CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211215Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 211215
Supporting document/s:	001, 002
Applicant's letter date:	September 26, 2018
CDER stamp date:	September 27, 2018; December 28, 2018; January 18, 2019
Product:	Bivalirudin injection ready to use
Indication:	Anticoagulant in percutaneous transluminal coronary angioplasty and percutaneous coronary intervention
Applicant:	Maia Pharmaceuticals, Inc
Review Division:	Division of Cardiovascular and Renal Products
Reviewer:	Elizabeth Hausner DVM
Supervisor/Team Leader:	Xuan Chi MD, PhD
Division Director:	Norman Stockbridge MD, PhD
Project Manager:	Bridget Kane, MS

Template Version: September 1, 2010 (Modified by DCRP: Nov. 30, 2016)

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of N211215 are owned by Maia Pharmaceuticals, Inc. or are data for which has Maia Pharmaceuticals, Inc. obtained a written right of reference.
Any information or data necessary for approval of NDA211215 that Maia Pharmaceuticals, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA211215.

TABLE OF CONTENTS

(Note: All tables and figures are those of the reviewer unless stated otherwise.)

1 Executive Summary

1.1 Introduction (and Clinical Rationale)

Maia Pharmaceuticals has submitted a new drug application for bivalirudin injection, 5 mg/ml as a 505(b)(2) application. This relies on the findings of safety and efficacy for the listed drug Angiomax(bivalirudin) for injection, approved as NDA 020873. The reference drug is a lyophilized drug product that must be reconstituted for use and then diluted for injection. The proposed drug is a ready to use (RTU) formulation.

1.2 Brief Discussion of Nonclinical Findings

The continuous infusion study using bivalirudin subject to accelerated degradation produced no findings of toxicological significance. The in vitro hemolysis study did not show appreciable differences in hemolysis of human blood when compared to Angiomax.

1.3 Recommendations

1.3.1 Approvability

From the nonclinical perspective, this can be approved.

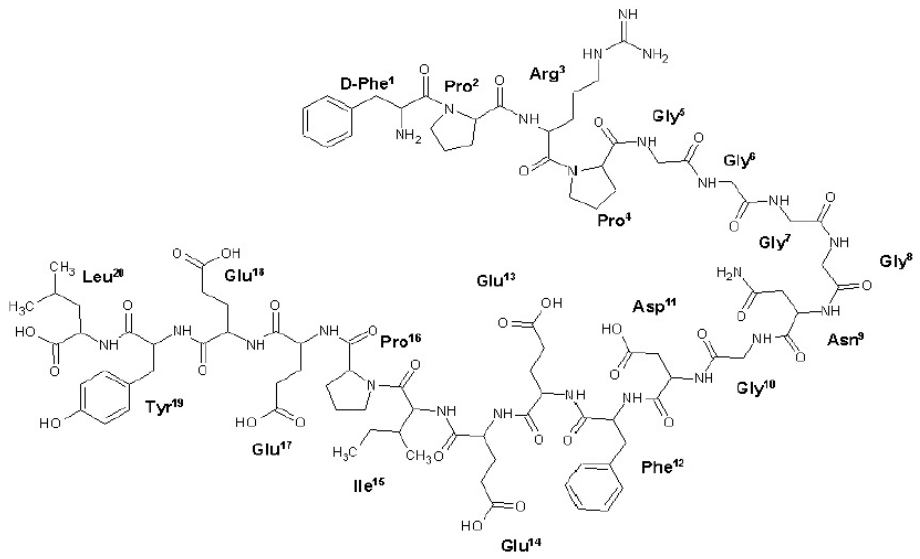
1.3.2 Additional NonClinical Recommendations

None.

1.3.3 Labeling

The nonclinical sections of the label appear to be the same as the reference label drug. Section 8.1 appears to have been updated to the new format.

2 Drug Information

CAS Registry Number (Optional)	12870-60-0
Generic Name	bivalirudin
Code Name	bivalirudin
Chemical Name	D-Phenylalanyl-L-prolyl-L-arginyl-L-prolyl-glycyl-glycyl-glycyl-glycyl-L-asparaginyl-glycyl-L-aspartyl-L-phenylalanyl-L-glutamyl-L-glutamyl-L-isoleucyl-L-prolyl-L-glutamyl-L-glutamyl-L-tyrosyl-L-leucine, trifluoroacetate salt
Molecular Formula/Molecular Weight	$C_{98}H_{138}N_{24}O_{33}$ (free base) 2179.0 g/mol (monoisotopic mass)
Structure or Biochemical Description	
Pharmacologic Class	Anti-coagulant via direct thrombin inhibition

2.1 Drug

The drug is a 20 amino acid peptide analog of hirudin. This consists of the hirudin active site-binding domain and the fibrinogen-binding domain linked by four glycine residues. Both binding sites must be present for the peptide to have activity.

2.2 Relevant INDs, NDAs, BLAs and DMFs

Reference label drug: NDA 20873
DMFs: (b) (4)

2.3 Drug Formulation

Table 5: Comparison of Inactive Ingredients: Listed Drug versus MAIA Product

Listed Drug (ANGIOMAX (bivalirudin) for Injection, 5 mg/mL)		MAIA Product (Bivalirudin Injection, 5 mg/mL)	
Ingredient	**Amount/vial**	**Ingredient**	**Amount/50 mL**
		Sodium Acetate trihydrate, USP	40 mg
Mannitol, USP	125 mg	Polyethylene Glycol 400, NF	5000 mg
Sodium Hydroxide, NF	Q.S to pH 5-6	Glacial Acetic Acid, USP or Sodium hydroxide NF	Q.S to pH 5.25±0.25
Water for Injection, USP	Removed during lyophilization	Water for Injection, USP	Q.S to 50 mL

2.4 Comments on Novel Excipients

There are no novel ingredients in the formulation. The Division of Hematology and Oncology Products agreed that no additional studies were needed to support the levels of inactive ingredients in the proposed formulation. DCRP also agreed with this position in meeting minutes from the pIND126394, dated July 24, 2018.

3. Consistent with prior guidance from DHP at the Pre-IND meeting, does the Agency agree that there are no novel inactive ingredients in MAIA's formulations? (Sponsor Question 5)

FDA Preliminary Response:
Yes, we agree.

