Leids Universitair
Medisch Centrum

Translational research: what, why, how and with whom??

Annemieke Aartsma-Rus

March 2018

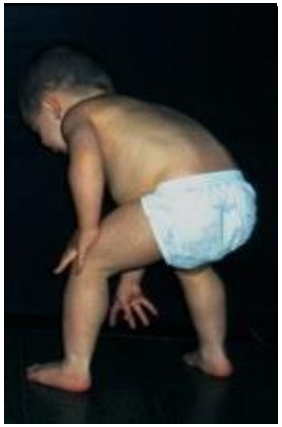
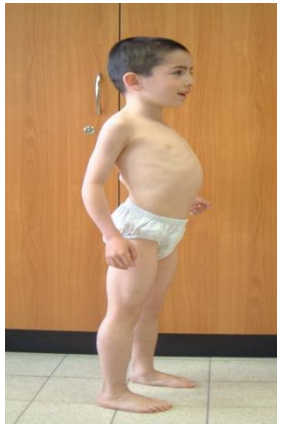
PARIS

Outline talk

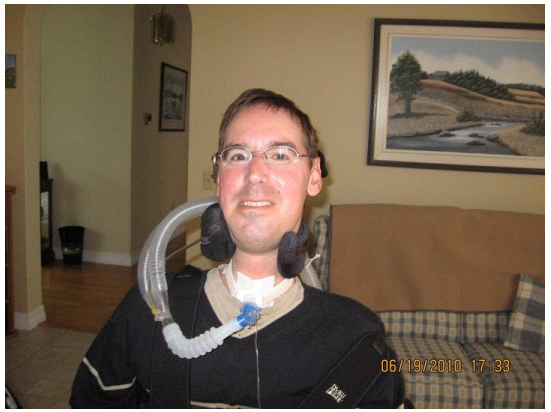
Use therapy development for DMD as a showcase

- Patient community involvement
- The need for timely tool development
- The importance of involving all stakeholders
- The importance of good communiciation
- Bilateral education → trilateral education
- Can we learn from our mistakes?

Duchenne Muscular Dystrophy



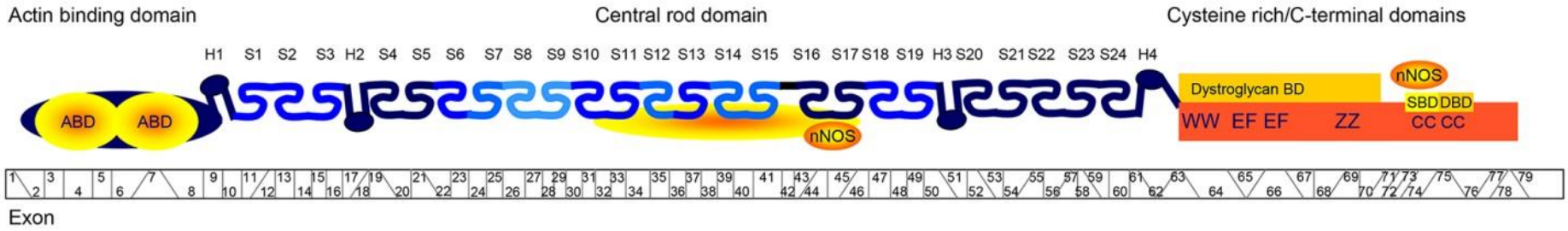
Steps towards a marketed drugs

- Fundamental research
- Proof-of-concept studies
- Pre-clinical studies
- Clinical trials
- Marketing authorization (regulators, EMA)
- Health insurance/implementation
- Post marketing studies (MEB)

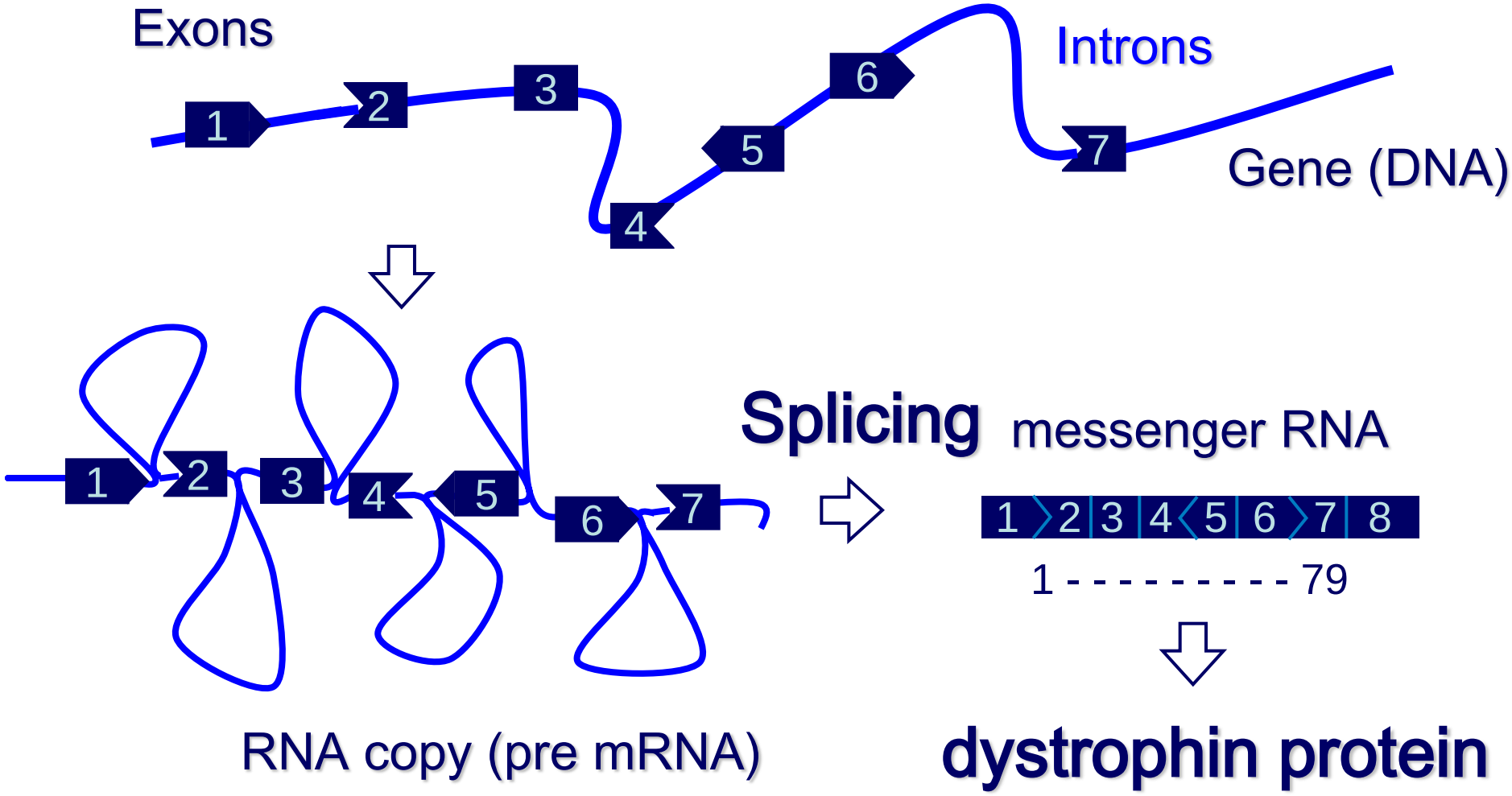
Duchenne Muscular Dystrophy

Step 1: Fundamental research ($$)

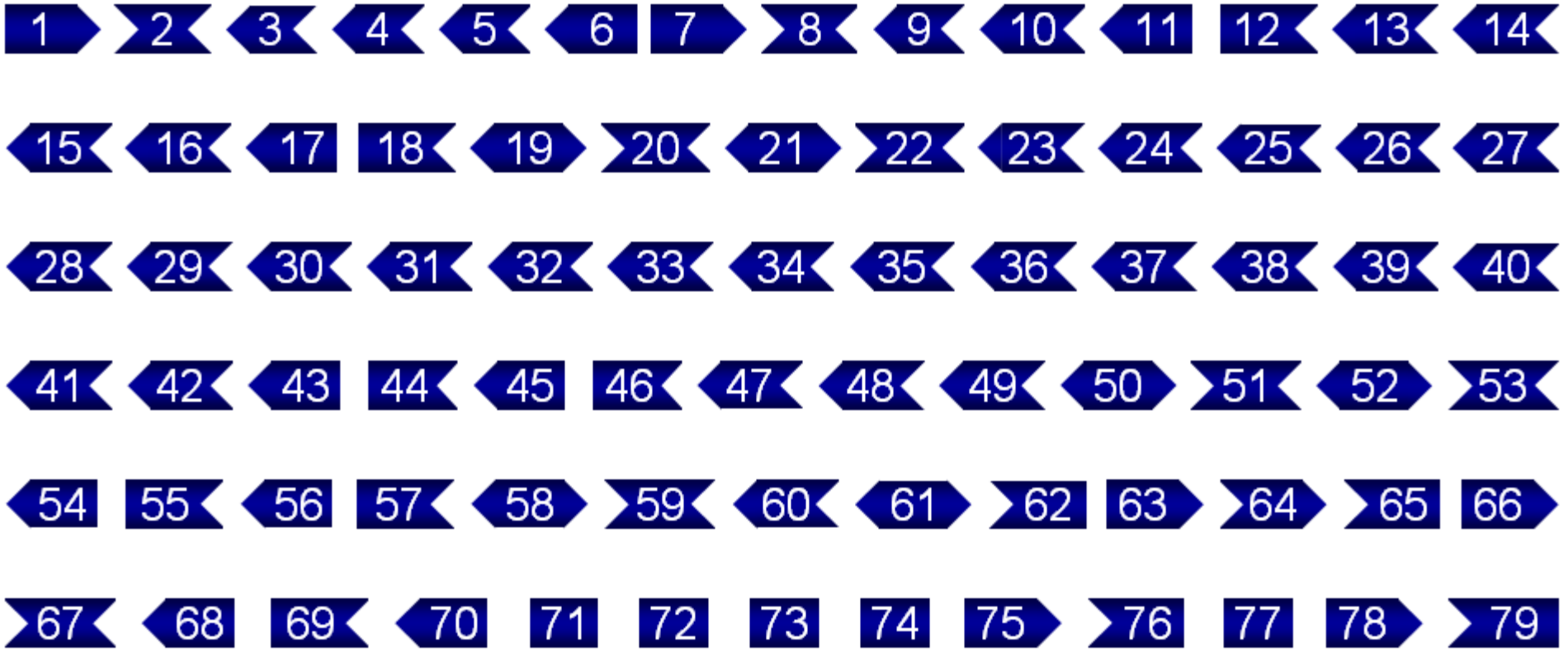
- DMD patients lack dystrophin protein
- BMD patients have altered dystrophins
- Acts as shock absorber
- Connects muscle cytoskeleton to connective tissue
- Functional domains located at beginning and end



