ASX Announcement

21 May 2020

Antisense ATL1102 Final Phase II DMD Results Meet Primary Endpoint and Exceed Expectations on Secondary Endpoints

- **Primary endpoint met with confirmation of drug's safety and tolerability**
- **Strong effects on secondary endpoints on activity markers and disease progression**
- **Improvement or stabilisation across different measures of motor function & strength**
- **Activity on the targeted CD49d immune cells consistent with drug's proposed mechanism of action**
- **New MRI data suggests stabilisation of percentage of fat in muscles and preservation of functional muscle mass**
- **International KOLs are supportive of Phase IIb plans**
- **Submission made to European Medicines Agency for Scientific Advice on Phase IIb design**

Antisense Therapeutics ("ANP" or the "Company" ASX:ANP | US OTC:ATHJY) is pleased to advise that the Phase II clinical trial of ANP's immunomodulatory therapy, ATL1102 for Duchenne Muscular Dystrophy (DMD) has met its primary endpoint confirming the safety and tolerability of ATL1102 for advancement into a potentially pivotal Phase IIb clinical trial.

Importantly, the final trial results have also confirmed the drug's positive effects on the secondary trial endpoints that assessed the drug's activity and efficacy including measuring the effects on immune cell numbers in the blood and measuring the participants' functional capacity as evaluated via Performance of Upper Limb Test (PUL2.0), grip and pinch strength and distal mobility (using the MyoSet, MyoGrip, MyoPinch and MoviPlate tools, respectively).

Additionally, the Company is very pleased to report that MRI assessment of the upper limb muscles of the patients with DMD has also shown the drug's apparent beneficial effects in stabilising the fat fraction percentage within the muscles of the forearm (increase in fat levels is another key marker of disease progression in non-ambulant DMD boys). The data shows a stabilisation in the percentage of fat in the forearm muscles and an increase/maintenance of functional muscle mass, which is both outstanding and unexpected for a drug treating the inflammation (and not the muscle dystrophin loss).

Results overview

The primary objective of the ATL1102 trial was to assess the safety and tolerability of 25 mg of ATL1102 administered once weekly (subcutaneous injection) for 24 weeks in nine non-ambulatory DMD participants. ATL1102 was assessed to be generally safe and well tolerated. No Serious Adverse Events were reported with no safety concerns expressed by the Data Safety Monitoring Board. There were no participant withdrawals from the study. The most commonly reported adverse events have related to the subcutaneous administration of the drug, mainly injection site erythema and skin discoloration which were generally regarded as mild and either resolved or were close to resolution at the end of the monitoring period. Overall, ATL1102 demonstrated an excellent safety profile in this trial.

> *Dr Ian Woodcock, Paediatric Neurologist and Honorary Fellow at The Murdoch Children's Research Institute, Melbourne and the Principal Investigator of the ATL1102 Phase II DMD trial said, "the study met its primary endpoint showing ATL1102 to be safe and well tolerated with no serious adverse events being reported and no participant withdrawing from the study. With very few treatment options for boys with Duchennes who are no longer ambulant, it has been great to enable the boys to participate in this clinical trial and I am most encouraged by the outcomes of the study".*

ATL1102 is an inhibitor of CD49d expression on certain immune cells (e.g. T lymphocytes). It has been reported in research literature that patients with DMD who have a greater number of CD4+ and CD8+T lymphocytes with high levels of CD49d have more severe and rapid disease progression. ATL1102 is the

only drug in clinical development for DMD targeting CD49d and one of a very limited number of treatments being tested in non-ambulant boys with DMD.

In assessing the effects of ATL1102 on immune cell numbers in the blood of participants, the immune cell data has shown a consistency in the mean reductions in the number of lymphocytes including T-lymphocytes (i.e. CD3+, CD3+CD4+, CD3+CD8+ and importantly, those expressing CD49d) measured from baseline to week 8, 12 and 24 (end of dosing) with a rebound of these markers to around starting levels post dosing at week 28. As previously reported, the mean number of CD3+CD49d+ T cells (i.e. mostly CD3+CD4+CD49d+ and CD3+CD8+CD49d+cells) at week 24 is statistically significantly lower vs week 28 (p=0.030 paired T test) suggesting the drug is working through its targeted mechanism of action. We further report that the mean number of NK lymphocytes (CD3-CD16+CD56+) and NK lymphocytes expressing CD49d+ at week 8,12 and 24 is statistically significantly lower vs baseline using a mixed model for repeated measurements (p=0.018), with comparable NK lymphocyte numbers at week 28. This data demonstrates the drug's positive effects on modulating CD49d+ lymphocytes in the blood during treatment.

As reported in December 2019, the PUL2.0 data showed that 7 of the 9 participants demonstrated either increases or no change in their PUL2.0 scores from baseline over 6 months, with a positive mean change of 0.9 (95% CI: -1.33, 3.11) in this key parameter indicative of disease stabilization. This contrasts to the losses in PUL2.0 reported in the published literature in longer term (1 year plus) studies (Pane et al 2018). Similarly, MyoGrip and MyoPinch assessments using the Myoset system showed a significant improvement in muscle strength compared to the loss of muscle strength reported in the Ricotti et. al. 2016 publication in a similar non-ambulant patient population on corticosteroids assessed over 6 months. MoviPlate data (an assessment of muscle function), has also demonstrated improvements in a majority of the participants with a mean increase from baseline to 6 months of 1.9 points (95% CI: -6.08, 9.85).

> *Dr Jean-Yves Hogrel, PhD, Director of the Neuromuscular Physiology and Evaluation Laboratory, Institute of Myology, France, a developer of the MyoSet assessment tools stated that "First, I would like to highlight the quality of the data that proves the expertise and dedication of evaluators in following standardised operating procedures. The intra-individual variability is very moderate and reflects this measurement quality. My observations based on the MyoSet data from the study suggest that the patients were generally stable."*

Overall, the study has shown that ATL1102 treatment results in consistent improvements or stabilisation across the different measures of motor function and strength.

In a post hoc analysis of the data, there appears to be a correlation between the individual patient PUL2.0 scores at the end of dosing (week 24) and their week 24 vs week 28 CD4+CD49d+ T cell changes. Of the eight participants with normal starting levels of lymphocytes, six demonstrated either an improvement or maintenance in their PUL2.0 scores and had a 'rebound' in the CD4+CD49d+ T cells at week 28, while two of the eight participants who had a loss of PUL2.0 at week 24 did not see a rebound in these cells at week 28 vs week 24. This data suggests that the drug is working through a targeted CD49d mechanism of action with down-modulation of CD4+CD49d+ T cells during treatment providing clinical benefit, with the two patients not responding at 24 weeks, potentially requiring longer and/or higher dosing to see similar effects. While this correlation was only observed with the PUL2.0 disease progression parameter (the expected primary efficacy endpoint for future trials), it is the Company's view that as PUL2.0 assesses the performance of a large group of muscles of the upper body (unlike Myoset which specifically assesses grip and pinch strength and distal mobility) it is appropriate to draw out this correlation as it may be a helpful future prognosticator of response to therapy.

