OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 20-839/S051	Submission Date: July 15, 2010
Brand Name	Plavix®
Generic Name	clopidogrel bisulfate
Pharmacometrics Reviewer	Kevin Krudys, Ph.D.
Pharmacometrics Team Leader	Pravin Jadhav, Ph. D.
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OCP Division	Division of Clinical Pharmacology 1
OND Division	Division of Cardio-Renal Drug Products
Applicant	sanofi-aventis U.S. Inc.
Formulation; strength(s) dosed in the trial	Reconstituted solution at (b) (4); 0.2 mg/kg/day
Indication for this supplement	Reduction of all-cause mortality and shunt-related morbidity in neonates or infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt
Review Type	Pediatric Supplement

1 EXECUTIVE SUMMARY

Plavix® (clopidogrel bisulfate) is indicated in adult patients with acute coronary syndrome or recent myocardial infarction, stroke or established peripheral arterial disease. In this application, the sponsor has submitted data in response to the pediatric written request. The application consists of a bioavailability study, a dose-ranging pharmacodynamic study and an efficacy study in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary shunt. The purpose of this review is to evaluate data supporting safety and efficacy of clopidogrel and aspirin in neonates and infants. This review does not address the adequacy of the contents of this application to satisfy the terms of the written request. (b) (5)

1.1 Recommendations

Pediatric Plavix® dosing recommendations can not be derived because an effective dose has not been identified in the clinical studies. The clopidogrel dose (0.2 mg/kg) used in the pivotal CLARINET study was potentially inadequate to demonstrate efficacy. The dose selection was based on response to ADP-induced platelet aggregation targeting similar proportional reduction to that of adults. This strategy is potentially flawed because the baseline responses among neonates, infants and adults are remarkably different. Furthermore, the formulation used in the CLARINET study was administered via naso-jejunal route in most of the neonates, thus potentially leading to decreased bioavailability, as clopidogrel is practically insoluble at neutral pH. If clopidogrel or another drug in the same class is considered for future evaluation for this indication, the pivotal trial should include multiple doses, one of which must achieve drug levels similar to those observed in adult patients at the approved dose. Also, the impact of different routes of administration on the bioavailability must be taken into consideration.

1.2 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Sanofi-aventis is seeking an additional six months exclusivity for Plavix® based on data submitted in response to the pediatric written request. The application consists of data from three studies:

1. A bioavailability study (BDR4580) comparing a liquid formulation suitable for pediatric administration to a 75 mg Plavix® tablet
2. A dose-ranging study (PICOLO) to determine the dose of clopidogrel achieving 30% to 50% inhibition of 5 μM ADP-induced platelet aggregation in neonates and infants/toddlers at risk for thrombosis.
3. A placebo-controlled, double-blind efficacy study (CLARINET) of 0.2 mg/kg clopidogrel in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary shunt.

The results of CLARINET failed to show a statistically significant difference in the frequency of the primary efficacy endpoint of death, stent thrombosis, or cardiac procedure prior to 120 days considered as thrombotic in nature (20.5% for placebo, vs.

19.1% for 0.2 mg/kg/day clopidogrel).

(b) (4)

1.4 Question Based Review

This review will address the key questions listed below. For a complete review of the clinical pharmacology of clopidogrel in the adult application, please refer to Dr. Uppoor's original review (October 15, 1997).

1.4.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The key design features of the two studies evaluating dose-response and efficacy are summarized below:

PICOLO

PICOLO was a dose-ranging study in neonates (less than or equal to 30 days old) and infants/toddlers (1 to 24 months of age) at risk of thrombosis to determine the dose of clopidogrel achieving a mean 30% to 50% inhibition of 5 μM ADP-induced platelet aggregation. A total of 92 patients were selected to receive one of four doses of clopidogrel (0.01, 0.1, 0.15 and 0.2 mg/kg/day) or placebo. Concomitant aspirin was administered at the investigator's discretion. Pharmacological activity was assessed after at least 7 consecutive days of daily administration of clopidogrel, with a maximum of 28 days. Plasma pharmacokinetic samples were collected from 47 of 65 patients treated with clopidogrel on Day 1 for determination of plasma concentrations of the inactive carboxylic acid metabolite (SR26334).

