

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-873

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 20-873 SUPPL #
Trade Name Angiomax™ Generic Name bivalirudin

Applicant Name The Medicines Company HFD- 180
Approval Date December 15, 2000

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/ X / NO / /

b) Is it an effectiveness supplement? YES / / NO / X /

If yes, what type(SE1, SE2, etc.)?

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / X / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / X / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? 5
Years.

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / / NO / /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No – Please indicate as such).

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA =

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA =

NDA =

NDA =

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II. Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / ___ / NO / ___ /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / ___ / NO / ___ /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / ___ / NOT ___ /

If yes, explain:

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / ___ / NO / ___ /

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product. i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES / ___ / NO / ___ /

Investigation #2 YES / ___ / NO / ___ /

Investigation #3 YES / ___ / NO / ___ /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES / ___ / NO / ___ /

Investigation #2 YES / ___ / NO / ___ /

Investigation #3 YES / ___ / NO / ___ /

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND = ___ YES / ___ / ! NO / ___ / Explain: _____

Investigation #2 !
IND = ___ YES / ___ / ! NO / ___ / Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
YES ___ / Explain _____ ! NO / ___ / Explain _____

Investigation #2

YES / ___ / Explain _____ ! NO / ___ / Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study?
(Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / ___ / NO / ___ /

If yes, explain: _____

Signature of Preparer
Title: Regulatory Health Project Manager

Date

Signature of Office of Division Director

Date

NDA 20-873
Hirulog[®] (bivalirudin) Injection
Section 2 - Draft Labeling

13.0 PATENT INFORMATION

U.S. Patent Number: 5,196,404

Date of Issue: March 23, 1993

Patent Owner: The Medicines Company

The statement of the patent attorney and the relevant sections of the patent are provided in this section.

NDA 20-873

Hirulog[®] (bivalirudin) Injection

Section 2 - Draft Labeling

14.0 PATENT CERTIFICATION

In accordance with 21 CFR §314.50(I) this section is not applicable as this is not a 505(b)(2) application.

HALE AND DORR LLP
COUNSELLORS AT LAW

60 STATE STREET, BOSTON, MASSACHUSETTS 02109
617-526-6000 • FAX 617-526-3000

WAYNE A. KROWN, PH.D.

617-526-6030
wayne.krown@haldorr.com

3 December 1997

VIA FACSIMILE

Mr. Tom Lategan
The Medicines Company
One Cambridge Center
Cambridge, MA 02142

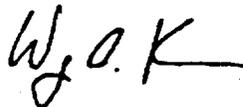
Re: Patent claims covering Hirulog™

Dear Tom:

As you requested, I reviewed the structure of Hirulog™, as set forth in your Investigators Brochure, as well as the specification and claims of U.S. Patent No. 5,196,404, which is exclusively licensed to The Medicines Company. Based upon this review and my conversation with you concerning dosing and mechanism, I conclude that your Hirulog™ formulation, as a composition of matter, is covered by claims 1-6, 9, 13, 14, 16 and 21 of U.S. Patent No. 5,196,404.

Please call me if you have any further questions about this matter.

Sincerely,



WASHINGTON, DC

BOSTON, MA

LONDON, UK*

HALE AND DORR LLP INCLUDES PROFESSIONAL CORPORATIONS
*BONICK HALE AND DORR INTERNATIONAL (AN INDEPENDENT JOINT VENTURE LAW FIRM)

NDA 20-873

Hirulog® (bivalirudin) Injection

Section 2 - Draft Labeling

16.0 DEBARMENT CERTIFICATION

The following is the debarment statement provided by The Medicines Company.



THE MEDICINES COMPANY

DEBARMENT CERTIFICATION

On behalf of the Medicines Company, I hereby certify that we did not and will not use in any capacity the services of an individual, partnership, corporation, or association debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug and Cosmetic Act in connection with NDA 20-873 for Hirulog ®(bivalirudin).

Clive Meanwell, M.D.
The Medicines Company

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 20873 Trade Name: HIRULOG(BIVALIRUDIN)250MG IV/IV INFUSION
Supplement Number: Generic Name: BIVALIRUDIN
Supplement Type: Dosage Form: INJ
Regulatory Action: NA Proposed Indication: Anticoagulant in patients undergoing percutaneous transluminal coronary angioplasty.

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission?

 NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Status
Formulation Status
Studies Needed
Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
11/10/98 Studies needed: None.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER,
JULIEANN DUBEAU

Signature JS

Date 11/10/98

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 20873 **Trade Name:** HIRULOG(BIVALIRUDIN)250MG IV/IV INFUSION

Supplement Number: **Generic Name:** BIVALIRUDIN

Supplement Type: **Dosage Form:** INJ

Regulatory Action: AE **Proposed Indication:** Anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA).

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

 NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Does Not Apply
Formulation Status
Studies Needed
Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

11/10/98 Studies needed: None. 10/28/99 Requested in action letter that the firm submit their pediatric drug development plan or request a waiver with supporting information and documents.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JULIEANN DUBEAU

Signature JS/ _____ Date 10/28/99

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 20873 Trade Name: HIRULOG(BIVALIRUDIN)250MG IV/IV INFUSION
Supplement Number: Generic Name: BIVALIRUDIN
Supplement Type: Dosage Form: INJ
Regulatory Action: AE Proposed Indication: Anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA).

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

 NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Does Not Apply
Formulation Status
Studies Needed
Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

11/10/98 Studies needed: None. 10/28/99 Requested in action letter that the firm submit their pediatric drug development plan or request a waiver with supporting information and documents. 4/24/00 Firm requested a waiver of pediatric studies for all age groups in a submission dated 11/11/99. Waiver granted. See M.O. review dated 2/8/00.

4/24/00 Firm requested a waiver for all age groups. Waiver granted.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JULIEANN DUBEAU

Signature

/s/

Date

4/24/00

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: 020873 Trade Name: ANGIOMAX 250MG IV/IV
Supplement Number: 000 Generic Name: BIVALIRUDIN
Supplement Type: N Dosage Form:
Regulatory Action: NA COMIS Indication: AS AN ANTICOAGULANT FOR PATIENTS UNDERGOING TRANSLUMINAL CORONARY ANGIOPLASTY PROCEDURES
Action Date: 11/18/98

Indication # 1 Anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA).

Label Adequacy: Does Not Apply

Formulation Needed: NO NEW FORMULATION is needed

Comments (if any): 11/14/00: Firm requested a waiver of pediatric studies for all age groups in a submission dated 11/11/99. Waiver granted. See Medical Officer review dated 2/8/00.

Lower Range	Upper Range	Status	Date
0 months	16 years	Waived	

Comments: The sponsor's request for waiver of the pediatric assessment requirement is reasonable as this indication is almost exclusively applicable to only the adult population (see 2/8/00 M.O. review).

This page was last edited on 11/14/00

Signature: *IS/*

November 14, 2000
Date

G. ESTABLISHMENT INSPECTION: ACCEPTABLE

14-NOV-2000

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Page 1 of 2

Application: NDA 20873/000	Priority: 1S	Org Code: 180
Stamp: 23-DEC-1997 Regulatory Due: 17-JAN-2001	Action Goal:	District Goal:
Applicant: THE MEDICINES COMPANY	Brand Name: ANGIOMAX 250MG IV/IV	Established Name:
1 CAMBRIDGE CENTER STE 407	Generic Name: BIVALIRUDIN	Dosage Form: INJ (INJECTION)
CAMBRIDGE, MA 02142	Strength: 250 MG	
<hr/>		
FDA Contacts: J. DUBEAU (HFD-180) 301-827-7310 , Project Manager		
A. SHAW (HFD-180) 301-827-7310 , Review Chemist		
E. DUFFY (HFD-150) 301-594-5765 , Team Leader		

Overall Recommendation:

ACCEPTABLE on 14-NOV-2000 by M. GARCIA (HFD-322) 301-594-0095
WITHHOLD on 09-MAY-2000 by M. GARCIA (HFD-322) 301-594-0095
WITHHOLD on 07-DEC-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: _____

DMF No:
AADA No:

Profile: SVS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-NOV-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: _____

Establishment: _____

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-OCT-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: _____

Establishment: _____

DMF No:
AADA No:

Profile: CTL OAI Status: NONE

Responsibilities: _____

Last Milestone: **OC RECOMMENDATION**
Milestone Date: **14-NOV-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: _____

DMF No: _____
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **31-OCT-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON FILE REVIEW**

Responsibilities: _____

H. LIST OF CHEMISTRY DEFICIENCIES AND COMMENTS None

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELECON

DATE: December 14, 2000

APPLICATION NUMBER: NDA 20-873, Angiomax™ (bivalirudin) Injection

BETWEEN:

Name: Ms. S. Loar; Senior Director, Regulatory Affairs
Phone: (617) 225-9099
Representing: The Medicines Company (TMC)

AND

Name: Ms. J. DuBeau, Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Revision of timeframe for submission of final report of postmarketing commitment study

BACKGROUND: In a December 1, 2000, letter to the Agency, TMC committed (postmarketing) to completing Study TMC 98-10 entitled "Anticoagulant Therapy with Bivalirudin to Assist in the Performance of Percutaneous Coronary Intervention in Patients with Heparin-Induced Thrombocytopenia. An Open Label Study of Bivalirudin for Heparin-Induced Thrombocytopenia (HIT) or Heparin-Induced Thrombocytopenia and Thrombosis Syndrome (HITTS)" and submitting the full report for that study. However, there was no date identified for submitting the final study report. The firm initially committed to submitting the final study report within 54 months of approval.

TODAY'S PHONE CALL: Ms. Loar was called and requested to commit to submitting the final study report within 36 months of approval. The firm agreed and the call was then concluded.

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager

MEMORANDUM OF MEETING MINUTES

Meeting Date: December 12, 2000
Time: 9:00 AM – 9:30 AM
Location: Parklawn Building, Room 6B-45
Sponsor: The Medicines Company
Application: NDA 20-873; Angiomax™ (bivalirudin) Injection
Proposed Indication: Anticoagulant in conjunction with aspirin in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA).
Type of Meeting: Pre-Approval Safety Conference between the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) and the Office of Post-Marketing Drug Risk Assessment (OPDRA) (Division of Drug Risk Evaluation II) (HFD-440)
Meeting Chair: Dr. Lilia Talarico; Division Director
Meeting Recorder: Ms. Julieann DuBeau; Regulatory Health Project Manager

Review Division Attendees/Titles:

Dr. L. Talarico; Division Director
Dr. K. Robie-Suh; Hematology Team Leader
Ms. J. DuBeau; Regulatory Health Project Manager

OPDRA Attendees/Titles:

Dr. K. Uhl; Acting Division II Director
Ms. A. Corken; Safety Evaluator
Ms. M. Dempsey; Project Manager

Division of Drug Marketing, Advertising, and Communications Attendee/Title:

Ms. P. Staub; Reviewer

Meeting Objectives:

To provide a routine, formal mechanism for communications between the Office of Drug Evaluation (ODE) review divisions and the Office of Post-Marketing Drug Risk Assessment (OPDRA) risk evaluation divisions prior to approval of a new chemical entity (NCE) or certain other applications in order to:

1. Ensure that OPDRA is aware of potential post-marketing safety problems of drugs about to be approved,
2. Consider, jointly, the need for any special post-marketing analyses or post-marketing safety studies or other evaluations to be implemented by or agreed to by the sponsor prior to the

approval of a drug product, and

3. Determine if there is any special information or feedback that the ODE review division would like from the OPDRA risk evaluation division during the immediate post-launch life of the soon-to-be-approved drug product.

Discussion Points:

In the NDA database, there are approximately 2,600 patients who have received Angiomax™ for PTCA and about 2,800 patients who have received Angiomax™ for other indications [such as acute myocardial infarction (HERO-2 trial)].

Bleeding Adverse Events

Angiomax™ had fewer total bleeding adverse events and fewer major bleeding adverse events compared with heparin in controlled clinical trials in PTCA. However, the majority of the clinical trials were completed prior to 1995 using heparin regimens, which may have been more aggressive than is the current standard of care. Ongoing studies continue to suggest less bleeding with Angiomax™ than with the heparin comparator.

Other Issues

Angiomax™ has a relatively short half-life (25 minutes to 3.5 hours, depending on renal function). There is no antidote for the drug product and it is not antigenic.

Post-Marketing Commitment

The firm has committed to completing Study TMC 98-10 entitled "Anticoagulant Therapy with Bivalirudin to Assist in the Performance of Percutaneous Coronary Intervention in Patients with Heparin-Induced Thrombocytopenia: An Open Label Study of Bivalirudin for Heparin-Induced Thrombocytopenia (HIT) or Heparin-Induced Thrombocytopenia and Thrombosis Syndrome (HITTS)" and submitting the full report for that study.

Action Items:

None.

Minutes Preparer: _____

Chair Concurrence: _____

MEMORANDUM OF TELECON

DATE: December 11, 2000

APPLICATION NUMBER: NDA 20-873, Angiomax™ (bivalirudin) Injection

BETWEEN:

Name: Ms. S. Loar, Senior Director, Regulatory Affairs

Phone: (617) 225-9099

Representing: The Medicines Company (TMC)

AND

Name: Ms. J. DuBeau, Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Timeframe for submission of final report of postmarketing commitment study

BACKGROUND: In a December 1, 2000, letter to the Agency, TMC committed (postmarketing) to completing Study TMC 98-10 entitled "Anticoagulant Therapy with Bivalirudin to Assist in the Performance of Percutaneous Coronary Intervention in Patients with Heparin-Induced Thrombocytopenia: An Open Label Study of Bivalirudin for Heparin-Induced Thrombocytopenia (HIT) or Heparin-Induced Thrombocytopenia and Thrombosis Syndrome (HITTS)" and submitting the full report for that study. However, there was no date identified for submitting the final study report.

TODAY'S PHONE CALL: Ms. Loar was called and requested to provide a timeframe in which TMC can commit to providing the final study report for the above referenced study. She stated that the final study report would be submitted within 54 months of approval. The call was then concluded.

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager

/s/

Julie DuBeau
12/11/00 01:12:26 PM
CSO

MEMORANDUM OF TELECON

DATE: December 5, 2000

APPLICATION NUMBER: NDA 20-873, Angiomax™ (bivalirudin) Injection

BETWEEN:

Name: Ms. S. Loar; Senior Director, Regulatory Affairs
Ms. J. Barton; Director, Regulatory and Scientific Affairs
Dr. C. Meanwell; CEO

Phone: (617) 225-9099

Representing: The Medicines Company

AND

Name: Ms. J. DuBeau; Regulatory Health Project Manager
Dr. L. Talarico; Division Director
Dr. V. Raczkowski; Office Deputy Director

Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Request for proprietary name change

BACKGROUND:

On November 17, 2000, per Dr. Raczkowski's request, Ms. DuBeau called Ms. Loar and requested that the firm propose a new proprietary name. Ms. DuBeau stated that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has the following concerns regarding the current proprietary name "Angiomax". (1) The term "angio" indicates a vascular use and thus, future approved indications may render this trademark misleading (2) There is a proposed efficacy claim associated with the proposed name due to the term "max", (3) The term "angio" encodes the indication and thus, adversely affects DDMAC's ability to enforce reminder advertisements under 21 CFR 202.1(e)(2)(i) and 21 CFR 201.100(f). On November 21, 2000, Ms. Loar requested a teleconference to defend the proprietary name "Angiomax" including justification (see attached November 21, 2000 correspondence from firm).

TODAY'S PHONE CALL:

Ms. Loar began the telephone conversation by stating the steps taken thus far in trademarking the name "Angiomax". In July 1999, the firm began the patent and trademark process after receiving a June 21, 1999, Agency letter stating that the name was acceptable with reservation. The process was initiated worldwide in 31 countries, 15 of which were under the European Union system. The name to date has been approved in three countries, one of which is New Zealand, where the drug product is approved. The patent and trademark office accepted the

name in September 2000. The firm is waiting for the registration certificate, at which point the proprietary name will be registered. Dr. Raczkowski reiterated the DDMAC concerns as listed in the BACKGROUND section above, and acknowledged the firm's arguments. He concluded that the proprietary name "Angiomax" may be retained; however, he stressed the importance and obligation of the firm to ensure fair balance in accordance with 21 CFR 202 when advertising. The call was then concluded.

