

11.0 APPENDIX
(October 21, 1997)

11.1 APPENDIX 1

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Pini M, Aiello S, Manotti C, Pattacini C, Quintavalia R, Poli T et al. *Low molecular weight heparin versus warfarin in the prevention of recurrence after deep vein thrombosis.* Thrombosis and Haemostasis. 1994; 72:191-9. (V.36, p.306).

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APPENDIX 2

11.2 APPENDIX 2: STUDY 2091

1. LIST OF PARTICIPANTS

1. LIST OF CENTERS IN CANADA, INVESTIGATORS AND NUMBER OF PATIENTS ASSIGNED

Center, Investigator	No. H/E	Center, Investigator	No. H/E
Center for Clinical Research, Halifax, Nova Scotia. David Anderson, M.D.	74 38/36	Maisonneuve, Centre d'hematologie. Montreal, Quebec. Jeannine Kassis, M.D.	27 15/12
St. Joseph's Hospital, London, Ontario, William F. Brien, M.D.	9 4/5	Victoria Hospital, London, Ontario. M.J. Kovacs, M.D.	35 19/16
Hematology Department, University Hospital, London, Ontario, Moirra Cruickshank, M.D.	13 8/5	Montreal General Hospital, Dpt. Hematology, Montreal, Quebec. Jacques R. Leclerc, M.D.	38 18/20
Centre de Resherche, Cardiovascular Recherche Lab., Hotel Dieue. Montreal, Quebec. Jean Cusson, M.D.	22 11/11	Cancer Center, Hamilton, Ontario. Mark Levine, M.D.	80 39/41
Dept. d'Hematologie, Hopital du Saint-Sacrament. Quebec, Quebec. Christine Demers, M.D.	41 22/19	St. Joseph's Hospital, McMaster Clinic. Hamilton, Ontario. Peter J. Powers, M.D.	9 3/6
Centre Hospitalier de L'Universite Laval, Laurier Saint-Foy, Quebec. Louis Desjardins, M.D.	24 11/13	Hamilton General Hospital, McMaster Clinic. Hamilton, Ontario. Alexander Turpie, M.D.	47 25/22
Sunnybrook Hospital, University of Toronto Clinic, Toronto, Ontario. William Geerts, M.D.	30 16/14	St. Paul's Hospital, Emergency Department. Vancouver, B.C. John H. Ward, M.D.	3 0/3
McMaster University, Dpt. of Medicine, Hamilton, Ontario. Jeffrey Ginsberg, M.D.	48 24/24	General Hospital, Health Sciences Center. St. John, Newfoundland. Lucinda A. Whitman, M.D.	1 1/0
		TOTAL= Centers: 16, Patients: 501(H=254/E=247)	

From Table 1 (Vol. 22, pp. 13-15), and Table 4 (vol.22, p.35). H=heparin. E=enoxaparin

2. NARRATIVES FOR PATIENTS WHO DIED

Early Deaths During the Follow-up Period (Day 7-30)

Prior to death, one patient (pt#162002) developed new thrombosis in the contralateral leg (Day 13). She died of "pancreatic cancer" on day 20. This case can be classified as enoxaparin efficacy "failure."

1. A patient (pt#102004) died on Day 17, following intracranial hemorrhage (Day 5) while on enoxaparin therapy. This is a safety failure.

2. A patient (pt#064008) died on Day 11 due to massive gastrointestinal hemorrhage (autopsy confirmed). This hemorrhage was noticed on Day 11 as hematemesis leading to discontinuation of warfarin. He received enoxaparin for six days. This may be classified as safety failure.

3. A patient (pt#021017) with "active lung cancer" received full enoxaparin treatment for bilateral leg thrombosis. She died on Day 30 while on therapy with warfarin due to cancer progression. No autopsy was performed. This case was probably not related to the study medication.
4. A patient (pt#112013) with lung cancer received heparin for 11 days. On day 19 he experienced moderate hematuria. On Day 21 he died due to cancer progression. No autopsy was performed. This case may be included in safety failure.
5. A patient (pt#041010) with liver cancer, was found to have bilateral thrombosis on day 13 (five days after completion of 8 days heparin treatment). On Day 18 he experienced intra-abdominal hemorrhage and was treated with vitamin K to reverse excess warfarin anticoagulant activity. He died on Day 19 due to this hemorrhage. It is a case of safety failure (warfarin)

Summary: All early deaths during the follow-up period of 7-30 days, may be caused by study failures, either insufficient efficacy (extension of DVT, or PE), or insufficient safety (hemorrhage).

