INTRODUCTION

Thromboembolic events are significant sources of morbidity and mortality that often necessitate long-term anticoagulation therapy. Although a variety of effective anticoagulants exist, heparins, heparinoids, and most direct thrombin inhibitors are available as injectable formulations and are typically unsuitable for long-term use.

Warfarin (Coumadin, Bristol-Myers Squibb), an oral vitamin K antagonist, has been the primary agent utilized in long-term anticoagulation therapy. Despite its ability to reduce and treat thromboembolic events, warfarin therapy has several limitations, including a slow onset of action; a narrow therapeutic range; variable patient responses; and numerous interactions with drugs, herbal medications, and foods containing vitamin K.1 As a result of this agent’s pharmacokinetic (PK) and pharmacodynamic (PD) limitations, patients receiving warfarin often require frequent monitoring to ensure optimal efficacy and safety. In recent years, efforts have been focused on the development of new oral anticoagulants with further predictable PK and PD profiles, which may reduce the need for vigilant monitoring.1

Thrombin has been identified as an essential target of therapy because of its pivotal role in the coagulation process. Thrombin is responsible for the conversion of soluble fibrinogen to fibrin; clot stabilization through activation of factor XIII and the formation of cross-linkage among fibrin molecules; and the generation of additional thrombin through activation of factors V, VIII, and XI.2 Direct thrombin inhibitors (DTIs) are an innovative class of anticoagulants that bind directly to thrombin to inhibit its actions and impede the clotting process.2 Although clinically available DTIs are parenteral agents, efforts are being concentrated in the development of an oral DTI.

Ximelagatran (Exanta, AstraZeneca) was a promising oral DTI that had been studied in numerous clinical trials and received approval for venous thromboembolism prophylaxis in Europe.3 However, in data submitted to the U.S. Food and Drug Administration (FDA), liver enzyme elevations were observed in patients receiving prolonged therapy for more than 35 days.3,4 Based on central and local laboratory data, the incidence of alanine aminotransferase (ALT) levels greater than three times the upper limit of normal (ULN) was 7.9% for the ximelagatran group and 1.2% for the comparators. The incidence of ALT levels greater than five times the ULN was 4.7% and 0.5% in the ximelagatran and comparator groups, respectively, and the incidence of ALT levels greater than 10 times the ULN was 1.9% and less than 0.1%, respectively.

Aspartate aminotransferase (AST) levels also increased in conjunction with ALT levels.4 As a result of these safety concerns, an FDA advisory committee recommended against the approval of ximelagatran in the U.S.2 In 2006, AstraZeneca announced its decision to withdraw ximelagatran from the market and to terminate its development.2

Dabigatran etexilate (Rendix, Boehringer Ingelheim) is a new oral DTI that is currently being studied in clinical trials. Several phase 2 studies have been completed with encouraging results, and recruitment is being conducted for several phase 3 studies. This article presents a review of the currently available information on this investigational product.

CHEMICAL STRUCTURE

Figure 1A,B illustrates the chemical structures of ximelagatran and dabigatran.

Disclosure: Dr. Abrams and Dr. Marzella have no commercial or industrial relationships to disclose in regard to this article.
Dabigatran etexilate (BIBR 1048) is an oral pro-drug of dabigatran (BIBR 953 ZW), a low-molecular-weight (LMW) DTI. Dabigatran is a specific, competitive, reversible univalent inhibitor of fibrin-bound and free-thrombin that binds to the active site of thrombin to inhibit its actions and to interrupt the coagulation process.

**PHARMACOKINETICS**

Dabigatran etexilate is rapidly converted to its active form, dabigatran, after oral administration. In healthy volunteers, the PK profile is characterized by a time to peak plasma (T_{max}) concentration within two hours, an absolute bioavailability of 3.5% to 5%, a bi-exponential distribution phase, and a terminal half-life of 14 to 17 hours after multiple-dose administration (Table 1).

Cytochrome P450 (CYP 450) isoenzymes are not involved with the metabolism of dabigatran, and dabigatran does not appear to inhibit or induce the activity of these isoenzymes. Dabigatran is excreted primarily via the renal system and is conjugated to activated glucuronic acid to form an acylglucuronide conjugate.

With phase 2 and 3 clinical studies currently ongoing, the PK profile of dabigatran in specific patient populations has not yet been completely elucidated.

