EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report under Article 46

Angiox

International non-proprietary name: bivalirudin

Procedure No. EMA/H/C/000562/A46/0025

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Introduction

This report covers the following post-authorisation commitments undertaken by the MAH: The Pharmacokinetic / pharmacodynamic (PK/PD) simulation analysis of bivalirudin in children which used patient data from study TMC-BIV-07-01. The study was conducted in accordance with a formal FDA Written Request dated 07 May 2007 in support of a request for a determination of paediatric exclusivity and a potential labelling change. This measure was proposed as part of the assessment of a PIP which was subsequently withdrawn. However, at the time the PIP was withdrawn the MAH had initiated this Measure 2 from the PIP and has now submitted this report.

Bivalirudin (Angiox®) has been developed by The Medicines Company and is a highly specific, short-acting anticoagulant which works via reversible, bivalent, direct thrombin inhibition (ATC code B01AE06).

Bivalirudin is a 20-amino acid, synthetic peptide which inhibits thrombin by binding to both the catalytic site and to the anion-binding (substrate recognition) exosite of thrombin. In nonclinical studies, bivalirudin was shown to inhibit both free (fluid-phase) and clot-bound thrombin, prevent thrombin-induced generation of fibrin and further activation of the clotting process, and inhibit thrombin-induced platelet activation, aggregation, and granule release.

Bivalirudin was first authorised for use in the European Union (EU) in September 2004 via the Centralised Procedure. It is currently authorised for use in the adult population in the following therapeutic indications:

- As an anticoagulant in adult patients undergoing percutaneous coronary intervention (PCI) including patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI;
- Treatment of adult patients with unstable angina (UA)/non-ST segment elevation myocardial infarction (NSTEMI) planned for urgent or early intervention.

In adult patients, bivalirudin should be administered with aspirin and clopidogrel.

There is no relevant indication for use of bivalirudin in children less than 18 years old.

Regulatory background

In September 2009, the Marketing Authorisation Holder (MAH) submitted the results of the paediatric study TMC-BIV-07-01 for bivalirudin, in accordance with Article 46 of Paediatric Regulation (EC) No. 1901/2006, as amended (Procedure ref no. EMEA/708429/2009). The study was conducted under a written request from Food and Drug Administration (FDA). At the time of this submission, the MAH requested suspension of the detailed review of the data until such time as it could be assessed as part of a paediatric investigation plan (PIP) for the product. In their opinion adopted on the 22 October 2009, The European Medicines Agency (EMA) agreed that no changes to the Summary of Product Characteristics (SmPC) were required at that time.

A first PIP was voluntarily submitted by the MAH on 14 February 2011. In the final opinion adopted on 8 June 2012 (EMEA-001065-PIP01-10) the Paediatric Committee (PDCO) recommended to grant a product-specific waiver for the treatment of atherosclerosis for all subsets of the paediatric population, but to refuse the use of bivalirudin as an anticoagulant in paediatric patients undergoing percutaneous intravascular procedures for congenital heart disease. The MAH subsequently submitted a second PIP (EMEA-001065-PIP02-12) on 05 October 2012 taking into account the comments from PDCO on the

first PIP. The PIP was agreed by PDCO on the 11 January 2013. It was subsequently withdrawn by the MAH on 13 March 2013 (EMA/PDC0/783995/2012). However, at the time the PIP was withdrawn the MAH had initiated Measure 2 from the PIP, which was the pharmacokinetic/pharmacodynamic (PK/PD) simulation analysis of bivalirudin in children which used patient data from study TMC-BIV-07-01.

This clinical overview is submitted in support of the submission of the paediatric data obtained in the PK/PD modeling study based on patient data from study TMC-BIV-07-01 in accordance with the requirements described in Article 46 of the Paediatric Regulation (EC No. 1901/2006).

The MAH states that, in accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance for bivalirudin and therefore are not required to take further regulatory action on the marketing authorisation.

Clinical pharmacology aspects

Methods – analysis of data submitted

PK/PD Simulation Analysis Objectives

- To develop a population PK/PD model to describe the concentration effect relationship for bleeding and thrombosis for bivalirudin; to establish a target concentration range and target anticoagulation level;

- To identify and characterise patient demographic factors that influence the variability in the pharmacokinetics and pharmacodynamics of bivalirudin;

- To estimate the magnitude of unexplained variability in bivalirudin pharmacokinetics and pharmacodynamics;

- To evaluate the model performance of the pharmacodynamic model(s) developed for bivalirudin;

- To develop a weight based dose schedule for paediatric subjects based on weight stratifications;

- To improve coverage and reduce variability of Angiomax exposure in paediatric populations.

