CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-484

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION — NDA

NDA #: 20-484

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Drug Class: 1S

Applicant: DuPont Pharmaceuticals Company

Name of Drug: Innohep (tinzaparin sodium) injection

Indication: For treatment of deep vein thrombosis (DVT); [redacted]

Documents Reviewed: NDA 1.1, 1.58-1.159 Dated June 30, 1999
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Statistical Reviewer: Milton C. Fan, Ph.D.

Medical Reviewer: This review has been discussed with medical officer, Ruyi He, M.D.

Key Words: One study, non-inferiority trial, interim analysis, multiplicity, and sensitivity analysis

I. Background

In this NDA, the applicant is seeking approval of tinzaparin for two indications:

1). the treatment of acute deep vein thrombosis (DVT) with or without pulmonary embolism (PE) when administered in conjunction with warfarin.

2) [redacted]

II. Treatment of Acute Deep Thrombosis

Two controlled studies (DMP 702-900 and DMP 702-904) and one uncontrolled study (DMP 702-928) have been submitted to support the efficacy of tinzaparin for the treatment of acute DVT, with and without PE, when administered in conjunction with warfarin.

In study DMP 702-900, patients had documented acute, proximal DVT at study entry and about 30% had lung scan abnormalities consistent with co-existent PE. The study started on December 15, 1988 and ended on April 22, 1992.

In Study DMP 702-904, patients presented with acute symptomatic PE, of which a half had objectively-documented, co-existent, proximal DVT. The study started on July 15, 1995 and ended on November 5, 1996.

This review will address only the two controlled efficacy studies (DMP 702-900, DMP 702-904).

A. Study DMP 702-900

1. Description of Study

This trial was a multi-center (17), double-blinded, randomized, parallel-group study. The study was conducted in North America. The objective of this study was to compare the efficacy and safety of low molecular weight (LMW) heparin (tinzaparin), given subcutaneous once daily without laboratory monitoring with continuous intravenous unfractionated heparin (monitored using aPTT) for the initial treatment of patients with acute proximal deep-vein thrombosis.

This trial was designed to demonstrate that s.c. tinzaparin was no less effective than continuous IV heparin.

Patients having acute proximal-vein thrombosis documented by venography (thrombosis of the popliteal or more proximal deep veins of the leg) were enrolled and randomized to receive one of the following treatment regimens:

1) Continuous intravenous unfractionated heparin monitored using the aPTT (1.5 – 2.5 control value).
2) Subcutaneous LMW heparin (tinzaparin) given in a fixed dose of 175 F X_aI units/kg body weight once daily.

Randomization to treatment groups was based on a computer-generated, randomized allocation prepared in blocks of two in each of the four strata at each site. Stratification was performed by center according to the presence/absence of a history of DVT/PE and the presence/absence of bleeding risk.

The initial treatment period began on the day of randomization (Day 0) and ended on the last day of treatment with tinzaparin or unfractionated heparin (generally Day 5). All patients in both groups received therapy with warfarin (p.o.) for 90 days starting on Day 2 of initial therapy, and treatment with either intravenous heparin or subcutaneous LMW heparin was discontinued on the sixth day.

The study's primary efficacy analysis was based on the cumulative 90 day incidence of objectively confirmed thromboembolic events (recurrent DVT/PE). Patients with signs or symptoms of DVT underwent impedance plethysmography (IPG) and, if this was positive, also underwent venography. Patients with signs or symptoms of PE underwent ventilation perfusion lung scanning and/or pulmonary angiography.

The observed frequencies of recurrent venous thromboembolism and bleeding complications between the treatment groups were compared using Fisher's Exact test. If no statistically significance differences were detected, the 95% confidence interval on the observed difference in the frequency of recurrent venous thromboembolism between the treatment groups was calculated using the normal approximation to the binomial distribution.

Subcutaneous tinzaparin would be considered as effective as continuous intravenous unfractionated heparin if any observed difference in the incidence of recurrent venous thromboembolism between these two regimens did not exceed 5 to 6% in favor of heparin.

Based on an expected incidence of recurrence of 5% in both groups, approximately 80 to 100 patients per treatment group were required to provide sufficiently narrow confidence intervals to exclude a true difference in the incidence of recurrent venous thromboembolism of 5 to 6% or more in favor of intravenous unfractionated heparin. The applicant chose a more conservative sample size of 200 patients per group to ensure a definitive conclusion could be made about the effectiveness of tinzaparin, even if the observed recurrence rates varied slightly from the hypothesized rate of 5%.