Splicing


Exons
1
2
3
4
5
6
7
Introns
Gene (DNA)
Splicing
messenger RNA
1 2 3 4 5 6 7 8
1 - - - - - - - - - 79
RNA copy (pre mRNA)
dystrophin protein

Dystrophin exons



Exon 48-50 deletion

Disrupted reading frame

↓

Protein translation truncated prematurely

↓

Dystrophin not functional

Becker: reading frame maintained

Reading frame not disrupted

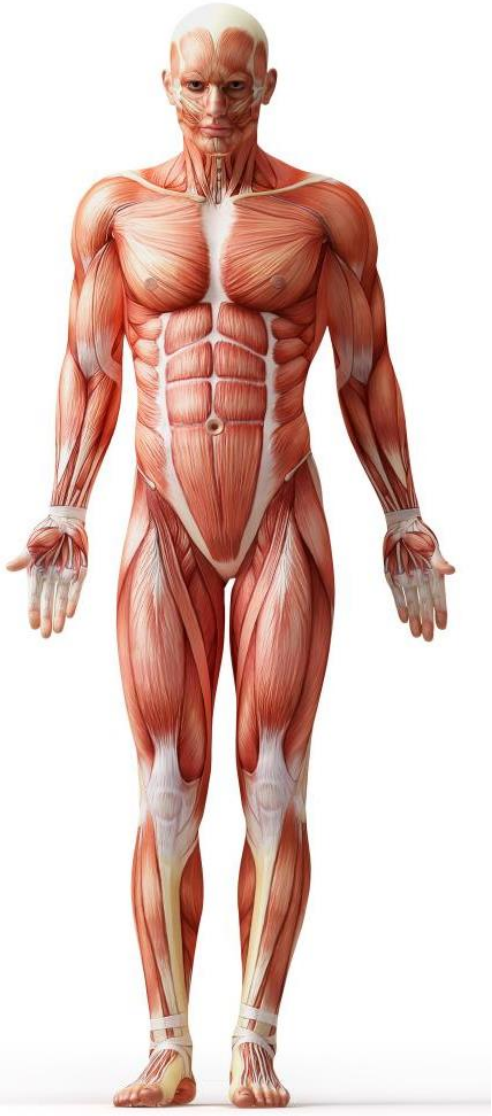
↓

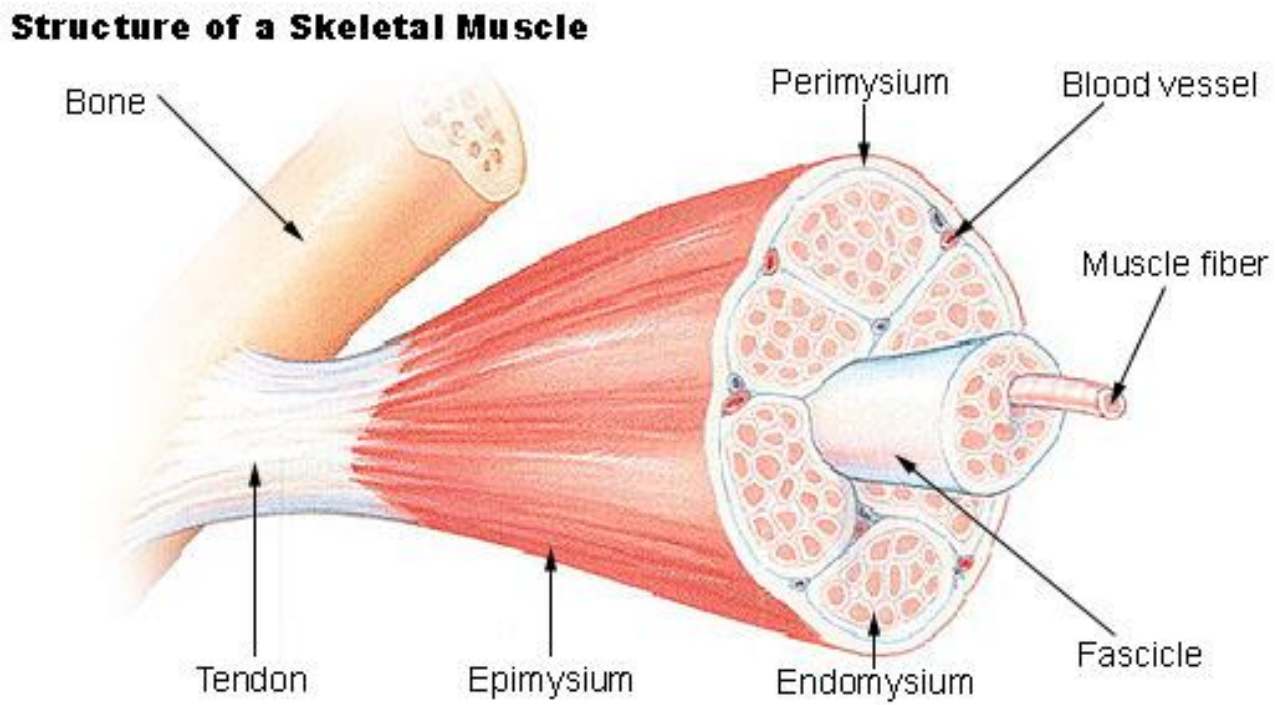
Protein translation continues

↓

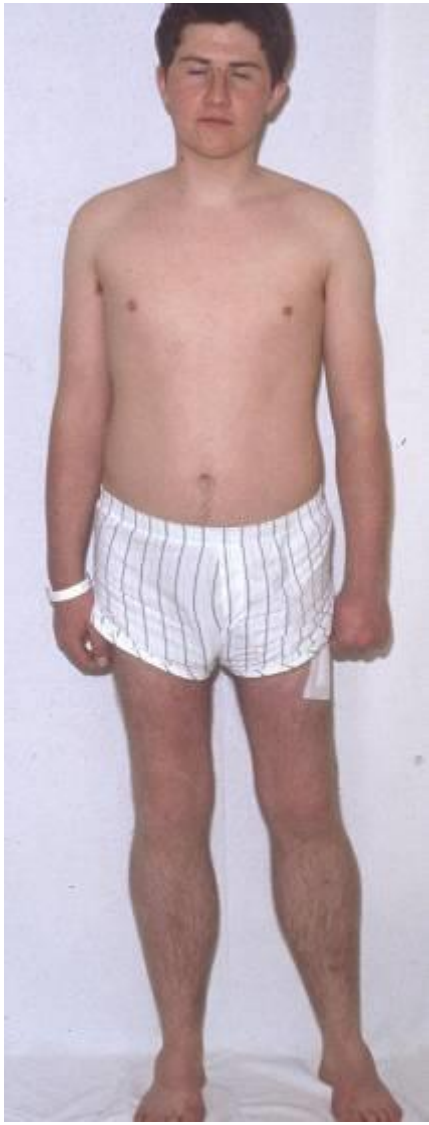
Dystrophin partly functional

Challenges for DMD therapy





Duchenne vs Becker



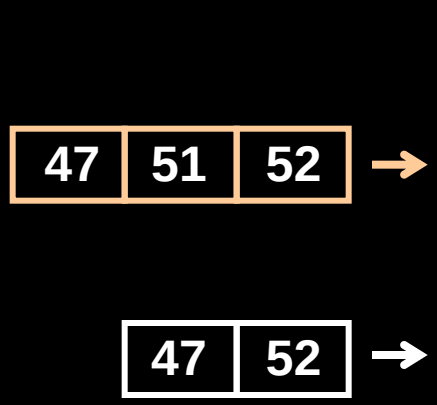
Exon skipping to restore reading frame

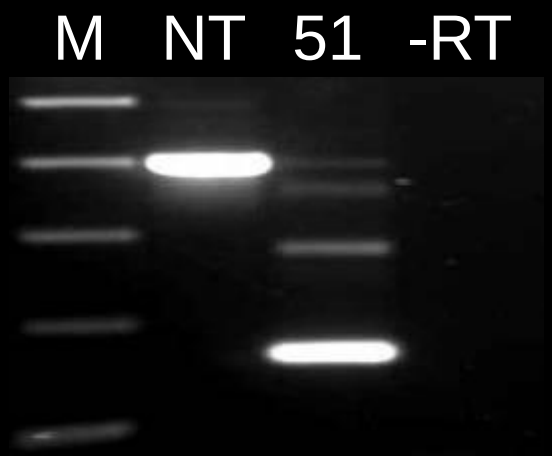
Reading frame restored

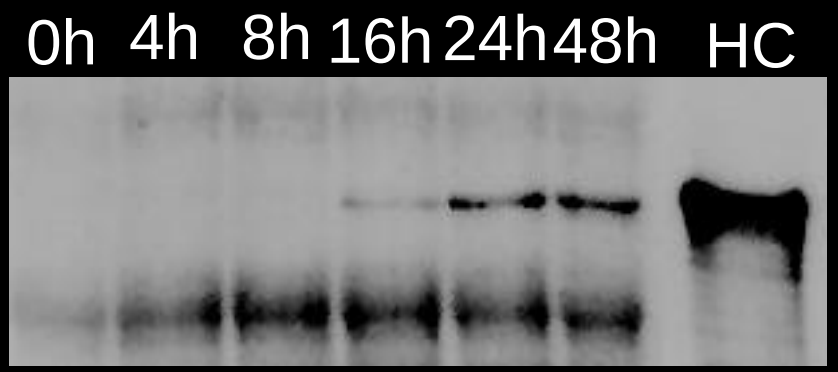
Partially functional dystrophin

Idea → Experiments $$$

Step 1: DMD cells start making dystrophin

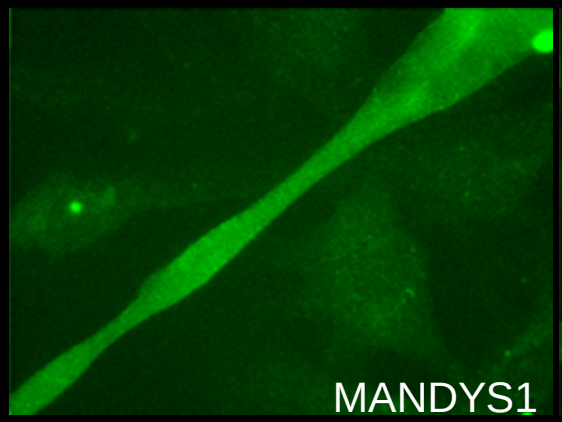


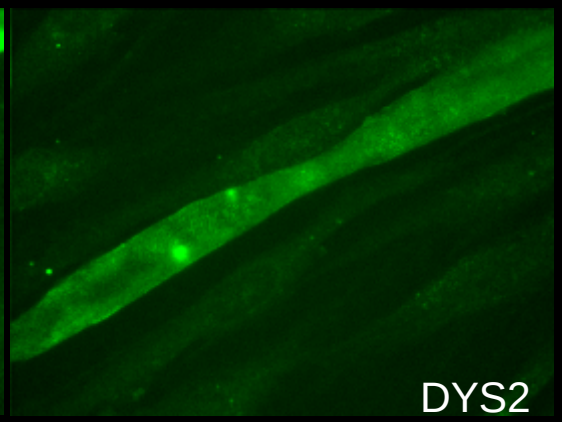




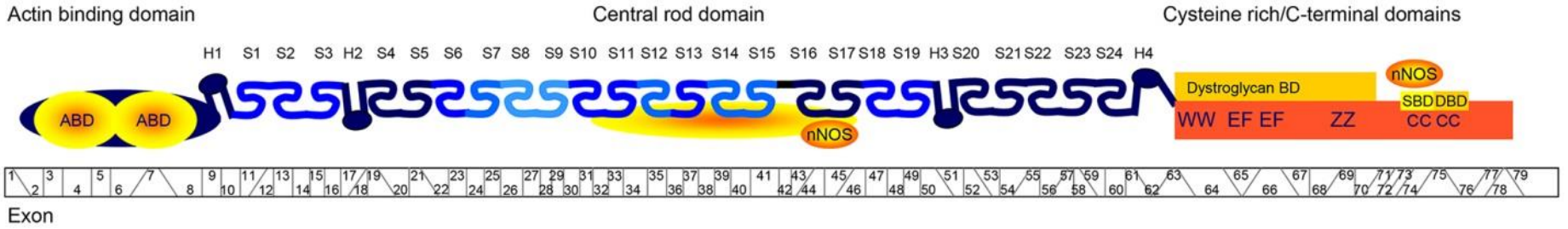
NT

48 post transfection





Mutation specific approach



hotspot

Exon	All mutations	Deletions
51	**14%**	**21%**
45	9.0%	13%
53	8.1%	12%
44	7.6%	11%
50	3.8%	5.6%
43	3.1%	4.5%
8	2.0%	2.9%

