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BAYN.DE - Bayer AG Investor Conference Call to Discuss Findings from the Phase III PATENT-1 and CHEST-1 Studies of Riociguat Presented at CHEST

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PRESENTATION

Operator

Ladies and gentlemen, thank you for standing by. Welcome to the conference call of Bayer AG for investors and analysts on October 24, 2012 to discuss findings from the Phase III PATENT-1 and CHEST-1 studies of riociguat presented at CHEST.

Throughout today's recorded presentation, all participants will be in a listen-only mode. The presentation will be followed by a question and answer session. (Operator Instructions).

I would now like to turn the conference over to Mr. Alexander Rosar, Head of Investor Relations of Bayer AG. Please go ahead, sir.

Alexander Rosar ***- Bayer AG - Head of IR***

Thank you, Cleo. Ladies and gentlemen, good afternoon, and thank you for joining our call.

It's our great pleasure to share exciting findings on two riociguat Phase III studies; PATENT-1 and CHEST-1, review. Data was presented earlier this week in a late-breaking abstract session at the annual meeting of the American College of Chest Physicians in Atlanta.

With me on the call are Kemal Malik, Head of Global Developments at Bayer Healthcare Pharmaceuticals; and Frank Misselwitz, Head of the Therapeutic Area Cardiovascular and Coagulation in the Global Clinical Development.

Before I hand over to Kemal, I'd also like to draw your attention to the forward-looking statement wordings. *(See "Disclaimer" chart at the end of this transcript)***.**

Thank you. Kemal?

Kemal Malik ***- Bayer Healthcare Pharmaceuticals - Head of Global Developments***

Thank you, Alexander. Ladies and gentlemen, I'd also like to welcome you.

Pre-program, we studied riociguat in two different forms of pulmonary hypotension. Let's look at pulmonary arterial hypertension, or PAH. It's a potentially life-threatening disease for which, despite the availability of several acute therapies, prognosis for patients remains poor.

Indeed, we studied riociguat in chronic thromboembolic pulmonary hypertension, or CTEPH; a truly devastating condition for which, so far, no pharmacological therapies have been approved.

Now I'll turn to the key findings. Both studies met their primary endpoint of a statistically significant improvement in the change from baseline in the six-minute walk test versus placebo. In addition, the two trials also met key and clinically relevant secondary endpoints. In both trials, riociguat was shown to be safe and well tolerated.

Now, ladies and gentlemen, let me emphasize that our results show, for the first time, that a drug can demonstrate robust efficacy in both PAH and CTEPH.

Let me put our findings into perspective. Pulmonary hypertension describes the constellation of severe and progressive diseases that are associated with increased pulmonary vascular resistance; reduction in exercise capacity; increased right ventricular heart failure; and premature death.

Several forms of pulmonary hypertension are heterogeneous. Importantly, pharmacological treatments are only approved to treat one of the various types of pulmonary hypertension, which is known as pulmonary arterial hypertension.

In other words, about 90% of patients with PH are in desperate need for a treatment, as there are no approved drugs available. Therefore, the unmet medical need in pulmonary hypertension remains significant.

So let's look at riociguat. Riociguat is first-in-class stimulator of an enzyme called soluble guanylate cyclase, or sGC. This enzyme facilitates the production of cyclic guanosine monophosphate, or cGMP, which is a secondary messenger in the cells of the vessels. Increased levels of cGMP lead to widening of the vessels and, in turn, a lowering of the local blood pressure.

A natural ligand for sGC is nitric oxide. However, nitric oxide is sometimes low in patients with pulmonary hypertension. A drug that just prevents degradation of cGMP, like a PDE5 inhibitor, may not properly work under these conditions because the signal that is needed to induce sufficient levels of cGMP at the beginning of the cascade is not there.

Riociguat acts in two ways. Firstly, it is able to stimulate the soluble guanylate cyclase independently from nitric oxide. As mentioned, this is an important prerequisite to treat forms of pulmonary hypertension where nitric oxide is absent, scarce, or responsiveness to nitric oxide is disturbed.

And secondly, by increasing the sensitivity of soluble guanylate cyclase to nitric oxide, riociguat is able to amplify the effects of the low levels of nitric oxide that may still exist in some areas.

The key findings that I've just shared with you indicate that this innovative principle translates into real clinical benefits.

Frank Misselwitz will now explain the studies in detail to you.

Frank Misselwitz - ***Bayer AG - Head of Therapeutic Area Cardiovascular and Coagulation, Global Clinical Development.***

Thank you, Kemal. On this slide, you can see the PATENT-1 study as a randomized double-blind, multi-center placebo controlled study to evaluate the efficacy of riociguat and the treatment of patients with pulmonary arterial hypertension who were either treatment naive, so these patients received oral riociguat as a monotherapy; or patients who were stable while on treatment with an endothelin receptor antagonist, or a prostacyclin analog. Those patients received riociguat in combination with the ERA or prostacyclin.

We titrated riociguat in two-week intervals, according to the peripheral systolic blood pressure over the first eight weeks of treatment, in doses of 0.5 mg increments, from 1 mg up to 2.5 mg, three times a day. After the titration phase, riociguat was provided as a maintenance therapy for additional four weeks.

Patients completing this PATENT-1 study were then given the opportunity to enroll in a long-term extension called PATENT-2. The primary efficacy outcome was the placebo-corrected change in the six-minute walking distance from baseline at week 12. Secondary outcomes included hemodynamic parameters; WHO functional class; time to clinical worsening; quality of life assessments; and, of course, safety.

