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REPORT SYNOPSIS

Name of Sponsor/Company: Daiichi Sankyo, Inc. and Eli Lilly and Company	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Test Product: Prasugrel hydrochloride (CS747, LY640315)		
Name of Active Ingredient: Prasugrel		
Title of Study:	A Pharmacodynamic Evaluation of Switching from Ticagrelor to Prasugrel in Subjects with Stable Coronary Artery Disease: 2nd Switching Antiplatelet Agents. CS747S-B-U4003 (SWAP 2)	
Phase of Development:	4	
Study Period:	First subject first visit date: 26 Mar 2012 Last subject last follow-up date: 13 Feb 2013	
Investigator(s):	[redacted] List of remaining study Investigators is in Appendix 16.1.4	
Study Center(s):	United States (US): 8 sites, United Kingdom (UK): 4 sites (in addition, 1 site did not randomize any subjects)	
Publication (reference):	None	
Study Objectives/Hypothesis:	PRIMARY OBJECTIVE: To compare the pharmacodynamic (PD) effects, expressed as $P2Y_{12}$ reaction units (PRU) by the VerifyNow® P2Y12 assay, in subjects treated with a prasugrel 10 mg daily (QD) maintenance dose (MD) (Arms A + B) and in subjects treated with ticagrelor 90 mg twice daily (BID) MD (Arm C), after 7 days of randomized study treatment. SECONDARY OBJECTIVES: • To compare the PD effects, measured by the vasodilator-stimulated phosphoprotein (VASP) assay (platelet reactivity index [PRI]), in all subjects treated with prasugrel 10 mg QD MD (Arms A + B) and in subjects treated with a ticagrelor 90 mg BID MD (Arm C) after 7 days of randomized treatment. • To compare the PD effects, measured using the VerifyNow® Assay device-reported and calculated percent inhibition in subjects treated on Arms A + B and in subjects treated on Arm C after 7 days of randomized treatment. • To compare the PD effects, in terms of PRU, VerifyNow® Assay device-reported and calculated percent inhibition, and PRI, in subjects treated on Arm A (prasugrel 60 mg LD + 10 mg QD MD) and in subjects treated on Arm C (ticagrelor 90 mg BID MD), at these time points: 2, 4, 24, and 48 hours and 7 days of	

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	randomized study treatment.
	• To compare the PD effects, in terms of PRU, VerifyNow® Assay device-reported and calculated percent inhibition, and PRI in subjects treated on Arm B (prasugrel 10 mg QD MD) vs. Arm C (ticagrelor 90 mg BID MD), at these time points: 2, 4, 24, and 48 hours and 7 days of randomized study treatment.
	• To assess and to compare the percentage of subjects with HPR after 2, 4, 24, and 48 hours and 7 days of randomized study treatment. The HPR will be defined in accordance with the following platelet inhibition level cut-off:
	  • a) ≥ 208 PRU by the VerifyNow® P2Y12 assay;
	  • b) ≥ 230 PRU by the VerifyNow® P2Y12 assay;
	  • c) > 50% PRI by the VASP assay.
	
	SAFETY OBJECTIVE*:*
	To evaluate the safety and tolerability of switching subjects from ticagrelor to prasugrel.
	
	EXPLORATORY OBJECTIVE*:*
	To determine the potential influence of pre-run-in baseline, pre-randomization baseline, age, body mass index (BMI), weight, gender, and presence of diabetes on platelet function after 7 days of randomized study treatment.
	
	STUDY HYPOTHESIS*:*
	The primary hypothesis in this study was that platelet inhibition (as measured by VerifyNow® P2Y12) after 7 days of randomized treatment would be noninferior (using 45 PRU as the noninferiority margin for the upper limit of the confidence interval [CI] for the treatment difference) in subjects who switched from ticagrelor to prasugrel compared with subjects treated continuously on ticagrelor.

