CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-839/S-051

MEDICAL REVIEW(S)

MEMORANDUM

From: Martin Rose, MD, JD, Medical Officer, DCRP
To: Pediatric Exclusivity Board
CC: Norman Stockbridge, MD
Stephen Grant, MD
Alison Blaus
Re: Pediatric Exclusivity for Clopidogrel, NDA 20839 – Additional Information
Date: 10 January, 2010

This memorandum summarizes information obtained since the last Board meeting in which clopidogrel was discussed. This includes Steering Committee and closed Data Monitoring Committee meeting minutes, further review of pediatric formulation issue, and additional information from DSI regarding CLARINET site inspections in the US and Argentina.

CLARINET Steering Committee (SC) meeting minutes

The CLARINET SC minutes reveal:

- Concern among members of the SC regarding the dose of clopidogrel selected for use in CLARINET;
- No evidence that FDA's concerns about the implications of the reduced reactivity to ADP of platelets in the CLARINET target population was communicated to the SC; and
- No evidence that the SC was aware of the potential implications of the differences between the formulation used in CLARINET and the ones used in PICOLO and the bioavailability study.

The first CLARINET SC meeting was held on November 12, 2006. There were a number of presentations regarding the prior pediatric studies and the PWR. (b) (4) (PI for PICOLO and SC member) presented the PICOLO results. The minutes state, "Some of the investigators pointed out that the dose chosen in phase III may be too small…"

We have been informed by several SC members that it was their understanding that FDA had accepted the use of the dose of 0.2 mg/kg/day for the CLARINET trial. Despite the fact that the Pediatric Written Request requirements were discussed, as well as the results of the EOP2 meeting held in 2006, there is no evidence in the SC minutes that the SC was informed about our concerns expressed at the EOP2 that reduced baseline platelet responsiveness to ADP stimulation in newborns and infants might affect the "premise for the [CLARINET] study," and that our acceptance of the data supporting use of the 0.2 mg/kg/day dose was contingent on the submission of data showing similar platelet responses to 5 µM ADP in the CLARINET target population and adults.

In addition, with regard to formulation issues, the SC was informed that the PWR required the sponsor to "Find a pediatric formulation (liquid formulation) and conduct a bioavailability study," and that this was "done". This was shown in a slide presentation of the PWR status at the first and several subsequent SC meetings. There is no evidence in the SC meeting minutes that the SC was made aware of the major differences among the formulation used in the bioavailability study and the similar (but not identical) formulation used in PICOLO, versus the one used in the CLARINET study. This issue is discussed further below.

CLARINET Data Monitoring Committee (DMC) closed meeting minutes

The DMC meeting minutes indicate that this committee became concerned over the course of the study about the possibility that the dose of clopidogrel used in CLARINET was too low because the rate of bleeding was similar in the clopidogrel and placebo arms. Meetings where information about the similarity of the bleeding rates in the two treatment arms was discussed are summarized below. Note that concern about the implications of the bleeding data was not immediately expressed.

The minutes of the meeting held on October 5, 2007 note that, "The bleeding events are well balanced between the two groups." At this point, there was no evidence of concern. The available data for this meeting came from 167 randomized patients, constituting 18% of the final study population of 906 randomized patients.

Bleeding was next mentioned at the meeting of 15 April 2008, when it was noted that, "Overall, there is a very low number of SAEs related to bleeding and nothing different than what would be expected in this population." At this point, data from 390 randomized patients (43%) was available.

At the next DMC meeting, held July 22, 2008, concern about the implication of the similar bleeding rates in the two arms was expressed: "There are slightly more SAEs in the clopidogrel group than the placebo group (47% versus 39%). However there is no difference in bleeding events (5.2% versus 5.4%). It is surprising that there are not more bleeding events in the clopidogrel group – the DMC members raised the hypothesis that possibly the dose is not high enough which could also explain the lack of effect." At this point, data from 496 patients (55%) were available.

The next DMC meeting was held on September 19, 2008. The concerns from the earlier meeting were reiterated: "There are slightly more SAEs in the clopidogrel group than the placebo group (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." At this point, there were 571 randomized patients (63%).

At the following DMC meeting, held November 26, 2008, it was noted that, "There is no difference in bleeding events between the two treatment groups (16% clopidogrel versus

19% placebo). The difference that one would expect to see is not seen. As a comparison, 2% of the patients not taking ASA had a bleeding event versus 15% of those taking ASA." At this point, there were 599 randomized patients (66%).

The next DMC meeting was held on February 11, 2009. It was noted that, "There is no difference in bleeding events between the two treatment groups (15% clopidogrel versus 18% placebo)." At this point, there were 703 randomized patients (78%).

The following DMC meeting was the last one where bleeding rates were discussed. It was noted that, "There is no difference in bleeding events (16% clopidogrel versus 18% placebo) or SAE bleeding events (5.8% compared to 6.1%) between the two treatment groups although that clopidogrel group did have more severe bleeding events (25% compared to 14%)."

There is no evidence that bleeding rates were discussed at the final two DMC meetings, which were held in June and August of 2009.

Although there was obvious concern about the implications of the similar bleeding rates in the two arms among the DMC members, there is no evidence that this was communicated to the SC or the sponsor. The recommendation of the DMC was consistently to allow the study to proceed as planned.

Formulation issues

The bioavailability of the formulation used CLARINET was not evaluated, even though the CLARINET formulation differed from the previous formulations in ways that might have led to reduced bioavailability. We believe that the failure to evaluate the bioavailability of the CLARINET formulation is not consistent with good scientific practices.

Details of the characteristics of the clopidogrel solution formulations used in the sponsor's program are displayed in Table 1.

Table 1 -- Formulations used in the clopidogrel pediatric studies

	BDR4580 – Comp. bioavailabilty study	PDY4422 – PICOLO	EFC-5314 – CLARINET
Form	[redacted] (b) (4)		
Final concentration			
pH			
Constituted pH			
Buffer			
Solubilizer/emulsifier			
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 [redacted] (b) (4)

The BDR4580 and PICOLO formulations [redacted] (b) (4) Solubility of clopidogrel, which is poorly soluble in all but highly acidic aqueous media, [redacted] (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, [redacted] (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. Pharmaceutical equivalence is based on similarity of the

active ingredient(s), dosage form, route of administration and strength or concentration. It does not necessarily imply similarity in bioavailability. An assumption of similar bioavailabilty may be justified with respect to the BA of the BDR4580 formulation and the PICOLO formulation. Both of these were (b) (4) , and 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 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, 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 procures.

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.

It was inappropriate to assume that the CLARINET formulation is equivalent in bioavailabilty 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 thus may be invalid because of reduced bioavailability. Reduced BA of clopidogrel in the CLARINET formulation could explain the lack of increased bleeding in subjects randomized to clopidogrel and the negative results for the primary endpoint.

We think there is a substantial question regarding the bioavailability of the CLARINET formulation. It would have been prudent to have done a BA study with this formulation, which what we think any sponsor developing a formulation for adults would have done in the same situation. We have asked OPS for their opinion on this issue; I hope to have this before the Board meeting on January 13.

Appendix I, copied from the Quality Overall Summary in the sponsor's labeling supplement, includes additional information on formulations used in the clopidogrel pediatric program.

Additional CLARINET site inspection information

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 1and 2, respectively. Only two of the US sites and one of the Argentinean sites administered aspirin to study patients. Note that data were not provided to us in a uniform way.

Table 2. 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 3. 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 we have from these sites indicate that in general, there were substantial delays from initiation of aspirin therapy to randomization. In all cases, aspirin route of administration was either oral or via feeding tube; no rectal aspirin was used. Data on initiation of feeding comes only from the Argentinean sites; the delay from initiation of feeding to randomization was substantial. At the one site in Argentina from which we have data for both initiation of aspirin and feeding, delays between initiation of feeding and randomization tended to be longer than the delays between initiation of aspirin and randomization.

As we stated previously, the delay in randomization reduced the study's ability to detect a beneficial effect on thrombotic events occurring soon after surgery, when events are most frequent. It not known whether the efficacy of anti-thrombotic therapy is greater in early than in late events in congenital heart surgery patients, as it is in adult patients. However, since only about ½ of patients were randomized within 2 weeks of surgery, the study's power to show an effect on early events was substantially reduced. If the effect of clopidogrel is greatest in the first few weeks after surgery, then the study may have been underpowered due to the delays in randomization.

We have received letters from several academic physicians associated with the trial, who argue strongly that it would have been very difficult to perform the trial with more stringent criteria regarding the timing of randomization. They state that it may be necessary to delay initiation of an *additional* antiplatelet agent when a patient is hemodynamically unstable or at risk for additional surgery. They argue that the trial was large and needed to have many sites to complete enrollment in a reasonable period. It seems clear to us that some sites were able to randomize early, while others seemed to consistently choose not to. We still think that it would been preferable for the protocol to be more specific about when randomization should occur (e.g., within 2 days of the time of initiation of oral or enteric aspirin therapy or attainment of goal feeds, whichever occurred first). However, it is possible that the study may have been very hard to perform in a timely manner if site enrollment were limited to centers that were committed to randomization on such a schedule. Nonetheless, we think the sponsor should have made additional efforts to enroll patients earlier after surgery, as we described in earlier communications to the Board. If those efforts were counterproductive in terms of enrollment, they might have been justified reverting to the original eligibility criteria; i.e., giving the investigators discretion to enroll patients at any time they thought appropriate up to the age limit on enrollment (92 days).

Recommendation: Our recommendation is unchanged: Pediatric exclusivity should be denied because of the following issues in the design and execution of the pediatric program, each of which was inconsistent with good scientific principles:

- Failure to evaluate the bioavailability of the formulation used in CLARINET, which differed substantially form those used in previous pediatric studies, and may have been less bioavailable.
- Use of a dose of clopidogrel in CLARINET that was too low to be effective or to cause increased bleeding. While the sponsor claims that we agreed to use of this dose, our agreement was contingent on the submission of data showing similar platelet responsiveness to ADP stimulation in the CLARINET target population and in adults, which was not submitted.
- Delayed randomization in CLARINET, which reduced the study's power to show an effect on early thrombotic events and may have made the study underpowered. The sponsor could have done considerably more to prevent delays in randomization.

