Early, initial data from C3391001, a first-in-human safety study of PF-06939926, a mini-dystrophin gene therapy for the potential treatment of DMD.

Parent Project Muscular Dystrophy

JOIN THE FIGHT. END DUCHENNE.

Michael Binks MD

VP Rare Disease Clinical Research

Pfizer Worldwide Research, Development and Medical

28th June 2019

Disclaimer

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- This presentation includes forward-looking statements about, among other things, development of Pfizer's Rare Disease products and product candidates, including mini-dystrophin gene therapy (PF-06939926), and its potential benefits, that are subject to substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Additional information regarding these factors can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2018 and in our subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors that May Affect Future Results", as well as in our subsequent reports on Form 8-K, all of which are filed with the US Securities and Exchange Commission (SEC) and available at www.sec.gov and www.pfizer.com.

- The forward-looking statements in this presentation speak only as of the original date of this presentation, and we undertake no obligation to update or revise any of these statements.

Pfizer's commitment to gene therapy

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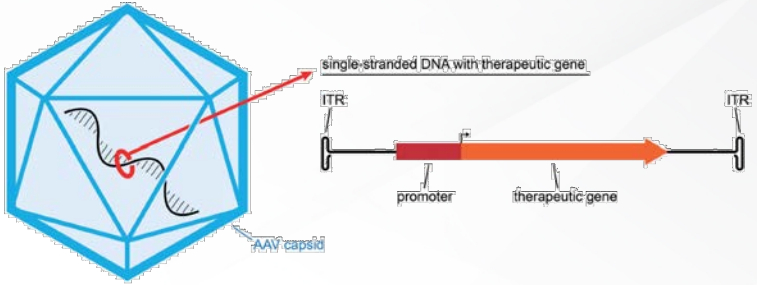
Pfizer believes that gene therapy for single gene disorders is on the cusp of becoming a robust therapeutic modality in a variety of diseases, and it is a major focus of our efforts in rare disease.

We hope that our continued innovation and collaborations with academia, industry and patients will continue to transition potential gene therapies from scientific concept into breakthroughs that change patients' lives.

AAV = Adeno-associated virus



Tretiakova, A. et al. Nature Outlook, 2018
https://www.nature.com/magazine-assets/d42473-018-00307-6/d42473-018-00307-6.pdf

PF-06939926 Capsid-transgene-promoter combination

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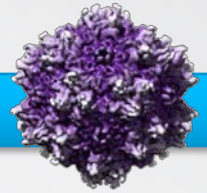
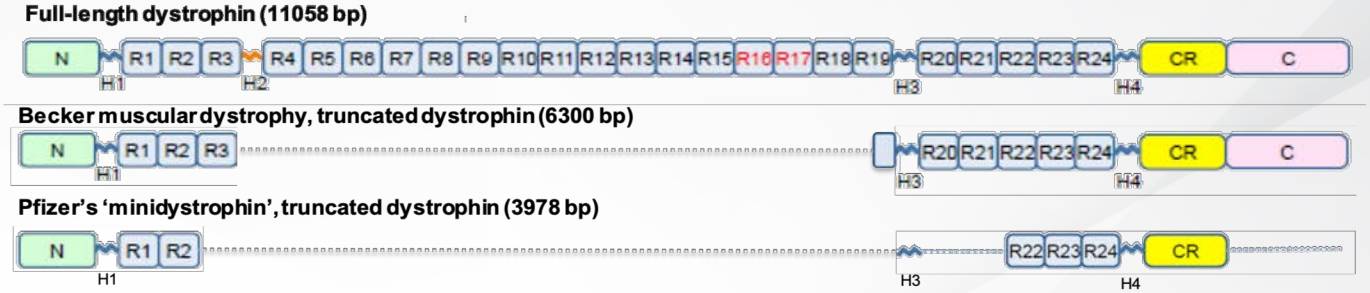
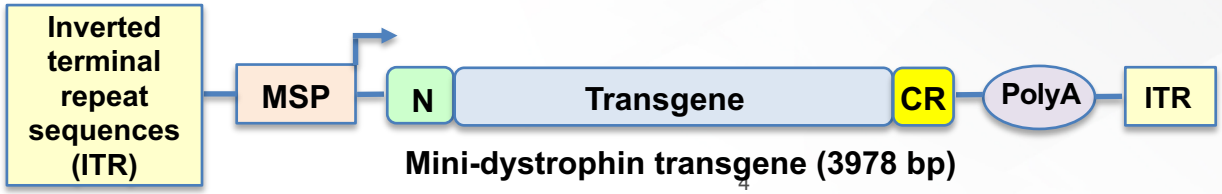
AAV9 capsid serotype



Mini-dystrophin transgene – *derived from mutation of patient with mild form of Becker muscular dystrophy*