Study Design/Methodology:	This was a Phase 4 multicenter, open-label (blinded PD results), randomized (1:1:1), 3-arm parallel-design study of subjects ≥ 18 to < 75 years of age with stable coronary artery disease (CAD). The study compared the PD effects (platelet inhibition) of prasugrel 10 mg QD MD and ticagrelor 90 mg BID MD, as assessed by the VerifyNow® P2Y12 and VASP assays.

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	The study consisted of a 3 to 5 day ticagrelor run-in phase (ticagrelor 180 mg LD followed by 90 mg BID MD) followed by randomized treatment on 1 of 2 prasugrel regimens or continued ticagrelor as follows: • Arm A - Prasugrel 60 mg LD, followed by prasugrel 10 mg QD MD • Arm B - Prasugrel 10 mg QD MD • Arm C - Ticagrelor 90 mg BID MD All subjects must have been taking low dose acetylsalicylic acid (ASA) (75 mg to 150 mg QD) for at least 7 days prior to Screening (Visit 1), and must have continued the same regimen throughout the study. ASA was not supplied by the Sponsor and was not considered an investigational drug in this study. Blood samples for platelet activity were collected prior to the ticagrelor LD (pre-run-in baseline), before the first dose of randomized drug (pre-randomization baseline), and at 2, 4, 24, and 48 hours, and 7 days after the first dose of randomized treatment. PD evaluations of platelet function by VerifyNow® P2Y12 and VASP assays were performed on samples from each time point.
Duration of Treatment for Individual Subject:	Up to 15 days
Number of Subjects:	Planned: 105 Screened: 167 Enrolled/Randomized: 120 enrolled/110 randomized Completed/Discontinued: 106 completed/4 discontinued. Subject completion included Screening procedures, a final study visit, and a follow-up telephone call 2 weeks after the final study visit.
Diagnosis and Main Criteria for Study Entry:	Subjects had to satisfy all of the following main criteria to be included in the study: 1. Male or female; age ≥ 18 years and < 75 years 2. Weight ≥ 60 kg 3. On low-dose ASA therapy (75 mg to 150 mg daily) for at least 7 days prior to Screening (Visit 1) and able to maintain the same ASA dosing regimen from the Screening visit through the final study visit 4. Stable CAD. CAD was defined as any of the following: a. History of a positive stress test b. Previous coronary revascularization including percutaneous coronary intervention (PCI), stent, or coronary artery bypass graft (CABG)

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c. Angiographic demonstration of CAD (at least 1 lesion ≥ 50 percent)

d. Presence of at least moderate plaque by computed tomography (CT) angiography

e. Electron beam CT coronary artery calcification score ≥ 100 Agatston units

5. If female, may have been enrolled if one of the following 3 criteria were met:

   a. Had a hysterectomy or tubal ligation at least 6 months prior to signing the informed consent form (ICF)

   b. Post-menopausal for at least 1 year

   c. If of childbearing potential, would practice 1 of the following methods of birth control throughout the study: oral, injectable, or implantable hormonal contraceptives; intrauterine device; diaphragm plus spermicide; or female condom plus spermicide. Methods of contraception that were not acceptable were partner's use of condoms or partner's vasectomy

6. Able and willing to provide written informed consent before entering the study

Subjects who met any of the following criteria were disqualified from entering the study:

1. Defined need for ADP receptor inhibitor therapy. This included, but was not exclusive to:

   a. Being within ≤ 12 months of an ACS event (UA, NSTEMI, or STEMI) regardless of initial treatment (that is, invasive vs. noninvasive)

   b. Subjects who underwent angioplasty within 12 months including bare metal stent and/or a drug eluting stent

   c. Having had any stent placed in an unprotected left main coronary artery or in the last patent artery within the last 12 months