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager

Attachment: November 21, 2000, correspondence

Dubeau

REVIEW MEMORANDUM

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

Rev

Date: May 24, 2000

From: Arthur B. Shaw, Ph.D., Review Chemist, Division of
Gastrointestinal and Coagulation Drug Products, HFD-180

/S/ 5/25/00

Through: Liang Zhou, Chemistry Team Leader, Division of
Gastrointestinal and Coagulation Drug Products, HFD-180

/S/ 5/26/00

To: NDA 20-873 BC Amendment May 17, 2000

Subject: Additional Information Request Concerning Thrombin
Inhibition Assay

During a recent inspection at Ben Venue Laboratories (BVL), the manufacturer of the finished drug product Angiomax®, the inspector noticed that data for the assay for thrombin inhibition _____ showed that some of the assay results were out of specification for individual tests. However the assay values were within specification when averaged over triplicate determinations. The applicant was asked to submit a copy of the latest version of the assay, which they did in this amendment.

In an e-mail dated May 16, 2000, the inspector, Fred Lochner wrote:

[REDACTED]

This new information can be provided as part of their response to our approvable letter dated May 11, 2000.

cc:

NDA 20-873

HFD-180/NDA 20-873

HFD-180/LTalarico

HFD-181/JDuBeau

HFD-180/LZhou

HFD-180/KRobieSuh

HFD-180/AShaw

HFR-CE4525/FLochner

Draft init. By:Lzhou 05/25/00

[REDACTED]

T 21/12/2000

MEMORANDUM OF TELECON

DATE: May 22, 2000

APPLICATION NUMBER: NDA 20-873; Angiomax™ (bivalirudin) Injection

BETWEEN:

- Name: Dr. C. Meanwell; CEO and President
- Dr. J. Villiger; Clinical Pharmacology
- Dr. J. Richards; Regulatory
- Dr. R. Robson; Consultant, Nephrologist and Clinical Pharmacologist
- Dr. D. Sica; Consultant, Clinical Pharmacologist

Phone: (617) 225-9099

Representing: The Medicines Company (TMC)

AND

- Name: Dr. L. Talarico; Division Director
- Dr. S. Doddapaneni; Biopharmaceutics Team Leader
- Mr. J. Hunt; Biopharmaceutist
- Ms. J. DuBeau; Regulatory Health Project Manager

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Firm's resubmission in response to May 11, 2000, approvable action letter

BACKGROUND:

TMC submitted a new drug application on December 23, 1997, for Angiomax™ (bivalirudin) Injection, a synthetic thrombin inhibitor. The firm received an approvable action letter on May 11, 2000, (see attached) which includes deficiencies in the following areas: biopharmaceutics; chemistry, manufacturing, and controls (CMC); and labeling. The firm requested this teleconference to discuss their planned resubmission in response to the approvable action letter, specifically the biopharmaceutics deficiencies.

TODAY'S PHONE CALL:

The firm stated that they would respond fully to items I.A., I.B., and I.C. as listed in the May 11, 2000, action letter. Regarding item I.D., the firm requested guidance on how recruitment of patients with severe renal disease undergoing angioplasty in Study No. TMC-98-09 could be expedited. Mr. Hunt suggested that the firm modify their existing TMC-98-09 protocol to allow enrollment of patients with severe renal disease not necessarily

undergoing angioplasty. The firm stated that they will amend their current protocol to allow recruitment of ten patients, mixed gender, with severe renal impairment to receive a loading dose of 1mg/kg and an infusion of .5 mg/kg/hr to steady state. The amended protocol will be faxed to the Agency for comment with an expected implementation date of early June 2000. The firm projects that the data will be analyzed and ready for submission in mid-July 2000 along with their complete response to the May 11, 2000, action letter. Dr. Talarico reminded the firm that the labeling must provide adequate information about the use of the drug in patients with renal impairment. The call was then concluded.

JS/ 6/2/00
Julfeann DuBeau, RN, MSN
Regulatory Health Project Manager

Attachment: May 11, 2000, action letter

cc: Original NDA 20-873
HFD-180/Div. File
HFD-180/DuBeau
HFD-180/Talarico
HFD-870/Hunt
HFD-870/Doddapaneni
HFD-103/Rackowski
R/d Init: Talarico 5/22/00
R/d Init: Hunt 5/23/00
R/d Init: Doddapaneni 6/1/00
JD/May 22, 2000 (drafted)

TELECON

Memorandum

Date: 9 May 2000

From: David E. Morse, Ph.D. /S/
Asc. Director (Pharm./Tox.), Office of Drug Evaluation III

To: Victor Raczkowski, M.D.
Deputy Director, Office of Drug Evaluation III

Florence Houn, M.D.
Director, Office of Drug Evaluation III

Cc: Lillia Talarico, M.D., Dir., DGCDP (HFD-180)
Jasti Choudary, Ph.D., TL Pharm./Tox., DGCDP (HFD-180)
Tim Robison, Ph.D., Pharm./Tox., DGCDP (HFD-180)

Subject: NDA 20-873
ANGIOMAX® (bivalirudin) Injection
Review of Pharm./Tox. Information and Sections of Proposed Product Label

I. Materials Included in Review

1. Pharm./Tox. Reviews of NDA 20-873, dated 27 Jul. 1998 and 14 Sept. 1999, written by Timothy W. Robison, Ph.D.
2. NDA 20-873 Approval Package, with Draft Product Labeling (dated 25 May 2000).

II. Comments Regarding the Product Label

1. Reference to the Trade name for bivalirudin (i.e., ANGIOMAX®) should be eliminated from the discussion of all non-clinical studies in the product label, unless those studies were specifically conducted with the clinical drug formulation to be marketed. All discussions of non-clinical studies conducted with other than the clinical drug formulation should make reference to the generic compound name of 'bivalirudin.'
2. Under the heading of "Carcinogenesis, Mutagenesis and Impairment of Fertility" it is recommended that:
 - reference to the "AMES" assay be revised as "in vitro bacterial cell reverse mutation assay (AMES test)" for consistency with the descriptive information included in subsequent sections of the sentence, and
 - the final sentence of the paragraph be simplified to read,
 - "Fertility and general reproductive performance in rats were unaffected by subcutaneous doses of bivalirudin up to 150 mg/kg/day, about 1.6 times the dose on a body surface area basis (mg/m²) of a 50 kg person administered the recommended dose of 15 mg/kg."
3. Under the heading of "Pregnancy Category" it is recommended that the first sentence of the paragraph be revised to read:

III. Comments and Conclusions

1. A review of the action package for NDA 20-873, ANGIOMAX® Injection, suggests that the product has been adequately evaluated in multiple non-clinical safety studies up to 1 months duration for approval of the requested indication (short-term intravenous administration immediately preceding and following [up to 24 hours] PTCA).
2. The preclinical data do not suggest of a risk of congenital malformations or other alterations to fetal growth or viability for patients administered ANGIOMAX® during or immediately preceding pregnancy. However, because animal data are not always predictive of the human response, some residual level of risk can not be excluded based on the available animal data.
3. A slight increase in the incidence of embryoletality (evident as pre- and/or post-implantation resorptions) was seen in rodents administered bivalirudin by subcutaneous injection at 500 mg/kg/day. Maternal toxicity, as evidenced by reduced weight gain during gestation, was seen in the pregnant animals and may account for aspects of the alterations in fetal mortality. Since pre-implantation and early post-implantation losses may occur prior to the recognition of human pregnancy, these endpoints are extremely difficult to study in typical clinical settings. Thus, the risk for adverse effects in humans may be inestimable except on the basis of animal data, which is suggestive of a low level of risk. A discussion of this potential reproductive risk should be included in the product label under the heading of "Impairment to Fertility" and may include reference to the effects potentially being related to maternal toxicity.