Bladen et al, Hum Mut 2015

Communication

- Not applicable to all patients
- Patient education
- Explain how approach works
  - www.exonskipping.nl
  - www.dmd.nl/gt/dance
- **Realistic expectations**
- **Slows down disease progresion**
- **Not a cure**

Is this what patients want?

Parent Project Muscular Dystrophy
LEADING THE FIGHT TO END DUCHENNE

Leading Article
The Patient - Patient-Centered Outcomes Research
February 2015, Volume 8, Issue 1, pp 19-27

First online: 19 December 2014

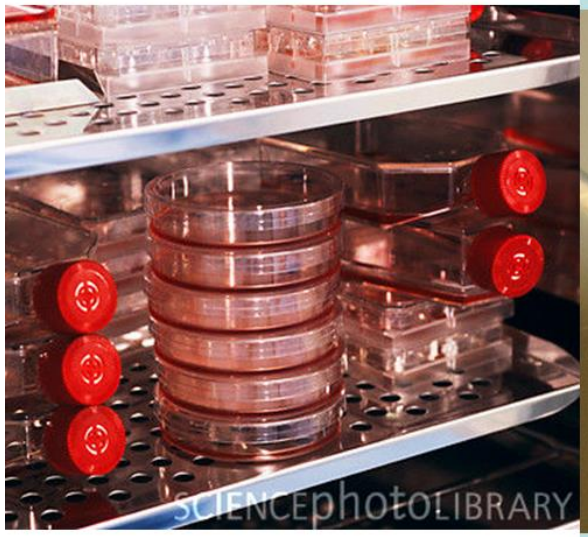
Caregiver Preferences for Emerging Duchenne Muscular Dystrophy Treatments: A Comparison of Best-Worst Scaling and Conjoint Analysis

Ilene L. Hollin, Holly L. Peay, John F. P. Bridges

Article Metrics

Therapeutic development

Cultured Cells



- First test
- Feasibility
- Small numbers
- No circulation
- No immunity
- No organs

Animal models

- *Mdx* mouse
- No dystrophin
- Organs, immunity

Limitation

- Regenerates well
- High metabolism

Patients

Phase 1/2

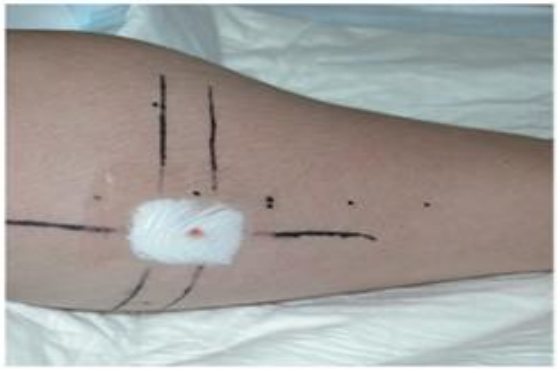
- Safety
- No control group

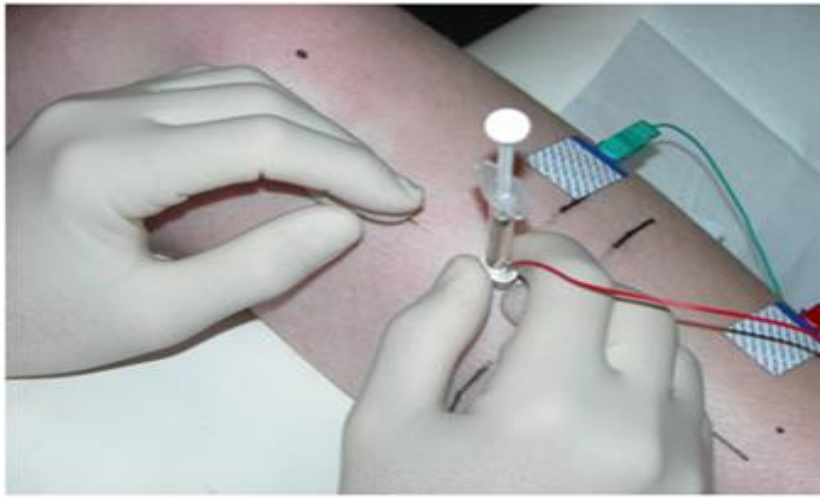
Phase 2-3:

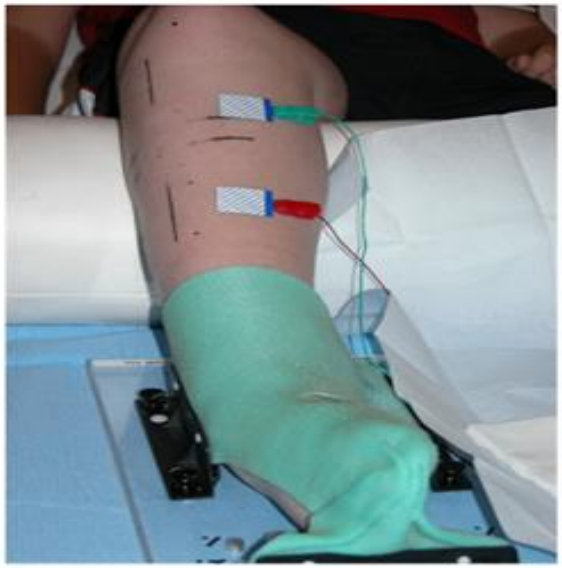
- Effective?
- Long term safety?

