Prevention and treatment of thromboembolic disorders

The present invention relates to the field of blood coagulation, more specifically it relates to a method of treating a thromboembolic disorder by administering a direct factor Xa inhibitor once daily in oral dosage form to a patient in need thereof, wherein the factor Xa inhibitor has a plasma concentration half life indicative of a bid or tid administration interval, e.g. of 10 hours or less.

Blood coagulation is a protective mechanism of the organism which helps to "seal" defects in the wall of the blood vessels quickly and reliably. Thus, loss of blood can be avoided or kept to a minimum. Haemostasis after injury of the blood vessels is effected mainly by the coagulation system in which an enzymatic cascade of complex reactions of plasma proteins is triggered. Numerous blood coagulation factors are involved in this process, each of which factors converts, on activation, the respectively next inactive precursor into its active form. At the end of the cascade comes the conversion of soluble fibrinogen into insoluble fibrin, resulting in the formation of a blood clot. In blood coagulation, traditionally the intrinsic and the extrinsic pathways, which end in a joint reaction path, are distinguished. Here factor Xa, which is formed from the proenzyme factor X, plays a key role, since it connects the two coagulation paths. The activated serine protease Xa cleaves prothrombin to thrombin. The resulting thrombin, in turn, cleaves fibrinogen to fibrin, a fibrous/gelatinous coagulant. In addition, thrombin is a potent effector of platelet aggregation which likewise contributes significantly to haemostasis.

Maintenance of normal haemostasis - the balance between bleeding and thrombosis - is subject to a complex regulatory mechanism. Uncontrolled activation of the coagulant system or defective inhibition of the activation processes may cause formation of local thrombi or embolisms in vessels (arteries, veins) or in heart cavities. This may lead to serious disorders, such as myocardial infarction, angina pectoris (including unstable angina), vascular re-occlusions and restenoses after angioplasty or aortocoronary bypass, stroke, transitory ischaemic attacks, peripheral arterial occlusive disorders, pulmonary embolisms or deep vein thromboses; herein below, these disorders are collectively also referred to as thromboembolic disorders. In addition, in the case of consumption coagulopathy, hypercoagulability may – systemically - result in disseminated intravascular coagulation.

These thromboembolic disorders are the most frequent cause of morbidity and mortality in most industrialised countries. Estimates place the annual incidence of VTE in excess of 1 case per 1,000 persons [White, R.H. The epidemiology of venous thromboembolism. Circulation 107 (Suppl.1),14-18 (2003)]. About 1.3 - 4.1 persons in 1,000 experience a first stroke [Feigin, V.L., Lawes, C.M., Bennett, D.A., Anderson, C.S. Lancet Neurol. 2, 43-53 (2003)], and about 5 in 1,000

persons a myocardial infarction annually [Fang, J, Alderman, M.H. Am. J. Med 113, 208-214 (2002)].

The anticoagulants, i.e. substances for inhibiting or preventing blood coagulation, which are known from the prior art have various, often severe disadvantages. Accordingly, in practice, an efficient treatment method or prophylaxis of thromboembolic disorders is very difficult and unsatisfactory.

In the therapy and prophylaxis of thromboembolic disorders, use is firstly made of heparin, which is administered parenterally (intravenously or subcutaneously). Owing to more favourable pharmacokinetic properties, preference is nowadays more and more given to low-molecular-weight heparin. Since heparin inhibits a plurality of factors of the blood coagulation cascade at the same time, the action is non-selective. Moreover, there is a high risk of bleeding.

A second class of anticoagulants are the vitamin K antagonists. These include, for example, 1,3-indanediones, and especially compounds such as warfarin, phenprocoumon, dicumarol and other coumarin derivatives which inhibit the synthesis of various products of certain vitamin K-dependent coagulation factors in the liver in a non-selective manner. Owing to the mechanism of action, however, the onset of the action is very slow (latency to the onset of action 36 to 48 hours). It is possible to administer the compounds orally; however, owing to the high risk of bleeding and the narrow therapeutic index, a time-consuming individual adjustment and monitoring of the patient are required.

