

PRO S ENSA

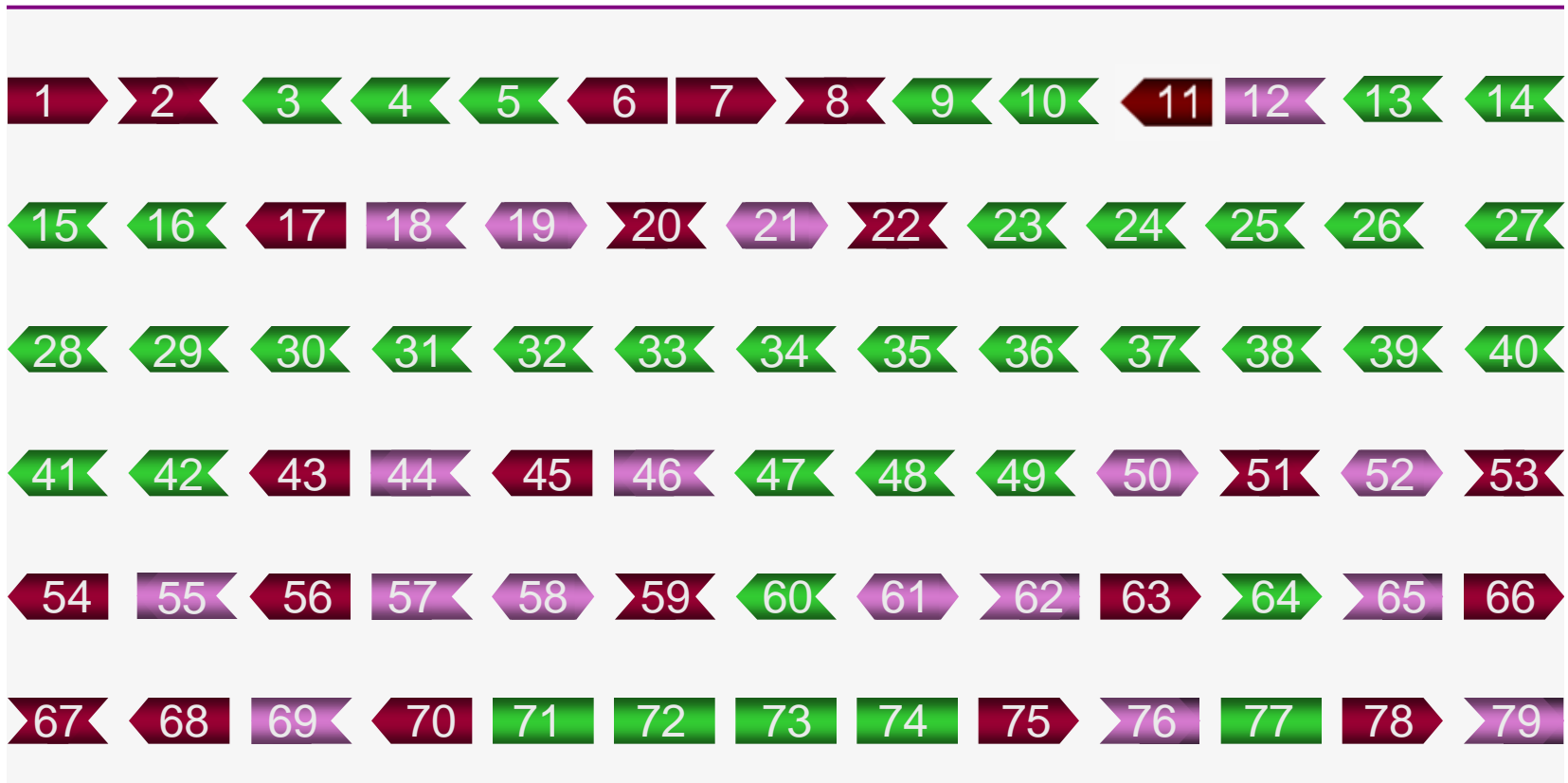


## The Prosensa exon-skipping programme

**Action Duchenne Conference, London**  
November 5th, 2011

Giles Campion; SVP R&D, CMO,

# The Dystrophin Gene



Aartsma-Rus & van Deutekom, Antisense Elements (*Genetics*) Research Focus, 2007 Nova Science Publishers

Exon skipping can restore the reading frame

# DMD boys need a menu of drugs



Exon	Applicable to deletions of exon(s)	% of deletions in the LDMD <sup>1</sup>
51	13-50, 29-50, 43-50, 45-50, 47-50, 48-50, 49-	24.6%
45	12-44, 18-44, 44, 46, 46-47, 46-48, 46-49, 46-51, 46-53, 46-55, 46-59, 46-60	15.8%
53	10-52, 42-52, 43-52, 45-52, 47-52, 48-52, 49-52, 50-52, 52	1
44	3-43, 5-43, 6-43, 10-43, 14-43, 17-43, 22-43, 28-43, 30-43, 33-43, 34-43, 35-43, 36-43, 37-43, 38-43, 40-43, 41-43, 42-43, 45, 45-54, 45-68	1
46	19-45, 21-45, 43-45, 45, 47-54, 47-56	8
52	8-51, 51, 53, 53-54, 53-55, 53-57, 53-59, 53-60,	7
43	44, 44-46, 44-47, 44-48, 44-49, 44-51, 44-53	7
50	51, 51-52	6
8	3-7, 4-7	3
2	3-7	2
<b>Total</b>		<b>7</b>





# Prosensa Menu

November 5th, 2011

**PRO051/ GSK 2402968**

In phase III clinical trials

**PRO044**

Phase I/II

**PRO045**

Phase I 2012

**PRO053**

Phase I 2012

**PRO055/52**

Preclinical

Clinical  
Testing only



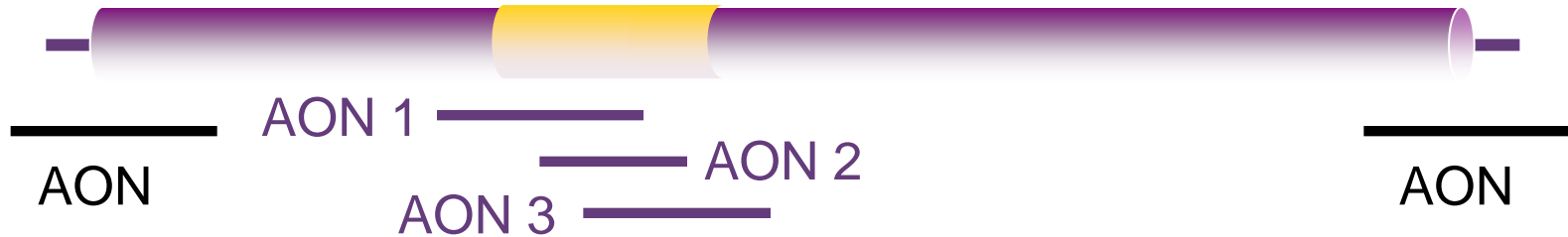
# The ProSensa Recipe Book

A decorative yellow wave graphic that spans across the top of the slide, starting from the left edge and ending under the title.

