begins on page 004. Page numbers for sections 13-19 in the overall index have been omitted. Further, there is no range for volume and page numbers. See 21 CFR 314.50(b).

d. The firm used the same volume numbering system for the CMC Presubmission and the NDA submission. For example, according to the overall index, volume 1.1 refers to the Table of Contents, Draft Labeling, and Summary as well as and to CMC Drug Substance and Drug Product.

e. The Table of Contents in the clinical section for the individual study reports does not list content of each volume.

f. There is no reference to specific page numbers for the following DMFs: [redacted] Under 21 CFR 314.50(g)(1), a reference to information is required to identify the file by name, reference number, volume, and page number in the agency's records where the information can be found.

2. Note:

a. The 356h form is incomplete. Under the "Cross References" section, there is no reference to IND [redacted] (Novastan®) to which many of the clinical studies were submitted. On page 2 of the form, there is a check mark next to item 4 (CMC), however, only some of the CMC volumes that were included in the CMC Presubmission (6/27/97) were resubmitted with the NDA submission (8/11/97).

b. LOAs for the following DMFs were not placed behind the 356h form in the archival or the chemistry review copies: [redacted]

c. The volume numbering system on the archival jackets differs from the volumes referenced in the overall index. For example, where the index refers to volume 1.70, the archival jacket is 2.70. For the convenience of the reviewers, the correct volume numbering system on the archival jackets is listed below.

CMC Presubmission (submitted/received 6/27/97):

Volumes 1.1-1.8

NDA Submission (submitted 8/11/97, received 8/15/97):

Volume 2.1
Volume 2.2 - does not exist according to the firm
Volumes 2.3-2.10 - exactly the same as the CMC presubmission volumes according to the firm.
Volumes 2.11-2.129
Volumes 2.129A
Volumes 2.130-2.139
Volumes 2.139A,B,C,D,E,F,G
Volumes 2.140-2.151
Volumes 2.151A,B,C,D,E,F,G,H,I,J,K
Volumes 2.152-2.154
Volumes 2.154A,B
Volumes 2.155-2.160
Volumes 2.160A
Volumes 2.161-2.167
Volumes 2.168-2.200 - do not exist according to the firm
Volumes 2.201-2.283

B. Clinical and Statistical Section: All elements listed in the "Guideline for the Format and Content of the Clinical and Statistical Sections of the New Drug Applications" (July 1988) are addressed except for the following:

1. Information Request:

a. There is no reference to specific page numbers for the "Location of Study Report" and "Location of Patient Data" sections of the investigator tables.

b. The following are not included in the Clinical Pharmacology Studies tables: investigator, starting date of study, age range, reference to CRFs, and product code.

c. Study reports for "ARG-230" and "ARG-231" could not be located. Under 21 CFR 314.50(d)(5)(ii) and (6)(i), a description and analysis of each controlled clinical study pertinent to a proposed use of the drug, including the protocol and a description of the statistical analyses used to evaluate the study must be provided in both the clinical and statistical sections of the NDA.

2. Note:

The ISE begins in volume 2.147 on page 16 and the ISS begins in volume 2.150 on page 229.

C. Summaries: All elements listed in the "Guideline for the Format and Content of the Summary for New Drug and Antibiotic Applications" (February 1987) are addressed.

Conclusions

The following information, if deemed necessary by the appropriate reviewers can be requested from the firm:

1. Revise the overall index to include correct volume numbers (i.e. starting with volume 2.1 and stating which volumes do not exist) and page numbers. The CMC volume numbers in the index should be referred to as either 1.1-1.8 or 2.3-2.10, but not both.

2. Revise the Table of Contents in the clinical section for the individual study reports to include the content of each volume.

3. Reference specific page numbers for the following DMFs: [redacted]

4. Reference specific page numbers for the "Location of Study Report" and "Location of Patient Data" sections of the investigator tables.

5. Revise the Clinical Pharmacology Studies tables to include: investigator, starting date of study, age range, reference to CRFs, and product code.

6. Locate or provide study reports for "ARG-230" and "ARG-231".

/S/ 9/12/97
Julieann DuBeau, RN,MSN
Regulatory Health Project Manager

cc:
Original 20-883
HFD-180/Div. Files
HFD-180/DuBeau

HFD-180/Talarico
HFD-180/Sizer
HFD-180/Duffy
HFD-180/Al-Hakim
HFD-180/Choudary
HFD-180/Antonipillai
JD/September 11, 1997 (drafted)
JD/9/12/97/c:\wpfiles\rev\20883709.rjd

ADMINISTRATIVE REVIEW

MEMORANDUM OF MEETING MINUTES

Meeting Date: January 11, 2000
Time: 9:00 AM – 10:00 AM
Location: Parklawn Building, Room 6B-45

Sponsor: Texas Biotechnology Corporation

Application: NDA 20-883; Novastan® (argatroban) Injection

Proposed Indication: Use in patients with heparin-induced thrombocytopenia who require anticoagulation.

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. S. Aurecchia; Deputy Division Director
Dr. K. Robie-Suh; Hematology Team Leader
Dr. A. Farrell; Medical Officer
Ms. J. DuBeau; Regulatory Health Project Manager

OPDRA Attendees/Titles:

Ms. J. Staffa; Acting Division II Director
Ms. A. Corken; Safety Evaluator
Dr. C. McCloskey; Epidemiologist
Mr. Z. Li; Epidemiologist
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:

Cardiac Adverse Events

In the firm's pivotal clinical trial ("ARG-911") there was a slightly higher incidence of cardiac deaths and arrhythmias in the argatroban treated group. Therefore, cardiac adverse events would be the signal that the division would be most interested in having OPDRA monitor. The drug product is approved in Japan and has been used in approximately 5,000 patients without incidence of cardiac adverse events, according to the firm. The Division will request that ODE III consider asking the firm to commit (phase IV) to further cardiac testing (i.e., in vitro electrophysiologic testing, in cardiac compromised animal models, and the collection of information on cardiac adverse events).

Other Issues

According to the firm, there is no drug-drug interaction between argatroban and erythromycin. However, there is potential for drug-drug interactions between argatroban and other drug products metabolized by the liver. The safety database indicates that bleeding is an adverse event, which is common to this class of drug products. There may be an increased risk of bleeding when argatroban is given concomitantly with antiplatelets, thrombolytics, and other anticoagulants.

Nomenclature

The trademark review, consulted to OPDRA on December 6, 1999, is pending.

Action Items:

Ms. Corken will search the AERS and World Health Organization (WHO) databases for adverse reaction reports on Novastan® Injection.

Ms. Dempsey will provide consult conclusions to the reviewing division by January 14, 2000.

Minutes Preparer /S/ 1/24/00

Chair Concurrence: /S/ 1-24-00

cc: Original NDA 20-883
HFD-180/Div. Files
HFD-180/Meeting Minutes files
HFD-180/DuBeau
HFD-180/Talarico
HFD-180/Robie-Suh
HFD-180/Farrell
HFD-180/Aurecchia
HFD-440/Staffa
HFD-440/Corken
HFD-440/McCloskey
HFD-440/Li
HFD-440/Dempsey
HFD-42/Staub
R/d Init: Talarico 1/24/00
JD/January 24, 2000 (drafted)

MEETING MINUTES

CSO/DuBeau

MEMORANDUM OF MEETING MINUTES

Meeting Date: July 14, 1998
Time: 1:00 PM - 2:30 PM
Location: Conference Room Q, Parklawn Building

Application: NDA 20-883
Novastan® (argatroban) Injection

Type of Meeting: Other: Discussion of "Not Approvable" Issues

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. H. Gallo-Torres; Gastrointestinal Team Leader
Dr. K. Robie-Suh; Medical Officer
Ms. J. DuBeau; Regulatory Health Project Manager

Division of Biometrics III (HFD-720)

Dr. A. Sankoh; Acting Statistical Team Leader

Office of Drug Evaluation III (HFD-103)

Dr. P. Botstein; Acting Office Director

External Constituent Attendees and titles:

Texas Biotechnology Corporation

Mr. D. McWilliams; President and CEO
Dr. R. Dixon; Vice President, Research
Mr. G. Knappenberger; Senior Director, Clinical and Regulatory Affairs

