

# Exhibit A

# FINAL TRANSCRIPT

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## Event Transcript

**RHHBY - Roche Conference Call - Phase II CERA Data in Renal Patients**

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## RHHBY - Roche Conference Call - Phase II CERA Data in Renal Patients

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### PRESENTATION

**Operator**

Good afternoon. This is the (indiscernible) conference operator. Welcome and thank you for joining the Roche conference call on CERA Phase II Data in Renal Patients presented at ASM. As a reminder, all participants are in a listing only mode only mode and the conference is being recorded. After the presentation, there'll be an opportunity to ask questions. (OPERATOR INSTRUCTIONS).

At this time, I'd like to turn the conference over to Dr. Karl Mahler (ph), head of Investor Relations Hoffman-La Roche in Basel.

**Dr. Karl Mahler - Roche - Director of Investor Relations**

Good afternoon to all parties here in Europe and good morning to all parties in North America. On behalf of Roche, I would like to welcome you to our telephone conference call.

We're excited to discuss with you today the result of our Phase II study of Roche's new anemia drug CERA in diabetes patients with chronic anemia. The results seem to demonstrate that this new chemical entity is of a potency (sic) and sustained (indiscernible) activity with longer dosing intervals. As you are aware, this data was presented on Saturday at the American Society of Metrology conference in San Diego.

To go over the results of this study, I have a direct pleasure in introducing us to John Michalidis, who is the Business Director of the (indiscernible) CERA at Roche. John will briefly cover the anemia market opportunity in CERA.

Dr. Steven Fishbane, Director (indiscernible) services (indiscernible) the director in the division of (indiscernible) and Associate Chairman in the Department of Medicine at Winthrop's (ph) University hospital New York and Dr. Fishbane is actually joining us from his office in New York. Dr. Fishbane will explain that CERA preclinical and Phase I data.

Dr. Iain Macdougall is an ecologist (ph) and is a senior lecturer at the Renal Unit Kings College in London. Dr. Macdougall will discuss CERA's mechanism of action and will cover the CERA Phase II data. After the short presentations, we will follow with a Q&A session. Where we can address your questions to any of the members of the team.

Now, I would like to handover to John. John, please?

**John Michalidis - Roche - Business Director**

Good afternoon, everyone. Good morning, everyone.

You all have, I hope, the slide presentation, and I would like to take you not to the first slide after the agenda. I would just like to touch on very briefly the strategic rationale we have behind the development of CERA. Of course, we believe that CERA is an important competitor in the area of anemia management, not only in the USA, where we believe we have

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a strong patent situation; we have recently been given a patent in the U.S. We also believe it will be a strong competitor in Europe, particularly in light of the context of generics that will be entering the European market in the later half of this decade, as well as Japan, where CERA will be a strong competitor, not only against other epoetins but also against genericized Epogen.

If I can move to the next slide, CERA, as you may well know, now is an acronym that we have used standing for Continuous Erythropoiesis Receptor Activator. This is an innovative chemical entity that we have designed rationally that has been able to deliver not only a prolonged half-life but also other clinical benefits that we hope to pursue in Phase III. We have started to understand that the molecule is acting differently at the receptor sites, suggesting a unique mode of action. We believe this is a technological advance in Erythropoiesis stimulation and as I said, it's designed to deliver sustained correction of anemia in patients in both the renal segment and the oncology segment.

As I've already mentioned, a patent has been issued in the U.S.; it was issued in June of this year and we're very confident of developing this molecule for worldwide launch, including the US.

What I'd like to do now is move to the mechanism of action and handover to Dr. Macdougall, who'll take you through the first part of this presentation.

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### Iain Macdougall - Roche

Thanks, John. Good morning and Good afternoon to everybody on line at the moment.

If we can just move onto the next slide. First of all, just before discussing the mechanism of action, I think we would like to look at the difference in the structure of the two molecules. On the right is the slide -- you can see the computer-generated model for EPO. The dark blue area is the protein (indiscernible) molecule the lighter blue (indiscernible) carbohydrate chains that are touch to the molecule. On the left there, you see CERA, which is a much, much larger molecule with a huge big polymer chain to the left-hand side but yet retaining the receptor-binding component of the molecule obviously in order to stimulate (indiscernible), so that's compared to the molecule.

Now, if you move onto the mechanism of action, I don't know if this is going to work; this is where technology might have outstripped the opportunity to do a sort of worldwide (inaudible)

conference call. Those of you that are watching this online will be able to see the animation. Those of you that have downloaded a hard copy will actually miss out on this, unfortunately, but that is EPO stimulating a (indiscernible) in the sector, as we've known for the last ten years or so.

If we compare this to CERA, CERA does indeed also stimulate the (indiscernible). You can see here that three molecules of CERA attaching to -- (technical difficulty) -- (indiscernible) stimulating (indiscernible) but because of the lower affinity this CERA molecule can (indiscernible) a sector and then may have the opportunity to find two subsequent points in the receptor, so you get a more continues stimulation of erythropoiesis that is believed to account for its unique mechanism of action.

