

Current progress and preliminary results with the systemic administration trial of AVI-4658, a novel Phosphorodiamidate Morpholino Oligomer (PMO) skipping dystrophin exon 51 in Duchenne muscular dystrophy (DMD).

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Update: Study completed; final clinical data currently being analyzed

Sponsor:



Principal Investigators: Professor F Muntoni, Institute of Child Health
at University College London, UK

Professor K Bushby, Royal Victoria Infirmary
Newcastle University, UK

Sub-Investigators: Dr S Cirak, Institute of Child Health, UCL, UK

Dr M Guglieri, Royal Victoria Infirmary, Newcastle, UK

Additional funding from:



- Study Design
 - Open-label, multiple dose, dose-ranging study
 - Route: IV infusion over 60 minutes, weekly for 12 weeks
 - Dose(s): 0.5 mg/kg, 1 mg/kg, 2 mg/kg, 4 mg/kg, 10 mg/kg and 20 mg/kg

- Study Population
 - Ambulatory DMD patients ≥ 5 and ≤ 15 years of age
 - Must have evidence of dystrophin defects consistent with DMD based on muscle biopsy analysis
 - Two sites in United Kingdom (Great Ormond Street Hospital in London and Royal Victoria Infirmary in Newcastle)

- Study Purpose
 - Determine the safety of the drug
 - Determine the dosage level that elicits an increase of at least 10% dystrophin-positive fibers (confirmed via immunofluorescent microscopy)
 - Determine dystrophin production by Western blot

AVI-4658 Study 28: Patient Drug Exposure

Cohort	Subject No.	Age	Genotype	GCS	ACEi	Doses Received	Cumulative Dose (mg)
1	101	10	Del 48-50	Y	N	12	186
1	102	9	Del 45-50	Y	Y	12	171
1	103	8	Del 49-50	Y	N	12	228
1	104	8	Del 48-50	Y	N	10 of 12	180
2	105	6	Del 45-50	Y	N	12	327
2	106	6	Del 48-50	Y	N	12	255
3	201	13	Del 49-50	Y	N	12	1,113
3	107	10	Del 49-50	Y	N	12	924
4	108	10	Del 48-50	N	N	11 of 12	2,797
4	202	10	Del 52	Y	N*	7*	862
4	206	10	Del 45-50	Y	N	12	1,349
5	109	6	Del 49-50	Y	N	12	3,181
5	203	13	Del 47-50	Y	Y	12	6,207
5	204	13	Del 49-50	Y	N	12	4,866
5	110	7	Del 48-50	Y	N	12	2,670
6	205	10	Del 49-50	Y	Y	12	10,788
6	111	10	Del 45-50	Y	N	12	7,600
6	112	7	Del 45-50	Y	N	12	6,218
6	207	10	Del 45-50	Y	N	11	6,790

219
Doses
Given

Subject declined biopsy

*Subject discontinued treatment, started on ACEi but remained under observation in study

AE	Number	(%)
URTI	8	42
Headache	8	42
Back pain	7	37
Rhinitis	7	37
Fall	5	26
Myalgia	4	21
Tachycardia	3	16
Abdominal pain	3	16
Nausea	3	16
Vomiting	3	16
Arthralgia	3	16
Influenza like illness	3	16
Dizziness	3	16
Fatigue	2	11
Upper abdominal pain	2	11
Disease progression	2	11
Vessel puncture site bruise	2	11
Bronchitis	2	11
Viral infection	2	11
Lumbar vertebral fracture	2	11
Procedural pain	2	11
Pain in extremity	2	11
Cough	2	11
Haematoma	2	11

