Leids Universitair Medisch Centrum

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

Annemieke Aartsma-Rus

June 2025

Disclosures

- Employed by Leiden University Medical Center (LUMC), which has patents on exon skipping technology, some of which are licensed to BioMarin and sublicensed to Sarepta. As co-inventor, I am entitled to a share of royalties

- Ad hoc (past) consultant for: AstraZeneca; BioMarin Pharmaceuticals; Dyne; Eisai; Eli Lilly; Galapagos (Alpha Anomeric, Global Guidepoint and GLG consultancy, Grunenthal, Wave and BioClinica); PTC Therapeutics; REGENXBIO; Sarepta Therapeutics; SpliSense; Takeda & Italfarmaco. Remuneration paid to LUMC

- Member of the scientific advisory boards of: Hybridize Therapeutics; Sarepta Therapeutics; Silence Therapeutics & Sapreme. Remuneration paid to LUMC

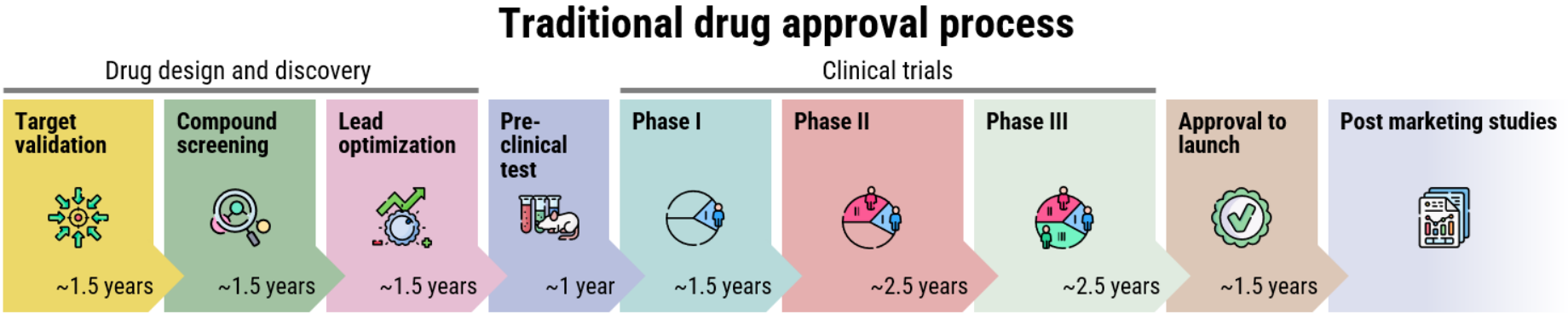
- LUMC received speaker honoraria from: Alnylam; BioMarin Pharmaceuticals; Pfizer; Italfarmaco, PTC Therapeutics

Learning objectives:

- Understand why patients should be included in translational research in each stage
- Understand how patients can be included
- Understand what happens when patients are not sufficiently included
- Use Duchenne as a paradigm but learnings apply to all rare diseases

How can patients be involved in therapy development

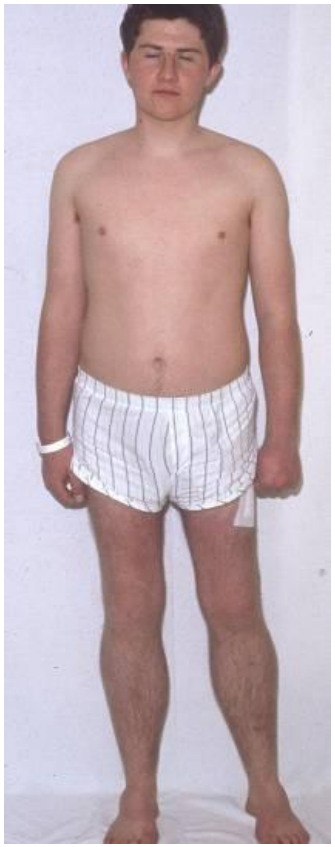
Therapeutic development stages



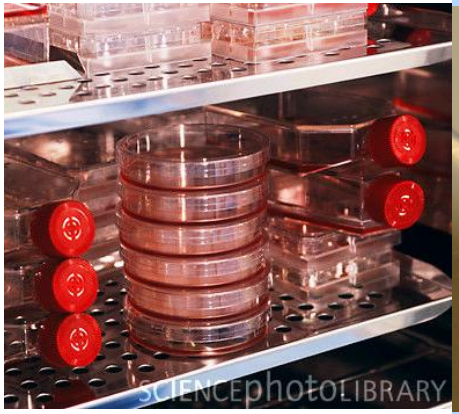
Therapeutic development

- From cell to animal models to clinical trials
- All steps are important to show proof of concept (does it work in model system?)
- Next step is always more complicated
- Success early on is no guarantee for succes in subsequent steps

