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Quick Pulse

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THE FDA'S CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE REJECTS ASTRAZENECA'S EXANTA

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September 10, 2004

It was clear from the advisory committee's briefing documents that AstraZeneca would have a difficult time getting panel – and probably full FDA – approval for Exanta (ximelagatran), and the actual meeting went even worse than expected. The panel determined nearly unanimously that Exanta is not safe and that the benefits do not outweigh the risks in any of the three proposed indications. The panel was concerned about liver damage and possibly a heart attack risk when used short-term. It is now virtually certain that the FDA will not approve Exanta, and the outlook for an approvable letter also is dim. There is little question that AstraZeneca will have to do additional trials to get approval for even a highly restrictive label. But will more trials resolve the safety issues? And will AstraZeneca want to invest further in this drug?

Exanta is a fixed-dose, oral, twice-daily anticoagulant. It is a prodrug of melagatran, a potent, reversible, competitive, and direct inhibitor of thrombin. AstraZeneca is seeking FDA approval to market Exanta to adults for three indications:

1. **VTE-T:** Short-term prevention in patients undergoing total knee replacement (TKR) surgery – at a dose of 36 mg BID for 7-12 days. Support for this came from the EXULT-A and EXULT-B trials.
2. **VTE-P:** Long-term secondary prevention of VTE after standard treatment for an episode of acute VTE – at a long-term dose therapy of 24 mg BID for 18 months. Support for this came from the THRIVE-III trial.
3. **AF:** Prevention of stroke and other thromboembolic complications associated with atrial fibrillation (AF) – at a life-long dose of 36 mg BID. Support for this came from the SPORTIF-III and SPORTIF-V trials.

Exanta would compete with warfarin in all these indications. For VTE in TKR patients, two subcutaneous injection agents are FDA-approved: (1) Sanofi-Aventis's Lovenox (enoxaparin sodium), a low molecular weight heparin (LMWH), and (2) Sanofi-Aventis's Arixtra (fondaparinux sodium), a synthetic inhibitor of activated Factor X (Xa). Only warfarin is approved for long-term thrombo-prophylaxis after treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE), or for chronic thrombo-prophylaxis in patients with AF.

AstraZeneca's clinical studies were designed to demonstrate that Exanta, without coagulation monitoring or dosage adjustment, offers:

- **Superiority** to placebo in long-term secondary prevention of VTE.
- **Superiority** to warfarin in prevention of VTE in patients undergoing knee replacement surgery.
- **Non-inferiority** to warfarin in prevention of stroke associated with AF.

THE FDA PERSPECTIVE

Unofficially, an FDA official said the Agency is taking the unmet medical need aspect for this drug seriously, and the Agency would like to approve Exanta because it is oral and the first new anticoagulant in a long time, especially since there is nothing close behind Exanta in the pharmaceutical industry pipeline. However, the agency is struggling with safety issues.

Exanta and melagatran were studied in five major trials plus 77 additional clinical studies involving 30,698 patients, and 17,593 of these received Exanta or melagatran. Long-term, 6,931 patients received ximelagatran (5,024 for at least six months and 3,509 for at least one year).

In the briefing documents and oral presentations, the FDA laid out its problems and concerns with Exanta, both on efficacy and on safety. The FDA statistician concluded that Exanta:

- Is superior to warfarin (1) at 36 mg BID (but not 24 mg BID) for short-term treatment of VTE and/or all-cause mortality and (2) at 24 mg BID for longer-term treatment of VTE.
- Is not safer than warfarin.
- Is not non-inferior to warfarin for AF.

Among the FDA concerns with Exanta are:

- **Hepatotoxicity.** FDA reviewers are worried about the safety of both short-term and long-term Exanta use, particularly with regard to hepatotoxicity.
  - **Short-term**. In the TKR studies, an imbalance in ALT >3xULN was observed at the follow-up visit (approximately six weeks after surgery) in Exanta patients. The Agency does not know whether delayed onset of severe liver injury could occur after short-term Exanta treatment because no additional, routine study visits were conducted in the TKR trials.
  - **Intermediate-term**. The Agency anticipates physicians will want to treat some TKR patients for a longer period (>12 days) with Exanta, but is concerned that the risk of severe liver injury could increase with longer duration of ximelagatran therapy, even during the first month. Thus, the FDA reviewer concluded, "'Short-term' duration of use after TKR would need to be strictly limited to prevent potential severe liver injury."
  - **Long-term.** In the long-term trials, the initial signs of liver injury during the first month of Exanta therapy in 6 of 37 patients who went on to develop severe liver injury (ALT >3xULN and bilirubin >2xULN) suggest that severe liver injury can potentially begin during the first month of treatment.
- **Risk management.** The FDA reviewers questioned the adequacy of AstraZeneca's proposed risk management program for hepatotoxicity.
- **Myocardial infarction** (MI). The agency found a possible increased risk of MI/coronary artery disease (CAD).
- **Overall risk:benefit assessment**.
- **Bleeding.** A lack of methods to control excessive bleeding with Exanta should it occur.

Indication #1: Short-Term Use at 36 mg BID for 7-12 days.

A dose of 36 mg BID was requested for short-term therapy (7-12 days) of:

- Venous thromboembolism (VTE), defined as deep vein thrombosis (DVT).
- Pulmonary embolism (PE).
- Both VTE and PE.

a. Efficacy: Exanta met the primary endpoint of incidence of total VTE and/or all-cause mortality. The FDA concluded that Exanta was superior to warfarin in reducing total VTE and/or all-cause mortality [21.7% Exanta and 30.2% for warfarin ($p<0.001$)], but a pooled analysis of the two trials found the benefit was mainly due to a reduction in asymptomatic distal DVT **diagnosed by venography** and this was "**not clinically meaningful**." There were no clinically or statistically significant differences between ximelagatran and warfarin groups in reducing the frequency of proximal DVT, PE, and/or all-cause mortality.

