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Quick Pulse

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FDA Advisory Committee Recommends Approval of First New Oral Anticoagulant in 55 Years

Silver Spring, MD
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The FDA's Cardiovascular and Renal Products (Cardio-Renal) Advisory Committee recommended approval of Johnson & Johnson/Bayer's Xarelto (rivaroxaban) for the prevention of blood clots in orthopedic surgery. However, the level of concern within the FDA over possible liver toxicity still may delay approval beyond the FDA action (PDUFA) date, which is May 28, 2009.

J&J is seeking FDA approval of rivaroxaban, an oral Factor Xa inhibitor that it is developing in conjunction with Bayer, for use in the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery. They are asking for a recommended dose of 10 mg taken orally once daily without any laboratory monitoring or dose adjustment, given for 35 days after hip replacement surgery and 14 days after knee replacement surgery.

If approved, rivaroxaban would be the first oral anticoagulant approved by the FDA since warfarin (Coumadin) in 1954. Rivaroxaban is expected to be widely used off-label and long-term for atrial fibrillation. However, the FDA, the company, and the advisory committee members all urged that, if it gains final FDA approval, it only be used on-label in appropriate patients until and unless there is more long-term data, particularly liver safety data.

Rivaroxaban is a hematology drug, so it is being reviewed by the Division of Medical Imaging and Hematology, but because of the safety issues, officials from the FDA's Office of Surveillance and Epidemiology (OSE) were also at the panel meeting. The panel included 18 voting members – 3 cardiologists, 3 orthopedic surgeons, 2 nephrologists, a toxicologist, a pharmacologist, an infectious disease specialist, a gastroenterologist, a biostatistician, a pulmonologist, a neurosurgeon, an anticoagulation specialist, a consumer rep, and a patient advocate as well as a non-voting industry representative.

Xarelto was developed under a special protocol assessment (SPA) with the FDA, which generally ensures approval unless a safety issue arises – and that appears to be what happened here. The FDA is concerned about possible liver toxicity, though it also raised questions about the lack of long-term data (yet) and the overall risk:benefit profile of the drug. A key FDA point was that even one case of Hy's Law – alanine aminotransferase (ALT) >3xULN + bilirubin >2xULN with no other explanation – is "ominous," and 2 cases are "fatal to the drug." However, there have been no confirmed Hy's Law cases yet.

J&J officials and experts did an excellent job presenting the rivaroxaban data. They were knowledgeable and responsive to the panel and the FDA. They weren't arrogant, and they were very clever. They used the FDA's own draft criteria for liver toxicity to defend rivaroxaban, and they scored points by noting out that AstraZeneca's Exanta (ximelagatran), an earlier oral anticoagulant that failed to get FDA approval because of liver toxicity, had shown an early signal – elevated ALT 0.53% – at 12 weeks while rivaroxaban's data to date have shown only 0.16%.

J&J estimated that, in a patient population of 10,000, use of rivaroxaban instead of enoxaparin (Sanofi-Aventis's Lovenox) would result in 504 fewer total venous thrombolic events (VTE) but an excess of 64 major or clinically-relevant bleeding events. Put another way, for every major or clinically-relevant bleed resulting from rivaroxaban therapy, 8 total VTE events would be prevented. J&J called this a highly positive benefit-to-risk ratio for rivaroxaban.

Apparently, the panel was convinced. Panel members:

- Generally agreed the **current data are sufficient** for approval, even given the potential hepatotoxicity. The panel was heavily influenced by new data from the recently completed, six-month, Phase II ATLAS trial that showed no increase in liver enzyme elevations vs. placebo even though FDA officials warned them that this was preliminary data that the FDA had not analyzed yet.
- Agreed that **longer-term data are not needed** before approval.
- Voted 15 to 2 that the **risk:benefit is favorable**.
- Voted 9 to 5, with 3 abstentions, that a **lower dose is not needed**.

The FDA also appeared to be less concerned with the company's risk management program than the briefing documents suggested. There weren't even any questions for the panel about that.

J&J officials were very pleased with the panel results. Dr. Rafel (Dwaine) Rieves, director of the FDA's Division of Medical Imaging and Hematology Products, Center for Drug Evaluation and Research (CDER), said his take-away message from the panel was: "On the whole, my sense was that most of the members were comfortable with the existing data…We (internally at the FDA) will talk about this. Everyone hears something different. And the reviews are ongoing and not completed yet. There is not a definitive answer yet (on whether the data are sufficient for approval). My perception is the committee is favorable to the existing data, but the actual outcome of the review is pending."

BACKGROUND

Both the American College of Chest Physicians (ACCP) and the American Academy of Orthopaedic Surgeons (AAOS) have issued guidelines for DVT/PE prevention.

- The AAOS guidelines focus on the prevention of PE balanced against the risk for major bleeding and peri-operative complications (such as post-operative bleeding that requires re-operation), emphasizing the relative rarity of symptomatic PE, fatal PE, and death in clinical studies and concluding that there is not much difference among the various chemoprophylaxis regimens (e.g., enoxaparin) and mechanical prophylaxis [e.g., intermittent pneumatic compression (IPC)] alone or IPC + aspirin. AAOS recommends doctors tailor PE prophylaxis to the patient's risk factors as well as the risk for major bleeding and that they consider IPC.
- The ACCP guidelines recognize IPC as useful but also cite the difficulties with compliance and the generally more limited clinical data supporting its use. ACCP recommends the "routine" use of chemoprophylaxis such as Lovenox, unless the patients are at high risk for bleeding, in which case IPC is recommended. The AACP recommends against the use of aspirin as the sole method of thromboprophylaxis in total hip replacement (THR) and total knee replacement (TKR) patients.

The Exanta experience appears to have made the FDA a little gun-shy. FDA reviewers noted that the Cardio-Renal Advisory Committee rejected Exanta "based in large part upon signals of liver toxicity (predominantly in the long-term studies), signals of cardiovascular risks (such as myocardial infarction) as well as questionable efficacy in the short-term studies. Exanta was not marketed in the U.S. but was sold in Europe until there was further evidence of liver toxicity in a hip surgery study. AstraZeneca then withdrew Exanta from the worldwide market. On the more positive side, there are more short-term data with rivaroxaban than Exanta.

Four drugs currently have FDA-approval for prophylaxis of DVT/PE in orthopedic surgery, and none are oral. Warfarin (Coumadin) is also used off-label.

1. Sanofi-Aventis's Lovenox (enoxaparin).
2. GlaxoSmithKline's Arixtra (fondaparinux).
3. Pfizer/Eisai's Fragmin (dalteparin).
4. Unfractionated heparin.

Despite the availability and widespread use of these effective agents, clinically symptomatic VTE is still the most common serious complication following elective THR and TKR, occurring in about 2%-3% of patients. More than 700,000 THR and TKR procedures are performed in the U.S. annually and are expected to increase. Most patients receive some form of anticoagulant prophylaxis, but only 47% of THR patients and 61% of TKR patients get the correct dose for the minimum time (10 days).

THE FDA PERSPECTIVE

In opening comments, Dr. Rieves emphasized that this review of rivaroxaban is for only one of the five indications which J&J and Bayer are investigating rivaroxaban. He emphasized that the hepatotoxicity with Exanta was not noted in the "shorter duration hip/knee surgery indication" trials but only in the longer-term atrial fibrillation trials.

Dr. Rieves noted, "Our preliminary review supports rivaroxaban's efficacy, based on the reduction of VTE…The main challenge in our view is predominantly related to safety and how (that) impacts the overall risk:benefit consideration." He is seeking panel guidance on three issues: bleeding, severe hepatotoxicity, and the role of ongoing clinical study data in assessing safety.

