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OVERVIEW:

Company Summary

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PRESENTATION

Operator

Welcome to the Regeneron conference call to discuss its factor XI development program. My name is Shannon, and I will be your operator for today's call. (Operator Instructions)

Please note that this conference call is being recorded. I will now turn the call over to Ryan Crowe, Senior Vice President, Investor Relations. You may begin.

Ryan Crowe - Regeneron Pharmaceuticals Inc - Senior Vice President-Investor Relations

Thank you, Shannon. Good morning, and welcome to the inaugural Regeneron Roundtable Investor Event. The first in a series of presentations that will spotlight key opportunities across our pipeline. Today, we will focus on our Factor XI development program, which began initial Phase III studies earlier this year.

Today's roundtable features key R&D leaders from Regeneron, including Dr. George Yancopoulos, Board Co-Chair, President and Chief Scientific Officer; Dr. Andres Sirulnik, Senior Vice President and Clinical Development Unit Head, Hematology; and David -- Dr. David Gutstein, Vice President and Global Program Head, Hematology.

Before we begin, I would like to remind you that remarks made today may include forward-looking statements at Regeneron, and each forward-looking statement is subject to risks and uncertainties that could cause actual results and events to differ materially from those projected in such statements.

A description of material risks and uncertainties can be found in Regeneron's SEC filings. Regeneron does not undertake any obligation to update any forward-looking statements whether as a result of new information, future events or otherwise.

With that, I will turn the call over to George.

George Yancopoulos - Regeneron Pharmaceuticals Inc - President, Chief Scientific Officer, Director

Thank you, Ryan. I'll begin with a brief introduction to Regeneron's hematology pipeline, highlighting recent progress in key programs. Andres will then provide an overview of our Factor XI program, outlining the unmet need in anticoagulation, the rationale behind our dual antibody strategy as well as the genetic support that validates our approach.

Then David, who leads the Factor XI clinical program at Regeneron, will present preclinical data as well as clinical data from the ROXI-VTE-I and II studies in venous thromboembolism prevention post knee replacement surgery, which we just presented this past weekend at the American Heart Association 2025 Conference.

David will also share for the first time preliminary results from our proof of mechanism, ROXI-CATH and GI bleed studies, which provide additional support for our broad clinical development program, details for which David will also reveal today.

Finally, Ryan will briefly discuss the commercial opportunity for our Factor XI antibodies before opening up the call for any questions you may have on this program.

Regeneron's hematology and hem/onc pipeline spans multiple areas, including hematologic malignancies, coagulation disorders, transplantation and immunomodulation, complement and other emerging areas with assets across early, mid- and late stages of development.

This pipeline is a result of decades of research and investment, recently culminating our first approved hem-onc medicines, most notably Lynozyfic, a BCMAxCD3 bispecific for late-stage multiple myeloma in both the US and Europe and Ordspono, a CD20xCD3 bispecific for late-stage follicular lymphoma and diffuse large B-cell lymphoma in Europe.

The Lynozyfic development program will be the topic of our next Regeneron Roundtable scheduled for December 10.

Another exciting program in our hematology pipeline is for complement inhibition. We've recently announced positive Phase III data for cemdisiran, our siRNA monotherapy targeting C5. Cemdisiran demonstrated competitive efficacy and safety profile with differentiated every three-month subcutaneous dosing in generalized myasthenia gravis. In the pivotal NIMBLE study, cemdisiran demonstrated, at week 26, a 2.3-point placebo-adjusted improvement in the Myasthenia Gravis Activities of Daily Living, or MG-ADL total score -- the highest placebo-adjusted reduction observed among C5 inhibitors in their respective pivotal trials. Our U.S. regulatory submission is planned for the first quarter of 2026, pending discussions with the FDA.

In paroxysmal nocturnal hemoglobinuria, or PNH, we have previously presented data from the lead-in cohort of our ongoing pivotal trial comparing our combination of an siRNA and antibody to the current standard of care, ravulizumab. Among other endpoints, the study is assessing the changes in lactate dehydrogenase or LDH, the key biomarker PNH disease activity from baseline to week 26.

We showed that our Regeneron combination reduced LDH more than the ravulizumab comparator with almost all patients treated with the combo achieving disease control. Moreover, when we took the 20% of patients treated with ravulizumab who failed to reach LDH normalization after 26 weeks and then switched them to our C5 combination... Once again, almost all were able to rapidly and durably reach the normal range for LDH, giving us increased confidence that this combination could become the new standard of care for PNH with pivotal data available in early 2027.

But for today, we turn our focus to our Factor XI program, which includes two investigational antibodies, REGN7508 that targets the catalytic domain of Factor XI and REGN9933 that targets the A2 domain.

As you'll hear from the team, trial results are consistent with the prospective design of these antibodies to have distinct profile, one to provide stronger anticoagulation and the other to have a lower risk of bleeding, potentially allowing physicians to tailor anticoagulant therapy for patients with different risk profiles. The data, as you'll hear, will support our vision for this program, which is to offer a tailored approach to anticoagulation therapy for patients with differing risk profiles.

With that, I will turn the call over to Andres.

