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(54) Title: METHODS OF TREATMENT AND PREVENTION

(57) Abstract: Disclosed are methods for the treatment and/or prevention of thromboembolic disorders, comprising administering 4-methyl-2-oxo-2H-1-benzopyran-7-yl-5-thio-β-D-xylopyranoside in effective amounts.

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METHODS OF TREATMENT AND PREVENTION

Field of the Invention

The present invention relates to a method for treating and/or preventing
5 thromboembolic disorders, comprising administration of 4-methyl-2-oxo-2H-1-benzopyran-
7-yl-5-thio- β -D-xylopyranoside in effective amounts to a patient in need thereof.

In particular embodiment, the thromboembolic disorder is thromboses associated
with atrial fibrillation, e.g., nonvalvular atrial fibrillation ("NVAF"). In another embodiment,
the thromboembolic disorder is venous thromboses, e.g., associated with orthopedic
10 surgery such as knee or hip replacement surgery.

Background of the Invention

Many medical problems relate to thromboses. For example, atrial fibrillation
("AF"), myocardial infarction ("MI"), heart failure, surgery (especially major orthopedic
15 surgery, including knee or hip replacement surgery), valvular heart disease, coronary
artery disease, peripheral arterial occlusive disease, cerebrovascular disease, various
cancers, and diabetes are associated with thrombogenesis and/or embolism, which can
result in stroke or myocardial infarction.

In particular, patients undergoing major orthopedic surgery such as total hip
20 arthroplasty ("THA") have a high risk of developing thromboembolic complications in the
immediate post-operative period. In addition, NVAF is a common cardiac dysrhythmia,
with increased prevalence in the aging population. Subjects with NVAF are at an overall
4-5 times greater risk of ischemic stroke and thromboembolic events, with subgroups
having lower or higher risk. See Singer DE, Albers GW, Dalen JE, Go AS, Halperin JL,
25 Manning WJ. Antithrombotic Therapy in Atrial Fibrillation - The seventh ACCP Conference
on antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126:429S.

Thrombosis within the venous system is mostly related to blood stasis and
endothelial damage, leading to activation of the clotting system. Most ischemic strokes
associated with atrial fibrillation are probably due to embolism of stasis-associated thrombi
30 forming in the left atrium and particularly its appendage (see, e.g., Fuster, V. et al., 1997.
Hemostasis, thrombosis, fibrinolysis, and cardiovascular disease. Heart Disease,
Braunwald E 1809-1842. Philadelphia, PA: WB Saunders Company).

As thromboses consist of platelets, fibrin (and often erythrocytes), various
approaches have been taken for the prevention and/or treatment of thromboses, including
35 the use of antiplatelet drugs, anticoagulant drugs, and thrombolytic agents. See, e.g.,
A.D. Blann et al., *BMJ* Vol. 325, Oct 5, 2002, 762-765.

Anticoagulants are designed to inhibit or antagonize one or more aspects of the coagulation cascade, in order to ultimately inhibit the formation of fibrin. These effects may be achieved by targeting thrombin, which acts on fibrinogen and factor XIII to form fibrin and crosslinked fibrin polymer, respectively. For example, an anticoagulant may be designed to limit functional prothrombin synthesis, attenuate thrombin generation, or inhibit formed thrombin. For example, warfarin inhibits the synthesis of factors dependent on vitamin K, i.e., prothrombin, factors VII, IX and X, protein C, and protein S. Heparin binds to antithrombin III thereby inactivating thrombin IIa, factor IXa, and factor Xa (unfractionated heparin having action against XIIa, XIa, IXa, VIIa and thrombin; low molecular weight heparin ("LMWH") having action primarily against Xa). Direct thrombin inhibitors like melagatran, argatroban, and hirudin bind directly in the thrombin active site and thereby inhibit its formation.

One thrombin inhibitor that is present endogenously in the circulation is Heparin Cofactor II ("HCII"). HCII is Serpin (serine protease inhibitor) activated by glycosaminoglycans ("GAG(s)"), including heparin, heparin sulfate, and dermatan sulfate. It has been reported that HCII is capable of inhibiting both fibrin-bound and clot-bound thrombin. See, e.g., J. A. Huntington et al., *TRENDS in Pharmacological Sciences*, Vol 24, No 11, Nov 2003 589-595; G. Mascellani et al., *Thrombosis Research*. 84(1):21-32, Oct 1, 1996.

Anti-thrombotic therapy for deep vein thromboses ("DVT") prophylaxis includes primarily LMWH, with some usage of warfarin. Antithrombotic prophylaxis has been routinely indicated in patients undergoing major orthopedic surgery such as THA. It has been recommended by international guidelines (Grade 1A Recommendation) that prophylaxis with either LMWHs or adjusted-dose warfarin (international normalized ratio ["INR"] target = 2.5; range of 2.0 to 3.0) be administered for 7 to 10 days following surgery for elective hip or knee replacement.

Current treatment for the prevention of stroke in the NVAF population with one or more risk factors for stroke is oral anticoagulation, and warfarin is the current standard of care for such treatment. Numerous studies (AFASAK, BAATAF, EAFT, CAFA, SPAF I and SPINAF) have demonstrated the benefit of warfarin versus aspirin or placebo in the prevention of stroke in subjects with atrial fibrillation with one or more risk factors for stroke. These studies reported decreased mortality and a reduction in stroke, embolic event rates and death when NVAF subjects were treated with warfarin, compared to placebo or aspirin. While warfarin has been proven to be beneficial in reducing stroke and thromboembolic events, physicians face numerous challenges in managing NVAF subjects treated with warfarin. Maintaining the INR within an appropriate therapeutic

range (2.0 – 3.0) is critical for the prevention of stroke while minimizing bleeding risk and is often difficult in part due to numerous food and drug interactions. Deviations of INR outside the therapeutic range for NVAf subjects often cause the subject to be under protected for stroke or at risk for hemorrhage. Currently, there is an unmet need for an effective, oral anti-thrombotic treatment with decreased food and drug interactions and decreased monitoring compared to warfarin.

In addition, the recommended treatment for atrial fibrillation patients with a low/intermediate risk for stroke is 325 mg aspirin, once daily (according to the American College of Chest Physicians (“ACCP”) and American Heart Association (“AHA”)/European Society of Cardiology (“ESC”)/American College of Cardiology (“ACC”) guidelines).

The above and additional background relating to antithrombotic prophylaxis is provided by:

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Bergqvist D, Benoni G, Bjorgell O, et al. Low molecular weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. *New Engl J Med*, 1996;335:696-700;

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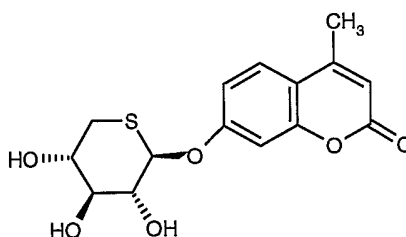
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Orally active β -D-thioxylosides have been proposed as anticoagulants. See Millet J, Theveniaux J, Brown NL. The Venous Antithrombotic Effect of LF 1351 in the rat following oral administration. *Thromb & Haemost* 1992;67:176-179; Millet J, Theveniaux J, Brown NL. The Venous Antithrombotic profile of Naroparcil in the rabbit. *Thromb & Haemost* 1994;72:874-879; Bellamy F, Horton D, Millet J, Picart F, Samreth S, Chazan JB. Glycosylated derivatives of benzophenone, benzhydrol, and benzhydryl as potential venous antithrombotic agents. *J Med Chem* 1993;36:898-903; Masson PJ, Coup D, Millet J, Brown NL. The effect of the b-D-Xyloside Naroparcil on circulating plasma glycosaminoglycans. *J Biol Chem* 1995;270:2662-2668; Lohmander S, Madsen K, Hinek A. Secretion of proteoglycans by chondrocytes. *Archives of Biochemistry and Biophysics* 1979;192:148-157; Masson P, Theveniaux J, Coup D, Grégoire T, Vaillot M, Dupouy D, Sié P, Boneu B, Millet J. Further studies on the mechanism for the antithrombotic effects of naroparcil, an orally active thioxyloside compound. *Thromb & Haemost* 1999;81:945-950; Martin NB, Masson P, Sepulchre C, Theveniaux J, Millet J, Bellamy F.

Pharmacologic and biochemical profiles of new venous antithrombotic b-D-Xyloside derivatives: Potential antiathero/thrombotic drugs. *Seminars in Thrombosis and Hemostasis* 1996;22:247-253.

The compound, 4-methyl-2-oxo-2H-1-benzopyran-7-yl-5-thio- β -D-xylopyranoside is depicted by the following chemical structure:



25

and is alternatively referred to herein as "odiparcil" or "Compound A". Odiparcil and its preparation is disclosed in U.S. Patent No. 5,169,838, issued to Samreth et al. on Dec 8, 1992. This patent discloses, inter alia, the use of the disclosed benzopyranone- β -D-thioxyloside compounds in the treatment of venous and arterial thrombosis, and treatment and prevention of diseases associated with circulatory disorders.

30

Without intending to be bound or limited by theory, the mechanism of action of odiparcil is postulated to involve an increased biosynthesis of GAGs and subsequent elevation of anti-IIa activity via HCII, leading to prevention of thrombosis. Anti-IIa activity, expressed in dermatan sulphate units, may serve as a pharmacodynamic marker of the anti-thrombotic effect of odiparcil. See, e.g., JA Huntington, Journal of Thrombosis & Haemostasis. 1(7):1535-49, Jul 2003, and Masson, PJ et al., The effect of the β -D-xyloside naroparcil on circulating plasma glycosaminoglycans, J. Biol Chem 1995; 270:2662-2668.

Odiparcil has shown efficacy when administered orally in experimental models of venous and arterial thrombosis, and limited effects on coagulation parameters and bleeding times in animals. In animal thrombosis models using odiparcil, anti-thrombotic activity has been correlated with anti thrombin (anti-IIa) activity expressed in dermatan sulphate units. Based on preclinical studies in the rabbit and rat, it is estimated that steady state, anti-IIa trough levels in the range of ≥ 0.5 ug (e.g., 0.5 to about 6, 0.5 to about 4, 0.5 to 3.5, 0.5 to 2 μ g) dermatan sulfate/mL plasma may correlate with significant benefits in treating and/or preventing thromboembolism. For example, ID₅₀s in these animal models (e.g., 0.75 – 2.2 ug/ml) provide a target anti-IIa activity for clinical development. It is especially predicted that an anti-IIa trough level of ≥ 1 ug, more especially ≥ 2 ug, dermatan sulfate/mL plasma, may correlate with significant benefits in treating and/or preventing thromboembolism. Pharmacokinetic-pharmacodynamic modeling suggests that mean trough concentrations of approximately 0.25-0.4 ug odiparcil/mL plasma may produce an anti-IIa trough level of ≥ 1 ug dermatan sulfate/mL plasma, and that mean trough concentrations of about 0.5-0.8 ug odiparcil/mL plasma may produce an anti-IIa trough level of ≥ 2 ug dermatan sulfate/mL plasma.

The specific anti-thrombotic activity of odiparcil, which is similar to the selective inhibition of thrombin observed with dermatan sulphate that also activates HCII (Ofosu FA, Modi GJ, Smith LM, et al. Heparin sulphate and dermatan sulphate inhibit the generation of thrombin activity in plasma by complementary pathways. Blood, 1984;64:742-7), may result in a reduced bleeding risk compared with vitamin K antagonists, unfractionated, low molecular weight heparins (LMWHs) and direct thrombin inhibitors, while providing anti-thrombotic efficacy.

Based on the foregoing, odiparcil may be useful in the treatment and/or prevention of thromboembolism, particularly venous thromboembolism ("VTE") such as in acute or extended prophylaxis for prevention of VTE following orthopaedic surgery (e.g., knee or hip arthroplasty), and/or thromboembolism associated with atrial fibrillation (e.g., NVAf).

The present invention relates to a method of treating and/or preventing VTE following orthopaedic surgery, comprising administering an effective amount of odiparcil to a patient in need thereof.

5 The invention also relates to a method of treating and/or preventing thromboses associated with atrial fibrillation, particularly NVAf, comprising administering an effective amount of odiparcil to a patient in need thereof.

Other aspects of the invention will be apparent to those having ordinary skill in the art.

10 Summary of the Invention

The present invention relates to a method of treating and/or preventing thromboembolic disorders, comprising administering an effective amount of odiparcil to a patient in need thereof.

15 In one aspect, the present invention relates to a method of treating and/or preventing VTE, particularly following orthopaedic surgery (e.g., knee or hip arthroplasty), comprising administering an effective amount of odiparcil to a patient in need thereof.

In one aspect, the present invention relates to a method of treating and/or preventing thromboembolism associated with atrial fibrillation, particularly NVAf, comprising administering an effective amount of odiparcil to a patient in need thereof. In 20 one embodiment, the patient is at low or intermediate risk of stroke. In another embodiment, the patient is at high risk of stroke.

In one embodiment, the odiparcil is administered in combination with aspirin or a heparin.

25 In particular embodiments, the odiparcil, and aspirin as applicable, is administered in an oral dosage form, such as tablets and/or capsules.

In particular embodiments, the odiparcil is administered in an amount of from about 125 to about 1000 mg per day. In some embodiments, the odiparcil is administered about every 12 or 24 hours. In some embodiments, the odiparcil is administered in an amount of about 250, about 375 or about 500 mg twice daily.

30 The odiparcil is administered for a period sufficient to treat and/or prevent the thromboembolic disorder. In some embodiments, the odiparcil is administered to treat acute thromboembolic disorders, e.g., for up to about 3 to 6 weeks (e.g., 1 to about 30 days, including about 8 to 12 days) following orthopaedic surgery. In some embodiments, the odiparcil is administered to treat a chronic thromboembolic disorder, e.g., for one or 35 more months or years.

Brief Description of the Drawings

Figure 1 represents 95% confidence intervals for incidence of VTE in a study of extended prophylaxis of VTE with odiparcil following THA.

Figure 2 represents box plots illustrating anti-IIa activity data in different treatment groups at baseline and trough samples in a study of extended prophylaxis of VTE with odiparcil following THA.

Figure 3 represents box plots illustrating anti-IIa activity data in different treatment groups at baseline and steady state trough samples in a study of extended prophylaxis of VTE with odiparcil following THA.

Figure 4 represents the dose-related effects of warfarin and odiparcil on thrombus formation and ex vivo pharmacodynamic indices.

Figure 5 represents the dose-related effects of warfarin and odiparcil on bleeding time and blood loss.

Figure 6 is a representative tracing demonstrating the effect of odiparcil on thrombin induced platelet aggregation.

Figure 7 represents the effect of protamine sulfate on odiparcil induced anti-thrombin and antithrombotic activity.

Detailed Description of the Invention

The present invention relates to a method of treating and/or preventing thromboembolic disorders comprising administration of an effective amount of odiparcil to a patient in need thereof.

The term "thromboembolic disorder" refers to disorders associated with inappropriate or undesired thromboses formation, resulting in undesired venous or arterial blockages or constriction of blood flow at the primary site of thrombosis and/or, in the case of embolisms, a more remote site. In the case of an embolism, the initial thrombus which is formed, fragments at least partially and the part to fragment off (embolus) is transported in the plasma where it can sometimes occlude a remote blood vessel, often resulting in serious or even fatal consequences.

