REFINITIV STREETEVENTS

EDITED TRANSCRIPT

REGN.OQ - Regeneron Pharmaceuticals Inc to Host Investor Call

EVENT DATE/TIME: DECEMBER 14, 2023 / 1:30PM GMT

OVERVIEW:

Company Summary

REFINITIV

CORPORATE PARTICIPANTS

George D. Yancopoulos Regeneron Pharmaceuticals, Inc. - Co-Founder, President, Chief Scientific Officer & Co-Chairman

L. Andres Sirulnik Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences, Hematology

Ryan Crowe Regeneron Pharmaceuticals, Inc. - VP of IR

CONFERENCE CALL PARTICIPANTS

Carter Lewis Gould Barclays Bank PLC, Research Division - Senior Analyst

Christopher Joseph Raymond Piper Sandler & Co., Research Division - MD & Senior Research Analyst

David Reed Risinger Leerink Partners LLC, Research Division - Senior MD

Hartaj Singh Oppenheimer & Co. Inc., Research Division - Research Analyst

Nicole Germino Truist Securities, Inc., Research Division - Associate

PRESENTATION

Operator

Welcome to the Regeneron Pharmaceuticals ASH 2023 Investor Conference Call. My name is Shannon, and I'll be your operator for today's call. (Operator Instructions) Please note that this conference is being recorded.

I will now turn the call over to Ryan Crowe, Vice President, Investor Relations. You may begin.

Ryan Crowe - Regeneron Pharmaceuticals, Inc. - VP of IR

Thank you, Shannon. Good morning, good afternoon, and good evening to everyone listening around the globe. Welcome to Regeneron's ASH 2023 investor call.

I'd like to remind you that remarks made on today's call may include forward-looking statements about Regeneron's business and research and development programs, anticipated milestones, and regulatory matters. Each forward-looking statement is subject to risks and uncertainties that could cause the actual results and events to differ materially from those projected in that statement. A more complete description of these and other material risks can be found in Regeneron's SEC filings. Regeneron does not undertake any obligation to update publicly any forward-looking statements, whether as a result of new information, future events or otherwise.

Joining me today are Dr. George Yancopoulos, Board Co-Chair, Co-Founder, President and Chief Scientific Officer; and Dr. Andres Sirulnik, Senior Vice President, Hematology Clinical Development. On today's call, George will provide an overview of our progress toward becoming a global oncology and hematology leader, as well as a novel treatment approach for controlling severe allergy for which pre-clinical data was published yesterday in the Science Translational Medicine Journal. Andres will then provide select updates across our hematology clinical pipeline, which includes programs that are in varying stages of clinical development. Hematology is becoming a bigger part of Regeneron's pipeline, as demonstrated by the approximately 20 presentations across 6 investigational medicines at this year's American Society of Hematology Conference, as well as other recent clinical data updates. After our prepared remarks, we'll open the call for Q&A.

I'll now pass the call over to George. Go ahead.

George D. Yancopoulos - Regeneron Pharmaceuticals, Inc. - Co-Founder, President, Chief Scientific Officer & Co-Chairman

Thank you, Ryan, and thanks to everyone who is joining today's call. Next slide. Thank you. Before we focus specifically on the recent clinical advancements and data updates in hem-onc and hematology, I'd like to first discuss Regeneron's overall strategy and progress towards developing important breakthroughs in oncology and immuno-oncology.

We are applying more than 3 decades of scientific innovation in developing medicines that have the potential to advance the standard of care for patients with cancer. Our oncology portfolio is built around 2 foundational approaches: so-called conventional antibodies, including our approved PD-1 inhibitor, LIBTAYO, and other checkpoint inhibitors, as well as our investigational bispecific antibodies, in particular, 2 different classes of bispecific antibodies, CD3 bispecifics, and costim bispecifics. All of these are being evaluated both as monotherapies and in logical combinations to address a variety of challenges. Together, our pipeline provides us with unique combinatorial flexibility to develop potentially synergistic treatments for a wide range of solid tumors, blood cancers, but a variety of other medical conditions as well. As I said, our hematology-oncology research is focused likewise on antibodies and bispecifics that are being investigated as monotherapies and in various combinations. Within classical hematology, our research and collaboration to develop potential treatments include explorations in -- with antibody medicines alone and in combinations with siRNAs, gene editing and gene knockout technologies.

Next slide, please. Today, we're going to discuss our programs across -- our progress across many clinical programs. Hematology is becoming an ever-increasing part of Regeneron's robust and differentiated pipeline, now with 10 programs in clinical development and 1 approved product. With the technology and capabilities to discover new targets and potentially combine agents to maximize potency utilizing various modalities, including the antibodies, the bispecifics, siRNA, CRISPR, as well as gene insertion efforts, we see our hematology efforts continue to be a larger part of our overall clinical efforts in the year to come.

Today, Andres will discuss data presented at ASH and covered in recent press releases for linvoseltamab in multiple myeloma and odronextamab in lymphoma. Both assets are in late-stage development for relapsed and refractory patients, and we are simultaneously in the process of evaluating these antibodies in earlier lines of treatment. Andres will also discuss our broadening C5 complement opportunity using the world's first antibody plus siRNA combination. Andres will also share some new groundbreaking data in PNH from an exploratory cohort from our ongoing Phase III trial. The data further increases our confidence in the combination's unique clinical profile, supports broadening our development strategy for complement mediated diseases, and using this innovative antibody siRNA combination approach to address other diseases with high unmet need as well. Finally, we will be highlighting some of our exciting clinical assets that are in various stages of early development within our expanding hematology pipeline. These include our Factor XI antibodies in thrombosis, our TMPRSS6 antibody for iron overload deficiencies, and our CRISPR gene editing and gene insertion efforts in ATTR and hemophilia B.

Next slide, please. Before I turn it over to Andres, let me take a moment to highlight a very recent publication that was featured just yesterday on the cover of Science Translational Medicine that speaks to our efforts to potentially cure allergy using novel combination approaches. What I'll tell you will highlight how we intelligently try to mix and match the right reagents to really make a difference in unaddressed medical situations. In this particular case, this combination will involve one of the bispecifics that Andres will highlight in our efforts in multiple myeloma as well. This exciting project in allergy has been many years in the making, and I am pleased to introduce it today.