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2. Received thienopyridine therapy within 30 days
3. Planned coronary revascularization at any time during the trial
4. Presence or history of any of the following: ischemic or hemorrhagic stroke; TIA; intracranial neoplasm; arteriovenous malformation or aneurysm; intracranial hemorrhage; head trauma (within 3 months of study entry)
5. History of refractory ventricular arrhythmias or with an increased risk of bradycardic events (eg, subjects without a pacemaker who had sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardic-related syncope)
6. History of evidence of congestive heart failure (New York Heart Association Class III or above) within 6 months prior to Screening
7. Severe hepatic impairment
8. History of uric acid nephropathy
9. Uncontrolled hypertension, or systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg at Screening
10. Severely impaired renal function, defined as glomerular filtration rate < 30 mL/minute or on dialysis
11. Bleeding Risk Exclusion Criteria:
    a. Presence of any known contraindication to treatment with an anticoagulant or antiplatelet agent
    b. Presence of active internal bleeding or history of bleeding diathesis (eg, hematemesis, melena, severe or recurrent epistaxis, hemoptysis, hematuria, or intraocular bleeding)
    c. Presence of active peptic ulcers
    d. Known prior history or presence of thrombocytopenia (platelet count < 100 000/mm3) or thrombocytosis (platelet count > 500 000/mm3) or recent history (within 6 months) of hemoglobin < 10 mg/dL
    e. International normalized ratio (INR) > 1.5 at

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screening

f. History of major surgery, severe trauma, fracture, or organ biopsy within ≤ 3 months of screening

g. Evidence of active hepatic disease or any of the following:

i. Positive for antibody to human immunodeficiency virus

ii. Positive for antibody to hepatitis C virus

iii. Positive hepatitis B surface antigen

iv. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), or gamma-glutamyltransferase (GGT) ≥ 3 × the upper limit of normal (ULN) or bilirubin ≥ 2 × ULN at Screening (ULNs based on laboratory reference ranges)

12. Prior/Concomitant Therapy Exclusion Criteria:

a. Received non-ASA antiplatelet agents, anticoagulants, Factor Xa inhibitors, direct or indirect antithrombins, or Glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors at the time of screening or anytime during study participation.

b. Used or planned to use fibrinolytic agents ≤ 7 days before screening or anytime during study participation

c. Received treatment with nonsteroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors exceeding 3 doses per week

d. Used or planned to use strong inhibitors or inducers of CYP3A4 < 10 days before screening or anytime during study participation

e. Received treatment with > 40 mg per day or either simvastatin or lovastatin at screening or any time during study participation

13. General Exclusion Criteria:

a. Employed at investigative site, with direct affiliation

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with the study, or immediate family of investigative site personnel directly affiliated with the study. (Immediate family was defined as a spouse, parent, child, or sibling, whether biological or legally adopted)

b. Employed by Daiichi Sankyo, Inc. (DSI), Eli Lilly, or the Contract Research Organization (CRO) representing the Sponsor

c. Was currently enrolled in, or discontinued within the last 30 days from, any clinical study involving an investigational drug or device

d. Previously completed or withdrew from this study

e. If female, had any of the following

   i. Positive serum pregnancy test at Visit 1

   ii. Had given birth ≤ 90 days before screening criteria were met

   iii. Was currently breast-feeding

   iv. Was planning to become pregnant during the study

f. Had clinically significant laboratory test result(s) at the time of screening, as determined by the Investigator

g. Had known allergies or intolerance to ASA, prasugrel, ticagrelor, or their excipients

h. Had evidence, as judged by the Investigator, of significant active neuropsychiatric disease, alcohol abuse, or drug abuse

i. Was unwilling to be available for the duration of the study and to abide by the research unit policy and procedure and study restrictions

j. Had any condition that, as judged by the Investigator, would place the subject at increased risk of harm if he/she participated in the study

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Investigational Product and Comparator Information:

Prasugrel:

Dosage Form: 10-mg film-coated tablets

Route of Administration: Oral

Lot Number.: [redacted]

Packaging Information: Supplied in 34-count high-density polyethylene (HDPE) bottles

Ticagrelor:

Dosage Form: 90-mg film-coated tablets

Route of Administration: Oral

Lot Number.: [redacted]

Packaging Information: Supplied in 14-count blister packs for the UK, and in 10-count blister packs for the US

Criteria for Evaluation:

Efficacy: PD assessments were used as a surrogate for efficacy

Pharmacokinetics/Pharmacodynamics:

PRIMARY PD VARIABLE:

