CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-839/S-051

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW

Office of New Drugs Quality Assessment

Application No.:	NDA 20-839/Supplement S-051 IND 34,663 (Clopidogrel Bisulfate)	**Reviewer:** Angelica Dorantes, Ph.D	
Submission Date:	July 15, 2010	**Supervisor:** Patrick J. Marroum, Ph.D	
Division:	DCRP	**Date of Review:**	January 11, 2011
Sponsor:	sanofi-aventis U.S. Inc.		
Trade Name:	Clopidogrel Bisulfate	**Type of Submission:** Efficacy Supplement ES-051 (Pediatric Exclusivity Request)	
Generic Name:	Plavix		
Indication:	Plavix is a P2Y12 platelet inhibitor indicated for: • Acute coronary syndrome • Recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease. Plavix has been shown to reduce the combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.		
Formulation/strength	Tablets/ 75 mg		
Route of Administration	Oral		
Type of Review:	**Evaluation of the pediatric formulation used in the CLARINET pivotal trial**		

SUBMISSION:

Plavix® (clopidogrel bisulfate) Tablets were approved by the Agency under NDA 20-839 on November, 17 1997. Plavix is an inhibitor of ADP-induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. In NDA 20-839/ Efficacy Supplement ES-051, sanofi-aventis is seeking the approval of additional six months exclusivity for Plavix® Tablets based on the data submitted in response to the pediatric written request. Data from the three following studies were provided in the ES-051 submission:

- A bioavailability study (BDR4580) comparing a liquid formulation suitable for pediatric administration to a 75 mg Plavix® tablet
- 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.
- 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 the CLARINET clinical study 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 bisulfate).

BIOPHARMACEUTICS:

The purpose of the Biopharmaceutics review is to evaluate the data supporting the acceptability of the pediatric formulation of clopidogrel bisulfate used in the pivotal clinical trial CLARINET and provide a recommendation.

Plavix Formulation: The formulation of the commercial Plavix 75 mg Tablets is presented in the following Table.

(b) (4)

[redacted]

Pediatric Formulations: The development history and overview of the clinical formulation used in the pivotal pediatric clinical trial, CLARINET are provided in the next summary tables containing all the formulation changes performed during the development of this pediatric formulation.

Pediatric Formulations - History of Formulation Changes

Clopidogrel Bisulfate - Active Powder		
Development Phase	**Dosage strength (expressed as base)**	**Formulation changes**

(b) (4)

[redacted]

Solvent for oral solution		
Development	**Deliverable**	**Formulation changes**
		(b) (4)

For the Phase 3 study intended for up to 1 year of treatment in neonates and infants, a (b) (4) multi-dose palatable constituted oral solution was developed. (b) (4)

Overview - Pediatric Formulation Development

	PHASE 1	PHASE 2	PHASE 3
Treatment Duration	**Single dose - Adults**	**7 to 28 days - Children**	**Up to 1 year - Children**
			(b) (4)

BIOAVAILABILITY Information:

The next table describes the composition of the three formulations used in the BA and pediatric studies.

Formulations Used in the Clopidogrel Pediatric Studies

	BDR4580 – BA Study	PDY4422 PICOLO Trial	EFC-5314 CLARINET Trial
Form	[redacted] (b) (4)		
Final concentration			
Constituted pH			
Buffer			
Solubilizer			
Flow enhancer			
Bioavailability Studies	**Yes** (Solution vs. Plavix tablet in adults)	**No**	**No**

BA Study: Study BDR4580 conducted in 2002, evaluated the relative bioavailability between the commercial clopidogrel formulation (Plavix® tablets, 75 mg) and the 75 mg solution of Clopidogrel (SR25990C) following single oral administration to young healthy men. The results from the BA study showed that the pediatric-solution formulation and Plavix® tablets commercial formulation were not bioequivalent with respect to Cmax of the inactive clopidogrel metabolite. The rate of absorption of the inactive metabolite of clopidogrel was higher when the drug was administered as solution when compared with the tablet, resulting in a 15% higher mean Cmax (90% CI 1.02, 1.30) and a shorter Tmax. The compared treatments were bioequivalent in terms of extent of absorption (AUCs) of inactive clopidogrel metabolite.

