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STATISTICAL REVIEW(S)



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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OFFICE OF BIostatISTICS

STATISTICAL REVIEW AND EVALUATION
Clinical Studies

NDA/Serial Number: NDA20839/S-051
Drug Name: PLAVIX[®] (clopidogrel bisulfate SR25990)
Indication: Cyanotic Congenital Heart Disease Palliated with a Systemic-
to-Pulmonary Artery Shunt
Applicant: Sanofi Aventis U.S. LLC
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Biometrics Division: Biometrics I, HFD-710
Statistical Reviewer: Yeh-Fong Chen, Ph.D.
Concurring Reviewers: James Hung, Ph.D.

Medical Division: Division of Cardio-Renal Drug Products, HFD-120
Clinical Team: Martin Rose, M.D., HFD-110
Stephen Grant, M.D., HFD-110
Project Manager: Alison Blaus, HFD-110

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1. EXECUTIVE SUMMARY

This supplement NDA was submitted to fulfill the Pediatric Written Request (PWR), originally dated October 15, 2001 and was later amended on August 24, 2007 for Plavix[®] Tablets. The objective of this pediatric program was to evaluate the efficacy of clopidogrel 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 shunt and to review all available safety data of clopidogrel in children.

Based on three interim and the final analysis, data from the only efficacy study (EFC5314/CLARINET) did not show that clopidogrel has an effect in reducing all-cause mortality and shunt-related morbidity in neonates or infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt.

Due to the unexpectedly similar bleeding event rates between the clopidogrel 0.2 mg/kg dose group and placebo, a concern of insufficient dose used was raised and a letter was sent to the sponsor for clarification. The sponsor insisted that the chosen dose is endorsed by the Platelet Aggregation Committee, Steering Committee and FDA. The statistical reviewer found that based on the sponsor provided closed meeting minutes for the first interim analysis, the sponsor was indeed informed repeatedly that the used dose could be too low to demonstrate clopidogrel's efficacy.

2. INTRODUCTION

2.1 OVERVIEW

This supplement NDA was submitted to fulfill the Pediatric Written Request (PWR), originally dated October 15, 2001 and was later amended on August 24, 2007 for Plavix[®] Tablets. The objective of this pediatric program was to evaluate the efficacy of clopidogrel 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 shunt and to review all available safety data of clopidogrel in children.

In this submission, the sponsor submitted a relative bioavailability study (i.e., BDR4580), a dose-ranging pharmacodynamic study (i.e., PDY4422/PICOLO), and a Phase 3 safety and efficacy study (i.e., EFC5314/CLARINET) in support of this sNDA. In this statistical review, only Study EFC5314/CLARINET will be evaluated. Study EFC5314 was titled as "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 (e.g. modified Blalock Taussig shunt) "

Study EFC5314/CLARINET was an event driven trial. All patients were followed from randomization to the earliest of shunt thrombosis or next surgical procedure for correction of the congenital heart disease, or death, or 1 year (365 days) of age, or a common study end date (CSED), defined as a date when it was projected that 172

primary events would have occurred. Due to the limited knowledge and therapeutic experience in this patient population, three interim analyses were performed during the trial to evaluate the effect of clopidogrel on the primary efficacy endpoint, with the potential to end the trial if there was a clear efficacy advantage for clopidogrel.

Based on the results of three interim analyses and the final analysis, the sponsor concluded that the study showed no statistically significant differences between the two 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 [Final analysis of relative risk reduction is 11.1%, 95%CI is (-19.2, 33.6) and p-value is 0.4340] or among the components of the primary endpoint, except for death, for which there was a little trend for fewer events with clopidogrel.

2.2 DATA SOURCES

The sponsor's original submission including data file and clinical study reports are stored in the following link: <\\Cdsub1\evsprod\NDA020839\0068>. The sponsor's response to FDA's request regarding their SAS programs and subgroup analysis results for countries are stored in the following link: <\\Cdsub1\evsprod\NDA020839\0081>.

3. STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 Description of Study EFC5314 (CLARINET)

Study EFC5314 was titled as “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)”. The study was conducted in 134 sites worldwide.

Note that the following study description was based on the sponsor's clinical study report. Any major study discrepancy between the study report and protocol will be discussed in the section of statistical reviewer's findings.

3.1.1.1 Study Objectives

Primary Objective

The primary objective of this study was to evaluate the efficacy of clopidogrel 0.2 mg/kg once daily 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.

Secondary Objectives

The secondary objective of this study was to assess the safety of clopidogrel 0.2 mg/kg once daily in the study population.

3.1.1.2 Study Design

This was a prospective, multinational, randomized, placebo-controlled, double-blind, parallel group clinical study of clopidogrel versus placebo in neonates or infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt. The study was event driven. A minimum of approximately 490 patients were planned to be randomized to get 172 events

Eligible patients were to be randomized and treated with the study drug as early as possible following shunt placement. During the study, randomized patients may have received concomitant background therapy, with or without ASA, as per usual practice at each site.

All patients were followed from randomization to the earliest of shunt thrombosis or next surgical procedure for correction of the congenital heart disease, or death, or 1 year (365 days) of age, or a common study end date (CSED) defined as a date when it was projected that 172 primary events would have occurred.

Due to the limited knowledge of this patient population, three interim analyses (at approximately 40%, 60%, and 80% of the maximum number of required events) were to be performed during the trial to evaluate the effect of clopidogrel on the primary efficacy endpoint, with the potential to end the trial in the case of a clear efficacy advantage for clopidogrel. All interim analyses were conducted by the DMC-associated independent biostatistician.

Since EFC5314/CLARINET was an event driven trial, the CSED was planned to occur at the time the target number of events was reached. For ethical reason, it was decided by the Steering Committee that the last patients enrolled would have at least 3 months of follow-up period. So the CSED was determined to be on 25-Jan-2010 when it was projected that 172 primary events had occurred in the study.

Due to the difficulty in obtaining blood samples in children, the pharmacokinetic/ pharmacodynamic substudies planned to be proposed in EFC5314/CLARINET were not performed.

3.1.1.3 Primary Efficacy Variable(s)

The primary efficacy variable was the time to first occurrence of any component of the primary composite endpoint of:

- Any death;
- Shunt thrombosis requiring intervention;
- 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.

Note that there was no secondary efficacy variables defined in the protocol.

3.1.1.4 Sponsor's Efficacy Analysis Plan

Primary analysis:

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 corresponding 95% CI was estimated using Cox's proportional hazards model.

