Drugs of the Future 2005, 30(9): 877-885

CCC: 0377-8282/2005
DOI: 10.1358/dof.2005.030.09.938760

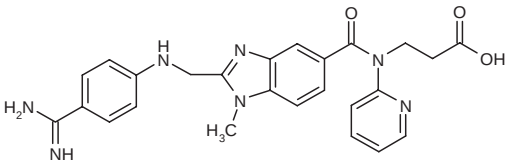
Dabigatran/Dabigatran Etexilate

Prevention of DVT
Prevention of Ischemic Stroke
Thrombin Inhibitor

Dabigatran
Prop INN

BIBR-953

N-[2-(4-Amidinophenylaminomethyl)-1-methyl-1*H*-benzimidazol-5-ylcarbonyl]-*N*-(2-pyridinyl)-β-alanine



$C_{25}H_{25}N_7O_3$
Mol wt: 471.5114

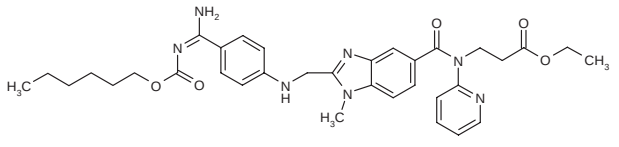
CAS: 211914-51-1

EN: 300695

Dabigatran Etexilate
Prop INNM

BIBR-1048

N-[2-[4-[*N*-(Hexyloxycarbonyl)amidino]phenylaminomethyl]-1-methyl-1*H*-benzimidazol-5-ylcarbonyl]-*N*-(2-pyridyl)-β-alanine ethyl ester



$C_{34}H_{41}N_7O_5$
Mol wt: 627.7335

CAS: 211915-06-9

EN: 305702

Abstract

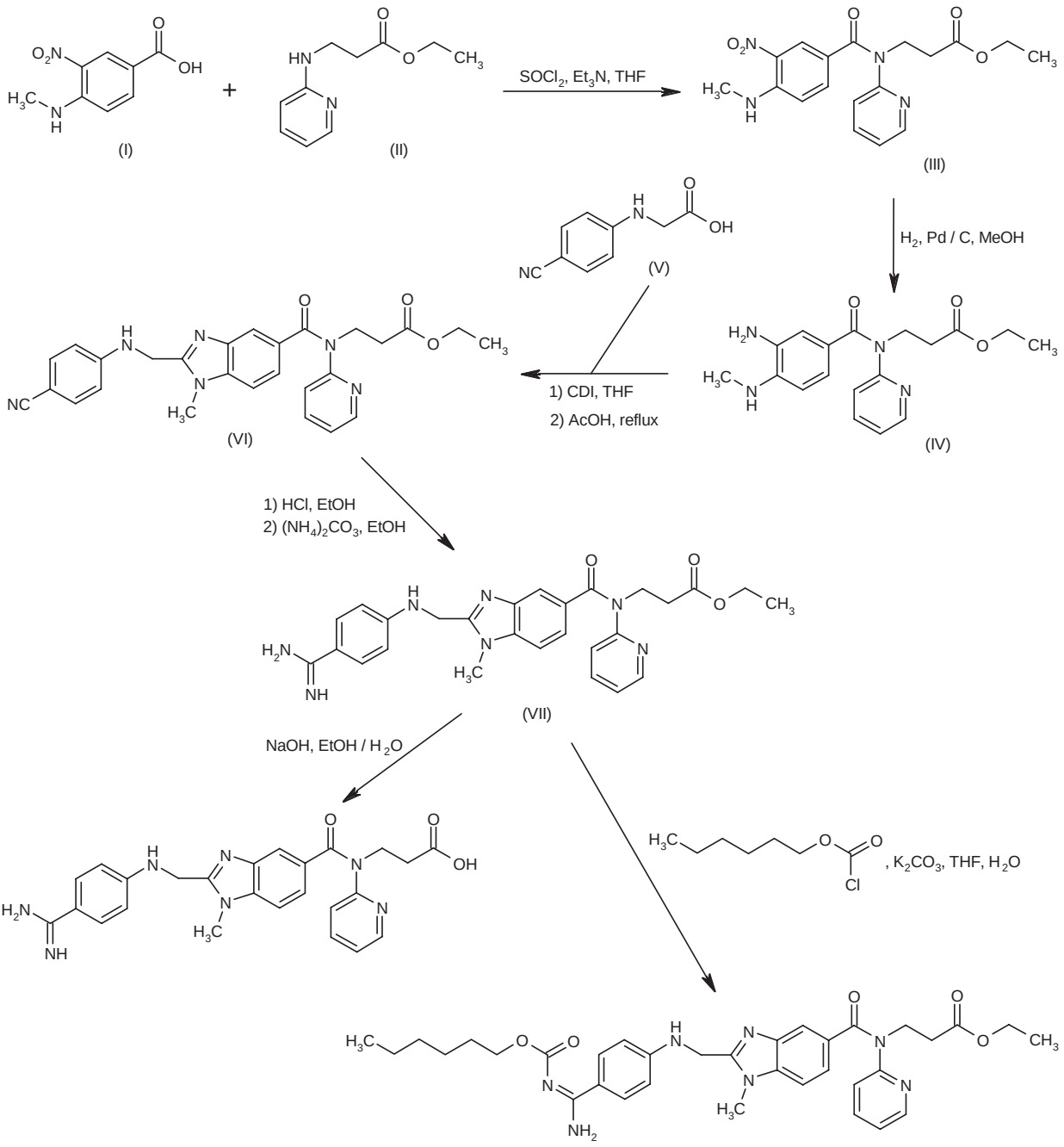
Because of the crucial role of thrombin in the coagulation cascade and platelet activation, the enzyme is a primary target for the development of anticoagulant and antithrombotic drugs. The peptidomimetic dabigatran and its oral double prodrug dabigatran etexilate are univalent direct thrombin inhibitors. Pharmacological studies indicate that dabigatran potently interferes with the coagulation cascade, being highly selective for thrombin over most other serine proteases. Dabigatran and dabigatran etexilate have proven to be well tolerated *in vivo* in animal models. Pharmacokinetic studies indicate that thrombin activity is dose-dependently inhibited following administration of the prodrug. Pharmacokinetic and pharmacodynamic parameters increase proportionally with dose. Food delays but does not affect the extent of absorption of the agent. Clinical studies indicated good safety. Higher plasma levels of dabigatran were associated with a lower incidence of deep venous thrombosis (DVT). Moreover, dabigatran etexilate at the doses examined has proven to be safe and effective in the treatment of venous thromboembolism (VTE) compared with other anticoagulants such as warfarin.