IV. Summary

A review of the action package for NDA 20-873, ANGIOMAX® Injection, suggests that the product has been adequately evaluated in multiple non-clinical safety studies for approval of the requested indication. The proposed product label, with possible revision as suggested in the preceding section, adequately reflects the safety data for this product.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: April 20, 2000

FROM: Director Division of Gastrointestinal and
Coagulation Drug Products, HFD-180 15 4-21-00

TO: NDA 20-873

THROUGH: Director, Office of Drug Evaluation III
Deputy Director, Office of Drug Evaluation III

SUBJECT: Resubmission of NDA 20-873: Anjomax (Hirulog) for
anticoagulation of patients undergoing PTCA for
Unstable Angina

Resubmission: November 11, 1999; December 20, 1999;
January 7, 2000; March 15, 2000

Background:

NDA 20-873 was initially submitted on December 23, 1997 for the approval of bivalirudin (Angiomax, Hirulog) as anticoagulant for patients undergoing PTCA for Unstable Angina (UA).

The proposed indication was based on two clinical trials of similar design, C92-304-1 and C92-304-2, entitled: 'A Multi-center, Double-blind, Randomized Study to Compare the Safety and Efficacy of BG8967 (Bivalirudin) with Heparin in Patients with Unstable Angina Undergoing Percutaneous Transluminal Coronary Angioplasty (PTCA)'.

A total of 2318 and 2354 patients were randomized to either bivalirudin or heparin in the two studies. The randomization was stratified by whether the patient had experienced an acute MI within 4 hours to 2 weeks prior to randomization. All patients received Aspirin, 325 or 300 mg/day.

The primary objective of the studies was to demonstrate the superiority of bivalirudin compared to heparin in preventing thrombotic complications in patients with UA undergoing PTCA. Efficacy was determined by the composite endpoint of 'procedural failure', defined as the occurrence of any of the following events during hospitalization:

- Death
- Documented MI, not present on admission, confirmed by at least 2 of the following criteria: angina >30 minutes, CK or CPK \geq UNL and CK-MB $>4\%$, new Q-wave or LBBS

- Clinical cardiac changes requiring revascularization (PTCA or CABG) or placement of IABP
- Angiographic evidence of decreased coronary blood flow (Established closure TIMI 0-1 or Impending Closure TIMI 0-2)

Secondary efficacy endpoints were:

- Incidence of each individual components of procedural failure
- Incidence of procedural failure in patients receiving heparin within 1 hour prior to study drug;
- Clinical events (death, MI, need for angiography, need for revascularization, need for re-hospitalization due to ischemic symptoms, evidence of restenosis).

Treatment group differences for rates of procedural failure were analyzed using the likelihood ratio test for logistic regression adjusted for site, post-MI, age, multi-vessel disease, degree of stenosis and treatment.

Safety was assessed primarily in terms of clinically significant bleeding.

NDA 20-873 has undergone three review cycles. The following review addresses primarily the third and latest submission dated 11/11/99. The initial review of NDA 20-873 and the subsequent re-submission cycles are briefly summarized in this review. Additional information on the initial submission and on the re-submissions is provided by the medical reviews by Dr. Kathy Robie-Suh dated 10/5/1998, 9/25/1999, and 2/3/2000; by the statistical reviews by Dr. Mushfiqur Rashid dated 10/2/1998, 10/13/1999, 3/15/2000; and by my secondary review memorandum dated 10/13/1999.

Initial Submission (December 23, 1997):

The efficacy data from the pivotal clinical trials failed to show the anticipated superior efficacy of bivalirudin over heparin in the overall patient population. No statistically significant difference between treatment groups was observed for the overall population in both studies. Lower incidence of procedural failure was observed in the post-MI population in both studies, which achieved statistical significance only in study C92-304-2.

The results are summarized in the following table.

Incidence of procedural failure

Study	Patients (n) Total		No. Procedural Failure (%)		Total No. Post MI Patients (%)		No. Post-MI Procedural Failure (%)	
	Hir.	Hep.	Hir.	Hep.	Hir.	Hep.	Hir.	Hep.
C92-304-1	1071	1060	77 (7.2)	90 (8.5)	206 (19)	203 (19)	10 (4.9)	18 (8.9)
C92-304-2	1091	1090	83 (7.6)	87 (8.0)	163 (15)	169 (16)	9* (5.5)	22* (13.0)

*p-value - 0.017

In both pivotal studies, more than 60% of patients received heparin up to one hour prior to study drug and more than 40% of patients continued heparin for longer than 12 hours. Approximately 25% of patients received open-label heparin after discontinuation of study drug, mostly within 8 hours from discontinuation of study drug and for longer than 12 hours.

The incidence of any bleeding and of major bleeding was significantly lower in the bivalirudin group (p=0.0001) compared with the heparin group.

On 10-23-199, the NDA was presented at a Cardiorenal Advisory Committee meeting. The issues discussed in great detail by the Committee members included the appropriateness of the heparin regimen used in the studies compared to that currently used for PTCA, particularly in regard to the observed difference in hemorrhagic complications; the potential confounding role of the non-study heparin administered before and after PTCA; and inability to clearly determine non-inferiority of bivalirudin to the comparator unfractionated heparin.

The Advisory Committee voted 5 to 3 against approval of bivalirudin for the requested indication.

On November 18, 1998, the sponsor was issued a non-approval letter for NDA 20-873 citing, beside other non-clinical deficiencies, the failure to demonstrate the benefit of bivalirudin over heparin for the primary efficacy endpoint of procedural failure. The sponsor was advised to conduct another study to confirm the efficacy and safety superiority of bivalirudin compared to heparin in post-MI patients undergoing PTCA. The lower incidence of bleeding complications observed in the bivalirudin groups was acknowledged, however it could not be excluded that it was due to the intensity of the heparin regimen used in the studies and to the inadequate aPTT monitoring.

On January 15, 1999, a meeting was held with the sponsor to discuss the clinical deficiencies. The Agency recommended that the sponsor should establish the efficacy of heparin in PTCA by

estimating the treatment effect of heparin relative to placebo and, consequently, demonstrate that the clinical effects of bivalirudin exceed this effect.

Cycle 2 (March 3, 1999):

On March 3, 1999, the sponsor responded to the non-approvable letter with a re-submission of NDA 20-873 containing the following additions and revisions:

- A summary of the anticoagulant, antithrombotic and clinical effectiveness of bivalirudin from Phase II studies to support a dose relationship for bivalirudin.
- Estimation of the clinical effect of bivalirudin and heparin in PTCA compared to an imputed placebo. Data from three literature reports were presented for this purpose.
- Data supporting the greater safety of bivalirudin for hemorrhagic complications in PTCA for UA.
- New analyses of the two pivotal clinical trials.

Demonstration of anticoagulant and antithrombotic effect of bivalirudin was based on the results of a combined analysis of two dose-ranging studies of bivalirudin in 291 patients undergoing PTCA. Evidence of dose-response in these studies was based on dose-response effect on coagulation tests (aPTT, ACT).

To support the hypothesis that bivalirudin is equivalent or non-inferior to heparin and superior to placebo, the sponsor estimated the treatment effect of heparin relative to placebo in PTCA in order to demonstrate that the clinical effect of bivalirudin exceeded the effect of heparin relative to placebo. Data from three observational published studies¹ and from a meta-analysis of two dose-ranging studies in PTCA² were provided to establish the clinical effect of heparin relative to placebo and the superiority of bivalirudin to an imputed placebo. Since no placebo-controlled studies of heparin have ever been performed in patients undergoing PTCA, inadequate heparinization was used as comparator to establish the efficacy of heparin when administered at dose regimen appropriate to provide adequate anticoagulation.

To demonstrate that bivalirudin can be as clinically effective as heparin in PTCA, the sponsor provided revised analyses of the efficacy results of the two pivotal studies of NDA 20-873 (C92-304-1/2) based on new definitions of the efficacy parameters. The following post-hoc changes in the definition of the efficacy

parameters were introduced: 1) change in definition of MI; 2) change of primary efficacy parameter from the composite of death, MI, revascularization and abrupt vessel closure (AVC) to that of death, MI and revascularization; 3) change in the time of assessment of the primary endpoint from during hospitalization to a period of 7 days or-end of hospitalization.

