Save the date for the 30th World Muscle Society Congress in Vienna, Austria.


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# Results from 15 mg/kg single dose PGN-EDODM1 cohort of FREEDOM-DM1- a Phase 1 study in people with myotonic dystrophy 1 (DM1).

Johanna Hamel[2], Jean-Denis Brisson[3], Hanns Lochmuller[4], Thurman Wheeler[5], Jacinda Sampson[6], Namita A. Goyal[7], Nicholas Johnson[8], Jeffrey Statland[9], James B Lilleker[10], Chris Turner[11], Gerald Pfeffer[12], Jennifer Shoskes[1], Ashling Holland[1] Brijesh Garg[1], Gregory Song[1], Pallavi Lonkar[1], Shaoxia Yu[1], Patricia Fraser[1], Jane Larkindale[1]

1. PepGen Inc., Boston, MA, USA 2. University of Rochester, Rochester, NY, USA 3. CIUSSS du Saguenay-Lac-Saint-Jean, Canada 4. Ottawa Hospital Research Institute, Canada 5. Massachusetts General Hospital, Boston, MA, USA 6. Stanford University Medical Center, Stanford, CA, USA 7. University of California - Irvine Medical Center, Irvine, CA, USA 8. Virginia Commonwealth University Health System, VA, USA 9. University of Kansas Medical Center (KUMC), KS, USA 10. Manchester Academic Health Science Centre, UK 11. University College London Hospital, UK 12. University of Calgary, Canada

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# Disclosure

Dr. Lochmuller is a site PI for the Freedom 1 and Freedom 2 trials

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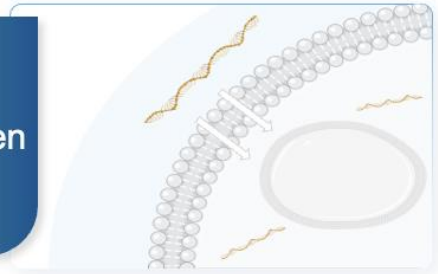
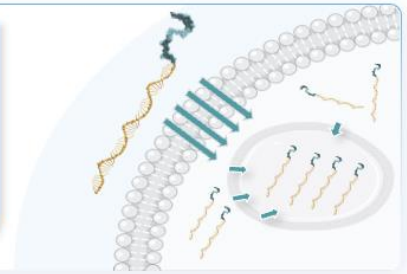
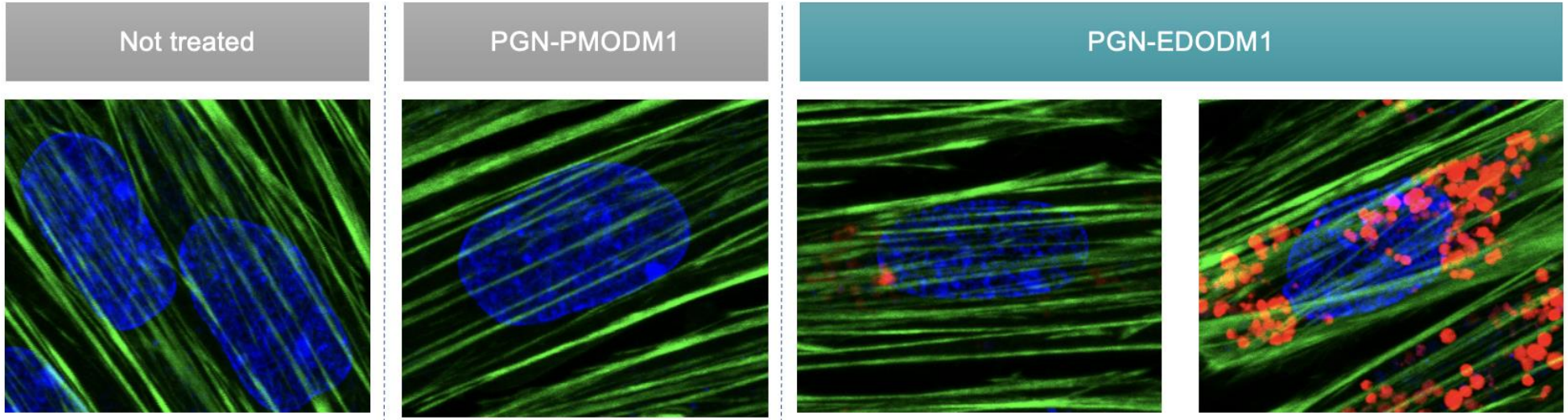
# Enhanced Delivery Oligonucleotide Platform Enhances Nuclear Delivery and Uptake of Oligonucleotides