CLARINET

The primary objective of CLARINET was to evaluate the efficacy of clopidogrel 0.2 mg/kg once daily (n=467) vs. placebo (n=439) for the reduction of all-cause mortality and shunt-related morbidity in neonates or infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt. Patients were planned to be randomized and treated with study drug as soon as possible following shunt placement. Concomitant aspirin therapy was administered at the investigator's discretion. Patients were followed from randomization to the earliest of shunt thrombosis or next surgical procedure for correction of congenital heart disease, death, one year, or the common study end date. No pharmacokinetic or pharmacodynamic assessments were included in this study.

1.4.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

PICOLO
The primary efficacy variables were the percent inhibition of maximum extent and rate of 5μM ADP-induced platelet aggregation calculated as the mean % change from baseline to steady state at each dose level. These variables have been used in adult PK/PD studies and are considered a reasonable biomarker of the pharmacological effect of clopidogrel.

CLARINET
The response endpoints comprising the primary efficacy endpoint were death, shunt thrombosis requiring intervention or hospitalization for bi-directional Glenn procedure or any cardiac-related intervention prior to 120 days of age following an event or a shunt narrowing considered of thrombotic nature. These endpoints were chosen because they reflect mortality and clinically relevant morbidity for this population. No pharmacokinetic or pharmacodynamic markers were collected in CLARINET.

1.4.3 What are the characteristics of the exposure-response relationships for efficacy?

The mean percent inhibition of maximum platelet aggregation increases in a dose-related manner. The mean percent inhibition of maximum platelet aggregation in neonates was 13%, 25%, 36% and 62% for the 0.01, 0.1, 0.15, and 0.2 mg/kg clopidogrel dose groups, respectively. In infants, the mean percent inhibition of maximum platelet aggregation was -28%, 15% and 41% for the 0.01, 0.1 and 0.2 mg/kg clopidogrel dose groups respectively (Table 1). Similar results were observed for the rate of ADP-induced platelet aggregation and inhibition.

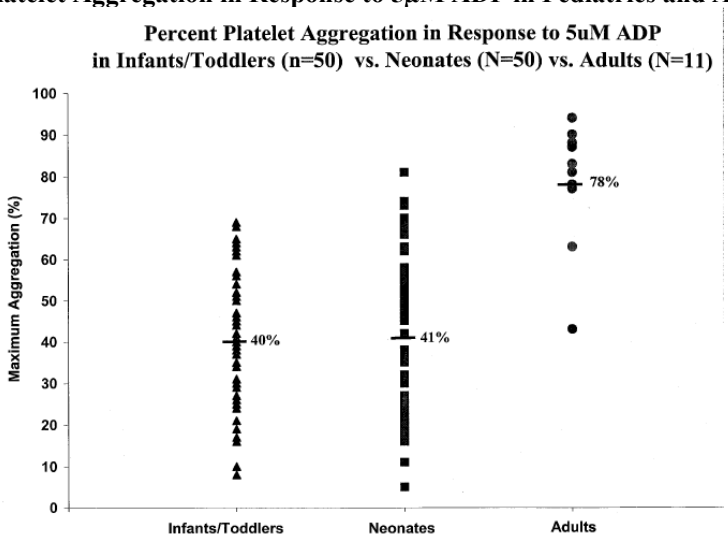
Table 1. Summary of maximum extent of ADP-induced platelet aggregation and inhibition by age group

