2. STUDY SYNOPSIS

Name of Company: Eisai Inc.	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: FRAGMIN® Injection	Referring to Module 5 of the Dossier	
Name of Active Ingredient: Dalteparin sodium	**Volume:** **Page:**	

Study Title

Dalteparin sodium injection (FRAGMIN®), multicenter, open label, single-arm, long term (52 weeks) study (DALTECAN) for understanding safety and efficacy in subjects with malignancies and symptomatic venous thromboembolism (FRAG-A001-401)

Investigator(s)/ Site(s)

Multicenter: 44 sites in Austria (6), Canada (8), Netherlands (2), Spain (5), and the United States (23).

Publication (Reference)

An abstract is being prepared for the American Society of Hematology annual meeting in December 2013.

Study Period

30 Jun 2009 to 15 Mar 2012

Phase of Development

Phase 4

Objective(s)

The primary objective of the study was to determine the rate of major bleeding events in cancer subjects receiving extended treatment with dalteparin sodium injection greater than 6 months and up to 12 months for prevention of recurrent symptomatic venous thromboembolism (VTE).

Secondary objectives were to determine (for all subjects and according to baseline renal function): 1) the rate of symptomatic recurrent VTE (proximal deep-vein thrombosis [DVT] and or pulmonary embolism [PE]) during treatment; 2) time to symptomatic recurrent VTE; 3) the rate of minor bleeding events; 4) time to first major bleeding event; 5) time to first bleeding event (any bleeding event); and 6) the safety and tolerability of extended treatment with dalteparin sodium.

Additional objectives included an evaluation of the utility of measuring anti-factor Xa (anti-Xa) activity to manage dose adjustment in subjects who presented with or developed severe renal impairment (creatinine clearance [CrCl] < 30 mL/min).

Methodology

The first multinational prospective randomized clinical trial in a general cancer population to show the clear superiority of low molecular weight heparin (LMWH) therapy for secondary prophylaxis compared with standard-of-care therapy in cancer subjects with symptomatic DVT, PE, or both was the CLOT study ["Randomized Comparison of Low Molecular Weight Heparin (dalteparin sodium, FRAGMIN®) versus Oral Anticoagulant Therapy for Long Term Anticoagulation in Cancer Subjects with Venous Thromboembolism"]. Eligibility criteria for this 6-month trial included a diagnosis of cancer and acute, symptomatic proximal DVT of the lower extremity, PE, or both. In this study, dalteparin sodium significantly reduced the risk of recurrent VTE without increasing the risk of major bleeding or any bleeding.[13] As there were no data on dalteparin sodium treatment beyond six months in this patient population, the FRAG-A001-401 study was designed to evaluate the safety and efficacy of dalteparin sodium treatment for up to 52 weeks in subjects with cancer and VTE.

This was an international, multicenter, single-arm, open-label, 52-week study designed to evaluate the safety and efficacy of dalteparin sodium in cancer subjects receiving extended treatment with dalteparin sodium (> 6 months) for the prevention of recurrent VTEs, including subjects with severe renal impairment. Enrollment was to be stopped when 338 subjects had been enrolled or 203 enrolled subjects had completed 6 months of treatment, whichever occurred first.

The study included a screening period of up to 96 hours. During this period, subjects with active malignancy and a newly diagnosed, symptomatic proximal DVT of the lower extremity, PE, or both, were screened and the diagnosis of DVT and/or PE was documented. Active malignancy was defined as a diagnosis of cancer, other than basal cell or squamous cell carcinoma of the skin, within 6 months before enrollment; receipt of any treatment for cancer within the previous 6 months; or documented recurrent or metastatic cancer.

Starting at the baseline visit/Day 1 of the treatment period, eligible subjects received 200 IU/kg of dalteparin sodium once daily for the first 4 weeks of the study. Beginning at Week 4, the dosage of dalteparin sodium was decreased to 150 IU/kg per day for the remaining 48 weeks. Subjects (except those with severe renal insufficiency) returned to the clinic for efficacy and safety assessments at Weeks 1, 4, 8, 12, 24, 36, 48, and 52, and had telephone contacts at Weeks 16, 20, 28, 32, 40, and 44. Subjects with severe renal insufficiency returned to the clinic for monthly visits.