Naked oligonucleotides not efficiently taken up into muscle cells & nucleus



EDOs enhance nuclear delivery of oligonucleotide therapeutics



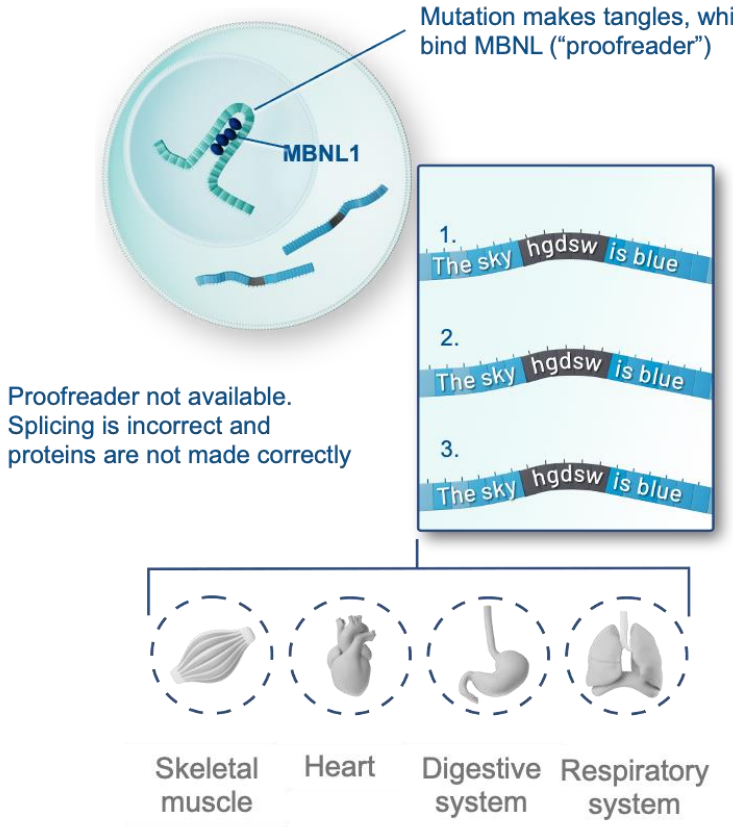



PGN-EDODM1 / Actin / Nucleus

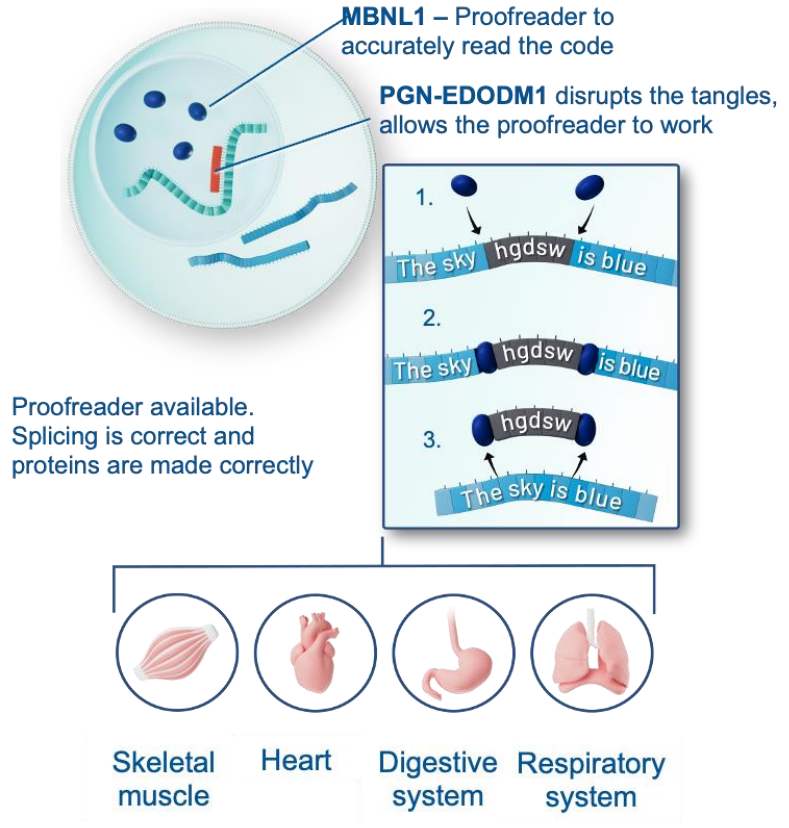
Immortalized myoblasts from a healthy individual or a DM1 patient with 2600 CTG repeats were cultured then differentiated for 4 days into myotubes and then treated with fluorescently tagged PGN-PMODM1 (PMO) or PGN-EDODM1 (PPMO) at concentrations detailed above. Cells were visualized by confocal microscopy 24h after treatment.

# PGN-EDODM1 Mechanism of Action - Approach in DM1

## DM1



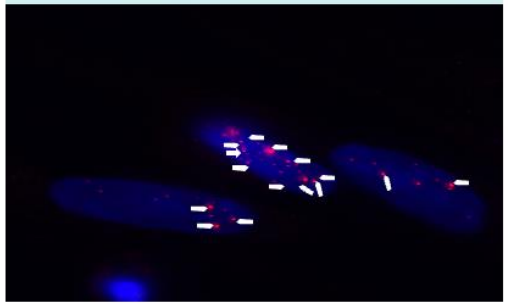

## DM1+ PGN-EDODM1



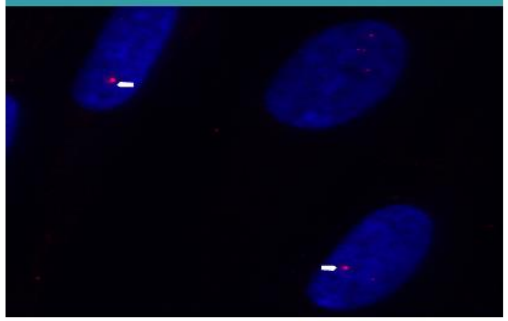
# PGN-EDODM1 Reduced Foci, Liberated MBNL1 and Corrected Mis-Splicing in Patient Cells with Long CTG Repeats

