

Development of PGN-EDODM1, a novel enhanced delivery oligonucleotide that targets the root cause of myotonic dystrophy type 1



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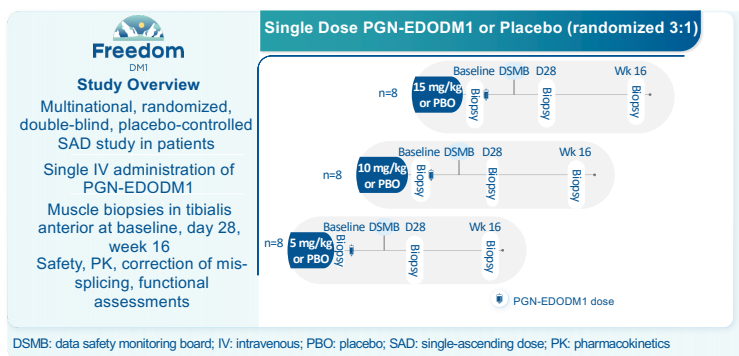
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INTRODUCTION

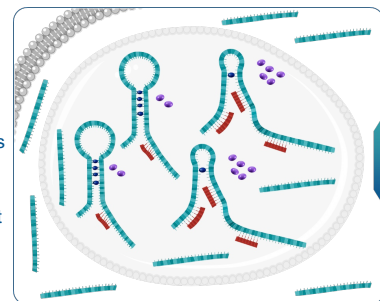
- PepGen's enhanced delivery oligonucleotide (EDO) cell-penetrating peptide technology is engineered to optimize tissue delivery and nuclear uptake of therapeutic oligonucleotides.
- PGN-EDODM1 is being evaluated for the treatment of myotonic dystrophy type 1 (DM1).
- PGN-EDODM1 has been evaluated in multiple nonclinical models including DM1 human derived muscle cells, the HSA^{LR} mouse model of DM1 and in wild-type mice and nonhuman primates.
- 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. Both studies have been approved by regulators. FREEDOM-DM1 (NCT06204809) is complete, FREEDOM2-DM1 (NCT06667453) is ongoing.

FREEDOM-DM1 STUDY DESIGN (NCT06204809)



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



BASELINE AND DEMOGRAPHIC CHARACTERISTICS

Some variability between cohorts as expected in the DM1 population.

Mean (SD)	Placebo (N=6)	5mg/kg PGN-EDODM1 (N=6)	10 mg/kg PGN-EDODM1 (N=6)	15 mg/kg PGN-EDODM1 (N=6)
Age (years)	35.5 (10.4)	36.3 (9.0)	34.7 (8.2)	28.5 (9.0)
Sex (female)	5 (83)	3 (50)	3 (50)	2 (33)
Weight (kg)	59.2 (12.2)	67.3 (19.7)	65.8 (16.6)	71.5 (14.1)
BMI (kg/m ²)	21.0 (3.4)	22.8 (5.0)	22.8 (5.7)	23.6 (5.5)
vHOT (s) (mean, middle finger)	12.6 (5.9)	12.6 (7.3)	9.3 (2.8)	9.5 (5.8)
Grip strength max PPN (R)	43.49 (19.14)	36.97 (15.03)	28.71 (15.19)	47.24 (13.04)
Grip strength max PPN (L)	43.28 (20.25)	44.92 (18.12)	32.27 (14.29)	54.44 (16.23)
Splicing Index	65.1 (17.7)	73.7 (15.2)	53.6 (26.0)*	51.6 (24.0)
DM1-ACTIVc	42.8 (8.6)	40.7 (6.7)	47.3 (3.7)	45.0 (5.1)
10MWRT (s)	4.0 (1.3)	3.9 (1.5)	4.4 (1.5)	3.8 (1.2)

*n=5 as biopsy data unavailable for one person. SD: standard deviation; BMI: body mass index; PBO: placebo; vHOT: video hand opening time; sec: second; 10MWRT: 10-meter walk run test