Dalteparin sodium was provided as multidose vials for dosing during the first 4 weeks and as single-dose prefilled syringes for the remainder of the trial. Dose adjustments were permitted during the study, and guidance was provided for those subjects who presented with severe renal insufficiency at baseline or developed severe renal insufficiency during the study, and for subjects with thrombocytopenia.

Efficacy evaluations consisted of the documentation of suspected recurrence of DVT and PE events and the documentation of central venous thrombosis (CVT) events. Safety evaluations included adverse events (AEs), major and minor bleeding events, and laboratory assessments. Plasma anti-Xa levels were also evaluated for those subjects who presented with severe renal impairment at baseline or developed severe renal impairment during the study. Bleeding events and VTEs were adjudicated by a Central Adjudication Committee (CAC).

The original protocol was amended twice, and a correction was issued to Amendment 1.

Number of Subjects (Planned and Enrolled)

Approximately 50 sites were to participate in the study in order to enroll approximately 338 VTE subjects who met all of the study criteria. Enrollment was to be stopped when 338 eligible subjects were enrolled or 203 subjects had completed 6 months of treatment, whichever occurred first.

A total of 344 subjects were screened and 338 enrolled into the study. There were 334 subjects who received at least one dose of dalteparin sodium (safety population) and 109 subjects completed the study.

Diagnosis and Main Criteria for Inclusion

Eligible subjects were males or females at least 18 years of age with active malignancy and newly diagnosed, symptomatic proximal DVT of the lower extremity, PE, or both. Eligible subjects had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

Proximal DVT of the lower extremity was diagnosed on the basis of evidence of thrombus in the popliteal or more proximal veins by computed tomography (CT) scan, compression ultrasonography, or contrast venography. A diagnosis of pulmonary embolism (PE) required verification by radionuclide ventilation-perfusion lung scanning, helical CT, or pulmonary angiography.

Inclusion criteria:

- Subjects must have been greater than or equal to 18 years of age.
- Male and female subjects were eligible for enrollment.
- Female subjects were either of nonchildbearing potential as a result of surgery, radiation therapy, menopause (had been in menopause for at least 1 year), or of childbearing potential and willing to adhere to an acceptable method of pregnancy prevention.
- Subjects had newly diagnosed, symptomatic proximal DVT of the lower extremity, PE, or both.
- Subjects had active malignancy defined as a diagnosis of cancer (excluding basal cell or squamous cell carcinoma of the skin) within 6 months before enrollment, receipt of any treatment for cancer within the previous 6 months, or documented recurrent or metastatic cancer.

- Prior to enrollment, subjects had not received therapeutic doses of heparin or LMWH for greater than 96 hours (or more than 8 doses within 96 hours) or oral anticoagulant therapy for greater than 48 hours (or more than 2 doses within 48 hours).
- Subjects had an ECOG performance status of 0, 1, or 2.
- Subjects had a life expectancy of greater than 6 months.
- Subjects had a platelet count greater than 75,000 mm^3.
- Subjects were not on any oral anticoagulant therapy for concomitant disease with the exception of acetylsalicylic acid (ASA). No other systemic anticoagulants were allowed during the study with the exception of institution-specific intravenous line patency protocols.
- Subjects had no active or serious bleeding episodes within 2 weeks prior to study entry.
- Subjects were able to comply with scheduled follow-ups.
- Subjects gave written informed consent.

Exclusion criteria:

- Subjects who had a high risk of serious bleeding (e.g., recent neurosurgery within 30 days, history of intracranial hemorrhage, acute gastroduodenal ulcer).
- Subjects who were on hemodialysis.
- Subjects who had a prior placement of a Greenfield filter or other device to prevent embolization of DVTs.
- Subjects with a known contraindication to the use of heparin (e.g., heparin-induced thrombocytopenia).
- Subjects with a known hypersensitivity to heparin, dalteparin sodium, other LMWHs, or pork products.
- Subjects who were currently participating in another clinical trial involving anticoagulation therapy (with the exception of ASA, in the 30 days prior to study entry), or were actively using any investigational drugs/treatments 30 days prior to study entry involving anticoagulation therapy (with the exception of ASA $\leq$ 3 times per day).
- Subjects who were pregnant or breast feeding.
- Subjects with uncontrolled hypertension characterized by a sustained systolic pressure greater than 170 mm Hg and/or diastolic pressure greater than 100 mm Hg.
- Subjects with a serious concomitant systemic disorder (for example, active infection including HIV or cardiac disease) that in the opinion of the investigator would have compromised the subject's ability to complete the study.
- Any condition that made the subject unsuitable in the opinion of the investigator.
- Subjects with leukemia or myeloproliferative syndrome.