Briefing documents

In briefing documents prepared for the panel, the FDA raised a number of concerns with rivaroxaban (BAY 59-7939). The FDA clearly was seriously concerned about the safety of rivaroxaban, potential off-label use, and what appeared to be an arrogant attitude by the sponsors toward safety. J&J apparently had rejected two FDA "suggestions:" one for a lower dose option and another for a Risk Evaluation and Mitigation Strategy (REMS). The Agency appears worried it might have another Exanta on its hands. Remember Exanta failed to get FDA approval and was later pulled from the European market due to liver toxicity. However, Exanta toxicity generally showed up only in the longer-term studies, and there are no completed longer-term studies of rivaroxaban yet, and the FDA appeared to want to wait for that longer-term data before making a final decision. The FDA also showed its high level of concern with liver toxicity by putting hepatotoxicity on the agenda as a separate item with its own time period for panel review.

The FDA laid out its concerns quite succinctly in the topics for panel discussion, but the focus is on liver toxicity, bleeding, risk management, and the risk:benefit equation. The FDA reviewers concluded, "FDA's preliminary review finds the clinical data most solid for a risk of bleeding (including potential fatal bleeding)…The risks for liver injury/hepatotoxicity and other toxicities are less clear. FDA's Office of Surveillance and Epidemiology noted that, without more fully characterized signals – perhaps from the ongoing long-term studies – the effectiveness of most risk mitigation strategies is limited." This suggests that the FDA is concerned that a REMS cannot solve the safety issues with rivaroxaban, which makes it harder for the Agency to approve it.

Rivaroxaban was studied in four Phase III clinical trials (the RECORD studies) to see if it prevented DVT and PE in patients undergoing THR or TKR surgery. Nine additional clinical studies – including EINSTEIN, MAGELLAN, ROCKET-AF, J-ROCKET-AF, and ATLAS – are currently ongoing to assess the drug's effects in multiple other settings. ATLAS actually is completed, but the FDA considers it ongoing because the Agency does not yet have the full results.

The FDA reviewers' concerns were:

1. **The degree of efficacy** – the robustness and clinical meaningfulness of the efficacy data, considering:
   - The ~12,000 patients in the RECORD trials, VTE (proximal or distal DVT) was statistically lower for rivaroxaban than enoxaparin (Sanofi-Aventis's Lovenox, which is injected).
   - The main rivaroxaban benefit in the RECORD trials was a reduction in the venographic detection of VTE, an endpoint which the FDA recognizes but which is a surrogate endpoint that has been used for approval of other anticoagulants.
   - Symptomatic DVT and/or PE were very uncommon events, and symptomatic VTE/death was statistically lower with rivaroxaban than enoxaparin (0.6% vs. 1.3%).
   - Intermittent pneumatic compression (IPC) was not allowed during the peri-operative period, so there are no data on the efficacy of rivaroxaban when IPC is used.
   - ~85% of RECORD patients were OUS, which have gotten concomitant medications different from what is typically used in the U.S.

Dr. Min Lu, a medical reviewer in the FDA's Division of Medical Imaging and Hematology Products, CDER, concluded: "Overall, rivaroxaban demonstrates efficacy in prophylaxis of total VTE in patients undergoing elective hip or knee replacement surgeries. The absolute risk reduction of rivaroxaban for total VTE was 2.6% for total hip replacement surgery (RECORD 1 study), and 3.2% for total knee replacement surgery (RECORD 4 study) compared to the currently available product (enoxaparin) with a similar treatment duration. The difference between the two treatments was mostly due to ***asymptomatic*** DVT. These results were based on 67% of all randomized population. There was no significant difference for the symptomatic VTE between the two treatments."

2. **Bleeding risk –** estimated to be low but about twice the rate with enoxaparin. The clinical importance of the bleeding risks associated with rivaroxaban, considering:
   - All categories of bleeding (e.g., "major" or "any bleeding") were numerically higher with rivaroxaban vs. enoxaparin (0.39% vs. 0.21%).
   - One rivaroxaban patient developed gastric bleeding and died vs. no bleeding deaths with enoxaparin.
   - Since European approval of rivaroxaban in September 2008, at least two patients have had non-fatal bleeding events.

- A dose ranging study found a two-fold increase in rivaroxaban exposure resulted in a five-fold increase in the risk of major bleeding.
- Two clinical pharmacology studies showed a "clinically relevant" prolongation of bleeding time with rivaroxaban + clopidogrel (Sanofi-Aventis's Plavix) and suggested an increased risk for bleeding with rivaroxaban in patients with moderate-to-severe renal or hepatic impairment and in patients on a variety of concomitant medications.
- The FDA asked the companies to develop a lower dose rivaroxaban tablet or a scored 10 mg tablet to permit downward dose titration in special populations at higher risk of adverse events, but the company has regarded this modification as "unnecessary." FDA reviewers declared that the 10 mg dose is "appropriate" for most patients, but the concern is for patients with impaired renal function, etc.

The FDA statistical reviewer found: "There is a trend toward increased incidence of bleeding events in the rivaroxaban group compared to the enoxaparin group. Especially, the incidence of major or non-major clinically-relevant bleeding events…were statistically significantly increased in the rivaroxaban group."

The reviewers concluded, "Rivaroxaban…increases the incidence of bleeding in comparison with the active control, enoxaparin…It is known (from the label) that the most common side effect associated with using enoxaparin is the risk of bleeding. The evidence that administration of rivaroxaban could lead to bleeding events in significantly more patients relative to enoxaparin amplifies this safety concern for rivaroxaban in comparison to placebo in the setting of prophylaxis of DVT and PE following THR or TKR surgery."

3. **Liver toxicity** – the sufficiency of the available data to characterize the risk for liver injury or toxicity, considering:
   - The liver toxicity of AstraZeneca's Exanta, which was initially approved in Europe and later withdrawn for liver toxicity – and which never gained FDA approval.
   - Long-term rivaroxaban studies are ongoing at higher than proposed doses.
   - The concerning Hy's Law-like (but not confirmed) cases in RECORD – 0.15% with rivaroxaban vs. 0.11% with enoxaparin. Four Hy's Law patients on rivaroxaban died vs. 2 on enoxaparin.

Dr. Lu said 27 additional Hy's Law-like cases (ALT >3xULN + bilirubin >2xULN) have been reported in five of the ongoing studies. These included 4 on rivaroxaban, 3 on placebo, 3 on warfarin, and 17 that haven't been unblinded. One of those rivaroxaban patients died of liver failure, and the autopsy findings raised concerns of likely drug-induced toxic injury to a liver advisory panel member. She noted, "Because enoxaparin control has been known to cause benign liver enzyme elevation and such elevations are fully reversible…the comparison of liver enzyme elevation between the two treatments would not eliminate the concerns of possible serious liver toxicity for rivaroxaban...Previous experience with Exanta…suggested even short-term tolerance does not necessarily predict long-term safety…(With rivaroxaban), 92% of patients were exposed to <35 days of rivaroxaban treatment, and only 6% (635 patients) were exposed to rivaroxaban for 3 months…Therefore, the long-term safety data from ongoing studies…will be needed to fully evaluate the hepatotoxicity for rivaroxaban."

4. **Lack of long-term data** – the importance, if any, of obtaining the final clinical data from the ongoing clinical studies of prolonged rivaroxaban administration, considering:
   - The risks are unknown for prolonged administration of rivaroxaban for potential "off-label" uses (e.g, anticoagulation among patients with atrial fibrillation).
   - Prior to the panel J&J was proposing what the FDA described as only "routine" risk management, rejecting the idea of a Risk Minimization Action Plan (RiskMAP, now known as a REMS) because the company believed "routine risk assessment and risk minimization measures, targeted educational activities, and outreach programs can adequately address all the potential safety risks."

