

Medical Officer's Review

(b) (4)

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Pediatric Written Request – clopidogrel for the reduction of the incidence of thrombosis in children with systemic to pulmonary artery shunts for palliation of cyanotic congenital heart disease (submitted in eCTD format only).
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RPM: Alison Blaus
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OPC reviewer: Elena Mishina
Biometric reviewer: Yeh Fong Chen
Sponsor: sanofi aventis
Product: Plavix (clopidogrel bisulfate)

1 Executive summary

This submission is (b) (4) the amended final PWR for clopidogrel dated 24 Aug. 2007 regarding a development program for clopidogrel for use in the reduction of the incidence of thrombosis in children with systemic to pulmonary artery shunts for palliation of cyanotic congenital heart disease. (References to “the PWR” shall mean the aforementioned PWR unless otherwise specified.) The submission contains (b) (4)

No new indication or formulation is proposed for marketing. (b) (4)

The studies performed by the sponsor in its pediatric development meet the literal requirements of the PWR. However, the sponsor ignored one of the advice terms in the PWR: “Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.” Of the three formulations (all were solutions) used in the pediatric program studies, only one (used only in the initial comparative BA study in adults) was evaluated with respect to BA. The other two formulations, including one used in the Phase 2 PD dose-finding study (PICOLO) and one used in the safety and efficacy study (CLARINET) were not evaluated for bioavailability. The PICOLO formulation was quite similar to the Phase 1 formulation. The CLARINET formulation was quite different from both previous formulations, and there are reasons to believe that its BA may have been less than that of the other formulations due to the possibility of precipitation of clopidogrel in the non-acidic environment of the small intestine. While it is not certain that the BA of CLARINET formulation is less than of

the other solutions used in the pediatric program, the level of concern is certainly great enough to warrant performance of a BA study. The lack of such information for the formulation used in the single safety and efficacy study (which showed no significant difference between clopidogrel and placebo for the primary efficacy endpoint as well for the rate of bleeding, findings that are consistent with lack of sufficient exposure to clopidogrel), constitutes lack of accordance with good scientific principles, (b) (4)

OCP has suggested that clopidogrel is absorbed to a considerable extent in the stomach and duodenum. In adult volunteers, the pH the duodenum varied over the course of a day, but was usually 4 or more; clopidogrel is very poorly soluble at these levels of pH. I am unaware of relevant data in pediatric patients. Additional input from OCP and perhaps the sponsor would be useful. Nonetheless, the uncertainty about the BA of the CLARINET formulation is sufficient to conclude at this time that a BA study should have been done.

There were other problems with the design and execution of the sponsor's studies that lead to the conclusion that these studies were not conducted in accordance with good scientific principles. The first is that there were substantial delays in the randomization for many patients in CLARINET. About 49% of patients were randomized more than two weeks after their index surgery, and 23% were randomized more than four weeks after their surgery. Primary event rates are higher in the first few weeks after surgery than later, but the study was event driven. Thus, late study entry would be problematic only if there was a differential effect of clopidogrel on early vs late events, and there is no evidence of such a differential. Notably, study data do not demonstrate an effect of time from surgery to randomization on the primary endpoint results, but the study was not powered for this analysis. However, the delays in randomization must have reduced the study's power to detect an effect of study treatment on early events. Data from DSI's site inspections reveals that patients given aspirin tended to be randomized considerably after the patient was started on oral or enteric aspirin therapy; the two drugs could have been started at the same time. The sponsor could have prevented these delays by revising the protocol's language about the timing of randomization and/or by targeted, aggressive site management, neither of which were attempted.

Another area of concern is that the sponsor failed to appropriately make us aware of PD data that were requested by the Division that suggested that patients in the target population had substantially reduced platelet aggregation responses to ADP compared to adults, and thus might not get as much benefit from clopidogrel as adults with increased risk for thrombosis. If we had been aware of the data, we might have requested additional PD data from children, changed our view of the appropriate dosing paradigm, or possibly even determined advised the sponsor that further study in target indication would be futile. The sponsor did submit the requested data, but in a manner that reduced the likelihood that we would identify it as what we requested. We are not blameless here, (b) (4)

Nonetheless, the sponsor's conduct was not in accordance with good scientific principles.

Finally, the above defects in the pediatric program, particularly those affecting CLARINET, led us to determine that the study's results are inconclusive and that they neither confirm nor rule out a beneficial effect of clopidogrel for the shunt palliation indication. The sponsor's pediatric program thus failed to meet the program's underlying goal as expressed in the PWR, which is to "... provide guidance for the use of clopidogrel in the reduction of the incidence of thrombosis in children with systemic to pulmonary artery shunts for palliation of cyanotic congenital heart disease." The results of the flawed CLARINET study provide no definitive guidance on the use of clopidogrel for the target indication (b) (4). Thus,

the pediatric program as a whole fails to fairly respond to the PWR.

Recommendation:

(b) (4)

2 Background -- Shunt palliation and thrombosis

Heart defects are the most common birth defects as well as the most common cause of birth defect related deaths. It is estimated that 1 out of 124 infants are born with heart defects in the US, or about 35,000 such births per year. Repair of some heart defects is performed immediately in the neonatal period. However, some babies with CCHD such as the hypoplastic left heart syndrome, may be treated in stages. The first stage, often performed within days of diagnosis, is a palliative procedure with placement of a systemic to pulmonary artery shunt (STPAS) to provide blood flow to the lungs. Such shunts may be created with synthetic materials or with re-routed native vessels such as a subclavian artery. The take-off point of these shunts may be the aorta, a thoracic vessel such as the left subclavian artery, or the ventricle supplying the systemic circulation (which may be the only functional ventricle), in which case the shunt is termed a Sano shunt. The insertion point is usually a proximal pulmonary artery.

The shunt is maintained until the patient is ready for more extensive heart and vascular surgery. In patients with hypoplastic left heart syndrome (HLLS), usually the most common form of CCHD, the next stage procedure is generally performed after age 4 months because earlier procedures are thought to have worse outcomes, although not all authorities agree on this point. The second procedure for HLLS patients is usually a bi-directional Glenn procedure, which creates an anastomosis between the vena cavae and a pulmonary artery, bypassing the heart. The STPAS is then unnecessary to provide blood flow to the lungs and is taken down at this point.

The STPAS is prone to thrombotic occlusion, which may be sudden or gradual. Many authorities recommend the use of aspirin to prevent shunt thrombosis on the basis of observational data; no controlled studies have been performed. Nonetheless, the current guidelines of the American College of Chest Physicians suggest that antiplatelet therapy is beneficial for patients with STPAS, as well as those with Fontan procedures, heart valves, or cardiac assist devices, and also for patients with ischemic stroke or Kawasaki disease. Authorities recommend the start of aspirin therapy at various times soon after shunt placement surgery, ranging from the day of surgery (given rectally at first, then switched to oral or via feeding tube (enteric)) to within 3 days of surgery (oral or enteric) or when goal feeds are attained (oral or enteric). Despite the widespread use of aspirin after STPAS placement, thrombosis remains a problem. In a recent publication, rate of death and thrombotic complications following STPAS placement was about 38% in the first year.¹

Because the sponsor and FDA agree that the study failed to establish a benefit of clopidogrel for use in shunt palliation, the safety and efficacy data in the supplement will be reviewed in an abbreviated fashion.

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¹ Li JS, Yow E, Berezny KY et al. Clinical outcomes of palliative surgery including a systemic-to-pulmonary artery shunt in infants with cyanotic congenital heart disease: does aspirin make a difference? *Circulation* 2007;116:293-297.

3 The Pediatric Written Request

Discussions between the Division and the sponsor about a pediatric development program for the shunt palliation indication began in early 2000. A formal PWR for a shunt palliation program was issued on 15 October 2001. This was followed up by the modified, amended final PWR on 24 August 2007. The final PWR clearly states that it supersedes the original PWR, so it will be focus of the following discussion.

The verbatim elements of the PWR and a point-by point analysis of whether they were met are provided in the tabular “Annotated PWR” (Appendix 1). A summary description of the PWR follows:

The substantive part of the PWR led off with a goal expressed as follows: “The requested data will provide guidance for the use of clopidogrel in the reduction of the incidence of thrombosis in children with systemic to pulmonary artery shunts for palliation of cyanotic congenital heart disease.”