Test Treatment, Dose, Mode of Administration, and Batch Number(s)

The study medication used for this study was dalteparin sodium injection (FRAGMIN®).

Dalteparin sodium for the initial 4-week treatment period was provided as a solution for subcutaneous daily injection in multidose vials with preservative (benzyl alcohol); the intended dose during this 4-week period was 200 IU/kg. Subjects administered this formulation using graduated, latex-free, insulin-type syringes (accurate to 0.01 mL). For the remainder of the study duration (48 weeks), dalteparin sodium was provided in prefilled preservative-free syringes that contained a single dose of the drug to be administered subcutaneously daily; the intended dose during Weeks 5-52 was 150 IU/kg. Guidelines for dose modification throughout the study were based on the subject's clinical condition. The study drug was provided as multidose vials of 95,000 IU/3.8 mL total dose and volume or (25,000 IU/1 mL), and single-dose prefilled syringes for subcutaneous daily injection.

Reference Therapy, Dose, Mode of Administration, and Batch Number(s)

Not applicable.

Duration of Treatment

This study included a 52-week treatment period. Eligible subjects received 200 IU/kg of dalteparin sodium once daily for the first 4 weeks of the study. Beginning at Week 4, the dosage of dalteparin sodium was decreased to 150 IU/kg

per day for the remaining 48 weeks.

Assessments

Efficacy

Efficacy was assessed by documentation of DVT, PE, and CVT events. Proximal DVT of the lower extremity and PE were diagnosed at baseline by the investigator. Suspected recurrence was documented with the same method used at baseline. In the case of fatal PE, documentation by autopsy was acceptable. Central venous thrombosis was documented by contrast venography or ultrasonography.

Pharmacokinetics

Plasma trough anti-Xa activity was measured in subjects with severe renal impairment. For subjects presenting with severe renal impairment at baseline, blood samples were collected prior to Day 4 dosing to establish baseline anti-Xa levels. Anti-Xa levels for these subjects were monitored throughout the study as follows:

- To assess for bioaccumulation of dalteparin sodium, trough anti-Xa levels were checked prior to the next dose. The trough anti-Xa levels had to be less than 0.4 IU/mL.
- If the anti-Xa level was above 0.4 IU/mL, the dose of dalteparin sodium was reduced.
- The anti-Xa measurement was repeated after 3-4 additional doses.
- Subjects with severe renal impairment were monitored every 4 weeks through Week 52/early termination.

Recommended dose adjustments for subjects with severe renal impairment were provided.

For subjects with normal or moderately impaired renal function at baseline whose CrCl declined to less than 30 mL/min during the course of the study, dalteparin sodium adjustments were permitted to maintain appropriate anti-Xa levels (i.e., trough anti-Xa levels of < 0.4 IU/mL). As soon as a subject was determined to have developed severe renal impairment (estimated CrCl < 30 mL/min), the trough anti-Xa levels were monitored as described above.

Pharmacogenomics/Pharmacogenetics

Not applicable.

Safety

Safety assessments consisted of the evaluation of the subject's major and minor bleeding events; monitoring and recording all AEs and serious adverse events (SAEs); clinical laboratory tests; periodic measurement of vital signs; and performance of physical examinations as detailed in the protocol. Safety evaluations included characterization of AE frequency, severity, and relationship to study drug. Safety laboratory assessments included complete white blood cell count with differential, platelet count, hemoglobin, and serum clinical chemistries (including liver function tests and electrolytes).

Major and minor bleeding events were identified based on the subject's medical history, physical examination, vital signs, clinical laboratory tests, CT scan, and AE reporting. A bleeding event was defined as **major** if it was clinically overt AND satisfied 1 of the following criteria:

1. A decrease in hemoglobin of 20 g/L (2.0 g/dL)
2. Bleeding leading to transfusion of 2 or more units of packed red cells
3. Bleeding occurring at a critical site (intraocular, spinal/epidural, intracranial, retroperitoneal, or pericardial bleeding)
4. Bleeding leading to death

All other clinically overt bleeding events not meeting any of the above criteria were classified as **minor**.

