

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: **20-873** Submission Date(s): **4/3/09, 4/29/09**
Brand Name **Angiomax[®] Injection**
Generic Name **Bivalirudin**
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Sponsor **The Medicines Company**
Relevant IND(s) **076855**
Submission Type; Code **Efficacy Supplement (Pediatric), S-019, Priority Review**
Formulation; Strength(s) **250 mg single-use vial**
Indication **Anticoagulant used in patients receiving concomitant aspirin with 1) unstable angina undergoing PTCA or PCI and 2) with or at risk of HIT or HITTS, undergoing PCI.**

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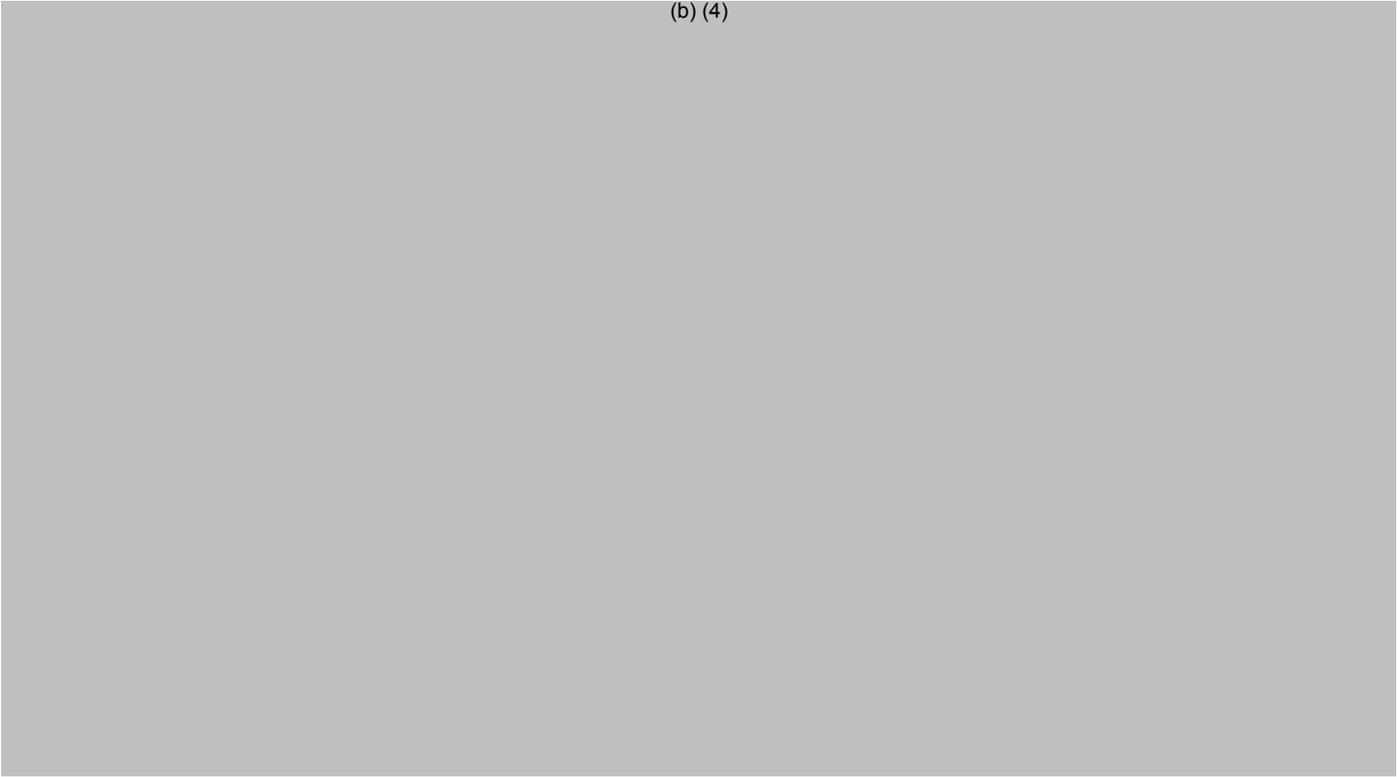
1 Executive Summary

Angiomax is a direct thrombin inhibitor that is approved for use as an anticoagulant in adults undergoing percutaneous transluminal coronary angioplasty (PTCA), percutaneous coronary intervention (PCI) or with, or at risk of, heparin-induced thrombocytopenia/heparin-induced thrombocytopenia thrombosis syndrome (HIT/HITTS) undergoing PCI.

This efficacy supplement was submitted in response to a formal Written Request by the United States (US) Food and Drug Administration (FDA) requiring the applicant to conduct an evaluation of bivalirudin in pediatric patients with congenital heart disease using same dosing regimen as approved in adults (0.75 mg/kg IV bolus followed by 1.75 mg/kg/h IV infusion for the length of the PCI). The objective of this study was to assess the PK, PD and safety of bivalirudin in this patient population and to provide dosing guidelines for the use of bivalirudin as an anticoagulant in this patient population. A PK/PD analysis compared these pediatric data with that of adult data from a study of adult patients undergoing PTCA.

Exposure of bivalirudin was found to be lower in pediatrics compared to adults receiving the proposed dose of 0.75 mg/kg IV bolus followed by 1.75 mg/kg/h IV infusion. The mean steady state concentration for pediatrics was 38 - 62% lower than the adults after the same dosing regimen. The effect on the activated clotting time (ACT) was found to be concentration dependent. However, the concentration-ACT relationship was not similar between pediatrics and adults. Younger pediatrics, especially less than 6 months old were found to be more sensitive to bivalirudin in terms of ACT. Despite lower sensitivity in these pediatric patients, steady state ACT will be lower than in adults due to lower exposures. All pediatrics patients produced ACT within the target range (200-400 sec) but the steady state ACT was consistently lower (17-36 seconds lower) than in adults.

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1.1 Recommendation

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1.2 Post Marketing Requirements

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1.3 Comments to the Applicant

(b) (4)

1.4 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Angiomax is a direct thrombin inhibitor that specifically binds to both the catalytic site and to the anion-binding exosite of circulating and clot-bound thrombin. Bivalirudin is approved for use as an anticoagulant in adults for: 1) Patients with unstable angina undergoing PTCA, 2) Patients undergoing PCI with provisional use of glycoprotein IIb/IIIa inhibitors (GPIs), and 3) Patients with, or at risk of, HIT/HITTS undergoing PCI.

This efficacy supplement was submitted in response to a formal Written Request by the United States (US) Food and Drug Administration (FDA), pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act. The Written Request received from the FDA on May 7, 2007, required primary data from a study in the pediatric population plus a review of other available data on the use of bivalirudin in children. The main requirement of the Written Request was to conduct an evaluation of bivalirudin in pediatric patients with congenital heart disease.

The requested study design was a prospective, open-labeled, single-arm, multicenter trial to assess the PK/PD and safety of bivalirudin as a procedural anticoagulant in the pediatric population undergoing percutaneous intravascular procedures for congenital heart disease. The objective of this study was to assess the PK, PD and safety of bivalirudin in this patient population and to provide dosing guidelines for the use of bivalirudin as an anticoagulant in this patient population. Enrollment included 110 patients ranging in age from birth up to 16 years, with 11 neonates, 33 infants/toddlers, 32 young children, and 34 older children, to complete treatment and study evaluations. Both noncompartmental analysis (NCA) and population PK modeling were used to describe the PK of bivalirudin in the pediatric patient population. The primary pharmacodynamic biomarker measured was ACT (Hemochron[®]) using blood obtained at the same time and from the same source line used for collecting PK samples.

A PK/PD analysis compared these pediatric data with that of adult data from Study TMC-98-09 (adult patients undergoing PTCA). A population PK/PD analysis was also conducted to characterize the disposition of bivalirudin and to allow exploration into the effects of several patient-specific covariates on PK and PD of bivalirudin in the pediatric patient population.

PK of bivalirudin was best described by a two compartment model with first order elimination. Weight was the most significant covariate which explained the interindividual variability in clearance and volume of distribution. Creatinine clearance also explained 20% of the

interindividual variability in clearance after adjusting for weight. No other covariates were identified to effect bivalirudin PK. Interindividual variabilities in central clearance and volume of distribution after adjusting for covariates were 22 and 19%, respectively. The affect of Angiomax on activated clotting time (ACT) was found to be concentration dependent. However, the PK/PD (ACT) relationship was not similar between pediatrics and adults. Younger pediatrics, especially less than 6 months old were more sensitive to bivalirudin in terms of ACT. Age was the only covariate identified on EC_{50} . Interindividual variabilites in EC_{50} and R_0 (baseline ACT) were 21 and 14% , respectively.

The exposures in pediatrics were lower when compared to adults with same dosing regimen. Younger pediatrics were more sensitive with lower EC_{50} than adults. (b) (4)

The steady state ACT with the sponsor's proposed dosing regimen was within the target range (200-400 sec). This target range was decided after consulting with the medical reviewer and also searching literature. (b) (4)

The median ACT in the REPLACE trial (pivotal trial conducted for approval of bivalirudin in adult patients undergoing PCI at the proposed dose of 0.75 mg/kg IV bolus followed by 1.75 mg/kg IV infusion over 4 hours) after 5 min, which can be considered to be representative of steady state ACT, was 358 sec (Inter-quartile range: 320-400 sec). Bivalirudin was also evaluated in patients with unstable angina undergoing PTCA (percutaneous transluminal coronary angioplasty) following 2.5 mg/kg/h IV infusion. Angiomax dose was not titrated to ACT, however ACT was measured at 5 and 45 min. The median ACT after 5 and 45 min was 345 sec (95% CI: 240-595) and 346 sec (95% CI: 269-583) after initiation of the dosing.

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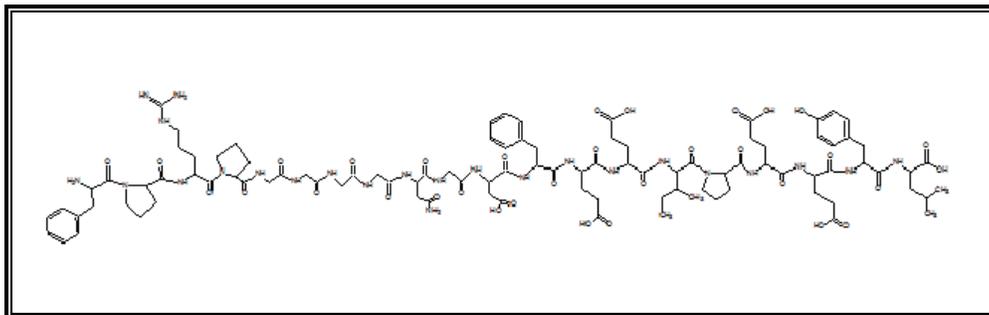
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2 Question Based Review

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?



Established name: bivalirudin

Molecular Weight: 2180 daltons (anhydrous free base peptide)

Molecular Formula: $C_{98}H_{138}N_{24}O_{33} \cdot C_2HF_3O_2 \cdot H_2O$

Chemical Name: D-phenylalanyl-L-prolyl-L-arginyl-L-prolyl-glycyl-glycyl-glycyl-glycyl-L-asparagyl-glycyl-L-aspartyl-L-phenylalanyl-L-glutamyl-L-glutamyl-L-isoleucyl-L-prolyl-L-glutamyl-L-glutamyl-L-tyrosyl-L-leucine trifluoroacetate (salt) hydrate

Solubility: “readily soluble in water” per 11/19/98 OCP review by Arzu Selen, Ph.D.

Product: Angiomax is supplied in single-use vials as a white lyophilized cake, which is sterile. Each vial contains 250 mg bivalirudin, 125 mg mannitol, and sodium hydroxide to adjust the pH to 5-6 (equivalent of approximately 12.5 mg sodium). When reconstituted with Sterile Water for Injection the product yields a clear to opalescent, colorless to slightly yellow solution, pH 5-6.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Angiomax directly inhibits thrombin by specifically binding both to the catalytic site and to the anion-binding exosite of circulating and clot-bound thrombin. Thrombin is a serine proteinase that plays a central role in the thrombotic process, acting to cleave fibrinogen into fibrin monomers and to activate Factor XIII to Factor XIIIa, allowing fibrin to develop a covalently cross-linked framework which stabilizes the thrombus; thrombin also activates Factors V and VIII, promoting further thrombin generation, and activates platelets, stimulating aggregation and granule release. The binding of Angiomax to thrombin is reversible as thrombin slowly cleaves the Angiomax-Arg3-Pro4 bond, resulting in recovery of thrombin active site functions.

In *in vitro* studies, Angiomax inhibited both soluble (free) and clot-bound thrombin, was not neutralized by products of the platelet release reaction, and prolonged the activated partial thromboplastin time (aPTT), thrombin time (TT), and prothrombin time (PT) of normal human plasma in a concentration-dependent manner. The clinical relevance of these findings is unknown.

Angiomax is indicated for:

1. Percutaneous transluminal coronary angioplasty (PTCA)
 - As an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA).
2. Percutaneous coronary intervention (PCI)
 - With provisional use of glycoprotein IIb/IIIa inhibitor (GPI) as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI).
 - Patients with, or at risk of, heparin induced thrombocytopenia (HIT) or heparin induced thrombocytopenia and thrombosis syndrome (HITTS) undergoing PCI.

Angiomax in these indications is intended for use with aspirin and has been studied only in patients receiving concomitant aspirin

2.1.3 What are the proposed dosage(s) and route(s) of administration?

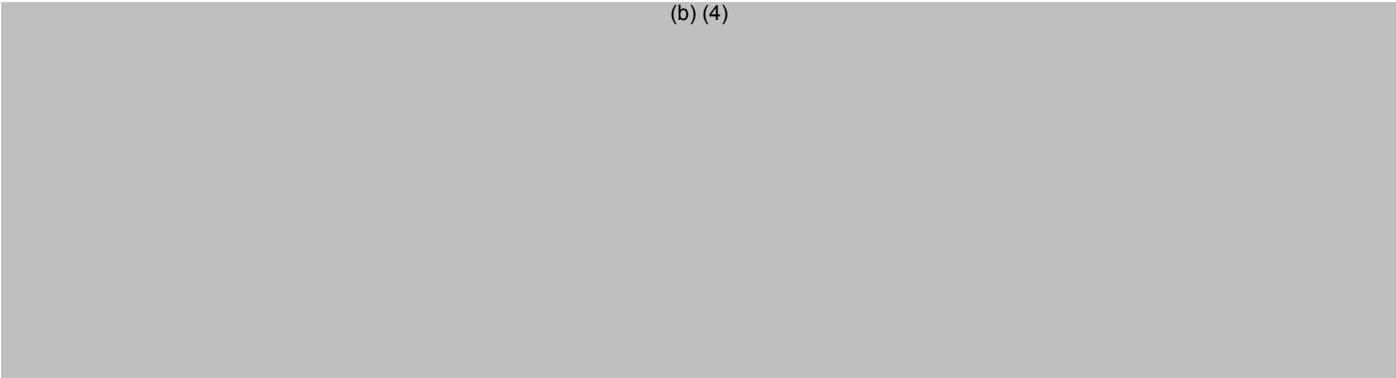
The recommended dose of Angiomax is an IV bolus dose of 0.75 mg/kg. This should be followed by an infusion of 1.75 mg/kg/h for the duration of the PCI procedure. Five min after the bolus dose has been administered, an activated clotting time (ACT) should be performed and an additional bolus of 0.3 mg/kg should be given if needed. GPI administration should be considered in the event that a decreased TIMI flow (0 to 2) or slow reflow; dissection with decreased flow; new or suspected thrombus; persistent residual stenosis; distal embolization; unplanned stent; suboptimal stenting; side branch closure; abrupt closure; clinical instability; or prolonged ischemia is present.

