Conference Transcription

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CONFERENCE DETAILS

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Chairperson:	Alexander Rosar
Speakers:	Kemal Malik Frank Misselwitz

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ACT Operator

Ladies and gentlemen thank you for standing by. Welcome to the conference call of Bayer AG for investors and analysts on 11 December 2007. To review data on Rivaroxaban presented at this year's ASH annual meeting.

Throughout today's recorded presentation all participants will be in a listen-only mode. The presentation will be followed by a question and answer session. If any participant has difficulty hearing the conference please press *0 on your telephone for operator assistance. I would now like to turn the conference over to Mr Alexander Rosar, head of investor relations of Bayer AG. Please go ahead sir.

Alexander Rosar

Thank you Pat. Ladies and gentlemen good afternoon. Thank you for joining us today to review the exciting results of our Xarelto development programme. Firstly on the call are Dr Kemal Malik our Chief Medical Officer and Dr Frank Misselwitz; Frank is heading our cardiovascular development team. Before handing over to Kemal and Frank for their introduction, I'd like to remind you that during this call we will make forward-looking statements which are based on our beliefs and assumptions as of today. Thank you Kemal.

Kemal Malik

Thank you Alexander. Good afternoon and good morning to you ladies and gentlemen, it's a great pleasure to discuss with you the key findings of our Xarelto development programme. What I want to do - what we want to do during the course of this call is give you an outline of the data, outline the exposure we have in terms of patients, but also then focusing particularly on the liver safety because I know this has been a topic of some discussion and we want to give you full data and transparency on this issue.

I think it is fair to say that Xarelto is a major advance in a new era of anticoagulant therapies and it does genuinely have the potential to overcome the constraints of currently available therapies. More than 24,000 patients have been involved in our completed Phase 2 programme and involved so far in our Phase 3 programme. Almost 50,000 patients are expected to be enrolled in the Xarelto development programme which will evaluate Xarelto in the prevention and treatment of a broad range of acute and chronic blood clotting disorders.

Based on the data collected so far, Xarelto truly holds the potential to set new standards of care in the prevention and treatment of thrombotic disorders. And I want to make three very important points. Firstly in the RECORD 1, 2 and 3 studies Xarelto demonstrated consistently superior efficacy compared to Enoxaparin, which is the current standard of care in the prevention of venous blood clots in patients undergoing major orthopaedic surgery. Secondly, in these trials Xarelto demonstrated a safety profile with low bleeding rates similar to Enoxaparin and no drug related liver toxicity was observed. Thirdly, as of today we have investigated Xarelto in 2,400 patients between three to six months and we have not seen any untoward drug related effects in the liver. And those three points are very important. We have got consistent superiority from our record programme; we have got a safety profile in terms of bleeding rates which is comparable to Enoxaparin; and we have seen no untoward effects in the liver.

But as I always say when I speak to you, although we are truly excited by the results, a more definitive statement on safety can only be based on the availability of the data from long-term exposure to Xarelto in the VT treatment and stoke prevention atrial fibrillation programmes.

So let me now go into some of the details. In all of the record studies published so far once daily Xarelto consistently demonstrated superior efficacy compared to Enoxaparin with a similar rate of bleeding. In RECORD 1 and 2, Xarelto was compared to Enoxaparin in approximately 7,000 patients undergoing hip replacement surgery. Xarelto was administered in both studies at 10 mg for five

weeks versus Enoxaparin which was administered for five weeks in the RECORD 1 study and ten to 14 days in the RECORD 2 study. In both studies, Xarelto significantly reduced the relative risk of deep vein thrombosis, so called DVT, non-fatal pulmonary embolism or all-cause mortality which was the primary efficacy end point versus the standard of care. It did this by 70% in RECORD 1 and by 79% in RECORD 2. These are clearly outstanding results.

Superiority was also demonstrated in the secondary end point which was the composite of proximal DVT, non fatal pulmonary embolism and VT related death. Xarelto reduced the risk of these events by 88% in both studies. These data confirmed the findings of the RECORD 3 study which was first presented at the ISTH in July this year. In all record trials Xarelto demonstrated safety similar to Enoxaparin. It's especially important to understand that five weeks administration of Xarelto results in a similar profile to Enoxaparin with respect to the safety end point of major and non-major bleeding, even though an Enoxaparin was used for five weeks in RECORD 1 and only for ten to 14 days in the RECORD 2 study. These findings are again consistent with the RECORD 3 safety data.

These results underscore that Xarelto does have the potential to be regarded as an excellent choice for anti-coagulation. But not unreasonably, and rightly, you may ask yourself why are we so confident about liver safety. Frank will now explain in more detail how we're performing our trials and the liver safety data. Thank you Frank.