Importantly the MRI data assessing the fat fraction percentage of the muscles of the dominant forearm of the participants has delivered a further most positive finding with the data showing a slight mean reduction in these levels compared to the significant increases in fat fraction reported in the Ricotti 2016 publication with the comparison showing to be statistically different on some of the MRI parameters. The change in percentage fat fraction from baseline to 24 weeks was (mean (SD); Median) -0.5 (6.6); 1.4 for the central reading and corroborated by the proximal and distal readings (-2.1 (7.1); -0.4 and -5.1 (14.6); 2.0, respectively). Furthermore, the lean muscle area (i.e. non-fat) showed a change from baseline to 24 weeks (Mean (SD); Median) of 13.9 mm^2 (SD: 112.5); 5.8 mm^2, indicating a maintenance of and possible increase in functional muscle mass. This is a somewhat unexpected but highly encouraging observation for a drug treating the inflammation and not the muscle dystrophin loss (the exon skipping drug's target).

Dr Valeria Ricotti MD, Researcher and Honorary Clinical Lecturer, Great Ormond Street Institute of Child Health University College London, UK, stated that "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."

Further data analyses performed by Dr Jean-Yves Hogrel looking at the correlation between MRI results for remaining muscle area (removing the fat fraction) with the results of the MyoGrip assessments for the individual participants has shown a highly significant positive correlation between these measures.

Dr Hogrel stated that "this positive correlation of remaining muscle area (the lean muscle), with grip strength suggests a consistency of the results across the different parameters of muscle structure and muscle force."

Quality of Life (PedsQL) questionnaires were completed by parents of the younger boys in the study and by two of the teenage boys. Both the teens that completed the questionnaire showed a mean improvement in all the domains; problems of daily activities, treatment management, problems with communication and worry. The results for the younger patients where the parents completed the questionnaire also showed improvements in daily activities and treatment domains but increased problems with communication and worry domains.

Respiratory parameters (FVC and PEF) were also measured. As noted in the December 2019 announcement in our experts' view the variability in this data makes it difficult to draw any meaningful conclusions on this parameter, which is best assessed in larger studies of 12 months and longer. Nevertheless, with the PEF assessment a slight mean increase in percentage predicted PEF was observed which is consistent with the data observed for the other parameters.

Professor Thomas Voit MD, Director, NIHR GOSH Biomedical Research Centre, UK had this to say about the trial results and the efficacy being observed in this Phase II trial of ATL1102: "The data certainly suggests an overall 'stabilisation' in disease progression at the very least which of itself is a very positive clinical outcome. MRI data confirms the positive changes at a muscular/cellular level and supports the observed physical stabilisation/improvements in muscle strength and function. The consistency of positive clinically relevant effects of ATL1102 treatment across muscle measures of structure, strength and function are very pleasing and provide great encouragement for the treatment of non-ambulant patients with DMD".

The results are highly supportive of the Company's plans for a Phase IIb clinical trial of ATL1102 in DMD. Scientific Advice meetings held with three European regulatory authorities affirmed the agencies' general acceptance of the proposed trial efficacy endpoints (PUL2.0, MyoSet), safety monitoring plan, dosing duration (12 months) and the use of higher doses. The Company has made a submission to the European Medicines Agency for Scientific Advice with the results of their evaluation due mid-year, which will then direct the Company on its preparation and submission of its clinical trial application.

Our international Key Opinion Leaders and advisors are encouraged by the results of functional endpoints (physical parameters) that demonstrate strong initial efficacy. Measurements of a number of functional parameters indicate that a majority of the boys experienced either improvement or no deterioration in several upper body measurements. These results compare favourably with data reported in a variety of historical studies of progressive and continuous deterioration in physical function in non-ambulant patients with DMD over time.

Dr Gil Price M.D., ANP's Consultant Medical Director, said: "In a small study with nine boys of only six months duration at a single low dose we not only achieved our primary endpoint of safety we also i) achieved significance in demonstrating an effect on our secondary endpoint relating to modulation of CD49d; ii) achieved positive outcomes in the important upper body function parameter of the PUL 2.0 test, and finally iii) achieved fat fraction percentage reduction in important upper body muscles. That each of these three effects were observed in an initial study in DMD boys at the lowest dose where we might have anticipated a biological effect is truly surprising and highly encouraging".

Next steps

The Company is extremely delighted by the trial results and our international experts' support which provides encouragement to move ATL1102 into a Phase IIb trial.

European Medicines Agency Scientific Advice due mid-year is the next milestone in preparation for submission of clinical trial application for a Phase IIb trial in Europe and UK. The Company is also in the process of preparing submissions for Orphan Drug Designation for ATL1102's use in DMD in the US and the EU.

As ANP continues to prepare for a Phase IIb, the Company will look to gain a deeper understanding of the drug's effects. This activity is likely to include further laboratory analysis of retained serum to attempt to tease out more insight on broader inflammatory processes and a deeper analysis of our data against the natural history of the disease with key experts.

In parallel, encouraged by observations of the anti-inflammatory actions of ATL1102, ANP is now also investigating other potential diseases including those that are inadequately controlled with corticosteroids such as other muscular dystrophies and neurological conditions. As previously advised, the Company is working on selecting and prioritising new indications where it is best positioned to leverage its expertise, intellectual property and relationships with clinical experts involved in treatment of those diseases.

Mark Diamond, CEO of Antisense Therapeutics said: "Our focus is to continue planning and to methodically and efficiently move our DMD program through Phase IIb in Europe. There is great interest in the DMD space. As we gain further certainty from the regulatory process on the parameters of the next trial, which may lead to early market approval, we will assess funding and trial management options and also engage in discussions with interested potential partners ahead of commencement of Phase IIb. This will allow the Company to consider the most advantageous way to proceed with the pivotal trial on its own or with a partner. Potential partners' input into the trial program may also be beneficial for future commercialisation plans. The Company is now in the process of confirming the manufacture of additional clinical supplies of ATL1102 and will provide further updates in due course".

This announcement has been authorised for release by the Board.

ATL1102 Phase II DMD results presentation webinar

For the results presentation webinar to be held at 9:00AM (AEST) on Friday 22 May | UK 12AM | US PDT 4:00PM: EDT 7.00PM (Thursday 21 May) and details of how to register online please follow this link:

https://us02web.zoom.us/webinar/register/WN_DCVk0mvJQr28qqHviPLG-Q

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About Antisense Therapeutics Limited (ASX:ANP | US OTC:ATHJY) is an Australian publicly listed bio-pharmaceutical company, developing and commercialising antisense pharmaceuticals for large unmet markets. The products are in-licensed from Ionis Pharmaceuticals Inc. (NASDAQ:IONS), world leaders in antisense drug development and commercialisation. ATL1102 (injection) has successfully completed a Phase II efficacy and safety trial, significantly reducing the number of brain lesions in patients with relapsing-remitting multiple sclerosis (RRMS). ATL1103 drug designed to block GHr production successfully reduced blood IGF-I levels in Phase II clinical trials in patients with the growth disorder acromegaly. The Company is conducting a Phase II clinical trial of ATL1102 in patients with DMD at the Royal Childrens Hospital, Melbourne.