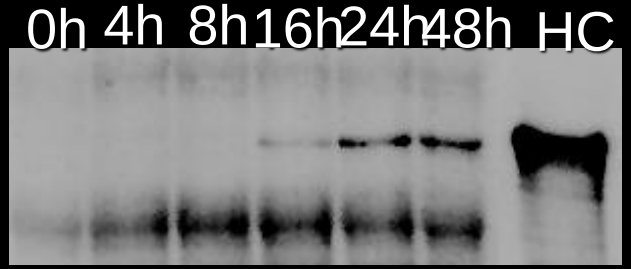
Duchenne vs Becker: treatment idea



Therapeutic development for Duchenne

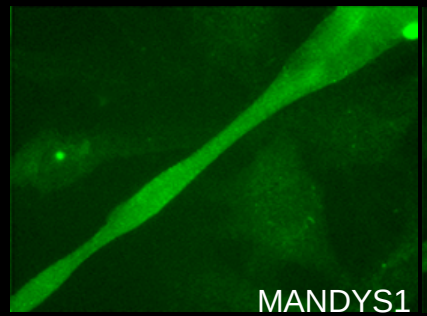
Cultured Cells	Animal models	Patients
		
• First test • Feasibility • Small numbers • No circulation • No immunity • No organs	• Mostly mice • Genetic model • Organs, immunity Limitation • Regenerate well • High metabolism	Phase 1/2 • Safety • No control group Phase 2-3: • Effective? • Long term safety?

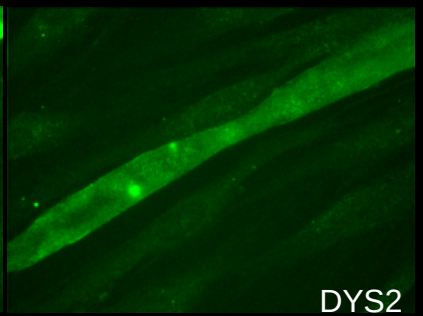
DMD cells start making dystrophin



NT

48 post treatment





Communication

- Not applicable to all patients (mutation specific)
- 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

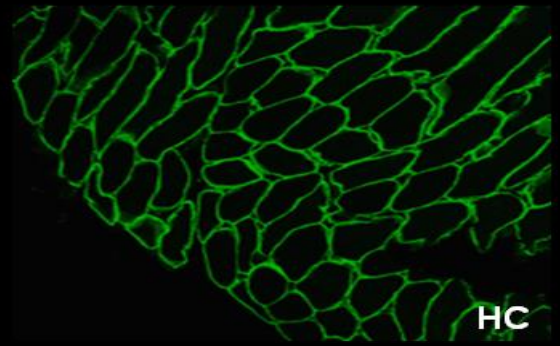
First online: 19 December 2014

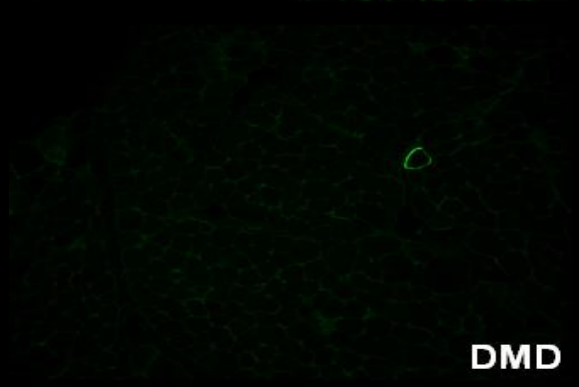
Caregiver Preferences for Emerging Duchenne Muscular Dystrophy Treatments: A Comparison of Best-Worst Scaling and Conjoint Analysis

