CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 020430

Trade Name : ORGARAN INJECTION

Generic Name: Danaproid Sodium Injection

Sponsor : Organon, Inc.

Approval Date: **December 24, 1996**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020430

APPROVAL LETTER

Oliver

DEC 24 1996

NDA 20-430

DEC 24 1996

Organon Inc.
Attention: Ms. Edwina L. Muir
375 Mount Pleasant Avenue
West Orange, New Jersey 07052

Dear Ms. Muir:

Please refer to your new drug application dated September 8, 1994, received September 9, 1994, and your resubmission dated December 29, 1994 (received December 30, 1994) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Orgaran™ (danaparoid sodium) Injection.

We acknowledge receipt of your submissions dated September 12 and November 18, 1996, submitted in response to our July 24, 1996 approvable letter. The User Fee goal date for this application is May 19, 1997.

This new drug application provides for 750 anti-Xa units of Orgaran™ Injection to be administered twice daily subcutaneously for the prophylaxis of post-operative deep venous thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing elective hip replacement surgery.

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on November 18, 1996. Accordingly, the application is approved effective on the date of this letter.

We request that in the ADVERSE REACTIONS section, in the "Blood Loss and Transfusions" table, the phrase "Transfusions (units PRBs)" be changed to "Transfusions (units PRBCs)" in the next printing of the package insert and be reported as an editorial change in the annual report.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Karen Oliver, Project Manager, at (301) 443-0487.

Sincerely yours,

Paula Botstein MD 12/24/96

Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-430
HFD-180/Div. files
HFD-180/CSO\K.Oliver
HFD-180/S.Fredd
HFD-180/L.Talarico
HFD-180/E.Duffy
HFD-180/A.Ali-Hakim
HFD-180/J.Choudary
HFD-720/M.Huque
HFD-720/M.Al-Osh
HFD-870/L.Kaus
HFD-870/R.Pradhan
HFD-160/P.Cooney
HFD-160/C.Vincent
HFD-002/ORM (with labeling)
HFD-103/Office Director
HFD-101/L.Carter
HFD-820/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)

FR 12/27/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020430

FINAL PRINTED LABELING

Incidence of Adverse Experiences (≥2%)
DVT and PE Prophylaxis Indication
All Patients Treated

Adverse Experience	ORGARAN™ N=2383 N(%)	Placebo N=276 N(%)	Warfarin N=421 N(%)	Other N=1163 N(%)
Injection Site Pain	327(13.7)	53(19.2)	0(0.0)	153(13.2)
Pain	207(8.7)	0(0.0)	202(48.0)	20(1.7)
Fever	173(7.3)	1(0.4)	150(35.6)	21(1.8)
Nausea	98(4.1)	3(1.1)	79(18.8)	13(1.1)
Urinary Tract Infection	96(4.0)	3(1.1)	27(6.4)	65(5.6)
Constipation	83(3.5)	0(0.0)	73(17.3)	3(0.3)
Rash	51(2.1)	0(0.0)	25(5.9)	5(0.4)
Infection	51(2.1)	3(1.1)	0(0.0)	47(4.0)

OVERDOSAGE

Symptoms/Treatment: Accidental overdosage following administration of ORGARAN™ (danaparoid sodium) Injection may lead to bleeding complications. The effects of ORGARAN™ on anti-Xa activity cannot be antagonized with any known agent at this time. Although protamine sulfate partially neutralizes the anti-Xa activity of ORGARAN™ and can be safely co-administered, there is no evidence that protamine sulfate is capable of reducing severe non-surgical bleeding during treatment with ORGARAN™. In the event of serious bleeding, ORGARAN™ should be stopped and blood or blood product transfusions should be administered as needed. Withdrawal of ORGARAN™ may be expected to restore the coagulation balance without rebound phenomenon.

Single subcutaneous doses of ORGARAN™ at 3800 anti-Xa units/kg (20.5 times the recommended human dose based on body surface area) and 15200 anti-Xa units/kg (82 times the recommended human dose based on body surface area) were lethal to female and male rats, respectively. Symptoms of acute toxicity after intravenous dosing were respiratory depression, prostration and twitching.

DOSAGE AND ADMINISTRATION

Usual Adult Dosage:

In patients undergoing hip replacement surgery, the recommended dose of ORGARAN™ (danaparoid sodium) Injection is 750 anti-Xa units twice daily administered by subcutaneous injection beginning 1–4 hours pre-operatively, and then not sooner than two hours after surgery. Treatment should be continued throughout the period of post-operative care until the risk of deep vein thrombosis has diminished. The average duration of administration in clinical trials was 7 to 10 days, up to 14 days. Patients with serum creatinine ≥ 2.0 mg/dL should be carefully monitored.

Administration:

ORGARAN™ (danaparoid sodium) Injection is intended for subcutaneous administration and should not be administered by intramuscular injection. Subcutaneous injection technique: Patients should be lying down and ORGARAN™ Injection administered by deep subcutaneous injection using a fine needle (25 to 26 gauge) to minimize tissue trauma. Administration should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held gently between the thumb and forefinger: the skin fold should be held throughout the injection and should neither be pinched nor rubbed afterwards.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

ORGARAN™ (danaparoid sodium) Injection is supplied in:

— Ampules containing 0.6 mL (750 anti-Xa units) of danaparoid sodium: boxes of 10, NDC 0052-0830-11

— Disposable prefilled syringes containing 0.6 mL (750 anti-Xa) units of danaparoid sodium: boxes of 10, NDC 0052-0830-61. Each ORGARAN™ prefilled syringe is affixed with a 25 gauge x 5/8 inch needle.

Storage:

— Ampules should be stored at temperatures of 2°–30°C (36°–86°F).

— Syringes should be stored at a refrigerated temperature of 2°–8°C (36°–46°F).

— Protect from light.

Caution: Federal law prohibits dispensing without a prescription.

Organon

Organon Inc.
West Orange, N.J. 07052

Printed in USA

5310150 11/96

ORGARAN™
(danaparoid sodium) Injection

5310150 11/96

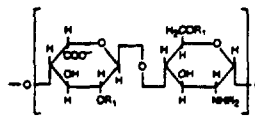
DESCRIPTION

ORGARAN™ (danaparoid sodium) Injection is a sterile, glycosaminoglycuronan antithrombotic agent. The active components of ORGARAN™, isolated from porcine intestinal mucosa, are heparan sulfate (~84%), dermatan sulfate (~12%) and a small amount of chondroitin sulfate (~4%). The average molecular weight is approximately 5500 Daltons.

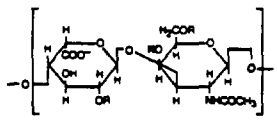
ORGARAN™ is intended for subcutaneous injection. Each prefilled syringe or ampule contains 750 anti-Xa units in 0.6 mL solution. ORGARAN™ Injection is made isotonic with sodium chloride, adjusted to pH 7 with hydrochloric acid, or sodium hydroxide. ORGARAN™ Injection contains 0.15% (w/v) sodium sulfite to prevent discoloration of the solution. The structural formula of the main repeating disaccharide units is as follows:

Structural Formula:

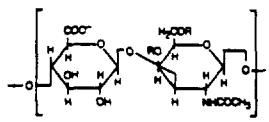
Main Repeating Disaccharide Units:



Heparan Sulfate: R_1 = H or SO_3^-, R_2 = $COCH_3$ or SO_3^-



Dermatan Sulfate
R = H or SO_3^-



Chondroitin Sulfate

CLINICAL PHARMACOLOGY

Pharmacodynamics: *Effect on Coagulation Factors:* ORGARAN™ (danaparoid sodium) Injection is an antithrombotic agent. ORGARAN™ prevents fibrin formation in the coagulation pathway via thrombin generation inhibition by anti-Xa and anti-IIa (thrombin) effects. The anti-Xa: anti-IIa activity ratio is greater than 22. Inactivation of factor Xa is mediated by antithrombin-III (AT-III) while factor IIa inactivation is mediated by both AT-III and heparin cofactor II (HC II). ORGARAN™ has only minor effect on platelet function and platelet aggregability.

Measurements of Hemostasis: Because of its predominant anti-Xa activity, ORGARAN™ (danaparoid sodium) has little effect on clotting assays (*e.g.*, prothrombin time [PT], partial thromboplastin time [PTT]). ORGARAN™ has minimal effect on fibrinolytic activity and bleeding time.

Pharmacokinetics: The pharmacokinetics of ORGARAN™ (danaparoid sodium) Injection have been described by monitoring its biological activity (plasma anti-Xa activity) since no specific chemical assay methods are currently available for the components of ORGARAN™.

By subcutaneous route of administration, ORGARAN™ was approximately 100% bioavailable, compared with the same dose administered intravenously. The maximum anti-Xa activity (Tmax) occurred at approximately two to five hours.

For single subcutaneous doses of 750, 1500, 2250, and 3250 anti-Xa units of ORGARAN™ the mean peak plasma anti-Xa activities were 102.4, 206.1, 283.9, and 403.4 mU/mL, respectively. The mean value for the terminal half-life (T1/2) was about 24 hours and the clearance was 0.36 L/hour. Clearance was affected by body surface area in that the higher the body surface, the faster the clearance. ORGARAN™ is mainly eliminated via the kidneys. In patients with severely impaired renal function, the half-life of elimination of plasma anti-Xa activity may be prolonged, therefore, monitoring such patients carefully is recommended.

Clinical Trials: In a European multicenter double-blind trial, ORGARAN™ (danaparoid sodium) was compared with placebo in 196 patients undergoing elective hip replacement surgery. The administration of ORGARAN™ for 7 to 14 days post-operatively significantly reduced the overall incidence of DVT to 15% (15/98 patients) compared to the incidence of 57% (56/98 patients) observed with placebo.

Number (%) of Patients with DVT*
Intent-to-Treat

	ORGARAN™ N=98	Placebo N=98	p-value[a]
Proximal: N (%)	8 (8)	26 (27)	0.001
Distal: N (%)	14 (14)	51 (52)	<0.001
Overall: N (%)	15 (15)	56 (57)	<0.001

*A patient may be counted more than once (proximal and/or distal)

[a]Using the Cochran Mantel-Haenszel test

In a United States multicenter trial, ORGARAN™ was compared with warfarin in 396 patients undergoing elective hip replacement. A significant reduction in the overall incidence of DVT was observed with ORGARAN™ (14.6%; 29/199 patients) compared with warfarin (26.9%; 53/197 patients), p=0.003.

Number (%) of Patients with DVT[a]
Intent-toTreat

	ORGARAN™ N=199	Warfarin N=197	p-value[b]
Proximal[c]: N (%)	3 (1.5)	8 (4.1)	0.13
Distal[d]: N (%)	28 (14.1)	49 (24.9)	0.007
Overall[e]: N (%)	29 (14.6)	53 (26.9)	0.003

[a] By positive venogram only
[b] Using the Cochran Mantel-Haenszel test
[c] Popliteal, iliac, and femoral
[d] Calf
[e] A patient may be counted more than once (proximal and distal)

INDICATIONS AND USAGE
ORGARAN™ (danaparoid sodium) Injection is indicated for the prophylaxis of post-operative deep venous thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients undergoing elective hip replacement surgery.

CONTRAINDICATIONS
ORGARAN™ (danaparoid sodium) Injection is contraindicated in the following conditions: severe hemorrhagic diathesis, e.g., hemophilia and idiopathic thrombocytopenic purpura; active major bleeding state, including hemorrhagic stroke in the acute phase; hypersensitivity to ORGARAN™; Type II thrombocytopenia associated with a positive *in vitro* test for antiplatelet antibody in the presence of ORGARAN™ injection. ORGARAN™ is contraindicated in patients with known hypersensitivity to pork products.

WARNINGS
General: ORGARAN™ (danaparoid sodium) Injection is not intended for intramuscular administration. Since a specific standard for the anti-Xa activity of ORGARAN™ is used, the anti-Xa unit activity of ORGARAN™ is not equivalent to that described for heparin or low molecular weight heparin. Therefore, ORGARAN™ cannot be dosed interchangeably (unit for unit) with either heparin or any low molecular weight heparin.

Miscellaneous: ORGARAN™ (danaparoid sodium) Injection contains sodium sulfite which may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic patients.

Hemorrhage: Hemorrhage can occur at virtually any site in patients receiving ORGARAN™ (danaparoid sodium). An unexplained fall in hematocrit and/or fall in blood pressure should lead to serious consideration of a hemorrhagic event. ORGARAN™, like anticoagulants, should be used with extreme caution in disease states in which there is increased risk of hemorrhage, such as severe uncontrolled hypertension, acute bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, non-hemorrhagic stroke, shortly after brain, spinal or ophthalmological surgery and post-operative indwelling epidural catheter use.

PRECAUTIONS
General: The risks and benefits of ORGARAN™ (danaparoid sodium) Injection should be carefully considered before use in patients with severely impaired renal function or hemorrhagic disorders (see ***DOSAGE AND ADMINISTRATION***).

Laboratory Tests: ORGARAN™ (danaparoid sodium) Injection has only a small effect on factor IIa (thrombin) activity, therefore, routine coagulation tests (e.g., Prothrombin Time [PT], Activated Partial Thromboplastin Time [APTT], Kaolin Cephalin Clotting Time [KCCT], Whole Blood Clotting Time [WBCT], and Thrombin Time [TT]) are unsuitable for monitoring ORGARAN™ activity at recommended doses.

Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with ORGARAN™.

Thrombocytopenia: ORGARAN™ (danaparoid sodium) Injection shows a low cross-reactivity with antiplatelet antibodies in individuals with Type II heparin-induced thrombocytopenia. No cases of white clot syndrome or cases of Type II thrombocytopenia have been reported in clinical studies for the prophylaxis of DVT in patients receiving multiple doses of ORGARAN™ up to 14 days.

Drug Interactions: In clinical studies for the prophylaxis of DVT, no clinically significant drug interactions have been noted in the following drugs: digoxin, cloxacillin, ticarcillin, chlorthalidone, and pentobarbital.

ORGARAN™ (danaparoid sodium) Injection should be used with caution in patients receiving oral anticoagulants and/or platelet inhibitors. Monitoring of anticoagulant activity of oral anticoagulants by Prothrombin Time and Thrombotest is unreliable within 5 hours after ORGARAN™ Injection administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long term studies in animals have been performed to evaluate the carcinogenic potential of ORGARAN™ (danaparoid sodium) Injection. ORGARAN™ was not genotoxic in the Ames test, the *in vitro* CHL/HGPRT forward gene mutation assay, the *in vitro* CHO cell chromosome aberration test, the *in vitro* HeLa cell unscheduled DNA synthesis (UDS) test or the *in vivo* mouse micronucleus test. ORGARAN™ at intravenous doses of up to 1090 anti-Xa units/kg/day was found to have no effect on fertility or reproductive performance of male and female rats. This dose is 5.9 times the recommended human subcutaneous dose based on body surface area (50 kg body weight and 1.46 m^2 body surface area assumed).

Pregnancy: Teratogenic effects. Pregnancy Category B: Teratology studies have been performed in pregnant rats at intravenous doses up to 1600 anti-Xa units/kg/day (8.7 times the recommended human dose based on body surface area) and pregnant rabbits at intravenous doses up to 780 anti-Xa units/kg/day (6 times the recommended human dose based on body surface area) and have not revealed evidence of impaired fertility or harm to the fetus due to ORGARAN™. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether ORGARAN™ (danaparoid sodium) is excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when ORGARAN™ is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of ORGARAN™ (danaparoid sodium) Injection in pediatric patients have not been established.

ADVERSE REACTIONS
The following table summarizes adverse bleeding events that occurred in clinical trials which studied ORGARAN™ (danaparoid sodium) Injection compared to placebo, warfarin, and others (heparin, heparin/DHE, acetylsalicylic acid, dextran, and low-molecular weight heparins).

Blood Loss and Transfusions
DVT and PE Prophylaxis for Orthopedic Hip Surgery
All Patients Treated

Blood Loss and Transfusions	Total N	ORGARAN™	Placebo	Warfarin	Other[a]
Total (728 Males; 1675 Females)		(N) Mean±SD	(N) Mean±SD	(N) Mean±SD	(N) Mean±SD
Intraoperative Blood Loss (mL)					
Males	596	(330) 694±555	(27) 586±737	(141) 689±499	(98) 754±661
Females	1259	(686) 486±430	(66) 416±252	(219) 471±306	(288) 530±456
Postoperative Blood Loss (mL)					
Males	580	(318) 954±879	(45) 908±812	(88) 817±585	(129) 1056±1055
Females	1256	(639) 700±778	(122) 715±520	(80) 619±352	(415) 798±779
Transfusions (units PRBs)					
Males	462	(258) 2.6±1.8	(35) 2.7±1.4	(87) 2.5±1.4	(82) 2.9±2.1
Females	1152	(604) 2.6±1.7	(92) 2.8±1.4	(177) 2.1±1.1	(279) 2.8±2.0

[a] "Other" includes the following active reference agents: heparin, heparin/DHE, acetylsalicylic acid, dextran, and low-molecular weight heparins.

Total N = Total number of patients with available data across all treatment groups.
n = The number of patients with available data in each respective treatment group and by gender.

Other: The following table summarizes adverse events that occurred at a frequency greater than, or equal to, 2% of patients in clinical trials for the prophylaxis of DVT and PE following elective hip surgery which studied ORGARAN™ (danaparoid sodium) Injection compared to placebo, warfarin, and others (dextran, heparin/DHE, aspirin).

Incidence of Adverse Experiences (≥2%)
DVT and PE Prophylaxis for Elective Hip Surgery
All Patients Treated

Adverse Experience	ORGARAN™ N=645 N(%)	Placebo N=135 N(%)	Warfarin N=243 N(%)	Other N=168 N(%)
Fever	143(22.2)	1(0.7)	138(56.8)	3(1.8)
Nausea	92(14.3)	3(2.2)	78(32.1)	8(4.8)
Constipation	73(11.3)	0(0.0)	70(28.8)	2(1.2)
Injection Site Pain	49(7.6)	4(3.0)	0(0.0)	34(20.2)
Rash	31(4.8)	0(0.0)	18(7.4)	2(1.2)
Pruritus	25(3.9)	1(0.7)	14(5.8)	0(0.0)
Peripheral Edema	21(3.3)	0(0.0)	19(7.8)	4(2.4)
Insomnia	20(3.1)	0(0.0)	32(13.2)	0(0.0)
Vomiting	19(2.9)	3(2.2)	20(8.2)	3(1.8)
Joint Disorder	17(2.6)	0(0.0)	15(6.2)	0(0.0)
Headache	17(2.6)	1(0.7)	13(5.3)	0(0.0)
Urinary Tract Infection	17(2.6)	1(0.7)	5(2.1)	5(3.0)
Edema	17(2.6)	0(0.0)	14(5.8)	2(1.2)
Asthenia	15(2.3)	0(0.0)	10(4.1)	1(0.6)
Dizziness	15(2.3)	0(0.0)	14(5.8)	0(0.0)
Anemia	14(2.2)	3(2.2)	5(2.1)	5(3.0)
Urinary Retention	13(2.0)	0(0.0)	14(5.8)	1(0.6)

In addition, the following table summarizes adverse events that occurred at a frequency greater than, or equal to, 2% of patients in clinical trials for the prophylaxis of DVT and PE which studied ORGARAN™ (danaparoid sodium) Injection compared to placebo, warfarin, and others (heparin, heparin sodium, heparin calcium, enoxaparin, dalteparin, dextran, heparin/DHE, aspirin).

Muir

JUL 24 1996

NDA 20-430

Organon Inc.
Attention: Ms. Edwina Muir
375 Mount Pleasant Avenue
West Orange, New Jersey 07052

Dear Ms. Muir:

Please refer to your September 8, 1994 new drug application and your resubmission dated December 29, 1994 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Orgaran™ (danaparoid sodium) Injection.

We acknowledge receipt of your amendments dated December 20, 1995 and January 3 and 24, February 6, March 11, April 8 and 19, and June 18, 1996.

We have completed the review of this application as submitted with draft labeling, and it is approvable. However, before this application may be approved, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed marked-up draft labeling, with additional information requested in the ADVERSE REACTIONS section, the "Other" subsection.

In addition, submit package inserts, with appropriate English translations, from all countries in which Orgaran™ is currently marketed, and provide information regarding any foreign safety-related regulatory actions.

Please submit sixteen copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of that FPL may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting safety reports, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of

occurrence of bleeding events, thrombocytopenia, and of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Karen Oliver
Regulatory Health Project Manager
Telephone: (301) 443-0487

Sincerely yours,

Paula Botstein MD 7/24/96

Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

EXCLUSIVITY SUMMARY for NDA # 20-430 **SUPPL #** _____

Trade Name Orgaran Injection **Generic Name** danaparoid sodium

Applicant Name Organon Inc. **HFD-** 180

Approval Date December 24, 1996

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES / X / NO / ___ /

   b) Is it an effectiveness supplement?

   YES / ___ / NO / ___ /

   If yes, what type? (SE1, SE2, etc.) SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES / X / NO / ___ /

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ ! NO /___/ Explain: _____

! _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

! _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ | NO /___/ Explain _____

_____ | _____

_____ | _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

Karin Owen
Signature

Dec 17, 1996
Date

Title: Regulatory Health Project Manager

Signature of Division Director

12/26/96
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

CERTIFICATION

Pursuant to Section 306 (k)(1) of the Federal Food, Drug and Cosmetic Act, the undersigned certifies that Organon Inc. did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [Section 306 (a) or (b)], in connection with the New Drug Application for Orgaran™ (danaparoid sodium), NDA. 20-430.

Patrick J. Osinski
Vice President

ITEM 13/14
PATENT INFORMATION AND CERTIFICATION

PROPOSED 21 CFR 314.53

314.53 (c) (1)

(i) U.S. PATENT NO. - 5,164,377

EXPIRATION DATE - NOVEMBER 17, 2009

(ii) TYPE OF PATENT - DRUG

(iii) NAME OF PATENT OWNER OF RECORD

Akzo N.V.
Arnhem, The Netherlands

(iv) NAME OF ATTORNEY

Mr. William Blackstone
Organon Teknika Corporation
Patent Department
1330-A Piccard Drive
Rockville, Maryland
20850-4373

Organon
ORGANON Inc.

314.53 (c) (2)

(i) Original Certification

The undersigned certifies that the drug and formulation or composition of ORGARAN™ (danaparoid sodium) is claimed and/or covered by U.S. Patent Number 5,164,377. This product is the subject of this application for which approval is being sought.

Patrick J. Osinski
Vice President

Orgaran

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-430 Trade (generic) names Orgaran (danaparoid sodium) Injection

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Karen Steiner
Signature of Preparer

June 24, 1996
Date

cc: Orig NDA
HFD-180/Div File
NDA Action Package

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020430

MEDICAL OFFICER REVIEW

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA No.: 20-430

Sponsor: Organon, Inc.

AUG - 7 1995

Drug: Orgaran (Org 10172)

Class: Glycosaminoglycan, antithrombotic

Indications: Thromboprophylaxis in hip replacement

Related Applications: IND

First Submission Date: 9-8-94

Re-submission Date: 12-29-1994

Date of NDA Filing: 2-28-1995

Medical Reviewer: Lilia Talarico, M.D.

Review Completed: 7-27-1995

BACKGROUND INFORMATION

Postoperative deep vein thrombosis (DVT) and pulmonary embolism (PE) are major complications for patients undergoing orthopedic hip surgery. Both DVT and PE may be clinically asymptomatic initially and the non-invasive methodologies used in clinical diagnosis are insensitive and unreliable for early diagnosis.
In the absence of thromboprophylaxis, DVT has been reported in approximately 40% to 60% of the patients undergoing either elective hip replacement or surgery for a fractured hip, whereas PE has been reported to occur in approximately 3% to 12% of these patient populations. Serious or fatal PE may arise in an otherwise well - convalescing patient.
The rationale for thromboprophylaxis following orthopedic hip surgery is based on the potentially fatal nature of PE and its origin from DVT. Thromboprophylaxis after hip or knee replacement surgery with low molecular weight heparins, such as enoxaparin, has significantly reduced the incidence rates of DVT.

Org 10172 is a glycosaminoglycan isolated from the same starting material as unfractionated heparin and low molecular weight heparins,

both of which, however, are excluded during the extraction procedure. Org 10172 inhibits the coagulation cascade predominantly by enhancing the antithrombin III (AT-III) mediated inhibition of factor Xa. Unlike heparin, Org 10172 is not inactivated by endogenous heparin-neutralizing factors (e.g., histidine-rich glycoproteins and platelet-factor-4) and has minimal or no effect on platelet activation.

Org 10172 was developed with the aim of providing a superior benefit/risk ratio (thrombosis prevention/bleeding enhancement) than other currently available antithrombotic regimens.
Orgaran has been evaluated for thromboprophylaxis in high risk general surgery, orthopedic surgery, non-hemorrhagic stroke and for anticoagulation in hemodialysis.
The clinical evaluation of Orgaran has been conducted in part under IND . Eleven clinical trials, 9 in US and 2 in Canada were sponsored by Organon Inc. under IND A total of 81 clinical studies were completed outside the U.S. not under IND NV Organon has five ongoing clinical studies as of June 1, 1993.

On September 8, 1994, Organon Inc submitted NDA 20-430 for the approval of Org 10172 (Orgaran 750 anti-Xa U bid, s.c., for up to 14 days postop. with the first dose preop.) for thromboprophylaxis in hip replacement . Seven controlled studies, 3 in patients undergoing elective hip replacement and 4 in patients with were submitted with the NDA. While the 3 clinical trials in hip replacement were comparable for design and dose regimen of Org 10172,

On June 7, 1995, the sponsor submitted a 120 day safety update and the final report of study #86030 comparing Org 10172 to unfractionated heparin in elective hip replacement surgery. The study was ongoing at the time of the NDA submission.

The Clinical Data are located in volumes 2.109-2.263 of the NDA submission. The data from study 86030 are located in vol. 7.2-7.6.

NDA 20-430 : Index of Clinical Data

* Studies of Thromboprophylaxis in hip replacement surgery.

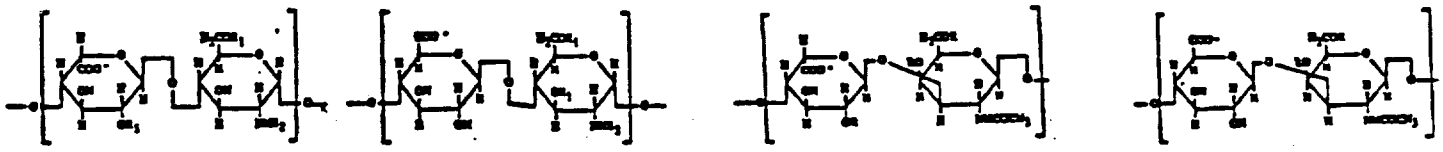
The medical review of NDA 20-430 includes only the studies performed to assess the efficacy and safety of Org 10172 for prophylaxis of DVT in elective hip replacement surgery.
The following volumes of the NDA were reviewed: v 2.3; v.2.109;

v.2.200-2.205 and 2.325-2.359 for study 004-023, v.2.209-2.212 and 2.363-2.368 for study 85140, v.2.223-2.225 and 2.387-2.400 for study 86002, v.7.2-7.6 for study 86030; v.2.254 and v.2.255 for the Integrated Summaries of Efficacy and Safety.

Pharmacologic Class of Org 10172

The drug substance ORG 10172 (Danaparoid sodium-USAN) is a natural mixture of LMW sulfated glycosaminoglycuronans derived from porcine intestinal mucosa. The mixture consists of ~84% heparan sulfate, ~12% dermatan sulfate and ~4% of chondroitin sulfate. The average MW of Org 10172 is 5500 daltons (range 4000-8000 daltons).
The chemical structure of Org 10172 is shown below:

Main Repeating Disaccharide Units:



Heparan Sulfate: R_1 = H or SO_3^-, R_2 = $COCH_3$ or SO_3^-

Dermatan Sulfate

Chondroitin Sulfate

Org 10172 is isolated from porcine intestinal mucosa, the same starting material as heparin and LMW heparins. However, heparin and heparin fragments are excluded in the extraction procedures of Org 10172, as confirmed by its structural analysis of the repeating disaccharide composition and anti-Xa/anti-IIa activity levels.

Org 10172 inhibits coagulation by enhancing the AT-III mediated inhibition of factor Xa. Approximately 5% of the heparan sulfate has high affinity and about 95% has low affinity for AT-III.
In the absence of specific analytic methods for the in vitro or ex vivo assay of Org 10172, the drug is characterized by anti-Xa activity. One mg of Org 10172 has 11.0 to 17.0 U of anti-Xa and not more than 0.5 anti-IIa U (anti-Xa/anti-IIa ratio >22).

The drug substance Org 10172 is manufactured by
The drug product Orgaran (Org 10172 injection) is manufactured and distributed in 1 mL ampules or glass syringes by Organon Inc..

Preclinical Pharmacology and Toxicology

Preclinical animal studies performed with Org 10172 showed that:

1) The absolute bioavailability of s.c. Orgaran is nearly 100%;
2) Org 10172 is not metabolized by the liver;
3) The kidney plays a significant role in the elimination of Org 10172 (by anti-Xa activity);
4) The pharmacokinetics are linear with respect to dose;
5) Org 10172 (anti-Xa activity) has a $T_{1/2}$ longer than heparin;
6) The anti-Xa $T_{1/2}$ is independent of route of administration;
7) The T_{max} is - 2-5 h after a s.c. dose in dogs and humans;
8) The volume of distribution is the blood compartment;
9) The effect of Org 10172 on PT, APTT, and TT is minimal.

Studies with various animal models of thrombosis show that Org 10172 had a dose-related antithrombotic effect when administered either i.v. or s.c.. In the stenosed vessel model in rabbits, the thromboprophylactic effect of Org 10172 was demonstrable for up to 12 hours after single s.c. dose while the effect of heparin was of shorter duration.

The animal studies showed that Org 10172 prevents thrombus formation and extension mainly by inhibiting fibrin formation and rendering any preformed thrombus less thrombogenic.

Org 10172 was found to cause less bleeding than heparin probably because of its minimal or no effect on platelet function.
Org 10172 showed no systemic toxicity at thromboprophylactic doses in all animal species tested.

Clinical Pharmacology

The PK profile of Org 10172 has been obtained in normal subjects, cardiac catheterization patients and patients with renal failure on hemodialysis. Approximately 1800 subjects received single or multiple i.v. or s.c. doses of Org 10172.

One of the 28 pharmacology studies was conducted in U.S. under IND
In this study, Org 10172 was administered to 24 healthy volunteers at the dose of 750 anti-Xa U i.v. and 750, 1500, and 2250 anti-Xa U s.c.. This study defined both the bioavailability and dose proportionality of Org 10172.

In the non-U.S. studies, i.v and s.c. Org 10172 was evaluated in males and females, and in elderly. Drug-drug or drug-antidote interaction and PK studies were performed. One study determined the effects of Org 10172 on the liver. Urine anti-Xa activity was measured in some

study for renal excretion of Org 10172.

The PK of Org 10172 were determined on seven different batches in three studies. A dose-dependent linear relationship between iv or sc doses of Org 10172 and plasma anti-Xa activity was demonstrated. The half-life of Org 10172 based on anti-Xa activity was independent of route of administration; the mean $\alpha T_{1/2}$ was 2.6 hours and the $\beta T_{1/2}$ was approximately 25 hours.
The absolute bioavailability of Org 10172 based on anti-Xa activity was approximately 100% for the subcutaneous route. Maximal concentration after s.c. administration was achieved at 3-3.5 hours. The peak urine concentration of anti-Xa activity occurs approximately six hours after a single intravenous bolus dose of Org 10172. After 12 hours about 65% of the total anti-Xa activity was excreted in the urine. The peak values for anti-Xa activity during steady state with repeated iv bolus doses administered once-daily were approximately 55% higher than those corresponding to single intravenous bolus doses. A possible circadian rhythm cannot be excluded. The covariates of age, gender, and weight were not found to be important for Org 10172.

The pharmacodynamic effects of Org 10172 on blood coagulation were assessed in terms of anti-Xa activity, anti-thrombin activity (anti--IIa), and thrombin-generation inhibiting activity (IIaGI), and routine coagulation tests(APTT, PT, TT, WBCT, and Thrombotest). A single i.v. dose up to 800 anti-Xa units of Org 10172 or s.c. doses up to 2250 anti-Xa U did not produce any detectable plasma anti-IIa response. Subcutaneous doses up to 3,250 anti-XaU or repeated doses did not prolong the APTT, PT, TT, or WBCT. Repeated iv doses up to 3,200 anti-Xa units had only minimal effect on the APTT and none on the PT and TT. Repeated s.c. doses did not prolong the APTT, PT, or TT. Continuous iv infusion up to 180 anti-Xa units per hour only slightly prolonged the APTT and WBCT.

