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Human Medicines Evaluation Division

Workshop on the role of pharmacokinetic and pharmacodynamic measurements in the use of direct oral anticoagulants

Workshop Proceedings

23 November 2015 at the European Medicines Agency, 30 Churchill Place, Canary Wharf, London, UK, meeting room 3A

The aim of the workshop was to bring together experts and stakeholders to discuss the utility of PK and PD measurements in the clinical use of the direct oral anticoagulants (DOACs). The objectives were to improve the understanding of:

1. Problems related to the use of DOACs in clinical practice, in the overall population of patients, in subgroups of patients at particular risk of bleeding or underexposure, and in patients presenting with a major bleeding or with a need for acute surgery or other invasive interventions
2. Need to further guide clinical decision-making on dose adjustment during routine use, when major bleedings occur, or when the need for acute surgery emerges
3. Recommendations regarding PK and PD measurements that can be implemented based on the current data
4. Gaps in the knowledge on PK and PD measurements of DOACs
5. Analytical methods, their validity, availability in the European Union and current use
6. Priorities in future research in the field of PK/PD measurements of DOACs

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Proceedings

A summary of the presentations held at workshop is provided below.

Opening

Welcome to the participants

Presenter: Dr Enrica Alteri (EMA)

Dr Enrica Alteri, Head of the Human Medicines Evaluation Division, welcomed the workshop participants and underlined the unique opportunity of bringing together patients' representatives, clinicians, academics, regulators and industry.

Dr Alteri stressed that the workshop is not intended to be a consultation on a regulatory guideline in the making or either an ongoing regulatory procedure but that it is about starting a process of scientific reflection.

This workshop stemmed from the awareness that the EMA, as scientific secretariat, can and must provide support to a purely scientific endeavour in order to gain a better insight into the knowledge accumulated in the past few years in the field of direct oral anticoagulants. This insight will help to shape the thinking about future research and guide clinical decision-making.

DOACS have been welcomed as an important therapeutic progress, because their relative ease of use is supposed to provide an advantage over other medicines. However, concerns about bleeding events have been raised, and these concerns are linked to the questions addressed during the workshop.

One of the main goals of the workshop was to find an answer for some relevant questions such as:

What are the real problems in clinical practice associated with oral anticoagulant treatment?

What analytical methods are currently used, how valid and how available are they in EU?

What are the gaps in knowledge and what research is more likely to fill them?

In view of the objectives that were set out for the workshop, and always keeping the focus on patients, the expectation was to pave the way for future discussions and to make progresses that can also help ultimately to address whether or not regulatory actions may be needed.

Session 1: The oral anticoagulant landscape - setting the scene.

This session aimed to set the stage for the workshop and stimulate later discussion. It should delineate the problems in clinical practice associated with oral anticoagulant treatment.

Patient perspective

Presenter: Christine Dehn (German Heart Foundation)

Christine Dehn, Assistant to the chief editor of HERZ HEUTE and HERZBLATT, the German Heart Foundation's (GHF) quarterly magazines, gave an overview of the patient perspective including the reality of being on an oral anticoagulant and the issue of monitoring.

Christine provided insight into the work of the German Heart Foundation (GHF) and explained why the GHF is able to give feedback on patient's concerns.

She explained where the GHF receives the information from, how does it reach the patient and how will the patient provides feedback to the GHF.

Christine also described the most important questions asked by patients related to DOACs. Most relevant questions are:

- Would my therapy be safer if the extent of anticoagulation would be controlled?
- Is my anticoagulation within the desired therapeutic range?
- If I take other drugs: What is their influence on the effectivity of DOACs?
  This question is frequently asked by elderly and multimorbid patients.
- Why did I have a stroke? Was my DOAC dosage too low?
- I've suffered severe bleeding. Was my DOAC dosage too high?
- I'm afraid to have an accident or to have an emergency operation. Will doctors know how to counteract my anticoagulation?
- Is there an antidote?
- What do I have to do before having a planned operation or dental intervention? My doctor and/or dentist seems not to be able to give me any reliable information/advise.

Clinician perspective

Presenter: Prof Menno Huisman (Department of Thrombosis and Hemostasis, Leiden University Medical Centre)

Prof Menno Huisman from the Leiden University Medical Centre Leiden in the Netherlands provided the clinician perspective on the challenging patients and the difficult clinical situations.