## FOCI REDUCTION

Not treated (NT)



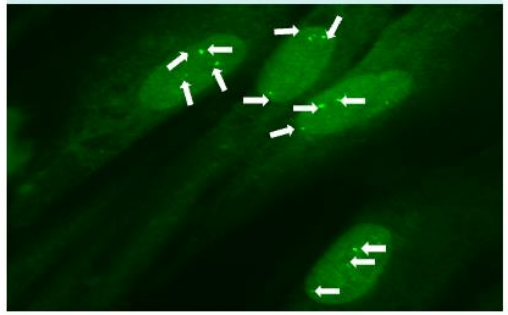
PGN-EDODM1 treated



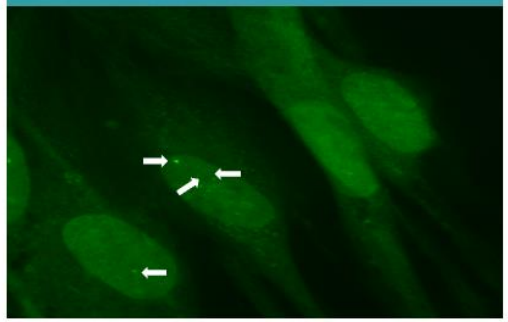
**54%**
reduction in toxic foci

## MBNL1 LIBERATION

Not treated (NT)

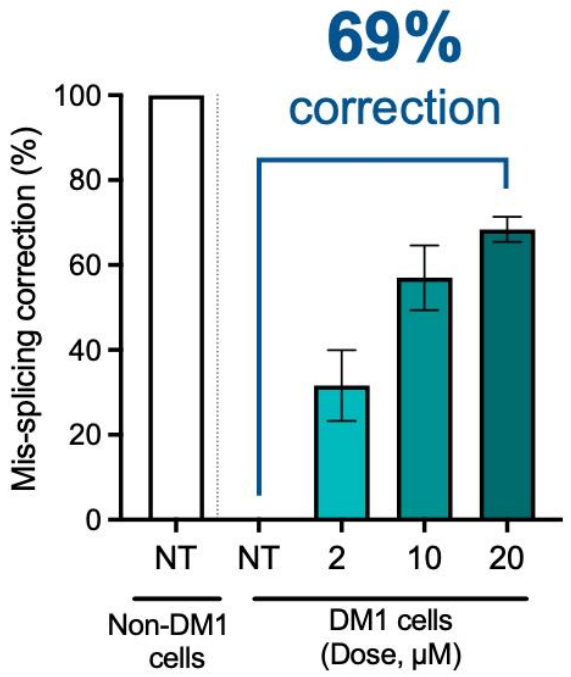


PGN-EDODM1 treated



## MIS-SPLICING CORRECTION

***Across multiple transcripts***

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Immortalized myoblasts from healthy individual or DM1 patient with 2600 CTG repeats were cultured then differentiated for 4 days into myotubes. Treatment with peptide-PMO conjugates at concentrations given. Cells were harvested for analysis 24h after treatment. RNA isolation, RT-PCR and capillary electrophoresis (QIAxcel) analysis was performed. Visualization with FISH and immunofluorescence microscopy. Mean ± SD; n = 5 per group.

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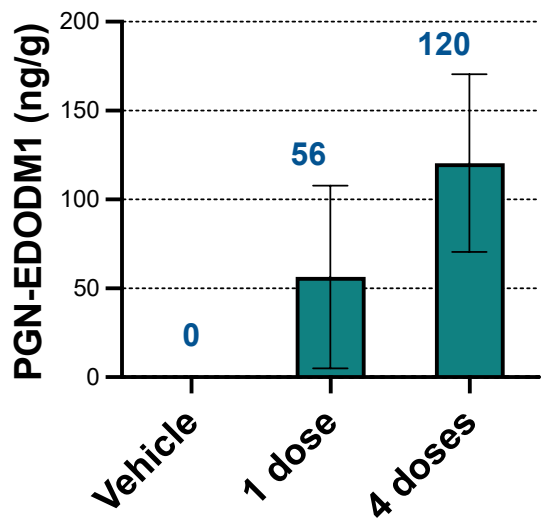
# Multiple Doses of PGN-EDODM1 Led to Greater Improvement in Splicing Correction and Myotonia vs Single Dose in Preclinical Studies