The assumption of proportional hazards in the Cox model was examined using two different models with non-proportional hazards. First, the hazard was allowed to vary monotonically over time by adding a regression parameter, β_2 , to the standard Cox model. The hazard function was $h(t) = h_0(t) \exp(\beta_1 + \beta_2 \log(t))$,

where $h_0(t)$ is the baseline hazard and β_1 is the treatment effect. In the second approach, the hazard ratio was assumed to be constant within each of three time periods, 0-3 months, 3-6 months, and 6-12 months, but allowed to vary between these periods. The three hazard ratios were compared using a Wald test.

Other analyses of the primary variables:

The time to the first occurrence of any component of the primary efficacy variable, using only the Investigator's assessment of the thrombotic nature of the cardiac procedure component, was analyzed using the statistical methodology described above.

Each component of the primary efficacy variable, death (or heart transplant), shunt thrombosis, and 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, was analyzed using the same methodology as described for the primary endpoint.

The sponsor also performed the following exploratory analyses, but the results are not reported in this review.

- The incidence of each method used to confirm a diagnosis of shunt thrombosis (marked decrease of murmur, impairment of flow, surgical observation, post-mortem observations and progressive cyanosis needing an urgent repeat shunt or a revascularization procedure) was summarized in each treatment group using counts and percentages. The denominator used in the calculation of the percentages was the number of patients with a diagnosis of shunt thrombosis. No statistical testing was performed.
- The incidence of each type of cardiac procedure performed prior to 120 days of age (cavo-pulmonary anastomosis, surgical biventricular repair, any alternative palliation and heart transplantation) and the incidence of the events/symptoms leading to the cardiac procedure prior to 120 days were summarized separately in each treatment group using counts and percentages. The denominator, used in the calculation of the percentages, was the number of patients with a cardiac procedure prior to 120 days of age. The incidence of elective and non-elective cardiac related procedures was summarized in each treatment group using counts and percentages for all patients who had a cardiac related procedure. No statistical testing was performed.
- The results of the adjudication of the thrombotic nature of the bi-directional Glenn procedure or any cardiac-related intervention prior to 120 days of age was summarized in each treatment group by Investigator's assessment using counts and percentages. The denominator used for the calculation of percentages was the number of adjudicated events. No statistical testing was performed.
- Causes of death were summarized in each treatment group using counts and percentages. No statistical testing of these incidence rates was performed.

Determination of Sample Size

The sample size for this phase 3 study was derived using data collected in a registry. This database registry was compiled from some of the sites participating in the PICOLO phase 2 dose ranging study. Fifteen centers in the United States, France, and Germany were requested to prospectively and retrospectively gather information, using a standard form, on events occurring in their patients with a Blalock-Taussig shunt or any systemic-to-pulmonary artery shunt. Investigators provided data on patients who had a shunt placement between 2001 to 2004, specifically reporting the age of subsequent death, shunt thrombosis (including repeat shunt procedure), or urgent bi-directional Glenn/hemi-Fontan surgery <4 months of age. Follow-up data were provided through 1 year after the initial shunt placement.

Based on the data collected (912 patients with an initial shunt placement at the age of 3 months or less who were followed to 1 year of age [i.e., for 9-12 months]), the observed overall (regardless of initial procedure type) event rate for the primary endpoint in the control group was expected to be around 40%.

This phase 3 study was an event-driven trial and was conducted using a sequential design planned to include 3 interim analyses in order to evaluate the effect of clopidogrel on the primary efficacy endpoint with the potential to end the trial in the case of a clear efficacy advantage for clopidogrel. The trial assumptions used for determining the number of events included a power of 80% to detect a 30% relative reduction in the primary event rate (28% rate in the test group), and a 5% overall type 1 error rate. The maximum number of primary events required was 172. The actual sample size was then dependent on the observed overall event rate.

Given the previous registry event rate observed, an initial recruitment of a minimum of 490 patients (245 per treatment group) was planned but it was anticipated that patient recruitment would continue until enough patients were enrolled to achieve a total of 172 primary endpoint events. The common study end date was defined as the date when it was projected that 172 primary events would have occurred.

The difference between the events assessed in the registry and the ones defined in the EFC5314/CLARINET study (deaths during the first year after shunt palliation in the registry and only death as a first event in EFC5314/CLARINET; and any early cardiac-related procedure prior to 120 days of age in the registry and only early cardiac intervention of thrombotic nature adjudicated by an independent committee in EFC5314/CLARINET) explains why the recruitment needed to go far beyond 490 to reach the target of 172 events.

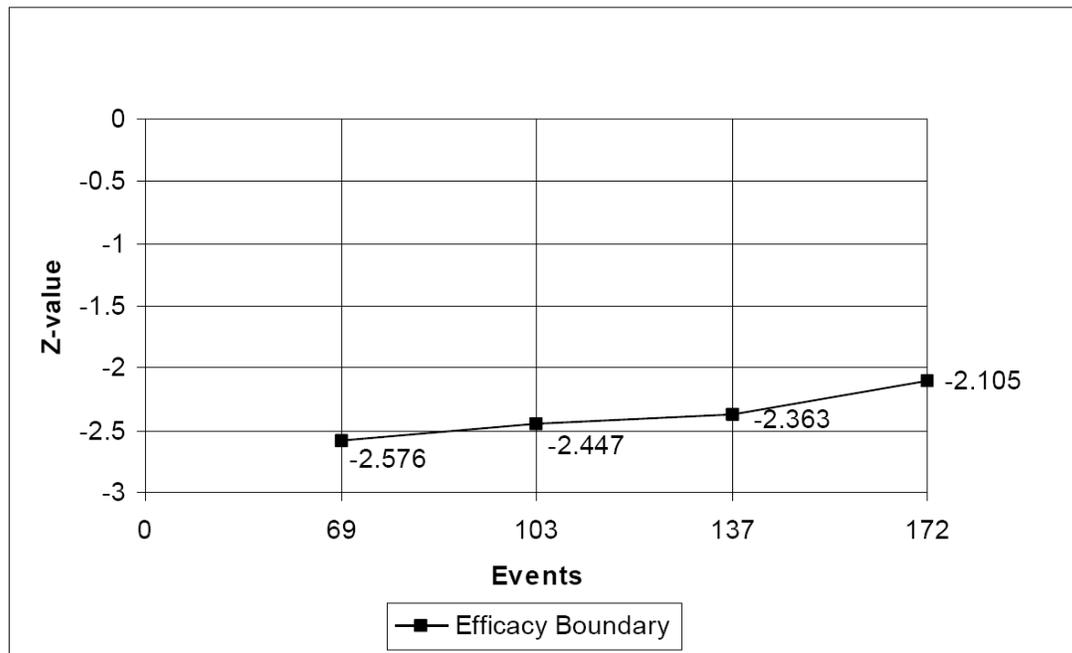
Overall 906 patients were randomized in the EFC5314/CLARINET study and 179 primary events occurred.