Study Design

Study TMC-BIV-07-01 was a Phase IIb, prospective, open-label, single-arm, multicentre trial to assess the PK/PD and safety of bivalirudin as a procedural anticoagulant in the paediatric population undergoing intravascular procedures for congenital heart disease.

The paediatric population included patients from birth up to 16 years including at least 10 neonates, 20 infants/toddlers, 20 young children and 10 older children.

Subjects (with glomerular filtration rate >30 mL/min) received 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. Pharmacokinetic sampling (0.5 to 2 mL blood) was collected at the following nominal times: baseline, 5 minutes post- bolus, every 30 minutes during the procedure, just before discontinuation of infusion, and 10 and 30 minutes post- cessation of infusion. Time matched activated clotting times (ACT) values were also collected.

Database

Exposure, thrombotic, and bleeding event data were merged from data provided for study TMC-BIV-07-01. Data included the subject identity, age, weight, gender, total bolus dose, total infusion dose, total infusion duration, steady-state concentration (Css) which was based on individual estimates of clearance from the previously developed PK model, creatinine clearance (CrCL) and GFR and bleeding or thrombotic events coded as 0 (none) and 1 (occurred).

The best pharmacokinetic model identified in the previously conducted analysis was a one compartment disposition model with IV bolus loading dose and IV zero order infusion maintenance dose, with first order elimination from the central compartment. The model was parameterized for CL and V. Covariate factors describing the effect of weight on both CL and V were also included. IIV was described for all pharmacokinetic parameters, with a term describing the correlation between CL and V. The final forms of the equations for the parameters of the model are given below.

$$CL = \theta_1 \bullet \left(\frac{Weight}{80}\right)^{\theta 3} \bullet \exp(\eta_1)$$

$$V = \theta_2 \bullet \left(\frac{Weight}{80}\right)^{\theta 4} \bullet \exp(\eta_2)$$

Weight substantially affected the pharmacokinetics of bivalirudin. A listing of the final parameter estimates for TMC-BIV-0701 is given in the table:

Table 1 Parameter Estimates and Associated Standard Errors for Final Pharmacokinetic Model for TMC-BIV-0701

Parameter (Units)	Population Mean (SE*)		%CV Inter-Individual Variability (SE*)	
CL (L/h)	θ_1	17.4 (4.2)	η_1	24.5 (19.7)
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)		
CCV2 Residual Error TMC-BIV-0701 (as %CV)		22.8 (10.7)		
Additive Residual Error 2 TMC-BIV-0701 (as SD)		716 (9.0)		

* - SE expressed as %CV
CCV=constant coefficient of variation; CV=coefficient of variation; CL=clearance; SD=standard deviation; SE=standard error; V=volume of distribution

Table 2 Summary Diagnostics for Exposure Response Evaluation, All Treatment Durations (n=105)

Demographic (Unit)	Mean	SD	Median	Min	Max
Total Dose (ug)	56033	64075	36240	4300	461780
CL (L/hr)	8.32	4.86	7.51	1.86	29.52
V (L)	2.52	1.88	2.081	0.500	11.48
Infusion duration (hr)	0.95	0.81	0.82	0.167	6.08
Model estimated Css (ug/L)	4376	1512	4419	1478	8587
Obs Css (ug/L)	3752	1424	3693	651	7911
Age (yr)	4.65	4.41	3.46	0.005	15.15
HT (cm)	98.36	34.52	96	48	176
WT (kg)	20.22	18.06	14.8	2.6	108
BSA (m2)	0.72	0.43	0.63	0.188	2.30
SCR	0.43	0.16	0.40	0.20	0.90
CRCL (mL/min)	141.48	54.37	141.12	36.75	301
GFR (mL/min)	103.22	30.31	103.2	35.12	184.9
SEX	Male 57		Females 48		
GROUP	10	33	31	31	

Graphical Assessment

Prior to conducting the model based evaluation, the data were evaluated graphically. For this evaluation, measures of exposure such as dose or Css were grouped into several equally sized “bins”. The objective is to have approximately the same number of observations in each bin, with sufficient numbers of observations per bin (e.g. at least 10) so that the standard error of the frequencies is generally low. However there had to be sufficient bins (e.g. at least 10) in order to be able to visualize a smooth transition from bin to bin to see trends in the data. There were no placebo groups in the present database so each bin represented an increasing level of drug exposure.