So, if you move on now to what is actually making CERA different, the preclinical and Phase I programs have been complete. It suggests that perhaps CERA has unique mechanism of action at the receptor site; it has a very long half-life (indiscernible) intravenously and subcutaneously. It has increased bioavailability compared to both epoetin and epoetins alfa and seems to be a more potent and prolonged stimulate (indiscernible) erythropoiesis.

Moving on now to the slide shows the Phase II renal data, starting with (indiscernible), the Phase II data supports the hypothesis that CERA has a longer half-life, allowing expanded dosing intervals. There have been no safety concerns -- (technical difficulty) -- program to date. There's good hemoglobin control within the target range that (indiscernible) look for, which is somewhere in the region of between 11 and 12.5 g per dl. There's been a few dose adjustments required. It's always (indiscernible) to make some dose adjustments because of the (indiscernible) patients but there have been no concerns with large amounts of dose adjustments required.

If you can move onto the next slide, and again, basically, if we look at -- I think we should now handover to Dr. Fishbane.

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### Steven Fishbane - Roche

Thanks, Iain. Thanks, John. I am now looking at slide number 12, which is titled "CERA Preclinical Studies Pharmacodynamic Intolerability Studies", to make sure that we're all on the same slide. This slide details some of the preclinical program that where studies (sic) conducted in animals to understand better the pharmacodynamic, pharmacokinetic and tolerability issues with the drug. You see here that there's five studies in mice, two in rats, a study in nephrectomized rats -- rats who've had

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their kidneys at least partially removed, and a study in dogs. Studies, of course, have been by both major routes of administration, subcutaneous and intravenous, and in a variety of dose ranges, and we will try to give you a little flavor for some of the studies.

In the next slide, which is slide numbered 13, this is titled "CERA Preclinical Studies Effect On Reticulocytes In Rats". Reticulocytes, you may be aware, are the first circulating form of mature red blood cells. They circular for about 24 hours before maturing into red blood cells, and they are a very good indicator -- since they are in the circulation for a shorter period of time than red cells -- of the effect of erythropoietic (ph) agents. What you see here are five lines for the various doses in drugs, giving the reticulocyte numbers.

I'm going to ask you to focus first here on the lowest line. If you have a color slide, it will be green. The lowest line shows that, in rats, in controls or just administered vehicle, that the percentage of total red blood cells that were reticulocytes average between approximate 5 and 10 percent.

The next line above that, which is grey if you have a color slide, is for epoetin dose to 2.5 (indiscernible) per kilogram three times per week. You'll see that, compared to controls, there is, of course, an increase in reticulocytes based on the erythropoietic (ph) effect of epoetin.

The next line, which is in the color red, is for CERA administered at the same dose, so the same amount of protein for CERA 2.5 (indiscernible) per kilogram, but instead of three times per week as for epoetin, you see the dosing here as once per week and the results in terms of reticulocytes are almost exactly the same, almost superimposable to the line for epoetin given three times per week.

Above that is a blue and gold line for higher doses of CERA, and this is simply to show that indeed there is an important dose-effect response as you go to higher dose levels. So there is a sustained increase in reticulocytes with CERA at different dose levels, and the dosing interval appears to be extended compared to epoetin.

The next slide, which is slide number 14, and this is titled "CERA Preclinical Studies' Effect on Reticulocytes in Mice". SC means subcutaneous rather than intravenous is a five-week study. What you see here in the red line, we are going to look at epoetin again given three times per week, and the red line shows a reticulocyte (ph) site response that ranges between 1 and approximately 6 percent. The good news here is that CERA,

in the blue line, given at the same dose but just once every two weeks, had a very similar response in terms of reticulocytes with a range of between 1 and 8 percent. In the gold line, you see going out to higher dose of CERA that there was even greater response. But this study shows that CERA induces similar erythropoietic responses to epoetin but with less frequent dosing, in this case, extending to once every two weeks.

The next slide, then, will summarize and animal studies, and I've given you just a brief flavor by saying that CERA is a more potent stimulator of erythropoiesis, or red blood production, than epoetin based both in terms of the magnitude and the duration of response. CERA has a lower systemic clearance than epoetin and that results in longer elimination half-life; in rats, it's approximately a two-fold increase and in dogs, approximately a seven-fold increase compared to epoetin. So, the preclinical program suggests a feasibility of a longer clinical dosing interval.

The next slide, this is slide number 16 in my group. It's titled "CERA Phase I Pharmacokinetics (ph)". The subtitle "Half-Life" suggests less frequent dosing. Let's look here half-lives for different erythropoietin drugs. We have a pretty good understanding, at this point, regarding these characteristics. I'm going to focus now on Column One, which are the names of the drugs, CERA, darbepoetin (ph) and the epoetin data analysis. The second column -- and let's look at the actual results intravenously. CERA now we know has a half-life of approximately 133 hours. That compares to darbepoetin alfa, which is 25.3 hours, epoetin alfa and beta, which range between 6.8 and 8.8 hours. When these drugs are administered subcutaneously, the SEC, which is our last column here, CERA has a half-life of approximately 137 hours. This shows you, I think, an important piece of information here, which is that, given (indiscernible) intravenously, the half-life appears to be about the same, whereas darbepoetin has a half-life of 48 hours and the epoetins, given subcutaneously, range between 19 and 24 hours.

