FREEDOM-DM1: Nonclinical Data Support the Phase 1 Study Design to Assess Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of PGN-EDODM1 in Adults with Myotonic Dystrophy Type 1 (DM1)

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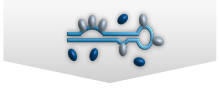
INTRODUCTION

- 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 DM1**.
- DM1 is a multi-systemic disease that has a **significant impact on the quality of life.**
- Pharmacological activity of PGN-EDODM1 was evaluated in DM1 cells, the HSA^{LR} mouse model of DM1 and in wild-type (WT) mice and non-human primates (NHPs).
  - **Reduction of toxic foci and liberation of MBNL1** observed in DM1 patient cells
  - In the HSA^{LR} DM1 mouse model, **robust mis-splicing correction and reversal of myotonia** observed with a single dose; durable mis-splicing corrections observed through 24 weeks
  - **Enhanced mis-splicing correction, reversal of myotonia and increased levels of tissue delivery** observed with repeat dosing in DM1 mouse
  - **PGN-EDODM1 is not designed to degrade** CUG-containing transcripts, including DMPK – a potentially important safety feature
  - Observed to be **well-tolerated through 90 mg/kg** in single dose NHP GLP toxicology studies

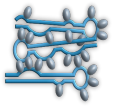
PEPGEN'S NOVEL APPROACH TO DM1

DM1 PATHOLOGY

***DMPK* transcript CUG repeat hairpin loops bind MBNL1 and form cross-linked foci**

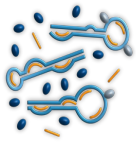


Expanding toxic foci trap more MBNL1



MBNL1 COMPETITION

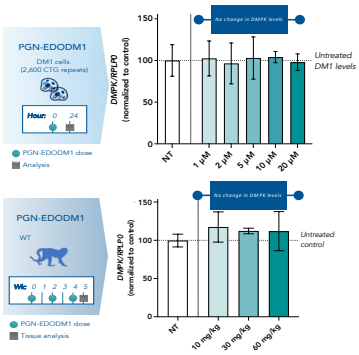
PGN-EDODM1 binds mutant DMPK transcript, reducing toxic foci



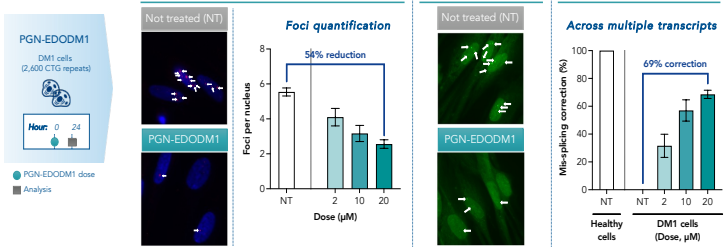
- Binding of PGN-EDODM1 liberates MBNL1, restoring physiological splicing
- ***DMPK* transcript retained; role in cellular processes uninterrupted**

denotes free (active) MBNL1, denotes bound (inactive) MBNL1, denotes PGN-EDODM1.

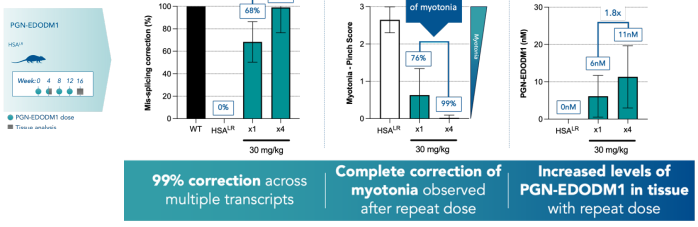
PGN-EDODM1 DID NOT TARGET *DMPK* FOR DEGRADATION



PGN-EDODM1 REDUCED RNA FOCI, LIBERATED MBNL1 AND CORRECTED MIS-SPLICING IN DM1 CELLS



PGN-EDODM1 SIGNIFICANTLY INCREASED CORRECTION OF MIS-SPLICING IN HSA^{LR} MICE WITH REPEAT DOSING



99% correction across multiple transcripts

Complete correction of myotonia observed after repeat dose

Increased levels of PGN-EDODM1 in tissue with repeat dose

We believe that nonclinical data in DM1 cells, HSA^{LR} mice and non-human primates support the **continued clinical development of PGN-EDODM1 and planned FREEDOM-DM1 clinical study**

FREEDOM-DM1 PHASE 1 STUDY DESIGN

OBJECTIVES

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

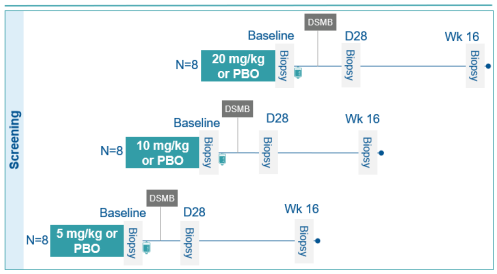
Freedom DM1

FREEDOM-DM1 study overview

- Ph1 global, randomized, double-blind, placebo-controlled SAD study in patients*
- Single IV administration of PGN-EDODM1
- Muscle biopsies at baseline, day 28, week 16
- Initial functional assessments, correction of mis-splicing and safety data anticipated in 2024

OPEN in CANADA

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



Note: Clinical plans are subject to alignment with regulatory authorities. PBO=Placebo; Study drug dose

SAD = single ascending dose

*IND for FREEDOM-DM1 study of PGN-EDODM1 in people with DM1 is currently on clinical hold with the FDA. PepGen is working to address FDA's feedback. FREEDOM-DM1 has been approved in Canada and we are pursuing the advancement of PGN-EDODM1 in additional geographies.

KEY INCLUSION CRITERIA

- Male or female between 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 ≥Grade 4 in bilateral tibialis anterior (TA) muscles at Screening

KEY EXCLUSION CRITERIA

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