	Placebo	Clopidogrel			
		0.01 mg/kg	0.1 mg/kg	0.15 mg/kg	0.2 mg/kg
Neonates	(N=7)	(N=3)	(N=8)	(N=6)	(N=10)
Baseline					
Mean (SD)	43.3 (18.6)	37.3 (6.8)	43.9 (22.1)	35.0 (10.8)	52.3 (18.0)
Median	38.0	35.0	37.0	34.0	49.0
Range	21.0 – 73.0	32.0 – 45.0	22.0 – 74.0	20.0 – 49.0	24.0 – 82.0
Steady-state					
Mean (SD)	36.0 (14.7)	33.0 (12.5)	28.1 (11.8)	21.2 (8.2)	18.1 (9.2)
Median	33.0	29.0	29.0	20.0	17.5
Range	13.0 – 59.0	23.0 – 47.0	9.0 – 45.0	13.0 – 36.0	5.0 – 32.0
% Inhibition [a]					
Mean (SD)	15.4 (20.3)	13.1 (19.6)	24.5 (43.2)	36.4 (27.5)	62.1 (24.5)
Median	21.0	9.4	25.2	47.4	67.7
Range	-20.0 – 38.1	-4.4 – 34.3	-60.9 – 71.9	-15.0 – 58.3	8.3 – 86.1
P-value		0.9272	0.6432	0.3182	0.0138
Difference from placebo [95% CI]		-2.37 [-53.95,49.21]	9.01 [-29.67,47.70]	20.94 [-20.64,62.53]	46.67 [9.84,83.51]
Infants/Toddlers	(N=9)	(N=5)	(N=10)	(N=0)	(N=15)
Baseline					
Mean (SD)	51.1 (17.5)	43.0 (17.5)	36.6 (14.6)	N.A.	48.3 (12.1)
Median	47.0	41.0	30.5		52.0
Range	24.0 – 84.0	21.0 – 68.0	19.0 – 65.0		29.0 – 66.0
Steady-state					
Mean (SD)	49.6 (11.8)	49.2 (12.0)	28.4 (12.0)	N.A.	26.8 (8.3)
Median	51.0	44.0	30.0		28.0
Range	26.0 – 62.0	38.0 – 68.0	10.0 – 47.0		16.0 – 46.0
% Inhibition [a]					
Mean (SD)	-10.6 (60.6)	-28.4 (52.3)	14.5 (39.8)	N.A.	40.7 (26.1)
Median	0.0	-8.6	13.6		46.2
Range	-158.3 – 51.2	-100.0 – 20.6	-34.6 – 78.3		-24.3 – 68.2
P-value		0.3969	0.1490		0.0018
Difference from placebo [95% CI]		-17.80 [-59.49,23.89]	25.11 [-9.24,59.45]		51.25 [19.74,82.77]

Source: PICOLO Clinical Study Report, P-52, Table (8.1.1.1)1

It should be noted that baseline (prior to clopidogrel administration) response to ADP-induced platelet aggregation, however, is not the same in neonates as it is in adults. Infants and neonates exhibit a baseline response that is approximately half that of adults (Figure 1). The utility of a mean 30% to 50% inhibition of 5 µM ADP-induced platelet aggregation in PICOLO for dose selection is therefore in question. (b) (5)

Figure 1. Percent Platelet Aggregation in Response to 5µM ADP in Pediatrics and Adults



1.4.4 What are the characteristics of the exposure-response relationships for safety?

The primary safety event associated with clopidogrel treatment is bleeding. At the doses studied in PICOLO, a dose-response relationship for bleeding events, defined as "any bleeding", was not observed. The only bleeding event in neonates occurred in the placebo group. In infants/toddlers, one bleeding event occurred in the placebo, 0.1 mg/kg and 0.2 mg/kg treatment groups each. In CLARINET, a similar proportion of patients had any bleeding in the placebo (20.18%) and 0.2 mg/kg clopidogrel (18.75%) treatment groups. Together, these results suggest that the clopidogrel exposures studied in PICOLO and CLARINET may be too low to elicit a significant anti-platelet response reflected in increased efficacy or bleeding.

1.4.5 Are the drug concentrations achieved in pediatric patients similar to observed adult concentrations at the approved dose?

