



# FORCE™ Platform Delivers Exon Skipping PMO, Leads to Durable Increases in Dystrophin Protein in *mdx* Mice and Is Well Tolerated in NHPs

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Muscle Study Group Annual Scientific Meeting | Oct. 1, 2021

Ravi, living with DMD



# Forward-Looking Statements

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# Agenda

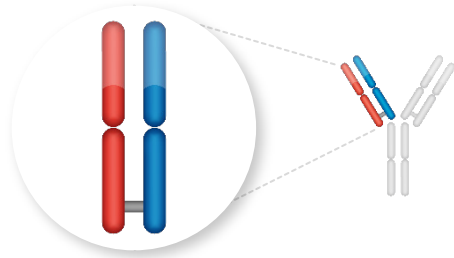
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- FORCE platform to enable muscle-targeted delivery of oligonucleotides
- Application of FORCE platform for the treatment of DMD
  - Functional benefit in the *mdx* mouse model
  - FORCE platform achieves high level dystrophin expression across cardiac and skeletal muscle in *mdx* model
- On path to clinical translation with DYNE-251
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  - Significant exon skipping in NHP cardiac and skeletal muscles
  - NHP toxicology results support advancement of DYNE-251 into the clinic

# Dyne FORCE™ Platform: Modern Oligo Therapeutics for Muscle Diseases

## ANTIBODY

Proprietary Fab targets TfR1 to enable muscle delivery

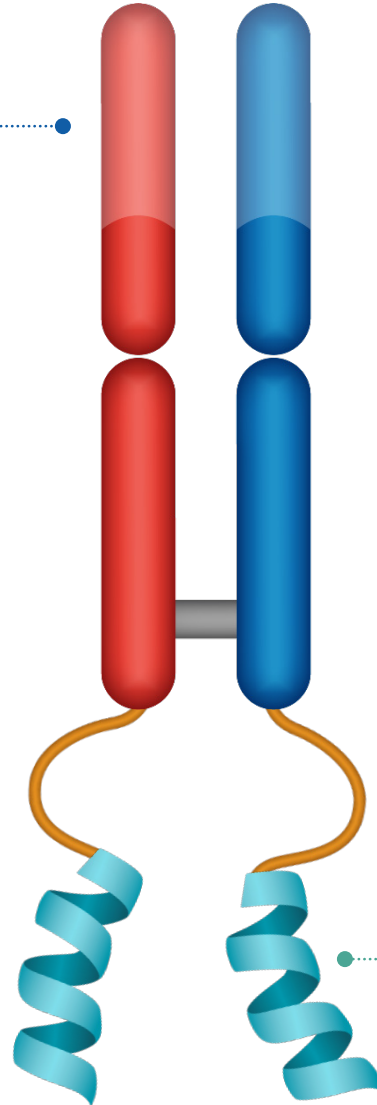


## LINKER

Clinically validated, enables precise conjugation of payloads to a single Fab

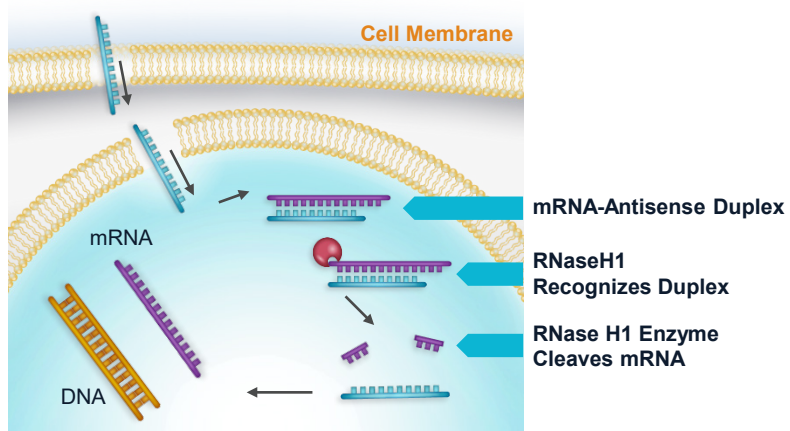
## PAYLOAD

Modularity enables rational selection of payload to target the genetic basis of disease

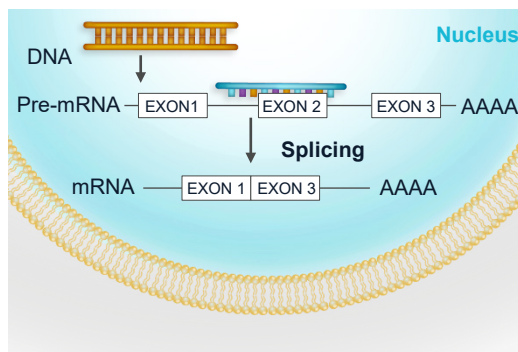


# Rationally Select Payload to Target Genetic Basis of Disease

## ASO acts in the nucleus and cytoplasm

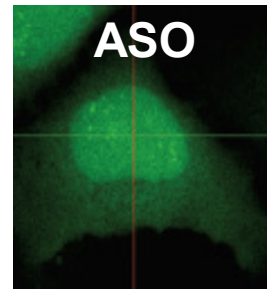


## Splice-modulating ASO

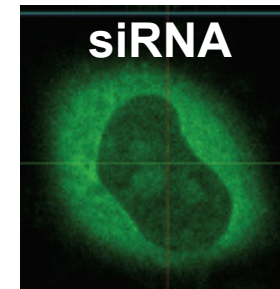


Single-Stranded Antisense

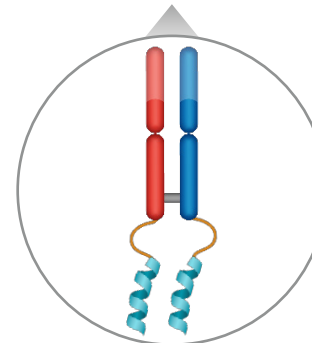
## Subcellular distribution of ASO and siRNA



Nuclear localization

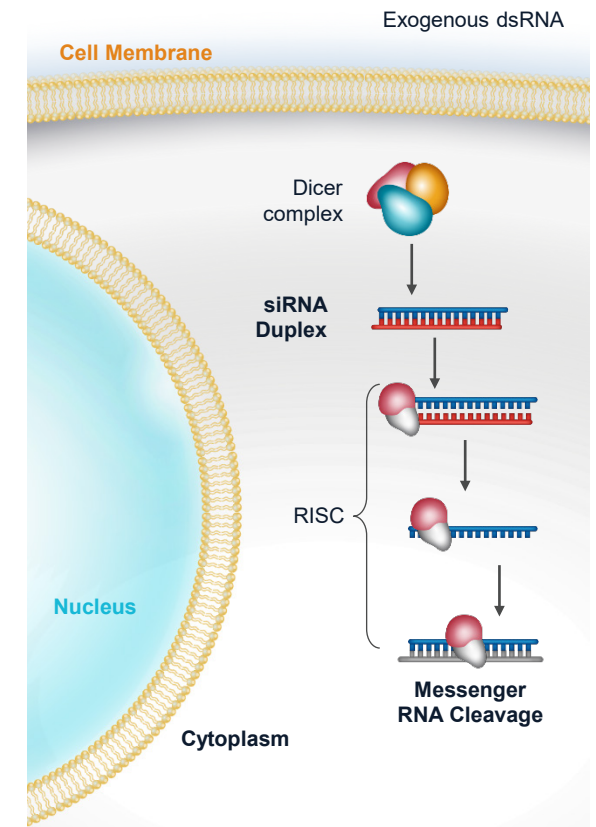


Cytoplasmic localization



**FORCE** delivers **ASO** payload for nuclear targets, **siRNA** payload for cytoplasmic targets

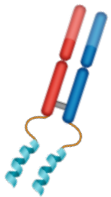
## siRNA acts in the cytoplasm



Double-Stranded Antisense (siRNA)

# FORCE Platform Designed to Deliver Significant Advantages

**Stop or Reverse  
Disease  
Progression**



## **Targeted Muscle Delivery**

Leverages TfR1 expression on skeletal, cardiac and smooth muscle



## **Targets Genetic Basis of Disease**

Rationally select payloads to match target biology



## **Redosable Administration**

Potential for individualized patient titration and longer-term efficacy



## **Enhanced Tolerability**

Targeted delivery limits systemic drug exposure



## **Extended Durability**

Potential for prolonged disease-modifying effects, enabling less frequent dosing



## **Reduced Development and Manufacturing Costs**

A single Fab and linker utilized across all programs

# Building a Global DMD Franchise of Transformative Therapies



## Overview

- Mutation in the *DMD* gene that encodes for dystrophin
- Onset in first few years of life
- Life expectancy ~30 years



## Clinical Presentation

- Muscle weakness
- Progressive loss of function
- Loss of ambulation
- Respiratory/cardiac failure



## Population

- ~12,000 - 15,000 (US)
- ~ 25,000 (Europe)



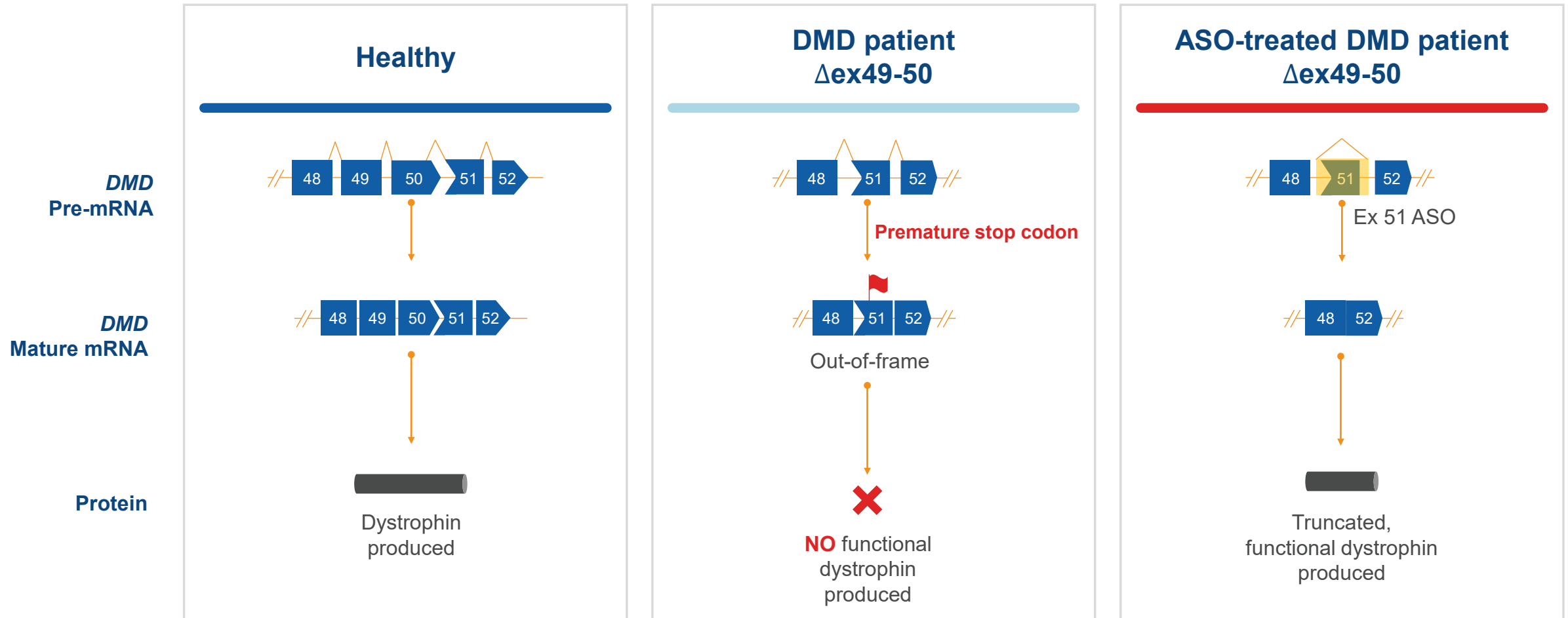
## OUR APPROACH

### Best-in-class Targeted Exon Skipping

Increase dystrophin expression and enable less frequent dosing to potentially **stop or reverse disease progression**