The definition of MI required two of the following: 1) Q-waves or LBBB on ECG, 2) substantial elevation of cardiac enzymes ≥ 2 x ULN and CK-MB $\geq 4\%$, or 3) prolonged chest pain >30 minutes.

AVC was removed from the efficacy parameters because of being subject to individual interpretation of angiographic findings, often not confirmed by independent reviewers. The sponsor contends that AVC is no longer used as endpoint, rather, the triple endpoint of death, MI and urgent revascularization is the standard primary outcome for clinical trials of acute coronary syndromes.

- 1) Narins et al, Circulation 93:667, 1996
Ferguson et al, JACC 23:1061, 1994
Mc Gary et al, Am Heart J 123:1445, 1992
- 2) Phase II studies C92-041 and C92-301 (TIMI-7)

The analysis of the results using the revised definition of MI and the revised endpoints still failed to show statistically significant superiority of bivalirudin over heparin in each of the two studies. However, when a combined analysis of the two studies was performed using the revised composite endpoint (revised MI definition and hospitalization period), a p-value of 0.043 by Fisher's exact test was achieved.

The statistical superiority of bivalirudin compared to heparin in the post-MI population persisted in the revised analysis (odd ratio 0.47, 95% CI 0.26-0.84).

To demonstrate the anticoagulant/antithrombotic effects of bivalirudin in acute coronary syndromes, the sponsor provided a meta-analysis of studies performed in ischemic heart diseases including dose-ranging studies, a study in UA/non-Q-wave MI, the two PTCA studies, and two MI studies in a total study population of 4,965 patients. An odd ratio for heparin versus placebo of 0.25 (95% CI 0.0017-0.37) was assumed and an odd ratio for bivalirudin versus heparin of 0.78 (95% CI 0.62-0.99) was calculated from the meta-analysis of the two pivotal PTCA clinical trials using the revised primary endpoints and the revised definition of MI. Based on the above assumptions, the sponsor has calculated an odd ratio for bivalirudin versus imputed placebo of $0.25 \times 0.78 = 0.197$ (95% CI 0.13-0.31) and calculates that bivalirudin has at least 75% of heparin efficacy.

To address the issue of the open-label heparin administered to about 20% of patients, the sponsor provided data on the incidence

of procedural failure in patients who did not receive any heparin before and after study drug. The incidence of procedural failure for patients who did not receive open-label heparin was similar in the two study drug treatment groups (bivalirudin or heparin). However, the incidence of procedural failure for the patients who did not receive heparin was higher (18% and 16.6% for bivalirudin and heparin respectively) than in the overall study population (6.2% and 7.8% for bivalirudin and heparin respectively). The significance of this difference was unclear since the use of heparin was not randomized and its indication was not described.

The sponsor did not provide any new data to prove the initial hypothesis of superiority of bivalirudin over heparin in PTCA, rather new analyses were performed to establish the efficacy of heparin in PTCA and to determine that bivalirudin can provide similar effective anticoagulation for PTCA.

Based on summary discussion of the above issues and re-analyses of efficacy data, an approvable letter for the indication for use as an anticoagulant in patients with Unstable Angina undergoing PTCA was issued on October 28, 1999. The letter identified a number of Clinical, CMC, and Biopharmaceutical deficiencies. The letter stated that: 'Although these pieces of evidence provided collectively assist in bringing the Agency closer to a determination that Angiomax is safe and effective for use as an anticoagulant in patients with unstable angina undergoing PTCA, these data do not provide substantial evidence of effectiveness consisting of adequate and well controlled clinical trials.'

The sponsor was advised to perform an additional adequate and well-controlled clinical trial that would demonstrate either superiority or non-inferiority of bivalirudin to a conventional dose regimen of heparin.

Cycle 3 (November 11, 1999)

The sponsor responded to the approvable letter on 11-11-99 addressing the CMC, the Biopharmaceutical, and the Clinical and Statistical issues. A safety update was also submitted.

In this submission, the indication for bivalirudin was changed to 'Bivalirudin is indicated as an anticoagulant for patients undergoing PTCA for UA presenting within two weeks of MI'.

A meeting was requested by the sponsor. On 12-13-1999, the Division of GICDP held a teleconference with the sponsor to discuss the clinical issues that would be addressed at the meeting, namely, the heparin regimen used as comparator in the two clinical trials, the use of open-label heparin, and the

rationale for the effectiveness of bivalirudin in the sicker population of post-MI patients undergoing PTCA.

On February 4, 2000, a meeting was held to discuss the approvable action for Angiomax for anticoagulation of patients undergoing PTCA. The objective of the meeting was to discuss the use of bivalirudin in three clinical settings:

1. in patients with UA and recent MI (post-MI population) undergoing PTCA.
2. in patients with UA undergoing PTCA,
3. in patients with UA undergoing PTCA to allow the procedure to be performed.

In addition, the sponsor was asked to address the use of open-label heparin in the two clinical trials, namely, to respond to the Agency's concern whether the open-label administration of heparin in patients who had not reached an endpoint could have prevented an event. The Agency noted that this would tend to cause the two treatments to look "equivalent", but the effect on a showing of 'near superiority' was not clear.

The discussion of the above clinical points is summarized here.

1) The use of bivalirudin in the clinical setting #1 (post-MI population) would be based on the statistically significant superiority of efficacy of bivalirudin over heparin in one of the two studies and on both studies combined on the post-MI population. However this population was small, consisting of approximately only 20% of the overall population. The interpretation of this finding of greater efficacy in the sicker population was problematic since the analysis was not pre-specified and the primary endpoint was not achieved in the overall population.

2) The use of bivalirudin in the clinical setting #2 (overall UA population undergoing PTCA) would be based on a claim of non-inferiority of bivalirudin versus heparin and supported by the totality of evidence indicating that heparin is effective. The sponsor was asked to submit data from additional trials that had compared bivalirudin plus abciximab (ReoPro) versus Heparin plus abciximab in patients undergoing PTCA with or without stents (CACHET trial).

3) The use of bivalirudin in the clinical setting #3 (periprocedural us) would be supported by the demonstration that anticoagulation during PTCA is necessary. The anticoagulant effect of bivalirudin has been clearly characterized.

At the conclusion of the meeting, the sponsor was requested to submit the following for review in cycle 3:

1. Further detailed information on those patients who received heparin prior to experiencing an endpoint in the two C-2-304 trials.
2. The protocol, including the prospective study analysis plan, and full study report from the CACHET trial.

Additionally, the sponsor was advised to demonstrate the effectiveness of heparin in acute coronary syndromes and vascular interventions by providing information on randomized comparisons of heparin with placebo, no treatment, or other treatments in unstable angina and in coronary arterial diagnostic procedures (angiography).

An amendment to the NDA was submitted on March 15, 2000 in response to the Agency's request for information from the February 4, 2000 meeting.

By way of an introduction to the submission, a summary of the body of evidence for support of the effectiveness and safety of bivalirudin in the clinical settings of patients with UA undergoing PTCA was provided.

Evidence of Bivalirudin efficacy: Bivalirudin has been evaluated in dose ranging studies and in efficacy trials in patients across the spectrum of ischemic heart disease (stable angina, unstable angina and myocardial infarction patients, with or without percutaneous coronary intervention).

The clinical investigations performed with bivalirudin in ischemic heart disease are listed in the following table.