The available data suggest that pediatric blood levels were much lower than levels in adult patients receiving the approved dose of 75 mg. This conclusion is based on two observations:

- The geometric mean SR26334 C_{max} (measurement on Day 1 between 0.17 and 3 hours post-dose) from 5 neonate patients in PICOLO receiving the 0.2 mg/kg dose was 0.03 mg/L. According to the relative BA study, the mean C_{max} of SR26334 following a single 75 mg dose in healthy adult male volunteers ranged from 2.8 to 3.3 mg/L. This difference is remarkable, even after taking into account the small pediatric sample size, wide sampling window for C_{max} and the fact that only the inactive metabolite was measured.
- The approved adult dose is 75 mg, which corresponds to approximately 1 mg/kg. The dose tested in CLARINET was 0.2 mg/kg, one fifth of the adult per kg dose.
- In the CLARINET study, the formulation was a 67% w/w sucrose solution of

clopidogrel bisulphate (1mg/mL) whose pH was adjusted to 2.1. In a substantial fraction of neonates the dose was administered via naso-jeujunal route. Given that clopidogrel is practically insoluble around neutral pH, the bioavailability can be expected to be decreased and contribute to lack of efficacy. It should be noted that PK was not assessed in the CLARINET study.

1.4.6 Was there a dose-response relationship between aspirin dose and the primary efficacy endpoint in the placebo arm in CLARINET?

The relationship between aspirin dose and the primary efficacy endpoint was weak (Figure 2). A strong dose-response relationship in the placebo arm would have provided evidence of efficacy for aspirin alone. Aspirin dose in Figure 2 was computed by dividing the first aspirin dose (mg) by average weight. A similar relationship was also observed when aspirin dose was calculated as the median aspirin dose from baseline to end of study. Subgroup analysis suggested that placebo patients with concomitant aspirin use had a lower event rate than patients not receiving aspirin (Table 2). It should be noted, however, that patients were not randomized to aspirin use, but received aspirin based on investigator discretion. This may confound any observed relationship. For example, it may be possible that clinicians prescribed a higher aspirin dose in patients they judged more likely to have an event. Or conversely, it is possible that the sickest patients were not given aspirin because clinicians thought the patient was not well enough to tolerate it.

Figure 2. Relationship between aspirin dose and incidence of primary efficacy endpoint.

