ADVISORY COMMITTEE BRIEFING DOCUMENT

Oncologic Drugs Advisory Committee Meeting

September 6, 2006

DALTEPARIN SODIUM (FRAGMIN®) NDA 20 – 287 S – 035

PROPOSED INDICATION: "…FOR EXTENDED TREATMENT OF SYMPTOMATIC VENOUS THROMBOEMBOLISM [VTE (PROXIMAL DVT AND/OR PE)] TO REDUCE THE RECURRENCE OF VENOUS THROMBOEMBOLISM (VTE) IN PATIENTS WITH CANCER."

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ALT (SGPT)	Alanine aminotransferase (serum glutamate-pyruvate transaminase)
ACCP	American College of Chest Physicians
AST (SGOT)	Aspartate aminotransferase (serum glutamate-oxaloacetate transaminase)
aPTT	Activated partial thromboplastin time
Anti-FXa	Anti-Factor Xa activity
BID	Twice Daily
CAC	Central Adjudication Committee
CI	Confidence Interval
CTMG	Clinical Trials Methodology Group
CVT	Central venous thrombosis of the upper limb(s), neck, or chest
CRF	Case Report Form
DVT	Deep vein thrombosis
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ – C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
FRIC Study	Fragmin in Unstable Coronary Artery Disease Study
FRISC Study	Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease Study
F_{1+2}	Plasma prothrombin fragment 1+2
GGT	Gamma-glutamyl transpeptidase
HIT	Heparin-induced thrombocytopenia
HR	Hazard Ratio
INR	International Normalized Ratio
ITT	Intent-to-treat
IV	Intravenous
LMWH	Low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTC	National Cancer Institute-Common Toxicity Criteria
OAC	Oral anticoagulant
ODAC	Oncologic Drugs Advisory Committee
PE	Pulmonary embolism
PF4	Platelet factor 4
PT	Prothrombin time
qD	Once Daily

SAE	Serious adverse event
SC	Subcutaneous
TAT	Thrombin-antithrombin complex
TFPI	Tissue factor pathway inhibitor
TT	Thrombin time
UCAD	Unstable Coronary Artery Disease
UFH	Unfractionated heparin
ULN	Upper Limit of Normal
USPI	United States Package Insert
VTE	Venous thromboembolism

1. EXECUTIVE SUMMARY

Dalteparin sodium (Fragmin®) is a low molecular weight heparin (LMWH) first marketed in 1985 in Germany, and approved in the United States in 1994. In the United States, dalteparin is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in various clinical situations (e.g., after hip replacement and abdominal surgery) and also indicated for prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin therapy. Dalteparin is administered once daily by subcutaneous injection and does not require monitoring of its anticoagulant effects by a laboratory test of coagulation. This briefing document addresses the use of dalteparin in patients with cancer and venous thromboembolism.

Patients with cancer are known to have a high risk of venous thromboembolism (VTE). In clinical trials using vitamin K antagonist oral anticoagulants (OAC) for prevention of recurrence of VTE, patients with cancer have had a higher incidence of recurrent thrombosis and bleeding than patients without cancer (Hutten BA et al, 2000; Prandoni P et al, 2002). Standard treatment of VTE is initial therapy with either unfractionated heparin or LMWH followed by long-term treatment with oral anticoagulants. Warfarin is the most common vitamin K antagonist OAC used in North America and is considered the drug of choice for treatment of VTE after initiation of therapy with a heparin. The only alternatives are extending LMWH or unfractionated heparin (UFH) therapy which are given by subcutaneous injection or intravenous infusion respectively. Management of OAC therapy can be problematic in patients with cancer, in whom vomiting, malnutrition, hepatic dysfunction and drug interactions can lead to unpredictable levels of anticoagulation. Moreover blood monitoring of the anticoagulant effects is required, but may be difficult in patients with cancer who have poor venous access.

The "Randomized **C**omparison of **L**ow-Molecular Weight Heparin Versus **O**ral Anticoagulant Therapy for Long Term Anticoagulation in Cancer patients with Venous **T**homboembolism" (CLOT study) was a randomized, open-label, controlled, multicenter, multinational study designed to compare the efficacy and safety of dalteparin and OAC therapy in patients with active malignancy who had experienced an acute symptomatic proximal lower limb DVT and/or a PE. The primary objective of this study was to compare the effect of dalteparin to OAC in the prevention of symptomatic recurrence of VTE in patients with cancer. The secondary objectives were to compare the two treatment groups in terms of development of symptomatic DVT, CVT (Central Venous Thrombosis) and/or PE, bleeding events and survival. The primary endpoint was the recurrence of VTE during a 6 month treatment period. In comparison to OAC therapy, dalteparin provided a 52% reduction in the risk of VTE recurrence (p=0.0017). From a total of 676 patients enrolled (338 patients per group), 27 (8%) patients had recurrent thromboembolism in the dalteparin arm compared to 53 (15.7%) patients in the oral anticoagulant comparator arm. There was no significant difference in major bleeding (dalteparin: 6% and OAC: 4%) or any bleeding (dalteparin: 14% and OAC: 19%). Mortality rates at 6 months were also similar with 39 % in the dalteparin arm and 41% in the OAC arm dying during the 6 month treatment period.

The CLOT Study was published in the New England Journal of Medicine in 2003 (Lee AY et al, 2003) and contributed to the recommendation in the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy that most patients with DVT and cancer undergo treatment with LMWH for at least the first 3 to 6 months of long term treatment (Buller et al, 2004).

A supplemental NDA (S-035) was submitted to FDA for the addition of the indication "extended treatment of symptomatic venous thromboembolism [VTE (proximal DVT and/or PE)], to reduce the recurrence of VTE in patients with cancer" to the Dalteparin US Package Insert. Supportive data for this new indication was primarily based on the CLOT Study. In discussions with FDA during the review of the sNDA, two main points arose regarding the CLOT Study data: mortality while patients were "on treatment" and robustness of the analysis of the primary endpoint. These points have been addressed in detail within this briefing document and are summarized below.

Although there was no expectation that dalteparin treatment would increase survival in this group of patients with cancer, mortality was a secondary endpoint. Mortality was analyzed by an ITT analysis in patients over the 6 month treatment period, and also summarized in patients while "on-treatment" (defined as up to 1 day after permanent discontinuation of therapy). There were a total of 131 and 137 deaths over the first 6 months in the dalteparin and OAC arms, respectively, and the survival curves did not differ (2-sided log-rank test, p=0.56). The vast majority of these deaths were due to the underlying cancer. There were a total of 59 deaths in the dalteparin arm and 21 deaths on the OAC arm while subjects were "on-treatment"; however, there is a reasonable explanation for this difference in "on-treatment" mortality. In the "on-treatment" analysis, deaths subsequent to discontinuation of study drug were censored. The Sponsor describes in this document that this censoring is informative: the reason for a death being censored (e.g., study drug being discontinued) is related to the death itself, due to the clinical management of the patients in the OAC arm. Patients with terminal cancer often are too ill to continue oral anticoagulant therapy because of difficulties with both oral intake and monitoring of oral anticoagulant effects. A second source of bias was the differences in frequency of recurrent VTEs. The higher rate of VTE in the OAC arm corresponded to more deaths being censored in the OAC arm further biasing the "on-treatment" mortality data. Hence, the analysis of "on-treatment" deaths is biased by informative censoring and does not provide a basis for conclusions on the mortality associated with the two treatments.

Regarding the robustness of the analysis of the primary endpoint, the similarity between the rates of "on-treatment" deaths and first VTE recurrence raises the question of whether deaths in the study impacted the analysis of the primary endpoint of recurrent VTE. The Sponsor believes that the Intention-To-Treat (ITT) analyses over the 6-month study period of the CLOT Study for the primary endpoint of venous thromboembolism (VTE) yields valid and unbiased results. Censoring of VTEs in patients who died without a VTE did not impact the analysis of time to VTE in the two treatment groups since the timing and main cause of death (underlying cancer) were similar in both treatment groups and there is no reason to believe that the probability of VTE for the patients who died without a VTE would have differed in the two treatment groups.

The characteristics of the CLOT study meet criteria set forth in the May 1998 FDA guidance entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products", as a large, randomized, controlled, multicenter, multinational trial with prospectively determined clinical and statistical analytic criteria. The open-label design of the study may be viewed as a limitation. Although double-blinding is as an optimal strategy to minimize bias, this study was designed as an open-label study because of the nature of the study population, differing methods of administration of the study drugs, and the need for active therapeutic monitoring. The Sponsor found double-blinding difficult to justify in patients whose quality of life may already be compromised from cancer. In order to minimize bias, all reported primary and secondary outcome events, including VTEs, deaths and bleeding episodes, were adjudicated by a blinded Central Adjudication Committee. The use of dalteparin for the initiation of anticoagulation in the control arm of the study may also be viewed as a limitation of the trial as there were no LMWHs approved for use in cancer patients. This was carefully considered by the CLOT Steering Committee as there were no LMWHs approved for use in cancer patients. The use of UFH or another LMWH as part of the comparator was ultimately not adopted because the introduction of additional variables may have had a confounding effect on the interpretation of the study result. Regarding the results of the CLOT Study, the effect of dalteparin, in comparison to OAC therapy, was statistically significant and the treatment effect was consistent across subgroups of cancer patients with solid tumors with or without metastatic disease. The treatment effect was also significant when adjusted for factors prognostic of outcome. The Sponsor, however, acknowledges that the treatment effect was not consistent in a subgroup of patients with hematological malignancies, possibly due to the small numbers of these patients in the trial. While the Sponsor believes that the data from this single trial provides sufficient evidence to support the proposed indication, the Sponsor has also committed to conducting one additional post-approval study in cancer patients with non-metastatic solid tumors presenting with acute, symptomatic, proximal lower limb DVT, PE or both.

Patients with active malignancy have a higher rate of thromboembolism than the general population. Although treatment regimens are recommended by the American College of Chest Physicians (ACCP), there are currently no approved medications for treatment of VTE in patients with cancer in the United States. The results of the CLOT trial show that for patients with cancer and newly diagnosed symptomatic proximal deep vein thrombosis and/or pulmonary embolism, extended treatment with dalteparin reduces the recurrence of these events and has a favorable risk/benefit profile, and therefore would offer patients with cancer an improved treatment option to reduce the risk of VTE.

2. PRODUCT OVERVIEW

Dalteparin sodium is a low molecular weight heparin (LMWH) the functional differences of which from conventional unfractionated heparin (UFH) are a higher anti-Factor Xa (anti-FXa) activity and a lower anti-Factor IIa activity. The main advantages of using dalteparin sodium compared with conventional UFH reside in its improved bioavailability and prolonged half-life, thus allowing a once daily subcutaneous (SC) injection. Moreover, no routine monitoring of the anticoagulant effects of dalteparin sodium activity is required compared to UFH.

Dalteparin is approved in over 80 countries worldwide. Many indications approved across the world are for thromboprophylaxis (in patients undergoing surgery; in patients with unstable coronary artery disease; and in patients with acute renal failure or chronic renal insufficiency during hemodialysis and hemofiltration). However, dalteparin is also approved in many regions, including countries within the European Union (EU), for the treatment of DVT and PE. Dalteparin is currently approved for the proposed indication, for the extended treatment of symptomatic venous thromboembolism [VTE (proximal DVT and/or PE)] to reduce the recurrence of venous thromboembolism (VTE) in patients with cancer, in 19 countries, including Canada, Austria, Finland and Denmark.

2.1. Product Description

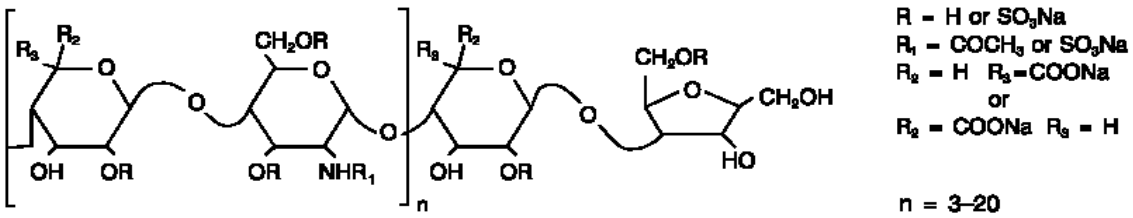
Dalteparin sodium (Fragmin®).

2.2. Chemical Name and Structure

Dalteparin sodium Injection is a sterile, low molecular weight heparin (LMWH). Dalteparin sodium is produced through controlled nitrous acid depolymerization of sodium heparin from porcine intestinal mucosa followed by a chromatographic purification process. It is composed of strongly acidic sulphated polysaccharide chains (oligosaccharide, containing 2,5-anhydro-D-mannitol residues as end groups) with an average molecular weight of 5000 and about 90% of the material within the range 2000-9000. The molecular weight distribution is:

< 3000 Daltons	3.0-15%
3000 to 8000 Daltons	65.0-78.0%
> 8000 Daltons	14.0-26.0%

Structural Formula



2.3. Proposed Indication

Dalteparin sodium is also indicated for the extended treatment of symptomatic venous thromboembolism [VTE (proximal DVT and/or PE)], to reduce the recurrence of VTE in patients with cancer.

2.3.1. Currently Approved Indications in the United States

Dalteparin sodium is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE):

- In patients undergoing hip replacement surgery;
- In patients undergoing abdominal surgery who are at risk for thromboembolic complications;
- In medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

Dalteparin sodium is also indicated for the prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin therapy.

See Appendix 1 for the United States Package Insert (USPI).

2.3.2. Approval History

The regulatory approval history of the product in the USA is as follows –

- Dalteparin sodium NDA 20-287 was approved December 22, 1994, for prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing abdominal surgery who are at risk for thromboembolic complications.
- sNDA approved March 30, 1999, for prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing hip replacement surgery.
- sNDA approved May 25, 1999, for the prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin therapy.
- sNDA approved December 10, 2003, for prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

The summary of significant FDA regulatory interactions for the sNDA for the proposed indication in patients with cancer follows –

- March 16, 2004, Pfizer submitted a sNDA for a new indication for the extended treatment of symptomatic venous thromboembolism [VTE (proximal DVT and/or PE)], to reduce the recurrence of VTE in patients with cancer.
- January 14, 2005, FDA advised Pfizer of the “approvable” status of the sNDA. Deficiencies to be addressed included a summary and analysis by treatment duration and

dose from the dalteparin safety database to more accurately assess possible risk with higher doses and longer treatment duration in patients both chronically and not chronically ill. In addition, post-marketing studies in renal impairment, hematologic malignancies, non-metastatic tumors, and pediatric patients were requested; as well as a request to consider further studies to investigate how best to transition patients from dalteparin to OAC.

- September 14, 2005, Pfizer filed an amendment to the pending sNDA in response to the Approvable Letter dated January 14, 2005.

- March 7, 2006, Teleconference with FDA Division of Medical Imaging and Hematology Products (DMIHP) regarding concern over "on-treatment" mortality imbalance in the CLOT trial. Pfizer was informed of the impending action letter, which would detail the list of FDA questions.

- March 15, 2006, FDA Non-Approvable Letter received.

- May 2, 2006, Teleconference with FDA regarding the "on-treatment" mortality data in the CLOT trial. The FDA acknowledged that informative censoring was a plausible explanation for the imbalance in "on-treatment" deaths and then raised a question of whether mortality is a competing risk which may have biased the interpretation of the analyses of the primary endpoint.

- June 9, 2006, Teleconference with FDA DMIHP. FDA informed Pfizer of their decision to take the discussion of the data from the CLOT study to the Oncologic Drugs Advisory Committee (ODAC).

- June 13, 2006, FDA Pfizer meeting to further discuss the interpretation of the CLOT trial regarding safety and efficacy results. FDA noted that input from the Oncologic Drugs Advisory Committee (ODAC) would assist in determining the overall approvability of the indication.

2.4. Dosage Form, Route of Administration and Dosing Regimen

2.4.1. Currently Approved Dosing Regimen in the United States

Hip Replacement Surgery:

In patients undergoing Hip replacement surgery with a risk of thromboembolic complications, the recommended dose of dalteparin sodium is 2500 IU administered by s.c. injection 1 to 2 hours prior to surgery and repeated once 4 to 8 hours following surgery. This is followed by 5000 IU once daily postoperatively. The usual duration of administration is 5 to 10 days after surgery; up to 14 days of treatment with dalteparin sodium have been well tolerated in clinical trials.

Abdominal Surgery:

In patients undergoing abdominal surgery with a risk of thromboembolic complications, the recommended dose of dalteparin sodium is 2500 IU administered by s.c. injection once daily, starting 1 to 2 hours prior to surgery and repeated once daily postoperatively. The usual duration of administration is 5 to 10 days.

In patients undergoing abdominal surgery associated with a high risk of thromboembolic complications, such as malignant disorder, the recommended dose of dalteparin sodium is 5000 IU s.c. the evening before surgery, then once daily postoperatively. The usual duration of administration is 5 to 10 days. Alternatively, in patients with malignancy, 2500 IU of dalteparin sodium can be administered s.c. 1 to 2 hours before surgery followed by 2500 IU s.c. 12 hours later, and then 5000 IU once daily postoperatively. The usual duration of administration is 5 to 10 days.

Dosage adjustment and routine monitoring of coagulation parameters are not required if the dosage and administration recommendations specified above are followed.

Medical Patients with Severely Restricted Mobility during Acute Illness:

In medical patients with severely restricted mobility during acute illness, the recommended dose of dalteparin sodium is 5000 IU administered by s.c. injection once daily. In clinical trials, the usual duration of administration was 12 to 14 days.

Unstable Angina and Non-Q-Wave Myocardial Infarction:

In patients with unstable angina or non-Q-wave myocardial infarction, the recommended dose of dalteparin sodium injection is 120 IU/kg of body weight, but not more than 10,000 IU, subcutaneously (s.c.) every 12 hours with concurrent oral aspirin (75 to 165 mg once daily) therapy. Treatment should be continued until the patient is clinically stabilized. The usual duration of administration is 5 to 8 days. Concurrent aspirin therapy is recommended except when contraindicated.

See Appendix 1 for USPI.

2.4.2. Proposed Dosing Regimen

First 30 Days:

In patients with venous thromboembolism and cancer, the recommended dosing of dalteparin sodium is as follows: for the first 30 days of treatment administer dalteparin sodium 200 IU/kg total body weight subcutaneously (s.c.) once daily. The total daily dose should not exceed 18,000 IU.

Months 2 to 6:

Administer Dalteparin sodium at a dose of approximately 150 IU/kg, s.c. once daily during Months 2 through 6. The total daily dose should not exceed 18,000 IU.

2.5. Dalteparin in Acute VTE

There is extensive clinical trial and post-marketing experience establishing the safety and efficacy of dalteparin sodium in the prophylaxis and treatment of VTE. For a brief outline please see Appendix 2.

3. CANCER AND VENOUS THROMBOEMBOLISM (VTE)

3.1. Epidemiology of Thromboembolism in Patients with Cancer

The association between venous thromboembolism (VTE) and cancer is well established and was first described in 1867 by Trousseau. In spite of the limited understanding of the pathophysiology of VTE in cancer patients, the etiology of VTE in this patient population is known to be multifactorial: tumor-related mechanisms (e.g., release of pro-coagulants by tumor cells or macrophages-tissue factor), patient-related risk factors (e.g., advanced age, surgery, periods of immobilization, infections) and anti-cancer treatment related thrombogenic effects (e.g., chemotherapy, endocrine treatments and other anti-cancer therapies and vascular catheters) (Durica SS, 1997). Epidemiological data indicate that the annual incidence of a first episode of VTE in the general population is 117/100,000 with over 200,000 first life time cases reported each year in the United States (Silverstein MD et al, 1998). Studies evaluating the risk of VTE after a cancer diagnosis have reported that a diagnosis of cancer alone is associated with a fourfold to sevenfold increase in the risk of venous thrombosis, while chemotherapy increases the risk six fold (Blom JW et al, 2005; Heit JA et al, 2000).

The incidence and time course of symptomatic VTE in patients with different types and stages of cancer is largely unknown. Clinical trials data in women with early-stage breast cancer estimated the incidence of VTE to be up to 4% in women with node-negative disease given chemotherapy plus tamoxifen (Fisher B, 1989) and up to 10% in women with node-positive disease on chemotherapy. Epidemiological studies using administrative hospital and cancer registry data have shown that incidence rates of thrombosis are higher during the first year after a cancer diagnosis and that advanced disease is the strongest predictor of VTE (Chew HK, et al 2006; Levitan N, et al 1999; Sallah S, et al 2002). Incidence rates for patients with local/regional disease were up to 5 per 100 patient-years during the first year of follow-up with the highest estimate found for pancreatic cancer. Rates in patients with advanced disease at diagnosis, were up to 20 per 100 patient-years with the highest rate found in patients with pancreatic cancer followed by stomach (11), bladder (8), uterine and kidney (6), lung (5) and ovarian, colorectal and melanoma cancers (4) (Chew HK, et al 2006). This epidemiological data indicate that thromboembolic disease occurs commonly in patients with many types of malignancies and provides insight into the time period when cancer patients are more susceptible to the development of VTE.

It is also known that age plays a synergistic role in the development of VTE. The overall incidence of cancer increases with age (Edwards BK, et al, 2002) and age-specific VTE rates have also been found to follow a similar pattern (Silverstein MD, et al 1998).

Another relevant aspect that needs special consideration in the evaluation of VTE burden in cancer refers to the higher risk of VTE recurrence observed in cancer patients when compared to those without an underlying malignancy and to the threefold greater cumulative probability of death found in cancer patients when compared to patients with VTE not associated with malignancy (Levitan N, et al 1999).

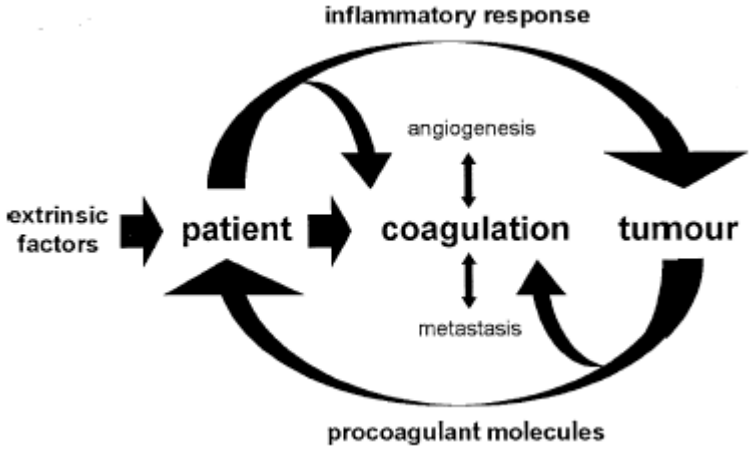
In summary, the clinical implications of the increased rate of VTE incidence and VTE recurrence in cancer patients, together with their impact on the patient's quality of life and ultimately on the patient's survival, suggest that improvements in the management of VTE in this highly susceptible patient' population is needed.

3.2. Pathophysiology of VTE in the Cancer Population

Development of VTE is a dynamic process, characterized by simultaneous progression and resolution of thrombus that ultimately favors the formation of clinically significant thrombosis. Patients may present with symptoms of DVT alone, PE alone or both, however whether there is a biological reason for the differences in presentation is unknown. The precise relationship between DVT and PE is unproven. However, because evidence suggests that DVT often precedes PE, these conditions are considered different clinical expressions of a single pathophysiological spectrum and anticoagulant therapy is the treatment of choice for both conditions (Girard, 1999).

