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PRESENTATION

Operator

Thank you for standing by. Welcome to the Merck & Co. Investor Event at ACC.23/WCC. (Operator Instructions) This call is being recorded. If you have any objections, please disconnect at this time.

I would like to turn the meeting over to Mr. Peter Dannenbaum, Vice President, Investor Relations. Sir, you may begin.

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

Thank you very much. Good evening, everyone. Welcome to Merck's Investor Event here at the American College of Cardiology in conjunction with the World Congress of Cardiology. Thank you to all of you in the room here who have made the effort to be with us here in New Orleans, and thanks to everyone that's listening in on the webcast. We're very excited to have this opportunity to speak to you about the significant data that we presented today. During today's call, a slide presentation will accompany our speakers' prepared remarks, and that presentation has been posted to our website.

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 United States 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, 2022, 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 evening. Merck undertakes no obligation to update any forward-looking statements.

Our presenters today will be Dr. Dean Li, President, Merck Research Laboratories; Dr. Joerg Koglin, Vice President, Global Clinical Development Cardiovascular and Respiratory; and Dr. Eliav Barr, Senior Vice President, Head of Global Clinical Development and Chief Medical Officer. Dean will kick off our presentation with a few opening comments, Joerg will follow with data highlights, and then Eliav will wrap up with some closing remarks. Following prepared remarks, we'll take your Q&A and we'll also include Chirfi Guindo, Chief Marketing Officer, Human Health; and Jannie Oosthuizen, President, Human Health U.S.

I will now turn the stage over to Dean.

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

So thank you, Peter. It's a privilege to share the stage with my clinical colleagues and my commercial colleagues as we share the work of our teams. Now a year ago, I spoke to many of you about our cardiovascular pipeline and as it progressed into the later stages of clinical development. And our aspiration then and now is to meaningfully address great unmet needs such as heart failure, thrombosis, atherosclerotic cardiovascular disease and pulmonary arterial hypertension.

We have made important progress throughout our portfolio. In heart failure, we've made progress in our [various C trial] and VICTOR trial. In our thrombosis efforts, we've made inroads in our MK-2060 late-stage clinical development program. But the focal point of this event and our time at ACC is on pulmonary hypertension, and it's the sotatercept, the active in signaling inhibitor, which is interdicting with a pathway identified by human genetics as a cause for PAH. We will also have a brief discussion on MK-5475 as well. In terms of atherosclerotic cardiovascular disease, we will be talking about PCSK9, a proven molecular mechanism for lowering LDL cholesterol.

So let me just get to the top line results that were presented today at ACC, and Joerg will give a more detailed description. So the top line for sotatercept is we have a 6-minute walk distance improvement of greater than 40 meters. We have reductions in pulmonary vascular resistance shown here. We have reductions in important biomarkers such as proBNP. But very importantly, we have substantial reduction in time to clinical worsening or death of an 84% risk reduction.

Now these trial met primary and 8 -- primarily in 8 out of 9 of the secondary endpoints, and I know that Joerg will give additional color. I think some of the comments that were made by others today during the session and also during the follow-up session is the possibility that this could be a potentially transformative option for patients in this, as it was quoted a landmark trial.

In relationship to MK-0616, our PCSK9 inhibitor, that is oral and daily, there was a reduction of LDL cholesterol, up to 60% -- 60.9%. We had reductions in ApoB and non-HDL-C and the ability to reach LDL goal. And we have transitioned this program from Phase I to Phase III in less than 18 months.

So let me just turn the stage over to Joerg as he goes in more detail, especially for many of the people who might have missed the presentation at ACC. Joerg?

Joerg Koglin - *Merck & Co., Inc. - VP of Global Clinical Development*

Thank you, Dean. Hello, and good evening from New Orleans. Thanks for being here. Having attended ACC for 30 years as a cardiologist, this year's meeting might be the most exciting one for me. So results from 2 of our development programs, both as late-breaking trial presentations and both with the promise that they might not only improve, but could potentially transform the way patients are treated. That is as exciting as it gets.

Over the next few minutes, I will summarize key findings from these 2 studies. The results are also available through simultaneous publications in today's New England Journal of Medicine for the sotatercept active inhibitor program; and in the Journal of the American College of Cardiology for MK-0616, our PCSK9 inhibitor.

Let's start with sotatercept and the STELLAR study. Primary pulmonary arterial hypertension is a rapidly progressive and fatal disease. It often affects women in their prime of life. In the U.S. alone, PAH is estimated or is diagnosed in roughly 40,000 patients. Current treatment options consist of combinations of various vasodilators, and these therapies are good in reducing symptoms and improving exercise capacity. Beyond that, the [staggering] mortality has really not changed over the last 2 decades.

PAH is a disease of vessels that transport blood from the right side of the heart through the lungs in order to get oxygenated. In PAH, these blood vessels become sickened and narrowed limiting the blood flow, and this abnormal narrowing of these vessels is caused by an imbalance in factors that controls growth of smooth muscle cells in the pulmonary vessel wall.

Sotatercept is the first of a new class of activin signaling inhibitors that's proposed to rebalance these factors by trapping signaling molecules that otherwise would lead to the overgrowth of these narrowing vessels. Sotatercept directly targets the underlying cellular mechanisms that contribute to the narrowing of the lungs blood vessels in PAH patients. In the Phase II study, PULSAR, which was also published in the New England Journal in 2023. So products have resulted in a very profound reduction in PVR. And based on these results, we embarked on multiple Phase III studies. The first of these studies, STELLAR was presented earlier today by Professor Harper.

STELLAR enrolled 323 patients to receive use of placebo or sotatercept titrated from 0.3 to 0.7 milligram per kilogram body weight and administered every 3 weeks through a subcutaneous injection. The study enrolled a broad fairly advanced patient population. Half of the patients were oral functional class III. That means they experience severe limitations even with normal daily chores. So patients were very well treated. Over 60% of those patients were on triple PAH background therapy. And this is typically a patient population that is very hard to further improve.

This result shows the -- or this slide shows the results for the primary endpoint, the change in 6-minute walk distance. 6-minute walk distance is a well-established and widely-accepted registrational endpoint in PAH patients. It assesses exercise capacity. It's also used by physicians to follow individual patients and their treatment progress. The control group is in gray. The treatment group is in green. The X-axis shows time from baseline to week 24, and the Y-axis shows the change in 6-minute walk distance. We observed mean change from placebo over this time period was a reduction in 6-minute walk distance by 1.4 meters. We observed mean change for sotatercept was an increase of 40.2 meters. To correct for outliers, we use the Hodges-Lehmann method as an established approach to compare the 6-minute change between groups. The modeled improvement of sotatercept over placebo was 40.8 meters, a result that's both statistically and clinically very meaningful.