Discussion at the Meeting:
No further discussion.

4. Consistent with prior guidance from DHP at the Pre-IND meeting, does the Agency agree that no additional studies are needed to support the levels of the inactive ingredients used in MAIA's formulation? (Sponsor Question 6)

FDA Preliminary Response:
Yes, we agree.

Discussion at the Meeting:
No further discussion.

FDA Preliminary Response:
The meeting document refers to an evaluation of the activity of the degradation fragments. We request that you submit this information as well as the hemolysis and toxicology study reports listed under Module 4 of Attachment 2.

However, a question was raised by another review discipline as to adequate justification for the safety of the proposed level of PEG400. This is the subject of SDN 002.

2.5 Comments on Impurities/Degradants of Concern

Related Substances of Bivalirudin Specified in the Drug Substance Specification and/or the USP-PF Monograph

(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

Patients undergoing percutaneous coronary intervention. Dosing regimen is 0.75mg/kg intravenous bolus dose followed by 1.75 mg/kg/hour intravenous infusion for the duration of the procedure. The duration of the infusion may be extended to 4 hours in patients with ST segment elevation myocardial infarction (STEMI) (b) (4)

2.7 Regulatory Background

In June , 2015, the sponsor discussed their proposed development plans with DHOT (minutes dated June 30, 2015). This pre-IND was transferred to the Division of Cardiovascular and Renal Products on April 23, 2018 as a bivalirudin product with similar indications was approved under the 505(b)(2) pathway in December 2017 in DCRP.

The authorized generic for the listed drug (Sandoz bivalirudin for injection) was used as the comparator substance in the nonclinical studies with the Agency's concurrence.

3 Studies Not Reviewed

Not applicable.

4 Pharmacology

4.1 Primary Pharmacology

Bivalirudin is an anticoagulant with reversible, direct thrombin activity. Bivalirudin binds both the catalytic site of thrombin and the fibrinogen-binding site. It has also been noted that bivalirudin can bind both soluble(free) and clot-bound (fibrin-bound) thrombin. Both binding domains must be present for the peptide to retain its activity.

4.2 Secondary Pharmacology

Not applicable.

4.3 Safety Pharmacology

Not applicable.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Bivalirudin undergoes degradation through three main pathways:

1.succinimide formation and deamidation at Asn[9](Asparagine)
2.Succinimide formation and hydrolysis at Asp[11] (aspartic acid)
3. intramolecular aminolysis (hydrolysis) at the Pro2-Arg3 bond

(b) (4) degradants from these pathways:

(b) (4)

[Asp9]-bivalirudin

(b) (4)

[1-11]-bivalirudin
[12-20]-bivalirudin

(b) (4)

Within the body, bivalirudin is catabolized extensively. Approximately 20% of full length bivalirudin and some degradants are excreted in the urine. The primary route of removal is by catabolism. The initial in vivo degradation is hydrolysis of the N-terminal dipeptide, (b) (4)

Bivalirudin is also slowly hydrolyzed by thrombin and other circulating proteases at the Arg3-Pro4 bond. The primary metabolite of this is [4-20]-bivalirudin, which is reportedly not active due to loss of affinity for the catalytic activity site of thrombin. Up to 61 potential catabolites have been identified and are presumed to be small fragments or amino acids of bivalirudin. In vivo, the ultimate fate of bivalirudin is breakdown into individual amino acids which are recycled to the body pool (Warkentin and Koster, 2005). As described in the EMEA's Scientific Discussion of Angiox (2005):

> The differences in the fate of the ^{3}H in the N-terminal dipeptide and the ^{14}C in the rest of the molecule, suggest that the parent compound is metabolised early and extensively. The similarity of the data

whether the ^{14}C is placed in the glycine spacer only or evenly distributed along the 18-amino acid C-terminal portion indicates that the initial reaction is the hydrolysis of the N-terminal dipeptide. This is supported by the clear separation of the ^{3}H and ^{14}C activity by iso-electric focusing of urine from a rat treated with bivalirudin with the ^{14}C label in the glycine spacer. Bivalirudin is stable in citrated plasma from rat, cynomolgus monkey and man *in vitro* and, therefore, proteolysis must occur at an extravascular site. Published data for other small peptides suggest that this could be the kidney. A study in which the N-terminal dipeptide was administered indicated that this is metabolised in the kidneys.

The ^{14}C label was initially cleared from plasma in parallel with the ^{3}H label, but was widely distributed to tissues with prolonged maintenance of a low plasma level. There was an uptake into skeletal muscle and skin and a later appearance in the small intestine. These findings are consistent with breakdown of the peptide by non-specific proteinases with the fragments entering the amino acid pool.

Excretion of the breakdown products of bivalirudin is almost exclusively in the urine in rat and cynomolgus monkey. Excretion of ^{3}H activity was rapid, almost all within the first 4 h. Low recovery of ^{14}C is consistent with incorporation of the amino acids from the C-terminal peptide into newly synthesised protein.

Sponsor's summary of major degradants and activity

Table 1: Degradation Fragments of Bivalirudin*

Common Name	Site of Degradation	Degradation Mechanism	Thrombin Inhibition Activity** (%)
			(b) (4)