Figure 1 illustrates the mechanisms of thrombogenesis in cancer patients. It shows the different processes between the tumor and the patient that act to promote a hypercoagulable state. Tumors can produce procoagulant molecules that can activate coagulation either directly or indirectly by bringing about an inflammatory response. The inflammatory response can then result in tumor cells further releasing procoagulants. In addition to the patient-tumor interactions (see Figure 1) extrinsic factors, such as surgery or chemotherapy, can further enhance this hypercoagulable process. There is also mounting evidence that tumor-induced coagulation activation and fibrin formation are intrinsically involved in tumor angiogenesis, growth and metastasis (Lee, 2002)

Figure 1. Mechanisms of thrombogenesis in patients with cancer:



Multiple and interdependent processes between the tumor and the patient act to promote a hypercoagulable state (Lee 2002).

Extrinsic factors also contribute to hypercoagulability in cancer patients, e.g. various forms of cancer treatment, venous stasis, and direct vessel trauma. Many cytotoxic agents have been reported to cause thromboembolic disease. Besides cytotoxic therapy, hormonal agents used for cancer treatment are also associated with thrombosis. These include: estrogens, selected estrogen receptor modulators (e.g., tamoxifen) and antiandrogenic compounds. Radiotherapy can also cause direct endothelial damage and elicit an inflammatory response. Other extrinsic factors that promote a hypercoagulable state in cancer patients include: restricted mobility because of their malignancy or an underlying disease; co-morbid conditions such as hospitalization and surgery; venous stasis from compression of vessels due to large tumor bulk or adenopathy; and any direct trauma to vessels from surgery or catheterisation. The mechanisms that have been proposed to explain how stasis promotes thrombosis are poor clearance of activated clotting factors and localized endothelial hypoxia, resulting in damage to the endothelial lining (Lee, 2002).

Many of the sequelae of VTE (acute symptoms, post-phlebitic syndrome) can be particularly problematic in cancer patients who are either receiving complicated multi-modality therapy or are experiencing significant morbidity because of their underlying tumor burden.

3.3. VTE Treatments and Outcomes in the Cancer Population

Standard treatment of acute VTE is initial therapy with either unfractionated heparin or low molecular weight heparin (LMWH) followed by long-term treatment with oral anticoagulants.

Management of oral anticoagulation therapy can be very problematic in patients with cancer in whom vomiting, malnutrition, hepatic dysfunction and drug interactions can lead to unpredictable levels of anticoagulation. Moreover invasive procedures and chemotherapy-induced thrombocytopenia may require interruption of anticoagulant therapy and poor

venous access may make adequate monitoring difficult. All these difficulties lead to suboptimal anticoagulation, which may be the cause for the significant recurrent episodes of VTE seen in this population.

However, even when "adequate" anticoagulant levels are achieved with maintenance of therapeutic international normalized ratio (INR) levels, cancer patients still have a higher risk of recurrent thrombosis than patients without cancer (Hutten 2000). This "OAC resistance" is attributed to the aggressive hypercoagulable state induced by malignancies and their treatments. In VTE trials where secondary prophylaxis with oral anticoagulants (OAC) has been used, cancer patients have a 2- to 3-fold higher risk of recurrent thrombosis and a 2- to 6-fold higher risk of bleeding relative to patients without cancer (Table 1). This was first documented in small studies (Chan, 1992; Clarke-Pearson, 1983; Moore, 1981), and more recently in larger studies reported over the last few years (Table 1). In several of these studies a higher rate of VTE recurrence in cancer patients was observed despite the fact that a greater proportion of subjects with cancer had therapeutic anticoagulation (or conversely a smaller proportion of subjects with cancer than subjects without cancer received sub-therapeutic anticoagulation and still had more VTE recurrence (e.g., the INR was <2)) (Prandoni, 2002; Merli, 2001; The Columbus Investigators, 1997).

Table 1. VTE Recurrence in Patients with Cancer

Author	N	VTE Recurrence Rate	
		With Cancer	Without Cancer
Prandoni (2002)	842 (181 with cancer)	20.7%*	6.8%*
Merli (2001)	900 (141 with cancer)	8.5%**	3.8%**
The Columbus Investigators (1997)	1021 (232 with cancer)	8.6%**	4.1%**

*12 month recurrence rate; **3 month recurrence.

The best evidence that demonstrates OAC resistance in cancer patients comes from a combined analysis of 2 thrombosis studies in patients with symptomatic proximal DVT and/or PE, treated with either UFH/OAC or LMWH/OAC for at least 5 days (Hutten, 2000). Results showed a significantly (p=0.003) higher incidence of recurrent VTE for the 264 cancer patients (27.1 per 100 patient-years; 95% CI: 14.8 to 45.4) compared to the 1039 non-cancer patients (9.0 per 100 patient-years; 95% CI: 5.6 to 13.8) which was independent of the adequacy of International Normalized Ratio (INR) control. The incidence of VTE recurrence in patients without cancer was comparable to that seen in prior publications.

Despite the marked difference in clinical course, standard treatment for VTE in both cancer and non-cancer patients for the past two decades has consisted of UFH or LMWH for initial treatment and long-term oral anticoagulation with a Vitamin K antagonist for secondary prophylaxis. UFH or LMWH is administered for 5-7 days and then discontinued when the OAC-induced INR elevation is consistently in the therapeutic range (between 2.0-3.0). For patients with life-threatening PE or extensive thrombosis, longer initial treatment with UFH or LMWH (7-10 days) is sometimes recommended (Lee, 2000). While the duration of OAC for non-cancer patients with VTE is generally 3-6 months, the duration of OAC for cancer patients with VTE is usually much longer. The exact duration must take into account a number of factors including extent of malignancy, life expectancy, performance status and

administration of hormonal or chemotherapy. Although no trial has directly addressed the duration of OAC therapy in cancer patients with VTE, the general recommendation is that patients should continue with treatment when there is evidence of active cancer or ongoing cancer treatment (Buller et al, Chest ACCP guidelines 2004). Hence, patients with extensive cancer are usually treated with OAC indefinitely (often until death), while patients without evidence of active cancer are treated for a minimum of 3-6 months (Lee, 2000).

These data indicate that treatment outcomes of VTE in cancer patients are worse when compared with non-cancer patients with VTE. Cancer patients are more likely to experience increased morbidity and mortality when treated with standard interventions. While secondary prophylaxis with OAC is effective in reducing recurrence to some degree, approximately one-third of cancer patients still suffer from recurrent VTE or bleeding. In a cancer patient undergoing complicated multi-modality treatment, recurrent VTE can increase morbidity, which leads to cancer treatment interruptions. In addition, maintaining the INR in the therapeutic range with OAC is complicated by the use of concomitant medications and patient nutritional status, difficulty with venous access, and the need to interrupt therapy for procedures (Hutten, 2000; Levine, 2003).

Secondary prophylaxis with LMWH may be a more effective alternative to oral anticoagulation therapy in cancer patients (Lee AYY et al, 2003). Unlike OACs, LMWHs have predictable pharmacokinetics, and drug interactions (Weitz J et al, 1997) and poor gastric absorption is not a concern with them. Other advantages of LMWH are that the therapeutic dosage is dependent on body weight and laboratory monitoring is not routinely required. Due to the rapid onset of action and predictable clearance, LMWHs are also convenient for patients who require frequent interruptions to anticoagulant therapy.

VTE in cancer patients, as described above, represents a difficult clinical problem. Results from studies conducted by the Sponsor investigating the use of dalteparin in the treatment of acute VTE provided the possibility that dalteparin may be of help in cancer patients with this condition. Results from 4 key studies out of the 10 conducted, investigating a dose of dalteparin identical to that used in the initial period of the CLOT study (200 IU/kg qD), had demonstrated that dalteparin is safe and effective in this setting (See Appendix 2).

Although dalteparin was approved for a number of indications using regimens for less than one month, there was safety data from long-term studies in cancer patients [CATHETER (Study 98-FRAG-076)] [1]and in patients with unstable coronary artery disease (UCAD) [FRIC[2] (Study CTN 91-128), FRISC (Study TRN 91-115), and FRISC[3] II (Study 95-FRAG-025)], investigating treatment regimens of dalteparin longer than 1 month. These studies demonstrated that dalteparin would be safe for use for longer durations, thus providing a

[1] CATHETER = known only as the "CATHETER" study.

[2] FRIC = Fragmin in Unstable Coronary Artery Disease;

[3] FRISC = Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease;

rationale for a study for dalteparin to prevent the recurrence of VTE in patients with cancer (Appendix 2).

In conclusion, current therapy with UFH/LMWH followed by OAC is an inadequate and inconvenient treatment regimen in cancer patients with VTE. Given cancer patients are a growing population, there is an urgent and unmet medical need to find a more efficacious, safe and convenient alternative to treat VTE in oncology patients.

4. DALTEPARIN IN CANCER PATIENTS: THE CLOT STUDY

4.1. Introduction

The CLOT study [Randomized **C**omparison of **L**ow-Molecular-Weight Heparin (Dalteparin) Versus **O**ral Anticoagulant Therapy for Long-Term Anticoagulation in Cancer Patients with Venous **T**hromboembolism], is the pivotal study supporting the proposed indication for extended treatment of symptomatic venous thromboembolism [VTE (proximal DVT and/or PE)] to reduce the recurrence of venous thromboembolism (VTE) in patients with cancer.

The CLOT study was conducted by a Steering Committee that included experienced trialists, hematologists and oncologists and it was coordinated by the independent Clinical Trials Methodology Group (CTMG) at McMaster University, an internationally respected and highly experienced research group in the Henderson Research Centre, Hamilton, Ontario, Canada. The trial was a Phase 3, randomized, open label, controlled, multi-center, multinational study. A total of 676 patients were planned to be enrolled. A summary of the key study design characteristics and findings is presented below.

4.2. Methods

The CLOT trial was designed to evaluate the efficacy and safety of dalteparin in preventing recurrent venous thromboembolism in patients with cancer.

4.2.1. Study Objectives and Endpoints

4.2.1.1. Study Objectives

Primary Objective

The primary objective of this study was to compare the effect of dalteparin to OAC in the prevention of symptomatic recurrence of VTE in cancer patients with acute, symptomatic, proximal lower limb deep vein thrombosis (DVT), pulmonary embolism (PE) or both.

Secondary Objectives

The secondary objectives were to compare the 2 treatment groups in terms of:

- Development of symptomatic DVT, or PE, or central venous thrombosis of the upper limb(s), neck, or chest (Central Venous Thrombosis [CVT])

- Survival
- Bleeding events
- General safety
- Quality of life (QOL) (Canadian sub-study)

4.2.1.2. Study Endpoints

Primary Endpoint

The primary endpoint, symptomatic VTE, was defined as the first objectively documented occurrence of either of the following during the 6-month study period:

- Symptomatic lower limb DVT
- Symptomatic PE

Secondary Endpoints

The secondary endpoints were:

- A composite endpoint defined as the first occurrence of symptomatic, and objectively documented lower limb DVT, or PE, or CVT during the 6-month study period
- Survival over 6 and 12 months
- Major bleeding events during the treatment period as defined below.
- Any bleeding events (major and minor bleedings) during the treatment period.
- The type, incidence, severity, relatedness of adverse events, and abnormalities of hematology, coagulation, and blood chemistry studies.
- Measures of QOL (EORTC QLQ C-30) during the treatment period (Canadian sub-study)

Criteria for diagnosing VTE

Patients presenting with signs and symptoms suggestive of recurrent VTE were investigated according to pre-specified diagnostic algorithms and diagnosed based on objective testing. Positive results on venography or compression ultrasonography (CUS) were accepted for the diagnosis of lower limb DVT, as these methods have been shown to give comparable results (Lensing, 1989; Heijboer, 1993).

The accepted tests for the diagnosis of PE were: pulmonary angiography, ventilation perfusion (V/Q) lung scintigraphy, V/Q lung scintigraphy combined with CUS or

venography or thoracic, contrast-enhanced spiral computerized tomography (CT). These approaches have been validated in previous studies (Hull, 1983; Hull, 1994; The PIOPED Investigators, 1990; Hansell, 1998; Mayo, 1997; Remy-Jardin, 1996).

A more detailed description of the diagnostic criteria used for VTE is provided in Appendix 2.

Bleeding

All bleeding events occurring during the time the patients were "on-treatment" and up to 48 hours after permanent discontinuation of study medication were reviewed and adjudicated by the Central Adjudication Committee.

Bleeding events were classified as *major*, defined as events that were clinically overt and satisfied one of the criteria listed below, or *minor*, defined as all the other overt hemorrhagic events that did not meet the criteria for classification as a major bleeding.

The criteria for a major hemorrhagic event were:

- A decrease in hemoglobin of ≥20 g/L over a 24-hour period
- Bleeding leading to transfusion of ≥2 units of packed red cells
- Retroperitoneal, intracranial, intraspinal, intraocular, or pericardial bleeding documented by objective investigation
- Bleeding leading to death

In addition to this classification, all bleeding episodes were graded according to the NCI-CTC (National Cancer Institute-Common Toxicity Criteria) version 2.0 for adverse event reporting.

Adverse Events

All adverse events, regardless of causality, occurring during the adverse event-reporting period were recorded. Severity of adverse events was graded according to the NCI-CTC version 2. The investigators were also instructed to record any untoward event of any severity that occurred subsequent to the adverse event-reporting period if deemed possibly related to study drug. Symptoms associated with the administration of chemotherapy or radiotherapy were also to be reported as adverse events, as well as any clinically significant laboratory abnormality (e.g., NCI-CTC grade 3 or 4) or a worsening of a clinically significant laboratory abnormality already present at baseline. Since recurrent VTE, central venous thrombosis, death, and bleeding of any severity were major outcome events for the study that were recorded and analyzed separately, they were not required to be recorded in the CRF (Case Report Form) Adverse Event form. Among the adverse events recorded, dalteparin-related events such as bruising and local reactions at dalteparin injection sites were to be carefully monitored

Outcomes Research (Quality of Life)

Eligible and consenting patients enrolled in Canada participated in a substudy requested by the Health Protection Branch of Canada. The objective of this substudy was to assess whether different types of long-term anticoagulant therapy could influence the QOL of cancer patients with acute venous thromboembolism.

The selected QOL questionnaire was the EORTC QLQ C-30 (version 3), an integrated system and a widely accepted tool for assessing QOL in cancer patients (Aaronson et al, 1993).

4.2.2. Study Population

The main entry criteria for the study required that eligible patients were ≥16 years of age, diagnosed with a documented active malignancy (excluding basal cell or squamous cell carcinoma of the skin) and had experienced an acute, symptomatic, objectively verified, proximal lower limb DVT and/or a PE. The inclusion of patients with PE was based on review of published studies in which dalteparin and other LMWHs had been used successfully to treat PE (see Appendix 2).

4.2.3. Study Procedures

The study was a phase III, randomized, open-label, controlled, multicenter, and multinational trial in cancer patients with acute, symptomatic, proximal lower limb DVT, PE, or both. Randomization was centralized and stratified with regard to participating sites. Patients were randomly assigned in a 1:1 ratio to receive dalteparin or OAC therapy at the time of confirmed VTE diagnosis. Treatment continued until the occurrence of symptomatic VTE, unacceptable toxicity/adverse event, the physician or patient decided to discontinue therapy, or the completion of the 6-month treatment as per protocol. Patients were followed for VTEs for the first 6 months after randomization during which they received treatment with the study drugs (known as the 6 month treatment/study period) and followed for overall survival for all of the 12 months of the study. An independent, blinded Central Adjudication Committee reviewed all the primary and secondary outcome events, including VTEs, deaths and bleeding events. The Central Adjudication Committee was composed of leading experts in the field of venous thromboembolism. Event validation was based on standardized criteria, pre-specified in the protocol and in the Adjudication Manual. An independent, external safety committee chaired by the Director of the National Cancer Institute of Canada Clinical Trials Group also monitored the study.

4.2.4. Treatment Regimens

Experimental Arm:
Month 1: dalteparin was administered SC once daily, at a dose of 200 IU/kg.
Month 2-6: dalteparin was administered SC once daily, at a dose of approximately 150 IU/kg.

Control Arm:
Dalteparin was commenced at a dose of 200 IU/kg on Day 1-5 and until the INR was between 2.0-3.0 for 2 consecutive days. OAC (e.g. warfarin or acenocoumarol) was started on the first or second day of treatment and administered for the remaining 6-month study period.

All patients received subcutaneous (SC) 200 IU/kg dalteparin once daily for at least 5 days as initial therapy. Treatment continued until the occurrence of symptomatic VTE, unacceptable toxicity/adverse event, the physician or patient decided to discontinue therapy, or the completion of the 6-month treatment as per protocol. Patients receiving OAC were monitored at frequent intervals (minimum of every two weeks) to maintain the INR in the therapeutic range of 2.0-3.0.

4.2.4.1. Open Label Design Rationale

The CLOT Study was an open-label trial. A double-blind double-dummy design would have required that patients randomized to dalteparin undergo 6 months of frequent blood monitoring for INR measurements, and patients randomized to OAC would have required daily placebo SC injections over the same time period. In order to account for lack of INR changes in the patients randomized to dalteparin and oral placebo, a complex and potentially unsafe system of masking treating physicians to INR results and providing OAC dose adjustment through a third party would have been required.
While a blinded design was not used, a number of quality-control measures were put into place:

- Objective criteria and diagnostic procedures were defined to ensure that patients had qualifying VTEs at study entry.
- Dalteparin-treated patients were interviewed with the same frequency as those patients who were receiving OAC in order to maintain equal frequency of contact.
- Symptom criteria for initiation of investigation for suspected VTE recurrence were pre-specified.
- Diagnostic algorithms for evaluation of suspected VTE recurrence were pre-specified.
- Assessment of critical outcome events, including VTEs, bleeding events, and deaths were performed by the independent Central Adjudication Committee masked to patient treatment. The primary and secondary analyses were based on the Central Adjudication Committee assessments, not those of the investigators.
- Procedures for sample size adjustment based on interim masked treatment results were prespecified in the protocol (Amendment 3).

4.2.4.2. Dose Considerations

No specific dose ranging studies have been conducted with dalteparin in the proposed indication. However, doses for use in the CLOT study were chosen after careful consideration of benefit and risk in the existing Sponsor database and evidence from a number of published studies in the acute and long term VTE settings over more than a decade of experience.

The risk of recurrent VTE is known to be highest in the first month after an initial occurrence (The Columbus Investigators, 1997; Koopman, 1996; Simonneau, 1997) – a situation exacerbated in cancer patients (Prandoni, 2002). This increased risk is reflected in the dosing regimen that has developed for the use of dalteparin in acute VTE studies conducted over the previous 10 years. A series of pilot studies conducted by the Sponsor (see Appendix 2), and published reports by Meyer (1995) and Kuijer (1995), investigated the use of twice daily doses of 120 IU/kg SC dalteparin in the acute VTE setting. These studies were superseded by Sponsor study 91-96-544 which established the equivalent efficacy of a 200 IU/kg qD SC dosing regimen compared to a 100 IU/kg twice daily (BID) SC dosing regimen. Thus, in subsequent randomized studies by the Sponsor (93-96-549, 94-96-235 and 94-96-414), and Kovacs (2000, 2001), an initial dose of 200 IU/kg qD SC with concomitant OAC was employed in the acute period and this regimen was therefore selected for use in the CLOT study. Subsequently this scientific experience was reviewed in the American College of Chest Physician's (ACCP) Consensus Conference on Anti-thrombotic Therapy (Hyers, 2001). Guidelines from the ACCP recommend a dose of 200 IU/kg qD SC, not to exceed 18,000 IU per day, for the initial treatment of acute VTE. Analysis of data from CLOT indicates that the critical period in which most VTE recurrences were reported was indeed within the first few weeks of the study.

After 1 month, the 200 IU/kg qD SC dose used in the dalteparin arm of CLOT was lowered to 150 IU/kg SC qD. This reduction in dose is consistent with the lower risk of recurrent VTE seen in the chronic treatment period (Prandoni, 2002), coupled with the requirement to reduce the risk of bleeding in this susceptible population.

The selected comparator arm (acute use of LMWH and chronic use of an OAC) is an accepted standard therapy for acute and long term treatment of VTE (Lee, 2000; Hyers, 2001; Hirsh, 2002; Buller, 2004). The administration of dalteparin 200 IU/kg qD SC as initial treatment of acute VTE in the control arm was appropriate, as LMWHs including dalteparin had been documented to be effective in this setting (Lindmarker, 1994; Fiessinger, 1996; Luomanmäki, 1996) and dalteparin had been registered for acute DVT treatment by the time of study initiation in all the participating countries except the United States.

Patients experiencing chemotherapy-induced thrombocytopenia leading to platelet counts $<50{,}000/mm^3$ had their dalteparin or OAC treatment interrupted until the platelet count recovered above $50{,}000/mm^3$. For platelet counts between $50{,}000\text{-}100{,}000/mm^3$, dose adjustment was made according to patient weight if they were receiving dalteparin, or INR if they were receiving OAC. Once the platelet count recovered to $\geq 100{,}000/mm^3$, dalteparin or OAC was re-instituted at full dose. Dosage was also adjusted in the event of significant renal

failure (defined as a creatinine level >3 x the upper limit of normal) in patients receiving dalteparin.

4.2.4.3. Initial Treatment (Use of study agent in both arms for initial 5 days of treatment)

When the CLOT Study was designed, the standard treatment for VTE was unfractionated Heparin (UFH) followed by OAC, however several studies had by then, shown similar long-term clinical outcomes with LMWH when compared with UFH in this setting (Levine et al 1996; Koopman et al 1996). A large study by Hull and colleagues showed lower rates of recurrence and bleeding when LMWH was compared to UFH (Hull et al, 1992). Several meta-analyses had also suggested that LMWH resulted in fewer episodes of recurrence and bleeding than UFH (Siragusa et al, 1992; Gould et al 1999). In the CLOT Study LMWHs were utilized in both treatment arms as they were considered equivalent to UFH in the treatment of VTE. Unlike UFH, LMWH offered these patients with malignancies the significant benefit of being treated in an outpatient setting. Dalteparin was chosen as the LMWH in the comparator arm as well because at that time there were no LMWHs approved for use in cancer patients and dalteparin had been documented to be effective in this setting (Lindmarker, 1994; Fiessinger, 1996; Luomanmäki, 1996). At the time of study initiation dalteparin had been registered for acute DVT treatment in all the countries participating in the CLOT Study except for the United States.

4.2.5. Statistical Analysis

The sample size for this study was based on the estimated risk of 20% for recurrent venous thromboembolism during 6 months of follow-up among subjects receiving oral anticoagulation therapy. In order to detect a 50% reduction in risk with a power of 0.85 and experiment-wise two-sided alpha of 0.05, it was determined that 70 primary outcome events would be required for the primary analysis. It was estimated that 247 subjects per treatment arm would be required to generate the 70 events allowing for 20% mortality during the study period. A blinded reassessment of the sample size was conducted twice during the trial to evaluate the assumption of the recurrent VTE rate, and resulted in an increase in the required sample size to 338 subjects per treatment arm (676 total).

Two analysis populations were defined. The Intention-to-Treat (ITT) population included all patients who were randomized, regardless of the treatment received. The As-Treated population included all subjects who received at least one dose of study medication.

All analyses were based on the first occurrence of each of the primary and secondary outcome events during the 6-month study period (including deaths during an additional 6-month follow-up period). All events were assessed by the Central Adjudication Committee in a blinded fashion, with the exception of deaths occurring in the 6-12 month follow-up period. The time-to-first-event of the primary outcome (recurrent VTE) and the secondary outcomes (major bleeding; any bleeding [major and minor]; VTE or CVT; and death) was described using the Kaplan-Meier method for each treatment group, and treatment groups were compared using the log-rank test. A 2-sided 0.05 significance level was used.

