These Clinical Trial Results are provided for informational purposes only.

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Name of Sponsor/Company: Daiichi Sankyo Pharma Development	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Test Product: DU-176b	Volume: Page:	
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		

Title of Study:	A Phase 2, randomized, parallel group, multi-center, multi-national study for the evaluation of safety of four fixed dose regimens of DU-176b in subjects with non-valvular atrial fibrillation
Phase of Development:	Phase 2
Study Period:	First subject randomized date: 02 Jul 2007 Last subject last follow-up date: 18 Jun 2008
Investigator(s):	A total of 107 investigative sites randomized subjects in this study. Information about all participating Investigators is provided in Appendix 16.1.4.
Study Center(s):	This study was conducted (randomized subjects) at 23 investigative sites in North and South America, 18 investigative sites in Eastern, Western, and Central Europe, 32 investigative sites in Russia, and 34 investigative sites in Ukraine.
Publication (reference):	Weitz JI et al. Randomized, parallel group, multicenter, multinational study evaluating safety of DU-176b compared with warfarin in subjects with nonvalvular atrial fibrillation. Paper presented at: 50th American Society of Hematology Annual Meeting; December 7, 2008. Guigliano R et al. The relationship between oral factor Xa (FXa) inhibitor DU-176b pharmacokinetics (PK) and the probability of bleeding events (BE) in patients with atrial fibrillation (AF). Accepted for oral presentation at the International Society of Thrombosis and Hemostasis; July 15, 2009.

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Study Objectives:

The primary objective was to evaluate the safety of four fixed dose regimens of DU-176b (30 mg once daily [qd], 30 mg twice daily [bid], 60 mg qd, and 60 mg bid) in subjects with non-valvular atrial fibrillation (NVAF). Warfarin was included as an active control. Evaluation of bleeding events and liver enzyme/bilirubin abnormalities were the primary focus of the safety evaluation.

Secondary objectives included the following:

- Evaluation of the incidence of major adverse cardiovascular events (MACE): stroke (ischemic or hemorrhagic), systemic embolic events (SEE), myocardial infarction (MI), cardiovascular death, and hospitalization for any cardiac condition
- Evaluation of the effects on biomarkers of thrombus formation: D-dimer and prothrombin fragments 1 and 2 (F1 and F2).
- Evaluation of the PK of DU 176 including known metabolites in subjects receiving DU-176b.
- Evaluation of the effects on PD biomarkers (anti FXa activity, endogenous FXa activity, prothombin time [PT], international normalized ratio [INR], prothrombinase induced clotting time [PiCT], and thrombin generation using the calibrated automated thrombogram [CAT-TG]) in subjects receiving DU-176b.

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Study Design/Methodology:	This was a randomized, double-blind (DU-176b) and open-label (warfarin), parallel group, multi-center, multi-national study. The Investigator, all subjects, and the Sponsor were blinded to the exact DU-176b dose regimen, but not to whether the treatment was DU-176b or warfarin. Subjects were randomly assigned to one of the following five treatment groups in a 1:1:1:1:1 ratio: • DU-176b 30 mg once daily (qd), • DU-176b 30 mg twice daily (bid), • DU-176b 60 mg qd, • DU-176b 60 mg bid, • Warfarin (qd dosage adjusted to maintain INR between 2.0 and 3.0, inclusive). An independent data monitoring committee (IDMC) of external experts was organized to monitor the study data in an unblinded manner to protect the safety of the subjects and to advise the Sponsor in case of any signals of safety concern. In addition, an independent Clinical Events Committee (CEC) was organized to evaluate and adjudicate all bleeding events based on review of blinded data. The CEC adjudicated all bleeding events and categorized them as major, clinically relevant non-major, or minor bleeding based on pre-specified definitions.
Duration of Treatment for Individual Subject:	The duration of treatment for an individual subject was 3 months. The total duration of participation, including screening and follow-up, for an individual subject was approximately 5 months.

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Number of Subjects:

Planned: 1000

Randomized: 1146

- DU-176b 30 mg qd: 235
- DU-176b 30 mg bid: 245
- DU-176b 60 mg qd: 235
- DU-176b 60 mg bid: 180
- Warfarin: 251

Completed/Discontinued: 889 subjects completed all protocol-specified study visits / 257 subjects discontinued the study (including 3 subjects never given study drug).

