## FREEDOM-DM1: Phase 1 Study Design to Assess Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of PGN-EDODM1 for Myotonic **Dystrophy Type 1**



PepGen

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### INTRODUCTION

- The Enhanced Delivery Oligonucleotide (EDO) platform is engineered to optimize the tissue penetration, cellular uptake and nuclear delivery of oligonucleotide therapeutic candidates.
  - Limited delivery and distribution of unconjugated oligonucleotides to affected tissues limits their activity in DM1.
- **PGN-EDODM1** is an EDO under investigation for the treatment of people with Myotonic Dystrophy type 1 (DM1).
- DM1 is a multi-systemic disease that has a significant impact on physical function and quality of life.
- PGN-EDODM1 was evaluated in multiple nonclinical models including DM1 human

# **PEPGEN'S NOVEL APPROACH TO DM1 MBNL1 COMPETITION PGN-EDODM1** binds to the CUG repeats in the DMPK transcript, reducing toxic foci

• Binding of PGN-EDODM1 liberates MBNL1,

**DM1 PATHOLOGY** 

DMPK transcript CUG repeat hairpin loops bind MBNL1 and form foci



- derived muscle cells, the HSA<sup>LR</sup> mouse model of DM1 and in wild-type (WT) mice and non-human primates (NHPs).
- FREEDOM-DM1, a Phase 1 single-ascending dose clinical study in participants with DM1, is underway in USA, Canada and UK.



Expanding foci trap more MBNL1

- restoring physiological splicing
- DMPK transcript retained; role in cellular processes uninterrupted

\ denotes PGN-EDODM1

#### **ROBUST PRECLINICAL EVALUATION OF PGN-EDODM1**

#### **REPEAT DOSING OF PGN-EDODM1 IN HSALR MICE ENHANCED CORRECTION OF PGN-EDODM1 REDUCED TOXIC FOCI, LIBERATED MBNL1 AND CORRECTED MIS-SPLICING IN DM1 CELLS** MIS-SPLICING, REVERSED MYOTONIA AND INCREASED MUSCLE DELIVERY PGN-EDODM1 PGN-EDODM1 PGN-EDODM1 dose PGN-EDODM1 dose Hour: 0 24 Week:0 4 8 12 16 HSALR DM1 cells Analysis Tissue/myotonia analysis (2,600 CTG repeats) **TOXIC FOCI REDUCTION MBNL1 LIBERATION MIS-SPLICING CORRECTION MIS-SPLICING CORRECTION REVERSAL OF MYOTONIA TISSUE CONCENTRATION** Across multiple transcripts **Pinch test** Across multiple transcripts **Skeletal muscle** Not treated (NT) Not treated (NT) Foci quantification **1.5**x 99% 100-54% reduction 30 Correction of (%) 69% correction **68% 2.2x** (%) myotonia 80ction 80 **WU** 20 10 SS nucleus 13nM Pinch ( 60-60 **76%** 6nM -splicing per 40 PGN-EDODM1 PGN-EDODM1 40-Foci 20 Š 20-2-**99%** Mis-0% **OnM** WT HSA<sup>LR</sup> x1 HSA<sup>LR</sup> x4 x1 x4 HSA<sup>LR</sup> x4 x1



Healthy		DM <sup>*</sup>	1 cells	5
NT	NT	2	10	20

30 mg/kg	30 mg/kg	30 mg/kg
<b>99% correction</b> across multiple	<b>Correction of myotonia</b> observed	Increased levels of PGN-EDODM1 in
transcripts	after repeat dose	tissue with repeat dose

### PHASE 1 STUDY (FREEDOM-DM1) CLINICAL DESIGN

### **OPEN in USA, CANADA & UK** FREEDOM-DM1: PHASE 1 Single ascending dose (SAD) Preliminary data expected in second half of 2024

- Being conducted in people with DM1 •
- Randomized, double-blind, placebo-controlled • trial
- Key anticipated readouts: Functional assessments, correction of mis-splicing, safety data

Freedom N=8 DM1

#### Single Dose PGN-EDODM1 or Placebo (randomized 3:1)



PBO: Placebo; 📋 Study drug dose

#### **STUDY OBJECTIVES**

- **PRIMARY**: To evaluate the safety and tolerability of PGN-EDODM1 after a single dose
- **SECONDARY**: To evaluate the pharmacokinetics (PK) of PGN-EDODM1 after a single dose
- SELECT KEY EXPLORATORY:
  - Correction of mis-splicing • Functional assessments

#### **KEY ELIGIBILITY CRITERIA**

#### **KEY INCLUSION**

- Male or female between the ages of 18 and 50 years, inclusive
- Confirmed diagnosis of DM1, defined as having a repeat sequence in the DMPK gene with at least 100 CTG repeats
- Medical Research Council (MRC) score of  $\geq$  Grade 4 in bilateral tibialis anterior (TA) muscles at Screening

#### **KEY EXCLUSION**

- Congenital DM1
- Known history or presence of any clinically significant conditions that may interfere with study safety assessments

#### CONCLUSION

- Robust nonclinical data in DM1 cells, HSA<sup>LR</sup> mice and NHP support further development of PGN-EDODM1 in clinical studies
- The Phase 1 FREEDOM-DM1 study is designed to assess the safety and tolerability of PGN-EDODM1 and provide an initial assessment of the effect of PGN-EDODM1 on functional assessments and mis-splicing