we can now be a lot more certain about the benefit deflazacort and, to certain extent other CSs, provide DMD patients. Without a profit motive, these trials never would have been conducted, such that there is plus side to the formal regulatory approval of deflazacort. This is actually a much more common strategy in the pharmaceutical industry than you would think.

Given the lack of data behind all but one of the currently marketed DMD drugs and the old and relatively poor performing nature of the other relative to generic competition, it is really quite easy to argue that we are no more advanced in the treatment of DMD, than we were in August of 2014.

Drugs in Development for DMD

Figure 10 provides a list of all of the significant therapeutics we could identify that are in clinical development for DMD. Because companies like to keep their activities quiet you can never be sure that you have a complete list. Additionally, it is not uncommon for a company to maintain it is developing a drug for a particular condition even after it has determined the drug will never be able to produce the data required for approval. They do this to avoid the hit to the share price they would take if they announced they were discontinuing development of the drug. It is surprising how often it works. Eventually, the drug just disappears off of their pipeline or they magically find another disease to study the drug in. **Overall, we are confident we included all of the main therapeutic candidates being developed for DMD, excluding those who do not seem to be serious about their endeavours**.

2022 and 2023 will be big a couple of big years in the DMD space, based the drugs in development for DMD in figure 10 and the dates on which they expect to complete particular trials.

We talked extensively about the three gene therapies earlier in this report. We have not mentioned the primary endpoints of the trials, though. Pfizer and Sarepta are both using change from baseline in NSAA over 52 weeks compared to placebo for their phase III trials, while Solid Biosciences' primary endpoint is using the change from its baseline in micro-dystrophin expression protein as determined by muscle biopsy.

Daiichi Sankyo's decision to pursue an exon 45-skipping drug is slightly odd, given there are two exon-skipping drugs on the market that do the same thing, however, we believe a not-for-profit is footing a large amount of the bill for the drug's development. In a short press release on 13 January 2021, the company said that DS-5141b was safe and that increased expression of dystrophin

was found in all patients in a phase I/II study (NCT02667483) of the drug (Daiichi Sankyo Press Release 13 January 2021). The clinical trial listed in the table is a long-term extension study derived from the phase I/II study. Other than that, Daiichi has said little about the drug. The primary endpoint of the company's current phase II trial is safety and tolerability, while the main efficacy-related endpoint is the six-minute walk test.

Sarepta's SRP-5051 consists of eteplirsen conjugated to a cell-penetrating peptide, which a journal article described as being developed because of the controversially low levels of dystrophin it produces and that unmodified phosphorodiamidate morpholino oligomer antisense nucleotides have limited efficacy in the heart (Sheikh & Yokota (2021) Arch Toxicol). Though true, an additional reason Sarepta is developing SRP-5051 is because eteplirsen is not proving efficacious in the pivotal trial it needs to perform in to fulfil its obligation to the FDA when eteplirsen was granted an accelerated approval or, at least, that is our take on the scenario. Sarepta announced the results of a phase II study of SRP-5051 on 4 May 2021, stating that SRP-5051 produced eight times the amount of dystrophin when dosed weekly for 3-months compared to eteplirsen (SRPT Press Release 4 May 2021). This turns out to be 3.52% of the expression levels seen in healthy and less than the 4.81% produced by NS Pharma's vitolarsen. It is also worth remembering that the dystrophin produced by SRP-5051 is mutated and will not have 3.52% of the function of normal dystrophin. Sarepta's current phase II trial of SRP-5051 has a co-primary endpoint of safety and tolerability, as well as change from baseline in dystrophin protein level.

Pamrevlumab, developed by Fibrogen, is a developmental compound that is lower risk than gene therapy, has strong science behind it, a solid MOA and a real shot at finding a long-term role in the treatment of DMD patients.

Figure 10. Therapies Currently in Development for DMD.

Drug	Company	Mechanism of Action	Stage of Development	Age Range of Patients - Years	Current Clinical Trials	Trial Size	Expected Completion Date
fordadistrogene movaparvovec	Pfizer	AAV9 Gene Therapy	Phase III	4 to 7	NCT04281485	99	February 2023
SRP-9001	Sarepta Therapeutics	AAV9 Gene Therapy	Phase III	4 to 7	NCT05096221	120	October 2023
SGT-001	Solid Biosciences	AAV9 Gene Therapy	Phase I/II	4 to 17	NCT03368742	16	December 2023
SRP-5051	Sarepta Therapeutics	Exon 51 Skipping	Phase II	7 to 21	NCT04004065	60	September 2023
DS-5141b	Daiichi Sankyo Co	Exon 45 Skipping	Phase II	5+	NCT04433234	8	March 2022
ATL1102	Antisense Therapeutics	Antisense anti-CD49d	Pivotal	Non-ambulant	To be advised	114	August 2024
pamrevlumab	Fibrogen	Anti-CTGF Antibody	Phase III	12+ 6 to 11	NCT04371666 NCT04632940	90 70	August 2022 January 2023
bocidelpar	Astellas Pharma	Modulator of peroxisome proliferator-activated receptor δ	Phase I	8 to 16	NCT04184882	18	March 2022
ifetroban	Cumberland Pharmaceuticals	Thromboxane/prostanoid receptor antagonist	Phase II	7+	NCT03340675	48	July 2023
vamorolone	Santhera Therapeutics & ReveraGen BioPharma	Anti-inflammatory steroid analogue	Phase IIb	4 to 7	NCT03439670	121	Complete
givinostat	Italfarmaco	Pan-histone deacetylase inhibitor	Phase III	6 to 17	NCT02851797	179	March 2022
CAP-1002	Capricor Therapeutics	Cardiosphere-derived cells	Phase III	10+	NCT05126758	68	June 2023