5. **Risk:benefit** – whether the benefits of rivaroxaban outweigh the risks, given that:
   - ~800,000 Americans underwent total joint replacement (TJR) in 2005, and rivaroxaban is likely to be widely used because of the convenience of its oral administration and no need for anticoagulation monitoring as with warfarin.
   - Several products are currently marketed for use in the prophylaxis of VTE in TJR patients.
   - The proposed rivaroxaban label generally refers to using "caution" when administering rivaroxaban to patients with renal insufficiency or patients who are concomitantly receiving drugs that may affect hemostasis (e.g., NSAIDs).
   - The proposed label notes that rivaroxaban is "not recommended" for use in patients who are receiving certain medications that interfere with the drug's metabolism or in patients with kidney failure. The proposed label also contraindicates rivaroxaban in "patients with hepatic disease associated with a coagulopathy leading to a clinically relevant bleeding risk."

- The sponsors are not proposing a REMS, though the FDA could require that on its own.
- In the RECORD trials, rivaroxaban had a numerically higher rate of cardiovascular (CV) events, including stroke, as well as abnormal creatinine values. FDA reviewers noted that CV events – MI, ischemic stroke, CV death, or unexplained death – was uncommon in the RECORD studies individually or pooled, but a numeric imbalance in the occurrence of ischemic stroke (0.08% vs. 0.02%) occurred in the follow-up period, "While the rates are low, the imbalance in the occurrence of ischemic stroke in the follow-up period, combined with a general pattern in which most of the rivaroxaban CV events occurring early in the follow-up period (within 10 days following study drug discontinuation) somewhat suggests that ***rivaroxaban may be associated with an increased tendency for thrombotic events in the early post-treatment period***. However, the numbers of patients with these events were very small, and the data appear inconclusive."

Primary Endpoint Results in RECORD Trials

Trial	Composite of all VTE (DVT, non-fatal PE, or death)		p-value
	Rivaroxaban n=6,183	Enoxaparin n=6,200	
RECORD-1	1.1%	3.7%	<0.05
RECORD-2	2.0%	9.3%	<0.05
RECORD-3	9.6%	18.9%	<0.05
RECORD-4	6.9%	10.2%	<0.05

Safety in RECORD Trials

Adverse event	Rivaroxaban N=6,183	Enoxaparin n=6,200	p-value
Any treatment-emergent adverse event	68%	69%	---
Any treatment-emergent serious adverse event	7%	9%	---
Any adverse event resulting in drug discontinuation	4%	5%	---
Death	<1%	<1%	---
ALT elevation	0.3%	0.2%	---
ALT >3xULN + bilirubin >2xULN	0.15% (4 deaths)	0.11% (2 deaths)	---
Ischemic stroke	5 patients	1 patient	---
Abnormal creatinine	10%	8%	---
Bleeding			
Major bleeding	0.39%	0.21%	Nss, 0.08
Bleeding-related death	1 patient	0	---
Major bleeding + surgical site bleeding	1.80%	1.37%	Nss, 0.06
Major or non-major clinically-relevant bleeding	3.19%	2.55%	0.04
Any bleeding event	7.02%	6.47%	Nss, 0.3

Other Efficacy Results in RECORD Trials

Measurement	Rivaroxaban vs. enoxaparin			
	RECORD-1	RECORD-2	RECORD-3	RECORD-4
DVT	0.8% vs. 3.4%	1.6% vs. 8.2%	9.6% vs. 18.2%	6.3% vs. 9.0%
Non-fatal PE	0.3% vs. <0.1%	0.1% vs. 0.5%	0 vs. 0.5%	0.5% vs. 0.8%
Death	0.3% vs. 0.3%	0.2% vs. 0.7%	0 vs. 0.2%	0.2% vs. 0.3%
Proximal DVT	<0.1% vs. 2.0%	0.6% vs. 5.1%	1.1% vs. 23.%	0.8% vs. 1.5%
Distal DVT	0.8% vs. 1.7%	1.3% vs. 5.6%	9.0% vs. 17.8%	5.9% vs. 8.6%
Main secondary endpoint: Major VTE (proximal DVT, non-fatal PE VTE-related death)	Rivaroxaban superior	Rivaroxaban superior	Rivaroxaban superior	Rivaroxaban non-inferior but not superior

The FDA pointed out that the rivaroxaban treatment effect was mainly due to differences in the venographic outcomes, with a reduction in the rates of both proximal and distal DVT, but the "major rivaroxaban treatment effect related to a reduction in proximal DVT detected on venography."

Panel presentation

Dr. Kathy Robie-Shu, medical officer/team leader in the FDA's Division of Medical Imaging and Hematology Products, CDER, provided an overview of DVT and PE treatment in patients undergoing TKR or THR surgery. The issues she emphasized for the panel to consider were:

- Efficacy – venography endpoints were accepted
- Safety – enoxaparin and liver test abnormalities and the appropriateness of a fixed dose for "special populations"
- Regulatory – this is the first oral and has the potential for "extended prophylaxis"

Dr. Lu discussed the safety and efficacy of rivaroxaban. She said there were no important imbalances in the baseline characteristics in the RECORD studies for rivaroxaban vs. enoxaparin. On liver safety she noted that the FDA draft guidance – the same guidance J&J referenced – on liver toxicity warns, "The finding of one Hy's Law case in clinical trials is ominous. Finding two is highly predictive of a potential for severe drug-induced liver injury."

She didn't dispute J&J's figures on the incidence of ALT/TB (total bilirubin) elevations in RECORD, but she pointed out that there was an imbalance of patients with ALT >3xULN + bilirubin >2xULN: 5 vs. 2, and two of these rivaroxaban patients died vs. none with enoxaparin. In the ongoing clinical studies 27 patients have had ALT >3xULN + TB >2xULN:

- 6 in unblinded studies: 3 for rivaroxaban, 3 for the comparator.
- 21 in blinded studies where selective unblinding showed 1 for rivaroxaban and 4 for the comparator.

Dr. Lu also pointed to an imbalance in ischemic stroke with rivaroxaban in RECORD: 0.19% vs. 0.11%.

Dr. Lu's conclusions were:

- *Do the data show efficacy?* Yes, we regard the data supporting the drug's efficacy, based on total VTE.
- *Does rivaroxaban increase bleeding?* Yes. The risk of major and non-major bleeding is increased with rivaroxaban.
- *Does rivaroxaban increase the risk for hepatotoxicity?* We cannot exclude the possibility.
- *Is there increased thrombotic CV risk after rivaroxaban discontinuation?* The data do not exclude this possibility.

Qing Xu, PhD, a statistical reviewer in the FDA's Office of Biostatistics, reviewed the rivaroxaban data analysis. She said the data from the RECORD studies demonstrate the efficacy of rivaroxaban for prophylactic anticoagulation after THR/ TKR surgery. Her question, though, was the extent of the benefit. She said the ***clinically important*** endpoint is symptomatic VTE – not just total VTE which was the primary endpoint – and there was no confirmatory hypothesis test in the statistical analysis plan for each RECORD study, so "any comparison of rivaroxaban with enoxaparin in terms of this endpoint is exploratory and, at best, hypothesis-generating." And she noted that the symptomatic VTE rate was numerically lower with rivaroxaban in all 4 RECORD trials. She added, "Clearly we can see rivaroxaban as numerically higher bleeding than enoxaparin, for all types of bleeding."