- PRU by VerifyNow® P2Y12 assay for prasugrel 10 mg QD MD (Arm A + B) and ticagrelor 90 mg BID MD (Arm C) after 7 days of randomized treatment

SECONDARY PD VARIABLES:

- PRI by the VASP assay 2, 4, 24, 48 hours, and 7 days after first randomized study treatment.
- PRU by the VerifyNow® P2Y12 assay 2, 4, 24, and 48 hours after first randomized study treatment.
- VerifyNow® assay device-reported and calculated percent inhibition 2, 4, 24, and 48 hours, and 7 days after first randomized study treatment.
    a. Calculated percent inhibition - defined for time point t as:
    $100 \times (\text{baseline PRU} - \text{PRU}_t)/\text{baseline PRU}$,
    where baseline is the pre-run-in baseline and PRU_t is the VerifyNow® P2Y12 assay value at time point t.
- Percentage of subjects with HPR, defined as a) ≥ 208 PRU or b) ≥ 230 PRU by the VerifyNow® P2Y12 assay, or c) > 50% PRI by the VASP assay, 2, 4, 24, and 48 hours, and 7 days after first randomized study treatment.

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Safety: Adverse events (AEs), clinical laboratory parameters, vital signs, and physical examinations. Bleeding events were to be reported as AEs. All serious AEs (SAEs) were to be reported according to the SAE reporting procedure for Investigators.

Other: Not applicable.

Statistical Methods:

The Treated Population was defined as all subjects who received at least 1 dose of randomized study medication. The Treated Population was used for safety analysis. Available data for subjects in the Treated Population was used for analysis of all secondary PD endpoints. The Primary population was used for the analysis of the primary and secondary PD endpoints. The Primary population was defined as all subjects who received at least 1 dose of randomized study drug and had valid PRU data at both the randomization visit (Visit 3, pre-dosing) and end-of-treatment (Visit 6). A subject was considered to have valid PRU data for primary PD analyses if he/she did not have any of these protocol deviations:

Deviations Prior to Randomization:

a. Subject missed more than 2 doses (consecutive or nonconsecutive) of ticagrelor during the run-in phase
b. Subject's VerifyNow® blood draw at Visit 3 pre-randomization was outside the window of 12 ± 4 hours after the last run-in dose of ticagrelor
c. Subject missed the LD of ticagrelor and 1 or more MD of ticagrelor during the run-in phase (if the subject missed the LD but took all scheduled MD in the run-in phase, the subject was not automatically excluded from the Primary Population)

Deviations Post Randomization:

a. Subject missed more than 1 dose of prasugrel (if randomized to prasugrel Arm A or B)
b. Subject missed more than 2 doses (consecutive or nonconsecutive) of ticagrelor (if randomized to ticagrelor Arm C)
c. Subject's VerifyNow® blood draw at final visit (Visit 6) was outside of the protocol-specified time window (12 ± 4 hours after taking the final dose of ticagrelor, 24 ± 4 hours after taking the final dose of prasugrel)
d. Subject did not have valid PRU data for Visit 6
e. Subject did not have valid PRU data for Visit 3 pre-dosing
f. Subject's final visit took place outside the Day 8 to Day 11 window

The primary PD analysis compared device-reported PRU measured using the Accumetrics VerifyNow® P2Y12 device between the combined prasugrel treatment groups and the ticagrelor treatment group.

The primary PD analysis was accomplished using an analysis of covariance (ANCOVA) model including treatment as a main effect and pre-randomization baseline PRU as a covariate. Treatment

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was modeled as a binary main effect ([A + B] vs. C). The least-square (LS) mean difference in PRU between the groups and the corresponding 2-sided 95% confidence interval (CI) for the difference was presented. Summary statistics including n, mean, standard deviation, median, minimum, and maximum for the combined prasugrel treatment groups and the ticagrelor treatment group were presented. Subgroup analyses were provided for gender, diabetic status, and BMI category ($\geq$ 30 kg/m^2 and < 30 kg/ m^2).