To evaluate the treatment effect after adjusting for potential prognostic factors assessed at study entry (e.g., age, performance status, type of VTE, previous history of VTE, active cancer chemotherapy), a supporting analysis for the primary efficacy outcome of recurrent VTE was conducted employing the Cox proportional hazard regression model.

Deaths from any cause during the 6-month study period and during the 12-month post randomization period were collected, summarized with Kaplan-Meier methods and compared with the log-rank test. Additionally, deaths were summarized based on time of occurrence as "on-treatment" (defined as occurring within 1 day after last dose of study medication) or "off-treatment".

A quality of life sub-study was conducted in the Canadian sites and patient information was collected by means of the EORTC QLQ-C30 (version 3) questionnaire. Differences from baseline in the two groups were compared using repeated measures analysis of variance.

Adverse events were coded and classified according to MedDRA version 2.3.

4.3. Study results

4.3.1. Study Population

From May 1999 until October 2001, 676 patients (338 per treatment arm) were randomized at 48 sites in Canada, Australia, the United States, New Zealand, and Europe. Three subjects randomized to OAC did not receive study medication. Baseline characteristics and prognostic factors were well-balanced between the two arms (Table 2). Most patients had a solid tumor cancer diagnosis (90%) with metastatic disease (75%). The distribution of tumor types was generally comparable in the 2 arms with the most common primary tumor histologies being breast, gastrointestinal, and lung. At entry into the study the qualifying VTE event in approximately two thirds of patients was symptomatic proximal DVT only, while in the remaining patients the qualifying event was both symptomatic proximal DVT and PE, or PE only.

Table 2. Patient Characteristics at Baseline: Demography (ITT Population)

	Dalteparin N=338		OAC N=338		Total N=676	
	N	**%**	**N**	**%**	**N**	**%**
Age Distribution						
<65 years	182	53.8	182	53.8	364	53.8
≥65 years	156	46.2	156	46.2	312	46.2
Age Median [Range] (years)	64 [22-85]		64 [28-89]		64 [22-89]	
Weight Median [Range] (kg)	74 [39-132]		73 [40-128]		73 [39-132]	
Gender						
Male	159	47.0	169	50.0	328	48.5
Female	179	53.0	169	50.0	348	51.5
Performance Status (ECOG)						
0	80	23.7	63	18.6	143	21.2
1	135	39.9	150	44.4	285	42.2
2	118	34.9	122	36.1	240	35.5
3 †	5	1.5	3	0.9	8	1.2
Tumor Type						
Solid Tumor	298	88.2	308	91.1	606	89.6
Gastrointestinal ‡	64	18.9	68	20.1	132	19.5
Breast	59	17.5	49	14.5	108	16.0
Lung	40	11.8	50	14.8	90	13.3
Prostate	25	7.4	22	6.5	47	7.0
Brain	14	4.1	13	3.8	27	4.0
Cervix	14	4.1	10	3.0	24	3.6
Pancreatic *	13	3.8	16	4.7	29	4.3
Uterus	13	3.8	2	0.6	15	2.2
Ovary	11	3.3	16	4.7	27	4.0
Bladder	10	3.0	19	5.6	29	4.3
Testicle	1	0.3	2	0.6	3	0.4
Other	33	9.8	42	12.4	75	11.1
Hematological Tumor	40	11.8	30	8.9	70	10.4
Non-Hodgkin's Lymphoma	22	6.5	15	4.4	37	5.5
Hodgkin's Lymphoma	5	1.5	2	0.6	7	1.0
Leukemia	8	2.4	4	1.2	12	1.8
Multiple myeloma	4	1.2	8	2.4	12	1.8
Solid Tumor Status						
No evidence of tumor	36	(12.1) §	33	(10.7) §	69	(11.4) §
Localized at primary site, no evidence of metastases	39	(13.1) §	43	(14.0) §	82	(13.5) §
Metastatic	223	(74.8) §	232	(75.3) §	455	(75.1) §
Hematological Tumor Status						
Not in Complete Remission	38	(95.0) ¶	29	(96.7) ¶	67	(95.7) ¶
Complete Remission	2	(5.0) ¶	1	(3.3) ¶	3	(4.3) ¶
Tumor Treatment (last 6 weeks)						
Antineoplastic Treatment	217	64.2	194	57.4	411	60.8
Palliative Treatment	54	16.0	50	14.8	104	15.4
Radiotherapy	58	17.2	56	16.6	114	16.9
Surgery	37	10.9	50	14.8	87	12.9
None	55	16.3	64	18.9	119	17.6

Abbreviations: ECOG = Eastern Collaborative Oncology Group; OAC = oral anticoagulant

† Patients with ECOG performance status of 3 were enrolled prior to Amendment 3 and therefore were eligible.

‡ Gastrointestinal tumors include: colorectal, colon, duodenum, rectal, esophageal, stomach, gastroesophageal, and gastric cancers. Figures reported in the table include also those tumor types reported under "Other" tumor

* Figures reported in the table include also 1 patient in the dalteparin arm and 1 patient in the OAC arm who were reported under "Other" tumor

§ Percentage was calculated versus the number of patients with solid tumors

¶ Percentage was calculated versus the number of patients with hematologic tumors

Source: Tables T2.1, T2.2, T2.6, T2.8, T2.9, T2.10, T2.11 from CLOT CSR

4.3.2. Anticoagulant Therapy (Duration of Therapy)

The duration of treatment was slightly longer in the dalteparin patients than in the OAC patients [median (range): 176 (1-205) days versus 167 (1-237) days, respectively]. Overall, 180 patients in the dalteparin arm and 163 patients in the OAC arm completed the full 6 months of treatment. The most common reasons for discontinuation of study medication were death and confirmed acute VTE. Reasons for all discontinuations are shown in Table 3.

Table 3. Reasons for Discontinuation of Study Medication (As-treated Population)

	Dalteparin sodium N=338		**OAC N=335**		**Total N=673**	
	N	%	N	%	N	%
Patients who completed treatment	180	53.3	163	48.7	343	51.0
Patients who discontinued	158	46.7	172	51.3	330	49.0
Death	56	16.6	24	7.2	80	11.9
Underlying cancer	52	15.4	17	5.1	69	10.3
Fatal PE	3	0.9	5	1.5	8	1.2
Fatal bleeding	1	0.3	0	0.0	1	0.1
Other	0	0.0	2	0.6	2	0.3
Confirmed acute VTE	21	6.2	47	14.0	68	10.1
DVT	12	3.6	35	10.4	47	7.0
PE	7	2.1	10	3.0	17	2.5
CVT of upper limb	2	0.6	2	0.6	4	0.6
Contraindication to anticoagulation	12	3.6	25	7.5	37	5.5
Bleeding	10	3.0	19	5.7	29	4.3
Other	1	0.3	6	1.8	7	1.0
Missing	1	0.3	0	0.0	1	0.1
Adverse event	17	5.0	19	5.7	36	5.3
Abnormal bloodwork	4	1.2	4	1.2	8	1.2
Abnormal investigation results	1	0.3	1	0.3	2	0.3
Patient decision / withdrawal of consent	20	5.9	14	4.2	34	5.1
Other	27	8.0	38	11.3	65	9.7
Underlying cancer	17	5.0	21	6.3	38	5.6
Investigator decision	1	0.3	5	1.5	6	0.7
Patient unable to swallow	0	0.0	4	1.2	4	0.6

Source: Table T1.4 and Appendices 3.1.1, 3.1.2, 3.6.3 of CLOT Clinical Study Report

Overall, the OAC-treated patients were considered to have received adequate anticoagulation as the INR was >2.0 for 76% of the total treatment time. For the OAC-treated patients, the mean proportion of total treatment time within, above and below the INR therapeutic range was 51.4%, 24.6% and 24.0% respectively. Of note, the distribution of the mean proportion of total treatment time above, below or within the INR therapeutic range did not differ between the OAC patients with and without a recurrent VTE and was comparable to that reported in other trials of long-term OAC in patients with VTE (Prandoni, 2002; Hutten, 2000).

4.3.3. Efficacy

Efficacy results were summarized and analysis conducted on the Intent-to-Treat (ITT) population, defined as all randomized subjects.

4.3.3.1. Primary Efficacy Endpoint: Recurrent Venous Thromboembolism

4.3.3.1.1. Primary Analysis

A total of 27 (8.0%) dalteparin patients and 53 (15.7%) OAC patients, experienced at least 1 adjudicated, symptomatic DVT and/or PE during the 6 month treatment period (see Table 4 and Figure 2). The primary comparison of the time to first VTE recurrence over the 6 month treatment period was highly significant in favor of dalteparin (two-sided log-rank test, p=0.0017), and the estimated cumulative probability of recurrence at 6 months was reduced from 0.172 in the OAC arm to 0.087 in the dalteparin arm. The reduction of the risk of VTE recurrence over 6 months was 52% in the dalteparin arm relative to the OAC arm (Hazard Ratio (HR)=0.48; 95% CI, 0.30-0.77).

Nearly one third of the subjects in each group (111 dalteparin and 97 OAC) died without having a VTE and were thus censored at the time of death in the analysis of time to first VTE. In both arms 95% of the deaths were adjudicated to have been caused by underlying cancer. The potential impact of this censoring on the analysis of this endpoint is discussed further in Section 4.4.3.

Table 4. Timing of First VTE (Intention-to-Treat population)

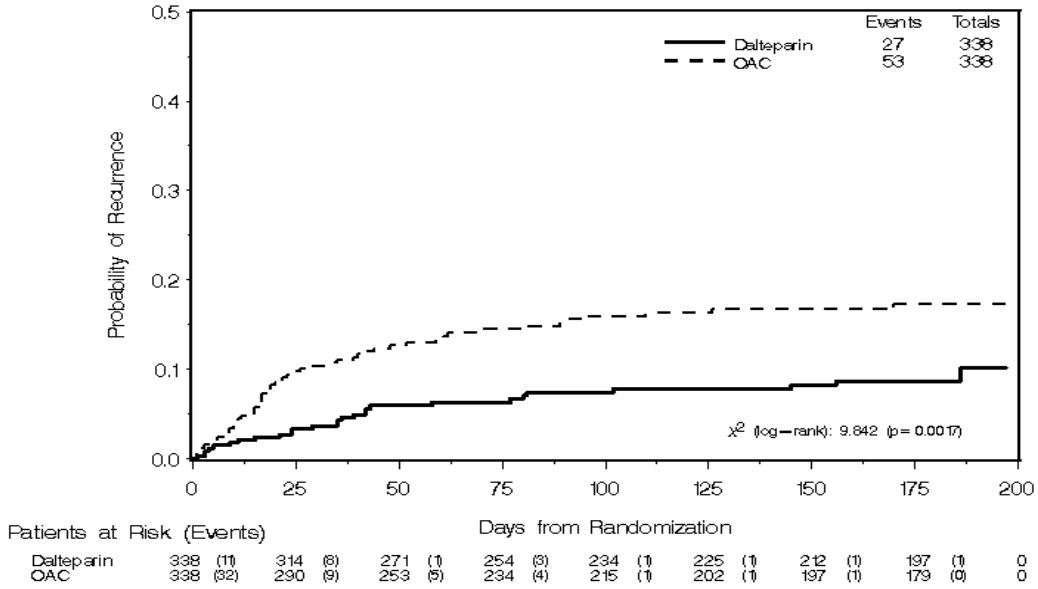
Study Period	**DALTEPARIN**			**OAC**		
	Dalteparin 200 IU/kg (max. 18,000 IU) sc qd x 1 mo, then 150 IU/kg (max. 18,000 IU) s.c. dq x 5 mo			**Dalteparin 200 IU/kg (max 18,000 IU) s.c. qd x 5-7 d and OAC for 6 mo (target INR 2.0-3.0)**		
	Number at Risk	**Patients with VTE**	**%**	**Number at Risk**	**Patients with VTE**	**%**
Total	338	27	8.0%	338	53	15.7%
Week 1	338	5	1.5%	338	8	2.4%
Weeks 2-4	331	6	1.8%	327	25	7.6%
Weeks 5-28	307	16	5.2%	284	20	7.0%

* Three patients in the Dalteparin group and 5 patients in the OAC group experienced more than 1 VTE over the 6 month study period

Source: Pfizer data on file

During the first week of anticoagulation treatment in which both groups were treated with dalteparin, there were 5 (1.5%) and 8 (2.4%) VTE in the dalteparin and OAC arms, respectively. Over the first 4 weeks, the incidence of recurrent VTE was less in the dalteparin arm (11 events) compared to the OAC arm (33 events). The major difference in favor of dalteparin evolved over the first 6 weeks of treatment, and was maintained throughout the six months of the study. The timing of VTE recurrences by treatment is shown by 25-day intervals under Figure 2.

Figure 2. Time to First Recurrent Adjudicated-Positive VTE during the 6 Month Study Period - Kaplan-Meier Curves (ITT Population)



Source: Figure F5.1 of CLOT Clinical Study Report

4.3.3.1.2. Supportive Analyses

A number of supportive analyses were conducted on the primary endpoint of time to recurrent VTE to demonstrate the robustness of the primary analyses.

Cox Proportional Hazards Models

A Cox model was used to explore the influence of potential prognostic factors on treatment difference for the primary efficacy outcome. Prognostic factors that were considered for the COX model are listed in Table 5. In the initial univariate analyses, the type of qualifying thrombotic event at study entry (i.e. DVT or PE ± DVT), as well as chronic (i.e. chronic immobilization, paralysis) or transient (i.e. surgery within the last 12 weeks, major trauma) risk factors, did not influence the risk of first VTE recurrence at 6 months. In addition, country did not influence the risk of first VTE recurrence (Table 5).

The variables selected for inclusion in the multivariate Cox model are shown in Table 6. The results obtained from this model supported the primary analysis and showed that the treatment effect of dalteparin remained highly significant after adjusting for factors found to be prognostic for outcome. The adjusted hazard ratio of dalteparin to OAC for recurrent VTE was 0.509 (95% CI: 0.319-0.812).

In the multivariate analysis (Table 6), the risk of first VTE recurrence over 6 months was lower in the patients with no evidence of metastasis as compared with patients with metastatic disease (p=0.004). The type of primary tumor also seemed to be a predictive factor of VTE recurrence; patients with lung or gastrointestinal cancer showed a higher risk

of developing a VTE recurrence than patients with breast cancer. Age was also predictive of VTE recurrence; the risk was significantly higher in younger patients (p=0.005).

Table 5. Recurrence Rate According to Prognostic Factors (ITT Population)

		Dalteparin (N=338)			OAC (N=338)		
Factors	**Category**	**Pts at risk**	**Pts with VTE**	**Rate**	**Pts at risk**	**Pts with VTE**	**Rate**
Race	White	**322**	**26**	**8.1**	**322**	**51**	**15.8**
	Non-White	**16**	**1**	**14.3**	**16**	**2**	**12.5**
Age at entry (years)	<50	48	7	14.6	53	14	26.4
	50-<60	84	8	9.5	75	10	13.3
	60-<70	103	10	9.7	96	18	18.8
	≥70	103	2	1.9	114	11	9.6
Gender	Male	159	15	9.4	169	33	19.5
	Female	179	12	6.7	169	20	11.8
Country	Canada	126	10	7.9	129	20	15.5
	United States	58	3	5.2	60	8	13.3
	Italy	34	4	11.8	33	4	12.1
	Australia/New Zealand	81	7	8.6	79	18	22.8
	The Netherlands	22	2	9.1	19	2	10.5
	Spain	16	1	6.3	17	1	5.9
ECOG Performance Status	0	80	7	8.8	63	7	11.1
	1	135	8	5.9	150	21	14.0
	2	118	12	10.2	122	24	19.7
	3	5	0	0.0	3	1	33.3
Type of tumor	Hematological	40	4	10.0	30	0	0.0
	Solid tumor	298	23	7.7	308	53	17.2
Type of solid tumor	Breast	59	2	3.4	49	2	4.1
	Gastrointestinal	79	7	8.9	85	14	16.5
	Lung	40	5	12.5	50	18	36.0
	Genitourinary	77	4	5.2	78	10	12.8
	Other	43	5	11.6	46	9	19.6
Extent of solid tumor	Non metastatic	75	3	4.0	76	5	6.6
	Non metastatic including hematological §	115	7	6.1	106	5	4.7
	Metastatic	223	20	9.0	232	48	20.7
Prior anti-neoplastic medication	Yes	217	17	7.8	194	28	14.4
	No	121	10	8.3	144	25	17.4
Prior radiotherapy	Yes	58	4	6.9	56	10	17.9
	No	280	23	8.2	282	43	15.2
Prior surgery	Yes	37	2	5.4	50	6	12.0
	No	301	25	8.3	288	47	16.3
Qualifying episode of VTE	DVT only	235	21	8.9	230	38	16.5
	PE ± DVT	103	6	5.8	108	15	13.9
Previous VTE	Yes	35	3	8.6	32	2	6.3
	No	303	24	7.9	306	51	16.7
Chronic risk factor	Yes	36	3	8.3	36	3	8.3
	No	302	24	7.9	302	50	16.6
Transient risk factor	Yes	134	11	8.2	136	15	11.0
	No	204	16	7.8	202	38	18.8
Other risk factor	Yes	64	6	9.4	51	8	15.7
	No	274	21	7.7	287	45	15.7
Currently smoke	Yes	33	6	18.2	42	11	26.2
	No	303	21	6.9	294	41	13.9

Abbreviations: CNS = central nervous system;
§ The level "non-metastatic" as reported in the CLOT clinical study report Table T6.5 also included the 70 patients with hematologic tumors (40 dalteparin patients; 30 OAC patients).

Table 6. Time-to-First VTE Recurrence at 6 Months – Results of Final Cox Model (ITT Population)

Factors	Category	Risk Ratio	95% CI	p value
Treatment	Dalteparin versus OAC	0.509	(0.319, 0.812)	0.005
Age at baseline	Continuous	0.973	(0.955, 0.992)	0.005
Type of tumor	GI versus Breast	4.562	(1.347, 15.444)	0.015
	Lung versus Breast	9.424	(2.802, 31.694)	<0.001
	GU versus Breast	3.033	(0.868, 10.596)	0.082
	Hematological versus Breast	4.740	(0.934, 24.064)	0.061
	Other versus Breast	6.553	(1.879, 22.856)	0.003
Extent of tumor	Non metastatic versus metastatic	0.334	(0.158, 0.706)	0.004
Currently smoke	Yes versus No	1.627	(0.931, 2.843)	0.088

Source: CLOT Clinical Study Report, Table T6.1.1. GI = gastrointestinal; GU = genitourinary.

Approximately 90% of the patients entered into the study had a solid tumor diagnosis and the remaining 10% of patients had a hematological malignancy. Therefore, the Cox model was reproduced for those patients with a solid tumor, in an attempt to increase homogeneity in the evaluation of the prognostic factors. The results of the model performed in the solid tumor patients only were comparable with those obtained for the overall population.

Subgroup Analyses

The CLOT study was designed to examine the safety and efficacy of dalteparin and OAC in a variety of cancer patients. The inclusion criteria in the study did not specify the type or extent of the cancer, and the randomization was not stratified by these variables. Hence analyses of particular tumor types or characteristics do not have adequate power to draw specific conclusions. An examination of subgroups can still be of interest in supporting the overall conclusions of the efficacy of dalteparin, but when the number of events are small the results must be interpreted with caution. Table 5 summarizes the rate of VTE recurrence according to a variety of patient and tumor characteristics.

The vast majority of subjects had solid tumors, and across the different types of solid tumors the rates of VTE recurrence for the dalteparin group were consistently lower than for the OAC group. A relatively small number of subjects (40 dalteparin and 30 OAC) had hematologic tumors, and only 4 (all in the dalteparin group) reached the primary endpoint of VTE. These numbers are too small to reach any conclusions.

The majority of subjects in the CLOT study with solid tumors had metastatic disease, and the results for this group were consistent with the overall results. The results for patients with non-metastatic solid tumors were in the same direction, but the number of events were small (3 and 5 in the dalteparin and OAC groups, respectively). When the subjects with hematological cancers are included in the number with non-metastatic disease, the rate of VTE in the dalteparin group is somewhat higher than in the OAC group, but the numbers of events (7 and 5 in the dalteparin and OAC groups, respectively) are still small.

The vast majority of subjects enrolled in the CLOT study were white. The number of non-whites (16 in each group) and the small number of events (1 on dalteparin and 2 on OAC) do not allow conclusions to be drawn about the efficacy of dalteparin in this subgroup.

4.3.3.2. Secondary Endpoints

4.3.3.2.1. Symptomatic Lower Limb DVT, PE, or new Central Venous Thrombosis (CVT)

Diagnosis of a new CVT was combined with the primary composite outcome events for a new composite endpoint, resulting in 2 and 1 events being added to the dalteparin and OAC arms respectively. The estimated probability of first recurrent symptomatic composite endpoint of DVT, PE or new CVT at 6 months was reduced from 0.175 in the OAC arm to 0.095 in the dalteparin arm. The time to first occurrence of this endpoint over the 6-month study period was highly significant in favor of dalteparin treatment (2-sided log-rank test, p=0.0028).

4.3.3.2.2. Other Secondary Endpoints

A total of 231 (90.6%) of 255 eligible subjects were assessed on Quality of Life, 116 in the dalteparin arm and 115 in the OAC arm. In the subset of patients completing a baseline and at least one on-treatment assessment (75% dalteparin patients and 69.5% OAC patients), there were changes in several of the scales measured by the EORTC QLQ C-30 (Aaronson et al 1993) during the treatment period. Generalized conclusions could not be drawn given the limited sample size from a single country, the multiplicity of testing, and the confounding effect of concomitant medications and interventions.

Secondary endpoints of bleeding and death are described in the next section.

4.3.4. Safety

Safety results for the CLOT Study are reported for the As-Treated population, defined as all subjects who received at least one dose of study medication. Three patients randomized to the OAC arm did not receive study medication. Hence safety information was summarized for 338 and 335 patients, in the dalteparin and OAC groups, respectively.

4.3.4.1. Bleeding

A Central Adjudication Committee (CAC) reviewed all bleeding events that occurred during treatment and within 48 hours of permanent discontinuation of study medication over the 6 month study period. Bleeding events not occurring within this time frame were excluded from the secondary endpoint analysis but were included as adverse events. Bleeding events were adjudicated into 2 categories.

- Major Bleeds (bleeding events that met the pre-specified criteria for major bleeding), or
- Any Bleed (bleeding events that met the pre-specified criteria for major or minor bleeding)

A bleeding event was considered major if it: 1) was accompanied by a decrease in hemoglobin of ≥ 2 g/dL in connection with clinical symptoms; 2) occurred at a critical site

(intraocular, spinal/epidural, intracranial, retroperitoneal, or pericardial bleeding); 3) required transfusion of ≥ 2 units of blood products; or 4) led to death. Minor bleeding was classified as clinically overt bleeding that did not meet criteria for major bleeding.