2. Applicant's Analysis

A total of 438 patients were randomized, 216 to receive tinzaparin and 222 to receive unfractionated heparin. Of these, 435 patients (216 tinzaparin and 219 heparin) received at least one dose of active study medication and were included in the intent-to-treat (ITT) population.

Of the 435 randomized and dosed patients, 73 (17%) patients were withdrawn prematurely from the study, 30 (14%) patients from the tinzaparin group and 43 (20%) patients from the heparin group. Overall, approximately two-thirds of the patients who withdrew did so because of an adverse event, the majority of these adverse events were serious adverse events or bleeding.

Seven (3%) tinzaparin and 15 (7%) heparin patients had no venogram at study entry. In the tinzaparin treatment group, there were three (1%) patients with no perfusion lung scan at entry. In the heparin treatment group, there were seven (3%) patients with no perfusion lung scan at entry. In the tinzaparin group, five (2%) patients had no or inadequate testing of a suspected recurrent thromboembolic event. In the heparin group, there was seven (3%) patients who had no or inadequate testing of a suspected recurrent thromboembolic event.

The summary of treatment assignment by stratification variable is given below.

Summary of Treatment Assignment by Stratification Variable
Study DMP 702-900

Strata Variable		Treatment	
Bleeding Risk	History of DVT/PE	Tinzaparin	Heparin
Low	No	129	135
	Yes	30	32
High	No	47	43
	Yes	10	12

Obtained by this reviewer from Applicant's SAS data set D900.Adjud..

As seen from the above, the distribution of patients across randomization strata was comparable for the two treatment groups. Approximately 75% of patients were at a low-risk of bleeding and approximately 80% had no history of DVT/PE.

Three (1%) patients in the tinzaparin treatment group and eight (4%) patients in the heparin treatment group with baseline platelet counts below 150 x 10^9/L were incorrectly stratified to the low bleeding risk group. In addition, one (<1%) patients in the tinzaparin treatment group was incorrectly randomized as having no history of thromboembolism despite having a history of PE. For analysis, these patients were evaluated in the stratum to which they were randomized.

The intent-to-treat (ITT) population included all patients randomized into the study that received at least one dose of active study drug.

Efficacy variables were assessed throughout the 90 days following the start of treatment medication. All efficacy analyses dealing with death and thromboembolic events (recurrent DVT pr PE) were based on Committee adjudicated events unless otherwise specified.

The primary efficacy analysis compared the 90-day cumulative incidence of thromboembolic events (DVTs and PEs combined) in the two treatment groups, using Fisher's Exact test as specified in the protocol.

The two treatment groups were also compared for death, and the 90-day cumulative incidence of two composite endpoints (thromboembolic events plus all deaths or thromboembolic event plus abrupt deaths only) using Fisher's Exact test.

Event rates were also compared by the Chi-square test. Time-to-event analyses through 90 days were performed for recurrent thromboembolic events, mortality, and the composite endpoints by the Kaplan-Meier survival estimates; between treatment effects were tested by the log-rank statistic.

2.1 Treatment Group Comparability

Attached Table 1 presents the demographic and baseline characteristics of all patients included in the ITT population.

As seen from Attached Table 1, the two treatment groups were similar with regard to most demographic characteristics and thromboembolism characteristics. However, the majority of patients in the tinzaparin group were male (61%) compared with equal numbers of males and females (50%) in the heparin group (p=0.034).

The majority (55%) of patients in the tinzaparin group were at least 65 years of age (mean age 62.6 years) while the majority (54%) in the heparin group were less than 65 years of age (mean age 59.2 years, p=0.042).

Patients in the tinzaparin groups were slightly taller than those in the heparin group (171.3 vs. 168.4, p=0.031).

2.2 Applicant's Analysis of the Primary Efficacy Variable

The primary efficacy analysis was the 90-day cumulative incidence of recurrent thromboembolic events (DVT and /or PE).

2.2.1 Efficacy Analysis by Investigator's Read

The results of applicant's analysis of the recurrent thromboembolic events for the suspected events reported by the study investigators are given below.

Thromboembolic Event Rates for Suspected Events Reported by Investigators Study DMP 702-900

	Tinzaparin (N=216)	Heparin (N=219)	Difference (Hep-Tin)	P-value	95% C.I.
Recurrent Thromboembolic Event	30 (13.9%)	34 (15.5%)	1.6%	0.685	(-5.01%, 8.29%)
DVT	19 (8.8%)	23 (10.5%)	1.7%	0.627	(-3.84%, 7.25%)
PE	16 (7.4%)	14 (6.4%)	-1.0%	0.709	(-5.78%, 3.75%)

P-value was obtained by Fisher's Exact test.
Copied from Table D.1.8, page 246, Vol. 39.

