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Results From The CONNECT1-EDO51 Phase 2 Study Of PGN-EDO51 In People With Duchenne Muscular Dystrophy Amenable To Exon 51 Skipping

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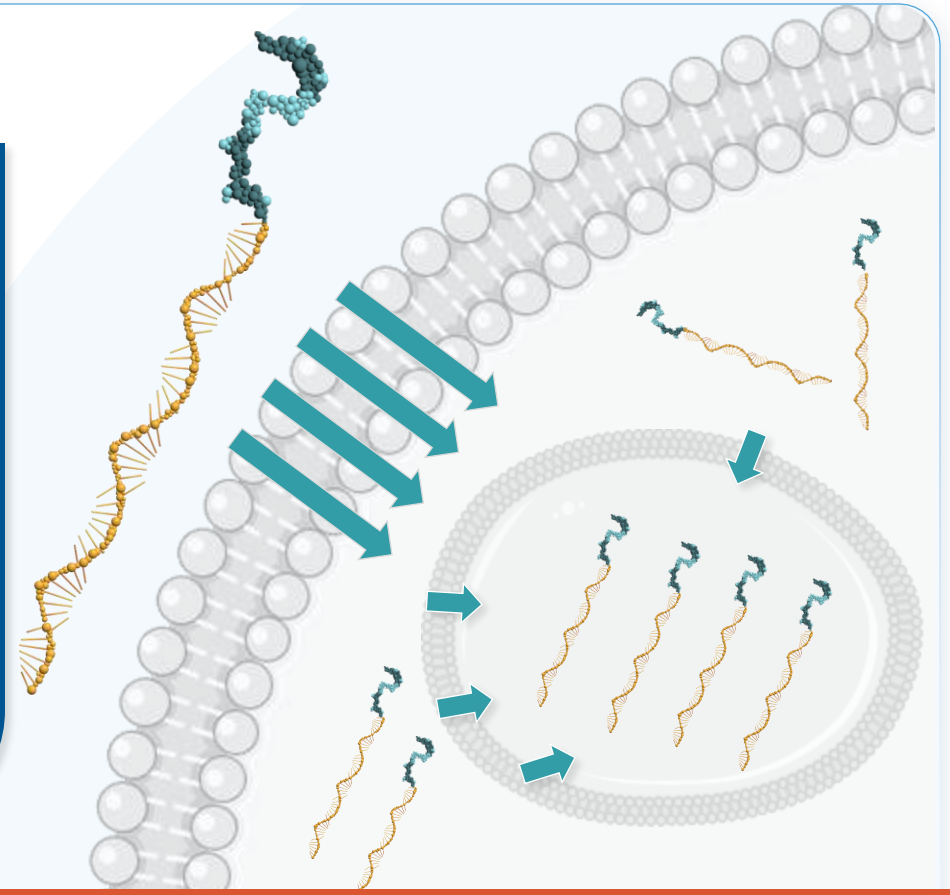
Disclosure

-Consultancy for: Biogen, Hoffman-LaRoche, Novartis, Regenxbio, and Solid Biosciences

-Principal trial (funds to institution) for: Biogen, Dyne Therapeutics, Hoffman-LaRoche, Italfarmaco, Novartis, PepGen, PTC Therapeutics, Regenxbio, Sarepta, Solid Biosciences

PepGen's Enhanced Delivery Oligonucleotide (EDO) Technology is Engineered to Optimize Tissue Delivery and Nuclear Uptake of Therapeutic Oligonucleotides

PGN-EDO51 is PepGen's investigational clinical candidate for the treatment of Duchenne muscular dystrophy (DMD) amenable to exon 51 skipping



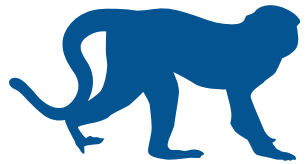
PGN-EDO51 Nonclinical Studies And Healthy Volunteer Study Provided Evidence That Supported Evaluation In People With DMD

Nonclinical

mdx mice

High levels of exon skipping and dystrophin were measured in *mdx* mice given a single dose of PGN-EDO51.

