ASX Announcement

18 November 2019

Additional preliminary data from the ATL1102 Phase II DMD trial presented at the Action Duchenne International Conference 2019

Antisense Therapeutics ("ANP" or the "Company") is pleased to advise that additional preliminary data analyses from the seven patients who have completed their 24 weeks of dosing in the ATL1102 Phase II DMD clinical trial was presented by Dr Ian Woodcock, the Principle Investigator of the ATL1102 Phase II trial at the 2019 Action Duchenne International Conference, Hinkley, UK on 15 November 2019. A copy of the presentation follows this announcement.

The new clinical data (in addition to preliminary data reported by ANP on 18 September 2019) presented by Dr Woodcock included a more detailed safety overview and re-confirmation that no Serious Adverse Events (SAEs) have been reported to date and that the Data Safety Monitoring Board continues to have no safety concerns.

In regard to the trial's secondary endpoints that assess drug efficacy in terms of its effects on disease processes and progression (being the type of endpoints required for future product registration), Dr Woodcock presented new data on the functional capacity of the participants as evaluated via Performance of Upper Limb Test (PUL2.0). PUL is a functional scale specifically designed for assessing upper limb function in DMD with the aim of reflecting the proximal to distal progression of muscle weakness typically observed in DMD. It includes three domains (shoulder, mid- and distal), each including items exploring activities easily related to activities of daily living that both patients and clinicians regard as relevant.

The PUL data presented by Dr Woodcock showed that the majority of participants have demonstrated either increases or no change in their PUL2.0 scores from baseline after 24 weeks of dosing with ATL1102 suggestive of an overall improvement in a key parameter of disease progression.

Muscle strength was also evaluated (as previously reported) via MyoGrip and MyoPinch assessments using the Myoset system with the data continuing to show an apparent improvement in muscle strength based on observed mean changes from baseline compared to the loss of muscle strength reported in the literature in similar patient populations.

These results continue to appear highly supportive of the Company's clinical development program, with plans for a Phase IIb clinical trial of ATL1102 in DMD presently being reviewed with European regulatory authorities at Scientific Advice (SA) meetings. The Company expects to report on these interactions after it receives written responses following the meetings.

The Company is consulting with internationally recognized DMD experts in regard to the ongoing development of ATL1102 and the Phase IIb clinical trial including Professor Thomas Voit MD, Director, NIHR GOSH Biomedical Research Centre, UK who is participating in all the planned SA meetings. Dr Voit had this to say about the preliminary trial results and their bearing on Phase IIb planning: "I am most encouraged by the preliminary data that is emerging from the Phase II clinical trial of ATL1102 in non-ambulant DMD patients in particular its safety profile and apparent positive effects on disease progression endpoints that will be employed in the follow on clinical trial. There are a very few treatment alternatives being developed for the non-ambulant DMD population, so I would expect that these preliminary findings should help facilitate productive interactions with the regulatory authorities on a hopefully expedited development path to market for such an underserved patient group."

The ATL1102 Phase II DMD trial remains ongoing with dosing in all patients to be completed this month.

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About Antisense Therapeutics Limited (ASX: ANP) is an Australian publicly listed biopharmaceutical 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 DMD patients 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 RR-MS patients. 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 Company is undertaking a clinical trial of ATL1102 in patients with Duchenne Muscular Dystrophy. The open label six-month dosing trial of ATL1102 in nine non-ambulant patients with DMD aged between 10 and 18 years is being conducted at the neuromuscular centre of the Royal Children's Hospital (RCH) which operates the largest clinic in the southern hemisphere treating children with DMD. The primary endpoints of the trial relate to the safety and tolerability of ATL1102. The efficacy of ATL1102 will also be assessed in terms of its effects on disease processes and progression (e.g. the upper limb strength and function of the boys). 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 wheelchair bound 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.