- Choosing the best ingredients
- Manufacturing large quantities
- Preclinical testing
- Obtaining permission
- Clinical trials
- Approval

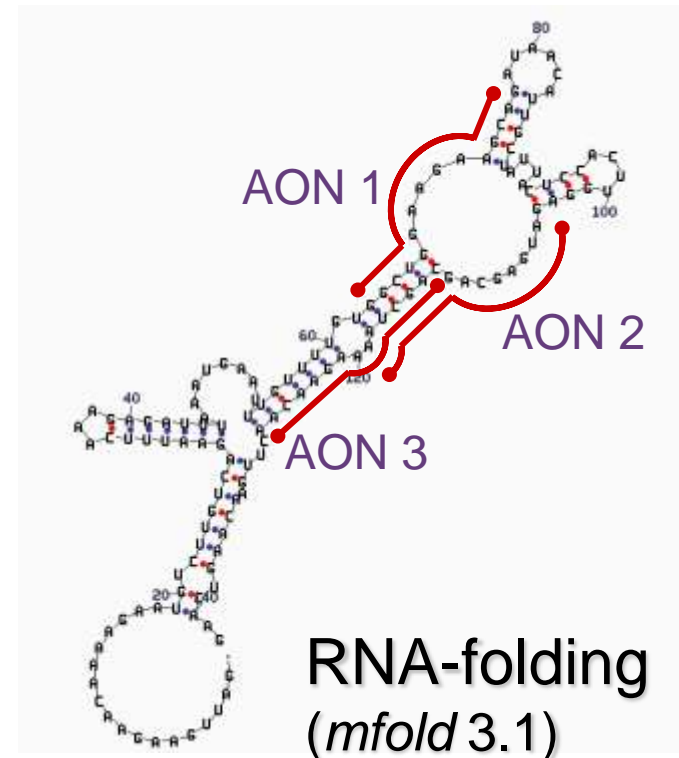
# Choosing the best ingredients: AON Design

## Exon-internal splicing regulatory element



### Targeting exon-internal sequences:

- likely to interfere with binding of splicing factors
- relatively simple design
- > 65% effective
- high specificity and sensitivity



