Novel Combination of Pozelimab and Cemdisiran (Poze-Cemdi) Achieved Greater Control of Intravascular Hemolysis in Patients with Paroxysmal Nocturnal Hemoglobinuria Compared to Ravulizumab

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Head-to-head exploratory cohort of a Phase 3 trial showed first-in-class poze-cemdi combination treatment helped patients achieve and maintain greater disease control, as measured by lactate dehydrogenase (LDH) levels, compared to standard-of-care ravulizumab

Five patients receiving ravulizumab did not achieve meaningful LDH control compared to one patient receiving poze-cemdi; after switching to the combination, four of the five previously treated with ravulizumab achieved LDH control

A separate registrational cohort is ongoing, investigating poze-cemdi against eculizumab

TARRYTOWN, N.Y., Dec. 07, 2024 (GLOBE NEWSWIRE) -- Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced positive updated Phase 3 data of an exploratory cohort from the ACCESS-1 trial investigating its first-in-class pozelimab and cemdisiran (poze-cemdi) combination treatment against ravulizumab, a standard-of-care complement factor 5 (C5) inhibitor, in patients with paroxysmal nocturnal hemoglobinuria (PNH). Results were shared during an oral session at the American Society of Hematology (ASH) 2024 Annual Meeting and support continued development of poze-cemdi in PNH, including in a separate registrational cohort, as well as in other complement-mediated diseases. Poze-Cemdi is a first-in-class combination of an antibody and an siRNA targeting C5: pozelimab is a fully human monoclonal antibody designed to block the activity of C5, while cemdisiran is an investigational siRNA therapeutic that reduces circulating levels of C5.

PNH is an ultra-rare, chronic, life-threatening complement-mediated blood disorder. People with PNH have an acquired genetic mutation in which red blood cells are destroyed (known as hemolysis) by the complement system, which is part of the innate immune system. The lysed red blood cells release lactate dehydrogenase (LDH), which is a biomarker used to measure the degree of hemolysis. Hemolysis causes a range of symptoms including fatigue, shortness of breath, and life-threatening blood clots. Inhibition of C5, a protein involved in complement system activation, is an established treatment approach to prevent intravascular hemolysis, which occurs inside blood vessels; LDH can be used to determine the effectiveness of C5 inhibition. Addressing intravascular hemolysis is a critical treatment approach to reducing the symptoms and risk of life-threatening complications of PNH.

“C5 inhibitors are widely considered the mainstay of PNH treatment, but a proportion of patients still do not achieve adequate control of intravascular hemolysis, may experience residual anemia, and may feel significant treatment burden, as many of these therapies require clinic or home visits for intravenous delivery,” said Christopher Patriquin, M.D., MSc, Assistant Professor of Medicine, Hematology, at the University of Toronto, hematologist at University Health Network and a trial investigator. “In this Phase 3 exploratory cohort, the complementary mechanisms of pozelimab and cemdisiran enabled complete, rapid, uninterrupted and durable inhibition of terminal complement throughout the dosing interval. The combination helped more patients achieve target LDH levels compared to the current standard-of-care C5 inhibitor, with the added benefit of infrequent four-week subcutaneous delivery that has potential for self-administration. These data validate this novel combination approach, and we look forward to results from the registrational cohort, which if repeated, could help transform what may be possible for many people with PNH.”

Updated results from an exploratory arm (Cohort A) of the ACCESS-1 trial, as well as interim results from a follow-on, open label extension (OLE) were presented at ASH. Patients were naïve to complement inhibition, with the primary endpoint of Cohort A being percent change in LDH at 26 weeks. LDH is a well-accepted biomarker of intravascular hemolysis that measures how effective a treatment is at inhibiting the destruction of red blood cells and has also demonstrated a correlation to clinical outcomes.[1] Adequate control of hemolysis is defined as LDH levels of ≤1.5 times upper limit of normal (ULN), while normalization is defined as ≤1 times ULN, respectively.

