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Clinical Study Summary: Study H7T-MC-TABN

A Randomized, Double-Blind, Cross-Over Study Comparing the Pharmacodynamic Response in Subjects with Acute Coronary Syndrome Receiving 14 Days 10-mg Maintenance Dose Prasugrel (LY640315) versus14 Days 150-mg Maintenance Dose Clopidogrel After Using a 900-mg Loading Dose of Clopidogrel to Reduce Ongoing Platelet Activation – The ACAPULCO Study

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Title of Study: A Randomized, Double-Blind, Cross-Over Study Comparing the Pharmacodynamic Response in Subjects with Acute Coronary Syndrome Receiving 14 Days 10-mg Maintenance Dose Prasugrel (LY640315) versus 14 Days 150-mg Maintenance Dose Clopidogrel After Using a 900-mg Loading Dose of Clopidogrel to Reduce Ongoing Platelet Activation – The ACAPULCO Study

Investigator(s): This multicentre study included 1 principal investigator.

Study Center(s): This study was conducted at 4 centers in 1 country.

Length of Study:
Date first subject randomized: 28 March 2007.
Date last subject completed: 31 October 2007.

Phase of Development: 2

Objectives:

The primary objective of this study was to establish superiority of a prasugrel 10-mg daily maintenance dose (MD) compared with a clopidogrel 150-mg daily MD as assessed by mean maximum platelet aggregation (MPA) to 20 μM adenosine diphosphate (ADP) at the end of two 14-day treatment periods in subjects with acute coronary syndrome (ACS).

The secondary objectives were to compare, at the end of two 14-day treatment periods, a prasugrel 10-mg daily MD with a clopidogrel 150-mg daily MD in subjects with ACS as assessed by:

- Mean MPA to 5 μM ADP.
- Mean Residual Platelet Activity (RPA) to 5 μM and 20 μM ADP.
- Phosphorylation status of vasodilator-associated stimulated phosphoprotein (VASP) expressed as the mean platelet reactivity index (PRI %).
- P2Y12 reaction units (PRU) and % inhibition using the VerifyNowTM P2Y12 (VN-P2Y12) device.
- Percentage of pharmacodynamic "poor responder" subjects (by various responder criteria).
- Mean inhibition of platelet aggregation (IPA) and Inhibition of residual platelet aggregation (IRPA) to 5 and 20 μM ADP.
- The safety and tolerability of the daily MD of prasugrel versus clopidogrel, including but not limited to:
  - Bleeding events classified according to Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria.
  - Safety of 14 days of a prasugrel 10-mg daily MD initiated after a clopidogrel 900-mg loading dose (LD).

Additional secondary objectives included

- To assess correlations between platelet function measures (MPA to 20 μM diphosphate ADP, PRU using the VN-P2Y12, and PRI %).
- To estimate the effect on platelet aggregation of the 900-mg clopidogrel load and of changing from a clopidogrel 900-mg LD to the initial 14 days of MD (prasugrel 10-mg or clopidogrel 150-mg).

Study Design: This was a randomized cross-over study in which subjects received a LD of clopidogrel and aspirin in an open-label phase, followed by a double-blind, randomized, daily MD, cross-over phase in

which subjects were randomly assigned to the sequence prasugrel 10-mg followed by clopidogrel 150-mg or to the sequence clopidogrel 150-mg followed by prasugrel 10-mg.

Number of Subjects:
Planned: 70 subjects so at least 60 subjects completed the study.
Randomized: 56 subjects randomized.
Completed: 41 subjects completed the study per protocol. Enrollment was suspended on 22 Oct 2007 following results of the TRITON-TIMI 38 study, which suggested excess bleeding risk in populations not excluded from this study (age ≥75 years, body weight <60 kg and history of TIA/stroke). The lower number of subjects who completed the study per protocol than were randomized is largely explained by the earlier than planned final study visits due to the suspension. The study was not resumed because it was determined that sufficient data was available for analysis. This was based on a revised sample size calculation from results of a similar crossover study (PRINCIPLE TIMI 44) that became available near the time that this study was suspended.

Main Criteria for Inclusion:
Patients, aged 18 to 84 years inclusive, with ACS who have planned treatment, as part of standard of care, with a 900-mg LD of commercially available clopidogrel.