The recommended dose of Angiomax in patients with HIT/HITTS undergoing PCI is an IV bolus dose of 0.75 mg/kg. This should be followed by a continuous infusion at a rate of 1.75 mg/kg/h for the duration of the procedure.

Continuation of the Angiomax infusion following PCI for up to 4 hours post-procedure is optional, at the discretion of the treating physician. After four hours, an additional IV infusion of Angiomax may be initiated at a rate of 0.2 mg/kg/h, for up to 20 hours, as needed. Angiomax is intended for use with aspirin (300-325 mg daily) and has been studied only in patients receiving concomitant aspirin.

The infusion dose of Angiomax may need to be reduced, and anticoagulant status monitored in patients with renal impairment. Patients with moderate renal impairment (30-59 mL/min) should receive 1.75 mg/kg/h. If the creatinine clearance is less than 30 mL/min, reduction of the infusion rate to 1.0 mg/kg/h should be considered. If a patient is on hemodialysis, the infusion should be reduced to 0.25 mg/kg/h. No reduction in the bolus dose is needed.

(b) (4)



2.2 General Clinical Pharmacology

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

See Section 4.2. The study design of study TMC-BIV-07-01 was a prospective, open-labeled, single-arm, multicenter trial to assess the PK/PD and safety of bivalirudin as a procedural anticoagulant in the pediatric population undergoing percutaneous intravascular procedures for congenital heart disease. The objective of this study was to assess the PK, PD and safety of bivalirudin in this patient population and to provide dosing guidelines for the use of bivalirudin as an anticoagulant in this patient population. Enrollment included 110 patients ranging in age from birth up to 16 years, with 11 neonates, 33 infants/toddlers, 32 young children, and 34 older children, to complete treatment and study evaluations. Both non-compartmental analysis (NCA) and population PK modeling were used to describe the PK of bivalirudin in the pediatric patient population. The primary pharmacodynamic biomarker measured was ACT (Hemochron®) using blood obtained at the same time and from the same source line used for collecting PK samples.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The approved product labeling for Angiomax states that, in adults, IV bivalirudin produces dose-dependent prolongation of anticoagulant activity as measured by activated partial thromboplastin time (aPTT), thrombin time (TT), prothrombin time (PT), and activated clotting time (ACT). Prolongation of clotting times is positively correlated with plasma drug concentrations. The choice of ACT is reasonable given the clinical environment of the study.

ACT is an accepted method for evaluating coagulation status and assessing PD activity in adults and is considered a suitable surrogate measure for confirming the presence of anticoagulation during vascular interventions. It is important to note that although ACT is a useful indicator that the patient has received bivalirudin through a rise in ACT values from baseline, ACT levels have not been predictive of thrombotic or bleeding events in previous studies in the setting of catheter-based procedures at a fixed dose of bivalirudin.¹

In response to an FDA request for increased guidance for investigators with respect to ACT values, additional text was added by the applicant as a protocol amendment explaining that ACT was not a precise measure of anticoagulant status but that ACT levels below 200 seconds may indicate inadequate anticoagulation and measures should be taken to establish correct dosing and receipt of drug.

The adequacy of ACT monitoring is more questionable in pediatric patients because ACT is influenced by factors more likely to occur in infants and neonates undergoing coronary bypass for congenital heart repair.² However, the approved labeling for commercially available

¹ Marmor JD. Direct versus indirect thrombin inhibition in percutaneous coronary intervention. *J Invasive Cardiol.* 2002; Suppl B:8B-18B.

² Codisoti M, Ludlam CA, Simpson D, Mankad PS. Individualized Heparin and Protamine Management in Infants and Children Undergoing Cardiac Operations. *Ann Thorac Surg* 2001;71:922–8.

transcatheter atrial septal closure devices recommend a targeted ACT > 200 seconds.³ Moreover, American College of Chest Physicians recommend a target ACT between 250-350 sec in patients undergoing PCI.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. See Section 2.6

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The pediatric study was not an efficacy study. ACT is a PD biomarker used to evaluate the anticoagulation effect of bivalirudin. There were some thrombotic events observed in the pediatric study. A trend of higher thrombotic events was associated with lower exposures (See section 2.2.4.2 for details).

This section describes and compares the PK-PD of pediatrics and adults. Effect on activated clotting time (ACT) was found to be concentration dependent as shown in **Figure 1** (left panel). However, the PK-PD is not similar between pediatrics and adults. The concentration-ACT relationship was best described by an E_{max} model. Younger pediatrics, especially less than 6 months old were found to be more sensitive to bivalirudin in terms of ACT. (b) (4)

Figure 1 (left) shows the observed concentrations vs. ACT in pediatrics and adults. It is evident from the figure that pediatrics less than 6 months have a steeper concentration-ACT relationship when compared to other groups. This was further supported by inclusion of age as a significant covariate on EC_{50} which explained 28% of the interindividual variability in EC_{50} (from 29% to 21%). **Figure 1** (right) shows that EC_{50} increases with age and achieves 80% of adult value (4940 ng/ml) in approximately 2 years.

³ Product information. CardioSEAL® septal occlusion system. 1999. (http://www.accessdata.fda.gov/cdrh_docs/pdf/H990005c.pdf)

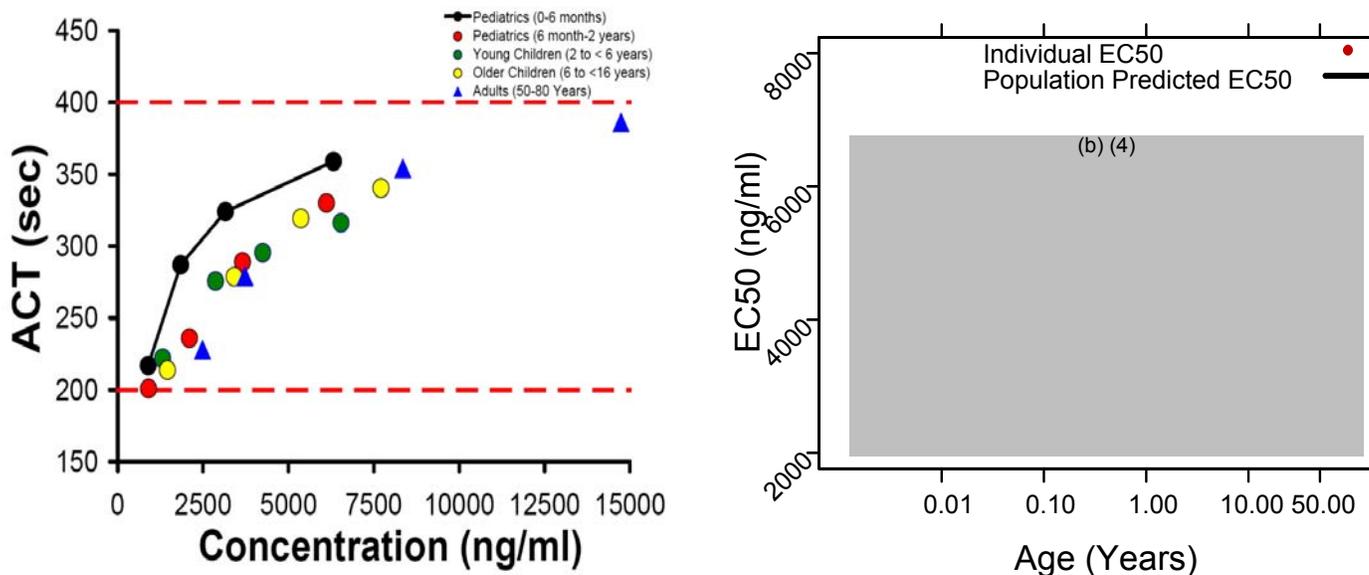


Figure 1: Observed concentration-ACT relationship in various pediatric subgroups (Left panel) and Age-EC₅₀ relationship (Right panel).

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

The applicant reports that two patients (one young child and one older child) had a hematoma >2.5 cm that qualified as a major bleeding event; there were no other major bleeding events; 12 patients had minor bleeding. Eight per protocol patients (9 safety population) had a thrombotic event either during the procedure (n=3) or during hospital stay (n=5) following discontinuation of study drug. The thrombotic event occurred in the sheath in seven of the eight per protocol patients (8/9 safety population). The remaining thrombotic event occurred in a Blalock Taussig shunt.

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Flushing of vascular insertion sheaths, typically with unfractionated heparin, is a standard technique in the catheterization laboratory to keep insertion sheaths clear of thrombus and allow devices to be inserted through the vessel. Since the protocol stated that unfractionated heparin could not be administered during the treatment period, if a sheath flush was needed, either 0.9% saline or a 0.1 mg/mL bivalirudin flush solution was used. The bivalirudin flush was based on published information for use in adult cardiopulmonary bypass surgery for arterial lines and graft storage. The bivalirudin flush is not an approved use per the approved labeling.

(b) (4)

Table 3: Influence of bivalirudin flush dose versus normal saline or no flush dose on thrombotic events

Event	Neonates ≤ 30 days n/N(%)	Infants 31 days to <2 yrs n/N(%)	Young Children 2 to <6 yrs n/N(%)	Older Children 6 to <16 yrs n/N(%)	Total n/N(%)
Any thrombosis at any time through 30 days					
All patients	2/11(18.2)	4/33(12.1)	2/32(6.3)	1/34(2.9)	9/110(8.2)
Patients with bivalirudin flush	0/3 (0.0)	1/15 (6.7)	0/17 (0.0)	0/18 (0.0)	1/53 (1.9)
Patients with saline or no flush	2/8*# (25.0)	3/18# (16.7)	2/15 (13.3)	1/16 (6.3)	8/57 (14.0)

*1 Event prior to receiving study drug

1 Event >1 hr after completion of infusion

Source: Applicant's Study report TMC BIV 07 01 Table 19

(b) (4)

2.2.4.3 Dose this drug prolong the QT or QTc interval

Not applicable to this SE (pediatric) submission.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

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. Sponsor only tested one dosing regimen in pediatrics which is 0.75 mg/kg IV bolus followed by 1.75 mg/kg/h IV infusion. This is also the approved dosing regimen of bivalirudin in adults. (b) (4)

. In the adult clinical trial, the mean ACT at 5 min, which is representative of steady state ACT in adults was 358 sec compared to 305 sec (Range: 251-372 sec) for pediatrics. (b) (4)

Figure 2 shows the mean ACT-time profiles for pediatrics in different age groups compared to adults with 0.75 mg/kg IV bolus followed by 1.75 mg/kg/h IV infusion. There is early fluctuation in the ACT-time profile for pediatrics due to different PK disposition (See **Figure 1** of the Pharmacometric review in section 4.4.1) of bivalirudin compared to adults. Moreover, the steady state ACT in pediatrics is consistently lower than adults at the proposed dosing regimen.