As seen from table above, there was no significant difference between treatments with regard to recurrent thromboembolic events. It can also be seen that tinzaparin could be up to 5% worse than heparin.

2.2.2 Adjudicated Efficacy Decision

Twelve of 44 (3 of 19 form the tinzaparin treatment group and 9 0f 25 from the heparin treatment group) suspected DVTs were adjudicated as a definite DVT. Nine of 34 (3 of 18 from the tinzaparin treatment group and 6 of 16 from the heparin treatment group) suspected PEs were adjudicated as a definite PE. Overall, 16% (6 of 37) of the suspected recurrent thromboembolic events that occurred within the tinzaparin treatment group and 37% (15 of 41) of the suspected events that occurred within the heparin treatment group were confirmed by the Adjudication Committee.

The number of adjudicated DVTs and PEs compared with the total number of suspected events are given below.

Tabulation of Adjudication Decisions by Efficacy Variable
Study DMP 702-900

		Tinzaparin Adjudication Decision		Heparin Adjudication Decision	
Suspected Event	Total Event	No Event	Event	No Event	Event
Suspected Recurrent DVT	44	16	3	16	9
Suspected PE	34	15	3	10	6
All Recurrent Thromboembolic Event	78	31	6	26	15

Compile from Table 6.1, page 101, Vol. 36

The most common reason in both treatment groups for which an event was rejected as a DVT was "a normal IPG." The most common reason in the tinzaparin group for which an event was rejected as a PE was "no new defects on lung scan." The most common reason in the heparin group for which an event was rejected as a PE was "no objective testing was performed."

The results of applicant's analysis of the adjudicated recurrent thromboembolic events are given below.

Primary Efficacy Analysis: Thromboembolic Event Rates
Study DMP 702-900

	Tinzaparin (N=216)	Heparin (N=219)	Difference (Hep-Tin)	P-value	95% C.I.
Recurrent Thromboembolic Event	6 (2.8%)	15 (6.8%)	4.1%	0.071	(0.07%, 8.07%)
DVT	3 (1.4%)	9 (4.1%)	2.7%	0.141	(-0.34%, 5.78%)
PE	3 (1.4%)	6 (2.7%)	1.4%	0.503	(-1.32%, 4.02%)

P-value was obtained by Fisher's Exact test.
Copied from Table 6.4, page 104, Vol. 36.

As seen from the table above, the treatment difference in the recurrent thromboembolic event did not reach statistical significance. However, the 95% confidence interval on the difference in events clearly excludes a difference of greater than the protocol-defined criteria of 5% to 6% in favor of heparin.

The superiority of tinzaparin was supported by time to event analysis for the recurrent thromboembolic event (p=0.048 log-rank test).

2.2.3 Homogeneity of Treatment Effect

Due to the large number of centers, the small sample size of the majority of the centers, and the low incidence of thromboembolic events, the applicant pooled results from the 17

centers into seven centers. It was required that pooled centers have at least two patients with an event in order to have valid center by treatment interaction test. The medium sized centers were pooled together by geographic location. The small centers were pooled with the larger centers that did not have at least one event per treatment group by geographic location whenever possible. Large centers that had at least one event per treatment group were used alone.

The incidence of thromboembolic events by pooled centers is summarized in Attached Table 2. The applicant performed DerSimonian and Laird random effects method to test of homogeneity of treatment effects. The test for homogeneity of treatment effects across pooled centers indicated there was statistically significant treatment by center interaction at the significance level of 20% (p=0.182).

2.2.4 Subgroup Analysis

Treatment groups were compared using the Chi-square test, rate difference and the 95% CI on the difference for the following factors: age (<65 years vs. ≥65 years); sex (male vs. female); race (white vs. other); prospectively defined stratification variables bleeding risk (high vs. low) and history of DVT/PE (yes vs. no); history of cancer (an important risk factor); and pulmonary embolism on baseline lung scan (defined as segmental or greater defects).

The results of subgroup analysis are summarized in Attached Table 3.

As seen from Attached Table 3, there were significantly fewer recurrent thromboembolic events in the tinzaparin group compared with the heparin group among patients with no history of cancer and among whites.