Recently, a novel therapeutic approach for the treatment and prophylaxis of thromboembolic disorders has been described. This novel therapeutic approach aims to inhibit factor Xa [cf. WO-A-99/37304; WO-A-99/06371; J. Hauptmann, J. Stürzebecher, Thrombosis Research **1999**, *93*, 203; S.A.V. Raghavan, M. Dikshit, „Recent advances in the status and targets of antithrombotic agents" *Drugs Fut.* **2002**, *27*, 669-683; H.A. Wieland, V. Laux, D. Kozian, M. Lorenz, „Approaches in anticoagulation: Rationales for target positioning" *Curr. Opin. Investig. Drugs* **2003**, *4*, 264-271; U.J. Ries, W. Wienen, „Serine proteases as targets for antithrombotic therapy" *Drugs Fut.* **2003**, *28*, 355-370; L.-A. Linkins, J.I. Weitz, „New anticoagulant therapy" *Annu. Rev. Med.* **2005**, *56*, 63-77]. It has been shown that, in animal models, various both peptidic and nonpeptidic compounds are effective as factor Xa inhibitors.

In general, oral application is the preferable route of administration of a drug, and a less frequent dose regimen is desirable. In particular, once daily oral application is preferred due to favourable convenience for the patient and for compliance reasons. However, this goal is sometimes difficult to achieve depending on the specific behaviour and properties of the drug substance, especially its

plasma concentration half life. "Half life" is the time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50 % (Goodman and Gillmans "The Pharmacological Basis of Therapeutics" 7th Edition, Macmillan Publishing Company, New York, 1985, p 27).

When the drug substance is applied in no more than a therapeutically effective amount, which is usually preferred in order to minimize the exposure of the patient with that drug substance in order to avoid potential side effects, the drug must be given approximately every half live (see for example: Malcolm Rowland, Thomas N. Tozer, in "Clinical Pharmacokinetics, Concepts and Applications", 3rd edition, Lea and Febiger, Philadelphia **1995**, pp 83).

In the case of multiple dose application the target plasma concentration (approximate steady state) can be reached after 3 to 5 half lives (Donald J. Birkett, in "Pharmacokinetics Made Easy", McGraw-Hill Education: 2000; p 20). At steady state the concentrations of drugs which rise and fall during each interdose interval are repeated identically in each interdose interval (Goodman and Gillmans "The Pharmacological Basis of Therapeutics" 7th Edition, Macmillan Publishing Company, New York, 1985, p 28).

Surprisingly, it has now been found in patients at frequent medication that once daily oral administration of a direct factor Xa inhibitor with a plasma concentration half life time of 10 hours or less demonstrated efficacy when compared to standard therapy and at the same time was as effective as after twice daily (bid) administration.

Therefore, the present invention relates to a method of treating a thromboembolic disorder comprising administering a direct factor Xa inhibitor no more than once daily for at least five consecutive days in an oral dosage form to a patient in need thereof, wherein said inhibitor has a plasma concentration half life of 10 hours or less when orally administered to a human patient.

The present invention further relates to the use of an oral dosage form of a direct factor Xa inhibitor for the manufacture of a medicament for the treatment of a thromboembolic disorder administered once daily for at least five consecutive days, wherein said inhibitor has a plasma concentration half life of 10 hours or less when orally administered to a human patient.

In a preferred embodiment, the present invention relates to 5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide (I), a low molecular weight, orally administrable direct inhibitor of blood clotting factor Xa (see WO-A 01/47919, whose disclosure is hereby included by way of reference) as the active ingredient.

Compound (I) is an active site directed, competitive, direct factor Xa inhibitor [E. Perzborn, J. Strassburger, A. Wilmen, J. Pohlmann, S. Roehrig, K.-H. Schlemmer, A. Straub; *J Thromb*

Haemost **2005**; DOI: 10.1111/j.1538-7836.2005.01166.x]. (I) acts directly on factor Xa, that means independently from a cofactor (such as Antithrombin III, the cofactor of heparins). The antithrombotic effect is attributed to the inhibition of factor Xa.

Furthermore, (I) binds to the active site of factor Xa in the S1- and S4 pockets [S. Roehrig et al. 228th ACS National Meeting, Philadelphia, August 22-26, 2004, MEDI-156].