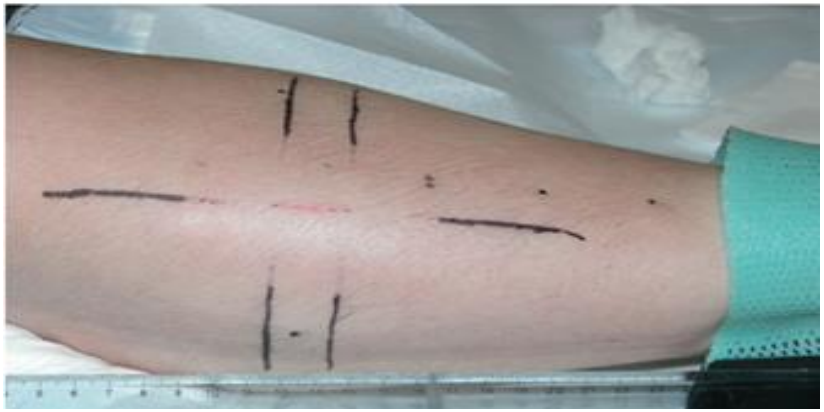
Step 2: first clinical trial

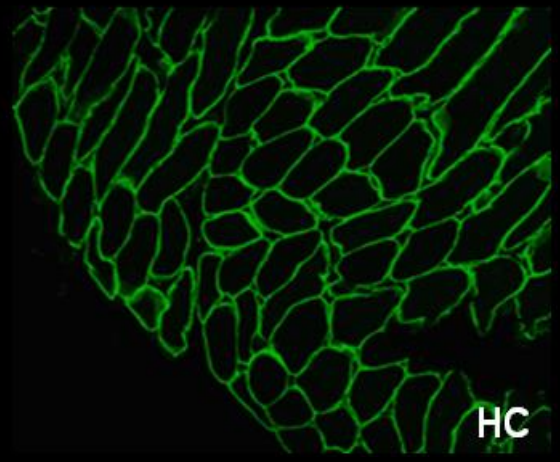
Clinical development

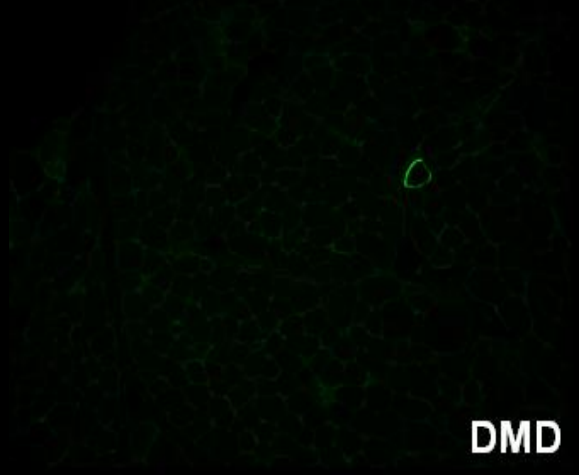









HC

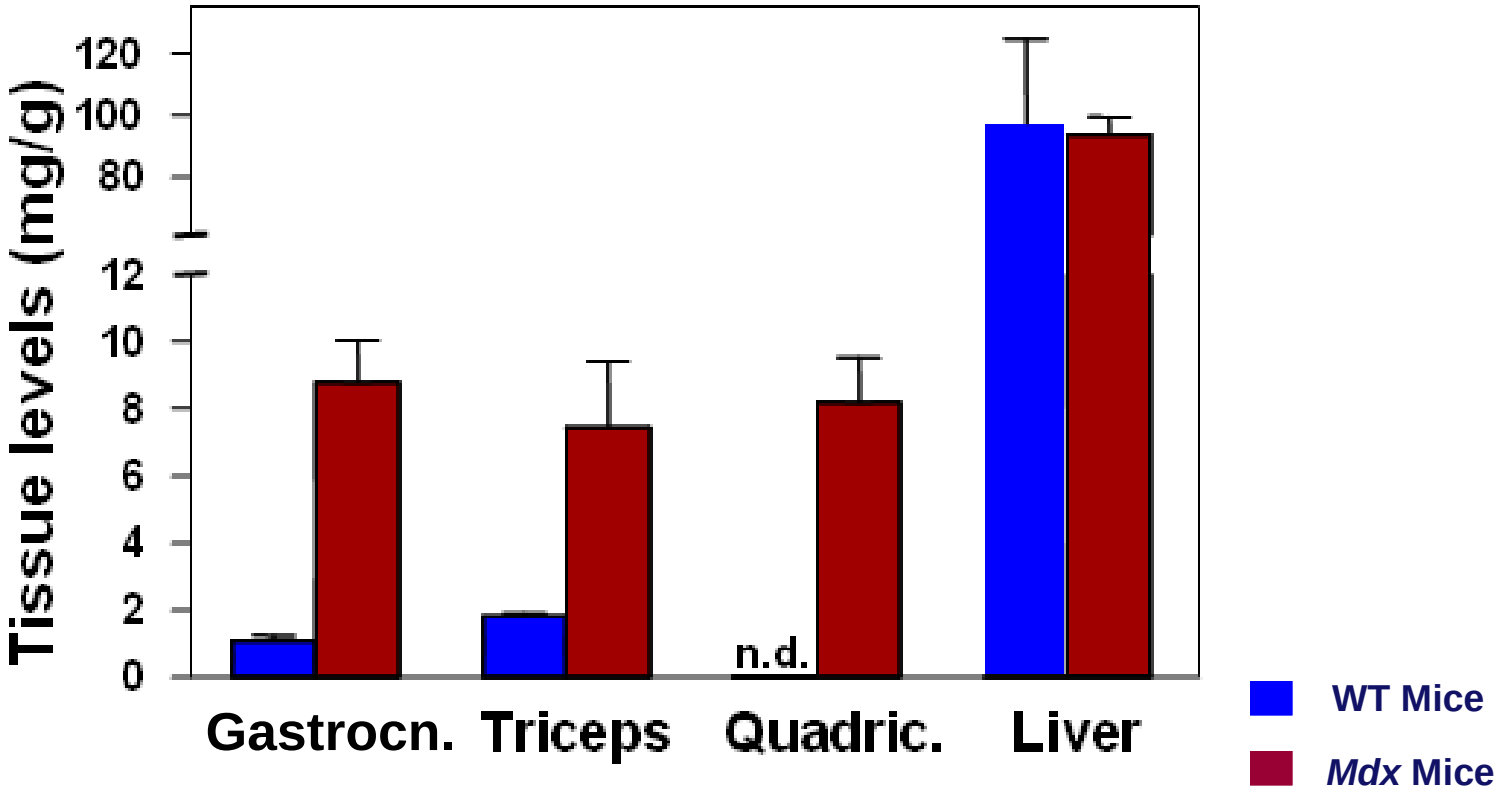

DMD

Step 3: mouse models

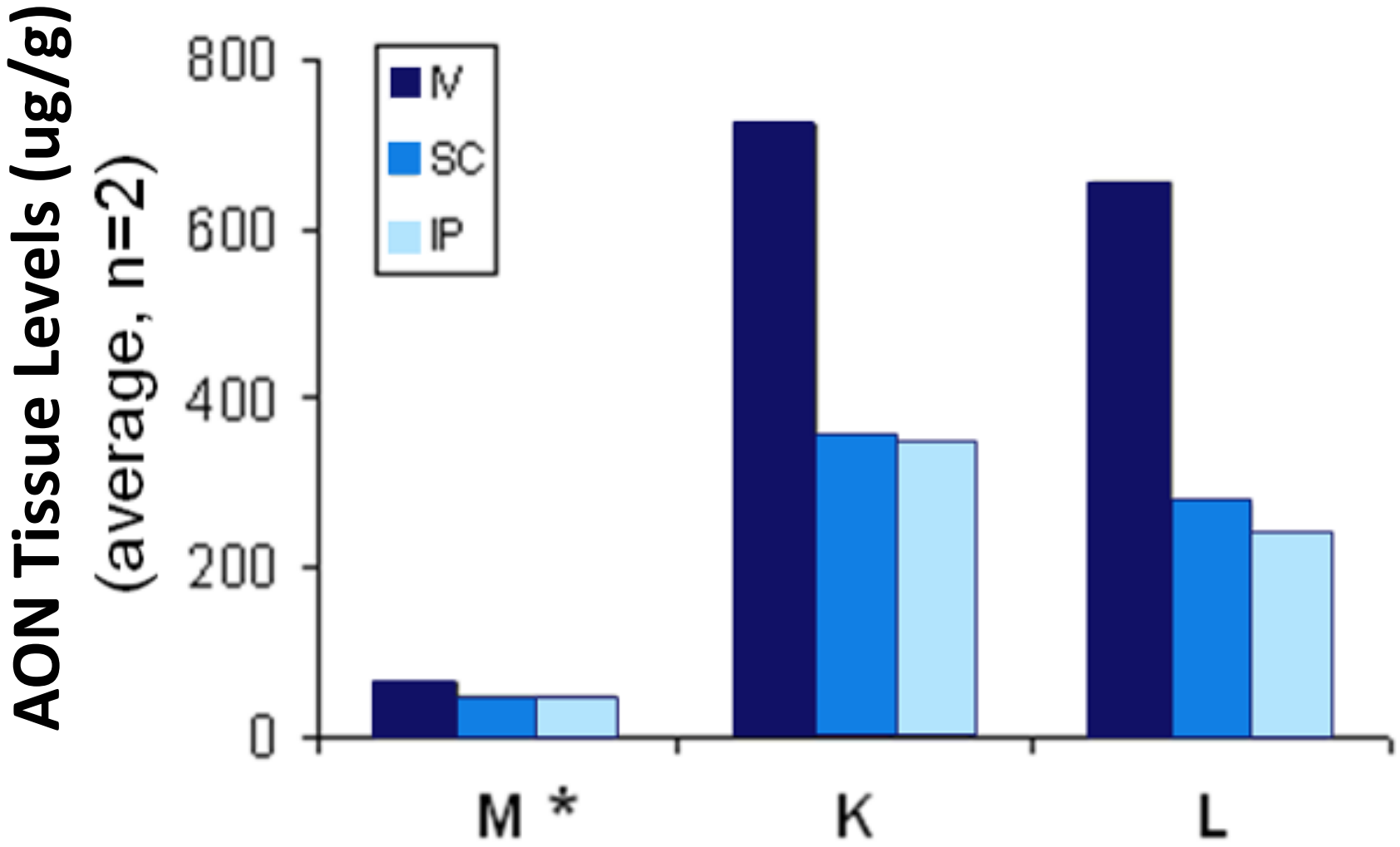
- *No animal model is perfect – that does not mean they are not useful*
- Spontaneous mutation in mouse dystrophin
- No dystrophin production
- Dystrophic muscles
- Milder phenotype
- Test systemic delivery