Consultants

Dr. B. Lewis; Loyola University Medical Center
Dr. D. Wallis; Loyola University Medical Center
Dr. J. Kelton; McMaster University Medical Center
Dr. J. Herson; Applied Logic Associates
Dr. S. Berkowitz; Duke University Medical Center

SmithKline Beecham Pharmaceuticals

Dr. C. Blumhardt; Vice President and Director, US Regulatory Affairs
Ms. C. Clark; Director, US Regulatory Affairs
Ms. N. Blackman; Senior Statistician, Biostatistics and Data Sciences
Mr. B. Ilson; Director, Clinical Research and Development
Dr. S. Sheth; Associate Director, Clinical Pharmacology
Dr. N. Shusterman; Vice President and Director, Cardiovascular Therapeutic Unit, Clinical Research, Development, and Medical Affairs
Dr. D. Miller; Director, Biostatistics and Data Sciences

Background:

Texas Biotechnology Corporation submitted a new drug application on August 11, 1997, for Novastan® (argatroban) Injection, a synthetic thrombin inhibitor, with the following proposed indication: Anticoagulant therapy in patients with heparin-induced thrombocytopenia. The firm received a Not Approvable letter on May 8, 1998, which includes deficiencies in the following areas: clinical/statistical; chemistry, manufacturing, and controls (CMC); and microbiology. The Agency's advice is that the firm either identify and analyze an appropriate historical control, or conduct an additional study comparing argatroban to a currently approved therapy for heparin-induced thrombocytopenia (HIT) and thrombosis syndrome (HITTS) in patients who need anticoagulation. The firm responded to the CMC and microbiology deficiencies in two amendments to the NDA dated July 8 and 20, 1998. The firm has requested this meeting to discuss the clinical/statistical deficiencies as outlined in the Not Approvable letter and plans to fully respond to the letter later this year.

Meeting Objectives:

1. To discuss the issues related to the current file.

2. To discuss the planned amendment in which all stated deficiencies will be addressed.

Discussion Points:

In response to the firm's questions in their June 22, 1998, submission (background package for the meeting), the following agreements were reached after discussion. The format provides the firm's questions (1-6), followed by the Agency's responses in bolded lettering.

1. We solicit the Agency's input on the approach to be used in the selection of new historical controls. (Refer to pages 13-19 in the background package).

   - **After discussion of the retrospective historical control created by Dr. Bruce Lewis and the registry created by Dr. Diane Wallis, it was decided that Dr. Wallis' registry is acceptable for use as the new historical control.**

   - **Provide CRFs of the registry patients.**

   - **Consider an independent, blinded, third party to review the selected registry for diagnosis and outcome of each patient.**

   - Dr. Lewis reiterated some of the points raised in the April 9, 1998, letter addressed to Dr. Talarico (see attached) which describes reasons why the Loyola historical control included in the original NDA, should not be used. The firm proposes to use Dr. Wallis' registry for the new historical control. Dr. Wallis' registry (January 1991 - December 1993) includes 116 serologically confirmed HIT patients who were prospectively selected. According to the firm, thus far, 102 of the 116 patients meet the inclusion/exclusion criteria as defined in the original phase III protocol. Dr. Robie-Suh suggested a side-by-side comparison of the registries regarding inclusion/exclusion criteria to determine comparability of groups. Dr. Talarico requested that the firm describe where the 116 patients in Dr. Wallis' registry originated from (i.e., overall number of patients who were tested for HIT). Overall, Dr. Talarico stated that the proposed new historical control plan as described, i.e. all patients with a positive HIT serological test, may be acceptable.

2. We solicit the Agency's comments on the proposal to validate the clinical validity of the subclassification of death as "thrombotic" or "due to underlying disease." (Refer to page 20 in the background package).

   - **Please note that "all cause" death will be part of the primary efficacy analysis. In your secondary efficacy analysis, you can separate death into "due to underlying disease" or "thrombotic".**

   - The firm stated that it is difficult to show statistical significance if "all cause" death is part of the analysis of a trial with a historical control. There may be a clinical benefit even though mortality between the argatroban-treated group and historical control group is similar. Dr. Talarico stated that it is difficult to identify the exact

cause of death without an autopsy. In addition, statistical significance with "all cause" death is not expected, however, greater deaths in the argatroban-treated group is unacceptable. The two groups must be comparable and the composite primary endpoint of new thrombosis, amputation, and all cause death must show directionality. Dr. Talarico stated that subgroup analyses could be performed (e.g. sepsis, cancer, trauma) to assess the outcomes in the two groups in relation to the major underlying conditions. The firm questioned whether they could change the primary endpoint to a thrombotic composite endpoint. Dr. Talarico stated that the endpoint should not be revised at this late date and should remain the primary endpoint as specified in the original phase III protocol. In response to a question from Dr. Sankoh, the firm stated that a clinical study comparing argatroban to a currently approved therapy to show equivalence in terms of safety and efficacy is not mathematically feasible, requiring enrollment of several thousand patients.

3. We solicit the Agency's comments on the proposal to avoid the opportunity for enrichment to occur, in the population for HIT patients who already experienced a thrombotic event, when selecting historical controls. (Refer to pages 21-22 in the background package).

   - **It is acceptable to use all serologically confirmed HIT patients, however, please divide them into patients who had an initial thrombotic event and patients who developed a secondary or new thrombosis on heparin.**

4. We solicit the Agency's comments regarding obtaining the following claim: "Novastan is indicated as anticoagulant therapy in patients suspected of or known to have heparin-induced thrombocytopenia or associated thrombosis in order to prevent further thromboembolic complications."

   - **Consider the wording in the following proposed indication: "Novastan is indicated as anticoagulant therapy in patients** with **heparin-induced thrombocytopenia** and **associated** thromboembolic disease **in order to prevent further thromboembolic complications."**

   - **The indication for HIT without thromboembolism (i.e. to prevent thromboembolism) will require a study of this patient population randomized to treatment and no treatment.**

5. We solicit comments from the Division regarding the proposed content/format of the upcoming amendment.

   - **Include CRFs and CRTs for the historical control. Provide patient narratives for deaths.**

- **Provided unannotated labeling on diskette in MS WORD 97 and certify that the information contained on the diskette is identical to that submitted in hard copy.**

- **Provide a detailed Table of Contents, and corresponding volume/page numbers.**

6. We solicit the Agency's comments regarding the approach and full plan for the statistical section of the upcoming amendment. (Refer to pages 25-28 in the background package).

   - **In the primary efficacy analysis, provide the absolute treatment effect difference between the argatroban-treated patients and the historical control patients. In addition, provide 95% confidence intervals based on the absolute treatment effect difference.**

   - **In the secondary efficacy analysis, include all deaths for any cause, both before and after 37 days. Deaths due to thrombotic events can be analyzed as secondary efficacy.**

   - In addition, the secondary efficacy analysis should provide information for **composite events at the following time points: 7, 14, 21, 28, and 37 days. We suggest the use of Kaplan-Meier Curves with both Log Rank and Wilcoxon Rank Sum statistics.**

Minutes Preparer: /S/ 8/11/98

Chair Concurrence: /S/ 8/11/98

Attachment: April 9, 1998, letter from Dr. Bruce Lewis to Dr. Lilia Talarico

cc: Original NDA 20-883
HFD-180/Div. Files
HFD-180/Meeting Minutes files
HFD-180/CSO/DuBeau
r/d Init: Talarico 8/7/98, 8/11/98
JD/August 6, 1998 (drafted)
JD/8/11/98/

MEETING MINUTES

DuBeau

MEMORANDUM OF MEETING MINUTES

Meeting Date: October 2, 1997
Time: 11:00 AM - 12:00 Noon
Location: Conference Room 6B-45, Parklawn Building

Application: NDA 20-883
Novastan® (argatroban) Injection

Type of Meeting: 45-Day Filing Meeting

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; Acting Division Director
Dr. K. Sizer; Medical Officer
J. Choudary; Pharmacology Team Leader
Dr. I. Antonipillai; Pharmacologist
Dr. E. Duffy; Chemistry Team Leader
Dr. A. Al-Hakim; Chemist
Ms. J. DuBeau; Regulatory Health Project Manager

Division of Biometrics III (HFD-720)

Dr. A. Sankoh; Statistician

Division of Pharmaceutical Evaluation II (HFD-870)

Dr. R. Pradhan; Pharmacokineticist
Dr. C. Cronenberger; Pharmacokineticist

Division of Scientific Investigations (HFD-340)

Dr. R. Young; Medical Officer
Dr. M. Skelly; Pharmacokineticist

Office of New Drug Chemistry II (HFD-820)

Dr. J. Gibbs; Office Director

Background:

Texas Biotechnology Corporation submitted this NDA on August 11, 1997, (received August 15, 1997) for Novastan® (argatroban) Injection with the following proposed indication: anticoagulant therapy in patients with heparin-induced thrombocytopenia. The Chemistry, Manufacturing, and Controls (CMC) section of the application was submitted and received on June 27, 1997, as a Presubmission to the NDA. The filing date for this application is October 14, 1997.