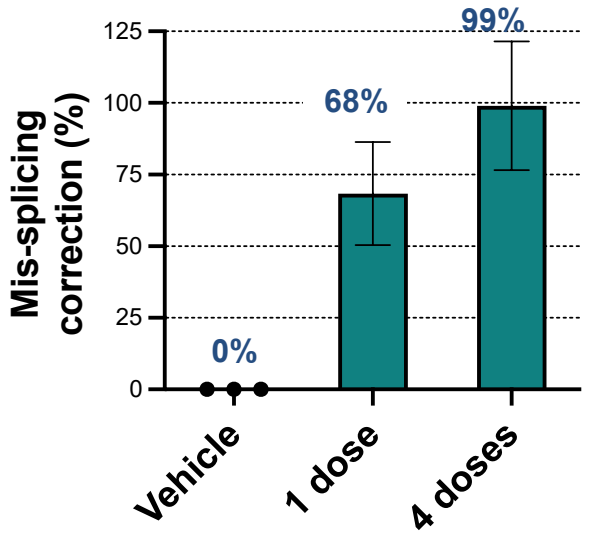
## Tissue Concentration

### Skeletal muscle



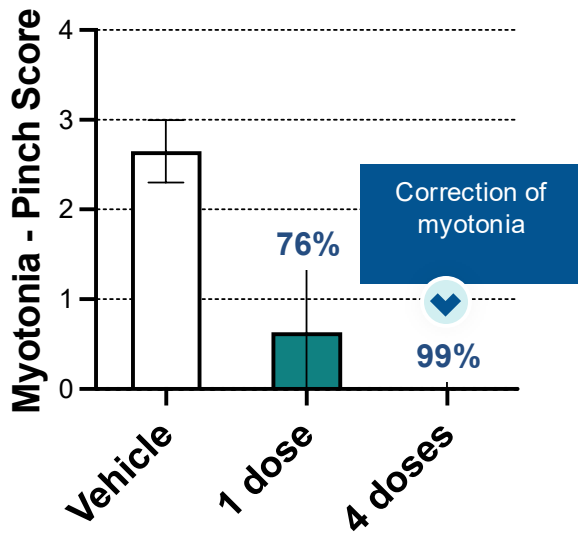

## Mis-Splicing Correction

### Across multiple transcripts




## Correction of Myotonia

### Pinch test




Protocol: HSA$^{LR}$ mice received 1 or 4 doses of PGN-EDODM1, with 4-week intervals between doses. Skeletal muscle tissues were collected 4 weeks post-final dose. Skeletal muscle tissue concentration was measured by fluorescent based HPLC method. Graph is presented as mean ± SD; n = 8-12 per cohort. Mis-splicing analysis considers multiple transcripts. Graph is presented as mean ± SD; n = 8-12 per cohort per transcript. Action myotonia evaluation (pinch test) was performed 4 weeks post-final dose. Grade 3 = Clear sign of myotonia strong AND reproducible, Grade 2 = Clear sign of myotonia, strong OR reproducible, Grade 1 = Clear sign of myotonia but non reproducible, Grade 0 = No sign of myotonia. Graph is presented as mean ± SD; n = 12-43 per cohort.