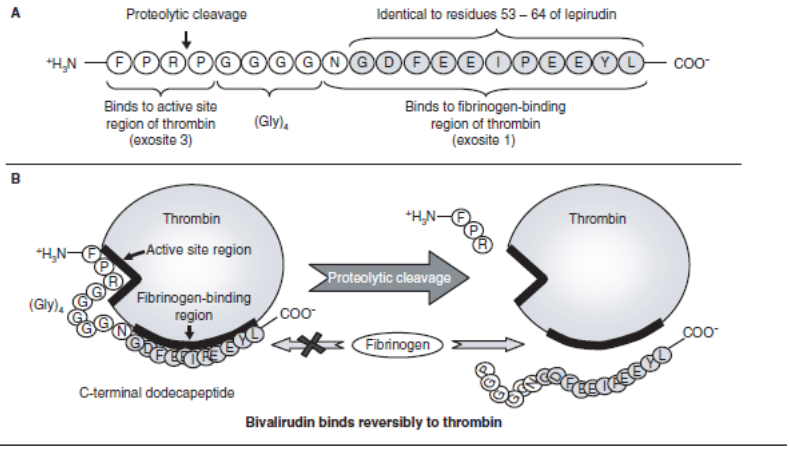


Figure 1. The structure of bivalirudin. A) Bivalirudin is comprised of 20 amino acids, with an N- (amino-) terminal D-Phe-Pro-Arg-Pro (F-P-R-P) region that binds with high affinity to the active site region (exosite 3) of thrombin; a $(gly)_4$ (G4) "spacer" region; and a C- (carboxy-) terminal Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu dodecapeptide (N-G-D-F-E-E-I-P-E-E-Y-L) that binds to the fibrinogen-binding region (exosite 1) of thrombin. The eleven C-terminal amino acids (shaded circles) correspond exactly to the 53 – 64 amino acid sequence of lepirudin. Highly-specific, noncompetitive binding between bivalirudin and thrombin results. The heparin-binding region (exosite 2) of thrombin is not shown. However, proteases, such as thrombin cleave the Arg3-Pro4 of bivalirudin, leading to loss of antithrombin activity. **B)** Initially, there is bivalent binding of bivalirudin to thrombin, as shown. Following cleavage at Arg3-Pro4, the N-terminal sequence of bivalirudin no longer binds to thrombin, leaving the residual C-terminal dodecapeptide with greatly-reduced binding affinity for thrombin exosite 1. Thus, the bivalirudin remnant transforms to a competitive inhibitor of thrombin. Other substrates (e.g., fibrinogen) can compete with, and displace, bivalirudin, thus allowing thrombin to resume its prohaemostatic functions.
D: Asp, aspartic acid; E: Glu, glutamic acid; F: Phe, phenylalanine; G: Gly, glycine; I: Ile, isoleucine; L: Leu, leucine; N: Asn, asparagine; P: Pro, proline; R: Arg, arginine; Y: Tyr, tyrosine.
Reprinted with permission from BARTHOLOMEW JR: Bivalirudin for the treatment of heparin-induced thrombocytopenia. In: *Heparin-Induced Thrombocytopenia (3rd edn)*. Warkentin TE, Greinacher A (Eds), Marcel Dekker, New York, US (2004). Copyright Taylor and Francis, Boca Raton, Florida.

5.2 Toxicokinetics

Validation of method BTM-2218-RO for determination of bivalirudin in rat plasma (sodium citrate) by LC-MS-MS.

Sodium citrate rat plasma was the matrix. The internal standard used was (b) (4). Bivalirudin and the internal standard were extracted from rat plasma using a protein precipitate technique. (b) (4)

The linearity was reported as r^2 of 0.9954 over a dynamic range of 50-25000ng/ml (LLOQ 50 ng/ml). Average recovery of the analyte was 93.5% and of the internal standard 96.0%. Sponsor's summary of results

QC Inter-run precision range (%CV)	9.8	4.0 to 8.7
QC Inter-run accuracy range (%Bias)	-1.6	-11.1 to -6.0
QC sample short-term stability	6.5 hours at room temperature	
Processed sample stability	118.5 hours at room temperature	
Reinjection reproducibility	63.5 hours at room temperature	
QC sample freeze/thaw stability	4 freeze (-20 °C)/thaw cycles 4 freeze (-70 °C)/thaw cycles	
QC sample long-term storage stability	34 days at -20 °C and -70 °C	
Dilution integrity	190000 ng/mL diluted 10-fold	

The limit of blank was not listed but from the description, blank selectivity is similar.

Matrix Effect	IS-normalized Matrix factor = 0.98± 0.11 at 150 ng/mL with %CV = 11.2% IS-normalized Matrix factor = 1.04 ± 0.04 at 19000 ng/mL with %CV = 3.8%
2% Hemolyzed QC precision range (%CV)	1.6 to 6.6
2% Hemolyzed QC accuracy range (%Bias)	-4.7 to 2.7
Blank Selectivity	The selectivity evaluation met the acceptance criteria: five out of the six matrix lots had no significant baseline interference (≥ 20.0% of the lower limit of quantitation, LLOQ for bivalirudin or ≥ 5.0% of the mean IS peak area of the accepted calibration standards and QC samples) was detected at the retention times of the analyte or the IS in any of the rat plasma lots.
Whole Blood Stability	120 minutes in an ice-water bath (0-4 °C) and room temperature
Batch Size	126 samples
Carryover Evaluation	All of the double blank samples that were evaluated for carryover met the acceptance criteria (analyte peak areas were < 20.0% of the lower limit of quantitation, LLOQ for bivalirudin and IS peak areas were < 5.0% of the mean IS peak area of the accepted calibration standards and QC samples).
Interference from Analyte on IS	There was no significant interference detected from the analyte on the internal standard.

Freeze thaw cycles: samples were considered stable if the mean of the obtained concentrations at each level was within ±15% of the nominal concentrations and the %CV was no more than 15%.
At -20C, the %CV was 12.9% and the % bias was -13%
Where %CV (precision) was defined as [SD/(mean measured concentration)] x 100 and
% bias (accuracy) was defined as([(mean measured concentration)-nominal concentration)]/nominal concentration) x 100.
At -70C, the %bias is -14.7% and %CV is 6.0.

6 General Toxicology

6.2 Repeat-Dose Toxicity

14-day continuous infusion study in rats
(b) (4) study number: BS92RH
(b) (4) location: (b) (4)
Maia reference number: MAIA-BVN-17-TOX-002
GLP: yes
Test article: lot number AJZ603, purity 85.9%. Note, an expiration date was not assigned to the test material because it was intentionally degraded beyond what is considered acceptable for release. This was done to test the toxicity of the degradants. The test article was evaluated at the start, middle and end of the study and demonstrated to be stable. The dose formulation concentration verification analysis was performed and confirmed the dose formulations.

Note: the lot of bivalirudin injection used here in the hemolysis study (lotAJZ603) was manufactured using the clinical manufacturing process and was formulated the same as the clinical material:

aqueous solution containing 5 mg/ml of bivalirudin (equivalent to average of 5.5 mg bivalirudin trifluoroacetate)
in 0.8 mg/ml sodium acetate(trihydrate)
100 mg/ml polyethylene glycol 400
pH 5.0 – pH 5.5

Comparator drug: authorized generic Bivalirudin marketed by Sandoz, Inc.