Current Approved  
Exon 51 Therapies  
Only Increased  
Dystrophin  
Production  
**<1%**

# ASO-Mediated Exon Skipping: Mechanism for Disease Correction





# Agenda

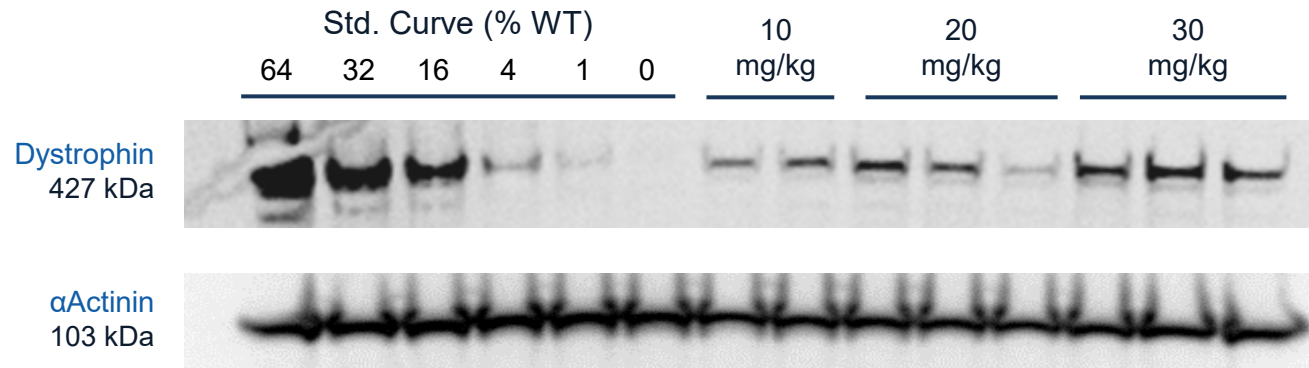
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# FORCE Dose-Dependently Increased Dystrophin Expression

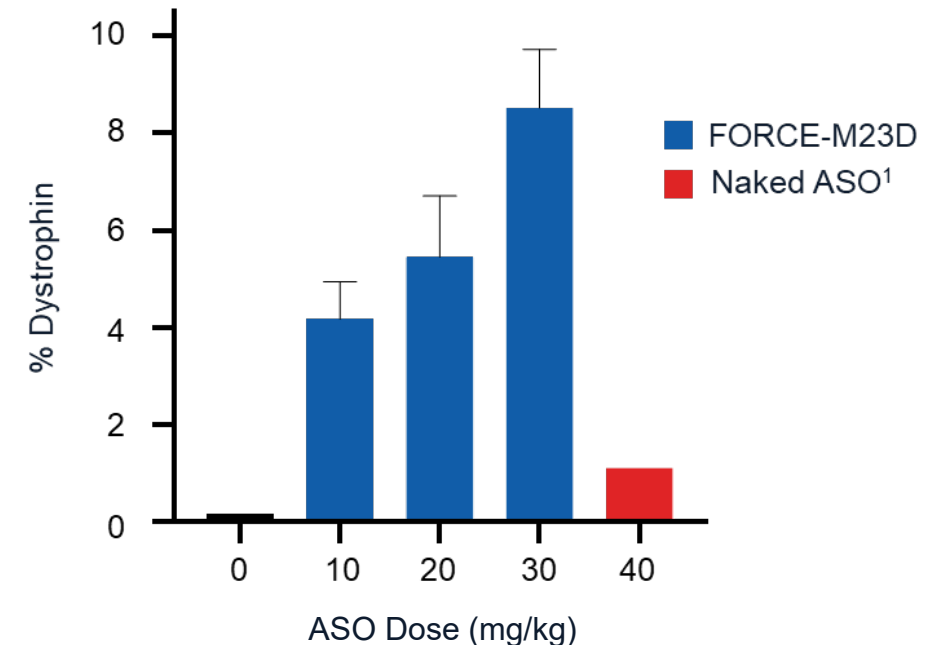


## Dose-Dependent Increase in Dystrophin Expression



Standard curve - Used pooled WT protein and pooled mdx protein,  
% indicates amt. of WT spiked into sample

## Restored Dystrophin Expression

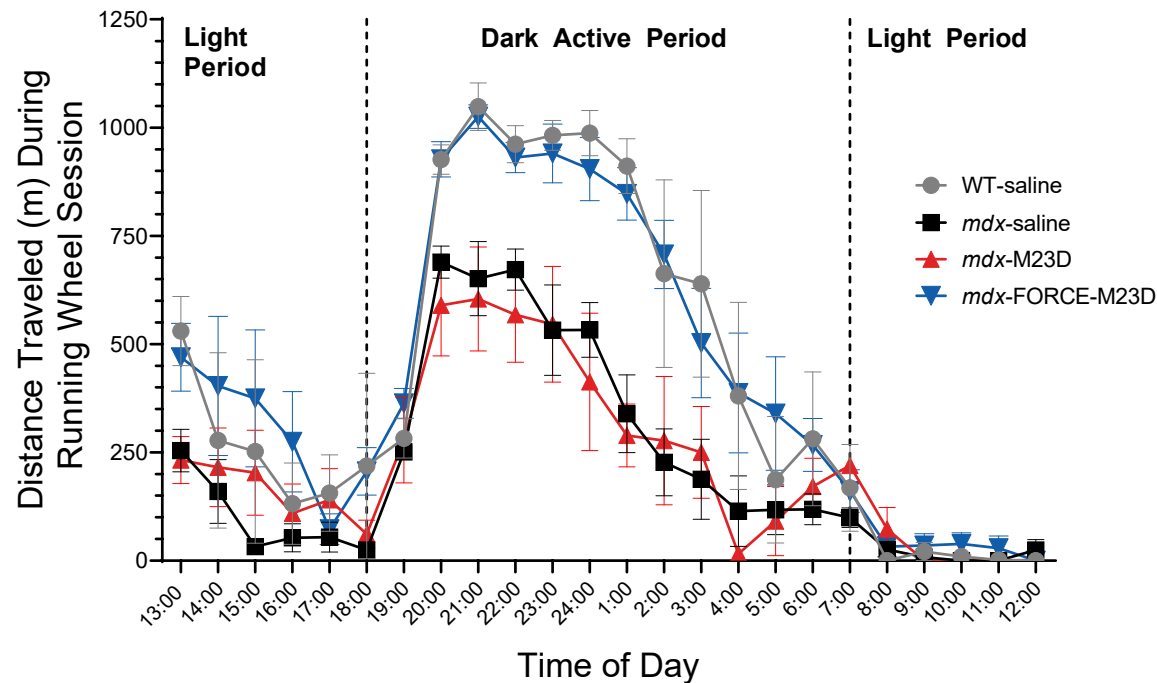


# FORCE Demonstrated Functional Benefit with a Single Dose



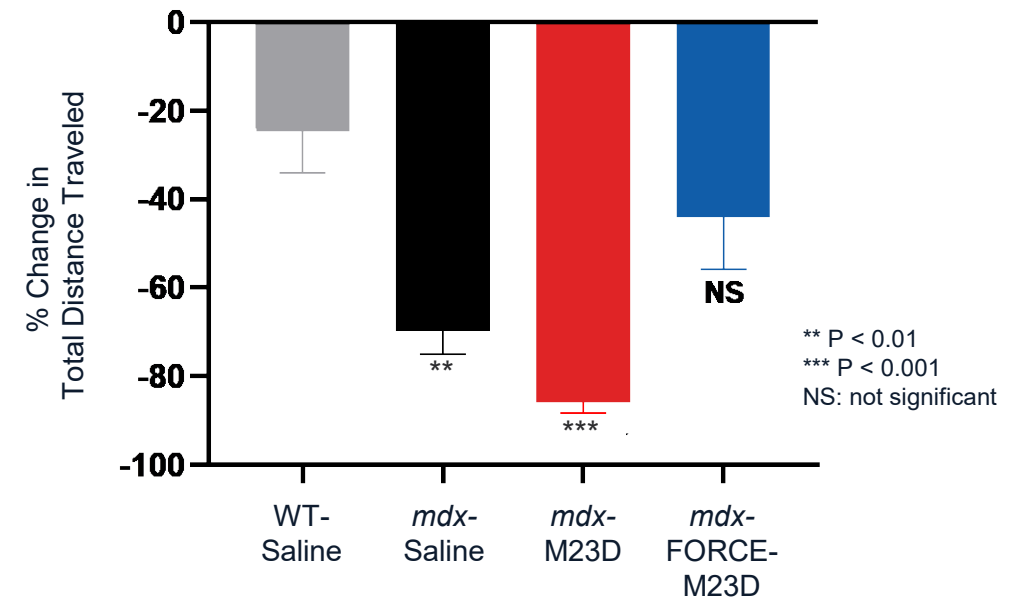
## Distance Traveled in Home Cage Running Wheel

(Assessed 4 weeks after treatment)



