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# Systemic administration of AVI-4658 a Phosphorodiamidate Morpholino Oligomer (PMO) restores dystrophin expression in selected Duchenne Muscular Dystrophy (DMD) boys in a dose dependent manner

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XII International Congress of
Neuromuscular Diseases
Naples, Italy


## Francesco Muntoni

Dubowitz Neuromuscular Centre
UCL Institute of Child Health
London, UK


Newcastle University

MRC Medical Research Council
Centre for Neuromuscular Diseases

# Francesco Muntoni: disclosures

- Full time academic position since 1993:
  Current position: Professor of Paediatric Neurology at University College London

- PI and Sponsor of a phase I/IIa clinical trial using IM exon 51 AVI antisense PMO in DMD (2005-2008)
- PI and AVI collaborator of a phase I/IIa trial of systemic exon 51 antisense PMO in DMD (2009-2010)

- One of the UK sites for the PTC124 clinical trial in DMD (2008-2010)
- One of the UK sites for the GSK/ Prosensa DMD114117 (2OME exon 51 antisense)

- Ad hoc consultant for AVI-Biopharma (SAB for AVI-4658 development) and for Genzyme (Ataluren)

# Background

- ~ 70% of DMD boys have out of frame deletions
- Antisense oligonucleotides (AO) induce exon skipping and restore the reading frame in DMD boys with eligible deletions
- Skipping of particular exons corrects a series of different mutations
- Skipping exon 51 → corrects ~13% of all DMD boys
- Skipping 9 other exons → corrects › 70% of DMD boys

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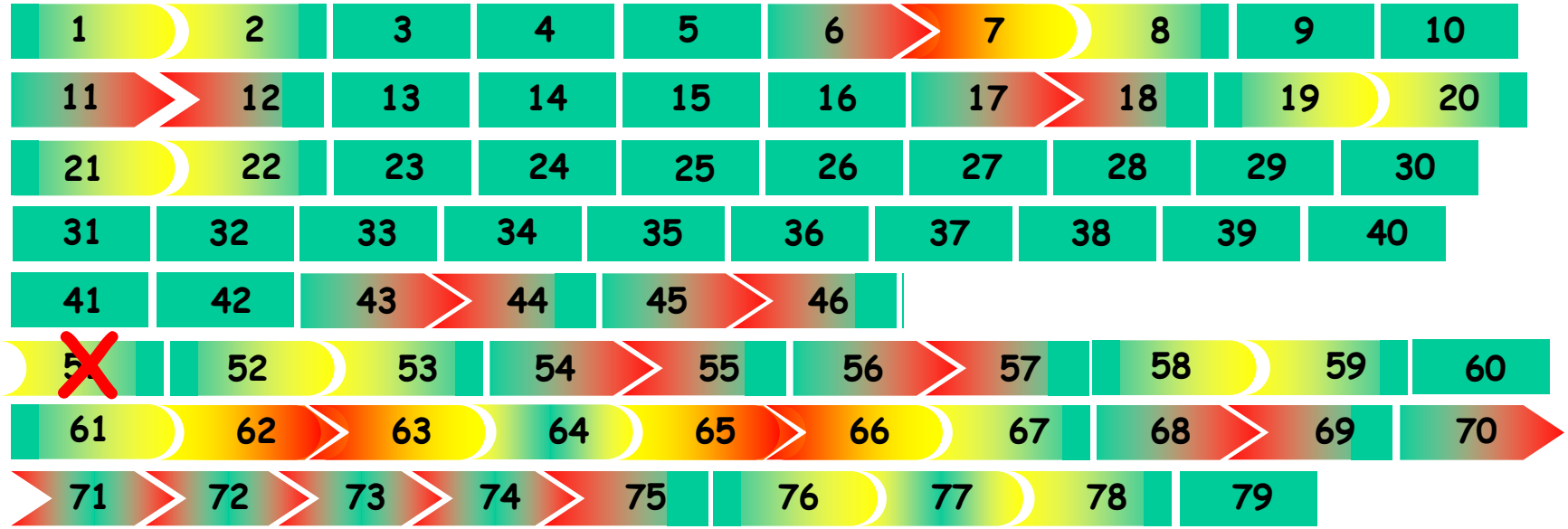
# Dystrophin Exon Boundaries



