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Antisense Therapeutics (ANP)

Promising treatment for a devastating disease

27 October 2020

Speculative Investment

Recommendation: Outperform

Our View

Antisense (ANP) reported very encouraging signs of efficacy from a small Phase II study of the fatal inherited muscle wasting disease Duchenne muscular dystrophy (DMD). Patients treated with lead drug ATL1102 for 6 months showed improvement in upper limb function and preservation of muscle mass, in marked contrast to the progressive deterioration that is the hallmark of the disease. The company plans to initiate a randomised Phase IIb study of ATL1102 in non-ambulant (wheelchair bound) DMD patients in Europe in H121. ANP has received positive feedback from European regulators regarding key aspects of the study, including that the study could potentially support an application for marketing approval in Europe if the results are positive. The company is also working to determine the appropriate clinical development and regulatory path in the US. We initiate coverage with an Outperform recommendation and a valuation of $134m, $0.27/sh (undiluted), or $0.23/sh fully diluted for a potential capital raise to fund the est. $20m European Phase IIb trial.

Key Points

ATL1102 stops the VLA-4 integrin connection that allows inflammatory cells to survive, proliferate and migrate across the vessel walls into the muscle tissue where they attack damaged and non-damaged muscle fibres. Its efficacy in reducing inflammation was confirmed in a previous randomised trial in multiple sclerosis, where it significantly reduced inflammation and disease progression.

Improved muscle function in DMD patients treated with ATL1102 – in a recent Phase IIa study that treated 9 boys with advanced DMD with ATL1102 for 24 weeks, the boys showed improvement or stabilisation in measures of upper limb strength and function. The most impressive result, in our view, was the average 0.9 point improvement in the validated Performance of the Upper Limb (PUL) 2.0 scale observed in ATL1102 treated patients, compared to the ongoing deterioration in PUL scores reported for DMD patients in the 6 other studies that we examined. The impressive PUL 2.0 results were supported by improvement or stabilisation of scores for the MyoSet test set, a validated suite of tools to assess strength and endurance of the upper limb.

Improvements in muscle structure as well - subjects in the ATL1102 Phase II study showed an average decrease in MRI measurements of forearm fat fraction as well as preservation of muscle mass, in contrast to the increase in fat fraction reported from other DMD studies. As DMD progresses, damaged muscle fibres are progressively replaced by fat, so the reduction in fat fraction is further evidence that ATL1102 is effectively combatting the disease. MRI measurement of fat fraction is an objective measure of disease progression that is independent of patient motivation or level of effort, so it is not subject to a placebo effect.

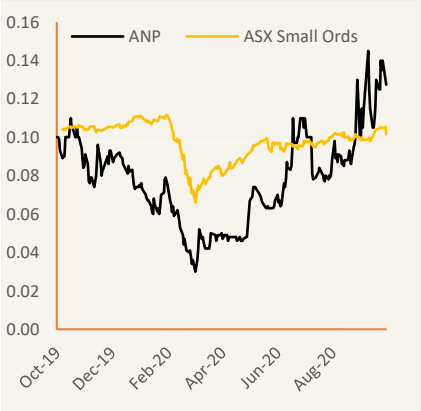
Premium pricing for DMD products – the DMD market is expected to be worth US$4.1bn by 2023. As is common for rare diseases, DMD treatments command high prices. Prices in the US for the three DMD treatments approved in the past 4 years range from US$63,000 to US$300,000 per patient per year, with list prices reportedly as high as US$892,000 per patient per year.

Eligible for a valuable Rare Pediatric Disease Priority Review Voucher - In September the FDA granted rare pediatric disease (RPD) designation for ATL1102 for the treatment of DMD. This means that if ATL1102 gains FDA approval it may be eligible for the award of a priority review voucher (PRV), which can be freely traded and which have recently sold for around US$100m. Legislation to extend the RPD PRV program to September 2026 is now before the US Senate. ANP is in discussions with KOLs and regulatory consultants about the best path for development of ATL1102 in the US.

Summary (AUD)

Market Capitalisation	**$61.1m**
Share price	**$0.125**
52 week low	$0.16
52 week high	$0.03
Cash as at 30 September 2020	$3.1m

Share price graph (AUD)



Key Financials (AUDm)

	FY20A	FY21E	FY22F
Revenue	0.7	1.8	3.5
R&D	(2.2)	(4.8)	(12.4)
SG&A	(4.3)	(1.6)	(1.6)
EBITDA	(5.8)	(4.6)	(10.5)
Reported NPAT	(5.9)	(4.6)	(10.4)
NPAT Adj.	(5.9)	(4.6)	(10.4)
EPS Adj. (c)	(1.3)	(0.8)	(1.5)
PE ratio (x)	n/a	n/a	n/a
DPS (c)	0.0	0.0	0.0
EV/Sales	n/a	n/a	n/a
EV/EBITDA (x)	n/a	n/a	n/a
ROE	n/a	n/a	n/a

Antisense Therapeutics - Summary of Forecasts — ANP $0.125

PROFIT & LOSS SUMMARY (A$m)

Year end June	FY19A	FY20A	FY21E	FY22F
Sales, royalties, milestones	0.0	0.0	0.0	0.0
Other (includes R&D tax rebate	0.6	0.7	1.8	3.5
Total Revenue	**0.6**	**0.7**	**1.8**	**3.5**
Growth (pcp)	n/a	26.3%	141.0%	96.5%
R&D Expenses	(1.8)	(2.2)	(4.8)	(12.4)
CoGS + SG&A expenses	(1.8)	(4.3)	(1.6)	(1.6)
EBITDA	**(3.0)**	**(5.8)**	**(4.6)**	**(10.5)**
Dep'n/Other Amort'n	(0.0)	(0.1)	(0.0)	(0.0)
EBIT	**(3.0)**	**(5.9)**	**(4.6)**	**(10.5)**
Net Interest	0.1	0.0	0.0	0.2
Pre-Tax Profit	**(2.9)**	**(5.9)**	**(4.6)**	**(10.4)**
Tax Expense	0.0	0.0	0.0	0.0
Minorities	0.0	0.0	0.0	0.0
NPAT	**(2.9)**	**(5.9)**	**(4.6)**	**(10.4)**
Growth (pcp)	-	-	-	-
Adjustments	0.0	0.0	0.0	0.0
NPAT Reported	(2.9)	(5.9)	(4.6)	(10.4)

PER SHARE DATA*

Year end June	FY19A	FY20A	FY21E	FY22F
EPS (c) - Reported	**(0.8)**	**(1.3)**	**(0.8)**	**(1.5)**
Growth (pcp)	n/a	n/a	-37.5%	90.3%
EPS (c) - Adjusted	(0.8)	(1.3)	(0.8)	(1.5)
Growth (pcp)	n/a	n/a	-37.5%	90.3%
Gross CF per share (c)	(0.8)	(0.9)	(1.0)	(1.7)
NTA per share (c)	0.7	0.9	3.0	2.7
Dividend (c)	0.0	0.0	0.0	0.0
Franking	0.0	0.0	0.0	0.0

KEY RATIOS

Year end June	FY19A	FY20A	FY21E	FY22F
Current ratio (x)	4.2	6.5	38.8	37.7
Net Debt : Equity (%)	n/a	-86.6%	-89.9%	-80.4%
Net Debt: EBITDA (x)	1.0	0.7	3.8	1.4
ROE (%)	n/a	n/a	n/a	n/a
ROIC (%)	n/a	n/a	n/a	n/a
Dividend Payout Ratio (%)	n/a	n/a	n/a	n/a

VALUATION MULTIPLES

Year end June	FY19A	FY20A	FY21E	FY22F
Reported PE Ratio (x)	**n/a**	**n/a**	**n/a**	**n/a**
Adjusted PE Ratio (x)	**n/a**	**n/a**	**n/a**	**n/a**
Dividend Yield (%)	0.0%	0.0%	0.0%	0.0%
EV/Sales (x)	n/a	n/a	n/a	n/a
EV/EBITDA (x)	n/a	n/a	n/a	n/a
EV/EBIT (x)	n/a	n/a	n/a	n/a

CAPITAL RAISING ASSUMPTIONS

Year end June	FY19A	FY20A	FY21E	FY22F
Shares Issued (m)	48.5	68.7	152.0	63.3
Issue Price (A$)	0.00	0.08	0.125	0.15
Net Cash Raised (A$m)	1.5	5.2	19.0	9.5

BALANCE SHEET SUMMARY

Year end June	FY19A	FY20A	FY21E	FY22F
Cash + Cash Equivalents	2.9	4.1	17.5	15.2
Receivables	0.6	0.7	1.7	3.5
Inventories	0.0	0.0	0.0	0.0
Other	0.2	0.5	0.5	0.5
Total Current Assets	3.7	5.2	19.6	19.1
Inventories	0.0	0.0	0.0	0.0
PP&E	0.0	0.0	0.0	0.0
Intangibles	0.0	0.0	0.0	0.0
Other	0.0	0.1	0.1	0.1
Total Non-Current Assets	0.0	0.1	0.1	0.2
TOTAL ASSETS	**3.7**	**5.4**	**19.8**	**19.2**
Accounts Payable	0.6	0.3	0.0	0.0
Borrowings	0.0	0.1	0.1	0.1
Provisions	0.3	0.4	0.4	0.4
Other	0.0	0.0	0.0	0.0
Total Current Liabilities	0.9	0.8	0.5	0.5
Borrowings	0.0	0.0	0.0	0.0
Provisions	0.0	0.0	0.0	0.0
Other	0.0	0.0	0.0	0.0
Total Non-Current Liabilities	0.0	0.0	0.0	0.0
TOTAL LIABILITIES	**0.9**	**0.8**	**0.5**	**0.5**
TOTAL EQUITY	**2.8**	**4.5**	**19.3**	**18.7**

CASH FLOW SUMMARY

Year end June	FY19A	FY20A	FY21E	FY22F
EBIT (excl Abs/Extr)	**(3.0)**	**(5.9)**	**(4.6)**	**(10.5)**
Add: Dep'n & Amort'n	0.0	0.1	0.0	0.0
Other non-cash items	0.4	(2.0)	2.0	2.8
Less: Tax paid	0.0	0.0	0.0	0.0
Net Interest	0.1	0.0	0.0	0.2
Change in Rec.	(0.6)	(0.1)	(1.0)	(1.7)
Change in Inv.	0.0	0.0	0.0	0.0
Gross Cashflows	(2.9)	(3.9)	(5.6)	(11.8)
Capex	2.4	(0.0)	(0.0)	(0.0)
Free Cashflows	(2.9)	(4.0)	(5.6)	(11.8)
Share Issue Proceeds	1.5	5.2	19.0	9.5
Other	2.4	(0.1)	0.0	0.0
Dividends Paid	0.0	0.0	0.0	0.0
Net Cash Flow	**1.0**	**1.2**	**13.4**	**(2.3)**
FX Effect on Cash	0.0	0.0	0.0	0.0