## Distance Traveled in Open Field Following Hind Limb Fatigue Challenge

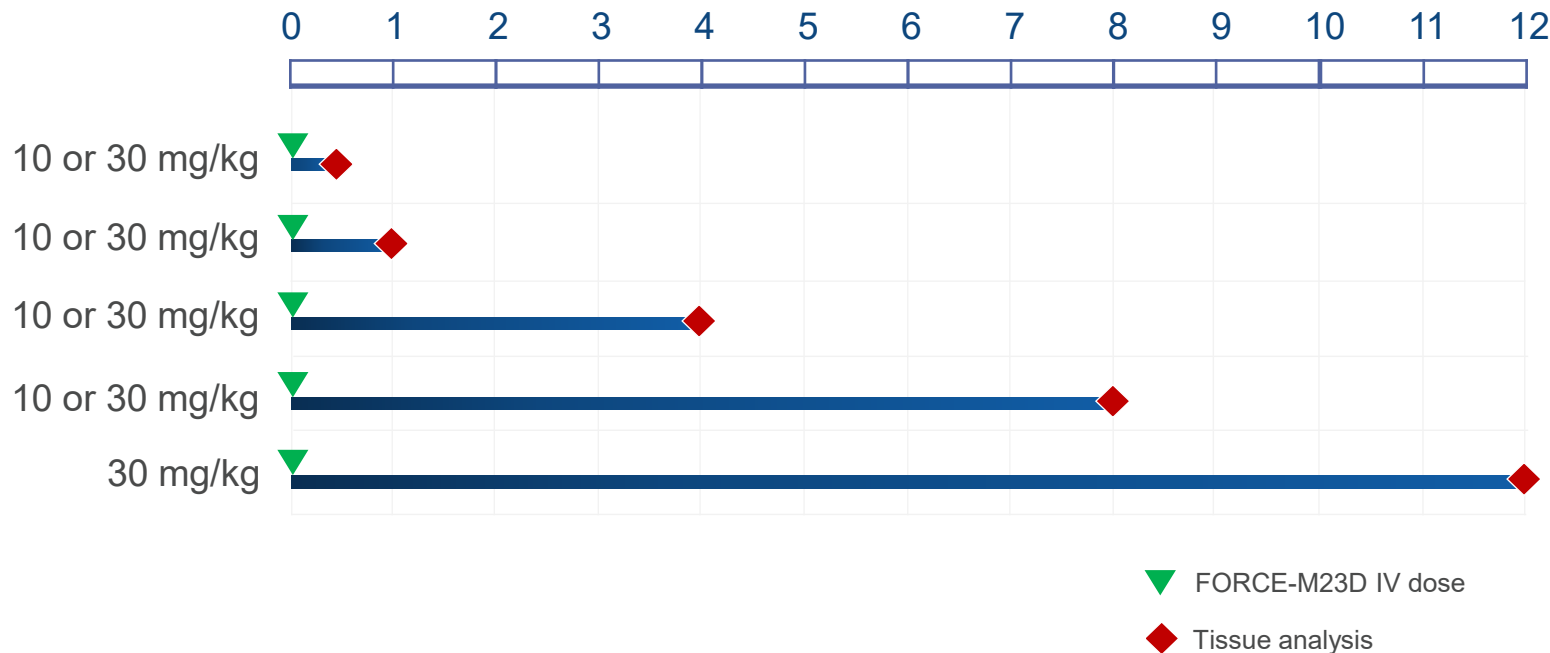
(Assessed 2 weeks after treatment)



# Study Evaluated Dynamic of FORCE on Dystrophin Expression up to 12 Weeks After a Single Dose



## Study Timeline (Weeks)



## Endpoints

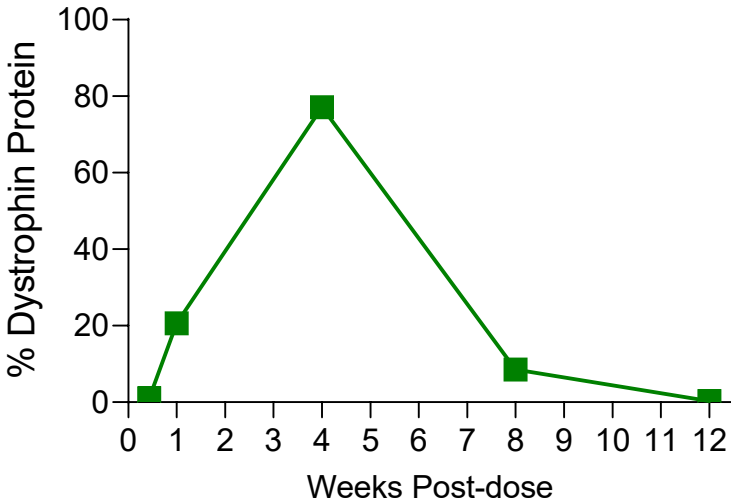
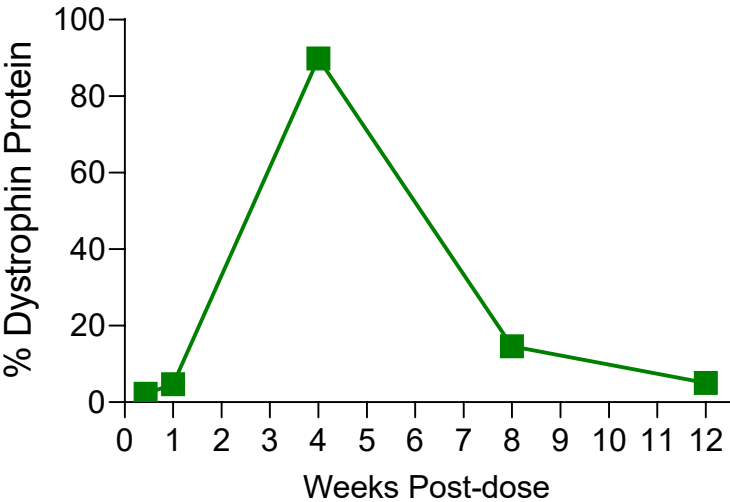
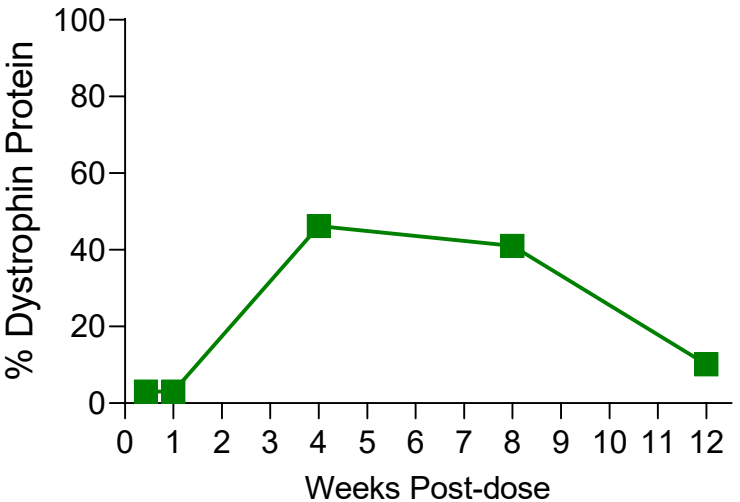
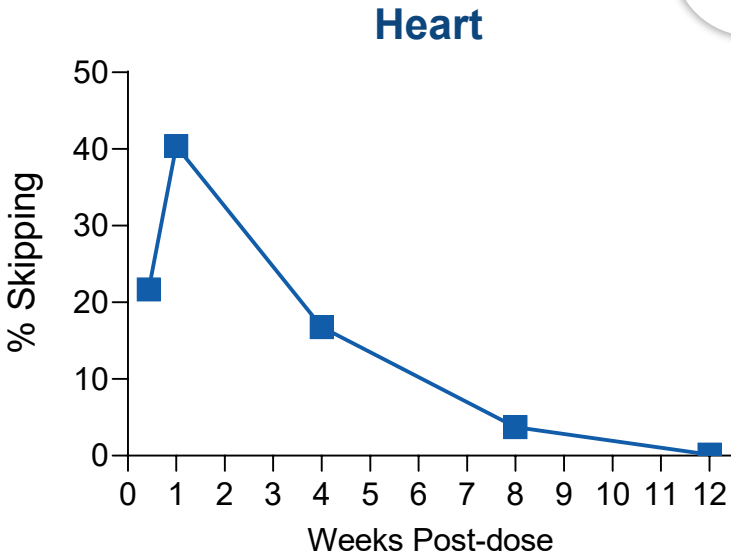
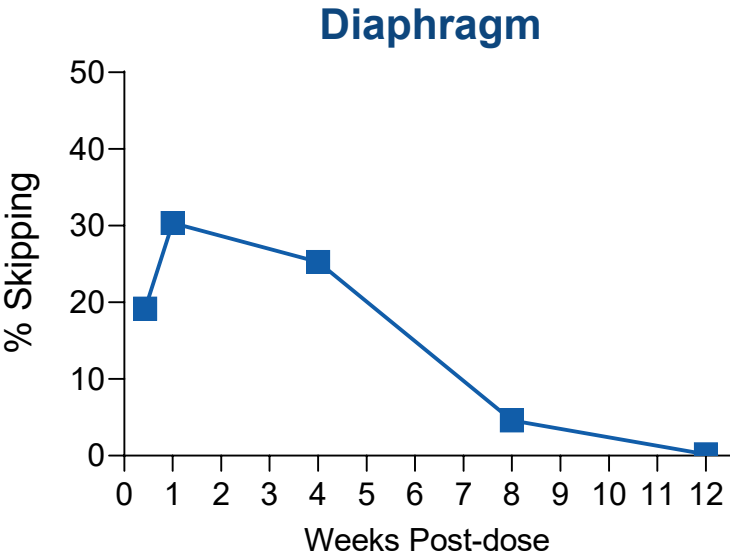
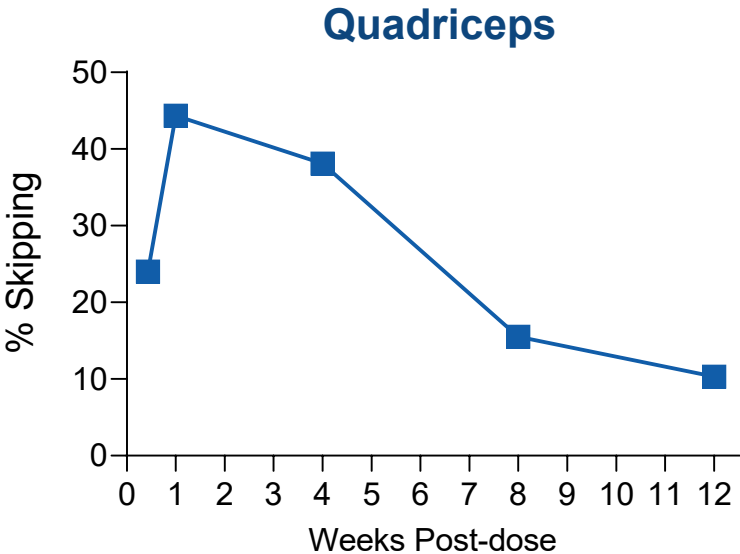
- ASO muscle concentration
- Exon skipping by PCR
- Dystrophin protein by WB
- Dystrophin localization by IF

