461P

Evaluation of PGN-EDODM1: FREEDOM-DM1 and FREEDOM2-DM1 Clinical Trials in Myotonic Dystrophy Type 1

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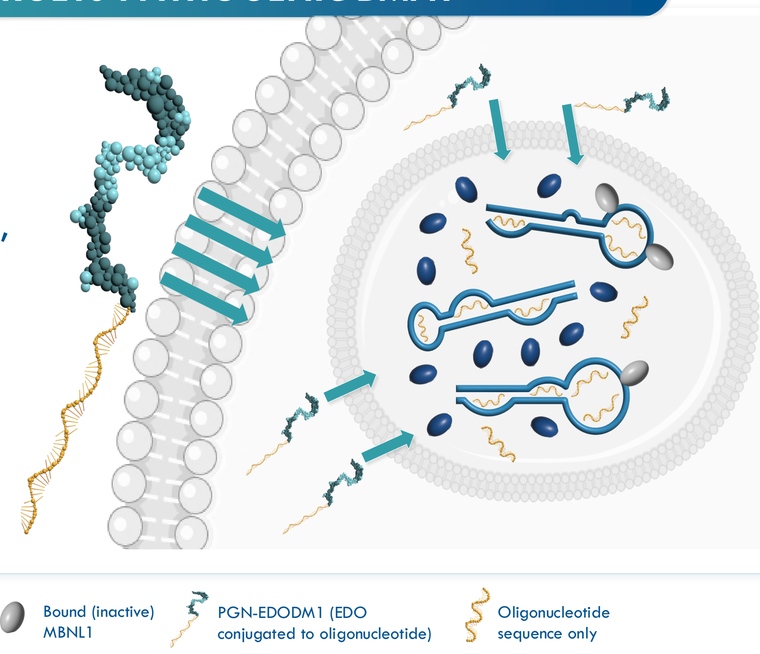
INTRODUCTION

- 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 restricts their activity in DM1.
- **PGN-EDODM1** is an EDO under investigation for the **treatment of people with myotonic dystrophy type 1 (DM1)**.
- DM1 is a multi-systemic disease that has a **significant impact on physical function and quality of life.**
- 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 mice and non-human primates.
  - See poster Holland et al 440P "Nonclinical data for PGN-EDODM1 demonstrated nuclear delivery, mechanistic and meaningful activity for the treatment of DM1"
- FREEDOM-DM1, a Phase 1 single-ascending dose (SAD) clinical study in participants with DM1, is underway in USA, Canada and UK. FREEDOM2, a Phase 2 multiple-ascending dose (MAD) study in participants with DM1 has been cleared in Canada and the UK.

PGN-EDODM1 TARGETS PATHOGENIC *DMPK*

PGN-EDODM1 binds pathogenic CUG *DMPK* transcript loops, reducing toxic foci, and liberating MBNL1 to restore normal splicing



CLINICAL STUDY DESIGNS

Freedom DM1

Open in US, Canada and UK

- Phase 1 randomized, double-blind, placebo-controlled SAD study in patients
- Key anticipated readouts: functional assessments, correction of mis-splicing, safety data

Freedom 2 DM1

Multinational Study Initiated

- Phase 2 randomized, double-blind, placebo-controlled MAD study in people with DM1
- Expect to initiate dosing of FREEDOM2 clinical trial in 2H:2024
  - IV administration of PGN-EDODM1 every 4 weeks up to 12 weeks
  - Key anticipated readouts: functional assessments, correction of mis-splicing, safety data

KEY ELIGIBILITY CRITERIA

KEY INCLUSION

- Male or female between the ages of 18 and 50 years, inclusive for FREEDOM, 16 to 60 for FREEDOM2
- 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