In one aspect, the thromboembolic disorder is thromboses associated with atrial fibrillation, including NVAf.

In another aspect, the thromboembolic disorder is thromboses following orthopedic surgery, including VTE, such as but not limited to deep vein thrombosis ("DVT"), symptomatic VTE, and pulmonary embolism ("PE"). In particular embodiments, the surgery is total or partial hip or knee replacement surgery.

In another aspect, the present invention relates to a method of treating and/or preventing a thromboembolic disorder comprising administering a combination of odiparcil and aspirin. In a particular embodiment, the disorder is thromboses associated with atrial fibrillation, including NVAf.

5 By "administered", "administration" and the like is meant administration of a therapeutically effective dose of the active compound(s) (including in the form of corresponding pharmaceutical composition(s) thereof) to a patient in need thereof.

By "therapeutically effective dose" herein is meant a dose that produces the effects for which it is administered.

10 By "effective amount" is meant that amount of a compound (and/or corresponding pharmaceutical composition), which upon administration to a patient in need thereof provides a clinically desirable result in the treatment and/or prevention of a thromboembolic disorder. For example, an effective amount may inhibit partially or completely the formation of thromboses, including decreasing the size, weight and/or
15 occurrence of thromboses. In regard to combinations of odiparcil and another active such as described herein (including aspirin), an effective amount refers to an amount of the combined actives or their corresponding composition(s) which upon administration to a patient in need thereof provides a clinically desirable result in the treatment and/or prevention of a thromboembolic disorder.

20 "Patient" includes both mammals and other animals. Thus the methods are applicable to both human therapy and veterinary applications. In one embodiment the patient is a mammal, and in a particular embodiment the patient is a human.

The term "odiparcil" as used herein refers to the β -D-xylopyranoside and is normally provided consisting substantially of that enantiomer. In alternative embodiments,
25 the odiparcil used herein has at least 60% of the D-xylopyranoside configuration; or at least 70%; or at least 80%; or at least 90%; or at least 95%; or at least 98%; or at least 99% of that configuration. Odiparcil as referred to herein is preferred as its β -anomer. In alternative embodiments, odiparcil as used herein is at least 60% of its β -anomer; or at least 70%; or at least 80%; or at least 90%; or at least 95%; or at least 98%; or at least
30 99% of its β -anomer. Odiparcil also includes all crystalline forms of the β -D-xylopyranoside.

The term "aspirin" as used herein refers to acetyl salicylic acid. Aspirin is readily available from commercial sources, generally in oral dosage forms such as tablets, caplets, capsules, powders, and the like. For example, aspirin marketed under the brands
35 ST. JOSEPH (McNeil Consumer), ECOTRIN (GlaxoSmithKline Consumer), and ASPIRIN

REGIMEN BAYER (Bayer Healthcare), ASPIRINE UPSA (Bristol-Myers Squibb), or equivalents thereof, may be used herein.

The term "combination" as used herein in reference to co-administration of odiparcil with another active, includes fixed dose combinations wherein the particular dosage form comprises both odiparcil and the other active.

The term "combination" may also refer to the use of odiparcil and another active in separate dosage forms. In one embodiment, both actives are contained within a single packaging unit, but are in separate dosage forms. In another embodiment, the separate dosage forms are contained in separate packaging units.

For purposes of the methods of this invention, the term "combination" can refer to the administration of a dosage form comprising both odiparcil and another active. "Combination" in this regard also applies to administration of odiparcil and the other active wherein the odiparcil and other active are administered as separate dosage forms and wherein said administration may be substantially simultaneous or sequential, providing only that the combination is being administered for the treatment of a thromboembolic disorder. In one embodiment, the actives are administered in such a way that at least at some point, the odiparcil and other active are simultaneously present in the subject's plasma.

The phrase "co-therapy" (or "combination-therapy"), in defining use of odiparcil and another active, may include the following examples:

administration of each active agent in a sequential manner in a regimen to provide beneficial effects of the drug combination; and/or

co-administration of each active agent in a substantially simultaneous manner (e.g., as in a single dosage form having a fixed ratio of these active agents or in multiple, separate dosage forms for each agent, etc.).

In one embodiment of combinations and co-therapy of the present invention, odiparcil is used in combination with aspirin. In another embodiment, odiparcil is used in combination with a heparin, e.g., LMWH or unfractionated heparin.

Unless otherwise stated, the term "about" includes but is not limited to the express value which is modified by the term, e.g., "about 1" includes 1.

The odiparcil, and aspirin or other active as applicable, may be administered in the form of a pharmaceutical composition. The pharmaceutical composition may further comprise one or more inactive ingredients or additional active ingredients, e.g., pharmaceutically acceptable excipients, and the like. As used herein, the term "pharmaceutically acceptable" means a compound which is suitable for pharmaceutical use. When applicable, the odiparcil and aspirin or other active may be in the same or

separate pharmaceutical compositions. Thus the present invention encompasses a pharmaceutical composition comprising an effective amount of odiparcil and aspirin, and a pharmaceutically acceptable excipient.

5 The active(s) and composition(s) may be provided in any dosage form suitable for the desired administration route. For example, administration may be peroral, lingual, sublingual, buccal, rectal, topical, intravenous, intraarterial, intracardiac, subcutaneous, intranasal, transdermal, intramuscular, or intraperitoneal. The mode of administration, and thus the type of dosage form, may be the same or different for the odiparcil and aspirin when used in combination according to some aspects of the present invention. Examples
10 of suitable dosage forms may be tablets (including caplets), capsules, powders, elixirs, syrups, solutions, suspensions, and others such as are known in the art.

The pharmaceutical composition(s) may comprise a wide variety and percentage of excipient(s) depending upon the particular drug, drug combination and/or method of delivery contemplated. Various excipients and their use in pharmaceutical compositions
15 are described, for example, in Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (e.g., 2nd Ed., Editors A. Wade and P.J. Weller, 1994); Handbook of Pharmaceutical Additives, Gower (e.g., M. and I. Ash, 1995); and Remington, The Science and Practice of Pharmacy, Lippincott Williams & Wilkins (e.g., 20th Edition, Editor A. Gennaro et al., 2000).

20 In the case of a solid oral dosage form (such as, for example, capsules, tablets, or dry powder), the formulation may contain one or more excipients selected from starches, sugars, diluents, lubricants, disintegrants, binders, fillers, polymers (including rate-controlling polymers, swelling polymers, matrix polymers), glidants, pigments, colorants, dyes, waxes, coating agents, disintegrants, effervescent agents, floating agents, film-
25 formers, stabilizing agents, suspending agents, viscosity-increasing agents, bulking agents, vehicles, adsorbents, anti-caking agents, humectants, plasticizers, solvents, preservatives, tonicity agents, surfactants, emulsifying agents, wetting agents, flavoring agents, sweetening agents, and other excipients such as are known in the art. Those skilled in the art will recognize that an excipient may possess one or more properties, such
30 as described above.

Solid oral dosage delivery forms may be coated or uncoated, and when coated, said coating might be, for example, a non-enteric coating or an enteric coating. In one embodiment, the odiparcil solid dosage form is coated; in a further embodiment, the coating is non-enteric. In one embodiment, the aspirin solid dosage form is uncoated.

35 For administration by injection, the formulation will generally comprise a carrier which is typically a sterile aqueous solution, sometimes containing in addition to water

other ingredients such as sugars, preservatives, salts, buffers, etc. Injectable suspensions may also be prepared wherein a suspending agent is chosen along with a selected liquid vehicle carrier.

5 The pharmaceutical compositions of the invention may be prepared according to conventional pharmaceutical blending, compounding or mixing techniques. Such methods are well known in the art. For example, suitable techniques are described in Remington, The Science and Practice of Pharmacy, supra.

10 In one embodiment, the odiparcil is provided in a solid dosage form. In a particular embodiment, the odiparcil is in the form of a tablet, further comprising a swelling polymer, a matrix polymer, a floating agent, and optionally a diluent, binder, glidant, and/or lubricant (e.g., in a modified release formulation). Such a composition is suitably prepared by, in one or more steps, combining the components, blending the components together until appropriately homogeneous, and compressing the mixture into tablets. In one embodiment, the composition is prepared using a wet granulation method, such as are 15 well known in the art. For example, the odiparcil, a portion of the diluent, binder, and sufficient amounts of a granulating fluid such as water are combined, granulated, dried and milled to form granules. The granules are then combined with the remaining components and the mixture is compressed into tablets.

For example, odiparcil tablets suitably comprise from about 5 to about 60% of 20 odiparcil, based on the total weight of the tablet (unless otherwise stated, % compositions herein are based on the total weight of the composition). In particular embodiments, the composition comprises from about 30 to about 50%, especially from about 35 to about 50%, e.g., about 37 to about 48%, odiparcil. In particular embodiments, odiparcil tablets comprise about 125 to about 500 mg odiparcil (including about 125, 150, 200, 250, 375, 25 400, or 500 mg odiparcil). In some embodiments, odiparcil tablets comprise about 250, 375, or 500 mg odiparcil.

In a particular embodiment, the odiparcil tablets are elongated, i.e., oblong (e.g., in the form of caplets). Caplets tend to promote ease of taking the medication and treatment compliance, and are particularly useful for dosage units containing higher active 30 concentrations.

In one embodiment, the aspirin is microencapsulated with ethylcellulose and further comprises lactose monohydrate and glycerine behenate.

In one embodiment the method is for the treatment and/or prevention of thromboses following orthopedic surgery, including VTE (e.g., DVT, symptomatic VTE, 35 and PE). In particular embodiments, the surgery is total or partial hip or knee replacement surgery.

In another embodiment the method is for the treatment and/or prevention of thromboses associated with atrial fibrillation, particularly NVAf. In one embodiment, the method is for the prevention of stroke in atrial fibrillation.

5 In a particular embodiment the patient is one with chronic atrial fibrillation at high risk for stroke. This may include patients who have had a previous ischemic stroke, transient ischemic attack ("TIA"), or systemic embolism; patients greater than 75 years of age; patients with moderately or severely impaired left ventricular function and/or chronic heart failure; and patients with a history of hypertension or diabetes.

10 In another embodiment, the patient is one with chronic atrial fibrillation at low or intermediate risk for stroke. This may include patients: (1) ≤ 60 years of age with no heart disease; (2) ≤ 60 years of age with heart disease but no risk factors (i.e., heart failure, left ventricular ejection fraction less than 35%, diabetes, history of hypertension, and prior embolic event); or (3) ≥ 60 yrs and ≤ 75 years of age with no risk factors and no heart disease.

15 It will be appreciated that treatment includes acute treatment or prophylaxis as well as the alleviation of established symptoms (e.g., a chronic disorder).

In regard to combinations of odiparcil and aspirin or another active, the odiparcil and aspirin or other active may be administered simultaneously or sequentially. The therapeutic agents can be formulated as separate compositions that are administered at
20 the same time or sequentially at different times, or the therapeutic agents can be administered in a single composition, provided that the active agents are not incompatible with other active agents or the formulation, or otherwise undesirably combined in a single composition.

25 Thus, the present invention is not limited in the sequence of administration; the odiparcil may be administered either prior to, at the same time with or after administration of the aspirin or other active.

In one embodiment administration is sequential. For example, the monitoring physician or health care worker may find it preferable to administer one of the components followed by a set period, or followed by a period determined on the basis of some
30 determination or monitoring, and after that period administer the other component. This process may be repeated. Thus, the administration, where sequential, may occur over a number of iterations and with an order and frequency that is determined as the circumstances and judgment might dictate. When the administration is sequential, in one
35 embodiment the second drug will be administered at a time where the patient being treated still has at least some of the first drug in his or her system (e.g., in plasma).

In one embodiment, the odiparcil and aspirin are administered substantially simultaneously in part and/or sequentially in part. For example, about one half of the total daily dose of odiparcil is administered substantially simultaneously with the total daily dose of aspirin, and the other half of the total daily dose of odiparcil is administered sequentially at a different time.

The odiparcil, or odiparcil and aspirin or other active, is administered in an amount effective to treat or prevent a thromboembolic disorder. The optimal amount of a drug to be administered depends upon a particular combination and/or composition contemplated, the particular thromboembolic disorder being treated and its severity, relevant patient characteristics (sex, weight, age, general health including the presence or absence of other conditions, diet, etc), the mode of delivery (e.g., systemic vs local), the time of administration, drug interactions, etc.

In particular embodiments, from about 125 mg to about 1000 mg of odiparcil is administered per day. For example, about 125, 250, 300, 375, 400, 500, 750, 800 or 1000 mg of odiparcil are administered per day. In some embodiments, about 250, 300, 375, 400, 500, 750, or 800 to about 1000 mg of odiparcil (including but not limited to the foregoing examples) are administered daily.

For example, at least about 0.1 mg, to about 50 mg of odiparcil per kilogram patient body weight may be administered per day. In particular embodiments, at least about 1 or 2 mg, to about 5, 10, 15, 20, 25, 30 or 35 mg odiparcil per kilogram patient body weight are administered per day.

In particular embodiments, the odiparcil is administered once daily or twice daily (e.g., about every 8-16, 10-14, or 12 hours). For example, the above-mentioned daily doses are split for twice daily administration (e.g., 1000 mg per day administered as a 500 mg dose twice a day, or as two 250 mg dosage units twice a day, and the like).

In particular embodiments, each odiparcil dose is administered in 1-4 dosage units. In a particular embodiment, each dose is administered as a single dosage unit. For example, each dosage unit may comprise about 250, 375, 400, or 500 mg odiparcil.

In particular embodiments, about 250, 375, 400, or 500 mg odiparcil is administered twice daily (for a total daily dose of about 500, 750, 800 or 1000 mg).

In one embodiment, the odiparcil is administered at least once a day, including a morning dose.

In one embodiment, the odiparcil is administered in the fasted state (i.e, on an empty stomach, e.g., at least about 1 hour before eating or about 2 or more hours after eating). In another embodiment, the odiparcil is administered with food ("in the fed state"); e.g., concurrently with or shortly before or after eating a meal (e.g., within about 20-30

minutes after eating, e.g., within about 5 minutes of completing a meal). Administering odiparcil with food tends to increase its systemic exposure and the maximum plasma concentration.

5 The aspirin or other active used in combination with odiparcil is generally used in accordance with its prescribing information. For example, aspirin may be administered in an amount of from about 50 to about 325 mg per day (including but not limited to about 100 to about 100 mg per day; 50, 75, 80, 81, 100, 160, 162.5, and 325 mg/day). The total daily dose may be achieved, e.g., in one or more doses per day (e.g., 1-6 doses per day). In one embodiment, about 325 mg of aspirin are administered per day, generally as a
10 single dose. LMWH, such as enoxaparin, may for example be administered in an amount of about 30 mg BID or about 40 mg daily.

Notwithstanding the particular dosages herein, it may nevertheless be advisable to use other dosages due to a particular mode of administration, patient weight or physiological function, severity of disorder, etc. Accordingly, it might in some cases be
15 preferred to use an amount of the drug(s) which may fall outside these particular embodiments.

