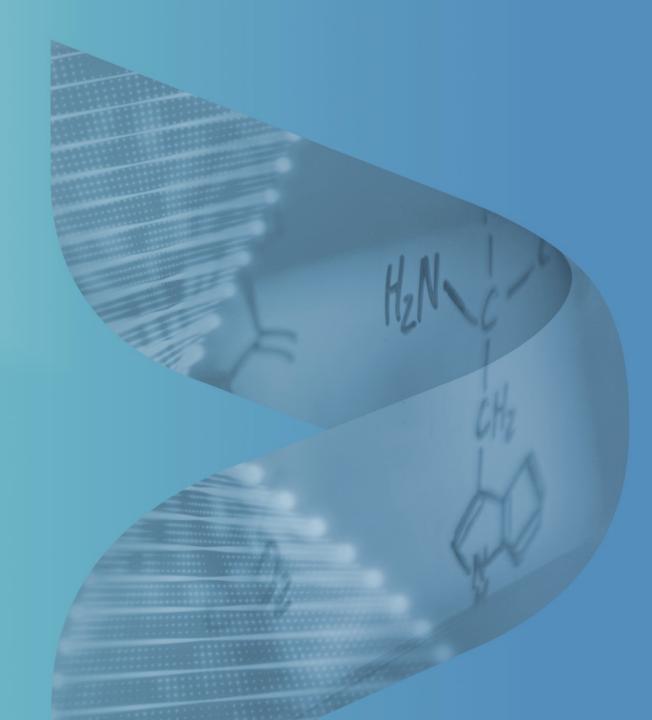


# EMPOWERING OLIGONUCLEOTIDE THERAPEUTICS

# COMPANY PRESENTATION JUNE 2022



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# A NEXT-GENERATION OLIGONUCLEOTIDE DELIVERY PLATFORM WITH THE POTENTIAL TO TRANSFORM PATIENT OUTCOMES

Our **Enhanced Delivery Oligonucleotide (EDO)** platform is engineered to offer enhanced therapeutic activity and improved tolerability

**Rare disease, clinical-stage** company with potentially significant value inflection points anticipated over next 24 months:

DMD Ph1 HNV data YE22 DMD & DM1 clinical POC 2024



Designed to achieve greater skeletal & cardiac muscle penetrance; extensive portfolio of product candidates for the treatment of multiple neuromuscular diseases (NMD)

Lead assets, PGN-EDO51 and PGN-EDODM1, target a potentially large market opportunity, with ~130k patients\* across Duchenne muscular dystrophy (DMD) exon 51 and myotonic dystrophy type 1 (DM1) in US/EEA/JP



\*DMD patient numbers: 15k US + 25k EEA + 5k JP whole population (range used: Crisafulli et al – 7.1/100k males; Orphanet – 4.78/100k pop). Exon 51 population 13% of total. DM1 patient numbers: 1 in 8,000 (Johnson et al); 40k US + 75k EEA + 15k JP.

# PEPGEN: EXPERIENCED TEAM OF COMPANY BUILDERS, SCIENTISTS, AND CLINICIANS

#### Management team



(Director)

RACAPITAL

(Director)

S<sup>0</sup>C<sup>X</sup>I<sup>F</sup>E<sup>0</sup>N<sup>R</sup>C<sup>D</sup>E



(Chair)

2 Alnylam

i Immuneering

IMAGO

(Director)

Pardes Biosciences

## WE ARE BUILDING ON FDA-APPROVED EXON 51 SKIPPING MODALITIES TO DEVELOP THE NEXT GENERATION OF OLIGO TX

### APPROVED EXON 51 PMO

Drug	Sponsor	Exon	Dystrophin restoration*	
EXONDYS 51® (eteplirsen)	Sarepta Therapeutics	Exon 51	0.44%	
<b>2021 sales: \$454M</b> (US & Israel)**				

### PEPGEN'S STEP CHANGE

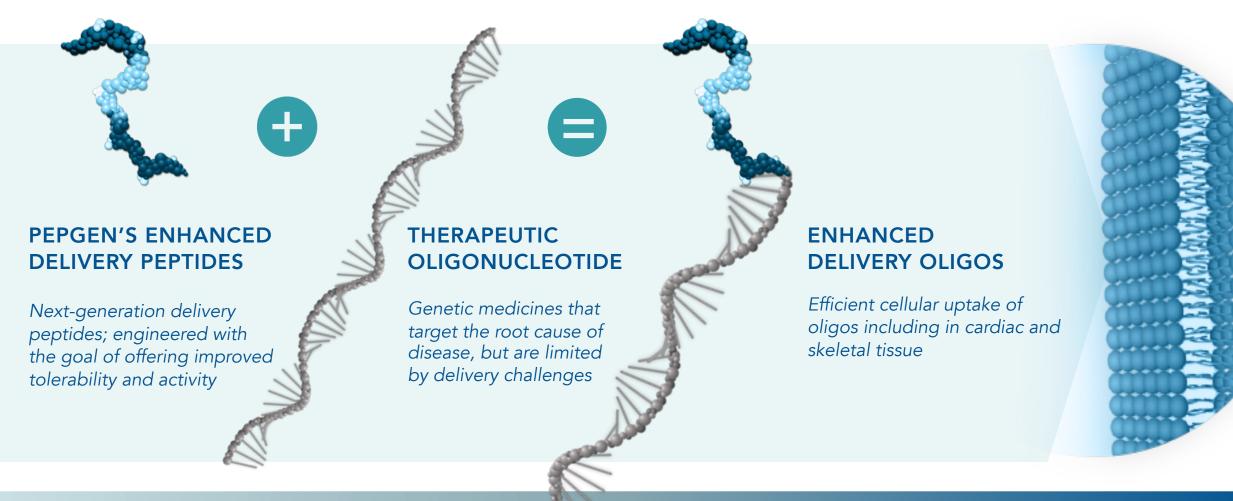
- Enhanced delivery to skeletal muscle (inc. diaphragm), cardiac muscle and the CNS
- Greatest exon skipping potency at tolerable target dose levels compared to any approved exon 51 therapeutic or known development candidate\*\*\*
- Potential for greater dystrophin production
- Enhanced balance between activity and tolerability compared to early delivery peptides
- Robust & scalable manufacturing



\* Clinical data included in drug label (FDA). \*\*Source: Sarepta 2021 10K filing. \*\*\* Based on a head-to-head comparison with the most clinically-advanced peptide-conjugated oligonucleotide therapeutic in NHP, and on cross-trial comparisons with publicly-available data for other preclinical approaches in NHP.