Studies supporting effectiveness of bivalirudin in ischemic heart disease

STUDY #	CENTERS	DIAGNOSIS	PROCEDURE	BIVALIRUDIN		CONTROL GROUP	
				N	Rx	N	Rand.
C92.304-1/2	Multictr	UA	PTCA	2161	Heparin	2151	Yes
C90-301	Multictr	UA	None	250	Placebo	160	Yes
C93-309	Multictr	UA	None	68	Heparin	65	Yes
TMC99-05	Multictr	UA	PTCA + stent	30	Heparin	30	Yes
C90.041	Multictr	CAD/PCI	PTCA	291	Dose steps		No
TMC97.01B/C	Multictr	CAD/PCI	PTCA + stent	144	Heparin	164	Yes
TMC97-01A	Multictr	CAD/PCI	PTCA + stent	30	Heparin	30	Yes
TMC98.20	Singlectr	CAD/PCI	PTCA + stent	15	Heparin	15	Yes
C92.307	Multictr	AMI	None	272	Heparin	140	Yes
C90.018	Singlectr	AMI	None	90	Heparin	30	Yes

Zegers E, Mcursing BJ, Verheugt FWA. Routine heparinization during coronary arteriography. Is it still indicated?. J Am Coll Cardiol (supplement) 2000-, 35: 42 (abstract).

These studies have provided evidence of bivalirudin activity as an anticoagulant and of its clinical effectiveness and safety during the acute manifestations of ischemic heart disease. The sponsor states that since these clinical syndromes are closely related, the theoretical basis for use of an anticoagulant drug are similar, the underlying mechanism of disease is the same, and the endpoints studied are similar, each study supports and confirms the other.

The sponsor has submitted the following six lines of evidence supporting the efficacy of bivalirudin in PTCA:

1. Bivalirudin is associated with fewer ischemic events than heparin following PTCA
2. Heparin is effective
3. Bivalirudin is not inferior to heparin and superior to imputed placebo in PTCA for UA
4. Relationship between bivalirudin dosing (including placebo doses) and clinical outcome supports effectiveness conclusions
5. Results in high-risk patient groups in Phase 3 PTCA trials supports effectiveness conclusions
6. The CACHET study supports conclusions of effectiveness

1. Bivalirudin is associated with fewer ischemic events than heparin following PTCA

In the two principal clinical trials of bivalirudin in PTCA, the composite incidence of pre-specified clinical endpoints death, Q-wave MI and revascularization was reduced from 6.6% on heparin to 5.4% on bivalirudin during the first 7-days in hospital (p-value 0.077, odds ratio 0.82 with 95% CI 0.62-1.02). When blindly adjudicated non-Q wave MI events (assessed at the time of original adjudication but not included in study reports) were added, the composite of clinical events was reduced from 7.9% on heparin to 6.2% on bivalirudin (p-value 0.039, odds ratio 0.78, 95% CI 0.62-0.99). Furthermore, 90-days after treatment, the cumulative incidence of death, MI or revascularization was reduced from 17.4% on heparin to 15.2% on bivalirudin (p-value 0.043).

The sponsor has summarized the results of the combined analyses of the two pivotal trials of the NDA as shown in the following table.

Event	Bivalirudin N=2161 n (%)	Heparin N=2151 n (%)	Effect Size %	p-value

In Hospital:				
Procedure Failure	160 (7.4)	177 (8.2)	-10	0.313
Major hemorrhage	79 (3.7)	199 (9.3)	-60	<0.001
Up to 7 days:				
Death, MI, revasc.	116 (5.4)	143 (6.6)	-19	0.07
Death, MI (Q+non-QW) or revasc *	135 (6.2)	169 (7.9)	-20	0.039
90 days:				
Death, MI, revasc	329 (15)	375 (17)	-13	0.043
180 days:				
death, MI, revasc	484 (22)	512 (24)	-6	0.273

•Modified endpoints

2. Heparin is effective

The sponsor points out that given the fact that thrombosis is the pathophysiologic event in ACS, it should be possible to link anticoagulant effect to clinical effectiveness. Double-blind, placebo-controlled trials of heparin have established that heparin-induced anticoagulation measured as a prolongation of activated partial thromboplastin time (APTT) or activated clotting time (ACT) reduces the risk of death or MI in patients with UA. Furthermore, anticoagulation is clearly needed during instrumentation of coronary arteries.

Heparin has been shown to be effective in ACS. When compared to placebo and aspirin in controlled trials of Unstable Angina (two randomized, double-blind studies by Telford and Wilson, and Theroux et al), heparin reduced the risk of fatal and non-fatal MI and it is clinically effective in PTCA as demonstrated by case-control trials and by analyses of heparin-ACT-response data.

A recent overview of 15 randomized and observational studies among 120,000 patients established that failure to anticoagulate with heparin is associated with 2-fold increase in the risk of death or MI following diagnostic angiography. Failure of adequate anticoagulation (APTT or ACT at least twice normal) would increase the risk of death, MI or need for urgent revascularization associated with more invasive procedures of angioplasty.

Meta-analysis of heparin in coronary angiography

OUTCOME	HEPARIN (N=83,085)	No HEPARIN (N=38,889)	RRISK	95% CI	P-VALUE
Death	102 (0.12%)	91 (0.24%)	1.91	1.43-2.52	0.0001
MI	127 (0.15%)	121 (0.31%)	2.03	1.59-2.61	0.0001

The efficacy of heparin in PTCA was determined in three case-controlled studies of PTCA patients which examined clinical outcomes relative to heparin response measured by ACT or APTT. In each study there was a strong inverse correlation between anticoagulant response and the subsequent risk of clinical ischemia. Investigators at the Duke Clinical Research Institute performed a meta-analysis of these studies to estimate the clinical effectiveness of heparin. The odds-ratio of experiencing death, MI or revascularization on heparin versus an imputed placebo was 0.25 with 95% CI 0.17-0.37 indicating that adequately dosed heparin reduces the risk of death, MI or revascularization by approximately 75% compared to treatment that does not reach a minimum threshold of anticoagulation.

A meta-analysis of large double-blind randomized PCI trials (including EPIC, EPILOG, EPISTENT, CAPTURE, IMPACT-II and C92-304-1 & 2), have shown that the effectiveness of heparin increases with dose. High-dose heparin was associated with significantly less frequent clinical ischemic events (8.1%) than lower-dose heparin (10.2%) (odds ratio 0.78, 95% CI 0.65-0.93, p-value 0.006). Further, an inverse relationship has been demonstrated between likelihood of ischemic events on heparin and ACT levels during PTCA. The lowest event rate was associated with an ACT of 350-400 seconds.

3. Bivalirudin is not inferior to heparin and is superior to imputed placebo in PTCA for UA

The sponsor claims that the non-inferior efficacy of bivalirudin to heparin can be inferred by the fact that bivalirudin was "almost superior" to high-dose heparin in the pivotal trials and, since high-dose heparin is superior to low-dose heparin and since any heparin is superior to no treatment or placebo, bivalirudin is non-inferior to heparin and is superior to placebo.

In order to conclude that bivalirudin may be inferior to heparin, one would have to assume that heparin has practically no benefit

over placebo, or actually causes ischemic complications in association with PCI.

The CACHET trial compared bivalirudin versus heparin with abciximab in patients undergoing PCI + stenting. It has been well established that heparin + abciximab is clinically effective in this setting. The EPISTENT trial showed that the combination of heparin + abciximab was superior to heparin + placebo. Therefore the demonstration that the use of bivalirudin in the CACHET trial, which was similar in design to the EPISTENT trial, preserved the benefit associated with heparin + abciximab supports a conclusion of non-inferiority to heparin alone.

4. Relationship between bivalirudin dosing (including placebo doses) and clinical outcome supports effectiveness conclusions

Two dose-finding studies performed in Phase-2 provide supportive evidence of bivalirudin effectiveness in unstable angina and PTCA. Both trials compared "active" bivalirudin doses (which at least doubled coagulation times) to "inactive" lower doses that simulated placebo.

Study C92-301 was a multicenter, double blind, randomized, parallel group design in 410 patients with unstable angina or non-Q wave MI. Patients were randomized to a very low dose of bivalirudin constituting placebo or one of three doses of bivalirudin. There was a dose-dependent increase in APTT throughout treatment. The incidence of death and MI in patients during hospitalization was 10% for placebo and 3.2% for active doses of bivalirudin (p-value 0.009); the difference was sustained at 6-weeks (p-value 0.014). The relative decrease of 68% was similar to that observed in placebo-controlled trials of heparin.

