O45

FREEDOM-DM1: A Phase 1, Placebo-Controlled Single Ascending Dose Study to Evaluate PGN-EDODM1 in People with Myotonic Dystrophy Type 1 (DM1)

Jennifer Shoskes[1], Johanna Hamel[2], Jean Dennis Brisson[3], Hanns Lochmuller[4], Thurman Wheeler[5], Jacinda Sampson[6], Namita Goyal[7], Jane Larkindale[1], Brijesh Garg[1], Gregory Song[1], Pallavi Lonkar[1], Stephen Babcock[1], Shaoxia Yu[1], Patricia Fraser[1], Michelle Mellion[1]

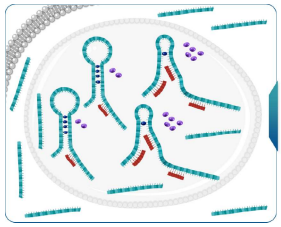
1. PepGen Inc. 2. University of Rochester, Rochester, NY 3. CIUSSS du Saguenay-Lac-Saint-Jean, Canada 4. The Ottawa Hospital, Canada. 5. Massachusetts General Hospital, Boston MA 6. Stanford University Medical Center, Stanford CA 7. University of California - Irvine Medical Center, Irvine CA

INTRODUCTION

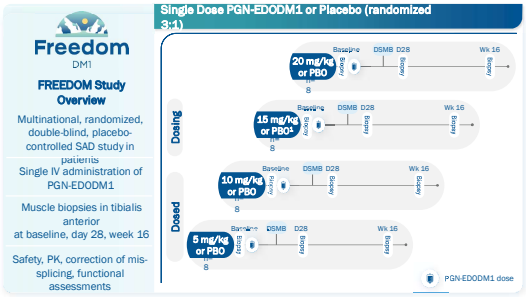
- PepGen's enhanced delivery oligonucleotide (EDO) cell-penetrating peptide technology is engineered to optimize tissue delivery and nuclear uptake of therapeutic oligonucleotides.
- PGN-EDODM1 is being evaluated for the treatment of myotonic dystrophy type 1 (DM1).
- PGN-EDODM1 has been evaluated in multiple nonclinical models including DM1 human derived muscle cells, the HSA^{LR} mouse model of DM1 and in wild-type mice and nonhuman primates.
  - See Poster P48 "Nonclinical Data for PGN-EDODM1 Demonstrated Mechanistic and Meaningful Activity for the Potential Treatment of DM"
- The PGN-EDODM1 clinical development program includes FREEDOM-DM1, a randomized, double-blind placebo-controlled single ascending dose study and FREEDOM2-DM1, a randomized, double-blind placebo-controlled multiple ascending dose study (NCT06204809 and NCT06667453, respectively). Both studies have been approved by regulators and are ongoing.

MECHANISM OF PGN-EDODM1

- PGN-EDODM1 is engineered to bind selectively to the pathogenic CUG repeat expansion present in *DMPK* transcripts
- This reduces the ability of these CUG repeats to form hairpin loops and sequester RNA splicing proteins, including MBNL1
- Liberated MBNL1 restores correct splicing



STUDY DESIGN



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

STUDY RESULTS

Baseline and Demographic Characteristics

	Mean (SD) or n (%)		
	Placebo (n=4)	5 mg/kg (n=6)	10 mg/kg (n=6)
Age (years)	39.0 (10.9)	36.3 (9.0)	34.7 (8.2)
Female, n (%)	3 (75%)	3 (50%)	3 (50%)
BMI (kg/m^2)	20.0 (3.3)	22.8 (5.0)	22.8 (5.7)
Splicing Index	72.3 (16.3)	73.7 (15.2)	53.6* (26.0)
vHOT – middle finger (sec)	14.1 (5.6)	12.6 (7.3)	9.3 (2.8)
10MWRT (sec)	4.3 (1.6)	3.9 (1.5)	4.4 (1.5)

*n=5 as one participant sample showed splicing index outside the pre-specified assay range at Baseline (no detectable mis-splicing)
SD: standard deviation; BMI: body mass index; PBO: placebo; vHOT: video hand opening time; sec: second; 10MWRT: 10-meter walk run test

Favorable Emerging Safety Profile of PGN-EDODM1[1]

Summary of Treatment Emergent Adverse Events (TEAEs) n(%)	5 mg/kg (n=8)[2]	10 mg/kg (n=8)[2]	Total (n=16)[2]
Any TEAE	4 (50.0)	6 (75.0)	10 (62.5)
Any related TEAE	1 (12.5)	3 (37.5)	4 (25.0)
Any SAE	1 (12.5)	2 (25.0)	3 (18.8)
Any related SAE	0	1 (12.5)	1 (6.3)
Any AESI or dose limiting toxicities	0	0	0
Any TEAE leading to study withdrawal	0	0	0
Any TEAE leading to death	0	0	0