In one embodiment, treatment with odiparcil is preceded by an initial treatment with an anticoagulant at standard regimen, e.g., low molecular weight heparin or unfractionated heparin (e.g., tinzaparin, enoxaparin, dalteparin, ardeparin). Initial treatment with an
20 anticoagulant is suitably utilized for acute VTE (e.g., DVT) therapy, e.g., in orthopaedic surgeries. Initial treatment with anticoagulant is suitably started post-surgery, suitably once adequate hemostasis is achieved (generally within 12-24 hours). Such initial treatment may be continued as needed, for example, for about 24 hours or for several days, e.g., up to 2 or 3 weeks, including 6-10 or 7-10 days, post-surgery. In one
25 embodiment, initial treatment is started before surgery, e.g., about 9-24 hours prior.

The odiparcil, or odiparcil and aspirin or other active, is administered for a period sufficient to treat or prevent a thromboembolic disorder, including acute and extended treatment. Duration of treatment will vary depending upon the particular thromboembolic disorder being treated, the patient being treated, the treatment setting, etc. In some
30 cases, treatment might consist of a single administration.

In some embodiments, the active(s) will be administered multiple times over a period of time sufficient to meet the needs of the particular situation.

In some extended treatment regimens, the odiparcil, or odiparcil and aspirin or other active, is given regularly or fairly regularly, for the entire duration of the patients
35 need, without limit. In one embodiment, the period of treatment is for more than one year. In other embodiments, the odiparcil or odiparcil and aspirin is given regularly or fairly

regularly for a period of from about 1 to 365 days; from about 1 and 180 days; from about 1 to 120 days; from about 1 to 90 days; from about 1 to 60 days; or from about 1 to 30 days (e.g., up to about 2, 4, 5, 6, 7 or 8 weeks). Treatment for months or years may be particularly suitable for thromboembolic disorders which are typically chronic, such as those associated with atrial fibrillation. Treatment in the order of days to about 2 or 3 months may be particularly suitable for thromboembolic disorders following orthopedic surgery.

In particular embodiments the odiparcil, or odiparcil and aspirin or other active, is administered for a period of from between 6, 7, or 8 days to 10, 11, or 12 days (e.g., 6-10, 7-10 or 8-12 days). In another embodiment, odiparcil is administered for a period of from about 1 to 60 days, e.g., 1 to 30 or 35 days, or 6-12 days, after an initial treatment with anticoagulant (e.g., LMWH) (such as described herein). Such methods may be particularly useful for acute treatment and prevention of VTE (e.g., DVT).

In one embodiment of the treatment and/or prevention of thromboses following orthopedic surgery, the administration of odiparcil is initiated as soon as possible following surgery (e.g., once adequate hemostasis is achieved, generally within about 24 hours, e.g., about 12 hours or about 6 hours after surgery). In a particular embodiment administration of odiparcil is initiated no later than 12 hours following completion of surgery.

In some embodiments, the odiparcil, or odiparcil and aspirin or other active, is administered on a need to treat basis. Accordingly, under such a regimen, the active(s) may not be administered regularly, but rather may be administered according to the need of the particular individual. In such a scenario, the individual being treated might be treated once, or a number of times and the effect of the treatment monitored, measured or otherwise diagnosed, and if necessary, additional treatment undertaken as needed or desired.

EXPERIMENTAL

Example 1: Clinical study - Prevention of Venous Thromboembolism following Total Knee Replacement Surgery

A multi-center, double-blind, double dummy, randomized, dose ranging, comparator-controlled trial to assess the efficacy, safety, and tolerability of odiparcil in subjects who undergo total knee replacement ("TKR") surgery is conducted. Subjects will receive odiparcil or warfarin. The study will consist of a screening period, a 10 +/- 2 day double-blind study medication period and two (2) follow-up visits, one at 14±2 days and the second at 28±2 days after discontinuation of study medication. The treatment period

includes randomization (day 1), in-hospital days on medication, and discharged days on medication. On the first day of the treatment period, eligible subjects are randomized to study medication following surgery.

5 Following primary elective TKR, subjects will receive either 250mg, 375mg or 500mg odiparcil q12h for 10 +/- 2 days or dose adjusted warfarin for 10 +/- 2 days. Study medication should be started as soon as possible following TKR surgery, but no later than 12 hours following completion of surgery. Study medication should be taken with food, i.e, it should not be taken on an empty stomach.

10 Subjects may be male or female ≥ 35 years of age who are scheduled for primary elective unilateral total knee arthroplasty (i.e., first time the knee is being replaced on the operative side). Subjects on the study will not be taking any other antithrombotic drug therapy such as a vitamin K antagonist, heparin (standard unfractionated or low molecular weight), heparinoid, direct thrombin inhibitor, GPIIb/IIIa receptor antagonist, thrombolytic agent, dextran, aggrenox, clopidogrel, or ticlopidine. Subjects will not use compression
15 stockings or intermittent pneumatic compression.

Any subject presenting with symptoms suggestive of PE or DVT at any time prior to randomization will be objectively assessed for symptomatic VTE and may remain a candidate for randomization if VTE is ruled out.

20 Following successful total knee replacement surgery, subjects will be assessed for any occurrence of VTE, major bleeding or clinically relevant non-major bleeding. If in the opinion of the surgeon or investigator the subject experienced a VTE, major bleed or is deemed inappropriate for the study, the subject should not be randomized to the study.

25 Subjects will be assessed for VTE at screening, prior to randomization, during treatment, and at the end of the study (day 10 $\pm$ 2) or early withdrawal. Any subject who remains asymptomatic for VTE at the end of the study or at early withdrawal will receive a bilateral venogram.

Any subject who becomes symptomatic for VTE including PE during the treatment period should be objectively assessed to confirm the presence or absence of VTE. Symptoms of DVT may include but are not limited to pain or swelling in the legs, and
30 symptoms of PE may include shortness of breath or difficulty in breathing. If a VTE is confirmed then the subject should be withdrawn from the study medication. Subjects who are symptomatic and objectively confirmed by a method other than venography (including compression ultrasound ("CUS") for VTE or ventilation-perfusion ("V/Q") scan for PE, spiral computerized tomography ("CT") or some other objective method) will not receive a
35 bilateral venogram. All events will be adjudicated by an independent central adjudication committee ("ICAC").

Efficacy will be assessed by the incidence of total VTE (proximal and distal DVT, non-fatal PE and death due to VTE). This includes any asymptomatic DVT assessed by mandatory bilateral venography at the end of the study or at early withdrawal, symptomatic DVT confirmed by objective testing, or symptomatic PE confirmed by objective testing at any time during the study. Any deaths related to VTE that occur during the study or any patients withdrawn from the double-blind treatment period due to objectively confirmed symptomatic VTE will be included in the incidence.

Bilateral venography should be performed within 12 h of the last dose of oral medication according to a modification of the Rabinov and Paulin technique, requiring at least nine (9) images per leg. See Rabinov K, Paulin S. Roentgen. Diagnosis of venous thrombosis in the leg. Arch Surg 1972; 104: 134–44; Kalebo P, Anthmyr BA, Eriksson BI, Zachrisson BE. Phlebographic findings in venous thrombosis following total hip replacement. Acta Radiol 1990; 31: 259–63; Kalebo P, Ekman S, Lindbratt S, Eriksson BI, Pauli U, Zachrisson BE. Percentage of inadequate phlebograms and observer agreement in thromboprophylactic multicenter trials using standardized methodology and central assessment. Thromb Haemost 1996; 76: 893–6; and Kalebo P, Anthmyr BA, Eriksson BI, Zachrisson BE. Optimization of ascending phlebography of the leg for screening of deep vein thrombosis in thromboprophylactic trials. Acta Radiol 1997; 38: 320–6.

If a patient taking metformin will undergo venography, metformin will be stopped the day before the patient undergoes venography and may not resume until 48 hours after venography. The venography should be performed in a semiupright position (preferably 60% elevation from horizontal), using adequate volumes of contrast media (preferably 100 mL per leg), and without the use of lower limb tourniquets. Venograms will be judged adequate for evaluation if they demonstrate bilaterally complete visualization of all deep veins or if a DVT was found.

Symptomatic DVT during hospitalization or follow-up may be confirmed by ultrasound or venography.

DVT will be diagnosed by the ICAC using set criteria. DVT may be diagnosed, for example: when a constant intraluminal filling-defect is seen on at least two images. Proximal DVT is defined as DVT in or above the popliteal vein. PE is diagnosed by ventilation–perfusion (“V/Q”) scintigraphy, pulmonary angiography or spiral computerized tomography (“CT”) based on accepted criteria for diagnosis (See Biello DR, Mattar AG, McKnight RC, Siegel BA. Ventilation–perfusion studies in suspected pulmonary embolism. Am J Roentgenol 1979; 133: 1033–7).

Subjects experiencing symptoms of a PE will undergo ventilation–perfusion scintigraphy, pulmonary angiography or spiral computerized tomography (CT) of the

chest. Symptoms of PE include chest pain, dyspnea, hemoptysis, syncope, tachypnea, and a widened A-a DO₂ difference (See Tierney LM Jr, Messina LM. 2000. Blood Vessels and Lymphatics. Current Medical Diagnosis and Treatment 2000, Tierney LM Jr, McPhee SJ, Papadakis MA. p 467. New York: Lange Medical Books/McGraw Hill).

5 Subjects experiencing symptoms of DVT will undergo CUS or a venogram. If CUS findings confirm a proximal DVT, a venogram is not required, otherwise the subject will undergo bilateral venography to diagnose DVT. Symptoms of DVT include calf pain or tightness, slight edema of the involved calf, distension of the superficial venous collaterals, tenderness over the femoral and iliac veins and marked edema of the involved leg, and
10 cyanotic skin in severe obstruction (See Chestnutt MS, Prendergast TJ. 2000. Lung. Current Medical Diagnosis and Treatment 2000, Tierney LM Jr, McPhee SJ, Papadakis MA. p 264. New York: Lange Medical Books/McGraw-Hill).

All subjects without objectively confirmed VTE will undergo mandatory bilateral venography on day 10±2 or at early withdrawal from study medication.

15 All subjects will participate in a population pharmacokinetic ("PK") analysis. Blood samples (approximately 2-3 mL) will be collected for analysis as follows: day 3 (i.e. predose (i.e., 15 minutes prior to dosing administration), 2, 4, 8, 10, and 12 hours post dose), day 5 (predose) and day 10 (predose). Samples will be collected in an EDTA tube and immediately chilled in ice. Plasma will be separated by centrifugation and frozen at
20 approximately -20°C.

A pharmacodynamic ("PD") assessment will be based on anti IIa activity. In all subjects, an additional blood sample (approximately 3 mL) will be collected at the time of other blood sampling as follows: Baseline, day 3 (i.e. predose, 2, 4, 8, 10, and 12 hours post dose), day 5 (predose), and day 10 (predose) for the assessment of anti-factor IIa
25 activity. Samples will be collected in 3.8% sodium citrate tubes and immediately chilled in ice. Plasma will be centrifuged and frozen at approximately -20°C.

The pharmacodynamic response is determined by measurement of the biomarker anti-IIa to detect changes in coagulability, and the relationship between odiparcil dosage, PK, and anti IIa activity is characterized. For example, anti-IIa levels following periods of
30 treatment, and proportions of subjects having defined anti-IIa levels (e.g., at least 0.75 ug/mL, at least 2ug/mL) following periods of treatment, are assessed.

The pharmacokinetics and pharmacodynamics of odiparcil in the study can be evaluated as described herein.

35 The study medication will consist of 250mg, 375mg or 500mg odiparcil tablets and matching placebo as well as overencapsulated warfarin. Warfarin will be supplied at strengths of 1mg and 5mg, with placebo to match.

Odiparcil (250 mg) is provided as aqueous film-coated, bi-convex, modified release, round tablets. The 500 and 375 mg strength odiparcil is provided as aqueous film-coated, modified release, bi-convex caplets. Placebo tablets are provided to match the 250 mg, 375 mg and 500 mg active tablets.

- 5 The odiparcil tablets may be prepared using a wet granulation method. For example, a granulation is prepared using about 90% odiparcil, 7% microcrystalline cellulose (e.g., Avicel PH102 (NF)), 3% Povidone (e.g., Kollidon 30 (USP)), and purified water (USP) qs (purified water is used in the process and is removed by drying). The granules are prepared using a high-shear granulator (e.g., 25L T.K. Fielder) followed by
- 10 fluid bed drying (e.g., Glatt GPCG 5/9) and milling (e.g., Co-Mil). Solid materials are screened (nominal 20 mesh using vibratory sieve if necessary) and transferred to the granulator in the following order: about half the odiparcil, the Avicel PH102, the povidone K30, and the remainder of odiparcil. The mix is blended using low main impeller speed and chopper setting for about 2 minutes. Water sufficient for granulation is slowly added
- 15 and the mass is mixed to granulate (e.g., about 3 min). The granules are then dried, e.g. to a moisture content of $\leq 5\%$ (by loss at 105C), milled and screened through the mill using a nominal 039 screen and washer (spacer) size 250+200. (Using a Fitch sieve shaker, not more than 5% should be retained on a 20 mesh screen and not less than 20% should pass through a 100 mesh screen.) The milled granulation is screened through a 20 mesh
- 20 screen.

Odiparcil tablets for use in the study may be prepared, nominally according to the following compositions:

Formula	1A	1B	1C
Tablet strength:	500 mg	375 mg	250 mg
Total tablet weight (uncoated)	1060 mg	850 mg	640 mg
	%	%	%
Odiparcil Granulation	52.4	49	43.4
Sodium carboxymethylcellulose 7H3SF (Aqualon) (USP)	9	10.6	12.5
hydroxypropyl methylcellulose 2208 (Methocel K100M Premium) (USP)("hypromellose")	1.4	1.2	1.6
sodium bicarbonate (USP)	12	11.2	10
microcrystalline cellulose Avicel PH 200(NF)**	23.6	26.7	31.2
colloidal silicon dioxide Cab-O-Sil (NF)	0.8	0.7	0.7
magnesium stearate vegetable grade (NF)	0.8	0.6	0.6

5 Formula 1A:

500 mg strength odiparcil tablets may be prepared nominally as follows. The microcrystalline cellulose (Avicel PH200) and colloidal silicon dioxide are combined. This blend, and the NaCMC, Na bicarbonate, hypromellose, and magnesium stearate are separately screened through a nominal 30 mesh screen. In the following order, these components are added to a suitable blender (e.g., a PK blender): about half the granules, the NaCMC, the microcrystalline cellulose/colloidal silicon dioxide, the Na bicarbonate, and the hypromellose. The remainder of the granules are added and the mix is blended until sufficiently uniform, e.g., for 10 min at 25 RPM. The magnesium stearate is then added and blended into the mixture until sufficiently uniform, e.g., for 3 min at 25 RPM. The mixture is compressed into biconvex caplets using a suitable press with about 0.38" x 0.72" punches and dies. The caplets are coated with Opadry White YS-1-7706-G (Colorcon, West Point PA) (comprising titanium dioxide, hypromellose, PEG, polysorbate 80), in an amount of about 1.8-1.9%, based on the weight of the uncoated tablet.