# Choosing the best sequence

Sequence characteristics



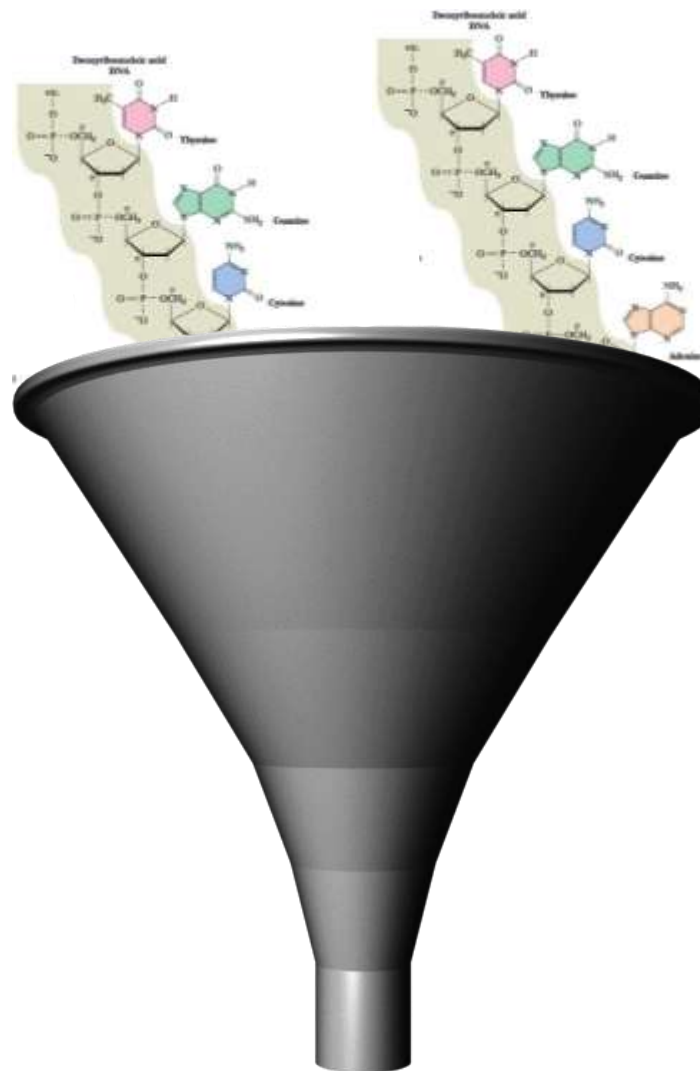
PK, ability to scale up



In vitro safety



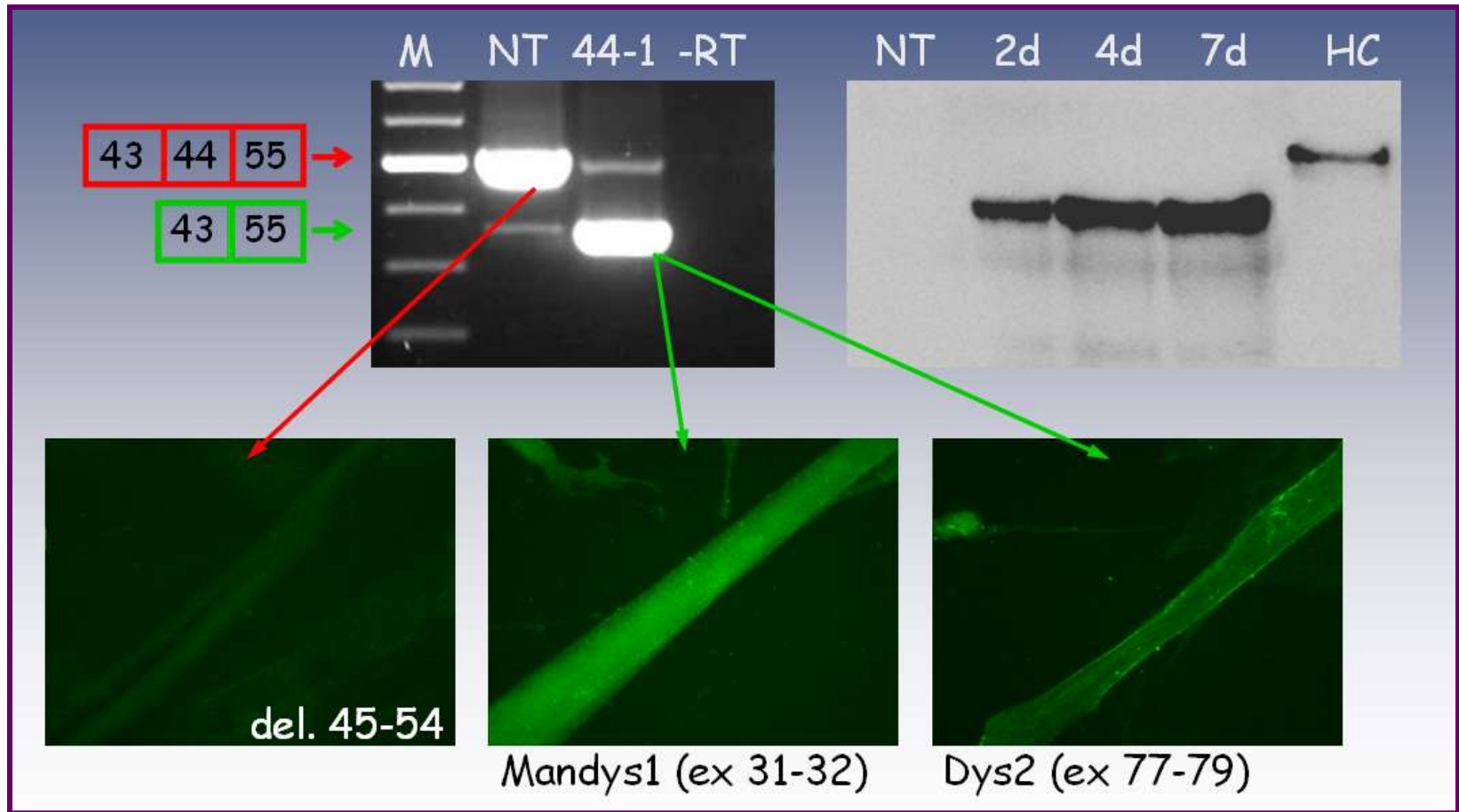
In vivo safety



## Choose the best chemistry

- Prosensa compounds are **2'O-Me-PS RNA oligonucleotides**
- Positively charged, good cell penetration
- Long muscle half life -29 days for PRO051/GSK2402968
- **Extensive safety data** available for this class of compounds in >3000 patients for different indications
- Commercial manufacture feasible

# Exon 44 Skipping in the Test Tube using in Patient Muscle Cells



# Testing in the transgenic hDMD Mouse (IM)

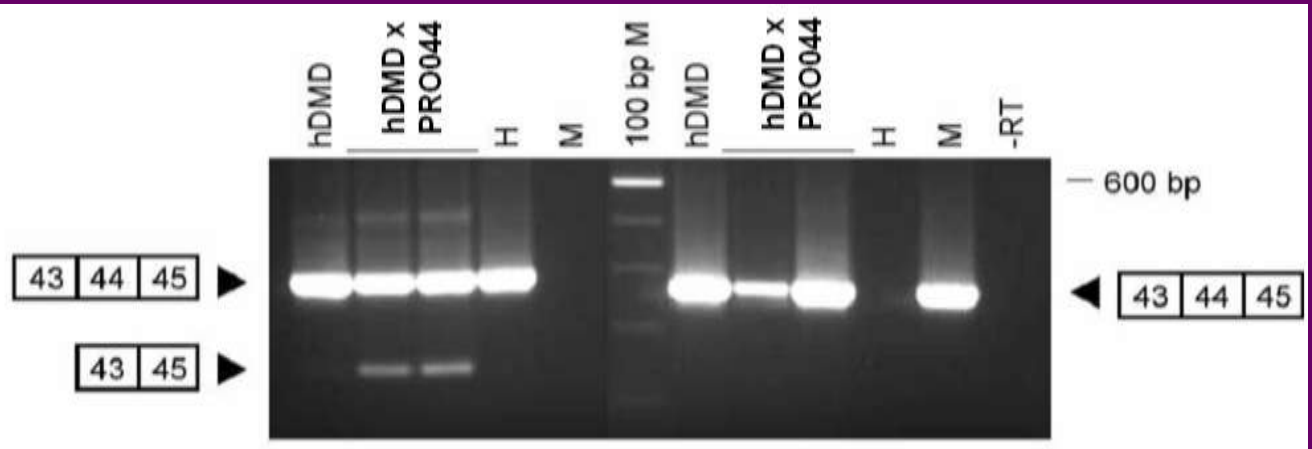
Mouse

hDMD

Human

## hDMD Mouse Model

- test human-specific AONs in vivo
- test sequence-specificity of AONs (mouse vs. human sequence)



# Making Enough Drug

- About 80 synthetic steps!
- Synthesis of material at increasing quantity
  - Studies in the test tube
  - Preclinical studies
  - Safety assessment
  - Clinical trials
- Process development
- Stability testing
- Impurity profile



# Fill and finish

- Turn final drug substance into drug product
- Final liquid formulation
- Sterility
- Available volume for injection
- Light sensitivity, storage
- Stability assessment



