M151

CONNECT1-EDO51 and CONNECT2-EDO51: Phase 2 Study Designs to Evaluate Safety and Efficacy for Duchenne Muscular Dystrophy Amenable to Exon 51 Skipping

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PepGen

INTRODUCTION

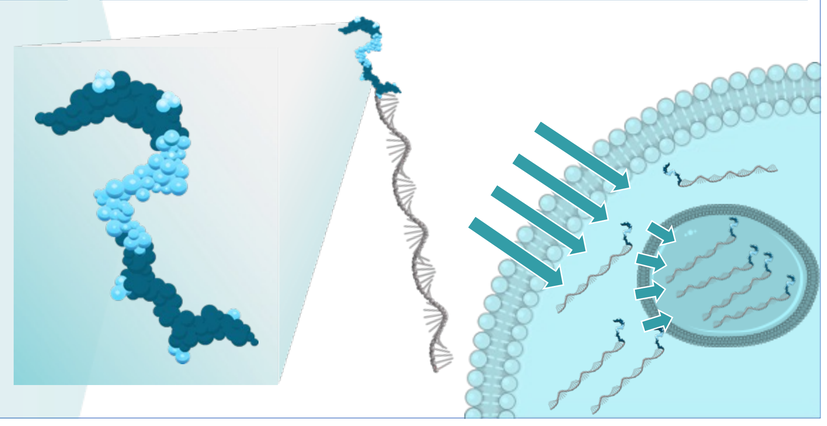
- PGN-EDO51 is PepGen's clinical-stage candidate-Enhanced Delivery Oligonucleotide (EDO) for the treatment of Duchenne muscular dystrophy amenable to an exon 51 skipping approach
- Our EDO platform is engineered to optimize the tissue penetration, cellular uptake and nuclear delivery of oligonucleotide therapeutics
  - Unconjugated oligonucleotides are not readily distributed to muscle and are not efficiently taken up into cells and the nucleus
- Two doses of 30 mg/kg EDO-peptide conjugated to PMO in non-human primate (NHP) resulted in >70% muscle nuclei positive for oligonucleotide
- PGN-EDO51 in NHPs and PGN-EDO23 (murine analogue) in mice showed robust exon skipping, in addition to dystrophin production (in *mdx* mouse)
  - See poster S17 "Single- and Repeat-Dose Nonclinical Data for PGN-EDO51 Demonstrated Potential for the Treatment of Duchenne Muscular Dystrophy (DMD)"
- Phase 1 healthy volunteer (HV) study showed the highest levels of mean exon 51 skipping following a single dose in humans*
  - 6-fold higher compared with an investigational PPMO**
  - Tolerable emerging safety profile

*Comparative statement based on cross-trial comparison of Phase 1 healthy volunteer (HV) data of single-dose administration of EDO51 with publicly-available Phase 1 HV data following a single dose of vesleteplirsen **PPMO SRP-5051 (vesleteplirsen) in clinical development

PepGen's EDO Peptides
Designed for enhanced uptake and improved tolerability

- Two poly-Arg domains where the number of arginines have been minimized are interspersed with non-natural amino acids to confer greater peptide stability
- Hydrophobic core coupled with poly-Arg domains contributes to endosomal escape
- Peptide sequence is linear with a length of less than 20 amino acids and is designed to be non-immunogenic

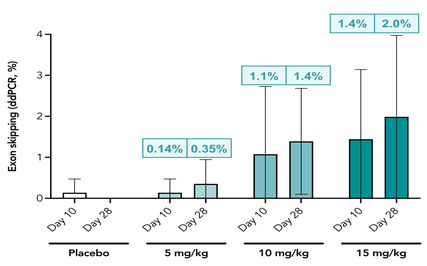
PepGen's EDOs
Designed to increase nuclear uptake of oligos in muscle and other target tissues



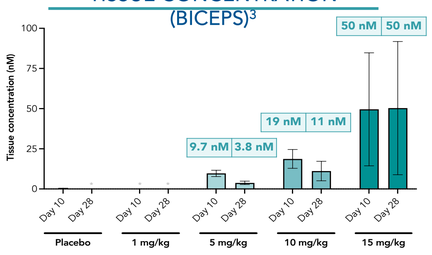
Based on Pre-clinical and Phase 1 data, a Phase 2 clinical program initiated in 2023

PHASE 1 STUDY RESULTS[1]

EXON SKIPPING (BICEPS)[2]

