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BAYN.DE - Bayer AG Investor Conference Call on Finerenone Data at the ESC Congress 2015

EVENT DATE/TIME: AUGUST 31, 2015 / 12:00PM GMT

OVERVIEW:
Co. updated on findings from the ARTS-HF study evaluating finerenone vs. eplerenone in patients with worsening chronic heart failure with diabetes and/or chronic kidney disease.

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PRESENTATION

Operator

Ladies and gentlemen, thank you for standing by. Welcome to Bayer's investor and analyst conference call on finerenone. (Operator Instructions).

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

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

Welcome. Also on behalf of my colleagues to our call during which we want to review findings from the finerenone ARTS-HF Phase 2 study. Data there presented earlier in the hotline session at the ESC Congress in London.

With me on the call are Joerg Moeller, Head of Global Development at Bayer Healthcare, and Frank Misselwitz, Head of Global Clinical Development Cardiovascular.

Before I hand over to Joerg, I would also like to draw your attention to the forward-looking statements. (See "Disclaimer" chart at the end of this transcript).

Thank you. Joerg?

Joerg Moeller - ***Bayer AG - Head of Bayer HealthCare Global Development***

Thank you, Alexander. Ladies and gentlemen, I also would like to welcome you to our IR call.

Finerenone is a novel third-generation mineralocorticoid receptor antagonist or MR, that we develop in two indications, heart failure and diabetic kidney disease or DKD. The results of a dose findings study in DKD, the ARTS-DN study have been reported earlier this year. Now in ARTS-HF, we studied various doses of finerenone versus a eplerenone which is approved in standard of care to treat patients with heart failure and reduced ejection fraction.

I now would like to cover the key findings. In ARTS-HF, finerenone decreased levels of surrogate marker NT-proBNP to a similar extent as eplerenone and a mounting body of evidence exists in the literature demonstrating that intra-individual changes of this marker may be a predictor of clinical events. The observed incidence of the composite endpoints, all-cause death, cardiovascular hospitalization or the emergency presentation for worsening chronic heart failure was lower with finerenone doses

except for the 2.5 to 5 milligram arm then with eplerenone. All doses of eplerenone were well-tolerated and treatment-emergent at those events occurred with a similar incidents in the eplerenone group and the finerenone group.

Let me put these findings into clinical perspective. Finerenone and eplerenone are approved gamma rays that have shown to be able to reduce mortality and morbidity in patients suffering from heart failure with reduced ejection fraction. However, their side effect profile prevents many physicians from using these agents broadly in daily clinical practice. It is true that eplerenone has the active comparator in ARTS-HF because of its large and well described evidence base in this indication.

Further to this those two MRAs have substantial differences in terms of receptor selectivity and the effect on glucose and [cortisol] metabolism with a more favorable profile for eplerenone. Both Spironolactone and eplerenone are not approved for treating kidney diseases.

Frank Misselwitz will now review the details of the ARTS-HF study. Frank?

Frank Misselwitz - ***Bayer AG - Head of Global Clinical Development Cardiovascular***

Thank you, Joerg. So here we see the study objective of the design of the ARTS-HF study that both a randomized double-blind, double-dummy and multicenter study to assess safety and efficacy of different doses of Finerenone in patients with an emergency presentation at the hospital because of worsening chronic heart failure with left ventricle systolic dysfunction and concomitantly either type 2 diabetes mellitus with or without chronic kidney disease or chronic kidney disease alone. And the test was versus the active competitor drug eplerenone.

Overall, treatment duration was planned for 90 days. Initially patients were randomized 1 to 1 to 1 in the week following the emergency to hospital to receive finerenone once daily at a dose of 2.5 milligrams or 5 milligrams or finerenone every second day at a dose of 25 milligrams.

Once approximately 300 patients were randomized, the safety and tolerability for example, the incidence of hyperkalemia and adverse events related to worsening renal function of the initial doses were assessed by an independent Data & Safety Monitoring Board. Based on the safety and tolerability assessments, the DSMB decided that additional preplanned treatment arms could be introduced, finerenone 7.5 milligrams, then up titrated to 15 milligrams; finerenone 10 milligrams, up titrated for 20 milligrams; and lastly Finerenone 15 milligrams, up titrated to the same dose of 20 milligrams.

Let me now go through the planned study endpoint. The primary efficacy endpoint for the responder analysis with a change in the surrogate marker of efficacy NT-proBNP of more than 30% from baseline to day 90. In order to further support the potential effects from the surrogate parameter, clinical events were also included as secondary endpoints considering that clinical events may be expected in those high risk populations even in the relatively short timeframe of 90 days.

Please bear in mind that ARTS-HF was a Phase 2 dose finding trial and therefore it is clearly not powered as an outcome trial for these clinical events.

Let me now review the baseline demographics. Over 1000 patients were randomized into the study. Notably 74% of the patients in all finerenone arm combined completed the study versus 64% of those receiving the approved comparator drug, eplerenone. As you can see here, the baseline demographic risk factors are well distributed amongst the various groups and clearly indicate a high risk population.

The next slide we see the mean potassium concentration and the estimated glomerular filtration rate that were also similar between the groups at baseline.