The DU-176b 60 mg bid regimen was discontinued before the completion of the study in accordance with a recommendation made by the IDMC on 14 Jan 2008. The IDMC recommendation was based on an unfavorable balance of risk and benefit for this specific regimen. At the time of the IDMC's recommendation, 180 subjects were randomized to DU-176b 60 mg bid. No additional subjects were randomized to this group. For subjects already in this group, study drug was discontinued and subjects were followed until the end of the study.

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Diagnosis and Main Criteria for Study Entry:	Key Inclusion Criteria: Subjects (aged 18 to 85 years; male or female) with documented NVAF with a $CHADS_2$ index score of at least 2, and with or without previous treatment with warfarin and/or aspirin were eligible for the study. Key Exclusion Criteria: Subjects with mitral valve disease or previous valvular heart surgery; contraindication for anti-coagulants; conditions associated with high risk of bleeding; acute coronary syndromes (ACS), percutaneous coronary intervention (PCI), MI, stroke, or coronary artery/cardiac/other major surgery within the previous 30 days; active infective endocarditis; or life expectancy < 12 months were not eligible for the study.
Investigational Product and Comparator Information:	All study medications were administered orally. DU-176b (30 mg film-coated tablets): Lot # [redacted], Placebo to match DU-176b: Lot # [redacted] Warfarin (1, 2.5, and 5 mg tablets): Lot # 1 mg: [redacted]

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Study Endpoints and Evaluations:

Safety:

The primary objective was evaluation of safety, and the primary safety variables were the incidences of the following:

- Bleeding events: Major, clinically relevant non-major, or minor as adjudicated by a treatment-blinded CEC based on pre-specified definitions for bleeding categories.
- Liver enzyme elevations (alanine transaminase / aspartate transaminase [ALT/AST] ≥ 3 x upper limit of normal [ULN]) or total bilirubin (TBL) elevations (≥ 2 x ULN), or both.

Other safety variables included incidence of treatment-emergent adverse events (TEAEs), deaths, serious adverse events (SAEs), and discontinuations from study drug due to adverse events and clinical laboratory assessments.

Other Secondary Endpoints:

The incidence of MACE (stroke [ischemic or hemorrhagic], SEE, MI, cardiovascular death, and hospitalization for any cardiac condition) was a secondary (efficacy) objective in this study.

Biomarkers of thrombus generation (D-dimer and prothrombin fragments F1 and F2) were to be assessed for all subjects.

Population pharmacokinetics (PK) and pharmacodynamics (PD) endpoints were assessed only in subjects randomized to DU-176b dosage regimens. PK endpoints consisted of plasma concentrations of DU-176 and known metabolites. PD endpoints included anti-FXa activity, endogenous FXa activity, PT, INR, PiCT, and CAT-TG.

A subset of subjects, those who signed the pharmacogenomics (PGx) informed consent form, had blood samples banked for possible future genomic analyses.

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Statistical Methods:

The sample size was determined based on the precision of the estimated incidence of 1) major plus clinically relevant non-major bleeding and 2) liver enzyme plus bilirubin abnormalities. If the actual incidence is 3% for either item 1 or item 2, then 200 subjects per group (1000 total) would provide an estimate of the incidence with a precision of 2.36% (95% confidence interval [CI] of 0.64% to 5.36%).

The primary analysis was based on subjects in the Safety Analysis Set. All subjects who received at least one dose of study drug and had at least one post-dose safety assessment were included in the safety analysis set.

The proportion of subjects with major plus clinically relevant non-major bleeding (as adjudicated by the CEC using pre-specified definitions) and the proportion of subjects with elevated liver enzymes plus bilirubin were estimated for each treatment group with a 95% confidence interval (CI). The differences between DU 176b dose regimens and between each DU-176b dose regimen and warfarin were estimated with a 95% CI.

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA, version 10.1). Treatment-emergent adverse events (TEAEs) were defined as events not seen at baseline and events that worsened if present at baseline. The incidences of TEAEs were summarized for the Safety Analysis Set by treatment group, by relationship to the study drug, and by severity. Deaths, other SAEs, and AEs leading to study drug discontinuation were summarized. Absolute values and changes from baseline for clinical laboratory tests were summarized by treatment.