2.3 Applicant's Analysis of Secondary Efficacy Variables

The treatments were also compared with respect to all-cause mortality and abrupt death. All-cause mortality was introduced after the protocol was finalized, but before the first case was reviewed. All deaths occurring during the 90-day study period were included in the analyses.

Two composite endpoints were considered: all deaths and thromboembolic events (DVT's and PEs) and abrupt deaths and thromboembolic events. The incorporation of composite endpoint analyses followed discussions with the FDA at a pre-NDA meeting in June 1992.

2.3.1 Efficacy Analysis by Investigator's Read

Results of the secondary efficacy analyses of death and the composite endpoints of death plus thromboembolic events and abrupt death plus thromboembolic events for the suspected events reported by the study investigators are summarized below.

Death and Composite Endpoints for Suspect Events Reported by Investigators
Study DMP 702-900

	Tinzaparin (N=216)	Heparin (N=219)	Difference (Hep-Tin)	P-value	95% C.I.
Death	10 (4.6%)	21 (9.6%)	5.0%	0.061	(0.16%, 9.76%)
Abrupt Death	3 (1.4%)	13 (5.9%)	4.5%	0.019	(1.05%, 8.04%)
Composite Endpoint I (Death, DVT, and PE)	37 (17.1%)	47 (21.5%)	4.3%	0.275	(-3.07%, 11.74%)
Composite Endpoint II (Abrupt Death, DVT, and PE)	31 (14.4%)	40 (18.3%)	3.9%	0.300	(-3.02%, 10.85%)

P-value was obtained by Fisher's Exact test.
Copied from Table D.1.8, page 247, Vol. 39.

As seen from table above, the treatment difference in the all cause death did not reach statistical significance. However, the 95% confidence interval on the difference in events clearly excludes a difference of greater than the protocol-defined criteria of 5% to 6% in favor of heparin. There was a treatment difference in favor of tinzaparin in the abrupt death. There was no significant difference between treatments with regard to composite endpoint I (death, DVT and PE) and composite endpoint II (abrupt death, DVT and PE).

2.3.2 Efficacy Analysis Based upon Adjudicated Events

Results of the secondary efficacy analyses of death and the composite endpoints of death plus thromboembolic events and abrupt death plus thromboembolic events are summarized below.

Secondary Efficacy Analysis: Death and Composite Endpoints
Study DMP 702-900

	Tinzaparin (N=216)	Heparin (N=219)	Difference (Hep-Tin)	P-value	95% C.I.
Death	10 (4.6%)	21 (9.6%)	5.0%	0.061	(0.16%, 9.76%)
Abrupt Death	3 (1.4%)	13 (5.9%)	4.5%	0.019	(1.05%, 8.04%)
Composite Endpoint I (Death, DVT, and PE)	15 (6.9%)	30 (13.7%)	6.8%	0.027	(1.08%, 12.43%)
Composite Endpoint II (Abrupt Death, DVT, and PE)	8 (3.7%)	23 (10.5%)	6.8%	0.008	(2.02%, 11.58%)

P-value was obtained by Fisher's Exact test.
Copied from Table 6.5, page 106, Vol. 36.

As seen from the table above, the treatment difference in the all cause death did not reach statistical significance. However, the 95% confidence interval on the difference in events clearly excludes a difference of greater than the protocol-defined criteria of 5% to 6% in favor of heparin. There was a treatment difference in favor of tinzaparin in the abrupt

death, composite endpoint I (death, DVT and PE) and composite endpoint II (abrupt death, DVT and PE).

3. Reviewer's Evaluation

3.1 Stratification

The stratification was not pre-specified in the protocol. The slightly imbalance on gender and age might be due to overstratification.

This reviewer performed analyses of recurrent thromboembolic event using Mantel-Haenszel method adjusted for gender and age (<65 vs. ≥65). The resulting p-values were 0.054 and 0.068 for gender and age, respectively.

3.2 Reviewer's Comments on Adjudicated Efficacy Decision

The use of the adjudicated efficacy decision was not pre-specified in the protocol. The adjudicated efficacy decision favors tinzaparin. There was a disproportionate number of adjudicated recurrent thromboembolic events (p=0.043); 6 of 37 (16%) of the suspected recurrent thromboembolic events that occurred within the tinzaparin treatment group compared to 15 of 41 (37%) of the suspected events that occurred within the heparin treatment group.

3.3 Superiority of Tinzaparin over Heparin

This study was designed as a non-inferiority trial. It was pre-specified in the protocol that tinzaparin would be as considered as effective as unfractionated heparin if any observed difference in the incidence of recurrent venous thromboembolism between these regimens did not exceed 5% to 6% in favor of heparin. It should be noted that this would allow tinzaparin to be up to 33% worse than heparin..