The effect of Org 10172 on other parameters concerned with bleeding, thrombus formation and lysis were investigated, including:
. Platelet count;
. Platelet aggregation;
. Platelet release/activation;
. Platelet adhesion; and
. Bleeding time, and effect on clot stability.

Org 10172 had no effect on the platelet count when given for up to 14 days. Immune-mediated thrombocytopenia as that seen with heparin therapy, was not reported in the study population with the administration of Org 10172.

Org 10172 had no effect on <u>in-vitro</u> platelet adhesiveness or aggregation in response to a number of physiological agonists. The effect on thrombin-induced aggregation was due to the small

anti-thrombin activity of Org 10172. Unlike heparin, Org 10172 does not appear to influence platelet release, particularly PF4 and is not neutralized by PF4. No consistent effect on the bleeding time was seen after iv or sc doses of Org 10172.
Org 10172 iv or sc has no effect on the concentrations of the major clotting factors and did not lower the levels of AT-III and HC-II.
Org 10172 did not affect fibrinolytic activity.

Org 10172 has only a small effect on the release of triglyceride lipases and no effect on aldosterone production.

In the phase II program, 10 dose-response studies for DVT prophylaxis following orthopedic hip surgery were performed to establish the minimum effective dose (as assessed by the DVT and PE development) and the maximum safe dose (as judged by bleeding complications). In addition, 12 dose-ranging studies of DVT prophylaxis in patients undergoing general surgery were performed to evaluate the risk/benefit of Org 10172 in conditions such as surgery for non-malignant disorders, major surgery for malignancies and TURP, and to select the dose regimen to be used for prophylaxis of DVT following hip surgery. Seven dose-finding trials for other indications were performed.

In an early dose-ranging study for DVT/PE prophylaxis in hip surgery, an iv dose of 800 anti-Xa U of Org 10172 followed by an infusion of 100 or 183 anti-Xa U/h for 6 days produced a C_{max} of 0.5 anti-Xa U/mL in 3 of 5 treated subjects. All three subjects experienced unacceptable post-operative bleeding at the surgical site leading to premature termination of the study.
An i.v. dosing safety study of bolus doses of 800, 1,600, or 2,400 anti-Xa U of Org 10172 b.i.d. performed in patients undergoing TURP showed that blood loss at the surgical site was greatest with peak anti-Xa levels > 0.5 U/mL. Based on the above two studies, the maximum anti-Xa level for DVT and PE prophylaxis in surgical was set at no greater than 0.5 anti-Xa U/mL.
Phase II dose-response studies for DVT/PE prophylaxis in hip surgery, non-orthopedic surgery, and non-hemorrhagic stroke showed that the s.c. twice-daily dose of 750 anti-Xa units Org 10172 results in steady-state peak levels of about 0.20 U/mL.
Dosing levels >750 anti-Xa units, b.i.d., s.c., offered little gain in the reduction of DVT and a linear increase in the frequency of bleeding complications.

Based on the Phase II studies, the regimen of Orgaran 750 anti-Xa U s.c. q12h for up to 14 days post-operatively with the first dose given pre-operatively was selected to provide prophylaxis for all patients at risk of DVT. In surgical patients, prophylaxis with Org 10172 began pre-operatively had minimal effect on peri-operative bleeding.

Cross-Reactivity with Anti-Heparin Antibodies

Org 10172 is chemically distinct from both heparin and the LMWHs and contains no detectable heparin or heparin fragments. The cross-reactivity of Org 10172 with heparin-induced antibodies was evaluated in 225 Heparin-Induced-Thrombocytopenia (HIT) patients from a "compassionate-use" program. Nine out of 48 patients tested (18.4%) who had a positive Org 10172 cross-reactivity were never administered Org 10172. Five of the 177 patients (2.8%) with initially negative Org 10172 cross-reactivity tests developed thrombocytopenia after the administration of Org 10172 and were shown on repeat testing to have developed cross-reactivity. Thus, 53 of 225 (23.5%) patients with verified HIT had positive cross-reactivity. The cross-reactivity of Org 10172 with anti-heparin antibodies was lower than that of the various LMWH which approaches 100%.

Phase III Clinical Trials: Thromboprophylaxis in Hip Replacement

Four phase III clinical trials (#004-023, #85140, #86002, #86030) assessed the safety and efficacy of Org 10172 at the dose of 750 anti-Xa U bid for the prophylaxis of DVT/PE in hip replacement surgery. One study was conducted in the U.S. (#004-23), one in the Netherlands (#85140), one in Switzerland and Germany (#86002), and one in Italy (#86030). The U.S. study was conducted under IND

The formulation of Org 10172 used in the orthopedic trials was similar to that used in the PK studies and to the to-be-marketed formulation, except for the presence of sodium sulfite, anti-Xa concentration, and fill volume in some studies.

The patient population of the four controlled clinical trials were similar and consisted largely of Caucasian elderly women.

In all the studies, the primary efficacy parameter was the occurrence of DVT as determined by bilateral or unilateral venography (VG) performed at exit or earlier, if clinically indicated. A secondary efficacy parameter was the occurrence of PE.
In all studies, most patients has a follow-up evaluation of DVT/PE.

Venograms were adjudicated by an independent panel.

Efficacy analyses were performed on the Intent-to-Treat (ITT) and on the Evaluable population. The ITT included all patients with at least one dose of study drug, underwent specified surgery, and at least one post-surgery efficacy evaluation. The Evaluable group included patients who met all inclusion/exclusion criteria with no major protocol deviations.

Protocol No. 004-023 (vol. 2.200-2.205)

Study Title: A multicenter randomized open-label assessor-blind evaluation of Org 10172 bid versus Warfarin qd as a prophylaxis for DVT in patients undergoing elective hip replacement surgery.

Study Design: The study was performed at 14 centers in U.S. and included only patients undergoing elective hip replacement.

Patients with prior hip surgery within 1 year, hypertension, renal failure, weight <90 or > 300 lbs, coagulopathies, use of NSAID or other anti-platelet drugs within 72 hours, history of GI bleeding, intolerance to study drugs (warfarin, heparin-like drugs, contrast media, iodine), current DVT, or intracranial or ocular hemorrhage within 12 months were not eligible.
Patients were randomized after the screening process and treatment groups were stratified by study center.

The assessment schedule for the study is shown in Table 1(v.200,p.31)

TABLE 1
ASSESSMENT SCHEDULE

Days in Study	Screen Day	Surgery Day 1	2	3	4	5	6	7	8
History/ Demographics	X[1]								
Physical Examination	X[1]								X[4]
Bleeding Assessments[3]		X	X	X	X	X	X	X	X[4]
Bruising Measurement	X			X[4]					X[4]
ECG	X[1]								
Biochemistry	X[1]								X[4]
Hematology	X[1]								X[4]
Hemostasis: - PT (one stage)[5] - PTT - Bleeding Time	X X X[6]	X	X	X	X	X	X	X	X[4]
Urinalysis	X[1]								X[4]
Duplex Scanning	X[1]				X[4]				X[4]
Venography[7]									X[4]
Ventilation/Perfusion Lung Scan[7]									
Adverse Experiences		X	X	X	X	X	X	X	X

1 May be performed up to 1 week prior to the surgery day.
2 When indicated by positive duplex scan (for proximal thrombosis) or exit from the study.
3 Intraoperative and postoperative bleeding assessment as well as skin, mucous membranes, and urine examination for blood loss.
4 May be performed ± 1 day.
5 Daily PT determinations were performed in warfarin-treated patients only. Screening and exit PT determinations were performed in all patients.
6 Bleeding Time measurements were performed at the discretion of the investigator.
7 Only when indicated in patients with clinical symptoms suggestive of pulmonary embolism and in patients with a DVT confirmed by venography or suggested by duplex scanning (unless contrary to investigator's clinical practice).

Both study medications, Org 10172 (lot #CP087143 and #CP091090) and warfarin were supplied to each study centers by Organon Inc..

Org 10172 and warfarin were started prior to surgery.
Org 10172 was started 1-4 hours before surgery and the second dose given not earlier than 2 hours after surgery. Dosing was then continued twice daily from day 2 to day 8 or to until discharge. Warfarin therapy was started with a dose of 10 mg on the day before surgery, dosage was adjusted according to daily PT to 1.3-1.5 x control and continued for 8 days or to discharge.

Based on the expected incidence rate of DVT of 30% in the warfarin-treated group and 16% in the Org 10172-treated group, 432 patients were initially calculated to yield 310 efficacy evaluable patients. Due to the greater than expected rate of dropout and protocol violations, the protocol was subsequently amended to increase the total number of patients enrolled to 486.

Assessment of Efficacy and Safety

Efficacy evaluation (occurrence of DVT) included daily clinical assessment, Doppler Ultrasound (DUS) on day 4 $\pm$ 1 and at exit and exit bilateral venography (VG) on study days 6-8 or within 24 hours of the last dose of study drug. VG was to be performed at any time if indicated by clinical symptoms or positive DUS.

The protocol included an interim analysis to compare the DUS and VG in the first 100 patients who had both assessments, however this was not done because of lack of correlation between the two tests. For the purpose of the efficacy analysis, the diagnosis of DVT was based primarily on the interpretation of the VG which were blindly reviewed by each of the three members of the Adjudicating Committee.

As the study was multicenter, the techniques and the interpretations of the DUS and VG were specified in the protocol.
The protocol required that all patients with positive VG should undergo lung scan for evaluation of PE, this, however was not always carried out.

Major bleeding was defined as intraoperative transfusion of $\geq$ 4 units of blood or of > 2 units at any other one time, blood loss requiring reoperation, reduction in Hgb of 30% or more over a three day period, bleeding into a major organ (eye, lung, brain), more than 2 significant GI or GU bleeding, spontaneous recurrent hematomas or repeat bleeds.

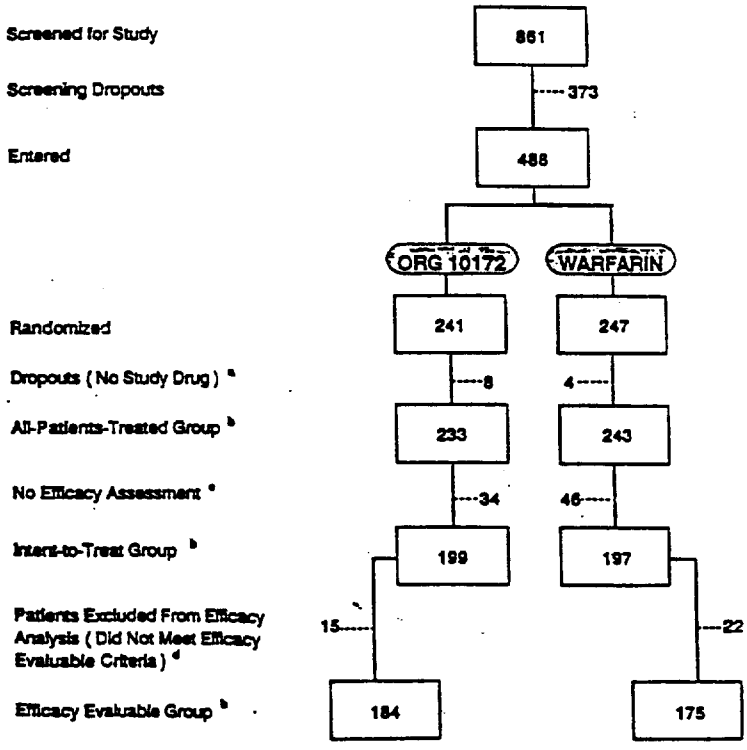
All adverse clinical experiences were classified according to severity, relation to the study drug, action taken and outcome.

Patients who experienced a DVT or a major bleeding event (study endpoints) at any time in the study were discontinued and considered as completers. Patients who received study drug for at least 6 days without DVT or major bleeding (i.e. early discharge) were considered as completers. A follow up at 1, 2, and 3 months postop. was obtained to record deaths or late thromboembolic events.

The data were analyzed in the Intent-To-Treat group which consisted of all randomized patients who had hip replacement, at least one dose of study drug and at least a unilateral VG, and in the Evaluable group, which was defined as the ITT group and having met all inclusion/ exclusion criteria without major protocol violations.
The All-Treated group included all randomized patients who received at least one dose of study drug regardless of any efficacy evaluation. This group was used for safety analyses.
Between-treatment comparison tests for both efficacy and safety were two-tailed with statistical significance of p-value <0.05.

The disposition of the patients is shown in Fig 2. (v.200,p.80)

FIGURE 2
DISPOSITION OF PATIENTS



Patients were excluded at screening mainly for refusal to participate, use of disallowed medications, contraindications, recent hip surgery, and cancellation of surgery.
Eight patients randomized to Org 10172 and 4 randomized to warfarin were excluded from the All-Treated group because did not receive any medication.
A total of 80 patients were excluded from the ITT because venography was not performed, their distribution according to treatment and study center is shown below:

Study Center	Treatment	
	Org 10172	Warfarin
#2	2/6	3/6
#3		2/10
#4	9/25	9/26
#5	2/35	6/35
#6	2/17	4/19
#7		1/5
#8	3/44	2/46
#9		3/15
#11	1/17	2/18
#12	10/41	12/41
#13	3/14	1/14
#14	2/3	1/3
Excluded/All Treated:	34/233(14.5%)	46/243(18.9%)

More warfarin-treated patients failed to undergo VG, however, no significant differences were noted between treatment groups at any of the study centers.
The majority of patients underwent VG at exit (day 7-8).

The patients excluded from the Efficacy Evaluable population are summarized in table 6. (v.200, p.89-91)

Patients with minor protocol deviations, as determined by Organon Inc., remained eligible for inclusion in the Efficacy Evaluable group. The patients with "minor" protocol deviations were: females of child bearing age, patients with hypertension, chronic DVT, receiving ionic contrast medium, not terminated for major bleeding, re-randomized, abnormal exit laboratory tests or missing baseline PT/APTT, improperly dosed preoperatively, using TEDS, unilateral VG, no repeat DUS, no V/Q scan after positive VG, prolonged dosing, prior hip surgery <12m.
The patients with "minor" protocol deviations allowed to enter the efficacy evaluable groups are shown in table 7 (v.200, p.93).

TABLE 6
PATIENTS EXCLUDED FROM EFFICACY EVALUABLE GROUP*

Patient	No. of Days on Study Drug	Reason for Exclusion
Org 10172 (15 of 199 Patients)		
Center 2 (2 of 4 Patients)		
209	7	Interfering concomitant medication.
212	7	Interfering concomitant medication.
Center 3 (1 of 8 Patients)		
309	7	No adjudicated venogram.[b]
Center 6 (1 of 15 Patients)		
618	7	Disallowed pretrial medication.
Center 8 (2 of 41 Patients)		
8066	6	Disallowed pretrial medication; Interfering concomitant medication.
808	8	No adjudicated venogram.
Center 9 (1 of 16 Patients)		
913	8	Use of TEDS® for prolonged periods; Improperly scheduled pre-op dose.
Center 10 (1 of 4 Patients)		
1008	8	Interfering concomitant medication.
Center 11 (2 of 16 Patients)		
1125	8	Hip surgery within previous 12 months.
1132	7	Disallowed pretrial medication.
Center 12 (5 of 31 Patients)		
1215	9	Disallowed pretrial medication.
1223	7	Interfering concomitant medication.
1228	8	Missed doses;[b] Interfering concomitant medication.
1236	8	Disallowed pretrial medication.
1283	8	Disallowed pretrial medication.

TABLE 6 (CONTINUED)
PATIENTS EXCLUDED FROM THE EFFICACY EVALUABLE GROUP*

Patient	No. of Days on Study Drug	Reason for Exclusion
Warfarin (22 of 197 Patients)		
Center 4 (2 of 17 Patients)		
450	7	Disallowed pretrial medication.
452	10	Interfering concomitant medication.
Center 5 (3 of 29 Patients)		
501	6	Interfering concomitant medication.
507	7	Disallowed pretrial medication.
511	6	No adjudicated venogram.*
Center 6 (2 of 15 Patients)		
636	8	Use of TEDS® for prolonged periods.
637	7	Disallowed pretrial medication.
Center 8 (2 of 44 Patients)		
8070	8	Improperly scheduled preop dose.
8084	8	Interfering concomitant medication.
Center 9 (7 of 12 Patients)		
901	6	Use of TEDS® for prolonged periods.
909	6	Disallowed pretrial medication.
914	6	Use of TEDS® for prolonged periods.
915	7	Interfering concomitant medication. Use of TEDS® for prolonged periods.
918	8	Use of TEDS® for prolonged periods.
924	8	Preoperative dose warfarin less than 10 mg required.
930	6	Preoperative dose warfarin less than 10 mg required.
Center 11 (2 of 16 Patients)		
1130	8	Disallowed pretrial medication.
1133	8	Disallowed pretrial medication.
Center 12 (2 of 29 Patients)		
1243	8	Disallowed pretrial medication.
1265	7	No preoperative dose.
Center 13 (2 of 13 Patients)		
1315	8	Interfering concomitant medication.
1321	9	Disallowed pretrial medication.
TOTAL NUMBER OF PATIENTS EXCLUDED FROM THE EFFICACY EVALUABLE GROUP = 37		

TABLE 7
MINOR PROTOCOL DEVIATIONS[a] -- EFFICACY EVALUABLE GROUP

Protocol Deviations	Org 10172 (N)	Warfarin (N)
Females of Child-Bearing Potential Females were to be either postmenopausal greater than 1 year or with hysterectomy and/or bilateral tubal ligation for at least 6 months prior to enrollment.	3	2
Uncontrolled Hypertension Serious uncontrolled hypertension was defined as systolic BP > 180 mmHg or diastolic BP > 110 mmHg with treatment.	1	1
Use of Ionic Contrast Medium For consistency among centers, a low ionic strength contrast medium such as Omnipaque was to be used.	14	4
Major Bleeds Not Terminated[b] A patient experiencing a major bleed was to be terminated from the study as having reached a study endpoint.	2	1
Re-Randomization of Patients Patient received a preoperative dose; surgery was canceled. Patient re-entered after at least a one week wash-out period.	2	0
Exit Laboratory Assessment Outside Treatment Window Exit laboratory assessments were to be performed ± 24 hr last dose of study drug.	20	21
Missing Either PT and PTT at Screen Screen PT and PTT were to be performed within 1 week of study entry.	8	12
Improperly Scheduled Preoperative Dosing Org 10172 patients dosed from 45-265 minutes prior to surgery. Warfarin patients dosed not more than 15 hours 40 minutes prior to surgery.	8	17
Chronic DVT Chronic DVT adjudicated as no acute DVT.	1	1
Use of TEDS® For Brief Period[b] Use of TEDS® for brief period in recovery room before removal by study coordinator.	0	1
Unilateral Venography Venography assessment performed on one leg as opposed to the protocol requirement of both legs.	26	30
Non-Repeated Duplex Ultrasonography Equivocal duplex findings were to be repeated within 24 hr.	9	9
Absent V/Q Scan After Positive Venography Positive venography finding by investigator was to be followed by V/Q scan for PE evaluation.	14	34
Prolonged Dosing[c] Patients were to receive study drug for a maximum of six-eight days.	9	4
Prior THR < 12 Months Before Current THR[d] Current THR was required to be at least 12 months after prior THR.	0	1

There were no significant differences between treatment groups for demographic and baseline characteristics in both ITT and evaluable groups (Table 8, v.200, p. 96).

TABLE 8
DEMOGRAPHICS AND BASELINE CHARACTERISTICS — INTENT-TO-TREAT GROUP

	Org 10172				Warfarin				
	N	Mean	Median	Range	N	Mean	Median	Range	p-Value[a]
Age (yr)	199	67	68	37-91	197	66	68	23-88	(0.79)
Weight (kg)	199	79	79	44-132	197	80	79	41-136	(0.87)
Height (cm)	198	169	168	140-193	196	170	170	127-196	(0.70)
Gender:									
Male	90				102				0.19
Female	109				95				
Race:[b]									
Caucasian	192				184				0.16
Black	6				9				
Asian	0				1				
Other	1				3				
Side of Surgery:									
Right	89				113				0.02[c]
Left	110				83				
Both	0				1				
Length of Surgical Procedure (min): (Including Anesthesia)	199	172	155	55-465	197	173	160	50-545	(0.57)
Type of Surgical Procedure:									NA
Total Hip Replacement	199				197				
Bipolar Hip Replacement	0				0				
Other	0				0				
Type of Anesthesia									0.82
General Only	170				164				
Spinal/Epidural (Regional Only)	9				11				
Mixed (General and Spinal)	20				22				
History of DVT									0.20
Documented: Clinically	4				1				
Venogram	4				1				
Unknown	2				3				
Location: Proximal (Thigh; Popliteal)	5				1				
Distal (Calf)	5				4				
Unknown	3				0				
History of PE									0.17
Documented: Clinically	1				3				
Pulmonary Angiogram	0				0				
Lung Scan	1				1				
Unknown	0				1				
Recent Mobility (In the Last Month)[d]									
Bedridden	0				0				
Mobile With Aid	96				95				1.00
Mobile Without Aid	103				102				

Includes patients with available data.

a Age, weight, height, and length of surgery analyzed using ANOVA based on ranks (p-values in parentheses). Categorical data analyzed using Cochran Mantel-Haenszel Test.
b Race analyzed as either Caucasian or Non-Caucasian.
c Statistically significant at $p \leq 0.05$
d Mobility analyzed as Bedridden, Mobile With Aid, or Mobile Without Aid.
NOTE: Information was derived from Data Listings 1, 2.2, and 10.1.

Efficacy Analysis

The overall incidence of DVT as diagnosed by VG is summarized in the following tables for the ITT and for the Evaluable groups.

Number (%) of patients with DVT[a]
Intent-to-treat group

	Org 10172 N=199	Warfarin N=197	p-value[b]
Proximal[c] : N (%)	3 (1.5)	8 (4.1)	0.13
Distal[d]: N (%)	28 (14.1)	49 (24.9)	0.007
Overall[e] : N (%)	29 (14.6)	53 (26.9)	0.003

Number (%) of patients with DVT[a]
Efficacy Evaluable group

	Org 10172 N=184	Warfarin N=175	p-value[b]
Proximal[c] : N (%)	3 (1.6)	7 (4.0)	0.19
Distal[d]: N (%)	27 (14.7)	46 (26.3)	0.007
Overall[e] : N (%)	28 (15.2)	49 (28.0)	0.003

[a] By positive venogram only.
[b] Using CMH test.
[c] Popliteal, iliac, and femoral.
[d] Calf
[e] A patient may be counted more than once (proximal and distal)

The intent-to-treat analysis included VGs of 3 patients evaluated only by investigator and site of DVT was assigned from the CRFs. In the Efficacy evaluable group, diagnosis of DVT and site of DVT were by final adjudication.

The incidence of DVT was statistically significantly higher in the warfarin group (p=0.003 for both ITT and evaluable groups). In the ITT analysis, the relative risk reduction of DVT in the Org 10172 group was 45.7% and the estimate of relative risk (odds ratio) for overall DVT in the warfarin group was 2.070 (95% CL 1.214

to 3.529). The estimates of relative reduction and relative risk of DVT were similar in the evaluable group.
The incidence rate for proximal DVT was lower in the Org 10172 group compared to the warfarin group, but the difference was not statistically significant.

The side on which the DVT occurred in relation to the side of surgery is shown below:

Study Drug	Total N	Side of DVT relative to side of surgery			
		Both Sides N(%)	Same side N(%)	Opposite side N(%)	Unknown side of DVT N(%)
Org 10172	29	8(27.6%)	15(51.7%)	4(13.8%)	2(6.9%)
Warfarin	53	9(17.0%)	26(49.1%)	14(26.4%)	4(7.5%)

Exploratory analyses within each treatment group were performed to assess the possible effect of several variables and risk factors on the incidence of DVT.

Within each treatment group, no relationship was found for:
- Incidence of DVT by age (≥70 years vs <70 years);
- Incidence of DVT by gender (males vs females);
- Incidence of DVT by missing at least 2 consecutive doses or 3 non-consecutive doses.
- Incidence of DVT by ideal body weight (>30% over ideal body weight by gender vs not > 30% over ideal body weight);

Exploratory analysis within each of the treatment groups indicated statistical significance in the Org 10172-treated but not warfarin-treated patients for the incidence of DVT by duration of surgery (time from start of anesthesia to end of surgery; > 130 minutes vs < 130) minutes). For Org 10172-treated patients, this was statistically significant in both ITT group (p=0.02) and in the Evaluable Group (p=0.04).

For both the ITT and the Evaluable Group, logistic regression was used to determine the treatment effect on the incidence of DVT with the following risk factors as covariates: age, intraoperative blood loss, duration of surgery, transfusions, history of DVT/PE, degree of mobility, gender, weight, Hgb..

Only treatment and gender (male gender and warfarin treatment) for the

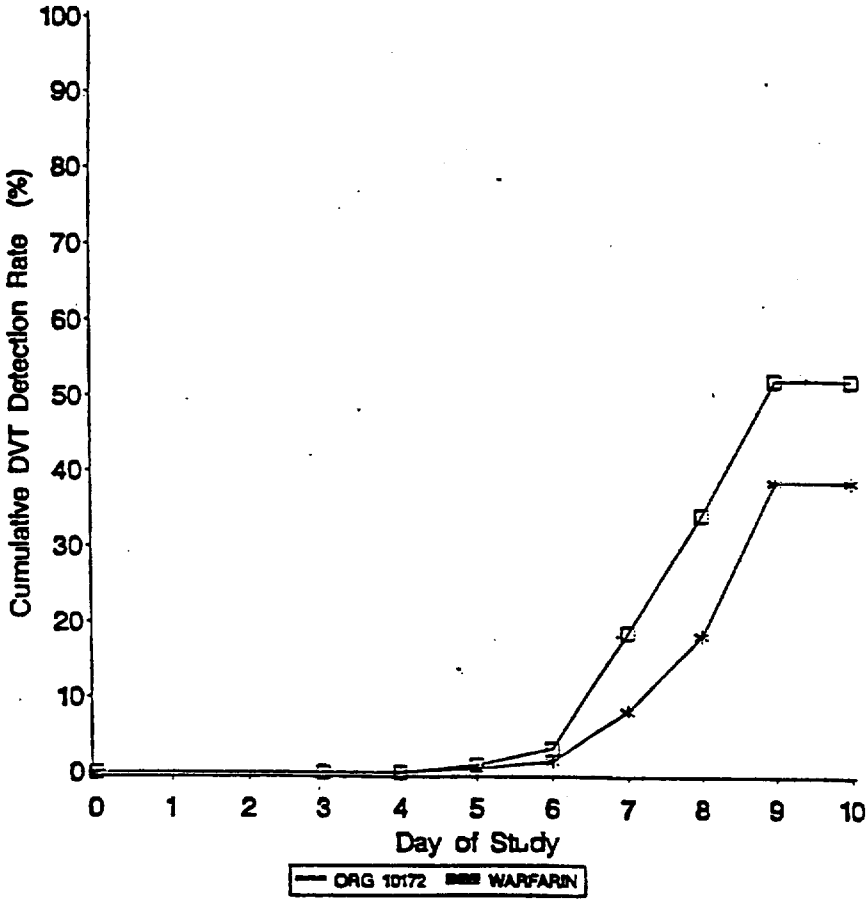
ITT and only treatment, gender, and weight (male gender, warfarin treatment, weight >30% IBW) for the Evaluable population were significant at the p=0.05 level.

Life Table estimates of the cumulative DVT detection rate showed a statistically significant difference in the two treatment groups (p=0.001 in ITT and p=0.002 for the evaluable groups respectively). The cumulative rate of detection of DVT on day 7 (fig 3, v.200, p.120) was 18.3% for Org 10172 and 18.7% for warfarin (56.2% RR).

FIGURE 3

LIFE TABLE ESTIMATES OF CUMULATIVE DVT DETECTION RATES (%)

INTENT-TO-TREAT GROUP



Five patients, 3 Org 10172 and 2 warfarin, had clinical symptoms of PE. The diagnosis was confirmed only in one warfarin patient.

A very poor agreement of outcomes between Doppler Ultrasound (DUS) and VG was observed. A concordance analysis of 392 patients who underwent both procedures showed the following results:

- Negative DUS and Negative VG= 305
- Positive DUS and Positive VG= 1
- Negative DUS and Positive VG= 80
- Positive DUS and Negative VG= 6

All patients in both groups received concomitant medications. Twenty patients, 11 in the Org 10172 group and 9 in the warfarin group, received disallowed medications such as ASA or other antiplatelet drugs (Toradol) and anticoagulants. Eleven of these patients underwent VG and were included in the ITT analysis.

From the total 476 All-Treated patients (233 Org 10172- and 243 warfarin-treated), 65 were discontinued. The distribution of the discontinued patients between the treatment groups and the reason for discontinuation are shown in the following table (v.200,p.135).

Reasons given for Discontinuation[a]	Org 10172 N=233	Warfarin N=243	p-value[b]
Rapid Recovery and Discharge	0	2	0.19
Physician withdrawal	2	3	0.67
Minor bleeding event	1	0	0.32
Insufficient compliance	24	26	0.82
Death	1	0	0.3
Other	1	5	1.12
Overall Total	29	36	0.4

[a] As given on the End of Trial Form
[b] Using CMH test.

The 233 patients in the Org 10172 group and the 243 patients in the warfarin group were exposed to study treatment for a mean of 7.1 and 6.8 days, respectively.

Safety Analysis

A total of 246 patients experienced bleeding, 240 patients experienced minor bleeding and 14 patients (7 in the Org 10172 group and 7 in the warfarin group) experienced major bleeding (table 23, p.0142). Ten of the 14 patients with major bleeding were from two centers. Eight patients (3 Org 10172- and 5 warfarin-treated) experienced major intraoperative bleeding during revision of prior hip replacement with duration of the operation ranging from 5 hr to >10 hr compared to the median duration of 2.5 hr for hip replacement.

TABLE 23
PATIENTS WITH MAJOR BLEEDING[a] —
ALL-PATIENTS-TREATED GROUP

Center-Patient	Study Day[b]	Medication Day[c]	Description of Event
Org 10172			
2-206	3	3	Patient bled from operative site when drain was removed on Day 3 and required transfusion of 3 units autologous PRBC. Patient received 1 pre- and 2 postoperative doses; study drug was withheld on Day 3.
4-425	1	1	Patient experienced severe[d] blood loss (4670 ml) during surgery (revision, 8 hr 30 min) requiring a transfusion of 4 units autologous PRBC. Only one preoperative dose of study drug was administered.
4-428	1	1	Patient experienced severe[d] blood loss (2900 ml) during surgery (bipolar hip arthroplasty plus revision, 5 hr 15 min) requiring transfusion of 4 units PRBCs. Only one preoperative dose of study drug was administered.
4-441	5	5	Hemoglobin decreased from 13.2 g/dL to 8.3 g/dL over a three-day period (Day 2 - Day 5). Investigator retained patient in study through Day 7; patient received 7 days of study drug.
4-460	1	1	Patient had 1 minor bleed during surgery (revision, 4 hr 30 min, 3 units autologous PRBC transfused); 1 major bleed during the perioperative period (Day 1) (3 units autologous PRBC transfused); and 1 minor bleed on Day 2 (2 units PRBC transfused). Investigator retained patient in study through Day 8; patient received 8 days of study drug.
5-508	1	1	Patient experienced severe[d] blood loss (5500 ml) during surgery (revision, 8 hr 15 min) requiring a transfusion of 6 units PRBCs, 4 units platelets and 2 units autologous blood. Only one preoperative dose of study drug was administered.
8-8059	5	5	Hemoglobin decreased from 9.5 g/dL to 6.9 g/dL over a three-day period (Day 2 - Day 5). Surgery was revision of prior THR.

