PepGen Announces Positive Initial Results, Including Robust Splicing Correction, from Ongoing FREEDOM-DM1 Trial in Patients with DM1

February 24, 2025

– Significant mean splicing correction of 29.1% following a single dose of PGN-EDODM1 at 10 mg/kg –

– PGN-EDODM1 observed to have favorable emerging safety profile –

– Conference call scheduled today at 8:00 a.m. ET –

BOSTON--(BUSINESS WIRE)--Feb. 24, 2025-- PepGen Inc. (Nasdaq: PEPG), a clinical-stage biotechnology company advancing the next generation of oligonucleotide therapies with the goal of transforming the treatment of severe neuromuscular and neurological diseases, today announced initial positive clinical data from the 5 and 10 mg/kg dose cohorts in the ongoing FREEDOM-DM1 Phase 1 trial investigating PGN-EDODM1 in myotonic dystrophy type 1 (DM1).

“These results far exceeded our expectations for splicing correction following a single dose of PGN-EDODM1. Mis-splicing is the underlying cause of DM1 pathology, and we believe the mean splicing correction observed at 28 days following a single dose of PGN-EDODM1 at 10 mg/kg in the FREEDOM clinical trial surpasses those reported to date in multi-dose clinical trials of up to nine months in duration in patients with DM1. We believe this is a strong indicator of our EDO technology’s potential to deliver therapeutic oligonucleotides to the nucleus and PGN-EDODM1’s potential to address the underlying cause of disease,” said James McArthur, PhD, President and CEO of PepGen. “We believe these results provide initial validation of PGN-EDODM1's ability to selectively bind the pathogenic CUG-repeat *DMPK* RNA and we look forward to evaluating PGN-EDODM1 with more doses over longer time periods in our FREEDOM2-DM1 multiple ascending dose study. Based on these initial results, we aim to build on the significant correction of mis-splicing observed in this single-dose study to potentially provide improved functional benefit for patients who currently have no available approved therapeutic options.”

FREEDOM Results for the 5 mg/kg (n=8) and 10 mg/kg (n=8) Dose Cohorts

Splicing, Muscle Tissue Concentration and Functional Data:

- Mean splicing correction from evaluable participants was 12.3% and 29.1% at 5 mg/kg (n=6) and at 10 mg/kg (n=4)[1,2], respectively, as measured by the 22-gene panel[3] at 28 days post-dosing.
- Dose-dependent increase in muscle tissue concentrations of PGN-EDODM1 was observed at 5 mg/kg (n=6) and at 10 mg/kg (n=5)[1] at day 28.
- While single-dose studies have not demonstrated improved functional outcomes in DM1 patients, the Company collected data from these cohorts and believes these data showed positive early trends in some functional outcome measures. The Company believes robust splicing correction with PGN-EDODM1 has the potential to lead to meaningful functional improvements with repeat dosing over time.

Safety and Tolerability Data:

- PGN-EDODM1 was observed to have a favorable emerging safety profile in the 5 and 10 mg/kg cohorts through the data cut-off date of December 3, 2024, which has continued through the date of this release. There were no adverse events related to electrolytes or renal biomarkers. Most of the treatment emergent adverse events were mild or moderate in severity.
- There was one treatment-related serious adverse event of abdominal pain in the 10 mg/kg cohort that was potentially confounded by use of a prohibited, off-label drug taken on the morning of PGN-EDODM1 dosing.

“These initial results from the FREEDOM clinical trial are highly encouraging. The emerging safety profile is very promising. The dose-dependent splicing correction may suggest that the drug gets into the muscle and effectively binds to the target. Mis-splicing is central to the cause of DM1, and correcting mis-splicing may improve functional outcomes for DM1 patients over time. With this in mind, I am particularly excited by the levels of splicing correction seen after only a single dose of PGN-EDODM1. Based on previous work, I believe that these effects could be stronger as levels of the drug build up with repeat dosing,” said Dr. Johanna Hamel, Associate Professor of Neurology, Pathology and Laboratory Medicine at the University of Rochester Medical Center.

The Company expects to report results from the FREEDOM 15 mg/kg cohort in the second half of 2025 and from the FREEDOM2 5 mg/kg cohort in the first quarter of 2026.

Conference Call Details

PepGen will host a conference call and webcast today at 8:00 a.m. ET to review the FREEDOM data. To access the call, please dial (800) 218-2154 and provide the Conference ID 8807881. A live webcast of the presentation will be available on the Events & Presentations section of the PepGen investor website, investors.pepgen.com.

About PGN-EDODM1

PGN-EDODM1, PepGen's investigational candidate in development for the treatment of DM1, utilizes the Company's proprietary EDO technology to deliver a therapeutic oligonucleotide that is designed to restore the normal splicing function of MBNL1, a key RNA splicing protein. PGN-EDODM1 is designed to directly address the deleterious effects of cytosine-uracil-guanine (CUG) repeat expansion in the dystrophia myotonica protein kinase (*DMPK)* transcripts which sequester MBNL1, by binding to the pathogenic CUG trinucleotide repeat expansion present in the *DMPK* transcripts, disrupting the binding between the CUG repeat expansion and MBNL1. We believe this mechanism will allow the *DMPK* transcripts to continue performing their normal function within the cell, while also liberating MBNL1 to correct downstream mis-splicing events. We believe that this innovative therapeutic approach has considerable advantages over oligonucleotide modalities that rely on knockdown or degradation of the *DMPK* transcripts. The U.S. Food and Drug Administration has granted PGN-EDODM1 both Orphan Drug and Fast Track Designations for the treatment of patients with DM1.