The next slide, slide number 17, will conclude the Phase I section by saying there is a dose-dependent erythropoietic response after both intravenous and subcutaneous administration. The prolonged half-life suggests that less frequent dosing with CERA is possible. The drug was quite well tolerated in Phase I and very importantly, there were no anti-erythropoietic antibodies observed in any subject receiving the drug.

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**John Michalidis** - Roche - Business Director

Thank you, Dr. Fishbane. I would like to now handover to Dr. Macdougall to take us through the Phase II results.

**Iain Macdougall** - Roche

I'd like to apologize for my enthusiasm for this exciting new molecule getting carried away and almost doing Steven's job.

If we move onto the Phase II efficacy results in which -- coming to the study that has the code name BA16260, which is an exploratory open label multi-symptom Phase II study. Basically, this required patients to be stable for six weeks with hemoglobin maintained in the range of 9 to 13 grams per day, (indiscernible) is really for safety reasons. There was a running period of four weeks for screening and then there were three different dose levels that you'll see building. These were .15 micrograms per kilogram per week -- actually, if we just build the rest of the slide -- .30 micrograms per kilogram per week and then finally .45 micrograms per kilogram per week.

Each of these different dose levels had three subsets of patients, one subset of patients with once weekly administration of CERA, the second subset had once every two weeks and the third subset had once every three weeks. The dose was not allowed to be altered for the first six weeks of treatment. Then after six weeks, there was an extension phase for another six weeks, which is shown in these yellow bars. But after the initial six weeks, the Data Safety Monitoring Board met to discuss the next appropriate dose escalation. The dose escalation went from .15 to .3. I might point out that at one stage, it was expected that the third dose (indiscernible) would have gone up to 0.6, but this was deemed to be too high a dose in terms of safety, and so the third dose level came in at 0.45 micrograms per kilogram per week.

If we move onto the results, so just (indiscernible) criteria fairly standard for any anemia treatment trial. Patients were adults over 18 years, all with chronic renal anemia. They could be either on hemodialysis for one month minimum or peritoneal dialysis for two months. They had a stable chemical during the run-in phase and hemoglobin in the range of age to 8 to 11 at the end of the run-in period. They had to have adequate iron status, as detailed by CERA (indiscernible), over 100 and a T-stat greater than 20 percent and they had to have no previous treatment with any erythropoietic agents within the last three months. Neither could they have any blood transfusions during the last three months or anticipating needing one in the next three

months, and they had to have a life expectancy greater than six months.

Now, we look at the results. In the left-hand part of this slide, which I hope you're on, which is entitled "CERA Effectively Increased Hemoglobin Per Protocol Six Weeks Treatment by Dose Group", you could see the median plus or minus inter-quartile range change from baseline in hemoglobin over time. You could see that in all three dose levels -- the low, which is shown I think in Orange, although I'm not sure if the colors are actually projected on the slide. I'm looking at the low is in orange, the intermediate is light blue and the high dose here is in violet. You can see that in all three dose levels, there is a progressive increase in hemoglobin over the first six weeks of treatment with the highest rise really in the high dose here.

If you look the right hand part of this slide, you see the mean plus or minus the standard error increase in hemoglobin over this period. You can see that there isn't any significant difference between any of these dose levels, although clearly the intermediate dose is giving a higher nonsignificant increase compared to the low dose (indiscernible) no difference.

If you compare individually, there is a significant difference for both of the intermediate and high doses versus the lower dose. Next, if we look at the progressive rise in hemoglobin now for the 12 weeks in this study, just to remind you that the dose could not be altered over the first six weeks but dose adjustments could be made after this period. Again, you can see that this progressive rise in hemoglobin has continued in all three dose levels, low, the intermediate and the high.

If we look now at 12 weeks in mean hemoglobin increase, comparing lower dose of roughly about 1.5 g per dl over the 12 weeks -- the rise in hemoglobin -- compared to 2.6 for the intermediate dose and 2.4 for the high dose. So basically, the efficacy in this study was fairly well proven.

The safety -- there were no serious adverse events that were related to study treatment. There were two patients withdrawn due to adverse effects; one of these was a drug toxicity not related to CERA and one of these was a (indiscernible) hemorrhage, but there were no serious adverse events related to the treatments.

There were two decks, none that were related to study treatment and there was the absence of any antibodies against (inaudible) CERA in this study.

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So in conclusion for the Phase II study, subcutaneous CERA in anemic dialysis patients corrected the anemia effectively. It did achieve a hemoglobin response at the lowest dose, but there was an enhanced response with higher doses. It allows for different dosing frequencies -- once a week, once every two weeks, and once every three weeks -- without significantly affecting the hemoglobin response. And this drug was indeed well-tolerated in this study.