**CLINICAL TRIALS**

**BISTRO I**

Boehringer Ingelheim Study in Thrombosis I (BISTRO I), an open-label, multicenter, sequential, dose-escalating trial, was conducted in 314 patients undergoing total hip replacement in Sweden and Norway. The primary objective of this study was to investigate the therapeutic range of dabigatran etexilate to determine optimal dosing for future studies.

The primary safety outcome was the rate of major bleeding events during the treatment phase. Major bleeding was defined as clinically overt bleeding, associated with a decline of greater than 20 g/L in hemoglobin, and leading to the need for blood transfusions of 2 units or more of packed red blood cells. The criteria also included retroperitoneal, intracranial, intraocular, or intraspinal bleeding.

Minor bleeding events were also evaluated; these included all events that were not covered in the definition of major bleeding.

The primary efficacy outcome was the rate of venous thromboembolic (VTE) events in each group. VTE included deep vein thrombosis (DVT) detected by venography, symptomatic and objectively confirmed VTE, and pulmonary embolism (PE). Monitoring of drug plasma concentrations was performed in all patients to assess drug exposure and determine the PK profile of dabigatran in patients receiving dabigatran etexilate. The investigators used the correlation between the blood coagulation parameters, activated partial thromboplastin time (aPTT) and Ecarin clotting time (ECT), and the plasma concentration of dabigatran to determine the PD profile for dabigatran etexilate. (Ecarin clotting time is an assay for hirudin, an anticoagulant.)

Table 1 Pharmacokinetic Properties of Dabigatran

<table>
<thead>
<tr>
<th>Administration</th>
<th>Orally</th>
<th>Within 2 hours</th>
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<tbody>
<tr>
<td>Peak plasma concentration</td>
<td>12 hours</td>
<td></td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>14–17 hours</td>
<td></td>
</tr>
<tr>
<td>Terminal half-life</td>
<td>No apparent CYP 450 isoenzyme induction or inhibition</td>
<td></td>
</tr>
<tr>
<td>Metabolism</td>
<td>Kidney</td>
<td></td>
</tr>
<tr>
<td>Clearance</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Reversal antidote</td>
<td>• Signs and symptoms of bleeding</td>
<td></td>
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<tr>
<td>Monitoring</td>
<td>• Liver enzyme monitoring</td>
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</table>
| Data for the 289 patients who received at least one dose of the study drug. In terms of safety, no major bleeding events were observed according the predefined criteria. However, the study was discontinued at the 300-mg twice daily dose level because two patients experienced bleeding episodes from multiple sites within a few days of receiving treatment. Both of these patients had approximate creatinine clearance (CrCl) levels of less than 50 mL/minute.

Although no major bleeding events occurred, a dose–response relationship was noted for the incidence of bleeding events that necessitated transfusions. Approximately 7% of patients had a bleeding event requiring a blood transfusion, and all bleeding events occurred in the six groups receiving the highest doses (100–300 mg twice daily, 150 mg daily, and 300 mg daily).

On average, 71% of patients experienced a minor bleeding event. No dose-dependent relationship was noted for non-bleeding adverse drug events (ADEs). AST and ALT levels were elevated for all doses, with large and small increases occurring randomly across the various dosing levels. No deaths were reported during the study.

In terms of efficacy, the overall rate of DVT was 12.4%. The patients receiving dabigatran 12.5 mg twice daily had the highest percentage of total and proximal DVT rates (20.8% and 12.5%, respectively). Although PE and symptomatic DVT did not occur in any of the patients during the treatment phase, two patients

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*Not routinely performed.

CYP = cytochrome.

developed a symptomatic DVT in the follow-up period.

Plasma concentrations of dabigatran generally peaked after two hours. However, absorption of the first dose was delayed in approximately 53% of patients, and peak concentrations were not reached until four to six hours after administration. Upon further analysis, the investigators observed no relationship between low dabigatran concentrations on the day of surgery, the dose received, and the development of DVT.

The data analysis also demonstrated a direct relationship between low CrCl levels and increased plasma concentrations. This relationship was especially pronounced when CrCl levels were below 50 mL/minute. High variability of plasma levels and area-under-the-curve (AUC) concentrations were noted among patients.

In terms of the PD profile, a close correlation was observed between the prolongation of aPTT and Ecarin clotting time and plasma concentrations of dabigatran. The correlation between Ecarin clotting time and plasma concentrations was linear, whereas the prolonged aPTT increased in a nonlinear fashion as dabigatran levels increased.

In conclusion, dabigatran etexilate demonstrated overall safety over a broad range of doses, with the therapeutic window falling above 12.5 mg twice daily and below 300 mg twice daily. The study authors indicated that future developments would need to focus on optimizing oral absorption and determining the timing of the first dose.