Further increases were observed with repeated doses every 4 weeks.



Cynomolgus monkey

High levels of exon skipping was measured in monkeys given a single dose of PGN-EDO51.

Further increases were observed with repeated doses every 4 weeks.

Clinical

Healthy volunteers

A randomized single-ascending dose study in healthy volunteers demonstrated that PGN-EDO51 had an acceptable safety profile.

Dose dependent levels of oligonucleotide delivery and exon skipping were measured in muscle 28 days post-dose.

CONNECT1*: Designed To Establish Proof-of-concept in People with DMD

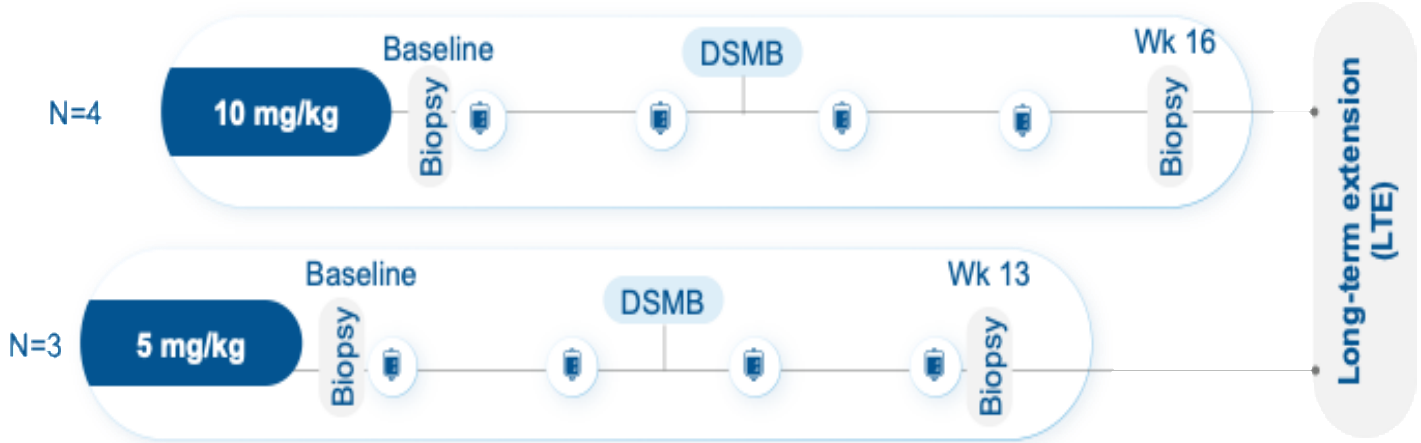
Connect 1
EDO51

* ClinicalTrials.gov number, NCT06079736.

Design

- Multi-center study only in Canada
- Participants with DMD (n=7) with exon 51 skippable mutation
- Ages ≥6 and ≤16 years
- Ambulatory and non-ambulatory

Open label study in people with DMD amenable to exon 51 skipping therapy



PGN-EDO51 IV administration every 4 weeks

DSMB: data safety and monitoring board

Endpoints

- Safety and tolerability
- Dystrophin
- Muscle tissue concentration of PGN-EDO51
- Exon skipping