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

Article Metrics

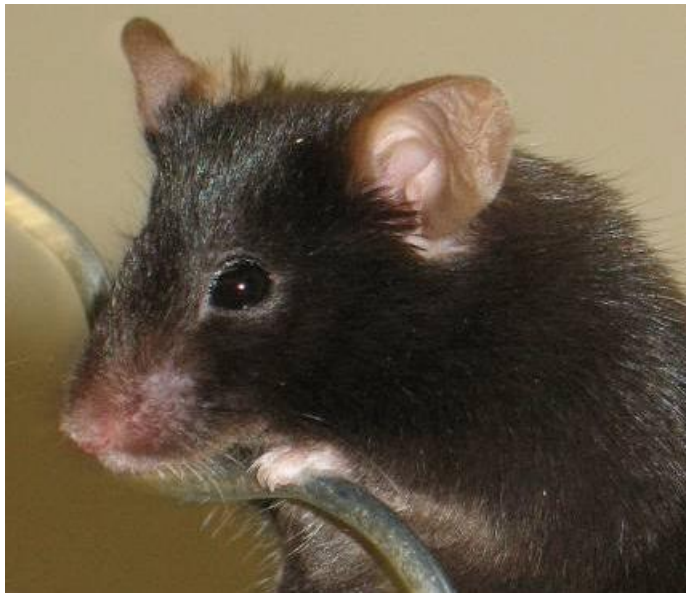
Clinical development: industry


HC


DMD

Mdx mouse model

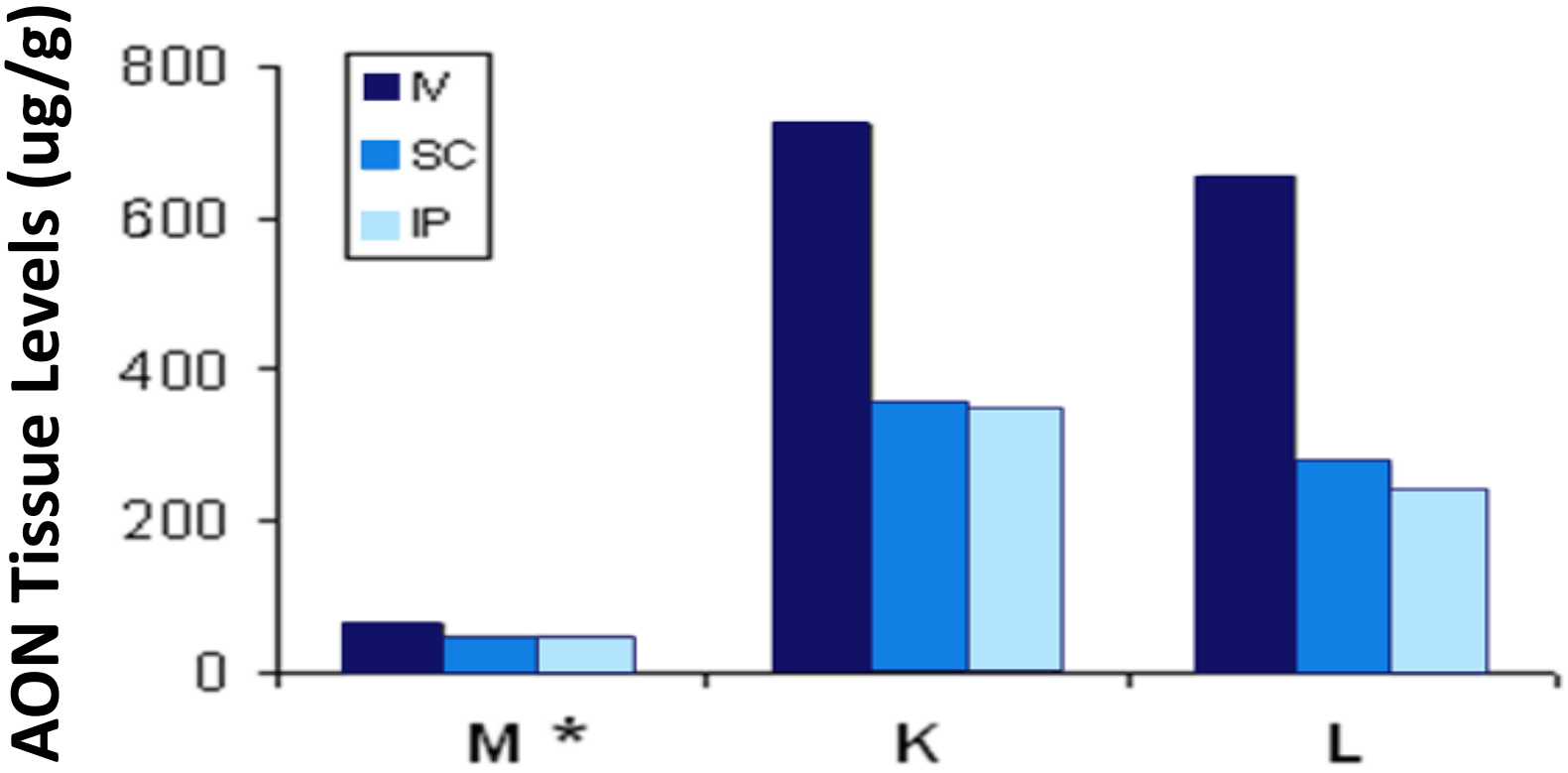
- No animal model is perfect, that does not mean they are not useful
- Spontaneous mutation
- Dystrophic muscles
- Milder phenotype
- Test systemic delivery
- Dystrophic muscle takes up compound better



Side note on poor translatability mouse human

- Proof of concept vs preclinical studies
  - Is my hypothesis correct?
  - If so: optimization needed towards trials
    - Dose, regimen, administration route etc
    - Use wild type references
  - Some trials initiated after proof-of-concept
  - Suboptimal trials
    - This is not the fault of the animal model

Intravenous or subcutaneous?