Baseline characteristics were very well balanced between the treatment arms. And on the six-minute walking distance, for instance, the mean baseline performance was 361 meters in the riociguat, and 368 meters in the placebo arm.

In addition, more than 40% of patients in either group were in functional class 2, and about the same proportion of patients in functional class 3 respectively.

This baseline data indicates a stable and, compared to benchmark trials, relatively healthy study population.

Let me now turn to the primary endpoint. The PATENT study met its primary efficacy endpoint of significantly improving the six-minute walking distance after 12 weeks of treatment versus baseline. The six-minute walk test is an accepted indicator and a validated prognostic (technical difficulty), and has been used in all the registration trials to date in PAH.

In the riociguat arm of the study, the improvement in exercise capacity started rapidly and continued for the entire 12-week treatment duration. Importantly, the improvements were observed to the same extent in both treatment-naive patients, those who were on riociguat monotherapy, as well as in patients treated with a combination of an ERA, or a non-IV prostacyclin analog, plus riociguat.

Let us turn to the secondary endpoints now. We have observed, furthermore, robust and clinically meaningful improvements across the secondary endpoint. While it provides the p-value and illustrates the consistency and robustness of our finding, I want to highlight in particular the significant improvements in WHO functional class, as well as in time to clinical worsening; an important indicator for morbidity and mortality.

On the safety part, it was demonstrated that riociguat was well tolerated, with a good safety profile in patients suffering from pulmonary arterial hypertension, when used as a monotherapy, also in combination. Of note, only adverse events related to the expected pharmacodynamic action of riociguat were observed.

In PATENT-2, patients who completed the 12-week treatment, as I told you, were eligible to enroll into this longer-term extension study.

We conducted an exploratory analysis at week 12 in the extension study, and we are pleased to report that the six-minute walking distance improved further in the riociguat arm. These improvements are consistent with this finding, were also observed in the former placebo arm upon switching over to riociguat. We plan to show these findings in greater detail at one of the major meetings next year.

So let me summarize the PATENT-1 findings. The efficacy results were significant and robust across the primary and secondary endpoints. Importantly, the improvements in the six-minute walk test were not limited to treatment-naive patients receiving riociguat as a monotherapy. They were also significant for those patients who received riociguat on top of an endothelin receptor antagonist, or a non-IV prostacyclin analog.

Riociguat was well-tolerated, with a good safety profile in PAH patients; again, both as a monotherapy, but also in the combination.

In addition, further improvements in the six-minute walking distance have been observed in a first exploratory analysis in the still-ongoing extension study, PATENT-2, after 24 weeks.

So this is already really good data. But let me now switch gears and move onto the study in chronic thromboembolic pulmonary hypertension, CTEPH, the CHEST trial.

We think that these results represent a breakthrough study and illustrate the potential of our novel approach of sGC stimulation. Endpoints in the CHEST-1 trial are similar to the PATENT study that we just discussed. Let me, therefore, only briefly explain the aspects that differ from the PATENT design.

Firstly, riociguat was administered as a monotherapy only, as there are no approved medical treatments for patients with CTEPH. Combination with any drugs approved for pulmonary arterial hypertension treatment was not allowed. However, patients could have undergone pulmonary endarterectomy; a surgical procedure in which the blood vessels of the lungs are cleared from scars and clot materials.

The study included patients with CTEPH, which was either inoperable or which was persistent or reoccurred after surgery. Baseline characteristics were balanced between the treatment arms. 60% to 70% of the patients were in functional class 3 at baseline.

Let me turn to the primary outcome of the CHEST-1 trial. CHEST is the first pivotal study ever that met its primary efficacy endpoint. The slide shows a significant improvement in the six-minute walking distance in patients suffering from CTEPH.

The onset of the treatment effects is rapid. Improvement versus baseline and versus placebo starts immediately after initiation of treatment.

As I mentioned before, the surgical procedure called pulmonary endarterectomy is the only cure for this condition, and is a treatment standard today. However, a considerable number of patients with CTEPH are non-operable; and in some of these patients, pulmonary hypertension persists or reoccurs after surgery had been performed.

In tests, we could demonstrate, and this is shown here on this slide, that the improvements in exercise capacity were observed consistently in both populations; inoperable patients, as well as in patients with persistent or recurrent PH after surgery.

In the larger population of inoperable patients, this improvement was statistically significant in the smaller group of patients with recurrent or persisting PH. A clinically meaningful trend was seen after 16 weeks of treatment.

As in PATENT, patients who completed the 16-week treatment were eligible to enroll into the long-term extension for a continuation of treatment. Preliminary data from the still ongoing long-term extension study indicates not only sustainability of the effect, but even further improvements, as you can see here.

Improvements consistent with this finding were also observed in the form of placebo arm upon switching over to active riociguat. As said, we plan to show detailed findings at one of the major meetings next year.

Riociguat also showed statistically significant improvement in relevant secondary endpoints, including the hemodynamic parameter, pulmonary vascular resistance; the bio-market NT-proBNP; as well as WHO functional class.

Additional measures were then tested in a hierarchical testing procedure. The percent of patients with a clinical worsening who went on this study was 2.3% in the riociguat treated patients, and 5.7% in the placebo group; a trend in favor of riociguat.

As in in the PAH population, riociguat was well tolerated in patients with CTEPH. Most frequent adverse events included headache and dizziness, which were observed more frequently in patients receiving riociguat, whereas other frequent adverse events, like peripheral edema [or CAF], occurred more frequently in the placebo arm of the trial.

As in the PATENT study, the safety profile of riociguat was benign, and closely related to its pharmacodynamic.