Busby 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

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

Action Duchenne - 15 & 16 November 2019

Ian Woodcock, Nuket Desem, George Tachas, Monique Ryan

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ATL1102

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

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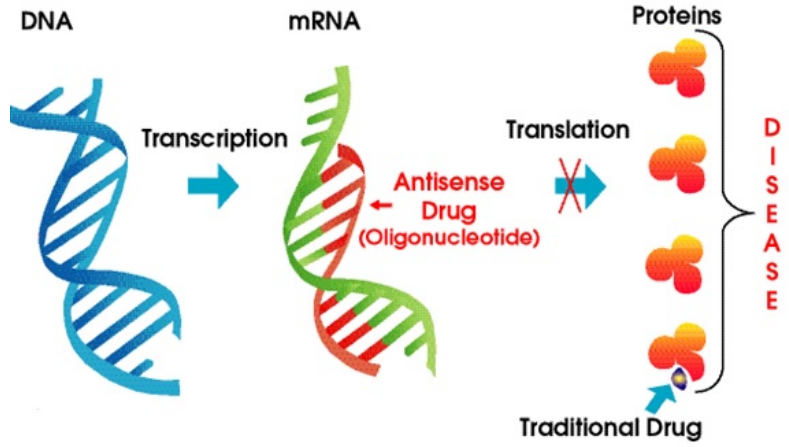
ATL1102

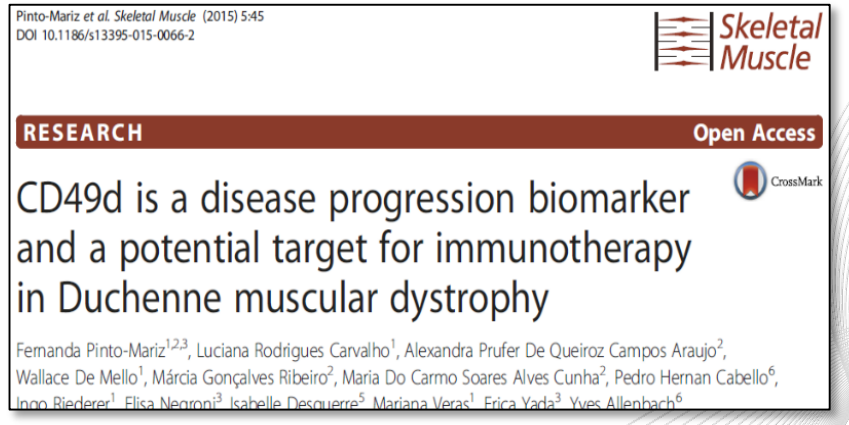
- ATL1102 is a 2'MOE gapmer antisense oligonucleotide drug to integrin a_4 RNA (CD49d alpha subunit of VLA-4), an adhesion molecule expressed on most human leukocytes
- ATL1102 is designed to inhibit CD49d expression on lymphocytes and thereby reduce their survival, activation and migration from the 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 MCRI 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
  - the primary efficacy endpoint for the study
- 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 MCRI Phase II Study

Current Status

Participant Visit Status

Study Visit	Screen	Wk 1	Wk 3	Wk 5	Wk 7	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Follow up
No. of Participants	11*	9	9	9	9	9	9	9	9	9	9	9	9	7	6

- Six participants have completed the study
- Of the currently ongoing participants:
  - Total of 7 have completed dosing at the end of Sept 2019
  - 8th and 9th participants completing dosing during early Nov 2019
  - The Last Participant Last Visit for the study will be beginning of Jan 2020
- No participants withdrawn from the study

* 2 Screen Failures

ATL1102 MCRI 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 MCRI Phase II Study

Safety Overview

An Independent Data and Safety Monitoring Board (DSMB) provides safety oversight for the study.

- The DSMB consists of 3 paediatricians and a biostatistician, the DSMB is chaired by A/Professor Andrew Kornberg, MD.
- The DSMB evaluate safety data on an ongoing basis and based upon the evaluation, issue formal recommendations for continuation/modification/discontinuation of the study to the sponsor
- Based on their review of the data to date, the DSMB have no safety concerns.