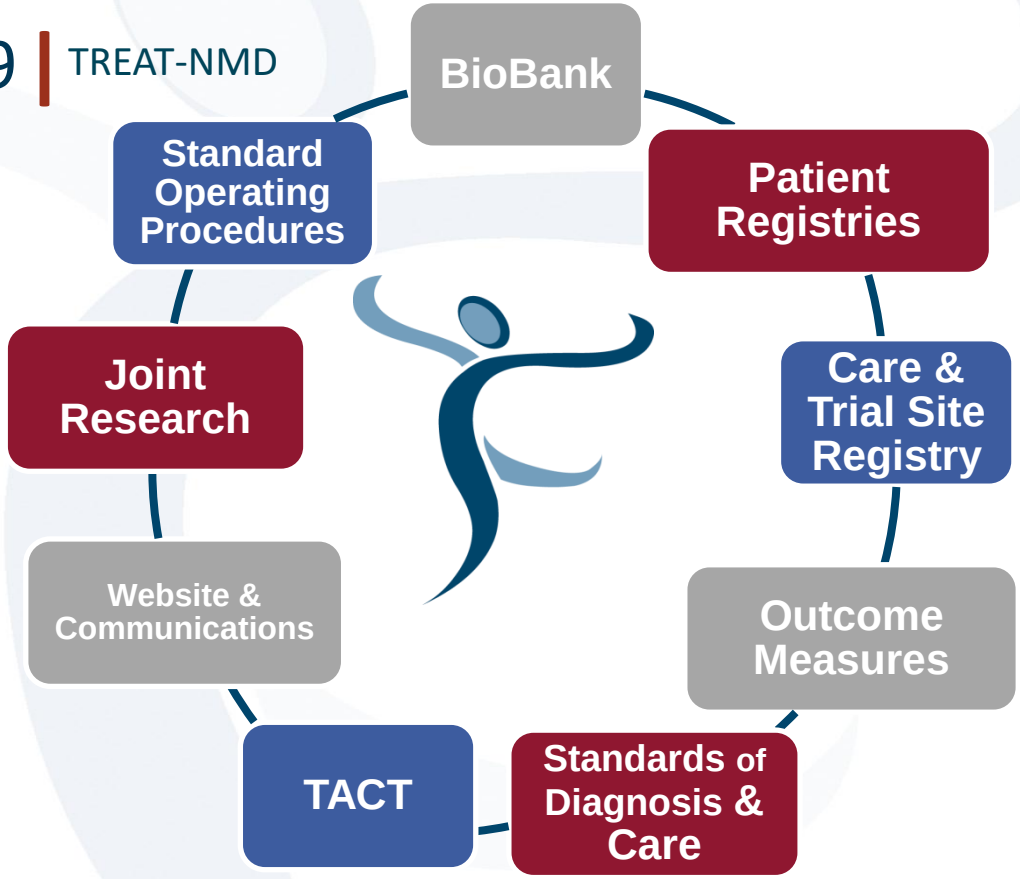


What delivery route would you choose?

After extensive mouse studies → 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

Current Chair Heather Gordish-Dressman

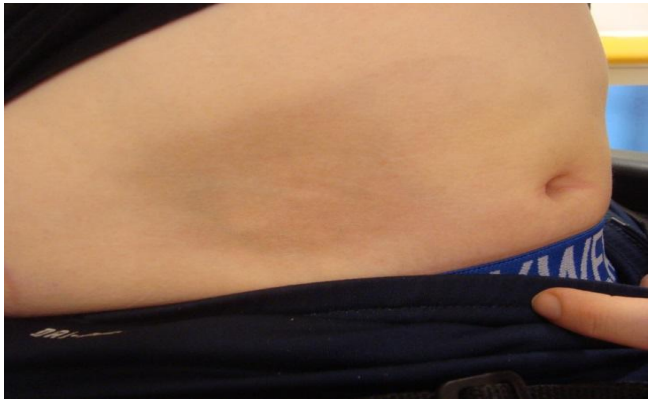
www.treat-nmd.eu

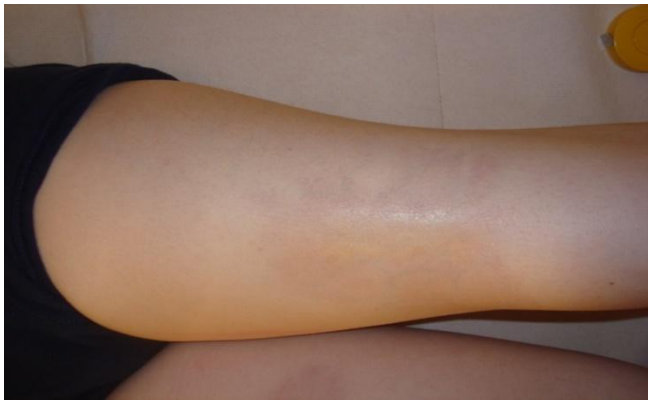
Trials were initiated (2008-2010)

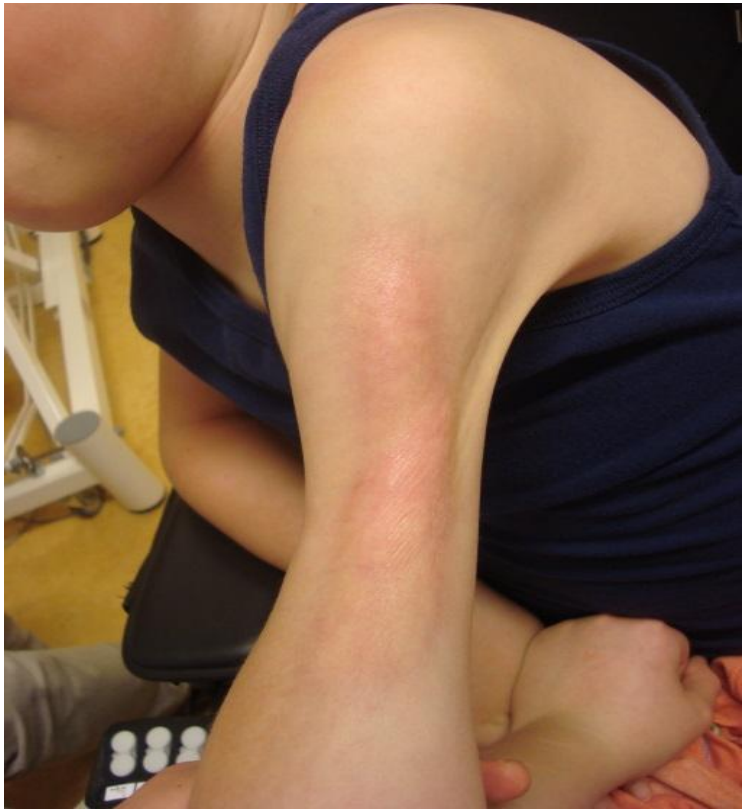
Prosensa → Lisenced exon 51 skipping drug to GSK