Formula 1B

375 mg strength odiparcil tablets may be prepared, e.g., in a like manner as described for Formula 1A, and coated with Opadry White YS-1-7706-G, in an amount of about 2% based on the uncoated tablet weight. In a modification, the sieved components are blended in the following manner: the hypromellose, and about 10% each of the NaCMC, MCC/SiO₂, and Na bicarbonate are blended; about 50% each of the remaining NaCMC, MCC/SiO₂, and Na bicarbonate are blended in; about half the granulation, and the remainder of each of the NaCMC, MCC/SiO₂, Na bicarbonate, and granulation are blended in (all the foregoing blending steps being, e.g., about 10 minutes at 24 +/- 3 rpm); and the magnesium stearate is blended in (e.g., about 3 minutes at 24 +/- 3 rpm). The mixture is compressed into tablets using, e.g., a Stokes Tripact press with about 0.38" X 0.72" punches and dies.

Formula 1C

250 mg strength odiparcil tablets may be prepared nominally as follows. 1199 g of the microcrystalline cellulose Avicel PH200 and 27 g of the colloidal silicon dioxide are combined. 480 g NaCMC, the MCC/SiO₂ blend, 383 g Na bicarbonate, and 60 g hypromellose are separately screened through a #30 mesh screen in that order. In the following order, these components are added to a PK crossflow blender: about 833.5 g of the granules of Example 1, the NaCMC, microcrystalline cellulose/colloidal silicon dioxide, Na bicarbonate, hypromellose, and about another 833.5 g of the granulation (to total 1667 g). The mix is blended for 10 min at 25 RPM. 24 g of magnesium stearate is passed through a #30 mesh screen, added to the blender and mixed for 3 min at 25 RPM. The mixture is compressed into 640 mg round, biconvex tablets using a Stokes B2 press with 1/2" standard punches and dies. The tablets are coated with Opadry White YS-1-7706-G, in an amount of about 3% based on the uncoated tablet weight.

The comparator warfarin is provided as overencapsulated Warfarin Sodium Tablets, 1 mg and 5 mg strength. The capsules used to overencapsulate are pink, opaque, hard gelatin capsules (size DB-AA) containing a white powder and the warfarin tablet. The placebo comparator capsules visually match the active overencapsulated Warfarin Sodium Tablets and Capsules.

Warfarin will be dose adjusted to a target INR of 2 to 3 at the investigator's discretion according to their own practice and subject status. A pre-dose INR will be taken and subsequent INRs should be monitored on days 2 and 3 of treatment and then as needed (assuming the subject has not reached the target INR level and been placed on a maintenance dose by day 3) to achieve the target INR of 2-3. Subjects should be placed

on a maintenance dose of warfarin after the subject has achieved an INR within the target INR range. If the subject has not reached a maintenance dose, then further INR measurements should be taken. Subjects will then remain on the maintenance dose and have the INR checked again on day 10 of treatment or at early withdrawal.

- 5 Total VTE incidence after each dose of odiparcil and warfarin will be determined. Other analyses may include but not be limited to: relative risk of any VTE after each dose of active, trend in total VTE incidence, anti-IIa activity, and active plasma concentrations.

PK Methodology:

- 10 Plasma samples are assayed for odiparcil using a protein precipitation method followed by LC/MS/MS analysis (e.g., lower limit of quantification 5.00 ng/mL for a 50 µL aliquot plasma). The odiparcil is isolated from human plasma by protein precipitation with acetonitrile and quantified by LC/MS/MS using a Turbo IonSpray interface. Positive ion multiple reaction monitoring (MRM) is employed for the MS/MS detection of odiparcil and
15 the internal standard, odiparcil [¹³C₄].

 The following materials, methods and equipment, or suitable equivalents, are utilized.

Human plasma (EDTA as anticoagulant) - Biological Specialty Corporation (Colmar, PA)

Formic Acid, (88%)

- 20 Acetonitrile, HPLC grade

Water, HPLC grade, Milli-Q System, Millipore Co. (Bedford, MA) ("Millipore water")

Ammonium Formate (reagent grade)

Dimethyl Sulfoxide (DMSO)

Ammonium formate buffer - 0.631 g Ammonium formate dissolved in about 800 mL

- 25 Millipore water, pH adjusted to 3.0 with formic acid, final volume brought to 1 liter with water, solution filtered through a 0.20 µm Nylon 66 filter.

Rheos 4000, quaternary pumping system with degasser, (Flux Instruments AB (Karlskoga, Sweden)) is used to deliver mobile phase

3 x 100 mm, 3 µm Genesis C18 column (Jones Chromotography, Lakewood, Colorado)

- 30 preceded by a 0.5 µm pre-column filter

Perkin Elmer Series 200 autosampler (Concord, Ontario, Canada).

Mobile phase - 40/50/10 (v/v) mixture of acetonitrile, Millipore water and 10 mM ammonium formate buffer (pH 3.0); flow rate 400 µL/min, introduced into the mass spectrometer source without post column split.

- 35 API 3000 triple quadrupole mass spectrometer (Perkin Elmer Sciex Instruments (Concord, Ontario, Canada)), coupled to the HPLC via a Turbo IonSpray interface: set in positive ion

mode to select the protonated molecules $[M+H]^+$ at m/z 325 (odiparcil) and m/z 329 (internal standard) by the first quadrupole filter (Q1); these selected ions (precursor ions) are collided with nitrogen gas in the second quadrupole (collision cell, Q2) to generate product ions at m/z 177 (odiparcil) and m/z 181 (internal standard); the product ions are monitored through the third quadrupole (Q3) before being detected by the electron multiplier.

Sample Control (version 1.3, PE/Sciex) for data acquisition; MacQuan (version 1.4, PE/Sciex) for automatic data processing.

Primary Stock of odiparcil- at least 2 mg of odiparcil dissolved in DMSO to give a standard stock solution of 1.0 mg/mL.

Working Standard Solutions - Serial dilutions of odiparcil calibration and validation primary stock solutions are prepared in acetonitrile/water (50/50, v/v) to give working solution concentrations of 100 ug/mL, 10 ug/mL, 1.0 ug/mL, and 0.1 ug/mL.

Internal Standard Stock – at least 2 mg of odiparcil [$^{13}\text{C}_4$] in DMSO to give a solution of 1.0 mg/mL odiparcil [$^{13}\text{C}_4$].

Working odiparcil [$^{13}\text{C}_4$] solutions - stock solution of odiparcil [$^{13}\text{C}_4$] is diluted with acetonitrile to give a solution of 10 ug/mL, which is used to make a final solution of 250 ng/mL in acetonitrile.

PD Methodology:

The samples are assayed for dermatan sulfate concentration equivalents using a chromogenic assay technique, based on modifications of a method reported in the publication "A Simple Method to Measure Dermatan Sulfate at Sub-Microgram Concentrations in Plasma" by D. Dupouy, P. Sie, F. Dol and B. Boneu in Thrombosis and Haemostasis, 1988, 60:236-239.

Dermatan sulfate is a glycosaminoglycan found in abundance in human tissues, especially in skin, blood vessels and heart valves. Dermatan sulfate exhibits anticoagulant activity by indirectly inhibiting thrombin as it is formed in plasma. Dermatan sulfate activates heparin cofactor II (HCII), a plasma protease inhibitor which specifically inhibits thrombin but not other proteases involved in hemostasis. Plasma levels of dermatan sulfate may increase in response to the administration of odiparcil. Therefore, plasma dermatan sulfate concentration may prove to be a useful biomarker for measuring anti-thrombotic activity after administration of odiparcil.

The following materials, methods and equipment or suitable equivalents are utilized.

- Tris-HCl - Sigma Chemical Co.(Cat.# T-3253), St. Louis, MO
 Dermatan sulfate - Celsus Laboratories, Inc. (Cat.# DS-03122) Cincinnati, OH
 Bentonite - Sigma Chemical Co.(Cat.# T-3253), St. Louis, MO
 Stachrom HCII Assay Kit - American Bioproducts Co. (Cat. # 851), Parsippany, NJ
 5 Heparin Cofactor II - Haematologic Technologies, Inc.(Cat.# HCII-0190) Essex Junction, VT
 HPLC Water - Sigma Chemical Co.(Cat.# 27,073-3), St. Louis, MO
 1N NaOH - Sigma Chemical Co.(Cat.# 930-65), St. Louis, MO
 Combi-tips – Eppendorf (Brinkman), (Cat. #22-49-510-1), Westbury, NY
 10 Safe-Lock 0.5 mL centrifuge tubes - Eppendorf (Brinkman), (Cat. #22-36-361-1), Westbury, NY
 Microplate reader - Dynex technologies (MRX), Chantilly, VA.
 Titer Plate Shaker, Model 4625 - Lab-Line Instruments, Inc., Melrose Park, IL
 Multichannel pipette, pipettors – Eppendorf (Brinkman), Westbury, CT
 15 EDOS 5221 Automatic Pipetter - Eppendorf (Brinkman), Westbury, CT
 Rotating Incubator, Model 4628GM - Lab-Line Instruments, Inc., Melrose Park, IL
 Microtiter plates - Nunc (Cat.# 439454) Nalge NUNC International, Naperville, IL
 Microtiter plate covers – Becton Dickinson (Falcon 3073), Oxnard, CA
 Microcentrifuge - Jouan (Model A-14), Winchester, VA

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Reagent Preparation:

- 0.02 M Tris, pH 7.4 - 3.15 g Tris-HCl dissolved in 900 mL of deionized H₂O, pH adjusted to 7.4 with 1N NaOH, solution diluted to a final volume of 1L with deionized H₂O.
 10 % Bentonite Suspension - 10 g of Bentonite is added to 80 mL of 0.02 M Tris, pH 7.4,
 25 mixed, diluted to a final volume of 100 mL and stored at 4-8°C.
 Heparin Cofactor II, 10 ug/mL- 492 uL of HPLC water is added to a vial containing 8 uL of Heparin Cofactor II stock to give a concentration of 200 ug/mL. 50 uL of this HCII solution is added to 950 uL HPLC water and vortexed (remaining 200 ug/mL solution is stored at 4-8°C).
 30 Thrombin- 2 mL of HPLC water is added to a vial of thrombin from the Stachrom HCII kit and mixed well, to give a final concentration of 2.75 Units/mL.
 Substrate- 2 mL of HPLC water is added to a vial of Thrombin Substrate from the Stachrom HCII kit and mixed well, to give a final concentration of 1.25 umol/mL.
 Dermatan Sulfate - Dermatan sulfate is prepared to a concentration of 100 ug/mL in HPLC
 35 water.

Plasma Standards:

Normal plasma contains endogenous low levels of dermatan sulfate. In order to construct a standard curve, dermatan sulfate is added to pooled plasma (equal volumes of plasma from 4 normal volunteers) to give a concentration of 16.00 ug/mL above the endogenous level. Serial dilutions of the 16.00 ug/mL standard are prepared to yield concentrations of 8.00, 4.00, 2.00, 1.00, 0.50, 0.25 ug/mL above endogenous level. The plasma pool without addition of dermatan sulfate is used for the 0.00 ug/mL standard. The standards are dispensed in 200 uL aliquots in 0.5 mL Safe-Lock Eppendorf tubes and stored at -80°C.

Assay procedure:

The Bentonite suspension is mixed on a stir plate for 30 min at room temperature. 200 uL of each plasma sample to be analyzed is dispensed into a 0.5 mL Safe-Lock Eppendorf tube. 200 uL of Bentonite suspension is added to each sample and standard tube (thawed to room temperature). The tubes are vortexed for 15 seconds, incubated for 5 minutes at room temperature, then centrifuged at 14,000 rpm for 2 min. 25 uL of HPLC water, 25 uL of Bentonite treated plasma or standard, and 50 uL of Heparin Cofactor II is added in that order to appropriate wells in the microtiter plate. Standards and samples are assayed in duplicate. The plate is covered, mixed for 15 – 30 seconds on the Titer-Tek rotator at 500 rpm at room temperature, then incubated for 10 min. at 150 rpm at 37°C using the Rotating Incubator. 25 uL of Thrombin is added per well. The plate is covered, mixed and incubated for 10 min. at 150 rpm at 37°C using the Rotating Incubator. 50 uL of substrate is added per well, then the plate is incubated at room temperature for 20-30 min. The plate is read using the DS-EP.asy program on the plate reader with the absorbance measured at 405 nm.

Using Revelation software version 3.04 in the microplate reader, the standard curve values are plotted using a sigmoidal fit. Sample values are obtained by software analysis and interpolation from the standard curve.

Example 2: Clinical study – Odiparcil + aspirin vs Placebo + aspirin in NVAF

A randomized, double-blind, double dummy, parallel group, placebo controlled, multi-center dose ranging study is conducted to assess the pharmacokinetics, pharmacodynamics (as defined by anti-IIa activity), safety and tolerability of odiparcil in non-valvular atrial fibrillation patients at a low/intermediate risk for stroke. Eligible patients are randomized to receive either odiparcil (250 mg, 375 mg or 500 mg) or placebo twice daily for 16 weeks in addition to aspirin, 325 mg once daily also for 16 weeks.

The PD response is determined by measurement of the biomarker anti-IIa to detect changes in coaguability, and the relationship between odiparcil dosage, PK, and anti IIa activity is characterized. For example, anti-IIa levels following periods of treatment, and proportions of subjects having defined anti-IIa levels (e.g., at least 0.75 ug/mL, at least 2ug/mL) following periods of treatment, are assessed.

Pharmacokinetic parameters are evaluated and correlated to safety and efficacy endpoints.

Incidence of ischemic stroke, transient ischemic attack (TIA) and systemic embolism over the course of the study is determined.

The study consists of a one week screening period, a 16 week treatment period and a 30 day follow-up period.

Study subjects are those who have a diagnosis of chronic non valvular atrial fibrillation with a low or intermediate risk for stroke within 6 months of the screening visit confirmed by either electrocardiogram (ECG) or telemetry (Subjects diagnosed with paroxysmal atrial fibrillation (AF), persistent AF or permanent AF may participate. Subjects with atrial flutter are excluded. The study excludes subjects with NVA secondary to other reversible disorders such as thyrotoxicosis.).

A subject is considered at a low or intermediate risk for stroke if one of the following applies:

Subject ≤ 60 years of age with no heart disease;
Subject < 60 years of age with heart disease but no risk factors (defined as: heart failure, left ventricular ejection fraction less than 35%, diabetes, history of hypertension and prior embolic event);
Subject ≥ 60 yrs and ≤ 75 years of age with no risk factors and no heart disease.

Subjects should not have had previous myocardial infarction, stroke (ischemic or hemorrhagic), TIA or other cardiovascular event, mechanical prosthetic valve or rheumatic valvular disease, history of hypertension (defined as medical treatment for the disease within the past year), diabetes (defined as medical treatment for the disease within the past year) or prior embolic event. Also, subjects are those not having LVEF less than 35%, and not requiring treatment with Class III anti-arrhythmic drugs.

Subjects are not receiving during the study any other anti-thrombotic drug therapy including vitamin K antagonist, heparin (standard unfractionated or low molecular weight), heparinoid, direct thrombin inhibitor, GPIIb/IIIa receptor antagonist, thrombolytic agent, intravenous dextran and clopidigrel; amiodarone; dofetilide; or a calcium channel blocker.

