Clinical Setting #2

Dr. Temple suggested that the claim of noninferiority of the overall population might be supported by the totality of the evidence that heparin is effective. He noted that the CRAC had not had an opportunity to consider fully the firm's argument in support of heparin's effectiveness because these arguments were developed by the firm and presented to the Agency in large part after the CRAC meeting. Dr. Raczkowski requested that the firm submit full study reports of the CACHET trial of bivalirudin/abciximab (ReoPro) versus heparin/abciximab in patients undergoing PTCA or stenting to support the noninferiority claim further (see Attachment 2, slide 31-32 for CACHET trial details).

Clinical Setting #3

Regarding the potential indication of peri-procedural use, Dr. Raczkowski stated that this indication would focus on the technical aspects of performing PTCA. Such an indication would likely not specifically mention clinical outcomes (i.e., the drug would not be indicated for reducing the likelihood of death, MI, or the need for urgent revascularization), although data on such clinical outcomes would likely be captured in some fashion in the Clinical Trials section of the package insert. The firm would have to use animal data, clinical data, and/or literature to support the point that anticoagulation during PTCA is necessary. Dr. Houn stated that it is clear that Angiomax™ has anticoagulant properties.

The firm stated that they do not want to return to the CRAC and would accept any of the 3 potential uses of Angiomax™ in any of these clinical settings outlined by Dr. Raczkowski.

In conclusion, Dr. Raczkowski requested that the firm submit the following three items for review in cycle 3:

1. further detailed information on those patients who received heparin prior to experiencing an endpoint,
2. the protocol, including the prospective study analysis plan, and full study report from the CACHET trial, and
3. a copy of the overheads presented at today's meeting.

The Agency will then review the entire body of evidence for support of the safety and effectiveness of Angiomax™.

Dr. Houn requested that all communication regarding this application be funneled through the project manager in the Division.

Minutes Preparer: /S/ 3/2/00

Chair Concurrence: /S/ 3/2/00

Attachments/Handouts: (1) December 13, 1999, Memorandum of Telecon
(2) Overheads presented at the meeting (#39).

cc: Original NDA 20-873
HFD-180/Div. Files
HFD-180/Meeting Minutes files
HFD-180/CSO/DuBeau
HFD-180/Robie-Suh
HFD-715/Rashid
HFD-715/Flyer
HFD-180/Talarico
HFD-103/Raczkowski
R/d Init: Raczkowski 2/28/00, 2/29/00, 3/2/00
R/d Init: Houn 2/22/00
R/d Init: Temple 2/14/00
R/d Init: Talarico 2/10/00
R/d Init: Robie-Suh 2/15/00
R/d Init: Flyer 2/22/00
JD/February 9, 2000 (drafted)

MEETING MINUTES

DuBeau

MEMORANDUM OF TELECON

DATE: December 13, 1999

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

BETWEEN:

Name: Dr. T. Lategan; Regulatory Affairs
Dr. C. Meanwell; CEO and President
Ms. P. Collins; Associate Director of Drug Safety
Ms. N. Buc; External Consultant
Dr. R. Califf; Duke University, Clinical

Phone: (617) 225-9099

Representing: The Medicines Company (TMC)

AND

Name: Ms. J. DuBeau; Regulatory Health Project Manager
Dr. L. Talarico; Division Director
Dr. K. Robie-Suh; Hematology Team Leader
Dr. P. Flyer; Statistical Team Leader
Dr. M. Rashid; Statistician

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Firm's resubmission in response to October 28, 1999, approvable action letter

BACKGROUND:

TMC submitted a new drug application on December 23, 1997, for Angiomax™ (bivalirudin) Injection, a synthetic thrombin inhibitor, with the following proposed indication: anticoagulant in patients with unstable angina (UA) undergoing percutaneous transluminal coronary artery procedures. The firm received a not approvable action letter on November 18, 1998, which included deficiencies in the following areas: clinical/statistical; biopharmaceutics; and chemistry, manufacturing, and controls (CMC). The firm responded to the not approvable action letter on April 28, 1999. The firm received an approvable action letter on October 28, 1999, which included deficiencies in the following areas: clinical/statistical; biopharmaceutics; and CMC. The firm's resubmission to the approvable letter was submitted November 11, 1999, and received November 12, 1999. The resubmission was determined to be a complete response and

classified as Class 2. The FDAMA due date for review cycle three is May 12, 2000. An industry meeting is scheduled with the firm on January 25, 2000. Dr. Talarico requested this teleconference to provide direction to the firm regarding the remaining clinical/statistical issues after cursory review of the firm's resubmission, which will provide a framework for discussion at the planned industry meeting.

TODAY'S PHONE CALL:

Dr. Talarico acknowledged that the firm is now pursuing a narrower indication of "Anticoagulant in patients undergoing percutaneous coronary angioplasty for UA presenting within two weeks of myocardial infarction." She reiterated her concern that the post-MI subgroup was prespecified for comparability of groups, not to determine efficacy in this subpopulation. In addition, the fact that all statistical analyses were done post-hoc.

Dr. Talarico requested that the firm address the following clinical/statistical issues regarding Angiomax.

1. The inadequacy of the Heparin regimen used, which is not conventionally accepted. The bleeding advantage of Angiomax may be attributed to the high dose of Heparin administered.

2. The accountability of Heparin usage after discontinuation of Angiomax. The firm identified approximately 25 % of patients who received Heparin to maintain line patency or due to procedural failure. The Medical Officer can only account for approximately 11 % of patients who received Heparin for line patency or procedural failure. Dr. Talarico requested that the firm account for the other approximately 14 % of patients. Specifically, the dose, duration, timing, and reason for administration of Heparin. This information is important since efficacy is assessed over time during hospitalization. In addition, the potential use of Heparin after discontinuation of Angiomax needs to be addressed in the labeling.

3. The rationale for Angiomax's effectiveness in a sicker post-MI subgroup but not in the overall population studied. In addition, the merit in using Angiomax and aspirin alone when GP IIb/IIIa inhibitors are available. The firm can present preliminary data from other ongoing clinical trials regarding use of Angiomax with GP IIb/IIIa inhibitors.

4. The labeling which only addresses the post-MI subgroup in the Clinical Trials section. This is misleading since the post-MI subgroup comprises only approximately 20% of the entire population in each of the two pivotal clinical trials. The firm should address the overall population studied (e.g., there was no superiority of Angiomax over Heparin for the overall population).

Ms. DuBeau requested that the firm address the above issues in their background package for the January 25, 2000, industry meeting which must be received two weeks prior to the meeting. The call was then concluded.

/S/ 12/16/99

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager

/S/ 12-16-99

cc: Original NDA 20-873
HFD-180/Div. File
HFD-180/DuBeau
HFD-180/Talarico
HFD-180/Robie-Suh
HFD-715/Flyer
HFD-715/Rashid
HFD-103/Raczkowski
Rd Init: Talarico 12/14/99
JD December 14, 1999 (drafted)

TELECON

Attachment

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: November 30, 1999

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

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

To: Lilia Talarico, M.D. Division Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Subject: Classification of Resubmission dated November 11, 1999 for NDA 20-873

This memo explains why The Medicines Company's (TMC's) November 11, 1999 resubmission of their NDA 20-873 for Angiomax does not qualify as a Class 1 Resubmission, from a CMC point of view.

In a Guidance document published on May 14, 1998, entitled "Classifying Resubmissions in Response to Action Letters.," the FDA specified criteria for classifying resubmissions when the Agency has sent an action letter. A Class 1 resubmission, under FDAMA and PDUFA 2, has a performance goal of a 2 month review time, while a Class 2 resubmission has a performance goal of 6 months.

The Guidance states:

"II.B. CLASS 1 RESUBMISSION

A Class 1 resubmission is a resubmission that includes the following items only (or combination of these items):

1. Final printed labeling
2. Draft labeling
3. Safety updates submitted in the same format, including tabulations, as the original safety submissions with new data and changes highlighted (except when large amounts of new

information, including important new adverse experiences not previously reported with the product, are presented in the resubmission it will be a Class 2 resubmission).
4. Stability updates to support provisional or final dating periods.
5. Commitments to perform phase 4 studies, including proposals for such studies.
6. Assay validation data.
7. Final release testing on the last 1-2 lots used to support approval.
8. A minor re-analysis of data previously submitted to the application (determined by the Agency as fitting the Class 1 category).
9. Other minor clarifying information (determined by the Agency as fitting the Class 1 category).
10. Other specific items may be added later as the Agency gains experience with the scheme. These will be communicated through guidance for industry."

Much of the CMC information in the resubmission does not meet these criteria. The resubmission contains, among other items, a proposal for revisions in the manufacturing procedure, a revision in the analytical method, and revisions in [redacted] for the manufacture and testing of the drug substance in response to a deficiency letter.

Furthermore the Guidance also states:

"II.C. CLASS 2 RESUBMISSION

- A Class 2 resubmission is a resubmission that includes any other items, including any item that would warrant presentation to an advisory committee. Any submission that would warrant a re-inspection is considered to fall into the category of a Class 2 resubmission."