So basically, if we look at the status of the CERA development program, the preclinical program is complete, which Steve has already talked about. Some of the ongoing work in this area suggests that those repeated attachments and rapid release of CERA, the receptor sites and hence the (indiscernible) in CERA, which stands for more continuous erythropoietic receptor activator than you get for other (indiscernible).

The Phase I in healthy volunteers is complete. The Phase II program is nearing completion, both in kidney disease and cancer, and the Phase III program is about to be initiated in the first quarter of next year.

The goals for Phase III in renal are focusing mainly on the renal side, I guess, because both Steve and myself are (inaudible). But the plan is for simultaneous approval of CERA, in both the U.S. and the European Union, as an indication for renal anemia. That's going to be the primary indication in chronic kidney disease patients. This will be the whole spectrum of chronic kidney disease, which will include hemodialysis patients, peritoneal dialysis patients and those patients that have not yet reached the need for any dialysis -- what we now call CKD, or Chronic Kidney Disease patients. In both the correction and the maintenance phases, both intravenous and subcutaneous routes will be used, the intravenous in hemodialysis and peritoneal dialysis. The subcutaneous again in hemodialysis, peritoneal dialysis and CKD. Obviously, (indiscernible) the hypothesis that has been generated -- that less-frequent dosing intervals will be required for this new molecule.

So really, we believe that CERA could be taking anemia management into a new era. We've had effective erythropoietic agents around for around 15 years now, but this could be the beginning of a new era in terms of molecules that may have a unique mechanism of action at the receptor site that, as Steve has already said, leads to a potency (ph) and more prolonged stimulation of erythropoiesis. We believe that it may offer the opportunity for longer dosing intervals with potential for administration up to every three or four weeks, which has advantages for quite a number of patients, perhaps particularly the CKD population. It would appear to (indiscernible)

predictable dose-dependent specific erythropoietic responses in this population of patients. Interestingly also, the comparable erythropoietic responses after the main two weeks of administration, the IV and the subcutaneous route, and it does seem to be well-tolerated with not one single report to date of antibody development to this molecule.

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### Unidentified Speaker

That concludes our slide presentation. I would like to open the call now for questions.

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## QUESTIONS AND ANSWERS

### Operator

This is the conference call operator. We will now begin the question-and-answer session. (OPERATOR INSTRUCTIONS) Catherine Arnold (ph), Bear Stearns.

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### Catherine Arnold - Sanford Bernstein - Analyst

It's Catherine Arnold (ph) from Sanford Bernstein. I have two questions; one relates to molecular structure and the second relates to the Phase III program.

If you could first tell me specifically how the protein molecule CERA differs from native EPO. Is it merely a difference in addition or in the carbohydrate chains, or is there a change to amino acid configuration which relates to just specifically amino acid change, or is it related to amino acid configuration related to a carbohydrate chain being actually linked onto the amino acid? So I'd like a little bit more detail there.

Then if you could just describe the scale and the structure of the Phase III program for CERA. I'd be interested in your thoughts on not just renal but also oncology, if you could provide that?

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### Unidentified Speaker

Perhaps if we tackle the mode of actions first in the molecule? Dr. Macdougall?

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**Iain Macdougall** - Roche

Well, in relation to some of the questions you raised, there are no differences in the amino acid structure in contrast to what you suggested; nor are there any differences in (indiscernible) pattern. That is sometimes contrast to, clearly, what was achieved with Aranesp, where an additional two glycostolation chains were added to the molecule. There are no additional glycostolation (ph) chains in CERA. Obviously there's the additional massive polymer that is attached but there are no changes in amino acid. So I hope that answers the question about the structure of it. John, do you want to take the Phase III program?

**Catherine Arnold** - Sanford Bernstein - Analyst

Yes, could I follow-up on that? In terms of the -- is there not an addition of a linked chain of repeated carbohydrates --?

**Iain Macdougall** - Roche

(Multiple Speakers) -- the polymer, yes. That's the polymer.

**Catherine Arnold** - Sanford Bernstein - Analyst

how does that affect the amino acid residues and the differences versus traditional EPO?

**Iain Macdougall** - Roche

The amino acid residue is altered. You're right; there is this enormous repeating carbohydrate chain, which is the polyethylene glycol polymer. That is attached to the erythropoits (ph) and molecule at the two sites. One of these sites is the end terminus of the molecule and the other main site is the lysine 52 amino acid residue on the molecule. But these have not been altered in any way. These are linked by a linkage chemistry, which is actually an SBA link, but there are no changes in the amino acid to make this polymer attach. Does that answer your question?

**Catherine Arnold** - Sanford Bernstein - Analyst

Yes, thank you.

**John Michalidis** - Roche - Business Director

I might take the second part of your questions regarding Phase III for renal and oncology.