The proportion of subjects experiencing MACE during the 3-month treatment period was summarized by treatment group with a 95% CI for the Safety Analysis Set.

Population PK/PD analyses, including examination of possible relationships between drug exposure and incidence of bleeding, were done.

Summary of Results:

Demography: There were no statistically significant differences in demographic or other baseline characteristics across treatment groups. The mean age ranged from 64.7 to 66.0 years. The mean weight ranged from 87.78 kg to 88.95 kg. Most subjects were male (~60%). Most of the subjects (~60%) were warfarin-naïve and approximately half of the subjects were on aspirin therapy at study entry. The majority of subjects were Caucasian (~98.0%) and from Eastern Europe (over 90%). Across all treatment groups, ~36% of subjects had a $CHADS_2$ score ≥ 3, ~20% of subjects had diabetes, ~95% of subjects had hypertension, ~65% of subjects had ischemic heart disease, ~90% of subjects had heart failure, and ~20% had a past stroke or TIA.

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Bleeding Events:

Bleeding events, as adjudicated and categorized by the CEC, are summarized in the table below.

Bleeding Category	DU-176b Daily Dose				Warfarin (N = 250)
	30 mg qd (N = 235)	30 mg bid (N = 244)	60 mg qd (N = 234)	60 mg bid (N = 180)	
All Bleeding, n (%)	13 (5.5)	31 (12.7)	17 (7.3)	33 (18.3)	20 (8.0)
p-value	0.367	0.104	0.864	0.002	
Major or CR non-major bleeding, n (%)	7 (3.0)	19 (7.8)	9 (3.8)	19 (10.6)	8 (3.2)
p-value	1.000	0.029	0.807	0.002	
Major bleeding, n (%)	0 (0.0)	5 (2.0)	1 (0.4)	6 (3.3)	1 (0.4)
p-value	1.000	0.119	1.000	0.023	

P-value is for DU-176b vs. warfarin.

- The DU-176b 60 mg bid group had the highest incidence of bleeding. This group was discontinued before the completion of the study based on the IDMC recommendation and no additional subjects were randomized to this treatment group. The differences between this group and the warfarin group for incidence of all bleeding events and incidence of major plus clinically relevant bleeding events were statistically significant.
- The DU-176b 30 mg bid group had a statistically higher observed incidence than the warfarin group for major plus clinically relevant non-major bleeding events.
- The DU-176b 60 mg qd group had observed incidences similar to the warfarin group for all bleeding events combined and each of the bleeding categories. There were no statistically significant differences between the two groups.
- The DU-176b 30 mg qd group had a numerically lower observed incidence than the warfarin group for all bleeding events combined and similar incidences for major plus clinically relevant non major bleeding events. There were no statistically significant differences between the two groups.
- The DU-176b bid groups had higher incidences of bleeding than the DU-176b qd groups.
- The DU-176b 30 mg and 60 mg qd regimens were well tolerated.

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Bleeding Events continued:

- Thirteen subjects (12 on DU-176b and 1 on warfarin) experienced major bleeding during the treatment period. For the DU-176b-treated subjects, all major bleeds, except one, were in the two bid treatment groups (60 mg bid and 30 mg bid). For the DU-176b-bid groups, including the 60 mg bid group terminated by the IDMC, major bleeding included gastrointestinal bleeding (7 subjects), intracranial bleeding (3 subjects), vaginal bleeding (1 subject), and epistaxis (subject also had major gastrointestinal bleeding). There was only one subject with major bleeding (spontaneous intracranial) in the DU-176b 60 mg qd group. No subject in the DU-176b 30 mg qd group experienced major bleeding. The warfarin-treated subject with major bleeding had epistaxis. Only 2 subjects (both in the DU-176b 30 mg bid group) died as a result of major bleeding (hemorrhagic stroke and intracranial bleeding).
- For bleeding events resulting in discontinuation, reported as SAEs, and those requiring transfusion, the highest incidences of the study were observed in the DU-176b 60 mg bid group.