# FREEDOM: Phase 1 PGN-EDODM1 Single-Ascending Dose Study Design

Freedom
DM1

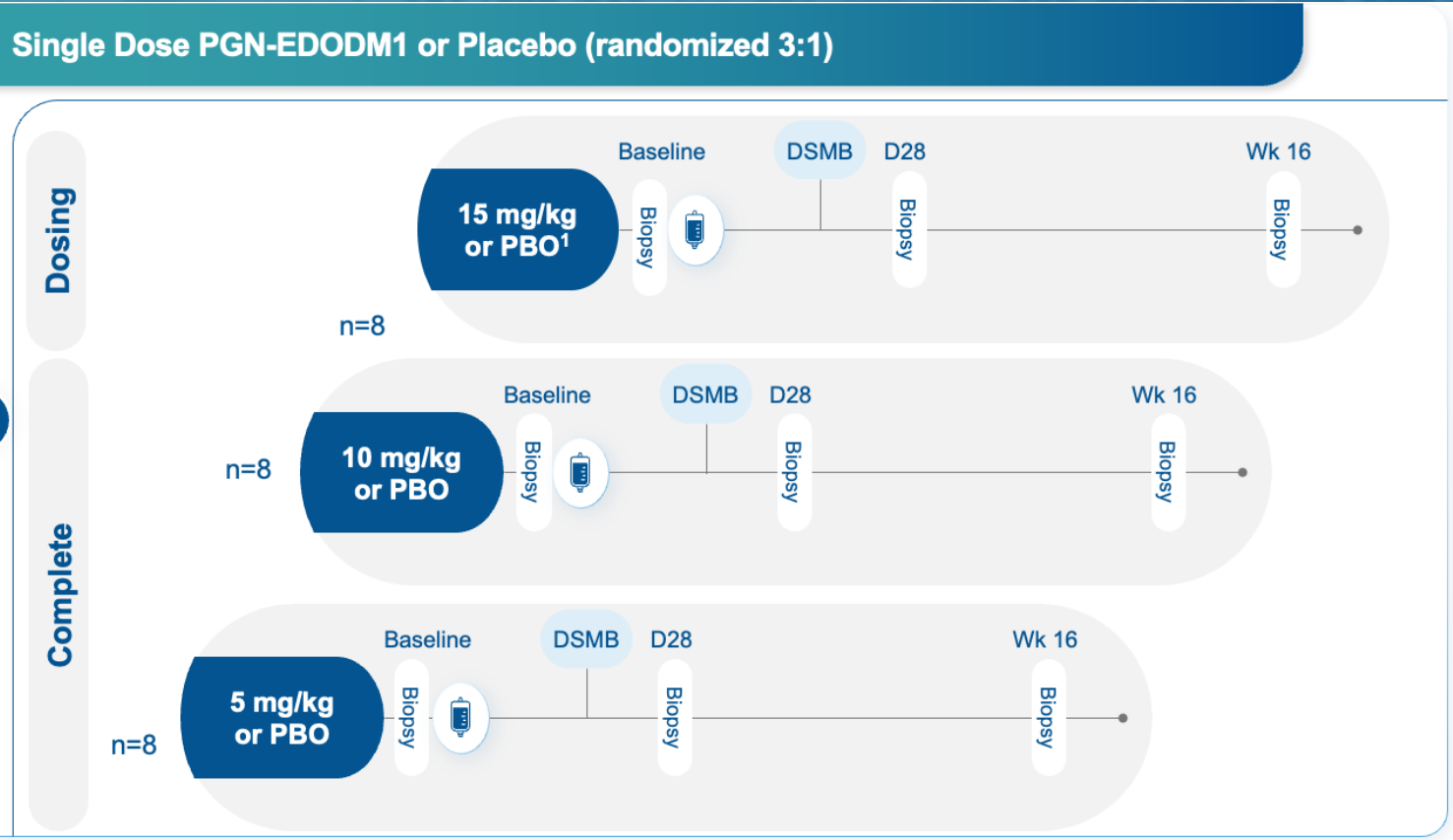
## FREEDOM Study Overview

Multinational, randomized, double-blind, placebo-controlled SAD study in people with DM1

Single IV administration of PGN-EDODM1

Muscle biopsies in tibialis anterior at Baseline, Day 28, Week 16

Safety, PK, correction of mis-splicing, initial functional assessments




1.15 mg/kg cohort added to expand pharmacokinetic and pharmacodynamic understanding
DSMB: data safety monitoring board; IV: intravenous; PBO: placebo; SAD: single-ascending dose; PK: pharmacokinetics

# DM1 Pathology Due to Spliceopathy: PGN-EDODM1 Produces Unprecedented Splicing Correction in DM1 Patients

## FREEDOM STUDY GOALS:

### PRIMARY: SAFETY

- ☑ Favorable emerging safety profile

### EXPLORATORY: PD (SPLICING)

- ☑ Unprecedented splicing correction achieved with single dose

## Mis-Splicing is the Known Cause of DM1

## Highest Splicing Correction Ever Reported in Patients

- **53.7% mean splicing correction** observed following single 15 mg/kg dose
- **100% of patients** in 15 mg/kg cohort demonstrated splicing correction
- Repeat doses of PGN-EDODM1 could deliver **greater splicing correction**

Splicing correction comparison is based on cross trial comparisons for exploratory purposes

# Favorable Emerging Safety Profile of PGN-EDODM1

## PGN-EDODM1 Generally Well-Tolerated at 15 mg/kg: *

- All treatment related TEAEs were mild or moderate in severity
  - All renal biomarker-related AEs were asymptomatic, transient (~48hrs) and resolved without intervention
- No electrolyte-related adverse events
- No treatment-related SAE
- No interventions required[1]
- No discontinuations
- Transient and reversible kidney biomarker movement in 1 patient qualified as a DLT as defined by the protocol and resolved without intervention; classified as a mild AE
- 1 moderate injection site reaction led to partial dose[2]
- 1 SAE related to biopsy procedure – unrelated to PGN-EDODM1
  - Tibial arterial pseudoaneurysm – alternative biopsy needle now employed in study

**Cohorts Include Placebo & Active**

| Summary of Treatment Emergent Adverse Events (TEAEs) | 5 mg/kg (n=8)* n(%) | 10 mg/kg (n=8)* n(%) | 15 mg/kg (n=8)* n(%) |
|---|---|---|---|
| Any related TEAE | 1 (13) | 3 (38) | 4 (50) |
| • Mild/Moderate<br>• Severe | 1 (13)<br>0 | 2 (25)<br>1 (13) | 4 (50)<br>0 (0) |
| Any Serious Adverse Event (SAE) | 1 (13) | 2 (25) | 1 (13) |
| Any related SAE | 0 | 1 (13) | 0 (0) |
| Any TEAE leading to study withdrawal, dose modification or dose interruption | 0 | 0 | 1 |
| Any TEAE leading to death | 0 | 0 | 0 |