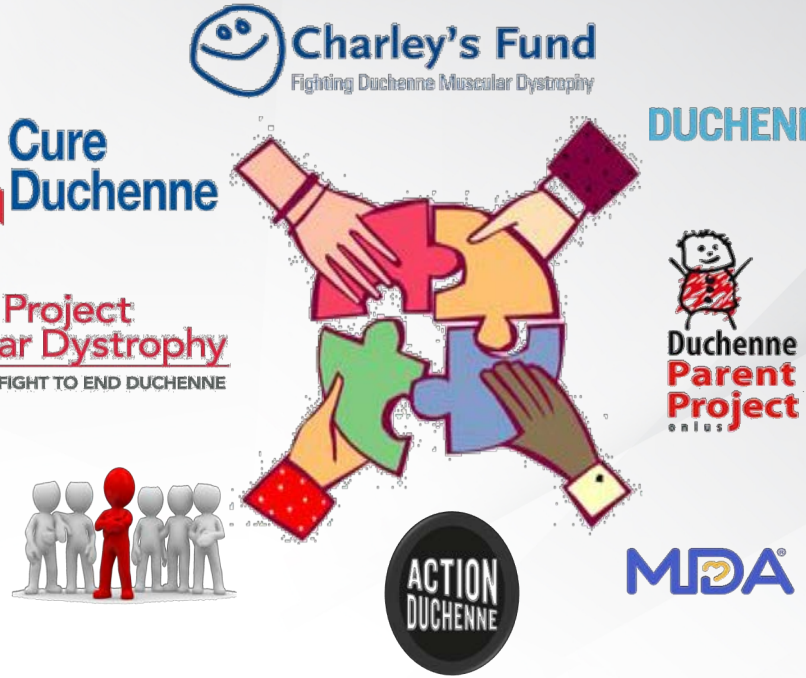


Human muscle specific promoter (MSP)



PF-06939926 Development Program

Incorporating Patient Perspective



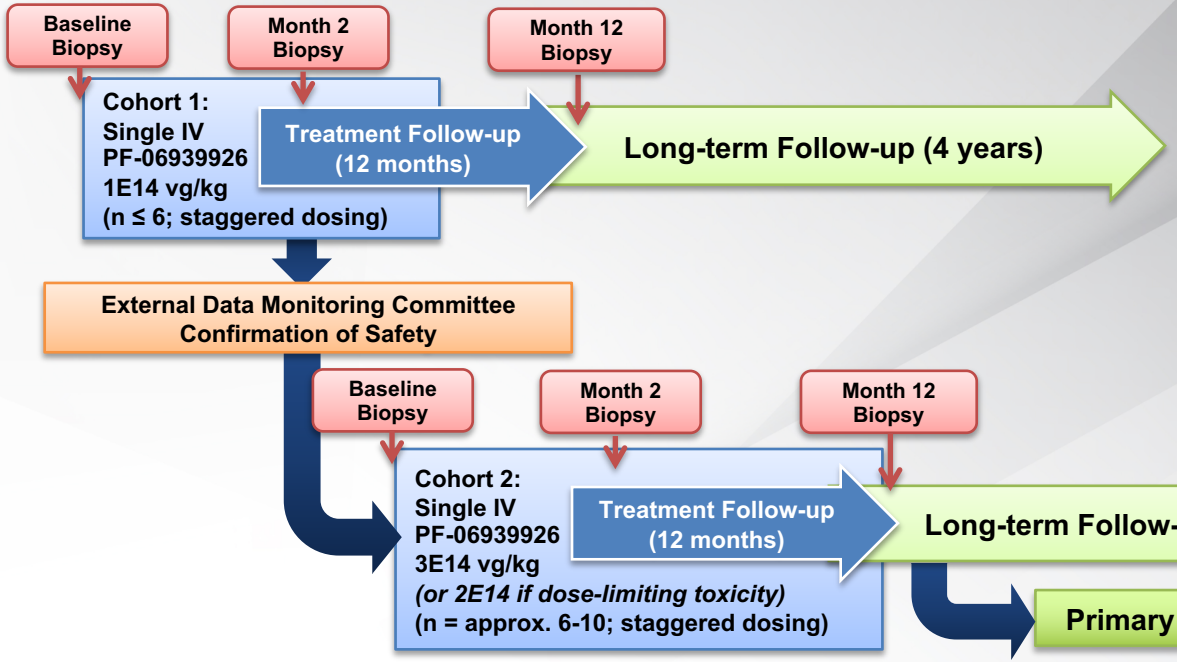
Design features informed by advocacy organizations:

- **Informed consent process**
- **Participant selection**
- **Travel support**
- **Steroid management**
- **Biopsy collection, handling, and follow-up care**
- **Activity monitoring**
- **External data monitoring committee membership**
- **Communications**
- **Data sharing**

Thanks for keeping us informed of what matters to patients!

C3391001: Phase 1b Safety Study

(ClinicalTrials.gov: NCT03362502)



INVESTIGATIVE SITES:

- *Russell Butterfield, MD, PhD*
  University of Utah
- *Perry Shieh, MD, PhD*
  UCLA
- *Edward Smith, MD*
  Duke University

- **Participants:** 5-12 year old boys with DMD:
  - Ambulant and on daily glucocorticoids
  - AAV9 NAb (-)
- **Single intravenous (IV) infusion**
- **Staggered dosing for both cohorts**

- **Primary endpoint:** Safety through 12 months
- **Secondary endpoints:**
  - Mini-dystrophin concentration and distribution
  - Long-term safety (through 5 years)
- **Exploratory endpoints**
  - CK/Function/MRI/activity

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C3391001: Phase 1b Safety Study:
List of All Adverse Drug Reactions (ADR)*

Adverse Drug Reactions	Subjects Number
System Organ Class Coded (MedDRA Preferred) Term	Treated (N = 6) n (%)
Gastrointestinal disorders	
Nausea	4 (66.7)
Vomiting	4 (66.7)
Metabolism and nutrition disorders	
Decreased appetite	3 (50.0)
Infections and Infestations	
Pyrexia (Fever)	2 (33.3)
General disorders and administration site conditions	
Fatigue	2 (33.3)
Renal and urinary disorders	
Acute kidney injury	1 (16.7)

Source: Reported for study C3391001 as of 15May2019.