Andres Sirulnik - Regeneron Pharmaceuticals Inc - Senior Vice President and Clinical Development Unit Head, Hematology

Thank you, George. To begin, I'd like to address several key questions on our Factor XI development program: is there still a meaningful unmet need in anticoagulation? If so, why target Factor XI? And finally, what differentiates Regeneron's approach from other Factor XI-targeting agents in development?

First, regarding the unmet need. Today, the global anticoagulation market is approximately $20 billion, primarily driven by stroke prevention in patients with atrial fibrillation. Yet, only about half of patients who should be treated with anticoagulation therapy receive standard of care direct oral anticoagulants, or DOACs, due to bleeding concerns that are associated with this class. A therapy with comparable efficacy and lower bleeding risk could unlock the untreated half of the market and drive switches from DOAC.

Importantly, we see an even greater opportunity in other areas where anticoagulants are currently underutilized, such as venous thromboembolism and arterial thrombosis. Furthermore, the risk-benefit profile of these new therapies may open up previously untapped opportunities where anticoagulation is not presently considered given the elevated risk of bleeding. A safer therapy could transform these indications and substantially expand the commercial opportunity.

But why target Factor XI for anticoagulation therapy?

As you can see in the diagram on the right side of the slide, Factor XI sits at a strategic point in the coagulation cascade, making it an attractive target for selective inhibition. Inhibiting Factor XI, which is in the proximal intrinsic pathway, can block amplification and propagation of pathologic clots, such as those seen in venous thromboembolism, while preserving the extrinsic pathway, which is essential for hemostasis and wound healing. In contrast, targeting Factor X, as DOACs do, disrupts both pathways, and as a result, increases bleeding risk.

Finally, we believe Regeneron's approach is differentiated from other Factor XI targeting agents in development, based on preclinical analysis, early clinical data, and our two mechanistically distinct antibodies that can tailor therapy based on an individual's patient's needs.

Let's now focus on the unmet need, which remains significant despite the availability of current treatments. Today's anticoagulants, including DOACs and low-molecular-weight heparins are effective, but as we mentioned earlier, their use is limited by bleeding risk. In the US alone, the anticoagulation market exceeds 15 billion [dollars], driven primarily by stroke prevention in atrial fibrillation. Yet, approximately half of the addressable population is not actively treated due to bleeding concerns.

Beyond atrial fibrillation, the treatment gap is even larger in other indications such as venous thromboembolism and atrial thrombosis, where anticoagulant use is minimal for the same reason. In contact-mediated thrombosis, we are still dependent on older standards of care, warfarin and heparin, which carry substantial bleeding risk. A therapy that delivers strong antithrombotic efficacy with substantially lower bleeding risk versus currently available medicines could transform care in these settings and open up new commercial opportunities.

With our two differentiated antibodies, Regeneron aims to address these unmet needs and expand treatment into areas where anticoagulation is currently underutilized or not even considered.

Let's now turn to the genetic evidence supporting our Factor XI development strategy, a critical underpinning for our program.

Analyses performed by the Regeneron Genetics Center, or RGC, along with published epidemiological studies, show that individuals with naturally occurring deficiencies in Factor XI have a significantly reduced risk of venous thromboembolism and cardio-embolic stroke with minimal increased bleeding risk. This supports the idea the Factor XI inhibition can deliver antithrombotic benefit while preserving hemostasis.

More specifically, the RGC analyzed associations of two types of factor 11 gene variants with clinical outcomes. Factor 11 gain of function, which includes people with increased Factor XI levels and Factor 11 partial loss of function, which includes people with decreased Factor XI levels. These variants allows us to evaluate the effect of Factor XI levels on thrombotic risk across large, diverse populations.

As shown on this slide, individuals with Factor 11 gain of function variant, had a 16% increased risk of VTE and a 10% increased risk of cardioembolic stroke. In contrast, Factor 11 loss of function variant is protective, with carriers exhibiting a 31% decreased risk of VTE and a 27% decreased risk of cardioembolic stroke.

These findings reinforce our therapeutic hypothesis that lowering Factor XI levels can reduce thrombotic risk while maintaining a favorable bleeding profile. Importantly, this genetic evidence helped guide our indication selection, focusing on conditions for which the evidence is strongest.

Notably, in arterial thrombosis indications like myocardial infarction and large artery atheroembolic stroke, the genetic data supporting a benefit for Factor XI deficiencies less convincing.

Thus, human genetic data supports Factor XI as a target for VTE and cardioembolic stroke, but additional validation is needed for arterial thrombosis.

Taken together, our insights from genetics enabled us to prioritize indications with the most compelling validation such as venous thromboembolism and SPAF, while continuing to generate data in other areas, including arterial thrombosis, where initial genetic signal is less clear.

This data-driven approach remains central to how we advance our Factor XI program and many other programs across the Regeneron pipeline.

Building on the genetic rationale, I'd now like to explain further while we are pursuing two mechanistically distinct Factor XI antibodies in our development program.

Our approach is rooted in patient centricity. Anticoagulation needs very significantly across indications and patient populations. Some require maximum anticoagulation potency, while others will be well served with moderate anticoagulation activity, but with no increased bleeding risk.

This is why we've designed two antibodies with differentiated therapeutic profiles.

