# Summary ID# 9495

## Clinical Study Summary: Study H7T-MC-TABR

## A Pharmacokinetic and Pharmacodynamic Comparison of Prasugrel (LY640315) versus Clopidogrel in Aspirin-Treated Subjects with Stable Atherosclerosis

Date summary approved by Lilly: 24 February 2009

**Title of Study:** A Pharmacokinetic and Pharmacodynamic Comparison of Prasugrel (LY640315) versus Clopidogrel in Aspirin-Treated Subjects with Stable Atherosclerosis.

**Number of Investigators:** This 2-center study included 2 principal investigators.

**Study Centers:** This study was conducted at two centers in one country.

**Length of Study:** 31 March 2006 to 06 December 2006 | **Phase of Development:** 1b

**Objectives:**

Primary objective: To compare the pharmacodynamic effect of a prasugrel 60 mg loading dose (LD) with a clopidogrel 600 mg LD, as assessed by change in mean maximal platelet aggregation (MPA) to 20 µM adenosine diphosphate (ADP) at 2 hours after LD administration, in aspirin-treated subjects with stable atherosclerosis.

Secondary objectives:

- To assess the pharmacodynamic effects (using MPA and inhibition of platelet aggregation [IPA] to 20 and 5 µM ADP) of a prasugrel 60-mg LD plus aspirin compared with a clopidogrel 600-mg LD plus aspirin at 0.5, 1, 2, 4, and 24 hours after LD administration.
- To assess the pharmacodynamic effects (using MPA and IPA to 20 and 5 µM ADP) of a 10-mg daily maintenance dose (MD) of prasugrel plus aspirin compared with a 75-mg daily MD of clopidogrel plus aspirin at pre-dose trough concentrations (timepoints) on Day 14 ± 3 days and Day 29 ± 3 days.
- To compare the rate of pharmacodynamic nonresponders for the LD and daily MD of prasugrel versus clopidogrel, using objective thresholds from a previously developed Bayesian model for classification of nonresponders (referred to as pharmacodynamic poor responders in this clinical study summary).
- To characterize the pharmacokinetics of the active metabolites after a LD and during daily MD of prasugrel and clopidogrel.
- To further assess the safety and tolerability for the LD and daily MD of prasugrel versus clopidogrel when co-administered with aspirin in subjects with stable atherosclerosis.
- To assess and compare vasodilator-associated stimulated phosphoprotein (VASP) phosphorylation and other exploratory flow cytometric biomarkers of platelet activation for the LD and daily MD of prasugrel versus clopidogrel when co-administered with aspirin.
- To assess the levels of ADP-induced IPA using light transmission aggregometry (LTA) in platelet-rich plasma compared with a recently approved point-of-care device for monitoring IPA in whole blood (Accumetrics Verify Now™ $P2Y_{12}$).
- To assess whether the variable IPA observed with clopidogrel reflects receptor heterogeneity with respect to inhibition of the $P2Y_{12}$ ADP receptor by the active metabolite of clopidogrel.

**Study Design:** Randomized, double-blind, double-dummy, two-arm parallel group study in subjects with stable atherosclerosis.

**Number of Subjects Receiving Drug:**

A total of 110 subjects (101 males and 9 females) entered the study, with 55 subjects receiving at least one dose of prasugrel and 55 subjects receiving at least one dose of clopidogrel. One subject was withdrawn during the prasugrel dosing regimen, and three subjects were withdrawn during the clopidogrel dosing regimen.

**Diagnosis and Main Criteria for Inclusion:**

Male and female subjects with a history of stable coronary artery disease, aged 40 to 75 years, inclusive.

**Study Drug, Dose, and Mode of Administration:**

Prasugrel was administered orally as a single 60-mg LD and as daily 10-mg MDs, with matching placebo. Prasugrel was provided as 10 mg tablets. Matching placebo was provided as tablets. Aspirin was administered orally as a daily 75-mg tablet.