**Adverse drug reactions are adverse events (AEs) suspected to be caused by the investigational product.*

C3391001: Phase 1b Safety Study:
Gastrointestinal Adverse Drug Reactions (ADR)

Symptoms started 1-2 days after receiving PF-06939926

- Nausea and vomiting (n=4)
  - Vomiting fully resolved within 2 to 5 days; nausea within ~1 week
    - Treated with oral antiemetic (ondansetron)
    - 1 participant required hospital admission for IV anti-emetics and fluids*
  - Reduced appetite (n=3): resolved without intervention ~1 to 3 weeks

➢ NOTE: Study amended to include additional safety monitoring at clinical research site during first week after treatment

**Classified as a Serious Adverse Event (SAE) and resulted in protocol-driven pause to enrollment and review with External Data Monitoring Committee (E-DMC).*

○ *Serious Adverse Events include **any** event that requires hospital admission*

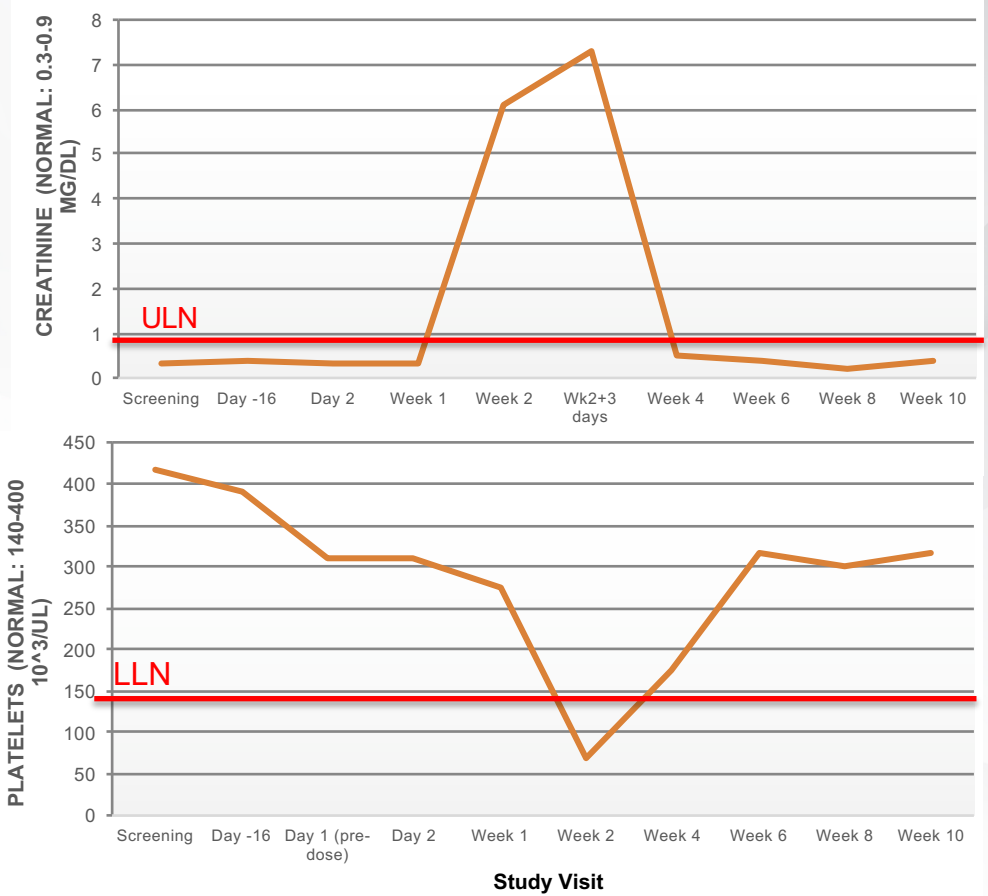
C3391001: Phase 1b Safety Study:
Serious Adverse Events (SAE) in two participants

1. **Nausea and Vomiting (n=1): *discussed on previous slide***
2. **Acute renal injury with complement activation (n=1)***

- **Routine week 2 assessment** (Day 11 relative to administration of PF-06939926)
  - Asymptomatic
  - Labs showed elevated BUN, creatinine, and uric acid detected.
    - Additional tests: Haptoglobin, C3 and C5b-C9 abnormal

- **Admitted to site pediatric intensive care unit (PICU)**
  - Vital signs normal on admission, but noted no urine output ~2 days;
  - Suspected complement mediated nephropathy, akin to atypical hemolytic uremic syndrome (aHUS), although remained clinically well

C3391001: Phase 1b Safety Study:
Management of the acute renal injury serious adverse event

