Bayer

Investor Conference Call on Rivaroxaban

28 August 2017

Opening Remarks

Oliver Maier

Head of Investor Relations

Thank you very much, everybody, for joining our call today. It's a great pleasure to share some exciting findings from the rivaroxaban COMPASS phase III study with you. Data were presented yesterday, during two hotline presentations at the ESC conference in Barcelona. You are probably also aware that the study results have been published simultaneously in the *New England Journal of Medicine*. In addition, a paper on the study rationale and design was published in the *Canadian Journal of Cardiology* earlier this month.

With me on the call are Jörg Möller, our Head of Global Development at Pharmaceuticals, and Frank Misselwitz, the Head of the Therapeutic Area Thrombosis and Haematology at Bayer. Frank and Jörg will start with a presentation, go through some slides with some prepared remarks, and then we will have a Q&A session at the end. Before I hand over to Jörg, I would like to draw your attention to the forward-looking statements that are part of the presentation and the remarks we have prepared this morning. With no further ado here, I'm going to hand it over to you.

See disclaimer

Overview of the Phase III COMPASS Trial

Jörg Möller

Head of Global Development at Pharmaceuticals

Thank you, Oliver. Ladies and gentlemen, I would also like to welcome you and thank you for joining our call. It is indeed a great pleasure to present and discuss the data from the phase III COMPASS trial, where we have studied rivaroxaban at a dose of 2.5 milligrams twice a day in combination with aspirin 100 milligrams once a day, and rivaroxaban 5 milligrams twice daily alone compared to aspirin 100 milligrams once a day, in patients with chronic stable coronary or peripheral arterial disease, or CAD or PAD.

The COMPASS study was designed to investigate whether rivaroxaban with or without aspirin could further reduce the first occurrence of major adverse cardiac events, or MACE, defined as

cardiovascular death, myocardial infarction or stroke in patients with CAD or PAD, and here are the key findings.

Rivaroxaban 2.5 milligrams twice a day, which we're going to call the vascular dose to clarify the low dose compared to normal anticoagulation dose, plus aspirin 100 milligrams once daily showed a 24% relative risk reduction in major adverse cardiovascular events compared with aspirin 100 milligrams once a day alone. The benefit shown in the combined efficacy endpoint was mainly driven by a significant 42% relative risk reduction in stroke and 22% in cardiovascular death. Rivaroxaban vascular dose 2.5 milligrams twice daily plus aspirin 100 milligrams once daily also reduced the risk of heart attack by 14%; however, this result was not statistically significant.

This regimen demonstrated a favourable 20% improvement in the pre-specified net clinical benefit, which was defined as the composite of stroke, cardiovascular death, myocardial infarction, fatal bleeding or symptomatic bleeding into a critical organ. Overall bleeding incidence rates were low, although major bleeding was increased. There was no significant increase in fatal or intracranial bleeding.

Importantly in the PAD patient population, major adverse limb events such as chronic limb ischaemia, which can lead to amputation, were reduced significantly. Patients included in the study already received guideline recommended therapy for hypertension, high cholesterol and diabetes. All finding were consistent across regions and subgroups.

Now, I want to put this finding into context and explain why these results are so important. Cardiovascular disease, which includes CAD and PAD, is responsible for approximately 17.7 million deaths every year, representing 31% or about a third of all global deaths. Additionally, patients with cardiovascular disease have a reduction in life expectancy of over seven years on average. CAD and PAD are caused by atherosclerosis, a chronic, progressive disease which is characterised by a build-up of plaque in the arteries. Patients with these conditions are at risk of thrombotic events, which may lead to disability, limb amputations and loss of life.

Aspirin, statins, angiotensin modulators and beta-blockers are effective and widely used for cardiovascular prevention in patients with CAD, and the first three classes of these drugs are also effective in patients with PAD. However, despite the use of these therapies as many as 5% to 10% of patients experience recurrent vascular events each year.

Various antiplatelet regimens, including clopridogrel, ticagrelor and voraxapar, have been tested as alternatives to aspirin alone for long-term secondary cardiovascular prevention. While these antiplatelet agents yield benefits, none of these approaches has been shown to reduce mortality. Long-term treatment with a vitamin K antagonist, alone or in combination with aspirin, is superior to aspirin for secondary prevention after acute myocardial infarction but substantially increases bleeding, including intracranial bleeding, and did not reduce mortality. Against this background, a more effective antithrombotic strategy with an acceptable bleeding risk is needed and could have major benefits for the large population of patients with stable cardiovascular disease.

In this context, rivaroxaban 2.5 milligrams twice daily in combination with aspirin 100 milligrams once daily demonstrated unprecedented results in the COMPASS trial. A 5 milligrams twice daily dose of rivaroxaban was also investigated in the trial, but did not reach the primary endpoint. Thus, for the purpose of this call, we're going to focus on the rivaroxaban 2.5 milligrams twice daily dose plus aspirin compared to aspirin only. With that, I would like to hand over to Frank to review the details of the COMPASS trial, Frank.