The manufacturer of the finished drug product, Ben Venue Laboratories (BVL), was issued a FDA form 483, listing GMP deficiencies. They responded to the 483. TMC, in their resubmission, states that there are no changes in the manufacturing process and that a re-inspection is not required or necessary. This is incorrect. The re-inspection is warranted because there are outstanding issues from the 483. A response to a 483 does not preclude a re-inspection. The investigator has informed me that he needs to re-inspect the plant. It appears from the 483 that the deficiencies at BVL are not confined to specific problems in the manufacturing procedure or analytical

method. There are fundamental GMP problems involving how changes to manufacturing procedures and analytical methods are handled.

Therefore, contrary to TMC's assertion, a re-inspection of the BWL plant is necessary.

In summary, this resubmission should be classified as a Class 2 because 1) there are significant manufacturing changes and 2) a re-inspection is necessary.

cc:
NDA 20-873
HFD-180/NDA 20-873
HFD-180/KRobie-Suh
HFD-180/SAurecchia
HFD-181/JDubeau
HFD-820/JGibbs
HFD-810/SKoepke
HFD-180/LZhou

NOV 19 1999

MEMORANDUM

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

DATE: November 19, 1999

FROM: Pharmacology Team Leader
Division of Gastrointestinal and
Coagulation Drug Products
HFD-180

SUBJECT: NDA 20,873 (ANGIOMAX/Bivalirudin) Amendment Dated November 11, 1999 - Response to Approvable Letter Dated October 28, 1999.

TO: NDA 20,873

In amendment dated November 11, 1999, the sponsor provided their response to the Agency's October 28, 1999 approvable letter. Sponsor complied with suggested changes in the preclinical portions of the draft labeling with the exception of two errors. They are reproduced below followed by evaluations and the corrected versions:

Carcinogenesis, Mutagenesis, Impairment of Fertility

Sponsor's Version

"Carcinogenesis, mutagenesis, and impairment of fertility:

No long-term studies in animals have been performed to evaluate the carcinogenic potential of ANGIOMAX™. Bivalirudin displayed no genotoxic potential in the [redacted] in vitro Chinese hamster ovary cell forward gene mutation test (CHO/HGPRT), the in vitro human lymphocyte chromosomal aberration assay, the in vitro rat hepatocyte unscheduled DNA synthesis (UDS) assay, and the in **vitro** rat micronucleus assay. Fertility and general reproductive performance in rats were unaffected by subcutaneous dose of bivalirudin up to 150 mg/kg/day [redacted] 1.6 times the dose on a body surface (mg/m^2) basis for a 50 kg person given the recommended dose of 15 mg/kg [redacted]

Evaluation

The rat micronucleus assay was listed as an in vitro assay. This is incorrect. It is an in vivo assay. Some editorial changes are also needed.

Corrected Version

"Carcinogenesis, Mutagenesis, Impairment of Fertility:

No long-term studies in animals have been performed to evaluate the carcinogenic potential of ANGIOMAX™. Bivalirudin displayed no genotoxic potential in the [redacted] in vitro Chinese hamster ovary cell forward gene mutation test (CHO/HGPRT), the in vitro human lymphocyte chromosomal aberration assay, the in vitro rat hepatocyte unscheduled DNA synthesis (UDS) assay, and the in vivo rat micronucleus assay. Fertility and general reproductive performance in rats were unaffected by subcutaneous dose of bivalirudin up to 150 mg/kg/day, about 1.6 times the exposure on a body surface (mg/m^2) basis, of a 50 kg person of average height (1.46 m^2 body surface area) given the recommended human dose of 15 mg/kg [redacted]

Pregnancy. Teratogenic Effects. Pregnancy Category

Sponsor's Version

"Pregnancy Category B:

[redacted]

Corrected Version

"Pregnancy. Teratogenic Effects. Pregnancy Category B.

Teratogenicity studies have been performed in rats at subcutaneous doses up to 150 mg/kg/day (1.6 times the recommended human dose based on body surface area) and rabbits at subcutaneous doses up to 150 mg/kg/day (3.2 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to bivalirudin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly

/S/

Jasti B. Choudary, B.V.Sc., Ph.D.

cc:
NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Robison

JBC/hw/11/19/99

DuBeau

MEMORANDUM OF TELECON

DATE: November 4, 1999

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

BETWEEN:

Name: Dr. T. Lategan; Regulatory Affairs
Dr. C. Meanwell; CEO and President
Ms. P. Collins; Associate Director of Drug Safety
Ms. N. Buc; External Consultant

Phone: (617) 225-9099

Representing: The Medicines Company (TMC)

AND

Name: Ms. J. DuBeau; Regulatory Health Project Manager
Ms. B. Collier; Associate Director of Regulatory Affairs; ODE III
Dr. L. Talarico; Division Director
Dr. V. Raczkowski; Office Director; ODE III

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Firm's resubmission in response to October 28, 1999, approvable action letter

BACKGROUND:

TMC submitted a new drug application on December 23, 1997, for Angiomax™ (bivalirudin) Injection, a synthetic thrombin inhibitor, with the following proposed indication: anticoagulant in patients with unstable angina (UA) undergoing percutaneous transluminal coronary artery procedures. The firm received a not approvable action letter on November 18, 1998, which included deficiencies in the following areas: clinical/statistical; biopharmaceutics; and chemistry, manufacturing, and controls (CMC). The firm responded to the not approvable action letter on April 28, 1999. The firm received an approvable action letter on October 28, 1999, which included deficiencies in the following areas: clinical/statistical; biopharmaceutics; and CMC. The firm requested this teleconference to discuss their planned resubmission in response to the October 28, 1999, approvable action letter.

TODAY'S PHONE CALL:

Dr. Meanwell stated that the firm plans to submit a complete response to the October 28, 1999, approvable action letter on November 12, 1999, and requests that their resubmission be classified

as Class 1. Ms. DuBeau stated that Dr. Talarico would determine whether the firm's resubmission is a complete response and whether it is classified as Class 1 or 2 once the resubmission is received. Ms. DuBeau referred the firm to the following Guidance for Industry: "Classifying Resubmissions in Response to Action Letters" (April 1998). Dr. Raczkowski stated that the Office could not specify a timeframe for issuance of an action letter in the next (third) review cycle but noted that the resubmission will probably be classified as Class 2, which have six-month review times. However, Dr. Raczkowski stated that the Division/Office would review the firm's resubmission as expeditiously as possible and that the review would not necessarily take six months. In response to a question from Ms. DuBeau, the firm stated that they have addressed all of the manufacturing facility deficiencies and are ready for reinspection. Ms. DuBeau requested that the firm include these statements in the cover letter of their resubmission. Dr. Meanwell stated that he would be requesting a narrower indication of "Anticoagulant in patients undergoing percutaneous coronary angioplasty for UA presenting within two weeks of myocardial infarction." Dr. Raczkowski stated that the firm could request a narrower indication, which will imply that the broader indication is withdrawn. In addition, this does not preclude the firm from formally appealing the broader indication. The call was then concluded.

FOLLOW-UP:

The firm's resubmission was submitted November 11, 1999, and received November 12, 1999. The resubmission was determined to be a complete response and classified as Class 2 (see attached CMC memo dated November 30, 1999, for justification). The firm was notified of their complete. Class 2 response on December 2, 1999. The FDAMA due date for review cycle three is May 12, 2000.

/S/ 1/7/00

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager

Attachment: November 30, 1999, CMC memo

/S/ 1-7-00

cc: Original NDA 20-873
HFD-180/Div. File
HFD-180/DuBeau
HFD-180/Talarico
HFD-103/Collier
HFD-103/Raczkowski
R/d Init: Raczkowski 12/16/99
JD December 13, 1999 (drafted)

TELECON

Memorandum

Date: 27 October 1999 /S/

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

To: 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 12 Oct. 1999).

II. 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 embryolethality (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.