This was followed by a description of the data needed to implement the goal:

- Performance of a steady-state pharmacodynamic (PD) dose-ranging study in pediatric patients at risk for thrombosis who are in the age groups treated with a systemic to pulmonary artery shunt (neonates, age < 1 month, and infants/toddlers, age 1-24 months). This trial will provide for the selection of an appropriate dose for an efficacy and safety, placebo-controlled study in patients with systemic to pulmonary artery shunts.
 - The goal of this study is to identify a dose providing steady state inhibition of platelet aggregation similar to that observed in adults taking clopidogrel (i.e., 30 to 50% inhibition of ADP-induced platelet aggregation).
 - The initial three doses used in the study must span a 10-fold range; however, if the lowest dose group provides little or no effect in the first few patients, modification of this dosing plan is acceptable in order to establish more rapidly which doses of clopidogrel have effects on platelet aggregation in the population.
- Completion of an event-driven efficacy and safety placebo-controlled clopidogrel study in patients with systemic to pulmonary artery shunts. An age appropriate dosage form should be used.
 - Dose levels for use in this study will be determined by a joint agreement between the sponsor and the Division, based upon the dose-response data in the pilot dose-ranging study.
 - As there is no standardized care in this patient population, additional therapy must be in accordance with the usual practice of the institution (i.e. plus or minus concomitant aspirin).
 - A composite primary endpoint was specified:
 - Death from any cause
 - 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 thrombotic in nature.
 - A relative risk reduction of 30% is acceptable for the power calculations.
- Submission of a supplement summarizing all data available on the use of clopidogrel in patients undergoing STPAS placement, as well as a comprehensive safety evaluation of

clopidogrel use in children. This should include a summary of the published literature and also formal analyses of the available published and unpublished safety information. Examples of sources for unpublished safety information include institutions or organizations that systematically collect such data as part of their healthcare delivery to pediatric populations.

- Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults. This was not highlighted in the PWR letter, so it was advice, rather than a requirement.

With the exception of bioavailability data for the (differing) formulations used in the Phase 2 and efficacy and safety studies, all of requested specific data items were submitted. The solution formulation used in the safety and efficacy study differed in important ways from the formulations used in the earlier pediatric studies. It was never evaluated for bioavailability. There are reasons to believe it might have been substantially less bioavailable than those formulations. This means that patients in the safety and efficacy study may not have had sufficient exposure to clopidogrel. Also, the goal of the PWR – to provide guidance on the use of clopidogrel for the target indication of shunt palliation -- was not met due to flaws in the design and execution of the required safety and efficacy study. These defects and others are discussed below.

4 Reports of studies submitted by the sponsor

4.1 Bioavailability Study BDR4580

The sponsor's first major initiative in the development program was to develop an age-appropriate formulation. The pediatric formulation used in BDR4580 was a (b) (4) (formulation SR25990C). Each dosing unit contained the equivalent of 75 mg clopidogrel base plus excipients (b) (4).

BDR4580, performed at a single center in France in 2002, was a single-dose oral bioavailability study in 24 healthy male volunteers age 18-40 years, comparing clopidogrel solution (75 mg, SR25990C) to a commercial Plavix 75 mg tablet. This study was not required by the PWR, but was important to the program. The study had a straightforward open-label, randomized, crossover design and analysis plan. The two single-dose treatment periods were separated by a 14 day washout. The solution was prepared extemporaneously. Study drug was given at 8 AM under fasting conditions with 200 mL water. The first meal each treatment day was at noon. From T0 to T48 (hours), 22 blood samples were drawn for PK analysis. The bioavailability of the 2 formulations was assessed using the pharmacokinetic parameters of the main circulating metabolite of clopidogrel (SR26334).

Key PK results are shown in Table 1 (reproduced from the study report).

²(b) Pursuant to an agreement with the Division, Module 3 (Quality) was not submitted as part of the supplement under review, but the submission included a Quality Overall Summary with summary information about the various formulations used in the sponsor's pediatric program.

Table 1. PK parameters of SR26334 in study BDR4580 (N=24)

Pharmacokinetic Parameter Mean (CV%)	Solution	Tablet	Ratio estimate _b	90% CI of Ratio Estimate
C _{max} (ng/ml)	3252 (26)	2762 (22)	1.15	[1.02;1.30]
t _{max} (h)	0.5	0.75	-0.14	[-0.25;-0.09]
AUC _{last} (ng.hr/mL)	8061 (21)	7723 (18)	1.04	[1.01;1.07]
AUC (ng.h/mL)	8186 (21)	7919 (17) _c	1.04	[1.01;1.07]
t _{1/2Z} (h)	8.34 (16)	8.39 (22) _c	NC	NC

NC=Not calculated

a Median values for t_{max}

b Geometric mean values of the ratios (solution / tablet) for C_{max}, AUC_{last} and AUC and Hodges-Lehmann estimator of the difference (solution - tablet) for t_{max}

c n=23

The data indicate that the point estimate for the solution C_{max} was 15% higher and the t_{max} was 15 minutes sooner than for the tablet. AUC and AUC_{last} were higher also higher for the solution, but the differences from the tablet were quite small.

The sponsor decided to move forward with the solution formulation, which would be intended for either oral or upper GI feeding tube administration pediatric patients. Note that this was the only bioavailability study in the pediatric package; each of the three studies reported in the supplement used a different (b) (4) solution of clopidogrel (b) (4) but only the solution described above was evaluated in a bioavailability study. The sponsor assumed that all the (b) (4) solutions would have similar bioavailability. This validity of this assumption is under review by Clinical Pharmacology.

Reviewer comment: The decision to move ahead with a (b) (4) solution with the BA characteristics of the solution used in BDR4580 was reasonable, but the sponsor's assumption that all 3 of the solutions used in the pediatric program had similar bioavailability (made without BA testing of the last two formulations) may not have been reasonable.

4.2 Pharmacodynamic study PDY4422 (title: 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))

This randomized, double-blind, placebo-controlled Phase 2 study was intended to satisfy the PWR's requirement for a dose-finding PD study. It was performed from January 2004 to April 2006, and enrolled 92 patients at 22 centers in 6 countries in North America and Western Europe.

The clopidogrel formulation used in this study was similar to the one used in BDR4580 except that (b) (4) during the course of the study. This formulation was not evaluated in a comparative PK study, but PK samples were drawn during the study.

Reviewer comment: This reviewer believes the differences between the BDR4580 (bioavailability study) formulation and the final PICOLO formulation are unlikely to affect bioavailability. This issue is under review by CP.

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 μ M ADP-induced platelet aggregation in neonates or infants/toddlers at risk for thrombosis.

The secondary objectives of the study were to assess pharmacokinetics (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. Additionally, in patients with a total body weight above 3 kg, changed by Amendment 01 to above 5 kg as per Investigator judgment, the percent inhibition of maximum extent and rate of aggregation of 5 μ M thrombin receptor activating peptide (TRAP)-induced platelet aggregation was determined.

Study patients were neonates (less than or equal to 30 days of age) or infants/toddlers (up to 24 months of age) at risk for thrombosis (eg, patients with a Blalock-Taussig shunt, Kawasaki disease, or vascular stent, or any pathological condition that required antiplatelet therapy).

The planned doses of clopidogrel for assessment were 0.01, 0.1 and 1.0 mg/kg/day by mouth or by feeding tube (enteric) for up to 28 days. Dosing was started at the lowest dose (with randomization to drug or placebo) and then escalated after unblinded review of data by the Pharmacodynamic Assessment Committee (PAC), with endorsement by DSMB. Escalation could occur before the completion of 12 patients at a dose level if PD effects with concurrence by the PAC, DSMB and the study Steering Committee at (but only PAC and DSMB concurrence were needed to escalate early out of the first dose level). Randomization was 3:1 (drug to placebo); it was planned to collect efficacy data from 9 patients on drug and 3 on placebo at each dose level in each of the two age strata (neonates and infants/toddlers), for a total of 6 x 12 = 72 patients.

The primary efficacy criterion was percent inhibition of maximum extent and rate of aggregation of 5 μ M ADP-induced platelet aggregation. In patients above 3 kg (later amended to 5 kg) body weight, the percent inhibition of maximum extent and rate of aggregation of 5 μ M TRAP-induced platelet aggregation were also determined. The target level of platelet aggregation inhibition was 30-50%, similar that achieved with a 75 mg dose of clopidogrel in adults. 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.

Blood samples for the determination of the plasma concentrations of SR26334 were collected on:

- Day 1, T0.17 to 0.5 h, T1 to 3 h, T6 to 12 h, and T12 to 24 h post dosing;
- Day 7 to 28.

PK parameters could be analyzed for any randomized and treated patient.

4.2.1 Pharmacodynamic results

There were 92 patients randomized; 86 of these received at least one dose of study drug and comprised the safety population. Efficacy (PD) data was obtained from 73 patients (72 were planned) and PK data from 66.

Because platelet aggregation with the 0.1 mg/kg dose was approaching target levels, the next dose level was 0.2 mg/kg in infants/toddlers and 0.15 mg/kg in neonates. Also, there were 10 neonates contributed efficacy data at the 0.2 mg/kg dose level. This was the highest dose level used in the study in either age group.