The study also met the next 8 out of 9 prespecified secondary endpoints. These endpoints were tested in a hierarchical manner. These endpoints were chosen to assess the impact of sotatercept on disease hemodynamics, on disease severity and outcomes, on biomarkers that correlate with the prognosis of the disease and on patient-reported outcomes. And I will talk about 4 of those endpoints in a little bit more detail.

Until now, the best that existing therapies could do is to delay the progression of the disease. Sotatercept is the first investigational drugs that actually showed an improvement in a substantial subset of patients. The multicomponent improvement endpoint counts the number of patients that need all 3 of the following clinically very relevant parameters. These patients have to meet -- have show an improvement in 6-minute walk distance by at least 30 meters. They have to show a reduction in NT-proBNP, a prognostically relevant marker for right heart strain by at least 30%. And they have to show an improvement in functional class. 38.9% of all patients, 4 out of 10 patients showed this level of improvement in the sotatercept group, and that compared to only 10.1% in the placebo group.

Pulmonary vascular resistance or the resistance by the pulmonary circulation to blood flow remained essentially unchanged, slight (inaudible) increase in the placebo group. Sotatercept resulted similar to Phase II in a profound reduction in PVR. The chronic increase in strain on the rate heart through increasing difficulty to pump blood through the ever-narrowing pulmonary circulation then leads to right heart failure, right heart failure is the leading course of death in PAH.

NT-proBNP is a circulating biomarker for cardiac wall stream, and so we assess the impact of sotatercept or placebo on NT-proBNP. What we showed was a slight increase in NT-proBNP in the placebo group and a very profound reduction in NT-proBNP in the sotatercept group, suggesting substantial unloading of the right ventricle. Perhaps most profound were the findings for time to clinical worsening, which includes death.

Shown here are the Kaplan-Meier curves with the -- our placebo group, again in gray. The treatment group in green. And the X-axis is again the time course. What you see here is the Kaplan-Meier curves separate early. Separation increases and then is maintained over time. With a median follow-up of 30. -- sorry, 2.7 weeks. The hazard ratio of only 0.16 equates to a reduction in the risk for death and worsening by 84%. This is an effect size that has not been observed with any other PAH study.

This result is further supported when looking at the individual components of this endpoint. The difference in time to death or the non-adverse, non-fatal clinical worsening event was really supported by each of the components, a reduction in death, a reduction numerically in patients that were hospitalized for PAH, a reduction in deterioration of PAH, and a reduction in the need for additional rescue therapy.

On the safety side, sotatercept was well tolerated with numerically lower levels of discontinuations due to treatment-emergent adverse events and a lower rate numerically of serious AEs. The overall AE profile was consistent with previous studies with adverse events that were generally mild and manageable without the need to discontinue therapy.

Over 99% of the patients, 162 out of the 163 patients in the Sotatercept, were able to reach the maximal dose of 0.7 milligram per kilogram body weight. Proactively monitored as mechanism-based AEs of special interest, we observed an increased incidence in typically minor bleeding. These were typically minor nose or gum bleeds. Which we were able to see a slightly higher rate of telangiectasia or spider veins. These are thin widened vessels in the skin. And we saw changes in red blood cell and thrombocyte counts. These changes were typically -- these changes typically didn't require any medical interaction. Only in 6 cases did these changes trigger an only intermittent reduction in dose, and these changes did not lead to any treatment discontinuation in our study.

So in summary, the therapy with sotatercept resulted in an improvement in 6-minute walk distance by 40.8 meters. It resulted in a reduction of PVR by 26.7% and resulted in a reduction in NT-proBNP by 62.6%, and it resulted in a reduction in the risk for death or a clinical worsening event by 84%. These data suggest that sotatercept on top of stable background therapy may provide a potentially transformational treatment option in PAH. We are now working with urgency to get these results formally presented to regulatory agencies.

So let me switch to our PCSK9 program. Today's presentation by Professor Valentine reviewed the results of the Phase II dose finding study for MK-0616, our novel oral PCSK9 inhibitor developed in patients with hypercholesterolemia. What is the context of this development program? Cardiovascular deaths remains the leading course of deaths worldwide. The majority of these death events is caused by atherosclerotic events such as myocardial infarctions and stroke. Elevations in LDL remains a leading risk factor for atherosclerotic events. And while existing anti-lipid therapy has shown a solid reduction in cardiovascular risk in well-controlled clinical studies to up to 30%, enormous residual cardiovascular risk remains. Recognizing this residual risk guideline committees worldwide continue to move the treatment goal for LDL lower and lower. And at the same point of time with the existing therapy, only a minority of patients reaches these treatment goals.

So inhibition of PCSK9 has been identified as the most effective drug intervention to reduce LDL-cholesterol. 3 injectable PCSK9 inhibitors are available. Nevertheless, high price, access barriers and the need for repeated injections often by a health care provider have limited the real-world use. The availability of an oral PCSK9 inhibitor would have the potential to reduce access barriers for this mechanism. However, today there are no oral PCSK9 inhibitors available.

Using our novel macrocyclic peptide platform, our discovery team was able to develop MK-0616, a cyclic peptide with antibody-like potency and selectivity at 100th of the size of an antibody. Given together with a naturally occurring permeation enhancer, oral MK-0616 one tablet per day is able to reach exposures that reduced PCSK9 by over 90%. The goal of this program is to develop the most prudent LDL lowering pill that could be accessed by a broad patient population, which may allow substantially more patients to reach their treatment goals and thereby help to reduce the global burden of atherosclerotic disease.

The study was designed to define the optimal dose for future Phase III development. 381 patients were enrolled into 1 of 4 dose groups or placebo. The study included treatment-naive patients as well as patients with intermediate and high doses of statin background therapy. The primary endpoint was the percent change in LDL from baseline to week 8 compared to placebo. So graph on the left shows the placebo-corrected results for the 4 treatment groups with a clear dose response. Each group showed a significant reduction over placebo. Not shown here but shown in the manuscript, near complete efficacy was already accomplished by around week 2. That was the first treatment visit after drug initiation. It was maintained over the entire 8-week treatment period. The observed LDL reduction was up to 60.9%, with a suggested (inaudible) were between 18 and 30 milligrams. The results were generally consistent across all prespecified subgroups. The effect size appears to compare well with the efficacy of injectable PCSK9 inhibitors.

The secondary endpoint means change in apolipoprotein B and the mean change in non-HDL-C. Represented additional markers of atherosclerotic risk and the dose reduction in these measures further support the findings for the primary endpoint. The percent reduction from baseline for ApoB was up to 51.8%. The mean reduction for non-HDL-C was up to 55.8%. The study also looked at the proportion of patients in each treatment arm who achieved protocol prespecified LDL-C goals.

Looking at treatment guidelines. That's the time of study design. These goals were set based on the presence of, or the risk for atherosclerotic cardiovascular disease. Only 9.3% of the patients in the placebo group, and remember, most of these patients were on statin background therapy, reached these goals, whereas goal attainment was achieved in up to 90.8% of the patients in the MK-0616 dose.