4. Specific comments related to the product label follow:

- Reference to the brand 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.'
- It is recommended that all interspecies dose comparisons included in the product label be based on pharmacokinetic parameters (i.e., AUC, C_{max} or other relevant parameter) unless there is clear scientific justification for the use of another scaling method (i.e., allometric scaling or nominal dose), or there is insufficient pharmacokinetic data to allow for interspecies dose comparisons.
- It is recommended that the reference to "preclinical experience" which is included in the "Clinical Pharmacology" section of the proposed product label (see pages 2 and 3) be removed, as this information is: a) redundant with clinical use experience reported under "Pharmacodynamics" on page 3, and b) relate to negative effects observed in animal studies, the lack of effects not being critical to the safe use of the drug product (21CFR 201.57 Subparts b(1) and b(2)ii).
- It is recommended that the references to "non-clinical study results" contained in paragraphs 1 and 2 under "Precautions – Drug interactions" be removed from the product label or moved to the section on "Clinical Pharmacology," as this information is: a) redundant with paragraph 3 under this heading, and b) relates to a lack of adverse effects observed in animals (which is not critical to the safe use of the drug product). In accordance with 21CFR 201.57 Subpart f(4)i, "this subsection of the labeling shall contain specific practical guidance for the physician on preventing clinically significant drug/drug and drug/food interactions that may occur in patients taking the drug."
- The section/reference to "Reproductive and developmental toxicity" included as paragraph #2 on page 10 under "PRECAUTIONS" should be removed, as its insertion at this point in the product label does not conform with 21CFR 201.57 Subparts f(5 and 6).
- Under the heading of "Carcinogenesis, Mutagenesis and Impairment of Fertility" it is recommended that:
  - reference to the "AMES" assay be included after "reverse mutation test"
  - the text "hypoxanthine-guanine phophoribosyl transferase" be eliminated,
  - the text "in vitro rat micronucleus assay" should be corrected to read "in vivo rat micronucleus assay",
  - the sentence related to the in vitro and in vivo genotoxicity study results be divided into two shorter sentences, and
  - the final sentence of the paragraph should be simplified to read,
    - "up to 1.6 times the dose" (i.e., remove "which is"), and
    - "for a 50 Kg person given the recommended dose of 15 mg/kg (555 mg/m^2)."
- Under the heading of "Pregnancy Category" it is recommended that:
  - reference to teratogenicity studies having been conducted in "pregnant rats" and "pregnant rabbits" should be simplified as "teratogenicity studies … in 'rats' and 'rabbits'."
  - reference to "developmental toxicity" as an adverse fetal effect be eliminated or rewritten, as it does not appear to be adequately supported by the reproductive toxicology study results.
- Under the heading of "Overdosage" it is suggested that single dose studies in mice and monkeys at 1.1 and 2.2 times the human recommended dose are not informative

for the treatment of drug overdoses (given the lack of observed effects), and present potentially conflicting information given that repeat dose animal studies (referenced in the Fertility and Pregnancy sections of the label) were conducted at higher multiples of human exposure.

5. If the data are available, consideration should be given to the inclusion of information on breast milk drug concentration and potential neo-natal drug exposure in woman administered ANGIOMAX® during lactation.

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

TACHLICD

MEMORANDUM

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

DATE: October 13, 1999

FROM: Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

TO: NDA 20-873

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

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

Background

Anticoagulation with heparin and antiplatelet drugs is conventionally used in patients undergoing PTCA to prevent thrombotic complication that may affect the outcome of the procedure. However, no controlled studies have been performed to determine the optimal dose or duration of heparin anticoagulation. Heparin exerts its anticoagulant activity by enhancing the activity of AT-III. Significant intra- and inter-individual variability to the effect of heparin is observed because of variable AT-III binding sites, absorption to endothelium and circulating molecular complexes and neutralization by anti-heparin protein such as platelet Factor 4. A further limitation of heparin is its inability to neutralize fibrin-bound thrombin and platelet-bound Fact Xa.

In addition to hemorrhagic adverse events, heparin can induce an immunologic adverse reaction with Heparin-Induced Thrombocytopenia and thrombotic complications.

Bivalirudin is a 20 aminoacid synthetic peptide similar to the naturally occurring leech hirudin. Bivalirudin is a potent, specific and reversible inhibitor of circulating and clot-bound alpha-thrombin. Its antithrombin effect is independent of AT-III and is not neutralized by PF4. Bivalirudin has a short half-life of 46 minutes.

Bivalirudin has been evaluated for its efficacy and safety as anticoagulant and antithrombotic regimen in 15 clinical trials, mostly in acute coronary syndromes.

NDA 20-873: Initial submission

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

NDA 20-873 was based on the results of two pivotal clinical trials of similar design: '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)'.

The two clinical trials (C92-304-1 and C-304-2) enrolled 2318 and 2354 patients respectively, randomized to either bivalirudin or heparin. 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 studies were described in details in the review of the initial NDA submission and will only be summarized briefly in this review.

The primary objective of the studies was to demonstrate 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 during hospitalization of any of the following events:

- 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 LBBB;
- Clinical deterioration of cardiac origin 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 the 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).

Safety was assessed primarily in terms of clinically significant bleeding.

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.

The incidence of procedural failure during hospitalization for the ITT population is summarized i- the following table.

Incidence of procedural failure

Study	Patients (n) Total		# procedural failure (%)		Total # Post-MI patients (%)		# 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

There was no statistically significant difference between the two treatment group for the overall study population in both studies. The odd ratio and corresponding 95% for procedural failure were not significant in either study: 0.835; 95% CI 0.608,1.146 for study C92-304-1 and 0.951; 95% CI 0.695,1.30 for study C92-304-2.

In both studies, the incidence of procedural failure in the post-MI subgroup was lower in the bivalirudin group than in the heparin group; the difference was statistically significant in study C92-304-2 (OR: 0.39; 95% CI=0.178,0.857).

The incidence rates of the individual components of procedural failure for the entire study population are summarized in the following table.

Incidence of individual components of procedural failure

Study	Death		MI		Revascularization		EAVC		IAVC	
	Hir.	Hep.	Hir.	Hep.	Hir.	Hep.	Hir.	Hep.	Hir.	Hep.
C92-304-1	3 .3%	1 .1%	21 2%	28 2.6%	49 4.6%	65 6.1%	22 2.1	29 2.7%	8 .7%	9 .8%
C92-304-2	6 .5%	5 .45%	23 2.1%	24 2.1%	47 4.3%	57 5.2%	23 2.1%	24 2.2%	11 1%	2 .2%

In study C92-304-2 the incidence of impending abrupt vessel closure (IAVC) was significantly lower in the heparin group (p-value= 0.008). No statistically significant difference was noted for any of the other endpoints in both studies.

In the post-MI study population, significantly more MIs occurred in the Heparin group (p=0.0007) in study C92-304-1 and more revascularization were required in the Heparin group (p=0.027) in study C92-304-2.

Efficacy analyses of the combined data from both studies showed no statistical significance in favor of bivalirudin in the overall study

In both studies, the incidence of any bleeding and of major bleeding was significantly lower in the bivalirudin group (p=0.0001).

On 10-23-99, the NDA was presented and discussed at a Cardiorenal Advisory Committee meeting. The issues discussed in great detail by the Committee members included the heparin regimen used in the two studies in the context of current medical practice with regard to PTCA and the use of non-study heparin before and after PTCA.

The results of the studies had failed to show superiority to heparin and it was concluded that the data had also failed to demonstrate non-inferiority of bivalirudin to the comparator regimen.

The safety advantage of bivalirudin as manifested by a lower incidence of major hemorrhagic complications was attributed to the degree of heparinization used.

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.

On January 15, 1999, a meeting with the sponsor was held to discuss the clinical deficiencies. The Agency recommended that the sponsor consider estimating the treatment effect of heparin relative to placebo in PTCA and demonstrate that the clinical effects of bivalirudin exceed this effect.

NDA 20-873: Resubmission

On March 3, 1999, the sponsor resubmitted NDA 20-873 with the following additions and revisions:

- A summary of the clinical effects of bivalirudin including:
  - analyses and meta-analysis of 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,
- a review of the data supporting the greater safety of bivalirudin for hemorrhagic complications in PTCA for UA.
- new analyses of the two clinical trials (C92-304-1 and C92-304-2)

The above issues were reviewed and discussed in detail in the medical review by Dr. Robie-Suh and in the statistical review by Dr. Rashid. This review will address only the revised analyses of the efficacy data.

The sponsor has not submitted any new information to prove the initial hypothesis of superiority of bivalirudin over heparin in PTCA, but has provided revised analyses to establish the efficacy of heparin in PTCA and to determine that bivaliurudin can provide effective anticoagulation for PTCA.

The following post-hoc changes in the definition of efficacy parameters from the two pivotal clinical trials 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.

A revised definition of MI was introduced to increase the sensitivity by requiring two of the following: 1) Q-waves or LBBB on ECG, 2) substantial elevation of cardiac enzymes =>2x ULN and CK-MB =>4%, or 3) prolonged chest pain >30 minutes.

The removal of AVC from the efficacy parameters was based on the sponsor's determination that AVC is 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.

The analysis of the results using the revised definition of MI still failed to show statistically significant superiority of bivalirudin over heparin. The analysis of the results using the revised efficacy endpoint also failed to achieve statistical significance for bivalirudin superiority.

When a meta-analysis of the two studies was performed using the revised composite endpoint with the revised MI definition and for the revised hospitalization period, a p-value of 0.043 by Fisher's exact test was achieved. The results of this analysis are summarized in the following table.

Efficacy Analysis of Revised Primary Endpoint

Study	Number of patients with revised procedural failure (%)			
	Bivalirudin	Heparin	p-value	Odd Ratio (95% CI)
C92-304-1	69/1071 (6.4)	84/1060 (7.9)	0.208	0.80 (0.57-1.11
C92-304-2	66/1090 (6.0)	85/1091 (7.7)	0.129	0.77 (0.55-1.07)
Meta-analysis	135/2161 (6.2)	169/2151 (7.8)	0.043	0.78 (0.62-0.99)

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

Notably, more than 60% of patients in both trials received heparin up to one hour prior to initiation of study drug and more that 40% received heparin for longer that 12 hours prior to initiation of study drug. About 24-30% of patients received heparin after discontinuation of study drug, most of them within 8 hours from discontinuation of study drug and for longer than 12 hours.