Platelet aggregation data are displayed in Tables 2 and 3 (reproduced from the study report).

Table 2. PICOLO – Platelet aggregation data (neonates and infants/toddlers combined)

	Placebo (N=16)	Clopidogrel			
		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

For both age strata combined, the 0.2 mg/kg dose was associated with 49.3% (27.2) mean platelet inhibition (SD), significantly better than placebo (0.8% (48.0)), $p < 0.0001$). Neonates, with a mean platelet aggregation inhibition of 62.1% (24.5), slightly larger responses to clopidogrel than infants/ toddlers, with a mean inhibition of 40.% (26.1). Because the target range of 30-50% inhibition of aggregation was approximated in each age group at a dose of 0.2 mg/kg, the study was stopped when these results became available.

Table 3. PICOLO – Platelet aggregation data by age stratum

Table (8.1.1.1) 1 - Summary of maximum extent of ADP-induced platelet aggregation and inhibition by age group (PP population)

	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]

PGM= SR25990C/PDY4422/CSR/BS/PGM RPT/i6pltagg1age.sas OUT= OUTPUT/i6pltagg1age.html (31MAY2006 – 14:18)

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

N.A. = not applicable

It is notable that the baseline platelet aggregation, about 40% for all studied patients, appears quite different from the roughly 80% value usually seen in adults. This suggests that the study patients, many of whom were STPAS patients, had platelets that responded relatively poorly to 5 µMol ADP in vitro. This will be discussed further below.

TRAP-induced platelet aggregation was 52.6% in neonates (n=1) and 11.8% in infants/toddlers (n=5) with the 0.2 mg/kg dose. There was an apparent dose response (data not shown).

4.2.2 Safety data

The safety profile of clopidogrel was acceptable. There were no severe bleeds in any study patient. Two patients in the placebo group and 2 in the clopidogrel group (at 0.01 and 0.2 mg/kg) experienced minor bleeding (e.g, blood in stool with no change in hematocrit or hemoglobin level). The most common AEs were non-bleeding GI disorders, mostly vomiting (9.5% in the placebo group vs. 40% for clopidogrel (all doses combined). There was no apparent dose response for vomiting.

Eight treatment-emergent serious adverse events occurred in 6 patients during the course of the study (3 serious adverse events in 3 patients receiving placebo and 5 serious events in 3 patients receiving active clopidogrel). In the placebo group, 1 case each of increasing congestive heart failure, sepsis, and shunt thrombosis was reported. In the clopidogrel treatment group, oxygen desaturation (at and 0.20 mg/kg), decrease in platelet count (at 0.01 mg/kg), and one patient with bradycardia hypotension and oxygen saturation (at 0.15 mg/kg) were reported. The last of these patients received 4 doses of the study drug and died after experiencing these events. The death was judged by the site investigator as unrelated to the study drug. Only the decrease in platelet count was considered “possibly related” to study treatment by the investigator.

4.2.3 PK data

Not all patients contributed PK data due to problems in obtaining blood from the babies enrolled in the study. Table 4 provides data on blood levels of SR26334 on the first dosing day at a time intended to approximate T_{max} . Metabolite blood levels were below the LLQ for all patients who received 0.01 mg/kg. Patients in the higher dose groups had less than dose proportional blood levels of SR26334 than the adults in BDR4580 who received 75 mg of clopidogrel either in solution or in a tablet (about 1 mg/kg).

Reviewer comment: Many of these may not have been true Cmax samples. The high mean for the 0.15 mg/kg group was said to be due to the results from one outlier.

Table 4. PICOLO -- Mean SR26334 Cmax values on day 1

10.1) 1 - Descriptive statistics of SR26334 C_{max} values (ng/mL) observed on Day 1 by dose level and age group

	Clopidogrel			
	0.01 mg/kg	0.1 mg/kg	0.15 mg/kg	0.2 mg/kg
Neonates				
N	2	6	6	5
Mean (SD)	BLQ	9.9 (3.31)	221 (426)	42.3 (35.7)
Geometric Mean	-	9.4	71.4	30.7
CV%	-	34	192	84
Infants/toddlers				
N	4	3	0	8
Mean (SD)	BLQ	17.5 (23.2)	-	53.4 (33.0)
Geometric Mean	-	19.5	-	38.7
CV%	-	133	-	62
Overall				
N	6	9	6	13
Mean (SD)	BLQ	12.4 (12.4)	221 (426)	49.2 (33.0)
Geometric Mean	-	11.3	71.4	35.4
CV%	-	101	192	67

SD = standard deviation

CV = coefficient of variation

BLQ = below the limit of quantification

4.3 Efficacy and safety study – EFC5314 – “International randomized double-blind clinical study evaluating the efficacy and safety of clopidogrel 0.2 mg/kg once daily versus placebo in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt (eg, modified Blalock Taussig shunt) (CLARINET)”

This was the single safety and efficacy study in the sponsor’s development program for clopidogrel. It was global, randomized, placebo-controlled, double-blind trial assessing the effects of clopidogrel 0.2 mg/kg/day by mouth or via feeding tube on a composite endpoint of death and thrombotic complications in neonates and infants/toddlers with CCHD who were surgically treated with a STPAS.

4.3.1 Formulation

The clopidogrel formulation used in this study was substantially different from the ones used in BDR 4580 (the comparative bioavailability study) and in PICOLO. The CLARINET formulation, like the PICOLO formulation, was not characterized for bioavailability. Table 5 describes features of the 3 formulations.

Table 5. Formulations used in the clopidogrel pediatric studies

	BDR4580 – Comp. bioavailability study	PDY4422 – PICOLO	EFC-5314 – CLARINET
Form	(b) (4)		
Final concentration			
pH			
Constituted pH			
Buffer			
Solubilizer			
Flow enhancer			
Bioavailability assessed?	Yes – vs. 75 mg Plavix tablet in adults	No	No

Comp. – comparative

Reconst. – reconstituted

* The formulation was changed during the course of PICOLO

(b) (4)

For additional discussion of the formulation issue, please refer to Sec. 4.4.1.

4.3.2 Design

CLARINET had 134 enrolling sites in 31 countries on every inhabited continent except Australia. The principal coordinating investigator and Chair of the Steering Committee was David Wessel of National Children’s Medical Center (Washington). The study ran from November 2006 to February 2010.

The primary objective was to evaluate the efficacy of 0.2 mg/kg/day of clopidogrel versus placebo 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. The secondary objective was to determine the safety of clopidogrel in the study population.

Patients were neonates or infants (age less than 93 days at randomization) with a STPAS for palliation of CCHD. Medically important exclusion included active bleeding or increased risk of bleeding due to bleeding disorders, AV malformations, previous intra-cranial bleed (Grade II-IV) or life-threatening hemorrhage, gestational age < 34 weeks, neutropenia, severe hepatic or renal failure (hepatic enzymes or creatinine > 2.5 x ULN for age), or inability to receive study drug orally or enterically (by feeding tube).

Eligible patients were to be randomized “as early as possible after shunt placement” to clopidogrel solution, 1mg/ML, at a dose of 0.2 mg/kg daily or placebo. The dose was to be adjusted for weight every 2 weeks up to the 12 week visit, and then every month. Dosing was to be maintained up to age 1 year, the next surgical procedure for the treatment of CHD, or the occurrence of a primary endpoint event. Treatment could be discontinued temporarily for AEs and restarted if appropriate in the judgment of the investigator. Patients were to be followed up until the final visit, defined as age of 1 year, the common study end date, occurrence of shunt thrombosis, or the next surgical procedure for CHD.

Use of the site’s customary anti-thrombotic regimen (heparin, LMW heparin, and/or aspirin in most cases) was allowed, but no concurrent use of non-study antiplatelet drugs other than aspirin was allowed. NSAID use was to be avoided as much as possible.

Study visits occurred at weeks 4, 12, 24, 36 and the final visit. Phone follow-up occurred at 2 week intervals until week 12 (except for visit weeks) and then every 4 weeks (except for visit weeks). and then every 4 weeks until the final visit.

The primary endpoint was the first occurrence of the composite endpoint of:

- Any death (or a heart transplant);
- 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. This component was adjudicated by a blinded adjudication committee.

Shunt thrombosis and the procedural hospitalization component of the endpoint were well-defined. There were no secondary efficacy endpoints.

Safety endpoints included AEs, SAEs, and bleeding events (captured on a specific CRF bleeding form). Bleeding intensity was classified as:

- Mild: any event that required no active intervention, other than withholding of medications or monitoring;
- Moderate: any event that required any medical intervention to treat bleeding or clot formation; or
- Severe: any event that required any procedural intervention to treat bleeding or clot formation (eg, corrective transfusion).