TABLE 23 (CONTINUED)
PATIENTS WITH MAJOR BLEEDING[a] —
ALL-PATIENTS-TREATED GROUP

Center-Patient	Study Day[b]	Medication Day[c]	Description of Event
Warfarin			
4-402	1	2	Patient experienced severe[d] blood loss (1800 ml) during surgery (revision, 4 hr 55 min) requiring transfusion of the following: 4 units autologous PRBCs during surgery, 1 unit autologous PRBC perioperatively, 2 units PRBC on Day 2 (minor bleed), and 1 unit PRBC on Day 3. Patient received preoperative and Day 1 study drug only (Day 2 not administered).
4-404	1	1	Patient experienced moderate[d] blood loss (1100 ml) during surgery (revision, 5 hr 15 min) requiring transfusion of 2 units PRBCs and 3 units autologous blood. Only one preoperative dose of study drug was administered.
4-417	1	2	Patient experienced severe[d] blood loss (1500 ml) during surgery (revision, 10 hr 14 min) requiring a transfusion of 5 units autologous blood. Postoperative coffee ground drainage from nasogastric tube evidenced in the recovery room. Only one preoperative dose of study drug administered.
5-516	2	2	Patient required a transfusion of 3 units autologous whole blood on Day 2. Hemoglobin decreased from a preoperative value of 11.3 g/dL (postoperative hemoglobin not available) to 7.8 g/dL (Day 2). Investigator retained patient in study through Day 6 (six days of study medication).
5-567	1	1	Patient experienced severe[d] blood loss (1500 ml) during surgery (revision, 7 hr 25 min) requiring a transfusion of 4 units autologous whole blood. Investigator retained patient in study through Day 4. Study drug was administered preoperatively as well as on Day 2, and on Day 4; Day 3 study drug was withheld.
6-626	4	5	Hemoglobin decreased from a postoperative value of 12.6 g/dL to 8.1 g/dL (Day 4). Patient exited after study drug was administered on Day 5.
9-921	1	1	Patient lost 2000 mL of blood during surgery (revision, 10 hr 25 min) and was transfused with 3 units PRBCs and 3 units autologous whole blood. Investigator retained patient in study through Day 6 (six days of study drug).

The surgical blood loss and transfusion requirements in the two treatment groups are summarized in tables 24 and 25. (p.0146/0147) A significantly greater number of Org 10172-treated patients received blood post-operatively compared to the warfarin-treated group (p=0.03 for therapeutic transfusion and p= 0.04 for all transfusion). The mean number of units of blood transfused was not significantly different in the two groups (1.7 vs 1.6 units).

TABLE 24
NUMBER OF PATIENTS WITH BLOOD LOSS AND
NUMBER OF PATIENTS GIVEN BLOOD TRANSFUSIONS
ALL-PATIENTS-TREATED GROUP

Parameter / Time Period	Org 10172		Warfarin		p-Value[3]
	N[2]	Frequency (%)	N[2]	Frequency (%)	Org 10172 vs. Warfarin
Blood Loss[4]					
Intraoperative	233	231 (99.1)	241	241 (100.0)	0.16
Perioperative[5]	176	159 (90.3)	186	167 (89.8)	0.85
Postoperative[6]	163	149 (91.4)	168	152 (90.5)	0.71
Total[7]	176	162 (92.0)	187	171 (91.4)	0.83
Therapeutic Blood Transfusions[8]					
Intraoperative	233	56 (24.0)	241	60 (24.9)	0.66
Perioperative[5]	233	27 (11.6)	252	32 (13.2)	0.63
Postoperative[6]	219	91 (41.6)	224	74 (33.0)	0.03[9]
Total[7]	239	103 (44.2)	243	93 (38.3)	0.12
All Blood Transfusions					
Intraoperative	233	64 (27.5)	241	67 (27.8)	0.84
Perioperative[5]	233	43 (18.5)	242	50 (20.7)	0.65
Postoperative[6]	219	144 (65.8)	224	127 (56.7)	0.01[9]
Total[7]	233	159 (68.2)	243	151 (62.1)	0.13

[1] Number of patients for whom this information was available.
[2] Using CMH procedures.
[3] All patients from Centers #9 and 12 have been excluded from the analysis of blood loss at the perioperative, postoperative, and total blood loss assessments due to a lack of consistent use of a drain.
[4] Up to midnight of operation day (recorded as "Postoperative" on the CRF).
[5] Total reported in Surgery/Blood Loss Form, Days 2-8 as applicable (excluding Intraoperative and Perioperative).
[6] Total reported in Surgery/Blood Loss Form (excluding Intraoperative).
[7] Does not include the routine return of a patient's own cells.
[8] Statistically significant at the 5% level.

TABLE 25
SUMMARY OF ESTIMATED BLOOD LOSS AND TRANSFUSIONS REQUIRED THROUGHOUT THE STUDY — ALL-PATIENTS-TREATED GROUP

Parameter Time Period	Org 10172					Warfarin					p-Value[b] Org 10172 vs Warfarin
	N[a]	Mean	SD	Min	Max	N[a]	Mean	SD	Min	Max	
Estimated Volume of Blood Loss (mL)[c]:											
Intraoperative	229	720.0	619.8			240	667.3	449.7			0.92
Perioperative[d]	158	389.9	241.0			164	420.2	362.4			0.33
Postoperative[e]	148	301.9	224.8			150	344.0	275.4			0.86
Total[f]	162	656.1	365.7			167	721.7	497.4			0.62
Therapeutic Blood Transfusions (No. of Units of PRBC)[g]:											
Intraoperative	56	1.7	1.2			60	1.8	1.1			0.96
Perioperative[d]	27	1.3	0.5			32	1.3	0.5			0.38
Postoperative[e]	91	1.7	0.7			74	1.6	0.6			0.11
Total[f]	103	1.9	0.9			93	1.7	0.8			0.08
All Blood Transfusions (No. of Units of PRBC):											
Intraoperative	64	1.6	1.1			67	1.8	1.1			0.99
Perioperative[d]	43	1.3	0.5			50	1.2	0.4			0.69
Postoperative[e]	144	1.7	0.7			127	1.6	0.7			0.07
Total[f]	159	1.8	0.8			151	1.8	0.8			0.10

a Sample size reflects only those patients who had a measurement for a particular parameter.
b Using two-way ANOVA based on ranks for continuous measures.
c All patients from Centers #9 and 12 have been excluded from the analysis of blood loss at the perioperative, postoperative, and total blood loss assessments due to a lack of consistent use of a drain.
d Up to midnight of operation day (recorded as "Postoperative" on the CRF).
e Total reported in Surgery/Blood Loss Form, Days 2-8 as applicable (excluding Intraoperative and Perioperative).
f Total reported in Surgery/Blood Loss Form (excluding Intraoperative).
g Does not include the routine return of a patient's own cells.

Logistic regression was used to determine the treatment effect on therapeutic and all transfusions with the risk factors of center, age, intraop. blood loss, gender, and Hgb levels as covariates. Of these, only center, age and gender were statistically significant for therapeutic transfusion while baseline Hgb, center, gender, and treatment were statistically significant for all transfusion.

Subjective, open label assessment of severe intra-, peri-, and post-operative bleeding by the investigators showed no difference between the two groups (17.4%, 1.9%, 0% for Org 10172, and 13.3%, 2.4%, 0.7% for warfarin group respectively).
The incidence of minor bleeding was similar in the two treatment groups: 52.4% in the Org 10172 group and 48.6% in the warfarin group. Hematuria occurred in 10 Org 10172- and in 8 warfarin-treated patients. Bruising was reported in about 38% of all patients and wound hematomas in 3 Org 10172 (1.3%) and 1 warfarin patient (0.4%). No significant differences in Hgb or Hct were reported for the two groups. The number of patients with clinically significant low outliers was similar for both groups (3 in each group).

Three Org 10172-treated patients and one warfarin-treated patient experienced serious adverse clinical experiences (ACE). None of the ACEs were attributed to study drug. One warfarin patient was withdrawn because of ACE. One Org 10172 patient died of arrhythmia.

The overall prevalence of ACEs. with the exception of bleeding, was in excess of 95% in both treatment groups (table 32, v.200, p.185).

TABLE 32
OVERALL ASSESSMENT OF ADVERSE CLINICAL EXPERIENCES
ALL-PATIENTS-TREATED GROUP

ACE Category	Org 10172 n (%) (N=233)	Warfarin n (%) (N=243)
Patients With at Least One ACE	224 (96.1)	232 (95.5)
Patients With at Least One Serious ACE[a]	3 (1.3)	1 (0.4)
Patients With at Least One Severe ACE	19 (8.2)	16 (6.6)
Patients With ACEs Contributing to Discontinuation[b,c]	0 (0.0)	2 (0.8)
Patients in Which the Relationship of ACE to Study Drug is Either Possible, Probable, or Definite	13 (5.6)	4 (1.6)

a As per 21 CFR 312.32.a.
b Includes all patients with an adverse experience for which action taken was dosage stopped. Patient #703 experienced chest pain and left calf tenderness which resulted in the dosage being stopped. However, this patient reached a study endpoint (PE) due to confirmatory evidence of PE (high probability V/Q scan).
c Patient #1206 experienced an ACE (chest pain) and was discontinued from the study. The patient was subsequently re-randomized as #1217. The ACE for Patient #1206 has not been included in the overall assessment of ACEs in the study.

The frequency of ACEs by body system is summarized in table 30 (p.165).

TABLE 30
FREQUENCY (%) OF PATIENTS WITH ADVERSE CLINICAL EXPERIENCES GROUPED BY BODY SYSTEM — ALL-PATIENTS-TREATED GROUP

Body System[a] (Relationship of ACE to Study Drug)[b]	Frequency (%)		p-Value[c] Org 10172 vs Warfarin
	Org 10172 (N = 233)	Warfarin (N = 243)	
Body as a Whole[d] (Related/Non-Related)	216 (93%) (3% / 89%)	216 (89%) (1% / 88%)	0.16
Cardiovascular System[e] (Related/Non-Related)	21 (9%) (0% / 9%)	21 (9%) (0% / 9%)	1.00
Digestive System (Related/Non-Related)	141 (61%) (1% / 60%)	138 (57%) (1% / 56%)	0.46
Hemic and Lymphatic System (Related/Non-Related)	1 (<0.5%) (0% / < 0.5%)	1 (<0.5%) (0% / < 0.5%)	1.00
Metabolic and Nutritional Disorders (Related/Non-Related)	34 (15%) (0% / 15%)	31 (13%) (0% /13%)	0.59
Miscellaneous (Related/Non-Related)	0	2 (1%) (0% / 1%)	0.50
Musculoskeletal System (Related/Non-Related)	19 (8%) (0% / 8%)	15 (6%) (0% / 6%)	0.48
Nervous System (Related/Non-Related)	59 (25%) (< 0.5% / 25%)	79 (33%) (0% / 33%)	0.09
Respiratory System (Related/Non-Related)	38 (16%) (<0.5% / 16%)	34 (14%) (0% / 14%)	0.52
Skin and Appendages (Related/Non-Related)	52 (22%) (3% / 19%)	41 (17%) (0% / 17%)	0.17
Special Senses (Related/Non-Related)	2 (1%) (0% / 1%)	2 (1%) (0% / 1%)	1.00
Urogenital System (Related/Non-Related)	43 (18%) (0% / 18%)	29 (12%) (0% / 12%)	0.05[d]
Overall (Related/Non-Related)	224 (96%) (6% / 91%)	232 (95%) (2% / 94%)	0.82

[a] Patient may be counted in more than one body system.
[b] "Related" refer to possible, probable, or definite, and "Non-Related" refers to unlikely or none.
[c] Using Fisher's exact test (two-tailed).
[d] Statistically significant at the 0.05 level.

There were no clinically important differences between treatments for shifts from baseline to last measurement for any biochemistry or hematology variables. No patients in any group developed thrombocytopenia.

Aside for the prolongation of PT in the warfarin group, no other changes in hemostatic parameters were noted.

Approximately 10% of the patients in each group were readmitted to the hospital at some time during the follow-up period. Four patients in the Org 10172 group developed DVT, each had a positive adjudicated exit VG and were included in the DVT efficacy analysis for the in-treatment period. One of the 5 warfarin patients with DVT had a positive adjudicated exit VG.

One Org 10173-treated patient and 3 warfarin-treated patients had clinical symptoms of PE in the post-treatment period. The diagnosis was confirmed in 2 of the warfarin patients by high probability lung scan in one and by angiogram in the other. None of the 2 patients had confirmed DVT. Both of the remaining 2 patients with symptoms of PE had a diagnosis of suspected PE only by abnormal V/Q scan.

COMMENTS:

The study was a multicenter, randomized, active control, open-label clinical trial comparing Org 10172 to warfarin for thromboprophylaxis in hip replacement surgery. Eligible patients were randomized to Org 10172 or to warfarin treatment on the day of surgery.

The efficacy endpoint was represented by development of a thromboembolic event, i.e., DVT diagnosed by VG or PE diagnosed by V/Q lung scan. Venograms were read by the investigator, but the final assessment of the VGs (positive or negative DVT) was made by an Adjudicating Committee blinded to treatment assignment. Most patients had Doppler US screening for DVT, however, the sensitivity of the test was unsatisfactory for the detection of clinically silent DVT as only one patient had both tests positive for DVT.

A total of 233 of 241 patients randomized to Org 10172 and 243 of 247 patients randomized to warfarin were treated. The ITT population did not include all randomized patients, rather it included randomized patients who were treated with study drug and had efficacy assessment. Consequently, of the 476 randomized and treated patients, 79 (34 Org 10172 and 46 warfarin patients) were excluded from the ITT analysis because of lack of efficacy assessment by VG.
Fifteen (15) additional patients in the Org 10172 and 22 in the warfarin group were excluded from the Efficacy-Evaluable group due to lack of adherence to protocol due mainly to the use of disallowed

medications or TED stocking.

In both ITT and Evaluable population analyses of efficacy, the incidence rates of DVT were significantly lower in the Org 10172-treated groups than in warfarin-treated groups: 14.6% vs 26.9% (p=0.003) in the ITT and 15.2% vs 28% in the Efficacy analyses.

More patients in the warfarin group (46 or 19%) than in the Org 10172 group (34 or 14.6%) were excluded from the ITT analysis because of lack of VG. However, no bias was detected for the exclusion of patients from either ITT or evaluable analyses.
In fact, when the patients missing VG are included in the ITT analysis with negative DVT endpoint (denominator), the incidence of DVT of 21.4% (53/247) in the warfarin group remained significantly higher than in the Org 10172. Of the patients excluded from the Evaluable analysis in the Org 10172 treatment group, one had positive VG and 14 had negative VG; whereas, of the 22 patients excluded from the Efficacy-Evaluable analysis in the warfarin group, four had positive VG and 18 had negative VG.

Fifteen study centers participated in the study with enrollment of patients ranging from 2 to 85 in number.
The distribution of patients by center, treatment and efficacy populations (ITT/Evaluable) are summarized in the following table.

Center	Number of patients by Study Center **Org 10172** ITT/Evaluable	**Warfarin** ITT/Evaluable
#2	4/2	3/3
#3	8/7	8/8
#4	16/16	17/15
#5	33/33	29/26
#6	15/14	15/13
#7	3/3	4/4
#8	41/39	44/42
#9	16/15	12/5
#10	4/3	5/5
#11	16/14	16/14
#12	31/26	29/27
#13	11/11	11/11
#14	1/1	2/2
Total	**199/184**	**197/175**

The number of patients with DVT by treatment group and by center for the all-treated and for the evaluable groups are shown below.

Number (%) of Patients with DVT by Treatment and Study Center
All-Treated Patients

Study Center	Treatment: Org 10172	Treatment: Warfarin
#2	0/4 (0.0%)	0/3 (0.0%)
#3	5/8 (62.5%)*	2/8 (25.0%)
#4	2/16(12.5%)	3/17(17.6%)
#5	5/33(15.2%)	8/29(27.6%)
#6	3/15(20.0%)	4/17(26.7%)
#7	0/3 (0.0%)	1/4 (25.0%)
#8	8/41(19.5%)	19/44(43.2%)
#9	3/16(18.8%)*	2/12(16.7%)
#10	1/4 (25.0%)*	1/5 (20.0%)
#11	1/16(6.0%)	4/16(25.0%)
#12	1/31(3.2%)	6/29(20.7%)
#13	0/11(0.0%)	2/13(15.4%)
#14	0/1 (0.0%)	1/2 (50.0%)
Total DVT	**29/199(14.6%)**	**53/197(26.9%)**

Number (%) of Patients with DVT by Treatment and Study Center

Study Center	Treatment: Org 10172	Treatment: Warfarin
#2	0/2 (0.0%)	0/3 (0.0%)
#3	4/7 (57.1%)*	2/8 (25.0%)
#4	2/16(12.5%)	3/15(20.0%)
#5	5/33(15.2%)	8/26(30.8%)
#6	3/14(21.4%)	4/13(30.8%)
#7	0/3 (0.0%)	1/4 (25.0%)
#8	8/39(20.5%)	17/42(40.5%)
#9	3/15(20.8%)*	1/5 (20.0%)
#10	1/3 (33.3%)*	1/5 (20.0%)
#11	1/14(7.1%)	3/14(21.4%)
#12	1/26(3.8%)	6/27(22.2%)
#13	0/11(0.0%)	2/11(18.2%)
#14	0/1 (0.0%)	1/2 (50.0%)
Total DVT	**28/184(15.2%)**	**49/175(28.0%)**

* Centers with DVT rates higher in the Org 10172.

More patients in the warfarin group than in the Org 10172 group developed DVT at most study centers except centers #3, #9 and #10. However, center #3 had unusually high incidence rate of DVT in the Org 10172 (5/8); center #10 had small patient population with only one event per treatment; center #9 had 28 patients and few events: 3 in the Org 10172 group and 2 in the warfarin group.

At study center #9, an imbalance was noted between the two treatment groups for the number of patients excluded from the Efficacy-evaluable group: 1 of 16 in the Org 10172 group versus 7 of 12 in the warfarin-group. Of the 7 warfarin-treated patients excluded, one had positive VG and 6 had negative VG. The patient with positive VG was excluded because of disallowed pretrial medication. Four of the 6 patients with negative VG excluded, 4 had prolonged use of TED stockings and 2 had received inadequate preoperative dose of warfarin. Inclusion of these 7 patients from study center #9 did not change the incidence rate of DVT for the warfarin group (27.6% vs 28%) or the difference between the two tratment groups which remains significantly higher in the warfarin- than in the Org 10172-treated group.

There was a poor correlation in the interpretations of the VGs between investigators and Adjudicating Committee (AC).
In the Org 10172-treated group, of the total 29 venograms adjudicated positive for DVT, 11 (38%) were read as positive by both investigators and AC, 17 (59%) were read as negative by the investigators and positive by the AC, 3 were read as positive by the investigators and negative by the AC. One VG was positive by the investigator but lacked adjudication.
In the warfarin-treated group, of the total 53 VGs adjudicated positive for DVT, 23 (43%) were read as positive by both investigators and AC, 30 (56%) were read as negative by the investigators and positive by the AC, 9 VGs were read as positive by the investigators and negative by the AC.
In both treatment groups, the diagnosis of DVT was missed by the investigators in 48% of the VG readings (false negative). The lack of correlation was similar in both treatment groups and does not appear to have introduced bias in favor of Org 10172. When the efficacy endpoint is analyzed in terms of incidence of investigator-diagnosed DVT (11% for the Org 10172 group versus 23% for the warfarin group), the difference between the two treatment groups is still statistically significant in favor of Org 10172.

Assessment of intra- peri- and post-operative bleeding by the investigators was subjective and unblinded. No statistically significant differences were reported between the two treatment groups.

Bleeding was also assessed in terms of amount of blood loss and transfusion requirement. Seven patients in each treatment group experienced major bleeding (defined as requiring transfusion of >4 U of blood). Eight of these 14 patients were operated for complex and lengthy revision of prior hip replacement.

No differences between the two groups for severe intra-, peri-, and post-operative bleeding were noted (17.4%, 1.9%, 0% for Org 10172 and 13.3%, 2.4%, 0.7% for warfarin group respectively). However, two center which included a total of 88 patients were excluded from this analysis due to inconsistent use of drains.

A statistically significant difference was noted for the number of patients requiring therapeutic and all blood transfusion in the postoperative period; more Org 10172-treated patients required transfusion, however the mean number of units of blood transfused (1.7 vs 1.6) was similar for the two groups.
Risk factors for postoperative bleeding were screen hemoglobin, center, gender and treatment.
Clinically significant reductions in hemoglobin were noted in three patients from each treatment group.
A high positive correlation for both treatment group was found between intraoperative blood loss and duration of surgery.

More than 95% of all patients experienced some ACE. There was no significant difference in incidence of severe or serious adverse clinical events (ACE) between the two treatment groups. Thirteen Org 10172-treated and 4 warfarin-treated patients had at least one drug-related ACE; in 8 of the 13 Org 10172-treated patients the drug-related ACE was fever.

Thromboprophylaxis with ASA, warfarin or sc heparin was continued after study termination in 99 patients, 33 from the Org 10172- and 63 from the warfarin-treated group. None of these patients developed DVT on follow up. Two thirds of these patients received warfarin for thromboprophylaxis, about one third received sc heparin and few patients received ASA. Twenty-sis (26) additional patients restarted thromboprophylaxis after an interval ranging from 3 to 54 days after discontinuation of study drug, 12 were from the Org 10172- and 14 from the warfarin-treated group. Among these 26 patients, 4 Org 10172- and 4 warfarin-treated patients developed clinical signs of DVT in the post-treatment period. The 4 Org 10172-treated patients had negative exit VG by the investigator subsequently read as positive by the AC. Two of the four warfarin-treated patients did not have exit VG, one patient had negative exit VG by the investigator subsequently read as positive by the AC, the fourth patient had negative exit VG by the AC. Two warfarin-treated patients had confirmed diagnosis of PE during the post-treatment period while not on thromboprophylaxis.

In conclusion, the study appear adequate and well-controlled.
The study showed that thromboprophylaxis with Org 10172 was superior to warfarin in hip replacement surgery for efficacy. Bleeding complications were similar in both treatment groups,
Although the study was open-label, there was no evidence of bias in favor of Org 10172.

Study Protocol No.85140 (NDA Vol.2.209-2.212)

Title of the Study: A randomized, double-blind, placebo-controlled, safety/efficacy study of Org 10172 administered s.c. twice daily for the prophylaxis of DVT in patients after elective hip surgery.

Investigators: Hamelynck KJ, Doets HC, Olsthoorn P, Winia WPCA, Marti RK, Besselaar PP, Cate JW ten.

Study Centers: Amsterdam, The Netherlands: Slotervaart Hospital, Prinsengracht Hospital, Academic Medical Center.

Study Period: September, 1986 to June, 1988

Report/Publication: SDG Release No 3405
Thromb Hemost 1989; 62: 129
Thromb Hemost 1989; 62: 520
Thromb Hemost 1989; 62: 1050-2
Thromb Hemost 1991; 65: 122-5
Haemostasis 1992; 22: 109-11
Thromb Haemost 1992; 67: 28-32

Test Product, Dose and Mode of Administration, and Batch:
Org 10172: 750 anti-Xa units (0.6 mL) containing sodium sulfite (0.9mg/0.6mL), sc, bid; Batch # CP 084126 and Batch # CP 084130. Injectable placebo: physiological saline (0.6mL) containing sodium bisulfite (0.9mg/0.6mL), sc, bid.

Summary of Study

Study Design: This was a randomized, placebo-controlled, double-blind, parallel-group study to compare the effects of Org 10172 (750 anti-Xa units) to placebo in patients undergoing elective hip replacement surgery for the first time on that hip.

A total of 220 patients admitted for THR surgery were enrolled and randomized; 218 patients, aged 30 to 91 years (mean 69 years), received study medication: 109 patients received Org 10172 and 109 patients received placebo. Study drugs were administered s.c. for a maximum of ten days or less if an adverse event or early hospital discharge led to premature withdrawal of trial treatment. The first dose was given immediately preoperatively. In patients receiving epidural anesthesia, no trial drug was administered if there was bleeding into the spinal tap and such patients were excluded from the study. The second dose was to be given on the evening of the surgery day (not less than four hours after the first dose). Thereafter, medication was to be given s.c. twice daily.

Approximately 20% of the patients were to receive a general anesthetic and about 80% were to receive epidural block according to procedures standardized for the participating centers.

Bilateral venography (VG) performed between 8 and 12 days postop. was the major study endpoint assessment. VG was performed earlier if DVT was suspected or if the patient reached a different study endpoint.

A minimum of 198 eligible male and female patients were to be enrolled in the study. Oral informed consent was obtained from all patients and noted on the Inclusion/Exclusion Checklist CRF.

Patients admitted for fractured hip surgery or other type of orthopedic surgery beside unilateral hip replacement, patients with abnormal preoperative IPG on one or both legs, history of bleeding, women of childbearing potential; mentally ill patients or patients with allergy to VG contrast medium were excluded from the study. Patients receiving ASA and/or oral anticoagulants in the week prior to operation or NSAIDs within 48 hours prior to surgery, or expected to receive ASA, oral anticoagulants and/or NSAIDs during the study period were not eligible for the study.

On the day of surgery, eligible patients were randomly assigned to treatment groups according to the Randomization Schedule provided by Organon International. Patients were stratified by hospital center.

Protocol Amendments: Two amendments to the protocol (Addendum I, October 16, 1986 and Addendum II, January 22, 1987) were approved by both the investigators and Organon International bv.

The following relevant additions/changes were introduced:

. If a patient refused the "Day 5" IPG and VG he/she was dropped out of the trial and replaced. If the patient refused the IPG, but allows routine VG then the patient was not replaced.

. If a patient dropped out with inadequate DVT assessments but had completed all bleeding assessments then the latter were analyzed."

The Organon International CRA monitored the study site at regular intervals of 3 to 11 weeks. All actions taken to correct deficiencies were documented by the CRA. At the conclusion of the study, the Organon International CRA checked all data and records of drug use. Completed case report forms (CRFs) were also reviewed at Organon International by the Data Quality Control (DQC) staff for missing or inadequate data. Data were entered and key verified using an in-house data management system that included consistency checks, logic checks, and edit checks. Data clarifications were documented on appropriate Data Entry Forms. In order to maintain a data audit trail, changes or corrections to study data were documented via these DQC forms which were reviewed and approved as indicated by the investigators. In some

cases, data documentation was captured by Organon International personnel on the separate DQC forms and related correspondence without entry of investigator-approved corrections onto original CRF sets. As a result, CRFs do not match information in the database in a straight-forward manner. The source of the corrected entry was recorded on the DMVF to assure traceability from the CRF to the database. Clinical Quality Assurance representatives from both Organon International and Organon Inc. visited the three study sites after this trial was completed to verify that the study was conducted in conformance with FDA regulations, GCPs, and Organon International Standard Operating Procedures.

Efficacy Assessment: The primary measure of efficacy was based on the assessment of Deep Vein Thrombosis (DVT) as originally recorded on the Thrombotic/Embolic Record and the Venography Assessment Form. The presence or absence of a DVT was assessed by routine bilateral VG on Days 8 to 12 or earlier if the IPG screening was abnormal or symptoms of DVT occurred.
All venograms were reviewed at the end of the study by a panel of three physicians not involved in the execution of the trial and unaware of the initial interpretation of the VG and of the patient treatment allocations. Their final decisions, if different from earlier decisions, were used as the absolute indicators of negativity, positivity or inadequacy of the VGs.

A secondary measure of efficacy was based on the assessment of Pulmonary Embolism (PE) as recorded on the Thrombotic/Embolic Record. Patients with clinically suspected PE were subjected to ventilation/ perfusion lung scanning.

Criteria for discontinuation of patients from the trial were classified by patient-related reasons (refusal; intercurrent illness or event; serious side effects, especially severe bleeding; DVT and/or PE; unacceptable laboratory results; death) and administrative reasons (data missing; protocol violations; unblinded assessments of DVT/PE endpoints; missing two consecutive or more than two non-consecutive doses).

A follow-up was to be obtained at 6-8 weeks.

Safety Assessment:

Intraoperative and Perioperative Bleeding assessment was based on the subjective evaluation by the surgeon and on the objective determination of the volume of blood loss, and volume of transfusions required during surgery and throughout the study.

Perioperative blood loss assessment included bleeding from drains, type of bleeding, estimated volume in mL, and whether a specific measure was taken to stop the bleeding and outcome. Transfusions/infusions given during the operation day were also entered on the Operation Day Record.

Postoperative Bleeding Events occurring after midnight of the operation day were recorded on the Post-Operative Bleeding Form. Each patient was assessed for bruising at the injection site.

Adverse Clinical Experiences (ACE): The Safety Group gathered all AE-related data from the CRFs without knowledge of the patients' trial treatment assignments. Both the investigator and Organon Internt. evaluated the causal relationship of the study drug to the adverse event. The Organon Internt. judgement of causality was made after the end of the trial, by the Safety Group according to pre-set criteria. In addition, adverse events meeting the criteria for a "serious unwanted event" (CFR 21: 312.32) were discussed before an Organon International Adverse Events Committee and a formal decision of causality was made and recorded on the Organon International ADR Evaluation Form.

Laboratory safety monitoring included Hematology, Biochemistry, Urinalysis, Hemostasis tests.

Statistical and Analytical Methods

Sample Size Calculations: The calculation of sample size was based on an expected incidence of 25 % thrombosis after total hip replacement in the Placebo Group and an expected 10% rate of thrombosis in the Org 10172-Treated Group. A sample size of 94 patients per treatment group was originally planned in order to demonstrate a statistically significant benefit of Org 10172 over placebo (at a two-tailed 5% level of significance and 80% statistical power). A minimum of 99 patients were to be recruited into each group.

Patient Populations: The Intent-to-Treat Group consists of all patients who were randomized to treatment, received at least one dose of study medication, had surgery, and had at least one efficacy evaluation postsurgery by venography.

The Efficacy Evaluable Group consists of all patients who were randomized to treatment, received at least one dose of study medication, had surgery, had at least one efficacy evaluation postsurgery by venography, met all inclusion/exclusion criteria, and had no major protocol deviation(s) that would interfere with the efficacy assessment.

The All-Patients-Treated Group includes all patients who were randomized to treatment and received at least one dose of study medication, including those who were never evaluated for efficacy.

Efficacy Analyses: The statistical methods actually used differed somewhat from the protocol. All tests were two-tailed at p-value =0.05. Between-treatment comparison with respect to incidence of DVT (as diagnosed by VG), was performed using the CMH procedures for 2x2xk tables, where k is the number of centers.
DVT incidence rates were further tabulated as proximal (above knee) and/or distal (below knee); and the side of the DVT occurrence was summarized in relation to the side of the operation.
Furthermore, the cumulative probability at a given day that a patient might exhibit a DVT (adjusting for patient withdrawal) was estimated using the Kaplan-Meier product-limit method. Logrank test was used to compare the survival (i.e., no DVT) curves of the treatment groups.

A separate analysis was done for the Efficacy Evaluable and Intent-to-Treat Groups.

Exploratory analyses were performed comparing the two treatment groups with respect to the incidence of DVT, for each type of anesthesia using Fisher's exact test.
The CMH test for 2x2xk tables, adjusting for k multiple centers or Fisher's exact test, was used for between-treatment comparisons of the proportion of patients other than study completers, who were discontinued from the study for each of several reasons and for all reasons combined.

Safety Analyses: The All-Patients-Treated Groups were analyzed for safety. All p-values are two-tailed and were considered statistically significant if $p < 0.05$.

Bleeding and Related Events were analyzed for treatment effect, using the CMH procedures for 2x2xk tables, where k is the number of centers. Descriptive statistics were computed for the amount (mL) of blood loss at various times throughout the study for each of the treatment groups.
The number of patients receiving blood transfusions (operation day and postoperative) was analyzed for treatment effect, using the CMH procedures for 2x2xk tables, where k is the number of centers.
Between treatment comparisons with respect to the volume of blood loss and blood transfusions (operation day, and postoperative) were performed using two-way ANOVA based on ranks, with treatment, center, and treatment-by-center interaction.

Within each of the treatment groups, hemoglobin and hematocrit versus time were plotted using boxplots. A separate plot was done for males

and females.
No formal statistical analysis was done for occurrence of hematuria, hematomas or bruising.

Adverse Clinical Experiences (ACEs): A between-treatment comparison of the proportion of patients reporting ACEs was done both by COSTART term and by body system, using either CMH procedures for 2x2xk tables, where k is the number of centers, or Fisher's exact test. The relationship of the ACE to the study medication was assessed.

Averse Laboratory Experiences (ALEs): Adverse laboratory experiences reported in the Safety Evaluation Form, or directly entered in the database by the Safety Group of the Medical Research and Development Unit at Organon International were examined and listed separately.

Hematology and Biochemistry: Hematology variables were measured at screening, Days 1, 2, and 5, and just prior to discharge. Biochemistry variables were measured only at screening and at exit. Shift tables were constructed for laboratory parameters to show categorical shifts from baseline (pretreatment) to the lowest and/or highest result during treatment. Between-treatment comparisons of these shifts were done using CMH procedures for 2x2xk tables, where k is the number of centers or Fisher's exact test.

