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Sponsor / Company: sanofi-aventis **Drug substance(s):** Clopidogrel	**Study Identifier:** NCT00821834 **Study code:** EFC10675

Title of the study: A randomized, double blind, parallel group study to investigate the safety of 12 weeks of clopidogrel 75 mg once daily with a 300 mg loading dose versus ticlopidine 100 mg twice daily in patients with stable angina or old (healed) myocardial infarction to which percutaneous coronary intervention is being planned - with extended treatment of clopidogrel 75 mg once daily for 40 weeks in a patients' subset

Study center(s): Ninety-five (95) active centers in Japan.

Study period:

Date first patient enrolled: 03 December 2008

Date last patient completed: 21 August 2010

Phase of development: 3

Objectives:

PRIMARY

- To evaluate whether 12 weeks of clopidogrel (a 300 mg loading dose followed by 75 mg once daily [o.d.]) is superior to ticlopidine (100 mg twice daily [b.i.d.]) in terms of lower risk of the safety events of interest in patients with stable angina (SA) or old myocardial infarction (OMI) to which percutaneous coronary intervention (PCI) is being planned.

SECONDARY

- To compare the incidence of adverse events, adverse drug reactions and bleeding events in patients treated with clopidogrel (a 300 mg loading dose followed by 75 mg o.d. for 12 weeks) versus ticlopidine (100 mg b.i.d. for 12 weeks).
- To compare the incidence of major adverse cardiac events (MACE) and major adverse cardiac and cerebrovascular events (MACCE) in patients treated with clopidogrel (a 300 mg loading dose followed by 75 mg o.d. for 12 weeks) versus ticlopidine (100 mg b.i.d. for 12 weeks).
- To evaluate the long-term safety (adverse drug reactions, adverse events, safety events of interest and bleeding events) of clopidogrel (75 mg o.d.) for a total of 52 weeks.
- To evaluate MACE and MACCE of clopidogrel (75 mg o.d.) for a total of 52 weeks.

Methodology: Multicenter, randomized, double blind, double dummy, parallel group study including a double-blind treatment period, followed by an open label treatment period for a subset of patients.

Number of patients:

Planned:

- 1st period (double-blind treatment): approximately 1000 (clopidogrel group: 500, ticlopidine group: 500)
- 2nd period (open label clopidogrel treatment): approximately 300.

Randomized: 1003 Treated: 999

Evaluated:

Safety and Efficacy:

931 (modified intent-to-treat [mITT] population, clopidogrel group: 466, ticlopidine group: 465)
999 (all treated population, clopidogrel group: 499, ticlopidine group: 500)
301 (long-term-evaluation [LTE] population, clopidogrel group: 158, ticlopidine group: 143)

Diagnosis and criteria for inclusion:

SA/OMI patients who met all of the following criteria:

1. Myocardial ischemic finding was proven by one or more of the followings within 2 months before randomization:

- Stress electrocardiogram (ECG) test
- Stress myocardial perfusion scintigraphy
- Stress echocardiogram
- Stress Magnetic Resonance Imaging (MRI)
- Event ECG test
- Holter ECG test

2. Either≥75% stenosis documented by coronary angiography (CAG) or severe stenosis confirmed by multi-slice computerized tomography (MSCT) angiography within 2 months before randomization.

3. PCI is being planned

Investigational product: Clopidogrel 75 mg tablets (or matching placebo)

Dose: a 300 mg loading dose followed by 75 mg once daily [o.d.]

Administration: Oral administration after breakfast as a rule

Background therapy: Aspirin 81-100 mg once daily should be administered during IP administration.

Duration of treatment:

- 1st period (double-blind treatment): 12 weeks
- 2nd period (open label clopidogrel treatment): 40 weeks (75 mg o.d until Week 52)

Duration of observation:

Screening period: maximum 2 weeks

Treatment period: 12 weeks (double-blind treatment - all patients) + 40 weeks (open label clopidogrel treatment - 300 patients)

Reference therapy: Ticlopidine 100 mg tablets (or matching placebo)

Dose: 100 mg twice daily [b.i.d]

Administration: Oral administration after breakfast and dinner as a rule

Background therapy: Aspirin 81-100 mg once daily should be administered during IP administration.

Criteria for evaluation:

Safety:

The primary endpoint was the elapsed time in days from the randomization to the first occurrence of the safety events of interest during the 1st 12-week treatment period (double-blind treatment period).