Sensitivity analysis was conducted to support the primary PD analysis using a subset of covariates. For the first planned sensitivity analysis, a regression analysis was performed to determine the potential influence of pre-run-in baseline, pre-randomization baseline, age (as a continuous variable), BMI, weight, gender, country, history of diabetes, history of hypertension, history of hyperlipidemia, and history of peripheral artery disease on platelet function after 7 days of randomized study treatment. Model selection was performed using a backward elimination procedure. The model that resulted from the backward selection process was used for the sensitivity analysis.

A second sensitivity analysis was performed to support the primary PD analysis by including subjects with blood draws for PRU outside the pre-specified windows at the final visit or Visit 3 pre-dosing.

Several secondary PD analyses were conducted that mirrored the approach used for the primary PD analysis. For these analyses, the ANCOVA model used was the same as that of the primary PD analysis, but used the pre-randomization baseline value corresponding to the response being modeled as the covariate. For the secondary PD variables, as well as the primary PD variable PRU, each prasugrel treatment was individually compared to the ticagrelor treatment group at each of the time points following the pre-randomization baseline time point.

For such time points, an ANCOVA model including treatment as a main effect and the relevant pre-randomization baseline value as a covariate was used to assess differences between treatment groups. Comparisons between groups were based on a model including data from all treatment groups. For all time points at which the response was measured, summary statistics including n, mean, SD, median, minimum, and maximum for the individual treatment groups and the combined prasugrel group were presented. For all time points after the pre-randomization baseline time point, LS means, standard errors for the LS means, 95% CIs for the LS means, the LS mean differences, and 95% CI for the LS mean differences were provided.

Summary:

Efficacy Results: Pharmacodynamic assessments were used as a surrogate for efficacy

Safety Results:

No unexpected safety issues were observed in this study. Drug-related ecchymosis occurred in 8 (10.7%) subjects receiving prasugrel and in 4 (11.4%) subjects receiving ticagrelor at the time of the event. However, none were SAEs or led to discontinuation from the study. All other drug-related treatment-emergent AEs (TEAEs) were experienced by 2 or fewer subjects while on prasugrel or ticagrelor.

One subject in ticagrelor Group C had a total of 4 SAEs during the study; the subject did not discontinue the study due to an SAE. None of the SAEs were considered to be related to study

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medication. The outcome for each event was recovered/resolved.

No clinically meaningful changes in hematology, blood chemistry, urinalysis, or coagulation were noted during the study.

Pharmacokinetic/Pharmacodynamic Results:

Table S1 presents the comparison of mean VerifyNow® device-reported PRU after 7 days of randomized treatment for subjects in the Primary Population treated with prasugrel and ticagrelor. The mean (SD) PRU was 95.6 (54.12) for prasugrel-treated subjects and 47.9 (47.59) for ticagrelor-treated subjects. The LS mean difference (95% CI) in the combined prasugrel group compared to the ticagrelor group was 46.0 PRU (24.9, 67.2). Since the upper limit of the CI of the LS mean difference was greater than 45 PRU, the PD response to prasugrel 10 mg QD MD was not deemed noninferior to that achieved by ticagrelor 90 mg BID MD.

Following adjustments for select baseline covariates in additional sensitivity analysis, the PRU results in the combined prasugrel and ticagrelor groups after 7 days of randomized treatment were identical to the primary analysis results.

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Table S1: Analysis of Mean $P2Y_{12}$ Reaction Units (PRU) Following 7 Days of Randomized Study Treatment - Primary Population

Time Point	Prasugrel Groups A + B (N = 65)	Ticagrelor Group C (N = 33)
Visit 3: Pre-Randomization Baseline		
n	65	33
Mean (SD)	48.8 (38.55)	44.7 (41.30)
Median	37.0	47.0
Min - Max	2 - 174	1 - 204
Visit 6: 7 Days Post First Randomized Dose		
n	65	33
Mean (SD)	95.6 (54.12)	47.9 (47.59)
Median	88.0	40.0
Min - Max	7 - 240	4 - 270
ANCOVA Results[1]		
LS Mean (SE)	95.0 (6.18)	49.0 (8.68)
LS Mean 95% CI	(82.7, 107.3)	(31.8, 66.2)
LS Mean Difference (SE)[2]	46.0 (10.66)	
LS Mean Difference 95% CI[3]	(24.9, 67.2)	

ANCOVA = analysis of covariance; BID = twice daily; CI = confidence interval; LD = loading dose; MD = maintenance dose; QD = once daily; SD = standard deviation; SE = standard error.