Meeting Objective:

To determine the fileability of this application.

Discussion Points:

I. Administrative

A. Filing Issues: None

B. Information Requests:

1. Proposed labeling on diskette in Word Perfect 6.1 using the three column format.

2. Revised, detailed Overall and Clinical Tables of Contents.

3. Revised 356h form which references IND ——— in the "Cross References" section.

II. Clinical

A. Filing Issues: None

B. Information Requests:

1. Plans for studying Novastan® (argatroban) Injection in the pediatric population.

2. Study reports for protocol ARG-230 entitled "A randomized, double-blind, study of two doses of NOVASTAN versus placebo as adjunctive therapy to ——— in acute myocardial infarction (AMI) study" and ARG-231 entitled "A randomized, single-blind, study of two doses of NOVASTAN versus heparin as adjunctive therapy to recombinant tissue

plasminogen activator (rt-PA) in acute myocardial infarction. MINT study."

3. Revised "Location of Study Report" and "Location of Patient Data" sections of investigator tables to reference specific page numbers.

4. Dr. Sizer stated that he will provide a list of additional requests to be forwarded to the firm.

III. Statistical

A. Filing Issues: None

B. Information Requests:

1. Stability and efficacy data on diskette in SAS data set format.

2. Efficacy results of the Two-sample Normalization Test.

3. Copy of all chapters from textbooks referenced in the application.

4. The location of the original ARG-911 (pivotal Phase III study) protocol as submitted to IND [redacted]

IV. Chemistry/Manufacturing/Controls (CMC)

A. Filing Issues: None

B. Information Requests:

1. Stability and light stability data out to 48 hours, on the resulting solution when Novastan® is added to the following diluents: 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, and Lactated Ringer's Solution, USP.

2. A request for withdrawal of the submitted Environmental Assessment and categorical exclusion from the Environmental Assessment in accordance with 21 CFR 25.15(d) [62 FR 40570 (August 28, 1997)].

V. Preclinical Pharmacology

A. Filing Issues: None

B. Information Request: List of all pharmacology and toxicology studies that were not previously submitted to IND [redacted]

VI. Biopharmaceutics

A. Filing Issues: None

B. Information Requests: Biopharmacological information and study summaries on diskette in ASCII file format.

VII. Division of Scientific Investigations (DSI)

A. Filing Issues: None

B. Information Requests: None

VIII. Microbiology

A. Filing Issues: None (see attached e-mail)

B. Information Requests: None

Conclusions:

It was decided to file the application. The administrative, clinical, statistical, CMC, preclinical pharmacology, and biopharmaceutics requests will be forwarded to the firm in an information request letter. A team planning meeting to include the medical officer, statistician, and scientific investigator will be scheduled in early December 1997. The PDUFA User-Fee goal date for this application is February 15, 1998. The individual reviewer due date for this application is January 1, 1998, since the application (1P) requires office level signature.

/S/ 10/9/97
Julieann DuBeau, RN, MSN
Regulatory Health Project Manager

Attachment: E-mail from Dr. Uratani (microbiologist)

cc: Original NDA 20-883
HFD-180/Div. Files
HFD-180/Minutes Files

HFD-180/CSO/DuBeau
HFD-180/Talarico
HFD-180/Sizer
HFD-180/Choudary
HFD-180/Duffy
HFD-180/Al-Hakim
HFD-180/Cowthran
HFD-870/Kaus
HFD-870/Cronenberger
HFD-720/Huque
HFD-720/Sankoh
HFD-340/Robert Young
HFD-340/M.Skelly
HFD-160/Cooney
HFD-160/Uratani
r/d Init: L.Talarico 10/7/97
JD/October 7, 1997 (drafted)
JD/10/9/97/

MEETING MINUTES

MEMORANDUM OF MEETING MINUTES

Meeting Date: May 21, 1997
Time: 9:30 AM - 11:00 AM
Location: Conference Room P, Parklawn Building

Application: IND [redacted]
NOVASTAN® (argatroban) Injection

Type of Meeting: Pre-NDA

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, Acting Division Director
Dr. K. Sizer, Medical Officer
Dr. N. Markovic, Medical Officer
Dr. J. Canchola, Medical Officer
Ms. J. DuBeau, Regulatory Health Project Manager

Division of Pharmaceutical Evaluation II (HFD-870)

Dr. L. Kaus, Pharmacokineticist-Team Leader
Dr. R. Pradhan, Pharmacokineticist-Reviewer

Division of Biometrics III (HFD-720)

Dr. A. Sankoh, Statistical Reviewer

External Constituent Attendees and titles:

Texas Biotechnology Corporation (TBC):

Dr. R. Schwarz Jr.; Vice President, Clinical Development and Regulatory Affairs
Dr. J. Becker; Senior Director, Clinical Research
Mr. G. Knappenberger; Senior Director, Clinical and Regulatory Affairs
Dr. R. Dixon; Vice President, Research
Mr. D. McWilliams; President
Dr. M. Hursting; Senior Clinical Scientist

Mr. J. Joffrion; Director, Clinical Operations
Mr. T. Massey; Senior Vice President, Drug Development, Coromed, Inc., Data Base Consultant
Dr. R. Scheldewaert; Director, Cardiovascular Program Strategy, Synthelabo Groupe
Ms. A. Evans; Biostatistician, Coromed Inc.
Dr. T. Kogan; Vice President, Chemistry Research

Loyola University Medical Center (Consultants)

Dr. J. Fareed; Professor of Pathology and Pharmacology/Director, Hemostasis and Thrombosis Research Laboratories
Dr. B. Lewis; Principal Investigator, ARG-911 Protocol

Background:

This IND was submitted December 8, 1988, by Genentech and subsequently transferred to TBC on July 26, 1993. The compound is a synthetic thrombin inhibitor derived from L-arginine. At therapeutic doses, it inhibits all physiologic effects of thrombin, including conversion of fibrinogen to fibrin, platelet aggregation, and activation of Factors XIII and VIII. NOVASTAN® is under development as a therapeutic agent for the treatment of thromboembolism associated with heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) as well as prophylaxis of thromboembolism in patients with heparin-induced thrombocytopenia (HIT). For the purpose of these minutes, in the clinical setting, both HIT and HITTS are referred to globally as HIT. The proposed indication for the NDA to be submitted will be for anticoagulant therapy in patients with HIT. The firm has requested this meeting to present the results of the single pivotal trial, Protocol No. ARG-911, entitled "An Open-label Study of NOVASTAN® (brand of argatroban) in Patients with Heparin-induced Thrombocytopenia (HIT) or Heparin-induced Thrombocytopenia and Thrombosis Syndrome (HITTS)," and to receive any Agency recommendations prior to submitting the application later this year.

Meeting Objectives:

1. Present preliminary results of the single Phase III pivotal trial.

2. Obtain Agency feedback on whether there is sufficient data available to submit an NDA in the near future.

3. Obtain Agency comments on the proposed content and format of the future NDA.

Discussion Points:

1. Overview of the design and preliminary results of the single Phase III pivotal trial (Protocol ARG 911).

The proposed NDA will contain a single, multi-center, inpatient, non-randomized, open-label, historically controlled study. The study compared 304 NOVASTAN®-treated patients (160 with HIT and 144 with HITTS) with 217 historically controlled patients (108 with HIT and 109 with HITTS). A dose range of 2.0 to 10.0 μg/kg/min of NOVASTAN® was administered intravenously for up to 14 days duration to target an APTT of 1.5 to 3.0 times baseline. The composite primary efficacy endpoint was new (i.e. not present at baseline) thrombosis, amputation (due to ischemic complications or other causes), and death (due to thrombosis or other causes) over the study period (drug infusion plus 30 days of follow-up). The primary safety endpoints were the incidence of major and minor bleeding. According to the firm, the composite primary efficacy endpoint was statistically significant ($p=0.008$) in the HITTS subgroup, but not in the HIT subgroup ($p=0.083$). Regarding safety, there was no increase in the incidence of major bleeding attributable to NOVASTAN®. However, there was an increase in minor bleeding that was neither clinically serious nor unexpected, and according to the firm, involved primarily minor drops in hematocrit or hemoglobin values (see attached overheads for definitions of major and minor bleeding).