Bleeding events were assessed by the investigator and adjudicated by the CAC. The critical documentation (imaging results, laboratory analyses) and study database (tables and listings of clinical data) to adjudicate the bleeding episodes for the study were provided by the sponsor to the CAC.

Statistical Methods

Significant changes to the planned analysis included the following: 1) all CAC adjudicated events were used for analysis, regardless of whether they were symptomatic events; 2) in the estimation of confidence intervals for the incidence rates and comparisons, the Exact method was used since it provided more conservative estimates as compared to the normal approximation method; and 3) except for some overall and subgroup summary of incidence rate as references, most analysis based on CAC-adjudicated events were not repeated for investigator-identified events.

SAMPLE SIZE

Approximately 338 subjects needed to be enrolled in the study to have an estimated 203 evaluable subjects completing at least 6 months of dalteparin sodium treatment. The sample size calculation was based on the desired precision (width of a 2-sided 95% confidence interval [CI]) for the estimate of the major bleeding incidence rate during 6 months of treatment. If the expected crude rate of major bleeding events was 5% at 6 months (from CLOT study data), 203 evaluable subjects completing 6 months of dalteparin sodium treatment were required with the precision level of 3% (half width of the 2-sided 95% CI for the incidence rate) using normal approximation.[13] Assuming a dropout rate of 40% at 6 months, approximately 338 subjects needed to be enrolled in the study.

ANALYSIS POPULATIONS

The following 4 analysis populations were used in the study:

- Safety population: all subjects who received at least 1 treatment with dalteparin sodium; the primary analysis population for all efficacy and safety endpoints
- Enrolled population: all subjects who were enrolled in the study (excluded screen failures)
- Per protocol (PP) population: all safety population subjects who did not have any major protocol deviations and finished the 12-month treatment period
- Severely renal-impaired population: all safety population subjects who presented with severe renal impairment at the screening visit or developed severe renal impairment during the study

PRIMARY EFFICACY ANALYSES

For the primary efficacy endpoint, the incidence of symptomatic adjudicated new or recurrent VTE (DVT/PE), the following analyses were performed based on the safety population.

The primary efficacy analysis was the estimation of the incidence of subjects with VTE during the 7^{th} to 12^{th} month (greater than 6 months and up to 12 months) study treatment period, which was summarized together with the 2-sided 95% CI. The denominator for the rate was all safety population subjects who did not experience the event within the first 6 months of treatment and remained under study observation for the event at the beginning of the 7th month of the study. Confidence intervals, exact Clopper-Pearson, were based on the F distribution.

The CAC-adjudicated VTEs and deaths were entered in the study database and used in the efficacy analysis.

The proportion of subjects with recurrent VTE of the leg/lower extremity or lung during the 12-month study period were summarized. The proportion of subjects with new or recurrent lower limb DVT, PE, or CVT occurring while the subject was on treatment with dalteparin sodium was summarized together with the 2-sided 95% CI.

Time to first objectively documented DVT, PE, or CVT and the time from the date of first treatment to the date of first objective documentation of VTE were estimated using the Kaplan-Meier method.

A Cox proportional hazard regression model was employed to assess the relative risk of VTE with prognostic factors of age, sex, primary site of cancer, chemotherapy status, previous history of VTE, performance status, and baseline body mass index (BMI) included in the model.

The primary analysis for the estimation of the incidence of subjects with adjudicated new or recurrent VTE during the 7 to 12 month period, as outlined above, was repeated in the PP population.

SECONDARY EFFICACY ANALYSES

The incidences of adjudicated new or recurrent VTE during 1 to 6 month, 1 to 12 month, 2 to 6 month, and 2 to 12-month study periods, and the monthly incidences were summarized similarly; the results were presented together

with the primary efficacy analysis.

The investigator's assessments for VTEs were collected and used as secondary assessments in the analyses. The incidence of subjects with investigator-identified new or recurrent VTE and adjudicated DVT/PE/CVT were analyzed using methods similar to those of the primary efficacy endpoint.

Time to first occurrence of adjudicated new or recurrent VTE and DVT/PE/CVT was analyzed using the Kaplan-Meier method. The event-free rates for the intervals of 1 to 6 months, 2 to 6 months, and 7 to 12 months were also presented using Kaplan-Meier estimates, with the number of subjects at risk during the specified period of time and censoring taken into account.