- 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

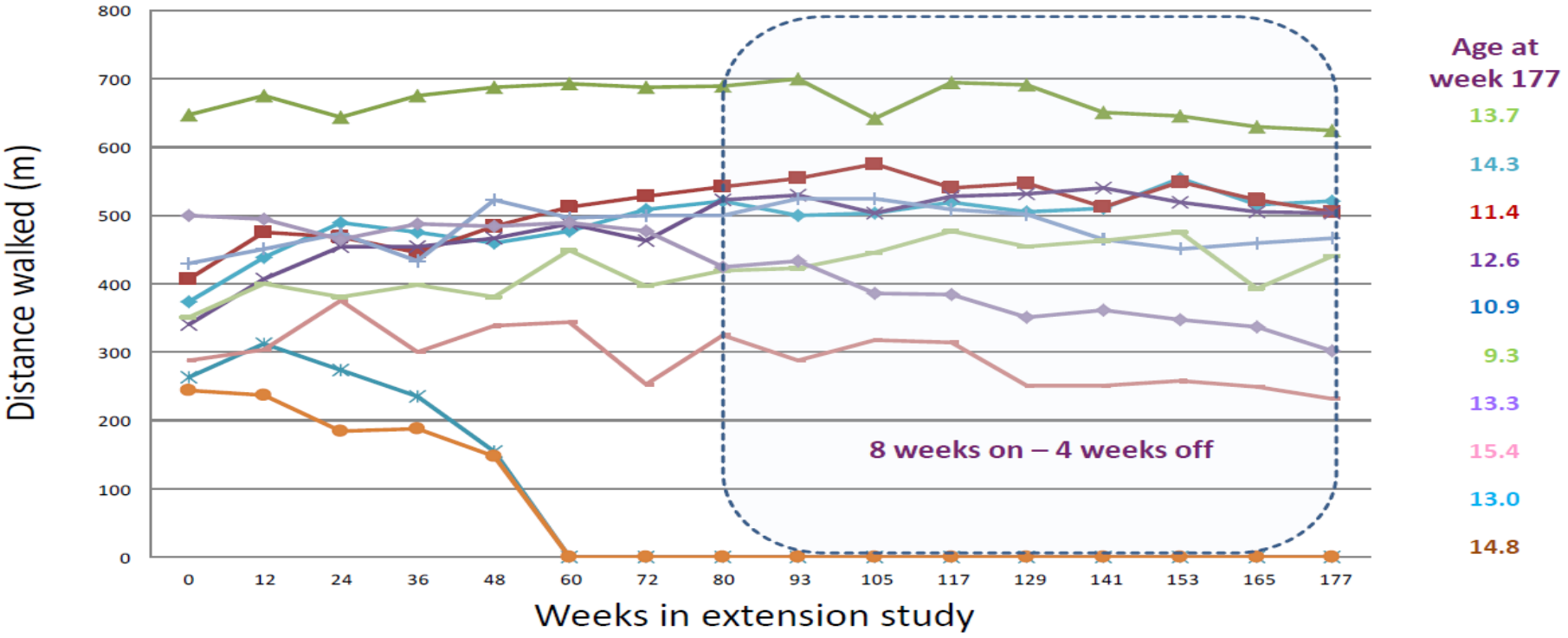
Side effects seen: skin reactions