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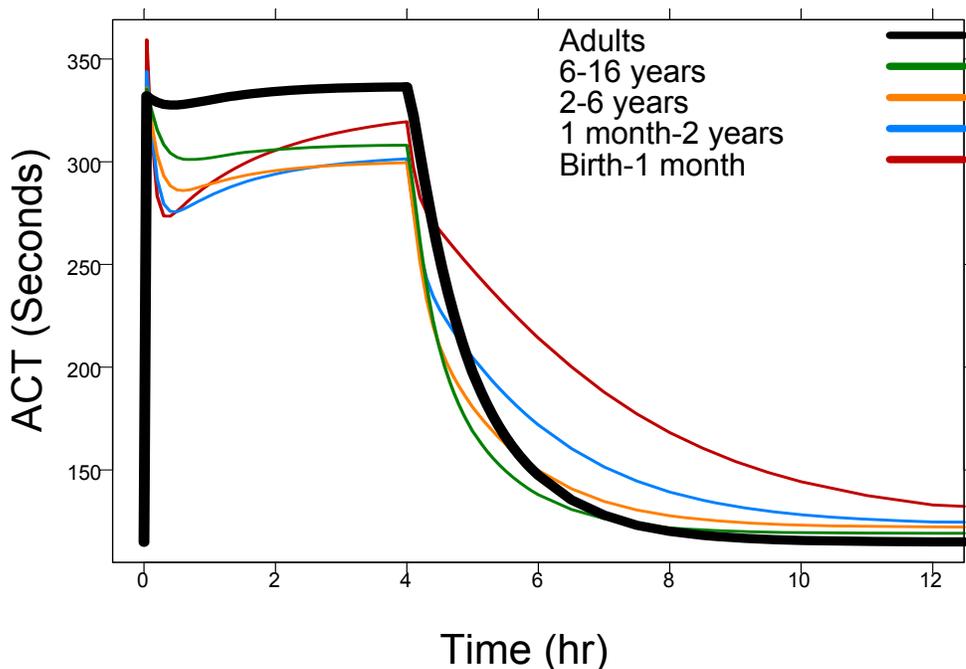
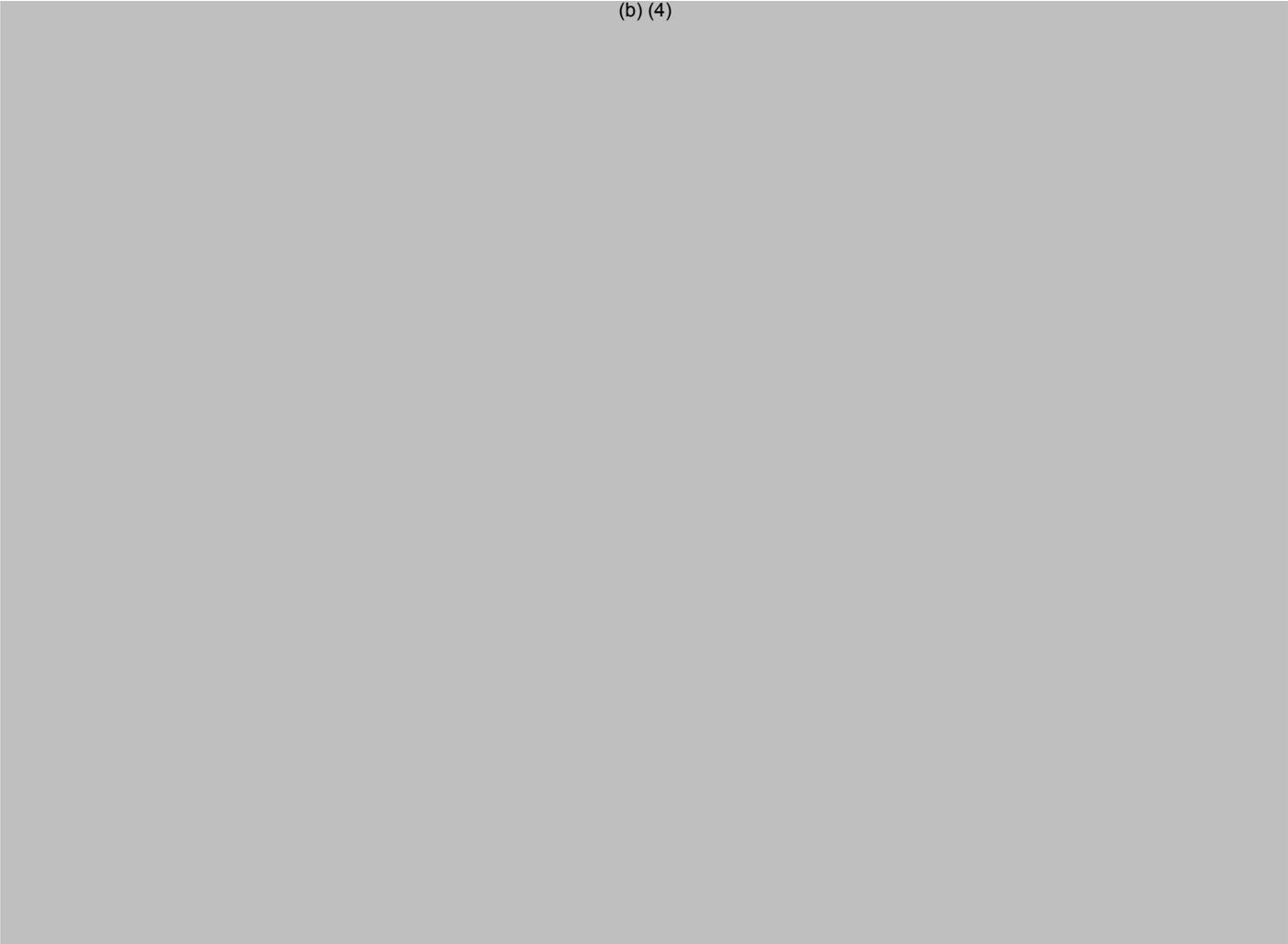


Figure 2: Mean ACT-time profiles for pediatrics and adults showing lower steady state ACT in pediatrics at the proposed dose of 0.75 mg/kg IV bolus followed by 1.75 mg/kg IV infusion over 4 hours.

The median ACT in the REPLACE trial (pivotal trial conducted for approval of bivalirudin in adult patients undergoing PCI at the proposed dose of 0.75 mg/kg IV bolus followed by 1.75 mg/kg IV infusion over 4 hours) after 5 min, which can be considered to be representative of steady state ACT, was 358 sec (Inter-quartile range: 320-400 sec). Bivalirudin was also evaluated in patients with unstable angina undergoing PTCA (percutaneous transluminal coronary angioplasty) following 2.5 mg/kg/h IV infusion. Angiomax dose was not titrated to ACT, however ACT was measured at 5 and 45 min. The median ACT after 5 and 45 min was 345 sec (95%CI: 240-595) and 346 sec (95%CI: 269-583) after initiation of the dosing. As seen in **Figure 2**, the mean steady state ACT for pediatrics is between 299 and 319 sec.

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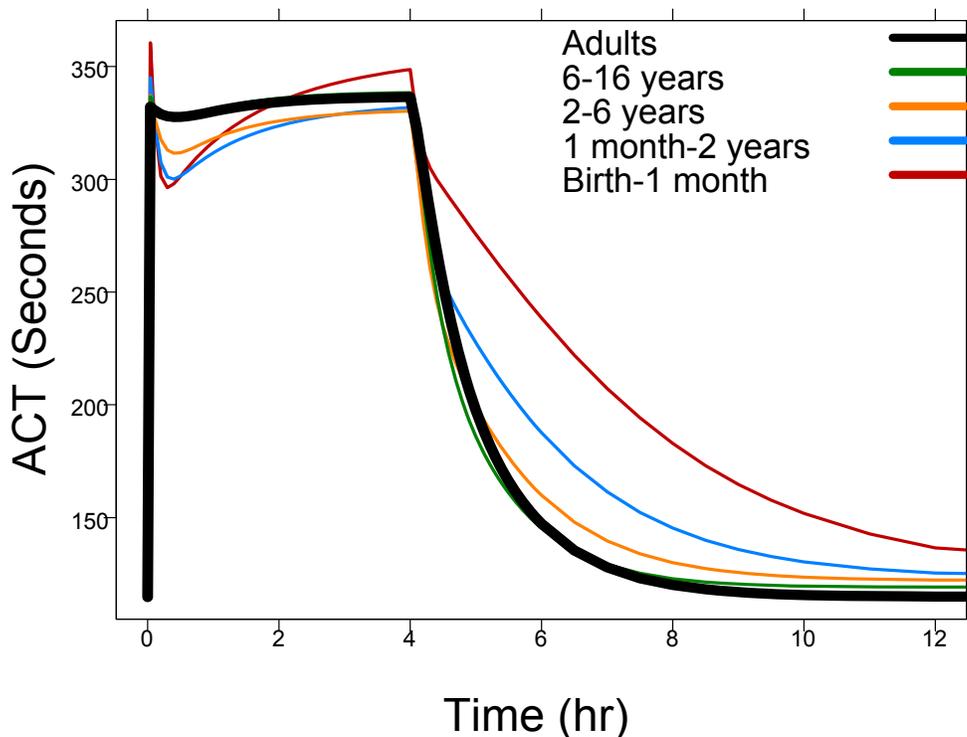


Figure 3: Mean ACT-time profiles for pediatrics and adults showing similar steady state ACT in pediatrics at the modified dosing regimen with same IV bolus dose (0.75 mg/kg) but increase in infusion rate to 2.5 mg/kg/h.

2.2.5 PK characteristics of the drug and its major metabolite

2.2.5.1 What are the single dose and multiple dose PK parameters?

In the pediatric study submitted in support of this application bivalirudin was administered as an IV bolus (0.75 mg/kg) followed by infusion (1.75 mg/kg/h) for the duration of the surgery. PK of bivalirudin was best described by a two compartment model with first order elimination. Weight was the most significant covariate which reduced the interindividual variability in central CL and volume of distribution from 75 and 98, to 28 and 19%, respectively. The exposures in pediatrics were lower when compared to adults (see Section 4.4.1). Elimination half life, especially in younger pediatrics is prolonged due to decreased clearance. The individual clearance estimates calculated from population PK and NCA were in close agreement (**Table 4** and **Table 7**). Volume of distribution increased with increasing weight. (See section 4.4.1 for details). The PK parameters in pediatrics stratified by age group are presented below in **Table 4**.

Table 4: PK Parameters [mean (SD)] of bivalirudin in pediatrics

	Neonates (≤30d)	Infants/ toddlers (31d - <2y)	Young children (2y - <6y)	Older children (6y - <16y)
† C_{ss} (ng/mL)	2534 (1569)	3467 (1890)	4277 (1319)	5331 (1496)
* Clearance (L/h)	1.8 (0.4)	3.8 (1.4)	6.9 (1.9)	12.9 (4.9)
* Elimination half-Life (min)	90 (16.1)	61 (11.8)	47 (5.6)	40 (3.6)

* Based on individual estimates from the population PK model

† Concentration at steady state based on average of concentrations between 15 min post infusion to end of the infusion.

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The optional use of a second bolus of bivalirudin, as outlined in the adult dosing recommendation, was not part of the dosing plan for study submitted in support of this application. Two subjects did receive a second bolus (0.75 mg/kg). For PT102008, the infusion was delayed after the first bolus and thus an additional bolus and infusion were administered again at 40 min. For PT101001 both a bolus dose and infusion were administered initially. An additional bolus for this patient was administered after checking the ACT at 30 minutes which was lower than expected (176 sec). A descriptive evaluation of these two patients (**Figure 4**) suggests that the 5 min ACT did not predict the need for an additional bolus.

(b) (4)

Figure 4: Time versus concentration and ACT for two patients that received an additional bolus dose of bivalirudin.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Not applicable to this SE (pediatric) submission.

2.2.5.3 What are the characteristics of drug absorption?

Not applicable to this SE (pediatric) submission.

2.2.5.4 What are the characteristics of drug distribution?

Not applicable to this SE (pediatric) submission.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Not applicable to this SE (pediatric) submission.

2.2.5.6 What are the characteristics of drug metabolism?

Not applicable to this SE (pediatric) submission.

2.2.5.7 What are the characteristics of drug excretion?

Not applicable to this SE (pediatric) submission.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Not applicable to this SE (pediatric) submission.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

Not applicable to this SE (pediatric) submission.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Not applicable to this SE (pediatric) submission.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Weight was the most significant covariate which described between subject variability (BSV). **Figure 5** shows relationship between individual predicted clearance overlaid with model prediction. Creatinine clearance further reduced the BSV in clearance from 28 to 21% after adjusting for weight. This is in accordance with the elimination mechanism of bivalirudin in which 20% of the total elimination is through renal route.

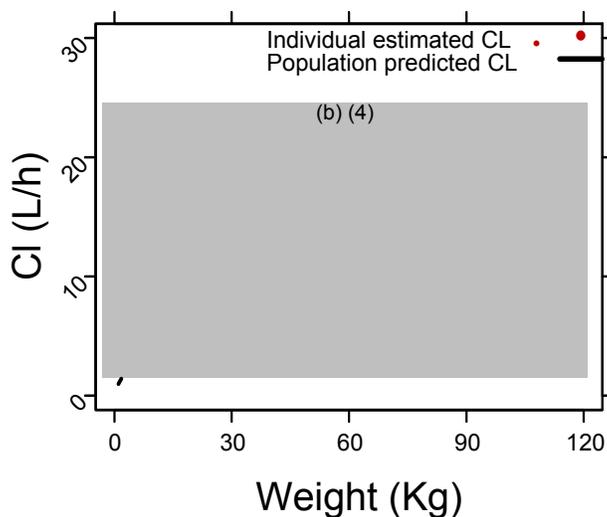


Figure 5: Effect of weight on bivalirudin clearance over the observed range of weight.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly

Not applicable to this SE (pediatric) submission.

2.3.2.2 Pediatric patients

See section 2.2.4.3 for recommended adjusted infusion rate (2.5 mg/kg/h) to match steady state ACT in adults.

2.3.2.3 Gender

Not applicable to this SE (pediatric) submission.

2.3.2.4 Race

Not applicable to this SE (pediatric) submission.

2.3.2.5 Renal impairment

Not applicable to this SE (pediatric) submission.

2.3.2.6 Hepatic impairment

Not applicable to this SE (pediatric) submission.

2.3.2.7 What pregnancy and lactation use information is there in the application?

Not applicable to this SE (pediatric) submission.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Not applicable to this SE (pediatric) submission.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Not applicable to this SE (pediatric) submission.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Not applicable to this SE (pediatric) submission.

2.4.2.3 Is the drug an inducer of CYP enzymes?

Not applicable to this SE (pediatric) submission.

2.4.2.4 Is the drug an inhibitor of CYP enzymes?

Not applicable to this SE (pediatric) submission.

2.4.2.5 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Not applicable to this SE (pediatric) submission.

2.4.2.6 Are there other metabolic/transporter pathways that may be important?

Not applicable to this SE (pediatric) submission.

2.4.2.7 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Not applicable to this SE (pediatric) submission.

2.4.2.8 What other co-medications are likely to be administered to the target patient population?

Not applicable to this SE (pediatric) submission.

2.4.2.9 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Not applicable to this SE (pediatric) submission.

2.4.2.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Not applicable to this SE (pediatric) submission.

2.4.2.11 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

Not applicable to this SE (pediatric) submission.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

Not applicable to this SE (pediatric) submission.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Not applicable to this SE (pediatric) submission.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

Not applicable to this SE (pediatric) submission.

2.5.2.1 What data support or do not support a waiver of *in vivo* BE data?

Not applicable to this SE (pediatric) submission.

2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

Not applicable to this SE (pediatric) submission.

2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

Not applicable to this SE (pediatric) submission.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not applicable to this SE (pediatric) submission.

2.5.4 When would a fed BE study be appropriate and was one conducted?

Not applicable to this SE (pediatric) submission.

2.5.5 How do the dissolution conditions and specifications ensure *in vivo* performance and quality of the product?

Not applicable to this SE (pediatric) submission.

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Not applicable to this SE (pediatric) submission.

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable to this SE (pediatric) submission.

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable to this SE (pediatric) submission.

2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

Not applicable to this SE (pediatric) submission.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Plasma bivalirudin concentrations were determined by validated high performance liquid chromatography – tandem mass spectrometry (HPLC/MS/MS) assay (**Table 5**).