## Tissues analyzed

- Quadriceps
- Diaphragm
- Heart



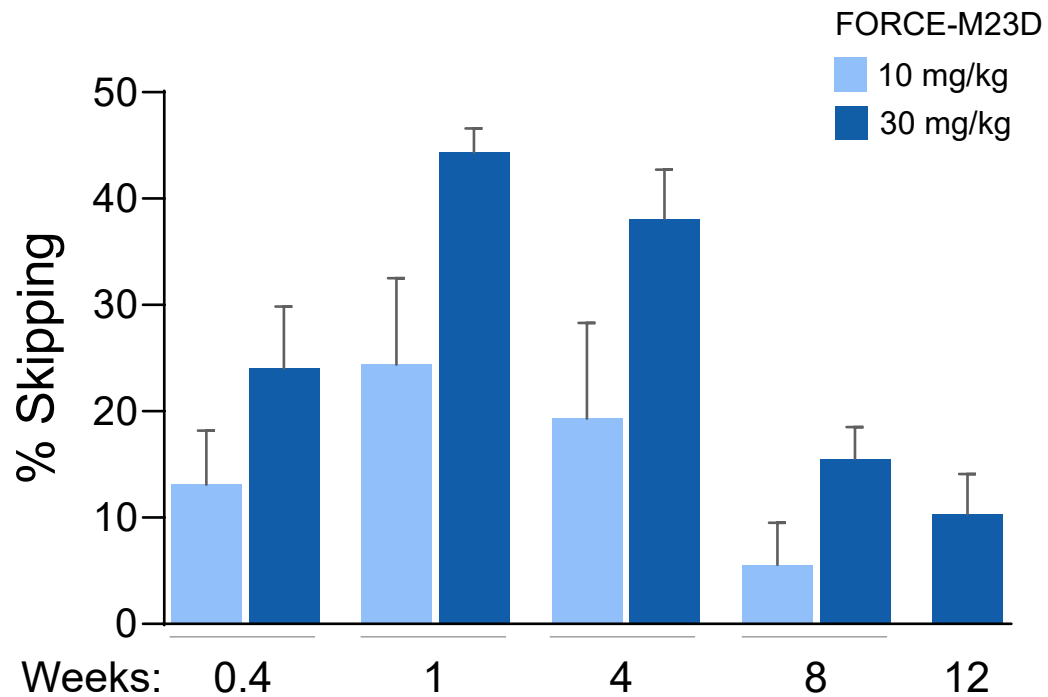
# FORCE Achieved Robust and Durable Skipping and Dystrophin Expression in Cardiac and Skeletal Muscle



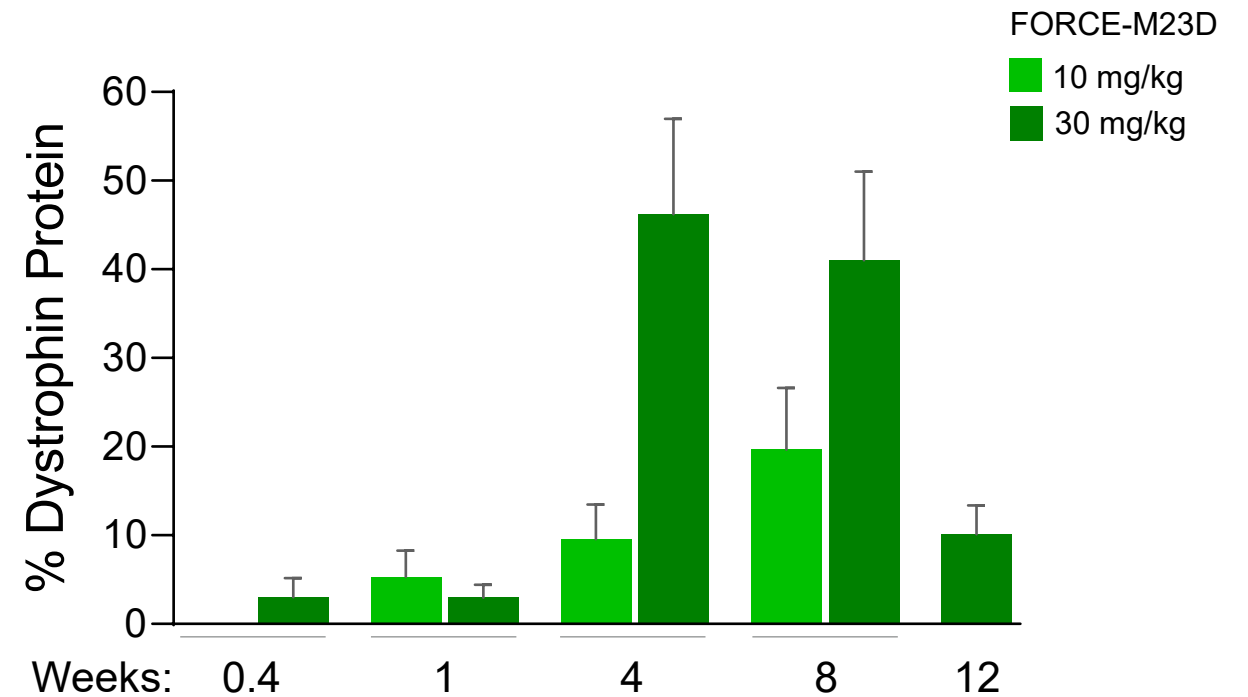
# FORCE Achieved Robust and Durable Skipping and Expression of Dystrophin in Quadriceps