REGN9933, our A2 antibody binds to the A2 domain on Factor XI, blocking its activation by Factor XII, effectively mimicking Factor XII deficiency. This antibody could be optimal for settings where bleeding risk tolerance is low, including patients with atrial fibrillation who are not candidates for DOACs, as well as those with PICC lines or peripheral artery disease.

REGN7508, our Cat antibody, blocks the catalytic domain of Factor XI and consequently results in robust anticoagulation activity. It is being pursued broadly across all indications including those where efficacy is paramount, such as total knee replacement and cancer-associated VTE.

As illustrated in the table, each antibody offers a distinct balance of anticoagulation potency and bleeding risk.

This tailored strategy allows us to match the right molecule to the right patient population.

Let me now turn the call over to David, who will review the preclinical and clinical data we have generated to date for each of these programs. David?

David Gutstein - Regeneron Pharmaceuticals Inc - Vice President and Global Program Head, Hematology

Thank you, Andres. Let's take a closer look at how these antibodies performed in preclinical assays and how their profiles compare to other Factor XI targeting agents in development. In these studies, both Regeneron antibodies demonstrated more complete inhibition of Factor XI activity compared to other investigational agents, including competitors' small molecules and monoclonal antibodies.

This was assessed using two key assays, activated partial thromboplastin time, or aPTT, and the thrombin generation assay. As shown on the slide, Regeneron's antibodies achieved robust aPTT prolongation and complete suppression of thrombin generation at clinically relevant concentrations.

This suggests a more complete blockade of the intrinsic pathway, which is critical for preventing pathologic clot formation. Importantly, small molecule inhibitors required significantly higher concentrations to reach similar anticoagulant activity, which may increase the risk of off-target effects.

In contrast, our antibodies achieved strong inhibition at lower concentrations, demonstrating their exquisite potency and specificity, thus supporting their favorable clinical profile. These preclinical data, combined with our genetic insights provide a robust foundation for our clinical development strategy.

Let's now cover clinical data just presented at the American Heart Association 2025 Annual Meeting, including results from the ROXI-VTE-I and ROXI-VTE-II studies.

Our Phase II studies in total knee replacement, ROXI-VTE-I and ROXI-VTE-II were randomized, open-label, active-controlled trials designed to evaluate the efficacy and safety of our Factor XI antibodies, administered as a single dose at 12 to 24 hours post-surgery versus standard of care anticoagulants, dosed starting at 12 to 24 hours post-op, as recommended, with mandatory venogram imaging of the leg veins at up to 12 days post-surgery.

The primary endpoint was adjudicated VTE through day 12 with enoxaparin as the primary comparator and apixaban as an exploratory calibrator arm in the ROXI-VTE-I study only. The principal safety outcome was major or clinically relevant nonmajor bleeding. The primary endpoint analysis for ROXI-VTE-I and II used a Bayesian approach, defining superiority if the posterior probability exceeded 95%. These results, which were published in The Lancet concurrently with the AHA presentation, support the predicted efficacy of both antibodies and validate our dual approach.

Pooled analysis confirm predicted efficacy differences between our catalytic and A2 antibodies. Our catalytic antibody demonstrated a numerically lowest VTE rate compared to both apixaban and enoxaparin, while the A2 antibody demonstrated a numerically lower VTE rate compared to enoxaparin.

There were no major or clinically relevant nonmajor bleeds in any arm of either study.

Minor bleeding and transfusion rates were low and comparable across groups and were in line with expected rates in the operative setting. No serious adverse events were attributed to study drug.

We expanded our early development program to evaluate Factor XI inhibition in additional indications beyond postsurgical VTE prevention.

Let's now walk through preliminary data from ROXI-CATH and our GI bleed studies. The ROXI-CATH study evaluated our A2 and catalytic antibodies in patients with indwelling catheters, a population at risk for catheter-associated thrombosis. With over half of participants enrolled at the time of this analysis, we have mostly cancer patients who have high thrombotic burden.

In this study, patients with peripherally inserted central catheters or PICC lines, were administered a single dose of either the A2 antibody, the catalytic antibody or placebo at the time of catheter placement and then monitored for two weeks with ultrasound imaging for the presence of clot on the catheter.

Interim results at 50% enrollment show promising efficacy for both antibodies, with the catalytic antibody achieving a 66% relative risk reduction in clot detection versus placebo and the A2 antibody showing a 47% reduction versus placebo.

These interim results represent the strongest evidence to date supporting Factor XI inhibition in a setting beyond postoperative VTE prevention and provide a compelling rationale to advance into Phase III trials that will evaluate prevention of cancer-associated VTE as well as PICC and other contacts related thromboses, areas were more effective options with lower bleeding risk are needed.

Moving on to the second set of new data, which provides further insights into the safety profile of our dual antibody approach. These data are from a Phase Ib study that was conducted in healthy volunteers to quantify subclinical gastrointestinal bleeding risk with aspirin therapy, a common background treatment that can increase bleeding risk, either alone or in combination with a DOAC or one of our Factor XI antibodies.

Participants were randomized to receive aspirin alone, aspirin plus rivaroxaban, a Factor Xa DOAC, or aspirin plus one of our Factor XI antibodies. Using fecal occult blood testing, the study measured incremental blood loss over baseline.