Once the number of bins had been determined, and the data were sorted, frequencies of events by grade were calculated for each bin. These frequencies were plotted against the median exposure associated with each bin. If a trend was visible in the graphical evaluation, model based evaluations were then conducted.

Model Based Evaluation

The probability of bleeding or thrombotic events in relation to exposure was evaluated by binomial logistic regression. The binary linear logistic model used to describe the observed trends in the probability of experiencing a bleeding or thrombotic event is given below.
P{Y|exposure}=B0+B1*DRUG+B2*factor+.

In this linear model, the baseline probability B0 describes the likelihood of a patient experiencing bleeding or thrombotic event without exposure to bivalirudin. B1 is the adjusted probability in excess of the baseline of experiencing that event given drug exposure and DRUG is the measure of bivalirudin

exposure. Other covariate factors may be added in with additional adjustments to the baseline probability.

Once a base model estimating the probability of an event occurring without drug exposure was established, the ability of drug exposure to explain variability was tested. Covariates including dose, and Css were assessed, and time functions to incorporate the cumulative effect of treatment (i.e. a higher probability of thrombus or bleeding event with longer procedure times). The acceptance criteria for covariate inclusion into the adverse event model included reduction in the objective function of at least 10.8 points ($p<0.001$) and a reduction or at least no increase in the unexplained variability in the model.

Model Evaluation

Once a logistic function describing the probability of an adverse event was established, credible intervals were generated for the probability curves using non-parametric bootstrapping. 1000 bootstrap data sets were created from the original data set and the model was re-evaluated using the new data sets. The resulting bootstrap parameter estimates were used to reconstruct a family of probability curves. At each Css value for the curve, the upper and lower 2.5% values were removed, resulting in 95% credible intervals for the population mean probability of an adverse event in relation to drug exposure.

Model performance was evaluated graphically, by comparing the model-based estimations of the probability of experiencing an event against the binned pooled data based estimates. Models were also evaluated based on their predictive performance using a sum of squares calculated from the residuals.

Simulation Evaluation for Dose Recommendation

Simulations of expected concentrations targeted to achieve concentrations that were sufficiently high to minimize the likelihood of thrombotic events (Css of 6500 µg/L) were conducted. Simulations using a more complete range of weights (2 to101 kg) from 568 virtual subjects derived from the US Centers for Disease Control (CDC) Growth Charts [10], representing subjects from birth to age 20 years. Although certain geographic variations in the growth charts may exist, the use of the CDC growth charts for the PK simulation is still appropriate because the primary covariate reflective of exposure is weight, which was used for the evaluation of various dose strategies. Parameter precision was not incorporated for these simulations.

200 simulated replicates were conducted for several dose regimens listed in Table 3 and the 95% prediction intervals were generated. Prediction intervals were compared graphically against the prediction intervals generated for subjects weighing 75 kg or higher receiving the labeled dose. Dose regimens that produced similar prediction intervals were selected as feasible for use in pediatric subjects. All scenarios involved administration of a bolus dose followed by a 1 hour infusion and two hours simulated sampling.

Table 3 Simulation Scenarios Tested for Pediatric Dosing

Scenario No	Description
1	Labeled Adult Dose (0.75 mg/kg bolus followed by 1.75 mg/kg/hr IV infusion)
2	Perfect Dose (calculated based on virtual individual weights to achieve a target Css of 6500 µg/L
3	4 Strata Dosing: 0 -6 kg, 6-12 kg, 12-25 kg, 25-50 kg with subjects weighing more than 50 kg receiving the Labeled Adult Dose
4	5 Strata Dosing: 0-3 kg, 6-12 kg; 12-25 kg, 25-50 kg w ith subjects weighing more than 50 kg receiving the Labeled Adult Dose

Results

Graphical Assessment

Thrombus Events

Plots of several measures of bivalirudin exposure and key covariates such as age and weight versus the frequency of thrombus events were provided. A trend towards a higher frequency of this event with decreasing Css was noted. However in the other factors assessed (total dose, infusion duration, weight and age) no trends were noted.