RECOMMENDATION:

ONDQA-Biopharmaceutics has reviewed the biopharmaceutic information supporting the pediatric-solution formulation of clopidogrel used in the pivotal clinical trial CLARINET provided in NDA 20-839/ Efficacy Supplement ES-051 for Plavix® Tablets and has the following comments:

Reviewer Comments:

1. ***It should be noted that at the time the BA study was conducted (2002) the assay for the active metabolite was not available. However, currently it is feasible to measure the parent compound and the active metabolite. Therefore, if we were to evaluate this BA study to currents standards, it would not be acceptable.***

2. ***Although, the pediatric formulation used in the CLARINET trial is a solution, it includes*** [redacted] (b) (4) ***is an inactive ingredient that has an effect on the small intestine transit (SIT) time and influences the bioavailability of the formulations, independently if they are solid dosage forms (tablets/capsules) or solutions. Increasing the rate of SIT reduces the time available for drug absorption and may contribute to impaired absorption of luminal contents. Therefore, the incorporation of an excipient like*** [redacted] (b) (4) ***into a pharmaceutical formulation would lead to reduced bioavailability.***

3. ***Additionally, there are other factors that may had affected the bioavailability of the formulation used in the CLARINET trial such as; 1) the lack of*** [redacted] (b) (4) ***in the formulation, 2) the precipitation of clopidogrel in the non-acidic environment of the small intestine, 3) the fact that the formulation used in***

the CLARINET study was administered via naso-jejunal route in some of the neonates. It is not known whether the pediatric clopidogrel solution administered via a naso-gastric or naso-jejunal tube results in the same bioavailability as the oral administration. The sponsor did not present any data to address this issue. At present, it is not known what levels of clopidogrel are achieved when the solution is administered through these routes.

4. ***The sponsor states that the all the clinical formulations developed and used during the pediatric program consisted of clopidogrel bisulfate in solution. Therefore, these formulations are considered pharmaceutical equivalent*. The sponsor is not correct, because the concentration of the active ingredient is different (b) (4) and the route of administration for some of the pediatric subjects was different (oral vs. naso-gastric or naso-jejunal tube), therefore, the formulations used in the pediatric program cannot be considered to be pharmaceutically equivalent. In addition of that the formulation used in the CLARINET trial also presents a potential bioavailability/bioequivalence problem. Therefore, the formulations used in the pediatric program are not pharmaceutically equivalent, nor therapeutically equivalent**.***

   Pharmaceutical Equivalents: *Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration.*

   ***Therapeutic Equivalents:** Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2)they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that(a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; (5) they are manufactured incompliance with Current Good Manufacturing Practice regulations.*

5. ***Although, the pediatric-formulation used in the BA study and the pediatric formulation used in the CLARINET pediatric-pivotal clinical trial are both solution formulations; because 1) the formulations are different, 2) the concentration of the active drug is different, 3) the percentage of (b) (4) an inactive ingredient presenting a potential bioavailability/bioequivalence problem is different, and 4) the route of administration was different for some pediatric patients; these formulations are not pharmaceutically nor therapeutically equivalent. Therefore, the pediatric formulation used in the pediatric trial CLARINET cannot qualify for a BA/BE waiver.***

6. ***In conclusion, contrary to the recommendation given in the pediatric written request* that clearly states that the relative bioavailability of the formulation to-be-used in clinical studies (each study) should be characterized; the applicant never evaluated the bioavailability of the pediatric formulation used in the CLARINET trial, neither the impact that the route of administration could have on the bioavailability of this pediatric formulation.***

   Pediatric Written Request - FORMULATION ISSUES
   The studies described below should use an age-appropriate formulation of clopidogrel. The relative bioavailability of this formulation should be determined, compared with the marketed formulation of clopidogrel. Full study reports of any relative bioavailability studies should be submitted to the Agency. If an age-appropriate formulation cannot be developed, complete documentation of your attempts and a detailed explanation of why the attempts were unsuccessful should be submitted. Under these circumstances, the use of a solid dosage form suspended in food or other formulations can be used, if it is standardized, palatable, and shown in adults to be of acceptable relative bioavailability (compared with the marketed product).