Generally Well Tolerated

- No Drug Related SAEs
- AEs not dose dependent or drug related at doses studied

2 SAEs reported:

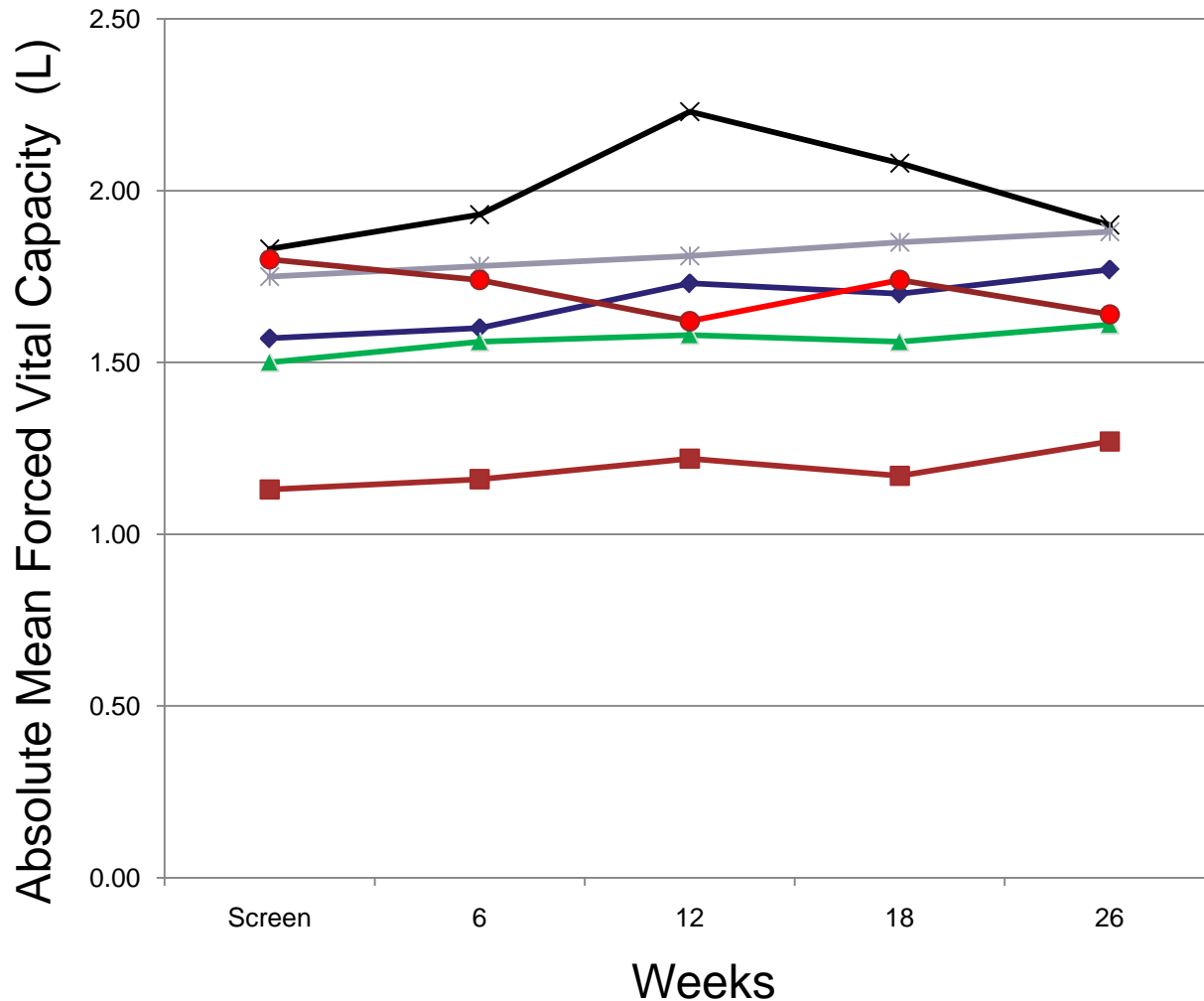
Both unrelated to drug in 14 week follow-up:

- 1 post-operative nausea and vomiting
- 1 ankle fracture

1 Withdrawn from Rx:

•Subject detection of asymptomatic deteriorating cardiomyopathy* after 7 weeks of Rx (elevated troponin). Sinus tachycardia noted on dosing visits from first dose onward. Cardiomyopathy noted in ~6m before study.