Table 4 Thrombus Event Frequency Based Probabilities for Css

Thrombus Count	No Observations	Observed Frequency	Median Css (µg/L)
1	10	0.10	2137
2	10	0.20	2611
1	10	0.10	3020
4	10	0.40	3649
0	10	0.00	4065
0	11	0.00	4516
0	11	0.00	4879
0	11	0.00	5239
0	11	0.00	5793
0	11	0.00	7271

Bleeding Events

Plots of several measures of bivalirudin exposure and key covariates such as age and weight versus the frequency of thrombus events were also provided. There were no trends noted between metrics of exposure (Css, total dose and infusion duration) and the frequency of bleeding. However the bleeding frequency was higher in subjects that were heavier or older (Table 5), suggesting a slight trend which was slightly more evident with age.

Table 5 Bleeding Event Frequency Based Probabilities for Age

Bleeding Count	No Observations	Observed Frequency	Median Age (yr)
1	10	0.1	0.04
0	10	0	0.38
0	10	0	0.81
1	10	0.1	1.49
1	10	0.1	2.43
4	11	0.36	4.19
1	11	0.091	5.34
2	11	0.182	6.44
2	11	0.182	9.84
2	11	0.182	13.89

Model based evaluation

Thrombus Events

The model building table for thrombus events was presented. Models 1 through 6 investigate the effects of covariates such as glomerular filtration rate (GFR) in addition to steady state concentration (Css). None of these combined models performed better than Css. The only covariate identified which

was predictive of the probability of a thrombus event was Css. Model building was halted at this point and model evaluation was initiated.

Table 7 Final Parameter Estimates for Thrombus Model

Parameter		Population Value (standard error as CV%)	Bootstrap Lower 2.5% CI	Bootstrap Median	Bootstrap Upper 95% CI
Baseline probability	θ1	0.484 (172.1)	0.0011	0.532	0.981
Drug Effect	θ2	-0.798 (25.6)	-1.13	-0.817	-0.5945

The drug effect parameter was estimated with good precision; the baseline probability parameter was not well estimated. The bootstrap confidence intervals reflect the parameter precision. In this model, the probability of a thrombus event increases with decreasing exposure (Css) to bivalirudin. A plot of the probability curves for the probability of thrombus events with the associated 95% bootstrap interval and overlaid with binned observed data is presented in Figure 11. In this figure it can be seen that the probability curves are associated with the observed data and reflect observed probability of thrombus. The confidence intervals are reassuringly narrow as well. A plot of the same information scaled at higher bivalirudin concentrations is presented in Figure 12. In this latter figure, it can be seen that the probability of thrombus falls to approximately 1% at bivalirudin concentrations in excess of 6500 µg/L, making this concentration an appropriate lower target concentration for paediatric dosing regimens.