7. ***Overall, without having the data from a bioavailability study (****i.e., four way crossover study****) evaluating; 1) the BA of the approved Plavix® tablets vs. the pediatric formulation used in the CLARINET study using the oral route of administration, 2) the BA of the approved Plavix® tablets given by oral route vs. the pediatric formulation used in the CLARINET study administered by naso-gastric tube, and 3) the BA of the approved Plavix® tablets given by the oral route vs. the pediatric formulation used in the CLARINET study administered by naso-jejunal tube, one could speculate that these differences would not result in differences in bioavailability (resulting in dissimilar exposures), but one would never be able to provide a complete answer for the following relevant questions;***

   - ***WHY DID THE CLARINET TRIAL FAIL?***
   - ***WAS THE FAILURE DUE TO THE USE OF AN INADEQUATE FORMULATION?***
   - ***WAS THE ROUTE OF ADMINISTRATION A MAJOR CONTRIBUTOR TO THE TRIAL FAILURE?***

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: NDA 20-839/ES-051, M. Rose

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

/s/

ANGELICA DORANTES
01/12/2011

PATRICK J MARROUM
01/12/2011

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.
Clinical Pharmacology Reviewer	Elena V. Mishina, Ph.D.
Clinical Pharmacology Team Leader	Rajanikanth Madabushi, Ph.D.
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. A separate memo evaluating dose selection strategy in the context of the written request is provided in APPENDIX 3 of this review.

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).

1.3 Detailed Labeling Recommendations

Pharmacokinetic or pharmacodynamic information is not to be added to the label.

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.

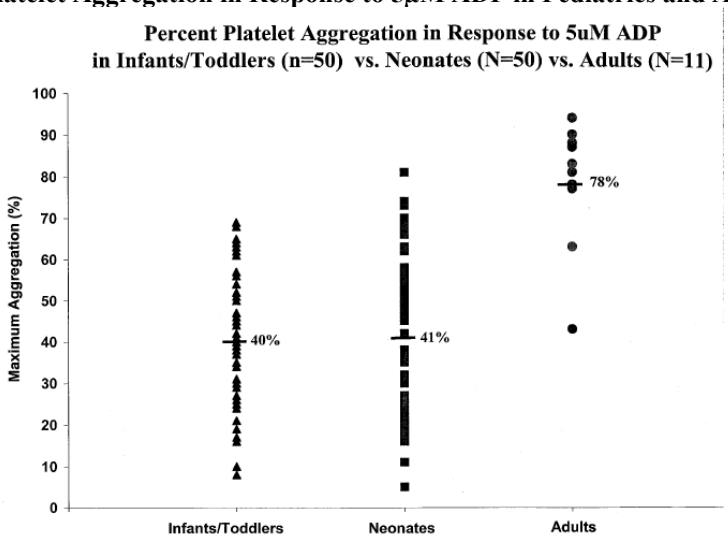
Table 1. Summary of maximum extent of ADP-induced platelet aggregation and inhibition by age group

	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. For a further discussion of this issue, please refer to Dr. Madabushi's memo (APPENDIX 3. Office of Clinical Pharmacology Memorandum).

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 (b) (4)

(b) (4). 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.