ATL1102 appears to be generally well tolerated:

- No Serious Adverse Events (SAEs) have been reported
- No participants have been withdrawn from the study for safety related reasons
- A total of 126 Treatment Emergent Adverse Events (TEAEs) have been reported by all 9 participants to date. Seventy-two (72) were associated with injection site reactions (ISR), 24 ISR TEAEs were reported for one participant.
- Of the 126 TEAEs, 98 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.

ATL1102 MCRI Phase II Study

Safety Overview - Treatment Emergent Adverse Events (TEAEs)

TEAEs (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%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Injection site erythema	8 (88.9%) [52]
Injection site pain	5 (55.6%) [7]
Injection site swelling	3 (33.3%) [6]
Pyrexia	3 (33.3%) [5]
Injection site bruising	4 (44.4%) [4]
Injection site reaction	2 (22.2%) [3]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Skin discolouration	7 (77.8%) [8]
GASTROINTESTINAL DISORDERS	
Vomiting	2 (22.2%) [4]
Constipation	2 (22.2%) [2]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Nasal congestion	2 (22.2%) [2]
Oropharyngeal pain	2 (22.2%) [2]
NERVOUS SYSTEM DISORDERS	
Migraine	2 (22.2%) [2]

ATL1102 MCRI Phase II Study

Safety Overview - TEAEs

TEAE of skin discolouration on the abdomen observed in 7 of the 9 participants dosed to date in the study:

- The onset of the skin discolouration on the abdomen of participants ranged from Day 29 to Day 120 of the study.
- There appears to be no pain, no itchiness, no discomfort and no skin breakdown associated with the skin discolouration.
- None of the participants experiencing the skin discolouration wished to withdraw from the study.
- One participant (01-004) has been reviewed by the RCH dermatology department and the skin discolouration was assessed/confirmed as a post inflammatory hyperpigmentation and that no further management was required.

ATL1102 MCRI Phase II Study

Safety Overview – DSMB Recommendations

- DSMB for the study have been closely reviewing the skin discolouration observed in the participants and have recommended that:
  - It was not considered a safety issue and therefore the study should continue.
  - Participants are referred to a dermatologist for assessment
  - The Participant Information and Consent Form be updated to include the skin discolouration observation. The updated PICF has been approved by the MCRI Ethics Committee.
  - Participants to be followed up into the longer term to document persistence or resolution of the changes.
  - DSMB have recommended serial photographs of the hyperpigmentation should be obtained, where possible, for review in the future.

ATL1102 MCRI Phase II Study

Overview of Efficacy Parameters - Preliminary Data

The Secondary Objectives of the study include evaluation of efficacy parameters for which preliminary data has become available and include:

- 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
  - Early indications of an immunomodulatory effect have been observed where T-cell numbers (in particular those expressing the CD49d, the biological target of ATL1102) are trending downward during the 24-week treatment phase while returning to around starting levels post dosing.
- Effects of ATL1102 on functional capacity in participants with DMD
  - Evaluation of muscle function via Performance of Upper Limb Test (PUL 2.0)
  - Evaluation of muscle strength via MyoGrip and MyoPinch assessments (using the Myoset System)

    - data presented on the following slides
- Effects of ATL1102 on respiratory function in participants with DMD
  - Includes % predicted Peak Expiratory Flow (PEF) and % predicted Forced Expiratory Volume (FVC)