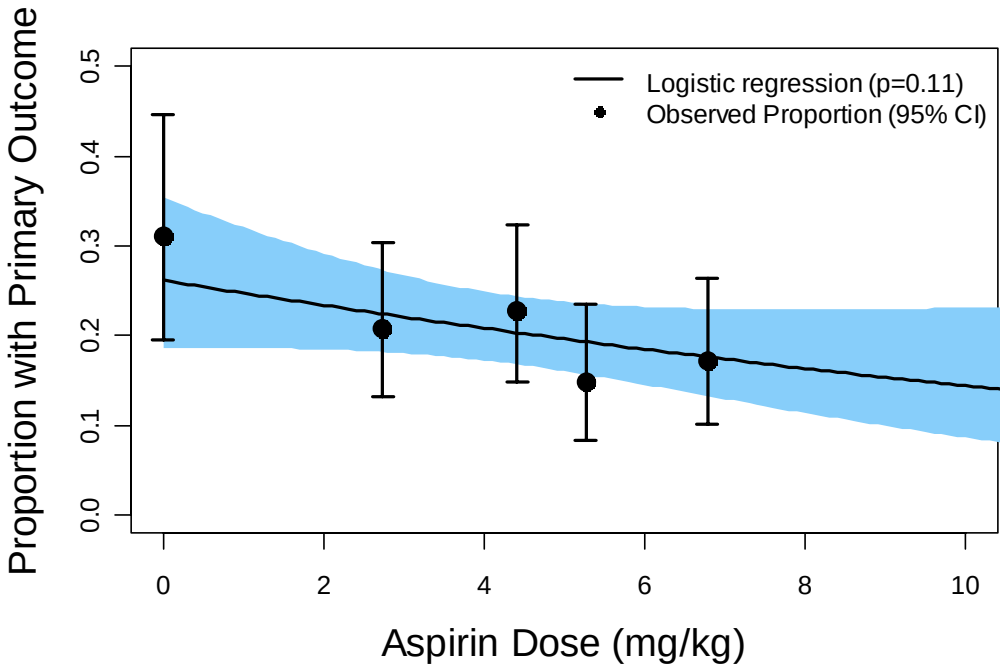


Table 2. Summary of primary outcome by concomitant aspirin use

Interaction Variable	Subgroup	Placebo	Clopidogrel 0.2 mg/kg/day	Hazard Ratio (95% CI)	p-value for interaction
ASA use	No (N=110)	18 (31.6%)	13 (24.5%)	0.71 (0.35 to 1.45)	0.2452
	Yes (N=796)	72 (18.8%)	76 (18.4%)	0.94 (0.68 to 1.30)	
ASA (mg/kg)	No intake (N=110)	18 (31.6%)	13 (24.5%)	0.71 (0.35 to 1.45)	
	≤ 3 mg/kg [a] (N=138)	11 (17.5%)	11 (14.7%)	0.78 (0.34 to 1.81)	
	> 3 to ≤ 5 mg/kg (N=312)	33 (22.1%)	33 (20.2%)	0.91 (0.56 to 1.48)	
	> 5 to ≤ 10 mg/kg (N=310)	25 (16.2%)	28 (17.9%)	1.05 (0.61 to 1.81)	
	> 10 mg/kg (N=36)	3 (18.8%)	4 (20.0%)	0.99 (0.21 to 4.58)	

1.5 APPENDIX 1. Clinical Pharmacology Review: BA/BE Study

Study Report # BDR4580: Bioavailability			
Title	Relative bioavailability study between 75 mg tablet and 75 mg solution of Clopidogrel (SR25990C) after single oral administration to young healthy men. Open, crossover, randomized and monocenter study		
Link	\\Cdsesub1\evsprod\NDA020839\0068\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\bdr4580		
Objectives	Bioequivalence ☐ Bioavailability ☒		
Study Design	Parallel ☐ Crossover ☒ A monocenter, single dose, open-label, randomized, 2-sequence, 2-period, crossover study. The 2 single oral drug administration periods were separated by a 14-day washout (inclusive of the treatment period).		
Formulation		**Test**	**Reference**
	Dosage Form	solution (b) (4) [redacted]	commercial clopidogrel formulation tablet (Plavix)
	Dosage Strength	75 mg	75 mg
	Batch #.	CL-04719 (b) (4) [redacted]	AR034588

<table>
<tr><td>PK Sampling</td><td>Pre-dose, and 0.17, 0.33, 0.5, 0.75, 1.0, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 30, 36 and 48 hours after clopidogrel administration.
Reviewer's comment:
Based on prior information, the above sampling scheme is adequate to capture the Cmax and to get an estimate of $AUC_{0\text{-}last/\infty}$ of inactive metabolite of clopidogrel.</td></tr>
<tr><td>PK Measurements</td><td>Clopidogrel inactive metabolite SR26334 was assayed for pharmacokinetics.
Reviewer Comment:
At the time of the study conduct (2002), the assay for the active metabolite was not available. Pediatric Written Request (original, 10/15/2001 and amended, 8/24/2007)) does not require the sponsor to report PK parameters of the active moiety</td></tr>
<tr><td>Statistical Method</td><td>Parameters were summarized by mean, standard deviation (SD), coefficient of variation (CV), minimum and maximum for each formulation. Log-transformed values of AUClast, AUC and Cmax and rank-transformed values of tmax were analyzed with a linear mixed effects model: Parameter = Sequence + Subject (Sequence) + Period + Treatment + Error. For AUClast, AUC and Cmax, estimates with 90% confidence intervals (CIs) for formulation ratios were obtained by first computing differences in estimates within the mixed model framework, and then converting to the ratio of adjusted geometric means by the antilogarithmic transformation. Bioequivalence to be concluded if the ratio 90% CI was included within the bioequivalence reference interval [0.80, 1.25]. For tmax, a 90% distribution-free CI for formulation differences was calculated based on the Hodges-Lehmann approach. Within-subject, between-subject and total-subject SDs were estimated by equating observed and expected means squares within the model framework used for treatment comparison.</td></tr>
<tr><td>Population</td><td>
<table>
<tr><td>Total Participants</td><td>Males</td><td>Females</td><td>Completed</td><td>Withdrawn</td></tr>
<tr><td>Healthy volunteers</td><td>24</td><td>0</td><td>24</td><td>0</td></tr>
</table>
</td></tr>
</table>