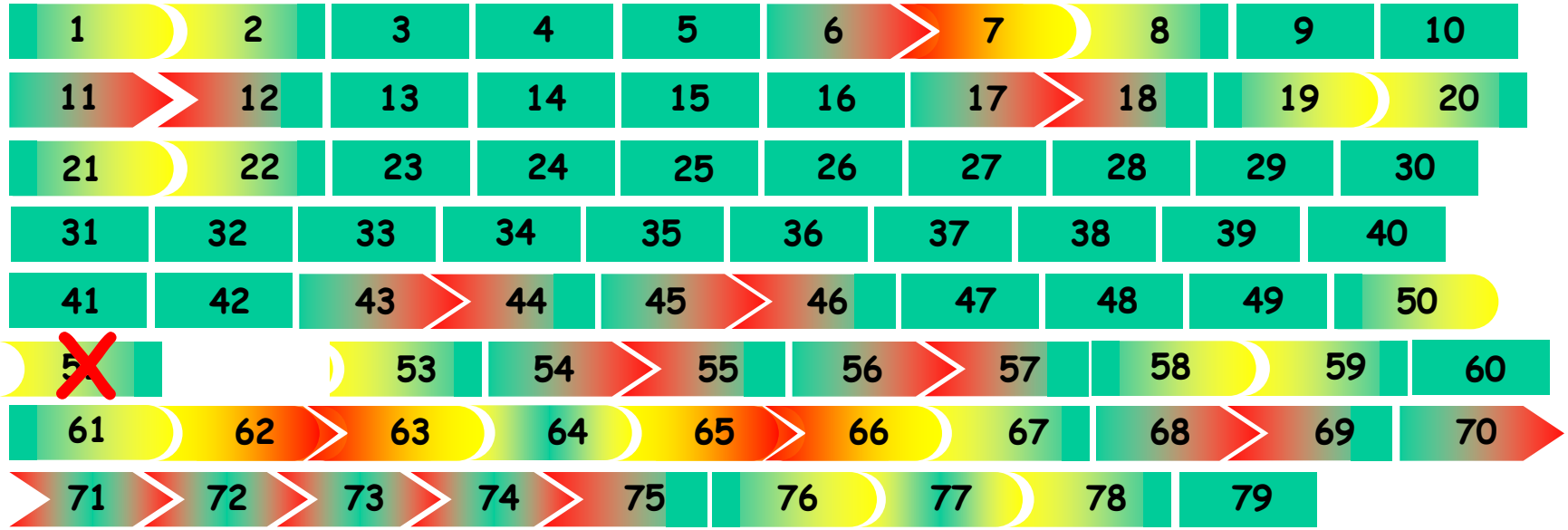

= 123 / 123 Codon Boundary

= 1 / 23 Codon Boundary

= 12 / 3 Codon Boundary

Courtesy of Steve Wilton

# Dystrophin Exon Boundaries



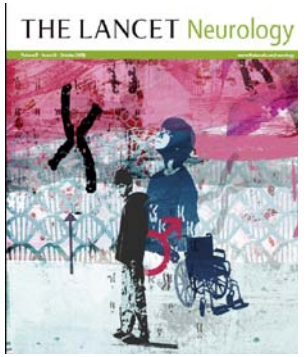

= 123 / 123 Codon Boundary

= 1 / 23 Codon Boundary

= 12 / 3 Codon Boundary

Courtesy of Steve Wilton

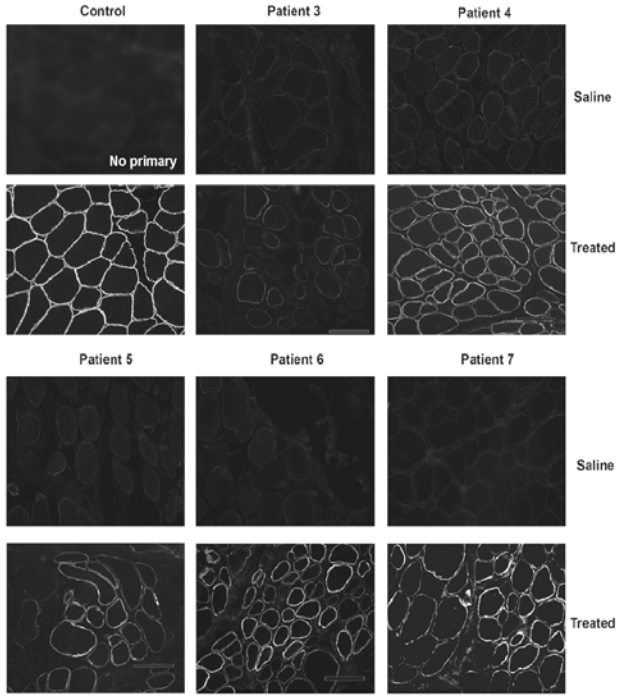
# Background: AVI-4658 morpholino AO exon 51 IM trial