Adding the catalytic or A2 antibody to background aspirin did not increase bleeding risk compared to aspirin alone.

In fact, a pooled analysis showed a 14% lower bleeding signal for our Factor XI antibodies combined with aspirin compared to rivaroxaban plus aspirin, reinforcing the favorable safety profile of our Factor XI antibodies. These findings support our hypothesis that our Factor XI antibodies are associated with substantially reduced bleeding risk compared to DOACs, which we believe will also be demonstrated across all of our planned Phase III indications.

Now turning to our Factor XI development plan. With strong genetic, preclinical, and early clinical data, we've initiated a broad pivotal development program spanning multiple indications, including VTE prevention post total knee replacement, prevention and treatment of cancer-associated VTE, stroke prevention in atrial fibrillation, PICC-associated thrombosis, and peripheral arterial disease post revascularization.

For stroke prevention, we evaluate both patients who are eligible for DOAC therapy and those who are not. Noncandidates for DOACs include individuals with a history of bleeding events or those identified as having a high bleeding risk as determined through shared decision-making with their physicians.

Each indication in our Phase III program is prioritized based on the strength of genetic, preclinical and early clinical validation. We start with those supported by the most compelling evidence and progressively expand into more exploratory settings, guided by our data-driven approach. Indications depicted on the slide are the initial indications that we plan to advance.

The development program has the potential to expand into additional areas as we generate more data. Such as secondary stroke prevention or other conditions for which DOACs are currently indicated. The catalytic antibody is being pursued across all indications while the A2 antibody is focused on settings with the highest bleeding risk, aligning with their mechanisms of action and enabling a tailored approach to patient needs.

Enrollment is underway in several trials with pivotal readouts for post total knee replacement VTE expected starting in 2027, creating a potential fast-to-market opportunity.

With that, I will pass the call back to Ryan for a discussion of the commercial opportunity and closing remarks.

Ryan Crowe - Regeneron Pharmaceuticals Inc - Senior Vice President-Investor Relations

Thanks, David. Our preclinical and clinical data generated to date as well as our genetic findings position Regeneron to compete in established anticoagulation markets and unlock new segments where bleeding risk has limited adoption, creating the potential for a significant long-term growth opportunity.

Our dual antibody strategy enables us to address a wide range of patient needs. The Cat antibody is being pursued broadly, while the A2 antibody is reserved for patients with higher bleeding risk sensitivity. By tailoring our Factor XI antibodies to distinct patient needs, we can address both high potency and high safety segments, differentiating our program from competitors and maximizing the number of addressable patients.

Patients undergoing total knee replacement face significant risk of venous thromboembolism. With nearly 2 million procedures annually in the US, even a single dose intravenous therapy could represent a meaningful opportunity to simplify adherence and improve real-world outcomes. Regeneron's Factor XI program is the only one in Phase III for orthopedic venous thromboembolism prophylaxis in the US, aiming to deliver next-generation anticoagulation with strong efficacy and a better bleeding profile for standard and high-risk patients.

Moving to cancer-associated venous thromboembolism. Patients with cancer face a markedly elevated risk of venous thromboembolism, up to 50 times higher than the general population, making thrombosis the second leading cause of death in these patients only after cancer progression itself. Despite guidance recommendations, primary prophylaxis remains highly underused and current options for secondary prevention carry significant bleeding risk.

With nearly 1 million US patients annually affected by cancer-associated thrombosis, a biweekly Factor XI therapy administered with an at-home auto injector with a favorable safety profile could transform care and unlock a multibillion-dollar market. Regeneron's program is uniquely positioned to address both primary prophylaxis and secondary prevention, offering tailored anticoagulation for this high-risk population.

Next, atrial fibrillation is a leading cause of stroke with patients up to 5 times more likely to experience a stroke compared to the general population. Despite the availability of DOACs, only about half of eligible patients receive anticoagulation therapy, primarily due to bleeding concerns.

With an estimated 8 million atrial fibrillation patients in the US by 2036, biweekly self-administered Factor XI therapy delivered via autoinjector that maintains efficacy while minimizing bleeding risk could significantly expand treatment adoption and unlock a multibillion dollar market.

Regeneron's program is designed to serve both DOAC candidates and noncandidates, offering a broad approach to stroke prevention. Finally, peripheral artery disease, or PAD, patients undergoing lower extremity revascularization faced a high risk of major adverse limb events.

Yet, anticoagulant use remains extremely low, only around 4% due to bleeding concerns. With more than 300,000 US patients receiving revascularization annually, an alternate to current therapies with a lower bleeding risk could transform outcomes and unlock a $1 billion-plus market opportunity. Regeneron's program is the only one evaluating Factor XI inhibitors in this setting, aiming to deliver next-generation anticoagulation that reduces limb complications [with a] favorable safety profile.

Now moving to some closing remarks before taking questions. Regeneron's tailored factor XI approach is designed to meet diverse patient needs across a range of thrombotic conditions. 2027 marks a key inflection point with pivotal data expected in post-TKR-VTE. This could enable us to pursue a fast-to-market path, establishing a foothold in orthopedic venous thromboembolism prophylaxis.

