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Clinical Study Summary: Study H7T-MC-TABL

PRasugrel IN comparison to Clopidogrel for Inhibition of PLatelet Activation and AggrEgation (PRINCIPLE) – TIMI 44

Date summary approved by Lilly: 24 February 2009

Title of Study: PRasugrel IN comparison to Clopidogrel for Inhibition of PLatelet Activation and AggrEgation (PRINCIPLE) – TIMI 44.

Investigator(s): This multicenter study included 15 principal investigators.

Study Center(s): This study was conducted at 14 study centers in 4 countries.

Length of Study: 10 months Date first subject enrolled: 24 August 2006 Date last subject completed: 20 June 2007	**Phase of Development:** 2

Objectives:

Primary Objectives:

- To compare the inhibition of platelet aggregation (IPA) with 20 µM adenosine diphosphate (ADP) measured at 6 hours (± 30 minutes) after prasugrel 60-mg loading dose (LD) versus clopidogrel 600-mg LD in subjects in the "on-treatment population" (consists of all subjects who received the LD of study drug) who did not receive a glycoprotein (GP) IIb/IIIa antagonist.
- To compare the IPA with 20 µM ADP measured after 14 ± 2 days of prasugrel 10-mg daily maintenance dose (MD) versus the IPA after 14 ± 2 days of clopidogrel 150-mg daily MD in the "on-treatment population" who received PCI regardless of GPIIb/IIIa antagonist use (this included subjects receiving prasugrel and clopidogrel, in either order, during crossover).

Secondary objectives:

- To compare the IPA with 20 µM ADP measured at approximately 2 hours after prasugrel 60-mg LD versus clopidogrel 600-mg LD in subjects in the "on-treatment population" who did not receive a GPIIb/IIIa antagonist.
- To compare overall safety and tolerability of prasugrel 60-mg LD and 10-mg daily MD versus clopidogrel 600-mg LD and 150-mg daily MD after 14 ± 2 days in treated subjects who received PCI. Safety measures include, but are not limited to the following: non-coronary artery bypass graft (CABG)-related Thrombolysis in Myocardial Infarction (TIMI) Study Group major bleeding, non-CABG-related TIMI life-threatening bleeding, and non-CABG-related TIMI minor bleeding.
- To compare overall safety and tolerability of the following dosing regimens: prasugrel 60-mg LD and 10-mg daily MD for 14 ± 2 days with crossover to clopidogrel 150-mg daily MD for 14 ± 2 days versus clopidogrel 600-mg LD and 150-mg daily MD for 14 ± 2 days with crossover to prasugrel 10-mg daily MD for 14 ± 2 days in treated subjects who received PCI. Safety measures include, but are not limited to the following: non-CABG-related TIMI major bleeding, non-CABG-related TIMI life-threatening bleeding, and non-CABG-related TIMI minor bleeding.
- To compare prasugrel (60-mg LD, 10-mg daily MD) versus clopidogrel (600-mg LD, 150-mg daily MD) in the occurrence of major adverse cardiac events (MACE) after 14 ± 2 days in treated subjects who received PCI.
- To compare prasugrel versus clopidogrel on additional measures of platelet inhibition including, but not limited to thienopyridine hyporesponsiveness, vasodilator-stimulated phosphoprotein (VASP), biomarkers of inflammation, and biomarkers of platelet activation.
- To compare prasugrel (60-mg LD, 10-mg daily MD) versus clopidogrel (600-mg LD, 150-mg daily MD) in measures of myonecrosis (creatine kinase-myocardial bands [CK-MB] isoform, troponin) following PCI.

Study Design: This was a multicenter, randomized, parallel, double-blind, double-dummy, crossover, active comparator-controlled study in subjects undergoing cardiac catheterization with planned elective PCI with coronary stenting.

Number of Subjects:
Planned: Approximately 180 subjects
Randomized: 201 subjects total—
102 prasugrel/clopidogrel (55 had PCI and received MD medication)
99 clopidogrel/prasugrel (57 had PCI and received MD medication)
Completed: 198 subjects total—
101 prasugrel/clopidogrel subjects (54 had PCI and received MD medication)
97 clopidogrel/prasugrel subjects (55 had PCI and received MD medication)

Main Criteria for Inclusion: Subjects were eligible if they were undergoing cardiac catheterization with planned elective PCI (where the coronary anatomy was suitable) for an indication of chest pain and/or anginal equivalent, if the treating physician considered the symptoms to be related to coronary ischemia. Subjects could be of either sex and at least 18 years old.

Study Drug, Dose, and Mode of Administration: Prasugrel 60-mg LD, given orally as six 10-mg tablets and 8-placebo tablets, followed by 10-mg MD (given orally daily as one 10-mg tablet and 2-placebo tablets) for 14 ± 2 days. Subjects who were randomized to receive clopidogrel LD crossed over after 14 ± 2 days MD treatment to receive prasugrel 10-mg MD (given orally daily as one 10-mg tablet and 2-placebo tablets) for 14 ± 2 days.

