

<p><i>These results are supplied for informational purposes only.</i></p> <p><i>Prescribing decisions should be made based on the approved package insert in the country of prescription</i></p>	
<p>Sponsor/company: sanofi-aventis</p> <p>Generic drug name: Clopidogrel</p>	<p>ClinicalTrials.gov Identifier:</p> <p>Study Code: L_9317</p> <p>Date: 15 July 2008</p>

Title of the study:	Clopidogrel 600 mg and 300 mg as a loading dose prior to percutaneous coronary intervention And Serum Troponin Level Elevation (CASTLE): A Pilot Study. L_9317	
Investigator(s):	<p>Dr. Efraín Gaxiola</p> <p>Address: Avenida Hidalgo 930, Zona Centro, 44290 Guadalajara, Jalisco MÉXICO</p> <p>Tel: +52 33 3827 1668 Fax: +52 33 3827 1670 e-mail: efraingaxiola@yahoo.com</p>	
Study center(s):	<p>Country: Mexico</p> <p>Active centers: 9</p>	
Publications (reference):	No publications were done	
Study period:	Phase of development:	
Date first patient/subject enrolled: 01-May-2004	IIIb	
Date last patient/subject completed: 20-Feb-2006		

Objectives:	<p align="center">- Primary Objective(s)</p> <p>Primary endpoint: Incidence of post-percutaneous coronary intervention elevation of troponin T at all measured time points.</p> <p align="center">- Secondary Objective(s)</p> <p>a) Composite endpoint of death, MI, cardiovascular death and urgent TVR (target vessel revascularization) at hospital follow-up (before hospital discharge).</p> <p>b) Composite endpoint of death, MI, cardiovascular death, re-hospitalization and urgent TVR (target vessel revascularization) within first 28 days.</p> <p>c) Incidence of troponin T elevation after intervention in patients with normal baseline troponin T.</p> <p>d) Median peak values of CK, CK-MB and troponin T</p> <p>e) Rescue therapy with platelet IIb/IIIa inhibitor during procedure</p> <p>f) Post-procedure MI using CK or CK-MB ≥ 3 times normal</p>																										
Methodology:	Multicenter, prospective, randomized, parallel groups, comparative trial.																										
Number of patients/subjects:	Planned: 234	Randomized: 155	Treated: 147																								
Evaluated:	Efficacy : 147	Safety: 147	<table border="1" data-bbox="582 1200 1342 1854"> <thead> <tr> <th colspan="2" data-bbox="582 1223 1342 1256">Number of Patients</th> </tr> </thead> <tbody> <tr> <td data-bbox="582 1272 1117 1305">Enrolled</td> <td data-bbox="1117 1272 1342 1305">155</td> </tr> <tr> <td data-bbox="582 1335 1117 1368">Not randomized to treatment</td> <td data-bbox="1117 1335 1342 1368">8</td> </tr> <tr> <td data-bbox="582 1397 1117 1431">Randomized to study treatment</td> <td data-bbox="1117 1397 1342 1431">147</td> </tr> <tr> <td data-bbox="582 1460 1117 1494">Treated</td> <td data-bbox="1117 1460 1342 1494">147</td> </tr> <tr> <td data-bbox="582 1523 1117 1556">Completed</td> <td data-bbox="1117 1523 1342 1556">124</td> </tr> <tr> <td data-bbox="582 1585 1117 1619">Discontinued</td> <td data-bbox="1117 1585 1342 1619">23</td> </tr> <tr> <td colspan="2" data-bbox="582 1648 1342 1682"><i>Assessed for safety:</i></td> </tr> <tr> <td data-bbox="582 1711 1117 1744">Adverse Events</td> <td data-bbox="1117 1711 1342 1744">147</td> </tr> <tr> <td data-bbox="582 1774 1117 1807">Laboratory tests</td> <td data-bbox="1117 1774 1342 1807">147</td> </tr> <tr> <td colspan="2" data-bbox="582 1836 1342 1870"><i>Assessed for efficacy:</i></td> </tr> <tr> <td data-bbox="582 1899 1117 1933"></td> <td data-bbox="1117 1899 1342 1933">105</td> </tr> </tbody> </table>	Number of Patients		Enrolled	155	Not randomized to treatment	8	Randomized to study treatment	147	Treated	147	Completed	124	Discontinued	23	<i>Assessed for safety:</i>		Adverse Events	147	Laboratory tests	147	<i>Assessed for efficacy:</i>			105
Number of Patients																											
Enrolled	155																										
Not randomized to treatment	8																										
Randomized to study treatment	147																										
Treated	147																										
Completed	124																										
Discontinued	23																										
<i>Assessed for safety:</i>																											
Adverse Events	147																										
Laboratory tests	147																										
<i>Assessed for efficacy:</i>																											
	105																										
Diagnosis and criteria for inclusion:	Patients having symptomatic coronary artery disease with objective evidence of ischemia or patients undergoing stent implantation																										