Laboratory parameters were measured locally.

The primary efficacy analysis was to be performed on the ITT population of all randomized patients. The relative efficacy of clopidogrel versus placebo was assessed using a two-sided log-rank test and served as the primary test of treatment effect. The time to the first occurrence of any component of the primary efficacy variable, including any adjudicated components, was used in the analysis. All patients who remained event free were to be followed until their planned study end date regardless of whether or not they permanently discontinued study drug prior to this date. Treatment effect, expressed as the relative risk reduction (RRR) (clopidogrel versus placebo), and its 95% CI was estimated using Cox's proportional hazards model.

The study was powered to detect a 30% reduction in RR; the placebo event rate was assumed to be 40%. The study was event driven; the target number of primary endpoint events was 172; the expected number of patients to be enrolled was about 490.

4.3.3 Patients

The actual event rate was about half the expected rate of 40%, requiring 906 patients to be randomized (467 to clopidogrel and 439 to placebo); of these 900 were treated (464 in the clopidogrel arm and 436 in the placebo arm). There were 179 primary endpoint events. Study follow-up was excellent; only 2 patients in the clopidogrel and 1 patient in the placebo arm were lost to follow-up, and an additional 7 and 4 patients, respectively, withdrew at the parent/guardian's request. All other patients completed follow-up. Eighty percent of treated patients in the clopidogrel arm and 82% in the placebo arm completed treatment per the protocol; the remainder discontinued permanently.

The treatment arms were similar with respect to age at randomization, gender, race, weight and height. They were also similar with regard to disease-related factors, including nature of the underlying congenital heart defect, type of shunt palliation, use of CP bypass, shunt size, age at shunt palliation, and prior and concomitant aspirin use. Overall about 84% of patients received aspirin in the 10 days prior to randomization and 88% of patients received aspirin concomitantly with study drug.

Despite the protocol's stipulation that randomization should occur "as early as possible after shunt placement", 23% of patients were randomized more than 4 weeks after their shunt placement procedure (Table 6). The treatment arms were similar in this regard. The impact of the possible impact of this issue on study outcomes (b) (4) will be discussed below.

Table 6: CLARINET: Time from shunt placement to randomization (randomized patients)

	Placebo (N=439)	Clopidogrel (N=467)	All
(N=906)			
Weeks from shunt palliation to randomization [n (%)]			
≤ 1 week	116 (26.4%)	113 (24.2%)	229 (25.3%)
> 1 to ≤ 2 weeks	105 (23.9%)	126 (27.0%)	231 (25.5%)
> 2 to ≤ 4 weeks	117 (26.7%)	119 (25.5%)	236 (26.0%)
> 4 weeks	101 (23.0%)	109 (23.3%)	210 (23.2%)

Note: one patient who had shunt palliation after randomization was included in this table.

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4.3.4 Efficacy results

Results for the primary endpoint showed no statistically significant difference between the treatment arms (Table 7). The point estimate the risk reduction with clopidogrel was 11%. Overall the event rate was about 20%, about half of the expected rate in the placebo group. Rates for the three individual components of the component primary endpoint are also displayed.

Table 7: Primary composite endpoint analysis and results for individual components (randomized patients).

	Placebo (N=439)	Clopidogrel 0.2 mg/kg/day (N=467)
Primary Outcome ^a	90 (20.5%)	89 (19.1%)
Death ^b	60 (13.7%)	51 (10.9%)
Shunt thrombosis	21 (4.8%)	26 (5.6%)
Cardiac procedure < 120 days considered as thrombotic nature	9 (2.1%)	12 (2.6%)
Log-rank test p-value		0.4340
Relative Risk Reduction (%) (95% CI)		11.1 (-19.2 to 33.6)

^a Death (including heart transplant), 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 shunt narrowing considered of thrombotic nature based on the adjudication committee whichever came first. Only the first event was counted.

^b Death included 78 cardiovascular deaths and 33 non cardiovascular deaths.

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4.3.5 Safety results

The most common adverse event was bleeding. There was no difference between the groups in the rate of bleeding or severe bleeding (Table 8).

Table 8. Incidence of bleeding events by severity (safety population)

	Clopidogrel		Difference (%) (95% CI)	p-Value ^a
	Placebo (N=436)	0.2 mg/kg/day (N=464)		
Any	88 (20.18%)	87 (18.75%)	-1.43 (-6.83 to 3.97)	0.5871
Mild	53 (12.16%)	44 (9.48%)	-2.67 (-6.96 to 1.61)	0.1962
Moderate	20 (4.59%)	24 (5.17%)	0.59 (-2.45 to 3.62)	0.6841
Severe ^b	15 (3.44%)	19 (4.09%)	0.65 (-2.05 to 3.36)	0.6068

^a Chi-square

^b Two severe bleeding AEs were fatal, one in each treatment group.

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Reviewer comment: The lack of any notable differences between the treatment groups in terms of efficacy or bleeding is consistent with our concerns that the, the dose of clopidogrel may have been too low in CLARINET, CLARINET patients' platelets responded poorly to clopidogrel, and/or delays in randomization may have reduced CLARINET's power to demonstrate an effect of clopidogrel on the primary endpoint. These issues will be discussed in Sec. 4.4 Our concern that the CLARINET formulation may have had poor bioavailability compared to the PICOLO formulation has already been discussed.

4.4 Problems with the design and execution of CLARINET

CLARINET had 3 major flaws that may have affected the outcome of the trial.

4.4.1 Use of an untested clopidogrel formulation that differed substantially from the formulation used in the Phase 2 dose-finding study

The formulation used CLARINET was not subjected to any evaluation of bioavailability. It was assumed to be equivalent to the formulations used in the previous pediatric studies, even though the CLARINET formulation differed from the other formulations in ways that might have lead to reduced bioavailability. The failure to evaluate the bioavailability of the CLARINET formulation was inconsistent with good scientific practices.

Details of the characteristics of the clopidogrel solution formulations used in the sponsor's program are displayed in Table 5, copied from Sec. 4.3.1.

Table 5 (reproduced). Formulations used in the clopidogrel pediatric studies

	BDR4580 – Comp. bioavailability study	PDY4422 – PICOLO	EFC-5314 – CLARINET			
Form	(b) (4)					
Final concentration						
pH						
Constituted pH						
Buffer						
Solubilizer/emulsifier						
Flow enhancer	(b) (4)					
Bioavailability assessed?				Yes – vs. 75 mg Plavix tablet in adults	No	No

Comp. – comparative

Reconst. – reconstituted

* The formulation was changed during the course of PICOLO

(b) (4)

The BDR4580 and PICOLO formulations

(b) (4)

Solubility of clopidogrel, which is poorly soluble in all but highly acidic aqueous media

(b) (4)

The CLARINET formulation, which was intended to go home with the patient from the hospital and be used as long as one year

(b) (4)

The PWR advises that: “Bioavailability of **any formulation used in the studies** should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults” [emphasis added]. However this was done for only one of the three different formulations used in the sponsor’s pediatric program. The BDR4580 formulation was compared to marketed Plavix tablets in adults in a classic crossover BA study and was demonstrated to have very slightly better BA than the tablet, with somewhat faster absorption. The other two formulations were not evaluated for BA. The sponsor states in the supplements Quality Overall Summary:

“All the clinical formulations developed and used during the pediatric program consisted of clopidogrel bisulfate in solution. Therefore, these formulations are considered pharmaceutically equivalent.”

No other rationale was provided for the lack of BA information for the PICOLO and CLARINET formulations. In this reviewer’s opinion, the sponsor’s equivalency assumption may be justified with respect to the BA of the BDR4580 formulation and the PICOLO formulation. Both these

(b) (4)

were probably not highly dependent upon maintenance of a highly acidic pH for continued solubility of clopidogrel. However, the highly acidic CLARINET formulation

(b) (4)

so it the solubility of clopidogrel probably was dependent on maintenance of acid pH. It is notable that most drugs are absorbed in the small intestine, which is a neutral to alkaline environment. I understand that OCP believes that there may be

substantial absorption of clopidogrel in the stomach and duodenum, based on its short Tmax. However, available data from adult volunteers indicates that the pH of the duodenal bulb (the closest part of the duodenum to the pylorus, which would be expected to be the most acidic) varies within subjects but is usually 4 or more,³ which would be associated with very poor solubility of clopidogrel, and consequent risk of precipitation. More distal regions of the duodenum would be expected to be even more alkaline. I was unable to find data on duodenal pH from healthy neonates or infants or those undergoing surgical procedures.

