

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-883

CORRESPONDENCE

June 20, 2000

Lilia Talarico, M.D.
Division of Gastrointestinal & Coagulation Drug Products
Food & Drug Administration
Document Control Room 6B - 24
5600 Fishers Lane
Rockville, Maryland 20857

Re: New Drug Application 20-883
TRADEMARK™ (argatroban) Injection
General Correspondence: Phase IV Commitments
Volume 7.5



Texas Biotechnology
Corporation

7000 Fannin
Houston, TX 77030

Telephone 713-796-8822

Dear Dr. Talarico:

Please refer to your letter dated June 13, 2000 regarding Phase IV commitments for Trademark™ (argatroban) Injection. As specified in your letter, Texas Biotechnology Corporation (TBC) agrees to conduct the following studies:

- ✓ 1. Pharmacokinetic and safety studies in pediatric subjects to allow for appropriate dosing instructions in this population.
- ✓ 2. The following *in vitro* cardiac electrophysiologic studies:
 - Action potential study in rabbit purkinje fibers,
 - Voltage clamp studies in isolated ventricular myocytes for determining effects on potassium, sodium and calcium currents,
 - Effects on HERG Channels in transfected human cells *in vitro*.
- ✓ 3. The following studies in cardiac compromised animal models:
 - Anesthetized dog model to study regional myocardial blood flow and contractile function distal to a severe flow-limiting stenosis of the left circumflex coronary artery,
 - Induced heart failure model in dogs.

If you have any questions regarding this submission, please contact me at 713-796-8822 ext. 117.

Sincerely,

Daniel J. Thompson
Director of Regulatory Affairs

NDA 20-883

Texas Biotechnology Corporation
Attention: Mr. Daniel J. Thompson
7000 Fannin, Suite 1920
Houston, Texas 77030

JUN 13 2000

Dear Mr. Thompson:

Please refer to your new drug application (NDA) dated August 11, 1997, received August 15, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADEMARK (argatroban) Injection.

We also refer to your submission dated April 20, 2000, in which you committed to conducting Phase 4 studies as specified below.

1. A pharmacokinetic and safety study in pediatric subjects to allow for appropriate dosing instructions in this population, and to consult with the Agency on the design of such a study prior to its initiation.
2. Appropriate *in vitro* cardiac electrophysiologic studies and studies in cardiac compromised animal models.

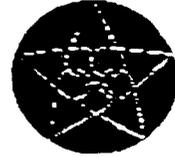
Regarding commitment 2 above, in addition to your proposed single *in vitro* electrophysiology study to determine the effect of argatroban on action potential in rabbit purkinje fibers, conduct the following: (a) voltage clamp studies in isolated ventricular myocytes for determining effects on potassium, sodium, and calcium currents, and (b) effect on HERG Channels in transfected human cells *in vitro*.

Regarding commitment 2 above, use the following cardiac compromised animal models for studying the effects of argatroban:

- (a) Anesthetized dog model to study regional myocardial blood flow and contractile function distal to a severe flow-limiting stenosis of the left circumflex coronary artery (Buck, J.D. et al, American Journal of Cardiology 44: 657-663, 1979) and Gross G. J. et al, Journal of Cardiovascular Pharmacology 1: 139-147, 1979).
- (b) Induced heart failure model in dogs (Kittleson, M.D. and Hamlin, R.L., American Journal of Veterinary Research, 44: 1501-1505, 1983).

June 1, 2000

Lilia Talarico, M.D.
Division of Gastrointestinal & Coagulation Drug Products
Food & Drug Administration
Document Control Room 6B - 24
5600 Fishers Land
Rockville, Maryland 20857



Re: New Drug Application 20-883
TRADEMARK™ (argatroban) Injection
General Correspondence: Commercial Batch Size
Volume 7.3

Texas Biotechnology
Corporation

Dear Dr. Talarico,

As indicated in NDA 20-883, Volume 7.1, the commercial batch size for TRADEMARK™ Injection was revised from the initially anticipated batch size of _____ to a smaller batch size of _____. The initially anticipated batch size of _____ was reported in Volume 1.1, Section A: Chemistry, Manufacturing, and Controls, Subsection 2, Drug Product, Section 2.d. (6) of the original NDA.

In response to the recent question regarding the commercial batch size, we wish to clarify that the _____ batch size is a theoretical or target batch size. In the solution compounding procedure for this product, before the final batch weight q.s. step, an in-process assay for argatroban is performed; and based on this assay value, the final batch weight for each batch is calculated. The final batch weight is achieved by adding sufficient quantity Water for Injection so that the theoretical amount of argatroban will be 100% of the label claim. Recently, we have successfully manufactured three validation batches of this product, and the final bulk solution weights have ranged from _____.