Beyond VTE, the program aims to compete with DOAC in established markets like atrial fibrillation, while also expanding into underutilized segments, including DOAC noncandidates, cancer-associated VTE, PAD, and PICC associated thrombosis. This differentiated strategy positions Regeneron to build a new class of anticoagulants, with the potential to deliver strong efficacy, reduced bleeding risk, and simplified dosing across multiple indications.

This concludes our prepared remarks. Thank you for your attention. We will now open the call for Q&A.(Conference Instructions). We ask that you limit your questions to the scope of this call, our Factor XI development program. Shannon, can we please go to our first question.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions)

Brian Abrahams, RBC Capital Markets.

Brian Abrahams - RBC Capital Markets Inc - Managing Director

Hey, good morning. Thanks for taking -- for hosting this and for taking my question. Just maybe a question on the ROXI-VTE studies. I noticed that both antibodies appeared to lower both the major VTE rate and the rate of proximal DVT.

So just kind of wondering if there's -- what the implications of that might be in terms of potential to ultimately be superior to the Factor Xs. And then just along those lines, we noticed also that there was maybe a little an outlier for patients enrollment from Latvia. Just wondering if, once you corrected for that outlier, what the results of the second study would have been?

David Gutstein - Regeneron Pharmaceuticals Inc - Vice President and Global Program Head, Hematology

Thank you for the question. So the question around how would we compare against DOACs with our antibodies. So you can see that the efficacy of the catalytic antibody is numerically superior to both of the benchmarks that we used: enoxaparin, a low-molecular-weight heparin, and apixaban, which is a Factor Xa DOAC. And this is very encouraging. It's also consistent with some of the competitor data out of the Factor XI space.

So consistently, Factor XIs are performing very well in this model of post TKR venous thromboembolism prevention. The A2 antibody interestingly came in right along the lines of the standard of care comparators, enoxaparin and apixaban, which suggests that Factor XI is playing a major role in this process.

By blocking Factor XI completely with the catalytic, we're generating the best efficacy you're seeing, and the A2, which blocks specifically XIIa activation of XI is still achieving comparable efficacy to standard of care in this setting. So this is really novel and very exciting finding supporting Factor XI in this space.

We were not powered to generate formal significance against apixaban, but clearly numerically we're comparing very favorably. In terms of the regional differences in terms of how we recruited this study... These findings were consistent geographically. So we did have a fair number of patients coming in from Eastern Europe and the results there were consistent across the study.

George Yancopoulos - Regeneron Pharmaceuticals Inc - President, Chief Scientific Officer, Director

And I think it's worth just emphasizing something that both David and Andre pointed out, which is, in this field, it's not really efficacy which is the major driver of use, or moreover of lack of use. It's really the risk of bleeding. And so the most powerful anticoagulants are not really used in these spaces. Why? Because the surgeons and the patients don't want to risk the bleeding.

So as both Dave and Andres pointed out, if we can deliver agents that have comparable efficacy, let alone even better, but just comparable in the ballpark to see, but with much lower rates of bleeding, this will really open up the opportunity to the vast majority, the vast majority of patients who are not getting the most powerful anticoagulant.

So let me remind you, in the United States, the standard of care in this thing is aspirin, okay? Why? Not because they're driving for the strongest anticoagulant because they're so afraid of the bleeding. And I think this is something that a lot of people are missing. That in this field, what is driving lack of use, which is really the problem, we could be saving a lot of events, and even a lot of lives, if we could use these agents more broadly. But, without this risk of bleeding, which can also lead to catastrophic events, and that's the whole value proposition here.

As you're seeing, we have agents. They may even be better, but they're certainly comparable to the standards of care. And as you heard, the genetics and so forth are arguing this is a much safer pathway that can really open up enormous opportunities in this setting that we're talking about post total knee replacement as well as other settings as well, where the powerful agents are not being used.

Ryan Crowe - Regeneron Pharmaceuticals Inc - Senior Vice President-Investor Relations

Okay. Thank you, George and David. Shannon, let's move to the next question, please.

Operator

Tyler Van Buren, TD Cowen.

Tyler Van Buren - Cowen and Company LLC - Analyst

Hey guys, thanks very much for the presentation. Certainly, a lot to consider across the indications. But I guess based upon George's comments just now, do you guys ultimately expect the safer A2 domain antibody to be the larger product? And what do you think needs to be shown in terms of improvement in bleeding in the pivotal trials? Is there a numerical bar you're looking for? Or will it be powered for statistical significance?

George Yancopoulos - Regeneron Pharmaceuticals Inc - President, Chief Scientific Officer, Director

Well, we will require larger studies to really understand and see bleeding risk. Right now, it is actually quite possible that the catalytic antibody has very little, if any, bleeding risk. That is the dream scenario because it is, as you've just seen, potentially one of the most powerful anticoagulants that one could be using.

However, for those patients in those individuals. If there's any bleeding risk at all, they may choose to use an agent that might have a little less anticoagulation capability, but might have itself no bleeding risk. So the data will speak to it, but this is why we're trying both agents, not because we prospectively are even sure which profile will fit which patient.

But this will allow, based on the data, physicians and patients to make their choices and what could be better? I mean if you've treated patients in this area and so forth, you would know that one of the first questions that physicians and the patients are always grappling with, well, the risk of clotting? Oh, the risk of bleeding, what should we do?