# THE POWER OF EDOs

Enhanced Delivery Oligonucleotides are well-characterized therapeutic PMO oligonucleotides conjugated to proprietary delivery-enhancing peptides



# SCALABLE EDO TECHNOLOGY DESIGNED TO ENABLE BROAD PORTFOLIO

PROGRAM	INDICATION TARGET	DISCOVERY	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	NEXT ANTICIPATED MILESTONE
PGN-EDO51	Duchenne muscular dystrophy Exon 51						YE22 Ph1 HNV topline clinical data
PGN-EDODM1	Myotonic dystrophy type 1 DMPK						1H23 IND submission
PGN-EDO53	Duchenne muscular dystrophy Exon 53						2H22 NHP exon skipping data
PGN-EDO45	Duchenne muscular dystrophy Exon 45						2H22 Candidate nomination
PGN-EDO44	Duchenne muscular dystrophy Exon 44						2H22 Candidate nomination

#### FUTURE PIPELINE OPPORTUNITIES

Additional neuromuscular indications

Neurologic indications





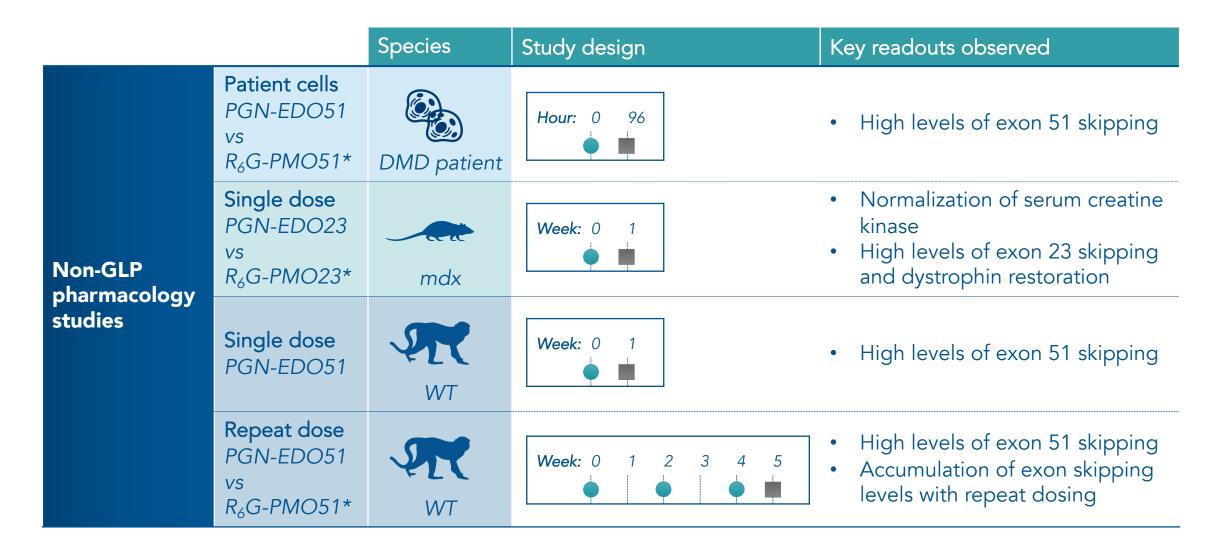
# PGN-ED051 FOR DUCHENNE MUSCULAR DYSTROPHY

### DUCHENNE MUSCULAR DYSTROPHY IS A DEBILITATING, PROGRESSIVE MUSCLE-WASTING DISEASE

ROOT CAUSE OF DISEASE	SYMPTOMATOLOGY & NATURAL HISTORY	EXON 51 PATIENT POPULATION*	EXON 51 THERAPEUTIC LANDSCAPE
<ul> <li>Caused by mutations in the dystrophin gene</li> <li>Absence of dystrophin leads to muscle degeneration</li> </ul>	<ul> <li>Progressive loss of function, including ambulation</li> <li>Cardiac &amp; respiratory conditions</li> <li>Lifespan ~25 years</li> </ul>	~2,000 (US) ~3,200 (EEA) ~700 (JP)	<ul> <li>Exondys51® approved in US on the basis of &lt;1% dystrophin restoration</li> <li>Not approved in EEA or JP</li> </ul>



# THE ACTIVITY OF OUR EDO PLATFORM IN DMD HAS BEEN EVALUATED IN MULTIPLE PRECLINICAL MODELS

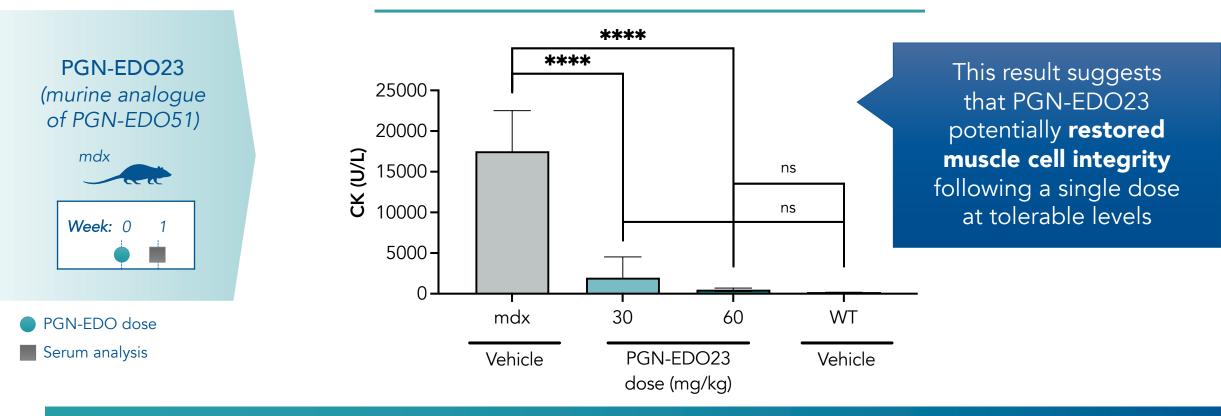




\*R<sub>6</sub>G-PMO51 is R<sub>6</sub>G peptide conjugated to eteplirsen. R<sub>6</sub>G-PMO23 is R<sub>6</sub>G peptide conjugated to murine exon 23-skipping sequence.