For (I) a plasma concentration half life of 4-6 hours has been demonstrated at steady state in humans in a multiple dose escalation study (D. Kubitza et al, Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of Bay 59-7939, an oral, direct Factor Xa inhibitor, in healthy male subjects. Blood 2003, 102: Abstract 3004)

In a clinical study in patients undergoing total hip replacement (THR), the efficacy of (I) is measured by the occurrence of deep vein thrombosis (DVT) after THR surgery. According to the Sixth ACCP Consensus Conference on Antithrombotic Therapy (Chest 2001; 119: 132S-175S) the DVT rate (prevalence) after THR surgery is as follows:

	Prevalence (%)	(95 % Confidence intervall)
Placebo	54.2	(50-58)
Low dose heparin	30.1	(27- 33)
LMWH *	16.1	(15-17)

* LMWH = Low Molecular Weight Heparin

After 7 to 9 days of once daily administration of 30 mg (I) to 73 patients undergoing THR surgery, a DVT rate of 12.3 % has been observed (LMWH comparator was 16.8 %). Administration of (I) was also safe and well tolerated.

The once daily dose of (I) was also compared to different doses of (I) which have been administered twice daily (bid). By comparing the total daily doses administered it could also be demonstrated that after once daily administration efficacy on one hand and major bleeding, an expected side effect on the other hand, match well the expected effects after twice daily administration (for a discussion of further details see the experimental part).

The present invention further relates to a packaged pharmaceutical composition comprising a container containing a rapid-release tablet comprising 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide, said container furthermore containing instructions for using said rapid-release tablet to treat a thromboembolic disorder.

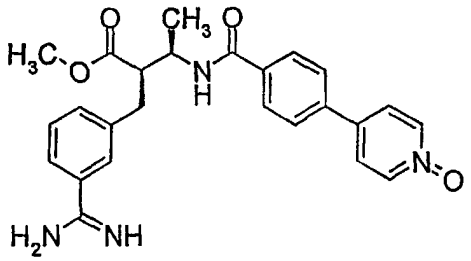
In a preferred embodiment, said packaged pharmaceutical composition, comprising a container containing a rapid-release tablet comprising 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide, said container furthermore containing instructions for administering said rapid-release tablet at a frequency of once daily.

In another preferred embodiment, the present invention relates to one of the following compounds:

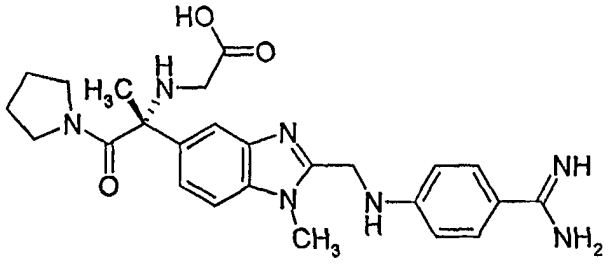
- **AX-1826** [S. Takehana *et al. Japanese Journal of Pharmacology* **2000**, *82* (Suppl. 1), 213P; T. Kayahara *et al. Japanese Journal of Pharmacology* **2000**, *82* (Suppl. 1), 213P]

- **HMR-2906** [XVIIth Congress of the International Society for Thrombosis and Haemostasis, Washington D.C., USA, 14-21 Aug **1999**; Generating greater value from our products and pipeline. Aventis SA Company Presentation, 05 Feb **2004**]

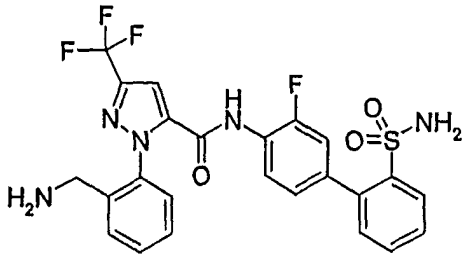
- **Otamixaban (FXV-673, RPR-130673)** [V. Chu *et al. Thrombosis Research* **2001**, *103*, 309-324; K.R. Guertin *et al. Bioorg. Med. Chem. Lett.* **2002**, *12*, 1671-1674]



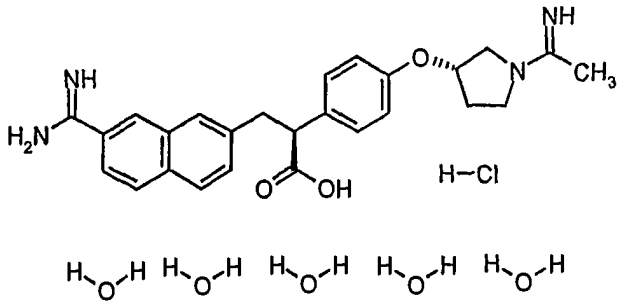
- **BIBT-986 (prodrug: BIBT-1011)** [American Chemical Society - 226th National Meeting, New York City, NY, USA, **2003**]