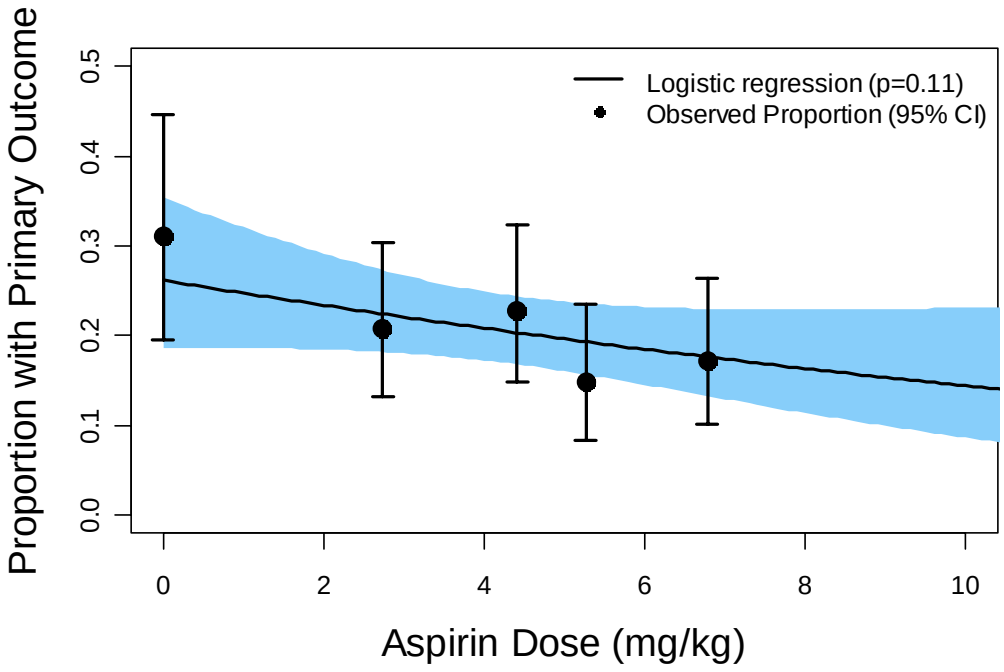


Table 2. Summary of primary outcome by concomitant aspirin use

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) (b) (4)	commercial clopidogrel formulation tablet (Plavix)
	Dosage Strength	75 mg	75 mg
	Batch #.	CL-04719 (b) (4)	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:

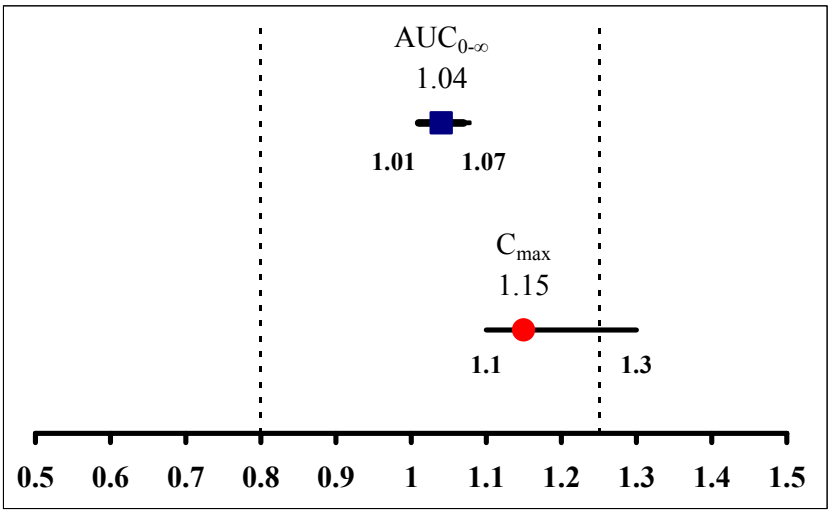


Figure 3. Results of statistical analysis. X-axis represents the geometric mean ratios. The fine broken vertical lines represent 80-125% BE limits. Data is represented as geometric mean ratio of BE metrics. Cmax, AUC_{0-last}, $AUC_{0-\infty}$) with 90% CI around the point estimate

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)	
	$AUC_{0\text{-}\infty}$, 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
			(b) (4)

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

1.7 APPENDIX 3. Office of Clinical Pharmacology Memorandum

MEMORANDUM
DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE:	October 25, 2010
FROM:	Rajanikanth Madabushi, Ph.D., Team Leader DCP1, Office of Clinical Pharmacology (OCP).
TO	Lawerence J Lesko, Ph.D., Director, OCP.
THROUGH:	Mehul U Mehta, Ph.D., Director, DCP1, OCP. Jogarao VS Gobburu, Ph.D., Director, DPM, OCP.
SUBJECT:	Office position with regard to the dose selection of clopidogrel based on the results of **P**latelet aggregation **I**nhibition in **C**hildren **o**n Cl**o**pidogrel (**PICOLO**) study.
REFERENCE:	NDA 20839/S051

The efficacy of clopidogrel (0.2 mg/kg) in children was evaluated in a multinational, randomized, placebo-controlled, double-blind, event driven trial (**CLARINET**), involving 906 neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt. The study showed no statistically significant differences between the treatment groups in the incidence of the primary efficacy endpoint of death, shunt thrombosis, or cardiac procedure prior to 120 days considered to be of a thrombotic nature or among the components of the primary endpoint, except for death, for which there was a trend for fewer events with clopidogrel.
The dose selected for the CLARINET trial was based on a dose-ranging PD study (PICOLO) in neonates and infants/toddlers at risk for thrombosis. Hence it is important to understand whether the dose selection was appropriate based on the results of the PICOLO study.

Conclusion:
Based on the results of the PICOLO study and the baseline differences, a different strategy for dose selection could have been adopted.