Results:

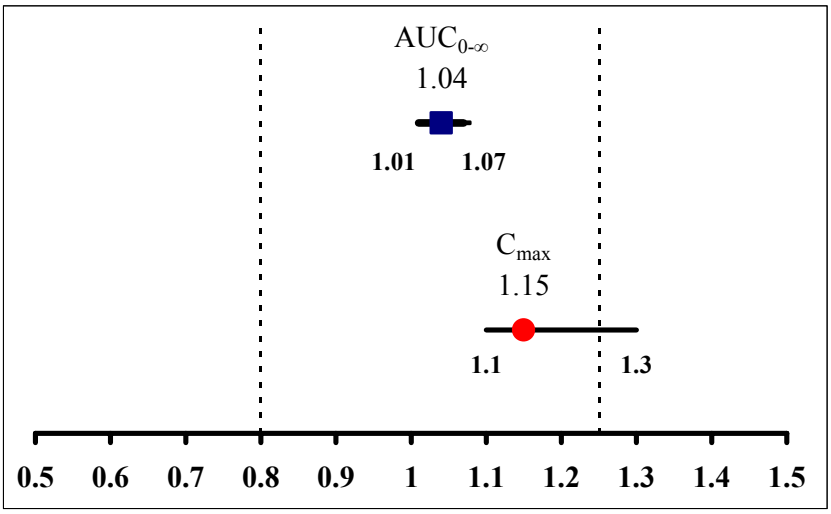


Figure 3. Results of statistical analysis. X-axis represents the geometric mean ratios. The fine broken vertical lines represent 80-125% BE limits. Data is represented as geometric mean ratio of BE metrics. Cmax, AUC_{0-last}, $AUC_{0-\infty}$) with 90% CI around the point estimate

Site Inspection

Performed: Yes ☐ No ☒

Assay Method

The performance of the assay method during study sample analysis is summarized in the table below

Analyte	SR26334, Inactive Metabolite
Method	LC-MS/MS
LLOQ, ng/mL	5
Range, ng/mL	5.0 to 1000
QCs, ng/mL	5, 10, 100, 1000
Accuracy/Bias, %	-5.89, -4.89, -4.26, -2.79
Precision, % (95% CI)	11.6(8.31, 19.1), 5.22(3.75, 8.62), 3.13(2.46, 5.69), 3.52(2.70, 7.06)

Reviewer Comment:

Accuracy and precision values for all QC values were within the acceptance criteria (< 15% of the true value); therefore, the assay validation is acceptable.

PK Parameters

Table 3. Mean (CV%) pharmacokinetic parameters of SR26334 (N=24)

Mean Parameter Value (CV,%)	Solution	Tablet
C_{max}, ng/mL	3252 (26)	2762 (22)
t_{max}[1], hr	0.5	0.75

$AUC_{0\text{-last}}$, ng.hr/mL	8061 (21)	7723 (18)
$AUC_{0-\infty}$, ng.hr/mL	8186 (21)	7919 (17) [2]
$t_{1/2z}$, hr	8.34 (16)	8.39 (22) [2]
[1]Median values; [2]N=23		

Safety	Only one subject #250001021 experienced a non treatment-emergent adverse event (TEAE), considered not related to the study drug by the sponsor: moderate facial paralysis 12 days after the administration of the solution and lasting 10 days. The subject fully recovered without concomitant treatment. There were no serious adverse events (SAEs), or AEs leading to treatment discontinuation during the study period.
Conclusion	The solution and tablet formulations were not bioequivalent with respect to Cmax of inactive clopidogrel metabolite: the rate of absorption of inactive metabolite of clopidogrel was higher when the drug was administered as the solution compared with the tablet, resulting in a 15% higher mean Cmax (90% CI 1.02, 1.30) and a shorter median tmax (-0.14h). The compared treatments were bioequivalent in terms of extent of absorption (AUCs) of inactive clopidogrel metabolite.