Interim Analysis

Due to the limited knowledge and therapeutic experience in this patient population, 3 interim analyses were performed during the trial to evaluate the effect of clopidogrel on the primary efficacy endpoint, with the potential to end the trial if there was a clear efficacy advantage for clopidogrel. All interim analyses were conducted by the DMC-associated statistician and the data were only given to the DMC.

The study was designed with 80% power and an overall type I error rate of 5%. Stopping boundaries were specified by selecting amounts of cumulative error probability (alpha spending function; 0.5% at each interim look) to be used at each of the analyses (calculated using EAST software, version 5.1) (see Figure 1 below). A total of 4 analyses (3 interim plus the final) were planned at approximately 40%, 60%, 80% and 100% of 172 required primary efficacy events.

Figure 1. Efficacy Stopping Boundaries for Three Interim analyses and the Final Analysis



Source: Sponsor's Figure 1 of CSR.

The first interim analysis was planned to occur after 69 primary events were observed. The trial would stop for efficacy if the observed z-value was less than -2.576 (nominally a p-value of 0.005). The second and third interim analyses were planned to occur after 103 and 137 primary events, respectively, were observed. While the overall type I error rate was 5%, the significance level at the final analysis would be 0.035, reflecting an adjustment for the interim analyses.

The initial protocol had included both futility and efficacy boundaries but was amended to remove the futility stopping boundary at the request of the FDA, and so subsequent changes were made on the efficacy stopping boundary, final significance level, and required number of primary events. Safety aspects were monitored every two months throughout the study by the DMC. The DMC would inform the Steering Committee and recommend stopping the study early only if, in their judgment, the risks to patients outweighed the potential benefits of treatment.

Subgroup Analysis

The incidence of the primary outcome was summarized for a number of subgroups of clinical interest to examine their potential effects. These subgroups included age, age categories (neonates versus infants), gender, race, age at shunt palliation (≤ 1 week and > 1 week), delay between shunt palliation and randomization, type of initial surgery (MBTS with Norwood, MBTS without Norwood, Sano with Norwood, Sano without Norwood, Central with Norwood, Central without Norwood, and stent with ductal arteriosus), and type of congenital cardiac defect (hypoplastic left heart syndrome, pulmonary atresia, tetralogy of Fallot, tetralogy of Fallot with pulmonary atresia, tricuspid atresia, other

single ventricle, other 2 ventricles, and Ebstein's anomaly), prior use of ASA, and concomitant use of ASA. The concomitant use of ASA was of clinical interest even though these subgroups were defined on the basis of post-randomization assessments and could be confounded with treatment effect. Given the number of subgroups considered and the possibility of small numbers of patients in some subgroups, the subgroup analyses should be interpreted with caution.

To examine the relationship between the treatment effect and the subgroups of most clinical interest, the time to the first occurrence of the primary endpoint was analyzed using the Cox proportional hazards model with terms for treatment, subgroup factor (covariate), and the treatment-by-subgroup interaction, and a test for interaction was performed. The number of patients with outcomes, estimated risk reductions, and associated 95% CIs were calculated within each of the subgroups generated from these analyses.

Note that no adjustments for multiplicity were made for the primary endpoint, except as described for the interim analyses. In the final analysis, statistical significance was claimed for the primary endpoint if the computed p-value was <0.035 .

Handling of dropouts or missing data

In the primary analysis, any patient, who was event free and withdrawn from the study, was censored at the date at which his/her status was last known (i.e., date of last assessment when data on components of the primary endpoint were available).

3.1.2 Disposition of Patients and Baseline Characteristics

Table 3.1.1 and Table 3.1.2 show the patient disposition and baseline characteristics, respectively. As shown in Table 1, among 906 patients randomized in the EFC5314/CLARINET study, 467 (51.5%) were in the clopidogrel group and 439 (48.5%) were in the placebo group. More patients in the clopidogrel group permanently discontinued the study drug than in the placebo group (24.1% versus 18.3%, $p = 0.0341$). The sponsor stated in the report that based on data in adults, when a patient was scheduled to undergo elective surgery, it was recommended that the study drug be discontinued 5 days prior to surgery. Due to the fear of bleeding, most surgeons decided to discontinue treatment more than 10 days prior to the second stage palliation procedure, leading to classification as "other causes" of permanent discontinuation. In addition, the most common reasons for permanent discontinuation of study drug were other reasons and AEs. For other reasons, mostly due to Investigators' decisions to stop earlier than the recommended window before surgery; 36 patients in the clopidogrel group and 27 in the placebo group.

Table 3.1.1 Sponsor's Summary of Patient Disposition Based on Safety Population

	Placebo (N=439)	Clopidogrel 0.2 mg/kg/day (N=467)
Randomized and treated	436 (99.3%)	464 (99.4%)
Completed study treatment period ^a	356 (81.7%)	352 (75.9%)
Permanently discontinued study drug	80 (18.3%)	112 (24.1%)
Adverse event	31 (7.1%)	34 (7.3%)
Lost to follow-up	0	0
Subject's request	10 (2.3%)	24 (5.2%)
Other reason ^b	39 (8.9%)	54 (11.6%)

^a Denominator for this row and following rows was the number of patients in the safety population

^b Most common other reasons were investigator's decision to stop > 10 days prior to surgery and medical decision.

Source: Sponsor's Table 5 of CSR.

Table 3.1.2 Sponsor's Summary of Patients' Demographic Baseline Characteristics

	Placebo (N=439)	Clopidogrel 0.2 mg/kg/day (N=467)	All (N=906)
Age(days)			
Number	439	467	906
Mean (SD)	36.0 (22.5)	36.1 (22.3)	36.1 (22.4)
Min : Max	1 : 92	3 : 92	1 : 92
Age (days) [n(%)]			
≤ 30	223 (50.8%)	238 (51.0%)	461 (50.9%)
> 30 to ≤ 92	216 (49.2%)	229 (49.0%)	445 (49.1%)
Gender [n(%)]			
Female	185 (42.1%)	198 (42.4%)	383 (42.3%)
Male	254 (57.9%)	269 (57.6%)	523 (57.7%)
Race [n(%)]			
Caucasian	312 (71.1%)	327 (70.0%)	639 (70.5%)
Black	30 (6.8%)	28 (6.0%)	58 (6.4%)
Asian/Oriental	61 (13.9%)	72 (15.4%)	133 (14.7%)
American Indian or Alaska Native	29 (6.6%)	34 (7.3%)	63 (7.0%)
Native Hawaiian or Pacific Islander	1 (0.2%)	0	1 (0.1%)
Other	6 (1.4%)	6 (1.3%)	12 (1.3%)
Hispanic or Latino [n (%)]	104 (23.7%)	116 (24.8%)	220 (24.3%)
Weight (kg)			
Number	439	467	906
Mean (SD)	3.5 (0.7)	3.4 (0.7)	3.5 (0.7)
Min : Max	2 : 6	2 : 6	2 : 6
Height (cm)			
Number	385	406	791
Mean (SD)	51.8 (4.6)	51.4 (4.4)	51.6 (4.5)
Min : Max	34 : 95	36 : 69	34 : 95

Source: Sponsor's Table 9 of CSR.

