T309

PGN-EDODM1 Single- and Repeat-Dose Nonclinical Data Indicated Mechanistic and Meaningful Activity for Potential Treatment of Myotonic Dystrophy Type 1 (DM1)

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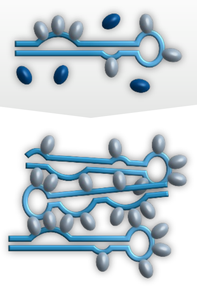
INTRODUCTION

- 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 quality of life.**
- Limited delivery and distribution of unconjugated oligonucleotides to affected tissues limits their potential effectiveness 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 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

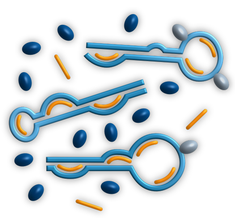
DMPK transcript CUG repeat hairpin loops bind MBNL1 and form foci



- Expanding foci trap more MBNL1

MBNL1 COMPETITION

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

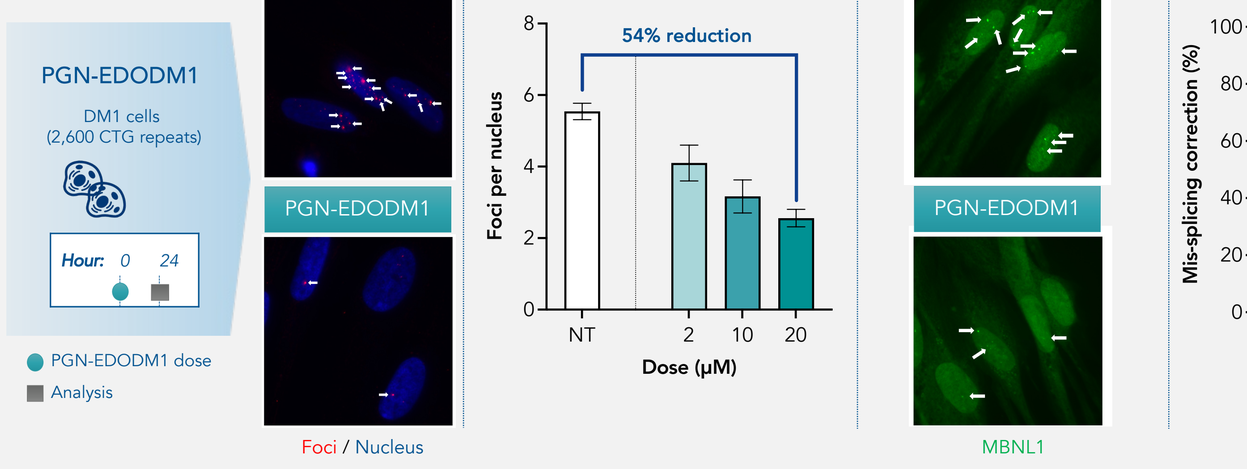


- Binding of PGN-EDODM1 liberates MBNL1, restoring physiological splicing
- *DMPK* transcript retained; role in cellular processes uninterrupted

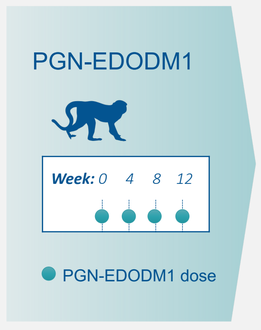
denotes free (active) MBNL1 | denotes bound (inactive) MBNL1 | denotes PGN-EDODM1