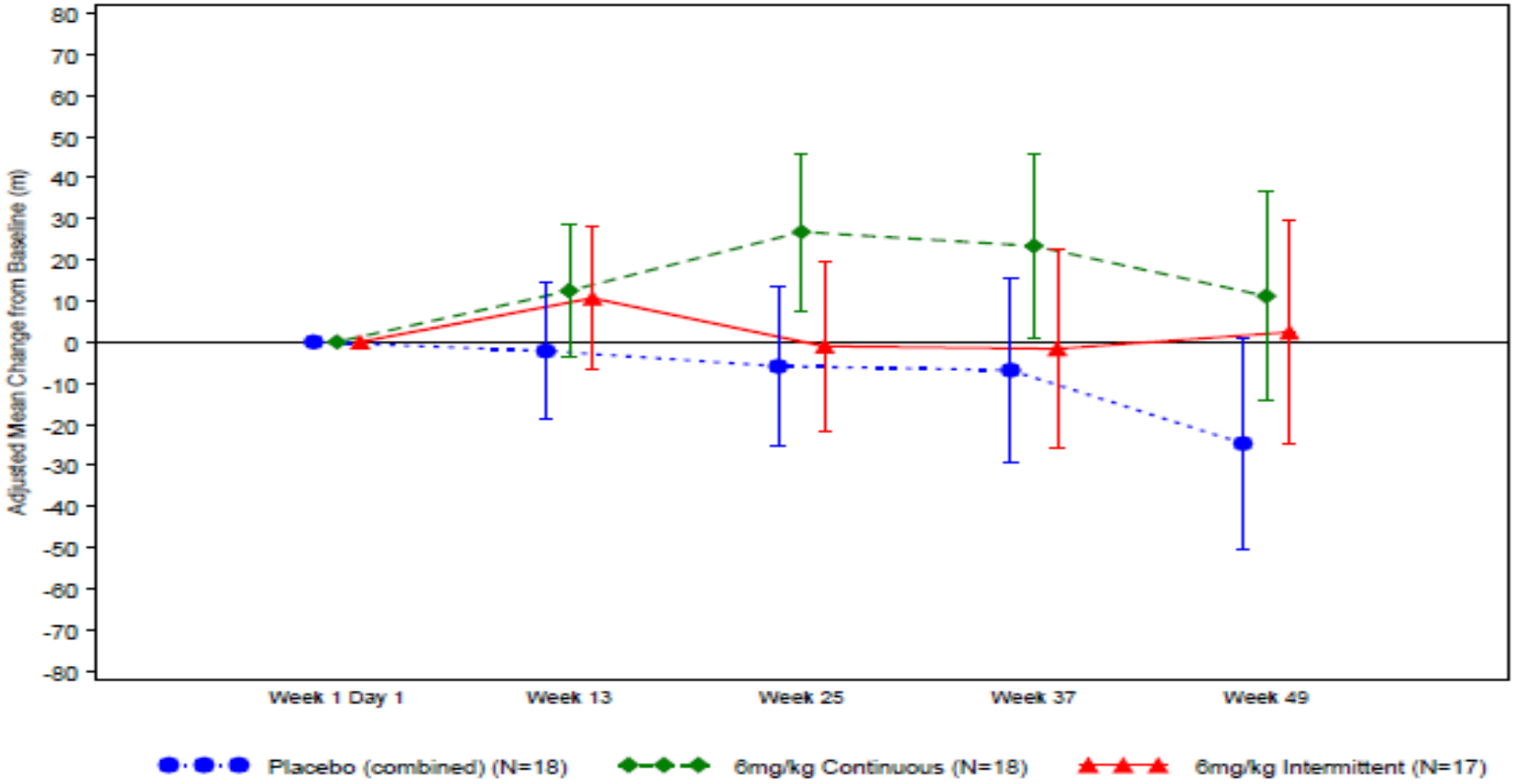


Open label study after dose escalation



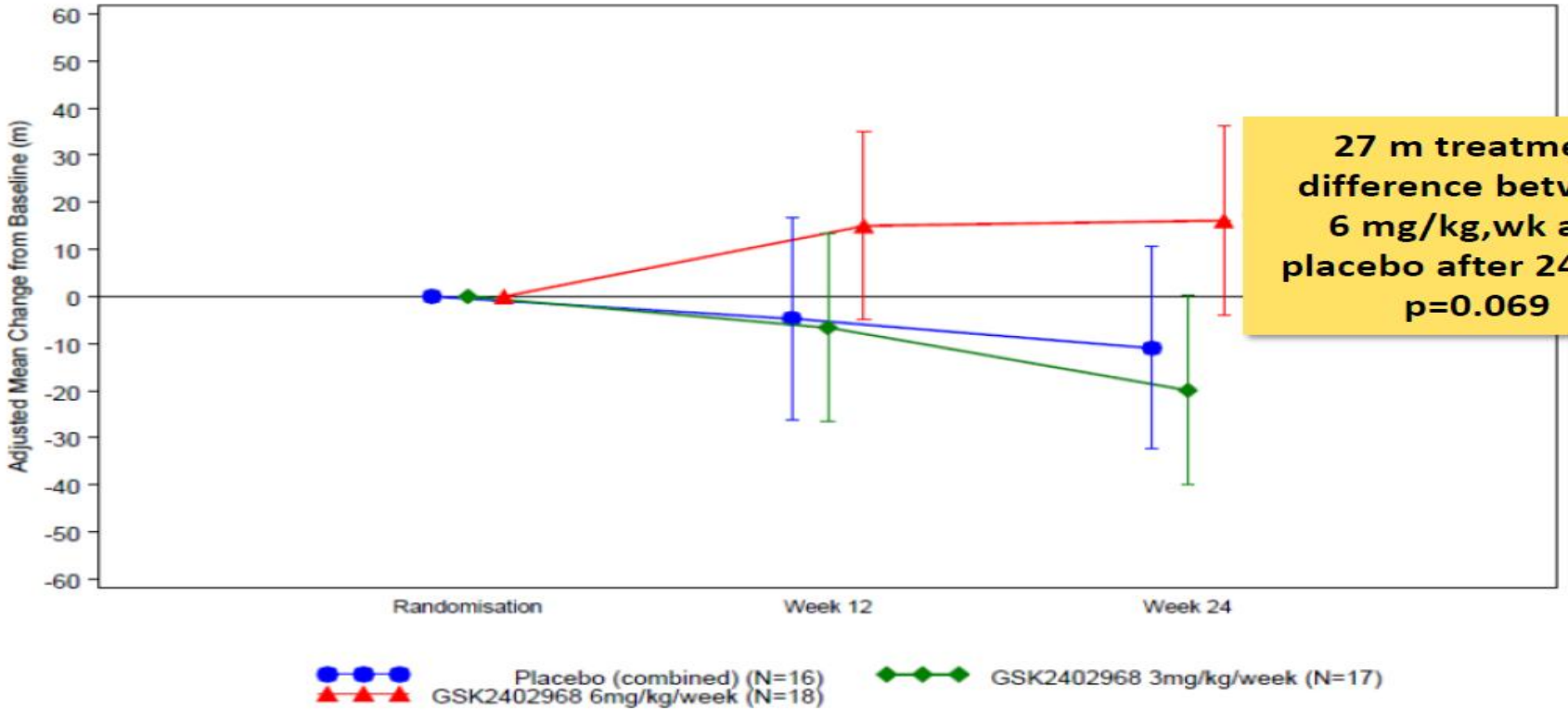
Do you think this treatment is effective

