REFINITIV STREETEVENTS

EDITED TRANSCRIPT

MRK.N - Merck & Co Inc Cardiovascular Event

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OVERVIEW:

MRK provided detailed overview of its broad and growing cardiopulmonary pipeline and portfolio and gave further insight into its ongoing late-stage clinical programs in atherosclerosis, heart failure, pulmonary arterial hypertension and thrombosis.

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PRESENTATION

Operator

Good morning. My name is Grace Lacker, and I'll be your conference operator today. At this time, I would like to welcome everyone to the Merck & Co., Inc.'s Cardiovascular Investor Event. (Operator Instructions) I would now like to turn the call over to Peter Dannenbaum, Vice President of Investor Relations. Please go ahead.

Peter Dannenbaum *- Merck & Co., Inc. - VP of IR*

Thank you, Grace, and good morning, everyone. Welcome to Merck's Cardiovascular Investor Event. We are excited to have this opportunity to speak to you today about our broad and growing cardiovascular portfolio. During today's call, a slide presentation will accompany our speakers' prepared remarks. This presentation is posted to the Investor Relations section of Merck's website.

Speaking on today's call will be Eliav Barr, Senior Vice President, Head of Global Clinical Development and Chief Medical Officer; Arpa Garay, Chief Marketing Officer, Human Health; Joerg Koglin, Vice President, Global Clinical Development, Cardiovascular and Respiratory; Dean Li, President, Merck Research Laboratories; and Fiona Marshall, Senior Vice President, Discovery, Preclinical and Translational Medicine. The full biographies of the speakers can be found in the appendix of the accompanying slide presentation.

Now moving to the agenda. Dean will start with a strategic overview. Joerg, Eliav and Fiona will then discuss the scientific attributes of our cardiovascular pipeline candidates, while Arpa will discuss the commercial opportunity for each. Fiona will provide detail on Merck's cardiovascular discovery efforts, and then Dean will wrap up with some closing remarks. Following prepared remarks, we will hold a Q&A session.

Before we get started, we would like to remind you that some of the statements that we make during today's call may be considered forward-looking statements within the meaning of the safe harbor provision of the U.S. Private Securities Litigation Reform Act of 1995. Such statements are made based on the current beliefs of Merck's management and are subject to significant risks and uncertainties. If our underlying assumptions prove inaccurate or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Our SEC filings, including Item 1A in our Form 10-K for the year ended December 31, 2021 identify certain risk factors and cautionary statements that could cause the company's actual results to differ materially from those projected in any of our forward-looking statements made this morning. Merck undertakes no obligation to publicly update any forward-looking statements. With that, let me turn it over to Dean.

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Thank you, Peter, and a warm welcome to everyone calling in for our cardiovascular event today. At Merck, we have a proud legacy of translating breakthrough science into medicines that, over the years, have served to alter the trajectory of cardiovascular disease. I am intimately familiar with many of these products from the pioneering studies demonstrating their clinical benefit from my own experience as a cardiologist. That background also makes me especially passionate about the subject of today's proceedings.

Now our company's unique heritage in cardiovascular disease can be traced back to the development of chlorothiazide in 1958. Since chlorothiazide, teams of distinguished scientists and clinicians have delivered a series of practice-changing medicines, including the first statin, MEVACOR; the first angiotensin receptor blocker, Losartan; the first selective cholesterol absorption inhibitor, ezetimibe; as well as the ACE inhibitor, enalapril; and the widely used statin, simvastatin; and more recently, the soluble guanylate cyclase stimulators, Adempas and VERQUVO, as part of our collaboration with Bayer, to name a few.

Despite advances in our scientific understanding, progress in diagnosis, prevention and treatment and improved health education, cardiovascular disease remains an epidemic. The magnitude of this health burden was recently summarized by Tom Frieden who is the former director of the CDC in The Wall Street Journal, who noted that in the first 2 years since its outbreak, COVID-19 killed more than 10 million. In the same 2 years, cardiovascular disease killed an estimated 35 million.

At Merck, we are focusing our efforts where the needs are greatest, and we feel we have the greatest opportunity to positively impact patients' lives, including: heart failure with the progressive nature of disease means that despite current therapies, approximately 50% of diagnosed patients will not live past 5 years; pulmonary arterial hypertension, where again, progressive disease kills close to half of patients within 5 years of diagnosis; thrombosis, where patients with end-stage renal disease, who have elevated incidence of thrombotic events and a high risk of bleeding, have limited therapeutic options; and finally, atherosclerosis, where despite therapeutic options, evidence indicates a significant portion of patients fail to reach their LDL cholesterol lowering goals, putting them at elevated risk of a major cardiovascular event.

As this slide indicates, we have grown and advanced our cardiovascular programs over the past year. We continue to generate value from our long-standing soluble guanylate cyclase partnership with Bayer. In 2021, we received approval for VERQUVO in the United States and the EU. In the United States, VERQUVO is indicated to reduce the risk of cardiovascular death and heart failure hospitalization, following a hospitalization for heart failure or need for outpatient intravenous diuretics in certain adults.

In addition, our discovery efforts have yielded a compelling internal pipeline of candidates, which are now steadily emerging from earlier stages of development. Where appropriate, we have also sought to augment and complement these assets through strategic business development transactions as exemplified by the recent acquisition of Acceleron Pharmaceuticals.

With our exceptional scientific expertise, data-driven approach and strong clinical development execution, we are uniquely positioned to provide a meaningful impact for patients with at least 8 potential new approvals by 2030. Now let me just turn it over to Arpa quickly to provide an indication of what these approvals could represent from a commercial perspective.

Arpa Garay - *Merck & Co., Inc. - CMO for Merck Human Health*

Thank you, Dean. By focusing in areas of high unmet need, as Dean just described, we believe our assets will translate into a significant commercial opportunity. The initial indications for the assets we are highlighting today as well as an expanded indication for VERQUVO are expected to launch in the 2024 to 2028 time line. As we think about the additional indications associated with these assets, where studies are currently underway or being planned, we believe the overall peak commercial revenue opportunity for our cardiovascular portfolio exceeds $10 billion approaching the mid-2030s. We have previously indicated that sotatercept in Phase III clinical trials for pulmonary arterial hypertension has multibillion-dollar peak commercial revenue potential as well.

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Yes. So before I turn to Joerg for the main event, I wish to take a moment to explain a general principle regarding our approach to the clinical pipeline and its development. This is a strategy that is apparent from our extensive work across oncology with KEYTRUDA, Lynparza and Lenvima as well as more recently with WELIREG. It is a strategy relevant to candidates throughout our therapeutic areas.

First, we follow the science with a laser focus on addressing patient needs. Once we commit to a molecule or mechanism or platform, we advance the program to demonstrate unambiguous promotable attributes in a defined patient population and to establish a clinical beachhead. Having observed a meaningful benefit, we subsequently seek to expand, deepen and extend beyond the initial clinical beachhead. In the case of a novel molecule, this means evaluating the benefit to broader patient populations where there is pathobiological rationale for activity.

In the case of the technology platform, we apply the technology to other diseases and therapeutic areas. I would invite you to consider this framework as my fellow presenters outline each program not just in the context of how we are establishing the beachhead but also where downstream opportunities to expand, deepen and extend our impact to more patients exist. So with no further ado, I will now turn it over to Joerg to kick off regarding our exciting work on the clinical development of VERQUVO. Joerg?

Joerg Koglin

Thank you, Dean. Even under optimized standard of care with improved chronic heart failure therapies, heart failure remains a progressive disease. Rather than as a continuous process, heart failure progresses through episodes with acute decompensation requiring intravenous therapies or hospitalizations. In fact, even on the current optimized therapies, every minute, an average of 20 more patients are hospitalized for heart failure worldwide.

Equally important, even after successful re-stabilization through intravenous therapies and in-hospital care, these patients continue to have a higher risk for future events. In the U.S. alone, every year, 900,000 hospitalizations are caused by worsening chronic heart failure. After successful initial re-stabilization and discharge from the hospital, in a recent data set, 27% of these patients will be rehospitalized within the subsequent 30 days. 1 out of 2 patients end up again in the hospital within 60 days. 18% of these patients die within the following year. After 5 years, approximately half of these patients will be dead.

This part exceeds the morbidity and mortality in the broader stable heart failure population where direct development has been focused over the last decades. Worsening chronic heart failure represents one of the largest unmet clinical needs in cardiovascular medicine. This is where our excitement around sGC stimulation comes in, building on de novo prize-winning research around the role of nitric oxide signaling in cardiovascular health, sGC stimulation could be the first mechanism with the potential to address the underlying root cause of progressing heart failure.

While oxidative stress and endothelial dysfunction has been shown to decrease nitric oxide signaling leading to relative cyclic GMP efficiency, sGC stimulators have been shown to reverse some of these effects. The development of multiple sGC stimulators for the treatment of pulmonary hypertension or worsening chronic heart failure has been the focus of our development collaboration with Bayer.

Following very promising effects observed in a Phase II study called SOCRATES-REDUCED conducted by our partners at Bayer, Merck led the 5,050-patient VICTORIA outcome study of vericiguat in patients with chronic heart failure with reduced ejection fraction enrolled after a recent heart failure hospitalization or recent need for outpatient IV therapy due to heart failure worsening. In the VICTORIA study, we successfully demonstrated that the treatment with vericiguat reduced the risk of subsequent heart failure hospitalizations or cardiovascular events.