About ATL1102 ATL1102 is an antisense inhibitor of CD49d, a subunit of VLA-4 (Very Late Antigen-4). Antisense inhibition of VLA-4 expression has demonstrated activity in a number of animal models of inflammatory disease including asthma and MS with the MS animal data having been published in a peer reviewed scientific journal. ATL1102 was shown to be highly effective in reducing MS lesions in a Phase IIa clinical trial in patients with RR-MS. The ATL1102 Phase IIa clinical data has been published in the medical Journal ***Neurology*** (Limmroth, V. et al Neurology, 2014; 83(20): 1780-1788).

About ATL1102 DMD Trial The Phase II clinical trial of ATL1102 in patients with Duchenne Muscular Dystrophy was an open label six-month dosing trial of ATL1102 administered SC at 25mg per week in nine non-ambulant patients with DMD aged between 10 and 18 years. The trial was conducted at the neuromuscular centre of the Royal Children's Hospital (RCH) in Melbourne, Australia. The primary endpoints of the trial related to the safety and tolerability of ATL1102. The efficacy of ATL1102 was also assessed in terms of its effects on disease processes and progression (e.g. the upper limb strength and function of the boys). Given the exploratory nature of this first trial in boys with DMD, it was not powered to see a statistical difference on these disease progression endpoints, which would be expected in future longer-term clinical studies in a larger number of patients. However, highly encouraging positive trends across multiple parameters have been reported in this Phase II clinical trial. Further details on the trial are available here on the Australia and New Zealand Clinical Trials Registry.

About DMD Duchenne Muscular Dystrophy (DMD) is an X-linked disease that affects 1 in 3600 to 6000 live male births (Bushby *et al*, 2010). DMD occurs as a result of mutations in the dystrophin gene which causes a substantial reduction in or absence of the dystrophin protein. Children with DMD have dystrophin deficient muscles and are susceptible to contraction induced injury to muscle that triggers the immune system which exacerbates muscle damage as summarized in a publication co-authored by the Director of the FDA CDER (Rosenberg et al, 2015). Ongoing deterioration in muscle strength affects lower limbs leading to impaired mobility, and also affects upper limbs, leading to further loss of function and self-care ability. The need for wheelchair use can occur in early teenage years for patients on corticosteroids with a mean age of 13, with respiratory, cardiac, cognitive dysfunction also emerging. Patients with a greater number of immune T cells expressing high levels of CD49d have more severe and progressive disease and are non-ambulant by the age of 10 despite being on corticosteroid treatment (Pinto Mariz et al, 2015). With no intervention, the mean age of life is approximately 19 years. The management of the inflammation associated with DMD is currently addressed via the use of corticosteroids, however they are acknowledged as providing insufficient efficacy and are associated with significant side effects. As a consequence, there is an acknowledged high need for new therapeutic approaches for the treatment of inflammation associated with DMD.

Rosenberg AS, Puig M, Nagaraju K, *et al*. Immune-mediated pathology in Duchenne muscular dystrophy. *Sci Transl Med* 2015, 7: 299rv4.

Bushby et al for the DMD Care Consideration Working Group/ *Diagnosis and management of Duchenne muscular dystrophy, part 1* Lancet Neurol. **2010** Jan;9(1):77-93 *and part 2* Lancet Neurol. **2010** Feb;9(2):177-89 .

Pinto-Mariz F, Carvalho LR, Araújo AQC, *et al*. CD49d is a disease progression biomarker and a potential target for immunotherapy in Duchenne muscular dystrophy. *Skeletal Muscle* 2015, 5: 45-55.

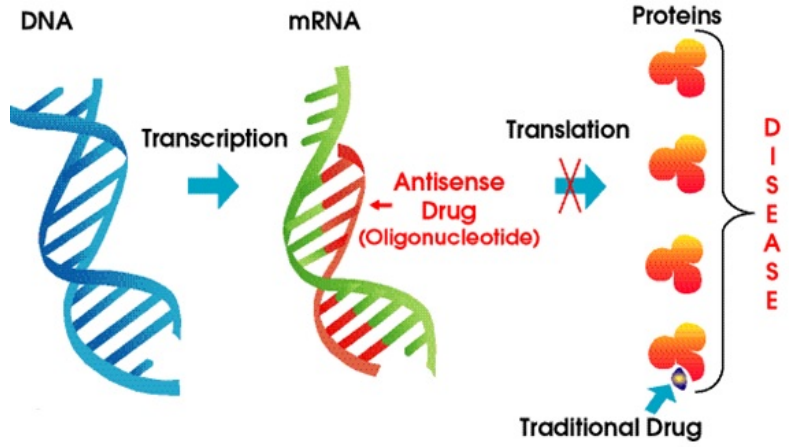
ATL1102 Phase II Non-Ambulant DMD Study (1102-DMD-CT02)

ATL1102

- Improved therapies are needed to ameliorate DMD severity & delay disease progression

ATL1102

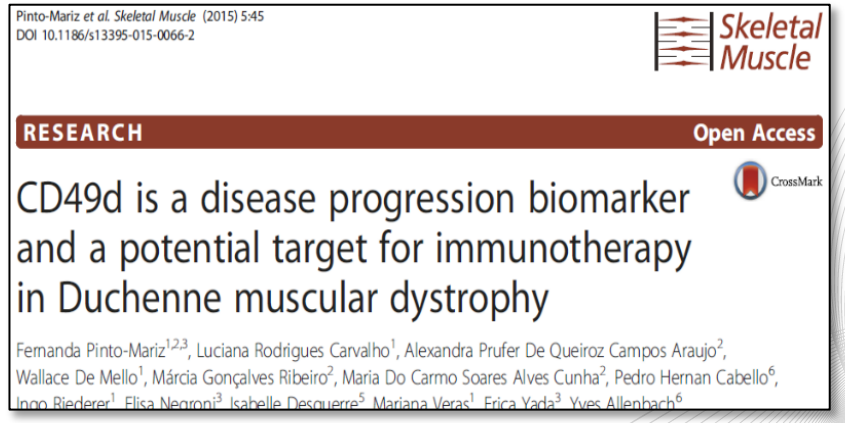
- ATL1102 is a 2'MOE gapmer antisense oligonucleotide drug to integrin a_4 RNA (CD49d alpha subunit of VLA-4), an adhesion molecule expressed on most human leukocytes
- ATL1102 is designed to inhibit CD49d expression on lymphocytes and thereby reduce their survival, activation and migration from the blood into sites of inflammation
- ATL1102 is an immunomodulatory antisense drug to human CD49d RNA which has completed a successful Phase IIa trial in Multiple Sclerosis (MS) patients [Limmroth V et al Neurology 2014, 11:83 (20) 1780-8]



WHY ATL1102 FOR DMD?