Table 5: Assay methodology

Equipment	LC/MS/MS	Sciex API 4000 with Shimadzu LC pump and autosampler
	Software	Analyst data acquisition software (Version 1.4)
	Column	YMCBasic, 50 x 4.6 mm, 3 micron
	Centrifuge	Beckman GS-6R
	Switch Valve	Valco Instruments
	Analytical Balance	capable of weighing 0.00001g
Standards and Reagents	Bivalirudin	Overall Purity: 97.8%
	(b) (4)	
HPLC conditions:	Mobile phase:	30:70 Acetonitrile 10.1% formic acid (v/v)
	Flow rate:	0.4 mL/min (splitless)
	Injection volume:	10 µL
	Needle wash solvent:	Mobile phase
MS/MS conditions: Bivalirudin	Parent ion m/z:	1090.9

	Product ion m/z:	227.1
	Dwell time:	400msec.
	Pause time:	5 msec.
	Retention time:	-2.1 min
MS/MS conditions (b) (4) (internal standard):	Parent ion m/z:	1097.9
	Product ion m/z:	199.1
	Dwell time:	200msec.
	Pause time:	5 msec.
	Retention time:	-2.1 min

Source Adapted from Applicant report FL05-TMC-TR199

Bivalirudin was extracted by protein precipitation from human plasma. Sample extracts were analyzed using a Sciex API 4000 tandem mass spectrometer fitted with a TurboIonSpray source. The method involved the addition of internal standard to an aliquot of sample followed by the extraction of bivalirudin by protein precipitation using methanol. The sample was centrifuged at 3000 rpm for 5 minutes and the resulting supernatant was reconstituted with 0.1% formic acid. The reconstituted solution was injected onto the HPLC/MS/MS system for analysis. Validation results are provided in **Table 6**.

The method was modified for Study TMC-BIV-07-01 (Method AM-098-R1) to allow for the use of either sodium citrate or K2EDTA as the anticoagulant, as well as to decrease the preparation volumes, to make the method suitable for pediatric studies. Validation results are provided in **Table 6**.

Table 6: Validation parameters for methods AM-098-R0 & AM-098-R1

Analytes	Bivalirudin
Internal standard (IS)	(b) (4)
Method description	Precipitation
Limit of quantitation (ng/mL)	500 ng/mL (LLOQ) 25000 ng/mL (ULOQ)
Average recovery of Bivalirudin (%)	85.9
Average recovery of IS (%)	85.7
Standard curve concentrations (ng/mL)	500,1000,1500,2500,10000,15000,20000,25000
QC concentrations (ng/mL)	1500,10000,20000
QC Intraday precision range (%)	Day 1: 3.8 to 5.0 Day 2: 4.8 to 10.5 Day 3: 3.2 to 4.5
QC Intraday accuracy range (%)	Day 1: 110.4 to 114.8 Day 2: 94.4 to 96.8 Day 3: 100.5 to 104.5
QC Interday precision range (%)	7.4 to 9.7
QC Interday accuracy range (%)	102.4 to 105.3
Intra batch accuracy(Method AM-098-R1)	95.4% to 103.9%
Intra batch precision (Method AM-098-R1)	2.0% to 3.6%
Bench-top stability (hrs)	6 hours @ room temperature
Stock stability (days/hours)	6 hours @room temperature See Section 6 Analytical Note
Processed stability (hrs)	84 hours @ room temperature
Freeze-thaw stability (freeze-thaw cycles)	3 freeze-thaw cycles
Long-term storage stability (days)	See Section 6 Analytical Note
Dilution integrity	250000 ng/mL diluted 20 times
Selectivity	No interfering peaks noted in blank plasma samples

Source Adapted from Applicant report FL05-TMC-TR199 & FL05-TMC-TR199A2

2.6.2 Which metabolites have been selected for analysis and why?

None. There are no known active metabolites.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total concentration was measured. This was appropriate for this submission because bivalirudin does not bind to plasma proteins other than thrombin per 11/19/98 OCP review by Arzu Selen, Ph.D.

2.6.4 What bioanalytical methods are used to assess concentrations?

See Section 2.6.1.

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

See Section 2.6.1. The linearity of the method was evaluated within the standard concentration range of 500- 25000 ng/mL. The calibration lines were weighed $1/x^2$ and linear interpolation was used to quantify the QC and test samples. Calibration curves were accepted on the basis that the calibration curve exhibited a correlation coefficient of greater than or equal to 0.98 for a minimum of six points. These findings appear reasonable and consistent with the guidance “Bioanalytical Method Validation.”⁴

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

See Section 2.6.1.

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

See Section 2.6.1. These findings appear reasonable and consistent with the guidance “Bioanalytical Method Validation.”⁵

2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

See Section 2.6.1. These findings appear reasonable and consistent with the guidance “Bioanalytical Method Validation.”⁵

2.6.4.5 What is the QC sample plan?

See Section 2.6.1. A set of quality control (QC) samples (three concentrations) were run with each batch of study samples. Batch analysis was accepted on the basis that sufficient QC sample results lay within the acceptance criteria (Standards were rejected if they were greater than $\pm 15\%$ (all standards but the LLOQ) or $\pm 20\%$ (LLOQ only) of the nominal concentration).

The accuracy of sample dilution was verified by the performance of dilution quality control samples (See Section 2.6.1).

⁴ Guidance for Industry: Bioanalytical Method Validation. Issued 5/2001. (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf>).

3 Detailed Labeling Recommendations

4.1.2 Patient Product Labeling

None submitted

4.2 Overview of Study Designs

Study ID: Study name Study design Country (no. sites) Location	Study objectives Angiomax dose regimen, Batch or Lot no.	No. patients enrolled/completed/PK evaluable (M/F)
<p>TMC-BIV-02-04:</p> <p>Pilot dose finding and efficacy study of Angiomax® (bivalirudin) as primary anticoagulation in infants under six months with thrombosis</p> <p>Study Design: Prospective, open-labeled, single-arm, multicenter trial</p> <p>Country: United States (2 centers)</p> <p>Location: Module 5.3.5.1</p>	<p>Objectives:</p> <ul style="list-style-type: none"> To assess the safety of bivalirudin in infants under 6 months with arterial or venous thrombosis To determine the dose of bivalirudin required to achieve adequate anticoagulation as measured by ACT or aPTT in this patient population To determine the outcome of patients on bivalirudin with respect to thrombus resolution and bleeding complications as compared to patients on UFH or LMWH based on historical data <p>Dose Regimen and batch no: One of three IV bolus doses: 0.125 mg/kg, 0.25 mg/kg or 0.5 mg/kg One of two initial infusion doses: 0.125 mg/kg/h or 0.25 mg/kg/h Lot numbers 239980 and 273786</p>	<p>Enrolled: 16 (7M/9F) Completed: 15 (7M/8F) PK evaluable: 7 (5M/2F)</p>
<p>TMC-BIV-07-01:</p> <p>Bivalirudin (Angiomax®) as a procedural anticoagulant in the pediatric population undergoing intravascular procedures for congenital heart disease</p> <p>Study Design: Prospective, open-labeled, single-arm, multicenter trial</p> <p>Country: United States (11 centers)</p>	<p>Objectives:</p> <ul style="list-style-type: none"> To determine the plasma concentrations of bivalirudin • To determine the PD of bivalirudin, as measured by ACT To provide dosing guidelines for the use of bivalirudin as an anticoagulant during percutaneous intravascular procedures in pediatric patients To evaluate the safety of bivalirudin in pediatric patients <p>Dose Regimen and batch no: IV bolus 0.75 mg/kg followed by an IV infusion of 1.75 mg/kg/h. Batch 896014.</p>	<p>Neonates (Birth ≤30days) Enrolled:11 (6M/5F) Completed:11 (6M/5F) PK evaluable:10 (5M/5F)</p> <p>Infants/toddlers (31 days to <24 mo.) Enrolled:33 (15M/18F) Completed:33 (15M/18F) PK evaluable:33 (15M/18F)</p> <p>Young children (2 to <6 years) Enrolled:32 (15M/17F) Completed:32 (15M/17F) PK evaluable:31 (14M/17F)</p> <p>Older children (6 to <16 years) Enrolled:34 (14M/20F) Completed:33 (13M/20F) PK evaluable:31 (14M/17F)</p>
<p>TMC-98-09:</p> <p>The influence of dose, gender and kidney function on bivalirudin pharmacokinetics and pharmacodynamics in patients</p>	<p>Objectives:</p> <ul style="list-style-type: none"> To determine bivalirudin CL and PD (ACT) in angioplasty patients at the recommended bivalirudin dose 	<p>Normal renal function (GFR≥90 mL/min): Enrolled: 8 (6M/2F) Completed: 8 (6M/2F) PK evaluable: 8 (6M/2F)</p> <p>Mild renal impairment</p>

<p>undergoing PTCA</p> <p>Study Design: Multicenter, open- label serially recruiting trial</p> <p>Country: New Zealand and Australia (2 centers)</p>	<ul style="list-style-type: none"> • To determine if bivalirudin CL and PD are dose-dependent • To determine if bivalirudin CL and PD are dependent on kidney function and gender • To assess the proportion of unchanged bivalirudin that is cleared renally <p>Dose Regimen and lot no: 1 mg/kg bolus followed by 2.5 mg/kg/h infusion for 4 hours, then infusion of 0.5 mg/kg/h for a further 4 hours <i>Patients with moderate renal impairment:</i> each infusion duration was extended to 6 hours Lot no. 41692</p>	<p>GFR 60-89 mL/min): Enrolled: 11 (6M/5F) Completed: 11 (6M/5F) PK evaluable: 11 (6M/5F)</p> <p>Moderate renal impairment (GFR 30-59 mL/min): Enrolled: 7 (6M/1F) Completed: 6 (5M/1F) PK evaluable: 6 (5M/1F) Mean age 63 years (50-78)</p>
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4.3 Individual Study Reviews

4.3.1 Pediatric Study

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: Bivalirudin (Angiomax®) as a Procedural Anticoagulant in the Pediatric Population Undergoing Intravascular Procedures for Congenital Heart Disease

Study period: 8 August 2007 to 2 August 2008

Reviewer Comments:

(b) (4)

Table 7: PK parameters of bivalirudin in pediatrics.

Age Group	C _{max} (ng/mL)	AUC _{0-t} (ng*h/mL)	C _{avg} (ng/mL)	T _{1/2} (h)	CL (mL/min/kg)	CL (L/h)
Neonates ≤30 days	4876 (3240) [n = 9]	4462 (4936) [n = 8]	3235 (1642) [n = 8]	0.25 (0.09) [n = 5]	11.2 (4.3) [n = 5]	2.52 (1.09) [n = 5]
Infants 31 days - <2 yrs	6124 (2750) [n = 32]	4325 (2957) [n = 30]	3775 (1492) [n = 30]	0.27 (0.06) [n = 22]	10.1 (4.0) [n = 22]	4.90 (1.94) [n = 22]
Young Children 2 yrs - <6 yrs	6628 (2353) [n = 30]	6244 (4758) [n = 30]	4651 (1508) [n = 30]	0.30 (0.08) [n = 28]	7.63 (2.32) [n = 28]	8.02 (2.69) [n = 28]
Older Children 6 yrs - <16 yrs	7188 (2133) [n = 31]	6757 (4745) [n = 30]	5291 (1549) [n = 30]	0.28 (0.06) [n = 25]	5.98 (1.30) [n = 25]	14.0 (5.7) [n = 25]

Source: Study report TMC-BIV-07-01, Table 13

Table 8: Steady state concentrations (ng/ml) of bivalirudin in pediatrics following 0.75 mg/kg IV bolus and 1.75 mg/kg/h infusion.

	Neonate	Infant	Young	Older	All
N	6	27	25	24	82
Mean (SD)	2534 (1569)	3467 (1890)	4277 (1319)	5331 (1496)	4191 (1793)
95% CI	887.6 to 4181	2719 to 4214	3733 to 4821	4699 to 5963	3797 to 4585

Table 9: Steady state ACT (sec) of bivalirudin in pediatrics following 0.75 mg/kg IV bolus and 1.75 mg/kg/h infusion.

	Neonate	Infant	Young	Older	All
N	6	27	25	24	82
Mean (SD)	292.2 (60.98)	282.4 (57.05)	292.1 (32.30)	311.2 (39.12)	294.5 (46.39)
95% CI	228.2 to 356.2	259.8 to 304.9	278.7 to 305.4	294.7 to 327.7	284.3 to 304.7

Name of Sponsor/Company: The Medicines Company	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: Angiomax®		
Name of Active Ingredient: Bivalirudin		
Title of Study: Bivalirudin (Angiomax®) as a Procedural Anticoagulant in the Pediatric Population Undergoing Intravascular Procedures for Congenital Heart Disease		
Principal Investigators: Ziyad M. Hijazi, MD, MPH, FACC Rolando Zamora-Salinas, MD		
Study Center(s): Multicenter 11		
Publications (reference): None		
Studied period (years): Date first patient enrolled: 15 August 2007 Date last patient completed: 02 August 2008	Phase of development: IIb	
Objectives: The purpose of this study was to generate clinical data on the use of bivalirudin as an anticoagulant in pediatric patients during percutaneous intravascular procedures for the management of congenital heart disease. The study objectives were as follows: <ul style="list-style-type: none"> • To determine the plasma concentrations of bivalirudin following administration of doses described below in pediatric patients • To determine the pharmacodynamics (PD) of bivalirudin, as measured by the activated clotting time (ACT), following administration of doses described below in pediatric patients • To provide dosing guidelines for the use of bivalirudin as an anticoagulant during percutaneous intravascular procedures in pediatric patients • To evaluate the safety of bivalirudin in pediatric patients by evaluating bleeding, thromboses, and other serious adverse events (SAEs) 		
Methodology: This was a prospective, open-labeled, single-arm, multicenter trial		
Number of Patients (Planned and Analyzed): 75 patients (planned); 110 patients (enrolled and analyzed).		

