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Single- and Repeat-Dose Nonclinical Data for PGN-EDO51 Demonstrated Potential for the Treatment of Duchenne Muscular Dystrophy (DMD)

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INTRODUCTION

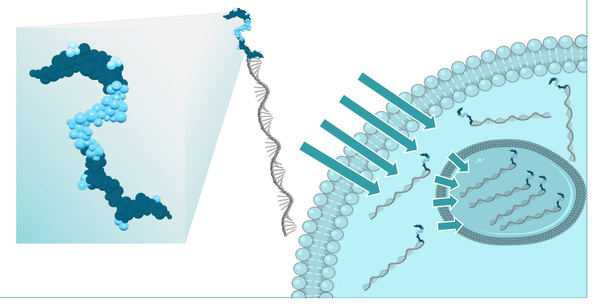
PGN-EDO51 is PepGen's Phase 2 clinical-stage Enhanced Delivery Oligonucleotide (EDO) candidate for the treatment of people with DMD amenable to exon 51 skipping. It is the first of a series of investigational therapies based on our EDO platform. PepGen has evaluated the potential of PGN-EDO23 (mouse equivalent) in the *mdx* mouse model of DMD and PGN-EDO51 in non-human primates (NHP) and showed robust exon skipping both following single- and repeat-dosing in both models and robust dystrophin production in *mdx* mice.

ENHANCED DELIVERY OLIGONUCLEOTIDES

PEPGEN'S EDO Peptides
Modified for enhanced uptake and improved tolerability

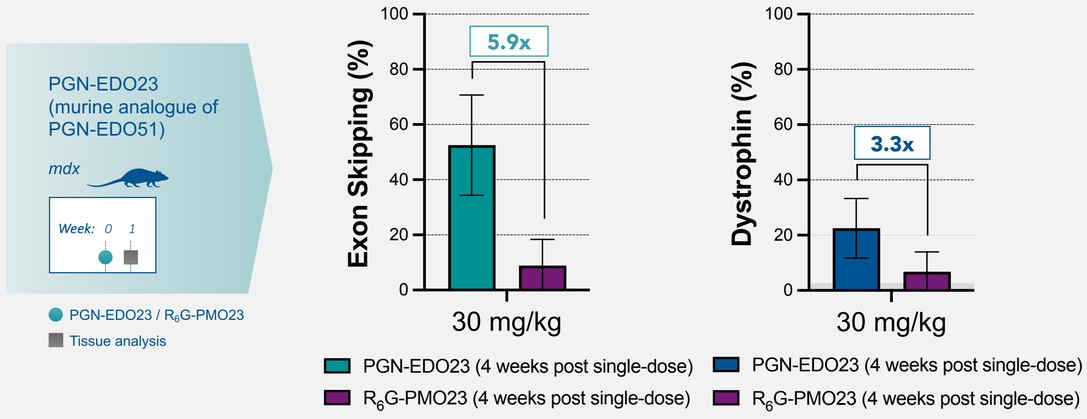
- Two poly-Arg domains where the number of arginines have been minimized are interspersed with non-natural amino acids to confer greater peptide stability
- Hydrophobic core coupled with poly-Arg domains contributes to endosomal escape
- Peptide sequence is linear with a length of less than 20 amino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

ENHANCED DELIVERY OLIGONUCLEOTIDES (EDOs)
Designed to increase nuclear uptake of oligos in muscle tissue



MDX MOUSE MODEL USING MOUSE EQUIVALENT OF PGN-EDO51 (PGN-EDO23)

IMPROVED PHARMACOLOGY OBSERVED WITH PGN-EDO23 IN *MDX* MODEL - BICEPS

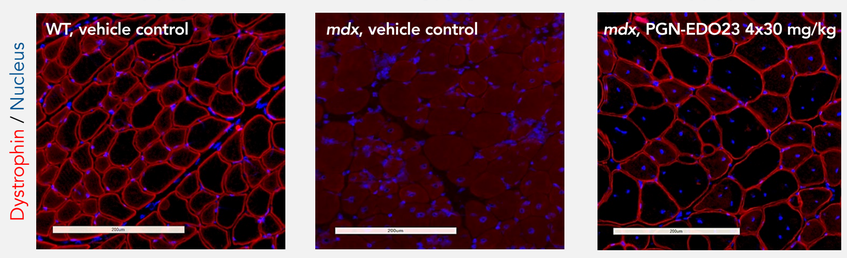


*R_6G-PMO23 is R_6G peptide conjugated to murine exon 23-skipping sequence.

ACCUMULATION OF EXON SKIPPING AND DYSTROPHIN FOLLOWING REPEAT-DOSE - BICEPS

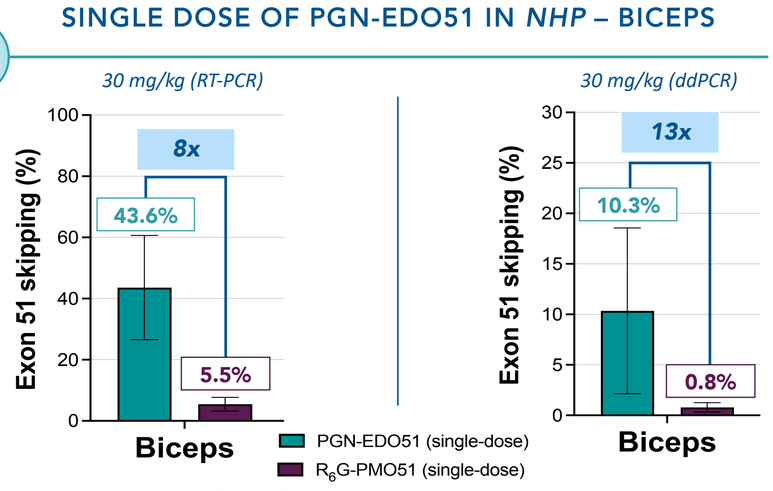
- Single dose of PGN-EDO23 in *mdx* mice resulted in high levels of exon 23 skipping (RT-PCR) and dystrophin in biceps.
- Improved pharmacology was observed in *mdx* biceps with PGN-EDO23 in comparison to R_6G-PMO23.
- Repeat-dosing with PGN-EDO23 in *mdx* mice every four weeks for a total of four doses resulted in the highest exon 23 skipping levels (RT-PCR) and dystrophin production compared to single dose.
- Uniform distribution of dystrophin in biceps following repeat dose in *mdx* mice.
- **Data support our belief that repeat dosing with PGN-EDO51 every 4 weeks has the potential to result in meaningful levels of dystrophin production and clinical benefit.**

