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Clinical Study Summary: Study H7T-MC-TAAL

A Comparison of CS-747 and Clopidogrel in Acute Coronary Syndrome Subjects who are to Undergo Percutaneous Coronary Intervention/TIMI 38

Date summary approved by Lilly: 25 March 2009

Title of Study: A Comparison of CS-747 and Clopidogrel in Acute Coronary Syndrome Subjects who are to Undergo Percutaneous Coronary Intervention/TIMI 38	
Investigator(s): This multicenter study included 717 principal investigators.	
Study Center(s): This study was conducted at 725 study centers (8 investigators had 2 study sites) in 30 countries.	
Length of Study: 33 months Date of first subject enrolled: 05 November 2004 Date of last subject completed: 22 July 2007	**Phase of Development:** 3

Objectives:

Primary Objective:

The primary objective of this study was to test the hypothesis that prasugrel co-administered with aspirin was superior to clopidogrel co-administered with aspirin in the treatment of subjects with acute coronary syndromes (ACS) who were to undergo percutaneous coronary intervention (PCI), as measured by a reduction in the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke at study end.

Secondary Objectives:

Efficacy Objectives:

The secondary efficacy objectives were to compare prasugrel with clopidogrel with respect to:

- The risk of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke through 90 days.
- The risk of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke through 30 days.
- The risk of cardiovascular death, nonfatal myocardial infarction, or urgent target vessel revascularization through 90 days.
- The risk of cardiovascular death, nonfatal myocardial infarction, or urgent target vessel revascularization through 30 days.
- The risk of all-cause death, nonfatal myocardial infarction, or nonfatal stroke at study end.
- The risk of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or rehospitalization for cardiac ischemic events at study end.
- The risk of definite or probable stent thrombosis per ARC (Academic Research Consortium) definition at study end.

Safety Objectives:

The safety objectives of this study were to compare prasugrel with clopidogrel with respect to:

- The risk of non-coronary artery bypass graft (Non-CABG) Thrombolysis in Myocardial Infarction Study Group (TIMI) Major bleeding in subjects receiving prasugrel or clopidogrel.
- The risk of Life-Threatening bleeding (a subset of Non-CABG-related TIMI Major bleeding) in subjects receiving prasugrel or clopidogrel.
- The risk of Non-CABG-related TIMI Minor bleeding in subjects receiving prasugrel or clopidogrel.
- The overall safety and tolerability of prasugrel administration based on clinical findings, laboratory values, and the occurrence of treatment-emergent adverse events.

Study Design: This was a Phase 3, multicenter, randomized, parallel-group, double-blind, double-dummy, active-controlled study. The study population included subjects with ACS (subjects with unstable angina and non-ST-segment elevation myocardial infarction [UA/NSTEMI] with TIMI risk score ≥3 or ST-segment elevation myocardial infarction [STEMI]) who were to undergo PCI. The study design incorporated a loading dose (to occur prior to the completion of the PCI procedure), followed by once-daily maintenance dosing (to start after the PCI procedure). The study continued until all of the following was attained:

1) A median treatment period of at least 12 months.
2) All subjects completed at least 6 months of follow-up.
3) At least 875 UA/NSTEMI subjects reached the primary endpoint.

Number of Subjects:
Planned: Approximately 13000 ACS subjects.
Randomized: 13619 (6820 prasugrel, 6799 clopidogrel).
Randomized and included in analysis: 13608 (6813 prasugrel, 6795 clopidogrel). (Note: 11 subjects who were randomized did not complete informed consent and were therefore excluded from the efficacy analyses.)
Completed: 12804 (6403 prasugrel, 6401 clopidogrel).

Main Criteria for Inclusion: All subjects, male or female, enrolled in this study were at least 18 years of age, presented with ACS, and were to undergo PCI.

Study Drug, Dose, and Mode of Administration: Prasugrel, supplied as 10-mg tablets, administered orally as a one-time 60-mg loading dose, followed by a once-daily 10-mg maintenance dose.

Comparator, Dose, and Mode of Administration: Clopidogrel, supplied as 75-mg tablets, administered orally as a one-time 300-mg loading dose, followed by a once-daily 75-mg maintenance dose.