On the risk:benefit equation, she concluded that there is:

- Evidence of efficacy of rivaroxaban for anticoagulation prophylaxis in terms of total VTE.
- No evidence of superiority of rivaroxaban vs. enoxaparin for the composite symptomatic VTE or death.
- Consistent evidence of an increased risk of bleeding for rivaroxaban vs. enoxaparin.

Dr. Kate Gelperin, a medical officer in the FDA's Office of Surveillance and Epidemiology (OSE), CDER, reviewed the Agency's ongoing evaluation of a potential severe liver injury signal in the rivaroxaban trials. She noted that Hy's Law-like cases – even very few of them – have often predicted post-marketing serious liver injuries. The estimated mortality is at least 10%. She cited 2 examples:

- **Warner Lambert's (now Pfizer's) Rezulin (troglitazone)**, which was withdrawn from the market after 19 cases of irreversible liver failure. Only 1.9% of patients had ALT >3xULN, and only 0.2% (5 patients) had ALT >30xULN (who turned out in retrospect to be suspected Hy's Law cases).
- **AstraZeneca's Exanta (ximelagatran)**, which was never approved in the U.S. and was withdrawn from the European market due to liver failure. She noted that "no signal for severe liver injury was detected in short-term orthopedic trials, but a strong signal was seen in long-term AFib (atrial fibrillation) trials."

In looking at the RECORD 1-4 data, she offered these comments:

- The current labeling for enoxaparin warns that ALT >3xULN has been reported in 5.9% of patients, and the elevations are generally considered irreversible.
- A J&J expert, Dr. Paul Watkins of the University of North Carolina, Chapel Hill, "presented a different causality assessment, and the FDA has not separately adjudicated these cases; but of 9 cases, 7 were considered possibly related to drug by the liver advisory panel vs. only 3 of the enoxaparin cases."

Dr. Gelperin said the OSE conclusion and recommendation are:

- "A potential signal for severe liver injury with rivaroxaban has not been fully characterized at this time."
- "Complete assessment, fully evaluating pertinent safety data from long-term clinical trials should be undertaken."

Christopher Tornoe, PhD, from the FDA's Office of Clinical Pharmacology, CDER, reviewed the clinical pharmacology of rivaroxaban. He said the bottom line is:

- There is a shallow dose-response.
- The risk of major bleeding increased with increasing rivaroxaban dose/exposure.
- The special populations at risk for clinically-relevant increases in exposure are moderate-to-severe hepatic patients, patients using strong CYP3A4/P-gp inhibitors, and patients with mild-to-moderate renal impairment + moderate CYP3A4/P-gp inhibitors.
- Lower dose strengths are the best option for addressing increased exposure and the risk of bleeding in special populations – and will allow a larger patient population to receive this treatment.

Symptomatic VTE (DVT or PE) and Death in RECORD Trials

Trial	Symptomatic VTE + Death		FDA meta-analysis *	
	Rivaroxaban	Enoxaparin	Hazard ratio	Favors
RECORD-1 (hip)	0.45%	0.67%	0.593	Rivaroxaban
RECORD-2 (hip)	0.41%	1.6%	2.135	Enoxaparin
RECORD-3 (knee)	0.66%	2.1%	0.251	Rivaroxaban
RECORD-4 (knee)	0.79%	1.4%	0.685	Rivaroxaban

* A different statistical approach

JOHNSON & JOHNSON'S PERSPECTIVE

J&J officials and experts did a very thorough, well-organized, and well-orchestrated presentation. They had a large contingent of experts and officials on hand, and they were able to answer or address every question the panel posed.

Briefing documents

In briefing documents prepared for the panel, J&J officials emphasized that rivaroxaban was studied "extensively" – in >50 Phase I studies (with 1,129 rivaroxaban subjects evaluated for safety), four Phase II studies in joint replacement surgery (2,232 rivaroxaban subjects evaluated for safety and efficacy), and four Phase III studies in joint replacement surgery (6,183 rivaroxaban subjects evaluated for safety and efficacy). They concluded, "The results of this program support the efficacy and safety of the fixed 10 mg once daily dosing regimen of rivaroxaban in the proposed indication. Safety data from other clinical studies in other indications, some of which are still ongoing and/or include longer-term dosing, are also supportive."

Compliance with Anticoagulation Regimens

Drug	THR patients	TKR patients
Overall	47%	61%
Warfarin	33%	48%
Low molecular weight heparin (e.g., enoxaparin)	63%	72%

The advantages that J&J emphasized were:

- Once daily dosing.
- Predictable pharmacokinetic (PK) profile.
- Low potential for drug-drug or drug-food interactions.
- No laboratory monitoring or dose adjustments required.

In contrast to the FDA reviewers who found the major benefit was in asymptomatic patients, J&J argued that ***symptomatic*** VTE or death from all causes was statistically significantly lower with rivaroxaban (0.57% vs. 1.32%, hazard ratio 0.42, p<0.001), "This difference was due to an approximately 2- to 3-fold lower incidence with rivaroxaban of all components of the primary endpoint and was consistent for both the THR and TKR studies separately. The cumulative incidence rate curves for rivaroxaban and enoxaparin began to separate shortly after surgery and continued to diverge throughout the entire treatment period with no evidence for any loss of efficacy during the follow-up period."

J&J also contended that asymptomatic distal DVTs tend to progress to proximal DVTs, symptomatic DVTs, and/or PE, "Therefore, the symptomatic event results observed in the RECORD program are entirely consistent with the venographic endpoint results of total VTE and major VTE… Rivaroxaban demonstrates statistically significant superior efficacy for both asymptomatic and symptomatic events compared with enoxaparin after both THR and TKR surgery."

J&J rebutted the FDA's safety concerns, noting:

- **Bleeding** was less with rivaroxaban than enoxaparin in a pooled analysis of the RECORD trials (0.18% vs. 0.37%) for rivaroxaban compared with enoxaparin. The effect "in most subgroups was directionally consistent with the effect observed in the overall population. In addition, the relative risk of bleeding for rivaroxaban compared with enoxaparin was not substantially influenced by concomitant medication use (including NSAIDs)."
- **CV "rebound"** after rivaroxaban treatment was "rare" (0.26%).
- **Liver safety** "has been carefully evaluated in the rivaroxaban development program, and the protection for drug-induced liver injury with rivaroxaban is low."
  - "The incidence of ALT >3xULN did not increase with dose and was lower on rivaroxaban compared to enoxaparin."
  - "In the pooled RECORD studies, (ALT >3xULN was) lower on rivaroxaban."
  - "It is important to note that enoxaparin…is known to be associated with benign ALT elevations."
  - "ALT >3xULN with TB >2xULN was similar in the two groups…(suggesting) that the potential for drug-induced liver injury with rivaroxaban is low."
  - "Additional data from ongoing studies…provide further evidence with respect to the liver safety of rivaroxaban…As of December 5, 2008, a total of 5,865, and 1,557 subjects have been exposed to rivaroxaban for >180 days, and >360 days respectively…The (Phase II) ATLAS-ACS-TIMI-46 study …in patients with acute coronary syndromes (ACS)…received the study drug for six months. In this study, the incidence of ALT >3xULN was similar on rivaroxaban (3.7%) vs. placebo (4.5%)."

The company-proposed risk management program includes, "in addition to routine risk minimization measures…to further assess and mitigate the identified and potential risks…(and) to address the potential for off-label use." The following measures were mentioned:

- Labeling, including a black box warning similar to enoxaparin in patients undergoing spinal/epidural anesthesia or spinal puncture that rivaroxaban increases the risk of spinal or epidural hematoma, which may cause long-term or permanent paralysis.
- Patient package insert.
- Routine pharmacovigilance practices.
- Enhanced pharmacovigilance activities for specific adverse events of interest.