DXB valuation summary

	Probability (%)	Valuation (A$m)	Valuation A$/share
ATL1102 RoW non-ambulant DMD	25%	56.9	0.12
ATL1102 US non-ambulant DMD	20%	42.7	0.09
ATL1102 Ambulant DMD	20%	31.6	0.06
SG&A to 2024	-	(17)	(0.00)
Portfolio total	-	129.5	0.26
Cash end FY20	-	4.1	0.01
Total Valuation	-	133.6	0.27

Overview

Antisense Therapeutics' lead drug, ATL1102 blocks a key inflammatory signal which facilitates survival, proliferation and migration of white blood cells from the bloodstream to the site of inflammation. The inflammatory signal is integrin α4, also known as CD49d, the alpha subunit of VLA-4, an adhesion molecule expressed on most leukocytes (white blood cells). ATL1102 is an antisense oligonucleotide drug that triggers the breakdown of the messenger RNA (mRNA) that carries the instructions for integrin α4 from the nucleus to the site of protein synthesis in the cytoplasm, thereby inhibiting the expression of integrin α4 on the cell surface, as shown in Exhibit 1. Antisense in-licenced ATL1102 from Ionis Pharmaceuticals (NASDAQ:IONS), which has commercialised 3 drugs based on its antisense technology.

ANP originally investigated ATL1102 as a treatment for multiple sclerosis (MS). ANP showed in a Phase II trial completed in 2008 that ATL1102 was effective in reducing the development of new lesions in MS patients.[1] The efficacy was comparable to that of the marketed MS drug Tysabri, which targets the same VLA-4 pathway but via a different mechanism. ANP out-licenced ATL1102 to Teva in February 2008, but Teva returned the rights in March 2010, in part due to the need to conduct additional animal toxicology studies before progressing to the next stage of clinical development. ANP completed the additional animal safety studies but has not yet been able to attract another partner to fund further development of ATL1102 in MS. However, the company continues to explore opportunities to develop ATL1102 in this indication.

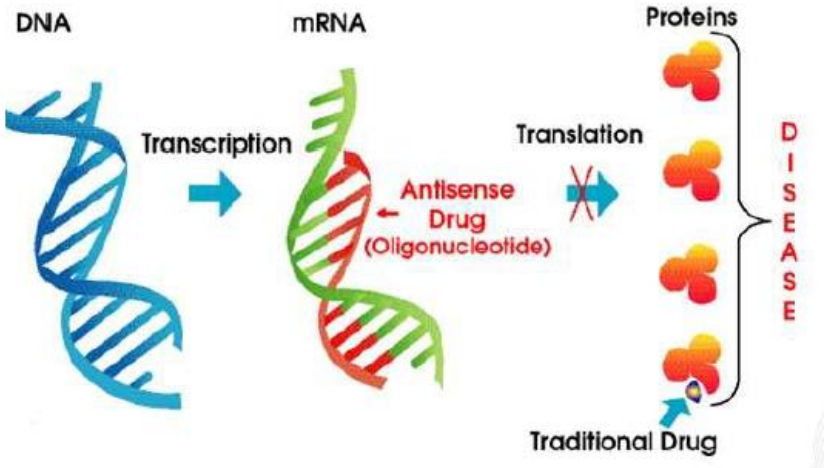
The company pivoted to developing ATL1102 as a treatment for the fatal inherited neuromuscular disease known as Duchenne muscular dystrophy (DMD) after a study published in 2015 identified CD49d as a promising therapeutic target in that condition. The study reported that levels of CD49d positive T cells (or lymphocytes) were elevated in boys suffering from DMD, and that high levels of CD49d positive T cells were associated with more rapid progression of the disease.

Given the lack of effective therapies for this fatal condition, the company identified DMD as a promising commercial opportunity that potentially offered a faster route to market and which would require fewer and smaller clinical studies. This has allowed ANP to keep control of the development program for ATL1102, rather than depending on a development partner. Treatments for orphan diseases like DMD attract high prices and the global market for DMD drugs is expected to be worth US$4.1bn by 2023.

ANP recently reported encouraging signs of efficacy from a single-arm Phase IIa study of ATL1102 in 9 boys with DMD who were confined to a wheelchair (ie non-ambulant). After 24 weeks of treatment with ATL1102, the boys showed improvement or slower-than-expected decline in measures of upper limb strength and function. There were also improvements in a number of biomarkers including reductions in targeted populations of inflammatory cells, preservation of muscle mass and reductions in the fat percentage in forearm muscles.

Buoyed by these encouraging results, ANP plans to initiate a randomised controlled Phase IIb study of ATL1102 in non-ambulant DMD patients in H121. Feedback from European regulators suggests that this study could be the basis for an application for conditional approval, if the results are positive.

Exhibit 1: ATL1102 inhibits expression of the CD49d protein by degrading the CD49d mRNA



Source: Antisense

[1] Limmroth et al Neurology 2014, 11:83 (20) 1780-8

Ground-breaking study showed CD49^{hi} T cells are a biomarker for rapid DMD progression

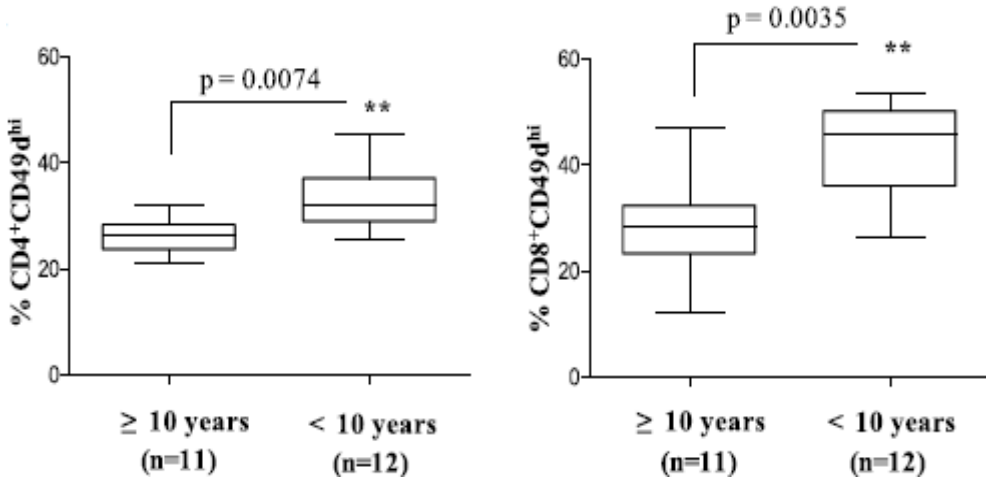
ATL1102 blocks the production of integrin α4, the alpha subunit of the integrin VLA-4, also known as CD49d. CD49d plays a key role in recruiting lymphocytes and monocytes (white blood cells) to migrate from the bloodstream to the site of inflammation in surrounding tissue, where they promote and perpetuate inflammation.

A study by Pinto Mariz and colleagues published in 2015 found that there was a strong association between the proportion of T cells expressing high levels of CD49d and the severity of symptoms in boys suffering from the DMD.

They found that the proportion of T cells (T lymphocytes) expressing high levels of CD49d (CD49^{hi}) was significantly elevated in boys with more advanced DMD who could only walk slowly (<1m/s) or were wheelchair bound. In contrast, the proportion of CD49dhi T cells in DMD boys who could walk relatively quickly (>1m/s) was similar to the levels in age-matched healthy controls. These findings were true for both CD4+ (helper) and CD8+ (cytotoxic) T cells.

The researchers also found that boys with a high proportion of Cd49^{hi} T cells at the start of the study were more likely to become wheelchair bound by 10 years of age due to rapidly progressing disease, as shown in Exhibit 2.

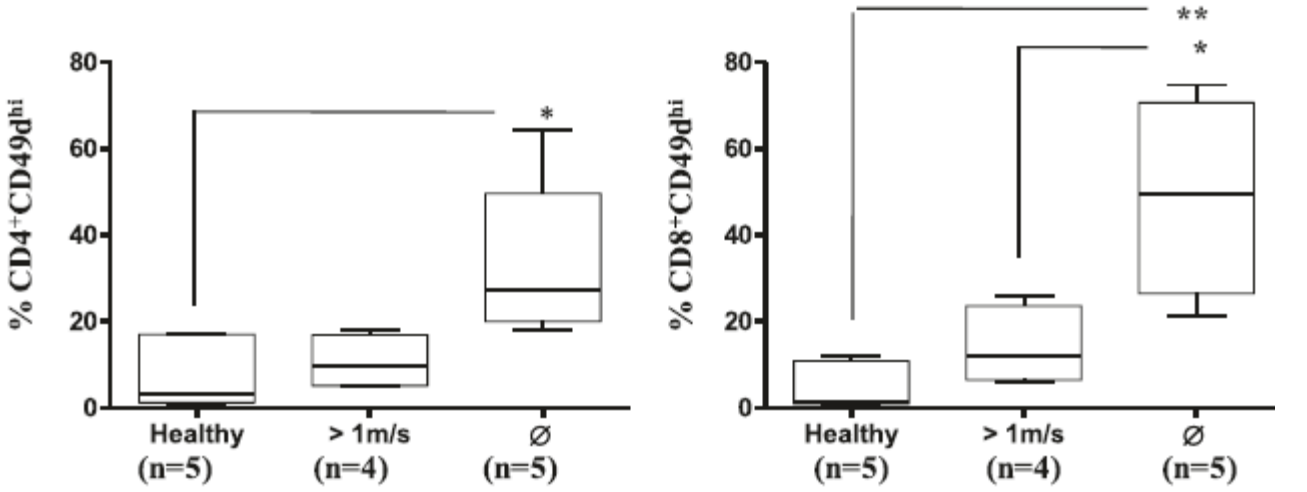
Exhibit 2: Boys with who lost mobility before age 10 had higher proportions of CD49d^{hi} T cells in the bloodstream



*Source: Pinto-Mariz et al 2015, Fig 1. Notes: Cd4^{+}= helper T cells; CD8^{+}= cytotoxic T cells; The number of DMD patients analysed in each group shown in brackets; *p < 0.05, **p < 0.01, ***p < 0.001 .*

CD49d plays a key role in the attachment of lymphocytes to the blood vessel wall and subsequent migration through the blood vessel wall into the surrounding tissue. Pinto Mariz et al found that CD49dhi T cells from wheelchair bound boys migrated faster through a layer of endothelial cells (ie the cell that line blood vessels) in a model of cell migration within tissues than cells from healthy boys or those with less advanced disease, as shown in Exhibit 3.