Data from the Phase III COMPASS Trial

Dr Frank Misselwitz

Head of the Therapeutic Area Thrombosis and Haematology

Thank you, Jörg. COMPASS is a double-blind, double-dummy, placebo-controlled, randomised trial that's been conducted at 602 centres in 33 countries. As Jörg already mentioned, the trial evaluated rivaroxaban at a dose of 2.5 milligrams twice daily in combination with aspirin 100 milligrams once a day, or rivaroxaban 5 milligrams twice daily as a monotherapy, compared with aspirin 100 milligrams once a day, for the prevention of cardiovascular death, stroke or myocardial infarction among persons with a history of stable CAD or PAD.

COMPASS is also evaluating pantoprazole 40 milligrams once a day compared with placebo for the prevention of upper gastrointestinal tract complications in those not receiving a proton pump inhibitor at the inclusion of the trial. This part of the trial is continuing.

After an initial run-in period, subjects were randomised in a 1:1:1 ratio to receive: rivaroxaban 2.5 milligrams twice daily and aspirin 100 milligrams once a day; or rivaroxaban 5 milligrams twice daily as monotherapy; or aspirin 100 milligrams once daily alone, as the comparator arm, of course,, also their matching placebos.

COMPASS was planned as an event-driven trial to collect at least 2,200 primary efficacy outcomes during a planned duration of approximately three to four years. Interim analysis were planned when 50% and 75% of the events were reached. The ITT principle was very strictly followed. In other words, the primary analysis set for efficacy was the intent-to-treat set, consisting of all randomised subjects.

Patients were eligible if they met the criteria for CAD and/or PAD. Patients with CAD who were aged below 65 years of age also had to have documented atherosclerosis involving at least two vascular beds or at least two additional risk factors, including current smoking, diabetes mellitus, renal dysfunction, heart failure or non-lacunar ischaemic stroke at least one month earlier. Those at high risk of bleeding, recent stroke or prior haemorrhagic or lacunar stroke, severe heart failure, advanced stable kidney disease, those requiring dual antiplatelet therapy, anticoagulation, or other antithrombotic therapy, or non-cardiovascular conditions deemed by the investigator to be associated with a poor prognosis were excluded. Generally, patients included in the trial were on guideline recommended therapy for hypertension, high cholesterol and diabetes.

Let me now turn to the primary outcomes of the trial. The primary outcome was the reduction of the composite of cardiovascular death, stroke or myocardial infarction, which we call the MACE outcome – major acute coronary events. The main safety outcome was a modification of the International Society on Thrombosis and Homeostasis, or ISTH, criteria for major bleeding, and included fatal bleeding, symptomatic bleeding in a critical organ, bleeding into a surgical site requiring reoperation, and bleeding leading to hospitalisation, including presentation to an acute care facility even without overnight stay. Unlike the ISTH criteria, we considered all bleeding leading to presentation to an acute care facility or hospitalization as a major bleed.

Three secondary outcomes were specified: first, the composite of coronary heart disease death, ischaemic stroke not all stroke, myocardial infarction or acute limb ischaemia; the second of those

secondary outcomes was a composite of cardiovascular death, again ischaemic stroke only, myocardial infarction or acute limb ischaemia; and last, but certainly not least, all-cause mortality. The pre-specified net clinical benefit outcome was the composite of cardiovascular death, stroke, myocardial infarction, fatal bleeding or symptomatic bleeding into a critical organ.

In total, 27,395 individuals were randomised to antithrombotic treatment. For the primary efficacy outcome, rivaroxaban vascular dose of 2.5 milligrams twice daily plus aspirin 100 milligrams once a day was clearly superior to aspirin 100 milligrams once a day alone for the prevention of MACE events, demonstrating a relative risk reduction of 24%. All components consistently contributed to the overall primary outcome. Remarkably, this drug combination yielded a significant 42% relative risk reduction in the risk of stroke and a significant 22% relative reduction in the risk of cardiovascular death.

Let's turn to the secondary efficacy outcomes. As you can see here, on the secondary efficacy outcomes, rivaroxaban 2.5 milligrams twice daily plus aspirin 100 milligrams once a day, compared with aspirin 100 milligrams once a day, reduced all-cause mortality by 18%. The pre-specified net clinical outcome was improved by a statistically significant 20%.

On the secondary endpoints of the composites of myocardial infarction, acute limb ischaemia, ischaemic stroke and coronary heart disease death, or cardiovascular death respectively, rivaroxaban 2.5 milligrams twice daily plus aspirin 100 milligrams once a day was superior compared to aspirin alone in reducing the relative risk of these secondary outcomes by 28% and 26% relative risk reduction respectively. The results were consistent across the components of these secondary outcome measures.