About the FREEDOM Clinical Program

FREEDOM-DM1 is a multinational, randomized, double-blind, placebo-controlled Phase 1 single ascending dose study, enrolling up to approximately 32 adult participants with DM1 in multiple geographies including the United States, the United Kingdom and Canada, to evaluate the safety and tolerability of PGN-EDODM1. Per the protocol, PGN-EDODM1 was administered at starting doses of 5 mg/kg and 10 mg/kg with subsequent dose escalation to 15 mg/kg, and potentially in the future to 20 mg/kg, based upon evaluation by a safety committee of safety data from the prior dose cohort(s). Muscle biopsies are being conducted at baseline, at day 28 and at week 16. In addition to safety and tolerability, oligonucleotide muscle concentrations, splicing correction and functional outcome measures are being assessed at day 28 and at week 16 following a single dose of PGN-EDODM1.

FREEDOM2-DM1 is a Phase 2 randomized, double-blind, placebo-controlled, multiple ascending dose clinical trial evaluating PGN-EDODM1 in approximately 24 adult participants with DM1 in Canada, the United Kingdom, and potentially other geographies, including the United States, subject to regulatory clearances.

About Myotonic Dystrophy Type 1

Myotonic dystrophy type 1 is a monogenic, autosomal dominant, progressive disorder that primarily affects skeletal, cardiac and smooth muscles, with central nervous system symptoms also being evident. Globally, the prevalence of DM1 is estimated to be 1 in 8,000 people, with approximately 40,000 patients in the United States, 75,000 patients in Europe and 15,000 patients in Japan.

DM1 patients can suffer from various manifestations of disease including myotonia, or a temporary rigidity due to the inability to relax muscles, muscle weakness, cardiac abnormalities, respiratory problems, fatigue, gastrointestinal complications, early cataracts, and cognitive and behavioral impairments. For patients with more severe forms of DM1, life expectancy is reduced due to increased mortality rates resulting from pulmonary and cardiac complications.

About PepGen

PepGen Inc. is a clinical-stage biotechnology company advancing the next generation of oligonucleotide therapies with the goal of transforming the treatment of severe neuromuscular and neurological diseases. PepGen’s Enhanced Delivery Oligonucleotide (EDO) platform is founded on over a decade of research and development and leverages cell-penetrating peptides to improve the uptake and activity of conjugated oligonucleotide therapeutics. Using these EDO peptides, we are generating a pipeline of oligonucleotide therapeutic candidates designed to target the root cause of serious diseases.

For more information, please visit www.pepgen.com. Follow PepGen on LinkedIn and X.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended. These statements may be identified by words such as “aims,” “anticipates,” “believes,” “could,” “estimates,” “expects,” “forecasts,” “goal,” “intends,” “may,” “plans,” “possible,” “potential,” “seeks,” “will,” and variations of these words or similar expressions that are intended to identify forward-looking statements. Any such statements in this press release that are not statements of historical fact may be deemed to be forward-looking statements. These forward-looking statements include, without limitation, statements regarding the therapeutic potential and safety profile of PGN-EDODM1, including as it relates to data from the 5 and 10 mg/kg cohorts of the FREEDOM-DM1 study, the potential of our EDO platform to deliver higher levels of oligonucleotide to the nuclei, our expectations regarding the potential for significant correction of mis-splicing with more doses of PGN-EDODM1 over a longer treatment period to potentially provide improved functional benefit for patients with DM1, the expected timing for additional data reports from our FREEDOM trial and the initial data report from our FREEDOM2-DM1 trial, any functional improvements that may result from robust splicing correction with PGN-EDODM1, dose-dependent increases in splicing suggesting that PGN-EDODM1 is getting into the muscle and effectively binding to the target, and ongoing and planned regulatory interactions.

Any forward-looking statements in this press release are based on current expectations, estimates and projections only as of the date of this release and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to risks related to: delays or failure to successfully initiate or complete our ongoing and planned development activities for our product candidates, including PGN-EDODM1; our ability to enroll patients in our clinical trials, including FREEDOM and FREEDOM2; that our interpretation of clinical and preclinical study results may be incorrect, or that we may not observe the levels of therapeutic activity in clinical testing that we anticipate based on prior clinical or preclinical results; our product candidates, including PGN-EDODM1, may not be safe and effective or otherwise demonstrate safety and efficacy in our clinical trials; adverse outcomes from our regulatory interactions, including delays in regulatory review, clearance to proceed or approval by regulatory authorities with respect to our programs, including clearance to commence planned clinical studies of our product candidates, or other regulatory feedback requiring modifications to our development programs, including in each case with respect to our FREEDOM and FREEDOM2 programs; changes in regulatory framework that are out of our control; unexpected increases in the expenses associated with our development activities or other events that adversely impact our financial resources and cash runway; and our dependence on third parties for some or all aspects of our product manufacturing, research and preclinical and clinical testing. Additional risks concerning PepGen’s programs and operations are described in our most recent annual report on Form 10-K that is filed with the SEC. PepGen explicitly disclaims any obligation to update any forward-looking statements except to the extent required by law.

This release discusses PGN-EDODM1, an investigational therapy that has not been approved for use in any country, and is not intended to convey conclusions about its efficacy or safety. There is no guarantee that PGN-EDODM1 or any other investigational therapy will successfully complete clinical development or gain regulatory authority approval.

1. One participant's biopsy was not collected at day 28 due to pseudoaneurysm in connection with the biopsy procedure.
2. One participant's sample showed a splicing index outside the pre-specified assay range at both baseline and day 28 (no detectable mis-splicing) and was excluded from the analysis.
3. Provenzano et al., The Splice Index as a prognostic biomarker of strength and function in myotonic dystrophy type 1, *J Clin. Invest*. 2025

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