Exhibit 3: CD49d^{hi} T cells from wheelchair-bound boys migrated more quickly through a layer of endothelial (blood-vessel) cells than T cells from healthy boys or those with milder disease



*Source: Pinto-Mariz et al 2015, Fig 1. Notes: Cd4$^+$= helper T cells; CD8$^+$= cytotoxic T cells; The number of DMD patients analysed in each group shown in brackets; ϕ indicates wheel-chair bound boys; *p < 0.05, **p < 0.01.*

While DMD is an inherited disease caused by mutations in the dystrophin gene, the immune inflammatory response also contributes to disease progression in DMD patients. The results reported by Pinto Mariz indicate that CD49d plays an important role in the pathogenesis of DMD and therefore suggest that targeting CD49d might be an effective way to reduce inflammation-mediated muscle damage and slow progression of the disease.

ATL1102 showed encouraging efficacy in a Phase IIa study in non-ambulant DMD boys

ANP investigated the use of ATL1102 as a treatment for DMD in a Phase IIa study of ATL1102 in 9 non-ambulant (wheelchair bound) DMD patients at the Royal Children's Hospital, Melbourne. In this open label, single arm study, the boys were injected with 25mg of ATL1102 once per week for a period of 24 weeks, with 8 of the 9 subjects also continuing to receive corticosteroid treatment throughout the study period. The trial assessed the safety and tolerability of ATL1102 and also its efficacy in terms of its effects on muscle strength and function as well as examining blood and imaging markers of inflammation and muscle damage.

Antisense reported top line data from the Phase IIa study in December 2019 and presented the final study report in May this year. ATL1102 was assessed to be safe and well tolerated and there were no participant withdrawals from the study. The most commonly reported adverse events were mild redness and skin discolouration at the injection site, which either resolved or were close to resolution at the end of the study. There were no reports of reduction in platelet counts (thrombocytopaenia) which has been reported in some studies which administered high doses of other oligonucleotide therapies.

There were consistent reductions in the number of lymphocytes, including T cells, in the bloodstream over the 24-week treatment period, with a rebound to slightly above the starting levels at week 28. The mean number of CD49 positive T cells was statistically significantly lower at week 24 vs week 28, demonstrating that ATL1102 modulated CD49+ lymphocytes in the blood during treatment, in line with the expected mode of action.

The outcomes in the key measures of efficacy in the study were very encouraging, with either improvement or slower-than-expected decline in measures of upper limb strength and function. Furthermore, there was a reduction in fat percentage in forearm muscles on MRI scans, whereas studies of the natural history of the disease show a steady increase as dying muscle fibres are replaced by fat.

The impact on measures of respiratory function was inconclusive. One measure, peak expiratory flow, did not decline at all over the course of the study (a better than expected outcome), while the other measure, forced vital capacity (FVC), declined faster than expected. However, these measures of respiratory function are highly variable, so data on substantially more subjects over a longer period of treatment would be required to draw any conclusions.

Professor Thomas Voit MD, Director, NIHR GOSH Biomedical Research Centre, UK, who is a widely-published DMD researcher, observed that "Disease stabilisation or indeed improvement in functional scores in non-ambulant DMD boys is almost unheard of and a very encouraging result. This is even more meaningful as these results have been obtained using different independent measures and over a relatively short trial time of 24 weeks…"

Impressive improvement in PUL 2.0 upper limb function score

In our view the most impressive result in the Phase IIa study of ATL1102 was the average 0.9 point improvement in PUL 2.0 scores observed in ATL1102 treated patients, compared to the deterioration in scores reported for non-ambulant DMD patients in other studies.

PUL 2.0 (performance of the Upper Limb) is a validated 42-point functional scale specifically designed for assessing upper limb function relating to everyday life in patients with DMD (Exhibit 4). The items within the scale were identified to be clinically meaningful, important to patients and relevant to everyday life. The scale involves scoring performance in a range of activities such as picking up coins, lifting and stacking cans, tracing a path, pushing on a light switch or lifting hands to their mouth; higher scores indicate better performance. The original PUL 1.2 scale (with a maximum score of 74) was developed at an international workshop in 2012 (Mercuri et al 2012); the ATL1102 trial assessed performance using the revised PUL 2.0 scale which has a maximum score of 42.[2]

The FDA has recommended the use of PUL 2.0 as a primary efficacy endpoint in Phase III studies that include non-ambulant DMD patients. A wide range of activities has been included in PUL 2.0 in order to avoid "ceiling" and "floor" effects and thus make it relevant to both ambulant and non-ambulant boys.

Exhibit 4: PUL 2.0 measures 3 dimensions of upper limb – the shoulder, elbow and wrist/hand

Source; Taylor Collison Research, Capricor Therapeutics company announcement. NB The exhibit illustrates most items of the PUL 1.2 assessments, almost all of which are included in PUL 2.0; notable changes include that PUL 2.0 does not use light cans in the middle level items and that tearing paper becomes a wrist/hand level task in PUL 2.0. Shoulder level items include tasks performed both with and without weights.

ANP recently presented an analysis at the World Muscle Society (WMS) Virtual Congress 2020, which compared the PUL 2.0 scores in the ATL1102 study to scores from a matched control group from a natural history cohort of DMD patients in Rome, Italy, identified using the same inclusion criteria used to enrol patients in the ATL1102 Phase II study (the Rome cohort).

As Exhibit 5 shows, in the Rome cohort PUL 2.0 scores declined on average by 2.0 points over a 6-month period, compared to the 0.9 point improvement over the same period in the ATL1102 study. The difference between the change in PUL 2.0 scores in the ATL1102 trial and in the Rome cohort was statistically significant.

We identified two other studies that reported changes in PUL 2.0 scores in non-ambulant DMD patients. In the first study, which reported the natural history of 90 boys, PUL 2.0 scores declined on average by 2.2 points over 12 months, equivalent to a decline of 1.1 points over a 6 month period. In the second cohort, 8 boys in the placebo arm of the HOPE Phase II study of CAP-1002, PUL 2.0 scores declined by 2.3 points over 6 months.[3]

As exhibit 5 shows, the average decline in these 3 cohorts of patients over a 6 month period was 1.8 points, a marked contrast to the 0.9 point improvement in the ATL1102 study.

We also identified three additional studies that reported changes in the original PUL 1.2 scale over a 6 or 12 month period[4,5]. In each of those studies the mean PUL score also declined over the 6 or 12 month period.

[2] Mayhew et al. Developmental Medicine & Child Neurology 2020, 62: 633–639. DOI: 10.1111/dmcn.14361

[3] Capricor Therapeutics announcement

[4] Ricotti et al 2016, PLosOne, 11(9) e0162542

Cross trial comparisons should always be treated with caution because there may be differences in the study design or unidentified differences between the patient populations. While bearing in mind this proviso, we find it very encouraging that mean PUL scores showed a progressive decline in the 5 other cohorts examined but improved in patients treated with ATL1102. In fact, PUL 2.0 scores improved or remained stable in 7 of the 9 subjects in the ATL1102 study, as shown in Exhibit 6.

The company also noted that there appears to be a relationship between changes in CD49d+ T cells and PUL 2.0 scores.

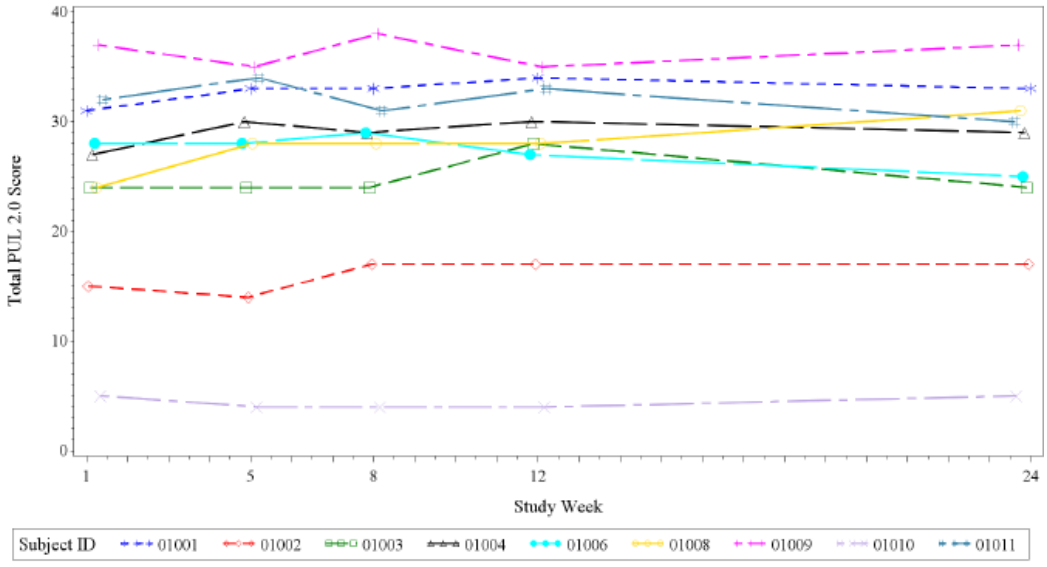
The fact that there were only 9 subjects in the ATL1102 trial means that the confidence intervals around the estimates of treatment effects are wide. The 95% confidence interval for the change in PUL 2.0 score ranges from a decline of 1.33 points to an improvement of 3.11 points. This tells us that if the study was repeated a large number of times that there is a 95% probability that the average change in PUL 2.0 score would lie in this range. It is encouraging that even at the bottom of the confidence interval (ie -1.33 points) the change in PUL 2.0 scores would be superior to the average decline in the three other cohorts in Exhibit 5.

Exhibit 5: Change in total PUL 2.0 upper limb muscle function and strength score over 6 months

Measure	ANP change after 24 weeks treatment with ATL1102 (mean, 95% CI)	Mayhew et al 2020 12-month change pro rata to 6 months	Matched Rome cohort (WMS) (mean, SD)	Capricor CAP-1002 HOPE Phase II 6 months (mean, SD)	Average of non-ATL1102 studies
PUL 2.0 score	0.9 (-1.33, 3.11)	-1.1	-2.0 (3.0)	-2.3 (1.5)	-1.8

Source: Taylor Collison research. NB 95% CI= 95% confidence interval; SD= standard deviation; higher PUL 2.0 score= less disability.