Synthesis

Condensation of 4-(methylamino)-3-nitrobenzoic acid (I) with 3-(2-pyridylamino)propionic acid ethyl ester (II) by means of $SOCl_2$ and TEA in THF gives the corresponding carboxamide (III), which is reduced at the nitro group with H_2 over Pd/C in methanol to yield the 3-amino-4-(methylamino)phenyl derivative (IV). Acylation of compound (IV) with 2-(4-cyanophenylamino)acetic acid and CDI in THF and subsequent cyclization in refluxing acetic acid affords the benzimidazole derivative (VI), which is submitted to a Pinner reaction with HCl gas/EtOH and ammonium carbonate in EtOH to provide the amidino derivative (VII). Finally, dabigatran is obtained by hydrolysis of the ester group of compound (VII) with NaOH in ethanol/water and dabigatran etexilate is obtained by acylation of the

L.A. Sorbera, J. Bozzo, J. Castañer. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of Dabigatran and Dabigatran Etexilate



amidino group of compound (VII) with hexyl chloroformate by means of K_2CO_3 in THF/H_2O (1, 2). Scheme 1.

Introduction

Thrombin, an extracellular trypsin-like serine protease, plays a dual role in the development of thrombotic events: it is not only a regulator of fibrin clot formation, but is also a potent inducer of platelet activation and aggregation. Also known as activated factor II (FIIa), thrombin is the final enzyme in the coagulation cascade. The first event initiating blood coagulation after tissue injury is the exposure of blood to tissue factor (TF), a transmembrane protein that binds activated factor VII (FVIIa), which is present in trace amounts in circulating blood. This complex catalyzes the activation of FIX and FX. FIXa then binds to FVIIIa to form a complex that activates FX. The principal role of FXa after being activated by TF-FVIIa is to generate small amounts of thrombin in

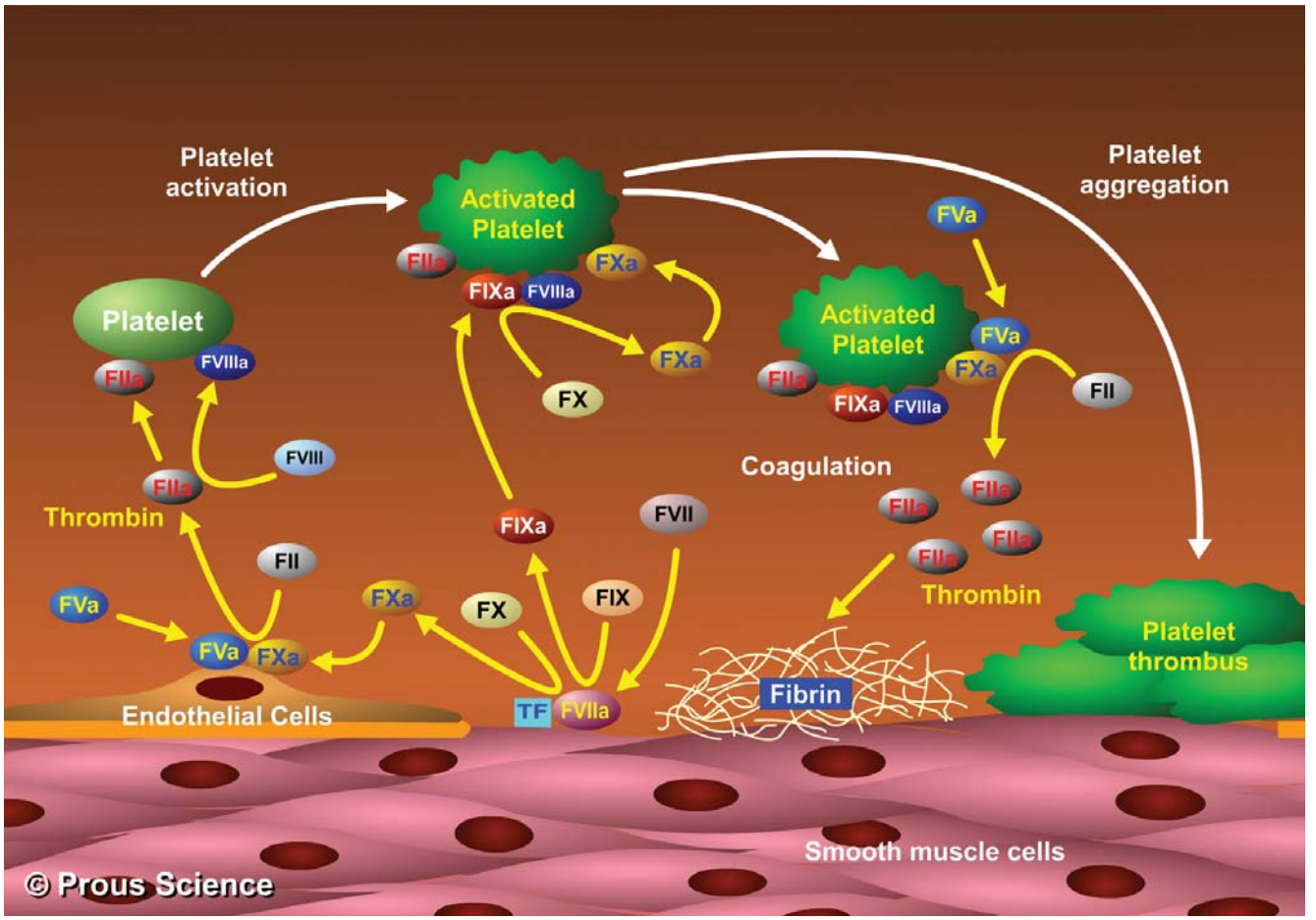


Fig. 1. Dual role of thrombin in coagulation and platelet aggregation. After damage of vessel endothelium, contact occurs between blood and tissue factor (TF) exposed on subendothelial cells. This leads to the activation of small amounts of prothrombin (FII) to thrombin (FIIa), which locally activates platelets. Thrombin activates FVII, which in turn directly activates FX on the surface of locally activated platelets. FXa promotes coagulation by binding to FVa on the platelet membrane surface to form the prothrombinase complex. This complex converts large amounts of prothrombin to thrombin, which converts fibrinogen to fibrin. Activated platelets adhere to and aggregate on the damaged vessel wall. Together with the polymerized fibrin strand, aggregated platelets form a stable thrombus.

the proximity of platelets, enhancing their activation. Moreover, FXa promotes coagulation by binding to FVa on membrane surfaces to form the prothrombinase complex. This complex first converts prothrombin (FII) to thrombin (FIIa), which then converts fibrinogen to fibrin. Fibrin then polymerizes, forming the strand network of the developing clot. Through positive feedback and activation of FVa, FVIIIa and FXI, thrombin enhances its own production (3-5). A model of these interactions is summarized in Figure 1.