Name of Sponsor/Company: The Medicines Company	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: Angiomax®		
Name of Active Ingredient: Bivalirudin		
<p>Diagnosis and Main Criteria for Inclusion:</p> <p>At least 75 patients ranging in age from birth up to 16 years were to be enrolled, complete treatment and study evaluations. At least 10 neonates, 20 infants/toddlers, 20 young children and 10 older children were to be included according to the definitions below:</p> <ul style="list-style-type: none"> • Neonates (Birth ≤30days) • Infants/toddlers (31 days to <24 months) • Young children (2 years to <6 years) • Older children (6 years to <16 years) <p>At least 50% of the cases in the study were to involve implantation of a device, either for closure of cardiac defects (such as atrial septal defect), or endovascular stenting (such as stenting of pulmonary vessels). The remainder of the procedures were to be diagnostic catheterizations, or other interventions such as balloon dilation procedures for treatment of aortic coarctation or valve stenosis.</p> <p><u>Inclusion criteria</u></p> <p>Patients were eligible for inclusion in this study if they satisfied the following criteria:</p> <ul style="list-style-type: none"> • Male and non-pregnant females, with an age range of birth up to 16 years • Expected to undergo a percutaneous intravascular procedure for the management of congenital heart disease • Written informed consent from a legal guardian/parent • Life expectancy of at least 15 days at study entry • Assent of the patient if older than 8 years, whenever possible • Do not meet any exclusion criteria 		

Name of Sponsor/Company: The Medicines Company	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Angiomax [®]	Volume: Page:	
Name of Active Ingredient: Bivalirudin		
Exclusion criteria		
<p>Patients were excluded if they met any of the following criteria:</p> <ul style="list-style-type: none"> • History of intracerebral bleed (neonates confirmed by an ultrasound head scan prior to procedure), or cerebral arteriovenous malformation or any prior bleed with neurological deficit • Known congenital or acquired bleeding or clotting disorder • Patients undergoing renal dialysis • Weight < 2.5 kg • Gastrointestinal or genitourinary bleeding within the last 2 weeks excluding normal menstrual cycles • Cerebrovascular accident within 6 months, or any cerebrovascular accident with a residual neurological deficit • Confirmed pregnancy at time of enrollment or breast feeding (females of child-bearing potential) • Known allergy to bivalirudin or hirudin-derived drugs, or known sensitivity to any component of bivalirudin • Any condition that in the investigator's opinion constituted a contraindication to participation in the study, or caused inability to comply with the study requirements • Participation in another investigational therapeutic drug or investigational therapeutic device trial within 30 days of starting study • Patients who had been receiving warfarin therapy and whose international normalized ratio (INR) was >1.5 immediately prior to the procedure • Patients who could not be discontinued from unfractionated heparin (UFH) at least 30 minutes prior to study drug bolus • Patients who had received a dose of low molecular weight heparin (LMWH) within 8 hours prior to study drug bolus • Patients previously enrolled in the study 		
Dose and Mode of Administration, Batch Number:		
<p>All patients were treated with Angiomax[®] (bivalirudin) for injection - Batch Number 896014.</p> <p>Patients were to received an intravenous (IV) bolus dose of 0.75 mg/kg immediately followed by an IV infusion of 1.75 mg/kg/h for the duration of the procedure;</p> <p>Investigators had the option of providing a maintenance dose of 0.25 mg/kg/h for as long as necessary post-procedure up to 72 hours. The Pharmacy Manual provided for use of a 0.1 mg/mL bivalirudin flush dose.</p>		
Duration of Treatment: Patients were to be monitored closely during the procedure and for the first 48 hours post procedure or until hospital discharge. Follow-up was to continue for at least 30 days after consent. If a patient experienced an SAE, he/she would be followed until resolution of the SAE even if that time was greater than 30 days.		
Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable.		

Name of Sponsor/Company: The Medicines Company	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Angiomax [®]	Volume: Page:	
Name of Active Ingredient: Bivalirudin		
<p>Criteria for Evaluation:</p> <p>The study endpoint evaluations were as follows:</p> <ul style="list-style-type: none"> • The pharmacokinetics (PK) and PD of bivalirudin • The incidence of bleeding and/or thrombotic events up to 30 days post-procedure • Changes in platelet count from baseline to end of study <p><i>Adverse events:</i></p> <p>Adverse events (AEs) and SAEs were to be collected up to 30 days post consent. All SAEs were followed to resolution.</p>		
<p>Statistical Methods: Population PK/PD analysis of bivalirudin concentration and ACT data was conducted in pediatric patients and compared with that of adults. A descriptive analysis of outcomes was compiled in regard to success or failure of the performance of the procedure. Listings of AEs and descriptive analyses of AEs and other safety data were compiled.</p>		
<p>SUMMARY – CONCLUSIONS</p> <p>Bivalirudin provided anticoagulant effect without unexpected safety concerns. All evaluable patients had detectable serum plasma levels of bivalirudin post drug administration with subsequent elevations of ACT values from baseline. The occurrence of thrombosis and bleeding events were low.</p> <p><u>PK/PD results:</u></p> <p>Results from the non-compartmental analysis of this pediatric study demonstrated that:</p> <ul style="list-style-type: none"> • There is a trend toward an increase in mean C_{max}, mean AUC_{0-t}, and mean C_{avg} with increasing age from neonates to older children when bivalirudin was administered as a weight-based dose. • Weight-normalized clearance (mL/min/kg) was higher in neonates than older children, decreasing slightly with increasing age. • The half-life of bivalirudin was shorter in neonates and increased with increasing age. <p><u>Safety results:</u></p> <ul style="list-style-type: none"> • There were no deaths during the course of this study. • Two patients (one young child and one older child) had a hematoma >2.5 cm that qualified as a major bleeding event; there were no other major bleeding events; 12 patients had minor bleeding. • Eight per protocol patients had a thrombotic event either during the procedure (n=3) or during hospital stay (n=5) following discontinuation of study drug. • Five patients had procedural complications that did not impact on procedural success (ie, completion of procedure) and that were unrelated to thrombosis or bleeding. • SAEs occurred in 11 patients; one event was considered by the investigator as possibly drug related. Decreased pedal pulse, catheter site hemorrhage, abnormal pulse and nausea were the most frequently reported non-serious AEs (8.2%, 7.3%, 6.4% and 5.5%, respectively). • Five patients had nadir platelet counts <150 k/μL and a \geq50% decreased from baseline values. All 5 events were associated with infections (n=2) or repeat cardiac procedures (n=3) and occurred between Days 5 and 30. • Laboratory values and vital signs were unremarkable. <p><u>Conclusions:</u> Based on PK/PD outcomes and major clinical endpoint outcomes, bivalirudin, when administered as a weight-based IV bolus dose of 0.75 mg/kg followed by an infusion dose of 1.75 mg/kg/h in pediatric patients</p>		

Name of Sponsor/Company: The Medicines Company	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: Angiomax [®]		
Name of Active Ingredient: Bivalirudin		
undergoing percutaneous intravascular procedures, provides anticoagulation without unexpected safety concerns across the entire age spectrum evaluated in this study.		
Date of the Report: FINAL 09 February 2009		

4.4 Pharmacometrics Review

4.4.1 Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

Application Number	NDA 20873 SE5 (Pediatric Supplement)
Submission Number (Date)	April 3, 2009
Compound	Angiomax injection (Bivalirudin)
Clinical Division	OND/OODP/DDOP
Primary PM Reviewer	Nitin Mehrotra, Ph.D.
Secondary PM Reviewer	Christoffer W. Tornoe, Ph.D.

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1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The following key questions were addressed in this pharmacometrics review.

1.1.1 Is bivalirudin exposure similar between adult and pediatric patients?

No, exposure of bivalirudin in pediatrics is lower in pediatrics compared to adults when receiving the proposed pediatric dose of 0.75 mg/kg IV bolus followed by 1.75 mg/kg/h IV infusion for 4 hours. The mean C_{max} at 4 h for pediatrics is 38 - 62% lower than adults.

Figure 1 shows the mean concentration-time profile for bivalirudin in adults compared to pediatrics following 0.75 mg/kg IV bolus followed by 1.75 mg/kg/h infusion for 4 h. The exposure increases consistently from neonates (birth-one month) to infants (1 month-2 years), young children (2-6 years), older children (6-16 years), and adults (51-78 Years).

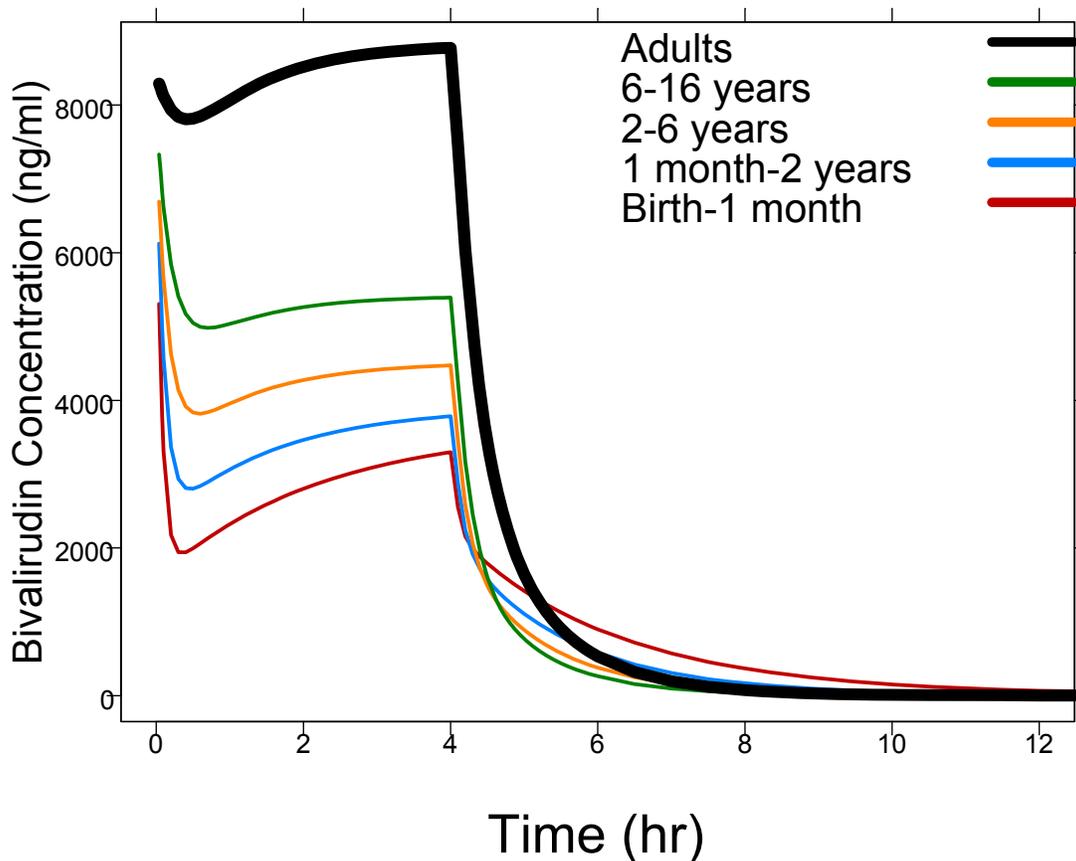


Figure 1: Mean concentration time profile of bivalirudin in each pediatric age group compared to adults after 0.75 mg/kg IV bolus followed by 1.75 mg/kg/h IV infusion.

(b) (4)

(b) (4)

1.1.2 Is the PK-PD (ACT) relationship for bivalirudin similar between adult and pediatric patients?

No, the PK-PD is not similar between pediatrics and adults. Effect on activated clotting time (ACT) was found to be concentration dependent as shown in **Figure 2** (left panel). The concentration-ACT relationship was best described by an E_{max} model. Younger pediatrics, especially less than 6 months old were found to be more sensitive to bivalirudin in terms of ACT. (b) (4)

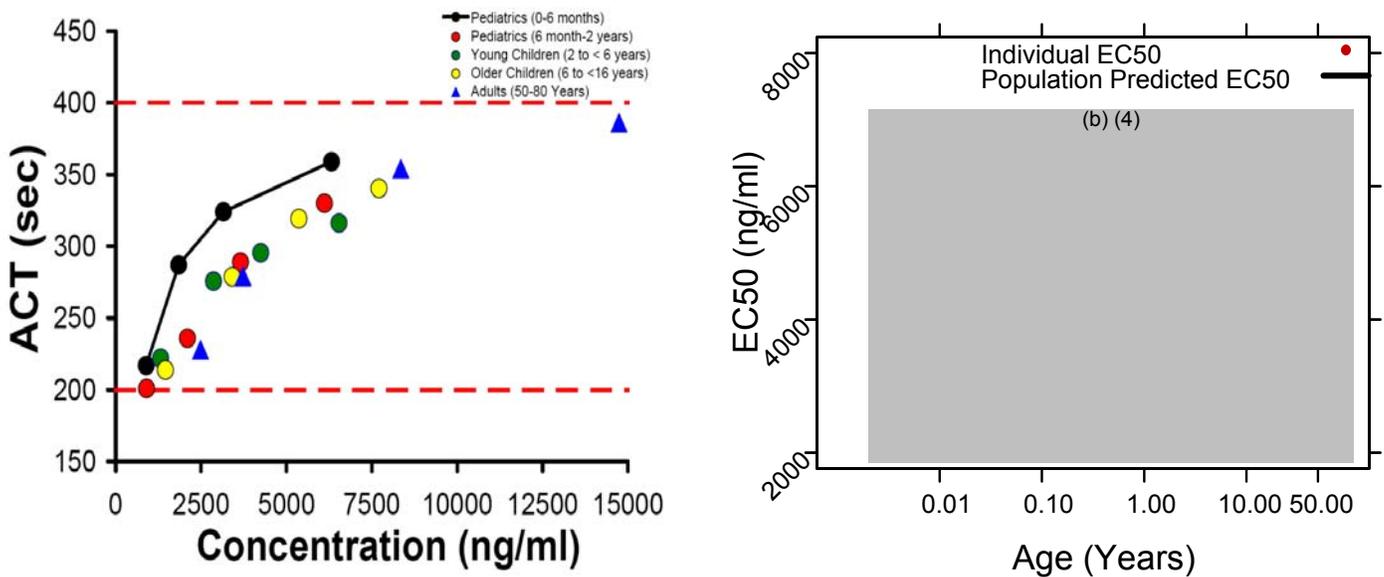
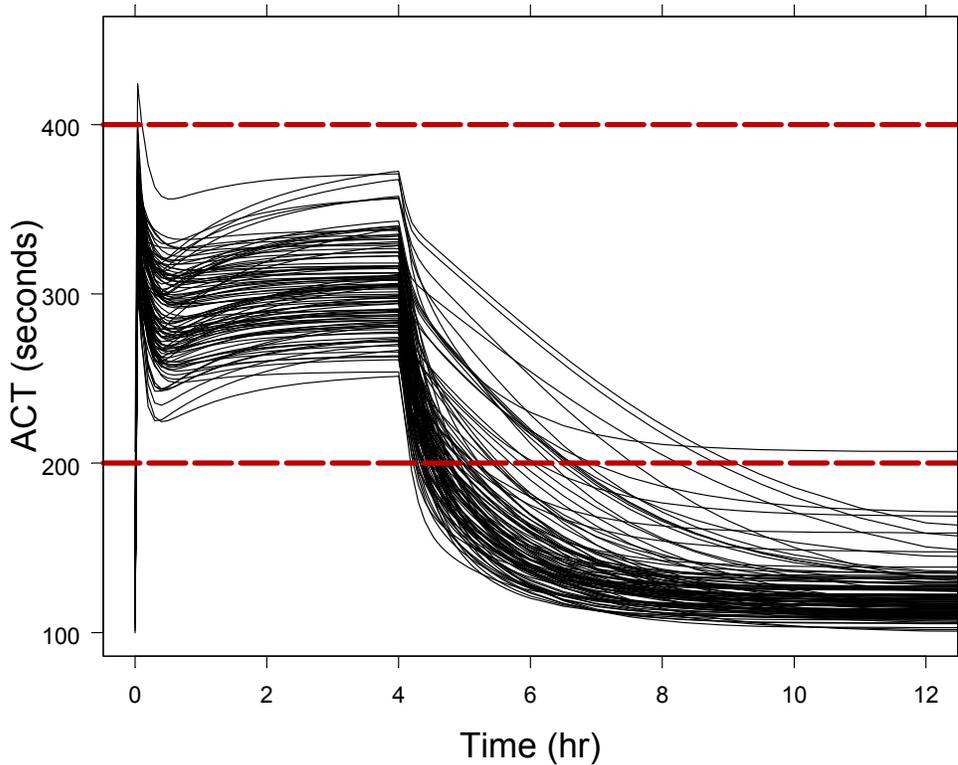


Figure 2: Observed concentration-ACT relationship in various pediatric subgroups (Left panel) and Age-EC₅₀ relationship (Right panel).