4.3.4.1.1. Major Bleeding

Nineteen dalteparin patients (5.6%) experienced 22 major bleeding events and 12 OAC patients (3.6%) experienced 13 major bleeding events during treatment (Table 7). The time to the first occurrence of a major bleeding event did not differ significantly between the two treatments (two-sided log-rank test, p=0.28). One fatal bleeding event (hemoptysis in a patient with lung cancer) occurred during treatment in the dalteparin arm. Four dalteparin and 3 OAC patients developed major bleeding events in clinically critical sites (i.e. retroperitoneal, intracranial, intraspinal, intraocular, and pericardial; and 10 dalteparin (2.9%) and 5 OAC patients (1.5%) permanently discontinued treatment due to a major hemorrhagic event. In the dalteparin arm, the single fatal bleeding event and the four critical-site bleeding events were associated with the anatomic location of the patient's underlying tumor. In the OAC arm, there was no obvious association between the primary tumor location and the critical bleeding site.

Table 7. Frequency of Adjudicated Major Bleeding Events during Treatment (As-treated Population)

	Dalteparin N=338		**OAC N=335**	
	n	%	n	%
At least one major bleeding event	19	5.6	12	3.6
Fatal bleeding event §	1	0.3	0	0.0
Critical sites ‡	4	1.2	3	0.9
Retroperitoneal	2	0.6	1	0.3
Intracranial	1	0.3	2	0.6
Pericardial	1	0.3	0	0.0
Other	15	4.4	9	2.7

§ Fatal bleeding event: Patient 701-004 (hemoptysis)
‡ Critical sites were defined a priori as: retroperitoneal, intracranial, intraspinal, intraocular, and pericardial

Source: Table T8.2 of CLOT Clinical Study Report

Most of the OAC patients who experienced a major bleeding event had an INR measurement at the time of the occurrence; 7 of the 13 major bleeding events occurred when the INR was within or below the therapeutic range of 2.0-3.0. Four of the major bleeding events in the OAC arm occurred during the first week of treatment. The majority of major bleeding events in the dalteparin arm occurred in the first month of treatment, in the period where patients received 200 IU/kg, SC daily (13 patients in Month 1 versus 9 patients in Months 2-6).

4.3.4.1.2. Any Bleeding

A total of 63 and 71 bleeding episodes (major or minor) occurred in the dalteparin and in the OAC arm respectively: 12 patients in the dalteparin arm and 6 patients in the OAC arm experienced multiple episodes of bleeding during treatment (in the dalteparin arm 8 patients

had two episodes, 3 patients had three episodes and 1 patient had 4 episodes; in the OAC arm 4 patients had two episodes and 2 patients had three episodes).

The proportion of patients with any bleeding (bleeding events that met the pre-specified criteria for major or minor bleeding) was higher in the OAC arm (18.5%) than the dalteparin arm (13.6%), two-sided log-rank test, p=0.049 (Table 8). The difference in the occurrence of any bleeding event in favor of dalteparin became evident after approximately 3 months of treatment.

A Cox model was used to explore the influence of potential prognostic factors on the time to first bleeding event, including the adjudicated major and minor events. When adjusted for baseline factors found to be prognostic for any bleeding, the hazard ratio of dalteparin to OAC for the occurrence of any bleeding was 0.625 (95% CI: 0.417-0.938; p=0.023). This result was mainly due to adjustment for the value of creatinine at baseline (abnormal versus normal values).

Table 8 summarizes by treatment the number of patients with major and any bleeding events during treatment intervals of 1 week, 2-4 weeks, and 5-28 weeks. During the second through fourth weeks of treatment, major bleeding was experienced by more patients in the dalteparin arm [9/332 (2.7%)] than by patients in the OAC arm [1/321 (0.3%)]. Only one bleeding event (hemoptysis in a patient in the DALTEPARIN arm at Day 71) was fatal.

Table 8. Timing of Bleeding Events (Major and Any) (As Treated population)

Study period	DALTEPARIN 200 IU/kg (max. 18,000 IU) sc qd x 1 mo, then 150 IU/kg (max. 18,000 IU) s.c. qd x 5 mo			OAC Dalteparin 200 IU/kg (max 18,000 IU) s.c. qd x 5-7 d and OAC for 6 mo (target INR 2.0-3.0)		
	Number at risk	Patients with Major Bleeding*	Patients with Any Bleeding*	Number at risk	Patients with Major* Bleeding	Patients with Any Bleeding*
Total during study	338	19 (5.6%)	46 (13.6%)	335	12 (3.6%)	62 (18.5%)
Week 1	338	4 (1.2%)	15 (4.4%)	335	4 (1.2%)	12 (3.6%)
Weeks 2-4	332	9 (2.7%)	17 (5.1%)	321	1 (0.3%)	12 (3.7%)
Weeks 5-28	297	9 (3.0%)	26 (8.8%)	267	8 (3.0%)	40 (15.0%)
* Patient with multiple bleeding episodes with any time interval were counted only once in that interval. Patients with bleeding events in multiple intervals are counted once in each interval						

Source: Pfizer data on file

4.3.4.2. Mortality

The CAC adjudicated all deaths that occurred during the 6-month treatment period and categorized the cause of death as (1) underlying cancer, (2) fatal PE, (3) fatal bleed, or (4) other.

The reasons for deaths occurring from 6 to 12 months after randomization were determined by the investigators, and are grouped in categories that differ from those used by the CAC.

4.3.4.2.1. Mortality During 6-Month Treatment Period

During the 6-month treatment period there were 131 deaths in the dalteparin arm and 137 deaths in the OAC arm; the majority in both groups (90.8% and 90.5%, respectively) were adjudicated as due to the underlying cancer (Table 9). The overall survival during this period was not different between treatment groups (log rank test, p=0.56) (Figure 3). The frequency of death due to non-cancer related reasons was low and comparable between the 2 arms [12 of 338 dalteparin patients (3.6%); 13 of 335 OAC patients (3.9%)]. Fatal PE was the adjudicated cause of death in 6 dalteparin and 8 OAC patients; 1 dalteparin and 1 OAC patient experienced fatal PEs after having a first recurrence of VTE, hence these fatal PEs were not included in the primary analysis. Fatal bleeding was the cause of death in 3 dalteparin (1 hemoptysis, 1 cerebellar hemorrhage, and 1 gastrointestinal hemorrhage) and 1 OAC patient.

Eighty subjects were categorized has having died while "on-treatment" (defined as within 1 day after last dose of study medication), 59 (17.5%) in the dalteparin arm and 21 (6.3%) in the OAC arm. Additional analyses conducted to better understand this difference are discussed in Section 4.4.2. The frequency of "on-treatment" deaths due to non-cancer related reasons was low [5 dalteparin patients (1.5%); 7 OAC patients (2.1%)]. PE was fatal in 4 dalteparin and 5 OAC patients, and bleeding was the adjudicated reason of death in 1 dalteparin patient (hemoptysis).

4.3.4.2.2. Mortality During 12-Month Post-Randomization Period

During the 6-12 months survival assessment period there were an additional 59 deaths in the dalteparin arm and 57 deaths in the OAC arm (Table 9); as in the 6 month study period, the majority occurred due to reasons related to underlying cancer. The frequency of death due to non-cancer related reasons was low and comparable between the 2 arms during the 6-12 month interval period [14/338 dalteparin (4.1%) and 12/335 OAC patients (3.6%)]. During the post 6 month survival follow-up of the study, the non-cancer related reasons for death consisted mainly of infection (5 dalteparin and 3 OAC patients), renal disorders (3 dalteparin and 1 OAC patients), and cardiac disorders (3 dalteparin patients). One case of fatal bleeding occurred in the OAC arm.

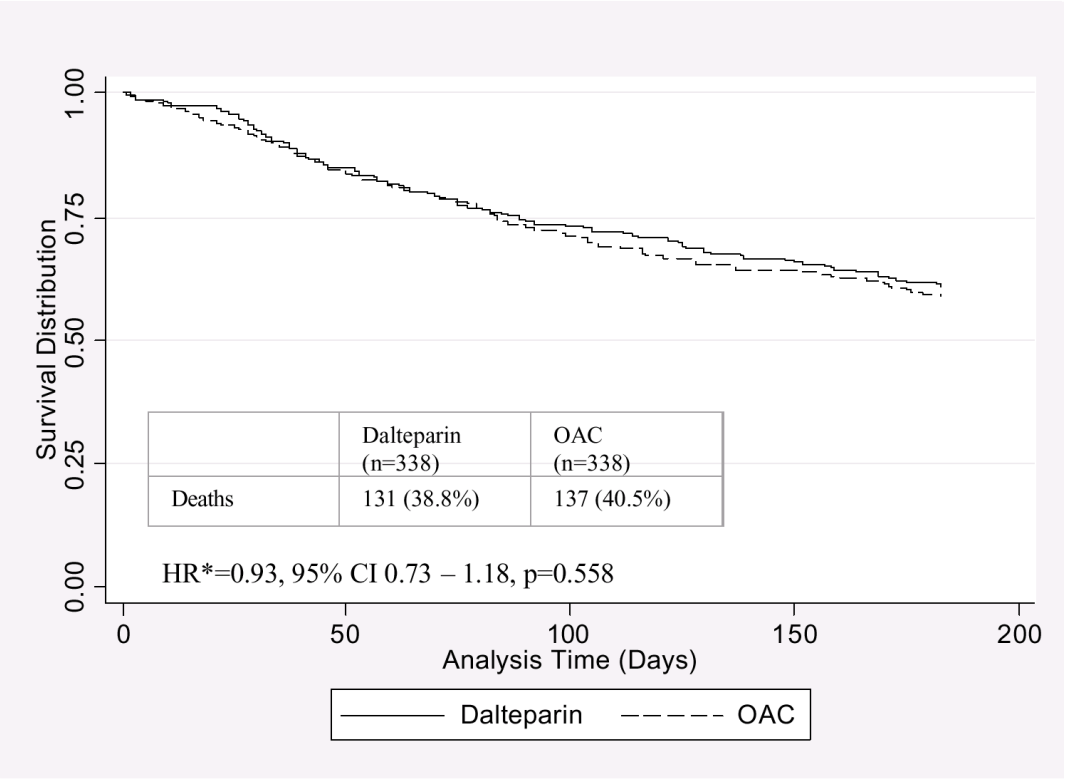
Overall, a total of 190 dalteparin patients (56.2%) and 194 OAC patients (57.9%) died over the entire 12 month period (Table 6), and the 12-month survival rate was similar between treatments (log rank test, p=0.57).

Table 9. Summary of Deaths (As-treated Population)

Primary Cause of Death	Dalteparin N=338						OAC N=335					
	On Treatment		Off treatment		Total		On Treatment		Off treatment		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Total	59	17.5	131	38.8	190	56.2	21	6.3	173	51.6	194	57.9
Patients with adjudicated cause of death (first 6 months)												
All	59	17.5	72	21.3	131	38.8	21	6.3	116	34.6	137	40.9
Underlying cancer	54	16.0	65	19.2	119	35.2	14	4.2	110	32.8	124	37.0
Fatal PE	4	1.2	2	0.6	6	1.8	5	1.5	3	0.9	8	2.4
Fatal bleed	1	0.3	2	0.6	3	0.9	0	0.0	1	0.3	1	0.3
Other	0	0.0	3	0.9	3	0.9	2	0.6	2	0.6	4	1.2
Patients without adjudicated cause of death (from 6 to 12 months)												
All	---	---	59	17.5	59	17.5	---	---	57	17.0	57	17.0
Underlying cancer	---	---	45	13.3	45	13.3	---	---	45	13.4	45	13.4
Infection	---	---	5	1.5	5	1.5	---	---	3	0.9	3	0.9
Cardiac disorders	---	---	3	0.9	3	0.9	---	---	0	0.0	0	0.0
Renal disorders	---	---	3	0.9	3	0.9	---	---	1	0.3	1	0.3
Respiratory disorders	---	---	1	0.3	1	0.3	---	---	1	0.3	1	0.3
Bleed	---	---	0	0.0	0	0.0	---	---	1	0.3	1	0.3
Other	---	---	1	0.3	1	0.3	---	---	3	0.9	3	0.9
Unknown	---	---	1	0.3	1	0.3	---	---	3	0.9	3	0.9

Source: Tables T7.13, Table T9.7 and Appendix 3.6.3 of CLOT Clinical Study Report.

Figure 3. Survival Distribution during Six-Month Treatment Period by Treatment ITT Population



* Treatment with OAC as reference

Source: Pfizer data on file

4.3.4.3. Adverse Events

The adverse event profile in both treatment arms was consistent with that expected in a clinical study enrolling cancer patients, many of whom were receiving concomitant cancer therapy and the majority of whom had metastatic disease.

The vast majority of patients reported at least 1 treatment-emergent adverse event, with a comparable frequency between the dalteparin and OAC arms (84.0% versus 85.5%, respectively). This high rate of adverse events seen in both groups is not surprising given that a majority of patients had advanced cancer. Overall, no major differences between the 2 treatments were apparent. In each treatment arm, events related to General Disorders and Administration Site Conditions, Gastrointestinal Disorders, and Investigations were the most frequently reported, affecting nearly 40% of patients. Within System Organ Classes, the most frequently reported adverse events were nausea (21.4% dalteparin and 17.5% OAC patients), vomiting (13.6% and 16.0%, respectively), and fatigue (16.0% and 18.7%, respectively). See Table 10.

Table 10. Frequency of Treatment-Emergent Adverse Events by System Organ Class - Any Drug Relationship, Worst CTC Grade by Patient (As-treated Population)

System Organ Class	Dalteparin N=337				OAC N=331			
	Any Grade		Grade ≥3		Any Grade		Grade ≥3	
	N	%	N	%	N	%	N	%
At least one adverse event	283	84.0	201	59.6	283	85.5	212	64.0
Blood and Lymphatic System Disorders	78	23.1	47	13.9	74	22.4	35	10.6
Cardiac Disorders	52	15.4	16	4.7	65	19.6	17	5.1
Ear and Labyrinth Disorders	10	3.0	2	0.6	7	2.1	2	0.6
Endocrine Disorders	0	0.0	0	0.0	2	0.6	0	0.0
Eye Disorders	10	3.0	3	0.9	11	3.3	4	1.2
Gastrointestinal Disorders	129	38.3	53	15.7	146	44.1	66	19.9
General Disorders and Administration Site Conditions	142	42.1	54	16.0	142	42.9	61	18.4
Hepato-biliary Disorders	33	9.8	10	3.0	35	10.6	10	3.0
Immune System Disorders	4	1.2	1	0.3	2	0.6	1	0.3
Infections and Infestations	83	24.6	33	9.8	90	27.2	41	12.4
Injury and Poisoning	20	5.9	7	2.1	20	6.0	7	2.1
Investigations	137	40.7	56	16.6	134	40.5	69	20.8
Metabolism and Nutrition Disorders	88	26.1	40	11.9	80	24.2	37	11.2
Musculoskeletal, Connective Tissue and Bone Disord.	90	26.7	22	6.5	81	24.5	20	6.0
Neoplasm Benign and Malignant	62	18.4	50	14.8	36	10.9	31	9.4
Nervous System Disorders	72	21.4	27	8.0	78	23.6	28	8.5
Psychiatric Disorders	49	14.5	14	4.2	37	11.2	19	5.7
Renal and Urinary Disorders	31	9.2	14	4.2	37	11.2	17	5.1
Reproductive System and Breast Disorders	9	2.7	2	0.6	10	3.0	1	0.3
Respiratory, Thoracic and Mediastinal Disorders	80	23.7	37	11.0	100	30.2	48	14.5
Skin & Subcutaneous Tissue Disorders	63	18.7	5	1.5	56	16.9	4	1.2
Social Circumstances	2	0.6	1	0.3	1	0.3	0	0.0
Surgical and Medical Procedures	23	6.8	16	4.7	25	7.6	17	5.1
Vascular Disorders	40	11.9	20	5.9	46	13.9	17	5.1

Abbreviations: OAC = oral anticoagulant
Source: Table T9.1 CLOT CSR

Serious adverse events (SAEs) were reported at similar frequencies in the dalteparin and OAC arms (47.2% versus 44.4%, respectively). In the majority of cases, the investigators and the Sponsor concluded that the event was not causally related to the study drug. A total of 37 patients in each arm (approximately 11%) experienced at least 1 SAE that was judged as study drug related in the clinical database.

A similar proportion of dalteparin and OAC treated patients were hospitalized at least once during the study (30.8% versus 28.1%, respectively).

At least 1 adverse event was reported to cause permanent discontinuation of the study drug in 63 (18.7%) and 62 patients (18.7%) in the dalteparin and OAC arm, respectively. A comparable number of patients in the 2 arms withdrew from treatment due to at least 1 drug-related adverse event (8.3% dalteparin patients and 8.8% OAC patients).

4.3.4.4. Clinical Laboratory Evaluation

No major difference was observed between the 2 treatments in the hematology findings. Only thrombocytopenia of any grade and, in particular, of grade 3 was reported in slightly more dalteparin than OAC patients (5.6% versus 3.0%, respectively). With the exception of the INR values for patients treated in the OAC arm, clinically relevant changes in coagulation parameters were not frequently observed. As expected, the INR values increased as soon as the OAC treatment started and mean values remained within the therapeutic range of 2.0-3.0 over time; INRs were not affected by dalteparin treatment.

Abnormalities of liver transaminases occurred in approximately 30-40% of patients. Grade 3-4 elevations• of ALT and AST occurred in 4.1% and 3.0% of patients respectively in the dalteparin group and 2.1% and 0.9% in the OAC group respectively.

4.3.4.5. Overdoses

Six dalteparin and 5 OAC patients mistakenly received higher than planned doses of dalteparin. These were mostly due to dose miscalculations. The highest dose allowed was 18,000 IU/day, but the actual doses received ranged from 23,400 to 100,000 IU/day. Approximately half of these patients received only 1 dalteparin overdose, usually during the initial treatment period, when patients were supplied with multi-dose vials of the drug. The clinical courses for the patients receiving overdoses was unremarkable except for 1 patient who experienced a major bleeding event (retroperitoneal hemorrhage) during concomitant OAC therapy; this patient also had a supra-therapeutic INR.

4.4. Interpretation and Discussion of Results

4.4.1. Efficacy of Dalteparin to Reduce the Recurrence of Symptomatic VTE

In the CLOT trial the reduction in VTE was apparent within the first 30 days of treatment and was maintained for the duration of the study. However, this raises the question of whether the early benefit is due to the higher dose of dalteparin in the first month of treatment.

Doses for use in the CLOT study were chosen after careful consideration of benefit and risk in the existing Sponsor database. Evidence from a number of published studies in the acute

• Grade 3 elevation: > 5 – 20 x Upper Limit of Normal (ULN); Grade 4 elevation: > 20 x ULN (NIC-CTC)

and long term VTE settings over more than a decade of experience were also considered. The risk of recurrence of VTE is highest in the first month (The Columbus Investigators, 1997; Koopman, 1996; Simonneau, 1997), a situation which is even truer in cancer patients (Prandoni, 2002). This increased risk is reflected in the dosing regimen that was developed for the use of dalteparin in acute VTE studies conducted over the previous 10 years. A series of pilot studies conducted by the Sponsor (see Appendix 2), and published reports by Meyer (1995) and Kuijer (1995), investigated the use of twice daily doses of 120 IU/kg SC dalteparin in the acute VTE setting. These studies were superseded by Sponsor study 91-96-544 which established the equivalent efficacy of a 200 IU/kg qD SC dosing regimen compared to a 100 IU/kg twice daily (BID) SC dosing regimen. Thus, in subsequent randomized studies by the Sponsor (93-96-549, 94-96-235 and 94-96-414), and Kovacs (2000, 2001), an initial dose of 200 IU/kg qD SC with concomitant OAC was employed in the acute period and this regimen was therefore selected for use in the CLOT study. The finding in the CLOT Study where benefit was mostly seen in the first 30 days of treatment reveals the veracity of this approach.

After 1 month, the 200 IU/kg qD SC dose used in the dalteparin arm of CLOT was lowered to 150 IU/kg SC qD. This reduction in dose is consistent with the lower risk of recurrent VTE seen in the chronic treatment period (Prandoni, 2002), coupled with the requirement to reduce the risk of bleeding in this susceptible population.

4.4.2. "On-Treatment" Mortality

As noted in Section 4.3.4.2.1, although the total 6 month mortality is almost identical in the two treatment groups, the distribution of the deaths differs between the treatment groups with respect to the 'on- and off- treatment' categorization specified in the statistical analysis plan. In this section the Sponsor will discuss the results of additional analyses and summaries conducted to demonstrate two major sources of bias in this "on-treatment" analysis: (1) informative censoring due to clinical management of terminal cancer patients, and (2) differences in the frequency of VTE recurrence.

It is useful to note that the vast majority of deaths in the first 6 months of study were judged by the blinded adjudication committee to be due to cancer (119/131 in the dalteparin arm and 124/137 in the OAC arm). Hence progression of the underlying cancer clearly plays a role in any discussion of mortality in this study.

4.4.2.1. Informative Censoring in "On-Treatment" Mortality

Figure 4 shows the Kaplan-Meir curves for the subset of events identified as "on-treatment" deaths. "On-treatment" deaths include all deaths out to 1 day after stopping study treatment. Thus, subsequent deaths are censored by this definition (Piantadosi, 2005).

The problem with this analysis is that this censoring is informative: the reason for a death being censored (e.g., study drug being discontinued) is related to the death itself, due to clinical management of the patients in the OAC arm. As cancer patients become sicker and approach death, they often have difficulty with oral intake, and INR management of the oral agent in these patients becomes clinically problematic. Oral anticoagulation treatment is

extremely difficult to manage in terminal patients. Frequent blood tests are required for adequate monitoring, and vomiting, liver dysfunction and drug interactions can lead to unpredictable levels of anticoagulation along with its attendant dangers, in spite of proper monitoring. In addition, the anticoagulant effect occurs more than 24 hours after dosing, making dose adjustment difficult and delaying the effect of dose discontinuation, especially dose discontinuation for a bleeding complication. Dalteparin, on the other hand, by virtue of its subcutaneous route of administration, its predictable anticoagulant response, its advantage of not requiring laboratory monitoring, and its lack of interaction with diet and other medications, allows cancer patients who are dying to continue anticoagulant therapy until they die or are in the very terminal stage. Moreover, for patients who wish to die at home, it is impossible to continue warfarin therapy because of the requirement for laboratory monitoring whereas treatment with dalteparin remains a viable treatment option, even in home or hospice setting. In the clinical setting, medical personnel would discontinue oral anticoagulants in patients who they deem terminal and often switch them over to parenteral agents like LMWH for ease of management and safety. Thus, more patients in the OAC arm would have tended to discontinue study drug before death than patients in the dalteparin arm, who received subcutaneous injections.

This explanation is supported by the data on reasons for discontinuation. Table 11 summarizes the reasons for discontinuation of study medication for those subjects who died more than one day after their last dose. The top portion of the table summarizes the reasons indicated by the investigator based on categories provided on the case report forms. The "other" category allowed the investigator to supply free text to specify the reason for discontinuation. The lower portion of the table summarizes the reasons for discontinuation based on a blinded (where possible) Sponsor review of the free text responses provided by the Investigators. In addition, predefined categories from the CRF were collapsed into similar concepts related to either the primary endpoint or issues related to clinical management of the patient. Reasons for discontinuation that were not related to one of the above concepts (e.g., patient withdrew consent, patient chooses not to continue) were re-categorized as "other". Categories created under the concept of "Clinical Management" were based on an examination of the free text reasons given by the investigator for discontinuation of study medication. Although conducted in a cancer population, the objective of the CLOT study was to assess the use of dalteparin and OAC for the prevention of recurrent VTE; it was not designed to assess any of the traditional endpoints used in the development of cancer drugs. Consequently, this study did not prespecify the capture of data specifically related to cancer progression.