Dose escalation study, 2 groups (0.09mg; 0.9 mg)

- 7 patients, age 10-17
- EDB muscle injection (one saline, one AO)
- Bilateral muscle biopsy after 3 weeks

*Trial started December 07; completed December 2008*




Local restoration of dystrophin expression with the morpholino oligomer AVI-4658 in Duchenne muscular dystrophy: a single-blind, placebo-controlled, dose-escalation, proof-of-concept study

Maria Kinali*, Virginia Arechavala-Gomeza*, Lucy Feng, Sebahattin Cirak, David Hunt, Carl Adkin, Michela Guglieri, Emma Ashton, Stephen Abbs, Petros Nihoyannopoulos, Maria Elena Garralda, Mary Rutherford, Caroline Mcculley, Linda Popplewell, Ian R Graham, George Dickson, Matthew J A Wood, Dominic J Wells, Steve D Wilton, Ryszard Kole, Volker Straub, Kate Bushby, Caroline Sewry, Jennifer E Morgan, Francesco Muntoni

| | Untreated | | Treated | |
|---|---|---|---|---|
| | Total | Positive | Total | Positive |
| 3 | 443 | 21 (5%) | 377 | 182 (49%) |
| 4 | 662 | 2 (<1%) | 792 | 623 (79%) |
| 5 | 475 | 2 (<1%) | 263 | 116 (44%) |
| 6 | 554 | 5 (1%) | 404 | 264 (65%) |
| 7 | 405 | 3 (<1%) | 262 | 164 (63%) |

# Method

Systemic Administration trial of AVI-4658; a Novel Phosphorodiamidate Morpholino Oligomer (PMO) skipping exon 51 in Duchenne muscular dystrophy

# Method
# AVI-4658-28: Trial Design

- 6 Cohorts Dose Escalation
  - 0.5, 1.0, 2.0, 4.0, 10.0 and 20.0 mg/kg
  - 1 h intravenous infusion
  - Weekly x 12 weeks
  - Open-label, no randomization
- Follow-up
  - First review and post Rx Biopsy at 14 wks (2 weeks after last dose)
  - Further F/U at weeks 18, 22 and 26

# AVI-4658-28: Trial Design

**Patient eligibility:**

a. deletions that can benefit from skipping exon 51 [45-50; 47-50; 48-50; 49-50; 50; 52; 52-63]
b. Age 5-15
c. Ambulant
d. < than 5% revertrant fibres on muscle biopsy

**Primary outcomes**:

a. safety and tolerability;

**Secondary outcomes:**

a. pharmacokinetic (urine/ blood)
b. molecular efficacy (skipping; dystrophin on muscle biopsy)
c. clinical function, strength and endurance (myometry/ North Star functional scale/ timed tests/ 6MinWalk/Activity monitors/ FVC)