*3 other patients reported cardiomyopathy at baseline (and receiving ACEi);
4 other patients recorded high troponin during study and 1 at baseline

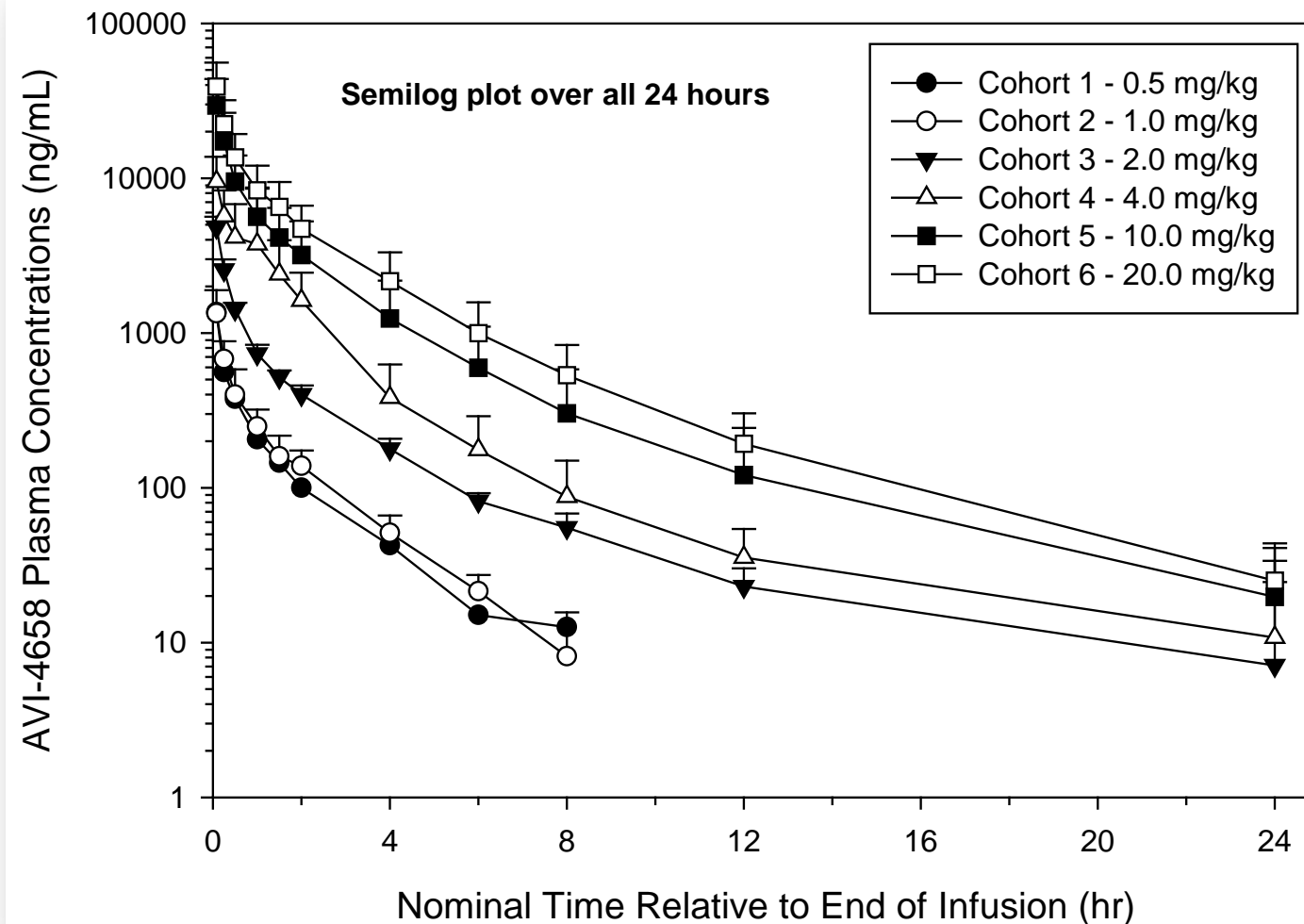


Pulmonary Function Tests

- FEV₁ and FVC stable all cohorts throughout 26 wk observation period
- No adverse effect noted

- ◆ Cohort 1 (0.5mg/kg)
- Cohort 2 (1.0mg/kg)
- ▲ Cohort 3 (2.0mg/kg)
- ✕ Cohort 4 (4.0mg/kg)
- ✱ Cohort 5 (10.0mg/kg)
- Cohort 6 (20.0mg/kg)

Mean (SD) Concentrations of AVI-4658 versus Nominal Elapsed Time Averaged Across Weeks 1, 6, 12



