PGN-EDODM1 Nonclinical Data Demonstrated Mechanistic and Meaningful Activity for the Potential Treatment of Myotonic Dystrophy Type 1 (DM1)

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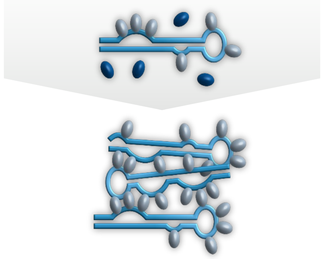
INTRODUCTION

- The **Enhanced Delivery Oligonucleotide (EDO)** platform is **engineered to optimize the tissue penetration, cellular uptake and nuclear delivery** of oligonucleotide therapeutic candidates.
- DM1 is a multi-systemic disease that has a **significant impact on the quality of life.**
- 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**.
- PGN-EDODM1 was evaluated in multiple nonclinical models including DM1 cells, the HSA^{LR} mouse model of DM1 and in wild-type (WT) mice and non-human primates (NHPs).

PGN-EDODM1 IS DESIGNED TO LIBERATE MBNL1 WITHOUT REDUCING *DMPK* LEVELS

DM1 PATHOLOGY

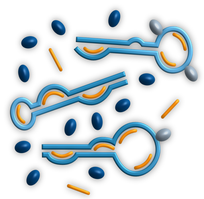
DMPK transcript CUG repeat hairpin loops bind MBNL1 and form foci



Expanding foci trap more MBNL1

MBNL1 COMPETITION

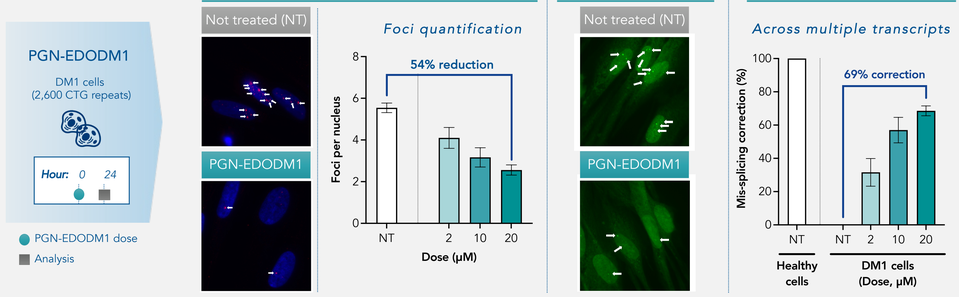
PGN-EDODM1 binds CUG repeats in *DMPK* transcript, reducing foci



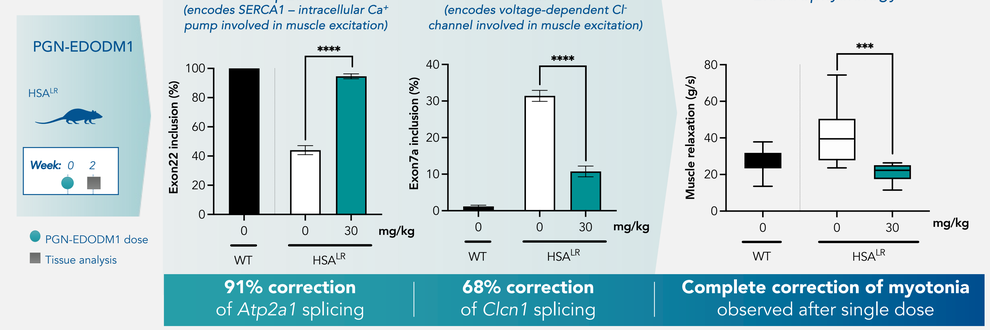
- Binding of PGN-EDODM1 liberates MBNL1, restoring physiological splicing
- *DMPK* transcript retained; role in cellular processes uninterrupted

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

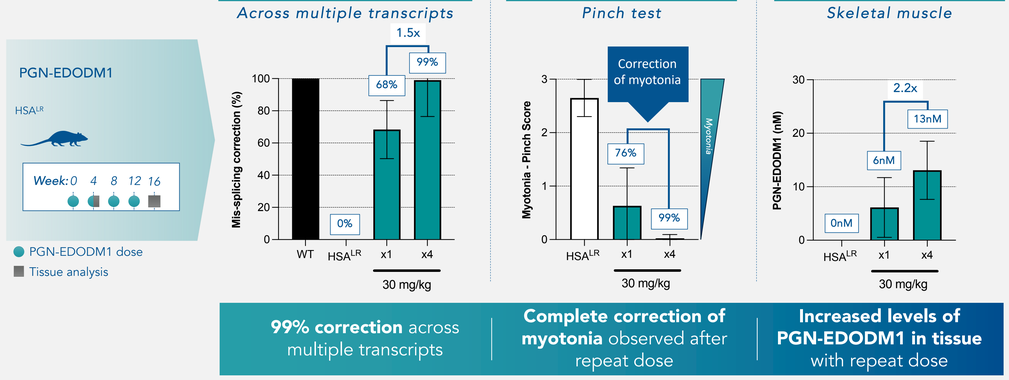
PGN-EDODM1 REDUCED FOCI, LIBERATED MBNL1 and CORRECTED MIS-SPLICING IN DM1 CELLS



A SINGLE DOSE OF PGN-EDODM1 ACHIEVED CORRECTION OF MIS-SPLICING AND MYOTONIA IN HSA^{LR} MODEL

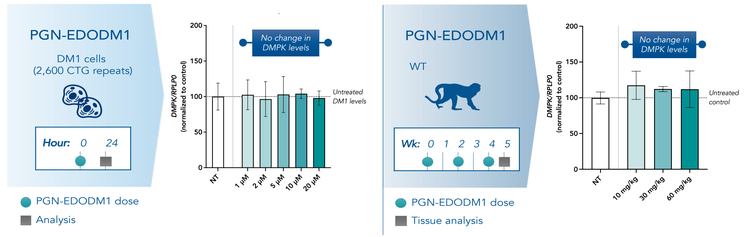


REPEAT DOSING OF PGN-EDODM1 IN HSA^{LR} MICE ENHANCED CORRECTION OF MIS-SPLICING, REVERSED MYOTONIA AND INCREASED MUSCLE DELIVERY



PGN-EDODM1 DID NOT TARGET *DMPK* FOR DEGRADATION

DMPK TRANSCRIPT LEVELS



FREEDOM-DM1 PHASE 1 CLINICAL STUDY

OPEN IN CANADA

FREEDOM-DM1: PHASE 1
Single ascending dose (SAD): Interim data expected to read out in 2024

- To be conducted in DM1 patients
- Randomized, double-blind, placebo-controlled trial
- Key anticipated readouts: **Functional assessments data, correction of mis-splicing data, safety data**

Freedom DM1

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

SUMMARY AND CONCLUSIONS

- **PGN-EDODM1** resulted in **reduction of foci and liberation of MBNL1** in DM1 cells
- In the HSA^{LR} DM1 mouse model, **robust mis-splicing correction and reversal of myotonia** was 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*
- Observed to be **well-tolerated through 90 mg/kg in single dose NHP GLP toxicology studies**
- **FREEDOM-DM1 Phase 1** randomized, double-blind, placebo-controlled **SAD study in patients** is **open in Canada**
- Nonclinical data in DM1 cells, HSA^{LR} mice and non-human primates support the **continued clinical development of PGN-EDODM1 and planned FREEDOM-DM1 Phase 1 clinical study*.**

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

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