EXPLORATORY EFFICACY ANALYSES

The rates of subjects with adjudicated new or recurrent VTE, as well as adjudicated DVT/PE/CVT, were analyzed using a logistic regression model with prognostic factors to assess the odds of events in response to these prognostic factors.

A Cox proportional hazard regression model was used for time to first occurrence of adjudicated new or recurrent VTE and time to first occurrence of adjudicated DVT/PE/CVT, with prognostic factors to assess the relative risk of VTE or DVT/PE/CVT in response to these prognostic factors.

Prognostic factors for exploratory efficacy analysis included age; sex; baseline tumor type and stage; baseline BMI, chemotherapy, and ECOG status; and previous history of VTE. All prognostic factors were entered into the model at once and no multiplicity adjustment on individual p-values was applied.

Based on adequate sample sizes, the analyses described above were performed for the following subgroups defined by baseline status with subgrouping factor removed from the model where applicable: tumor type and stage; ECOG performance status score; renal function; and chemotherapy status. Additionally, the analyses were repeated for subjects whose renal function deteriorated from baseline.

PRIMARY SAFETY ANALYSES

The primary study endpoint was the primary safety endpoint, which was the incidence rate of adjudicated major bleeding events during the 2 to 6 months and 7 to 12 month study period. The CAC assessment of major bleeding was used as the primary assessment for analysis and the investigator's assessment was used as a secondary safety assessment.

The incidence of adjudicated major bleeding events was the number of subjects with the event divided by the total patient-months at risk during the specified period of time. This applied to all safety endpoints of incidence type in this study.

The primary safety analysis was a comparison of the rates of major bleeding events for the intervals of 2 to 6 months and 7 to 12 months. The difference was summarized together with the 2-sided 95% CI.

- The incidence was calculated as the number of subjects with adjudicated major bleeding events divided by the total subject-months at risk, during the 7 to 12 month period. The 2-sided 95% CI was calculated using a normal approximation to the binomial distribution. In case no event was observed during an interval, the upper 95% CI was estimated as 3/N, where N was the total number of subjects at risk at the beginning of the interval.
- The difference between the 2 to 6 and 7 to 12 month incidences was assessed using a 2-sided 95% CI, based on the normal approximation for the difference in the 2 proportions.

SECONDARY SAFETY ANALYSES

The secondary analyses of the incidences of major bleeding events during 1 to 6 months, 1 to 12 months, 2 to 12 months study periods, and the monthly incidence rates were summarized similarly to the primary analysis; the results were presented together with the primary analysis.

The incidence rate of investigator-identified major bleeding events as determined by the investigator, any bleeding events (including adjudicated and investigator-identified major and minor events), and fatal bleeding events were analyzed in methods similar to those of the primary safety endpoint.

Time to first occurrence of adjudicated and investigator-identified major bleeding events, any bleeding events, and

fatal bleeding events were estimated using the Kaplan-Meier method, along with 2-sided 95% CIs based on the log-log transformation of the survival function. The event-free rates for the intervals of 1 to 6 months, 2 to 6 months, and 7 to 12 months were also presented using Kaplan-Meier estimates, taking into account the number of subjects at risk during the specified period of time and censoring.

EXPLORATORY SAFETY ANALYSES

The incidences of adjudicated and investigator-identified major bleeding events, any bleeding events (including adjudicated and investigator-identified major and minor events), and fatal bleeding events were analyzed using logistic regression models with prognostic factors to assess the odds of events in response to these prognostic factors.

Cox proportional hazard regression models for the time to first occurrence of adjudicated and investigator-identified major bleeding events, any bleeding events, and fatal bleeding events, with the prognostic factors, were used to assess the relative risk of bleeding events in response to these prognostic factors.

Prognostic factors for the exploratory safety analyses included age, sex, baseline chemotherapy status, and baseline platelet count. All prognostic factors were entered into the model at once and no multiplicity adjustment on individual p-values was applied.

Based on adequate sample sizes, the analyses described above were performed for the following subgroups based on baseline status as exploratory analyses, in which case the subgrouping variable was not to be included as a covariate for the model: metastatic tumor status and type; ECOG performance status score; renal function status; and chemotherapy status. Additionally, the analyses were repeated for subjects whose renal function deteriorated from baseline.