Also, some patients in CLARINET may have received clopidogrel via a naso-jejunal (NJ) enteric feeding tube, at least initially; but data to document this is lacking. With NJ tube administration, the administered solution would be immediately mixed in alkaline fluids when it reached the jejunum. To the extent that clopidogrel, administered by mouth or a feeding tube, reaches the small intestine, the CLARINET formulation may be problematic in terms of having reduced BA. This issue will be explored by OCP.

It may thus be inappropriate to assume that the CLARINET formulation is “pharmaceutically equivalent” to the other formulations, including most critically the PICOLO formulation which was used in the study that determined the dose of clopidogrel to be used in CLARINET. The assumptions underlying the dose selected for use in CLARINET may be invalid. Reduced BA of clopidogrel in the CLARINET formulation could explain the trial’s negative results for the primary endpoint and the lack of evidence of excess bleeding.

4.4.2 Delays in randomization

The CLARINET protocol specified that, “Patients should be randomized and treated as early as possible following shunt placement.” In congenital heart surgery patients who receive a systemic-to-pulmonary artery shunt, administration of aspirin starting in the immediate post-operative period is used routinely at major centers to prevent shunt thrombosis, based on case series data. Various post-operative landmarks have been suggested as start times for post-operative aspirin therapy, including the evening of the day of surgery (1 mg/kg rectally), within 3 days of surgery (for oral treatment), the day of extubation (oral treatment), and when goal feeds have been attained and heparin is discontinued (oral treatment). In one large series of 546 modified and classical Blalock-Taussig shunt (BTS) procedures at one institution, the rate of shunt failure (echocardiographically proven complete occlusion or occlusion to the extent that blood flow was “insignificant”) was 9.3%; about 1/5 of these (1.8% of shunts) occurred early (before hospital discharge) and the remainder were classified as late (after discharge). Early shunt failure occurred in about 1% of modified BTS shunts, despite use of postoperative oral aspirin at age-specific doses in all patients who received these shunts (7); early shunt failure in patients who received post-operative aspirin has been described in a recent review of the use of catheter based interventions for shunt occlusion (6). The premise of CLARINET was that clopidogrel might be useful to reduce risk of thrombosis (early or late) that occurs in patients taking aspirin and those who do not. It is logical to initiate treatment with clopidogrel at the same time that aspirin would be started, which is what we thought the sponsor intended by using the words “as early as possible” in the protocol.

However, this is not what occurred. In about ¾ of patients in CLARINET, more than 1 week elapsed between shunt placement surgery and randomization to clopidogrel or placebo, and in nearly ¼ of patients, randomization did not occur until more than 4 weeks after surgery. The

³ McCloy RF, Greenberg GR, Baron JH. Duodenal pH in health and duodenal ulcer disease: effect of a meal, Coca-Cola, smoking, and cimetidine. *Gut* 1984;25:386-392.

range of time for this parameter was 0 to 84 days (one other patient was randomized before surgery, a protocol violation). In the vast majority of patients, treatment with study drug was initiated on the day of randomization or the next day; the range of time from shunt placement to initiation of study treatment was 1 to 90 days. Table 6 (reproduced from Sect. 4.3.3) provides a breakdown of the time from shunt placement to randomization in CLARINET in 4 strata of patients corresponding roughly to quartiles.

Primary endpoint data for these 4 strata are shown in Table 9. Hazard ratios for clopidogrel vs placebo across the strata are roughly similar. There was no significant interaction ($p=0.94$) between treatment and time to randomization for this analysis. Note that the value provided in the Sponsor's table (duplicated below as Table 4) for the p-value of the interaction, 0.4163, actually is the value of the Wald chi-square statistic. Thus, we have no evidence from the study data that the delays from surgery to randomization affected the trial outcome. Likewise, there is no evidence from in the literature other than expert opinion to suggest that late initiation of anti-thrombotic therapy after shunt palliation is problematic.

Table 6 (reproduced): CLARINET -- Time from shunt placement to randomization

	Placebo (N=439)	Clopidogrel (N=467)	All (N=906)
Weeks from shunt palliation to randomization [n (%)]			
≤ 1 week	116 (26.4%)	113 (24.2%)	229 (25.3%)
> 1 to ≤ 2 weeks	105 (23.9%)	126 (27.0%)	231 (25.5%)
> 2 to ≤ 4 weeks	117 (26.7%)	119 (25.5%)	236 (26.0%)
> 4 weeks	101 (23.0%)	109 (23.3%)	210 (23.2%)

Note: one patient who had shunt palliation after randomization was included in this table.

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Table 9 – CLARINET -- Primary outcome results by time from shunt placement to randomization (randomized patients)

Interaction Variable	Subgroup	Placebo	Clopidogrel 0.2 mg/kg/day	Hazard Ratio (95% CI)	p-value for interaction
Days from shunt palliation to randomization ^a	≤ 1 week (N=229)	26 (22.4%)	24 (21.2%)	0.94 (0.54 to 1.63)	0.4163
	>1 and ≤ 2 weeks (N=231)	21 (20.0%)	23 (18.3%)	0.81 (0.45 to 1.46)	
	>2 and ≤ 4 weeks (N=236)	25 (21.4%)	22 (18.5%)	0.82 (0.46 to 1.46)	
	> 4 weeks (N=210)	18 (17.8%)	20 (18.3%)	1.03 (0.55 to 1.96)	

Note: One patient had shunt palliation one day after randomization. This patient was included in the ≤ 1 week group.

Note: One patient with shunt palliation date but no shunt type specified was included in this table.

^a Days from shunt palliation to randomization was included in the model as continuous.

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Note that the event rates for patients tended to fall as time from surgery to randomization increased, although the change was not dramatic. Biostatistics was not able to calculate the study's power to detect a significant interaction between treatment and time from shunt placement to randomization, but it probably was not large. It is possible that the high rate of late randomization and treatment may have biased the study against finding a treatment effect by including few patients at risk for early thrombosis. On the other hand, the study was event-driven, and more than the required number of events were accrued (172 events required; 179 events accrued). One would have to posit a beneficial effect of clopidogrel on early events, but not late events, for the delays in randomization to have affected the study outcome. AS noted above, we know of no evidence to confirm or refute the possibility of such a differential effect. The sponsor believes there was no such differential effect, but offers no evidence other than the opinion of its experts.

Nonetheless, the high rate of delayed randomization represents a flaw in the study that might have affected the results. Only 51% of the patients were randomized in the first two weeks after surgery, meaning that the study's true power to detect a beneficial effect of clopidogrel on early shunt thrombosis was greatly reduced from what it would have been if patients had been started on clopidogrel at the same time that initiation of aspirin is recommended by some authorities.

This problem was noted by the study's Steering Committee during the study and communicated to the investigators on several occasions. In a study newsletter sent to the investigators on 31 October 2007, about one year after the first patient entered the study, David Wessel, MD, the chair of the Steering Committee, wrote:

"We also reviewed blinded data about patient characteristics, and have found that more than 50% of patients are randomized more than 2 weeks after the initial surgery. As you may know, the greatest incidence of adverse thrombotic or fatal events after shunt palliation occurs in the early post-operative period. We are convinced that if clopidogrel is effective in this patient population, then these early thrombotic or fatal events may potentially be avoided. We therefore strongly recommend that patients entering the trial are randomized as soon as possible after shunt palliation, as soon as they are able to tolerate oral medications."

Dr. Wessel's admonition had little effect. The data in Table 6 indicate that at the end of the study, 74.7% of subjects had been randomized more than one week after surgery, and 49.7% were randomized more than 2 weeks after surgery. It seems clear that the protocol's requirement that "Patients should be randomized and treated as early as possible following shunt placement" was often ignored. This defect could and should have been prevented through more rigorous design (such as a hard limit on the number of days from shunt placement to the start of study drug) and/or rigorous monitoring and enforcement of the requirement to start study drug soon after surgery.

We asked DSI to inspect 5 sites with average to long mean times from surgery to randomization to determine when aspirin therapy was started and other relevant details about post-operative care and reasons for delays in randomization. Three of the sites were in the US and two were in Argentina. Data for US sites and Argentinean sites are displayed in Tables 10 and 11, respectively. Only two of the US sites and one of the Argentinean sites administered aspirin. Note that data were not provided to us in a uniform way.

Table 10. CLARINET field inspection data – US sites

PI / Site location	Days from surgery to randomization Mean (SD) / Median (range)	Days from aspirin initiation to randomization* Mean (SD) / Median (range)	Days from first feeds to randomization # Mean (SD) / Median (range)
Tugertimur / Orlando, FL (N=24)	34.3 (20.8) / 35.5 (5 to 79)	17.0 (18.2) / 14.5 (0 to 78)	No data
Sullivan / Louisville, KY (N=11)	36.6 (15.5) / 38 (15 to 63)	29.1 (16.3) / 29 (4 to 60)	No data
Pizzaro / Wilmington, DE (N=8)	Mean – 25.7 Range – 8 to 60	No use of aspirin	No data

*Aspirin route at initiation was oral or enteric (not rectal) in each patient at sites where it was used.