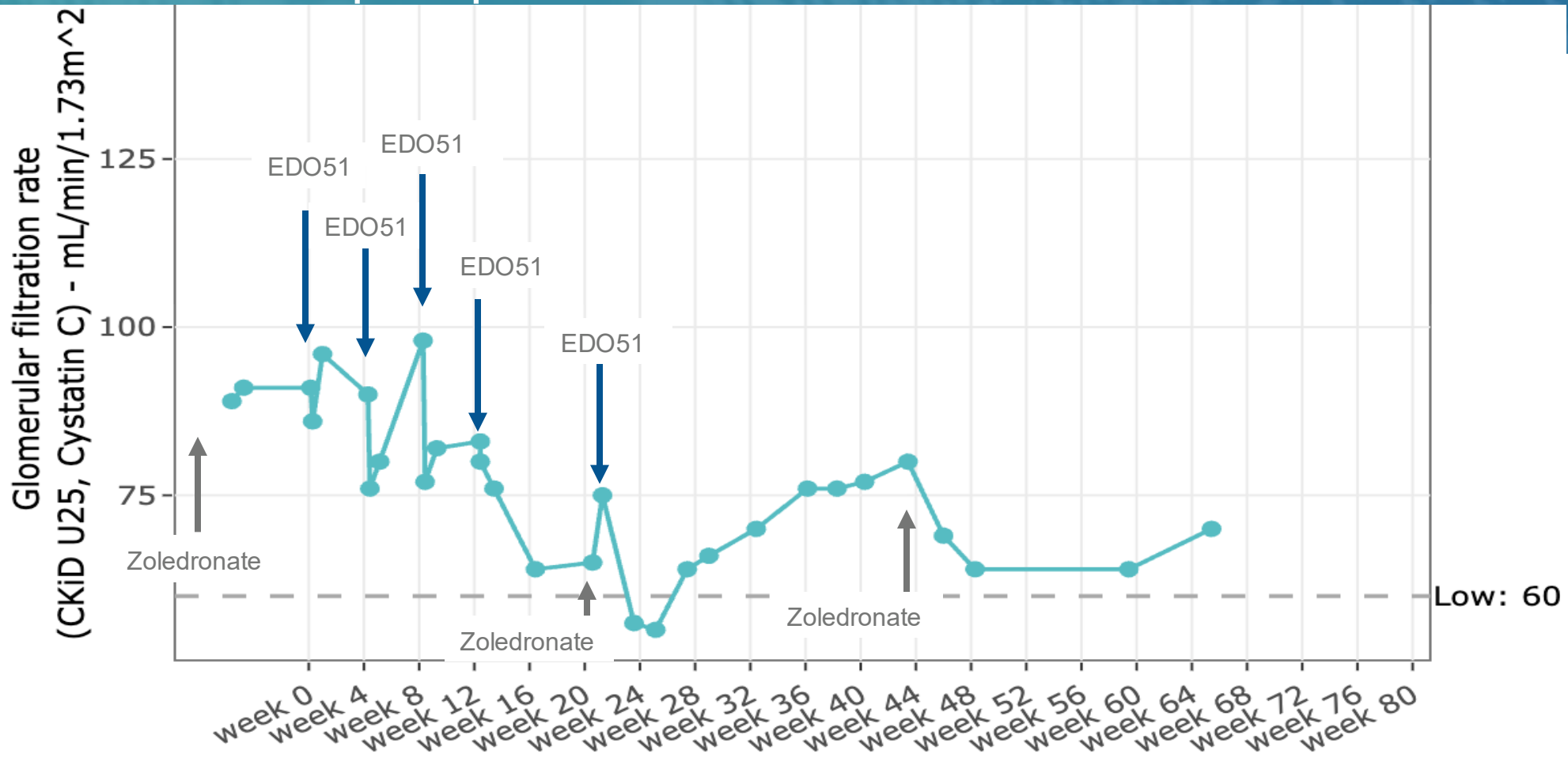
PGN-EDO51 Was Generally Well Tolerated with Repeat Doses of PGN-EDO51

	Cohort 1 5 mg/kg (n=3)	Cohort 2 10 mg/kg (n=4)
Any TEAE, n (%)	3 (100)	3 (75)
Related to study drug Mild Moderate Severe	2 (67) abdominal pain/flatulence (1), creatinine increased (1) 0 0	3 (75.0) nausea (3), vomiting (2), hypomagnesemia (2), eGFR decrease (1) 0 0
Any subjects with occurrence of an SAE or severe related AE	0	0
AEs leading to dose modification/ discontinuation/ interruption	0	1 (25.0)
AEs leading to death	0	0

- All treatment emergent adverse events (TEAEs) were mild
- 2 participants with mild (grade 1) hypomagnesemia at 10 mg/kg
  - Recovered with oral supplementation
  - Asymptomatic
  - No hypokalemia
  - Did not re-occur in the time of the study
- 1 dose interruption due to eGFR decreased
  - Confounded by semi- annual zoledronic acid rx for corticosteroid induced osteoporosis