In Cohort A, patients were randomized to receive either poze-cemdi or ravulizumab. The ravulizumab arm generally responded as would be expected based on historical clinical trial data, which indicate that 44% of treated patients did not achieve LDH normalization (≤1 x ULN).[2] Results for those treated with poze-cemdi (n=25), compared to ravulizumab (n=23), were as follows:

- **96% achieved adequate LDH control (≤1.5 x ULN) across study visits** (weeks 8-26) on average with poze-cemdi, compared to 80% with ravulizumab. At 26 weeks, 5 patients receiving ravulizumab, compared with 1 patient receiving poze-cemdi, did not achieve meaningful LDH control.
- **93% achieved LDH normalization (≤1 x ULN) across study visits** (week 8-26) on average with poze-cemdi, compared to 65% with ravulizumab.
- **84% decrease in LDH from baseline** at week 26 with poze-cemdi compared to 74% with ravulizumab.

- **The CH50 profile observed with poze-cemdi demonstrated complete and uninterrupted inhibition of terminal complement**, compared to the profile for ravulizumab showing loss of inhibition at the end of the dosing interval.

After week 26, all patients who completed ACCESS-1 could enroll in a follow-on OLE trial and receive poze-cemdi, including those who initially received ravulizumab (n=19). At the start of the OLE, 68% (n=13) of patients treated with ravulizumab had adequate LDH control. After switching to poze-cemdi, 95% of patients (n=18) achieved LDH control. This included 4 of 5 patients who had failed to achieve LDH control while on ravulizumab.

The safety profile of poze-cemdi was generally consistent with approved C5 inhibitors. During ACCESS-1, treatment-emergent adverse events (TEAEs) occurred in 84% of patients treated with poze-cemdi, compared to 87% treated with ravulizumab. The most common TEAEs (≥10%) for poze-cemdi compared to ravulizumab were headache (28% vs. 17%), upper respiratory tract infection (12% vs. 9%), nausea (12% vs. 4%), anemia (12% vs. 9%), fatigue (8% vs. 13%) and cough (4% vs. 13%). Serious adverse events (SAEs) occurred in two patients receiving poze-cemdi that were considered unrelated to treatment by the investigator. This included one patient who had post-traumatic cellulitis that resolved with treatment while continuing poze-cemdi. The second patient experienced a fever, seizure and hemolytic crisis within one week of the first dose of the combination that also resolved while continuing poze-cemdi; the patient later had a fatal SAE of sepsis and disseminated intravascular coagulation on day 130.

In the OLE, among patients who switched to poze-cemdi from ravulizumab, 68% experienced TEAEs, with the most common being non-serious, mild to moderate injection-site reactions. There were no TEAEs consistent with type 3 hypersensitivity reactions due to large drug-target-drug immune complexes after switching from ravulizumab to poze-cemdi, which have been observed when switching between other C5 inhibitors. There were also no fatal TEAEs, and no patients discontinued therapy due to an adverse event.

The potential use of pozelimab and cemdisiran for the treatment of PNH is investigational and has not been approved by any regulatory authority.

About the Pozelimab and Cemdisiran Clinical Trial Program
Pozelimab and cemdisiran are being evaluated in separate Phase 3 trials for several complement-mediated disorders, including PNH, myasthenia gravis (MG) and geographic atrophy (GA).

PNH: ACCESS-1 is a randomized, active-controlled study comprised of two cohorts, evaluating poze-cemdi in patients with PNH who are naïve to, or have not recently received, complement inhibitor therapy. The first cohort (Cohort A) is an exploratory cohort examining the combination administered subcutaneously as a maintenance regimen every four weeks compared to ravulizumab delivered as a maintenance regimen every eight weeks by intravenous infusion. Cohort B is a registrational cohort examining poze-cemdi against eculizumab. Patients in both cohorts may participate in a follow-on OLE study (ACCESS-EXTENSION) assessing the long-term safety and efficacy of the combination, including in patients who switch from ravulizumab or eculizumab.

MG: NIMBLE is a randomized, double-blind placebo controlled trial evaluating poze-cemdi as well as cemdisiran monotherapy in patients with generalized MG.

GA: SIENNA is a randomized, double-blind, placebo controlled trial evaluating poze-cemdi as well as cemdisiran monotherapy in patients with GA secondary to age-related macular degeneration.

For more information, visit the Regeneron clinical trials website, or contact clinicaltrials@regeneron.com or +1 844-734-6643.