As shown in Table 3.1.2, the demographic and baseline characteristics were similar between the 2 treatment groups. The majority of patients enrolled were Caucasian (70.5%) and male (57.7%), with a mean age of 36.1 days at the time of randomization.

3.1.3. Sponsor's Efficacy Analysis Results

3.1.3.1 Primary Efficacy Analysis

Table 3.1.3 shows the sponsor's summary of frequency of the primary outcome. As shown in the table, a total of 89 (19.1%) patients in the clopidogrel group and 90 (20.5%) patients in the placebo group experienced a primary efficacy endpoint of death, shunt thrombosis, or cardiac procedure prior to 120 days considered to be of thrombotic nature by the EAC, resulting in a non-significant relative risk reduction of 11.1% in favor of clopidogrel (95%CI: -19.2, 33.6; p = 0.4340). The sponsor also calculated the Kaplan-Meier cumulative event rates at selected time points during the study. As shown in Table 3.1.4, they noted that the non-significant benefit of clopidogrel was early and was maintained throughout the duration. The sponsor's graph of the event rate over time for the primary outcome was shown in Figure 2.

Table 3.1.3 Sponsor's Summary of Frequency of Primary Outcome

	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.

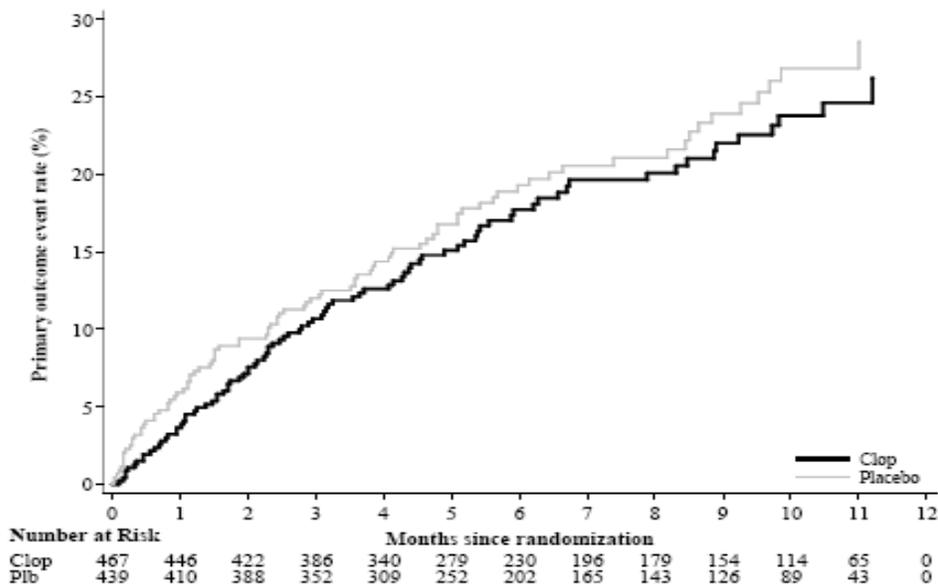
Source: Sponsor's Table 20 of CSR.

Table 3.1.4 Sponsor's Summary of Cumulative Event Rates for Primary Outcome

Time (Months)	Placebo (N=439)	Clopidogrel 0.2 mg/kg/day (N=467)	Absolute Difference (%) (95% C.I.)
0.5	4.10	1.93	2.17 (-0.06 to 4.41)
1	5.93	3.65	2.28 (-0.51 to 5.08)
2	9.39	7.57	1.83 (-1.82 to 5.48)
3	12.01	10.69	1.32 (-2.85 to 5.49)
4	14.37	12.61	1.77 (-2.77 to 6.31)
6	19.30	17.71	1.58 (-3.88 to 7.04)
9	23.93	22.02	1.91 (-4.60 to 8.42)
12	28.55	26.19	2.36 (-6.10 to 10.82)

Source: Sponsor's Table 21 of CSR.

Figure 2 Sponsor's Graph of Event Rate over Time For the Primary Outcome



Source: Sponsor's Figure 6 of CSR.

3.1.3.2 Secondary Efficacy Analyses

Investigator-Reported Outcomes

Table 3.1.5 shows the sponsor's summary of frequency of primary outcome as reported by the investigators. As shown in the table, the sponsor concluded that there was no statistically significant difference between the two treatment groups in the incidence of components of the primary efficacy endpoint as reported by the investigators.

Table 3.1.5 Sponsor's Summary of Frequency of Primary Outcome as Reported by the Investigators

	Placebo (N=439)	Clopidogrel 0.2 mg/kg/day (N=467)
Primary Outcome ^a	83 (18.9%)	79 (16.9%)
Death	61 (13.9%)	52 (11.1%)
Shunt thrombosis	21 (4.8%)	27 (5.8%)
Intervention < 120 days	1 (0.2%)	0
Log-rank test p-value		0.3168
Relative Risk Reduction (%) (95% CI)		14.6 (-16.3 to 37.2)

^a Death (including heart transplant)/shunt thrombosis requiring intervention/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. Only the first event was counted.

Source: Sponsor's Table 22.

Drug-Drug Interactions

Tables 3.1.6 and 3.1.7 show the sponsor's summary of primary outcome by both prior ASA use and concomitant ASA first use, respectively. As shown in the table, the sponsor concluded that there were no interactions between treatment and prior or concomitant ASA use.