Sources: M.Sinatra Research

Pamrevlumab is an anti-connective tissue growth factor (CTGF) monoclonal antibody that binds CTGF and prevents it from interacting with other proteins. Chen et al (2020) Front Cell Dev Biol have recently written a review on CTGF and the function of its various domains. It is not the easiest paper to read, but it does make you realise that its biology is well understood. It is a matricellular protein or, rather, a non-structural ECM protein that is produced by cells in response to various signals, several cytokines and, in particular, transforming growth factor (TGF). CTGF, in turn, interacts with and influences several cell membrane receptors, binds to several extracellular matrix proteins and induces the production of many of the cytokines that induce its expression, creating a positive feedback loop. It induces cellular trans-differentiation of cells into myofibroblasts, including myoblasts, which, in turn, increase ECM deposition. Fibrogen's interest in CTGF is that it is associated with virtually all fibrotic pathology and, as mentioned, fibrotic tissue replaces muscle tissue in DMD. In DMD, elevated expression levels of CTGF are found in the skeletal muscles of patients and, in the mouse model of DMD, the levels of CTGF correlate with the number of necrotic foci in the muscles and the expression levels of several fibrotic markers. Also, in the mouse model of DMD, inhibition of TGF or CTGF, reduces ECM deposition and the level of fibrosis. Fibrogen is strongly backing pamrevlumab and has it in phase III trials for pancreatic cancer and idiopathic pulmonary fibrosis, in addition to phase III trials in ambulatory and non-ambulatory DMD patients. Fibrogen's hypothesis appears to be that in DMD, the persistent activation of myofibroblasts leads to the excess production of

extracellular matrix proteins leading to fibrosis, and the production of CTGF in response to the inflammation and, in particular, TGF activation in DMD patients' muscles, mediates this process. Fibrogen moved pamrevlumab into these two-phase III trials based on a single-arm phase II trial in non-ambulant DMD in which several clinical parameters, including PUL score, were numerically better than those found in a natural history cohort by Ricotti et al (2019) Neuromuscl Disord. The primary endpoint for Fibrogen's phase III trial in non-ambulant boys (NCT04371666) is a change in the total score of PUL2.0, while the primary endpoint for the phase III trial in ambulant boys is a change in NSAA linearized total score (NCT04632940).

Vamorolone is mentioned consistently throughout the literature and it is hoped it will be the better CS that physicians desperately want. US-based ReveraGen discovered vamorolone and it is being developed in collaboration with Santhera Therapeutics who own the worldwide rights to the compound for all indications. The compound is believed to repress the expression of NF-κB and increase the expression of other anti-inflammatory genes associated with the standard CSs, while it does not repress the expression of those genes unrelated to inflammation (Heier et al (2019) Life Sci Alliance). Additionally, rather than having an agonist effect on the mineralocorticoid receptors it is thought to have an antagonistic one. Several reviews talk about it very positively (Hoffman (2020) Handb Exp Pharmacol; Duan et al (2021) Nat Rev Dis Primers; Kourakis et al (2021) Orphanet J Rare Dis) and there are almost certainly additional ones, as well. In a phase I trial in healthy volunteers, vamorolone was safe and well tolerated at all dose levels, while showing pharmacokinetic and metabolic profiles similar to prednisone (Hoffman et al (2018) Steroids). However, it did not have the safety concerns or adverse event profile of prednisone. A phase IIa trial in ambulant children aged four to seven years, vamorolone demonstrated the same safety profile and met the primary outcome of improved muscle function (Hoffman et al (2019) Neurology). The study was a phase IIb, double blind, randomised, controlled trial with six groups over 24 and 48 weeks. (NCT03439670). The groups were randomised 2:2:1:1:1:1 or n= 30, 30, 15, 15, 15, 15. For the 24-week comparisons, the prednisone and placebo groups were combined, resulting in four groups of 1:1:1:1 for the 24-week readout. The groups were as follows:

1) Vamorolone 2.0mg/kg/day for the duration of the study.
2) Vamorolone 6.0mg/kg/day for the duration of the study.
3) Prednisone 0.75mg/kg/day for 24 weeks followed by a 4-week transition period and then vamorolone 2.0mg/kg/day for 20 weeks.
4) Prednisone 0.75mg/kg/day for 24 weeks followed by a 4-week transition period and then vamorolone 6.0mg/kg/day for 20 weeks.
5) Placebo daily for 24 weeks followed by a 4-week transition period and then 20 weeks' treatment with 2.0 mg/kg/day of vamorolone.
6) Placebo daily for 24 weeks followed by a 4-week transition period and then 20 weeks' treatment with 6.0 mg/kg/day of vamorolone.

The initial 24 weeks of the study was to compare the two doses of vamorolone, prednisone and placebo to each other, while the last 20/24 weeks of the study, depending on the arm a patient was randomised to, was to assess the persistence of the effect of vamorolone and intra-patient difference between prednisone, the two doses of vamorolone and to collect further data on patients who initiate vamorolone from no intervention (I.e., the placebo groups).

The primary endpoint was the Time to Stand Test (TTSTAND) at 24 weeks comparing the difference from baseline of the 6.0mg/kg/day vamorolone group to the placebo group. Secondary endpoints at 24 weeks included TTSTAND, Time to Run/Walk Test (TTRW), six-minute Walk Test (6MWT) comparing 2.0mg/kg/day and 6.0mg/kg/day to placebo. Comparisons at 24 weeks included comparisons between the two doses of vamorolone and the prednisone group. Largely, the same parameters were tested at 48 weeks, but included a Time to Climb Test (TTCLIMB) and the NSAA.

The study met its primary endpoint TTSTAND with 6.0mg/kg/day significantly superior to placebo (p=0.002) (Santhera & ReveraGen, Press Release, 1 June 2021). The study also met the secondary endpoints for both vamorolone dose groups which were significantly superior to placebo for the 6WMT and the TTRW. No significant differences were seen between vamorolone and prednisone across the above endpoints. The company stated that vamorolone showed a favourable safety and tolerability profile. The number of treatment-emergent adverse events were similar between the vamorolone dose groups and were numerically lower than that for prednisone. Importantly, in a comparison of clinically-relevant adverse events, as defined by the EMA, vamorolone at 6.0mg/kg/day was superior to prednisone (n=6 vs n=19, respectively, p=0.02).