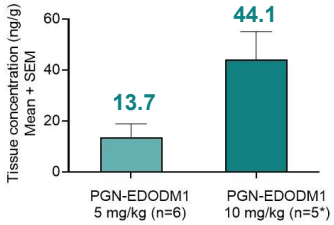
PGN-EDODM1 was Generally Well Tolerated, with Most TEAEs Mild or Moderate in Severity

- All treatment related TEAEs:
  - Nausea (n=2), vomiting (n=1), dizziness (n=1), headache (n=1), feeling hot (n=1), abdominal pain (n=1)
- SAE related to study drug:
  - Abdominal pain (10 mg/kg) potentially confounded by use of prohibited, off-label drug taken on the morning of PGN-EDODM1 dosing[2]
- SAEs unrelated to study drug:
  - Appendicitis (5 mg/kg)
  - Right anterior tibial artery pseudoaneurysm (10 mg/kg) in connection with biopsy procedure
- No adverse events related to electrolytes or renal biomarkers

1. As of December 3, 2024. 2. Includes all participants (placebo and PGN-EDODM1 treated); cohorts remain blinded 3. Data Safety Monitoring Board reviewed event and recommended continuation of study/dosing. SAE: serious adverse event; AESI: adverse event of special interest

Dose-Dependent Increase in Muscle Tissue Concentration Following Single Dose

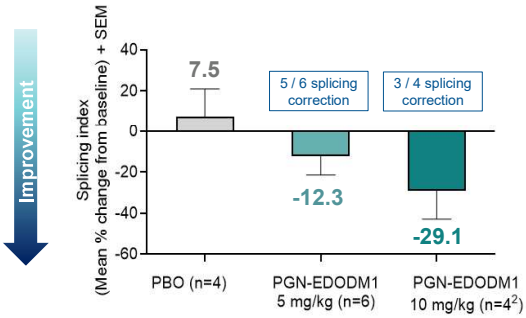
Muscle Tissue Concentration at Day 28



* One participant's biopsy was not collected at Day 28 due to pseudoaneurysm in connection with biopsy procedure
SEM: standard error of the mean; Placebo tissue concentration was below level of quantification

Dose Dependent Splice Correction Following a Single Dose, with Mean 29% Splicing Correction at 10 mg/kg

Splicing Index Changes: 22-Gene Panel[1] at Day 28

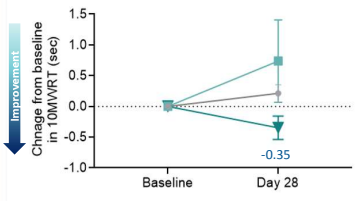


Each person with splicing correction in 10 mg/kg cohort showed >17% correction

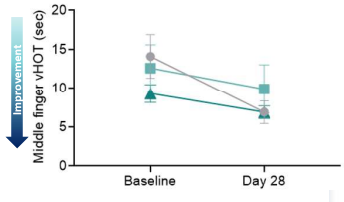
1.Provenzano et al, The Splice Index as a prognostic biomarker of strength and function in myotonic dystrophy type 1, *J Clin. Invest.* 2025
2.In 10 mg/kg cohort: One participant's biopsy was not collected at Day 28 due to pseudoaneurysm in connection with biopsy procedure and one participant's sample showed splicing index outside the pre-specified assay range at Baseline and Day 28 (no detectable mis-splicing) and was excluded from the analysis.

Functional Outcome Data After Single Dose Showed Variable Response

10MWRT at Day 28



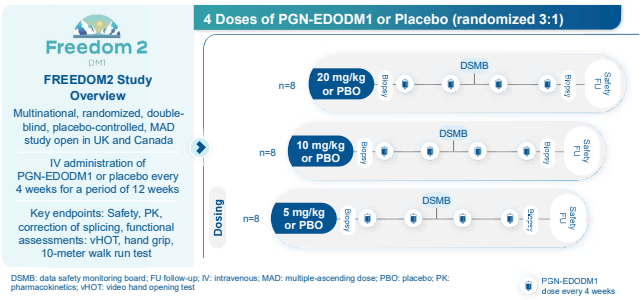
Myotonia (vHOT) at Day 28



10MWRT: 10-meter walk run test; vHOT: video hand opening time; PBO: placebo

PBO (n=4) | PGN-EDODM1 5 mg/kg (n=6) | PGN-EDODM1 10 mg/kg (n=6)

FREEDOM2-DM1 Multiple-Ascending Dose (MAD) Study Underway



DSMB: data safety monitoring board; FU follow-up; IV: intravenous; MAD: multiple-ascending dose; PBO: placebo; PK: pharmacokinetics; vHOT: video hand opening test

CONCLUSIONS

- PGN-EDODM1 demonstrated a favorable emerging safety profile in people with myotonic dystrophy type 1
- There was a dose dependent increase in drug tissue concentration observed in first two cohorts from 5 mg/kg to 10 mg/kg
- PGN-EDODM1 produced dose dependent increases in mean splicing correction following single dose with ~29% at 10mg/kg and ~12% at 5 mg/kg
- The FREEDOM-DM1 study results support the continued development of PGN-EDODM1 for the treatment of DM1

Disclosures: All PepGen authors are employees of PepGen Inc. and hold PepGen equity