The summary of the exposure to drug and impurities, based on this report, is:

Dose of bivalirudin (mg/kg/day)	36	100	258
Dose of collective impurities (mg/kg/day) contained within drug dose	(b) (4)		

Sprague Dawley CD® rats, 10/sex/group, 10-11 weeks at start of dosing.

Group	Treatment	Number of animals			
		Main study		TK study[b]	
		Male	Female	Male	Female
1	Control	10	10	6	6
2	Placebo for MAIA Bivalirudin Injection	10	10	6	6
3	MAIA Bivalirudin Injection	10	10	6	6
4	MAIA Bivalirudin Injection	10	10	6	6
5	MAIA Bivalirudin Injection	10	10	6	6
6	Sandoz Bivalirudin for Injection[e]	10	10	6	6

[a] Doses represent active ingredient

[b]TK animals used for toxicokinetic blood sampling only.

Treatment groups: 0(0.9% sodium chloride or sodium acetate trihydrate/polyethylene glycol 400/glacial acetic acid to adjust pH/sterile water for injection
36, 100, 258 mg/kg/day MAIA bivalirudin partially degraded to (b) (4)% impurities
258 mg/kg/day Sandoz bivalirudin
Infusion rate: 2.5 ml/kg/hour for all groups, continuously administered for 14 days

Satellite animals were used for toxicokinetics, 3/sex/group/timepoint. Timepoints were 5 minutes and 24 hours post-infusion.

The sponsor notes that studies were conducted under NDA20873 to qualify degradants and synthesis impurities (b) (4). The duration of the present study is based on the duration of the nonclinical studies performed by the Innovator company, The Medicines Company. The duration of the study was also agreed upon with the FDA as part of the pre-IND meeting for pIND 126394.

Dose selection:

The low dose was chosen based on the no observed adverse effect level established for the listed drug, in study P8967-94-13 (NDA20-843(Angiomax for Injection), also a 14-day intravenous toxicity study. The mid-dose was based on the maximum daily dose specified for Angiomax for injection in the listed drug package insert (15mg/kg). The high dose of 250 mg/kg was the highest dose used in Study P8967-94-02 (intravenous toxicity of (b) (4) and is 2.5-fold higher than the human equivalent dose using a conversion factor of 6.2.

A question was asked about the level of polyethylene glycol used in the formulation. Therefore, additional detail will be included here.

MAIA Bivalirudin Injection was prepared for administration by dilution with the placebo to achieve the desired concentrations for Groups 3 and 4, or administered as is (undiluted) for Group 5. The comparator article was reconstituted in 5 mL of Sterile Water for Injection and diluted in 45 mL of the control article (0.9% Sodium Chloride Injection) to achieve the label concentration (5 mg/mL); the reconstituted and diluted comparator article was then subsequently diluted to the target concentration (~ 4.3 mg/mL) for Group 6.

The Placebo for MAIA Bivalirudin Injection was prepared by dissolving Polyethylene Glycol 400 NF (100 mg/mL) and Sodium Acetate (trihydrate) USP (0.8 mg/mL) in an initial quantity of Sterile Water for Injection, and adjusting the pH to 5.25 ± 0.10 with Glacial Acetic Acid USP, before diluting to the final concentration with Sterile Water for Injection, q.s (1 mL).

The vehicle for the test article was described as the clinical formulation (b) (4) Relative exposure is summarized in the reviewer's table below.

Rat exposure to polyethylene glycol 400(PEG):
2.5ml / Kg.hr x 100 mg PEG / ml x 24 hours = 6000 mg PEG/kg/24 hours 2000 mg/kg/8 hours
Human exposure: 300 mg/kg/8 hours

Homogeneity, stability, and concentration were determined from samples taken from top, middle, and bottom of each dose formulation.

Group	Treatment	Dose (mg/kg/day)	Concentration (mg/mL)	Dose (mg/kg/hr)	Infusion Rate (mL/kg/hr)
1	Control Article - 0.9% Sodium Chloride Control	0	0	0	2.5
2	Placebo for MAIA Bivalirudin Injection	0	0	0	2.5
3	MAIA Bivalirudin Injection	36	0.60	1.5	2.5
4	MAIA Bivalirudin Injection	100	1.67	4.18	2.5
5	MAIA Bivalirudin Injection	~258	~4.3	~10.75	2.5
6	Comparator Article - Sandoz Bivalirudin for Injection	~258	~4.3	~10.75	2.5

In life observations included behavioral and signs, body weight, food consumption, ophthalmoscopy. At time of euthanasia, blood was collected for hematology, coagulation and clinical chemistry. Urine was obtained also.

At necropsy, gross observations were made, organ weights determined, and tissues collected for histopathology. An adequate list of tissues was reported.

Results

Exposure to impurities

Impurities were evaluated. The Sandoz comparator contained approximately (b) (4)% impurities. The intentionally degraded new material contained approximately (b) (4)% impurities as shown in the sponsor's table below.

Sample	Assay (mg/mL)	Related Substances (%) Known Impurities
		(b) (4)
Day 1	4.37	
Day 7	4.32	
Day 15	4.33	

Sample	Assay (mg/mL)	Related Substances (%) Unknown Impurities	Σ RRT	Total
		(b) (4)		(b) (4)
Day 1	4.37			
Day 7	4.32			
Day 15	4.33			

Limit of Quantitation: (b) (4)%

ND: Not detected

There is a difference in the qualified levels of impurities listed in the table in the body of the report and the table in the Appendix. Both are shown below.

From body of the report:

Text Table 7-1: Degradants and Qualified Levels in MAIA Bivalirudin Injection

Degradant	Levels in Test Article (%)			Qualified Level (%)
	Day 1	Day 7	Day 15	
(b) (4)				

From the certificate of analysis in the appendix(p.491):

(b) (4)

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Homogeneity and measured concentrations were within the pre-specified acceptable range of %RSD±10%. The measured concentration for the highest dose was at the edge of the acceptable range.