The 48-week results showed that the efficacy of vamorolone was sustained across multiple endpoints, and that switching from prednisone to vamorolone restored the growth trajectory and reduced behavioural changes. Patients who switched from placebo to vamorolone demonstrated improvement in multiple efficacy parameters without an apparent increase in treatment-emergent adverse events. With all patients on vamorolone, 98% completed the period from 24 to 48 weeks. Overall, 121 boys commenced the trial, 114 started the second 24 weeks and 112 completed the trial. The company plans to commence a rolling NDA to the FDA in Q1 2022. In a rolling application, allowed under the Fast Track Status if the FDA agrees to it, sections of the NDA can be submitted to the FDA as they are completed, whereas under a normal NDA, the entire NDA must be submitted at the one time. This will considerably speed up the agency's review of the application. The companies plan to submit a full MAA to the EMA by the end of Q2 CY22.

Based on the results the companies have made available in their press releases, it is highly likely vamorolone will be approved.

Bocidelpar from Astellas Pharmaceuticals is thought to modulate the peroxisome proliferator-activated receptor δ (PPAR-δ, often referred in the literature as PPAR-β/δ). PPAR-δ is one of three broad groups of PPARs, which live in the nucleus of a cell where the chromosomes reside. They act to control gene expression much in the way the CS-GR does, by binding specific sites on the DNA in the promoter region of various genes. Of the three groups of PPARs, PPAR-δ is the one that is most abundantly found in skeletal muscle (reviewed in Manickam et al (2020) Int J Mol Sci; Manickam & Wahli (2016) Biochimie; Ljubicic et al (2014) FASEB). It is involved in multiple tasks comprising lipid metabolism, mitochondrial function promoting fuel use, and muscle fibre-type changes associated with increased performance. Astellas has said very little about the compound or its MOA. The only mention of the compound in the literature is a paper on the phase I trial the company ran in healthy subjects (Ito et al (2021) Muscle Nerve). That paper mentions a potential benefit on mitochondrial dysfunction seen in DMD patients, which would make bocidelpar an agonist of PPAR-δ. The literature backs up that claim, implicating PPAR-δ in mitochondrial biogenesis. However, the literature also highlights its role in lipid metabolism, myogenesis, myocyte regeneration and myocyte plasticity, effectively promoting a switch from fast (type II or glycolytic or anaerobic) twitch fibres to slow (type I or oxidative or aerobic) twitch fibres. Slow twitch fibres are thought to be more tolerant of the lack of dystrophin in DMD patients and, consequently, it is a therapeutic route that has been tried, but not yet successful. We will have to wait for Astellas to release more information on bocidelpar or for additional publications by researchers with a better understanding of the molecule. Astellas is a successful and is valued at ~USD30 billion and is in that tier of companies that cannot afford to fund programs just for the knowledge they main gain from them. There is no choice but to take the compound seriously.

The PPAR-δ is thought to play a crucial role in regulating cellular metabolic functions that contribute to maintaining energy balance in the DMD myocytes (Liu et al (2018) Int J Mol Sci). Astellas' hypothesis is that by modulating PPAR-δ, bocidelpar will have a beneficial effect on the mitochondrial dysfunction observed in the muscle of DMD patients. It has published the results of a phase I trial in healthy subjects (Ito et al (2021) Muscle Nerve), which has led to the phase I trial it is currently conducting in DMD patients. Astella's phase I trial has a primary endpoint of safety and tolerability and all of the trial's secondary endpoints are related to safety.

Ifetroban from Cumberland Pharmaceuticals is another interesting one. The thromboxane/prostanoid receptor is thought to act in cardiac tissue to increase heart rate, trigger cardiac arrhythmias and cause myocardial ischemia. Cumberland's hypothesis is that activation of the thromboxane/prostanoid receptor in DMD patients leads to cardiomyopathy and, ultimately, heart failure and that ifetroban, as an antagonist of the receptor, can slow the degeneration of the heart in DMD patients (West et al (2019) J Am Heart Assoc). The FDA was impressed enough with the company's findings with ifetroban, providing it with USD1 million in funding toward the clinical trial Cumberland is conducting (1st FDA-funded DMD Study Now Recruiting Patients to Test Ifetroban, Muscular Dystrophy News Today, 26 August 2021). Cumberland is listed on the NASDAQ under the ticker symbol CPIX and has a market capitalisation of USD86.5 million, which makes it a nano-cap by US standards and it indicates US investors do not give it much chance of success. Having said that, it may have just overlooked more exciting opportunities. The primary endpoint of its phase II trial is safety and tolerability, although as secondary endpoints it will be looking at change from baseline in left ventricular ejection fraction and change from baseline in forced expiratory volume in one second.

The last two companies do not have a lot of chance of success.

It is hard to know where to start with givinostat from Italfarmaco. The company's phase III trial is fully enrolled and is expected to be completed in approximately four months. According to the US National Cancer Institute (NCI) givinostat is a pan histone deacetylase (HDAC) inhibitor that is thought to have anti-inflammatory, anti-angiogenic and antineoplastic activities (NCI Definition of givinostat). Histones are involved in the organisation and higher structure of basic DNA into chromatin. In short, histones are broadly involved in gene regulation, unacetylated histones result in a "tight" structure of chromatin, which inhibits gene expression, while acetylated histones results in a looser structure, which promotes gene expression. Italfarmaco patented givinostat in 1997 and, since then, the company has trialled, or is trialling, it in 18 clinical trials, based on ClinicalTrials.gov entries. Since clinical trials performed outside the US do not have to be entered into the ClinicalTrials.gov data base, the number of trials could be considerably higher. Of those 18 studies, three are in DMD and two are in BMD. Givinostat has also been studied in polycythemia vera, chronic myeloproliferative neoplasms, polyarticular course juvenile idiopathic arthritis, juvenile idiopathic arthritis, Hodgkin's lymphoma, chronic lymphocytic leukemia, Crohn's disease, multiple myeloma and autoinflammatory syndromes. Givinostat was trialled in a single-arm phase I trial in DMD prior to commencing the phase III trial (Bettica et al (2016) Neuromuscl Disord). **In that study givinostat did not improve outcomes, such as the six-minute walk test and North Star Ambulatory Assessment and in its phase III trial it is using the unusual primary endpoint of the mean change in four standard stair climb test results between baseline and 18 months.** To us it seems likely that a pan HDAC inhibitor that has broad effects on gene transcription is likely to cause a wide-range of changes in cellular activity that may suggest the drug could have activity in a wide variety of diseases states. At the end of the day, its activity isn't specific enough to have a significant clinical impact on a disease. Givinostat's probability of success in its current phase III trial is low.