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| **Comparator, Dose, and Mode of Administration:**<br>Clopidogrel was administered orally as a single 600-mg LD and as daily 75-mg MDs, with matching placebo. Clopidogrel was provided as 75 mg tablets. Matching placebo was provided as tablets. Aspirin was administered orally as a daily 75-mg tablet. |
| **Duration of Treatment:**<br>Subjects received either prasugrel as a single 60-mg LD followed by 10 mg daily MDs for 28 ± 3 days or clopidogrel as a single 600-mg LD followed by 75 mg daily MDs for 28 ± 3 days. All subjects were on a background of daily 75 mg aspirin. |
| **Variables:**<br>Safety: Adverse events, clinical laboratory evaluations, and physical examinations.<br>Pharmacodynamic: Blood samples were collected for the assessment of platelet aggregation, VASP phosphorylation, other biomarkers of platelet activation, and spiking experiments with the active metabolite of clopidogrel.<br>Pharmacokinetic: Blood samples were collected for the determination of plasma concentrations of the prasugrel active metabolite (R-138727), prasugrel inactive metabolites (R-95913, R-106583, and R-119251), and the clopidogrel active metabolite (R-130964). |
| **Evaluation Methods:**<br>Analytical: Platelet aggregation was measured using LTA with 20 and 5 µM ADP, and 1 mM arachidonic acid as the agonists, and the Accumetrics VerifyNow™ $P2Y_{12}$ (VN-$P2Y_{12}$) and aspirin (VN-ASA) devices. VASP phosphorylation was measured using flow cytometry and reported as platelet reactivity index (PRI). Other biomarkers of platelet activation were measured using flow cytometry in unstimulated samples and in samples stimulated with 20 and 5 µM ADP. Plasma concentrations of prasugrel and clopidogrel metabolites were assayed using validated liquid chromatography with tandem mass spectrometric detection (LC/MS/MS) methods.<br>Pharmacokinetics: Plasma concentration versus time data for prasugrel and clopidogrel active metabolites following LD and daily MDs were graphically summarized.<br>Statistical: The primary endpoint was the mean change in MPA to 20 µM ADP at 2 hours post LD. Prasugrel and clopidogrel were compared at each timepoint from platelet aggregation data collected using LTA, the Accumetrics VerifyNow™ VN-$P2Y_{12}$ and VN-ASA devices, VASP phosphorylation, and additional biomarkers of platelet activation. Pharmacodynamic poor responders rates and aspirin resistance were assessed for prasugrel and clopidogrel. Variability between treatments was compared for LTA. Relationships between LTA, VN-$P2Y_{12}$ and VASP were investigated, and correlation coefficients calculated. For the active metabolite spiking experiment, blood samples had the active metabolite of clopidogrel added and evaluated by LTA using ADP to 20 and 5 µM ADP and PRI (VASP) at baseline (pre LD) and at Day 29 ± 3 days. The results from these samples were compared to samples not treated with active metabolite collected at the same timepoints. Subject characteristics and the number of adverse events were compared between treatments. |

## Summary:

Pharmacodynamics:

- Following a LD of 60-mg prasugrel, the change from baseline in MPA to 20 µM ADP using the LTA method was statistically significantly higher ($p<0.001$) compared to a LD of 600-mg clopidogrel at 2 hours postdose.
- Following a LD of 60-mg prasugrel, the MPA to 20 µM ADP was statistically significantly lower ($p<0.001$) and the IPA to 20 µM ADP was statistically significantly higher ($p<0.001$) compared to a LD of 600-mg clopidogrel at all timepoints. The nadir of the mean MPA occurred by 2 hours postdose for both the 60-mg LD of prasugrel and 600-mg LD of clopidogrel, with minimal change thereafter following the LDs.

 

