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Sponsor/Company : Sanofi **Drug substance** : Clopidogrel (SR25990)	**Study Identifiers** : NCT00862420 **Study Code** : SFY10810

Title of the study:

A randomized, double blind, parallel group study to investigate the safety of 12 weeks of clopidogrel 75 mg/day versus ticlopidine 200 mg/day in patients with peripheral arterial disease - with extended treatment of clopidogrel 75 mg/day for 40 weeks

Study center(s): 52 In Japan

Study period:

Date first patient enrolled: 06 February 2009

Date last patient completed: 12 May 2011

Phase of development: Phase 3

Objectives:

Primary

To evaluate whether 12 weeks of clopidogrel (75 mg once daily [o.d.]) is superior to ticlopidine (200 mg o.d.) in terms of lower risk of the safety events of interest in patients with peripheral arterial disease

Secondary

To compare the risk of bleeding adverse events, serious adverse events and overall safety of clopidogrel (75 mg o.d. for 12 weeks) with ticlopidine (200 mg o.d. for 12 weeks)

To compare the risk of vascular events of clopidogrel (75 mg o.d. for 12 weeks) with ticlopidine (200 mg o.d. for 12 weeks)

To document the long-term safety (bleeding adverse events, serious adverse events, safety events of interest and overall safety) of clopidogrel (75 mg o.d.) for a total of 52 weeks

To document the vascular events of clopidogrel (75 mg o.d.) for a total of 52 weeks

Methodology:

Randomized, double-blind, double dummy, parallel group study for the 1st period (12 weeks), and multicenter, open study for the 40-week extension period. All patients who finished the double-blind treatment for 12 weeks (1st period) were transferred to the long-term open treatment (2nd period) until Week 52 regardless of the treatment group in the 1st period.

Number of patients: Planned: 400

Randomized: 431

Treated: 431

Evaluated:

Efficacy: 431

Safety: 431

Diagnosis and criteria for inclusion:

Patient with documented symptomatic peripheral artery disease (PAD) (one or both of the following 2 criteria had to be satisfied):

- current intermittent claudication with ankle brachial index (ABI) <0.90, or
- a history of intermittent claudication together with previous related intervention in a leg (angioplasty, atherectomy, bypass graft, other vascular intervention including amputation, etc.).

Investigational product: Clopidogrel /clopidogrel placebo

Formulation: clopidogrel: 75 mg film-coated tablets

clopidogrel placebo: film-coated tablets indistinguishable from the active clopidogrel tablets

Administration: oral

Dose: clopidogrel: 75 mg once daily

clopidogrel placebo: not applicable

Reference therapy: Ticlopidine/ticlopidine placebo

Formulation: ticlopidine: 100 mg film-coated tablets

ticlopidine placebo: film-coated tablets indistinguishable from the active ticlopidine tablets

Administration: oral

Dose: ticlopidine: 200 mg once daily

ticlopidine placebo: not applicable

Duration of treatment:

1st period (double-blind treatment): 12 weeks

2nd period (open clopidogrel treatment): 40 weeks (after Week 12, one tablet of clopidogrel 75 mg o.d.)

Duration of observation:

Screening period: maximum 4 weeks

Treatment period:

1st period (double-blind treatment): 12 weeks

2nd period (open clopidogrel treatment): 40 weeks

Criteria for evaluation:

Primary endpoint:

Safety during the 1st period (double-blind treatment):

The elapsed time in days from the randomization to the first occurrence of the safety events of interest until Week 12 (1st period).

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

- Clinical significant bleeding (non-traumatic hemorrhage that results in death or requires inpatient hospitalization or prolongation of existing hospitalization) for which a causal relationship to the Investigational Product could not be ruled out by the Investigator
- Blood disorders (leukopenia, neutropenia or thrombocytopenia) for which a causal relationship to the Investigational Product could not be ruled out by the Investigator
- Hepatic dysfunction (elevated AST, ALT, γ-GTP, ALP or total bilirubin and jaundice) for which a causal relationship to the Investigational Product could not be ruled out by the Investigator
- Other serious adverse drug reactions that meet the following criteria and for which a causal relationship to the Investigational Product could not be ruled out by the Investigator
  - Resulted in death
  - Was life-threatening
  - Required inpatient hospitalization or prolongation of existing hospitalization
  - Resulted in persistent or significant disability/incapacity

Secondary endpoints:

Safety during the 1st period (double-blind treatment):

The elapsed times in days from the randomization to the first occurrence of each following event until Week 12 (1st period) for:

- Bleeding adverse events
- Serious adverse events
- Adverse events
- Adverse drug reaction