Pharmaceutical Profile of the Oral Capsule in Total Hip Replacement

Because of the unfavorable PK profile of the tablet formulation of dabigatran etexilate, a multi-particulate pellet formulation was developed and studied in healthy volunteers and in patients undergoing total hip replacement. The goal of these phase 1 and phase 2 studies was to determine the PK profile of the new formulation.

The primary endpoints were the rate and extent of absorption, as defined by the AUC versus time curve, the maximum peak plasma concentrations (Cmax), and the Tmax. Patient safety monitoring was performed throughout both studies.

**Phase 1**

The phase 1 PK study was performed in 18 healthy volunteers in a three-way crossover study design that included males between 18 and 55 years of age with a body mass index (BMI) between 18.5 and 30 kg/m². Treatment sequences consisted of a dabigatran 150-mg capsule, administered after an overnight fasting period, in conjunction with pantoprazole (Protonix, Wyeth) 40 mg twice daily, started two days before administration of the study drug and following a high-fat, high-calorie breakfast.

PK parameters were determined via plasma concentration versus time curves obtained from serial blood sampling over a 72-hour period after administration of the study drug.

Results were analyzed for all 18 subjects who had been randomly assigned to treatment and who had completed the trial. Co-administration with food demonstrated a delayed absorption of dabigatran etexilate, with the median Tmax increasing from two to four hours. This delay did not result in decreased drug exposure, as expressed by a relatively unchanged AUC (904 ng • hours/mL, fasted; 895 ng • hours/mL, fed) and Cmax (111 mg/mL, fasted; 106 mg/mL, fed).

In contrast to these findings, co-administration with pantoprazole resulted in both a lower AUC (904 ng • hours/mL, fasted; 705 ng • hours/mL, fed) and Cmax (111 mg/mL, fasted; 74.5 mg/mL, fed). The Tmax remained unchanged.

The mean terminal half-life was decreased in both the pantoprazole and the fed patients, compared with the fasted patients: 7.8 hours (pantoprazole), 7.7 hours (fed), and 8.7 hours (fasted).

**Phase 2**

Phase 2 was an uncontrolled, open-label, multicenter PK study (BISTRO Ib) that was conducted in 62 consecutive patients scheduled for total hip replacement surgery in 11 sites in Sweden and Norway. Patients received a single oral dose of 150 mg of dabigatran etexilate one to three hours after surgery. All concomitant medications prescribed and given at the investigator’s discretion were considered acceptable.

All patients received a dose of enoxaparin (Lovenox, Sanofi-Aventis) 40 mg subcutaneously in the evening or early morning prior to surgery. Continued VTE prophylaxis was given at the discretion of the investigator, and subsequent doses were given for a minimum of 10 hours after administration of the study drug.

The investigators determined PK parameters by using plasma concentration versus time curves obtained from serial blood sampling over a 24-hour period after the study drug was administered. There were four pre-determined PK acceptance criteria for future use of the capsule formulation in the postoperative period (Table 2).

The results of 39 patients were analyzed and reported. In the majority of enrolled patients, the onset was immediate, with plasma levels of dabigatran measurable within one hour of administration. However, absorption was delayed by four to six hours following administration.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Pharmacokinetic Criteria for Patients Taking the Oral Capsule Formulation of Dabigatran</th>
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<tr>
<td>1.</td>
<td>The time to onset of absorption had to be less than 6 hours.</td>
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<tr>
<td>2.</td>
<td>A median Tmax had to be achieved within 10 hours after drug administration.</td>
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<tr>
<td>3.</td>
<td>The average AUC had to be greater than 50% of the mean observed steady-state AUC in BISTRO I for the 150-mg/day dose (AUCss 1,022 ng • hours/mL).</td>
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<tr>
<td>4.</td>
<td>Fewer than 30% of the patients had to have an AUCss of less than 50% of the AUCss in BISTRO I.</td>
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AUCss = area-under-the-curve concentration at steady state; AUC0–24 = AUC concentration from time zero to 24 hours; BISTRO = Boehringer Ingelheim Study in Thrombosis; Tmax = time to maximum concentration.

tion in two patients.

The C\text{max} (mean, 75.8 ng/mL) occurred at a median T\text{max} of six hours, although the investigators noted that the T\text{max} in 13 patients exceeded 10 hours.

The mean AUC was comparable to that of healthy volunteers (962 ng \cdot hours/mL and 904 ng \cdot hours/mL, respectively). Inter-individual variability was also high in this study, with coefficients of variation greater than 65% for both the C\text{max} and AUC\text{0-24}.