As seen in Table 11, more OAC (67) than dalteparin (42) subjects were discontinued due to reasons related to clinical management. Specifically, more than twice as many OAC patients (26) were discontinued due to deterioration of their condition or inability to take their oral medication as dalteparin patients (12). All of these subjects are censored in the analysis of "on-treatment" mortality.

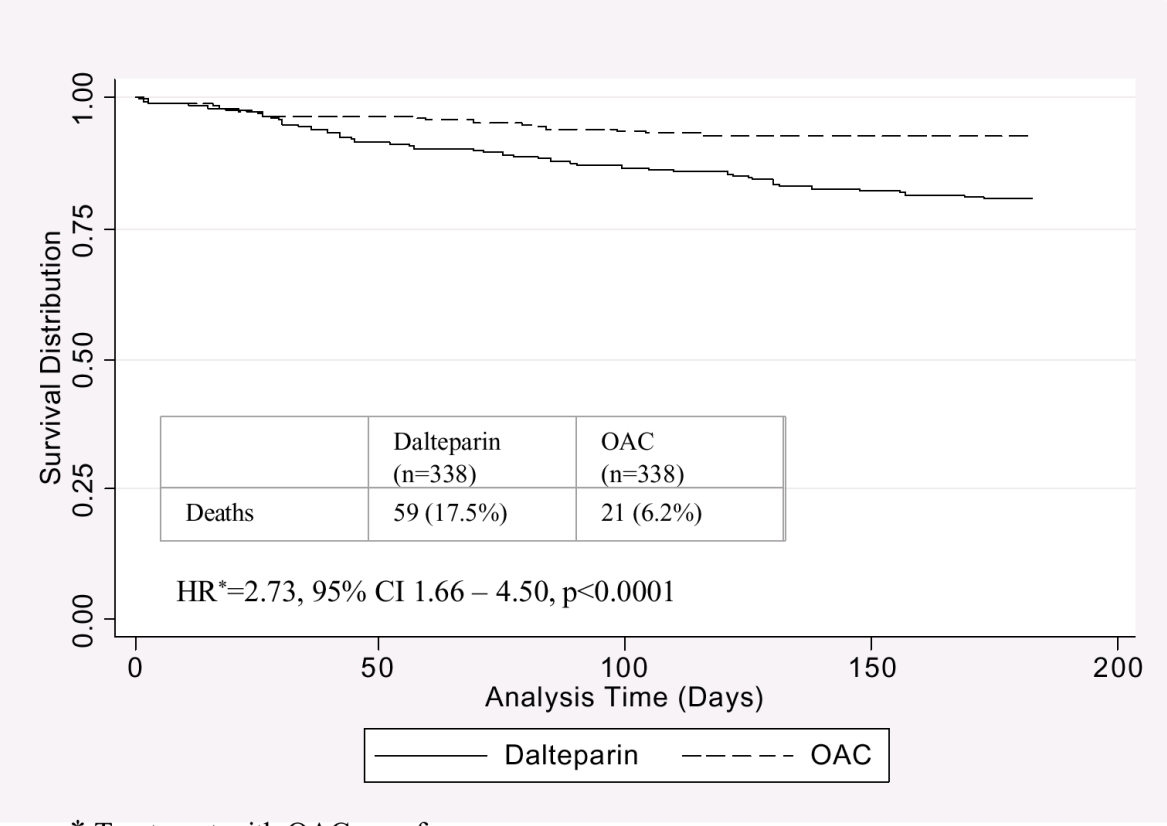
Table 11. Reasons for Discontinuation of Study Medication for Patients who Died "Off-Treatment"* During the 6 Month Treatment Period

	Dalteparin N=338	OAC N=335
	N (%)†	N (%)
Deaths 'Off-Treatment'	72 (21.3)	116 (34.6)
Reason for Discontinuation per Case Report Form		
Confirmed acute VTE	8 (2.4%)	27 (8.1%)
Confirmed acute PE	4 (1.2%)	5 (1.5%)
Confirmed central VT upper limb	0 (0.0%)	2 (0.6%)
Contraindication to anticoagulation	10 (3.0%)	15 (4.5%)
Adverse event	12 (3.6%)	15 (4.5%)
Abnormal blood work	2 (0.6%)	4 (1.2%)
Abnormal investigation result	1 (0.3%)	0 (0.0%)
Patient chooses to discontinue	10 (3.0%)	10 (3.0%)
Patient withdrew consent	2 (0.6%)	1 (0.3%)
Death	1 (0.3%)	5 (1.5%)
Other	21 (6.2%)	31 (9.3%)
Unknown	1 (0.3%)	1 (0.3)
Reason for Discontinuation as Categorized by Sponsor		
Primary endpoint	12 (3.6)	32 (9.6)
Central venous thrombosis	0 (0.0)	2 (0.6)
Clinical management	42 (12.4)	67 (20.0)
Cannot take PO medication	0 (0.0)	4 (1.2)
Deterioration in condition due to cancer / Impending death	12 (3.6)	22 (6.6)
Disease progression	5 (1.5)	4 (1.2)
Contraindication / abnormal blood work	12 (3.6)	21 (6.3)
Adverse event	13 (3.8)	16 (4.8)
Other‡	18 (5.0)	15 (4.5)

* "Off-Treatment" is defined as more than 1 day after the last dose of study medication.
† % is based on As Treated population
‡ Includes the following CSR defined categories: patient withdrew consent, patient chooses to discontinue, unknown, and "other" not reclassified elsewhere.
Source: Pfizer data on file

Further support for the argument that the "on-treatment" analysis of mortality is biased is found by examination of alternative definitions of "on-treatment." When the definition is expanded to include all deaths up to 14 days after discontinuation of study drug, as shown in Figure 5, the mortality difference is no longer significant. This sensitivity to the definition of "on-treatment" clearly demonstrates the significance of informative censoring.

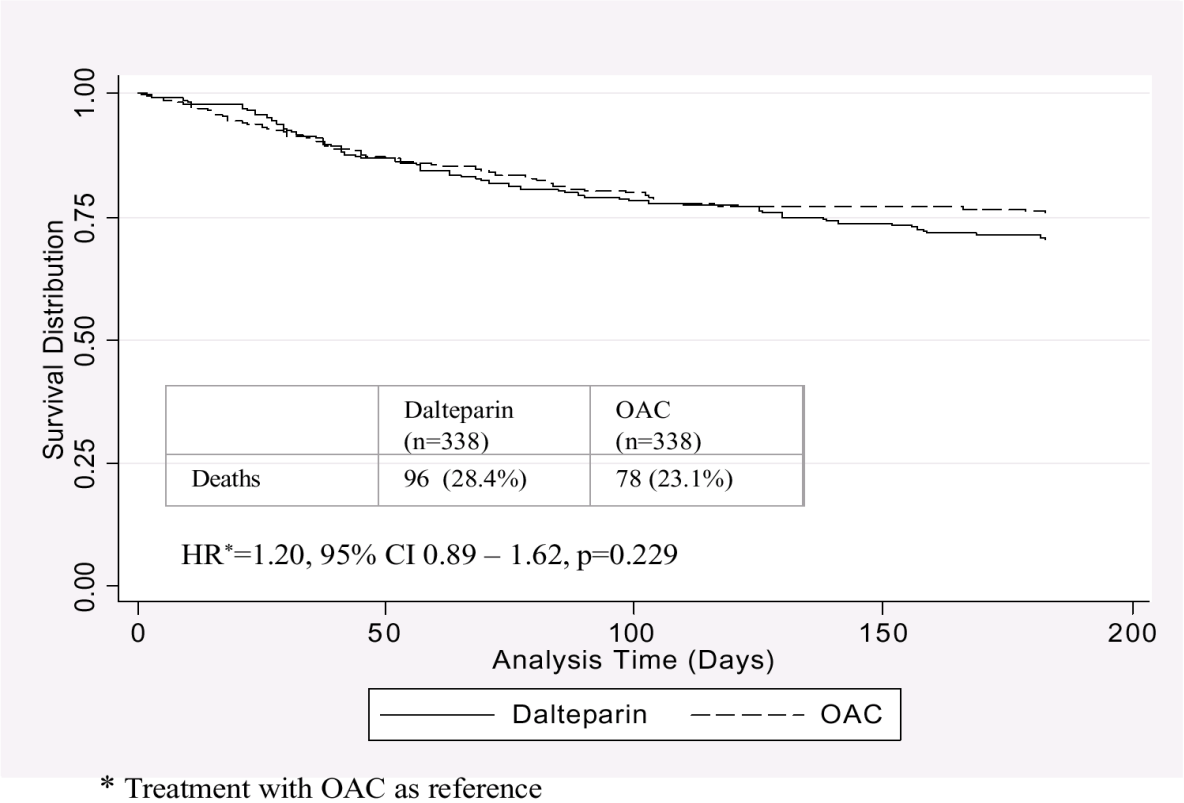
Figure 4. "On-Treatment" Survival Distribution During Six-Month Treatment Period By Treatment Observations Censored 1 Day Post-Treatment Withdrawal ITT Population



* Treatment with OAC as reference

Source: Pfizer data on file

Figure 5. "On-Treatment" Survival Distribution During Six-Month Treatment Period By Treatment Observations Censored 14 Days Post-Treatment Withdrawal ITT Population



* Treatment with OAC as reference

Source: Pfizer data on file

4.4.2.2. Differences in Frequency of Recurrent VTEs

The "on-treatment" analysis also suffers from an additional censoring bias. Study drug was discontinued for patients who developed recurrent VTEs or CVTs at the time of the event and consequently these patients are censored from the "on-treatment" mortality analysis. Hence the higher rates of VTE on the OAC arm than in the dalteparin arm corresponded to more deaths being censored in the OAC arm in the ""on-treatment"" analysis of mortality. Table 11 shows that 32 OAC but only 12 dalteparin patients were discontinued due to reaching the primary endpoint.

4.4.2.3. Conclusion Regarding "On-Treatment" Mortality

The Sponsor has demonstrated that the "on-treatment" analysis of mortality represents a biased estimate of the difference in the distribution of deaths in the two treatment groups. Hence, the 6 month overall mortality analysis presented in Figure 3 is the only valid way to assess mortality differences in the two treatment arms.

4.4.3. Robustness of the Analysis of the Primary Efficacy Endpoint

4.4.3.1. Censoring of VTEs Due to Death

The primary endpoint in the CLOT study, recurrent VTE, was selected so that the results would provide clear support for the most effective treatment used in this trial in cancer patients. There was no reasonable expectation that dalteparin would improve overall survival in this terminally ill population. However, because these patients represented a sick population, it was anticipated that a fair proportion of the patients would die of their underlying disease before experiencing the primary endpoint, and this was in fact the case. In order to focus specifically on these agents in the prevention of recurrent VTEs, patients who died without experiencing a VTE were censored on the date of death in the primary and supportive analyses of time to VTE. Hence it is important to consider the potential impact of those deaths on the analysis of time to VTE.

The Sponsor believes that the Intention-To-Treat (ITT) analyses over the 6-month study period of the CLOT Trial for the primary endpoint of venous thromboembolism (VTE) yields valid and unbiased results. The estimated hazard ratios (HR) for VTE are unbiased estimates of the relative event rates in the two treatment arms. Mortality is a competing risk with the occurrence of VTE and mortality censors the occurrence of VTE. However, the mortality censoring is noninformative with regard to the relative event rates of VTE in the two treatment groups.

The cumulative 6-month mortality is very similar in the two treatment groups and as shown in Figure 3 the survival curves show no difference at any time over the 6-month observation period. Thus, the censoring of VTE over the 6-month observation period due to mortality is the same in the two treatment groups. Under this condition, for censoring due to mortality to bias the relative hazard rate of VTE, it would have to affect the probability of VTE differentially in the treatment groups. There is no *a priori* reason to suspect a differential effect and it is not plausible when the cause of death (primarily underlying disease) is also similar in the two treatment groups.

Although there is no plausible reason for a differential effect, it is useful to examine hypothetical biases of this type in order to show the robustness of the CLOT efficacy results. The details of this analysis are provided in Appendix 3. These hypothetical cases show that even under strong assumptions of informative censoring the dalteparin benefit on VTE remains significant.

4.4.3.2. Subgroup Analyses

As discussed in Section 4.3.3.1.2, although the CLOT study was not designed to address questions about specific tumor types or underlying disease characteristics, the rate of recurrent VTE was higher for patients treated with OAC than those treated with dalteparin in most of the subgroups examined. One exception was in the comparison of the two treatments

when patients with non-metastatic solid tumors were combined with hematological cancers, although the numbers of VTEs were small (7/115, 6.1% and 5/106, 4.7% in the dalteparin and OAC groups, respectively). The Sponsor has committed to conducting one additional post-approval study in patients with non-metastatic solid cancers and VTE.

4.4.3.3. Conclusion on the Robustness of the Analysis of the Primary Efficacy Endpoint

The analysis of the primary endpoint in the CLOT study, recurrent VTE, provides robust support for the efficacy of dalteparin in cancer patients.

4.5. Conclusions of the CLOT Study

Results from the CLOT study demonstrate that a regimen of dalteparin (200 IU/kg qD for 1 month, then 150 IU/kg qD for up to 5 months) is effective in reducing the recurrence of VTE in cancer patients. The main conclusions from the CLOT study are:

- There was a clinically important reduction (52%) in the risk of symptomatic VTE recurrence when compared to OAC treatment - a result that was highly significant (p=0.0017). The treatment effect of dalteparin also remained highly statistically significant after adjusting for factors found to be prognostic for outcome.

- Results from the secondary composite endpoint of the first recurrent symptomatic DVT, PE, or CVT at 6 months further supported the results of the primary efficacy endpoint.

- No difference in survival was found between treatments in either the 6 month treatment period or the 12 month post-randomization period.

- Overall the incidence of bleeding was similar between the two groups. The difference in the incidence of major bleeds was not statistically significant.

5. SUMMARY & CONCLUSIONS

5.1. Discussion

General Principles of Trial Design

The essentials of an adequate and well-controlled clinical trial, as recognized by the scientific and medical community, include clearly defined objectives, a design that permits a valid comparison with an appropriate control to provide quantitative assessment of drug effect, a method of selection of subjects which ensures that subjects have the disease being studied, a method of assigning patients to treatment and control groups which minimizes bias, measures to minimize bias on the part of subjects, observers and analysts (e.g., blinding), well defined and reliable assessment of subjects' response and analysis of results adequate to assess effects of the drug, including appropriate statistical methods.

The CLOT Trial: Assessment of Strengths and Potential Limitations

The CLOT Study was a randomized, open-label, controlled, multicenter, multinational study in patients with active malignancy and documented VTE. The Sponsor believes that this study is an adequate and well-controlled trial and provides sufficient evidence to support the proposed indication for the following reasons (also discussed in detail in Section 4):

- The study had a clear objective to compare the efficacy and safety of long-term dalteparin treatment to long-term OAC therapy in cancer patients with acute, symptomatic DVT, PE or both, as well as a clear method of analysis.

- Patients selected were required to have a documented active malignancy and have had experienced an acute, symptomatic, objectively verified DVT and/or PE.

- The dose of dalteparin and the duration of treatment were selected based upon data demonstrating that the increased risk of recurrence of VTE is highest in the first month after initial occurrence, the efficacy of dalteparin 200 IU/Kg in the treatment of acute VTE (see Section 4.2.4.3), and the increased risk of VTE recurrence in patients with cancer compared to patients without cancer (see Section 3.3)

- Patients were randomly assigned to each treatment group by a centralized procedure stratified with regard to study sites.

- In order to minimize bias, an independent blinded Central Adjudication Committee reviewed and adjudicated all the primary and secondary outcome events, including VTEs, deaths and bleeding events.

- Analysis of results based on methods outlined in a prespecified statistical analysis plan demonstrated a 52% reduction in the risk of symptomatic VTE recurrence when compared to OAC treatment (p=0.0017). The treatment effect of dalteparin also remained statistically significant after adjusting for factors found to be prognostic for outcome.

Potential limitations of the trial include the open label design and the use of dalteparin in both arms for the initial 5 days of treatment. The rationale for these aspects of the study design are as follows:

- Although blinding of patients and investigators is as an optimal strategy to minimize bias, this study was designed as an open-label study because of the nature of the study population. The Sponsor found double-blinding difficult to justify in patients whose quality of life may already be compromised from cancer. As noted above, in order to reduce bias, all primary and secondary outcomes were adjudicated by a Central Adjudication Committee blinded to treatment assignment.

- The CLOT Steering Committee carefully considered whether to adopt UFH or a comparator LMWH as acute therapy in the control arm. However, the use of UFH or a comparator LMWH was ultimately not adopted because the introduction of additional

variables may have had a confounding effect on the interpretation of study results, there were no LMWHs approved for use in cancer patients and dalteparin had been documented to be effective in this setting (see Section 4.2.4.3).

CLOT Results and Interpretation of Mortality Data

As described in detail in Section 4.4, the effect of dalteparin on the primary endpoint VTE was statistically significant, with a 52% relative reduction in risk of VTE in the dalteparin group compared to the OAC group. Although there was no expectation that dalteparin would increase survival in this group of patients with cancer, mortality was a secondary endpoint. In the ITT analysis of mortality during the 6 month treatment period, mortality did not differ between the dalteparin and OAC groups as clearly shown by the nearly identical survival curves (Figure 3). When a subset of deaths determined to be "on-treatment" were examined, in which "on-treatment" was defined as patients who were taking the assigned study treatment or had discontinued the study treatment within one day of death, there was an imbalance in "on-treatment" deaths. However, as noted in Section 4.4.2, the "on-treatment" mortality data are biased by informative censoring related to the clinical management of patients with terminal cancer who often are too ill to continue oral anticoagulant therapy because of difficulties with both oral intake and monitoring of oral anticoagulant effects. A second source of bias was the differences in frequency of recurrent VTEs. The higher rate of VTE in the OAC arm corresponded to more deaths being censored in the OAC arm further biasing the "on-treatment" mortality data.

The question of whether deaths in the study impacted the analysis of time to VTE should also be considered when interpreting the results of the CLOT trial. As explained in Section 4.4.3.1, censoring of VTEs in patients who died without a VTE did not impact the analysis of time to VTE in the two treatment groups since the timing and main cause of death (underlying cancer) were similar in both treatment groups and there is no reason to believe that the probability of VTE for a subject who died without VTE would have differed in the two treatment groups.

Use of a Single Study to Support an Effectiveness Claim

The CLOT study fulfills many of the characteristics of a single study that may be adequate to support an effectiveness claim noted in the May 1998 FDA guidance entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products". The CLOT study was a large, randomized, controlled, multicenter, multinational study with prospectively determined clinical and statistical analytic criteria. All primary endpoints were adjudicated by a central committee that was blinded to treatment allocation. Effect of dalteparin on the primary endpoint was statistically significant with a persuasive p value of 0.0017. The results were consistent across a variety of study subsets. The effect was not consistent in a small subset of patients with hematological malignancies, possibly because of the small numbers of these patients in the trial.

To further support the evidence shown in the CLOT study, the Sponsor has also committed to conducting one additional post-approval study in cancer patients with non-metastatic solid tumors presenting with acute, symptomatic, proximal lower limb DVT, PE or both.

5.2. Benefits and Risks

Cancer patients, especially those with advanced disease, frequently receive multiple interventions in an attempt to manage cancer-related symptoms, provide clinical benefit, and to prolong life when possible. In the cancer patient, VTE creates other significant complications, including additional adverse symptoms and the need for anticoagulation that can interfere with cancer treatment. Currently, the treatment for newly diagnosed proximal DVT and/or PE does not differ between cancer and non-cancer patients. In cancer patients, however, standard secondary prophylaxis with OAC is not optimal, in terms of both efficacy and bleeding, relative to patients without cancer. Secondary prophylaxis with OAC is further complicated by difficulties in maintaining a therapeutic INR due to drug interactions, malnutrition, nausea and vomiting, and the need to interrupt OAC for invasive procedures. Another consequence for the patient is that the INR must be closely monitored resulting in frequent venipunctures and clinic visits.

The objective of the CLOT study was to address recurrent VTE and its associated morbidity experienced by cancer patients with VTE by testing a new treatment regimen of dalteparin compared to OAC therapy. The majority of the enrolled patients in the CLOT study had advanced solid tumors, were symptomatic from their cancer, and most were receiving active therapy for their cancer. In this regard the conclusions of the CLOT Study are widely applicable to oncology practices.

The primary efficacy analysis shows a highly significant reduction in the risk of VTE recurrence over 6 months in the dalteparin arm relative to the OAC arm (52% reduction in risk; p=0.0017). The effect of dalteparin on VTE was consistent in sub-groups of cancer patients with different types of solid tumors, with or without metastatic disease. The treatment effect was not, however, consistent in a subgroup of patients with hematological cancer. These numbers were too small to reach any conclusion.

Results from the CLOT study confirmed that treatment within the first month is critical to reduce VTE recurrence. In this period, the risk of bleeding (while being kept to an acceptable minimum) can be considered secondary to prevention of VTE recurrence and was addressed in the CLOT study by use of the higher 200 IU/kg qD dose of dalteparin. Thus, while the incidence of major bleeding was higher in the first month in the dalteparin arm (5.6%) compared with the OAC arm (3.6%), the number of VTE recurrences was substantially less in the dalteparin arm (11 recurrences) than the OAC arm (33 recurrences) in this period, supporting this approach. In the subsequent 5 month chronic treatment period of CLOT, the dose of dalteparin was lowered to 150 IU/kg qD, reflecting the known decreased risk of VTE recurrence and the need to minimize bleeding over a long duration. In this period, the major bleeding rate and VTE recurrence rate of patients in the dalteparin group was comparable or lower than the rates of major bleeding and VTE recurrence in patients in the OAC group.

The overall adverse event profile was comparable in the two groups. As anticipated, mortality did not differ between the two treatment groups in ITT analyses of deaths during the 6 months of treatment (Figure 3) and the 6 months following treatment. The differences observed in deaths "on-treatment" can be explained by informative censoring. The Sponsor therefore concludes that overall mortality was comparable in the dalteparin and OAC groups.

5.3. Conclusion

Currently there is no FDA-approved treatment for VTE in patients with cancer and off-label regimens with OAC therapy provide suboptimal outcomes. The results of the CLOT Study indicate that for cancer patients with symptomatic, newly diagnosed proximal DVT and/or PE, extended treatment with dalteparin significantly reduces the recurrence of VTE compared to OAC and has a favorable risk/benefit profile. The Sponsor believes the approval of dalteparin for the proposed indication [extended treatment of symptomatic venous thromboembolism (VTE) (proximal DVT and/or PE), to reduce the recurrence of VTE in patients with cancer], based on the CLOT Study data, would provide these patients with a safe, effective and viable treatment option.

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Appendix 1. Fragmin USPI

Appendix 2. Dalteparin in the Prophylaxis and Treatment VTE

Appendix 3. Censoring of Primary Endpoint in the CLOT Study

Fragmin®
dalteparin sodium injection

For *Subcutaneous* Use Only

SPINAL/EPIDURAL HEMATOMAS

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (also see **WARNINGS, Hemorrhage** and **PRECAUTIONS, Drug Interactions**).

DESCRIPTION

FRAGMIN Injection (dalteparin sodium injection) is a sterile, low molecular weight heparin. It is available in single-dose, prefilled syringes preassembled with a needle guard device, and multiple-dose vials. With reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard, each syringe contains either 2500, 5000, 7500, or 10,000 anti-Factor Xa international units (IU), equivalent to 16, 32, 48, or 64 mg dalteparin sodium, respectively. Each vial contains either 10,000 or 25,000 anti-Factor Xa IU per 1 mL (equivalent to 64 or 160 mg dalteparin sodium, respectively), for a total of 95,000 anti-Factor Xa IU per vial.