CAP-1002 being developed by Capricor comprises adult stem cells derived from endomyocardial biopsies, which are then expanded ex-vivo (Smith et al (2007) Circulation). The general theory around adult stem cell therapies is that, rather than functioning by developing into new tissue, replacing that which has been damaged, they have a strong anti-inflammatory effect through signals they send to nearby cells. CAP-1002 has previously been studied in a 25-patient randomised, controlled, phase I/II trial of DMD patients with cardiomyopathy, after which it was studied in an 18-patient phase II trial of patients with varying dystrophies, including Duchenne. The phase I/II in DMD patients with cardiomyopathy has been published (Taylor et al (2019)

Neurology) with the authors concluding " intracoronary CAP-1002 in DMD appears safe and demonstrates signals of efficacy on both cardiac and upper limb function for up to 12 months". These signals of efficacy included a reduction in damage to the heart and a significant improvement in mid-distal PUL1.2. The company recently announced the results of its phase II trial, stating that the trial had met its primary endpoint with a significantly better mid-level PUL1.2 score, slowing its decline by 71% (Capricor Press Release 24 September 2021). Additional positive endpoints included a significantly better PUL2.0 score and cardiac ejection fraction. It would be interesting to know why it used two different versions of PUL in the one trial, particularly when PUL2.0 is the FDA and EMA accepted primary endpoint in non-ambulant DMD. There also appears to have been some cherry-picking of results that were released to the market. It would also be nice to understand why the ClinicalTrials.gov entry (NCT03406780) states that the trial was undertaken in patients with multiple dystrophies, but the press release states the trial was undertaken in DMD patients. The study's primary endpoint is mean change from baseline in full PUL 2.0 at month 12-months. These results seem too good to be true, while the discrepancies we have been able to find without even closely looking at the company or its trial results, give us pause. **We cannot see this therapy being approved by any major regulatory body**. Investors agree with our view, since the company, which trades under the ticker symbol CAPR, has a market capitalisation even lower than that of Cumberland Pharmaceuticals at USD79.7 million.

To recap, the truly promising compounds in development for DMD are:

- Pamrevlumab - targets CTGF and aims to reduce the level of fibrosis in DMD patients.
- Vamorolone - a CS with an antagonistic effect on the mineralocorticoid receptors, rather than an agonist effect, and is being developed as the better CS.
- Bocidelpar - thought to be a modulator of PPAR-δ and by modulating the receptor, DMD myocyte mitochondria should maintain a healthier state.
- Ifetroban - an inhibitor of thromboxane/prostanoid receptor (which is thought to be over-stimulated in DMD patients, leading to cardiac issues).

Gene therapies are high risk, high reward. In our view, they may be too risky and their efficacy, if successful, will likely be underwhelming.

While the exon-skipping drug from Sarepta results in greater production of dystrophin than the approved Sarepta drugs, it is still only producing a relatively small amount of dystrophin (circa 10% of the expression levels seen in healthy individuals), and won't have 10% of the function of normal dystrophin. This does not seem to be enough to make a clinical difference. With the drugs in development, and the crop to come through, you have to wonder where the technology is heading.

Non-Ambulant DMD: Addressable Market Size, Relevant Pricing Indicators and The Potential for Competition

Addressable Market Sizes

As an orphan indication, the DMD market is small on a per-patient basis. According to the US National Institute of Neurological Disorders and Stroke (NINDS), approximately 1 in every 3,500 to 6,000 live males born have DMD, making it the most common form of muscular dystrophy (NINDS DMD).

The best study we could find, which estimated the global birth prevalence (highly analogous to incidence) and prevalence of DMD, was a systematic review and meta-analysis of the literature published in 2020, which included all studies published up until 1 October 2019 (Cristafulli et al (2020) Orphanet J Rare Dis). The estimate of birth prevalence (essentially, incidence) was based on the assessment of 29 studies conducted between 1977 and 2019. The estimate of prevalence was based on the assessment of 22 studies conducted between 1977 and 2016. The authors claim, and we think they are likely correct, that this was the first systematic review and meta-analysis of the literature with respect to the global epidemiology of DMD.

This study found a birth prevalence of 19.8 per 100,000 live male births [95% Confidence Intervals: 16.6 – 23.6]. This translates into **1 in every 5,050 males (**the high-end estimate being 1 in 4,237 and the low-end being 1 in 6,024). A separate earlier study found that only 74% of DMD cases diagnosed were done so using acceptable genetic testing methods, leaving the possibility that some cases of DMD are being mistaken for other muscular dystrophies and vice versa (Mah et al (2011 (2011) Can J Neurol Sci). Genetic testing for specific DMD mutations was not available when the early studies included in the systematic review were conducted. Once the tests became available, they steadily improved. As such, the later studies included in the systematic analysis were likely more accurate than the earlier ones. As would be expected for a disease that is purely genetic, there is no evidence that the incidence of DMD has been increasing or decreasing over time.

Incidence does not equal prevalence. Since prevalence represents the absolute number of live patients with a disease, that is the more important number. Cristafulli et al (2020) Orphanet J Rare Dis found a DMD prevalence of 7.1 per 100,000 males [95% Confidence Intervals: 5.0 – 10.1] or 1 in 14,085 males (the high-end estimate being 1 in 10,000 males and the low-end estimate being 1 in 21,739). Prevalence estimates are, of course, lower than incidence estimates because DMD patients' average life span is considerably shorter than the average person. Remember that the lifespan of DMD patients has been increasing, with DMD patients born before 1970 surviving an average of 25.8 years and those born afterward living an average of 41.0 years, based

on a study published in 2013 (Kieny et al (2013) Ann Phys Rehabil Med). While the authors of the systematic review did not comment on it, by eyeballing the forest plot of the studies examined in the review there is no obvious trend toward an increasing prevalence of DMD. This is something you would expect if the average lifespan of DMD patients was increasing over the ~35-year study period. Interestingly enough, the systematic review went back until the same year (1977) that research studies regarding the use of CSs in DMD patients began to appear. Still, you have to assume that the average life span of DMD has been increasing based on Kieny et al (2013) Ann Phys Rehabil Med, such that the prevalence estimate from the systematic review is likely to be an under-estimate of the current prevalence.