PGN-EDO dose

## MDX MICE: A SINGLE DOSE OF PGN-EDO23 WAS OBSERVED TO NORMALIZE CREATINE KINASE, A MARKER OF MUSCLE DAMAGE



#### SERUM CREATINE KINASE

PGN-EDO23 utilizes the same EDO delivery peptide as our clinical candidate

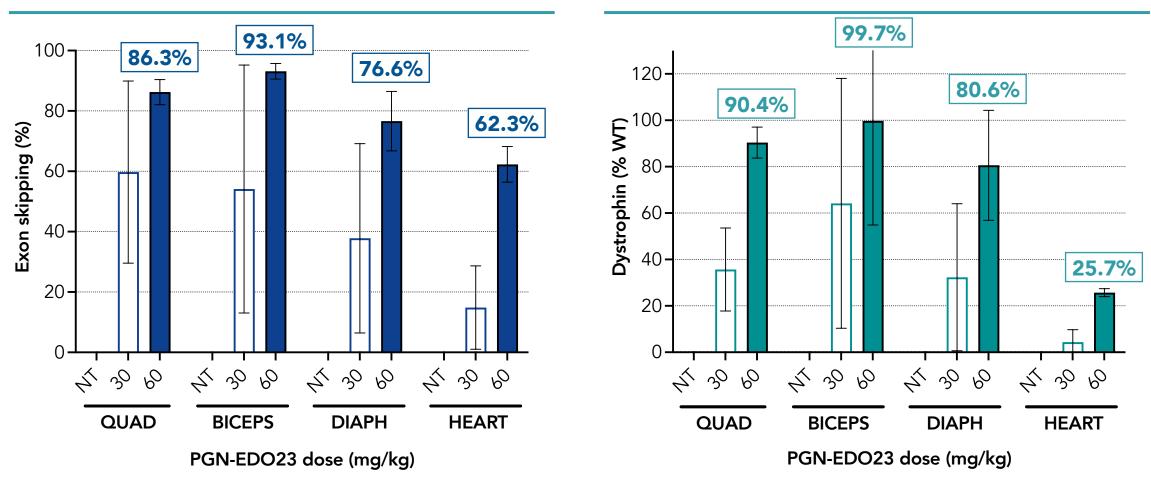


Protocol: peptide-PMO conjugate and a saline control were administered intravenously (IV) to mdx and WT mice; serum creatine kinase measured 7 days after injection. Mean ± SD; \*\*\*\* =  $p \le 0.0001$ ; **ns** =  $p \ge 0.05$ ; n = 3 for control groups and 5 for treated group.

## MDX MICE: ROBUST DYSTROPHIN RESTORATION OBSERVED 7 DAYS AFTER A SINGLE, GENERALLY WELL-TOLERATED DOSE OF PGN-EDO23

EXON SKIPPING

DYSTROPHIN



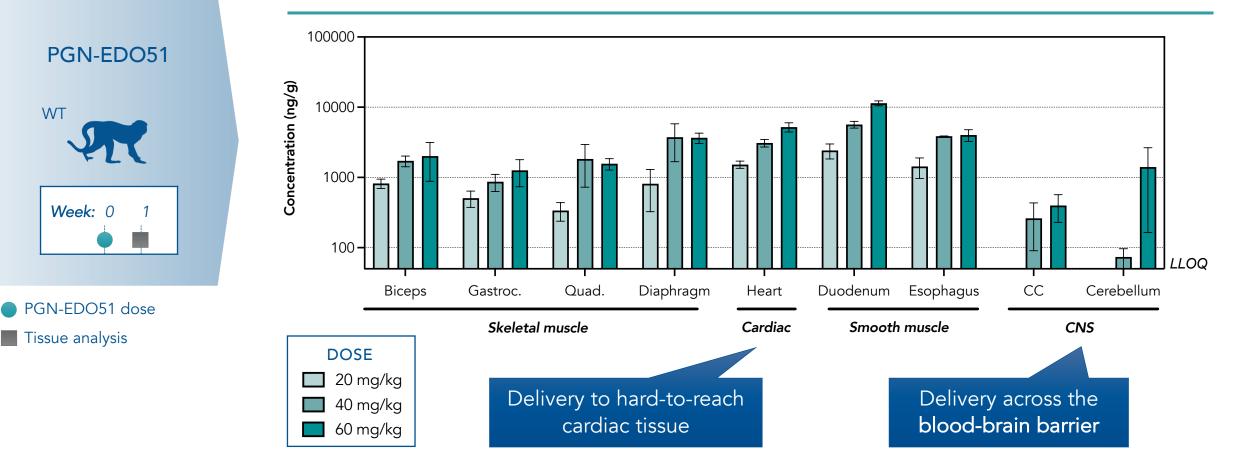


Protocol: peptide-PMO conjugate and a saline control were administered intravenously (IV) to mdx and WT mice; exon skipping and dystrophin restoration measured 7 days after injection. Mean  $\pm$  SD; n = 3 for control groups and 3 for treated

groups. NT = not trea

## NHP: BIODISTRIBUTION DATA EXHIBITED ROBUST EDO DELIVERY ACROSS KEY NEUROMUSCULAR TISSUE TYPES

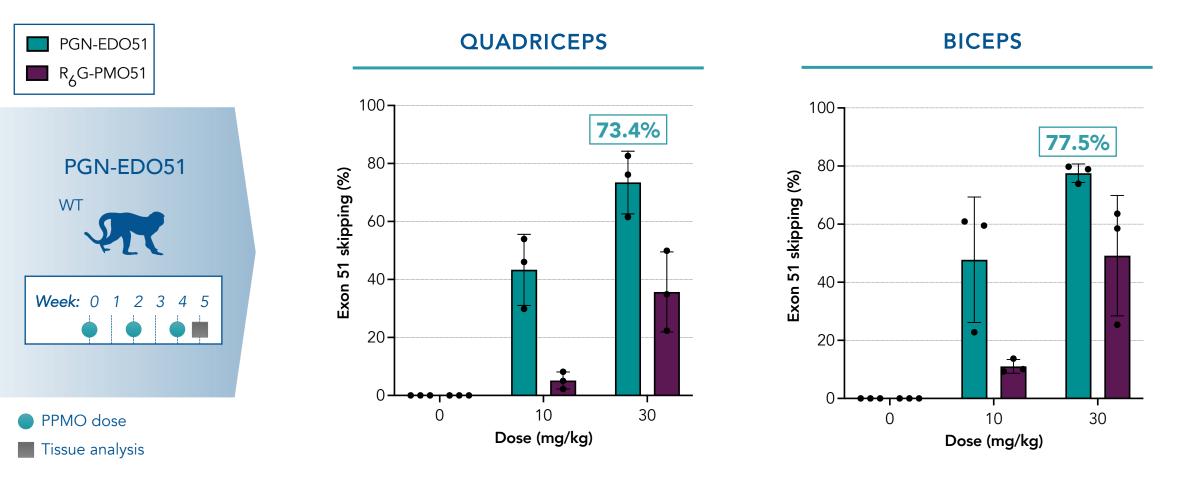
### **TISSUE PMO QUANTIFICATION**





Protocol: NHPs received one slow bolus IV infusion on Day 1, study was terminated on Day 8 and PMO levels were quantified in key tissues. Shown as mean ± SEM; n = 2 per group. CC = cerebral cortex; LLOQ = lower limit of quantification.