No interim analysis was planned or conducted for this study.

Results

Subject Disposition/Analysis Sets

A total of 344 subjects were screened and 6 subjects were screen failures due to a failure to meet all inclusion and/or exclusion criteria. Of the 338 subjects who were enrolled, 4 withdrew prior to receiving a dose of study medication (2 subjects withdrew consent and 2 subjects withdrew due to health deterioration). A total of 334 patients received at least 1 dose of study medication; these subjects were included in the safety population.

The screening visit was completed by 334 subjects; 85% (n = 284) of these subjects completed the 4-week visit (Visit 4), 56.3% (n = 188) completed the 24-week visit (Visit 9), and 32.6% (n = 109) completed the 52-week visit (Visit 16).

A total of 185 subjects completed the first six months of study treatment and continued into the second six months of treatment. Premature discontinuation from the study was documented for 229 subjects. The most common primary reasons for discontinuation were death (33.2%), AE (26.2%), and subject no longer willing to participate in the study (18.3%).

The number of subjects included in each analysis population follows: enrolled population (338 subjects), safety population (334 subjects), PP population (297 subjects), and severely renal-impaired population (19 subjects). The safety population was the primary analysis population for all efficacy and safety endpoints.

The median age of all subjects was 64 years and the majority (89.8%) of subjects were white. The most common category of cancer at baseline was solid tumor (91.6%), with a majority of subjects having adenocarcinoma (53.3%), metastasis (including local recurrence, 62.6%), and stage III or stage IV disease (20.4% and 39.8%, respectively).

Baseline characteristics that were more common among subjects who continued into the second 6 months than those who discontinued during the first 6 months were: male sex (53.0% vs. 43.6%), colorectal cancer (15.1% vs. 8.1%), prostate cancer (8.1% vs. 2.0%), and ECOG performance status of 0 (35.7% vs. 22.1%). Characteristics that were more common in the earlier cohort were: stage IV disease (49.7% vs. 31.9%), distant metastasis (66.4% vs. 49.2%), ECOG status of 2 (27.5% vs. 15.1%), lung cancer (20.8% vs. 13.5%), and pancreatic cancer (16.1% vs. 3.8%).

Previous histories of PE, DVT, or both were each reported by less than 10% of all subjects. At baseline, all 344 subjects had qualifying episodes of VTE: 49.1% of subjects had episodes of DVT, 38.9% had PEs, and 12.0% had DVT combined with PE.

Efficacy

There were 65 subjects with suspected (investigator identified) new or recurrent VTE episodes, including all VTE events regardless of whether they were confirmed by the CAC or through objective diagnosis by the investigator. The CAC adjudication process reduced the total number to 37 subjects with events during the study (1 to 12 month time period), which was the same number of events identified by investigators, and the incidence of the events was highest during the first month of the study (5.7%, 95% CI [3.5%, 8.7%]) compared to any other month during the study.

The primary efficacy endpoint was the incidence of adjudicated symptomatic and objectively documented new or recurrent VTE of the leg/lower extremity or lung (DVT and/or PE) during the 7 to 12 month (> 6 months and up to 12 months) study period. During the 7 to 12 month time period, 8 (4.1%) subjects experienced an adjudicated new or recurrent VTE compared to 29 (8.7%) subjects during months 1 through 6. Regression analysis of the incidence of adjudicated VTE did not reveal significant effects for any prognostic factor. Caution should be exercised that even though separation issues were circumvented with technical maneuvers described in the statistical analysis plan, occasional extreme odds ratios or hazard ratios should always be referred together with the confidence limits and p-values during interpretation. Differences in the general pattern of the incidence of VTEs were not observed following review of the sensitivity analysis, which repeated the primary analysis using the PP population.

The mean (standard error [SE]) time to first occurrence of adjudicated new or recurrent VTE was 294.1 (4.87) days with the majority (88.9%) of observations being censoring time; the Kaplan-Meier estimate for median time to first occurrence had not been reached at the time of the analysis. An analysis of time to first occurrence of adjudicated new or recurrent VTE with prognostic factors did not demonstrate a significant effect on the time to first occurrence for any factor.