Systemic studies in *mdx* mice

AON levels in muscle and Liver



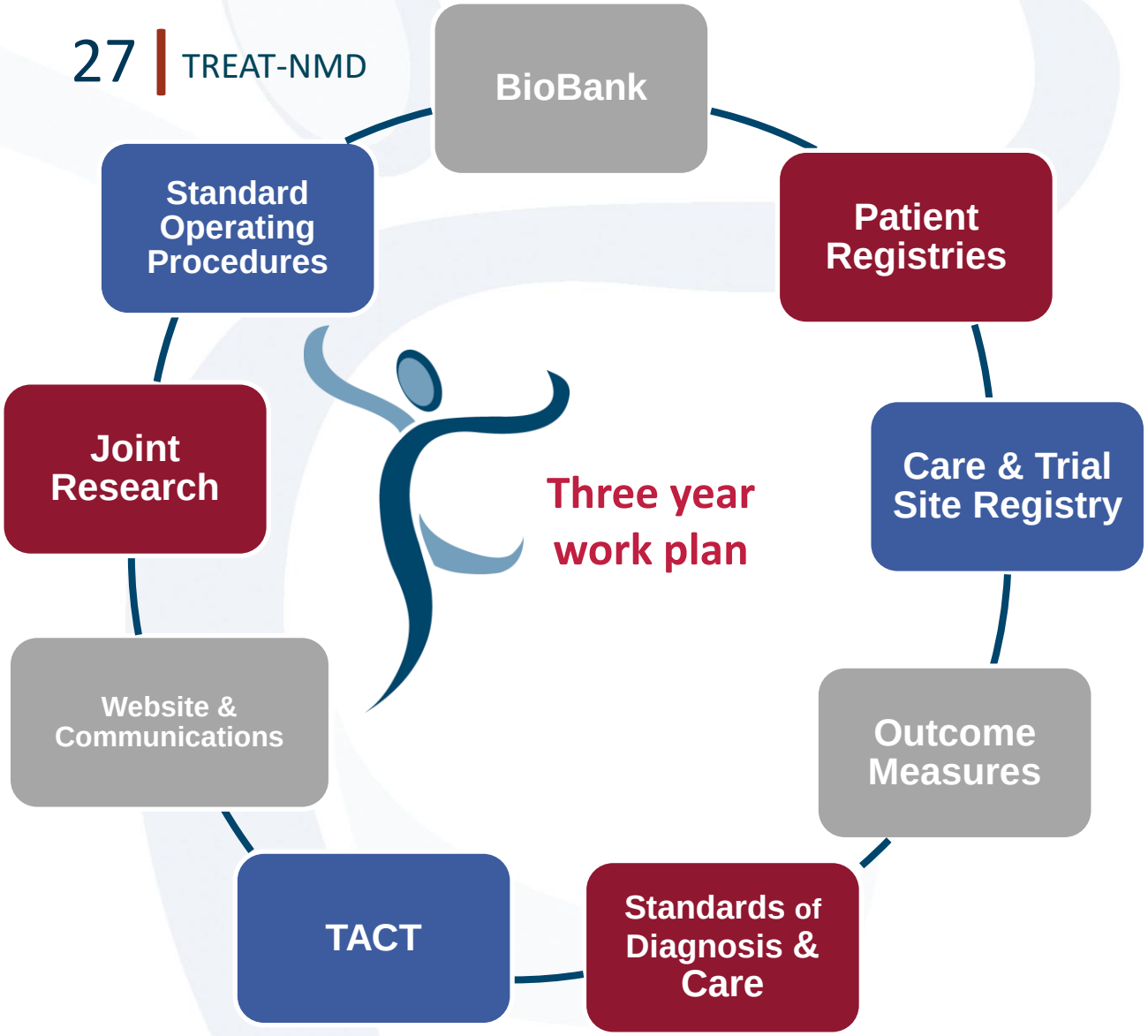
Delivery routes



Step 4: Systemic efficacy trials

How are drugs approved?

- For rare diseases European Medicines Agency (EMA) approves drugs
- Regulators base approval on benefit/risk analysis
- Need to show ‘clincial benefit’ for patients
- Need tools
  - Outcome measures
  - Natural history data



TREAT-NMD
Neuromuscular Network

2007-2011
EU funded Network

2012 onwards
Alliance funded through multiple streams with global partners & membership

Governance

Chair – Kevin Flanigan
Vice Chair – Filippo Buccella

Executive Committee
Supported by academic advisory board ("task force") of NMD leaders

www.treat-nmd.eu

Trials were initiated (2008-2010)

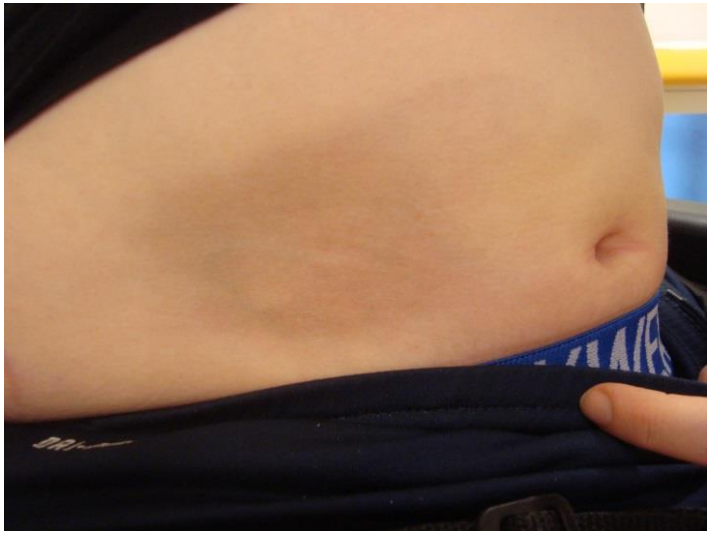
- Subcutaneous delivery
- 2a: Dose escalation (n=12)
- 2b: Dose regimen (n=51)
- 2b: Dose comparison (n=51)
- 3: Efficacy study (n=186)
- Open label extension study for each
- Primary endpoint: 6 minute walk test

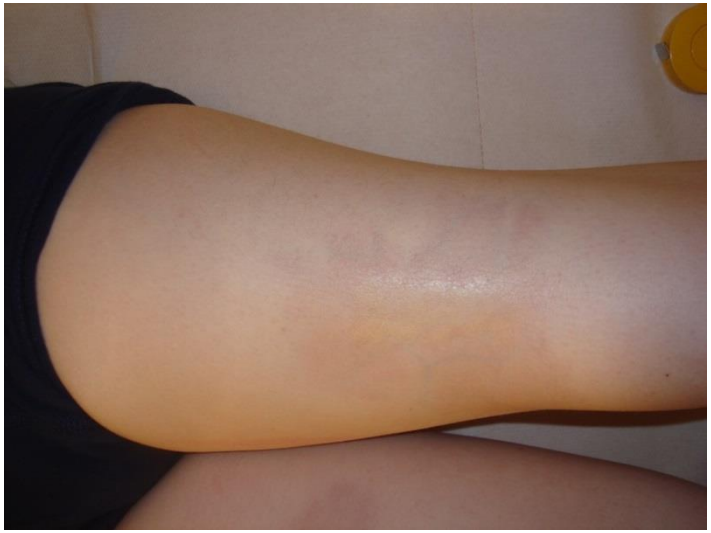
BIOMARIN®

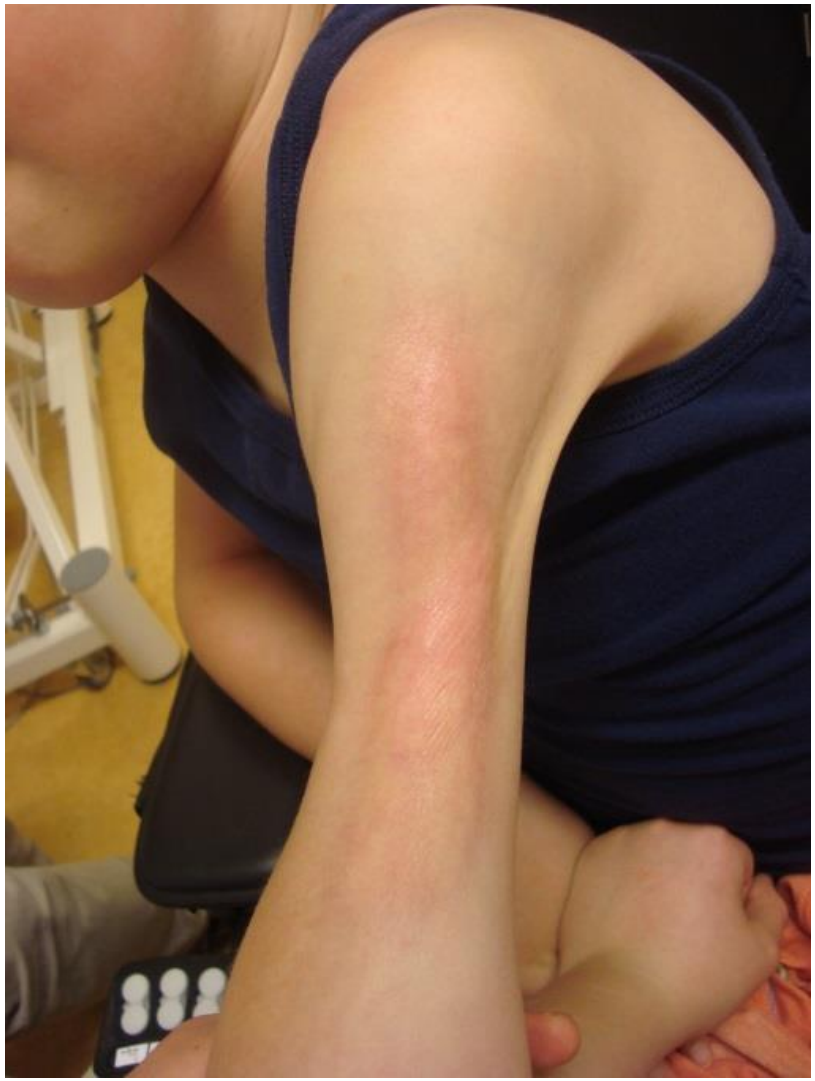
Side effects observed

- Local injection reactions
  - Known effect of subcutaneous delivery of PS AONs
  - Intraveneous delivery: no injection reactions
- Proteinuria (reversible during treatment breaks)
- Thrombocytopenia in some patients