In this high-risk patient population, the statistically significant relative risk reduction translated to an absolute reduction of 4.2 events per 100 patient-years or as arguably the most relevant parameter for patients and physicians, a number needed to treat of only 24. These results published in the New England Journal of Medicine formed the basis for our Priority Review by the FDA in January 2021. Subsequently, VERQUVO has been approved in over 50 countries worldwide, including Japan and EU and has been included in European and, as recently as this weekend, U.S. treatment guidelines.

So what's next for vericiguat? After establishing the benefit of treatment initiation following a recent hospitalization event in the VICTORIA study, we are now evaluating the potential for expanded use into a population with more stable disease by trying to show that the initiation of the drug even earlier in a patient's journey prior to a worsening event could show equal or larger relative benefit. This hypothesis is based on some intriguing post-hoc analysis in VICTORIA that were published last year.

In modeling the outcome of a functional baseline NT-proBNP, a marker of heart failure severity and stability, patients with lower NT-proBNP at baseline indicative of earlier or more stable disease states provided evidence for an even larger treatment effect with vericiguat. Working with a team of academic advisers, we initiated the VICTOR outcome study in November last year. The study focuses on chronic heart failure patients without a recent decompensation event, a population more similar to other recent large heart failure studies evaluating other compounds.

As an event to create some outcome trial, around 6,000 patients will be randomized to receive vericiguat versus placebo 1-on-1 with time to the first event of CV death or heart failure hospitalization as the primary endpoint. The study is off to a great start with more than 60% of the sites worldwide up and running and more than 500 patients already enrolled at this time. For now, we estimate study completion somewhere around early 2025. Now I will turn it over to Arpa, who will talk about the commercial opportunity.

Arpa Garay - *Merck & Co., Inc. - CMO for Merck Human Health*

Thank you, Joerg. The commercial outlook for VERQUVO remains positive due to double-digit market growth as well as continued high unmet need in both the high-risk population for which the product is currently approved as well as a broader stable HFrEF population that is currently under investigation, as Joerg described. Despite a crowded and rapidly evolving market with significant changes to treatment guidelines, VERQUVO remains to be the only product indicated exclusively to reduce the risk of CV death and heart failure hospitalization in symptomatic chronic heart failure patients following a worsening heart failure event. And it has demonstrated efficacy on top of standard of care.

We expect to see future growth through increased access, adoption and geographic expansion as we launch in more markets around the world. And pending the potential successful completion of the VICTOR study, we see the possibility of tripling the addressable population from an estimated global prevalence of 4 million patients with the existing indications to a potential 12 million patients with the potential label expansion. Now let me turn it over to Eliav, who will discuss our pulmonary arterial hypertension canvas.

Eliav Barr - *Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories*

Thank you, Arpa. So let's turn our attention to pulmonary arterial hypertension. Now pulmonary hypertension is defined as high blood pressure in the arteries that lead from the right side of the heart to the lungs. As blood travels into the lungs, it's oxygenated and then it passes to the left side of the heart where it distributes oxygen to the rest of the body.

Now one cause of pulmonary hypertension is pulmonary arterial hypertension or PAH. PAH is a rare disease caused by proliferation of cells in the walls of arteries in the lung, leading to narrowing and abnormal constriction. PAH strikes women more than men. Symptoms begin in the prime of adult life. The heart is increasingly unable to deliver sufficient blood to the lungs, leading to a deficit in delivery of oxygenated blood to the rest of the body, first during exercise and then even at rest. So patients experience increasingly severe breathlessness and limitations in mobility. Eventually, their only recourse is lung transplant. Most patients die from complications of right heart failure.

Now PAH is a rapidly progressive disease. The 43% 5-year mortality rivals that of some of the most feared forms of cancer. Current PAH therapies treat the symptoms of the disease by dilating arteries. These medicines can improve exercise capacity but they have 2 major limitations. They don't change the course of the disease, so patients experience increasingly severe symptoms. They also don't really specifically dilate the pulmonary circulation. They dilate both the pulmonary and systemic circulation, and that causes low blood pressure that limits tolerability and the ability to induce sufficient vasodilation in the lungs.

Now our PAH pipeline aims to address each of these deficits. Now this gets us to the recent acquisition of Acceleron Pharma. The exciting science and early clinical data around sotatercept has been on our radar screen for some time. The emerging Phase II data provided important preliminary evidence that sotatercept has the novel mechanism with the potential to transform the treatment of PAH and perhaps other forms of pulmonary hypertension.

In 2021, we finally saw an opportunity to add this program to our pipeline through an acquisition.

So what's so special about sotatercept? Now as I noted before, blood vessel dilators improve the symptoms of PAH but they do not impact the underlying disease process, so patients continue to progress towards death. In PAH, there is an overproliferation of pulmonary arterial muscle cells, resulting in progressive thickening of the pulmonary vessels and narrowing of the vessel lumen. This dysfunctional process is thought to be mediated by an imbalance in factors that regulate the thickness of the pulmonary vessel wall.

Proliferation or the signal to thicken the pulmonary vessel wall is driven by circulating Activin A and that's shown on the left side of that diagram. Anti-proliferative proteins signal a need to reduce the thickness of the vessel wall by modulating the BMP-2 receptor, and that's on the right side the green box. In the PULSAR study, we showed that sotatercept binds Activin A so that reduces circulating Activin levels. And as expected, we also demonstrated in that study that sotatercept had no impact on expression of the BMP-2 receptor. So our ongoing trials will examine whether reduction in pro-proliferative Activin A levels induced by sotatercept without changing the anti-proliferative signaling can improve symptoms and slow the progression of disease, which may ultimately improve survival.

Now preclinical models demonstrate the potential of sotatercept to maintain proper vessel wall architecture. Here, we evaluated the effect of a sotatercept analog in the Sugen 5416 hypoxia rat model, which really mimics the course of human PAH. So if you look at the left side of the panel, you can see the thin walls and wide lumens of blood vessels in a healthy lung. And then you go to the middle panel, induction of PAH in the rat leads to vessel wall thickening, which narrows the vessel lumen. Animals with induced PAH were then treated with either placebo or RAP-011, which is the rodent equivalent of sotatercept.

So now if you look at the right side, you can see what the effect of therapy was. And in the upper right, rats given placebo showed further thickening of blood vessel walls and narrowing of the lumen. On the other hand, animals treated with sotatercept on the bottom right had reversion of blood vessel architecture back to normal. Normal vessels, wide open lumens. So this preclinical experiment supported the decision to further investigate the potential for sotatercept to reverse pulmonary vascular disease that underlines PAH.

And so we conducted the PULSAR study. And so the objective of the sotatercept clinical program is to demonstrate the drug's effect on pulmonary arterial walls, improves the -- and prolongs lives of patients with PAH. And the first step was to demonstrate the potential for sotatercept to normalize the pressure in the pulmonary blood vessels in patients with PAH. In this way, we're improving exercise capacity. And as you see, the PULSAR study provided evidence of this benefit.

In this study, 106 patients with moderate PAH who are optimized on standard of care therapy were randomized to receive either placebo or 1 of 2 doses of sotatercept for 24 weeks. The primary endpoint was a change in pulmonary vascular resistance, which is a measure of the resistance

that must be overcome for blood to flow through the lung vasculature. Treatment with sotatercept resulted in statistically significant and clinically meaningful reductions in pulmonary vascular resistance, and that means that the right side of the heart had a lot less work to do to get blood to flow through the lungs.

The impact of this improvement is shown in the results of the 6-minute walking distance test, which is the standard Phase III efficacy endpoint for PAH drugs. Individuals in the pooled sotatercept group were able to improve their walking distance by 25 meters relative to placebo, which is a striking improvement. On the basis of these results, which were published in the New England Journal of Medicine in April of last year, FDA and EMA granted sotatercept Breakthrough and Prime Designations, respectively.

Now once the primary endpoint of PULSAR had been reached, those patients who were given placebo were crossed over to active drug, and patients that were receiving sotatercept continued their therapy. The benefits of sotatercept was shown to continue over longer periods of time, and patients receiving placebo who then crossed over to sotatercept were able to achieve the benefits observed in those studies -- observed in those who started sotatercept at the start of the study.

So as you see on the left-hand side of the panel, we see changes in 6-minute walking distance at 48-week time point, including the open-label extension. In the top, patients who started sotatercept were able to gain a bit more benefit with longer therapy, while placebo patients who crossed over sotatercept were able to increase their walking distance substantially. The middle panel, we see, shows the effects of drug treatment on levels of NT-proBNP, which is a hormone released by the heart in response to heart failure. Again, longer durations of therapy with sotatercept resulted in sustained reductions in this biomarker for heart failure. Crossover from placebo to active drug resulted in large reductions in the hormone's levels. And you can see a similar pattern was observed with pulmonary vascular resistance.

So based on the PULSAR results, we embarked on an extensive Phase III development program to evaluate sotatercept across the spectrum of patients with PAH. These studies work together to create a comprehensive program covering end-stage, mid-stage and early-stage disease. STELLAR is the pivotal registration study, our beachhead in the fight against PAH. It is designed to determine whether sotatercept improves exercise capacity as measured by 6-minute walking distance among patients with mid-stage disease who are on stable optimized standard of care.

ZENITH is meant to deepen the body of evidence with sotatercept. The study evaluates patients with more severe disease who are at high risk of death. The intent is to determine whether sotatercept can reduce the risk of hospitalizations for PAH, lung transplant or death in these seriously ill patients. Finally, HYPERION is designed to extend the population benefiting from sotatercept. This study is enrolling individuals who are recently diagnosed with PAH and are in intermediate or high risk for disease progression. The goal here is to demonstrate a positive impact on disease progression. The endpoint of time to clinical worsening, which is defined as the combined incidence of significant worsening of exercise capacity, hospitalization for PAH, lung transplantation or death.