In support of this indication, AstraZeneca completed three Phase III studies vs. warfarin with a total of 5,284 patients: EXULT-A (36 mg BID), EXULT-B (36 mg BID), and SH-TPO-0006 (24 mg BID). They were designed to demonstrate that Exanta, without coagulation monitoring or dosage adjustment, offers **superiority** to placebo in long-term secondary prevention of VTE.

The FDA cited several major problems with using warfarin as the active comparator in these trials:

- Warfarin is not approved for this short-term indication.
- Warfarin takes longer (about 3-5 days) to reach a therapeutic level, while Exanta reaches therapeutic levels within hours.
- Mean days of exposure were longer with Exanta (8.1 days vs. 6.7 days for warfarin).
- 33.1% - 35.2% of patients receiving warfarin had an INR less than 1.8 at postoperative Day 3, and 24.0% - 26.9% of patients receiving warfarin had an INR less than 1.8 at end of treatment (Days 7 - 12). Because of the superiority study design, however, efficacy results for Exanta may still be acceptable, since warfarin may be considered to be placebo.

b. Safety: Bleeding, liver toxicity, and MI/CAD were noted. The conclusions were that there is a two-fold higher incidence of major bleeding events, a higher incidence of ALT >3xULN, a potential for duration of treatment to be >12 days in clinical practice, and a ~3-fold higher incidence of acute MI/CAD.

FDA View of Exanta Bleeding Events with Short-Term Use

Adjudicated bleeding events	Exanta 36 mg BID n=1,913	Exanta 24 mg BID n=1,097	Warfarin (dose adjusted) n=2,978
Major or minor bleeding	5.1%	5.7%	4.3%
Major bleeding	0.9%	0.9%	0.5%
Fatal bleeding	0.1%	0	0

FDA View of Liver Toxicity with Short-Term Use

EXULT-A+B Trials	Exanta 36 mg BID	Warfarin
Patients with ALAT >3xULN		
7-12 days	.72%	1.0%
4-6 week follow-up	0.45	0.05%

FDA View of MI/CAD Adverse Events with Short-Term Use

Adverse Events	EXULT-A+B Trials	
	Exanta n=2,677	Warfarin n=1,907
MI	16 patients (0.60%)	4 patients (0.21%)
Other CAD (angina/ischemia)	4 patients (0.15%)	1 patient (0.05%)
TOTAL	20 patients (0.75%)	5 patients (0.26%)

Indication #2: Long-Term Use at 24 mg BID for 18 months for VTE-P.

A dose of 24 mg BID was requested for longer-term therapy (18 months), after standard treatment for an episode of acute VTE. The only trial supporting this indication was the 18-month THRIVE-III (SH-TPV-0003) study of 1,233 patients (468 on Exanta 24 mg BID and 435 on placebo).

a. Efficacy: The FDA concluded that Exanta met its primary endpoint in this trial, significantly reducing the recurrence rate of symptomatic, objectively confirmed VTE vs. placebo at 18 months.

18-Month Results of THRIVE-III

Measurement	Exanta 24 mg BID	Placebo	p-value
VTE events	12	71	---
Primary endpoint: Cumulative risk of VTE	2.8%	12.6%	<.0001
PE events	2	23	---
Secondary endpoint: All-cause mortality	1.1%	1.4%	Nss

b. Safety: No specific safety issues were raised about this trial.

Indication #3: Long-Term Use at 36 mg BID for >12 months for AF.

The proposed dose for the prevention of stroke and other thromboembolic complications associated with AF was 36 mg BID life-long. Two pivotal, non-inferiority Phase III studies of 36 mg BID vs. warfarin in a total of ~7,300 patients were conducted, SPORTIF-III and SPORTIF-V.

a. Efficacy: The FDA questioned the efficacy of Exanta in AF. SPORTIF-III and SPORTIF-V produced divergent results, and the FDA concluded that the pre-specified 2% non-inferiority margin in AF trials was too liberal. An FDA reviewer concluded: "Based on one double-blind study of Exanta versus…warfarin, there is very little evidence that Exanta is effective at reducing the risk of the combined incidence of stroke or systemic embolic events…We have a scenario where the magnitude of the effect of warfarin versus placebo is not precisely known for this patient population. Moreover, warfarin was numerically better than Exanta (using the point estimate) in the double-blind study, and the difference was nearly statistically significant." The FDA statistician agreed: "Exanta was not shown to be superior to warfarin in either the open-label study (SPORTIF-III) or the double-blind study (SPORTIF-V). The margin for concluding non-inferiority (a risk difference of 2%) was too large and was calculated based on an assumed event rate that was much larger than was observed in SPORTIF-V. The efficacy results of the two studies were quite different...There is no obvious reason for the difference in the efficacy results between the two studies based on patient demographics. The only obvious difference between the two studies is that one was open-label and the other double-blind."

FDA View of the 12-Month Results of SPORTIF-III and SPORTIF-V

Measurement	SPORTIF-III (open-label)		SPORTIF-V (randomized)	
	Exanta 36 mg BID	Warfarin	Exanta 36 mg BID	Warfarin
Primary endpoint: Composite of all strokes (fatal and non-fatal)	1.64%	2.29% (p=.10)	1.61% (p=.133)	1.16%

In these SPORTIF trials, AstraZeneca used a pre-specified non-inferiority margin of 2% in the event rate. However, the FDA commented, "This margin was not agreed to by the Agency and its derivation from referenced historical trials is unclear. A margin of that size could leave open the possibility that ximelagatran is only half as effective as warfarin and still be considered 'non-inferior'…While the two studies could be considered 'successes' based on the sponsor's pre-specified margin, the margin chosen was too liberal." In another

document, the FDA noted, "The lower limit of the confidence interval (the best case scenario for Exanta) would give a miniscule benefit to Exanta over warfarin. The upper limit is below the non-inferiority margin of 2% that was pre-specified by the sponsor, but reflects a potential loss of about 1% of the effect of warfarin. The non-inferiority margin of 2% may be too liberal and earlier letters from the FDA to the sponsor conveyed this."