And as we said, in some of these settings, they settle for aspirin, okay? So having two choices here based on the data will open up, we believe, really unanticipated opportunities in so many different settings. And in many settings where these agents are not utilized at all. I mean Ryan didn't even talk about the commercial opportunity in terms of central catheters, which is another very, very huge opportunity.

Once again, there's millions of patients in the United States that utilize these. And very often, it's a serious procedure to replace one of these. And of course, once it clots, it's associated with many risks and problems as well. So just being able to deal with the millions of patients in preventing having to replace these because they clot and cause problems with the patients, would provide enormous new benefit in a major unmet space. Why aren't they used here -- because of the risk of bleeding.

So we have really two shots on goal to balance the risk profile as judged by the physician and patient tailored to each particular situation, we think this really has the opportunity to entirely change the field of how anticoagulants are used across so many fields of medicine where right now, they could be used, but they're not being used.

Ryan Crowe - Regeneron Pharmaceuticals Inc - Senior Vice President-Investor Relations

Okay. Let's move to the next question please, Shannon.

Operator

Dave Risinger, Leerink Partners.

David Risinger - Leerink Partners LLC - Analyst

Thanks very much and thanks for hosting this session today. So how do you think about the magnitude of Factor XI inhibition that is required to match Factor Xa apixaban efficacy in atrial fibrillation. And can you please reframe the inhibition that 7508 delivers relative to 9933?

David Gutstein - Regeneron Pharmaceuticals Inc - Vice President and Global Program Head, Hematology

Thanks for that question. So the level of Factor XI inhibition that it will take versus Factor Xa; a couple of points. First of all, we're entering into cardioembolic stroke or atrial fibrillation based on the strength of the human genetic data very clearly showing that Factor XI deficiency is associated with protection against cardioembolic stroke to the same degree as venous thromboembolism, showed very strong data there.

Now Factor XI, this mechanism gives us the advantage because we know that the bleeding signal with complete Factor XI deficiency is very well characterized in -- through the epidemiology of Factor XI inhibition, or deficiency rather, that we know what that phenotype looks like.

And it's basically a modest bleeding phenotype, mostly with provoked bleeding. It is there, but it's nothing compared to complete factor deficiency of Factor X or the other factors that are associated with more severe hemophilias that are associated with spontaneous hemorrhage. In other words, we can completely inhibit Factor XI, and we could top out on the bleeding risk in a way that we'd be very acceptable in terms of patient management.

Factor Xa, you can't do that. So for Factor XI, the goal of our program is to completely inhibit Factor XI throughout the treatment period and to achieve the maximal efficacy through this mechanism. We can do this with the catalytic because we achieved near complete or complete inhibition of Factor XI in a way in which none of the competitors do.

So we have the strongest mechanism in order to do that. So the catalytic antibody 7508 as you mentioned, can completely inhibit Factor XI with what we're seeing so far is an acceptable bleeding profile. Factor Xa, you can't completely inhibit the Factor because of this bleeding risk.

Even at clinically relevant doses of DOACs, we're seeing unacceptable bleeding in the stroke prevention in Afib space to the point where it's estimated up to half of the people who should qualify for anticoagulant therapy are not being treated. And even those half that are being treated may be treated with lower doses or may have to stop because of bleeding complications. So this is a major area of medical need that we're seeing Factor XI space as potentially being able to address.

George Yancopoulos - Regeneron Pharmaceuticals Inc - President, Chief Scientific Officer, Director

I don't want to sound like a broken record. Based on that question, I just have to point it out again. There's many ways to win in terms of providing more benefits to the community here. One is, of course, we may actually produce better anticoagulation, but we don't have to. If we achieve similar anticoagulation, but a much lower bleeding risk, it will provide enormous benefit to this whole community and will dramatically increase use.

Not only will it be used with comparable efficacy in the patients who are already taking a DOAC, but it will also be utilized in those 50% of patients who are not taking anything, even if we don't have as good efficacy, but if the bleeding risk as the genetics suggest is much lower, then once again, it will provide another option for the patients already on a DOAC. But of course, it will provide an option for the many patients, 50% or more, who're not taking any of these agents right now. So there's multiple ways here of winning in terms of delivering much needed important benefit to patients.

Ryan Crowe - Regeneron Pharmaceuticals Inc - Senior Vice President-Investor Relations

Let's move to the next question, please, Shannon.

Operator

Geoff Meacham, Citi.

Ross Fladeland Citi Research - Associate Analyst

Hi guys, It's Ross on for Geoff. I guess our question is, what was the latest timeline for the development of the subcu formulations of the inhibitors? And also, both 9933 and 7508 will be advanced for subcu?

David Gutstein - Regeneron Pharmaceuticals Inc - Vice President and Global Program Head, Hematology

So in our major indications that we're looking at, and we have already profiled for you the major Phase III programs that are going forward. We are taking forward in the postoperative space an IV formulation because after total knee, that's a single injection after the operation, but we are testing subcu there as well. So we're prepared now to take forward the subcu. In the cancer space, that's going to be subcu dosing.