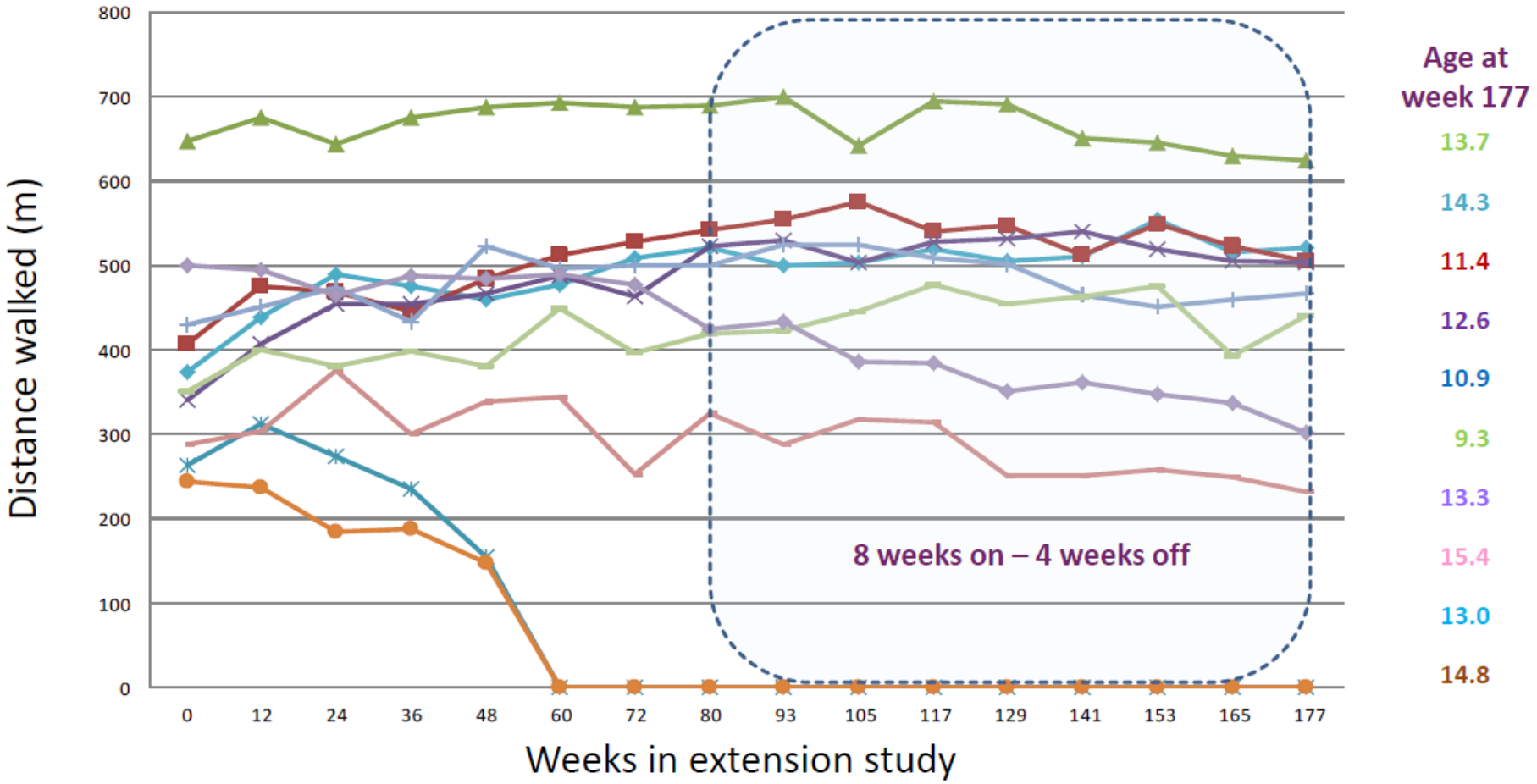
Drisapersen - skin reactions



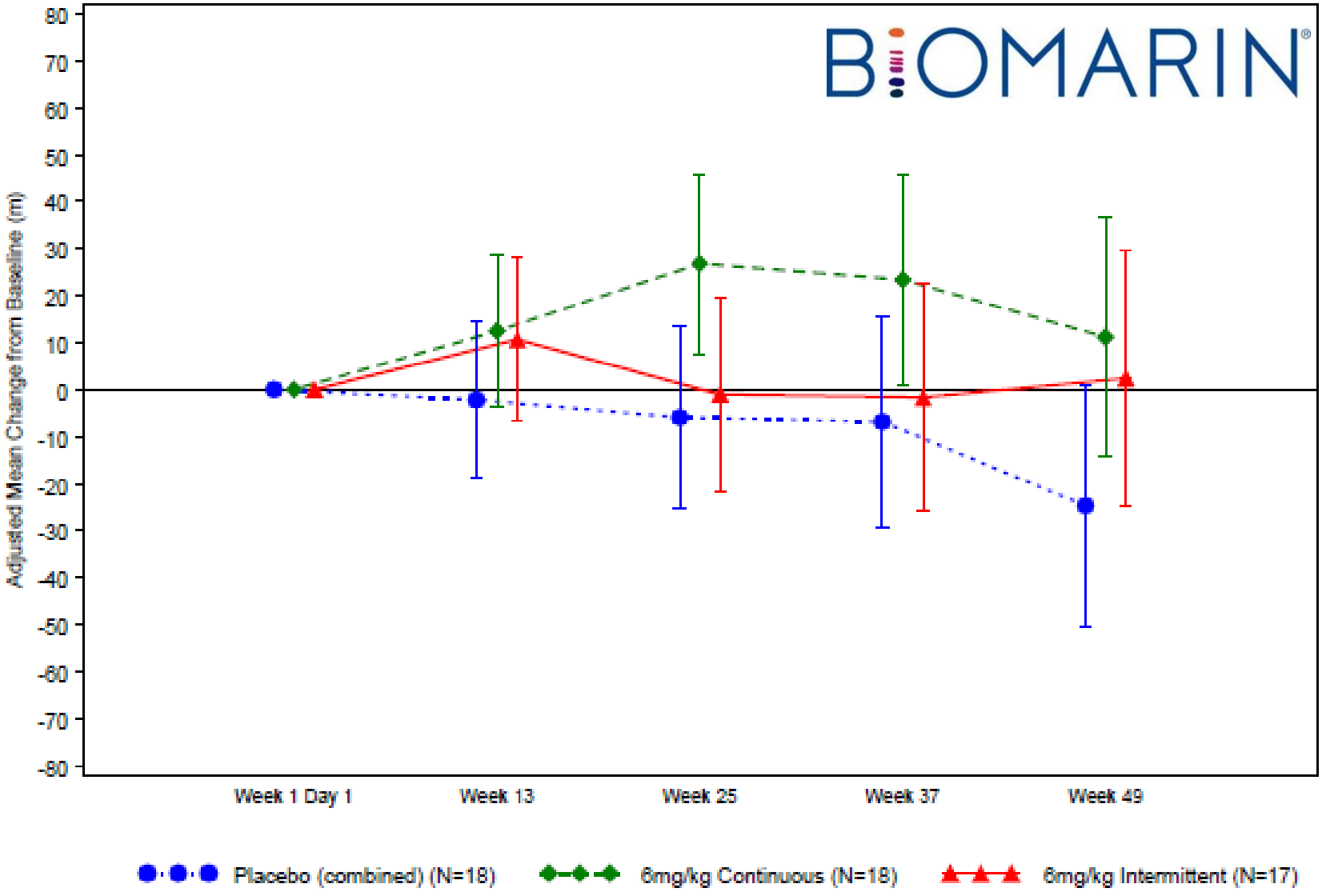




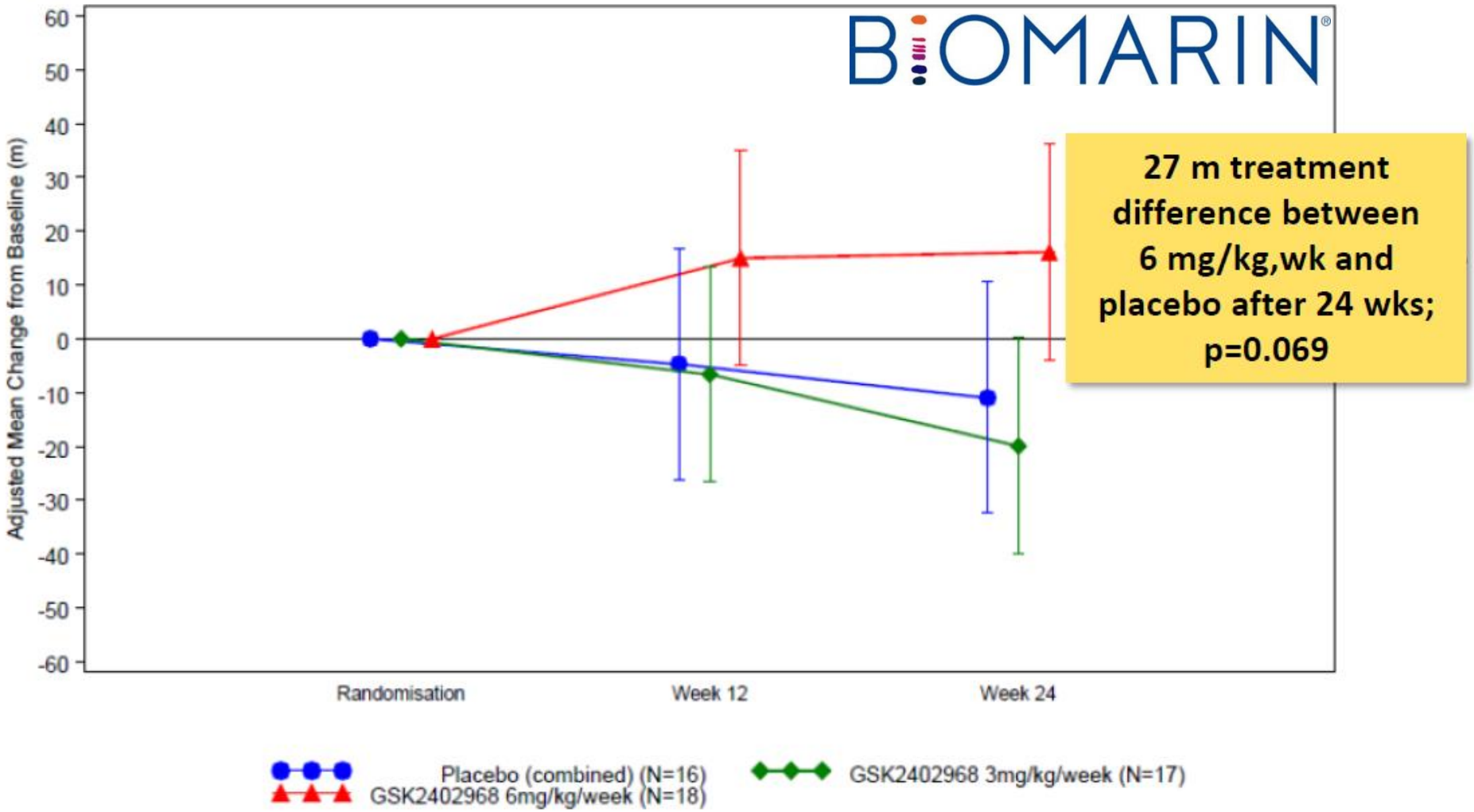
Open label study after dose escalation



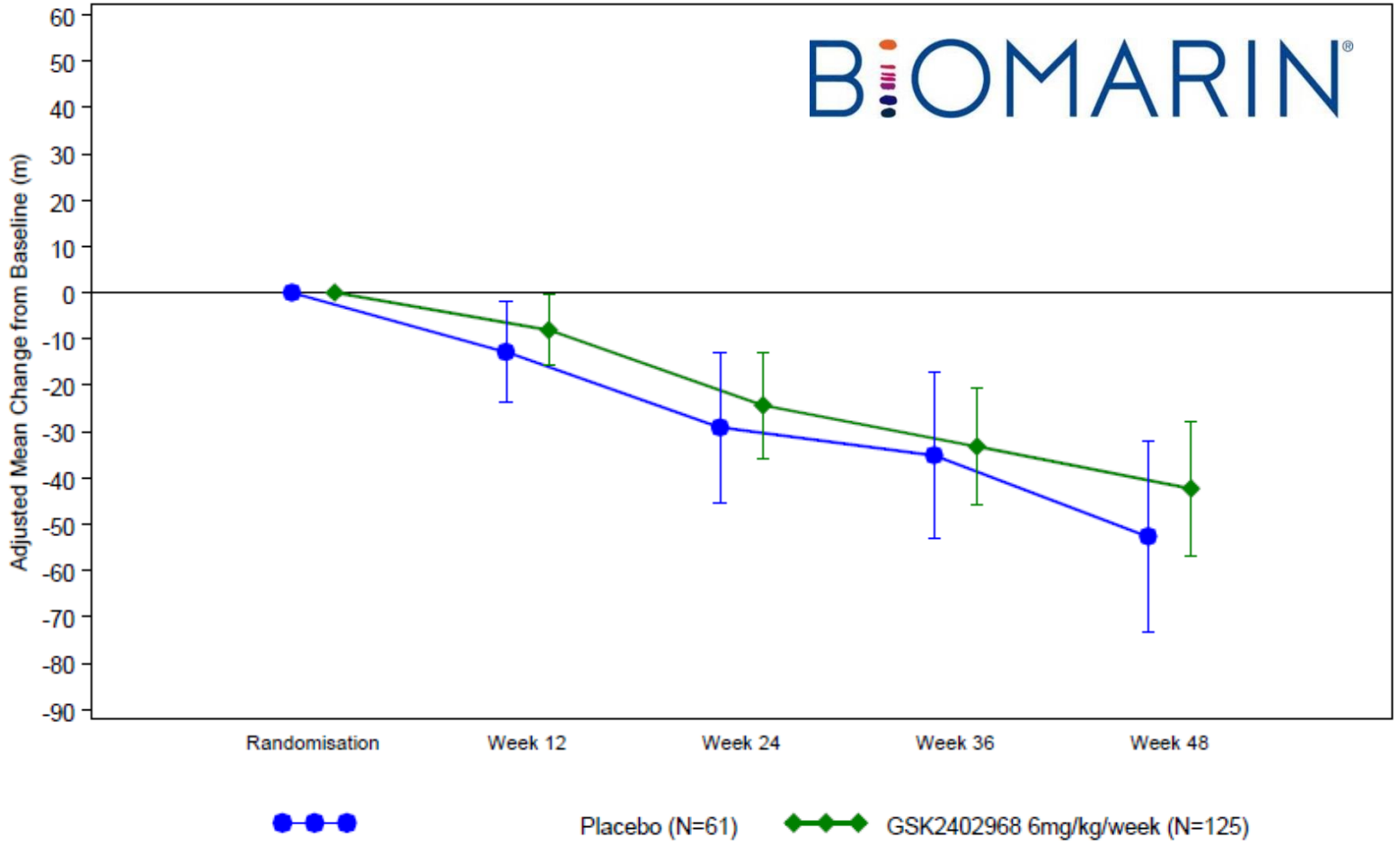
Phase 2b. Dose regimen study



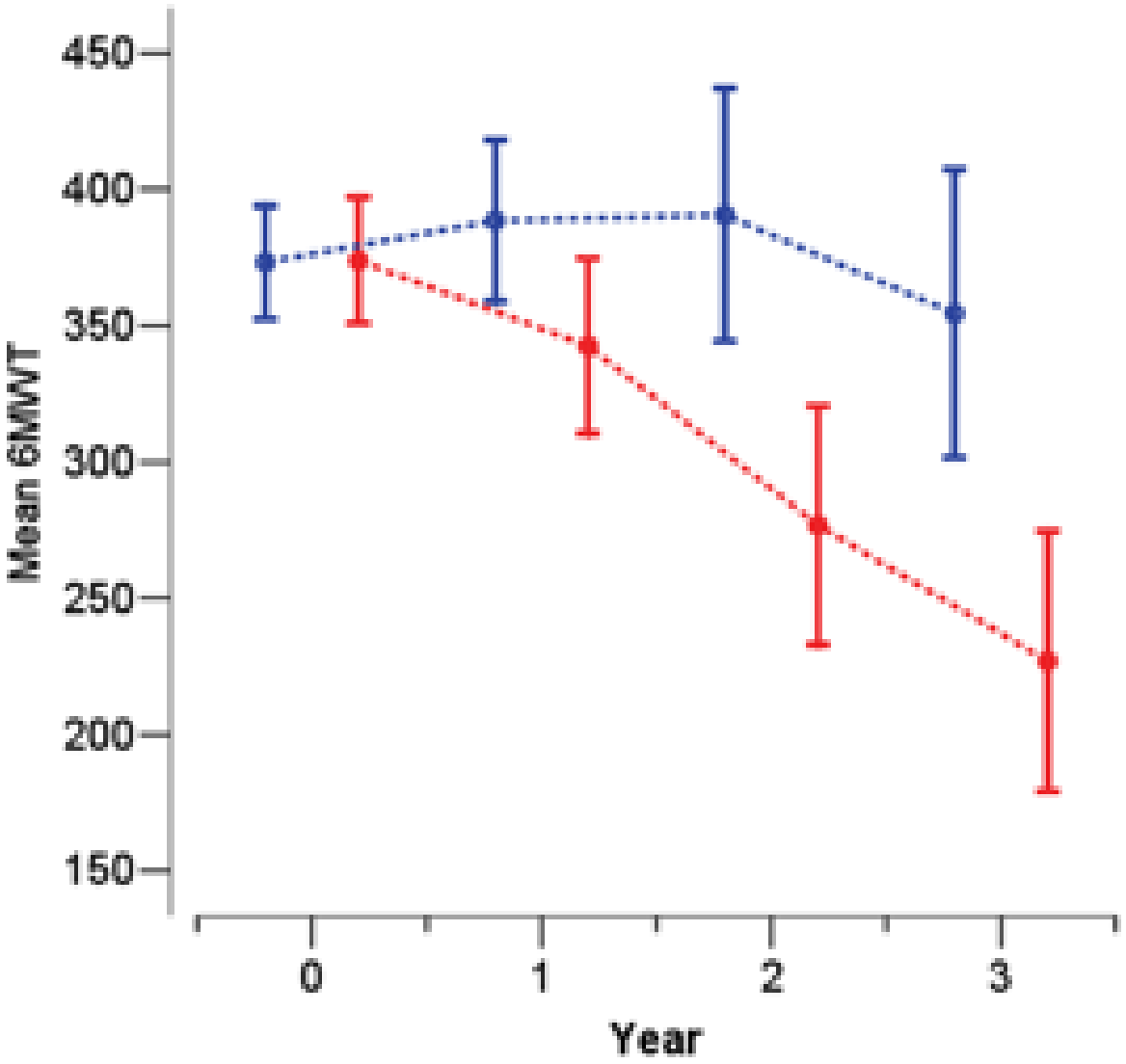
Phase 2b. Dose comparison



Phase 3. Efficacy study



What we know now



Blue: below 7
Red: above 7

In hindsight

- Information too limited to allow set up ideal trial
- Limited information on 6MWT
  - Variation
  - Progression in different age ranges
- Power calculations impossible
- Selection of ideal cohort impossible
- Difficult to pick up minor treatment effect

Is this the end?

- Phase 3 population more advanced disease
  - See more response in younger patients
  - See more response in early stage patients
- Open label studies: effect clearer after 2 years
- Applied for FDA approval: not granted
- EMA application withdrawn
  - Limited benefit vs side effects
- Exon 44, 45 and 53 skipping programms stopped
- Focus on next generation AONs

Collateral benefits

PUL test: developed WITH patients

13 | AFMTELETHON | cost | Muscular Dystrophy Campaign | Parent Project Muscular Dystrophy | United Parent Projects Muscular Dystrophy | TREAT-NMD Neuromuscular Network

Clinical meaning of current PUL items

Shoulder abduction flexion to and above shoulder height	→	Access to cupboards, book shelves, using hair dryer, combing hair
Hands to mouth	→	Self feed
Hand(s) to table from lap	→	Independence to reach things on a table from a chair
Move weight on table	→	Classroom activities, feeding table use, board games
Lifting light cans	→	Reaching across a table to get something
Lifting heavy cans	→	Putting things away, getting things out
Remove lid from container	→	Can access items in a container
Tearing paper	→	Simulates two handed activity like opening letters or crisps
Tracing path	→	Simulates writing
Push on the light	→	Simulated activities that require application of pressure with fingers e.g. door bell
Supination	→	Giving and receiving of money
Picking up coins	→	Handling money
Placing finger on number diagram	→	Simulating use of a key pad eg text and phone and remote
Finger grip items	→	Simulates fine motor activities accessing technology that requires minimal finger movement

Trilateral education

- Regulators are no experts in any rare disease
- DMD field no expert in regulatory affairs
- Stakeholder meetings organized to learn each others language and perspective and plan for future
  - Patients/parents
  - Academics
  - Regulators
  - Industry