The activation of human platelets by thrombin is mediated by the protease-activated receptors PAR1 and PAR4 (6). Thrombin irreversibly cleaves the extracellular *N*-terminal of the receptor, unmasking a peptide fragment sequence (SFLLRN for PAR1 and GYPGQV for PAR4), which acts as a tethered ligand that can bind to the body of and autoactivate PAR1 or PAR4. PAR1-induced platelet activation appears to be predominant, while PAR4-induced platelet responses are less pronounced. Activated PAR1 and PAR4 are coupled to and transduce signals through multiple G-proteins, although Gq appears to be the primary signaling-mediated pathway. Gq stimulates inositol phosphate metabolism and intracellular calcium levels to activate platelets. PAR1 and PAR4 also couple to the G12/13 pathway, which triggers Rho-dependent phosphorylation of the myosin light chain, contributing to the rearrangement of the platelet cytoskeleton. The Gi pathway also appears to be necessary for platelet activation by PAR1 or PAR4. Gi regulates the production of cAMP through the inhibition of adenylyl cyclase, the enzyme catalyzing the conversion of ATP to cAMP. High levels of cAMP oppose platelet activation by blocking intracellular calcium mobilization (5, 7). A scheme of the different signaling pathways and platelet responses triggered by thrombin is shown in Figure 2.

Because of the crucial role of thrombin in the coagulation cascade and platelet activation, the enzyme is a primary target for the development of anticoagulant and antithrombotic drugs. Both direct and indirect thrombin inhibition strategies are currently available. Indirect

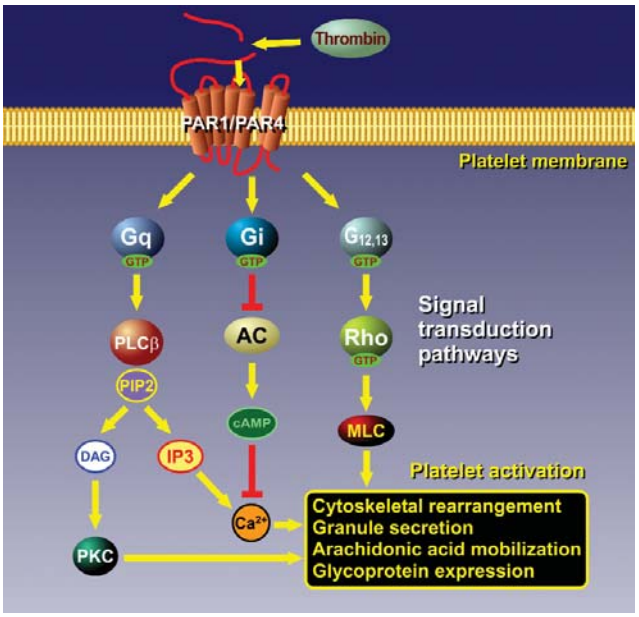


Fig. 2. Signal transduction pathways triggered by thrombin binding to its receptors PAR1 and PAR4. Thrombin partially cleaves the extracellular part of its receptor, unmasking a portion that binds to and activates the body of the receptor. Activated PAR1 and PAR4 are coupled to and transduce signals through Gq, Gi and G12/13 pathways, finally leading to platelet activation manifested by means of several metabolic responses. PLCβ: phospholipase C β; PIP2: phosphatidylinositol bisphosphonate; DAG: diacylglycerol; IP3: inositol triphosphate; PKC: protein kinase C; AC: adenylyl cyclase; MLC: myosin light chain.

thrombin inhibition via suppression of precursor coagulation proteins is associated with undesirable properties such as bleeding and interpatient dosing variability. In contrast, selective direct thrombin inhibitors are not associated with these undesirable effects since they bind directly to thrombin and block its interactions with its substrates. Low-molecular-weight heparins (LMWH) indirectly inhibit thrombin by strongly catalyzing the function of antithrombin (8). Although there is less interpatient variability with LMWH, they are ineffective against clot-bound thrombin and may cause thrombocytopenia (9, 10). In contrast, direct thrombin inhibitors act independently of antithrombin, so they can inhibit thrombin bound to fibrin or fibrin degradation products (10, 11). Direct thrombin-inhibiting drugs can block the action of the enzyme by binding to three domains: the active site or catalytic site and two exosites (12, 13).

The peptidomimetic dabigatran (BIBR-953) and its oral double prodrug dabigatran etexilate (BIBR-1048) are highly selective univalent direct thrombin inhibitors that block thrombin by binding only to the active site solely via hydrophobic interactions (1). The launched products argatroban and melagatran (and its produg ximelagatran) are also univalent direct thrombin inhibitors, while recombinant hirudins and bivalirudin are bivalent inhibitors. Studies indicate that dabigatran appears to exhibit a better safety profile than its competitors. Dabigatran is currently undergoing phase III development for the prevention of deep venous thrombosis (DVT) after surgical intervention and for the prevention of stroke in patients with atrial fibrillation. Several other direct thrombin inhibitors are currently under clinical development, as shown in Table I.