It is possible to take the numbers from the systematic review and calculate some absolute estimates of the number of live males with DMD today. Looking at the EU first, there were an estimated 219.0 million males in the EU in 2019 (Eurostat, European Commission, Accessed 18 December 2021). This gives us an absolute figure of 15,548 live DMD males presently in EU. In the US in 2019, there were an estimated 161.5 million males (US Census Bureau, QuickFacts, Accessed 18 December, 2021), which give us an estimated absolute number of live DMD males of 11,465 at present. At a world level, there were an estimated 3.97 billion males in 2021, giving us a global prevalence for DMD in males of 281,860 at present. However, while the estimates for the EU and the US are most likely underestimates of the prevalence based on the increasing lifespan of DMD patients, the global estimate is almost certainly an over-estimate. The reason is that the documented increasing lifespan is based on first world numbers. The third world almost certainly hasn't experienced the same increasing lifespan and may not have increased at all, due to the comparatively lower quality of healthcare in the third world. From a valuation perspective, it is the EU and the US that really count, although Japan is one of the seven largest pharmaceutical markets, as well. Japan can also be a tricky one for western pharmaceutical companies.

Our estimates above and the figures used to calculate the absolute market potential of each drug in figure 11 fail to recognise that DMD therapeutics are only indicated for DMD patients of certain ages. Most DMD drugs, for example, are not indicated for children under the age of 5-years. By making some assumptions and using generally available statistics, we can, however, adjust for those factors. We can estimate the population of DMD boys under the age of 5-years by substituting the live birth prevalence of DMD for the prevalence of DMD, and by assuming a death rate between those ages of zero and that statistics from a couple of years ago will be applicable into the future. The population of the EU was 447.0 million in 2019 (Eurostat, European Commission, Accessed 18 December 2021) and the number of live births was 9.5 per thousand inhabitants (Destatis, Press Release #262, 13 July 2020). Moreover, the ratio of male to female live births was 1.056 (Data, The World Bank, Accessed 18 December 2021). From these numbers we can derive that there were ~2,505,560 males born in the EU that year. Using the birth prevalence from above of 1 in 5,050, the number of live males born with DMD that year ~496. That provides us with an estimate of ~2,480 DMD males in the EU born in 2019 and that give us a number we can then subtract from our overall DMD prevalence above, from which we derive a number of ~13,068 males with DMD in the EU. Using similar numbers from the US, we find an estimate of ~380 males born with DMD each year and an overall estimate of the number Males with DMD under the age of 5-years of ~1,900. Thus, we would estimate the US population of DMD males 5-years and older at ~9,565

A little more difficult is how you calculate the number of ambulant and non-ambulant DMD patients. To do this, you need to address the question in a similar fashion to the way we addressed the number of DMD patients under 5-years old. Finding a good number to use for the average age a DMD patient becomes non-ambulant is not overly easy and also depends on how non-ambulance is defined. The most recent systematic review of the literature would only go so far as to say that the average of age of loss of ambulation tended to range between 10 and 14-years of age. When we have to use numbers like these, we tend to use a simple of the two numbers. As such, we would do our calculations using an average age of loss of ambulation of 12-years old. Therefore, we estimate the ambulant DMD population suitable for a therapeutic for males 5-years and older at 8 multiplied by the estimated absolute number of males born each year with DMD in the region of interest. **We end up with absolute ambulant DMD patient populations 5-years and older of ~3,968 in the EU and ~3,040 in the US**. Obviously, we have assumed a mortality rate of zero for this calculation, too.

Estimating the non-ambulant DMD population is then just a matter of subtracting our estimates for the number of DMD patients under the age of 5-years and those aged 5 to 12-years of age from the absolute number of males with DMD in the relevant population. **Thus, our estimate for the non-ambulant DMD population in the EU is ~9,100, while for the US it is ~6,525**.

It is possible to refine many of the numbers further, for example, by taking a closer look at the mortality data for DMD males up to 12-years old, inclusive. The law of diminishing returns, however, does start to apply and the error we would be adding to our estimates by not refining them further would likely be dwarfed by the error just in the initial birth prevalence and prevalence numbers that we started with.

The take home message, though, is that the non-ambulant market is larger than the ambulant market. Whether it will stay that way is an open question. The answer will be dependent much more so on the success of the therapeutics in development for DMD, than those that have already been approved.

Relevant Pricing and Market Size Information

Figure 11 contains a range of information regarding pricing for the currently approved drugs for DMD and one drug used off-label to treat the disease. **This information needs to be treated with extreme caution because some of the assumptions made are not realistic but are used for illustrative purposes only.**

Firstly, list prices and an assumption about the average weight were used in the calculation of the yearly cost of each drug. With the exception of the generic drug prednisone, pharmaceutical companies rarely, if ever, realise the list price for protected drugs (those with some form of market exclusivity) they sell. Protected drugs are subject to a gross-to-net discount and pharmaceutical companies have often recorded gross revenue, as calculated based on list prices, in their financial statements and a number for net revenue, which is the money they receive for the drug. Transparency statements by some pharmaceutical companies are giving the public a much better view of how much they actually receive for their protected drugs. Eli Lilly, for example, increased its average list prices by 3.4% in 2020, but the average prices it realised for its medications declined by -5.3% (Drug Channels Report, 14 April 2021). Overall, this meant that its gross-to-net discount actually increased by 8.7%. For their protected drugs, Lilly's gross-to-net discount is 60%. That is, if the list price for a drug is $100,000 per year, they bring in revenue of only $40,000 for that drug. Janssen's gross-to-net discount is 53% and Merck & Co's is 45.5%, among others.