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Liver Enzyme and Total Bilirubin Abnormalities:

The number (%) of subjects with liver enzyme and/or bilirubin abnormalities is summarized in the table below.

	DU-176b Daily Dose				
Laboratory Test	**30 mg qd (N = 235)**	**30 mg bid (N = 244)**	**60 mg qd (N = 234)**	**60 mg bid (N = 180)**	**Warfarin (N = 250)**
Any Elevation	5 (2.1)	4 (1.6)	8 (3.4)	7 (3.9)	8 (3.2)
ALT, N	230	235	229	172	245
Total ≥3 x ULN	3 (1.3)	2 (0.9)	6 (2.6)	3 (1.7)	3 (1.2)
AST, N	230	235	229	172	245
Total ≥3 x ULN	2 (0.9)	2 (0.9)	3 (1.3)	2 (1.2)	2 (0.8)
TBL, N	230	235	229	172	245
Total ≥2 x ULN	2 (0.9)	3 (1.3)	1 (0.4)	5 (2.9)	4 (1.6)
ALT and/or AST, N	230	235	229	172	245
ALT or AST ≥3 x ULN	3 (1.3)	2 (0.9)	7 (3.1)	3 (1.7)	4 (1.6)
(ALT or AST) and TBL, N	230	235	229	172	245
(ALT/AST ≥3 x ULN) and (TBL ≥2 x ULN)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.6)	0 (0.0)

- The numbers (%) of subjects with ALT ≥ 3 x ULN or AST ≥ 3 x ULN or TBL ≥ 2 x ULN at any time after the first dose of study drug were low across all treatment groups.
- The number of subjects with ALT or AST ≥ 3 x ULN ranged from 2 to 7 subjects (0.9% to 3.1%) across all treatment groups. The number of subjects with TBL ≥ 2 x ULN ranged from 1 to 5 subjects (0.4 to 2.9%) across all treatment groups.
- With each parameter considered separately, there were no statistically significant differences between any DU-176b group and the warfarin group, and no statistically significant differences between any two DU-176b groups.
- There were two subjects (Subject IDs: 20060002 and 40290006 [1 in each of the DU-176b bid groups]) who experienced concomitant but not persistent elevations of ALT or AST ≥ 3 x ULN and TBL ≥ 2 x ULN. At the same time as the elevated ALT/AST and TBL, both subjects also had ALP > 2 x ULN, suggesting cholestasis rather than drug-induced hepatocellular injury. Independent hepatologists' review of these cases concluded that one subject had acute cholecystitis and the other had a dilated bile duct confounded by chronic heart failure and anemia.

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Other Safety Assessments:

- Deaths: Fourteen subjects (6 [2.6%] in the 30 mg qd DU-176b group, 4 [1.6%] in the 30 mg bid DU-176b group, 1 [0.4%] in the 60 mg qd DU-176b group, 0 in the 60 mg bid DU-176b group, and 3 [1.2%] in the warfarin group) died during the study: 8 deaths occurred while the subject was on study drug, 5 occurred as a results of events during the post-treatment follow-up period, and 1 occurred during the follow-up period as a result of an event that began the day after the last dose of study drug (i.e., on the last day of the treatment period). All deaths resulted from cardiovascular conditions such as MI, coronary artery disease, cardiac failure, stroke, pulmonary embolism, or sudden death. This is not unexpected considering the medical history (hypertension, atrial fibrillation, heart failure, ischemic heart disease, diabetes, and stroke/TIA) of the subject population.
- SAEs: Sixty-four (5.6%) subjects in the Safety Analysis Set had at least one SAE that was treatment-emergent. The incidences of such SAEs in the DU-176b 30 mg qd and warfarin treatment groups were similar (3.4% and 4.4%, respectively). The DU-176b 30 mg bid and 60 mg qd groups had similar incidences of such SAEs (6.6% and 6.4%). The DU-176b 60 mg bid group had the highest incidence (7.8%) of SAEs. Almost all SAEs were also reported in at least one of these other categories: MACE, bleeding, liver abnormalities, deaths, and AEs leading to study drug discontinuation.
- Discontinuations Due to AEs: Fifty eight (5.1%) subjects had TEAEs leading to study drug discontinuation. The majority of such TEAEs were also either a MACE or a major and/or clinically relevant non-major bleeding event. The DU-176b 60 mg bid group had the highest incidence of discontinuation due to AEs (8.3%). The incidences of withdrawals due to AEs in the 30 mg qd, 30 mg bid, and 60 mg qd DU-176b groups were 5.1%, 4.5%, and 6.0% of subjects, respectively. The warfarin group had a lower incidence (2.4%) of such events. It is important to note that warfarin was given as an open-label therapy; this plus the knowledge that the IDMC recommended discontinuation of the DU-176b 60 mg bid regimen may have biased the early withdrawals to some extent.
- The overall incidence of TEAEs was similar across treatment groups with 39.8% to 46.0% of subjects in each group having at least one event. Most TEAEs in all treatment groups were mild or moderate in severity and not considered related to study drug.