Frank Misselwitz

Thank you Kemal. Ladies and gentlemen, close monitoring of the effects of Xarelto on the liver has been, and will continue to be, a very high priority in our clinical development programme as safeguarding patient safety is paramount. Our goal is very clearly to ensure that there are sufficient data to establish that Xarelto does not induce liver toxicity and death or does not require liver monitoring. In general, safety across the entire programme is assessed in a standardised fashion. Protocols for all programmes include guidelines for subject management and for liver safety monitoring, this includes a repeat testing schedule for liver function abnormalities should they occur. Parameters, thresholds, as well as a schedule for measurements, has been discussed and agreed upon in a special protocol assessment with the FDA and other agencies.

We measure aminotransferases, enzymes involved in the metabolism of amino acids like alanine aminotransferase or ALT and aspartate aminotransferase, AST. These enzymes are usually present within the liver cells and elevated levels in the plasma may indicate a breakdown of liver cells and leakage of these enzymes into the circulation. In addition we also measure alkaline phosphatase or AP. AP levels for instance increase with bile obstructions; bile duct obstructions due to gallstones for instance.

We also measure bilirubin in all patients. Bilirubin is a waste product of red blood cell breakdown. It occurs at either an indirect, sometimes called free or unconjugated bilirubin, and then in the liver cells it is converted or conjugated to direct bilirubin making it more to soluble and permitting its excretion. An increase of unconjugated bilirubin indicates an extrahepatic cause whereas elevation of conjugated bilirubin may indicate liver injury. Therefore bilirubin is a very valuable laboratory parameter for monitoring liver function.

So how are these data from these analysis to be interpreted? Firstly it is important to detect and characterize any pathological changes and, if observed, to see whether the incidence of these changes in the Xarelto treated patients would be different from those treated with the active comparator drug, in this case Enoxaparin.

Secondly, the time pattern and the relative increase of some lab parameters over others, may be specific either for an intra hepatic cause such as hepatitis or drug induced liver injury or B) an extra hepatic cause such as gallstones, bleeding events or the re-absorption of large haematomas resulting form surgical bleeding.

There is also a regulatory relevance with respect to the data interpretation. The FDA recently provided guidance on assessment of drug induced liver injury to the industry. An important predictor for a drug induced liver injury under this guidance is a case according to the so-called Hy's Law. Let

me comment on the three prerequisites that need to be fulfilled until the finding of the liver can be categorised as a drug induced liver injury.

First it's important to understand that generally in the population treated there needs to be a clearly higher incidence of ALT elevations of threefold or greater above the upper limit of normal compared to placebo or compared to the active control agent. And among subjects showing such aminotransferase elevations, the total bilirubin must also be concomitantly increased to twofold of upper limit of normal. But so far this is only a laboratory finding and it's very important to understand that there must be also a third category fulfilled in order to qualify. And the third factor is very important. No other reason than exposure to the test drug is evident to explain the combination of increased ALT and total bilirubin.

Such other confounding reasons may include hepatitis, pre-existing or acute liver disease or another drug capable of causing the observed injury or other causes like blood transfusion, gallstones or Gilbert's syndrome.

A confounding factor actually may also be the surgery itself. In patients undergoing major orthopaedic surgery due to the very often large amount of blood transfusion, haematoma absorptions etc, but also non-surgical patients for instance and patients with Gilbert's disease, the total bilirubin may be increased without any liver involvement. For this reason it is recommended to determine the conjugated bilirubin and the ratio of conjugated to total bilirubin. If this ratio is greater than 50%, an involvement of the liver is likely. According to this definition of a Hy's Law case, we focus on patients with a combined increase of ALT, more than threefold upper limits are normal, plus total bilirubin more than twofold upper limit of normal and the ratio of conjugated bilirubin versus total bilirubin greater than 50%. And, of course, then the lack of any alternative explanation. This definition has been discussed and is agreed upon by authorities and it is part of our special protocol assessment with the FDA.

We are convinced, ladies and gentlemen, that both the frequent measurement of liver function parameters and information of the investigator, the independent data safety monitoring board and in addition to that an independent blinded advisory panel are important measures that help us to assess and handle any safety issues if they occur appropriately.

We are currently investigating Xarelto in chronic settings in Phase 3 clinical trials for the treatment of venous thromboembolism, the EINSTEIN-VTE, DVT and PE as well as the EINSTEIN extension studies. as well as an indication called stroke prevention and atrial fibrillation, the ROCKET AF study. Here, treatment duration is planned for an average of 18 months. There is also a large Phase 2 dose finding study underway and well advanced in secondary prevention of ACS, the ATLAS ACS TIMI 46 trial where the treatment duration is set for up to six months.