% Skipping by PCR



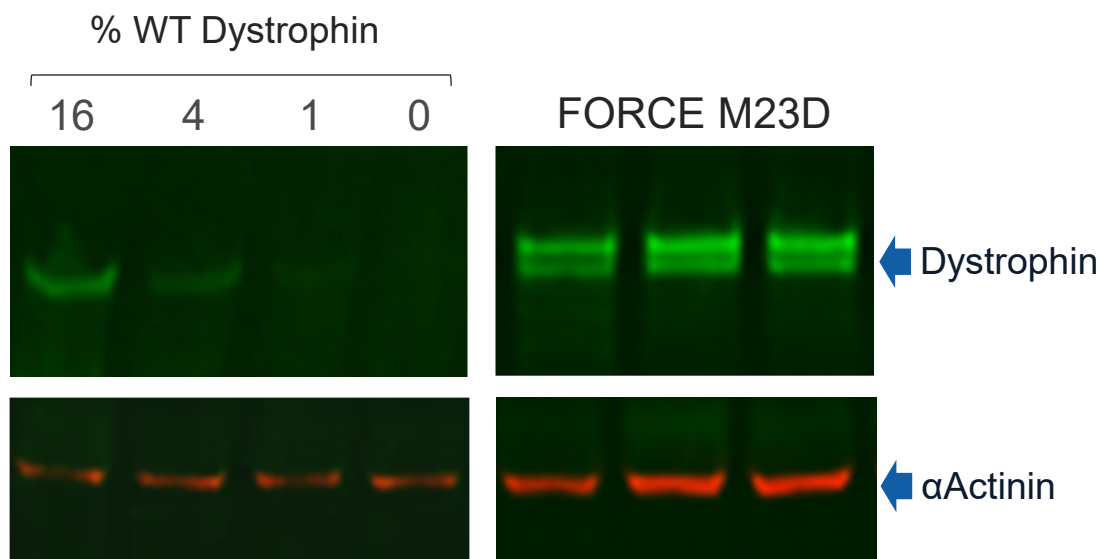
Dystrophin by WB



# FORCE Achieved Robust Dystrophin Expression and Localization to Sarcolemma in Quadriceps at 8 Weeks

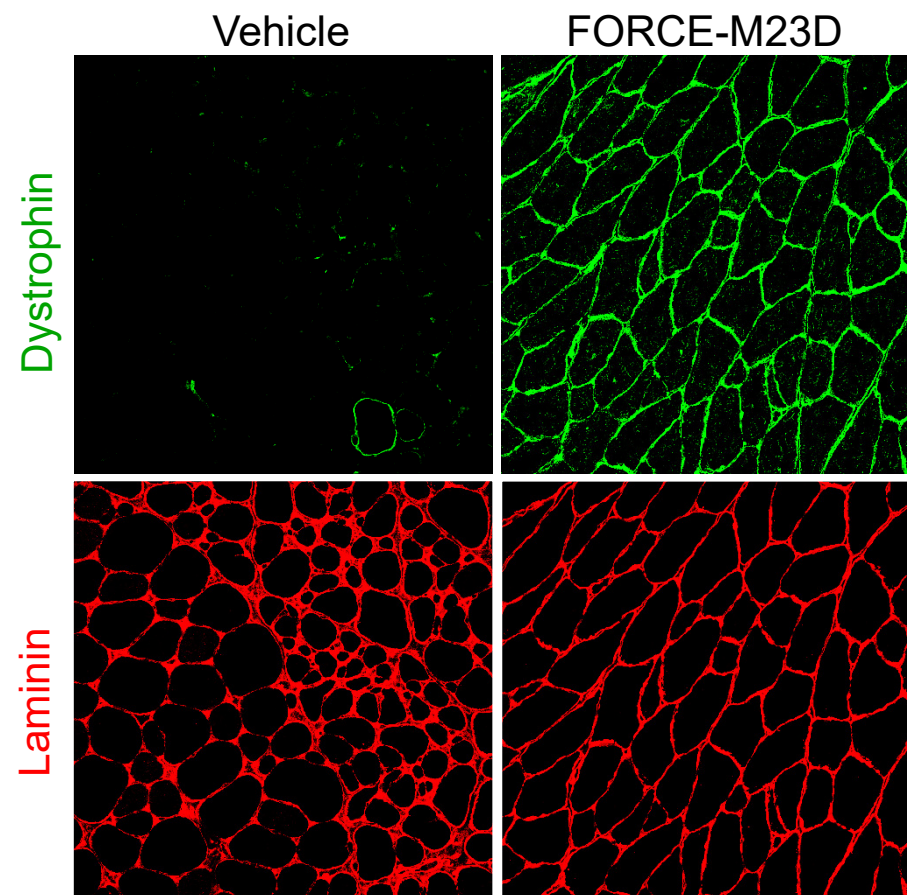


**Dystrophin Expression by WB**  
**30 mg/kg 8 Weeks Post-Dose**



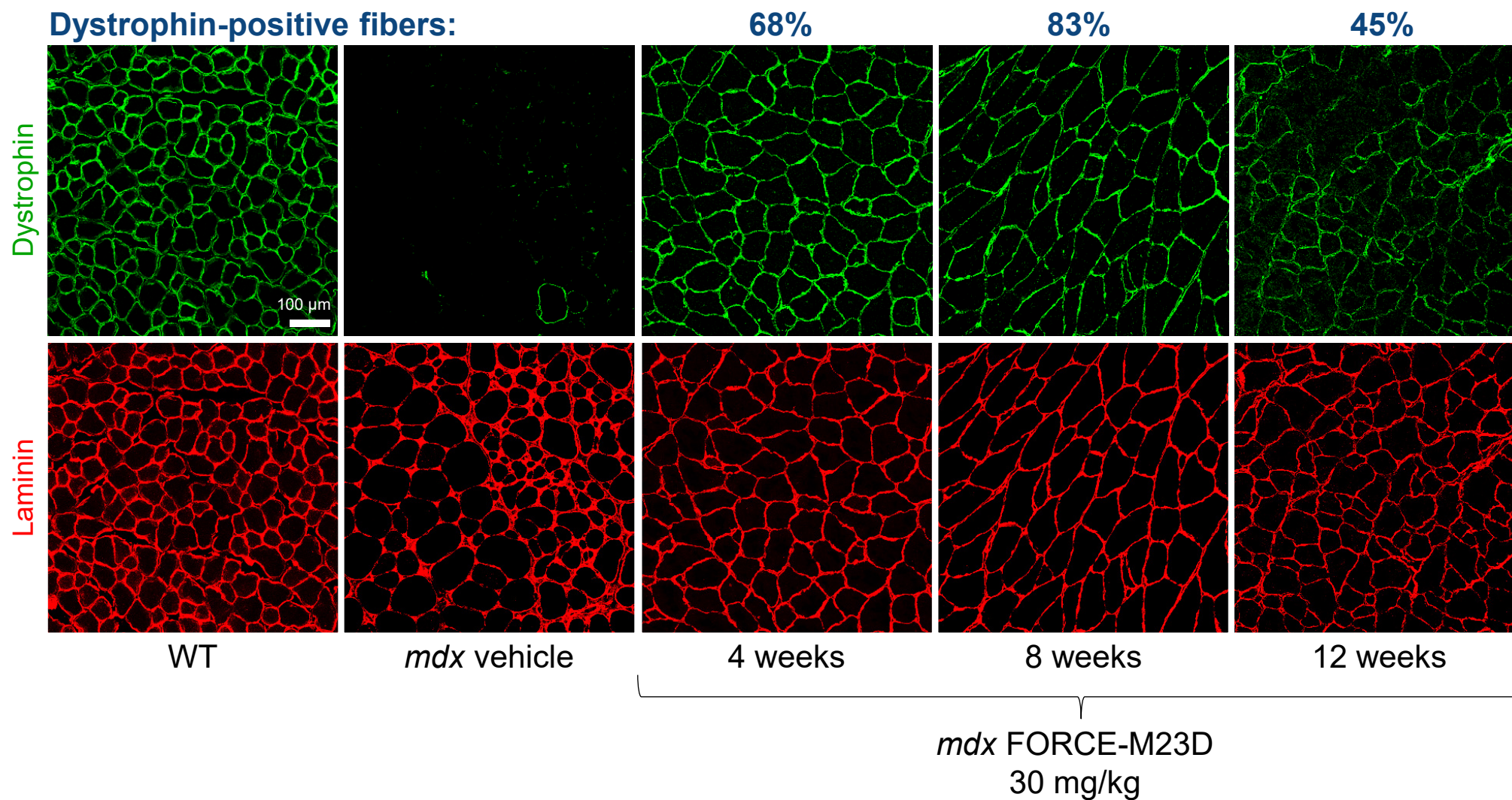
41% of wild-type dystrophin

**Dystrophin Localization to Sarcolemma**



83% dystrophin-positive fibers

# FORCE Achieved Durable Dystrophin Localization to Sarcolemma in Quadriceps

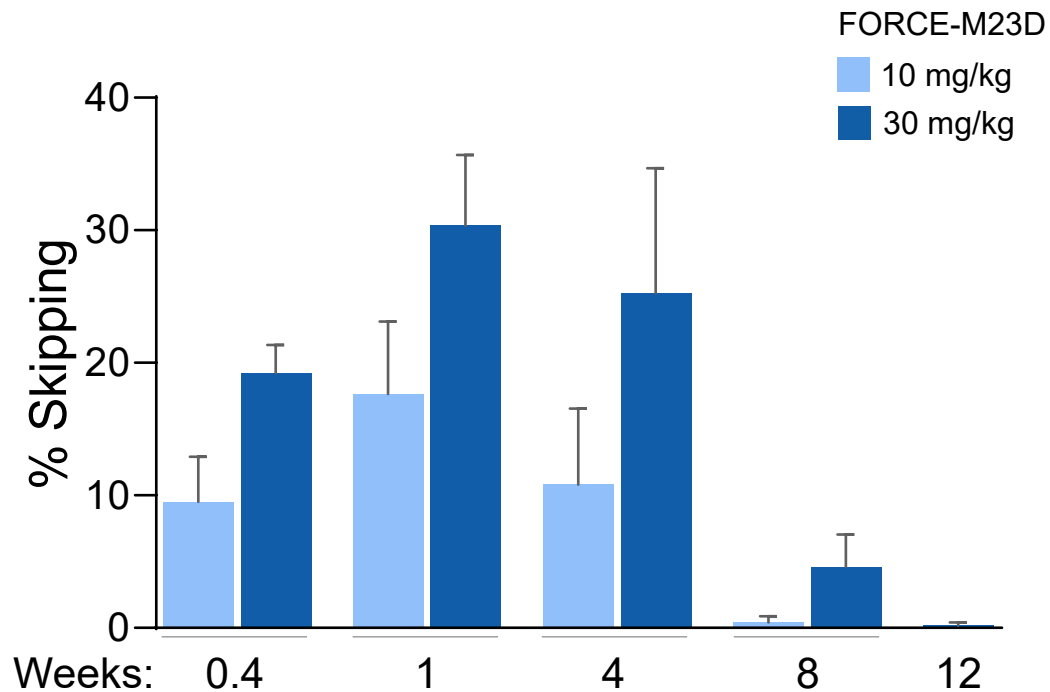




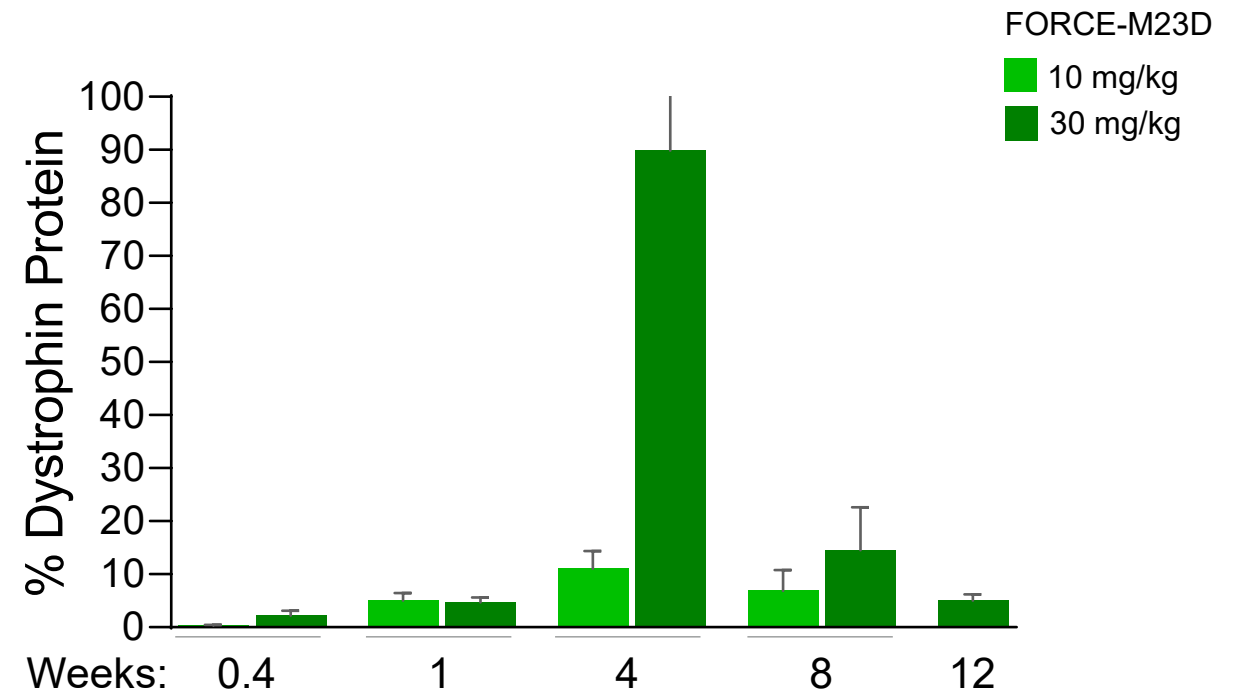
# FORCE Achieved Robust and Durable Skipping and Expression of Dystrophin in Diaphragm