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Major Adverse Cardiovascular Events (Efficacy):

This study was not designed to evaluate efficacy. The incidence of stroke/SEE was very low in all groups. There were four subjects with strokes in warfarin group compared with only one or two in each of the DU-176b treatment groups.

The incidence of MACE was 2.4% for warfarin-treated subjects and 2.5% across all DU-176b treated subjects. With such low incidences, no conclusions regarding efficacy can be drawn. In any case, the study was not powered to detect differences in MACE incidence across the treatment groups.

PK and PD variables:

The pharmacometric analyses were conducted to better understand the PK across the study population, the relationship between PK parameters and bleeding incidence relationship and the differences in bleeding incidences (DU-176b bid regimens vs. DU-176b qd regimens). These pharmacometric analyses confirmed similar total exposure expressed as AUC_{inf} between the DU-176b 60 mg qd and 30 mg bid regimens. In addition, logistic regression analyses indicated that the steady state minimum (trough) concentrations ($C_{min,ss}$) best predicted the probability of bleeding.

The PD data (anti FXa activity, endogenous FXa activity, PT, INR, PiCT, CAT TG, D-dimer, and prothrombin fragments F1+2) will be reported in a CSR addendum.

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Conclusions:

The primary objective of this study was to evaluate the safety of 3-month treatment with DU-176b in moderate to high risk patients with NVAF. This study was not designed to evaluate efficacy.

Overall, DU-176b 30 mg qd and 60 mg qd dosage regimens were well tolerated with lower or similar incidences of bleeding compared with warfarin therapy.

Subjects treated with DU-30 mg bid and 60 mg bid regimens had higher bleeding incidences compared with subjects on warfarin therapy.

The DU-176b 60 mg bid regimen was considered unsafe by the IDMC due to an unfavorable benefit/risk ratio.

Subjects treated with DU-176b 30 mg qd and 60 mg qd regimens had lower bleeding incidences than those treated with the 30 mg bid or 60 mg bid regimens.

The overall incidence of liver enzyme and bilirubin abnormalities was low in this study and there was no significant difference between treatment groups. There were no significant or clinically relevant signals of drug-induced hepatocellular injury in this relatively small study.

This study was not designed to evaluate efficacy. The incidence of stroke/SEE was very low in all groups. There were four subjects with strokes in the warfarin group compared with only one or two in each of the DU-176b treatment groups. There were too few subjects with MACEs during the treatment period (from first dose to the end of treatment visit) to draw any clinically meaningful conclusion.

All deaths reported in this study were due to cardiovascular conditions which are expected in this subject population.

The pharmacometric analyses were conducted to better understand the PK across the study population, the relationship between PK parameters and bleeding incidence relationship and the differences in bleeding incidences (DU-176b bid regimens vs. DU-176b qd regimens). These pharmacometric analyses confirmed similar total exposure expressed as AUC_{inf} between the DU-176b 60 mg qd and 30 mg bid regimens. In addition, logistic regression analyses indicated that the steady state minimum (trough) concentrations ($C_{min,ss}$) best predicted the probability of bleeding. This may explain the higher bleeding incidences observed in the DU-176b 30 mg bid group compared with the DU-176b 60 mg qd group.

Overall, the DU-176b 30 mg qd and 60 mg qd regimens were safe and well tolerated by subjects with AF treated for 3 months in this Phase 2 study.

Date of the Report: 17 Sep 2009