Figure 11 Thrombus Model Probability Curves

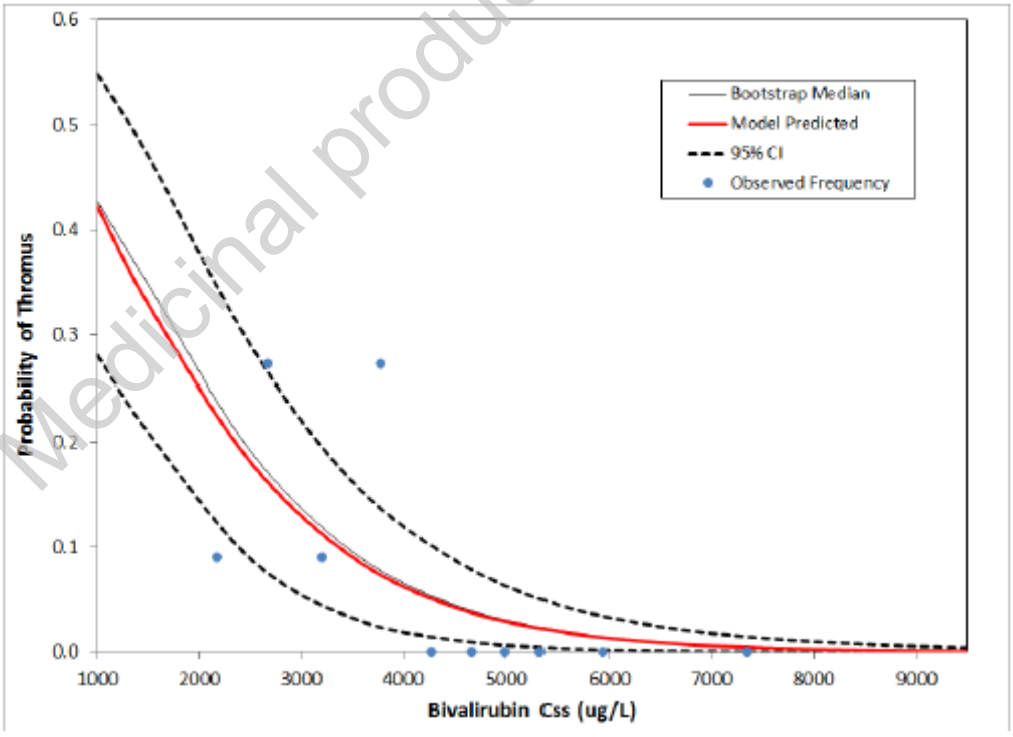
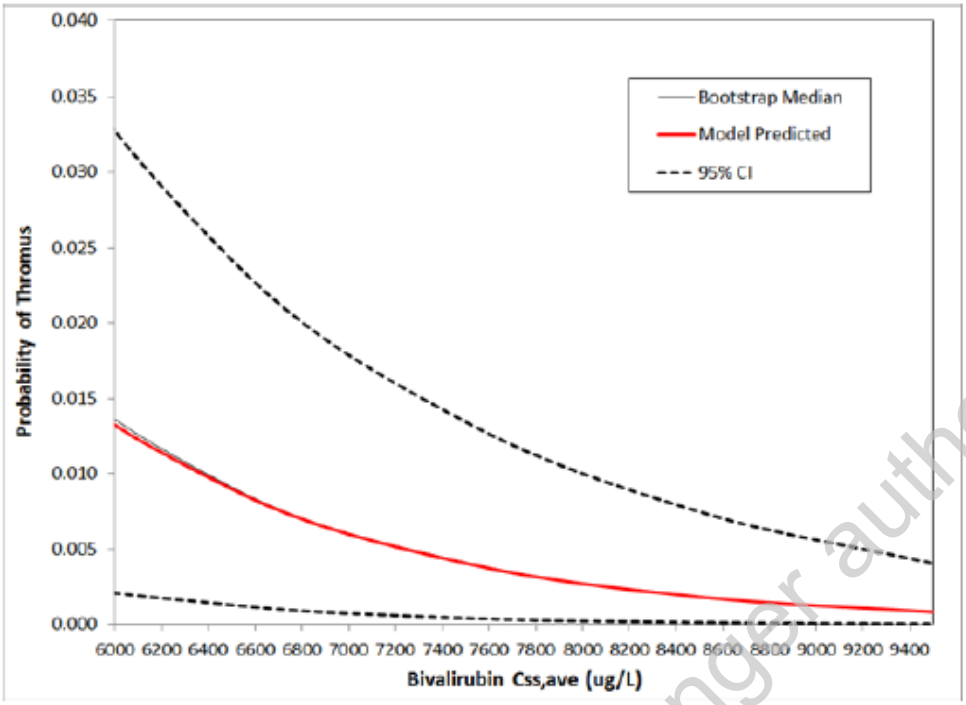