Ladies and gentlemen, let me now summarize the findings of the test trial.

Riociguat was the first ever drug that demonstrated clinical efficacy in a pivotal study in patients with CTEPH. It met the primary efficacy endpoint by demonstrating a statistically significant and clinically relevant improvement in the six-minute walk test.

Riociguat also showed statistically significant improvements in relevant secondary endpoints. Importantly, riociguat works in both inoperable patients, and in patients with residual or recurrent CTEPH post the surgical procedure.

Riociguat was well tolerated. There's a good safety profile in patients with CTEPH. And the efficacy benefits were further improved in an exploratory analysis in the long-term extension trial.

With that, I would like to hand over to Kemal again.

Kemal Malik - ***Bayer Healthcare Pharmaceuticals - Head of Global Developments***

Thank you, Frank. Ladies and gentlemen, let me, as always, express my sincere thanks to the patients and physicians who have been involved in this large clinical program; and congratulate our team for their hard work, dedication, and commitment to this disease area.

I'd like to summarize what we have achieved in our clinical development program for riociguat so far.

We have demonstrated, for the first time, that a drug can actually demonstrate clinical efficacy in Phase III studies in different forms of pulmonary hypertension. That is the most significant aspect, we think, as riociguat, if granted approval, may become the first pharmacological treatment option for patients with CTEPH.

We previously reported positive results from small [single] generating studies in patients with two forms of PH, owing to lung disease. The data that we have obtained so far in our clinical program for our first sGC stimulator, riociguat, suggests that there may be a potential for this approach in additional indications.

So what are the next steps? Well, we plan to present additional data from the riociguat program, the Phase II Left study, in patients with pulmonary hypertension as a result of left ventricular dysfunction, at this year's American Heart Association meeting.

We target submitting our applications for marketing authorization in pulmonary arterial hypertension, PAH, and CTEPH in the first half of 2013. And, in addition, we plan to update all of you on our potential further steps in the riociguat development program during the first half of next year.

With that, I'd like to pass you back to Alexander again.

Alexander Rosar - ***Bayer AG - Head of IR***

Thank you, Frank and Kemal. Before opening the Q&A, I would like to make you aware that an on-demand version of the call will be available on our website later today. With this on-demand version, we also plan to provide some additional slides on the clinical studies.

With that, we would now like to listen to your questions.

QUESTION AND ANSWER

Operator

Thank you. Ladies and gentlemen, at this time, we will begin the question and answer session. (Operator Instructions). Mr. Race.

Tim Race - ***Deutsche Bank - Analyst***

Tim Race, Deutsche Bank. Congratulations on the clinical data. First question is just on CTEPH indication. Obviously, it's not -- it's a new indication, as such, as there's been no other drugs and so the market isn't quite developed yet. The numbers or incident figures you gave, just could you help us understand a little bit more how -- what proportion of patients do you estimate are actually currently getting surgery? What proportion are actually getting diagnosed properly? And what proportion are currently getting treated off label with, perhaps, the ERAs, or with [Ratio], or something of that ilk?

Then, just moving onto the PAH indication, obviously, that's more of an established market. It's in transition with lots of therapies either going generic, or new therapies coming to the market. Based on the data that you've provided, how do you think riociguat can differentiate itself there? And where's the natural positioning for the drug?

And then just, perhaps, if you could just talk on the safety profile, perhaps the GI tolerability and the systemic hypertension. Is -- in terms of the wider usage and perhaps the halo effect in off-label usage, do you think any of the side effects you've seen are going to be a barrier for regulatory purposes there, and -- or concerns there?

Kemal Malik - ***Bayer Healthcare Pharmaceuticals - Head of Global Developments***

Thanks, Tim. Frank, why don't you kick off and talk a little bit about CTEPH; the operability in terms of patients; and, perhaps, the safety profile? And then, I'll come in and talk about the profiling of the drug.

Frank Misselwitz - ***Bayer AG - Head of Therapeutic Area Cardiovascular and Coagulation, Global Clinical Development.***

Sure, happy to answer those questions. Tim, good question.

With regard to the proportion of non-operable patients, or patients with residual disease, let me start answering that question with the numbers from the trial, knowing that the real life data may look slightly different.

In the trial, we had performed a very rigorous assessment of the operability with the 24/7 availability of a central adjudication committee. And we found that, from all patients initially screened, approximately 37% were not eligible because they were deemed to be operable.

So that is in the situation of an assessment by the worldwide leading surgical centers to cure that disease. And it is very clear that in real life the proportion of patients with CTEPH not being operated is approximately up to 50%; much higher than the 37% observed in the clinical trial. So that is the proportion to start with.

Commenting on the safety part, as you noted, we have seen, in a relatively small percent of patients, GI side effects, as you noted. They were mostly mild to moderate and essentially did not lead, in a large percentage, to stopping the treatment. So they are very well handled and not dramatic in the proportion, nor in severity.

Hypertension; you may have noted, Tim, that the most significant expression, syncarpy/pre-syncarpy, was really not different and even, in the PATENT trial in particular, more frequent in the placebo arm compared to the actively treated patients.

So the hypotensive episodes were mostly asymptomatic, not associated with any clinical symptomatology, and were just picked up in the titration phase when patients were -- frequently measured their peripheral systemic blood pressure. So also here we are actually quite confident that this is a typical to-be-expected side effect due to the fact that the mode of action involves [phase of] dilation, and we do not expect any hurdles in the clinical uptake based on that.