As we manufacture additional batches of this product in the near future, we will gain a better understanding of the magnitude of the variability in the batch weight. At that time, we will be able to assign a firm range for the batch weight instead of using the current 21.49-kg target batch weight.

If you have any questions, please contact me at (713) 796-8822 ext. 117.

Sincerely,

Daniel J. Thompson
Director of Regulatory Affairs

NDA 20-883

MAY 11 2000

Texas Biotechnology Corporation
Attention: Daniel J. Thompson
7000 Fannin, Suite 1920
Houston, TX 77030

Dear Mr. Thompson:

We acknowledge receipt on May 4, 2000, of your May 3, 2000, resubmission to your new drug application (NDA) for Acova (argatroban) Injection.

This resubmission, along with your April 20, 2000, submission, contains additional information submitted in response to our February 18, 2000, action letter.

We consider this a complete class 1 response to our action letter. Therefore, the primary user fee goal date is July 4, 2000, and the secondary user fee goal date is September 4, 2000.

If you have any questions, call me at (301) 827-7310.

Sincerely,

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Archival NDA 20-883

HFD-180/Div. Files

HFD-180/J.DuBeau

HFD-180/Talarico

HFD-103/Raczkowski

DISTRICT OFFICE

JD/May 11, 2000 (drafted)

JD/5/11/00/

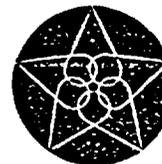
/S/ 5/11/00

CLASS 1 RESUBMISSION ACKNOWLEDGEMENT (AC)



December 28, 1999

Julieann DuBeau
Food and Drug Administration
5600 Fishers Lane
Document Control Room 6B-24
Rockville, MD 20857



Re: New Drug Application 20,883
Novastan[®] (argatroban) Injection Concentrate
Response to Biopharmaceutical Questions

*Texas Biotechnology
Corporation*

*7000 Fannin
Houston, TX 77030
Telephone 713-796-8822*

Dear Ms. DuBeau:

In response to our telephone conversation on December 17, 1999 regarding the questions from the Biopharmaceutics reviewer, I have included reports and other information that should answer all of his/her questions. The questions being answered are listed below and are a literal transcription from our telephone conversation.

1. For plasma samples analyzed by ~~LC~~ and MS in protocol SKF002 and by RIA in SKF003, the limits of quantification are stated as 5ng/ml for LC and MS and 1ng/ml for RIA. No other validation data are provided. For each protocol, please provide the following validation information:
 - A. Linearity range
 - B. Precision (intra-day and inter-day)
 - C. Accuracy (intra-day and inter-day)
 - D. Specificity

RESPONSE: Tab 1:

- A. SKF002: Copy of the report regarding determination of argatroban in human plasma by LC/MS/MS, and a copy of the report regarding determination of dehydroargatroban in human plasma by LC/MS/MS.
- B. SKF003: Copy of the validation report RIA analysis of digoxin in heparinized human plasma, and a copy of the validation report method ICD 11.2 RIA analysis of digoxin in human urine.

2. The Investigational Batch Size in SKF001, SKF002, and SKF003 and the proposed Commercial Batch Size of this drug product should be submitted for review.

RESPONSE: Tab 2:

- A. The investigational batch sizes for SKF001, SKF002 and SKF003 are as follows:

NOTE: There were 5 registration lots of Novastan[®] that are identical in their manufacturing. They are M245PF, M246PF, M020PJ, M021PJ, and M295PK (reference Volume 1.1, presubmission CMC, June 27, 1997, page 043-also attached, see # 1 below).

1. SKF001: copies of page 02 and 017 of the clinical report, which specifies the lot number for this protocol as M246PF (Volume 2, March 1999 submission). As noted above, this registration lot is identical to M295PK, documented on page 28, 29, and 43 in Volume 1.1 of the presubmission of CMC information submitted June 27, 1997, copies provided. Also see number 2 and 3 below for copies of pages from the batch record for Lot No. M295PK.
2. SKF002: copies of page 205 and 218 from the clinical report, which specifies the lot number for this protocol as M295PK (Volume 3, March 1999 submission). Also copies of pages from Attachment 2, which is the Batch Production and Control Record for Novastan, Lot No. M295PK (Volume 1.2, Attachment 2, page 007 of the presubmission of CMC information, June 27, 1997).
3. SKF003: copies of page 96 and 108 from the clinical report, which specifies the lot number for this protocol as M295PK (Volume 4, March 1999 submission). Also copies of pages from Attachment 2, which is the Batch Production and Control Record for Novastan, Lot No. M295PK (Volume 1.2, Attachment 2, page 007 of the presubmission of CMC information, June 27, 1997).