## NHP: EXON SKIPPING LEVELS OF >70% OBSERVED IN SKELETAL MUSCLE AT 30 MG/KG

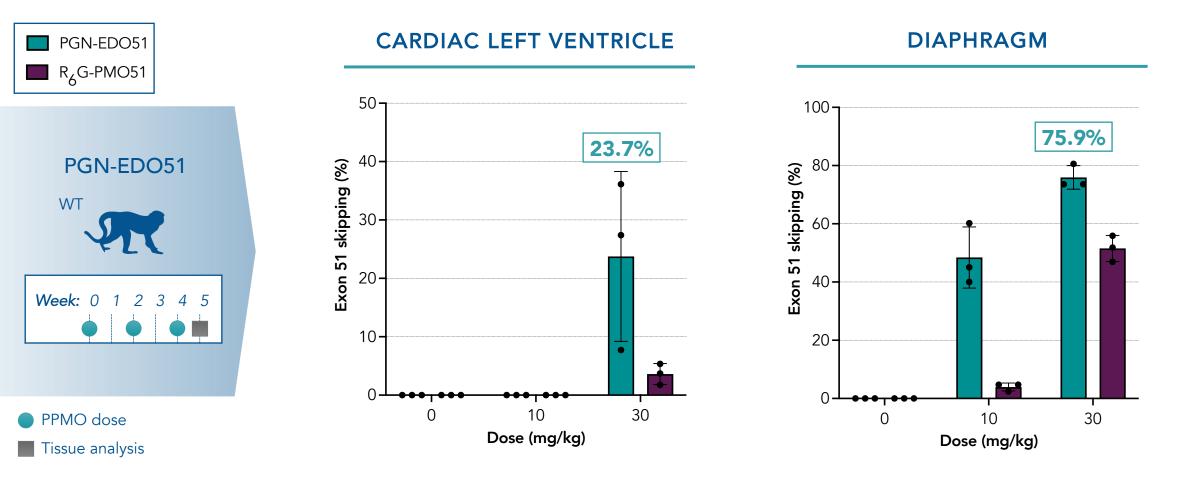


### 10 mg/kg of PGN-EDO51 was approximately as potent as 30 mg/kg of R<sub>6</sub>G-PMO\*



Protocol: PGN-EDO51 and  $R_6G$ -PMO were administered to NHP by IV infusion over 30 min at the doses indicated (n=3). Q2W, three doses administered, saline control. Tissues were harvested 7 days after final administration. Shown as mean ± SD; n = 3 per group. Study was not powered for statistical significance. \*Believed to be structurally equivalent to SRP-5051.

# NHP: PGN-EDO51 EXHIBITED GREATER ACTIVITY IN HEART AND DIAPHRAGM OVER $R_6G$ -PMO

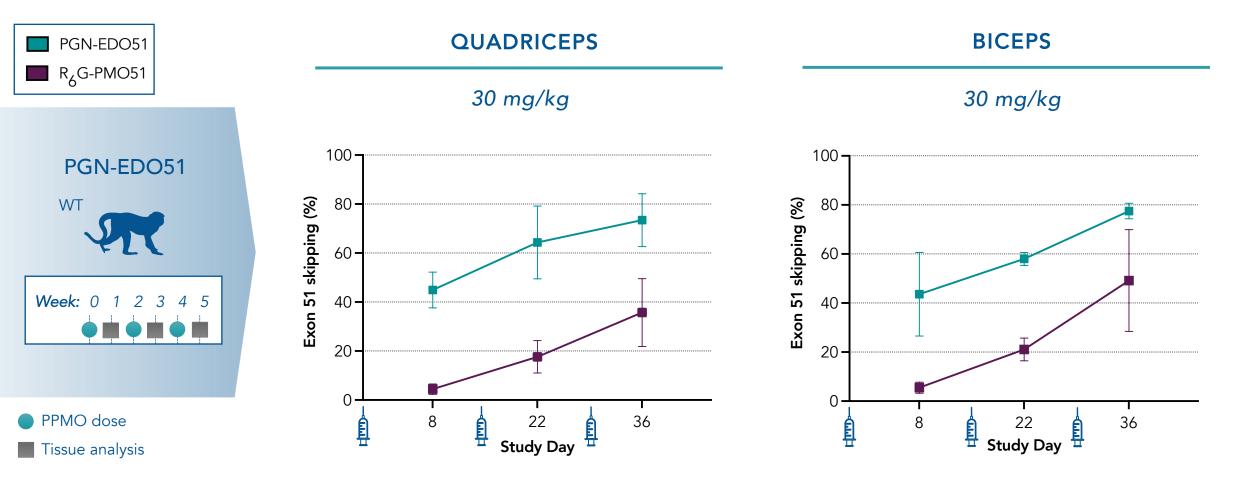


### A single dose of 20 mg/kg of PGN-EDO51 afforded 19% exon 51 skipping in whole heart



Protocol: PGN-EDO51 and  $R_6G$ -PMO were administered to NHP by IV infusion over 30 min at the doses indicated (n=3). Q2W, three doses administered, saline control. Tissues were harvested 7 days after final administration. Shown as mean ± SD; n = 3 per group. Study was not powered for statistical significance.

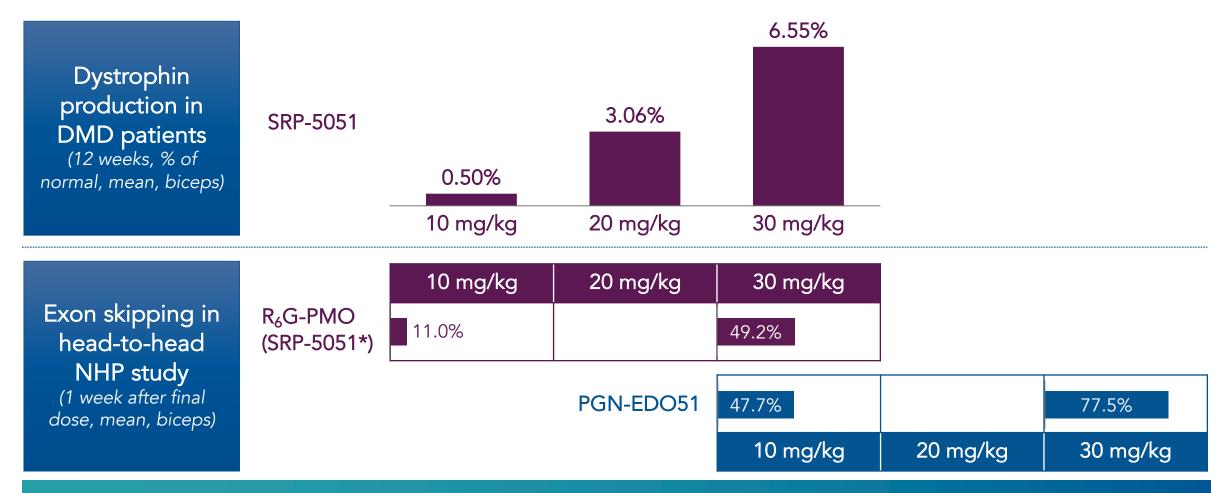
### NHP: EXON SKIPPING LEVELS ACCUMULATED WITH REPEAT DOSE ADMINISTRATION OF PGN-EDO51





Protocol: PGN-EDO51 and  $R_6G$ -PMO were administered to NHP by IV infusion over 30 min at the doses indicated (n=3). Q2W, three doses administered, saline control. Biopsies taken 7 days after each administration; terminal samples collected 7 days after final dose. Study not powered for statistical significance. Data shown as mean ± SD; n = 3 per group.