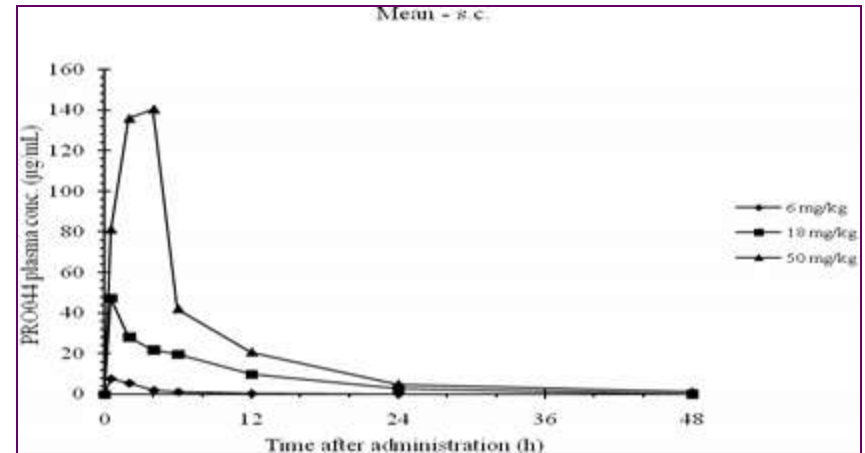
# Preclinical Studies

## Pharmacokinetics and distribution studies

- Cold and radio-labelled studies
- Develop method for measuring drug levels in muscle

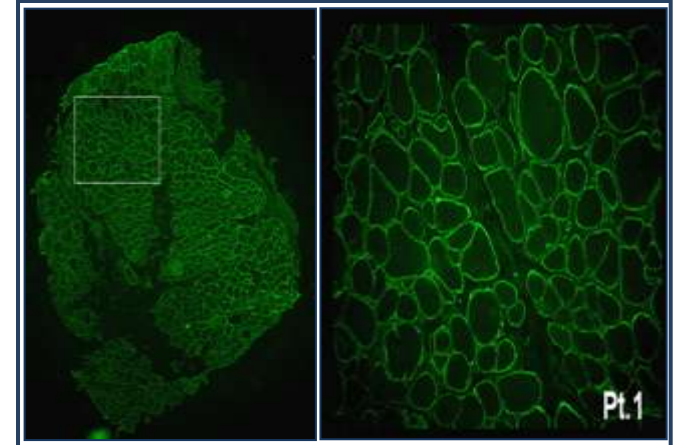
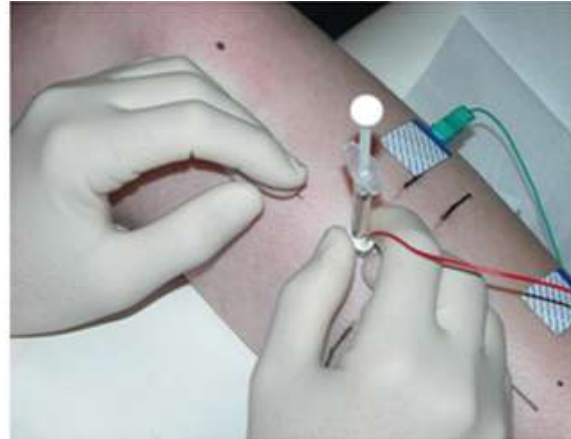
## Long term safety assessment studies

- Help determine human safety monitoring programme
- Needed before chronic dosing studies can occur



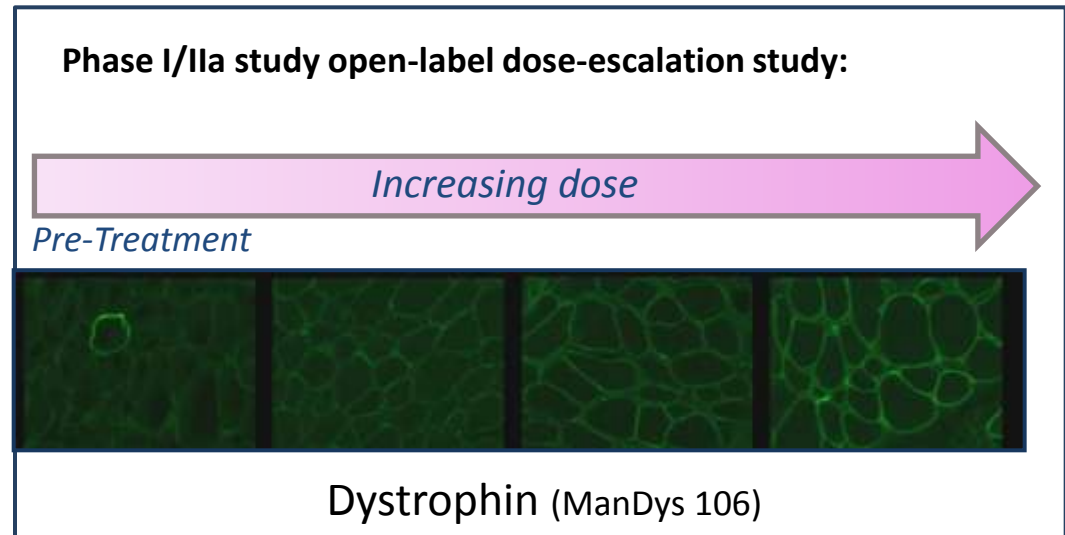
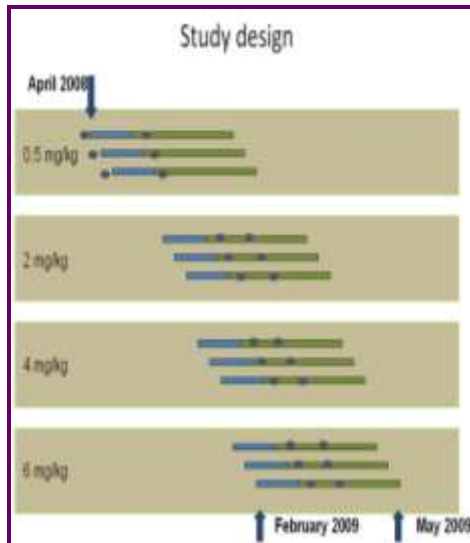
# Proof of concept (molecular)

Local



[van Deutekom et al., 2007]