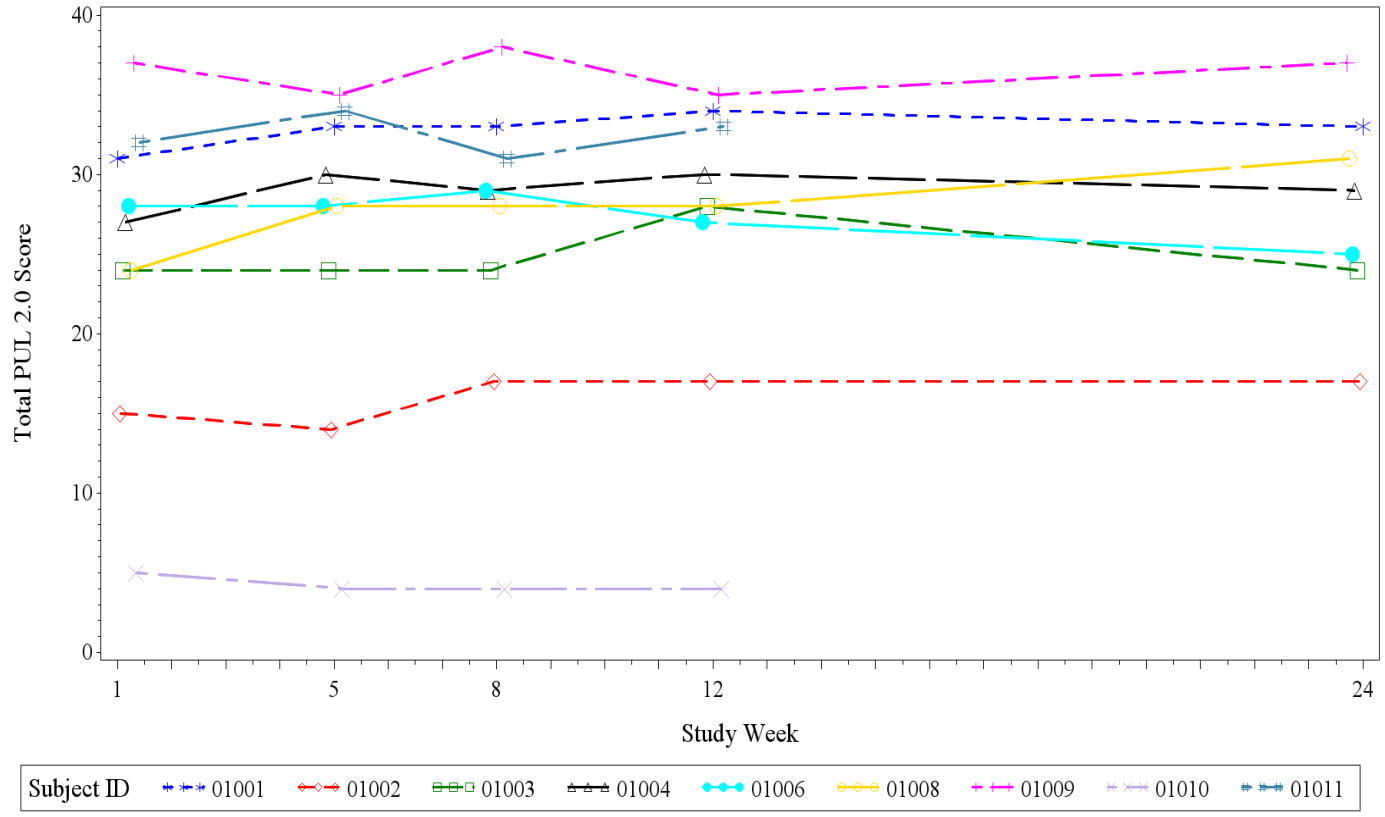
    - data presented on the following slides

ATL1102 MCRI Phase II Study

Efficacy Parameters – Preliminary Data

Performance of Upper Limb Module for DMD version 2.0 (PUL 2.0 for DMD)

Change from Baseline to Week 24	
Participant No.	**PUL 2.0**
01-001	+2
01-002	+2
01-003	0
01-004	+2
01-006	-3
01-008	+7
10-009	0
01-010	
01-011	
Mean Change (95% CI)	1.4 (-1.39, 4.25)