We also have SOTERIA in which patients of all trials of sotatercept continue to receive the drug, enabling assessment of the drug's long-term safety, tolerability and efficacy.

Now we wanted to provide you a little bit more detail on STELLAR study, which is the first registration study for sotatercept. As you can see, the study is designed to evaluate sotatercept in patients with PAH and moderate range of disabilities, this is WHO Functional Class II or III. 284 patients were meant to be randomized to receive placebo or sotatercept titrated from 0.3 to 0.7 milligrams per kilogram every 3 weeks. The primary endpoint is change in 6-minute walking distance, which is the registration endpoint recognized by FDA in the majority of other regulatory authorities.

In essence, the study is designed to replicate the findings of the Phase II PULSAR study with greater precision in the larger patient population. Enrollment was exceptionally fast, remarkable during a period where COVID-19 disrupted many trials. The enthusiasm of investigators and the patients has been palpable. We expect the results to read out before the end of the year.

Now at current PAH, we just treat the symptoms of the disease by dilating arteries and arterials. These medicines can improve exercise capacity, but again, as I mentioned earlier, they have 2 major limitations. Current drugs don't change the course of disease so patients continue to deteriorate. So this is where sotatercept fits in. It targets key factors involved in vascular modeling process. So it's really designed to slow or prevent disease progression.

But current drugs also nonspecifically dilate the pulmonary and systemic circulation, and they cause low blood pressure that limits tolerability and the ability to induce sufficient vasodilation in lungs. Our inhaled sGC stimulator, MK-5475, aims to address this problem.

Now as we've discussed, PAH is a disease that primarily affects blood vessels in the lungs. So the ideal medicine would increase blood flow to the lungs -- the ideal medicine to increase blood flow to the lungs should have the effect targeted to the lungs without any systemic effect. All orally-delivered therapies for PAH dilate the systemic circulation. Because of this, hypotension can be a dose-limiting effect. It's a balance between blood vessel dilations in the lung to improve exercise tolerance versus the reduction in the level of systemic blood pressure that may cause the patient to feel lightheaded. To maximize drug delivery, many of the drugs are titrated slowly to build systemic tolerance.

Finally, many of the current drugs have substantive barriers to use, including drug-drug interactions and bleeding risk. So our chemists went about developing a drug called MK-5475, which is an sGC stimulator with the potential to be formulated for delivery by inhalation. The mechanism of action for MK-5475 is sGC stimulation, which is the same mechanism used in Adempas, a drug that we co-market with Bayer. This drug already is approved for PAH and chronic thromboembolic pulmonary hypertension.

MK-5475 is administered with a proven device, a dry powder inhaler built on the technology used in ASMANEX inhaler previously commercialized by Merck. The promise of this approach would be a different route of administration, no need for titration, the potential to combine this approach with other mechanisms, and importantly, improve 6-minute walking distance when added to background therapy.

Now we became excited about MK-5475 based on preclinical experiments, one of which we show here. We compared the delivery of MK-5475 via inhalation on the left or by mouth on the right in that same Sugen 5416 hypoxia rat model I discussed previously. We looked at systemic and pulmonary vascular resistance as well as systemic and pulmonary arterial blood pressure. As you can see on the left, inhalation resulted in lowering of pulmonary vascular resistance and pulmonary pressure, but systemic resistance and systemic blood pressure were minimally impacted, exactly as we hypothesized. And on the right, you can see that oral therapy results in drops in blood pressure, both in the pulmonary and systemic circulation. So this is a good example of why inhalation was very, very important. So these data led us to early clinical studies that were quite promising.

Now to optimize clinical trial efficiencies, we were able to agree with agencies on an operationally seamless Phase II/Phase III approach, allowing us to conduct Phase II and Phase III cohorts under 1 combined study protocol. The ongoing Phase II cohort will help us to select and dose using changes in pulmonary vascular resistance as the primary endpoint. This will be followed by a Phase III cohort, seeking initial approval based on 6-minute walking distance, with a long-term extension that captures additional endpoints relative to guidelines, committees and to payers.

With that, let me turn it over to Arpa, who will talk about the commercial opportunities for sotatercept and MK-5475 in this important indication of PAH.

Arpa Garay - *Merck & Co., Inc. - CMO for Merck Human Health*

Thank you, Eliav. Merck's PAH portfolio has the potential to transform the way PAH is managed and to really establish Merck as the leader in serving patients suffering from PAH, a rare disease with a high mortality rate. We expect the category to continue to grow, and we're confident that our PAH portfolio can play a significant role in this often fatal and rapidly progressive disease.

We have 3 important assets as part of our portfolio today. We have Adempas, which is currently commercialized in partnership with Bayer, and it continues to be a growth opportunity in both PAH as well as chronic thromboembolic pulmonary hypertension. Thus far, it has demonstrated double-digit worldwide growth with over $1 billion in global sales in 2021. Assuming our studies are successful, the additional 2 assets that Eliav has just covered are also important pieces of our portfolio in PAH. First, sotatercept offers the potential to tackle PAH as the first and only non-vasodilator that addresses the underlying disease instead of treating the symptoms only.

The second asset, our inhaled sGC, MK-5475, has the potential to be a best-in-class vasodilator, offering a novel administration pathway and different dosing regimen that can be potentially used with PDE5, which are a current standard of care that approximately 60% of patients are currently treated with.

As a reminder, the PAH market is currently managed with a combination treatment paradigm. Despite the advances in treatment options and usage of combination approaches, there is still a 43% mortality rate at 5 years. Health agencies, clinicians and payers recognize the need for additional treatment options within PAH as a result. And we expect that payers will continue to prioritize access to these medical advancements in order to serve patients suffering from this rare disease.

What I hope you see here is that the Merck PAH portfolio is complementary, including both best-in-class vasodilators as well as a non-vasodilator in sotatercept that has the potential to treat underlying disease. And these assets can potentially be used not only in combination with other approved PAH therapies but also in combination with each other. And this allows us to focus on creating a market-leading rare disease customer engagement model.

Merck's industry-leading PAH portfolio, as you'll hear, has the potential to treat a broad range of PAH patients across the patient's journey, covering Groups 1 to 4, which reinforces the multibillion-dollar potential for the Merck PAH portfolio. Now let me hand it back to Eliav to talk about some of these expansion opportunities for both sotatercept and MK-5475.

Eliav Barr - *Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories*

Thanks, Arpa. The focus of the discussion so far has been on PAH. However, for sotatercept and MK-5475, there are opportunities to expand further into additional areas of unmet need. For sotatercept, there's an opportunity to evaluate its impact in the treatment of patients with combined post-capillary and pre-capillary pulmonary hypertension caused by heart failure with preserved ejection fraction. There are currently no marketed therapies indicated for these patients.

We have a Phase II trial called CADENCE that is evaluating sotatercept's impact in these patients. The primary endpoint is pulmonary vascular resistance with a key secondary endpoint of 6-minute walking distance. For MK-5475, given its differentiated approach to targeting therapy directly into the lungs, we're evaluating whether it could have additional impact in patients with pulmonary hypertension associated with chronic obstructive pulmonary disease or COPD. The prognosis is particularly poor for those COPD patients who develop pulmonary hypertension.

Now I'll turn it over to Joerg who will talk about MK-2060 which targets Factor XI. Joerg?

Joerg Koglin

Thank you, Eliav. Let's switch topics to anticoagulation and our Factor XI program. Cardiovascular diseases such as ischemic stroke or heart attacks are caused by blood clots. While the last 70 years of research have given us ever more effective agents that prevent such clots, all these agents are associated with increased risk of life-threatening bleeding. In large part, this is explained by the fact that the cascade of protein factors that control immuno-stasis and thrombosis are highly intertwined and overlapping with a common final pathway. All existing anticoagulants target this common pathway, which explains why antithrombotic efficacy remains connected with bleeding liability.

Arguably, the development of an effective anticoagulant that does not bleed might be one of the remaining holy grails in clinical medicine. While we would argue that existing anticoagulants such as Factor Xa inhibitors might offer a clinically sufficient therapeutic window in lower-risk patients, such as patients with atrial fibrillation or after knee or hip replacement, there are other populations with substantially higher bleeding risks for whom existing anticoagulants still are not a good option.

Our initial efforts are focusing on patients with end-stage renal disease and the need for hemodialysis, who have an enormous risk for life-threatening thrombotic events such as stroke, myocardial infarctions or venous thromboembolisms. At the same time, these patients have substantially higher risk for bleeding, limiting the use of other anticoagulants.

For a number of reasons, Factor XI inhibition comes with the potential to offer effective anticoagulation with minimal risk for clinically meaningful bleeding. Factor XI is an integral component of what is called the intrinsic pathway of the physiologic coagulation cascade. Patients with inherited forms of Factor XI deficiency, patients with so called hemophilia C, has been shown to have a lower risk for thrombotic events without elevated

risk for major bleeding. In Factor XI knockout mouse models, there is a lower rate of thrombosis with no apparent increased bleeding. And this is further confirmed by a number of other Factor XI programs using treatment modalities, such as small molecules or antisense oligonucleotides in other patient populations, which in recent Phase II readouts have shown good anticoagulation with a safety profile that in small Phase II studies seem comparable or even better to their respective control groups.