We believe that combining our very successful medicine, DUPIXENT, which is the world's leading biologic for a variety of allergic conditions -- it's approved in asthma, atopic dermatitis, eosinophilic esophagitis, nasal polyps, as well as other conditions. But by itself, though it addresses these allergic conditions, it doesn't cure allergy itself. But we realized and just announced that we believe that by combining DUPIXENT with our investigational BCMAxCD3 bispecific, we could potentially address and potentially cure severe allergies by eliminating the supply of a specific antibody type produced by the immune system known as immunoglobulin E, which is known to be the key driver of allergic conditions such as severe food allergies, which are increasing in prevalence and in severity.

The persistence of IgE in atopic patients is partly due to long-lived IgE-producing plasma cells that maintain serological memory to allergens, as was actually realized and described by our scientists a couple of years ago. The good news is that these long-lived IgE-producing plasma cells found in the bone marrow could be susceptible to plasma cell targeted therapeutics, which is where our BCMAxCD3 bispecific, linvoseltamab, comes in. As you can see from the charts on the right side of this Slide #7, treatment with linvoseltamab over a fixed duration can rapidly deplete long-lived plasma cells, thereby transiently eliminating IgE. The problem with using this BCMAxCD3 bispecific alone is that as soon as you stop treatment,

these IgE-producing plasma cells get quickly reconstituted from memory cells. However, these memory cells to produce IgE have to undergo class switch, which is driven by interleukin-4 and interleukin-13, which are blocked with DUPIXENT. So, by first, eliminating the cells with the BCMAxCD3 bispecific, and then permanently blocking IL-4 and IL-13 signaling with DUPIXENT, we can specifically block the class switching to IgE and cause persistent reduction in IgE levels and prevent the generation of new IgE-producing cells and thus eliminate the allergy-causing cells and keep them from coming back. These results are very exciting, and we are planning to start a clinical program in the coming year, exploring the combinatorial approach of linvoseltamab treatment over a fixed short duration, followed by continued maintenance treatment with DUPIXENT in patients with severe food allergies.

So, with this example of how we combine our innovative agents to address unmet medical need, I'd like to turn over the call to Andres, who will provide a comprehensive overview on -- update on our hematology-oncology as well as our classical hematology portfolio. Andres?

L. Andres Sirulnik - Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences, Hematology

Thank you, George, and thank you to everyone joining the call today. Let me continue the discussion on linvoseltamab, where we highlight some recent data in multiple myeloma. At the recent ASH Meeting, we presented longer-term data from the ongoing LINKER-MM1 trial in patients with relapsed/refractory multiple myeloma. The median duration of follow-up for those data was approximately 8 months. In a separate press release on December 7, we also announced the updated registration-enabling data from this pivotal trial with longer-term median follow-up of 11 months. This dataset will underpin our BLA filing, which is planned for later this month, and the MAA submission, which is -- we have planned in the first half of next year. We will briefly touch upon this data over the next few slides, as we are confident in linvoseltamab as a potential best-in-class BCMA bispecific and are continuing development in early lines of therapy.

Starting with efficacy, linvoseltamab demonstrated deep and durable response rates in patients with relapsed/refractory multiple myeloma, even in those patients with difficult-to-treat disease. At the primary analysis with a median follow-up of 11 months, a 71% objective response rate was observed in patients treated at a dose of 200 milligrams, as assessed by an independent review committee, with 46% of patients achieving a complete response or better. Importantly, as the graph depicts, we continue to see a [trend] of responses deepening over time with longer-term follow-up. These response rates and complete response rates represent the highest observed across the BCMA bispecific class. Responses occurred early, deepened with time and have shown durability. The median time to achieve a partial response or better was rapid, at 1 month. Patients achieved a very good partial response or better after a median of 2.6 months, with a median time to complete response or stringent complete response of 7.6 months. The median duration of response had not been met at 8 months of follow-up.

Linvoseltamab showed a generally manageable safety profile with infection being the most commonly reported adverse event. Importantly, the majority of patients did not develop CRS, with CRS reported in 46% of patients and most of those being Grade 1 events. We continued to observe that most CRS occurred during the step-up dosing period, most commonly after the first dose and before the first full dose at week 3. There was one Grade 3 adverse event during the step-up dosing, but no other Grade 3 or higher CRS events were observed. For those patients that do experience CRS, it typically occurred and resolved within 24 hours. So, based on the 11-month cut data, linvoseltamab has a compelling and differentiated profile relative to other FDA-approved BCMA bispecifics. As we have indicated, this recent linvoseltamab data cut will serve as the basis for upcoming regulatory filings in the U.S. and in Europe.

In summary, with this differentiated efficacy and safety profile, favorable monitoring schedule and potential for every 4-week dosing, linvoseltamab is posed to be a competitive agent in multiple myeloma, pending regulatory approval.

We are rapidly advancing our clinical development program into early lines of therapy and in multiple myeloma precursor disorders. The LINKER-MM3 confirmatory Phase III study evaluating linvoseltamab monotherapy compared to a current standard of care regimen is enrolling. Trials in early lines of disease are underway or planned. We are initiating trials in precursor multiple myeloma in patients with high-risk smoldering myeloma and MGUS, and we are also planning studies in second-line light chain amyloidosis.

In conclusion, we are rapidly initiating confirmatory studies and advancing studies into early lines of therapy and early stages of the disease.

Now, to odronextamab, where we're presenting data from the Phase II ELM-2 study in both follicular lymphoma and diffuse large B-cell lymphoma. Odronextamab is an off-the-shelf CD20xCD3 bispecific effective in patients with both indolent and aggressive lymphomas. At ASH, we presented data from the final analysis for DLBCL and a prespecified interim analysis for follicular lymphoma, both of which continue to show deep and durable responses and a manageable safety profile. Our BLA for both indications was accepted by the FDA early this year and assigned a PDUFA date of March 31, 2024, supported by our confirmatory Phase III OLYMPIA program. A regulatory decision in Europe is expected in the second half of 2024.

Moving to the data presented at ASH and starting with follicular lymphoma. With 128 patients available for efficacy at the prespecified interim analysis and a median follow-up of 18 months, an overall response rate of 81% was observed in heavily pretreated and highly refractory patients, of whom, 91% achieved a complete response. 73% of all patients achieved a complete response, the highest CR rate observed for these late-line patients across the class. Responses appear to be durable with a median duration of response of 22.6 months and nearly 2 years median duration of complete response. Median PFS was 21 months across all patients. Complete responders achieved a median PFS of nearly 28 months, demonstrating a promising outlook for the many patients who achieved a complete response.