Exhibit 6: Total PUL 2.0 upper limb muscle function and strength score in individual subjects at each time point



Source: Antisense. Note higher score = less disability

MyoSet upper limb function scores stable or improved

The ATL1102 study also assessed changes in upper limb function measured using the MyoSet tests, a suite of validated tools to assess strength and endurance of the upper limb. The MyoPinch and MyoGrip tools measure, respectively, pinch strength and grip strength. MoviPlate is a tapping device designed to measure endurance of the upper limb.

Over the course of 24 weeks of treatment with ATL1102 grip strength, pinch strength and MoviPlate score either improved or remained stable, as shown in Exhibit 7. Exhibit 7 also shows that, in contrast, grip strength declined in each of the 4 other studies that we identified that used these tools, while pinch strength either declined or was stable. Only 1 out of 3 studies reported an improvement in MoviPlate scores, but the average improvement in MoviPlate scores was less than was observed in the ATL1102 study.

[5] Ricotti et al 2019, Neuromuscular Disorders 29(4);261-268

The main takeout is that the outcomes on each of these measures of upper limb function in patients treated with ATL1102 was better than would be expected based on the results of the historical studies.

Exhibit 7: Change in MyoGrip, MyoPinch and MoviPlate scores in ATL1102 Phase II and other DMD studies

	ANP change after 24 weeks treatment with ATL1102 (mean, 95% CI)	Ricotti (2019) annual change pro rata to 6 months	Hogrel (2016) 12-month change pro rata to 6 months	Ricotti (2016) 6 months (mean, 95% CI)	Seferian (2020) annual change pro rata to 6 months	Average of non-ATL1102 studies
Grip strength (kg)	0.2 (-0.25, 0.67)	-0.2	-0.16	-0.5 (-1.01, 0.002)	-0.14	-0.25
Pinch strength (kg)	0.0 (-0.18, 0.19)	-0.04	-0.04	-0.38 (-0.53, -0.22)	-0.09	-0.14
MoviPlate score	1.9 (-6.08, 9.85)		-0.8	4.7 (2.0, 7.4)	-0.60	1.1

Source: Taylor Collison research. NB 95% CI= 95% confidence interval; higher score= less disability.

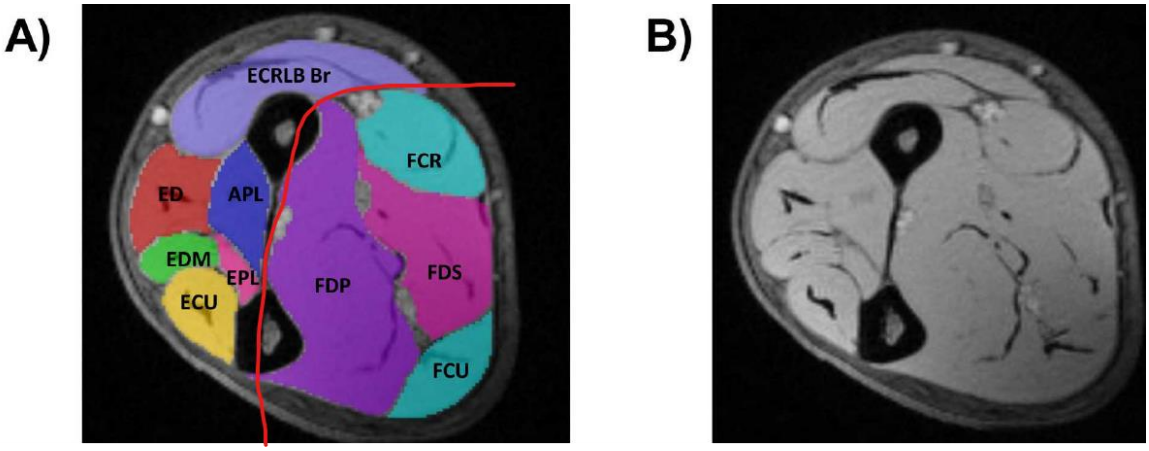
ATL1102 preserved muscle mass and reduced fat fraction in MRI scans

ANP reported a number of different MRI measures of muscle volume and fat fraction from the Phase II DMD study. We focus here on the measure of the percentage of fat within the muscle because in our survey of the scientific literature we found considerable support for the use of muscle fat fraction (fat %) as measured by MRI as an objective measure of disease progression.

As DMD progresses and damaged muscle fibres die they are gradually replaced by fat, and so the fat fraction within the muscles increases. Techniques have been developed to measure the fat fraction using MRI scans. Fat fraction has the advantage that it is an objective measure that does not rely on the degree of effort by the subject. This means that it is not influenced by the level of motivation of the subject and so is unlikely to be influenced by a placebo effect. This is an important attribute in a single arm study with no control group.

ANP reported detailed fat fraction results for scans from the middle for the forearm. It reported fat fraction separately for the volar (flexor) muscle group (volar means on the same side as the palm of the hand) and for the dorsal (extensor) muscles, as well as the average fat fraction across all the muscle groups. Exhibit 8 shows the location of the major forearm muscles; the 4 volar muscles are to the right of the red line in the exhibit and the 6 dorsal muscles on the left.

Exhibit 8: Forearm muscle segmentation (A) and MRI image (B) from a healthy boy



Source: Ricotti et al 2016 doi:10.1371/journal.pone.0162542.g001. Notes: volar muscles are to the right of the red line; individual muscles labelled Extensor carpi ulnaris (ECU), extensor digiti minimi (EDM), extensor digitorum (ED), extensor pollicis longus (EPL), abductor pollicis longus (APL), extensor carpi radialis longus/brevis and brachioradialis (ECRLB Br). VOLAR compartment: flexor digitorum profundus and flexor pollicis longus (FDP), flexor digitorum superficialis and palmaris longus (FDS), flexor carpi ulnaris (FCU), flexor carpi radialis (FCR).

Subjects in the ATL1102 Phase II study showed an average decrease in forearm fat fraction as well as preservation of muscle mass, in contrast to the increase in fat fraction reported from other studies of DMD patients, as shown in Exhibit 9. The confidence intervals are quite wide, indicating that there was considerable variation between patients in this measure. Despite this, ANP reported that the difference in the mean change in middle (central) dorsal fat fraction between the ATL1102 study and a historical study in a similar population of non-ambulant patients (Ricotti et al 2016) was statistically significant (p=0.001). A

similar study by Hogrel and colleagues reported that the muscle fat fraction in the volar (flexor) muscle compartment increased by 3.2% over 12 months (equivalent to a 1.6% increase every 6 months), further evidence that muscle fat fraction typically increases over time in the absence of effective therapy[6].

Exhibit 9: Change in forearm muscle fat fraction % over 6 months in ATL1102 Phase II and other DMD studies

	ANP change after 24 weeks treatment with ATL1102 (mean, 95% CI)	Hogrel (2016) 12-month change pro rata to 6 months	Ricotti (2016) 6 months (mean, 95% CI)	Average of non-ATL1102 studies
Volar fat fraction (%)	-0.57 (-7.8, 6.7)	1.6	0.7 (-1.8, 3.3)	1.2
Dorsal fat fraction (%)	-0.88 (-3.4, 1.7)		5.5 (2.7, 8.3)	
Total forearm fat fraction (%)	-0.52 (-5.6, 4.6)		3.9 (1.9, 5.7)	

Source: Taylor Collison research. NB 95% CI= 95% confidence interval.

Putting MRI changes in fat fraction in context

While MRI fat fraction is a relatively new measure, it has been shown to correlate well with clinical measures of muscle function and strength in non-ambulant DMD patients. For example, Hogrel et al (2016) reported that increase in forearm fat fraction over the course of one year was highly correlated with reductions in upper limb muscle strength and function.

We identified two further studies that compared MRI measurement of fat fraction with functional measures of performance in DMD patients. While these studies mainly looked at MRI assessment of leg muscles, one of the reports noted that findings in arm and leg MRI were similar.

Nagy et al 2020 looked at longitudinal reliability of outcome measures in patients with DMD. While they were looking at MRI assessment of thigh muscles in ambulant patients, it is noteworthy that they concluded that mean fat fraction was the most sensitive and powerful marker of disease progression that they evaluated.

Willcocks 2017 examined over 100 ambulant boys, looking at MRI and other measures of leg muscle structure. They concluded that MRI fat fraction of the vastus lateralis and the biceps femoris long head muscles were both good objective measures of disease progress in ambulant boys with DMD.

While fat fraction is a biomarker rather than a direct measure of clinical benefit, the fact that it is an objective measure of changes in muscle structure makes it a useful tool for assessing responses to treatment, in our view. It is encouraging that subjects in the ATL1102 study experienced improvement in this objective measure in addition to improvements in the PUL 2.0 and MyoSet functional measures.

Our overall view of the ATL1102 DMD trial results

While the efficacy results from the Phase IIa study are very encouraging, the small number of subjects means that the confidence intervals (error margins) of the estimates of efficacy are wide. Despite this limitation, the trial results provide the best evidence we have of the true effect of ATL1102. If the efficacy of ATL1102 is confirmed in the planned randomised placebo-controlled study, it would become one of the few drugs with demonstrated efficacy in improving or preserving function in DMD patients.

Planning underway for a potentially pivotal randomised Phase IIb of ATL1102 in Europe

ANP plans to undertake a randomised Phase IIb study of ATL1102 in non-ambulant DMD patients in Europe. Feedback from regulators indicates that if the study is successful it could be the basis for an application for approval in Europe. The trial could also potentially recruit patients in Australia and New Zealand.

The company announced on 30 July that it had received feedback from the European Medicines Agency (EMA) on the appropriateness of key trial design parameters. The randomised trial will include a placebo arm and an arm dosing patients with 25mg of ATL1102 per week, the dose that was used in the recent Phase IIa study at the Royal Children's Hospital in Melbourne. The company has also proposed dosing at higher levels (up to 100mg/week), and the EMA advised the company to provide further rationale for the selection of the higher dose levels. The company's partner, IONIS, is undertaking modelling work to support the administration of higher doses in the trial. We expect the Phase IIb trial to also include one or two additional arms dosing patients at doses higher than 25mg/week, which would increase the trial size to 105 to 140 subjects. Subjects will be treated for one year to assess the efficacy of ATL1102 over a longer time frame.

We expect PUL 2.0 to be the primary endpoint, given the efficacy seen in the Phase IIa study and the fact that is assesses functions that are clinically meaningful, important to patients and relevant to everyday life. Assessments of upper arm strength with the MyoGrip and MyoPinch are likely to be included as secondary endpoints.