MK-2060 is a monoclonal antibody administered intravenously, which is the preferred route for patients with end-stage renal disease requiring regular hemodialysis. MK-2060 is designed to work through a dual mechanism of action, both blocking the activation of Factor XI as well as the downstream activity of activated protein. The early development studies of MK-2060 was well tolerated with good target engagement and pharmacodynamic effects warranting the start of further dose-finding studies in Phase II.

With the ultimate goal of developing an anticoagulant that would reduce major thrombotic cardiovascular events in patients with ESRD or end-stage renal disease, our Phase II study of MK-2060 uses prevention of thrombosis through arteriovenous graft access for dialysis as its surrogate for dose selection. This study is off to a very good start with enrollment currently ahead of plan, signaling general excitement in the field around this project. With this time-to-event study, we hope for the appropriate number of events to accrue in the first half of 2023.

As mentioned, we are using AV graft failure as a surrogate endpoint for dose selection in Phase II. Patients with dialysis through AV grafts have an exceptionally high rate of graft thrombosis every year. It has been shown that AV graft data correlates reasonably well with other arterial and venous thrombotic events in these patients. This very efficient approach to dose selection has been reviewed and supported by major regulatory authorities. If MK-2060 is successful in Phase II, we would hope to move this program into Phase III in an outcome study in a broader ESRD population on dialysis to evaluate the impact of our antibody on major thrombotic cardiovascular events such as myocardial infarction, ischemic stroke, pulmonary embolisms, deep vein thrombosis or acute limb ischemia.

If positive, the Phase II study would also trigger further consideration of additional formulation options such as for subcutaneous administration that could facilitate expansion into additional indications such as other stages of advanced renal disease. Now Arpa will talk about the commercial potential for MK-2060.

Arpa Garay - *Merck & Co., Inc. - CMO for Merck Human Health*

Thank you, Joerg. What we're excited about is that MK-2060 is likely to be the first Factor XI/Factor XIa in development for end-stage renal disease patients who, as you heard, are at higher risk for CV events. They have 20x the risk of CV death, 6x higher risk of stroke, 5x higher risk of myocardial infarctions as well. As we focus on this specific population with an area of high unmet need, we believe MK-2060 has a substantial runway, with a potential for clear differentiation from the rest of the market through an IV formulation which is anticipated to be able to integrate into existing in-center dialysis patient care and the potential to offer anticoagulation without significant bleeding liability, which remains an unmet need in this population where there is currently no standard of care.

If we are successful in showing efficacy in the hard-to-treat end-stage renal disease area, this helps to provide confidence that other indications may offer the promise of future growth potential. For example, expanding into a broader CKD population or the chronic kidney disease population through life cycle management could afford an opportunity approximately 2.5x the size of the end-stage renal disease population.

Reduction of major thrombotic events would enable Merck to have a meaningful impact on cardiovascular disease at a global scale. And we can do this by impacting atherosclerotic cardiovascular disease, which is a leading cause of cardiovascular mortality. I will now hand it off to Fiona to talk about MK-0616, our oral PCSK9 inhibitor.

Fiona Marshall - *Merck & Co., Inc. - Head of Neurosciences*

Thank you, Arpa, and good morning, everybody. I'd like to introduce you to our oral PCSK9 inhibitor program, MK-0616, and share with you why we are excited about this program. As you heard earlier from Dean, Merck has a long-standing legacy in the area of hypercholesterolemia with the early development of statins that have been so important in helping patients by reducing their LDL cholesterol levels.

Despite the benefit from the use of statins, there is still a very substantial cardiovascular risk which can be attributed to a number of different factors that include the remaining high levels of LDL cholesterol. There is, as you know, a very well-established link between high levels of LDL cholesterol and the development of atherosclerosis. Importantly, data have shown that following treatment with existing options, the more LDL cholesterol is reduced, the greater the reduction in cardiovascular event risk.

Now despite current treatments, millions of patients around the world are still not meeting the targets set forth in the guidelines. As you can see in the panel on the right, with the real-world study data from the European Union, according to the 2016 European Society of Cardiology guidelines, less than half of patients reached their LDL cholesterol target, while only 1/4 met their goals according to the newer 2019 guidelines. Goal attainment is similarly poor in the United States as well as other parts of the world. And consequently, high LDL cholesterol continues to account for millions of deaths worldwide each year.

Our objective has been to develop a highly-effective oral cholesterol-lowering therapy while improving upon efficacy and safety profile seen with existing oral treatments. The PCSK9 has emerged as an important target for lowering LDL cholesterol to prevent atherosclerosis. Now despite tremendous efforts, there are no oral PCSK9 inhibitors on the market today. This has been particularly challenging to achieve due to the complex nature of the PCSK9 protein.

PCSK9 has a key role in cholesterol homeostasis by regulating the levels of the LDL receptor, which is responsible for the uptake of cholesterol into cells. Upon binding of PCSK9 to LDL receptors, the PCSK9 protein stimulates LDL receptor degradation, and this results in fewer LDL receptors on the cell surface. Genetics has shown that mutations in PCSK9 can alter the risk of cardiovascular disease. So gain-of-function mutations that result in higher LDL cholesterol levels therefore increase the risk of cardiovascular events.

Now in contrast, people who have loss-of-function mutations in PCSK9 have lower LDL cholesterol and demonstrate markedly decreased cardiovascular risk. So correspondingly, inhibition of PCSK9 function causes an increase in the number of LDL receptors, facilitating the clearance of LDL cholesterol from the circulation.

As you know, there are a number of injectable PCSK9 inhibitors on the market, which have been shown to reduce LDL cholesterol by 50% to 60%. However, despite their strong safety and efficacy profile, use has been limited, and this is due to access and adherence challenges as a result of the need for multiple repeated injections by trained health care providers. So the challenge has been to identify compounds that have the potential to be potent inhibitors of PCSK9 but with properties suitable for oral administration.

To achieve this, we decided to pursue a macrocyclic peptide strategy. The starting points are identified by screening large libraries of cyclic peptides using messenger RNA display technology. And this led to the identification of tricyclic peptide leads that were then optimized by Merck chemists using 3-dimensional protein structure-based design and advanced computational techniques. The flat surface of the protein makes PCSK9 difficult to drug with conventional small molecules, but it is actually well suited to cyclic peptides.

And then further iterations of chemistry gradually improved the potency, the stability and other drug-like properties, ultimately leading to MK-0616. MK-0616 has actually similar potency in binding to PCSK9 as a monoclonal antibody, which are given by injection and so it works in a similar way. But it is less than 100th of the size of the antibody. And importantly, this means it can be given orally as a tablet when it's combined with permeation enhancers. In addition, it can be made by simple chemical synthesis, which lowers the cost of production greatly relative to biologic manufacturing systems. Nonclinical safety studies supported further development with no clinically relevant adverse events observed to date.

Now I would like to tell you about the Phase I data from our MK-0616 clinical program. First and foremost, safety and tolerability of once-daily MK-0616 were assessed in a Phase I single- and multiple-ascending dose studies. No serious adverse events were observed and the results supported continued development.

Next, in order to understand whether MK-0616 achieved the desired target engagement, namely its ability to bind PCSK9, we measured 3 PCSK9 levels in blood samples, and this is shown in the top panel. As you can see, MK-0616 produced a rapid reduction in free PCSK9 levels to greater than 90% at baseline and this was sustained over 24 hours. Importantly, as illustrated here, this translated to greater than 60% further reduction in LDL cholesterol by day 14 in participants already receiving statin therapy.

In summary, MK-0616 has the potential to be differentiated from other oral LDL cholesterol-reducing therapies on the market based on its promising safety and efficacy profile. And importantly, as an oral treatment, it has the ability to overcome barriers currently associated with the use of injectable PCSK9 inhibitors.

So based on these promising Phase I results, we now have initiated Phase IIb dose-ranging studies in patients with hypercholesterolemia, including those at risk of or with established atherosclerotic cardiovascular disease. The study is designed to evaluate the efficacy and safety of MK-0616 in patients who have elevated LDL cholesterol either with or without statin therapy. Primary endpoint of the study will be the percent reduction of LDL cholesterol at 8 weeks. We've started randomizing patients into the study in March, and we anticipate a primary completion date in early 2023.

As we think about MK-0616, we plan to seek approval based on LDL cholesterol lowering for secondary prevention in high-risk patients that have also considered starting. And we're also considering starting an outcome study in parallel. With that, let me turn over to Arpa, who will talk more about the commercial opportunity for MK-0616.

Arpa Garay - *Merck & Co., Inc. - CMO for Merck Human Health*

Thank you, Fiona. Despite a multitude of approved therapies, there continues to be a significant unmet need with a large population of patients at risk for heart attacks and strokes due to suboptimal lipid control. In just the U.S., EU and Japan alone, there are more than 40 million patients currently at risk and potentially a significant amount more around the world.

Even with extensive use of statins, what we're seeing is that 70% of patients continue to not be at goal. MK-0616 has the potential to be the most effective LDL-lowering pill that could transform the way cholesterol is managed around the world. Customer insights from early market research have really reinforced our excitement around MK-0616, showing that approximately half of clinicians signal a strong interest in an oral dosing option.

With Merck's legacy in this category, it truly positions us well to make a meaningful impact for patients. And we fully intend to move rapidly with the goal of securing first-mover advantage in the oral PCSK9 market. Now let me hand it back to Fiona to talk about our approach to cardiovascular discovery research.

Fiona Marshall - *Merck & Co., Inc. - Head of Neurosciences*

Thank you, Arpa. It is an exciting time to work in discovery research with significant advances in enabling technologies that allow us to explore mechanisms underlying cardiovascular disease and to identify new drug targets. Our aim is to target fundamental mechanism for the cause of the disease with a long-term aim for disease modification rather than just symptomatic treatment. We focus on human biology, utilizing a combination of clinical data, genetics and human cellular models.