Text Table 6.1.2-1.: Homogeneity Concentrations

Group	Nominal Concentration (mg/mL)	Measured Concentration (% of Nominal)			%RSD			Mean Concentration of 3 Levels (% of Nominal)	Mean %RSD of 3 Levels
		Top	Mid	Bot-tom	Top	Mid	Bot-tom		
3	0.6	100.5	100.0	100.0	0.3	0.2	0.2	100.2	0.3
4	1.67	100.6	100.3	100.6	0.1	0.5	0.6	100.5	0.4
6	4.3	91.4	91.3	91.4	0.8	0.3	0.1	91.4	0.4

* For the homogeneity testing, the comparator article was prepared by transferring the contents of the reconstituted vial to 50 mL of control article, and subsequently diluting to 4.3 mg/mL in the control article.

Unscheduled mortality was reported for 4 rats in the main study group and 4 rats in the toxicokinetic group.

Main study	Toxicokinetic study
2 males, 250 mg/kg/day bivalirudin	1 female found dead day 3
1 male given 250 mg/kg/day Sandoz comparator	I female euthanized day 7
1 control female: death attributed to gavage accident	1 female euthanized after failure to collect sample (catheter failure)
	1 male found dead day 14

The 2 males given bivalirudin showed black material in the stomach, jejunum, ileum, and colon, consistent with digested blood. Ulceration was not noted in the GI tract. In one of these males, the lungs were discolored red and microscopically were shown to contain increased aggregates of alveolar macrophages with hemoglobin crystals. The dark material in the GI tract and hemoglobin crystals in the lung were consistent with hemorrhage as was pallor of skin and organs, considered to be due to blood loss. Centrilobular necrosis was present in the liver, and was attributed to hypoxia secondary to blood loss.

Clinical signs were reported for all groups of animals, including the controls. These signs included decreased activity, hunching, abnormal color or pallor, piloerection, irregular breathing. The majority of these observations were attributed to the animals who died ahead of schedule.

The causes of death and the clinical signs were considered related to exaggerated pharmacology of the test material.

The ophthalmologist's report stated that the findings were common incidental observations in this species.

Males: Ophthalmoscopy findings

	Negative control	Vehicle control	MAIA bivalirudin (Dose in mg/kg)			Sandoz bivaliridun
			36	100	250	250
# examined	10	10	10	10	8	9
Iritis/uveitis	0	0	1	0	0	0
Vitreous hemorrhage	0	0	0	1	0	1

Females: Ophthalmoscopy findings

	Negative control	Vehicle control	MAIA bivalirudin (Dose in mg/kg)			Sandoz bivaliridun
			36	100	250	250
# examined	9	10	10	10	10	10
Iritis/uveitis	0	0	0	0	0	0
Vitreous hemorrhage	0	0	0	0	0	0
Posterior capsular cataract	0	0	0	0	1	0

Body weight: Males

In the first seven days, the high dose group of Maia bivalirudin gained somewhat less than the control and comparator groups. The comparator group gained slightly less weight than the test article groups over the 15 day course of the study. There is no dose-related relationship apparent over the entirety of the study.

group		Group /Sex		Change 1-7	Change 1-14	Change 1-15
Negative control		Statistics test		Wi	Wi	Wi
		1M	Mean	28	64	57
			SD	17.2	17.1	18.1
			N	10	10	10
Vehicle control						
		2M	Mean	31	64	64
			SD	14.5	24.3	14.7
			N	10	10	9
MAIA Bivalirudin Injection	36					
		3M	Mean	30	60	53
			SD	8.9	13.4	14.2
			N	10	10	10
	100					
		4M	Mean	32	68	61
			SD	12.0	12.0	12.9
			N	10	10	10
	258					
		5M	Mean	21	67	62
			SD	25.7	10.5	13.1
			N	10	8	8
Sandoz bivalirudin 258						
		6M	Mean	30	55	51
			SD	11.6	19.6	19.5
			N	10	9	9

Bodyweight: females

The drug-treated females gained slightly less than the control groups in the first seven days but were similar to the mean gain reported for the comparator group. Over the 14 days of the study there appears to be a dose-related effect for mean weight gain.

group		Group /Sex		Change 1-7	Change 1-14	Change 1-15
Negative control		Statistics test		Sh	Wi	Wi
		1F	Mean	10	26	24
			SD	14.5	9.8	8.9
Vehicle control			N	10	9	9
		2F	Mean	14	31	27
			SD	10.0	13.6	16.6
MAIA Bivalirudin Injection	36		N	10	10	10
		3F	Mean	9*	28	23
	100		SD	4.4	6.4	5.3
			N	10	10	10
	258	4F	Mean	6*	24	20
			SD	10.1	9.9	8.8
			N	10	10	10
Sandoz bivalirudin 258		5F	Mean	7*	23	22
			SD	6.4	14.8	12.0
			N	10	10	10
		6F	Mean	6	21	19
			SD	5.6	7.4	7.0
			N	10	10	10

Hematology

Both males and females showed slight increase in absolute reticulocyte counts. If more than normal variability, this may reflect blood loss. There were no changes in total white blood cell counts and no apparent changes within the differentials. There were minor fluctuations in the hematology data without a dose-response relationship that may have been reflective of inflammation or infection associated with the catheters.

		males		females	
		RBC x10^6/uL	RETIC x10^9/L	RBC x10^6/uL	RETIC x10^9/L
Negative control	Mean	7.93*	251.9	7.57	172.1
	SD	0.271	57.21	0.474	46.11
	N	10	10	7	7
Vehicle control	Mean	8.28	282.0	8.05	185.9
	SD	0.431	65.91	0.398	36.87
	N	10	10	10	10
MAIA 36 mg/kg	Mean	8.34	271.3	7.75	257.7
	SD	0.329	39.70	1.074	111.21
	N	9	9	9	9
MAIA 100 mg/kg	Mean	8.20	273.9	7.84	227.5
	SD	0.389	38.20	0.462	50.99
	N	9	9	8	8
MAIA 250 mg/kg	Mean	8.05	305.0	7.56	251.2*
	SD	0.452	26.40	0.583	73.58
	N	5	5	10	10
Sandoz 250 mg/kg	Mean	7.95	303.5	8.00	209.8
	SD	0.380	92.40	0.439	54.01
	N	9	9	9	9

Clinical Chemistry

Both sexes of rats showed decreases in serum glucose at 100 mg/kg and 250 mg/kg. Both changes were statistically significant at $p<0.05$ and $p<0.01$ respectively in males. Only the change at the high dose was statistically significant in the females.