Kemal Malik - ***Bayer Healthcare Pharmaceuticals - Head of Global Developments***

Thanks, Frank. And also, added to that, the regulatory [point], we have a very strong risk benefit profile; positive risk benefit profile.

If I talk specifically, Tim, to your question about PAH, I would emphasize the robustness of the data that we generated; a very strong dataset in terms of six-minute walk distance, in pretreated and well as treatment naÃ¯ve patience. And the point that Frank made earlier about the significant improvements in WHO functional class, as well as time to clinical worsening, these are important indicators of morbidity and mortality.

Clearly, the two indications are different. In PH, there are other approved drugs. With the data we've generated in PATENT, I think that gives us a competitive position.

But really the icing on the cake, and clearly the thing that we're all terribly excited about within Bayer, are the data that we've seen in CTEPH. The fact that no other drug has been shown in a randomized control clinical trial to have statistically significant results, and the fact that we've shown this with quite marked results, really does differentiate this agent from all existing agents. As I said, I think this really is potentially a very game changing move in this area.

Tim Race - ***Deutsche Bank - Analyst***

Okay, understood. Thank you.

Operator

Mr. Jain.

Sachin Jain - ***Bank of America Merrill Lynch - Analyst***

Sachin Jain, Bank of America Merrill Lynch. Three questions, please. First, just a high level mechanistic question. Any thoughts from your side as to why you've seen better data in CTEPH than PAH, whereas, obviously, existing agents it's the other way around?

And then mechanistically, any indications as to why the effect accumulates with time in those exploratory analyses? Again, I think with PD5s we haven't seen that, so any early thoughts on that?

Secondly, Kemal, in your final slide you alluded to further trials potentially. Could you just give us a feel as to where you're going with that? Would that be further datasets to build in CTEPH or CTEPH and PAH? Where would the focus be?

And then finally on CTEPH guidelines. I think they were last updated in 2009, and PAH therapy is recommended or is discussed there. Would you expect that to be removed and just to be replaced with a riociguat? Thank you.

Kemal Malik - ***Bayer Healthcare Pharmaceuticals - Head of Global Developments***

Sachin, thanks. Frank, why don't you kick off with the question about the mechanistic background and guidance we can gain for our efficacy results in PH, and I guess specifically in CTEPH, and the time factor on the efficacy? Then, I'll follow up with something about further development and guidance.

Frank Misselwitz - ***Bayer AG - Head of Therapeutic Area Cardiovascular and Coagulation, Global Clinical Development.***

Thanks. Right, Kemal, we'll be happy to do that. Sachin, why we are better in the CTEPH environment compared to PATENT, well, I think the answer here is relatively easy. It's driven by a number of components.

First, the PATENT trial was a mixture of treatment-naive patients and pretreated patients, and a combination of therapy with ERAs or prostacyclin analogs. And, of course, having had in the mixture of patients in PATENT approximately half of the patients being treatment naive and the other half pretreated that, of course, means that overall the benefit is slightly smaller.

But, importantly, it's also related to the severity of disease. Given the fact that CTEPH patients are very often progressing more into their disease before they actually will be correctly diagnosed and potentially undergo surgery, these patients, at average, just if you look at the split of functional classes and baseline, six-minute walk distance, were slightly more diseased. And what we see in general, across the program, is that the more diseased the more severe patients actually have a greater benefit from the treatment that's riociguat.

We actually see that also in the PATENT, if you have a split between the less severe versus the more severe patients, so the more severe patients are always associated with a greater benefit.

Why do we see a further improvement accumulating over time? Well, this has a number of reasons. We believe that, first of all, the treatment period chosen in our trials was relatively short. You may have noticed that at 12 weeks in PATENT and 16 weeks in CHEST, which, in part, was driven, particularly in PATENT, by our belief that it is not good to actually randomize patients to a placebo comparator in an indication where, actually, other treatments are available. Hence, this relatively short observation time.

Obviously, and we have seen that very clearly, further improvements are possible. That actually clearly shows that the mode of action is not just laser dilation. But there is something in addition to that which is really driven by the mode of action, by the stimulation of the sGC access, and that involves entire remodeling, entire fibrotic effects, and these kick in in the longer term.

Kemal Malik - ***Bayer Healthcare Pharmaceuticals - Head of Global Developments***

Thanks, Frank. Sachin, if I turn to your next question, which was about further development. I guess the reason why we're so excited by the CTEPH data are, obviously, that within CTEPH, because nothing else had ever been shown to work, we're working. But also, it's a segue to the fact that we can work in other causes of pulmonary hypertension other than PAH.

From what I said earlier, the vast majority of patients with pulmonary hypertension don't have approved treatment options. And CTEPH, for us, is a marker of the fact that we work in this really high-risk medical need area, but also opens up the possibility of working in other areas in which pulmonary hypertension is associated.

We will be presenting the left data, pulmonary hypertension secondary to left ventricular dysfunction, the Phase II study, at the American Heart Association. And, naturally, we're now going to explore the full clinical utility of riociguat and see what the possibilities are in the other areas, and we'll update on that clinical program in the first half of next year.

In terms of guidelines, I don't think it's unreasonable, in an age of evidence-based medicine, that if we are, with our agent, the agent that has been shown in a randomized Phase III clinical trial to be the ones who have generated these data then I don't think it's unreasonable that we should get high priority and treatment guidelines when other agents haven't done so.

That having been said, we don't write the treatment guidelines. Those are in the hands of the great and the good. I think the great and the good will be impressed by the data from CTEPH, but that is a bit out of our control.

But if there is fairness and justness and evidence-based medicine, we would imagine that we would hold premier position if and when approved in CTEPH.