Study C90-041 was a multicenter, open label, sequential group, and dose escalation study in patients undergoing elective PTCA. Six bivalirudin dose levels were tested. There was a dose dependent increase in ACT throughout treatment. The overall incidence of death, MI, urgent revascularization or abrupt vessel closure was 3.6% (5/139) for the doses associated with a two-fold increase in the baseline ACT and 12.5% (19/152) for lower doses (p = 0.006).

Each of these studies showed a relationship between bivalirudin plasma concentration and anticoagulant effect as well as a dose-dependent reduction in clinical endpoints. A meta-analysis of the 701 patients enrolled in these trials showed a reduction of the objective endpoints of death and MI with "active" bivalirudin doses (odds ratio 0.31; 95% CI 0.14-0.68, p-value 0.003).

Other double-blind heparin-controlled trials in ischemic heart disease have shown evidence of superior effects to heparin.

In double-blind randomized trials of bivalirudin versus heparin in acute MI patients undergoing thrombolysis (C90-018 and C92-307), restoration of full coronary artery blood flow (TIMI-III) was accomplished significantly more frequently among patients randomized to bivalirudin.

An overview of all trials that randomized bivalirudin versus heparin was reported in Circulation, November 1992. Combined data from 4973 patients showed that bivalirudin was associated with a significant reduction in the composite endpoint of death or MI (odds ratio 0.73, 95% CI 0.57-0.95, p-value 0.02).

5 Results in high-risk patient groups in Phase-3 PTCA trials supports effectiveness conclusions

In the two pivotal studies, the sub-population of patients who had experienced an acute MI within two weeks (741 patients) experienced a 55% reduction in the primary endpoint (odds ratio 0.45, 95% CI 0.25-0.79), including 66% reduction in the clinical components of death, MI and revascularization (odds ratio 0.34, 95% CI 0.17-0.66). Further, each individual major clinical component (death, MI, revascularization and major hemorrhage) was reduced significantly.

The acceptance of these findings was questioned by the Agency since they were observed in a sub-population of sicker patients when only a modest improvement had been observed in the overall patient population. The sponsor argues that the findings in combination with separate randomization and significant treatment-by-stratum interactions observed for post-MI patients, are at least strongly supportive of the overall conclusion that bivalirudin is not inferior to heparin. In addition, when the post-MI group was compared with imputed placebo, the odds ratio for death, MI or revascularization for bivalirudin versus heparin was 0.13 (95% CI 0.05-0.37 with a p-value <0.0001) in trial C92-304-1; 0.06 (CI 0.05-0.36 with a p-value <0.0001) in trial C92-304-2; and 0.08 (CI 0.04-0.18, p-value <10⁻¹⁰) for the combined C92-304-1 and C92-304-2 data analysis.

6. Data from the CACHET trial support conclusions of effectiveness

The EPISTENT trial has demonstrated that the combined use of abciximab to low dose heparin (70 u/kg) provides effective anticoagulation regimen in elective or urgent PCI with stenting, as measured by death, MI or revascularization at 7- or 30-days.

However, this benefit was associated with a 10% relative increase in the risk of hemorrhage.

In the CACHET trial, treatment with bivalirudin + stent was associated with a lower combined incidence of death, MI, revascularization or major hemorrhage compared to low-dose heparin (70 u/kg), abciximab + stent.

Comparison of the EPISTENT and CACHET trial data for death, MI, revascularization at 7-days supports the conclusion that bivalirudin is not inferior to abciximab + low-dose heparin (70 µg/kg) in PTCA with stenting and that bivalirudin preserves the beneficial effect shown in the EPISTENT trial by abciximab with low-dose heparin (70 µg/kg) over low-dose heparin (100 µg/kg) alone. These data therefore support the conclusion that bivalirudin is superior to low-dose heparin (100 µg/kg) used in current PCI practice.

Open-label use of heparin

In regard to the issue of open-label use of heparin, the sponsor stated that it occurred during the blinded phase of the trial, most of the times after an endpoint had been reached and in most cases for medical management. The use of open-label heparin was balanced between treatments groups.

In order to support the assessment of non-inferiority of bivalirudin to heparin by ensuring assay sensitivity in the pivotal trials, the sponsor assessed whether the use of open-label heparin may have had a confounding effect on the study's ability to demonstrate a treatment difference.

In the absence of placebo controlled data from randomized trials for the indication, or data from randomized patients treated only with bivalirudin without open-label heparin, matched reference trials (EPILOG and EPISTENT) were used to determine the expected outcome for ischemic events following PCI for patients enrolled in the NDA pivotal trials. The two reference studies were selected because they evaluated patients for open-label use of heparin, they clearly defined the use of heparin outside the study drug regimen, and they were comparable to the NDA pivotal studies C92-304. Data from the reference trials were used to establish the expected response in heparin-treated patients with and without concomitant open-label heparin.

The observed response profiles in the pivotal trials were consistent with the expected response profile from the reference trials. In both reference and study trials, patients with risk factors had higher incidence of events. This resulted in the

higher incidence of events in the population receiving open-label heparin than in patients not requiring open-label heparin.

The results indicate that the concomitant use of open-label heparin did not reduce the assay sensitivity of the pivotal trials C92-304 and did not influence the observed differences between patients randomized to the two treatment groups.

The findings are consistent with the results of a randomized trial which showed no difference between patients treated with or without additional heparin following heparin for PCI (Kong DF, Califf RM, Post-procedure heparin. American Heart J, 136 (2): 352, 1998. In this report, a meta-analysis of 6 trials including 2186 patients treated with heparin for PCI and then randomized to receive additional heparin following uncomplicated procedures. The combined odds ratio for ischemic complications (death, MI, urgent revascularization and abrupt vessel closure) for patients randomized to additional heparin was 0.91 (95% CI 0.45-1.84).

Summary and conclusions

The protocol's prespecified objectives of statistically significant superiority of bivalirudin over heparin for the composite endpoint of death, MI and need for revascularization in patients undergoing PTCA were not met. However, the overall results across all studies show consistent evidence that bivalirudin is: (1) an effective, highly specific and reversible inhibitor of thrombin with more predictable and consistent anticoagulant activity than heparin; (2) markedly better than no treatment or imputed placebo and at least as effective as heparin in the setting of percutaneous coronary intervention.

None of the many pre-clinical or clinical studies performed with bivalirudin provide any contrary evidence to these conclusions. Bivalirudin was never shown to be significantly less effective than heparin. The studies submitted indicate that, based on confidence intervals, bivalirudin is no more than 1-2% less effective than heparin.

Reduction in bleeding risk compared to heparin was repeatedly demonstrated. No other serious adverse events were observed with bivalirudin administration.

A clinically significant advantage of bivalirudin over heparin emerges when the outcome of PCI is assessed in terms of ischemic and hemorrhagic complications.

Bivalirudin is recommended for approval for the following indication. Anticoagulant in patients with Unstable Angina (UA) undergoing percutaneous transluminal coronary angioplasty (PTCA).

Although the CACHET trial provided evidence of non-inferiority of bivalirudin versus heparin in PCI with stenting and when used in combination with GPIIb/IIIa inhibitors, no sufficient evidence has been provided to allow such information to be included in the labeling.

The results observed in the post-MI subgroup are not adequate, without additional confirmation, for a claim of superiority over heparin.

The sponsor must be asked to revise the DOSAGE and ADMINISTRATION section of the labeling to conform with the information on bivalirudin administration provided in the Clinical Trials section.

Before the application may be approved, the sponsor must address Biopharmaceutical and CMC deficiencies presently pending.