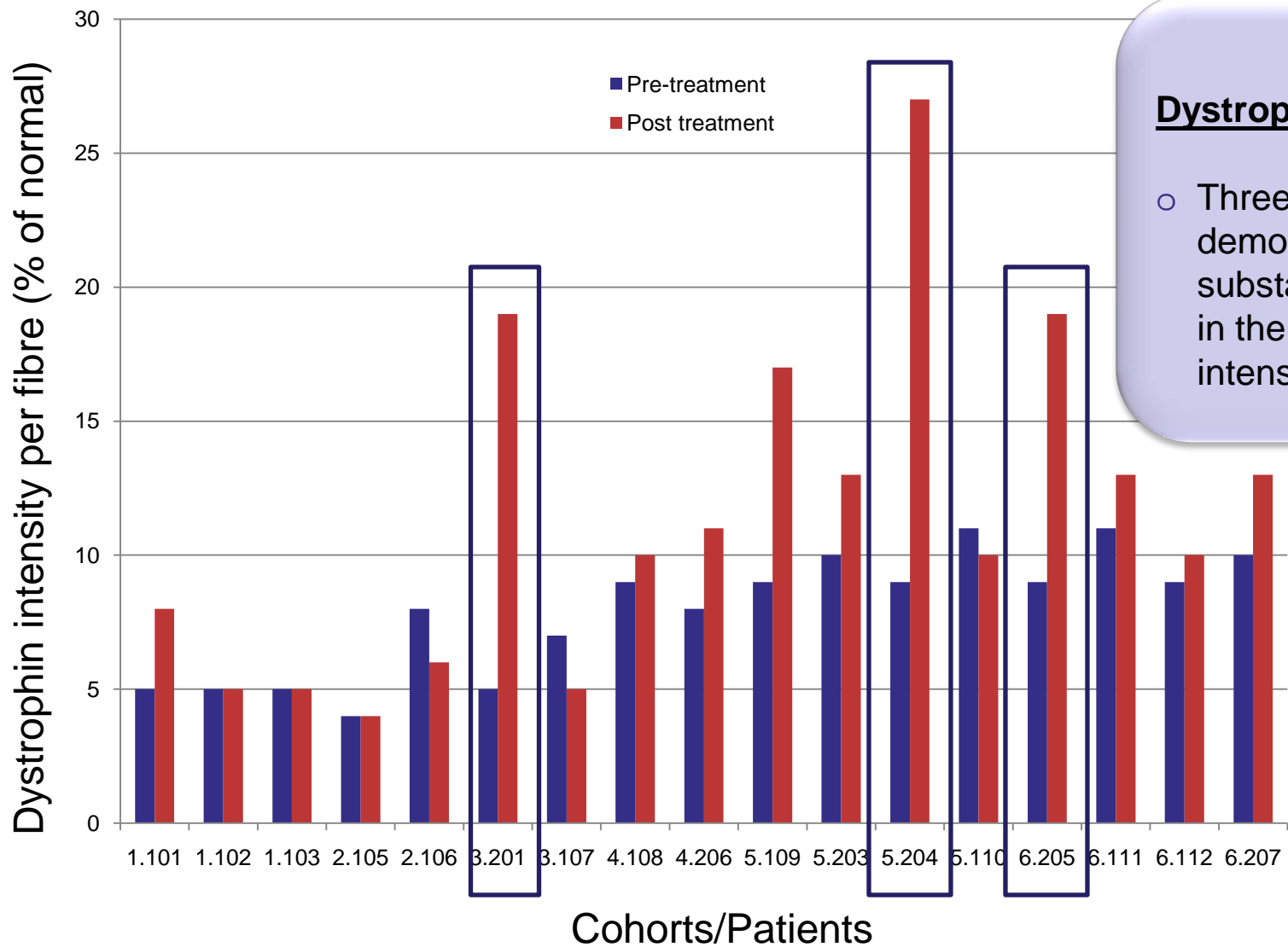
Dystrophin Positive Fibers (% of Normal)

Cohort	Subject	Pre (%)	Post (%)
1	101	1	1
1	102	3	0
1	103	1	7
2	105	0	0
2	106	5	1
3	201	1	21
3	107	1	5
4	108	5	4
4	206	1	1
5	109	3	6
5	203	0	7
5	204	1	15
5	110	2	6
6	205	3	55
6	111	3	5
6	112	3	8
6	207	5	7

Note: Patient 104 (Cohort 1) declined post-treatment biopsy and is not listed above.
Patient 202 (Cohort 4) withdrew from treatment after 7 doses and is not listed above.