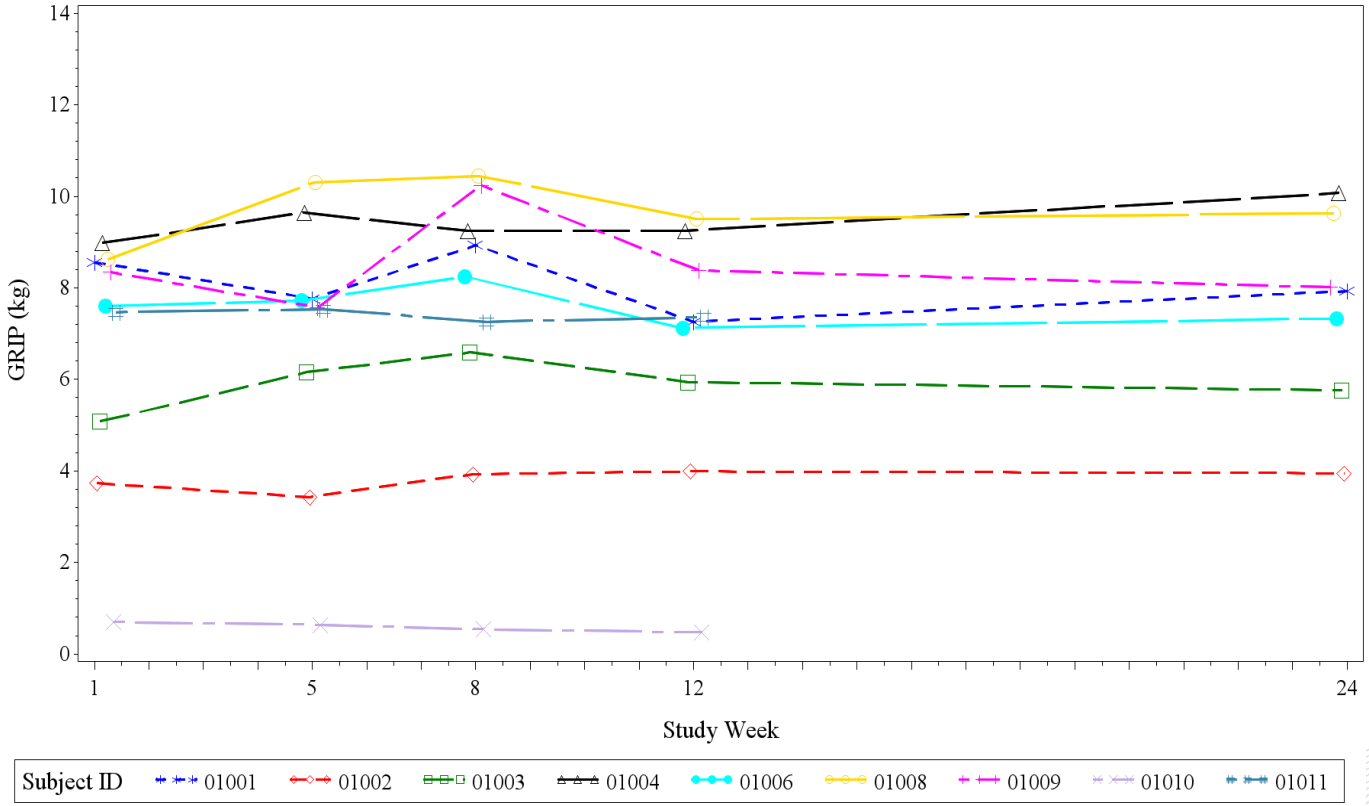
Please note: Higher score = less disability

ATL1102 MCRI Phase II Study

Efficacy Parameters – Preliminary Data

Myoset Measures – MyoGrip (absolute (kg) and % Predicted by Age)

Change from Baseline to Week 24		
Participant No.	**MyoGrip (dom) (Kg)**	**MyoGrip (dom) (% Pred)**
01-001	-0.63	-4.49
01-002	0.22	0.49
01-003	0.68	1.02
01-004	1.09	1.01
01-006	-0.27	0.60
01-008	1.00	1.11
10-009	-0.33	-3.75
01-010		
01-011		
Mean Change (95% CI)	0.3 (-0.38, 0.89)	-0.7 (-2.95, 1.47)