- Following daily MDs of 10-mg prasugrel, the MPA to 20 μM ADP was statistically significantly ($p<0.001$) lower and the IPA to 20 μM ADP was statistically significantly ($p<0.001$) higher compared to daily MDs of 75-mg clopidogrel at predose trough timepoints on Days 14 and 29.
- Following a LD of prasugrel, all subjects, except one, were PD responders, based on achieving a change from baseline in MPA to 20 μM ADP of ≥15 percentage points at 2 hours post-LD or 4 or 24 hours post-LD. Following daily MDs of prasugrel, 51 of 54 subjects were PD responders.
- Following a LD of clopidogrel, approximately half of the subjects were PD poor responders. Approximately 1 out of 4 subjects (26%) were consistently PD poor responders across all LD timepoints following clopidogrel. Following MDs of clopidogrel, approximately half of subjects were poor responders and generally comprised the same subjects who were poor responders following the LD.
- The between-subject variability, based on the variance of IPA to 20 and 5 μM ADP, was lower for prasugrel compared to clopidogrel (post-LD and during MDs), and the difference in variance between the two treatments was statistically significant at 2 ($p=0.015$) and 24 hours ($p=0.025$) post-LD for IPA to 20 μM ADP, and at 2 ($p=0.004$), 4 ($p=0.003$) and 24 ($p=0.018$) hours post-LD for IPA to 5 μM ADP.
- Following a LD and MDs of prasugrel, the device reported % inhibition of PRU with the VN-$P2Y_{12}$ assay was statistically significantly higher ($p<0.001$) compared to a LD and MDs of clopidogrel at all timepoints.
- The IPA to 20 μM ADP using the LTA method generally correlated with the % inhibition of PRU using the VN-$P2Y_{12}$ assay.
- Following a 60-mg LD and 10-mg MDs prasugrel, the reduction in PRI with the VASP phosphorylation assay was statistically significantly greater ($p<0.001$) compared to a 600-mg LD and 75-mg MDs of clopidogrel at all timepoints.
- There was a moderate correlation between MPA to 20 μM ADP (LTA) and PRI (VASP phosphorylation).
- Following a LD and MDs of prasugrel, the reduction in P-selectin (CD62P), based on mean fluorescence intensity (MFI) stimulated with 20 μM ADP, was statistically significantly greater ($p<0.001$) compared to a LD and MDs of clopidogrel at all timepoints. Similar results were obtained for other cytometric biomarkers (CD154, annexin-V and PAC-1) stimulated with 20 and 5 μM ADP, with significantly greater reduction in biomarker levels for prasugrel compared to clopidogrel. There were no significant differences between dosing regimens at most timepoints for biomarkers from unstimulated samples, and for platelet-leukocyte aggregates.
- The MPA to 20 μM ADP and PRI following the addition of clopidogrel's active metabolite to blood samples taken pre-LD and Day 29 was reduced compared to the MPA and PRI measured in untreated blood samples taken after the 600-mg LD of clopidogrel for all subjects (PD responders and poor responders).

Pharmacokinetics:

- Following administration of a prasugrel LD, mean peak concentration of prasugrel's active metabolite occurred earlier (30 minutes) and was approximately 4.7-times higher than clopidogrel's active metabolite following clopidogrel LD administration. Similarly, active metabolite peak concentrations were consistently higher (approximately 2.7-times) after daily MDs of prasugrel than those following clopidogrel MDs.

Safety and Tolerability:

- A total of 110 Caucasian subjects (101 males and 9 females) aged 47 to 75 years, inclusive, participated in the study. The mean age (prasugrel 62 years, clopidogrel 64 years) and body weight (prasugrel 87.3 kg, clopidogrel 84.3 kg) were similar for the two dosing regimens.
- A total of 110 subjects were enrolled into the study, with 55 subjects receiving at least one dose of prasugrel and 55 subjects receiving at least one dose of clopidogrel. A total of 106 subjects completed the study according to the protocol with two subjects (one randomized to prasugrel and one randomized to clopidogrel) withdrawn due to the physician's decision and two subjects (both randomized to clopidogrel) withdrawn due to the subject's decision.

 

- No deaths occurred in this study.
- No SAEs occurred in subjects treated with prasugrel.
- No subjects discontinued due to AEs.
- The incidence of adverse events (all causalities) did not vary greatly between the prasugrel and clopidogrel dosing regimens, and most adverse events were mild or moderate in severity (as determined by the investigator). However, the incidence of adverse events (drug-related) was higher for the prasugrel dosing regimen (predominantly minor bleeding events) compared to clopidogrel.
- No clinically significant changes in clinical laboratory evaluations emerged in subjects taking prasugrel.