APPENDIX 1 – Formulation information from the Sponsor's Overall Quality Summary

Table 2 - Formulation development overview

	Phase 1	Phase 2	Phase 3
Treatment duration	Single dose	7 to 28 days	up to 1 year
	Adults	Children	Children

(b) (4)

APPENDIX 1 – Formulation information from the Sponsor's Overall Quality Summary

Table 3 - History of formulation changes – (b) (4)

Development Phase	Dosage strength (expressed as base)	Formulation changes
(b) (4)		

Table 4 – History of formulation changes – (b) (4)

Development Phase	Deliverable volume	Formulation changes
(b) (4)		

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/s/

MARTIN ROSE
05/02/2011

Medical Officer's Review of a Pediatric Labeling Supplement

Martin Rose MD, JD CDER/OND/DCRP

NDA:	020839, S051
Supporting Document #:	Initial: SD 307 (eCTD 0068)**;** amendments: SD 313, 316 – 319, 321 – 24
Submission type:	Labeling Supplement / Complete Response to 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).
Submission date:	15 July 2010
Review type	Priority
PDUFA target:	15 Jan 2011
Review date:	22 December 2010
RPM:	Alison Blaus
Quality reviewer	Kasturi Srinivasachar
OPC reviewer	Elena Mishina
Biometric reviewer	Yeh Fong Chen
Sponsor:	sanofi aventis
Product:	Plavix (clopidogrel bisulfate)

1 Executive summary

This submission is a complete response to 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 proposed labeling revisions to reflect the results of the sponsor's safety and efficacy study for the target indication, which failed to show a benefit of clopidogrel. No new indication or formulation is proposed for marketing. The sponsor is requesting Pediatric Exclusivity, specifically, a six month extension of listed patents.

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, contrary to the requirements for granting Pediatric Exclusivity. This reviewer also believes that this conduct rises to the level of failure to "fairly respond to the written request", as required for the grant of Pediatric Exclusivity. 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, and this issue probably could not fairly stand on its own as a reason to deny pediatric exclusivity. 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, a result that that we propose to indicate in labeling. Thus,

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

Recommendation: We should approve the sponsor's labeling supplement with labeling that describes the inconclusive nature of the results of CLARINET as discussed above. The Division should recommend to the Pediatric Exclusivity Board that FDA should deny Pediatric Exclusivity for clopidogrel.

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 SPTAS 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. The major focus of the review will be whether the requirements for the award of pediatric exclusivity have been met.

[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) .[2]

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] The sponsor did not request approval of a pediatric formulation. 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 μM 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 5μM 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 μM 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 μM 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)

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

[a] neonates only

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. bioavailabilty 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 and the award of Pediatric Exclusivity 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.
PGM=DEVOPS/SR25990C/EFC5314/CSR/REPORT/PGM/i4ishunt.sas OUT=REPORT/OUTPUT/i4ishunt_i.rtf (05MAR2010 - 15:34)

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.
PGM=DEVOPS/SR25990C/EFC5314/CSR/REPORT/PGM/i6eff1.sas OUT=REPORT/OUTPUT/i6eff1_i.rtf (10MAR2010 - 17:34)

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			
	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.

PGM=DEVOPS/SR25990C/EFC5314/CSR/REPORT/PGM/i7tebe1_max2.sas OUT=REPORT/OUTPUT/i7tebe1_max2_i.rtf (01JUN2010 - 17:27)

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. bioavailabilty study	PDY4422 – PICOLO	EFC-5314 – CLARINET
Form	[redacted] (b) (4)		
Final concentration			
pH			
Constituted pH			
Buffer			
Solubilizer/emulsifier			
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 [redacted] (b) (4) ."

The BDR4580 and PICOLO formulations [redacted] (b) (4) . Solubility of clopidogrel, which is poorly soluble in all but highly acidic aqueous media, [redacted] (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, [redacted] (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 [redacted] (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 [redacted] (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 procures.

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.
PGM=DEVOPS/SR25990C/EFC5314/CSR/REPORT/PGM/i4ishunt.sas OUT=REPORT/OUTPUT/i4ishunt_i.rtf (05MAR2010 - 15:34)

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.
PGM=DEVOPS/SR25990C/EFC5314/CSR/REPORT/PGM/i6eint_ishunt_5.sas OUT=REPORT/OUTPUT/i6eint_ishunt_5_i.rtf (17MAY2010 - 8:16)

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 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 form 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 "Patients should be randomized preferably as soon as they are hemodynamically stable and able to receive the drug orally / enterically" (version dated 06 MARCH 06/ DRAFT 01, submitted 09 March 2006 (IND 34,663 SN 0622). 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

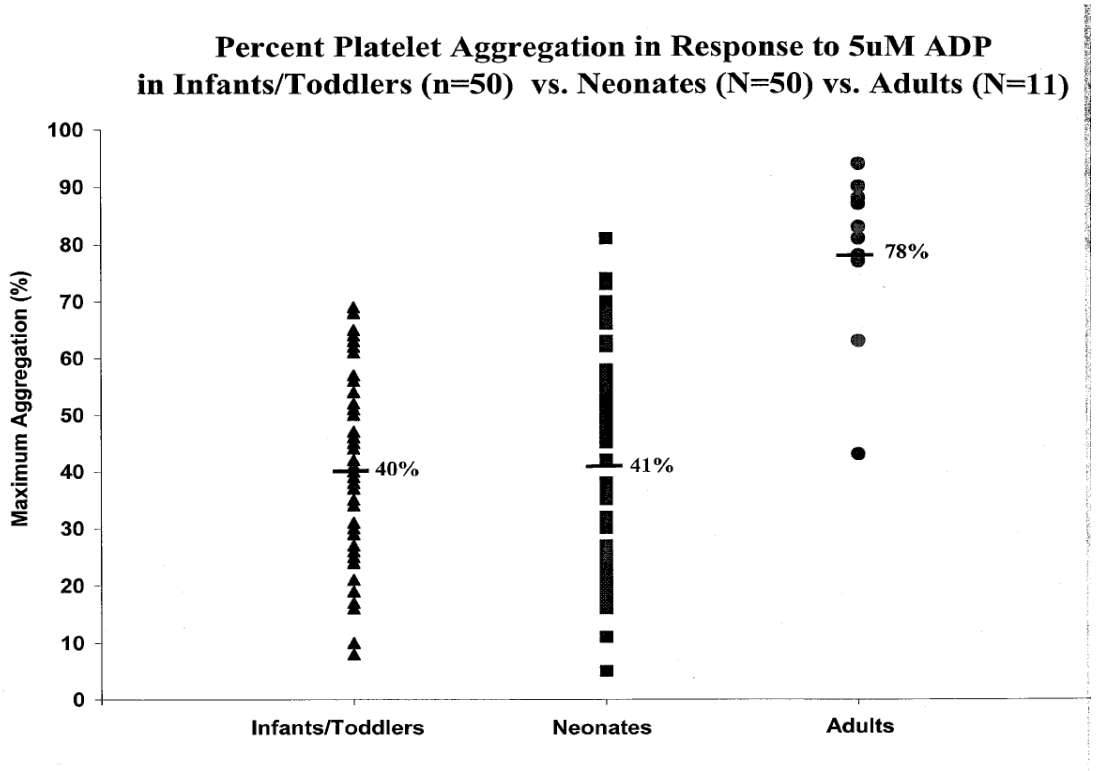
further studies of clopidogrel in this patient population should not be performed because of the low probability of success.

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 μM 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 μM 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 μM), 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 μM 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 while preparing for the first Pediatric Exclusivity Board meeting. 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 μM 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 μM 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." The data in the Sponsor's "Clarification of Meeting Minutes" submission show that the platelet aggregation responses of neonates and infants/toddlers are indeed markedly less than adults. The implications of this difference should have been clear to the Sponsor. 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. This issue by itself does not seem sufficient to support denial of Pediatric Exclusivity. 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:
    - Premier Perspective™ Comparative Research Database (Premier), and
    - The Normative Health Informatics (NHI) database.

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

5 Pediatric Exclusivity

5.1 *Standards for the award of Pediatric Exclusivity*

Sec. 505A of the FDCA, added by FDAMA in 1997, describes procedures for the grant of Pediatric Exclusivity. Sec. 505A(c) of the FDCA stipulates that: "….if the Secretary … makes a written request to the holder of an approved application under section 505(b)(1) for pediatric studies (which shall include a timeframe for completing such studies), the holder agrees to the request, such studies are completed using appropriate formulations for each age group for which the study is requested within any such timeframe, and the reports thereof are submitted and accepted in accordance with subsection (d)(3)….", the applicant may be awarded an additional 6 months of marketing exclusivity in certain circumstances.

Sec. 505A(d)(3) provides in its entirety:

> "Meeting studies requirement -- Not later than 180 days after the submission of the reports of the studies, the Secretary shall accept or reject such reports and so notify the sponsor or holder. The Secretary's only responsibility in accepting or rejecting the reports shall be to determine, within the 180-day period, whether the studies fairly respond to the written request, have been conducted in accordance with commonly accepted scientific principles and protocols, and have been reported in accordance with the requirements of the Secretary for filing."

It is my understanding that all the requirements of both subsections (c) and (d)(3) must be met for the FDA to grant Pediatric Exclusivity. Failure to meet any one or more of these requirements means that FDA should deny Pediatric Exclusivity.

5.2 *Application of the Sec. 505A standards to the clopidogrel pediatric submission*

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. This reviewer believes that with the exception of the issue discussed in Sec. 5.2.3, any one of these problems, standing alone, is sufficient to deny Pediatric Exclusivity in this case.

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 and thus contrary to Sec. 505A(d)(3).

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, and were thus contrary to subsection (d)(3).

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. The sponsor's conduct with regard to these data, standing alone, probably could not fairly support denial of Pediatric Exclusivity. However, the sponsor's conduct was not in accordance with good scientific principles and was thus contrary to subsection (d)(3).

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," as required by subsection (d)(3).

6 Recommendation

We should approve the sponsor's labeling supplement with labeling that describes the inconclusive nature of the results of CLARINET as discussed above. The Division should recommend to the Pediatric Exclusivity Board that FDA should deny Pediatric Exclusivity for clopidogrel.