1.1.3 Does the proposed dosing regimen produce ACT in the target range (200-400 sec)?

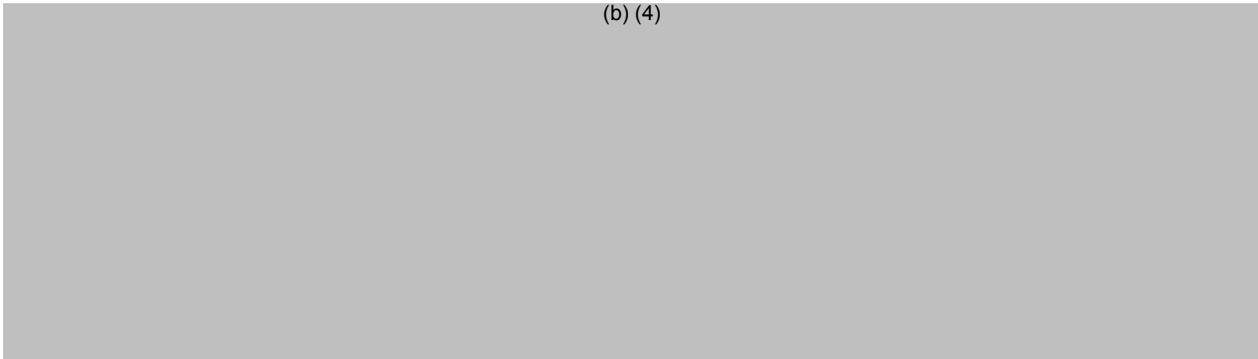
Yes, the proposed dosing regimen would produce steady state ACT within the target range (ACT between 200-400 sec, **Figure 3**) for 100% of the pediatric patients.

Figure 3: 100% of pediatric patients achieved steady state ACT in the target range (200-400 sec) with same adult dose of 0.75 mg/kg IV bolus followed by 1.75 mg/kg/h IV infusion



1.1.4 Is sponsor's dosing regimen appropriate in pediatric patients?

(b) (4)



(b) (4)

compared to adults with 0.75 mg/kg IV bolus followed by 1.75 mg/kg/h IV infusion.

(b) (4)

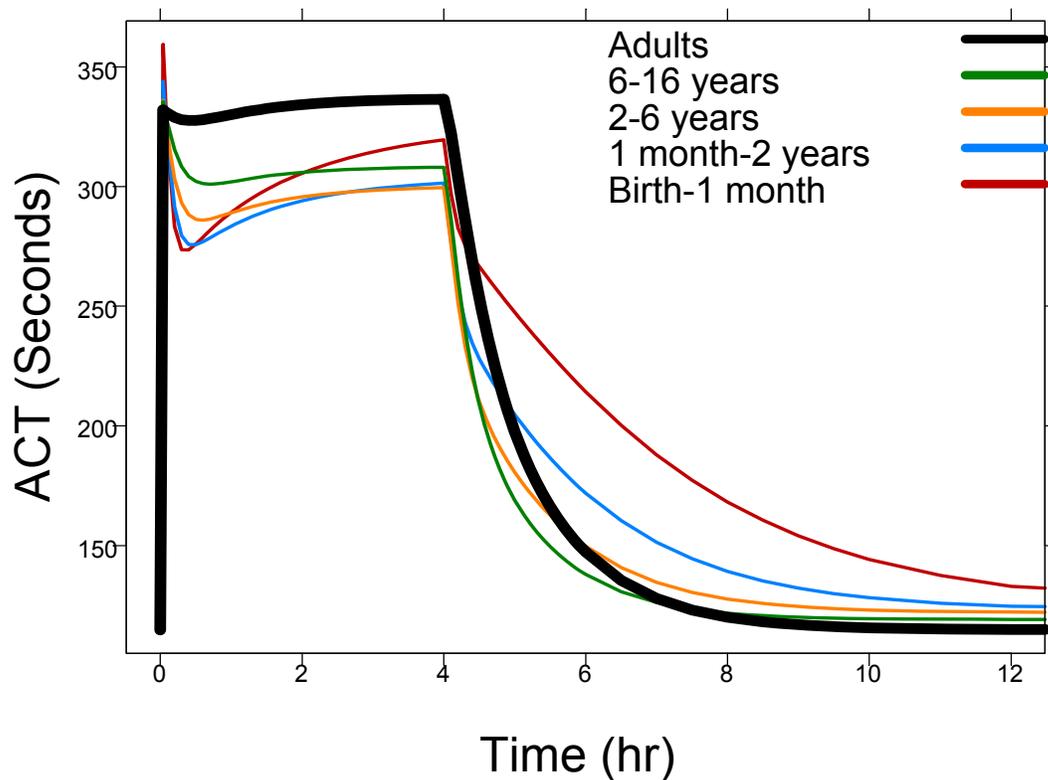
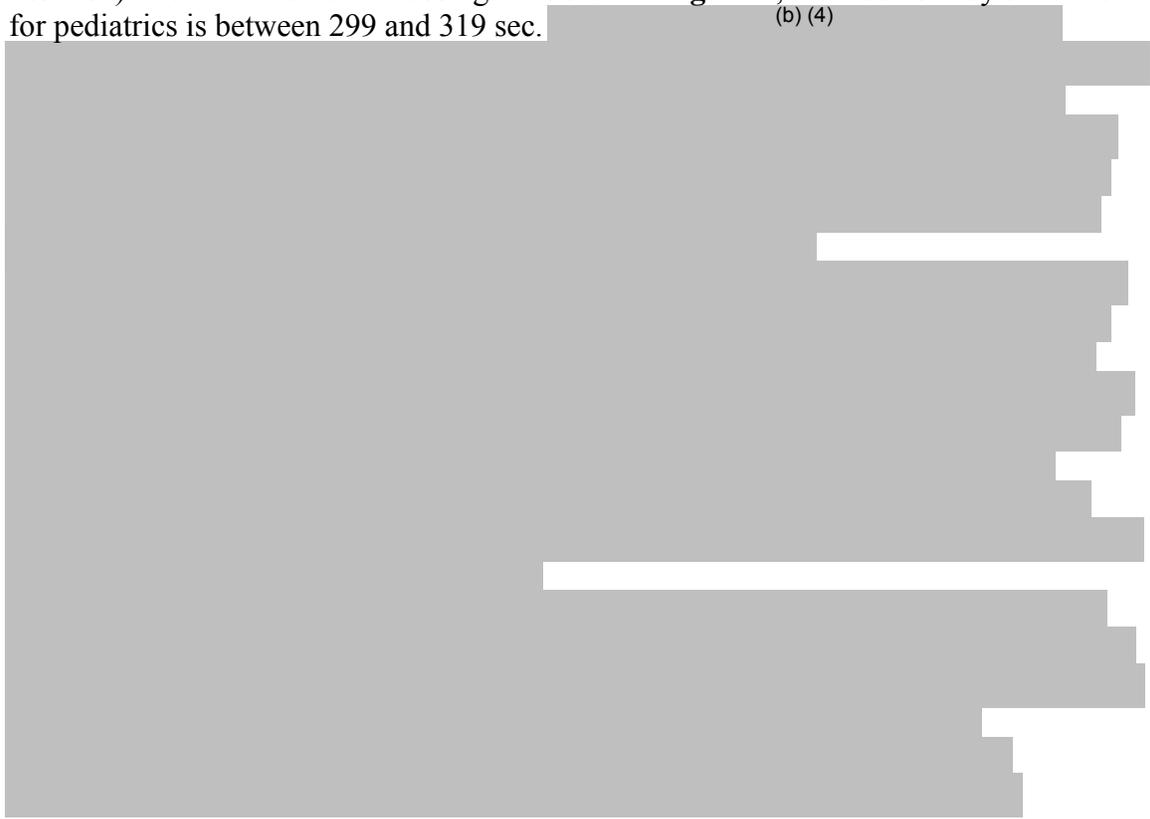


Figure 4: Mean ACT-time profiles for pediatrics and adults showing lower steady state ACT in pediatrics at the proposed dose of 0.75 mg/kg IV bolus followed by 1.75 mg/kg IV infusion over 4 hours.

The median ACT in the REPLACE trial (pivotal trial conducted for approval of bivalirudin in adult patients undergoing PCI at the proposed dose of 0.75 mg/kg IV bolus followed by 1.75 mg/kg IV infusion over 4 hours) after 5 min, which can be considered to be representative of steady state ACT, was 358 sec (Inter-quartile range: 320-400 sec). Bivalirudin was also evaluated in patients with unstable angina undergoing PTCA

(percutaneous transluminal coronary angioplasty) following 2.5 mg/kg/h IV infusion. Angiomax dose was not titrated to ACT, however ACT was measured at 5 and 45 min. The median ACT after 5 and 45 min was 345 sec (95%CI: 240-595) and 346 sec (95%CI: 269-583) after initiation of the dosing. As seen in **Figure 4**, the mean steady state ACT for pediatrics is between 299 and 319 sec. (b) (4)



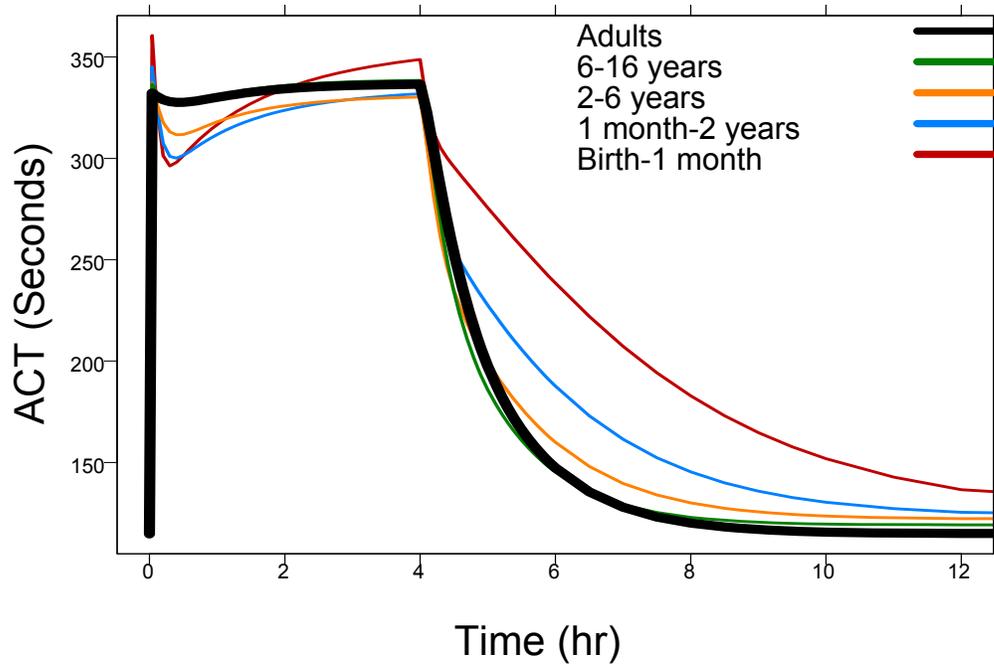


Figure 5: Mean ACT-time profiles for pediatrics and adults showing similar steady state ACT in pediatrics at the modified dosing regimen with same IV bolus dose (0.75 mg/kg) but increase in infusion rate to 2.5 mg/kg/h.

1.1.5 Is more frequent ACT monitoring needed in pediatrics?

(b) (4)



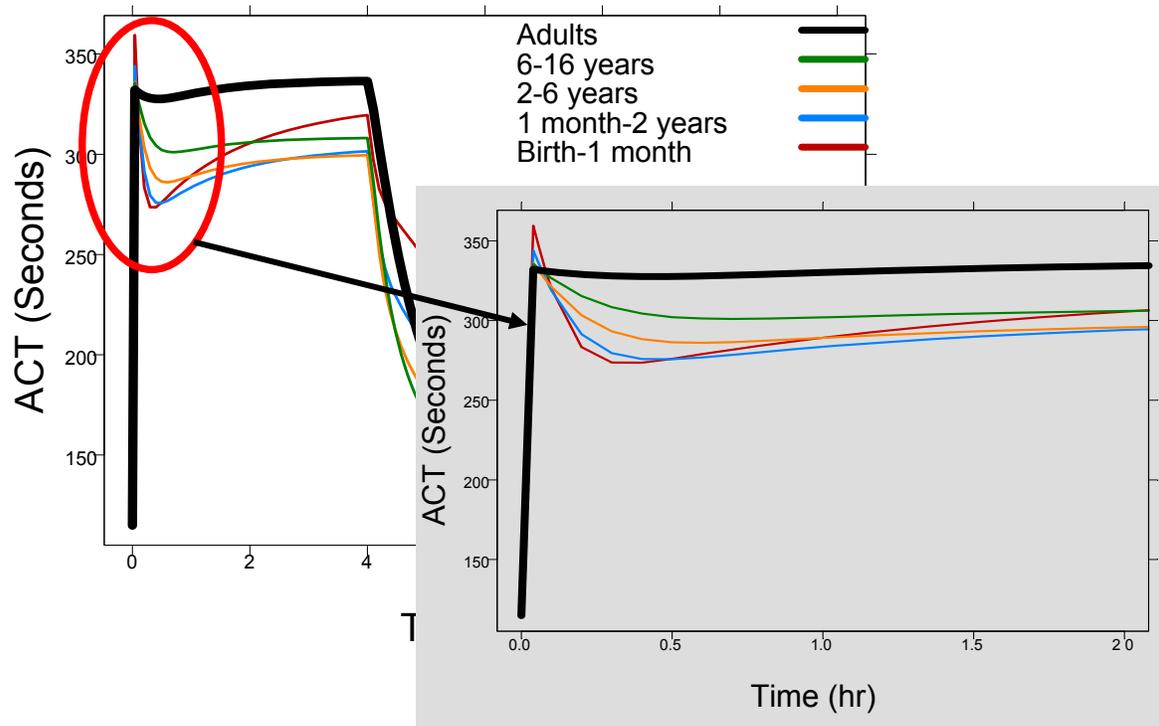


Figure 6: Steady state for ACT is not achieved until 1.5-2 h in pediatrics.