On the safety side, the PCSK9 inhibitor was generally well tolerated and overall lower rate of AEs discontinuation due to AEs or serious AEs. There was -- for none of those categories, any dose response and looking at the serious adverse events, there was no clear trend across treatment arms or towards specific organ classes. None of these serious adverse events were deemed related to study drug by the investigator.

The one death was unfortunately due to a motor vehicle accident. There was no AEs that increased in a dose-dependent manner. The most common AE in the study was COVID-19 infection. The study was run during the pandemic. The gastrointestinal AEs here, again, without any dose response were all nonserious, generally well tolerated and typically did not lead to discontinuation of the drug.

So in summary, all inhibition of PCSK9 with MK-0616, doses from 6 to 30 milligrams provided significant and clinically very meaningful reductions in LDL cholesterol with an effect size and a risk/benefit profile that's well comparable to injectable PCSK9 inhibitors. These results strongly support further development of MK-0616, which could widen access to effective oral LDL lowering and help improve attainment of guideline recommended LDL goals as a mean to reduce cardiovascular risk.

With that, I will hand it over to Dr. Eliav Barr, our Chief Medical Officer.

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

Well, thanks, Joerg. And again, thank you for coming to New Orleans and for being on the phone. What I'm going to do is I'm going to summarize Joerg's review of the data on sotatercept and MK-0616 and then bringing forward to what the future is going to be for clinical programs in the pipeline.

So as Joerg mentioned, sotatercept has the potential to profoundly change the treatment for PAH. It's a first-in-class active and signaling inhibitor. It's the first of a potential new drug, new class of therapies that target the underlying pathophysiology of PAH. And I think it's fair to say that the efficacy findings in the STELLAR trial were robust, actually pretty stellar.

Compared to placebo, you've heard this before, but it's just worth mentioning, patients who received sotatercept experienced substantial improvements in 6-minute walking distance, markedly reduced risk of clinical worsening or death and substantial improvement in measures of right ventricular stress. And this is important because most patients die -- with PAH die from right heart failure. Clinical benefit was observed in the primary endpoint in the other measures regardless of background therapy or disease severity. Therapy was generally well tolerated, with the safety profile consistent with prior studies.

Now we intend to build on the results of the STELLAR study to expand our understanding of how sotatercept help patients with a broader range of pulmonary hypertension. For sotatercept, we've already initiated 2 additional Phase III trials: the HYPERION trial, which evaluates sotatercept in newly-diagnosed intermediate and high-risk PAH patients; and then the ZENITH trial, which evaluates sotatercept in patients with advanced PAH at high risk of death. We're trying to pull them away from the bit that they're facing with advanced disease. We're also expanding the studies of the drugs, in different kinds of pulmonary hypertension, especially that pulmonary hypertension associated with left heart disease.

Now our efforts aren't just limited to sotatercept. They include MK-5475, which is our inhaled guanyl -- soluble guanylate cyclase stimulator. Now this drug has the potential to be a first-in-class pulmonary selective vasodilator. Now as you know, currently available vasodilators or pulmonary hypertension can dilate the preliminary vessels, but they all have a dose-limiting toxicity of also dilating the systemic circulation. So it causes low blood pressure in patients feel very faint, and that impacts the ability of the drug to actually do anything from a symptom relief point of view.

Inhaled delivery of 5475 is different because it's got the potential to deliver the right doses of inhaled vasodilator, right to the pulmonary vasculature that needs to be dilated. And so the relative concentration of the drug in the lung is much higher than the circulation Therefore, you can really get high levels of vasodilation without impacting systemic blood pressure and hypertension.

Oops, sorry. So we've initiated 2 trials of MK-5475. The first is in pulmonary arterial hypertension, so in a population not terribly dissimilar from what we reported today. And then the second in patients who have pulmonary hypertension in the context of chronic obstructive pulmonary disease, a very important set of patients for whom there's really nothing available.

Now shifting over to atherosclerotic cardiovascular disease in 616. I think the data that were presented at ACC and so nicely by Joerg today, show the really strong potential of MK-0616 as a new way to improve LDL-cholesterol reduction and a means to democratize access to this important class of disease. MK-0616 is the first -- is potentially the first oral PCSK9 inhibitor, and that's an important innovation because it will reduce the access that patients have and the market has shown us has occurs, when patients try to access PCSK9 inhibition. The Phase II data that we saw today really demonstrate that MK-0616 therapy is quite effective in reducing lipids to the levels that are consistent with those observed with the various injectables. And the safety profile was favorable across the different doses (inaudible).

Now based on the Phase IIb results, we anticipate looking at a very large clinical program, which we'll initiate in the second half of '23. We plan on 3 kinds of studies. The first are going to be lipid-lowering trials. These are the traditional trials that look at the highest primary prevention and secondary prevention patients and examine the effect of the drug on LDL-cholesterol levels over a period of time. They're designed to look at efficacy with respect to LDL cholesterol reduction and other measures of lipids and also safety and tolerability.

The second kind of study that we'll do is the cardiovascular outcomes trial. Although this mechanism of action is really very, very well validated and has been repeatedly demonstrated to improve outcomes, we also want to be able to look at our own trial, our own drug and to examine the effect of the drug on outcomes, both in high-risk primary prevention patients as well as in secondary prevention patients.

And then finally, we're going to have a set of supportive studies that, in aggregate, will seek to look at MK-0616 in specific subgroup of patients and also in combination with other drugs that are used for cholesterol lowering.

So I want to just finish by saying that from a broader point of view, this really -- today's presentations really represent an acceleration of our cardiovascular efforts, and we've made great progress towards our goal of creating meaningful medicines that will transform and improve the outcomes of patients with a variety of cardiovascular disease.

Our cardiovascular portfolio is growing and advancing with a potential of about 8 approvals by 2030. And as we noted, we anticipate that this pipeline will provide over $10 billion in revenue by the mid-2030s, and so we're really excited about being back in cardiovascular medicine and really making contributions to patients.

And with that, I'll turn it over to Peter for your comments.

QUESTIONS AND ANSWERS

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

Thank you, Eliav. We're ready to get started with the Q&A. We're going to take questions here in the room first. Steve and Domini have mics. So please wait for a mic, and announce your name and firm when you get the mic. And then we'll go in a few minutes, we'll go to questions on the webcast. So Chris Shibutani.

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

Thank you very much, and thank you for hosting this event. Very comprehensive, and the data, obviously. Congratulations. Chris Shibutani from Goldman Sachs. On sotatercept, I think as we think about the time to clinical worsening endpoint. Can you help us decode, to any extent possible, so that we can attempt in our efforts to extrapolate the potential results for both HYPERION and ZENITH. When we think about those primary endpoints, they really center on time to clinical worsening. In particular, the ZENITH study, it seems to have the primary endpoint of time to all-cause death and PAH-related hospitalization with a more severe patients. Whereas in HYPERION, it's more broad. So if we are trying to assess the potential future based upon this data set, any granular insights would be really helpful.