In order to build depth of expertise in each of our therapeutic areas, we focus on specific cell types or pathways relevant to disease. In the case of our cardiometabolic group, the areas of focus include inflammation, fibrosis, vascular dysfunction as well as tissue dysfunction and remodeling. The benefit of working in a company like Merck is that we can bring together all of these new capabilities in target discovery, with advanced chemistry and biologics that match the target with the optimal modality, thus enabling the rapid translation of new discoveries to clinical assets with the potential to bring benefit to patients.

Our drug discovery portfolio includes validated targets such as PCSK9 where we can use Merck's advanced drug discovery capabilities to find new and improved therapeutics as well as novel proprietary targets. Using human cell models such as organoids, combined with screening technologies such as CRISPR, we can screen and identify new targets. Target classes that were previously considered difficult to drug can now be matched to the relevant modalities, whether this is conventional small molecules, biologics or macrocyclic peptides.

A critical component of our work in discovery and translational medicine is to ensure a deep understanding of the relationship between target modulation and drug dose response. And this is done through advanced preclinical models such as humanized mice, careful experimental medicine and rigorous clinical pharmacology linked to biomarkers of efficacy. I think this approach was well illustrated by the PCSK9 example.

Another example is shown in this slide, which was an early clinical study of our inhaled soluble guanylate cyclase activator, MK-5475. The goal for this molecule, as you've heard, is to enable selective pulmonary arterial vasodilation. And in this translational medicine study, we used functional respiratory imaging technology, which uses high-resolution CT scans and computational fluid dynamic technology, enabling noninvasive measurement of the entire respiratory system. And this provides more detailed information than conventional lung function tests. You can see in these images the improvement in blood flow to the lung following inhalation of MK-5475.

As we continue to advance our discovery research, we are establishing a number of innovative hubs that focus on particular therapeutic areas, combined with expertise in specific therapeutic modalities. Most recently, we've established research sites in London, Cambridge, Massachusetts and in South San Francisco. The new site in San Francisco is our center for cardiometabolic disease discovery research. Here, research scientists are located with drug discovery experts and with business development colleagues that allow us to connect with the strong communities with biotech and academia in these local areas.

In summary, it's a very exciting time to lead discovery research here at Merck, where we have the potential to fundamentally alter the course of many grievous diseases, including cardiovascular disease. And with that, let me turn the call back to Dean to provide some closing remarks.

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Thank you, Fiona, and thank you for your attention, all of you. As I mentioned in my opening remarks and as you have observed throughout this session, first, once we identify a novel pathway molecule or technology platform, we seek to establish a clinical beachhead with the first indication in a defined patient population. Second, based on the data from the study, we identify opportunities to expand the label population, deepen the response and broaden the label claim and extend with the next generation in dosing schedules, routes of administration and new patient populations.

And you heard today about the importance of the sGC pathway. As Joerg mentioned, some of the work had demonstrated the role of nitric oxide to the sGC pathway in cardiovascular health and disease, evidence demonstrating the benefit of VERQUVO in reducing cardiovascular mortality or heart failure hospitalization illustrates the potential of this mechanism and provide strong rationale for selectively targeting the lungs with our inhaled sGC stimulator for the treatment of pulmonary arterial hypertension.

Sotatercept has the potential to be the first disease-modifying agent in pulmonary arterial hypertension. And data from the STELLAR trial will inform our plans to potentially expand into additional stages of PAH and left heart disease. Our Factor XI program is focused initially on patients with end-stage renal disease on hemodialysis. Thrombosis and hemostasis present clinical conundrums for these patients, especially given their high prevalence of hypertension, coronary artery disease, stroke and atrial fibrillation, the threat of excessive bleeding severely limits their therapeutic options.

And finally, as we just talked, when you think about the cyclic peptide platform, we envision that protein targets normally reserved for large molecules of biologics can now be targeted by small molecule chemistry. We can start with an oral form of PCSK9 inhibition because of the large unmet need, but this platform or this program provides a proof point to conceive of many other potential applications that might be addressed using this important chemistry platform.

Now as Arpa mentioned at the beginning of the presentation, the initial indication for the assets we are highlighting today as well as expanded indications for VERQUVO are expected to launch in the 2024 to 2028 time line. Now including additional indications associated with these assets, where studies are underway or being planned, we believe the overall peak commercial revenue opportunity for our cardiovascular portfolio exceeds $10 billion approaching the mid-2030s.

Now in closing, Merck has a storied legacy in developing therapies for cardiovascular disease, which remains the single largest cause of mortality worldwide. With our differentiated portfolio and industry-leading capabilities, we are uniquely positioned to positively impact cardiovascular

mortality and morbidity. I'm extremely excited by the opportunity to build upon our broad legacy in cardiovascular disease and look forward to providing updates on our pipeline in the future. Now I will hand the call back to Peter to manage the Q&A session.

Peter Dannenbaum - *Merck & Co., Inc. - VP of IR*

Great. Thank you, Dean. Grace, we are ready to begin the Q&A session. (Operator Instructions)

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Your first question comes from the line Chris Schott from JPMorgan.

Christopher Thomas Schott - *JPMorgan Chase & Co, Research Division - Senior Analyst*

Thanks so much for hosting the day-to-day and digging into the pipeline. I just had 2 quick ones here. I guess just first on the PCSK9, obviously, it seems like a really interesting opportunity. Can you just elaborate a bit on how long you see it taking to run the LDL study, assuming successful Phase II data? I'm just trying to get my hands around is kind of like a 2026, 2027 launch time line, assuming all goes well, a reasonable way to think about this? Or is there any ability to accelerate those time lines? So just any color there would be appreciated.

And then the second one is just thinking about business development priorities within cardiovascular. You've obviously brought a few assets in-house. But post-Acceleron, I guess, is the focus here more on smaller deals, given the state of the pipeline? Or would you consider a larger deal? And maybe more specifically within there, is it -- is the focus later-stage assets, earlier? Is it technology platforms? I'm just trying to get any color as you think about kind of further kind of building upon the portfolio you have today.

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

So this is Dean. Why don't I have Joerg answer the question about the PCSK9 clinical trial time line? I would emphasize that there is a long history or a well-worn history of how one thinks about, for example, the first approval based on biomarkers, followed later on by outcomes. But why don't we handle that first, Joerg, and then I'll handle the broader business development question?

Joerg Koglin

Yes. Thank you, Dean. So our Phase IIb study, as Fiona mentioned, has started earlier in the first quarter. We expect as we learn about the Phase II results somewhat in the early part of 2023, that will be the right time point then to go into a Phase III program. And as Dean just mentioned, we assume that the initial approval will be based on standard LDL studies. The limiting factor for all these is to accrue enough safety data. That's where we are right now, and I think we'll communicate the time lines of our Phase III studies at a later point of time.

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Yes. In relationship to the business development, I just probably would want to make maybe 2 points. The first is, this past year, we've made, for example, forays with Pandion and with Acceleron. And the reason I like those deals is because they really accelerate our ability, in one case, to affect immunology and the other, affect cardiovascular. But they're also built on internal insights and programs that give us a situation where we believe that we are not just interested in the program but we have advantages as the advantaged owner of such programs. So I just want to emphasize that. And this is something no different than how we thought about any other therapeutic area.

The second point is we look at lots of different assets, but we do it from the point of whether we can make a substantial impact on patients' lives. And so within the cardiovascular but also throughout all the therapeutic areas, I don't know that we're constrained or contained by a certain size. It's really where we want to focus and where we think the unmet need.

I will put something out there, which is although we're focused on the cardiovascular session here, I would say that metabolic disease is something that's really advancing. And the sort of the intersection between inflammation and immunology in those fields are really important. And although they're not really cardiovascular, we've made substantial business development deals in relationship to that intersection focusing on NASH. But that intersection between inflammation and metabolic diseases often show up in cardiovascular disease. So those are places that we're interested in. But basically, we're going to follow where we think we can make the biggest impact, where the science is compelling and where we think that we are the advantaged owners of such a business development deal.

Operator

Your next question comes from the line of Carter Gould from Barclays.

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

A couple for me on 5475. So I guess when we think about COPD, what's the gating steps there? The Phase I was done earlier this year according to clinicaltrials.gov. And you're highlighting the indication here, so I'm assuming you liked what you saw. Should we view the Phase II portion of INSIGNIA as informing the dose might carry forward in PH-COPD? Just trying to understand any dependency there and if you can match how fast you move forward with INSIGNIA. And then bigger picture, when you think about 5475, should we think about that ultimate opportunity more weighted to PAH or the Group 3 space, given the limitations of systemic vasodilators, given the ventilation perfusion mismatch you alluded to?

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Yes. So why don't I have Joerg answer that specific question in relationship to how we think about COPD, and then I'll ask Eliav to take that broader question that you've placed in front of us.

Joerg Koglin

Yes. So PH-COPD, as you appreciate, is a completely new indication, so there is no blueprint in how to develop drugs there. So for us, it is important to move after a Phase I study that focus on hemodynamic effects. Through the proper steps of product development, our next step will be a proof-of-concept study where we want to make sure that in this patient population, these hemodynamic effects also translate into clinically meaningful effects. So we'll assume that the continuation of the program will be posted in clinicaltrials.gov during the remainder of this year.