Sachin Jain - ***Bank of America Merrill Lynch - Analyst***

Thank you very much.

Operator

Mr. Leuchten.

Michael Leuchten - ***Barclays Capital - Analyst***

Michael Leuchten, Barclays. Thank you for taking my questions. Two really; one on PATENT-1. Just going back to what Frank was saying about the healthy patient population, if I looked at the slides correctly there's 55% of patients are in functional class 3, but only 50% overall are treated -- or 50% overall are treatment naive. That seems a bit odd and a conflict here.

Also, the subgroup of patients that have received PCA, the control patients are seeing a 40-meter decrease in the six-minute walk distance, so I just wonder whether you could comment a little bit more on the patient population from that perspective.

And then the second question on the CHEST-1 trial. The six-minute walk distance appears to be flattening a little bit and the time to clinical worsening was not statistically significant. Can you talk about the duration of responses? Is it actually sustainable? Or do you see a peak and then a flattening or a decrease thereafter, which brings down the statistical significance on time to clinical worsening? Thank you.

Kemal Malik - ***Bayer Healthcare Pharmaceuticals - Head of Global Developments***

Thanks, Michael. Frank, could I ask you to try both of those?

Frank Misselwitz - ***Bayer AG - Head of Therapeutic Area Cardiovascular and Coagulation, Global Clinical Development.***

Certainly, try to do that. Let's first start, Michael, with the PATENT inclusion and the question you raised about the percentage of patients being in functional class 3, and relative to the proportion of patients being treatment naive.

I think the fact here is that when you compare and benchmark overall the severity of disease in PATENT and try to benchmark that across the trials in PAH in the last couple of years you will see that the baseline parameters of the patients enrolled in PATENT-1 is more towards the less diseased patients.

It is fully captured in the spectrum of all the benchmark trials, but it is slightly more towards the less diseased patients. And that, as you rightly said, is expressed in the split between functional class at baseline. It is also, as a matter of fact, highlighted in the baseline six-minute walk distance with these patients.

So the fact that we have approximately half of the patients being treatment naive is -- I don't believe it's contradictory to that because clinical reality in many countries is that those patients are relatively late diagnosed. We have patients actually with an early diagnosis and then being submitted to become patients in the clinical trial.

And in terms of pretreatment, we see that most of the pretreatments, also in registries outside our clinical trials, are really pretreatment with ERAs, followed by PDE5 inhibitors.

So I think given the natural cause of disease, the difficulties in diagnosis, it's not unreasonable having this kind of patient split. So I would not necessarily assume that every patient with functional class 3 has to necessarily be pretreated already with another drug. That is just not reflective of clinical reality.

In terms of the CHEST data and why do we believe the -- or what is our data on the longer-term effect and why the time to clinical worsening was not significant in itself as a secondary outcome, well, that's relatively straightforward and easy to answer.

We do see continuous improvements over the first, roughly, six months of treatment, with very substantial improvement in the six-minute walk distance and other parameters. This is then for [towing], and we don't see in the active arm any big fluctuations or further decreases. So that is very stable.

And what we are going to report next year in terms of the longer-term data, the CHEST-2 data, that we are able now also, as Professor Ghofrani said in the meeting -- we actually have now up to five-year chronic data for patients who were included in the Phase II and are still in the extension trial. And they can be -- approximately half of them can still be handled with riociguat monotherapy.

So, indeed, we believe that the long-term effect is very promising and there is no decrease over a longer time.

So why is the time to clinical worsening not significant in this trial? Well, it's a secondary endpoint. The trial was not powered for that.

It's very obvious that also the observation time of 16 weeks is, of course, not long enough to capture enough clinical outcome events in those patients. But, as I mentioned, the numbers are actually quite good. We have in the CHEST trial the same trend with regard to the proportion of patients having had a clinical worsening event, and this number simply numerically is halved in the patients treated with riociguat.

So given the small number of patients in the trial, that has not become significant. But there is a very clear and pronounced, and when you compare the two trials, PATENT and CHEST, very consistent effect on the time to clinical worsening.

Michael Leuchten - ***Barclays Capital - Analyst***

Thank you.

Operator

Mr. Vosser.

Richard Vosser - ***JPMorgan - Analyst***

Richard Vosser, JPMorgan. A few questions, please. Just on the -- you mentioned the titration regimen. I just wondered if you could comment on -- you talked about every two weeks, but how difficult is this titration regimen really to do, given the risk of hypertension, thinking particularly in terms of the PAH setting here? Clearly, there's nothing else in CTEPH, so that's less relevant.

Second question. Just thinking about the discussion with regulators, just if you could give us some light on how the regulators are now thinking of the six-minute walk test in PAH.

I think feedback that I've heard from CHEST is that a lot of the doctors are now starting to comment that morbidity, mortality, is the way to go. So just some context here on how the regulators may be thinking about that, and also whether the European regulators need a head-to-head trial for PAH.

And then finally, just looking at the CHEST data and the exploratory analysis going forward, the number of patients decreases going forward, potentially because it's exploratory, I suppose, that you have -- all the patients haven't reached that point. But if there are any dropouts contributing to the reduction in the patient number, could you just give us an idea of the reasons why patients are dropping out, if that is indeed the case?

Thanks very much.

Kemal Malik - ***Bayer Healthcare Pharmaceuticals - Head of Global Developments***

Richard, thank you. Frank, could you take the question on titration and its applicability and ease, particularly within the pulmonary arterial hypertension setting; and also, talk about the CHEST data and the impact or not of dropouts? And then, I'll finish off with the regulatory bit.