**Conclusions:**

- The mean change in MPA to 20 μM ADP at 2 hours after a 60-mg LD of prasugrel (decrease of 42 percentage points) was significantly greater than the decrease in MPA after a 600-mg LD of clopidogrel (decrease of 18 percentage points) in aspirin-treated subjects with stable atherosclerosis.
- Following a 60-mg LD of prasugrel, the MPA to 20 and 5 μM ADP was significantly lower and the IPA to 20 and 5 μM ADP was significantly higher than after a 600-mg LD of clopidogrel at all timepoints. The onset of platelet inhibition was more rapid after a LD of prasugrel compared to clopidogrel, although the nadir of the mean MPA to 20 μM ADP was achieved at 2 hours after prasugrel (31%) and clopidogrel (55%) with minimal change thereafter. The mean IPA to 20 μM ADP at 2 hours post LD was 57% for prasugrel and 25% for clopidogrel.
- Following daily 10-mg MDs of prasugrel, the MPA to 20 and 5 μM ADP was significantly lower and the IPA to 20 and 5 μM ADP was significantly higher compared to daily 75-mg MDs of clopidogrel at predose trough timepoints on Day 14 ± 3 and Day 29 ± 3. On both days, mean MPA to 20 μM ADP was approximately 42% for prasugrel and 54% for clopidogrel, and mean IPA to 20 μM ADP was approximately 42% for prasugrel and 26% for clopidogrel.
- Following administration of a prasugrel 60-mg LD, peak concentrations of prasugrel's active metabolite occurred earlier and were approximately 4.7-times higher than clopidogrel's active metabolite following clopidogrel 600-mg LD administration. Similarly, metabolite peak concentrations were consistently higher (approximately 2.7-times) after daily 10-mg MDs of prasugrel than those following clopidogrel 75-mg MDs. Thus, the higher levels of platelet inhibition demonstrated with a LD and MDs of prasugrel were associated with generation of higher levels of prasugrel's active metabolite.
- The rate of pharmacodynamic poor responders, based on the pre-specified Bayesian classification, was low following a 60-mg LD and daily 10-mg MDs of prasugrel, with ≤5% of subjects showing poor response after a LD or MDs (pre-defined as change in MPA from baseline of <15 percentage points to 20 μM ADP).
- The rate of pharmacodynamic poor responders was significantly higher following a 600-mg LD and daily 75-mg MDs of clopidogrel, with approximately 40 to 50% of subjects showing a poor response after the LD and/or MDs. A poor pharmacodynamic response to the clopidogrel LD was generally also associated with poor pharmacodynamic response during subsequent clopidogrel MD administration.
- The between-subject variability, based on the variance of IPA to 20 and 5 μM ADP, was lower for prasugrel compared to clopidogrel (post-LD and during MDs), and the difference in variance between the two treatments was statistically significant following the LD but not following MDs. The within-subject variability, based on subject ranges in IPA to 20 μM ADP, was similar for prasugrel and clopidogrel following the LD and during MDs.
- The adverse event profile of prasugrel did not vary greatly to the clopidogrel dosing regimen, although the incidence of minor bleeding-related events was higher for the prasugrel dosing regimen (mostly minor bleeding and/or bruising related to venipunctures).
- The % inhibition of PRU reported by the Accumetrics VerifyNow™ $P2Y_{12}$ (VN-$P2Y_{12}$) point-of-care device after a 60-mg LD of prasugrel (93% to 94%) was significantly higher than after a 600-mg LD of clopidogrel (44% to 49%) at 2 and 24 ± 4 hours postdose. The device-reported % inhibition of PRU following daily 10-mg MDs of prasugrel (73% to 76%) was significantly higher

 

compared to daily 75-mg MDs of clopidogrel (41% to 43%) at predose trough timepoints on Day 14 ± 3 and Day 29 ± 3.

- There was a correlation between the platelet aggregation results measured using the light transmission aggregometry (LTA) method versus the Accumetrics VerifyNow™ $P2Y_{12}$ assay (VN-$P2Y_{12}$). However, at higher levels of $P2Y_{12}$ inhibition, platelet aggregation measured by VN-$P2Y_{12}$ was maximally inhibited and could not distinguish differences in IPA indicated by the LTA method.
- Following a 60-mg LD and daily 10-mg MDs of prasugrel, the reductions in PRI (as measured by VASP) and other flow cytometric biomarkers of platelet activation (P selectin, CD 40 ligand, annexin-V binding and PAC-1 Mab binding, stimulated with 20 and 5 μM ADP) were significantly greater than following a 600-mg LD and daily 75-mg MDs of clopidogrel at most time points.
- The in vitro addition of clopidogrel's active metabolite into blood samples resulted in a further decrease in MPA for all subjects receiving clopidogrel, including subjects who were pharmacodynamic poor responders. This indicates that the variable inhibition of platelet aggegration observed with clopidogrel does not reflect receptor heterogeneity with respect to inhibition of the $P2Y_{12}$ ADP receptor by clopidogrel's active metabolite. Rather, it indicates that pharmacodynamic poor response to clopidogrel is related to pro-drug absorption and/or metabolic generation of clopidogrel's active metabolite.