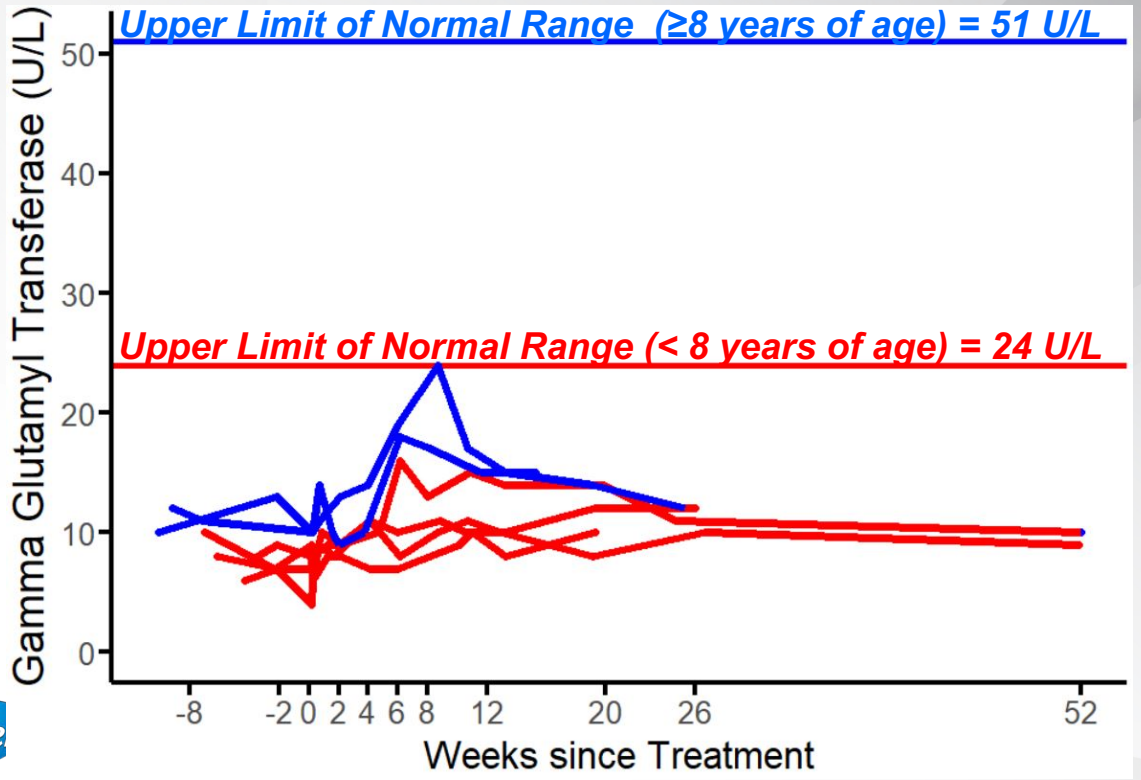


- Hemodialysis treatments repeated every 3-4 days until discharge;
- IV eculizumab (Soliris) - 2x, 1 week apart;
- Discharged 11 days after admission
- Platelets and creatinine normalized 15 days after admission and event deemed resolved
- **AAV9 NAb titer at 2 weeks > all other participants at 4 week**

- *Resulted in protocol-driven pause to enrollment and review with External Data Monitoring Committee (E-DMC), who endorsed proposed additional safety monitoring.*
- *Reported in full to FDA; no clinical hold applied.*
- *Comprehensive case report in preparation for publication*

C3391001: Phase 1b Safety Study:
No evidence of acute liver injury to date

Gamma Glutamyl Transferase (GGT) Results



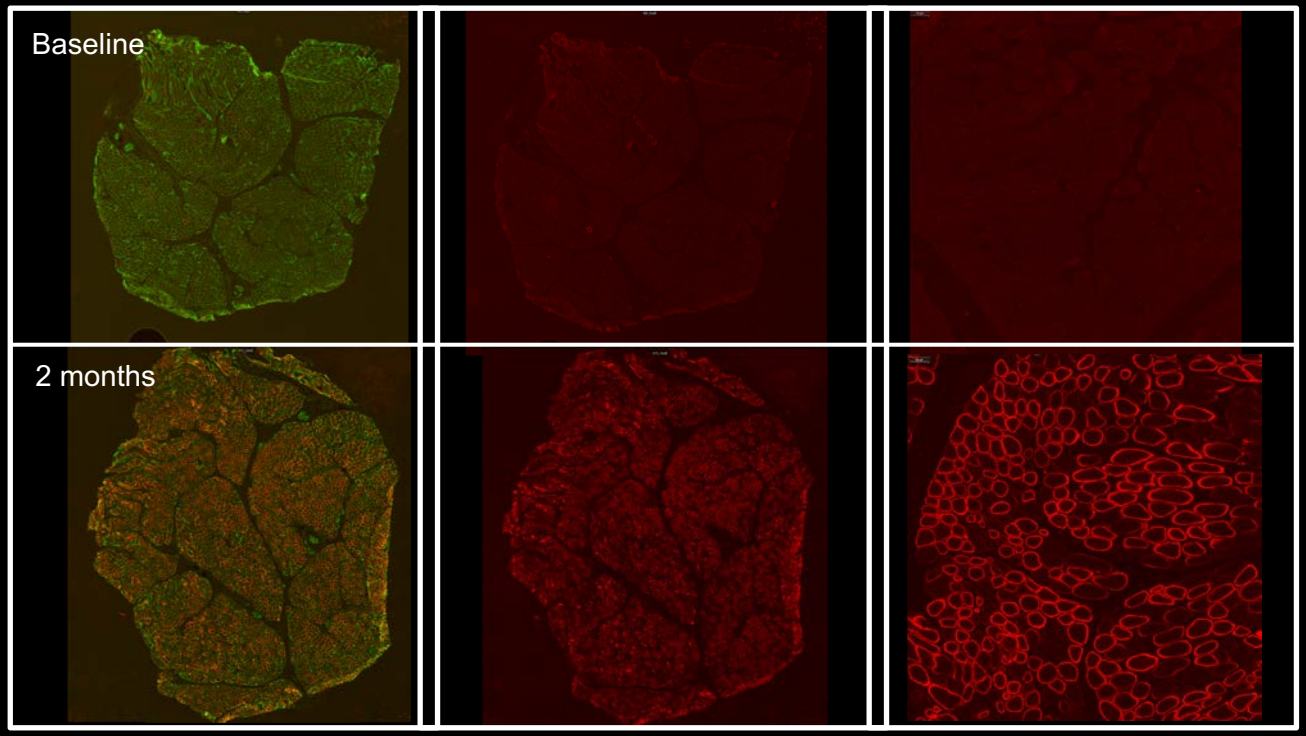
Glutamate dehydrogenase (GLDH):

- *Transient elevation >2x the upper limit of normal seen in single participant during acute renal injury event*
- *Hepatic expert on E-DMC agreed not indicative of drug-induced liver injury*

C3391001: Phase 1b Safety Study:
Preliminary results from Secondary and Exploratory Endpoints