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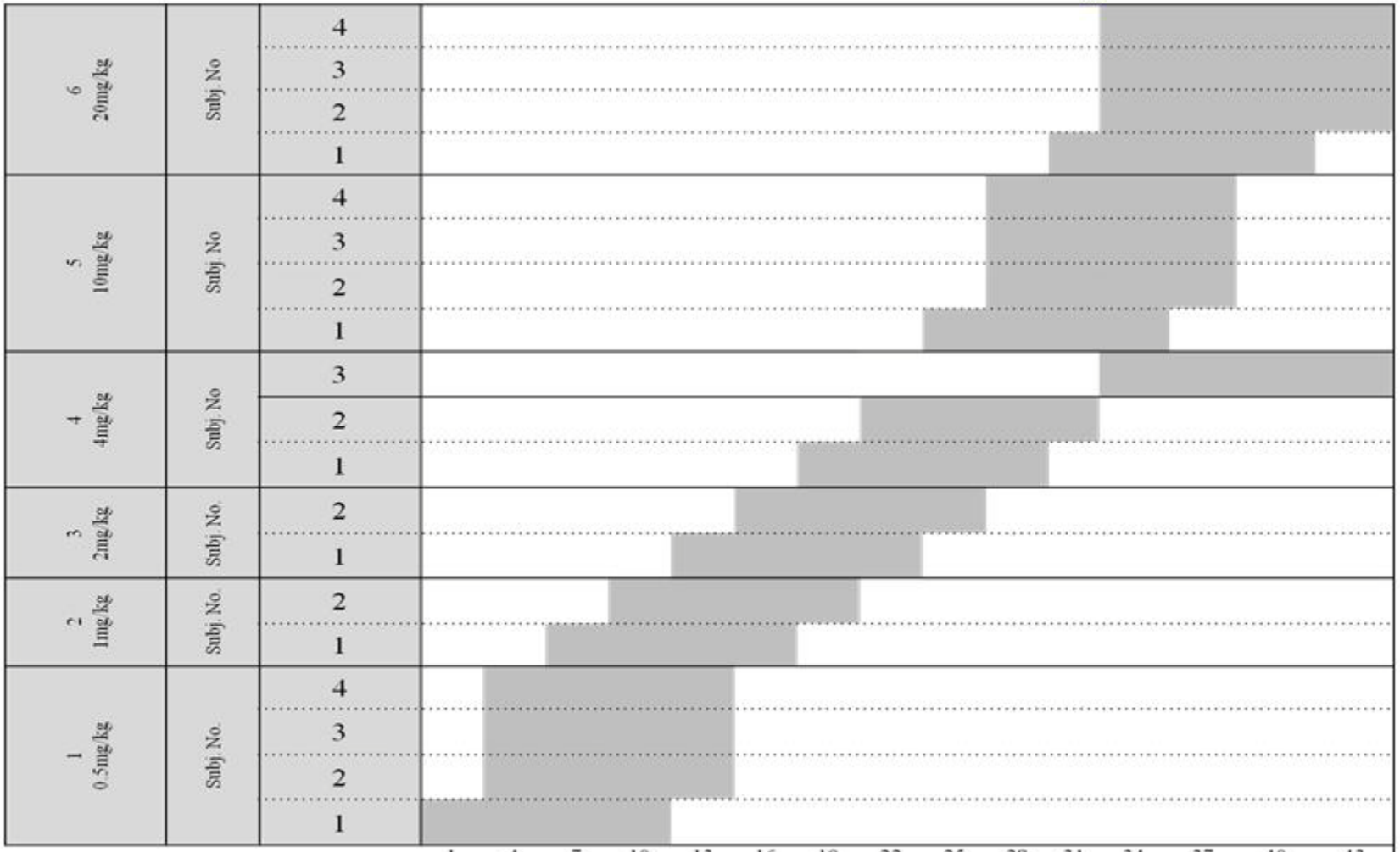
# AVI-4658-28: Trial Design




DSMB reviews ↑ ↑ ↑ ↑ ↑ ↑

03.10

# Results: safety

- AVI-4658 well tolerated by IV administration
- No adverse safety signal
- Maximum single dose of 900mg and maximum cumulative dose of 10,813mg
- 2 drug unrelated SAE
  - -1 leg fracture
  - -1 post operative nausea and vomiting

In addition -1 patient in cohort 4 with worsening disease-related cardiomyopathy, withdrawn from treatment after 7 doses (stabilised on ACEi/β-blocker)

# Results: Patient demographics, genotypes and cumulative exposure to AVI-4658

| Coh r't | Subject No. | Age | Genotype | GCS | ACEi | Doses received | Cumulative dose (mg) |
|---|---|---|---|---|---|---|---|
| 1 | 101 | 10 | Del 48-50 | Y | Y | 12 | 186 |
| 1 | 102 | 9 | Del 45-50 | Y | N | 12 | 171 |
| 1 | 103 | 8 | Del 49-50 | Y | N | 12 | 218 |
| 1 | 104 | 8 | Del 48-50 | Y | N | 10 of 12 | 180 |
| 2 | 105 | 6 | Del 45-50 | Y | N | 12 | 326 |
| 2 | 106 | 6 | Del 48-50 | Y | N | 12 | 255 |
| 3 | 201 | 13 | Del 49-50 | Y | N | 12 | 1113 |
| 3 | 107 | 10 | Del 49-50 | Y | N | 12 | 924 |
| 4 | 108 | 10 | Del 48-50 | Y | N | 11 of 12 | 2801 |
| 4 | 202 | 10 | Del 52 | Y | N* | 7* | 864 |
| 4 | 206 | 10 | Del 45-50 | Y | N | 12 | 1342 |
| 5 | 109 | 6 | Del 49-50 | Y | N | 12 | 3036 |
| 5 | 203 | 13 | Del 47-50 | Y | N | 12 | 6207 |
| 5 | 204 | 13 | Del 49-50 | Y | N | 12 | 4866 |
| 5 | 110 | 7 | Del 48-50 | Y | N | 12 | 2664 |
| 6 | 205 | 10 | Del 49-50 | Y | Y | 12 | 10813 |
| 6 | 111 | 10 | Del 45-50 | Y | N | 12 | 6982 |
| 6 | 112 | 7 | Del 45-50 | Y | N | 12 | 5673 |
| 6 | 207 | 10 | Del 45-50 | Y | N | 12 | 6710 |