Pivotal scientific publication confirming CD49d as a potential target for DMD therapy

- DMD patients with greater number of circulating T cells with high levels of CD49d (CD49dhi) expression have both more severe & rapid progression of disease [Pinto-Mariz et al Skeletal Muscle 2015, 5: p45-55]
- Corticosteriods (CS) appear to have no effect on CD49dhi T cell numbers
- CS treatment does not modulate CD49d expression on T cells in MS
- Non-ambulant DMD patients have greatest number of CD49d high expressing T cells


Pinto-Mariz *et al. Skeletal Muscle* (2015) 5:45
DOI 10.1186/s13395-015-0066-2

Skeletal Muscle

RESEARCH Open Access

CD49d is a disease progression biomarker and a potential target for immunotherapy in Duchenne muscular dystrophy

Fernanda Pinto-Mariz[1,2,3], Luciana Rodrigues Carvalho[1], Alexandra Prufer De Queiroz Campos Araujo[2], Wallace De Mello[1], Márcia Gonçalves Ribeiro[2], Maria Do Carmo Soares Alves Cunha[2], Pedro Hernan Cabello[6], Ingo Riederer[1], Elisa Negroni[3], Isabelle Desguerre[5], Mariana Veras[1], Erica Yada[3], Yves Allenbach[6]

ATL1102 Phase II Study Overview (1102-DMD-CT02)

Study Title: A Phase 2 open label study to determine the safety, efficacy and pharmacokinetic profile of weekly dosing of ATL1102 in patients with non-ambulatory Duchenne Muscular Dystrophy. (ACTRN12618000970246)

Primary objective:

To assess the safety and tolerability of 25 mg of ATL1102 administered once weekly (s.c. injection) for 24 weeks in non-ambulatory participants with DMD.

Secondary objectives:

To evaluate the

- lymphocyte-modulatory potential of ATL1102 in participants with DMD
- PK profile of ATL1102 in participants with DMD
- effects of ATL1102 on functional capacity in participants with DMD
- effects of ATL1102 on respiratory function in participants with DMD
- effects of ATL1102 on quality-of-life in participants with DMD

Design:

Single-centre, open-labelled study conducted at the Murdoch Children's Research Institute (MCRI), Melbourne, Australia

Sample size:

9 participants

Target population:

- participants diagnosed with DMD and have been non-ambulatory for at least 3 months
- 10 to 18 years of age
- body weight of more than 25 kg and less than or equal to 65 kg

ATL1102 Phase II Study

Participant Demographics

Summary of Participant Demographics, DMD Disease History and Corticosteroid Medication

Characteristic	Category	Statistic	ATL1102 N = 9
Gender	Male	n (%)	9 (100)
Race	Native Hawaiian or Other Pacific Islander	n (%)	1 (11.1)
	White	n (%)	8 (88.9)
Ethnicity	Non-Hispanic and Non-Latino	n (%)	9 (100)
Age (years)		Mean (SD)	14.9 (2.1)
		Median (range)	14.0 (12 - 18)
Weight (kg)		Mean (SD)	52.7 (9.8)
Height (cm)		Mean (SD)	141.1 (10.0)
BMI		Mean (SD)	27.1 (7.4)
Time since non-ambulant (years)		Median (range)	2.2 (0.6 – 9.2)
Corticosteroid Medication	Yes	n (%)	8 (88.9)
	Prednisolone		*3 (33.3)*
	Deflazacort		*5 (55.6)*
	No	n (%)	1 (11.1)

ATL1102 Phase II Study

Safety Overview – *Study Met Primary Endpoint*

ATL1102 appears to be generally safe and well tolerated:

- No Serious Adverse Events (SAEs) have been reported
- No participants have been withdrawn from the study
- A total of 136 Treatment Emergent Adverse Events (TEAEs) have been reported by all 9 participants.
  - Of the 136 TEAEs, 114 were considered to be Related to the study medication (including possibly, probably, definitely and unlikely) and 22 considered to be Not-Related by the Investigator.
  - The 9 participants reported 131 TEAEs that were considered to be mild in severity. A total of 2 participants reported 2 TEAEs of moderate severity and 3 TEAEs that were considered to be severe.
- The most commonly reported TEAEs were injection site erythema, skin discolouration, injection site pain, injection site bruising and injection site swelling.
  - All Injection site reactions and skin discolouration TEAEs were reported to be mild in severity.
  - Participants were followed up to monitor the skin discolouration, which resolved (4 participants) or were resolving (2 participants) in all participants at the end of the study.

ATL1102 Phase II Study

Safety Overview - Treatment Emergent Adverse Events (by MedDRA Preferred Term) Reported in ≥ 2 Participants

SYSTEM ORGAN CLASS Preferred Term	All N=9 Participants (%) [Events]
Participants reporting any AEs	9 (100.0%) [136]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Injection site erythema	8 (88.9%) [59]
Injection site pain	5 (55.6%) [7]
Injection site swelling	3 (33.3%) [6]
Injection site bruising	4 (44.4%) [4]
Pyrexia	2 (22.2%) [4]
Injection site reaction	2 (22.2%) [3]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Skin discolouration	6 (66.7%) [7]
GASTROINTESTINAL DISORDERS	
Vomiting	2 (22.2%) [4]
Constipation	2 (22.2%) [2]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Cough	2 (22.2%) [2]
Nasal congestion	2 (22.2%) [2]
Oropharyngeal pain	2 (22.2%) [2]
INFECTIONS AND INFESTATIONS	
Lower respiratory tract infection	2 (22.2%) [2]
Nasopharyngitis	2 (22.2%) [2]
NERVOUS SYSTEM DISORDERS	
Migraine	2 (22.2%) [2]

ATL1102 Phase II Study

Overview of Efficacy Parameters

The Secondary Objectives of the study include evaluation of the following efficacy parameters:

- Lymphocyte-modulation potential to be determined by assessing number and percentages of lymphocytes, CD4+ and CD8+ T cells and, CD4+ CD49d and CD8+ CD49d T cells
- Effects of ATL1102 on functional capacity in participants with DMD
  - Evaluation of muscle function via Performance of Upper Limb Test (PUL 2.0) and Moviplate assessments (using the Myoset System)
  - Evaluation of muscle strength via MyoGrip and MyoPinch assessments (using the Myoset System)
- Effects of ATL1102 on respiratory function in participants with DMD
  - Includes % predicted Peak Expiratory Flow (PEF) and % predicted Forced Expiratory Volume (FVC)
- Effects of ATL1102 on quality-of-life in participants with DMD

ATL1102 Phase II Study

Overview of Efficacy Parameters

Lymphocyte-modulation potential to be determined by assessing number and percentages of lymphocytes, CD4+ and CD8+ T cells and, CD4+ CD49d and CD8+ CD49d T cells