The date of first full feeds or goal feeds (oral or enteral) was used preferentially in the calculation. If that was not available, the date of first feeds (oral or enteral) was used.

Table 11. CLARINET field inspection data – Argentinean sites

PI / Site location	Days from surgery to randomization Mean (range)	Days from aspirin initiation to randomization* Mean (SD) / Median (range)	Days from first feeds to randomization # Mean (SD) / Median (range)
Marantz / Buenos Aires (N=22)	26 (3 to 78)	(N=9) 10.2 (13.4) / 6 (-1 to 46)	(N=13) 18.5 (22.7) / 8 (-1 to 74)
Somoza / Cordoba (N=9)	45.4 (26 to 72)	No use of aspirin	30.4 (13.7) / 28 (11 to 54)

*Aspirin route at initiation was oral or enteric (not rectal) in each patient at sites where it was used.

The date of “full” feeds or “goal” feeds (oral or enteral) was used preferentially in the calculation. If that was not available, the date of first feeds (oral or enteral) was used.

The data indicate that both US sites that used aspirin had mean and median times from surgery to randomization of longer than 30 days. The Orlando site had a mean time from aspirin start to randomization of 17 days, while for the Louisville site the analogous time was 29 days. The Louisville site had a policy of not randomizing patients until the post-operative intracardiac line had been discontinued and there was no bleeding. Clearly, the site allowed aspirin use prior to that milestone. Neither site received any directed communication about late randomization from the sponsor. Waiting for the patient to stabilize was the most common underlying reason for delays in randomization.

At the two Argentinean sites, the mean time from surgery to randomization was 26 and 45 days in Buenos Aires and Cordoba, respectively. The mean time from aspirin initiation to randomization was about 10 days at the one site where aspirin was used (Buenos Aires), but the distribution is skewed by an outlier; the median is 6. The substantial length of the time from surgery to randomization after surgery in Cordoba was related to the surgeon's desire to know the shunt was "permeable" (which appears to mean patent) and the strict criteria he used for that determination, as well as a deliberately drawn out informed consent process. In Buenos Aires, most patients who had their surgery at the investigational site were randomized quickly (these are the patients who received aspirin). However, more than half the patients were referred from other hospitals where the patient had shunt placement surgery, and these patients tended to be randomized many days after surgery. Data on aspirin use and times to feeding were scant on the patients referred to the Buenos Aires site from other surgical centers. Neither of the Argentinean sites received targeted communications regarding their randomization practices.

For the sites for which we have data on the days that oral or enteral feeding (either full or initial feeding) was initiated, the time between the onset of feeding and the day of randomization tended to be longer than the times between initiation of aspirin and randomization.

Note that the inspection results are from a small fraction of the enrolling sites. However, the data suggest that aspirin was administered relatively soon after surgery at the inspected sites, reasonably in line with published reports. This suggests that other sites using aspirin may have done the same.

The delays from start of aspirin therapy to randomization seem inappropriate. Aspirin and clopidogrel were administered in the same way for essentially the same purpose, and have the same important risks. There is no sound medical reason to start them at different times as a general practice in a clinical study, although the informed consent process might delay the start of an experimental treatment for a short time. While a surgeon might want to delay the start of a second anti-platelet agent in a particular patient in practice due to risk/benefit considerations, in a clinical study such discretion is problematic. These delays should not have been permitted in CLARINET. Such patients should not have been randomized. However, the sponsor did not admonish any site about late randomization.

After we received the supplement under review, we asked the sponsor: "*....Please provide us with details about any efforts you made to encourage investigators to enroll subjects earlier and provide the rationale for the delays in randomization seen in CLARINET. Please explain why you did not amend the protocol to exclude patients who were more than two weeks post-shunt surgery once you became aware of this issue.*" Our questions, the sponsors' responses, and this reviewer's comments on those responses are included in an appended review (Appendix 2). The sponsor's important responses and our comments on them are included here. The sponsor indicated:

1. The precise time of randomization was left to the judgment of the investigator in order to ensure that patients received the best medical care. Patients were typically under the care of pediatric cardiac specialists who were in the best position to make that judgment.
2. Not specifying a fixed interval reflected a safety concern. Infants with cyanotic congenital heart disease (CCHD) are unstable in the post-operative period. Oral administration of medications sometimes may not be initiated until hemodynamics are stable to avoid complications. These patients may be too sick to take oral medications.
3. Some investigators did not randomize early after surgery because patients were unstable or receiving intensive support.

4. Some investigators were concerned about starting blinded antiplatelet therapy if repeat surgery might be needed.
5. Some investigators were concerned about asking parents, who might be overwhelmed by their baby's surgery, for consent to be in a study.

Reviewer comment: These babies may indeed have been quite ill. However, nearly ¼ of patients in this study were randomized more than 4 weeks after surgery, with some randomized more than two months after surgery. It seems unlikely that all of them were unable to take oral medication until their randomization date. One paper from a US children's hospital indicates that in patients having the Norwood procedure, one of the most complex and risky procedures for infants with CCHD, the goal is start oral aspirin therapy to prevent shunt thrombosis no later than 3 days after surgery. Data from DSI inspections of several sites indicates that randomization occurred days to weeks after the start of oral or enteric aspirin. There is no good medical reason to delay start of study drug after the start of oral or enteric aspirin.

Regarding efforts made to encourage investigators to enroll subjects early, the Sponsor responded that it had send newsletters and other communications about the importance enrolling patients early after surgery. We had already seen these documents. The sponsor indicated that no site or investigator was ever singled out for late enrollment and asked to do better.

Regarding the issue of modifying the protocol, the Sponsor wrote:

“The question of a protocol amendment to exclude patients who were more than two weeks after surgery was never raised by the Steering Committee nor was this topic raised by the DMC, and the study was intended to reflect real-world management of these patients. Also, this was an event driven trial. Clinical experts on the steering committee believed that events occurring at any time after surgery might be prevented by clopidogrel.”

Reviewer comment: The initial version of the protocol submitted to us stated that (b) (4)

Also, the protocol might have specified that patients should be randomized and treated with study drug at the same time that oral or enteric aspirin is initiated, if the site treats shunt patients with aspirin.

If such language had been implemented and enforced, we believe that fewer patients would be have been enrolled late. As it was, only ¼ of patients were enrolled in the first week after surgery, when event rates (including death) are highest. Death and event rates drop steadily in the first few weeks after surgery, although not all deaths are thrombotic in nature. Nonetheless, the study's power to detect an effect on events in this period was probably considerably lower than it would have been with different protocol language. Also, while the Sponsor indicates that its experts stated their opinion that events occurring at any time after surgery might be prevented by clopidogrel, this was speculation -- clopidogrel has never been shown to prevent thrombotic events in shunts. The possibility exists that clopidogrel could have differential effects on early vs. late shunt occlusion, which have different mechanisms. In adults, the effect of clopidogrel on the prevention of CV events (relative to placebo) in acute ACS patients diminishes over time: in the CURE study in patients with NSTEMI or unstable angina, the effect of clopidogrel relative to placebo was largely established in the first 3 weeks after randomization, which occurred a mean of 14 hours after the onset of chest pain, and maintained over 1 year. Also, babies with shunt placement face the highest risk of death early after surgery, and are thus at greatest need

for effective therapy. The Sponsor could and should have enrolled more patients in the first two to three weeks after surgery to learn about the risks and benefits of clopidogrel in the shunt patients at highest risk of death.

Even though we have no evidence that the delays in randomization affected the outcome, the delays reduced the study's power to detect a difference on the rate of early events, which is when the death and thrombotic event rate is highest. The substantial rate of late randomization in CLARINET represents flaws in the design and/or execution of the study that are not consistent with good scientific principles.

4.4.3 The sponsor had data that platelets from pediatric patients in the target population responded poorly to stimulation by ADP and failed to emphasize these data to FDA

Clopidogrel, a thienopyridine, is an inhibitor of P2Y₁₂, the ADP receptor on the surface of platelets. ADP agonism at P2Y₁₂ triggers platelet aggregation by making platelets sticky and adhere to each other and to collagen, leading to the formation of a platelet plug. Activated platelets also release their contents of their granules, which include several clotting factors, ADP and other agents that recruit other platelets to the aggregating mass, helping to form a thrombus. By inhibiting the triggering action of ADP by blocking its receptor on platelets, clopidogrel reduces the risk of thrombotic events in its indicated conditions and possibly other conditions. ADP is one of several activators of platelets; blockade of P2Y₁₂ does not affect initial platelet activation by other mediators, such as collagen.