The presentation described the guide for indication and dosing of DOACs. He also gave three examples of challenging patients in which lab testing may prove useful, and also provided some thoughts on the necessity for routine monitoring of DOACs. In his opinion neither lab testing at the start of DOACs nor routine lab monitoring of DOACs is necessary.

Presenter: Prof Peter Svensson (Centre for Thrombosis and Haemostasis, SUS, Malmö)

Prof Peter Svensson from Skane University Hospital in Sweden discussed further the clinician perspective on the management of DOACs in clinical practice, including the efficacy/safety of the DOACs and the way these agents are handled in his hospital.

The presentation started with a brief introduction regarding the indication for treating patients with DOACs including patient population for atrial fibrillation and venous thrombosis.

The presentation included a discussion on the different properties of DOACs as well as the different methods that can be used in clinical practice to measure DOACs.

Prof Svensson talked about how he handles the DOACs in his clinical practice that includes more than 12.000 patients on oral anticoagulants and how and why it was decided to follow them i.e. kidney function test.

He also discussed his views on why warfarin is an ideal drug to monitor and why DOACs should not be routinely monitored or measured. The presentation included a small study that illustrated how to use laboratory methods for drugs that can interfere with the concentration of DOACs.

Knowledge about the DOACs different characteristics and how this information can help in "bridging" certain clinical situations was illustrated. Clinical situations where measuring the DOACs can be proved to be useful were also discussed.

Session 2: What can we do now and what are the gaps in our knowledge?

This session aimed to present the most up-to-date data and discuss gaps in current knowledge about the possibility of implementing targeted PK and PD measurements in subgroups of patients at increased risk.

The direct thrombin inhibitor (dabigatran etexilate)

Presenter: Dr Marie Louise Schougaard Christiansen (Danish Medicines Agency)

Dr Marie Louise Christiansen, clinical assessor for the Danish Medicines Agency, gave a presentation on the direct thrombin inhibitor, dabigatran.

Dr Christiansen noted that the current Summary of Product Characteristics (SmPC) for Pradaxa lists no recommendation for routine anticoagulant monitoring and provides no therapeutic range. However, coagulation test thresholds are provided where therapy may be associated with an increased risk of bleeding. The EPARs for both the AF and DVT/PE indications acknowledge some additional value of coagulation testing. They emphasize that coagulation tests can only serve to define a theoretical risk of bleeding but not to define a therapeutic range. Thus, the conclusions in the EPAR did not translate into a recommendation of routine use of coagulation tests. The CHMP accepted that selection of doses could be based on characteristics such as age, concomitant medication, renal function and other clinical attributes.

New knowledge regarding possibly added value of the application of coagulation tests obtained since then stems primarily from the article by Reilly et al (J Am Coll Card. 2014 Feb 4;63(4):321-8). This presents analyses of data derived from the RE-LY study which found that 110 mg bid of Pradaxa was associated with significantly less bleeding than both warfarin and 150 mg bid of Pradaxa. Compared with 110 mg bid, exposure to dabigatran was increased by 36% when using 150 mg bid. This led to a 39% reduction in the primary endpoints of strokes/SEE but caused a 16% increase in major bleeding.

Reilly et al investigated the association between plasma conc. of dabigatran and efficacy and safety outcomes and explored factors affecting the variability of plasma conc. of dabigatran and their impact on outcome events. Peak and trough samples at steady state collected in the RE-LY study were used to determine drug conc. at 1-month post-randomisation in subjects in the Pradaxa arms. It was found that trough plasma conc. of dabigatran following 150 mg bid were approx. 41% higher than following 110 mg bid. Important covariates were renal function and age (highly correlated). Those experiencing a major bleed had approx. 55% higher plasma conc. than those with no bleeds.

Reilly et al found that the risks of both major bleeding and ischaemic stroke/SEE after treatment with Pradaxa in AF patients were related to trough conc. of dabigatran. The conc. range for either dose in the RE-LY study ranged over 5-fold for the 10th and 90th percentiles suggesting a wide therapeutic range. Both safety and efficacy outcomes were correlated with plasma conc. of Pradaxa, but no single plasma conc. range was proposed by the authors which provided optimal benefit-risk for all patients.

Reilly et al concluded that a subset of AF patients may improve their benefit-risk balance with Pradaxa by a tailoring of the dose.

Regulators are left with a number of questions. Should the formal establishment of a therapeutic range for plasma conc. for dabigatran be pursued? Is the arbitrary therapeutic range indicated in the RE-LY study of approx. 50-200 ng/mL sufficient? How many measurements would be sufficient if plasma monitoring was to be recommended? How should we regard the results of other researchers whose recommendations are not uniform regarding the possible need for monitoring of plasma conc. and/or dose tailoring of Pradaxa?

The direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)

Presenter: Dr Antonio Gomez-Outes (Spanish Agency of Medicines and Medical Devices)

Dr Antonio Gomez-Outes, medical assessor for cardiovascular and respiratory drugs at the Spanish Medicines Agency, presented the direct factor Xa inhibitors.

In recent years, several direct-acting oral anticoagulants (DOAC) have become available for use in Europe and other regions in indications related to prophylaxis and treatment of venous and arterial thromboembolism. They include the oral direct thrombin inhibitor dabigatran etexilate (Pradaxa) and the oral direct FXa inhibitors rivaroxaban (Xarelto,), apixaban (Eliquis), and edoxaban (Lixiana/Savaysa). Factor Xa inhibitors share similar pharmacological characteristics including a predictable dose response and few drug–drug interactions (unlike vitamin k antagonists) but lack widely available monitoring tests for measuring its anticoagulant activity. The main differences in clinical data are due to different clinical developments resulting in different posologies (twice-daily vs. once-daily) and adjustments [body-weight; Creatinine Clearance (CrCl); P glycoprotein (PgP inhibitors/inducers, etc)]. Recently, concern has emerged that measurement of drug concentration or anticoagulant activity might be necessary when using these drugs to tailor the dose to help to optimise their relative risk and benefit in individual patients. An important question is whether tailoring the dose to optimise drug concentrations and patient outcomes could be accomplished by modification of the dose on the basis of clinical features alone, as currently included in the product information (e.g.: renal function, weight and/or concomitant treatments with metabolic inhibitors/inducers). Measurement of anticoagulant activity or drug concentration might be potentially necessary (but the benefit is unknown) in some situations: a) To protect vulnerable patients from excess drug concentrations and bleeding risk; b) To protect individual patients from lack of efficacy (e.g.: combination of factors decreasing exposure: high CrCl, obesity, PgP/CYP3A4 inducers); c) In emergency situations: bleeding (e.g.: to confirm “toxic” levels and guide therapy), need for urgent invasive procedures, including thrombolysis or surgery. These latter situations (bullet-point c) are those in which a potential benefit of TDM could be greater.

Limited clinical data available on the PK/PD/efficacy-safety relationship for FXa inhibitors, suggest a flat dose-response for thrombosis/embolism [significant decrease in plasma levels (and anti-Xa activity) not associated to a significant increase in thromboembolism] and a steeper dose-response for bleeding: increase in exposure associated to exponential increase in bleeding. Therefore, the main concerns seem to be related to an increased risk of bleeding at increased exposure, but lack of efficacy is also of concern, particularly in patients with combined clinical factors resulting in low plasma concentrations. In addition, these analyses have limitations, including the population level used (concentrations and anti-Xa activity not measured in all patients; measurements at single time-points; correlated with outcomes that occurred throughout the duration of the trials), lack of data about changes in concentration/activity that may occur overtime and lack of measurements at the time of

the event (thrombosis/bleeding). Another uncertainties refer to the identification of the PK/PD parameter that correlates best with efficacy and safety (drug levels: average concentration, peak, trough; Anti-Xa: peak, trough) and the validation of the assay kit to be used. Dr Gomez pointed that even if we have the "best" PK/PD marker for monitoring drug activity and a validated assay, it is difficult to define a "therapeutic range" due to several reasons: a) Variability in anti-Xa activity depending on patients characteristics (e.g.: renal function) as well as by indication; b) Different clinical situations may require different intensity of anticoagulation (e.g.: baseline risk of thrombosis, concomitant use of antiplatelet drugs, etc.). Finally, a clinical trial to confirm that TDM guided DOAC anticoagulation therapy could improve outcomes versus current DOAC dosing according to clinical factors seems unfeasible. All these issues make challenging the introduction of recommendations about laboratory monitoring of the direct FXa inhibitors in the currently approved product information, as well as deciding which additional clinical data do we need to improve current knowledge.

Session 3: The analytical part

This session aimed to present the analytical methods and challenges to determine concentrations or the anticoagulant activity of DOACs.

The direct thrombin inhibitor (dabigatran etexilate)

Presenter: Prof François Mullier (University of Namur, Namur Thrombosis and Hemostasis Centre and L'Université catholique de Louvain)

Prof Francois Mullier, Founder member and coordinator of the Namur Thrombosis and Hemostasis Centre in Belgium discussed the analytical issues for the direct thrombin inhibitor, dabigatran.