Dystrophin response

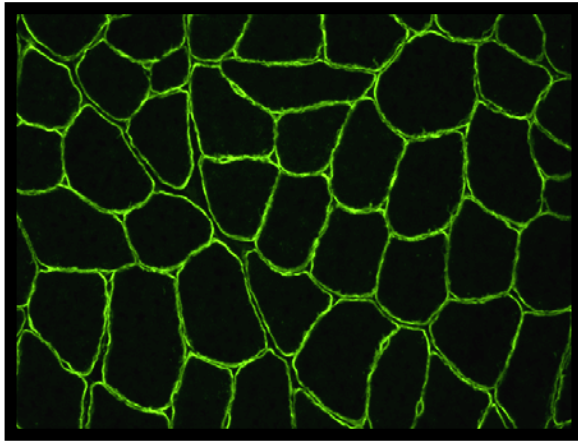
- All patients in the 10 & 20 mg/kg cohorts (Cohorts 5 and 6) demonstrated generation of new dystrophin-positive muscle fibers
- Three patients demonstrated substantial ($\geq 10\%$ increase) generation of new dystrophin-positive muscle fibers



Dystrophin response

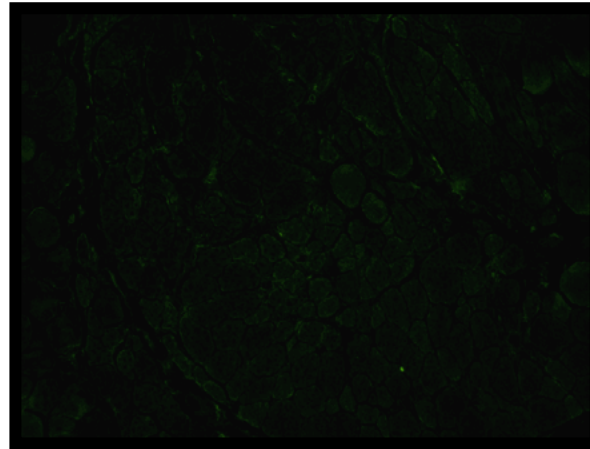
- Three patients demonstrated substantial increases in the dystrophin intensity/fibre

Normal Subject



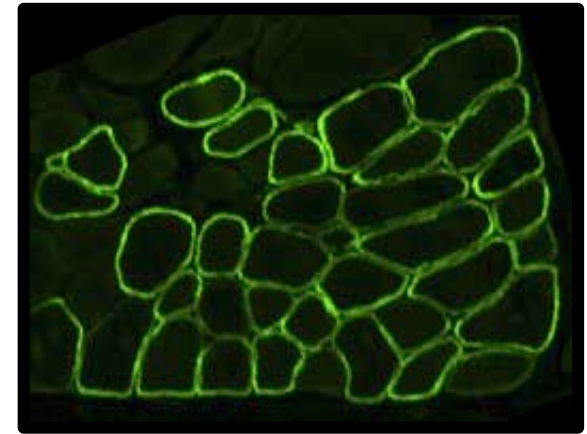
- Mandys 106 Antibody stain = nominal 100%