In the PWR, the sponsor was asked to conduct a PD study to find a dose of clopidogrel that produced the same degree of maximal inhibition of platelet aggregation stimulated by 5 µM ADP as observed in adults with recommended maintenance dose of clopidogrel (i.e., 75 mg/day). Specifically, the Sponsor was asked to identify a clopidogrel dose in the target population that produces 30-50% inhibition of baseline platelet aggregation, as is observed in adults. The Sponsor was asked to test at least a 10-fold range of doses with the initial 3 doses. To satisfy this request, the sponsor conducted study PDY4422 (PICOLO) in neonates (i.e., age ≤ 30 days) and infants/toddlers (age 31 days – 2 years), The study data indicated that the dose of 0.2 mg/kg/day was determined to meet the standard set by the PWR.

In the Division's preliminary response to a question about the need for further PD studies in the Sponsor's pre-meeting package for the EOP2 meeting held on July 12, 2006, where the PICOLO data and the plans for the proposed CLARINET study were discussed, the sponsor was asked to provide additional data: "What is the level of platelet aggregation achieved with 5 micrograms [sic] of ADP as a function of age (neonates to adults)?"

At the meeting, there was additional clarification: "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." (FDA EOP2 meeting minutes, dated 8 August 2006).

The rationale behind the question and the further comments at the meeting is that if the platelet aggregation response to ADP (in the absence of any antithrombotic drug) were to be substantially reduced in the target population compared to adults, then the efficacy of an ADP receptor blocker like clopidogrel might be reduced. This might make it more difficult to show efficacy, possibly necessitating an increase in study size, or it might lead to a conclusion that

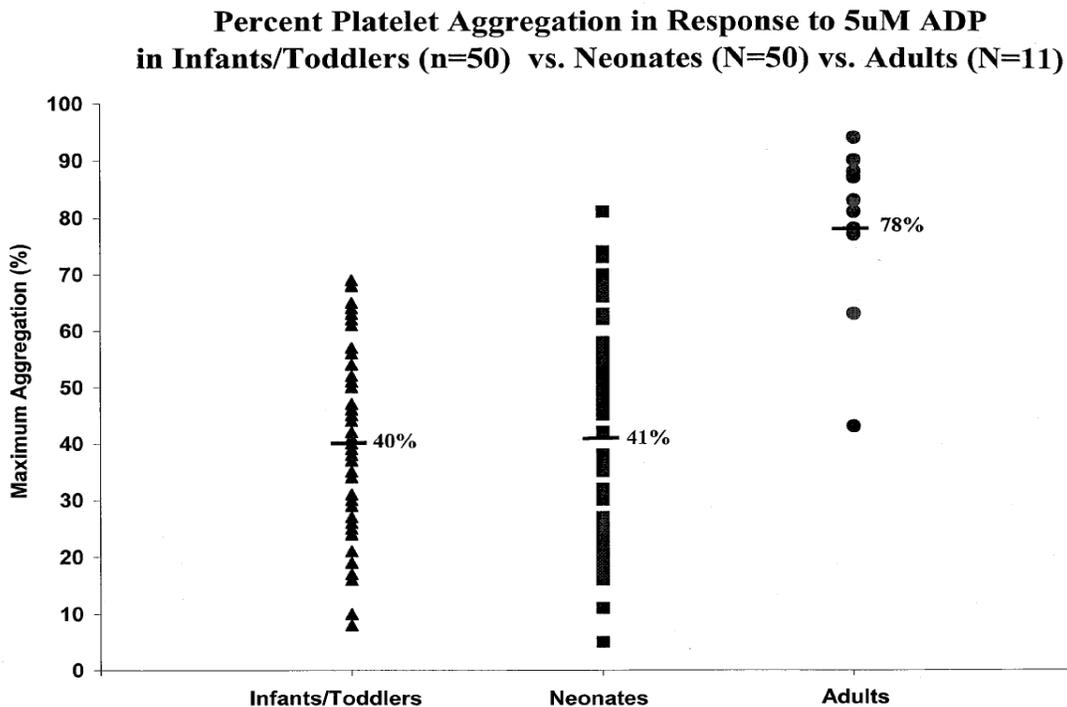
further studies of clopidogrel in this patient population should not be performed because of the low probability of success.

On October 13, 2006, after receiving FDA's minutes of the EOP2 meeting described above, the Sponsor made a submission styled as a "Clarification of Agency Meeting Minutes" to the clopidogrel IND, 034663 (Serial 658). This was received in White Oak on October 16. The opening paragraph of the cover letter indicates that the sponsor wanted clarification of the Agency's minutes of the EOP2 meeting. The submission asked for clarification of aspects of the original PWR and proposed to amend it. Between information regarding clarification of issues arising at the EOP2 meeting, the sponsor included 3 brief paragraphs in response to the Agency's request for age-comparison platelet aggregation responses to 5 μ M ADP. The data were summarized as follows by the Sponsor:

"The data show a greater degree of variability in the neonates and infant/toddler group versus the adult population and a decreased responsiveness to ADP in these groups as compared to adults. "

The data discussed above were provided in a figure in an Appendix to the submission (Figure 1). The mean platelet aggregation resulting from the addition of 5 μ M ADP (without clopidogrel or any other antithrombotic) was 41% in neonates (N=50); 40% in infants/toddlers (N=50), and 78% in adults (N=11). All data points in adults appear to be above the means in the other groups, and only one of the 99 data points in children appeared to be above the mean in adults. The pediatric data came from PICOLO, so we know the methodology; we know nothing about the methodology for the adult data.

Figure 1



These data are somewhat inconsistent with published literature regarding platelet aggregation in children. The weight of the published evidence is that newborns have reduced platelet aggregation responses compared to adults to low concentrations of ADP (such as 5 μ M), not unlike the Sponsor's findings, but that adult-level responses are reached within about 10 days after birth or less (1), (2),(3). This inconsistency was never explained or even mentioned by the Sponsor.

The submission contained no discussion whatsoever of the implications of these data for the proposed CLARINET efficacy and safety study or the pediatric program as a whole. The Sponsor did not ask for any feedback on the data. On November 3, 2006, less than 3 weeks after we received the Sponsor's platelet aggregation data, the first patient entered the CLARINET study.

These data raise the question as to whether there is a substantial reduction in the platelet aggregation response to 5 μ M ADP in neonates and infants/toddlers as compared to adults. The data, which should be confirmed in a study with consistent and well-described methodology, suggest that in the very young, ADP may not be a powerful stimulator of platelet aggregation, and that blocking ADP with drugs like clopidogrel may not be as beneficial in preventing thrombosis as it is in adults. If true, this would have important implications for the pediatric development program, including reduced effect size or even lack of benefit, as well as reduced bleeding risk.

This submission was not reviewed when it was submitted, and Division management was not informed of the above data on platelet aggregation. We never responded to the Sponsor regarding these data. We noted these data [REDACTED] (b) (4) [REDACTED]. Nonetheless, the Sponsor should have flagged these data for us in 2006 and discussed their implications with us.

CLARINET was a negative study. The results for the primary endpoint, the time to the first event of composite of death, shunt thrombosis and cardiac procedure of a thrombotic nature (i.e., for a thrombotic cause) at age < 120 days were similar for clopidogrel vs. placebo, with event rates of 19.1% vs 20.5%, respectively. The RR reduction was 11.1%, with a 95% CI of -19.2 to 33.6%. (log rank p=0.43, see Table 7, Sec. 4.3.3).

The bleeding data from CLARINET also indicate similarity of clopidogrel and placebo (see Table 8, Sec. 4.3.5). The similarity of the treatment groups for bleeding rates is inconsistent with placebo-controlled studies of the long-term use of clopidogrel in adults, which consistently show that clopidogrel causes excess bleeding. However, these findings of similarity of clopidogrel and placebo in CLARINET are consistent with our view of the implications of the platelet aggregation data in Figure 1, which show a reduced impact of ADP agonism on platelet aggregation in neonates and infants/toddlers. This would be expected to be associated with reduced benefit in terms of thrombosis rate and less bleeding risk. This was observed in CLARINET, where neither the benefit nor risk of clopidogrel differed from placebo.

After submission of the supplement now under review, we asked the sponsor several questions relating to the PD data discussed above (see Appendix II for the questions, the sponsor's responses, and this reviewer's comments on those responses). The sponsor made the following major substantive points about the data and their significance; this reviewer's comments follow each response:

1. Reduced responsiveness of platelets to ADP stimulation is normal in the very young;

Reviewer comment: This assertion is not an adequate response because it does not deal with FDA's basic concern that reduced levels of agonism of a ligand might imply a reduced benefit from specific antagonism of the same ligand in a biological process with multiple potential agonist ligands.