On the primary safety outcome, bleeding events were low in all arms. Rivaroxaban 2.5 milligrams twice daily plus aspirin, compared with aspirin, significantly increased major bleeding, which was mainly due to an increase in bleeding leading to hospitalisation. Most of the excess major bleeding was into the gastrointestinal tract. Importantly, the combination rivaroxaban 2.5 milligrams and aspirin, did not show a significant increase in fatal or intracranial bleeds compared to aspirin alone.

The consequence of using this specific modified ISTH definition of major bleeding was that, due to globally different hospitalisation patterns for the management of bleeding, more bleeding events were classified as major. When compared to the GUSTO severe or TIMI major bleeding definitions, there are more major bleeding events across all treatment arms in the COMPASS trial driven by hospitalisations. With this limitation in mind of the modified ISTH definition, cross-trial comparisons are still possible for fatal bleeding and intracranial bleeding. Although there was also a significant increase in major bleeding as defined using the non-modified ISTH scale, incidence rates using this definition were approximately one third lower when compared to those obtained when using the modified ISTH criteria.

The effects of rivaroxaban vascular dose plus aspirin on the primary outcome and on major bleeding in this trial were consistent among subgroups as defined by age, sex, region, ethnicity, body weight, renal function and history of cardiovascular risk factors including their smoking status, hypertension, diabetes and dyslipidaemia. Results in participants who met the eligibility criteria for CAD and for those who met the eligibility criteria for PAD were also very consistent and are being reported separately.

Ladies and gentlemen, rivaroxaban at a vascular dose of 2.5 milligrams twice daily used in combination with aspirin 100 milligrams once a day was significantly more effective than aspirin alone in reducing the occurrence of the composite outcome of cardiovascular death, myocardial infarction and stroke.

The substantial treatment effect of the 24% relative risk reduction in cardiovascular events was driven by the components of cardiovascular death and stroke, with relative risk reductions of 22%

and 42%, respectively. An 18% improvement in survival mirrored the result of the cardiovascular death component of the primary outcome. Modified ISTH major bleeding was increased significantly, but there was no significant increase in fatal or intracranial bleeds. The net clinical benefit – a composite of stroke, cardiovascular death, myocardial infarction, fatal bleeding or symptomatic bleeding in a critical organ – was clearly positive.

Overall, the dual pathway inhibition with rivaroxaban at a vascular dose of 2.5 milligrams twice daily combined with aspirin provides a larger relative risk reduction than dual anti-platelet strategies. This drug combination represents a substantial improvement to aspirin alone in the management of patients for secondary prevention of chronic stable CAD and PAD. Once approved, this treatment regimen could have the potential to change the standard of care for the secondary prevention of chronic stable CAD and PAD patients for the benefit of these patients. With that, I would like to hand over back to Jörg.

Summary

Jörg Möller

Head of Global Development at Pharmaceuticals

Thank you, Frank. Ladies and gentlemen, we are truly excited by these impressive results of the COMPASS trial. These data exceeded our already-high expectations. The COMPASS study is the first of its kind; no other NOAC has been studied in this patient population and the magnitude of these results clearly shows the benefit rivaroxaban could bring to patients diagnosed with CAD and/or PAD.

In the ROCKET AF trial, we have investigated the potential of rivaroxaban to reduce the risk of stroke in patients with atrial fibrillation, and in COMPASS rivaroxaban demonstrated a significant reduction in the risk of stroke in CAD or PAD patients. With that, rivaroxaban is the only factor Xa inhibitor to demonstrate a reduction of the risk of stroke in patients with or without atrial fibrillation. We will now work with the regulatory authorities to make this treatment option available to patients as soon as possible. With that, I would hand back to Oliver.

Questions and Answers

Oliver Maier

Thank you, Jörg. Thank you, Frank, for the presentation of these impressive data. I think with that we are ready to open the call for the Q&A session.

Richard Vosser, JPMorgan

Thanks for taking my question. It's Richard Vosser from JPMorgan. First question: the presenter at the 'meet the trialists' session for COMPASS yesterday suggested that the lack of a statistically significant benefit on MI could be due to competing endpoints. I just wondered if you could give your perspective there and whether this is, in any way, a concern for you in relation to the data.

The second question: as you highlighted, the excess bleeding seems to come from the GI tract. I just wondered if you could talk about your expectations for the PPI subgroup study and whether that could shed some light to further reduce and manage GI bleeds to a greater extent.

Thirdly, I just wondered if you could give your perspective on the potential of the opportunity in CAD and PAD, given the magnitude of the MACE benefit, the CV death benefit and the all-cause mortality benefit. What are you thinking now? Thanks very much.