Pre-treatment



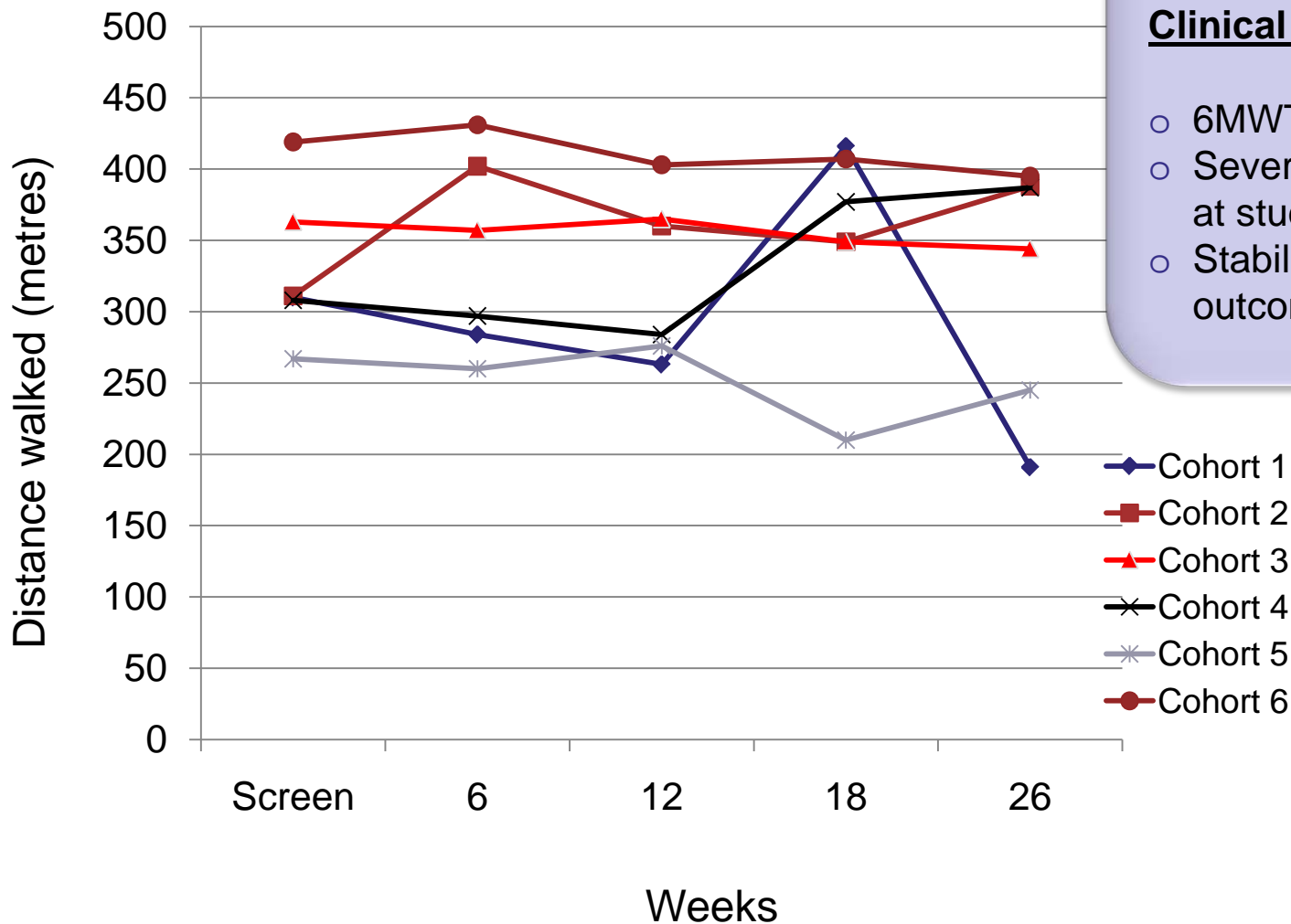
- Subject 205 before study, dystrophin positive fibres, revertants ~3%

Post-treatment



- Subject 205 after 12 weekly infusions of AVI-4658 at 20 mg/kg, increase in dystrophin positive fibres to ~55%
- Cumulative dose 10,788mg