2. Reduced responsiveness of platelets to ADP stimulation does not affect the dose selection rationale;

Reviewer comment: This assertion was made by the sponsor's consultants without any rationale and without dealing with FDA's basic concern, expressed in my comments on response #1.

3. FDA agreed to the strategy of dose finding used by the sponsor (i.e., find a dose that results in 30%-50% inhibition of 5 μ M ADP-induced platelet aggregation, and FDA agreed that the 0.2 mg/kg dose met those criteria.

Reviewer comment: FDA's acceptance of 0.2 mg/kg/day as the as the dose to be used in CLARINET was not final, but was plainly a qualified acceptance. The appropriateness of the standard of 30-50% inhibition of platelet aggregation was contingent on the submission of data showing similarity between adults and neonates in terms of the platelet aggregation response to 5 μ M ADP. The EOP2 minutes indicate that Dr. Stockbridge said, "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."

*_____ (b) (4) _____
_____. The Sponsor should not have started the CLARINET study until this issue was discussed with us and fully resolved.*

4. *The sponsor states that it understood Dr. Stockbridge's FDA's requests for information platelet aggregation as follows: "Our understanding of the purpose of the Division/Dr. Stockbridge's request for an analysis of ADP agonist responses (using PICOLO data in neonates and infants/toddlers compared to adults) was to help FDA decide if there was a need for a PD study in older pediatric age groups based on similarity of pharmacodynamic response in neonates and infants/toddlers compared to adults." The Sponsor goes on to say FDA's comments were made in connection with the Sponsor's question regarding the need to study PD responses in older children.*

Reviewer comment: We are puzzled as to why the sponsor interpreted our comments in this way. Dr. Stockbridge said, "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." We don't understand how this statement, which mentions only neonates and adults, could be construed as relating to the need to perform PD studies in older children. Also, It should be noted that at the EOP2 meeting, we indicated to the sponsor that they would not have to study PD responses of older children because we agreed with them that shunt placement for CCHD is rare in the older pediatric patient groups, and only patients less than 1 year old would be in CLARINET (in fact, the age limit at randomization was 93 days). Given all this, the sponsor's stated understanding of our remarks remains puzzling.

As noted in our comments on response #1, if the platelets of neonates aggregate poorly in response to ADP, then an inhibitor of ADP action might not be very effective in preventing aggregation. Such data might trigger a request for additional PD studies, or possibly a decision that a Phase 3 study would be futile. If the Sponsor was perplexed by the meaning of Dr. Stockbridge's statement, the prudent and obvious course of action would be have been to discuss this issue with us in a direct and frank manner. This never occurred.

5. The sponsor and the PICOLO Steering Committee did not consider altering the expected effect size in CLARINET (and thereby increasing the target number of events and the expected sample size) because of the PD evidence discussed above because the effect of such alterations in PD on the efficacy of clopidogrel was not known.

Reviewer comment: It is true that the effects of the PD alterations in the target population on clinical efficacy were not known. However, in a conservative approach intended to maximize the likelihood of the success of the trial, one might assume that the effect size would be reduced, leading to appropriate adjustments in sample size. The record is clear that FDA was concerned about this possibility at the time of the EOP2 meeting in 2006. If the Sponsor had discussed this issue with us, we might have recommended an assumed effect size lower than the 30% reduction figure that was specified in the final amended PWR of 24 August 2007 to be used for power and sample size calculations of the safety and efficacy study, or we might have told the Sponsor not to perform the safety and efficacy study without additional PD information.

However, the sponsor did eventually submit the requested PD information, albeit months after they received it. We did not review the information data at that time, so the Division is not blameless. (b) (4)

Nonetheless, the sponsor's failure to consider the implications for CLARINET of the reduced responsiveness of the patients' platelets to ADP stimulation or to appropriately bring the PD information to our attention is not in accordance with good scientific principles.

4.5 Additional information required by the PWR

The PWR required the sponsor to include with its submission a comprehensive safety evaluation of the use of clopidogrel in children that was "more than a summary of the published literature...." This was submitted in the supplement under review, and consists of information from:

- The clinical studies performed as part of the clinical pediatric plan (i.e., PICOLO and CLARINET)
- Spontaneous post-marketing events reported to the sponsor on the use of clopidogrel in children since the first marketing authorization
- Two single center registries:
 - From Boston, MA; and
 - From Leuven, Belgium.
- Published literature, including BOSTON, LEUVEN and PICOLO study publications, as well as other publications;
- Data from two US claims databases:
 - (b) (4)
 - (b) (4)

Reviewer comment: This information satisfied the terms of the PWR and in general supports the use of clopidogrel in pediatric patients.

As noted above, there were three major problems with the design and execution of CLARINET, The implications of these will be considered serially. The overarching failure of the pediatric program to meet the primary goal of the PWR will also be discussed. (b) (4)

5.2.1 Unknown bioavailability of the CLARINET formulation

The PWR advised the sponsor to evaluate the bioavailability of each formulation used in the studies in its pediatric program. In developing the CLARINET formulation, the sponsor made major changes to the PICOLO formulation that increased the likelihood that clopidogrel would not be available for absorption in the small intestine. The dose used in CLARINET was based on the results of PICOLO. If the bioavailable of the CLARINET formulation was less than the PICOLO formulation, as we think is possible, the dose of clopidogrel in CLARINET would have been suboptimal. Accordingly, the sponsor should have performed a comparative bioavailability study of the CLARINET formulation or at a minimum, provided drug exposure data from CLARINET, which it did not do. The failure to collect and submit information on bioavailability of a new and substantially changed formulation is not fairly responsive to the written request. In addition, the conduct of the sponsor in this regard is not in accordance with good scientific principles (b) (4)

Note that is conclusion is based on the likelihood that there is a substantial question about the BA of the CLARINET formulation relative to that of the PICOLO formulation. Input form OCP is important regarding this issue.

5.2.2 Delays in randomization in CLARINET

Nearly one quarter of patients in CLARINET were randomized more than 4 weeks after their shunt placement surgery. It is not known if clopidogrel's effects on early vs late shunt thrombosis are similar. At the sites we inspected, in nearly every case where aspirin was given to patients in the post-operative period, it was initiated orally or enterically days to weeks before study drug. There is no good medical reason not to start these drugs at the same time in a clinical study. The delays in randomization were tolerated by the sponsor, who never admonished a single investigator about late randomization. The study's randomization instructions in the protocol could have been more specific, and set firm limits on the amount of time between the index surgery and randomization, and the sponsor could have done more to modify the behavior of the investigators. While we have no data to that the delays in randomization affected the study outcome, we cannot rule out that it did not. The sponsor's actions here reduced the study's power to show an effect on events occurring in the first few weeks after surgery, which when the event rate is highest and when patients most need protection from thrombotic events. The sponsor's acts here were was not in accordance with good scientific principles, (b) (4)

5.2.3 Failure to acknowledge pharmacodynamic data that suggested clopidogrel might not be useful for the target indication or which might affect the dosing paradigm.

The sponsor was on notice that the Division was concerned that PD data showing that ADP agonism is reduced in the CLARINET target population compared to adults might affect the premise of the pediatric program, because reduced agonism of ADP might imply reduced efficacy (and also reduced bleeding risk) of an ADP inhibitor. The sponsor had such data, and did not appropriately bring them to our attention. The data might have prompted us to request additional PD data, to rethink the dosing decision paradigm, or event to determine that development programs should be scrapped for futility. The sponsor's failed to bring these data to our attention in an appropriate manner, but the data were submitted to us.

As noted earlier, we failed to recognize these data when they were submitted. (b) (4)

5.2.4 Failure of the pediatric development program to meet the overall goal of the PWR.

The PWR indicates that the overall goal of the sponsor's pediatric development program should be to "... provide guidance for the use of clopidogrel in the reduction of the incidence of thrombosis in children with systemic to pulmonary artery shunts for palliation of cyanotic congenital heart disease." Because of the flaws in the development program discussed above, the results of the sponsor's safety and efficacy study, CLARINET, are inconclusive. They neither confirm nor rule out a beneficial effect of clopidogrel on the complications of shunt thrombosis. Thus, the flaws in the development program have caused the program to fail to meet its underlying purpose of providing guidance on how to use clopidogrel in children with STPAS. Thus, this reviewer believes it is appropriate to conclude that the sponsor's studies did not "fairly respond to the written request," (b) (4)

6 Recommendation

[REDACTED] (b) (4)

Appendix 1 – Annotated Pediatric Written Request

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(CCI/TS) immediately following this page

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

/s/

MARTIN ROSE
12/23/2010

SHARI L TARGUM
12/27/2010