% Skipping by PCR



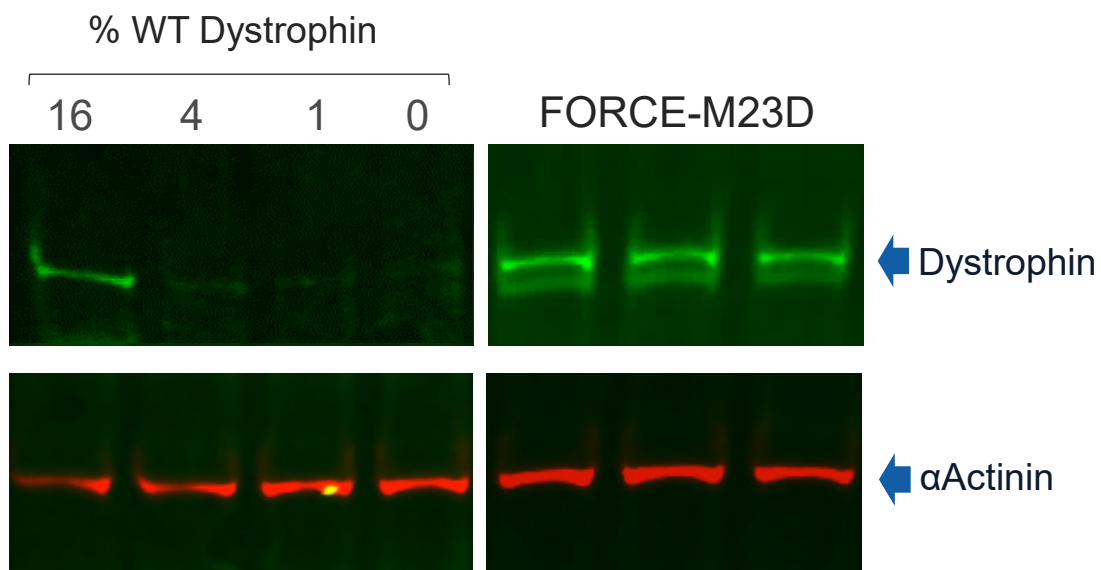
Dystrophin by WB



# FORCE Achieved Robust Dystrophin Expression and Localization to Sarcolemma in Diaphragm at 4 Weeks

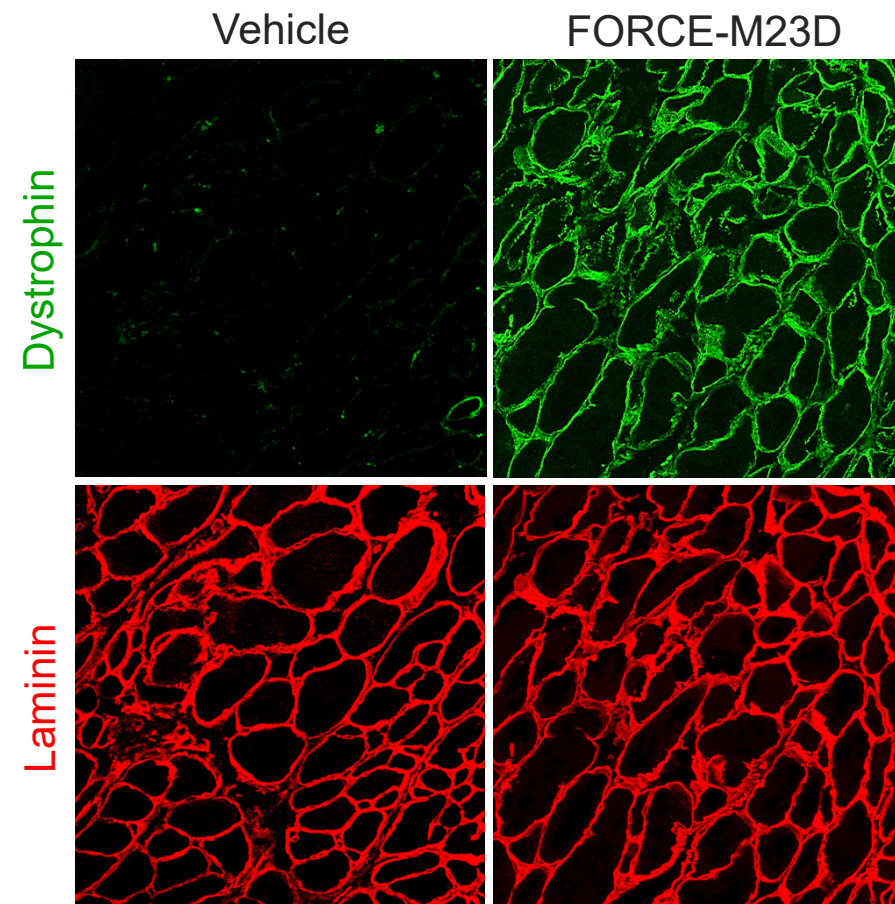


## Dystrophin Expression by WB 30 mg/kg 4 Weeks Post-Dose



90% of wild-type dystrophin

## Dystrophin Localization to Sarcolemma

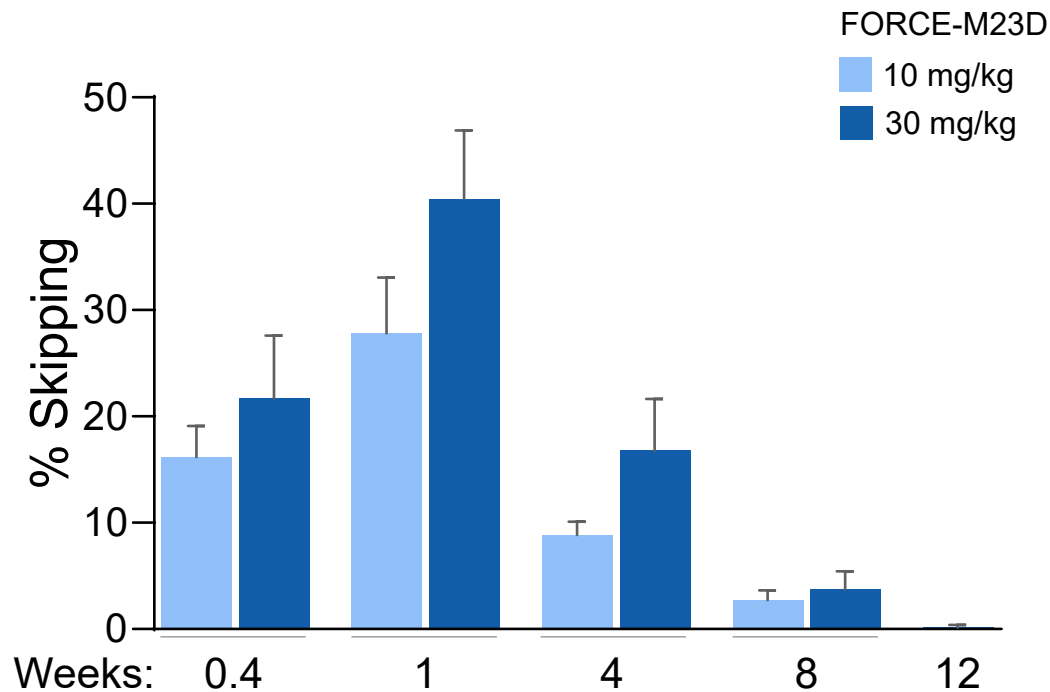


~80% dystrophin-positive fibers

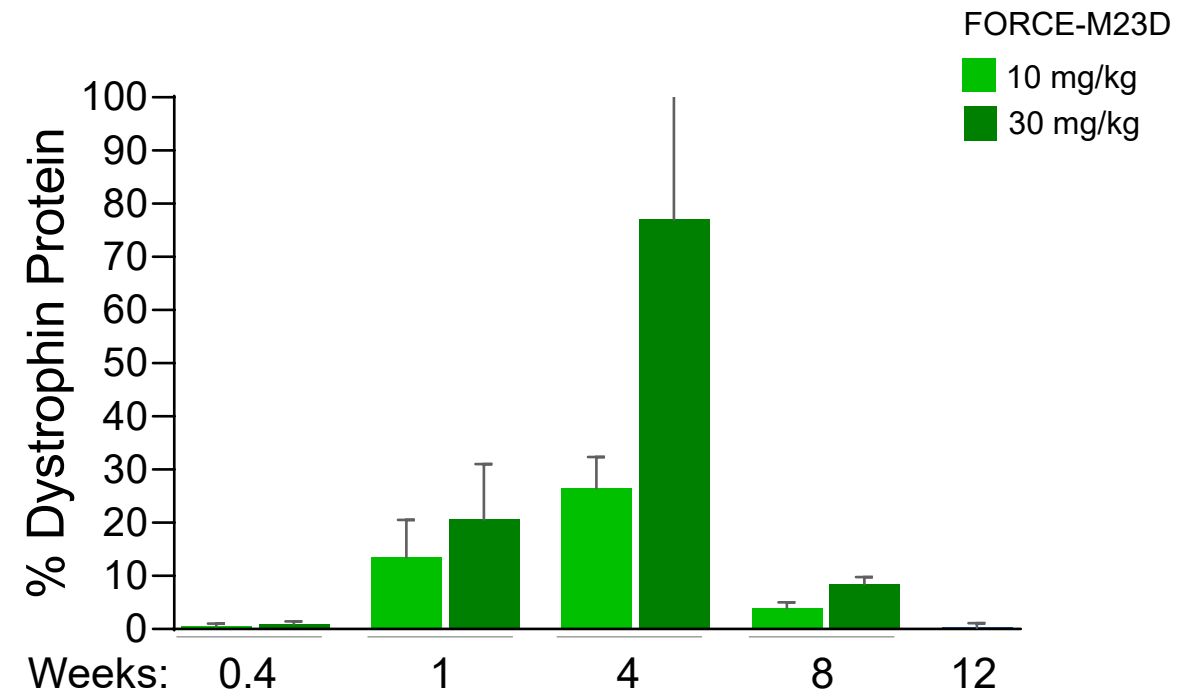
# FORCE Achieved Robust and Durable Skipping and Expression of Dystrophin in Heart