Investigational product:	Clopidogrel	
Dose:	300 / 600 mg of loading dose of Clopidogrel	
Administration:	Group 1: 300-mg loading dose of clopidogrel given ≥ 6 and ≤ 24 hours before PCI. Group 2: 600-mg loading dose of clopidogrel given ≥ 6 hours and ≤ 24 before PCI. Group 3: 600-mg loading dose of clopidogrel given immediately (≤ 45 minutes) before PCI.	
Duration of treatment: 28 days	Duration of observation: Based on investigators judgement 6 and 12 months post-PCI	
Reference therapy:	NA	
Criteria for evaluation:		
Efficacy:	Primary endpoint: Incidence of post-percutaneous coronary intervention elevation of troponin T at all measured time points.	
Safety:	Adverse events reported by the patient/subject or noted by the investigator, standard hematology and blood chemistry.	
Statistical methods:	<p>The primary efficacy variable is the proportion of patients with an increase in troponin T at 8, 16 or 24 hours after PCI. When troponin T level is higher than 0.1 ng/mL, it is considered increased.</p> <p>In order to analyze the primary efficacy variable, a χ^2 test will be used to determine if there is an association between treatment variables and an increase or not in troponin T.</p> <p>As exploratory analysis, proportion comparison tests among the 3 treatments will be performed.</p>	

<p>Summary:</p>	<p>Analysis populations</p> <p>The analysis populations were assigned according to the following:</p> <p><u>Safety</u></p> <p>The patient's population for safety analysis consisted of all those patients who received at least one active treatment dose.</p> <p>The safety population consisted of 147 patients (94.84%)</p> <p><u>Efficacy</u></p> <p>Efficacy analysis population per Protocol consists of all patients with no mayor protocol violations and that had baseline Troponin T determinations, and at 8, 16 and 24 h post-PCI (or those that did not have the baseline Troponin I determinations, and at 8, 16, and 24 h after PCI).</p> <p>The efficacy population per protocol consisted of a total of 105 (67.74%) patients. The primary efficacy analysis was performed with the efficacy population per protocol</p> <p>Patients were included in 9 Investigational sites. 155 patients were enrolled in the study. 8 patients (5.16%) were not randomized to treatment group.</p> <p>The study consisted of a 10-visit schedule: Visit 1 was the baseline; visits 2 and 3 during and, at the end of the PCI; the visits 4, 5, and 6 were at 8, 16 and 24 hours post- PCI; visit 7 at hospital discharge and visit 8, 28 days post-PCI. The study termination was considered up to this visit; the visits 9 (6 months post-PCI) and 10 (1 year post-PCI) were optional</p> <p>From 155 patients enrolled in the study, 124 (80%) patients completed the study and, 23 were early discontinued for different reasons</p> <p><i>Demographic data.</i> 101 (68.71%) patients were males and 43 (29.25%) were females; gender was not registered in 3 patients. The patients mean age was 62 years, with a standard deviation of 11.13 years (range: 34 to 93 years).</p> <p>The angiography was not previously performed in 110 (75%) patients. 78 patients (53%) were reported for unstable angina, being the most frequent ones those of recent onset or post-infarction. Angina classification was performed in 54 (36.73%) patients; the most frequent was the class II angina (mild)</p> <p><u>Measurements for Visit 2 (during PCI).</u></p> <p>The results for this visit and the next one are reported for the efficacy population per protocol.</p> <p>Cardiac catheterization. The stenosis percentage data showed a high variability as indicated by the coefficient of variation, particularly for the left Trunk Stenosis., Cx Stenosis percentage and the CD Stenosis percentage.</p> <p>PCI results.</p>
------------------------	---

A total of 155 segments in 105 patients in the population per protocol underwent PCI. The segments that were more treated were the proximal anterior descending and the middle third of the anterior descending artery in the three groups.

The unfractionated heparin (in bolus) was the most used in 99 patients, whereas the low molecular weight heparin was the least used (5 patients).

The pre-PCI stenosis mean (visual and angiographic) was about 80% and, the post-PCI mean was between 2.76% and 15.10%

For the type of lesion the result of the procedure was successful in 98.68% cases; there was one partial success and two failures. The final TIMI and PMT were mostly in 3.

There were few complications. The most frequent complication was observed in 8 (5.16%) cases of lateral branch transient closure.

Efficacy results:

Primary endpoint.

The primary endpoint was calculated based on the proportion of patients with Troponin T elevation (or Troponin I).