Test Product, Dose, and Mode of Administration:
Open-label phase:
A 900-mg clopidogrel LD was administered orally as either a single or cumulative (for subjects who received a clopidogrel LD less than 900-mg as part of their emergency care) dose.
Aspirin was similarly administered as a single or cumulative LD of 250 to 500-mg, either orally or intravenously prior to randomization.
Randomized, daily MD, cross-over phase:
Prasugrel was administered orally as a daily 10-mg MD.
Aspirin was administered orally as a daily dose of ≤100-mg/day.

Reference Therapy, Dose, and Mode of Administration:
Clopidogrel was administered orally as a daily 150-mg MD.

Duration of Treatment:
In the open-label phase (Visits 1 and 2: Day 0 up to Day 2), a LD of up to 900-mg clopidogrel and a dose of 250 to 500-mg aspirin were administered. In the cross-over phase (beginning at Visit 2) subjects were randomly assigned to either prasugrel 10-mg daily MD or clopidogrel 150-mg daily MD for 14±2 days. At Visit 3 (Day 15±2), the subject was switched to the alternative MD treatment for a further 14±2 days.
All subjects received oral daily aspirin ≤100-mg during the cross-over phase.

Variables:
Safety: Adverse events, vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory evaluations, and physical examinations.
Pharmacodynamic: Blood samples for the assessment of platelet aggregation and VASP phosphorylation. A centralized laboratory performed all platelet function assessments.

Evaluation Methods:
Analytical: Platelet aggregation was measured using LTA with 5 and 20 μM ADP, and 0.2 mg/mL arachidonic acid as the agonists, and the VerifyNow™ P2Y12 (VN-P2Y12) and aspirin (VN-ASA) assays. VASP phosphorylation was measured using flow cytometry and reported as PRI %.
Statistical: The primary end point was the mean MPA to 20 μM ADP after 14±2 days of maintenance dosing for the combined MD periods, using an analysis of covariance (ANCOVA) crossover model, with treatment, study site, and study period as fixed effects and subject as a random effect. The same model was also applied for other outcomes based on LTA, the VN-P2Y12, and VASP phosphorylation.
Pharmacodynamic responder rates, based on LTA and VASP criteria, were assessed for prasugrel and clopidogrel.
Comparisons of the variability between treatments were assessed by comparing standard deviations using an F-test.
Results obtained prior to administration of the 900-mg clopidogrel LD and at 6 to 18 hours post-clopidogrel LD were compared for MPA, RPA, IPA, and IRPA to 5 and 20 μM ADP, VASP, and the VN-P2Y12 and VN-ASA devices.
Relationships between LTA, VN-P2Y12, and PRI % were assessed using scatter plots and correlation coefficients.
A subgroup analysis for the primary efficacy endpoint was performed for subjects on chronic clopidogrel treatment when enrolled and reloaded with 900-mg clopidogrel versus subjects without prior clopidogrel treatment.
Subject characteristics and the number of adverse events were compared between treatments.

Summary

Demographics and Disposition:

Fifty-six subjects (47 males and 9 females) were randomly assigned to blinded treatment with either prasugrel 10-mg or clopidogrel 150-mg daily MD with daily aspirin (29 prasugrel 10-mg and 27 clopidogrel 150-mg). A total of 54 (46 males and 8 females) randomized subjects received MD treatment, as 2 randomized subjects were withdrawn after randomization and prior to the first MD administration due to self-withdrawal and physician's decision, respectively. Of the 54 subjects who were randomized and received at least one MD of clopidogrel or prasugrel, 41 subjects (22 prasugrel 10-mg/clopidogrel 150-mg and 19 clopidogrel 150-mg/prasugrel 10-mg) completed the study according to the protocol.

The mean age and body weight were similar for the subjects randomized to each of the two MD dosing sequences. Medical history was typical for the prevalence of major coronary artery disease risk factors in an ACS population, with the exception of a low incidence of hyperlipidemia. There were no statistically significant differences between study treatment sequences in medical history.

Pharmacodynamics:

The primary efficacy measure conclusion is:

- For the combined MD periods, 10-mg prasugrel demonstrated statistically significantly lower MPA with 20 μM ADP compared to 150-mg clopidogrel after 14 ± 2 days of daily MD treatment (26.2% for prasugrel versus 39.1% for clopidogrel; $p<.001$).

Further conclusions:

- For each MD period, prasugrel 10-mg demonstrated statistically significantly lower MPA with 20 μM ADP than clopidogrel 150-mg.