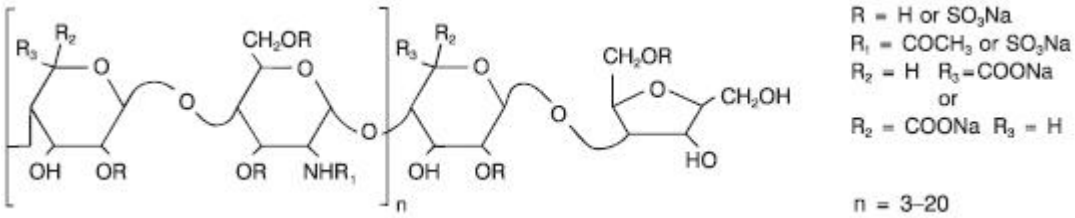
Each prefilled syringe also contains Water for Injection and sodium chloride, when required, to maintain physiologic ionic strength. The prefilled syringes are preservative free. Each multiple-dose vial also contains Water for Injection and 14 mg of benzyl alcohol per mL as a preservative. The pH of both formulations is 5.0 to 7.5.

Dalteparin sodium is produced through controlled nitrous acid depolymerization of sodium heparin from porcine intestinal mucosa followed by a chromatographic

purification process. It is composed of strongly acidic sulphated polysaccharide chains (oligosaccharide, containing 2,5-anhydro-D-mannitol residues as end groups) with an average molecular weight of 5000 and about 90% of the material within the range 2000–9000. The molecular weight distribution is:

<	3000 daltons	3.0–15%
	3000 to 8000 daltons	65.0–78.0%
>	8000 daltons	14.0–26.0%

Structural Formula



CLINICAL PHARMACOLOGY

Dalteparin is a low molecular weight heparin with antithrombotic properties. It acts by enhancing the inhibition of Factor Xa and thrombin by antithrombin. In man, dalteparin potentiates preferentially the inhibition of coagulation Factor Xa, while only slightly affecting clotting time, e.g., activated partial thromboplastin time (APTT).

Pharmacodynamics:

Doses of FRAGMIN Injection of up to 10,000 anti-Factor Xa IU administered subcutaneously as a single dose or two 5000 IU doses 12 hours apart to healthy subjects do not produce a significant change in platelet aggregation, fibrinolysis, or global clotting tests such as prothrombin time (PT), thrombin time (TT) or APTT. Subcutaneous (s.c.) administration of doses of 5000 IU bid of FRAGMIN for seven consecutive days to patients undergoing abdominal surgery did not markedly affect APTT, Platelet Factor 4 (PF4), or lipoprotein lipase.

Pharmacokinetics:

Mean peak levels of plasma anti-Factor Xa activity following single s.c. doses of 2500, 5000 and 10,000 IU were 0.19 ± 0.04, 0.41 ± 0.07 and 0.82 ± 0.10 IU/mL, respectively, and were attained in about 4 hours in most subjects. Absolute bioavailability in healthy volunteers, measured as the anti-Factor Xa activity, was 87 ± 6%. Increasing the dose from 2500 to 10,000 IU resulted in an overall increase in anti-Factor Xa AUC that was greater than proportional by about one-third.

Peak anti-Factor Xa activity increased more or less linearly with dose over the same dose range. There appeared to be no appreciable accumulation of anti-Factor Xa activity with twice-daily dosing of 100 IU/kg s.c. for up to 7 days.

The volume of distribution for dalteparin anti-Factor Xa activity was 40 to 60 mL/kg. The mean plasma clearances of dalteparin anti-Factor Xa activity in normal volunteers following single intravenous bolus doses of 30 and 120 anti-Factor Xa IU/kg were 24.6 ± 5.4 and 15.6 ± 2.4 mL/hr/kg, respectively. The corresponding mean disposition half-lives are 1.47 ± 0.3 and 2.5 ± 0.3 hours.

Following intravenous doses of 40 and 60 IU/kg, mean terminal half-lives were 2.1 ± 0.3 and 2.3 ± 0.4 hours, respectively. Longer apparent terminal half-lives (3 to 5 hours) are observed following s.c. dosing, possibly due to delayed absorption. In patients with chronic renal insufficiency requiring hemodialysis, the mean terminal half-life of anti-Factor Xa activity following a single intravenous dose of 5000 IU FRAGMIN was 5.7 ± 2.0 hours, i.e. considerably longer than values observed in healthy volunteers, therefore, greater accumulation can be expected in these patients.

CLINICAL TRIALS

Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction:

In a double-blind, randomized, placebo-controlled clinical trial, patients who recently experienced unstable angina with EKG changes or non-Q-wave myocardial infarction (MI) were randomized to FRAGMIN Injection 120 IU/kg every 12 hours subcutaneously (s.c.) or placebo every 12 hours s.c. In this trial, unstable angina was defined to include only angina with EKG changes. All patients, except when contraindicated, were treated concurrently with aspirin (75 mg once daily) and beta blockers. Treatment was initiated within 72 hours of the event (the majority of patients received treatment within 24 hours) and continued for 5 to 8 days. A total of 1506 patients were enrolled and treated; 746 received FRAGMIN and 760 received placebo. The mean age of the study population was 68 years (range 40 to 90 years) and the majority of patients were white (99.7%) and male (63.9%). The combined incidence of the double endpoint of death or myocardial infarction was lower for FRAGMIN compared with placebo at 6 days after initiation of therapy. These results were observed in an analysis of all-randomized and all-treated patients. The combined incidence of death, MI, need for intravenous (i.v.) heparin or i.v. nitroglycerin, and revascularization was also lower for FRAGMIN than for placebo (see Table 1).

Table 1

Efficacy of FRAGMIN in the Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction

Indication	Dosing Regimen	
	FRAGMIN 120 IU/kg/12 hr s.c.	**Placebo** q 12 hr s.c.

All Treated Unstable Angina and Non-Q-Wave MI Patients	746	760
Primary Endpoints - 6 day timepoint Death, MI	13/741 (1.8%)[1]	36/757 (4.8%)
Secondary Endpoints - 6 day timepoint Death, MI, i.v. heparin, i.v. nitroglycerin, Revascularization	59/739 (8.0%)[1]	106/756 (14.0%)

[1] p-value = 0.001

In a second randomized, controlled trial designed to evaluate long-term treatment with FRAGMIN (days 6 to 45), data were also collected comparing 1-week (5 to 8 days) treatment of FRAGMIN 120 IU/kg every 12 hours s.c. with heparin at an APTT-adjusted dosage. All patients, except when contraindicated, were treated concurrently with aspirin (100 to 165 mg per day). Of the total enrolled study population of 1499 patients, 1482 patients were treated; 751 received FRAGMIN and 731 received heparin. The mean age of the study population was 64 years (range 25 to 92 years) and the majority of patients were white (96.0%) and male (64.2%). The incidence of the combined triple endpoint of death, myocardial infarction, or recurrent angina during this 1-week treatment period (5 to 8 days) was 9.3% for FRAGMIN and 7.6% for heparin (p=0.323).

Prophylaxis of Deep Vein Thrombosis in Patients Following Hip Replacement Surgery:

In an open-label randomized study, FRAGMIN 5000 IU administered once daily s.c. was compared with warfarin sodium, administered orally, in patients undergoing hip replacement surgery. Treatment with FRAGMIN was initiated with a 2500 IU dose s.c. within 2 hours before surgery, followed by a 2500 IU dose s.c. the evening of the day of surgery. Then, a dosing regimen of FRAGMIN 5000 IU s.c. once daily was initiated on the first postoperative day. The first dose of warfarin sodium was given the evening before surgery, then continued daily at a dose adjusted for INR 2.0 to 3.0. Treatment in both groups was then continued for 5 to 9 days postoperatively. Of the total enrolled study population of 580 patients, 553 were treated and 550 underwent surgery. Of those who underwent surgery, 271 received FRAGMIN and 279 received warfarin sodium. The mean age of the study population was 63 years (range 20 to 92 years) and the majority of patients were white (91.1%) and female (52.9%). The incidence of deep vein thrombosis (DVT), any vein, as determined by evaluable venography, was significantly lower for the group treated with FRAGMIN compared with patients treated with warfarin sodium (28/192 vs 49/190; p=0.006) [see Table 2].

Table 2
Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery

Indication	Dosing Regimen	
	FRAGMIN 5000 IU qd[1] s.c.	**Warfarin Sodium** qd[2] oral
All Treated Hip Replacement Surgery	271	279

Patients		
Treatment Failures in Evaluable Patients		
DVT, Total	28/192 (14.6%)[3]	49/190 (25.8%)
Proximal DVT	10/192 (5.2%)[4]	16/190 (8.4%)
PE	2/271 (0.7%)	2/279 (0.7%)

[1] The daily dose on the day of surgery was divided: 2500 IU was given two hours before surgery and again in the evening of the day of surgery.

[2] Warfarin sodium dosage was adjusted to maintain a prothrombin time index of 1.4 to 1.5, corresponding to an International Normalized Ratio (INR) of approximately 2.5.

[3] p-value = 0.006

[4] p-value = 0.185

In a second single-center, double-blind study of patients undergoing hip replacement surgery, FRAGMIN 5000 IU once daily s.c. starting the evening before surgery, was compared with heparin 5000 U s.c. tid, starting the morning of surgery. Treatment in both groups was continued for up to 9 days postoperatively. Of the total enrolled study population of 140 patients, 139 were treated and 136 underwent surgery. Of those who underwent surgery, 67 received FRAGMIN and 69 received heparin. The mean age of the study population was 69 years (range 42 to 87 years) and the majority of patients were female (58.8%). In the intent-to-treat analysis, the incidence of proximal DVT was significantly lower for patients treated with FRAGMIN compared with patients treated with heparin (6/67 vs 18/69; p=0.012). Further, the incidence of pulmonary embolism detected by lung scan was also significantly lower in the group treated with FRAGMIN (9/67 vs 19/69; p=0.032).

A third multi-center, double-blind, randomized study evaluated a postoperative dosing regimen of FRAGMIN for thromboprophylaxis following total hip replacement surgery. Patients received either FRAGMIN or warfarin sodium, randomized into one of three treatment groups. One group of patients received the first dose of FRAGMIN 2500 IU s.c. within 2 hours before surgery, followed by another dose of FRAGMIN 2500 IU s.c. at least 4 hours (6.6 ± 2.3 hr) after surgery. Another group received the first dose of FRAGMIN 2500 IU s.c. at least 4 hours (6.6 ± 2.4 hr) after surgery. Then, **both** of these groups began a dosing regimen of FRAGMIN 5000 IU once daily s.c. on postoperative day 1. The third group of patients received warfarin sodium the evening of the day of surgery, then continued daily at a dose adjusted for INR 2.0 to 3.0. Treatment for all groups was continued for 4 to 8 days postoperatively, after which time all patients underwent bilateral venography.

In the total enrolled study population of 1501 patients, 1472 patients were treated; 496 received FRAGMIN (first dose before surgery), 487 received FRAGMIN (first dose after surgery) and 489 received warfarin sodium. The mean age of the study population was 63 years (range 18 to 91 years) and the majority of patients were white (94.4%) and female (51.8%).

Administration of the first dose of FRAGMIN after surgery was as effective in reducing the incidence of thromboembolic events as administration of the first dose of FRAGMIN before surgery (44/336 vs 37/338; p=0.448). Both dosing regimens of FRAGMIN were

more effective than warfarin sodium in reducing the incidence of thromboembolic events following hip replacement surgery.

Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery in Patients at Risk for Thromboembolic Complications:

Abdominal surgery patients at risk include those who are over 40 years of age, obese, undergoing surgery under general anesthesia lasting longer than 30 minutes, or who have additional risk factors such as malignancy or a history of deep vein thrombosis or pulmonary embolism.

FRAGMIN administered once daily s.c. beginning prior to surgery and continuing for 5 to 10 days after surgery, was shown to reduce the risk of DVT in patients at risk for thromboembolic complications in two double-blind, randomized, controlled clinical trials performed in patients undergoing major abdominal surgery. In the first study, a total of 204 patients were enrolled and treated; 102 received FRAGMIN and 102 received placebo. The mean age of the study population was 64 years (range 40 to 98 years) and the majority of patients were female (54.9%). In the second study, a total of 391 patients were enrolled and treated; 195 received FRAGMIN and 196 received heparin. The mean age of the study population was 59 years (range 30 to 88 years) and the majority of patients were female (51.9%). As summarized in the following tables, FRAGMIN 2500 IU was superior to placebo and similar to heparin in reducing the risk of DVT (see Tables 3 and 4).

Table 3

Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery

Indication	Dosing Regimen	
	FRAGMIN 2500 IU qd s.c.	**Placebo** qd s.c.
All Treated Abdominal Surgery Patients	102	102
Treatment Failures in Evaluable Patients		
Total Thromboembolic Events	4/91 (4.4%)[1]	16/91 (17.6%)
Proximal DVT	0	5/91 (5.5%)
Distal DVT	4/91 (4.4%)	11/91 (12.1%)
PE	0	2/91 (2.2%)[2]

[1] p-value = 0.008

[2] Both patients also had DVT , 1 proximal and 1 distal

Table 4

Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery

Indication	Dosing Regimen	
	FRAGMIN	**Heparin**

	2500 IU qd s.c.	5000 U bid s.c.
All Treated Abdominal Surgery Patients	195	196
Treatment Failures in Evaluable Patients		
Total Thromboembolic Events	7/178 (3.9%)[1]	7/174 (4.0%)
Proximal DVT	3/178 (1.7%)	4/174 (2.3%)
Distal DVT	3/178 (1.7%)	3/174 (1.7%)
PE	1/178 (0.6%)	0

[1] p-value = 0.74

In a third double-blind, randomized study performed in patients undergoing major abdominal surgery with malignancy, FRAGMIN 5000 IU once daily was compared with FRAGMIN 2500 IU once daily. Treatment was continued for 6 to 8 days. A total of 1375 patients were enrolled and treated; 679 received FRAGMIN 5000 IU and 696 received 2500 IU. The mean age of the combined groups was 71 years (range 40 to 95 years). The majority of patients were female (51.0%). The study showed that FRAGMIN 5000 IU once daily was more effective than FRAGMIN 2500 IU once daily in reducing the risk of DVT in patients undergoing abdominal surgery with malignancy (see Table 5).

Table 5

Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery

Indication	**Dosing Regimen**	
	FRAGMIN 2500 IU qd s.c.	**FRAGMIN** 5000 IU bid s.c.
All Treated Abdominal Surgery Patients[1]	696	679
Treatment Failures in Evaluable Patients		
Total Thromboembolic Events	99/656 (15.1%)[2]	60/645 (9.3%)
Proximal DVT	18/657 (2.7%)	14/646 (2.2%)
Distal DVT	80/657 (12.2%)	41/646 (6.3%)
PE		
Fatal	1/674 (0.1%)	1/669 (0.1%)
Non-fatal	2	4

[1] Major abdominal surgery with malignancy

[2] p-value = 0.001

Prophylaxis of Deep Vein Thrombosis in Medical Patients at Risk for Thromboembolic Complications Due to Severely Restricted Mobility During Acute Illness:

In a double-blind, multi-center, randomized, placebo-controlled clinical trial, general medical patients with severely restricted mobility who were at risk of venous thromboembolism were randomized to receive either FRAGMIN 5000 IU or placebo s.c. once daily during Days 1 to 14 of the study. The primary endpoint was evaluated at Day 21, and the follow-up period was up to Day 90. These patients had an acute medical condition requiring a projected hospital stay of at least 4 days, and were confined to bed during waking hours. The study included patients with congestive heart failure (NYHA

Class III or IV), acute respiratory failure not requiring ventilatory support, and the following acute conditions with at least one risk factor occurring in > 1% of treated patients: acute infection (excluding septic shock), acute rheumatic disorder, acute lumbar or sciatic pain, vertebral compression, or acute arthritis of the lower extremities. Risk factors include > 75 years of age, cancer, previous DVT/PE, obesity and chronic venous insufficiency. A total of 3681 patients were enrolled and treated: 1848 received FRAGMIN and 1833 received placebo. The mean age of the study population was 69 years (range 26 to 99 years), 92.1% were white and 51.9% were female. The primary efficacy endpoint was defined as at least one of the following within Days 1 to 21 of the study: asymptomatic DVT (diagnosed by compression ultrasound), a confirmed symptomatic DVT, a confirmed pulmonary embolism or sudden death.

When given at a dose of 5000 IU once a day s.c., FRAGMIN significantly reduced the incidence of thromboembolic events including verified DVT by Day 21 (see Table 6). The prophylactic effect was sustained through Day 90.

Table 6
Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis in Medical Patients with Severely Restricted Mobility During Acute Illness

Indication	Dosing Regimen	
	FRAGMIN 5000 IU qd s.c.	**Placebo** qd s.c.
All Treated Medical Patients During Acute Illness	1848	1833
Treatment failure in evaluable patients (Day 21)[1] DVT, PE, or sudden death	42/1518 (2.77%)[2]	73/1473 (4.96%)
Total thromboembolic events (Day 21)	37/1513 (2.45%)	70/1470 (4.76%)
Total DVT	32/1508 (2.12%)	64/1464 (4.37%)
Proximal DVT	29/1518 (1.91%)	60/1474 (4.07%)
Symptomatic VTE	10/1759 (0.57%)	17/1740 (0.98%)
PE	5/1759 (0.28%)	6/1740 (0.34%)
Sudden Death	5/1829 (0.27%)	3/1807 (0.17%)

[1] Defined as DVT (diagnosed by compression ultrasound at Day 21 + 3), confirmed symptomatic DVT, confirmed PE or sudden death.
[2] p-value = 0.0015

INDICATIONS AND USAGE

FRAGMIN Injection is indicated for the prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin therapy (as described in CLINICAL TRIALS, Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction).

FRAGMIN is also indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE):

- In patients undergoing hip replacement surgery;
- In patients undergoing abdominal surgery who are at risk for thromboembolic complications;
- In medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

CONTRAINDICATIONS

FRAGMIN Injection is contraindicated in patients with known hypersensitivity to the drug, active major bleeding, or thrombocytopenia associated with positive *in vitro* tests for anti-platelet antibody in the presence of FRAGMIN.

Patients undergoing regional anesthesia should not receive FRAGMIN for unstable angina or non-Q-wave myocardial infarction due to an increased risk of bleeding associated with the dosage of FRAGMIN recommended for unstable angina and non-Q-wave myocardial infarction.

Patients with known hypersensitivity to heparin or pork products should not be treated with FRAGMIN.

WARNINGS

FRAGMIN Injection is not intended for intramuscular administration.

FRAGMIN cannot be used interchangeably (unit for unit) with unfractionated heparin or other low molecular weight heparins.

FRAGMIN should be used with extreme caution in patients with history of heparin-induced thrombocytopenia.

Hemorrhage:

FRAGMIN, like other anticoagulants, should be used with extreme caution in patients who have an increased risk of hemorrhage, such as those with severe uncontrolled hypertension, bacterial endocarditis, congenital or acquired bleeding disorders, active ulceration and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal or ophthalmological surgery.

Spinal or epidural hematomas can occur with the associated use of low molecular weight heparins or heparinoids and neuraxial (spinal/epidural) anesthesia or spinal puncture, which can result in long-term or permanent paralysis. The risk of these events is higher with the use of indwelling epidural catheters or concomitant use of additional drugs affecting hemostasis such as NSAIDs (see boxed WARNING and ADVERSE REACTIONS, Ongoing Safety Surveillance).

As with other anticoagulants, bleeding can occur at any site during therapy with FRAGMIN. An unexpected drop in hematocrit or blood pressure should lead to a search for a bleeding site.

Thrombocytopenia:

In clinical trials, thrombocytopenia with platelet counts of < 100,000/mm^3 and < 50,000/mm^3 occurred in < 1% and < 1%, respectively. In clinical practice, rare cases of thrombocytopenia with thrombosis have also been observed.

Thrombocytopenia of any degree should be monitored closely. Heparin-induced thrombocytopenia can occur with the administration of FRAGMIN. The incidence of this complication is unknown at present.

Miscellaneous:

The multiple-dose vial of FRAGMIN contains benzyl alcohol as a preservative. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. Because benzyl alcohol may cross the placenta, FRAGMIN preserved with benzyl alcohol should not be used in pregnant women (see **PRECAUTIONS, Pregnancy Category B, Nonteratogenic Effects**).

PRECAUTIONS

General:

FRAGMIN Injection should not be mixed with other injections or infusions unless specific compatibility data are available that support such mixing.

FRAGMIN should be used with caution in patients with bleeding diathesis, thrombocytopenia or platelet defects; severe liver or kidney insufficiency, hypertensive or diabetic retinopathy, and recent gastrointestinal bleeding.

If a thromboembolic event should occur despite dalteparin prophylaxis, FRAGMIN should be discontinued and appropriate therapy initiated.

Drug Interactions:

FRAGMIN should be used with care in patients receiving oral anticoagulants, platelet inhibitors, and thrombolytic agents because of increased risk of bleeding (see **PRECAUTIONS, Laboratory Tests**). Aspirin, unless contraindicated, is recommended in patients treated for unstable angina or non-Q-wave myocardial infarction (see **DOSAGE AND ADMINISTRATION**).

Laboratory Tests:

Periodic routine complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with FRAGMIN. No special monitoring of blood clotting times (e.g., APTT) is needed.

When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) are relatively insensitive measures of FRAGMIN activity and, therefore, unsuitable for monitoring.

Drug/Laboratory Test Interactions:

Elevations of Serum Transaminases:

Asymptomatic increases in transaminase levels (SGOT/AST and SGPT/ALT) greater than three times the upper limit of normal of the laboratory reference range have been reported in 1.7 and 4.3%, respectively, of patients during treatment with FRAGMIN. Similar significant increases in transaminase levels have also been observed in patients treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin. Since transaminase determinations are important in the differential diagnosis of myocardial infarction, liver disease and pulmonary emboli, elevations that might be caused by drugs like FRAGMIN should be interpreted with caution.

Carcinogenicity, Mutagenesis, Impairment of Fertility:

Dalteparin sodium has not been tested for its carcinogenic potential in long-term animal studies. It was not mutagenic in the ***in vitro*** Ames Test, mouse lymphoma cell forward mutation test and human lymphocyte chromosomal aberration test and in the ***in vivo*** mouse micronucleus test. Dalteparin sodium at subcutaneous doses up to 1200 IU/kg (7080 IU/m^2) did not affect the fertility or reproductive performance of male and female rats.

Pregnancy: Pregnancy Category B.

Teratogenic Effects:

Reproduction studies with dalteparin sodium at intravenous doses up to 2400 IU/kg (14,160 IU/m^2) in pregnant rats and 4800 IU/kg (40,800 IU/m^2) in pregnant rabbits did not produce any evidence of impaired fertility or harm to the fetuses. 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.

Nonteratogenic Effects:

Cases of "Gasping Syndrome" have occurred when large amounts of benzyl alcohol have been administered (99–404 mg/kg/day). The 9.5 mL multiple-dose vial of FRAGMIN contains 14 mg/mL of benzyl alcohol.

Nursing Mothers:

It is not known whether dalteparin sodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FRAGMIN is administered to a nursing mother.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:

Of the total number of patients in clinical studies of FRAGMIN, 5204 patients were 65 years of age or older and 2123 were 75 or older. No overall differences in effectiveness were observed between these subjects and younger subjects. Some studies suggest that the risk of bleeding increases with age. Postmarketing surveillance and literature reports have not revealed additional differences in the safety of FRAGMIN between elderly and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised, particularly in geriatric patients with low body weight (< 45 kg) and those predisposed to decreased renal function (see also **CLINICAL PHARMACOLOGY** and **General** and **Drug Interactions** subsections of **PRECAUTIONS**).