Treatment Groups: A = prasugrel 60 mg LD, followed by prasugrel 10 mg QD MD; B = prasugrel 10 mg QD MD; C = ticagrelor 90 mg BID MD.

1 ANCOVA model included treatment as a main effect and pre-randomization baseline as a covariate. The combined prasugrel groups were modeled as a single treatment.

2 LS mean difference was computed as (A+B) - C.

3 If the upper limit of the CI for the mean difference was not greater than 45 PRU, then the PD response to prasugrel 10 mg QD MD was deemed noninferior to that achieved by ticagrelor 90 mg BID MD.

Source: Post-text Table 15.4.1.1

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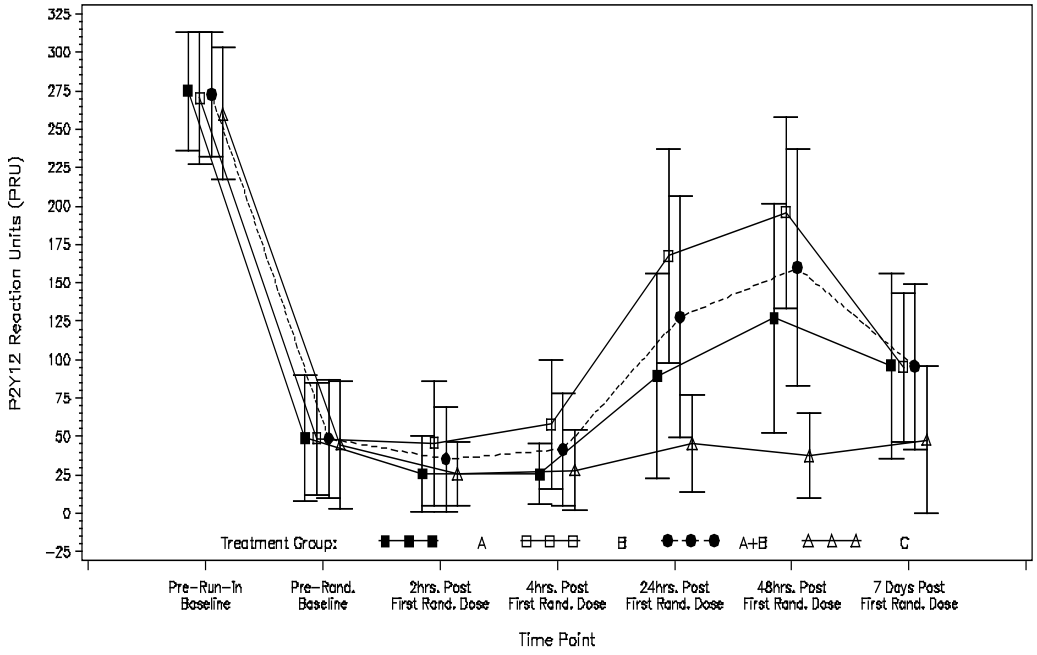
Figure S1 displays the mean subject time profiles of PRU after 2, 4, 24, 48 hours, and 7 days of randomized treatment for subjects treated with prasugrel and ticagrelor.

Figure S1: Time Profile of Mean (SD) $P2Y_{12}$ Reaction Units - Primary Population



BID = twice daily; hrs = hours; LD = loading dose; MD = maintenance dose; QD = once daily; Rand = randomized.

Treatment Groups: A = prasugrel 60 mg LD, followed by prasugrel 10 mg QD MD; B = prasugrel 10 mg QD MD; C = ticagrelor 90 mg BID MD.

Errors bars ± 1 standard deviation about the group mean.