- Drug packaging strategies.
- Commercialization strategies.
- Education and outreach programs.
- Postmarketing utilization study.
- Postmarketing observational study (OUS).

J&J's conclusion was, "The favorable benefit:risk profile of rivaroxaban in DVT and PE prophylaxis after THR and TKR has been demonstrated throughout the RECORD program. Each of the four RECORD studies successfully demonstrated superiority in reducing the incidence of total VTE vs. the comparator…Consistent reductions were also seen in major and symptomatic VTE. These occurred at the expense of a modest increase in bleeding events, most of which had relatively lesser clinical impact than the VTE events…Analyses of the clinical importance of the symptomatic VTE events vs. bleeding events indicate that the events prevented by rivaroxaban are, in general, of greater clinical impact than the bleeding events that occur as a result of treatment, further solidifying the favorable benefit:risk profile of rivaroxaban. Keeping in mind that enoxaparin is an accepted part of standard therapy in the proposed setting of THR/TKR, the results present a compelling argument that the benefit:risk balance of rivaroxaban is favorable. Considering the number of THR and TKR surgeries, the potential public health benefit is substantial."

The presentation to the panel

Dr. Richard Friedman, an orthopedic surgeon from the Medical University of South Carolina (MUSC), reviewed the current use of anticoagulants in total joint arthroplasty (TJA). He pointed out that >300,000 THA and >500,000 TKAs are performed yearly. Patients are admitted on the day of surgery, with a mean length of stay of 3.1 days. VTE prophylaxis is mainly an outpatient event.

Dr. Gary Peters, vice president, J&J, reviewed the rivaroxaban development program. He cited the 52 Phase I studies, 4 Phase II studies, and 4 Phase III (RECORD) studies in the "comprehensive" rivaroxaban program. He said:

- QD and BID dosing were explored, with no clear efficacy and safety differences.
- Efficacy was not strongly related to dose but reduced proximal DVT with increasing dose.
- Bleeding dose was similar to enoxaparin for total daily doses of ≤20 mg.
- "To our knowledge this is the first agent to show a reduction in symptomatic VTE vs. enoxaparin."
- Total daily doses of 5 mg to 60 mg were tested.

Dr. Peters offered these comments on safety:

- There were 2 fatal bleeding events with rivaroxaban. "One was a fatal GI bleed after 6 days of therapy in a patient also getting 2 prescription NSAIDs and an OTC medication containing aspirin."
- Patients in some subgroups (e.g., fragile, age >75, moderate renal impairment) "have documented efficacy benefit and bleeding risk similar to overall."
- "We recommend rivaroxaban not be administered concomitantly with ketoconozole."
- "We do not believe patients with cirrhosis and impaired hepatic (function) should receive rivaroxaban."
- The situations where patients should not be able to take rivaroxaban are likely to be "few."

Advantages and Disadvantages of Current Prophylaxis for VTE

Therapy	Advantages	Disadvantages
Warfarin	Oral Efficacious	INR monitoring Food/drug interactions Slow onset and offset Bleeding complications
LMWH, fondaparinux	Fixed dose, QD No food/drug interactions Safe Efficacious	Injectable Cost vs. warfarin
IPC	Efficacious in TKA if worn 19 hours/day No effect on bleeding Safe	No efficacy in THA alone Not efficacious if worn 13 hours/day Restricted to in-hospital use only Limited use with early PT and D/C

Rivaroxaban Safety in Pooled RECORD Trials

Measurement	Rivaroxaban n=6,183	Enoxaparin n=6,200	Hazard ratio
Any death	0.21%	0.40%	---
Any treatment-emergent serious adverse event	6.57%	8.52%	---
Any adverse event resulting in permanent discontinuation	3.72%	4.65%	---
Any fatal bleeding event	0.03% *	0	---
Critical organ bleeding event	0.05%	0.08%	---
Major bleeding event	0.39%	0.21%	1.84
Major bleeding combined with surgical site bleeding events	1.80%	1.37%	1.31
Major or non-major clinically-relevant bleeding event	3.19%	2.55%	1.25
Any bleeding event	7.02%	6.47%	1.08

* 2 patients died

Rivaroxaban Efficacy Results in Pooled RECORD Trials

Measurement	Rivaroxaban	Enoxaparin	p-value	Hazard ratio
Symptomatic VTE or death	0.57%	1.2%	<0.001	0.42
Symptomatic DVT	0.31%	0.79%	---	0.39
Symptomatic PE	0.16%	0.31%	---	0.52
Death	0.13%	0.26%	---	0.50

On liver safety, Dr. Peters pointed out:

- Rats, mice, and dogs at levels at least 29-times the human dose did not show liver toxicity. "The (animal studies) do not indicate rivaroxaban has the potential for liver toxicity in humans."
- The liver toxicity signal with Exanta was seen at 12 weeks in an AFib study. Rivaroxaban has been studied in twice as many AFib patients (ATLAS-ACS-TIMI-46 trial) with no signal.
- In all completed Phase II and III studies, ALT >3xULN + bilirubin >2xULN is 0.16% for rivaroxaban vs. 0.14% with the comparator. In contrast, with Exanta, the rates were 0.53% vs. 0.08% for its comparator.

Rivaroxaban Liver Safety in Pooled RECORD Trials

Measurement	Rivaroxaban n=6,131	Enoxaparin n=6,131
ALT >3xULN	2.48%	3.70%
ALT >5xULN	0.91%	1.27%
ALT >8xULN	0.29%	0.33%
ALT >10xULN	0.16%	0.15%
ALT >20xULN	0.03%	0.02%
ALT >3xULN + bilirubin >2xULN	0.16%	0.16%

Dr. Watkins, a liver expert, reviewed the hepatic safety of rivaroxaban. He started by pointing out the chemical structures of Exanta and rivaroxaban are different: Exanta is a direct thrombin inhibitor and a prodrug metabolite to melagatran while rivaroxaban is a Factor Xa inhibitor. He then went through the six ALT deaths in great detail, offering other explanations for the deaths such as gastric cancer, pancreatitis, etc. He concluded, "It is unlikely that rivaroxaban-induced liver injury caused these fatalities."

He offered a complicated analysis of liver injury using a method developed by an FDA safety official, Dr. Gerald del Pan, and he used the FDA definition of Hy's Law in a draft guidance on drug-induced liver injury to make the claim that there are no patients in the rivaroxaban program that can be classified as Hy's Law.

The Hy's Law definition he used was:

1. The liver injury should be hepatocellular in nature – alkaline phosphatase (ALP) <2xULN.
2. There should be no more likely alternative cause than drug-induced liver injury.
3. There should be more frequent ALT elevations >3xULN in the treated group vs. the control (referred to as "Temple's Corollary," after Dr. Robert Temple, director of the FDA's Office of Medical Policy and director of the FDA's Office of Drug Evaluation, CDER.

Dr. Watkins said, "My conclusion – which is shared by other liver experts – is that a liver safety signal is not evident from the clinical trial database for rivaroxaban."

- No deaths should be attributed to rivaroxaban liver toxicity.
- There was no imbalance in clinically important liver injuries between rivaroxaban vs. enoxaparin in the RECORDS program or vs. true placebo in the ATLAS clinical trial.
- There was no evidence of increased ALT elevations relative to placebo in the ATLAS trial.

Dr. Peter DiBattiste, Cardiovascular Therapeutics Area Head, Johnson & Johnson Pharmaceutical Research and Development, who was also the J&J "team leader" at the panel meeting, then outlined the company's proposed risk management (assessment and minimization) program for rivaroxaban, and it was exactly as laid out in the briefing documents but with slightly more detail.