The incidence of procedural failure in the revised analysis of patients who did not receive any heparin before and after study drug was similar in the two treatment groups (about 20%). The incidence of procedural failure for the patients who did not receive heparin was higher (18% and 16.6% for bivalirudin and heparin respectively) that in the meta-analysis of the overall study population (6.2% and 7.8 7% for bivalirudin and heparin respectively in the meta-analysis). The significance of this difference is unclear since the use of heparin was not randomized and its indication was not described.

To support the hypothesis that bivalirudin is equivalent or non-inferior to heparin, the sponsor has estimated the treatment effect of heparin relative to placebo in PTCA based on historical data from three published reports in order to demonstrate that the clinical effect of bivalirudin exceeded the effect of heparin relative to placebo.

Data from three observational published studies and from a meta-analysis of two dose-ranging studies in PTCA were provided to establish the clinical effect of heparin relative to placebo and the superiority of bivalirudin to an imputed placebo. As no placebo-controlled studies have ever been performed in patients undergoing PTCA, inadequate heparinization was used to determine the efficacy of adequate heparinization.

To demonstrate the anticoagulant/antithrombotic effects of bivalirudin, the sponsor has 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 x 0.78 = 0.197 (95% CI 0.13-0.31) and calculates that bivalirudin has at least 75% of heparin efficacy.

Conclusions

The sponsor has resubmitted NDA 20-873 for the use of bivalirudin in patients undergoing PTCA. The sponsor has not provided any new information 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 bivaliurudin can provide similar effective anticoagulation for PTCA.

The data presented in this resubmission are derived from re-analyses of the original data with various revisions. A new definition of MI was introduced, abrupt vessel closure (AVC) was removed from the composite primary endpoint of procedural failure, the time to endpoint was changed to 7 days. Only with these modifications and by combining the two pivotal clinical trials, a borderline statistically significant difference for bivalirudin compared heparin was demonstrated (p-value = 0.043; odd ratio 0.78; 95% CI 0.62-0.99). These results are, however, inadequate to establish convincingly the superiority of the bivalirudin regimen. It must also be noted that the results are confounded by the uncontrolled administration of heparin to both treatment groups prior to initiation and following termination of study drug.

As shown in the NDA, only in the post-MI population a statistically significant advantage for bivalirudin over heparin was demonstrated in one study with numerical superiority shown in the second study. These data are, however, of limited significance due to the small patient population.

Although it is conventionally used and acknowledged as effective for thromboprophylaxis during PTCA and other acute coronary syndromes, heparin is not approved for these indications. Heparin has been used at various doses and regimens, however, no standardized regimen in terms of dose or duration has been established for cardiac indications.

Data were presented to support the efficacy of heparin in PTCA and, even though the pivotal studies were not designed for equivalence of non-inferiority, analyses were performed to show that bivalirudin is not inferior to heparin for PTCA. The data to show the efficacy of heparin were based on a comparison of adequate versus inadequate heparin regimen. These data are acceptable since no placebo controlled studies have been performed or will ever be performed to confirm the efficacy of heparin for PTCA or any vascular surgery. The studies submitted indicate that, based on confidence intervals, bivalirudin is no more that 1-2% less effective than heparin.

Antithrombotic therapy for cardiac indication has evolved over time with the introduction of new antiplatelet drugs. In fact, the dosage and regimen of heparin has required adjustment when used in conjunction with GPIIb/IIIa inhibitors (abcibimax) due to the serious hemorrhagic complications that occurred when used at the same regimen as with aspirin. The efficacy and safety of heparin have been tested when used in combination with new and more effective platelet inhibitors,

therefore the clinical assessment of efficacy and safety of new anticoagulant/antithrombotic agents should not be limited to the proof of superiority to the heparin/aspirin regimen.

The available evidence of the effectiveness of heparin in cardiac syndromes, however convincing, is not adequate for its approval for PTCA and for labeling in terms of dose and duration of administration. Consequently, equivalence or proof of non-inferiority to heparin cannot lead to the approval of bivalirudin for PTCA. Approval of bivalirudin as alternative to heparin could be considered for limited indications in PTCA patients with history of heparin intolerance or heparin-induced thrombocytopenia. There is no reason to believe that these patients would respond to bivalirudin differently from other PTCA patients.

The sponsor should consider further investigation of the use of bivalirudin for PTCA in post-MI patients. In addition, further investigations of bivalirudin for PTCA should also assess the efficacy and, particularly, the safety of this drug when used concomitantly with new antiplatelet drugs (GPIIb/IIIa inhibitors).

/S/

Lilia Talarico, M.D.

cc:
NDA 20-873
HFD-180
HFD-180/LTalarico
HFD-180/KRobie-Suh
HFD-181/JDuBeau
HFD-103/FHoun
HFD-103/VRaczkowski
f/t 10/15/99 jgw
N/20873910.0LT

DuBECA

MEMORANDUM OF TELECON

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

Date: July 16, 1999

Between: Clive A. Meanwell, M.D., Ph.D.
The Medicines Company
One Cambridge Center
Cambridge, Massachusetts 02142

and

Kathy M. Robie-Suh, M.D., Ph.D.
Medical Team Leader, Hematology, HFD-180

Subject: NDA 20-873 (Hirulog)

At the request of Dr. Talarico I returned Dr. Meanwell's telephone call of yesterday. He said he had called to ask how the review of the firm's response to the non-approvable letter for Hirulog was going. I told him the submission is under active review, but that we will need some additional information which will be detailed in an information request letter to be sent out on Monday, July 19th. I briefly described the information being requested as per my 7/12/99 memo. He stated that there should not be a problem with promptly providing the tabulations, the Safety Update and the tabulation of patients exposed to heparin.

He stated that he would appreciate it if we could fax a copy of the letter to him when we get ready to send it out. He thanked us heartily for returning his call.

The telephone call was terminated.

cc: Orig. NDA 20-873
HFD-180 Div. File
HFD-180 DuBeau
HFD-180 Robie-Suh
HFD-180 Talarico
HFD-180 Meyer

/S/ 7/21/99

MEMORANDUM

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

Date: July 12, 1999

From: Kathy M. Robie-Suh, M.D., Ph.D.
Medical Team Leader, HFD-180

Subject: NDA 20-873
HIRULOG (bivalirudin)

To: Director, Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

To continue review of the sponsor's response to the Division's nonapproval letter the following additional information is needed.

Clinical:
For Study C92-304-1 and Study C92-304-2 separately:

1. Provide a listing by treatment of patients who were not judged to have MI in the study report but who are now being classified as having had an MI.

2. Provide a tabulation of all patients who received no heparin prior to study and who received no heparin after discontinuation of the study drug, including in that tabulation: patient number, site, treatment, age, gender, yes/no for post-MI, yes/no for procedural failure (by original study definition and by the revised definition), yes/no for each component of procedural failure (including AVC and including MI by both the protocol specified definition and the revised definition), exact ACT values at baseline; exact ACT values during treatment, and days in hospital. For this subpopulation, provide a calculation of procedural failure by the protocol specified definition and for the new composite endpoint using the revised MI definition at 7 days or end of hospitalization.

3. Provide a Safety Update for bivalirudin.

Statistical:
For the comparisons between bivalirudin and heparin treatment groups:

1. Provide an estimate of the difference in proportions, Fisher's exact test, odds ratios, standard errors of the difference in proportions, standard errors of odds ratios, confidence intervals for the composite endpoint (death, revised MI, revascularization or AVC) during hospitalization period for Study C92-304-1, C92-304-2 and C92-304-1/2).

2. Provide an estimate of the difference in proportions, Fisher's exact test, odds ratios, standard errors of the difference in proportions, standard errors of odds

ratios, confidence intervals for the composite endpoint (death, original MI, revascularization or AVC) during 7-day or hospitalization period for Study C92-304-1, C92-304-2 and C92-304-1/2).

3. Provide an estimate of the difference in proportions, Fisher's exact test, odds ratios, standard errors of the difference in proportions, standard errors of odds ratios, confidence intervals for the composite endpoint (death, revised MI, or revascularization) during hospitalization period for Study C92-304-1, C92-304-2 and C92-304-1/2).

4. Provide an estimate of the difference in proportions, Fisher's exact test, odds ratios, standard errors of the difference in proportions, standard errors of odds ratios, confidence intervals for the composite endpoint (death, revised MI, revascularization or AVC) during 7-day or hospitalization period for Study C92-304-1, C92-304-2 and C92-304-1/2).

5. Data diskette with revised MI, procedural failures (death, revised MI, revascularization or AVC), three-component procedural failures (death, revised MI or revasuclarization).

/S/

Kathy M. Robie-Suh, M.D., Ph.D. 7/12/99

cc:
NDA 20-873
HFD-180/Division File
HFD-180/JDuBeau
HFD-180/KRobie-Suh
HFD-720/MRashid
HFD-720/PFlyer

Record of a Telephone Communication

Date: 12 May 1999
To: The Medicines Company
Contact: Mr. Tom Lategan
Telephone: (617) 225-9099
Initiated by: Patricia F. Hughes, Ph.D.
Reference: NDA 20-873 Amendment dated 22 April 1999 for Hirulog
Purpose of communication: To obtain container/closure integrity data

Mr. Tom Lategan at The Medicines Company was contacted by telephone to obtain container/closure integrity data not included in the Amendment dated 22 April 1999.