- **DPC-602** [J.R. Pruitt et al. *J. Med. Chem.* **2003**, *46*, 5298-5313]



- **DX-9065a** [T. Nagahara *et al. J. Med. Chem.* **1994**, *37*, 1200-1207]

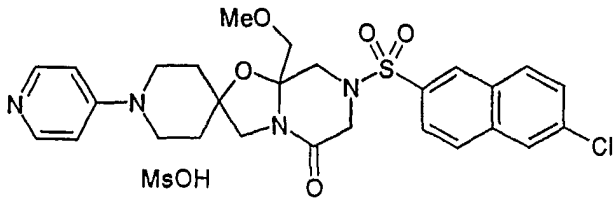


- **DU-176b** [Y. Morishima *et al. Blood* **2004**, *104*, 11, ASH 2004 (Abst 1862); T. Fukuda *et al. Blood* **2004**, *104*, 11, ASH 2004 (Abst 1852); T. Furugohri *et al. Blood* **2004**, *104*, 11, ASH 2004 (Abst 1851)]

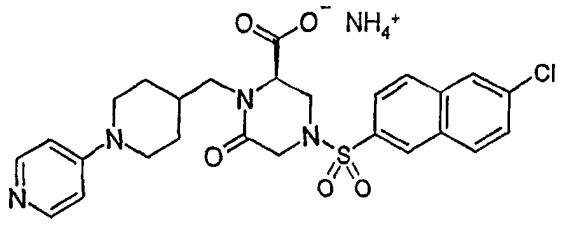
- **813893** [Proteinase Inhibitor Design - Fourth SCI-RSC Symposium, Proteinase **2004**: Strategies for New Medicines (Part I), London]

- **KFA-1982 (prodrug of KFA-1829)** [T. Koizumi *et al. Journal of Thrombosis and Hemostasis* **2003**, 1 Suppl 1, P2022]

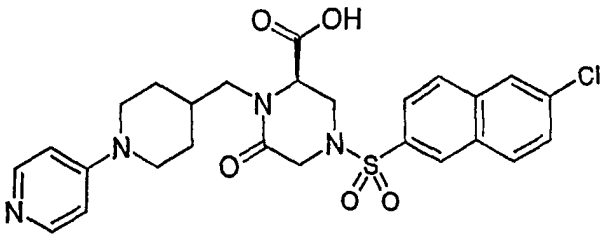
- **M-55532** [H. Nishida *et al.* 228th ACS National Meeting, Philadelphia, August 22-26, **2004**, MEDI-251; H. Nishida *et al. Chem. Pharm. Bull.* **2004**, *52*, 406-412, *dito* 459-462]



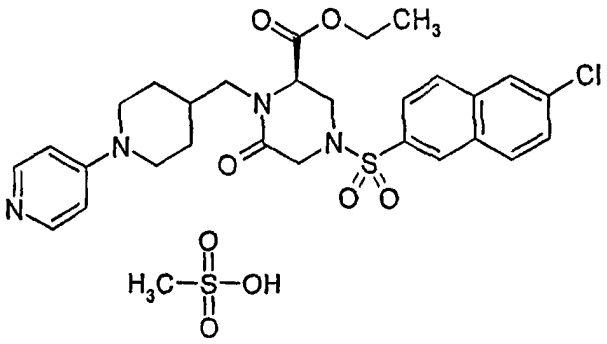
- **M-55555** [H. Nishida *et al.* 16th Int Symp Med Chem, Bologna, 18-22 Sept **2000**, Abst PA-125]



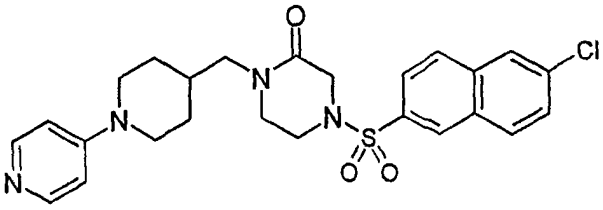
- **M-55551** [H. Nishida *et al. Chem. Pharm. Bull.* **2002**, *50*, 1187-1194]