Prof Mullier said that thanks to their ease of use and their similar or superior safety/efficacy profiles versus warfarin, direct oral anticoagulants (DOACs) have now widely reached the market of anticoagulation. These compounds are usually given at fixed doses without routine coagulation monitoring. However, accumulating evidence suggest that an assessment of the response at the individual level in some specific situations could improve the benefit-risk ratio of DOACs, including dabigatran etexilate (Pradaxa). Thus, in certain patient populations, i.e. acute or chronic renal impairment or multiple drug interactions, measurement of drug exposure may be useful to ensure an optimal treatment response. More specific circumstances such as patients experiencing a haemorrhagic or thromboembolic event during the treatment duration, patients who require urgent surgery or an invasive procedure at risk of bleeding, or patients with a suspected overdose could benefit from such a measurement. This presentation aimed at providing guidance on how to best estimate the concentration of dabigatran using laboratory assays in daily practice. Systematic review, national and international recommendations and results of external quality control were presented. The performances (accuracy, precision, sensitivity, specificity, linearity, available external control, standardization, calibration and availability) of activated partial thromboplastin time, thrombin time and specific assays were displayed. The importance to develop accurate assays for measurement of low plasma dabigatran concentrations in the perioperative management of patients on dabigatran etexilate, was also addressed. Finally, based on the current evidence, recommendations were proposed to eventually update the regulatory documents available to health care professionals.

The direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)

Presenter: Dr Steve Kitchen (Sheffield Haemophilia and Thrombosis centre and UK NEQAS Blood Coagulation)

Dr Steve Kitchen, Lead clinical scientist from the Department of Coagulation, RHH, Sheffield Teaching Hospitals, discussed the analytical challenges in measuring concentrations of Rivaroxaban, Apixaban and Edoxaban.

Dr Kitchen said that the concentrations of rivaroxaban, apixaban and edoxaban in patient blood samples can all be determined using liquid tandem high performance chromatography/ mass spectometry (LC-MS/MS). This method requires highly specialised equipment and expertise and currently is available in a very limited number of centres in Europe (and elsewhere). This is likely to remain the case in future. One of the best sources of information on current practices and assay availability is external quality assessment or proficiency testing schemes. The UK National External Quality assessment scheme (UK NEQAS) for Blood Coagulation (BC) is one such programme. There are others in Europe. Around 1000 laboratories currently participate in UK NEQAS of which approximately 650 are in the UK. The remaining centres include more than 40 in Ireland and more than 60 in Portugal with participants in many other European countries. A survey of practice in May 2014 indicated that approximately 7% of participating centres had established assays for apixaban and 20% had established assays for rivaroxaban. Only one centre was using the LC-MS/MS assay. All others were using anti Xa assays in which a solution of activated factor X (FXa) is added to plasma after which any drug present with ability to neutralise Xa may neutralise some of the added Xa. Residual Xa is then quantified by adding a substrate that generates yellow colour. The assay is made specific for a particular drug by use of specific calibrants and requires information about which drug the patient is taking so that the appropriate assay can be used. Such anti Xa assays for rivaroxaban and apixaban are commercially available from several diagnostic companies and are CE marked for use in the EU. At the time of writing no commercial edoxaban anti Xa assay is available but one diagnostic company reported on the performance of an assay in December 2014 and anticipate launching soon. Other companies are likely also developing such an assay. The vast majority of medium or large laboratories in the UK, and most EU countries have analysers already in place capable of performing such anti Xa assays. Some prediction of future assay availability can be made based on the situation related to low molecular weight heparin. It has been useful to determine anti Xa in a minority of patients on LMWH therapy but after several decades of use less than 40% of hospital labs have the anti Xa assays for LMWH available as such full on site availability of anti Xa for rivaroxaban or apixaban is unlikely to occur. One or two Uk centres have made apixaban and rivaroxaban assays available 24 hr/7 days a week but most have not. NEQAS data suggest that the various commercial assays are subject to some variability, particularly at trough levels of the drug.

Session 4: Future perspectives. What could be done?

This session aimed to discuss ways to fill the gaps in our knowledge about PK/PD measurements as well as how to better use the available data. Future scenarios on how knowledge can be obtained should be depicted.

Academic perspective

Presenter: Prof Hugo ten Cate (Maastricht University Medical Centre)

Prof Hugo ten Cate, Head of the Thrombosis Expertise Centre at Maastricht University Medical Centre in the Netherlands, spoke about perspectives to optimise use of DOACs including future research.