The analyses of the incidence of investigator-identified VTE and the incidence and time to first adjudicated

DVT/PE/CVT showed results similar to those for adjudicated VTE events.

Certain subgroups demonstrated efficacy findings that differed from the safety population. Compared with subjects with early-stage tumors and normal renal function at baseline, subjects with late-stage tumors and normal renal function at baseline had significantly lower odds of experiencing an adjudicated bleeding event (odds ratio 0.306; p-value = 0.0490).

Subjects in the following subgroups defined at baseline had a shorter mean (SE) time to first occurrence of adjudicated new or recurrent VTE when compared with the safety population (294.1 [4.87] days): early-stage tumors (196.6 [8.26] days); mild and moderate-to-severe renal impairment (217.1 [5.48] days and 225.2 [11.62] days, respectively); and subjects not undergoing chemotherapy (217.5 [6.61] days). In addition, subjects with no renal function deterioration from baseline had fewer days to first occurrence of adjudicated new or recurrent VTE than the safety population (221.7 [4.38] days vs. 294.1 [4.87] days). Among subjects with normal renal function at baseline, a significantly longer time to first occurrence of adjudicated new or recurrent VTE was observed in subjects with late-stage tumors vs. subjects with early-stage tumors (hazard ratio = 0.340; p-value = 0.0475).

Levels of anti-Xa were used to monitor the anticoagulant effect of dalteparin sodium in the 19 subjects who presented with or developed severe renal impairment during the study. In an analysis that included only the severely renal-impaired subjects who eventually achieved the target anti-Xa levels (n = 12), a correlation between the dose of dalteparin sodium needed to maintain factor Xa inhibition at 0.5 ± 0.5 IU/mL and baseline CrCl was not evident due to the small size of sample data.

In terms of overall compliance with study medication administration, most subjects were at least 80% compliant (100% compliance: 47.9% of subjects and 80% to <100% compliant: 47.3%). The majority of subjects who completed the first 6 months of the study and continued into the second 6 months were generally at least 80% compliant (80% to < 100% compliant: 66.5%).

Pharmacokinetics, Pharmacodynamics Pharmacogenomics/Pharmacogenetics

Levels of anti-Xa were analyzed using data from all the subjects in the severely renal-impaired population. The dose of dalteparin sodium needed to maintain factor-Xa inhibition at 0.5 ± 0.5 IU/mL was analyzed in only the severely renal-impaired subjects who eventually achieved the target anti-Xa levels (n = 12 out of a total of 19 severely renal-impaired subjects). The mean (SD) dose of dalteparin sodium needed to maintain factor Xa inhibition at 0.5 ± 0.5 IU/mL was 12,537 (2980) IU, and mean (SD) baseline CrCl was 44.5 (29.27) mL/min. The correlation between the dose of dalteparin sodium needed to maintain factor Xa inhibition and baseline CrCl was not statistically significant (Spearman rank correlation coefficient = 0.3368; p = 0.2843).

Safety

The primary safety endpoint, which was also the primary study endpoint, was the incidence of adjudicated major bleeding events during the 7 to 12 month (> 6 months and up to 12 months) study period. This incidence was 0.7%, 95% CI (0.3%, 1.4%), which was less than the incidence during the initial 6 months of the study (1.7%, 95% CI [1.1%, 2.4%]) and during every other time period analyzed greater than 1 month. No significant difference in the incidence of adjudicated major bleeding events was observed between the periods 1 to 6 months and 7 to 12 months (95% CI [-2.9%, 4.8%]), or between the periods 2 to 6 months and 7 to 12 months (95% CI [-3.7%, 4.5%]). The highest incidence of adjudicated major bleeding events was during the first month of the study (3.6%, 95% CI [1.9%, 6.2%]).

During the 7 to 12 month period, the incidence of investigator-identified major bleeding events was 0.6%, 95% CI (0.3%, 1.3%), and the incidence of any adjudicated bleeding event was 2.7%, 95% CI (1.7%, 4.0%). The incidence pattern by time period was similar to adjudicated major bleeding events. Two subjects had fatal bleeding events, occurring at 4 and 9 months.