In a second telephone communication, Mr. Lategan stated that the protocol included in the original application has not been executed. Mr. Lategan stated that the protocol will be executed and data will be submitted in an amendment in four to six weeks.

/S/ 12/May/'99

Patricia F. Hughes, Ph.D.
Review Microbiologist /S/ 5/17/99

DuBeau

MEMORANDUM OF TELECON

DATE: May 6, 1999

APPLICATION NUMBER: NDA 20-873; Hirulog® (bivalirudin) Injection

BETWEEN:

Name: Mr. T. Lategan; Regulatory Affairs
Mr. J. Richards; Manufacturing
Mr. T. Wright; Manager of Logistics
Dr. B. Crouthamel; Pharmacokinetic Consultant

Phone: (617) 225-9099

Representing: The Medicines Company (TMC)

AND

Name: Ms. J. DuBeau; Regulatory Health Project Manager
Dr. E. Duffy; CMC Team Leader
Dr. A. Shaw; Chemist

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Linkage between drug product used in pivotal clinical trials and the drug product to-be-marketed

BACKGROUND:

TMC submitted a new drug application on December 23, 1997, for Hirulog® (bivalirudin) Injection, a synthetic thrombin inhibitor, with the following proposed indication: Anticoagulant in patients with unstable angina (UA) undergoing percutaneous transluminal coronary artery procedures (PTCA). The proposed indication was based on two pivotal clinical trials: Studies C92-304-1 and C92-304-2, two 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 Hirulog® 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 Meeting. The committee members voted (5-no, 3-yes) that they could not recommend approval for the use of Hirulog® (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. The firm responded to the Not Approvable letter on April 28, 1999. The user-fee goal date for cycle #2 is October 28, 1999. The Division initiated this teleconference to inquire about the linkage between the drug product used in the pivotal clinical trials and the drug product to-be-marketed.

TODAY'S PHONE CALL:

Dr. Duffy stated that the firm has yet to provide a linkage between the drug product used in the pivotal clinical trials and the drug product to-be-marketed. In response to a question from Dr. Duffy, the firm stated that they do have retain samples from pivotal clinical trial lots however the samples have been frozen at -75° for approximately six years. The to-be-marketed formulation is lyophilized. In response to a question from Dr. Shaw, the firm stated that they do have a bridging study between the frozen and lyophilized formulations (Study C93-316). The firm agreed to establish the chemical equivalence of the frozen retain samples from lots used in the pivotal clinical trials to the to-be-marketed lyophilized drug product. Dr. Duffy requested that the firm provide a side-by-side comparison of the two formulations using the following specifications: assay and impurities by Method 931-00-24A/B; absorbance scan; thrombin inhibition activity (anti-IIa); sequencing; and mannitol content. Dr. Duffy reassured the firm that biopharmaceutics would not request use of retain samples for a Phase I PK/PD study due to sterility assurance issues (i.e. six year old retain samples). The firm agreed to perform the side-by-side comparison and submit the results to the NDA. The call was then concluded.

/S/ 8/3/99
Jillieann DuBeau, RN, MSN
Regulatory Health Project Manager

cc: Original NDA 20-873
HFD-180 Div. File
HFD-180 DuBeau
HFD-180 Shaw
HFD-180 Duffy
r.d Init: Duffy 8/2/99
r.d Init: Shaw 8/2/99
JD August 2, 1999 (drafted)

/S/ 8/3/99

TELECON

CSO/DuBeau

MEMORANDUM OF TELECON

DATE: February 18, 1999

APPLICATION NUMBER: NDA 20-873; Hirulog® (bivalirudin) Injection

BETWEEN:

Name: Clive Meanwell; CEO, The Medicines Company (TMC)
Alistair Wheeler; Senior Advisor, TMC
[redacted]
Ralph D-Agostino; Professor, Boston University
David Kong; Fellow, Duke University Medical Center
Victor Hasselback; Duke University Medical Center

Phone: (617) 225-2397

Representing: TMC

AND

Name: Ms. J. DuBeau; Regulatory Health Project Manager
Dr. L. Talarico; Division Director
Dr. K. Robie-Suh; Medical Officer
Dr. A. Farrell; Medical Officer
Dr. M. Rashid; Statistician, Division of Biometrics II
Dr. M. Welch; Acting Deputy Director, Division of Biometrics II

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Statistical methodology submitted in February 4, 1999, correspondence to NDA 20-873

BACKGROUND:

TMC submitted a new drug application on December 23, 1997, for Hirulog® (bivalirudin) Injection, a synthetic thrombin inhibitor, with the following proposed indication: anticoagulant in patients with unstable angina (UA) undergoing percutaneous transluminal coronary artery procedures (PTCA). The proposed indication was based on two pivotal clinical trials: Studies C92-304-1 and C92-304-2, two 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 Hirulog® 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 Meeting. The committee members voted (5-no, 3-yes) that they could not recommend approval for the use of Hirulog® (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 Hirulog®, compared to heparin, in post-MI patients undergoing PTCA for the treatment of UA.

An industry meeting was held on January 15, 1999, to discuss the clinical and statistical deficiencies as outlined in the Not Approvable letter. Since the firm was unable to demonstrate the superior efficacy and safety of Hirulog® compared with heparin in patients with UA undergoing PTCA in either of the two pivotal studies, the Agency suggested several possible strategies. The firm decided to pursue the strategy described below. To potentially support a noninferiority claim of Hirulog® to heparin with the existing data, the firm must demonstrate that heparin is "active." The firm should provide evidence to establish and quantitate the beneficial effect of heparin compared to placebo on death, MI, urgent revascularization, and abrupt vessel closure in patients undergoing PTCA for the treatment of UA. Then the firm can extrapolate the efficacy margin between heparin and Hirulog®.

On January 26, 1999, the firm requested this teleconference to discuss their methodology used to impute a placebo event rate, and the resulting argument for non-inferiority of heparin. On February 4, 1999, at the Division's request, the firm submitted their proposed detailed methodology.

TODAY'S PHONE CALL:

Dr. Rashid stated that the framework for the proposed methodology as presented in the firm's February 4, 1999, submission, is acceptable. In addition to what the firm has proposed, Dr. Rashid requested that the firm perform the Fisher's Exact and Mantel-Haenszel test statistics, and provide treatment effect size based on absolute difference and the corresponding 95% Confidence Interval based on differences in proportions. Dr. Welch requested that the firm provide details of the formula used, derivation, and references.

Dr. Robie-Suh stated that the firm must show that heparin is "active" and vastly superior to placebo. She stated that there is a clinical concern with the submitted methodology since the firm has revised the clinical outcome definition (endpoint), timeframes to clinical outcome, and hypothesis from superiority to non-inferiority. She reminded the firm that the Agency approves

drug products based on adequate and well-controlled clinical trials, not post-hoc analyses that are supportive.

The firm stated that they will respond to the clinical/statistical section of the Not Approvable within the next two weeks. The information to be submitted will contain new analyses, but no new data. The call was then concluded.

/S/ 3/9/99

Julleann DuBeau, RN, MSN
Regulatory Health Project Manager

cc: Original NDA 20-873
HFD-180/Div. File
HFD-180/DuBeau
HFD-180/Robie-Suh
HFD-180/Talarico
HFD-715/Rashid
rd Init: Rashid 3/8/99
rd Init. Talarico 3/8/99
JD March 8, 1999 (drafted)

TELECON

MEMORANDUM OF MEETING MINUTES

Meeting Date: January 15, 1999
Time: 3:00 PM – 5:00 PM
Location: Conference Room L, Parklawn Building

Application: NDA 20-873
Hirulog® (bivalirudin) Injection

Type of Meeting: Type "B" Meeting: Post Issuance of Not Approvable Letter (End of Review Conference)

Meeting Chair: Dr. Lilia Talarico

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. K. Robie-Suh; Medical Officer
Dr. J. Schmeling; Medical Officer
Dr. A. Farrell; Medical Officer
Dr. A. Shaw; Chemist
Ms. J. DuBeau: Regulatory Health Project Manager

Division of Biometrics II (HFD-715)

Dr. A.J. Sankoh; Statistical Team Leader

Division of Pharmaceutical Evaluation II (HFD-870)

Dr. D. Lee; Biopharmaceutics Team Leader
Mr. J. Hunt; Deputy Director, Biopharmaceutics
Dr. A. Selen; Biopharmaceutist

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. V. Raczkowski; Acting Office 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. A. Wheeler; Medical Advisor

Consultants

Dr. R. Califf; Professor of Medicine, Director of the Duke Clinical Research Institute
Dr. R. D'Agostino; Professor of Mathematics and Statistics, Boston University
Dr. E. Topol; Professor of Cardiology, Director of the Cleveland Clinic Foundation
Dr. B. Chaitman; Professor of Cardiology, St. Louis University
Ms. N. Buc; Outside Counsel, Buc and Beardsley, Washington

[redacted]

Background:

The Medicines Company submitted a new drug application on December 23, 1997, for Hirulog® (bivalirudin) Injection, a synthetic thrombin inhibitor, with the following proposed indication: Anticoagulant in patients with unstable angina (UA) undergoing percutaneous transluminal coronary artery procedures (PTCA). The proposed indication was based on two pivotal clinical trials; Studies C92-304-1 and C92-304-2, two 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 Hirulog® 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 Meeting. The committee members voted (5-no, 3-yes) that they could not recommend approval for the use of Hirulog® (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 Hirulog®, compared to

heparin, in post-MI patients undergoing PTCA for the treatment of UA. The firm has requested this meeting to discuss the clinical and statistical deficiencies as outlined in the Not Approvable letter.