Source: Post-text Figure 15.4.13.4.

At early time points, the mean PRU was lower in subjects receiving prasugrel LD (prasugrel Group A) vs. MD only (prasugrel Group B). At 24 hours following randomization, the mean (SD) PRU Group A was 83.4 (63.97) in prasugrel Group A and 168.2 (67.97) in prasugrel Group B. The mean (SD) PRU at 48 hours was 120.2 (71.33) in prasugrel Group A and 198.3 (61.85) in prasugrel Group B. At 24 and 48 hours, the P-value for the LS mean difference between prasugrel groups A and B was < 0.001. Similar to 7 days after randomization, the mean (SD) PRU in ticagrelor Group C at 24 hours was 45.4 (31.85) and at 48 hours was 37.6 (27.46), which was lower than subjects in prasugrel groups A and B.

The analysis of mean PRU with the inclusion of subjects with out-of-window blood draws yielded similar results.

In comparing subjects treated with prasugrel by gender, the mean PRU after 7 days of randomized

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treatment was higher in females than males; however, females treated with ticagrelor had a lower mean (SD) PRU than males. In males, the mean PRU was 90.8 (49.25) for subjects treated with prasugrel and 51.6 (51.78) in subjects treated with ticagrelor. The LS mean difference (95% CI) in PRU in the combined prasugrel group compared to the ticagrelor group was 39.8 (15.9, 63.8). In females, the mean (SD) PRU was 107.2 (64.41) for subjects treated with prasugrel and 36.5 (31.07) in subjects treated with ticagrelor. The LS mean difference (95% CI) in PRU in the combined prasugrel group compared to the ticagrelor group was 61.2 (11.4, 110.9).

The mean PRU after 7 days of randomized treatment was comparable in subjects with or without diabetes. In subjects with diabetes, the mean (SD) PRU was 103.1 (52.18) in subjects treated with prasugrel and 46.2 (23.66) in subjects treated with ticagrelor. The LS mean difference (95% CI) in PRU in the combined prasugrel group compared to the ticagrelor group was 50.3 (2.4, 98.1). In subjects without diabetes, the mean (SD) PRU was 90.9 (55.42) in subjects treated with prasugrel and 48.2 (51.00) in subjects treated with ticagrelor. The LS mean difference (95% CI) in PRU in the combined prasugrel group compared to the ticagrelor group was 43.9 (18.3, 69.5).

In comparing subjects in the different BMI categories after 7 days of randomized treatment, subjects treated with prasugrel in the BMI category ≥ 30 kg/m^2 had a higher mean PRU than subjects in the BMI category < 30 kg/m^2. In contrast, subjects treated with ticagrelor in the BMI category < 30 kg/m^2 had a higher mean PRU than subjects in the BMI category ≥ 30 kg/m^2. In subjects with a BMI category < 30 kg/m^2, the mean (SD) PRU was 87.9 (53.92) in subjects treated with prasugrel and 52.1 (54.63) in subjects treated with ticagrelor. The LS mean difference (95% CI) in PRU in the combined prasugrel group compared to the ticagrelor group was 38.6 (6.6, 70.5). In subjects with a BMI category ≥ 30 kg/m^2, the mean (SD) PRU was 100.7 (54.34) in subjects treated with prasugrel and 38.2 (24.64) in subjects treated with ticagrelor. The LS mean difference (95% CI) in PRU in the combined prasugrel group compared to the ticagrelor group was 49.2 (15.6, 82.8).

Although the LS mean difference between prasugrel and ticagrelor did not meet the noninferiority objective, the rates of HPR for subjects treated with prasugrel or ticagrelor using the PRU cutoff of ≥ 208 or ≥ 230 were similar after 7 days of randomized treatment. At the early time points of 24 and 48 hours, the rates of HPR PRU ≥ 208 and ≥ 230 were greater in prasugrel Group B vs. prasugrel Group A. At 24 hours, the P-values for Groups A vs. B for the rates of HPR PRU ≥ 208 and ≥ 230 were 0.007 and 0.03, respectively. At 48 hours, the P-values for Groups A vs. B for the rates of HPR PRU ≥ 208 and ≥ 230 were 0.03 and 0.005, respectively.