Dr. DiBattiste concluded: "Considering all of the data together, rivaroxaban has a compelling benefit:risk when used for prophylaxis of DVT and PE in patients undergoing elective THR or TKR. We believe the public health benefits clearly outweigh the risks."

Public Witness

There was only one public witness at this panel meeting: **David Henry, National Alliance for Thrombosis and Thrombophilia** (NATT), who is himself a warfarin user because of a PE. He said, "The reluctance to follow evidence-based guidelines by orthopedic surgeons is of great concern to us…We don't understand why orthopedists don't implement prophylaxis to a greater extent than they do." He read a letter from Tom Hogan, NATT's secretary who had recently had hip replacement surgery, in which Hogan wrote, "I'm truly dumbfounded that anticoagulation therapy was not routine at (my) hospital…Products like rivaroxaban may well be the wave of the future."

Panel Questions for the FDA and J&J

There has been a lot of back and forth on technical statistical issues. The FDA biostatistician, Dr. James Neaton from the University of Minnesota, has been fairly friendly to the J&J analyses, and less receptive to the FDA statistical approach.

One of the key points that seemed to impress the panel was the 6-month data on ~1,200 patients (800 rivaroxaban, 400 comparator) in the recently completed and unblinded, six-month Phase II ATLAS trial in acute coronary syndrome patients. Only part of this data has been submitted to the FDA so far. J&J said the incidence of ALT >3xULN was similar on

rivaroxaban (3.7%) vs. placebo (4.5%) in this trial, and several panel members seemed to find this reassuring.

J&J's liver expert, Dr. Watkins, said, "I put a lot of faith in the ATLAS data…I can't conceive of a reason why you wouldn't detect an ALT signal in that period. Is 6 months enough? More data are always better, but I'm not aware of any drug that had a problem and didn't demonstrate ALT issues within a six-month trial."

However, Dr. Rieves, head of the FDA division overseeing this drug, commented, "The charge to the committee is (to consider rivaroxaban) based on the RECORD studies and studies before that…That is the agreement (with J&J) and the charge to the committee. We are not ramping up our review… They (J&J) submitted data a month ago (from ATLAS)…It is not the final data. We asked about the ongoing studies (in our questions to the panel). ATLAS, from our perspective, is an ongoing study. We do not have the final data. That is >3,000-patient…It seems ATLAS is very important, but we all need time to review it. The data shouldn't be coming in piecemeal just before a decision time…The agreement was to focus on RECORD and the studies that preceded that."

Asked if ATLAS (II) would suffice if the committee recommends more long-term data, Dr. Rieves said it would, but it is a matter of timing. If the FDA is to make a decision by the PDUFA date, then it probably cannot be made on ATLAS, "We are on a time clock to make a decision on how the application was submitted, not how it was modified. We can't work that way. We can review the data once it is ready to review, but we have to work out the logistics…The conclusion may be that we can't come to a definitive conclusion at this time in the absence of long-term data…but we shouldn't make a decision on long-term (safety) based on 'some' data."

A Phase III ATLAS-ACS-TIMI-46 trial began in December 2008. It is a global study that will enroll ≤16,000 patients. That data are expected to be available in 2011, but it is an event-driven trial, so timing could change.

There was also "debate" over the adjudication of some of the liver-associated deaths. An FDA reviewer took one view (concern, possible liver toxicity), and the company and its liver experts took another (no liver toxicity proven). An FDA expert, Dr. John Senior, said, "This (type of determination) is a fine art, not a science yet, so we have to be careful about the adjudication…I am impressed with the ATLAS data, which I saw for the first time this morning…It looks good, but I want to see more. I'd like to see the long-term data. We should have learned a lesson from ximelagatran (Exanta). We didn't see the signal (with that) in the short-term or the two-week knee study, but we did begin to see the problem at >5 weeks in AFib. I'd like to see those (long-term rivaroxaban) data before I'm convinced there is no signal…If it can be shown the drug is saving more lives than it is risking, then I would think a reduction in mortality would trump the risk of liver injury. But I haven't been convinced those data are real. I think we need to see that…I would like to see a drug approved that really saves lives and has more benefit than risk."

Dr. Sanjay Kaul from Cedars-Sinai Heart Institute in Los Angeles had some tough questions for the panel on the value of the drug vs. the harm. He was trying to get a handle on the relevance of VTEs vs. bleeding by estimating case benefit and case fatality rates.

Panel chair Dr. Michael Lincoff, an interventional cardiologist from the Cleveland Clinic, wondered why J&J didn't have anyone from the company liver advisory panel which adjudicated the liver diseases address the panel, "It is striking you had a liver panel and never presented any of the data from that panel." J&J didn't directly respond.

J&J officials also defended their choice of the 10 mg QD dose. They insisted there is no significant added benefit from higher doses but an increased risk of bleeding. And they said that a lower dose did not have the efficacy of the 10 mg dose. An official said, "We would like to keep exposure to 10 mg BID and lower range…We had very good efficacy with (10 mg in) all the four (RECORD) studies and a favorable safety profile as well. In Phase II we looked at BID dosing and splitting the dose. The efficacy and safety are not very different. There was nothing definitive, but we didn't see differences between BID and QD…and that has been our experience in ATLAS… which is a little counter-intuitive."

Dr. Lincoff also expressed surprise at the lack of compliance by orthopedic surgeons with prophylaxis guidelines. He asked why that is: Is it compliance or concern about bleeding into the joint? If it is convenience, rivaroxaban might help; if not, it probably wouldn't help boost orthopedic surgeon compliance. Dr. Harry Skinner, an orthopedic surgeon from the University of California, Irvine, said it is surgeon focus on wound draining or re-operation, not stroke or MI. Dr. Michael Mayor, an orthopedic surgeon from Dartmouth Hitchcock Medical Center, said, "When I had my knee replaced, I was on prophylaxis, and I was reluctant to given myself injections. It is difficult to get patients to subscribe to an injectable. I think it would be a significant advantage to have a more convenient technique." Dr. Brian Gage from Washington University School of Medicine added, "Orthopedic surgeons don't target an INR of 2.0-3.0. It is clear the primary reservation of orthopedic surgeons is the fear of hemorrhage, and to the degree that is true, rivaroxaban doesn't directly address that."

Just before the panel began discussion of the FDA questions, Dr. Richard Pazdur, director of the FDA's Office of Oncology Drug Products – and Dr. Rieves boss – addressed the panel. He talked about the ATLAS trial and the "convenience" of rivaroxaban, redirecting the panel a bit. In fact, his comments appeared to have substantial influence on the panel's deliberations afterwards:

- "A lot of focus has been on the (regulatory) timeline. What we are really interested in is doing the right thing. If in your discussion and deliberation, you think we need

to review this (ATLAS) data, we want to hear that. If to make a characterization on this drug – even for short-term – we need this additional data, we want to hear from you…There are regulatory ways of handling that. It is not an issue of a deadline or a timeline. It is doing the right thing. If we need more time to review this data or to even have the entire trial, we can do that."

- "On the issue of convenience, the Food and Drug Law states safety and efficacy. It doesn't weigh anywhere in there convenience. In making a regulatory decision, you have to first make up in your mind, 'Do you have a safe and effective drug here?' Then, you can consider convenience. But only after you make up your mind that this is a safe and effective drug. If we start on approving more convenient drugs without certainty on safety and efficacy, we could be approving more convenient toxic placebos. The issue here is safety and efficacy first. Then, you could get into any discussion of convenience."
- "First, you are to be certain in your mind this drug is safe and effective for the indication. If you feel you can't make that decision now and need more data from the Coumadin-controlled trials, we want to hear that. It is not about a PDUFA deadline. And it is not about convenience. It is about safety and efficacy. That has to be decided first, and then discussion of convenience can be entertained."