Let me now come to the results as the safety results, treatment emergent adverse events. All doses of finerenone had a similar safety profile to eplerenone and are well-tolerated. Incidence of treatment emergent adverse events are similar between the eplerenone group and oral finerenone dose group. As hyperkalemia is seen as a specific problem for spironolactone and eplerenone at their approved dosages, we wanted to look next specifically on changes in the serum potassium concentration. The mean change from baseline to day 90 in serum potassium concentration was greater in the eplerenone group, an increase of 0.262 millimoles per liter, than each of the finerenone dose groups where we have seen a dose dependency with significantly lower levels compared to eplerenone observed in the lower doses.

Although it is clearly too early to draw a definitive conclusion from the findings, we think it is encouraging and clearly warrants further investigation in a Phase 3.

Let me now come to patients with hyperkalemia and an EGFR decrease of greater than 40%. Hyperkalemia is defined as serum potassium concentration of more or equal of 5.6 millimoles per liter at any time post baseline was observed in 44 patients with an approximately similar distribution amongst the finerenone dose groups and the eplerenone group.

The same holds true for the observed reductions of the estimated glomerular filtration rate of greater than 40%.

Let me now come to the primary endpoint results. As said earlier, we performed a responder analysis for the biomarker of cardiac decongestion NT-proBNP. Patients responded equally well to finerenone and to eplerenone. The proportion of patients who had an NT-proBNP decrease of more than 30% at day 90 compared with baseline was similar in the finerenone groups and the eplerenone group.

Our analysis focused both on the data of all individual finerenone doses as well as on the dose trend across the different finerenone doses. The finerenone doses did not show a large decline of surrogate marker NT-proBNP than the active competitor. While the primary endpoint, mainly the change of NT-proBNP was not significantly different between the comparator drug and finerenone, the reduction in mortality and admissions by finerenone and comparative to eplerenone if confirmed and further adequately powered large-scale prospective randomized studies, could have important public health and health cost implication.

Let me now display the clinical composite endpoints. We were somewhat positively surprised by the magnitude of the reduction of cardiovascular events in this study, specifically mortality in the finerenone 10 to 20 milligram group which appears to be the optimal dose. We observed a strong trend to less events with higher doses for the secondary clinical outcome.

The incidence of the composite endpoint for all-cause death, cardiovascular hospitalization or emergency presentation for worsening chronic heart failure at day 90 was lower in all finerenone groups compared with the eplerenone group except for the lowest dose of finerenone 2.5 to 5 milligrams group.

The Kaplan Meier curves for all groups are shown on this slide. On the next slide, we see the effect on all-cause cardiovascular hospitalization broken into subgroups consistent with the effect from the composite endpoints with a hazard ratio of 0.56 and a confidence interval not crossing unity, similar findings for the 10 to 20 milligram finerenone dose group versus eplerenone were observed for the individual components.

On the left-hand side you see the cumulative probability for all-cause debts for eplerenone, pooled finerenone, and the finerenone 10 to 20 milligram dose group. The two incidents (inaudible) for the full finerenone group, the black line, as well as the 10 to 20 milligram finerenone dose group, that is at the red line, separated strongly.

On the right hand of that slide we illustrate all cardiovascular hospitalizations for the same groups. For cardiovascular hospitalizations we see a nominal improvement for the comparator with the indicated hazard ratios.

Let me now turn to patient reported outcomes on quality of life, another very important outcome that we investigated in our ARTS-HF trial.

The topline is that patients reported outcome results mirror the efficacy results versus strong results for the 7.5 to 15 milligrams and the 10 to 20 milligram dose groups of finerenone. The results of the KCCQ and the EQ-5D-3L questionnaire supported those for hospitalization and mortality with the greatest patient reported improvements observed in the finerenone 7.5 to 15 milligrams once a day and 10 to 20 milligrams once a day group.

In the KCCQ, the mean improvement in total symptom score from baseline to visit 9 in the full analysis that was numerically larger in the finerenone 7.5 to 15, namely 29.3 than in the 10 to 20 milligram dose groups namely 28.3 compared with eplerenone reaching a score of 24.3 resulting in a clinically meaningful treatment difference finerenone versus eplerenone of 5 and 4 points respectively.

The treatment differences seen for the KCCQ symptom score are reflected in the KCCQ clinical summary score with a treatment difference of 3.4 and 3.0 score points in the 7.5 to 15 and 10 to 20 milligrams once a day group respectively. There seems to be a stronger effect versus eplerenone in the KCCQ clinical summary score than seen in recent heart failure trials in a stable heart failure population. LCZ696 showed an improvement of 0.95 points at eight months and Ivabradine had a 1.8 point improvement at 12 months.

Ladies and gentlemen, I would like to summarize now the results from the ARTS-HF Phase 2 study. In patients hospitalized for worsening chronic heart failure with reduced ejection fraction with type 2 diabetes mellitus and/or chronic kidney disease, finerenone decreased the biomarker of congestion I should say NT-proBNP to a similar extent as did eplerenone from baseline to day 90. The observed incidence of the composite endpoints that are a composite of all-cause deaths, cardiovascular hospitalization or emergency presentation for worsening chronic heart failure at day 90 was lower with all finerenone doses except at the very lowest 2.5 to 5 milligram dose arm than compared to eplerenone, with the lowest incident observed in the finerenone 10 to 20 milligram dose group.