## WE BELIEVE PGN-EDO51 HAS ROBUST POTENTIAL TO PRODUCE DYSTROPHIN IN PATIENTS



Sarepta has initiated a pivotal trial for SRP-5051



Source: SRPT Momentum updates, 07Dec20 and 03May21, dystrophin measured by Western blot. PepGen NHP protocol: PGN-EDO51 and R<sub>6</sub>G-PMO were administered to NHP by IV infusion over 30 min at 10 and 30 mg/kg indicated (n=3). Q2W, three doses administered, saline control. Tissues were harvested 7 days after final administration. Shown as mean. \*Believed to be structurally equivalent to SRP-5051.

## PGN-EDO51 WAS GENERALLY WELL-TOLERATED AT CLINICALLY-RELEVANT DOSE LEVELS

### TOLERABILITY PROFILE AT TARGET DOSE LEVEL

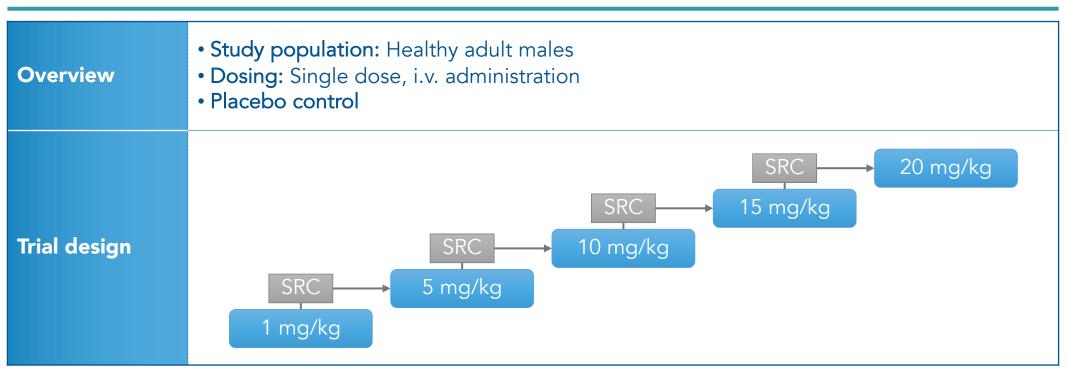
GLP	Single dose 28D		<ul> <li>No mortality and no SAEs</li> <li>No adverse microscopic observations</li> <li>No adverse impacts on clinical chemistry markers</li> </ul>
	Single dose 28D	R	<ul> <li>No mortality and no SAEs</li> <li>No adverse microscopic observations</li> <li>No adverse impacts on clinical chemistry markers</li> </ul>
Non-GLP	Immunogenicity screen		<ul> <li>No significant immunotoxicity flag in human peripheral blood mononuclear cells</li> </ul>

CTA accepted: Health Canada has reviewed our preclinical safety dataset and authorized Ph1 initiation



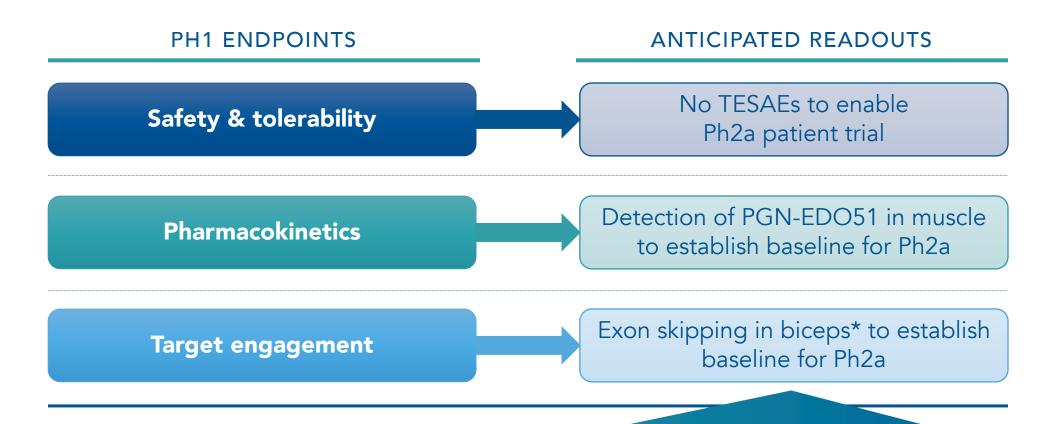
## HEALTH CANADA HAS AUTHORIZED THE INITIATION OF OUR ONGOING PH1 TRIAL IN HEALTHY NORMAL VOLUNTEERS FOR PGN-ED051

### PH1 HEALTHY NORMAL VOLUNTEER (HNV) TRIAL DESIGN





## ONGOING PH1 HNV TRIAL POTENTIALLY ENABLES 2023 PH2A TRIAL IN DMD PATIENTS AND COULD ESTABLISH BASELINE FOR KEY ENDPOINTS



Sarepta reported median exon skipping levels of <0.2% for SRP-5051 in HNV; exon skipping in DMD patients was >10x higher at the same dose level\*\*



TESAEs = Treatment-Emergent Serious Adverse Events. \* Assayed 10 days post-dose \*\* Source: SRPT Momentum updates, 07Dec20 and 03May21, measured by ddPCR. Exon skipping in DMD patients reported following three doses Q4W in a multiple ascending dose trial.