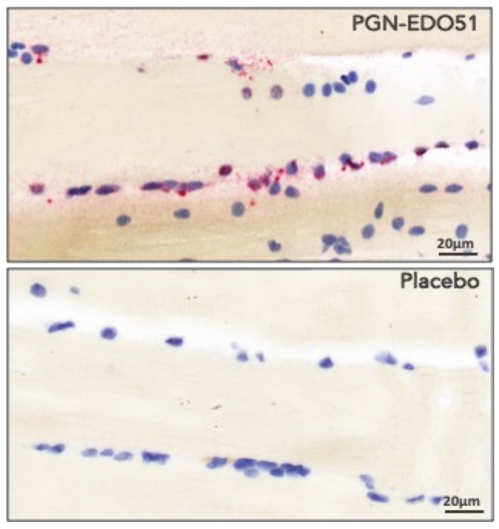


TISSUE CONCENTRATION (BICEPS)[3]



1. Protocol PGN-EDO51-101: Phase 1, first in human, randomized double blind, placebo controlled single ascending dose study in healthy adult volunteers. Single dose of either PGN-EDO51 or Placebo were administered by IV infusion at doses indicated. Participants were followed for 28-day period following dose administration to evaluate safety, tolerability, PK, and PD. Needle biopsies of biceps muscle were taken on Day 10 and Day 28.
2. Exon skipping measured by ddPCR. Shown as mean ± SD; n = 6 PGN-EDO51: 2 Placebo per cohort (n = 5 for D10 at 15 mg/kg).
3. Tissue concentration measured by ELISA. Shown as mean ± SD; n = 6 PGN-EDO51: 2 Placebo per cohort (n = 5 for D10 at 15 mg/kg). Asterix indicates that values were under the lower limit of quantitation.

PGN-EDO51(10mg/kg) DETECTED IN HUMAN MUSCLE NUCLEI



Red- PMO Blue-Nuclei

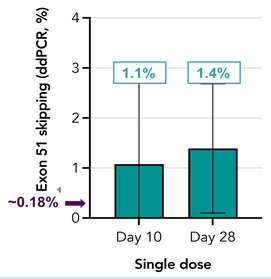
Preliminary partial data from RNAScope analysis showing PMO51 can be detected in muscle nuclei of healthy volunteers in PGN-EDO51-101 Phase 1 study. Biceps muscle biopsies collected and analyzed 28 days after single dose at 10mg/kg or placebo.

PRE-CLINICAL DATA WITH MONTHLY REPEAT DOSING SUPPORTS CLINICAL DOSING

COMPARISON BETWEEN HUMAN SINGLE- AND REPEAT-DOSE IN NHP

HV SINGLE DOSE PGN-EDO51

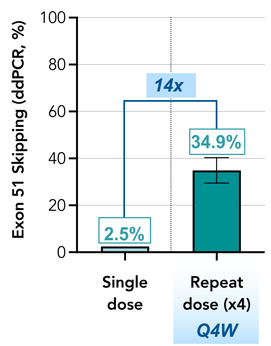
10 mg/kg, ddPCR
All AEs were generally mild & reversible



~6x higher than previously reported following a single dose

NHP SINGLE VS. REPEAT [2]

Biceps, 20 mg/kg, ddPCR



PATIENT REPEAT DOSE

Studies initiated in 2023

People with DMD in phase 2 MAD studies will be dosed **Q4W**

We believe this NHP data supports potential for meaningful increases in exon skipping under this dosing regimen

Phase 1 data showed the highest levels of mean exon 51 skipping seen in humans after a single dose, supporting further development

1. SRP-5051 (vesleteplirsen) 20 mg/kg HV data from Momentum update, 07Dec20 (comparative statements for human data are based on cross-trial comparisons).
2. NHP protocol: Single (30 min) or repeat (60 min) IV doses with PGN-EDO51 were administered in male NHP. For repeat dose evaluation, NHP received 4 doses with 4-week intervals between doses. Tissue samples were collected 1-week post-final dose as indicated on graphs. Exon skipping was assessed by ddPCR. Graph is presented as mean ± SD; n = 3-8 per group.
HV: Healthy Volunteers, AE: Adverse Event,, PCR: Polymerase Chain Reaction

The Phase 2 Multiple Ascending Dose (MAD) Clinical Program eligibility, objectives and design

PEPGEN'S PHASE 2 CLINICAL PROGRAM*

OPEN

CONNECT1-EDO51
Ph2 open-label MAD study in patients *(opened in 1H 2023)*

Connect 1 EDO51

- 3-month Q4W dosing
- Dystrophin, Exon skipping, and Safety data expected mid - 2024

PLANNED

CONNECT2-EDO51
Ph2 randomized, double-blind, placebo-controlled MAD study in patients

Connect 2 EDO51

- 6-month Q4W repeat dosing
- Exon skipping, dystrophin and safety data
- Functional measures
- Designed to provide potential path to accelerated approval

* All eligible participants who have completed the Multiple Ascending Dose (MAD) period will have the opportunity to participate in the long-term extension (LTE) to receive intravenous (IV) infusions of PGN-EDO51 for an additional 104 weeks.