Meeting Objective:

To agree on the most efficient further activities required to enable approval and ensure strong data support for proposed labeling.

Discussion Points:

The firm gave a presentation (see attached overheads presented at the meeting).

Since the firm was unable to demonstrate the superior efficacy and safety of Hirulog® compared with heparin in patients with UA undergoing PTCA in either of the two pivotal studies, the Agency suggested the following possible strategies.

1. To potentially support a noninferiority claim of Hirulog® to heparin with the existing data, the firm must demonstrate that heparin is "active." The firm should provide evidence to establish and quantitate the beneficial effect of heparin compared to placebo on death, MI, urgent revascularization, and abrupt vessel closure in patients undergoing PTCA for the treatment of UA. Then the firm can extrapolate the efficacy margin between heparin and Hirulog®.

2. Another strategy would be to conduct an additional clinical trial, prospectively designed, to demonstrate superior efficacy and safety of Hirulog®, compared with heparin, in post-MI patients undergoing PTCA for the treatment of UA. The composite endpoint could be death and MI. Depending on the results of this trial, the firm could get a limited indication of anticoagulant in post-MI patients undergoing PTCA for the treatment of UA.

3. The Agency suggested additional clinical trials with Hirulog® in the following populations: Heparin-induced thrombocytopenia (HIT), heparin-induced thrombocytopenia and thrombosis syndrome (HITTS), and patients taking GP IIb/IIIa inhibitors. The firm stated that they are currently investigating the use of Hirulog® in patients with HIT/HITTS.

In conclusion, the firm stated that they would consider the above strategies.

Minutes Preparer: /S/ 2/8/99

Chair Concurrence: /S/ 2-8-99

Attachments/Handouts: Overheads presented at the meeting (#39).

cc: Original NDA 20-873
HFD-180/Div. Files
HFD-180/Meeting Minutes files
HFD-180/CSO/DuBeau
HFD-180/Robie-Suh
HFD-715/Rashid
HFD-180/Talarico
R/d Init: Talarico 2/8/99
JD/February 8, 1999 (drafted)

MEETING MINUTES

MEMORANDUM

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

Date: November 16, 1998

From: Kathy M. Robie-Suh, M.D., Ph.D.
Medical Officer, HFD-180

Subject: NDA 20-873
Hirulog Injection for use in percutaneous transluminal angioplasty (PTCA) – Information needed on use in renally impaired patients

To: Director, Division of Gastrointestinal and Coagulation Drug Products (HFD-180) /S/ 11-16-98

Hirulog (bivalirudin) is cleared predominantly via the kidneys. In the NDA the sponsor included Study C93-313, an open-label pharmacokinetic/pharmacodynamic study of Hirulog infused for 4 hrs at a rate of 0.5mg/kg/h in 39 subjects having various degrees of renal failure as follows:

- normal renal function - GFR $\geq$90 mL/min/1.73m^2
- mild renal failure - GFR 60-89 mL/min/1.73m^2
- moderate renal failure - GFR 30-59 mL/min/1.73m^2
- severe renal failure - GFR <30 mL/min/1.73m^2
- dialysis-dependent subjects requiring maintenance hemodialysis at least twice per week

Results of this study are shown in the table below:

Study C93-313: PK/PD Parameters in Patients with Various Degrees of Renal Failure

	Normal Renal Function (n=8)	Mild Renal Impairment (n=8)	Moderate Renal Imapirment (n=7)	Severe Renal Impairment		Dialysis Dependent	
				0.5mg/kg/h (n=8)	0.25mg/kg/h (n=2)	Off dialysis 0.5mg/kg/h (n=8)	Off dialysis 0.25 mg/kg/h (n=4)
Pharmacokinetic Parameters:							
t_{max} (h)	2.7	3.5	3.7	3.3	4.0	3.7	3.8
C_{max} (ng/ml)	2110.3	2495.8	4026.0	6161.3	2149.0	5397.4	3135.8
$AUC_{0-2\infty}$ (h.ng/mL)	7610.5	9245.9	18473.1	29225.6	15613.3	37874.2	21708.3
Half-life (h)	0.52	0.68	1.49	2.03	2.90	3.53	3.18
Clearance (mL/min/kg)	4.58	4.94	2.50	1.46	1.57	1.04	0.92
Vd (L/kg)	0.20	0.22	0.23	0.20	0.22	0.27	0.19
aPTT:							
t_{max}	2.7	2.7	2.7	2.7	3.0	3.6	3.2
E_{max}	58.3	44.7	56.8	79.4	57.1	84.4	54.2
E_{AUC}	237.8	180.6	245.3	364.9	279.2	478.5	306.7

sponsor's table, NDA Vol. 1.49, p.194

C_{max} and AUC_{0-28} appeared to increase with increasing severity of renal failure. The maximum effect (E_{max}) appeared to be greater in patients with severe renal failure as compared to those with normal renal function. Hirulog was well-tolerated by subjects with renal failure in this study. The sponsor concluded that dosage adjustment of Hirulog would seem indicated in patients with moderate and severe renal failure. Howeve., a dosing scheme for patients with renal impairment submitted by the sponsor October 19, 1998 was found to be inadequately supported by the available data (see FDA Clinical Pharmacology and Biopharmaceutics review, ASelen, 11/98). That review recommends that the sponsor conduct a pharmacokinetic/pharmacodynamic study in patients renal impairment, including a control group of normal subjects.

Patients having significant renal impairment (serum creatinine >3.0 g/dl) were excluded from the main clinical efficacy studies of Hirulog in PTCA submitted in the NDA (Studies C92-304-1 and C92-304-2). In designing a future clinical trial for this indication the sponsor should consider including patients having at least moderate renal failure and assessing blood levels of the drug, clotting parameters and other safety measures in these patients. Also, I agree with FDA Clinical Pharmacology and Biopharmaceutics that an additional pharmacokinetic/pharmacodynamic study in patients with significant renal insufficiency should be done to allow adequate labeling for dosing Hirulog in these patients.

/S/

Kathy M. Robie-Suh, M.D., Ph.D. 1/11/99

cc:
NDA 20-873
HFD-180/Division File
HFD-180/JDuBeau
HFD-180/KRobie-Suh
HFD-880/ASelen

MEMORANDUM

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

DATE: November 2, 1998

FROM: Director Division of Gastrointestinal and Coagulation drug Products

TO: NDA 20-873

THROUGH: Acting Director Office of Drug Evaluation III

SUBJECT: NDA 20-873: Hirulog for anticoagulation of patients undergoing PTCA for Unstable Angina

Due to the risk of thromboembolic complications secondary to coronary instrumentation, disruption of the intimal layer and exposure of thrombogenics structures, PTCA cannot be performed without adequate anticoagulation. The risk of procedural complication is increased in patients undergoing PTCA for Unstable Angina (UA).

The conventional anticoagulant regimen for PTCA consists of heparin and aspirin, however, no controlled studies have been performed to determine the optimal dose or duration of heparin anticoagulation.

Although widely used, heparin exhibits considerable limitations as anticoagulant. Heparin is an indirect anticoagulant which act by enhancing the activity of the naturally occurring AT-III. Heparin is an heterogeneous mixture of molecules of variable pharmacologic properties, has unpredictable activity due to variable AT-III binding sites and absorption to endothelium and circulating molecular complexes, and is neutralized by anti-heparin protein such as platelet Factor 4. Consequently, considerable intra- and inter-variability of effect are observed. A further limitation of heparin is its inability to neutralize fibrin-bound thrombin and platelet-bound Fact Xa. A clinically important complication of heparin therapy is Heparin-Induced Thrombocytopenia and its thrombotic complications.

Direct anti-thrombin compounds such as Hirudin, hirudin analogues and other synthetic antithrombin compounds may offer advantages over heparin due to high specific activity, lack of dependence on AT-III for their activity, ability to inactivate clot-bound thrombin, lack of interaction with neutralization by anti-heparin molecules, lack of interaction with platelets and antibodies formation.

Hirulog (BG8967) is a synthetic 20 aminoacid peptide similar to hirudin. Hirulog is a potent and specific direct inhibitor of alpha-thrombin (circulating and clot-bound), independent of AT-III and not neutralized by PF4. Hirulog differs from hirudin in that its binding to thrombin is reversible resulting in recovery of thrombin binding sites. Hirulog has a short half-life of 46 minutes. The anticoagulant activity of Hirudin is dose-related and related to plasma drug concentration.