[6] Hogrel et al 2016, Neurology;86:1022–1030

The company plans to submit its Paediatric Investigational Plan (PIP) to the EMA Paediatric committee (PDCO) in the current quarter. The company will look to address the EMA scientific advice recommendations and confirm Phase IIb trial design through its PIP application. The Phase IIb trial application will be submitted after receiving initial PDCO feedback. The company expects to commence the trial in H121.

The company applied for Orphan Drug Designation (ODD) for ATL1102 for the treatment of DMD in Europe in August. If granted, ODD would confer 10 years of market exclusivity in the EU, and pediatric orphan designation a further 2 years .

Potentially eligible for a valuable Pediatric Rare Disease Priority Review Voucher from the FDA

The company has engaged with key opinion leaders, advocacy groups and regulatory consultants in the US and is working to determine the appropriate clinical development and regulatory path for ATL1102 in DMD in the US. The company has previously submitted an Investigational New Drug (IND) application to the FDA for the conduct of a Phase IIb trial in MS patients, and received notification from the FDA that the study could proceed at a 25mg/week dose for 6 months under a partial hold introduced by the FDA. In view of this feedback, we suspect that the company may need to conduct additional long term animal safety studies if it wants to treat patients in the US for a longer time (such as a year) or at higher doses. Therefore, we suspect that any trial that recruited US-based subjects would be a separate study to the proposed European trial.

On the other hand, a well-conducted trial that recruited subjects in Europe and Australia could potentially be used as the basis for an application for marketing approval in the US, despite the FDA's preference for trials to include US-based subjects if possible.

Antisense has applied for ODD in the US, which would confer 7 years of market exclusivity in the US, if granted. Separately, in September the FDA granted rare pediatric disease (RPD) designation for ATL1102 for the treatment of DMD. The RPD designation means that if ATL1102 gains FDA approval it would be eligible for the award of a priority review voucher (PRV) which can be used to shorten the FDA review process by as much as 4 months.

Under the sunset clause in the current act authorising the pediatric rare disease priority review voucher program, ATL1102 would need to be approved by 30 September 2022 in order to qualify for a PRV. However, legislation to extend the program by a further 4 years, known as the Creating Hope Reauthorization Act, passed by the US House of Representatives on 30 September 2020 with bipartisan support. The legislation is co-sponsored by 43 lawmakers, including 23 Democrats and 20 Republicans. We conclude from this that there is a good chance that the legislation will also be passed by the Senate and approved by the President. If the legislation becomes law, ATL1102 would be eligible for a PRV if it is approved before 30 September 2026, which is achievable under the current development timeline.

To date the FDA has awarded 22 PRVs for rare paediatric diseases. PRVs have sold for between US$65m and US$350m. Recent prices for PRVs have been around US$100m; for example, in February 2020 Vifor Pharma purchased a PRV from Sarepta therapeutics for US$111m.

DMD overview

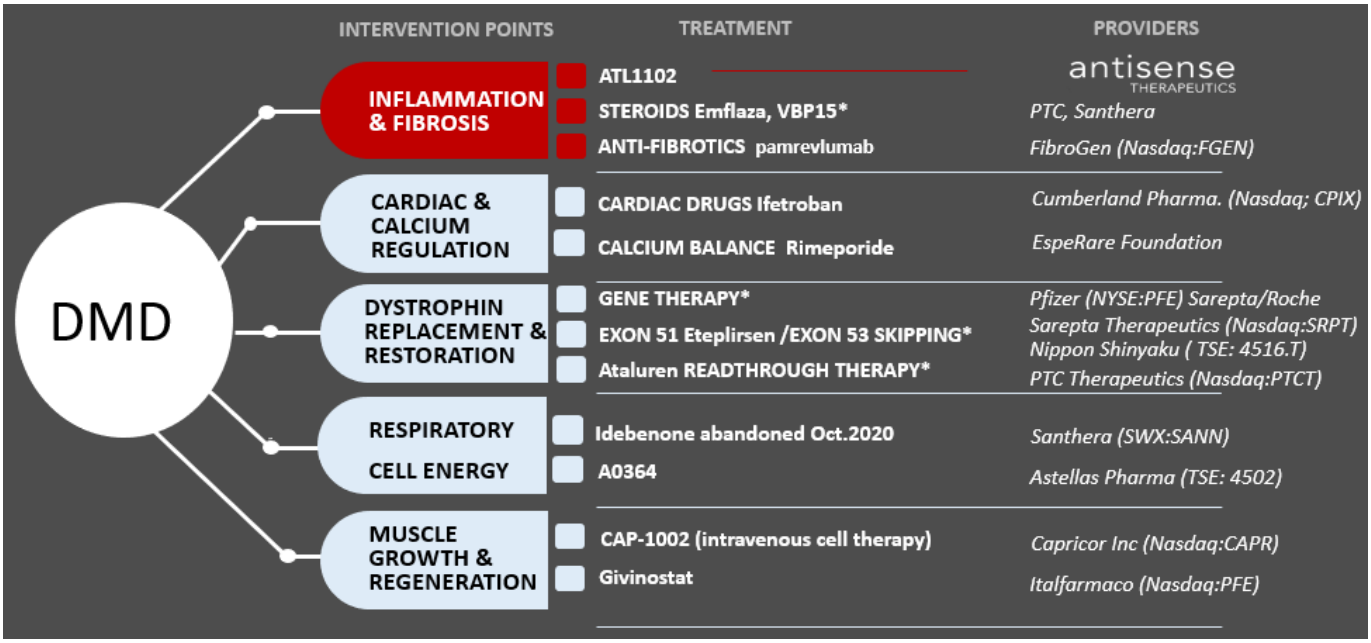
DMD is one of the most devastating and most common inherited neuromuscular diseases. It results from a defective gene responsible for producing the key muscle protein dystrophin. The gene mutation dramatically reduces production of the dystrophin protein, which strengthens and protects muscle fibres from damage as they contract and relax. Without dystrophin, muscle cells easily become damaged and die, resulting in progressive muscle weakness, loss of walking ability, heart and breathing failure and premature death. DMD has an X-linked recessive inheritance pattern because the gene for dystrophin is carried on the X chromosome. DMD almost exclusively affects boys, as they have only one copy of the X chromosome.

DMD has been estimated to effect one in 3,500[7] to 6,300[8] live male births. A recent meta-analysis estimated that the pooled global incidence of DMD was 19.8 per 100,000, equal to one in 5050 live male births[9]. The meta-analysis also estimated that that the global DMD prevalence was 7.1 cases per 100,000 males in the overall population. Based on this estimate of prevalence, we estimate that there are approximately 11,600 DMD patients in the US and 17,500 patients in the EU (including the UK). Despite the best available treatment, the need for wheelchair use can occur in the early teenage years, with an average age of 13. Between 36% and 48% of DMD patient are estimated to be non-ambulant.

Several different classes of drug therapies are either in use or in development for managing aspects of the disease in DMD patients, as shown in Exhibit 10. We discuss the classes of drugs that are relevant to ATL1102 in the sections below. Drugs to support cardiac function are also an important aspect of managing DMD, but they are not relevant to ATL1102 and so are not discussed here. The effects of the different classes of drugs tend to be complementary.[10]

[7] Emery 1991, Neuromuscul Disord 1 (1) 19- 29
[8] Ryder et al. 2017, Orphanet Journal of Rare Diseases 12:79
[9] Crisafulli et al. 2020, Orphanet Journal of Rare Diseases 15:141 https://doi.org/10.1186/s13023-020-01430-8
[10] Cordova et al 2018, Front. Genet. 9:114. doi: 10.3389/fgene.2018.00114

Exhibit 10: ATL1102's potential place in the treatment of DMD



*Source: Antisense. * New anti-inflammatory steroids, dystrophin restoration and gene therapies are only being tested in ambulant boys.*

Drugs to manage inflammation are a key plank of DMD treatment

One of the key challenges in treating DMD is managing the inflammation-mediated muscle damage that contributes to the progression of the disease. Corticosteroids are the only treatment approved for the broad DMD population, but they are associated with significant side effects including bone fragility, suppression of the immune system and suppression of growth hormone production.

Despite the long-term safety concerns associated with steroids, the drugs have a multipronged mechanism. This mechanism significantly prolongs lifespan, so it is unlikely to be replaced in the near future. The key drugs in development to treat inflammation in DMD patients are shown in Exhibit 11.

ATL1102 aims to further reduce inflammation-mediated muscle damage over and above that achieved with corticosteroids, with 8 of the 9 patients on corticosteroids in the completed Phase II trial. It could also potentially be used as an alternative to corticosteroid therapy in patients who are unable to tolerate the side effects of corticosteroids.

Emflaza (deflazacort), a corticosteroid that was approved by the FDA in 2017, was launched at a list price of US$89,000 per year. In 2019, the Institute for Clinical and Economic Review (ICER) estimated that the annual cost of Emflaza for a 40kg boy in the US was US$62,900, based on the Federal Supply Schedule price.[11] Emflaza efficacy is comparable to standard corticosteroid therapy, but with an improved side effect profile.

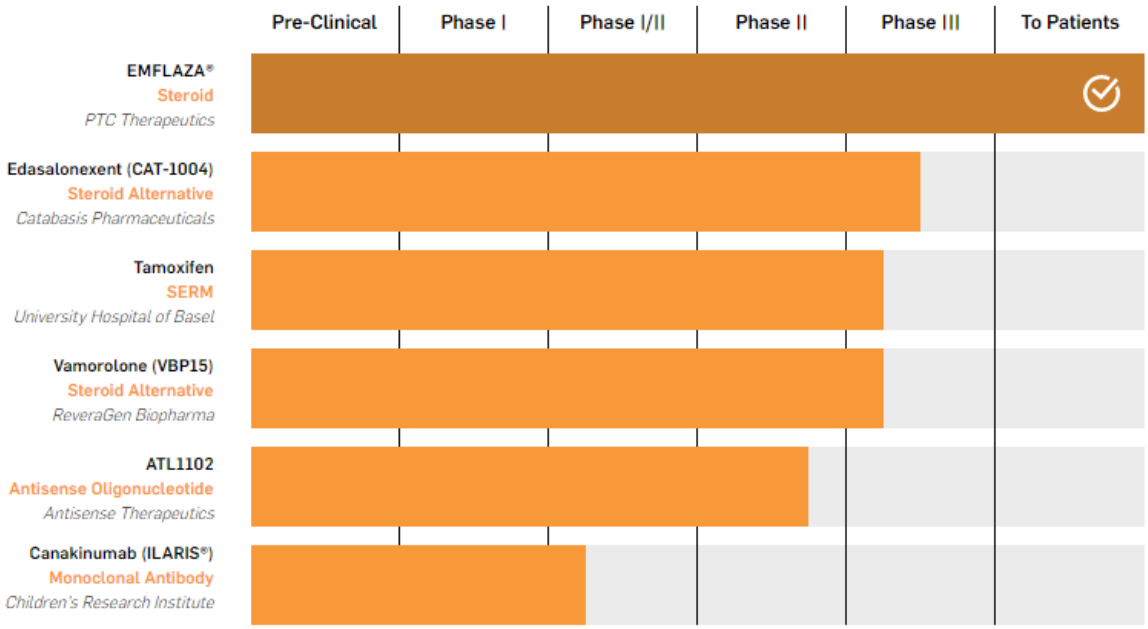
Another steroid alternative, edasalonexent (Catabasis Pharmaceuticals), was being investigated in a Phase 3 trial called PolarisDMD (NCT03703882) in 131 ambulant boys with DMD aged 4 to 7 who were not being treated with corticosteroids. However, Catabasis announced on 27 October that edasalonexent failed to meet its primary endpoint in the Phase III trial and that development has been terminated.