1.2 Recommendations

(b) (4)

1.3 Label Statements

Refer to Section 3 of the Clinical Pharmacology Review for detailed labeling recommendations.

2 Pertinent Regulatory Background

Angiomax[®] (bivalirudin) is indicated for use as an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA). Angiomax with provisional use of glycoprotein IIb/IIIa inhibitor (GPI) is indicated for use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI). Angiomax is indicated for patients with, or at risk of, heparin induced thrombocytopenia (HIT) or heparin induced thrombocytopenia and thrombosis syndrome (HITS).

undergoing PCI. The recommended dose of Angiomax is an IV bolus dose of 0.75 mg/kg. This should be followed by an infusion of 1.75 mg/kg/h for the duration of the PCI procedure. Five min after the bolus dose has been administered, an activated clotting time (ACT) should be performed and an additional bolus of 0.3 mg/kg should be given if needed.

Sponsor conducted a PKPD study (TMC-BIV-07-01) in pediatrics in response to the written request issued by the FDA. The study design was a prospective, open-labeled, single-arm, multicenter trial to assess the PK/PD and safety of bivalirudin as a procedural anticoagulant in the pediatric population undergoing percutaneous intravascular procedures for congenital heart disease. 110 pediatric patients were enrolled across birth-16 years and activated clotting time (ACT) was the PD biomarker measured in the study. Patients with a glomerular filtration rate (GFR) ≥ 30 mL/min were to receive an IV bolus dose of 0.75 mg/kg immediately followed by an IV infusion of 1.75 mg/kg/h for the duration of the procedure. Patients with a GFR < 30 mL/min were to receive an IV bolus dose of 0.75 mg/kg immediately followed by an IV infusion of 1.0 mg/kg/h for the duration of the procedure.

3 Results of sponsor analysis

A population PK/PD analysis was conducted to characterize the disposition of bivalirudin from data collected during the conduct of two clinical studies, TMC-98-09 and TMC-BIV-07-01 (**Table 1** and **Table 2**). The description of TMC-BIV-07-01 is provided in Section 2. Study TMC-98-09 was designed to evaluate the influence of dose, gender and kidney function on bivalirudin PK in adult patients receiving PTCA. Bivalirudin dosing was also given intravenously using the following dose regimen: patients with GFR > 30 mL/min, subjects received an IV bolus dose of 1.0 mg/kg immediately followed by an IV infusion of 2.5 mg/kg/h for 4 hours, followed by an IV infusion of 0.5 mg/kg/h for an additional 4 hours. This population analysis afforded the exploration into the effects of several patient-specific covariates on PK and PD of bivalirudin in the pediatric patient population. The objectives of this population PK/PD analysis were to develop population PK and PK/PD models to describe concentration time data arising from the two studies of bivalirudin in adult and pediatric patients, to describe the relationship between bivalirudin concentrations and ACT response, to identify and characterize patient factors that influence PK and PD variability, and to estimate the magnitude of unexplained variability in bivalirudin PK and PD in this patient population.

3.1 Methods

PK and PD (ACT) data was available from 105 pediatric and 26 adult patients. Rich PK and PD data was available from adults while pediatrics contributed to sparse PK/PD data. Demographic characteristics for adult and pediatric patients are given in **Table 1** and **Table 2**.

Table 1: Study characteristics for TMC-98-99

Baseline Characteristics (units)	Mean (SD)	Median	Range
Age (years)	68.19 (8.60)	65	50.5 – 77.8
Weight (kg)	82.15 (14.22)	79.5	47 – 116
Height (cm)	NA	NA	NA
Body surface area (m ²)	NA	NA	NA
Creatinine clearance* (mL/min)	82.53 (32.03)	78.35	33.9 – 150
Glomerular filtration rate* (mL/min/1.73m ²)	82.61 (32.02)	75.7	34.3 - 150
Sex	Males = 18; Females = 8		

*Calculated creatinine clearance value capped at 150 mL/min as a reasonable upper limit

(Source : Population PK-Pharmacodynamics report, Section 4.2.2, Table 8, Page 998)

Table 2: Study characteristics for TMC-BIV-07-01

Demographics/ Baseline characteristics	Neonates ≤30 days (N=10)	Infants 31 days to <2 yrs (N=33)	Young Children 2 to <6 yrs (N=32)	Older Children 6 to <16 yrs (N=31)	Total (N=106)
Age (years) (median)	0.027 (10.0 days)	0.9 (329 days)	4.7	11.1	3.7
Sex, n (%)					
Male	5(50.0)	15(45.5)	15(46.9)	14(45.2)	49(46.2)
Female	5(50.0)	18(54.5)	17(53.1)	17(54.8)	57(53.8)
Race, n/N (%)*					
Asian	0(0.0)	0(0.0)	1(3.4)	0(0.0)	1(1.0)
Black or African American	0(0.0)	8(25.0)	10(34.5)	7(23.3)	25(24.8)
White	10(100)	24(75.0)	18(62.1)	23(76.7)	75(74.3)
Ethnicity, n/N (%)^a					
Hispanic or Latino	1(10)	2(6.1)	4(12.9)	1(3.3)	8(7.7)
Not Hispanic or Latino	9(90)	31(93.9)	27(87.1)	29(96.7)	96(92.3)
Weight (kg)					
Mean±SD	3.6±0.7	8.2±2.5	17.9±5.6	40.9±19.8	20.3±18.0
Median	3.5	8.0	15.9	34.7	14.9
Min, Max	3, 5	4, 12	11, 32	15, 108	3, 108
Serum Creatinine (mg/dL)					
Mean ± SD	0.49±0.11	0.302±0.087	0.403±0.090	0.585±0.144	0.433±0.156
Median	0.5	0.3	0.4	0.57	0.4
Min, Max	0.3, 0.6	0.2, 0.6	0.2, 0.6	0.4, 0.9	0.2, 0.9
GFR (mL/min/1.73m²)					
Mean ± SD	47.55±13.61	105.2±28.5	114.91±26.32	106.71±18.83	103.14±30.18
Median	43.86	103.2	113.41	108.36	103.2
Min, Max	35.1, 74.5	42.6, 172.0	78.8, 184.9	67.6, 140.8	35.1, 184.9

(Source : TMC-BIV-07-01 study report, Section 10., Table 7, Page 38)

3.2 Conclusions

Pharmacokinetic model

- The PK of bivalirudin was best described by a one compartment model with linear CL. This model includes inter-individual variability (IIV) terms for CL and V, with covariance between these random effects.
- Weight was the only covariate found to explain variability in bivalirudin PK. Neither age, nor renal function (creatinine clearance) were identified as covariates in the population PK model.

$$CL = \theta_1 \cdot \left(\frac{Weight}{80} \right)^{\theta_3} \cdot \exp(\eta_1)$$

$$V = \theta_2 \cdot \left(\frac{Weight}{80} \right)^{\theta_4} \cdot \exp(\eta_2)$$

- A dual residual error model was employed to describe each study separately.
- Model was qualified using visual predictive check and bootstrapping was performed to assess the precision of PK parameters.

Pharmacodynamic model

- The ACT-time data were well described by the final PD model, a direct effect stimulatory E_{max} model. The ACT was prolonged in all patients, from neonates to older children as well as adults with increasing bivalirudin concentrations.
- The model was parameterized for a baseline ACT value (E_0), a maximal change in ACT (E_{max}) and the concentration at half maximal effect (EC_{50}). This model includes IIV terms for E_0 and EC_{50} . IIV for E_{max} could not be estimated (values approached 0) and therefore was not included in the model.

$$E_0 = \theta_5 \cdot \left(\frac{AGE}{50} \right)^{\theta_8} \cdot \exp(\eta_3)$$

$$E_{max} = \theta_6$$

$$EC_{50} = \theta_7 \cdot \exp(\eta_4)$$

$$E(t) = E_0 + \frac{E_{max} \cdot C_p}{EC_{50} + C_p}$$

- A dual residual error model was employed to describe each study separately.
- Effect of age on E_0 was the only covariate identified such that E_0 decreased with increasing age.

- Model was qualified using visual predictive check and bootstrapping was performed to assess the precision of PD parameters.

Parameter estimates for pharmacokinetic and pharmacodynamic model are provided in **Table 3** and **Table 4**, respectively.

Table 3: Summary of NONMEM parameter estimates for the final PK model

Parameter (Units)	Population Mean (SE*)		%CV IIV (SE*)	
	CL (L/h)	θ_1	17.4 (4.2)	η_1
Effect of Weight	θ_3	0.534 (4.5)		
V (L)	θ_2	8.4 (4.8)	η_2	19.8 (33.9)
Effect of Weight	θ_4	0.852 (3.6)		
CCV Residual Error TMC-98-09 (as %CV)			12.7 (3.6)	
Additive Residual Error TMC-98-09 (as SD)			316 (19.4)	
CCV2 Residual Error TMC-BIV-07-01 (as %CV)			22.8 (10.7)	
Additive Residual Error 2 TMC-BIV-07-01 (as SD)			716 (9.0)	

* - SE expressed as %CV

CCV=constant coefficient of variation; CV=coefficient of variation; CL=clearance; IIV-inter-individual variability; SD=standard deviation; SE=standard error; V=volume of distribution.

Source: Source: Population PK-Pharmacodynamic analysis report, Table 12, Pg 1017

Table 4: Summary of NONMEM parameter estimates for the final PD model

Parameter (Units)	Population Mean (SE*)		%CV Inter-Individual Variability (SE*)	
	E0 (sec)	θ_5	115 (3,5)	η_3
Effect of Age	θ_8	-0.049 (10.8)		
E _{max} (sec)	θ_6	349 (1.8)	--	NE
EC50 (ug/L)	θ_7	4640 (7.0)	η_4	22.7 (37.5)
Additive Residual Error (as SD) for TMC-98-09			15.94 (6.5)	
Additive Residual Error (as SD) for TMC-BIV-07-01			40.50 (4.2)	

* - SE expressed as %CV

E0=baseline activated clotting time value; EC50=the concentration at which half maximal response is achieved; E_{max}= maximal response; NE= Not Estimated; SD=standard deviation; SE=standard error.

Source: Population PK-Pharmacodynamic analysis report, Table 17, Pg 1045

Reviewer's comments on sponsor's population PK and PK/PD models:

(b) (4)

Pharmacokinetic model:

(b) (4)

Pharmacodynamic model:

(b) (4)

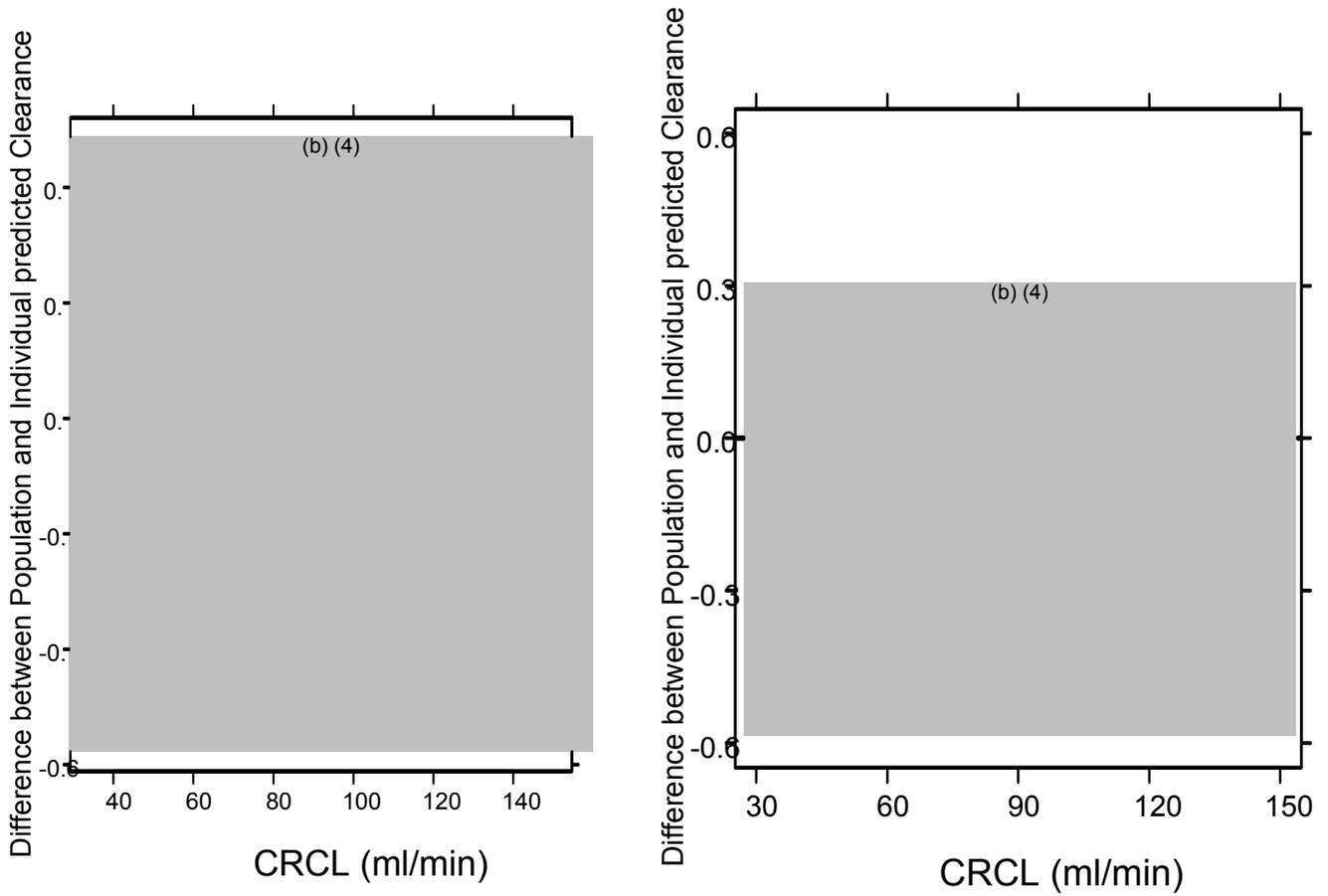


Figure 7: CRCL does seem to affect CL of bivalirudin. Left panel shows ETA (CL) vs CRCL plot for both adults and pediatrics while right panel shows ETA (CL) vs CRCL plot for adults only.