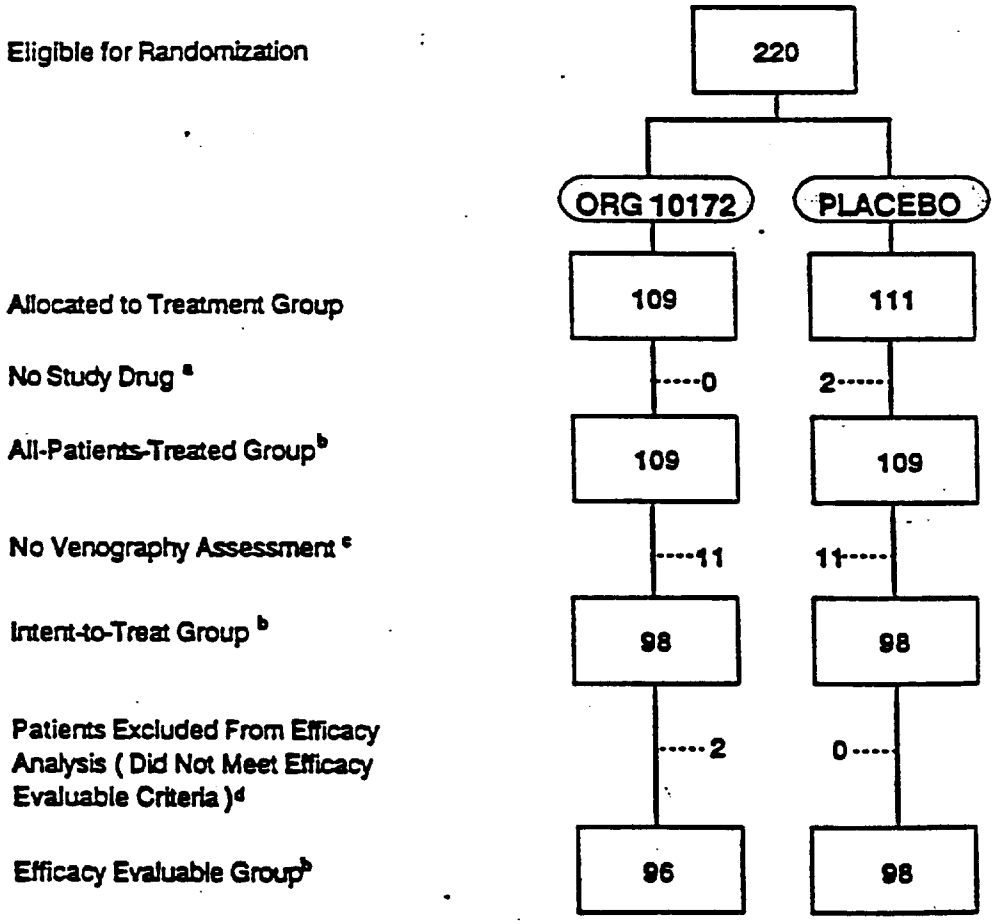
Hemostasis: Bleeding time and Thrombotest were measured at screening, anti-Xa, APTT, and platelets were also measured at Days 2 and 5, and at exit. Descriptive statistics (including mean and standard deviation) of hemostasis parameters for each treatment group were calculated at baseline and last measurement. The mean percent changes from baseline to last measurement were calculated for each treatment group. Platelet count were also examined as a measure of hemostasis, using boxplots.

Post-Treatment Evaluation included the number of patients who developed DVT or PE, the number of patients on anti-coagulant therapy, and the mean time from drug discontinuation to post-treatment contact. Post-treatment deaths occurring during this follow-up period were tabulated.

STUDY RESULTS

Disposition of Patients: Two hundred and twenty patients were eligible for randomization to one of two treatment groups (Org 10172 or placebo). Of the 218 treated patients, 22 did not have bilateral VG for the assessment of DVT during the study treatment period. The remaining 196 patients (98 patients in the Org 10172 Group and 98 patients in the Placebo Group) were included in the ITT Group. The All-Patients-Treated Group consisted of 109 Org 10172-treated patients and 109 placebo-treated patients .
The disposition of the study patients is summarized in fig.2.

FIGURE 2
DISPOSITION OF PATIENTS



Eleven patients did not meet the criteria for inclusion in the Efficacy Evaluable Group, as determined by the Organon Inc. Medical Monitor. However, all but two of these 11 patients were already excluded from the ITT Group as they did not have a VG assessment during the study treatment period. The remaining two patients (Patients #30 and 89, both from the Org 10172-treated group) were excluded from the Efficacy Evaluable Group because of disallowed pretrial medication and missed doses respectively.

The patients excluded from the Efficacy analysis are shown in table 7 (v. 2.209, p.85)

TABLE 7
PATIENTS EXCLUDED FROM THE EFFICACY EVALUABLE GROUP

Center - Patient (Treatment Group)	No. of Days on Study Drug	Reason for Exclusion
Patients With Venography Assessment		
1 - 30 (Org 10172)	9	Disallowed pretrial medication.[b]
1 - 89 (Org 10172)	9	Missed doses.[a]
Patients With No Venography Assessment[c]		
1 - 15 (Placebo)	2	Disallowed concomitant medication.[b]
1 - 27 (Org 10172)	1	Interfering concomitant medication.[d]
1 - 50 (Org 10172)[e]	1	Interfering pretrial and concomitant medication.[d]
1 - 75 (Org 10172)	3	Interfering concomitant medication.[d]
1 - 108 (Org 10172)	2	Disallowed concomitant medication.[b]
1 - 123 (Placebo)	1	Disallowed concomitant medication.[b]
1 - 136 (Placebo)	1	Disallowed concomitant medication.[b]
1 - 161 (Org 10172)	1	Disallowed concomitant medication.[b]
3 - 240 (Placebo)	1	Disallowed concomitant medication.[b]

[a] Patient missed three non-consecutive doses, according to the Daily Data Card CRF. (As per Section VI.C., a patient missing two consecutive or more than two non-consecutive doses was to be discontinued from the study.)
[b] As per protocol exclusion criteria; see also Section IV.B.3. and Table 22.
[c] Therefore, these patients were excluded from the Intent-to-Treat Group; see also Table 6.
[d] As per Section VI.C., use of other drugs or treatments interfering with trial treatment was a criterion for discontinuation. The Organon Inc. Medical Monitor has determined that pretrial or concomitant medications taken by these patients were included in this category.
[e] Patient did not have venography during the treatment period; see also Table 6.

Deviations from Protocol:
1. Diagnostic Testing/Assessments: The follow-up evaluation was not specifically addressed, however, an IPG was to be performed at the 6-8 week follow-up visit and a CRF was provided to record events occurring in the follow-up period. However, no information regarding the follow-up IPG was collected on the Follow-Up Form or entered in the database. The time of the follow-up visit spanned from 13 to 302 days following the administration of the last dose of study medication.
2. Inclusion/Exclusion Criteria: Ten patients [6 in the Org 10172 Group (#27, 30, 50, 75, 108, and 161) and 4 in the Placebo Group (#15, 123, 136, and 240)] received continued therapy with NSAIDs or oral anticoagulants, or other medications including heparin and dextran. Two patients (#6 and 29) who were randomized to the Placebo Group did not undergo THR (surgery was changed during the operation).
One patient (#224) from the Placebo-Treated Group with a prolonged baseline APTT (30% outside of the normal range) of no clinical significance was included in all analyses.
3. Dosing Schedule: One Org 10172-treated patient (#89) missed three nonconsecutive doses and was excluded from the Efficacy Evaluable Group. According to the protocol, study treatment was to proceed for a maximum of ten days but 8 patients [4 from the Org 10172 Group (#36, #121, #157, and #211) and 4 from the Placebo Group (#156, #212, #221, and #233)] received study drug for 10.5 or 11 days.
4. Type of Anesthesia: According to the protocol, patients were to receive either general or epidural anesthesia. In Center 2 (PH), 61 patients (29 Org 10172-treated and 32 placebo-treated patients) received psoas block anesthesia. In Center 3 (AMC), 16 patients (8 Org 10172- and 8 placebo-treated) received psoas block anesthesia.
5. Randomization and Blinding: The following patients received allocation numbers assigned to another center: Patients #001, #002 at Center 2 (PH) instead of at Center 1 (SH); Patients #161, #162 at Center 1 (SH) instead of at Center 2 (PH); Patients #223-#240 at Center 3 (AMC) instead of at Center 2 (PH).

Demographic and Other Patient Characteristics: For both the ITT and Efficacy-Evaluable Groups, there was no statistically significant difference between the two treatment groups with regard to age, sex, height, length of operation, type of anesthesia, and cigarette smoking. Information on race was not collected in this study.

A statistically significant center by treatment interaction was noted for patient weight in both the ITT and Evaluable Groups. In Centers 1 and 3, which accounted for 68% of patients, the difference in mean weight was relatively small and without an impact on the study results. The pattern of alcohol consumption differed in Center 2 from the other two centers, however Center 2 contributed only 32 % of the total study population.

Efficacy Results

1. Deep Venous Thrombosis (DVT)

All 196 patients in the ITT Group and 194 patients in the Evaluable group underwent bilateral VG for the diagnosis of DVT during day 8-12 of the study treatment period. A total of 189 patients from the ITT Group and 188 from the Evaluable group had IPG between study Day 5 and 10. Only patient #92, in the Org 10172-Treated Group, had positive IPG on Day 7, however, the VG done on the next day was negative.

For the ITT Group, the overall incidence of DVT was significantly lower in the Org 10172-treated Group ($p<0.001$) than in the placebo group. Fifteen percent of Org 10172-treated patients (15 of 98 patients) developed DVT compared with 57% of the placebo patients (56 of 98 patients).

Number (%) of Patients with DVT*
Intent-to-Treat

	Org 10172 N=98	Placebo N=98	p-Value[a]
Proximal; N (%)	8 (8)	26 (27)	0.001
Distal; N (%)	14 (14)	51 (52)	<0.001
Overall; N (%)	15 (15)	56 (57)	<0.001

*A patient may be counted more than once (proximal and/cr distal)
[a] Using CMH test

For the ITT group, the Org 10172-treated patients experienced a relative reduction of 70% and 73 % for proximal and distal DVT, respectively, as compared with the placebo patients. Similarly, in the Evaluable Group, the overall incidence of DVT was statistically significantly lower ($p<0.001$) for the Org 10172-treated patients [15 of 96 patients (16%)] than for the placebo-treated patients [56 of 98 patients (57%)]. This represents a relative reduction of 72%.

The side on which a DVT occurred (proximal and/or distal) in relation to the side of surgery is shown in the following table.

Study Drug	Total Number of Patients with DVT N	Side of DVT		
		Both Sides N (%)	Same Side as Surgery N (%)	Opposite to Side of Surgery N (%)
Org 10172	15	7 (47)	2 (13)	6 (40)
Placebo	56	22 (39)	19 (34)	15 (27)

Exploratory Analyses: The possible effect of type of anesthesia on incidence of DVT was examined using Fisher's exact test. Two methods of regional anesthesia were used: epidural anesthesia and psoas compartment block with additional inhalation anesthesia.
The incidence of proximal, distal and overall DVT was significantly lower in the Org 10172 patients compared to placebo for all types of anesthesia except epidural where the incidence of proximal DVT in the Org 10172 group was numerically lower than in the placebo-treated group, but the difference was not statistically significant.

Life Table Estimates: In addition to incidence determination, the cumulative probability of DVT was determined for each treatment group. The cumulative probability of detecting a DVT by Day 12 was 37.4% for the Org 10172-treated patients versus 86.3% for the placebo-treated patients. Thus, a 56.6% reduction in the risk of occurrence of DVT was demonstrable in the Org 10172-treated patients, as compared with the placebo-treated patients, on Day 12. Figure 3 shows the cumulative probability of DVT detection (Kaplan-Meier estimate) for each treatment group. The comparison of DVT-free survival curves showed a highly significant difference ($p < 0.001$) between the two treatment groups. The initial flat portion of the curve corresponds to study days when no VG assessments for DVT were carried out. Similar results were seen in the Efficacy Evaluable Group.

2. Pulmonary Embolism (PE)

One patient in the Placebo-Treated Group (#199) had clinical symptoms of PE on Day 8. The diagnosis was not confirmed, however, bilateral VG on Day 9 was positive for proximal and distal DVT in the left leg.

Concomitant Medications: Analgesics, antibiotics, or cardiovascular drugs) were administered to near 100% of patients. Ten patients received disallowed pretrial or concomitant medications: Six patients received NSAIDs or anticoagulants, 2 patients received concomitant dextran, one patient received acenocoumarol, and one patient received heparin and dextran. Three patients took a low dose of an antimalarial agent (hydroxychloroquine) for the treatment of rheumatoid arthritis in the week before surgery. All of the above patients, except one who was excluded from the Evaluable group, had been excluded from the Intent-to-Treat Group.

Reasons for Discontinuation: Of 218 patients who received study medication, 22 patients (11 Org 10172 and 11 placebo-treated), representing 10.1% of the study population, were discontinued from the study. There were no significant differences between the two treatment groups for any of the reasons for discontinuation, nor for the number of patients discontinued in each category.
Patients with DVT diagnosed by routine VG on Days 8 to 12 (no clinical

suspicion of DVT) wereconsideredd completers. Two patients in the placebo group were discontinued for "Inadequate Treatment Effect" on Study Day 8: patient #159 for DVT and patient #199 for PE.

No patients in either treatment group was discontinued for an adverse clinical or laboratory event or for a bleeding event.

Safety Results:

The safety analysis included all patients who received at least one dose of study medication (All-Patients-Treated Group).
The mean exposure to Org 10172 or placebo was 9.30 and 9.17 days, respectively. Patient #89 missed three non-consecutive doses of Org 10172 and was excluded from the efficacy evaluable analysis.

Analysis of Excessive Blood Loss:

The frequency of patients with excessive blood loss (as per the investigator's subjective evaluation) and the percentage of patients requiring transfusion are shown in the following table (Table 25, v.2.209, p.128).

NUMBER OF PATIENTS WITH EXCESSIVE BLOOD LOSS AND NUMBER OF PATIENTS GIVEN BLOOD TRANSFUSION

	ORG 10172		Placebo		p-value
	N	Frequency %	N	Frequency %	Org 10172 vs Placebo
Incisional Bleeding	109	0	108	1 (1%)	0.33
Intraop. bleeding	109	0	108	2 (2%)	0.16
Periop. bleeding	108	0	107	0	
Postop. bleeding	105	1 (1%)	106	0	0.3
Oper.Day transfus.	108	77 (71%)	107	82 (77%)	0.41
Postop.Day transf.	104	21 (20%)	105	17 (16%)	0.45

The estimated volume of blood loss and number of transfusions required throughout the study treatment period are summarized in table 26 (v.2.209, p.130). There was no statistically significant difference between the two treatment groups.

TABLE 26
SUMMARY OF ESTIMATED BLOOD LOSS AND TRANSFUSIONS REQUIRED DURING THE STUDY TREATMENT PERIOD- ALL-PATIENTS-TREATED GROUP

	Org 10172					Placebo					p-Value[b]
	N[a]	Mean	S.D.	Minimum	Maximum	N	Mean	S.D.	Minimum	Maximum	Org 10172 vs Placebo
Estimated Volume of Blood Loss (mL):											
Intraoperative	45	505.6	233.6			36	666.7	644.5			0.32
Perioperative[c]	107	479.2	268.3			105	522.4	251.6			0.94
Total Postoperative[d]	96	247.1	211.7			99	252.2	168.8			0.45
Blood Transfusions (Volume (mL) of RBC containing transfusions):[e]											
During Operation Day	77	1226.0	419.1			82	1271.3	493.8			0.91
Total Postoperative	21	1130.5	627.8			17	1270	570.9			0.48

[a] Sample size reflects only those patients who had a measurement for a particular parameter at a particular time.
[b] Using two-way ANOVA based on ranks for continuous measures.
[c] Up to midnight of operation day, reported in Operation Day Record.
[d] Total reported on postoperative bleeding forms.
[e] Volume of RBC-containing transfusions = volume of whole blood transfusions plus two times the volume of packed cell transfusions.

Changes in Hemoglobin and/or Hematocrit: Hemoglobin (Hgb) levels fell on Day 2 by about 19 g/L for Org 10172-treated males and by about 18 g/L for placebo-treated males; and by about 18 g/L for Org 10172-treated females and by about 15g/L for placebo-treated females. Boxplots for Hgb and for Hct reveal no clinical differences between the treatment groups.

Patients With Clinically Significant Laboratory Outliers: Of the patients who had outliers equal to or outside of the 1.5x interquartile range, 10 patients had Hgb values that were considered clinically significantly low: 6 Org 10172-treated patient (#10, 76, 95, 157, 168, 200) and 4 placebo-treated patients (#37, 116, 219, 180). Five patients had hematocrit values during treatment that were considered clinically significantly low: Org 10172-treated Patients #10, 76, 200, and placebo-treated Patients #37, 219. The total number of patients with at least one outlier Hgb or Hct considered to be clinically significantly low was 6 Org 10172-treated and 4 placebo-treated.

Adverse Clinical Experiences (ACEs)

Study Deaths: No patient died during the study treatment period. Two patients from the Org 10172 Group (#14, 189) died during the post-treatment follow-up period. One of these patients (#189) had DVT and PE recorded at autopsy.

Incidence of ACEs: The distribution of patients with ACEs in each body system as assessed by the investigators is shown in the table below. The assessment of ACE by Organon Int. was similar.

Body System Relationship to Study Drug: Related,Unrelated, Unknkown	Frequency (%)		p-value
	Org 10172 (N=109)	Placebo (N=109)	Org 10172 vs Placebo
Body as a Whole	8 (7%)	6 (6%)	0.78
Cardiovascular System	5 (5%)	2 (2%)	0.45
Digestive System	2 (2%)	2 (2%)	1
Skin and Appendages	1 (1%)	2 (2%)	1
Urogenital System	1 (1%)	1 (1%)	1
Overall Related, Unrelated, Unknown	13(12%) 1, 6, 6	10 (9%) 1, 4, 5	0.66

The systems with the highest incidence rates were Body as a Whole and Cardiovascular System which had incidence rates ≥5 % for at least one treatment group. The incidence rates in each body system were comparable for Org 10172- and placebo-treated patients.

Overall Assessment of ACEs: The overall assessment of ACEs is given in the following table. At least one ACE was reported by 13 (11.9%) Org 10172-treated patients and 10 (9.2%) placebo-treated patients. None of the ACEs were reported as severe. No patient in either treatment group was discontinued for an ACE. Eleven (11) patients, 5 (4.6%) Org 10172-treated patients and 6 (5.5%) placebo-treated patients reported 14 ACEs, all of which were possibly drug related, according to the Organon International (Safety Group) judgement of causality.

ACE Category	Org 10172		Placebo	
	N	%	N	%
Total Patients	109	NA	109	NA
Patients with at least one ACE	13.0	11.9	10.0	9.2
" with at least 1 severe ACE	0.0	0.0	0.0	0.0
" Discontinued due to ACE	0.0	0.0	0.0	0.0
Possible, probable, definite relationship to study drug by investigator assessment	1.0	0.9	1.0	0.9
Possible, probable, definite relationship to study drug by Organon inc. assessment	5.0	4.6	6.0	5.5

Eight patients had a change in ECG from normal at screen to abnormal at last assessment [seven patients (7.4%) in the Org 10172-Treated Group, (#14, 62, 86, 89, 93, 101 and 132), and one patient (1.1%) in the Placebo-Treated Group (#65)]. These changes were considered non-diagnostic by the Organon Inc. Medical Monitor and related to the patients' medical histories.

Laboratory Parameters: No patient from either treatment group was discontinued because of ALEs. No significant differences between treatments for shifts from baseline to during-treatment maximum or minimum values were observed for any of the hematology and biochemistry variables. A statistically significant difference between treatments was demonstrated for the downward shift for

erythrocytes: 78 of 102 (76%) of Org 10172-treated patients and 62 of 105 (59%) placebo-treated patients ($p < 0.01$).

The mean anti-Xa level at last measurement was 0.16 ± 0.07 U/mL in the Org 10172-treated group and 0.05 ± 0.10 U/mL in the placebo group. No changes in APTT values were noted from baseline and between treatments.

Post-Treatment Follow-Up Evaluation

Follow-up was available for 216 (99.1%) patients. The time of the follow-up evaluation ranged from 13 to 247 days past the last administration of study medication for patients in the Org 10172 Group and 23 to 302 days past the last dose of study medication for the Placebo Group.

Two patients (#205 and 232) from the Org 10172-Treatment Group had a DVT reported at the post-treatment follow-up evaluation. Patient #205 was found to have DVT 16 days after ending study drug. The patient was not on anticoagulant therapy. Patient #232 developed a DVT in the operated leg, as confirmed by VG four days after ending study drug.

At follow-up, 10 of 95 patients (10.5%) in the Org 10172-treated group and 28 of 74 patients (37.8%) in the placebo group were on anticoagulant therapy.

Two deaths were reported during the post-treatment evaluation, both from the Org 10172-Treatment Group (Patients #14 and 189). Patient #14 died of colorectal cancer with no thromboembolic events recorded during the study or at autopsy. Patient #189 had no evidence of DVT or PE during the study, however, had PE and DVT at autopsy.

COMMENTS

The study was a multi-center, randomized, double-blind, placebo controlled, parallel group clinical trial to assess the efficacy and safety of Org 10172 in patients undergoing elective hip replacement. Treatment was started immediately before surgery and continued to a maximum of 10 days. The study was conducted between 1986 and 1988 when the placebo control group was still acceptable.

Three centers participated in the study with the enrollment of 120, 62, and 16 patients respectively. No imbalance is noted for patient distribution between treatment groups or for demographic and surgical characteristics. Blinding was maintained at randomization and throughout the study. Levels of anti-Xa activity which would be expected to be elevated only in the Org 10172-treated group, and thus

identified the treatment assignment, were not available to the investigators.

No imbalance was noted for patients exclusion between treatments and among study centers.

The presence or absence of DVT was assessed by bilateral venography (VG) on Study Days 8 to 12, or earlier if indicated by clinical suspicion of DVT or by an abnormal IPG result.
VGs were read blindly by the investigators and by the an independent panel of three physicians also blinded to treatment assignment. The reading of the VGs by the panel represented the final diagnosis. Non-invasive tests for DVT (IPG) were found to be of no value for the diagnosis of DVT in asymptomatic patients.

The results of this study demonstrated that the incidence rate of DVT of 15% (15/98) in the Org 10172-treated group was significantly lower ($p < 0.001$) than the rate of 57% (56/98) in the placebo group for both ITT and Efficacy-evaluable analyses. Similarly, statistically significant reductions occurred for both proximal DVT (8% for Org 10172-treated patients versus 27% for placebo-treated patients), $p = 0.001$ and distal DVT (14% for Org 10172-treated patients versus 52% for placebo-treated patients, $p < 0.001$). This statistically significant reduction in DVT incidence in patients given Org 10172 represents a relative reduction of 74%.

The cumulative probability of exhibiting a DVT by day 12 was 37.4% for the Org 10172-treated patients versus 86.3% for the placebo-treated patients equal to a 56.6% reduction in the risk of occurrence of DVT in the Org 10172-treated patients.

The difference in DVT rates between the two treatment groups remained highly statistically significant when the ITT analysis included <u>all</u> the randomized patients regardless of any efficacy evaluation.

Approximately 50% of the DVT-negative VG readings by the investigators were read as positive by the panel. Most of the DVT-positive VG readings by the investigators were also read as positive by the panel. The incidence rates of DVT for the Org 10172-treated groups at the three centers were 13.1% (8/61), 20% (6/30) and 12.5% (1/8) respectively. The incidence rates of DVT for the placebo groups at the three centers were 64.5% (35/59), 56,2% (18/32) and 37.5% (3/8) respectively.

Pulmonary embolism was not diagnosed in any patient from either treatment group during the treatment period.

After completion of the study, thromboprophylaxis was continued in 10 Org 10172-treated patients and was started in 20 placebo patients.

Seven of the 10 Org 10172-treated patients and 17 of the 28 placebo patients on post-study thromboprophylaxix had been diagnosed with DVT.

Two Org 10172-treated patients developed DVT in the follow up period. Both patients had negative exit VG and were not on post-study thromboprophylaxix.

Two Org 10172-treated patients died in the follow-up period, one patient had colon cancer and the second patient was found to have DVT and PE at post-mortem examination. The latter patient had negative exit VG and was not on post-study thromboprophylaxis.

A total of 10 patients, 6 from the Org 101072-treated group and 4 from the placebo group received concomitant disallowed medications, mainly NDAIDs. However, the effect of such medications on the patient's efficacy outcome could not be assessed because all of them except one had been excluded from ITT group for lack of VG evaluation.

Treatment with Org 10172 was generally well tolerated. The overall incidence of adverse experiences in this study was low and similar for Org 10172- (11.9 %) and Placebo-treated (9.2%) groups. Adverse events were considered by the investigator to be related to study medication in 0.9% of the patients in each treatment group and by the Organon International in 5 % of Org 10172-treated patients and 6 % of placebo-treated patients. No unexpected adverse events were reported during the study in either treatment group.

No patient in either treatment group experienced serious ACEs or was discontinued from the study due to an ACE.

Bleeding events were assessed subjectively based on the investigator's evaluation and objectively by direct measurement of blood loss volume and transfusions. There were no statistically significant differences between the two treatment groups in estimated intraoperative, perioperative, or total postoperative blood loss or transfusion requirements during the study treatment period. In the investigator's subjective judgement, excessive bleeding occurred in 1 (0.9%) Org 10172-treated patient and 2 (1.8%) placebo-treated patients during the study. Six org 10172-treated patients developed a hematoma, which was not clinically significant.

No patient was discontinued the study for bleeding-related event.

In conclusion, the study indicates that Org 10172 is safe and effective in reducing the risk of thromboembolic events following elective hip replacement surgery.

Study Protocol No. 86002 (NDA vol. 2.223-2.225)

Title: A randomized, assessor blind study to compare the safety and efficacy of Org 10172 with Heparin/DHE in the prophylaxis of DVT in patients undergoing elective hip surgery.

Summary of Study Protocol: The study was an open-label, assessor-blinded study performed at three centers in Switzerland. The study was monitored by a contract research organization and, after completion of the trial, by NV Organon CQA.

Study treatment was started 2-3 hours before surgery or anesthesia and was continued for 9-11 days unless a study endpoint occurred earlier. After completion of the study treatment period and after the VG, all patients received anticoagulant therapy with warfarin.

Study endpoint for efficacy was the development of a thromboembolic event (TE) as DVT or PE. Patients were monitored for DVT by Doppler scanning performed on alternate days. Bilateral venography (VG) was to be performed on all patients between day 9 and 11 or earlier if indicated. VGs were initially read by the local radiologist blinded to patients's condition and treatment and subsequently by the panel of the three radiologists also blinded to patients identity.

The efficacy results were analyzed by ITT and in the evaluable population. The results from the 3 centers were pooled for analysis with no separate analysis of each center results. The statistical methods of analyses were those actually used in the study and differed from the study protocol adjusting for multiple centers.

A total of 309 patients were randomized sequentially according to a randomization list provided by NV Organon: 154 to Org 10172 (750 anti-Xa U sc bid) and 155 to heparin-dihydroergotamine (heparin 5000 U with 0.5 mg dihydroergotamine mesylate sc bid). The sample size was calculated based on expected incidence rates of DVT of more than 25% in the heparin/DHE group and 10% or less in the Org 10172 group. All randomized patients were treated. Six Org 10172-treated patients and 8 Heparin/DHE-treated patients did not have VG performed and were excluded from ITT analysis. One patient in the Org 10172 received two doses of heparin/DHE on day 6, 15 Heparin/DHE patients and 6 Org 10172 patients continued to receive study medication for 1 to 5 days after diagnosis of DVT.

Safety was assessed in terms of bleeding complications, transfusion requirements and by occurrence of any other adverse event.

In general, demographics and other patient characteristics were similar in the two groups except for a larger proportion of females in the heparin/DHE group (104/147 vs 87/148, p=0.02).

Efficacy Results: The number of patients with DVT is summarized in the following table.

NUMBER (%) OF PATIENTS WITH DVT AS DETERMINED BY VENOGRAPHY
INTENT-TO-TREAT GROUP

	Org 10172 (N=148)	Heparin.DHE (N=147)	p-value
Proximal N (%)	7 (5%)	10 (7%)	0.442
Distal N (%)	25 (17%)	45 (31%)	0.005
Overall N (%)	25 (17%)	47 (32%)	0.002

The majority of DVTs in both treatment groups were ipsilateral to surgery, bilateral DVTs occurred in 32% (8/25) of Org 10172 patients and in 23.4% (11/47) Heparin/DHE patients.

During the treatment period, three heparin/DHE and three Org 10172 patients were evaluated for PE, the diagnosis was confirmed in one patient in each treatment group.

Approximately 20% of patients in each group discontinued for reasons other than completion of trial. Five patients in the Org 10172 group and 4 in the Heparin/DHE group discontinued for protocol violations.

NUMBER OF PATIENTS DISCONTINUED AND REASON FOR DISCONTINUATION

Reason for discontinuation	Org 10172 N=154	Heparin/DHE N=155	p-value[a]
Subject well	23	22	0.9
Inadequate Treatment Effect	0	2	0.16
Side Effect	3	5	0.66
Protocol Violation	5	4	0.71
Inadequate Compliance	1	1	0.98
Reasons Unrelated to Trial	0	2	0.16
Overall Total[b]	30	33	0.65

[a]Using CMH test
[b]A patient may be counted in more than one category

Two patients in the Org 10172 and 8 patients in the Heparin/DHE group had DVT reported in the post-treatment period.

Safety Results: All treated patients entered in the safety analysis. Approximately 75% of patients received study drug for 9-11 days. Bleeding was assessed subjectively during surgery and objectively in terms of blood loss and transfusion requirement.

NUMBER OF PATIENTS WITH EXCESSIVE BLOOD LOSS
NUMBER OF PATIENTS TRANSFUSED

	Org 10172		Heparin/DHE		p-Value
	N	Frequency %	N	Frequency %	Org10172 vs Heparin/DHE
Incisional blood loss	154	9 (6%)	155	6 (4%)	0.38
Intraop. blood loss	154	15 (10%)	155	9 (6%)	0.16
Periop. blood loss	154	5 (3%)	154	9 (6%)	0.25
Postop. blood loss	154	4 (3%)	152	3 (2%)	0.71
Transfusion on oper. day	154	148 (96%)	154	140 (91%)	0.06
Transfusion postop. days	154	50 (32%)	152	42 (28%)	0.36

There were no significant differences between treatments for incidence of excessive bleeding or transfusion requirement.
One Org 10172 and one heparin/DHE patient discontinued treatment because of bleeding complications.

The incidence rates of other adverse clinical events were similar in the two treatment groups. It is of note that the relationship of ACE to study drug was positive in only two heparin/DHE patients by the investigator assessment, whereas it was positive in 35 (22.7%) of the Org 10172 patients and in 38 (24.5%) of the heparin/DHE patients by the NV Organon assessment.

There were no differences in the incidence of laboratory abnormalities and no patients were discontinued due to laboratory abnormalities.

There were no death in either group for the entire duration of the study. Twc patients, one in each treatment group, developed heparin-induced thrombocytopenia while on unfractionated heparin therapy for DVT.

Comments: The study compares Org 10172 to Heparin/DHE for DVT prophylaxis following hip replacement surgery. The comparator regimen used in this study is not approved in US for any indication due to safety concerns. This study was reviewed only as a supportive study of the efficacy of Org 10172.

The study was open-label with randomized treatment assignment provided by NV Organon for the three participating centers. The efficacy endpoints consisted of DVT diagnosed by VG which were assessed blindly by the three radiologists from the three participating centers.

Thromboprophylaxis with Org 10172 in elective hip replacement reduced the incidence rate of DVT compared to Heparin/DHE (17% vs 32%). The Heparin/DHE group included more females than the Org 10172 group ($p=0.02$). However no increased incidence of DVT in females was noted in study 004-023 where gender interaction was assessed.

Follow up was available for more than 95% of patients. Nearly 87% of Org 10172- and 90% of Heparin/DHE-treated patients were continued on some regimen of post-study thromboprophylaxis. During the follow up period, 2 Org 10172- and 8 Heparin/DHE-treated patients developed DVT 6 weeks to 11 months after the end of the study. Thromboprophylaxis had been continued in 7 of the 8 patients. The 2 Org 10172 and 6 Heparin/DHE patients had negative exit VGs, the remaining 2 Heparin/DHE patients had recurrence of DVT during the follow up period.

One Org 10172 patient and one Heparin/DHE patient experienced PE in the post-treatment period. Both patients had DVT during the study and were fully anticoagulated with heparin. The Org 10172 patient (#94) developed bilateral PE and thrombocytopenia 11 days after starting heparin. The test for heparin-induced platelet aggregation was not performed. The Heparin/DHE patient (#89) developed arterial thrombosis and thrombocytopenia two days after heparin therapy. It is not possible to determine whether heparin/DHE contributed to the arterial thrombosis in patient #89. The test for heparin-induced platelet aggregation was negative in patient #89. Nevertheless, the possibility of HIT cannot be excluded as the platelet count rose to normal after discontinuation of heparin in both patients.