The pozelimab and cemdisiran combination is being developed under an agreement with Alnylam Pharmaceuticals, Inc.

About Regeneron in Hematology
At Regeneron, we're applying more than three decades of biology expertise with our proprietary *VelociSuite*® technologies to develop medicines for patients with diverse blood cancers and rare blood disorders.

Our blood cancer research is focused on bispecific antibodies that are being investigated both as monotherapies and in combination with each other and emerging therapeutic modalities. Together, they provide us with unique combinatorial flexibility to develop customized and potentially synergistic cancer treatments.

Our research and collaborations to develop potential treatments for rare blood disorders include explorations in antibody medicine, gene editing and gene-knockout technologies, and investigational RNA approaches focused on depleting abnormal proteins or blocking disease-causing cellular signaling.

About Regeneron's *VelocImmune* Technology
Regeneron's *VelocImmune* technology utilizes a proprietary genetically engineered mouse platform endowed with a genetically humanized immune system to produce optimized fully human antibodies. When Regeneron's co-Founder, President and Chief Scientific Officer George D. Yancopoulos was a graduate student with his mentor Frederick W. Alt in 1985, they were the first to envision making such a genetically humanized mouse, and Regeneron has spent decades inventing and developing *VelocImmune* and related *VelociSuite*® technologies. Dr. Yancopoulos and his team have used *VelocImmune* technology to create a substantial proportion of all original, FDA-approved or authorized fully human monoclonal antibodies. This includes

REGEN-COV® (casirivimab and imdevimab), Dupixent® (dupilumab), Libtayo® (cemiplimab-rwlc), Praluent® (alirocumab), Kevzara® (sarilumab), Evkeeza® (evinacumab-dgnb), Inmazeb® (atoltivimab, maftivimab and odesivimab-ebgn) and Veopoz® (pozelimab).

About Regeneron
Regeneron (NASDAQ: REGN) is a leading biotechnology company that invents, develops and commercializes life-transforming medicines for people with serious diseases. Founded and led by physician-scientists, our unique ability to repeatedly and consistently translate science into medicine has led to numerous approved treatments and product candidates in development, most of which were homegrown in our laboratories. Our medicines and pipeline are designed to help patients with eye diseases, allergic and inflammatory diseases, cancer, cardiovascular and metabolic diseases, neurological diseases, hematologic conditions, infectious diseases, and rare diseases.

Regeneron pushes the boundaries of scientific discovery and accelerates drug development using our proprietary technologies, such as *VelociSuite*®, which produces optimized fully human antibodies and new classes of bispecific antibodies. We are shaping the next frontier of medicine with data-powered insights from the Regeneron Genetics Center® and pioneering genetic medicine platforms, enabling us to identify innovative targets and complementary approaches to potentially treat or cure diseases. For more information, please visit www.Regeneron.com or follow Regeneron on LinkedIn, Instagram, Facebook or X.

