# NDA 21-686
# Ximelagatran (H376/95)

## Indication: Prevention of stroke and thromboembolic complications associated with atrial fibrillation

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*NOTE: This is a preliminary/draft review that is not intended to provide any recommendations on the approvability of NDA 21,686. Any opinions expressed in the review do not necessarily reflect those of the Division/Office.*

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Executive Summary

I. Recommendations

A. Recommendation on Approvability

The sponsor of NDA 21-686 is currently seeking approval of ximelagatran (H376/95) for 3 different indications. The indication that is the focus of this review is the prevention of stroke and other thromboembolic complications associated with atrial fibrillation. Two pivotal phase 3 studies (SPORTIF III and SPORTIF V) have been submitted in support of the stated indication. The two studies are active controlled studies designed to show that ximelagatran is non-inferior or "as efficacious as" treatment with warfarin, the current standard of care. The active controlled, non-inferiority design of the SPORTIF studies makes interpretation of efficacy relatively more complicated compared to a design involving a placebo control. An important step in interpreting the effectiveness of ximelagatran in the SPORTIF studies is to understand the benefit of warfarin relative to placebo. The benefit of warfarin relative to placebo was derived from several placebo controlled trials conducted approximately 10 to 15 years ago and published in the peer reviewed medical literature. A summary of these studies is discussed in detail elsewhere in this review. Based on these studies, the relative risk reduction for stroke appears to be approximately 64% (95% CI → 47%, 75%).

The 2 SPORTIF studies compared the effectiveness of a fixed dose of ximelagatran, 36 mg administered twice a day, to warfarin, targeting an INR of 2 – 3 in patients with nonvalvular atrial fibrillation and at least one additional risk factor for stroke. SPORTIF III and SPORTIF V were similar in design except that the former was open-label while the latter was blinded. The primary endpoint was a composite of all strokes (ischemic and hemorrhagic) and systemic embolic events. The sponsor pre-specified a non-inferiority margin of 2% in the event rate. Ximelagatran would be called non-inferior if an excess of 2% per year in the event rate relative to warfarin could be confidently excluded. A margin of this magnitude could leave open the possibility that ximelagatran was only half as effective as warfarin and still be considered non-inferior to warfarin. The magnitude of this non-inferiority margin was not formally agreed upon by the reviewing division within the Agency and marked as a point of future review/discussion.

The two SPORTIF studies produced divergent results despite similar designs. In SPORTIF III, the primary event rate was numerically higher in the warfarin arm compared to the ximelagatran arm. In SPORTIF V, the primary event rate was numerically higher in the ximelagatran arm compared to the warfarin arm. Comparing the event rates in the common arm of both SPORTIF studies, the rate in the ximelagatran arm was practically the same in both studies while the event rate in the warfarin arm varied by nearly two-fold. The variable event rate on warfarin in the two studies could potentially be attributed to the fact that patients in the two studies were slightly different at baseline. Patients in SPORTIF V were slightly older, had lower blood pressures on average, had fewer patients with histories of transient ischemic attacks (TIA's) or strokes, and had greater consumption of HMG CoA reductase inhibitors than did patients enrolled in SPORTIF III. It is puzzling why differences in patient populations of both studies would lead to differences in event rates in the warfarin arms while leaving the event rate in the ximelagatran arms unaffected. In such a setting where two similarly designed studies produce divergent results, I would favor the results from a double-blind study.

In terms of safety, liver toxicity as assessed by serum aminotransferase abnormalities occurred approximately 6 times more often on ximelagatran compared to warfarin and was consistent across both trials. There was one well documented case (and most probably a second case) of drug induced liver failure leading to coagulopathy and death among the approximately 3700 patients randomized to ximelagatran. Intense protocol mandated liver enzyme monitoring did not prevent serious liver toxicity in these two cases although in some other cases it did prevent serious adverse outcomes. These two cases highlight the possibility that liver enzyme monitoring as a risk management strategy may not be entirely fool proof. In terms of major bleeding events, the total number of bleeds was numerically lower in the ximelagatran arm of both studies. In neither of the studies did the difference achieve statistical significance. The majority of major bleeds in both studies were due to bleeding with a fall in the hemoglobin level of $\geq$ 2g/dL or due to overt bleeding requiring $\geq$ 2 units of whole blood. Bleeding events leading to death were relatively few in both studies and similar in the two treatment arms.

With respect to dosing, there is a strong correlation between the oral clearance of melagatran (the active metabolite of ximelagatran) and creatinine clearance. Thus exposure to melagatran will be affected by renal impairment. Varying degrees of renal impairment are expected in the patient population for which this therapy is targeted and will potentially be a significant factor affecting exposure to melagatran. There is a clear relationship between higher exposures to melagatran and increased risk of major bleeds and elevations in aminotransferases. A strategy of fixed dosing as is being proposed for ximelagatran is concerning.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The sponsor has proposed a risk management program that is intended to minimize the risk of severe hepatic injury that could occur in the setting ximelagatran use. One of the key features of this program involves liver enzyme (ALAT) monitoring. The method of monitoring proposed in the risk management plan is similar in intensity to the monitoring that was conducted in the pivotal clinical trials. Unfortunately, the relatively intense liver enzyme monitoring in the clinical trials did not prevent two cases of drug induced liver failure/death in the SPORTIF V study.

The experience of the FDA in using liver enzyme monitoring as a risk management tool has been disappointing particularly in the case of troglitazone. Troglitazone was an antidiabetic agent that was approved in 1997 but taken off the market in 2000 because of numerous cases of liver failure reported post marketing. Despite labeling changes, Dear doctor letters and other risk management strategies, baseline testing of liver enzymes was conducted in less than one-half of the patients that were started on troglitazone (Graham et al JAMA 2001;286:831-833).

## II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

One of the indications that ximelagatran is being developed for is the prevention of stroke and other thromboembolic complications associated with atrial fibrillation. Two pivotal phase 3 studies have been submitted in support of the stated indication. In the atrial fibrillation development program a total of approximately 7,300 patients were followed for an average of

1.4 years. The two studies were active controlled studies designed to show that ximelagatran is "non-inferior" to treatment with warfarin, the current standard of care. The 2 SPORTIF studies compared the effectiveness of fixed doses of ximelagatran 36 mg administered twice a day versus warfarin, targeting an INR of 2 – 3 in patients with nonvalvular atrial fibrillation and at least one additional risk factor for stroke.

B. Efficacy

SPORTIF III and SPORTIF V are two Phase III, active control, non-inferiority studies that were provided in support of NDA21-686. Both studies compared the effectiveness of a fixed dose of ximelagatran, 36 mg administered twice a day to warfarin targeting an INR of 2 to 3 in patients with nonvalvular atrial fibrillation and at least one additional risk factor for stroke. The studies were very similar in design except that SPORTIF III was open label while SPORTIF V was double-blind. The primary endpoint was the composite of all strokes (fatal and non-fatal) and systemic embolic events. The sponsor pre-specified a non-inferiority margin of 2% points in the event rate in both studies. 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." In both studies, the efficacy of ximelagatran was within the sponsor's pre-specified non-inferiority margin of 2% and it was concluded by the sponsor that ximelagatran was as efficacious as warfarin. While the two studies could be considered "successes" based on the sponsor's pre-specified margin, the margin chosen was too liberal.

The two SPORTIF studies produced divergent results despite their similar designs and patient populations studied. In SPORTIF V, the event rate was higher in the ximelagatran arm compared to the warfarin arm while in SPORTIF III, the event rate was higher in the warfarin arm compared to the ximelagatran arm. Comparing the event rates in common arm of both studies, the event rate in the ximelagatran arm of both SPORTIF studies were similar at approximately 1.6%. However, the event rate in the warfarin arm varied by almost two-fold: 1.2% in SPORTIF V versus 2.3% in SPORTIF III. Differences in the patient populations in the two studies at baseline could be a possible explanation of the differences in the event rate in the treatment arms. However, it is difficult to explain why such differences would lead to differences in event rates in the warfarin arm while leaving the event rate in the ximelagatran arm unaffected. In a setting where two similarly designed studies produce divergent results, I would favor the results from a double-blind study. It is important to note that the event rate in both studies was primarily driven by the occurrence of ischemic strokes. More than 80% of the events in both studies were ischemic strokes.

C. Safety

In SPORTIF III, there were a total of 145 deaths that occurred on drug or during the follow-up period: 75 Ximelagatran, 70 Warfarin. In SPORTIF V, there were a total of 237 deaths occurring on drug or during the follow-up period: 116 Ximelagatran, 121 Warfarin. The etiologies of deaths were consistent with what is to be expected from an elderly population with co-morbidities. The most common etiologies of death included sudden death, heart rate and rhythm disorders, myocardial infarctions, and congestive heart failure.

In terms of serious adverse events (SAE's) not leading to death, the reporting rate was lower in SPORTIF III compared to SPORTIF V. The etiologies of the SAE's not leading to

death were also consistent with what would be expected in an elderly population. The most common etiologies of SAE's included congestive heart failure, cerebrovascular disorders, myocardial infarctions, GI hemorrhage, pneumonia, and angina pectoris.

Discontinuations due to adverse events were numerically greater in the ximelagatran arms of both SPORTIF studies. The most common reason for study drug discontinuation from ximelagatran was liver and biliary system disorders. The frequency of aminotransferase abnormalities was significantly higher on ximelagatran compared to warfarin regardless of the criteria used to define abnormal (e.g. ALAT or ASAT > 3x ULN, > 5x ULN, or > 10 x ULN). The majority of patients that developed liver enzyme abnormalities did so beginning 2 to 4 months after starting ximelagatran therapy. There was one case of a biopsy documented drug induced liver failure leading to death. There was a second probable case of drug induced liver failure leading to coagulopathy and subsequently death. In addition there were multiple cases of aminotransferase abnormalities greater than 3 times the upper limit of normal temporally associated with a bilirubin increase of greater than 2 times the upper limit of normal. The cases fitting the description of "Hy's Law" and their associated narratives are listed in the Appendix of this review. In most of these cases the patients were asymptomatic. Liver enzyme abnormalities returned to normal after drug discontinuation in these patients.

In terms of major bleeding events, the total number of bleeds was numerically lower in the ximelagatran arm of both SPORTIF studies. In neither of the studies did this difference achieve statistical significance. The majority of major bleeds in both studies was due to bleeding with a fall in the hemoglobin level of greater than or equal to 2 g/dL or due to overt bleeding requiring $\geq$ 2 units of whole blood.

D. Dosing

A fixed dose of ximelagatran 36mg bid was studied in the SPORTIF trials. The sponsor's preliminary labeling proposes for the use of fixed doses of ximelagatran without recommending dose adjustment.

There is a strong correlation between creatinine clearance and the apparent oral clearance of melagatran, the active metabolite of ximelagatran. As creatinine clearance decreases, there is a proportional decrease in melagatran clearance. In the sponsor's proposed labeling there are no provisions for dose adjustment in patients with varying degrees of renal impairment. The proposed labeling would only contradict the use of ximelagatran in patients with a creatinine clearance less than 30 ml/min. Not allowing for dose adjustment in renal impairment may compromise safety because the risk of serious adverse events increases as the exposure to drug increases as shown in Table I and Table II below.

Table I below shows that as the exposure to melagatran increases as measured by the area under the plasma concentration time curve increases, the cumulative risk of major bleeding increases by a factor of about 4 fold.

**Table I: Cumulative risk of major bleeding with increasing exposure of study drug in SPORTIF III/V**

| Study | AUC value | Cumulative | 95%CI |
|---|---|---|---|

| (SPORTIF III/V) | | | Risk (%) | Lower (%) | Upper (%) |
|---|---|---|---|---|---|
| | Lowest 5% | 2.06 | 1.00 | .64 | 1.37 |
| | Lowest 25% | 2.77 | 1.29 | 0.89 | 1.70 |
| | Median | 3.46 | 1.65 | 1.21 | 2.10 |
| | Highest 75% | 4.38 | 2.29 | 1.74 | 2.85 |
| | Highest 95% | 6.19 | 4.37 | 3.05 | 5.69 |

Obtained from Table 27 of Summary of Clinical Pharmacology Studies Study Report

Similar to the previous table, Table II below shows that as the exposure to melagatran increases, the cumulative risk of hepatotoxicity (as measured by an ALAT > 3x ULN) increases. The increased risk of toxicity with increased exposures to melagatran appears to be slightly less pronounced for hepatotoxicity than that for major bleeding.

**Table II: Cumulative risk of ALAT >3x ULN with increasing exposure of study drug in SPORTIF III/V**

| Study (SPORTIF III/V) | | AUC value | Cumulative Risk (%) | 95%CI Lower (%) | Upper (%) |
|---|---|---|---|---|---|
| | Lowest 5% | 2.06 | 5.13 | 4.02 | 6.23 |
| | Lowest 25% | 2.77 | 5.59 | 4.64 | 6.55 |
| | Median | 3.46 | 6.08 | 5.22 | 6.94 |
| | Highest 75% | 4.38 | 6.80 | 5.83 | 7.77 |
| | Highest 95% | 6.19 | 8.47 | 6.38 | 10.6 |

Obtained from Table 27 of Summary of Clinical Pharmacology Studies Study Report

E. Special Population

Just under 1/3 of the patients randomized in the SPORTIF studies were females. The direction and magnitude of the ximelagatran effect with respect to the primary efficacy endpoint was similar in males and females.

Less than 5% of the study population in the SPORTIF studies was Black and thus limited conclusions can be made of efficacy or safety of ximelagatran in that population.

It was not unexpected that both SPORTIF studies randomized predominantly a geriatric population with a mean age of just over 70 years as the prevalence of atrial fibrillation increases with increasing age.

Melagatran, the active metabolite of ximelagatran is predominantly excreted in the urine unchanged. Thus, patients with severe renal impairment can have up to 5 times the exposure compared to those with normal renal function.

There are no adequate and well controlled studies of ximelagatran use in pregnant women. Reproductive toxicity studies with ximelagatran in pregnant rats, rabbits, and minipigs have been conducted and have not shown any risk of harm to the fetus at doses that do not produce maternal bleeding. Please refer to the Pharmacology/Toxicology review for further details.

Clinical Review

## III. Introduction and Background

### A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose Regimens, Age Groups

Proposed trade name: EXANTA®

Drug Class: Reversible, oral thrombin inhibitor

Proposed indications: The sponsor is seeking a total of 3 indications. Two of the indications are related to the prevention and treatment of venous thromboembolism. The third indication that is the purpose of this review is "prevention of stroke and other thromboembolic complications associated with atrial fibrillation."

Dose/Regimen: Fixed dose of 36 mg orally twice daily

Age groups: Older adults will be the primary recipients of this therapy. The prevalence of atrial fibrillation is much higher in older adults than in younger adults. Chronic ximelagatran therapy has not been studied in pediatric populations because atrial fibrillation is a rare, atypical arrhythmia in children.

### B. State of Armamentarium for Indication(s)

EXANTA is the first in a new class of oral anticoagulants. The primary mechanism of action involves reversible inhibition of thrombin. The most commonly used oral anticoagulants worldwide are the vitamin K antagonists. Warfarin is an approved Vitamin K antagonist that is available in the U.S. Warfarin is generally recognized as a very effective oral anticoagulant. Its main side effect is risk of bleeding that is predictable from its pharmacologic action. One drawback of using warfarin is that it requires therapeutic drug monitoring to ensure that efficacy is being maximized while minimizing bleeding risk.

### C. Important Milestones in Product Development

**Table III: Important milestones in Product development**

| | |
|---|---|
| January 16, 1998 | Patent issue date |
| August 14, 1998 | IND filed for the oral tablet formulation of ximelagatran |
| June 16, 2000 | End of Phase 2 meeting to discuss SPORTIF protocols |
| July 14, 2003 | Pre-NDA meeting |
| October 9, 2003 | Meeting to discuss risk management strategies |

| | |
|---|---|
| December 23, 2003 | NDA filed to Division of GI/Coagulation Drug Products |

## IV. Clinically Relevant Findings from From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Please refer to the Medical Officer Review by Dr. Ruyi He (Primary Medical Officer in Division of GI/Coagulation Drug Products) for further details.

## V. Human Pharmacokinetics and Pharmacodynamics

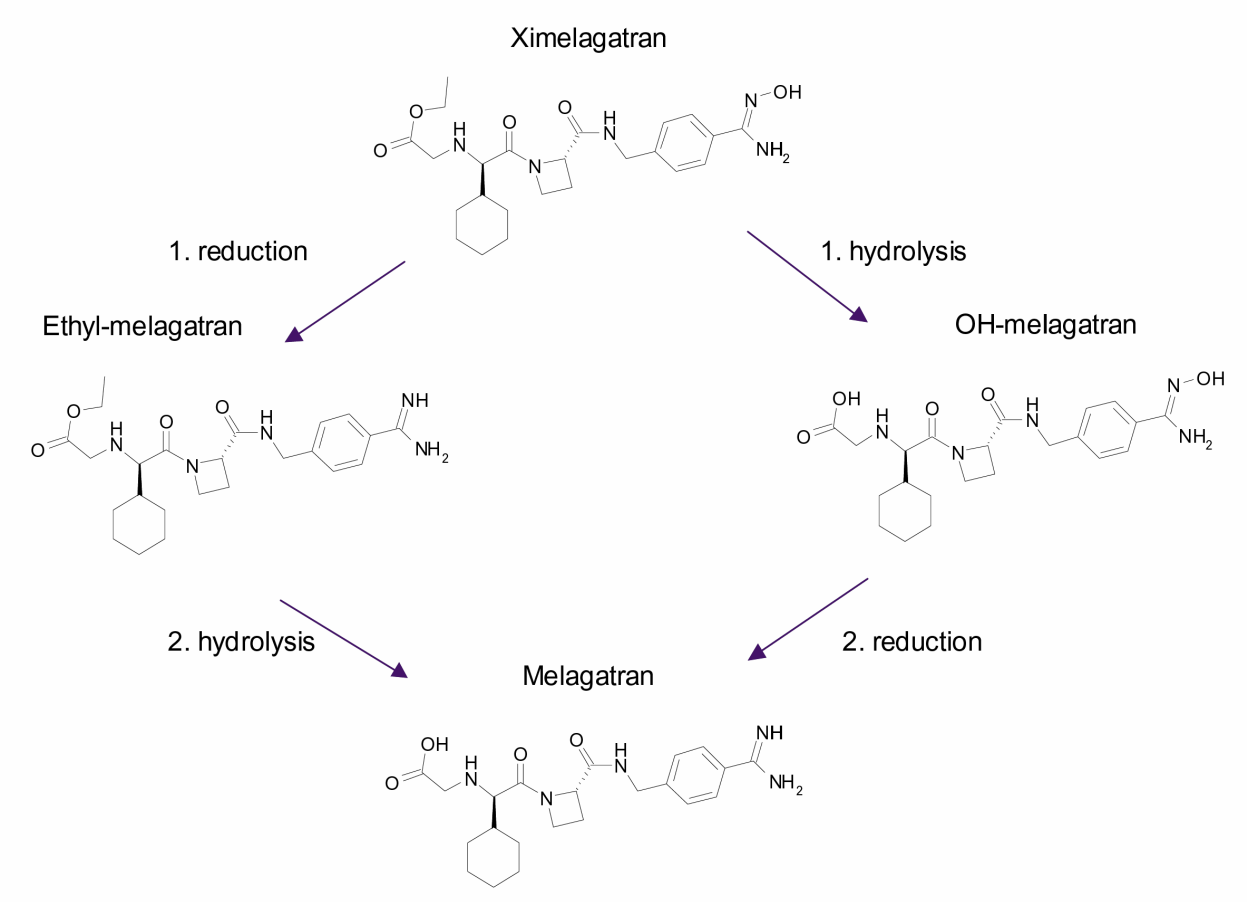
Please refer to the Clinical Pharmacology, Biopharmaceutics Review for details.

Melagatran is a potent, competitive and reversible direct inhibitor of the serine protease α-thrombin. Thrombin converts fibrinogen to fibrin in the coagulation cascade. In addition thrombin also produces platelet aggregation. Inhibition of thrombin by ximelagatran prevents thrombus development and reduces platelet aggregation. Melagatran inhibits both free and fibrin-bound thrombin and thrombin-induced aggregation of platelets.

### A. Pharmacokinetics

Ximelagatran is a prodrug, which after oral administration yields melagatran as the dominant metabolite. As shown in Figure 1 below, there are two intermediate metabolites in the pathway from the prodrug to melagatran: ethyl-melagatran and OH-melagatran. Ximelagatran and OH-melagatran are essentially inactive as thrombin inhibitors while melagatran and ethyl-melagatran are both active inhibitors of thrombin. The formation of melagatran primarily occurs via formation of the OH-melagatran intermediate metabolite. The formation of melagatran via ethyl-melagatran is a relatively minor pathway.

**Figure 1: The metabolic pathways of ximelagatran for the formation of melagatran (Figure taken from Figure 1 of Summary of Clinical Pharmacology Studies).**




The conversion (hydrolysis) from ximelagatran to OH-melagatran is rapid and mediated primarily by esterases. The reduction reaction from OH-melagatran to melagatran is a reduction reaction through a yet unidentified metabolic pathway. No cytochrome P450 enzymes have been identified in the reduction of OH-melagatran to melagatran.

Ximelagatran, melagatran, ethyl-melagatran, or OH-melagatran has not been shown shown to inhibit human drug metabolizing enzymes in various in vitro studies (e.g. human liver microsomes). In vivo studies in rats showed that ximelagatran did not induce P450 enzymes that were studied.

Melagatran is eliminated primarily by excretion in urine with a renal clearance that corresponds to the glomerular filtration rate.

**Summary of key pharmacokinetic (PK) findings in healthy subjects**

- The pharmacokinetics are dose proportional
- The bioavailability is approximately 20%
- The half-life of melagatran is approximately 3 hours

- Inter-individual variability in exposure: CV = 20%, while intra-individual variability in exposure: CV = 10%
- Melagatran is main excreted unchanged in urine

**Summary of key PK findings in patients**

- The pharmacokinetics are dose proportional
- The half-life of melagatran is approximately 5 hours
- Inter-individual variability in exposure: CV = 50%, Intra-individual variability in exposure: CV = 25%

**Effects of renal impairment on PK of melagatran**

The effects of renal impairment on ximelagatran PK were evaluated in an open-label, randomized, single dose study. Subjects enrolled in this study were given single oral doses of Ximelagatran 24 mg. Plasma concentrations and amount of melagatran, the active metabolite of ximelagatran, excreted in urine were measured up to 24 hours post dose.

Study subjects were between the ages of 20 to 80 yeas old and were enrolled into 3 groups. Note that the creatinine clearance (CrCL) was calculated according to the Cockcroft & Gault formula.

Group 1 CrCL > 50 ml/min/1.73m$^2$
Group 2 CrCL 20-30 ml/min/1.73m$^2$
Group 3 CrCL 10-19 ml/min/1.73m$^2$

12 subjects were enrolled into Group 1 and this group was considered as having normal renal function. Groups 2 and 3 were lumped together as one group and were considered as having renal impairment. There were a total of 12 subjects in these 2 groups. In Group 1, the mean Cr CL (using Cockcroft Gault) was 107.7 $\pm$ 24.3 ml/min (min 63.9 ml/min and max 151.1 ml/min). In groups 2 and 3, the mean CrCL was 27.1 $\pm$ 9.7 ml/min (min 13.9 ml/min and max 43.1 ml/min).

The effects of renal impairment on melagatran PK are summarized in **Table IV** below. As shown in the table, the exposure to melagatran in terms of AUC is approximately 5 fold higher in patients with renal impairment compared to "Normals." Similarly $C_{max}$ is about 2 fold higher.

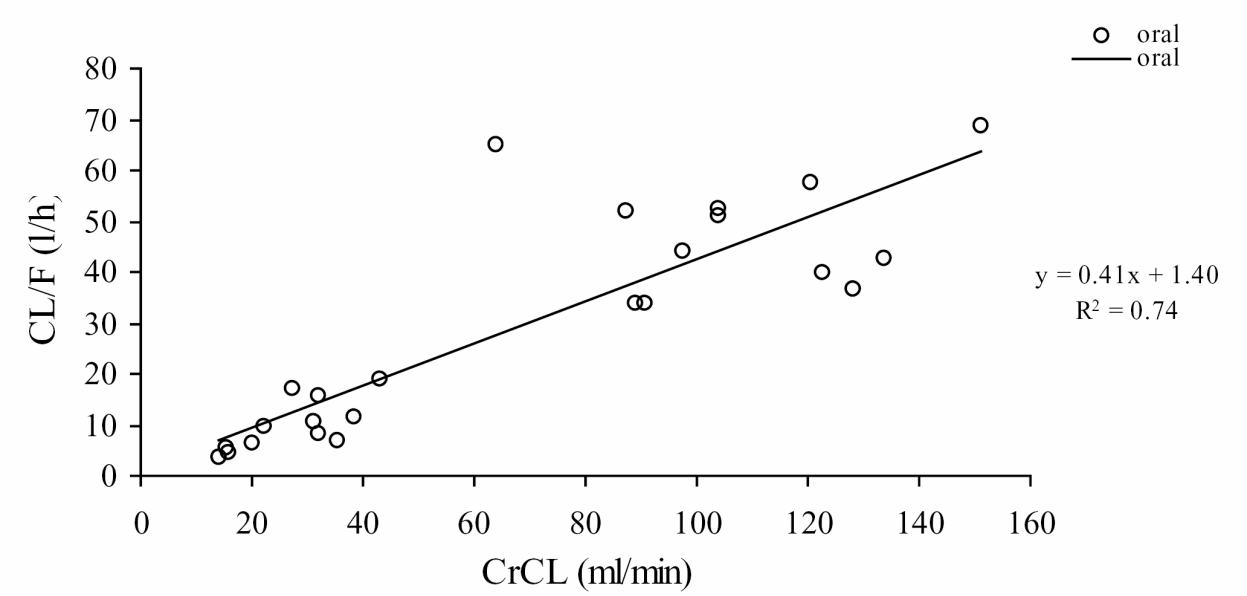
**Table IV: Effects of renal impairment on the pharmacokinetics of melagatran, the active metabolite of ximelagatran. Values represent the ratio of subjects with renal impairment to patients with normal renal function.**

| Variable | Group comparison | Estimate | 95% CI | |
|---|---|---|---|---|
| | | | Lower | Upper |
| AUC | Renally impaired/normal | 5.33 | 3.76 | 7.56 |
| $C_{max}$ | Renally impaired/normal | 1.83 | 1.42 | 2.37 |
| t1/2 | Renally impaired/normal | 2.60 | 2.07 | 3.26 |
| $F_{rel}$ | Renally impaired/normal | 1.32 | 1.04 | 1.67 |
| CL/F | Renally impaired/normal | 0.188 | 0.132 | 0.266 |
| CLR | Renally impaired/normal | 0.106 | 0.065 | 0.173 |

Data in this table obtained from synopsis report of study SH-TP1-0026

The oral clearance (CL/F) of melagatran correlates very well with CrCL calculated using Cockcroft Gault as shown in Figure 2 below. This type of relationship makes justification of a fixed dose of ximelagatran for all patients rather problematic particularly in the setting of increased risk of serious adverse events with increasing exposure to drug.

**Figure 2: Mean CrCL (ml/min) versus CL/F (l/h) after oral ximelagatran administration (This figure taken from Figure 11:9 of Sponsor's Clinical Pharmacology Study Report for study SH-TP1-0026)**




**Effect of hepatic impairment on PK of melagatran**

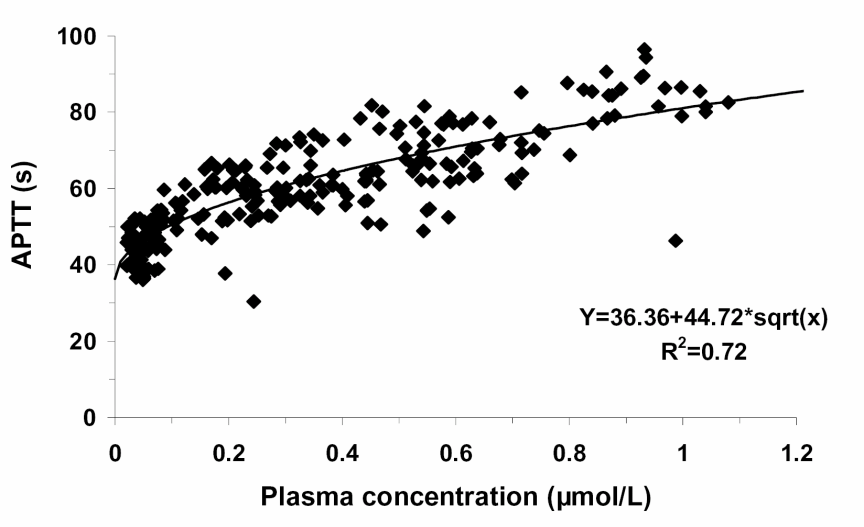
An open-label, single dose study was conducted in patients with hepatic impairment and controls matched in terms of age, sex, and weight. A total of 12 liver patients and 12 controls were studied. The subjects ranged in age from 45-69 years. Among the patients with hepatic impairment, 7 had mild impairment (Child Pugh A) while 5 had moderate impairment (Child Pugh B). The results of this study showed that the pharmacokinetics of melagatran were similar in patients with or without hepatic impairment.

B. Pharmacodynamics

Melagatran, the active metabolite of ximelagatran, prolongs the activated partial thromboplastin time (aPTT) and INR ratio. Melagatran is an inhibitor of thrombin which happens to be Factor II in the coagulation cascade. aPTT is prolonged by abnormalities in factors involved in the intrinsic coagulation cascade (e.g. FVIII, FIX, XI, XII, etc), fibrinogen, and also factors in the common pathway (e.g. FII, V, X). Prolongation of aPTT occurs in a concentration dependent manner and is non-linear. The relationship between melagatran concentrations and aPTT

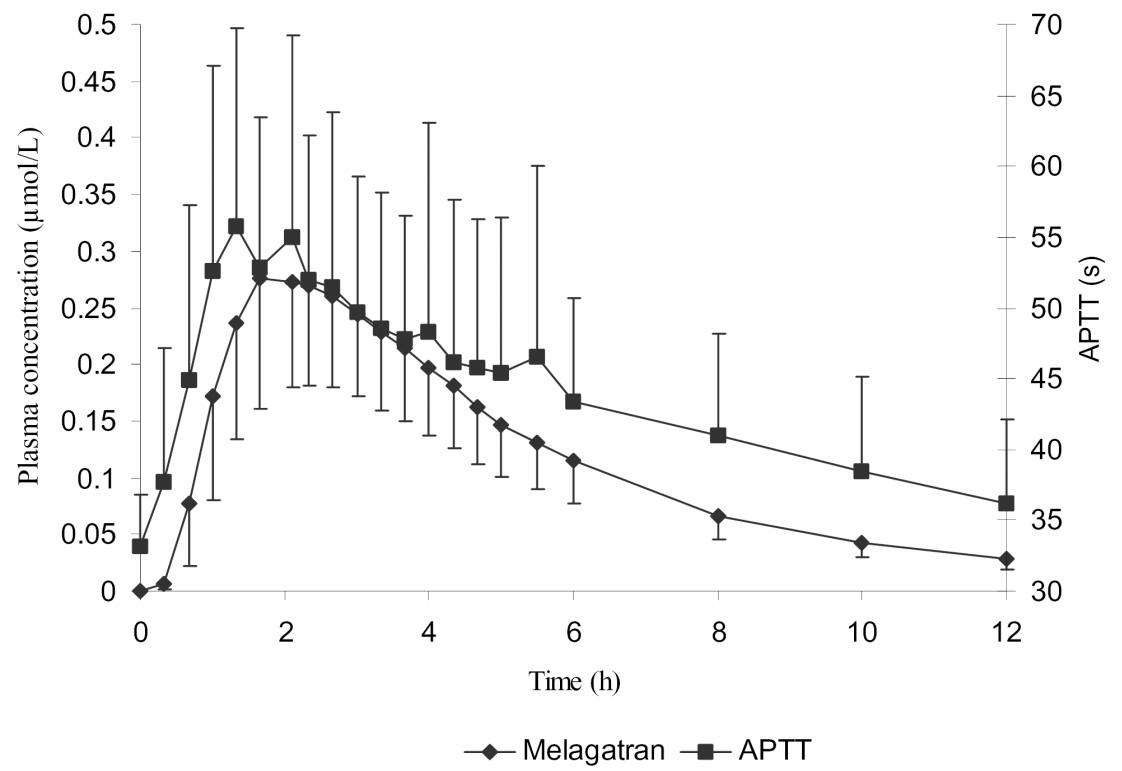
prolongation is illustrated in Figure 3 and Figure 4 below. It is important to note that the pharmacodynamic data in the figures below has been generated from healthy subjects.