The rates of HPR using the PRU cutoff of ≥ 208 or ≥ 230 were significantly higher at early time points of 24 and 48 hours in the combined prasugrel group vs. the ticagrelor group. At 24 hours, the P values for the combined prasugrel group vs. the ticagrelor group for the rates of HPR PRU ≥ 208 and ≥ 230 were 0.01 and 0.03, respectively. At 48 hours, the P values for the combined prasugrel group vs. the ticagrelor group for the rates of HPR PRU ≥ 208 and ≥ 230 were < 0.001 and 0.002, respectively.

After 7 days of randomized treatment, the rates of HPR using the PRI cutoff of > 50% were greater in subjects treated with prasugrel (15.5%) vs. ticagrelor (3.4%). At 24 and 48 hours, the rates of HPR using the PRI cutoff of > 50% were greater in prasugrel Group B vs. prasugrel Group A. At 24 and

Name of Sponsor/Company: Daiichi Sankyo, Inc. and Eli Lilly and Company	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Test Product: Prasugrel hydrochloride (CS747, LY640315)		
Name of Active Ingredient: Prasugrel		

48 hours, the P-values for Groups A vs. B for the rates of HPR with the PRI cutoff of > 50% were 0.001 and < 0.001, respectively.

In additional analyses, after 7 days of randomized treatment, the mean (SD) PRI by VASP was higher in subjects treated with prasugrel: 35.6 (22.22) in prasugrel Group A and 29.8 (14.83) in prasugrel Group B vs. 20.1 (17.83) in ticagrelor Group C. The LS mean difference (95% CI) in PRI in prasugrel groups A and B compared to ticagrelor Group C was 19.0 (8.4, 29.5) and 9.3 (-0.8, 19.3), respectively.

After 7 days of randomized treatment, the device-reported mean (SD) percent inhibition by VerifyNow® was lower in subjects treated with prasugrel: 65.7 (19.48) in prasugrel Group A and 65.6 (17.87) in prasugrel Group B vs. 80.8 (18.46) in ticagrelor Group C. The LS mean differences (95% CI) in percent inhibition in prasugrel groups A and B compared to ticagrelor Group C were -15.4 (-24.1, -6.7) and -15.6 (-24.2, -7.1), respectively.

After 7 days of randomized treatment, the mean (SD) calculated percent inhibition was lower in subjects treated with prasugrel: 65.1 (19.34) in prasugrel Group A and 65.2 (18.36) in prasugrel Group B vs. 80.4 (20.26) in ticagrelor Group C. The LS mean difference (95% CI) in calculated percent inhibition in prasugrel groups A and B compared to ticagrelor Group C was -15.7 (-25.2, -6.2) and -15.7 (-24.9, -6.5), respectively.

Overall, these results indicate that the PRU response to prasugrel did not meet the noninferiority primary objective. However, the HPR rates in subjects treated with prasugrel were similar to the HPR rates in subjects treated with ticagrelor after 7 days of randomized treatment using the PRU cutoff of ≥ 208 or ≥ 230.

Other Results: Not applicable

Conclusions:

Switching from ticagrelor to prasugrel did not meet its primary objective of demonstrating noninferiority based upon the VerifyNow® P2Y12 test not achieving < 45 PRU in the upper limit of the confidence interval for the treatment difference. These data suggest a potential PD interaction between ticagrelor and prasugrel that appears to be partially mitigated with administration of a LD of prasugrel. The optimal timing between the discontinuation of ticagrelor and administration of a LD of prasugrel remains to be determined.

No unexpected safety issues were observed in this study. The incidences of both hemorrhagic and non-hemorrhagic TEAEs were numerically lower in subjects receiving prasugrel compared to ticagrelor. Subjects receiving a prasugrel LD (prasugrel Group A) showed a slightly lower incidence of TEAEs and more consistent inhibition of platelet aggregation than those who did not receive a prasugrel LD (prasugrel Group B).

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