Dr. Sankoh noted that there is an imbalance between the historically controlled population and the NOVASTAN®-treated population, with the latter being more medically compromised at baseline (e.g. incidences of underlying disease and pre-existing conditions). The firm stated that it was difficult to identify patients with HIT/HITTS retrospectively for the historically controlled population. In addition, the historically controlled population represented the full spectrum of the disease, whereas the NOVASTAN®-treated population represented only those with more serious disease.

Dr. Markovic noted a baseline covariate of Warfarin use and requested that the firm separately analyze patients with Warfarin and non-Warfarin use.

In response to a question from Dr. Talarico, the firm stated that approximately 70% of the patients experienced an increased incidence of minor bleeding with a decrease in hemoglobin, between 0-2 g/dl. Dr. Talarico requested that the firm separate out spontaneous bleeding from bleeding due to other causes (e.g. epistaxis, hematoma) when analyzing the safety data. In addition, Dr. Markovic requested that the firm separately analyze patients with platelet counts above and below 30 K/mm^3. In response to a question from Dr. Talarico, the firm stated that approximately half of the patients who experienced major bleeding discontinued treatment.

The firm stated that the proposed indication is as anticoagulant therapy in patients with HIT. Dr. Talarico stated that the firm needs to determine the use of the drug as an anti-thrombin or as an anticoagulant (e.g. CPB, dialysis). In addition, the population (HIT) needs to be specifically defined (i.e. "active" versus "latent HIT"). The firm stated that approximately 90% of the patients are "active" (present heparin exposure) and 10% have a history of HIT. Dr. Talarico reminded the firm that the approved indication will be based upon the pivotal study contained in the application, with the study results represented in the CLINICAL TRIALS section of the package insert.

2. Statistical presentation of the data.

Dr. Sankoh noted that efficacy results using the Two-sample Normalization Test were different than the One-sample Normalization Test. He stated that the results should be similar. Regarding survival analysis of patients with HIT/HITTS for all-cause mortality, Dr. Sankoh agreed with the use of the Cox proportional hazards model to adjust for the imbalance between the historically controlled population and the NOVASTAN®-treated population. In response to a question from Dr. Sankoh, the firm stated that they were unable to detect any imbalance between centers. Dr. Sankoh requested that in the summary of results, the firm provide results by time points (i.e. 10 day intervals) as well as confidence intervals. In addition, Dr. Sankoh requested that the firm separate out thrombosis present at baseline and new thrombotic complications when presenting the results.

3. Biopharmaceutical presentation of the data.

Dr. Pradhan requested that the firm characterize the pharmacokinetics (PK) of argatroban individual isomers in humans. In response to a question from Dr. Pradhan, the firm stated that information regarding the one major metabolite "M1" will be provided in the NDA. Dr. Pradhan reminded the firm that the major and active/toxic metabolites PK need to be discussed in the context of humans including a summary of the correlation between animals and humans. In addition, Dr. Pradhan stated that the PK in patients on dialysis (severe renal impairment) should be provided in the NDA as well as any possibility of population PK parameters estimation or PK-Pharmacodynamic relationship analysis. Regarding Protocol No. ARG-112, entitled "Comparative, Randomized, Three-Way Crossover Drug-Drug Interaction Study of NOVASTAN® (brand of argatroban) Concentrate and Heparin in Healthy Volunteers," the firm needs to explain how the concentration or activity of heparin was studied.

4. Administrative issues.

The firm stated that they are anticipating a July NDA submission with possible pre-submission of the CMC section in June. Dr. Talarico stated that the application status

(i.e. standard or priority) will be determined after receipt of the NDA. The firm was encouraged to request, in writing, a waiver of the requirement to submit paper copies of Case Report Forms and Tabulations, thus, submitting this information electronically. Dr. Talarico reminded the firm to provide a detailed Table of Contents and full references in the annotated labeling. Dr. Sankoh requested that statistical information be provided in SAS data set format (6.10). Dr. Pradhan requested that biopharmacological information and study summaries be provided in ASCII file format. In response to a question from Dr. Talarico, the firm stated that their two manufacturing facilities, Mitsubishi in Japan and [redacted] will be ready for inspection upon NDA submission.

Recommendations/Conclusions:

1. Consider the imbalance between the historically controlled population and the NOVASTAN®-treated population when analyzing the data.

2. Separately analyze patients with the following:

   (a) Warfarin and non-Warfarin use

   (b) Spontaneous and other causes of bleeding

   (c) Platelet counts above and below 30 K/mm^3.

3. Refine the proposed indication and represent study results in the CLINICAL TRIALS section of the package insert.

4. In the summary of results, provide results by time points (i.e. 10 day intervals) as well as confidence intervals. In addition, stratify thrombosis present at baseline and new thrombotic complications. Provide statistical information in SAS data set format (6.10).

5. Characterize the PK of argatroban individual isomers in humans as well as the major and active/toxic metabolites PK in the context of humans, including a summary of the correlation between animals and humans. In addition, provide the PK in patients on dialysis (severe renal impairment) and population PK parameters estimation or PK-Pharmacodynamic relationship analysis. Regarding Protocol No. ARG-112, explain how the concentration or activity of heparin was studied. Provide biopharmacological information and study summaries in ASCII file format.

Minutes Preparer: /S/ 6/12/97

Chair Concurrence: /S/ 6/12/97

MEMORANDUM OF MEETING MINUTES

Meeting Date: February 26, 1997
Time: 2:00 - 3:30 p.m.
Location: Conference Room. 6B-45, Parklawn Building

Application: IND [redacted] NOVASTAN® (argatroban) Injection

Type of Meeting: CMC Pre-NDA meeting

Meeting Chair: John Gibbs, Ph.D.

Meeting Recorder: Michael Folkendt

FDA Attendees, titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Arthur Shaw, Ph.D.; Chemistry Reviewer
Michael Folkendt; Project Manager

Division of New Drug Chemistry II (HFD-820)
John Gibbs, Ph.D.; Director

External Constituent Attendees and titles:

Texas Biotechnology Corporation (TBC)
Richard P. Schwarz, Ph.D.; Vice President, Clinical Development & Regulatory Affairs
Richard A.F. Dixon, Ph.D.; Vice President, Research and Development
Timothy P. Kogan, Ph.D.; Vice President of Chemistry and Biophysics
Gary D. Knappenberger; Senior Director, Clinical and Regulatory Affairs
Trish Woodard, Ph.D.; Associate Director Pharmaceutical Development
Marcie J. Hursting, Ph.D.; Senior Clinical Scientist

Beckloff & Associates (consultant to Texas Biotechnology Corporation)
Michael C. Beckloff; President and Chief Executive Officer
J. Thomas Stoklosa, Ph.D.; Executive Director, Pharmaceutical Sciences

Background:

This IND was submitted on December 8, 1988, by [redacted] and subsequently transferred to Texas Biotechnology Corporation (TBC) on July 26, 1993. NOVASTAN® (argatroban) Injection is a synthetic thrombin inhibitor derived from L-arginine. NOVASTAN® has been under development as a therapeutic agent for the treatment (anticoagulation) of thromboembolism associated with heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) as well as prophylaxis of thromboembolism in patients with heparin-induced thrombocytopenia (HIT). Past meetings with the firm concerning this drug include an end of Phase II meeting held on April 2, 1996 and a Phase III advice meeting held on January 7, 1997. In preparation for the submission of the NDA in late June 1997, the firm has requested (on January 10, 1997) this meeting to discuss a number of issues related to the chemistry section of

the proposed NDA. On February 14, 1997, the firm submitted a four volume background package for this meeting.