Appendix 1 – Annotated Pediatric Written Request

Pediatric Exclusivity Determination for NDA 20-839, Plavix® (clopidogrel bisulfate)
Based on Amended Pediatric Written Requested Dated 24 Aug 2007

Written Request Items	Information Submitted/Sponsor's Response
STRATEGY	
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. The following pediatric development plan will implement this goal	See below for specific written request items and responses, and see attached memorandum for information regarding the scientific merit of the Sponsor's pediatric development program and the value of the data obtained by the Sponsor to "provide data on the use of clopidogrel" for the relevant pediatric indication.
1. Performance of a steady-state pharmacodynamic (PD) dose-ranging study in pediatric shunt patients who are in the age groups using the 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.	This study was completed (No. PDY4422, "**P**latelet aggregation **I**nhibition in **C**hildren **O**n c**LO**pidogrel (PICOLO): Dose-ranging pharmacodynamic assessment of platelet aggregation inhibition with clopidogrel in children of Blalock-Taussig shunt age categories (neonates and infants/toddlers)" This was a multi-center, randomized, double-blind, placebo-controlled study performed in neonates (n=32) and infants/toddlers (n=33), originally intended to evaluate the PK & PD of 3 doses of clopidogrel: 0;01, 0.1, and 1.0 mg/kg. Based on study data, 4 doses were evaluated: 0.01, 0.1, 0.15, and 0.2 mg/kg.
2. Completion of an efficacy and safety placebo-controlled clopidogrel study in patients with systemic pulmonary artery shunts.	This study was completed (No. 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 (e.g. modified Blalock Taussig shunt)" (CLARINET).
3. Submission of a supplement summarizing all data available on the use of clopidogrel in patients undergoing systemic to pulmonary artery shunt placement [STPASP] ….. …..as well as a comprehensive safety evaluation of clopidogrel in children.	The supplement (S-51) was received on 7/15/2010 and was accepted for filing on 9/9/2010, with a user fee goal date of 1/15/2011. The Pediatric Exclusivity 90 day due date is 10/13/2010. The summary contains information available to the Sponsor regarding STPASP from its own studies and other sources (see below for details regarding this information). The comprehensive safety evaluation was submitted in the Supplement, and consists of information from: • The clinical studies performed as part of the clinical pediatric plan (i.e.,

Written Request Items	Information Submitted/Sponsor's Response
	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: − Boston registry in the USA; − Leuven registry in Europe; • Published literature, including BOSTON, LEUVEN and PICOLO study publications, as well as other publications; • Data from two US claims databases: Premier Perspective™ Comparative Research Database (Premier) and the Normative Health Informatics (NHI) database.
The safety evaluation in children receiving clopidogrel must include more than a summary of the published literature…..	See the cell immediately above for sources of safety information.
….and includes 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.	All the information described above was analyzed by the Sponsor and included in the submitted Supplement.
TRIAL DESIGN AND GENERAL CONSIDERATIONS	
DOSE-RANGING PHARMACOKINETIC/PHARMACODYANMIC STUDY: Pharmacodynamic data must be obtained from a dose-ranging study in pediatric patients at risk for thrombosis (including patients with therapeutic shunts of any kind) and who are in the same age range (neonates and infants/toddlers) as patients in the efficacy study.	PD data were obtained in the PICOLO study. Major inclusion criteria were: a) neonates less than or equal to 30 days of age and infants/toddlers up to 24 months of age; b) patients must have had either a Blalock-Taussig shunt or any systemic to pulmonary artery shunt or have a potential therapeutic benefit from clopidogrel because of a related pathological condition requiring anti-platelet therapy such as but not limited to Kawasaki disease, vascular stent, Glenn shunt or Fontan physiology.
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).	Overall mean % platelet inhibition in PICOLO for placebo and the 0.01, 0.1, 0.15 and 0.2 mg/kg/day clopidogrel doses was 0.8, -12.8, 18.9, 36.4 and 49.3, respectively. The 0.15 mg/kg/day dose was given only to neonates. Mean % inhibition with 0.2 mg/kg/day, the dose selected for the efficacy and safety study, was 62.1 in neonates and 40.7 in infants/toddlers.
The initial three doses used in the study must span a 10-fold range;	The study was originally intended to evaluate the PK & PD of 3 doses of

Written Request Items	Information Submitted/Sponsor's Response
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.	clopidogrel: 0.01, 0.1, and 1.0 mg/kg/day. Based on early interim study data, 4 doses were evaluated: 0.01, 0.1, 0.15, and 0.2 mg/kg/day.
The results of this study will be the basis for the choice of the single dose to be used in the efficacy and safety study.	Based on the final study data, the Sponsor proposed 0.2 mg/kg/day clopidogrel as the dose for the efficacy and safety study. The Division responded: *"We believe you have adequately identified a dose of clopidogrel in neonates and toddlers that achieves about 50% inhibition of ADP-induced platelet aggregation."* (FDA minutes of EOP2 meeting held 12 July 2006, dated 8 August 2006). See the attached memorandum for additional comments on the Sponsor's platelet aggregation studies and dosing plan that are relevant to the scientific merit of the Sponsor's efficacy and safety study.
EFFICACY AND SAFETY STUDY Dose levels for this study will be determined by a joint agreement between you and the Division, based upon the dose-response data in the pilot dose-ranging study.	This requirement was met (see information in the row immediately above).
This must be a placebo-controlled, double blind clinical study in pediatric patients (neonates and infants/toddlers) receiving a systemic to pulmonary artery shunt for palliation of congenital heart disease. Patients must be randomized to clopidogrel (once per day at the determined dose) or to placebo following shunt placement, and then treated up to the time of the next surgical procedure for correction of their congenital heart disease. The study drug must be stopped in the following situations: • Occurrence of any component of the primary efficacy endpoint • The next surgical procedure is to be carried out • Discontinuation is needed for management of an adverse event • The parents or guardian request withdrawal • The investigator decides that discontinuation is in the best interest of the patient As there is no standardized care in this patient population,	The CLARINET study was performed. It was a placebo-controlled, double blind clinical study in pediatric patients (neonates and infants, i.e., age ≤ 92 days at study entry) receiving a systemic to pulmonary artery shunt for palliation of congenital heart disease. Patients were randomized to clopidogrel 0.2 mg/kg po once daily "as early as possible" following shunt placement. Study drug was stopped in case of: • Occurrence of one of the components of primary efficacy end point • The next surgical procedure for correction of the congenital heart disease. • **Patient reached age 365 days,** • **Occurrence of the common study end date.** • Discontinuation is needed for management of an adverse event• • The parents or guardian request withdrawal

Written Request Items	Information Submitted/Sponsor's Response
additional therapy must be in accordance with the usual practice of the institution (i.e. plus or minus concomitant aspirin).	• The investigator's decision that discontinuation is in the best interest of the patient Additional therapy was in accordance with the usual practice of the institution (i.e. plus or minus concomitant aspirin).
The primary efficacy endpoint is the first occurrence of any component of the primary composite endpoint of: • 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.	The primary efficacy variable was the occurrence of any component of the composite endpoint of: • Any death; • Shunt thrombosis requiring intervention; • Hospitalization for bi-directional Glenn procedure or any cardiac-related intervention prior to120 days of age following an event or a shunt narrowing considered of thrombotic nature.
STATISTICAL CONSIDERATIONS	
Since there are closely related indications in adults, a claim in children would be supported by one study with an observed effect on the primary end point significant at $p < 0.05$. Your initial estimate of the sample size should be based upon sound estimates of the event rate and the usual statistical considerations. Your study must be powered to be able to detect a "clinically meaningful" treatment benefit on the primary end point. The study should use a population judged to be of adequate size, based on sound estimates of the effect size and usual statistical considerations. A relative risk reduction of 30% is acceptable for the power calculations. As there is no way to derive an assured event rate, the study must be event-driven; you must recruit until, based on the observed overall event rate, enough patients are enrolled to achieve the targeted number of events. A full statistical analysis plan, including detailed plans for handling missing data, must be acceptable to the Division prior to first planned interim analysis.	A single Phase 3 study (CLARINET) was planned and performed in children as noted above. Per the prospective statistical plan: "At the final analysis, statistical significance will be claimed for the primary endpoint if the computed p-value is <0.035." Three interim analyses were planned, with an alpha error spend of 0.005 per analysis. CLARINET was an event driven trial. The sample size calculation was based on a database registry conducted at 15 sites in the US, France, and Germany that participated n the PICOLO Phase 2 dose ranging study. In this registry, data corresponding to the planned Phase 3 primary endpoint events were collected for patients with a Blalock-Taussig shunt or any systemic-to-pulmonary artery shunt. The estimated placebo event rate was 40%, and the study was powered at the 80% level to detect a 30% RR in event rate. 174 primary endpoint events would be required; the sponsor estimated that 490 patients would be needed. Such a plan was submitted to the Division in a timely manner and was deemed to be acceptable (see Submission to IND 034663, 10 April 2008; Serial No. 0753 and the Sponsor's response to the Agency's comments on the SAP, 09 June 2008; Serial No. 0775; and FDA's letter to the Sponsor, 03 Sept. 2008, declaring the statistical plan to be "acceptable".)
EXTRAORDINARY RESULTS	

Written Request Items	Information Submitted/Sponsor's Response
In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected, useful results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.	Not Applicable
RECRUITING	
Both the dose ranging and the efficacy/safety studies should be performed in patients of both sexes in the pediatric age groups above, approximately evenly distributed among the relevant pediatric age groups to the extent possible given the patient population. The recruitment scheme should be designed to encourage broad enrollment with respect to gender and race.	In the PICOLO Phase 2 pharmacodynamic study, 92 children were randomized, 86 received study drug, and 73 received study drug and had baseline and steady-state platelet aggregation data (the Per Protocol (PP) population). Baseline characteristic for the PP population are as follows Age: ≤ 30 days, 46.6%, >30 days to ≤ 24 months, 53.4% Gender: Female, 39.7%, male, 60.3% Race: Caucasian, 84.9.5%, Black,5.5 %; Asian, 1.4%; Native American, 2.7%; Other , 5.5% Ethnicity: Hispanic or Latino, 11.0%, In the CLARINET Phase 3 study, 906 children were randomized. Baseline characteristic for all randomized patients are as follows Age: ≤ 30 days, 50.9%, >30 to ≤ 92 days, 49.1% Gender: Female, 42.3%, male, 57.7% Race: Caucasian, 70.5%, Black, 6%, Asian, 14.7%, American Indian or Alaska Native, 7.0%, Native Hawaiian or Pacific Islander, 0.1%; Other 1.3% Ethnicity: Hispanic or Latino, 24.3%,
DRUG INFORMATION	
Use an age-appropriate formulation in the effectiveness study described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children.	For the Phase 1 bioequivalence study in adults (BDR4580, "Relative bioavailability study between 75 mg tablet and 75 mg solution of Clopidogrel (SR25990C) after single oral administration to young healthy men Open, crossover, randomized and mono center study" and

Written Request Items	Information Submitted/Sponsor's Response
This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.	for the dose ranging Phase 2 study in children (PICOLO), a single dose 5 mg/mL constituted oral solution was used: • Dose-proportional formulations were developed (75 mg of clopidogrel base in 15 mL for Phase 1 study and 25 mg in 5 mL for the Phase 2 study). (b) (4) . For the efficacy and safety study with up to 1 year of treatment in neonates and infants (CLARINET), a multidose palatable (b) (4) constituted oral solution was developed. • (b) (4) .
Development of a commercially marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval. If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate	The Sponsor does not plan to commercialize a pediatric formulation; therefore Module 3 was not included in the Supplement. Not Applicable.