Systemic

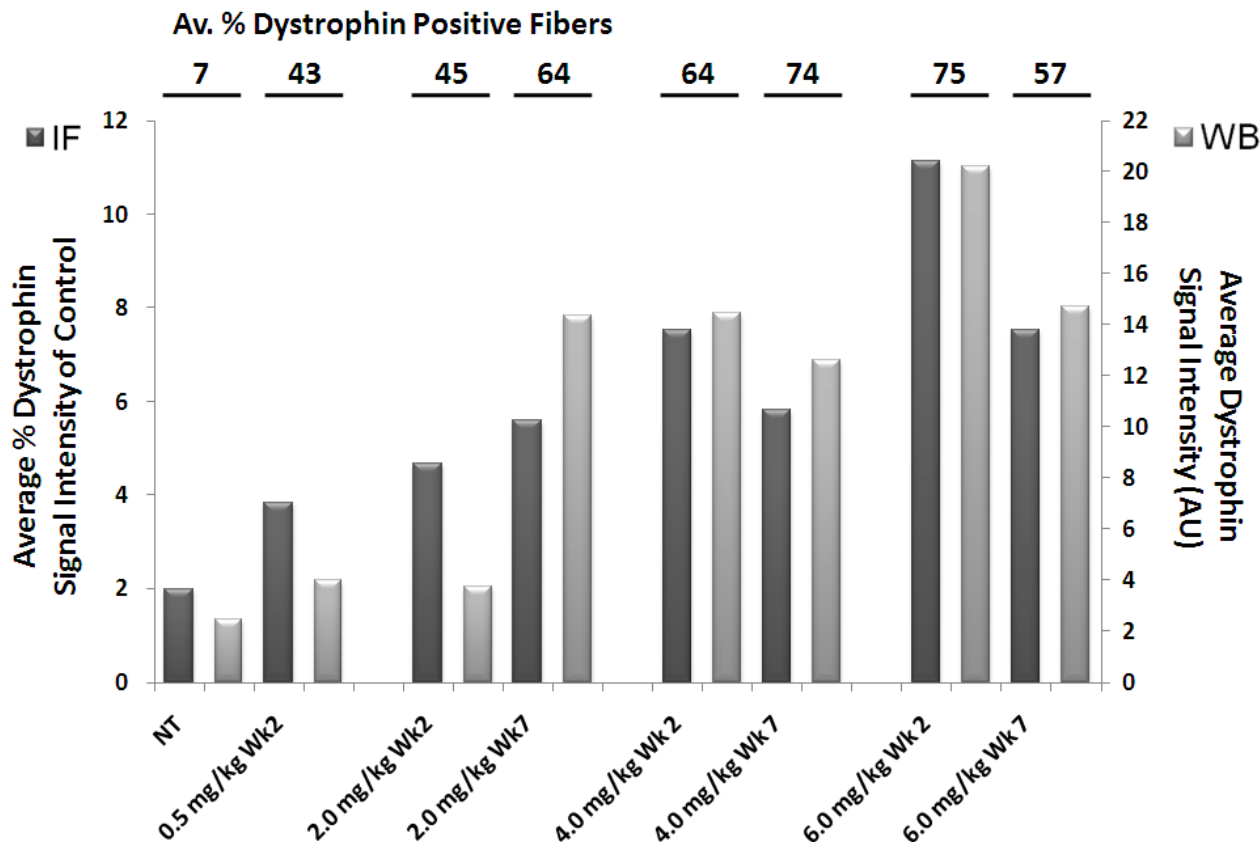


Dystrophin (ManDys 106)

1. Van Deutekom JC et al. N Engl J Med. 2007;357:2677–86.
2. Goemans NM et al. N Engl J Med. 2011; Mar 23

# Dose dependent increase in dystrophin expression

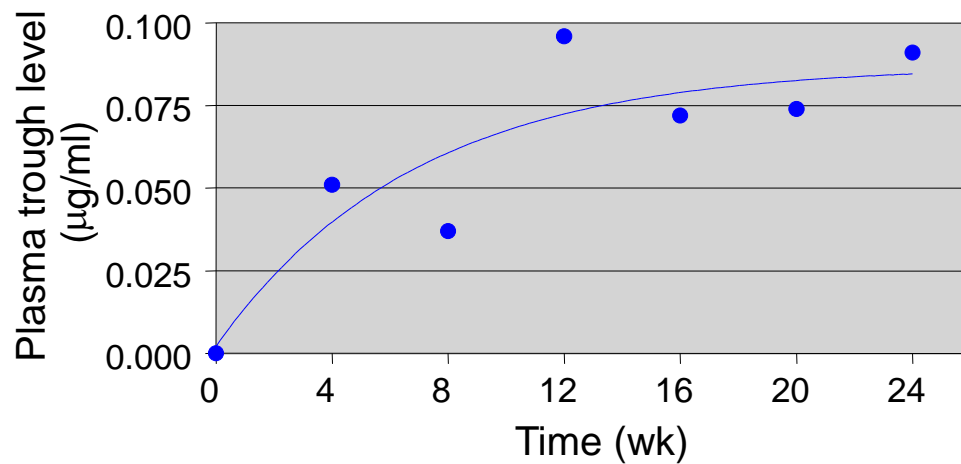
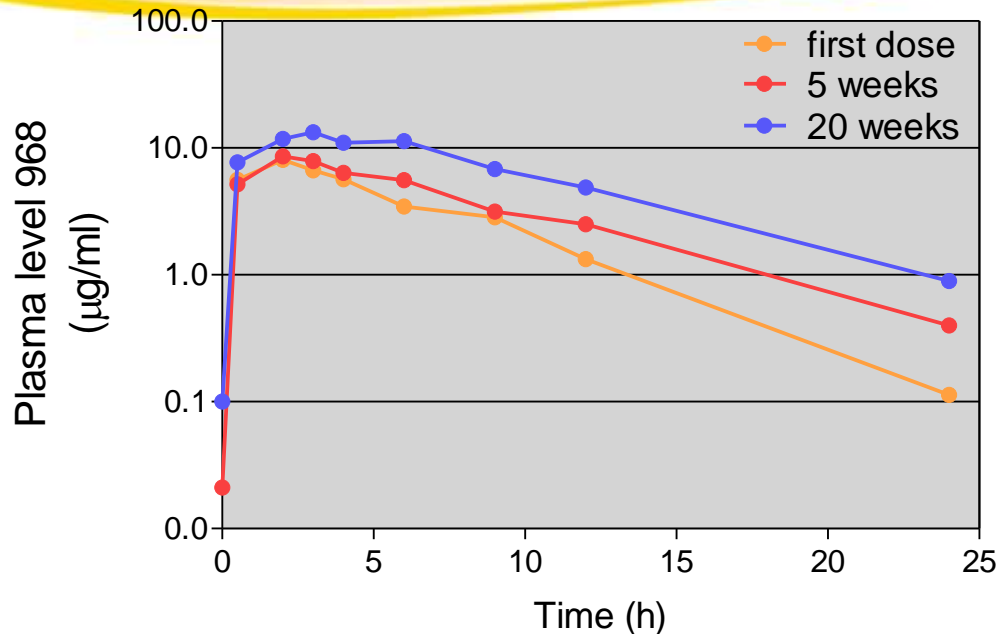
- Increased percentage of positive fibres detected by IF
- Increased signal intensity detected by IF and WB