# PEPGEN HAS RECEIVED REGULATORY AUTHORIZATION TO INITIATE A PH1 HEALTHY NORMAL VOLUNTEER (HNV) TRIAL FOR PGN-EDO51

	2022	2023	2024
Anticipated milestones	<ul> <li>2Q: First HNV dosed in Ph1 trial</li> <li>YE: Ph1 clinical safety, oligo delivery &amp; exon skipping topline data</li> </ul>	<ul> <li>1H: IND filing</li> <li>1H: Initiation of Ph2a DMD patient clinical trial</li> </ul>	<ul> <li>Safety and dystrophin data in DMD patients (Ph2a)</li> </ul>
Overview	<ul> <li>HNV study will assess safety and tolerability, oligo delivery &amp; exon skipping</li> <li>Study is being conducted in Canada</li> </ul>	<ul> <li>Study will assess safety and tolerability, exon skipping and dystrophin in DMD patients</li> <li>Safety readouts from HNV study anticipated to support MAD initiation at higher dose levels</li> <li>Precedents suggest that exon skipping readouts will be higher in patients than in HNVs at the same dose level</li> <li>Anticipate that study will be conducted in multiple geographies, including U.S.</li> </ul>	





# PGN-EDODM1 FOR MYOTONIC DYSTROPHY TYPE 1 (DM1)

# MYOTONIC DYSTROPHY TYPE 1 IS A PROGRESSIVE, DEBILITATING NEUROMUSCULAR DISORDER WITH GREAT UNMET NEED

ROOT CAUSE OF	SYMPTOMATOLOGY	PATIENT POPULATION**	THERAPEUTIC
DISEASE	& NATURAL HISTORY		LANDSCAPE
<ul> <li>Due to a CTG repeat expansion mutation in the DMPK gene</li> <li>Leads to downstream dysregulation of a broad set of proteins</li> </ul>	<ul> <li>Myotonia, muscle weakness, GI issues</li> <li>CNS symptoms*, cardiac &amp; respiratory abnormalities</li> <li>Wide range in age of onset, life expectancy 45 – 60 years</li> </ul>	~40,000 (US) ~75,000 (EEA) ~15,000 (JP)	<ul> <li>No approved disease- modifying therapeutics</li> <li>Standards of care focused on symptom management</li> </ul>



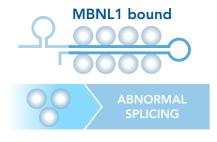
# PEPGEN'S PLATFORM DELIVERS STERIC BLOCKING ASOs TO RESTORE CELLULAR FUNCTION IN DM1

### DM1 CAUSED BY CUG TRIPLET EXPANSION HAIRPIN LOOP IN DMPK RNA SEQUESTERING MBNL1 PROTEIN

### WITHOUT TREATMENT



CUG repeats form 'hairpin loops' in the *DMPK* RNA, which sequester a key RNA processing protein (MBNL1)



Downstream mis-splicing events and aberrant protein expression gives rise to disease phenotypes

#### WITH PGN-EDODM1 TREATMENT



PGN-EDODM1 binds toxic CUG repeats in *DMPK* RNA and blocks MBNL1 binding

#### MBNL1 free



Downstream splicing patterns are restored

PGN-EDODM1 is designed to restore MBNL1 functions and correct downstream mis-splicing events

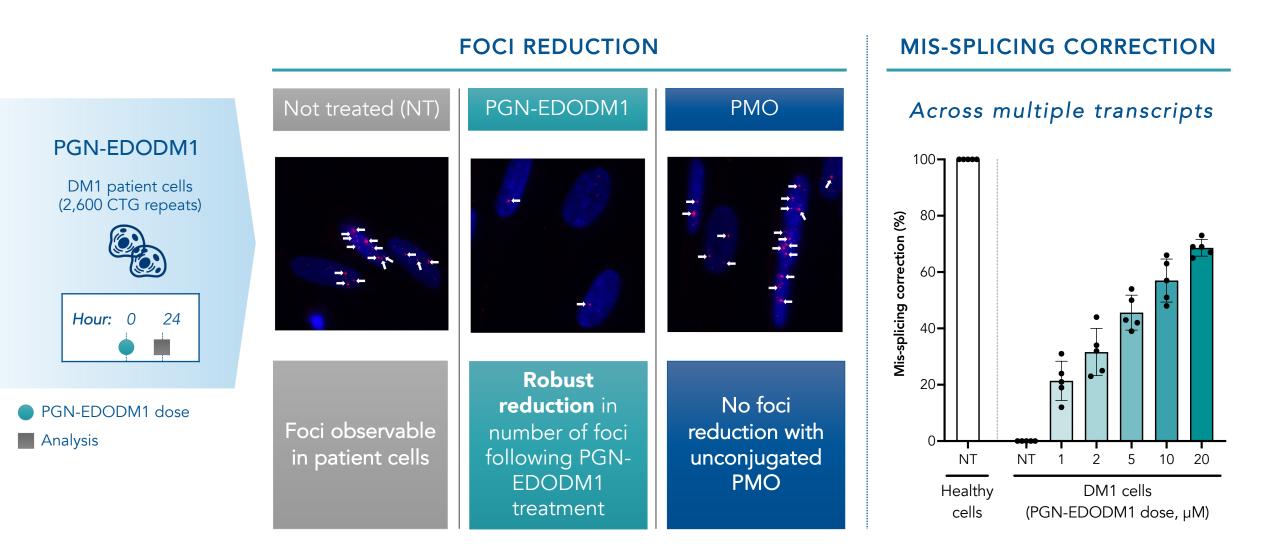


# THE PHARMACOLOGY OF PGN-EDODM1 HAS BEEN EVALUATED IN MULTIPLE PRECLINICAL MODELS

		Species	Study design	Key readouts observed
	Patient cells PGN-EDODM1	DM1 patient	Hour: 0 24	<ul> <li>Reduction in nuclear foci</li> <li>Correction of downstream transcript mis-splicing</li> </ul>
Non-GLP pharmacology studies	Single dose PGN-EDODM1	HSALR	Week: 0 1 2	<ul> <li>Correction of downstream transcript mis-splicing</li> <li>Normalization of myotonia</li> </ul>
	Duration of effect PGN-EDODM1	HSALR	Week: 0 12 24	<ul> <li>Correction of downstream transcript mis-splicing for at least 24 weeks post-dose</li> </ul>
Non-GLP dose- range finding	Single dose PGN-EDODM1	WT	Week: 0 1	In progress
(DRF) studies	<b>Repeat dose</b> PGN-EDODM1	WT	Week: 0 1 2 3 4 5	• In progress

**PepGen** 

# PGN-EDODM1 REDUCED PATHOGENIC NUCLEAR FOCI AND CORRECTED DOWNSTREAM TRANSCRIPT MIS-SPLICING

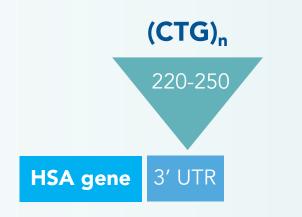


**PepGen** 

Immortalized myoblasts from healthy individual or DM1 patient with 2600 CTG repeats were cultivated then differentiated for 4 days. Treatment with PMO or peptide-PMO conjugates at concentrations given. Cells were harvested for analysis 24h after treatment. Visualisation with FISH and immunofluorescence. RNA isolation, RT-PCR and capilliary electrophoresis (QIAxcel) analysis. Mean ± SD; n = 5 per group.