Blood samples (2 mL) for the assessment of population pharmacokinetics are collected from all subjects. The PK blood samples are collected into tubes containing

EDTA and immediately chilled in ice. Plasma is separated by centrifugation (preferably refrigerated)(e.g., 3000 rpm for approximately 10 minutes at 4°C) within 30 minutes following the blood draw. Plasma is then transferred immediately to appropriate specimen containers and frozen at approximately -20°C until time of drug analysis. Plasma samples may be analyzed for odiparcil in accordance with the methodology described herein.

Blood samples (approximately 3 mL) for evaluation of anti-IIa via HCII are collected into 3.8% sodium citrate tubes. Plasma is separated, packaged and stored as for the PK samples. The plasma samples are assayed for anti-IIa activity via chromogenic techniques in accordance with the methodology described herein.

A PD sample is collected just before the first morning dose at the beginning of the treatment period. PK and PD samples are obtained during the treatment period at week 1 (just before morning dose and 0.5-3 hrs after that dose); week 3 (7-12 hrs after the morning dose); week 4 and 8 (just before the morning dose); and week 16 (just before the morning dose and 4-6 hrs after that dose).

Odiparcil tablets/caplets and matching placebo are supplied and may be prepared using methods and nominally as described in Example 1. Open label 325 mg aspirin is provided in commercially packaged containers. Aspirin may be Aspirine UPSA, 325 mg available from Bristol-Myers Squibb.

The subjects are randomized in a 1:1:1:1 ratio to receive either:

Odiparcil 250 mg bid, po and aspirin 325 mg qd, po;
Odiparcil 375 mg bid, po and aspirin 325 mg qd, po;
Odiparcil 500 mg bid, po and aspirin 325 mg qd, po; or
Placebo bid, po and aspirin 325 mg qd, po.

In addition to the aspirin and active odiparcil, subjects receive matching placebo for the other two odiparcil dose levels. Subjects are instructed to self dose with the assigned odiparcil product twice a day, with food, with approximately 12 hours between doses, and aspirin 325 mg once daily, for a total of 16 weeks.

The pharmacokinetics and pharmacodynamics of odiparcil in the study can be evaluated as described in Example 1.

Example 3 – Extended prophylaxis of thromboembolism with odiparcil

A study was conducted to assess the efficacy, safety and tolerability of extended prophylaxis of thromboembolism with odiparcil. The study involved 28 days of extended prophylaxis with odiparcil, in patients (male or female ≥ 35 years of age) who had undergone primary elective unilateral THA (i.e., first time the hip is being replaced on the operative side) followed by 7-10 days of low molecular weight heparin (LMWH)

prophylaxis prior to initiation of odiparcil treatment. Following LMWH prophylaxis, eligible subjects were randomized to odiparcil 125 mg twice daily (BID), odiparcil 500 mg BID, or matching placebo. The study was a 28-day, multicenter, double-blind, placebo-controlled, adaptive dose-response trial.

5 Following THA, subjects received 7-10 days of LMWH prophylaxis during a run-in period. The LMWH therapy was initiated as soon as adequate hemostasis was achieved following the THA, generally within 24 hours, depending on local practice. Subjects who had undergone primary elective THA, received 7-10 days of LMWH prophylaxis, and had no symptomatic evidence of VTE were eligible for randomization to receive one of the
10 three treatment arms (odiparcil 125 mg BID, odiparcil 500 mg BID, or matching placebo) for 28 days.

The odiparcil was administered as a No. 0 opaque-white (white #9) capsule containing 125 mg or 250 mg of uniform, white to off-white granules of odiparcil. Placebo capsules were matched for weight, shape and color, comprising uniform white to off-white
15 granules.

The granules were prepared using a high-shear granulator followed by fluid bed drying and milling nominally according to the following composition:

	125 mg odiparcil unit dose (mg)	250 mg odiparcil unit dose (mg)	Placebo (mg)	
	%w/w target	%w/w target	%w/w target	Function
odiparcil	45	90	0	Active
Microcrystalline cellulose (Avicel PH102)	52	7	97	Diluent
Povidone K30	3	3	3	Binder
Water	Qs*	Qs*	Qs*	Granulating liquid

* purified water removed by drying.

20

The granules were blended with magnesium stearate (lubricant; passed through a nominal 20-40 mesh screen using a vibratory sieve if required to de-aggregate), e.g., for 3 minutes at 24.4 RPM, or sufficient speed and/or time to achieve 60 +/- 10 revolutions, and filled into capsules according to the following target formulations:

25

	125 mg odiparcil unit dose (mg)	250 mg odiparcil unit dose (mg)	Placebo (mg)
Corresponding granules	277.8	277.8	325.7
Magnesium stearate	2.8	2.8	3.3
Total weight unit dose	280.6	280.6	329

Two bottles of medication were dispensed to provide 31 days of twice-daily study medication, which was sufficient for 28 days of double-blind treatment. Subjects were assigned to take one capsule from each bottle twice daily on an empty stomach,

5 according to the following regimen:

Regimen	Bottle 1	Bottle 2
odiparcil 125 mg BID	125 mg	Placebo
odiparcil 500 mg BID	250 mg	250 mg
Placebo BID	Placebo	Placebo

226 subjects were randomized to a treatment group and took at least one dose of study medication (79 to the placebo group, 72 to the odiparcil 125 mg BID group, and 75

10 to the odiparcil 500 mg BID group). The majority of the randomized subjects (198) completed the study (i.e., received study medication for 28 +/- 3 days) (70 in the placebo group, 60 in the odiparcil 125 mg BID group, and 68 in the odiparcil 500 mg BID group).

Subject demographics and baseline characteristics were comparable among the three treatment groups (54.4% men, mean age 66 years, mean body mass index ("BMI" =

15 $\text{weight}/(\text{height}/100)^2$ at screening) = 29.0 kg/m²), predominantly Caucasian). The three treatment groups were well balanced with respect to the types of surgery (cemented (69%), hybrid, or uncemented) and anesthesia (general (54.4%) vs regional) used for THA.

All of the randomized subjects had received some form of medication prior to their

20 enrollment into the study. Anti-thrombotic agents, other than LMWHs, were the most frequently reported class of prior medications (LMWH experience was not collected as a prior medication).

The proportion of randomized subjects who received concomitant medication during the on-therapy period was comparable among the three treatment groups: 78, 71, and 73 subjects in the placebo, odiparcil 125 mg BID, and odiparcil 500 mg BID groups, respectively. The most frequently reported concomitant medications were multiple
5 ingredient analgesics, paracetamol, and multiple ingredient vitamins.

36 subjects had anti-thrombotic agents listed as concomitant medications during the on-therapy period: 12, 13, and 11 subjects in the placebo, odiparcil 125 mg BID, and odiparcil 500 mg BID groups, respectively. 24 of these subjects took acetylsalicylic acid. Subjects who used an oral form of acetylsalicylic acid for more than seven consecutive
10 days were excluded from the efficacy evaluation. For all but two of the subjects who received concomitant anti-thrombotic agents other than acetylsalicylic acid, the agent was either 1) started (first dose administered) on the last day of the on-therapy period, or 2) stopped (last dose administered) on the first day of the on-therapy period (the two subjects were not included in the efficacy evaluable population).

15 Over 94% of the randomized subjects were considered compliant (took $\geq 80\%$ and $< 120\%$ of the study medication) while participating in the double-blind phase of the study. The proportion of subjects who were not in compliance (took $< 80\%$ or $\geq 120\%$ of study medication) was similar across all treatment groups. Non-compliant subjects were excluded from the efficacy evaluable analysis.

20 Subjects were assessed at Days 1, 3 (± 1 day), 5 (± 1 day), 7 (± 1 day), 10 (± 1 day), 14 (± 2 days), 21 (± 2 days), and 28 (± 3 days) and at a follow-up visit 14 (± 2) days post-therapy. The primary efficacy endpoint was the incidence of venous thromboembolism (VTE) events during the 28 (± 3)-day treatment period. Secondary endpoints were the incidences of the types of VTE (DVT, symptomatic VTE, PE), and
25 anti-IIa activity via heparin cofactor II.

The baseline value for any parameter, other than laboratory parameters, was the most recent measurement taken just prior to taking the first dose of double-blind study medication. The baseline visit occurred on the last day of the subject's 7-10 days of LMWH prophylaxis following THA. For any parameter that was not assessed at the
30 baseline visit (e.g., height, weight), the last available assessment at the study screening visit was considered as the baseline value. For each subject and for each laboratory parameter the endpoint value was defined as the last non-missing value in the on-therapy period.

Efficacy analysis was based on adjudication of VTE events by an independent
35 central adjudication committee (ICAC). The ICAC adjudicated mandatory venography, reviewed and adjudicated the clinical and diagnostic investigations associated with the

evaluation of reported, suspected symptomatic DVT and/or PE outcome events, and reviewed and classified the cause of any reported deaths. If an investigator recorded a VTE event that was not adjudicated as a VTE event by the ICAC, it was not counted as a VTE event.

5 All efficacy data was analyzed descriptively. The VTE event rates for each treatment group were described as 95% confidence intervals around the proportion of events. Pairwise comparisons of odiparcil against placebo were analyzed as 95% confidence intervals around the relative risk. The relative risks were calculated for each odiparcil treatment group as the percentage of subjects in the odiparcil group with a VTE
10 divided by the percentage in the placebo group.

VTE data was analyzed using the evaluable population. The anti-IIa data was analyzed using the intent-to-treat population (i.e., subjects who had at least one dose of study medication).

Incidence of VTE events during the 28 (± 3)-day treatment period included
15 asymptomatic DVT assessed by bilateral venography on Day 28 or at early withdrawal (if applicable), symptomatic DVT confirmed by compression ultrasound or venography, or symptomatic PE confirmed by perfusion/ventilation scanning (VQ scanning), pulmonary angiography, or spiral computed tomography (CT) of the chest.

Assessments for symptomatic VTE were performed at baseline and at Days 7, 14,
20 21, and 28 (or early withdrawal). Bilateral venography was performed at Day 28 or early withdrawal; venography was not required for subjects with objectively confirmed symptomatic PE or symptomatic DVT.

Symptomatic deep vein thrombosis: Subjects experiencing symptoms of DVT were required to undergo CUS or a venogram. If CUS findings confirmed a proximal DVT,
25 a venogram was not required, otherwise the subject underwent bilateral venography to diagnose DVT. Symptoms of DVT included calf pain or tightness, slight edema of the involved calf, distension of the superficial venous collaterals, tenderness over the femoral and iliac veins and marked edema of the involved leg, and cyanotic skin in severe obstruction (Tierney LM Jr, Messina LM. Blood Vessels and Lymphatics. Current Medical
30 Diagnosis and Treatment 2000, Tierney LM Jr, McPhee SJ, Papadakis MA. New York: Lange Medical Books/McGraw Hill, 2000:467).

Asymptomatic deep vein thrombosis: All subjects without objectively confirmed VTE were required to undergo mandatory bilateral venography on Day 28 or at early withdrawal from study medication. If a DVT was objectively confirmed, study medication
35 was discontinued and treatment initiated according to local practice.

Pulmonary embolism: Subjects experiencing symptoms of a PE underwent a ventilation/perfusion scan (V/Q scan) or spiral CT of the chest. Symptoms of PE included chest pain, dyspnea, hemoptysis, syncope, tachypnea, and a widened alveolar-arterial difference in oxygen (A-a DO₂ difference). In subjects who had a non-high probability V/Q scan or normal findings on spiral CT, further testing was to be performed using CUS. If CUS did not confirm a proximal DVT, then serial CUS, venography, or pulmonary angiography was to be performed. Positive findings were considered diagnostic for PE; negative findings were considered to exclude PE. If a suspected PE was objectively confirmed, study medication was discontinued and treatment initiated according to local practice.

A subject was considered to have experienced a VTE if the VTE event occurred at any time following the first dose of study medication through the Day 28 visit.

Any subject who entered the study and received one dose of study medication but did not, for any reason, complete the 28 ($\pm$ 3)-day treatment period was considered a withdrawal. Any such subjects with objectively confirmed VTE as the cause of withdrawal were included in the efficacy analyses.

135 subjects (54, 38, and 43 subjects in the placebo, odiparcil 125 mg BID, and odiparcil 500 mg BID treatment groups, respectively) were efficacy evaluable and were included in the primary efficacy analysis.

The incidence of VTEs was highest in the placebo group, and showed a tendency to decrease in the odiparcil treatment groups. The relative risk ratio decreased in subjects on odiparcil therapy. No formal statistical comparison among the treatment groups was made (because of the small sample size coupled with the low event rate, the observed percentages would have been very different if one more or less event had been observed in any given dose group; the results of a formal statistical analysis would be overly sensitive to any change in the data). See Table 1 and Figure 1.

Table 1: Incidence of Venous Thromboembolism (VTE) in the Efficacy Evaluable Population

Treatment Group	Total Subjects	Incidence of VTE			Relative Risk for VTE	
		Total VTEs	Percent VTE	95% CI for % VTE	Relative Risk	95% CI
Placebo	54	4	7.41	(2.06 , 17.89)		
odiparcil 125 mg BID	38	2	5.26	(0.64 , 17.75)	0.71	(0.14 , 3.68)
odiparcil 500 mg BID	43	1	2.33	(0.06 , 12.29)	0.31	(0.04 , 2.71)

Abbreviations: CI = confidence interval.

Note: The efficacy evaluable population is defined as only those subjects who took at least one dose of study medication, did not violate the protocol, and had an evaluable venogram following 28 +/- 3 days of treatment. In addition, subjects who were withdrawn from the study with an adjudicated diagnosis of symptomatic VTE were included in the evaluable population.

Secondary analyses of the adjudicated incidences of DVT, proximal DVT, symptomatic VTE, and PE were conducted on the evaluable population. Secondary endpoints are summarized descriptively by treatment group in Table 2. Any deaths due to a VTE, symptomatic DVTs, PEs, and asymptomatic DVTs were all analyzed as the percentage of subjects experiencing the event by treatment group. The percentage of subjects who had either a symptomatic DVT or PE were tabulated by treatment group as having a symptomatic VTE. Because of the low overall incidence of VTEs, clinical interpretations of this descriptive analysis were not feasible.

Table 2: Incidence of Venous Thromboembolism (VTE), Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE) and Death Due To VTE in the Efficacy Evaluable Population

	Placebo	odiparcil 125 mg BID	odiparcil 500 mg BID
Type of VTE, n (%)	n = 54	n = 38	n = 43
Total VTE	4 (7.41)	2 (5.26)	1 (2.33)
Asymptomatic DVT:	3 (5.56)	2 (5.26)	0
Non-proximal	2 (3.70)	0	0
Proximal	1 (1.85)	2 (5.26)	0
Symptomatic DVT:	1 (1.85)	0	1 (2.33)
Non-proximal	1 (1.85)	0	1 (2.33)
Proximal	1 (1.85)	0	0
PE	0	0	0
Death Associated with VTE	0	0	0
Symptomatic VTE	1 (1.85)	0	1 (2.33)

5 Anti-IIa activity was measured as a possible surrogate marker for efficacy. For the assessment of anti-IIa activity, blood was collected at baseline and on Days 5, 7, 14, and 21 (approximately 3 mL in 3.8% sodium citrate tubes, which was centrifuged, and stored until analyzed).