Safety during the 52 weeks treatment of clopidogrel:

The elapsed times in days from the randomization to the first occurrence of each following event until Week 52 (2nd period)

- Bleeding adverse events
- Serious adverse events
- Safety events of interest
- Adverse events
- Adverse drug reaction

Efficacy during the 1st period (double-blind treatment):

- Vascular events:
  - Combined outcome event cluster of cerebral infarction (CI), myocardial infarction (MI), or other cardiovascular (CV) death
  - Combined outcome event cluster of CI, MI, other CV death, or hospitalization due to ischemic event (except that not to accompany exacerbation of disease/symptoms)
  - Combined outcome event cluster of CI, MI, other CV death, or any hospitalization (except that not to accompany exacerbation of disease/symptoms)

Efficacy during the 52 weeks treatment of clopidogrel:

- Vascular events (as above)

Statistical methods:

Analysis population

All randomized population: any patient who was allocated to a randomized treatment regardless of whether the treatment kit was used or not, analyzed according to the treatment group allocated by randomization.

All treated population: all randomized population who actually received at least one dose or partial of a dose of Investigational Product (IP) analyzed according to the treatment actually received.

Primary analysis:

For the safety events of interest until Week 12 (1st period), comparison between clopidogrel and ticlopidine groups was performed using log-rank test stratified by the randomization stratification factors with two-sided 5% significance level on all randomized 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 the randomization stratification factors 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 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 all randomized population.

Analyses of general safety data

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

All Adverse Events (AEs) were coded using the version 14.0 of MedDRA. Treatment-emergent Adverse Events (TEAEs) were defined as AEs 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 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:

Primary endpoint

The risk of first safety events of interest up to Week 12 was statistically significantly lower in the clopidogrel group than in the ticlopidine group (p<0.0001, stratified log-rank test). The cumulative incidences of the first safety event of interest at Week 12 were 2.4% and 13.6%, for clopidogrel and ticlopidine groups, respectively. The adjusted hazard ratio was 0.161 (95%CI, 0.062 to 0.416). The difference was mainly due to a greater incidence of hepatic dysfunctions in the ticlopidine group.

Analysis of time to first safety event of interest - All randomized population – 1st period

	Clopidogrel (N=215)	**Ticlopidine (N=216)**
Number of events, n (%)	5 (2.3%)	30 (13.9%)
Cumulative incidence (95% CI)[a] at Week 4	0.009 (0.000 to 0.022)	0.037 (0.012 to 0.063)
Cumulative incidence (95% CI)[a] at Week 8	0.009 (0.000 to 0.022)	0.117 (0.074 to 0.161)
Cumulative incidence (95% CI)[a] at Week 12	0.024 (0.003 to 0.044)	0.136 (0.090 to 0.182)
Stratified Log-rank test p-value[b]	<0.0001	-
Adjusted Hazard ratio (95% CI)[c]	0.161 (0.062 to 0.416)	-
Un-stratified Log-rank test p-value[d]	<0.0001	-
Un-adjusted Hazard ratio (95% CI)[e]	0.159 (0.062 to 0.410)	-

[a] *Kaplan-Meier technique with Greenwood's variance estimation*

[b] *Log-rank test for treatment group with background antiplatelet therapies, history of myocardial infarction and/or ischemic cerebrovascular disorder and concomitant diabetes mellitus at baseline as stratum,* [c] *Estimated using Cox proportional hazard model with treatment group, background antiplatelet therapies, history of myocardial infarction and/or ischemic cerebrovascular disorder and concomitant diabetes mellitus as factors*

[d] *Unstratified Log-rank test for treatment group* [e] *Estimated using Cox proportional hazard model with treatment group as a factor*

Composition of first safety event of interest - All randomized population - 1st period

	Clopidogrel (N=215)	Ticlopidine (N=216)
Any safety event of interest	5 (2.3%)	30 (13.9%)
Clinically significant bleeding	0	1 (0.5%)
Spontaneous	0	1 (0.5%)
Post procedural	0	0
Blood disorder	1 (0.5%)	5 (2.3%)
Leukopenia	0	3 (1.4%)
Neutropenia	1 (0.5%)	5 (2.3%)
Thrombocytopenia	0	0
Hepatic dysfunction	3 (1.4%)	24 (11.1%)
Elevated AST	1 (0.5%)	4 (1.9%)
Elevated ALT	0	5 (2.3%)
Elevated gamma-GTP	2 (0.9%)	20 (9.3%)
Elevated ALP	0	0
Elevated total bilirubin	0	0
Jaundice	0	0
Other serious adverse drug reaction [a]	1 (0.5%)	1 (0.5%)
Results in death	0	0
Is life-threatening	0	0
Requires inpatient hospitalization or prolongation of existing hospitalization	1 (0.5%)	1 (0.5%)
Results in persistent or significant disability/incapacity	0	0

[a] Meeting one of the following criteria: Results in death, or Life-threatening or, Requires inpatient hospitalization or prolongation of existing hospitalization or, Results in persistent or significant disability/incapacity.
Note: A patient can be counted in several categories when multiple events occurred on the same day as first event.