PGN-EDODM1 WAS GENERALLY WELL TOLERATED¹

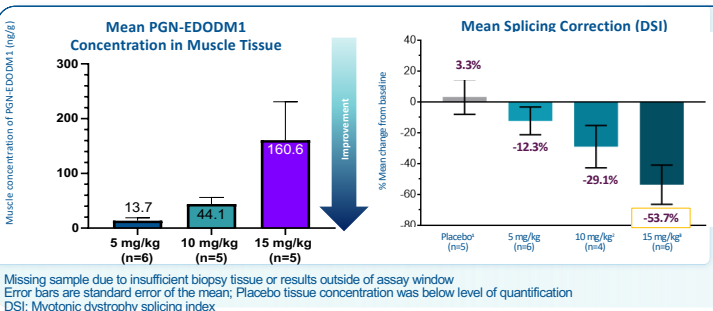
	Placebo (n=6) N (events)	Cohort 1 5 mg/kg (n=6)	Cohort 2 10 mg/kg (n=6)	Cohort 3 15 mg/kg (n=6)	Total (n=24)
Any TEAE, n (events)	5 (16)	3 (20)	4 (16)	5 (18)	17 (70)
Any TEAE by Max Severity					
Mild	2	1	2	3	8
Moderate	3	1	0	2	6
Severe	0	1	2	0	3
Any related TEAE, n (events)	1 (3)	1 (1)	2 (4)	4 (14)	8 (22)
Any SAE (event)	1(2)	1 (1)	2 (2)	0 (0)	4 (5)
Any related SAE	0	0	1 (1)	0	1(1)
Any AESI	0	0	1(1)	2 (2)	3
Any DLT	0	0	0	1	1
Any TEAE leading to study withdrawal	0	0	0	0	0
Any TEAE leading to death	0	0	0	0	0

1. As of database lock on December 23, 2025. TEAE: treatment related adverse event, SAE: serious adverse event, AESI: adverse event of special interest. DLT: dose limiting toxicity

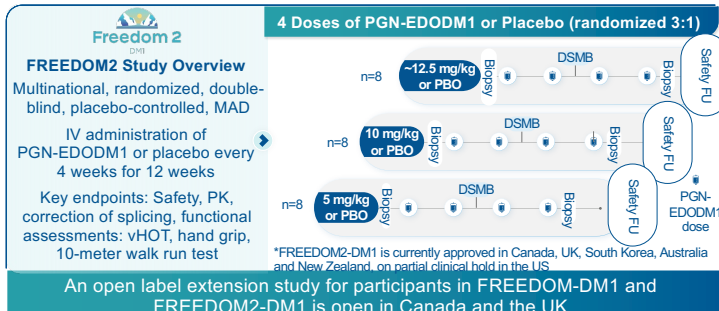
TEAEs Primarily Mild to Moderate Across Cohorts:

- Most frequent TEAEs: nausea, nasopharyngitis, and headache
- No electrolyte-related TEAEs or hypomagnesemia observed across dose cohorts
- No renal-related TEAEs observed at 5 and 10 mg/kg
 - DLT at 15 mg/kg involving a transient decrease in eGFR(cys), resolved without intervention
 - Asymptomatic transient changes in renal biomarkers resolved without intervention
- One drug-related hypersensitivity reaction (rash) during infusion at 15 mg/kg, resolving within 2 hours with oral antihistamines
- One drug-related SAE of severe abdominal pain at 10 mg/kg, confounded by off-label medication use on the day of dosing

DOSE-DEPENDENT INCREASES IN DRUG CONCENTRATION AND SPLICING CORRECTION 28 DAYS POST-DOSE



MULTIPLE ASCENDING DOSE STUDY, FREEDOM2-DM1, IS CURRENTLY ENROLLING (NCT06667453)*.



CONCLUSIONS

- PGN-EDODM1 was generally well-tolerated in people with myotonic dystrophy type 1 at doses showing pharmacodynamic activity
- Dose dependent increases in mean splicing correction following single doses of PGN-EDODM1: ~12% at 5 mg/kg, ~29% at 10 mg/kg and 54% at 15 mg/kg
- The FREEDOM-DM1 study results support the continued development of PGN-EDODM1 for the treatment of DM1 in the repeat dose study, FREEDOM2-DM1, which is ongoing

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