Within Study Deaths (Day 31-90)

Nineteen deaths occurred within study day 31-90. Eight of them (42%) occurred during ten late study days (day 78-87). Seven were in the heparin/warfarin group. One was in the enoxaparin/warfarin group. The following selection from narratives is given to show difference to early deaths.

- 1-6. A patient (pt#011027) completed 6-day heparin treatment for popliteal DVT. She died of glioblastoma multiform on day 83.
There is no data to consider this death related to the study drug.
- 2-7. A patient (pt#043002) with carcinoma of the liver, received 5-day heparin therapy for proximal DVT. On day 31 she was found with another DVT and received only warfarin. She died on day 87, due to liver cancer. In this case the primary anticoagulant therapy was insufficient to prevent recurrence of DVT. Study drug failure.
- 3-8. A patient (pt#062006) with metastatic ovarian cancer received 6-day heparin treatment for proximal DVT. She was discontinued from warfarin therapy for "other" reasons. She died on Day 81 due to cancer progression. There is no data to consider this death as related to the study medication.
- 4-9. A patient (pt#071002) with pancreatic cancer received 6-day heparin treatment for proximal thrombosis. On Day 28 another DVT occurred and she was hospitalized. The patient died on Day 82 due to pancreatic cancer. Study drug failure.
- 5-10. A patient (pt#082007) with multiple myeloma received 7-day heparin treatment for DVT. On Day 36 he was admitted to hospital for treatment of myeloma related hypercalcemia. On Day 81 he was found to have pneumonia. On Day 84 he was discovered to have DVT in the opposite leg and, because of no apparent clinical symptoms, he was returned home, where he died. The exact date is not known. Study drug failure.
- 6-11. A patient (pt#091028) received 6-day heparin treatment for proximal DVT. On Day 2 she was diagnosed with lung cancer. On day 22 she developed a recurrent DVT. It was repeated on Day 55. The patient died on Day 85 due to pulmonary cancer. No autopsy was performed. Study drug failure.
- 7-12. A patient (pt#124007) with gliosarcoma received 5-day heparin for DVT. On day 22 he experienced a serious confusion. Hemorrhage was not ruled out. The patient died on Day 78 due to cancer progression. Possible safety failure.

8-13. A patient (pt#091007) with bladder cancer (stage C) received 6-day enoxaparin for proximal DVT (iliac and leg). Beginning Day 63 the patient experienced severe GI symptoms followed with dehydration. He died on Day 83 due to cancer progression. No autopsy was performed. There is no data that this death may be influenced by the study medication.

Comment: Although the cause of death was considered not to be related to study medications, patients who died during this period, had experienced study failure in more than 60%. Efficacy failure (recurrence of DVT) occurred in 4 (50%) of patients. Safety failure (major hemorrhage) occurred in 12.5%. In one third of patients (37.5%) have no data.

Post-Study Deaths (Day 91-180)

Fifteen deaths occurred between days 91-180. This period is within the original six-month follow-up (changed to three months with amendment to the protocol). According to the sponsor, during this period there was a poor compliance of patients to continue warfarin therapy and undergo control visits.

1-14. A patient (pt#011008) with prostate cancer received 7-day heparin/warfarin treatment for proximal DVT. He died on day 185 from DIC following massive GI hemorrhage and intracranial hemorrhage on day 180. No information of warfarin therapy at this time is provided. No autopsy was performed.

2-15. A patient (pt#011012) received 6-day heparin/warfarin treatment regimen for DVT. She died on day 107 due to cardiopulmonary arrest and chronic lymphatic leukemia. No autopsy was performed.

3-16. A patient (pt#012013) with lung cancer received 10-day heparin/warfarin regimen for DVT. On day 33 she had recurrent DVT. On day 88 she had an arterial thrombosis. She died on day 91 due to cancer progression. No autopsy was performed. No data for INR or warfarin at this time are provided.

4-17. A patient (pt#021014) with prostatic cancer received 7-day heparin/warfarin regimen for iliac DVT. On day 15 he had recurrent DVT. He died on day 209 due to cancer progression (bony metastasis, femur fracture). No autopsy was performed.