The FDA statistician concluded, "The method that the sponsor used to define the hypothesis for non-inferiority is not valid because it was based on an assumed event rate that was very different from what was actually observed in the trials. A more reliable way of defining the hypotheses would be based on the risk ratio. Using the same distributional assumption that the sponsor used (exponential event times), the confidence interval for the risk ratio is (0.91, 2.12). Therefore, the SPORTIF-V trial does not rule out a two-fold risk in the Exanta group compared to the warfarin group…There is a pretty good case from this data that warfarin is actually superior to Exanta…and no evidence that Exanta is non-inferior to warfarin unless one uses a very large margin that is not supported by the historical studies of warfarin compared to placebo."

b. Safety: Liver toxicity, withdrawal, and MI/CAD were all FDA concerns. It could not be ruled out that the risk of stroke/SEE was two-fold greater vs. warfarin. The FDA reviewer cited ***three case studies where Exanta patients died of coagulopathy or liver failure***. He concluded there is a higher incidence of severe liver injury – including three deaths – despite LFT monitoring, a higher incidence of withdrawal due to adverse events, and a higher incidence of acute MI/CAD with Exanta in the VTE population.

FDA View of Exanta Liver Toxicity with Long-Term Use

ALT elevation	Exanta n=6,948	Comparators n=6,230
ALT >3xULN	7.8%	1.1%
ALT >3xULN + bilirubin >2xULN	0.53%	0.08%

FDA View of Exanta Discontinuations Due to Adverse Events with Long-Term Use

Adverse Event	Exanta n=6,931	Comparators n=6,216
Total discontinuations for adverse events	17.2%	12.9%
LFT abnormal	4.6%	0.3%
Bleeding	1.2%	1.9%
Cerebrovascular disorder	1.0%	0.9%
DVT/PE	0.6%	1.8%

An FDA official from the Division of Drug Risk Evaluation noted that:

- Substantial risk of severe liver injury was seen with long-term exposure.
- 1 in 200 Exanta patients experienced severe liver injury (0.5% vs. 0.08% with comparator).
- Fatal liver injuries occurred.
- 39% of patients failed to discontinue the study drug when specified (due to increased ALT).
- There was a rapid tempo to the liver injury. In some cases, near normal ALT rose to very high levels in <30 days, and a rise of bilirubin occurred after stopping the drug.
- Currently, there are no risk management tools proven to prevent the risk for rapidly progressive severe hepatic injury (based on FDA experience with drugs that cause idiosyncratic liver injury). Limiting the usage of a drug on a population basis has been associated with a marked decrease in reports of liver failure post-marketing (e.g., trovafloxacin, pemoline). The experience with Rezulin (Pfizer, troglitazone) and Duract (Wyeth, bromfenac) show that the track record for transaminase monitoring to prevent severe drug-induced liver injury has not been convincingly demonstrated.

An expert from the University of North Carolina also addressed the liver toxicity issue, noting:

- Drugs capable of causing idiosyncratic severe hepatocellular injury:
  - Have increased incidence of ALT elevations >3xULN vs. placebo
  - The majority of patients experiencing ALT elevations are not at risk of developing significant liver injury
- ALT elevations are not very predictive. The concern rises with the higher the ALT (>8xULN) or when accompanied by hypersensitivity signs or symptoms. "Hy's Law" states that ALT >3xULN combined with bilirubin >1.5xULN is the most predictive "signal."
- The take-home messages are:
  - Isolated ALT elevations are difficult to interpret, but >8xULN or elevations associated with hypersensitivity signs and/or symptoms raise concern
  - The highest concern is bilirubin elevations in a setting of a hepatocellular injury (high ALT, ~nl alk phos)
  - The ability to predict true liver risk from safety databases is imperfect

Overall Safety

Short-term (<35 days) Safety

The FDA concluded: "These studies raised some safety concerns for use of oral ximelagatran 36 mg BID for 7-12 days after surgery (beginning the morning after surgery) in the prevention of VTE in patients undergoing elective knee replacement surgery. There is a potential risk of higher coronary artery disease adverse events, including acute

myocardial infarction. Potential for long-term use (>12 days) that will cause liver toxicity is high. Also, major bleeding events were more common in patients treated with ximelagatran than in patients treated with warfarin."

Longer-term Safety (> 35 days)

The FDA concluded: "Considering ximelagatran as an anticoagulant with potential to treat MI, these results are worrisome…Based on the observation of Hy Zimmerman (Hy's Law) that at least 10% of individuals with severe drug-induced liver injury progress to liver failure, liver transplant, or death, ximelagatran-associated fatal liver injury or liver failure could occur in as many as 1 in 2,000 patients treated long-term."