Comments	• The bioequivalence and/or relative bioavailability between the solution and tablet formulation for the parent compound clopidogrel and for its active metabolite which is responsible for the pharmacodynamic effect is not established with this study. • The compositions of the formulation used in the relative BA study and the PICOLO and CLARINET studies are different (see the table below). While the differences in the formulation between the relative BA study and the PICOLO study are not significantly different, the formulation used in the CLARINET study is significantly different.

Table 2 - Formulation development overview

	Phase 1	Phase 2	Phase 3
Treatment duration	Single dose	7 to 28 days	up to 1 year
	Adults	Children	Children
Powder	(b) (4)		
Solvent			
Constitut solution			

(1) (b) ( )
(2) Initial solvent formulation for phase 2 (CMC amendment n°0433)
(3) Subsequent solvent formulation for phase 2 (CMC amendment n°0498)

Source: Table 2 of the sponsor report Quality Overall Summary-CMC-CL-2010-02698 2.0

- The aim of the relative BA study in the adults is to assess the impact of change in the formulation that is intended for administration in other pediatric studies. The current study did not assess the impact of the phase 3 formulation on the bioavailability of either clopidogrel's active metabolite of the main circulating metabolite. Since the formulations in adults were intended to be administered via oral route, the results of the relative BA study with Phase 1 - 3 formulations is unlikely to be different. The Phase 1/2 formulations contain (b) (4) while the pH of the Phase 3 formulation is (b) (4) rendering the solubility of clopidogrel in stomach and duodenum. It should be noted that the solubility of clopidogrel is highest at (b) (4) (see the table below). It is not unreasonable to expect that most of the absorption of clopidogrel occurs in stomach and duodenum based on the tmax of clopidogrel, active metabolite and SR26334 (30 – 45 mins) (Source: Dr. Uppor's review dated Oct 15, 1997, Dr.Mishina's review dated 2nd Nov, 2009).

- Differences in the relative bioavailability between Phase 1/2 and Phase 3 formulations can be expected in the CLARINET study as most of the neonates received clopidogrel via naso-jejunal route (email communication by Dr.Martin Rose on 12/20/2010). It should be noted that the Phase 3 formulation neither contains (b) (4) The pH of jejunum is 7 – 9 and the solubility drastically decreases to less than 1 mg/mL at pH above 3 and is practically insoluble at neutral pH (see table below). Thus, one can expect a lower bioavailablility when the Phase 3 formulation is administered via naso-jejunal route. This could be one of the factors for the lack of efficacy of clopidogrel.

(b) (4)

Source: Dr. Uppoor's review dated Oct 15, 1997

1.6 APPENDIX 2. Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
make.aspirindoseresponse.R	Aspirin dose-response analysis	Reviews\Ongoing PM Reviews\Clopidogrel_NDA20839_KMK\ER Analyses\ASA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KEVIN M KRUDYS
12/22/2010

ELENA V MISHINA
12/23/2010

PRAVIN R JADHAV
12/23/2010

RAJANIKANTH MADABUSHI
12/23/2010

Note: On Pages 3, 8 and 14, it is stated that "a substantial fraction fraction of neonates recieved NJ adminstration of clopidogrel "based on an email communication by Dr. Martin Rose.
In a later email Dr. Rose (22nd Dec, 3:25 PM) communicated that based on the available data, the proportion of patients recieving NJ administration of clopidogrel cannot be documented, hence, one cannot state that "a substantial proportion of neonates recieved NJ administration".