As we've shown this morning, the renal program -- the renal Phase III program is about to begin. We have a suite of studies that we are initiating for both hemodialysis and CKD in both correction and maintenance. We will be looking at those intervals up to a month, and we will be also comparing reference arms for both EPO alfa and darbepoetin alfa. There will be approximately 1,700 patients in these Phase III program. It's a worldwide program and will be conducted in many countries across the world, including the U.S.

In regard to the oncology program, we are currently in Phase II in oncology. We do not anticipate entering Phase III in oncology until approximately this time next year.

**John Michalidis** - Roche - Business Director

Can we take the next question, please?

**Operator**

(indiscernible) from Bain (ph) Capital.

**Unidentified Speaker**

Thanks for taking my question and congratulations on the results. I'm curious to know -- in the past, you've expressed confidence that you're planning to develop CERA for both the European international markets and the United States. Given that (indiscernible) is not currently launched in the United States and that the amino acid sequence of (indiscernible) and CERA appear to be identical, what leads you to believe that the intellectual property estate (ph) surrounding CERA will differ from that that's been involved in the (indiscernible) IP disputes with Amgen, etc.?

**John Michalidis** - Roche - Business Director

Perhaps I will take that question. There were two pieces of information for which we feel confident. The first is the fact that we believe we have a new chemical entity with unique properties at the receptor site that confers a number of clearly unique properties, both preclinically and clinically.



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The second point is that we have been successful in gaining a patent in the U.S. and at least the U.S. Patent Office has recognized the utility and novelty of the molecule. Both of these pieces of information make us confident that we will be able to take this molecule to market, both in the U.S. and in the EU.

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### Operator

Richard Jarvis (indiscernible).

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### Richard Jarvis - - Analyst

Good afternoon. This is a question for John, I guess. John, I wonder if you could just tell us briefly, what are the other Phase II studies you have ongoing at present? What sort of different populations are you looking at? What are the different dose frequencies? Are you looking at anything above four weeks at the present?

Also, with regards to the confidence you've expressed about antibody production, what are the total number of patients so far exposed to CERA? Could you comment on the data released by Amgen over the weekend regarding once-every-four-week dosing of Aranesp, please?

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### John Michalidis - Roche - Business Director

Okay, thank you. Let me first address the Phase II data, the other data that you referring to. We have shown you our subcutaneous Phase II data. There is Phase II data in maintenance, which we will be presenting at ADTA (ph) next year. The Phase II data for oncology, as I said before, is ongoing and will not be presented until the latter part of next year.

In regards to antibodies and the number of patients, I think I am correct in saying we have exposed approximately several hundred patients so far, including healthy volunteers, to CERA and have not seen antibodies yet.

The third part of your question I may hand over to Dr. Macdougall.

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### Iain Macdougall - Roche

The third part related to the suggestion that perhaps Aranesp can be given once a month and there is indeed a poster at this meeting that you're obviously aware of that suggests that Aranesp can be given once a month.

I have two problems with this from a scientific point of view. One is that the doses were not very clear in terms of the requirements of Aranesp for once a month; that was not very clear from the work. I think the most concerning part of this study was the inclusion criteria. In order to get into this study, you had to be a patient who was stable on once every two weeks of Aranesp to even get into the study. I think Steve and I would both agree that the CKD population has got stable patients in them but the vast majority of patients are very unstable and are not able to get (indiscernible) with 172 (inaudible) Aranesp. So that's the point of this study; they were looking at highly select patients who were very stable, on twice a week Aranesp, and indeed 88 percent of them could get down to once a month Aranesp. That is not the majority of CKD patients that we see in clinical practice.

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### Operator

Ratna Padia (ph), Merrill Lynch.

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### Ratna Padia - Merrill Lynch - Analyst

Good afternoon. Ratna Padia (ph) from Merrill Lynch. I just had a few quick questions to ask. With regards to the Phase III study for the renal and oncology indications, can you just clarify whether you are pairing studies to show noninferiority to Aranesp and Eprex (ph)?

The second question is whether you could sort of give us some idea as to the data you plan to present at Ash (ph) later -- this next month?

Finally, sort of why, in this study, did you not include patients who were dosed at monthly intervals?

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### John Michalidis - Roche - Business Director

I may take those questions. Your last question first -- why a monthly interval was not used in the study presented here. The 260 study was a correction study. Monthly intervals have been used in some of the other studies that we will be presenting to you (indiscernible) say early next year.

Your second question related to Phase III, the specific statistical analysis of Phase III. At this point, I have no comment to make about that until we initiate Phase III; we will be initiating Phase III very early next year. At that time, I will be happy to discuss that further with you. (multiple speakers).

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Your third question was (indiscernible). The Doddard Ash (ph) will be presented -- will be on multiple myeloma. It's a Phase I/II study. The true Phase II studies will be presented later next year.

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**Ratna Padia** - *Merrill Lynch - Analyst*

I just had one follow-up question. With the Phase III study, are you going to be looking at six months duration or one year duration in terms of the length of the study on active treatments?

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**John Michalidis** - *Roche - Business Director*

You mean the total length of Phase III?

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**Ratna Padia** - *Merrill Lynch - Analyst*

Yes, of the active treatments.