- **Immunofluorescence**
  - Distribution of mini-dystrophin in muscle fibers in muscle biopsy
  - Measured by digital image analysis of microscope images
- **Liquid chromatography mass spectrometry (LCMS)**
  - Concentration of (mini-)dystrophin in muscle biopsy
- **NorthStar Ambulatory Assessment**
  - 17-item rating scale used to assess motor function abilities in children

A



Low Magnification Laminin
Dystrophin

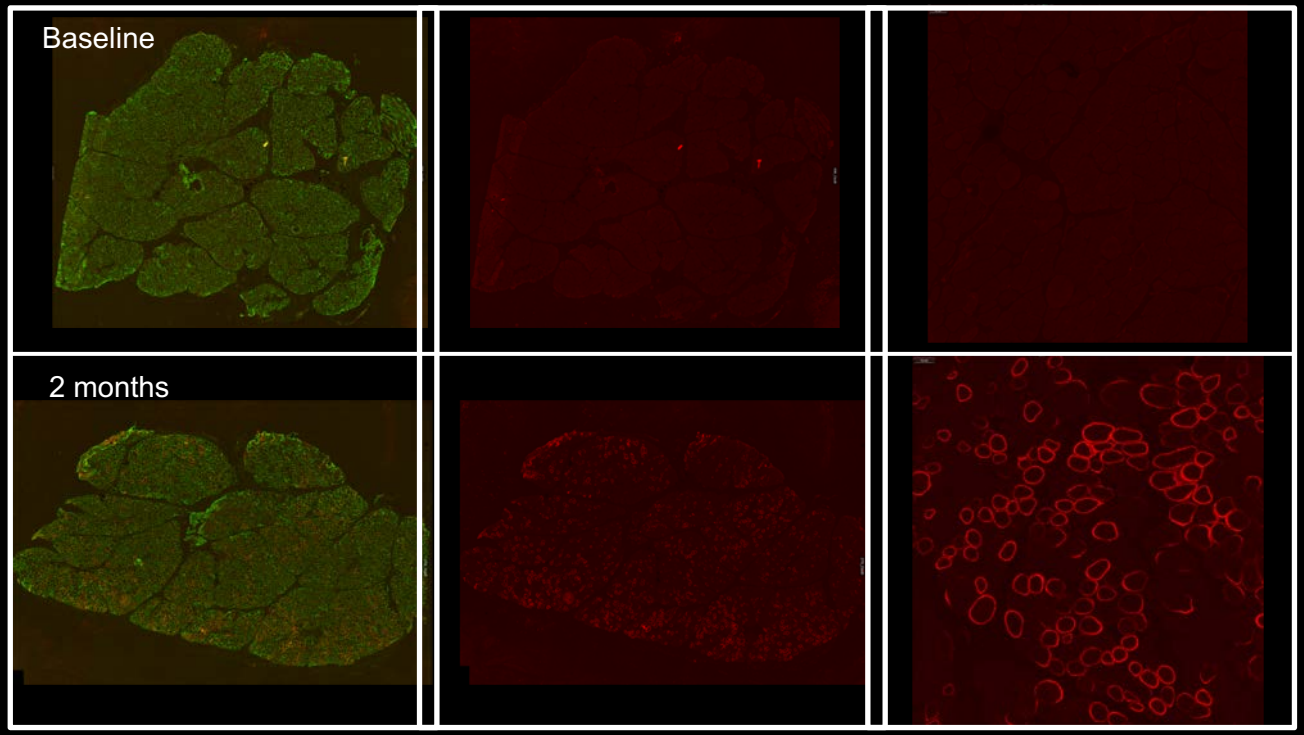
Low Magnification
Dystrophin

High Magnification
Dystrophin

Laminin is a marker of skeletal muscle cell membrane

3E14vg/kg dose

B



Low Magnification Laminin
Dystrophin

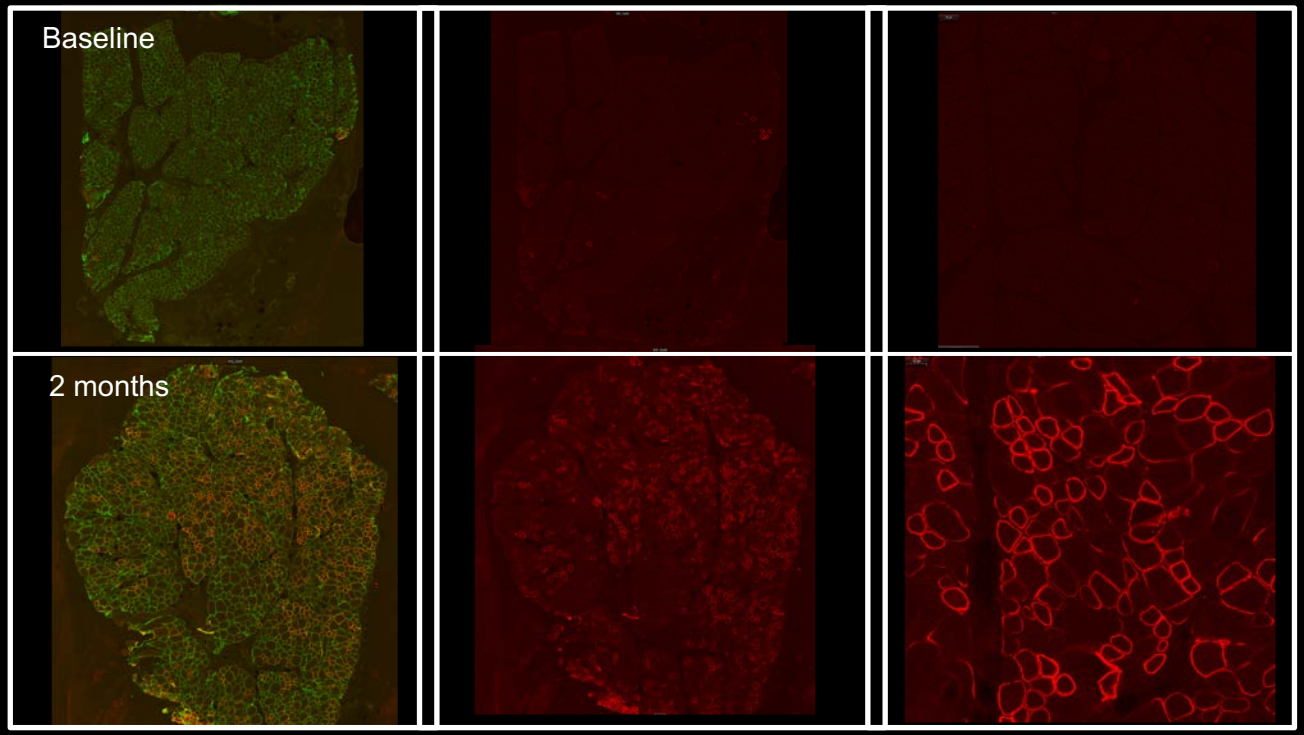
Low Magnification
Dystrophin

High Magnification
Dystrophin

Laminin is a marker of skeletal muscle cell membrane

3E14vg/kg dose

C



Low Magnification Laminin
Dystrophin

Low Magnification
Dystrophin