5-18. A patient (pt#022001) received 6-day heparin/warfarin regimen for iliac DVT. On day 177 she had "ischemic bowel" and was operated. She died of respiratory failure (possible PE) on day 184. No autopsy was performed. Data about warfarin or INR level at this time are not provided.

6-19. A patient (pt#074002) with pancreatic cancer received 1-day heparin/warfarin treatment for proximal DVT. She was discontinued from study medication because of hematemesis considered to be a major hemorrhagic event. She died on day 116 due to cancer progression. No autopsy was performed.

7-20. A patient (pt#091025) with AIDS received 6-day heparin/warfarin regimen for DVT. On day 87 he was hospitalized because of fever. He died on day 92. No autopsy was performed.

8-21. A patient (pt#153) received 5-day heparin/warfarin regimen for proximal DVT. On day 22 he had a recurrent DVT (new clot, and PE). On day 25 the patient was diagnosed with cancer (metastatic pulmonary carcinoma). He died on day 153 due to cancer progression. No autopsy was performed. Data for warfarin and INR levels at this time are not provided.

9-22. A patient (pt#011011) received 6-day enoxaparin/warfarin regimen for DVT. On day 91 she underwent surgery for bowel obstruction. On day 94 she experienced PE. On day 108 she had a retroperitoneal hemorrhage. On day 114 she had sepsis and peritonitis. She died the same day. No data of warfarin and INR levels at this time are provided. Autopsy was not performed.

10-23. A patient (pt#011019) received 7-day enoxaparin/warfarin regimen for proximal thrombosis. On day 62 he was diagnosed to have a diffuse, large cell lymphoma. At this time recurrence of DVT was noted and he received a Greenfield filter. A pseudomembranaceous colitis followed chemotherapy. He died on day 120 in a hypovolemic shock "due to lymphoma progression." No autopsy was performed.

11-24. A patient (pt#011020) with lung cancer with brain metastases received 9-day enoxaparin/warfarin regimen for proximal DVT. On day 17 he had recurrent DVT (another enoxaparin treatment). On day 100 he died due to cancer progression. No data for warfarin or INR levels at this time are provided. No autopsy was performed.

12-25. A patient (pt#012006) with prostatic cancer received 7-day enoxaparin/warfarin regimen for DVT. On day 62 he developed anemia requiring transfusions. Warfarin was withheld and he recovered. He died on day 112 due to cancer progression. No autopsy was performed.

13-26. A patient (pt#045002) was hospitalized for hip replacement. A DVT was found on venography. He received 7-day enoxaparin/warfarin regimen. On day 53 he was found to have a cecum carcinoma. He died on day 163 due to cancer progression.

14-27. A patient (pt#064002) with lung cancer received 5-day enoxaparin/warfarin regimen for iliac DVT. On day 13 he was found to have DVT recurrence. He was treated with vitamin K and streptokinase and he recovered. On day 153 he died due to progression of lung cancer. No autopsy was performed.

15-28. A patient (pt#122004) received 7-day enoxaparin/warfarin regimen for proximal DVT. On day 123 he was found to have metastatic adenocarcinoma. The same day he died. No autopsy was performed.

3. NARRATIVES ON PATIENTS WHO DISCONTINUED STUDY DUE TO SERIOUS ADVERSE EVENTS.

A patient (pt#042003) developed DVT after prostatic surgery. He was randomized on heparin/warfarin regimen. On day 2-5 he experienced macrohematuria, and further therapy was discontinued.

A patient (pt#05402) developed DVT after radical cystoprostatectomy due to bladder cancer. He was randomized to receive heparin/warfarin. On day 3 the patient experienced a bleeding duodenal ulcer. The study drug was discontinued.

A patient (pt#074004) with DVT received a 5-day heparin/warfarin regimen. On day 66 the patient experienced a septic shock and DIC with melena, and nasogastric return. He recovered from the event and continued with warfarin. On day 79 he experienced intracranial hemorrhage and "endocarditis." Warfarin was stopped permanently.

A patient (pt#122042) with stomach and liver cancer received 8-day heparin/warfarin regimen for proximal DVT. On day 74 he experienced hematemesis. Warfarin was stopped permanently.