Salient Points:
- Given the baseline differences to ADP agonism between neonates, infants/toddlers and adults, it is not clear as to why the sponsor did not reconsider their dose selection strategy. Several hypotheses can be put forward to explain the impact of the differences in PD response at baseline.

- The platelets of newborns and children do not differ significantly from those of adults in number[1]. However, platelets derived from neonates display a decreased response to platelet agonists such as collagen, thrombin, ADP, and epinephrine[2,3]. These differences in platelet activation have been shown to be, at least in part, the result of impaired receptor-mediated signal transduction in thromboxane synthesis, G protein-mediated response, and intracellular calcium mobilization [2,3,4]. Sponsor states that these results suggest that lower weight-adjusted dose may be required in neonates to achieve the same level of platelet inhibition compared to older children and adults. It should be noted the American College of Chest Physicians (ACCP) recommends Aspirin at a dose of 1 – 5 mg/kg/day for pediatric patients having a modified Blalock-Taussig shunt (Grade 2C). This dose is reasonably similar to that used in adults (81 mg – 325 mg/day).
- Given that the baseline responses to ADP induced platelet aggregation are different, it is not unreasonable to expect a 30 % - 50% inhibition of platelet aggregation to result in different clinical effects in adults and neonates, infants/toddlers. This provides basis for studying higher doses.
- In the PICOLO study, 8 of the enrolled subjects were not randomized as the baseline response to 5 μM ADP was less than 20%. Based on the hypo-responsiveness one can hypothesize that the ADP-dependent path way is not a prominent pathway to inhibit platelet aggregation in neonates and infant.

- Initially the doses planned for PICOLO study were 0.01 mg/kg, 0.1 mg/kg and 1 mg/kg. This was based on the WR issued in 2001. The WR stipulated, the initial 3 doses used in the study should have provided a 10-fold difference between dose levels. However, if the lowest dose group provided little or no effect in the first few patients, modification of this dosing plan was acceptable in order to establish more rapidly doses of clopidogrel with effects on platelets aggregation in the population. The actual administered doses were 0.01, 0.1, and 0.2 mg/kg, and 0.15 mg/kg in neonates. It should be noted that the initial 3 doses studied do not provide a 10-fold difference between the dose levels. There is no clear rationale for the choice of 0.2 mg/kg.
- Even though it is not unreasonable to choose 5μM ADP (most of the adult PK/PD studies have been conducted with 5 μM and 10 μM ADP as agonists) as the agonist, there is no clear rationale for the choice. Given the baseline findings, it would have been appropriate to explore various concentrations of the ADP and select the appropriate concentration of ADP that would provide reasonably similar baseline response.

---

[1] Israels SJ, Rand ML, Michelson AD. Neonatal platelet function. Seminars in Thrombosis and Hemostasis 2003;29 (4):363-71.
[2] Israels SJ, Michelson AD. Antiplatelet therapy in children. Thromb Res 2006;118:75-83.
[3] Rajasekhar D, Kestin AS, Bednarek FJ, Ellis PA, Barnard MR, Michelson AD. Neonatal platelets are less reactive than adult platelets to physiological agonists in whole blood. Thrombosis and Hemostasis 1994;72(6):957-63.
[4] Israels SJ, Cheang T, Robertson C, McMillan EM, McNicol A. Impaired signal transduction in neonatal platelets. Pediatr Res 1999;45(5):687-91.

Regulatory History:
Following the completion of the PICOLO study, the sponsor submitted the protocol for the CLARINET study for Special Protocol Assessment (May 10, 2006). The sponsor stated that the PICOLO study formed the basis for dose selection. The sponsor also indicated that three doses (0.01, 0.1 and 0.2mg/kg per day) had been tested in 30 infants and 20 neonates and the dose of 0.2 mg/kg per day was found to be the dose to achieve a mean of 30-50% inhibition of ADP-induced platelet aggregation. It should be noted that the results of the PICOLO study were not available for complete review at this time. This was followed by an EOP2 meeting with sponsor on July 12th, 2006 for further discussions. As a part of the preliminary responses to the questions, the following was communicated by the Agency on July 6th, 2006:

"Does the Division agree that the pharmacodynamic findings in neonates and infants/toddlers are comparable to that in adults and that no additional PD studies are required in the three other pediatric age groups?
Preliminary Response:
We believe you have adequately identified a dose of clopidogrel in neonates and toddlers that achieves about 50% inhibition of ADP-induced platelet aggregation.
We ask that you give a response to the following questions:
What is the level of platelet aggregation achieved with 5 micrograms of ADP as a function of age (neonates to adults)?
It appears that the target dose of clopidogrel would be about 0.2 mg/kg in neonates, while it is about 1 mg/kg in adults. How do you propose to justify dose selection for children of intermediate age?"