All doses of finerenone were well tolerated with a similar incidence of treatment emergent adverse events in the eplerenone group and finerenone dose groups. Hyperkalemia was observed with balanced distribution across the finerenone groups and eplerenone groups, with a mean change from baseline to day 90 in serum potassium concentration was nominally greater than in the eplerenone group than in each of the finerenone dose groups respectively.

With that I would now like to hand over to Joerg again.

Joerg Moeller - ***Bayer AG - Head of Bayer HealthCare Global Development***

Thank you, Frank. Ladies and gentlemen, I would now like to cover our plans for Phase 3 where we plan to conduct three events driven outcome trials.

Finerenone demonstrated meaningful effects on clinical outcome parameters versus eplerenone in our heart failure ARTS-HF study and a significant reduction of albuminuria compared to standard of care in patients with a clinical diagnosis of diabetic kidney disease in our ARTS-DN trial. Therefore we would like to study the effects of finerenone further in three upcoming events driven outcome studies. We are right now in active discussions with health authorities and aim to enroll the first patients by the end of this year.

Now I would like to share some more details on the plan design starting with the Phase 3 FINESSE heart failure trial design. In the FINESSE heart failure trial, we plan to assess finerenone versus eplerenone in heart failure patients. The primary objective of the study is to test if finerenone is superior to eplerenone in delaying time to first occurrence of the composite endpoint defined as cardiovascular death or hospitalization for heart failure in patients with chronic heart failure according to the New York Heart Association Class II to IV and reduced ejection fraction. Patients will have additional risk factors such as type 2 mellitus and /r chronic kidney disease. So we intend to enroll a population of patients at a higher risk of cardiovascular morbidity and mortality.

It is planned to test finerenone versus eplerenone in several thousand patients and patients previously taking a mineralocorticoid receptor antagonist, in those patients the investigator will choose the starting dose as indicated on this slide. Patients unlikely to benefit from the study because they have unfavorable heart failure will be excluded from the study.

Now I want to switch to our plan in diabetic kidney disease. The initiation of two Phase 3 studies in diabetic kidney disease is based on the successful phase 2b ARTS-DN study which was presented earlier this year at the World Congress of Nephrology in March. The addition of finerenone to the standard of care treatment resulted in significant reduction of albuminuria without adversely affecting serum, potassium or kidney function.

We plan to conduct two placebo-controlled studies that focus on the unmet medical need in diabetic kidney disease. Individuals with DKD have a far greater likelihood of cardiovascular death than progression to end stage renal disease.

In the FIGARO-DKD study, we will primarily assess whether finerenone treatment may reduce cardiovascular events and in the FIDELIO-DKD trial we plan to study finerenone's potential to slow renal disease progression in patients. The primary endpoint here will be a composite of kidney failure, decrease in glomerular filtration rate and renal death. We will enroll patients with micro and macro albuminuria, also referred to as high and very high albuminuria in our trials and with this cover the full spectrum of patients with DKD. Both trials will be placebo-controlled on top of standard of care, ie RAS blockers as steroidal MRAs are not approved in this indication.

Based on today's database on two large Phase 2b studies and earlier studies we conducted, we target to position finerenone as the best in class in heart failure and first in class in diabetic kidney disease.

With that I would like to finish my remarks and we are now happy to answer your questions.

QUESTION AND ANSWER

Operator

(Operator Instructions). Richard Vosser.

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

It is Richard Vosser from JPMorgan. A few questions please. At the presentation of the ARTS data today, the discussant was postulating whether 1.1% reduction in hyperkalemia was enough to warrant substantial treatment uptake eventually? Could you just give us an idea of your discussions with key opinion leaders on that point please?

Second question, just on the mortality benefits or the hint of mortality benefits that we have seen, if you could give your perspective on the fact that we are seeing a mortality benefit without any benefits on blood pressure or NT-proBNP versus eplerenone or spironolactone, just what do you think is driving that mortality benefit, your confidence on being able to reproduce that in Phase 3?

And just a perspective again, the discussant pointed out that there was no dose response in the benefit and I think the higher doses had a lower benefit over eplerenone on the mortality endpoint that were looked at.

And then just one quick question on the decision around using an ACE as the background treatment in Phase 3 FINESSE heart failure trial rather than Entresto. I can understand that the gold standard at the moment is ACE but potentially when this trial finishes, Entresto could be very well-established so how do you think that is going to affect both enrollment and the results at the end of the trial? Thanks very much.

Joerg Moeller - ***Bayer AG - Head of Bayer HealthCare Global Development***

Thank you, Richard. I want to give the days start and then hand over to Frank. So I think as we all know, the challenge in Phase 2 in heart failure is typically the trial is underpowered to indicate direction of what it needs to show in Phase 3, namely mortality and morbidity. So that is the reason why in addition to NT-proBNP we selected quite a number of additional secondary exploratory endpoints. And I have to say when I saw the results for the first time what really struck me was the consistency of the results that we saw in the data. Literally all parameters showing into very consistent direction of benefit of finerenone. I think that as encouraging as it can be given the limitations one typically has in designing Phase 2 studies in heart failure.

I would now like to hand over to Frank to cover some of the more specific details of your question.