- B. The proposed Commercial Batch size of this drug product is _____ with theoretical yield _____ each (see copy of e-mail to and from Catherine Clark and Richard Simpson of SmithKline Beecham).

3. In SKF001 under the "Assay Method" for INR determination, the following is stated: "Prothrombin time tests _____ method on file) were performed at CPU using two different thromboplastins." A description of the assay methods "on file" needs to be submitted for review.

RESPONSE: Tab 3:

A copy of SmithKline Beecham's Standard Operating Procedure for performing prothrombin times.

*Texas Biotechnology
Corporation*

I hope that these responses are what the Biopharmaceutics reviewer is looking for. Please contact me if you need any additional information or clarification at 713-796-8822 ext. 117.

Sincerely,



Daniel J. Thompson
Director, Regulatory Affairs

Du BEAU

NDA 20-883

Texas Biotechnology Corporation
Attention: John McMurdo, M.D.
7000 Fannin Street, Suite 1920
Houston, Texas 77030

AUG 17 1999

Dear Dr. McMurdo:

We acknowledge receipt on August 16, 1999, of your August 13, 1999, resubmission to your new drug application (NDA) for Novastan® (argatroban) Injection.

This resubmission contains additional clinical, statistical, and biopharmaceutics information submitted in response to our May 8, 1998, action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is February 16, 2000.

If you have any questions, contact me at (301) 827-7310.

Sincerely,

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Archival NDA 20-883

HFD-180/Div. Files

HFD-180/J.DuBeau

HFD-180/Talarico

HFD-180/Robie-Suh

HFD-180/Farrell

HFD-715/Flyer

HFD-715/W.J.Chen

HFD-870/D.Lee

DISTRICT OFFICE

JD/August 17, 1999 (drafted)

JD/8/17/99:

CLASS 2 RESUBMISSION ACKNOWLEDGEMENT (AC)

/S/8/17/99

DuBeau

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

DATE: August 17, 1999
FROM: Julieann DuBeau, RN, MSN; Regulatory Health Project Manager
SUBJECT: Submissions to the NDA
TO: File NDA 20-883 [Novastan® (argatroban) Injection]

10/8/17/99

NDA 20-883 was submitted on August 11, 1997 (received August 15, 1997). The firm received a Not Approvable action on May 8, 1998. The firm's March 17, 1999, submission (received March 19, 1999) was coded a major amendment and considered a complete response to the Not Approvable letter. However, the firm informed the Division that there were statistical errors in the March 17, 1999, submission. The firm was given the choice of receiving another Not Approvable letter (review cycle 2), or resubmitting the complete response to the action letter again with correction of the errors. The firm chose the latter approach. Thus, the March 17, 1999, submission (received March 19, 1999) was recoded as a minor amendment. A complete response to the Not Approvable letter was submitted on August 13, 1999, (received August 16, 1999). Therefore, the new goal date for review cycle 2 is February 16, 2000.

- Cc:
- Original NDA 20-883
- HFD-180/DuBeau
- HFD-180/Talarico
- HFD-180/Robie-Suh
- HFD-180/Farrell
- HFD-715/Flyer
- HFD-715/W.J.Chen
- HFD-870/D.Lee
- JD/August 17, 1999 (drafted)
- JD/8/17/99

Dudley

NDA 20-883

Texas Biotechnology Corporation
Attention: John McMurdo, M.D.
7000 Fannin Street, Suite 1920
Houston, Texas 77030

MAY 13 1999

Dear Dr. McMurdo:

Please refer to your pending August 11, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Novastan® (argatroban) Injection.

We also refer to your resubmission dated March 17, 1999, containing among other things, a new historical control group for the pivotal clinical trial ARG-911 and the final study results of ARG-915.

We are reviewing the Clinical Statistical section of your submission and have the following information requests regarding study ARG-911, study ARG-915, and the new historical control.

I. Please provide a diskette with a SAS data set for the following variables, and add any other efficacy related variables which you utilized to conduct the efficacy analyses:

PROTOCOL - Protocol number.

INVEST - Investigator ID.

CENTERG - Center groups: group A (or Center A), Group B (or Center B), or Group C (or Center C) as you defined it (submission dated 3/17/99, volume 74, page 66).

PATID - Patient identification number.

GROUP: ARG (ARG911 or ARG915) for argatroban group or HC for historical control as you defined it.

POP: HIT or HITTS as you defined it.

ITT - Y if patient was in the intent-to-treat population; N otherwise.

EVALU - Y if patient was in the evaluable population as defined in your document; N otherwise.