Selected dose:  
**6 mg/kg**

Tissue levels of  
 GSK2402968 in  
 muscle biopsy at  
 this dose:  
**6.9 ± 1.9 µg/g**

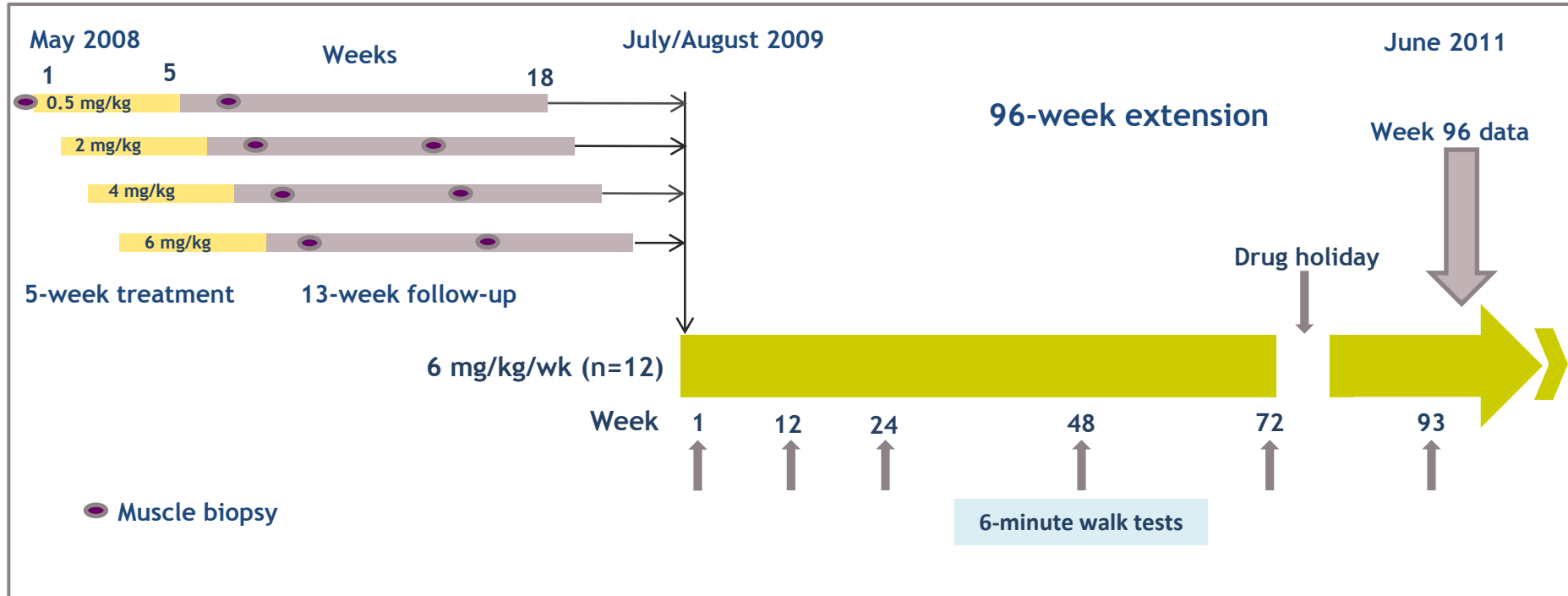
# Pharmacokinetic Profile



## Profile features

- $T_{max}$  2–3 hours
- Rapidly cleared from plasma
- Distribution to muscle tissue
- Increasing pre-dose trough levels

# Longer administration for indication of functional benefit



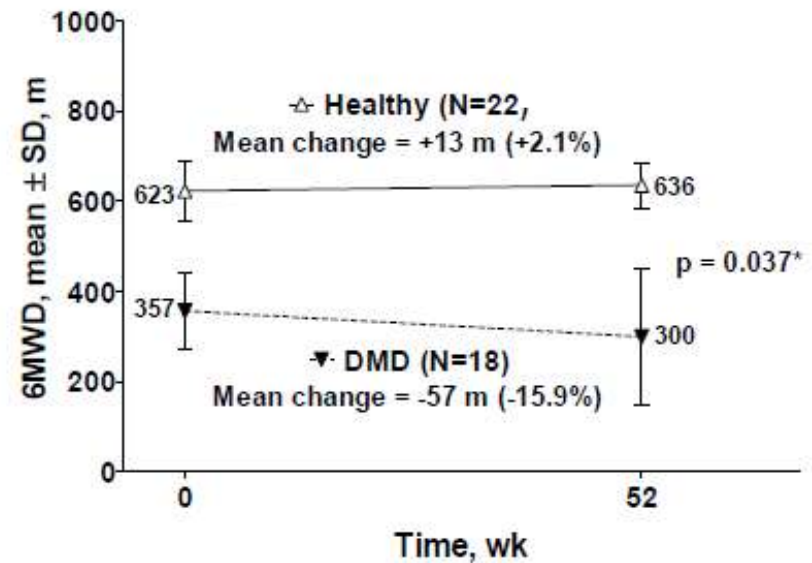
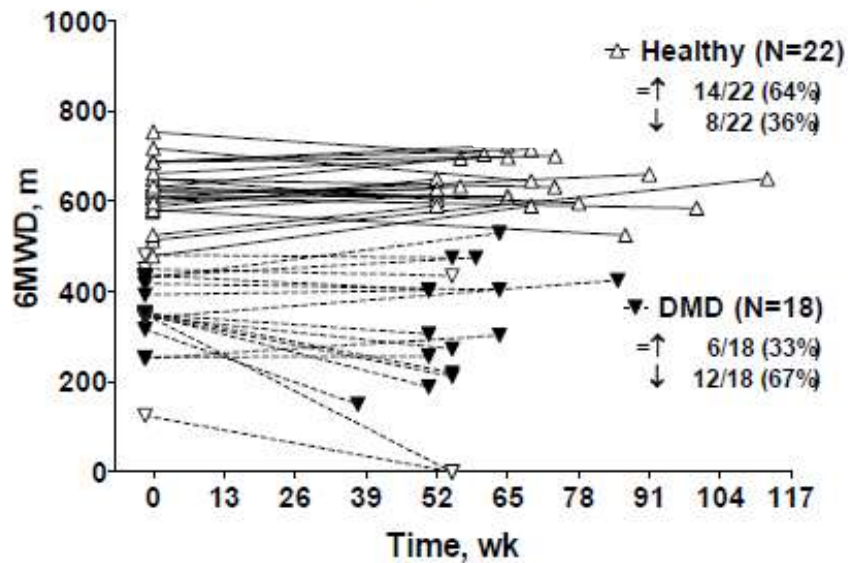
## Endpoints