Secondary endpoints of the first period

Regarding first bleeding adverse events up to Week 12, no statistically significant difference was observed between the clopidogrel and ticlopidine groups (p= 0.4478, stratified log-rank test). The cumulative incidences of the first events at Week 12 for clopidogrel and ticlopidine groups were 8.4% and 7.0%, respectively.

Regarding other secondary safety endpoints up to Week 12, clopidogrel treatment was associated with a significant lower risks of first adverse events and adverse drug reactions compared with the ticlopidine treatment (p=0.0026 and p<0.0001, respectively, stratified log-rank test). There was no significant difference in terms of first serious adverse events between the clopidogrel and ticlopidine groups (p=0.6805, stratified log-rank test).

Secondary endpoints of the overall period

For the long-term safety, the cumulative incidences of first bleeding adverse events at Week 52 for the clopidogrel (CLOP-CLOP) and ticlopidine (TIC-CLOP) groups were 19.1% and 19.8%, respectively. The occurrence rate of first bleeding adverse events was constant on the long-term exposure. The cumulative incidences of the first safety event of interest at Week 52 for clopidogrel (CLOP-CLOP) and ticlopidine (TIC-CLOP) groups were 4.8% and 17.5%, respectively. The difference was mainly due to the high incidence observed in the ticlopidine (TIC-CLOP) group related to 1st period. After switching from ticlopidine to clopidogrel at Week 12, the occurrence rate of safety events of interest for the ticlopidine (TIC-CLOP) group was consistent with that for the clopidogrel (CLOP-CLOP) group with minimum increase of incidence. For other secondary safety endpoints, the cumulative incidences of first SAEs and AEs at Week 52 were 16.7% and 90.8% in the clopidogrel (CLOP-CLOP) group, 19.0% and 94.2% in the ticlopidine (TIC-CLOP) group, respectively. The cumulative incidences of the first adverse drug reactions at Week 52 in clopidogrel (CLOP-CLOP) group and ticlopidine (TIC-CLOP) group were 27.7% and 45.3%, respectively. The difference was mainly due to the high incidence observed in the ticlopidine (TIC-CLOP) group related to 1st period.

Efficacy results:

Regarding the first vascular events up to Week 12 , no statistical significant differences between the 2 treatment groups were observed in the 3 composite endpoints (CI/MI/Other CV death, p=0.1539; CI/MI/Other CV death/Hospitalization due to ischemic event, p=0.9553; and CI/MI/Other CV death/Any hospitalization, p=0.9534; stratified log-rank test). Concerning the composite of first CI/MI/Other CV death, there were 2 events (one fatal CI and one non-fatal MI) in the ticlopidine group, and no event in the clopidogrel group. The cumulative incidences of composite of first CI/MI/Other CV death at Week 12 for the clopidogrel and ticlopidine groups were 0% and 0.9%, respectively. Regarding the composite of first CI/MI/Other CV death/Hospitalization due to ischemic event, the cumulative incidences at Week 12 for the clopidogrel and ticlopidine groups were the same (0.9% each).

Regarding the long-term efficacy, the cumulative incidences of composite of first CI/MI/Other CV death at Week 52 for the clopidogrel (CLOP-CLOP) and ticlopidine (TIC-CLOP) groups were 0.5% and 3.9%, respectively. Two patients in the clopidogrel (CLOP-CLOP) group and 8 patients in the ticlopidine (TIC-CLOP) group experienced this composite endpoint up to Week 52. The most frequently observed first events in both groups were CIs which were observed during the 52-week treatment. The occurrence rates of this composite endpoint were constant throughout the 52-week treatment in the 2 groups. Regarding the composite of first CI/MI/Other CV death/Hospitalization due to ischemic event, the cumulative incidences at Week 52 for the clopidogrel (CLOP-CLOP) and ticlopidine (TIC-CLOP) groups were 4.3% and 4.4%, respectively. Also, the occurrence rates of this composite endpoint were constant on the long-term exposure in both groups.

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