440P

Nonclinical Data for PGN-EDODM1 Demonstrated Nuclear Delivery, Mechanistic and Meaningful Activity for the Potential Treatment of DM1

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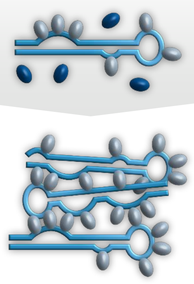
INTRODUCTION

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

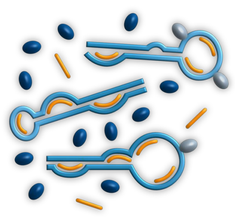
***DMPK* transcript CUG repeat hairpin loops bind MBNL1 and form foci**



- **Expanding foci trap more MBNL1**

MBNL1 COMPETITION

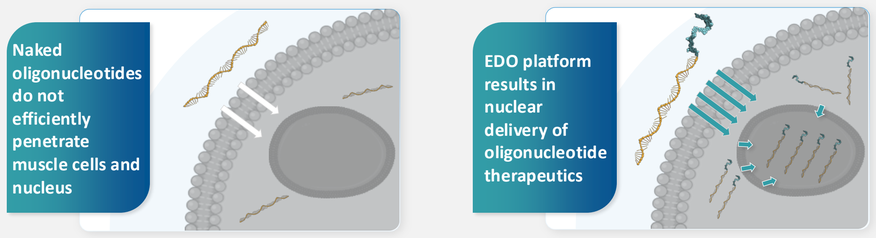
PGN-EDODM1 binds to the CUG repeats in the *DMPK* transcript, reducing toxic foci



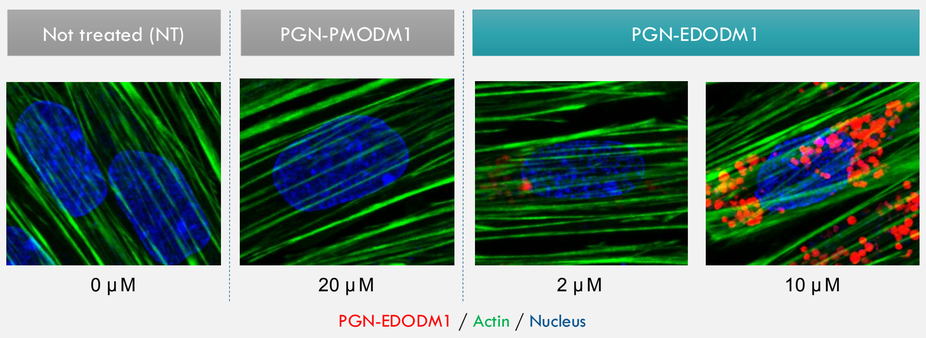
- Binding of PGN-EDODM1 liberates MBNL1, restoring physiological splicing
- ***DMPK* transcript retained; role in cellular processes uninterrupted**