Frank Misselwitz - ***Bayer AG - Head of Therapeutic Area Cardiovascular and Coagulation, Global Clinical Development.***

Excellent, will do. So, Richard, a couple of very good questions. The titration regimen is nothing particularly exciting, difficult, or new. We all know when you have systemic hypertension, not pulmonary but systemic hypertension, that you will be given, say, a beta-blocker to start with, and that is going to be up-titrated and dosed.

There's nothing magic about it. That is to be done in everyday clinical practice. And the same holds true here for pulmonary hypertension. So you just adjust based on the effect or on side effects. It's a simple measurement, and we don't believe that there is any difficulty in performing that.

It's a very severe disease. Patients are under close surveillance anyhow. And we have not experienced in the setting of our clinical trial that there is any difficulty in performing that part of the titration.

As a matter of fact, it has been highlighted by Hadi Ghofrani in the original presentation, 90% of patients in both trials have reached the two highest doses, which actually is a testament to the good safety profile of the drug, and that --

Basically, again, the same applies. You would not start with the highest possible dose of the beta-blocker because of potential side effects; you actually consider a slight up-titration. So I think that part is not a big deal at all.

Talking about your specific question about the CHEST data and the denominator in the longer-term dropping, yes, of course, there are a couple of patients dropping out. Of course, there is mortality, albeit very low. So in the longer run people -- patients may die. They may stop due to other reasons, just because they relocate to a different town, etc. But importantly, and I want to highlight that, we have had this very rigorous operability assessment.

A couple of patients initially were deemed inoperable, and that was driven by the very severe underlying disease. So after improvement during treatment with riociguat, those patients actually improved in their general health status, and were then in some cases deemed to be operable, and hence be operated on, because this is the only cure for patients with CTEPH. So we believe that this is the important reason.

And another technical reason is that this trial is still ongoing. And, of course, the data presented here are simply technically dated to a certain cut-off date, which then also translates into certain denominators over a longer time.

Kemal Malik - ***Bayer Healthcare Pharmaceuticals - Head of Global Developments***

Thanks, Frank. Richard, let me talk to you about the regulatory situation. The clinical programs in both PAH and CTEPH were discussed [prior] with the regulatory authorities, both in the US and in Europe, and there was endorsement of the primary endpoint chosen. Subsequently, and as part of our ongoing discussions leading to the regulatory filing, we've discussed with the authorities there's no untoward signals. I think it is a validated and accepted endpoint in terms of these studies, which they are comfortable with.

Clearly, other agents have presented some data at the same meeting, and we can talk about the significance or not of those data perhaps on another date. But certainly, in terms of six-minute walk distance, this is an accepted endpoint which we have discussed and the authorities' clear feedback to us has been endorsement.

Clearly, we're going to enter a regulatory process and there will be discussion as we go through that process, but we're very comfortable with the endpoints chosen.

Specifically also to your question, in Europe we haven't been asked to run a comparator study.

Richard Vosser - ***JPMorgan - Analyst***

Brilliant. Thank you very much.

Kemal Malik - ***Bayer Healthcare Pharmaceuticals - Head of Global Developments***

Thanks, Richard.

Operator

Mr. Weston.

Matthew Weston - ***Credit Suisse - Analyst***

Matthew Weston, Credit Suisse. Two questions, if I can, please; both really, I guess, boiling down to commercial potential.

So in terms of treatment duration, you've made some comments about five-year patients in the follow up on the Phase II study. You've also made the comments about treat to surgery. Particularly in CTEPH, how do you see riociguat likely to be positioned? Is it a drug we should think of in terms of a treat to surgery setting? Or is it one where we can think of in terms of long term utility? And, if so, what duration do you think we will over time find patients using?

And then secondly, I realize it's very early to talk about price, but clearly within the PAH market there are a number of price points, some of which are about to change very soon with drugs moving to generic status. You clearly highlighted the differentiated nature of the efficacy in CTEPH, should we also think of that meaningfully transitioning into a differentiated price relative to current therapies on the market?

Kemal Malik - ***Bayer Healthcare Pharmaceuticals - Head of Global Developments***

Thanks for your question. I'll take the question on the price in commercial first. And then, Frank, perhaps you can talk about the CTEPH medical positioning and, based on the data which is in inoperable and operable patients, where you see this drug having its clinical utility base on the Phase III data.

You're absolutely right, it's too early to talk about price. The focus of our organization at the moment is a bit of celebration, generating what we think are excellent data. But really a focus on the regulatory submissions in the first half of next year to make this what we think is a breakthrough medication available for patients around the world. So that's really where we're focusing as an organization.

We're not really in a position to talk about pricing and the commercial potential of the asset.

Clearly, the markets are different; self-evidently. You have other treatment options in PAH, and some of them are going off patent. In CTEPH, we have white space, and we see a very significant opportunity in CTEPH. But really, to be fair, I think it's premature to talk about differential pricing and commercial expectations at this stage. Please bear with us. We will give an update on the potential in the first half of next year.

Frank Misselwitz - ***Bayer AG - Head of Therapeutic Area Cardiovascular and Coagulation, Global Clinical Development.***

Right, if I then can kick in alluding to the position in treat to surgery or not, and these type of questions. Basically, I think one thing has to be very clear; unlike other forms of pulmonary hypertension, the chronic thromboembolic form is the only group of PAH patients with a potential cure, and that is surgery. And we should really highlight that, and should really work together with surgeons in the long run making sure that all patients who are deemed to be operable will undergo the surgery as soon as possible, and as fast as possible.