As of April 4, 2025 (last participant's LTE D1 visit)

Reduced eGFR in One Participant at 10mg/kg; Potentially Associated With Concomitant Use of Bisphosphonates



Biomarker Changes After Single Doses of PGN-EDO51 Predicted Repeat Dose Results

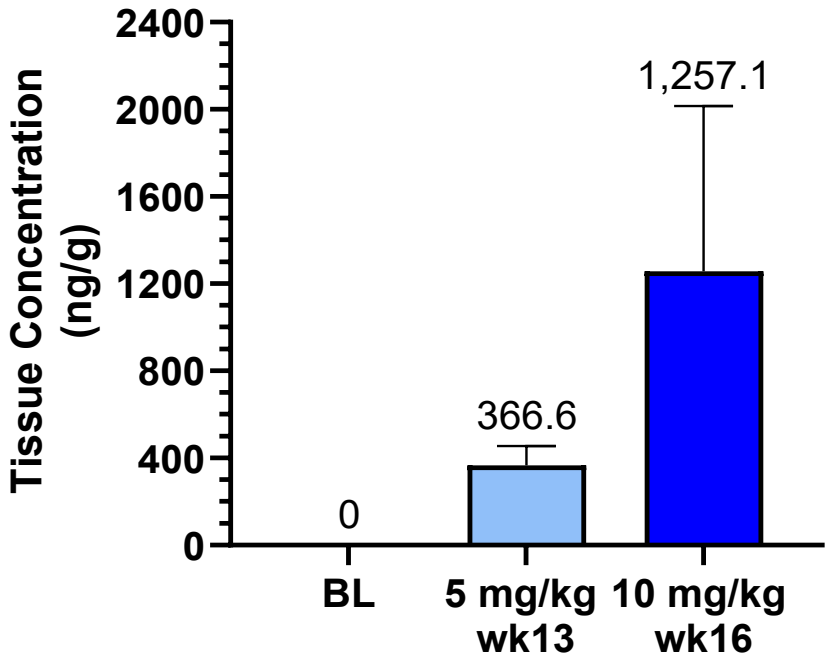
	Single Dose PGN-EDO51 (HV)	Repeat Dose PGN-EDO51 (DMD)
5 mg/kg	• No changes in serum magnesium • No changes in creatinine, • No changes in eGFRcys	• No changes in serum magnesium • Increases in creatinine (1/4 mild AE in OLE) • No changes in eGFRcys,
10 mg/kg	• Decreases in serum magnesium (3/6, 2-5 days) • Increases in creatinine (3/6, 1-9 days) • No changes in eGFRcys 3 AEs of renal impairment	• Decreases in serum magnesium (2/4; recovered with oral Mg*) • Increases in creatinine (1/4), • Decreases in eGFRcys (1/4) 1 dose stopped due to decreased eGFR
15 mg/kg	• Decreases in serum magnesium (5/6, 2-28 days)* • Increases in creatinine (6/6, 1-11 days) • Decreases in eGFRcys (3/6, 2-11 days) 3 AEs of renal impairment and 3 AEs of AKI (1 an SAE)	

*2 HVs at 15 mg/kg and 2 people with DMD at 10 mg/kg were characterized as having hypomagnesemia.