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

Joerg can make some more comments, and I may add something on top. Joerg?

Joerg Koglin - *Merck & Co., Inc. - VP of Global Clinical Development*

Good. So you appreciate that the patient population in ZENITH and the patient population in HYPERION is overlapping, but still different from what we studied in STELLAR when for the broad overall PAH patient population ZENITH, these are really patients with really high risk score. Many of those patients are already on a transplant waiting list. This is going to be a hard outcome study. It's time to death and PAH hospitalization.

In STELLAR, when you look at the overall results, with just the 32.7 week follow-up. You saw 6 versus 2 and 7 versus 0. Of course, we went in there and we're trying to squeeze out in that small sample size and how did the patients in the higher risk group do. And so that, I think, further supports our assumptions of, yes, in ZENITH, we should have a chance to detects that in a reasonable time period.

Time to clinical worsening in HYPERION. There, the objective is a different one. The objective is to figure out how early in a patient journey should you actually start with sotatercept. Remember, in STELLAR as the median time from diagnosis to the patient ends up in the study was 8 to 9 years. These are well-treated patients. Typically, they tried everything else. Now the question is if it works there, how early should you actually start it in a patient population?

In HYPERION, all patients are just diagnosed within the last 12 months. We still mandate that they start with the guidelines required combination therapy of vasodilators. Time to clinical worsening there will be more driven through the components of need-for-rescue therapy or deterioration of PAH. This is a much lower risk patient population. But again, when we look at the STELLAR results, when we tease out the patients with lower risk, when we look at those components, we believe, yes, that's a study that has a very reasonable probability of success.

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

So I would just add one -- just a couple of things having to do with the time between worsening on HYPERION because really ZENITH is a hard endpoint trial. It's going to be whether we can salvage patients who are really heading towards one transplant. The -- initially, the expectation was that HYPERION was being necessary to show a benefit in time of clinical worsening. We just didn't realize how incredibly effective sotatercept was, and so the data here are just pretty extraordinary and I think unequivocal.

The question that I've heard a lot of key scientific leaders talk about is what their earlier intervention might actually be even further beneficial, and the reason for that is that perhaps in earlier stages the disease is more dynamic. There's more activity going on unless, let's say, fibrosis and kind of end-stage vessel behavior. So it may very well be the case that in earlier trials -- the earlier patients, we might get an even further improvement in time to clinical worsening. Time will tell, but we're really enthusiastic about the trial.

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

All right. Next question. Chris Schott.

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

Great. Maybe just following up on sotatercept. Can you just talk about logistics of 40,000 patients in the U.S.? How many of those are you able to go after post STELLAR? I mean it seems like we saw a very strong signal, kind of whether you're on dual or triple, and I guess just with the kind of not-so-great standard of care currently. Do we need to wait for HYPERION to get access to that? Or can we offer a majority of the patients just with what you have currently?

And then maybe just a quick follow-up on PCSK9. Can you talk about the food effect seen with the drug and how you're kind of managing through that? It seems like just in the diabetes setting with the GLP-1s, the food effect was a pretty big hurdle to get some patients of injectables on to orals. So I'm just wondering, is it different in the situation? Or how you kind of manage through that?

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

So why don't we have Jannie take your first question, and then I'll have Joerg speak about the food effect, and I may make some comments. Jannie?

Jannie Oosthuizen - *Merck & Co., Inc. - Senior VP & President Merck U.S. Human Health*

Yes. Thanks, Chris. That's a good question. So in terms of -- if you think about how PAH is treated in the U.S., it's a very concentrated treatment setup in terms of a few less than 150 specialized centers around PAH, where most of these patients are treated. I mean this is the tight community of experts, specialists, most people consisting of pulmonologists, but also cardiologists with a specific focus on PAH. So I think the ability to get to the majority of these patients is going to be fairly efficient through a few centers and a highly connected treatment community that obviously is very much aware of the data that played out today already.

I think the other thing is if you look at the patient population within STELLAR, it is pretty much the patient population that exists out there, right? So I think it's going to be the discussion over the next few weeks and months to see exactly how (inaudible) and general treatment physicians are thinking or the treatment health care professionals are thinking about where to use data states in the context of the patients that they have today.

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

Joerg, did you want to take the 0616 question?

Joerg Koglin - *Merck & Co., Inc. - VP of Global Clinical Development*

Sure. So we're pretty advanced with our clinical pharmacology program, and we learned given with the permeation enhancer is that absorption is better if you put 30 minutes between taking the drug in the morning and then taking in foods. That was the recommendation that was used in Phase II. Those are the results that you've seen here, and I think that will be the recommendation as we take this into late-stage development into Phase III.

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

I'll just make some really quick questions -- comments. The sotatercept data will potentially change how people think about PAH, and they may actually change how people diagnose as well. So one of the things that I wonder is oftentimes, 40,000 patients, that's what you think. And all of a sudden, you have a medicine that substantially changes the course. And it might, it might change how people think about how for example, a woman who comes in with no known coronary artery disease, sort of risk factors with no asthma comes in a short of breath and how fast people will start trying to drive to diagnosis. What I would say at this point is, the time to diagnosis is, something that could be substantially improved, and we are hoping that the excitement around sotatercept may catalyze that.

The second issue that I would say in relationship to MK-0616 is, at least from my practice, when I used to practice the patient population often has other oral daily drugs that they're taking. This is a patient population that may be taking a baby aspirin a day, maybe taking a statin, may be taking a beta blocker and ACE inhibitors and all of this. And at least the time that I sort of limited time that I was on the awards, one of the things that we often did is we would have it once a day, but you take one set at night and one set in the morning. And those drugs that change your hemodynamic status, you would take in the morning. And things like aspirin or maybe a PCSK9, you would take at night. So at least in my mind, when you look at the adverse effects, I don't know that it has a big impact. You can do it 30 minutes. But the way that you pace a patient through reality, I think this is -- this will be something that can easily be handled through the practice of medicine.

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

Great. Next question. One more from this side, then we'll go to the other side. Daina?

Daina Graybosch - *SVB Leerink, LLC*

I wonder if you could talk about how AE's dose alterations and compliance events fell across the treatment period in STELLAR. And from that study and anything you see in the open-label extension, whether there are certain events that you think may be more important as we get to more chronic dosing. I'll take that.

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

Joerg?

Joerg Koglin - *Merck & Co., Inc. - VP of Global Clinical Development*

I can get started. So the mechanism -- so one observation expected mechanism is the increase in red blood cells counts. We see that developing over the first few weeks, and then patients are stable. I mean increase in hemoglobin that we observed in the study was 1.3 milligram per deciliter. And as I pointed out, it was an increase in this patient population. Remember, hemoglobin increases the oxygen-carrying capacity in patients that don't have enough of that. That was generally well acceptable. Our protocol defined intervention routes. I mentioned that a few patients had to be down-titrated. We're much more conservative than what most of our PAH sites with use in clinical practice.