Table 3.1.6 Sponsor's Summary of Primary Outcome by Prior ASA Use

Interaction Variable	Subgroup	Placebo	Clopidogrel 0.2 mg/kg/day	Hazard Ratio (95% CI)	p-value for interaction
ASA use	No (N=146)	16 (23.5%)	11 (14.1%)	0.56 (0.26 to 1.21)	0.4002
	Yes (N=760)	74 (19.9%)	78 (20.1%)	0.97 (0.70 to 1.33)	
ASA (mg/kg)	No intake (N=146)	16 (23.5%)	11 (14.1%)	0.56 (0.26 to 1.21)	
	≤ 3 mg/kg ^a (N=135)	13 (18.8%)	13 (19.7%)	1.08 (0.50 to 2.33)	
	> 3 to ≤ 5 mg/kg (N=323)	35 (22.6%)	35 (20.8%)	0.84 (0.53 to 1.35)	
	> 5 to ≤ 10 mg/kg (N=261)	24 (18.8%)	26 (19.5%)	1.02 (0.58 to 1.77)	
	> 10 mg/kg (N=41)	2 (10.5%)	4 (18.2%)	1.94 (0.35 to 10.6)	

^a Only one patient was in "≤ 1 mg/kg" category with no primary events. This patient was combined into "> 1 to ≤ 3 mg/kg" category.

Source: Sponsor's Table 27 of CSR.

Table 3.1.7 Sponsor's Summary of Primary Outcome by Concomitant ASA First 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)	

^a Only one patient was in "≤ 1 mg/kg" category with no primary events. This patient was combined into "> 1 to ≤ 3 mg/kg" category.

Source: Sponsor's Table 28 of CSR.

3.1.3.3 Interim Analysis

The sponsor's three interim analysis results are shown in Table 3.1.8. As described in the clinical study report, the first interim analysis was carried out when 79 primary events were reached, the second interim analysis was carried out when 103 primary events were reached, and the third interim analysis was carried out when 140 primary events were reached. For all three interim analyses, since there were no major safety concerns and the efficacy boundary was not crossed. Therefore, the DMC recommended continuing the study as planned.

Table 3.1.8 Sponsor's Interim Analysis Results

Interim Analysis	Number of Events (%)			Relative Risk Reduction & 95% C.I. (Clopidogrel vs Placebo)	Observed Z-Value
	Placebo	Clopidogrel 0.2 mg/kg/day	Total		
1	39 (16)	40 (16)	79 (16)	-1.3% (-57.5%, 34.8%)	0.058
2	50 (17)	53 (17)	103 (17)	-1.9% (-49.9%, 30.8%)	0.091
3	67 (18)	73 (18)	140 (18)	-1.6% (-41.5%, 27.1%)	0.003

Source: Sponsor's Table 3 on Page 50 of CSR.

Reviewer's Note: The sponsor's all three interim analysis results showed that patients in clopidogrel 0.2 mg/kg/day had similar number of primary outcome events as the patients in placebo did.

3.1.1.5 Statistical Reviewer's Findings and Comments

1. Basically, the statistical reviewer confirmed the sponsor's primary efficacy analysis results for Study EFC5314/CLARINET including those from three interim analyses. It was concluded that the clopidogrel did not have an effect in reducing rates of all-cause mortality and shunt-related morbidity in neonates or infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary shunt.
2. The medical reviewer found that the protocol of Study EFC5314/CLARINET specified that neonates were to be randomized as early as possible following shunt palliation. Nonetheless, almost half of the subjects were randomized more than 2 weeks after surgery and 23 % were randomized more than 4 weeks after surgery. During a pre-NDA meeting, the sponsor was asked to perform the interaction test for treatment and the days from shunt palliation to randomization. The sponsor's analysis results are shown in Table 4.2.2 of this review. The statistical reviewer noted that the sponsor's p-values was not correct. Instead of 0.4163, the statistical reviewer's p-value is 0.9371.

The sponsor noted that they treated patients' days from shunt palliation to randomization as a continuous variable, which is not suitable. Analyzing data by the Cox regression model, this variable should be grouped as a categorical variable. Strictly speaking, to make certain that the results are interpretable, the proportional hazard ratio assumptions should also be checked even though based on either result, the conclusion is that no interaction between treatment and patients' days from shunt palliation to randomization was observed.

3. Regarding the bleeding endpoint, it is very surprising to note that, patients in clopidogrel group showed a similar number of bleeding events as the patients in placebo group (See Table 3.2.2) did. For patients who had mild bleeding, those who took clopidogrel even had a smaller event rate than those who took placebo. This raised a concern that whether the sponsor used a proper dose in this trial.

In an FDA internal pediatric board meeting for determining the approval of granting the pediatric exclusivity held on October 5, 2010, the decision was made to issue a letter to the sponsor (dated October 14, 2010) for clarifying two major problems. One

problem is regarding the time of patients who were randomized after having the shunt palliation surgery and the other problem is regarding the dose selection procedure and the appropriateness of the chosen dose.

For the 2nd question, the sponsor emphasized that prior to initiation of this program, there was very limited data available about antiplatelet therapy in children. They also noted that ‘The 0.20 mg/kg dose identified in PICOLO was endorsed by the Platelet Aggregation Committee, Steering Committee and FDA and then was assessed in the efficacy study (CLARINET)’.

After reviewing the sponsor’s three interim analysis results and related meeting minutes, this reviewer found that in the sponsor provided closed meeting minutes (dated September 19, 2008) for the first interim analysis, it was mentioned that ‘There was slightly more SAEs in the clopidogrel group than the placebo (49% versus 41%). However there is little difference in bleeding SAEs (5.4% versus 5.0%). It is surprising that there are not more bleeding events in the clopidogrel group – the DMC members continue to raise the hypothesis that possibly the dose is not high enough which could also explain the lack of effect.’

Based on the sponsor’s response to the first question for the Pediatric Board Information Request, where it was mentioned that “The DMC was charged with making appropriate recommendations to the SC regarding the conduct or potential discontinuation of the trial.”, it appears that the sponsor and the Steering Committee were indeed informed about the possibility that 0.20 mg/kg dose could be too low to show efficacy and this information was given repeatedly and at the very early stage.

3.2 EVALUATION OF SAFETY

3.2.1 Sponsor’s Safety Analysis Plan

The review of safety and tolerance of the drug were performed on the safety population.

Incidences of treatment-emergent adverse events (TEAEs), serious TEAEs and events leading to non-CV death, AEs leading to treatment discontinuation, and bleeding AEs were summarized for each treatment group. The rates of TEAEs were compared between treatment groups using Pearson’s chi-square test.

Similar summary tables for AEs and SAEs were provided during pre-treatment and post-treatment periods. Pre-treatment AEs that led to treatment discontinuations were summarized.

All TEAEs and severe TEAEs related to abnormal hepatic function, abnormal renal function, allergic reaction, rashes, white blood cell count abnormalities, and platelet count abnormalities were summarized for each treatment group using counts and percentages.

Listings of all AEs, SAEs, AEs that resulted in discontinuation of study drug, and bleeding events by patient were provided.