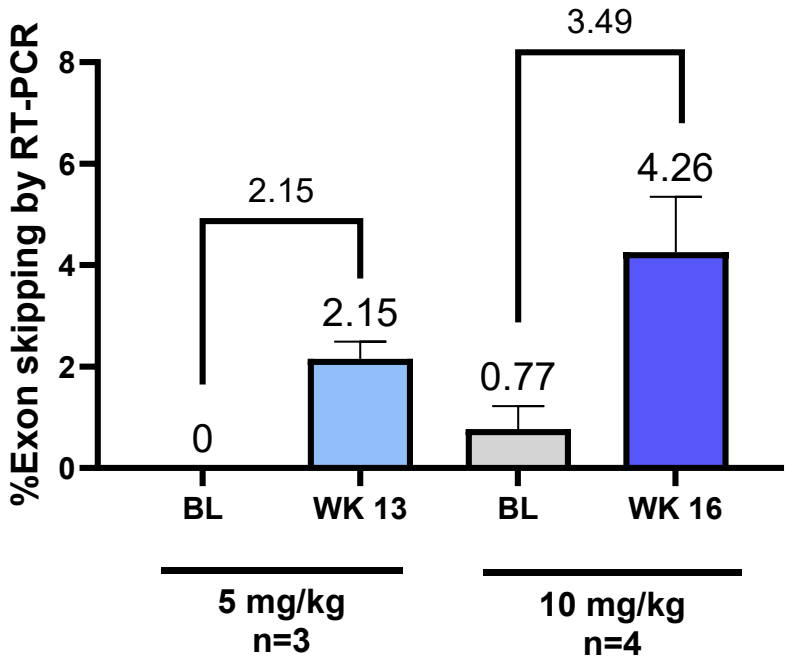
BUN: Blood Urea Nitrogen, eGFRcys: Estimated Glomerular Filtration rate (cystatin C), ULN: Upper Limit of Normal, LTE: Long Term Extension, AE: Adverse Event, AKI: Acute Kidney Injury, SAE: Serious Adverse Event.

PGN-EDO51 Resulted In Dose-dependent Increases In Exon Skipping And Tissue Concentration In People With DMD

PGN-EDO51 Tissue Concentration



Exon Skipping by RT-PCR

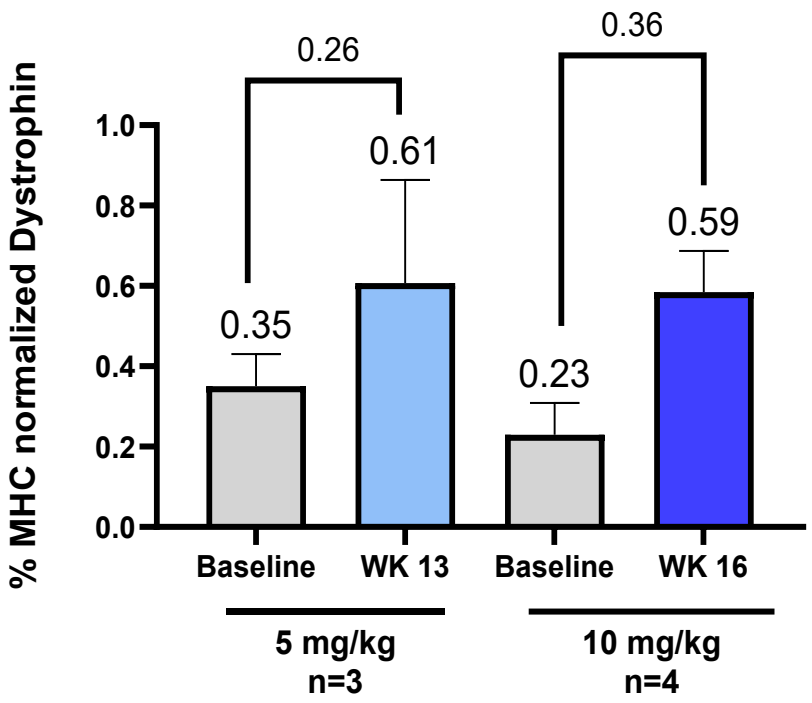


Muscle biopsies were collected at week 13 in Cohort 1 (5mg/kg), and at week 16 in Cohort 2 (10 mg/kg)