Pharmacological Actions

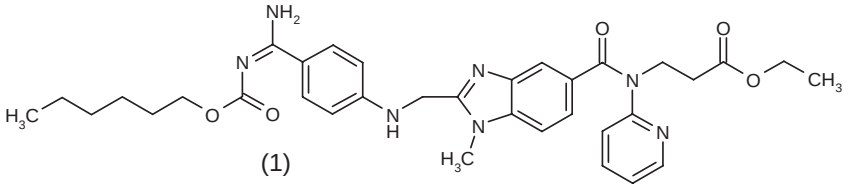
Dabigatran, the active component of the double prodrug dabigatran etexilate, inhibited human thrombin *in vitro* with an IC_{50} value of 0.0093 μM and a K_i value of 4.5 ± 0.2 μM. The agent was highly selective for thrombin over most other serine proteases. With the exception of trypsin (K_i = 50.3 ± 0.3 nM), the K_i values for dabigatran against other human serine proteases, including FXa, FVIIa, FXIa, plasma kallikrein, plasmin, two-chain urokinase, tissue-type plasminogen activator (t-PA), C1 esterase and activated protein C, were at least 700-fold higher than that obtained against thrombin. Results from other *in vitro* experiments demonstrated that dabigatran interfered with the coagulation cascade over the concentration range of 0.001-10 μM. Humans were the most sensitive species in the activated partial thromboplastin time (aPTT) coagulation assay, where an ED_{200} value of 0.23 ± 0.021 μM was obtained. In contrast, guinea pigs and rats were the most sensitive species in coagulation assays for ecatrin clotting time (ECT; ED_{200} = 0.090 ± 0.008 μM) and prothrombin time (PT; ED_{200} = 0.56 ± 0.058 μM), respectively. Concentration-dependent prolongation of clotting times (aPTT, ECT, PT) was observed in all species. ECT was the most sensitive to concentration, followed by aPTT and PT (1, 14).

Dabigatran and dabigatran etexilate exhibited potent anticoagulant effects and were well tolerated *in vivo* in rats, rabbits, dogs and rhesus monkeys. The aPTT of rats treated with 1 and 3 mg/kg i.v. dabigatran was prolonged up to 2 and 3 h, respectively. The aPTT was also significantly prolonged in rats treated with dabigatran 0.35 mg/kg s.c., with maximum effect (2.2-fold) seen 15 min postdosing and sustained for 1 h postdosing; intraduodenal administration of the agent only weakly prolonged aPTT. In contrast, oral administration of the prodrug dabigatran etexilate caused a dose-dependent prolongation of aPTT in all species. For example, following a single oral dose of the prodrug (1, 2.5 and 5 mg/kg) in rhesus monkeys, aPTT was prolonged 1.9-, 2.3- and 3.1-fold, respectively, at 2 h postdosing. Significant aPTT prolongations of 1.4-, 1.6- and 1.7-fold, respectively, were observed at 8 h postdosing (1, 15).

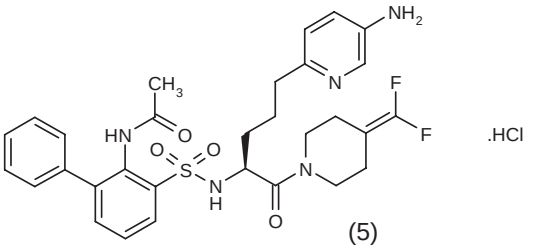
The antithrombotic and anticoagulant effects of both dabigatran (0.01, 0.03, 0.05 and 0.1 mg/kg i.v.) and dabigatran etexilate (5, 10, 20 and 30 mg/kg p.o. starting 30 min or up to 7 h prior to venous thrombosis induction) were examined in a rat model of venous thrombosis (*i.e.*, venous stasis of the vena cava + TF administration). Treatment with dabigatran dose-dependently decreased dry clot weight (9.1 ± 1.5, 6.8 ± 2.7, 3.3 ± 1.4 and 0 mg,

Table I: Highly selective direct thrombin inhibitors currently under active clinical development (from Prous Science Integrity®).

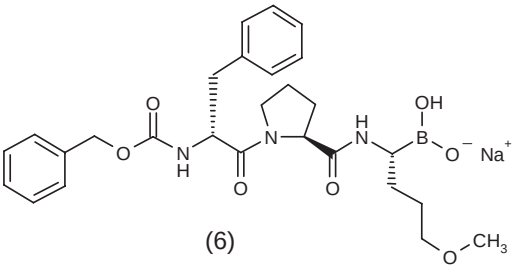
Drug	Source	Phase
1. Dabigatran etexilate	Boehringer Ingelheim	III
2. AZD-0837*	AstraZeneca	II
3. MCC-977*	Mitsubishi Pharma	II
4. Pegmusirudin*	Speedel; Abbott	II
5. SSR-182289	Sanofi-Aventis	II
6. TGN-255	Trigen	II
7. TGN-167	Trigen; Eurand	I



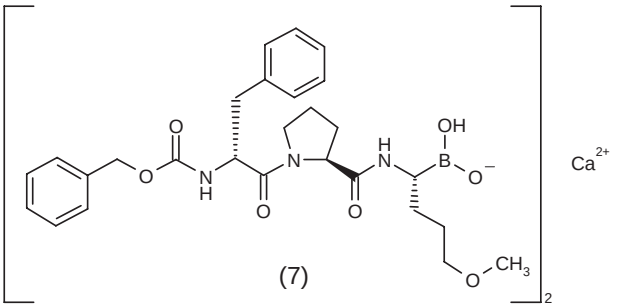
(1)



(5)



(6)



(7)

*Structure not available

respectively, *vs.* 10.3 ± 1 mg in controls; ED_{50} = 0.033 mg/kg). Moreover, pretreatment with dabigatran etexilate dose- and time-dependently reduced clot formation (1.7 ± 0.7, 0.8 ± 0.6, 0 and 0 mg, respectively, *vs*. 9 ± 0.7 mg in controls). The prodrug appeared to have a rapid onset of action since maximum reductions were observed when pretreatment was initiated only 30 min before induction of thrombosis. Both agents dose-dependently prolonged aPTT. Results from experiments using a rat tail incision bleeding time model indicated that single bolus doses of 0.1 and 0.3 mg/kg of dabigatran etexilate did not significantly prolong predose bleeding time, although significant prolongation of bleeding time was observed with higher doses of 0.5 and 1 mg/kg (doses 5-10-fold higher than the maximum therapeutically effective dose) (16).