Meeting Objectives:

Discussion of the following three specific issues outlined in the January 10, 1997 meeting request:

1. The drug product used in the clinical trial were packaged in glass ampules. The marketed product are/will be packaged in glass vials with a coated stopper. A bioequivalency study has been conducted with one lot of the clinical product and the first production batch of the to be marketed product (see protocol ARG-108; submitted on 10/7/96; Serial Number 109). What, if any, additional equivalence data will be required?

2. As part of the transfer of the drug product to the production facility, analytical methods have been upgraded and validated (see submission dated 11/13/96, serial number 112). Is this documentation adequate? Are there any additional manufacturing requirements or documentation needed for the proposed NDA.

3. As part of the November 13, 1996 submission (serial number 112), a request for waiver of a complete Environmental Assessment (EA) was submitted based upon the small quantity of the product produced annually. Will this statement suffice for the EA section of the proposed NDA?

Discussion Points (bullet format):

1. Information on the drug substance and drug product:

   Argatroban drug substance is manufactured by Mitsubishi Chemical Corporation, Kashima Plant in Dashima-gun, Ibaraki-ken, Japan. The DMF for its manufacture is [redacted]

   NOVASTAN® drug product is a mixture of diastereoisomers of argatroban with a ratio of 65:35 for 21-(R)-Argatroban: 21-(S)-Argatroban. The firm stated that, assuming the drug acts via thrombin inhibition, the S-stereoisomer is about twice as potent as the R-stereoisomer. The firm stated that separation of the diasterioisomers is extremely difficult and time consuming (over three weeks) and that there is no commercially available assay for the individual diasterioisomers. Analysis of six drug substance lots from Mitsubishi indicates very good batch to batch diasterioisomer ratio consistency. In response to an Agency question, the firm stated that the NDA will contain *in-vitro* and *in-vivo* (in small animals) information on the individual stereoisomers. In addition, the firm stated that there is no statistical difference in clearance rate between the stereoisomers.

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

conditions). The firm stated that it plans to amend the NDA in November with 12 month data for five of the six lots of drug product. Because Lot # M225RB will only have one month of data at the time of original NDA submission in June, the firm was advised to wait until the November amendment to submit data for this lot.

The following additional assays, controls, and data were requested:

a. Because pH is important to control, add a pH in-process control and release specification (based on data).

[redacted]

c. Include data on drug product light sensitivity. The firm stated that photostability was done in the amber vials.

5. Concerning the EA section of the NDA:

The firm was advised to follow regulations and guidance for submission under Teir 0. The firm was reminded that permits for air, water, and solid wastes be included in the EA. In addition, the firm was requested to address the handling/disposal of returned drug product in the EA.

Decisions, Conclusions, and Recommendations:

1. The NDA is scheduled for submission in late June, 1997.

2. The NDA will contain *in-vitro* and *in-vivo* (in small animals) information on the individual stereoisomers.

3. The NDA will include extraction data on the alternate stopper to support its use.

4. The firm will include in the NDA a justification for the use of [redacted]

5. The firm will include in the NDA information on the formulation development solubility curves. The firm will conduct a study on the effect of pH on the solubility of the drug product. The firm was also recommended to conduct a study on forced [redacted] degradation and its effect on the solubility.

6. Because Lot # M225RB will only have one month of stability data at the time of original NDA submission in June, the firm was advised to wait until the November amendment to submit data for this lot.

7. The firm was requested to add a pH in-process control and release specification (based on data) and an assay for [redacted]

8. The firm will include in the NDA data on the drug product light sensitivity.

9. The firm will follow regulations and guidance for submission of the EA under Teir 0. The firm will address the handling/disposal of returned drug product as well as include updated permits for air, water, and solid wastes in the EA.

10. Additional requests made of the firm:

    a. Include in the NDA a table of impurity levels found in the lots used for the toxicology studies.

    b. Compound I is the major metabolite and degradation product. The firm should include a correlation of relative retention times of this compound with those of forced degradation.

    c. It was recommended that the firm conduct a container/closure integrity study by microbial intrusion at the end of the stability study.

    d. The firm will ensure that the methods use the same name throughout the NDA.

Minutes Preparer: /S/ 5/12/97

Chair Concurrence: /S/ 5/12/97

Attachments/Handouts: Copies of overheads presented.

cc: Original
HFD-180/Div. Files
HFD-180/Meeting Minutes files
HFD-180/CSO/J.Dubeau
HFD-180/A.shaw, E.Duffy
HFD-820/J.Gibbs

Drafted by: MF/May 9, 1997/32460705.0mf
Initialed by: A.Shaw 5/9/97
J.DuBeau 5/12/97
J.Gibbs 5/12/97
final: 5/12/97

MEETING MINUTES

MEMORANDUM OF MEETING MINUTES

Meeting Date: April 2, 1996
Time: 1:30 - 3:30
Location: Conference Room I, Parklawn Building

Application: [redacted]
NOVASTAN (argatroban) Injection

Type of Meeting: End of Phase II

Meeting Chair: Dr. Stephen B. Fredd

Meeting Recorder: Ms. Julie DuBeau, Consumer Safety Officer

FDA Attendees, titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180):
- Dr. Stephen Fredd-Division Director
- Dr. Lilia Talarico-Medical Officer
- Dr. John Gibbs-Team Leader, Chemistry
- Ms. Julie DuBeau-Consumer Safety Officer
- Ms. Kati Johnson-Consumer Safety Officer

Division of Biometrics (HFD-720):
- Dr. Mohammad Huque-Team Leader, Statistics

External Constituent Attendees and titles:

Texas Biotechnology Corporation (TBC):

- Mr. David McWilliams-President and CEO
- Dr. Richard Schwarz-Clinical Development, Regulatory Affairs
- Dr. Richard Dixon-Research
- Dr. Jean-Claude Becker-Clinical Research
- Mr. Gary Knappenberger-Regulatory Affairs
- Mr. Jim Joffrion-Clinical Operations
- Dr. Jay Herson-Consulting Statistician
- Dr. Marcie Hursting-Senior Clinical Scientist
- Dr. Timothy Kogan-Senior Director of Chemistry
- Dr. Bruce Lewis-Principal Investigator, Loyola University Medical Center

Background:

This IND was submitted December 8, 1988, by Genentech and subsequently transferred to TBC on July 26, 1993. The compound is a synthetic thrombin inhibitor derived from L-arginine. At clinically useful doses, it inhibits all physiologic effects of thrombin, including conversion of fibrinogen to fibrin, platelet aggregation, and activation of Factors XIII and

VIII. The firm requested an End of Phase II meeting to discuss the progress of ongoing clinical studies which will provide the basis for a future NDA submission for the treatment of thromboembolism associated with heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) and prevention of thromboembolism in patients with heparin-induced thrombocytopenia (HIT). The pre-meeting package dated April 2, 1996, also contained a proposed package insert.

Meeting Objective:

Provide the Agency with an overview of Study ARG-911 entitled, "An Open-Label Study of NOVASTAN in Patients with HIT and HITTS". The patients to be enrolled in the study will be equally divided into a "prophylactic" population (HIT) and "treatment" population (HITTS). The initial NOVASTAN dose is 2 mcg/kg/min, which can be escalated according to predefined guidelines, until aPTT is in the desired therapeutic range (1.5 to 3 times control). Once this dose is determined, patients are maintained on this dose until there is clinical resolution of the underlying condition, anticoagulation is provided or NOVASTAN treatment has been given for 7 days.

Discussion Points, Study ARG-911:

1. The Agency was updated as to the status of the study. According to Dr. Lewis, a total of 57 patients have been enrolled who received NOVASTAN, either for treatment or for prophylaxis of thrombosis, 33 of which have been diagnosed with HIT; and 24, HITTS. With regard to any unsatisfactory outcomes at 30 days, there were no events (death, limb amputation, new thrombosis) in approximately 70% of both the HIT and HITTS patients as compared to historical controls.

2. The use of historical control was discussed. According to Dr. Lewis, they have assumed a 30-35% mortality rate and 25-30% amputation rate in untreated patients. The study has been sized to achieve a 50% reduction in mortality and the firm has calculated that approximately 60 patients will be required.

Conclusions, Study ARG-911:

1. The firm was advised to pre-define the historical control for HIT and HITTS separately by which efficacy of NOVASTAN will be judged.