Bleeding complications were similar for the two groups and no unexpected ACEs were reported. A discrepancy was noted between investigators' and NV Organon's assessment of study drug-related ACE, however there appeared to be no bias in favor of Org 10172.

Study Protocol No. 86030 (NDA vol. 7.2-7.6)

Title of the study:

A randomized assessor blind study of Org 10172 twice daily administration sc and twice daily low dose sc heparin in the prophylaxis of DVT in patients undergoing elective hip surgery.

Study Summary:

The study was designed as a randomized, parallel-group, assessor blind safety and efficacy study comparing Org 10172 750 anti-Xa units s.c. twice daily with a 5000 IU heparin s.c. twice daily regimen.

In this parallel group study, 120 patients were originally to be randomized to either the Org 10172 or the low dose heparin. Because of new data on the expected incidence of DVT in the heparin control group and because of slow recruitment, a second study center (Parma) was enlisted and the number of patients was increased to 170.

In both treatment groups, study drug was initiated 2-3 hours before the start of surgery or, if epidural or spinal anaesthesia was given, 2-3 hours before the anaesthetic procedure. The treatment was continued up to the time of the bilateral venography (VG) which was performed on Day 9,10 or 11.

The following criteria excluded patients from participation in study: Patients undergoing surgery other than for hip replacement, patients with bleeding diathesis or abnormality on the hemostasis screening profile (platelets count <, 150.000/mm3 but >100.000/mm3 were allowed), renal impairment, severe hypertension, hepatic failure i.e. PT (one stage prothrombin time) > 1.3 x the upper limit of the normal range, previous CVA, women of child bearing potential, use of anticoagulants or antiplatelet drugs during the 8 days before surgery, patients with a known allergy to contrast media or to heparin, patients with positive screening IPG examination.

Randomization lists for each center were provided by N.V. Organon. Patients were randomized according to this list after informed consent had been obtained. Org 10172 (lot CP 084133, 087143 and 091129) and Heparin (lot CP 085161 and 090I06) were supplied by N.V. Organon, Oss, The Netherlands.

The study protocol was amended to increase the number of patients and to include a second study center, to include patients with thrombocyte count <150.000/mm3 but > 100.000/mm3, and to eliminate the requirement for IPG for DVT screening because of its lack of specificity and sensitivity.

Efficacy Evaluation

Assessment of deep vein thrombosis (DVT) and Pulmonary Embolism (PE)
IPG was performed on both legs at screening and on Days 5 and 8. Due to low yield of positivity from DVT monitoring by IPG, this test was discontinued in July 1991 after a total of 105 patients were screened.

Bilateral venography (VG) was performed on each patient on the morning of treatment Day 9, 10 or 11, or earlier if clinical signs of DVT occurred or the IPG suggested the presence of a DVT. The hospital radiologist was responsible for the interpretation of the VG.

If a VG performed before Day 9 showed the presence of DVT, the patient had reached an end-point. Patients with a negative VG performed before Day 6 were to continue study drug treatment, but a second VG was to be done on Day 9, 10 or 11. If a phlebogram performed on or after Day 6 was negative for DVT another VG was to be made on the other limb.

Lung ventilation/perfusion scans or a pulmonary angiogram were made if signs or symptoms, suggestive of the presence of a PE developed.

Safety Evaluation

Assessments of bleeding and related events: Intra-operative bleeding and blood loss was estimated by the surgeon. The volumes of transfusions and/or infusions were recorded.

Post-operative bleeding was assessed by daily recording of blood volumes collected via drains. Blood and blood products transfusions given during the peri-operative and postoperative periods were recorded. In addition, Hgb and Hct values were assessed on each day during the first three post-operative days, on Day 4 or 5, on Day 6, 7 or 8 and on Day 9, 10 or 11.

Adverse experience (AE): All clinical and laboratory AEs were recorded with severity grading and drug attribution.
All AEs which occurred during the study period were coded according to the "International monitoring of adverse reactions to study drugs: adverse reactions terminology" of WHO. The same AE reported more than once in a patient was counted as one AE.

Patients with AEs causing early termination and drug related AEs (assessed by the investigator as very likely or definitely drug-related) were described individually in the final repost.

Reasons for discontinuation
1. Patient related reasons
   a. Emergence of a severe or prolonged intercurrent illness which
   b. Emergence of serious adverse event and/or severe bleeding.
   c. Occurrence of laboratory results indicated serious AE.
   d. The occurrence of DVT or PE.

Patients in whom the study treatment was prematurely stopped for reasons other than unacceptable and/or severe bleeding or DVT/PE were considered drop-outs. Subjects discontinued because of bleeding were not included in the statistical analysis of DVT and PE. Drop-outs because of DVT or PE were included in the analysis of bleeding for the days data is available.

2. Administrative reasons (drop-outs)
   a. Essential data missing which cannot be recovered.
   b. Major protocol violations
   c. Patients given incorrect drug and/or dosage more than once,

Patients were to be replaced if the study treatment was prematurely stopped for reasons other than excessive bleeding or the development of deep vein thrombosis or pulmonary embolism.

Deviations from the protocol: Patients who had no VG or a negative VG on the not operated leg only, were excluded from ITT DVT analysis.

The following criteria for protocol deviations were relaxed after closing the study and the following patients were included in the Per-Protocol analysis:

1) All patients having completed 8 or more days of treatment (or less, if positive for DVT) because the duration of hospitalization was often shorter than the protocol-required minimum 9 days.

2) Patients with VG performed on the operated leg only, whether positive for DVT or not (on the assumption that the operated leg is most at risk of DVT development).

3) Patients with VG performed on the non-operated leg only, if positive for DVT.

4) Patients with venography performed after the last treatment day because VG was performed 1-3 days after the last treatment day in few patients of practical reasons.

5) Patients receiving concomitant therapy with ASA and antiplatelet drugs because a recent interaction study of Org 10172 and ASA which did not suggest that the concomitant use of aspirin and/or NSAID's could have influenced the safety and efficacy parameters of this study. These medications were equally distributed over the two treatment groups.

6) One patient with a prothrombin time of 1.39 times the control value and patients with a diastolic blood pressure of 105 mmHg.

Post-treatment evaluation: Patients were scheduled to be seen by the investigator approximately 6 weeks after the study medication was stopped to assess late occurrence of bleeding or thrombi-embolic complications.

Statistical and analytical methods

Study population: On the basis of $\alpha=0.05$ (two-sided) and $\beta=0.10$ a number of 80 patients in each treatment group was considered likely to detect a difference in the incidence of DVT of at least 20%.

Subjects data sets: Subject data sets were analyzed as follows:

1) All subjects randomized group
2) All subjects treated group: randomized patients who received at least one dose of study medication.
3) The Intention-to-Treat group: those patients in whom the following conditions were fulfilled:
   a) Inclusion in the all subjects treated group
   b) Patients who were operated
   c) Patients with at least a VG of the operated leg. Patients with a VG of the not-operated leg only were included if this was positive for DVT.
4) The Efficacy-Evaluable (Per-Protocol) Group: those patients in whom the following conditions were fulfilled:
   a) Inclusion of the patient in the ITT population.
   b) The patient has completed 8 or more days of treatment or less than 8 days if he or she has had a VG which was positive for DVT.
   c) The patient was not a major protocol violator

Analyses of Efficacy: Venogram results were the basis of the analysis for the incidence of DVT in the ITT and the Per-Protocol population. A between-treatment group comparison with respect to the incidence of any DVT and of proximal DVT adjusted for center differences was performed using the CMH test. Estimates of the relative risk of DVT with associated 95% confidence intervals were calculated for Org 10172 versus low dose heparin using the MH method with test-based confidence intervals. In the same way an estimate for the relative risk of proximal DVT (with or without distal DVT) was calculated. Because the study was extended with a second center, the center effect and the center by treatment interaction were investigated by logistic regression (analysis of deviances).
The (possible) effect of the covariate blood transfusion (autologous or heterologous) on the incidence of DVT was assessed.

Analyses of Safety: Adverse Events and Bleeding: The numbers of subjects with at least one adverse experience by body system and dictionary term were tabulated per treatment group.

Summary statistics of the volumes of blood loss and of blood transfusions during the operation, after the operation and overall, per treatment group and per center were calculated. Differences between the treatment groups across the centers were analyzed by applying the Cochran-Mantel-Haenszel test adjusted for center. Differences between the centers were analyzed by means of a Wilcoxon 2-sample test.
Assessments of pre- and post-operative bleeding complications and transfusion requirements were made, however, the protocol did not distinguish between major and minor bleeding complications. Bleeding complications were listed and tabulated under adverse experiences.

Analyses of Laboratory Data: Descriptive statistics, including baseline values, changes from baseline and relative changes from baseline, were calculated for the following parameters:
Biochemistry: creatinine, SGPT (=ALAT).
Hematology: hemoglobin, hematocrit, leucocytes,thrombocytes.
These laboratory parameters were analyzed for treatment differences using a CMH test adjusting for center. The relative change from baseline of the last scheduled assessment (2 Day 9) was used for comparison. The remaining biochemical, hematological and hemostasis parameters were listed only.

Demographic and other Patient characterization: Summary statistics for the ITT group were calculated per treatment group and study center for baseline and operation characteristics. The treatment groups overall and per center were checked for imbalances of these variables. As the ITT and the Per-protocol group differed for only 4 patients, the latter population was not presented in separate tables.

Listings have been made of pretrial and concomitant medication used by each patient.

Study Results

Disposition of patients: The numbers of patients randomized per center, per treatment group and their suitability for Per-Protocol and/or ITT efficacy analysis are summarized in Table 1.
In total 200 patients were randomized to one of the two treatment groups. All randomized patients had received at least one dose of study medication; therefore all were eligible for the safety analysis.

A total of 26 patients were excluded from the ITT analysis because of lack of VG. A total of 14 patients were excluded from the Per-Protocol analysis because of major protocol violations other than no or incomplete VG. Ten of these patients were already excluded from the ITT analysis because of the absence of or incomplete VG.
In total 30 treated patients (16 in the Org 1017~ group and 14 in the

low dose heparin group) were excluded from the Per- Protocol analysis for efficacy.

Table 1: Number of Subjects per Treatment Group and Center

Treatment Center	Subjects Randomized N	Subjects Treated N	Intent-to-Treat N	Per-Protocol N
Org 10172				
Perugia	80	80	66	64
Parma	20	20	20	20
Total	100	100	86	84
Heparin				
Perugia	80	80	68	67
Parma	20	20	20	19
Total	100	100	88	86

Deviations from the protocol

The following patients were considered minor protocol deviators and were included in the Per-Protocol analysis:

1) Thirty-five patients (17 in the Org 10172 group and 18 in the heparin group) treated beyond Day 11 (up to Day 15) and 2 patients (in the Org 10172 group) treated for 8 days only.

2) Five patients (42, 47, 48, 203, 210) with VG of the operated leg only. It was considered that the operated leg has the greater risk for DVT.

3) One patient with VG only of the non-operated leg positive for DVT (194, heparin group), whereas one with a negative result (215, heparin group) was excluded from both analyses.

4) The two patients (113 and 118) who had VG (positive results) before the last dosing date (but on or after Day 8).

5) Five patients had VG after the last dosing date. Of these, two patients (22 and 189) had VG on day 12 i.e. one day beyond the in the protocol permissible period.

6) One patient (206) had a PT of 16.8", 1.39 times the control value of 12.1". The patient had no other abnormalities

7) Five patients (80, 94, 157, 181 and 194) with diastolic BP of 105 mmHg at baseline and no other abnormalities.

Of the 200 patients randomized, 26 were excluded from the ITT group and 4 additional patients (total of 30) were excluded from the Per-Protocol group. These exclusions were made before the blind was broken. The distribution of these exclusions was similar over the two treatment groups.

Table 3 lists the patients excluded from Per-Protocol analysis because of major protocol violations (other than no VG).

Table 3: Subjects with major protocol violations (reasons other than no venography). Excluded from the Per Protocol group.

Group: Org 10172

Centre	Subject	Last day on study drug	Reason for exclusion
Perugia	18*	4	Less than 8 days of treatment
Perugia	36	6	Less than 8 days of treatment
Perugia	145*	1	Less than 8 days of treatment
Perugia	181	10	Child-bearing potential (age 51, menstruating)
Perugia	212*	6	Less than 8 days of treatment
Perugia	213*	11	Forbidden medication (5000 IE x 2 Calciparine subcutaneously, one day before the operation)

Group: Heparin

Centre	Subject	Last day on study drug	Reason for exclusion
Perugia	27*	1	Less than 8 days of treatment (no operation)
Perugia	28	11	Thrombocytopenia at baseline (platelet count below 100 x 10^9/L)
Perugia	46*	7	Less than 8 days of treatment
Parma	114	12	Thrombocytopenia at baseline (platelet count below 100 x 10^9/L)
Perugia	148*	1	Less than 8 days of treatment
Perugia	152*	1	Less than 8 days of treatment (no operation)
Perugia	156*	1	Less than 8 days of treatment
Perugia	174*	11	No morning or evening dose on days 2 and 3 (Trial stopped because of low Hb-value; trial medication erroneously restarted after two days).

* subjects where no venography was performed (excluded from the Intention to Treat group)

Blind broken during study: Because of minor differences in color between the treatment solutions it is possible that the nursing staff, was aware of the allocated treatments. However all assessments of efficacy and of intra- and post-operative bleeding and adverse events were made blindly. Eligible patients received their study number in a sequential order and treatment was allocated according to the randomization list.

Subjects Discontinued: Table 5 gives lists the early treatment discontinuations before Day 8, which occurred in 9 patients. Both treatment groups were comparable with respect to the drop-out rate. For none of the patients was the treatment "prematurely" discontinued because of the presence of DVT.
All early discontinuations are included in the safety analysis.

Table 5: Reasons for treatment discontinuation before day 8

Group: Org 10172

Centre	Subject	Last day on study drug	Reason for discontinuation
Perugia	18	4	Forbidden comedication (Indomethacine)
Perugia	36	6	False positive IPG
Perugia	145	1	Forbidden comedication (Indomethacine)
Perugia	212	6	Haematemesis (gastric endoscopy showed an old duodenal ulcer)

Group: Heparin

Centre	Subject	Last day on study drug	Reason for discontinuation
Perugia	27	1	No operation (patient refuses cooperation after allergic reaction)
Perugia	46	7	Patient refuses cooperation.
Perugia	148	1	Forbidden comedication (Indomethacine)
Perugia	152	1	Operation not done (osteolytic lesion in left femur)
Perugia	156	1	Forbidden comedication (Indomethacine)

Demographic and other Subject characteristics

Demographic data at baseline: The ratio of women to men is approximately 2:1. Statistically relevant differences ($p<0.05$) between the treatment groups were:

1) Cardiovascular diseases other than MI and angina were less frequent in the Org 10172 than in the heparin group: 30% vs 45%.
2) A past history of GI diseases was more frequent in the Org 10172 group than in the low dose heparin group: 42% vs 25%.
3) Dysfunction of the Respiratory System was more frequent in the Org 10172 group than in the low dose heparin group: 13% vs 4%.

No relevant differences in demographic parameters or surgical characteristics were observed between the treatment groups. Statistically relevant differences ($p<0.05$) in patient characteristics at baseline between centers were:

1) Subject demographics
   a) Age (mean age: Parma = 4.2 years more than in Perugia).
   b) Weight (mean weight: Parma 5.1 kg less than in Peruqia).
2) Present and past illness
   a) In Parma "other relevant disorders" in the present and past were more frequently reported than in Perugia.
   b) Past respiratory disease was reported more frequently in Parma than in Perugia.
3) General health information
   a) Patients in Perugia less often reported the use of drugs during the 2 weeks prior to the start of the study than patients in Parma (47% and 70% respectively).
4) Operation details
   a) In Parma 25 patients received autologous blood transfusion and 13 patients heterologous transfusion while in Perugia only heterologous blood transfusion were given.

The patients in Parma were somewhat less healthy than in Perugia.

Extent of exposure to treatment and Dosing compliance: The average treatment duration for all treated patients was similar for both treatment groups (approximately 10 days).

Concomitant medication: All patients had concomitant medications. After closing of the study, it was decided to include in the Per Protocol analysis, the patients who had used ASA and/or NSAID's during the study. However, the study treatment had been discontinued in 4 patients given indomethacin concomitantly (2 patients in the Org 10172 group and 2 in the low-dose heparin group). One patient (213) had been given heparin 5000 IU. twice daily up to the day before surgery. This patient was excluded from the Per-Protocol analysis.

Efficacy Results

Assessments of deep vein thrombosis: The decision on whether a DVT was present or not was made for all patients by two fully blinded expert radiologists who reviewed the VGs.

Distal and proximal DVT: In the ITT analysis, the lowest incidence of DVT was observed in the Org 10172 group: 21% compared to 35% in the heparin group. This difference was statistically significant (p=0.032). The difference in the incidence of DVT between the two treatment groups for the Per-Protocol population was similar: 21% and 36% for the Org 10172 and the heparin group respectively (p = 0.028) as none of the four patients in the ITT group who were excluded from the Per Protocol analysis had a DVT.

The relative risk of experiencing a DVT in the Org 10172 group, compared with that in the heparin group was 0.59 with 95% the CI ranging from 0.37 to 0.96.

A statistically significant difference in the incidence of DVT was observed between the two centers: in Perugia 23% of the overall total number of patients in both treatment groups experienced a DVT, compared to 45% of the patients in Parma (p = 0.009). However, at both centers, the incidence of DVT was lower in the Org 10172 group compared to the heparin group. As the analysis was done adjusting for a possible center effect, the difference in incidence of DVT between the centers did not affect the comparison of DVT incidence between treatment groups especially as no center x treatment interaction could be observed with respect to the occurrence of DVT (p=0.91).

Proximal DVT (with or without distal DVT): In the ITT group the lowest incidence of proximal DVT, with or without distal DVT, is observed in the Org 10172 group: 8.1% compared to 16% in the heparin group. This difference is not statistically significant (p=0.12). The relative risk for proximal DVT, using the Mantel-Haenszel method for the Org 10172 and the heparin group is 0.51 but its 95% confidence interval is 0.22-1.18. There were no statistically significant differences between the centers with regard to the occurrence of proximal DVT (p=0.53) nor for the center x treatment interaction (p=0.96) when using a logistic regression method (analysis of deviances).

Assessment of pulmonary embolism: One heparin patient (# 22) had evidence of PE as detected on a V/Q lung scan performed on Day 11.

The frequencies of total and proximal DVT by treatment and by center for the ITT population of 174 patients are summarized below.

Occurrence of DVT by treatment and by center
Intent-To-Treat Group

Treatment / Center	DVT				Total N	No Venography N
	Total		Proximal			
	N	%	N	%		
Org 10172						
Perugia	11	16.7	5	7.6	66	14
Parma	7	35.0	2	10.0	20	0
Total	18	20.9	7	8.1	86	14
Heparin						
Perugia	20	29.4	10	14.7	68	12
Parma	11	55.0	4	20.0	20	0
Total	31	35.2	14	15.9	88	12

Between treatment comparison for total DVT (CMH adjusted for center)
Chi-square (df=1) 4.602 P-value=0.032
Relative Risk (MH): Org 10172 vs Heparin=0.592 (95% CI:0.366-0.956)
P-value center effect on occurrence of DVT: 0.009
P-value center-treatment interaction effect on occurrence of DVT: 0.91

Between treatment comparison for proximal DVT (CMH adjusted for center)
Chi-square (df=1) 2.462 P-value=0.117
Relative Risk (MH): Org 10172 vs Heparin=0.511 (95% CI:0.221-1.182)
P-value center effect on occurrence of DVT: 0.526
P-value center-treatment interaction effect on occurrence of DVT: 0.96

Safety Results

Assessment of bleeding and related events

Excessive bleeding: The following table gives the numbers of patients with excessive blood loss in each treatment group.

Blood loss	Org 10172	heparin
Incisional	1	3
Intra-operative	3	2
Post-operative~	4	3
Total**	6	7

** Number of patients with at least one excessive bleeding irrespective of time point of occurrence.

Intra-operative blood loss: The intra-operative blood loss was comparable for both treatment groups (median values 350 ml in each group). The CMH test to detect differences between treatments (adjusted for multiple centers) did not show statistically significant differences. However, statistically significant differences in intra-operative blood loss were found between the centers (Wilcoxon test $p < 0.001$). The median value (both treatments combined) for Parma (600 ml) was twice the value for Perugia (300 ml).

Post-operative bleeding: The medians of the volumes of post-operative blood loss were 700 ml and 750 ml for the Org 10172 and the heparin treatment group respectively. The difference between the treatment groups was not statistically significant ($p=0.603$, CMH test). The median of the volume of post-operative blood loss by center (the two treatments taken together) was 730 ml and 700 ml for Perugia and Parma respectively. The difference was not statistically significant.

Total overall blood loss: The volume of total blood loss was the sum of the intra-operative and post-operative blood loss. The median values were the same for both treatment groups (1100 ml). The median values of total blood loss per center (both treatment groups combined) were 1090 ml for Perugia and 1305 ml for Parma. The difference was statistically significant ($p=0.001$) and was due to the different intra-operative blood loss volumes.
The median values of total blood loss in Perugia and in Parma were not significantly different in the two treatment groups (CMH test adjusted for center).

Blood transfusions:

Transfusions on the day of operation: On the operation day, 96 patients from the Org 10172 group and 94 from the heparin group, received blood transfusions. When data of both centers are combined, the median values of blood transfusions for the Org 10172 and the heparin groups are 575 ml and 600 ml respectively. The differences between the treatment groups across the two centers are not statistically significant ($p=0.807$, CMH test). However, significant differences between the centers were observed. The median value of the volume of blood transfusions (the two treatments combined) for Parma (1615 ml) is more than three times that of Perugia (500 ml). This difference was statistically significant ($p<0.001$). In Perugia the median volumes of blood transfusion were 500 ml and 600 ml for the Org 10172 and the heparin group respectively. In Parma the median values were 1490 ml and 1690 ml for the Org 10172 and the heparin group respectively.

Transfusions after the operation day: Five patients in each treatment group received blood transfusion after the day of the operation. Due to the small number of patients, no statistical tests were performed.

Overall volume of blood transfusions: The median values were 550 ml and 600 ml for the Org 10172 and the heparin group respectively. The median value of the total volume of blood transfused for Parma (1700 ml) was more than three times that of Perugia (500 ml). This difference was statistically significant (p~0.001). In Perugia the median values of the total volumes of blood transfusions were 500 ml and 600 ml for the Org 10172 and the heparin group respectively. In Parma the median values of the total volumes of blood transfusions were 1659 ml and 1800 ml in the Org 10172 and the heparin group respectively. Table 41 summarizes the differences in volumes of blood transfusions between both treatments on the operation day, after the operation day and the overall total transfusion volume, per center and in total.

Autologous versus heterologous blood transfusions Twenty five patients in Parma received transfusions of autologous blood whereas in Perugia only heterologous blood transfusions were given (see also Table 17). The incidence of DVT (in Parma) in the group of patients who received autologous blood was (40%) not statistically different from that in the patients who received heterologous blood (62%).

Bleeding complications: For six patients in the Org 10172 group adverse events with a bleeding aspect were reported: melaena (2), purpura (7, 109 and 128), hematoma (26) and hematemesis (212). For two patients in the low dose heparin group adverse events with a bleeding aspect were reported: hematoma (28 and 114). None of these 8 adverse experiences were regarded as serious (SAE); one adverse experience (2) was regarded as drug-related.

The protocol did not distinguish between major and minor bleeding complications. However in only one patient (212, Org 10172 group) the treatment was terminated before Day 8 (on Day 7) because of bleeding complications (hematemesis). Gastro-duodenoscopy revealed a duodenal ulcer. The investigator did not consider that a relationship of the bleed with the Org 10172 treatment was likely.

Bruising at the injection site occurred in 46% and 62% of patients in the Org 10172 and the heparin group respectively. No hematoma which was produced by local injections were reported by the investigators.

Adverse Events

Serious Adverse Events (SAE): There were no serious adverse events and no deaths.
Adverse Events (AE) causing early termination of study medication: In patient 212 (Org 10172 group) the study medication was stopped on Day 6 because of hematemesis secondary to a duodenal ulcer. In Patient 27 (Heparin group) the treatment was stopped after the first injection because an allergic reaction probably related to ceftriaxone.
Drug-related adverse events: Patient 2 (Org 10172 group) experienced melaena, nausea and vomiting. Patient 111 (Org 10172 group) had an erythematous cutaneous rash on Day 6. Patient 22 (Heparin group) had fever on Day 10. Patient 194 (Heparin group) had on Day 10 a marked fall in the thrombocyte count (Days 0, 1, 2, 4 and 10 respectively 293, 320, 271, 246 and 86x109/L). On the 10th day, the VG showed a proximal DVT. The fall in thrombocytes and the development of the DVT were attributed to heparin induced thrombocytopenia (HIT).

Laboratory parameters
1. Markedly abnormal laboratory values (values outside the Organon "safety range")
Biochemistry parameters: No significant differences between the treatment groups are seen in the number of patients with at least one value outside the safety range for the serum Creatinine and the SGPT values.
Hematology parameters: Hgb values lower than 9.5 g/dl measured after the start of treatment, were seen in 36% and 38% of the Org 10172 and the heparin group respectively. Hematocrit values <32% were seen in 73% and 67% of the Org 10172 and the heparin group respectively.
The numbers of patients with at least one Hgb or Hct value which was lower than the safety range after the start of treatment did not differ between the two treatment groups. No significant differences between the treatment groups were seen in the number of patients with at least one value outside the safety range for the leucocyte and thrombocyte counts. One patient in the Org 10172 group (8) and one patient in the heparin group (28) developed a thrombocyte count below $75x10^9/L$ after the start of treatment.

2. Changes from baseline
Biochemistry parameters: The summary values for Creatinine did not show any relevant change over the treatment period for both treatment groups. The summary values for SGPT show in both treatment groups a rise from baseline) for Day 3-4-5 and Day 6-7-8 and 2-9. This increase was statistically significantly higher at Day 9 and beyond in the heparin

group as compared to the Org 10172 group ($p<0.05$).
Hematology parameters: The summary values for Hgb and Hct show the expected reductions after the operation. The difference in the mean relative change from baseline between the treatment groups was small and clinically and statistically insignificant.

The summary values for platelets showed the expected fall in number during the first 5 days after the operation and the subsequent overshoot recovery during days 6-7-8 and 9 or beyond. This pattern of platelet count changes was similar for both treatment groups.

Three patients developed marked thrombocytopenia (of which 2 patients had platelet counts $<75x10^9/L$) during one or more treatment days:
Patient 8 (Org 10172 group) had a platelet count of $163x10^9/L$ at baseline, which increased to $214x10^9/L$ on the operation day, but dropped to $50x10^9/L$ the day after. Treatment with Org 10172 was continued and the thrombocytes began to rise again, eventually reaching $330x10^9/L$ on Day 8.
Patient 28 (Heparin group) had a platelet count of $71x10^9/L$ at baseline, which dropped to $60x10^9/L$ on the operation day, rising to $76x10^9/L$ on Day 2, and dropping again to $60x10^9/L$ on Day 4. The heparin treatment was continued and the platelet began to rise a second time, eventually to $114x10^9/L$ on Day 11.
Patient 194 (Heparin group) had a marked fall in platelet count on day 10 (293, 320, 271, 246 and $86x10^9/L$ on days 0,1,2,4,10 respectively). On the 10th day the VG showed a proximal DVT. The fall in platelets and the development of the DVT were likely due to heparin induced thrombocytopenia (HIT).

Plasma anti-Xa values Samples of plasma anti-Xa were collected; however these have not been assayed.

Follow-up: Eighty nine patients from the Org 10172 group and 87 patients from the heparin group attended for an outpatient follow-up examination. Follow-up information by telephone only was obtained from a further 8 patients. In the Org 10172 group and the heparin group, 6 and 11 patients respectively had signs of DVT on clinical examination at follow-up. There was no further evaluation to confirm the presence of DVT in these patients.

One patient (Patient 74 heparin group) with diagnosis of a DVT at the end of the study experienced a PE on post-study day 29.

Comments

In this study the efficacy and safety of Org 10172 (750 anti-Xa units b.i.d., s.c.) for prophylaxis of venous thrombi-embolism in patients undergoing elective hip replacement surgery were compared with standard heparin (5000 IU heparin b.i.d., s.c.). Both treatments were started 2-3 hours before surgery and were continued for at least 8 days.

It must be noted that the comparator regimen (unfractionated heparin) is not approved for this indication and, moreover, it was given at a dose clearly inadequate for thromboprophylaxis in high risk orthopedic surgery.

The diagnosis of DVT was made in all patients on the basis of positive VG. As previously reported from other studies, IPG was totally unreliable as screening diagnostic tests in patients with clinically silent DVT.

Because of an unexpectedly low recruitment rate the study was extended to a second center where 40 of the total of 200 randomized patients were recruited. At both centers. the incidence of DVT in the ITT and in the Per-Protocol population was lower in the Org 10172 group than in the heparin group: 21% vs 35%, p-value=0.03. The heparin regimen used as comparator is ineffective for the prophylaxis of DVT/PE in high risk orthopedic surgery and should be considered close to placebo.

The two treatment groups were not fully matched for previous or present medical conditions. Most of the differences, except for cardiovascular diseases (other than MI or angina), were unlikely to have significantly influenced the study outcome and no correlation was found between presence of CV disease and development of DVT in the study population.

The incidence of DVT in both treatment groups was higher at the Parma center where the study population was older than at the Perugia center.

Both treatments were well tolerated: no deaths or other serious adverse events were reported. At both centers, no differences were observed between intra-operative, post-operative and total-blood loss and the transfusion requirements between the treatment groups. However, the intraoperative and total median volume of blood loss was statistically significantly larger in Parma than in Perugia. A much larger difference between the two center was noted for volume of blood transfusion on operation day when the median volume of blood transfused at the Parma center was approximately three fold that of the Perugia center for both treatment groups. However, it must also be noted that 66% of patients

at the Parma center received autologous blood during the peri-operative period and this was included in the overall volume of blood transfused.

The post-operative levels of Hgb were similar in the two treatment groups. In the Org 10172 group, 15 patients had Hgb levels below 9.0 g/dL, compared to 14 in the heparin group; 5 patients had levels below 8.0 g/dL compared to 7 in the heparin group; and 2 patients had levels below 7.0 g/dL. compared to 1 in the heparin group.

In conclusion no differences between the treatment groups in operation-related blood loss and blood transfusions were observed, but differences were noted between the two centers.

Adverse events other than bleeding included one case of erythematous rash in a Org 10172-treated patient and a case of HIT with thrombosis in a heparin-treated patient.
Two patients in the heparin group developed PE, one during and one after the period of study medication.

In one patient from the Org 10172 group the treatment had to be terminated because of hematemesis from a duodenal ulcer. In another patient the heparin medication was stopped for an allergic reaction following administration of Ceftriaxone. No unexpected adverse events were reported during the study.

INTEGRATED SUMMARY OF EFFECTIVENESS

SUMMARY AND COMPARISON OF EFFICACY DATA FROM FOUR INDIVIDUAL STUDIES

Four controlled studies have been conducted to assess the efficacy and safety of Org 10172 for thromboprophylaxis after elective hip replacement surgery. Two studies appear to be adequate and well - controlled and two studies are supportive in providing substantial evidence that Org 10172 is efficacious and has its intended effect for the prophylaxis of DVT in patients undergoing orthopedic hip surgery. The four studies include a placebo controlled, double-blind, multicenter trial (#85140) carried out in The Netherlands, one active-controlled, assessor-blind, multicenter U.S. trial (#004-023), comparing the efficacy of Org 10172 with warfarin sodium, and one other active controlled non-U.S. multicenter study (#86002, assessor-blind) assessing the effect of Org 10172 versus heparin/DHE. The final report of an additional study, #86030 (Org 10172 versus heparin), completed after the NDA submission of 12-19-1994, was submitted with an update of safety on June 7. 1995.

The efficacy of Org 10172, expressed in terms of reduction in the incidence rates of DVT/PE, compared to that seen in the comparator groups, are summarized in the following tables.