Short-Term (<35 days) Administration of Exanta

Measurement	Exanta 36 mg BID n=1,913	Exanta 24 mg BID n=1,097	Warfarin n=2,226	p-value
≥1 adverse event	>55%	>55%	N/A	---
Bleeding	17%	23%	15%-20%	
Deaths	12 patients (including 2 fatal bleeds at 36 mg)		6 patients	---
Fatal events in which PE could not be excluded			0.3%	---
Discontinuations due to adverse events	2.6%	3.1%	2.0%-2.1%	---
Major bleeding	0.9%		0.5%	---
Major/minor bleeding	5.1%		4.1%	---
Alanine aminotransferase (ALAT) elevation	2.1%	1.4%	1.3%-1.5%	---
CAD events leading to discontinuation	.75%		.26%	.02800
MI	.60%		0.21%	.04951

The ALAT elevation increases typically occurred from 1-6 months after the initiation of Exanta. Before and after this time frame, the incidence of ALAT increase was similar to that of warfarin or placebo. Asian patients were found to have a decreased risk (p=0.0038), but several other groups of patients had an increased risk:

- Post acute coronary syndrome (ACS) (p=0.0009)
- VTE-treatment (p=0.0003)
- Female patients (p=0.0002)
- Low BMI (<27 kg/m2) (p<0.0001)
- Concomitant treatment with statins (p=0.019)

Although a single factor identified above may not be strong enough to eliminate the subgroup population, the FDA said **consideration may be given to contraindicating ximelagatran in patients who have two or more risk factors**, such as a female patient with low body weight or who is taking a statin.

Longer-Term (>35 days) Administration of Exanta

Measurement	Exanta 20-60 mg (median 370 days) n=6,931	Exanta 20-60 mg (≥6 months) n=5,024	Exanta 20-60 mg (≥12 months) n=3,509	Warfarin (median 455 days) n=4,967	Placebo n=1,249
Deaths during treatment	112 patients			112 patients	
Deaths after treatment	166 patients			165 patients	
MI (non-fatal) during treatment	26.3%			27.1%	
Non-fatal serious adverse event after treatment	5.5%			4.3%	
Discontinuations	17.2% (mostly due to ALAT elevations)			12.9%	
Discontinuations due to CAD	0.6%			0.3%	
Thrombolic events	0.4%			1.3%	
ALAT ≥3xULN	7.8% (546 patients)			1.1% (74 patients)	
Bilirubin ≥ 2xULN and ALAT >3xULN	0.53% (37 cases; 9 deaths – 24.3%) relative risk: 6.6%			0.08%	
CAD adverse events	7.0% for AF patients 1.3% for VTE-T patients 2.6% for VTE-P patients			6.7% for AF patients 0.1% for VTE-T patients 2.0% for VTE-P patients	

Risk Management

To address the FDA's safety concerns, AstraZeneca proposed a risk minimization action plan, RiskMAP. This would involve ALT-monitoring similar to that used during clinical development. That consisted of baseline and monthly ALT assessments, with more frequent testing and discontinuation linked to different ALT levels. The proposed RiskMAP is an education-based system reinforced by a complementary, interconnected set of materials and programs that emphasize and support compliance with the ALT-testing and management algorithm. It includes special packaging.

The RiskMAP program was field-tested with physicians and their hospital/office staff, pharmacists, and patients/ caregivers.

It assumes:

1. Severe hepatic injury will be preceded by an increase in ALT.
2. Appropriate ALT testing will identify individuals with elevated ALT levels, triggering the increased frequency of such testing for these individuals.
3. Cessation of Exanta, in accordance with the proposed ALT-testing algorithm, will minimize the risk of developing severe hepatic injury.

The FDA did not find AstraZeneca's risk minimization plan, RiskMAP, sufficient. The concerns were that:

- Stopping Exanta when ALT levels rise too far might not prevent liver failure and death.
- Testing compliance.

The FDA reviewer wrote in the briefing documents:

- "RiskMAP does not address the possible risks of delayed hepatotoxicity after short-term use with ximelagatran, or the risk of MI. In addition, reversal of excessive ximelagatran-induced bleeding was not addressed…Cases of severe liver injury and a case of fatal liver injury continued to be observed after the implementation of the revised algorithm. More conservative algorithms were not tested, so **it remains unknown whether timely discontinuation with any ALT elevation can prevent irreversible life-threatening liver injury with ximelagatran."**
- "The sponsor has not provided sufficient evidence about whether timely transaminase monitoring and early discontinuation of the drug at the first signs of liver toxicity could prevent severe liver injury and associated fatalities with ximelagatran."
- "Even if evidence were sufficient to support the claim that monitoring can reduce the risk of severe liver injury and associated fatalities, the sponsor's projected lower adherence with recommended ALT monitoring in clinical use has the potential to result in a higher rate of severe liver injury and liver failure/fatal liver injury than was observed in clinical development."
- "The demonstrated severity and rate of hepatotoxicity is substantial with long-term treatment with ximelagatran. Since no adequate mechanism to prevent or limit this toxicity has been demonstrated, there is no basis for proposing RiskMAP tools to reliably limit hepatotoxicity risk in individual patients."

If a limited label were given to Exanta, the FDA appeared to suggest that a RiskMAP could be applied, writing: "Should it be determined that ximelagatran offers selected populations of patients sufficient benefits to counter the hepatotoxicity risk, consideration should be given to a restrictive RiskMAP that would limit risk on a population basis. One example might be a performance-linked access system with a registry for patients entering long-term ximelagatran therapy." The safety reviewer also recommended that if Exanta is approved for short-term use for prevention of VTE, a risk management program should be implemented that limits therapy to 12 days maximum.

AstraZeneca's Perspective

In its briefing documents and in the oral presentation, AstraZeneca emphasized the unmet need that Exanta would address:

- More than 60% of the 960,000 cardiovascular (CV) deaths in the U.S. in 1999 were caused by thrombotic disease.
- VTE (DVT+PE) is the third most common CV disease.
- The population at greatest risk for VTE is those undergoing major lower extremity orthopedic surgery and those who experience major trauma or spinal cord injury.
- The risk for DVT after TKR surgery is greatest within the first 2 weeks after surgery. Without treatment, the prevalence of total DVT at 7-14 days after TKR surgery is 40%-84%, with proximal DVT rates from 9%-20%.
- Atrial fibrillation, the most common sustained arrhythmia, affects 4% of people over age 60 and 10% of those over age 80 and is often associated with stroke.