Figure 12 Thrombus Probability Curve at High Bivalirudin Concentrations



Bleeding Events

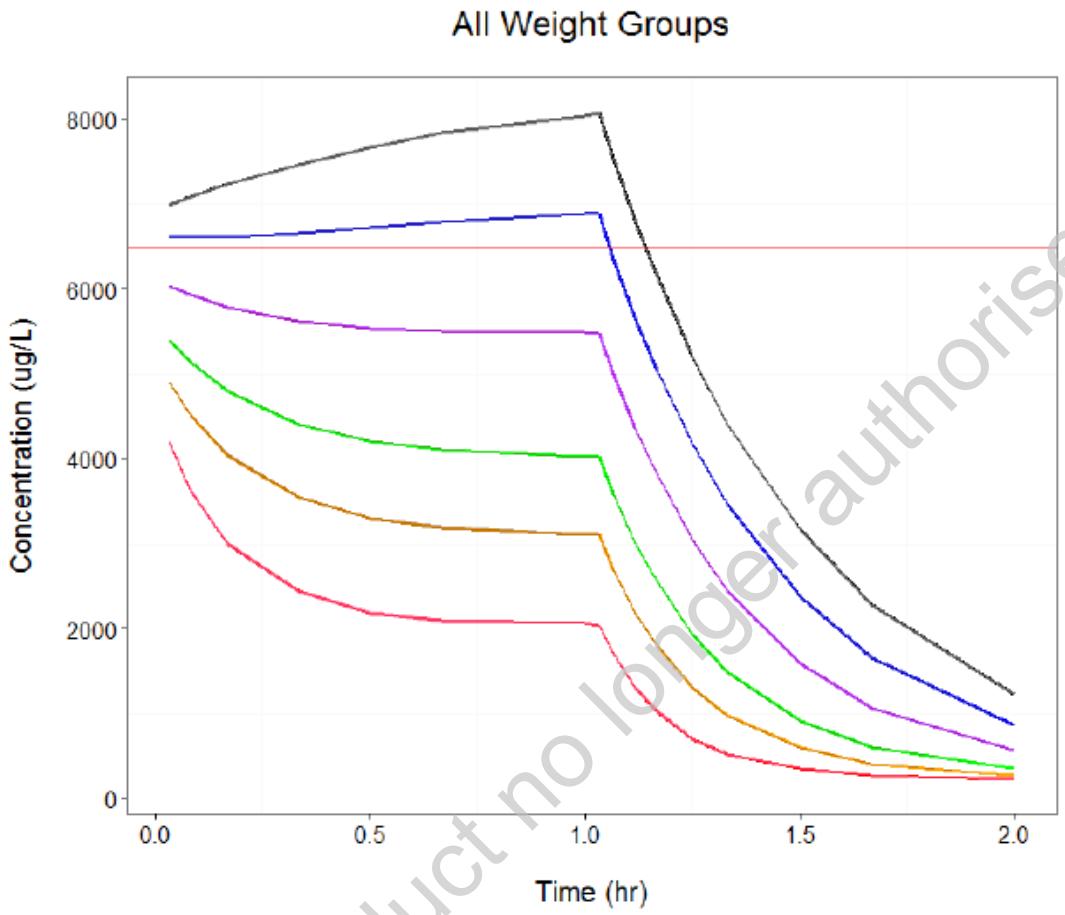
The model building tables for the binomial logistic regression evaluation were presented and no covariates were identified that met the criteria for inclusion as being predictive of the probability of a bleeding event.

This is consistent with the graphical assessment which identified weak trends for age and weight. Thus the final model was the base model and bivalirudin exposure does not appear to be related to the probability of bleeding events. Model development was halted at this time and no further exploration of model results was conducted.

Simulations for Dose Evaluation

Simulated concentration time profiles for bivalirudin versus time were provided by weight. Figure 14 shows a comparison of the median simulated concentrations by age group, showing a progressively lower concentration achieved on average as subject weight decreases. This finding is expected because the effect of weight on bivalirudin clearance is not linear (see Table 1). Weight groups from 50-75 kg and over 75 kg appear to reach the target concentration for more than half of the simulated subjects and are reflective of exposures seen in approved use in adults.

Figure 14 **Comparison of Median Simulated Bivalirudin Concentration Time Profiles for the Labeled Dose**



Key: red line is less than 6 kg, orange line is 6-12 kg, green line is 12-25 kg, purple line is 25-50 kg, blue line is 50-75 kg and black line is greater than 75 kg. The horizontal red line is the target concentration of 6500 µg/L.