220 doses administered

Difficulties with IV cannulation

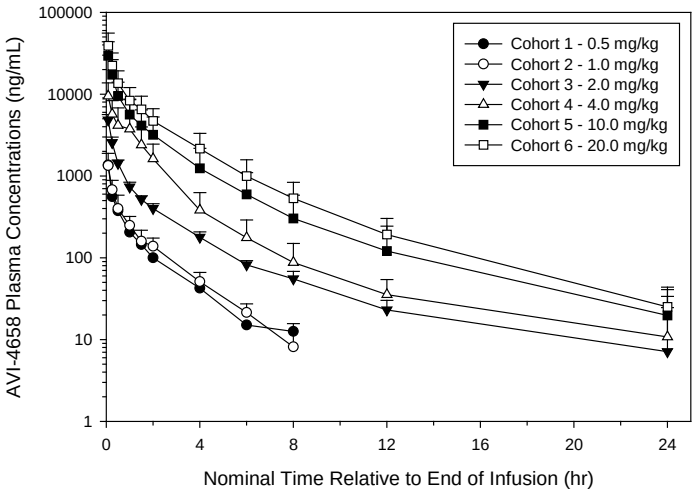
*Withdrawn from study, progressive DCM

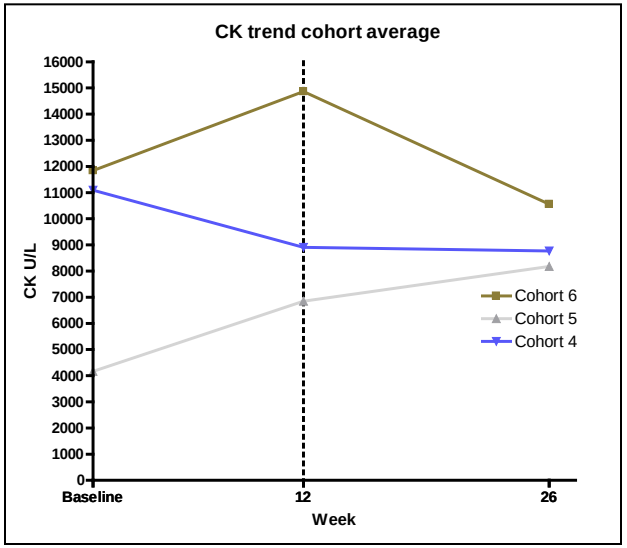
# Results: safety and PK

| Description of Adverse Event* | No. Subjects | No. Events |
|---|---|---|
| Headache | 8 | 14 |
| Rhinitis | 4 | 5 |
| URTI/viral | 6 | 8 |
| Abdominal pain | 3 | 6 |
| Hordeleum/Skin infection (tinea) | 1 | 2 |
| Osteopenia | 1 | 1 |
| Backache | 1 | 1 |
| Sunstroke | 1 | 1 |
| Insect bite/Sting | 2 | 2 |
| Muscle pain | 4 | 5 |
| Deteriorating cardiomyopathy** | 1 | 1 |
| Fatigue | 3 | 3 |
| Painful joint | 1 | 1 |
| Nausea/Vomiting | 3 | 3 |
| Fever | 2 | 2 |
| Dizziness | 2 | 2 |
| Pallor | 1 | 1 |
| Bruise | 3 | 5 |

*At last safety meeting (Cohort 6 expansion): 23 November 2009

* *Previously, Subject 202 had several episodes of sinus tachycardia reported as AEs. A reassessment of pre-trial Echos has revealed evidence of cardiomyopathy in 2008. (not an exclusion criterion for this study) Fluctuation and elevation of cardiac troponin and decrease ejection fractional fractional shortening on Echo were new events.