**Figure 3: Relationship between aPTT levels and plasma concentrations of melagatran (obtained from Figure 18 of the Sponsor's Summary of Clinical Pharmacology Studies).**



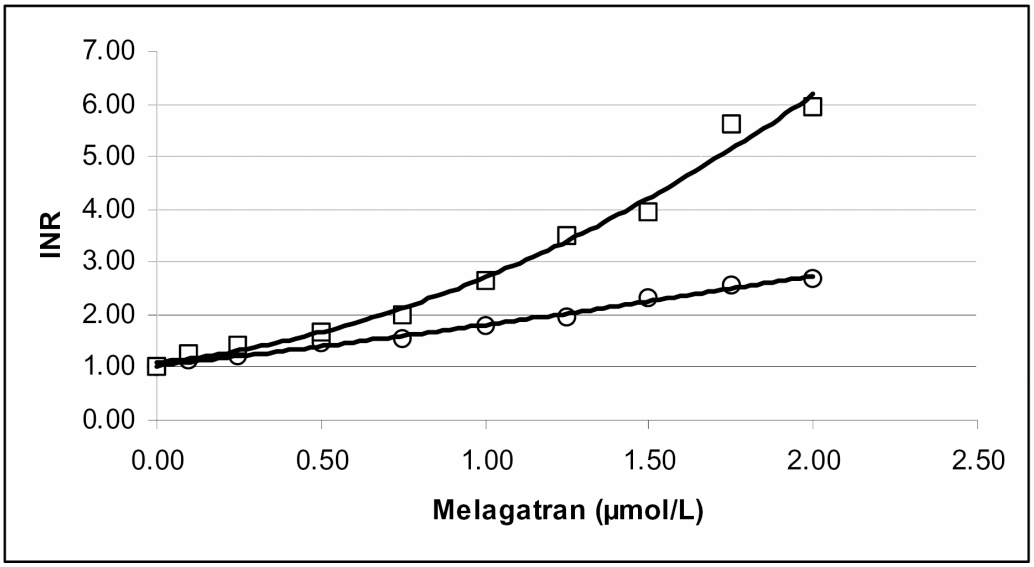

As shown in **Figure 4** below, after oral dosing with ximelagatran, the aPTT starts to prolong within 20 minutes of dosing and peak prolongations are observed 2 hours post dosing. The effect of ximelagatran on aPTT at the end of 12 hours is approximately at the same level seen pre-dose. Based on this figure it appears as though a once a day dosing strategy would be sub-optimal. It can not be determined from this trial whether a more than twice a day dosing regimen would result in greater efficacy compared to twice a day dosing.

**Figure 4: Relationship between the PK time course of melagatran and the PD time course of aPTT (obtained from Figure 19 of the Sponsor's Summary of Clinical Pharmacology Studies)**




In addition to effects on aPTT, ximelagatran can also affect the prothrombin time (PT) and INR. In vitro studies in human plasma have demonstrated that the PT was prolonged by melagatran but that the corresponding INR varied considerably depending on the ISI of the thromboplastin. It is predicted that INR's of approximately 1.2 to 1.8 are expected at steady-state trough and peak plasma concentrations of melagatran in atrial fibrillation receiving 36 mg bid. At very high plasma melagatran concentrations the INR ranged from approximately 2.8 to 6 depending on the ISI of the thromboplastin used. Figure 5 below summarizes the relationship between melagatran plasma concentrations and INR based on an in vitro study using two different thromboplastins with differing ISI levels.

**Figure 5: INR values plotted versus plasma melagatran concentration (Figure obtained from Figure 27 of Summary of Clinical Pharmacology Studies)**




Data derived from the individual non-clinical Report 1767-01 in Module 4.
The figure shows a prolongation of INR values using an ISI of 1.9 or 1.08 for Thrombomat (○) and Thromborel S (□), respectively.

## VI. Description of Clinical Data and Sources

### A. Overall Data

The sources of data used in generating this review include:

- Electronic NDA submission for N21686
- Sponsor's reply to an Information Request dated March 23, 2004, June 3, 2004
- NDA21686 4-month Safety Update Report

## B. Tables Listing the Clinical Trials

**Table V: Summary of the clinical trials submitted in support of the atrial fibrillation indication**

| | |
|---|---|
| SPORTIF V<br>"Efficacy and Safety of the Oral Direct Thrombin Inhibitor H376/95 Compared with Dose-Adjusted Warfarin (Coumadin) in the Prevention of Stroke and Systemic Embolic Events in Patients with Atrial Fibrillation." | • Pivotal Phase 3 study<br>• Randomized, **Double-blind**<br>• **U.S. and Canada**<br>• Active control (warfarin INR 2 – 3)<br>• Fixed dose ximelagatran 36 mg bid<br>• Patients with nonvalvular atrial fibrillation + at least one additional risk factor for stroke |
| SPORTIF III<br>"Efficacy and Safety of the Oral Direct Thrombin Inhibitor H376/95 Compared with Dose-Adjusted Warfarin (Coumadin) in the Prevention of Stroke and Systemic Embolic Events in Patients with Atrial Fibrillation." | • Pivotal Phase 3 study<br>• randomized, **Unblind**<br>• **Europe and Asia**<br>• Active control (warfarin INR 2 – 3)<br>• Fixed dose of ximelagatran 36 mg bid<br>• Population of patients with nonvalvular atrial fibrillation + at least one additional risk factor for stroke |
| SPORTIF II, SPORTIF IV | • Non-pivotal, phase 2 studies<br>• Unblind with respect warfarin arm<br>• Dose ranging (20 mg, 40mg, 60mg)<br>• Active control (warfarin INR 2 – 3)<br>• Primarily designed to assess long term safety of ximelagatran |

## C. Postmarketing Experience

No post-marketing safety data are available. Marketing authorization was received in France in December 2003 for the prevention of venous thromboembolism (VTE) in patients undergoing hip or knee replacement surgery. However, ximelagatran has not yet obtained full approval by the European Union and thus is not commercially available as of April 2004.

## D. Literature Review

The studies in support of the efficacy of ximelagatran (H376/95) are active control, non-inferiority trials. The active control chosen for both studies was warfarin titrated to an INR of 2 to 3. One aspect in trying to understand whether ximelagatran is non-inferior to warfarin is to understand the efficacy of warfarin over placebo.

Table VI below summarizes a total of 6 randomized controlled trials of warfarin in patients with chronic, non-rheumatic atrial fibrillation. The 6 studies (or portions of them) listed in the table were used to derive the benefit of warfarin relative to placebo. Please refer to Dr. John Lawrence's Statistical Review for further details regarding the benefit of warfarin over placebo to use in the non-inferiority analysis.

*Similarities and differences in terms of study design*

In terms of study design, 2 of the listed studies were blinded while 4 were unblind. One of the SPORTIF trials was blinded while the other was not. Also in terms of design, the studies differed significantly from each other and from the SPORTIF studies with respect to the target INR (e.g. BAATAF Target INR 1.5 – 2.7, AFASAK Target INR 2.8 – 4.2). In the SPORTIF studies the target INR was 2 – 3.

Lack of blinding may be less problematic for "hard" endpoints such as death or severely disabling stroke. However, lack of blinding may be more problematic when evaluating "softer" endpoints such as TIA's.

*Similarities and differences with respect to patient demographics*

Patients in the 6 listed warfarin studies were similar in age and gender to those patients in the SPORTIF studies. However, in 5/6 listed studies, fewer patients had a prior history of stroke/TIA compared to the SPORTIF studies. In addition, there were fewer patients with a history of hypertension in the 6 warfarin studies compared to the SPORTIF studies.

*Similarities and differences with respect to endpoints*

The definitions of stroke varied in some of the studies. For example in the Veterans Affairs Stroke Prevention study ($5^{th}$ study in Table VI), stroke was defined as a new neurologic deficit that persisted for longer than 12 hours. Most other studies used a new neurologic deficit lasting $\geq$ 24 hours to define stroke. The AFASAK study ($1^{st}$ study in Table VI) defined a "minor stroke" as a focal neurologic deficit lasting more than 24 hours but less than one week. Most of the other studies did not define such a subgroup of patients. Also in terms of differences in endpoints, the EAFT study included death from vascular disease and non-fatal MI in its primary endpoint and thus the overall event rate was significantly higher in that study compared to either of the SPORTIF studies.

It is important to note that in many of the studies listed in Table VI, intracranial bleed/hemorrhage was not included as part of the primary efficacy endpoint but was rather a secondary endpoint or assessed as a safety endpoint. On the other hand, in the two SPORTIF studies, the primary endpoint included all strokes both ischemic and hemorrhagic. In addition, the two SPORTIF studies did not include TIA's as part of their primary endpoint unlike what was done in the AFASAK study. Hemorrhagic strokes or TIA's did not occur in large numbers in any of the studies listed in Table VI.

In summary, it seems acceptable to use the studies listed in Table VI to define the benefit of warfarin relative to placebo despite differences in study design, endpoints, target INR's, and patient population. Based on the 6 studies in this table, the benefit of warfarin over placebo appears to be a rather large 64% (95% CI → 47%, 75%) relative risk reduction. The studies listed in Table VI clearly suggest that warfarin is an effective oral anti-coagulant in terms of preventing the composite endpoint of stroke and systemic embolic events.

**Table VI: Summary of randomized controlled trials of warfarin in patients with atrial fibrillation**

| Study | Population studied | Design | Endpoints | Results (based on primary endpoint) |
|---|---|---|---|---|
| AFASAK Study[a]<br><br>(n = 335 randomized to warfarin) | Chronic, non-valvular atrial fibrillation;<br><br>Median age = 72.8 years; 53% male; 6% with previous stroke or TIA; 32% with hypertension | Randomized, Unblinded, placebo-controlled<br><br>Study duration was 2 years or until "end of trial"<br><br>Target INR range = 2.8 – 4.2 | 1° = Stroke, TIA, embolic complication to viscera and extremities | There were a total of 5 events in the warfarin arm (incidence rate as reported in the manuscript = 2.0% / year). The 5 events included 4 "disabling strokes" and 1 "fatal" stroke.<br><br>There were a total of 21 events in the control (placebo) arm (incidence rate as reported in the manuscript = 5.5 % / year). The 21 events included 3 TIA's, 2 minor strokes, 3 non-disabling strokes, 7 disabling strokes, 4 fatal strokes, 2 visceral emboli.<br><br>INR between 2.8 and 4.2 → 42% of time<br>INR > 4.2 → 0.6% of time<br>INR < 2.4 → 26% of time |
| BAATAF Study[b]<br><br>(n = 212 randomized to warfarin) | Chronic, non-valvular, non-Rheumatic atrial fibrillation;<br><br>Mean age = 68.5 years; 75% male, 3% with previous stroke; 51% with hypertension | Randomized, Unblinded, controlled (control group consisted of patients that received no treatment or ASA per their choice)<br><br>Target INR range = 1.5 – 2.7 (INR's | 1° = Ischemic stroke<br><br>(TIA's were not counted as endpoints)<br><br>Major bleeds were also counted and defined in the manuscript | Follow-up in the warfarin arm was 487 patient-years; There were a total of 2 ischemic strokes during this time (0.41%/ year) that included 1 stroke classified as "severe."<br><br>Follow-up in the control arm was 435 patient-years; There were a total of 13 ischemic strokes during this time (2.98%/year) that included 5 that were classified as "severe."<br><br>In terms of "major bleeds", there were 2 on warfarin (including 1 fatal intracranial bleed) and 1 in the control arm as reported in the text.<br><br>INR between 1.5 to 2.7 → 83% of time |

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| | | were checked every 3 weeks during study) | | INR > 2.7 → 9% of time<br>INR < 1.5 → 8% of time |
| CAFA Study[c]<br><br>(n = 187 randomized to warfarin) | Chronic atrial fibrillation;<br><br>Mean age = 68 years; 76% males, 3.2% with previous stroke or TIA; 43.3% with history of hypertension | Randomized, Double-Blind, Placebo-controlled<br><br>Target INR range = 2 – 3 | 1° = Ischemic strokes (except lacunar), systemic embolism to the gut, legs, kidneys or arm, intracranial or fatal hemorrhage<br><br>2° = TIA's, lacunar infarctions, major bleeding, minor bleeding, death | Mean follow-up period was 15.2 months<br><br>Primary endpoint<br>A total of 8 events occurred in the warfarin arm = 3.4%/patient-year. Of the 8 events, 5 were nonlacunar strokes, 1 was a non-CNS embolic event, 1 was an intracranial hemorrhage, and 1 was "other" fatal hemorrhage.<br><br>A total of 11events occurred in the control arm (incidence as reported in the manuscript = 4.6% / patient-year. Of the 11 events, 9 were nonlacunar strokes and 2 were non-CNS embolic events.<br><br>Secondary endpoint<br>A total of 13 events occurred in the warfarin arm while a total of 10 occurred in the control arm (excluding bleeding events)<br><br>A total of 5 major bleeds occurred in patients in the warfarin arm compared to 1 major bleed in a patient in the control arm.<br><br>INR between 2 to 3 → 43.7%<br>INR > 3 → 16.6%<br>INR < 2 → 39.6% |
| SPAF Study[d] | Nonrheumatic atrial fibrillation; | Randomized, Unblinded, | 1° = Ischemic stroke, systemic | Primary endpoint<br>For the primary endpoint, the total patient-years of |

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| (n = 210 randomized to warfarin) | Mean age = 65 years; 74% males; 8% with previous stroke or TIA; 49% with history of hypertension | controlled (placebo)<br><br>Target INR range = 2.0 – 4.5 | embolism<br><br>2° = Intracerebral hemorrhage, TIA's, MI's, mortality | observation were 260 on warfarin and 244 on placebo.<br><br>In the warfarin arm there were a total of 6 events - event rate is 2.3%/patient-year. This includes 4 minimally disabling strokes and 2 moderate to severely disabling strokes.<br>In the placebo arm there were a total of 18 events on placebo<br>- event rate is 7.4%/patient-year. This includes 10 minimally disabling strokes, 7 moderate to severely disabling strokes, and 1 systemic embolic event.<br><br>Secondary endpoints<br>There was one intracerebral hemorrhage on warfarin and none on placebo. There were 3 TIA's on warfarin and 4 on placebo. There were 2 myocardial infarctions on warfarin and 2 on placebo. There were 6 deaths in the warfarin arm and 8 on placebo.<br><br>In terms of "relevant bleeding" there were a total of 3 cases in the warfarin arm and 1 in the placebo arm<br><br>INR 2 to 4.5 → 71% of all values<br>INR > 4.5 → 5%<br>INR < 2 → 23% |
| VA Stroke prevention Study[e]<br><br>(n = 260 randomized to | Nonrheumatic atrial fibrillation;<br><br>Mean age = 67 years; 100% males, 0% with history of stroke; 55% with history of hypertension | Randomized, Double-Blind, Placebo-controlled<br><br>Target INR | 1° = Cerebral infarction<br><br>2° = cerebral hemorrhage and death | Primary endpoint<br>Mean follow-up in the warfarin arm was 1.8 years while mean follow-up in the control arm was 1.7 years.<br><br>There were a total of 4 primary events in the warfarin arm including 3 patients with minor impairment and 1 patient with a fatal stroke. Incidence = 0.9% /patient- |

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| warfarin) | | range = 1.4 – 2.8<br><br>INR's were checked monthly | Systemic embolic events were not assessed in this study<br><br>Major bleeding was defined in the manuscript | year.<br><br>There were a total of 19 events in the control (placebo) arm including 9 patients with no impairment post stroke, 7 with minor impairment, 2 with major impairment, and 1 fatal stroke. Incidence = 4.3%/patient-year.<br><br>Secondary endpoint<br>Cerebral hemorrhage occurred in 1 patient in the warfarin arm versus 0 patients in the control arm. The total number of deaths was 15 in the warfarin arm and 22 in the control arm.<br><br>INR 1.4 to 2.8 → 56% of time<br>INR > 2.8 → 15% of time<br>INR < 1.4 → 29% of time |
| EAFT Study[f]<br><br>(n = 225 randomized to warfarin) | Nonrheumatic atrial fibrillation with history of TIA or stroke within 3 months of study onset<br><br>Mean age = 71 years; 59% males, 44% with history of hypertension | Randomized, Unblinded, controlled (placebo)<br><br>Target INR = 2.5 – 4.0<br><br>(warfarin was not the anticoagulant necessarily given to all patients) | 1° = Death from vascular disease, non-fatal stroke, non-fatal MI, systemic embolism;<br><br>2° = death from all causes, all strokes and major thromboembolic events<br><br>"Major bleed" was defined in manuscript. | Primary endpoint<br>There was a total of 507 patient-years follow up in the anticoagulation arm and 405 patient-years follow up in the control arm. There were a total of 43 events in the anticoagulation arm and a total of 67 events in the control arm. The event rate equals 8.5% in the anticoagulation arm and 16.5% in the control arm. The components of the primary endpoint driving the composite were mainly nonfatal stroke and vascular death.<br><br>In terms of major and/or fatal bleeding, there were 13 events in the anticoagulation arm and 3 events in the control arm.<br><br>INR 2.5 to 4 → 59 % of time |

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|---|---|---|---|---|
| | | | | INR > 4 → 9% of time<br>INR < 2.5 → 32% |

[a]Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. Lancet 1989;1:175-8.

[b]Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. N Engl J Med 1990;323(22):1505-11.

[c]Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian atrial fibrillation anticoagulation (CAFA) study. J Am Coll Cardiol 1991;18:349-55.

[d]Stroke Prevention in Atrial Fibrillation Investigators (SPAF). Stroke Prevention in Atrial Fibrillation Study. Final results. Circulation 1991;84:527-39.

[e]Ezekowitz MD, Bridgers SL, James KE, Carliner NH, Colling CL, Gornick CC, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veteran Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators (SPINAF). N Engl J Med 1992;327:1406-1412.

[f]European Atrial Fibrillation Trial Study Group. Secondary prevention of vascular events in patients with non-rheumatic atrial fibrillation and recent transient ischaemic attack or minor ischaemic stroke. Lancet 1993;342:1255-1262.

## VII. Clinical Review Methods

### A. How the Review was Conducted

I spent the majority of time reviewing the two pivotal SPORTIF trials submitted in support of the chronic use of ximelagatran in patients with atrial fibrillation. Relatively less time was spent in reviewing SPORTIF II/IV, as this was a smaller, non-pivotal, dose ranging study. Each of the SPORTIF trials was reviewed separately. The efficacy and safety data from the 2 SPORTIF studies were not pooled as one was a blinded study while the other was not. In addition, the results particularly with respect to efficacy were different in the two studies.

With respect to safety, I spent relatively more time reviewing hepatobiliary adverse events. Case narratives of all hepatobiliary serious adverse events and discontinuations due to hepatobiliary AE's in both SPORTIF trials were read in detail by the reviewer. Line listings of the causes of death from both studies were reviewed and narratives from selected cases of death were read in depth.

### B. Overview of Materials Consulted in Review

The materials used in this review include the electronic NDA submissions, Sponsor's responses to Information requests, Literature references, and Sponsor's 4 month safety update.

### C. Overview of Methods Used to Evaluate Data Quality and Integrity

I evaluated the case narratives for selected AE's and cross checked the statements in the narratives with Case Report Forms (CRF) for consistency. It is important to note that in at least one instance the case narrative referred to abnormal or elevated liver enzyme values but no such documentation was reported in the CRF. The reason was that only liver enzymes obtained at pre-specified time points and measured by the Central Lab were recorded in the CRF. Local lab tests of liver enzymes were not recorded in the study database regardless of whether they were abnormal or not.

One study site in SPORTIF V was evaluated by the Division of Scientific Investigation (DSI) where the source documents were reviewed and compared to the case report forms. In addition, DSI reviewed inclusion and exclusion criteria, protocol deviations, and also adverse event reporting. One study site in the SPORTIF III study is also to be inspected by DSI.

The sponsor's analysis of the primary endpoint in SPORTIF V was re-analyzed and confirmed by the statistical reviewer Dr. John Lawrence. The primary endpoint in SPORTIF III was not re-analyzed and confirmed by Dr. Lawrence.

### D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The studies conducted were performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice.

E. Evaluation of Financial Disclosure

The sponsor submitted FDA Form 3454 for each of the two pivotal studies, SPORTIF III and SPORTIF V. In Form 3454, the sponsor attested that they had not entered into any financial arrangements with investigators whereby the value of compensation to the investigator could be affected by the outcome of the study. The sponsor also certified that each investigator/sub-investigator in the study was required to disclose to the sponsor whether the investigator had a proprietary interest in the product or a significant equity interest in the sponsor. Finally the sponsor also certified that no investigator was the recipient of significant payments of other sorts.

The sponsor received financial disclosure forms in the vast majority of investigators/sub-investigators. There were 4 sub-investigators that participated in SPORTIF III that did not complete financial disclosure forms. These 4 sub-investigators had moved from their respective facilities and no forwarding addresses were available. These 4 sites enrolled 39 (1.1%) of the 3410 patients randomized. There were 5 investigators that did not complete financial disclosure forms despite attempts to contact them by the sponsor. These 5 investigators enrolled a total of 64 (1.9%) of the 3410 patients randomized.

Two investigators in SPORTIF III, disclosed that they held "significant equity interest" as defined by 21CFR54.2. The first of these investigators was Dr. Bertil Olsson, who was co-chair of the Executive Steering Committee and Principal investigator at center 312. Center 312 randomized 33 patients. The second investigator was Dr. Jan Hysing, a sub-investigator at site 253. This center randomized 15 patients.

I do not believe the financial disclosure issues discussed above significantly impacted the study outcomes as the number of patients enrolled at each center was a small fraction of the total number of subjects randomized.

## VIII. Integrated Review of Efficacy

A. Brief Statement of Conclusions

SPORTIF III and SPORTIF V are two Phase III, active control, non-inferiority studies that were provided in support of NDA21-686. Both studies compared the effectiveness of a fixed dose of ximelagatran 36 mg administered twice a day to warfarin targeting an INR of 2 to 3 in patients with nonvalvular atrial fibrillation and at least one additional risk factor for stroke. The studies were very similar in design except that SPORTIF III was open label while SPORTIF V was double-blind. The primary endpoint was the composite of all strokes (fatal and non-fatal) and systemic embolic events. The sponsor pre-specified a non-inferiority margin of 2% points in the event rate in both studies. 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."

The two studies produced divergent results despite their similar designs. In SPORTIF V, the event rate was higher in the ximelagatran arm compared to the warfarin arm while in SPORTIF III, the event rate was higher in the warfarin arm compared to the ximelagatran arm. In both studies, the efficacy of ximelagatran was within the sponsor's pre-specified non-inferiority margin of 2%. Comparing the event rates in the common arm of both studies, the rate in the

ximelagatran arm was approximately the same at 1.6%/year. However, the event rate in the warfarin arm varied nearly 2-fold between the studies: 1.2% in SPORTIF V and 2.3% in SPORTIF III. Differences in the patient populations in the two studies at baseline could be a possible explanation of the differences in the event rate in the treatment arms. Patients in SPORTIF V were slightly older, had lower blood pressures on average, had fewer patients with histories of transient ischemic attacks (TIA's) or strokes, and had greater consumption of HMG CoA reductase inhibitors than did patients enrolled in SPORTIF III. However, it is difficult to explain why such differences would lead to differences in event rates in the warfarin arm while leaving the event rate in the ximelagatran arm unaffected. In a setting where two studies produce divergent results, I would favor the results from the double-blind study. The event rate in both studies was primarily driven by the occurrence of ischemic strokes. More than 80% of the events in both studies were ischemic strokes.

B. General Approach to Review of the Efficacy of the Drug

SPORTIF III and SPORTIF V were the two studies submitted in support of efficacy. Each of these studies was reviewed separately as the former was unblinded while the latter was a blinded study.

C. Detailed Review of Trials by Indication

1. SPORTIF V

Study Title: "Efficacy and Safety of the Oral Direct Thrombin Inhibitor H376/95 Compared with Dose-Adjusted Warfarin (Coumadin) in the Prevention of Stroke and Systemic Embolic Events in Patients with Atrial Fibrillation"

*a. Study dates*

Date first patient enrolled: July 24, 2000
Date enrollment ended: December 7, 2001
Date study closure procedures began: January 13, 2003
Date final patient completed study: June 19, 2003
Date of Clinical Study Report: October 9, 2003

*b. Protocol amendments:*

Table VII below summarizes the date at which the original protocol was issued along with the dates of all subsequent amendments to the original protocol. Below Table VII are listed the summaries of each protocol amendment.

**Table VII: Summary of the issue dates of the original protocol and protocol amendments to Study 0005**

| Version of Protocol or Protocol Amendment | Date of issue |
|---|---|
| Original Protocol | May 19, 2000 |
| Approval amendment 1 | July 18, 2000 |
| Approval amendment 2 | July 11, 2001 |
| Approval amendment 3 | October 31, 2001 |
| Approval amendment 4 | August 8, 2002 |
| Approval amendment 5 | November 7, 2002 |

Amendment 1:

- Additional pregnancy testing was to be done at 3 month intervals
- Occult bleeding determined by the laboratory would not be classified as a minor bleed
- Recommendations for managing patients that may experience ALT elevations were broadened to include all liver enzymes (e.g. ALAT, ASAT, alkaline phosphatase, and bilirubin). In addition, treatment discontinuation would be considered if there is a rapid increase in liver enzymes to > 5x ULN.
- A melagatran PK sample was to be obtained from patients with persistent LFT elevations.
- The study was to remain open until the sponsor collected a minimum of 2000 patient-years of exposure data per treatment arm.

Amendment 2:

- A sub study to measure pancreas volumes and plasma CCK concentrations was added
- Definitions of lone atrial fibrillation and prosthetic heart valves were clarified
- Clarifies the exclusion of a patient with known intracardiac thrombus
- Clarifies that the intent to treat population (ITT) includes all randomized patients regardless of whether the study medication had been taken.
- Clarifies the data to record once a patient had discontinued study medication. Once a patient prematurely discontinued the study the adverse events (AE's) that were to be recorded included the primary events of stroke and systemic embolic events in addition to death. After premature study drug discontinuation, patients were contacted via phone on a monthly basis to ascertain these events. It was not necessary to record other AE's.
- The timing of the study medication on the day of a point of care INR determination was clarified
- The limit on the period of study drug interruption was clarified. There were 30 consecutive days (60 days for cardioversion) during which a patient was allowed to temporarily discontinue study drug. During the course of the entire study, a patient could be temporarily off study drug for a total of 60 non-consecutive days.
- The concomitant medications to be recorded in the 14 day period following a serious adverse event was clarified

Amendment 3

- The total number of patients randomized and the total number of sites was increased. The Data Safety Monitoring Board (DSMB) noted that the aggregate primary event rate was substantially below what was anticipated. Based on this information from the DSMB, the Executive Steering Committee (ESC) recommended increasing exposure to

5000 patient-years via increasing both duration of patient exposure and through an increase in the total number of subjects enrolled in the trial.

- The time period for enrollment was increased
- Instructions were revised for management of patients with elevated liver enzymes. Patients with LFT's > 2x ULN would undergo weekly LFT testing until the affected entity returns to below the ULN or the baseline measurement. Patients with an LFT elevation > 3x ULN will have a blood sample drawn for extensive liver function testing. If the affected entity did not demonstrate a tendency to decrease or an alternative reason for the elevation was found, patients were to be withdrawn from study drug. Patients with an LFT > 5x ULN were to be withdrawn from study drug.

Amendment 4

- A new plan for the transition from study medication to open label warfarin at the termination visit was implemented to provide additional protection against too little anticoagulation.
- The amendment provided clarity regarding the frequency of measurement of full safety laboratory values and INR's.
- There was also clarification as to when to obtain blinded and unblinded INR's during interruptions of study medication.

Amendment 5

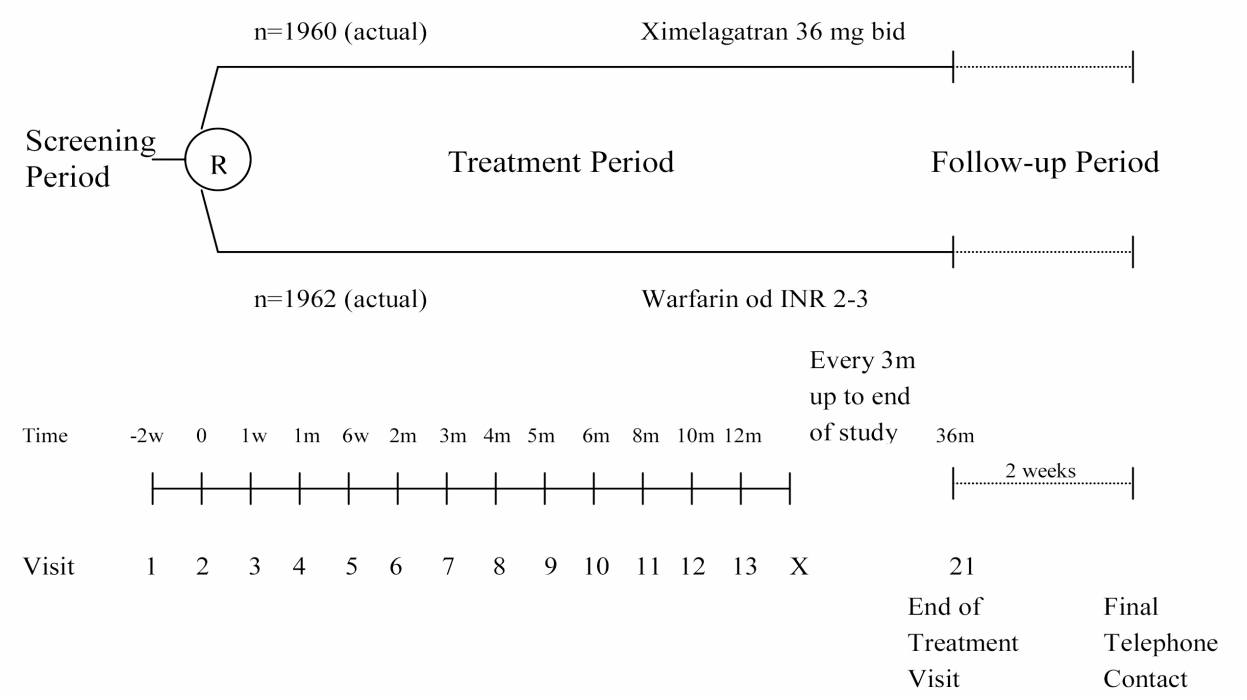
The treatment period of "active" patients and the follow-up period of "inactive" patients (those prematurely discontinued) were increased to a maximum of 36 months. Consequently additional office visits and procedures were added.

*c. Study Design:*

SPORTIF V was a multi-centered, randomized, double-blind, double-dummy, active controlled (warfarin), parallel group study in patients with chronic, non-valvular atrial fibrillation (AF). This study was conducted primarily in the United States and Canada.

The study randomized a total of 3922 patients. The treatment period ranged between 12 to 36 months. As shown in Figure 6 below, patients were randomized to either fixed doses of Ximelagatran 36 mg bid or to Warfarin titrated to an INR of 2 to 3 via monthly blood tests.

**Figure 6: Study Schema for SPORTIF V (Figure taken from Figure 1 of SPORTIF V CSR)**




Patients that prematurely discontinued study medication (e.g. to bleeding or hepatobiliary AE) were not withdrawn from the trial but were followed up via monthly telephone contacts until the end of the study with regard to primary events (e.g. strokes and SEE's) and death. Patients that discontinued from study medication and withdrew from study were not followed for primary efficacy endpoints or death.

Patients were stratified based on aspirin use and a previous history of stroke/TIA.

The primary analysis consisted of events adjudicated by the CEAC. Events that were "suspected" by the study site investigator were eligible for adjudication. If an event was not "suspected" it would not have been forwarded to the CEAC for adjudication.

If an investigator suspected an event, an initial fax describing the event was to be sent to the CEAC committee within 24 hours of the knowledge of the event. The initial fax was followed up with more complete forms within 14 days of knowledge of the event. Data that were to be submitted to the CEAC for purposes of adjudication could have included documentation of the patient's history and physical exam, discharge summary, neurology consultation, CT scans, Angiograms, X-rays, ECG's, or appropriate enzyme levels.

The CEAC was to work in accordance with the principles described in a written charter. Pairs of primary reviewers were to independently assess each event and if in agreement, this adjudication would be accepted. In cases of disagreement, a second, final review would be performed by a third independent reviewer.

The trial included a Data Safety Monitoring Board (DSMB), Clinical Events Adjudication Committee (CEAC), and an Executive Steering Committee (ESC).