Now, moving to diffuse large B-cell lymphoma, at the final analysis, 127 patients were evaluable for efficacy with a median follow-up of 30 months. The objective response rate in these heavily pretreated, highly refractory patients was 52%, with 32% of patients experiencing a CR. Of note, 61% of patients who responded to therapy experienced a complete response. These responses were durable, particularly in complete responders. The median duration of complete response was 18 months, and the median progression-free survival for complete responders was 20 months. Consistent objective response rates were observed in a prospective study in a separate cohort of post CAR-T patients. This is important because a significant portion of patients are refractory to CAR therapies and currently have limited additional treatment options. We are pleased with the efficacy observed in both follicular and diffuse large B-cell lymphoma, including in post CAR-T patients and believe these results position odronextamab well in a competitive market.

Odronextamab has demonstrated a generally manageable safety and tolerability profile. Our step-up dosing regimen significantly improved CRS with no Grade 4 or 5 CRS events observed in patients using this regimen. Across both follicular and diffuse large B-cell lymphoma, there was 1 low-grade ICANS event reported in a patient -- in a follicular lymphoma patient, which was not associated with CRS. Infections were common, which is to be expected given the heavily pretreated patient population and the mechanism of action of odronextamab. However, most infections were Grade 3 or lower. Overall, odronextamab showed an acceptable tolerability profile, underscored by the significant portions of both follicular and DLBCL patients who completed initial dosing cycles and maintenance of patient-reported quality of life outcomes. This tolerability profile also supports our proposed maintenance dosing regimen, which, per protocol, allows for patients with a durable CR of 9 months or longer to transition from every 2-week dosing to every 4-week dosing, a great benefit to the many patients who are able to achieve a complete response.

Now, we have a broad development plan for odronextamab, with a confirmatory Phase III OLYMPIA program now enrolling patients in early lines of therapy. We are enrolling in studies evaluating odro both with and without chemotherapy and hope to find ways to accelerate timelines for these studies, including using surrogate endpoints to shorten time to readouts. In addition, we are applying our unique CD28 costim platform to potentially improve on the profile of odro by combining it with a CD22xCD28 antibody. This study is now enrolling in diffuse large B-cell lymphoma patients and may provide long-term differentiation and enhanced benefits to patients. We're excited about the prospects of odro in these indications and look forward to our PDUFA date in March and a potential commercial launch shortly thereafter.

Our competitive efficacy and safety profile, including high complete response rates in follicular and consistent diffuse large B-cell lymphoma response rates, regardless of CAR-T experience, allows for unique commercial positioning if approved. The potential launch of odronextamab will allow Regeneron to establish itself in the hematology-oncology market, prepare for a potential launch for linvoseltamab in myeloma, and is one of several important steps forward for the Regeneron oncology commercial organization.

I'd like now to discuss classical hematology, where we have a robust and advancing pipeline across various blood disorders. Let me start with pozelimab and cemdisiran and our C5 program. One increasingly important opportunity we have is our C5 program, as it is the first of its kind combination of an antibody with an siRNA therapeutic for a specific target. Our systemic approach utilizes the combination of pozelimab and cemdisiran to target C5 to inhibit complement activation. The siRNA reduces the production of C5 protein in the liver, where the majority of C5 is synthesized, and the antibody blocks activation of the residual C5 protein in the circulation. We have data to suggest, the combination approach will provide complete, rapid and durable inhibition that is not achievable with other therapies, even at higher doses. We believe complete and

sustained C5 inhibition results in optimal efficacy and better control of breakthrough hemolysis. Also, our antibody plus siRNA combination has the potential for reduced dosing in a highly convenient monthly self-administered subcutaneous formulation.

Here you can see, our C5 program continues to advance with pivotal data readouts across various indications expected in the coming years. Additionally, we are formally announcing today that we intend to move forward with a Phase III program for this combination in geographic atrophy. Today, for the first time, we are presenting 26-week data from an exploratory cohort of PNH patients from our ongoing Phase III trial. Based on these interim results, patients treated with pozelimab and cemdisiran combination achieved a greater control of intravascular hemolysis compared with ravulizumab. The combination, in comparison to ravulizumab, led to average LDH levels of 0.8 versus 1.2x the upper limit of normal with 91% versus 73% of patients maintaining adequate control of hemolysis through week-26. With these first interim Phase III results, a novel combination of pozelimab and cemdisiran led to the normalization of [LDH] levels in almost all patients.

Digging into the data further, here, we present the individual patient data from the exploratory cohort. When compared to ravulizumab, pozelimab and cemdisiran combination demonstrated complete and sustained controls in almost all patients, while more patients in the ravulizumab arm were uncontrolled. This promising PNH data supports accelerated development in PNH and other [complement-mediated] disorders. To date, we have enrolled over 180 patients in our studies and are advancing rapidly. Building upon the evidence of an encouraging data to date for our C5 combination, we are announcing that we are rapidly moving forward to explore a potential systemic approach to geographic atrophy. Recently approved treatment options look to locally inhibit C3 or C5 to help regulate complement activation and slow its downstream effect in the eye. Our approach, using the pozelimab-cemdisiran [combination] seeks to systemically inhibit complement activation, which is associated with vision loss in GA.

We believe our approach has significant and unique advantages over the recently approved agents, as demonstrated in the table on Slide 28. We are rapidly advancing 2 Phase III pivotal trials that will begin in the first half of 2024, with more details to be provided on trial design once final regulatory feedback has been incorporated.

In conclusion, we are excited about the commercial prospects of our C5 combination, which we think could meaningfully improve upon the standards of care across PNH, MG and GA.

Now, I will briefly introduce our efforts in targeting Factor XI for coagulation disorders and our near-term development plans. While the approaches for preventing pathological blood clotting have advanced in recent years, there is still a substantial unmet need for prevention of thrombosis with minimal bleeding risk. Current standard of care, the Direct Oral anticoagulants, or DOACs, are targeting Factor X. They are generally effective at reducing thrombotic events but do carry a serious, potentially fatal bleeding risk. Next-generation anticoagulation efforts, including efforts at Regeneron, are focused on targeting Factor XI. Better anticoagulation agents could expand the market, as well as improve current market penetration seen with DOACs.