NUMBER (%) OF PATIENTS WITH DVT*

INTENT-TO-TREAT GROUP					
	Org 10172 N=531	Warfarin N=197	Placebo N=98	Hepar/DHE N=147	Heparin N=88
Proximal	25 (4.7%)	8 (4.1%)	26 (27%)	10 (7%)	14 (16%)
Distal	79 (14.9%)	49 (24.9%)	51 (52%)	45 (31%)	29 (33%)
Overall	87 (16.4%)	53 (26.9%)	56 (57%)	47 (32%)	31 (35%)

*A patient may be counted more than once (proximal and distal)

NUMBER (%) OF PATIENTS WITH DVT*

	EFFICACY EVALUABLE GROUP				
	Org 10172[@] N=280	Warfarin N=175	Placebo N=98	Hepar/DHE N/A	Heparin N=86
Proximal	11 (3.9%)	7 (4.0%)	26 (27%)	N/A	14 (16%)
Distal	41 (14.6%)	46 (26.3%)	51 (52%)	N/A	29 (34%)
Overall	43 (15.3%)	49 (28.0%)	56 (57%)	N/A	31 (36%)

*A patient may be counted more than once (proximal and distal)
[@]Number include patients from studies #004-023, #85140,

In all studies, Org 10172 was superior to the comparator regimen with a difference which was statistically significant for distal and total DVT. In study 85140, the incidence of proximal DVT was statistically significantly lower in the Org 10172 group than in the placebo group. In the remaining three studies, the incidence of proximal DVT was also lower in Org 10172-treated patients than in the active control groups, although these differences wwere not statistically significant.

The incidence of PE in the Org 10172-treated patients pooled from all 4 studies was 1.03% (6/582) compared to 0.82% (2/243) for warfarin, 0.92% (1/109) for placebo, 1.13% (1/88) for heparin, and 1.93% (3/155) for heparin/DHE. The differences were not statistically significant.

Exploratory and risk factor analyses performed in the individual studies showed no relationship between most risk factors and DVT. In the pivotal study #004-023, no relationship was found within each treatment group between age, gender, body weight, missed doses and incidence of DVT. A statistically significant difference was found within each of the treatment groups only for incidence of DVT by duration of surgery ($\geq$ 120' vs $\leq$ 120').
For the pivotal study #85140, an exploratory analysis was performed to compare the two treatment groups with respect to the incidence of DVT and each type of anesthesia (epidural, psoas block or general).
For patients in both ITT and Evaluable groups treated with Org 10172, a statistically significant reduction in proximal DVT (p=0.002) as compared to placebo-treated patients was noted in those receiving psoas block. For patients receiving general anesthesia, the incidence of proximal, distal and overall DVT was significantly lower for Org 10172-treated patient than for placebo-treated patients.

INTEGRATED SUMMARY OF SAFETY

SUMMARY AND COMPARISON OF SAFETY DATA FROM ALL STUDIES

In addition to the initial proposed NDA indication of "DVT and PE Prophylaxis Following Orthopedic Hip Surgery" which included hip replacement Org 10172 has been evaluated for efficacy and safety in several other controlled and uncontrolled non-orthopedic surgery studies ("Other Studies" or "Non- Indication Studies") including the following clinical situations:

TABLE 34
STUDY GROUPINGS AND NUMBER OF PATIENTS
ALLOCATED TO TREATMENT (ALL TREATMENT GROUPS)[a]

Study Grouping	Number of Patients/Subjects Randomized to a Study	Number of Patients/Subjects Who Did Not Receive Treatment	Number of Patients/Subjects Treated[b]
Indication			
DVT and PE Prophylaxis for Orthopedic Hip Surgery			
U.S.	938	18	920
Non-U.S.	1491	7	1484
Total	2429	25	2404
Other Studies			

TABLE 35
SUMMARY OF PATIENTS BY TREATMENT GROUP
ALL PATIENTS TREATED[a]

Study Grouping	Total Number of Patients	Treatment			
		Org 10172	Placebo	Warfarin	Other[b]
DVT and PE Prophylaxis for Orthopedic Hip Surgery					
U.S.	920	517	5	386	12
Non-U.S.	1484	750	168	0	566
Total	2404	1267	173	386	578
Other Studies[c]					
Total	2231[a]	1449[a]	132[a]	35[a]	615[a]

[a]Data from Studies #004-022, 004-500/004-500(OL), 62001, 62002, 82030 Part I, 83065, 84011, 85019, 86008, 86030, 87018, and the de Boer publication (de Boer et al., 1992) are not included in this table. Also not included are 190 patients in crossover studies in which patients received Org 10172 and at least one reference agent in the treatment sequence.
[b]"Other" treatment includes the following reference agents: heparin, heparin/DHE, acetylsalicylic acid (ASA), dextran, and low-molecular weight heparins.
[c]"Other Studies" includes all patients studied, except those in the DVT and PE Prophylaxis for Orthopedic Hip Surgery Group and those excluded (see Footnote "a" above) from this table.

Of the 2429 patients from 17 Orthopedic Surgery Studies, 1267 received Org 10172 for DVT/PE prophylaxis, the remaining 1161 subjects received placebo or active reference agents (warfarin, heparin, heparin/DHE, ASA, Dextran, or LMWH). A total of 1449 from the 2231 patients entered in Other Studies received Org 10172.

In 8/17 Orthopedic studies, Org 10172 was administered at the dose of 750 anti-Xa U/bid sc, in the remaining 9 studies, Org 10172 was administered at various doses, ranging from 500 to 1500 anti-Xa U qd or bid or by infusion. The majority of patients from the Orthopedic Studies received Org 10172 for 7 to 11 days with the highest number being treated for 10 days. The duration of treatment was variable in the Other Studies because of different indications.

A total of 70 deaths occurred among the 2404 patients from the Orthopedic Studies (2.9%). Twenty-eight of the deaths occurred among the Org 10172-treated patients (2.2%), 7 in the warfarin group (1.8%), 2 in the placebo group (1.15%), and 23 among the others control treatments (3.97%). None of the deaths occurring in the Org 10172 group were considered to be related to the drug.
There were 155 deaths among the 2231 patients from the Other Studies (6.9%); 98 death occurred in the Org 10172 group (6.8%), 8 in the placebo group (6.0%), and 49 in the other control groups (7.96%).

In the Orthopedic Studies, 131/2404 patients (5.4%) experienced serious adverse events (SAE) involving mostly the Body as a Whole, the Cardiovascular, GU, Respiratory systems. Only one episode of skin rash was considered definitely related to Org 10172. The frequency of SAE and the frequency of drug-related SAE for the whole Orthopedic Studies population are summarized in table 38 (v. 2.3, p.346).

TABLE 38
ASSESSMENT OF ADVERSE EXPERIENCES BY TREATMENT
DVT AND PE PROPHYLAXIS FOR ORTHOPEDIC HIP SURGERY
ALL PATIENTS TREATED

Indication	Org 10172		Placebo		Warfarin		Other*	
	Frequency of Patients With AEs	Frequency of Patients With Drug-Related AEs	Frequency of Patients With AEs	Frequency of Patients With Drug-Related AEs	Frequency of Patients With AEs	Frequency of Patients With Drug-Related AEs	Frequency of Patients With AEs	Frequency of Patients With Drug-Related AEs
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
DVT and PE Prophylaxis for Orthopedic Hip Surgery								
U.S. (920 Patients)	370/517 (71.6)	56/517 (10.8)	4/5 (80.0)	1/5 (20.0)	313/386 (81.1)	23/386 (6.0)	0/12 (0.0)	0/12 (0.0)
Non-U.S. (1484 Patients)	263/750 (35.1)	115/750 (15.3)	30/168 (17.9)	26/168 (15.5)	0/0 (-)	0/0 (-)	212/566 (37.5)	65/566 (11.5)
Total (2404 Patients)	633/1267 (50.0)	171/1267 (13.5)	34/173 (19.7)	27/173 (15.6)	313/386 (81.1)	23/386 (6.0)	212/578 (36.7)	65/578 (11.2)

*"Other" includes the following reference agents: heparin, heparin/DHE, acetylsalicylic acid (ASA), dextran, and low-molecular weight heparins.

SAE were experienced by 1.7% of the study population from the Other Studies. In the Org 10172-treated group, the incidence of SAE was 1.4% (21/1449).

The changes in laboratory data for patients in the Orthopedic and Other Studies were unremarkable and not clinically significant.

Bleeding events assessed in terms of blood loss and replacement are summarized in table 48 (v.2.255, p. 274) for the overall population of the Orthopedic studies.

The hematological laboratory abnormalities reported for the overall population of the Orthopedic studies are summarized in table 55 (v.2.255, p.283).

TABLE 48 (CONTINUED)
BLOOD LOSS AND TRANSFUSIONS
DVT AND PE PROPHYLAXIS FOR ORTHOPEDIC HIP SURGERY
ALL PATIENTS TREATED

Blood Loss and Transfusions	Total N	Org 10172	Placebo	Warfarin	Other*
Total (728 Males; 1675 Females)		(n) Mean±SD	(n) Mean±SD	(n) Mean±SD	(n) Mean±SD
Intraoperative Blood Loss (mL)					
Males	596	(330) 694±555	(27) 586±737	(141) 689±499	(98) 754±661
Females	1259	(686) 486±430	(66) 416±252	(219) 471±306	(288) 530±456
Postoperative Blood Loss					
Males	580	(318) 954±879	(41) 908±812	(88) 817±585	(129) 1056±1055
Females	1256	(639) 700±778	(122) 715±520	(80) 609±352	(415) 798±779
Transfusions (Units PRBCs)					
Males	462	(258) 2.6±1.8	(15) 2.7±1.4	(87) 2.5±1.4	(82) 2.9±2.1
Females	1152	(604) 2.6±1.7	(92) 2.8±1.4	(177) 2.1±1.1	(279) 2.8±2.0

*"Other" includes the following active reference agents: heparin, heparin/DHE, acetylsalicylic acid, dextran, and low-molecular weight heparins.

Total N = Total number of patients with available data across all treatment groups.
n= The number of patients with available data in each respective treatment group and by gender.

TABLE 55
MEAN VALUES FOR HEMATOLOGY PARAMETERS
DVT AND PE PROPHYLAXIS FOR ORTHOPEDIC HIP SURGERY
ALL PATIENTS TREATED

Component		Males				Females			
		Org 10172	Placebo	Warfarin	Other[a]	Org 10172	Placebo	Warfarin	Other[a]
Hgb (g/L)	N[b]	360	44	117	126	789	122	199	393
	Entry	137.6	139.3	130.5	138.6	125.4	128.3	118.9	130.3
	Last Measurement	111.0	118.4	110.4	115.7	108.9	114.8	105.9	110.5
HCT	N[b]	344	41	116	125	748	108	200	382
	Entry	0.41	0.43	0.39	0.41	0.38	0.39	0.36	0.39
	Last Measurement	0.33	0.36	0.34	0.34	0.33	0.35	0.33	0.33
RBC ($x10^{12}$/L)	N[b]	307	44	93	91	592	121	85	272
	Entry	4.5	4.7	4.3	4.5	4.2	4.4	3.9	4.3
	Last Measurement	3.6	4.0	3.6	3.8	3.6	3.9	3.4	3.7
Platelets ($x10^9$/L)	N[b]	359	44	115	126	774	123	195	393
	Entry	249.1	258.5	277.6	220.3	269.0	252.4	290.2	249.8
	Last Measurement	381.3	399.6	357.1	351.8	404.8	350.5	387.5	363.9

[a] "Other" includes the following active reference agents: heparin, heparin/DHE, acetylsalicylic acid, dextran, and low-molecular weight heparins.
[b] Patients with data available.

Less than 1% of the overall patient population of the Orthopedic studies experienced bleeding designated as serious adverse events. The incidence and severity of bleeding in the patient population from Other Studies were comparable for the Org 10172-treated group compared to patients in the placebo, warfarin and other groups.

The frequency of discontinuation of study drug due to bleeding events for the overall population of the Orthopedic Studies is summarized in table 57 (v. 2.255, p. 291).

No significant drug-demographics and drug-disease interactions were observed for bleeding events.

TABLE 57
DISCONTINUATIONS OF STUDY DRUG DUE TO BLEEDING EVENTS BY TREATMENT
DVT AND PE PROPHYLAXIS FOR ORTHOPEDIC HIP SURGERY
ALL PATIENTS TREATED

	Org 10172 n/N (%)	Placebo n/N (%)	Warfarin n/N (%)	Other[a] n/N (%)
U.S. Studies	12/517 (2.3)	0/5 (0.0)	4/386 (1.0)	0/12 (0.0)
Non-U.S.Studies	14/750 (1.9)	2/168 (1.2)	NA	12/566 (2.1)
Total	26/1267 (2.1)	2/173 (1.2)	4/386 (1.0)	12/578 (2.1)

[a]"Other" includes the following active reference agents: heparin, heparin/DHE, acetylsalicylic acid, dextran, and low-molecular weight heparins.

n = Number of patients with at least one bleeding event.
N = Number of "All Patients Treated" with the designated study drug.
NA = Not applicable.

Additional data from studies that were ongoing at the time of the NDA submission were submitted in a 120 Day Safety Update on 6-7-1995. With the completion of one Orthopedic Study (86030) and 6 non-Orthopedic studies, the total number of study subjects has increased to 6507: 2604 from 17 studies of "DVT and PE Prophylaxis in Orthopedic Surgery" and 3903 from "Other Studies".

At the cutoff date of the Safety Update, 12-31-1994, the total number of patients treated with Org 10172 was 3349: 1367 from the Orthopedic studies and 1981 from Non-Indication Studies. The distribution of the study population, as of the time of the Safety Update, is summarized in table 3 (v.7.1, p.36).

No new adverse events were reported in these additional studies. The overall incidence rates of clinical and laboratory were similar to that presented for the NDA Integrated Summary of Safety.

TABLE 3
SUMMARY OF SUBJECTS BY TREATMENT GROUP
ALL SUBJECTS TREATED[a]

Study Grouping	Total Number of Subjects	Treatment			
		Org 10172	Placebo	Warfarin	Other[b]
DVT and PE Prophylaxis for Orthopedic Hip Surgery					
U.S.					
Integrated Summary of Safety Information	920	517	5	386	12
Additional Subjects 120-Day Safety Update	0	0	0	0	0
Non-U.S.					
Integrated Summary of Safety Information	1484	750	168	0	566
Additional Subjects 120-Day Safety Update	200	100	0	0	100
Sub-Totals					
Integrated Summary of Safety Information	2404	1267	173	386	578
Additional Subjects 120-Day Safety Update	200	100	0	0	100
Total DVT and PE Prophylaxis for Orthopedic Hip Surgery	2604	1367	173	386	678

CONCLUSIONS FROM CONTROLLED CLINICAL STUDIES

Based on the data obtained from four controlled clinical trials with Org 10172, administered twice daily as a sc injection of 750 anti-XaU for the prophylaxis of DVT in patients undergoing hip replacement surgery, it may be concluded that the clinical advantages of Org 10172, when compared to other antithrombotic regimens, are as follows:
1) A significant reduction in the incidence of DVT following orthopedic hip surgery when compared to warfarin, heparin/DHE, unfractionated heparin, or placebo;
2) Consistent results in the prophylaxis of DVT following orthopedic hip surgery with a dose of 750 anti-Xa units, s.c., b.i.d., in patients with multiple risk factors for DVT;
3) The incidence of proximal DVT in replacement hip patients treated with Org 10172 is lower than in patients administered placebo, warfarin, heparin/DHE, or heparin. The difference is statistically significant for placebo.
4) No requirements for laboratory control for monitoring the antithrombotic effects;
5) A safety profile similar to placebo and other active comparator regimens.
6) A lower cross-reactivity with heparin-induced antibodies than LMWH.

Commercial Marketing Experience and Foreign Regulatory Action

As of 12-31-1993, Org 10172, under the trade name of Orgaran, has been approved for prevention of postoperative thromboembolism in patients undergoing general or orthopedic surgery in 10 countries, is currently marketed in 2 and planned for marketing in more. In Switzerland, Organon is also approved as anticoagulant in patients with HIT. Approval of Orgaran is pending in additional countries. Approval (indications unspecified) has been denied in Germany because the data available were not considered adequate by the BGA to establish the benefit/risk ratio, and in Finland because the preparation was not found to be appropriate to its purpose (indication unspecified) since the comparative studies did not show equivalence to other similar products and because the price of the product was excessive.

Proposed Package Insert Labeling

The proposed labeling submitted with the NDA must be revised in order to pertain to the indication for thromboprophylaxis in hip replacement surgery.

RECOMMENDATIONS:

Org 10172 (Orgaran, Danaparoid Sodium) has been shown to be safe and effective for thromboprophylaxis in patients undergoing elective hip replacement surgery. In four controlled clinical trial, the administration of Orgaran at the dose of 750 anti-Xa U sc bid with the first dose given preoperatively and continued for an average duration of 7-10 days postoperatively, produced a statistically significant reduction in incidence of DVT when compared to placebo, warfarin, heparin, and heparin/DHE. At the dose regimen used, Orgaran exhibited a favorable safety profile.

Orgaran is recommended for approval for thromboprophylaxis in elective hip replacement surgery. The recommended dose regimen for the above indication is 750 anti-Xa U sc bid for an average duration of 7-10 days postoperatively and with the first dose given preoperatively.

Lilia Talarico, M.D.

cc:
NDA 20-430
HFD-180
HFD-180/SFredd
HFD-180/LTalarico
HFD-181/CSO
HFD-180/JChoudary
HFD-180/JGibbs
f/t 8/2/95 jgw
MED\N\20430508.0LT

8/7/95

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Medical Officer's Review

DEC 13 1997

NDA #	20-430
Sponsor:	Organon Inc.
Drug:	Orgaran™ (Danaparoid Sodium)
Class:	Low Molecular Weight Sulfated Glycosaminoglycuronans (Heparinoid)
Indications:	Thromboprophylaxis in patients undergoing elective hip replacement surgery.
Submission:	Safety Update
Date of Submission:	11-18-1996
Date Received (CDER):	11-19-1996
Medical Reviewer:	Lilia Talarico, M.D.
Date of Review:	12-12-1996

BACKGROUND INFORMATION:

NDA 20-430 was submitted on 12-19-1994 for the approval of Orgaran for thromboprophylaxis in patients undergoing elective hip replacement surgery. Orgaran is an antithrombotic agent derived from porcine intestinal mucosa after heparin extraction. Orgaran is a mixture of low-molecular weight sulfated glycosaminoglycuronans.

A total of 107 studies were undertaken In the clinical development of Orgaran to assess its safety and/or efficacy in various groups of subjects requiring anticoagulant therapy. Ninety (90) of these studies with safety and efficacy data available were reported in the "Integrated Summary of Safety" (ISS) and 14 studies without Case Report Forms or other data verification were reported in "Other Studies and Information." Additional safety information was included in the 120-Day Safety Update submitted during the NDA review.

Following the Agency's approvable letter of July 24, 1996, the sponsor has submitted a safety update report for Orgaran.

No new studies for the use of Orgaran in orthopedic surgery have been performed and none of the studies reported in this safety update are part of the original proposed indication of DVT and PE Prophylaxis for Orthopedic Hip Surgery. The report summarizes the data for subjects outside of the DVT and PE Prophylaxis for Orthopedic Hip Surgery indication for whom additional data have become available since the cutoff date of the " 120-Day Safety Update" (December 31, 1994) up to July 31, 1996.

The studies presented in this safety update include three of the 90 studies reported in the Orgaran NDA "Integrated Summary of Safety" (ISS), six Japanese studies that were reported in the NDA "Other Studies and Information" report and three additional Japanese studies reported after the "120-Day Safety Update" for which new data have become available since the cutoff date of December 31, 1994.

The 12 non-indication studies presented in this document fall within the following original ISS groupings:

- DVT and PE Prophylaxis (Excluding Orthopedic Hip Surgery)--Study 86008;
- Heparin Sensitivity--Study 004-500/004-500 OL;
- Management of Acute or Progressing Ischemic Stroke--Study 004-022; and
- Other Studies--Japanese Studies 1-9.

The characteristics of each of these 12 studies are summarized in Table I.

5 pages
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The 90 studies reported in the NDA "Integrated Summary of Safety" included 5,309 subjects who received at least one dose of study medication. The 120-Day Safety Update included 1,199 additional subjects and the 197 heparin sensitivity subjects. The total number of subjects treated to date as part of clinical trials is 6,704; of these, 2,604 were in the DVT and PE Prophylaxis for Orthopedic Hip Surgery indication studies (920 U.S. and 1,684 non-U.S.) and 4,100 in "Non-Indication Studies."

The number of patients allocated to treatment in the various study groupings are shown in Table 2

TABLE 2
STUDY GROUPINGS AND NUMBER OF SUBJECTS ALLOCATED TO TREATMENT (ALL TREATMENT GROUPS)[a] AS OF JULY 31, 1996

Study Grouping	Number of Subjects or Subjects Treated[b] (Integrated Summary of Safety Information)	Number of Additional Subjects Treated[b] (120-Day Safety Update)	Number of Additional Subjects Treated (This Safety Update)	Total Subjects Treated[b]
Indication				
DVT and PE Prophylaxis for Orthopedic Hip Surgery[c]				
U.S.	920	—	—	920
Non-U.S.	1484	200	—	1684
Total	2404	200	—	2604

Within the DVT/PE prophylaxis for Orthopedic Hip Surgery indication studies, 2,604 subjects were treated with Orgaran or one of the reference agents as of July 31, 1996. Of these patients, 1,367 have received Orgaran; 173 placebo, 386 warfarin, and 678 other regimens.

Within the non-indication studies, 3,027 subjects were treated with Orgaran or one of the reference agents as of July 31, 1996. A total of 1,982 patients have received Orgaran, 137 placebo, 35 warfarin, and 873 other (including heparin, heparin/DHE, acetylsalicylic acid (ASA), dextran, and low molecular weight heparins).

Table 3 shows the various treatments of all the subjects who received study drugs.

TABLE 3
SUMMARY OF SUBJECTS BY TREATMENT GROUP
ALL SUBJECTS TREATED[a]

Study Grouping	Total Number of Subjects	Treatment			
		Orgaran™	Placebo	Warfarin	Other[b]
DVT and PE Prophylaxis for Orthopedic Hip Surgery					
U.S.					
Integrated Summary of Safety Information	920	517	5	386	12
Additional Subjects 120-Day Safety Update	0	0	0	0	0
Additional Subjects This Safety Update	0	0	0	0	0
Non-U.S.					
Integrated Summary of Safety Information	1484	750	168	0	566
Additional Subjects 120-Day Safety Update	200	100	0	0	100
Additional Subjects This Safety Update	0	0	0	0	0
Sub-Totals					
Integrated Summary of Safety Information	2404	1267	173	386	578
Additional Subjects 120-Day Safety Update	200	100	0	0	100
Additional Subjects This Safety Update	0	0	0	0	0
Total DVT and PE Prophylaxis for Orthopedic Hip Surgery	2604	1367	173	386	678

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B. Literature Search of Publications

Organon Inc. conducted an electronic literature search of publications from the cutoff dat of the ISS (July 27, 1993) to August 2, 1996 to identify publications not listed in the ISS or 120-Day Update. All relevant additional publications found were based on the studies already presented in the ISS, the 120-Day Safety Update, or in this update.

CONCLUSIONS

No new or unanticipated adverse events have been observed in this follow up period. The adverse events reported in this Safety Update were related to the underlying conditions in which Orgaran was evaluated: heparin-induced thrombocytopenia, DIC (7 of the 9 Japan studies). The safety of Orgaran for thromboprophylaxis in acute or progressing ischemic stroke cannot be assesses as the study is still blinded to treatment assignment, however, the study Data and Safety Monitoring Committee has allowed the continuation of the study.

Lilia Talarico MD

Lilia Talarico, M.D.

cc:
NDA 20-430
HFD-180
HFD-180/SFredd
HFD-180/LTalarico
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
f/t 12/13/96 jgw
MED\N\20430612.0LT

12/13/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020430

STATISTICAL REVIEW

Typed

STATISTICAL REVIEW AND EVALUATION

Date: SEP 15 1995

NDA #: 20-430
Applicant: Organon Inc.
Name of Drug: Orgaran(danaparoid sodium) injection
Indication: Prophylaxis of deep venous thrombosis(DVT) in patients undergoing orthopedic hip surgery.
Documents Reviewed: Vol. 2.1-2.3, 2.199-2.205, 2.209-2.212 2.254-2.255 dated November 8, 1994; vol 3.5 dated September 15, 1994 vol 3.4 dated January 5, 1995 and 1 vol dated May 22, 1995.

The issues in this review have been discussed with medical officer, L. Talarico, M.D.

I. Introduction/Background

This review addresses Study #004-23 (U.S.)and Study #85140 (The Netherlands) which the sponsor has submitted for claiming safety and efficacy of Org 10172 (danaparoid sodium) for the prophylaxis of deep venous thrombosis (DVT) in patients undergoing orthopedic hip surgery.

The primary measure of efficacy was based on the assessment of DVT. The development of DVT was assessed by duplex scanning and confirmed by bilateral venography on Days 8-12, unless clinical suspicion of a DVT occurred earlier or a positive impedance plethysmography (IPG) result was obtained. IPG scans were performed between Days 5-10. The venogram were subdivided into proximal-vein or distal-vein thrombosis only, or both categories. All venogram were reviewed at the end of the study by an independent panel who had no knowledge of the patients' treatment allocations. The decisions of this panel formed the basis for assessing the presence or absence of a DVT.

A secondary measure of efficacy was based on the assessment of Pulmonary Embolism (PE). Only patients with clinically suspected PE and/or DVT suggested by duplex scanning or confirmed by

venography were to be subjected to ventilation/perfusion lung scanning using standard techniques (unless contrary to the investigator's practice). If needed, selective pulmonary angiography was to be used to establish the diagnosis.

The efficacy analysis in studies #004-023 and #85140 was done for both Intent-To-Treat (ITT) and Efficacy Evaluable Groups. The sponsor defined the ITT group as all patients who were randomized to treatment, received at least one dose of study medication, had elective hip surgery and had at least a unilateral venogram during the treatment period. Efficacy Evaluable group is a subset of the ITT Group, who additionally met all inclusion/ exclusion criteria, and had no major protocol violation that would interfere with the efficacy assessment.

In addition the sponsor defined an All-Patients-Treated Group to includes all patients who were randomized to treatment and received at least one dose of study medication, including those who were never evaluated for efficacy. Data from these patients was used for the analysis of incidence rates of adverse clinical experiences.

The sponsor's definition of the ITT group is narrower than the usual one, which does not require a patient to undergo an efficacy evaluation. The effect of this definition difference on the efficacy of the treatment is addressed in Sections V.A.II. and V.B.II.

The dose regimen selected in Phase III program was based on Phase II dose-finding studies in patients undergoing either orthopedic hip surgery or general surgery, using doses ranging from 480 to 1250 anti-Xa units, s.c., b.i.d. Table 1, attached, summarizes the incidence and percentage of DVT/PE and major/serious bleeding occurring at various doses of Org 10172 in these studies.

The results of these studies, as presented in Table 1, showed that for dose levels >750 anti-Xa units, there was little gain in

the reduction of DVT, but the frequency of bleeding complications showed a small, but linear increase. Consequently the dose regimen of 750 anti-Xa units, b.i.d., s.c. is considered to provide orthopedic hip surgery patients with the optimum benefit/ risk ratio in terms of DVT prophylaxis.

II. Description of Studies

II.A. Study # 004-023 (U.S.)

This was randomized, open-label, assessor-blind, warfarin-control, multicenter trial. There were 15 centers to be involved in this study. However center 1 had only one randomized patient and this patient did not receive study drug, and center 15 was initiated but never enrolled patients.

The primary objective of this study was to compare the efficacy of Org 10172 (s.c. q 12 h doses of 750 anti-Xa units) versus warfarin (oral dose of 10 mg within 12 hr prior to surgery), followed by daily doses on Days 1 through 8 or until discharge, in the prevention of DVT in patients undergoing elective hip replacement surgery.

The secondary objective of this study were: a) to assess the safety (intra-and postoperative major and minor bleeding) of Org 10172 versus warfarin in patients undergoing elective hip replacement surgery; and b) to compare the efficacy of Org 10172 versus warfarin in prevention of clinically significant PE in these patients.

Inclusion criteria include: 1) Patients undergoing elective hip replacement surgery who have given written informed consent; 2) Male or females, over 18 years of age; 3) Females of non-childbearing potentials.

II.A.I. Study Population:

Table 2, attached, illustrates the disposition of patients in study #004-023. This table shows that out of the total 861 patients who were screened, 373 patients were excluded at screening stage. Thereafter, 476 patients in the All-Patients-Treated Group received study medication (223 Org-10172 and 243 warfarin). The patients were to be stratified by hospital center. Comments about the randomization are given in Section V.A.I.

There were 80 patients (34 Org 10172-treated and 46 warfarin-treated) excluded from the ITT Group for protocol violations, because no venography or no elective hip surgery was performed. Furthermore, there were 37 patients (15 Org-10172 treated and 22 warfarin-treated) with violation of some exclusion criteria and consequently they were ineligible for inclusion in the Efficacy Evaluable Group. As a result, the Efficacy Evaluable Group consisted of 184 patients in the Organon-treated group and 175 patients in the Warfarin-treated group.

II.A.II. Demographic and Baseline Information:

Table 3 presents a summary of demographic parameters as well as baseline variables affecting DVT, including length and type of surgery, history of DVT and PE, type of anesthesia, and recent mobility for the ITT Group. Table 4 presents similar information for the Efficacy Evaluable Group.

There were no statistically significant difference between the treatment groups with respect to age, gender, height or weight in either study group. For the baseline variables, the only characteristic that differed significantly between the two treatments in the ITT group is the side of surgery ($p=0.02$). For the Efficacy Evaluable group the p-value for this variable was 0.06.

II.B. Study # 85140 (The Netherlands)

This was a multi-center (3 centers), randomized, double-blind, placebo-control, parallel-group study. The objectives of the study is to investigate whether 750 anti-Xa of Org 10172, s.c., administered to patients undergoing elective hip replacement surgery are:

1) Efficacious in DVT prophylaxis as compared with placebo;
2) well tolerated and safe when compared with placebo , with respect to both intra-and postoperative bleeding complications.

The study medication is to be administered at 12 hours intervals, beginning with one preopertion dose and to be continued for a total of 10 days or until a study endpoint is reached.

Inclusion criteria include: 1) Admission to the hospital for THR surgery for the first time on that hip; 2) Patients considered fit for surgery with anti-coagulant cover; and 3) Patients giving informed consent.

II.B.I. Study Population:

Table 5, attached, illustrates the disposition of patients in study #85140. This Table shows that there were 220 patients enrolled and randomized to the two treatment groups. 218 patients received study medication. Of these 22 patients did not have bilateral venography for the assessment of DVT during the study period. The remaining 196 patients(98 in the Org 10172- group and 98 in the placebo group) had an efficacy assessment for DVT.

II.B.II. Demographic and Baseline Information:

Tables 6 and 7, attached, compare the demographic as well as baseline characteristics, related to surgery, for the ITT and the Efficacy Evaluable Groups, respectively. For both groups there was no statistically significant difference between the

treatments with respect to age, gender, height, side of the operation, length of the operation, type of anesthesia, and cigarette smoking.

A statistically significant center by treatment interaction was noted for patient weight in both the ITT and the Efficacy Evaluable Groups. Center 2 had a higher mean difference in weight, between the Org 10172 and placebo patients, than the other two centers. Also, there was a higher percentage of alcohol consumers in placebo treated patients in center 2 compared to the average of the other two centers (91% versus 56%). As centers 1 and 3 account for 68% of the patients in the ITT and Efficacy Evaluable groups, the sponsor believed that the center by treatment interaction will not have an impact on the study results. Center by center results will be discussed in Section V.B.III.

III. Sponsor's Analysis:

Separate statistical analysis was done for the ITT and the Efficacy Evaluable Groups. The statistical methods used for the analysis were as follows.

III.A. Comparability of Treatment Groups:

Between-treatment comparisons with respect to continuous baseline variables were performed using two-way analysis of variance (ANOVA), based on ranks, with center, treatment, and center by treatment interaction. Between-treatment comparisons with respect to categorical baseline variables were performed using Cochran-Mantel-Haenszel(CMH) procedures, adjusting for multiple centers.

III.B. Efficacy:

I- Between-treatment comparisons with respect to the incidence of DVT (as diagnosed by venography) was performed using the CMH procedures for 2x2xk tables, where k is the number of centers.

The denominator for this analysis included patients who had venography during the treatment period in study 004-023 and during the 48 hours of the last dose of study medication in Study 85140. In addition, for Study 004-023, 95% Confidence limits for the difference in DVT incidence rates between Org 10172 and warfarin was computed.

DVT incidence rates were further tabulated as proximal and/or distal and the side of the DVT occurrence was summarized in relation to the side of the operation.