But it's very clear -- and actually, in that context, we don't want to position the drug as a bridge prior to surgery because any potential delay would actually withhold a potentially curable surgery from the patient.

The point I made earlier, that patients who were previously graded as inoperable may improve upon treatment with riociguat and then became curable or surgically eligible, that is a relatively minor percentage of patients. That may be true, but it does not change the statement I made before.

But there are clearly patients who are inoperable because of distal disease, or recurrent disease, even after they have undergone a pulmonary endarterectomy. And those patients of course will benefit from treatment with riociguat. And that is not a niche; this is actually, I think, in clinical reality roughly half of the patients.

Matthew Weston - ***Credit Suisse - Analyst***

Thank you very much.

Operator

Mr. Wendorff.

Daniel Wendorff - ***Commerzbank - Analyst***

Daniel Wendorff, Commerzbank. Thanks for taking my questions. Two are remaining, if I may. One refers to the potential use of riociguat in PAH. Could you already potentially comment on how you think you could differentiate the product versus the existing treatment landscape, i.e., is it more important to focus on safety profile, or on certain efficacy and parameters?

Second question would be in terms of positioning the drug in the two different indications amongst physicians. Is there a difference in between how you would have to market it in terms of doctor groups, or in terms of doctors centers/hospitals? That would be very helpful to get a bit more information there. Thank you very much.

Kemal Malik - ***Bayer Healthcare Pharmaceuticals - Head of Global Developments***

I think on the first one, from what we've said, we think we have a very competitive profile in PAH. Quite how this aggregates, if and when we get approval, obviously will remain to be seen.

But I think in terms of the data we have generated, I think it's very competitive, both in terms of the primary endpoint, which is six-minute walk distance, but also the strong secondary endpoints that were alluded to earlier in time to clinical worsening, etc. I think the ultimate positioning, I think we're going to have to wait to comment on, to be honest.

Frank, can you make some comments on the second question?

Frank Misselwitz - ***Bayer AG - Head of Therapeutic Area Cardiovascular and Coagulation, Global Clinical Development.***

Well, with regard to the positioning and the two indications, whether we believe that there are different target audiences, etc., first of all, it should be very clear that now, for the first time, a drug has shown the ability to improve exercise capability, but also functional class, and even time to clinical worsening in two different distinct groups of PH patients; and, in particular, in CTEPH patients, where actually no medical therapy so far has been shown to be successful, and there is no approval.

Does it lead to a different positioning or approach in terms of addressing this with our target audiences? In the bigger scheme of things, no.

But importantly, as I said earlier, in the CTEPH part it will also, importantly, depend on the way how we interact with the surgeons. Because we actually want to do that in a very close co-operation, showing that patients should be operated as soon as possible, and if deemed inoperable then of course be treated with riociguat. But I don't think that there will be basically a large difference in the approach to those two different indications.

Daniel Wendorff - ***Commerzbank - Analyst***

Okay, thank you very much.

Operator

Mr. Cespedes.

Florent Cespedes - ***Exane BNP Paribas - Analyst***

Florent Cespedes, Exane BNP Paribas. Thank you for taking my questions. Two quick ones. First, on PAH, could we have an idea on why we see that there is such a small difference on the primary endpoint on the naive and pretreated patients on the PAH trial?

And second question, on the CTEPH trial could we have any idea on why there is only a trend on some secondary endpoints in CTEPH, i.e., like time to clinical worsening? Could it be due to the fact that the product is more [potent] on the inoperable patients? Do we have an idea of the split of this population on this secondary endpoint? Thank you.

Kemal Malik - ***Bayer Healthcare Pharmaceuticals - Head of Global Developments***

Great thank you. I'd ask Frank to comment them. On your question on CTEPH, as Frank said on one of the earlier questions, these were secondary endpoints. The study wasn't powered for these. The fact that we see strong trends and the numbers all head in the right direction is very encouraging, but clearly this was a study that wasn't powered for these secondary endpoints.

Frank, if you want to add to that, but also talk about the differential in naive versus pretreatment in the first part of the question.

Frank Misselwitz - ***Bayer AG - Head of Therapeutic Area Cardiovascular and Coagulation, Global Clinical Development.***

Right. Well, let me start with the CTEPH question. So why are secondary endpoints where found to be non-significant in the overall study, and then which leads whether they would become significant, considering the non-operable group, where we have seen a larger benefit for the primary outcome.

I think basically the question is that we believe that it has to be done with great caution in terms of analyzing subgroups of subgroups of subgroups. And the overall trial was obviously also, relative to the PATENT trial, relatively small, which then automatically leads to, at best, very clear trends in secondary outcomes, but not necessarily having enough statistical power to prove that some change, which may be in reality existing, can be proven statistically significant.

So to answer your question in particular, we have not yet performed any analysis on the subgroup of treatment of -- sorry, non-operable patients for a variety of secondary endpoints. But, in general, we should temper expectations because these subgroups are getting relatively small.

So I think we have -- importantly, when you assess all the subgroup analysis by analysis for heterogeneity, we do not see positive interaction p-value indicating that any of the subgroups would fundamentally behave different. And, hence, we believe that overall the consistent finding from the main trial can be, and should be, translated into any of the subgroups, albeit the magnitude of the effect may slightly differ.

Coming now to the PAH trial, the question about naive versus pretreated patients, the difference between those two subgroups, with regards to the six-minute walk distance, was, indeed, small.