Targeting Factor XI is supported by genetic evidence from people with Factor XI deficiency and preclinical data, as well as early clinical data. Furthermore, our clinical results demonstrated that our investigational Factor XI antibodies show higher specificity compared to small molecules [that are] Factor XI inhibitors that are currently in development, as well as more complete Factor XI blockade compared to competitor antibodies in development. Based on this preclinical data and healthy volunteer data, which we are planning to present next year, we decided to advance this program on a rapid path to registration trials starting in 2024 or early 2025. Further support for this approach should come next year when we are hoping to show results of the Phase II proof-of-concept study for REGN9933, evaluated for prevention of VTE, or venous thromboembolism, after knee replacement surgery.

Now, to our TMPRSS6 program in iron overload disorders for which healthy volunteer data were presented at the ASH meeting. Targeting the liver transmembrane protein, TMPRSS6 is a promising strategy for addressing disorders that result in iron overload such as beta-thalassemia. Our TMPRSS6 blocker, REGN7999, improved red cell health and reduced hepatic iron loading in a mouse model of beta-thalassemia. At ASH, we showed that the mechanism of action is replicated in healthy humans. Single ascending doses of REGN7999 caused dose-dependent, rapid, deep and durable reductions in serum iron levels, as you can see in the chart on the right side of Slide 33. We are planning on proceeding with a proof-of-concept study in non-transfusion dependent beta-thalassemia in the second half of 2024. Key unmet need for the iron overload disorders is for therapies

that are more potent, less toxic and more convenient for patients compared to standard of care iron chelators, which carry numerous black box warnings.

Finally, I wanted to briefly address our exciting in vivo gene editing efforts using CRISPR technology. As you know, we and Intellia are employing CRISPR to potentially treat a variety of diseases. Systemic gene knockout approach is pioneered by knocking out the TTR gene in patients with transthyretin amyloidosis. We and Intellia have shown impressive proof-of-concept clinical trial results in ATTR with both cardiomyopathy and polyneuropathy, and TTR knockout is the first systemic genome editing approach that has been cleared by the FDA to proceed to a Phase III study. Also exciting is our ongoing pursuit of a more technically challenging approach of using CRISPR for targeted gene insertion, initially for Factor IX to potentially treat patients with hemophilia B. With this approach, we are proceeding with IND-enabling studies, and exciting preclinical data were presented at ASH.

As we have disclosed previously, our first-ever systemic CRISPR gene knockout has shown exciting results in both manifestations of ATTR. Phase III program in ATTR with cardiomyopathy has been initiated, and we are pleased to announce, a trial site opened just this week. A summary of the MAGNITUDE study design is shown on the right-hand side of this slide.

With targeted gene insertion, our vision is to provide a one-time durable treatment that can restore Factor IX expression even when given to young patients, something that currently-approved gene therapies are not able to achieve. At ASH, we presented exciting preclinical data in primates and mice that provide support for this approach. In primates, even with successful Factor IX gene insertion in low percentage of albumin loci, robust, clinically-relevant Factor IX activity could be measured in the plasma of the animals. Experiments in neonatal mice showed that CRISPR enabled durable and stable Factor IX expression through adulthood, while genes introduced through episomal AAV gene therapies were rapidly lost within weeks of administration. Taken together, this finding showed that a robust and durable expression of Factor IX is possible with this genome editing approach, including in states of rapid liver growth such as in the pediatric population. We are currently conducting a lead-in study called HONEY-B for patients with hemophilia B. These patients will be potential candidates for our interventional study for which we are planning on submitting IND and CTA by the end of this year.

I will now turn the call back over to George for some closing remarks.

George D. Yancopoulos - Regeneron Pharmaceuticals, Inc. - Co-Founder, President, Chief Scientific Officer & Co-Chairman

Thank you, Andres, for reviewing our very exciting advances in hematology-oncology and in hematology. Clearly, you guys have been making incredible progress across a variety of diseases and modalities, and we are excited about making real breakthroughs for so many with so much need here. As you showed us, linvoseltamab demonstrated potential best-in-class efficacy in the primary analysis, and we believe it's highly differentiated from the competition. And as you told us, a U.S. regulatory filing is planned by the end of this year, this month.

Odronextamab, as you showed, continues to show favorable durable responses and a competitive profile ahead of our March 31, 2024 PDUFA date in both follicular lymphoma and diffuse large B-cell lymphoma, with studies ongoing and earlier lines of therapy. You showed us the combination data with the C5 antibody and the C5 siRNA showing robust knockdown -- unprecedented knockdown and clearing of C5 in an investigational cohort of patients from a pivotal study in PNH, paving the way not only in this indication, but for potentially pivotal studies in other important settings such as geographic atrophy, where there is an enormous need to try to avoid all the side effects from intravitreal injections such as occlusive retinal vasculitis, which your treatment has the potential to deliver.

You showed us data on the 2 Factor XI antibodies, presenting an opportunity to improve on the current standard of care for anticoagulation, with initial data from our Phase II study coming next year and plans for rapid advancement into pivotal studies. You showed a first-in-class opportunity with our TMPRSS6 antibody for the treatment of iron overload disorders. And you showed exciting gene editing approaches using our CRISPR platform with Intellia, first, the editing of the amyloidosis ATTR-causing gene in cardiomyopathy and peripheral neuropathy; and next, [inserting] hemophilia B in a novel way to address all those patients in need.

So, I'd just like to highlight how many first-in-the-world stories have been coming out from Regeneron and are reflected in everything that you told us. Just to remind everybody, we put the first CD3 bispecific into the clinic several years ago. We put the first costim bispecific in the clinic

several years ago. You updated us on the data and emerging programs with those. You told us today about the first antibody and siRNA combination ever done with very exciting combination data. I want to remind everybody that the TTR data you showed us in collaboration with Intellia is the first example of CRISPR-based gene editing performed in vivo in living human beings with incredible data, greater than 90% knockdown of the pathological gene. And you showed us the next hopefully first-in-class program, which is the combination of using CRISPR and our novel gene insertion technology to address hemophilia B. So, a lot of innovation, a lot of first-in-the-world advances and a lot of data suggesting that you're really making a difference in so many different patients' lives.