The antithrombotic and anticoagulant effects of dabigatran (0.03, 0.1, 0.3 and 0.5 mg/kg i.v.) and dabigatran etexilate (1, 3, 5, 10 and 20 mg/kg p.o. 2 h prior to induction of thrombosis) were further examined in a rabbit model of venous thromboembolism (*i.e*., chemically induced local endothelial damage of both jugular veins with reductions in blood flow in a vessel segment). Administration of dabigatran dose-dependently decreased clot weight (23 ± 3.9, 11.6 ± 2.8, 4.7 ± 1.6 and 2.5 ± 0.6 mg, respectively, *vs.* 32.5 ± 2.4 mg in controls; ED_{50} = 0.066 mg/kg) and dose-dependently prolonged aPTT. Dose-dependent reductions in clot weight were also observed following oral administration of dabigatran etexilate, with significant effects observed at doses of 5, 10 and 20 mg/kg (16.2 ± 5, 0.94 ± 0.7 and 0 mg, respectively, *vs*. 38.2 ± 2.2 mg in controls); treatment with the prodrug also prolonged aPTT. Pretreatment with 10 mg/kg p.o. dabigatran etexilate starting 1, 2, 3, 5 and 7 h before thrombosis induction significantly decreased clot weights at all times (1.9 ± 1.3, 0.9 ± 0.7, 2.6 ± 1.8, 10.3 ± 2.3 and 18.5 ± 4.4 mg, respectively) (17).

Pharmacokinetics

The pharmacokinetics of dabigatran were studied in rats (2.6 mg/kg) and rhesus monkeys (3 mg/kg) administered [^{14}C]-labeled dabigatran etexilate as the methanesulfonate salt. In rats, peak plasma levels of total radioactivity were approximately 300 ng Eq/ml, with a terminal half-life of 1.7 h; the respective values for dabigatran were 200 ng/ml and 1.1 h. The great majority (88%) of the radioactivity was eliminated in the feces via the bile by 24 h after dosing. The major metabolite in bile was identified as dabigatran. In monkeys, peak plasma levels of total radioactivity (dabigatran + glucuronide) and dabigratan were 140 and 50 ng/ml, respectively, with a $t_{1/2}$ for total radioactivity of 6 h. Again, most of the radioactivity (80%) was eliminated in the feces within 48 h. In feces, parent compound and dabigatran accounted for most of the radioactivity, and dabigatran was also detected in urine (18).

The effects of fasted and fed states and pantoprazole coadministration on the pharmacokinetics of single-dose dabigatran etexilate (150 mg p.o. as capsules) were examined in an open-label, crossover phase I study in 18 healthy male volunteers. Although food did not affect the extent of absorption of the agent, absorption was delayed (median t_{max} increased from 2 to 4 h) and the intersubject variability for dabigatran C_{max} and $AUC_{0-\infty}$ values was decreased from 42% to 24% and from 44% to 21%, respectively. Mean dabigatran AUC and C_{max} values were reduced (AUC = 705 ng.h/ml *vs*. 904 and 895 ng.h/ml in fasted and fed states, respectively; C_{max} = 74.5 ng/ml *vs*. 111 and 106 ng/ml, respectively) in the presence of pantoprazole (19) (Table II).

The pharmacokinetics of single doses of dabigatran etexilate (150 mg p.o. as capsules) were also studied in a multicenter, open-label phase II (BISTRO Ib) trial conducted in 59 patients undergoing total hip replacement. The agent was administered 1-3 h following surgery. An immediate onset of absorption was observed, with adequate plasma levels achieved at 1 h postdosing; only 2 patients had a delay in absorption (4 and 6 h, respectively). The onset of absorption was not affected by coadministration of opioids. Dabigatran C_{max} (75.8 ng/ml) was reached between 1 and 24 h postdosing (median t_{max} = 6 h). The mean $AUC_{0-24\ h}$ for dabigatran was comparable to values obtained in healthy subjects (962 and 904 ng.h/ml, respectively). Intersubject variability for C_{max} and AUC values was high (19) (Table II).

The pharmacokinetics of dabigatran following the administration of multiple doses of dabigatran etexilate (150 mg p.o. b.i.d. for 7 days) were examined in a total of 36 healthy elderly (65-87 years) male and female subjects, 18 of whom were also receiving pantoprazole (40 mg b.i.d.). Dabigatran was rapidly absorbed, with a median t_{max} of 3 h. Coadministration of pantoprazole reduced the AUC values for dabigatran by 20-24%. Steady-state plasma levels were achieved after 2-3 days, with a terminal $t_{1/2}$ of approximately 12 h. Geometric mean stea dy-state trough plasma levels were 78 and 65 ng/ml, respectively, in the absence and presence of pantoprazole. AUC values in females were 20-30% higher than in males. The inter- and intrasubject variability of dabigatran pharmacokinetic parameters was low to moderate, with respective coefficients of variation of 21-28% and 11-15%. Pharmacodynamic examination of aPPT and ECT revealed a close correlation with dabigatran plasma concentrations. It was concluded that the pharmacokinetics of dabigatran in elderly subjects following administration of its prodrug are reproducible and not significantly altered by gender or pantoprazole coadministration (20) (Table II).

Two phase I clinical trials evaluated the pharmacokinetics of single and multiple doses of dabigatran etexilate as an oral solution in healthy volunteers. In subjects administered single doses of 10, 30, 100, 200 and 400 mg, drug was rapidly absorbed and converted to dabigatran. Mean peak plasma levels of dabigatran were 8.3, 21, 79, 126 and 243 ng/ml, respectively, reached at 1.25-1.75 h, followed by biphasic decline with terminal elimination half-lives of 8.2-10.4 h after doses of 100-400 mg. C_{max} and AUC increased proportionally with dose. In the placebo-controlled multiple-dose study, subjects received doses of 50, 100, 200 and 400 mg t.i.d. for 6 days. Steady state was reached on day 3 and moderate drug accumulation was observed. Peak plasma levels at steady state were 61, 187, 355 and 663 ng/ml, respectively, and were reached in a mean of 1.5 h, with a mean terminal elimination half-life of 7.25, 13.3, 17.0 and 16.2 h, respectively, after doses of 50, 100, 200 and 400 mg. Steady-state C_{max} and AUC increased proportionally with dose. Interindividual variability was low in both studies (21) (Table II).

The pharmacokinetics of dabigatran after administration of dabigatran etexilate (50, 150 or 300 mg p.o. b.i.d. for 12 weeks) with or without aspirin (81 or 325 mg/day) or warfarin (adjusted to INR of 2.0-3.0) were evaluated in a randomized, dose-finding trial conducted in 502 patients with atrial fibrillation on stable warfarin treatment and with at least 1 additional risk factor for thromboembolic events. Dabigatran trough plasma concentrations increased proportionally with dose (mean steady-state trough plasma concentrations = 32.5, 98.9 and 210 ng/ml, respectively). Interpatient variability of plasma concentrations was high (coefficient of variation = 73-80%). Trough plasma concentrations of dabigatran were increased in patients with creatinine clearance below 50 ml/min due to prolonged elimination of the agent. Pharmacodynamic parameters (aPTT, ECT) were closely correlated with dabigatran plasma levels. The aPTT was dose-dependently prolonged from 32-34 s to 39.5, 49.4 and 58.8 s for the respective dabigatran etexilate doses, and ECT increased from 32-33 s to 43.3, 67.4 and 104 s, respectively. Interpatient variability for aPTT and ECT was low to moderate (coefficient of variation = 17-23% and 22-47%, respectively) (22).