The following responses were provided by the sponsor in response (Meeting Minutes DARRTS date: 8/8/2006):

Sponsor comments :

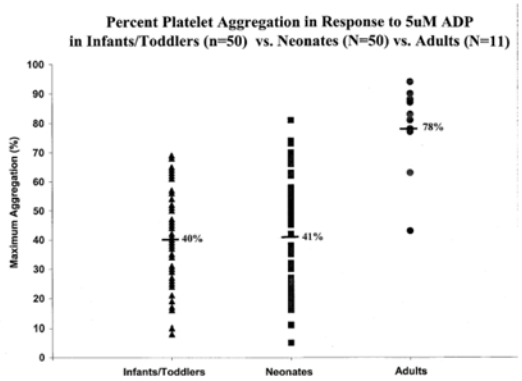
- **These age groups are outside of the scope of the indication mentioned in the written request**
- **There is no homogeneous population in older age groups where clopidogrel may be used**
- **The applicability of the previously determined 0.2 mg/kg dose outside of the pulmonary-systemic shunt indication cannot be assessed as not only the age but also the condition may impact on platelet reactivity and inhibition**
- **Therefore, the sponsor suggests that the evaluation of the 3 older age groups be waived from the written request**

The Agency reiterated the need for understanding the baseline response and the role it plays in selecting doses for the efficacy trial ((Meeting Minutes DARRTS date: 8/8/2006):

*"**Dose range and study of other age groups***

Dr. Stockbridge asked the sponsor to provide data from their platelet inhibition study to show the agonist effect of ADP in neonates. If the response in neonates is similar to that in adults, then the dose range seems reasonable. If it is markedly less than in adults, the premise for the study may need to be reconsidered."

On October 26th, 2006, sponsor provided clarification to of Agency's minutes. In addition to other issues discussed, the sponsor provided the following in response to the above comment:



It should be noted that no attempts were made to highlight the differences in baseline response to 5 µM ADP between neonates, infants/toddlers and adults. Further, the need to reconsider the premise of the study in light of the results was not justified. There is no documented review by the OCP in response to this information.

An amended Written Request (WR) was issued on 24th August, 2007. The amendment addressed the issues related to the PK/PD measurements and the need to study other age groups. The issue of dose selection was not addressed at this time.

Brief description of PICOLO study:
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. A total of 116 patients were enrolled into the study of which 92 were randomized. Steady-state (7 days of treatment) pharmacodynamics information was available in 73 patients (N = 34 infants and N = 39 infants/toddlers).
The patients were randomized to receive one of the 4 doses of clopidogrel (0.01, 0.1, 0.15 and 0.2 mg/kg per day) or placebo. The dose of 0.15 mg/kg in neonates was recommended by the steering committee following the results of 0.2 mg/kg.

The primary objective of this study was a PD assessment to determine the dose of clopidogrel to achieve a mean 30 to 50% inhibition of 5 μM ADP-induced platelet aggregation (ie, to provide inhibition of platelet aggregation similar to that observed with 75 mg in adults) in neonates and infants/toddlers at risk for thrombosis. The key results of the study are presented in the table below:

Table 1: Summary of maximum extent of ADP-induced platelet aggregation and inhibition by age group (PP population). *[Source: Sponsor report CSR_BDY-PDY4422-EN-E01.pdf, Table 8.1.1.1 on page 52]*

	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]

[a] % inhibition = [100 * (baseline – steady state)/baseline]

Similar results were seen with the rate of ADP-induced platelet aggregation for neonates. The percent inhibition was comparatively lower in infants/toddlers (38% compared to placebo). Based on the above results the sponsor concluded that at a dose of 0.2 mg/kg clopidogrel achieved the target of 30 to 50% inhibition of 5 μM ADP-induced platelet aggregation in neonates or infant/toddlers at risk of thrombosis.

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".