Duration of Treatment: Six to 15 months (until the subject's study termination or 464 days from randomization, whichever was earlier). Median treatment duration of study was 14.5 months.

Variables:
Efficacy:
The primary efficacy measure was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke at study end.
Secondary efficacy measures included:

- The composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke through 30 days and 90 days post randomization.
- The composite of cardiovascular death, nonfatal myocardial infarction, or urgent target vessel revascularization through 30 days and 90 days post randomization.
- The composite of all-cause death, nonfatal myocardial infarction, or nonfatal stroke at study end.
- The composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or rehospitalization for cardiac ischemic events at study end.
- Definite or probable (Academic Research Consortium definition) stent thrombosis at study end.

Safety:
Safety measures included:

- Non-CABG-related TIMI Major, Minor, and Life-Threatening bleeding.
- Assessment of adverse events, including serious adverse events and treatment-emergent adverse events, laboratory tests, vital signs, and electrocardiograms.

Evaluation Methods:

Statistical:

Efficacy analyses were carried out using the intent-to-treat dataset, consisting of all randomized subjects. The safety analyses were carried out using the treated dataset that included all subjects who received at least 1 dose of study drug, either a loading dose or maintenance dose.

An independent Clinical Endpoint Committee (CEC) adjudicated, in a blinded fashion, all efficacy and safety endpoints that were reported by the investigator according to the procedures and the criteria described in the CEC Charter. These included CEC adjudicated deaths, cardiac ischemic events, cerebrovascular events, stent thrombosis, urgent target vessel revascularization (UTVR), rehospitalization for cardiac ischemic event, and bleeding endpoints according to TIMI classification (Major, Life-Threatening, Minor, Minimal, or no bleed). The CEC also adjudicated whether or not a bleeding event was CABG-related.

The primary efficacy endpoint analyses were conducted using the Gehan-Wilcoxon test from a time-to-first event analysis. All other key efficacy and safety analyses were conducted using the log-rank test from a time-to-first event analysis. In the time-to-first event analyses of the composite endpoints, a subject reaching any component of the composite endpoint was considered to have reached that endpoint. In analyzing non-composite endpoints, a subject reaching only the specific endpoint was considered to have reached the endpoint (whether or not it was the first endpoint to occur). Subjects experiencing multiple occurrences of an endpoint were censored at the time of first occurrence. That is, for the purpose of time to-first event analysis, a subject was not considered to be at-risk for the specific endpoint after the first occurrence. Given the importance of preventing recurrent events (some subjects experienced events such as myocardial infarction and bleeding more than one time), a comparison of the average number of events per 100 subjects was conducted using Poisson Regression models with the subject's duration of follow-up as an offset variable. With the exception of interaction effects, two-sided p-values $<.05$ were used in determining statistical significance in all analyses. Interaction effects were deemed to be statistically significant when two-sided p-values were $<.10$.

All efficacy and safety analyses were carried out for subjects with UA/NSTEMI, subjects with STEMI, and all subjects with ACS (UA/NSTEMI/STEMI). Analyses, including all subjects with ACS, included clinical presentation UA/NSTEMI versus STEMI as a stratification factor in the time-to-first event analyses. The study was intended to continue until an estimated 875 subjects with UA/NSTEMI reached one of the events described in the triple composite endpoint (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke), a median duration of therapy of at least 12 months was achieved, and a minimum follow-up of 6 months was achieved. Contingent upon establishing superiority of prasugrel in the composite efficacy endpoint in subjects with UA/NSTEMI, superiority of prasugrel was to be evaluated in all subjects with ACS with the view of establishing superiority in the STEMI population.