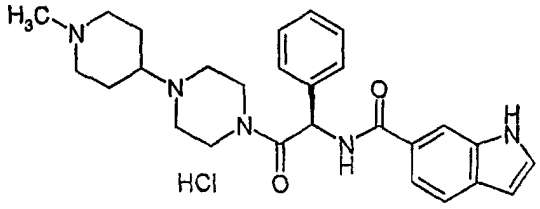
- **M-55190** [H. Nishida *et al.* 16th Int Symp Med Chem, Bologna, 18-22 Sept **2000**, Abst PA-125]



- **M-55113** [H. Nishida *et al. Chem. Pharm. Bull.* **2001**, *49*, 1237-1244]



- **LY517717** [S. Young, Medicinal Chemistry-12th RSC-SCI Symposium, 7-10 September **2003**, Cambridge, UK; M. Wiley *et al.* 228th ACS National Meeting, Philadelphia, August 22-26, **2004**, MEDI-252 & 254]



- **YM-150** [Research and development pipeline. Yamanouchi Pharmaceutical Co Ltd, Company World Wide Web site, 11 Feb 2004]

In another preferred embodiment, the present invention relates to direct active site directed factor Xa-inhibitors which bind to the active site of factor Xa in the S1- and S4 pockets as does (I). Such a binding mode is also reported for compounds cited in the following references whose disclosure, preferentially the compounds disclosed therein, is hereby included by way of reference:

- M. Nazare et al. Bioorg. Med. Chem. Lett. 2004, 14, 4191-4201; dito 2801-2805; Y.-M. Choi-Sledeski et al. J. Med. Chem. 2003, 46, 681-690;
- M. Adler et al. Biochemistry 2002, 41, 15514-15523; Y.L. Chou et al. Bioorg. Med. Chem. Lett. 2003, 13, 507-511;
- M.L. Quan et al. J. Med. Chem. 2004, online ASAP jm0497949; DPC602: J.R. Pruitt et al. J. Med. Chem. 2003, 46, 5298-5313; DPC 423: D.J.P. Pinto et al. J. Med. Chem. 2001, 44, 566-578;
- N. Haginoya, J. Med. Chem. 2004, 47, 5167-5182;
- S. Young, Medicinal Chemistry - 12th RSC-SCI Symposium, 7-10 September 2003, Cambridge, UK; M. Wiley et al. 228th ACS National Meeting, Philadelphia, August 22-26, 2004, MEDI-252 & 254;
- W.W.K.R. Mederski et al. Bioorg. Med. Chem. Lett. 2004, 14, 3763-3769;
- P. Zhang et al. Bioorg. Med. Chem. Lett. 2004, 14, 983-987, dito 989-993;
- H. Nishida et al. Chem. Pharm. Bull. 2004, 52, 406-412, dito 459-462;
- J.A. Willardsen et al. J. Med. Chem. 2004, 47, 4089-4099.

For the purpose of the present invention as disclosed and described herein, the following terms and abbreviations are defined as follows.

The term "treatment" includes the therapeutic and/or prophylactic treatment of thromboembolic disorders.

The term "direct factor Xa inhibitor" means an inhibitor that acts directly on factor Xa, independently of a cofactor (such as Antithrombin III, the cofactor of heparins). The anti-thrombotic effect is hereby attributed to the inhibition of factor Xa.

The term "thromboembolic disorders" includes in particular disorders as the acute coronary syndrome spectrum as ST Segment Elevation Myocardial Infarction (STEMI) (also known as Q-wave MI), Non ST Segment Elevation Myocardial Infarction (NSTEMI) (also known as Non Q-wave MI) and unstable angina (UA), as well as stable angina pectoris, vascular re-occlusions and restenoses after angioplasty or aorto-coronary bypass, peripheral arterial occlusion disorders, pulmonary embolisms, or deep vein thromboses, renal thrombosis, transitory ischaemic attacks and stroke, inhibition of tumor growth and development of metastasis, treatment of disseminated intravascular coagulation (DIC) and the so-called "economy class syndrome", especially in patients with risk of venous thrombosis, atherosclerotic diseases, inflammatory diseases, as rheumatic diseases of the musculoskeletal system, Alzheimer's disease, inhibition of old-age macula-degeneration, diabetic retinopathy, diabetic nephropathy and other microvascular diseases.