The DSMB was composed of the following members:

- Prof. Robert Hart (Chairman), Department of Medicine (Neurology), University of Texas Health Science Centre, USA.
- Prof. David DeMets, Department of Biostatistics, University of Wisconsin Medical School, USA.
- Prof. Gudrun Boysen, Bispebjerg Hospital, Neurologisk Afd, Denmark.
- Prof. Desmond Julian, London, UK.

The CEAC was composed of the following members listed below. All were based at University Hospital in Dresden, Germany.

- Prof. Rüdiger von Kummer (Chairman) Department of Neuroradiology
- Dr. Angela Müller, Department of Neuroradiology
- Dr. Dirk Mucha, Department of Neuroradiology
- Prof. Heinz Reichmann, Department of Neurology
- Dr. Georg Gahn, Department of Neurology
- Dr. Thomas Schwarz, Department of Internal Medicine
- Dr. Alexander Schmeisser, Department of Cardiology
- Olaf Wunderlich (Administrator)

The Executive steering committee members included:

- Jonathan Halperin, MD (Co-chairman), Mount Sinai Medical Center, New York, USA
- Bertil Olsson, MD PhD (Co-chairman) University Hospital, Lund, Sweden
- Gregory Albers, MD,Stanford Stroke Center, Palo Alto, USA
- Hans Christoph Diener, MD, PhD, University of Essen, Germany
- Palle Petersen, MD, PhD, University Hospital of Copenhagen, Hvidovre Hospital, Hvidovre, Denmark
- Alec Vahanian, MD Hospital Tenon, Paris, France
- Margaretha Grind, MD, PhD, AstraZeneca R&D Charnwood, UK
- Lars Frison, PhD, AstraZeneca R&D Molndal, Sweden
- Stephen Partridge, PhD, AstraZeneca R&D Charnwood, UK
- Mark Nevinson, BPharm (Secretary) AstraZeneca R&D Charnwood, UK
- Jay Horrow, MD, AstraZeneca LP, Wilmington, DE, USA

*d. Rationale for doses selected*

Rationale for warfarin dose:
Warfarin is the most widely used oral anticoagulant worldwide. Treatment guidelines recommend the use of long-term oral anticoagulant therapy, aiming for an INR of 2 – 3, for all patients who are at high risk of stroke. Over anticoagulation increases the risk of bleeding events while under anticoagulation increases the risk of ischemic stroke. Warfarin has proven to be highly effective at preventing strokes and SEE in previous placebo controlled clinical trials.

Please refer to Section VI D "Literature Review" for further details regarding placebo controlled studies involving warfarin.

Rationale for ximelagtran dose:
The sponsor took into consideration an array of data in selecting the fixed dose of 36 mg bid used in both SPORTIF studies. These include:

- A phase 2 study (SPORTIF II), suggested that there were fewer minor bleeding events in the 20 and 40 mg bid dose groups relative to a 60 mg bid dose group. In addition, there was some concern about possible dose related increase in liver enzyme abnormalities based on SPORTIF II.
- A phase 2 study conducted in patients for the prevention of venous thromboembolism showed enhanced efficacy of doses of 24 mg bid versus doses of 12 mg bid.
- Pre-clinical thrombosis models showing that acceptable antithrombotic effect was achieved at plasma concentrations of 0.05 to 0.5 mmol/L.
- Capillary bleeding time study showed that mean plasma levels of 0.31 mmol/L caused a small, non-significant prolongation of bleeding time.

*e. Blinding/Randomization*

A double-dummy technique was used to preserve blinding during this trial. Real INR values and warfarin doses were entered into a centralized interactive voice response system (IVRS) that would issue a standardized report containing a real INR value if the patient was randomized to warfarin or a sham value if the patient was randomized to ximelagatran (H736/95).

At the End of Treatment visit, a plan was implemented by the sponsor that retained study blinding while transitioning patients from ximelagatran to warfarin. This was necessary for patients in the ximelagatran arm because of the risk of reduced anti-coagulation due to the quick offset of ximelagatran and the slow onset of open-label warfarin (details of this plan are in the sponosor's clinical study report).

A centralized and automated IVRS was used to manage the randomization process, allowing for stratification factors, and to aid the efficient distribution of study drugs.

### *f. Pre-specified Study Objectives*

Primary objective:

To determine whether H376/95 is non-inferior compared to dose-adjusted warfarin aiming for an INR 2.0 – 3.0 for the prevention of all strokes (fatal and non-fatal) and systemic embolic events in patients with chronic non-valular AF.

Secondary objectives:

- To compare the efficacy of H376/95 to that of dose-adjusted warfarin aiming for an INR 2.0 – 3.0 for the combined endpoint of prevention of death, non-fatal strokes, non-fatal systemic embolic events and non-fatal acute myocardial infarction (AMI).
- To compare the efficacy of H376/95 to that of dose-adjusted warfarin aiming for an INR 2.0 – 3.0 for the combined endpoint of prevention of ischemic strokes, TIA's, and systemic embolic events
- To assess the safety of H376/95 compared to dose-adjusted warfarin aiming for INR 2.0 – 3.0 with an emphasis on major and minor bleeding events and any treatment discontinuations

Tertiary objectives

- To compare the efficacy of H376/95 and dose-adjusted warfarin aiming for an INR 2.0 – 3.0 for the prevention of all strokes with a poor outcome (defined by a Modified Rankin score of > 3 at 3 months post-stroke or a Barthel score of < 60 at 3 months post-stroke).
- To compare the efficacy of H376/95 and dose-adjusted warfarin aiming for an INR 2.0 – 3.0 for the prevention of all strokes and systemic embolic events in patients $\geq$ 75 years of age with AF and to compare this with patients below the age of 75 years.

It is important to note that patients that prematurely discontinued study medication but agreed to remain in the study were followed up for primary events (e.g. strokes and SEE's) and death via regular telephone contact.

### *g. Definitions of study endpoints*

**Definition of stroke and TIA:**
Stroke was defined as the abrupt onset over minutes to hours of a focal neurological deficit persisting for more than 24 h and caused by altered cerebral circulation in the distribution of a cervical or cerebral artery. If the focal neurological deficit lasted for less than 24 h, the event was classified as a TIA. Patients that died within 30 days of the onset of the stroke were regarded as having had a fatal stroke. Patients who had a stroke and then died 30 or more days after the onset of the stroke were regarded as having non-stroke death.

**Definition of stroke with poor outcome:**
A stroke was defined as having a poor outcome if it met 1 or more of the following criteria:

• An increased (relative to baseline) Modified Rankin score to =3 at 3 months post stroke
• A Barthel score of <60 at 3 months post-stroke
• A fatal stroke. This component was not specified in the protocol, but added in the statistical analysis plan (SAP) before unblinding of study data;

**Definition of Systemic embolic events (SEE's):**
SEE was defined as abrupt vascular insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms, eg, atherosclerosis instrumentation. In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities should be made with caution and requires arteriographic demonstration of abrupt arterial occlusion.

**Definition of acute myocardial infarction:**
AMI was defined as the presence of at least 2 of the following:

- Typical retrosternal chest pain indicating AMI for at least 20 minutes
- Electrocardiogram showing changes typical of AMI
- Elevation of the cardiac enzyme creatine phosphokinase, myocardial band (CK-MB) or troponin to more than twice ULN.

The occurrence of AMI was documented only in patients that were on study drug at the time of the event.

**Definition of Major Bleed:**
Major bleed was defined as one or more of the following:
• Fatal bleeding
• Clinically overt bleeding associated with a fall in hemoglobin of 20 g/L (2 g/dL) or more
• Clinically overt bleeding leading to transfusion of 2 or more units of whole blood or erythrocytes
• Bleeding in areas of special concern, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial or atraumatic intra-articular bleeding.

Subdural and epidural bleeds, but not intracerebral bleeds were treated as major bleeds. Intracerebral bleeding events were handled in the same way as stroke and were not documented on the "Major Bleed" Form. Major bleeds were reported only for active patients at the time of the event.

**Definition of Minor Bleed:**

Any bleeding event other than a major bleed was considered a minor bleed. Bleeding events initially characterized by the investigator as a major bleed but subsequently rejected by CEAC, as such, were considered minor bleeds.

*h. Inclusion/Exclusion Criteria*

**Inclusion Criteria**

1. Chronic non-valvular AF (constant or paroxysmal) verified by at least 2 ECG readings in the last year separated by at least one week; the second ECG being carried out within the 2 weeks prior to randomization. Historical evidence of the first ECG showing AF (i.e. tracing available in patient notes) is required. In addition one of the items under 2 must be present.

2. At least one of the following risk factors for stroke:

- Hypertension requiring anti-hypertensive treatment, and which is below 180/100 mmHg on randomization
- Age =75 years
- Previous cerebral ischemic attack (stroke or TIA)
- Previous systemic embolism
- Left ventricular dysfunction (either LVEF <40% or symptomatic CHF)
- Age =65 years AND coronary artery disease
- Age =65 years AND diabetes mellitus.

3. Aged 18 years or older.

4. Willing and able to give signed informed consent.

**Exclusion Criteria**

1. Stroke within the previous 30 days or TIA within the previous 3 days.

2. The following conditions associated with increased risk of bleeding:

- History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleed
- Overt gastrointestinal bleed in the previous year
- Endoscopically verified ulcer disease in the previous 30 days
- Major surgical procedure or trauma in the previous 30 days
- Persistent blood pressure =180/100 mmHg (with or without antihypertensive therapy)
- Hemorrhagic disorder.

3. Lone AF (atrial fibrillation in the absence of overt cardiovascular disease or precipitating illness).

4. Transient AF caused by reversible disorders, e.g. current thyrotoxicosis, pulmonary embolism.

5. Rheumatic valve disease, a prosthetic heart valve or valve surgery.

6. Active endocarditis.

7. Diagnosis of current atrial myxoma or left ventricular thrombus.

8. Hospitalization for acute coronary syndromes or percutaneous coronary artery intervention within the last 30 days.

9. Planned cardioversion (electrical or chemical).

10. Concomitant treatment with antiplatelet or fibrinolytic agents (or use of these within 10 and 30 days, respectively, before randomization); other anticoagulant agents or continuous treatment with NSAID drugs. However, aspirin =100 mg/day is allowed during the whole study period.

11. Requirement for chronic anticoagulant treatment other than for atrial fibrillation

(eg repeated deep vein thrombosis, hereditary thrombophilia).

12. Renal impairment defined as a calculated creatinine clearance <30 mL/min

13. Active liver disease or persistent elevation of liver enzymes $\geq$ 2 times the upper limit of the normal level defined by central laboratories.

14. Anemia (Hb <100 $g*L^{-1}$) or a platelet count <100 x $10^9$ $L^{-1}$.

15. Childbearing potential (female patients should be at least 2 years post-menopausal, surgically sterile or using medically accepted contraceptive measures as judged by the investigator).

16. Pregnancy or lactation (see Section 10.2).

17. Drug addiction and/or alcohol abuse in the past 3 years.

18. Participation in any clinical study involving an investigational drug within one month prior to randomization; previous randomization in this study or any other 376/95 study.

19. Other diseases that give an estimated life survival less than 36 months as judged by the treating physician.

20. Inability to complete the study according to the protocol, eg inability to comply with the monitoring required for therapy control, significant mental impairment or geographic inaccessibility to a laboratory.

21. Previous significant disabling stroke (defined as Modified Rankin score =3).

22. Planned major surgery.

23. Allergy or intolerance to warfarin.

### *i. Statistical considerations (please refer to statistical review for details)*

**Major changes to planned analyses:**
Please refer to the statistical review by Dr. John Lawrence for further details regarding amendments to the statistical analysis plan.

The major changes to the planned analyses that were implemented prior to unblinding the database were:

- The methodology for the analysis of the primary endpoint was changed to a patient-years calculation assuming an exponentially distributed event rate.
- The definition of the ITT population was modified to include all randomized patients. The original protocol and SAP stated that patients needed two baseline ECG's demonstrating atrial fibrillation to be eligible for study entry.

The major changes to the planned analyses that were implemented after the database was unblinded were:

- AE's were counted in all periods where they occurred instead of only in the period when they started.
- The analyses of the tertiary objectives and liver function tests were performed for the ITT population instead of the OT analysis set.

**Analysis of primary endpoint:**
The primary objective of the study was to be addressed with an intention to treat (ITT) approach. In this approach, all randomized patients were included until the date of each patient's study closure visit or final contact, irrespective of their protocol adherence. The primary objective was to be addressed with a life table analysis. Primary events (e.g. all strokes or SEE's, and death) were reported for all patients in the trial including patients who had already suffered a study endpoint. For example, if a patient suffered an MI as a study endpoint (and assuming he/she did not withdraw consent), this patient would continued to be followed for the occurrence of death or a primary endpoint event such as stroke or SEE. For patients with multiple occurrences of events the time to first event was used. Each patient was counted once in any composite endpoint that included at least one of the events that the patient had experienced. In this non-inferiority trial, the margin of non-inferiority chosen was 2% points in the annual event rate of stroke and SEE.

As part of a sensitivity analysis, the primary objective was also analyzed using the On Treatment (OT) approach. This was done to examine the robustness of the primary analysis using the ITT approach. While the ITT approach is a conservative approach particularly when dealing with superiority study designs, the OT approach may be a more appropriate when trying to interpret the results of a non-inferiority study. The OT approach included all patients in the ITT population but only their time on active study drug was used for analysis. A maximum continuous interruption of up to 30 days without active study drug was allowed. For patients undergoing cardioversion, a maximum 60 continuous days of study drug interruption was allowed. A maximum of 60 accumulated days of interruption was also permitted.

**Analyses of the secondary and tertiary endpoints:**
Analyses related to the secondary and tertiary objectives, as well as descriptive and exploratory analyses were to be based on an On Treatment approach according to the statistical analysis plan. In this approach, all patients in the ITT population would be included as long as they remained on study medication. A maximum continuous interruption of up to 30 days without active study drug was allowed. For patients undergoing cardioversion, a maximum 60 continuous days of

study drug interruption was allowed. Any patient with a study drug interruption (H376/95 or warfarin) of more than 60 days would not be included in the On Treatment analysis.
It is important to note that in the clinical study report the sponsor analyzed the tertiary endpoint using the ITT population, a change from what was proposed in the statistical analysis plan. This change was implemented after the database was unblinded.

**Analysis of adverse events(AE's):**
AE's were actively collected up to the End of Treatment Visit. AE's that started in 1 time period and continued into a subsequent time period(s) were counted once in each period. This was a difference from the SAP where AE's were to be counted only in the period of onset. If an ongoing AE worsened in a subsequent period, it was reported as a new AE at the time of worsening and was then counted twice; at the time of initial onset and at the time of worsening onset.
All analyses of liver function tests were performed using the ITT analysis, which utilized the full time pattern for liver function elevations. This is a change from the SAP, which had specified the OT analysis.

**Other analysis considerations:**
No Analyses based on a per protocol approach were performed.
The sponsor was to make every effort to trace all patients until the very end of the study and to record their status with regard to occurrence of stroke, systemic embolism and mortality.

**Determination of Sample Size:**
It was estimated that the combined rate of ischemic stroke, hemorrhagic stroke and systemic embolism for patients in this study protocol would be 3.1% per year for both treatment groups. In order to obtain 90% statistical power, adopting a one sided $\alpha = 0.025$, approximately 1600 patient years of follow-up per treatment group would be necessary to establish a non-inferiority of H376/95 compared to adjusted-dose warfarin within 2% per year. Assuming an average follow-up of 16 months about 2400 patients would be required in total. In the protocol it was stated that if the aggregate event rate (stroke + SEE) was low, follow-up could be extended to ensure a minimum of 80 events.

**DSMB Interim safety analysis:**

The DSMB was to formally compare the two treatment arms for safety with respect to:

- All cause mortality
- All cause mortality, all strokes, and all systemic embolic events
- All strokes and all systemic embolic events
- Major bleeding

This was to be done when approximately 12.5%, 25%, 50%, and 75% of the expected total number of patient exposure years have been reached. Pre-determined stopping rules for a positive or a negative trend were described in a DSMB charter. No adjustments to the significance levels in the final statistical analyses of the primary, secondary or tertiary endpoints were made.

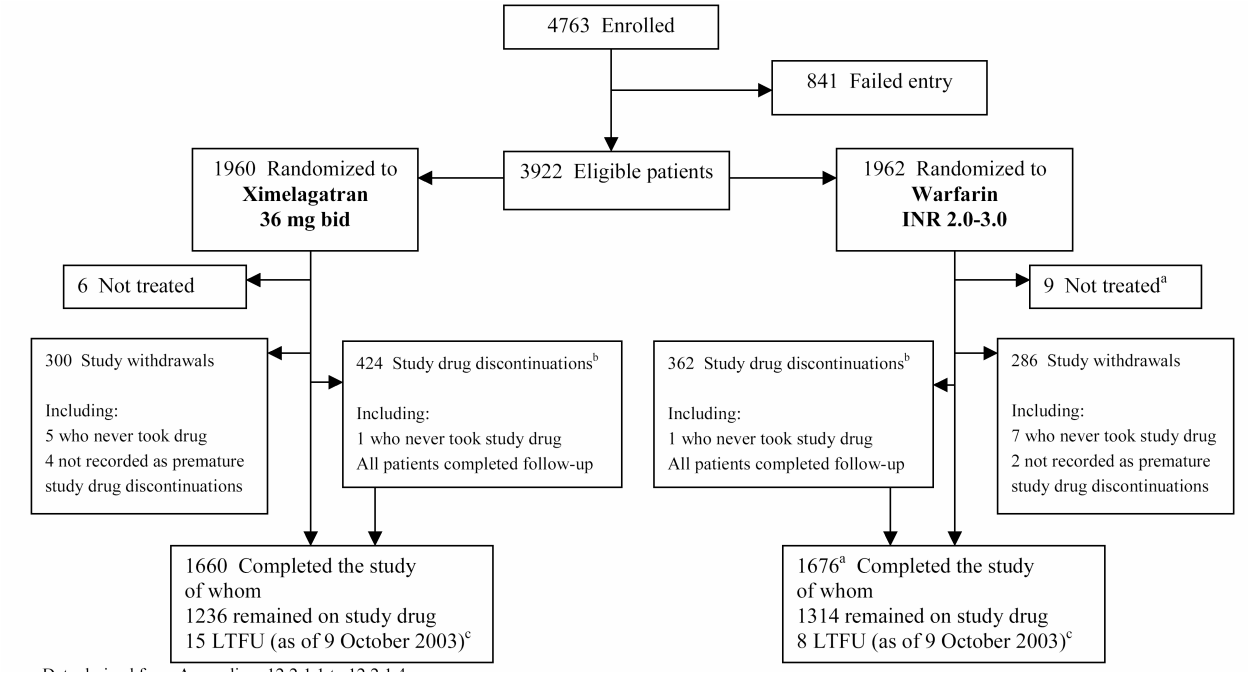
*j. Study patient disposition*

A total of 4763 patients were enrolled into the study from which 3922 were randomized. Patients were randomized from a total of 422 centers in the U.S. (n = 361) and Canada (n = 61). A total of 1960 and 1962 patients were randomized to H376/95 and warfarin respectively. These patients formed the ITT population.

The population used for the analysis of the safety data was equal to 3906 patients (3922 – 16). Of the 16 patients excluded in the safety population, 15 were randomized but never received study drug. One patient received a dose of study drug but no post-randomization data are available.

Please refer to Figure 7 below for a summary of patient disposition in SPORTIF V.

**Figure 7: Patient disposition in SPORTIF V (Figure taken from Figure 4 of SPORTIF V CSR)**




As seen in Figure 7 above, 841 patients were enrolled but not randomized. Approximately 2/3 of these patients were not eligible because they failed to meet inclusion/exclusion criteria. Sixty three percent of patients remained on ximelagatran at the time of study closure, while 67% remained on warfarin. A total of 300 patients prematurely withdrew from the ximelagatran arm while 286 did soon the warfarin arm.

As shown in Figure 7, there were a total of 586 study withdrawals that were pre-mature in SPORTIF V (300 ximelagatran, 286 warfarin). It is important to note that these patients were not followed up for primary endpoint events (e.g. stroke or SEE) or death. Although not shown in this review, the reasons for pre-mature withdrawal were similar in both study arms.

Unlike patients that pre-maturely withdrew from the study, patients that discontinued study drug were followed up for primary endpoint events or death. As shown in Figure 7 above, there were 424 study drug discontinuations in the ximelagatran arm and 362 study drug discontinuations in the warfarin arm.

As shown in Table VIII below, the total number of study drug discontinuations was greater on ximelagatran compared to warfarin by an absolute value of 3.7%. A large portion of this excess discontinuation on ximelagatran could be attributed to adverse events specifically liver enzyme abnormalities.

**Table VIII: Table summarizing the primary reason for discontinuing study drug (ITT population)[a]**

| Reason for study drug discontinuation | Ximelagatran N=1960 | | Warfarin N=1962 | | Total N=3922 | |
|---|---|---|---|---|---|---|
| Total | 720 | (36.7%) | 646 | (33.0%) | 1366 | (34.8%) |
| Eligibility criteria not fulfilled | 15 | (0.8%) | 8 | (0.4%) | 23 | (0.6%) |
| Adverse event | 238 | (12.1%) | 175 | (8.9%) | 413 | (10.5%) |
| Patient decision (Consent withdrawn from study drug) | 207 | (10.6%) | 197 | (10.0%) | 404 | (10.3%) |
| Endpoint events | | | | | | |
| Acute myocardial infarction | 10 | (0.5%) | 12 | (0.6%) | 22 | (0.6%) |
| Major bleed | 30 | (1.5%) | 41 | (2.1%) | 71 | (1.8%) |
| Stroke | 24 | (1.2%) | 24 | (1.2%) | 48 | (1.2%) |
| Systemic embolic event | 6 | (0.3%) | 5 | (0.3%) | 11 | (0.3%) |
| Transient ischemic attack | 16 | (0.8%) | 8 | (0.4%) | 24 | (0.6%) |
| Death | 44 | (2.2%) | 47 | (2.4%) | 91 | (2.3%) |
| Other | 130 | (6.6%) | 129 | (6.6%) | 259 | (6.6%) |

[a]The data in this table obtained from table 18 of SPORTIF V CSR

As shown in Table IX below, even after excluding patients with ALAT > 3x ULN, the total study drug discontinuation rate was numerically higher on ximelagatran compared to warfarin.

**Table IX: Comparison of total study drug discontinuation rates including and excluding patients with ALAT > 3x ULN[a]**

| | Ximelagatran | Warfarin | Totals |
|---|---|---|---|
| Total discontinuation rate (including patients with ALAT > 3x ULN) | 720/1960 (36.7%) | 646/1962 (33.0%) | 1366 (34.8%) |
| Total discontinuation rate (excluding patients with ALAT > 3x ULN) | 640/1843 (34.7%) | 635/1947 (32.6%) | 1275 (33.6%) |

[a]Data in this table obtained from Tables 18 and 19 of SPORTIF V CSR

After study closure activities, vital status and primary event status were unknown for a total of 226 subjects: 119 Ximelagatran, 107 warfarin. Efforts were made to contact these subjects and information related to the primary event or death was obtained on 203/226 subjects. In 188 of the 203 patients in whom follow-up information was available, the information was obtained prior to unblinding the database. In 15 of the 203 patient in whom follow-up information was available, the information was obtained after unblinding the database. Information on these 203 patients ***was not*** entered into the database. In these 203 patients, follow-up information revealed that there was one stroke in a patient that received warfarin. There were a total of 15 deaths (8 ximelagatran, 7 warfarin). A total of 23 patients (226 – 203) were lost to follow-up and for whom there is no primary event or vital status information.

*k. Protocol deviations*

In the clinical study report for SPORTIF V the sponsor summarizes 4 different classes of protocol deviations that occurred: Enrollment deviations, Study drug administration deviations, Deviations relating to interruption of study drug, Unblinding deviations. Each of these is summarized below.

**Enrollment deviations (violations of inclusion/exclusion criteria)**:

For Table X below, please refer to Section VII, C, 1, h ("Inclusion/Exclusion Criteria") for reference to each criteria #.

**Table X: Summary of inclusion/exclusion criteria violations by treatment groups (Please refer to inclusion/exclusion criteria section of this review to match the number with the description of the criteria)[a]**

| | **Ximelagatran (n = 1960)** | **Warfarin (n = 1962)** | **Total (n = 3922)** |
|---|---|---|---|
| Criteria # | Inclusion Criteria violations | | |
| 1 | 27 | 18 | 45 |
| 2 | 3 | 1 | 4 |
| Criteria # | Exclusion Criteria violations | | |
| 1 | 0 | 1 | 1 |
| 2 (bullet 1) | 0 | 3 | 2 |
| 2 (bullet 2) | 2 | 2 | 4 |
| 2 (bullet 5) | 0 | 1 | 1 |
| 3 | 1 | 0 | 1 |
| 5 | 2 | 2 | 4 |
| 8 | 1 | 0 | 1 |
| 9 | 1 | 0 | 1 |
| 10 | 2 | 0 | 2 |
| 12 | 5 | 2 | 7 |
| 13 | 4 | 1 | 5 |
| 14 | 3 | 4 | 7 |
| 17 | 0 | 4 | 4 |
| 21 | 1 | 1 | 2 |

[a]Data in this table obtained from Table 11.1.20 of SPORTIF V NDA submission

**Study drug administration deviations:**

The sponsor reported a drug shipment error in which a study drug (Coumadin 2.5 mg YY series) from a different AstraZeneca study bearing similar bottle numbers had been shipped to numerous sites. SPORTIF V and THRIVE V shared common bottle numbers and bottle appearances. Five patients were affected by this shipping error.

Drug dispensing errors resulted in 13 patients receiving a total of 14 bottles of the incorrect active medication. In 11 instances (8 ximelagatran, 3 warfarin), patients took both active medications together for various durations. In 2 instances, patients returned the incorrect bottles. No endpoints occurred during the time of dispensing error. Endpoints occurred for 3 of the 13 patients 6 months or more after the administration error and are unlikely to be related to the error.

**Deviations relating to interruption of study drug:**

A greater number of warfarin patients (61.6%) interrupted study drug for any duration compared with ximelagatran patients (41.7%) as shown in Table XI below. One of the factors that might

be responsible for the discrepancy in treatment interruption between the two groups is that patients in the warfarin arm with an INR > 3 would have their treatment interrupted until the INR had returned to less than 3. It is unclear if this was the only reason in the discrepancy between the two study arms or if there are other reasons.

**Table XI: Number (%) of patients by total days of treatment interruption, and treatment group[a]**

| Treatment interruption | Ximelagatran N=1952 | | Warfarin N=1952 | | Total N=3904 | |
|---|---|---|---|---|---|---|
| No interruption | 1138 | (58.3) | 749 | (38.4) | 1887 | (48.3) |
| Any interruption | 814 | (41.7) | 1203 | (61.6) | 2017 | (51.7) |
| 1 to 7 days | 463 | (23.7) | 660 | (33.8) | 1123 | (28.8) |
| 8 to 30 days | 274 | (14.0) | 431 | (22.1) | 705 | (18.1) |
| 31 to 60 days | 63 | (3.2) | 83 | (4.3) | 146 | (3.7) |
| >60 days | 14 | (0.7) | 29 | (1.5) | 43 | (1.1) |

[a]Data in this table obtained from Table 27 of SPORTIF V CSR.

**Unblinding deviations:**

Three patients were unblinded during the study. Two unblindings were intentional and one was unintentional.

**Intervals greater than 28 ± 3 days between INR measurements:**

As shown in Table XII below, more than 75% of patients had INR's measured at an interval of ≤ 31 days as specified in the protocol.

**Table XII: INR measurements for warfarin patients in SPORTIF V**

| INR measurement interval | Number (%) of INR measurements |
|---|---|
| Total number of INR measurements | 44108 (100) |
| Number of INR's with interval ≤31 days (<1 month) | 33758 (77) |
| Number of INR's with interval ≥31 days (at least 1 month) | 10350 (23) |
| Number of INR's with interval ≥ 31 but <61 days (between 1 and 2 months) | 10099 (23) |
| Number of INR's with interval 61 days (at least 2 months) | 251 (<1) |

Data in this table obtained from Table 6 of 5May2004 FDA Information request

*l. Demographics and other patient characteristics*

The characteristics of the patients enrolled in SPORTIF V are described in the Table XIII below. The majority of patients were males, Caucasians, and ≥ 65 years old. Approximately 75% had two or more risk factors for stroke (in addition to non-valvular atrial fibrillation). In general, the baseline characteristics were similar in the two treatment arms suggesting that randomization in the trial was successful.

Comparing the population in SPORTIF V to that in SPORTIF III, there were fewer non-smokers and more non-drinkers in the former compared to the latter study. In addition, the number of patients using aspirin at baseline was greater in SPORTIF V compared to SPORTIF III.

**Table XIII: Patient characteristics at screening: number (%) of patients by treatment group (ITT population)[a]**

| Characteristic | | Ximelagatran N=1960 | | Warfarin N=1962 | | Total N=3922 | |
|---|---|---|---|---|---|---|---|
| Sex | Male | 1365 | (69.9) | 1353 | (69.0) | 2718 | (69.3) |
| | Female | 595 | (30.4) | 609 | (31.0) | 1204 | (30.7) |
| Race | Caucasian | 1875 | (95.7) | 1888 | (96.2) | 3763 | (95.9) |
| | Black | 67 | (3.4) | 58 | (3.0) | 125 | (3.2) |
| | Oriental | 15 | (0.8) | 10 | (0.5) | 25 | (0.6) |
| | Other | 3 | (0.2) | 6 | (0.3) | 9 | (0.2) |
| Age | <65 | 383 | (19.5) | 401 | (20.4) | 784 | (20.0) |
| | ³65 to <75 | 739 | (37.7) | 741 | (37.8) | 1480 | (37.7) |
| | ³75 | 838 | (42.8) | 820 | (41.8) | 1658 | (42.3) |
| Number of unique stroke risk factors (In addition to AF) | 0 | 3 | (0.2) | 4 | (0.2) | 7 | (0.2) |
| | 1 | 490 | (25.0) | 509 | (25.9) | 999 | (25.5) |
| | 2 | 600 | (30.6) | 597 | (30.4) | 1197 | (30.5) |
| | 3 | 472 | (24.1) | 459 | (23.4) | 931 | (23.7) |
| | 4 | 274 | (14.0) | 273 | (13.9) | 547 | (13.9) |
| | 5 | 100 | (5.1) | 96 | (4.9) | 196 | (5.0) |
| | 6 | 20 | (1.0) | 21 | (1.1) | 41 | (1.0) |
| | 7 | 1 | (0.0) | 3 | (0.2) | 4 | (0.1) |
| Smoking | Non-smoker | 711 | (36.3) | 689 | (35.1) | 1400 | (35.7) |
| | Previous smoker | 1085 | (55.4) | 1108 | (56.5) | 2193 | (55.9) |
| | Occasional smoker | 27 | (1.4) | 31 | (1.6) | 58 | (1.5) |
| | Daily smoker | 137 | (7.0) | 134 | (6.8) | 271 | (6.9) |
| Alcohol use | No | 1151 | (58.7) | 1163 | (59.3) | 2314 | (59.0) |
| | Yes | 808 | (41.2) | 799 | (40.7) | 1607 | (41.0) |
| | Missing | 1 | (0.1) | 0 | (0.0) | 1 | (0.0) |
| Drinks per week | None | 1151 | (58.7) | 1163 | (59.3) | 2314 | (59.0) |
| | >0 to £5 drinks | 450 | (23.0) | 458 | (23.3) | 908 | (23.2) |
| | >5 to £10 drinks | 208 | (10.6) | 200 | (10.2) | 408 | (10.4) |
| | >10 to £15 drinks | 103 | (5.3) | 102 | (5.2) | 205 | (5.2) |
| | >15 to £20 drinks | 5 | (0.3) | 7 | (0.4) | 12 | (0.3) |
| | >20 drinks | 39 | (2.0) | 30 | (1.5) | 69 | (1.8) |
| | Missing | 4 | (0.2) | 2 | (0.1) | 6 | (0.2) |
| Undergone any major surgery | No | 452 | (23.1) | 501 | (25.5) | 953 | (24.3) |
| | Yes | 1506 | (76.8) | 1458 | (74.3) | 2964 | (75.6) |
| | Missing | 2 | (0.1) | 3 | (0.2) | 5 | (0.1) |
| Current ASA use | No | 1398 | (71.3) | 1393 | (71.0) | 2791 | (71.2) |
| | Yes | 542 | (27.7) | 544 | (27.7) | 1086 | (27.7) |
| | Missing | 20 | (1.0) | 25 | (1.3) | 45 | (1.1) |
| Rankin score | 0 | 1481 | (75.6) | 1479 | (75.4) | 2960 | (75.5) |
| | 1 | 310 | (15.8) | 311 | (15.9) | 621 | (15.8) |
| | 2 | 159 | (8.1) | 165 | (8.4) | 324 | (8.3) |
| | 3 | 6 | (0.3) | 5 | (0.3) | 11 | (0.3) |
| | 4 | 2 | (0.1) | 0 | (0.0) | 2 | (0.1) |
| | 5 | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| | Missing | 2 | (0.1) | 2 | (0.1) | 4 | (0.1) |

[a]Data in this table obtained from Table 29 of SPORTIF V CSR

Patients in the two treatment arms were also comparable with respect to various demographic factors listed in Table XIV below.