Hirulog has been evaluated for its efficacy and safety as anticoagulant and antithrombotic regimen in 15 clinical trials, mostly in acute coronary syndromes.

On December 23, 1997, the sponsor submitted NDA 20-873 for the approval of Hirulog as anticoagulant for patients undergoing PTCA for UA. The NDA was based on the results of two pivotal clinical trials that were performed using the same study protocol: '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)'.

As the two trials (C92-304-1 and C-304-2) were of similar design, they will be discussed concomitantly and in combination.

The primary objective of the studies was to demonstrate the safety and efficacy of Hirulog in patients undergoing PTCA for UA compared to similar patients treated with heparin.

Efficacy was determined using the composite endpoint of 'procedural failure' defines as the occurrence during hospitalization of any of the following:

- 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 LBBB;
- Clinical deterioration of cardiac origin 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 the 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.

The efficacy endpoints were classified by a Morbidity and Mortality Classification Committee (MMCC) which consisted of 5 of the principal

investigators.

Safety was assessed primarily in terms of clinically significant bleeding. Major bleeding events were intracranial, retroperitoneal, requiring transfusion of 2 or more units of blood.

In both studies, study populations of 2000 patients were calculated in order to detect, with at least 80% power and a two sided type I error rate of 5%, a 33% reduction in event rate in the Hirulog group compared to the heparin group. The studies were, therefore designed to show superiority of Hirulog compared to heparin.

Efficacy analyses were performed on the evaluable population and on the Intent-To-Treat (ITT) population defined as all patients randomized and receiving any study drug.

Patients were randomized in a 1:1 ratio to Hirulog or heparin. The randomization was stratified on the basis of whether the patient had experienced an acute MI with 4 hours to 2 weeks prior to randomization.

The heparin regimen consisted of an initial infusion over 4 hours of 15 U/kg/hr followed by a bolus dose of 175 U/kg and an infusion of 15 U/kg/hr over 14-24 hours. Two additional bolus doses of 60 U/kg were allowed if the ACT at 5 minutes was < 350 secs.

The Hirulog regimen consisted of an infusion of 2.5 mg/kg/hr over 4 hrs, followed by a bolus dose of 1.0 mg/kg and by an infusion of 0.2 mg/kg/hr for 14-24 hours. Bolus doses of placebo were given to maintain the double-blind design.
All patients received Aspirin, 325 or 300 mg/day.

In study 92-304-1, a total of 2318 patients were randomized and 2131 (92%) received study drug: 1071 received Hirulog and 1060 received Heparin. A total of 206 (19%) in the Hirulog group and 203 (19%) in the Heparin group were post-MI patients.

In study 92-304-2, a total of 2354 patients were randomized and 2181 (93%) received study drug: 1182 received Hirulog and 1172 received Heparin. A total of 163 (15%) in the Hirulog group and 169 (16%) in the Heparin group were post-MI patients.

The demographic and baseline characteristics of the two treatment groups in the two studies were essentially comparable, except for age difference in study 92-304-1 where the Heparin patients were younger.

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. The data for the overall patient population are summarized in the following table.

Incidence of Procedural Failure during Hospitalization (ITT Population)

Study	Patients (n) Total		# procedural failure (%)		Total # Post-MI patients (%)		# 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

There was no statistically significant difference between the two treatment group for the overall study population in both studies. The odd ratio and corresponding 95% for procedural failure were not significant in both studies: 0.835; 95% CI 0.608,1.146 for study C92-304-1 and 0.951; 95% CI 0.695,1.30 for study C92-304-2.

In the post-MI subgroup, the incidence of procedural failure was lower for the Hirulog group than in the Heparin group in both studies; the difference was statistically significant in study C92-304-2. The odd ratio and corresponding 95% CI in study C-92-304-2 were 0.39; 95% CI 0.178,0.857. In the same study, however, the odd ration for the non post-MI was 1.132.

No significant differences in procedural failure were noted between genders, for race or for age differences.

Secondary endpoints included incidence rates of individual components of procedural failure. The data are summarized in the following table.

Incidence of individual components of procedural failure (ITT analysis)

Study	Death		MI		Revascul-arization		EAVC		IAVC	
	Hir.	Hep.	Hir.	Hep.	Hir.	Hep.	Hir.	Hep.	Hir.	Hep.
C92-304-1	3 .3%	1 .1%	21 2%	28 2.6%	49 4.6%	65 61%	22 2.1	29 2.7%	8 .7%	9 .8%
C92-304-2	6 .5%	5 .5%	23 .6%	24 .5%	47 2.1%	57 2.2%	23 4.3%	24 5.2%	11 1%	2 .2%

The incidence of impending abrupt vessel closure was significantly lower in the heparin group (p-value= 0.008). No statistically significant difference was noted for any of the other endpoints in both studies.

Incidence of individual components of procedural failure in Post-MI patients

Study	Death		MI		Revascul-arization		EAVC		IAVC	
	Hir.	Hep.	Hir.	Hep.	Hir.	Hep.	Hir.	Hep.	Hir.	Hep.
C92-304-1	0 0	1 .34%	0 0	7 3.4%	7 3.4%	10 4.9%	3 1.5%	7 3.4%	2 1%	3 1.5%
C92-304-2	0 0	2 1.2%	2 1.2%	7 4.1%	4 2.5%	14 8.3%	3 1.8%	3 1.8%	2 1.2%	0 0%

Significantly more MIs occurred in the Heparin group (p-value=0.0007) in study C92-304-1 and more revascularization were required in the Heparin group (p-value=0.027) in study C92-304-2, however, the numbers were very small.

Efficacy analyses (ITT) performed on the combined data from both studies showed that the incidence of procedural failure for the ITT population were 7.4% (160/2161) for the Hirulog group and 8.2% (177/2151) for the Heparin group (p-value=0.31).
In the post-MI population, the incidence of procedural failure was reduced in the Hirulog group to 5.15% (19/369) compared to 10.7% (40/372) for the Heparin group. The difference was statistically significant (p-value=0.004).

Follow-up at 6 months was obtained for more than 95% of patients. No difference in incidence of events was noted between the two treatment groups in both studies.
No difference in events at 6 month follow-up was noted in the post-MI subgroups in both studies.

The data for the overall study population from each study are summarized in the following table.

Incidence of Clinical Events at 6 month Follow-up

Study	Death		MI		Revascul-arization		Rehospitali-zation for angina		Any Event	
	Hir.	Hep.	Hir.	Hep.	Hir.	Hep.	Hir.	Hep.	Hir.	Hep.
C92-304-1	20 2	15 1%	29 3%	22 2%	193 19%	201 19%	248 24%	236 23%	532 52%	507 49%
C92-304-2	17 2	11 1%	19 2%	22 2%	176 17%	181 18%	224 21%	234 23%	529 51%	533 52%

Safety was assessed primarily in terms of bleeding events. In both studies, both the incidence of major bleeding and of any bleeding were significantly lower in the Hirulog groups. The time to first occurrence of major bleeding also favored Hirulog.
The data are summarized in the following table.

Incidence of Bleeding Events

Study	Patients (n) Total		Major Bleeding (%)		Any Bleeding (%)		p-values	
	Hir.	Hep.	Hir.	Hep.	Hir.	Hep.	Any Bleed.	Major Bleed.
C92-304-1	1071	1060	47 (4)	113 (11)	593 (55)	864 (82)	.0001	.0001
C92-304-2	1090	1091	32 (3)	86 (8)	561 (51)	835 (77)	.0001	.0001

In the post-MI population, the incidences of any bleeding or major bleeding were also significantly lower in the Hirulog groups. The data are summarized in the following table.

Incidence of bleeding events in Post-MI Patients

Study	Patients (n) Total		Major Bleeding (%)		Any Bleeding (%)		p-values	
	Hir.	Hep.	Hir.	Hep.	Hir.	Hep.	Any Bleed.	Major Bleed.
C92-304-1	206	203	8 (3.8)	25 (12.3)	118 (57)	151 (74)	.0001	.0005
C92-304-2	163	169	1 (0.6)	19 (11.2)	78 (48)	115 (68)	.0002	.0001

Notably, more patients in the Heparin groups of both studies were discontinued from the study due to adverse events, mainly bleeding events. In study C92-304-1, 29 patients (2.7%) in the Hirulog group vs. 79 patients (7.4%) discontinued study drug for adverse events. In study C92-304-2. 18 patients (1.7%) in the Hirulog group vs. 65 patients (6.0%) in the Heparin group discontinued study drug for adverse events.

Comments and Recommendations:

Anticoagulation is necessary for prevention of procedural thrombotic complications of cardiovascular surgery and heparin is conventionally used for this purpose. Heparin is not specifically approved for the indication of PTCA and the most appropriate regimen for optimal efficacy and safety has not been established by controlled clinical trials. The introduction of various antiplatelet drugs for use in combination with anticoagulant regimens for acute coronary syndromes has required appropriate modifications of heparin dose and regimen in order to achieve greater efficacy without excessive bleeding complications.