The same is true for thrombocyte changes. If they develop, you see them early. With respect to telangiectasias, I think we're still learning. In PULSAR, so initially, we didn't see any telangiectasias. Only once we went out to sites and said mechanism-based, please look for that. We started to report those. So all the patients in PULSAR and now patients in STELLAR get rolled over in a long-term extension. I think that will help us to understand our telangiectasias occurring more over time, are they stable after a certain time period. I hope that answers your question.

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

Next question. Carter.

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

Great. Carter Gould, Barclays. Eliav, your characterization of the CVOT for 0616, it seems pretty, I'm not going to say aggressive, but ambitious. And certainly, it seems as though you're looking to differentiate not just on the oral nature, but also not run [48-2.0 or Odyssey 2.0]. And I think I heard you say going into primary prevention, too. Can you just expand how you think about differentiating versus those? And what I didn't hear is something, Merck used to be known really well for is fixed-dose combinations in PV studies. Can you talk about Merck's interest there?

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

Sure. So first and foremost, the design of our cardiovascular outcomes trial is still in discussion with internally and with FDA. But we see this drug as being a very important drug across a broad range of patients. This isn't a salvage drug. It's not for a drug for -- just for people who don't tolerate (inaudible) none of that. It's for people -- it's -- our interest is to broaden and democratize PCSK9 inhibition as a tool for obtaining -- for patients obtaining their LDL-cholesterol goals. And that means not just secondary prevention, but also primary prevention in high-risk patients, obviously, the beginning. But we think this is a really important drug so that patients reach their goal regardless of whether they're -- they've had an MI or other event or not.

In terms of fixed-dose combinations, we'll take a look at that. The important thing for us, first and foremost, is to be able to see how we do on top of a variety of standards of care. So in other words, not to just say only on statin or only one intervention, but a broad range. But the future will take us, I'm sure, to different places.

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

Great. Thank you. Next question. Vamil?

Vamil Divan - *Guggenheim Securities, LLC*

Vamil Divanon from Guggenheim. So 2 questions if I could. One, following up on the hemoglobin. I noticed the rate was much lower than we saw in Phase II, I think 5% versus 17%. I was just wondering, was there something different how patients are monitored or how -- define or anything along those lines? And then the second one, we talked about this briefly before, but just on the commercial preparation since it is a weight-based dose subcutaneous, I guess people have been giving it to themselves, how are you thinking about sort of how you provide that commercially.

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

Why don't we go to Joerg and Chirfi. Would you want to take the other question, Joerg, first and then Chirfi?

Joerg Koglin - *Merck & Co., Inc. - VP of Global Clinical Development*

So the protocol criteria in an exclusion criteria as a way how hemoglobin was managed, monitored how is the protocol responded to hemoglobin changes was similar to what was identical to PULSAR. So one difference is in PULSAR, remember, patients either receive 0.3, 0.7 milligrams. What we did in this study is we up-titrated on 2.7 milligrams. And so one can speculate perhaps that helps patients to accommodate a little bit better, but I think it's the only difference that I could come up with.

Chirfi Guindo - *Merck & Co., Inc. - Senior VP & CMO for Merck Human Health*

As far as commercial, I mean these patients are used to taking medicines that are fairly complicated to administer. This will not be the more complicated of the medicines that they take. But certainly, we continue to work on preference preparing the environment so that patients or physicians, you could have these physicians administered, high dose administer this drug, in a way that is safe, in a way that is simple, simple as possible going forward.

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

Yes. I would just add one more comment on top of Chirfi's. So it is weight-based. And Chirfi has told us -- told you, we're very confident in our ability to get this medicine, especially in this patient population. But your question also points out that further innovation on our part as to how we think about delivery systems and as such should be something that we intensely think about especially if we want to make this broadly available.

And I just want to reemphasize the most striking part of this story for me is what Eliav spoke about. If you talk about good remodeling or the field of regeneration, it is generally when you take those signaling cascade, you generally do not apply them 9 years after the diagnosis because there's all this negative remodeling going on. So the fact that we had such a profound impact despite starting that late I think, is really interesting.

In one of the commentary that was afterwards, there was a clear appetite of physicians to really ask the question should we really be waiting 5 and then 9 years afterwards and how soon can we put it, and so I just want to emphasize that point. And if that's how we're going to sort of bring that up in relationship of how much earlier from the time of diagnosis and the start of other medicines, I think we need to think carefully about further innovation that will make this drug extremely easy to access wherever you are in the world that you have this disease.

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

Okay. We'll take one more from the room, and then maybe front row here, and then we'll take a few from the phone line. I know there's a lot of questions, and we'll go past the hour because I want to try to get to everybody.

Hao Shen - *BofA Securities, Inc.*

This is [Hao] on for Geoff Meacham, Bank of America. And first of all, congratulations on the great data from sotatercept and MK-0616. So my question about the oral PCSK9 trial in 40% of patients is not on statin, and then only 25% of patients was on high-intensity statin. Just curious, like, are those patients just running out of options or are they -- maybe PCSK9 injectables? And then a quick follow-up on sotatercept. Are those bleeding events has any correlations with thrombocytopenia or hemoglobin increase?

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

I'll have Joerg, you take both of them?

Joerg Koglin - *Merck & Co., Inc. - VP of Global Clinical Development*

I can start with both of them. Yes. So first question was around 616. Help me again?

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

The intensity.

Joerg Koglin - *Merck & Co., Inc. - VP of Global Clinical Development*

Intensity.

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

Background statin.

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

Background statin versus...

Joerg Koglin - *Merck & Co., Inc. - VP of Global Clinical Development*

So in the Phase II study, it was important for us to just get essentially equal subpopulations. So we intentionally looked for 30%. We wanted to end up with a certain set, and I think we got pretty close to that. And like when you look at the Journal of the American College Publication, you also see the subgroup analysis. And in general, oral PCSK9 inhibition led to LDL reduction. So it was pretty comparable between subgroups. We observed the same distribution that you would observe with an injectable.

And then in terms of bleeding events with sotatercept, thrombocyte reductions, were actually fairly mild. We had 2 patients that very briefly dropped below 50,000 thrombocytes. Nobody required platelet infusions, and we didn't have any bleedings associated with that. Thrombocytes did not trigger any change in dosing in this study. And no, I think there was also no correlation with patients that have higher hemoglobin. But I think pathophysiologically, that would be also a lesser concern to start with.