ADVERSE REACTIONS

Hemorrhage:

The incidence of hemorrhagic complications during treatment with FRAGMIN Injection has been low. The most commonly reported side effect is hematoma at the injection site. The incidence of bleeding may increase with higher doses; however, in abdominal surgery patients with malignancy, no significant increase in bleeding was observed when comparing FRAGMIN 5000 IU to either FRAGMIN 2500 IU or low dose heparin.

In a trial comparing FRAGMIN 5000 IU once daily to FRAGMIN 2500 IU once daily in patients undergoing surgery for malignancy, the incidence of bleeding events was 4.6% and 3.6%, respectively (n.s.). In a trial comparing FRAGMIN 5000 IU once daily to heparin 5000 U twice daily, the incidence of bleeding events was 3.2% and 2.7%, respectively (n.s.) in the malignancy subgroup.

Unstable Angina and Non-Q-Wave Myocardial Infarction:

Table 7 summarizes major bleeding events that occurred with FRAGMIN, heparin, and placebo in clinical trials of unstable angina and non-Q-wave myocardial infarction.

Table 7
Major Bleeding Events in Unstable Angina and Non-Q-Wave Myocardial Infarction

Indication	Dosing Regimen		
Unstable Angina and Non-Q-Wave MI	**FRAGMIN** 120 IU/kg/12 hr s.c.[1]	**Heparin** i.v. and s.c.[2]	**Placebo** q 12 hr s.c.
Major Bleeding Events[3,4]	15/1497 (1.0%)	7/731 (1.0%)	4/760 (0.5%)

1 Treatment was administered for 5 to 8 days.
2 Heparin i.v. infusion for at least 48 hours, APPT 1.5 to 2 times control, then 12,500 U s.c. every 12 hours for 5 to 8 days.
3 Aspirin (75 to 165 mg per day) and beta blocker therapies were administered concurrently.
4 Bleeding events were considered major if: 1) accompanied by a decrease in hemoglobin of ≥2 g/dL in connection with clinical symptoms; 2) a transfusion was required; 3) bleeding led to interruption of treatment or death; or 4) intracranial bleeding.

Hip Replacement Surgery:

Table 8 summarizes: 1) all major bleeding events and, 2) other bleeding events possibly or probably related to treatment with FRAGMIN (preoperative dosing regimen), warfarin sodium, or heparin in two hip replacement surgery clinical trials.

Table 8
Bleeding Events Following Hip Replacement Surgery

Indication	FRAGMIN vs Warfarin Sodium		FRAGMIN vs Heparin	
	Dosing Regimen		Dosing Regimen	
Hip Replacement Surgery	**FRAGMIN** 5000 IU qd s.c. (n=274[2])	**Warfarin** Sodium[1] oral (n=279)	**FRAGMIN** 5000 IU qd s.c. (n=69[4])	**Heparin** 5000 U tid s.c. (n=69)
Major Bleeding Events[3]	7/274 (2.6%)	1/279 (0.4%)	0	3/69 (4.3%)
Other Bleeding Events[5]				
Hematuria	8/274 (2.9%)	5/279 (1.8%)	0	0
Wound Hematoma	6/274 (2.2%)	0	0	0
Injection Site Hematoma	3/274 (1.1%)	NA	2/69 (2.9%)	7/69 (10.1%)

1 Warfarin sodium dosage was adjusted to maintain a prothrombin time index of 1.4 to 1.5, corresponding to an International Normalized Ratio (INR) of approximately 2.5.
2 Includes three treated patients who did not undergo a surgical procedure.
3 A bleeding event was considered major if: 1) hemorrhage caused a significant clinical event, 2) it was associated with a hemoglobin decrease of ≥2 g/dL or transfusion of 2 or more units of blood products, 3) it resulted in reoperation due to bleeding, or 4) it involved retroperitoneal or intracranial hemorrhage.
4 Includes two treated patients who did not undergo a surgical procedure.
5 Occurred at a rate of at least 2% in the group treated with FRAGMIN 5000 IU once daily.

Six of the patients treated with FRAGMIN experienced seven major bleeding events. Two of the events were wound hematoma (one requiring reoperation), three were

bleeding from the operative site, one was intraoperative bleeding due to vessel damage, and one was gastrointestinal bleeding. None of the patients experienced retroperitoneal or intracranial hemorrhage nor died of bleeding complications.

In the third hip replacement surgery clinical trial, the incidence of major bleeding events was similar in all three treatment groups: 3.6% (18/496) for patients who started FRAGMIN before surgery; 2.5% (12/487) for patients who started FRAGMIN after surgery; and 3.1% (15/489) for patients treated with warfarin sodium.

Abdominal Surgery:

Table 9 summarizes bleeding events that occurred in clinical trials which studied FRAGMIN 2500 and 5000 IU administered once daily to abdominal surgery patients.

Table 9
Bleeding Events Following Abdominal Surgery

Indication	FRAGMIN vs Heparin				FRAGMIN vs Placebo		FRAGMIN vs FRAGMIN	
	Dosing Regimen				Dosing Regimen		Dosing Regimen	
Abdominal Surgery	**FRAGMIN** 2500 IU qd s.c.	**Heparin** 5000 U bid s.c.	**FRAGMIN** 5000 IU qd s.c.	**Heparin** 5000 U bid s.c.	**FRAGMIN** 2500 IU qd s.c.	**Placebo** qd s.c.	**FRAGMIN** 2500 IU qd s.c.	**FRAGMIN** 5000 IU qd s.c.
Postoperative Transfusions	26/459 (5.7%)	36/454 (7.9%)	81/508 (15.9%)	63/498 (12.7%)	14/182 (7.7%)	13/182 (7.1%)	89/1025 (8.7%)	125/1033 (12.1%)
Wound Hematoma	16/467 (3.4%)	18/467 (3.9%)	12/508 (2.4%)	6/498 (1.2%)	2/79 (2.5%)	2/77 (2.6%)	1/1030 (0.1%)	4/1039 (0.4%)
Reoperation Due to Bleeding	2/392 (0.5%)	3/392 (0.8%)	4/508 (0.8%)	2/498 (0.4%)	1/79 (1.3%)	1/78 (1.3%)	2/1030 (0.2%)	13/1038 (1.3%)
Injection Site Hematoma	1/466 (0.2%)	5/464 (1.1%)	36/506 (7.1%)	47/493 (9.5%)	8/172 (4.7%)	2/174 (1.1%)	36/1026 (3.5%)	57/1035 (5.5%)

Medical Patients with Severely Restricted Mobility During Acute Illness:

Table 10 summarizes major bleeding events that occurred in a clinical trial of medical patients with severely restricted mobility during acute illness.

Table 10
Bleeding Events in Medical Patients with Severely Restricted Mobility During Acute Illness

Indication	Dosing Regimen	
Medical Patients with Severely Restricted Mobility	**FRAGMIN** 5000 IU qd s.c.	**Placebo** qd s.c.
Major Bleeding Events[1] at Day 14	8/1848 (0.43%)	0/1833 (0%)
Major Bleeding Events[1] at Day 21	9/1848 (0.49%)	3/1833 (0.16%)

[1] A bleeding event was considered major if: 1) it was accompanied by a decrease in hemoglobin of ≥2 g/dL in connection with clinical symptoms; 2) intraocular, spinal/epidural, intracranial, or retroperitoneal bleeding; 3) required transfusion of ≥ 2

units of blood products; 4) required significant medical or surgical intervention; or 5) led to death.

Three of the major bleeding events that occurred by Day 21 were fatal, all due to gastrointestinal hemorrhage (two patients in the group treated with FRAGMIN and one in the group receiving placebo). Two deaths occurred after Day 21: one patient in the placebo group died from a subarachnoid hemorrhage that started on Day 55, and one patient died on day 71 (two months after receiving the last dose of FRAGMIN) from a subdural hematoma.

Thrombocytopenia: **See WARNINGS: Thrombocytopenia.**

Other:

Allergic Reactions:

Allergic reactions (i.e., pruritus, rash, fever, injection site reaction, bulleous eruption) and skin necrosis have occurred rarely. A few cases of anaphylactoid reactions have been reported.

Local Reactions:

Pain at the injection site, the only non-bleeding event determined to be possibly or probably related to treatment with FRAGMIN and reported at a rate of at least 2% in the group treated with FRAGMIN, was reported in 4.5% of patients treated with FRAGMIN 5000 IU qd vs 11.8% of patients treated with heparin 5000 U bid in the abdominal surgery trials. In the hip replacement trials, pain at injection site was reported in 12% of patients treated with FRAGMIN 5000 IU qd vs 13% of patients treated with heparin 5000 U tid.

Ongoing Safety Surveillance:

Since first international market introduction in 1985, there have been nine reports of epidural or spinal hematoma formation with concurrent use of dalteparin sodium and spinal/epidural anesthesia or spinal puncture. Five of the nine patients had post-operative indwelling epidural catheters placed for analgesia or received additional drugs affecting hemostasis. The hematomas caused long-term or permanent paralysis (partial or complete) in seven of these cases. One patient experienced temporary paraplegia but made a full recovery, and one patient had no neurological deficit. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

OVERDOSAGE

Symptoms/Treatment:

An excessive dosage of FRAGMIN Injection may lead to hemorrhagic complications. These may generally be stopped by the slow intravenous injection of protamine sulfate (1% solution), at a dose of 1 mg protamine for every 100 anti-Xa IU of FRAGMIN given. A second infusion of 0.5 mg protamine sulfate per 100 anti-Xa IU of FRAGMIN may be administered if the APTT measured 2 to 4 hours after the first infusion remains prolonged. Even with these additional doses of protamine, the APTT may remain more prolonged than would usually be found following administration of conventional heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60 to 75%).

Particular care should be taken to avoid overdosage with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactic shock are readily available. For additional information, consult the labeling of Protamine Sulfate Injection, USP, products. A single subcutaneous dose of 100,000 IU/kg of FRAGMIN to mice caused a mortality of 8% (1/12) whereas 50,000 IU/kg was a non-lethal dose. The observed sign was hematoma at the site of injection.

DOSAGE AND ADMINISTRATION

Unstable Angina and Non-Q-Wave Myocardial Infarction:

In patients with unstable angina or non-Q-wave myocardial infarction, the recommended dose of FRAGMIN Injection is 120 IU/kg of body weight, but not more than 10,000 IU, subcutaneously (s.c.) every 12 hours with concurrent oral aspirin (75 to 165 mg once daily) therapy. Treatment should be continued until the patient is clinically stabilized. The usual duration of administration is 5 to 8 days. Concurrent aspirin therapy is recommended except when contraindicated.

Table 11 lists the volume of FRAGMIN, based on the 9.5 mL multiple-dose vial (10,000 IU/mL), to be administered for a range of patient weights.

Table 11
Volume of FRAGMIN to be Administered by Patient Weight, Based on 9.5 mL Vial (10,000 IU/mL)

Patient weight (lb)	< 110	110 to 131	132 to 153	154 to 175	176 to 197	≥198
Patient weight (kg)	< 50	50 to 59	60 to 69	70 to 79	80 to 89	≥90
Volume of FRAGMIN (mL)	0.55	0.65	0.75	0.90	1.00	1.00

Hip Replacement Surgery:

Table 12 presents the dosing options for patients undergoing hip replacement surgery. The usual duration of administration is 5 to 10 days after surgery; up to 14 days of treatment with FRAGMIN have been well tolerated in clinical trials.

Table 12
Dosing Options for Patients Undergoing Hip Replacement Surgery

Timing of First Dose of FRAGMIN	Dose of FRAGMIN to be Given Subcutaneously			
	10 to 14 Hours Before Surgery	Within 2 Hours Before Surgery	4 to 8 Hours After Surgery[1]	Postoperative Period[2]
Postoperative Start	---	---	2500 IU[3]	5000 IU qd
Preoperative Start - Day of Surgery	---	2500 IU	2500 IU[3]	5000 IU qd
Preoperative Start - Evening Before Surgery[4]	5000 IU	---	5000 IU	5000 IU qd

1 Or later, if hemostasis has not been achieved.
2 Up to 14 days of treatment was well tolerated in controlled clinical trials, where the usual duration of treatment was 5 to 10 days postoperatively.
3 Allow a minimum of 6 hours between this dose and the dose to be given on Postoperative Day 1. Adjust the timing of the dose on Postoperative Day 1 accordingly.
4 Allow approximately 24 hours between doses.

Abdominal Surgery:

In patients undergoing abdominal surgery with a risk of thromboembolic complications, the recommended dose of FRAGMIN is 2500 IU administered by s.c. injection once daily, starting 1 to 2 hours prior to surgery and repeated once daily postoperatively. The usual duration of administration is 5 to 10 days.

In patients undergoing abdominal surgery associated with a high risk of thromboembolic complications, such as malignant disorder, the recommended dose of FRAGMIN is 5000 IU s.c. the evening before surgery, then once daily postoperatively. The usual duration of administration is 5 to 10 days. Alternatively, in patients with malignancy, 2500 IU of FRAGMIN can be administered s.c. 1 to 2 hours before surgery followed by 2500 IU s.c. 12 hours later, and then 5000 IU once daily postoperatively. The usual duration of administration is 5 to 10 days.

Dosage adjustment and routine monitoring of coagulation parameters are not required if the dosage and administration recommendations specified above are followed.

Medical Patients with Severely Restricted Mobility During Acute Illness:

In medical patients with severely restricted mobility during acute illness, the recommended dose of FRAGMIN is 5000 IU administered by s.c. injection once daily. In clinical trials, the usual duration of administration was 12 to 14 days.

Administration:

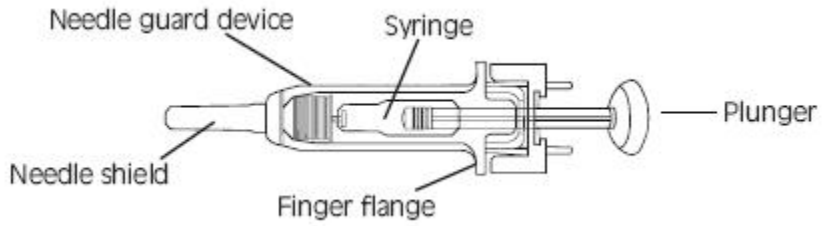
FRAGMIN is administered by subcutaneous injection. It must not be administered by intramuscular injection.

Subcutaneous injection technique: Patients should be sitting or lying down and FRAGMIN administered by deep s.c. injection. FRAGMIN may be injected in a U-shape area around the navel, the upper outer side of the thigh or the upper outer quadrangle of the buttock. The injection site should be varied daily. When the area around the navel or the thigh is used, using the thumb and forefinger, you **must** lift up a fold of skin while giving the injection. The entire length of the needle should be inserted at a 45 to 90 degree angle.

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

After first penetration of the rubber stopper, store the multiple-dose vials at room temperature for up to 2 weeks. Discard any unused solution after 2 weeks.

Instructions for using the prefilled single-dose syringes preassembled with needle guard devices:



Fixed dose syringes: To ensure delivery of the full dose, do not expel the air bubble from the prefilled syringe before injection. Hold the syringe assembly by the open sides of the device. Remove the needle shield. Insert the needle into the injection area as instructed above. Depress the plunger of the syringe while holding the finger flange **until the entire dose has been given**. The needle guard will **not** be activated unless the **entire** dose has been given. Remove needle from the patient. Let go of the plunger and allow syringe to move up inside the device until the entire needle is guarded. Discard the syringe assembly in approved containers.

Graduated syringes: Hold the syringe assembly by the open sides of the device. Remove the needle shield. With the needle pointing up, prepare the syringe by expelling the air bubble and then continuing to push the plunger to the desired dose or volume, discarding the extra solution in an appropriate manner. Insert the needle into the injection

area as instructed above. Depress the plunger of the syringe while holding the finger flange **until the entire dose remaining in the syringe has been given**. The needle guard will **not** be activated unless the **entire** dose has been given. Remove needle from the patient. Let go of the plunger and allow syringe to move up inside the device until the entire needle is guarded. Discard the syringe assembly in approved containers.

HOW SUPPLIED

FRAGMIN Injection is available in the following strengths and package sizes:

0.2 mL single-dose prefilled syringe, affixed with a 27-gauge x 1/2 inch needle and preassembled with UltraSafe Passive™ Needle Guard* devices.

Package of 10:

2500 anti-Factor Xa IU	NDC 0013-2406-91
5000 anti-Factor Xa IU	NDC 0013-2426-91

0.3 mL single-dose prefilled syringe, affixed with a 27-gauge x 1/2 inch needle and preassembled with UltraSafe Passive™ Needle Guard* devices.

Package of 10:

7500 anti-Factor Xa IU	NDC 0013-2426-01

1.0 mL single-dose graduated syringe, affixed with a 27-gauge x 1/2 inch needle and preassembled with UltraSafe Passive™ Needle Guard* devices.

Package of 10:

10,000 anti-Factor Xa IU	NDC 0013-5190-01

3.8 mL multiple-dose vial:

25,000 anti-Factor Xa IU/mL (95,000 anti-Factor Xa IU/vial)	NDC 0013-5191-01

9.5 mL multiple-dose vial:

10,000 anti-Factor Xa IU/mL (95,000 anti-Factor Xa IU/vial)	NDC 0013-2436-06

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP] .

Rx only

* UltraSafe Passive™ Needle Guard is a trademark of Safety Syringes, Inc.

Distributed by

Pharmacia & Upjohn Company
Division of Pfizer Inc, NY, NY 10017

Manufactured By:
Vetter Pharma-Fertigung
Ravensburg, Germany
(prefilled syringes)

Pharmacia N.V./S.A.
Puurs, Belgium
(multiple-dose vial)

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APPENDIX 2 FOR FRAGMIN ODAC BD

DALTEPARIN IN THE PROPHYLAXIS AND TREATMENT OF VTE

TABLE OF CONTENTS

TABLES

Appendix 2

1. Dalteparin in the prophylaxis and treatment of VTE

Acute treatment of DVT was one of the first indications developed for dalteparin. From 1984-1993, the Sponsor conducted a total of 10 studies (Table 1) in this indication, all in non-cancer patients.

Table 1. Pfizer Sponsored Studies with Dalteparin 1984-1993

Study	Objective	Type of Study	Patients	Experimental Treatment	Comparator
86-96-291	DVT (S&E)	MC, R, DB	56	DAL 0.5-0.8 Anti FXa U/mL SC + OAC	UFH 0.5-0.8 Anti FXa U/ml SC + OAC
88-96-259	DVT (S&E)	R, DB	194	DAL IV infusion INR 3.5-5.0	UFH IV infusion INR 3.5-5.0
88-96-297	DVT (S&E)	R	119	DAL 120 IU/kg BID SC + OAC	UFH 240 IU/kg/12 h IV infusion + OAC
88-96-484	DVT (S&E)	R	84	Two year clinical follow-up to Study 88-96-297	-
89-96-060	DVT (S&E)	MC, R	60	DAL 0.5-0.8 Anti FXa U/mL SC + OAC	UFH IV infusion INR 1.5-3.0 + OAC
91-96-389	DVT (S&E)	R	122	DAL 100 IU/kg BID SC	DAL Anti FXa 0.5-1.0 IU/ml
91-96-544	DVT (S&E)	R, C	101	DAL 100 IU/kg BID SC + OAC	DAL 200 IU/kg qD SC + OAC
94-96-414	DVT (S&E)	MC, R, C	204	DAL 200 IU/kg qD SC + OAC	UFH IV infusion + OAC
93-96-549	DVT (S&E)	MN, MC, R, C	330	DAL 200 IU/kg qD SC + OAC	UFH IV infusion + OAC
94-96-235	DVT (S&E)	MN, MC, R, C	268	DAL 200 IU/kg qD SC + OAC	UFH IV infusion + OAC

DVT = Deep Venous Thrombosis, S&E = Safety and Efficacy, MN = multinational, MC = multi-center, R = randomized, C = controlled, DB = double blind, DAL = dalteparin

The difference in venographic scores before and after treatment was the primary determinant of efficacy in the Sponsor's early DVT treatment studies. The Marder scoring system which is an established measure of efficacy in this setting (Breddin, 2001), was adopted as a common endpoint in these and subsequent dalteparin clinical studies. The Marder scoring criteria (Marder, 1977) was used to grade the extension and localization of venographic thrombi using a scale from 0 to 40, with 40 points indicating total occlusion and 0 points indicating no DVT. An "Improvement" was a decrease of 1 or more points on the Marder scale, while a "Progression" was an increase of 1 or more points on the Marder scale.

1.1. Criteria for Diagnosis of VTE

Patients presenting with signs and symptoms suggestive of recurrent VTE were investigated according to pre-specified diagnostic algorithms and diagnosed based on objective testing. Positive results on venography or compression ultrasonography (CUS) were accepted for the diagnosis of lower limb DVT, as these methods have been shown to give comparable results (Lensing, 1989; Heijboer, 1993). A suspected symptomatic lower limb DVT was confirmed if any of the criteria in Table 2 was met.

Table 2. Criteria for Diagnosing Lower Limb DVT Post-baseline

Previous Venogram Available	Previous Venogram Unavailable
1. A new intraluminal filling defect in ≥2 projections on venography. 2. ≥5 cm extension of an intraluminal filling defect previously seen on a venograms	1. A constant intraluminal filling defect in ≥2 projections on venography. 2. Conversion of a previously fully compressible proximal venous segment on the most recent CUS to non-compressibility of that segment (venography was required for calf DVT found on CUS).

Source: Section 6.5.1.2.1 of CLOT Clinical Study Report

A suspected symptomatic PE was confirmed if any of the criteria in Table 2 were met. The accepted tests for the diagnosis of PE were: pulmonary angiography, ventilation perfusion (V/Q) lung scintigraphy, V/Q lung scintigraphy combined with CUS or venography or thoracic, contrast-enhanced spiral computerized tomography (CT). These approaches have been validated in previous studies (Hull, 1983; Hull, 1994; The PIOPED Investigators, 1990; Hansell, 1998; Mayo, 1997; Remy-Jardin, 1996). See Table 3.

Table 3. Criteria for Diagnosing PE Post-baseline

Previous Pulmonary Angiogram Available	Previous Pulmonary Angiogram Unavailable
1. A new intraluminal filling defect on pulmonary angiography. 2. Extension of an existing defect on pulmonary angiography. 3. A new sudden cut-off of vessels >2.5 mm in diameter on a pulmonary angiogram.	1. An intraluminal filling defect on pulmonary angiography. 2. Sudden contrast cut-off of vessels >2.5 mm in diameter on a pulmonary angiogram. 3. A high probability V/Q scan which shows new or larger areas of segmental perfusion defects with ventilation mismatch in comparison to the baseline V/Q scan. 4. A non-high probability V/Q scan and satisfaction of the criteria for lower limb DVT. 5. A spiral CT scan showing new or unequivocal, unenhancing filling defect in the central pulmonary vasculature. 6. Evidence of PE at autopsy or a death within the 6 month study period that is attributable to PE.