Two adequate and well controlled studies have compared the efficacy and safety of Hirulog and Heparin (both in combination with aspirin) for prevention of fatal and non-fatal ischemic complications (procedure failure) secondary to PTCA. The objectives of the two studies were to

demonstrate that Hirulog was more effective than Heparin in preventing procedural failure in patients undergoing PTCA for UA. However, the superior efficacy of Hirolog was not demonstrated in either of the two studies, nor in the combined patient population from the two studies.

The efficacy results showed no significant difference in incidence of events between the two treatment groups. Post-hoc analyses were performed to demonstrate equality of the two regimens, however, the studies were not designed to show non-inferiority of Hirulog to Heparin.

Significantly lower rates of procedural failure were observed for the Hirulog-treated patients in the post-MI subgroup in study C93-304-2. However, the number of patients in this subgroup was small and the results were not replicated in study C92-304-1.

In both studies, significantly fewer bleeding events, including major bleeding, occurred with the use of Hirulog compared to Heparin and fewer patients in the Hirulog group discontinued treatment due to bleeding. However, this safety advantage may have resulted from increased bleeding risk in the Heparin group due to the Heparin regimen used for the studies. In fact, in both studies, more than 70% of patients in the Heparin group had ACT in excess of the conventional limit of 350 secs.

In view of the above observations, approval of Hirulog for anticoagulation in patients undergoing PTCA for the treatment of unstable angina is not recommended.

The sponsor should consider conducting an additional clinical trial, prospectively designed to demonstrate superior efficacy and safety of Hirulog compared to Heparin (at the dose and regimen currently used) in the high-risk population of post-MI patients undergoing PTCA for the treatment of unstable angina.

/S/

Lilia Talarico, M.D.

cc:
NDA 20-873
HFD-180
HFD-103
HFD-180/Talarico

CSO/Dubau

MEMORANDUM OF TELECON

DATE: September 30, 1998

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

BETWEEN:

Name: Dr. Clive Meanwell, CEO
Mr. Tom Lategan, Regulatory Affairs
Phone: (888) 422-7124 #237294
Representing: The Medicines Company

[redacted]

Name: Dr. Ralph D'Agostino, Biostatistics, Boston University
Dr. Robert M. Califf, Duke Clinical Research Institute (DCRI)
Dr. David Kong, DCRI
Dr. Kerry Lee, DCRI
Dr. John Bittl, Interventional cardiologist, Ocala Heart Institute
Representing: Other consultants

AND

Name: Ms. Melodi McNeil, Project Manager
Dr. Lilia Talarico, Division Director
Dr. Kathy Robie-Suh, Medical Reviewer
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Advisory Committee Background Package

BACKGROUND: This application was submitted December 23, 1997 by [redacted] (on behalf of The Medicines Company) to market Hirulog (bivalirudin) Injection as an anticoagulant in patients undergoing percutaneous transluminal coronary angioplasty (PTCA). The application is currently scheduled to be presented at the Cardio-Renal Advisory Committee (CRAC) meeting on October 23, 1998. In a September 25, 1998 submission the firm provided a draft advisory committee briefing package for Agency review and comment.

At Dr. Talarico's request, I arranged a teleconference with the firm to convey the Division's comments on the briefing package.

TODAY'S PHONE CALL: Dr. Talarico said that in general, the briefing package is acceptable, however, she and Dr. Robie-Suh requested clarification of several items in the submission. In response to a question, the sponsor's representatives said the study undertaken by the [redacted] (see page 97 of the briefing package) was not part of the original NDA. According to the sponsor, this information was submitted recently as part of the preparations for the CRAC. After some discussion, it was decided that the sponsor will revise the advisory committee briefing package to indicate that this study was not part of the NDA, and therefore has not been reviewed by the Division. Further, they indicated that the briefing package will only contain information from the NDA (with the exception of the [redacted] study, as noted), although they said other supplemental material might be part of either the firm's presentations or their responses to questions at the advisory committee meeting. Representatives from The Medicincs Company said the background package would be revised based on today's teleconference and a copy sent to the Division within the next few days. The call was then concluded.

/S/ 9/30/98
Melodi McNeil, Project Manager
Regulatory Health Project Manager

cc: Original NDA 20-873
HFD-180/Div. File
HFD-180/Talarico
HFD-180/Robie-Suh
HFD-180/DuBeau

TELECON

(20-873

MEMORANDUM OF TELECON

DATE: September 1, 1998

APPLICATION NUMBER: NDA 20-873; Hirulog® (bivalirudin) Injection

BETWEEN:

Name: Dr. C. Meanwell; CEO, The Medicines Company
Mr. T. Lategan; Project Manager, The Medicines Company
[redacted]

Representing: The Medicines Company [redacted]

AND

Name: Ms. J. DuBeau; Regulatory Health Project Manager
Dr. A. Sankoh; Biostatistics Acting Team Leader
Dr. M. Rashid; Biostatistics Reviewer
Dr. L. Talarico; Division Director
Dr. K. Robie-Suh; Medical Officer
Dr. E. Duffy; Chemistry Team Leader
Dr. A. Shaw; Chemistry Reviewer
Mr. J. Hunt; Biopharmaceutics Acting Team Leader

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Discussion of Clinical and Statistical Data Submitted in NDA 20-873

BACKGROUND:

Hirulog® (bivalirudin) Injection, a 20 amino acid synthetic peptide thrombin inhibitor, is under development for use as an anticoagulant in patients with acute myocardial infarction and in patients undergoing percutaneous transluminal coronary angioplasty (PTCA). There is currently a pending NDA under review for Hirulog® Injection (NDA 20-873) pursuing the latter indication. All pivotal clinical trials for this NDA were conducted under the IND [redacted] Biogen, Inc., the original sponsor of the IND, stopped clinical development of Hirulog® approximately two years ago for business reasons. In March 1997, the ownership of the IND was transferred from Biogen, Inc. to The Medicines Company (TMC). [redacted] is the contract research organization for TMC.

Two pivotal phase III trials were submitted in the NDA in support of the proposed indication. The first pivotal trial, Study C92-304-1, is a multicenter, double-blind, randomized comparison of Hirulog® and heparin for anticoagulation in patients with unstable angina undergoing PTCA. The primary efficacy endpoint is the combined incidence of death, myocardial infarction (MI), or revascularization. The firm claims that among all patients, there is no statistical significance between groups (Hirulog® and heparin) regarding the primary efficacy endpoint, however, the incidence of major bleeding is statistically significant between groups, favoring Hirulog®. In addition, the firm claims that among post-MI patients, there is statistical significance between groups regarding the primary efficacy endpoint, favoring Hirulog®. According to the firm, the same results were replicated in the second pivotal trial, Study C92-304-2, with an even higher statistical significance between groups regarding the primary efficacy endpoint (favoring Hirulog®) among the post-MI patients.

After the August 28, 1998, team meeting, Dr. Talarico requested that the firm be contacted to discuss the clinical and statistical data and results of the pivotal clinical trials, and to inform the firm that their NDA is scheduled to be discussed at the Cardio-Renal Advisory Committee (CRAC) on October 23, 1998.

TODAY'S PHONE CALL:

Dr. Talarico began the conversation by stating that the NDA will be presented on October 23, 1998, at the CRAC meeting. Dr. Robie-Suh stated that the primary analysis of the two pivotal clinical trials did not demonstrate superiority of Hirulog® over heparin with regard to the primary efficacy endpoint. The post-MI subgroup in Study C92-304-2 did show some effect, but not strong enough to demonstrate superiority to heparin. The firm agreed and added that the safety profile of Hirulog® is superior to heparin. Dr. Robie-Suh stated that the firm needs to assert efficacy by establishing that the heparin control group is "active" in patients undergoing PTCA. The firm stated that they have been working with the Cleveland Clinic in Ohio on a meta-analysis to demonstrate that heparin is "active" (see attached handouts faxed from the firm). The firm could not commit to when the meta-analysis would be available. Dr. Talarico advised the firm to submit a description of this analysis to the CRAC members in the background package by October 1, 1998. Drs. Robie-Suh and Sankoh requested that the firm submit any additional/updated clinical and statistical information that is available. In addition, they requested that the firm submit the meta-analysis data to the NDA prior to the CRAC meeting. This information will be formally reviewed prior to the CRAC if time permits. Dr. Talarico stated that if the firm submits a major amendment after September 23, 1998, the PDUFA user-fee goal date of September 23, 1998, may be extended by three months (March 23, 1999). Dr. Talarico stated that the clinical and statistical reviews of all clinical and statistical submissions to the NDA thus far will be finalized by September 30, 1998, to allow adequate time for review by the CRAC members. The firm committed to working swiftly with the Cleveland Clinical to complete the meta-analysis and include it in the background package for the CRAC meeting. The call was then concluded.

/S/ 9/10/98

Juneann DuBeau, RN, MSN
Regulatory Health Project Manager

Attachment: Handouts

cc: Original NDA 20-873
HFD-180/Div. File
HFD-180/Ms. J. DuBeau
HFD-180/Robie-Suh
r/d Init: Talarico 9/8/98
JD/September 4, 1998 (drafted)

TELECON