Jörg Möller

Thank you, Richard. Maybe I will start on the opportunity, then I will ask Frank to comment on the PPI study, which is still ongoing, and the 14% reduction in myocardial infarction. In terms of the opportunity, these are truly impressive data in our view. I tried to describe that this really has the potential for how patients diagnosed with CAD and PAD are being treated. However, at this point, it is a bit too early to speculate about the commercial impact. Our focus right now from a development perspective is to get approval, get these data in front of regulatory agencies and then of course, hopefully following an approval, execute a successful launch of Xarelto in these indications. These are clearly our next priorities. Frank, do you want to talk about PPI and MI?

Frank Misselwitz

Definitely, I'm happy to do it. Hello, Richard. Commenting on MI first, you noted the p-value as a non-significant p-value for MI, 0.14. That said, if you look at the hazard ratios, they were entirely consistent for all the components of the composite endpoint. Typically, you expect a significant result for the entire composite, but not necessarily for each of the components. That's why we basically have these composite outcomes, because we power the trial for the composite and not for the components. It actually is in itself a positive surprise to see that some of the components that drove that outcome are really, even as a standalone, highly significant. There's no particular surprise MI not being significant on its own; it's entirely consistent and goes along with the other components of the composite. If the trial would had gone further and simply had accrued more events towards the end of the trial, I think it would have easily reached significance as well.

To the other part of the question, you asked that, if you have competing risks, such as cardiac death or certain, let's say, unstable angina, etc., and would really assess it in on a more thorough way, what in total could be attributed to myocardial infarction, either fatal or non-fatal, or unstable angina. This post-hoc analysis did in fact show an even significant reduction of that endpoint. We believe it's entirely consistent. It's partly due to the early interruption of the trial. If you were to analyse in a post-hoc fashion all components that could attribute to coronary artery thrombosis then, actually, it's even significant.

To the other question, bleeding mainly being attributable to GI bleeding, this is not unexpected. We saw that in many trials with rivaroxaban. I want to point out though that the absolute rates of bleeding in this trial were, by far, lower when for instance compared to the ROCKET trial. We are using a very low dose here, or low in combination with aspirin. Bleeding rates on absolute terms

are very low, mainly driven by GI. Now, you're right we actually have this PPI comparison. Two thirds of the patients who had not had a PPI at entry into the trial were randomised to receive either a placebo or pantoprazole 40 milligrams. This comparison is ongoing as we speak and will continue until the scheduled end of the trial, next spring 2018. Everything else in terms of the outcome of that comparison is highly speculative, at this point in time. It's a double-blind comparison and I simply, as eager as you, await the data next spring to come.

Luisa Hector, Exane

Good afternoon. Luisa Hector from Exane. Thank you for the call. I have a couple of questions. I'm sort of just trying to think a little bit more about the eligible patient pool and I notice that just under 6% of patients were excluded during the run-in phase, due to adherence concerns. I wonder if you could touch upon that, the reasons for that, and maybe tie in with that where you see initial targeting for this treatment, because you're essentially adding on a drug rather than replacing. That's the first question.

Then on the GI bleeds, I appreciate it's lower, so you've had the experience in the AF indication, but just maybe a bit more colour on how they are managed and whether there was any particular impact on the patient. Was there any discontinuation linked to the GI bleed? Thank you.

Jörg Möller

Thank you, Luisa. Frank, do you want to take those questions?

Frank Misselwitz

Yes, I'm happy to take them. The patient pool, first of all: why did we do this run-in period and how many patients were basically dropping out during the run-in period? When you plan for a very long-term large clinical trial, which was planned to recruit patients over one and a half to two years, and then continue follow-up and treatment for another maybe three years, making it up to a total expected trial duration of five years, you need to make sure that you have patients in the trial who are compliant, who are willing to participate in such a long-term endeavour and are really willing to come back to the sites. Typically that was the experience of our folks at Bayer, but also at academic research organisations such as PHRI. You would be able to identify these types of patients who actually are not eligible for such a marathon run relatively early on in the trial, and that's why we designed the run-in period.

You would, number one, see patients who simply cannot tolerate aspirin, which is relatively rare and was not the primary point of the run-in. Importantly, you will be able to identify patients who simply cannot cope with a long-term research trial of that kind and would either be non-compliant or simply not willing to return so frequently to the hospital. Losing these approximately 6% of individuals doesn't change the overall population but it did, in the long run of the trial, enhance the compliance and adherence. Actually, the number of dropouts during the trial was exactly even slightly lower than we anticipated, because we anticipated approximately 10% of patients dropping out during year one and then, in each of the consecutive years, approximately 6%. As a matter of fact, we do see approximately 15% to 16% dropout rates finally, at the end of our trial, which exactly matches our expectations. That is so far to the patient pool.