Frank Misselwitz - ***Bayer AG - Head of Global Clinical Development Cardiovascular***

Hello, Richard. Let me first come quickly to (inaudible) the discussions today, his comments on the effect on hyperkalemia relative to finerenone. The point here is that it was not only about the hyperkalemia effect plus we know that it is not just in clinical practice eplerenone that is in use but also spironolactone and in our Phase 2a trial, we had studied directly the comparison versus spiro and found a very profound difference here on hyperkalemia, again dose-dependently.

So the other additional point I would want to make is that the unwanted and to some extent limiting side effect of steroidal MRAs are not limited to hyperkalemia but also includes a decrease of kidney function measured by the EGFR and this parameter was clearly seen at the lower frequency with the finerenone 10 to 20 milligram target dose group compared to eplerenone.

So we believe that there is overall clearly a very good safety profile but in addition to that owing to the question what will basically drive the use of finerenone in the market besides the safety profile, is clearly all for the effect that of course we are going to test the drug for superiority versus eplerenone. So we seek to demonstrate in a confirmatory way a superior outcome on the past clinical outcomes in the Phase 3 and this will come along with a balanced and well tolerated safety profile.

Let me also comment on the mortality benefits that you asked what drives it, because it has no effects on blood pressure and as you said, no effect on NT-proBNP. Let me correct that.

I mean it is a profound effect on lowering NT-proBNP but this profound effect wasn't in the dose finding trial larger compared to the very active comparator drug eplerenone. So we do see a profound effect when we would have compared say to placebo but it wasn't in that dose finding trial different to the active comparator drug.

How do we believe we can reproduce the binding in the Phase 3 trial? We believe that there are of course effects and we know from mineralocorticoid receptor antagonists that there are effects that are much longer lasting than the immediate effect after the acute decomposition and there are longer-term antifibrotic effects that you can see. There are longer-term effects in terms of providing a better safety profile compared to the existing steroidal drugs and this will drive what we believe in the long run is even better outcome on hard clinical outcomes compared to the comparator drug.

Now to your last question about the standard of care and baseline treatment in our upcoming Phase 3 trial whether or not we would also include Entresto here, it is very clear. We furthermore reiterate that and I know you have not asked for that, but we are not testing versus Entresto. Entresto will now gradually substitute for the ACE in heart so it will become an important part of the standard of care and we test our drug on top of standard of care. So clearly not a testing versus

and I understand that you have not asked for that but we will of course design the trial in a way that we have a sizable and informative subgroup of patients also tested on top of Entresto so that we will document safety and efficacy of that subgroup.

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

Brilliant. Thanks very much.

Operator

Peter Verdult.

Peter Verdult - ***Citigroup - Analyst***

It is Peter Verdult here from Citi. Just a couple of follow ons. Very keen just to push a bit more in terms of how the discussant was reviewing the data. You are taking what looks like the most efficacious dose into Phase 3 but he seems to suggest that the major driver for supporting Phase 3 would be showing a significant difference inhyperkalemia. So I am wondering how you sort of balance or square that circle in terms of the data that we have seen in Phase 2?

Perhaps maybe just going on to the trial design FINESSE or any subsequent analysis that you have done on ARTS-HF, if you just look at the diabetic patients that were enrolled in ARTS-HF, was there any difference in the primary or composite endpoints versus the overall study?

Also in terms of the Phase 3 FINESSE program, I think prior Phase 3 studies recruited about one-third of their patients that had diabetes. I'm wondering can you give us a sense of how concentrated the diabetic population would be in FINESSE?

And I'm just trying to clarify one thing regarding your comments around Entresto, I believe at a recent meet the management data I have been at, you have very much said that you would go against standard of care. So I just want to understand a bit better why or just clarify if a patient is on Entresto, will they be excluded from enrolling in the FINESSE study? Thanks.

Joerg Moeller - ***Bayer AG - Head of Bayer HealthCare Global Development***

Maybe let me start with your question regarding standard of care and what will be in and will be allowed. So basically the plan is to test in FINESSE heart failure on top of standard of care which as we know in heart failure typically consists of ACE inhibitor and ARB, a beta blocker maybe a diuretic and an MRA. And so in this case, finerenone would be tested on top of agents of this class with the exception of [on top an] MRA antagonist. And if during the conduct of FINESSE heart failure, Entresto will be used and we can expect it to be used and will become standard of care then of course finerenone would be also tested on top of LCZ696 meaning we are open to that development and if you remember how LCZ was developed, they compared against enalapril. So the competitive pressure of LCZ can be expected to push against ACE inhibitors and ARBs, but of course we would include Entresto now, and Entresto to be included during the conduct of FINESSE in heart failure if the treating physician considers this to be standard of care.

Peter Verdult - ***Citigroup - Analyst***

Thanks, so consistent with before? Thank you.

Joerg Moeller - ***Bayer AG - Head of Bayer HealthCare Global Development***

Frank, do want to cover the data on diabetic patients and how much enrichment we expect and see?

Frank Misselwitz - *Bayer AG - Head of Global Clinical Development Cardiovascular*

Certainly I will cover that. There are two points of your question, this was the enrichment of the patient population in terms of diabetes mellitus and the difference of hyperkalemia in the target dose of finerenone relative to eplerenone.