Secondly, in calculating the absolute maximum market potential for each drug, we have used the market size figures for the EU and US we calculated earlier, multiplied that number by the percentage of DMD patients a drug was relevant to, and then multiplied the resultant number by the list price of the drug. Only prednisone is available in both markets.

If any of the drugs were approved in the EU, it is likely that the price they would obtain in the region for their drug would be, on average, significantly lower than their list price given in the table and even significantly lower than the net price the companies realise. A US Government report into drug pricing, based on 79 drugs, found that US drug prices were nearly four times higher than the combined average price for 11 other similar countries (House Ways & Means Committee Press Release, September 2019). Many other studies can be found, which back up the findings of this report, although the gross to net discounting catches many out. The list price of Translarna of USD421,529 which is only sold in the EU compared to USD748,00 for each of Sarepta's three drugs which are only sold in the US bears out this discrepancy between US and EU pricing at a list price level. Unfortunately, we do not have any visibility into either drug at a net price level or, rather, the revenue they actually receive for the drug for treating an equivalent patient.

To inject some reality into this section, we can look at the revenues of two companies, PTC Therapeutics and Sarepta Therapeutics

As stated earlier, PTC's ataluren is the only therapeutic approved by the EMA for DMD, specifically 12% of patients with premature stop codon mutations. Ataluren is not supported by regulatory quality data and its approval by the EMA was conditional on the company completing the necessary trial required of it by the EMA. PTC also owns deflazacort, a drug that was first patented in 1965 and that has generic competition supported by clinical guidelines, but it is the only CS approved by the FDA for DMD which does carry some weight. Ataluren generated USD191.9 million in 2020 revenues and its Q3 CY21 revenues have shown growth of 54.8%. Deflazacort generated USD139 million in 2020 revenues and its Q3 CY20 revenues have grown by 22.3%. As a result, PTC has raised its CY2021 revenue guidance from USD370 to USD390 million to USD400 to USD420 million. These numbers can be compared to our calculated maximum market potential for those two drugs of USD4.2B. **Clearly, the two drugs are nowhere near our absolute market potential and they still would be even if ataluren was approved in the US and deflazacort had the same standing in the EU that it does in the US.**

Figure 11. FDA-Approved Therapies and Their Cost to Treat a 30 Kilogram Child per Year.

Brand Name	INN[1]	Company	Dosage Form	Yearly Cost[2] (USD) 30kg Male	Applicable % DMD Population	Reference	Absolute Maximum Market Potential – EU + US – Year[3] (USD)
Exondys 51	eteplirsen	Sarepta Therapeutics	Infusion	$748,000	14.0%	Aartsma-Rus (2009) Hum Mutat	2.829B
Vyondis 53	golodirsen	Sarepta Therapeutics	Injection	$748,000	7.7%	Bladen et al (2015) Hum Mutat	1.556B
Viltepso	viltolarsen	NS Pharma	Infusion	$733,200	10.1%	Bladen et al (2015) Hum Mutat	2.000B
Amondys 45	casimersen	Sarepta therapeutics	Infusion	$748,000	9.0%	Bladen et al (2015) Hum Mutat	1.819B
Emflaza	deflazacort	PTC Therapeutics	Suspension Tablet	$122,469 $90,628	100%	Emflaza Package Insert	2.878B
prednisone	prednisone[5]	Several	Tablet	$114.98	100%	Birkrant et al (2018) Lancet Neurol	0.003B
Translarna	ataluren	PTC Therapeutics	Granules for Suspension	$421,529	12%	Kellermayer (2006) Eur J Med Genet	1.366B

Sources: M.Sinatra Research

1 INN = International Non-proprietary Names; 2 New Drug Fact Blast, Conduent Business Solutions, 2021; 3 Some very significant assumptions have been made in calculating these figures, such that they are likely very much higher than they ever could be. See text for an explanation; 4 It is assumed that half of patients listed will use the suspension and half the tablet, as such an average of the two prices have been used; 5 While prednisone is not FDA approved for DMD it is recommended in professional body guidelines as a suitable alternative to deflazacort and, as such, likely sees some use in the treat of DMD males in the US and likely significantly greater use in the EU; 6 Price taken from List of Prescribable High Tech Medicines February 2021, Ireland and converted from Euro into USD using an exchange rate of 1 Euro = 1.12 USD as at 18 December 2021.

The situation is very much the same if we look at Sarepta's revenues. Its three approved DMD drugs, eteplirsen, golodirsen and casimersen were all granted accelerated approvals by the FDA. None of the drugs are supported by regulatory quality clinical data, but were, instead, granted their approvals based on minute increases in dystrophin. Sarepta does not break out its revenues by product, such that all we can look at are combined revenues for the three products. Those revenues were USD455.9 million in 2020. Those revenues have also been growing strongly, partly due to casimersen's accelerated approval granted by the FDA's in April 2021. Third quarter 2021 combined revenues for the drugs were USD166.9 million, which represent 33.3% growth on Sarepta's USD121.4 million in revenue recorded for the previous corresponding period. This growth has caused Sarepta to raise its full year 2021 revenue guidance from between USD565 million and USD575 million to between USD605 million and USD615 million. As with PTC Therapeutics, Sarepta is nowhere near the absolute market potential we calculated of USD6.2 billion, although, in fairness, it should be mentioned that golodirsen had only been on the market for 21 months and casimersen about 5 months when the third quarter ended. **Even if Sarepta's drugs were approved in the EU, they would still be a long way from our absolute market potentials**.