Patients in SPORTIF V were slightly older compared to patients in SPORTIF III – 71.6 years versus 70.2 years. In addition, the mean blood pressure at baseline for patients enrolled in SPORTIF V was lower compared to that for patients in SPORTIF III.

**Table XIV: Mean (±SD) of patient characteristics at screening (ITT population)[a]**

| | Ximelagatran (N = 1960) | Warfarin (N = 1962) | Total (N = 3922) |
|---|---|---|---|
| Mean Age (years) | 71.6 ± 9.2 | 71.6 ± 9.0 | 71.6 ± 9.1 |
| Mean Height (cm) | 173.0 ± 10.8 | 173.1 ± 10.6 | 173.1 ± 10.7 |
| Mean Weight (kg) | 90.1 ± 21.9 | 89.1 ± 21.3 | 89.6 ± 21.6 |
| Mean BMI ((kg/m$^2$) | 30.0 ± 6.6 | 29.6 ± 6.2 | 29.8 ± 6.4 |
| Mean estimated CrCL (mL/min) | 87.0 + 40.5 | 86.1 ± 38.3 | 86.6 ± 39.4 |
| Mean Sitting SBP (mm Hg) | 132.6 ± 17.7 | 132.4 ± 17.6 | 132.5 ± 17.7 |
| Mean Sitting DBP (mm Hg) | 77.4 ± 10.5 | 77.2 ± 10.3 | 77.3 ± 10.4 |

[a]Data in this table obtained from Table 30 of SPORTIF V CSR.

As shown in Table XV below, hypertension was by far the most prevalent risk factor in SPORTIF V. Less than 1/5 of the randomized patients had a prior history of stroke or TIA. The distribution of risk factors was similar between the two treatment arms.

In SPORTIF V, fewer patients had a history of stroke or TIA compared to patients in SPORTIF III: 18% versus 24%.

**Table XV: Number (%) of patients with the presence of the listed risk factor at study entry.**

| | Ximelagatran (N = 1960) | Warfarin (N = 1962) | Total (N = 3922) |
|---|---|---|---|
| Hypertension | 1584 (80.8) | 1582 (80.6) | 3166 (80.7) |
| Age > 75 years | 838 (42.8) | 820 (41.8) | 1658 (42.3) |
| History of stroke or TIA | 369 (18.8) | 348 (17.7) | 717 (18.3) |
| History of SEE | 92 (4.7) | 85 (4.3) | 177 (4.5) |
| Left ventricular dysfunction | 735 (37.5) | 788 (40.2) | 1523 (38.8) |
| Age ≥ 65 and CAD | 822 (41.9) | 803 (40.9) | 1625 (41.4) |
| Age ≥ 65 and DM | 389 (19.8) | 373 (19.0) | 762 (19.4) |

Data in this table obtained from Table 32 of SPORTIF V CSR

As shown in Table XVI below, the use of study medications at study entry was similar between the two treatment arms. Approximately 20% of the randomized patients were on aspirin at study entry and the majority of those were on doses less than 100 mg/day. In SPORTIF III, just under 30% of the randomized patients were on aspirin at study entry, the majority being on doses less than 100 mg/day. The use of HMG CoA reductase inhibitors at study entry was more prevalent in SPORTIF V (36.8%) than in SPORTIF III (19%).

**Table XVI: Number (%) of patients with concomitant medication use at study entry by treatment group (ITT population)[a]**

| Therapy[a] | Ximelagatran N=1960 | | Warfarin N=1962 | | Total N=3922 | |
|---|---|---|---|---|---|---|
| Vitamin K antagonists | 1617 | (82.5) | 1661 | (84.7) | 3278 | (83.6) |
| Heparin group | 15 | (0.8) | 4 | (0.2) | 19 | (0.5) |
| ASA £100 mg/day | 227 | (11.6) | 251 | (12.8) | 478 | (12.2) |
| ASA >100 mg/day | 160 | (8.2) | 135 | (6.9) | 295 | (7.5) |
| ASA (dose unknown) | 31 | (1.6) | 25 | (1.3) | 56 | (1.4) |
| Digoxin/Digitoxin | 1058 | (54.0) | 1056 | (53.8) | 2114 | (53.9) |
| Beta blockers | 972 | (49.6) | 937 | (47.7) | 1909 | (48.6) |
| Calcium antagonists | 754 | (38.5) | 743 | (37.8) | 1497 | (38.1) |
| Diuretics | 1274 | (65.0) | 1275 | (64.9) | 2549 | (65.1) |
| ACE inhibitors | 937 | (47.8) | 938 | (47.8) | 1875 | (47.8) |
| Angiotensin II-antagonists | 213 | (10.9) | 189 | (9.6) | 402 | (10.2) |
| Acetaminophen | 351 | (17.9) | 299 | (15.2) | 650 | (16.6) |
| Amiodarone | 83 | (4.2) | 94 | (4.8) | 177 | (4.5) |
| HMG CoA reductase inhibitors | 733 | (37.4) | 709 | (36.1) | 1442 | (36.8) |

[a]Data in this table obtained from Table 39 of SPORTIF V CSR.

Table XVII below shows the proportion of time patients took concomitant aspirin between the first and last dose of study drug. As discussed earlier in the inclusion/exclusion criteria, patients were permitted to take ASA < 100 mg/day during the trial. As shown in the table below, the overall percentage of time that patients in the ximelagatran arm were on aspirin during the study was greater than in the warfarin arm.

**Table XVII: Proportion of time patients took concomitant ASA between the first and last dose of study drug (ITT population)[a]**

| Proportion of time | Ximelagatran N=512 | | Warfarin N=535 | | Total N=1047 | |
|---|---|---|---|---|---|---|
| >0% to 25% | 160 | (31.3) | 178 | (33.3) | 338 | (32.3) |
| >25% to 50% | 22 | (4.3) | 28 | (5.2) | 50 | (4.8) |
| >50% to 75% | 22 | (4.3) | 18 | (3.4) | 40 | (3.8) |
| >75% to 100% | 308 | (60.2) | 311 | (58.1) | 619 | (59.1) |
| Overall % of time on ASA | 64.4 | | 60.4 | | 62.3 | |

[a]Data in this table obtained from Table 40 of SPORTIF V CSR.

As shown in Table XVIII below, the number of patients on the various listed medications between the first and last dose of study drug were similar in the 2 treatment arms.

**Table XVIII: Number (%) of patients using other cardiovascular medications between the first and last dose of study drug, by treatment group (ITT population)[a]**

| Medication[a] | Ximelagatran N=1960 | | Warfarin N=1962 | | Total N=3922 | |
|---|---|---|---|---|---|---|
| Digoxin/Digitoxin | 1122 | (57.2) | 1132 | (57.7) | 2254 | (57.5) |
| Beta blockers | 1149 | (58.7) | 1187 | (60.6) | 2336 | (59.6) |
| Calcium antagonists | 905 | (46.1) | 910 | (46.5) | 1815 | (46.2) |
| Diuretics | 1603 | (81.9) | 1681 | (85.9) | 3284 | (83.8) |
| ACE inhibitors | 1091 | (55.7) | 1121 | (57.2) | 2212 | (56.4) |
| Angiotensin II-antagonists | 301 | (15.4) | 296 | (15.1) | 597 | (15.2) |
| Acetaminophen | 654 | (33.4) | 642 | (32.7) | 1296 | (33.0) |
| Amiodarone | 130 | (6.6) | 139 | (7.1) | 269 | (6.9) |
| HMG CoA reductase inhibitors | 923 | (47.1) | 926 | (47.2) | 1849 | (47.1) |

[a]Data in this table was obtained from Table 41 SPORTIF V CSR.

*m. Primary endpoint results*

The results of the primary pre-specified endpoint from SPORTIF V are summarized in **Table XIX** below. The results of the sponsor's primary endpoint analysis was re-analyzed and confirmed by the statistical reviewer Dr. John Lawrence.

**Table XIX: Number of patients with stroke and/or SEE by treatment group (primary prespecified endpoint)[a]**

| Treatment group | Events[b,c] | Patient Years | Event Rate (%/year) | 95% CI Lower | 95% CI Higher | p-value |
|---|---|---|---|---|---|---|
| Ximelagatran | 51 | 3160 | 1.61 | 1.17 | 2.06 | |
| Warfarin | 37 | 3186 | 1.16 | 0.79 | 1.54 | |
| Ximelagatran – warfarin | | | 0.45 | -0.13 | 1.03 | 0.133 |

[a]Data in this table obtained from Table 45 of SPORTIF V CSR
[b]Events represent CEAC adjudicated events
[c]This table only informs of the number of patients with their first event. If a patient had more than one event, it is not reflected in this table.

As shown in Table XX below, the most striking finding was a total of 10 fatal strokes on ximelagatran versus 3 fatal strokes on warfarin. In terms of overall number of events, the majority of strokes were non-fatal and ischemic in nature. Relatively few were hemorrhagic in nature. SEE's were also relatively rare comprising less than 10% of the total number of primary events.

Table XX: Breakdown of primary endpoint by type of event and whether fatal or non-fatal[a].

| Endpoint event[b] | Ximelagatran N=1960 | | Warfarin N=1962 | | Total N=3922 | |
|---|---|---|---|---|---|---|
| Fatal stroke | 10 | (0.5) | 3 | (0.2) | 13 | (0.3) |
| Ischemic stroke | 8 | (0.4) | 3 | (2.0) | 11 | (0.3) |
| Hemorrhagic stroke | 2 | (0.1) | 0 | (0.0) | 2 | (0.1) |
| Non-fatal stroke | 38 | (1.9) | 34 | (1.7) | 72 | (1.8) |
| Ischemic stroke | 38 | (1.9) | 33 | (1.7) | 71 | (1.8) |
| Hemorrhagic stroke | 0 | (0.0) | 2 | (0.1) | 2 | (0.1) |
| Non fatal SEE | 6 | (0.3) | 1 | (0.1) | 7 | (0.2) |
| Total number of events | 57 | (2.9) | 40 | (2.0) | 97 | (2.5) |
| Total number of patients with at least 1 event | 51 | (2.6) | 37 | (1.9) | 88 | (2.2) |

[a]Data in this table obtained from Table 46 of SPORTIF V CSR.
[b]Patients are counted once in each category of event if they had one or more events of that type.

**Figure 8: Cumulative proportion of patients with stroke and/or SEE over time-estimated Kaplan-Meier curves (Figure taken from Figure 12 of SPORTIF V CSR).**

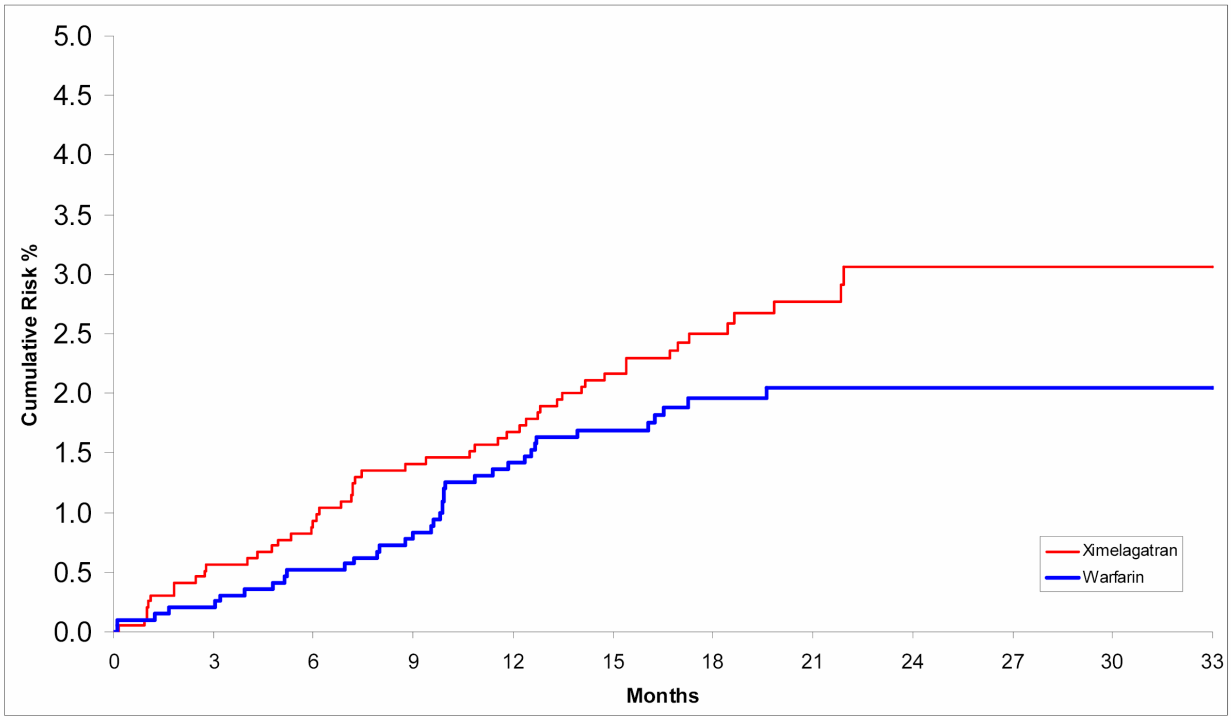
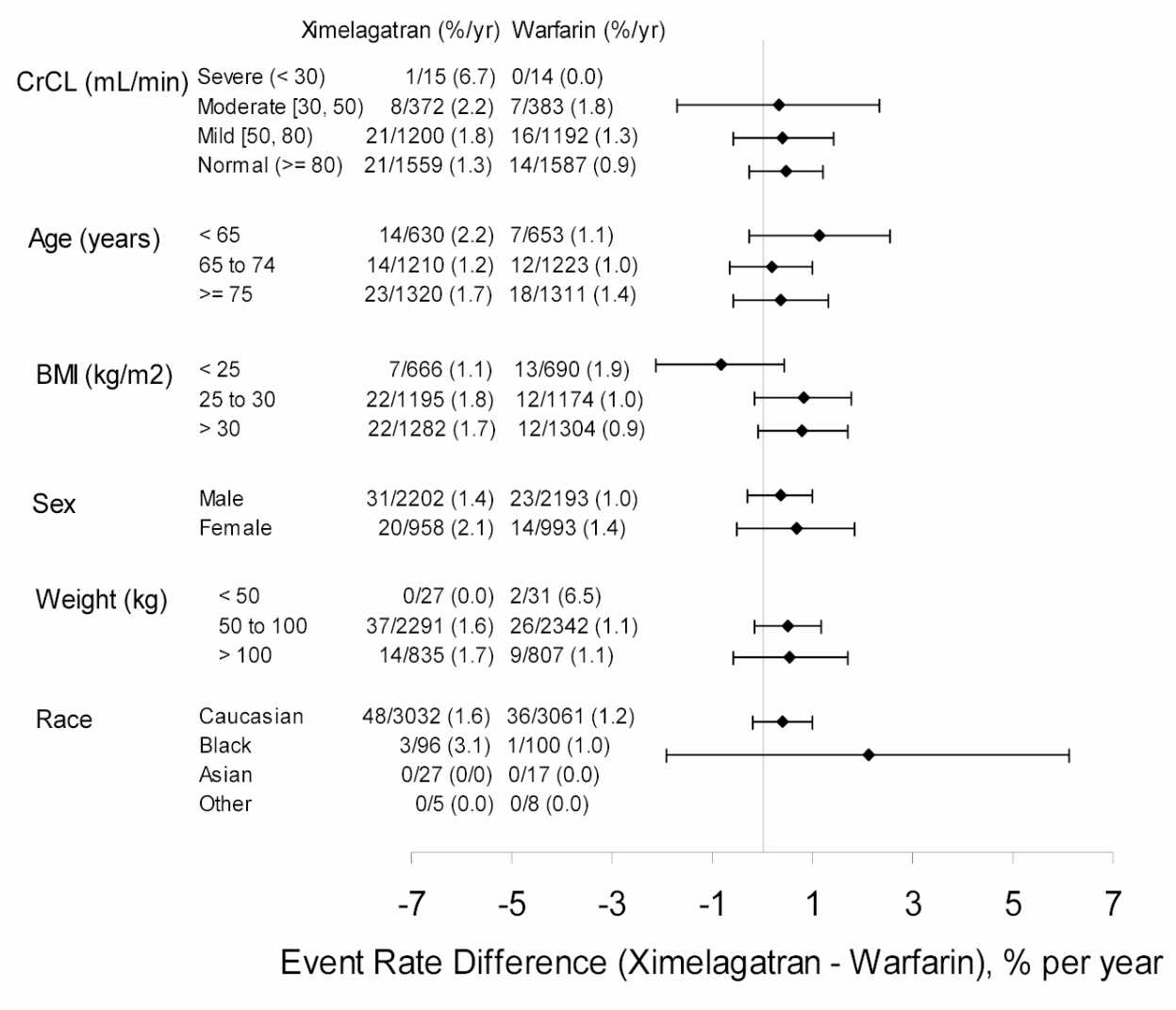



Figure 9 below summarizes the results of the primary endpoint as a function of various prognostic factors. The point estimates of the event rates were generally consistent across various subgroups and favored warfarin with the exception of patients with a BMI < 25.

Figure 9: Event rate difference (ximelagatran – warfarin) for the primary endpoint (stroke and/or SEE) according to prognostic factors (Figure taken from Figure 16 of SPORTIF V CSR)




*n. Secondary and Tertiary endpoint results*

The results of the secondary and tertiary endpoints are summarized in Table XXI through Table XXIV.

SECONDARY ENDPOINTS

Table XXI below summarizes the results of the secondary endpoint. There were a total of 229 patients with at least one event. However, the total number of events was 261 because of the fact that a patient could have had more than one event. Of the 229 patients with one event, just under 50% were deaths.

**Table XXI: Number of patients with all cause mortality/stroke/ SEE/AMI by treatment group (secondary prespecified endpoint based on OT analysis)[a]**

| Treatment | Events[b,c] | Patient years | Event Rate (%/year) | 95% CI Lower | 95% CI Higher | p-value |
|---|---|---|---|---|---|---|
| Ximelagatran | 110 | 2612 | 4.21 | 3.42 | 5.00 | |
| Warfarin | 119 | 2738 | 4.35 | 3.56 | 5.13 | |
| Ximelagatran – warfarin | | | -0.13 | -1.24 | 0.98 | 0.839 |

[a]Data in this table obtained from Table 58 of SPORTIF V CSR
[b]Events represent CEAC adjudicated events
[c]If a patient had more than one event, it is not reflected in this table. The total number of events was 127 and 134 on ximelagatran and warfarin respectively.

Table XXII below shows the results of one of the secondary prespecified endpoints which evaluated the number of patients with stroke/TIA/SEE. There were numerically more TIA's in the ximelagatran arm compared to the warfarin arm.

**Table XXII: Number of patients with ischemic stroke/TIA/SEE by treatment group (secondary prespecified endpoint based on OT analysis)[a]**

| Treatment | Events[b,c] | Patient Years | Event Rate (%/year) | 95% CI Lower | 95% CI Higher | p-value |
|---|---|---|---|---|---|---|
| Ximelagatran | 67 | 2606 | 2.57 | 1.96 | 3.19 | |
| Warfarin | 52 | 2728 | 1.91 | 1.39 | 2.42 | |
| Ximelagatran – warfarin | | | 0.66 | -0.14 | 1.47 | 0.115 |

[a]Data in this table obtained from Table 62 of SPORTIF V CSR
[b]Events represent CEAC adjudicated events
[c]If a patient had more than one event, it is not reflected in this table. The total number of events was 80 and 57 on ximelagatran and warfarin respectively.

## TERTIARY ENDPOINTS

It is important to note that the analysis of the tertiary endpoint was changed to include the ITT population ***after*** the database was unblinded.

**Table XXIII: Number of patients with strokes with a poor outcome by treatment group (tertiary prespecified endpoint based on ITT analysis)[a]**

| Treatment | Events[b] | Patient years | Event Rate (%/year) | 95% CI Lower | 95% CI Higher | p-value |
|---|---|---|---|---|---|---|
| Ximelagatran | 16 | 3190 | 0.50 | 0.26 | 0.75 | |
| Warfarin | 10 | 3207 | 0.31 | 0.12 | 0.51 | |
| Ximelagatran – warfarin | | | 0.19 | -0.12 | 0.50 | 0.246 |

[a]Data in this table obtained from Table 64 of SPORTIF V CSR
[b]Events represent CEAC adjudicated events

**Table XXIV: Number of patients with stroke or SEE as a function of age (<, ≥ 75 years of age) (tertiary prespecified endpoint based on ITT analysis)[a]**

| Age group | Treatment | Events[b] | Patient Years | Event rate (%/year) | 95% CI Lower | 95% CI Higher | p-value |
|---|---|---|---|---|---|---|---|
| Age ³75 Years | Ximelagatran | 23 | 1322 | 1.74 | 1.03 | 2.45 | |
| | Warfarin | 18 | 1311 | 1.37 | 0.74 | 2.01 | |
| | Ximelagatran - warfarin | | | 0.37 | -0.59 | 1.32 | 0.530 |
| Age <75 Years | Ximelagatran | 28 | 1840 | 1.52 | 0.96 | 2.09 | |
| | Warfarin | 19 | 1875 | 1.01 | 0.56 | 1.47 | |
| | Ximelagatran - warfarin | | | 0.51 | -0.22 | 1.23 | 0.187 |

[a]Data in this table obtained from Table 66 of SPORTIF V CSR
[b]Events represent CEAC adjudicated events

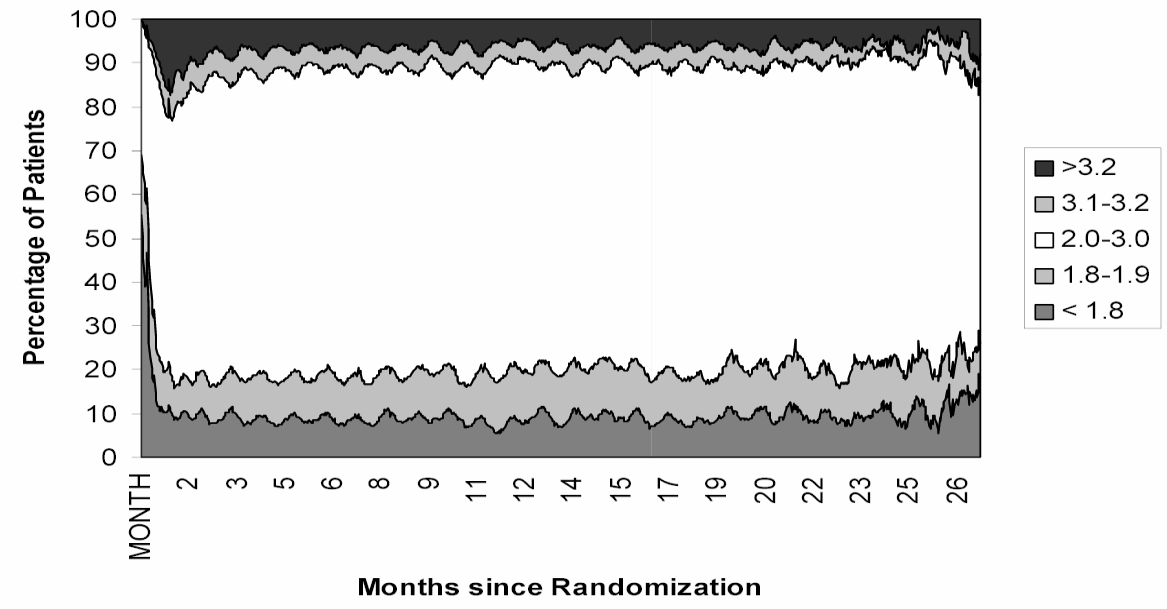
*o. Adequacy of anticoagulation in the warfarin arm*

The adequacy of anticoagulation in the warfarin group was assessed in the OT (on treatment) population. Overall, the number of patients in the warfarin group with an:

- INR < 2.0 occurred 20.3% of total time
- INR 2.0 to 3.0 occurred 68% of the time
- INR > 3.0 occurred 11.7% of the time

Figure 10 below shows the percentage of patients with INR's < 2.0, between 2.0 and 3.0, and > 3.0 as a function of time since randomization.

**Figure 10: Adequacy of anticoagulation as assessed by INR in patients assigned to warfarin (OT population); (Figure taken from Figure 23 of SPORTIF V CSR).**



In general, the adequacy of anticoagulation with warfarin in SPORTIF V was good and comparable to that seen in historical studies of warfarin. Please refer to Table VI for details of the adequacy of anticoagulation in studies involving warfarin. Using the AFASAK study as an example of the worst case scenario, the INR was in the "therapeutic" range (2.8 to 4.2) 42% of the time. In the best case scenario, the BAATAF study showed that the "therapeutic" range (1.5 to 2.7) was achieved 83% of the time.

A total of 172 (8.8%) of patients had intervals between INR measurements of more than 2 months.

2. SPORTIF III

Study Title: "Efficacy and Safety of the Oral Direct Thrombin Inhibitor H376/95 Compared with Dose-Adjusted Warfarin in the Prevention of Stroke and Systemic Embolic Events in Patients with Atrial Fibrillation"

SPORTIF III (SH-TPA-0003) was the second of the 2 pivotal Phase 3 studies submitted by the sponsor for the indication of prevention of stroke and SEE in patients with atrial fibrillation. SPORTIF III was very similar in design to SPORTIF V except for the aspect of blinding. The former was open-label while the latter was double-blind.

*a. Study dates*

Date first patient enrolled: July 25, 2000
Date enrollment ended: September 13, 2001
Date study closure procedures began: July 1, 2002
Date final patient completed study: September 30, 2002
Date of Clinical Study Report: September 26, 2003

*b. Protocol Amendments*

Table XXV below summarizes the date at which the original protocol was issued along with dates at which all subsequent amendments to the original protocol were issued. Below Table XXV are listed the summaries of each protocol amendment.

**Table XXV: Original Protocol and Protocol Amendment Issue dates for SPORTIF III**

| Version of Protocol or Protocol Amendment | Date of issue |
|---|---|
| Protocol Version 1 | March 8, 2000 |
| Protocol amendment 1 to Version 1 | May 3, 2000 |
| Protocol Version 2 | May 3, 2000 |
| Protocol Amendment 1 to Version 2 | October 30, 2001 |
| Protocol Amendment 1 to Version 3 | June 12, 2002 |

Amendment entitled: "Protocol amendment 1 to Version 1"

- Change in exclusion criteria relating to active liver disease and persistent elevation of liver enzymes has been changed from "more than 3 times the upper limit of normal" to"=2 times the upper limit of normal".
- Additional laboratory assessments, hematology and clinical chemistry, were scheduled at the following time points: 6 weeks, 2 months, 4, 5, 8, 10, 15 and 21 months. Additional clinic visits were added to accommodate the extra laboratory assessments.
- The protocol was amended to include specific instructions for the investigator to follow in the event of liver enzyme abnormalities. If, at any time during the study, the liver enzyme, S-ALAT (GPT) is =3 times the upper limit of normal (ULN) and this is confirmed in a repeat test then the patient will be recalled for a third check-up visit when a 14-15 mL blood sample will be drawn for extended liver function tests evaluating various etiologies for liver enzyme abnormalities. Once an increase of S-ALAT to > 3x ULN has been confirmed in a repeat test, weekly liver enzyme test check-ups, i.e. S-ASAT, S-ALAT, S-ALP and S-Bilirubin will be performed until S-ALAT is either less than 2x ULN or has returned to normal values.
- Specific instruction regarding when to discontinue a patient for liver enzyme abnormalities were added. A patient was to be discontinued from the study if repeated measurements showed that S-ALAT remains elevated 3 to 7x ULN during a 2-month period without any tendency to decrease or other clinical explanation being found. Any patient with a S-ALAT > 7x ULN at any time was to be discontinued from the study.
- The number of patients was increased from 2700 to 3000.
- The study start date was changed from April 2000 to July 2000.
- The treatment period was changed from 30 months to 26 months.

Amendment entitled: "Protocol amendment 1 to Version 2"

- The threshold for discontinuing a patient due to liver enzyme abnormalities was reduced. Patients with an increase of >5 times the upper limit of normal (ULN) in any liver enzyme test, i.e. S-ASAT, S-ALAT, S-ALP and S-Bilirubin, were to be withdrawn from study treatment, unless it was agreed with the AstraZeneca responsible physician that it is acceptable for the patient to remain on treatment.
- For any patient that showed a persistent elevation of ***any*** LFT (not just restricted to ALAT elevation) $\geq$3 times the ULN but $\leq$ 5 times the ULN for 8 weeks then study treatment must be discontinued.
- If an increase of $\geq$3 times ULN was seen in any LFT then the patient was to be recalled for a visit where further work-up occurred. No confirmation or repeat lab test was necessary to confirm the enzyme abnormality – unlike that required in Amendment 1 to Version 1.

Amendment entitled: "Protocol amendment 1 to Version 3"

- The following was added: "It is important that the final health status of all patients is known at the end of the study. For patients who withdraw from the study due to death, stroke or systemic embolic event, their final health status is considered known. Patients who withdraw completely from the study due to other reasons are considered to have an

unknown final health status. These patients will be contacted during the 3-month closeout period and will be asked to consent to provide follow-up information regarding their health status. If consent is provided, the patient will be asked to confirm that they are still alive and whether or not they have suffered a stroke or a systemic embolic event."

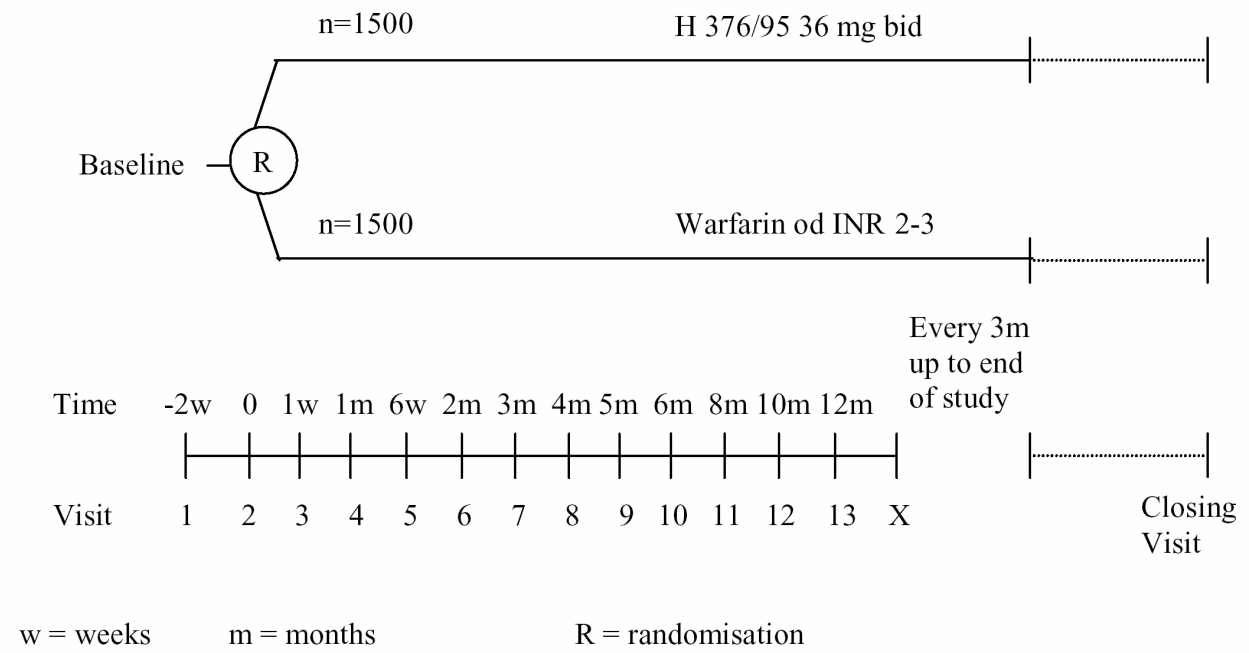
- With regards to the statistical analysis of the primary endpoint it was decided to analyze the primary endpoint with an Intention to Treat approach using adjudication from the Clinical Events Committee.

*c. Study Design:*

SPORTIF III was similar in design to SPORTIF V except that it was open-label. It was a randomized, active control, parallel group study in patients with non-valvular atrial fibrillation. SPORTIF III was conducted in Europe and Asia whereas SPORTIF V was conducted in the U.S. and Canada. Please refer to section VIII, C, 2, j for details of the countries that enrolled patients into this study.