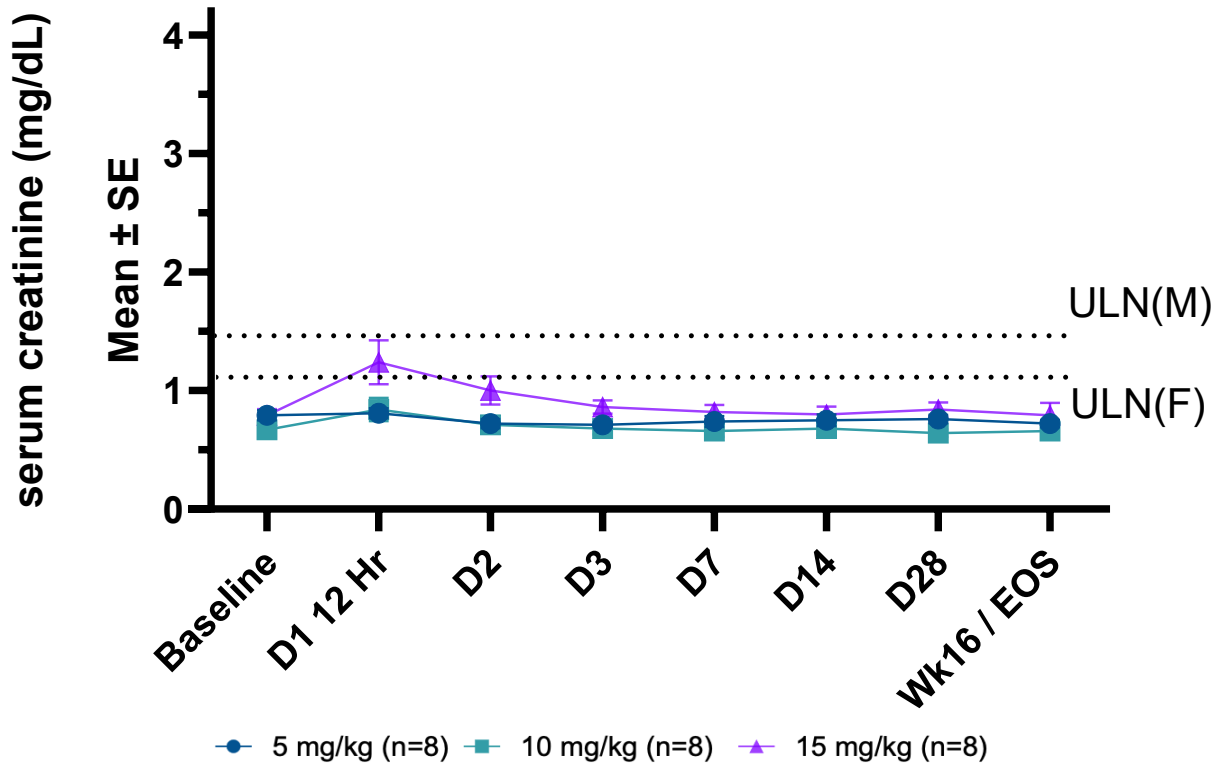


*Data collection ongoing for 15 mg/kg cohort; data current through Aug 5, 2025

1. With the exception of 1 patient who received oral OTC antihistamines
2. Data Safety Monitoring Board reviewed AE and recommended continuation of study/dosing