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

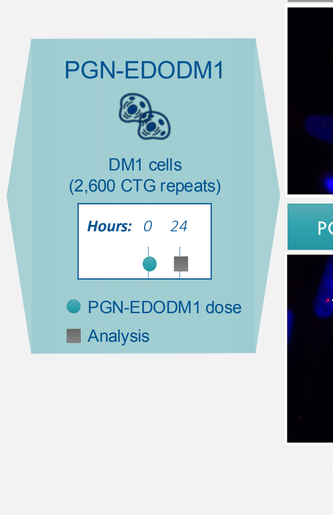
CELLULAR DELIVERY AND ACTIVITY DATA



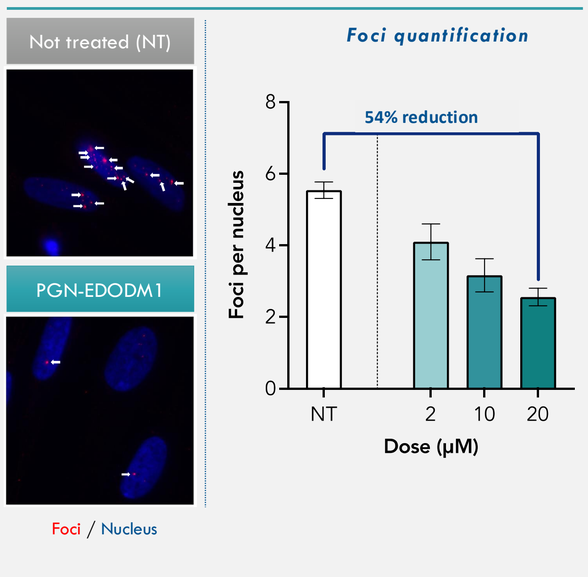
PGN-EDODM1 RESULTED IN HIGH LEVELS OF NUCLEAR DELIVERY IN DM1 MUSCLE CELLS



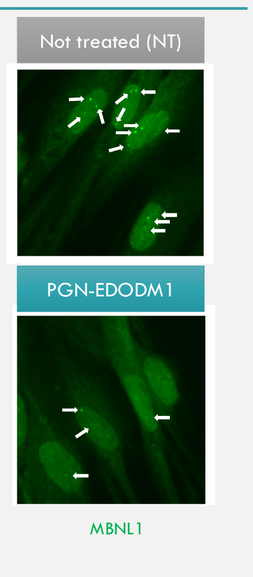
PGN-EDODM1 REDUCED TOXIC FOCI, LIBERATED MBNL1 AND CORRECTED MIS-SPLICING IN DM1 MUSCLE CELLS