Phase 2b. Dose regimen study



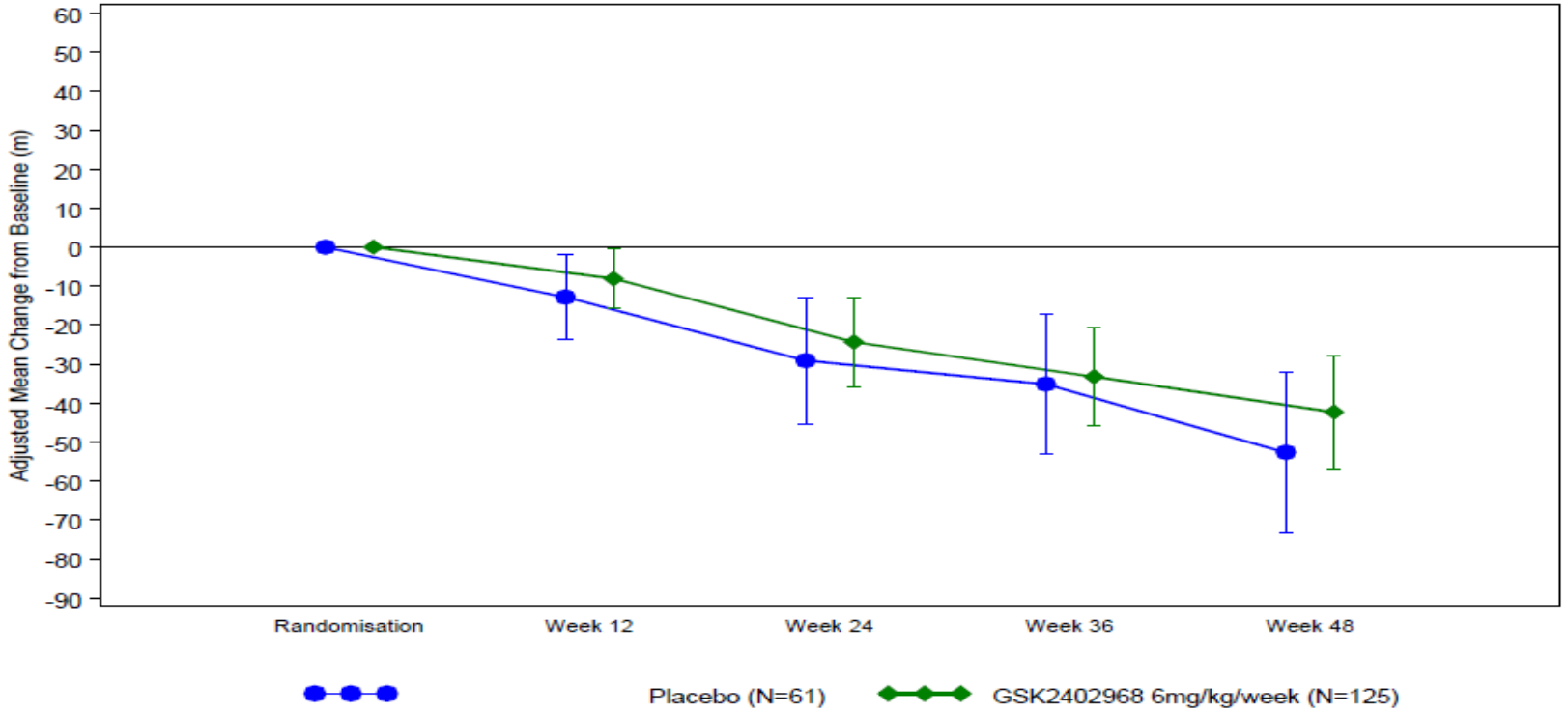
Do you think this treatment works?