Dose Group	Negative Control	Vehicle Control	MAIA Bivalirudin Injection			Sandoz Bivalirudin Injection
Dose (mg/kg/day)	1	2	3	4	5	6
			36	100	~258	~258

Group /Sex	T	GLU mg/dL	Group /Sex	GLU mg/dL
1M	Mean	88	1F	85
	SD	10.3		4.5
	N	10		7
2M	Mean	92	2F	84
	SD	9.4		9.0
	N	10		9
3M	Mean	84	3F	75
	SD	9.8		10.7
	N	10		9
4M	Mean	80*	4F	79
	SD	14.2		10.8
	N	10		8
5M	Mean	68**	5F	73*$
	SD	7.6		10.0
	N	7		9
6M	Mean	61	6F	82
	SD	6.5		7.0
	N	7		8

Appears this way on original

Coagulation

Prothrombin time (PT) and activated partial thromboplastin time (APTT) were unaffected in samples collected 24 hours after dosing. Thrombin time, as expected from the pharmacology, was increased in males. Thrombin time was not increased in females, perhaps indicating a difference in metabolism between male and female rats.

	Negative Control	Vehicle Control	MAIA Bivalirudin Injection			Sandoz Bivalirudin Injection
Dose Group	1	2	3	4	5	6
Dose (mg/kg/day)			36	100	~258	~258

Group /Sex		Occasion Termination	PT Seconds	APTT Seconds	TT Seconds
1F	Mean		17.0	15.9	28.5
	SD		0.29	1.60	2.87
	N		4	4	4
2F	Mean		16.7	15.1	28.0
	SD		0.78	1.18	2.37
	N		8	9	8
3F	Mean		16.3	16.0	28.0
	SD		1.56	1.85	2.18
	N		10	10	10
4F	Mean		17.1	14.5	27.0
	SD		3.92	2.31	2.57
	N		7	7	7
5F	Mean		15.2**	16.6$	28.7
	SD		0.69	1.30	1.59
	N		9	9	9
6F	Mean		15.1	18.7	31.0
	SD		0.69	1.59	2.54
	N		8	7	5

Group /Sex		Occasion Termination	PT Seconds	APTT Seconds	TT Seconds
1M	Mean		17.8	14.1	28.5
	SD		1.38	1.41	1.58
	N		8	8	8
2M	Mean		17.4	15.4	27.9
	SD		0.67	1.67	3.30
	N		9	9	9
3M	Mean		17.0	16.6	30.9*
	SD		0.93	0.84	2.48
	N		7	7	7
4M	Mean		16.4	15.8	30.9*
	SD		0.70	0.83	1.24
	N		6	6	4
5M	Mean		16.3	16.8	32.3**
	SD		0.40	1.45	1.36
	N		4	4	4
6M	Mean		15.8	16.7	29.7
	SD		0.66	2.18	1.60
	N		8	8	5

The sponsor proposed that due to the short half-life, it is common for coagulation parameters to return to normal within an hour after removal of the test article. Therefore, seeing little to no effect 24 hours after stopping the infusion was not unexpected. To determine whether bivalirudin remained active as administered, residual plasma from the 5-minute toxicokinetic samples was analyzed for coagulation parameters.

A second report, 8 pages, contained final coagulation data. For each parameter, PT, APTT, and TT, the bivalirudin injection shows a dose response effect on coagulation with results similar to the effect reported for the comparator compound. The sponsor's summary of results may be seen below.

Day 15, 5 minute coagulation								
Dose group		males			female			
		PT Seconds	APTT Seconds	TT Seconds	PT Seconds	APTT Seconds	TT Seconds	
Negative control	Mean	16.3	18.9	25.0	16.0	16.0	26.1	
	SD	0.51	6.18	0.28	0.64	1.27	1.13	
	N	3	3	2	3	3	2	
Vehicle control	Mean	17.7	15.3	26.9	15.8	14.5	25.3	
	SD	0.95	1.27	0.64	0.76	1.47	0.72	
	N	3	3	3	3	3	3	
Maia 36 Mg/kg	Mean	24.4**	30.0*	111.7**	20.3**	24.4	97.3**	
	SD	3.15	6.22	19.13	0.84	7.80	32.45	
	N	3	3	3	3	3	3	
Maia 100 mg/kg	Mean	28.3**	33.0*	154.4**	23.3**	40.0**	166.6**	
	SD	2.76	7.03	17.68	1.90	6.96	30.90	
	N	3	3	2	3	3	2	
Maia 258 mg/kg	Mean	55.1**	63.7**	206.0**	39.8**	57.8**	242.2**	
	SD	8.59	9.77					
	N	3	3	1	1	1	1	
Sandoz 258 mg/kg	Mean	49.4	57.7	197.6	41.3	65.7		
	SD	0.07	9.33	16.12	1.20			
	N	2	2	2	2	1		
* p<0.05 for Group 2 to 3, 4, 5 and Group 1 to 2 comparisons								
** p<0.01 for Group 2 to 3, 4, 5 and Group 1 to 2 comparisons								
$ p<0.05 for Group 5 to 6 comparison								
$$ p<0.01 for Group 5 to 6 comparison								

Organ weight data
No findings of toxicological significance.

Histopathology
The pathologist listed axillary, mesenteric, medial iliac, mediastinal, thymic, and tracheobronchial lymph nodes as having been examined as well as thymus, Peyer's patches and gut associated lymphoid tissue (GALT) in the standard list of tissues collected. There were no findings of toxicological significance in the data as reported.

Toxicokinetics

The plasma concentrations of bivalirudin were quantifiable at the first sampling time (5 minutes after dosing on day 15) for all animals but one. This animal was a female in the 250 mg/kg/day group.

Only 7 of 23 samples taken at 24 hours contained quantifiable amounts of bivalirudin (Range: 50.5-159 ng/ml). Females showed approximately 25% lower mean C5 values as compared to males receiving the same dose of MAIA bivalirudin or the Sandoz comparator.