2. Dr. Fredd recommended that the firm continue to enroll patients such that, upon completion, various subgroup analyses can be conducted to provide as much information as possible in the package insert. To assist the firm in financing continuing investigation, Dr. Fredd suggested that a separate, identical "treatment" protocol be submitted under 21 CFR 312.34.

3. Dr. Fredd recommended that the firm have a study population of adequate size to permit the assessment of efficacy and safety of NOVASTAN separately in the two groups versus their respective historical controls. He suggested that the HITTS group be concentrated on for the initial NDA.

Meeting Objective, Study ARG-216:

Provide an update as to the status of Study ARG-216. This study, entitled, "A Pilot, Open Label, dose Titration Study of NOVASTAN in Patients with Heparin-Induced Thrombocytopenia (HIT) Undergoing Percutaneous Transluminal Coronary Angioplasty or Atherectomy" plans to enroll 30 patients with documented HIT. Patients will receive an initial bolus dose of 350 mcg/kg and an initial infusion dose of 20 mcg/kg/min. The infusion dose will be titrated (not to exceed 40 mcg/kg/min) to reach an ACT of 300-450 seconds, then continued at that dose for the duration of the procedure. At the investigator's discretion, infusion could continue for 48 hours at a dose necessary to achieve an aPTT between 1.5 and 3 times control. Procedural success will be documented in addition to death, myocardial infarction, and bleeding/thrombotic complications.

According the Dr. Lewis, 16 patients with HIT who underwent PTCA with NOVASTAN anticoagulation have been enrolled to date. Procedural success was achieved in 15 of 16 subjects (pre-treatment stenosis = 86%, post-treatment stenosis = 17%), and adequate anticoagulation was achieved in all 16 patients. According to Dr. Lewis, the ACT average was 379 seconds 10 minutes after the bolus and infusion of 20 mcg/kg/min (3 patients) or 30 mcg/kg/min (11 patients).

Discussion Points, Study ARG-216:

1. The Phase II study was discussed. The adverse experiences observed to date were presented. According to the firm, they are very similar to those observed in patients undergoing angiography. For treatment of HITTS by NOVASTAN, it seemed reasonable to target an aPTT of 1.5 to 3 times control.

Meeting Objective:

Provide the Agency with an overview of Study ARG-310 to be initiated in 1996 to evaluate the efficacy of NOVASTAN in HIT/HITTS patients undergoing coronary interventional procedures. The study will enroll 30 patients who will be dosed to achieve an ACT of 300-450.

Discussion Points:

1. The limitation of enrollment to HIT and HITTS patients was discussed. Although it is logical to study the HIT/HITTS population, there is insufficient

safety information available to label against use in a broader population. The firm cited financial restraints in pursuing a generic anticoagulation indication. Following approval, the firm stated their intention to pursue additional indications. It was suggested that HITTS patients should be concentrated on for the initial indication.

2. The primary efficacy analyses were discussed (i.e. attainment of adequate anticoagulation versus procedural success).

Conclusion:

1. The firm stated their willingness to conduct Phase 4 studies in broader populations.

Meeting Objective:

The potential for Subpart E and "priority" drug designation.

Discussion Points:

1. The proposed package insert lists several indications. For HITTS, Dr. Fredd explained that drugs could be approved on the basis of a single study, provided that there is a mortality or severely debilitating efficacy endpoint with results that are compelling. He stressed that the company would need to make the case for one study. Beginning with applications received on or after October 1, 1996, applications designated as "priority" will have a 6 month review due date for the first action.

Conclusions:

1. It was Dr. Fredd's opinion that the treatment of patients with HITTS may qualify for evaluation under Subpart E regulations.

2. Since there is no death or amputation endpoints for the anticoagulation in HIT patients undergoing coronary interventions, Dr. Fredd informed the firm that this indication did not appear to qualify under Subpart E regulations.

Meeting Objective:

Obtain Agency feedback on specific portions of the chemistry, manufacturing and controls section of the NDA anticipated for submission in mid-1997.

Discussion Points:

1. The firm said that the final selection of the stopper to be used in the marketed product should be made within the next two months, and that the stability studies will be initiated as quickly as possible.

2. In response to a question from Dr. Gibbs, the firm said that the NDA will contain 6, 9 and 12 month stability data on 3 lots of drug product. Each lot will be one-tenth the size of the proposed commercial size lot.

3. The mechanism by which the proposed manufacturing revisions could be reviewed was discussed.

4. The firm plans to market the drug in an amber vial. In response to a question from Dr. Gibbs, the firm stated that stability studies conducted to date have not identified any light sensitivity.

Conclusions:

1. The firm was informed that a link between the formulation used in the clinical trials and that proposed for marketing will be required. Although the drug substance has consistently been manufactured by Mitsubishi, the drug product in the clinical studies has been manufactured by the University of Iowa, [redacted] will manufacture the drug for marketing.

2. Under the Prescription Drug User Fee Act of 1992, new drug applications are to be complete when submitted. To facilitate a rapid review, the firm was informed of the option to submit the manufacturing revisions to the IND, prior to submission of the NDA. Also, Dr. Gibbs requested that the firm provide specific references to any Drug Master Files.

3. Dr. Gibbs reminded the firm that starting in January 1998, firms will be required to provide 12 month stability data on three lots.

Minutes Preparer: [redacted] 4/30/96

Chair Concurrence: [redacted] 4/30/96

Attachment (hard copy of overheads distributed at meeting)

cc: Original
HFD-180/Div. Files
HFD-180/Minutes Files
HFD-180/CSO/DuBeau
HFD-180/Talarico
HFD-180/Gibbs
r/d Init: K.Johnson 4/24/96
r/d Init: S.Fredd 4/30/96
r/d Init: L.Talarico 4/30/96
JD/April 24, 1996 (drafted)

MEETING MINUTES

Collier

MEMORANDUM OF MEETING

Date: February 2, 1995

Application Number: [redacted]

Drug: Novastan (argatroban) Injection

Attendees:

Texas Biotechnology Corporation
Dr. John R. Plachetka, VP, Clinical Development
Ms. Karen L. Mancinelli, Manager, Regulatory Affairs and Project Management
Mr. Jim Joffrion, Manager, Clinical Development
Dr. Richard Dixon, VP, Research
Dr. Josh Baker, Biostatistician

Loyola University Medical Center
Dr. Jeanine M. Walenga, Asst. Professor Thoracic-Cardiovascular Surgery and Pathology
Dr. Bruce Lewis, Principal Investigator, HITTS Protocol (ARG-911)

[redacted]

FDA, Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Dr. Stephen Fredd, Director
Dr. Lilia Talarico, Medical Officer
Dr. Eugenie Triantas, Medical Officer
Dr. Nenad Markovic, Medical Officer
Ms. Bronwyn Collier, Consumer Safety Officer

FDA, Division of Biometrics (HFD-713)
Dr. Ferrin Harrison, Statistical Reviewer

FDA, Division of Biopharmaceutics (HFD-426)
Dr. R.S. Pradhan, Reviewer, Biopharmaceutics

BACKGROUND

Novastan (argatroban) Injection is a synthetic thrombin inhibitor derived from L-arginine. It is highly selective at clinically

useful doses, inhibiting all physiologic effects of thrombin, including conversion of fibrinogen to fibrin, platelet aggregation, and activation of Factors XIII and VIII. for Novastan was submitted December 8, 1988. The drug is under development for treatment of heparin induced thrombocytopenia (HIT) and as an adjunct to in acute myocardial infarction (AMI). The sponsor requested this meeting to discuss their proposed study in patients with HIT.

MEETING

Dr. Plachetka presented a brief history of the development of argatroban. It was synthesized and patented by Mitsubishi Chemical Industries Ltd. and Professor Okamoto of Kobe University. It has been marketed in Japan since 1991 by Mitsubishi Kasei Corporation for the treatment of peripheral arterial occlusive disease. An indication is currently pending in Japan for treatment of thrombotic stroke. The U.S. and Canadian marketing rights are held by Texas Biotechnology Corporation via and the European marketing rights are held by According to Dr. Plachetka, their primary focus for drug development in the U.S. is on cures and/or treatment for acute arterial diseases (e.g. cardiovascular indications, diseases of the blood vessel, injury).