Summary:

- In this study 13619 subjects with ACS from 30 countries were randomly assigned to either clopidogrel (one-time 300-mg loading dose, followed by once-daily 75-mg maintenance dose; n=6799) or prasugrel (one-time 60-mg loading dose, followed by once-daily 10-mg maintenance dose; n=6820) and treated until the subject's study termination or 464 days from randomization, whichever was earlier. There were 7 subjects randomly assigned to prasugrel and 4 subjects randomly assigned to clopidogrel without data available for inclusion in the final analysis dataset due to an incomplete informed consent document. The remaining subjects, those with available data, make up the intent-to-treat (ITT) analysis data set. The treated population (those receiving at least one dose of study drug) included 6741 subjects receiving prasugrel and 6716 subjects receiving clopidogrel. Of the intent-to-treat population, 12804 subjects (94.1%; All ACS population) completed the study (6403 [94.0%] prasugrel group; 6401 [94.2%] clopidogrel group; p=.587).

- The majority of subjects were male and Caucasian. The mean age was 61 years and the mean weight was 83 kg. Most baseline demographics and medical history variables were not statistically significantly different between treatment groups, with the exception of statistically significant differences in age (p=.038) and diabetic treatment (p=.024) in the STEMI population; sex in the All ACS population (p=.021); the use of angiotensin-converting enzyme inhibitors (ACEI) in the UA/NSTEMI (p=.002) and the All ACS (p=.003) populations; the number of subjects classified as Killip III (p=.006), or with rales on physical examination (more randomized to prasugrel compared to clopidogrel; p=.005) in the STEMI population; and the number of subjects with a history of transient ischemic attack (TIA) within one year (more randomized to clopidogrel) in the UA/NSTEMI (p=.036) and All ACS (p=.007) populations.

- There were no statistically significant differences between treatment groups for characteristics of index procedure and estimates of treatment compliance, except for the maximum activated clotting time (ACT) measured in the periprocedural period (the mean value was statistically significantly higher in subjects randomized to prasugrel compared to clopidogrel in the UA/NSTEMI population; p=0.034). Nearly all subjects received PCI as the index revascularization procedure, with less than 0.5% of subjects undergoing CABG as the index revascularization procedure. Of those subjects receiving PCI, the majority (approximately 96%) received a stent in at least one intervened lesion, with approximately 36% of the UA/NSTEMI and approximately 54% of the STEMI subjects receiving a glycoprotein (GP) IIb/IIIa inhibitor in support of the PCI.

- The incidence of the primary composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was statistically significantly lower in subjects randomized to prasugrel compared to clopidogrel in all 3 populations (UA/NSTEMI: 9.30% versus 11.23%, hazard ratio=0.820, p=.002; All ACS: 9.44% versus 11.49%, hazard ratio=0.812, p<.001; and STEMI: 9.84% versus 12.24%, hazard ratio=0.793, p=.019). The Kaplan-Meier curves for the primary composite endpoint continued to diverge throughout the study period.

- In subjects randomized to prasugrel compared to clopidogrel, a statistically significant reduction in the incidence of each of the pre-specified secondary composite endpoints (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke through 30 and through 90 days; cardiovascular death, nonfatal myocardial infarction, or urgent target vessel revascularization through 30 and through 90 days; all cause death, nonfatal myocardial infarction or nonfatal stroke through study end; cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or rehospitalization for a cardiac ischemic event through study end; and definite or probable stent thrombosis through study end) contained within the hierarchical analysis was observed in all 3 populations (UA/NSTEMI, All ACS, and STEMI).

- In all 3 populations (UA/NSTEMI, All ACS, and STEMI), there was no statistically significant difference in the incidence of cardiovascular death, all cause death, nonfatal stroke, or all stroke in

subjects randomized to prasugrel compared to clopidogrel. There were statistically significant reductions in subjects randomized to prasugrel compared to clopidogrel in all 3 populations (UA/NSTEMI, STEMI, and All ACS) in the incidence of nonfatal myocardial infarction ($p<.001$, $p=0.016$, and $p<0.001$, respectively) and all myocardial infarction ($p<.001$, $p=.016$, and $p<.001$, respectively), and in urgent target vessel revascularization in subjects randomized to prasugrel compared to clopidogrel in the UA/NSTEMI ($p<.001$) and All ACS ($p<.001$) populations.