PANEL CONSIDERATION OF FDA QUESTIONS

QUESTION 1. Do the available data preclude approval of rivaroxaban at this time for the prophylaxis of VTE among patients undergoing hip or knee replacement surgery due to the potential risk for severe hepatotoxicity?

The panel was mixed, but generally the answer was NO.

Panel comments included:

- *Dr. Sidney Wolfe, director of the Health Research Group of Public Citizen and the panel's consumer representative:* "We shouldn't rush into this…There are longer studies that will yield more and longer data. There aren't enough available data on the signal of hepatoxicity… Even though technically approval is for relatively short-term use, this has been exciting people for enough time that if it is approved, I would bet a large amount of money that within a short time it would be widely used off-label in a way we don't have data."
- *Dr. Ronald Fogel, a gastroenterologist from Chesterfield MI:* "I do not believe the data preclude the approval. The animal studies did not show any hepatotoxicity…However, I have reservations about whether the drug should be approved because:
  1. One probable case of hepatotoxicity is worrisome.
  2. There are six Hy's Law-criteria patients, and that does represent a signal we need to look at.
  3. I have safety concerns should the drug be approved ….about the adequacy with which patients will be dosed and observed.
  4. Is the study sample representative of the larger population? We never got the data on underlying liver disease or use of alcohol."
- *Dr. Emil Paganini, a nephrologist from Chesterland OH:* "This is short-term use. I think the data presented for that particular use is adequate to allow this to be approved."
- *Robert Dubbs from West Palm Beach FL, the patient advocate:* "I don't think you should preclude approval… I'm not able to put this all together and say there is a statistical problem with the study drug."
- *Dr. Skinner, an orthopedic surgeon:* "The data don't preclude approval…I think it is fairly safe from a bleeding standpoint, and I think some of the worries we hear around the table are from a group of doctors who are going to use it long-term, and I don't think we should be swayed by the potential for some doctors to use it off-label…The band-aid people (J&J) will price it high, and the insurance companies will do all they can to prevent us from using it, and the pharmacists will try to prevent us from using it, so I think long-term use is less of a problem than you think."
- *Panel chair Dr. Lincoff:* "I don't think the data preclude approval. I do wonder how much responsibility we have to protect against what is likely to be off-label use. The impetus to use this considerably longer than the label will be a lot…(That) is a reality. The Watkins (J&J) presentation showed very plausible reasons why many of these Hy's Law-like cases were not...but a blinded liver panel did suggest there were more likely related cases in the rivaroxaban group than control, so…there may be a question, and it would be nice to resolve that. The pending longer-term data…are good but haven't been the subject of a thorough review, so they don't preclude approval, but there is a note of caution."
- *Dr. Peter Gross, an infectious disease specialist from Hackensack University Medical Center:* "I don't think you can conclude rivaroxaban is (dangerous) until there is a head-to-head study with warfarin."
- *Edward Krenzelok, PharmD, a toxicologist from the University of Pittsburgh Medical Center:* "I think we would be prudent to recommend long-term surveillance to be sure this is not just background noise."
- *Dr. Henry Black, a nephrologist from New York University School of Medicine:* "Longer-term data are critical here, and we will have it, and we should ask for more."

- *Dr. Mori Krantz, a cardiologist from Denver CO:* "Overall, there were twice as many deaths with enoxaparin (as with rivaroxaban) in the safety database, and I think that is a little reassuring. I think, despite that, there is strong interest for all of us to follow this long-term – because troglitazone and ximelagatran are in our minds."
- *Biostatistician Dr. Neaton:* "I think we should deal with the data and the indication we have in front of us…There are always more data down the line."

QUESTION 2. The proposed rivaroxaban dose regimen is for a maximum of 14 (knee surgery) or 35 (hip surgery) days. Are the data from the ongoing (long-term) clinical studies essential to assess rivaroxaban safety prior to its approval for the prophylaxis of DVT and PE among patients undergoing hip or knee replacement surgery?

Consensus was NO.

Panel comments included:

- *Panel chair:* "The FDA is saying you can't be reassured by ATLAS."
- *Dr. Neaton:* "I'm happy there is post-approval randomized clinical trials, and that we will see the results down the line."
- *Panel Chair:* "If you hadn't seen the (ATLAS) data, would you feel as sanguine?"
- *Dr. Neaton:* "Yes, because of how this drug is proposed to be used, and I'm not going to speculate on how it is going to be used long-term off-label."
- *Dr. Gage:* "I would be comfortable with (use for) 14 days for TKR but not necessarily 35 days for THR if I hadn't seen ATLAS…When someone is undergoing knee surgery, we often prescribe anticoagulant therapy for 14 days. And knowing we have data to 35 days gives me confidence that knee patients will do well and be at low risk of liver toxicity. But patients undergoing hip surgery, I guess I have a little more reservations. They sometimes get more than 35 days (of prophylaxis), and we don't have much long-term data, so for them the question is not as clear."
- *Jurgen Venitz, a pharmacologist from Virginia Commonwealth University School of Pharmacy:* "The data on long-term studies are not essential, just helpful. So, they should not preclude approval."

QUESTION 3. Do the available clinical data demonstrate a favorable risk:benefit profile for rivaroxaban in the prophylaxis of VTE in patients undergoing hip or knee replacement surgery?

VOTE: 15 YES, 2 NO. (*1 member did not vote.*)

Panel comments included:

- *Dr. Darren McGuire, a cardiologist from the University of Texas Southwestern Medical Center in Dallas:* "I don't think venography is an acceptable endpoint going forward…My vote was largely driven by aggregated pooled data."
- *Dr. Fogel:* "I do have reservations on toxicity, but I don't think that it is strong enough to prevent approval."
- *Dr. Krenzelok:* "I do think this (rivaroxaban) provides patients with a more convenient way to dose."
- *Dr. Neaton, the biostatistician:* "I voted yes, and I think the risk:benefit profile laid out by the sponsor was very helpful in making my vote."
- *Dr. Wolfe (a NO vote):* "I voted no partly because of the statistical analysis where it was stated there is no evidence of superiority…Second, I am concerned about the bleeding. And third, I am very uncomfortable about the certainty of long-term use and the absence of long-term safety data on hepatotoxicity."
- *Panel chair:* "I think the data are actually compelling. The surrogate endpoints and harder endpoints line up… The net clinical benefit, including bleeding, is still beneficial. The liver signal is very weak and warrants continued surveillance in upcoming clinical trials and practice but does not preclude approval. And I would encourage on-label rather than off-label use."
- *Dr. Gage:* "Yes, but I would be uncomfortable if this drug were used in patients with possible liver disease or in patients at high risk of bleeding."
- *Dr. Krantz:* "I have some trepidation, but the trial design was excellent."
- *Dr. Paul McCormick, a neurosurgeon from Columbia University:* "The risk:benefit profile for the stated indications is very fair. As a neurosurgeon, I would not consider this medication in a neurosurgical population."
- *Dr. Kaul (another NO vote):* "Trials that use clinically important outcomes to assess both efficacy and safety would yield more relevant results…I had issues on the choice of endpoints…The FDA should provide updated guidance on whether venography endpoints are a valid surrogate for clinical practice…I had issues on pooling…I didn't see any signal that would exclude the possibility of hepatotoxicity and cardiotoxicity…I saw a risk:benefit that was a wash, and this is why I voted no."
- *Patient advocate:* "I felt the evidence for short-term use and the risk:benefit was compelling…As a chronic Coumadin user, I am excited by the prospect of not having to have blood drawn every two weeks."