- Positive immunomodulatory effects have been observed on lymphocytes, including T-Lymphocytes (i.e CD4 and CD8+ T cells) and NK lymphocytes including T and NK lymphocytes expressing CD49d (the biological target of ATL1102)
- A consistency in the mean reductions in the number of lymphocytes including T-lymphocytes (i.e. CD3+, CD3+CD4+, CD3+CD8+ and, importantly those expressing CD49d) measured from baseline to week 8, 12 and 24 (end of dosing) with a rebound of these T-cells to around starting levels post dosing at week 28
- The mean number of Lymphocyte at week 24 (at the end of dosing) is trending significantly lower vs week 28 (p= 0.051 paired T test)
- The mean number of CD3+CD49d+ T cells (i.e. mostly CD3+CD4+CD49d+ and CD3+CD8+CD49d+cells) at week 24 is statistically significantly lower vs week 28 (p=0.030 paired T test) suggesting the drug is working through its targeted mechanism of action
- The mean number of NK lymphocytes (CD3-CD16+CD56+) and NK lymphocytes expressing CD49d+ at week 8,12 and 24 is statistically significantly lower vs baseline using a mixed model for repeated measurements (p=0.018), with comparable NK lymphocyte numbers at week 28

This data demonstrates the drug's positive effects on modulating CD49d+ lymphocytes in the blood during treatment.

ATL1102 Phase II Study

Lymphocyte and T-cell Modulation Data

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)

antisense THERAPEUTICS

ATL1102 Phase II Study

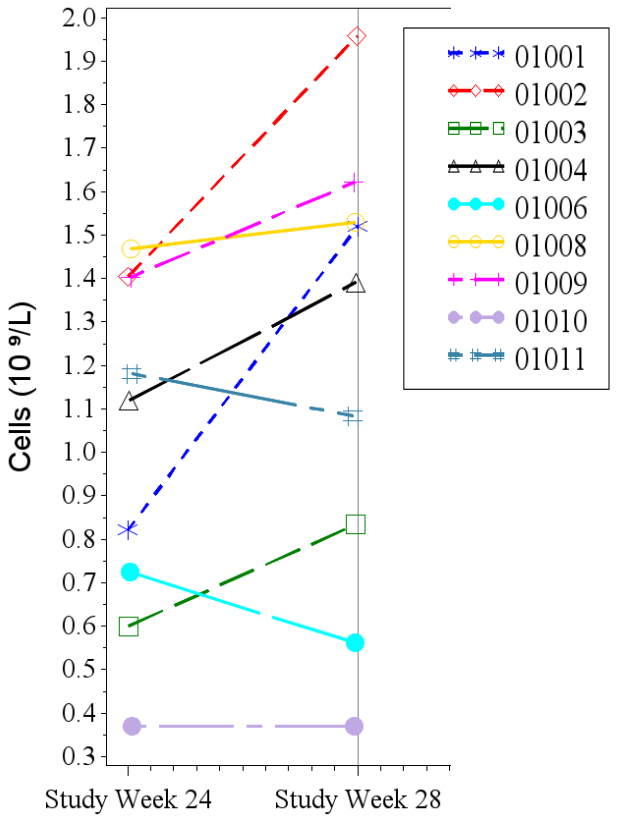
Individual PUL 2.0 and T-cell CD4+CD49d+ week 24 and 28 data*

- There appears to be a correlation between the individual patient PUL2.0 scores at the end of dosing (week 24) and their week 24 vs week 28 CD4+CD49d+ T cell changes
- Of the eight participants with normal starting levels of lymphocytes, six demonstrated either an improvement or maintenance in their PUL2.0 scores and had a 'rebound' in the CD4+CD49d+ T cells at week 28, while two of the eight participants who had a loss of PUL2.0 at week 24 did not see a rebound in these cells at week 28 vs week 24

* Performance of Upper Limb Module for DMD version 2.0 (PUL 2.0) assesses the performance of a large group of muscles of the upper body of patients

Change from Baseline	
Patient No.	PUL 2.0* change Week 24
01-001	+2
01-002	+2
01-003	0
01-004	+2
01-006	-3
01-008	+7
10-009	0
01-010	0
01-011	-2

Number of CD4CD49d+ Cells Over Time by Participant



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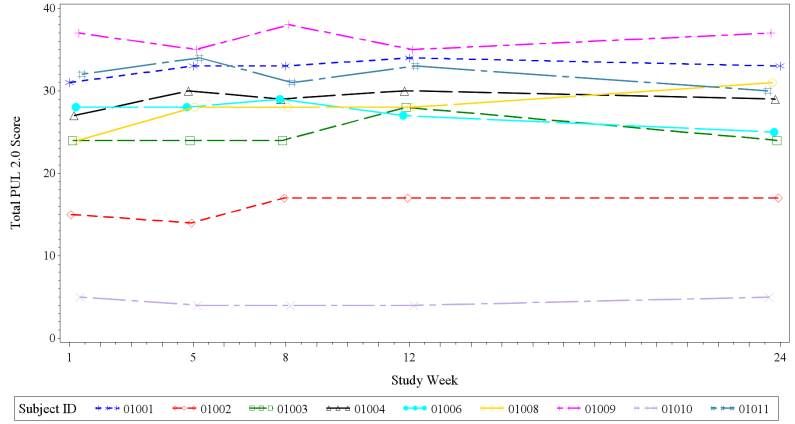
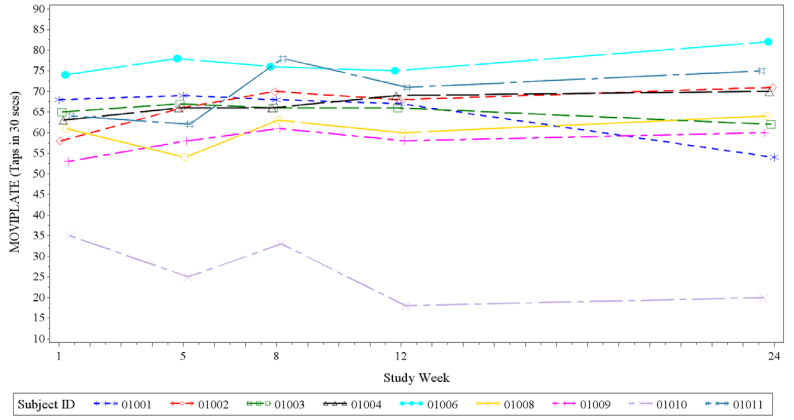
ATL1102 Phase II Study

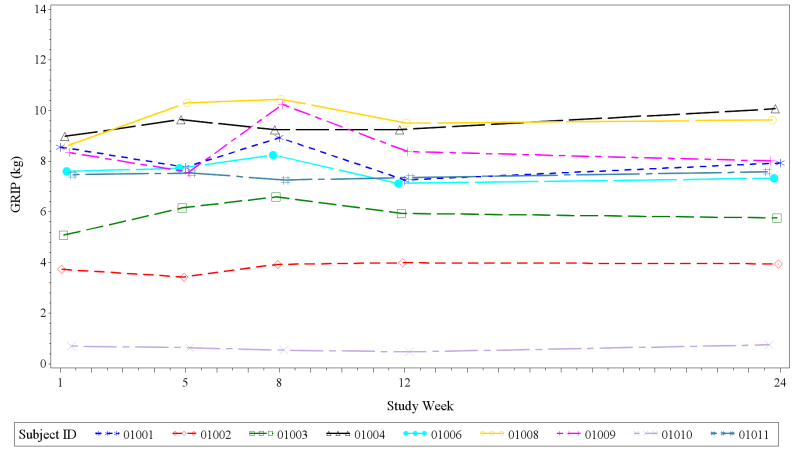
Efficacy Parameters – Muscle Function & Strength