10 The samples obtained on Days 14 and 21 were trough samples (i.e., taken prior to the medication). Figures 2 and 3 are box plots illustrating the distribution of data in each treatment group for baseline and these trough samples (In Figure 2: If the value was less than the lower limit of quantitation (LOQ = 0.25 µg/mL) then the value of 0.125 was imputed. The bottom and top edges of the box are 25th and 75th percentiles intersected by the median. The vertical line stretches from either side of the box to the 10th and 90th percentiles.)

15 The Days 5 and 7 samples were mixed samples (i.e., they could have been trough or peak samples).

20 Odiparcil elicited an increase in anti-IIa activity that appeared to be proportional to dose. Anti-IIa activity was detected in both odiparcil treatment groups at all visits (days 5, 7, 14 and 21), but was markedly elevated in the higher, 500 mg BID group. The median anti-IIa activity was 0.41 and 0.42 µg/mL at Days 14 and 21, respectively in the odiparcil

125 mg bid group and 3.52 and 3.64 µg/mL at Days 14 and 21, respectively in the odiparcil 500 mg bid group. Two subjects in the odiparcil 125 mg bid group experienced asymptomatic VTE at Day 21, having an anti-IIa activity of 0.32 and 2.14 µg/mL. One subject in the odiparcil 500 mg bid group experienced symptomatic VTE on Day 2; the anti-IIa activity was not determined.

Elevated anti-IIa activity was also demonstrated for both odiparcil treatment groups on Days 5 and 7. The tendency for higher values on Days 5 and 7 compared with Days 14 and 21 (trough samples) appears to be due to the difference in sampling.

As shown in Table 3, over 75% of subjects in the odiparcil 500 mg BID treatment group had steady state anti-IIa activity levels above 2 µg/mL at the Day 14 and Day 21 visits. These levels of anti-IIa activity have been shown to correspond to a therapeutic International Normalization Ratio (INR) in a rat model of venous thrombosis (see Example 4). Less than 7% of subjects in the odiparcil 125 mg BID achieved anti-IIa activity levels above 2 µg/mL at the Day 14 and Day 21 visits. See also Figure 3 (in which P= placebo, L= "low" dose 125 mg bid, and H= "high" dose 500 mg bid).

Table 3: Number and Percentage of Subjects with Anti-IIa Activity Greater Than 2 Micrograms per Milliliter

	Placebo	odiparcil 125 mg BID	odiparcil 500 mg BID
Visit	n/n (%) ¹	n/n (%) ¹	n/n (%) ¹
Baseline	0/ 77	0/ 69	0/ 71
Day 14	0/ 73	4/ 59 (6.78)	52/ 68 (76.47)
Day 21	0/ 68	3/ 56 (5.36)	49/ 64 (76.56)

n/n = Number of subjects with activity >2 µg/mL /number of subjects with nonmissing results.

Example 4 - Comparison of odiparcil to warfarin in a rat model of venous thrombosis, and other characterizations of odiparcil

The antithrombotic and bleeding profile of odiparcil was compared to warfarin in a rat model of venous thrombosis. Additionally, the ex vivo antithrombin and antiplatelet activity of odiparcil, and the potential of protamine sulphate to function as an antidote to odiparcil, were assessed.

Materials: Bentonite, H₂O₂, protamine sulfate, Adenosine diphosphate (ADP), Thrombin, and 3,3',5,5' tetramethylbenzidine were purchased from Sigma-Aldrich (St. Louis, MO), Heparin cofactor II from Haematologic Technologies (Essex Junction, VT), CBS61.50 from American Bioproducts (Parsippany, NJ), SpectrozymeTH from
5 Centerchem (Norwalk, CT), dermatan sulfate from Celsus Laboratories (Cincinnati, OH), Collagen reagent (equine tendon) from Helena Laboratories (Beaumont TX), odiparcil supplied by GlaxoSmithKline.

Deep Vein Thrombosis Model: The thrombotic stimulus in this model is through the mechanical restriction of blood flow, coupled with induced endothelial lesions in the
10 inferior vena cava brought on by the transient exposure to hypotonic saline. This model has been shown to result in thrombus formation which was sensitive to anticoagulants (and a more limited sensitivity to antiplatelet agents). See Millet J, Theveniaux J, Pascal M. A new experimental model of venous thrombosis in rats involving partial stasis and slight endothelium alterations. *Thromb Res* 1987;45:123-133; Feuerstein GZ, Toomey JR,
15 Valocik R, Koster P, Patel A, Blackburn MN. An inhibitory anti-factor IX antibody effectively reduces thrombus formation in a rat model of venous thrombosis. *Thromb & Haemost* 1999;82:1443-1445).

Both odiparcil and warfarin were administered prior to the thrombotic challenge, warfarin daily over 4 days, and odiparcil 3 hours prior to the challenge. The antithrombotic
20 activity of odiparcil had been shown previously to peak 2-4 hours following a single oral dose (not shown).

Male Sprague-Dawley rats (350-400 g) were anaesthetised with sodium pentobarbital (50 mg/kg, i.p.). The trachea was surgically exposed and an endotracheal tube (PE tubing 240) was inserted. The left carotid artery was cannulated for withdrawal
25 of blood samples at the end of the experiment. Blood was centrifuged at 3000 rpm for 10 minutes to obtain plasma for quantification of dermatan sulphate-like GAGs. For thrombus formation, a ventral midline incision was made and the descending vena cava was exposed and separated from the descending aorta. A suture was placed under the vena cava just distal to the renal veins and the vessel was tied against a 26g needle. The
30 vessel was then clamped with a non-serrated clamp just proximal to the iliac veins. The section of vena cava between the ligature and the clamp formed a "vena cava (venous) sac". Thrombus formation was induced by injecting 2.0 ml hypotonic saline (0.25%) into the venous sac using a second 26g needle attached to a syringe via PE20 tubing. After saline injection, the distal clamp was released and the 26g needle was removed from the
35 proximal ligature (time 0). The remaining suture restricts the vena cava to a 26g (opening) non-occlusive stenosis. The experiment continued for 60 minutes, after which blood

samples were collected, the animal was sacrificed, and the thrombus excised and its weight determined. A total of 8 rats were included in each arm of the study.

In vivo assessment of protamine sulfate ("PS") antidote potential: The venous thrombosis procedure utilized for this assessment was as described above, with the following modifications. For intravenous administration of PS, the right jugular vein was cannulated with a 22GA intravenous catheter (Becton, Dickinson, UT). PS infusion began 5 minutes prior to thrombus induction and continued for a total of 60 minutes (see dosing regimen for details).

Formulation & Dosing Regimen: Odiparcil was prepared as a suspension in 0.5% carboxymethylcellulose (15 mg/ml stock concentration), and administered by oral gavage 3 hours prior to thrombus induction. The dose groups were as follows: vehicle, 1.9 mg/kg, 3.8 mg/kg, 7.5 mg/kg, 15.0 mg/kg and 30 mg/kg (bleeding study only). For the in vivo protamine sulphate study, only a single dose of odiparcil (15 mg/kg) was administered. Protamine sulphate was prepared in saline and infused as a 1.0 mg/kg bolus (over 5 minutes) + 1.0 mg/kg infusion (over 55 minutes).

Warfarin (Aldrich; Milwaukee, WI) was prepared in 0.2 M NaHCO₃ (1mg/ml stock concentration). Warfarin administration was initiated by oral gavage 72 hours prior to the start of the study, followed by subsequent dosing at 24 hour intervals. The last dose was administered 1 hour prior to thrombus induction. The dose groups were as follows: vehicle, 0.06 mg/kg, 0.2 mg/kg and 0.6 mg/kg/day.

Bleeding Time Model: A rat tail transection model was used to assess hemostasis effects. This model has been shown to be sensitive to the effects of anticoagulants as well as antiplatelet agents. See, Dejana E, Villa S, de Gaetano G. Bleeding time in rats: A comparison of different experimental conditions. *Thromb & Haemost* 1982;48:108-111.

In a separate cohort of animals, bleeding was induced by tail transection of the anesthetized rat with a size 21 disposable scalpel blade 5mm from the tail tip. The bleeding tail was immediately placed in 1.0 liter of saline (37°C) where blood was collected. Bleeding was monitored visually until blood flow stopped for a complete 15 second interval, or if bleeding did not stop, for a maximum of 30 minutes. After recording the time to stop bleeding, the liter of saline plus collected blood was mixed. The samples were collected and frozen (-20°C) for blood volume/hemoglobin analysis.

Hemoglobin Analysis (Blood Loss): To quantitate and compare blood loss in the bleeding time experiments, the samples were assessed for hemoglobin content using a colorimetric hemoglobin detection assay. Determination of hemoglobin concentration was based upon the catalytic action of hemoglobin on the oxidation of 3,3',5,5'-tetramethylbenzidine (TMB) by hydrogen peroxide (H₂O₂). The rate of color formation in

this assay is proportional to the hemoglobin concentration and is detectable at wavelength of 600 nm. 3 μ L of each sample was added to 122 μ L TMB and 125 μ L H_2O_2 . Optical density readings were recorded 15 minutes after H_2O_2 addition. O.D.s derived from samples were compared to similarly prepared standards from known volumes of pooled rat blood and total blood loss per rat was calculated.

Coagulation tests: Blood samples withdrawn via the cannulated left carotid artery at the end of the stenosis period were collected in 2 ml vacutainer tubes containing 3.8% sodium citrate, mixed gently, and then centrifuged at 3000 rpm for 10 minutes at room temperature to separate plasma. Coagulation tests were then performed using the Dade Behring BCS Coagulation System (Newark, DE).

For measurement of the prothrombin time (PT), 50 μ L of plasma was combined with 100 μ L of Thromboplastin C Plus, and clotting monitored by absorbance at 570 nm to obtain time to clot formation.

International normalized ratio's (INRs) were determined according to manufacturer instructions using the following equation:

$$INR = R^{ISI}$$

Where R is the patient PT/normal PT, and where the ISI is the International Sensitivity Index of the reagent. For human warfarin therapy, the target INR range is between 2.0-3.0.

Platelet aggregation: Rats were administered 15 mg/kg odiparcil or vehicle by oral gavage four hours prior to blood withdrawal. Blood was drawn into 3.8% citrated vacutainers (9 parts blood: 1 part citrate) via a carotid artery cannula and centrifuged at 2000 rpm for 4 minutes to obtain platelet rich plasma (PRP). PRP was removed and pooled from all rats in the same treatment group. The remaining sample was then centrifuged at 3000 rpm for 10 minutes to obtain platelet poor plasma (PPP). A platelet count was obtained and adjusted to 200,000/ μ L by dilution with PPP (n=4/group/day). Measurement of platelet aggregation was determined using Chronolog platelet aggregometers (Chronolog Corp, Havertown, PA). All experiments were performed in duplicate under shear conditions (1000 rpm) at 37°C. Test concentrations included: 2-6 μ g/ml collagen, 1-10 μ M ADP, and 1-3 units/ml thrombin. Aggregation was measured as percent change in optical transmission where platelet-poor plasma (PPP) represents 100% transmission and untreated PRP represents 0% transmission.

Plasma dermatan sulfate assay: The assay is a modification of Dupouy D, Sié P, Dol F, Boneu B. A simple method to measure dermatan sulfate at sub-microgram concentrations in plasma. *Thromb & Haemost* 1988;60:236-239. An HCl assay kit (Diagnostica Stago, Parsippany, NJ) was used to determine the concentration of

dermatan sulfate-like GAGs in plasma samples obtained in the odiparcil venous thrombosis study. This assay was configured to detect HCII mediated thrombin inhibition as a function of dermatan sulfate concentration. A standard curve was prepared by spiking pooled rat plasma with purified dermatan sulfate (0-100ug/ml). This was added in equal volume to a 10% bentonite suspension prepared in 0.02 M Tris, pH 7.4. The bentonite step was used to defibrinate the plasma and remove endogenous antithrombin III (ATIII) and HCII. The combination was vortexed, incubated for 5 minutes at room temperature, and then centrifuged for 2 minutes at 14,000 rpm. After centrifugation, the plasma supernatant was removed and assessed for HCII-dependent antithrombin activity according to the manufacturer's instructions. In a 96 well plate, plasma supernatant was combined with 0.5 ug of HCII, mixed and incubated for 10 minutes at 37°C, followed by an additional 10 minute incubation with thrombin (0.1unit), and then finally residual thrombin activity detected using a thrombin specific chromogenic substrate (CBS61.50 – 0.36 mM) with an O.D. read-out at 405 nm. The standard curve was prepared by plotting the observed O.D. values (thrombin activity) as a function of the dermatan sulfate concentration and the data fit using a four parameter logistic regression model.

For odiparcil study samples, an identical protocol was followed with the exception that no dermatan sulfate was added to the plasma samples. The HCII mediated anti-IIa activity (residual thrombin activity - O.D. 405) of odiparcil or vehicle plasma samples were then used with the standard curve equation to calculate the dermatan sulfate-like equivalent activity (DS eq ug/ml) for each sample.

Effect of Protamine sulfate (PS) on Odiparcil - induced antithrombin activity: A desirable feature of any antithrombotic therapy is either rapid reversibility and/or an antidote. The ability of protamine sulfate to suppress odiparcil-induced antithrombin activity was determined using a modification of the HCII kit described above. The assay was performed with plasma from rats treated with 15 mg/kg odiparcil. In this modified assay, bentonite treated plasma was incubated with HCII for 10 minutes, followed by a 10 minute incubation with PS (0-20uM), and then finally an additional 10 minute incubation with thrombin. The addition of substrate, detection, and data analysis were as described above.

Data Analysis: Data were analyzed using the statistical software STATISTICA version 6, Data StatSoft, Inc.

Results:

1. Rat antithrombotic profiles of warfarin vs Odiparcil. See Figure 4 showing: A) warfarin on thrombus formation B) odiparcil on thrombus formation C) warfarin on the international normalized ratio (INR) D) odiparcil on dermatan sulfate equivalent (DSeq) production as

measured in the DS-HCII antithrombin assay (the dotted line in A & C represents the ID₆₅; **P < 0.01, ***P < 0.001, One-way ANOVA, Duncan's multiple range test, n = 8/dose). Oral administration of both warfarin and odiparcil produced dose-related suppression of thrombus formation with ID₅₀'s of 0.12 mg/kg and 3.2 mg/kg respectively (figure 4A & 4B).

- 5 The drugs had distinct antithrombotic profiles, with warfarin suppressing thrombus formation by 100% at the highest dose, whereas odiparcil antithrombotic activity plateaued between 65-70% inhibition of thrombus formation.

The effects on pharmacodynamic markers also demonstrated dose-dependence. Warfarin had abrupt and pronounced effects on the prothrombin time, extending the INR
10 to ~1.9 at the ID₅₀ and to ~3.0 at the ID₆₅ (figure 4C) and beyond assay limitations (> 10) at the ID₉₀. Given that the target INR for warfarin therapy in humans is in the range of 2.0 - 3.0, a therapeutically relevant dose-range of warfarin in this rat model would maximally suppress thrombus formation by approximately 65%.