Some of the benefits the company cited for Exanta included:

- No interaction with food or alcohol.
- No interaction with cardiac drugs such as digoxin, ACE inhibitors, organic nitrates, loop diuretics, beta-blockers, CCBs, amiodarone, ARBs, and statins – though interactions with erythromycin and azithromycin have been noted.
- No independent effect of race on pharmacokinetics.
- Elimination primarily by glomerular filtration.
- Not metabolized by, and does not inhibit, CYP450 isoenzymes.
- No need to monitor INR.
- Rapid onset of action precluding the need for bridging therapy with heparins when rapid anticoagulation is needed. The rapid offset of action allows for simple discontinuation of drug administration.

AstraZeneca also defended its use of a 2% non-inferiority margin in the SPORTIF trials, saying it was planned "in collaboration with an Executive Steering Committee (ESC) and DSMB composed of leaders of prior stroke prevention trials and statisticians with expertise in non-inferiority trials. In selecting the non-inferiority margin, AstraZeneca considered what difference in event rates would be clinically tolerable, accounting for the overall clinical profile of warfarin…The 2%/year absolute non-inferiority margin is clinically relevant, was pre-specified, and was conservatively

chosen. The non-inferiority margin was selected to represent an upper confidence interval (CI)...In addition, a putative placebo comparison was added as a prerequisite to non-inferiority analysis in each of the SPORTIF trials. The non-inferiority analysis was to be done only if ximelagatran was found to be statistically superior to placebo. This prerequisite analysis adds robustness to the conclusions drawn from the subsequent non-inferiority analysis."

Safety

➢ **Bleeding**. Both adjudicated major and investigator-reported bleeding adverse events were reported to be less with Exanta than with dose-adjusted warfarin, and no subgroups appeared to be at increased risk for bleeding events vs. warfarin.

➢ **Liver.** AstraZeneca had been claiming the ALT elevation issue with Exanta is in the range of ~6%, but in its FDA paper, the company wrote: "Long-term dosing with ximelagatran has been associated with ALT elevations in approximately 8% of patients." ALT elevations to >3xULN were described as mostly asymptomatic and reversible within the first six months of therapy. No hepatic signal was observed during short-term administration after orthopedic surgery.

ALT Elevations in Exanta Clinical Trials

Measurement	Exanta n=6,948	Comparator n=6,230
ALT >2xULN	12.4%	3.1%
ALT >3xULN	7.9%	1.2%
ALT >5xULN	4.7%	0.5%
ALT >10xULN	1.9%	<.01%
Bilirubin >2xULN	1.2%	1.1%
Bilirubin >3xULN	0.6%	0.3%
Bilirubin >5xULN	0.3%	0.1%
Bilirubin >10xULN	<.01%	<.01%
ALT >3xULN and bilirubin >2xULN	0.8%	1.0%

AstraZeneca's Benefit/Risk Evaluation of Exanta

Measurement	Warfarin	Exanta	Relative risk reduction	p-value
Net risk/benefit in prevention of VTE after TKR				
Primary events+major bleeding+death	30.5%	22.1%	28%	<.001
Net risk/benefit for long-term secondary prevention of VTE				
Primary events+major bleeding+death	14.4%	4.9%	66%	<.0001
Net risk/benefit for prevention of stroke in AF				
Primary events+major bleeding+death	6.2%	5.2%	16%	.042

Risk Management

Dr. Hamish Cameron, AstraZeneca's vice president in charge of Exanta, said the company would work with the FDA to strengthen its monitoring program. He said, "We believe the risk can be adequately managed." He also claimed the liver failure risk is lower than estimated by the FDA, "We do not believe the risk is as high as 1:2,000…In our post-marketing program, we are developing programs to reduce the risk to 1:10,000, and we think that is about the right ballpark…and we will be discussing those proposals with the FDA in an upcoming meeting."

PUBLIC WITNESSES

The public witnesses were divided in their recommendation to the Exanta advisory panel. There were no patients pleading for Exanta approval, but an official of the National Stroke Association and a Boston University professor who consults with AstraZeneca both urged approval. An Anticoagulation Steering Committee member also argued for approval, warning there is a substantial public health problem: non-treatment and sub-optimal of DVTs and AF with warfarin.

On the other hand, a Loyola University professor said, "We feel further studies are needed before approval for AF…Although it was judged non-inferior, the side effects may offset the non-inferiority status." A Colorado pharmacist wondered if there are unpublished (negative?) studies on Exanta, and he urged the panel – if they recommend approval – to also recommend very strict liver monitoring, labeling, and advertising restrictions.

Perhaps surprisingly, Public Citizen did not recommend outright rejection of Exanta. Dr. Peter Lurie of Public Citizen urged rejection of all except perhaps the longer-term VTE prevention (<18 months), "We find that the data submitted by the sponsors fail to establish the drug's efficacy for two of the three indications sought (VTE-T and VTE-P) and that the company's proposed risk management strategy is inadequate to optimally reduce the risks, particularly to the liver, associated with use for the third indication (AF).

Among the points he made were:

➢ **For VTE-T:**

- "Although two drugs (injectable enoxaparin and fondaparinux) are approved for this indication, the sponsor chose to compare ximelagatran to warfarin, which is not approved for this indication."
- "Any convenience advantage over the approved medications conferred by ximelagatran being an oral medication is diminished in this short-term, substantially inpatient setting."