The treatment difference in the recurrent thromboembolic event did not reach statistical significance in both analysis by investigator read and analysis by adjudicated read using pre-specified statistical method (Fisher's exact test).

Both composite endpoints I (death, DVT, and PE) and II (abrupt death, DVT, and PE) were specified post-hoc. The apparent superiority of tinzaparin (unadjusted p-value) over unfractionated heparin was shown in the adjudicated read analysis but not in the investigator read analysis.

3.4 Reviewer's Comments on Applicant's Homogeneity of Treatment Effects

The method of pooling of centers was not pre-specified in the protocol. The applicant's pooling was done post-hoc. The applicant performed the DerSimonian and Laird random effects method to test of homogeneity of treatment effects. For the incidence of thromboembolic events, the treatment by center interaction was significant at significance

level of 20% (p=0.182). As seen from Attached Table 2, all centers except Centers 1 and 6, showed a trend in favor of tinzaparin. Center 7 was the only center where the difference between treatment groups achieved statistical significance in favor of tinzaparin.

Hence the results in favor of tinzaparin in term of incidence of thromboembolic events were not consistent across the pooled centers. Furthermore, treatment difference would be non-significant if the analysis was adjusted for centers (p=0.122 by applicant's DerSimonia and Laird random effects method)

B. Study DMP 702-904

1. Description of Study

This trial was an open label, multi-center (57), randomized, and parallel-group study. This trial was conducted in France, Belgium and Switzerland. The study was not blinded, because of the different routes of drug administration. The objective of the design was to compare the efficacy and safety of tinzaparin (s.c.) with heparin (IV) in patients with PE; both groups received anticoagulant therapy (p.o.) for 90 days starting between Days 1 and 3.

Patients at least 18 years of age in France and Belgium and 20 years of age in Switzerland, weighting no more than 120 kg, with a clinically symptomatic pulmonary embolism confirmed by either perfusion ± ventilation lung scan, venous compression ultrasonography, ascending contrast venography or pulmonary angiography was eligible to be enrolled.

The study included two phases: Phase I (initial treatment) Day 1 to Day 8 and Phase II (long-term treatment) Day 9 to Day 90.
Patients were randomized to receive either tinzaparin or UFH. Central randomization, stratified by center was used.

> Tinzaparin in weight-adjusted dose: 175 Anti-Xa IU/kg, in one daily subcutaneous injection, not exceed 18,000 IU Anti-Xa in 24 hours.
>
> Unfractionated Heparin (UFH): APTT-adjusted dose to achieve a patient/control APTT ratio of between 2 and 3, administered in continuous intravenous infusion.

The primary efficacy variable was a composite endpoint consisting of critical events defined as the recurrence of symptomatic venous thromboembolism (PE or DVT), major bleeding, and death, due to any cause during the first 8 days of treatment (Phase I). These events were blindly adjudicated by the Critical Event Committee. Note: this endpoint is made up of a combination of efficacy and safety.

The secondary endpoints were every critical event (symptomatic venous thromboembolic recurrence, major bleeding, death) during phase I of the study and during the entire

duration of the study (phases I and II). The occurrence time would be determined separately for each critical event throughout the entire study.

Statistical analysis of the primary endpoint and of all the variables measured during the study was performed on an intention to treat basis for the randomized patients and for whom data was collected.

The statistical comparison between the two treatment groups was made using a type I error of 5% (α=0.05). All the test results were calculated using a two-sided p-value, including the primary endpoint. This is in contrast to the protocol in which a one-sided test was specified.

The primary endpoint and the occurrence rate of critical events were compared between two groups by a Chi-square or Fisher's exact test. The occurrence time was analyzed by a survival model and the Kaplan-Meier survival rate at 90 days.

All cases of critical events occurring during the study, such as clinically suspected thromboembolic events (PE or DVT), bleeding and deaths were submitted blindly to the Critical Events Committee composed of 3 members. The Committee exercised its functions according to the criteria specified in the protocol, and by reviewing all pertinent documents available, such as medical imaging, results of laboratory tests and autopsy reports. Adjudication of the events was determined by majority vote. The decision was final and binding and might not be modified in any way.

The expected frequency of failure with continuous IV UFH treatment is 15 ±5%. With a type I error of 5% (α=0.05) and with a power of 80% (type II error β=0.20), a sample of approximately 600 patients (300 per group) was chosen to ensure the detection of a significant reduction of frequency of 40 to 60% with tinzaparin for various predicted values of frequency with UFH.