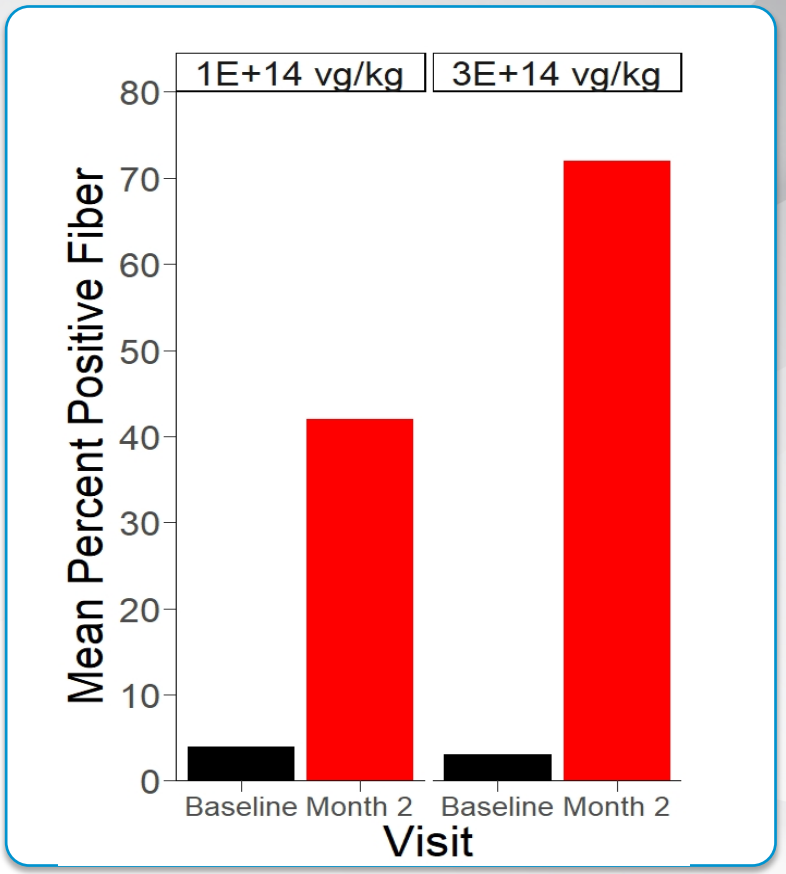
High Magnification
Dystrophin

Laminin is a marker of skeletal muscle cell membrane

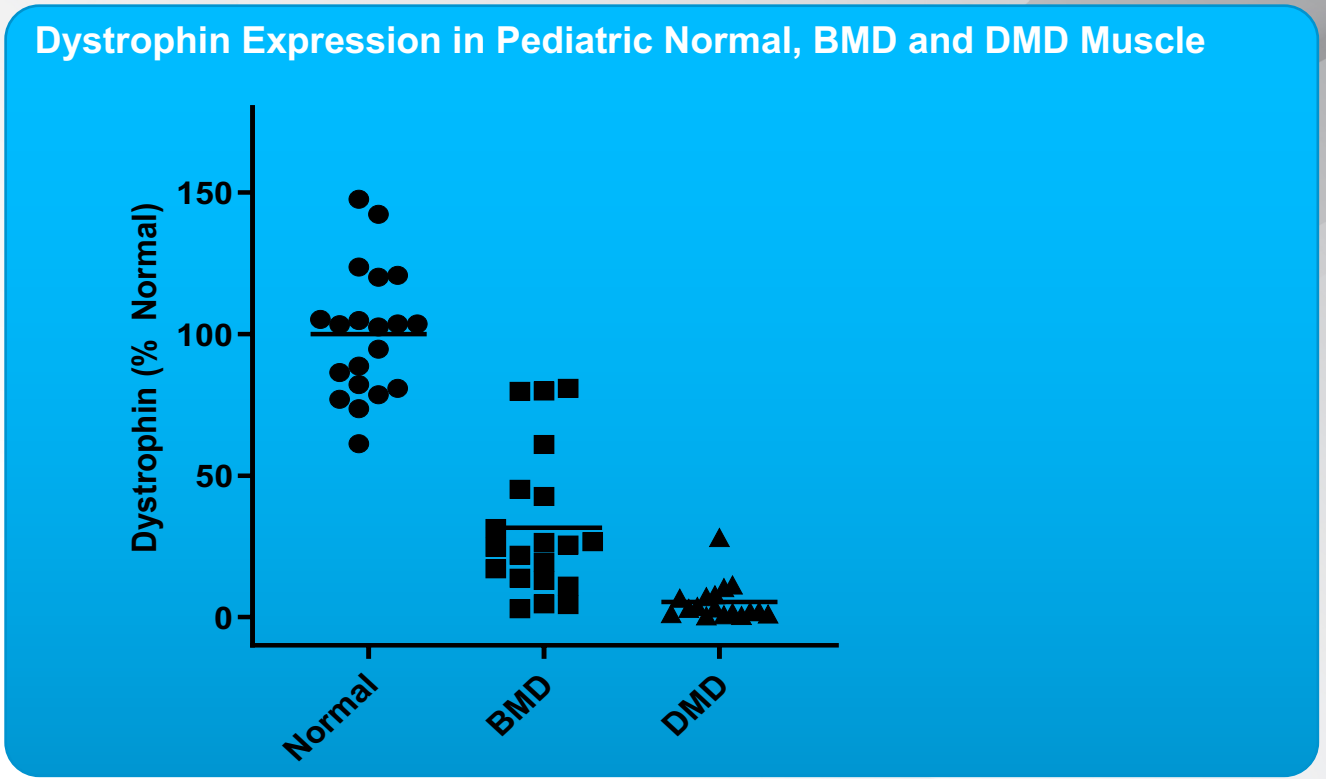
3E14vg/kg dose

C3391001: Phase 1b Safety Study: *Preliminary results*

Immunofluorescence Digital Image Analysis – *Percentage Positive Fibers*



Liquid chromatography mass spectrometry:
Novel assay enables sensitive and specific quantification across wide range of mini-dystrophin concentration



Why use LCMS for Dystrophin Measurement?

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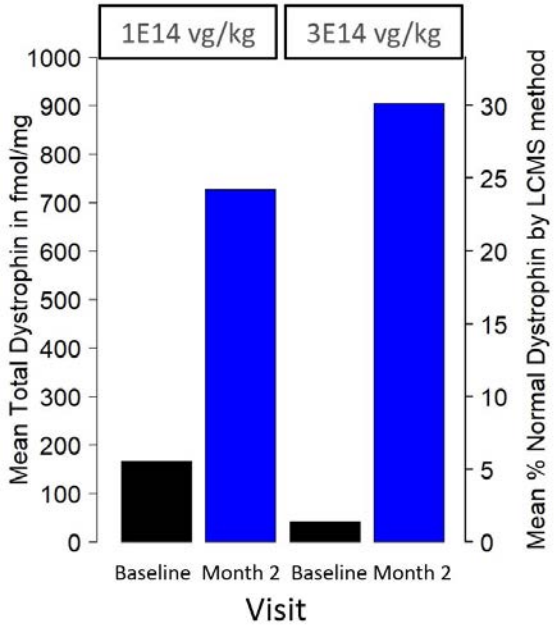
- **Recombinant mini-dystrophin standard**
  - Provides calibration for accurate quantitative performance and tight %CVs
- **Wide dynamic range**
  - Can measure tissues with low and high dystrophin expression within same assay run
- **High sensitivity**: Down to 0.5% Normal with low %CV
- **High selectivity achieved using 2 unique peptides:**
  - Peptide unique to mini-dystrophin to calculate tissue concentration expressed in fmol/mg total protein
  - Peptide common to full length dystrophin and mini-dystrophin to calculate % Normal
- **'Normal' dystrophin sample**:
  - Represented by well characterized non-dystrophic, pediatric skeletal muscle lysate pool (n=20)
- **Challenges encountered with Western Blot methods**:
  - Gel overloading
  - Membrane transfer efficiency
  - Non-specific binding of detection antibodies
  - Normalization to protein of much greater molecular weight

➢ **FDA is supportive of the development of our LCMS assay and agrees that it is "significantly improved over the Western Blot method".**

C3391001: Phase 1b Safety Study: *Preliminary results*
Mini-dystrophin concentration in Muscle Biopsy

Significant difference between baseline and post-treatment measures (p = .03)