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**John Michalidis** - *Roche - Business Director*

Again, this is something that we're in the process of finalizing with authorities and will be able to divulge that to you once that process has been done, which should be very early next year.

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**Operator**

Mr. Marcel Brand (ph), (indiscernible).

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**Marcel Brand** - *Analyst*

Good afternoon, gentlemen. One or two brief questions -- where do you see the advantage of a longer-acting EPO in renal terms, particularly in hemodialysis, where I think most patients get the drug anyway via the AV fistula? That is clearly also question one may raise regarding Aranesp (sic).

The second question is related to antibodies. How confident are you that the antibody test is validated in a decent fashion at this stage in development? I think that is sort of it. Thanks.

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**John Michalidis** - *Roche - Business Director*

If I could ask Dr. Fishbane to comment on the first part of the question, please.

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**Steven Fishbane** - *Roche*

That's a very good question relating to the potential advantages from the logistic standpoint of patient care. You asked about (indiscernible) chronic kidney disease with an emphasis on hemodialysis.

There are, with chronic kidney disease, approximately 40 times as many people as there are on hemodialysis, so I will start there first. There clearly is an opportunity that (indiscernible) troubles us in terms of our patients' experience. The EPO drugs have been a wonderful advance in terms of caring for these patients but the patients still have a terrific hardship in terms of having to not just see their nephrologist on a regular basis but their cardiologist and their chronologists, internist. And getting injections a couple times a week or once a week has been, I will tell you, a very substantial hardship for these patients, both in terms of having to come into the office in terms of the logistics of getting around, finding rides and managing to get the injections, so I think most nephrologists would agree that we haven't yet had the ideal erythropoietic agent for treatment of patients.

I suppose that our interest has been in trying to get to once every once every four weeks therapy. This is being tested with CERA since once every four weeks matches often how we already see the patients with advanced chronic kidney disease, so it wouldn't be an additional hardship.

You also asked about hemodialysis specifically, where you have access to the patients' circulation three times a week when the patient comes in for hemodialysis treatments. Epogen, which is used in the United States is the erythropoietic drug, is in fact, for the most part, given three times a week. You have access to the circulation of the patients there, so you don't have the same hardship in terms of traveling. The issues there tend to relate more to the nursing shortage in nephrology and having nurses -- in our main unit in Mineola, New York, we have 210 patients, so throughout the course of the week, we have 620 injections for EPO. You can imagine what it's like having nurses run around and inject the drug as frequently as they do.

We have a nursing shortage and there's a great interest in trying to get nurses back to doing the things that they are so valuable at -- assessment of patients and guaranteeing safety. So an extended duration clinical interval for dosing would be a benefit also in end-stage kidney disease.

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**Marcel Brand** - - Analyst

So even in IV? Okay.

**Unidentified Speaker**

Dr. Macdougall, would you like to add to that?

**Iain Macdougall** - Roche

Sure. I think Steve summarized the situation very well. Just to add to what Steve said, we look after patients who are on dialysis; we also look after patients who are not yet on dialysis. Anemia doesn't just develop when the patients go on dialysis; it becomes very apparent that anemia develops at an earlier stage of chronic kidney disease than perhaps we realized 10 or 15 years ago. These patients are therefore exposed to anemia for maybe quite some years before they end up on dialysis.

So just correcting the anemia when they end up on dialysis is not really the thing we should be trying to do. Clearly, for these patients that are not yet on dialysis, giving a drug three times a week, as Steve said, is an enormous hardship to them. If we can give a drug once a month perhaps in this population, these are the patients that might benefit the most from a drug that can be given every four weeks.

I agree also with Steve that for the hemodialysis units in the UK, we're very stretched (indiscernible) giving drugs regularly to patients on hemodialysis is really quite a hardship for them. Maybe giving a drug once a month will increase (inaudible) and save time considerably. (multiple speakers).

The only other point was ready the antibody test -- validity question. Can you just repeat the question again?

**Marcel Brand** - - Analyst

How much or to what degree you are confident that the antibody test to this new EPO molecule is validated?

**Iain Macdougall** - Roche

I think we can be fairly confident that it is. There's been (indiscernible) antibody developed against CERA's intact molecule, which is separate from antibodies simply against erythropoietin, so that is as much as I can say. This has been developed in-house as a robust antibody against CERA but as you are probably aware, it's actually very difficult doing antibody

tests, even against erythropoietin (ph), and it's been enormous (indiscernible) actually characterizing the antibodies and deciding which is the most appropriate antibody test for what is often a very low affinity antibody against the protein. (multiple speakers).

**John Michalidis** - Roche - Business Director

I can confirm that we do have validated antibody test. Next question, please.

**Operator**

Ken Haraqi (ph), (indiscernible) Securities.

**Ken Haraqi** - - Analyst

Thank you for taking my question. I have a couple of questions. First of all, just remind my memory -- how can you make this molecule? In the case of Epogen, (indiscernible) recombinant chronology. How can you make this CERA molecule?

