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

James Gilbert[1], Arnaud Klein[2], Pallavi Lonkar[1], Jeffrey Foy[1], Shaoxia Yu[1], Denis Furling[2], Ashling Holland[1]

[1]PepGen Inc., Boston, MA, USA, [2]Sorbonne Université, Inserm, Institut de Myologie, Centre de Recherche en Myologie, Paris, France

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.** There are **no approved therapies** that address the underlying cause of DM1.

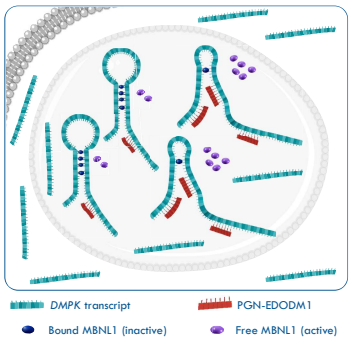
Limited delivery and distribution of unconjugated oligonucleotides to affected tissues limit their potential effectiveness in DM1.

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 an investigational EDO and is being evaluated in people with DM1 in a Phase 1 single ascending dose study (FREEDOM) and a Phase 2 multiple ascending dose study (FREEDOM2).

MECHANISM OF PGN-EDODM1

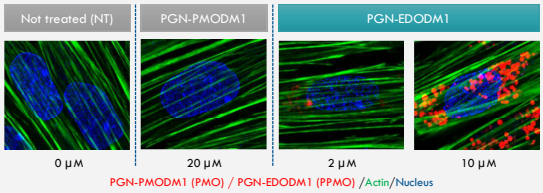
- **PGN-EDODM1** is engineered to bind selectively to the **pathogenic** CUG repeat expansion present in *DMPK* transcripts.
- This reduces the ability of these CUG repeats to form hairpin loops and sequester RNA splicing proteins, including MBNL1.
- Liberated MBNL1 restores correct splicing.

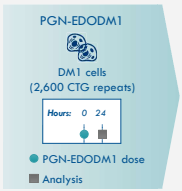


DMPK = myotonic dystrophy protein kinase, MBNL1 = muscleblind like splicing regulator 1

CELLULAR DELIVERY AND ACTIVITY DATA

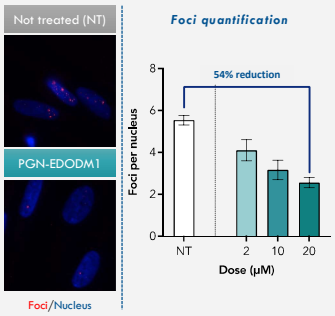
PGN-EDODM1 RESULTED IN HIGH LEVELS OF NUCLEAR DELIVERY IN DM1 MUSCLE CELLS





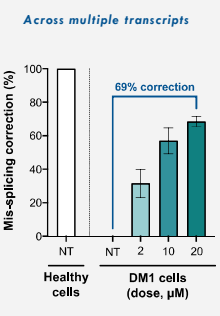
PGN-EDODM1 REDUCED TOXIC FOCI, LIBERATED MBNL1 AND CORRECTED MIS-SPLICING IN DM1 MUSCLE CELLS

TOXIC FOCI REDUCTION



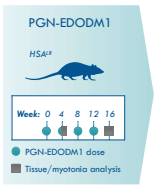
MBNL1 LIBERATION

MIS-SPLICING CORRECTION

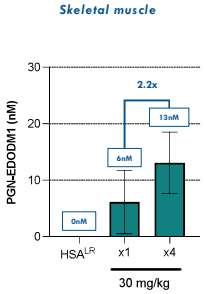


HSA^{LR} MOUSE MODEL AND NON-HUMAN PRIMATE (NHP) DATA

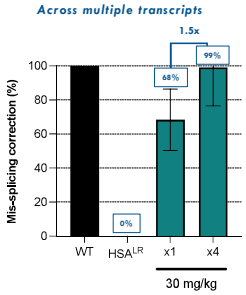
REPEAT DOSING OF PGN-EDODM1 IN HSA^{LR} MICE ENHANCED CORRECTION OF MIS-SPLICING, REVERSED MYOTONIA AND INCREASED MUSCLE DELIVERY



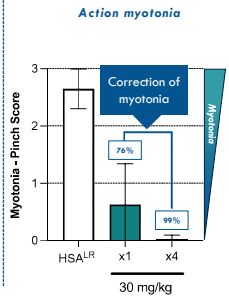
TISSUE CONCENTRATION



MIS-SPLICING CORRECTION

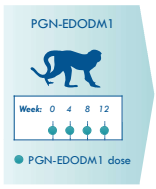


REVERSAL OF MYOTONIA

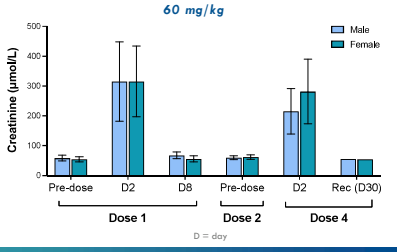


Increased levels of PGN-EDODM1 in tissue with repeat dosing | **99% correction** across multiple transcripts | **Complete correction of myotonia** observed after repeat dosing

FAVORABLE SAFETY PROFILE IN NHPs 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 postdose and did not worsen with repeat dosing.
- No adverse findings in the kidney after 60 mg/kg doses (Q4W; 4 doses).
- No notable hematologic or hepatic effects, no cardiovascular effects.

CONCLUSIONS & NEXT STEPS

- **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-derived 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 correction was observed **through 24 weeks.**
- **Increased levels of tissue delivery, enhanced mis-splicing correction** and **reversal of myotonia** were observed with repeat dosing in HSA^{LR} mice.
- **PGN-EDODM1 was well tolerated in 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 **enrolling 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 O45).

Disclosures: [1]Employees of PepGen Inc. and hold PepGen equity; [2]Work conducted under a sponsored research agreement