UNIFORM DISTRIBUTION OF DYSTROPHIN FOLLOWING REPEAT-DOSE - BICEPS



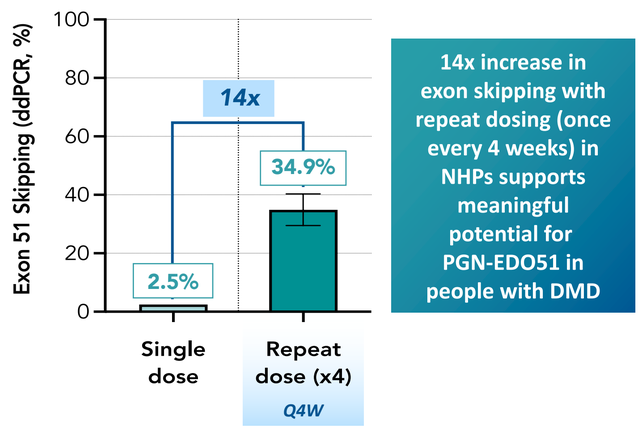
NON-HUMAN PRIMATE (NHP) PHARMACOLOGY AND TOLERABILITY USING PGN-EDO51

IMPROVED PHARMACOLOGY OBSERVED WITH A SINGLE DOSE OF PGN-EDO51 IN *NHP* – BICEPS



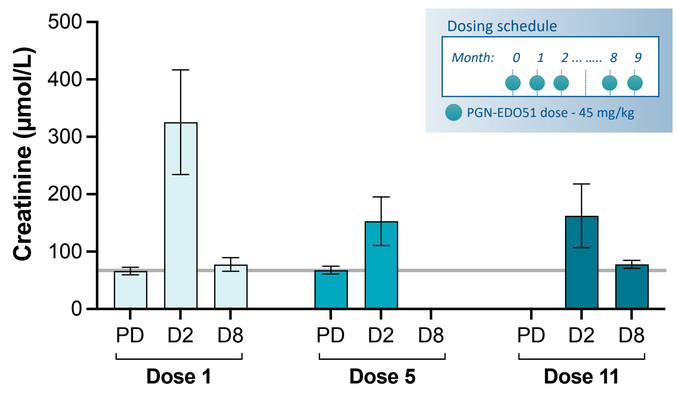
*R_6G-PMO51 is believed to be structurally equivalent to SRP-5051

DOSE-DEPENDENT ACCUMULATION OF EXON SKIPPED TRANSCRIPTS FOLLOWING REPEAT-DOSE - BICEPS



14x increase in exon skipping with repeat dosing (once every 4 weeks) in NHPs supports meaningful potential for PGN-EDO51 in people with DMD

GLP NHP TOXICOLOGY STUDIES SUPPORT CONTINUED CLINICAL DEVELOPMENT OF PGN-EDO51



SUPERIOR PHARMACOLOGY AND ACCUMULATION OF EXON SKIPPING FOLLOWING REPEAT DOSING

- Single dose of PGN-EDO51 in male NHPs resulted in significantly higher levels of exon 51 skipping in biceps over R_6G-PMO51 comparator PPMO.
- Repeat dosing resulted in dose-dependent accumulation of exon 51 skipping (by ddPCR) in biceps.
- The lower levels of exon 51 skipping (by ddPCR) in biceps observed after a single dose, significantly increased by 14-fold at 20 mg/kg with repeat dosing.
- **Data support our belief that repeat dosing with PGN-EDO51 once every 4 weeks has the potential to result in meaningful levels of dystrophin production and clinical benefit.**

In a chronic NHP study (Q4W; 11 doses total):

- Through 45 mg/kg, non-adverse, transient increases in serum creatinine were observed and were of lower magnitude with repeat dosing.
- Through 45 mg/kg, non-adverse minimal to moderate decreases were observed in serum magnesium.
- Through 45 mg/kg no changes in serum potassium and no adverse renal, hematologic, cardiovascular or hepatic effects were observed.

CONCLUSIONS & NEXT STEPS

These data demonstrate that single and repeat dosing of PGN-EDO23/PGN-EDO51 resulted in high levels of exon skipping and/or dystrophin production in the models shown and were observed to be well tolerated at clinically relevant doses.

The totality of the activity and safety data from nonclinical and clinical studies supports the continued development of PGN-EDO51 for the treatment of people with DMD amenable to exon 51 skipping.

A Phase 1 clinical trial assessing the tolerability of PGN-EDO51 in Healthy Volunteers is complete. The CONNECT1/CONNECT2 Phase 2 clinical program to investigate the effects of multiple doses of PGN-EDO51 in people with DMD amendable to exon 51 skipping has been initiated (see Poster M151).