2. Applicant's Analysis

Among 1482 PE patients evaluated, 612 patients were eligible and were randomized into study (304 to tinzaparin and 308 to heparin). Of the 612 randomized patients, 4 patients (3 tinzaparin and 1 heparin) did not receive treatment and 608 (301 randomized to tinzaparin and 307 randomized to heparin) patients received treatment.

The intent-to-treat (ITT) population included all patients randomized into the study who received at least one dose of active study drug. Patients in the ITT population were analyzed according to the treatment to which they were randomized. In addition, the efficacy measures were analyzed using a pure ITT population that included all randomized patients.

These 608 (301 in tinzaparin and 307 in heparin) treated patients (based on the treatment group assigned by randomization) constituted the ITT population.

Of the 608 patients in the ITT population, a subset of 312 patients (156 patients in each treatment group) had documented proximal DVT as a coexistent baseline condition; this group constituted the proximal DVT subgroup population.

Two patients (Patient 2503 and 4204) were randomized to receive heparin but were treated with tinzaparin. Thus, 303 patients actually received tinzaparin treatment while 305 patients received heparin. These 608 treated patients (based on treatment actually received) constituted the safety population.

Of 608 treated patients, 525 (86%) patients completed the study; 83 (14%) patients were withdrawn prematurely, 27 (4%) patients during the initial study period, and 56 (9%) patients during the long-term follow-up period. The most common reason for premature withdrawal was an AE.

One patient was randomized twice at Center 31 because of a power failure at the end of the first randomization. The investigator kept the second randomization and discarded the first. Five randomizations were performed manually by the emergency operator at RCTs.

2.1 Treatment Group Comparability

The demographic characteristics, risk factors, and medical/surgical history of patients in the ITT population are summarized by treatment in Attached Table 4.

As seen from Attached Table 4, the demographic characteristics of patients in the two treatment groups were comparable. While slightly more tinzaparin patients were smokers and more tinzaparin patients were considered obese, the two treatment groups were similar in their risk factors for thromboembolic disease.

Although slightly more tinzaparin patients experienced dyspnea (93% of tinzaparin patients vs. 86% of heparin patients), the two treatment groups in the ITT population were considered similar with regard to baseline clinical characteristics.

More tinzaparin patients received heparin at a curative dose level for more than 24 hours (but less than 36 hours) before enrollment in the study (16 tinzaparin patients vs. 7 heparin patients).

2.2 Applicant's Analysis of the Primary Efficacy Variable

The primary endpoint, a combination of efficacy and safety outcomes, was the evaluation (based on the blindly adjudicated events) of the occurrence rate of symptomatic recurrent venous thromboembolism (PE and/or DVT), major bleeding, or death during the initial treatment period (the first 8 days of the study).

The protocol specified that primary endpoint rates were to be compared between the two treatment groups using a one-sided Chi-square or Fisher's exact test. Although the protocol specified calculating a one-sided 95% confidence interval for the observed

difference of rates, a two-sided test was used to compare treatment groups and to calculate a two-sided 95% confidence interval.

2.2.1 Adjudication Process and Efficacy Decisions

All suspected recurrent thromboembolic event were evaluated and classified by the Critical Events Committee according to protocol-specified criteria. A suspected PE or DVT was confirmed ('yes" or "probable") or rejected ("no" or "doubtful") by the Committee.

Suspected major bleeding events were confirmed ("yes") or ("no") by the Critical Events Committee.

All deaths were reported and evaluated by members of the Critical Events Committee who were blinded to the patient's treatment assignment.

The Committee reviewed 128 suspected events; 122 of these events met the protocol-specified criteria for classification as suspected critical events (i.e., PE, DVT, death, and major bleed).

Overall, 8 of 71 suspected PEs were adjudicated as definite or probable PE and 18 of 19 suspected major bleeds were adjudicated as major bleeds. All six suspected DVTs and all 26 deaths were confirmed by the Committee.

The results of adjudication decisions by treatment group during the initial treatment period (Phase I), during the follow-up period (Phase II), and over the entire study period (Phase I and Phase II) are given below.