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

FREEDOM-DM1 STUDY OBJECTIVES

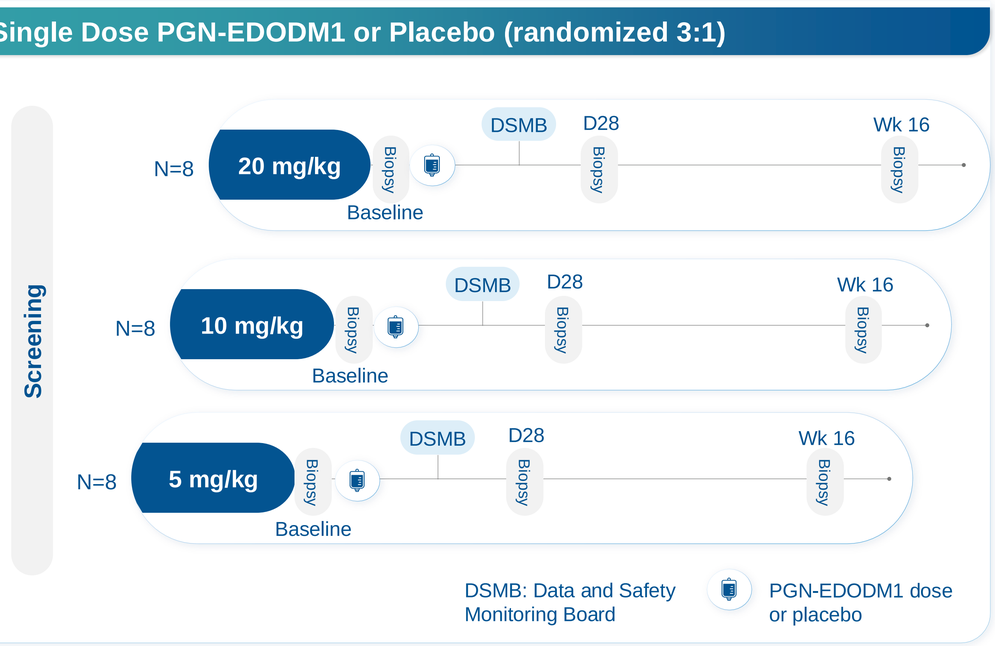
- **PRIMARY:** To evaluate the safety and tolerability of PGN-EDODM1 after a single dose
- **SECONDARY:** To evaluate the pharmacokinetics (PK) of PGN-EDODM1 after a single dose
- **SELECT KEY EXPLORATORY:**
  - To evaluate the tissue pharmacodynamic (PD) of PGN-EDODM1 after multiple administrations assessed by changes in splicing pattern of affected transcripts
  - To evaluate functional assessments

FREEDOM2-DM1 STUDY OBJECTIVES

- **PRIMARY:** To evaluate the safety and tolerability of PGN-EDODM1 after a multiple administrations
- **SECONDARY:**
  - To evaluate the PK of PGN-EDODM1 after multiple administrations
  - To evaluate the tissue pharmacodynamic (PD) of PGN-EDODM1 after multiple administrations assessed by changes in splicing pattern of affected transcripts
  - To evaluate functional assessments of myotonia, hand grip strength, and mobility

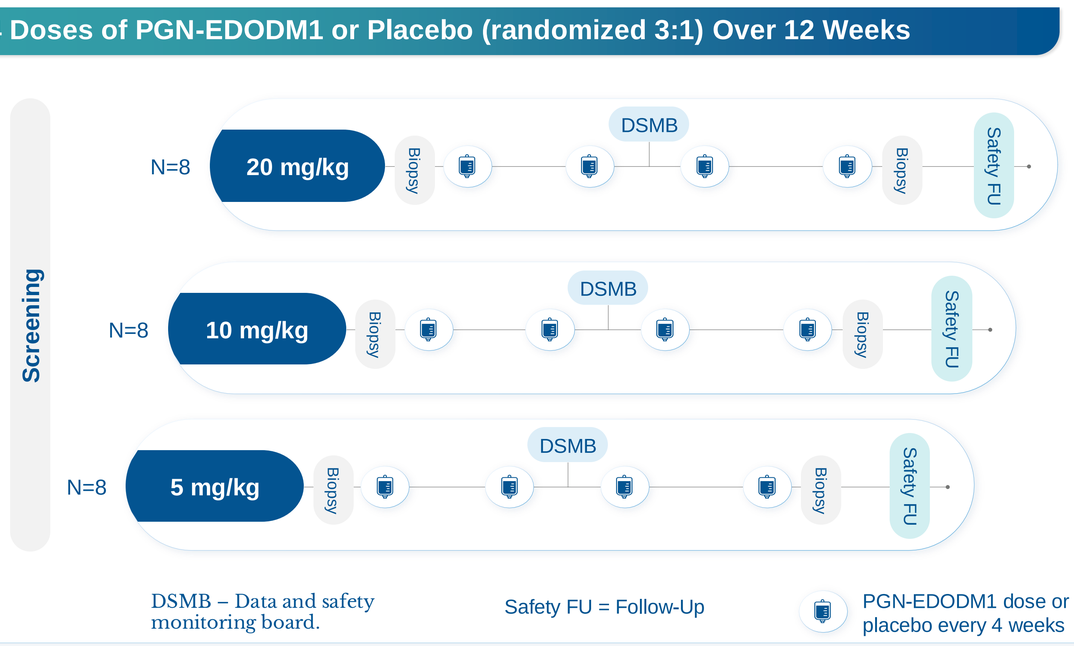
FREEDOM-DM1 STUDY DESIGN

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



FREEDOM2-DM1 STUDY DESIGN

4 Doses of PGN-EDODM1 or Placebo (randomized 3:1) Over 12 Weeks



CONCLUSION

- The FREEDOM-DM1 and FREEDOM2-DM1 studies are designed to support and advance the clinical development of PGN-EDODM1.