So let me first come to the diabetic mellitus and the other enrichment with chronic kidney disease. We expect just to put in a very general way, to see approximately the same kind of breakdown in terms of these concomitant diseases in the Phase 3 as currently studied in our Phase 2b trial and we have had approximately 20 -- 18% of patients with only diabetes mellitus but then of course there is a large group of another 26% of patients who had concomitantly the -- sorry, yes, I mean talking about diabetes mellitus with or without chronic kidney disease, we approximately have 60% in our population. We have approximately 70%, 73% of patients who have chronic kidney disease and of course we haven't talked about that specifically from 60%, 65% of patients with underlying ischemic heart disease. So it is a really high risk group of frequent comorbid conditions and this is basically also the breakdown we believe to have for the Phase 3.

And then the other question was about the difference of hyperkalemia relative to eplerenone and you pointed to the fact that yes, of course, this effect in the small dose finding trial was significantly different for the three lowest doses of finerenone but for the target dose of 10 to 20 milligrams which we are going to study further in the Phase 3, this difference was numerically there but it wasn't significant. But that was no surprise because of the small sample size and this will further increase by extending the trial duration because you have to keep in mind that the 90 day trial is relatively short for hyperkalemia events to occur and the longer you run the trial the more these curves will start to separate.

Operator

Matthew Weston.

Matthew Weston - *Credit Suisse - Analyst*

Thank you. It is Matthew Weston from Credit Suisse. Two questions please. The first on the Phase 3 FINESSE trial. So you have absolutely clarified that Entresto is allowed and I think you suggested you used the phrase a significant subgroup of patients would be expected to be on Entresto. The thing that surprises me is the size of the FINESSE study. So if you are only recruiting 4700 patients and only a subset of them may be on what is going to likely be standard of care at the time the trial reports out, isn't there a real risk that you don't have valid survival outcomes of finerenone in combination with Entresto? And can you just confirm whether or not that will be one of the requirements for stopping the trial, the statistical significance in the Entresto subgroup?

And then secondly, I guess a much bigger picture question, one thing that has always surprised me about the MRA market is that despite the superior safety of INSPRA, it only ever took a minute fraction of the market share relative to spironolactone. So how confident are you and particularly what gives you that confidence that the small benefits of finerenone over eplerenone will give you significant market share in this marketplace?

Joerg Moeller - *Bayer AG - Head of Bayer HealthCare Global Development*

Thank you. Maybe let me start with your second question and I will ask Frank to answer the first one.

I think it is important to keep in mind that in Phase 2a, we also collected data against spironolactone in DKD but also based on market research that we did, it appears especially in the West cardiologists have a preference for eplerenone which as we also alluded to in terms of the clinical evidence, there is just a stronger set of data compared to spironolactone which only was studied in an outcome study, the RALES trial that (inaudible) ran.

So clearly the evidence base for eplerenone is much stronger, that is probably also the reason why we see based on our discussions with cardiologists in the US in particular a stronger preference for eplerenone. And of course that is the reason why on the basis of having conducted trials in Phase 2 against both we selected eplerenone as the Phase 3 comparator here.

Frank, do want to cover the first question?

Frank Misselwitz - *Bayer AG - Head of Global Clinical Development Cardiovascular*

Yes, I have one addition to that very question before I then come to the other question. What you also have to understand is not just the relative use of eplerenone versus spironolactone, but also the enormous underutilization of MRAs overall. We know according to the use and that is true for the US in particular but also for other countries that only approximately one-third of patients of the eligible patients who should according to treatment guidelines you see in MRA actually do receive an MRA.

So what is going to happen with the safe and efficacious drug coming into that market that is basically then potentially the best in class drug of that MRA class is, that we first will see a much broader use so we are not necessarily cannibalizing on either spiro or eplerenone but we basically have the potential to increase the overall use. It is basically not so different from the market dynamics that you would currently observe with the while novel oral anticoagulant relative to warfarin. While the warfarin use is pretty stable in many countries what is happening is quite a substantial enlargement of the markets end use of anticoagulants. So we believe approximately the same is going to happen here.

Now let me turn to the other question you ask. Clearly Entresto will be allowed as the standard of care. The 4,700 patients will what we believe will clearly be large enough to recruit a substantial subgroup also of patients on top of Entresto. Of course a sample size calculation has not been done based on the subgroup analysis. This is not the way it has been done and we are not going to stop the trial for a potential survival benefit on top of Entresto. So that is clearly only a secondary analysis.

The point here is regardless of what we want to do, we only now see in the US starting an uptake of Entresto and many other countries still have a later approval and with the trial starting relatively soon, we of course are bound to the availability of Entresto in the market and whatever the ramp up in terms of some day to day use in clinical practice. So again in order to have a sizable subgroup, the typical guidelines from EMEA and FDA in terms of subgroup analysis would apply and I think the aim here is not to show a separate confirmatory value on top of Entresto but the consistency of that subgroup finding with the overall trial data.

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

Thank you. Is it possible to just have two quick follow-ups? The first around the existing MRAs and your comments about your desired profile for finerenone, I think at the moment the ACC guidelines only recommend eplerenone for those patients who have gynecomastia or impotence on spironolactone. Can you just confirm that your aim is that you would have a guideline position which would make you first in class of the MRAs?

Secondly, could you just give us an idea when with your statistical analysis you see the FINESSE trial reading out?