Vamorolone (VBP15, ReveraGen/Santhera Pharmaceuticals) is a corticosteroid alternative that hopes to retain the beneficial anti-inflammatory and muscle strengthening aspects of corticosteroids, while decreasing some of the undesirable side effects. A randomised Phase IIb study (NCT03439670) is comparing two doses of vamorolone to prednisolone (active control) and placebo groups in 121 boys aged 4-7. The trial is expected to read out in Q221.

The cancer drug Tamoxifen, a selective estrogen receptor regulator, is being investigated in a randomised Phase III study in ~70 ambulant DMD patients and a small number (6-20) of non-ambulant patients. The study (NCT03354039), which is sponsored by the University Hospital, Basel, Switzerland) commenced in June 2018 and is expected to complete in June 2022. Tamoxifen significantly improved muscle strength and reduced muscle fatigue in a mouse model of DMD, and is reported to have shown potential disease stabilisation under compassionate use in DMD patients.

[11] Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value - draft report; p49

Exhibit 11: Drugs that aim to reduce inflammation in DMD patients



Source: Parent Project MD https://www.parentprojectmd.org/duchenne-drug-development-pipeline/

Two other drugs in development that are relevant to ATL1102 because they target inflammation and/or fibrosis in non-ambulant DMD patients but are not listed in Exhibit 11 are discussed below.

The first drug, pamrevlumab (FG-3019, FibroGen), is an antibody drug that inhibits connective tissue growth factor (CTGF). CTGF is a pro-inflammatory protein involved in wound healing. A randomized Phase III study of pamrevlumab in 90 non-ambulant DMD patients was initiated in July 2020 and is expected to complete in September 2022. The primary endpoint is change in PUL 2.0 over 12 months of treatment. An open-label Phase 2 clinical trial (NCT02606136) is assessing the safety and efficacy of pamrevlumab in 21 non-ambulant DMD patients. Interim finding presented in 2019 showed that after one year of treatment respiratory function was better preserved than expected. PUL scores declined by 1.5 points over 12 months. Pamrevlumab is also being investigated in Phase III studies in idiopathic pulmonary fibrosis (IPF) and pancreatic cancer.

The second drug, CAP-1002 (Capricor Therapeutics) is an intravenous (iv) cell therapy composed of cardiosphere-derived cells (CDCs), a type of heart progenitor cells with the ability to generate mature cardiac cells. CDCs have been shown to have anti-inflammatory, and immune modulatory properties. Capricor's HOPE-2 randomised Phase 2 trial (NCT03406780) assessed the safety and effectiveness of CAP-1002 in 20 boys and young men in advanced stages of DMD who were being treated with steroids. Subjects received either CAP-1002 (8 patients) or placebo (12 patients) every 3 months for one year. Over 12 months, PUL 2.0 scores declined by 1.3 points in boys treated with CAP-1002 vs a decline of 3.7 points in boys on placebo; the difference just missed statistical significance (p=0.053). Boys treated with CAP-1002 had statistically significant relative improvements in cardiac function on measures such as left ventricular ejection fraction. The FDA has suggested Capricor use PUL 2.0 as the primary efficacy endpoint in support of a Biologics License Application (BLA) for ACP-1002. The FDA has encouraged Capricor to conduct a Phase III study in DMD, but the company is still in discussions with the FDA about the path forward.

We are not aware of any other drugs that are in late stage development in non-ambulant DMD patients.

Drugs that aim to restore or replace dystrophin production

The other significant class is drugs that aim to replace or restore production of the dystrophin protein, in most cases by producing a shortened but still functional form of the protein. Drugs in this class either aim to counteract the effect of the mutation to allow the body to produce dystrophin (mainly exon skippers) or are gene therapies that aim to deliver shortened versions of the dystrophin gene to muscle cells. Exhibit 12 summarises the main drugs in this category, including two exon skipping drugs that have received FDA approval.

While the exon skippers and other therapies that seek to address the genetic mutation may partially counteract the effect of the DMD mutations on dystrophin production and may slow disease progression, they are unlikely to provide a cure and are currently used to treat patients at the earliest stages of the disease. Drugs to treat the damaging effects of inflammation will still

be needed. In fact, by extending the life expectancy of DMD patients, the treatments that target dystrophin production are likely to increase the addressable market for anti-inflammatory therapies such as ATL1102.

Exon skippers and other therapies aiming to restore dystrophin production

The exon skipping drugs are based on technology developed at the University of Western Australia. Antisense oligonucleotides or 'molecular patches' are used to mask the exon that contains the mutation that causes DMD in that patient, so that it is ignored during protein production. This can allow a shortened but partially functional form of the dystrophin protein to be produced. The two exon skipping drugs that have been approved by the FDA are appropriate for mutations carried by around 20% of DMD patients. These drugs are used in young ambulant boys and are used on top of standard doses of corticosteroids to control inflammation.

The first of these drugs, Exondys 51 (eteplirsen), developed by Sarepta Therapeutics, which received accelerated approval from the FDA in 2016, induces skipping of exon 51. Approximately 13% of the total DMD population have gene deletions that are amenable to exon 51 skipping.

In December 12, 2019 the FDA granted accelerated approval to Vyondys 53 (golodirsen, Sarepta Therapeutics) to treat DMD patients who have a mutation of the dystrophin gene that is amenable to exon 53 skipping. It is estimated that about 8 percent of patients with DMD have this mutation.

The approval of both Exondys 51 and Vyondys 53 was controversial, because neither drug has been shown to produce clinical benefit in DMD patients, but were approved on the basis of modest increases in dystrophin production. For example, in a study involving 25 patients, treatment with Vyondys 53 for at least 48 weeks increased dystrophin levels, on average, from 0.10% of normal at baseline to 1.02% of normal.

Sarepta submitted an NDA submission for another exon skipping drug, Casimersin (SRP-4045) in June 2020. The FDA has granted a priority review and has assigned a Prescription Drug User Fee Act (PDUFA) target action date of February 25, 2021. Casimersin is a treatment for mutations that are amenable to exon 45 skipping.

According to Sarepta, Exondys 51 and Vyondys 53 both cost about $300,000 on average per patient a year, after taking into account rebates, discounts and compliance. However the list price appears to be substantially higher; an analysis of cost effectiveness by ICER estimated that the annual drug cost for treating a 40kg boy, including mark-up, was US$892,000.[12] Sarepta reported sales of US$381m for Exondys 51 in 2019, vs US$301m the preceding year.

Several other exon skippers are in development, as shown in Exhibit 12; Viltolarsen, another exon 53 skipper, was granted accelerated approval by the FDA in August.

The other drug in this class is Translarna (Ataluren, PTC Therapeutics). Translarna aims to correct the genetic mutation in DMD by a different mechanism to the exon skippers. In the case of Translarna the mutation that is targeted is a premature stop codon, the cause of DMD in approximately 10-15% of boys with the disease. Translarna missed statistical significance in on its primary endpoint, 6-minute walk distance, in a phase III study in 230 DMD patients. The FDA rejected an application for approval of Translarna in the US, but the drug received conditional approval in Europe in 2014 and was approved in Brazil in April 2019. Sales of Translarna totalled US$109m in 2019. The list price for Translarna in Europe is reported to be approx. €411,000 - €440,000 (~US$500,000).[13,14] However, as is the case for Exondys 51, the average reimbursed price is expected to be substantially lower.

Gene therapies to produced micro-dystrophins

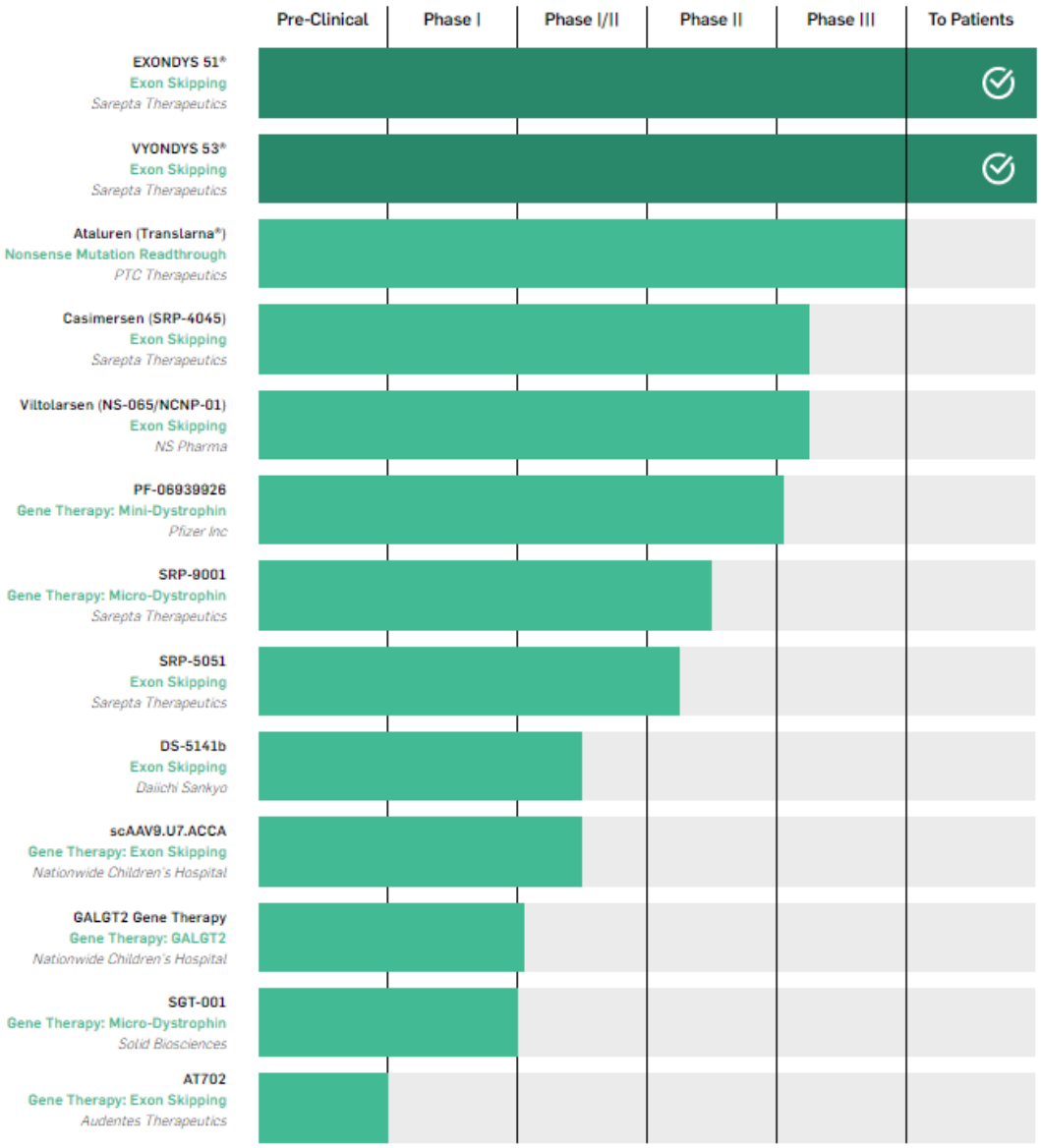
The other class of drugs that aim to replace dystrophin production is gene transfer therapies that aim to deliver shortened but functional versions of the dystrophin gene to muscle tissue for the targeted production of a micro-dystrophin or mini-dystrophin protein.