So, with that, good luck guys, and I'll turn it back over to Ryan.

Ryan Crowe - Regeneron Pharmaceuticals, Inc. - VP of IR

Thanks, George and Andres. We'll now open the call for Q&A, where George and Andres can address your questions. In order to address as many as possible, we ask that each caller limit themselves to one question and please keep the scope of your question limited to today's subject matter. Shannon, we'll take our first question, please.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Our first question comes from the line of Tyler Van Buren with TD Cowen.

Unidentified Analyst

This is Beth on for Tyler. Congrats on the new bispecific data as it continues to look significantly better. And today also at ASH, the remarks that you guys have helped lead development in the bispecific space. While the step-up dosing has markedly improved the safety profile, some physicians have remarked that the step-up dosing and need to split doses can be a nuisance. So, what can you do upon launch from a product perspective to make it easy for physicians to administer your bispecifics relative to the competitors already on the market?

L. Andres Sirulnik - Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences, Hematology

Thank you for your question. This is Andres. So, I think that it's important to first recognize that we don't have a label yet. And the way of administration, monitoring and so forth is yet to be determined. And we think that it is really key in terms of administration, the step-up regimen is that this particular regimen was able to deliver one of the lowest rates of cytokine release syndrome in the class, and it speaks to the tolerability of the regimen. And we also need to bear in mind that this only is in the first -- the complicated, that you call, administration occurs only in the first 3 weeks of treatment. Beyond that, we are moving to a convenient regimen of every 2 weeks, and even in patients that achieve a complete response, to a monthly administration.

George D. Yancopoulos - Regeneron Pharmaceuticals, Inc. - Co-Founder, President, Chief Scientific Officer & Co-Chairman

I think it's important to remind you that it's another first. We were the first to put CD3 bispecifics into the clinic. So, we were the first to see these rates of CRS. So, we were also the first to develop step-up dosing regimens. And we should also point out, as highlighted on Slide 14 that Andres showed you, for example, for linvoseltamab, it may be -- it's an important nuisance because patient safety comes first. This step-up regimen really that we introduced, the concept of step-up dosing is clearly revolutionary in terms of reducing CRS rates. But as you see, in terms of this nuisance, we don't know what we're going to ultimately get in the label and so forth. But what we think the required hospitalization is going to be many less days for our step-up regimen than for the competitors in the class right now. So, it's a necessary nuisance. It's very innovative. Once again, another innovation that we introduced, it dramatically drops CRS rates. So, it's very important for patients. And we believe certainly for the benefit that it

provides, it's an important process that patients and physicians will get through. But we think that we have made it, as seen here, from the hospitalization requirement, as convenient as possible for the patients, especially compared to the competitors in the class.

Operator

Our next question comes from the line of Robyn Karnauskas with Truist.

Nicole Germino - Truist Securities, Inc., Research Division - Associate

This is Nicole on for Robyn. So, we see great results with CAR-T [in] autoimmune [instances] due to the CAR's potency and ability to reset the B-cell repertoire. So, does linvo need to reset the B-cell compartment similarly in allergy? Or does it just need to keep overactivity at bay?

George D. Yancopoulos - Regeneron Pharmaceuticals, Inc. - Co-Founder, President, Chief Scientific Officer & Co-Chairman

Yes. So, first of all, let's just say that in autoimmune diseases, the depth that CAR-Ts seem to deliver is really no different than that delivered in bispecifics. Both of them are much deeper than what you would see with, for example, standard CD20 antibodies like rituxan. So, just as you would expect, just like multiple people are exploring CAR-T in autoimmune diseases, we are, of course, also exploring our large portfolio of B-cell-targeting bispecifics alone and in combination in autoimmune diseases. What we've actually shown in the allergy example that I showed you is that we could essentially deeply and completely eliminate essentially every single IgE-producing plasma cell in the body. We've now done this in animals definitively, and our early studies in the myeloma patients are very consistent with that. The only problem, as I said, is the IgE compartment is naturally and normally reconstituted for memory B-cells. The memory B-cells, however, sit in an IgG configuration. In allergic patients, though, because they have high body levels of IL-4 and IL-13, those memory B-cells, as they become plasma cells, as they reconstitute to plasma cells from the memory B-cell compartment, switch from IgG to IgE, and we can completely block that switching with Dupi. So, we believe we can deliver the deepest depletion and resetting of any B-cell compartment using any one of our bispecifics. In the allergy situation, we're using to eliminate all plasma cells, they immediately get reconstituted from the memory B-cell compartment, so you regain all your forgotten, missing IgGs, and by using DUPIXENT, you prevent any of those IgGs from becoming IgE. So, we're really excited about this. The data in both mice and non-human primates is incredible. I encourage you to read our recent cover paper in Science Translational Medicine. And we really believe, just like DUPIXENT has changed the face of so many allergic diseases, the combination of linvoseltamab and DUPIXENT could really be the key and the cure for so many people who are suffering from allergies.

Operator

Our next question comes from the line of Carter Gould with Barclays.

Carter Lewis Gould - Barclays Bank PLC, Research Division - Senior Analyst

Yes. Really, tons of information to go through. I feel like I need to ask around the GA disclosures, though. And can you talk about, first off, when we talked in the past around systemic options, some of these ophthalmic conditions, you pushed back on that in wet AMD. So, when you think about in GA, I guess the -- your willingness to use a systemic option, as well as any lessons from the preceding molecules that have gotten approved here, as you think about your Phase III program and designing that?

George D. Yancopoulos - Regeneron Pharmaceuticals, Inc. - Co-Founder, President, Chief Scientific Officer & Co-Chairman

Right. Well, in GA, in geographic atrophy, what has been seen now in commercial use of these intravitreally administered blockers of the complement pathways is that while they are just trying to prevent progression of a slow-progressing disease, they can acutely and catastrophically result in loss of vision in small but substantial fractions of patients. So, imagine this, you're taking a preventative treatment to prevent slow ongoing possibility

of blindness, and yet, you then can acutely suffer from catastrophic blindness. That's really raising a lot of concerns among physicians and patients in terms of using this approach. We believe that the systemic approach here will completely avoid the local toxicities that are raising all these concerns. In addition to this, we also remind you that almost all patients with geographic atrophy have it bilaterally. So, these patients are requiring injections in both eyes, both of them having the potential of suffering from these acute catastrophic local side effects, which will be avoided with the systemic approach. So, we believe that this could be an approach that really brings a lot of benefit to patients and allow for a less invasive and potential at-home treatment paradigm. There is always the possibility and the risk that by doing the systemic blockade of C5, and we know it in other indications and with other people's agents, that there is a risk of infections, which you can protect against. And we're trying to develop a mitigation plan so that the patients at highest risk perhaps would avoid this approach. But we are very excited about it because it's addressing a major problem with a major breakthrough. So, obviously, complement blockade is a major advance for these diseases, but there is obviously a major problem with bilateral delivery in so many patients for a chronic preventative approach.