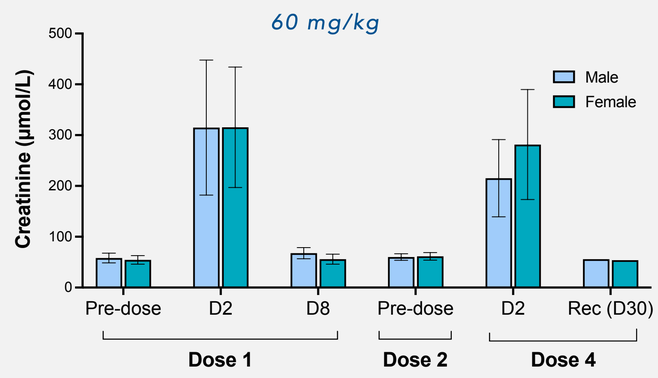
CELLULAR AND NON-HUMAN PRIMATE DATA

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



FAVOURABLE SAFETY PROFILE IN NHP SUPPORTED PROGRESSION TO CLINICAL STUDIES

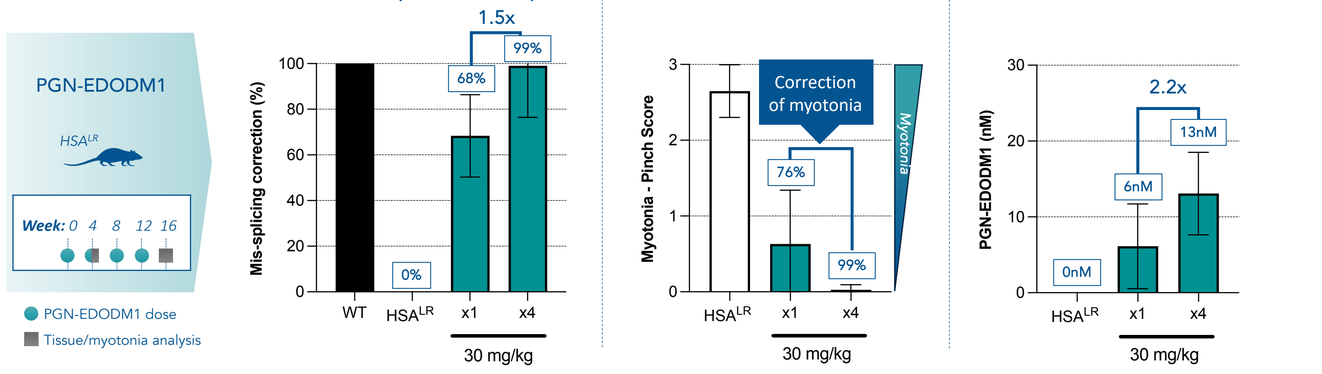




- Non-adverse transient increases in serum creatinine were observed at 60 mg/kg -resolved within a week postdose and did not worsen with repeat dosing.
- No adverse findings in the kidney after 4x Q4W 60 mg/kg doses.
- No notable hematologic or hepatic effects, no cardiovascular effects.

HSA^{LR} MOUSE MODEL DATA

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



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

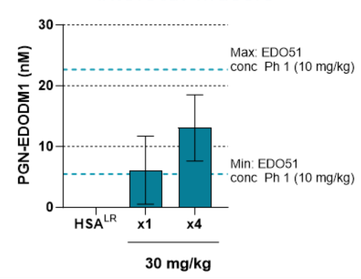
PGN-EDODM1 HAS THE POTENTIAL TO ACHIEVE CONCENTRATIONS IN PEOPLE WITH DM1 THAT COULD LEAD TO CLINICALLY-MEANINGFUL OUTCOMES

HSA^{LR} MOUSE

Robust mis-splicing correction and correction of myotonia were observed 28 days after a **single 30 mg/kg dose**

TISSUE CONCENTRATION

Skeletal muscle



PGN-EDO51 Ph1

Following a single 10 mg/kg dose of PGN-EDO51 in our Ph1 HV trial, **tissue concentrations were similar** to those measured for PGN-EDODM1 at 30 mg/kg in HSA^{LR} mouse

In healthy volunteers (HVs) EDO technology achieved a mean PGN-EDO51 PMO conc. >11nM following a single dose. We conclude that a single 10 mg/kg dose of PGN-EDODM1 in the Phase 1 clinical trial, FREEDOM-DM1, could achieve pharmacologically active dose levels in muscle. FREEDOM-DM1 trial is currently open for evaluation in people living with DM1 in the US, Canada and UK.

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 **reduction of toxic foci and liberation of MBNL1** in DM1 human muscle cells
- In the HSA^{LR} DM1 mouse model, **robust mis-splicing correction and reversal of myotonia** was observed with a single 30 mg/kg 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 HSA^{LR} DM1 mouse model
- **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 **open in Canada, the UK and the US**
- **Nonclinical data** in DM1 cells, HSA^{LR} mice and NHP support the **development of PGN-EDODM1 and FREEDOM-DM1 Phase 1 clinical study (see Poster T306)**