# Biochemical efficacy

All muscle biopsies perfectly preserved; no technical issues regarding the biochemical outcome measures

Exon skipping and dystrophin protein expression indicates a **clear dose response** with:

**i.** Minimal skipping but no detectable protein expression in cohorts 1 and 2

**ii.** Skipping and no detectable protein expression in patients in cohort 3 and 4, with the exception of one strong responder in cohort 3

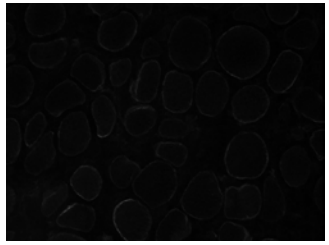
**iii.** Strong skipping in all boys in the 5th and 6th cohorts, **with clear protein expression** in 3/4 patients in cohort 5 and 3/4 patients in cohort 6.
In two of these 6 patients (one in each cohort) protein expression was considerably higher than the other patients

# Biochemical efficacy

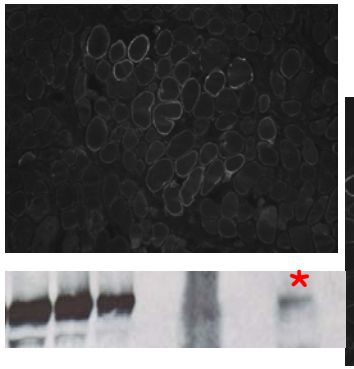
| | Skip | Immuno | Western |
|---|---|---|---|
| Cohort 1 : | ± | - | - |
| Cohort 2: | ± | - | - |
| Cohort 3: | + | + | + |
| Cohort 4 | + | - | - |
| Cohort 5 | + | + | + |
| Cohort 6 | + | + | + |

# Range of responses in dystrophin expression observed in AVI-4658 study 28

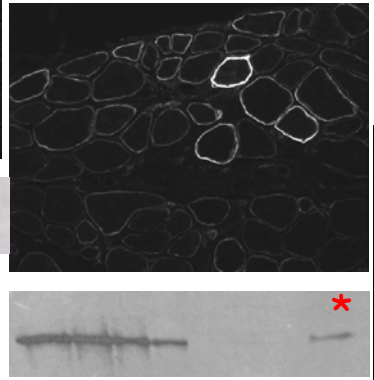
Untreated DMD



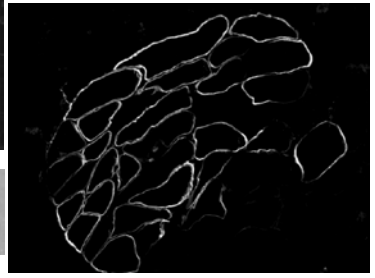
AVI-4658 treated
DMD case 109
10mg/kg
6% +ve fibres
17% intensity



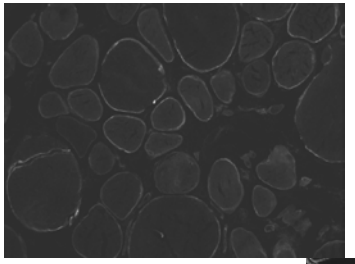
AVI-4658 treated
DMD case 204
10mg/kg
15% +ve fibres
27% intensity



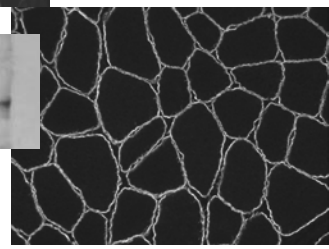
AVI-4658 treated
DMD case 201
2mg/kg
21% +ve fibres
19% intensity



AVI-4658 treated
DMD case 205
20mg/kg
55% +ve fibres
19% intensity

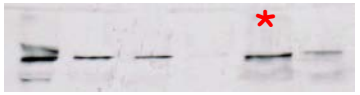


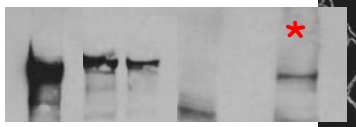
Control muscle











# Conclusion

AVI-4658 well tolerated by repeated IV administration up to doses of 20/mg/kg

Full clinical data 3Q2010

The level of dystrophin observed in the three patients with the highest response may be sufficient to enable muscle protection

Extension study and pivotal RCT study planned

# Acknowledgements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| | | |
|---|---|---|
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