Written Request Items	Information Submitted/Sponsor's Response
formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information. 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.	In BDR4580, which compared the bioavailability of a75 mg commercial tablet and 75 mg solution of clopidogrel after single oral administration to young healthy men, the ratio estimates [and 95% CI] for the solution relative to the tablet were: Cmax: 1.15 [1.02; 1.30]; AUC last: 1.04 [1.01; 1.07] AUC: same results as AUC last; and Tmax (in hours): 0.5 for solution, 0.75 for tablet. T ½ not calculated. A modest amount of PK data are available from the Phase 2 PICOLO study in neonates and infants/toddlers, but a non-compartmental analysis or a stand-alone population PK analysis was not feasible with the small number of samples/patients available..
GENERAL CONSIDERATIONS	
Labeling that may result from the study(ies): Draft labeling must be submitted with appropriate sections of the label changed to incorporate the findings of the studies. Format of reports to be submitted: You must submit full study reports, not previously submitted to the Agency, addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino. Although not currently required, we request that study data be	Revised labeling was submitted (b) (4) [redacted] Full reports were submitted as described above. In the safety and efficacy study in children, the Sponsor collected racial and ethnic information on the patients using the requested categories, **except that the term "Caucasian" was used instead of "White."** In the Phase 2 PICOLO study, the Sponsor used the requested ethnic category, but simplified the racial categories as follows: **Caucasian**, Black, Asian, **Native American**, and Other. There was no category corresponding to "Native Hawaiian or Pacific Islander"; there were no study sites in the regions where such persons are indigenous. We have a preliminary determination from DRRS that the submitted tabulated datasets of the Sponsor's PD study in children (PICOLO)

Written Request Items	Information Submitted/Sponsor's Response
submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/cder/regulatory/ersr/Studydata-v1.1.pdf and referenced in the FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications at http://www.fda.gov/cder/guidance/6766fnl.pdf.	appear to meet the SDTM standard. The Sponsor also submitted 2 sequences of tabulated datasets for its efficacy and safety study in children (CLARINET); one of these sequences (No. 68) appears to meet the SDTM standard, but the other sequence (No. 82) does not. The two sequences include the same patients; the second one may be an updated version of the first. In addition, the Sponsor has submitted analysis datasets for two registry studies (Boston and Leuven), but no tabulated data are included for these studies.
Timeframe for submitting reports of the study(ies): Reports of the above studies must be submitted to the Agency on or before July 31, 2011. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.	The reports were in the Supplement that was received in a timely manner on July 15, 2010.
Response to Written Request: As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.	Responses to the PWR letters from FDA were timely and contained the requested information. See IND 034663, Sponsor's Intent to Conduct Planned Studies, 22 October 2002, Serial No. 398 (Response to PWR re-issue letter of 02 July 2002; and Sponsor's Response to Written Request (Amendment 1) Intent to Conduct Planned Studies, 13 September 2007; Serial No. 0704 (Response to Amended PWR of 24 August 2007).
Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, "PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission, "PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission.	The following protocols in the Sponsor' pediatric development program were submitted to IND 034663 with appropriate language in the relevant cover letters: BDR4580; 18 March 2002; Serial No. 368 PICOLO (PDY4422); 09 January 2003; Serial No. 415 CLARINET (EFC5314); 29 August 2006; Serial No. 651 The Sponsor has not entered into a Written Agreement with FDA.
If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked, "PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission.	The Sponsor submitted a request to IND 034663 to amend the original Pediatric Written Request (PWR) on 13 October 2006; Serial No. 0658. The Agency issued an Amended PWR on 24 August 2007. The latter was the final PWR.

Written Request Items	Information Submitted/Sponsor's Response
You will be notified in writing if any changes to this Written Request are agreed upon by the Agency. As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov and http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.	The following trials conducted in the Sponsor's pediatric development program were registered on clinicaltrials.gov: PICOLO (PDY4422) NCT No. 00115375 CLARINET (EFC5314) NCT No. 00396877

Pediatric Exclusivity Determination for NDA 20-839, Plavix® (clopidogrel bisulfate)
Based on Amended Pediatric Written Requested Dated 24 Aug 2007

Written Request Items	**6.1** *Information Submitted/Sponsor's Response*
STRATEGY	
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. The following pediatric development plan will implement this goal	See below for specific written request items and responses, and see attached memorandum for information regarding the scientific merit of the Sponsor's pediatric development program and the value of the data obtained by the Sponsor to "provide data on the use of clopidogrel" for the relevant pediatric indication.
1. Performance of a steady-state pharmacodynamic (PD) dose-ranging study in pediatric shunt patients who are in the age groups using the 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.	This study was completed (No. PDY4422, "**P**latelet aggregation **I**nhibition in **C**hildren **O**n c**LO**pidogrel (PICOLO): Dose-ranging pharmacodynamic assessment of platelet aggregation inhibition with clopidogrel in children of Blalock-Taussig shunt age categories (neonates and infants/toddlers)" This was a multi-center, randomized, double-blind, placebo-controlled study performed in neonates (n=32) and infants/toddlers (n=33), originally intended to evaluate the PK & PD of 3 doses of clopidogrel: 0;01, 0.1, and 1.0 mg/kg. Based on study data, 4 doses were evaluated: 0.01, 0.1, 0.15, and 0.2 mg/kg.
2. Completion of an efficacy and safety placebo-controlled clopidogrel study in patients with systemic pulmonary artery shunts.	This study was completed (No. 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 (e.g. modified Blalock Taussig shunt)" (CLARINET).
3. Submission of a supplement summarizing all data available on the use of clopidogrel in patients undergoing systemic to pulmonary artery shunt placement [STPASP] ….. …..as well as a comprehensive safety evaluation of clopidogrel in children.	The supplement (S-51) was received on 7/15/2010 and was accepted for filing on 9/9/2010, with a user fee goal date of 1/15/2011. The Pediatric Exclusivity 90 day due date is 10/13/2010. The summary contains information available to the Sponsor regarding STPASP from its own studies and other sources (see below for details regarding this information). The comprehensive safety evaluation was submitted in the Supplement, and consists of information from: • The clinical studies performed as part of the clinical pediatric plan (i.e.,

Written Request Items	**6.1** *Information Submitted/Sponsor's Response*
	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: − Boston registry in the USA; − Leuven registry in Europe; • Published literature, including BOSTON, LEUVEN and PICOLO study publications, as well as other publications; • Data from two US claims databases: Premier Perspective™ Comparative Research Database (Premier) and the Normative Health Informatics (NHI) database.
The safety evaluation in children receiving clopidogrel must include more than a summary of the published literature…..	See the cell immediately above for sources of safety information.
….and includes 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.	All the information described above was analyzed by the Sponsor and included in the submitted Supplement.
TRIAL DESIGN AND GENERAL CONSIDERATIONS	
DOSE-RANGING PHARMACOKINETIC/PHARMACODYANMIC STUDY: Pharmacodynamic data must be obtained from a dose-ranging study in pediatric patients at risk for thrombosis (including patients with therapeutic shunts of any kind) and who are in the same age range (neonates and infants/toddlers) as patients in the efficacy study.	PD data were obtained in the PICOLO study. Major inclusion criteria were: a) neonates less than or equal to 30 days of age and infants/toddlers up to 24 months of age; b) patients must have had either a Blalock-Taussig shunt or any systemic to pulmonary artery shunt or have a potential therapeutic benefit from clopidogrel because of a related pathological condition requiring anti-platelet therapy such as but not limited to Kawasaki disease, vascular stent, Glenn shunt or Fontan physiology.
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).	Overall mean % platelet inhibition in PICOLO for placebo and the 0.01, 0.1, 0.15 and 0.2 mg/kg/day clopidogrel doses was 0.8, -12.8, 18.9, 36.4 and 49.3, respectively. The 0.15 mg/kg/day dose was given only to neonates. Mean % inhibition with 0.2 mg/kg/day, the dose selected for the efficacy and safety study, was 62.1 in neonates and 40.7 in infants/toddlers.
The initial three doses used in the study must span a 10-fold range;	The study was originally intended to evaluate the PK & PD of 3 doses of