And then in the atrial fibrillation space, that's subcu dose as well. For the catheter study that George mentioned, that's going to be dosed initially IV, but subsequent dose is subcu. And then for peripheral arterial disease, that's a subcu formulation as well. So we're prepared to take forward now, actually, we have studies ongoing with the subcu formulation. And then, both 9933 and 7508 are prepared to go forward with subcu very shortly as well.

Ryan Crowe - Regeneron Pharmaceuticals Inc - Senior Vice President-Investor Relations

Thanks, David. Next question, please.

Operator

Simon Baker, Rothschild & Company Redburn.

Simon Baker - Rothschild & Company Redburn - Analyst

Thank you for taking my question and thanks so much for hosting this call. In the Lancet paper that was published with this data, the authors highlight the potential for 9933 in preventing medical device triggered clotting, which is induced by Factor XII auto-activation. Is that an area of interest, it doesn't appear explicitly in the development program. I'm wondering if maybe by prespecified subgroups, you might be able to assess that in some of the studies. But any thoughts on the attractiveness of that would be much appreciated.

David Gutstein - Regeneron Pharmaceuticals Inc - Vice President and Global Program Head, Hematology

Yes. Thanks for the question. We're very interested in the area of contact mediated or medical device initiated thrombosis. This is an area where it's underserved in a major way through ongoing activity. And we're looking to address it directly. We have an ongoing Phase II, as we've shown you the initial data in PICC-associated thrombosis or catheter-associated thrombosis. And we are looking to extend those findings into Phase III as well.

So that's our first entry into the device-mediated thrombosis space. After this, there is a number of indications, including those in which you see much higher acuity. So we really want to have, again, this stepwise approach in which we're generating the validation data and then moving to expand into these areas. And this is part and parcel of that strategy.

After we establish efficacy here, you get into the higher acuity indications within the medical device space, sicker patients. A lot of times, they're dependent on warfarin or heparin for anticoagulation, which carry a very high bleeding risk. So there's a lot of need here, again, focused on the need for bleeding and where we think we can address it with Factor XI, which sits at the proximal point of the contact-activated coagulation pathway and could be a really great solution here for achieving efficacy and substantially reducing bleeding risk.

Ryan Crowe - Regeneron Pharmaceuticals Inc - Senior Vice President-Investor Relations

Thank you, David. Next question, please, Shannon.

Operator

Evan Seigerman, BMO Capital Markets.

Malcolm Hoffman BMO Capital Markets - Associate Analyst

Hi, Malcolm on for Evan. As a part of The Lancet paper published in the discussion highlighted that all agents assessed, including 9933, enoxaparin, apixaban, and 7508 all appear to be reasonably safe from a bleeding perspective. In the context of the knee replacement when you're considering the ROXI-ASPEN and APEX trials, are there specific patients you believe may be more vulnerable for VTE that you could highlight differences with 7508 for improving that bleeding risk. I appreciate it.

David Gutstein - Regeneron Pharmaceuticals Inc - Vice President and Global Program Head, Hematology

Thanks for that question. So in the VTE space, the postoperative VTE space, you're seeing in our Lancet paper that we did not see major or clinically relevant nonmajor bleeding across any of the study arms and differentiating on bleeding in this setting is going to be very difficult.

You've seen how we've tried to assess this in the Phase II space with our GI bleeding study and looking at -- and in that study, the GI bleeding study, we are not seeing an increase in bleeding risk with our antibodies on top of aspirin versus aspirin alone. The DOAC in that setting plus aspirin did increase bleeding versus aspirin alone and versus our antibodies on top of aspirin.

So you're seeing some of the supporting data there. In addition, ROXI-CATH, these are sicker patients. The catheter study is mostly cancer, but it also includes long-term antibiotic and parenteral nutrition patients. And these carry a higher risk of bleeding and in these patients we're going to do a full assessment of bleeding.

Again, this is just the interim data that you're seeing here. We had to do a full assessment once we have completed enrollment here. And so that's going to allow us to further flesh out the risk benefit for Factor XI inhibition in this space.

Going forward, again, across all of these indications, you're going to see a much better idea of the risk in terms of bleeding, and how 9933 / A2 mechanism may differ from the catalytic in terms of their profile and bleeding. We expect both of those antibodies are going to be substantially better than the current standard of care and one or the other of the Factor XI mechanisms may be more appropriate, depending on the specific patient cohort.

And just one further mention, you may have noticed that our Phase II ROXI-ATLAS study in atrial fibrillation patients has initiated and that is a study that's primarily looking at bleeding risk in the patients. So again, a lot of data coming in on bleeding.

George Yancopoulos - Regeneron Pharmaceuticals Inc - President, Chief Scientific Officer, Director

I think that what we should just once again provide a little bit of an overview here, which is that in these very small studies, you're not going to see bleeding with any of these agents with knee replacement. But when one looks at these large data collections, real-world analysis and so forth, these occur at the several percent level, which means when you have several million knee replacement, hip replacements a year, that corresponds to tens of thousands, hundreds of thousands of patients who are now undergoing serious bleeding events, which is what concerns obviously the surgeons as well as their patients.