Comparator, Dose, and Mode of Administration: Clopidogrel 600-mg LD, given orally as eight 75-mg tablets and 6-placebo tablets, followed by 150-mg MD (given orally daily as two 75-mg tablets and 1-placebo tablet) for 14 ± 2 days. Subjects randomized to receive prasugrel as the LD crossed over after 14 ± 2 days MD treatment to receive clopidogrel 150-mg MD (given orally daily as two 75-mg tablets and 1-placebo tablet).

Duration of Treatment: 29 ± 4 days of total treatment, comprising the first day of LD administration, followed by 14 ± 2 days MD treatment with either prasugrel or clopidogrel and then crossing over for an additional 14 ± 2 days MD treatment with the opposite treatment.

Variables:
Efficacy: The primary efficacy endpoints were:

- IPA with 20 μM ADP by light transmission aggregometry (LTA) at 6 hours (± 30 minutes) after LD of study drug.
- IPA with 20 μM ADP measured after 14 ± 2 days of prasugrel 10-mg daily MD and IPA after 14 ± 2 days of clopidogrel 150-mg daily MD, including subjects receiving prasugrel and clopidogrel, in either order, during crossover.

Safety: The primary safety measure was non-CABG-related TIMI significant bleeding, defined as the occurrence of TIMI major or minor bleeding in the treated population at the Day 15 visit.

Evaluation Methods:
Statistical:
The first primary efficacy endpoint was evaluated in subjects in the "on-treatment population" who did not receive a GPIIb/IIIa antagonist. These data were analyzed via analysis of covariance (ANCOVA) with factors for treatment group and pooled study site and a covariate for maximum platelet aggregation (MPA) value at baseline. The model allowed for differing variability of the response for prasugrel and clopidogrel.
The second primary efficacy endpoint was assessed in the "on-treatment population" who received PCI (this included subjects receiving prasugrel and clopidogrel, in either order, during crossover). These data were analyzed via a hierarchical ANCOVA model with factors for treatment, study phase, treatment order (sequence), subject within-treatment order as a random effect and pooled study site, and a covariate for MPA value at baseline. Again, the model allowed for differing variances in the 2 treatment groups. Analysis was conducted using PROC MIXED in SAS.
In order to preserve the Type I error rate, hypotheses were evaluated hierarchically with the comparison of mean IPA after 14 ± 2 days of daily MD contingent on previously showing a statistically significantly higher mean IPA for prasugrel at 6 hours after the LD.
For the primary safety endpoint (non-CABG-related TIMI significant bleeding up to Day 15 visit), no statistical test was applied due to the occurrence of a small number of events (2 out of 102 on prasugrel and 0 out of 99 on clopidogrel).
The incidence of other adverse events occurring in the 2 groups during Phase 1 (LD through first 14 ± 2 days MD in subjects that underwent PCI) of the study was compared using a logistic regression model containing a factor for study treatment, except in the case where the absolute number of events in each group was <10, in which case an equivalent exact logistic regression model was used. The difference between treatments in the incidence for data measured via a binary response occurring in the two 14 ± 2 days MD periods was assessed using an exact Prescott's test.

Summary:

Demographics / Disposition

The study population comprised subjects undergoing cardiac catheterization with elective PCI. A total of 201 subjects (191 Caucasian and 10 non-caucasian; 150 males and 51 females; mean age 63.9 years) participated in the study. Most demographic, cardiac history, and other baseline data variables were not statistically significant between treatment groups.

Of the 201 subjects randomized, 102 received prasugrel LD (55 underwent PCI) and 99 received clopidogrel (57 underwent PCI). Fifty-three subjects crossed over from prasugrel to clopidogrel and 55 crossed over from clopidogrel to prasugrel. Three subjects (1.5%) prematurely discontinued from the study (1 in the prasugrel/clopidogrel group while on prasugrel and 2 in the clopidogrel/prasugrel group while on clopidogrel). Of the 112 subjects who underwent PCI, 5 (4.5%) prematurely permanently discontinued study drug but completed the study visits. Two (3.6%) of the 55 prasugrel/clopidogrel subjects prematurely discontinued study drug, with one subject experiencing a non-bleed-related adverse event during the first (prasugrel) MD period, and one subject electing to stop taking study drug following crossover to clopidogrel. Three (5.3%) of the 57 clopidogrel/prasugrel subjects prematurely discontinued study drug. Two subjects did not receive a MD of study drug and 1 elected to stop taking study drug. An additional subject elected to stop taking study drug during the second (prasugrel) MD period.

Efficacy

Treatment with prasugrel (60-mg LD, 10-mg daily MD) compared to clopidogrel (600-mg LD, 150-mg daily MD) resulted in statistically significantly higher IPA (as assessed by all measures of platelet function) at all time points beginning 30 minutes following LD. This included the following primary efficacy measure conclusions:

- At 6-hours post-LD, prasugrel 60 mg demonstrated statistically significantly higher IPA with 20 μM adenosine diphosphate (ADP) compared to clopidogrel 600 mg (74.8% vs. 31.8%, $p<0.0001$).
- At 14 ± 2 days of daily MD treatment, prasugrel 10 mg demonstrated statistically significantly higher IPA with 20 μM ADP compared to clopidogrel 150 mg (55.5% vs. 40.6%, $p<0.0001$).