Written Request Items	**6.1** *Information Submitted/Sponsor's Response*
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.	clopidogrel: 0.01, 0.1, and 1.0 mg/kg/day. Based on early interim study data, 4 doses were evaluated: 0.01, 0.1, 0.15, and 0.2 mg/kg/day.
The results of this study will be the basis for the choice of the single dose to be used in the efficacy and safety study.	Based on the final study data, the Sponsor proposed 0.2 mg/kg/day clopidogrel as the dose for the efficacy and safety study. The Division responded: *"We believe you have adequately identified a dose of clopidogrel in neonates and toddlers that achieves about 50% inhibition of ADP-induced platelet aggregation."* (FDA minutes of EOP2 meeting held 12 July 2006, dated 8 August 2006). See the attached memorandum for additional comments on the Sponsor's platelet aggregation studies and dosing plan that are relevant to the scientific merit of the Sponsor's efficacy and safety study.
EFFICACY AND SAFETY STUDY Dose levels for this study will be determined by a joint agreement between you and the Division, based upon the dose-response data in the pilot dose-ranging study.	This requirement was met (see information in the row immediately above).
This must be a placebo-controlled, double blind clinical study in pediatric patients (neonates and infants/toddlers) receiving a systemic to pulmonary artery shunt for palliation of congenital heart disease. Patients must be randomized to clopidogrel (once per day at the determined dose) or to placebo following shunt placement, and then treated up to the time of the next surgical procedure for correction of their congenital heart disease. The study drug must be stopped in the following situations: • Occurrence of any component of the primary efficacy endpoint • The next surgical procedure is to be carried out • Discontinuation is needed for management of an adverse event • The parents or guardian request withdrawal • The investigator decides that discontinuation is in the best interest of the patient As there is no standardized care in this patient population,	The CLARINET study was performed. It was a placebo-controlled, double blind clinical study in pediatric patients (neonates and infants, i.e., age ≤ 92 days at study entry) receiving a systemic to pulmonary artery shunt for palliation of congenital heart disease. Patients were randomized to clopidogrel 0.2 mg/kg po once daily "as early as possible" following shunt placement. Study drug was stopped in case of: • Occurrence of one of the components of primary efficacy end point • The next surgical procedure for correction of the congenital heart disease. • **Patient reached age 365 days,** • **Occurrence of the common study end date.** • Discontinuation is needed for management of an adverse event• • The parents or guardian request withdrawal

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additional therapy must be in accordance with the usual practice of the institution (i.e. plus or minus concomitant aspirin).	• The investigator's decision that discontinuation is in the best interest of the patient Additional therapy was in accordance with the usual practice of the institution (i.e. plus or minus concomitant aspirin).
The primary efficacy endpoint is the first occurrence of any component of the primary composite endpoint of: • 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.	The primary efficacy variable was the occurrence of any component of the composite endpoint of: • Any death; • Shunt thrombosis requiring intervention; • Hospitalization for bi-directional Glenn procedure or any cardiac-related intervention prior to120 days of age following an event or a shunt narrowing considered of thrombotic nature.
STATISTICAL CONSIDERATIONS	
Since there are closely related indications in adults, a claim in children would be supported by one study with an observed effect on the primary end point significant at $p < 0.05$. Your initial estimate of the sample size should be based upon sound estimates of the event rate and the usual statistical considerations. Your study must be powered to be able to detect a "clinically meaningful" treatment benefit on the primary end point. The study should use a population judged to be of adequate size, based on sound estimates of the effect size and usual statistical considerations. A relative risk reduction of 30% is acceptable for the power calculations. As there is no way to derive an assured event rate, the study must be event-driven; you must recruit until, based on the observed overall event rate, enough patients are enrolled to achieve the targeted number of events. A full statistical analysis plan, including detailed plans for handling missing data, must be acceptable to the Division prior to first planned interim analysis.	A single Phase 3 study (CLARINET) was planned and performed in children as noted above. Per the prospective statistical plan: "At the final analysis, statistical significance will be claimed for the primary endpoint if the computed p-value is <0.035." Three interim analyses were planned, with an alpha error spend of 0.005 per analysis. CLARINET was an event driven trial. The sample size calculation was based on a database registry conducted at 15 sites in the US, France, and Germany that participated n the PICOLO Phase 2 dose ranging study. In this registry, data corresponding to the planned Phase 3 primary endpoint events were collected for patients with a Blalock-Taussig shunt or any systemic-to-pulmonary artery shunt. The estimated placebo event rate was 40%, and the study was powered at the 80% level to detect a 30% RR in event rate. 174 primary endpoint events would be required; the sponsor estimated that 490 patients would be needed. Such a plan was submitted to the Division in a timely manner and was deemed to be acceptable (see Submission to IND 034663, 10 April 2008; Serial No. 0753 and the Sponsor's response to the Agency's comments on the SAP, 09 June 2008; Serial No. 0775; and FDA's letter to the Sponsor, 03 Sept. 2008, declaring the statistical plan to be "acceptable".)
EXTRAORDINARY RESULTS	

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In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected, useful results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.	Not Applicable
RECRUITING	
Both the dose ranging and the efficacy/safety studies should be performed in patients of both sexes in the pediatric age groups above, approximately evenly distributed among the relevant pediatric age groups to the extent possible given the patient population. The recruitment scheme should be designed to encourage broad enrollment with respect to gender and race.	In the PICOLO Phase 2 pharmacodynamic study, 92 children were randomized, 86 received study drug, and 73 received study drug and had baseline and steady-state platelet aggregation data (the Per Protocol (PP) population). Baseline characteristic for the PP population are as follows Age: ≤ 30 days, 46.6%, >30 days to ≤ 24 months, 53.4% Gender: Female, 39.7%, male, 60.3% Race: Caucasian, 84.9.5%, Black,5.5 %; Asian, 1.4%; Native American, 2.7%; Other , 5.5% Ethnicity: Hispanic or Latino, 11.0%, In the CLARINET Phase 3 study, 906 children were randomized. Baseline characteristic for all randomized patients are as follows Age: ≤ 30 days, 50.9%, >30 to ≤ 92 days, 49.1% Gender: Female, 42.3%, male, 57.7% Race: Caucasian, 70.5%, Black, 6%, Asian, 14.7%, American Indian or Alaska Native, 7.0%, Native Hawaiian or Pacific Islander, 0.1%; Other 1.3% Ethnicity: Hispanic or Latino, 24.3%,
DRUG INFORMATION	
Use an age-appropriate formulation in the effectiveness study described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children.	For the Phase 1 bioequivalence study in adults (BDR4580, "Relative bioavailability study between 75 mg tablet and 75 mg solution of Clopidogrel (SR25990C) after single oral administration to young healthy men Open, crossover, randomized and mono center study" and

Written Request Items	**6.1** *Information Submitted/Sponsor's Response*
This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.	for the dose ranging Phase 2 study in children (PICOLO), a single dose 5 mg/mL constituted oral solution was used: • (b) (4)  For the efficacy and safety study with up to 1 year of treatment in neonates and infants (CLARINET), a multidose palatable (b) (4) constituted oral solution was developed. • (b) (4) 
Development of a commercially marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval. If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate	The Sponsor does not plan to commercialize a pediatric formulation; therefore Module 3 was not included in the Supplement. Not Applicable.

Written Request Items	**6.1** *Information Submitted/Sponsor's Response*
formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information. 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.	In BDR4580, which compared the bioavailability of a75 mg commercial tablet and 75 mg solution of clopidogrel after single oral administration to young healthy men, the ratio estimates [and 95% CI] for the solution relative to the tablet were: Cmax: 1.15 [1.02; 1.30]; AUC last: 1.04 [1.01; 1.07] AUC: same results as AUC last; and Tmax (in hours): 0.5 for solution, 0.75 for tablet. T ½ not calculated. A modest amount of PK data are available from the Phase 2 PICOLO study in neonates and infants/toddlers, but a non-compartmental analysis or a stand-alone population PK analysis was not feasible with the small number of samples/patients available..
GENERAL CONSIDERATIONS	
Labeling that may result from the study(ies): Draft labeling must be submitted with appropriate sections of the label changed to incorporate the findings of the studies. Format of reports to be submitted: You must submit full study reports, not previously submitted to the Agency, addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino. Although not currently required, we request that study data be	Revised labeling was submitted (b) (4) [redacted] s. Full reports were submitted as described above. In the safety and efficacy study in children, the Sponsor collected racial and ethnic information on the patients using the requested categories, **except that the term "Caucasian" was used instead of "White."** In the Phase 2 PICOLO study, the Sponsor used the requested ethnic category, but simplified the racial categories as follows: **Caucasian**, Black, Asian, **Native American**, and Other. There was no category corresponding to "Native Hawaiian or Pacific Islander"; there were no study sites in the regions where such persons are indigenous. We have a preliminary determination from DRRS that the submitted tabulated datasets of the Sponsor's PD study in children (PICOLO)

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submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/cder/regulatory/ersr/Studydata-v1.1.pdf and referenced in the FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications at http://www.fda.gov/cder/guidance/6766fnl.pdf.	appear to meet the SDTM standard. The Sponsor also submitted 2 sequences of tabulated datasets for its efficacy and safety study in children (CLARINET); one of these sequences (No. 68) appears to meet the SDTM standard, but the other sequence (No. 82) does not. The two sequences include the same patients; the second one may be an updated version of the first. In addition, the Sponsor has submitted analysis datasets for two registry studies (Boston and Leuven), but no tabulated data are included for these studies.
Timeframe for submitting reports of the study(ies): Reports of the above studies must be submitted to the Agency on or before July 31, 2011. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.	The reports were in the Supplement that was received in a timely manner on July 15, 2010.
Response to Written Request: As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.	Responses to the PWR letters from FDA were timely and contained the requested information. See IND 034663, Sponsor's Intent to Conduct Planned Studies, 22 October 2002, Serial No. 398 (Response to PWR re-issue letter of 02 July 2002; and Sponsor's Response to Written Request (Amendment 1) Intent to Conduct Planned Studies, 13 September 2007; Serial No. 0704 (Response to Amended PWR of 24 August 2007).
Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, "PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission, "PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission.	The following protocols in the Sponsor' pediatric development program were submitted to IND 034663 with appropriate language in the relevant cover letters: BDR4580; 18 March 2002; Serial No. 368 PICOLO (PDY4422); 09 January 2003; Serial No. 415 CLARINET (EFC5314); 29 August 2006; Serial No. 651 The Sponsor has not entered into a Written Agreement with FDA.
If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked, "PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission.	The Sponsor submitted a request to IND 034663 to amend the original Pediatric Written Request (PWR) on 13 October 2006; Serial No. 0658. The Agency issued an Amended PWR on 24 August 2007. The latter was the final PWR.