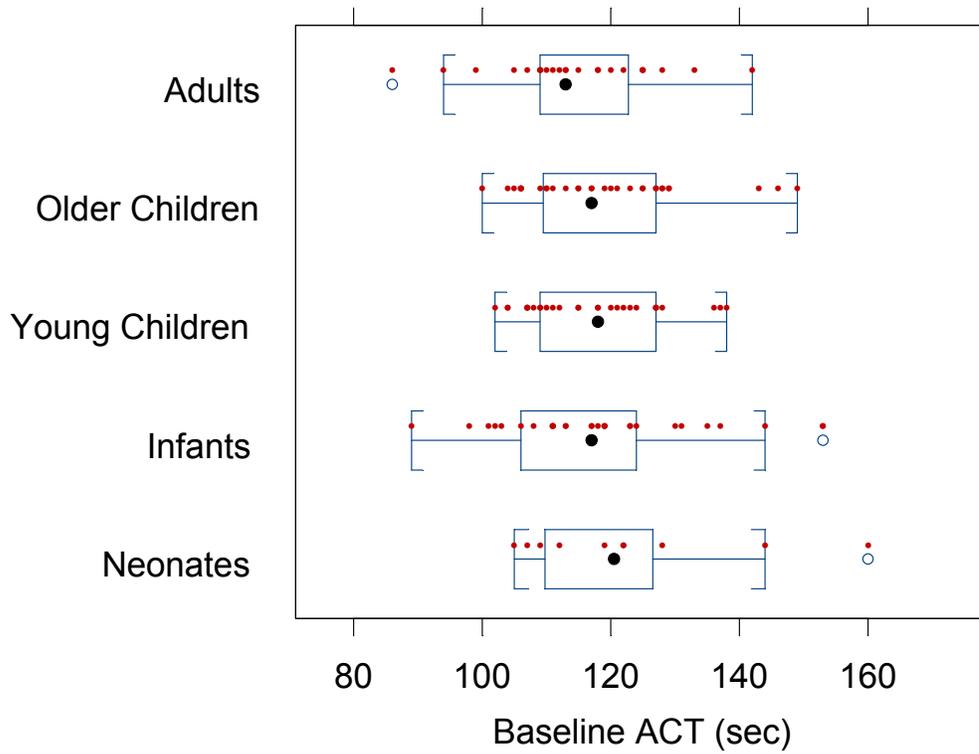


Figure 8: Similar observed baseline ACT among various subgroups in pediatrics and adults. Red dot represent baseline ACT for one patient.

4 Reviewer's Analysis

4.1 Population Pharmacokinetic analysis

(b) (4)

(b) (4)

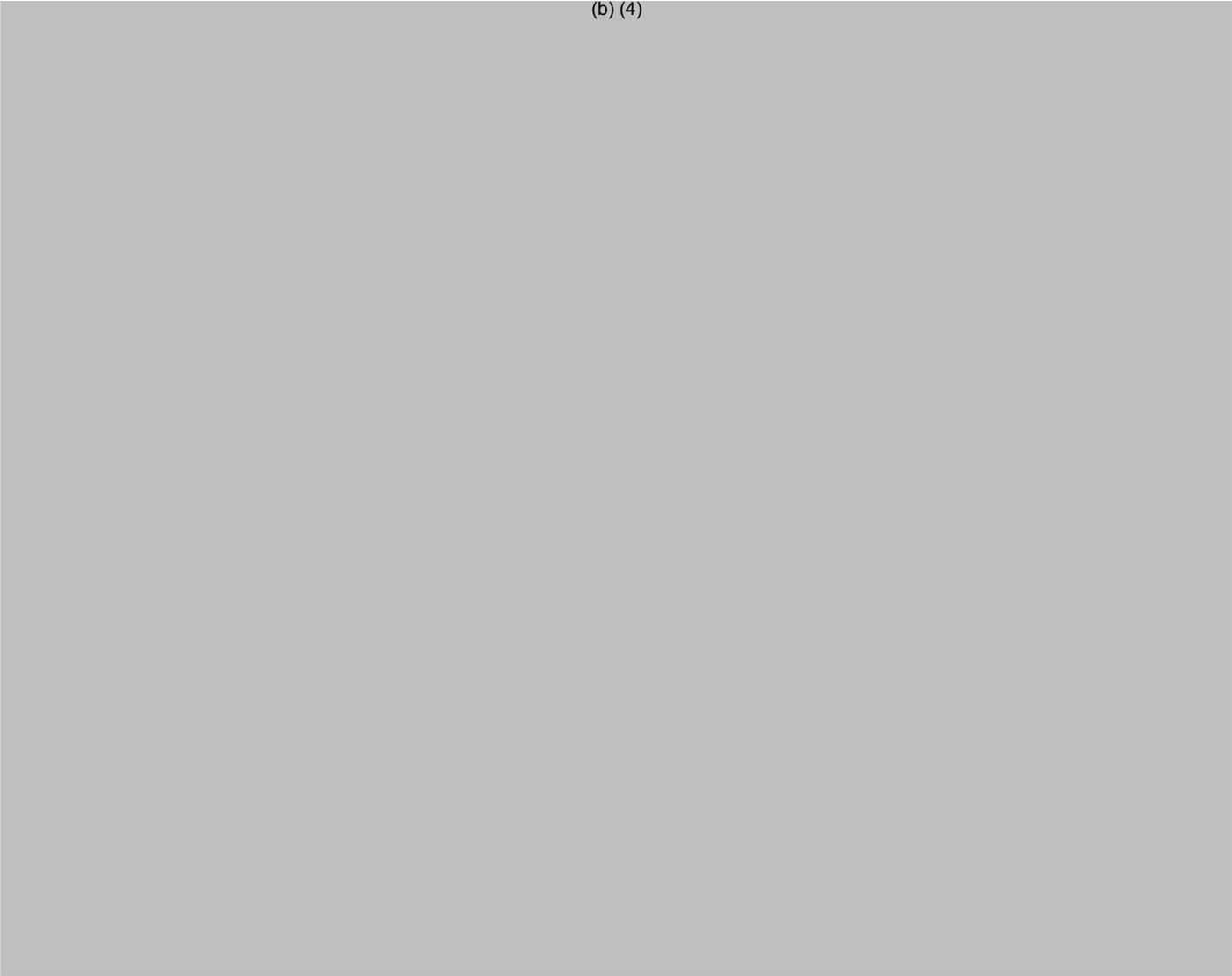
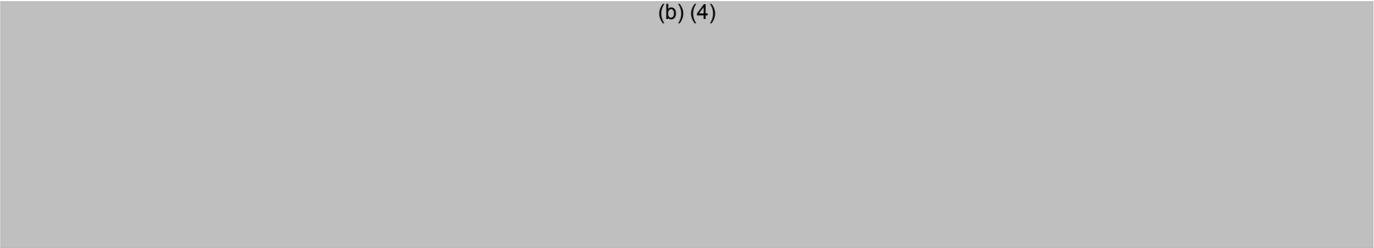


Figure 14: Goodness of fit plots from the reviewer's final covariate model

4.2 Population Pharmacokinetic-Pharmacodynamic analysis

(b) (4)



4.5 Cover sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

Information		Information	
NDA Number	20-873	Brand Name	Angiomax® Injection
OCPB Division (I, II, III)	5	Generic Name	bivalirudin
Medical Division	OND/OODP/DMIHP	Drug Class	Anticoagulant
OCPB Reviewer	Joseph A. Grillo, Pharm.D. Nitin Mehrotra, Ph.D.	Indication(s)	
		Anticoagulant used in patients receiving concomitant aspirin with 1) unstable angina undergoing PTCA or PCI and 2) with or at risk of HIT or HITTS, undergoing PCI.	
OCPB Team Leader	Young Moon Choi, Ph.D. Christoffer Tornoe, Ph.D.	Dosage Form	250 mg single-use vial
		Dosing Regimen	
		The recommended adult dose of Angiomax in patients with HIT/HITTS undergoing PCI is an IV bolus dose of 0.75 mg/kg. This should be followed by a continuous infusion at a rate of 1.75 mg/kg/h for the duration of the procedure.	
Date of Submission	4/3/2009	Route of Administration	Intravenous
Due Date of OCPB Review	9/4/2009	Sponsor	The Medicines Company
PDUFA Due Date	10/6/2009	Priority Classification	Priority Review
Division Due Date	9/6/2009		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1	1	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				

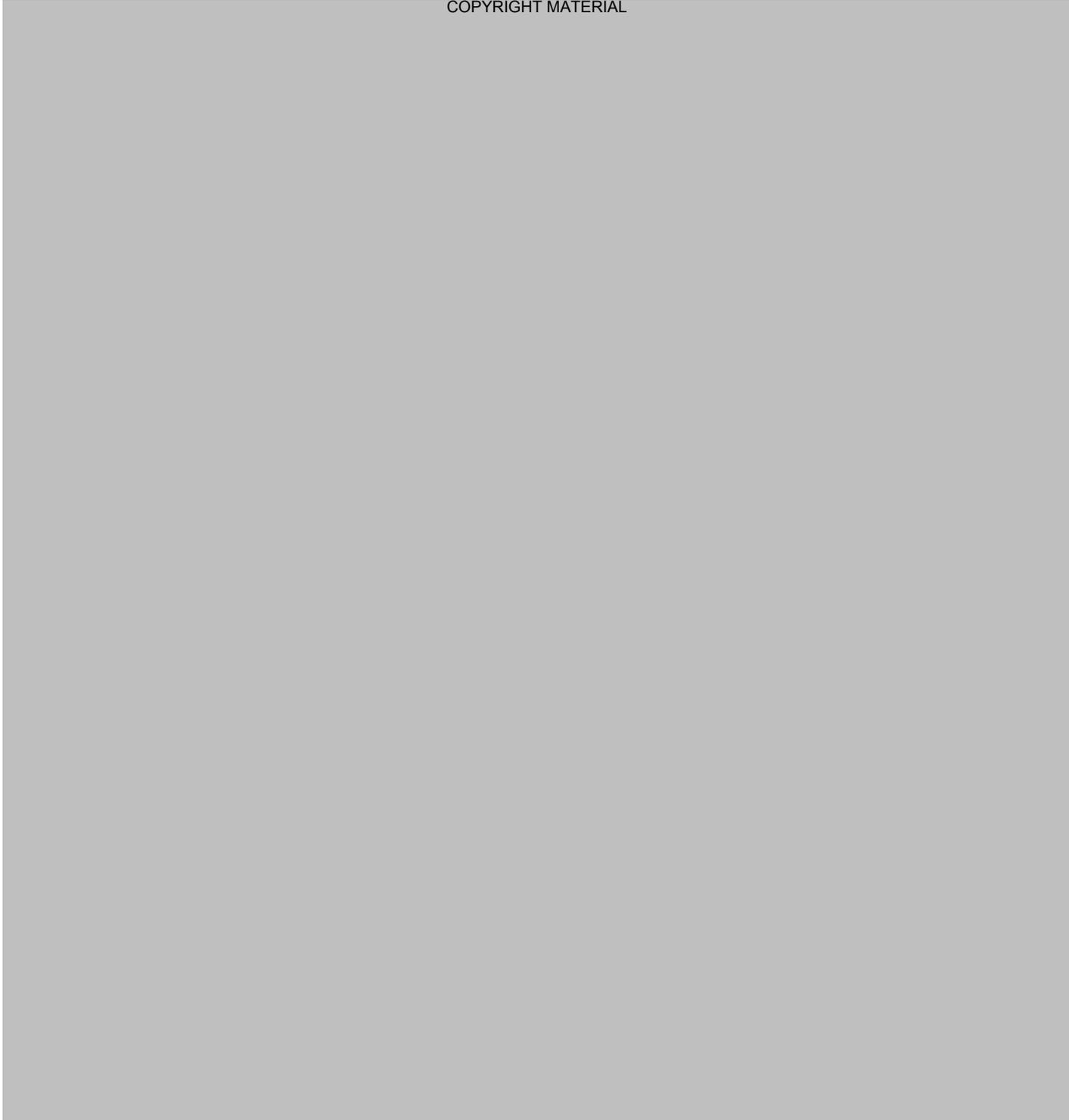
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	X	2	1	
geriatrics:				
renal impairment:	X	1	1	
hepatic impairment:				
PD:				
Phase 1:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	1	1	
Data sparse:	X	1	1	
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
In vitro PD bridge study				
Literature References		3	3	
Total Number of Studies		9	8	
Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	X			
Comments sent to firm?	X	<ul style="list-style-type: none"> • Requested winnonlin & Nonmem data sets and codes 		
QBR questions (key issues to be considered)		<ul style="list-style-type: none"> • Is bivalirudin exposure similar between adult & pediatric patients? • Is the exposure-response for bivalirudin similar in adult & pediatric patients? • Is there a relationship between exposure and safety? • Does the proposed dosing regimen in pediatrics results in ACT within the target range? • Is sponsor's proposed dosing regimen in pediatrics appropriate? 		
Other not included above				
Primary reviewer Signature and Date	/s/ Joseph A. Grillo, Pharm.D. & Nitin Mehrotra, Ph.D.			
Secondary reviewer Signature and Date	/s/ Young Moon Choi, Ph.D. & Christoffer Tornoe, Ph.D.			

4.6 Cited References

Direct Versus Indirect Thrombin Inhibition in Percutaneous Coronary Intervention

Jonathan D. Marmor, MD, FACC

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20873	SUPPL-19	THE MEDICINES CO	ANGIOMAX

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09/11/2009

CHRISTOFFER W TORNOE
09/11/2009