### HSALR MOUSE DISPLAYS MOLECULAR AND FUNCTIONAL DM1 PHENOTYPE





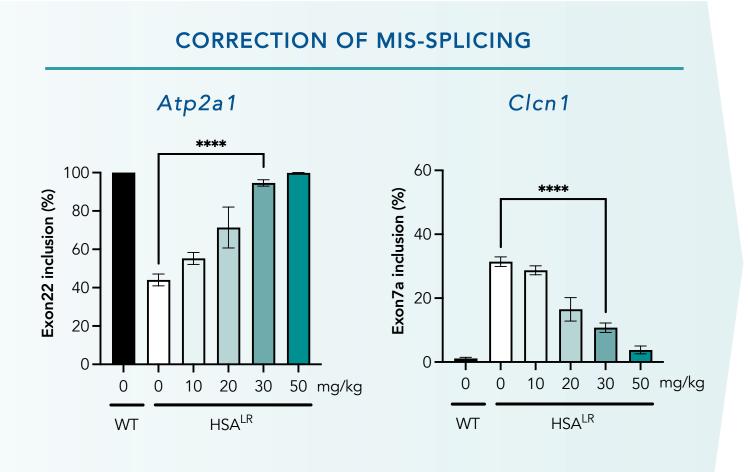
PepGen

### DM1 ASSOCIATED ABNORMALITIES

- Skeletal muscle specific CUGexp
- MBNL1 sequestration in the nucleus
- Downstream mis-splicing events
- Myotonia

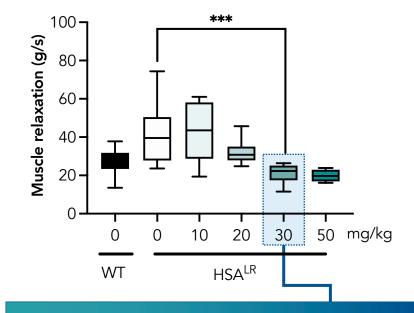


## HSALR: PGN-EDODM1 CORRECTED MOLECULAR AND FUNCTIONAL DM1 PHENOTYPE AT GENERALLY WELL-TOLERATED DOSES



### **REVERSAL OF MYOTONIA**

### Rate of muscle relaxation



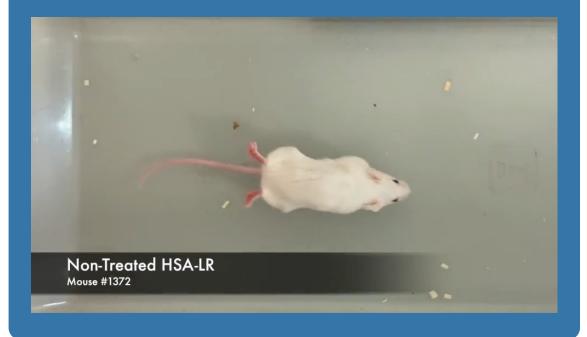
Correction of myotonia observed after a single dose of 30 mg/kg



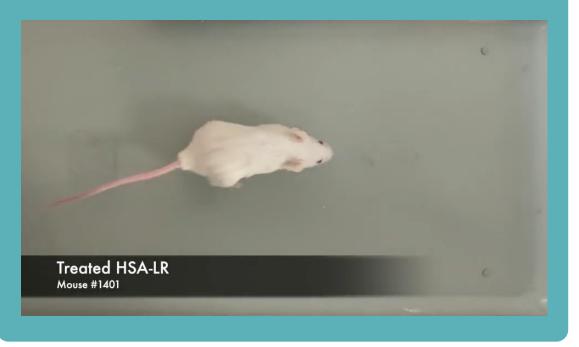
Protocol: PGN-EDODM1 was administered IV to HSALR at doses (mg/kg): 10, 20, 30 (n=8), 50 (n=4) against a saline control (n=16) and wild-type (WT) saline control (n=8). Myotonia assessed, tissues harvested 2 weeks post-administration. Mis-splicing data is guadriceps. Mean  $\pm$  SEM or min to max. \*\*\*\* =  $p \le 0.0001$ ; \*\*\* =  $p \le 0.001$ .

## HSALR: SPLICING CORRECTION TRANSLATED TO PHENOTYPIC IMPROVEMENT OF DM1 MICE TREATED WITH PGN-EDODM1

### UNTREATED HSALR



### TREATED HSALR

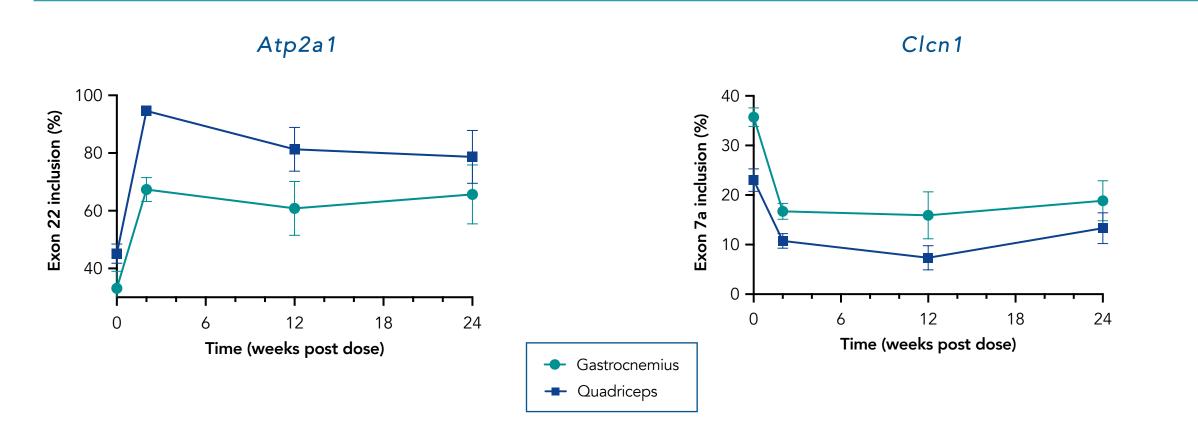




Protocol: PGN-EDODM1 was administered intravenously (IV) to WT and HSALR (DM1 mouse model) at 50 mg/kg (n=4-16); myotonia assessed two weeks post-administration.

### HSALR: SINGLE DOSE TREATMENT OF PGN-EDODM1 LED TO DURABLE IMPROVEMENTS IN SPLICING THROUGH 24 WEEKS

**CORRECTION OF MIS-SPLICING** 





Protocol: PGN-EDODM1 was administered intravenously (IV) to WT and HSALR (DM1 mouse model) at 30 mg/kg; gastrocnemius muscle harvested 2 (n=8), 12 (n=8) or 24 (n=5) weeks post-administration; graph plotted as mean  $\pm$ SEM; n = 7 for 0 timepoint. 8 for 2- and 12-week timepoints; 5 for 24-week timepoint.