LSI

Lilia Talarico, M.D.

cc:

HFD-180

HFD-180/LTalarico

HFD-103/F. Houn

HFD-103/V. Raczkowski

HFD-181/PM

f/t 4/21/00 jgw

N/20873004.0LT

MEMORANDUM OF MEETING MINUTES

Meeting Date: February 4, 2000
Time: 8:00 AM – 10:00 AM
Location: Conference Room C, Parklawn Building

Application: NDA 20-873
Angiomax™ (bivalirudin) Injection

Type of Meeting: Type "C" Meeting: Post Issuance of Approvable Letter (End of Review Conference)

Meeting Chair: Dr. Victor Raczowski

Meeting Recorder: Ms. Julieann DuBeau

FDA Attendees, titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Dr. L. Talarico; Division Director
Dr. S. Aurecchia; Deputy Division Director
Dr. K. Robie-Suh; Medical Officer
Dr. R. He; Medical Officer
Ms. K. Johnson; Supervisory Consumer Safety Officer
Ms. J. DuBeau; Regulatory Health Project Manager

Division of Biometrics II (HFD-715)

Dr. P. Flyer; Statistical Team Leader
Dr. M. Rashid; Statistician

Office of Drug Evaluation I (HFD-101)

Dr. R. Temple; Office Director and Associate Director for Medical Policy

Office of Drug Evaluation III (HFD-103)

Dr. F. Houn; Office Director
Dr. V. Raczowski; Office Deputy Director

External Constituent Attendees and titles:

The Medicines Company

Dr. C. Meanwell; Program Leader and President
Dr. T. Lategan; Program Leader for Regulatory Affairs
Dr. J. Villiger; Medical Advisor

Consultants

Dr. R. Califf; Professor of Medicine, Director of the Duke Clinical Research Institute
Dr. E. Topol; Professor of Cardiology, Director of the Cleveland Clinic Foundation
Ms. N. Buc; Outside Counsel, Buc and Beardsley, Washington
Mr. W. Kimball; Director of Biostatistics and Data Management, Quintiles Inc.
Ms. S. Gregoire; Vice President of Regulatory Affairs, Biogen Inc.

Background:

The Medicines Company submitted a new drug application on December 23, 1997, for Angiomax™ (bivalirudin) Injection (formerly known as Hirulog™ Injection), a synthetic thrombin inhibitor, with the following proposed indication: Anticoagulant in patients with unstable angina (UA) undergoing percutaneous transluminal coronary angioplasty (PTCA). The proposed indication was based on two Phase-3 clinical trials; Studies C92-304-1 and C92-304-2, which were multi-center, double-blind, active controlled clinical trials with identical protocols. The primary objective of the studies was to demonstrate the superior efficacy and safety of Angiomax™ compared with heparin in patients with UA undergoing PTCA. The primary composite efficacy endpoint was "procedural failure" comprising death, myocardial infarction (MI), urgent revascularization, and abrupt vessel closure. The primary safety endpoints were the incidences of major and minor bleeding.

The application was presented at the October 23, 1998, Cardiovascular and Renal Drugs Advisory Committee (CRAC) Meeting. The committee members voted (5-no, 3-yes) that they could not recommend approval for the use of Angiomax™ (bivalirudin) Injection as an anticoagulant in patients with UA undergoing PTCA. The firm received a Not Approvable letter on November 18, 1998, which included deficiencies in the following areas: clinical/statistical; biopharmaceutics; and chemistry, manufacturing, and controls (CMC). The Agency's advice in the Not Approvable letter regarding clinical and statistical deficiencies was to consider conducting an additional clinical trial, prospectively designed, to demonstrate superior efficacy and safety of Angiomax™, compared to heparin, in patients with recent myocardial infarctions (MIs) who were undergoing PTCA for the treatment of UA.

The firm fully responded to the Not Approvable letter on April 28, 1999, which began review cycle 2 for this application, and subsequently received an Approvable letter on October 28, 1999, which included deficiencies in the following areas: clinical/statistical; biopharmaceutics; and chemistry, manufacturing, and controls (CMC). The Agency's advice in the Approvable letter

regarding clinical and statistical deficiencies was to consider conducting an additional clinical trial, prospectively designed, in patients with UA undergoing PTCA or percutaneous coronary intervention, to demonstrate either superiority or non-inferiority/equivalence of Angiomax™, compared to heparin, as conventionally used and monitored.

The firm fully responded to the Approvable letter on November 12, 1999, which began review cycle 3 for this application. The action for cycle 3 is pending in the Agency with a PDUFA due date of May 12, 2000. In the firm's resubmission, the following indication is proposed:

"Anticoagulant for patients with UA undergoing PTCA within 2-weeks of myocardial infarction."

On December 13, 1999, after preliminary review of the firm's resubmission, the Agency initiated a teleconference with the firm to discuss remaining clinical/statistical issues (see Attachment 1, Memorandum of Telecon). These issues were to provide a framework for discussion at the planned industry meeting in the year 2000.

The firm has requested this "End-of-Review" conference to discuss clinical/statistical issues as outlined in the October 28, 1999, Approvable letter.

Meeting Objective:

To "learn from FDA whether it believes Angiomax can be approved for the post-MI indication based on the data in the NDA (i.e., without the need for additional studies) and to identify the appropriate pathway(s) for prompt review and approval as soon as possible following the meeting."

Discussion Points:

The firm gave a presentation to summarize the clinical context and data in order to provide support for their proposed indication in the post-MI subpopulation (although they also believed the indication for the broader population was viable), and to address issues raised by the Agency in the December 13, 1999, teleconference (see Attachment 2, overheads presented at the meeting).

Although the firm was unable to demonstrate that Angiomax™ was superior to heparin in patients with UA undergoing PTCA in either of the two Phase-3 studies, Dr. Raczowski stated that use of Angiomax™ in three clinical settings could serve as a framework for subsequent discussion.

1. Use of Angiomax™ in patients with UA and recent MIs who are undergoing PTCA. This discussion could be based on the evidence of superiority of Angiomax™ to heparin in this subgroup. This post-MI subgroup is the population specified in the sponsor's current proposed indication.
2. Use of Angiomax™ in patients with UA undergoing PTCA (i.e., its use in such patients

regardless of whether or not they had experienced recent MIs). This discussion could be based on the evidence of noninferiority of Angiomax™ compared to heparin in this population.

3. Use of Angiomax™ in patients with UA undergoing PTCA to allow the procedure to go forward. Dr. Raczkowski stressed that the Agency had had only preliminary internal discussions on such a use of Angiomax™.

To consider any of the above indications, Dr. Raczkowski stated that the firm needs to clarify the ancillary heparin use in the two Phase-3 clinical trials. Dr. Meanwell stated that in each of the two Phase-3 clinical trials, 21-22% of patients in each of the two trials received ancillary heparin. According to Dr. Meanwell, there is no evidence to suggest an effect of open-label heparin use on study endpoints. In response to a question from Dr. Temple, the firm stated that of the 21-22% of patients who received heparin, approximately 90% received heparin after an endpoint had occurred. Dr. Robie-Suh pointed out that this 90% of patients more accurately refers to those patients who received heparin after they had been "evaluated" for an endpoint event. That is, this 90% of patients includes those who had an endpoint event (i.e., death, MI, revascularization, abrupt vessel closure) before receiving open-label heparin as well as those who never had an event. Dr. Robie-Suh noted the Agency's concern that use of open-label heparin in patients who did not reach an endpoint could have prevented an event. This would tend to cause the two treatments to look "equivalent", but the effect on a showing of "near superiority" was not clear. The Agency asked that the firm submit any further information regarding this ancillary heparin use in patients who did not reach an endpoint.

Clinical Setting #1

Dr. Raczkowski continued the discussion by reiterating the following statements regarding the post-MI subgroup. In the post-MI subgroup there was statistical superiority of Angiomax™ over heparin in one of the two clinical trials, with a numerical trend toward superiority in the other trial. This superiority was based on a revised endpoint of death, MI, and revascularization at seven days. For this analysis the fourth component of the composite endpoint, abrupt vessel closure, was not included. Dr. Raczkowski indicated that the small number of patients in this subgroup was of concern to the Agency. Only approximately 20% of patients in the overall population in each of the Phase-3 trials were in this post-MI subgroup. He also stated that the interpretation of a positive finding in a subgroup in a secondary analysis is problematic in a trial in which the primary endpoint in the overall population has not been achieved. Dr. Flyer added that a conclusion of statistical significance in the post-MI group is difficult to establish for the following reasons: the subgroup analysis was not a prespecified analysis in the original protocol and the endpoint was changed post-hoc. Dr. Temple added that it would be difficult to demonstrate superiority persuasively in a retrospectively identified subgroup in a single study.