- Results similar to the primary endpoint analysis were seen for the combined MD periods for MPA with 5 μM ADP, RPA with 20 and 5 μM ADP, IPA with 5 and 20 μM ADP and IRPA to 20 μM ADP.
- The majority of subjects had higher MPA following the crossover from prasugrel to clopidogrel (19/23; 82.6%) and lower MPA following the crossover from clopidogrel to prasugrel (19/22; 86.4%), demonstrating a higher level of platelet inhibition with prasugrel than with clopidogrel.
- Prasugrel demonstrated a statistically significantly lower VASP PRI % than clopidogrel for the combined and individual MD periods.
- Prasugrel demonstrated a statistically significantly higher device-reported % inhibition and lower PRU using VerifyNow™ P2Y12 than clopidogrel for the combined and individual MD periods.
- Using various responder criteria, there was a significantly higher rate of poor response to clopidogrel (21.3 to 34.0%) than to prasugrel (2.0 % to 6.1%) ($p<.001$). In subjects with poor response to the clopidogrel 900-mg LD, 44-57% responded poorly to a clopidogrel 150-mg MD, while 86-90% responded to prasugrel 10-mg MD.
- There were high correlations between LTA and other platelet function measures utilized in this study: MPA to 20 μM ADP using the LTA method and PRU using the VN-P2Y12 assay (correlation coefficient of 0.8); MPA to 20 μM ADP using the LTA method and VASP PRI % (correlation coefficient of 0.7); and VASP PRI % and PRU using the VN-P2Y12 assay (correlation coefficient of 0.8).
- After MD treatment, prasugrel demonstrated statistically significantly lower MPA with 20 μM ADP compared to 6-18 hours after a clopidogrel 900-mg LD ($p=.011$), while clopidogrel 150-mg did not ($p=.847$).

Safety and Tolerability:

- There were no non-CABG related TIMI major or GUSTO severe/life-threatening bleeding events reported during the study and there were no discontinuations in the study related to an adverse event.
- There was no statistically significant difference between the number of subjects experiencing bleeding events, or classification of events by TIMI or GUSTO criteria by study treatment for the combined MD periods.
- There were few bleeding events reported during the study with the majority of the events occurring within 3 days of the clopidogrel LD (900 mg):
    - Eight subjects (14.3%) experienced a single bleeding event following the administration of the clopidogrel LD (900 mg) and prior to the first MD.
    - During the first MD period, two subjects (6.9%) randomized to prasugrel experienced 3 bleeding events and 2 subjects (7.4%) randomized to clopidogrel experienced 2 bleeding events. In 3 of these 4 subjects (one on prasugrel and 2 on clopidogrel), events occurred within the first 3 days of study drug treatment.

  - During the second MD period, one subject experienced a single bleeding event after crossing over from clopidogrel to prasugrel, while there no subjects experiencing bleeding events when crossing over from prasugrel to clopidogrel.

- Twenty-one (38%) of the 56 randomized subjects experienced a total of 39 adverse events following administration of the clopidogrel 900-mg LD.
- There was one death on the study. This subject's metastatic cancer recorded following the clopidogrel LD, and septic shock and fatal cardiac arrest, during a prasugrel MD period, were considered by the investigator to have no relationship to study drug.
- There was a total of 9 SAEs in 5 subjects (3 SAEs each in 2 subjects and 1 SAE each in 3 other subjects). Seven SAEs occurred during prasugrel treatment, while 2 SAEs occurred during clopidogrel treatment.

Conclusions:

For the combined MD periods, prasugrel 10-mg demonstrated statistically significantly lower MPA with 20 μM ADP compared to clopidogrel 150-mg after 14 ± 2 days of daily MD treatment (26.2% for prasugrel versus 39.1% for clopidogrel; $p<0.001$). Prasugrel also demonstrated higher platelet inhibition compared to clopidogrel on various secondary measures, including a significantly greater proportion of subjects who were poor responders to clopidogrel than to prasugrel using various pharmacodynamic responder criteria, and a statistically significantly lower MPA with 20 μM ADP compared to a 900-mg clopidogrel LD.

There were no TIMI Major or GUSTO Severe/Life-Threatening bleeding events nor was there any statistically significant difference in bleeding events, regardless of classification method, between study treatments. The majority of bleeding events was at vascular access sites related to cardiac catheterization procedures and occurred prior to study drug administration. The overall incidence of adverse events was not statistically different between the two study drugs.