Written Request Items	**6.1** *Information Submitted/Sponsor's Response*
You will be notified in writing if any changes to this Written Request are agreed upon by the Agency. As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov and http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.	The following trials conducted in the Sponsor's pediatric development program were registered on clinicaltrials.gov: PICOLO (PDY4422) NCT No. 00115375 CLARINET (EFC5314) NCT No. 00396877

Annotated Pediatric Written Request (Based on Amended PWR of 24 Aug 2007)

NDA 020839 /clopidogrel /SR25990 / Plavix

Written Request Items	**6.2** *Information Submitted/Sponsor's Response*
STRATEGY	
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. The following pediatric development plan will implement this goal	Not Applicable (see below for detailed items and responses)
1. Performance of a steady-state pharmacodynamic (PD) dose-ranging study in pediatric shunt patients who are in the age groups using the 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.	This study was completed (No. PDY4422, "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 was a multi-center, randomized, double-blind, placebo-controlled study performed in neonates (n=32) and infants/toddlers (n=33), originally intended to evaluate the PK & PD of 3 doses of clopidogrel: 0;01, 0.1, and 1.0 mg/kg. Based on study data, 4 doses were evaluated: 0.01, 0.1, 0.15, and 0.2 mg/kg.
2. Completion of an efficacy and safety placebo-controlled clopidogrel study in patients with systemic pulmonary artery shunts.	This study was completed (No. 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 (e.g. modified Blalock Taussig shunt)" (CLARINET).
3. Submission of a supplement summarizing all data available on the use of clopidogrel in patients undergoing systemic to pulmonary artery shunt placement [STPASP] …..	The supplement (S-51) was received on 7/15/2010 and was accepted for filing on 9/9/2010, with a user fee goal date of 1/15/2011. The 90 day Pediatric Exclusivity determination goal date is 10/13/2010. The summary contains information available to the Sponsor regarding STPASP from its own studies and other sources (see below for details regarding this information).
…..as well as a comprehensive safety evaluation of clopidogrel in children.	The comprehensive safety evaluation was submitted in the Supplement, and consists of information from the sponsor's studies in children, two retrospective observational studies, postmarketing AE information, and published reports.

Written Request Items	**6.2** *Information Submitted/Sponsor's Response*
The safety evaluation in children receiving clopidogrel must include more than a summary of the published literature…..	See above. The safety evaluation included reports of registry studies, an analysis of the sponsor's post-marketing data in children, and an analysis of published data.
….and include 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.	Such information was collected and reported. See Module 2; section 2.5, Clinical Overview [5.5 Data from the Two US Claims Databases] Module 5; section 5.3.5.4 [CV149-183] entitled, "Clopidogrel Bisulfate (Plavix) Use in children 18 years of age and younger: A Descriptive Study in Two Medical Claims Databases" Module 5; section 5.3.5.4 [BOSTON] entitled, "Use of Plavix in Pediatric Patients: Retrospective Registry." Module 5; section 5.3.5.4 [LEUVEN] entitled, "Use of Plavix in Pediatric Patients: Retrospective Registry." Module 5; section 5.3.6 [GPE-P-2010-0073 Summary of post marketing experience in pediatric use]These analyses were performed.
TRIAL DESIGN AND GENERAL CONSIDERATIONS	
DOSE-RANGING PHARMACOKINETIC/PHARMACODYANMIC STUDY: Pharmacodynamic data must be obtained from a dose-ranging study in pediatric patients at risk for thrombosis (including patients with therapeutic shunts of any kind) and who are in the same age range (neonates and infants/toddlers) as patients in the efficacy study.	Such data were obtained in the PICOLO study(see Module 5; section 5.3.4.2 [PDY4422] PICOLO, entitled, "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)". The study included: **"a) neonates less than or equal to 30 days of age and infants/toddlers up to 24 months of age;** **b) patients must have had either a Blalock-Taussig shunt or any systemic to pulmonary artery shunt or have a potential therapeutic benefit from clopidogrel because of a related pathological condition requiring anti-platelet therapy such as but not limited to Kawasaki disease, vascular stent, Glenn shunt or Fontan physiology.**
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).	Overall mean platelet inhibition in PICOLO with 0.2 mg/kd/d clopidogrel, the dose selected for study in Phase 3, was 49.3% (67.7% in neonates and 40.7% in infants/toddlers.

Written Request Items	**6.2** *Information Submitted/Sponsor's Response*
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.	The study was originally intended to evaluate the PK & PD of 3 doses of clopidogrel: 0;01, 0.1, and 1.0 mg/kg. Based on early interim study data, 4 doses were evaluated: 0.01, 0.1, 0.15, and 0.2 mg/kg ..
The results of this study will be the basis for the choice of the single dose to be used in the efficacy and safety study.	Based on the final study data, 0.2 mg/kg/day was selected for evaluation in the efficacy and safety study; the Division agreed to this selection.
EFFICACY AND SAFETY STUDY	
Dose levels for this study will be determined by a joint agreement between you and the Division, based upon the dose-response data in the pilot dose-ranging study	This requirement was met (see information in the row immediately above.
This must be a placebo-controlled, double blind clinical study in pediatric patients (neonates and infants/toddlers) receiving a systemic to pulmonary artery shunt for palliation of congenital heart disease. Patients must be randomized to clopidogrel (once per day at the determined dose) or to placebo following shunt placement, and then treated up to the time of the next surgical procedure for correction of their congenital heart disease. The study drug must be stopped in the following situations: • Occurrence of any component of the primary efficacy endpoint • The next surgical procedure is to be carried out • Discontinuation is needed for management of an adverse event • The parents or guardian request withdrawal • The investigator decides that discontinuation is in the best interest of the patient 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).	The CLARINET study was performed. It was a placebo-controlled, double blind clinical study in pediatric patients (neonates and infants/toddlers) receiving a systemic to pulmonary artery shunt for palliation of congenital heart disease. Patients were randomized to clopidogrel 0.2 mg/kg po once daily "as early as possible" following shunt placement. Study drug was stopped in case of: • Occurrence of one of the components of primary efficacy end point • The next surgical procedure for correction of the congenital heart disease. • **Patient reached age 365 days,** • **Occurrence of the common study end date.** • Discontinuation is needed for management of an adverse event• • The parents or guardian request withdrawal • The investigator's decision that discontinuation is in the best interest of the patient Additional therapy was in accordance with the usual practice of the institution (i.e, plus or minus concomitant aspirin).
The primary efficacy endpoint is the first occurrence of any	The primary efficacy variable was the occurrence of any component of

Written Request Items	**6.2** *Information Submitted/Sponsor's Response*
component of the primary composite endpoint of: • 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.	the composite endpoint of: • Any death; • Shunt thrombosis requiring intervention; • Hospitalization for bi-directional Glenn procedure or any cardiac-related intervention prior to120 days of age following an event or a shunt narrowing considered of thrombotic nature. This component was adjudicated by a blinded adjudication committee.
STATISTICAL CONSIDERATIONS	
Since there are closely related indications in adults, a claim in children would be supported by one study with an observed effect on the primary end point significant at $p < 0.05$. Your initial estimate of the sample size should be based upon sound estimates of the event rate and the usual statistical considerations. Your study must be powered to be able to detect a "clinically meaningful" treatment benefit on the primary end point. The study should use a population judged to be of adequate size, based on sound estimates of the effect size and usual statistical considerations. A relative risk reduction of 30% is acceptable for the power calculations. As there is no way to derive an assured event rate, the study must be event-driven; you must recruit until, based on the observed overall event rate, enough patients are enrolled to achieve the targeted number of events. A full statistical analysis plan, including detailed plans for handling missing data, must be acceptable to the Division prior to first planned interim analysis.	A single Phase 3 study (CLARINET) was planned and performed in children as noted above. Per the prospective statistical plan: "At the final analysis, statistical significance will be claimed for the primary endpoint if the computed p-value is <0.035." Three interim analyses were planned, with an alpha error spend of 0.005 per analysis. CLARINET was an event driven trial. The sample size calculation was based on a database registry conducted by at 15 sites participating in the PICOLO Phase 2 dose ranging study in the US, France, and Germany. In this registry, data corresponding to the planned Phase 3 primary endpoint events were collected for patients with a Blalock-Taussig shunt or any systemic-to-pulmonary artery shunt. The estimated placebo event rate was 40%, and the study was powered at the 80% level to detect a 30% RR in event rate. 174 primary endpoint events would be required, the sponsor estimated that 490 patients would be needed. Such a plan was submitted to the Division in a timely manner and was deemed to be acceptable (see Submission to IND 034663, 10 April 2008; Serial No. 0753 and the Sponsor's response to the Agency's comments on the SAP, 09 June 2008; Serial No. 0775
EXTRAORDINARY RESULTS	
In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected, useful results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request.	Not Applicable

Written Request Items	**6.2** *Information Submitted/Sponsor's Response*
If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.	
RECRUITING	
Both the dose ranging and the efficacy/safety studies should be performed in patients of both sexes in the pediatric age groups above, approximately evenly distributed among the relevant pediatric age groups to the extent possible given the patient population. The recruitment scheme should be designed to encourage broad enrollment with respect to gender and race.	In the CLARINET Phase 3 study, 906 children were enrolled. Baseline characteristic for all randomized patients are as follows Age: age ≤ 30 days, 50.9%, age >30 to ≤ 92 days, 49.1% Gender: Female, 42.3%, male, 57.7% Race: Caucasian, 70.5%, Black, 6%, Asian, 14.7%, American Indian or Alaska Native, 7.0%, Native Hawaiian or Pacific Islander, 0.1%; Other 1.3% Ethnicity: Hispanic or Latino, 24.3%,
DRUG INFORMATION	
Use an age-appropriate formulation in the effectiveness study described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.	For the Phase 1 bioequivalence study in adults (BDR4580, "Relative bioavailability study between 75 mg tablet and 75 mg solution of Clopidogrel (SR25990C) after single oral administration to young healthy men Open, crossover, randomized and mono center study" and for the dose ranging Phase 2 study in children (PICOLO), a single dose 5 mg/mL constituted oral solution was used: • (b) (4) For the Phase 3 study intended for up to 1 year of treatment in neonates and infants (CLARINET), a multidose (b) (4) constituted oral solution was developed. • (b) (4)