Joerg Moeller - ***Bayer AG - Head of Bayer HealthCare Global Development***

Let me start with the positioning question. Clearly our goal is to position finerenone as the first in class MRA antagonist in diabetic kidney disease because none of the other agents have been approved there for mainly reasons of their side effect profile. And our goal in heart failure is to position finerenone as a third-generation mineralocorticoid receptor antagonist as a best in class agent. And Frank has alluded to the fact that although spironolactone and eplerenone are drugs that have shown mortality benefits, they are relatively underused and the reason for their under usage is conference of treating physicians regarding their side effect profile. Hyperkalemia, as you mentioned (inaudible), our goal is with the third-generation mineralocorticoid receptor antagonist and higher selectivity and to the receptor to come up with a compound that overcomes these limitations and especially also with this type of side effect profile and hence we can expect if we show that in Phase 3 also a significant uptake of this agent compared to what we see right now in the usage of spironolactone and finerenone in the heart failure compilation.

For the readout question, this is an event driven study and you can see that we aimed for a highly enriched population of patients that has diabetes and or kidney disease but obviously we will run the study until we have reached the acquired amount of events according to the statistic analysis.

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

Okay, but we have no idea when that date -- when your plan points that date to?

Joerg Moeller

We have an idea that we haven't communicated yet.

Matthew Weston - *Credit Suisse - Analyst*

Okay, perfect. Many, many thanks indeed.

Operator

Mr. Gal.

Ronny Gal - *Bernstein - Analyst*

Good morning, good afternoon. This is Ronny Gal from Sanford Bernstein. Two questions, the first one regarding the quality of life data. We are seeing at least from your exhibits a fairly modest improvement in quality of life if you consider statistical analysis and there by your showing. You have stated that you believe this impact is significant or important. Can you give us a bit more color on this?

We also noticed that you have not presented here data showing the difference in the avoidance of the steroidal side effect that are common with eplerenone. Can you discuss what you have seen in terms of avoidance of those effects and will this be something to potentially show statistical significance on in your Phase 3 program?

Separately back to the question of survival, can you describe to us the mechanism, the hypothetical mechanism by which you believe finerenone actually has a survival benefit over eplerenone? It is just not clear from the data why that would be the case?

Frank Misselwitz - *Bayer AG - Head of Global Clinical Development Cardiovascular*

Let me first answer the quality of life question. You pointed out to the effect here that wasn't significant. Well again, the purpose of the dose finding trial for a secondary parameter was of course not to test things whether they are significant or not and neither was the trial powered for that. However, the observed differences in the important scoring scales of the KCCQ namely the total symptom score and also the more clinical summary score part were quite impressive.

Just to remind you that recently reported effects here for Entresto were 0.95 points of that scoring scale at eight months and Ivabradine had 1.8 points improvement and that compares here to 5 to 4 points in the two very effective dose arms of finerenone for the total symptoms and approximately 3 to 4 for the clinical summary score. So that is to say that the observed improvement and quality of life was substantial. It compared favorably and I will not say by no means in a significant way because the trial was not empowered for that, but it compares favorably even to very effective drugs just recently investigated and also tested for the same KCCQ score.

So we believe it is relevant and we know that there is general literature out there saying that as soon as you derive a difference of approximately 3 to 4 points this is really for the patient clinically meaningful. This is really enhancing activities of daily life, quality of life in general. So I think it is not -- although not significant on a nominal base, but again the trial was powered for that and we believe it is still a very important outcome shown here.

Joerg Moeller - *Bayer AG - Head of Bayer HealthCare Global Development*

Frank, do you want to cover steroidal side effects, the power structural changes?

Frank Misselwitz - *Bayer AG - Head of Global Clinical Development Cardiovascular*

Indeed. I mean the point here is just to remind us finerenone is a nonsteroidal MRA and that has a very high affinity and potency to work the receptor but importantly it has also a much higher selectivity and it does not address other receptor types that would become influenced by the steroidal MRAs. And we have seen zero incidents or (inaudible) or other steroidal related side effects in our dose finding trial. But again, this trial is not large enough to basically have final conclusions on this.

The other question you raised was how do we hypothesize a mortality benefit driven by MRA. First of all just to come back to the RADES study with spiro, here versus placebo, there was a very profound mortality benefit shown and we believe that the drug that is more potent and will be used consistently longer with a better adherence that we can even further enhance the mortality benefit.

Ronny Gal - ***Bernstein - Analyst***

Thank you very much.

Operator

Tim Race.

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

Tim Race from Deutsche Bank. So just a couple of questions. First of all just on hyperkalemia, can you just talk about what the current monitoring requirements are for patients on an MRA whether you expect based on the profile you are hoping for you would get any differences in terms of (inaudible) label? I presume not given that you do still (inaudible)?

Second, just on market size, could you just explain what you see as the number of patients with diabetes or chronic kidney disease with heart failure and also how big you think the relative population is for diabetic kidney disease relative to heart failure? Thank you.

Joerg Moeller - ***Bayer AG - Head of Bayer HealthCare Global Development***

Thank you, Tim. Frank, do want to give it a shot?

Frank Misselwitz - ***Bayer AG - Head of Global Clinical Development Cardiovascular***

I mean Tim, first to your question about the hyperkalemia and how often do we measure and what do we believe is the important differentiator here relative to standard of care or to steroidal MRA. The point here is that of course for the sake of the clinical trial, we had regular measurements, they are required also we believe in clinical practice for the DKD part so for the renal protective part but they are not deemed to be necessary on a regular basis in the heart failure population.