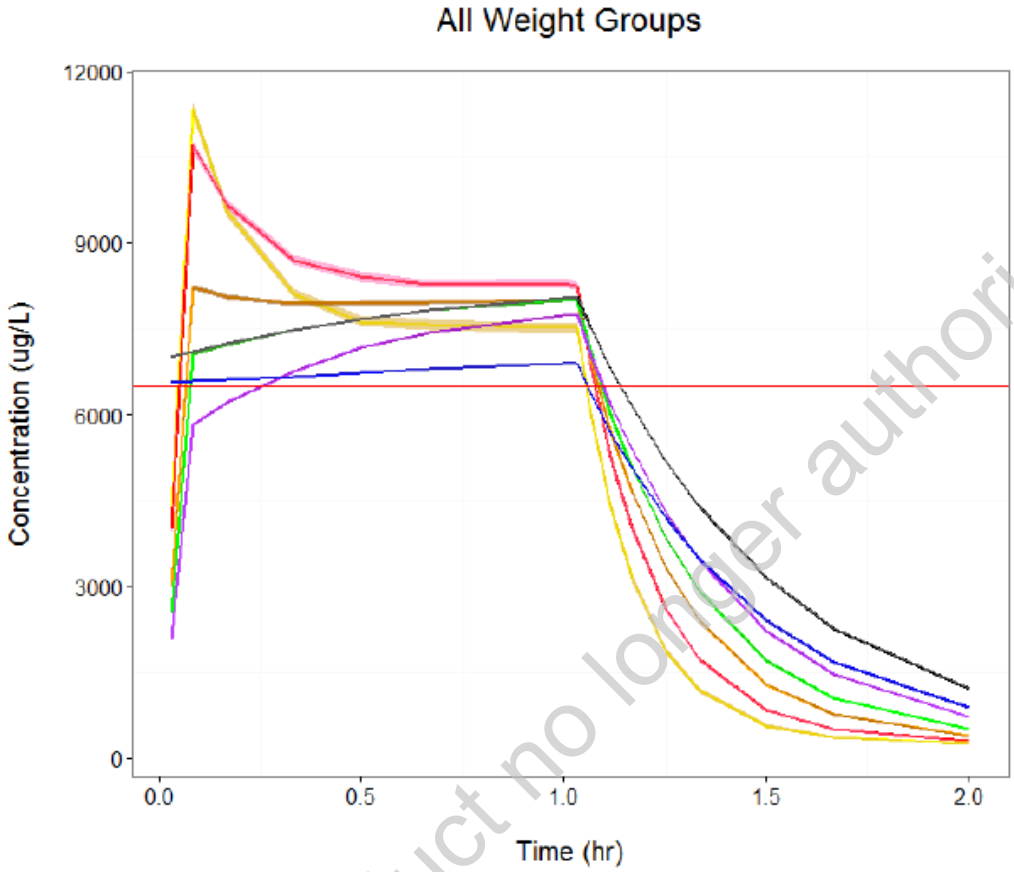
The best results were achieved with doses stratified for <3 kg, 3-6 kg, 6-12 kg, 12-25 kg, and 25-50 kg with subjects weighing over 50 kg receiving the labelled adult dose. The doses used for this simulation scenario are provided in Table 9. These doses were derived as the median of the individualized doses used from Scenario 2 by weight.

Table 9 Doses for Best Stratified Dose Regimen

Dose Type	Dose (µg)	Weight (kg)
IV Bolus	5000	< 3kg
Maintenance Infusion Rate (µg per Hour)	20000	< 3 kg
IV Bolus	7500	3-6 kg
Maintenance Infusion Rate (µg per Hour)	30000	3-6 kg
IV Bolus	11500	6-12 kg
Maintenance Infusion Rate (µg per Hour)	46000	6-12 kg
IV Bolus	15500	12-25 kg
Maintenance Infusion Rate (µg per Hour)	63000	12-25 kg
IV Bolus	22500	25-50 kg
Maintenance Infusion Rate (µg per Hour)	90000	25-50 kg

Plots of these simulated concentrations by weight group are provided in Figure 16. The lowest weight groups (weight less than 3 kg and weight 3-6 kg) have somewhat higher peak concentrations than the reference adult profiles, but do achieve the target concentration for the majority of subjects. Attempts were made to simulate without the IV bolus loading dose but the resulting concentration time profiles took too long (15 to 20 minutes, data not shown) to achieve steady state and were thus retained in the dose regimen. The ranges of concentrations for the other weight groups (6-12 kg, 12-25 kg, 25-50 kg) are in good agreement with adult concentrations. A plot of the median simulated concentrations for all weight groups is provided in Figure 16. As can be seen in this figure, the median simulated concentrations for all weight groups are comparable and are higher than the target.

Figure 16 **Comparison of Median Simulated Bivalirudin Concentration Time Profiles for the Weight-Stratified Dose By Weight Group**



Key: yellow line is weight 0-3 kg, red line is 3- 6 kg, orange line is 6-12 kg, green line is 12-25 kg, purple line is 25-50 kg, blue line is 50-75 kg and black line is greater than 75 kg. The horizontal red line is the target concentration of 6500 µg/L.

Rapporteur's overall conclusion and further action if required

The MAH provided the study report for PK/PD Modelling – TMC-BIV-07-01 and an Addendum to the Clinical Overview with a list of 6 references.

The Assessors considers that there are a number of limitations in this submission.