A patient (pt#011001) with prostatic cancer and recent orchideectomy was randomized on enoxaparin/warfarin regimen. On day 6 he experienced a hematoma of the hip, but the therapy continued. On day 90 he attempted suicide with overdose of oxazepam and warfarin. He recovered, but warfarin was discontinued permanently.

A patient (pt#011031) received 6-day enoxaparin/warfarin regimen. On day 7 she experienced a large abdominal wall hematoma (injection site?). Warfarin was permanently discontinued.

A patient (pt#012018) was randomized on enoxaparin/warfarin regimen for proximal DVT. On day 4 she experienced a large abdominal anterior wall hematoma (injection site!). Due to this event, the study was discontinued on day 6.

A patient (pt#143010) with lung carcinoma received 8-day enoxaparin/warfarin regimen. On day 47 he experienced melena, epistaxis, and macroscopic hematuria. Warfarin was discontinued temporarily.

Narratives on Patients Who Discontinued Because of VTE

A patient (pt#012003) received 7-day heparin warfarin regimen for DVT. On day 12 she became symptomatic and had positive leg scan for recurrent DVT. She recovered after another intravenous heparin treatment.

A patient (pt#016001) received 7-day heparin/warfarin regimen for proximal thrombosis. On day 7 she experienced recurrent DVT and was treated with vitamin K, oxycodone/acetaminophen, and morphine until recovery. On day 10 she experienced thrombocytopenia and was hospitalized. She received ferrous gluconate, orgaran, and ancrod until recovery. This thrombocytopenia was not considered as drug related (?) and discontinuation was related to recurrent DVT.

A patient (pt#091033) with ovarian cancer received 6-day heparin/warfarin regimen for proximal DVT. On day 29 she experienced recurrent DVT and recovered after in hospital treatment. On day 72 she experienced dyspnea, but PE was not considered. She was treated with oxygen and recovered "with sequelae."

A patient (pt#122040) received 6-day heparin/warfarin regimen for DVT. On day 14 she experienced recurrent DVT. She was hospitalized, treated and recovered.

A patient (pt#126001) with non-Hodgkin's Lymphoma received 5-day heparin/warfarin regimen. On day 29 he developed a recurrent proximal DVT. No information for further history is provided.

A patient (pt#016004) who was hospitalized for total abdominal hysterectomy with bilateral salpingoophorectomy received 6-day enoxaparin/warfarin regimen for treatment of DVT (confirmed by duplex ultrasonography). On day 12 she developed a recurrent thrombosis of the superficial femoral vein.

A patient (pt#042006) with carcinoma (unspecified but probably GI) received 6-day enoxaparin/warfarin regimen. On day 60 she had a recurrent DVT, was hospitalized and recovered. No action against carcinoma was taken (?).

A patient (pt#042007) with lymphoma received 5-day enoxaparin/warfarin regimen for proximal DVT. On day 57 he developed a recurrent DVT, was hospitalized and recovered.

A patient (pt#042009) with a history of DVT and recent orthopedic surgery (tibiostomy) received with interruption (due to acute renal failure) enoxaparin/warfarin regimen. Both drugs administration ended on day 17. On day 42 a new clot and recurrent DVT were found. He was hospitalized and recovered after warfarin.

A patient (pt#082002) with DVT received 6-day enoxaparin/warfarin regimen resulting in disease progress. She was transferred to heparin and recovered.

A patient (pt#112003) began enoxaparin/warfarin regimen for treatment of DVT. On day 2 she experienced PE. Enoxaparin was discontinued. She recovered.

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A patient (pt#122007) with promyelocytic leukemia (diagnosed on day 57 of the study) received 7-day enoxaparin/warfarin regimen for DVT. On day 33 she experienced PE symptoms (w/o confirmation). On day 79 she developed recurrent DVT. She was hospitalized up to day 147 mostly because of leukemia related events.

A patient (pt#126003) was hospitalized for treatment of glioblastoma multiforme. He was randomized to receive enoxaparin. On day 3 he was diagnosed to have HIT (serotonin-release assay). He finished enoxaparin on day 7. On day 43 he developed recurrent DVT, was hospitalized and recovered.

A patient (pt#143008) was randomized on enoxaparin/warfarin regimen for DVT. On day 3 he experienced recurrent DVT. On day 18 he experienced another recurrent DVT. No information on treatment of this patient between two episodes of DVT is provided.

APPEARS THIS WAY ON ORIGINAL

APPENDIX 3