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This press release includes forward-looking statements that involve risks and uncertainties relating to future events and the future performance of Regeneron Pharmaceuticals, Inc. ("Regeneron" or the "Company"), and actual events or results may differ materially from these forward-looking statements. Words such as "anticipate," "expect," "intend," "plan," "believe," "seek," "estimate," variations of such words, and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements concern, and these risks and uncertainties include, among others, the nature, timing, and possible success and therapeutic applications of products marketed or otherwise commercialized by Regeneron and/or its collaborators or licensees (collectively, "Regeneron's Products") and product candidates being developed by Regeneron and/or its collaborators or licensees (collectively, "Regeneron's Product Candidates") and research and clinical programs now underway or planned, including without limitation pozelimab (a fully human monoclonal antibody designed to block the activity of C5) in combination with cemdisiran (an investigational siRNA therapeutic targeting C5); the likelihood, timing, and scope of possible regulatory approval and commercial launch of Regeneron's Product Candidates and new indications for Regeneron's Products, such as pozelimab in combination with cemdisiran for the treatment of paroxysmal nocturnal hemoglobinuria as discussed in this press release as well as the treatment of other complement-mediated disorders (including myasthenia gravis and/or geographic atrophy); uncertainty of the utilization, market acceptance, and commercial success of Regeneron's Products and Regeneron's Product Candidates and the impact of studies (whether conducted by Regeneron or others and whether mandated or voluntary), including the studies discussed or referenced in this press release, on any of the foregoing or any potential regulatory approval of Regeneron's Products and Regeneron's Product Candidates (such as pozelimab in combination with cemdisiran); the ability of Regeneron's collaborators, licensees, suppliers, or other third parties (as applicable) to perform manufacturing, filling, finishing, packaging, labeling, distribution, and other steps related to Regeneron's Products and Regeneron's Product Candidates; the ability of Regeneron to manage supply chains for multiple products and product candidates; safety issues resulting from the administration of Regeneron's Products and Regeneron's Product Candidates (such as pozelimab in combination with cemdisiran) in patients, including serious complications or side effects in connection with the use of Regeneron's Products and Regeneron's Product Candidates in clinical trials; determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize Regeneron's Products and Regeneron's Product Candidates; ongoing regulatory obligations and oversight impacting Regeneron's Products, research and clinical programs, and business, including those relating to patient privacy; the availability and extent of reimbursement of Regeneron's Products from third-party payers, including private payer healthcare and insurance programs, health maintenance organizations, pharmacy benefit management companies, and government programs such as Medicare and Medicaid; coverage and reimbursement determinations by such payers and new policies and procedures adopted by such payers; competing drugs and product candidates that may be superior to, or more cost effective than, Regeneron's Products and Regeneron's Product Candidates (including biosimilar versions of Regeneron's Products); the extent to which the results from the research and development programs conducted by Regeneron and/or its collaborators or licensees may be replicated in other studies and/or lead to advancement of product candidates to clinical trials, therapeutic applications, or regulatory approval; unanticipated expenses; the costs of developing, producing, and selling products; the ability of Regeneron to meet any of its financial projections or guidance and changes to the assumptions underlying those projections or guidance; the potential for any license, collaboration, or supply agreement, including Regeneron's agreements with Sanofi and Bayer (or their respective affiliated companies, as applicable) and the agreement with Alnylam Pharmaceuticals, Inc. referenced in this press release, to be cancelled or terminated; the impact of public health outbreaks, epidemics, or pandemics (such as the COVID-19 pandemic) on Regeneron's business; and risks associated with intellectual property of other parties and pending or future litigation relating thereto (including without limitation the patent litigation and other related proceedings relating to EYLEA® (aflibercept) Injection), other litigation and other proceedings and government investigations relating to the Company and/or its operations (including the pending civil proceedings initiated or joined by the U.S. Department of Justice and the U.S. Attorney's Office for the District of Massachusetts), the ultimate outcome of any such proceedings and investigations, and the impact any of the foregoing may have on Regeneron's business, prospects, operating results, and financial condition. A more complete description of these and other material risks can be found in Regeneron's filings with the U.S. Securities and Exchange Commission, including its Form 10-K for the year ended December 31, 2023 and its Form 10-Q for the quarterly period ended September 30, 2024. Any forward-looking statements are made based on management's current beliefs and judgment, and the reader is cautioned not to rely on any forward-looking

statements made by Regeneron. Regeneron does not undertake any obligation to update (publicly or otherwise) any forward-looking statement, including without limitation any financial projection or guidance, whether as a result of new information, future events, or otherwise.

Regeneron uses its media and investor relations website and social media outlets to publish important information about the Company, including information that may be deemed material to investors. Financial and other information about Regeneron is routinely posted and is accessible on Regeneron's media and investor relations website (https://investor.regeneron.com) and its LinkedIn page (https://www.linkedin.com/company/regeneron-pharmaceuticals).

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[1] Schrezenmeier, H., Kulasekararaj, A., Mitchell, L. et al. Predictors for improvement in patient-reported outcomes: post hoc analysis of a phase 3 randomized, open-label study of eculizumab and ravulizumab in complement inhibitor-naive patients with paroxysmal nocturnal hemoglobinuria. *Ann Hematol* 103, 5-15 (2024).
[2] Ultomiris (ravulizumab) [package insert]. Boston, MA: Alexion Pharmaceuticals, Inc.; 2018.

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Source: Regeneron Pharmaceuticals, Inc.