The anti-thrombin effects of odiparcil were followed with the DS-HCII dependent
15 antithrombin assay. The readout in the assay was in DS equivalent units (ug/ml) (figure 4D). As measured in this assay, the production of DS-like activity correlated with the antithrombotic activity of the drug ($r^2 = 0.86$, P = 0.01). DS concentration ranged from ~2.0 ug/ml at the ID₅₀ to ~4.0 ug/ml at the ID₆₅ with maximal DS concentration plateauing between 4-6 ug/ml. Therefore, by comparison to warfarin, odiparcil induced DS levels of
20 2.0 – 4.0 ug/ml approximated the efficacy of warfarin when dosed to an INR of 1.9 - 3.0 in this rat venous thrombosis model. No ATIII dependent anti-thrombin activity was detected in odiparcil samples, nor were effects on aPTTs or PTs observed.

2. Bleeding profiles: See Figure 5 which shows: A & C) warfarin; B & D) odiparcil (*P < 0.05, **P < 0.01, One-way ANOVA, Duncan's multiple range test, n = 8/dose). Warfarin
25 caused a significant dose-dependent increase in bleeding time and blood loss, extending these indices at the ID₆₅ by 2.7 and 5.2 fold respectively (these data are consistent with previous reports, see MacIomhair M, Lavelle SM. The anticoagulant, antithrombotic and haemorrhagic effect of long-term warfarin on experimental venous and arterial thrombosis in the rat. I J M S 1996;165:213-218). At the highest dose (0.6mg/kg/day), the bleeding
30 time was prolonged to the experimental limit of 1800 seconds.

In contrast, odiparcil did not cause dose-related changes in bleeding time or blood loss. At the 30 mg/kg dose, a 2.4 fold increase in bleeding time was observed, (P = 0.045) however with no associated increase in blood loss.

3. Odiparcil effects on thrombin, ADP, and collagen induced platelet aggregation: To
35 evaluate potential effects of odiparcil on platelet function, platelets were collected as platelet rich plasma (PRP) from rats treated with odiparcil (15mg/kg) and vehicle. The

PRP was then tested in conventional platelet aggregation studies. By comparison to vehicle treated animals, platelets collected from odiparcil-treated rats did not respond differently to the platelet agonist ADP or collagen. ADP was tested in a range of 1-10 μ M and collagen from 1-8 μ g/ml. In contrast thrombin-induced aggregation and subsequent clot formation was blocked by the odiparcil treatment (Figure 6). Odiparcil completely prevented aggregation and clot formation induced by 1.0 unit/ml thrombin, and caused reversible aggregation at 2.5 units/ml thrombin.

4. Assessment of protamine sulfate as a potential Odiparcil antidote: See Figure 7 in which: A) (-)odiparcil indicates plasma sample collected from a control rat administered no odiparcil, (+)odiparcil indicates plasma samples collected from rats treated with 15 mg/kg odiparcil. The square symbols represent an assay order of addition of plasma followed by HCII, PS, and then thrombin as the last step prior to substrate addition. The triangle symbols represent an assay order of addition of plasma, HCII, thrombin, and then PS added as the last step; B) antithrombotic effects of odiparcil alone or combined with PS (see methods for details) (** significantly higher thrombus weight in comparison to odiparcil group ($P = 0.006$) and significantly reduced thrombus weight in comparison to vehicle group ($P = 0.02$), One-way ANOVA, Duncan's multiple range test, $n = 9-10/\text{group}$). The ability of protamine sulfate to neutralize the antithrombin and antithrombotic activity of odiparcil was assessed ex vivo and in vivo. In the ex vivo assessment, plasma collected from rats treated with odiparcil was tested for its ability to promote HCII mediated thrombin inhibition in the presence of an increasing concentration of protamine sulfate. Under the conditions of this assay, a 15 mg/kg dose of odiparcil maximally suppressed thrombin activity by approximately 40% (Figure 7A). PS, in a concentration-dependent manner completely suppressed odiparcil induced antithrombin activity. Importantly, if the assay order of addition was altered such that the HCII, GAG, thrombin association was allowed to occur prior to PS addition, then PS did not suppress the odiparcil induced antithrombin activity.

To further characterize these findings, PS was evaluated in vivo for its potential to neutralize the antithrombotic effects of odiparcil. The experimental protocol was as the previously described venous thrombosis studies, with the exception that PS administration was initiated 5 minutes prior to and then continued throughout the thrombus induction period. The PS dose and regimen were selected through a limited dose-finding optimization effort. The most effective dose and regimen tested are illustrated in Figure 7B. PS only partially neutralized (55%, $P = 0.006$) the antithrombotic effects of odiparcil. Unlike the in vitro observations, no dose or regimen tested in vivo completely neutralized the odiparcil antithrombotic activity.

In similar preclinical studies of heparin, PS has been shown to completely neutralize heparin activity. See, Racanelli A, Fareed J. Neutralization of the antithrombotic effects of heparin and Fraxiparin by protamine sulfate. *Thromb Res* 1992;68:211-222.

- 5 In previously published studies of purified dermatan sulfate, PS was shown to only partially neutralize dermatan sulfate. See, Sié P, Cremers B, Dupouy D, Caranobe C, Dol F, Boneu B. Neutralization of dermatan sulfate in vitro and in vivo by protamine sulfate and polybrene. *Thromb Res* 1989;54:63-74. Therefore, the odiparcil antithrombotic mechanism may at least in part be through the actions of dermatan sulfate-like GAGs.
- 10 Whether all of the antithrombotic activity of odiparcil is mediated by a DS-HCII antithrombin mechanism remains to be determined. Prior studies with purified preparations of chondroitin and dermatan sulfate suggested antithrombotic potential through profibrinolytic and antiplatelet mechanisms (Kariya Y, Sakai T, Kaneko T, Suzuki K, Kyogashima M. Enhancement of t-PA-mediated plasminogen activation by partially
- 15 defucosylated glycosaminoglycans from the sea cucumber *Stichopus Japonicus*. *J Biochem* 2002;132:335-343; Abbadini M, Zhu GJ, Maggi A, Pangrazzi J, Donati MB, Mussoni L. Dermatan sulphate induces plasminogen activator release in the perfused rat hindquarters. *Blood* 1987;70:1858-1860; Silver FH, Yannas IV, Salzman EW. Glycosaminoglycan inhibition of collagen induced platelet aggregation. *Thromb Res*
- 20 1978;13:267-277). However, no general suppression of platelet function was observed in these rat studies, only platelet activity mediated by thrombin was effected. The lack of any detectable ATIII mediated antithrombin activity, and the clear dose-dependent HCII mediated antithrombin activity, suggests that the odiparcil-induced GAG profile in the rat appears consistent with prior xyloside studies reporting a GAG induced profile that is
- 25 comprised predominantly of chondroitin and dermatan sulfate (Masson et al, *J Biol Chem* 1995; and *Thromb & Haemost* 1999, supra).

Overall, these studies suggest that PS may have utility as a neutralizing agent for odiparcil. Accordingly, the present invention encompasses the use of protamine sulfate to neutralize the antithrombin and/or antithrombotic activity of odiparcil.

- 30 In summary, following oral administration, both odiparcil and warfarin demonstrated dose-related suppression of thrombus formation. In vitro analysis of plasma from odiparcil treated rats demonstrated an increase in dermatan sulfate-like molecules at antithrombotic doses. This suggests increased heparin cofactor II activity yielding an increase in thrombin inhibition. This indicates that DS-HCII mediated antithrombin activity
- 35 could be used as a pharmacodynamic marker of odiparcil antithrombotic activity.

In addition, odiparcil and warfarin demonstrated a pronounced difference in their effect on bleeding time and blood loss. Odiparcil had no significant effect on bleeding time within an efficacious dose range and hemoglobin content analysis showed no significant blood volume loss. In contrast, warfarin significantly prolonged bleeding time in a dose range that overlapped antithrombotic effect and was accompanied by a significant loss in blood volume at doses ≥ 0.2 mg/kg.

These studies also indicate that protamine sulphate could be used to partially neutralize the activity of odiparcil.

These studies suggest that an antithrombotic approach based upon xyloside induction of circulating GAGs may have the potential to match the efficacy of warfarin without incurring a significant risk to hemostasis (e.g., related to a possible saturable mechanism, and/or availability of a neutralizing agent). In particular, the collective data indicates that odiparcil is an orally active antithrombotic which has the potential to match the efficacy of warfarin (e.g., when dosed to an INR of 2-3), without incurring a significant bleeding liability.

Since thrombosis within the venous system is mostly related to blood stasis and endothelial damage, leading to activation of the clotting system, efficacy in venous thrombosis could represent a marker of its efficacy in atrial thrombosis. Thus, the above demonstrations of efficacy of odiparcil in venous thrombosis could represent a marker of or suggest its efficacy in atrial thrombosis.

It is to be understood that the present invention is not limited to the embodiments illustrated hereinabove.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

It is to be understood that the present invention covers all combinations of particular and preferred groups described herein above. Particular examples or embodiments are non-limiting unless expressly described as such herein.

It will be apparent to those skilled in the art that various modifications may be made without departing from the spirit of the invention, such that the right is reserved to illustrated embodiments and all modifications coming within the scope of the following claims.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent

application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims.

What is claimed is:

1. A method of treating or preventing thromboembolic disorders, comprising administering to a patient in need of such treatment or prevention an effective amount of
5 odiparcil.
2. The method according to Claim 1 wherein the patient is a human.
3. The method according to claim 1 or 2, wherein the odiparcil is administered in an
10 amount of from about 125 to about 1000 mg per day.
4. The method according to claim 3, wherein the odiparcil is administered in an amount of from about 250 to about 1000 mg per day.
- 15 5. The method according to Claim 4, wherein the odiparcil is administered in an amount of from about 500 to about 1000 mg per day.
6. The method according to Claim 5, wherein the odiparcil is administered in an amount of about 250, about 375 or about 500 mg twice daily.
20
7. The method according to claim 1 or 2, wherein the odiparcil is administered so as to provide a steady state anti-IIa trough level of at least 0.5 μ g dermatan sulphate/mL plasma.
- 25 8. The method according to claim 7, wherein the odiparcil is administered so as to provide a steady state anti-IIa trough level of at least 2 μ g dermatan sulphate/mL plasma.
9. The method according to any preceding claim, wherein the odiparcil is administered about every 12 hours.
- 30 10. The method according to any preceding claim, wherein the odiparcil is administered in the form of a pharmaceutical composition further comprising a pharmaceutically acceptable excipient.

11. The method according to any preceding claim, wherein the thromboembolic disorder is venous thromboembolism (VTE) following orthopaedic surgery (for example, knee or hip arthroplasty).
- 5 12. The method according to Claim 11, wherein the odiparcil is administered for up to about 6 weeks following orthopaedic surgery.
13. The method according to Claim 11, wherein the odiparcil is administered for about 1 to about 30 days following orthopaedic surgery.
- 10 14. The method according to Claim 13, wherein the odiparcil is administered for about 8 to about 12 days following orthopaedic surgery.
- 15 15. The method according to any of claims 1-10, wherein the thromboembolic disorder is thromboses associated with atrial fibrillation (for example, non-valvular atrial fibrillation).
16. The method according to Claim 15 wherein the patient is at low or intermediate risk of stroke.
- 20 17. The method according to Claim 15 wherein the patient is at high risk of stroke.
18. The method according to Claim 15 wherein the method is for preventing stroke in atrial fibrillation.
- 25 19. The method according to any preceding claim, which is a combination therapy method of treating or preventing a thromboembolic disorder, comprising administering to a patient in need of such treatment or prevention an effective amount of odiparcil and aspirin or a heparin.
- 30 20. The method according to Claim 19, wherein the odiparcil and aspirin or heparin are separately administered in the form of a pharmaceutical composition comprising odiparcil and a pharmaceutically acceptable excipient, and a pharmaceutical composition comprising aspirin or heparin and a pharmaceutically acceptable excipient.