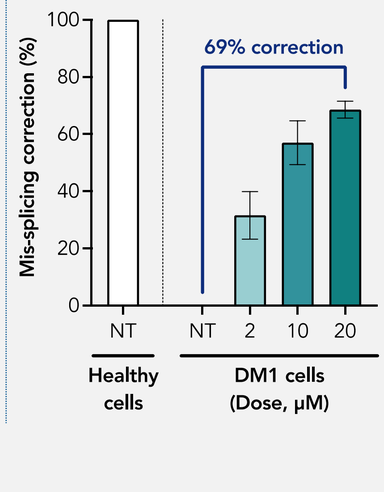
TOXIC FOCI REDUCTION



MBNL1 LIBERATION

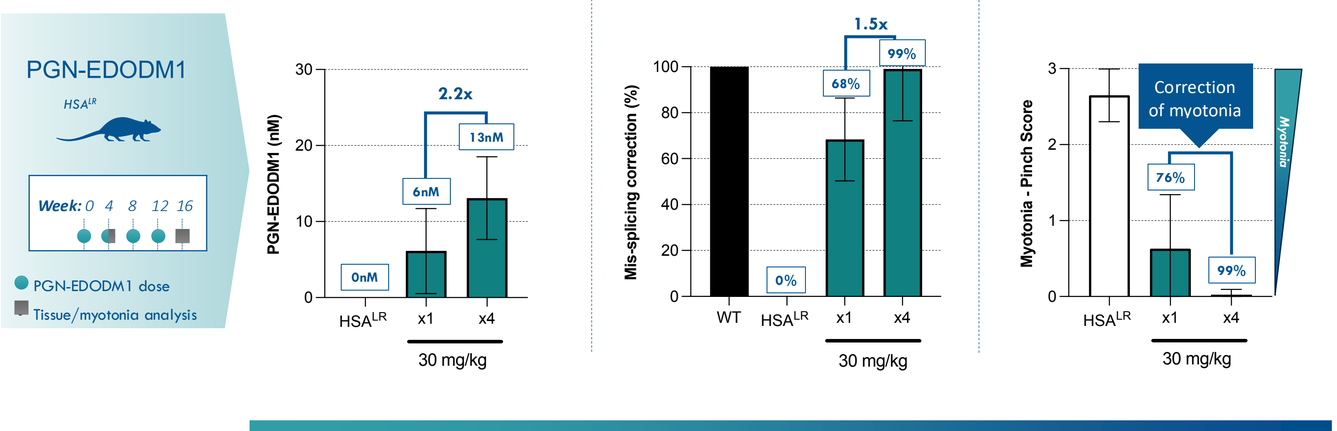


MIS-SPLICING CORRECTION



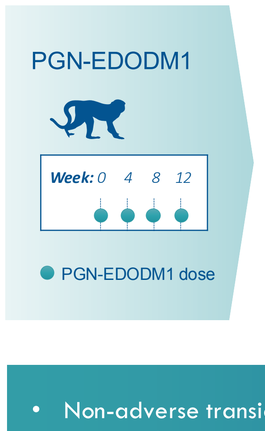
HSA^{LR} MOUSE MODEL AND NON-HUMAN PRIMATE (NHP) DATA

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

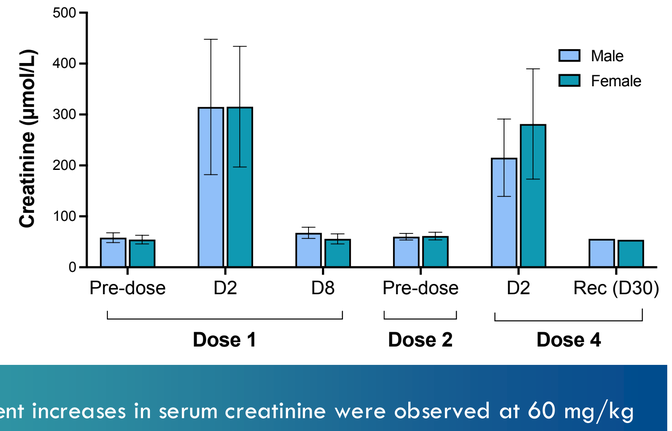


Increased levels of PGN-EDODM1 in tissue with repeat dose	**99% correction** across multiple transcripts	**Complete correction of myotonia** observed after repeat dose

FAVORABLE SAFETY PROFILE IN NHP SUPPORTED PROGRESSION TO CLINICAL STUDIES



SERUM CREATININE



- Non-adverse transient increases in serum creatinine were observed at 60 mg/kg and resolved within a week post dose and did not worsen with repeat dosing.
- No adverse findings in the kidney after 4x Q4W 60 mg/kg doses.
- No notable hematologic or hepatic effects, no cardiovascular effects.

SUMMARY AND CONCLUSIONS OF PGN-EDODM1 NONCLINICAL DATA

- **PGN-EDODM1** is **not designed to degrade *DMPK*,** the transcript where the pathogenic CUG expansion is located.
- **PGN-EDODM1** resulted in **nuclear delivery, reduction of toxic foci and liberation of MBNL1, and correction of mis-splicing** in DM1 human muscle cells.
- In the HSA^{LR} DM1 mouse model, **robust mis-splicing correction and reversal of myotonia** were observed with a single 30 mg/kg dose; durable mis-splicing corrections observed **through 24 weeks.**
- **Increased levels of tissue delivery, enhanced mis-splicing correction** and **reversal of myotonia** was observed with repeat dosing in HSA^{LR} mice.
- **Well-tolerated NHP GLP repeat-dose toxicity studies at 60 mg/kg; repeat dosing did not exacerbate increases in serum creatinine.**
- **FREEDOM-DM1 Phase 1** randomized, double-blind, placebo-controlled **Single Ascending Dose study in people with DM1** is **enrolling in Canada,** the **UK** and the **US.** **FREEDOM2 Phase 2** randomized, double-blind, placebo-controlled **Multiple Ascending Dose study in people with DM1** is **cleared in Canada** and the **UK.**
- **Nonclinical data** in DM1 cells, HSA^{LR} mice and NHP support the **development of PGN-EDODM1** and the **FREEDOM1-DM1 Phase 1 and FREEDOM2-DM1 Phase 2 clinical studies** (see **Poster 461P**).