And we believe that this is mainly due to the fact that whether a patient was pretreated with an endothelial receptor antagonist or a prostacyclin analog, we are adding a completely new mode of action, which is important, and which shows that you can still, even in a patient who is already pretreated with any array, in most of the cases you can still have a more or less as good effect on top of that as in the treatment naives.

I think it is, to sum up, a clear demonstration of an independent and complementary mode of action which we see here.

Florent Cespedes - ***Exane BNP Paribas - Analyst***

Okay. Thank you very much.

Operator

[Mrs. Esman].

Natasha Esman ***Analyst***

This is Natasha. Thank you for taking my question. I wanted to ask about PAH trial. You had several background therapies, could you give us some color on that; why these therapies exactly and not other therapies? Thank you.

Kemal Malik ***- Bayer Healthcare Pharmaceuticals - Head of Global Developments***

Frank, could I ask you to comment on the background therapies in PAH study?

Frank Misselwitz ***- Bayer AG - Head of Therapeutic Area Cardiovascular and Coagulation, Global Clinical Development.***

So, Natasha, just to understand the question right, I presume you meant to say the other PAH-specific therapies, like ERAs or prostacyclin analogs. Is this what you mean?

Natasha Esman ***Analyst***

Yes, exactly.

Frank Misselwitz ***- Bayer AG - Head of Therapeutic Area Cardiovascular and Coagulation, Global Clinical Development.***

Okay. So, yes, in fact we have allowed to include patients who are pretreated with an ERA or a non-IV prostanoid, which is actually mainly driven by the belief that we have a complementary mode of action in this case.

We have not considered patients who are pretreated with the PED5 inhibitor because of the fact that PED5 is working essentially on the same NO access. Although we believe that a dual mode of action of riociguat what we can add more here than a pure PED5 inhibitor, which, as we know, works insufficiently in the condition of NO deficiency. And we know that many of our patients with PAH have NO deficiency.

So, basically, to cut it short, ERAs and prostacyclin analogs were allowed. That captures a very large proportion of the patients, in reality. PED5s work exactly on the NO axis, but they may not work as good as riociguat in this particular setting as we have to assume that many of our patients have an NO deficiency, which would, at least theoretically, limit the ability of PED5 inhibitors to be active.

Natasha Esman ***Analyst***

Okay, thank you very much. And another question, if I may. In the second indication that you treated the CH --

Frank Misselwitz ***- Bayer AG - Head of Therapeutic Area Cardiovascular and Coagulation, Global Clinical Development.***

Chronic thromboembolic.

Natasha Esman ***Analyst***

Yes. Does this trial - is it enough for approval? Will you be doing any other pivotal trials? Could you give us some guidelines regarding the schedule of this?

Kemal Malik - ***Bayer Healthcare Pharmaceuticals - Head of Global Developments***

I'll take that one. Clearly, we're having the discussions with the regulatory authorities. From what I said earlier, we aim to file in both indications, PAH and CTPH, in the first half of next year. So we feel that the clinic program, as defined, is sufficient to proceed for approval in both indications.

And the further work, clearly we want to maximize the benefit of riociguat in different forms of pulmonary hypertension, and we'll update in the first half of next year on that.

But for the existing program and the existing indications, we feel that the program is sufficient for approval and we'll now enter the regulatory process.

Natasha Esman ***Analyst***

Okay, great. Thank you very much.

Operator

Mr. Leuchten.

Michael Leuchten - ***Barclays Capital - Analyst***

Thank you for taking my follow up. Two quick ones. Just because Frank just mentioned on the potential combination of PED5 and riociguat, do you have any data -- is there any data on your side that has looked at that, at least from a safety perspective?

And then a technical question. In terms of discontinuation in both trials, statistically, how were they treated for the six-minute walk distance? Was that an imputed value? Or was it last observation carried forward? And what do the regulators say to that, if it matters at all? Thank you.

Kemal Malik - ***Bayer Healthcare Pharmaceuticals - Head of Global Developments***

Frank, do you want to take that, and then I can chip in, if needs be?

Frank Misselwitz - ***Bayer AG - Head of Therapeutic Area Cardiovascular and Coagulation, Global Clinical Development.***

Yes, I can. So basically, to start with the discontinuation of patients and how this was handled in a statistical manner to calculate the primary endpoint, that has been pre-agreed with agencies.

So we had either the real value after 16 weeks of treatment in the CHEST trial, or 12 weeks in the PATENT trial. Or a patient, for whatever reason, had dropped out earlier, then this value was either the last observed carried forward or, say, for instance, if the patient died during the treatment course, then, of course, we imputed six-minute walk distance of zero.

And those imputed values at the end of the 16-week treatment duration, 12 weeks in PATENT and 16 in CHEST, was then used to be the primary endpoint.

Kemal, do you take the combi, or shall I do that as well?

Kemal Malik - ***Bayer Healthcare Pharmaceuticals - Head of Global Developments***

I can take the combi. I think it's fair to say we have limited data in combination with PED5 inhibitors. And so we'll obviously start the discussions with regulatory authorities, but the data set we have, in terms of combination with PED5 inhibitors, is very limited.

Michael Leuchten - ***Barclays Capital - Analyst***

Okay, thank you.

Operator

Excuse me, Mr. Rosar, there are no further questions at this time. Please continue with any other points you wish to raise.

Alexander Rosar - ***Bayer AG - Head of IR***

In this case, ladies and gentlemen, what remains to be said is thank you for being with us on the call. Thank you, my colleagues, for their contributions. And goodbye.

Operator

Ladies and gentlemen, this concludes the investor conference call of Bayer AG. Thank you for participating. You may now disconnect.