- The treatment benefit associated with prasugrel was preserved across the majority of the prespecified subgroups for the primary composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. There was no statistically significant evidence to suggest that the relative risk reduction with prasugrel compared to clopidogrel was influenced by sex. The relative risk reduction with prasugrel was greater in all 3 populations (UA/NSTEMI, STEMI, and All ACS) in subjects with diabetes ($p=.002$, $p=.080$, and $p<.001$, respectively) and those with age <75 years ($p<.001$, $p=.042$, and $p<.001$, respectively).

- There was no statistically significant difference in the treatment benefit observed in subjects receiving a GPIIb/IIIa inhibitor during the index procedure compared to subjects not receiving a GPIIb/IIIa inhibitor (in all 3 populations). In addition, the relative risk reduction with prasugrel compared to clopidogrel was preserved in subjects receiving drug-eluting stents, bare metal stents, or treated with angioplasty alone (the stent type did not statistically significantly influence the relative risk reduction seen with prasugrel compared to clopiogrel in all 3 populations). The relative risk reduction with prasugrel compared to clopidogrel was not affected by the use of a statin or the maximum daily dose of aspirin (in all 3 populations).

- A statistically significant interaction between treatment group and prior transient ischemic attack or stroke was observed for the primary composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke for the UA/NSTEMI ($p<.012$) and All ACS ($p<.015$) populations. For those subjects with a history of prior transient ischemic attack or stroke, the incidence of the primary composite endpoint was higher in subjects randomized to prasugrel compared to clopidogrel. This was primarily due to an increase in the incidence of stroke.

- The most common adverse drug reaction associated with prasugrel compared to clopidogrel was bleeding. Consistent with the increased incidence of bleeding complications, there was a higher incidence of premature study drug discontinuation for bleeding events in subjects treated with prasugrel. In the All ACS population, there was a statistically significantly higher incidence of Non-CABG-related TIMI Major bleeding in subjects treated with prasugrel including life-threatening and fatal events ($p=.029$). This higher incidence was observed in the UA/NSTEMI ($p=.022$), but not the STEMI population ($p=.645$). A risk factor for fatal bleeding appeared to be age $\geq$75 years. The most commonly reported locations of non-CABG-related TIMI Major bleeding were gastrointestinal, puncture site, intracranial hemorrhage (ICH), and retroperitoneal for both treatment groups. Although not statistically significant, the incidence of gastrointestinal and retroperitoneal bleeding was higher in subjects treated with prasugrel, while the incidence of ICH and puncture site bleeding were approximately the same between treatment groups.

- Non-CABG-related TIMI Major and non-CABG-related TIMI Minor bleeding events through 3 days after the loading dose were higher for subjects treated with prasugrel compared to clopidogrel although the absolute differences were not statistically significant for any of the populations. However, when combined, the incidence of non-CABG-related TIMI Major or Minor bleeding through 3 days after the first dose of study drug was statistically significantly higher in subjects treated with prasugrel compared to clopidogrel in the UA/NSTEMI population ($p=.041$).

- The most common provocation of bleeding through 3 days after the loading dose was related to instrumentation and the incidence was not statistically significantly different between treatment groups. The co-administration of a GPIIb/IIIa inhibitor with the loading dose increased the risk of bleeding in both prasugrel- and clopidogrel-treated subjects, particularly in the STEMI population.

The incidence of TIMI Major or Minor bleeding events was not statistically significantly different between treatment groups for subjects receiving GPIIb/IIIa inhibitors in both the UA/NSTEMI and STEMI populations.

- Through the entire at-risk period, there was a higher incidence of non-CABG-related TIMI Major or Minor, and TIMI Minimal bleeding events in subjects treated with prasugrel compared to clopidogrel. Risk factors for bleeding events in subjects treated with prasugrel appeared to be low body weight and age ≥75 years. These higher bleeding rates were consistent with higher exposure to the active metabolite of prasugrel in these subgroups.

- There were a greater number of Treatment-emergent Adverse Events (TEAEs) reported for subjects treated with prasugrel compared to clopidogrel in the System Organ Class: Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps). This difference was primarily due to more TEAEs related to colorectal cancer being reported for subjects treated with prasugrel compared to clopidogrel. At study end, malignancy related deaths were 21 (0.31%) in prasugrel and 17 (0.25%) in clopidogrel.