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

Okay, thank you.

Frank Misselwitz - ***Bayer AG - Head of Global Clinical Development Cardiovascular***

I think it is important, Tim, again as we discussed earlier that we see a relative under usage of [existing] agents and we see a significant potential if we come up with an agent that overcomes the limitations that physicians see namely the side effect profile and so we believe based on what we showed in two well-sized phase II B studies and in this A study, we have a profile that promises that we are able to hit the sweet spot there.

Operator

Maria Miemietz.

Maria Miemietz - ***Primeavenue - Analyst***

Maria Miemietz from Primeavenue. A quick follow-up question on the primary efficacy analysis from ARTS this morning. So if I understood the discussion correctly, the reason we did not see ITT data was because a substantial number of patients were lost to follow-up.

So I was just wondering if you can elaborate what proportion of patients did not have NT-proBNP data at 90 days and what the reasons were and how that may actually have affected the analysis?

Second question, I appreciate it is a bit early to discuss price but there was some commentary during the meet management that eplerenone would be a better benchmark than spironolactone. Do you think that the Entresto price can now also be considered a really good benchmark or do you just think that MRAs are just going to be constrained by the pricing of all the MRAs?

And then I was wondering since we are in heart failure, could I actually sneak in a question about the COMMANDER trial or is that the wrong forum here?

Joerg Moeller - ***Bayer AG - Head of Bayer HealthCare Global Development***

I think COMMANDER I would direct you to either our next meet management or specific questions with Xarelto. But today we want to specifically talk about finerenone and the data we presented earlier today.

Frank, do you want to comment on ITT and clarify A, the consistency of the results but also the situation of lost to follow up?

Frank Misselwitz - ***Bayer AG - Head of Global Clinical Development Cardiovascular***

The point here is that of course the primary endpoint in a Phase 3 trial is always measured in the ITT population and as randomized and that is very clear for Phase 3. In phase 2 of course particularly when the endpoint is a biomarker, you can only determine that endpoint in the population where the biomarker was measured. That does not mean that a patient in which you don't have a continuum of NT-proBNP measurements over time that these patients are dropouts or lost to follow-up, they aren't. We have a very low number of lost to follow-ups, etc.

But of course they would not be in the pre-specified analysis for (inaudible) protocol type of analysis of those in which we have all of the NT-proBNP measurements. We of course did and that may be the morning presentation today of the plenary was a bit misunderstanding or not that well expressed. We of course did all the respective sensitivity analysis with regards to the as randomized ITT population and we basically were able to show exactly the same outcome or the primary endpoint with no difference to the reported population of the patients of which we had all the measurements.

Just to be precise, the overall number of lost to follow-up in the trial was only eight patients.

Joerg Moeller - ***Bayer AG - Head of Bayer HealthCare Global Development***

Thank you, Frank. Maybe final comment on price, we obviously not commenting or theoreticizing on price right now other than to say that we believe based on what we mentioned before and based on the profile we see that finerenone is an attractive opportunity aiming a very high medical need condition and that is clearly what is getting us excited. We believe we can really have something that improves the situation and disease condition of patients with diabetic kidney disease and heart [failure].

Maria Miemietz - ***Primeavenue - Analyst***

Thank you very much.

Operator

Sachin Jain

Sachin Jain - ***BofA Merrill Lynch - Analyst***

It is Sachin Jain from Bank of America. Just a couple of wrap up questions please. Firstly, just to check could you just confirm the number of all-cause death and CV hospitalization events that actually were in the study at 90 days? I might have missed that.

Secondly, on the NT-proBNP endpoint your primary endpoint was the percentage of patients with a 30% reduction and the difference therein. Have you actually looked to the absolute difference in pro-BNP reduction between the two arms? Finally, obviously the study is powered for the efficacy endpoint. Can you just confirm that you are expecting to be powered for a difference in hyperkalemia in the Phase 3 study? Thank you.

Joerg Moeller - ***Bayer AG - Head of Bayer HealthCare Global Development***

Thank you. Let me pull up the number of deaths and hospitalizations in the trial just to give you exactly the precise number here and what we can see here is the following.

We have a total number of deaths in the eplerenone group of 15 clinically. And we see in the different doses of finerenone in the lowest dose 15, and seven in the middle and in the higher dose of 10 to 20 we see two of those events happening. So this is just to give an impression. And on day 90 that of course is substantially the more relevant number because it is while on treatment we see in the eplerenone group 9, and then in the middle groups of 5 or 7.5 to 10 or 15, we see four in each and in the 10 to 20, we see a target dose of one case.

Frank Misselwitz - ***Bayer AG - Head of Global Clinical Development Cardiovascular***

But just to repeat the number. Day 90 for while on treatment: eplerenone 9, and in the dose that we want to take forward into Phase 3, the 10 to 20, we had one and if you include the treatment follow-up period, then we had 15 in eplerenone as compared to two in the dose that we want to take forward in Phase 3.

And perhaps the cardiovascular hospitalization, to also give the exact number because we need to pull them up, so again, just to show what specifically the numbers are here at day 90 again the primary endpoints here also the cutoff, we have on eplerenone 58 CV hospitalizations and in the target dose of 10 to 20 we have 22. So 58 versus 22 and then of course intermediate numbers in the other dose which also show kind of the dose strength.