% Skipping by PCR



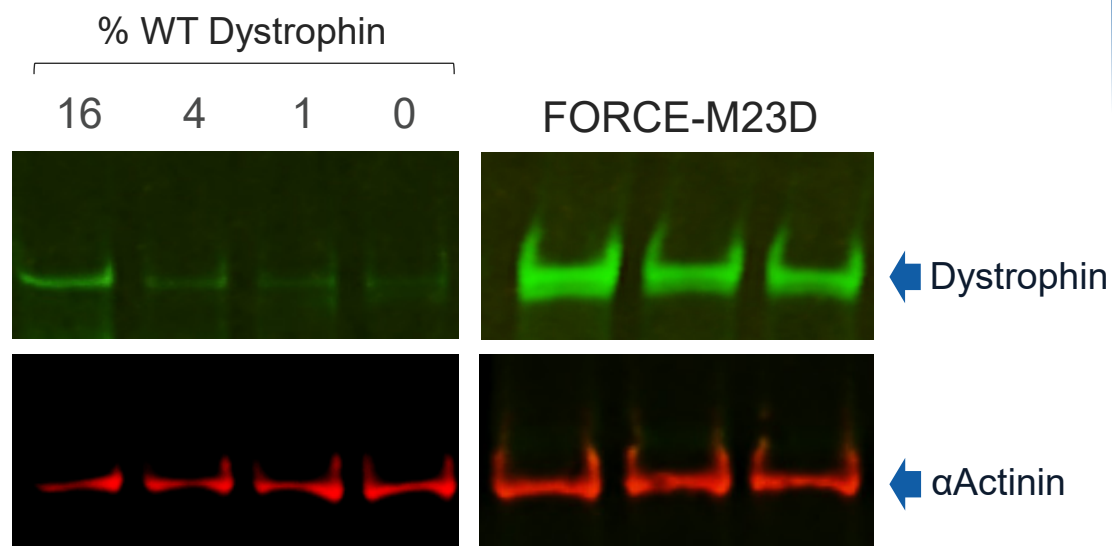
Dystrophin by WB



# FORCE Achieved Robust Dystrophin Expression and Localization to Sarcolemma in Heart at 4 Weeks

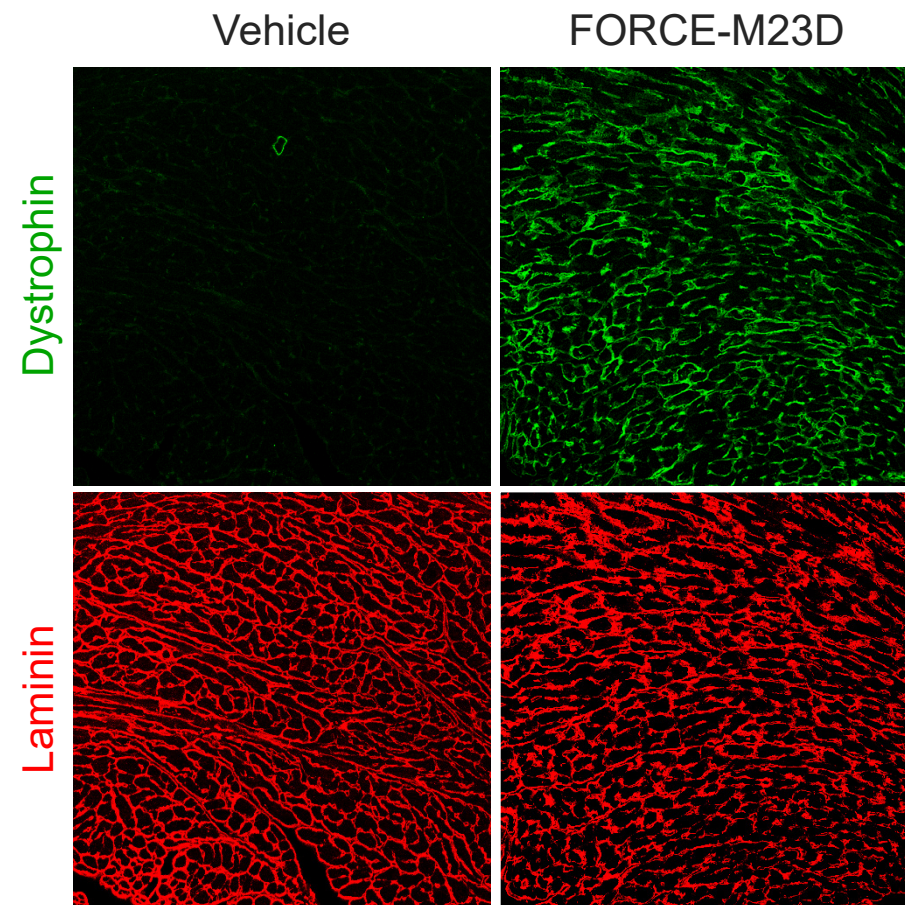


## Dystrophin Expression by WB 30 mg/kg 4 Weeks Post-Dose



78% of wild-type dystrophin

## Dystrophin Localization to Sarcolemma



~80% dystrophin-positive fibers



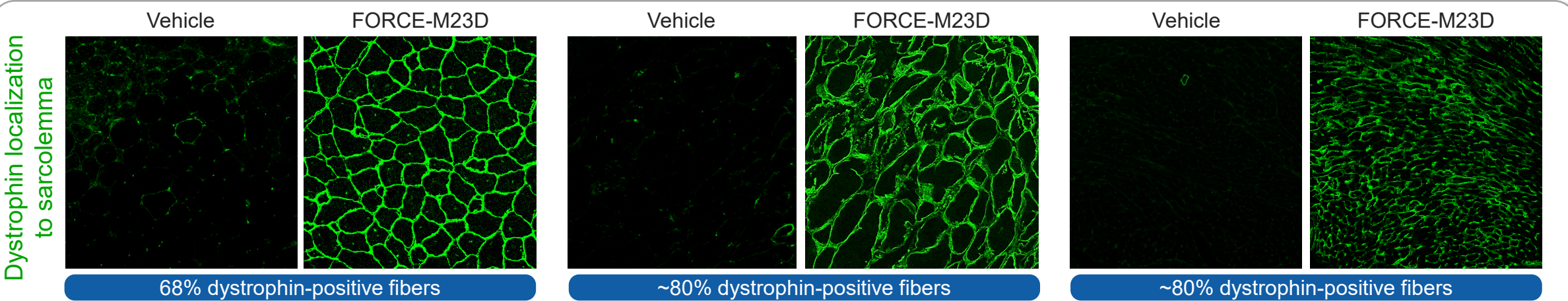
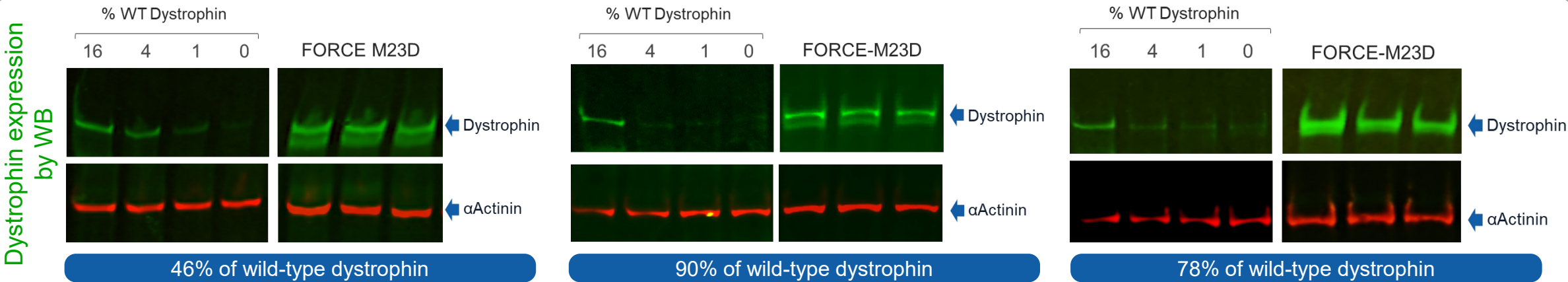
# FORCE Achieved Robust and Durable Dystrophin Expression and Sarcolemma Localization in Muscle