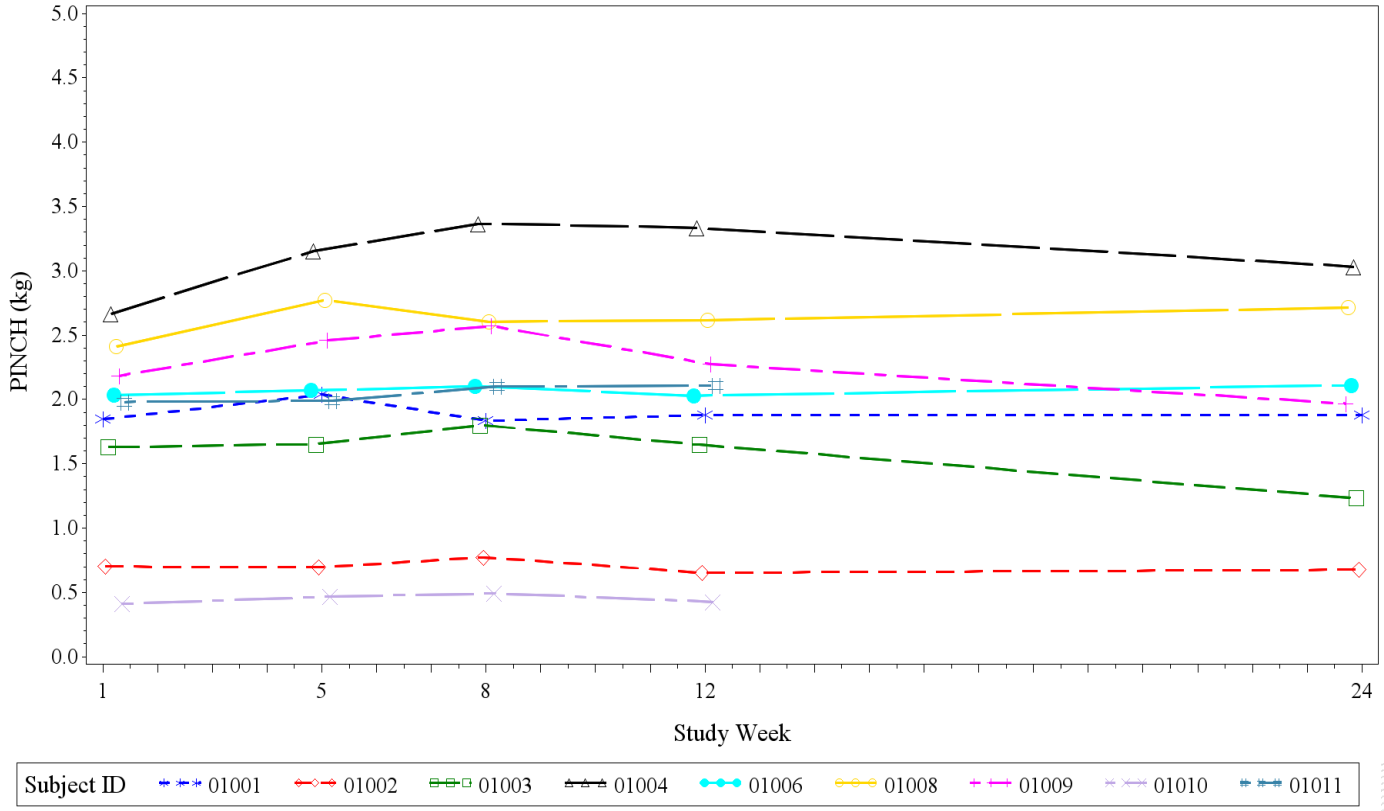


ATL1102 MCRI Phase II Study

Efficacy Parameters – Preliminary Data

Myoset Measures – MyoPinch (absolute (kg) and % Predicted by Age)