Targeting patient population, I think you clearly see in the eligibility criteria that we target patients with CAD and/or PAD, but really patients at a relatively higher risk. I wouldn't say highest-risk

patients, but an elevated risk because, if a patient was younger than 65 years of age, he or she had to have additional risk factors. In particular, this becomes evident when you look at what we call the poly-vascular patients or patient with atherosclerosis in two or more vascular beds. These are very interesting patients, representing quite a substantial proportion of our patients in the COMPASS trial.

To your question about the GI bleeds and how they have been managed and what were the consequences, of course, we had in general not just GI bleeds discontinuation due to bleeding but, overall, that wasn't a large percentage. Owing to the overall number of 16%, at average, who dropped out during the trial, only a small proportion of those dropped out due to a bleeding event.

The management of a GI bleed typically is emergency care facility at presentation of the patient, work up endoscopy. Typically, in some cases, surgical interventions via the endoscope procedure is required to pacify the site. Patients either then of course had all right to drop out from the trial or they were, after a certain period, again put into the trial. Both had happened and, generally speaking, many of our major bleeds were bleeds that actually could be treated effectively in a day clinic setting with no overnight stay. This is what I really want to emphasise here: regardless of whether there has been a GI bleed or, let's say, a nose bleed that had to be packed.

Jörg Möller

Thank you, Frank. As Frank has mentioned, treatment of these GI bleeds is mostly symptomatic. I want to emphasise that, in COMPASS, the overall bleeding incidence rates were really low and, while it is correct that major bleeding was increased, importantly, there was no significant increase in fatal or intracranial bleeding. That meant that we were able to demonstrate a favourable 20% improvement in the pre-specified net clinical benefit. That is a very important finding putting both benefit and potential harm into perspective.

Sachin Jain, Bank of America

Hi, it's Sachin Jain from Bank of America. A few questions, please, firstly just to follow on from the last topic. Given the screening criteria, what percentage of the CAD/PAD population do you think this study is applicable to? I think, Jörg, you mentioned 17 million patients addressable. What number of that does this study directly apply to?

Secondly, do you see any overlap or halo effect with the SPAF indicator from this data set? Is there any overlap in the patient population?

Thirdly, you've referenced the net clinical benefit a few times. Can you just clarify whether major GI bleeds were included within that net clinical benefit? I've heard back that it wasn't and, therefore, do you think that's fair?

Then my final question is for PCPs. I imagine PCPs is a fair proportion of the prescribing base for this indication. Do you think they will be as comfortable with the non-significant increases in fatal and intracranial bleeds as the key opinion leaders or cardiologists would be? Thank you.

Jörg Möller

Thank you, Sachin. Maybe I'll start describing what we think is the eligible patient population. The overall patient population that is diagnosed with CAD and/or PAD is very large, as we

mentioned. However, in the COMPASS trial, we covered a sub-population of the overall patient population that is diagnosed with CAD and/or PAD. For example in COMPASS, we have excluded patients who have atrial fibrillation and also those who were on dual antiplatelet therapy. We have, as Frank mentioned, included patients with CAD who were younger than 65 years only if they also had documented atherosclerosis involving at least two vascular beds or at least two additional risk factors. Based on this, we estimate that the potentially addressable patient population for COMPASS is about 30 million patients globally, round about.

To your second question on halo, I believe, actually, COMPASS nicely underlines the profile for Xarelto that we also have seen in other typical phase III studies before, where we could demonstrate clearly efficacious medical intervention with rivaroxaban, significantly addressing modifiable risk in these populations, but mostly only at the expense of an increase in minor bleeds that were addressable also with medical intervention. Importantly, as in ROCKET also in COMPASS, we could show that especially the most critical bleeds, fatal bleeds and bleeding into critical organs, intracranial bleeds were not increased. That is a very important message that will also make primary care prescribers more comfortable. Also, we have to realise that we are now some years into commercialisation of Xarelto. We have more 30 million patients treated globally, so prescribers know how to use these drugs and have built experiences. I think the clinical profile of rivaroxaban has again been underlined by these exciting data resulting out of COMPASS. Frank, do you want to address the question of Sachin on net clinical benefit?

Frank Misselwitz

Yes, I'm happy to do so. Sachin, the net clinical benefit did include fatal bleeds and bleeds into a critical organ, so a major GI bleed would only be included if it was fatal, otherwise not in this pre-specified definition. We really wanted to basically be balanced as to events of irreversible harm. There is this emerging and widely accepted concept of events of irreversible harm, both on the efficacy and on the safety side, to really derive an appropriate and balanced view of the net clinical benefit. Hence, we tried to focus here on really irreversible harm events and GI bleeds are often actually very well managed and without longer-term signalling.