Phase 2b. Dose comparison



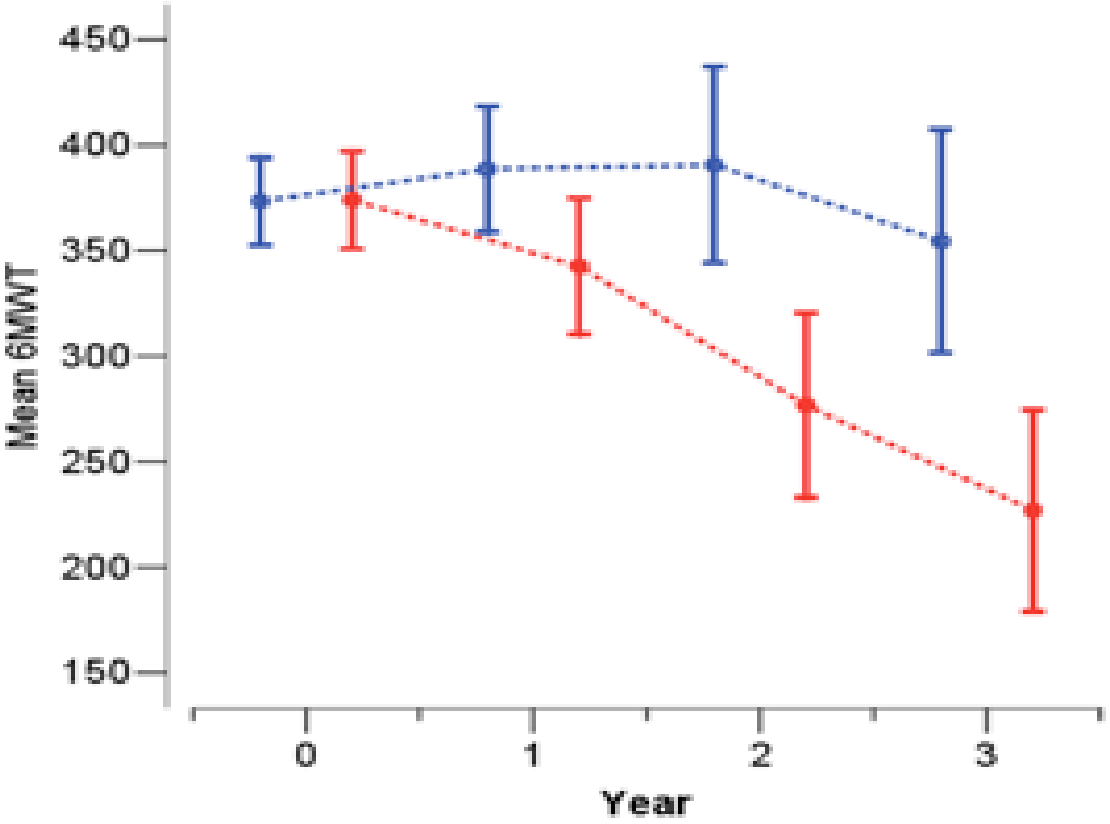
Do you think this treatment works?

Phase 3. Efficacy study



Do you think this treatment works?

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?

- GSK → Prosensa → BioMarin
- Phase 3 population more advanced disease
  - Response in subset eligible for phase 2 trials
- Applied for FDA approval: not granted
  - Limited benefit posthoc analysis vs side effects
- EMA application withdrawn
- Development of approach stopped
- Focus on next generation compounds
  - New trial ongoing for drisapersen 2.0

Collateral benefits

PUL test: developed WITH patients

13 | AFMTELETHON | ccost | 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
Policy View
SP
This version saved: 11:13, 21-Apr-16

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

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

Learning objectives:

- Understand why patients should be included in translational research in each stage → not doing this can lead to failures
- Understand how patients can be included in translational research
  - Developing outcome measures (what is clinically relevant)
  - Trial design
  - Trial participation
  - Advising EMA
  - (and many other ways)

Acknowledgements

Exon Skip group LUMC

Annemieke Aartsma-Rus
Maaike van Putten
Remko Goossens
Laura Heezen
Anne-Fleur Schneider
Davy van der Vijver
Nisha Verwey
Lizette van der Pijl
Sharon de Vries
Pietro Spitali
Tiberiu Stan
Sarah Engelbeen
Alper Yavas
Minou Verhaeg
Kayleigh Putker
Christa Tanganyika-de Winter
Lola van Doorne
Qirong Mao
Gertjan van Ommen †

SAREPTA THERAPEUTICS
entrada THERAPEUTICS
Duchenne UK
DEPARTMENT OF DEFENSE · UNITED STATES OF AMERICA
cost EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY
Duchenne Parent Project
ZonMw
SPIEREN voor SPIEREN
Prinses Beatrix Fonds VOOR SPIERZIEKTEN
TREAT-NMD Neuromuscular Network