Bivalirudin dose level (mg/kg/day)	Mean C_5 (ng/mL) Day 15		C_5/D [(ng/mL)/(mg/kg)] Day 15	
	Males	Females	Males	Females
36 (MAIA)	961 ± 283	593 ± 88	26.7	16.5
100 (MAIA)	2500 ± 200	1800 ± 300	25.0	18.0
~258 (MAIA)	7240 ± 120	5360*	28.1	20.8*
~258 (Sandoz)	7270**	6700**, ***	28.2**	26.0**, ***

*Based on one animal.
**Based on two animals.
***Data from animal 6633 are not included in the mean as the value was considered an outlier (the mean is 4467 if animal 6633 is included).

Incurred sample reanalysis was found on page 518. Nine out of the 68 study samples that were analyzed for bivalirudin were selected for ISR.

Table 1. Samples Selected from MAIA Study No. BS92RH for the ISR Evaluation of Method BTM-2218-R0 for Bivalirudin in Rat Plasma

Sample #	Treatment ID	Subject	Day Nominal	Nominal Time (min)
1	G3	3063	15	5
2	G3	3571	15	5
3	G3	3575	15	5
4	G4	4085	15	5
5	G4	4594	15	5
6	G5	5102	15	5
7	G5	5107	15	5
8	G6	6121	15	5
9	G6	6631	15	5

ACCEPTANCE CRITERIA OF ISR ANALYSIS

The percent difference (%Diff) of the result of the ISR analysis compared with that of the original analysis will be calculated as follows:

%Diff = (Repeat - Original)/(Mean of Original and Repeat) x 100

Acceptance Criterion: %Diff of at least 2/3 of all of the ISR samples should be within ±20%.

One sample of the nine did not meet acceptance criteria.

Table 8. ISR Results for Bivalirudin

Sample No.	Animal No.	Treatment Group	Day Nominal	Hour Nominal	Bivalirudin Concentration, ng/mL			%Difference
					Original Value	Repeat Value	Mean Value*	
1	3063	G3	15	0.08333	697	650	674	-7.0
2	3571	G3	15	0.08333	667	618	643	-7.6
3	3575	G3	15	0.08333	616	579	598	-6.2
4	4085	G4	15	0.08333	2730	2550	2640	-6.8
5	4594	G4	15	0.08333	2080	2150	2120	3.3
6	5102	G5	15	0.08333	7100	8960	8030	23.2
7	5107	G5	15	0.08333	7300	8790	8050	18.5
8	6121	G6	15	0.08333	7300	6920	7110	-5.3
9	6631	G6	15	0.08333	6650	6710	6680	0.9

ISR: Incurred Sample Reproducibility
*Mean value of original value and the repeat value.

Table 9. Performance of Bivalirudin QC Samples from the ISR Batch Run

Watson Run ID	QC Low 150 ng/mL	%Bias	QC Mid 5000 ng/mL	%Bias	QC High 19000 ng/mL	%Bias
3	151	0.7	5670	13.4	19200	1.1
	158	5.3	5390	7.8	18200	-4.2

Table 10. Performance of Bivalirudin Calibration Standards from the ISR Batch Run

Watson Run ID	Std 1 50.0 ng/mL	Std 2 100 ng/mL	Std 3 400 ng/mL	Std 4 2000 ng/mL	Std 5 10000 ng/mL	Std 6 15000 ng/mL	Std 7 20000 ng/mL	Std 8 25000 ng/mL
3	50.9	55.5*	342	2020	9940	15300	20900	26400
%Bias	1.8	NA	-14.5	1.0	-0.6	2.0	4.5	5.6

*Value was out of acceptance criteria and was excluded from the regression analysis.

Table 11. Calibration Curve Parameters of the ISR Batch Run for Bivalirudin

Watson Run ID	Slope	Intercept	Coefficient of Determination, R^2
3	0.000241	-0.009290	0.9952

9 Reproductive and Developmental Toxicology

Reproduction studies have been performed in rats at subcutaneous doses up to 150 mg/kg/day (1.6 times the maximum recommended human dose based on body surface area) and rabbits at subcutaneous doses up to 150 mg/kg/day (3.2 times the maximum recommended human dose based on body surface area). These studies revealed no evidence of impaired fertility or harm to the fetus attributable to bivalirudin. At doses of 500 mg/kg/day given subcutaneously to rats, litter sizes and live fetuses were reduced. Fetal skeletal variations were also reduced. Maternal toxicity was also noted at this dose.

10 Special Toxicology Studies

10.1 In vitro comparison of hemolysis induced by test and reference formulations of bivalirudin for injection in human whole blood

Conducting laboratory and location: (b) (4)

Study number(s): (b) (4) # NT46SB, MAIA # MAIA-BVN-17-TOX-003
Experimental start date: October 9, 2017
Drug lot number: AJZ603, 85.9% (4.3mg/ml of bivalirudin containing about (b) (4)% of degradants)
Vehicle: 0.8mg/ml sodium acetate USP, 100 mg/ml polyethylene glycol 400, glacial acetic acid or sodium hydroxide for pH adjustment to pH5.25±0.25 and water for injection, q. s., to 1 ml.

GLP compliance: Yes
QA statement: Yes

Purpose: To compare the hemolytic potential of a bivalirudin for injection in human(single donor) whole blood and determine if there were detectable differences compared to a formulation of Angiomax.

The concentration used, in the sponsor's words:

The *in vitro* hemolysis study was conducted using MAIA Bivalirudin Injection (Test Drug) at a concentration of 5 mg/mL. The testing was conducted by mixing whole human blood with drug product at 5 mg/mL in the ratio of 1 mL of blood to 0.75 mL of drug product. Thus, the drug product used "neat", and not diluted prior to use in the study. The final concentration of bivalirudin in the blood-drug product mixture was 2.14 mg/mL (5 mg/mL * 0.75 mL/1.75 mL = 2.14 mg/mL).

The goal was to achieve a final bivalirudin concentration that is approximately 2-fold higher than the theoretical in vivo worst case after adjusting for blood flow at the point of injection.