# PEPGEN IS ON TRACK TO FILE AN IND FOR PGN-EDODM1 IN 1H23

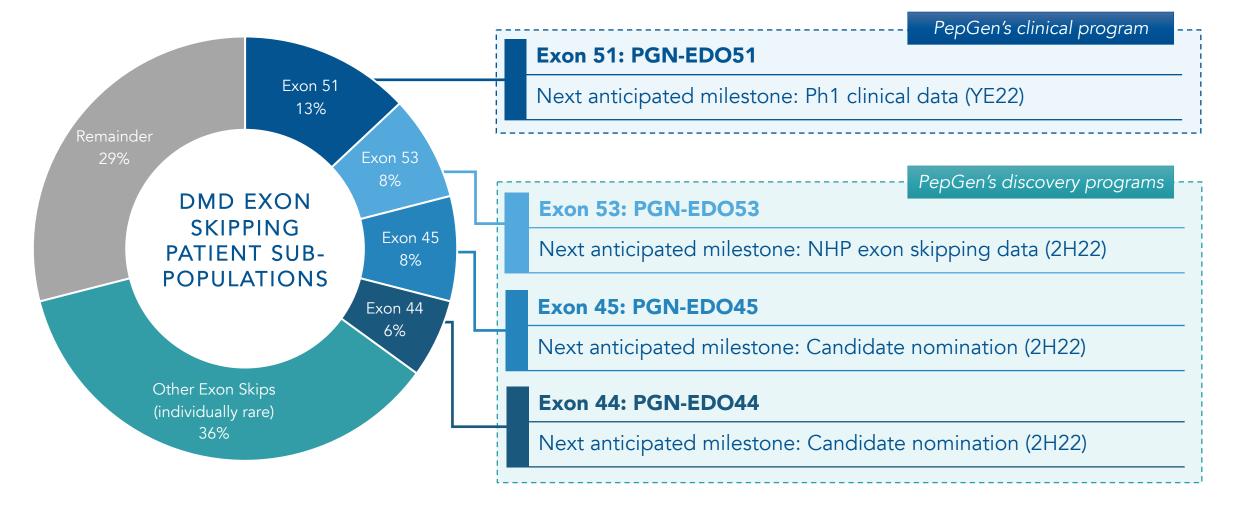
	2022	2023	2024
Anticipated milestones	<ul> <li>2Q: NHP dose range- finding study</li> <li>2H: IND-enabling studies</li> </ul>	<ul> <li>1H: IND filing</li> <li>1H: Initiation of Ph1/2 DM1 patient clinical trial</li> </ul>	<ul> <li>Safety and splicing data in DM1 patients (Ph1/2)</li> </ul>
Overview		<ul> <li>Aim of clinical studies is to assess safety, tolerability and efficacy of PGN-EDODM1 in DM1 patients</li> </ul>	





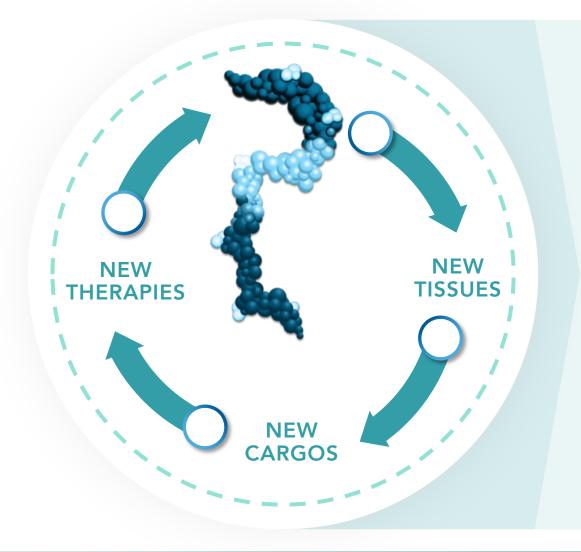
# EDO PIPELINE

# PEPGEN'S LEAD PROGRAM TARGETS LARGEST EXON SKIPPING PATIENT POPULATION IN DMD





# WE ARE HARNESSING THE POWER OF OUR EDO PLATFORM TO REACH NEW TISSUES, DELIVER NEW CARGOS, & DEVELOP NEW THERAPIES



### WE WILL LEVERAGE OUR EDO PEPTIDE PLATFORM TO:

- REACH NEW TISSUES
  - Explore full potential of EDO platform across multiple tissue types, including:
    - Deep brain structures via IT administration
    - Peripheral nerves via IV administration
    - Other tissue and cell types

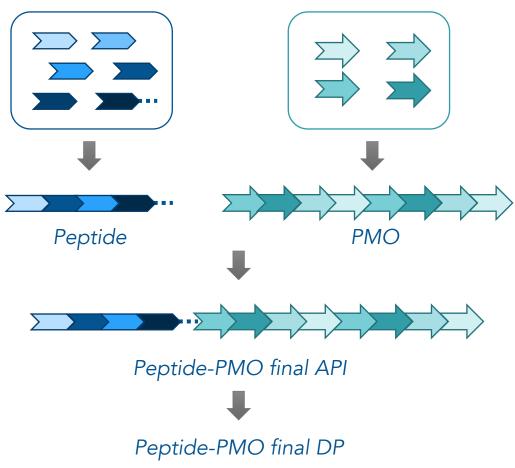
### DELIVER NEW CARGOS

- Utilize **modular nature** of EDO platform to evaluate new cargo technologies
- Explore potential for **non-PMO oligo** and small molecule delivery
- DEVELOP NEW THERAPIES
  - Identify opportunities for novel EDO therapeutics
  - Maximize EDO platform and pipeline value through strategic collaborations



# CURRENT MANUFACTURING CAPABILITIES DESIGNED TO SUPPORT ALL PLANNED CLINICAL TRIALS AND COMMERCIALIZATION

### Readily-available raw materials



### HIGHLIGHTS:

- Fully synthetic manufacturing process; no cellbased steps
- Product and intermediates are readily characterized
- Research to date suggests product has robust stability
- Multiple cGMP DP batches have been manufactured and released; material shipped to Ph1 site





# CONCLUSION

# THE FUTURE OF PEPGEN

2022	Ph1 tolerability, oligo delivery & exon skipping data in HNV anticipated
2023	Anticipate initiation of patient clinical trials for DMD & DM1
2024	<ul> <li>Anticipate clinical POC in two indications:</li> <li>Patient dystrophin data (DMD)</li> <li>Splicing data (DM1)</li> </ul>

- 5 NMD therapies in pipeline
- Work underway to **leverage EDO platform** to expand to new tissues and new indications
- An experienced team with a **deep commitment to the patient community**





# THANK YOU