- **For VTE-P:**
  - Ximelagatran does indeed appear to be superior to placebo for this condition…(but) the risks are significant."
  - "Troglitazone (Rezulin) had only a .9% incidence of ALTs >3xULN, compared to 0.6% on placebo… 7.6% (of Exanta patients) developed ALT >3xULN compared to 1.1% of patients receiving comparators …This rate (of serious hepatotoxicity) likely will be higher in clinical practice."
- **For AF:** "Approval of ximelagatran for this indication is not warranted."

On risk management, Dr. Lurie warned that compliance would be less in clinical practice than in the clinical trials. He urged that the FDA implement the following measures in adding to the company's RiskMAP risk management program if it does approve Exanta for any indication:

- Black box warning
- Mandatory patient registry for long-term users that would be linked to performance
- Patient-physician agreements
- Restrictions on promotion, distribution, and packaging.

THE ADVISORY COMMITTEE DISCUSSION AND DEBATE

The panel had a number of questions for AstraZeneca, but the company appeared either not to expect them or not to be well prepared. For instance, Dr. Steve Nissen of the Cleveland Clinic asked AstraZeneca officials: "Something extraordinary happened in SPORTIF-III and SPORTIF-V: The results favored Exanta in SPORTIF-III and favored warfarin in SPORTIF-V. That opposite effect on the point estimate is really unusual given the similarity of the trials…We are all looking at the briefing documents and trying to figure out what could have happened here…A 39% greater risk for warfarin in SPORTIF-III and a 39% greater risk for Exanta in SPORTIF-V. The only difference is one trial is blinded (SPORTIF-III) and one is not (SPORTIF-V)…So, most rational people will believe the blinded results, not the unblinded results...This is a real credibility issue...What is your reaction?"

An AstraZeneca official did not directly answer the question, responding, "In fact, there are many differences between SPORTIF-III and SPORTIF-V that confounded…those two trials:

1. One was done in Europe/Asia, and the other was in N. America, and practice issues may pertain.
2. SPORTIF-V patients more often had hypertension. Their BP was 6 mmHg lower on average than in SPORTIF-III patients.
3. There was artificially intense control of INR in SPORTIF-V relative to SPORTIF-III because in SPORTIF-III, there were >270 clinical labs conducting INR measurements but essentially two labs in SPORTIF-V, achieving some kind of standardization that is difficult to quantify.
4. The Exanta rates were identical in the two trials. The warfarin rates in the two trials appear disparate but are actually within the rates seen in prior stroke prevention trials. What we may be looking at here is another manifestation of the variability of warfarin.

Both Dr. Nissen and the panel's statistician, Dr. Tom Fleming of the University of Washington, hammered the company over the failure to directly answer Dr. Nissen's question. Dr. Fleming also focused on the overall survival rates in the THRIVE-III trial. AstraZeneca listed only five deaths with Exanta, but the FDA briefing documents claimed 10, and Dr. Fleming wanted to understand the difference. It turned out that AstraZeneca only reported the deaths on treatment, and the FDA used an ITT analysis, and by ITT, there were 10 deaths.

These and other panel members had tough questions, but AstraZeneca officials were offering few direct answers. Among the other topics the panel explored were:

Rebound after short-term use

- Dr. Nissen said, "Our concern is that there is some increased vulnerability when the drug is discontinued and that accounts for the increase in post-treatment events (MI, PE, and deaths)…It (rebound) really struck many of us on the committee as a problem."
- The chair said, "I am struck with a difference between the on-treatment and post-treatment frequency of major adverse CV events (in EXULT-A and EXULT-B). If you look at the number of MI or other cardiac events on drug vs. the comparator, the numbers were different but not all that different...but the number of events that occurred with Exanta post-treatment was greater as a percentage of the whole than was the case for the comparators…The really serious events – death, PE, and MI – look a lot worse on Exanta than on warfarin…This is a potentially remedial problem, so it is important to know (if there is a rebound effect)."
- An AstraZeneca official responded: "The numbers are higher in Exanta than the warfarin group. Unfortunately, those are really small numbers. Is this really a true difference? I would speculate that if it were true, we would see difference in long-term treatment trials because they are larger."

Trial design issues

- Discordance between SPORTIF-III and SPORTIF-V

- Lack of blinding in SPORTIF-III. Interestingly, an AstraZeneca official said this was because investigators would not agree to a blinded trial.

Acute liver failure

Patients recover ALT levels faster on drug than by discontinuing it (~28 days vs. ~40 days), and that puzzled some panel members.

- According to "Hy's Law," Exanta would be expected to have an acute liver failure rate of 1:2,000. Dr. Nissen asked AstraZeneca if that was a correct estimate, and an AstraZeneca official said, "It might be the highest, but we don't know the incidence…Our goal is to prevent any hepatic injury."
- A hepatologist who is an AstraZeneca consultant said, "I hope it will be better…It will be better."
- Asked about patients with ALT elevations who were successfully re-challenged with Exanta, the FDA's outside liver consultant, Dr. Paul Watkins of the University of North Carolina Medical Center, said, "The fact that you can do that is reassuring in the sense that…it argues strongly against a hypersensitivity reaction…It doesn't, however, mean that the elevation wasn't due to the drug…The current thinking is the few patients incapable of adapting (to elevated ALT) are the ones who go on to get progressive liver injury."

ALT Monitoring

The panel chair suggested that the panel is struggling with efficacy more than safety, "We don't know and won't determine what kind of risk management program you will develop...The issue (for us) will be that if you could develop one, is there something here worth giving to patients?"