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

I'll just add a comment. I mean just to reset, we are trying to make the most potent LDL lowering cholesterol medicine. Period. At the same time, that is happening, the guidelines appropriately is reducing the level of LDL. So we're trying to chase both at the same time. We're trying to make the most potent pill at the same time at the level of LDL has gone -- I don't know, you have to remind me, 130 to 110 to 90 to 70 to 55. And so that's what we're trying to do.

In some patients, we wonder whether the most potent LDL lowering cholesterol pill might be enough. But in other situations, you may need to combine it with others. And that possibility has not alluded us, and the possibilities laid out by the other gentlemen, and there's a question about fixed dose combination. As we learn more about how we look at those populations in Phase III, that may inform us in relationship to the other question that was asked.

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

Great. Does that get all your questions now? Yes, good. Okay. Calvin, can we take a few from the phone line, please?

Operator

Our next question comes from Tim Anderson, Wolfe Research.

Timothy Minton Anderson - *Wolfe Research, LLC - MD of Equity Research*

A couple of questions. If you think forward many years from now, peak for these products, I'm hoping you could say which products you think would be [bigger]. The major focus I think (inaudible) sotatercept, the data is fantastic, but that's a rare disease. Obviously, the size of the market is less, [not much bigger]. There's commercial dynamic honestly. I'm guessing consensus thinks that sotatercept will be bigger, but I'd appreciate any thoughts even if directional from you on that question.

And then the second on the adverse events for STELLAR, the impact on TTCW, it's great. Does that completely eliminate any concerns about some of these treatment-emergent adverse events? Or do you think there could be some residual concerns by prescribers about patients on this therapy when they've been on it for maybe 2 or 3 years?

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

So why don't we do this? Why don't we have the second question go first. And Joerg, you answered that. And then the first question about rolling the dice and saying what the commercial sort of thing, I'll leave it to Chirfi. And then I may make some broader comments after that. So Joerg?

Joerg Koglin - *Merck & Co., Inc. - VP of Global Clinical Development*

So thanks for the question. I think the context, PAH is a context where the current standard of care. All those drugs are essentially based by safety -- are dosed by safety. You up-titrate them until they are not tolerated anymore, they are not dosed by efficacy. All those rock-set safety profiles, they are pretty profound. I mean (inaudible) cycling, pick ERAs.

In that context, I think the safety profile that we observed with sotatercept is deemed by treating physicians and patients is typically well acceptable. And then you contrast that with the efficacy signal that we observed, we believe there is a very strong risk/benefit profile that the AE profile is typically well manageable. Doesn't typically require any changes in the way how the drug is dosed, and I think supports the use in this patient population.

Chirfi Guindo - *Merck & Co., Inc. - Senior VP & CMO for Merck Human Health*

So in terms of -- I love the question. Obviously, we believe that both have multibillion dollar potential. And the reason for that, obviously, is that they are both in their own way, pretty transformative. I mean you heard the scientific community today at ACC.

So if you think about sotatercept, [lot of] sotatercept. Jannie mentioned 40,000 patients in the U.S. You add Europe to that, you add Japan, you're talking 90,000 patients plus. And then the rest of the world will be obviously even more patients who are desperate for an option to treat their PAH. Despite the fact that you have many drugs available, you still have high mortality in the space, 43%. You saw that, and these are young women typically the prime of their age. They have -- they're professionals, they have families. So we believe that sotatercept given its transformative nature will really, really have a rapid uptake and achieve multibillion-dollar potential for the years to come.

Turning to MK-0616, as you heard from my colleagues, this is the opportunity that we have to really democratize access to PCSK9, right? So you provide the same efficacy, similar efficacy to the injectables in a way that is simple, in a way that is accessible around the world, global access. There are 40 million patients just in the U.S., Europe and Japan that are living with atherosclerosis secondary prevention. So initially, those are the patients that we're going to be targeting, right? And. Then over time, as we get the cardiovascular outcome data, we will have the opportunity for additional upside if you think about the primary prevention. So again, significant patient population. Of course, the price points are not going to be the same. But both innovations, both compounds, we believe, have multibillion dollars.

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

Yes. I just want to make a comment. Eliav who's a cardiologist and myself who's a cardiologist, you're asking us, which child do we think is more important, and that is a very difficult question to answer. I would just remind you that he trained at Michigan University Chicago, I trained at WashU. PAH is a rare disease, but it's not so rare that a cardiology fellow that sees these patients. So I just want to make sure everyone understands it.

The second thing is when they come in, I mean you're talking about generally women who are suffocating to death. I don't know how to explain that better than they are suffocating to death, and the fact that you see this type of data can have such a meaningful impact.

I would also remind you of the other comments that I made, which is I'm very surprised that how much -- how good the data is because from a basic science standpoint, you would not imagine that you could positively remodel the heart after 9 years, and it will be very interesting to see what happens as we look at other diseases that have right heart strain. So although it's in PAH, I would be a little bit -- we have to see what the data is from cadence to understand how big of an impact.

Anyone who's been doing cardiology recognizes that the number of patients that have reached their goal when they have risk factors of an LDL less than 55 is shockingly low, and so we just sit there and go from a global standpoint. There is (inaudible) whether you like that or not. And with that, the scourge of cardiovascular disease has increased. So the ability to make a meaningful impact, not just in the U.S. but globally, is something that I think the 3 of us think is just really important. So we love both our children.

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

There you go. Thank you, Tim. Calvin, another question, please?

Operator

Our next question comes from Colin Bristow, UBS.

Colin Nigel Bristow - *UBS Investment Bank, Research Division - Analyst*

Congrats on the really impressive data today. So a couple of follow-ons on sotatercept. Can you give us a little more color on the bleeding events in telangiectasias, both in terms of the severity and when these events were typically observed during the treatment course? And then more point of curiosity, but do you have any information on whether there is a correlation between the hemoglobin increases and the 6-minute walk improvement you saw during the trial?

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

Joerg and then Eliav make some comments about that.

Joerg Koglin - *Merck & Co., Inc. - VP of Global Clinical Development*

Sure. So I start with bleeding events. We have detailed AE tables in the New England Journal in the supplement. And then what you see there is really the bleeding events that we observed here were minor bleeding events. These are epistaxis, nose bleeds and gum bleeds. We're not talking about big gastrointestinal bleeding events or intracranial bleeding events. That's not what we observed in this study.

Telangiectasias, so we'll have to learn a little bit more about that. I think in principle, those spider veins are not a clinical concern. Many of those patients often are not even aware that they have those spider veins. When you proactively look for those, then physicians start to detect them. What you want to exclude is that telangiectasia with any other concomitant risk, there is a disease that's different from what we observed in this

study for telangiectasias go hand-in-hand with AVs, which means blood vessel malformations. We haven't observed this in this program. And then we'll learn more through the Soteria study and through the other studies that we do.