## Quadriceps

## Diaphragm

## Heart



# FORCE Distinctive Pharmacokinetic Profile Delivered Substantial and Durable Dystrophin Expression with a Single Dose



## Pharmacokinetics

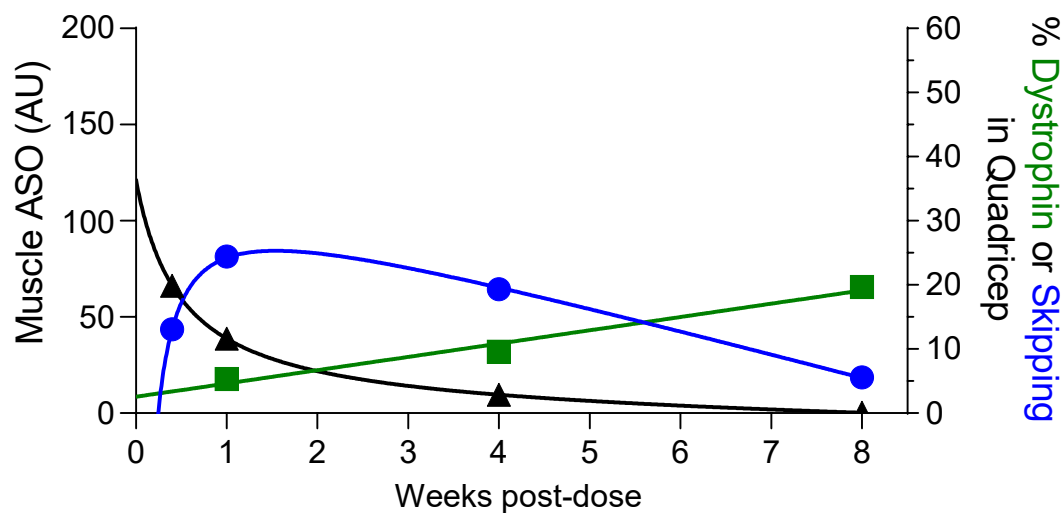
## Pharmacodynamics

Muscle ASO concentration

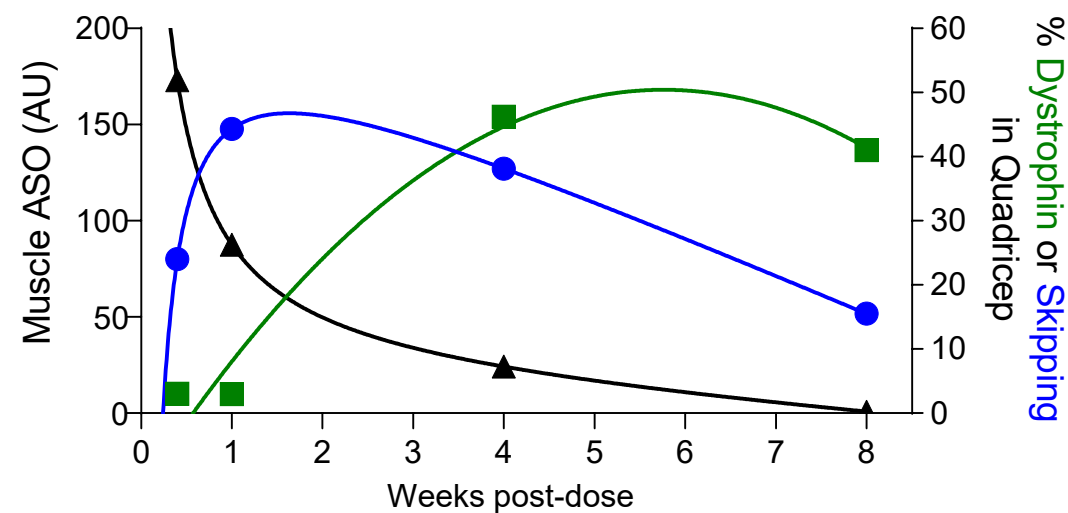
Exon skipping

Dystrophin restoration

FORCE-M23D 10 mg/kg



FORCE-M23D 30 mg/kg



▲ Muscle ASO | ● Skipping | ■ Dystrophin

# Agenda

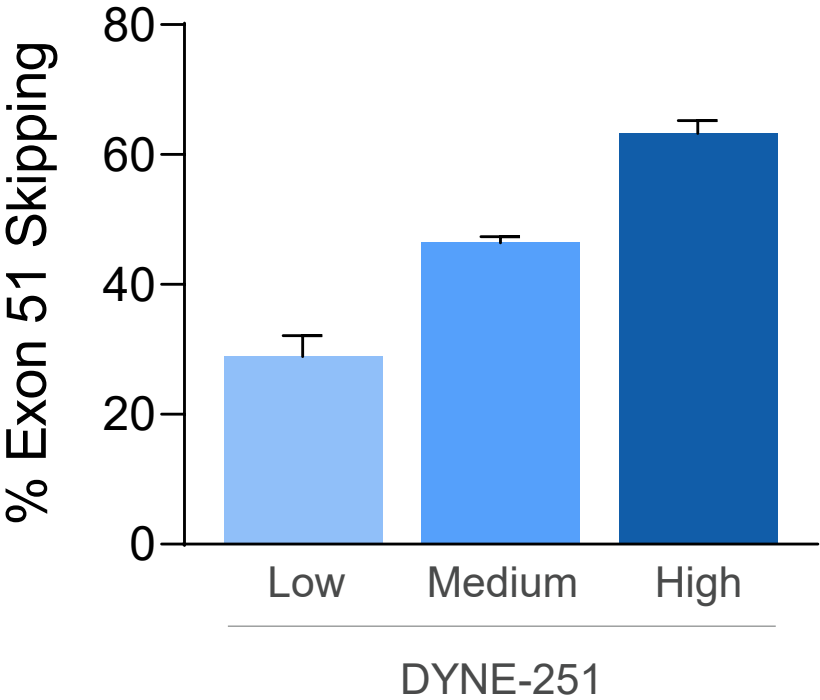
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# DYNE-251 Achieved Robust and Dose-Dependent Exon 51 Skipping in DMD Patient Myotubes

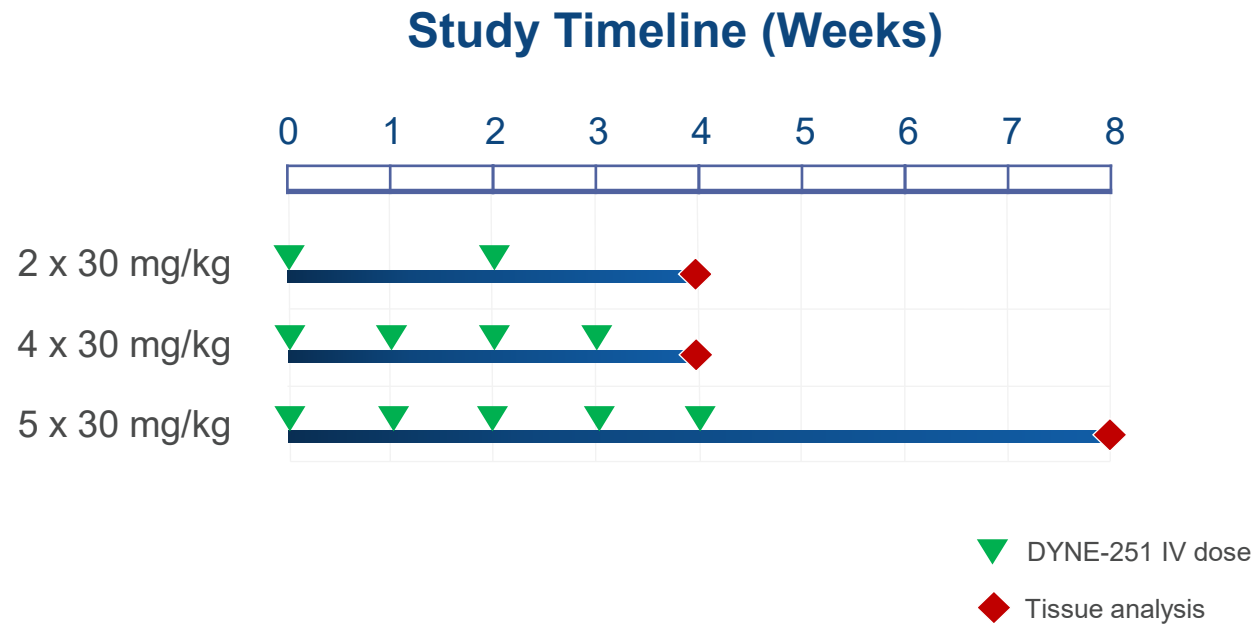


Exon 51 Skipping in del52 DMD Myotubes





# Dose Regimen Study in NHPs to Inform Clinical Dose



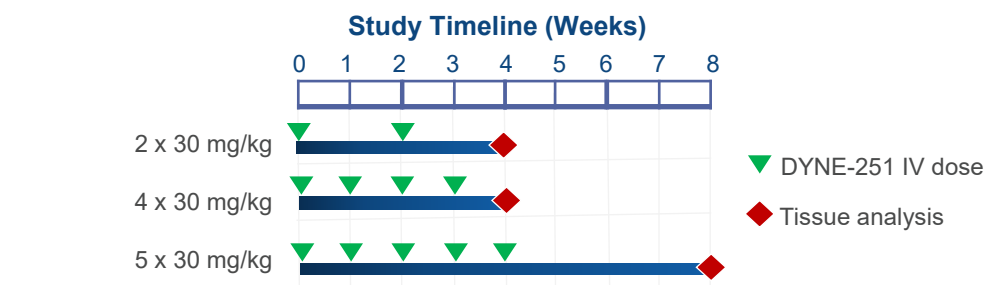
## Endpoints

- Exon skipping by PCR

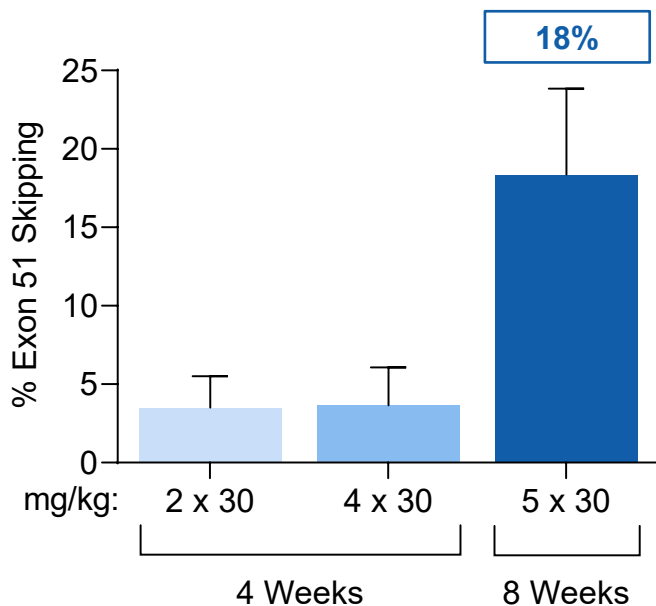
## Tissues analyzed

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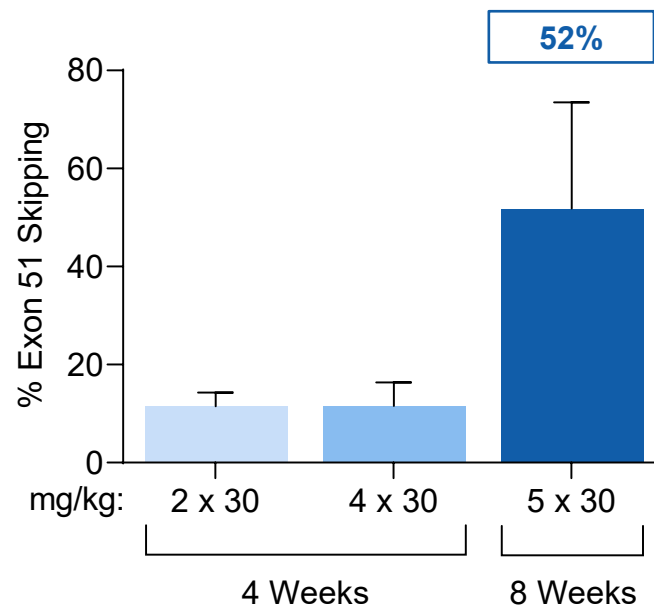
# DYNE-251 Achieved Robust Exon Skipping in NHP Skeletal and Cardiac Muscles



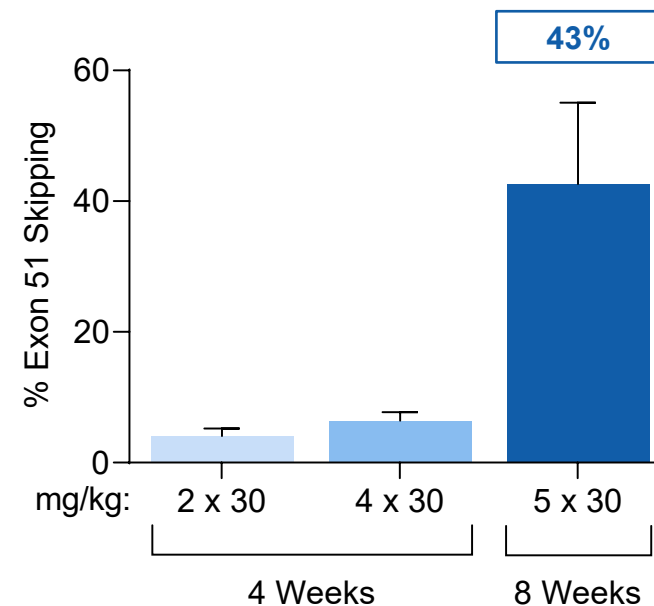
### Quadriceps



### Diaphragm



### Heart



# DYNE-251 NHP GLP Toxicology Results Demonstrated Favorable Safety Profile That Support Advancement to Clinic

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- No dose limiting toxicity observed after five weekly doses up to a maximally feasible dose
- No changes in cardiac, respiratory, neurologic or ophthalmic endpoints
- No effect on kidney function
- No effect on liver function
- No effect on coagulation
- NOAEL was identified at the highest dose tested

# Summary

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- In *mdx* mouse model FORCE achieved:
  - Dose-dependent, robust, and durable skipping and dystrophin expression
  - Long-lasting dystrophin localization to sarcolemma
  - Functional benefit
- DYNE-251 demonstrated robust and dose-dependent exon 51 skipping in DMD patient myotubes
- DYNE-251 demonstrated robust exon skipping in NHP cardiac and skeletal muscles
- NHP toxicology results support advancement of DYNE-251 into the clinic



Three INDs  
planned between  
Q4 2021 - Q4 2022

Targeting the genetic basis of serious muscle diseases to

**STOP OR REVERSE DISEASE PROGRESSION**

**FORCE**  
PLATFORM

**Robust**  
PIPELINE

**Delivering**  
FOR PATIENTS

**Exceptional**  
TEAM