Operator

Our next question comes from the line of Evan Seigerman with BMO Capital Markets.

Unidentified Analyst

[Malcolm Hoffman] on for Evan. I wanted to start -- you had started off by talking about the linvoseltamab and DUPIXENT combo for severe allergy. Could you talk a little bit more about the opportunity here? Maybe how many patients would potentially be eligible in the severely allergic patient population? And how would you consider this -- or would you consider this combo after something like a failed DUPIXENT use in monotherapy? Just want to get a sense of how you guys are going to be positioning this.

George D. Yancopoulos - Regeneron Pharmaceuticals, Inc. - Co-Founder, President, Chief Scientific Officer & Co-Chairman

Right. So, just to remind you, as we all know, DUPIXENT is now approved in 5 different allergic disease indications. That is -- and it's the leading, by new prescriptions, agent biologic in all of these settings, and it's first-in-class in 4 out of the 5 of these. It's really a remarkable story. But despite all that, DUPIXENT by itself does not reverse or cure allergy. Why? Because it does nothing to the long-lived existing IgE plasma cells. So, it treats other manifestations of allergic diseases, so in asthma, decreases exacerbations and dramatically improves lung function. In atopic dermatitis, it clears the skin and the itch and so forth. It shrinks and makes nasal polyps go away. We have in recent -- in eosinophilic esophagitis, it normalizes the anatomy of the esophagus and allows for normal swallowing and so forth. We've just released incredibly exciting data for chronic obstructive pulmonary disease, where we hope that will be the sixth indication approved for DUPIXENT. But by itself, it does not reverse allergies. And we -- our scientists, a few years ago, figured out why. Because once you have an IgE plasma cell, it's already undergone switching, and there's no more role for IL-4 or IL-13. That cell will just sit there and make IgE, and you'll be allergic for life. So, what our scientists realized is, well, we have to eliminate those cells somehow. And that's where the BCMA CD3 bispecific that you heard all about from Andres afforded us that opportunity. And the combination does 2 things. It acutely -- a one-time or short-term use by the BCMA bispecific will eliminate these cells, DUPIXENT will keep them from coming back. We are first going to be applying it to the sickest patients with the greatest need.

There's unfortunately a lot of individuals who have very severe allergies where they can actually be life threatening, where these people have suffered life-threatening anaphylactic reactions and so forth, or where they have so many allergies that it just restricts their lives and the ability to eat a normal diet and so forth, okay? So, those are the patients, and there are smaller numbers of those patients. Depending on the efficacy and safety that we see in the most dire patients, we can then expand out to patients with less severe forms of allergy. And it is quite possible it could grow to the many people. As we all know, allergy itself -- allergic diseases like atopic dermatitis and asthma, eosinophilic esophagitis, nasal polyps, they've been incredibly increasing in frequency to epidemic proportions, and that's why DUPIXENT is such an important drug. But as we also know, just conventional allergies, IgE-mediated allergies, are also achieving epidemic proportions. When I was growing up, a long, long time ago, less than 1% of the population had severe food allergies like peanut allergies. Now, the number of people who have severe allergies is escalating to tens and tens of millions. The fraction of those patients that we would be interested in addressing will, of course, depend on the efficacy and safety profile that we see in the sickest patients. So, as we often do in drug development, as we did in myeloma and as we did in lymphoma and so forth,

you start with the sickest patients. They're a small population. If it works there and it's effective and acceptably safe, then you move to the frontline patients. Allergy will be no different, except that in that space, we are totally alone and the leaders.

Ryan Crowe - Regeneron Pharmaceuticals, Inc. - VP of IR

Thank you, George. We'll know more about patient populations as we move forward with the program.

Operator

Our next question comes from the line of David Risinger with Leerink Partners.

David Reed Risinger - Leerink Partners LLC, Research Division - Senior MD

Thanks for the comprehensive updates, and congrats on the new data. So, my question is on your Factor XI programs. You have 2 candidates. Do you plan to choose 1 of the 2 for Phase III? And could you juxtapose your vision for Factor XI inhibition versus oral competitors?

L. Andres Sirulnik - Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences, Hematology

Thank you for your question. This is Andres. As you mentioned, we are developing 2 highly specific Factor XI monoclonal antibodies, each one with unique and different mechanism of action. I think that is important to highlight. And based on our preclinical work so far, these antibodies are demonstrating the expected pharmacology and provide optionality for clinical development. Now, we will complete 2 small proof-of-concept Phase II studies with a fast readout in venous thromboembolism, and we will data-driven -- we will make data-driven decisions as that data emerges. So I think it's a little bit early right now to say we choose one vis-a-vis the other, but I think that as development progresses, we'll make those decisions.

Now, you're asking how do we perform vis-a-vis oral or other Factor XI assets or drugs in development. I'll say that we have a highly specific antibodies that have performed very well in our preclinical models. In fact, in our pharmacodynamic in vitro testing, these antibodies have performed better than all other Factor XI antibodies. When we look at oral Factor XIs that are being tested, we believe that the specificity of the antibodies itself is a major advantage. For example, the [asundexian] may have been underdosed in a current study that recently read out. And, all small molecules will face a similar issue, which is balancing sufficiently high doses to inhibit Factor XI, but not too high doses to lose specificity for the factor. So, all in all, we think that the antibodies are the way to go. And we are very fortunate to have 2 very good antibodies with distinct mechanism of actions that will give us optionality for the future.