SPORTIF III randomized a total of 3410 patients. As shown in Figure 11, patients were randomized to either fixed doses of ximelagatran 36 mg bid or to adjusted dose warfarin, titrating to an INR of 2-3 via monthly blood tests.

**Figure 11: Study Schema for SPORTIF III (Figure obtained from Figure 1 of SPORTIF III CSR)**




w = weeks m = months R = randomisation

Stratification in SPORTIF III was based on:
Aspirin Use
Previous stroke/TIA
Country

Study duration: The study is to continue until 4000 patient years are collected and/or at least 80 primary endpoints are achieved.

The study included a DSMB, CEAC, and ESC. The members of the DSMB, CEAC and ESC were the same as in SPORTIF V and are listed in Section VIII, C, 1, c of this review.

*d. Rationale for doses selected*

Please refer to Section VIII, C, 1, d of this of this review for details.

*e. Blinding/Randomization:*

Unlike SPORTIF V, this study was conducted open-label. All primary events (stroke and systemic embolic events), secondary events (deaths, acute MI's, TIA's) and major bleeding events were adjudicated by a CEAC.

*f. Pre-specified study objectives*

The primary, secondary, and tertiary endpoints were almost identical to those in SPORTIF V. Please refer to Section VIII, C, 1, f of this review for details.

*g. Definitions of study endpoints*

Please refer to Section VIII, C, 1, g of this review for details

*h. Inclusion/Exclusion Criteria:*

The inclusion and exclusion criteria were identical to those is SPORTIF V. Please refer to Section VIII, C, 1, h of this review for details.

*i. Statistical Considerations (please refer to the statistical review for details):*

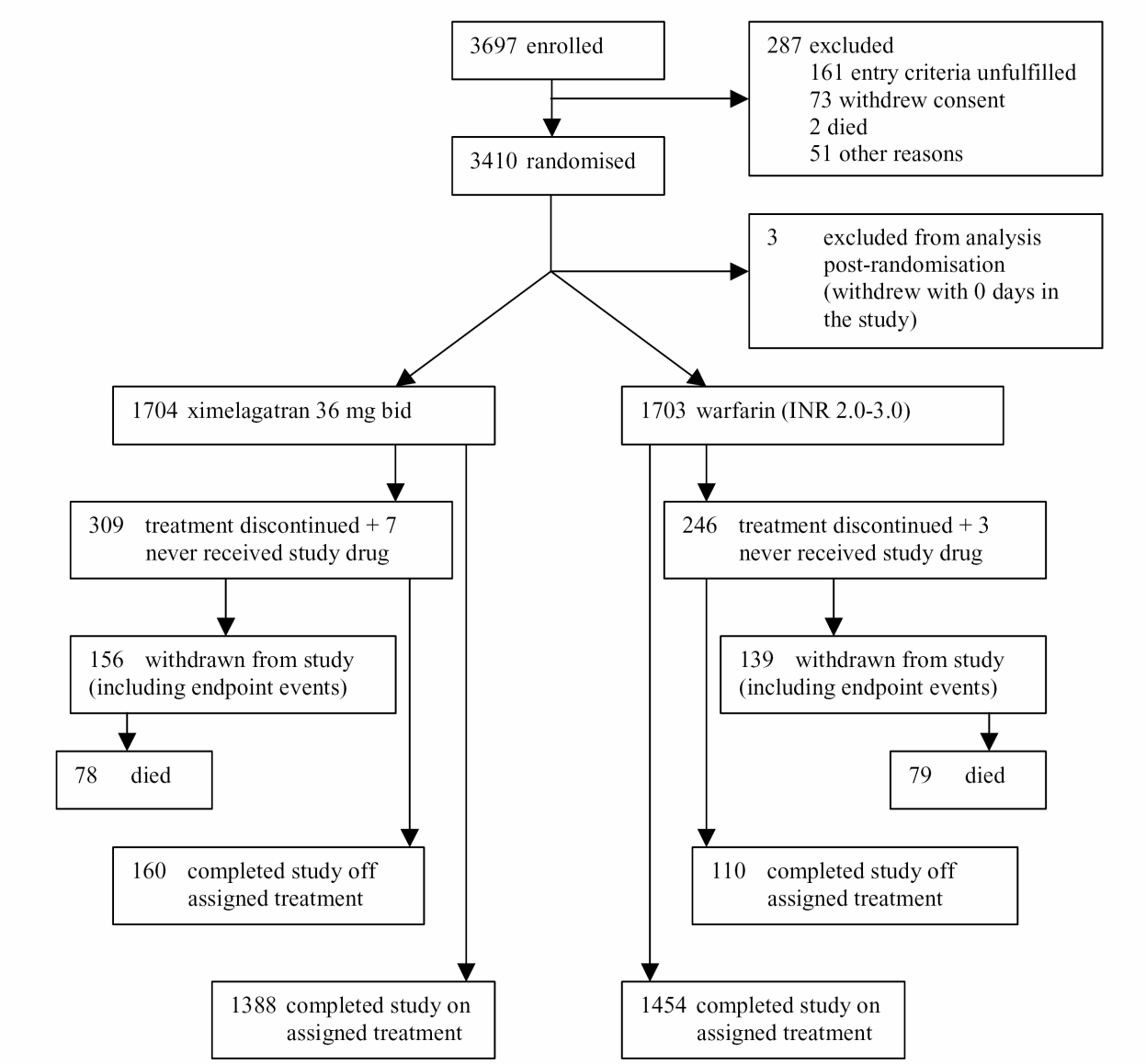
The general statistical considerations and sample size calculations were very similar for both studies. Please refer to Section VIII, C, 1, i of this review for further details.

*j. Study patient disposition*

Patients were enrolled from a total of 259 centers in 23 countries (Australia, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hong Kong, Hungary, Iceland, Ireland, Italy, Japan, Malaysia, New Zealand, Norway, Poland, Philippines, Portugal, Spain, Sweden, Taiwan and UK). A total of 3697 patients were enrolled from which 3407 patients were randomized and received at least one dose of study drug (1704 to ximelagatran and 1703 to warfarin).

As seen in Figure 12 below, 287 patients were enrolled but not randomized. The top two reasons for screening failures were eligibility criteria being unfulfilled and withdrawal of consent. A total of 81.5% of patients remained on ximelagatran at the time of study completion, while 85.4% of patients remained on warfarin at the time of study completion.

**Figure 12: Patient disposition in SPORTIF III (Figure obtained from Figure 4 of SPORTIF III CSR)**




Note: A further 10 patients (7 ximelagatran, 3 warfarin) died after withdrawal from, or completion of, the study, upto the administrative closure date (30 September 2002)

As shown in Table XXVI below, the total number of study drug discontinuations was greater on ximelagatran compared to warfarin by an absolute value of 4% and was consistent with the findings seen in SPORTIF V. A large portion of this excess discontinuation on ximelagatran could be attributed to adverse events (e.g. liver enzyme abnormalities).

**Table XXVI: Summary of the reasons for discontinuing study drug (ITT population)[a]**

| Reason for study drug discontinuation | Ximelagatran N=1704 | | Warfarin N=1703 | | Total N=3407 | |
|---|---|---|---|---|---|---|
| Total | 309 | (18%) | 246 | (14%) | 555 | (16%) |
| Adverse event | 132 | (8) | 61 | (4) | 193 | (6) |
| Patient decision (Consent withdrawn from study drug) | 49 | (3) | 49 | (3) | 98 | (3) |
| Endpoint events | 52 | (3) | 61 | (4) | 113 | (3) |
| Other | 29 | (2) | 30 | (2) | 59 | (2) |

[a]The data in this table obtained from table 15 of SPORTIF III CSR

As seen in Table XXVII below, even after excluding patients with ALAT > 3x ULN, the total drug discontinuation rate was slightly higher on ximelagatran compared to warfarin. Again, this pattern of study drug discontinuations was consistent with the pattern seen in SPORTIF V.

**Table XXVII: Comparison of total study drug discontinuation rates including and excluding patients with ALAT > 3x ULN[a]**

| | Ximelagatran | Warfarin | Totals |
|---|---|---|---|
| Total discontinuation rate (including patients with AL AT > 3x ULN) | 309/1704 (18%) | 246/1703 (14%) | 555/3407 (16%) |
| Total discontinuation rate (excluding patients with ALAT > 3x ULN) | 261/1597 (16%) | 242/1689 (14%) | 503/3286 (15%) |

[a]Data in this table obtained from Tables 15 and 16 of SPORTIF V CSR

In SPORTIF III, there were 97 patients with missing vital status or primary event data during study closure procedures. All these patients were asked to re-consent to provide follow-up information regarding the primary endpoint event or death. The results are summarized in

Table XXVIII below. The sponsor's attempt to collect vital status or primary event data during this process yielded no additional primary events or deaths. Note that 12 patients on ximelagatran and 15 patients on warfarin were lost to follow-up.

**Table XXVIII: Number of patients that discontinued the study and had missing vital status or primary event data at time of study closure procedures but were asked to re-consent to provide follow-up information.**

| | Ximelagatran (N =53) | Warfarin (N = 44) | Total (N = 97) |
|---|---|---|---|
| Provided re-consent | 19 (37.3%) | 14 (30.4%) | 33 (34%) |
| IEC approval not obtained prior to study closure | 14 (27.5%) | 11 (23.9%) | 25 (25.8%) |
| Refused to re-consent | 8 (15.7%) | 4 (8.7%) | 12 (12.4%) |
| Lost to follow-up | 12 (23.5%) | 15 (32.6%) | 27 (27.8%) |

Data in this table obtained from Table 14 of SPORTIF III CSR

*k. Protocol deviations*

There were no exclusions from any analyses due to protocol deviations.

Enrollment violations

The major inclusion criteria violations involved either criteria 1 (AF verified by 2 ECG's) or criteria 2 (at least one other risk factor for stroke). The most common exclusion criteria violation involved the use of disallowed concomitant medication.

**Table XXIX: Inclusion/exclusion criteria violations by treatment group**

| | **Ximelagatran (N = 1704)** | **Warfarin (N = 1703)** | **Total (N = 3407)** |
|---|---|---|---|
| Inclusion criteria violations | 9 | 7 | 16 |
| Exclusion criteria violations | 21 | 20 | 41 |

Study drug administration violation

There was one patient (#4167) that was assigned to receive warfarin but was treated with ximelagatran by the investigator. This patient is included in the warfarin group for the efficacy analyses but in the ximelagatran group for the analysis of AE's.

Violations relating to interruption of study drug

Table XXX below summarizes the cumulative duration of treatment interruption by treatment group. Slightly more patients on warfarin had treatment interruptions of any duration compared to patients on ximelagatran. These findings contrast to those in SPORTIF V, where there was a more pronounced discrepancy in the percentage of patients with treatment interruption between the two study arms.

**Table XXX: Number (%) of patients by total days of treatment interruption, and treatment group[a]**

| **Treatment interruption** | **Ximelagatran N=1952** | | **Warfarin N=1952** | | **Total N=3904** | |
|---|---|---|---|---|---|---|
| No interruption | 1208 | (71%) | 1139 | (67%) | 2347 | (69%) |
| 1 to 7 days | 313 | (18%) | 304 | (18%) | 617 | (18%) |
| 8 to 30 days | 143 | (8%) | 220 | (13%) | 363 | (11%) |
| 31 to 60 days | 31 | (2%) | 30 | (2%) | 61 | (2%) |
| >60 days | 9 | (1%) | 10 | (1%) | 19 | (1%) |

[a]Data in this table obtained from Table 20 of SPORTIF III CSR.

Intervals greater than 28 $\pm$ 3 days between INR measurements:

Per the protocol, patients were to have INR measurements every 28 $\pm$ 3 days. A total of 225 (13.2%) patients had at least one interval between INR measurements of more than 2 months.

*l. Demographics and other patient characteristics*

The characteristics of the patients enrolled in SPORTIF III are described in Table XXXI below. The majority of patients were males, Caucasians, and $\geq$ 65 years old. Approximately 69% had

two or more risk factors for stroke in addition non-valvular AF. Baseline characteristics between the two treatment arms were similar.

There were some notable differences in the baseline characteristics of the patients in SPORTIF III compared to SPORTIF V. On average, the patient population in SPORTIF III had fewer risk factors for stroke, was younger, and had fewer patients taking aspirin at the time of enrollment compared to SPORTIF V. In addition, SPORTIF III also had more patients that drank alcohol and more that never smoked. Finally there were a greater proportion of Oriental patients in SPORTIF III compared to SPORTIF V.

**Table XXXI: Patient characteristics at screening: number (%) of patients by treatment group (ITT population)[a]**

| | | **Ximelagatran N=1704** | **Warfarin N=1703** | **Total N=3407** |
|---|---|---|---|---|
| Sex | Male | 1158 (68%) | 1196 (70%) | 2354 (69%) |
| | Female | 546 (32%) | 507 (30%) | 1053 (31%) |
| Race | Caucasian | 1494 (88%) | 1500 (88%) | 2994 (88%) |
| | Black | 0 | 3 (0%) | 3 (0%) |
| | Oriental | 201 (12%) | 196 (12%) | 397 (12%) |
| | Other | 9 (1%) | 4 (0%) | 13 (0%) |
| Age | <65 | 386 (23%) | 397 (23%) | 783 (23%) |
| | [65,75) | 737 (43%) | 741 (44%) | 1478 (43%) |
| | >=75 | 581 (34%) | 565 (33%) | 1146 (34%) |
| Number of risk factors (in addition to AF) | 0 | 5 (0%) | 5 (0%) | 10 (0%) |
| | 1 | 508 (30%) | 544 (32%) | 1052 (31%) |
| | 2 | 612 (36%) | 572 (34%) | 1184 (35%) |
| | 3 | 370 (22%) | 378 (22%) | 748 (22%) |
| | 4 | 150 (9%) | 143 (8%) | 293 (9%) |
| | 5 | 52 (3%) | 51 (3%) | 103 (3%) |
| | 6 | 7 (0%) | 10 (1%) | 17 (0%) |
| Smoking | No | 844 (50%) | 857 (50%) | 1701 (50%) |
| | Previous smoker | 680 (40%) | 677 (40%) | 1357 (40%) |
| | Occasional smoker | 46 (3%) | 36 (2%) | 82 (2%) |
| | Habitual smoker | 134 (8%) | 133 (8%) | 267 (8%) |
| Does the patient drink alcohol | No | 835 (49%) | 852 (50%) | 1687 (50%) |
| | Yes | 869 (51%) | 851 (50%) | 1720 (50%) |
| Undergone any major surgery | No | 809 (47%) | 780 (46%) | 1589 (47%) |
| | Yes | 895 (53%) | 923 (54%) | 1818 (53%) |
| Is the patient taking aspirin | No | 1359 (80%) | 1344 (79%) | 2703 (79%) |
| | Yes | 345 (20%) | 359 (21%) | 704 (21%) |
| Modified Rankin score | 0 | 1319 (77%) | 1308 (77%) | 2627 (77%) |
| | 1 | 264 (15%) | 271 (16%) | 535 (16%) |
| | 2 | 114 (7%) | 119 (7%) | 233 (7%) |
| | 3 | 6 (0%) | 4 (0%) | 10 (0%) |
| | 4 | 1 (0%) | 1 (0%) | 2 (0%) |
| Alcohol consumption (units/week) | 0 | 838 (49%) | 856 (50%) | 1694 (50%) |
| | 0.1-5 | 460 (27%) | 484 (28%) | 944 (28%) |
| | 6-10 | 229 (13%) | 190 (11%) | 419 (12%) |
| | 11-15 | 82 (5%) | 91 (5%) | 173 (5%) |
| | 16-20 | 29 (2%) | 13 (1%) | 42 (1%) |
| | 21- | 66 (4%) | 69 (4%) | 135 (4%) |

[a]Data in this table obtained from Table 22 of SPORTIF III CSR

Table XXXII below summarizes some additional patient characteristics. As mentioned earlier, patients in SPORTIF III were younger than patients in SPORTIF V. In addition, patients in SPORTIF III, had a lower BMI compared to patients in SPORTIF V.

**Table XXXII: Mean (+SD) of patient characteristics at screening (ITT population)[a]**

| | Ximelagatran (N = 1960) | Warfarin (N = 1962) | Total (N = 3922) |
|---|---|---|---|
| Mean Age (years) | 70.3 ± 8.6 | 70.1 ± 8.6 | 70.2 ± 8.6 |
| Mean Height (cm) | 169.5 ± 9.8 | 170.1 ± 9.5 | 169.8 ± 9.6 |
| Mean Weight (kg) | 80.7 ± 16.8 | 81.7 ± 16.9 | 81.2 ± 16.9 |
| Mean BMI ($(kg/m^2)$) | 28.0 ± 4.9 | 28.1 ± 4.8 | 28.1 ± 4.9 |
| Mean estimated CrCL (mL/min) | 82.8 ± 31.9 | 83.3 ± 34.1 | 83.1 ± 33.0 |
| Mean SBP (mm Hg)[b] | 139.0 ± 17.9 | 138.6 ± 18.1 | 138.8 ± 18.0 |
| Mean DBP (mm Hg)[b] | 81.8 ± 9.7 | 81.9 ± 10.1 | 81.9 ± 9.9 |

[a]Data in this table obtained from Table 23 of SPORTIF III CSR.
[b]Blood pressure data was not provided in Sponsor's table but was obtained by analyzing the dataset "HRBP2" of SPORTIF III. Visit 1 blood pressure data were used to obtain baseline data.

Table XXXIII below summarizes the number of patients with presence of the listed risk factor in patients enrolled into SPORTIF III.

More patients in SPORTIF III had a history of stroke and/or TIA at study enrollment compared to patients in SPORTIF V (24% vs. 18%). However, fewer patients in SPORTIF III had a history of hypertension (72% vs. 81%) and left ventricular dysfunction (34% vs. 39%) compared to patients in SPORTIF V.

**Table XXXIII: Number (%) of patients with presence of the listed risk factor at study entry[a]**

| | **Ximelagatran (N = 1704)** | **Warfarin (N = 1703)** | **Total (N = 3407)** |
|---|---|---|---|
| Previous stroke | 265 (16%) | 254 (15%) | 519 (15%) |
| Systemic embolism | 74 (4%) | 77 (5%) | 151 (4%) |
| Previous TIA | 189 (11%) | 188 (11%) | 377 (11%) |
| Previous stroke and/or TIA | 417 (24%) | 405 (24%) | 822 (24%) |
| Hypertension | 1229 (72%) | 1230 (72%) | 2459 (72%) |
| LV dysfunction | 574 (34%) | 584 (34%) | 1158 (34%) |
| Diabetes mellitus | 370 (22%) | 377 (22%) | 747 (22%) |
| Age >=65 and DM | 288 (17%) | 290 (17%) | 578 (17%) |
| CAD | 682 (40%) | 675 (40%) | 1357 (40%) |
| Age >=65 and CAD | 581 (34%) | 558 (33%) | 1139 (33%) |
| Clinically significant bleeding | 78 (5%) | 68 (4%) | 146 (4%) |

[a]Data in this table obtained from Table 26 of SPORTIF III CSR

Table XXXIV below summarizes the medications that patients were using before randomization into the study. The use of the listed medications was similar at baseline in the 2 study arms. There was less use of Vitamin K antagonists (73% vs. 84%), diuretics (51% vs. 65%), and

HMG-CoA reductase inhibitors (19% vs. 37%) in SPORTIF III patients compared to SPORTIF V patients. There was a relatively higher use of low dose aspirin in SPORTIF III compared to SPORTIF V (21% vs. 12%).

**Table XXXIV: Number (%) of patients with concomitant medication use at study entry by treatment group (ITT population)[a]**

| | Ximelagatran N=1704 | Warfarin N=1703 | Total N=3407 |
|---|---|---|---|
| Antifibrinolytics | 0 (0%) | 1 (0%) | 1 (0%) |
| Vitamin K antagonists | 1266 (74%) | 1235 (73%) | 2501 (73%) |
| Heparin group | 62 (4%) | 57 (3%) | 119 (3%) |
| Aspirin <=100 mg | 348 (20%) | 356 (21%) | 704 (21%) |
| Aspirin >100 mg | 99 (6%) | 87 (5%) | 186 (5%) |
| Aspirin (dose unknown) | 51 (3%) | 35 (2%) | 86 (3%) |
| NSAID | 94 (6%) | 83 (5%) | 177 (5%) |
| Digoxin/Digitoxin | 928 (54%) | 934 (55%) | 1862 (55%) |
| Beta blockers | 774 (45%) | 816 (48%) | 1590 (47%) |
| Calcium antagonists | 578 (34%) | 565 (33%) | 1143 (34%) |
| Diuretics | 846 (50%) | 877 (51%) | 1723 (51%) |
| ACE inhibitors | 829 (49%) | 873 (51%) | 1702 (50%) |
| Angiotensin II-antagonists | 133 (8%) | 134 (8%) | 267 (8%) |
| Paracetamol | 91 (5%) | 82 (5%) | 173 (5%) |
| Amiodarone | 104 (6%) | 115 (7%) | 219 (6%) |
| HMG CoA reductase inhibitors | 310 (18%) | 329 (19%) | 639 (19%) |

[a]Data in this table obtained from Tables 30 and 31 of SPORTIF III CSR.

As shown in Table XXXV below, patients in the ximelagatran arm were more often on aspirin compared to patients in the warfarin arm during the course of SPORTIF III.

**Table XXXV: Proportion of time patients took concomitant ASA between the first and last dose of study drug (ITT population)[a]**

| | Ximelagatran N=369 | Warfarin N=334 | Total N=703 |
|---|---|---|---|
| >0-25% | 128 (35%) | 147 (44%) | 275 (39%) |
| 26-50% | 19 (5%) | 14 (4%) | 33 (5%) |
| 51-75% | 16 (4%) | 14 (4%) | 30 (4%) |
| 76-100% | 206 (56%) | 159 (48%) | 365 (52%) |
| overall % of time on aspirin | 64% | 54% | 59% |

[a]Data in this table obtained from Table 33 of SPORTIF III CSR

In general, the use of the listed medications during the study was similar in the 2 treatment arms as shown in Table XXXVI below. The most striking finding was the difference in use of HMG CoA reductase inhibitors between SPORTIF III and SPORTIF V patients: 27% of patients in SPORTIF III compared to 47 % of patients in SPORTIF V.

**Table XXXVI: Number (%) of patients using other cardiovascular medications between the first and last dose of study drug, by treatment group (ITT population)[a]**

| | Ximelagatran N=1697 | Warfarin N=1700 | Total N=3397[b] |
|---|---|---|---|
| Digoxin/Digitoxin | 961 (57%) | 980 (58%) | 1941 (57%) |
| Beta blockers | 828 (49%) | 896 (53%) | 1724 (51%) |
| Calcium antagonists | 647 (38%) | 655 (39%) | 1302 (38%) |
| Diuretics | 942 (56%) | 1012 (60%) | 1954 (58%) |
| ACE inhibitors | 880 (52%) | 947 (56%) | 1827 (54%) |
| Angiotensin II-antagonists | 174 (10%) | 201 (12%) | 375 (11%) |
| Paracetamol | 331 (20%) | 334 (20%) | 665 (20%) |
| Amiodarone | 106 (6%) | 119 (7%) | 225 (7%) |
| HMG CoA reductase inhibitors | 426 (25%) | 500 (29%) | 926 (27%) |

[a]Data in this table was obtained from Table 41 SPORTIF V CSR.
[b]This table excludes the 10 patients who did not receive any study drug.

*m. Primary endpoint results*

**Table XXXVII** below summarizes the results of the primary prespecified endpoint. The results of the primary endpoint analysis were taken directly from the sponsor's analysis and were not re-analyzed and validated by the reviewer.

**Table XXXVII: Number of patients with stroke and/or SEE by treatment group (primary prespecified endpoint)[a]**

| | Events[b] | Patient years | Event rate (%/year) | 95% CI Lower | Higher | p-value |
|---|---|---|---|---|---|---|
| Ximelagatran | 40 | 2446 | 1.64 | 1.13 | 2.14 | |
| Warfarin | 56 | 2440 | 2.29 | 1.69 | 2.9 | |
| Ximelagatran-Warfarin | | | -0.66 | -1.45 | 0.13 | 0.100 |

[a]Data in this table obtained from Table 39 of SPORTIF III CSR
[b]Events represent CEAC adjudicated events

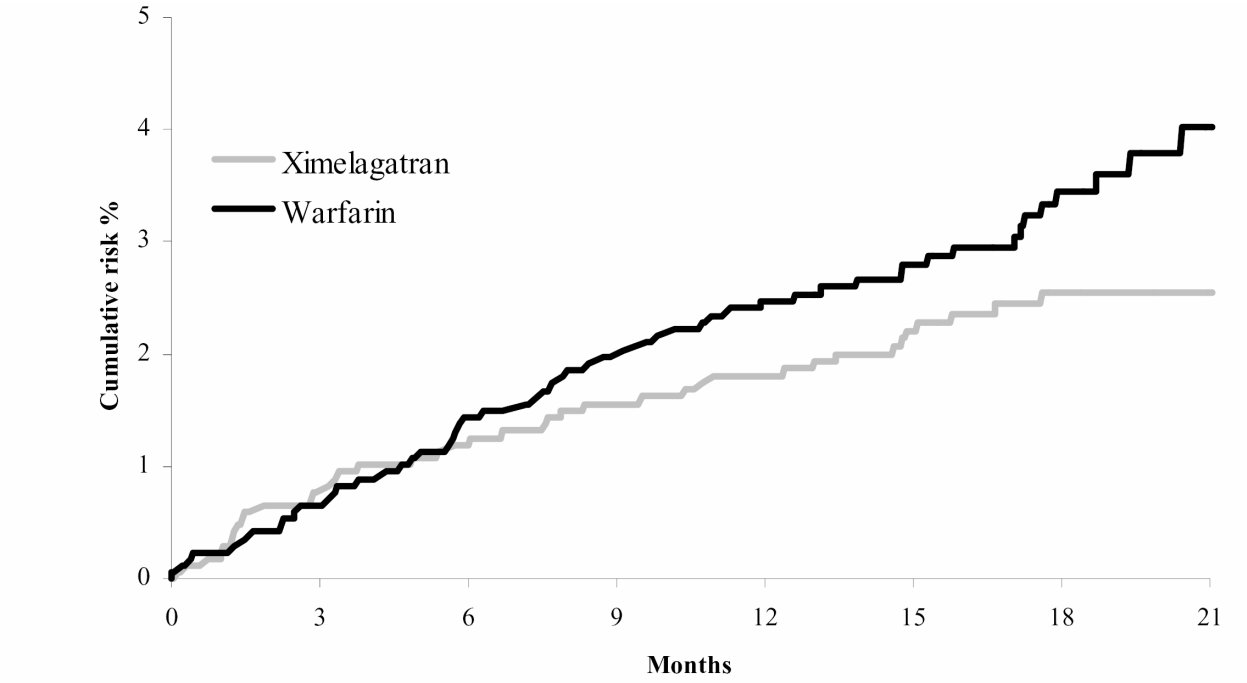
As seen in Table XXXVIII below, the vast majority (> 80%) of primary events that occurred were ischemic strokes. Hemorrhagic strokes and SEE accounted for less than 20% of the total number of events.

**Table XXXVIII: Listing of the individual components of the primary endpoint in SPORTIF III[a]**

| | Ximelagatran | Warfarin | Total |
|---|---|---|---|
| Hemorrhagic stroke | 4 (3) | 9 (5) | 13 (8) |
| Ischemic stroke | 32 (7) | 46 (4) | 78 (11) |
| SEE | 4 (2) | 2 (0) | 6 (2) |
| Total[a] | 40 (12) | 56 (9) | 96 (21) |

[a]Data in this table obtained from Table 40 of SPORTIF III CSR.

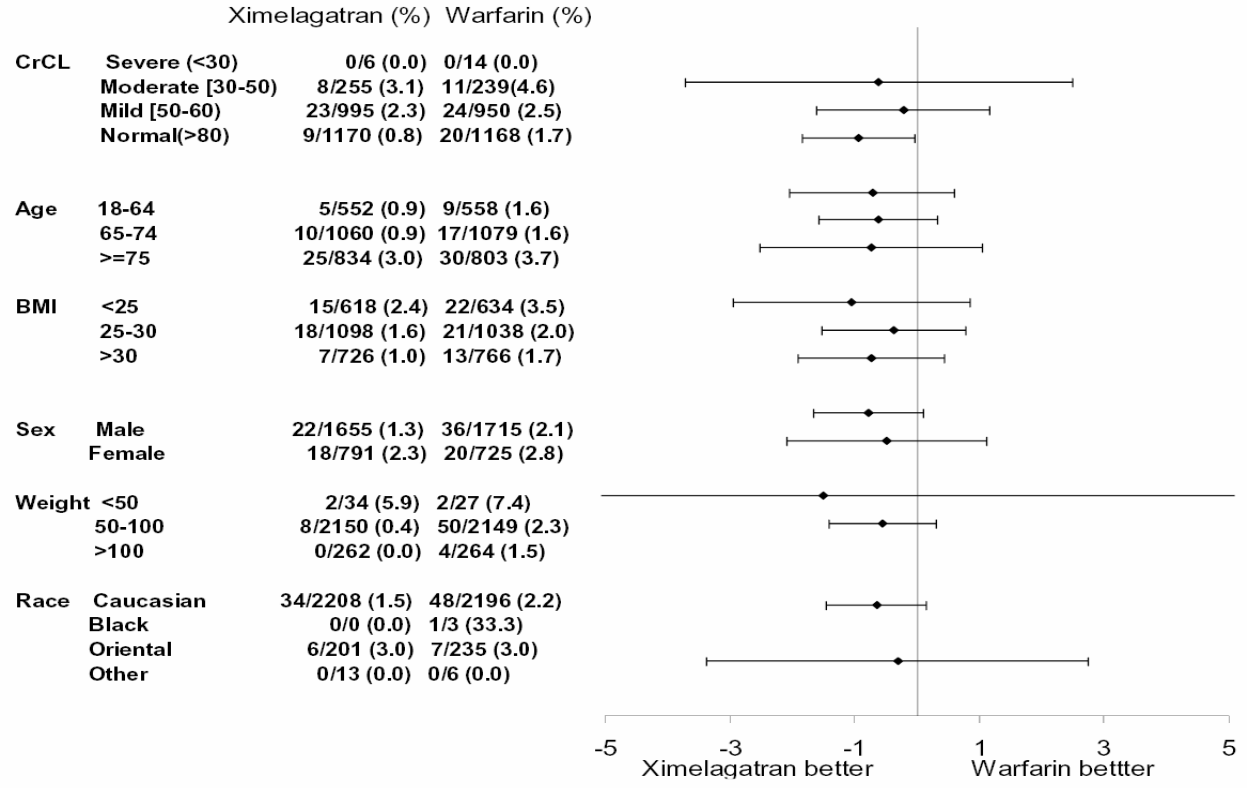
**Figure 13: Cumulative proportion of patients with stroke and/or SEE (primary endpoint) over time – estimated Kaplan-Meier curves (This figure obtained from Figure 12 of SPORTIF III CSR).**




| Patients at risk | | | | | |
|---|---|---|---|---|---|
| Ximelagatran | 1704 | 1625 | 1538 | 703 | 202 |
| Warfarin | 1703 | 1628 | 1540 | 692 | 172 |

As shown in Figure 14 below, the results in various sub-groups were consistent with the results of the general population.

**Figure 14: Event rate difference (ximelagatran – warfarin) for the primary endpoint (stroke and/or SEE) according to prognostic factors (This figure obtained from Figure 13 of SPORTIF III CSR).**




*n. Secondary and Tertiary endpoint results*

SECONDARY ENDPOINTS

The results of the secondary endpoint are summarized in Table XXXIX and Table XL below.

**Table XXXIX: Number of patients with all cause mortality/stroke/ SEE/AMI by treatment group (secondary prespecified endpoint based on OT analysis)[a]**

| | Events[b] | Patient years | Event rate (%/year) | 95% CI Lower | Higher | p-value |
|---|---|---|---|---|---|---|
| Ximelagatran | 96 | 2276 | 4.22 | 3.37 | 5.06 | |
| Warfarin | 116 | 2348 | 4.94 | 4.04 | 5.84 | |
| Ximelagatran-Warfarin | | | -0.72 | -1.95 | 0.51 | 0.261 |

[a]Data in this table obtained from Table 51 of SPORTIF III CSR
[b]Events represent CEAC adjudicated events
Ishcemic strokes/SEE/TIA

**Table XL: Number of patients with ischemic stroke/TIA/SEE by treatment group (secondary prespecified endpoint based on OT analysis)[a]**

| | Events | Patient years | Event rate (%/year) | 95% CI Lower | Higher | p-value |
|---|---|---|---|---|---|---|
| Ximelagatran | 48 | 2267 | 2.12 | 1.52 | 2.72 | |
| Warfarin | 67 | 2334 | 2.87 | 2.18 | 3.56 | |
| Ximelagatran-Warfarin | | | -0.75 | -1.67 | 0.16 | 0.109 |

[a]Data in this table obtained from Table 56 of SPORTIF III CSR

TERTIARY ENDPOINTS

It is important to note that the analysis of the tertiary endpoint was changed to include the ITT population *after* the database was unblinded.