Then also, in the future, is there any possibility to add more carbohydrate or pegylated to realize less-frequent administration? For example, let's see, once every three months or something?

Finally, do you have any plans to do so-called head-to-head study with Aranesp in Phase III trial? Thank you.

**John Michalidis** - Roche - Business Director

Perhaps I will start with the last question and then hand it to Dr. Macdougall for the molecule question.

We are exploring and pursuing a head-to-head comparison against Aranesp to something that we have a steering committee for that -- looking at the design. We will be pursuing this avidly and hope to be discussing this with authorities in the near future.

If I could hand you to Dr. Macdougall?

**Iain Macdougall** - Roche

Your question is really (indiscernible) make the molecule. Clearly, that's a bit of a trade secret. The technology is patented Roche technology and how you attach the polymer onto the protein. It's perhaps fair to say that this has been years and years of research. The process of attaching a polymer onto a protein is not an easy one; it's not something you can do your sort of

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backstreet laboratory back home, and it's required years and years of research in terms of the size of the polymer, whether it's a single chain polymer or a multiple-chain polymer, a branched-chain polymer with different molecular weights and different linkage chemistry.

Just to emphasize, there has been an extensive amount of research by Roche scientists over many years. It is patented Roche technology and (indiscernible) how you do it. Clearly, you'd have to ask Roche but I'm not exactly sure that they are going to tell you.

### Unidentified Speaker

Your third question related to adding more carbohydrates or pegylation to the molecule. I'm not sure what you were exactly asking. If you wouldn't mind repeating that?

### Ken Haraqj - - Analyst

As you know, in the case of Aranesp, they were successful to add more carbohydrate to realize less-frequent administration, so in the case of CERA in the future, is there any possible (indiscernible) carbohydrate or so-called pegylated something for CERA to realize the best frequency?

### John Michalidis - Roche - Business Director

I think the answer to that question is we have already tested many permutations of various molecules. The best one that we have come up with is CERA.

### Operator

Rudolph Clairveux (ph), (indiscernible).

### Rudolph Clairveux - - Analyst

Thank you for taking my question. Relating to Phase III program of CERA, I'm wondering if you've got already some discussion with the authorities about the batches of products you have to employ for the Phase III program. I'm wondering if it might require some batches coming from (indiscernible) plant to do these Phase III trial (sic)?

### John Michalidis - Roche - Business Director

I can confirm that our discussions with all authorities around the world have been finalized and our Phase III program will begin early next year with appropriate material from in-house.

### Rudolph Clairveux - - Analyst

When you mean appropriate material, it means that you have already (indiscernible) plans or if you are using (indiscernible) plans for doing this Phase III trial?

### John Michalidis - Roche - Business Director

We will be using material that has been approved by all authorities for use in Phase III.

### Operator

Nick Banner (ph), Jefferies.

### Nick Banner - Jefferies & Co. - Analyst

I wonder if you could -- maybe it's some information I missed but I wondered if you could tell me what the pharmacodynamic half-life is, please, of CERA, and compare that to Aranesp (indiscernible).

In addition, you are implying novelty of action at the EPO receptor. By that, do you suggest that the CERA is (indiscernible) receptors, for example? Rather than there being novelty at the level of the receptor, I just wonder whether there's the possibility that in fact it is just more of a pharmacodynamic effect and that you have prolonged exposure of the receptor to the liggins (ph) -- i.e., do you have a -- the pegylation is producing (indiscernible) on subcutaneous injection (inaudible) a depo effect. But I wonder if you could maybe go through the reasons why you believe you have novelty at the receptors.

Then finally, given the fact that you have a presumably prolonged activation at the receptors, do you see at all any at receptor (indiscernible) regulation, internalization, or do you see any (indiscernible) regulation of intracellular (indiscernible) mechanism?

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**John Michalidis** - Roche - Business Director

Perhaps I can take that one from you. You asked quite a large number of questions there.

In terms of the pharmacokinetics, there was a slide -- perhaps you missed it -- showing the relative half-life pharmacokinetically between the different operations, and you've differences, obviously, between intravenous and subcutaneous. If you look at just intravenous alone, you are talking about (indiscernible) roughly for the epoetins, 25 (indiscernible) for darbepoetin alfa, and up to 133 hours for CERA.

Now, in terms of the receptor interaction, all erythropoietic agents are requires to do (indiscernible) the receptor. At the present time, there is no other way of stimulating erythropoiesis physiologically pharmacologically except by diamarising (ph) the (indiscernible) the receptor. If you can diamarize (ph) the (indiscernible) receptor by whatever means, it looks as if you get the intracellular (indiscernible) process that then will allow proliferation and reduction of (inaudible) sales.

In terms of the unique mechanism of action, because CERA is such a large molecule, it has a lower affinity for the erythropoietic (indiscernible) receptors (indiscernible) natural (indiscernible), as you might expect. The hypothesis at the present time is that this lower affinity is not a disadvantage but, in fact, may be an advantage in that it allows the agonist, in this case CERA, to come off the receptor more easily because it is not as tightly bound and therefore, perhaps to hang around for awhile and potentially stimulant the receptor again.