To the other question, whether primary care providers would be satisfied with the non-significant slight numerical increase in fatal and critical organ bleeds, on that point the same would apply to aspirin alone. That is already a fact. In the important sub-populations, for instance of coronary artery disease, the increase of fatal or critical organ bleed was simply absent. There was even no numerical increase versus aspirin alone. We talk about very low percentages, in the range of 0.2%, and that is throughout the entire duration of the trial, which is on average close to two years. Whether they will tolerate it, I think they will take into consideration the potential very large benefit.

Maybe a last remark I want to make on that is we have seen the bleeding risk being or occurring earlier on in the trial. The bleeding hazard was relatively higher in the first year of the trial and then really tapered off massively, getting actually close to a hazard ratio of 1 in the later part of the trial; whereas the benefit, in terms of preventing thrombotic events, was constant over time. You can, by treating the patient longer, accrue more and more benefit over time.

Peter Verdult, Citi

Good afternoon. It's Peter Verdult from Citi. I have three questions, please. Firstly, just coming back to the GI bleeds, can you confirm whether you have or have not had a look, at the interim

stage, at the patients randomised to Protonix and whether there's been any impact on the overall result, as it relates to GI bleeding? That's question number one.

Question number two, could you just remind us, outside of the US, what the average daily treatment cost is for Xarelto across the approved doses?

Number three, I realise Dieter's not on the call, but could you make any initial comments regarding the commercialisation efforts required assuming, a year from now, you get an updated label? Is the intention to commercialise this with the existing sales force or will it require an increased investment from Bayer? Thank you.

Jörg Möller

Thank you, Peter. Frank, do you want to cover the GI bit?

Frank Misselwitz

I can start with the first question, yes. I'm happy to do so. Peter, the important and relevant question about whether or not we already had some glimpse into whether PPI works or not, it's a twofold answer to that. Number one, we analysed without breaking the blind to everyone at PHRI and at the sponsor level, as to whether there is an interaction in the sense of whether or not PPI would have an interference with the primary efficacy data. That has been analysed and the clear answer is there is no statistical interaction whatsoever between the use or not use of PPI with the efficacy of the drug, so that has been looked at. We have not and we remain to be fully blinded, as to any effect PPI may have on the safety. That simply cannot be answered. The only independent committee that is looking at it is the data management and safety board, and of course everyone else remains blinded to these data.

Jörg Möller

Peter, regarding your other two questions, Frank and I are from the development organisation, so I can't really comment on commercialisation cost and I ask for your understanding. I think what we can provide is, for example since you asked for daily treatment costs, one number is €2.5 daily as the wholesale acquisition cost. Those are data from Germany, but I'm at my limit when it comes to these commercial questions. I ask for your understanding.

Marietta Miemitz, Prime Avenue

Good afternoon. Marietta Miemitz from Prime Avenue. Thanks for taking my questions. I do actually have a whole bunch, to be honest. Following on from some earlier questions, I'd just be really grateful for some more help with patient segmentation. I appreciate it's too early to really gauge the commercial opportunity, but maybe just some high-level thoughts. Of the 30 million people who make the COMPASS enrolment criteria, do you have a rough split between the G7 and the emerging markets? Just generally based on your own analysis of the data and the discussions you've had with various physicians, in what proportion would you say it's really a no-brainer to give Xarelto based on the COMPASS data and what proportion would you say, just based on the bleeding profile, the low absolute benefit and just the conservatism that you see in the real world every day that they're quite unlikely to go into Xarelto in the coming years?

Maybe specifically on that point, do I read the sub-group analysis correctly that patients with PAD, but no concomitant CAD, don't actually get much of a benefit on the primary endpoint? How many patients would fall into that group in the real world? Would you still expect them to get Xarelto, just to avoid the limb events? Have you done a separate analysis based on the disease severity at all? Do you think that the milder patients within COMPASS will go for Xarelto? I would imagine that the milder that the patient is the lower the absolute efficacy benefit, but still the same bleeding profile. Maybe the motivation actually increases with disease severity.

The final segmentation question is, maybe just as a benchmark, can you remind us roughly what proportion of the 25 million SPAF patients in the world are now on some sort of a novel oral anticoagulant?

If I could have just a couple of commercial questions as well, you typically have to give price concessions to get a new indication reimbursed, so I was just wondering if there was any risk we could see a decline in Xarelto sales in the short term or has that actually been ruled out?

Maybe just one final question on the other PAD product you have in your pipeline, BAY 1193397: how does that compare to Xarelto and can you just give us a rough feel for the development timelines on that? Thank you very much.