The Kaplan-Meier estimate for median times to first occurrence of an adjudicated major bleeding event and first occurrence of any adjudicated bleeding event had not been reached at the time of analysis. Mean (SE) times to these events were 332.9 (5.25) days and 262.5 (8.52) days, respectively. The prognostic factors of age, sex, baseline chemotherapy status, and baseline platelet count showed no significant effect on the incidences of adjudicated major bleeding events or any adjudicated bleeding event, or on the times to these events. Adjudicated bleeding events were more common in subjects with the lowest categories of post-baseline platelet counts than for subjects with the highest category: 57.1%, 53.8%, and 52.1% for $< 50 \times 10^9$/L, $< 75 \times 10^9$/L, $< 100 \times 10^9$/L at least once, respectively, vs.

31.7% for ≥ 100 × 10^9/L at all times.

Subgroup analyses of bleeding events revealed no clinically meaningful patterns. Different subgroups showed variations from the safety population findings. The most common variation from the safety population was the occurrence of the highest monthly incidence of bleeding events during months other than the first (primary disease only, hematologic malignancy, ECOG performance status 2 or greater, mild and moderate-to-severe renal impairment, renal function deterioration, and no baseline chemotherapy). The second most common subgroup variation was a shorter mean time to first occurrence of bleeding events (primary disease only, ECOG performance status 2 or greater, mild and moderate-to-severe renal impairment, and no baseline chemotherapy). The small size of some of the subgroups limited interpretation of the findings. For example, the subgroups for hematologic malignancy, moderate-to-severe renal impairment, and ECOG performance status 2 or greater had 28, 34, and 70 subjects, respectively.

Median overall survival for the safety population was 405.0 days, 95% CI (335.0, –). Survival was not significantly different between subjects with bleeding events and subjects without bleeding events (p-value = 0.7606)

A total of 328 (98.2%) subjects reported TEAEs during the study. The most common preferred terms were injection site hematoma (27.2%), fatigue (26.9%), nausea (24.3%), edema peripheral (24.0%), and constipation (21.3%). The frequencies of very severe and severe TEAEs were 41.3% and 23.4%, respectively, and the most common preferred terms for these grades were disease progression (7.5%) and anemia (6.0%), respectively. The majority of subjects had TEAEs with a maximum causality rating of probably or possibly related to study drug (38.3% and 24.9%, respectively). For both ratings, the most common event was injection site hematoma (18.0% and 6.6%, respectively); this and other most common (≥ 1.0%) related TEAEs were conditions potentially associated with bleeding.

The frequencies of TEAEs leading to death, serious TEAEs, TEAEs leading to discontinuation of study drug, and TEAEs leading to change in dose of study drug were 34.7%, 63.8%, 36.8%, and 34.1%, respectively. For each category except TEAEs leading to dose change, the most common SOC was neoplasms benign, malignant, and unspecified (including cysts and polyps) (20.1%, 24.3%, and 12.3% for deaths, serious TEAEs, and TEAEs leading to discontinuation, respectively). Disease progression (under general disorders and administrative site conditions) was the most common, or second most common, event in each category of significant event, with frequencies of 7.8%, 8.7%, 4.2%, and 1.5% for deaths, serious TEAEs, TEAEs leading to discontinuation, and TEAEs leading to dose change, respectively. The most common events leading to discontinuation and dose change were pulmonary embolism (6.0%) and thrombocytopenia (8.1%), respectively.

Analyses of clinical laboratory test results over time showed small decreases in platelet count, leukocyte count, and absolute neutrophil count from baseline and small increases in serum creatinine from baseline. No other notable changes or trends in clinical laboratory tests over time were observed. The frequencies of shifts to a worse CTCAE grade of 3 or 4 during the study were generally low (most less than 5%). Analyses of changes in creatinine clearance in the severely renal-impaired population revealed no patterns or trends.

Systolic blood pressure showed decreases from baseline at several time points, the largest mean (SD) change from baseline being of -4.2 (18.13) mm Hg. No notable changes in other vital sign variables were observed.

Conclusions

Extending dalteparin therapy in patients with VTE and cancer beyond 6 months is not associated with an increase in bleeding compared to the initial period of therapy. The risks for developing major bleeding complications were greatest in the first month of therapy and decreased over the subsequent 11 months. The risk for VTE recurrence was also greatest in the first month after initiating dalteparin sodium, decreased subsequently thereafter, and remained low during the observation period. The compliance rate was high, confirming that an extended LMWH regimen with dalteparin sodium in cancer patients is feasible.

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