Indeed, as of to date, no evidence of untoward drug related effects on the liver attributable to Xarelto has been reported. All cases where we have observed concomitant increases of ALT greater than threefold upper limit of normal, together with an increased total bilirubin of more than twofold upper limit of normal did not fall under Hy's Law. These patients had either confounding factors like hepatitis, gallstones, tumours, palliative chemotherapy etc. Or the ratio of conjugated bilirubin versus the total bilirubin was less than 50%, or the time of the increase suggested that the effect was not attributable to the drug.

In our Phase 2 trials we reported four cases of concomitant increase in ALT and bilirubin. At that time we did not do the differentiation into the conjugated versus total bilirubin. There were two cases in the ODIXa knee VTE prevention trial occurring directly after surgery and rapidly normalising and two in the ODIXa hip trial. One patient in the ODIXa hip study had cholecystolithiasis**,** gallstones as a confounding cause. The other patient in the ODIXa hip study had a combined increase directly after surgery but the bilirubin normalised already on the next day when the increase was to be confirmed by a second lab test. The ALT normalised on the treatment rapidly and, as I said before, in the Phase 2 programme we did not determine on a regular basis the conjugated bilirubin. The other two patients did not show symptoms, remained on study medication and levels again resolved during the course of the study without stopping the medication.

In our extensive Phase 2 programme for the chronic indication, Xarelto was administered in roughly 900 patients for up to three months. Again in these studies we did not observe drug related liver toxicity. The data for one of the two trials, the ODIXa VTE trial or DVT trial are now published in circulation. In this study, three cases were already reported last year in September when we presented the results of the ODIXa DVT trial. Two of those patients who had received Xarelto had early elevations of transamination; one patient the day after initiation of treatment, the levels later returned to normal. In a second patient, levels were increased even before the first intake of study medication when treatment stopped immediately. This patient died two and a half weeks later of a carcinoma with liver metastases. In the third patient, medication got stopped after the individual had been diagnosed with Hepatitis B, with elevated liver transaminases. This patient has received two transfusions because of anaemia during palliative chemotherapy for a metastatic uterine sarcoma. The patient showed a very acute seroconversion during the study period and died of liver failure. Again all three cases did not fulfil the Hy's Law criteria.

In a second DVT treatment trial, the EINSTEIN DVT trial also for a treatment duration of three months, we did not observe effects on liver enzymes attributable to Xarelto. We have also observed five cases of elevated ALT of more than threefold upper limits of normal and elevations of bilirubin of more than fivefold **(ed. comment: correct is twofold)** upper limits of normal in the RECORD 1 to 3 trials. Two of these five patients were enrolled in RECORD 3 and the data has already been presented at the ISTH. Here, one patient has received multiple blood transfusions; the unconjugated bilirubin was elevated in the second patient suggesting an extra hepatic course of the increase. The patient remained on study medication and elevated levels resolved during the study.

Three additional cases first found in RECORD 1 and 2. The patient in RECORD 1 showed a fast increase after two days and a very quick resolution under treatment and the ratio of conjugated versus total bilirubin was below 50%, suggesting an extra hepatic reason. In RECORD 2, one of the patients had increased levels of aminotransferase and bilirubin already at the time of the first dose and remained on study medication. The higher of the increased level resolved. The other patient was diagnosed with an acute Hepatitis C.

So ladies and gentlemen to summarise our findings, we have a very tight safety monitoring programme in place that has been discussed and agreed upon with the authorities. All cases of concomitant increases of ALT and bilirubin that have been reported so far do not fall under Hy's Law. All cases have been discussed with the authorities and the cases had no impact on the clinical development programme.

With this, I would now like to thank you for your attention and turn back to Kemal again.

Kemal Malik

Thank you Frank. I hope that you realise that we've wanted to give you full transparency on this liver information and that’s why we've gone into it in such detail. Although we have a long way to go in our clinical programme, these data are truly building confidence. To date Xarelto is the most extensively studied oral direct Factor Xa inhibitor in development. As I said earlier more than 24,000 patients have been evaluated in the completed Phase 2 and ongoing Phase 3 programmes. In all our programmes, over 14,000 patients have been exposed to Xarelto to date. This adds up to an exposure of more than 1,500 patient years, and of these patients 2,400 have been treated between three and six months, and this is a timeframe when usually liver toxicity should be observed and a substantial number of patients in our programme have been treated for more than six months.

To date, and to repeat what we said earlier, no untoward drug related effects on the liver attributable to Xarelto have been reported. The longer term safety data that I've alluded to will be shared with the FDA upon submission of the VTE Prevention Programme in the United States which is planned for mid 2008.

In summary ladies and gentlemen, I do hope you share our excitement about Xarelto; the outstanding efficacy that has been demonstrated; the excellent safety profile in terms of bleeding; and the reassuring data that we've generated to date in terms of liver safety. And I'd like to thank you for your attention and now we're happy to try and answer any questions that you may have.