- Safety and tolerability
- Plasma and tissue pharmacokinetics
- Muscle biopsies: RNA and protein effects
- Muscle strength and function

## Safety and efficacy assessments

- Weekly: AEs, urinalysis (wk 1–16; then 2-weekly, wk 16–36; then 4–8-weekly, wk 36–48; then 2–5 weekly, wk 48–96)
- Monthly: safety biochemistry and haematology, thrombocytes, PK (to Week 24; weeks 76–96), ECGs

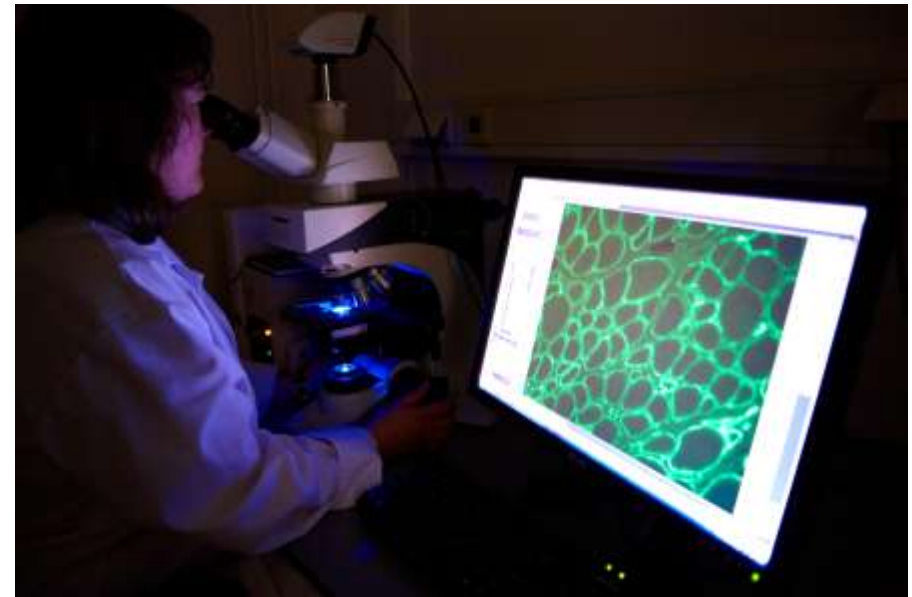
# The 6-minute walk test in DBMD: longitudinal observations compared with healthy controls (McDonald et al)



For those DBMD, aged >7 years at baseline, the mean change over 52 weeks was -115 m, with decreases in 9/10 boys

# Bioassays

- Muscle biopsy
  - Skipping
  - Dystrophin protein (IF, WB)
  
- Drug levels
  - Serum
  - Tissue
  
- Anti-dystrophin antibodies



# Patients for clinical trials

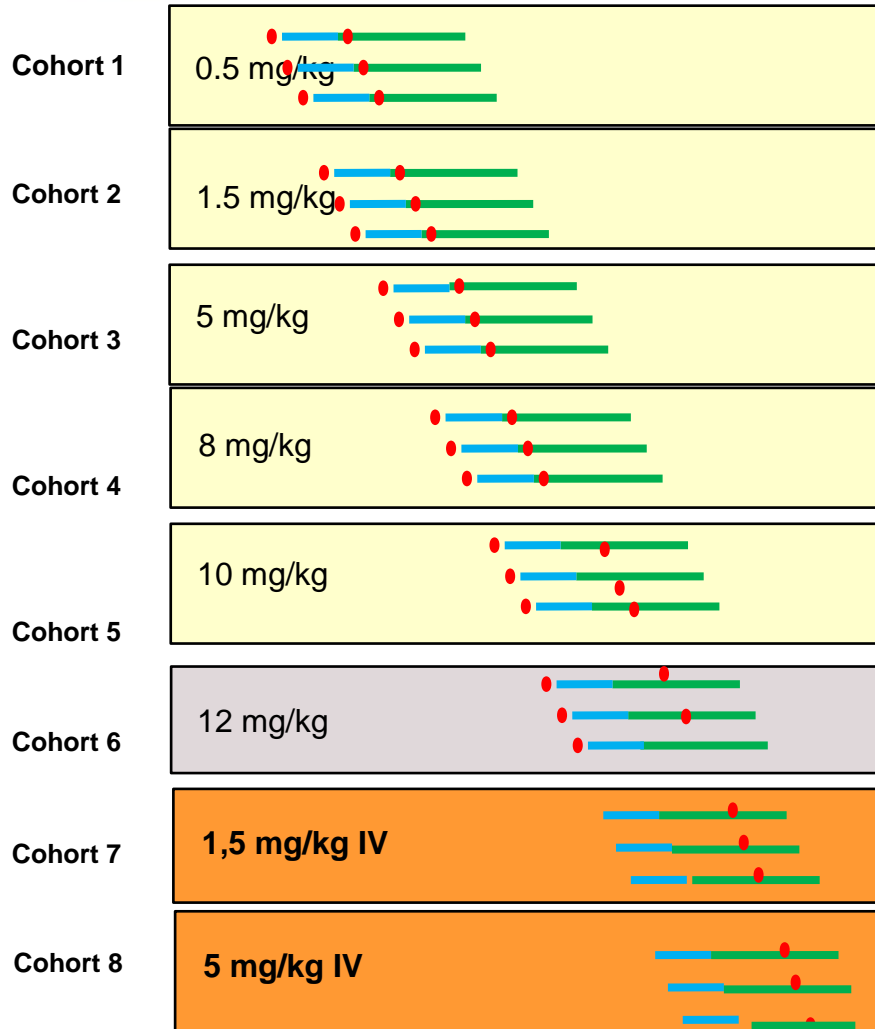
- Orphan drug Europe 50 : 100,000
- Ultra-orphan (NICE) 2 : 100,000
- PRO051/GSK2402968 0.5 : 100,000