VTE-T

The FDA argued that no clinically meaningful benefit was shown in VET-T (short-term prevention in patients undergoing TKR surgery – at a dose of 36 mg BID for 7-12 days). However, the panel disagreed**.** Among the panel comments were:

- "I think it is clinically meaningful…The sponsor should be congratulated for doing this (venograms)…However, though we have a hard event, is it a hard clinical event?"
- "I wouldn't dismiss the asymptomatic benefit."
- "In a clinical trial for a new molecule…as a clinician I would look at this as a continuum as opposed to separate subjects, so I would (agree) that there is clinical meaning to having distal venogram-detected DVTs."
- Chair Dr. Jeffery Borer of Cornell: "I, too, feel very concerned saying the benefit is not important."

VTE-P

The FDA contends there is an excess MI/CAD risk with VTE-P (long-term secondary prevention of VTE after standard treatment for an episode of acute VTE – at a long-term dose therapy of 24 mg BID for 18 months). An FDA expert explained, "If Exanta causes MI, it will do it in a very small percentage of patients…It is not like liver toxicity where you can see it so clearly (8% vs. 1%)…This difference is very small."

FDA Questions for the Advisory Committee – and the Panel Votes

The advisory panel rejected Exanta on safety and rejected all three proposed indications. With 12 voting members, here are the questions and the panel votes and comments.

Safety

1. What is your level of concern (none, low, moderate, high) for the risk of liver toxicity with use of ximelagatran:

a. For prevention of stroke and systemic embolic events in patients with atrial fibrillation? **HIGH**

b. For secondary prevention of venous thrombo-embolism after 6 month standard treatment for an episode of acute VTE? **HIGH**

c. For prevention of VTE in patients undergoing elective total knee replacement surgery?
MODERATE TO LOW, but the panel was concerned about the potential danger of dose creep, which they expect will happen if Exanta is approved.

Panel member comments included:

- "My level of concern is high. There is a 1:2,000 risk of acute liver failure…I'm also troubled by the fulminate nature of the liver injury seen, that it is difficult to predict even with monthly monitoring….My judgment from the three cases (deaths) is that all three are probably drug-related, so I think the risk is very high….It (Exanta) is about double the rate for troglitazone (Rezulin). So, the estimated risk exceeds that of an agent withdrawn for this issue. On short-term use, my assessment of the risk is lower. But I'm worried about a couple of other things I suspect the Agency also is worried about – duration of use and dose creep. You can say the drug can only be used for 12 days and not 13-14-15 days or longer, but I know my colleagues. If someone is on Exanta and doing well, they will keep the patient on it 20-30 days, etc. We don't have data on the delayed risk profile…My risk concerns are lower for short-term use, but they don't go away for short-term use because I'm concerned about dose creep."

- "In the long-term database, when you look at Hy's Law, there is a 0.5% increase (in liver toxicity), and…that means 1:2,000 will progress to liver failure, transplant, or death…(In AF) it is not as clear to me what the risk is...and I would like to know what happens after Week 6."
- "We didn't discuss whether ALT developed after discontinuation…so we can't say an absence of safety data says there is no or low risk."
- *Chair:* "Warfarin is a very, very difficult drug to use…I think the risk is high in a setting where it will be used for a long time…Whether that can be minimized with a monitoring program, I don't know."
- "The dilemma is that (the liver toxicity) is high for a small percentage of patients, and it is idiosyncratic…I hear this drug is good otherwise and probably preferable to Coumadin (warfarin) in many patients…It is important to find a way to monitor it to prevent the bad outcomes."
- "I will ignore the benefit that probably does exist for this medication…and I will follow Hy's Law…And duration creep is a real issue."

2. Based on currently available data, is it possible to identify patients who are at risk for developing severe liver toxicity after exposure to ximelagatran? **NO**

Panel member comments included:

- "We need more exposure to know if this is true."
- "The sponsor said there are no prognostic factors…so it is difficult to nail down this population…and AstraZeneca said there is no subgroup at greater risk."
- "It is not predictable…I sure wish it were because that would turn this whole thing around. It is a very small number of people who have the problem, but we just can't pick them out."

3. Did the sponsor's study procedures for monitoring and managing patients with regard to liver function adequately minimize the risk of severe liver injury and liver failure in the clinical studies? **UNANIMOUSLY NO**

Panel member comments included:

- "The protocol was good but not the implementation."
- "It was appropriate that they modified the (risk management) algorithm, but I was somewhat surprised about compliance."

4. Do you have other safety concerns regarding the long-term use of ximelagatran (e.g., cardiac)? Regarding the short-term use of ximelagatran? **YES for both, particularly cardiac safety, but some panel members were also concerned with bleeding.**

Panel member comments included:

- "I share the cardiovascular concern, but it is a low-moderate level of concern because I think it can be addressed in further studies and may be able to be eliminated with other data."
- "I have concerns, but they don't rise to the level of show stopper concerns…The issue of cardiovascular events is a concern if it is real…and probably the importance of this can be resolved with some additional data…On the one hand, the observations suggest an excess of cardiovascular events (both MIs and other generally softer cardiovascular events) and heart failure, which seems to be excessive in populations in whom they were unexpected. And if they were unexpected, then finding them is less compelling than if I had expected them…There was a tendency for things to look better on ximelagatran…so where I expected ximelagatran to look good, it did, and where I didn't expect it to look bad, it maybe looked bad….The absolute number of excess events seemed small, so I am not overwhelmingly concerned, but I am concerned enough to look a little further."
- "I have concerns about cardiac events more than the others."
- "This level of (cardiac) signal means it deserves future attention."
- "I don't see this as an extremely strong or hard signal…To my mind, the short-term signal may be a real issue…I think it relates to a more generic problem than all of us have seen."
- "I'm not yet fully convinced of a cardiac issue."

