These Clinical Trial Results are provided for informational purposes only.

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2. REPORT SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Daiichi Sankyo Pharma Development</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Name of Finished Product:
DU-176b</td></tr>
<tr><td>Name of Active Ingredient:
N-(5-Chloropyridin-2-yl)- N'-[(1S,2R,4S)-4-(N,N-dimethylcarbamoyl)-2-(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4 c]pyridine-2-carboxamido)cyclohexyl]ethanediamide p-toluenesulfonate monohydrate</td></tr>
<tr><td colspan="3">Title of Study:
A Phase 2a, Multi-Center, Multi-National, Open-label, Dose Ranging Study of the Efficacy, Safety, and Tolerability of Oral DU-176b Administered Once or Twice Daily in the Treatment of Adult Subjects Undergoing Total Hip Arthroplasty</td></tr>
<tr><td colspan="3">Investigators:
A total of 51 investigators participated in this study. A complete list of investigators is provided in Section 16.1.4.</td></tr>
<tr><td colspan="3">Study Center(s):
There were 61 study centers in Europe and North America.</td></tr>
<tr><td colspan="3">Publication (reference):</td></tr>
<tr><td colspan="2">Study Period:
First Subject Entered: 12 Jan 2005
Last Subject Completed: 16 Dec 2005</td><td>Phase of Development:
2a</td></tr>
<tr><td colspan="3">Objectives:
Primary:
To explore the relationship between the dose of DU-176b and the occurrence of venous thromboembolism (VTE) and bleeding in subjects undergoing total hip replacement surgery.
Secondary:
To assess the pharmacokinetics of DU-176b and its effects on coagulation parameters.</td></tr>
<tr><td colspan="3">Methodology:
DU-176b was administered as an oral dose for 7 to 10 days either once or twice per diem in adult male and female subjects following total hip replacement.</td></tr>
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Number of Subjects (Planned and Analyzed):

Planned number of subjects was up to 700 subjects treated to obtain 350 (50 per dose group) evaluable subjects.

The actual number of subjects dosed was 606.

Main Inclusion/Exclusion Criteria:

Adult subjects undergoing elective hip replacement surgery.

Test Product, Dose and Mode of Administration, Lot Number:

The drug was supplied as yellow film-coated tablets. Oral DU-176b at 15 mg bid, 30 mg qd, 30 mg bid, 60 mg qd, 60 mg bid, and 120 mg qd. The lot numbers were [redacted] (15 mg); [redacted], and [redacted] (both 30 mg).

Reference Therapy, Dose and Mode of Administration, Lot Number:

Not applicable.

Duration of Treatment:

7 to 10 days.

Criteria for Evaluation:

Efficacy:

Incidence of venous thromboembolism.

Safety:

Incidence of major bleeding.

Statistical Methods:

The incidence of VTEs was summarized by dose group with 90% confidence intervals. Venography results were summarized by dose group for result category, type, and location. Subgroup analysis for the incidence of VTE was performed for race, age, gender, and geographic location.

For the primary safety variable, the incidence of major bleeding events (based on adjudication committee interpretation) was summarized by dose regimen group with a 95% confidence interval. The relationship between doses of DU-176b and occurrence

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of major bleeding events was explored using logistic regression with biomarkers and subject demographics as covariates or factors.

All other safety data and demographic data were summarized with descriptive statistics.

SUMMARY-CONCLUSIONS

Disposition:

A total of 614 subjects were assigned to treatment, 606 subjects took at least one dose of study drug (safety population), and 526 (86.8%) subjects completed the study.

Demographics:

The mean and median age of all subjects in the safety population was 58.5 and 58.0 years, respectively. The majority of subjects were female, with 256 (42.2%) male subjects and 350 (57.8%) female subjects. The majority of subjects were White by race (578, 95.4%). The majority of subjects (400, 66.0%) were located outside of North America. The average height and weight of all safety population subjects was 167.32 cm and 78.65 kg, respectively, with a mean BMI of 28.10 kg/m^2.

Efficacy Result:

In the mITT and PP populations, the incidence of VTE ranged from 10.3% in the 30 mg bid group to 21.3% in the 120 mg qd dose group. There were no statistically significant differences between dose groups using the Fisher's exact test p-value for incidence of VTE across dose groups (mITT population, P=0.391; PP population, P=0.374), and the Cochran-Armitage trend test p-value for incidence of VTE across dose groups (mITT population, P=0.822; PP population P=0.939).