Safety events of interest (including any of the following):

- Clinically significant bleeding
- Leukopenia, neutropenia or thrombocytopenia occurring as adverse drug reaction
- Elevated liver function values (ALT, γ-GTP, ALP or total bilirubin elevation) occurring as adverse drug reaction
- Permanent investigational product discontinuation due to skin disorders, gastrointestinal disorders, bleeding, hepatic disorders, or significant decreases in such tests as leukocytes, neutrophils or platelets occurring as adverse drug reaction

Criteria for evaluation (cont'd):

The secondary safety endpoints were:

- The elapsed times in days from the randomization to the first occurrence of each following event during the 1st 12-week treatment period:

  Adverse events

  Adverse drug reactions

  Bleeding events of CURE definition (Life-threatening, Major, Minor bleeding)

  Bleeding events of GUSTO definition (Severe/Life-threatening, Moderate, Minor bleeding)

  Bleeding events of TIMI definition (Major, Minor, Minimal bleeding)

- The elapsed times in days from the randomization to the first occurrence of each following event during the 52-week treatment period (12-week double-blind treatment period + 40-week open label treatment period):

  Safety events of interest

  Adverse drug reactions

  Adverse events

  Bleeding events of CURE definition

  Bleeding events of GUSTO definition

  Bleeding events of TIMI definition

Efficacy:

The main efficay endpoints were:

- The elapsed time in days from the randomization to the first occurrence of major adverse cardiac events (MACE) during the 1st 12-week treatment period.

  MACE (the composite of the following):

  - All-cause mortality
  - Acute myocardial infarction
  - Revascularization (excluding revascularization related to the planned PCI)
  - Stent thrombosis

- The elapsed time in days from the randomization to the first occurrence of the MACE during the 52-week treatment period.

The other efficacy endpoints were:

- The elapsed time in days from the randomization to the first occurrence of major adverse cardiac and cerebrovascular events (MACCE) during the 1st 12-week treatment period.

  MACCE (the composite of the following):

  - All-cause mortality
  - Acute myocardial infarction
  - Revascularization (excluding revascularization related to the planned PCI)
  - Stent thrombosis
  - Ischemic stroke

- The elapsed time in days from the randomization to the first occurrence of the MACCE during the 52-week treatment period.

Statistical methods:

Analysis population

Modified ITT (mITT) population: randomized population who had the index PCI analyzed according to the randomized treatment.

All treated population: randomized population who did actually receive at least one dose or partial of a dose of IP analyzed according to the treatment actually received.

Long-term-evaluation (LTE) population: randomized population who completed the 1st period of study and enrolled the 2nd period had the index PCI analyzed according to the randomized treatment.

Analysis of primary endpoint

For the safety events of interest, comparison between clopidogrel and ticlopidine groups was performed using log-rank test stratified by aspirin pre-treatment with two-sided 5% significance level on mITT population. Cumulative incidence functions with 95% confidence interval were estimated using Kaplan-Meier technique and Greenwood's formula. Hazard ratio with 95% confidence interval was estimated using Cox model with treatment group and aspirin pre-treatment as factors.

Analysis of secondary endpoints

Secondary endpoints for 1st period were analyzed in the same manner as analyses of primary endpoint.

For endpoints for a long-term evaluation, cumulative incidence functions until Week 52 with 95% confidence intervals for each treatment group were estimated with Kaplan-Meier technique and Greenwood's formula on LTE population.

Analyses of general safety data

All summary tables were provided for the 1st period on the all treated population and all periods on the LTE population, unless otherwise specified.

All adverse events were coded using the version 13.0 of MedDRA. Treatment-emergent adverse events (TEAEs) were defined as adverse events s that developed or worsened under treatment (from the first study drug intake to 14 days after the last study drug intake). The frequency distributions of patients with TEAEs, treatment emergent serious adverse events (SAEs) and TEAEs leading to treatment discontinuation were provided by treatment.

For central laboratory parameters and vital signs, raw values and their changes from baseline across visits were summarized by treatment group. The numbers and percentages of patients presenting at least one post-baseline PCSA and post-baseline out-of-normal range value on the on-treatment period were summarized by parameter in each treatment group.

Summary:

Safety results:

In the primary analysis, stratified log-rank test to compare treatments in terms of the safety events of interest (clinically significant bleeding, blood disorder, elevated liver function values and permanent IP discontinuation) was statistically significant ($p<0.0001$). The incidences of the first safety event of interest at Week 12 for the clopidogrel and ticlopidine groups were 8.9% and 30.9% respectively. The hazard ratio in the clopidogrel group was 0.259 (95%CI, 0.187 to 0.359). Mainly elevated liver function values and permanent IP discontinuation contributed to the difference.