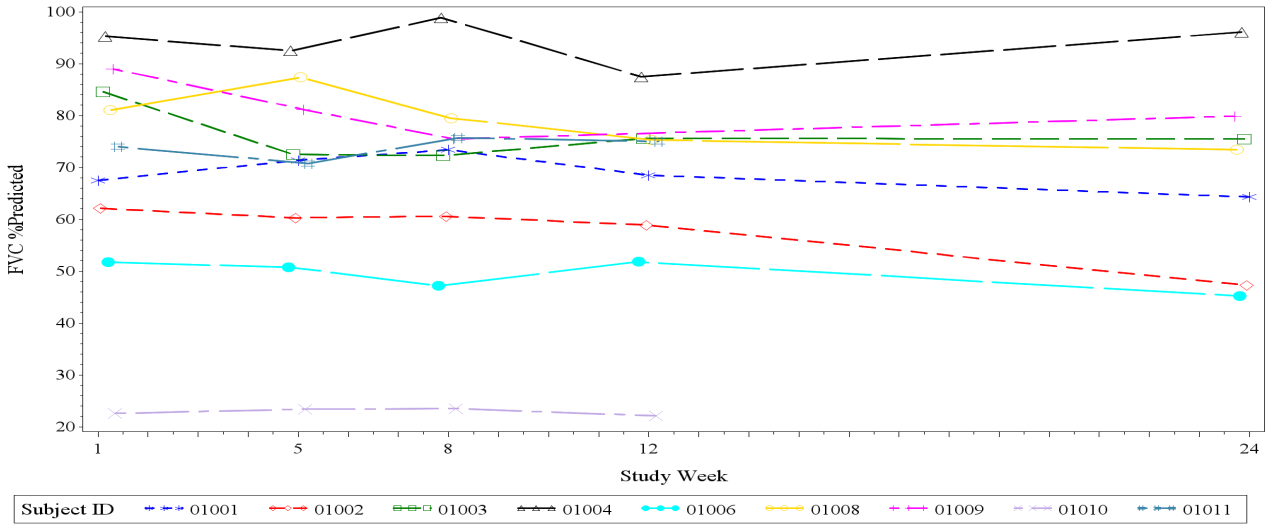
Change from Baseline to Week 24		
Participant No.	**MyoPinch (dom) (Kg)**	**MyoPinch (dom) (% Pred)**
01-001	0.03	-0.62
01-002	-0.02	-0.29
01-003	-0.40	-6.59
01-004	0.37	2.99
01-006	0.07	0.94
01-008	0.30	2.77
10-009	-0.22	-4.97
01-010		
01-011		
Mean Change (95% CI)	0.0 (-0.23, 0.27)	-0.8 (-4.23, 2.58)