Road to success: communication

THELANCETNEUROLOGY-D-16-00102R1
S1474-4422(16)30035-7
Embargo: [add date when known]

16TLN0102
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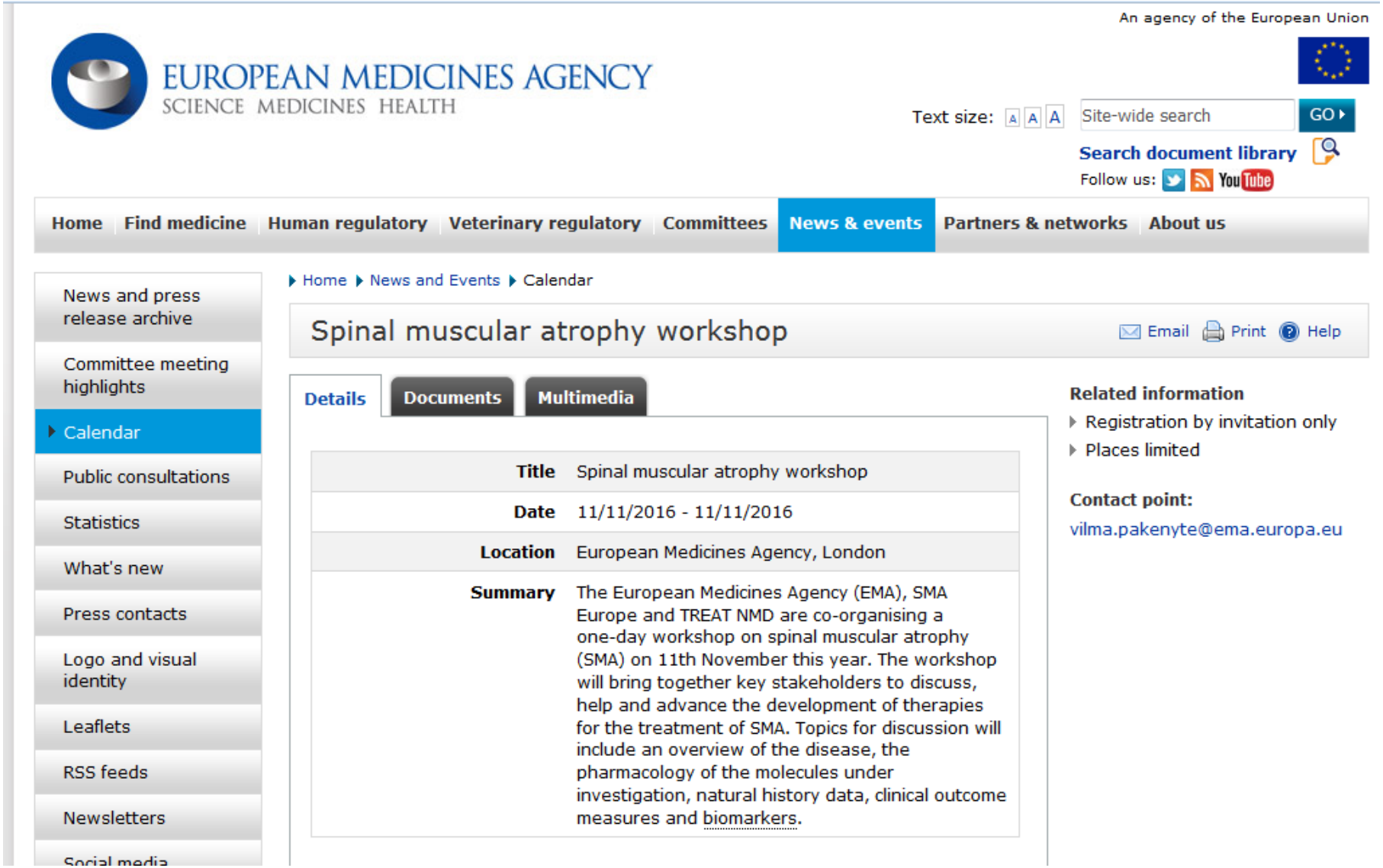
Stakeholder cooperation to overcome challenges in orphan medicine development: the example of Duchenne muscular dystrophy

Volker Straub, Pavel Balabanov, Kate Bushby, Monica Ensini, Nathalie Goemans, Annamaria De Luca, Alejandra Pereda, Robert Hemmings, Giles Campion, Edward Kaye, Virginia Arechavala-Gomeza, Aurelie Goyenvalle, Erik Niks, Olav Veldhuizen, Pat Furlong, Violeta Stoyanova-Beninska, Matthew J Wood, Alex Johnson, Eugenio Mercuri, Francesco Muntoni, Bruno Sepodes, Manuel Haas, Elizabeth Vroom, Annemieke Aartsma-Rus

Free copy available on Researchgate

Others are following example



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Spinal muscular atrophy workshop

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Title	Spinal muscular atrophy workshop
Date	11/11/2016 - 11/11/2016
Location	European Medicines Agency, London
Summary	The European Medicines Agency (EMA), SMA Europe and TREAT NMD are co-organising a one-day workshop on spinal muscular atrophy (SMA) on 11th November this year. The workshop will bring together key stakeholders to discuss, help and advance the development of therapies for the treatment of SMA. Topics for discussion will include an overview of the disease, the pharmacology of the molecules under investigation, natural history data, clinical outcome measures and biomarkers.

Related information

- Registration by invitation only
- Places limited

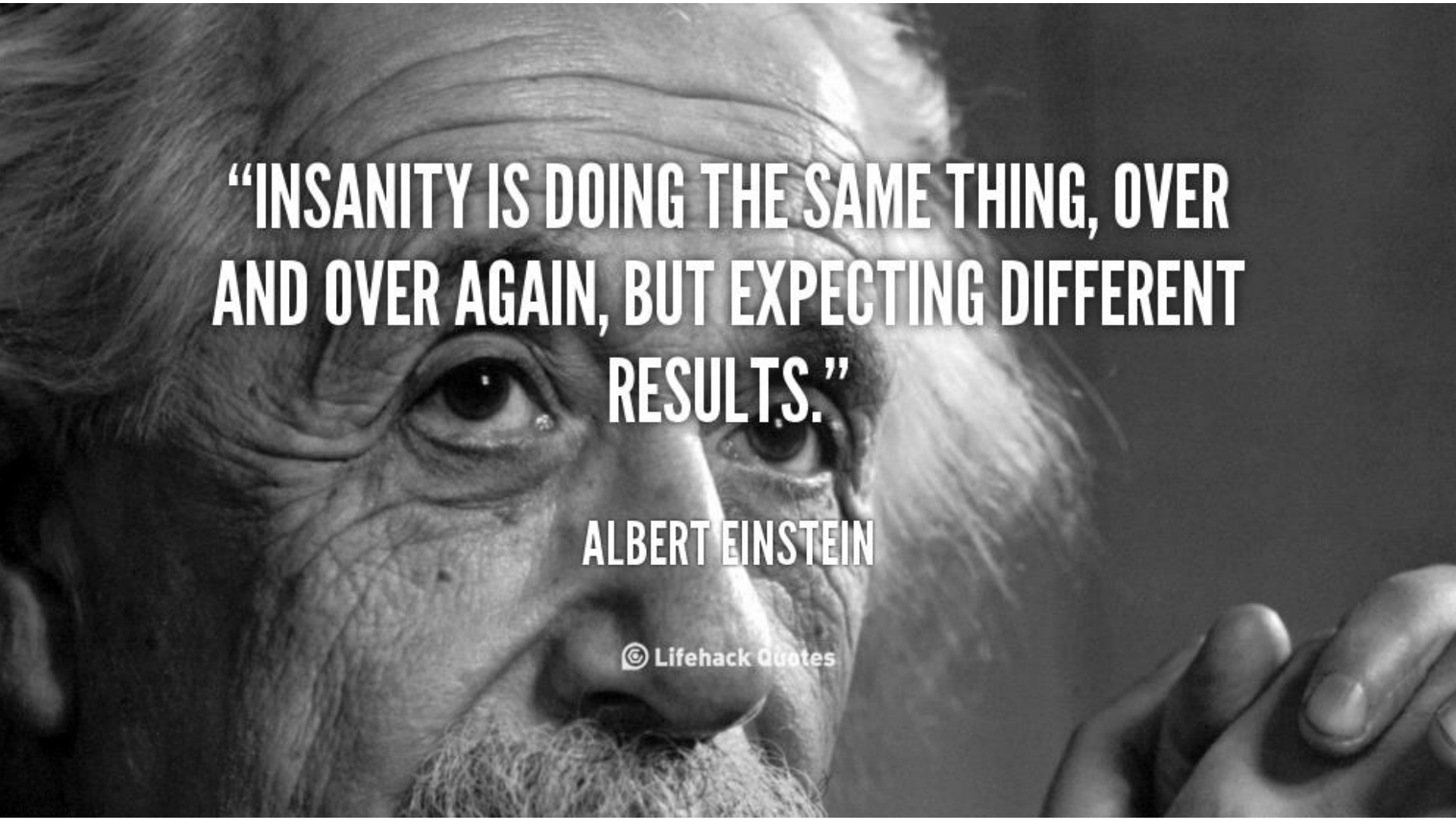
Contact point:

vilma.pakenyte@ema.europa.eu

Lessons learned by the field

- Have natural history data available (especially for your outcome measures)
- Suboptimal trial design can lead to false negative results (especially for low effective drugs)
- Develop outcome measures in parallel with therapeutic approach and involve patients
- Involve **all stakeholders** from an early stage
- Learn each other's language

Retrospective analysis



Current situation

FDA News Release

FDA grants accelerated approval to first drug for Duchenne muscular dystrophy

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For Immediate Release September 19, 2016

- No functional data available yet
- Approval based on minute increases in dystrophin
- Clear room for improvement
- Evaluation EMA pending

Acknowledgements

Exon Skip group

Annemieke Aartsma-Rus

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BioMarin Nederland

Judith van Deutekom, Nicole Datson

cost EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

Duchenne Parent Project

ZonMw

SPIEREN voor SPIEREN

Prinses Beatrix Fonds VOOR SPIERZIEKTEN

TREAT-NMD Neuromuscular Network