Interestingly, both PTC and Sarepta's revenues are ~10% of our calculated maximum market potentials. However, given golodirsen and, particularly, casimersen are young drugs, while ataluren has been on the market ~7.5 years and deflazacort only has a bit over two years remaining on its market exclusivity, future growth is definitely on Sarepta's side

Just to re-iterate, three of drugs (eteplirsen, golodirsen and casimersen) are only applicable to ~30.7% of the estimated ~11,465 DMD patients in the US, while another (ataluren) is only applicable to 12.0% of an estimated ~15,548 DMD patients in the EU. None of these drugs have regulatory quality data supporting their efficacy. The three drugs first mentioned only produce minute amounts of the desired protein relative to healthy individuals and they produce it in forms that almost certainly are not as functional as the protein produced by healthy individuals. The fourth drug mentioned has already failed two phase III randomised, controlled, trials in a combined 342 patients. The fifth drug, in terms of significant revenues, may be applicable at all DMD patients in the US, but it also has generic competition supported by professional body clinical guidelines. **This rather motley crew of drugs is set to generate combined calendar year 2021 revenues of ~USD1.02 billion with year-on-year growth of ~29.6%.**

Now, consider what a drug like ATL1102 with strong MOA data, solid safety data and a clinical use profile that includes every DMD patient in the EU and the US could generate if it were to deliver supporting efficacy from a pivotal trial. There is little question that we would be likely to see sales pass the USD1 billion mark in a couple of years and peak sales exceed USD2 billion, but by how much is really anybody's guess.

Yes, Antisense is only targeting the non-ambulant DMD market initially and, although it is the biggest of the two markets, the pathway to the ambulant market in the EU is already defined in a paediatric investigation plan agreed to by Antisense and the EMA and will be just a protocol amendment away, if that, for the US market.

The one thing Antisense has to do to get there is to generate solid efficacy data. Toward that point, think of the work that has gone into discussions with the EMA and the FDA. The feedback it has received. The European clinical trial design that has received the EMA's blessing and the NHP toxicology study protocol that has just been submitted to the FDA for its review. **This is a company that has all of its ducks in a row and must now simply execute**.

Suddenly, those market size estimates do not look nearly as silly fore ATL1102 as they do for the drugs in the table.

Competition and the Potential for it

Our beliefs are in line with the thoughts contained in the references we discussed earlier about the DMD market and the way it will evolve. Regardless of which drugs eventually demonstrate efficacy and gain marketing approval/authorisation, DMD patients will end up receiving several therapies.

The highly variable clinical manifestations currently seen with BDM appear to be due more to variation in other genes BDM patients have, than the particular mutation they have in the dystrophin gene. We suspect that those factors may well come into play in a patient's response to DMD drugs, as well. **Therefore, we also agree with the view that there will be considerable personalisation of treatments once there are several broadly applicable drugs on the market.**

We do not believe the three gene therapies currently in clinical trials are game changers. If one or more of them make it to market, and we do think that is a big if, they are likely to represent what amounts to highly variable incremental improvement in patient outcomes. New therapies will be needed for the clinical manifestations of DMD and BDM, where those gene therapies are found to be deficient and may well even be needed where the therapy does have some impact.

The net result of the variation we believe we will see in the response to new DMD therapies is that no one drug is likely to truly be useful in 100% of patients, or even close to that. CSs seem likely to continue to see considerable use, particularly if one with a better safety profile than those currently on the market is approved. The best other drugs will likely be able to do is provide a clinical benefit to, at a guess, 60% of patients in a world with two, three and maybe even four drug combinations. If a drug was really good and turned out to deal with an underlying problem common to almost every patient, that particular drug may be able to go a bit higher.

At this point, we only see competition between therapies sharing the same target, such as viltolarsen and casimersen, which both target Exon 45. Having said that, the expression advantage viltolarsen has over casimersen will likely mean casimersen won't be used much.

For ATL1102, with a completely unique MOA and target, plus a significant time advantage over any company that tries to develop a CD49d-targeting drug, the major determinant of use will be how broadly applicable CD49d is as a target in a background of other drugs and the magnitude of the clinical benefit it ends up providing. Overall, the drug appears to be in a good position to see considerable use. **The CD49d T-cells seems to ultimately be responsible for a lot of the clinical symptoms DMD patients experience and targeting them is a good strategy from an indirect competition point of view.** Few doctors are going to prescribe two drugs if one works just as well.

If ATL1102 and CSs can synergistically dial the immune response right down, they will be hitting the pathogenesis of DMD at an early stage and a lot of the problems, including the deposition of fibrous substances and fat, as well as a reasonable degree of cellular dysfunction, may cease to be. **If that were the case, ATL1102 would help many DMD patients and the revenues would likely flow very freely.**

ATL1102 and Additional Therapeutic Indications

Antisense has mentioned that it is exploring other possible indications for ATL1102 but has been short on specifics. It has indicated the ambulant DMD population, but that is obvious. It has also said fibrotic diseases, but that encompasses a lot of diseases. However, it is not entirely unreasonable to be short on specifics. Australian drug development has more than its fair share of companies that will say, yes, our drug is applicable to that disease, without having thought the opportunity through completely first. On occasion, they will give that answer before they have had a chance to Google wiki and the disease name to find out what it is. Choosing an indication to develop a drug for is not a trivial matter and we would almost certainly be wrong if we said Antisense should develop ATL1102 for this particular disease. However, we can take a look at the literature and see what the experts are speculating.

CD49d is more regularly referred to as the α4 integrin subunit and ATL1102 falls into the class of drug known as an integrin inhibitor. Essentially, what it comes down to is that wherever an α4 containing integrin is implicated in a disease state, there is a potential role for ATL1102. As this recent review Slack et al (2021) Nat Rev Drug Discov from Nature Reviews Drug Discovery indicates, our understanding of the biology of certain diseases and the role of integrins in them is starting to catch up to the fact that some integrin inhibitors have been around for quite a while. Usually, it is the other way around, in that our increased understanding of the biology of a disease leads to the development of a particular drug class.

In terms of diseases where α4 subunit-containing integrins are involved, you are specifically talking about two integrins. One is the α4β1 integrin, which is also known as VLA-4, as we have mentioned, it may also be referred to as lymphocyte homing receptor. The other is the α4β7 integrin, which is also known as LPAM-1 (lymphocyte Peyer's patch adhesion molecules). Natalizumab's activity in MS occurs through the α4 subunit of α4β1 integrin, while its activity in Crohn's disease is also through the α4 subunit of α4β7 integrin. Crohn's disease, of course, would be a potential opportunity for ATL1102, although, considering natalizumab was approved for the disease over a decade ago, you would have to think that Antisense has already thoroughly looked at that opportunity and decided against it. Another inflammatory bowel disease, ulcerative colitis, is a possible indication for ATL1102, however, vedolizumab (Entyio, Takeda Pharmaceuticals), another anti-α4β7 antibody, received an approval for that indication in 2014 and, again, you would have to think that Antisense has already had a good hard look at the opportunity.