**Table XLI: Number of patients with strokes with a poor outcome by treatment group (tertiary prespecified endpoint based on ITT analysis)[a]**

| | Events | Patient years | Event rate (%/year) | 95% CI Lower | Higher | p-value |
|---|---|---|---|---|---|---|
| Ximelagatran | 15 | 2464 | 0.61 | 0.3 | 0.92 | |
| Warfarin | 16 | 2467 | 0.65 | 0.33 | 0.97 | |
| Ximelagatran-Warfarin | | | -0.04 | -0.48 | 0.4 | 1.000 |

[a]Data in this table obtained from Table 58 of SPORTIF III CSR

**Table XLII: Number of patients with stroke or SEE as a function of age (<, ≥ 75 years of age) (tertiary prespecified endpoint based on ITT analysis)[a]**

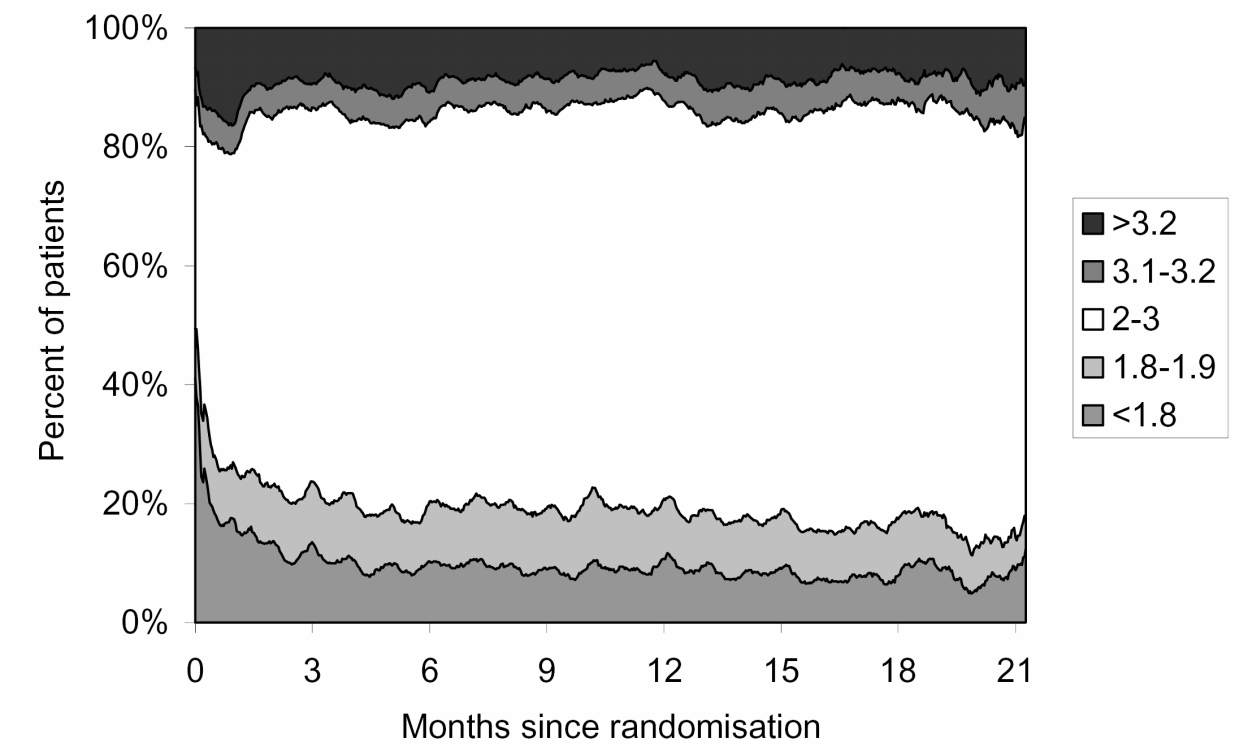
| | | Events | Patient years | Event rate (%/year) | 95% CI Lower | Higher | p-value |
|---|---|---|---|---|---|---|---|
| Age >=75 years | Ximelagatran | 25 | 834 | 3 | 1.82 | 4.17 | |
| | Warfarin | 30 | 803 | 3.73 | 2.4 | 5.07 | |
| | Ximelagatran-Warfarin | | | -0.74 | -2.52 | 1.04 | 0.415 |
| Age <75 years | Ximelagatran | 15 | 1612 | 0.93 | 0.46 | 1.4 | |
| | Warfarin | 26 | 1637 | 1.59 | 0.98 | 2.2 | |
| | Ximelagatran-Warfarin | | | -0.66 | -1.43 | 0.11 | 0.115 |

[a]Data in this table obtained from Table 60 of SPORTIF III CSR

*o. Adequacy of anticoagulation in the warfarin arm*

The adequacy of anticoagulation in the warfarin group was assessed in the OT population. Patients in SPORTIF III were within the targeted INR range of 2 to 3 for 66% of the time. This was very similar to the 68% of the time that the INR was within the range of 2 to 3 in SPORTIF V. A stable INR was achieved by month 2. Between month 2 and the end of the study, the percentage of time the INR was within the targeted range (2 to 3), ranged from a low of 64% to a high of 72%. Figure 15 below summarizes the percentage of time with INR's within the targeted range of 2 to 3, and also the percentage of time above and below this range. A total of 225 (13.2%) patients had at least one interval between INR measurements of more than 2 months and 62 (3.6%) patients had intervals of more than 3 months.

**Figure 15: Adequacy of anticoagulation as assessed by INR in patients assigned to warfarin (OT population) (This figure was obtained from Figure 25 of SPORTIF III CSR).**




D. Efficacy Conclusions

SPORTIF III and SPORTIF V are two Phase III, active control, non-inferiority studies that were provided in support of NDA21-686. Both studies compared the effectiveness of a fixed dose of ximelagatran, 36 mg administered twice a day to warfarin targeting an INR of 2 to 3 in patients with nonvalvular atrial fibrillation and at least one additional risk factor for stroke. The studies were very similar in design except that SPORTIF III was open label while SPORTIF V was double-blind. The primary endpoint was the composite occurrence of all strokes (fatal and non-fatal) and systemic embolic events. The sponsor pre-specified a non-inferiority margin of 2% points in the event rate in both studies. 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." In both studies, the efficacy of ximelagatran was within the sponsor's pre-specified non-inferiority margin of 2% and it was concluded by the sponsor that ximelagatran was as efficacious as warfarin. While the two studies could be considered "successes" based on the sponsor's pre-specified margin, the margin chosen was too liberal.

The two studies produced divergent results despite their similar designs. In SPORTIF V, the event rate was higher in the ximelagatran arm compared to the warfarin arm while in

SPORTIF III, the event rate was higher in the warfarin arm compared to the ximelagatran arm. Comparing the event rate in the common arm of both studies, the event rate in the ximelagatran arm of both studies was similar at approximately 1.6%. However, the event rate in the warfarin arm varied by almost two-fold: 1.2% in SPORTIF V versus 2.3% in SPORTIF III. Differences in the patient populations in the two studies at baseline could be a possible explanation of the differences in the event rate in the treatment arms. Patients in SPORTIF V were slightly older, had lower blood pressures on average, had fewer patients with histories of transient ischemic attacks (TIA's) or strokes, and had greater consumption of HMG CoA reductase inhibitors than did patients enrolled in SPORTIF III. However, it is difficult to explain why such differences would lead to differences in event rates in the warfarin arm while leaving the event rate in the ximelagatran arm unaffected. In a setting where two studies produce divergent results, I would favor the results from a double-blind study. The event rate in both studies was primarily driven by the occurrence of ischemic strokes. More than 80% of the events in both studies were ischemic strokes.

## IX. Integrated Review of Safety

### A. Brief Statement of Conclusions

The studies submitted in support of safety are SPORTIF III, SPORTIF V, and SPORTIF II/IV. The SPORTIF II/IV studies are not discussed in this section but are discussed in detail in the Appendix. The studies in aggregate exceeded the ICH E1 guidelines for safety exposure for drugs intended for chronic use. The exposure to ximelagatran in SPORTIF III and SPORTIF V was approximately 2300 and 2600 patient-years respectively.

In SPORTIF III, there were a total of 145 deaths that occurred on treatment or during the follow-up period: 75 Ximelagatran, 70 Warfarin. In SPORTIF V, there were a total of 237 deaths occurring on treatment or during the follow-up period: 116 Ximelagatran, 121 Warfarin. The etiologies of deaths were consistent with what is to be expected from an elderly population with co-morbidities. The common etiologies of death for patients enrolled in these studies included sudden death, heart rate and rhythm disorders, myocardial infarctions, and congestive heart failure.

In terms of serious adverse events (SAE's) not leading to death, the frequency of reporting of SAE's was similar in the 2 treatment arms in each of the SPORTIF studies. In general, the reporting rate was lower in SPORTIF III compared to SPORTIF V. The etiologies of the SAE's not leading to death were also consistent with what would be expected in an elderly population. The most common etiologies included congestive heart failure, cerebrovascular disorders, myocardial infarctions, GI hemorrhage, pneumonia, and angina pectoris.

Discontinuations due to adverse events were numerically greater in the ximelagatran arms of both SPORTIF studies. The most common reason for study drug discontinuation from ximelagatran was liver and biliary system disorders. The incidence of aminotransferase abnormalities was significantly higher on ximelagatran compared to warfarin regardless of the criteria used to define abnormal (e.g. ALAT or ASAT > 3x ULN, > 5x ULN, or > 10 x ULN). The majority of patients that developed liver enzyme abnormalities did so beginning 2 to 4 months after starting ximelagatran therapy. There was one case of a biopsy documented drug induced liver failure leading to death. There was a second probable case of drug induced liver failure leading to coagulopathy and subsequently death. In addition there were multiple cases of

aminotransferase abnormalities greater than 3 times the upper limit of normal temporally associated with a bilirubin increase of greater than 2 times the upper limit of normal. In most of these cases the patients were asymptomatic. Liver enzyme abnormalities returned to normal after drug discontinuation in these patients.

In terms of major bleeding events, the total number of bleeds was numerically lower in the ximelagatran arm of both SPORTIF studies. In neither of the studies did this difference achieve statistical significance. The majority of major bleeds in both studies was due to bleeding with a fall in the hemoglobin level of greater than or equal to 2 g/dL or due to overt bleeding requiring ≥ 2 units of whole blood.

Finally in terms of commonly reported adverse events, the most common reported adverse events on ximelagatran were respiratory infection, dizziness, accident/injury, purpura, and pain. The frequency of these adverse events was similar in the two treatment arms in both SPORTIF studies.

B. Description of Patient Exposure

As shown in Table XLIII below, the safety population in the 2 SPORTIF studies consisted of primarily Caucasian males with an average age of about 70 years.

**Table XLIII: Demographic description of Safety population**

| | **SPORTIF III[a]** | | **SPORTIF V[b]** | |
|---|---|---|---|---|
| | **Ximelagatran (N = 1698)** | **Warfarin (N = 1699)** | **Ximelagatran (N = 1953)** | **Warfarin (N = 1953)** |
| Male | 1153 (68%) | 1195 (70%) | 1361 (70%) | 1347 (69%) |
| Female | 545 (32%) | 504 (30%) | 592 (30%) | 606 (31%) |
| Caucasian | 1490 (88%) | 1497 (88%) | 1870 (96%) | 1879 (96%) |
| Black | 0 | 3 (0.2%) | 65 (3%) | 58 (3%) |
| Oriental | 199 (12%) | 195 (12%) | 15 (0.8%) | 10 (0.5%) |
| Mean age male (range) | 69.1 (30 – 89) | 68.9 (37 – 90) | 70.6 (35 – 97) | 70.4 (40 to 92) |
| Mean age female (range) | 72.6 (29-92) | 72.8 (46 – 90) | 73.7 (30 to 91) | 74.3 (35 to 92) |

Data in this table obtained from Table 72 (SPORTIF III CSR) and Table 79 (SPORTIF V CSR)

[a]A total of 3407 patients were formally randomized into this study. 10 of the randomized patients did not take the study drug and therefore a total of 3397 (1698 + 1699) were randomized and received at least one dose of study drug.

[b]A total of 3922 patients were formally randomized into this study. 15 of the randomized patients did not take the study drug. One patient took study drug but all contact was lost for this patient and thus did not provide safety data.

As shown in Table XLIV, the mean duration on study drug was similar between the 2 SPORTIF studies. The mean duration on study drug was greater on warfarin relative to ximelagatran and consistent across both studies. There were significantly more patients with an exposure duration ≥ 631 days in SPORTIF V compared to SPORTIF III. There was a difference in the mean post treatment follow-up between the 2 SPORTIF studies as shown below. In SPORTIF V there was a 14 day follow-up period for collecting AE's that began on the second day after the last dose of

study drug and continued until the 14th day after the last dose of study drug. SPORTIF III did not have such a pre-specified follow-up period.

**Table XLIV: Summary of Exposure Data**

| | **SPORTIF III Ximelagatran (N = 1698)** | **Warfarin (N = 1699)** | **SPORTIF V Ximelagatran (N = 1953)** | **Warfarin (N = 1953)** |
|---|---|---|---|---|
| Mean Duration on study drug in days (SD) | 485 (170) | 502 (145) | 478 (233) | 506 (212) |
| Mean Post treatment follow-up in days (SD) | 26 (27) | 33 (43) | 12 (2) | 12 (2) |
| Duration of exposure $\geq$ 91 days | 1584 (93%) | 1639 (97%) | 1738 (89%) | 1802 (92%) |
| Duration of exposure $\geq$ 361 days | 1443 (85%) | 1520 (90%) | 1459 (75%) | 1563 (80%) |
| Duration of exposure $\geq$ 631 days | 311 (18%) | 296 (17%) | 590 (30%) | 611 (31%) |

Data in this table obtained from Table 75 (SPORTIF III CSR) and Table

C. Methods and Specific Findings of Safety Review

1. Study population definitions

The definitions of the various safety populations are described below.

**Safety Population:** All patients with intake of at least 1 dose of study medication and for whom post-dose information was available were included in the safety population and used in the analysis of AE's. Patients in the safety population were analyzed according to the study treatment that they received. Other safety analyses, eg, laboratory values, were to be performed on the OT analysis set. The total safety population in SPORTIF III consisted of 3,397 patients (1698 X, 1699 W). The total safety population in SPORTIF V consisted of 3,906 patients (1953 X, 1953 W).

**OT analysis population:** The OT approach included all patients in the ITT population (i.e. all randomized patients) but only their time on active study drug was used for analysis. A maximum continuous interruption of up to 30 days without active study drug was allowed for patients to remain in the OT analyses (except for cardioversion, for which the patient was allowed to interrupt treatment for 60 continuous days). In addition, a maximum of 60 accumulated days of interruption was permitted. Patients who deviated from the above criteria had all subsequent data excluded from the OT analyses, although data obtained prior to the deviation were included, i.e., data were excluded from the time the criteria were violated. For the purposes of the analysis the time "On Treatment" started at randomization, hence patients with events after randomization but before the first dose intake were included.

**ITT analysis population:** All randomized patients were included in the ITT population until the date of each patient's study closure visit or final contact, irrespective of their protocol adherence to study treatment or other protocol procedures. For those patients who withdrew from the study, they were included up to the date of their study termination. This population was used primarily for the analysis of efficacy and therefore not necessarily applicable to safety.

2. Deaths

In SPORTIF V, there were a total of 239 deaths reported. Of these 239 deaths, 116 deaths were reported in the ximelagatran arm and 123 were reported in the warfarin arm. These 239 deaths, include 2 deaths (patients 5882 and 8818 both in the warfarin arm) that occurred approximately 2 months after study termination and therefore should not have been considered in the safety analysis. A total of 74 deaths occurred on treatment (33 X, 41 W). A total of 163 deaths occurred during the follow-up period (83 X, 80 W). Finally, as discussed above, 2 deaths occurred after the follow-up period (both in the warfarin arm) and therefore should not be considered in the final safety analysis. In summary, 74 + 163 + 2 = 239.

In SPORTIF III, a total of 168 patients died. Of these 168 deaths, 85 were reported in the ximelagatran arm and 82 were reported in the warfarin arm. Of these 168 deaths, 145 occurred during treatment or during the follow-up period (75 X, 70 W). 23 deaths occurred after withdrawal from the study and therefore were not required to be analyzed in the safety population.

Table XLV below lists the most common adverse events leading to death. The reporting format in the table below is as follows: The number shown before the parentheses represents the total number of events occurring on treatment and during follow-up. The first number in parentheses represents the total number of events on treatment while the second number in the parentheses represents the total number of events during follow-up.

The most common adverse events leading to death were not unexpected for the elderly population studied in these two trials.

**Table XLV: Listing of the most common adverse events leading to death**[a](PLEASE NOTE THAT NUMBER OF EVENTS RATHER THAN PERCENTAGES ARE REPORTED)

| | **SPORTIF III Ximelagatran (N = 1698)** | **Warfarin (N = 1699)** | **SPORTIF V Ximelagatran (N = 1953)** | **Warfarin (N = 1953)** |
|---|---|---|---|---|
| Total deaths[b] | 75 (48, 27) | 70 (42, 28) | 116 (33, 83) | 121 (41, 82) |
| Sudden death | 17 (16, 1) | 20 (19, 1) | 8 (6, 2) | 3 (0, 3) |
| Heart rate and rhythm disorders[c] | 6 (6, 0) | 3 (2, 1) | 26 (14, 12) | 31 (18, 13) |
| Myocardial infarction | 10 (6, 4) | 3 (0, 3) | 11 (5, 6) | 12 (7, 5) |
| Cardiac failure/Aggravated cardiac failure | 8 (4, 4) | 9 (4, 5) | 5 (0, 5) | 9 (2, 7) |

Note the format of reporting in this table: total number of reported deaths (deaths "during treatment period", deaths during follow-up or "post-treatment period")

[a]Data derived from table 84 of SPORTIF III CSR and table 96 of SPORTIF V CSR

[b]For SPORTIF III, as stated in the text above, there were 168 deaths recorded by the sponsor of which 23 occurred after study termination and therefore not included in this table. For SPORTIF V, there were 239 deaths recorded by the sponsor of which 2 occurred after study termination and therefore not included in this table.

[c] Includes terms coded as "cardiac arrest", "ventricular fibrillation", "arrhythmia", "ventricular arrhythmia" and/or "cardio-respiratory arrest"

3. Serious Adverse Events other than death

Table XLVI below provides a summary of the serious adverse events (SAE's) reported in SPORTIF III and SPORTIF V. The format of reporting in the table below is similar to that in the previous section dealing with deaths. The number shown before the parentheses represents the total number of events occurring on treatment and during follow-up. The first number in parentheses represents the total # of events on treatment while the second number in the parentheses represents the total #of events during follow-up.

Shown in the table below are SAE's that occurred with a frequency of $\geq$ 1% based on the ximelagatran arm. In addition, also shown are SAE's that occurred with a frequency < 1% but were $\geq$ 2x more common on ximelagatran versus warfarin.

The reporting of serious adverse events other than death was lower in both study arms of the open-label SPORTIF III study versus the double-blind SPORTIF V study despite correcting for patient-years of exposure. The most common serious adverse events not leading to death were cardiac failure, cerebrovascular disorders, and myocardial infarctions as would be expected in the target population studied. Hepatic enzyme abnormalities occurred with a greater frequency in the ximelagatran arm of both studies and are discussed in depth later in this review.

SAE's that occurred with a frequency < 1% but that were $\geq$2x higher on ximelagatran versus warfarin and consistent in both studies included peripheral ischemia, neuropathy, rectal carcinoma, and peripheral edema. These SAE'S are highlighted in the table below. Due to the small number of events, it is difficult to determine whether these findings represent noise in the data or a real signal.

**Table XLVI: Listing of serious adverse events not leading to death**[a, b, c, d, e] (PLEASE NOTE THAT NUMBER OF EVENTS RATHER THAN PERCENTAGES ARE REPORTED)

| | **SPORTIF III Ximelagatran (N = 1698)** | **Warfarin (N = 1699)** | **SPORTIF V Ximelagatran (N = 1953)** | **Warfarin (N = 1953)** |
|---|---|---|---|---|
| Total number of patients with non-fatal SAE's | 497 (474, 23) | 541 (525, 16) | 896 (600, 296) | 874 (609, 265) |
| Cardiac Failure/ Aggravated Cardiac failure | 35 (35, 0) | 69 (69, 0) | 122 (91, 31) | 139 (108, 31) |
| Cerebrovascular Disorder | 55 (52,3) | 79 (76, 3) | 97 (56, 41) | 78 (49, 29) |
| GI hemorrhage | 13 (12, 1) | 14 (14, 0) | 52 (31, 21) | 47 (25, 22) |
| Pneumonia | 23 (22, 1) | 23 (23, 0) | 32 (28, 4) | 53 (53, 0) |
| Myocardial Infarction | 25 (23, 2) | 14 (14, 0) | 39 (26, 13) | 48 (30, 18) |
| Angina Pectoris | 26 (26, 0) | 36 (35, 1) | 34 (25, 9) | 44 (36, 8) |
| Atrial fibrillation | 11 (11, 0) | 11 (11, 0) | 26 (24, 2) | 30 (21, 9) |
| Coronary artery disorder | 6 (6, 0) | 6 (4, 2) | 20 (20, 0) | 15 (15, 0) |
| Hepatic enzymes | 7 (6, 1) | 0 (0, 0) | 41 (21, 20) | 3 (2, 1) |

| | | | | |
|---|---|---|---|---|
| increased | | | | |
| Fracture | 1 (1, 0) | 5 (5, 0) | 30 (20, 10) | 28 (20, 8) |
| Chronic obstructive airways disease | 1 (1, 0) | 4 (4, 0) | 27 (19, 8) | 20 (15, 5) |
| Accident/Injury | 27 (27, 0) | 30 (30, 0) | 15 (11, 4) | 24 (21, 3) |
| | | | Adverse events with an frequency < 1% on the ximelagatran arm but occurring ≥ 2x more often on ximelagatran vs. warfarin in SPORTIF V (excluded are AE's where 2 or fewer patients were affected in the ximelagatran arm) | |
| Bronchitis | 3 (3, 0) | 2 (2, 0) | 17 (15, 2) | 6 (6, 0) |
| Infection | 1 (1, 0) | 8 (8, 0) | 11 (8, 3) | 4 (3, 1) |
| Renal function abnormal | NR | NR | 16 (9, 7) | 7 (6, 1) |
| Cardiomyopathy | 1 (1, 0) | 1 (1, 0) | 13 (8, 5) | 5 (4, 1) |
| Neoplasm NOS | 1 (1, 0) | 1 (1, 0) | 10 (7, 3) | 1 (1, 0) |
| Retinal Detachment | 1 (1, 0) | 1 (1, 0) | 6 (5, 1) | 0 (0, 0) |
| Peripheral ischemia | 2 (2, 0) | 1 (1, 0) | 9 (5, 4) | 2 (2, 0) |
| Confusion | 2 (2, 0) | 3 (3, 0) | 5 (4, 1) | 2 (1, 1) |
| Renal artery stenosis | NR | NR | 5 (4, 1) | 0 (0, 0) |
| Angina pectoris aggravated | 4 (4, 0) | 6 (6, 0) | 6 (4, 2) | 2 (2, 0) |
| Urinary bladder carcinoma | 0 (0, 0) | 4 (4, 0) | 6 (4, 2) | 1 (1, 0) |
| Neuropathy | 4 (4, 0) | 2 (2, 0) | 5 (4, 1) | 2 (1, 1) |
| Pulmonary carcinoma | 1 (1, 0) | 1 (1, 0) | 7 (3, 4) | 2 (1, 1) |
| Small cell lung cancer | NR | NR | 4 (3, 1) | 2 (1, 1) |
| Hypertension aggravated | NR | NR | 6 (3, 3) | 1 (1, 0) |
| Esophageal disorder | 1 (1, 0) | 0 (0, 0) | 3 (3, 0) | 1 (0, 1) |
| Esophagitis | 0 (0, 0) | 1 (1, 0) | 3 (3, 0) | 0 (0, 0) |
| Ventricular fibrillation | 1 (1, 0) | 3 (3, 0) | 4 (3, 1) | 2 (1, 1) |
| Renal failure NOS | 1 (1, 0) | 2 (2, 0) | 6 (3, 3) | 3 (0, 3) |
| Limb embolism | NR | NR | 6 (3, 3) | 0 (0, 0) |
| | Adverse events with an frequency < 1% on the ximelagatran arm but occurring ≥ 2x more often on ximelagatran vs. warfarin in SPORTIF III (excluded are AE's where 2 or fewer patients were affected in the ximelagatran arm) | | | |
| Retinal hemorrhage | 4 (4, 0) | 0 (0, 0) | (0, 0) | (1, 0) |
| Depression | 5 (4, 1) | 2 (2, 0) | 2 (1, 1) | 2 (1, 1) |
| Abdominal pain | 6 (5, 1) | 2 (2, 0) | 6 (6, 0) | 8 (7, 1) |
| Rectal hemorrhage | 7 (6, 1) | 1 (1, 0) | 3 (2, 1) | 5 (3, 2) |
| Cholecystitis | 7 (7, 0) | 2 (2, 0) | 5 (5, 0) | 14 (11, 3) |
| Diabetes mellitus | 4 (4, 0) | 2 (2, 0) | 2 (1, 1) | 5 (3, 2) |
| Gout | 3 (3, 0) | 1 (1, 0) | 5 (4, 1) | 3 (3, 0) |
| Hyponatremia | 3 (3, 0) | 0 (0, 0) | 5 (4, 1) | 4 (3, 1) |
| Hypertension | 5 (5, 0) | 1 (1, 0) | 0 (0, 0) | 2 (1, 1) |
| Tachycardia | 6 (6, 0) | 3 (3, 0) | 1 (1, 0) | 0 (0, 0) |
| Palpitations | 3 (3, 0) | 1 (1, 0) | 0 (0, 0) | 1 (1, 0) |
| Vertebrobasilar | 4 (4, 0) | 2 (2, 0) | NR | NR |

| | | | | |
|---|---|---|---|---|
| insufficiency | | | | |
| Intermittent claudication | 3 (3, 0) | 0 (0, 0) | NR | NR |
| Uterine prolapse | 3 (3, 0) | 0 (0, 0) | 1 (1, 0) | 0 (0, 0) |
| Rectal carcinoma | 4 (4, 0) | 2 (2, 0) | 2 (1, 1) | 1 (0, 1) |
| Peripheral edema | 3 (3, 0) | 1 (1, 0) | 2 (1, 1) | 1 (1, 0) |

[a]Note the format of reporting in this table: total number of reports of each adverse (events "during treatment period", events during follow-up or "post-treatment period")
[b]Events reported in this table are those that occurred with a ≥ 1% frequency in the ximelagatran arm ***or*** occurred with a frequency < 1% ***and*** were ≥ 2 fold higher in the ximelagatran arm relative to the warfarin arm
[c]Note that some patients had the same AE reported in both the "during tx" and "post tx" period because AE's were counted in all periods where they occurred instead of only in the period when they started
[d]Note that some patients had more than 1 serious adverse event.
[e]Data obtained from table 11.3.4.1.1 and 11.3.4.1.3 (SPORTIF V) and table 11.3.4.1.2 (SPORTIF III)
[f]NR = none reported

4. Discontinuations due to Adverse Events

Discontinuations of study drug were more common in the ximelagatran arm in both clinical trials. Table XLVII below lists the discontinuations due to AE's that occurred with an frequency of ≥ 1% based on the ximelagatran arm. In addition, also shown are SAE's that occurred with a frequency < 1% but were ≥ 2x more common on ximelagatran versus warfarin. The most common reason for study drug discontinuation was liver and biliary system disorders. This broad category included preferred terms such as hepatic enzyme increases, SGPT or SGOT increases, and abnormal hepatic function. These adverse events could explain a substantial portion of the uneven distribution of study drug discontinuations between the two study groups. Details of adverse hepatobiliary events are described later in this review.
The most common reasons for study drug discontinuation (≥ 1% frequency) in the ximelagatran arm were hepatic enzyme abnormalities and cerebrovascular disorders.

**Table XLVII: Listing of study drug discontinuations due to adverse events. Listed are the total number of AE's occurring at a frequency of ≥ 1% in the ximelagatran group or were ≥ 2x fold higher in the ximelagatran arm relative to the warfarin arm[a]** (PLEASE NOTE THAT NUMBER OF EVENTS RATHER THAN PERCENTAGES ARE REPORTED)

| | **SPORTIF III** | | **SPORTIF V** | |
|---|---|---|---|---|
| | **Ximelagatran (N = 1698)** | **Warfarin (N = 1699)** | **Ximelagatran (N = 1953)** | **Warfarin (N = 1953)** |
| Total number of patients with an AE leading to study drug discontinuation | 185 | 100 | 354 | 300 |
| Adverse events occurring with an absolute incidence of ≥ 1% in the ximelagatran arm of either SPORTIF III OR SPORTIF V | | | | |
| Hepatic enzymes increased | 20 | 0 | 39 | 4 |
| Cerebrovascular disorder | 21 | 18 | 36 | 26 |
| Hepatic function abnormal | 6 | 0 | 22 | 3 |
| | Corresponding events in SPORTIF III | | Adverse events with an incidence < 1% on the ximelagatran arm but occurring at a frequency ≥ 2x on ximelagatran vs. | |

| | | | warfarin in SPORTIF V (**excluded are AE's where 2 or fewer patients were affected in the ximelagatran arm**) | |
|---|---|---|---|---|
| Hematuria | 5 | 2 | 11 | 5 |
| Diarrhea | 1 | 1 | 10 | 5 |
| Fracture | 1 | 0 | 6 | 3 |
| Fatigue | 1 | 0 | 6 | 2 |
| Pain | 1 | 0 | 6 | 2 |
| Chest pain | 1 | 1 | 5 | 2 |
| Sudden death | 1 | 0 | 5 | 0 |
| Cardiomyopathy | 0 | 1 | 4 | 2 |
| Hemorrhage rectum | 2 | 0 | 4 | 0 |
| Ventricular fibrillation | 1 | 2 | 4 | 2 |
| Colon carcinoma | 2 | 1 | 3 | 0 |
| Renal failure NOS | 1 | 0 | 3 | 1 |
| Anxiety | NR[b] | NR[b] | 3 | 1 |
| | Adverse events with an frequency < 1% on the ximelagatran arm but occurring $\geq$ 2x more often on ximelagatran vs. warfarin in SPORTIF III (**excluded are AE's where 2 or fewer patients were affected in the ximelagatran arm**) | | Corresponding events in SPORTIF V | |
| Cardiac failure | 6 | 3 | 8 | 13 |
| Retinal hemorrhage | 3 | 0 | NR[b] | NR[b] |
| Hemoptysis | 3 | 0 | 1 | 2 |
| Epistaxis | 3 | 1 | NR[b] | NR[b] |

[a]Data in this table obtained from Table 11.3.5.1.1 of SPORTIF V CSR and Table 11.3.5.1 of SPORTIF III CSR.
[b]NR = none reported

5. Adverse Bleeding Events

The major bleeding events as adjudicated by the CEAC are presented in this section. As shown in Table XLVIII, there were a total of 147 adjudicated major bleeds in SPORTIF V and 70 in SPORTIF III. The bleeding event rates were markedly different between the two studies even after accounting for differences in patient-years of exposure. There were a total of 3 major bleeds that were fatal in each of the studies, SPORTIF III and SPORTIF V.

**Table XLVIII: Summary Table of Major bleeding events (Based on On Treatment – OT Analysis)[a].**

| | **SPORTIF III** | | **SPORTIF V** | |
|---|---|---|---|---|
| | **Ximelagatran** | **Warfarin** | **Ximelagatran** | **Warfarin** |
| Major Bleeds[b] | | | | |
| Patient Years | 2279 | 2347 | 2602 | 2724 |
| # of Events | 29 | 41 | 63 | 84 |
| | P = 0.228 | | P = 0.155 | |

[a]Data in this table obtained from Table 79 of SPORTIF III CSR and Table 87 of SPORTIF V CSR.
[b]CEAC adjudicated events

Kaplan-Meier curves for major bleeding events in SPORTIF III and SPORTIF V are shown in Figure 16 and Figure 17 below.