The most common ADEs were nausea and vomiting, although the investigators considered these ADEs to be related to the surgical procedure. One patient experienced moderate hypotension and a severe drop in hemoglobin, necessitating a blood transfusion, but these events were not considered to be related to the study drug. No patients died during the study.

As a result of both phase 1 and phase 2 studies, the investigators concluded that oral administration of a capsule formulation of dabigatran etexilate resulted in an acceptable PK profile in healthy volunteers and in patients undergoing total hip replacement.

**BISTRO II**

Boehringer Ingelheim Study in ThROMbosis II (BISTRO II) was a randomized, multicenter, parallel-group, double-blind, active-control trial.

The primary objective was to further investigate the dose–response relationship and the safety and efficacy of dabigatran etexilate for preventing VTE in patients undergoing total hip or total knee replacement. A secondary objective was to compare the safety and efficacy of various dosages of dabigatran etexilate with that of the LMW heparin, enoxaparin (Lovenox). Serial sampling of dabigatran concentrations was used to determine its PK parameters postoperatively.

The investigators determined efficacy by assessing the incidence of VTE, defined as symptomatic DVT, DVT detected by venography, or PE detected during the treatment period.

The primary safety outcome was major bleeding during the treatment period, defined as clinically overt bleeding associated with a hemoglobin decrease of greater than 20 g/L and leading to a blood transfusion of 2 or more units of packed red blood cells or whole blood; fatal retroperitoneal, intracranial, intracocular, or intraspinal bleeding; or bleeding warranting treatment cessation or leading to reoperation.

Clinically significant bleeding events were defined as spontaneous skin hematomata of 25 cm\(^2\) or more, wound hematomata of 100 cm\(^2\) or greater, epistaxis lasting longer than five minutes, spontaneous macroscopic hematuria or hematuria lasting more than 24 hours if associated with an intervention, spontaneous rectal bleeding, gingival bleeding for more than five minutes, and any other bleeding event judged to be significant.

Minor bleeding events were defined as those not meeting the definition or clinically relevant criteria of a major bleeding event.

Patients were randomly assigned to receive either oral dabigatran etexilate (n = 1,576) 50 and 150 mg twice daily, 300 mg once daily, or 225 mg twice daily or 40 mg of enoxaparin subcutaneously once daily (n = 397). Dabigatran etexilate was administered one to four hours after the completion of surgery or as soon as possible. The second dose was given after an interval of at least eight hours.

Enoxaparin was administered on the evening before surgery and was continued daily until the end of the treatment period. However, the first dose of enoxaparin might have been administered postoperatively, depending on regional guidelines. The treatment period was to last between six and 10 days until mandatory bilateral venography was performed.

An analysis of serial plasma concentrations after an initial oral dose given one to four hours after surgery (mean = 2.6 hours) demonstrated a slow dose-proportional rise to a mean C\text{max} of 24.5 to 132 ng/mL in an average of 3.7 to 4.5 hours. Steady-state conditions yielded a mean C\text{max} of 48 to 271 ng/mL in 2.3 to 2.9 hours.

A regression analysis revealed that a 5% rate of clinically relevant bleeding, a composite of major and clinically significant bleeding, corresponded to a C\text{max} of dabigatran of 40 ng/mL. On the basis of this finding, the first dose of dabigatran etexilate was predicted to be 75 mg, with a DVT rate of 13%.

Of the 1,973 randomized patients, 1,464 patients were included in the efficacy analysis. The population decreased, because 24 patients had never received treatment and 215 patients discontinued treatment prematurely.

In terms of efficacy, increasing doses of dabigatran etexilate were correlated with a significant dose-dependent decrease in the frequency of VTE (P < 0.001). The lowest rate of VTE occurred in patients receiving dabigatran 225 mg twice daily (13.1%); the highest rate of VTE occurred in the 50 mg twice-daily group (28.5%). No significant difference was observed with 300 mg once daily and 150 mg twice daily.

A post hoc analysis found that the incidence of VTE was significantly lower in patients who received their first dose of dabigatran etexilate within two hours (14.1%), in contrast to those receiving their initial dose beyond this period (22.4%) (P = 0.0005). The incidence of VTE was significantly reduced as follows:

- dabigatran 150 mg twice daily, 17.4%; enoxaparin, 24% (P = 0.04)
- dabigatran 300 mg once daily, 16.6%; enoxaparin 24% (P = 0.02)
- dabigatran 225 mg twice daily, 13.1%; enoxaparin, 24% (P = 0.0007)

Results were similar in both total knee and total hip surgery study arms.