The most advanced gene transfer therapy candidate is Sarepta's SRP-9001 micro-dystrophin. SRP-9001 uses a viral vector to transfect cardiac and skeletal muscle cells and express the micro-dystrophin gene. Initial data from the first 4-patient cohort of boys aged 3-7 showed 81% expression of dystrophin in muscle fibres 12 weeks post infusion and mean improvements of 7.0 points from baseline in the 34-point North Star Ambulatory Assessment two years after administration of the once-time treatment (NSAA scores were increased by 5.5 points from baseline at 1 year). A larger study, Study 102, has dosed 41 patients and is scheduled for a data read out of expression and functional data in early 2021.

[12] Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value - draft report; p49
[13] National Centre for Pharmacoeconomics, Ireland; p7. evaluation http://www.ncpe.ie/wp-content/uploads/2014/12/NCPE-summary-of-ataluren-1.pdf
[14] https://pharmaintelligence.informa.com/resources/product-content/2017/03/28/13/51/ptc-bids-farewell-to-translarna

The gene therapy drugs in development use adenovirus vectors to transfect the muscles cells in patients. A significant proportion of older boys carry antibodies against the adenovirus vectors, which may reduce the number of patients who are eligible for these treatments, if they are eventually approved.

Exhibit 12: Drugs that aim to restore or replace dystrophin production



Source: Parent Project MD https://www.parentprojectmd.org/duchenne-drug-development-pipeline/; Note viltolarsen was recently granted accelerated approval by the FDA.

Inhibiting leukocyte integrins effective in inflammatory diseases

Therapies that inhibit the activity of leukocyte integrins have been shown to be effective as treatments for multiple sclerosis, psoriasis and inflammatory bowel disease. The two treatments that are currently marketed both target integrins that incorporate the same α4 integrin subunit that is inhibited by ATL1102. The approved therapies are both monoclonal antibodies.

Tysabri (Natalizumab, Biogen) is a monoclonal antibody against CD49d, the α4 subunit in α4β1 integrin (VLA-4), which interacts with the vascular endothelium adhesion molecule VCAM-1, facilitating transmigration of white blood cells from the bloodstream to surrounding tissue. Tysabri is approved for treating multiple sclerosis and moderate to severe Crohn's disease.

Entyvio (vedolizumab), is a monoclonal antibody that binds to integrin α4β7. It was approved for treatment of both moderate-to-severe ulcerative colitis and moderate-to-severe Crohn's disease in 2014 in the US and Europe.

Tysabri generates US$1.9bn of annual sales despite fatal infection risk

Tysabri is approved to treat relapsing forms of multiple sclerosis (MS) and moderate to severe Crohn's disease. However, treatment with Tysabri increases the risk of getting a rare brain infection called progressive multifocal leukoencephalopathy (PML) that usually leads to death or severe disability. There is no known treatment, prevention, or cure for PML, but stopping treatment with Tysabri at the earliest stages of the disease before clinical signs are evident leads to improved outcomes.

The risk of getting PML is higher in patients who:

- have been infected by the John Cunningham Virus (JCV). JCV is a common virus that can cause PML in people who have weakened immune systems, such as people taking Tysabri. Patients can undergo a blood test to check if they have been infected with JCV before receiving Tysabri.
- have received Tysabri for a long time, especially for longer than 2 years
- have received immunosuppressant medications before they started receiving Tysabri

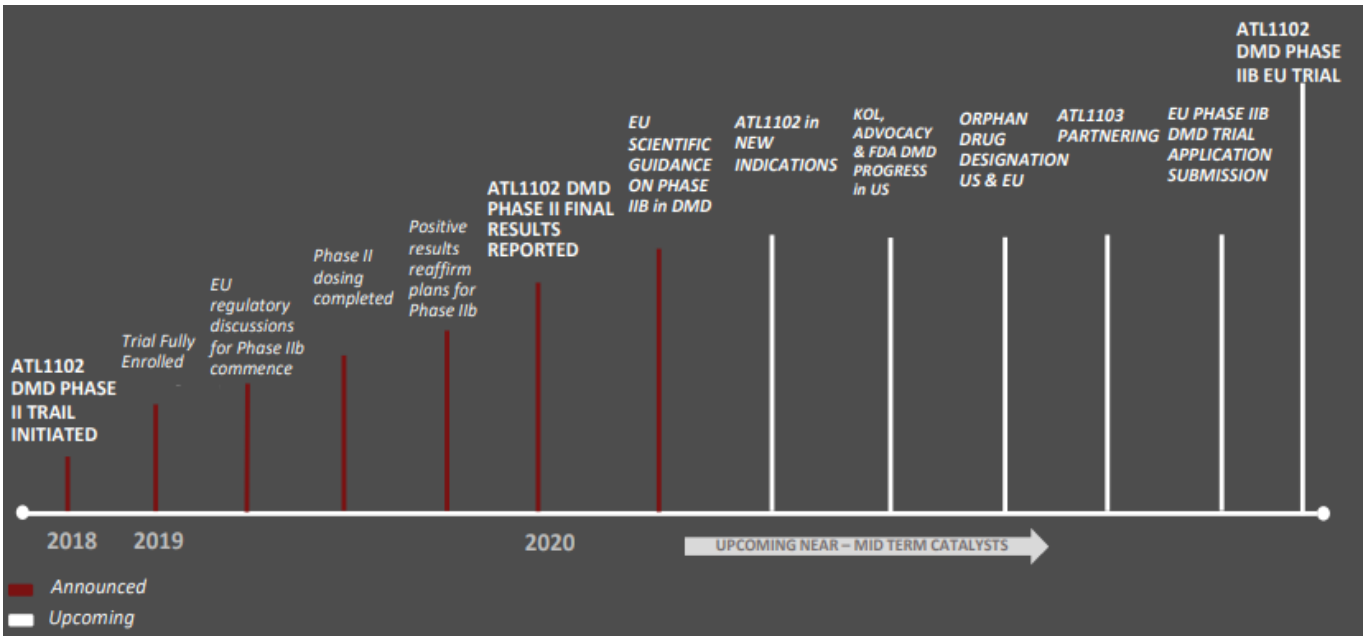
The risk of a patient who is being treated with Tysabri developing PML ranges from less than 1 in 10,000 for those who are negative for JCV virus antibodies to 1 in 1000 for patients who are JCV virus positive but have no other risk factors and 1 in 125 for patients in the highest risk categories. Because of the risk of PML, Tysabri is available only through a restricted distribution program. Despite the risk of PML and the restricted distribution program, Biogen reported Tysabri sales of US$1.9bn in 2019.

ATL1102 uses a different mechanism to Tysabri to reduce CD49d activity and there is no evidence to date that ATL1102 also increases the risk of PML, although it may do so. There was no evidence of JC virus activation in either of the Phase IIa trials of ATL1102 conducted to date. Given the very poor prognosis for DMD patients, we do not think that a modest risk of developing PML would deter patients from taking ATL1102, if future studies show the existence of such a risk. Only approximately 20-33% of 10-19 year olds carry JCV antibodies, so the majority of DMD patients would be expected to be at very low risk of PML.[15]

Upcoming catalysts

As Exhibit 13 shows, the key upcoming catalyst for ANP is the initiation of the European Phase IIb trial.

Exhibit 13: Near and medium term news flow



Source: Antisense

Patent applications could extend IP protection beyond 2040

In addition to patents covering the use of ATL1102 to treat MS patients, Antisense holds granted patents in the US (9,885,048) and Australia (20113017172) covering methods of using ATL1102 to reduce circulating leukocytes as observed in the Phase II DMD trial, which extend to 2031. It has filed US and international patent applications covering the use of ATL1102 to treat DMD, which would extend to 2039/2040 if granted. The patent term of the above patents or new patents if granted could potentially be

[15] White and Khalili 2011 The Journal of Infectious Diseases; 203:578–586

extended by up to 5 years once ATL1102 receives marketing approval. The key DMD patent applications are shown in Exhibit 14.

Exhibit 14: Key patent applications covering ATL1102 therapeutic uses and methods for treating muscular dystrophy

Territory	Application number	Status	Expiry (if granted)
US Continuation - in part	16/404561	Filed	2039
International	PCT/AU2018/051353	Filed	2039
International	PCT/AU2020/050445	Filed	2040

Source: Antisense annual report

Risks

Antisense is subject to clinical trial, regulatory and commercialisation risks common to all biotech companies. The key risk is the possibility that ATL1102 may fail to show statistically significant and clinically meaningful improvements in outcomes for DMD patients in future clinical trials. The encouraging indications of efficacy of ATL1102 in DMD were based on a small sample of only 9 patients in a single arm study, which increases the risk that the favourable results may have arisen due to chance rather than being due to the efficacy of the ATL1102 therapy.