Table 1: Drug Product Dosing, the Blood:Drug Product Ratio, and Calculated Bivalirudin Concentrations for a Worst Case (150 kg) Patient

Dosing/Study	Drug Administration Rate	Worst Case Blood Flow Rate	Blood:Product Ratio	Bivalirudin Concentration
Bolus	22.5 mL/3 min = 7.5 mL/min	28 mL/min	28:7.5 = 1:0.27	1.06 mg/mL*
Continuous Infusion during PCI	52.5 mL/hour (0.875 mL/min)	28 mL/min	10:0.875 = 1:0.0.0875	0.15 mg/mL*
In vitro hemolysis study (NT46SB)	[redacted]	[redacted]	1:0.75	2.14 mg/mL
Pharmacokinetics	Peak concentration after bolus = 3.2±0.7 µM (7.0±1.5 µg/mL)			

* Calculated as $(5 \times R_{inj})/(R_{inj} + Q_v)$

The justification above was discussed with the Agency during the Pre-NDA Meeting and found acceptable by the Agency (see **Nonclinical Question #1 of the Pre-NDA Meeting Minutes**).

Blood was mixed with either bivalirudin injection, Angiomax, vehicle or saline. Saponin (1%) was used as the positive control. Tubes were incubated at 37ºC for 30 minutes. Each sample was tested in triplicate. Tubes were then centrifuged and the supernatant tested for hemoglobin.

Calculation of hemolytic potential: Hemoglobin (Hb) concentration was determined by the Siemens Advia 120 in g/dl.

$$\% \text{ hemolysis} = \frac{(\text{Hb test sample} \times \text{dilution factor})}{(\text{Hb of donor})} \text{ x } 100$$

Sponsor's Summary of Hemolysis Results

Treatment	Replicate	Tube ID	Corrected Hb	% Hemolysis
Test Item 1:0.750 (Bivalirudin Injection)	1	101	0.0	0.0
	2	201	0.0	0.0
	3	301	0.0	0.0
Reference Item 1:0.750 (ANGIOMAX)	1	102	0.0	0.0
	2	202	0.0	0.0
	3	302	0.0	0.0
Test Item Vehicle 1:0.750 (Bivalirudin Injection Placebo)	1	103	0.0	0.0
	2	203	0.0	0.0
	3	303	0.0	0.0
Negative Control for hemolysis 1 (Saline)	1	104	0.0	0.0
	2	204	0.0	0.0
	3	304	0.0	0.0
Negative Control for hemolysis 2 (Whole blood only)	1	105	0.0	0.0
	2	205	0.0	0.0
	3	305	0.0	0.0
Positive Control for hemolysis (1% saponin)	1	106	7.4	99.1
	2	206	7.5	100.4
	3	306	7.5	100.4

11 Integrated Summary and Safety Evaluation

Brief Background / Introduction

Maia Pharmaceuticals has submitted a new drug application for bivalirudin injection, 5 mg/ml as a 505(b)(2) application. This relies on the findings of safety and efficacy for the listed drug Angiomax(bivalirudin) for injection, approved as NDA 020873. The reference drug is a lyophilized drug product that must be reconstituted for use and then diluted for injection. The proposed drug is a ready to use (RTU) formulation.

Pharmacology

The drug is a 20 amino acid peptide analog of hirudin. This consists of the hirudin active site-binding domain and the fibrinogen-binding domain linked by four glycine residues. Both binding sites must be present for the peptide to have activity. Bivalirudin is an anticoagulant with reversible, direct thrombin activity. Bivalirudin binds both the catalytic site of thrombin and the fibrinogen-binding site. It has also been noted that bivalirudin can bind both soluble(free) and clot-bound (fibrin-bound) thrombin.

Toxicology

There were no findings of toxicological significance in the studies presented. The effects in the repeat dose rat study appear to be related to exaggerated pharmacology or technical difficulties with the catheters.

(b) (4)

The use of a lot of bivalirudin subject to accelerated degradation did not produce new toxicity signals when administered continuously for 14 days and compared to the Sandoz product.

Immunogenicity was considered in several ways. The following components suggest that there was no discernible immunogenic reaction from a nonclinical perspective:

1. No effects in the hematology or differential data.
2. No apparent effects in the clinical chemistry (e.g., altered albumin to globulin ratio)
3. Histopathology. The pathologist listed axillary, mesenteric, medial iliac, mediastinal, thymic, and tracheobronchial lymph nodes as having been examined as well as thymus, Peyer's patches and gut associated lymphoid tissue (GALT) in the standard list of tissues collected. There were no findings of toxicological significance in the data as reported.

4. Toxicokinetics. A dose-proportional increase in exposure across dose groups. At the highest dose, the C5 (Concentration at 5 minutes) was very similar to the C5 for the Sandoz comparator drug. The majority of samples collected at 24 hours had no detectable bivalirudin, consistent with the expected short half-life.

5. Pharmacologic activity of the drug was apparent in the prolongation of coagulation parameters. This was determined in the auxillary coagulation study using residual plasma from the toxicokinetic study, collected at the 5minute time point.
6. Incurred sample reanalysis was within the prespecified parameters for acceptability.

Conclusions

The sponsor performed a repeat dose rat study and in vitro hemolysis with drug substance in which accelerated degradation had been deliberately achieved. This was to simulate a worst case scenario of degradation at the end of the usable shelf-life. The CMC reviewer raised a question about the potential for the degradation products to be immunogenic. Based upon the material presented in the repeat dose rat study with toxicokinetics, there was no discernible difference between the Maia bivalirudin and the Sandoz comparator. From the nonclinical perspective, there was no discernible difference from the comparator Angiomax product in the material provided with respect to any detectable immunogenic response.

12 References

Warkentin TE and A Koster 2005. Bivalirudin: a review.Expert Opinion on Pharmacotherapy 6:8,1349-1371,DOI:10.1517/14656566.6.8.1349.

Human Medicine European public assessment report (EPAR):Angiox
https://www.ema.europa.eu/en/medicines/human/EPAR/angiox
(accessed February 7, 2019).

13 Appendix/Attachments

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ELIZABETH A HAUSNER
02/20/2019 03:17:40 PM

XUAN CHI
02/20/2019 03:20:21 PM