George D. Yancopoulos - Regeneron Pharmaceuticals, Inc. - Co-Founder, President, Chief Scientific Officer & Co-Chairman

And just to add to that, I'm sure you all know these things are all proteases. The small molecules are blocking proteases. There are a lot of very closely related proteases, and it's impossible for these small molecules to be totally specific. And so, because of that, you can't dose them high enough to get 100% inhibition of the one protease you want, because if you do that, you're going to be partly inhibiting a whole bunch of other proteases which cause all of those problems. So, you have to underdose with the small molecules. Antibodies, because of their specificity, don't have that problem. Very interestingly, as Andres detailed for you guys, our 2 antibodies attack Factor XI at the very beginning of its action or at the end of its action. Those might have slightly different not only efficacies in the anticoagulation space, but also potential safety advantages. So, depending on how they perform, if they both perform well in the initial Phase II studies, we will probably move forward with both of them in pivotal studies. If one clearly outperforms the other, then we'd make a choice based on that data. But we believe we're in a really attractive position because, as Andres said, not only do we think antibodies are the way to go, but our antibodies, when compared in-house side by side with competitors, they performed much better, as is usually the case when you look at our VelocImmune-produced antibodies coming from our technologies compared with the one-off technologies that are usually used by other competitors. So, we're very excited about the potential for these programs to really change the practice of medicine in this space.

Operator

Our next question comes from the line of Salveen Richter with Goldman Sachs.

Unidentified Analyst

This is [Anoumid] on for Salveen. Congratulations on the progress. Just 2 questions from us. First on linvoseltamab, now that you have patients out to a median follow-up of 11 months, have you had the chance to look at a potential of -- potential loss of responses via BCMA antigen escape? And then, just a quick question on the linvo-Dupi combination, I guess given the safety and administration concerns with bispecific, do you think physicians that are treating the severe allergy patients would be receptive to the use of bispecifics in their patients? And what would you need to do to get them comfortable with this potential therapy?

George D. Yancopoulos - Regeneron Pharmaceuticals, Inc. - Co-Founder, President, Chief Scientific Officer & Co-Chairman

Well, let me start talking about allergy, and then I'm going to turn it over to Andres. So, in terms of the allergy, of course, this is why we're starting with the most severe patients. The other point is our preclinical data and where we're starting in humans is, to eliminate natural cells -- remember, it's always much harder to kill a tumor cell, and it's much, much harder to kill a refractory/relapsed myeloma cell than a naive virgin plasma cell. So, our preclinical data says that we will actually need much lower doses and for much shorter, maybe even single courses of treatment. But of course, we're going to go into a patient population where the benefit-risk will warrant even the amount of CRS that you see in the myeloma patients. But let me remind you, with our new step-up regimen that we use for myeloma, which is at higher doses than we plan to be using in the allergy patients, where you're trying to kill a much easier to kill non-malignant cell, even in those settings, you have very rare Grade 3s on the order of 1% or lower. They're all well controlled and have not led to any long-term negative sequelae. And the vast majority of CRS that you see are very mild things like mild temperature elevations and so forth. So, the CRS profile, particularly with our new and improved step-up regimen, are actually well tolerated. But we're going to the highest unmet need patients, where even that relatively mild nuisance and risk is warranted. And if the lower doses that we'll be using, those populations are even better tolerated, it'll of course allow broader usage in even milder and milder allergic patients. But time and data will tell. So, Andres?

L. Andres Sirulnik - Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences, Hematology

Yes. Thank you, George. To your question on loss of antigen expression in patients, we are actively investigating this and remain vigilant. We know that this has been reported for other BCMAs. So, we will be looking and reporting on the data in due course.

George D. Yancopoulos - Regeneron Pharmaceuticals, Inc. - Co-Founder, President, Chief Scientific Officer & Co-Chairman

I think it is worth just pointing out, the data that Andres showed to you is that, first of all, the swimmer plots, as they're shown or talked about on Slide 12, the patients progressively develop deeper and deeper responses with 46% of patients with 11-month follow-up ultimately becoming complete responders. And once you become a complete responder, you have a very long duration of action, duration of the response at that point. So, this all argues that if there is escape, it's very rare and would be very late in the whole time course. The data is very compelling on that. We've actually seen, as you might expect, because the responses are not as complete nor long-lasting in lymphoma, there we've actually characterized and seen that there are substantial examples of antigen escape there. But the data here speaks for itself. Yes, there may be rare and late escape, but with the percentage of complete responses, the fact that they continually deepen over time and that the average duration of a complete response is measured now in years, okay, it suggests that if it occurs, it's a relatively late and very minor problem for this incredible bispecific treatment.

L. Andres Sirulnik - Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences, Hematology

Yes. And, I just want to add that the loss of antigen has been reported actually frequently in GPRC5B treatment with that target, more so than the very rare occasions or circumstances in which it has been reported for loss of BCMA.

Operator

Our next question comes from the line of Christopher Raymond with Piper Sandler.

Christopher Joseph Raymond - Piper Sandler & Co., Research Division - MD & Senior Research Analyst

Just on the geographic atrophy program, George, I see that the LDH knockdown from the PNH data is a potential read-through to this program. But I know you guys have sort of hinted at this program for a while, and as I've talked to investors who've heard what you've said before, I think there's a bit of surprise that you could jump right into a Phase III program without data in actual GA patients. So, I'm just wondering if you could maybe flesh out a little bit more the supportive data you have for going right into GA and maybe frame the discussions you've had with FDA to get them comfortable with this approach.

George D. Yancopoulos - Regeneron Pharmaceuticals, Inc. - Co-Founder, President, Chief Scientific Officer & Co-Chairman

Well, I think the general way to look at it is, this is now a Phase III program in multiple indications. It's a Phase III program in PNH, and it's a Phase III program in myasthenia gravis. So, we have a lot of data, an extensive amount of data in this data set. The other point is that it actually, for this disease, for GA, despite the benefit that the approved treatments with complement inhibition have shown that the only way that you can show and demonstrate the benefit is in a relatively large Phase III because you need that many patients to show this approximately 15% to 20% decrease in the growth rate of GA because it is such a slow developing disease. So, the point is that we're already in Phase III with this program. We have a lot of experience. As Andres said, we have almost 200 patients in our Phase III trials right now, and we also treat a lot of patients at earlier stages. We've learned a lot about this, and the only way to get the answers in geographic atrophy is in Phase III. So we believe we are in a good position to be going forward here. But of course, the large studies, which [are what] are going to be required to actually demonstrate the benefit-risk ratio, which is ultimately what determines what the FDA is going to decide on here. So, that's what we're going to have to do to get real answers here. But we're very excited about this opportunity because it can really address a really unmet need here, which is, can you actually provide this protection? Can you slow the slow progression of this disease to blindness, but avoid these acute catastrophic events? And the acute catastrophic events are very limiting, obviously, in this space.