# PGN-EDODM1 Continues to Demonstrate Favorable Safety Profile

## PGN-EDODM1 Serum Creatinine in FREEDOM*



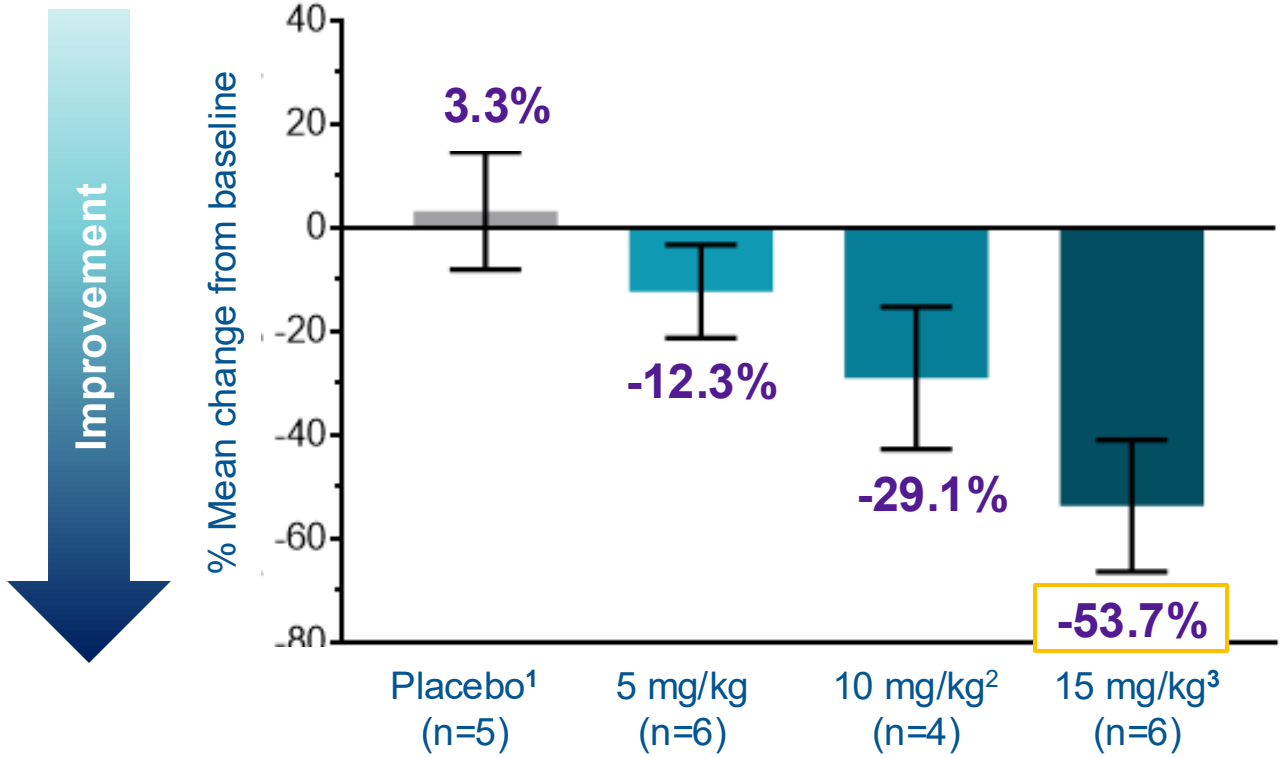

## KEY TAKEAWAYS:

- All kidney AEs were transient and mild or moderate
- No interventions required for kidney AEs
- No patients withdrew from study
- No hypomagnesemia observed at any PGN-EDODM1 dose

*Data collection ongoing for 15 mg/kg cohort; data current through Aug 5, 2025
BL: baseline; ULN: upper limit of normal; M: male; F: female

# PGN-EDODM1 Produced Mean 53.7% Splicing Correction Following Single 15 mg/kg Dose

## Splicing Index Changes: 22-Gene Panel* at D28




**100%**

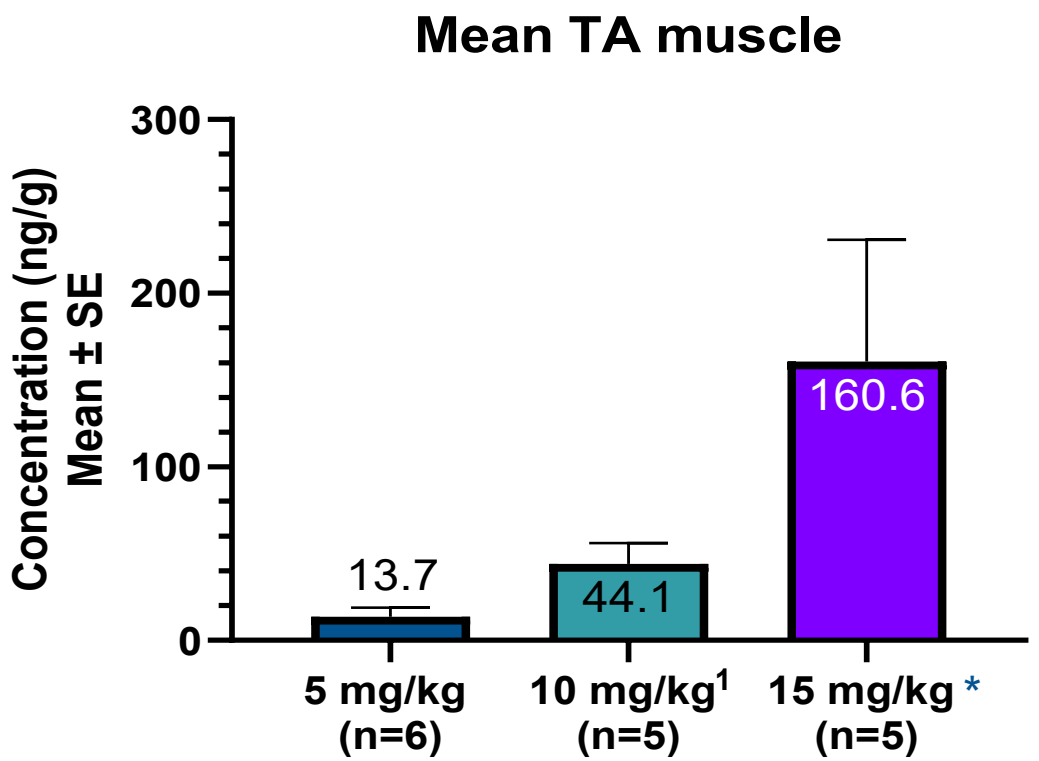
of patients in the 15 mg/kg cohort responded to treatment with PGN-EDODM1

* Provenzano et al., The Splice Index as a prognostic biomarker of strength and function in myotonic dystrophy type 1, J Clin. Invest. 2025

1. Placebo n=5 as biopsies were not obtained from one of the cohort 3 placebo patients due to biopsy associated complications on day 0.
2. One subject at 10 mg/kg biopsy was not collected at day 28 due to pseudoaneurysm in connection with biopsy and one participant's splicing index fell below the pre-specified assay range at baseline and at day 28 (indicating no detectable mis-splicing)
3. One subject at 15mg/kg received 77% of the dose and was still included in the splicing index change analysis for the cohort