Chemistry

Dr. Plachetka said that argatroban is not a protein. The molecule is one fifth the size of Hirudin and Hirulog. It is a racemate with a ratio of 65/35 and with unequal relative activity of the enantiomers. However, according to the firm, clinical data demonstrates that the ratio is constant. In response to Dr. Fredd's question, Dr. Plachetka said that it is extremely difficult to purify either enantiomer. Dr. Fredd advised that the question of relative activity and/or toxicity will have to address .

Pharmacology

According to the firm, argatroban specifically blocks thrombin-induced platelet aggregation, platelet adhesion,

vasoconstriction, and coagulation. It has an excellent toxicology profile and is active in several models of arterial, venous, and mixed thrombosis and is virtually devoid of any other activity at several times the proposed therapeutic doses. About 80% of the drug is hepatically metabolized with the remainder being excreted unchanged.

Dr. Plachetka reported that the pharmacokinetic and pharmacodynamic half-life is approximately 30 minutes. The half life of the alpha enantiomer is 8-10 minutes and for the beta enantiomer, ½ hour. The half-lives are dose dependent. He added that preliminary study results indicate that there does not appear to be a major shift in elimination rate in the elderly or other special populations. In response to Dr. Fredd's question, Dr. Plachetka said that they had intended to conduct a study in hepatically impaired patients but have encountered difficulties since this population has preexisting coagulopathies. Dr. Fredd suggested that some data on hepatically impaired patients could be gleaned from the proposed clinical studies.

Dr. Plachetka summarized the preclinical and clinical development of argatroban. The relative potency of the drug in animal models is dependent on dosing regimen. In a study designed to compare various bolus doses against similar doses of heparin, there were interesting differences relating to delay in ACT prolongation with heparin and a large difference in elimination, i.e. with argatroban there is a rapid diminishing of effect resulting in a highly predictable response for ACT. The dose response curve is relatively gentle with rapid onset and offset.

Dr. Plachetka presented data that demonstrates that argatroban prevents formation of platelet-rich thrombi with less effect on aPTT than either heparin or Hirudin. In response to Dr. Fredd's question, he said that there is very little variation in individual response to dose elevations compared with that seen with other anti-thrombins. Dr. Walenga commented that argatroban also has some effect on the vascular endothelium and does not affect platelet aggregation except for thrombin induced platelet aggregation. No effects on tissue factors have been observed. Further, Dr. Plachetka commented that, based on the dose response curves, the pharmacodynamic profile of argatroban indicates a comfortable therapeutic range. The firm concluded that argatroban

is well tolerated at doses of 1-40 mcg/kg/minute; the drug effects dose dependent prolongation of ACT, aPTT, and PT; and unlike heparin, it has similar dose response curves for aPTT, PT and ACT.

Dr. Fredd noted that the proposed study is in a subgroup of patients that has no alternative effective anticoagulant therapy. He suggested that a randomized controlled clinical trial be designed, with HIT patients as a subgroup, to support argatroban as an alternative therapy to heparin. Clinical trials should also include use in pediatric patients as well as investigations into drug interactions such as aspirin. Dr. Plachetka said that some drug interactions studies (preclinical and clinical) have been conducted, including a study with tPA in which no interactions were observed. An interaction study has not been conducted yet with aspirin.

Dr. Plachetka predicted that there may be some interactions with drugs metabolized by the P450 isoenzymes. *In vivo* studies have been done on some subgroups, such as Asians, which demonstrated no differences in bleeding times or pharmacokinetics. Dr. Fredd suggested that they should also explore whether there are any interactions between argatroban and aprotinin. Dr. Plachetka commented that argatroban is "a response type" drug with a rapid measure of anticoagulant effect and that the main issue to address will be how this equates to clinical efficacy. Dr. Fredd agreed that dosing recommendations, whether for titration or a fixed dose, must be related to clinical benefit.

Dr. Fredd said that any information on how much easier Novastan is to use over heparin is not appropriate. Dr. Plachetka agreed and suggested that the labeling should include information (no comparison) on the effects of the drug on ACT and aPTT. He added that their studies using heparin as a comparator were designed to confirm the pharmacodynamic profile of argatroban.

<u>HIT and HITTS</u>

Dr. Walenga presented an overview of HIT and HITTS. The diagnosis of HIT in patients administered heparin is based on a 50% decrease in platelet count, or, <100,000 platelets for 2 or more days for no apparent reason other than heparin. HIT is

divided into two categories; Type I consists of a transient fall in platelets immediately after heparin administration with no clinical complications, Type II occurs several days after heparin administration, corrects with cessation of heparin and occurs with rechallenge. It is observed in about 2-5% of patients receiving heparin which equates to 10,000 cases/year in the U.S. Sequelae include a range of symptoms from mild to severe hemorrhage or thrombosis affecting the extremities, heart, or brain. Antibody formation in HIT is mediated through the FcR11 receptor of platelets but is not heparin specific. HIT antibodies bind to the same epitope on both platelets and endothelial cells. Current management of HIT includes cessation of heparin administration anticoagulation as needed, plasmapheresis, thrombolysis, surgical clot removal, treatment with anti-platelet or anti-thrombotic agents. Dr. Walenga suggested that the best alternative for management of HIT is the thrombin inhibitors.

In response to Dr. Fredd's questions, Dr. Walenga reported that there is some anecdotal information indicating a higher incidence of HIT associated with heparin derived from bovine over porcine sources. In addition, she said that the assay they propose for HIT (HIPA test) will distinguish between Type 1 and 2 HIT, i.e. only Type 2 will appear as a positive result with the assay. Dr. Fredd suggested that the HIPA test could be used to determine patient eligibility for studies of HIT.

Dr. Lewis continued with a historical overview of HIT and HITTS, citing several reviews and studies including King and Kelton; Singer, et al; Leroy, et al; Demers, et al; Magnani; and Wallis, Lewis, Pifarre, and Scanlon. He concluded that thrombosis is a frequent complication of HIT that is not reduced with early detection and cessation of heparin. In addition, he suggested that the ideal anticoagulant to treat HIT should be rapid acting, safe, have potent antithrombin effects, be easily monitored, have a short half-life, and have no immunologic similarity to heparin.

In response to Dr. Fredd's question, Dr. Lewis stated that it is not possible to predict which patients will develop HIT, nor is the course of HIT avoidable. In Dr. Lewis' opinion, HIT patients should not be rechallenged with heparin because of the inability to predict which patients will develop thromboses. Dr. Fredd

suggested that several potential indications for the use of argatroban associated with HIT could be considered:

a. Use as an alternative anticoagulant to heparin.
b. Use as an alternate anticoagulant in patients likely to develop HIT.
c. Treatment of active thrombosis in HIT patients.
d. Use as an alternative anticoagulant in patients with a history of HIT,

Dr. Fredd advised that each indication would have to be developed individually. Dr. Talarico added that patients with HIT and patients with a history of HIT are distinct populations that should be statistically evaluated separately.

Proposed study of Argatroban in HIT

The objective of the proposed study of argatroban in HIT (ARG 911) is to evaluate the use of argatroban as an anticoagulant in patients with HIT and HITTS. It is designed to be a phase 2/3, open-label, historically controlled study of a variable dose of argatroban administered by continuous intravenous infusion in 100 patients. HITTS is defined as 1) platelets <100,000 or a 50% decrease in platelets after initiation of heparin therapy, with no apparent explanation other than HITTS, 2) presence of a documented arterial or venous thrombosis, and 3) confirmation with a positive HIPA test within 7 days of treatment with argatroban. The definition of HIT is the same as HITTS in the absence of thrombosis. The primary efficacy endpoints will be death, amputation, and development of new thrombosis. Secondary efficacy endpoints will be clinical ischemic syndromes, negative HIPA test, resolution of thrombocytopenia, and anticoagulant effect as evidenced by aPTT. Patients will also be monitored for bleeding. The dose will be initiated at 2 μg/kg/min and adjusted to achieve a therapeutic range of 1.5 to 3 times aPTT control (not to exceed 100 sec.). The treatment will continue for up to 7 days.

In response to Dr. Fredd's question, Dr. Plachetka said that patients with a positive HIPA test but without documentation of HIT or HITTS will be excluded from the study. Dr. Fredd commented that information on this subpopulation may be valuable

since, according to the historical information presented, 30% of patients with a positive HIPA test will develop thrombosis and sequelae of thrombosis. He encouraged them to study a full spectrum of patients that require alternative anticoagulants to heparin.