Jörg Möller

Thanks so much. Maybe, Frank, you want to take the question on PAD and the benefits PAD patients have in COMPASS. Maybe also talk a little bit about the sub-group question and then also the pipeline question. Before you do that, I want to take the first question. Unfortunately, I am not able to provide you with more colour on the breakdown of the 30 million people who we think are eligible and sort of like mimic the COMPASS eligibility criteria. I'm not able to provide you with more breakdown there, but what I want to emphasise is, clearly, Xarelto is the Xa inhibitor that has the broadest set of indications. Especially now in light of the COMPASS data, there is no other of the new oral anticoagulants that has been studied in this patient population. Clearly as we mentioned, the magnitude of the benefit demonstrated in COMPASS clearly shows what rivaroxaban could bring to patients diagnosed with CAD and PAD. Clearly rivaroxaban is the only factor Xa inhibitor to demonstrate a reduction of the risk of stroke in patients with or without atrial fibrillation. That is also what I would emphasise and what makes these data so special also when compared in the competitive setting.

Marietta Miemitz

I think that's all very clear, but I guess there's just an element of inertia in the real world. We're not going to see 30 million patients go on to the drug some time in the next three to five years, so that's why I also asked the benchmark question. What patients, what proportion of the a-fib population, in the whole world are still on warfarin or something else that's not a novel oral anticoagulant, despite the clear evidence?

Jörg Möller

I was about to address that. Following up, you are right we have seen a continued decline in the use of warfarin globally, if one looks at warfarin use. Round about globally, and this varies a little bit by region and country, but globally we are approaching 50% of warfarin use. Remember one and a half years ago, I would have answered that question with about 60-65% warfarin use, so we

are seeing a continuing decrease and we are seeing increasing shares of the new oral anticoagulants in the a-fib market.

Frank Misselwitz

That's, just to add, relatively homogenous in terms of geography. This is also documented when you look at data from contemporary registries, such as the GARFIELD registry, where you see that this is a trend you can actually quite evenly observe, be it Latin America, be it Asia-Pacific or the G7.

Let me tackle the question of PAD-only. You asked that this was a sub-group reported to have potentially a lower benefit. Well, I want to say atherosclerosis is really a generalised and systemic progressive disease. It is correct to say that it may become symptomatic in one particular vascular bed, manifesting itself as a coronary artery disease or a carotid artery disease or a peripheral artery disease. Most of the time, it really affects more than one vascular bed, so the sub-group of PAD-only you were referring to is only 9% of the patients. It's a very tiny, small sub-group and I wouldn't actually, just owing to the size of that sub-group, want to make any far-reaching statements that PAD alone wouldn't work. The majority of the PAD patients had concomitant atherosclerosis in other vascular beds. We have a very large group of patients with CAD and PAD; actually the majority of the PAD patients were both and the clearly derived a massive benefit, not only in terms of reducing MACE, but also in terms of reducing major adverse limb events and amputations.

In that regard, you asked the question where to use our sub-group analysis as to mild and more severe patients. We in part are still in the process of analysis that, as to comparing the outcomes to existing risk scores, such as a GRACE risk or REACH risk or TIMI risk scores, etc. That is work in progress, but what I can say, just to give an example, is when you look at the relatively younger patients, those aged below 65, they actually in absolute terms had the biggest benefit of 2% absolute reduction, with the smallest increase in all the major bleeding, according to the modified ISTH definition. This increase was as small as 0.2%, so 2% absolute decrease on the efficacy side, 0.2% absolute increase on ISTH modified major bleeding side. That is just to your point that is not always the most severe, most frail patients who would benefit most, but in this regard it was actually the patients with CAD and PAD who are younger and would actually accrue a very large lifetime benefit.

Marietta Miemitz

Weren't they the patients who were also the sicker ones in the trial, in a way, because they had to have more comorbidities, right?

Frank Misselwitz

That is true. That is correct, and maybe that is exactly the reason for this observation I was just referring to.

Damien Conover, Morningstar

This is Damien Conover calling from Morningstar. I have a question talking a little bit about some of the comments towards the end of the presentation, talking about the dual pathway inhibition with rivaroxaban and aspirin being a stronger relative risk reduction versus other dual antiplatelet

strategies. Could you talk about the key studies you're referencing there and some of the quantitative relative benefit, and anything we should keep in mind with some of the challenges with cross-trial comparisons?

One follow-up question is: do you have any numbers on the number of patients who are on dual pathway inhibition currently? Thank you.

Jörg Möller

Thanks so much, Damien. Frank, do you want to give it a shot?

Frank Misselwitz

I thought that the dual pathway inhibition, the best evidence is really from the series of ATLAS trials, our dose-finding ATLAS 1 and the phase III ATLAS 2 trial in acute patients, in incident patients with an acute coronary syndrome, clearly showing that there is a substantial benefit when you add an anticoagulant, in this case rivaroxaban, at the very low dose of 2.5 milligrams b.i.d. on top of, in this case, either aspirin alone or dual antiplatelet inhibition for most of the cases.