α4β1 is also important in B cells (immune cells that produce antibody-producing cells) and also appears to play an important role in B-cell malignancies (Härzschelet al (2020) Int J Mol Sci). These malignancies include Hodgkin's and non-Hodgkin's lymphoma, chronic lymphocytic leukemia, diffuse large B-cell lymphoma, follicular lymphoma, marginal zone B cell lymphoma, small lymphocytic lymphoma, mantle cell lymphoma and more than half a dozen rare B cell lymphomas.

Cancerous cells can also develop the ability to express α4β1, which appears to enhance its ability to metastasize (Schlesinger & Bendas (2015) Cancer Metastasis Rev). Obviously, α4β1 would also be important in terms of the homing to CD8+ T-cells and macrophages to tumours. The integrin has also been shown to play a role in angiogenesis and lymphangiogenesis and, possibly most interestingly, appears to play a role in chemoresistance by allowing tumour cells to adhere to each other and components of the ECM. While it is hard to imagine how the inhibition of α4β1 might be leveraged in some of the roles it might play in cancer, one certainly could envision giving patients a dose of an anti-α4β1 just prior to chemotherapy to try and reduce the development of chemoresistance.

HIV preferentially infects α4β7+ CD4+ T-cells (Lakshmanappa et al (2021) FEBS Lett), however, it is unclear how targeting α4 would result in a clinical improvement in the disease.

Antisense said, as we stated earlier, that it was assessing opportunities for ATL1102 in fibrosis and there appear to be a number of them. Both integrins, α4β1 and α4β7 are expressed by fibroblasts which use them to adhere to the ECM protein fibronectin. Fibroblasts contribute to the ECM by depositing collagen. A particular isoform of fibronectin, which contains a ligand both the α4β1 and α4β7 integrins is associated with pulmonary fibrosis, liver fibrosis, keloid scars and scleroderma. Moreover, blocking the integrins from binding those ligands, reduced a lot of signalling associated with the deposition of fibrotic and the actual deposition of

collagen (Zhang et al (2021) Int J Mol Sci). **A large-scale analysis of the changes in the levels of proteins ATL1102 results causes in DMD patients identified positive changes in the levels of LTBP4 and TSP-1, both of which are strongly involved in the fibrotic process.** These results support Antisense's assessment of ATL1102's potential utility in fibrotic diseases.

There are many more mentions particularly of α4β1 and its association with various diseases in the literature, but also some of α4β7. While we do not possess the knowledge or time to identify a particular opportunity for ATL1102, we can say with certainty that there appears to be plenty of potential opportunities for Antisense to evaluate.

Intellectual Property

To a certain extent, ATL1102's need for intellectual property is likely to be fairly low, given the regulatory exclusivities it 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 one year, but the point has 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. 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 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 eight of the 2020 ANP annual report, and includes a granted US patent covering ATL1102 methods of reducing circulating leukocytes to 2031, which can be extended for an additional five years.

Key Personnel

Over the last year, Antisense has appointed Dr Charmaine Gittleson, Ex-CSL veteran, as the new chairperson and Dr Gil Price, Antisense's Consultant Medical Director, has moved on to the board. Both appointments will likely prove highly valuable. Both have backgrounds and experience that enhance Antisense's corporate knowledge and experience in key areas relevant to the company's development of ATL1102 for DMD. Dr Gittleson's background in rare diseases is particularly relevant, as is Dr Price's experience as a long-time director of Sarepta Therapeutics, during the period in which it obtained the first approval of a DMD drug from the FDA via an accelerated pathway

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Dr Charmaine Gittleson, Chairperson
Dr Gittleson comes from a long stint at CSL, where she worked locally and in the US. During her tenure she held a wide variety of roles was responsible, at one time or another, for nearly every aspect of the clinical development process, while consistently moving up in the organisation to eventually serve as chief medical officer. Her background is particularly strong in the areas of clinical research, regulatory strategy development, medical safety and the ethics of drug development. Importantly, she is a proven leader in rare diseases, which will obviously be of significant benefit to Antisense as it develops ATL1002 for DMD.

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 CEO and managing director in 2001, Mr. Diamond was employed in the US as director, project planning/business development at Faulding Pharmaceuticals. Prior to this he was 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.

Dr Gil Price, M.D., Non-Executive Director and Consultant Medical Director
Dr Price's appointment significantly strengthens the board's clinical and scientific expertise, particularly in the area of DMD, as well as governance. Dr Price, as a physician, has been focussed on drug development, adverse drug reactions, drug utilisation and regulation. As a senior executive, his expertise spans clinical asset investment strategy, evaluation, financing and execution. Additionally, he was a director of Sarepta Therapeutics (2007-2016), the first company to obtain a DMD drug approval from the US FDA.

Dr Gary Pace, Non-Executive Director
Dr Pace has more than 40 years' experience in developing and commercialising 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. He 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' Experience spans research and discovery, as well as intellectual property. Since 2000, he has worked for Antisense Therapeutics, although in the earliest of years it was with a company related to Antisense Therapeutics. Prior to that, he worked for the law firm Griffith Hack and Co before moving on to Callinan Lawrie. Before moving into intellectual property law, Dr Tachas was a researcher at the Cancer and Transplantation (now the Austin Research Institute) at the University of Melbourne, where he gained his first experience with antisense oligonucleotides. Dr Tachas holds a PhD from the University of Melbourne and a Diploma of Intellectual Property Law.

Nuket Desem, Director of Clinical & 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 development director. Previously, Ms Desem was director clinical and regulatory affairs at Paranta Biosciences, and prior to that was senior manager development and regulatory affairs at Prana Biotechnology. She was also vice president clinical and regulatory affairs at Spinifex Pharmaceuticals

Antisense Therapeutics (ANP)

Comprehensive Research Report

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