Antisense faces significant funding risks. While the design of the upcoming European Phase IIb trial of ATL1102 in non-ambulant DMD patients has not been finalised and therefore the cost is not yet known, we estimate that it may need to raise substantial funds in the order of $20m to fund the study if it chooses to continue the development of ATL1102 without a development partner. There is a risk that it may not be able to raise the funds at a reasonable price, or at all. It had $3.1m of cash at 30 September.

Tysabri (natalizumab), a drug that inhibits the activity of CD49b (via different mechanism to ATL1102), is known to increase the risk of the fatal condition known as PML. It is not known whether ATL1102 will also increase the risk of PML. If any subjects in ATL1102 clinical trials develop PML, then this may result in interruption or suspension of clinical trials. Furthermore, if ATL1102 is shown increase the risk of developing PML, this may influence the uptake of ATL1102 (if approved).

Valuation

We initiate coverage of Antisense with a valuation of $134m or 27c per share (undiluted), based on a risk-adjusted discounted cash flow model, which includes our estimates of the future milestone payments and royalty streams for ATL1102, as listed in Exhibit 15. On a fully diluted basis, our valuation is 23c per share, after taking into account the options on issue, and a $20m capital raise that we model in FY21. Alternatively, Antisense may seek a partner to fund future trials of ATL1102.

We have extended our cash flow forecasts out to 2040, in the expectation that patents covering use of ATL1102 to treat DMD will be granted, but assume that sales will decline by 10% per year from 2036 onwards. The recent grant of Orphan Drug designation by the FDA brings seven years of market exclusivity for the DMD indication in the US; if it gains ODD in Europe then it would gain ten years of market exclusivity, and for pediatric ODD another 2 years in Europe. We assume a long-term exchange rate of US$0.70/A$ and apply a 12.5% discount rate.

We model Antisense out-licensing global rights to ATL1102 in a single transaction while the European DMD study is underway. We assume that the licence deal includes an upfront payment of US$85m and US$540m of milestone payments. We assume that 50% (US$270m) of the milestone payments are for the achievement of clinical and regulatory milestones, with the remaining 50% assumed to be based on sales hurdles. We split the US$85m upfront and US$270m clinical and regulatory milestones equally between European and US non-ambulant indications, adjusted with a 20-60% probability (60% probability of signing a license deal, 20% for US approval milestones). We do not include any potential sales-based milestones in our forecasts, and instead model a 20% gross royalty rate. The modelled deal terms are based on relevant benchmarks over the last few years (sourced from EvaluatePharma and a report produced by the industry group BIO).

We assume that ANP will pay one third of any licensing revenue received to partner IONIS, in line with the company's statements about the previous licencing deal with Teva. We note that, alternatively, ANP could choose to establish its own sales force and commercialise ATL1102 itself, in which case it would pay a mid-single digit royalty on net sales to IONIS.

The likely pricing for ATL1102 is difficult to determine as we do not yet know how effective it will be at delaying disease progression in DMD patients. Plausible ex-manufacturer pricing in the US, net of discounts and rebates, ranges from US$62,900 for Emflaza modelled by ICER to the average of US$300,000 per patient per year cited by Sarepta for Exondys 51. We model the net price of ATL1102 being US$150,000 per patient/year in the US, a 50% discount to Exondys 51, but acknowledge that eventual pricing could be substantially higher or lower than this figure. In Europe and other territories, we model a net price of US$100,000 per year, two thirds of the assumed US price.

Exhibit 15 shows our market assumptions for ATL1102 for non-ambulant DMD patients in Europe and the US, separately, plus a separate rNPV for use in earlier-stage ambulant boys. We have offset the risk-adjusted trial cost against revenue for the first two indications; we assume a partner would fund the clinical trial in ambulant boys.

Exhibit 15: Antisense risk-adjusted DCF base case valuation and assumptions

	Base case success likelihood (%)	rNPV (A$m)	rNPV/share (A$)	Assumptions
ATL1102 RoW non-ambulant DMD	25%	56.9	$0.12	Peak sales US$280m. Prevalence of 17,500 DMD patients, 45% non-ambulant, 25% penetration; pricing US$100k per patient; launch H2 2025; patents expire 2040; assume receives 13% net royalty after pay-away to IONIS. R&D cost: A$20m for pivotal Phase IIb Commencing H121, out-license while Phase IIb study is underway.
ATL1102 US non-ambulant DMD	20%	42.7	$0.09	Peak sales of US$290m. Assumes prevalence of 11,600 DMD patients, 45% non-ambulant, 25% penetration; pricing US$150k per patient; launch H2 2026; patents expire 2040; assume receives 13% net royalty. R&D cost: A$30m for pivotal Phase IIb commencing in H122.
ATL1102 Global ambulant DMD	20%	31.6	$0.06	Global peak sales in ambulant patients of US$580m; launch H2 2028; Prevalence, pricing and royalty assumptions as above; 55% ambulant, 20% penetration in ambulant patients; R&D cost for pivotal study commencing in H124 after top line data from European Phase IIb is available paid by licensee.
RPD Priority Review Voucher	10%	6.3	$0.01	Assumes a 50% probability that the legislation to extend the RPD PRV program passes into law and an FDA approval decision on ATL1102 is reached before new sunset date of September 2026; PRV sold for US$100m in 2026.
SG&A to 2024		-1.7	-$0.00	
Portfolio total		129.5	$0.26	
Cash end FY20		4.1	$0.01	
Enterprise total		133.6	$0.27	

Source: Taylor Collison research. Note: NPV adjusted for tax at an effective tax rate of 20%. We assume that the addressable markets grow at 3% per year

Key personnel

Antisense has a highly regarded board of directors with impressive pedigrees, including senior management and research positions at CSL. Of particular note is William Goolsbee, who was a director of Sarepta therapeutics from 2007 to 2016, including as Chairman from 2010 to 2014, giving him extensive insight into successful development of DMD therapeutics. Consultant Medical Director Dr Gil Price has also had extensive experience as a Director at Sarepta.

Robert Moses – Chairman

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

Mark Diamond – MD and CEO

Mark Diamond has over 30 years' experience in the pharmaceutical and biotechnology industry. Before joining Antisense Therapeutics Limited as MD and CEO in 2001, Mr. Diamond was employed in the US as Director, Project Planning/Business Development at Faulding Pharmaceuticals. Prior to this he 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.

William Goolsbee – Non-Executive Director

Mr. Goolsbee was founder, Chairman and Chief Executive Officer of Horizon Medical Inc. from 1987 until its acquisition by a unit of UBS Private Equity in 2002. Mr Goolsbee was a founding Director of ImmunoTherapy Corporation in 1993, and became Chairman in 1995, a position he held until overseeing the successful acquisition of ImmunoTherapy by AVI Biopharma, Inc. (now Sarepta Therapeutics) in 1998. Mr. Goolsbee served as Chairman of privately held BMG Pharma LLC, a pharmaceutical company, from 2006 through 2011 and of Metrodora Therapeutics until 2015. Mr Goolsbee has served as an Independent director of Helix BioMedix Inc since 2019 and was a Director of Sarepta Therapeutics Inc from 2007 until the end of 2016.

Dr Graham Mitchell – Non-Executive Director

Graham Mitchell was a former senior researcher at the Walter & Eliza Hall Institute, a Chief Scientist in Victorian Government Departments, and a Director of Research in the R&D Division of CSL. Dr Mitchell is currently Principal and CEO of Foursight Associates Pty Ltd.

Dr Gary Pace – Non-Executive Director

Dr Pace has more than 40 years of experience in the development and commercialization of advanced technologies in biotechnology, pharmaceuticals, medical devices and the food industries. He has long-term board level experience with both multi-billion and small cap companies. In 2003 Dr Pace was awarded a Centenary Medal by the Australian Government "for service to Australian society in research and development", and in 2011 was awarded Director of the Year (corporate governance) by the San Diego Directors Forum. In addition he has held visiting academic positions at the Massachusetts Institute of Technology and the University of Queensland. Dr Pace is an elected Fellow of the Australian Academy of Technological Sciences and Engineering and is currently a Director of Pacira Pharmaceuticals (NASDAQ: PCRX, TrovaGene Oncology (NASDAQ: TROV) and Simavita limited (ASX: SVA) and was formerly a Director of Invitrocue (ASX: IVQ) and ResMed Inc (ASX: RMD).

Nuket Desem - Director of Clinical & Regulatory Affairs

Ms Desem has over 25 years' experience in global regulatory affairs, clinical development and project management obtained through her roles within the pharmaceutical/biotechnology industry, including senior positions in various biotechnology companies. Nuket joined Antisense Therapeutics from Paranta Biosciences, where she held the position of Director Clinical and Regulatory Affairs. Prior to Paranta, Nuket was Senior Manager Development and Regulatory Affairs at Prana Biotechnology. Earlier, Nuket served as Vice President Clinical and Regulatory Affairs at Spinifex Pharmaceuticals and was responsible for the management of the company's regulatory and clinical trial programs. Spinifex was acquired by Novartis in 2015. Previously, Nuket spent over 10 years at CSL Limited in R&D and Regulatory Affairs. Nuket holds a Bachelor of Science (Honours) from La Trobe University and a Master of Business Administration (MBA) from Monash University.

Dr George Tachas - Director, Drug Discovery & Patents

Dr Tachas, received his Ph.D from the University of Melbourne in 1988 and a Diploma of Intellectual Property Law in 1994. Dr Tachas Ph.D studies (1984-88) were in gene transfer, cloning and characterising of genes important in immunology at the University of Melbourne. Dr Tachas' post-doctoral studies (1989-1991) were in the molecular and cellular biology of vascular smooth muscle cells in cardiovascular disease as Head of Molecular Biology at the Cardiovascular Research Unit of the University of Melbourne's Anatomy Department. Dr Tachas made the move to a leading Australian patent attorney firm, Griffith Hack and Co, in late 1991. In 1997 Dr Tachas planned to start up an antisense company, which lead to his roles as exclusive consultant first to Syngene Ltd and then to Antisense (2000-2001). Since the ASX listing of ANP Dr Tachas has directed the company's efforts in expanding its product pipeline and managing the company's IP portfolio.

Dr Gil Price M.D. – consultant Medical Director

Dr. Price is a clinical physician trained in internal medicine with a long-standing focus in drug development, adverse drug reactions, drug utilization and regulation. Dr. Price is an experienced biotech executive and entrepreneur with a depth of expertise across clinical asset investment strategy, evaluation, financing and execution. Over the years Dr. Price has served on multiple boards of public, private and not-for-profit entities; from 2007 to 2016, he was a non-executive director of Sarepta Therapeutics, Inc.

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