Venography results indicate the 30 mg bid group had the highest percentage (89.7%) of subjects with normal venography results, while the 120 mg qd group had the lowest percentage (78.8%). In both the mITT and PP population as a whole, there were no significant differences between dose groups in venography results by category as observed by the venogram adjudication committee.

Analysis of the incidence of VTEs by population subgroups in general showed no statistically significant trends of clinical relevance among subgroups. However, the sample size was too small on all these subgroups to make any statements of clinical relevance on any of these population factors.

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On the secondary efficacy variables of PT, INR, aPTT, and anti-FXa activity, there were minor numerical differences between dose groups on these factors, but none of the differences were clinically relevant. A logistic regression analysis of VTE on subject biomarkers and select demographics indicated there was a statistically significant relationship only between VTE and age, and between specific geographic locations; however, the sample size was too small to draw any clinically relevant conclusions on these factors.

Pharmacokinetic/Pharmacodynamic Results:

Based on a separate PK analysis of data from this study compared with data from studies using healthy volunteers, the PK of DU-176b in this study population was comparable with that of healthy volunteers. However, absorption of DU-176b in the subject population was slowed on the first day of dosing (up to 24 hours after the first dose) resulting in a mean delay of 2.9 hours in the time to the peak plasma concentration (T_{max}) relative to healthy volunteers (4.4 hours versus 1.5 hours). This is consistent with reduced gastrointestinal motility following major surgery.

Safety Results:

There were a total of 9 major bleeding events (1.5%) across all dose groups. Differences across dose groups on the number of incidents of major bleeding up to 11 days post-surgery were not statistically significant. The total number of clinically significant bleeding events across all dose groups was 12 (2.0%), while the total number of minor bleeding events was 9 (1.5%). Regression analysis of major bleeding events to subject biomarkers and selected demographics showed there were no statistically significant relationships between the incidence of major bleeding events and study drug dose levels or subject demographics, although a dose-dependent trend appeared to be present for all bleeding events combined.

A total of 364 subjects (60.1% of the safety population) experienced at least 1 AE (includes treatment-emergent AEs). The 60 mg qd group had the highest percentage of subjects with at least 1 AE (71, 71.7%), while the 30 mg qd group had the lowest percentage (33, 44.0%). There did not appear to be any clinically significant trends in the frequency or nature of AEs in general or across dose groups. Approximately 7% of subjects experienced an AE classified by the investigator to be an SAE, and only 4.3%

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of subjects experienced an AE that lead to study withdrawal. There was 1 death reported during the conduct of this study; autopsy findings indicated pulmonary embolism as the cause of death and the investigator assessed the event as possibly related to study drug. Adjudicated bilateral venogram obtained at the end of dosing was negative, thus the subject experienced a new thrombus 10 days post-study drug cessation.

Shifts from baseline in clinical laboratory findings included increases and decreases in a number of key laboratory parameters, possibly due to surgery alone or in combination with study drug dosing. However, without a control group, definitive clinical conclusions can not be made on this point. Analysis of select abnormal laboratory findings found there was no evidence of dose-induced hepatoxicity.

There were no clinically relevant changes in vital sign parameters between baseline and end of treatment. Categorical findings of 12-lead ECG parameters showed a majority of subjects had non-clinically significant abnormalities on ECGs. There did not appear to be a trend of increased QT_c interval with increased dosing. Changes in physical examination findings were minor with no trends of clinical relevance.

Conclusions:

- There were no statistically or clinically significant relationships between VTE incidence and any of the levels of study drug dosing as occurred in this study, although there were fewer DVTs in the 30 mg bid dose group compared with the other dose groups. Without prophylaxis, approximately 40 to 80% of these subjects will develop DVT after surgery. Approximately 4 to 10% will develop symptomatic pulmonary embolism (PE). The results of this study indicate VTE incidence ranges from 10.3 to 21.3%.
- Assessment of bleeding events also showed no clinically significant findings between study drug dosing and incidence of bleeding events, although a dose-dependent trend appeared to be present for all bleeding events combined.
- The PK of DU-176b in this study population was consistent with that found in healthy volunteers.
- Differences in coagulation parameters between dose groups were not

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clinically relevant.

- Safety analysis showed no clinically significant trends in the frequency and nature of AEs, clinical laboratory findings, ECG findings, vital sign parameters, and physical examination findings.
- Overall, once or twice daily oral doses of DU-176b 12 to 24 hours after hip replacement surgery were well-tolerated in this subject population.