Written Request Items	**6.2** *Information Submitted/Sponsor's Response*
	(b) (4) [redacted] .
Development of a commercially marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval. If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information. 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.	The Sponsor does not plan to commercialize a pediatric formulation; therefore Module 3 was not included in the Supplement. Not Applicable. In BDR4580, which compared the bioavailability of a75 mg commercial tablet and 75 mg solution of clopidogrel after single oral administration to young healthy men, the ratio estimates [and 95% CI] for the solution relative to the tablet were: Cmax: 1.15 [1.02; 1.30]; AUC last: 1.04 [1.01; 1.07] AUC: same as AUC last; and Tmax (hours, not ratio): 0.5 for solution, 0.75 for tablet. T ½ not calculated. A modest amount of PK data are available from the Phase 2 PICOLO study in neonates and infants/toddlers, but a non-compartmental analysis or a stand-alone population PK analysis was not feasible with

Written Request Items	**6.2** *Information Submitted/Sponsor's Response*
	the very small number of samples/patients available..
GENERAL CONSIDERATIONS	
Labeling that may result from the study(ies): Draft labeling must be submitted with appropriate sections of the label changed to incorporate the findings of the studies.	Revised labeling was submitted (b) (4)]
Format of reports to be submitted: You must submit full study reports, not previously submitted to the Agency, addressing the issues outlined in this request with full analysis, assessment, and interpretation.	Reports were submitted as described above.
In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.	All studies performed by the sponsor have the requested information regarding the race and ethnicity of the pediatric patients.
Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/cder/regulatory/ersr/Studydata-v1.1.pdf and referenced in the FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications at http://www.fda.gov/cder/guidance/6766fnl.pdf.	The supplement was received in a timely manner on July 15, 2010.
Timeframe for submitting reports of the study(ies): Reports of the above studies must be submitted to the Agency on or before July 31, 2011. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.	See above. All reports were submitted in a timely manner.
Response to Written Request: As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must	**Responses to the PWR were timely. See IND 034663, Sponsor's Intent to Conduct Planned Studies; Response to re-issue letter; 02 October 2002; Serial No. 398 and The Sponsor's Response to Written Request (Amendment 1) Intent to Conduct Planned Studies 13 September 2007; Serial No. 0704.**

Written Request Items	**6.2** *Information Submitted/Sponsor's Response*
indicate when the pediatric studies will be initiated. Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, "PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission, "PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission.	**Protocols submitted to IND 034663:** BDR4580; 18 March 2002; Serial No. 368 PICOLO (PDY4422); 09 January 2003; Serial No. 0415 CLARINET (EFC5314); 29 August 2006; Serial No. 0651 The Sponsor has not entered into a Written Agreement
If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked, "PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency. As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov and http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site	Sponsor submitted a request to IND 034663 to amend the original Pediatric Written Request (PWR) on 13 October 2006; Serial No. 0658. The Agency provided the Amended PWR on 24 August 2007. The following trials were registered on clinicaltrials.gov: CLARINET (EFC5314) NCT No. 00396877 PICOLO (PDY4422) NCT No. 00115375

Written Request Items	**6.2** *Information Submitted/Sponsor's Response*
http://prsinfo.clinicaltrials.gov/.	

Appendix 2 – Response to FDA communication dated 13 October 2010: Questions re Pediatric Exclusivity

Medical Officer's Review

Martin Rose MD, JD CDER/OND/DCRP

NDA:	020839
Supporting Document #:	S051 amendment, SN 0096
Submission type:	Response to FDA communication dated 13 October 2010: Questions re Pediatric Exclusivity
Submission date:	25 October 2010
Review date:	23 November 2010
RPM:	Alison Blaus
Manufacturer:	sanofi aventis
Product:	Plavix (clopidogrel bisulfate)

This document contains the Sponsor's responses to our queries relating to Pediatric Exclusivity issues, sent on 13 October 2010, arising out of the Pediatric Exclusivity Board meeting held on 5 October 2010. Each question to the Sponsor in our communication of 13 October 2010 is followed by a summary of the Sponsor's response, and then by the reviewer's comments regarding the response.

Question 1: *In your protocol for CLARINET you stipulated that subjects were to be enrolled "as early as possible" after shunt surgery. Nonetheless, almost half of the subjects were randomized more than 2 weeks after surgery and 23% were randomized more than 4 weeks after surgery. In a newsletter to the CLARINET investigators dated 31 October 2007, Dr. David Wessel, the CLARINET Steering Committee Chairman, wrote we "have found that more than 50% of patients are randomized more than 2 weeks after palliation surgery. As you may know the e greatest incidence of adverse thrombotic or fatal events after shunt palliation…" 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.*

Sponsor's response: The Sponsor made the following points in response to this question:

- 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.
- 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.
- Some investigators did not randomize early after surgery because patients were unstable or receiving intensive support.
- Some investigators were concerned about starting blinded antiplatelet therapy if repeat surgery might be needed.
- Some investigators were concerned about asking parents, who might be overwhelmed by

their baby's surgery, for consent to be in a study.

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.[1] We have asked DSI to search for information about when oral medications were started in study patients at the sites they are inspecting.

Regarding efforts made to encourage investigators to enroll subjects early, the Sponsor responded:

- In newsletters and other communications to the investigator team as a whole, the importance of enrolling patients early after surgery was stressed. Several examples of these communications were provided.

Comment: We have seen these examples already. When asked specifically if any investigator was told individually to improve his or her performance with respect to when patients were randomized, we were told verbally that this did not occur. No site was dropped from the study for this problem. In one case, an investigator (Dr. Kumar) asked at a pre-study visit on 6 July 2006 whether a hypothetical patient who already had first stage surgery, with second stage surgery planned expected in November or December, could be enrolled when the site opened (expected date: September 1, more than 7 weeks later). The Sponsor's response was that the patient would be qualified for enrollment any time before the second stage procedure.

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 "Patients should be randomized preferably as soon as they are hemodynamically stable and able to receive the drug orally / enterically" (version dated 06 MARCH 06/ DRAFT 01, submitted 09 March 2006 (IND 34,663 SN 0622). If this version had been implemented and this provision 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 weeks after surgery. The study's power to detect an effect on events in this period was probably much lower than it would have been with different protocol language. We have no information on why the language was changed. Also, while the Sponsor indicates that its experts opined 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 BT 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 weeks after surgery to learn about the risks and benefits of clopidogrel in the shunt patients at highest risk of death.

We have received information from DSI regarding 2 of the 5 scheduled inspections of CLARINET study sites. Both of the completed sites were in the US. At Dr. Tugertimur's site (Orlando FL, N=24), the mean time from surgery to randomization (in days) was 34.3 (SD 20.8), the median was 35.5, and the range was 5 to 79. For days between start of ASA therapy to randomization, the mean was 17.0 (SD 18.2), the median was 14.5, and the range was 0 to 78. The DSI inspector noted that "the delay in enrollment was due to the ability of subjects to tolerate and be administered (orally and enterically) study medications" according to the PI and study coordinator. However the data for the time from ASA start to randomization suggest that other factors may have played a role. The site received no targeted communications from the Sponsor about late randomization.

At Dr. Sullivan's site (Louisville, KY, N=11), the mean time from surgery to randomization (in days) was 36.6 (SD 15.5), with a median of 38, and a range of 15 to 63. For days between start of ASA therapy to randomization, the mean was 29.1 (SD 16.3), with a median of 29, and a range of 4 to 60. The DSI inspector noted that, "the subject was not considered for study randomization until after the intercardiac [sic] line had been removed and there was no bleeding." This was considered as a patient safety issue at the site. The inspector reported that she did not find evidence that the Sponsor or monitor encouraged the site to randomize subjects sooner after the shunt surgery. If the original protocol language about time of randomization had been implemented, indicating that randomization should occur when the patient was able to tolerate oral or enteric medication, this self-imposed delay until the intracardiac line was removed may not have been implemented, and randomization might have occurred earlier. Note: this last site was chosen for inspection because it had one of the longest mean delays in randomization of the US sites. It is notable that the site never received any targeted communications regarding excessive time to randomization. In fact, no site received such a communication, and none was dropped or otherwise penalized for such performance.

Question 2 [preamble]: *At the End of Phase 2 meeting held on 12 July 2006, you asked us if additional PD studies were required and in our preliminary response that you received prior to the meeting we asked: "What is the level of platelet aggregation achieved with 5 micrograms [sic] of ADP as a function of age (neonates to adults)?" You did not provide the requested information at the meeting. According to the meeting minutes, Dr. Stockbridge asked you "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." [Note: this is the preamble to 4 subsequent questions, a though d.]*

Sponsor's response: The Sponsor made the following points in response to this preamble:

- "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: This response makes no sense on its face. 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 are puzzled how this statement, which mentions only neonates and adults, could reasonably be construed as relating to the need to perform PD studies in older children. Dr. Stockbridge is clearly interested in whether the PD responses (i.e., inhibition of ADP induced platelet aggregation) differ between neonates and adults because inhibition of platelet aggregation is the mechanism of action of clopidogrel. 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 were genuinely 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.

We note that the Sponsor had data from the PICOLO study on clopidogrel- induced inhibition of ADP induced platelet aggregation platelet aggregation that it could have discussed at the EOP2 meeting in July 2006 or sooner (see the discussion related to Question 2d). Instead, the Sponsor submitted the requested data to IND in an October 2006 submission that was styled as a "Clarification of Agency Meeting Minutes." The data were described in 3 short paragraphs that were located on one page, in between two "Requests for Clarification" relating to other issues. There was one page in an appendix with figures showing platelet aggregation data points in children and adults. CLARINET, the Sponsor's safety and efficacy study that was under discussion at the EOP2 meeting, was begun several weeks later.

We believe the Sponsor knew, or at a minimum, suspected what Dr. Stockbridge intended in his request for data in 2006. However, the Sponsor did not discuss the issue at the EOP2 meeting in 2006 and never discussed it until they received our letter of 13 October 2010. Instead of discussing the issue with us openly, the Sponsor submitted the requested data in 2006 in a manner that seems intended to maximize the likelihood that the data would be overlooked.

The Sponsor made additional comments regarding the preamble that were repeated in its responses to Questions 2a through 2d; these are discussed serially below.

Question 2a: Please explain why you believe that a study of administering clopidogrel, an inhibitor of ADP-induced platelet aggregation, to reduce shunt thrombosis at a dose lower than that administered to adults is informative given ADP appears to be a much less potent agonist of platelet aggregation in neonates and infants/toddlers than in adults.