CONNECT1-EDO51 OBJECTIVES

PRIMARY

- To evaluate the safety and tolerability of PGN-EDO51 following multiple doses in male participants with DMD amenable to exon 51 skipping

SECONDARY

- To evaluate the levels of dystrophin in skeletal muscle following multiple doses of PGN-EDO51
- To evaluate the concentration of PGN-EDO51 in skeletal muscle following multiple doses
- To evaluate the pharmacokinetics (PK) of PGN-EDO51in plasma following multiple doses

CONNECT2-EDO51 OBJECTIVES

PRIMARY

- To evaluate the safety and tolerability of PGN-EDO51 following multiple doses in male participants with DMD amenable to exon 51 skipping
- To evaluate the levels of dystrophin in skeletal muscles following multiple doses of PGN-EDO51

SECONDARY

- To evaluate the PK of PGN-EDO51 in skeletal muscle following multiple doses
- To evaluate the pharmacokinetics (PK) of PGN-EDO51

KEY INCLUSION/EXCLUSION CRITERIA

INCLUSION

- Males by birth age ≥8 years of age for CONNECT1 and ≥6 years of age for CONNECT2 at the time of consent/assent
- Body weight ≥25 kg; BMI ≤32 kg/m^2 for CONNECT1 and ≤36 kg/m^2 for CONNECT2 at Screening
- Diagnosis of DMD with exon 51 skippable mutation
- Performance of Upper Limb (PUL) 2.0 entry score of ≥ 3 at Screening

EXCLUSION

- Initiation or change in doses of concomitant medications or herbal supplements (except for modifications to accommodate changes in weight)
- Left ventricle ejection fraction <45% as measured within 12 months of study start
- Forced vital capacity <40% predicted value

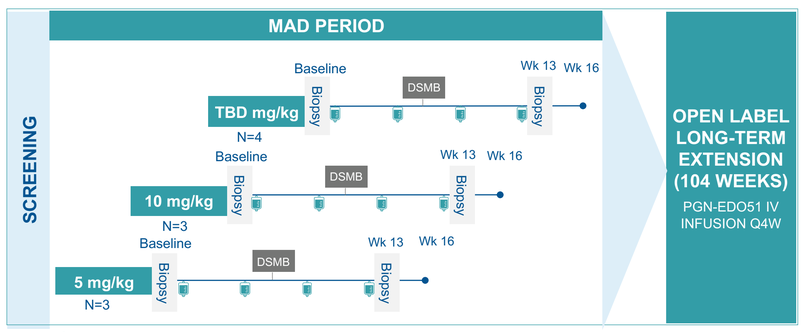
CONNECT1-EDO51 STUDY DESIGN

Connect 1 EDO51

CONNECT1 study overview

- Open-label study in people with DMD
- The study is open in Canada
- IV administration of PGN-EDO51 every 4 weeks
- Muscle biopsies at baseline and week 13
- Key endpoints: safety and tolerability, dystrophin, and exon skipping
- Data expected in 2024

PGN-EDO51 dosing Q4W for a treatment period of 12 weeks



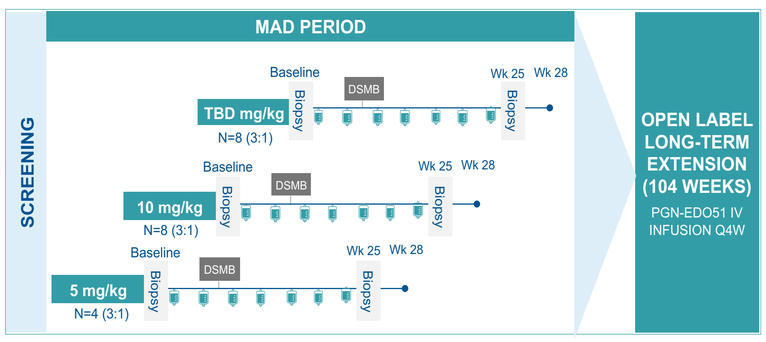
CONNECT2-EDO51 STUDY DESIGN

Connect 2 EDO51

CONNECT2 study overview

- A double-blind placebo-controlled (3:1) study in people with DMD
- The study will be multinational
- IV administration of PGN-EDO51 every 4 weeks
- Muscle biopsies at baseline and week 25
- Key endpoints: safety and tolerability, dystrophin, exon skipping
- Sites' initiation in 2024

PGN-EDO51 dosing Q4W for a treatment period of 24 weeks



Q4W: every 4 weeks, DSMB: data safety and monitoring board, IV: intravenous

CONCLUSION

The CONNECT1 & CONNECT2 clinical studies are designed to efficiently evaluate the potential safety and efficacy of PGN-EDO51 in a population of people with DMD amenable to exon 51 skipping.