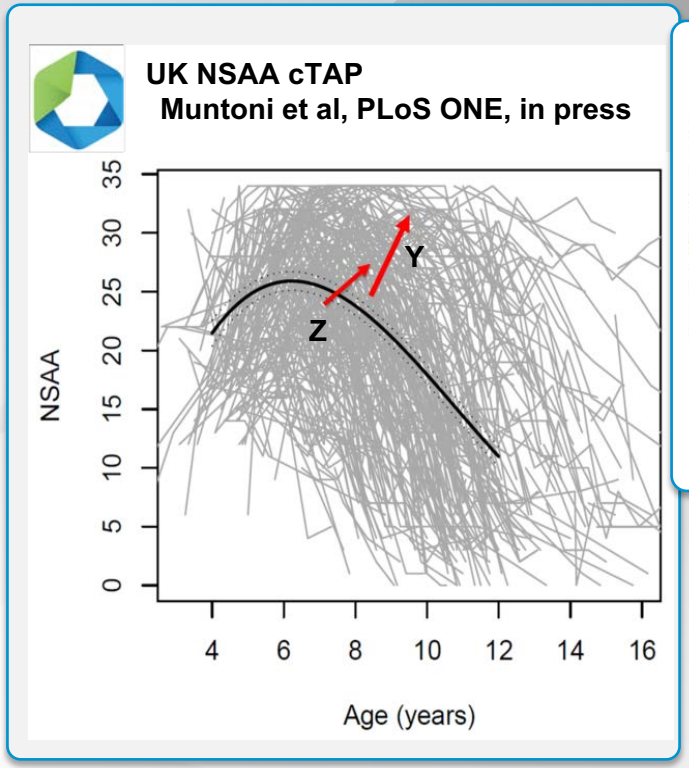
No standard for 'Normal' exists

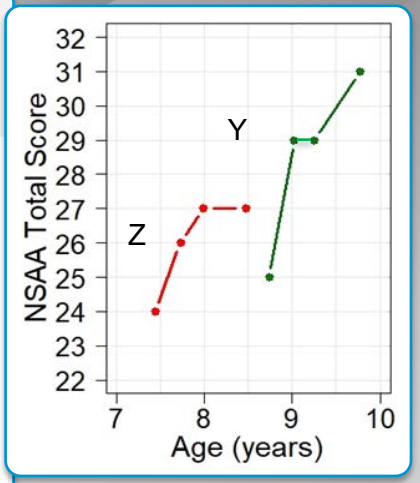
Same assays not comparable between labs without appropriate cross-validation

C3391001: Phase 1b Safety Study: *Preliminary results*
North Star Ambulatory Assessment (NSAA)

Caveats

- **Open label expectation bias**
- **NSAA data from the 2 participants who have completed 1 year**
  - Both received PF-06939926 at 1E14 vg/kg
  - Earlier timepoints confounded by glucocorticoid effects
- **Natural history is variable**
  - Rich data source in NSAA UK database
  - cTAP consortium prognostic modelling
  - Rate of progression associated with baseline age and function





→ = change (improvement) in of each of the 2 study participants' total score from baseline to 1-year post treatment

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Takeaways

Summary and Key Messages

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WHAT HAVE WE LEARNED TO DATE AND WARRANTS FURTHER INVESTIGATION?

- Initial data from multiple investigational sites on muscle fiber distribution, minidystrophin concentration and signs of potential clinical benefit are encouraging, but warrant further investigation
- Safety profile of the investigational therapy is acceptable for continued development
- LCMS is a sensitive and specific quantitative assay the development has been encouraged by regulators

WHAT ARE WE STILL LEARNING?

- Optimal management of the body's immune response to AAV
  - Immune responses to AAV occurred in all recipients and varied in magnitude
  - Clinical consequences of adverse immune response have been manageable
  - Research is ongoing to understand how to minimize risk and prevent immune reactions
- Sources of variability in measures of dystrophin

NEXT STEPS

- Planned Phase 3 program will leverage learnings from this ongoing Phase 1 trial
  - Global, randomized, placebo-controlled Phase 3 trial expected to begin in 1H 2020
  - Phase 1 results will inform decisions regarding optimal dose, administration, co-medication, patient selection and safety monitoring

Parent Project Muscular Dystrophy

JOIN THE FIGHT. END DUCHENNE.

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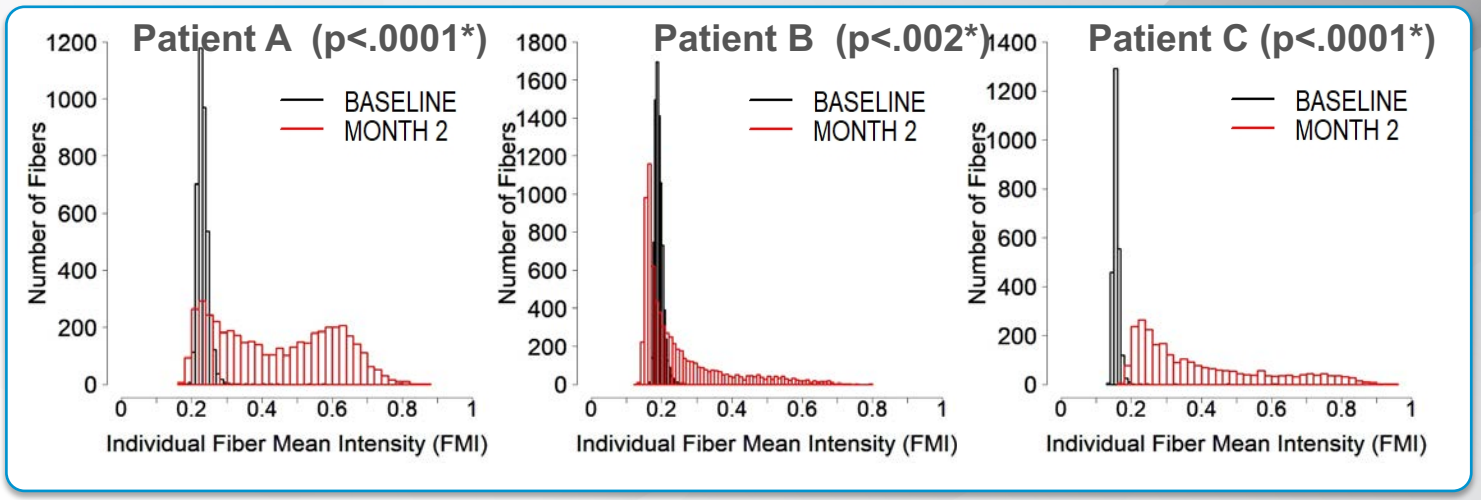
Questions?

C3391001: Phase 1b Safety Study: *Preliminary results*

Immunofluorescence Digital Image Analysis – *Percentage Positive Fibers*



*Statistically significant difference between baseline distributions of individual fiber mean intensity (FMI) and post-dose distributions at 2 months (3E14vg/kg) dose

Percentage +ve Fibers	Baseline (Day -16)	Month 2 (Day 60)
Mean	3%	72%

NOTE: Patient #s in random order (i.e. not necessarily in order in which they were enrolled and dosed to protect participant identities)