Included are also disorders derived from cardiogenic thromboembolism, for instance cerebral ischemic diseases, stroke, systemic embolism and ischemic attacks, especially in patients with acute, intermittent or persistent arrhythmia of the heart such as atrial fibrillation or alongside cardioversion, or in patients with valvular heart disease or artificial heart valves.

Moreover, included are also disorders derived from thromboembolic complications which can arise within patients with microangiopathic hemolytic anaemia, extracorporal circulation such as hemo-dialysis, or prosthetic heart valves as well as from thromboembolic complication, e.g. venous thromboembolism in tumor patients, in particular in patients undergoing surgical interventions, chemotherapy or radiotherapy.

Preferred is the treatment of acute coronary syndrome spectrum as ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI) and unstable angina, reocclusions after angioplasty or aortocoronary bypass, peripheral arterial occlusion disorders, pulmonary embolisms or deep vein thromboses, transitory ischaemic attacks and stroke.

Particularly preferred is the treatment of acute coronary syndrome spectrum as ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction

(NSTEMI) and unstable angina, reocclusions after angioplasty or aortocoronary bypass, pulmonary embolisms or deep vein thromboses and stroke.

The term "oral dosage forms" is used in a general sense to reference pharmaceutical products administered orally. Oral dosage forms are recognized by those skilled in the art to include such forms as liquid formulations, granules, gelcaps, hard gelatine capsules or sachets filled with granules, and tablets releasing the active compound rapidly or in a modified manner.

Tablets are preferred, in particular tablets rapidly releasing the active compound. In the context of the present invention, rapid-release tablets are in particular those which, according to the USP release method using apparatus 2 (paddle), have a Q value (30 minutes) of 75 %.

Very particularly preferred are rapid-release tablets containing 5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide as active ingredient. Preparation of such tablets is for example described in PCT/04/01289, whose disclosure is hereby included by way of reference.

The amount of active ingredient in the formulation will depend on the severity of the condition, and on the patient to be treated, as well as the compound employed. In the case of (I) as active ingredient, a dose of 1 to 100 mg, preferentially 2 to 50 mg, particularly preferred 5 to 30 mg can be applied.

The term "once daily" is well known by those skilled in the art and means administration of the drug once a day and includes the administration of one dosage form as well as administration of two or more dosage forms simultaneously or consecutively within a short time period.

In a preferred embodiment, one oral dosage form is administered once daily.

The invention is illustrated, but in no way limited, by the following example:

Experimental part (clinical trial)

Example 1

This was a dose guiding study for the direct factor Xa inhibitor (I). Objective of the study was the assessment of safety, tolerability, and efficacy of (I) at different oral doses (bid and od) compared with subcutaneously administered enoxaparin 40 mg in the prevention of venous thrombo-embolism.

642 patients were enrolled in this study and the treatment duration was 7 to 9 days.

The main inclusion criteria for the study were: men ≥18 years of age and postmenopausal women undergoing elective primary total hip replacement.

This was a prospective, randomized, open-label, active comparator controlled, multi-center and multi-national trial designed as a proof-of-principle dose-escalating study in patients undergoing elective primary total hip replacement.

Patients were consecutively to receive within each dose step either (I) or the active comparator drug, enoxaparin:

- one group receiving 2.5 mg (I) bid,
- one receiving 5 mg (I) bid,
- one receiving 10 mg (I) bid,
- one receiving 20 mg (I) bid,
- one receiving 30 mg (I) bid,
- and one receiving 30 mg (I) od.

(I) was administered orally as rapid release tablets.

The criteria for evaluation were:

a) The primary efficacy endpoint was a composite endpoint of

- Any deep vein thrombosis (DVT) (proximal and/or distal).
- Non-fatal pulmonary embolism (PE).
- Death from all causes.

The primary endpoint was evaluated 5 - 9 days after surgery. The analysis of the primary efficacy endpoint was solely based on the assessments made by the central adjudication committee which was blinded to the treatment allocation.

b) The main safety endpoint was the incidence of major bleeding events observed after the first intake of study drug and not later than 2 days after last intake of study drug. Major bleeding observed after this period was assessed separately.

The analysis of the primary safety endpoint was solely based on the classification made by the Safety Committee and Bleeding Committee which were both blinded to the treatment allocation.

Results:

The analysis of demographic data can be summarized as follows:

For subjects in the "valid for safety analysis" age ranged from 30 – 92 years, weight from 45 -150 kg, height from 145 – 195 cm, and BMI from 17.3 – 52.7 kg/m^2.