Hemoglobin. So -- and in principle, it's correct. Having a little bit more hemoglobin is not a bad thing for a patient with PAH. Actually, PAH physicians often supplement iron to increase hemoglobin. But the hemoglobin is not driving the benefits that you observe on 6-minute walk distance. What we've done in the PULSAR study is we actually used the exposure models to try to figure out how much of that 6-minute walk distance. This is a theoretical exercise. It's driven by hemoglobin. And we came up with something that would be around 4 meters. And so you contrast that to the 40.8 meters that we observed in this study, the increase in hemoglobin drives not the 6-minute walk distance. This is actually, by the way, it would work against your PVR. Higher hemoglobin gives you more PVR, not less, and we saw this impressive PVR effect.

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

Right. And just to amplify on that, I think that the hemoglobin increase that we saw was there, for sure. But I think where the dramatic results were in the decreases in right ventricular strain in the pulmonary vascular resistance, and I think that's a really important point that helps us to understand that this is really a meaningful benefit at the vessel wall and at the circulation itself.

In terms of bleeding, again, minor bleeding and time will be an important component. We'll be looking at how well people do over the course of the year. Soteria, which is the open label study, has been really instructive in that regard. And we see the patients have been on drug for quite some time now, and we'll continue to increase patients under observation. But I think that that's going to turn out in patients to be a nuisance more than a major event.

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

Thank you, Calvin. Back to the room. Question back here.

Jennifer M. Kim - *Cantor Fitzgerald & Co., Research Division - Large Cap and Biopharma Analyst*

Jennifer for Louise Chen at Cantor Fitzgerald. Maybe to start off with sotatercept. So are you going into your conversations with regulators possibly with the consideration of allowing a label that enables early intervention in patients? And if not, for HYPERION, is there an opportunity for an interim analysis or an earlier readout ahead of 2028? And then for the oral PCSK9, Dean, you were talking about delivery being important. You've talked about the macrocyclic peptide technology. Are there other targets that you're actively looking at? And I guess, what are the most important or attractive opportunities?

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

I'm going to have Joerg and Eliav answer the sotatercept question, and then I'll take the PCSK9 question.

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

Yes. So I think just to follow up on the question about FDA and early intervention, we are going to work with the FDA to determine what's the best path forward for sotatercept will be. The STELLAR trial, obviously, is the centerpiece of the regulatory submission, and so I think that that's going to be the centerpiece of what the product circular would look like. Although FDA, of course, is the final arbiter of that.

In terms of HYPERION, we always have interim analysis in our trials, and HYPERION was designed also in the context of -- our old thinking about tactic clinical worsening. That said, right now, the PCD data is in 28 and protocol completion date, primary completion date. So that's probably the best date for planning. But as I said, this drug surprised us a lot in a good way. So we look forward to seeing what the results of that study will show us. Dean?

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

Yes. So we -- I just want to just step back and just sort of emphasize what the design principles for PCSK9 was and is. So in 2018, we sat there and said, how are we going to do this? And what we recognize is the monoclonal antibodies into between the LDL receptor and the PCSK9 at a very specific place. So the design principle is why change that, and so the design principle was to make small molecule that could do precisely. When I mean precisely, I mean not just not just turn down PCSK9 but interdict with the monoclonal antibody dose interdict.

The other issue was you need to take something that's 150,000 belt in. And you need to make it smaller by 150, 100 fold and more, right? You have to, because if you can't do that, there's no chance of making it an oral. So that's what the teams were able to do. It allows you to make an oral. It allows you to make it daily. And it allows you to make it in a way that you don't require cold chain, which is absolutely required in my mind to make it have a global reach.

Now one of the issues that comes up is you can invent these molecules, and that's all nice, and you can get a science or a nature paper about it. But if we want global access, we need to be able to synthesize it at scale, at scale such that my colleagues down the line can offer it at a -- and accessing value price point similar to other oral small molecules. And so those were critical issues.

So we invented it, and we knew that we could do that. And given what I've just told you, that means that in Phase I, we already knew where we stood, right? You can just sit there and you can just take biomarkers and you know where you are. But we were not going to start a Phase IIb unless we knew that we could synthesize it in a way such that the access that we think is required for this is possible. it's that Jannie and Chirfi are in a position that when we talk about global access, we mean it.

And so what I can tell everyone is that we were not going to start a Phase IIb unless we knew that. Because the problem is if we don't know that and we get a Phase IIb, it's a little bit like the forbidden fruit in the Garden of Eden, right? So we know that we can make this and deliver this.

You asked another question, which is, will you see other molecules coming through our pipeline in the coming years? The answer is yes. And if you have suggestions of molecules you would like us to make,.

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

All right. Thank you, Jennifer. Next question, maybe back in the back corner.

Malcolm Hoffman - *BMO Capital Markets*

This is Malcolm Hoffman on for Evan Seigerman at BMO Capital Markets. The question we have is when I -- we think about the Phase III program for 0616, how will you approach the need for outcomes trials? These are critical for injectable medications but took a long time with reimbursement for very limited -- with very limited ahead of these data. How do you envision 0616 coexisting with other cholesterol lowering, non-statin therapeutics.

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

Do you want to take, Chirfi? Chirfi and Jannie? And then I'll just make a final point related to the mechanism of action. Chirfi and Jannie?

Chirfi Guindo - *Merck & Co., Inc. - Senior VP & CMO for Merck Human Health*

So you believe -- I gave you the (inaudible) secondary prevention of 40,000 in the U.S., Japan and Europe and obviously, a lot more around the world. And so 70% of those patients who are treated is a secondary prevention patients, patients who had an event and who have high cholesterol. 70% of them treated with a statin, including high-dose statin not a goal, right? So we believe that there's an opportunity to provide access to those

patients in the first instance, right? And then later on, as we get into the cardiovascular CVOT data, then we could move into primary prevention. This is kind of how we are planning forward for 0616.

Jannie Oosthuizen - *Merck & Co., Inc. - Senior VP & President Merck U.S. Human Health*

Yes. I mean I was going to say -- I mean I think there's a compelling case to be made, right? If you look at 85% of cardiovascular deaths, it's still driven by atherosclerotic cardiovascular disease, right? But less than 5% of patients today are getting an injectable PCSK9. And as Chirfi said, 70% of (inaudible) patients are not at goal. So I think there's a compelling argument. I have no doubt we have some policy work to do and guideline shifts that need to happen, and that's where the work is going to be focused in order to prepare this environment within which these therapies are broadly accessed by more patients. There's clearly an access issue today with injectable PCSK9 in terms of the treatment setting as well as the price point and how it's being managed. So I think we have significant opportunity to open that up in the U.S., and then as Dean said, LDF kicked it off with democratized access to PCSK9. That is really for Merck or MSDs throughout the world.

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

So I'll just remind the previous comments that I made. So when you have a new molecule or a new mechanism, there's always this question of how do you extrapolate what you see from a biomarker to outcomes, right? That's always a question that occurs. So when the PCSK9 antibodies came out, there was no evidence that lowering LDL by interdicting with PCSK9. Everyone knew it could affect LDL, but they didn't know that it could affect outcomes. That's been proven, right? That's been proven, and it's beautiful work by other companies who've done that, and we applaud that.