# Finding patients



# PRO044 Phase I/II study



Leiden University  
Medical Center



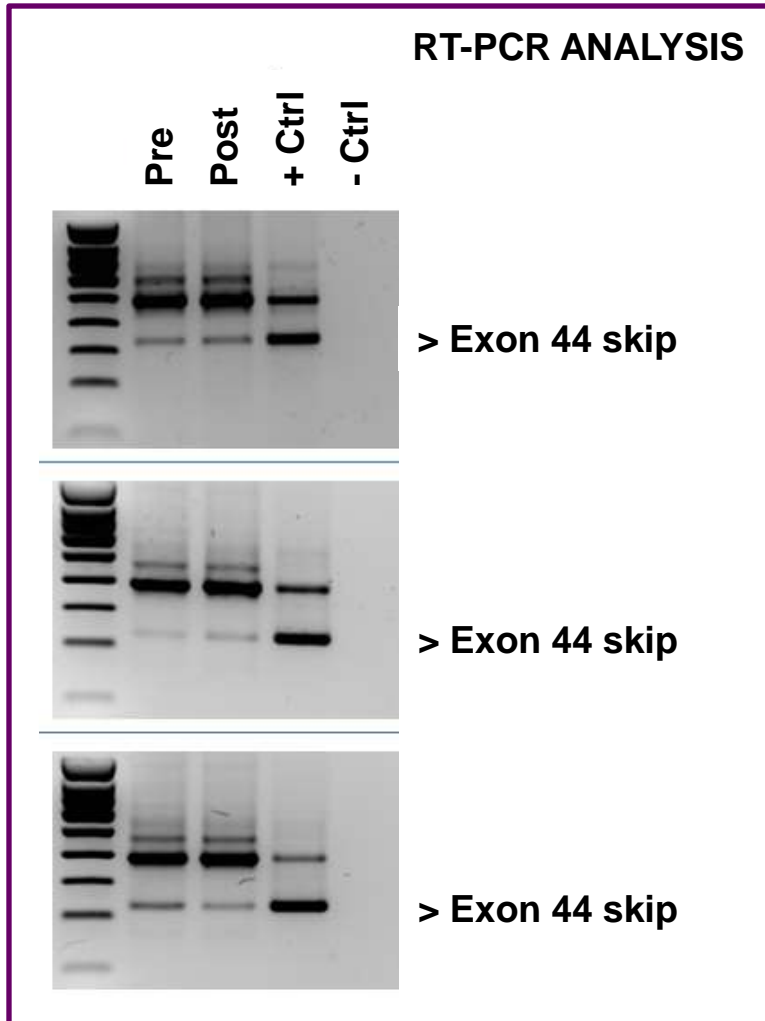
University of Ferrara



UNIVERSITY OF GOTHENBURG



# PRO044-CLIN-01: Muscle Biopsy Analysis



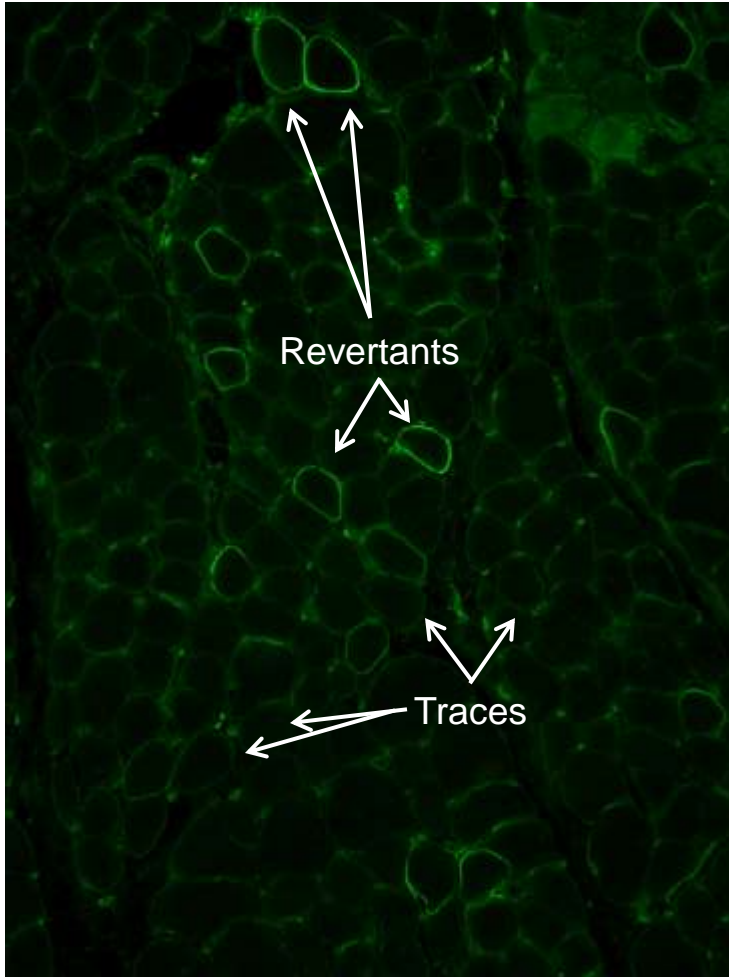
## Patient subpopulation specifics

General high level of spontaneous exon 44 skipping (“easy” exon to skip)

Relatively high number of “dystrophin-positive” revertant fibers

Interference of analysis of specific PRO044-induced exon 44 skipping: dependent on number of revertant fibers in pre vs post treatment biopsies

# PRO044-CLIN-01: Muscle Biopsy Analysis



## Patient subpopulation specifics

General high level of spontaneous exon 44 skipping (“rescue”)

Relatively high number of “dystrophin-positive” revertant fibers and fibers with trace dystrophin

These are to be distinguished from PRO044-induced positive fibers by **immunofluorescence analysis of cross sections** (not by Western Blot analysis of total protein homogenates)

## Drugs to skip other exons

- PRO045 and PRO053 in clinical studies 1<sup>st</sup> half 2012
- PRO052 and PRO055 in preclinical development
- Commitment to address rare exons

# Summary

- Prosensa committed to developing novel medicines for DMD
- Expertise in oligo design, manufacturing, preclinical and clinical development
- Key partnership with GSK to globalize reach and bring depth to portfolio
- 6 products in development (PRO051, PRO044, PRO045, PRO053, PRO055, PRO052)
- Early encouraging signs of clinical efficacy
- Extensive programme of controlled studies in different populations
- Committed to find a solution for rare exons

# Financial Support

## Venture Capital



## Other Partners