**Figure 16: Cumulative percentage of patients with major bleeding events over time – Estimated Kaplan-Meir Curves (OT analysis) for SPORTIF III study (Obtained from Figure 32 of Sponsor's SPORTIF III Clinical Study report)**

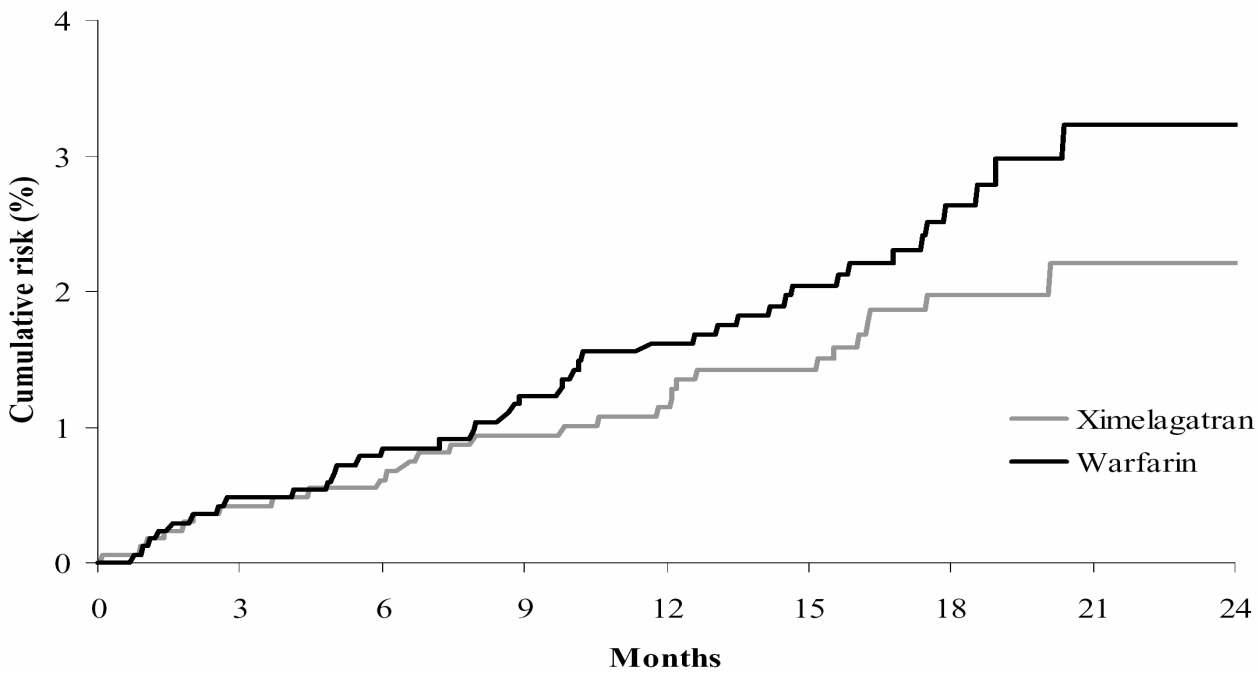
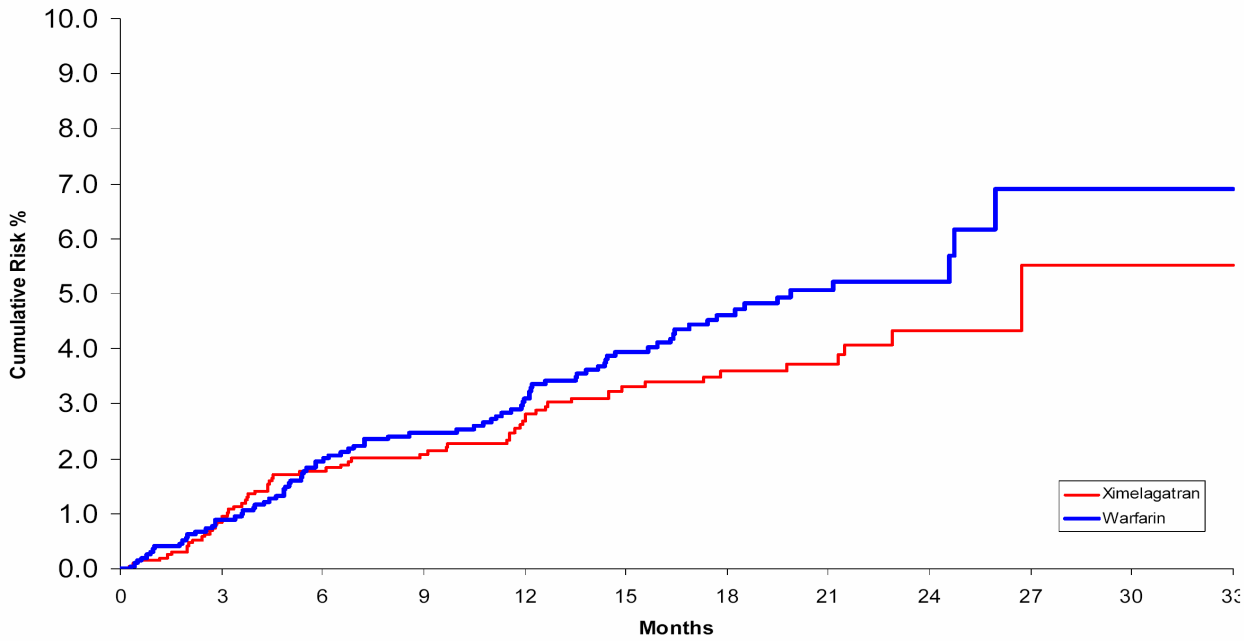



**Figure 17: Cumulative percentage of patients with major bleeding events over time; estimated Kaplan-Meier curves (OT Analysis). (Obtained from Figure 25 of Sponsor's SPORTIF V Clinical Study report)**



As shown in Table XLIX below, the majority of major bleeds in both SPORTIF studies were those defined by "overt bleeding with a fall in Hb of 2 g/dL or more."

**Table XLIX: Number of patients with major bleeding events according to the CEAC, by criteria for judgment according to local criteria assessed and by treatment group (OT analysis)[a].**

| | **SPORTIF III** | | **SPORTIF V[b]** | |
|---|---|---|---|---|
| | **Ximelagatran** | **Warfarin** | **Ximelagatran** | **Warfarin** |
| # of adjudicated events | 29 | 41 | 63 | 84 |
| Fatal Bleeds | 1 | 2 | 2 | 1 |
| Overt Bleeding with fall in Hb of 2.0 g/dL or more | 16 | 20 | 44 | 61 |
| Overt Bleeding requiring $\geq$ 2 units of whole blood | 4 | 8 | 23 | 34 |
| Critical site Bleeding[c] | 8 | 11 | 8 | 9 |

[a]Data from Tables 80 and 88 of SPORTIF III and V Clinical study reports respectively.
[b]For SPORTIF V, the "# of adjudicated events" represents total number of patients with at least one event. A major bleeding event may be counted under more than 1 criteria.
[c]Critical site bleeding includes intracranial, retroperitoneal, intraspinal, intraocular, pericardial or atraumatic intra-articular bleeding.

Table L below shows the location and subtypes of major bleeds.

**Table L: Locations/subtypes of major bleeds[a]**

| | **SPORTIF III** | | **SPORTIF V** | |
|---|---|---|---|---|
| | **Ximelagatran** | **Warfarin** | **Ximelagatran** | **Warfarin** |
| # of adjudicated events | 29[b] | 41[b] | 63[e] | 84[e] |
| Gastrointestinal | 16 | 16 | 29 | 33 |
| "Other" | 5[c] | 10[d] | 15 | 29 |
| Subdural Hematoma | 6 | 4 | | |
| Intraocular | 3 | 4 | 2 | 5 |
| Urinary | 0 | 4 | 5 | 5 |
| Retroperitoneal | 0 | 2 | 3 | 5 |
| Pericardial | 0 | 2 | 2 | 1 |
| Intra-articular | 0 | 1 | | |
| Intraspinal | 0 | 1 | | |
| Missing information | | | 8 | 12 |

[a]Data obtained from Table 11.3.2.18 of sponsor's Clinical Study report
[b]One patient in the ximelagatran group had 2 major events and 2 patients in the warfarin group had 2 major events. Therefore although the total number of patients with major bleeds where 29, the total number of events was 30. Similar for the warfarin group, the total number of patients was 41 but the total of bleeding events was 43.
[c]Other includes operative and post-op blood loss, arm bleed, leg bleed, scalp bleed, femoral neck fracture operation
[d]Other includes nose bleed, facial, cutaneous, bleeding from left inguinal catheterization channel, psoas muscle, arm (brachial hematoma)
[e]The number in this row represents the total number of patients with an event and not the total number of events. It is possible that one patient could have had more than one event.

In SPORTIF III, in various subgroups, most point estimates of major bleeds favored ximelagatran. Exceptions included patients with moderate renal dysfunction, patients with BMI < 25, female patients, and Oriental patients. Similar to SPORTIF III, In SPORTIF V, most point estimates favored ximelagatran. Exceptional subgroups were patients with moderate renal dysfunction and patients that weighed over 100 kg. Please refer to Figure 18 and Figure 19 below.

**Figure 18: Summary of safety comparison: ximelagatran vs. warfarin (difference in percent events, with 95% CI) for major bleed events, according to prognostic factors (OT analysis) (SPORTIF III) (Obtained from Figure 33 of SPORTIF III CSR).**

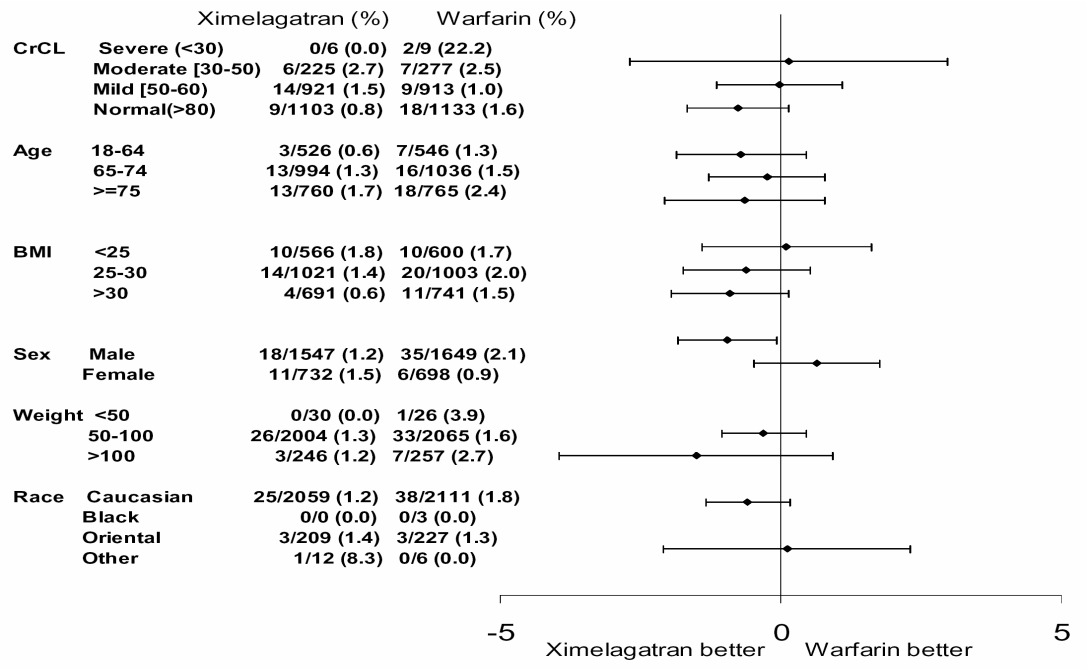
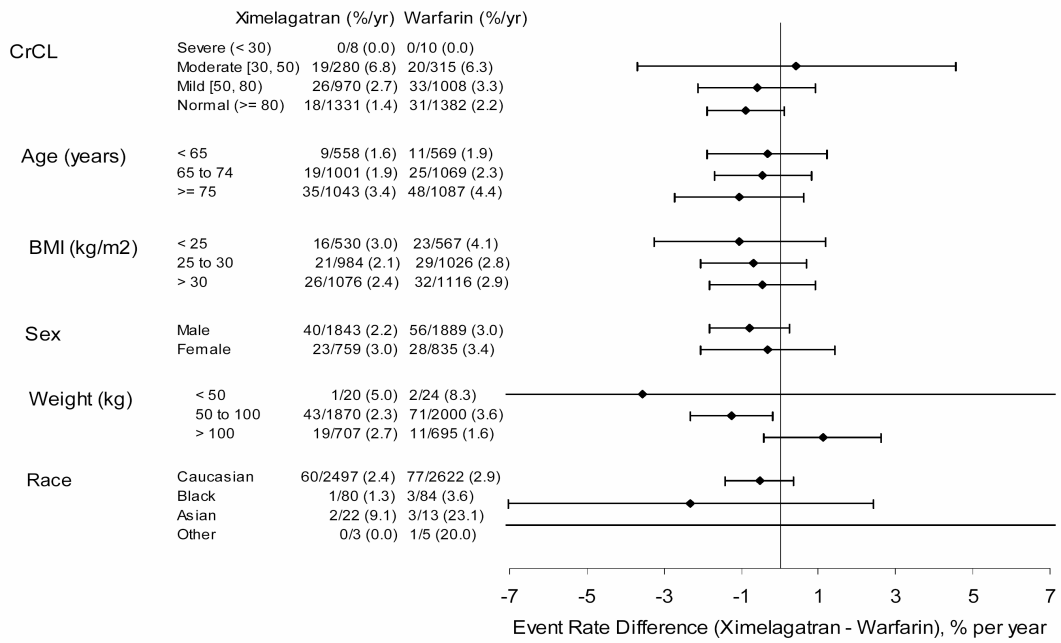


**Figure 19: Summary of safety comparison: ximelagatran vs. warfarin (difference in percent events, with 95% CI) for major bleed events, according to prognostic factors (OT analysis) (SPORTIF V) (Obtained from Figure 26 of SPORTIF V CSR)**




6. Hepatobiliary Adverse Events

The frequency of hepatic enzyme abnormalities is shown in Table LI below. There is clearly a greater frequency of aminotransferase abnormalities on ximelagatran relative to warfarin regardless of the cutoff level one considers abnormal. Although not shown in this review, there was a strong correlation between ALAT and ASAT enzyme abnormalities. The correlation between ALAT elevations and ALP or Bilirubin elevations was relatively poor.

**Table LI: Frequency of patients with elevated ALAT, ASAT, ALP, and Bilirubin (ITT population)[a]** (PLEASE NOTE THAT NUMBER OF EVENTS RATHER THAN PERCENTAGES ARE REPORTED)

| | **SPORTIF III** | | **SPORTIF V** | |
|---|---|---|---|---|
| | **Ximelagatran (N = 1704)** | **Warfarin (N = 1703)** | **Ximelagatran (N = 1960)** | **Warfarin (N = 1962)** |
| ALAT > ULN | 457 | 232 | 472 | 197 |
| ALAT > 2x ULN | 170 | 37 | 200 | 35 |
| ALAT > 3x ULN | 107 | 14 | 117 | 15 |
| ALAT > 5x ULN | 57 | 7 | 59 | 5 |
| ALAT > 10x ULN | 15 | 0 | 16 | 1 |
| ASAT > ULN | 326 | 172 | 342 | 140 |
| ASAT > 2x ULN | 109 | 29 | 112 | 21 |
| ASAT > 3x ULN | 60 | 13 | 60 | 10 |
| ASAT > 5x ULN | 28 | 5 | 25 | 2 |
| ASAT > 10x ULN | 11 | 1 | 9 | 1 |
| ALP > ULN | 250 | 222 | 325 | 291 |
| ALP > 2x ULN | 30 | 16 | 36 | 19 |
| ALP > 3x ULN | 13 | 4 | 12 | 3 |

| | | | | |
|---|---|---|---|---|
| ALP > 5x ULN | | | 5 | 0 |
| ALP > 10x ULN | | | 2 | 0 |
| Bilirubin > 1.5x ULN | 86 | 83 | 103 | 81 |
| Bilirubin > 2x ULN | 24 | 26 | 28 | 20 |
| Bilirubin > 3x ULN | 8 | 3 | 10 | 4 |
| Bilirubin > 5x ULN | 3 | 1 | 4 | 2 |
| Bilirubin > 10x ULN | | | 2 | 1 |

[a]Data from Table 87 of SPORTIF III CSR and Table 100 of SPORTIF V CSR

Table LII below shows that there were a greater number of patients with a bilirubin increase of > 2 times the upper limit in close temporal relationship to an elevated aminotransferase levels. Isolated elevations in aminotransferase levels are suggestive of a hepatocellular injury that may be reversible if the offending agent is removed. Elevations in aminotransferase levels in conjunction with an elevated bilirubin level can be a more ominous sign suggesting a disruption in synthetic liver function. The combination of elevated aminotransferase elevations in association with elevations in total bilirubin has been dubbed by the Agency as "Hy's Law." According to the Clinical White Paper on hepatotoxicity published in November 2000 "instances (even very few of them) of transaminase elevation accompanied by elevated bilirubin (even if obvious jaundice was not present) have been associated with, and have often predicted, post-marketing serious liver injuries (fatal or requiring transplant)." Several case narratives of patients that fulfill Hy's Law are described in the Appendix of this review.

**Table LII: Number of Patients with ALAT > 3x ULN followed by a bilirubin level > 2x ULN within one month of the elevated ALAT** (PLEASE NOTE THAT NUMBER OF EVENTS RATHER THAN PERCENTAGES ARE REPORTED) **.**

| | **SPORTIF III** | | **SPORTIF V** | |
|---|---|---|---|---|
| | **Ximelagatran** | **Warfarin** | **Ximelagatran** | **Warfarin** |
| # of patients with ALAT > 3x ULN | 107 | 14 | 117 | 15 |
| # of patients with Bilirubin > 2x ULN within one month of raised ALAT | 9 | 1 | 9 | 1 |

The time course of ALAT abnormalities is shown in Figure 20 and Figure 21 below. In both studies there were a large number of cases of ALAT abnormalities that appeared between 2 and 4 months post randomization.

**Figure 20: Cumulative risk of ALAT > 3x ULN versus time after randomization (ITT population) (Figure obtained from Figure 36 of SPORTIF III CSR).**

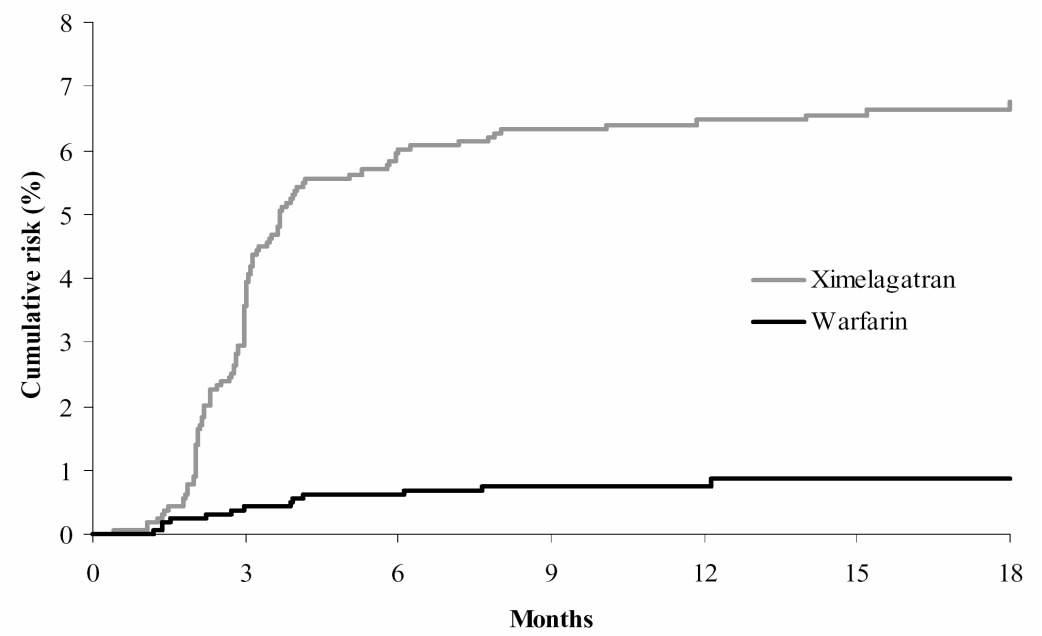



**Figure 21: Cumulative risk of ALAT > 3x ULN versus time after randomization (ITT population) (Figure obtained from Figure 33 of SPORTIF V CSR)**

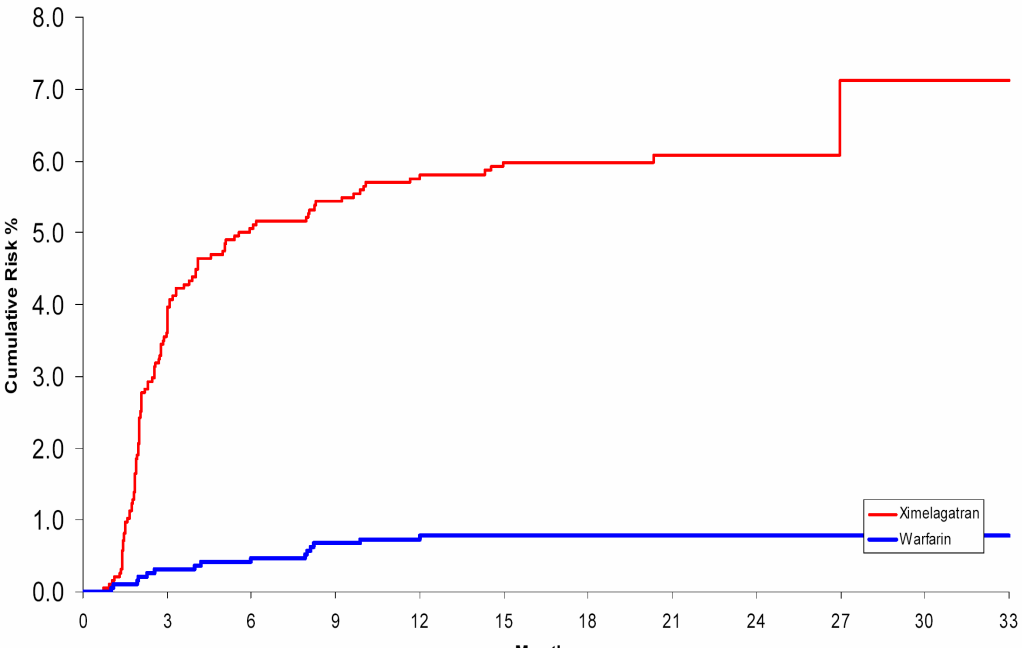
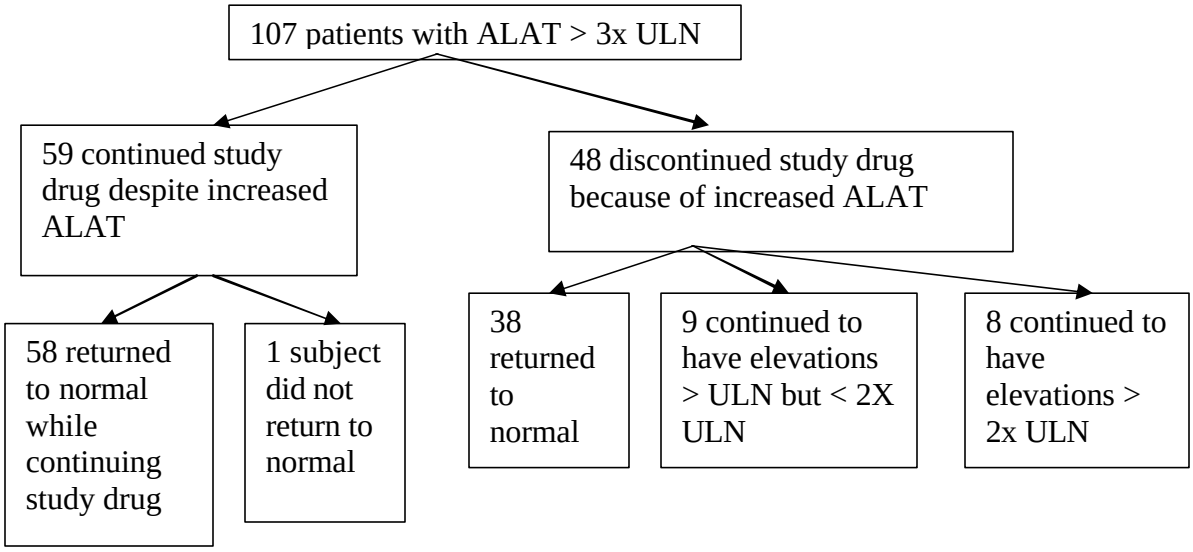



Figure 22 below summarizes the disposition of patients with ALAT > 3x ULN in SPORTIF III. 59 of the 107 ximelagatran patients with ALAT > 3x ULN were continued on treatment. Of these 59 patients, 58 returned to normal limits despite continuing ximelagatran therapy. 48 of

the 107 ximelagatran patients with ALAT > 3x ULN were discontinued from therapy. In 31 of these 48 patients, ALAT returned to normal limits. 9 of these 48 patients, had values that returned to < 2x ULN during the study while 8 of the 48 continued to have ALAT values > 2x ULN.

**Figure 22: Summary of patients on ximelagatran with an ALAT > 3x ULN in SPORTIF III**




In SPORTIF V, there were 117 ximelagatran treated patients with ALAT elevations > 3x ULN. It was not completely clear from the SPORTIF V CSR as to how many of these patients continued study drug despite an increased ALAT versus how many discontinued study drug because of an increased ALAT. Forty five of the patients that continued to be treated with study drug returned to normal spontaneously during the study period. Of the patients that discontinued study drug, 42 had returned to normal at the last available blood test or during follow-up.

Case Narratives of two patients with severe hepatotoxicity as manifested by evidence of hepatic synthetic dysfunction

Patient 7259:

An 80 y/o Caucasian male's medical history included hyperlipidemia, atrial fibrillation, hydronephrosis, urinary retention, fibromyalgia, coronary artery disease s/p CABG, and colon cancer.

Medications: digoxin, metoprolol, prednisone, tamsulosin

May 30, 2001: Baseline (screening)
June 11, 2001: Randomized to ximelagatran
August 6, 2001: At the month 2 visit, his liver enzymes were noted to be mildly elevated.

September 4, 2001: Further elevations in liver enzymes were noted compared to August 6. This led to weekly blood monitoring. In the case narrative, there was no documentation of this patient being symptomatic early on in association with a rise in liver enzymes. Patient was reported to be symptomatic only much later in his clinical course.

September 7, 2001: Study drug was discontinued. The liver enzymes continued to increase. Serologies for viral hepatitis (A, B, C, CMV, EBV, HSV) were not consistent with a recent viral infection. An ANA was also negative. An abdominal ultrasound showed a normal liver, gall bladder, and normal biliary tree.

September 24, 2001: The patient was referred to a hepatologist as an outpatient.

September 27, 2001: Transaminases peaked. A biopsy was performed revealing "severe active hepatitis with hepatocyte necrosis, areas of collapse and marked bile ductular proliferation consistent with acute submassive necrosis."

October 1, 2001: Patient noted to be coagulopathic with an elevated PT of 16.3 sec and an INR of 1.7.

October 2, 2001: Patient was hospitalized with jaundice but reportedly asymptomatic. Patient began therapy with prednisone 40 mg daily, vitamin K, and ranitidine.

October 8, 2001: Patient was discharged in stable condition.

October 29, 2001: During an outpatient visit, the patient complained of increasing fatigue over a 2 week period. Liver enzymes were noted to be improving and patient's dose of prednisone decreased to 15 mg daily. Patient was noted to have developed ascites, significant lower extremity edema and oliguria.

November 3, 2001: Patient found unresponsive at home.

An autopsy was conducted revealing a large duodenal ulcer with erosions. A small, friable and diffusely mottled liver was noted suggestive of severe diffuse hepatic necrosis.

**Table LIII: Pattern of liver enzyme progression for Patient 7259**

| | 5/30/01 | 7/9/01 | 8/6/01 | 9/4/01 | 9/12/01 | 9/19/01 | 10/4/01 | 10/10/01 | 10/29/01 |
|---|---|---|---|---|---|---|---|---|---|
| ALAT (U/L) | 16 | 14 | 103 | 970 | 1106 | 1440 | 1012 | 645 | 219 |
| ASAT (U/L) | 22 | 18 | 80 | 698 | 784 | 1296 | 671 | 411 | 175 |
| ALP (U/L) | 67 | 75 | 90 | 142 | 152 | 160 | 225 | 190 | 180 |
| Bili[a] (mg/dL) | 0.9 | 0.6 | 1 | 1.1 | 1.7 | 2.5 | 9 | 17.1 | 12.1 |

Data taken from Case Report Form and/or Case narrative
[a]Normal bilirubin range is 0 to 1.3 mg/dL

Patient 7859:

A 77 y/o Caucasian male's past medical history included alcohol abuse, cholecystectomy 1999, duodenal ulcer, bleeding in bladder, psychosis, gout, osteoarthritis, chronic obstructive pulmonary disease, pulmonary hypertension, pulmonary insufficiency, emphysema, idiopathic cardiomyopathy, mild tricuspid insufficiency, mild mitral insufficiency, sick sinus syndrome,

pacemaker insertion, hypertension, carotid stenosis, abdominal aortic aneurysm repair, coronary artery disease and benign prostatic hypertrophy.

Medications: carvedilol, magnesium oxide, ramipril, tamsulosin, vitamin b

| | |
|---|---|
| June 19, 2001: | Randomized to receive ximelagatran |
| October 15, 2001: | At the month 2 visit, elevated liver enzymes were noted. |
| October 17, 2001: | Patient "felt well" with no change in his dietary behavior and was able to travel to another city to visit his son. Patient was instructed to get liver enzymes checked in the city where he was visiting his son but apparently did not. |
| November 1, 2001: | Patient took the last dose of his study drug. |
| November 2, 2001: | Patient awoke with stomach pains and light-headedness. He had a bowel movement that produced a bloody stool. He was admitted to a hospital and was noted to be pale, hypotensive (76/45 mm Hg), and tachycardiac. Laboratory work-up revealed that the patient's hematocrit was 20, INR = 3.4, PT = 37 sec, PTT = 69 sec, and his albumin was 2 grams/dL. Plasma melagatran concentrations at admission revealed a value of 0.25 micromolar. Patient was admitted to the intensive care unit and treated with Vitamin K, packed red blood cells, fresh frozen plasma, cryoprecipitate and fluids. |
| November 3, 2001: | Patients anemia and coagulopathy improved with the medical ma nagement described above. The hematocrit increased to 27 while his INR decreased to 1.1, PT to 14 seconds, and PTT to 53 seconds. The patient underwent a gastroscopy that revealed a Billroth II anastomosis. There was evidence of bleeding in the pre-anastomotic area and epinephrine was injected to decrease bleeding. Later during the day, the patient's condition worsened when he developed respiratory failure necessitating tracheal intubation. Gastric suction produced 200 mL of blood. Patient became hemodynamically unstable and required vasopressors. Shock persisted despite further treatment with intravenous fluids, 2 packed red blood cells, 10 units fresh frozen plasma, and 1 unit of platelets. An operation was deemed futile, support was withdrawn, and patient died later that day. No autopsy was conducted. |

**Table LIV: Pattern of liver enzyme progression for patient 7859**

| | Baseline | 15Oct01 | 2Nov01 | 3Nov01 |
|---|---|---|---|---|
| ALAT (U/L) | 13 | 216 | 569 | 134 |
| ASAT (U/L) | 20 | 154 | 629 | 236 |
| ALP (U/L) | 125 | 156 | 173 | 49 |
| Bili (mg/Dl) | 1.1 | 1.3 | | 6.2 |

Data taken from Case Report Form and/or Case narrative

Similar to patient 7259, this patient has evidence for dysfunction in the liver's synthetic function. Assuming that this patient took his last dose of study medication in the evening of November 1$^{st}$, I would not expect this magnitude of elevation in the PT/INR from ximelagatran's pharmacologic effect. The plasma concentration in this patient at the time of hospitalization on November 2$^{nd}$ was reported as 0.25 μmoL/L. This concentration would not be expected to

produce an INR of 3.4 based on Figure 5 of this review. It is more likely that this elevation is due to synthetic dysfunction in the liver as opposed to a pharmacologic effect of ximelagatran. In addition, this patient was noted to have an elevated bilirubin of 6.2 on November 3rd further suggestive of synthetic dysfunction as opposed to a pharmacologic effect of ximelagatran.

Additional cases of ximelagatran associated hepatotoxicity that meet the criteria for Hy's Law are described in the Appendix, Section XIII B.