Prof ten Cate stated that non-vitamin K oral antagonists (NOAC) are rapidly replacing warfarin and other cumarin derivatives for the primary prevention of ischemic stroke in patients with non-valvular atrial fibrillation (AF). Based on large comparative trials the NOAC appear to have a similar or superior efficacy/safety profile. One caveat related to this conclusion is the fact that the comparator group on warfarin is composed from many different countries around the globe with highly variable quality of warfarin treatment. This may to some extend influence the interpretation and lead to the conclusion that warfarin is inferior in all aspects, including the risk of intracranial (i.c.) bleeding; however, even the risk of intracranial bleeding may still be acceptable and comparable to NOAC in well managed VKA countries like Sweden. In other words, there may still be room for improvement of NOAC treatment.

NOAC have the practical advantage of not requiring repeated blood testing for dose adjustment. Doses are selected based on patient characteristics, including age and renal function, which leads to a fixed dose regimen for most if not all patients. Annual or more frequent checks on side effects, complications, adherence and renal and liver functions are recommended by organisations such as European Society for Cardiology (ESC), but there is uncertainty as to the accurate implementation of such recommendations.

Prof ten Cate discussed two issues that merit more attention at this stage. First, the fixed dose concept derives from the assumption that a single dose of a drug is suitable in a wide range of patients. When we would assume that NOAC have proven benefits tested against suboptimal controlled warfarin, the conclusion should be that NOAC therapy need to be improved in order to demonstrate the real potential benefits. This should include aiming for improved selection of anticoagulants and optimal doses, based on PK assessments, in the individual patient. Second, long term use of NOAC is threatened by loss of adherence, especially in case of unmonitored therapy. Currently, there is no consensus on the long term management of potentially harmful anticoagulants in the absence of lab testing like with warfarin (which included additional management in the sting of anticoagulation clinics). Prof ten Cate concluded that this void needs to be addressed urgently.

Prof ten Cate also presented his perspective on further research to be undertaken to fill the knowledge gaps to allow for an optimised use of oral anti-coagulants in clinical practise.

Industry perspective

Presenter: Prof Jörg Kreuzer (Boehringer Ingelheim Pharma GmbH & Co. KG)

Fixed dose dabigatran etexilate demonstrated safety and/or efficacy advantages over well-controlled warfarin in clinical outcome trials for different approved indications. This was confirmed by large real world studies like FDA´s Medicare analysis.

The EU dabigatran label provides clear guidance on when to use 110 mg bid dosing and when to use 150 mg bid dosing and how to use individual patient risk factors or attributes which are routine parts of physician´s diagnosis (e.g. age) for dose decision. The EU label also contains information regarding measurement of dabigatran plasma levels in certain clinical situations. The plasma level is not for guidance on target dabigatran therapeutic concentration. Adjusting the level to a certain threshold

might lower bleeding risk but at the same time can lead to a significantly increased stroke risk. Several factors are known to impact bleeding and stroke risk, most notably age and renal function. Treatment decision and dose selection must be based upon individual patient characteristics as there is no single plasma concentration range that provides optimal benefit-risk for all patients.

For dabigatran PK data from multiple clinical trials, with over 8,000 patients from the RE-LY study alone, is available. This allowed to model a relation between plasma levels and bleeding or stroke. Confidence intervals in this analysis are huge as there are very few events that can be directly related to a plasma level. However, these on-treatment plasma levels do not allow for the prediction of an individual patient's risk. Based on the current data one therapeutic range applying to all patients or distinct subgroups cannot be defined. Only large randomized prospective trials in every subgroup of interest would allow to study a potential benefit of dose adjustment to a target plasma level (to be defined) on outcome. Sample size would be greater than 15,000 patients for a selected subgroup, duration therefore many years, and most importantly it would provide answers only on the subgroup of patients defined for this study.

However to obtain further knowledge, data on how to optimally treat additional patient populations or subgroups are being collected by BI in several ongoing clinical trials with dabigatran: RE-DUAL, RE-SPECT ESUS, RE-CIRCUIT, RE-VERSE AD (idarucizumab for reversal of dabigatran anticoagulation).

Presenter: Dr Scott Berkowitz (Bayer Pharma AG)

Dr Scott D. Berkowitz presented Bayer/Janssen perspective.