Table II: Pharmacokinetics of dabigatran following oral dosing of the prodrug in humans (from Prous Science Integrity®).

Dose (mg)	C_{max} (ng/ml)	C_{min} (ng/ml)	AUC (ng.h/ml)	t_{max} (h)	$t_{1/2}$ (h)
12.5 mg b.i.d.	10	5	75		
25 mg b.i.d.	18	8	146		
50 mg b.i.d.	43	19	308		
50 mg t.i.d.	61	20		1.5	7.3
100 mg s.d.	79			1.5	8.2
100 mg b.i.d.	104	44	787		
100 mg t.i.d.	187	58		1.5	13.3
150 mg s.d. *Fasted*	111		904	2.0	8.7
150 mg s.d. *Fed*	106		895	4.0	7.7
150 mg s.d. + *Pantoprazole*	75		705	2.0	7.8
150 mg o.d.	99	14	1020		
150 mg b.i.d.	146	73	1080	3.0	12.0
200 mg s.d.	126			1.5	9.8
200 mg b.i.d.	242	107	1880		
200 mg t.i.d.	355	109		1.5	17
300 mg o.d.	232	29	2200		
300 mg b.i.d.	338	182	2920		
400 mg s.d.	243			1.5	10.4
400 mg t.i.d.	663	242		1.5	16.2

C_{max}: peak plasma concentration; C_{min}: minimum plasma concentration; AUC: area under the concentration-time curve; t_{max}: time to reach peak plasma concentrations; $t_{1/2}$: elimination half-life.

Clinical Studies

The pharmacodynamics of dabigatran were studied in healthy male subjects following single- or multiple-dose dabigatran etexilate (10, 30, 50, 100, 200 and 400 mg p.o. t.i.d. as solution). Treatment was concluded to be safe. Hematoma and mild bleeding at venipuncture sites were reported in 2 of 8 and 6 of 8 subjects, respectively, receiving 200 and 400 mg t.i.d. These adverse events were considered to be treatment-related. Thrombin activity was dose-dependently inhibited following administration of the prodrug. Coagulation parameters obtained closely correlated with dabigatran plasma levels. Maximum prolongation of aPPT, PT, thrombin time (TT) and ECT occurred without delay, which is consistent with direct inhibition of thrombin, and at peak dabigatran plasma concentrations. Intersubject variability of aPTT, PT, TT and ECT was low (coefficient of variation = 6-11%). Maximum mean aPTT prolongations (ratios) were 1.46, 1.85, 2.31 and 3.02, respectively, for doses of 50, 100, 200 and 400 mg t.i.d. as compared to 0.92-1.05 for placebo, and mean steady-state trough aPTT ratios were 1.17, 1.42, 1.67 and 2.02, respectively, as compared to 0.99 for placebo (23).

The safety of dabigatran etexilate tablets (12.5, 25, 50, 100, 150, 200 and 300 mg p.o. b.i.d. or 150 or 300 mg p.o. once daily administered 4-8 h postsurgery for 6-10 days) was investigated in a multicenter, open-label, dose-escalating study (BISTRO I) in 314 patients undergoing total hip replacement surgery. Of the patients enrolled, 289 received at least 1 dose of the agent, 27 patients discontinued early (18 due to adverse events) and 262 patients completed the study. No serious bleeding events were observed. Two patients receiving 300 mg b.i.d. developed bleeding from multiple sites, which was associated with reduced renal clearance and prolonged pharmacodynamic parameters. Minor bleeding events were dose-related. The overall incidence of deep vein thrombosis (DVT) as determined from the 225 evaluable venograms was 12.4% (28 patients) and was not related to dose. Pharmacokinetic and pharmacodynamic parameters increased proportionally with dose. Higher plasma levels of dabigatran were associated with a lower incidence of DVT. Plasma levels of dabigatran were low in about 20% of the patients following the first dose, indicating that the tablet formulation should be further optimized. Dabigatran etexilate was concluded to have an acceptable safety profile with a therapeutic window above 12.5 mg and below 300 mg b.i.d. (24) (see Table II for pharmacokinetic data).

A multicenter, double-blind, randomized, parallel-group study (BISTRO II) compared the safety and efficacy of dabigatran etexilate (50, 150 or 225 mg b.i.d. or 300 mg once daily p.o. starting 1-4 h postsurgery and for 6-10 days) and enoxaparin (40 mg s.c. once daily starting 12 h prior to surgery) in patients undergoing total hip or knee replacement surgery. Of the 1,973 patients enrolled, 1,949 were treated and 1,464 were evaluable for efficacy. A significantly lower incidence of major bleeding was observed with dabigatran etexilate at the dose of 50 mg b.i.d. as compared to enoxaparin (0.3% *vs*. 2%). However, the incidence increased with dabigatran etexilate dose and the bleeding rate for the group given 300 mg once daily was almost significantly higher than that of the enoxaparin group (4.7% *vs*. 2%; $p = 0.051$). The incidence of venous thromboembolism (VTE) in patients

receiving dabigatran etexilate was dose-dependent and was 28.5%, 17.4%, 13.1% and 16.6%, respectively, at doses of 50 mg b.i.d., 150 mg b.i.d., 225 mg b.i.d. and 300 mg once daily compared to 24% in patients receiving enoxaparin. VTE rates were significantly lower compared to enoxaparin in groups receiving 150 and 225 mg b.i.d. and 300 mg once daily. It was concluded that dabigatran etexilate at the doses examined was safe and effective (25).