21. The method according to Claim 19, wherein the aspirin is administered in an amount of about 325 mg once daily.

Figure 1

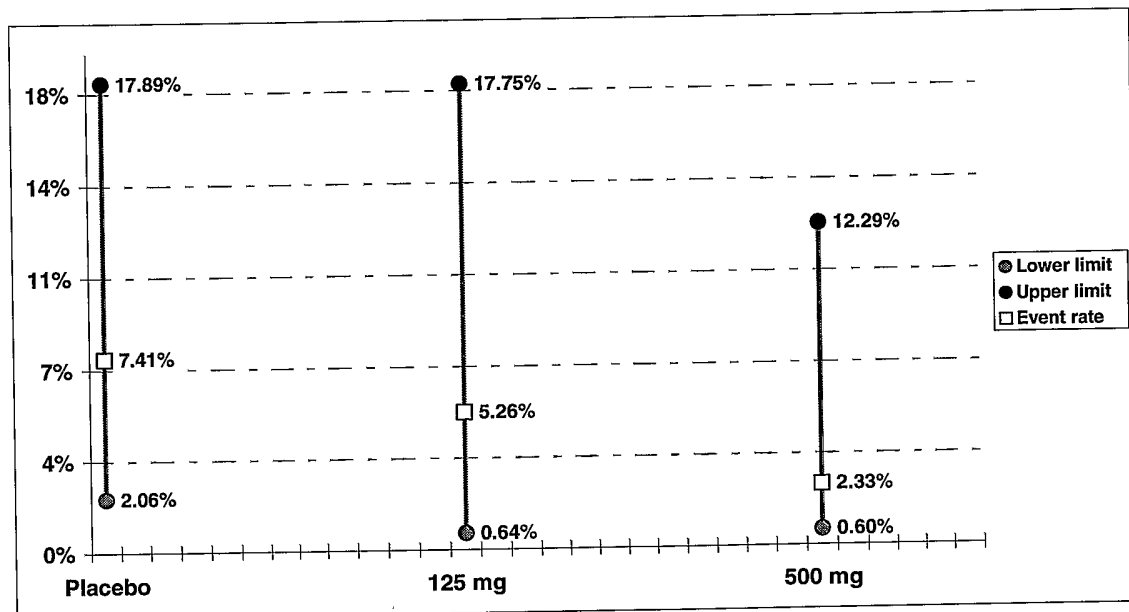


Figure 2

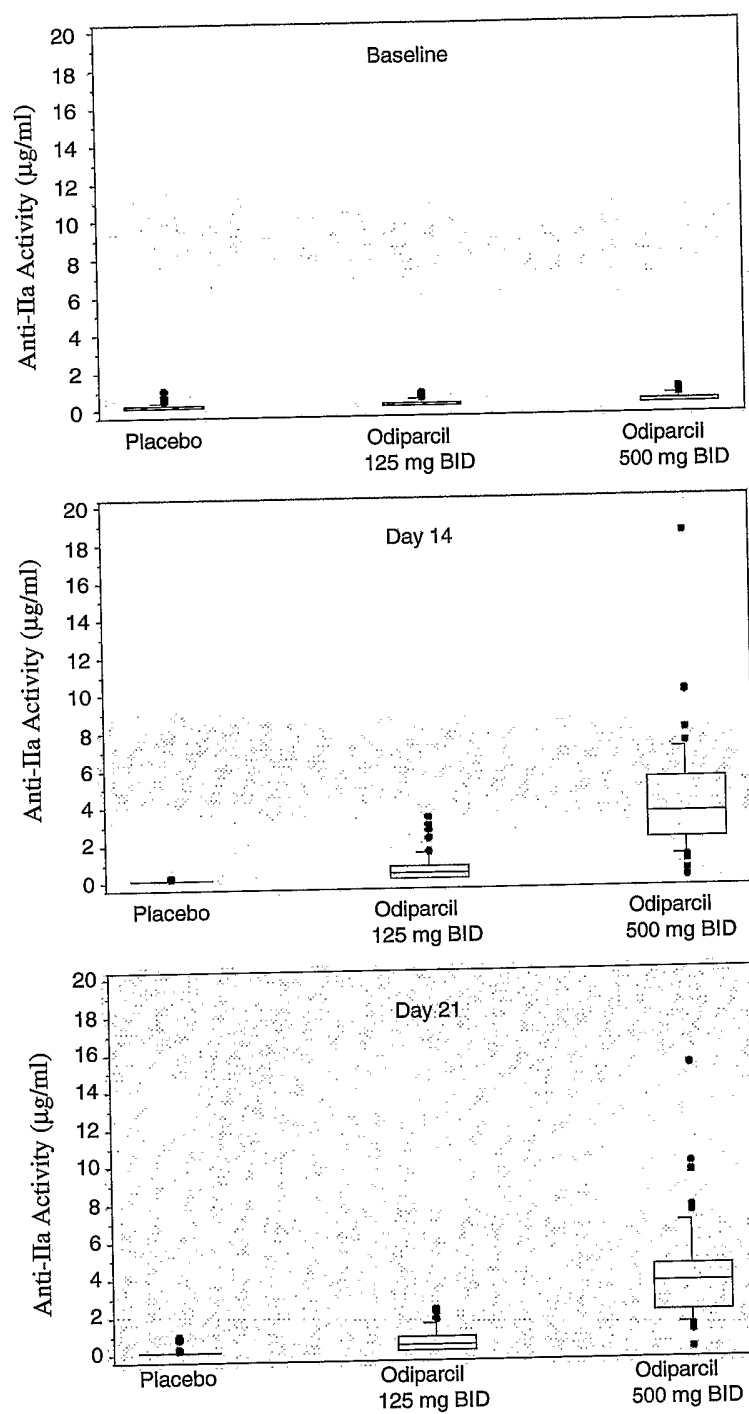


Figure 3

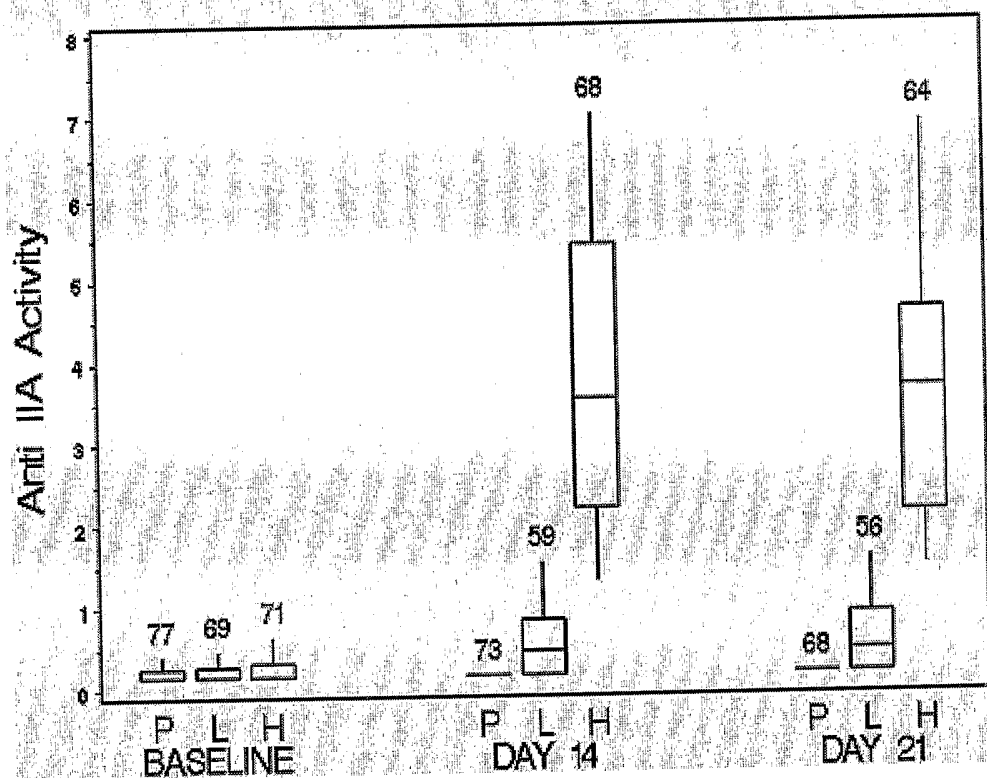


Figure 4

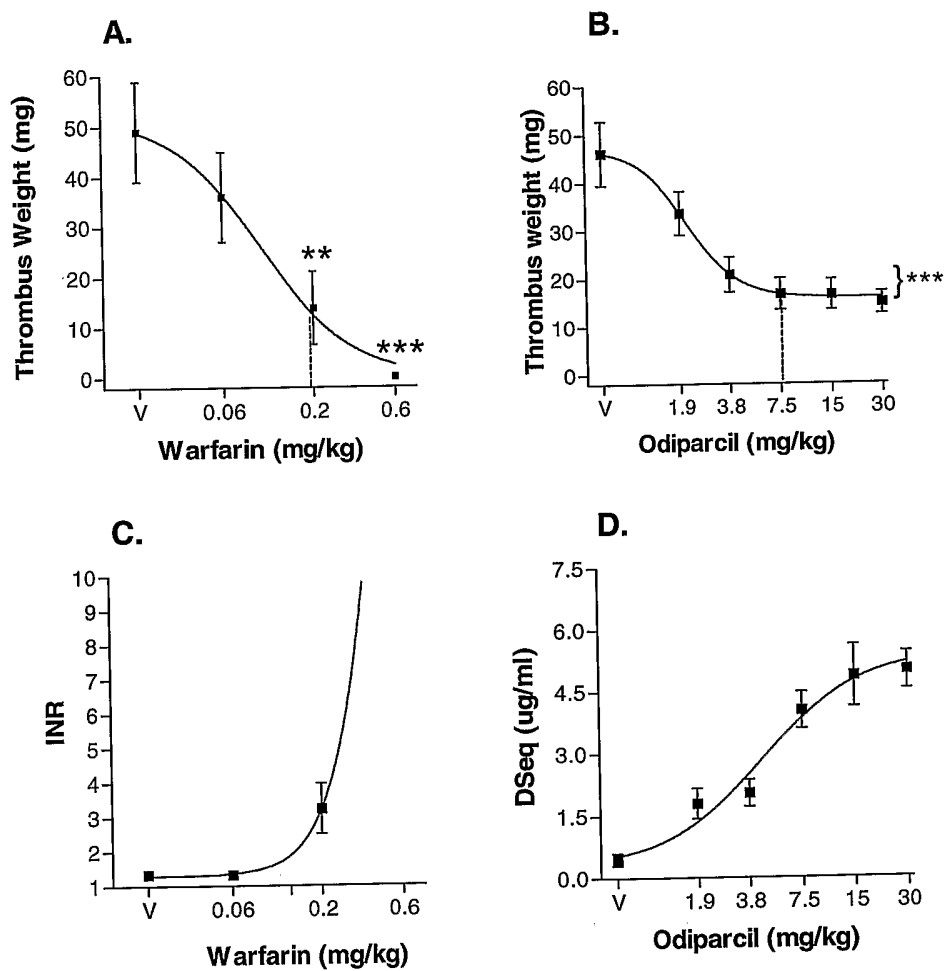


Figure 5

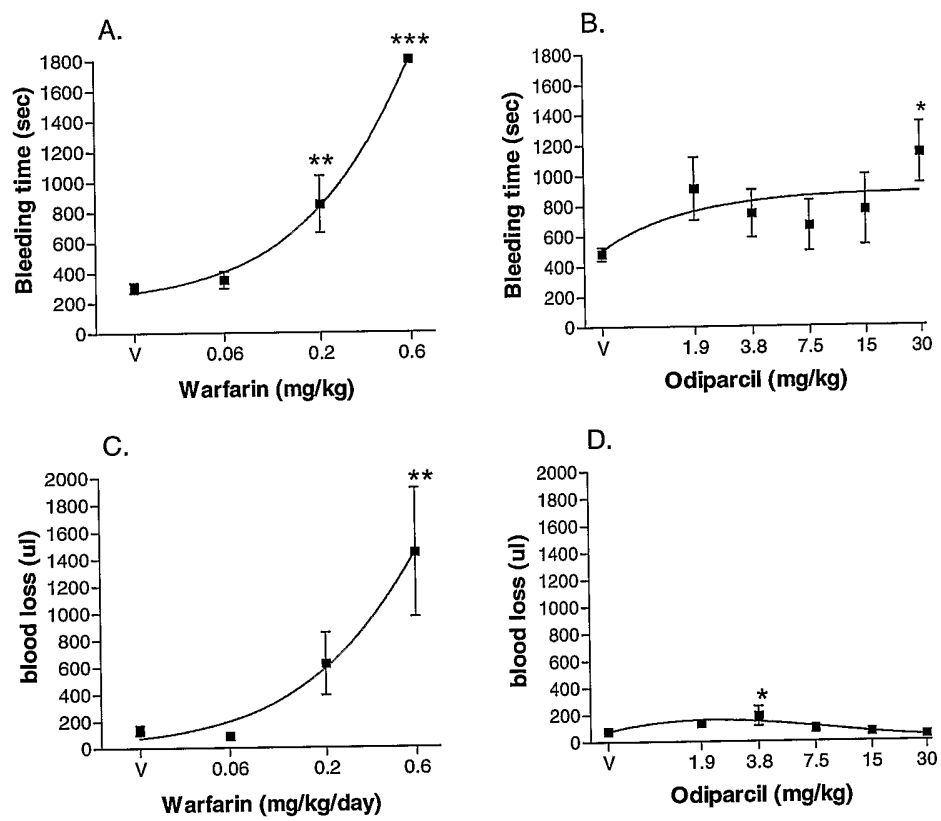


Figure 6

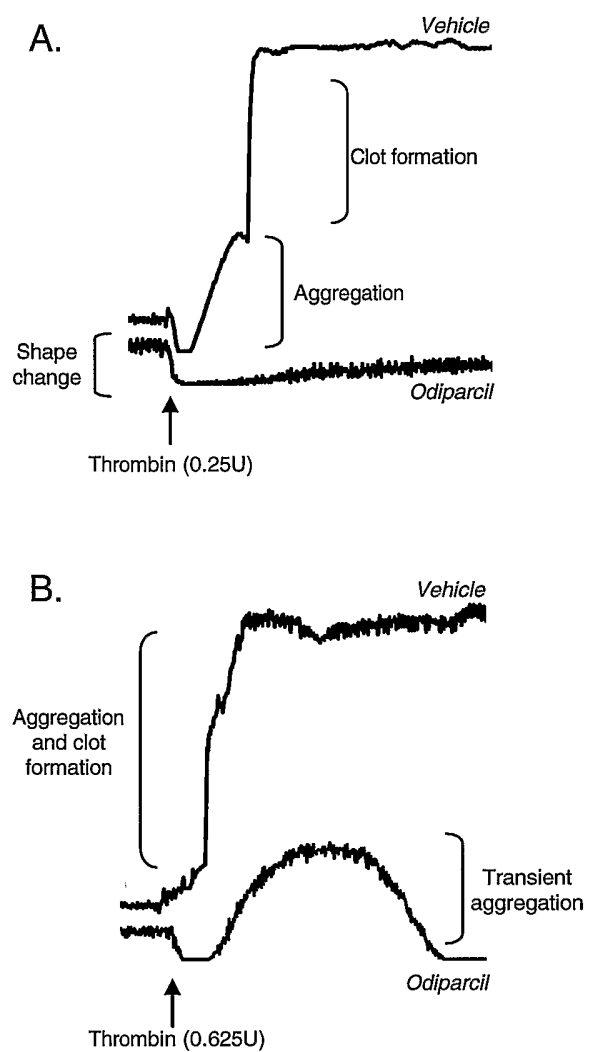
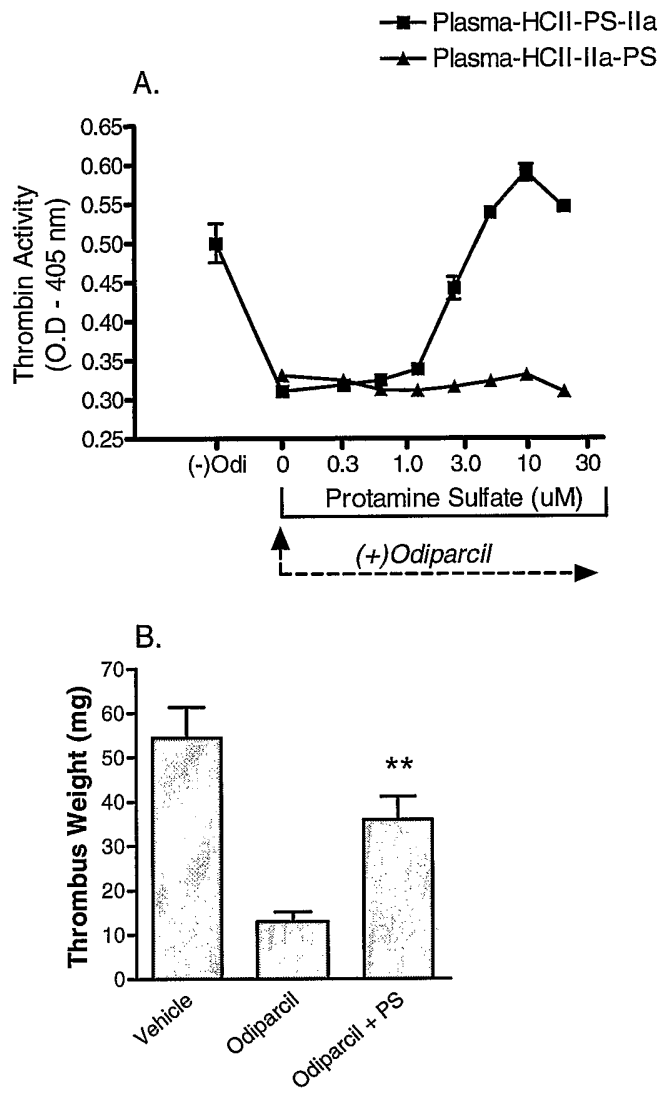


Figure 7



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/43602

A. CLASSIFICATION OF SUBJECT MATTER

IPC: A61K 31/38(2006.01)

USPC: 514/432

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/432

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,602,899 B1 (BARBEROUSSE et al.) 05 August 2003 (05.08.2003), see the entire document.	1-21



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

16 March 2006 (16.03.2006)

Date of mailing of the international search report

28 MAR 2006

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