Subgroup analyses

The incidence of any TEAE, and bleeding AEs was summarized for a number of subgroups of clinical interest to examine their potential effects. These subgroups included age, age categories (neonates versus infants), gender, race, age at shunt palliation (≤ 1 week and >1 week), delay between shunt palliation and randomization, type of initial surgery (MBTS with Norwood, MBTS without Norwood, Sano with Norwood, Sano without Norwood, Central with Norwood, Central without Norwood, and stent with ductal arteriosus), and type of congenital cardiac defect (hypoplastic left heart syndrome, pulmonary atresia, tetralogy of Fallot, tetralogy of Fallot with pulmonary atresia, tricuspid atresia, other single ventricle, other 2 ventricles, and Ebstein's anomaly), prior use of ASA, and concomitant use of ASA. The concomitant use of ASA was of clinical interest even though these subgroups were defined on the basis of postrandomization assessments and could be confounded with treatment effect. Given the number of subgroups considered and the possibility of small numbers of patients in some subgroups, the subgroup analyses should be interpreted with caution.

To examine the relationship between the treatment effect and subgroups of interest, the incidence of a TEAE or bleeding AE was analyzed using a logistic regression model incorporating terms for treatment, the subgroup factor, and treatment-by-subgroup interaction. A test for interaction was also performed.

Bleeding adverse events

The incidence of any bleeding AEs was summarized for a number of subgroups of clinical interest to examine their potential effects. These subgroups included age, age categories (neonates versus infants), gender, race, age at shunt palliation (≤ 1 week and >1 week), type of initial surgery (modified BTS with Norwood, modified BTS without Norwood, Sano with Norwood, Sano without Norwood, Central with Norwood, Central without Norwood, and stent with ductal arteriosus), and type of congenital cardiac defect (hypoplastic left heart syndrome, pulmonary atresia, tetralogy of Fallot, tetralogy of Fallot with pulmonary atresia, tricuspid atresia, other single ventricle, and other 2 ventricles), prior use of ASA, and concomitant use of ASA. The concomitant use of ASA was of clinical interest even though these subgroups were defined on the basis of post-randomization assessments and could be confounded with treatment effect. Given the number of subgroups considered and the possibility of small numbers of patients in some subgroups, the subgroup analyses should be interpreted with caution.

To examine the relationship between the treatment effect and subgroups, the incidence of any bleeding AEs was analyzed using a logistic regression model with terms for treatment, subgroup factor, and treatment-by-subgroup interaction. A test for interaction was also performed.

The number and percentage of patients who required intervention due to a bleeding adverse event and the number and percentage of patients with a bleeding episode associated with hemodynamic compromise were summarized for each treatment group. The types of bleeding and interventions were also summarized.

3.2.2 The Sponsor's Safety Analysis Results

Treatment-Emergent Adverse Events

The sponsor's overall summary of treatment-emergent AEs is shown in the following Table 3.2.1. They concluded that no significant difference was seen in the incidence of bleeding events between the clopidogrel and placebo groups. However, post-traumatic and surgical bleeding tended to be more frequent in the clopidogrel group.

Table 3.2.1 Sponsor's Overall Summary of Treatment-Emergent Adverse Events

	Placebo (N=436)	Clopidogrel 0.2 mg/kg/day (N=464)	Difference (%) (95% CI)	p-Value ^a
Any AE	310 (71.1%)	353 (76.1%)	5.0 (-1.0 to 11.0)	0.0903
Bleeding event ^b	88 (20.2%)	87 (18.8%)	-1.4 (-6.8 to 4.0)	
Non-bleeding event	222 (50.9%)	266 (57.3%)	6.4 (-0.3 to 13.1)	
Any SAE	196 (45.0%)	234 (50.4%)	5.5 (-1.3 to 12.2)	0.1002
Bleeding event ^b	32 (7.3%)	30 (6.5%)	-0.9 (-4.4 to 2.7)	
Non-bleeding event	164 (37.6%)	204 (44.0%)	6.4 (-0.3 to 13.0)	
SAE with an outcome of death	14 (3.2%)	16 (3.4%)	0.2 (-2.3 to 2.8)	0.8429
Bleeding event ^b	1 (0.2%)	1 (0.2%)	-0.0 (NC)	
Non-bleeding event	13 (3.0%)	15 (3.2%)	0.3 (-2.2 to 2.7)	
AE leading to permanent discontinuation	31 (7.1%)	34 (7.3%)	0.2 (-3.4 to 3.8)	0.8998
Bleeding event ^b	9 (2.1%)	9 (1.9%)	-0.1 (-2.2 to 1.9)	
Non-bleeding event	22 (5.0%)	25 (5.4%)	0.3 (-2.8 to 3.5)	

AE = adverse event; SAE = serious adverse event.

^a Chi-square

^b Patients having both a bleeding event and non-bleeding event AE are counted only in the bleeding event AE row

Source: Sponsor's Table on Page 6 of CSR.

3.2.2 Bleeding Assessments

Table 3.2.2 shows the sponsor's analysis results for treatment-emergent bleeding events by maximum intensity. Note that the bleeding was assessed based on the level of intensity as per the investigator's judgment. Based on the results, the sponsor concluded that the incidence of any treatment-emergent bleeding events was similar in the 2 treatment groups. The bleeding events were mainly mild or moderate and among severe bleeding, two events led to death, one patient in each treatment group.

Table 3.2.2 Sponsor's Analysis Results for Patients with Treatment-Emergent Bleeding Events by Maximum Intensity

	Placebo (N=436)	0.2 mg/kg/day (N=464)	Difference (%) (95% CI)	p-Value ^a
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.

Source: Sponsor's Table 36 of CSR.

The sponsor also displayed a table for patients with treatment-emergent bleeding adverse events by MedDRA system organ class regardless of incidence and by preferred term in at least one percent of patients in any treatment group. They noted that the incidence of any treatment-emergent bleeding events was similar between the two treatment groups. In addition, it was noted that bleeding events reported in more than 1% of the patients in the clopidogrel group were mainly of gastrointestinal origin or related to injury, poisoning and procedural complications, according to MedDRA system organ class coding. Gastrointestinal hemorrhage, hematochezia and post-procedural hemorrhage were the most frequently reported bleeding events in the clopidogrel group.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE AND AGE

4.1.1 For Primary Outcome Measure

Table 4.1.1 shows the sponsor's summary of primary outcome by demographic subgroup. As shown in the table, the sponsor concluded that there were no interactions between treatment and age, gender or race in the incidence of the primary efficacy endpoint. Numerically, however, there were fewer events in the clopidogrel group in patients ≤ 30 days and in males.