The safety and efficacy of dabigatran etexilate (50, 150 or 300 mg p.o. b.i.d. for 12 weeks) with or without aspirin (81 or 325 mg/day) or warfarin (adjusted to INR = 2.0-3.0), were examined in a randomized, dose-finding trial conducted in 502 patients with atrial fibrillation (median D-dimer levels = 72 ng/ml) on stable warfarin treatment and with at least 1 additional risk factor for thromboembolic events (see also 20). Of the patients enrolled, 464 completed the 12 weeks of treatment and 29 and 9 discontinued due to adverse events and other causes, respectively. Aspirin was terminated prematurely in the 300-mg dabigatran etexilate group due to excessive bleeding events (11% of patients). However, coadministration of aspirin in the other dose groups did not significantly increase bleeding events; only 2% and 8% of the patients, respectively, on 50 and 150 mg developed major or relevant bleeding events. The rate of bleeding events in the highest dose group in the absence of aspirin was comparable to in the other groups. Thromboembolic events were seen in 2, 0 and 1 patient, respectively, in the 50, 150 and 300 mg b.i.d. dose groups and in 0 patients in the warfarin group. The 150 mg b.i.d. dose of dabigatran etexilate was concluded to have the same anticoagulant activity as the higher dose and warfarin. None of the dabigatran etexilate doses significantly altered liver function tests. From the results of this study, dabigatran etexilate doses of 200-300 mg daily were recommended for phase III testing for the prevention of thromboembolic events in patients with atrial fibrillation (26).

Dabigatran etexilate is currently in phase III development for the prevention of DVT after surgical intervention and phase II/III for the prevention of stroke in patients with atrial fibrillation (27).

Source

Boehringer Ingelheim GmbH (DE).

References

1. Hauel, N.H., Nar, H., Priepke, H., Ries, U.J., Stassen, J.M., Wienen, W. *Structure-based design of novel potent nonpeptide thrombin inhibitors.* J Med Chem 2002, 45: 1757-66.

2. Hauel, N., Priepke, H., Ries, U., Stassen, J.M., Wienen, W. (Boehringer Ingelheim Pharma KG). *Disubstd. bicyclic heterocycles, their production and use as medicaments*. DE 19706229, DE 19751939, EP 0966454, JP 2001509815, US 2003004181, US 6087380, US 6469039, US 6710055, WO 1998037075.

3. Walsh, P.N. *Platelet coagulation-protein interactions*. Semin Thromb Hemost 2004, 30: 461-71.

4. Narayanan, S. *Multifunctional roles of thrombin*. Ann Clin Lab Sci 1999, 29: 275-80.

5. Heemskerk, J.W., Bevers, E.M., Lindhout, T. *Platelet activation and blood coagulation*. Thromb Haemost 2002, 88: 186-93.

6. Kahn, M.L., Nakanishi-Matsui, M., Shapiro, M.J., Ishihara, H., Coughlin, S.R. *Protease-activated receptors 1 and 4 mediate activation of human platelets by thrombin.* J Clin Invest 1999, 103: 879-87.

7. Trejo, J. *Protease-activated receptors: New concepts in regulation of G protein-coupled receptor signaling and trafficking*. J Pharmacol Exp Ther 2003, 307: 437-42.

8. Pineo, G.F., Hull, R.D. *Unfractionated and low-molecular-weight heparin. Comparisons and current recommendations.* Med Clin North Am 1998, 82: 587-99.

9. Kleinschmidt, K., Charles, R. *Pharmacology of low molecular weight heparins*. Emerg Med Clin North Am 2001, 19: 1025-49.

10. Weitz, J.I., Hudoba, M., Massel, D., Maraganore, J., Hirsh, J. *Clot-bound thrombin is protected from inhibition by heparin-antithrombin III but is susceptible to inactivation by antithrombin III-independent inhibitors.* J Clin Invest 1990, 86: 385-91.

11. Hauptmann, J., Sturzebecher, J. *Synthetic inhibitors of thrombin and factor Xa: From bench to bedside.* Thromb Res 1999, 93: 203-41.

12. Tulinsky, A. *Molecular interactions of thrombin*. Semin Thromb Hemost 1996, 22: 117-24.

13. Das, J., Kimball, S.D. *Thrombin active site inhibitors*. Bioorg Med Chem 1995, 3: 999-1007.

14. Stassen, J.M., Hauel, N.H., Nar, H., Ries, U.J., Priepke, H.W.M., Wienen, W. *Identification and in vitro characterization of BIBR 953 ZW, a novel synthetic low molecular weight direct thrombin inhibitor*. 18th Cong Int Soc Thromb Haemost (July 6-12, Paris) 2001, Abst P755.

15. Stassen, J.M., Hauel, N.H., Nar, H., Ries, U.J., Priepke, H.M.W. *Ex vivo anticoagulant activity of BIBR953ZW, a novel synthetic direct thrombin inhibitor and of its prodrug BIBR1048 MS in different animal species.* 18th Cong Int Soc Thromb Haemost (July 6-12, Paris) 2001, Abst P763.

16. Wienen, W., Nar, H., Ries, U.J., Priepke, H.W.M., Hauel, N.H., Stassen, J.M. *Effects of the direct thrombin inhibitor BIBR953ZW and its orally active prodrug BIBR1048MS on experimentally-induced clot formation and template bleeding time in rats.* 18th Cong Int Soc Thromb Haemost (July 6-12, Paris) 2001, Abst P761.

17. Wienen, W., Nar, H., Ries, U.J., Priepke, H.W.M., Hauel, N.H., Stassen, J.M. *Antithrombotic effects of the direct thrombin inhibitor BIBR953ZW and its orally active prodrug BIBR1048MS in a model of venous thrombosis in rabbits*. 18th Cong Int Soc Thromb Haemost (July 6-12, Paris) 2001, Abst OC853.

18. Busch, U., Schmid, J. *Pharmacokinetics of the synthetic direct thrombin inhibitor BIBR 953 ZW in different animal species.* 18th Cong Int Soc Thromb Haemost (July 6-12, Paris) 2001, Abst P766.

19. Stangier, J., Eriksson, B.I., Dahl, O.E., Ahnfelt, L., Nehmiz, G., Stahle, H., Rathgen, K., Svard, R. *Pharmacokinetic profile of*

the oral direct thrombin inhibitor dabigatran etexilate in healthy volunteers and patients undergoing total hip replacement. J Clin Pharmacol 2005, 45: 555-63.

20. Stangier, J., Stahle, H., Rathgen, K. Seitz, Ch. *Pharmacokinetics and pharmacodynamics of the direct thrombin inhibitor dabigatran in elderly healthy subjects*. 20th Cong Int Soc Thromb Haemost (Aug 6-12, Sydney) 2005, Abst P2207.