Operator

Our next question comes from the line of Hartaj Singh with Oppenheimer & Co.

Hartaj Singh - Oppenheimer & Co. Inc., Research Division - Research Analyst

Thanks for all the updates. I just had a question on your oncology programs. As you're moving up in multiple myeloma, at ASH, when we were there, there was a lot of update on CAR-T. And it seems that multiple myeloma, there's so many lines of treatment, sequencing the therapies could become very important. So, could you just talk about your late-stage programs and then how you kind of -- how would you move that up lines of therapy with all the trials going on?

L. Andres Sirulnik - Regeneron Pharmaceuticals, Inc. - SVP of Translational & Clinical Sciences, Hematology

Thank you for your question. We think, first, let me just start by saying that we think that the level of efficacy that we have [observed] with linvoseltamab is very encouraging. And I think hereof, the opportunity to move in early lines of therapy, not only in multiple myeloma, but potentially with an

aim to cure pre-malignant conditions such as MGUS or smoldering myeloma. This is -- when you look at again the data in the latest -- very heavily pre-treated patients, late lines of therapies, this data is unique. We are observing CR rates of 46%. These are deepening. These results may improve over time in terms of the CR rate. And we think that monotherapy in early lines is an opportunity for patients of receiving less toxic treatments. So, as I mentioned, not only we are moving into early lines of therapy in the myeloma space, but we are now accelerating our development in those conditions that give rise to multiple myeloma.

George D. Yancopoulos - Regeneron Pharmaceuticals, Inc. - Co-Founder, President, Chief Scientific Officer & Co-Chairman

[Let's just add], there's a lot of points to add to here, is, when you talk about CAR-T, and particularly if you're talking about the late-stage patients, these are very sick people, okay? In order to give them a CAR-T, you have to do 2 things. You have to essentially give them very high levels of chemotherapy for a month to clear space so the CAR-Ts can take. That causes a lot of morbidity and mortality to very sick people who are at high risk. And not only that, during that period of time, some of the patients actually progress and can no longer be eligible for the CAR-T therapy. And then, you then have to give them an engineered CAR-T therapy, and we know -- all know the access and manufacturing issues having to do with that. The concept of having something that has a similar level of efficacy that is off-the-shelf that you can start and give almost immediately without having to give them chemoablation in order to clear space and so forth, positions these things, we believe, especially with the efficacy levels that we showed, very attractively for this very sick population. And then, going to earlier lines of therapy, once again, would you rather have to go through chemoablation and all that for an earlier line of therapy? Or particularly, even, as Andres highlighted, which we're very excited about for pre-malignant conditions, with something that also has these risks that's been recently highlighted by the FDA of maybe being associated in the long term with T-cell malignancies, would you want to do that? Or would you want to take something that's much more convenient, doesn't put you through that and so forth, and has similar efficacy as a bispecific? So, we really think that if the data continues to evolve as it looks like it's evolving, we think that bispecs clearly are going to become the first wave of treatment that almost all patients in these spaces would get as compared to CAR-T. We think CAR-Ts are really -- they were a great proof of principle, they were a great approach, but we made a commitment a long time ago that they would eventually be displaced and replaced by agents that would have similar efficacy as we're now beginning to show, but much safer and much more convenient ways of being delivered. And as we said, certainly, if Andres' dream of going to the pre-malignant conditions really pertains, you're not going to be doing that with CAR-T, but you can very easily imagine doing it with a very short course temporary treatment of a very highly potent bispecific agent.

Operator

Our last question comes from the line of Brian Abrahams with RBC.

Unidentified Analyst

This is Joe on for Brian. Congrats on all the pipeline progress. So, for geographic atrophy, I know we touched on benefits related to ocular safety over intravitreal injection, but just trying to have a better understanding of additional benefits on the efficacy side as well. So, how established are the role of complement system locally in the eyes versus systemically in these patients? And are there any potential advantages of targeting C5 over C3? And did these patients have any other comorbidities driven by a complement system that can further benefit from systemic delivery?

George D. Yancopoulos - Regeneron Pharmaceuticals, Inc. - Co-Founder, President, Chief Scientific Officer & Co-Chairman

Yes, these are all great questions. I think that the point is that almost all of your C5 is coming from the liver, okay? And just in case there's minute amounts of it coming from anywhere else, the systemic antibody will take care of that. So, what you would expect, if anything, is that they should be more effective when you've completely blocked the C5 systemically. It should be more effective than local delivery, which as we all know and from our experience. We are the world leaders in intravitreal treatments and so forth. We have developed these high-dose, long-acting versions of EYLEA to allow them to act longer and longer and longer. And right now, the current C5 or complement treatments intravitreal are limited to every month or every 2-month treatment because they don't last long enough and they don't provide complete blockade. So we think, if anything, we should have higher efficacy. As I mentioned before, what we will have to straddle is, we won't have the local toxicities, the acute catastrophic

blindness that can be caused by local administration of inflammatory-causing agents. On the other hand, we'll have to balance the safety of systemic complement suppression, which is known to be associated with certain kinds of infections. And that's something that we're going to have to straddle. As I said, obviously, the standard with these C5 approaches is you pre-vaccinate patients against the infections that they become susceptible to. But we're also going to try to attempt mitigation approaches to protect against the individuals that we'd be most worried about. So, we do have a systemic safety concern. But from the efficacy point of view, from the convenience, from the avoidance of acute catastrophic blindness-causing events, we think there could be enormous advantages to this, especially since, as we said, most patients suffer from bilateral diseases, and so they have to get injections in both eyes either monthly or every other month, which is obviously a major burden, both from the convenience, but also from the acute catastrophic safety point of view.

Ryan Crowe - Regeneron Pharmaceuticals, Inc. - VP of IR

Okay. Thanks, George, and thanks to everyone for joining us today. Apologies to those that I wasn't able to get to in the queue. We're happy to follow up after the call. Everyone have a great day, and thanks again for joining us.

Operator

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