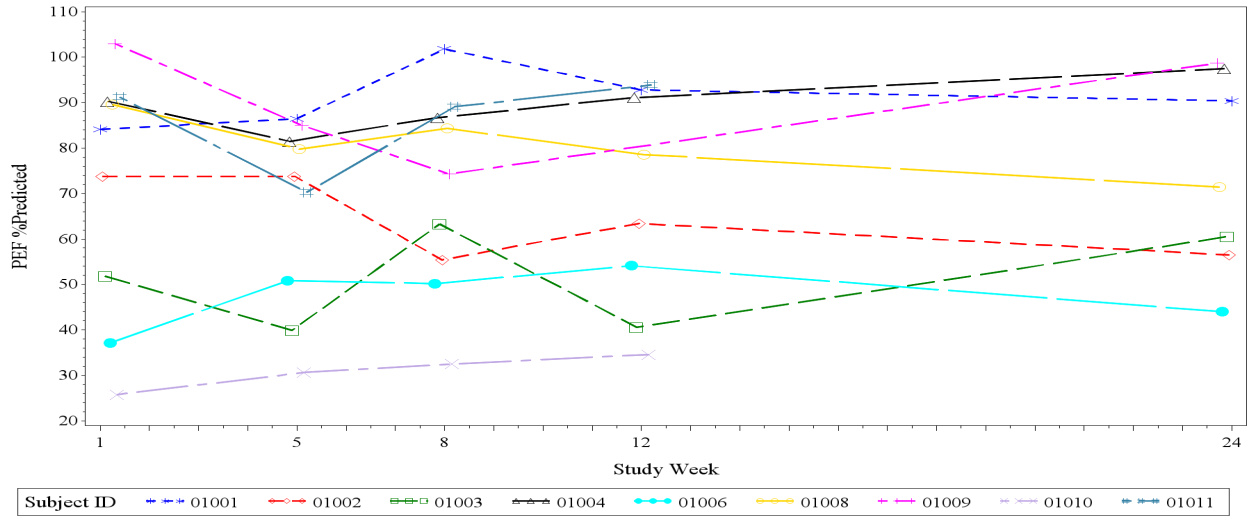


ATL1102 MCRI Phase II Study

Efficacy Parameters – Preliminary Data

Respiratory Function - % Predicted FVC, % Predicted PEF





Change from Baseline to Week 24		
Participant No.	**% Predicted FVC**	**% Predicted PEF**
01-001	-3.20	6.30
01-002	-14.8	-17.3
01-003	-9.10	8.70
01-004	0.80	7.20
01-006	-6.50	+6.90
01-008	-7.70	-18.2
10-009	-9.10	-4.30
01-010		
01-011		
Mean Change (95% CI)	-7.02 (-11.6,-2.53)	-1.53 (-12.5, 9.46)

ATL1102 MCRI Phase II Trial

Efficacy Parameters Overview – Preliminary Data

Comparison of ATL1102 Phase II study data with data in published literature

Description of Comparison	Published Data			ATL1102-DMD-CT02 Data		
	No. of Participants (n)	Mean Change at 6 Months	Variance	No. of Participants (n)	Mean Change at 6 Months	Variance
Total PUL2.0 Score - Change to Month 6 / Historical: Pane 2018*	90	-1.09	54.767	7	1.4	9.496
MYOGRIP - Change to Month 6 / Historical: Ricotti 2016	8	-0.5	0.361	7	0.3	0.407
MYOGRIP %pred - Change to Month 6 / Historical: Ricotti 2019*	29	-1.43	1.278	7	-0.7	5.505
MYOPINCH - Change to Month 6 / Historical: Ricotti 2016	9	-0.38	0.043	7	0	0.085
MYOPINCH %pred - Change to Month 6 / Historical: Ricotti 2019*	29	-1.12	2.488	7	-0.8	13.357
PEF%pred - Change to Month 6 / Historical: Ricotti 2019*	29	-2.4	26.822	7	-1.53	141.207
FVC%pred - Change to Month 6 / Historical: Ricotti 2019*	29	-2.74	7.050	7	-7.09	24.310

*In some cases 6 month historical results have been interpolated from 1 yr results

Ricotti et. al 2019 NeuroMuscular Disorders 29(4) 261-268 (results from Non-Ambulant cohort with 24 of 29 on CS)

Pane et. al 2018 PLoS One, 13(6) e0199223 (results from Non-Ambulant cohort with 52 of 90 patients on CS)

Ricotti et. al 2016 . PLoS One, 11(9) e0162542 (results from Non – Ambulant cohort of 8 patients all on CS)

ATL1102 MCRI Phase II Study

Summary of Safety and Efficacy Parameters - Preliminary Data

- ATL1102 appears to be generally safe and well tolerated in non-ambulant boys with DMD
  - No Serious Adverse Events (SAEs) have been reported
  - The DSMB, responsible for safety oversight of the study, have no safety concerns
  - To date the most commonly reported TEAEs were injection site erythema (8 participants), skin discolouration (7 participants), injection site pain (5 participants) and injection site bruising (4 participants)
- 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 preliminary data from the 7 participants recently completed dosing 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 preliminary data is also suggestive of an improvement in muscle function as assessed by the Performance of Upper Limb Test (PUL 2.0), where the majority of participants have demonstrated either improvements or no change in their PUL 2.0 scores from baseline after 24 weeks of dosing with ATL1102
- Promising preliminary results support continued development of ATL1102 for the treatment of DMD


QUESTIONS?