21. Stangier, J., Rathgen, K., Gansser, D., Kohlbrenner, V., Stassen, J.M. *Pharmacokinetics of BIBR 953 ZW, a novel low molecular weight direct thrombin inhibitor in healthy volunteers*. 18th Cong Int Soc Thromb Haemost (July 6-12, Paris) 2001, Abst OC2347.

22. Stangier, J., Nehmiz, G., Reilly, P., Ezekowitz, M., Petersen, K.-E., Simmers, T., Wallentin, L. *Pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran in a dose finding trial in atrial fibrillation*. 20th Cong Int Soc Thromb Haemost (Aug 6-12, Sydney) 2005, Abst OR271.

23. Stassen, J.M., Rathgen, K., Zimmermann, R., Wienen, W., Stangler, J. *Pharmacodynamics of the synthetic direct thrombin inhibitor BIBR953ZW in healthy subjects.* 18th Cong Int Soc Thromb Haemost (July 6-12, Paris) 2001, Abst OC160.

24. Eriksson, B.I., Dahl, O.E., Ahnfelt, L., Kalebo, P., Stangier, J., Nehmiz, G., Hermansson, K., Kohlbrenner, V. *Dose escalating safety study of a new oral direct thrombin inhibitor, dabigatran etexilate, in patients undergoing total hip replacement: BISTRO I.* J Thromb Haemost 2004, 2(9): 1573-80.

25. Eriksson, B.I., Dahl, O.E., Buller, H.R., Hettiarachchi, R., Rosencher, N., Bravo, M.-L., Ahnfelt, L., Piovella, F., Stangier, J., Kalebo, P., Reilly, P. *A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: The BISTRO II randomized trial.* J Thromb Haemost 2005, 3(1): 103-11.

26. Wallentin, L.C., Ezekowitz, M., Simmers, T.A., Pedersen, K.E., Stangier, J., Nehmiz, G., Reilly, P. *Safety and efficacy of a new oral direct thrombin inhibitor dabigatran in atrial fibrillation – A dose finding trial with comparison to warfarin*. Eur Soc Cardiol Cong (Sept 3-7, Stockholm) 2005, Abst P2949.

27. Boehringer Ingelheim Annual Report 2004.

Additional References

Di Nisio, M., Middeldorp, S., Buller, H.R. *Direct thrombin inhibitors*. New Engl J Med 2005, 353(10): 1028-40.

Ezekowitz, M.D. *Stroke prevention in atrial fibrillation: Anticoagulants and antithrombotics*. Am Heart Hosp J 2004, 2(4, Suppl. I): 31-5.

Stangier, J., Liesenfeld, K.H., Troconiz, Ch., Tillmann, I.F., Schaefer, H.G., Hermansson, K., Eriksson, B.I. *The effect of BIBR 953 ZW, the active form of the oral direct thrombin inhibitor BIBR 1048, on the prolongation of aPTT and ECT in orthopedic patients: A population pharmacodynamic study.* J Thromb Haemost 2003, 1(Suppl. 1): Abst P1917.

Eriksson, B.I., Dahl, O., Ahnfelt, L., Kalebo, P., Stangier, J., Nehmiz, G., Hermansson, K., Kohlbrenner, V. *Dose escalating safety study of a new oral direct thrombin inhibitor, BIBR 1048, in patients undergoing total hip replacement (THR).* Pathophysiol Haemost Thromb 2002, 32(Suppl. 2): Abst O124.

Garnett, C., Liesenfeld, K.H., Tillmann, C., Troconiz, I., Schaefer, H.G., Stangier, J., Lee, H. *Clinical trial simulation of the dose-response relationship of a direct thrombin inhibitor, dabigatran etexilate, in hip replacement patients*. 12th Meet Population Approach Group Eur (June 12-13, Verona) 2003, Abst 388.

Liesenfeld, K.H., Tillmann, I., Troconiz, I., Schaefer, H.G., Stangier, J. *Population pharmacodynamic analysis of dabigatran, the active form of the new oral direct thrombin inhibitor dabigatran etexilate (BIBR 1048), on the prolongation of aPTT and ECT in orthopaedic patients.* 12th Meet Population Approach Group Eur (June 12-13, Verona) 2003, Abst 387.

Liesenfeld, K.-H., Stangier, J., Garnett, C., Tillmann, C., Troconiz, I., Lee, H., Schaefer, H.G. *PK/PD-modeling (PK/PD) and clinical trial simulation (CTS) of early clinical data of a new oral direct thrombin inhibitor (dabigatran etexilate).* 14th Meet Population Approach Group Eur (June 16-17, Pamplona) 2005, Abst 787.

Stangier, J., Liesenfeld, K.-H., Tillmann, C., Troconiz, I., Schaefer, H.G. *Population pharmacokinetics/-dynamics of dabigatran, the active form of the new oral direct thrombin inhibitor dabigatran etexilate (BIBR 1048) in patients undergoing hip replacement*. 12th Meet Population Approach Group Eur (June 12-13, Verona) 2003, Abst 385.

Tillmann, C., Troconiz, I.F., Stangier, J., Liesenfeld, K.H., Schaefer, H.G. *Population pharmacokinetic analysis of the new oral thrombin inhibitor dabigatran etexilate (BIBR1048) in patients undergoing primary elective total hip replacement surgery.* 12th Meet Population Approach Group Eur (June 12-13, Verona) 2003, Abst 386.

Stangier, J., Nehmiz, G., Liesenfeld, K.H., Holzschuh, I., Hermansson, K., Svaerd, R., Dahl, O.E., Ahnfelt, L., Eriksson, B.I. *Pharmacokinetics of BIBR 953 ZW, the active form of the oral direct thrombin inhibitor BIBR 1048, in patients undergoing hip replacement*. J Thromb Haemost 2003, 1(Suppl. 1): Abst P1916.

Gustafsson, D. *Oral direct thrombin inhibitors in clinical development.* J Intern Med 2003, 254(4): 322-34.

Kikelj, D. *Peptidomimetic thrombin inhibitors*. Pathophysiol Haemost Thromb 2003/2004, 33(5-6): 487-91.

Heit, J.A *The potential role of direct thrombin inhibitors in the prevention and treatment of venous thromboembolism*. Chest 2003, 124(3): 40S-8S.

Bates, S.M., Weitz, J.I. *New anticoagulants: Beyond heparin, low-molecular-weight heparin and warfarin.* Br J Pharmacol 2005, 144(8): 1017-28.