Eliav Barr - *Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories*

Thanks, Joerg. This is Eliav. So from a broader point of view, I think both of these drugs, 5475 and sotatercept, have the ability to address pulmonary hypertension across a multiplicity of diseases and indications. One of the things that Merck has as an advantage in my mind is the ability to understand these new areas like pulmonary hypertension of COPD, like pulmonary hypertension associated with heart failure with preserved ejection fraction.

We also have, with sotatercept, a real foundational drug that will make tremendous progress in our fight against pulmonary arterial hypertension. But my expectation is that this is only the beginning, that other forms of pulmonary hypertension may benefit from sotatercept. So we're well positioned to build an important body of evidence to address the multiplicity of types of PH in addition to those first indications we've talked about today.

Operator

Next, we have Mara Goldstein from Mizuho.

Supawat Thongthip - *Mizuho Securities USA LLC, Research Division - Associate*

This is Supawat for Mara Goldstein. So just a quick question on VERQUVO. Can you characterize the current access for VERQUVO? And perhaps, what do you anticipate for this year and perhaps next year in 2023?

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Yes. Why don't we have Arpa take that question? Arpa?

Arpa Garay - *Merck & Co., Inc. - CMO for Merck Human Health*

Sure. Thank you for the question. So we remain optimistic about the potential for VERQUVO. Just an important thing to remember is when we launched VERQUVO, we had unfortunately just missed the window for Medicare Part D in the United States. So the current situation with access is we have fairly broad commercial access but limited Medicare D access in the United States, where 70% of our patients currently reside, right?

So from an access perspective, we are limited today in terms of the broadest patient population with Medicare Part D. That being said, we do expect to hit an inflection point later in '22 as well as '23 as we gain access to Medicare Part D across the United States. And if our commercial success is an indication, we do expect that access to be fairly broad over the coming months.

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Just really quickly, whether Joerg or Eliav want to just speak about the recent AHA/ACC guidelines. So Joerg, can you just emphasize what is different about the AHA/ACC as they evolve how they think about heart failure?

Joerg Koglin

Yes. Thank you, Dean. Obviously, we are excited about vericiguat now being recognized for the first time in the 2022 AHA/ACC/HFSA guidelines for the management of heart failure just published last Friday. We are encouraged that worsening heart failure is now recognized for the first time in the guideline as part of the trajectory of patients with Stage III heart failure. And vericiguat is the only drug that has been studied in this specific patient population, specifically, and is recommended in the guideline for patients with working chronic heart failure. Beyond that, we believe that the readout of the ongoing VICTOR study will continue to strengthen and expand the role of VERQUVO in future guideline updates.

Operator

Next, we half Steve Scala from Cowen.

Stephen Michael Scala - *Cowen and Company, LLC, Research Division - MD & Senior Research Analyst*

I have 2 questions. The $10-plus billion peak sales estimate by the mid-2030s, what portion is late-stage assets such as sotatercept and VERQUVO versus early-stage cardiovascular assets? And does it include anything not in development now? The second question is on MK-0616. How is it different than Novo's effort, both of which appear to use permeability enhancers to facilitate small intestine transport?

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Why don't we have that first question be by Arpa? And then when you're speaking about the molecule and how it's different and its structure is different, I'll have Fiona touch that. But Arpa?

Arpa Garay - *Merck & Co., Inc. - CMO for Merck Human Health*

Sure. So just to answer your first question around the $10 billion, as we think about the initial indications, so the initial indications that were covered today, most of those will be launched within the 2024 to 2028 time frame. So as we think about the proportion of the $10 billion that would come from the earlier indications, we're looking at over $5 billion coming from that set of opportunities. And then the remainder of the $10 billion would come from the expanded indications from studies that are already currently underway that we've discussed today. So this broader opportunity of $10 billion does not include any potential expansions of indications or business development or earlier-stage compounds that we did not review in today's session.

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Fiona?

Fiona Marshall - *Merck & Co., Inc. - Head of Neurosciences*

Yes. Thank you. So the other peptide that you're referring to is actually a shorter peptide and has a very different structure from our molecule in that it's designed to mimic part of the LDL receptor and bind to PCSK9 in that way. As I told you about our program, we designed this using the X-ray crystal structure of PCSK9 to then take a cyclic peptide that was optimized by structure-based design. And this produces a very unique incredibly high potency, actually picomolar potency, closer to the potency of a monoclonal antibody really than a sort of peptide type of drug. And then it would stabilize to allow to have the oral stability. Now until these go through clinical trials, then it's hard to sort of compare what level of efficacy they would have. But they are sort of mechanistically somewhat different.

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Yes. I would just emphasize, the mechanism that we're trying to sort of follow is the mechanism that we know works in the clinical arena, which is where the antibody disrupts LDL receptor and PCSK9 interaction. That's where our position has been focused on with this macrocyclic peptide. The concept that Fiona says is there are other ways to do this, but it's not sort of mimicking that antibody disruption.

I just would emphasize that we use this program because we think an oral PCSK9 is really important. But we also use this as a demonstration of how we can, with small molecule chemistry, essentially recreate many interactions that are known to be important in biology and medicine as been shown by what antibodies can disrupt. So we believe that our macrocyclic technology and peptide is "following" what the PCSK9 antibodies, and it also gives me a view to how all of us might be able to use this as we think of other targets normally relegated or normally focused by the biologic modality.

Peter Dannenbaum - *Merck & Co., Inc. - VP of IR*

Great. Thank you, Steve. Next question please, Grace.

Operator

Next, we have Mohit Bansal from Wells Fargo.

Mohit Bansal - *Wells Fargo Securities, LLC, Research Division - Senior Equity Analyst*

Maybe one -- a couple of questions. So one part -- one modality that is missing from your cardiovascular portfolio is siRNA and ASOs. Do you have any reservations about using them or it could be an area you explore in the future to build on this pipeline? Because there are quite a few of them coming up in the cardiovascular area. And then the other housekeeping question is, PCSK9 orals, can it be co-formulated with statins?

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

So I will make a shot at having Fiona talk about siRNA and ASO. I would just emphasize, we think all these different modalities are important. But in a situation where we can make an oral medicine that's extremely stable shelf life, can be sent to you through FedEx or through Amazon and this, it's really important. But I'll talk -- have her talk about the siRNA and ASO sort of question first and then I'll take the second question. Well, no, I'll have you also take the second question of the potential to co-formulate these orals in relationship to PCSK9 and oral, for example, with a statin.

Fiona Marshall - *Merck & Co., Inc. - Head of Neurosciences*

Yes. Thanks, Dean. So as Dean said, I think in each disease area, you have to think about the patient population and whether they're going to prefer to take an easy once-a-day oral or whether an injectable would be more relevant to the disease. So we always try to start with thinking about the patients and what would they prefer, what is going to be easier for the health care system to administer. And there's always that flexibility with an oral that you can stop taking it and if you have adverse events or that sort of thing.

That said, once you understand a lot about a target, then there's a huge convenience in some cases of having an injectable. So we are very interested in antisense and gene therapy approaches. And actually, we do have a collaboration in the siRNA area in the field of NASH. So we actually have 2 different targets that we haven't disclosed yet, but we do think that, that is a disease area where an antisense could be useful. So within the broader cardiometabolic disease, it's certainly something that we're interested in.

And so then moving on to the co-formulation, again, the benefit of having an oral therapy is that it has that advantage of co-formulating with other oral therapies, so this is certainly something that we would consider for the future.

Operator

Next, we have Andrew Baum from Citi.

Andrew Simon Baum - *Citigroup Inc., Research Division - Global Head of Healthcare Research and MD*

Yes. Sorry about that. Forgive me if I address something which was already answered earlier. I joined the call a little late. First question is on MK-2060. Could you talk to the possibility of dosing subcutaneously and anything about the therapeutic half-life plus any comparisons versus the [Adempas] molecule? And then second, in relation to your oral PCSK9, in the event that out-of-pocket caps do not get introduced to Medicare, isn't it going to be a struggle to get penetration in the large percentage of patients who would benefit from this drug, given the much lower financial friction as well as convenience benefits in the U.S. for inclisiran?

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Yes. So let me just have Joerg answer the question about the subcu formulation, and then I'll give Arpa a shot at the question in terms of the payer market and as such. Joerg?

Joerg Koglin

Yes. So the way how I would answer the question is as follows. I think we were trying to explain that our initial focus is on ESRD patients with hemodialysis. We identified that as an exceptionally high unmet clinical need that we would consider as a beachhead. These patients, on average, have a median pill burden of 19 tablets per day, so IV administration in those patients was clearly the preferred route of administration. So we believe that our MK-2060 program in that patient population, besides having the dual mechanism of action, is actually differentiated through the focus on an IV administration. That being said, as we will learn more about the Phase II results, we are already discussing additional efforts to work on the subcu formulation that would then allow us expansion into, for example, other end-stage kidney disease patients.

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Arpa?

Arpa Garay - *Merck & Co., Inc. - CMO for Merck Human Health*

Sure. So from an access perspective, I think it's important to just note the payers do recognize the unmet need that remains, with 70% of patients still not at goal. From our perspective, as we think about the opportunity with MK-0616, with the small molecule approach that we have, our goal is to ensure broad and equitable access where the notion of some of the barriers to access that the early injectable PCSK9s have faced could potentially be removed with the small molecule approach. So we are positioning our launch with a broad global equitable access strategy. And in terms of Medicare Part D reform, I will just remind you that Merck is supportive of it. But whether or not the reform happens, we will be taking that into consideration to ensure as many patients benefit as well.