The safety population included all patients who received at least one dose of the study drug (n = 1,949). Within the dabigatran groups, major bleeding episodes were significantly higher with 225 mg twice daily and 300 mg once daily than with 50 mg twice daily (P value not shown).

Four patients in the three highest-dose dabigatran etexilate groups required reoperation as a result of bleeding.

The rate of major bleeding was significantly lower in patients receiving dabigatran 50 mg twice daily (0.3%) than in those receiving enoxaparin (2%) (P = 0.047). However, there was a nonsignificant trend toward increased bleeding with dabigatran 150 mg twice daily, 225 mg twice daily, and 300 mg daily.

A total of 160 serious ADEs were reported during the treatment period. Ninety-nine patients discontinued treatment as a result of an ADE. Liver enzyme levels (AST and ALT) increased during treatment in all groups, but these
elevations were judged to be mild. No clinically relevant cases of thrombocytopenia were observed during the study.

Based on the results observed in this trial, the study authors concluded that dabigatran etexilate exhibited a post-operative dose–response relationship for efficacy and safety.

**ADVERSE DRUG REACTIONS**

Although the ADE profile of dabigatran etexilate has not been fully elucidated, according to the results of these studies, bleeding would be the most commonly anticipated ADE. It is unknown how dabigatran etexilate will compare with that of traditional anticoagulants in terms of the severity and risk of bleeding in patients.

As shown from previous clinical experience with ximelagatran, another safety concern with dabigatran etexilate is hepatoxicity. Elevations in liver enzymes have been observed in patients during clinical trials. Although these elevations have been considered mild, further studies are required to determine the clinical significance of these events.

**DRUG INTERACTIONS**

The potential for drug interactions in conjunction with dabigatran etexilate has not been extensively studied in clinical trials. However, interactions similar to that of warfarin seem unlikely, because the thrombin-specific mechanism of action reduces the likelihood of an effect on other vitamin K–specific clotting factors. In addition, CYP 450 isoenzymes are not involved in the metabolism of dabigatran, and dabigatran does not appear to inhibit or induce the activity of these isoenzymes. Thus, interaction with other CYP 450 substrates would not be expected.

On the basis of the results of the PK study evaluating the effect of coadministration of pantoprazole on the plasma concentrations and the AUC concentration of dabigatran, it appears that a high gastric pH decreases dabigatran exposure. Thus, it might be expected that proton pump inhibitors, histamine blockers, and other agents that increase gastric pH would interact with dabigatran etexilate.

Because dabigatran etexilate undergoes renal excretion primarily, drugs frequently associated with nephrotoxicity may result in elevated concentrations of dabigatran and an increased risk of bleeding in patients.

**PRECAUTIONS AND WARNINGS**

Appropriate precautions and increased monitoring will probably be required if dabigatran is administered under conditions associated with increased risks of bleeding, such as its use in patients with bleeding diathesis or other coagulation disorders; trauma; thrombocytopenia; a history of gastric or duodenal ulcers; and the concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDS), thrombolytic agents, and antiplatelet agents.

Patients with renal insufficiency may require dosage adjustments to decrease the risk of bleeding.

**DOSAGE AND ADMINISTRATION**

Although optimal dosing and administration schedules for dabigatran etexilate have not yet been determined, it appears that the dose will be between 100 and 225 mg daily. Additional studies are required to determine the specific dose that will provide the greatest reduction in thromboembolic events along with a minimal risk for bleeding.

**FUTURE TRIALS**

Boehringer Ingelheim, the developer of dabigatran etexilate, has launched a large clinical trial program under the name RE-VOLUTION. It is expected that this trial will involve more than 27,000 patients. The phase 3 trials covered under this umbrella will investigate the use of dabigatran etexilate in preventing primary and secondary VTE, treating acute DVT, and preventing stroke in atrial fibrillation, in comparison with warfarin or enoxaparin. Recruitment for many of these trials is under way.

**CONCLUSION**

In its current stage of clinical development, dabigatran etexilate shows promise in becoming the next orally available anticoagulant. Clinical trials have demonstrated timely efficacy without the safety concerns that have been associated with ximelagatran administration. Ongoing research will eventually confirm or refute these early findings and determine whether dabigatran etexilate has a role in the management of patients who require anticoagulation therapy and whether it might replace warfarin as the mainstay of therapy.

**REFERENCES**