And this is why since in these small initial studies, we can't see the differences, but we know they are there with the other agents, what -- the program have been trying to do, as David explained, is do these provoked bleeding studies, the data that we've shown you that shows that relatively in comparison these new Factor XI agents seem to have less associated bleeding that should be revealed in the much larger studies.

So we're using the provoke bleeding to support the genetics profiles and all the signs that you've heard, which will suggest that when you get to treating millions of patients, you now have the potential to save tens of thousands or hundreds of thousands of bleeding events per the millions of patients who undergo these operations every year.

And that's why they are not used. Not because you see bleeding in studies that have 50 or 100 patients, but because you see them when you're dealing with millions of patients a year, which is what we do as a medical community right now in the United States.

Ryan Crowe - Regeneron Pharmaceuticals Inc - Senior Vice President-Investor Relations

Okay, thank you, David and George. Shannon, we have time for two more questions, please.

Operator

William Pickering, Bernstein.

William Pickering - Sanford C Bernstein & Co LLC - Analyst

Hi, thank you for taking my question. In AFib, could you elaborate on the rationale for the development plan? It looks like the Phase II ATLAS study is going to complete after the Phase III EVEREST already starts. So just how will you use the info that you learned from ATLAS? Thank you.

David Gutstein - Regeneron Pharmaceuticals Inc - Vice President and Global Program Head, Hematology

So the Phase II ATLAS study, as you point out, has initiated already. And we are looking to initiate our noncandidate study and the candidate study EVEREST in partial parallel to the ATLAS study. So ATLAS plays a number of roles here in supporting the study. First of all, ATLAS is going to give critical information in terms of flushing out the risk/benefit with regard to bleeding risk.

The primary endpoint for this study is bleeding. We're focused on bleeding risk in the study, and that's going to give very important supportive data not only for atrial fibrillation, but also for the other programs that we're looking to potentially submit before we come to submission with atrial fibrillation.

So, very important supportive data. In terms of the atrial fibrillation program specifically, we are planning to have an interim in ATLAS to look at the bleeding profile there before initiating EVEREST. So ATLAS is going to give important information prior to the initiation of [EVEREST].

Ryan Crowe - Regeneron Pharmaceuticals Inc - Senior Vice President-Investor Relations

Thank you, David. Let's move to our last question, please, Shannon.

Operator

Chris Schott, JPMorgan.

Taylor Hanley - JPMorgan Chase & Co - Analyst

Hi, this is Taylor Hanley on for Chris. So we were hoping to touch on, I guess, the broader Factor XI development landscape. And we are expecting data from upcoming Phase IIIs from some of your competitors Bayer and Bristol. I'm just wondering, would any success or setbacks with those trials change how you'd approach your development programs? And how can you apply any of the learnings from their programs to your development program? Thank you.

David Gutstein - Regeneron Pharmaceuticals Inc - Vice President and Global Program Head, Hematology

Thanks for the question. We do have a very busy competitive space, and that's important. We feel that our agents achieve greater target engagement and effect on Factor XI than any of the competitors. So that's an important piece here, bringing forward a best-in-class compound in the catalytic antibody.

And then our A2 antibody in our in vitro studies has generated comparable effects to the competitors in terms of clot suppression. But mechanistically, it only hits the A2 domain, meaning that you have a differentiation potentially on the bleeding side. So the competitive data that's coming out, I believe the first set of data may be asundexian next in secondary stroke. This is going to be really important for the field to see what is the safety profile look like in this large study on top of aspirin in these patients.

Secondly, are we seeing an efficacy signal in secondary stroke compared to placebo? And this is -- so these are very important pieces that we're looking at in terms of the validation for going into arterial clot; milvexian after that one, looking at two large arterial indications, including MI in

secondary stroke plus their atrial fibrillation in candidates only. And then we have abelacimab as well, who we're seeing in cancer treatment and in noncandidates for anticoagulation in atrial fibrillation.

So all of these data reading out are going to give critical information in terms of validation. But within the context that, you're looking at with our catalytic antibody, a superior target engagement. And again, we're dosing our antibody with the goal of achieving complete targeting engagement throughout the treatment period. Which is going to be very hard to achieve with some of the competitors. So again, validation data, but within the context that we think we're bringing forward a best-in-class for this target.

George Yancopoulos - Regeneron Pharmaceuticals Inc - President, Chief Scientific Officer, Director

Remember, as David explained before, the small molecules like asundexian will not be able to achieve as complete Factor XI-specific inhibition, but it will also have off-target effects, which will increase bleeding. So it'd be very hard to read through their data. If they have less efficacy, it could be attributed to the fact that they are less well inhibiting the target -- the specific target, if they have more bleeding, that could be attributed to the fact that they inhibit other proteases in these cascades as well. So we will be integrating the data and trying to understand what it means, but it will not be directly reading necessarily on our program.

Ryan Crowe - Regeneron Pharmaceuticals Inc - Senior Vice President-Investor Relations

All right. Thank you, David and George. Unfortunately, that is all the time we have for today. Thanks to everyone who dialed in for your interest in Regeneron and our Factor XI program. We look forward to seeing next Regeneron Roundtable on December 10, where we plan to showcase the opportunities we have with in multiple myeloma and precursor conditions. Thank you once again and have a great day.

Operator

This concludes today's conference. Thank you for your participation. You may now disconnect.