Regarding patients with HITTS, Dr. Lewis stated that the current best available therapy is thrombolytics. The surgical approach to managing HITTS has a low success rate since surgery cannot be done without concurrent anticoagulant therapy. Therefore, a comparison will be made between HITTS patients treated with argatroban, HITTS patients treated with a combination of argatroban plus thrombolytics, and a historical control of HITTS patients treated with thrombolytic therapy alone.

Dr. Harrison commented that the proposed multiple endpoint will require statistical adjustment of the data. The firm stated that the primary endpoint is death and that the study will be powered for this. Dr. Fredd noted that the proposed primary endpoint(s) is acceptable and recommended that they carefully state, a priori, how the study will be evaluated. He continued, saying that the secondary endpoints should be able to indicate whether the drug, at a given dose or dose range is an effective anticoagulant. He also advised that, in order to indicate argatroban as an alternative to heparin the drugs would have to be demonstrated equivalent in each population heparin is indicated.

Dr. Fredd suggested that the study enroll patients undergoing surgery utilizing cardiopulmonary bypass dosed with argatroban in terms of aPTT/ACT and have the clinician/investigator determine whether adequate anticoagulation was achieved. This would provide a homogenous population for study of prevention of HIT/HITTS that would be less problematic to study than treatment of HIT/HITTS. Dr. Plachetka agreed that this approach may be feasible and will be considered.

Dr. Plachetka inquired whether a similar adequate anticoagulation/inadequate anticoagulation determination could be used for patients with pulmonary embolism and/or deep venous thrombosis. Dr. Fredd agreed that this approach may be acceptable, provided uniform standards are established to

objectively measure the effect. However, he cautioned that the dose for treatment of venous thrombosis may be different from arterial thrombosis since the dose would be an antithrombotic rather than an anticoagulant dose. Thus, the dose for each indication would have to be determined.

Miscellaneous Discussion

Dr. Plachetka inquired whether one pivotal study or two would be required to support an indication for Novastan. He cited the recent approval of Rheopro as an example where only one study was needed. Dr. Fredd explained that Rheopro is classified as a biologic and is regulated under the Public Health Service Act rather than the Food Drug and Cosmetic Act as drugs are. Support for an indication for Novastan will require at least two adequate and well controlled studies. However, he added that there are various methods for providing replication of results that may be considered, such as designing a large study so as to provide internal replication.

/S/ 6/6/95

CC:
Orig.
HFD-180
HFD-180/minutes file
HFD-180/L.Talarico
E.Triantas
N.Markovic
HFD-180/CSO/BCollier
HFD-713/F.Harrison
HFD-426/R.Pradhan
RD/Initial: S.Fredd 6/5/95
K.Johnson 5/31/95
BC/5/24/95

MEMORANDUM OF TELECON

DATE: July 12, 1999

APPLICATION NUMBER: NDA 20-883; Novastan (argatroban) Injection

BETWEEN:

Name: John McMurdo, M.D.;
Vice President, Clinical Development and Regulatory Affairs, Texas Biotechnology Corporation
Dan Thompson; Director Regulatory Affairs, Texas Biotechnology Corporation
Philip Brown, M.D.; Director Medical Affairs, Texas Biotechnology Corporation
Catherine Clark; Director Regulatory Affairs, Smith Kline Beecham (SKB)
Bernard Ilson, M.D.; Director, Clinical Research and Development SKB
Mark McCord-Amas; Project Director, SKB
Phone: (713) 796-8822, (X-139)

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Errors in the Statistical Analysis of Studies ARG-911 and ARG-915

Background

NDA 20-883, submitted August 11, 1997, provides for anticoagulation therapy in patients with heparin-induced thrombocytopenia (HIT). Efficacy is supported by the sole pivotal study, ARG-911, a multicenter, open-label, historically controlled, prospective study of 304 patients with HIT and HITTS (heparin-induced thrombocytopenia and thrombois syndrome) treated with argatroban. Study ARG-911 is supported by study ARG-915, an open-label extension of ARG-911 designed to collect additional safety information. A Not Approvable action was taken May 8, 1998 citing CMC and clinical deficiencies. A complete response was submitted March 17, 1999 and is under review. This application required Office level sign-off, and the PDUFA date is September 17, 1999.

In the course of his review, the clinical statistician Wen-Jen Chen noted that a patient in the time-to-event analysis in ARG-911 had been censored prior to the full follow-up time. In response to our call, the firm rechecked their data and discovered that 39 ARG-911 patients were similarly prematurely censored in the time-to-event analysis. This change resulted in 10% of patients being prematurely censored. The firm also rechecked the analysis for Study ARG-915. Although a similar error was not detected, the firm uncovered an additional error in ARG-915. As a result of, according to the firm, a programming error, primary endpoint events were not recorded in six patients. According to the firm, the net result of these errors is a small increase in significance in favor of argatroban in ARG-911 and a decrease in significance not in

favor of argatroban in ARG-915.

Today's Call

At the request of Dr. Houn, Director, Office of Drug Evaluation III, I conveyed the following:

1. The following additional information, as well as any additional information you are aware of, is required for the medical and statistical reviewers to evaluate the impact of these errors:

   A. revised analyses where the errors resulted in changes to the information currently submitted;
   B. revised data and tabulations;
   C. revised clinical and statistical reports;
   D. and, revised ISS and ISE.

2. At this time, all of the information necessary for the Agency to perform the complete and thorough review necessary, as requested in item #1, has not been submitted. It may be very difficult to meet the PDUFA due date of March 17 after the information is submitted.

3. Since this situation is the result of errors in the statistical analyses of studies ARG-911 and ARG-915, we propose reclassifying the March, 1999 submission to a General Correspondence, and restarting the resubmission clock when all of the revised information, as requested in item #1, has been submitted. That submission would be classified as a complete response to the May, 1998 Not Approval letter. We recommend resubmitting all information submitted since March, 1999 and highlighting the changes resulting from the errors.

4. Alternatively, a Not Approvable action is likely since we cannot rely on the present database.

5. We will be glad to work with you as necessary to discuss the reanalysis.

The call was then concluded.

/S/ 7/12/99

Brian Strongin
Regulatory Health Project Manager

cc: Original NDA 20-883
HFD-180/Div. File
HFD-103/F.Houn
HFD-180/Brian Strongin
HFD-180/L.Talarico
HFD-180/K.Robie-Suh
HFD-180/A.Farrell
HFD-180/J.Dubeau
HFD-715/P.Flyer
HFD-715/W.J.Chen

TELECON

CSO/DuBeau

MEMORANDUM OF TELECON

DATE: September 16, 1998

APPLICATION NUMBER: NDA 20-883; Novastan® (argatroban) Injection

BETWEEN:

Name: Mr. G. Knappenberger; Senior Director, Clinical Development/Regulatory Affairs
Phone: (713) 796-8822 x165
Representing: Texas Biotechnology Corporation (TBC)

AND

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

SUBJECT: September 14, 1998, facsimile regarding an alternative historical control proposal

BACKGROUND:

On August 11, 1997, Texas Biotechnology Corporation submitted an NDA for Novastan® (argatroban) Injection with the following proposed indication: Anticoagulant therapy in patients with heparin-induced thrombocytopenia (HIT). The firm received a NOT APPROVABLE letter on May 8, 1998, in which the Agency suggested that the firm either identify and analyze an appropriate historical control, or conduct an additional study comparing argatroban to a currently approved therapy for HIT/HITTS in patients who need anticoagulation. On July 14, 1998, a meeting was held to discuss the firm's strategy for identifying and analyzing an appropriate historical control. On September 14, 1998, the firm faxed the Agency a letter regarding an alternative historical control proposal (see attached facsimile).

TODAY'S PHONE CALL:

At the request of Dr. Talarico, the firm was contacted and informed that the alternative historical control proposal as presented in the September 14, 1998, facsimile is acceptable. The following points were conveyed to Mr. Knappenberger:

1. A written procedure should be followed by all clinical investigators.
2. A record should be provided of all cases identified by the clinical investigator, those where there is agreement/disagreement with TBC monitors, and the reasons should be documented.
3. Details should be provided of the Independent Medical Review Panel arbitration, case by case.

Mr. Knappenberger agreed. The call was then concluded.