QUESTION 4. Rivaroxaban clinical pharmacology data indicate that, based on systemic exposure, a lower dose would optimize benefit:risk in patients with renal and/or hepatic dysfunction and/or on CYP3A4, P-gp inhibitors. In addition to the proposed 10 mg dose of rivaroxaban, should a lower dose be available to treat this population?

VOTE: 5 YES, 9 NO, 3 ABSTAINED.

(The five YES votes were Dr. Wolfe, Dr. Venitz, Dr. Skinner, Dr. Paganini, and Dr. Mayor. The three abstentions were Dr. Kaul, Dr. Gage, and Dr. Fogel. One panel member did not vote.)

FDA officials argued that they don't need additional data to approve a lower dose, but the panel didn't really buy that, with several members saying they would want additional data first. However, J&J made a strong argument that, even though it is counterintuitive, the higher exposure with the 10 mg dose in "at risk" patient populations such as the renally impaired does not appear to cause increased safety concerns, and a lower dose may actually compromise safety.

Before the vote, the panel discussed a lower dose, and their comments included:

- The FDA's Dr. Tornoe, a pharmacologist, argued that there are patients where drug exposure is increased two-fold or more, so a lower dose should be available for those patients. He noted that the FDA doesn't necessarily need data on a lower dose to approve it and has done that in the past with other drugs.
- J&J officials insisted that this was a very small population (perhaps 5%) and that it would be better to deal with them by using a different drug, not lowering the rivaroxaban dose. An official said the company is also concerned that if a lower dose were available, people who should get the higher dose might be given the lower dose, "We are willing to discuss other options…but we favor the 10 mg dose (only)."
- *Dr. McGuire:* "I think if we had a lower dose alternative available, a surgeon would very commonly choose the 5 mg dose, and we may jeopardize patients…This is going to be a fairly expensive medication, and giving patients the opportunity to cut something in half and save money …could encourage patients to use a lower dose (to save money)…If I had a lower dose, I might be inclined to use it more off-label."
- *Dr. Gage:* "I can see not having a 5 mg, but if we don't have the option in older, sicker, more petite patients, we might regret it later…I would like to have the ability to break a 10 mg in half if I am taking care of a patient who is elderly, ESRD, or petite, so I don't cause harm."
- *Dr. Paganini:* "I think the availability of a lower dose would seem to be a nice thing to have in (some) patients."
- *Dr. Black:* "To use 5 mg, we have to study it."

After the vote, panel members offered these comments:

- NO – *Dr. Black, nephrologist:* "I'm concerned we may lose some efficacy, and I'm not sure we have that much less risk."
- NO – *Dr. McCormick, neurosurgeon:* "I think the disadvantages of a separate 5 mg tablet on the broad level outweigh the ability to titrate down. If the patient is seen as at increased risk of hemorrhage, the drug just shouldn't be used."
- NO – *Dr. Neaton, biostatistican:* "I am not persuaded by the precedent of other drugs…I don't think the issue has been vetted adequately…I don't think the Agency presented any evidence to support that decision."
- NO – *Dr. Swenson, pulmonologist:* "I think for those with increased risk of bleeding, there are alternatives available."
- NO – *Dr. McGuire, cardiologist:* "While that may reduce the bleeding risk, we may also jeopardize efficacy."
- NO – *Patient advocate:* "Although it may be a good thing, I don't think we have enough data to say it should be approved."
- YES – *Dr. Paganini, nephrologist:* "I think safety is more important than efficacy, and 5 mg is probably better for a safer drug rather than a more effective drug."
- YES – *Dr. Mayor, orthopedic surgeon:* "If a 5 mg dose is appropriate for some patients, I believe a 10 mg tablet that could be divided in half is a practical arrangement to make a 5 mg available."
- YES – *Dr. Skinner, orthopedic surgeon:* "I think there is a chance it might be dosed sooner (after surgery) if there were a 5 mg dose. I don't think anyone would give full dose 6 hours after surgery."
- YES – *Dr. Venitz, pharmacologist:* "There is evidence of an increased incidence of bleeding from drug/drug interactions that could be managed with a smaller dose."

FDA AND COMPANY REACTION TO THE PANEL MEETING

The FDA's Dr. Rieves said his take-away message from the panel was: "There were mixed responses, but, on the whole, my sense was that most of the members were comfortable with the existing data (without ATLAS)." Dr. Rieves insisted that the ATLAS data were not given to the FDA in a format that can be analyzed by the Agency, "The data with the original application are what we review. The data that come later are a snapshot, a summary. We will have summary data from ATLAS, but we don't get it to the same degree as the original data so…even though the (ATLAS) study is completed…the analysis is ongoing…We will get that data. It is a matter of timing…We will talk about this. Everyone hears something different. And the reviews are ongoing and not

completed yet. Whether ATLAS is determined essential or the ROCKET data are essential to an ongoing (FDA) decision, there is not a definitive answer yet…My perception is the committee is favorable to the existing data, but the actual outcome of the review is pending."

Asked when he expects to have the complete ATLAS analysis from J&J, Dr. Rieves said simply that, "I wish we knew that." However, J&J officials insisted the ATLAS trial is completed, and the final report is in progress. J&J's Dr. Peter DiBattiste said, "The relevant liver safety data have been unblinded…If we had a question about the potential for hepatotoxicity, we would not be moving forward in the way we are…In ATLAS, which was placebo-controlled, there was no evidence of 'Temple's Corollary' (a statistical warning sign of liver toxicity). That honestly gave us great confidence in moving forward."

Asked if it was his sense that the advisory committee wants the FDA to have the ATLAS data before making its final decision, Dr. Rieves said, "I think we will go back and talk internally about what each of us heard (from the panel)…But, in general, considering the response to the question (on whether the available data preclude approval at this time) and the overall vote, my perception is the committee was comfortable with the RECORD data plus the PK studies."

J&J's Dr. DiBattiste was "pleased" with the panel, "It was a good discussion. Many of the issues presented by us and the FDA were considered. My sense was that the general sentiment was that whatever might have been a concern was not an impediment to considering this indication for approval."

Asked if any additional steps are expected other than those outlined in the company's risk mitigation plan to inhibit off-label use of rivaroxaban long-term, Dr. DiBattiste said, "We definitely plan to implement the elements we listed in our risk assessment and mitigation plan. We will do packaging strategies, monitoring carefully for off-label use, share information with physicians, pharmacists, and patients (in the patient package insert). We will also interact with third payers, informing them on appropriate durations of use. Our strong interest is that this drug be used on-label for the indication we are filing for…We want to put this drug optimally in the hands of the patient who will derive benefit and strongly discourage use in populations that are inappropriate."

Asked about J&J's reluctance to agree to the FDA's request for either a 5 mg dose or the scoring of the 10 mg tablet, Dr. DiBattiste said, "In a number of subpopulations where one would predict increased exposure and one (might expect) an adverse risk:benefit impact, we didn't see it. In moderate renal insufficiency patients, in the elderly patients, in the fragile patients, all of those patients are predicted to have a higher exposure. Yet, in each one of those subgroups (799 patients the smallest), the benefit:risk was preserved…Certainly, there was no loss of benefit…That called into question an adjustment in dose based on clinical pharmacology data only. We have a genuine concern that if the dose were reduced, there might be a loss of benefit in the benefit:risk that we couldn't anticipate. Having said that…we do acknowledge there are some subpopulations where the exposure will be >2-fold greater, and there we agree 10 mg would not be appropriate, and we think those populations are smaller, and it is best to recommend against use in those patients."

Dr. DiBattiste said Bayer gets a 30% royalty on U.S. sales of rivaroxaban. Bayer also will help with U.S. sales by detailing "designated hospital accounts" in the U.S.

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