Regeneron to Advance Two Factor XI Antibodies into a Broad Phase 3 Program Following Positive Phase 2 Proof-of-concept Results

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Investigational REGN7508 (catalytic domain) and REGN9933 (A2 domain) are being evaluated for their potential to control thrombosis while minimizing bleeding risk in a variety of patient populations and clinical settings

Evaluated against current standards of care, single doses of REGN7508 and REGN9933 administered 12 to 24 hours after total knee replacement demonstrated robust antithrombotic effects

Phase 3 program to be initiated in 2025

TARRYTOWN, N.Y., Dec. 19, 2024 (GLOBE NEWSWIRE) -- Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced positive Phase 2 results for two novel monoclonal antibodies targeting distinct domains of Factor XI. REGN7508 (catalytic domain) is designed to maximize anticoagulant activity while minimizing bleeding risk, and REGN9933 (A2 domain) is designed to provide an additional option for patients with the highest bleeding risk who would otherwise not be candidates for currently available anticoagulants. Per the Phase 2 results, there was a robust antithrombotic effect for each antibody, and no clinically relevant bleeding was observed in any treatment arm.

“Our Factor XI antibodies targeting the catalytic and A2 domains were rigorously evaluated alongside current standards of care and showed clear evidence of antithrombotic effect with an encouraging safety profile after a convenient single dose,” said George D. Yancopoulos, M.D., Ph.D., Board Co-Chair, President and Chief Scientific Officer at Regeneron. “These latest Phase 2 results add to our preclinical data that showed prolongation of activated partial thromboplastin clotting time was greater with REGN7508 and similar with REGN9933, compared to other Factor XI-targeted agents. Together, these clinical and preclinical data, along with compelling genetic evidence, give us confidence in targeting multiple distinct domains of Factor XI to potentially offer tailored therapies for patients with different bleeding risk profiles and in a variety of treatment settings. We are eager to advance REGN7508 and REGN9933 into a broad Phase 3 program beginning in 2025.”

Regeneron conducted two open-label, active-controlled Phase 2 trials (ROXI-VTE-I and ROXI-VTE-II) in the same centers under similar protocols to evaluate REGN7508 and REGN9933 for the prevention of asymptomatic (detected by venogram between day 8 and 12) or symptomatic venous thromboembolism (VTE) after unilateral total knee arthroplasty. In ROXI-VTE-I, patients were randomized to receive either a single intravenous (IV) dose of REGN9933, daily enoxaparin, or twice daily doses of apixaban until the time of venography. In ROXI-VTE-II, patients were randomized to receive a single IV dose of REGN7508 or daily enoxaparin until the time of venography. In contrast to trials evaluating other Factor XI antibodies, administration of all treatments began 12 to 24 hours after surgery (generally one day post-operation) in both trials, consistent with the approved administration of the active comparators.

On the measure of VTE rates at venogram following surgery, a pooled analysis across both trials showed REGN7508 was superior to enoxaparin and non-inferior to apixaban, and REGN9933 was non-inferior to enoxaparin. All VTE events were asymptomatic, except for one symptomatic case of pulmonary embolism in the apixaban arm. Results were as follows:

	REGN7508	**REGN9933**	**enoxaparin**	**apixaban**		**Historical control (placebo)**[1]
Patients with VTE events	7% (8 of 113 patients)	17% (20 of 116 patients)	21% (36 of 175 patients)	12% (14 of 113 patients)		48% (43 of 89 patients)
Difference in VTE incidence (95% confidence interval)	REGN7508 vs enoxaparin: -14% (-21% to -6%)* REGN7508 vs apixaban: -5% (-13% to 2%)^ REGN9933 vs enoxaparin: -3% (-13% to 6%)^					

* Superiority met
^ Non-inferiority met with a margin of 9%

There was no major bleeding (including surgical site bleeding) or clinically relevant non-major bleeding in any arm; the only treatment-related adverse events (AE) in any arm was one case of minimal bleeding (contusion) reported in the enoxaparin arm of ROXI-VTE-I.

There were no treatment-related serious AEs (SAEs) in any arm. There were also no AEs in any arm leading to trial

discontinuation or dose interruption/modification, and no AEs of special interest or deaths in these trials. Across both trials, AE rates were generally similar among the treatment arms (ROXI-VTE-I: REGN9933=22%, enoxaparin=21%, apixaban: 25%; ROXI-VTE-II: REGN7508=22%, enoxaparin: 25%).

The safety and efficacy of REGN7508 and REGN9933 have not been evaluated by any regulatory authority.

About Thrombosis
Thrombosis, otherwise known as clot formation, is responsible for one in four deaths worldwide. Due to bleeding concerns, current standard-of-care anticoagulants are underutilized and current oral agents are often associated with poor adherence. There is an unmet need for treatments that can help prevent thrombosis without increased bleeding risk.

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 fully human monoclonal antibodies. This includes Dupixent® (dupilumab), Libtayo® (cemiplimab-rwlc), Praluent® (alirocumab), Kevzara®, Evkeeza® (evinacumab-dgnb), Inmazeb® (atoltivimab, maftivimab and odesivimab-ebgn) and Veopoz® (pozelimab-bbfg). In addition, REGEN-COV® (casirivimab and imdevimab) had been authorized by the FDA during the COVID-19 pandemic until 2024.

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 for over 35 years by physician-scientists, our unique ability to repeatedly and consistently translate science into medicine has led to numerous FDA-approved treatments and product candidates in development, almost all 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, hematologic conditions, infectious diseases and rare diseases.

Regeneron is accelerating and improving the traditional drug development process through our proprietary VelociSuite® technologies, such as VelocImmune, which uses unique genetically humanized mice to produce optimized fully human antibodies and bispecific antibodies, and through ambitious research initiatives such as the Regeneron Genetics Center®, which is conducting one of the largest genetics sequencing efforts in the world.

For more information, please visit www.Regeneron.com or follow Regeneron on LinkedIn.

Forward-Looking Statements and Use of Digital Media

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 REGN7508 and REGN9933, two novel monoclonal antibodies targeting distinct domains of Factor XI (together, the "Factor XI Product Candidates"); 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 any of the Factor XI Product Candidates); 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 any regulatory approval of any of the Factor XI Product Candidates; 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 any of the Factor XI Product Candidates) 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 (including the Phase 2 studies evaluating the Factor XI Product Candidates discussed in this press release) 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), 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] Fuji T, Fujita S, Tachibana S, Kawai Y. A dose-ranging study evaluating the oral factor Xa inhibitor edoxaban for the prevention of venous thromboembolism in patients undergoing total knee arthroplasty. J Thromb Haemost. 2010 Nov;8(11):2458-68. doi: 10.1111/j.1538-7836.2010.04021.x. PMID: 20723033.

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