Summary (cont'd):

Analysis of time to first safety event of interest for the 1st period - mITT population

	Clopidogrel (N=466)	Ticlopidine (N=465)
Number of events, n (%)	47 (10.1%)	159 (34.2%)
Cumulative incidence (95% CI)[a] at Week 4	0.041 (0.023 to 0.059)	0.100 (0.072 to 0.127)
Cumulative incidence (95% CI)[a] at Week 8	0.078 (0.053 to 0.102)	0.276 (0.235 to 0.317)
Cumulative incidence (95% CI)[a] at Week 12	0.089 (0.063 to 0.115)	0.309 (0.267 to 0.351)
Stratified Log-rank test p-value[b]	<0.0001	-
Adjusted Hazard ratio (95% CI)[c]	0.259 (0.187 to 0.359)	-
Un-stratified Log-rank test p-value[d]	<0.0001	-
Un-adjusted Hazard ratio (95% CI)[e]	0.259 (0.187 to 0.359)	-

[a] Kaplan-Meier technique with Greenwood's variance estimation, [b] Log-rank test for treatment group with aspirin pre-treatment as strata, [c] Estimated using Cox proportional hazard model with treatment group as the factor, stratified by aspirin pre-treatment, [d] Unstratified Log-rank test for treatment group [e] Estimated using Cox proportional hazard model with treatment group as the factor

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Composition of first safety event of interest for the 1st period - mITT population

	Clopidogrel (N=466)	Ticlopidine (N=465)
Any safety event of interest	47 (10.1%)	159 (34.2%)
Clinically significant bleeding	4 (0.9%)	3 (0.6%)
Blood disorder	7 (1.5%)	15 (3.2%)
Elevated liver function value	27 (5.8%)	136 (29.2%)
Permanent IP discontinuation	16 (3.4%)	56 (12.0%)

Note: A patient can be counted in several categories when multiple events occurred at the same day as first event.

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Summary (cont'd):

Regarding bleeding events (CURE definition) in mITT population, no statistical significant difference was observed between the clopidogrel and ticlopidine group (p=0.5292, stratified log-rank test). The incidences of the events at Week 12 for clopidogrel and ticlopidine groups were 1.3% and 0.9% respectively. In addition, GUSTO bleeding and TIMI bleeding showed consistent results with those of CURE bleeding.

Regarding adverse events in mITT population, no statistical significant difference was observed between the clopidogrel and ticlopidine group (p=0.0688, stratified log-rank test). The incidences of the adverse events at Week 12 for clopidogrel and ticlopidine groups were 68.8% and 76.1% respectively.

Regarding adverse drug reactions in mITT population, statistical significant difference was observed between the clopidogrel and ticlopidine group (p<0.0001, stratified log-rank test). The incidences of the events at Week 12 for clopidogrel and ticlopidine groups were 19.2% and 40.8% respectively.

For the long-term safety (safety events of interest, adverse drug reactions, adverse events, and bleeding events) of the clopidogrel 52-week treatment, there were no new findings. In addition no specific finding was observed in the 2nd period in the patients who stwiched from ticlopidine to clopidogrel (ticlopidine 12-week treatment followed by clopidogrel 40-week treatment).

Regarding overall safety, TEAEs leading to permanent treatment discontinuation for the 1st period were observed more in the ticlopidine group than the clopidogrel group (5.0% [25/499] in the clopidogrel group, 15.0% [75/500] in the ticlopidine group), and the main reason for this difference were the liver function abnormalities. For other safety (TEAE, treatment-emergent SAE, laboratory values, and vital signs), there were no significant findings.

Efficacy results:

Regarding cumulative incidence of MACE for the 1st period in mITT population, no statistical significant difference was observed between the clopidogrel group and the ticlopidine group (p=0.7899, stratified log-rank test). The incidences of the event at Week 12 for the clopidogrel and ticlopidine groups were 9.0% and 9.7% respectively. There were 36 myocardial infarctions in the clopidogrel group and 43 myocardial infarctions in the ticlopidine group, among them only one Q-wave myocardial infarction was reported in each group. The most frequently observed component of MACE in the 2nd period was revascularization.

Regarding cumulative incidence of MACCE for the 1st period in mITT population, no statistical significant difference was observed between the clopidogrel group and the ticlopidine group (p=0.5611, stratified log-rank test). The incidences of the event at Week 12 for the clopidogrel and ticlopidine groups were 9.0% and 10.4% respectively.

Regarding clopidogrel 52-week treatment, incidences of MACE and MACCE at Week 52 in LTE population were 16.7% and 17.4% respectively. On the other hand, those incidences of ticlopidine 12-week treatment followed by clopidogrel 40-week treatment were 23.5% and 24.2% respectively. In both treatment groups, index PCI-related acute myocardial infarctions were frequently observed within initial 2 weeks after randomization though revascularizations related to in-stent coronary artery restenosis were mainly observed from Week 28 to Week 44.

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