Increase in dystrophin protein detected by immunofluorescence at 20 mg/kg



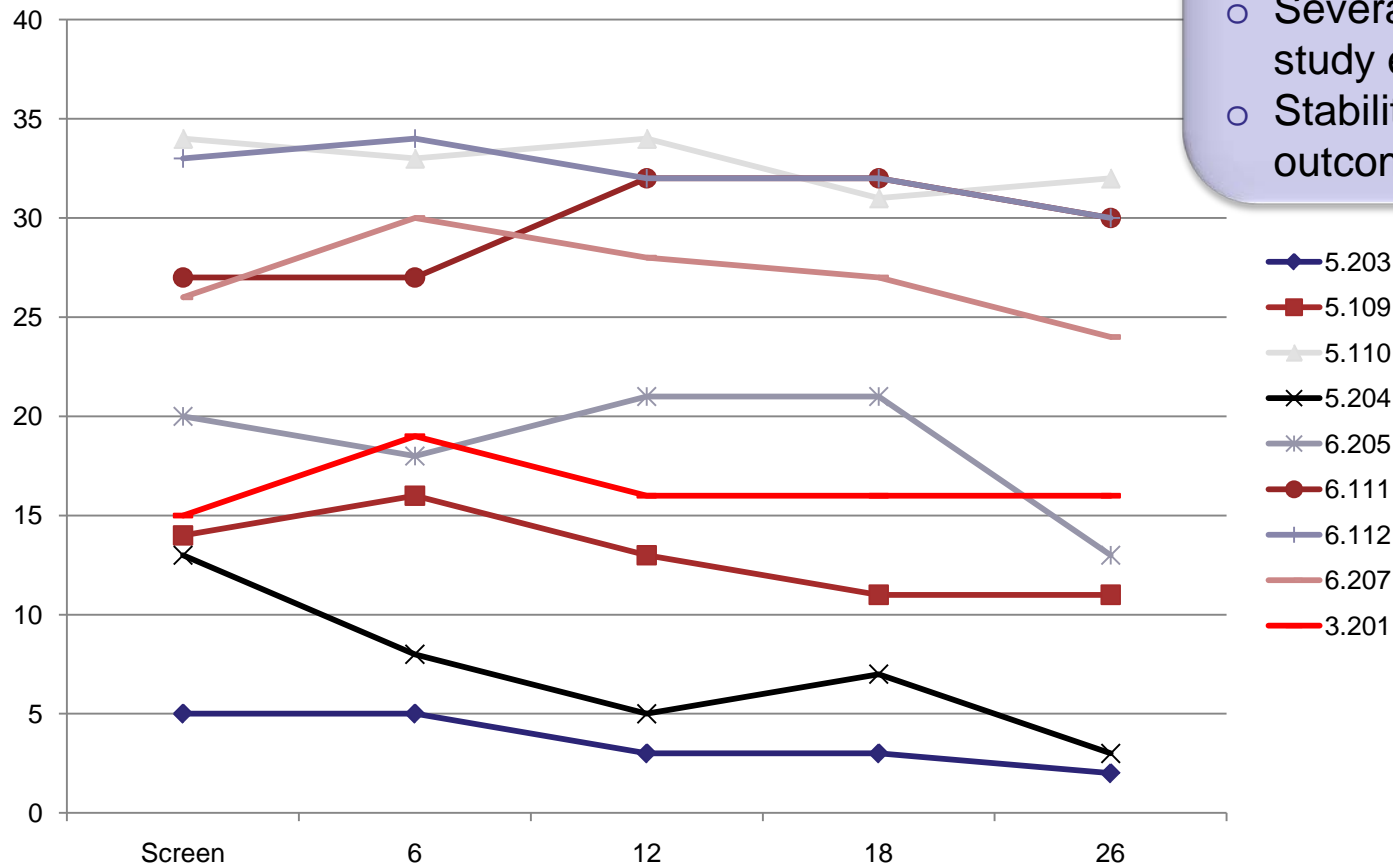
Clinical response

- 6MWT stable over 26wk
- Several barely ambulant at study entry
- Stability may be a good outcome

Individual results – Cohorts 5 (n=4) and 6 (n=4)
(at 10 and 20 mg/kg), and Subject 201 (2mg/kg)

Clinical response

- 6NSAA stable over 26wk
- Several barely ambulant at study entry
- Stability may be a good outcome



- AVI-4658 well tolerated - all 219 doses (up to 20mg/kg)
- AEs generally mild (63%) or moderate (32%), transient and unrelated (26%) or only possibly related (74%) to study drug.
- No adverse, clinically significant laboratory changes; No DRSAEs.
- Plasma PK – behaves as “small molecule”
 - Rapid renal clearance (up to ~60% 24hrs); short half life (1.6-3.6hrs)
- Dystrophin-positive muscle fibers >50% of normal in a DMD patient
 - All patients in the 10 & 20 mg/kg cohorts demonstrated generation of new dystrophin-positive muscle fibers
 - Three patients demonstrated substantial generation of new dystrophin-positive muscle fibers (1 each at 2.0, 10.0 and 20.0mg/kg)
- Clinical muscle function measures generally stable over 26 wks
- Current toxicology program supports human dosing up to 100 mg/kg