The Sponsor made the following points in response:

- The dose selected for CLARINET, 0.2 mg/kg/day, was shown in PICOLO to provide 30-50% platelet aggregation in response to 5 μM ADP.
- It does not matter that ADP appears to be a less potent agonist of platelet in the target age group than in adults. This state is normal for patients in the target age group. The lower baseline responsiveness of neonatal platelets might explain why the mg/kg dose of clopidogrel is lower in these patients. While infants/toddlers are less responsive than adults to ADP, they still respond. Platelets on infants/toddlers and neonates aggregate and contribute to thrombus. These arguments are backed by statements from two the Sponsor's consultants, (b) (4)

- The 5 μM ADP test is the most relevant test of platelet aggregation in neonates, and the same methodology would be used today.

Reviewer comment: The fact that reduced responsiveness to ADP in the CLARINET target population might be "normal" is not an adequate response. Dr. Stockbridge's concern was that a patient whose platelets aggregation response to ADP is reduced (yet aggregate in vivo and are involved in pathological thrombosis) might respond poorly to a drug that acts by inhibiting ADP dependent aggregation. The Sponsor's experts did not address this issue. A number of endogenous molecules cause platelets to aggregate. The data provided by the Sponsor in its October "Clarification of Meeting Minutes" submission suggest that ADP may be less important in triggering platelet aggregation in the CLARINET target population than it is in adults. This might not be a serious problem for the patients, who have other ways to trigger platelet aggregation. However, perhaps a different approach to picking a clopidogrel dose might be more appropriate than one based on data from (fully functional) adult platelet aggregation studies, or perhaps clopidogrel would be a poor choice of drug for these patients, and the CLARINET study was futile from the start. Because the Sponsor did not respond to us in an open and direct manner, these issues were never discussed.

Our concern was and remains that if the platelets of CLARINET patient population did not aggregate like those of adults in response to ADP (but still aggregated in vivo, as evidence by the incidence of thrombotic complications after surgery), then the therapeutic strategy of inhibiting platelet aggregation by an ADP blocking agent to prevent thrombosis might not work as well in these patients as in adults, or it might not work at all. This is not hindsight – we raised this issue prior to the 2006 EOP meeting and then again at the EOP meeting in July 2006. The Sponsor never addressed it in 2006, and still has never addressed it.

We note that the Sponsor could have studied the use of clopidogrel in other thrombotic conditions that affect children, such as sickle cell crises. These children would mostly be older, and might have ADP responses in platelet aggregation studies similar to adults. The data to suggest the potential benefit of platelet aggregation inhibiting drugs in sickle cell anemia was available to the Sponsor before the 2006 EOP2 meeting.

- The Sponsor states that the rationale for dose selection was agreed to FDA.

Reviewer comment: FDA's agreement to the Sponsor's dose selection was contingent on the Sponsor's submission of data showing that the target population has a platelet aggregation response to 5 μM ADP similar to the response in adults. However, the responses in the target population and adults are quite different. This issue is discussed in more detail in out comments relating to Question 2b.

Question 2b: You chose to administer a dose of 0.2 mg/kg/day in CLARINET based on the finding in the dose ranging study PICOLO that this dose produced an approximately 50% reduction in inhibition of baseline platelet aggregation in response to 5 μM ADP in neonates and infants/toddlers. This percentage reduction was chosen as a target based on the effect of clopidogrel in adults. Please explain why you believe that method for choosing a dose was appropriate even though the response of platelets to ADP appears to be reduced in neonates and infants/toddlers compared to adults.

In response the Sponsor made the following points:

- When the pediatric program began, there was little information on pediatric platelet function, including the level of optimal platelet inhibition.
- The Sponsor, FDA, and the [CLARINET] Steering Committee agreed to use 30-50% platelet inhibition for dose selection, as in adults. "The potential for neonatal and infants/toddlers [sic] platelets to respond differently to ADP was not considered a critical factor in this rationale."
- In PICOLO, target levels of inhibition of platelet aggregation were achieved with the 0.2 mg/kg dose, and higher doses were not tested, including the planned 1.0 mg/kg dose.
- During PICOLO, FDA was provided with unblinded data by Drs. (b) (4) (the Platelet Aggregation Committee Chair) and Dr. (b) (4), the DMC independent statistician from (b) (4) Dr. (b) (4) and the Chair of the Steering Committee believed the best dose had been reached, and the Sponsor received FDA input to confirm its acceptance of this dose before stopping enrollment in PICOLO.
- The Sponsor's experts, Drs. (b) (4), stated that the reduced responsiveness of PICOLO patients' platelets to ADP "does not impact the CLARINET dose selection rationale." However, they simply make this assertion without explaining why or dealing with FDA's concern that reduced levels of agonism of a specific ligand might imply reduced benefit from specific antagonism of the same ligand in a biological process with multiple potential agonist ligands.
- FDA agreed with the choice of dose for CLARINET.

Reviewer comment: FDA's acceptance of 0.2 mg/kg/day as the as the clopidogrel dose to be used in CLARINET was not final, but was plainly a qualified acceptance. As Dr. Stockbridge's statement makes clear, 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 µM ADP. He 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." The data in the Sponsor's "Clarification of Meeting Minutes" submission show that the platelet aggregation responses of neonates and infants/toddlers are indeed markedly less than adults. The implications of this difference should have been clear to the Sponsor. The Sponsor should not have started the CLARINET study until this issue was discussed with us and fully resolved.

Other points raised by the Sponsor in its response to 2b are similar to the Sponsor's points in response to 2a and are discussed in our comments following that request for information.

Question 2c: The reduced response of platelets to ADP in neonates and infants/toddlers might have been expected to have implications for the expected effect size of clopidogrel in CLARINET. Please provide your rationale for the choice of an expected effect size of 30% in light of these data.

In response, the Sponsor made the following points:

- The efficacy of clopidogrel, mostly given with ASA, in the CLARINET target population was unknown at the start of the study. Target risk reduction was discussed with FDA and a 30% reduction was deemed to be an acceptable target.

- The Sponsor and Steering Committee did not consider altering the expected effect size based on the reduced ADP responses in the target population because the effect of such alterations in PD on the clinical 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.

Question 2d: On October 12, 2006, you submitted to us a document (SN 658 to IND 34663) in response to queries we made at the July 2006 End of Phase 2 meeting. Please disclose to us the date you became aware of the information contained in that submission.

The entirety of the Sponsor's response was:

> "The Sponsor became aware of the information contained in the 12 October 2006 submission in response to queries made at the July 2006 End of Phase 2 meeting upon receipt of initial draft from Dr. (b) (4) on 27 July 2006. It was sent to the Agency in the 12 October 2006 submission. There was no further communication between the Agency and Sponsor on this point until the PWR was re-issued in August 2007."

Reviewer comment: The data submitted by the Sponsor on 12 October 2006 were data from the pediatric patients in PICOLO and data from 11 adults.

Baseline data from PICOLO may have been in the Sponsor's hands at some time prior to the first submission of the data from PICOLO to us, which was on 19 December 2005. While the Sponsor may have been blinded then to the results of randomized treatment, the information requested by FDA was data from untreated patients -- i.e., baseline data, which could have been reported by the Sponsor without breaking the blind. In any event, unblinded data from PICOLO probably were submitted by the Sponsor prior to 7 February 2006, when FDA stated to the Sponsor by telephone that a dose of 0.2 mg/kg/day dose was acceptable for CLARINET. Also, the unblinded results of PICOLO were discussed in the Sponsor's EOP2 meeting package that was submitted on 27 March 2006.

The Sponsor states that the adult data submitted on 12 October 2006 were provided to the Sponsor by Dr. (b) (4) on 27 July 2006. These data were collected in 2003 - 2004, according to information in reference in the submission, but may not have been available to the Sponsor until 2006. The Sponsor certainly had adult platelet aggregation data from other studies prior to the drafting of the PICOLO protocol in December 2002, although perhaps not obtained using the same assay as in PICOLO. These data served as the basis of the 30-50% target inhibition standard that was the basis of dose selection in PICOLO.[4]

[4] The PICOLO protocol (dated 16 December 2002) states in the introduction, "Dose-response can best be assessed from a comparison to the pharmacodynamic efficacy of clopidogrel observed in adult patients, which

Conclusion:

This submission does not change our views regarding the adequacy of the Sponsor's submission to support a grant of pediatric exclusivity. While the Sponsor's experts indicated that it is their opinion that the reduced response of the CLARINET target population's platelets to ADP should not have affected the response to clopidogrel, they provide no data or convincing rationale for this opinion. The never addressed our basic concern about the implications of substantially reduced ADP agonism for the success of a therapeutic strategy involving use on an ADP antagonist. We still have the same concern about the premise of the use of clopidogrel in the CLARINET target population that Dr. Stockbridge clearly expressed at the EOP2 meeting in 2006 and that was documented in the meeting minutes. This concern was never addressed by the Sponsor.

The Sponsor's actions in 2006 and the conduct of the CLARINET study are the basis of our conclusion that they did not conduct the pediatric program in a manner that is consistent with good scientific principles. In particular, they did not conduct their single safety and efficacy study, CLARINET, in a manner that shows intent to achieve the desired result – a showing that clopidogrel treatment had an effect on the primary study outcome of the composite of 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. The Sponsor failed to ensure that patients were randomized in the study early enough so that the study had adequate power to detect an effect of clopidogrel on death and thrombotic events occurring in the first week after surgery, when the event rate is highest. The Sponsor's handling of FDA's clearly stated concerns in 2006 about the possibly reduced efficacy of clopidogrel in the target population is likewise inconsistent with good scientific principles, and their rationale for avoiding a discussion of this issue with FDA seems disingenuous to us. Accordingly, a grant of pediatric exclusivity should be denied.

Reference List

(1) Pearl JM, Nelson DP, Schwartz SM, Manning PB. First-stage palliation for hypoplastic left heart syndrome in the twenty-first century. *Ann Thorac Surg* 2002;73:331-339.

produces 30 to 50% inhibition of ADP-induced platelet aggregation at steady-state at the usual daily dose of 75 mg." (p. 17).

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