The aim of the rivaroxaban clinical development program was to provide reliable anticoagulation without the need for routine monitoring for dose adjustment due to rivaroxaban's highly predictable pharmacokinetic/ pharmacodynamic (PK/PD) response. Potential covariates that influence PK were identified in the Phase I and confirmed in Phase II. Body weight and age showed small differences that were within the variability of the population, while a decrease in renal function showed increases in AUC that led to the adaptation of the rivaroxaban dose in the Stroke Prevention in Atrial Fibrillation indication.

In the Phase III program it was assessed how relevant these covariates are by evaluating their effect on clinical outcomes. The presented analysis of the Einstein program showed that patient characteristics such as renal impairment provide pertinent clinical information, and are important in evaluating the balance of safety and efficacy. To adjust the dose, which was confirmed in clinical outcomes trials for a given indication, based on a laboratory measurement of the anticoagulant effect of a DOAC, in an effort to decrease bleeding risk, may be associated with consequences on the side of efficacy.

The marketing authorization holder (MAH) has used patient characteristics and clinical outcomes in the program to inform on dose adaptation and has included information like dosing by indication, PK properties including plasma concentrations observed in clinical trials as well as information on variability in the European Xarelto labeling.

Regarding future perspectives, it was agreed that there is a general interest in the potential value of plasma concentration measurement and dose adaptation of DOACs in specific clinical situations. As there was no PK program in the rivaroxaban Phase III trials, a sophisticated modelling approach to perform Exposure Response analysis was described as a path forward. With this rivaroxaban Exposure Prediction model, it is the aim to perform Exposure Response analyses based on the simulated PK data and derive the Exposure Response for each indication.

It was highlighted by the MAH that extensive information on the PK and PD of rivaroxaban, which was a basis for the labeling approved by the regulatory authorities, is published.

Presenter: Dr Robert Knabb (BMS/Pfizer EEIG)

Dr Robert Knabb presented the future perspectives for Eliquis.

Apixaban has shown a favourable benefit risk profile and superiority in bleeding, efficacy, or both when compared to the standard of care in each of its approved indications. This was achieved without therapeutic drug monitoring and only minimal dose adjustment, in the case of stroke prevention in atrial fibrillation, where a simple, clinically based dose adjustment is used. On the basis of evidence from the pivotal trials of apixaban, BMS and Pfizer believe that it is important to consider not only the potential variability in exposures, but also the clinical conditions that may be associated with risks of bleeding or thromboembolic events. Population PK and exposure response modelling did not identify a therapeutic range for apixaban. In fact, results from the ARISTOTLE study for stroke prevention in nonvalvular atrial fibrillation showed that there was extensive overlap in concentrations between patients who experienced a bleeding event and those who did not. Apixaban is believed to have a broad therapeutic window, and has shown favorable results in clinically important subgroups that may have varying risks for bleeding or thromboembolic events. Guidance to physicians is provided in the Eliquis SmPC, which states that a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions. Predicted values for Cmax and Cmin, including median, 5th, and 95th percentiles from patients studied in pivotal trials in each of the approved indications are included in the SmPC as potential guidance. Ongoing studies and surveillance including new randomized trials, registries, and other real-world data are being closely evaluated to identify additional populations in whom the benefit-risk profile may differ from those in clinical trials, and to provide appropriate communication of this information.

Presenter: Dr Michele Mercuri, Vice President, Clinical Development, Daiichi Sankyo Pharma Development

Dr Mercuri stated that ENGAGE AF – TIMI 48 and Hokusai VTE demonstrated that LIXIANA is an effective and safe anticoagulant with a positive benefit and risk ratio. In response to the EMA request for information, Daiichi Sankyo (DS) confirmed that is currently working on four distinct activities that directly relate to the assessment of pharmacokinetic (PK) and pharmacodynamics measurements for the Direct Oral Anticoagulants (DOACS). Specifically, the continuous analysis and relevance of its large PK database, the evaluation for the use of anti-factor Xa activity, the assessment and further refinement of a test measuring the actual patients' coagulation status, and finally, the development of regimens for reversing the anticoagulation effects of DOACs. DS concurs with the clinicians' request for accurate information to deal with a few specific and critical medical situations—such as managing a life threatening bleed or a patient who need surgery for a trauma or other unanticipated reasons or a suspected overdose or a stroke requiring thrombolysis—where rapid decision making is required. However, DS does not believe that PK measurements are practical and useful for the clinical community. For this purpose, a dedicated effort shall be placed to develop simple, accurate and widely available tests of coagulation.