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Yes. I think it's important to emphasize, Fiona really focused on the ingenuity to make this molecule. This is a complex small molecule and we are also very confident that we can synthesize and manufacture this not at clinical scale but at commercial scale, such that this is something that we want to be as a small molecule. And the access to be able to do that is also deeply connected with the cost of goods related to how you make such a small molecule and we are confident in our ability to tackle that issue.

Operator

Next, we have Luisa Hector from Berenberg.

Luisa Caroline Hector - *Joh. Berenberg, Gossler & Co. KG, Research Division - Co-Head of Global Pharmaceutical Team*

I wanted to come back to the $10 billion peak sales and just confirm that, that is unadjusted sales number. And therefore, maybe to explore a little bit about the probability of success that you are assuming, is it fair to go with average probabilities of success, given the status? Or are there assets that you've highlighted today where you would expect a higher probability of success based on the science?

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Let's have Arpa take care of those commercial forecast questions.

Arpa Garay - *Merck & Co., Inc. - CMO for Merck Human Health*

So just simply, I would say the $10 billion -- the greater than $10 billion potential is unadjusted sales numbers. From a probability of success perspective, I'm going to hand it back to Dean, as obviously, some of these opportunities are with VERQUVO, for example, which is a more established product. So maybe you can comment.

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Yes. I mean, it's this question of how do you lay out the probability of success of any program, how do you look at a late stage or a later stage versus an earlier stage. The VERQUVO, we have approved Factor XI and sotatercept and inhaled soluble guanylate cyclase are moving quickly behind those programs. And then we have something that's earlier on, which is the PCSK9. And so we can sit there and adjust. What I would actually say is that the data to date in relationship, for example, for VERQUVO is we know that pathway works in a population that had yet been defined by our treatment and our treatment guidelines and so we've been able to establish that.

So we believe that is a "deemed" somewhat derisked molecule and mechanism, but whether it can be expanded to this other population is why we do the experiment. The sotatercept experiments look very promising, but essentially, the Phase III will have to be the Phase III. But there is strong Phase II data and not just one piece of Phase II data, there's a couple of Phase II data that give us the confidence to make the deal.

In relationship to the inhaled soluble guanylate cyclase, we do know. We do know that, that pathway and molecules in that pathway work. We also know what the problem is. And so we'll have to just see what the clinical data looks like. Factor XI, I think we'll see just our data and other people. And then the issue related to PCSK9 as a pathway and as a molecule, I think there's a clear pathway for PCSK9, and we are mimicking the interaction that we're seeking to disrupt, which is already sort of that proof of concept has already been laid out by the antibody.

So that's how I sort of, at a broad view, look at how we think about our sort of PTRS. We have other programs in the discovery space that are coming through later. And clearly, they have a much different profile in terms of their probability of success as they -- as we'll see what they look like in the clinic.

Operator

Next, we have Umer Raffat from Evercore ISI.

Umer Raffat - *Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research*

I wanted to focus on sotatercept for a second, if I may. First, I'm curious what percentage of the Phase III patients in STELLAR trial are on background triple therapy. I'm very curious what that percentage is. And how are you thinking about the inherent variability on 6-meter walk endpoint? Second, would your peak sales estimates on sotatercept look any different if the time to clinical worsening or survival endpoint does not hit? And then finally, I was quite intrigued that there was a recent exclusion criteria update on platelet counts less than 50,000. It was relatively recent and very late in the trial. And I'm curious, was there any thrombocytopenia finding or any sort of DSMB update from Phase III that prompted that?

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

So let me have Joerg take some of those first questions and maybe the latter question, I'd have Eliav provide a broader view. And then I'll -- to have Arpa touch from a commercial standpoint, the question of how does one think about the commercial, depending on the different clinical trials.

Joerg Koglin

Good. So STELLAR, obviously, while fully enrolled is an ongoing study, and we are in blinded medical monitoring. But as you recall, the [Balta] study showed even more promising results in patients that were on triple therapy and that were more advanced. And we see that now in the patient enrollment instead of we will have a fairly large component of patients that are already on triple therapy. This will be tested on top of standard of care.

With respect to thrombocyte changes, mechanistically, changes in thrombocytes are one of those safety endpoints that we proactively monitor. So far, the DSMB has not flagged any concerns there. And we'll learn more when the data reads out later this year. Eliav?

Eliav Barr - *Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories*

Thanks, Joerg. I would also add that the sotatercept studies and STELLAR, in particular, are -- have been extraordinary in terms of the retention of patients in how few discontinuations we've had. They are, so far, blinded, of course. The tolerability profile has been just exceptional and better than we expected from the perspective of dropouts and things that happened to patients over the course of time, especially in the context of COVID.

So I think that overall, the data that we're going to be able to get from STELLAR are very high quality. They'll be on patients with the right kind of background standard of care, very similar to what the PULSAR study showed. And so this will be a really good test of sotatercept, and we look forward to seeing the results.

More broadly speaking, you asked about the question about time to clinical worsening. I think that the -- overall, what's unique about sotatercept is its ability to potentially modify the disease underlying pulmonary arterial hypertension. And so when you think about long-term endpoints, time to clinical worsening, hospitalization or death, these are the kinds of endpoints that would be best impacted by those medicines that are actually impacting the pathology, the pathophysiology and not just doing symptom improvement or trying to ameliorate a progressive disease.

So while I can't tell you today what the results of the study that's ongoing will be, I think that we're uniquely positioned with sotatercept to address those questions. That's why I think the investigator community and the patient community have been clamoring for this drug. And enrollment was so brisk that it was difficult to cut it off. People were just running to the site to get on the study. Arpa, did you want to make any comments?

Arpa Garay - *Merck & Co., Inc. - CMO for Merck Human Health*

Sure. I think there was a specific question around potential commercial impact of not hitting the time to clinical worsening. In that scenario, I think what that would do is put our EU launches at risk if we don't hit that specific endpoint. That being said, we still see a blockbuster, multibillion-dollar potential with sotatercept.

And then just from a balance perspective, as Eliav mentioned, sort of the disease-modifying aspects of sotatercept, if we do hit in the ZENITH trial with the mortality benefit, we actually see significant upside to our assumed base case. So I think those 2 sort of balance each other out. But really, the commercial risk would be in the EU.

Operator

Next off, we have Chris Shibutani from Goldman Sachs.

Chris Shibutani - *Goldman Sachs Group, Inc., Research Division - Research Analyst*

Two questions, one on sotatercept. Is it your expectation that we'll see use across the entire spectrum of sort of disease classes as an add-on? Or do you expect to be positioning sota as a potential replacement for any of the drugs? Certainly across the Class II patients and III, we're seeing

multiple combination use meaningfully expand. And my second question, I'll give a little bit of love to 2060. Can we talk about how you might prioritize additional indications beyond end-stage renal disease? And to the extent that you do that, how important might a subcutaneous rather formulation be in pursuit of that? Is there some opportunity there in the broader spectrum for Factor XIa that you see potentially being a higher priority?

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Why don't I have Eliav take the sotatercept question and then have Joerg take a swing at the Factor XI question? Clearly, the data will define where we can go in all of these programs, but with that, Eliav, did you want to make a comment?

Eliav Barr - *Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories*

Sure. Actually, I think that the -- that we're interested in sotatercept being part of an overall strategy to improve outcomes and patients. So sotatercept would be probably on top of standard of care therapy. The idea here is to really transform the course of the disease and ensure that patients don't end up either home-bound, bed-bound or with more severe consequences.

And that's, by the way, why 5475 is such an important component of our strategy as well. By being able to have what we believe to be an extraordinary opportunity as a vasodilator plus disease-modifying opportunity, we really hope to transform the lives of patients with PAH. Joerg?

Joerg Koglin

So perhaps closing out the sotatercept discussion first and then I think the elegance of the development program is that you see 3 pivotal studies running in parallel. They will read out at different time lines. The HYPERION study actually is a study that will test -- does it make sense to start sotatercept early? As you saw in the slide deck, that study focuses on recently diagnosed patients. So that's an important contribution as to data results.

To your Factor XI question, you're absolutely right. Our initial focus is on patients that are on hemodialysis. For those patients, IV, clearly, is the preferred route of administration. But patients with end-stage renal disease or on hemodialysis, patients with CKD Stage IV, those are additional and even larger patient populations that cannot be appropriately anticoagulated at this point of time. And so as we are considering to expand into those patient populations, a subcutaneous formulation will be essential.

Operator

Next, we have Louise Chen from Cantor.

Louise Alesandra Chen - *Cantor Fitzgerald & Co., Research Division - Senior Research Analyst & MD*

So my first question for you is do you see any potential for your oral PCSK9 to be used in first-line treatment? And then secondly, how much do you think you need to spend in order to achieve that greater than $10 billion of sales as you approach the 2030s?

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Let me just -- let me take a shot at that oral PCSK9 question. I mean, what we're sort of positioning this is to be an oral PCSK9 medicine, to be a "first-in-class oral PCSK9." And there's a standard way of how you sort of build and demonstrate your efficacy. I think we'll have to look at those data. But I would also pose the possibility that we may be sitting on potentially one of the more or most effective oral LDL-lowering cholesterol medicines. And I think that provides a possibility of thinking about earlier lines of therapy.

But I think a lot of things have to play out in relationship to that. But we view this as a first-in-class oral PCSK9 drug that hopefully we can demonstrate and then also thinking about as potentially one of the most effective in reducing LDL cholesterol as an oral medicine. And that may lead to some adoption, and we'll have to see how the field moves and what the data looks like and what is the sort of investment required to get that done. But that has -- that is something that our aspiration is to strive for that.