II- The cumulative probability at a given day that a DVT was detected (adjusting for patient withdrawal) was estimated using the Kaplan-Meier product limit method. Logrank test was used to compare the survival (i.e., no DVT) curves of the treatment groups.

III- Within each treatment group, Fisher's exact test was used to perform exploratory analyses to examine the relationship between the incidence of DVT in Study # 004-023 and the following factors: age, gender, body weight and duration of surgery and missed doses; between the incidence of DVT and type of anesthesia in Study # 85140.

IV- Logistic regression was carried out in Study 004-023, to test for treatment effect using the following risk factors as covariates: duration of surgery, age, history of DVT and/or PE, gender and body weight.

V- Either the CMH procedure or Fisher's exact test was to be used to compare the treatment groups with respect to the incident of PE. However, since there was only one patient who had confirmatory evidence of PE in Study # 004-023, and only one suspected PE was reported in Study # 85140, no comparative statistical analysis was done.

III.C. Termination and Safety:

Finally, The CMH test, adjusting for k multiple centers, or Fisher's exact test, was used for between-treatment comparisons of the proportion of patients who were prematurely terminated from the study or to analyze the number of patients with major/minor bleeding or for comparing the adverse clinical experiences.

IV. Sponsor's Results:

IV.A. Study #004-023

IV.A.I. Comparison of DVT incidence rate:

Table 8 compares the incidence of DVT, detected by bilateral venography, for the Org-10172 and warfarin treatment groups.

Table 8/ Study #004-023
Summary of number (%) of patients with DVT

		Localization of DVT		
Treatment Group	N	Proximal(%)	Distal(%)	Overall(%)
i) Intent-to-Treat				
Org 10172	199	3(1.5)	28(14.1)	29(14.6)
Warfarin	197	8(4.1)	49(24.9)	53(26.9)
p-value		0.13	0.007	0.003
ii) Efficacy Evaluable				
Org 10172	184	3(1.6)	27(14.7)	28(15.2)
Warfarin	175	7(4.0)	46(26.3)	49(28.0)
p-value		0.19	0.007	0.003

Table 8 shows the overall incidence of DVT, as diagnosed by venography, in the ITT Group was statistically significantly lower (p=0.003) in the Org 10172-treated group than in the warfarin sodium-treated group. For this analysis group the

incidence of proximal DVT was lower in the Org 10172-treated patients (1.5%) than in warfarin sodium-treated patients (4.1%) but this difference was not statistically significant. Org 10172-treated patients did have a statistically significantly lower incidence of distal DVT, with p=0.007, than warfarin treated patients. The comparison for the Efficacy Evaluable Group in Table 8 are consistent with those of the ITT Group.

IV.A.III. Comparison of the Cumulative DVT Detection Rate:

Table 9, below, summarizes the life table estimates of cumulative DVT detection rate in the Org 10172- and warfarin- treated patients for the ITT and the Efficacy Evaluable Groups. Detailed about this comparison are given in Tables 9 and 10, attached, for the ITT and Efficacy Evaluable Groups, respectively.

Table 9/ Study #004-023
Life Table Estimates of the Cumulative DVT Detection Rates

	Org 10172			Warfarin		
Study Day	No.at Risk	No.with DVT	Cumulative Rate	No.at Risk	No.with DVT	Cumulative Rate
Intent to Treat						
4	199	0	0.000	196	0	0.0000
5	198	1	0.0051	195	2	0.0103
6	193	2	0.0154	184	4	0.0318
7	177	12	0.0821	168	27	0.1874
8	100	11	0.1831	89	17	0.3426
9	12	3	0.3873	11	3	0.5219
10	1	0	0.3873	2	0	0.5219
Overall		29		53		
p-value			0.001			
Efficacy Evaluable Group						
4	184	0	0.000	174	0	0.000
5	183	1	0.0055	173	2	0.0116
6	178	2	0.0166	166	3	0.0294
7	163	11	0.0830	153	26	0.1944
8	92	11	0.1926	79	15	0.3473
9	12	3	0.3945	9	3	0.5649
10	1	0	0.3945	1	0	0.5649
Overall		28			49	
p-value			0.002			

The results from Tables 9 show that, for either analysis group, there was statistically significant difference between the treatment groups with regard to the survival curve distribution (defined as "no DVT"). The p-values for the Intent-to-Treat and the Efficacy Evaluable groups are, respectively, 0.001 and 0.002.

Figures 1 and 2, attached, compare, the Kaplan-Meier product limit estimates of the cumulative DVT detection rate for both treatments for the Intent-to-Treat and the Efficacy Evaluable groups, respectively. The initial flat portion of the curve corresponds to study days when no venographic assessments for DVT were carried out.

IV.A.IV. Exploratory and Risk Factor Analysis for DVT

Exploratory analyses were performed to assess the relationship between the incidence of DVT and specified risk factors. This analysis indicated, for the ITT Group and the Efficacy Evaluable Group, that no relationship between the incidence of DVT and age(>70 years vs <70 years)or gender(males vs females) or missing at least 2 consecutive doses or 3 non-consecutive doses missing or body weight (>30% over ideal body weight by gender vs not >30% over ideal body weight).

The exploratory analyses indicated, however, a statistical significance for the incidence of DVT and duration of surgery (>130 minutes vs <130 minutes) in the Org-10172 treated patients. The p-values for the ITT Group and the Efficacy Valuable Group were 0.02 and 0.04, respectively.

Logistic regression was used, for both the ITT and the Efficacy Evaluable Groups, to determine the treatment effect and the incidence of DVT with the following risk factors as covariates: age, intraoperative blood loss, duration of surgery; blood

replaced at any time during the study, history of DVT or PE, degree of mobility, gender, body weight and hemoglobin.

For the ITT Group, only treatment and gender (i.e. being a male and being treated with warfarin) were statistically significant at the 0.05 level. For the Efficacy Evaluable Group, only treatment, gender and weight (i.e. being a male whose body weights is >30% over the ideal body weight and being treated with warfarin) were statistically significant at the 0.05 level. In Section V.A.IV. we discuss the findings of this analysis.

IV.A.V. Pulmonary Embolism (PE) Assessment:

Of the 396 patients in the ITT Group, 4 patients (3 Org 10172- and 1 warfarin- treated) presented with clinical symptoms suggestive of PE. One additional warfarin-treated patients who was not in the ITT group also presented with clinically suspected PE. Of the 5 patients, only 1 warfarin-treated patient had confirmatory evidence of a PE evidence based upon an abnormal, high probability V/Q scan. Since the incidence of PE was so small in this study, no formal statistical analysis was done.

IV.A.VI. Safety/ Adverse Clinical Experience(ACEs):

Table 10, attached, summarize the results of the analysis of major bleeding and related events by using (ANOVA and CMH procedure).

The results of Table 10 shows, aside from the postoperative therapeutic blood transfusions, there were no statistically significant differences between the two treatment groups.

Table 11, attached, compares the deaths/adverse clinical experience (ACEs) of the two treatments. The results of this table shows that no statistically significant differences between the two treatment groups with respect to deaths, serious ACEs or

discontinuation from the study due to ACEs. In addition, The sponsor indicated that all patients with serious ACEs were recovered, and that the investigators did not consider any of the ACEs or the death to be related to the study drugs.

IV.B. Study # 85140:

IV.B.I. Comparison of DVT incidence rate:

Table 12 compares the incidence of DVT, detected by bilateral venography, for the two treatment groups.

Table 12/ Study #85140
Summary of number (%) of patients with DVT

		Localization of DVT		
Treatment Group	N	Proximal(%)	Distal(%)	Overall(%)
i) Intent-to-Treat				
Org 10172	98	8(8%)	14(14%)	15(15%)
placebo	98	26(27%)	51(52%)	56(57%)
p-value		0.001	<0.001	<0.001
ii) Efficacy Evaluable				
Org 10172	96	8(8%)	14(15%)	15(16%)
placebo	98	26(27%)	51(52%)	56(57%)
p-value		0.001	<0.001	<0.001

The results of Table 12 show that for both analysis groups the overall incidence of DVT detected by venography was significantly lower in the Org 10172-treated patients in comparison to the placebo-treated patients ($p < 0.001$). Similarly, for both analysis groups, statistically significant reductions in the proximal as well as distal DVT occurred in the Org 10172-treated patients as compared with the placebo-treated patients ($p=<0.001$).

IV.B.II. Comparison of the cumulative DVT detection rate:

Table 13 compares the cumulative rate of DVT detection in the Org 10172 and placebo-treatment patients

Table 13/ Study # 85140

Life Table Estimates of the Cumulative DVT Detection Rates

	Org 10172			Placebo		
Study Day	No.at Risk	No.with DVT	Cumulative Rate	No.at Risk	No.with DVT	Cumulative Rate
Intent to Treat Group						
7	98	0	0.000	98	0	0.000
8	98	0	0.000	97	6	0.062
9	89	0	0.000	89	11	0.178
10	78	2	0.026	71	11	0.305
11	61	12	0.217	54	22	0.588
12	5	1	0.374	9	6	0.863
Overall		15		56		
p-value			<0.001			
Efficacy Evaluable Group						
7	96	0	0.000	98	0	0.000
8	96	0	0.000	97	6	0.062
9	89	0	0.000	89	11	0.178
10	77	2	0.026	71	11	0.305
11	61	12	0.217	54	22	0.588
12	5	1	0.374	9	6	0.863
Overall		15		56		
p-value			<0.001			

Figures 3 and 4, attached, compare the cumulative probability of DVT detection (Kaplan-Meier estimate) for the two treatment groups for the ITT and the Efficacy Evaluable groups, respectively. The comparison of DVT-free survival curves for the ITT Group showed a highly significant difference ($p<0.001$) between the two treatments. Similar results were seen in the Efficacy Evaluable Group analysis.

IV.B.III. Exploratory Analysis:

To assess the possible effect of type of anesthesia on the incidence of DVT, the two treatments were compared with respect to the incidence of DVT, for each type of anesthesia using Fisher's exact test. Table 14 presents the results of this analysis, for both the ITT and the Efficacy Evaluable Groups.

The comparison in Table 14 shows that statistically significant reductions in the incidence of DVT (proximal, distal and overall) occurred favoring Org 10172-treated as compared to placebo-treated patients ($p=0.002$) in the ITT Group. Similar results were observed for patients receiving general anesthesia in this analysis group. For patients receiving epidural, the reduction in the distal and overall DVT incidence was significant ($p=0.003$ and 0.001, respectively) but not for the proximal DVT. The findings of the comparison for the Efficacy Evaluable Group were similar to those of the ITT Group.

IV.B.III. Pulmonary Embolism (PE) Assessment:

Since only one Placebo-treated patient in the ITT Group has a suspected PE, and this was not confirmed, no statistical comparison was made between the two treatment groups.

IV.B.IV. Safety/ Adverse Clinical Experience (ACEs):

No patient in either treatment group died, or discontinued from the study due to ACEs, during the study treatment period.

In comparing bleeding and related events, the frequency of patients with excessive blood loss was very low for both treatment groups. Table 15 compares the percentage of patients with bleeding related events in the two treatment groups. The results of this comparison show no significant difference between the treatments with respect to the percentage of patients with excessive blood loss or blood transfusion. Similarly there was no statistically significant difference between the two treatment groups with respect to the estimated blood loss volume (intraoperative, perioperative, or total postoperative) or in the percentage of patients with other adverse clinical experiences.

V. Further Analysis /Comments

This section addresses this reviewer's comments about randomization and it presents results of additional analyses concerning the efficacy in each study.

V.A. Study# 004-023

V.A.I. Randomization:

Table 16, below, compares the pre-treatment assignments across centers and the actual treatment allocations.

Table 16/ Study # 004-0023
Differences Between Pre- and Actual- Treatment Allocation, Classified by Centers

Center	Total no. patients Assigned	Total no. patients Analyzed	patients on Org	patients on Warfarin	Comments [a,b]
1	1	0	1		
2	12	12	6	6	
3	19	18	9	10	
4	52	51	26	26	#429-436[a]
5	70	70	35	35	#547,548,563[a]
6	39	36	19	20	#627[a]
7	8	8	3	5	#707[a]
8	95	90	47	48	#8021-2,8301-8302[b]; #802,813,823,824,830[a]
9	32	31	16	16	
10	9	9	4	5	#1006[a]
11	35	35	17	18	
12	83	82	42	41	
13	29	28	15	14	
14	6	6	3	3	

[a] pre-assigned treatment number is not used
[b] a new treatment number is added

Table 16, shows that the deviations of the actual treatment allocations from the pre-treatment randomization schemes are small. In addition the sponsor explained some of these deviations as follows:

i) Two Org 10172-treated patients (#802 and 1206)) were withdrawn from the study and subsequently re-randomized at a later date. The first patient suffered an injury prior to study drug medication and the second developed chest pain prior to surgery and after receiving one preoperative dose of study drug. The first patient was re-randomized to the same allocation number after a 4-week wash-out period. To differentiate the two data sets for this patient, the sponsor recorded the first admission as #8021, and the second admission as #8022. Only #8022 is included in the All-Patients-Treated Group. Similarly, the second patient
was re-randomized as #1217 after an 8-day wash-out period. For analysis purposes, only the data for patient #1217 have been included in the All-Patient-Treated Group.

ii) One patient (#830) randomized to warfarin was withdrawn before receiving any preoperative study drug for having taken ASA prior to surgery. The study medication for this patient was subsequently administered to the next eligible patient. To differentiate these two patients, # 8301 was used for the first and #8302 was used for the second patient. Only patient #8302 has been included in the All-Patient-Treated Group.

As a result, the remaining deviations from the pre-assigned are within the limits of what one would expect to occur in carrying-out an actual clinical trial.

V.A.II. Effect of Change in the Definition of the Intent-to-Treat Group on the Efficacy Results:

The sponsor's definition of the Intent-to-Treat Group is narrower than the familiar one, since it requires at least one efficacy evaluation, as was indicated in Section 1. Below we compare the patients who were excluded from the two treatments and investigate whether the efficacy results were influenced by the modification in the definition of this analysis group. Table 18,

below, shows the patients who were excluded from the Intent-to-Treat and the Efficacy Evaluable Groups by center.

Table 17/ Study # 004-0023
Patients Excluded from the Intent-to-Treat and the Efficacy Evaluable Groups, by Center

	I) Intent-to-Treat Group[a]		II) Efficacy Evaluable Group	
Center	Org 10172	Warfarin	Org 10172	Warfarin
2	2/6(33%)	3/6(50%)	2/4(50%)	
3		2/10(20%)	1/8(13%)	
4	9/25(36%)	9/26(35%)		2/17(12%)
5	2/35(6%)	6/35(17%)		3/29(10%)
6	2/17(12%)	4/19(21%)	1/15 (7%)	2/15(13%)
7		1/5(20%)		
8	3/44(7%)	2/46(4%)	2/41 (5%)	2/44 (5%)
9		3/15(20%)	1/16 (6%)	7/12(58%)
10			1/4 (25%)	
11	1/17(6%)	2/18(11%)	2/16(13%)	2/16(13%)
12	10/41 (24%)	12/41(29%)	5/31(16%)	2/29 (7%)
13	3/14 (21%)	1/14(7%)		2/13(15%)
14	2/3 (67%)	1/3(33%)		
Total	34/233(14.6%)	46/243(18.9%)	15/199 (7.5%)	22/197 (11.2%)

[a] Reason for exclusion is no venography, which is the primary measure of efficacy.

Excluding centers with small patients, comparison of the patients excluded from each center, as presented in Table 17, does not reveal any pattern based on treatment allocation.

Since patients were excluded from the ITT because they did not have venography during the treatment period, therefore the number of DVT incidence remains as reported in Table 8. However, by disregarding the requirement that a patient would have to have at least a unilateral venogram to be included in the ITT Group, increases the number of patients exposed to the risk of DVT as shown in Table 18, below, which compares the efficacy for the Org-10172 and the warfarin treatment groups, under this scenario.

The results of Table 18 shows that the change in the definition of the ITT analysis group did not change the conclusion about the

efficacy of Org 10172 in comparison to warfarin as presented in Table 8.

Table 18/ Study #004-023
Re-analysis of Org 10172 Efficacy Results for the ITT Group, Disregarding the Requirement that a Patient Have at Least a Unilateral Venogram

Treatment Group	N	Localization of DVT Proximal(%)	Distal(%)	Overall(%)
Org 10172	233	3(1.3)	28(12.0)	29(12.5)
Warfarin	243	8(3.3)	49(20.2)	53(21.8)
p-value		0.146	0.016	0.007

V.A.III. Center-by-Center Results:

Table 19 compares the efficacy of Org-10172 versus Warfarin across centers. As the number of patients varies across centers, this reviewer combined centers in which the number of patients at risk of developing DVT is 8 or less, per treatment group.

Table 19 /Study #004-023
Number(%) of Patients With DVT by Treatment, Center and Analysis Group

	I) Intent-to-Treat Group:			II) Efficacy Evaluable Group		
Center	Org 10172	Warfarin	Warf-Org	Org 10172	Warfarin	Warf-Org
4	2/16(13%)	3/17(18%)	5%	2/16(13%)	3/15(20%)	7%
5	5/33(15%)	8/29(28%)	13%	5/33(15%)	8/26(31%)	16%
6	3/15(20%)	4/15(27%)	7%	3/14(21%)	4/13(31%)	10%
8	8/41(20%)	19/44(43%)	23%	8/39(21%)	17/42(41%)	20%
9	3/16(19%)	2/12(17%)	-2%	*		
11	1/16(6%)	4/16(25%)	19%	1/14(7%)	3/14(21%)	14%
12	1/31(3%)	6/29(21%)	18%	1/26(4%)	6/27(22%)	18%
13	0/11(0%)	2/13(15%)	15%	0/11(0%)	2/11(18%)	18%
2/3/7/10/14*	6/20(30%)	5/22(23%)	-7%	8/31(26%)	6/27(22%)	-4%
Overall	29/199(14.6%)	53/197(26.9%)	12.3%	28/184(15.2%)	49/175(20%)	4.8%

* Center 9 has 5 patients, thus combined with the grouped centers

Table 19 shows that almost across all centers the incidence of DVT in Org 10172-treated patients is consistently smaller than that of warfarin-treated patients. Only in center 9 and the combined group of small centers that the results show trend in the opposite direction. However, the difference in the DVT incidence rates are small (7% for the ITT Group and 4% for Efficacy Evaluable Group). Consequently, this reviewer considers the results are consistent across centers and combines these for further analysis.

V.A.III. Comparison of DVT Relative Risk:

Table 20 compares the estimate of relative risk (odd ratio) for the Org 10172 and warfarin treatments.

Table 20 / Study #004-023
Estimated Relative Risk, with 95% C.I., of Developing a DVT for Warfarin Treated Patients Relative to Those of Org 10172

	Treatment Group	
Localization of DVT	Intent-to-Treat	Efficacy Valuable
Overall	1.846 (1.241, 2.747)	1.840(1.226, 2.761)
Proximal	2.694 (0.766, 9.477)	2.453(0.674, 8.927)
Distal	1.768 (1.171, 2.668)	1.791(1.178, 2.723)

The results of Table 20 show that, for both the ITT and Efficacy Evaluable Groups, the overall risk of developing a DVT for warfarin-treated patients is more than twice that for Org 10172-treated patients. The 95% confidence limits for the relative risk does not include one, for either analysis group, indicating statistically significant difference between the two treatments in developing DVT. The findings for the distal DVT are similar.

V.A.IV. Risk Factors Associated with DVT Incidence:

The sponsor noted, for the ITT and the Efficacy Evaluable Groups, that the most significant risk factors, selected through the

stepwise regression procedure, were treatment, gender, weight, and duration of surgery. Of these, only treatment and gender, in addition to weight in the Efficacy Evaluable Group, were statistically significant at the 0.05 level.

However, the results of fitting the final logistic regression model, as presented in Table 21 below, shows that the significant factors associated with the development of DVT are treatment, Intraoperative Blood loss and to a less extent age.

Table 21/ Study 004-023
Results of Fitting Final Logistic Regression Model to the DVT Incidence Rate

	Intent-to-Treat Group				Efficacy Evaluable Group			
Variable	Estimate	SE	p-value	Odds Ratio	Estimate	SE	p-value	Odds Ratio
Intercept	-2.696	0.525	0.0001	0.07	-2.656	0.54	0.0001	0.07
Treatment	0.842	0.294	0.004	2.32	0.855	0.306	0.005	2.35
Blood loss	0.666	0.288	0.021	1.95	0.647	0.301	0.032	1.91
Age	-0.624	0.307	0.042	0.54	-0.666	0.323	0.040	0.51
Residual X^2 = 9.798 with 7 d.f., p= 0.20					X^2 = 10.35 with 7 d.f., p= 0.17			

V.B. Study # 85140

V.B.I. Randomization:

This study was planned to be conducted in two centers, but instead was carried out in three centers. Also some patients received allocation numbers assigned to another center. These deviations are shown in Table 22, below.

The sponsor stated that two of the co-investigators had joint appointments at the third added center. Furthermore, comparison with pre-randomization schedule showed patients received the same pre-assigned treatment, even when their allocation numbers were assigned to another center. Consequently, the small deviations

from what is planned in the protocol, as shown in Table 22, should not affect the efficacy results.

Table 22/ Study # 85140
Differences Between Pre- and Actual- Treatment Allocation, By Center

Planned Assignment		Actual Assignment	
Center	Patient sequence	Center	Patient sequence
1	1-160	1	3-136, 161-162
2	161-240	2	1-2,156-160,163-221
		3	223-240

V.B.II. Effect of Change in the Definition of the Intent-to -Treat Group on the Efficacy Results:

Analogous to the analysis done in Study 004-023, to investigate the effect of patients exclusion from the Intent to-Treat Group on the efficacy results of Org 10172, Table 23, below, presents a comparison of the patients excluded from the Intent-to-Treat and Efficacy Evaluable Groups, by center.

Table 23/ Study # 85140
Patients Excluded from the Intent-to-Treat and the Efficacy Evaluable Groups, by Center

	I) Intent-to-Treat Group[a]:		II) Efficacy Evaluable Group	
Center	Org 10172	Placebo	Org 10172	Placebo
1	8/68(11.8%)	8/66(12.1%)	2/60(3.3%)	0/58
2	2/32(6.3%)	2/34(5.9%)	0/30	0/32
3	1/9(11.1%)	1/9(11.1%)	0/8	0/8
Total	11/109(10.1%)	11/109(10.1%)	2/98 (2.0%)	0/98

[a] Reason for exclusion is no venography, which is the primary measure of efficacy.

The results of Table 23 does not reveal any selection bias for the exclusion of patients based on their treatment.

Table 24 presents the efficacy results of org 10172 for the Intent-to-Treat group after disregarding the requirement that a patients would have to have at least a unilateral venogram to be included in this analysis group.

Table 24/ Study # 85140
Re-analysis of Org 10172 Efficacy Results for the ITT Group, Disregarding the Requirement that a Patient Have at Least a Unilateral Venogram

		Localization of DVT		
Treatment Group	N	Proximal(%)	Distal(%)	Overall(%)
Org 10172	109	8(7%)	14(13%)	15(14%)
placebo	109	26(24%)	51(47%)	56(51%)
p-value		0.001	<0.001	<0.001

The Org 10172 efficacy results in Table 24 are similar to those in Table 12 . Consequently we conclude that the change in the definition of the Intent-to-Treat analysis group did not affect the efficacy of org 10172 versus placebo, as was the case in Study 004-023.

V.B.III. Center-by-Center Results:

Table 25 compares the efficacy of Org-10172 versus placebo for the three centers in this study.

Table 25 /Study #185
Number(%) of Patients With DVT by Treatment, Center and Analysis Group

	I) Intent to treat Group			II) Efficacy Evaluable Group		
Center	Org 10172	Placebo	Pla-Org	Org 10172	Placebo	Pla-Org
1	8/60(13%)	35/58(60%)	47%	8/58(14%)	35/58(60%)	46%
2	6/30(20%)	18/32(56%)	36%	6/30(20%)	18/32(56%)	36%
3	1/8 (13%)	3/8 (38%)	25%	1/8 (13%)	3/8(38%)	25%
Overall	15/98(15.3%)	56/98(57.1%)	41.8%	15/96(15.6%)	56/98(57.1%)	41.5%
Homogeneity test(B-D) p-value			0.612			0.646

The comparison in Table 25 shows that the org 10172 efficacy results are consistent across study centers.

V.B.VI. Comparison of DVT Relative Risk:

Table 26 presents the estimated relative risk (odd ratio), with 95% C.I., for developing DVT in the Placebo patients relative to those of org 10172.

Table 26/ Study #85140
Estimated Relative Risk, with 95% C.I., of Developing a DVT for Placebo Treated Patients Relative to Those of Org 10172

	Treatment Group	
Localization of DVT	Intent-to-Treat	Efficacy Valuable
Overall	3.733 (2.441, 5.710)	3.657 (2.392, 5.591)
Proximal	3.250 (1.643, 6.429)	3.184 (1.609, 6.301)
Distal	3.643 (2.317, 5.728)	3.569 (2.270, 5.610)

It can be seen from this Table that the risk of developing DVT for a placebo patient is more than three times that of an org 10172 treated patient. Since the 95% C.I. does not includes the value 1, the difference in the risks of developing DVT for two treatment is statistically significant.

VI. Overall Summary:

The results of the analyses of the two controlled trials (Study #004-023 Study #85140) have consistently shown a statistically significant decrease in the incidence of DVT in the Org 10172-treated patients compared to that of placebo- or warfarin-treated patients. In addition, the incidence of DVT for patients receiving Org 10172 was consistent in the two studies. Below is a list of the main findings of each study.

VI.A. Study #004-023:

The results of this study showed that a statistically significant reduction in the incidence of DVT for Org 10172-treated patients compared to that of warfarin-treated patients. The findings of this study can be summarized as follows:

i) The overall incidence of developing DVT in the org 10172-treated patient is significantly lower than that of the warfarin-treated patients (14.6% versus 26.9% for the ITT group, p=0.003). Considering the localization of the DVT, the results are highly significant in favor of Org 10172(p=0.007) for the distal DVT, but not so for the proximal DVT(p=0.13). Similar conclusions hold for the Efficacy Evaluable group (Table 8).

ii) The cumulative probability of developing a DVT in Org 10172 -treated patient is significantly lower than that of the warfarin treated group, p <0.001 for the ITT Group (Table 9 and Figure 1). Similar conclusion holds for the Efficacy Evaluable Group.

iii) The estimated relative risk of developing a DVT for a warfarin-treated patient is almost twice that of an organon - treated patient. Furthermore the 95% confidence interval for the odd-ratio does not include the value 1, indicating a statistically significant difference between the two treatments favoring Org 10172 (Table 20).

iv) The comparison of the DVT incidence rates for the Org 10172 and warfarin treatments are consistent across the study centers. Furthermore, the conclusion about the efficacy results of Org 10172 is not influenced by the sponsor's definition of the ITT, which requires a patient to have at least one efficacy evaluation to be included in this analysis group (Tables 18 and 19, respectively).

v) The incident of confirmed or suspected PE was very small(3 Org 10172- and 2 warfarin-treated patients) to make statistical

comparison for this secondary measure of efficacy meaningful (Section IV.A.V).

VI.B. Study # 85140:

The results of this study showed a statistically significant reduction in the incidence of DVT for Org 10172-treated patients compared to that of placebo-treated patients. The findings of this study can be summarized as follows:

i) The overall incidence of developing DVT in the ITT group was 57.1% for the placebo-treated patients compared to 15.3% for the org 10172-treated patients. The difference is statistically significant with p-value <0.001. Similar conclusion holds for the Efficacy Evaluable Group or the proximal and distal DVT (Table 12).

ii) The cumulative probability of developing a DVT in the org 10172 treated patients is significantly lower than that of the placebo-treated patients, p <0.001 (Table 13).

iii) The estimated relative risk of developing DVT for a placebo-treated patient is more than three times than that of the org 10172-treated patient. Furthermore, as Table 26 shows, the 95% confidence interval for the odd-ratio does not include the value 1, indicating a statistically significant difference between risks of developing DVT in the two treatments.

iv) The efficacy results of Org 10172 are consistent across study centers and are not influenced by the sponsor's definition of the ITT analysis group (Tables 24 and 25)

v) The incident of confirmed or suspected PE was very small (only 1 placebo treated patient) to make statistical comparison for this secondary measure of efficacy meaningful (Section IV.B.III).

VII. Overall Summary/ Conclusion:

The results of the analyses of the two controlled trials have consistently shown a statistically significant decrease in the incidence of DVT in the Org 10172-treated patients compared to that of placebo- or warfarin- treated patients. The p-values for comparing the overall DVT incidence rate in the ITT analysis group, were: <0.001 and 0.003, for the comparison with placebo (Study #85140) and the warfarin (Study #004-023) treated patients, respectively. Similar results were obtained when comparing the cumulative probability of developing a DVT, or analyzing the estimated relative risk of developing DVT.

The incidence of DVT for patients receiving Org 10172 in the ITT Group was consistent in the two studies (14.6% in Study #004-023 and 15.35% in Study #85140). In addition, within each study, efficacy results are, in general, consistent across study centers.

In summary the combined data from the two studies support the sponsor's claim about the efficacy of Org 10172 as a prophylaxis for DVT in patients undergoing orthopedic hip surgery.

M. Al-Osh 9/14/95
M. Al Osh, Ph.D.
Mathematical Statistician

Concur: Dr. Huque Huque 9/15/95
Dr. Dubey 9-15-95

cc:
Orig. NDA 20-430/Rx (one certified copy)
HFD-180/ Dr. Fredd
HFD-180/ Dr. Talarico
HFD-180/ Ms. Oliver
HFD-713/ Dr. Dubey [File DRU 1.3.2 NDA]
HFD-713/ Dr. Huque
HFD-713/ Dr. Al Osh

Aloshm/x4594/SERB/Alosh/9/7/95

Table 1

Benefit/Risk Relationship to Dose of Org 10172 Based on Phase II Dose-Finding Studies in Patients Undergoing Either Orthopedic Hip Surgery or General Surgery

Dose Org 10172 (bid,sc) or control	plasma Anti-Xa	DVT/PE		major/serious Bleeding	
		N	%	N	%
500 Anti-Xa Units	0.11	53	11.3	84	8.5
750 Anti-Xa Units	0.18	81	6.2	102	10.0
1000 Anti-Xa Units	0.26	73	5.5	79	14.1
1250 Anti-Xa Units	0.33	17	5.9	23	17.3
Warfarin/Heparin		67	9.0	88	10.4
Placebo		77	30.0	77	3.9

Table 2/ Study #004-023

Disposition of Patients

Patient Disposition	Treatment Group		
	Org 10172	Warfarin	Total
Eligible for randomization	241	247	488
No Study Drug	8	4	12
All patients-treated group	233	243	476
No venography assessment	34	46	80
Intent-to-treat Group	199	197	396
Excl.from Evaluable Group	15	22	37
Efficacy Evaluable group	184	175	359

Table 4/ Study #004-023

Demographic and Baseline Data: Efficacy Evaluable Group

	Org 10172				Warfarin				p-Value[a]
	N	Mean	Median	Range	N	Mean	Median	Range	
Age (yr)	184	67	68	37 - 88	175	66	68	32 - 88	(0.49)
Weight (kg)	184	79	79	44 - 132	175	81	79	41 - 136	(0.65)
Height (cm)	153	169	168	140 - 193	174	170	171	127 - 193	(0.66)
Sex:									0.16
Male	83				92				
Female	101				83				
Race:[b]									
Caucasian	177				163				0.20
Black	6				9				
Asian	0				1				
Other	1				2				
Side of Surgery:									
Right	82				97				0.06
Left	102				77				
Both	0				1				
Length of Surgical Procedure (min): (Including Anesthesia)	184	174	160	60-465	175	169	160	50-545	(1.00)
Type of Surgical Procedure:									NA
Total Hip Replacement	184				175				
Bipolar Hip Replacement	0								
Other	0								
Type of Anesthesia									
General Only	159				145				0.64
Spinal/Epidural (Regional Only)	8				10				
Mixed (General and Spinal)	17				20				
History of DVT									0.12
Documented: Clinically	4				1				
Venogram	4				0				
Unknown	2				3				
Location: Proximal (Thigh; Popliteal)	5				1				
Distal (Calf)	5				3				
Unknown	3				0				
History of PE									0.16
Documented: Clinically	1				3				
Pulmonary Angiogram	0				0				
Lung Scan	1				1				
Unknown	0				1				
Recent Mobility (In the Last Month)[c]									1.00
Bedridden	0				0				
Mobile With Aid	90				80				
Mobile Without Aid	94				95				

Includes patients with available data.