Table 4.1.1 Sponsor's Summary of Primary Outcome by Demographic Subgroup

Interaction Variable	Subgroup	Placebo	Clopidogrel 0.2 mg/kg/day	Hazard Ratio (95% CI)	p-value for interaction
Age (days) ^a	≤ 30 (N=461)	48 (21.5%)	43 (18.1%)	0.78 (0.52 to 1.18)	0.6357
	> 30 to ≤ 92 (N=445)	42 (19.4%)	46 (20.1%)	1.01 (0.67 to 1.54)	
Gender	Female (N=383)	37 (20.0%)	42 (21.2%)	1.04 (0.67 to 1.61)	0.3847
	Male (N=523)	53 (20.9%)	47 (17.5%)	0.80 (0.54 to 1.18)	
Race ^b	Caucasian (N=639)	55 (17.6%)	58 (17.7%)	0.97 (0.67 to 1.40)	0.4561
	Black (N=58)	12 (40.0%)	7 (25.0%)	0.62 (0.24 to 1.57)	
	Asian/Oriental (N=133)	10 (16.4%)	14 (19.4%)	1.14 (0.51 to 2.57)	
	American Indian or Alaska Native (N=63)	11 (37.9%)	9 (26.5%)	0.69 (0.28 to 1.66)	
	Other (N=13)	2 (28.6%)	1 (16.7%)	0.31 (0.03 to 3.61)	

Note: One patient of Native Hawaiian race was grouped in Other race

^a Age was included in the model as continuous.

^b All patients of a non-Caucasian race were grouped together for statistical testing since the proportion of Black, Asian/Oriental, American Indian or Alaska Native, Native Hawaiian or Pacific Islander and patients of 'other' ethnic origin was small.

Source: Sponsor's Table 23 of CSR.

4.1.2 For Bleeding Events

Table 4.1.2 shows the sponsor's subgroup analysis results for bleeding events. As shown in the table, they concluded that there were no significant interactions between baseline demographic covariates and treatment for the incidence of treatment-emergent bleeding events.

Table 4.1.2 Sponsor's Subgroup Analysis Results for Treatment Emergent Bleeding

Interaction Variable	Subgroup	Placebo	Clopidogrel 0.2 mg/kg/day	Odds Ratio (95% CI)	p-value for interaction
Age (days) ^a	≤ 30 (N=458)	45 (20.3%)	46 (19.5%)	0.95 (0.60 to 1.51)	0.2845
	> 30 to ≤ 92 (N=442)	43 (20.1%)	41 (18.0%)	0.87 (0.54 to 1.40)	
Gender	Female (N=378)	36 (19.7%)	39 (20.0%)	1.02 (0.62 to 1.69)	0.5663
	Male (N=522)	52 (20.6%)	48 (17.8%)	0.84 (0.54 to 1.30)	
Race ^b	Caucasian (N=635)	74 (23.9%)	65 (20.0%)	0.80 (0.55 to 1.16)	0.1251
	Black (N=58)	6 (20.0%)	7 (25.0%)	1.33 (0.39 to 4.60)	
	Asian/Oriental (N=131)	2 (3.3%)	8 (11.3%)	3.68 (0.75 to 18.0)	
	American Indian or Alaska Native (N=63)	4 (13.8%)	5 (14.7%)	1.08 (0.26 to 4.46)	
	Other (N=13)	2 (28.6%)	2 (33.3%)	1.25 (0.12 to 13.2)	

Note: One patient of Native Hawaiian race was grouped in Other race

^a Age was included in the model as continuous.

^b All patients of a non-Caucasian race were grouped together for statistical testing since the proportion of Black, Asian/Oriental, American Indian or Alaska Native, Native Hawaiian or Pacific Islander and patients of 'other' ethnic origin was small.

Source: Sponsor's Table 39 of CSR.

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

4.2.1 Shunt Palliation Surgery

Table 4.2.1 shows the sponsor's summary of primary outcome by type of initial surgery subgroup. Again, as shown in the table, the sponsor concluded that there were no interactions between treatment and type of initial surgery subgroups.

Table 4.2.1 Sponsor's Summary of Primary Outcome by Type of Initial Surgery Subgroup

Interaction Variable	Subgroup	Placebo	Clopidogrel 0.2 mg/kg/day	Hazard Ratio (95% CI)	p-value for interaction
Type of shunt palliation ^a	Modified BTS with Norwood (N=113)	8 (15.7%)	11 (17.7%)	1.17 (0.47 to 2.90)	0.3288
	Modified BTS without Norwood (N=509)	51 (20.2%)	42 (16.3%)	0.75 (0.50 to 1.13)	
	Sano with Norwood (N=114)	7 (13.0%)	16 (26.7%)	1.92 (0.79 to 4.69)	
	Sano without Norwood (N=7)	1 (50.0%)	2 (40.0%)	0.75 (0.07 to 8.42)	
	Central shunt (N=78)	8 (21.1%)	10 (25.0%)	1.06 (0.42 to 2.69)	
	Stent of ductus arteriosus (N=84)	15 (35.7%)	8 (19.0%)	0.51 (0.22 to 1.22)	
Age at shunt palliation ^b	≤ 1 week (N=427)	41 (19.8%)	47 (21.4%)	1.09 (0.72 to 1.66)	0.8622
	> 1 week (N=479)	49 (21.1%)	42 (17.0%)	0.73 (0.49 to 1.11)	

^a One patient did not have type of shunt palliation and was therefore not included in this subgroup analysis

Note: One patient had shunt palliation after randomization. This patient was included in this study

^b Age was included in the model as continuous.

BTS = Blalock-Taussig Shunt

Source: Sponsor's Table 24 of CSR.

Table 4.2.2 shows the sponsor’s analysis results for the primary outcome by days from shunt palliation to randomization. Again, as shown in the table, the sponsor concluded that there were no interactions between treatment and delay between shunt palliation and randomization subgroups. Please note that the statistical reviewer found that the sponsor p-value was calculated by treating patient’s days from shunt palliation to randomization as a continuous variable directly into the Cox regression model, with is not suitable. The statistical reviewer’s calculated p-value was 0.9371.

Table 4.2.2 Sponsor’s Summary of Primary Outcome by Days from Shunt Palliation to Randomization

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)	This is not correct.
	>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.

Source: Sponsor’s Table 25 of CSR.

4.2.2 Type of Congenital Cardiac Defect

Table 4.2.3 shows the sponsor’s summary of primary outcome by additional congenital cardiac defect subgroup. As shown in the table, there were no interaction between treatment and type of congenital cardiac defect subgroups in the incidence of primary efficacy endpoint.