Tabulation of Adjudication Decisions of Critical Events: ITT Population
Study DMP 702-904

Suspected Event	Total Event	Tinzaparin Adjudication Decision		Heparin Adjudication Decision	
		No Event[a]	Event[b]	No Event[a]	Event[b]
Initial Treatment Period					
PE	22	5	3	12	2
Death	7	0	4	0	3
Major Bleed	8	0	3	0	5
Other[c]	3	0	1	0	2
Follow-Up Period					
PE	49	31	1	15	2
DVT	6	0	2	0	4
Death	19	0	8	0	11
Major Bleed	11	1	4	0	6
Other[c]	3	0	1	0	2
Entire Study Period					
PE	71	36	4	27	4
DVT	6	0	2	0	4
Death	26	0	12	0	14
Major Bleed	19	1	7	0	11
Other[c]	6	0	2	0	4

[a]Includes those for which the adjudication decision was no event or doubtful event.
[b]Includes those for which the adjudication decision was a definite event or probable event.
[c]Critical events not defined as such in the protocol.
Copied from Table 6.1, page 127, Vol. 40.

2.2.2 Applicant's Analysis of Any Critical Event

The results of any critical event occurring during the initial 8-day treatment period are summarized by treatment groups are given below.

Occurrence of Any Critical Event During the Initial Treatment Period
(ITT Population)
Study DMP 702-904

Treatment	Any Critical Event	Diff (Hep-Tin)	p-value	95% C.I.
Tinzaparin	9/301 (2.99%)	-0.06	1.000	(-2.75%, 2.64%)
Heparin	9/307 (2.93%)			

P-value was obtained by Fisher's Exact test.
Copied from Table 6.2, Vol. 40.

As seen from table above, there was no treatment difference in any critical event during the initial treatment period. The confidence interval allows for up to a 3% difference in the treatments.

2.3 Applicant's Analysis of Secondary Efficacy Variables

The secondary endpoints of the study were:

1) the occurrence rate of each of these events (recurrent thromboembolic events, major bleeding, death) during the initial treatment period, the long-term follow-up period and over the entire study period.

2) the time of occurrence of each of these events during the entire study period (Days 1 to 90)

Time-to-event analyses evaluated the time to the first critical event over the entire study period using the Kaplan-Meier survival estimate. Between treatment effect was tested using the log-rank statistics.

Occurrence of Each Critical Event during the Initial Treatment Period

The results of each critical event occurring during the initial 8-day treatment period are summarized by treatment groups are given below.

Occurrence of Any Critical Event during the Initial Treatment Period (ITT Population) Study DMP 702-904

	Tinzaparin (N=301)	Heparin (N=307)	Difference	P-value	95% C. I.
DVT/PE Events	3 (1.00%)	2 (0.65%)	-0.35%	0.683	(-1.78%, 1.09%)
Death	4 (1.33%)	3 (0.98%)	-0.35%	0.723	(-2.05%, 1.34%)
Major Bleed	3 (1.00%)	5 (1.65%)	0.63%	0.725	(-1.18%, 2.44%)

Differences in event rates were calculated by heparin minus tinzaparin.
P-value was obtained by Fisher's Exact test.
Copied from Table 6.2, page 128, Vol. 40.

As seen from table above, there were no treatment differences in DVT/PE events, death, and major bleed during the initial treatment period.

Occurrence of Each Critical Event during Long-Term Follow-up Period and Entire Study Period

The results of each critical event occurring during the long-term follow-up period and over the entire study period are summarized by treatment groups in Attached Table 5.

As seen from Attached Table 5, there was no treatment difference in any critical event, TE, DVT, PE events, death, and major bleed during the long-term follow-up period and over the entire study period.

The time-to-event analysis showed no significant differences between treatment groups (p=0.570, log-rank test).

2.4 Subgroup Analyses

Subgroup analyses were performed for the primary endpoint for the following subgroups: patients with documented proximal DVT at baseline vs. patients without documented proximal DVT at baseline; patients with baseline PVOS<50% vs. patients with baseline PVOS ≥50%; patients aged <65 years vs. ≥65 years; male patients vs. female patients.

The results of subgroup analysis of overall critical event are given in Attached Table 6.

It was observed in the Attached Table 6 that overall critical event rates across treatment groups during the 90-day study period in older patients (i.e.,≥ 65 years) were slightly higher than those in younger patients (i.e., <65 years) (8.1% vs. 4.0%). The 90-day overall critical event rate was also slightly higher for female than for males (7.7% vs. 5.2%).

The event rates in the subgroup of patients with documented proximal DVT at baseline were low. The overall critical rates and the major bleed rates for this subgroup were, however, slightly higher than those for patients who did not have a documented proximal DVT at baseline.

3. Reviewer's Evaluation

This trial was an open label and not blinded study.

The sample size determination was based on a one-sided test. So, sample size might be inadequate to show superiority on a two-sided test.

