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Sponsor / Company: sanofi-aventis **Drug substance(s):** clopidogrel	**Study Identifier:** NCT00115375 **Study code:** PDY4422
Title of the study: Platelet aggregation Inhibition in Children On Clopidogrel (PICOLO) – Dose ranging pharmacodynamic assessment of platelet aggregation inhibition with clopidogrel in children of Blalock-Taussig shunt age categories (neonates and infants/toddlers)	
Study center(s): Total of 22 study centers in 6 countries: Canada, France, Germany, Italy, Belgium and United States	
Study period: Date first patient enrolled: 13-Jan-2004 Date last patient completed: 15-Apr-2006	
Phase of development: Phase II	
Objectives: Primary: The primary objective of this study was a pharmacodynamic assessment to determine the dose of clopidogrel to achieve a mean 30 to 50% inhibition of 5 µM ADP-induced platelet aggregation in neonates or infants/toddlers at risk for thrombosis. Secondary: The secondary objectives of the study were to assess pharmacokinetic (PK) and safety of clopidogrel when administered to neonates and infants/toddlers at the doses tested for demonstration of an appropriate inhibitory effect on ADP induced platelet aggregation.	
Methodology: A multicentre, randomized, double blind, placebo controlled dose finding study	
Number of patients: Planned: 72 Randomized: 92 Treated: 86 Evaluated for efficacy: 73, safety: 86	
Diagnosis and criteria for inclusion: Neonates (less than or equal to 30 days of age) or infants/toddlers (up to 24 months of age) at risk for thrombosis (eg, Blalock-Taussig shunt, Kawasaki disease, or vascular stent, or any pathological condition that required antiplatelet therapy).	

Investigational product: clopidogrel powder was to be reconstituted in 5 mL solvent to obtain a 5 mg/mL stock solution that was used undiluted or diluted to obtain the planned dose to be administered.

Dose: planned doses: 0.01. 0.1, and 1.0 mg/kg;
administered doses: 0.01, 0.1, 0.2 mg/kg in both age groups and 0.15 mg/kg only in neonates.

Administration: oral or enteric

Duration of treatment: A minimum of 7 days and a maximum of 28 days depending on the actual timing of the pharmacodynamic (PD) assessment with at least 7 consecutive days of treatment to reach steady state

Duration of observation: 7 to 34 days

Reference therapy: placebo (mannitol powder)

Dose: the same volume as used for the clopidogrel administration

Administration: oral or enteric

Criteria for evaluation:

Pharmacodynamic: Percent inhibition of maximum extent and rate of aggregation of 5 μM ADP induced platelet aggregation. In patients above 3 kg body weight, the percent inhibition of maximum extent and rate of aggregation of 5 μM TRAP induced platelet aggregation were also determined.

Safety: Adverse events (AEs), serious adverse events (SAEs), available laboratory tests at study drug treatment end, and bleeding.

Pharmacokinetics: The concentration of the inactive carboxylic acid metabolite of clopidogrel, SR26334, was measured in plasma when it was possible to obtain the necessary samples.

Statistical methods:

All patients who received the study drug were assessed for safety and tolerability.
Only randomized patients who had a baseline (pre-treatment) and a steady state (at least 7 consecutive days of treatment) assessment of platelet aggregation were included in the analysis of pharmacodynamic (PD) parameters.
However, available PK parameters and safety data were considered for any randomized and treated patient.

Steady state percent inhibition of maximum extent and rate relative to baseline (pre-treatment) results were summarized using descriptive statistics and compared between clopidogrel and placebo treated patients at each dose level and age category using analysis of variance (ANOVA). Statistical significance was claimed if the computed p-value was ≤ 0.05. Estimates and 95% confidence intervals (CI) for the difference between means were also calculated.

Summary:

Pharmacodynamic results:

Clopidogrel inhibited ADP-induced platelet aggregation in a dose-dependent manner. At a dose of 0.2 mg/kg, clopidogrel significantly reduced the maximum extent and the rate of ADP-induced platelet aggregation as compared to placebo with a mean percent inhibition of the maximum extent of platelet aggregation of 49.3%, which achieved the target of 30 to 50% inhibition of 5 µM ADP-induced platelet aggregation in neonates or infant/toddlers.

The table below summarizes the inhibition (expressed numerical and in %) of the maximum extent of ADP-induced platelet aggregation by clopidogrel in the overall population of neonates and infants/toddlers.

		Clopidogrel			
	Placebo (N=16)	**0.01 mg/kg (N=8)**	**0.1 mg/kg (N=18)**	**0.15 mg/kg[a] (N=6)**	**0.2 mg/kg (N=25)**
Baseline					
Mean (SD)	47.7 (17.8)	40.9 (14.0)	39.8 (18.1)	35.0 (10.8)	49.9 (14.6)
Median	46.0	38.0	31.5	34.0	51.0
Range	21.0 - 84.0	21.0 - 68.0	19.0 - 74.0	20.0 - 49.0	24.0 - 82.0
Steady-state					
Mean (SD)	43.6 (14.4)	43.1 (14.1)	28.3 (11.5)	21.2 (8.2)	23.3 (9.5)
Median	45.0	43.0	30.0	20.0	22.0
Range	13.0 - 62.0	23.0 - 68.0	9.0 - 47.0	13.0 - 36.0	5.0 - 46.0
% Inhibition[a]					
Mean (SD)	0.8 (48.0)	-12.8 (46.2)	18.9 (40.4)	36.4 (27.5)	49.3 (27.2)
Median	5.5	2.5	19.0	47.4	53.2
Range	-158.3 - 51.2	-100.0 - 34.3	-60.9 - 78.3	-15.0 - 58.3	-24.3 - 86.1
P-value		0.4445	0.1602	0.2139	0.0001
Difference from placebo [95% CI]		-12.28 [-44.16, 19.59]	17.99 [-7.29, 43.26]	20.94 [-12.76, 54.65]	49.26 [25.70, 72.82]

[a] neonates only

Safety results:

In the combined clopidogrel dose groups, 40% of the patients experienced at least one treatment-emergent AE (TEAE) with no dose relationship. In the placebo group, 28.6% of the patients experienced at least 1 TEAE. There were 4 patients (including 2 patients who received placebo) who experienced at least 1 bleeding during the study. None of the bleedings were severe. With regard to non-hemorrhagic AEs, the most frequently reported were gastrointestinal disorders with vomiting and diarrhea.

Pharmacokinetic results:

For ethical reasons in this population of very small children, we have not been able to collect enough blood samplings to assess correctly the pharmacokinetic.

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