I'll just recount, our molecule will lower LDF. Our molecule interdicts with the PCSK pathway. It doesn't just interdict with the PCSK9 pathway. It interdicts in the same biochemical means by which the antibodies work, right? This is not I'm going to do some other mechanism in relationship to PCSK9. With the biophysical and the biochemical level, we are doing what the antibodies. We have simply taken 150,000 antibody. And we've gone, poof, made at 1,500.

So when one thinks about what is the probability that this might be able to replicate the outcome style, I think if people think through that, I think that would be a reasonable way to think about it. I should also remind is that the access requires no co chain. This is something that can be mailed to you. This is something that you can go to your local Walgreens or CVS or something like this. This will be that easy to get. But in order to get back global access, we need to make it that at a price point that makes it accessible is possible. So you're right. But when we designed the principles in 2017, 2018, this is what we laid out.

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

Next question.

Cerena Chen - *Wells Fargo Securities, LLC*

This is Cerena on from Mohit Bansal of Wells Fargo. So I have 2 questions on sotatercept. One is on the AE. So given the rate of certain visible AEs, like epistaxis and telangiectasias, sorry about that. What do you think about the potential for an unblinding effect with the AEs? And then the second question is on the potential remodeling effect of sotatercept. When would we see the CT scan or vascular imaging data that would support this effect? And how would this data impact how early sotatercept is used in the treatment paradigm?

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

So I'll let Joerg take the first 2. But also this question of unblinding and all of this sort of thing, I'll let Eliav also speak to that as well.

Joerg Koglin - *Merck & Co., Inc. - VP of Global Clinical Development*

So what we do in clinical studies, for example, we blind the study personnel investigator to hemoglobin, precisely avoid that there would be some intentional or unintentional unblinding of individual patients.

With respect to telangiectasia, I mean you saw we had a 3.5% telangiectasia AE rate auto the placebo group. We see the same treatment effect in PULSAR at a time where we didn't look for a telangiectasia. They were not detected, Same treatment effect. I think that makes me a little bit more comfortable that what I observe is not confounded by any of those AEs.

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

Do you want to speak Eliav, just to profound and how many patients are getting accepted versus searching for telangiectasia and what percent?

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

Right. I think that the -- obviously, adverse experiences that are in balanced between the treatment group are things that we see sometimes with drugs based on the mechanism of action, but the event rate for those events were really pretty small. And what's also important in striking is that the actual measurements that we do, the values that we measure are objective measures. In other words, it's not about us saying we're going to do some sort of score, it's really more about how much piece we're going to walk, what is the pulmonary vascular resistance as measured in the Cath Lab. And then the NT-proBNP is simply a blood test. And so I don't believe that there was any cases where there might have been sort of this systematic potential for bias.

The other thing is epistaxis are pretty rare. I remember these folks are also getting a lot of (inaudible). So they get a lot of -- they have in usual course of practice to have a little bit of nosebleed. So I think the doctors were not looking at that as a mechanism-based thing.

In terms of trying to be able to tease out the mechanistic underpinnings of the drug in patients, I think that none of these tools is validated, frankly. And the best way to do this, and it's not exactly the same as in preclinical models. And in that -- in those models, which are pretty predictive, there was a pretty substantial remodeling in the right way. In other words, reversal of fibrosis and -- I'm sorry, reversal of thickening and then a return to a normal biology.

At the end of the day, time will tell. The most important thing is what the time to clinical worsening is. And when you think about it, hard endpoints was already improved with 300-some-odd patient trial. I mean it's pretty impressive. So I think that, that will be the ultimate demonstration that the drug is doing something more than just simply dilating blood vessels.

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

Great. Maybe last question here in the room.

Nishant Shailesh Gandhi - *Truist Securities, Inc., Research Division - Research Analyst*

All right. Nishant Gandhi for Robyn from Truist Securities. And congratulations on all the great data. So I have 2 questions with MK-0616. So first, just wondering in terms of GI side effects, whether you think these effects are mostly related to the overall oral drug and if they are like a class side effect in terms of PCSK9 in general.

And the second one is in one of the recently presented outcomes trial for LDL-C, over a period of time, they saw the placebo group started coming upwards over a period of time in one of the trial and whether you think that is an issue in your trial and if it needs addressing.

Joerg Koglin - *Merck & Co., Inc. - VP of Global Clinical Development*

I'll start with the placebo question. As a clinical trial, it is important to do everything you can do that your placebo group essentially. It's constant. You do that by mandating that patients are on background therapy for a longer time part. Sometimes we do a run-in. We didn't do this here. So we had a good experiment. So there was no wheel change in placebo LDL. So this is in a really stable patient population.

And then the second question, please help me again. Or is it first?

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

This was about GI side effects and what was the mechanism of action (inaudible) here.

Joerg Koglin - *Merck & Co., Inc. - VP of Global Clinical Development*

Yes. So we'll have to learn more about those GI side effects. The good news is they were rare, and they were mild. When you look through the table, there's no real dose response. So I think we'll need more than 381 patients observed over 8 weeks and then 8 weeks of safety follow-ups. So that will be a focus of our Phase III program. It is not a PCSK9 mechanism-based side effect. I mean the side effects that you see with injectables very often have to do with the injection itself, and that way how the drug is given. That's not our problem with the tablet. But PCSK9 inhibition doesn't mechanistically cause GI side effects.

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

Yes. Thank you very much, everybody, for attending, making the trip down here to New Orleans. Really appreciate it. Great questions. But let me turn it to Dean for any final comments.

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

Yes. So thank you all for making all the way to New Orleans to speak to us. This has been an important day for us, and I just want to make sure that we thank the patients and the investigators. But I also want to specifically call out for the sotatercept program. I really want to thank our colleagues at Acceleron, who really did -- were remarkable in the work that they've done prior to the merger acquisition, during the merger acquisition, and many of them have become more colleagues. And without that smooth transition, I'm not so sure that day would come for patients with PAH.

And for people who have seen patients with PAH, I mean it is a horrible disease, and the fact that we might be able to change the treatment paradigm is something that has all of us absolutely thrilled. For the PCSK9 program, I do, again, want to thank the sites and the investigators and the patients.

But we're all here in our suit, but I just also want to highlight those of us who are at Merck, who are in the engine room of the Starship Merck, and in that engine room are people who have done what I believe has been people have thought of making an oral PCSK9 for decades. And to be able to do that, and to be able to create it, and to be able to make a molecule that has a possibility of having that accessibility is just remarkable.

So I thank Eliav's teams and Joerg's teams and the product development team leaders for this, but I just want to make sure that I made a call out for all of our colleagues from Acceleron and all of our colleagues in the engine room of Merck. Thank you very much.