7. Most commonly reported adverse events (AE's)

Table LV below shows the most common adverse events reported during both the SPORTIF III and SPORTIF V trials. In the table are listed adverse events that occurred with a frequency of greater than or equal to 5% based on the ximelagatran arm. Also shown in the table are adverse events that occurred twice as often on ximelagatran compared to warfarin.

**Table LV: Most common AE's with an absolute frequency ≥ 5% (based on the ximelagatran arm) or were ≥ 2 fold higher than on the control group (warfarin)[a].**

| | **SPORTIF III** | | **SPORTIF V** | |
|---|---|---|---|---|
| | **Ximelagatran (N = 1698)** | **Warfarin (N = 1699)** | **Ximelagatran (N = 1953) N (%)** | **Warfarin (N = 1953) N (%)** |
| Respiratory infection | 312 (18.4) | 306 (18) | 438 (22.4) | 458 (23.5) |
| Purpura | 120 (7.1) | 130 (7.7) | 298 (15.3) | 428 (21.9) |
| Accident and/or injury | 147 (8.7) | 164 (9.7) | 314(16.1) | 381 (19.5) |
| Dizziness | 130 (7.7) | 152 (8.9) | 327 (16.7) | 312 (16.0) |
| Pain | 113 (6.7) | 123 (7.2) | 276 (14.1) | 320 (16.4) |
| Dyspnea | 114 (6.7) | 149 (8.8) | 265 (13.6) | 295 (15.1) |
| Diarrhea | 112 (6.6) | 106 (6.2) | 240 (12.3) | 242 (12.4) |
| Edema peripheral | 94 (5.5) | 109 (6.4) | 207 (10.6) | 247 (12.6) |
| Fatigue | 80 (4.7) | 67 (3.9) | 229 (11.7) | 222 (11.4) |
| Epistaxis | 117 (6.9) | 197 (11.6) | 151 (7.7) | 282 (14.4) |
| Chest pain | 99 (5.8) | 104 (6.1) | 197 (10.1) | 224 (11.5) |
| Back pain | 139 (8.2) | 144 (8.5) | 177 (9.1) | 218 (11.2) |
| Headache | 113 (6.7) | 110 (6.5) | 187 (9.6) | 185 (9.5) |
| Coughing | 105 (6.2) | 100 (5.9) | 183 (9.4) | 175 (9.0) |
| Arthralgia | | | 166 (8.5) | 163 (8.3) |
| Bronchitis | 95 (5.6) | 102 (6.0) | 158 (8.1) | 164 (8.4) |
| Nausea | | | 144 (7.4) | 160 (8.2) |
| Sinusitis | | | 139 (7.1) | 145 (7.4) |
| Rash | | | 128 (6.6) | 132 (6.8) |
| Urinary tract infection | | | 128 (6.6) | 130 (6.7) |
| Abdominal pain | | | 108 (5.5) | 137 (7.0) |
| Hematuria | | | 109 (5.6) | 105 (5.4) |
| Insomnia | | | 107 (5.5) | 116 ( 5.9) |
| Tooth disorder | | | 105 (5.4) | 75 (3.8) |
| Rhinitis | | | 106 (5.4) | 95 (4.9) |
| Dyspepsia | | | 104 (5.3) | 90 (4.6) |
| Hepatic enzymes increased | | | 90 (4.6) | 23 (1.2) |
| SGPT increased | | | 53 (2.7) | 12 (0.6) |
| Hepatic function | | | 50 (2.6) | 12 (0.6) |

| | | | | |
|---|---|---|---|---|
| abnormal | | | | |
| Angina Pectoris aggravated | | | 23 (1.2) | 10 (0.5) |
| Viral infection | 90 (5.3) | 76 (4.5) | | |

[a]Data in this table obtained from Table 78 of SPORTIF III CSR, and Tables 86 and 11.3.2.9 of SPORTIF V CSR.

8. Pancreatic Adverse Events

In preclinical studies, pancreatic hyperplasia was observed in rats. This is thought to be an effect specific to rats. Pancreatic adverse events were monitored in both clinical studies. There does not appear to be a difference between the two groups in terms of pancreatic cancer or pancreatitis serious adverse events as shown in Table LVI below.

**Table LVI: Summary of pancreatic adverse events in SPORTIF III and SPORTIF V**

| | **SPORTIF III** | | **SPORTIF V** | |
|---|---|---|---|---|
| | **Ximelagatran** | **Warfarin** | **Ximelagatran** | **Warfarin** |
| Pancreatic cancer | 0 | 0 | 0 | 3 |
| Pancreatitis SAE's | 1 | 3 | 2 | 2 |

In the SPORTIF V study a subset of patients underwent further monitoring for pancreatic adverse events via measurement of cholecystokinin plasma concentrations and pancreatic volumes via CT scans. A total of 62 patients in the ximelagatran group and 68 in the warfarin group were randomized into this sub-study. The results are shown below.

As shown in Table LVII below, there was marked variability in plasma CCK levels. In general there did not appear to be a significant difference in mean plasma CCK levels at month 3. At baseline, the median CCK plasma levels were 6.6 and 4.5 in the ximelagatran and warfarin arm respectively.

**Table LVII: Comparison of cholecystokinin plasma concentrations at month 3 in a subset of patients in the SPORTIF V study[a]**

| | **Ximelagatran (N = 56)** | **Warfarin (N = 63)** |
|---|---|---|
| Mean (picomolar) | 14.97 | 11.39 |
| Standard deviation (SD) | 18.32 | 16.51 |
| Minimum | 2.00 | 2.00 |
| Median | 6.63 | 4.50 |
| Maximum | 62.5 | 62.5 |

[a]Data taken from Table 110 of SPORTIF V clinical study report

As shown in Table LVIII below, there were similar magnitudes of changes in pancreatic volumes obtained via CT scans in the two treatment arms.

**Table LVIII: Pancreatic volume obtained via CT scan: mean change from screening to last available value. (SPORTIF V study)[a]**

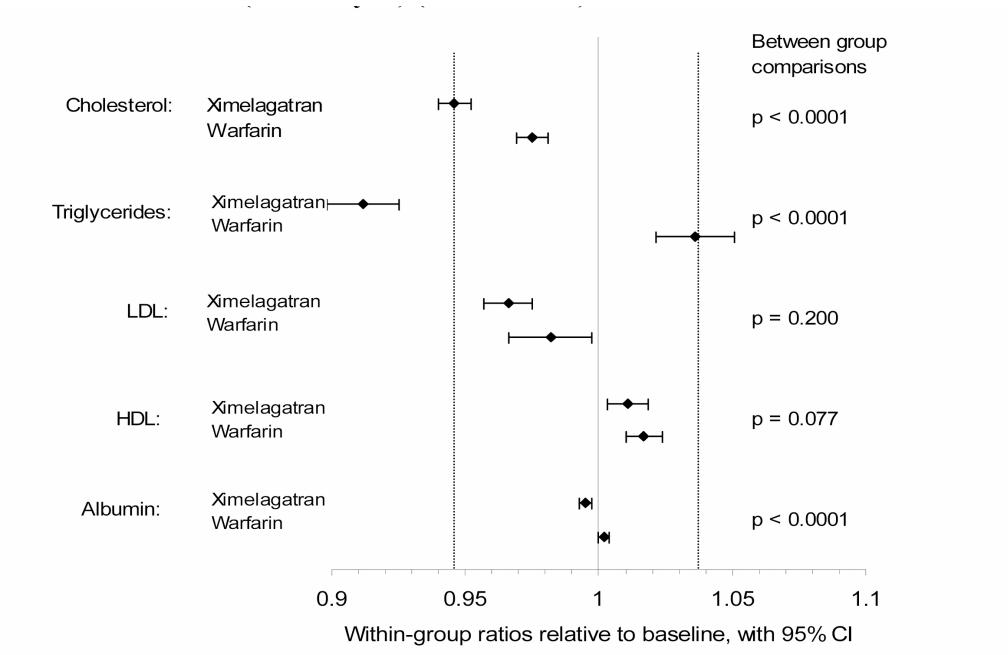
| | Ximelagatran | | | Warfarin | | |
|---|---|---|---|---|---|---|
| | **Screening** | **Month 12/ end of treatment** | **Change** | **Screening** | **Month 12/ end of treatment** | **Change** |
| N | 39 | 34 | 34 | 33 | 28 | 28 |
| Mean | 81.6 | 69.7 | -10.9 | 88.0 | 75.3 | -10.5 |
| SD | 30.8 | 25.3 | 13.6 | 28.1 | 27.9 | 13.9 |
| Minimum | 24.2 | 27.2 | -40.1 | 34.6 | 23.4 | -35.9 |
| Median | 80.9 | 61.0 | -11.3 | 86.1 | 75.2 | -11.5 |
| Maximum | 159.1 | 140.1 | 20.5 | 147.7 | 128 | 21.9 |
| P –value | | | 0.0001 | | | 0.0004 |

[a]Data taken from Table 111 of SPORTIF V clinical study report

9. Other Laboratory Test Adverse events

There was no obvious adverse safety signal with respect to laboratory tests that were noted in either SPORTIF III OR SPORTIF V except for the abnormalities in liver enzymes as discussed above. **Figure 23** below summarizes changes relative to baseline in several chemistry lab parameters that were noted in SPORTIF V. The findings shown in the figure below were consistent with the findings in SPORTIF III (not shown). There was a decrease in serum cholesterol, triglycerides, LDL and albumin in the ximelagatran group relative to baseline. Changes in cholesterol, triglycerides, and albumin in the ximelagatran arm were statistically significant compared to the warfarin arm. The clinical significance of these findings is unclear.

**Figure 23: Estimated within-group ratios relative to baseline (each patient's mean of all measurements post-randomization divided by baseline) with 95% CI. Between-group comparisons for those ratios made with unpaired t-test (OT analysis) (Figure taken from Figure 41 of SPORTIF V CSR).**



10. Adverse events related to vital signs, ECG, physical findings

There was no obvious adverse safety signal with respect to vital signs, ECG analysis, and physical exam findings.

D. Adequacy of Safety Testing

In general the safety testing performed by the sponsor appears to be adequate. The total and long-term exposure to ximelagatran in patients with atrial fibrillation exceeds the guidelines provided in ICH E1 for a drug intended for chronic use.

According to a recent draft ICH guidance on QT, all new drugs that are systemically bioavailable should have a clinical evaluation of their proarrhythmic potential. Such studies assessing QT/QTc interval prolongation should be randomized and double-blinded with concurrent placebo and positive controls. A positive control is necessary to ensure assay sensitivity exists in the trial being conducted. I wasn't able to find evidence that the sponsor conducted a study fitting this description. The sponsor has conducted studies in which they evaluated changes in the RR, QRS, PQ, or QT interval at the time of peak levels of melagatran and/or ximelagatran. The sponsor notes no significant correlation between the QT interval and plasma concentrations of study drug. However, it is unclear if the results from the study were truly negative or that the study lacked assay sensitivity.

Preliminary exposure-response relationships that have been performed based on existing data suggest that there is a relationship between higher exposure to melagatran, the active metabolite of ximelagatran, and risk of major bleeding or hepatotoxicity (ALAT > 3x ULN). It would be useful to know in a randomized control trial whether use of lower doses would reduce the risk of toxicity while still preserving efficacy.

E. Summary of Critical Safety Findings and Limitations of Data

X. Dosing, Regimen, and Administration Issues

Ximelagatran is a pro-drug that gets metabolized to melagatran, the active metabolite. The vast majority of melagatran is excreted unchanged in urine. There is a strong correlation between the oral clearance of melagatran and creatinine clearance as discussed earlier in this review. This relationship will have an impact on dosing and dosing regimen particularly if ximelagatran is a narrow therapeutic index drug. The risk of major bleeding can be significantly higher in patients with relatively high exposures to melagatran relative to patients with relatively low exposures. Similarly, the risk of ALAT > 3x ULN can also be significantly higher. Please refer to Table I and Table II of this review for further details. Knowing that there is a relationship between extent of exposure and the risk of serious adverse events suggests that safe use of ximelagatran could be improved through use of individualized dosing rather than fixed doses for all patients.

## XI. Use in Special Populations

### A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Approximately 31% of the patients randomized in each of the SPORTIF studies were females. The direction and magnitude of the ximelagatran treatment effect with respect to the primary efficacy endpoint was similar in males and females.

### B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Due to the nature of the disease, the population predominantly studied in the SPORTIF studies was an elderly one. The mean ages of patients studied were 70.2 and 71.6 years respectively. Approximately 77% and 80% of patients randomized in SPORTIF III and V respectively were $\geq$ 65 years old. The direction and magnitude of efficacy was similar in patients < 65 years of age, 65 to 74 years of age, and $\geq$ 75 years of age.

The vast majority of patients studied in SPORTIF III and SPORTIF V were Caucasian: 88% in SPORTIF III and 96% in SPORTIF V. 12% of the study population was identified as Oriental in SPORTIF III while 3% of the study population was identified as black in SPORTIF V. It is difficult to reliably make any conclusions regarding the efficacy or safety of ximelagatran in Orientals or Blacks because of the relatively few numbers of events in these patients.

### C. Evaluation of Pediatric Program

The sponsor requests that the requirements to conduct pediatric studies as per PREA (Pediatric Research Equity Act) be waived for the indication of prevention of stroke and SEE in patients with nonvalvular atrial fibrillation. The sponsor states that the estimated number of pediatric patients diagnosed with atrial fibrillation in the U.S. in 2002 is less than 1,500 children.

### D. Comments on Data Available or Needed in Other Populations

The sponsor has done studies in patients with renal and hepatic impairment. In brief, these studies showed that patients with renal impairment have altered significantly altered exposure to ximelagatran while patients with hepatic impairment do not. The results from these studies are summarized in the section on Clinical Pharmacology above.

## XII. Conclusions and Recommendations

### A. Conclusions

Ximelagatran is a reversible thrombin inhibitor that is being developed as an alternative oral anticoagulant to warfarin, the current standard of care. The indication that is the focus of this review is the prevention of stroke and other thromboembolic complications associated with atrial fibrillation. Two pivotal phase 3 studies (SPORTIF III and SPORTIF V) have been submitted in

support of the stated indication. The two studies are active controlled studies designed to show that ximelagatran is non-inferior or "as good as" treatment with warfarin.

The SPORTIF studies compared the effectiveness of a fixed dose of ximelagatran, 36 mg administered twice a day, to warfarin, targeting an INR of 2 – 3 in patients with nonvalvular atrial fibrillation and at least one additional risk factor for stroke. SPORTIF III and SPORTIF V were similar in design except that the former was open-label while the latter was blinded. The primary endpoint was the composite occurrence of all strokes (ischemic and hemorrhagic) and systemic embolic events. The sponsor pre-specified a non-inferiority margin of 2% in the event rate. Ximelagatran would be called non-inferior if an excess of 2% per year in the event rate could be confidently excluded. A margin of this magnitude could leave open the possibility that ximelagatran was only half as effective as warfarin and still be considered non-inferior to warfarin. The magnitude of this non-inferiority margin was not formally agreed upon by the reviewing division within the Agency and marked as a point of future review/discussion. The two SPORTIF studies produced divergent results despite similar designs. In such a setting I would favor the results from a double-blind study.

In terms of safety, liver toxicity as assessed by serum aminotransferase abnormalities occurred approximately 6 times more often on ximelagatran compared to warfarin and was consistent across both trials. There was one well documented case (and most probably a second case) of drug induced liver failure leading to coagulopathy and death among the approximately 3700 patients randomized to the ximelagatran arm of both studies. In terms of major bleeding events, the total number of bleeds was numerically lower in the ximelagatran arm of both studies. In neither of the studies did the difference achieve statistical significance. Bleeding events leading to death were relatively few in both studies and similar in the two treatment arms.

Melagatran, the active metabolite of ximelagatran, primarily excreted unchanged in the urine. There is a strong correlation between the oral clearance of melagatran and creatinine clearance. Exposure differences can be significant in the setting of renal impairment. Renal impairment is expected in the patient population for which this drug is targeted. There appears to be a relationship between higher exposures and increased risk of major bleeds and elevations in aminotransferases. Thus a fixed dosing strategy of ximelagatran could potentially be harmful if implemented.

B. Recommendations

## XIII. Appendix

A. Other Relevant Materials

SPORTIF II/SPORTIF IV STUDY

1. SPORTIF II

"Tolerability and Safety of the Oral Thrombin Inhibitor H376/95, Compared to Warfarin, as Stroke Prophylaxis with Atrial Fibrillation. A Dose-Guiding, Feasibility Multicenter Study"

SPORTIF II was a multi-center, randomized, parallel group, dose ranging, Phase II study that compared the safety and tolerability of ximelagatran (20, 40, or 60 mg bid) with warfarin, aiming for an INR of 2 – 3 in patients with nonvalvular atrial fibrillation. The study was double-blind with respect to ximelagatran dosing but unblinded with respect to warfarin administration. The inclusion/exclusion criteria were generally similar to those in SPORTIF III and V. The duration of treatment in this study was 12 weeks.

257 patients were randomized into the study (N's = 66, 64, 60 in Ximelagatran 20 mg, 40 mg, 60 mg bid respectively; N = 67 in warfarin). 254 actually received treatment. 207 patients completed treatment. The mean age of patients in the study was 69.5 years. The various treatment groups were fairly similar with respect age, gender, ethnicity, risk factors for Afib, use of medications at study entry, weight, and chronicity of Afib.

With regards to efficacy, in the ximelagatran arm, 1 patient (60 mg bid) experienced a TIA and 1 patient (60 mg bid) experienced an ischemic stroke. In the warfarin arm, 2 patients experienced TIA's. There were no reported events in the 2 lower dose groups of ximelagatran. There were no reported SEE's or hemorrhagic strokes during this 12 week study.

The safety in SPORTIF II is summarized in Table LIX below. Recall that 257 patients were randomized into SPORTIF II but 254 actually received treatment.

**Table LIX: Summary of safety findings from SPORTIF II study (shown are the numbers of patients with events)**

| | **Ximelagatran (H376/95) bid** | | | **Warfarin (N = 67)** | **Total** |
|---|---|---|---|---|---|
| | **20 mg (N = 66)** | **40 mg (N = 62)** | **60 mg (N = 59)** | | |
| Death | 1 | 0 | 0 | 0 | 1 |
| Major bleed | 0 | 0 | 0 | 1 | 1 |
| Total bleeds (major + minor) | 4 | 5 | 7 | 7 | 23 |
| Any LFT reported as AE | 3 | 6 | 4 | 1 | 14 |
| Discontinuation due to AE | 7 | 4 | 5 | 6 | 22 |

Data obtained from Tables 12.2:1, 12.2.2:1, 12.3.1.3:1, and 12.3.1.4:3

2. SPORTIF IV

"Long Term Treatment with the Oral Direct Thrombin Inhibitor H376/95, Compared to Warfarin, as Stroke Prophylaxis in Patients with Atrial Fibrillation. An Open 5-Year Follow-up Study"

SPORTIF IV was a follow on study to SPORTIF II. 167 patients from the SPORTIF II study initiated SPORTIF IV. The primary objective of SPORTIF IV was to evaluate the tolerability of long-term treatment with ximelagatran compared to warfarin. It was conducted as an open-label study. The study is still ongoing as of the time of submission of this NDA. The results from interim study reports are summarized below. The dose of ximelagatran given to patients in this

study was 36 mg bid (the proposed commercial formulation). The safety and efficacy findings from SPORTIF IV are summarized in Table LX below.

**Table LX: Summary of findings from the SPORTIF IV study**

| | Ximelagatran | Warfarin |
|---|---|---|
| Summary of results of the first two years of IV (includes endpoints that occurred in SPORTIF II); Results up to 30 June 01; | | |
| # of patients that entered SPORTIF IV | 125 | 42 |
| Deaths | 3 | 2 |
| Strokes | 2 | 2 |
| TIA | 1 | 2 |
| Major bleeds | 2 | 2 |
| Elevated liver enzymes reported as SAE's | 16 | 4 |
| Summary of results from the second two years of SPORTIF IV; ***New*** events occurring between 30 June 01 and 27 June 03; | | |
| # of patients entering this study period | 102 | 33 |
| Death | 9 | 2 |
| Stroke | 2 | 1 |
| TIA | 1 | 0 |
| Major bleeds | 2 | 2 |
| ALT >3x ULN | 1 | 0 |
| Summary of results from 27 June 03 through 27 March 04; ***New*** events occurring during this time period. | | |
| # of patients entering this study period | 85 | 30 |
| Death | 5 | 0 |

Data obtained from the text and various tables from SPORTIF IV Clinical study report dated 31 July 2003, SPORTIF IV Safety Update dated 21 October 03, 4-month safety update report (4-MSU) for EXANTA dated 22 April 2004.

B. Individual More Detailed Study Reviews (if performed)

The Clinical White Paper on Hepatotoxicity published in November 2000 references Dr. Hyman Zimmerman's observation, noting that the combination of a pure hepatocellular injury (transaminase elevation without much alkaline phosphatase elevation) and jaundice is particularly ominous, with about 10-15% of such patients who show such findings as a result of drug-induced injury going on to die. Case narratives of selected patients with markedly elevated aminotransferase levels and temporally related elevation in serum bilirubin levels and/or jaundice are described below.

**Patient 3174 (SPORTIF III)**

An 85 y/o Caucasian male's past medical history included atrial fibrillation, hypertension, diabetes mellitus and coronary heart disease

Medications: furosemide, glycerol trinitrate, human insulin, ramipril, zopiclone

February 27, 2001: Baseline visit

March 5, 2001: Randomized to receive ximelagatran 36 mg bid
April 30, 2001: Aminotransferase level elevation first noted by central lab. Patient was noted to have fatigue, troubling sleeping and nausea 13 days prior to ALT elevation.
May 23, 2001: Patient received last dose of study drug

This patient had an unrevealing work-up for his liver enzyme abnormalities including negative ANA, Smooth muscle antibodies, IgG and IgM CMV antibodies, and viral hepatitis titers. The patient's aminotransferase enzyme levels and bilirubin levels had normalized approximately 2 months post study drug discontinuation.

**Table LXI: Pattern of liver enzyme progression in patient 3174**

| | 3/5/01 | 4/2/01 | 4/17/01 | 4/30/01 | 5/16/01 | 5/28/01 | 6/8/01 | 6/19/01 | 6/26/01 |
|---|---|---|---|---|---|---|---|---|---|
| ALAT (U/L) | 35 | 29 | 39 | 325 | 470 | 599 | 510 | 265 | 147 |
| ASAT (U/L) | 30 | 29 | 50 | 315 | 509 | 680 | 458 | 205 | 123 |
| ALP[a] (U/L) | 196 | 234 | 360 | 708 | 610 | 523 | 502 | 408 | 334 |
| Bili[b] (μmol/L) | 15 | 10 | 14 | 15 | 27 | 28 | **49** | 28 | 18 |

Data taken from Case Report Form and/or Case narrative
[a]Normal alkaline phosphatase range is 20-125 U/L
[b]Normal bilirubin range is 0 to 22 μmol/L

**Patient 1967 (SPORTIF III)**

A 71 y/o Caucasian male's past medical history included atrial fibrillation, stroke, heart failure, and essential hypertension.

Medications: Carvedilol, digoxin, furosemide, potassium, trandolapril

November 22, 2000: Baseline visit in which baseline lab tests were done.
December 6, 2000: Patient was randomized to receive ximelagatran.
December 8, 2000: Two days after initiating study medication, the patient was noted problems of tiredness and problems with balance.
December 11, 2000: Patient had sudden onset of double-vision and dizziness and was admitted to the hospital. He was diagnosed as having a brain stem stroke by a neurologist. Study drug was stopped. During the course of hospitalization, the patient had several episodes of syncope causing his hospital stay to be prolonged. Also during the course of hospitalization, it was noted that the patient's liver enzymes were elevated. The patient was also noted to be jaundiced. An abdominal ultrasound was done revealing a few gallstones but no reports of obstruction in the case narrative.
December 18, 2000: The patient's condition improved, his liver enzymes were noted to be improving and he was discharged from the hospital.

An extended liver laboratory panel was remarkable for an elevated CMV antibody IgM, EIA. In the case narrative there was no description of this patient having fever, abdominal pain, nausea, vomiting, loss of appetite, etc. Blood work at baseline revealed no evidence of lymphocytosis.

**Table LXII: Pattern of liver enzyme progression for patient 1967**

| | Baseline (11/22/2000) | Early DC visit (12/14/2000) |
|---|---|---|
| WBC | 7.9 | 7.1 |
| Lymphocytes (%) | 24 | 21 |
| ALAT | 30 | 414 |
| ASAT | 26 | 195 |
| ALP[a] | 77 | 215 |
| Bili[b] (µmol/L) | 13 | 127 |

Data taken from Case Report Form and/or Case narrative
[a]Normal alkaline phosphatase range is 20-125 U/L
[b]Normal bilirubin range is 0 to 22 µmol/L

**Patient 7986 (SPORTIF V)**
An 81 y/o Caucasian female's past medical history included atrial fibrillation, hypertension, pericarditis, coronary artery disease, hyperlipidemia, mitral valve prolapse, and eye hemorrhages.

Medications: acetylsalicylic acid, ascorbic acid, tocopheryl acetate, retinol, zinc, calcium, vitamins, minerals, atenolol, atorvastatin, doxazosin, conjugated estrogens, furosemide, potassium chloride.

| | |
|---|---|
| August 23, 2001: | Patient was randomized to ximelagatran |
| October 04, 2001: | Patient was first noted to have elevated liver enzymes (see table below). Patient was asymptomatic despite liver enzyme abnormalities throughout the time the enzymes were elevated. |
| November 8, 2001: | Study medication discontinued |

A little more than one month after study drug discontinuation, the patient had an abdominal ultrasound that revealed cholelithiasis that was not considered clinically relevant. There was no evidence of biliary duct dilatation. The patient also had an extensive work-up ANA Antibody titer, Smooth Muscle antibody titer, CMV IgG and IgM, EBV IgG and IgM, Hep A, B, C that were not considered clinically significant.

**Table LXIII: Pattern of liver enzyme progression for patient 7986**

| | 8/16/01 | 9/20/01 | 10/4/01 | 10/17/01 | 10/25/01 | 11/8/01 | 11/21/01 | 11/29/01 | 12/7/01 | 1/10/02 |
|---|---|---|---|---|---|---|---|---|---|---|
| ALAT (U/L) | 24 | 20 | 60 | 120 | 220 | 689 | 673 | 548 | 329 | 46 |
| ASAT (U/L) | 16 | 16 | 37 | 120 | 182 | 670 | 648 | 529 | 307 | 55 |
| ALP (U/L) | 93 | 95 | 184 | 122 | 132 | 162 | 162 | 132 | 118 | 64 |
| Bili (mg/dL) | 0.7 | 0.8 | 1.0 | 0.7 | 1.4 | 1.4 | 2.3 | 2.7 | 2.2 | 1.2 |

Data taken from Case Report Form and/or Case narrative

**Patient 5402 (SPORTIF V):**

A 73 y/o Caucasian female's medical history included atrial fibrillation, coronary artery disease, carotid disease, pulmonary hypertension, mild chronic anemia, and chronic nocturia with a rectocystocele.

Medications: enalapril, conjugated estrogens, fexofenadine, iron, metoprolol

| | |
|---|---|
| December 12, 2000: | Patient was randomized to ximelagatran |
| January 23, 2001: | Elevated liver enzymes were noted (see Table below). Patient was asymptomatic despite liver enzyme elevations. |
| February 9, 2001: | Study drug was discontinued. An abdominal ultrasound revealed a normal liver, bile ducts, and pancreas. Extended liver laboratory investigations were unrevealing including ANA antibody, Smooth muscle antibody, CMV IgG and IgM, EBV IgG and IgM, Hepatitis A,B, C. |
| March 5, 2001: | Patient was seen in the Emergency department of a hospital for chest pain, epigastric discomfort, hematuria, and to rule out an MI. |
| March 8, 2001: | Patient was admitted to the hospital for weakness and lethargy. On physical exam, the patient had a blood pressure of 80-90/50 mm Hg. She was also noted to be jaundiced. Laboratory work-up revealed the patient to be anemic (hematocrit = 23). Patient also had guiaic positive stools. The patient was treated with vitamin K and 2 units of packed red blood cells. Further work-up during the hospitalization included an upper and lower GI endoscopy both of which were unrevealing in terms of an identifiable source of bleed. |
| March 15, 2001: | Patient was discharged in stable condition. |

**Table LXIV: Pattern of liver enzyme progression for patient 5402**

| | 12/5/00 | 1/9/01 | 1/23/01 | 1/30/01 | 2/6/01 | 2/20/01 | 3/5/01[a] | 3/8/01[a] | 4/12/01 |
|---|---|---|---|---|---|---|---|---|---|
| ALAT (U/L) | 36 | 30 | 196 | 282 | 448 | 492 | 1483 | 707 | 78 |
| ASAT (U/L) | 34 | 29 | 145 | 270 | 446 | 556 | 1586 | 528 | 90 |
| ALP (U/L) | 82 | 120 | 199 | 195 | 178 | 140 | 230 | 145 | 110 |
| Bili (mg/dL) | 0.4 | 0.4 | 0.6 | 0.5 | 0.7 | 0.9 | 2.9 | 5.6 | 1.8 |

Data taken from Case Report Form and/or Case narrative

[a]Labs on 3/5/01 and 3/8/01 were obtained from narrative in sponsors clinical study report for SPORTIF V. These lab values were not available in the Case Report Form of this patient.

**Patient 8387(SPORTIF V):**

An 80 y/o Caucasian females past medical history included atrial fibrillation, permanent pacemaker insertion, angina, coronary heart disease, bradycardia, torsades de pointes, hypertension, hyperlipidemia, osteoporosis, and hypothyroidism.

Medications: atenolol, calcium, digoxin, ergocalciferol, retinol, calcium carbonate, estrogen, furosemide, levothyroxine, sodium Phenobarbital, atropine methonitrate, glyceryl trinitrate, theophylline, papaverine, potassium chloride, ramipril

| | |
|---|---|
| October 10, 2001: | Patient was randomized to ximelagatran |
| December 10, 2001: | Elevated liver enzymes were noted. There were no reports that the patient was symptomatic in association with enzyme elevations. |
| December 14, 2001: | Study drug permanently discontinued and patient was started on open-label warfarin for stroke prophylaxis. Patient had an extensive liver work-up that was negative (including ANA antibody; Smooth muscle antibody; CMV; EBV; Hepatitis A,B, and C). |
| January 3, 2002: | Liver enzyme elevations peaked. The patient remained asymptomatic. |
| January 14, 2002: | After this date, there is evidence of improvement in bilirubin levels. Liver tests eventually returned to normal in this patient. |

**Table LXV: Pattern of liver enzyme progression for patient 8387**

| | Baseline | 7Nov01 | 10Dec01 | 17Dec01 | 27Dec01 | 3Jan02 | 10Jan02 | 14Jan02 | 22Jan02 | 11Feb02 |
|---|---|---|---|---|---|---|---|---|---|---|
| ALAT (U/L) | 8 | 8 | 128 | 270 | 590 | 729 | 527 | 410 | 245 | 53 |
| ASAT (U/L) | 15 | 17 | 180 | 447 | 1240 | 1419 | 1158 | 903 | 544 | 76 |
| ALP (U/L) | 74 | 72 | 77 | 82 | 131 | 141 | 155 | 170 | 199 | 137 |
| Bili (µmol/L) | 8 | 6 | 8 | 6 | 14 | **48** | **158** | **238** | 202 | 54 |

Data taken from Case Report Form and/or Case narrative

# Abbreviations:

aPTT = activated partial thromboplastin time
AE's = Adverse events
AF = Atrial Fibrillation
ALAT = Alanine Aminotransferase (also referred to as SGPT)
ANA = Antinuclear Antibody
AMI = Acute Myocardial infarction
ASAT = Aspartate aminotransferase (also referred to as SGOT)
ALP = Alkaline phosphatase
AUC = Area under the plasma concentration time curve
Bid = twice a day
Bili = Total bilirubin
CEAC = Clinical Events Adjudication Committee
CCK = cholecystekinin
CRF = case report form
CSR = clinical study report
CrCL = creatinine clearance
CV = Coefficient of variation
DSMB = Data Safety Monitoring Board
ECG = Electrocardiogram
ESC = Executive Steering Committee
H376/95 = ximelagatran
INR = International Normalized Ratio
ITT = Intention to Treat
IVRS = Interactive Voice response system
LFT's = liver function tests (this includes ALAT, ASAT, ALP, and Bilirubin)
MI = Myocardial infarction
PT = Prothrombin time
SAE = Serious Adverse Event
SAP = Statistical Analysis Plan
SEE = systemic embolic event
ULN = Upper limit of normal
WBC = white blood count
95% CI = 95% confidence interval