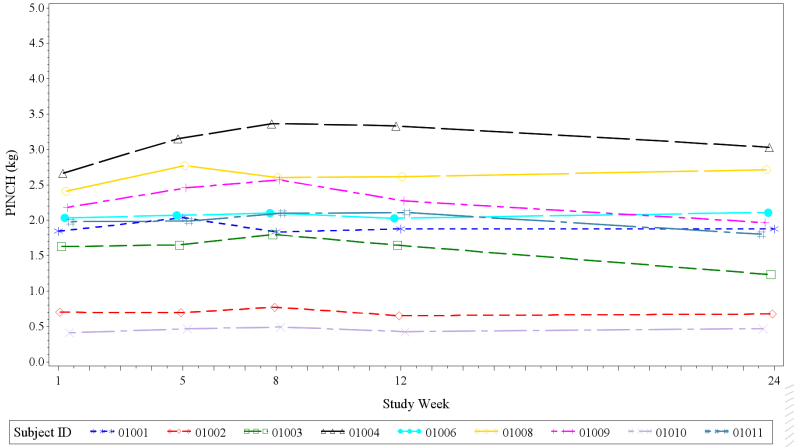
Mean change observed across multiple parameters following ATL1102 treatment suggest improvements or reductions in the declines that would be expected in patients with DMD over 6 months

Change from Baseline to Week 24	
Efficacy Parameter	**Mean Change (95% CI)**
PUL 2.0	0.9 (-1.33, 3.11)
MyoGrip (dom) (Kg)	0.2 (-0.25, 0.67)
MyoGrip (dom) (% Pred)	-0.7 (-2.33, 0.90)
MyoPinch (dom) (Kg)	0.0 (-0.18, 0.19)
MyoPinch (dom) (% Pred)	-1.0 (-3.56, 1.63)
MoviPlate Score (dom)	1.9 (-6.08, 9.85)









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ATL1102 Phase II Study

Efficacy Parameters Overview – Muscle Function & Strength; Clinical Interpretation

Composite Scores determined based on clinical relevance of the observed changes in Non-Ambulant DMD Integrating PUL2.0 Total Score, % Predicted MyoGrip, % Predicted MyoPinch and MoviPlate Score

	Change from Baseline to Week 24			
Patient No.	PUL 2.0	MyoGrip (dom) (% Pred)	MyoPinch (dom) (% Pred)	MoviPlate Score (dom)
01-001	+1	-1	0	-1
01-002	+1	0	0	+1
01-003	0	0	-1	0
01-004	+1	0	+1	+1
01-006	-1	0	0	+1
01-008	+1	0	+1	0
01-009	0	-1	-1	+1
01-010	0	0	0	-1
01-011	-1	0	-1	+1
Clinically Meaningful Stabilisation/Improvement	**7/9 Participants**	**7/9 Participants**	**6/9 Participants**	**7/9 Participants**
Mean Change (95% CI):	0.9 (-1.33, 3.11)	-0.7 (-2.33, 0.90)	-1.0 (-3.56, 1.63)	1.9 (-6.08, 9.85)

A clinically meaningful annual change was considered to be: for the PUL2.0 total score = 4 points, for the MyoGrip and MyoPinch = 3% and for the MoviPlate = 10 points.
A decline was captured as −1, unchanged measurements as 0 and improvement as +1.

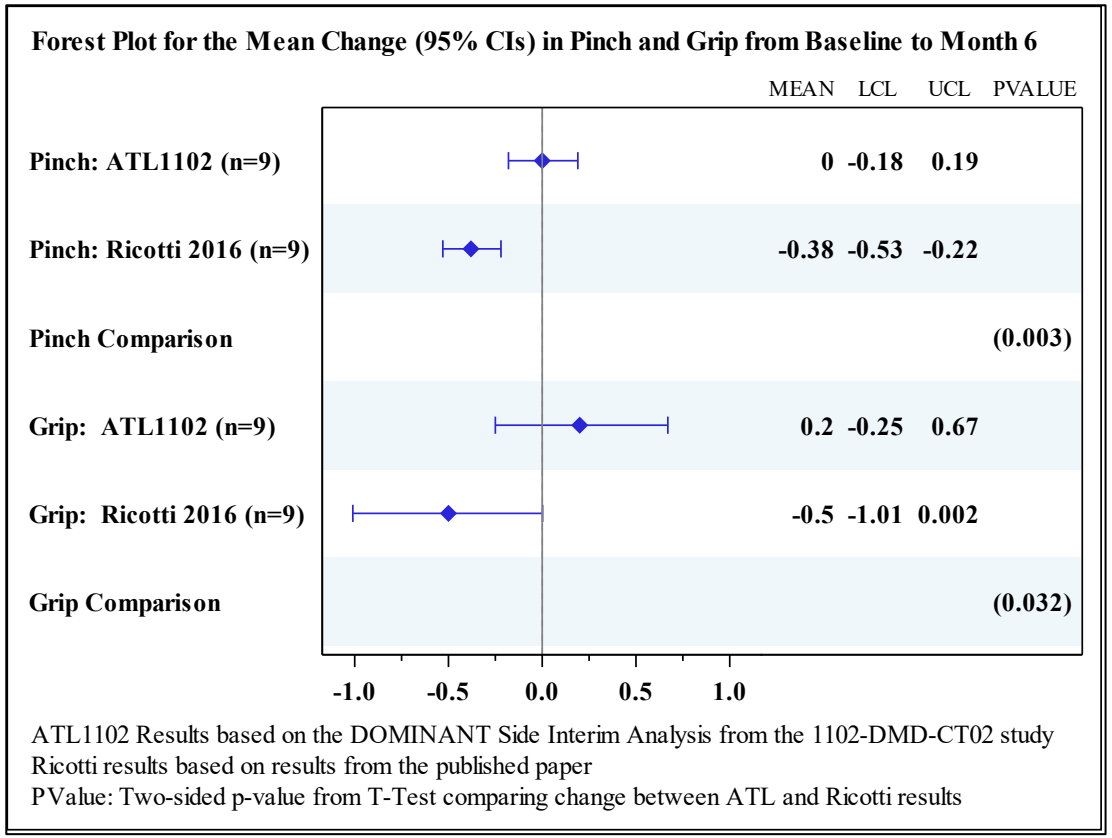
Based on the composite scores:

- No participants declined across all domains
- 3 participants remained stable across all domains, these participants showed no reduction in muscle strength and function parameters assessed in the study
- 7 of 9 participants have demonstrated clinically meaningful stabilisation /improvement on PUL2.0
- Overall stabilisation across muscle force/strength and function
  - 5/9 participants showed clinically meaningful stabilisation across both grip and pinch strength
  - 5/9 participants showed clinically meaningful stabilisation or improvement across both PUL2.0 and MoviPlate scores

ATL1102 Phase II Study

Efficacy Parameters Overview – Muscle Strength (MyoGrip & MyoPinch)

Comparison of ATL1102 Phase II study data with data in published literature (Ricotti et. al. 2016)



- *ATL1102 Phase II study data showing statistically significant improvements when compared to data in published literature*

Ricotti et. al 2016 . PLoS One, 11(9) e0162542 (are historical results from a Non – Ambulant cohort of 9 DMD patients all on CS for 6 months)

ATL1102 Phase II Study

Efficacy Parameters – Muscle Structure (MRI)

The MRI assessment of muscles of the dominant forearm showed:

- The mean change in percentage of Fat Fraction (of the central reading) was slightly reduced or stable across the 3 muscle groups (Volar, Dorsal and ECRLB-Br) and the overall Average Fat Fraction (FF).
- This finding was further supported by the reductions in % FF observed for the MRI proximal and distal readings.
- The observed stabilisation in % FF is not expected in the natural course of the disease.
- The stabilisation of the % FF combined with the observed increase/maintenance of the lean muscle mass suggests ATL1102 preserves functional muscle mass.

Change from Baseline to Week 24		
MRI CENTRAL READING	**Average Fat Fraction (%)**	**Total Remaining Muscle (Non-Fat) Area (mm^2)**
Mean Change (95% CI)	-0.52 (-5.6, 4.6)	13.9 (-72.6, 100.4)
Median Change	1.4	5.8

"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."

Dr Valeria Ricotti MD, Researcher and Honorary Clinical Lecturer, Great Ormond Street Institute of Child Health University College London, UK

ATL1102 Phase II Trial

Efficacy Parameters Overview – Muscle Structure (MRI)

Comparison of ATL1102 Phase II study data with data in published literature (Ricotti et. al. 2016)

Mean Change (95% CI) Screening/Baseline to Week 24/6 months				
MRI Parameter	N	ATL1102 Study Data	N	Published Data*
MRI CENTRAL READING				
Fat Fraction (%)				
Volar Muscle	9	-0.57 (-7.8, 6.7)	7	0.7 (-1.8, 3.3)
Dorsal Muscles#	9	-0.88 (-3.4, 1.7)	7	5.5 (2.7, 8.3)
ECRLB-Br	9	-0.12 (-6.4, 6.2)	7	6.1 (3.1, 9.2)
Average Fat Fraction	9	-0.52 (-5.6, 4.6)	7	3.9 (1.9, 5.7)
Cross Sectional Muscle Area -total (mm^2)	9	22.33 (-36.8, 81.4)	7	42.1 (-47.0, 131.2)
Remaining Muscle Area – total (mm^2)	9	13.9 (-72.6, 100.4)	7	-32.1 (-102.6, 38.1)
MRI PROXIMAL READING - Average Fat Fraction (%)#	9	-2.14 (-7.6, 3.3)	7	4.5 (2.7, 6.3)
MRI DISTAL READING - Average Fat Fraction (%)	7	-5.14 (-18.7, 8.4)^	7	2.2 (-0.05, 4.5)

*Ricotti et. al 2016 . PLoS One, 11(9) e0162542 (results from Non – Ambulant cohort of 7 patients all but one on CS)

^Distal Reading is Average of Dorsal and Volar Muscle (ECRL-Br not measurable)

T-Test analysis comparing the ATL1102 study data and the published data showed statistically significant differences for:

- MRI central reading mean change in percentage fat fraction from baseline to 6 months for the dorsal muscle group with a 2-sided p-value of 0.001
- MRI proximal reading mean change in average fat fraction percentage with a 2-sided p-value of 0.018

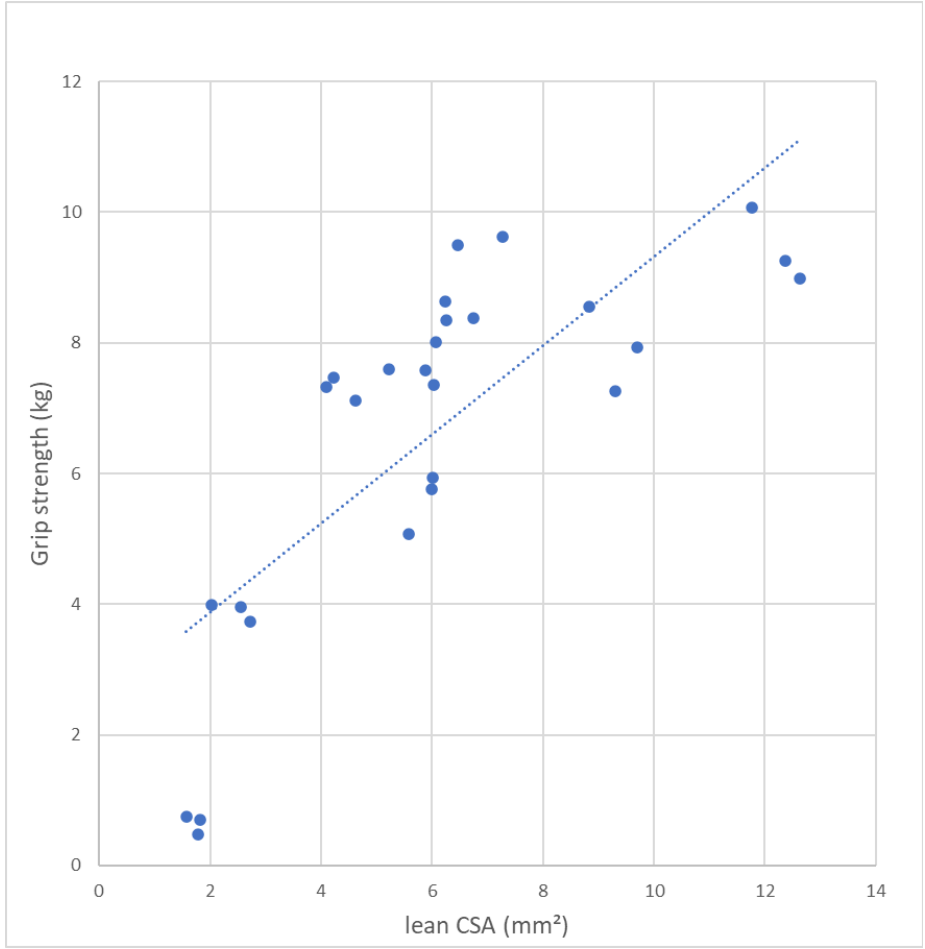
ATL1102 Phase II Trial

Efficacy Parameters Overview – Muscle Structure (MRI) & Strength (MyoGrip)

- Highly significant positive correlation observed between the MRI results for the lean muscle area (non-fat) and the MyoGrip results
- Confirms consistency of results across the different parameters of muscle structure and muscle force/strength

"this positive correlation of remaining muscle area (the lean muscle), with grip strength suggests a consistency of the results across the different parameters of muscle structure and muscle force."