Secondary efficacy measure conclusions include:

- Prasugrel demonstrated statistically significantly higher IPA with 20 μM ADP or 5 μM ADP at all time points during LD and MD periods compared to clopidogrel.
- At 30 minutes post-LD, IPA with 20 μM ADP for prasugrel 60 mg was comparable to 6-hours and 18- to 24-hours post-LD for clopidogrel 600 mg.
- Prasugrel demonstrated statistically significantly lower MPA at 20 μM or 5 μM ADP at all time points during LD and MD compared to clopidogrel.
- Prasugrel demonstrated statistically significantly lower MPA to 20 μM ADP at 30-minutes post-prasugrel 60 mg LD compared to baseline values.
- Prasugrel demonstrated mean IPA with 20 μM ADP >50% at all time points ≥2-hours post-LD.
- Prasugrel demonstrated statistically significantly higher VerifyNow™ P2Y12 percent inhibition at all time points during LD and MD periods (when measured) compared to clopidogrel.
- Prasugrel demonstrated statistically significantly lower VASP PRI % at all time points during LD and MD periods compared to clopidogrel.
- Prasugrel demonstrated statistically significantly lower thienopyridine hyporesponsiveness during the LD period and at 14 ± 2 days of MD treatment compared to clopidogrel.
- In both treatment groups, MACE was low at the Day 15 visit.
- No deaths or strokes occurred during the study.

Safety

The primary safety measure was non-coronary artery bypass graft (CABG)-related Thrombolysis in Myocardial Infarction (TIMI) Study Group significant bleeding, defined as the occurrence of TIMI major or minor bleeding in the treated population at the Day 15 visit. Additional safety assessments included bleeding events at any time during the study, other adverse events (serious and nonserious), and clinical laboratory evaluations.

- Two subjects prematurely discontinued prasugrel; however, no subject discontinued for an event of bleeding and 1 subject discontinued for the adverse event of deep vein thrombosis (DVT). Three subjects prematurely discontinued clopidogrel; however, no subject discontinued for an adverse event.
- During the LD period, no non-CABG-related TIMI major and 2 non-CABG-related TIMI minor bleeding events were reported in prasugrel-treated subjects and no non-CABG-related TIMI major or minor bleeding events were reported in clopidogrel-treated subjects. There were no non-CABG-related TIMI major or minor bleeding events reported after the LD period. Furthermore, no life-threatening bleeding events were reported during the study.
- During the LD period, 3 non-CABG-related TIMI minimal bleeding events were reported in prasugrel-treated subjects and no non-CABG-related TIMI minimal bleeding events were reported in clopidogrel-treated subjects. Furthermore, no non-CABG-related TIMI minimal bleeding events were reported after the LD period.
- Of the 5 non-CABG-related TIMI minor and minimal bleeding events in prasugrel-treated subjects, 2 TIMI minor and 2 TIMI minimal bleeding events were access site related and 1 TIMI minimal bleeding event was a right coronary artery perforation.
- More overall bleeding events (non-CABG-related TIMI minor, TIMI minimal and nonserious events) were reported in subjects taking prasugrel compared to clopidogrel. Between LD to Day 15 visit, 19 (18.6%) of the 102 prasugrel-treated subjects experienced a bleeding event. Between LD to Day 15 visit, 14 (14.1%) of the 99 clopidogrel-treated subjects experienced a bleeding event. This difference was not statistically significant. The majority of bleeding events in both treatment groups occurred within the first 4 days following LD.
- No deaths or strokes were reported during the study.
- The overall incidence of adverse events and serious adverse events (SAEs) was not statistically significantly different between subjects taking prasugrel and subjects taking clopidogrel.
- Three SAEs were considered related to study drug by either the investigator or the Sponsor. One occurred in a subject taking prasugrel (access site-related) and 2 occurred in subjects taking clopidogrel (hypotension and MI).
- Three SAEs (all MIs) met the definition for the major clinical efficacy measure of MACE (LD through Day 15 visit). Two events occurred in 2 subjects taking prasugrel (both peri-procedural) and 1 occurred in a subject taking clopidogrel, the later event being a subacute stent thrombosis (Day 3). One subject developed an MI (reported as an SAE) following crossover from prasugrel to clopidogrel.
- No subject experienced thrombocytopenia or neutropenia during the study.

Overall, bleeding complications were more common in subjects taking prasugrel compared to clopidogrel. This difference was not statistically significant. Of the 5 non-CABG-related TIMI minor and minimal bleeding events in prasugrel-treated subjects, 2 TIMI minor and 2 TIMI minimal bleeding events were

access site related and 1 TIMI minimal bleeding event was a right coronary artery perforation. No non-CABG-related TIMI minor or TIMI minimal bleeding complications were observed in subjects taking clopidogrel. The overall incidence of adverse events and serious adverse events (SAEs) were not statistically significant between the 2 study drugs.

Study TABL was not powered to detect differences in the incidence of MACE between the 2 treatment groups. The occurrence of MACE was too limited to draw any meaningful conclusions.