Joerg Moeller - ***Bayer AG - Head of Bayer HealthCare Global Development***

I think the other question was on absolute reduction of NT-proBNP.

Frank Misselwitz - ***Bayer AG - Head of Global Clinical Development Cardiovascular***

Yes, the absolute reduction is, I mean the point with NT-proBNP is a bit difficult and I will explain in the results methodologically why it is. First of all the numbers vary widely. This is a biomarker with quite a large variability from patient to patient and hence we have run the pro forma analysis rather than the analysis on mean value. What you ultimately ought to do because you have very, very high outliers to both the higher-end you often tend to use even logarithmarized NT-proBNP value to be more precise and that is basically then the reason the method to basically reduce the variability.

What I can say and maybe this is more informative for you is the ratio, so what is the ratio to baseline for the last on-treatment measurement of NT-proBNP and that was in the eplerenone 0.755, in other words the mean reduction was approximately 25%. And that was in the target dose of 10 to 20 milligrams 0.735 so pretty similar as I said.

It is also clear that there is at average say 25 to roughly 25% reduction of NT-proBNP. You should also keep in mind that this is of course compounded by the other factors because patients for instance who have atrial fibrillation as an underlying disease, their NT-proBNP levels are much less reactive and the same holds true for PKD in this patient group, the baseline but also the treatment effect on that biomarker are also tending to those higher levels. Is this answering your questions, Sachin?

Sachin Jain - ***BofA Merrill Lynch - Analyst***

Yes, perfect. And then just one left on (inaudible) Phase 3?

Joerg Moeller

We aren't going to power for these differences or -- I mean we are not powering for that because we actually will retain in terms of confirmatory testing the power for important clinical outcome.

Sachin Jain - ***BofA Merrill Lynch - Analyst***

Sorry, just to confirm so you are not powered clinically significance for phase 3?

Joerg Moeller - ***Bayer AG - Head of Bayer HealthCare Global Development***

You actually typically do not do that. I mean first of all in clinical randomized well-controlled clinical trials where there is a very close surveillance of patients, you will actually see the levels of AEs and SAEs in general and hyperkalemia in particular that are lower than in clinical practice. So even if you were to do that it would not be necessarily reflective of clinical reality in data preclinical practice. But that aside, you typically also for approvability reasons would not power a trial for safety outcomes but rather efficacy outcomes.

Sachin Jain - ***BofA Merrill Lynch - Analyst***

Very good, thank you.

Operator

Emmanuel Papadakis

Unidentified Participant

It is Emmanuel Papadakis from MainFirst. Just a couple of quick follow-ups. Firstly, on the dose selection, you are obviously going for the 10 to 20 milligrams. If you look at the data on key efficacy and safety endpoints, it looks like the 7.5 to 15 is equally efficacious and that is markedly better on safety. So if you just give us a bit more color on the driver of your thinking as to why the 10 to 20 is the dose to take forward that would be extremely helpful.

The second one was just around the market. I mean I imagine it is a pretty significant portion of the market for capturing in terms of Phase 3 FINESSE design for your heart failure patients with diabetes and kidney disease. But if you could just give us your estimate as to what percentage of the total HF RS population that captures that phase 3 design will capture that will be very helpful.

And then the last one was just if you could clarify, disclose whether you have had any regulatory input particularly from the FDA side into those Phase 3 designs and indeed the selection that you have taken forward? Thank you very much.

Joerg Moeller - ***Bayer AG - Head of Bayer HealthCare Global Development***

So let me start with the regulatory process. We have been and are in active discussions with the main regulatory agencies and we also plan to agree with the FDA on a special protocol assessment here to make sure we have an agreement on the trial parameters with the FDA so that is where we stand. And like I said, we expect to conclude these discussions in the very near term future and expect to have the first patients enrolled by the end of this year.

Frank Misselwitz - ***Bayer AG - Head of Global Clinical Development Cardiovascular***

Yes, I covered the broad population targeted for our Phase 3 investigations as well as the dose selection. It is correct to say that of course we start to see good efficacy in the dose ranging trial with the dose of 7.5 to 15. But obviously very good data from the 10 to 20 and particularly with regard to the clinical outcomes there seems to be a dose trend to increase efficacy for the 10 to 20.

What is important to note is of course the overall risk-benefit balance here for the three doses not just to select a dose that is particularly safe for hyperkalemia but also a dose in the long run which will be able to show profound efficacy also on anti-fibrotic anti-remodeling effect. And we know from preclinical work that the anti-fibrotic, anti-remodeling effect have a tendency to kick in at higher doses rather than lower doses. So for many considerations we believe that the 10 to 20 dose is the right dose.

The other question is in terms of what is the desired labeled indication for the Phase 3 study in the Phase 3. We are going to address the broad heart failure population and we know that of course in clinical reality there is also an overlap with comorbid conditions and health authorities are perfectly willing to accept an enrichment strategy for clinical trials. So basically we believe that the to be approved indications will be a broad heart failure population.

Unidentified Participant

Thanks very much.

Operator

There are no further questions at this time. Please continue within any other points you wish to raise.

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

In this case, ladies and gentlemen, also on behalf of my colleagues, we would like to thank you for being with us on the call, for your questions and the interest you have demonstrated in our developments. With that we are now saying goodbye.

Operator

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