In terms of the amount of resources that inject in relationship to move that forward, I don't know that we share the breakdown of our research and development investments by programs and therapies in relationship to that. And so this is something that we've been working on for the last 3 to 5 years, and it fits well within our investment thesis of our R&D organization as we've expressed it previously.

Peter Dannenbaum - *Merck & Co., Inc. - VP of IR*

Thanks, Louise. Just to follow up on that. We have a question via the webcast about the commercial footprint and whether it's sufficient to support the breadth of potential therapeutics discussed today, especially when considering the oral PCSK9. So maybe, Arpa, as a follow-on to Louise's question, we could address that question.

Arpa Garay - *Merck & Co., Inc. - CMO for Merck Human Health*

Yes, absolutely. So as we think about the U.S. market, we currently have an established footprint in heart failure with the commercial launch of VERQUVO. And the customer overlap between -- the primary customer overlap between MK-0616 and heart failure, we think it will be fairly broad. Outside of the U.S. as well as with the broader primary care community that could be prescribing MK-0616, our intent is to have a digital-first launch. So really leveraging our data and analytics capabilities to identify where are the greatest pockets of unmet needs from a patient perspective and then also leveraging our omnichannel capabilities to think about how we engage across the ecosystem between patients, clinicians and payers to make sure that we are getting the appropriate education awareness out there to get as many patients who need this product on the product without investing in large additional sales force capacity.

Operator

We have Geoff Meacham from Bank of America.

Alexandria Hammond - *BofA Securities, Research Division - Associate*

This is Alexandria on for Geoff Meacham. So on sotatercept, what are your expectations here in terms of treatment dynamics? And is it potentially disease -- and as it is potentially disease-modifying, how does that change your market expectations? And lastly, what are the opportunities outside of PAH?

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Did you want to -- Eliav, just answer just broadly outside of PAH. And I think we've reviewed some of this. And then potentially, Arpa?

Eliav Barr - *Merck & Co., Inc. - Chief Medical Officer & Head of Global Clinical Development of Merck Research Laboratories*

Sure. With respect to treatment dynamics just in broad terms, I mean, the first step with the STELLAR study, as we mentioned, is on top of background therapy, to optimize outcomes for PAH patients. The 2 other studies, ZENITH and HYPERION are designed to look at the impact of the drug on hard endpoints such as survival in the patients who are sickest. And then as Joerg mentioned a little earlier, to look at a broad population of early PAH with the idea of understanding how sotatercept might fit into the steps of therapy.

With respect to broader opportunities outside of pulmonary arterial hypertension, pulmonary hypertension is caused by a variety of different diseases. And we're already starting to evaluate sotatercept in pulmonary hypertension associated with heart failure with preserved ejection fraction as the subpopulation of that group. And those data will -- are being generated in the CADENCE setting and we'll see how the results look like.

But I think that there are going to be opportunities, not only there but elsewhere. And indeed, when we think about pulmonary hypertension, there's also a lot of overlap there with interstitial lung disease and disease associated with systemic sclerosis. And one of the other purchases that we -- one of the other great assets that we were able to get with Acceleron was [MK-2225], previously ACE-1334. And that drug also may have important opportunities in the pulmonary space. So we look forward to exploring sotatercept fully across the different spectrum of the entire spectrum of PAH but also in other pulmonary hypertension opportunities. And Arpa, maybe you can talk a little bit about the market?

Arpa Garay - *Merck & Co., Inc. - CMO for Merck Human Health*

Sure. So thank you for the question. As we think about -- I believe your question was if this truly is disease-modifying, what does that mean from a commercial perspective. I think as we get more and more data behind this product, if we do see that there is a mortality benefit in ZENITH, as an example, there is a potential for sotatercept to be used earlier in therapy as well as become the foundational backbone of PAH therapy over time. So as sotatercept accumulates additional positive data, if it does become the backbone of therapy, we do believe that there will be significant commercial upside to our current expectations.

Peter Dannenbaum - *Merck & Co., Inc. - VP of IR*

Great. Next question, please, Grace. And I think we have time for maybe 2 more questions.

Operator

Next up, we have Seamus Fernandez from Guggenheim.

Seamus Christopher Fernandez - *Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals*

So the first question is on 2060. Just wanted to understand the frequency of events that you would expect, and then how the severity of events can emerge in the ESRD patient population, such that we get a clear visibility on the types of events that can be prevented. And then separately, on 0616, just hoping that you could help us understand the bioavailability of the product. What's the -- what does the PK look like? Typically with peptides, we'll tend to see quite a high dose necessary or sequentially, multiple days of dosing to achieve a consistent bioavailability. Just wondering what the profile of the product looks like from a PK perspective.

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

So why don't I have Joerg touch the 2060 and then Fiona or Joerg, who wanted to touch the PK? Fiona, you can touch the PK issue in relationship to -- or the bioavailability and Joerg, you can follow up with any other suggestions after Fiona. But Eliav -- sorry, Joerg and then Fiona?

Joerg Koglin

Yes. So I'll start with the 2060 question. So we made the point that we selected ESRD patients with hemodialysis as our initial beachhead, our initial indication. In this patient population, the rate of major thrombotic cardiovascular events, it's roughly around 16% per -- or 16 events per 100 patient-years, so an enormous annual rate of thrombotic events that can be prevented. That is contrasted by a rate of major or clinically relevant nonmajor bleeding, that's somewhere between 10% and 11%, so that's the risk profile. That makes it, I think, a unique patient population where an anticoagulant without major bleeding liabilities could be established early on.

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Fiona, did you -- I think some of this was actually published in a publication in a poster.

Fiona Marshall - *Merck & Co., Inc. - Head of Neurosciences*

Yes. I think the important point here is that what we've been able to show already in the Phase I study, where we were looking at target engagement, is that following oral -- once-a-day oral dosing, we can get sustained reduction in LDL cholesterol. And the doses -- actually, the molecule is actually performing better from an oral absorption point of view than we expected. So we think that we can continue with a once-a-day oral dose and we can get the efficacy and target engagement that we're seeking.

Peter Dannenbaum - *Merck & Co., Inc. - VP of IR*

Thank you, Seamus. I think we'll take our last question.

Operator

Okay. And your last question comes from the line of Daina Graybosch from SVB Leerink.

Daina Michelle Graybosch - *SVB Leerink LLC, Research Division - Senior MD of Immuno-Oncology and Senior Research Analyst*

Thank you for the couple of hours. It's been very helpful. So first on the oral PCSK9, I want to ask about the selectivity of the macrocyclic peptides compared to monoclonal antibodies. You mentioned the potency is very high and similar -- you get similar selectivity as a monoclonal antibody. And do you expect any differential risk of any off-target effects with the oral versus the monoclonal?

And my second question on vericiguat and the VICTOR trial. Can you talk a little bit more about the background standard of care that will be in this trial? Will this be on top of SGLT2s in addition to Entresto or this is on top of Entresto and why you made that particular decision in VICTOR?

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Fiona first and then Joerg?

Fiona Marshall - *Merck & Co., Inc. - Head of Neurosciences*

Yes, I'll start with this. So the cyclic peptides have a significant footprint in the way that they interact with PCSK9. And then in the way that they're evolved through the, first of all, the messenger RNA display and then the chemistry optimization means that they have very, very high specificity for their target. So in a way, they're a bit like the monoclonal in terms of the point of interaction of the antibody with the target. So yes, they're very, very potent and also very selective.

Joerg Koglin

And with respect to your question around VICTOR, so in VICTORIA, we were already able to enroll a substantial number of patients on RNAs. That was an important objective. Of course, we wanted to understand that this is additive on top of RNAs as part of standard of care. And the results actually showed that the efficacy of vericiguat is there, independent of if the patient was on an RNA background or not.

With VICTOR, it will be important to capture appropriate standard of care background therapy. So we are trying hard on having enough patients on SGLT2s, having enough patients on RNAs and having enough patients on both. In the first 500 patients, we are tracking really well. But of course, the ability to include those drugs in clinical studies is dependent also on the geographic footprint. Our initial patients right now are coming predominantly out of the U.S. and Europe where it's easier to find patients on SGLT2s and RNAs.

Peter Dannenbaum - *Merck & Co., Inc. - VP of IR*

Yes. Great. Thank you, Daina. If there's anybody that has follow-up questions, we will be around all day today and the rest of the week. I'll turn it over to Dean to make a closing remark.

Dean Y. Li - *Merck & Co., Inc. - Executive VP & President of Merck Research Laboratories*

Yes. So I just -- we have a storied legacy in developing therapies for cardiovascular disease. And I think it's just really important that all of us recognize that it is still the single largest cause of mortality, so the ability for us to make a meaningful impact will be important for the world and for Merck.

I also wanted to emphasize that many of you I've spoken about to -- spoken to, have emphasized what our aspirations as a company, as a pipeline, as Merck Research Laboratories. We have focused on being the leading cancer company by 2025 and making that position enduring and durable in '28, 2030, 2035. But we've also talked about how we need to open up a little bit of the accelerator on many of our other programs, advancing foundational medicines and other therapeutic areas. This is just a snippet in relationship to cardiovascular and I hope that you see that.

And I think the third thing that we've always emphasized is not just cancer, not just in relationship to other therapeutic areas such as cardiovascular, but how we think about our internal pipeline and how that meshes with an external pipeline, which is on display in the cardiovascular portfolio as we've discussed. So I want to thank all of you for your attention, and we look forward to hosting other such events. And please, as Peter has said, any other questions that we didn't get to, please reach out to Peter and his team. Thank you very much.

Operator

Thank you, presenters. Ladies and gentlemen, this concludes today's conference call. You may now disconnect.