For subjects in the "valid for PP (per protocol) analysis" age ranged from 30 – 92 years, weight from 45 – 150 kg, height from 146 – 195 cm, and BMI from 17.3 – 37.7 kg/m^2.

a) Efficacy results:

An 7 – 9 -day treatment with (I) using a wide, 12-fold dose range [2.5 to 30 mg bid corresponding to total daily doses of 5 to 60 mg (I)] prevented venous thromboembolism (VTE) in adult subjects undergoing elective hip replacement compared with enoxaparin, thus confirming the proof-of-principle of (I) in this indication.

The reduction of the VTE incidence rates (primary composite endpoint comprising DVT, PE and death) by (I) was dose-dependent in the range from 2.5 to 20 mg bid with incidence rates declining from 22.2 % to 10.2 % compared with 16.8 % in the enoxaparin group. The incidence rate in the 30 mg od dose group was 15.1 % (Table 1-1).

On the basis of total daily doses the 30 mg once daily dose fits well into the dose dependance observed in the range of 2.5 to 20 mg bid, which corresponds to total daily doses of 5 to 40 mg.

Table 1-1: Incidence rate of primary efficacy endpoint and its individual components (PP population)

	Dose (I) 2.5 mg bid (N = 63)	Dose (I) 5 mg bid (N = 63)	Dose (I) 10 mg bid (N = 55)	Dose (I) 30 mg od (N = 73)
Primary efficacy, composite endpoint [n (%)]	14 (22.2 %)	15 (23.8 %)	11 (20.0 %)	11 (15.1 %)

	Dose (I) 20 mg bid (N = 59)	Dose (I) 30 mg bid (N = 46)	Enoxaparin 40 mg od (N = 107)
Primary efficacy, composite endpoint [n (%)]	6 (10.2 %)	8 (17.4 %)	18 (16.8 %)

Summary: The above data clearly demonstrate the efficacy of od administration of (I), namely fewer occurrence of composite endpoint events, i.e. fewer cases of DVT, PE or death compared to untreated conditions, and in the range of standard therapy. Furthermore, the od administration is surprisingly perfect in line with bid administration.

b) Safety results:

The number of post-operative major bleeding events increased with increasing (I) doses indicating a monotonous dose-response (table 1-2). However, it is important to note that there were neither fatal bleeds or bleeds in critical organs, nor clinically significant bleeds that could not be treated. Most bleeds adjudicated as major were related to the surgical site and no wound healing complications were reported in these subjects.

On the basis of total daily doses the 30 mg once daily dose fits very well into the dose dependence observed in the range of 2.5 to 30 mg bid which corresponds to total daily doses of 5 to 60 mg.

Table 1- 2: Incidence rates of post-operative bleeding events (safety population)				
	Dose (I) 2.5 mg bid (N = 76)	Dose (I) 5 mg bid (N = 80)	Dose (i) 10 mg bid (N = 68)	Dose (I) 30 mg od (N = 88)
Any major bleeding event [n (%)]	0 (0.0 %)	2 (2.5 %)	2 (2.9 %)	4 (4.5 %)
	Dose (I) 20 mg bid (N = 77)	Dose (I) 30 mg bid (N = 74)	Enoxaparin 40 mg od (N = 162)	
Any major bleeding event [n (%)]	5 (6.5 %)	8 (10.8 %)	0 (0.0 %) *	

* For LMWH in similar studies major bleeding rates of 1.5 – 5.3 % have been observed (Sixth ACCP Consensus Conference on Antithrombotic Therapy, Chest 2001; 119: 132S-175S).

Summary: The above data clearly demonstrate the safety of od administration of (I). The occurrence of any major bleeding events is low, approximately in the range of standard therapy and again perfectly in line with results from bid administration.

We claim

1. The use of a rapid-release tablet of the compound 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide for the manufacture of a medicament for the treatment of a thromboembolic disorder administered no more than once daily for at least five consecutive days, wherein said compound has a plasma concentration half life of 10 hours or less when orally administered to a human patient.

2. The use as claimed in Claim 1, wherein the thromboembolic disorder is ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI), unstable angina, reocclusion after angioplasty or aortocoronary bypass, pulmonary embolisms, deep vein thromboses or stroke.