Dr Jean-Yves Hogrel, PhD, Director of the Neuromuscular Physiology and Evaluation Laboratory, Institute of Myology, France



Note: MRI measurements taken at 3 timepoints for each participant.

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ATL1102 Phase II Trial

Efficacy Parameters Overview – Quality of Life (PedsQL)

Change from Baseline to Week 24 Mean Change (SD)				
PedsQL	**Communication Domain**	**Daily Activities Domain**	**Treatment Domain**	**Worry Domain**
PedsQL - Parent Report Transformed Domain Score	-10.7 (29.2)	4.3 (18.1)	5.4 (17.1)	-3.5 (25.1)
PedsQL – Teen Report Transformed Domain Score	8.3 (35.4)	10.0 (14.1)	9.4 (4.4)	2.1 (2.9)

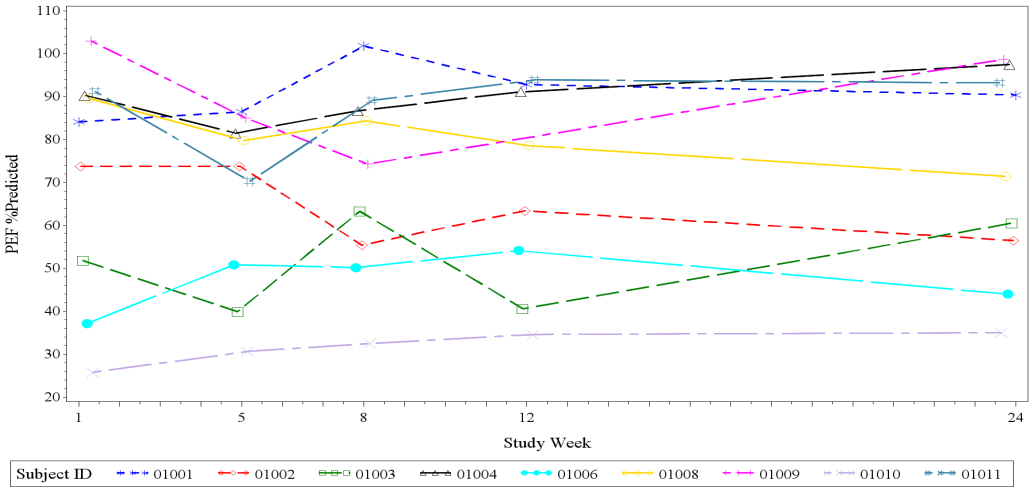
Quality of Life (PedsQL) questionnaires were completed by parents of the younger boys in the study and by two of the teenage boys

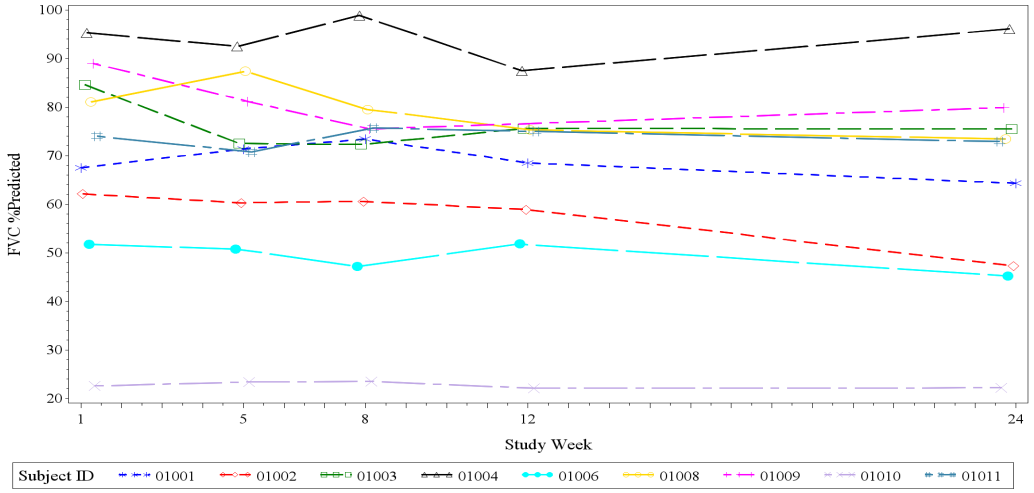
- Both the teens showed a mean improvement in all the domains
- The results for the younger patients where the parents completed the questionnaire also showed improvements in daily activities and treatment domains but increased problems with communication and worry domains

Interpretation is complicated by the inherent variability in the assessment tool.

ATL1102 Phase II Trial

Efficacy Parameters Overview – Respiratory Function





Change from Baseline to Week 24		
Respiratory Function	**% Predicted PEF**	**% Predicted FVC**
Mean Change (95% CI):	0.06 (-8.33, 8.44)	-5.68 (-9.60, -1.76)

- Difficult to draw any meaningful conclusions on this parameter due to variability in this data, which is best assessed in 12 month studies or longer and with a larger patient population
- Nevertheless, with the PEF assessment a slight mean increase in percentage predicted PEF was observed which is consistent with the data observed for the other parameters

ATL1102 Phase II Study

Conclusions

- ATL1102 appears to be generally safe and well tolerated in non-ambulant boys with DMD in this study
- ATL1102, a novel antisense drug being developed for the treatment of inflammation that exacerbates muscle fibre damage in DMD, appears to be demonstrating positive effects on disease progression parameters assessed for the study in non-ambulant boys with DMD
    - The data from the study shows an apparent improvement in muscle strength based on the observed mean change from baseline after 24 weeks of dosing with ATL1102 as assessed by MyoGrip and MyoPinch compared to the loss of muscle strength reported in the literature in similar patient populations
    - The data is also suggestive of an improvement in muscle function as assessed by the Performance of Upper Limb Test (PUL 2.0), where 7 of the 9 participants have demonstrated clinically meaningful improvements or stabilisation in their PUL 2.0 scores from baseline after 24 weeks of dosing with ATL1102
    - MRI data suggests stabilisation of percentage of fat in muscles and preservation of functional muscle mass confirming
- MRI data confirms the positive changes at a muscular/cellular level and supports the observed physical stabilisation/improvements in muscle strength and function
- Promising results support continued development of ATL1102 for the treatment of DMD

"The data certainly suggests an overall 'stabilisation' in disease progression at the very least which of itself is a very positive clinical outcome. MRI data confirms the positive changes at a muscular/cellular level and supports the observed physical stabilisation/improvements in muscle strength and function. The consistency of positive clinically relevant effects of ATL1102 treatment across muscle measures of structure, strength and function are very pleasing and provide great encouragement for the treatment of non-ambulant patients with DMD".

Professor Thomas Voit MD, Director, NIHR GOSH Biomedical Research Centre, UK