Table 4.2.3 Sponsor’s Summary of Primary Outcome by Additional Congenital Cardiac Subgroup

Interaction Variable	Subgroup	Placebo	Clopidogrel 0.2 mg/kg/day	Hazard Ratio (95% CI)	p-value for interaction
Type of congenital cardiac defect	Hypoplastic left heart syndrome (N=218)	21 (20.6%)	24 (20.7%)	0.94 (0.52 to 1.68)	0.5920
	Pulmonary atresia with intact ventricular septum (N=119)	11 (18.6%)	10 (16.7%)	0.95 (0.40 to 2.25)	
	Tetralogy of Fallot (N=65)	5 (19.2%)	4 (10.3%)	0.42 (0.11 to 1.58)	
	Tetralogy of Fallot with pulmonary atresia (N=118)	18 (31.6%)	11 (18.0%)	0.52 (0.25 to 1.11)	
	Tricuspid atresia (N=82)	10 (22.2%)	8 (21.6%)	0.88 (0.35 to 2.24)	
	Other single ventricle (N=128)	10 (16.7%)	17 (25.0%)	1.53 (0.70 to 3.35)	
	Other 2 ventricle (N=110)	9 (15.5%)	10 (19.2%)	1.16 (0.47 to 2.87)	
	Multiple congenital cardiac defects (N=64)	6 (20.0%)	5 (14.7%)	0.65 (0.20 to 2.14)	

Note: Ebsteins anomaly is not included as only 2 additional patients with no primary outcomes have this congenital cardiac defect

Source: Sponsor’s Table 26 of CSR.

4.2.3 Regions

Tables 4.2.4 and 4.2.5 show the sponsor's regional subgroup analysis results for US versus non-US and for multi-regions, respectively. Based on the results, the sponsor concluded that there was no interaction between US and non-US countries and treatment effect. The conclusions of the study are substantially the same in the US, non-US countries and in the overall study population. Basically, they concluded results do not support the use of clopidogrel 0.2 mg/kg once daily in US or in the rest of the world in children with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt.

Table 4.2.4 Sponsor's Summary of Primary Outcome by Country Subgroup (US vs. Non-US)

Interaction		No. (%) with Event			Hazard Ratio (95% CI)	p-Value for Interaction
Variable	Subgroup	Placebo	Clopidogrel 0.2 mg/kg/day			
United States	No (n=728)	74 (21.20)	73 (19.26)	0.88 (0.64 to 1.22)	0.8714	
	Yes (n=178)	16 (17.78)	16 (18.18)	0.96 (0.48 to 1.92)		

Source: Sponsor's Table 5 of Response to FDA Request.

Table 4.2.5 Sponsor's Summary of Primary Outcome by Region Subgroup

Interaction		No. (%) with Event			Hazard Ratio (95% CI)	p-Value for Interaction
Variable	Subgroup	Placebo	Clopidogrel 0.2 mg/kg/day			
Region	North America (n=189)	16 (16.84)	16 (17.02)	0.93 (0.47 to 1.87)	0.2407	
	Latin America (n=186)	32 (36.78)	25 (25.25)	0.68 (0.40 to 1.14)		
	Africa (n=36)	11 (64.71)	6 (31.58)	0.35 (0.13 to 0.95)		
	Asia (n=114)	10 (18.18)	13 (22.03)	1.13 (0.50 to 2.59)		
	Eastern Europe (n=56)	4 (16.00)	5 (16.13)	1.01 (0.27 to 3.79)		
	Western Europe & Israel (n=325)	17 (10.63)	24 (14.55)	1.38 (0.74 to 2.58)		

Note: Africa includes Egypt and South Africa.

Asia includes China, Hong Kong, India, Republic of Korea, Malaysia, Singapore, Taiwan, and Thailand.

Eastern Europe includes Hungary, Poland, and Russian Federation.

Latin America includes Argentina, Brazil, and Mexico.

North America includes Canada and United States.

Western Europe includes Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Portugal, Spain, Sweden, United Kingdom, and Israel.

Source: Sponsor's Table 6 of Response to FDA Request.

5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

- The sponsor's efficacy analysis results for the primary efficacy endpoint had been confirmed by the statistical reviewer. Based on the results from three interim and

the final analyses, it was concluded that clopidogrel did not show an effect in reducing the all-cause mortality and shunt-related morbidity in neonates or infants with cyanotic congenital heart disease palliated with systemic-to-pulmonary artery shunt.

- One major discrepancy between the sponsor's analysis results and the statistical reviewers is that the statistical reviewer found that for the interaction between patients' days from shunt palliation surgery to randomization and the study treatments, the sponsor calculated p-value was obtained by treating patients' days from shunt palliation surgery to randomization as a continuous variable directly in the cox regression model. Their p-value was 0.4163.

Due to the underlying proportional hazards assumption, this variable should be categorized to few categories for being analyzed in the Cox regression model. The p-value this reviewer found was 0.94 even though based on either results, the same conclusion, that no different efficacy findings among different groups of patients with different days from shunt palliation surgery to randomization, was made.

- Patients' in clopidogrel group had surprisingly similar bleeding event rate to those in placebo. A concern about using an improper dose in Study EFC5314/CLARINET has been raised to the sponsor. The sponsor insisted that the chosen dose is endorsed by the Platelet Aggregation Committee, Steering Committee and FDA.

This reviewer found that based on the sponsor's closed meeting minutes for the first interim analysis, the sponsor was indeed informed by the DMC that the 0.20 mg/kg dose could be too low to show clopidogrel's efficacy. It was also noted that the DMC had raised this concern to the sponsor at least twice and right after they saw the first interim analysis results.

5.2 CONCLUSIONS AND RECOMMENDATIONS

Data from Study EFC5314/CLARINET did not show that clopidogrel has efficacy in reducing neonates or infants' all-cause mortality and shunt-related morbidity for those with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt.

Due to the unexpectedly similar bleeding event rates between the clopidogrel 0.2 mg/kg dose group and placebo, a concern of insufficient dose used was raised and a letter was sent to the sponsor for clarification. The sponsor insisted that the chosen dose is endorsed by the Platelet Aggregation Committee, Steering Committee and FDA. The statistical reviewer found that based on the sponsor provided closed meeting minutes of the first interim analysis, the sponsor was indeed informed repeatedly that the used dose could be too low to demonstrate clopidogrel's efficacy.

Yeh-Fong Chen, Ph.D.
Mathematical Statistician

cc: NDA 20839
HFD-110/Dr. Stockbridge
HFD-110/Dr. Grant
HFD-110/Dr. Rose
HFD-110/Ms. Blaus
HFD-700/Ms. Patrician
HFD-710/Dr. Hung

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YEH FONG CHEN
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HSIEN MING J J HUNG
11/29/2010