I think your final comment was really regarding the possibility of tolerance and down-regulation due to the prolonged stimulation. There's absolutely no evidence at the present time in the clinical trials that you get down-regulation. This would be manifested clinically by perhaps an increase in the requirement for dosing, and Phase III studies will also look at this, but at the moment, in Phase II, there's no evidence that you're getting any tolerance in the patients that you're treating with CERA. I think this is perhaps a theoretical concern rather than a practical one at the present time.

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**Operator**

Andrew Fallows (ph), (indiscernible).

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**Andrew Fallows** - - Analyst

Actually, I'm going to ask probably a stupid question. Just on the oncology indications, I've noticed it's (inaudible) very much about frequency or lack of frequency of administration. But on the oncology side, might you be focusing more on the dose response effect, which seemed quite impressive in the animal data? Therefore, would that be more aimed at sort of more frequent or higher dosing levels?

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**John Michalidis** - Roche - Business Director

I think that's not a stupid question at all. I think that is something that we are focusing on and will continue to focus in the oncology indications, yes.

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**Operator**

Louisa Betts (ph), Lehman Brothers.

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**Louisa Betts** - Lehman Brothers - Analyst

I just wanted to check on the data that you show on a per protocol basis. Can you comment on how the data would look on an intent-to-treat basis and how many patients were excluded on a per-protocol basis, and for what reason?

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**Iain Macdougall** - Roche

The data don't really seem any different from the ITT analysis than the per-protocol. They were a few patients that were limited. Unfortunately, our patient population is a fairly thick population and to get no dropouts in any study in renal failure patients we wouldn't believe, so we did have some drop-outs; patients get transplanted; they die; we had one or two deaths.

None of this was related -- was believed by the investigators to be related to the administration of CERA. These were sort of things that happen to renal-failure patients, but it did allow for a few patients dropping out. It did not alter the results of the analysis between ITT or the per-protocol results.

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**Louisa Betts** - Lehman Brothers - Analyst

Okay, and the two patients that withdrew due to side effects, what were the side effects that they experienced?

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### Iain Macdougall - Roche

They were not related to the drug in any way, the two patients that had side effects. I don't know if Steve can remember the reason. At the moment, it just has slipped my mind what the two side effects were, but I remember from yesterday they were not related to study drug.

We have a few minutes left. I will take another question.

### Operator

(OPERATOR INSTRUCTIONS). Stephen Loren (ph), Legg Mason.

### Stephen Loren - Legg Mason - Analyst

Thank you. Most of my questions have been answered but very quickly, I was wondering if you could comment on the relative molecular weights of CERA versus native EPO and also versus Aranesp. At the same time, when you showed your preclinical data, you showed equivalent weight in terms of micrograms per kilogram. Is that on an effective-equivalence weight or is that actually on equivalent weight of drug substance?

### Iain Macdougall - Roche

In response to the molecular weights of the different erythropoietic agents, as you probably know, the molecular weights of erythropoietin or recombinant human erythropoietin is just over 30 kilo daltons (ph). The development of Aranesp did add to the molecular weight, and this put the molecular weights really up to around 38 kilo daltons (ph). The molecular weight of CERA is just over 60 kilodaltons (ph), so it's almost twice the size or almost exactly twice the size of erythropoietin, from just over 60 (indiscernible) erythropoietin is just over 30 kilodaltons (ph). That is the molecular weight.

The second part of your question related to the micrograms per kilogram dosing. Can I just clarify -- are you talking about the animal data or the human data?

### Stephen Loren - Legg Mason - Analyst

Actually, in both cases, just wondering -- in the animal data that you gave us, you are comparing EPO to CERA. Any time there is a comparison, is that on an actual-weight basis or an equivalent-weight basis of EPO contained?

### Iain Macdougall - Roche

I don't know if Steve wants to take that because he was commenting on the animal data.

### Steven Fishbane - Roche

I'm sorry, I was not able to hear the question.

### Stephen Loren - Legg Mason - Analyst

I'm just wondering, when you're comparing your doses for CERA versus EPO, whether or not that is on an equivalent weight based dosing, or -- (multiple speakers)?

### Steven Fishbane - Roche

Yes, thank you. It's based on protein weights, so it's an equivalent dose.

### Stephen Loren - Legg Mason - Analyst

Okay, so that's factoring out the effect of the PEG on the -- (multiple speakers)?

### Steven Fishbane - Roche

Absolutely.

### John Michalidis - Roche - Business Director

Thank you, ladies and gentlemen. At this point, we will close the conference call. Thanks very much for your questions.

### Unidentified Speaker

Allow me also to thank you in the name of Roche (indiscernible) John, Steve and Iain, and I hope that all questions could be addressed. Of course, thanks to all participants in the call and for the interest in Roche. Good-bye.

### Operator

Ladies and gentlemen, the conference call is now over. You may disconnect your telephones. Thank you for joining. Good-bye.

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