The hypothesized critical event rate of 15% was too high. The observed event rates in this study were low compared to the pre-study assumption. The sample size of 600 was inadequate to make any valid statistical assessment.

Without a pre-specified delta, it was difficult to state whether tinzaparin and heparin were equally effective in the treatment of patients with pulmonary emoblism.

3.1 Analysis of Composite Endpoint (Death/PE/DVT)

This reviewer performed analyses of the adjudicated and suspected occurrence of composite endpoint (death/PE/DVT) during the initial 8-day treatment period, during long-term follow-up and entire study period. The results of these analyses are given below.

Adjudicated Occurrence of Composite Endpoint (Death/PE/DVT)
(ITT Population)
Study DMP 702-904

Time Period	Tinzaparin	Heparin	Difference	P-value	95% C. I.
Initial Treatment	6/301 (2.00%)	5/307 (1.62%)	-0.38%	0.770	(-2.49%, 1.76%)
Long-term Follow-up	9/297 (3.03%)	14/304 (4.61%)	1.58%	0.396	(-1.48%, 4.63%)
Entire Study	14/301 (4.65%)	19/307 (6.19%)	1.54%	0.475	(-2.06%, 5.13%)

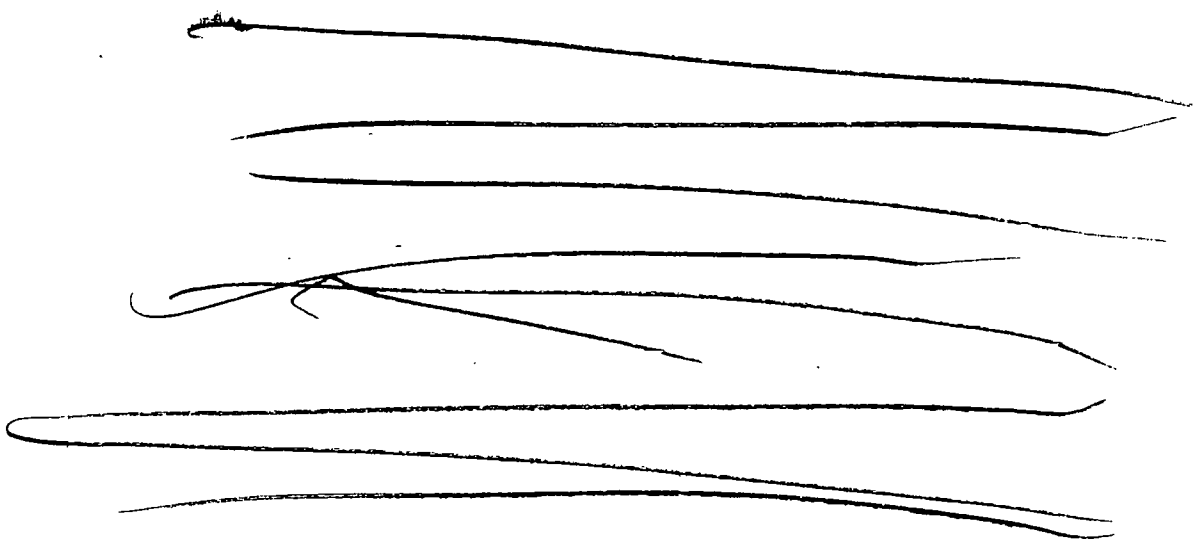
Differences in event rates were calculated by heparin minus tinzaparin.
P-value was obtained by Fisher's Exact test.

Suspected Occurrence of Composite Endpoint (Death/PE/DVT)
(ITT Population)
Study DMP 702-904

Time Period	Tinzaparin	Heparin	Difference	P-value	95% C. I.
Initial Treatment	12/301 (3.99%)	16/307 (5.21%)	1.22%	0.563	(-2.10%, 4.55%)
Long-term Follow-up	33/297 (11.11%)	29/304 (9.54%)	-1.57%	0.592	(-6.44%, 3.29%)
Entire Study	38/301 (12.62%)	43/307 (14.01%)	1.39%	0.635	(-4.02%, 6.78%)

Differences in event rates were calculated by heparin minus tinzaparin.
P-value was obtained by Fisher's Exact test.

As seen from the tables above for the adjudicated composite endpoint (death/PE/DVT), the confidence interval allows up to 6% difference in the treatments. The confidence interval for the suspected composite endpoint was wider that that for the adjudicated composite endpoint. It allows up to 7% difference in the treatments.



11 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.