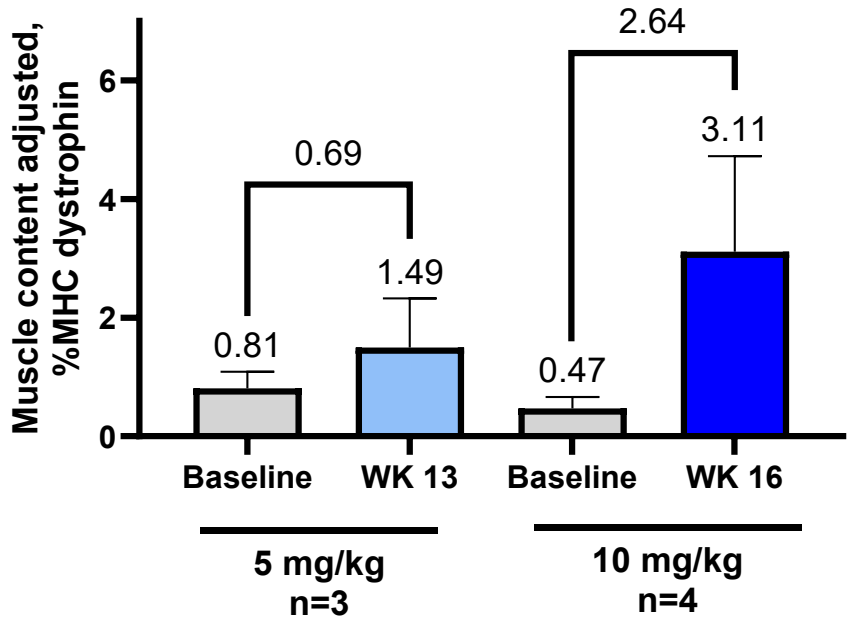
4 doses over 3 months

PGN-EDO51 Resulted In Modest Increases In Dystrophin Level At 10 mg/kg, Indicating Limited Pharmacodynamic Response.

Unadjusted Dystrophin



Adjusted Dystrophin



MHC: Myosin heavy chains

Muscle biopsies were collected at week 13 in Cohort 1 (5mg/kg), and at week 16 in Cohort 2 (10 mg/kg)

4 doses over 3 months

Conclusions

PGN-EDO51

- CONNECT1-EDO51 Phase 2 study results did not achieve target dystrophin levels
  - Observed acceptable emerging safety profile[1] – all treatment-related adverse events were mild
  - Mean maximal exon skipping of 4.26% (mean increase of 3.5%) after 4 doses of 10 mg/kg at 28 days post-dosing
  - Mean maximal dystrophin of 0.59% (mean increase of 0.36%) after 4 doses of 10 mg/kg at 28 days post-dosing
  - All treatment related adverse events were mild and reversible?
- Company voluntarily discontinuing development of PGN-EDO51 and intends to wind down all DMD-related research and development activities.
  - Unexpected low exposure and low dystrophin production suggest that we would need to give substantially higher doses to see clinically meaningful levels of dystrophin. Mild biomarker changes at 10 mg/kg contradicted substantial dose escalation.

1. Data cut off as of May 12, 2025

PGN-EDO51 Learnings for the PGN-EDODM1 Program

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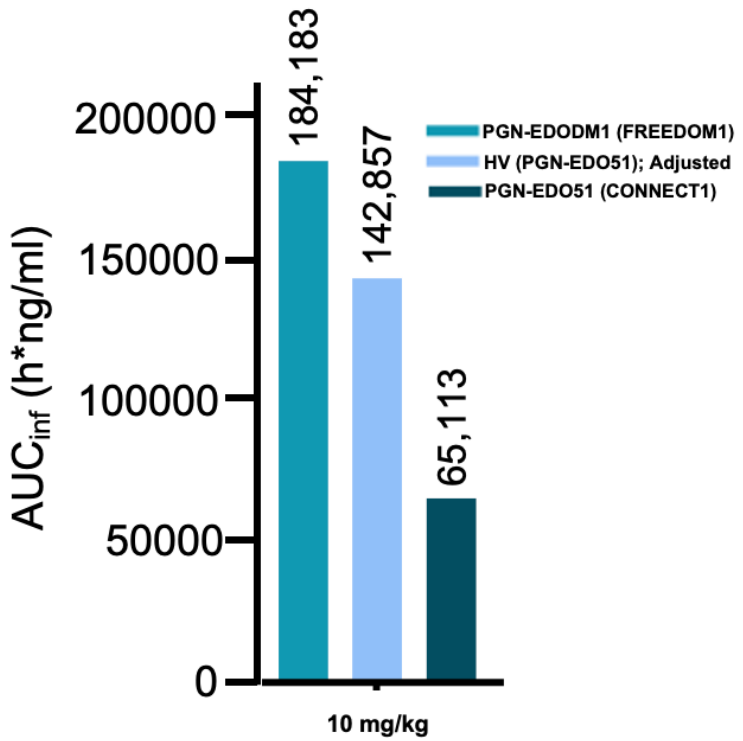
PGN-EDODM1 Demonstrates Greater Systemic Exposure in People with DM1 than PGN-EDO51 Did in People with DMD[1]