It makes a lot of sense, because we know that, whenever you have an atherosclerotic plaque and you have a rupture of that plaque there is both the coagulation pathway that is being activated and of course also the activation of platelets, of thrombocytes. Those processes are highly intertwined and we firmly believe – and this is also what has been highlighted by Dr Eugene Braunwald in his commentary in the hotline session, as well as in the editorial in *New England*. This is what makes it most efficient to use low doses to inhibit both of the pathways, the clotting pathway and the platelet pathway. If you pile up many drugs and even more potent drugs for just one of the pathways, you run the risk of increased risk of bleeding, while this is far less pronounced with this dual pathway.

In terms of the evidence to that, it is really the external validation from the ATLAS 2 trial, which by the way also did show a 52% relative risk reduction of all-cause morality over the two years of the trial duration. Now we have a second trial, basically in a continuum of patients. The ATLAS population was acute incidents directly after intervention; now we have the same findings very consistently in a prevalent, more stable patient population with chronic CAD. I think it's highly believable, it's very plausible and externally plausible.

Jörg Möller

Thank you, Frank. Maybe to add on that and also as we have mentioned during our explanation of the data, when one looks at the data generated in clinical studies with antiplatelet regimens – clopridogrel, ticagrelor, voraxapar – they have been tested in secondary prevention in similar settings. Importantly in those trials, none of these compounds has been shown to have an effect on mortality. As Frank has mentioned, that in my view also underlines the importance of addressing both pathways, as compared to just focusing on antiplatelets and basically going probably into higher doses there and thereby increasing the bleeding risk, but not being able to increase the benefit to a higher extent. This is also what sets COMPASS apart from other approaches using just antiplatelet regimens.

Wimal Kapadia, Bernstein

Just as a follow-on from an earlier question, can you talk a little bit about the difference in unmet medical need between the two populations, i.e. CAD versus PAD? My sense is that, within PAD, the unmet need is significantly higher and even aspirin is not really considered that effective. That seems slightly different in CAD, so I'm just trying to get a sense of the opportunities across the two populations. I appreciate there's significant overlap, but just want your thoughts on the difference in appetite across the two populations.

Just following on from that, can you be a bit more specific around the number of patients who have PAD alone within the 30 million population? Is it similar to the study, around 9% – just your thoughts there?

Finally, would you consider running Xarelto in combination with dual antiplatelet therapy within CAD, in an additional study? Thanks.

Jörg Möller

Thanks so much. Frank, do you want to take?

Frank Misselwitz

I'm happy to take the medical need question, PAD versus CAD. Well, first of all, as you rightly mention, most of them are going hand in hand and effectively have both. We included in our PAD analysis also those who came into the trial as CAD patients but then, upon baseline check-up, were identified to have a low ankle-brachial index, indicative of a PAD. Those were qualified as of course having both, CAD and PAD. The data are very consistent.

I think medically speaking it is very clear that, while the data are very consistent, for both populations who consistently benefit from the treatment, there are differences in the absolute risk reduction being higher in those who have both CAD and PAD. Owing to the medical need, I would concur saying that currently the unmet medical need certainly is larger in the PAD sub-population. We believe that, if you were to rank the absolute benefit, you would clearly have, at the tip of the iceberg, the poly-vascular patients who have atherosclerosis and more than one bed, which kind of automatically includes the PAD patients, but does not exclude the CAD patients. Then you work down that cascade, but having in mind that the hazard ratio for relative risk is very consistent.

Jörg Möller

Thank you, Frank. To your last question, in fact, if you look at the ATLAS programme we have tested rivaroxaban on top of dual antiplatelet therapy, in a more acute coronary heart disease setting. In the ATLAS 2-TIMI 53 study, which was also published in the *New England Journal* in 2012, those data were the basis for the approval of rivaroxaban in the ACS setting in round about 40 countries globally. These data have been available and, in a way, also nicely dovetailed, as Dr Braunwald yesterday alluded to, because also in the ATLAS 2-TIMI 51 study rivaroxaban could show a reduction in mortality that actually, in itself, even slightly exceeded what we are seeing in COMPASS. The data, not only within COMPASS but also across trials being conducted with rivaroxaban, are very consistent.

Closing Remarks

Oliver Maier

Head of Investor Relations

I would like to thanks Frank and Jörg for being available. Thanks for taking the time doing the presentation and the Q&A session, very much appreciated. I wish everybody the best and will talk to you guys soon. Thank you.

This Verbatim Document was produced by Ubiqus UK ❩ +44 (0) 20 7269 0370
http://www.ubiqus.co.uk / infouk@ubiqus.com

Cautionary Statements Regarding Forward-Looking Information

This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.