# Robust, Greater Than Dose-Proportional Increase in Muscle Tissue Concentration Following Single Dose

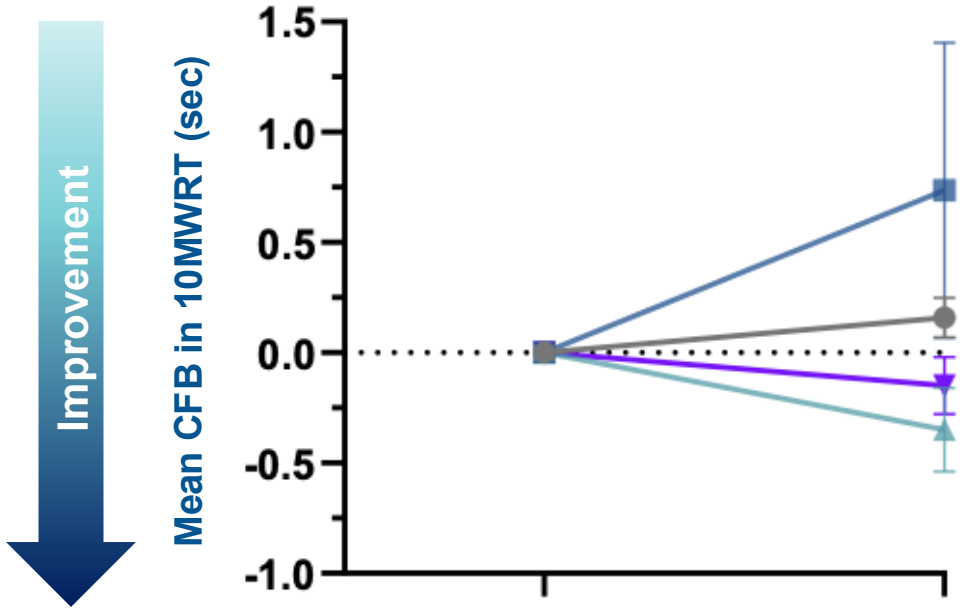
## Muscle Tissue Concentration at D28



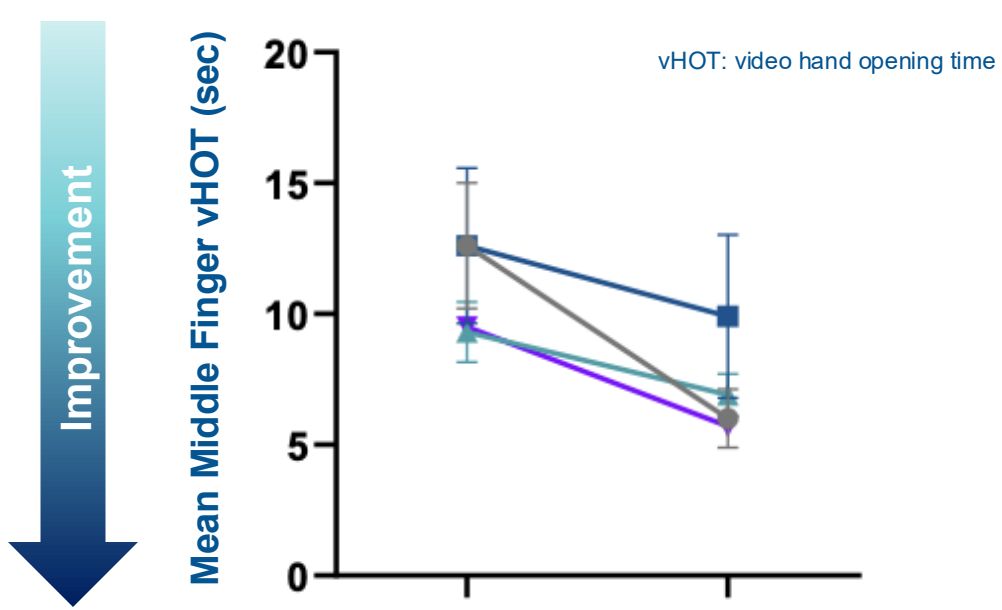

1. One subject at 10 mg/kg did not have biopsy collected at day 28 and was excluded from tissue quant analysis
*One subject at 15mg/kg received 77% of the full dose. Due to limited amount of biopsy, one subject at 15 mg/kg was excluded from tissue quant analysis

# Functional Outcomes After Single Dose

## 10-Meter Walk Run Test (10MWRT) at D28




## Myotonia (vHOT) at D28




Placebo (n=6) 5 mg/kg (n=6) 10 mg/kg (n=6) 15 mg/kg (n=6)

# Next Steps

## PHASE 1 FREEDOM (SAD)
*open in U.S., Canada and UK*

- **Completed patient dosing** in 15 mg/kg cohort
- Trial to conclude with 15 mg/kg cohort based on splicing, functional outcomes and blinded safety data observed to date

**UPCOMING MILESTONE:**

**Early Q4 2025:** FREEDOM 15 mg/kg clinical results

## PHASE 2 FREEDOM2 (MAD)
*open in Canada and UK*

- **Currently dosing** 5 mg/kg cohort
- Transitioning open FREEDOM clinical sites to FREEDOM2

**UPCOMING MILESTONE:**

**Q1 2026:** FREEDOM2 5 mg/kg clinical results

# Thank you!

**Clinical study participants and their families**

**Clinical site staff and investigators**

**Community and clinical advisors**

**Preclinical collaborators**

# Q&A

community@pepgen.com