Troponin elevation was considered according to the next limits:

- Troponin T: greater than 0.1 ng/ml
- Troponin I: greater than or equal to 0.2 ng/ml

In the χ^2 test there was no association between treatment and Troponin elevation (p value = 0.1246); however, after exploring the data there are fewer patients (17 cases: 48.57% of total per group) with Troponin elevation in group 2 (600 mg Clopidogrel ≥ 6 and ≤ 24 h prior to PCI) than in group 1 (300 mg Clopidogrel ≥ 6 and ≤ 24 h prior to PCI) and group 3 (600 mg Clopidogrel ≤ 45 min prior to PCI) 58.82% and 72.22% respectively.(table 1)

Table 1: Efficacy endpoint. Proportion of patients with Troponin T elevation (or Troponin I) at 8, 16 or 24 hours post-PCI

	Treatment groups			Total
	Group 1 *	Group 2	Group 3	
No elevation	14 (41.18%)	18 (51.43%)	10 (27.78%)	42
Elevation	20 (58.82%)	17 (48.57%)	26 (72.22%)	63
Total	34	35	36	105

* Group 1: 300-mg loading dose of clopidogrel given ≥ 6 and ≤ 24 hours before PCI.

Group 2: 600-mg loading dose of clopidogrel given ≥ 6 hours and ≤ 24 before PCI.

Group 3: 600-mg loading dose of clopidogrel given immediately (≤ 45 minutes) before PCI.

Secondary endpoints

Patients with a composite outcome event of death, MI and TVR during in-hospital follow-up (before hospital discharge): There were four outcome events distributed along the groups, because of this a Fisher exact test was performed to demonstrate the association between the treatment and the outcome event. The p-value was 1.00, therefore there is no statistical evidence for such association (table 2).

Table 2: Secondary Efficacy endpoint. a) Patients with a composite outcome event of death, MI y UTVR during in-hospital follow-up (before hospital discharge).

	Treatment groups			Total
	Group 1 *	Group 2	Group 3	
No outcome	33 (97.06%)	34 (97.15%)	34 (94.44%)	101
Outcome: MI, death, TVR	1 (2.84%)	1 (2.86%)	2 (5.56 %)	4
Total	34	35	36	105

* Group 1: 300-mg loading dose of clopidogrel given ≥ 6 and ≤ 24 hours before PCI.

Group 2: 600-mg loading dose of clopidogrel given ≥ 6 hours and ≤ 24 before PCI.

Group 3: 600-mg loading dose of clopidogrel given immediately (≤ 45 minutes) before PCI.

Due to the sample size the results in the current study will only be considered as exploratory.

	<p>The survival time for the composite outcome event of death, myocardial infarction, re-hospitalization and UTVR during the 28-day follow-up.</p> <p>In the efficacy population per protocol there were no outcome events.</p> <p>CK, CK-MB, Troponin T and Troponin I mean peak values.</p> <p>The mean peak values were calculated as the enzyme maximum value at 8, 16 or 24 hours after PCI.</p> <p>For the comparison between the mean peak values in the treatment group a Kruskal-Wallis test was performed. The resulting p-values were:</p> <table border="1" data-bbox="675 772 1193 967"> <thead> <tr> <th>Enzyme</th> <th>p-value</th> </tr> </thead> <tbody> <tr> <td>CK</td> <td>0.1440</td> </tr> <tr> <td>Troponin T</td> <td>0.3252</td> </tr> <tr> <td>Troponin I</td> <td>0.2575</td> </tr> </tbody> </table>	Enzyme	p-value	CK	0.1440	Troponin T	0.3252	Troponin I	0.2575
Enzyme	p-value								
CK	0.1440								
Troponin T	0.3252								
Troponin I	0.2575								
<p>Safety results:</p>	<p>The patient's population for safety analysis consisted of all those patients who received at least one active treatment dose. The safety population consisted of 147 patients (94.84%)</p> <p>Adverse Events: The assessment of adverse events was analyzed in 147 patients. There were a total of 21 adverse events, only 2 (1.36%) of them were serious. Two serious adverse events were observed: one patient in group 2 (600 mg Clopidogrel ≥ 6 and ≤ 24 h prior to PCI) died, and one patient in group 3 (600 mg Clopidogrel ≤ 45 min prior to PCI) required hospitalization</p> <p>The results regarding ASA dose are not available in the study and therefore, the influence on safety results (bleeding) cannot be determined.</p> <p>Laboratory parameters.</p> <p>The laboratory parameters (hematocrit, hemoglobin, leucocytes and platelets) were evaluated in visit 1 (baseline) and in visit 6 (24 hours post-PCI).</p> <p>In group 1 (300 mg Clopidogrel ≥ 6 and ≤ 24 h prior to PCI) no statistically significant changes were observed; in group 2 (600 mg Clopidogrel ≥ 6 and ≤ 24 h prior to PCI), there were significant changes in all the parameters; in group 3 (600 mg Clopidogrel ≤ 45 min prior to PCI) there was an increase in leucocytes (7.54 Vs 8.39 mm³) and platelet reduction (224234 Vs 213500 mm³).</p>								
<p>Date of report:</p>	<p>06-Jun-07</p>								