Systemic Exposure in Humans[2]



1. Patients (n=6) were dosed with either 10 mg/kg of EDODM1 or EDO51.
2. Plasma samples were analyzed by LC-MS for presence of PGN-EDODM1 PPMO or PGN-EDO51 PPMO as indicated.

Renal Biomarker Signals Were Observed at Lower Doses for PGN-EDO51 than PGN-EDODM1; and Were of Higher Magnitude and Longer Duration

	Single Dose PGN-EDO51 (HV)	Single Dose PGN-EDODM1 (DM1)
5 mg/kg	• No changes in serum magnesium • No changes in creatinine, • No changes in eGFRcys	• No changes in serum magnesium • No changes in creatinine, • No changes in eGFRcys
10 mg/kg	• Decreases in serum magnesium (3/6, 2-5 days) • Increases in creatinine (3/6, 1-9 days) • No changes in eGFRcys 3 AEs of renal impairment	• No changes in serum magnesium • No changes in creatinine, • No changes in eGFRcys
15 mg/kg	• Decreases in serum magnesium (5/6, 2-28 days)* • Increases in creatinine (6/6, 1-11 days) • Decreases in eGFRcys (3/6, 2-11 days) 3 AEs of renal impairment and 3 AEs of AKI (1 an SAE)	• Decreases in serum magnesium (3/6 for 12-48 hrs) • Increases in creatinine (4/6 for 12-24hrs), • Decreases in eGFRcys (1/6, for 12-24hrs) 1 met DLT criterion, GFR decrease

*2 HVs at 15 mg/kg were characterized as having hypomagnesemia. No AEs of hypomagnesemia occurred with PGN-EDODM1. N given are number outside of normal limits at any time point

BUN: Blood Urea Nitrogen, eGFRcys: Estimated Glomerular Filtration rate (cystatin C), ULN: Upper Limit of Normal, AE: Adverse Event, AKI: Acute Kidney Injury, SAE: Serious Adverse Event.

PGN-EDODM1 for Myotonic Dystrophy Type 1 Has A Wider Therapeutic Window than PGN-EDO51

	PGN-EDODM1 (Myotonic Dystrophy Type 1)	PGN-EDO51 (Duchenne Muscular Dystrophy)
MOA	**MOA: Steric Blockade** Binding 1 hairpin loop may release **multiple** MBNL1 proteins	**MOA: Frame Reading** Binding 1 preRNA produces **one** skipped RNA
Target Engagement	**Greater Target Engagement** Single 10 mg/kg dose produced mean **29%** mean correction of RNA splicing	**Lower Target Engagement** Four 10 mg/kg doses produced mean **3.5%** normal skipped RNA
Exposure	**Higher Exposure** **Higher exposure** achieved with PGN-EDODM1 in people with DM1 at 10 mg/kg	**Reduced Exposure** **Lower exposure** of PGN-EDO51 in people with DMD at 10 mg/kg
Safety	**Larger Safety Window** **Higher doses** reached before renal biomarker changes observed;	**Reduced Safety Window** Renal biomarker changes observed at **lower doses; changes were of greater magnitude and longer duration**

Thank You!

All the study participants and their families

The clinical investigators and their teams

- Dr. Hugh McMillan, MD, MSc, FRCPC
  Children's Hospital of Eastern Ontario (CHEO)
- Dr. Nicolas Chrestian, MD, FRCPC, CSCN
  CHU De Quebec-Universite Laval
- Dr. Hernan Gonorazky, MD, CSCN
  The Hospital for Sick Children (SickKids)

The Duchenne patient community