1. Although there is a possible indication for the product as an anti-coagulant in children, the Clinical Overview affirms that, '*There is no relevant indication for use of bivalirudin in children less than 18 years old,*' on page 4 and the indication is not sought. The FDA's written request for paediatric data is in line with the policy on requesting paediatric data and a PIP was submitted but then withdrawn and there is currently no PIP. No explanation has been provided for the subsequent withdrawal and re-submissions of multiple PIPs and the reasoning behind this submission has not been made clear in either document. Dosing information would be

useful in children to inform any off label use. In addition, the outcome of an assessment may have implications for the SmPC

2. The study report states that, '*This report summarizes the exposure/response analysis of Angiomax® (bivalirudin) in pediatric patients enrolled in study TMC-BIV-07-01,'* However, apart from listing exposure, thrombotic, and bleeding events (105 in 105 patients) as the data which was merged from data provided for study TMC-BIV-0701 in paediatric patients, the pharmacodynamic details have not been provided and cannot be correlated to the bioanalytical data provided.

3. The study report states that there were '*105 bleeding and thrombotic event observations from a total of 105 subjects*' (p.10), whilst the overview states that, *'… the exposure/response analysis of Angiomax® (bivalirudin) in paediatric patients (birth up to 16 years including at least 10 neonates, 20 infants/toddlers, 20 young children and 10 older children) enrolled in study TMC-BIV-07-01',* suggesting only 60 patients (p5), with no explanation for the discrepancy.

4. The age categories used for those 60 patients are in line with the WHO paediatric age categories. The Assessor is unable to comment on the possible additional 45 patients.

5. A brief summary of the study method was provided – GFR, bolus (0.75mg/kg) and infusion regimen (1.75 mg/kg/hr), use of dilute Angiox flush (0.1mg/mL) in some cases during the procedure (which was added to the total dosing) and sampling times for PK analysis and ACT measurement. However, the Assessor cannot comment on the adequacy of the method without the standard, more detailed Study Method and Bioanalysis information.

6. The study report states that there were '*105 bleeding and thrombotic event observations from a total of 105 subjects*' (p.10). However, without an idea of the adequacy of the study method, population characteristics, inclusion/exclusion criteria, ACT results or a more appropriate indication of what these events were, when they occurred and how serious they were, the PK data cannot be meaningfully interpreted in relation to pharmacodynamic effect, efficacy or safety.

7. The graphical representations and tables suggest lower thrombolytic events at higher concentrations, and no correlation with any exposure measure and bleeding events. The data for this clinical study was assessed in a previous assessment and was judged not to affect the overall benefit risk. The modelling of thrombolytic events has been used to develop a relationship with plasma concentration. However, the plot with observed values over-laid (figure 11) shows limited data and is not strongly supportive of a target of 6,500 ng/ml. However, it is agreed that thrombolytic events are limited above concentrations of 3649 ng/ml. Further support for the target value based on adult data should be provided.

8. A full POPPK report including diagnostic plots would be required to support the inclusion of the data in POPPK model and its use to simulate dosing regimens in children. Diagnostic plots should include predicted versus observed concentrations for the population and individual predictions, and WRES versus IPRED and time. These plots should be included for the full data set and a second set based solely on the data from the paediatric study. In addition plots showing observed versus predicted individual profiles for all paediatric subjects should be supplied. All available paediatric pharmacokinetic data should be included in the model.

9. The expected exponent for weight is 0.75 therefore it is agreed that the value of 1 used in the dose regimen in the clinical study would be expected to result in under exposure of the

younger children. However, the value of 0.534 from the model is low and requires further supporting plots. These plots should include plots of ETA(CL) versus weight in the basic and full model. In addition, the implications for the relationship with weight for dosing in adult populations should be discussed.

10. Further justification of the target concentration and of the POPPK model is required before the doses proposed in children can be considered. If this data supports the proposed posology this data could be included in section 5.2 of the SmPC.

Overall Conclusion

This submission appears incomplete; lacking crucial information from which a meaningful interpretation of the data provided can be made. It is considered that if satisfactorily presented the data could be used to inform a change of wording in the SmPC.

☒ PAC not fulfilled (not all commitments fulfilled) and further action required:

The MAH is required to submit by end 2014 the following variation(s). A population PKPD analysis utilising all available PK in children as per the standard in the EMA guideline Guideline on reporting the results of population pharmacokinetic analyses CHMP/EWP/185990/06.