Short-term Use: prevention of VTE in patients undergoing elective total knee replacement surgery

5. Do you recommend additional safety studies with longer follow-up to address the possibility of delayed occurrence of liver toxicity following short-term use? **UNANIMOUSLY YES, 30 days exposure with follow-up out to 90 days**

6. Regarding the potential risk of myocardial infarction/coronary artery disease (MI/CAD) with short-term exposure to ximelagatran (mean 8 days) in patients undergoing TKR, do you recommend further studies to assess the risk of MI/CAD? If yes, what type of study (ies) do you recommend? **YES, the recommendation was for a 30-day pre-approval study with 90-day follow-up as suggested in questions #5.**

Panel member comments included:

- "There is a statistically significant p-value in the short-term population that I can't make go away without more data…That (new study) doesn't need to be a large group…I see a signal which is a statistically significant excess of events that may be false…so I am looking for a study to confirm or

refute that doses used in the short-term trial will result in an excess short-term cardiovascular risk."

- "I argue that the trial should be in patients who appear to be low risk and not on cardiovascular medicines."
- "I don't feel the indication is for another short-term study…but I think there is need for education after approval and labeling to remind physicians to use aspirin appropriately."
- "I believe there is a signal requiring additional data, but it is challenging to find a practical design. This is a tantalizing molecule. I would like to define a population where it is clearly safe."
- *Chair:* "I'm not sure we need another short-term study… We are concerned about protracted use that probably would be the model in clinical practice…I think warfarin is a reasonable comparator because it is used clinically. I don't believe the statements that the comparator (warfarin) was unfair are really germane. This (warfarin) is the recommended treatment by a consensus panel even though it is not an approved indication."

7. Based on the currently available data, do you conclude that the benefits of ximelagatran for short-term use for prevention of VTE in patients undergoing TKR surgery outweigh its risks? **UNANIMOUSLY NO. The panel felt the benefits of Exanta did not outweigh the risks without additional data, although several panel members thought that some day it will be approvable.**

Panel member comments included:

- "First, we have an excess risk in pulmonary embolisms, death, and MI…so the proof of benefit is simply not there…It goes the wrong way. Secondly, we simply don't know what happens if you give this drug longer, and I have to believe it will be given for at least 30 days – and we don't know the risk of that…Third, warfarin is not burdensome for 30-day administration."
- "I think ultimately this drug should be approvable...I don't think we have sufficient information at this point to let that happen."
- "I share your enthusiasm, and I hope someday it will be able to be used…but I can't say it is appropriate now for…I'm not convinced the benefits outweigh the risk."

Long-term Use: secondary prevention of VTE after 6 months standard treatment for an episode of acute VTE

8. Based on the currently available data, do benefits of ximelagatran for secondary prevention of VTE (18 months) after 6 months standard treatment for an episode of acute VTE outweigh the risks for this indication? **NO 11, YES 1.**

Panel member comments included:

- "This is tougher…I hope this won't be viewed as excessively harsh…but if an agent has a serious risk of fatal toxicity in a range similar to drugs that had to be withdrawn for the market, then you have to show superiority over existing therapies…I'm convinced that to overcome the current burdens of liver failure problem, we need to see unequivocal superiority on outcomes…Equivalency is not sufficient when there is a 1:2,000 risk of fatal liver injury. We have data for this which is superiority data over placebo…but, basically, to make this indication approvable, I want to see superiority over another therapy, not over placebo."
- *Chair:* "I don't think we have data sufficient for approval for this now because the risk is a concern and not well-defined, and we don't know yet if we have an acceptable algorithm to minimize risk."
- "I don't think the public is ready to accept liver failure."
- "While I'm convinced it (Exanta) is better than placebo …the study was not designed in line with consensus guidelines. These patients were probably treated with Coumadin too briefly before they were enrolled, so they were studying a scenario that is not relevant to best practices…They (patients) should have been treated with Coumadin for a year before randomization to a new agent or placebo...So, there is not sufficient data."
- "This is a problematic drug…It has a lot of potential…but I want to see an algorithm to reduce the liver toxicity."

Long-term Use: prevention of stroke and systemic embolic events in patients with atrial fibrillation

9. Is the non-inferiority margin of 2% compared to warfarin adequate to ensure that ximelagatran is non-inferior to warfarin with respect to efficacy? **NO**

If no, what should the non-inferiority margin be for the indication of prevention of stroke and systemic embolic events in patients with atrial fibrillation? **The panel's statistician recommended a margin between 1.0 and 1.4.**

10. Based on the currently available data, do you conclude that the benefits of ximelagatran for long-term use for prevention of stroke and systemic embolic events in patients with AF outweigh its risk? **NO 11, YES 1.**

A panel member commented, "A future trial has to show superiority in light of what I see as a very serious toxicity."

WHAT HAPPEN'S NEXT?

After the panel votes, AstraZeneca VP Dr. Hamish Cameron was asked for his reaction. He said, "Obviously, we are disappointed…The issues with warfarin were highlighted, and

the hunger for a new treatment is there. Even though, it was a NO vote, there were caveats that with more data they could approve." He would not comment on whether his company will do those studies or abandon Exanta.

An FDA official said, "We heard from the committee that there is clear need for an oral alternative to warfarin, but we also heard strongly that there are serious safety concerns, especially liver and an unexplained hint of something going on that is cardiac in nature and maybe MI…The committee suggested some studies to look at MI…We didn't talk in great detail about risk management, but the panel felt it would be difficult to manage, but left it to us (the Agency)…Most of the committee felt it is not possible to identify in advance those patients most at risk (for liver failure)…There are very important problems that the sponsor will have to work on…I can't say at this time if they can be overcome."

♦