Source: Section 6.5.1.2.1 of CLOT Clinical Study Report

1.2. Initial Pilot Studies Establishing the Efficacy and Safety Profile of Dalteparin

Initial pilot studies 86-96-291, 88-96-259, 88-96-297, 88-96-484 and 89-96-060 were conducted in patients with either proximal or distal lower extremity DVT to establish the efficacy and safety profile of dalteparin. All patients received OAC for extended prevention of recurrence. Duration of treatment with dalteparin lasted between 5 and 10 days. These studies as a whole established that the efficacy and safety of dalteparin was comparable to UFH and provided the evidence to conduct further clinical studies that would develop a once-daily dosing regimen without laboratory monitoring for dose adjustments. Results from study 91-96-389 (Alhenc-Gelas, 1994) indicated that a fixed dose of dalteparin 100 IU/kg SC BID was at least as effective at improving Marder scores as the same therapy with monitoring of anti-FXa levels and dose adjustment over a 10 day treatment period. These results were consistent with emerging evidence in the 1990s that suggested the efficacy of LMWHs such as dalteparin was related to more than just their anti-FXa and anti-FIIa activity (Millet, 1996).

1.3. Randomized Trials of Single Daily Dosing of Dalteparin

Study 91-96-544 compared the effectiveness of dalteparin 200 IU/kg qD SC versus dalteparin 100 IU/kg BID SC. The difference in the frequency of Marder score changes on repeat venography between the 2 groups was not statistically significant (p=0.83). The results showed that dalteparin given qD SC in the treatment of acute DVT was an effective and safe alternative to a BID regimen (Holmstrom, 1992). This study indicated that the favorable efficacy and safety profile of dalteparin relative to the current standard of care could be maintained in a convenient, once-daily dosing regimen that required no laboratory monitoring.

Three further Sponsor studies were conducted to confirm these results: Studies 94-96-414, 93-96-549 and 94-96-235 were multi-center, randomized, controlled studies to compare the efficacy and safety of dalteparin in a fixed dose of 200 IU/kg SC qD versus a continuous intravenous (IV) infusion of UFH. The 200 IU/kg daily dosing of dalteparin followed by OAC in these 3 studies is the same as that used in the control arm of the CLOT study. A summary of the results is provided in Table 4.

1.3.1. Primary Efficacy Endpoint (Change in Marder Score)

The primary objective of each study was to compare the change in thrombus size (using Marder scores; Marder, 1977) before and after treatment. All studies were either of double blind design or employed study specialists blinded to treatment to assess the venograms.

Patients received a fixed dose of dalteparin (without monitoring for anti-FXa) of 200 IU/kg SC qD, or UFH dose adjusted to an activated partial thromboplastin time (aPTT) 1.5-3.0 times the control. Treatment lasted for 5-10 days. OAC therapy was started on the first or second day of treatment and dalteparin or UFH treatment was stopped when the OAC treatment had elevated the prothrombin time into the therapeutic range.

The study designs and populations in the 3 studies were sufficiently homogeneous to permit a meta-analysis (Lindmarker, 1995). In this meta-analysis the 95% CI for the treatment difference of the proportion of improved/unchanged venograms (Marder score) was -4.2 to +5.2, showing no statistically significant difference between dalteparin and UFH. The authors concluded that a fixed dose of once daily SC dalteparin was as equally safe and effective as continuous IV UFH in the initial treatment of DVT. A subsequent meta-analysis of 7 studies reached conclusions consistent with the Lindmarker analysis (Landorph, 1997). In summary, no significant differences in efficacy were noted between treatment with dalteparin and UFH in combination with OAC in any of the 3 studies.

Table 4. Summary of Studies Comparing Dalteparin 200 IU/kg SC qD to UFH in Acute Treatment of DVT

Study	No. Randomized	No. Evaluated Efficacy		Marder Score Change (% of patients)	
		DAL/OAC	UFH/OAC	DAL/OAC	UFH/OAC
93-96-549	330	92	98	Imp-51.1 Unch-37.0 Prog-12.0 p=0.152*	Imp-62.2 Unch-28.7 Prog-9.1
94-96-235	268	95	99	Imp-67.4 Unch-24.2 Prog-8.4 p=0.369*	Imp-61.6 Unch-26.3 Prog-12.1
94-96-414	204	91	89	Imp-60.4 Unch-34.1 Prog-5.5 p=0.62**	Imp-62.9 Unch-29.2 Prog-7.9
Total	802	278	286	Imp-59.7 Unch-31.7 Prog-8.6	Imp-62.2 Unch-28.7 Prog-9.1

Imp-improved, Unch-unchanged, Prog-progressed. * = Diff. between No. patients with improved Marder scores after treatment; ** = Diff. between No. patients with improved or unchanged Marder scores after treatment.

1.3.2. Secondary Efficacy Endpoints

A number of secondary endpoints were collected in the studies of the acute treatment of DVT, and were found to support the results of the primary endpoint.

Follow-up results taken at the 6 month time-point in studies 93-96-549, 94-96-414 and 94-96-235 indicated that unfavorable outcome (classified as death, other illness/complication, predisposing factor unknown at admission, recurrent thromboembolic event, or hospital treated after discharge) was similar in the dalteparin and UFH groups. Sixty dalteparin-treated patients (22%) and 78 UFH-treated patients (27%) experienced one of these unfavorable outcomes.

1.4. Published Reports of Dalteparin in Acute PE

Relative to DVT treatment there are less clinical trial data regarding LMWHs in the treatment of PE. Between 1995 and 2000 two in-patient studies were performed to compare dalteparin with different regimens for the treatment of acute PE.

- A randomized study in patients with acute, non-massive PE compared 29 patients who received 120 IU/kg dalteparin SC BID and 31 patients who received a continuous infusion of UFH 500 IU/kg/24 h subsequently adjusted to an aPTT 2-3 times control (Meyer, 1995) for 10 days. There was no PE recurrence in either group and the decrease in pulmonary vascular obstruction on perfusion lung scan between Day 0 to Day 10 was 17±13% in the dalteparin group and 16±33% in the UFH group.

- A randomized study in 87 patients with symptomatic PE compared patients treated with dalteparin 120 IU/kg SC BID or a UFH 5000 IU bolus followed by continuous IV infusion subsequently adjusted to an aPTT 1.5-2.5 times control (Kuijer, 1995). Although no additional safety data was provided in the publication, the authors concluded that treatment with fixed dose dalteparin was a satisfactory alternative to UFH in this setting.

In addition, Kovacs et al conducted 2 outpatient studies which included some PE patients:

- One hundred and eight outpatients diagnosed with PE (25 of whom also had cancer) received dalteparin 200 IU/kg qD SC for a minimum of 5 days and warfarin until the INR was therapeutic (>1.9) for at least 2 consecutive days (Kovacs, 2000). For all outpatients, the overall symptomatic VTE recurrence rate was 5.6%. There were 2/108 (1.9%) major bleeds. There were a total of 4 deaths (3.7%) with none due to PE or major bleeds. The authors concluded that outpatient management of PE with dalteparin and warfarin, as used in the control arm in the initial period of the CLOT study, was feasible and safe for the majority of patients.

- Kovacs (2001) reported a study in 417 outpatients with DVT and 80 with PE who were randomized with stratification for cancer or no cancer to receive dalteparin (200 IU/kg) or tinzaparin (175 IU/kg) and simultaneous OAC. LMWH was administered for a minimum of 5 days and stopped only after the INR was ≥ 2.0 for 2 consecutive days. The study was stopped early after a futility analysis revealed that the study was underpowered to be able to show a statistically significant difference between treatments. At this point the number of VTE recurrences was similar in both treatment groups (9 VTE recurrences in the dalteparin arm; 10 VTE recurrences in the tinzaparin arm).

Studies investigating treatment of PE or VTE with the LMWHs reviparin (The Columbus Investigators, 1997) and tinzaparin (Simonneau, 1997) versus dose-adjusted UFH, support the results from the studies mentioned above. In the Columbus study, similar rates of recurrent VTE were observed in VTE patients treated with reviparin or UFH over 12 weeks. In the Simonneau study, the combined number of patients with symptomatic PE who died, had symptomatic recurrent VTE or major bleeding was similar in the tinzaparin and UFH group up to Day 90.

Overall, published studies suggested that LMWHs, such as dalteparin, are safe and effective in the treatment of PE, and contributed to the introduction of LMWHs in this clinical setting and to the inclusion of patients with PE in the CLOT study.

1.5. Safety of Long Term Treatment with Dalteparin in Non Cancer Patients

Review of the labeling of other LMWHs and the existing literature on LMWHs (e.g. Hirsh, 2001; Leizorovicz, 1994) has identified 3 issues of particular clinical concern related to long term heparin use: (1) the risk of bleeding (major and minor), (2) the risk of

thrombocytopenia, (3) the risk of fractures (due to heparin-induced osteoporosis). The results from long term studies with dalteparin regarding these issues are discussed below.

1.5.1. Long Term Sponsor Studies

1.5.1.1. Study Design

Three long term dalteparin studies in non-cancer patients [FRIC (97-10-813)[1] (Klein et al 1997), FRISC (96-10-047)[2] (FRISC Study Group, 1996), and FRISC II (95-FRAG-025)] have been conducted by the Sponsor. These 3 studies investigated the use of dalteparin in patients with unstable coronary artery disease (UCAD). Although doses of dalteparin were lower in the chronic treatment period of these 3 studies than in the CLOT study, the duration of therapy in all 3 studies lasted between 45 and 90 days, thus providing meaningful long term safety data to support the results from the CLOT study.

In the 5-8 day acute treatment period, all patients in FRISC II received 120 IU/kg BID SC dalteparin, while patients in FRIC received open label dalteparin (120 IU/kg BID) or UFH, and patients in FRISC received double blind 120 IU/kg BID dalteparin or placebo. In the 45 day chronic treatment phase of FRIC and FRISC patients received double blind SC dalteparin (7500 IU qD) or placebo. The double blind chronic treatment phase of FRISC II was longer (90 days) and the dalteparin dose was greater (5000-7500 IU BID) than the respective durations and doses in the chronic periods of the FRIC or FRISC studies. In the chronic treatment phase of FRISC II, patients with no contraindications to early angiography/revascularization were randomized to an invasive or noninvasive revascularization strategy, while patients with contraindications to an invasive approach were assigned to the noninvasive strategy. Patients in all groups were then randomized to receive either placebo or dalteparin.

Patients in all 3 studies had a history of cardiovascular disease, including angina or myocardial infarction, at entry into the studies. Most patients were receiving concomitant medications to treat a number of underlying illnesses including hyperlipidemia, hypertension and diabetes mellitus. Treatment groups were well matched with regard to baseline characteristics.

1.5.1.2. Safety Issues

The incidence of bleeding events in all 3 studies was low. The initial treatment period (Days 1-8) of the FRIC and FRISC studies was characterized by a relatively higher major bleeding rate (1.2% and 0.8-6.3%) than in the longer chronic treatment period (0.5% and 0.3-2.0%). This may reflect a number of factors, including the relatively higher dose used in the initial treatment period and the fact that a patient's pre-disposition to a bleeding event is more likely to become apparent in the period shortly after treatment is started. Furthermore,

[1] FRIC = Fragmin in Unstable Coronary Artery Disease;

[2] FRISC = Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease;

as the FRIC and FRISC studies enrolled patients with unstable coronary events, this patient population is more likely to undergo invasive procedures early in the course of treatment. The incidence of minor bleeding events was only slightly higher in the chronic period of FRIC and FRISC than the acute period.

During the acute period of the FRISC study, a higher incidence of major bleeding (6.3%) was observed in the 150 IU/kg SC BID dalteparin group than had been observed in the dalteparin groups of other studies, leading to a decision to reduce the dose of dalteparin to 120 IU/kg BID. Though the incidence of bleeding declined once this dose reduction had been made, there is no clear evidence from these studies to suggest that the overall incidence of bleeding is indeed dose-related. Conversely, the incidence of major bleeding in the acute period of the FRISC II study (0.6-1.6%) was lower than in the chronic treatment period (2.3-3.7%), but this is likely to reflect the study design of the chronic period which mandated invasive procedures for many patients. Furthermore, analysis of the timing of major bleeding events in FRISC II indicated that there was no relationship between bleeding incidence and duration of treatment. The incidence of minor bleeding was also higher in the chronic period than the acute period.

The overall incidence of thrombocytopenia[**] in FRIC, FRISC and FRISC II was very low. Seven of the 10 cases of thrombocytopenia observed in dalteparin-treated patients in FRIC, FRISC and FRISC II occurred in the acute treatment periods of these studies. The low rate of thrombocytopenia was indistinguishable from that observed in patients receiving placebo.

The overall incidence of fractures in FRIC, FRISC and FRISC II was very low. No types of fracture were reported by >1 patient in FRIC or FRISC, and only 7 fractures were reported in the FRISC II study (of which 1 was deemed to be treatment related). Risk of fracture due to heparin-induced osteoporosis is not currently listed in the current USPI as a safety concern.

1.5.2. Long Term Studies Reported in the Literature

Ulander (2002) reported an open observational study in pregnant women with deep vein thrombosis (DVT). Most patients (29) had ultrasonographically confirmed DVT in the lower limbs, but 2 had DVT in the upper limbs. In 77% of cases the DVT was proximal. There were no statistical differences in maternal or neonatal data at baseline between the 2 groups, but the time-point in pregnancy for diagnosis of DVT tended to be earlier in the dalteparin group (21 weeks) than in the UFH group (27 weeks), although this was not statistically significant. Patients received either UFH (a mean dose of 25430 IU/day) or SC dalteparin (mean doses of 16,000 IU/day) from Day 1-7. After this period all patients received doses of SC dalteparin averaging around 7800 IU/24 h until delivery.

No thrombocytopenia or heparin-induced osteoporosis was reported, and only 1 dalteparin patient experienced a bleeding event.

[**] Defined as a platelet count $<100x10^9/L$

1.6. Safety of Dalteparin in the Acute VTE Setting

Doses of 200 IU/kg qD were given for 5-8 days in the 4 acute VTE studies (Studies 93-96-549, 94-96-235, 91-96-544 and 94-96-414). Unlike in Studies 93-96-549 and 94-96-235, major and minor bleeding events were not sub-classified in Studies 91-96-544 and 94-96-414. However, the overall rate of bleeding events was low (0-8%) and similar to rates observed in other studies.

Only 1 case of thrombocytopenia occurred in a dalteparin-treated patient in the 4 acute VTE studies. The treatment period employed in these studies was too short to result in any signs or symptoms of osteoporosis, and indeed no fractures were reported during any of the 4 studies.

1.7. Safety of Long Term Treatment with Dalteparin in Cancer Patients: The Catheter Study

The CATHETER study was a Phase 3, randomized, double blind, placebo controlled, multi-center, multinational trial in cancer patients who required placement of a central venous catheter (CVC) for administration of chemotherapy. Patients were randomly assigned in a 2:1 ratio to receive dalteparin 5000 IU or placebo (saline) subcutaneously qD for 16 weeks. Treatment continued until the occurrence of a catheter-related complication (CRC), a non-catheter-related thromboembolic event, unacceptable toxicity/adverse event, development of a prolonged PT/aPTT, or the completion of the 16 week period as per protocol. Of the 439 patients randomized to receive treatment, 425 actually received treatment.

The CATHETER study is notably different from the CLOT study in several respects. The CATHETER study was conducted in the primary thromboprophylaxis setting using a dalteparin dose that was significantly lower than those used in the CLOT study. A comparison of patient characteristics between the CLOT and CATHETER studies revealed that the CLOT study population was older and more debilitated. The frequency of patients ≥65 years was 46.2% in the CLOT study and 25.5% in the CATHETER study while the frequency of patients with an Eastern Cooperative Oncology Group (ECOG 2) performance status was 35.5% in the CLOT study and 10.7% in the CATHETER study.

Overall, the adverse event profile was consistent with the patient population under treatment. The vast majority of patients reported at least 1 treatment emergent adverse event, with a frequency comparable between dalteparin and placebo (89.5% dalteparin versus 86.4% placebo treated patients).

The frequency of patients reporting at least 1 drug-related event was relatively low in each group (20.4% versus 16.4% in the dalteparin and placebo arm, respectively). Overall, drug-related adverse events were mild or moderate in severity in the majority of the cases in both treatment arms. The incidence and the profile of adverse events reported as drug-related were comparable between dalteparin and placebo. As expected, the proportion of patients

who reported at least 1 drug-related reaction at the injection site was higher with dalteparin than with placebo (9.5% versus 2.9%, respectively). However, all the observed local reactions were mild or moderate in severity. Notably, the frequency of injection site reaction on dalteparin observed in this study was consistent with that reported in the CLOT study. The frequency of patients who reported at least 1 drug-related hemorrhagic event of any grade during the study was comparable between the 2 arms (17.5% dalteparin versus 15.0% placebo patients). Only 1 major bleeding event in the dalteparin arm and 1 in the placebo arm were confirmed by the Adjudication Committee.

Seventeen patients in the dalteparin group (6.0%) and 9 patients in the placebo group (6.4%) experienced thrombocytopenia during the study. Only 2 cases of thrombocytopenia were reported as related to dalteparin, a frequency lower than that reported in the placebo arm (0.7% versus 2.1%, respectively).

A total of 31 dalteparin treated patients (10.9%) and 18 placebo-treated patients (12.9%) died, most of them after the end of treatment (26 dalteparin and 15 placebo treated patients). Most deaths in each treatment group were due to tumor progression or cancer-related reasons and their frequency was comparable between the 2 arms.

The frequency of SAEs was similar in the 2 treatment arms (28.4% dalteparin- and 32.9% placebo-treated patients). A total of 6 SAEs in the dalteparin arm (2.1%) and 5 SAEs in the placebo arm (3.6%) were reported as drug related in either the clinical database or the drug safety and surveillance database.

At least 1 adverse event was reported to cause permanent discontinuation of the study drug in 40 (14.0%) and 22 (15.7%) patients in the dalteparin and placebo arm, respectively.

1.8. Dalteparin Post – Marketing Experience in VTE

It is estimated that over 46 million patients have been prescribed dalteparin for a number of indications related to treatment or prophylaxis of VTE. A search of Pfizer's safety database cumulatively through 30 April 2006 for dalteparin non-clinical study and solicited cases identified 3567 cases with adverse events. Of the 2976 cases reporting gender, there were 1857 females and 1119 males. In the 2463 cases reporting patient age, age ranged from neonate to 98 years with a mean age of 61.1 years. In the 2254 cases reporting case outcome, 1450 patients were recovered/recovering, 93 patients recovered with sequelae, 361 patients were not recovered, and 350 patients died. Case seriousness was assessed as non-serious in 1549 cases and serious in 2018 cases. MedDRA (version 9.0) Preferred terms reported in $\geq$ 2% of these 3567 cases included Thrombocytopenia (12.1%), Drug exposure during pregnancy (7.0%), Hematoma (6.1%), Pulmonary embolism (5.2%), Hemorrhage (4.7%), Injection site pain (3.1%), Cerebral hemorrhage (3.0%), Rash (2.6%), Deep vein thrombosis (2.4%), Drug ineffective (2.2%), Pruritus (2.2%), Injection site reaction (2.1%), Thrombocythemia (2.1%), and Gastrointestinal hemorrhage (2.0%). The majority of these preferred terms is considered expected according to the Fragmin (dalteparin sodium) United States Package Insert (Appendix 1) or are attributable to the patient's medical history, conditions and disease under treatment.

It can be concluded from this latest review of the safety database and from the previous Periodic Safety Update Reports (PSUR) provided to the FDA that the overall number of reported adverse events is low in comparison with the number of patients exposed, and the majority of events are expected reactions to the drug. No changes in severity of the suspected adverse drug reactions (serious and non serious) have been observed as compared with the known safety profile of dalteparin.

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APPENDIX 3 FOR FRAGMIN ODAC BD

CENSORING OF PRIMARY ENDPOINT IN THE CLOT STUDY

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Appendix 3

1. Censoring of Primary Endpoint in the CLOT Study

Let H_d and H_o be the 6-month cumulative hazard of a VTE in the dalteparin and OAC groups, respectively.

Let C be the proportion of the 6 month observation time censored due to mortality common to both groups.

Let $\theta_d H_d$ and $\theta_o H_o$ be the 6-month cumulative hazard (not observed) of a VTE over the time censored by mortality in the dalteparin and OAC groups, respectively. The parameter θ represents the proportional change in the 6-month cumulative hazard over the censored time.

The relative risk (RR) in the absence of censoring is:

$$[(1-C)\, H_d + C\, \theta_d\, H_d\,] / [(1-C)\, H_o + C\, \theta_o\, H_o\,]. \qquad (1)$$

Either in the presence of censoring or with $\theta_d = \theta_o$, equation (1) reduces to H_d / H_o, Therefore, unless θ_d and θ_o are not equal, the RR is the same with or without censoring. This is true even if the patients who were censored due to death had a higher (or lower) hazard rate of VTE. Consequently, the CLOT study yields an unbiased estimate of RR as long as the risk of VTE is affected in the same way in both treatment groups.

Hypothetical Informative Censoring

In order to show the robustness of the VTE results we examine the hypothetical informative censoring of the type $\theta_d H_d = \theta_o H_o$. This implies that dalteparin would have no benefit over the censored time.

As noted in the briefing document, the 6-month cumulative probability of VTE was estimated by the Kaplan-Meir method to be

$$P_d = 0.087 \text{ and } P_o = 0.172$$

for the dalteparin and OAC groups, respectively.

Using the relationship that

$$\log (1-P_d) = -H_d \quad \text{and} \quad \log (1-P_o) = -H_o$$

leads to $H_d = 0.091$ and $H_o = 0.189$

For the purpose of illustrating the robustness of the efficacy results to censoring by mortality we will assume 3 hypothetical cases; that the 6-month cumulative probability in patients censored by death is 0.346, 0.516 and 0.688, i.e., 2, 3 and 4 times the cumulative probability observed in the OAC group. The corresponding cumulative hazard ratio is increased by θ_o = 2.25, 3.84 and 6.16 in the OAC group and by θ_d =4.67, 7.97 and 12.80 in the dalteparin group.

For each of the 3 hypothetical cases the probability of a VTE over the censored time was calculated for each censored patient. These probabilities were summed over all censored patients within each treatment group to obtain the espected number of censored VTEs. Because the probability of a VTE was much greater in the first 30 days than the remaining time of the 6 month obsevation period, the cumultive hazard over the first 30 days and the cumulative hazard from days 30 to 180 were used in the calculations.

The expected number of VTEs were then added to the observed number of VTEs and analyzed for differences between treatment groups. The results of the 3 hypothetical examples follow Table 1.

Table 1. Hypothetical Cases of Informative Censoring

θ_o	θ_d	P		E			
OAC	**DAL**	**OAC**	**DAL**	**OAC**	**DAL**	**RR**	**p**
2.25	4.67	0.346	0.346	12.5	14.0	0.63	0.010
3.84	7.97	0.516	0.516	20.0	22.4	0.68	0.020
6.16	12.80	0.688	0.688	29.4	33.1	0.73	0.036

P is the 6 month probability of a VTE. E is the expected number of additional VTEs censored by death. RR is the relative risk obtained by the Mantel-Haenszel Method after adding the expected VTEs to the observed VTEs
OAC: oral anticoagulant; DAL: dalteparin

These hypothetical cases show the robustness of the significant benefit of dalteparin on VTE with regard to mortality censoring. Even if one assumes the 6 month probability of a VTE to be 0.688 in the patients censored by death (4 times the observed probability in the OAC group) the benefit in the dalteparin group would still be statistically significant. This is because the amount of censoring due to mortality is almost the same in the two treatment groups and because many of the patients who died did so after more than 30 days of treatment where the probability of a VTE was low relative to the initial 30 days.

We reiterate that there is no basis to assume that θ_d and θ_o are not equal. These analyses are presented only to show that even under strong assumptions of informative censoring the dalteparin benefit on VTE remains significant.

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