[a] Age, weight, height, and length of surgical procedure analyzed using ANOVA based on ranks (p-values in parentheses). Categorical data analyzed using Cochran Mantel-Haenszel test.

[b] Race analyzed as either Caucasian or Non-Caucasian.

[c] Mobility analyzed as Bedridden, Mobile With Aid, or Mobile Without Aid.

Table 5/ Study #85140
Disposition of patients

Patient Disposition	Treatment Group: Org 10172	placebo	Total
Eligible for randomization	109	111	220
No Study Drug	0	2	2
All patients-treated group	109	109	218
No venography assessment	11	11	22
Intent-to-treat Group	98	98	196
Excl.from Evaluable Group	2	0	2
Efficacy Evaluable Group	96	98	194

Table 6/ Study #85140
Demographic and Baseline Data: Intent-to-Treat Group

	Org 10172				Placebo				p-Values	
	N	Mean	Median	Range	N	Mean	Median	Range	a	b
Age (yr)	98	67	69	31-84	98	70	71	48-88	0.19	
Weight (Kg)	98	72	72	41-119	98	72	71	45-100	0.99[c]	
Height (cm)	98	165	164	150-196	98	167	167	150-187	0.26	
Sex										0.42
Male	21				26					
Female	77				72					
Side of Operation										0.95
Right	54				53					
Left	44				45					
Length of Operation (minutes)	98	93	87	36-210	98	93	89	44-190	0.59	
Type of Anesthesia[d]										0.58
Epidural	45				44					
General	15				14					
Psoas Block	37				40					
Cigarette Smoking										0.06
Yes	17				28					
No	81				70					
Alcohol Use:										0.15[c]
Yes	56				66					
No	42				32					

[a] Age, weight, height, and length of operation were analyzed using ANOVA based on ranks.
[b] Categorical data were analyzed using Cochran Mantel-Haenszel test.
[c] Significant center by treatment interaction (or non-homogeneity). Individual center summaries are presented in Appendix D.
[d] Data were not available for one Org 10172-treated patient.
Note: Information for this table was derived from Data Listings 1, 2, and 8.

Table 7/ Study #85140

Demographic and Baseline Data: Efficacy Evaluable Group

	Org 10172				Placebo				p-Values	
	N	Mean	Median	Range	N	Mean	Median	Range	a	b
Age (yr)	96	67	68	31-84	98	70	71	48-88	0.16	
Weight (Kg)	96	72	72	41-119	98	72	71	45-100	0.95[c]	
Height (cm)	96	166	164	150-196	98	167	167	150-187	0.28	
Sex										
Male	21				26					0.46
Female	75				72					
Side of Operation										
Right	53				53					0.92
Left	43				45					
Length of Operation (Minutes)	96	93	87	36-210	98	93	89	44-190	0.57	
Type of Anesthesia										
Epidural	44				44					0.57
General	15				14					
Psoas Block	37				40					
Cigarette Smoking										
Yes	16				28					0.05
No	80				70					
Alcohol Use:										
Yes	55				66					0.15[c]
No	41				32					

a Age, weight, height, and length of operation were analyzed using ANOVA based on ranks.

b Categorical data were analyzed using Cochran Mantel-Haenszel test

c Significant center by treatment interaction (or non-homogeneity). Individual center summaries are presented in Appendix D.

Table 10/ Study #004-023

Frequency (%) of patients with bleeding and related events

All-patients treated group

	Org-10172	warfarin	p-value
All-Treated Patients	233	243	
Major Bleeding	7 (3.0%)	7 (2.9%)	0.96
Minor bleeding	122(52.4%)	118(48.6%)	0.30
Severe Blood loss			
Intraoperative	40(17.4%)	32(13.3%)	0.24
Perioprative	3 (1.9%)	4 (2.4%)	0.78
Postoperative	0 (0)	1 (0.7%)	0.32
Therap.Blood Transfusions	103(44.2%)	93(38.3%)	0.12
Intraoperative	56(24%)	60(24.9%)	0.66
Perioprative	27(11.6)	32(13.2%)	0.63
Postoperative	91(41.6%))	74(33.0%)	0.03
Bruising Assessment	87(38.7%)	89(38.4%)	0.99

Table 11/ Study #004-023

Comparison of Patients Died/had Adverse Clinical Experience

All-Patients Treated Group

	Org-10172	warfarin	p-value
All-Treated Patients	233	243	
Study deaths	1(0.4%)	0	0.49
Serious ACEs	3(1.3%)	1(0.4%)	0.36
Discont.Due to ACEs	2(0.8%)	0	0.50

Table 14/ Study #85140

Number (%) of Patients with DVT By Type of Anesthesia

	Intent-to-Treat			Efficacy Evaluable		
Anesthesia	Org 10172	Placebo	p-value	Org 10172	Placebo	p-value
Epidural	45	44		44	44	
Proximal	8(18%)	12(27%)	0.319	8(18%)	12(27%)	0.446
Distal	8(18%)	21(48%)	0.003	8(18%)	21(48%)	0.006
Overall	9(20%)	24(55%)	0.001	9(20%)	24(55%)	0.002
General	15	14		15	14	
Proximal	0(0%)	5(36%)	0.017	0(0%)	5(36%)	0.017
Distal	0(0%)	10(71%)	<0.001	0(0%)	10(71%)	<0.001
Overall	0(0%)	11(79%)	<0.001	0(0%)	11(79%)	<0.001
Psoas Block	37	40		37	40	
Proximal	0(0%)	9(23%)	0.002	0(0%)	9(23%)	0.002
Distal	6(16%)	20(50%)	0.002	6(16%)	20(50%)	0.002
Overall	6(16%)	21(53%)	0.002	6(16%)	21(53%)	<0.001

Figure 1/ Study # 004-023
Life Table Estimates of the Cumulative DVT Rates
Intent-to-Treat Group

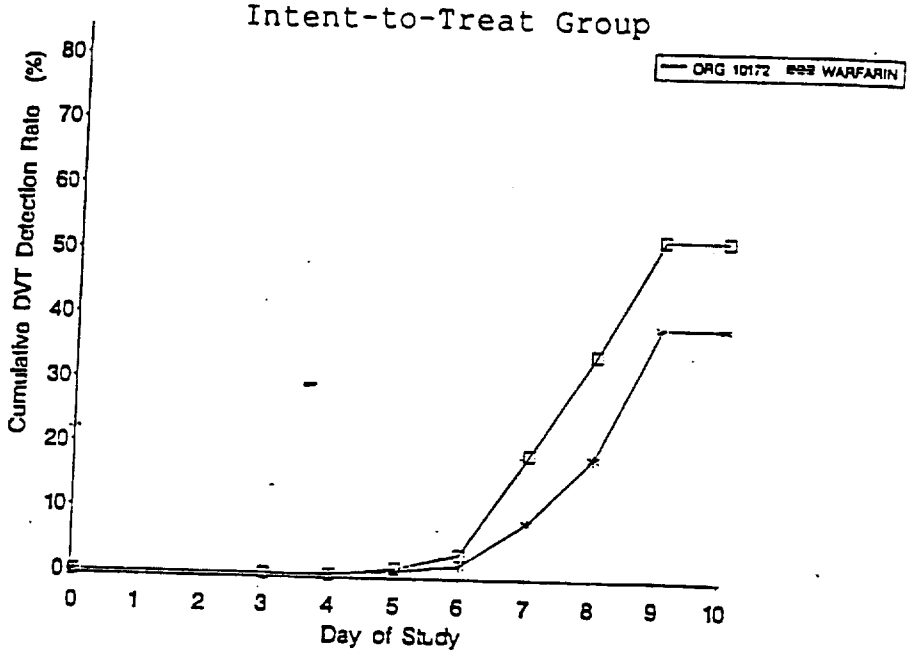


Figure 2/ Study # 004-023
Life Table Estimates of the Cumulative DVT Rates
Efficacy Evaluable Group

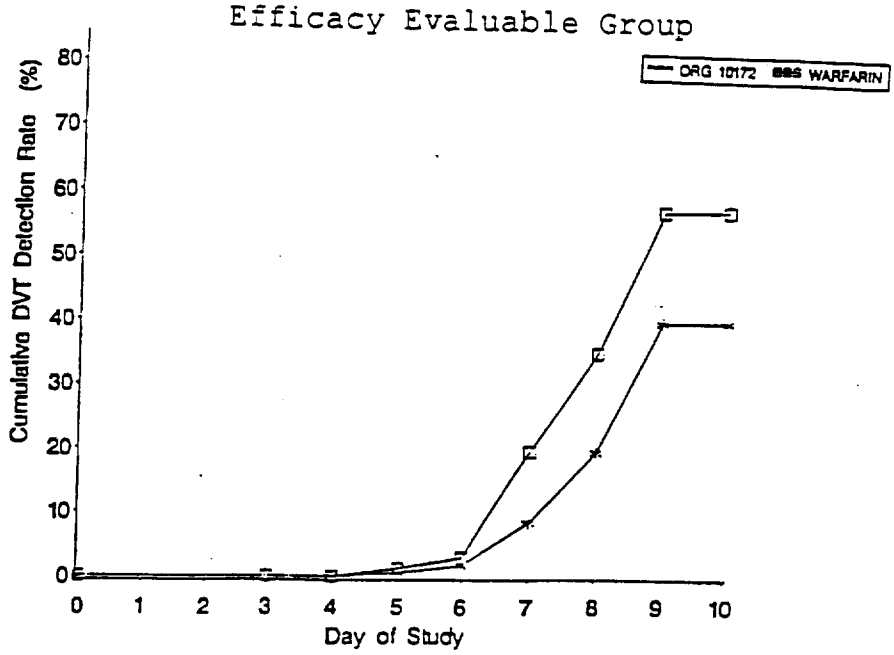


Figure 3/ Study # 85140
Life Table Estimates of the Cumulative DVT Rates
Intent-to-Treat Group

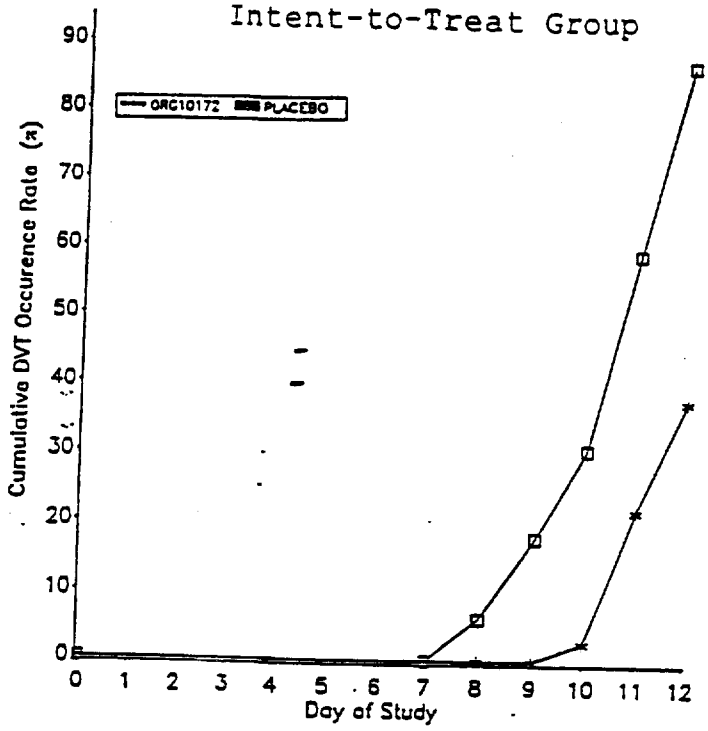
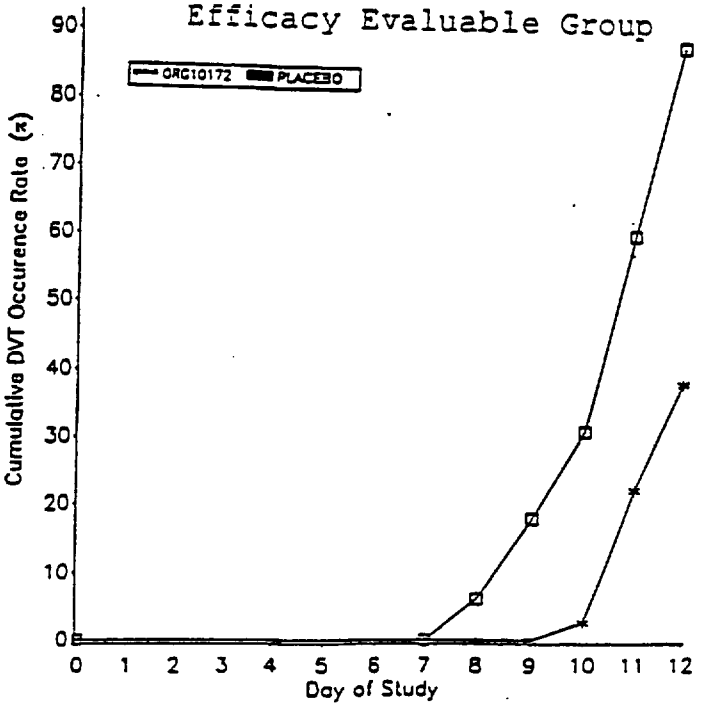


Figure 4/ Study # 85140
Life Table Estimates of the Cumulative DVT Rates
Efficacy Evaluable Group



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020430

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Clinical Pharmacology & Biopharmaceutics Review MAY 30 1996

NDA 20-430 (amendment BB) Submission Date: 04-19-96
Danaparoid Na Injection
Orgaran™
Sponsor: Organon Inc., 375 Mt. Pleasant Avenue, West Orange, NJ

Priority: 1S

Type of Submission: Sponsor's response to request from OCPB/DPEII

Reviewer: Rajendra S. Pradhan

Background: The sponsor has submitted additional information regarding original NDA 20-430 submission at the request of this reviewer. The request was conveyed to the sponsor through the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) and appeared in the OCPB/DPEII review of NDA 20-430 as follows:

Comments (to be sent to the firm):

1. In validation report for amidolytic assay for anti-Xa activity (used for study 004-025), specificity data/information on the assay was missing. This information should have been in table 28 according to the report; however, table 28 was missing.

2. In digoxin drug interaction study, the design does not permit to estimate the exact magnitude of interaction as Org was administered only once.

3. In assay validation, the sponsor needs to address the cross-reactivity and interference of simultaneously administered drug in drug interaction studies.

Sponsor's Response:

1. The sponsor has submitted the missing information on amidolytic assay for anti-Xa activity (used for study 004-025).

2. The sponsor acknowledge that the design of the digoxin drug interaction study may underestimate the exact magnitude of interaction.

3. The sponsor has addressed the 'cross-reactivity in assay' issue for acenocoumarol, ticarcillin, cloxacillin and aspirin

Comments:

1. The information provided on plasma anti-Xa activity benchtop stability and specificity is satisfactory

2. The sponsor's response is adequate. The Medical Officer (HFD-180) should please note that if digoxin and orgaran are simultaneously administered in patient who has been on digoxin, a greater than 14% decrease in $AUC_{0\text{-}24hr}$ and serum average concentration of digoxin could be expected.

3. The sponsor's response to the 'cross-reactivity in assay' issue for acenocoumarol, ticarcillin and cloxacillin is adequate. However, the sponsor's argument about comparing Cmax for anti-Xa activity (orgaran alone versus orgaran with aspirin) to test for cross reactivity/interference in assay is based on assumption that there is no pharmacokinetic drug interaction between orgaran and aspirin and therefore not completely valid.

Recommendation:

The Division of Pharmaceutical Evaluation II has reviewed the information provided by the sponsor on the assay validation and drug interaction and found this information to be acceptable. No further information is needed.

5/23/96

Rajendra S. Pradhan, Ph.D.
Division of Pharmaceutical Evaluation II

FT initialed by Lydia Kaus, Ph.D. LK 5/24/96

cc: NDA 20-430, HFD-180, HFD-870 (DPEII Chenme, Kaus, Pradhan), HFD-860 (DPEI Malinowski), HFD-880 (DPEIII Fleischer), HFD-340 (Viswanathan), HFD-850 (Chron, Drug, Reviewer), HFD-19 (FOI), HFD-850 (Lesko)

DWP

Clinical Pharmacology & Biopharmaceutics Review

NDA 20-430 Submission Date: 09-08-95 and 09-09-95
Danaparoid Na Injection
Orgaran™
Sponsor: Organon Inc., 375 Mt. Pleasant Avenue, West Orange, NJ NOV 21 1995

Priority: 1S
Type of Submission: NME **Reviewer:** Rajendra S. Pradhan

Synopsis: The sponsor has studied danaparoid Na (Org) pharmacokinetics using its anti-Xa activity as a surrogate marker, since no assay for the direct measurement of the components of Org in plasma exists. The sponsor has adequately studied the pharmacokinetics (single and multiple dose) and excretion of Org and has established the dose proportionality of Org. Acceptable studies have been performed in elderly population. Drug interactions between Org and acenocoumarol, digoxin, cloxacillin, ticarcillin, chlorthalidone and pentobarbital were studied. The sponsor has adequately validated the assay methods for anti-Xa activity and anti-IIa activity of Org. Formulations used in pharmacokinetic studies and pivotal clinical trials are adequately linked to to-be-marketed formulation. Pharmacokinetics of Org has been studied in males and females.

Recommendation: The sponsor's NDA 20-430 is acceptable for meeting the Division of Pharmaceutical Evaluation II's requirements, provided that comments are addressed satisfactorily by the sponsor.

Table of Content:

Background: Danaparoid Na (Org) is a mixture of sulfated glycosaminoglycuronans, consisting of heparan sulfate with high and low affinity to AT-III (about 84%), dermatan sulfate (about 12%) and chondroitin sulfate (about 4%). It is isolated from same starting material as heparin and low molecular weight heparins (porcine intestinal mucosa). However, during the extraction procedure heparin and heparin fragments have been excluded from Org. The absence of heparin has been confirmed by enzymatic degradation with chrondroitinase, heparinase and heparitinase followed by structural analysis of the repeating disaccharide composition and determination of anti-Xa/anti-IIa activity. The average MW of Org is approximately 5500 daltons. The sponsor is

proposing that Org has a better benefit (antithrombotic properties)/risk (bleeding enhancement) ratio than other standard antithrombotic regimens currently available.

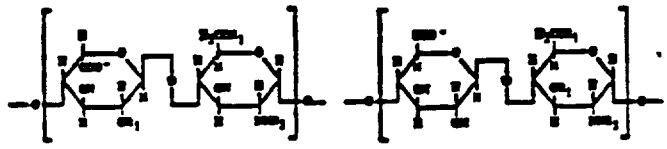
The sponsor has presented a set of twenty three pharmacokinetic study reports to seek approval of injectable Org. Only 11 study reports were considered important for reviewing. Others were considered less important or supportive in nature because: **a.** repetition of the objective of study, **b.** poor or no assay information or validation, **c.** simply not relevant.

The sponsor analyzed 12 studies (one U.S. and 11 non-U.S. integrated pharmacokinetic studies) using a newly developed Non-Linear Mix Effect modeling approach ( ) to directly estimate the population pharmacokinetics of Org.

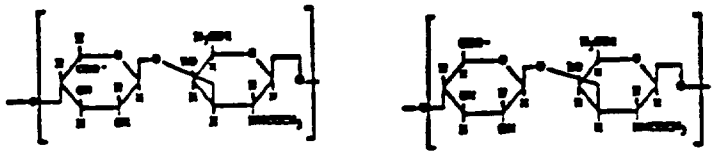
Org injection is proposed for the prophylaxis of post-operative deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing orthopedic hip surgery. The recommended dose is 750 anti-Xa units twice daily administered by subcutaneous (SC) injection. The proposed average duration of administration is 7 to 10 days.

Chemical Structure:

Main Repeating Disaccharide Units:



Heparan Sulfate: R_1 = H or SO_3, R_2 = $COCH_3$ or SO_3



Dermatan Sulfate

Chondroitin Sulfate

Summary of Bioavailability/Pharmacokinetics/Pharmacodynamics:

I Bioavailability

The absolute bioavailability of SC dose was nearly 100%. The estimates obtained in the population pharmacokinetic analysis concur with this estimate.

II Pharmacokinetics/Pharmacodynamics

Since Danaparoid Na (Org) is a mixture of sulfated glycosaminoglycuronans, consisting of heparan sulfate with high and low affinity to AT-III, dermatan sulfate and chondroitin sulfate, a radio-label-tagged mass-balance study was not conducted by the sponsor. However, based on anti-Xa activity it appears that Org was slowly absorbed after a SC administration with Tmax about 3 to 4 hours. The estimated mean absorption coefficient is 0.453 (1/hr) with intersubject variability of 14%. The mean volume of distribution at steady state of Org, in healthy volunteers is about 10 L. This indicates very limited distribution into extravascular tissue. The protein binding information on Org is not provided by the sponsor. The metabolic fate of Org is not studied but based on anti-Xa activity mean clearance of Org is 0.363 (L/hr) with intersubject variability of 26%. The estimated elimination half life is about 27 hr.

The following table summarizes the estimates from population pharmacokinetic analysis (carried out by this reviewer):

Parameter	Mean	CV on Mean = (SE/mean)*100	Interindividual Variation#	Variance	CV on Variance (SE/mean)*100
CL (L/hr)	0.363	3.5%	26.3%	0.069	19.9%
V2 (L)	4.15	1.6%	13.7%	0.016	20.2%
Ka (1/hr)	0.453	5.1%	27.2%	0.070	31.2%
Q (1/hr)	0.423	3.4%	26.7%	0.071	19.7%
V3 (L)	6.26	5.0%	26.1%	0.068	21.2%

Interindividual Variance = Sqrt ot Variance * 100

CL: Clearance, V2: Volume of central compartment, Ka: Absorption rate constant for SC route, Q: Inter-compartmental clearance, V3: Volume of peripheral compartment

Multiple Dose Kinetics: In study 81059, Org was administered QD for 5 days over 800-3200 anti-Xa U dose range in an open, group-comparative non-cross-over fashion. For individual subject pharmacokinetic profile, the AUC_{inf} after the first dose could predict $AUC_{ss}{}^{T}$ (area under curve at steady state over dosing period). The accumulation index for QD dosing is about 1.5. In study 83018, Org was administered BID at a daily dose of 1280 or 1920 anti-Xa U in non-cross-over fashion. The accumulation index for BID dosing ranged from 2.5 to 2.8. The

sponsor has defined different dosing regimen using SS simulations based on the parameters defined from this study (viz. 500 anti-Xa bid, 750 anti-Xa bid or 1000 anti-Xa bid). Studies 81059 and 83018 did not have assay validation information and therefore the estimated PK parameters for anti-Xa activity were reviewed subjectively.

Dose Proportionality: Org administered in single doses 750-2250 anti-Xa units in healthy adult males and females subcutaneously showed dose proportionality with respect to AUC_{last} and Cmax. The dose proportionality was also seen after single IV bolus doses up to 6400 anti-Xa units and after single SC doses upto 3250 anti-Xa units of Org, based on the population pharmacokinetic analysis.

III Special Populations

Patients with Renal Impairment: In absence of any mass balance information or not knowing what fraction of dose is eliminated renally, it becomes particularly important to know what effect renal impairment has on Org pharmacokinetics and pharmacodynamics. However, the sponsor has not address this issue in the current submission.

Patients with Hepatic Impairment: The sponsor has not carried out any study in hepatically impaired patients.

Elderly and Gender Difference: In cross-study comparison, differences in pharmacokinetic parameters between young and elderly (55 - 68 yr) were negligible.

	CL (ml/hr/Kg) (mean ± sd)
Young male	5.80 ± 1.40
Young female	6.12 ± 2.11
Elderly male	5.38 ± 1.79
Elderly female	5.41 ± 1.54

IV Drug Interactions:

A. Acenocoumarol: When Org was administered at a dose of 3250 anti-Xa U with acenocoumarol there was a reduction in plasma clearance of anti-Xa activity. This resulted in approximately 17% increase in AUC_{inf}. In brief, acenocoumarol was administered orally at doses of 6, 4, and 2 mg on days -1, 0 and 1 respectively. Starting on day 2 there was daily acenocoumarol administration in doses that were individually adjusted to keep the thrombotest values between 10% and 15%. When steady-state thrombotest values were reached (after at least 14 days of acenocoumarol administration), one dose of 3250 anti Xa units of Org was administered intravenously. Acenocoumarol administration was continued at the individually

adjusted dose for two more days.

B. Digoxin: Oral treatment with digoxin 0.25 mg once daily was given for eight days. With seventh dose of digoxin 3250 anti-Xa units of Org was administered intravenously. A seven percent (7%) increase in average clearance of anti-Xa activity was observed. In this study, after simultaneous administration of Org with digoxin, the 24 hr AUC and average serum concentration of digoxin was decreased by 14% (renal clearance was unchanged). Higher decrease in digoxin average serum concentration can not be ruled out for multiple administration of two drugs simultaneously. The plausible explanation is a change in the systemic clearance of digoxin. Digoxin did not influence the effects of Org on the coagulation tests.

C. Cloxacillin: Oral cloxacillin, 500 mg four times daily, was given for three days. Twenty four hour after the start of the cloxacillin treatment, 3250 anti-Xa units of Org were administered intravenously immediately after the fifth dose of cloxacillin dose. The half-life of anti-Xa activity was increased by 22%. However, the coagulation tests revealed no important interactions at the pharmacodynamic level.

D. Ticarcillin: When Org was administered as a IV dose of 3250 anti-Xa units with ticarcillin (IV, 2 gm six times daily), the anti-Xa activity AUC, AUC_{inf} and Cmax were decreased by 14.3%, 7.5% and 13.2% respectively. In this study, for ticarcillin, although the time course of the individual plasma level profiles was quite in agreement with expectations, the concentrations were about 10 times lower than anticipated on the basis of literature data[1].

E. Chlorthalidone: Oral treatment with chlorthalidone 100 mg (tablet) at 11:00 pm. was given in the evening, before the day of Org administration. The following morning, 3250 anti-Xa units of Org were administered intravenously. The pre-administration of chlorthalidone caused a modest increase (<20%) in Org's anti-Xa activity (AUC, Cmax). The coagulation tests revealed no important interactions at the pharmacodynamic level.

F. Pentobarbital: This study was carried out to evaluate effect of liver enzyme induction on Org (anti-Xa activity) pharmacokinetics. Liver enzymes were induced with QD doses of 100 mg of pentobarbital for 12 days, on day 11, 3250 anti-Xa units of Org were administered. The Org anti-Xa activity was not affected by phenobarbital induced metabolism in the liver as monitored by reduction in the half-life of antipyrine (used as a marker for liver enzymes). However, the variability in the Org's pharmacokinetic parameters (Cmax, AUCinf and CL) was higher when liver metabolism was induced by pentobarbital. The coagulation tests revealed no important interactions at the pharmacodynamic level.

G. Aspirin: This study was conducted to evaluate the acute effect of the combined medication

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1. Libke R. D. et. al. Ticarcillin vs. carbenicillin: Clinical Pharmacokinetics, Clin. Pharm. Ther. 1975; 17: 441-446

of aspirin on the bleeding time, platelet aggregation and hemostatic tests. Also to investigate the effect of subcutaneous "chronic" Org treatment on the restoration of platelet function following the inhibition of cyclo-oxygenase activity by aspirin ingestion. In this study, the subjects ingested 500 mg aspirin 14 and 2 hr before the administration of 3250 anti-Xa units of Org as an IV bolus injection at time 0. 7.5 hr later SC Org treatment BID, 750 anti-Xa units, was started and continued for 8 days. These dose levels reflect the normal dose of aspirin and the dose of Org recommended for clinical use for DVT (deep venous thrombosis) prophylaxis. The concomitant administration affected hemostatic parameters. Compared to pre-injection values, increased thrombin time values were seen after Org combined with aspirin at 15 min. APTT and PT values increased during Org alone and Org combined with aspirin treatments at 15 min and to a lesser extent at 90 min after the administration of Org. In 3 out of 8 subjects increase in bleeding time was seen (>15 min). There was no clear influence of Org on the inhibiting effect of aspirin on platelets. Aspirin did not influence Org's anti-Xa activity pharmacokinetic profile.

V Formulation:

All formulations used in pharmacokinetic program and in pivotal clinical studies are similar to the proposed marketed formulation with exception of Lot # CP081083 (used in two phase I pharmacokinetic studies viz. 84063 and 85035). The proposed marketed formulation can be considered bioequivalent to the formulations used in pivotal clinical trials.

General Comments (need not be sent to the firm):

1. In study 85026, drug interaction between Org and ticarcillin sodium, ticarcillin sodium at a dose of 2 mg six times a day showed plasma concentrations about 10 times lower than anticipated on the basis of literature data. In this study, the sponsor has used a validated assay (using quality control samples). The sponsor has shown the drug to be stable in whole blood during freezing and thawing cycles. The sponsor has also studied the absorption of ticarcillin on plastic components. However, no explanation could be given for the low ticarcillin concentrations seen in this study.

2. For studies 87020, 81059 and 83018 assay validation information for anti-Xa activity was not provided. The results in these studies are therefore interpreted only subjectively.

3. In study 85014, the calculated pharmacokinetic parameters for the total glycosaminoglycuronan are of very little clinical importance because Org is composed of several compounds and in plasma, different fragments of these compounds probably exist. Thus, for example Vd here does not have the same meaning as in other situations (eg. drug with a specific molecular structure).

Comments (to be sent to the firm):

1. In validation report for amidolytic assay for anti-Xa activity (used for study 004-025),

specificity data/information on the assay was missing. This information should have been in table 28 according to the report; however, table 28 was missing.

2. In digoxin drug interaction study, the design does not permit to estimate the exact magnitude of interaction as Org was administered only once.

3. In assay validation, the sponsor needs to address the cross-reactivity and interference of simultaneously administered drug in drug interaction studies.

Labelling Comments:

1. The proposed labeling states in the Pharmacokinetic section:

   However, the sponsor has not submitted any data/information to support . A comparison of Org clearance between young and elderly people show no difference. Elderly people usually show a lower CrCl than young. The sponsor should therefore justify this statement.

   In absence of any justification, the label should state: "Pharmacokinetics of Org has not been studied in renally impaired patients".

2. In study 87020, aspirin administration did not influence Org's anti-Xa activity. Similarly, simultaneous administration of Org and aspirin did not influence platelet aggregation. However, three out of eight subjects showed significant prolongation of bleeding time. Therefore, the label should state the possibility of prolonged bleeding time after concomitant administration of Org and aspirin.

3. The proposed label states in the Overdosage section:
   "Although protamine chloride partially neutralizes the anti-Xa activity of ORGRAN™ and can be safely co-administered, there is no evidence that protamine chloride is capable of reducing severe non-surgical bleeding during treatment with ORGARAN™".
   It should be noted that instead of protamine chloride, protamine sulfate is marketed in the United States.

4. The proposed labeling states in the Pharmacokinetic section:

   "The covariates age, gender and weight were not found to be important in describing the pharmacokinetics of ORGARAN™ based on anti-Xa activity".
   However, in the population pharmacokinetic analysis carried out by the sponsor and the one carried out by this reviewer show that height and weight were significant covariates.

Comment to the Medical Officer (HFD-180):

1. Under Drug Interaction, the sponsor has stated that no clinically significant drug interactions have been noted in the following concomitantly administered medication in clinical studies for the prophylaxis of DVT and PE following orthopedic hip surgery:

   antidiabetics (insulin and hypoglycemics), digitalis/digoxin, Ca channel blockers, diuretics, beta blockers, thyroid drugs, antibiotics for systemic use (broad spectrum penicillins, cephalosporins, aminoglycoside antibiotics), antiinflamatory and antirheumatic agents, muscle relaxants, anti-asthmatics, antipyretics (acetaminophen), opiate and non-opiate analgesics.

   Division of Pharmaceutical Evaluation II has information on Org's drug interaction potential only for following drugs:

   acenocoumarol, digoxin, cloxacillin, ticarcillin, chlorthalidone, pentobarbital and aspirin

   The medical officer (HFD-180) is requested to please comment on the safety of administering drugs mentioned in the proposed label under "Drug Interaction" that are different from those studied in the pharmacokinetic program.

   The medical officer (HFD-180) is also requested to comment on the clinical importance of the drug interactions seen in case of digoxin, cloxacillin and ticarcillin.

11-21-95
Rajendra S. Pradhan, Ph.D.
Division of Pharmaceutical Evaluation II

FT initialed by Lydia Kaus, Ph.D. LCK 11/21/95

cc: NDA 20-430, HFD-180, HFD-870 (DPEII Chenme, Kaus, Pradhan), HFD-860 (DPEI Malinowski), HFD-880 (DPEIII Fleischer), HFD-340 (Viswanathan), HFD-850 (Chron, Drug, Reviewer), HFD-19 (FOI)