TESTP - Y if patient was in the test-positive (SRA positive) population defined in your document; N otherwise.

GENDER - F for Female; M for Male.

Age - Patient age at baseline date (Unit: Years); baseline date was defined in your March 17, 1999, submission (volume 74, page 63).

Weight (Unit kg)

Height (Unit cm)

RACE

DPOUT - Y if patient dropped out of the study; N otherwise.

STUDYL - Time length for the patient participating in the study, calculated from the baseline date (Unit Day).

HIPA - Y if Heparin-Induced Platelet Aggregation was positive; N otherwise.

SRA - Y if Serotonin Release Assay was positive; N otherwise.

CIRSYSD - Y if patient had baseline circulatory system disease defined/generated in your History data set; N otherwise.

ENMD - Y if patient had endocrine, nutritional and metabolic disease defined/generated in your History data set; N otherwise.

INJPD - Y if patient had injury and poisoning disease defined/generated in your History data set; N otherwise.

RESPSD - Y if patient had respiratory system disease defined/generated in your History data set; N otherwise.

DIGSD - Y if patient had digestive system disease defined/generated in your History data set; N otherwise.

GENSD - Y if patient had genitourinary system disease defined/generated in your History data set; N otherwise.

MSCTD - Y if patient had musculoskeletal system and connective tissue disease defined/generated in your History data set; N otherwise.

MENTDD – Y if patient had mental disorder disease defined/generated in your History data set; N otherwise.

AMPUT – Y if patient had all-cause amputation event within 37 days from baseline date; N otherwise.

DAETH – Y if patient had all-cause death within 37 days from baseline date; N otherwise.

THROMB – Y if patient developed new thrombosis within 37 days from baseline date; N otherwise.

PRIENDE – First occurrence event (composite event) of all-cause amputation, all- cause death, and the development of a new thrombosis within 37 days from baseline date.

TAMPUT – Time to the all-cause amputation event, calculated form the baseline date.

TDEATH – Time to the all-cause death, calculated form the baseline date.

TTHROMB – Time to new developed thrombosis, calculated from the baseline date.

DIFF – Time to the first occurrence event (composite endpoint) of all-cause amputation, all-cause death, and the development of a new thrombosis within 37 days from baseline date.

Please leave one space between two adjacent variables.

II. Please provide a diskette with the SAS programs used to perform the statistical efficacy analyses, for the data sets from the three types of populations (ITT, EVALU, and TESTP), described in sections 9.7.1.3, 9.7.1.4, and 9.7.1.5 (volume 74, pages 64-67) of your March 17, 1999, submission. The above SAS programs should be modified to read data from the file requested in I. above.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider

your response prior to taking an action on your application during this review cycle.

If you have any questions, contact me at (301) 827-7310.

Sincerely,

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Archival NDA 20-883

HFD-180/Div. Files

HFD-180/J.DuBeau

HFD-180/Robie-Suh

HFD-180/Farrell

HFD-715/W.Chen

HFD-715/Al-Osh

DISTRICT OFFICE

R/d Init: Johnson 5/10/99

JD/May 10, 1999 (drafted)

JD/5/13/99/

/S/ 5/13/99

INFORMATION REQUEST (IR)

INFORMATION REQUEST

Date: May 6,1999

NDA: 20-883

Sponsor: Texas Biotechnology Corporation.

Drug: Novastan[®] (Argatroban) Injection.

Indication: : (i) Prevention of thrombosis in patients with heparin-induced thrombocytopenia (HIT) and
(ii) Treatment of patients with heparin-induced thrombocytopenia and thrombosis syndrome (HITTS).

Dear Ms. DuBeau:

In order to complete the review for Novastan[®] (Argatroban) Injection, In addition to the data I requested before (around April 20), I would like the sponsor to provide the following additional data for Study# ARG-911, Study# ARG-915, and the new historical control.

I. Please provide a SAS data set with the following variables :

PROTOCOL - Protocol number.

INVEST - Investigator ID.

CENTERG - Center groups: group A (or Center A), Group B (or Center B), or Group C (or Center C) as defined by the sponsor in page 66, Volume 74.

PATID - Patient identification number.

GROUP: ARG (ARG911 or ARG915) for argatroban group or HC for historical control as defined by the sponsor.

POP: HIT or HITTS as defined by the sponsor.

ITT - Y if patient was in the intent-to-treat population; N otherwise.

EVALU - Y if patient was in the evaluable population defined in the sponsor's document; N otherwise.

TESTP - Y if patient was in the test-positive (SRA positive) population defined in sponsor's document; N otherwise.

GENDER - F for Female; M for Male.

Age - Patient age at baseline date (Unit: Years); baseline date was defined in page 63, volume 74.

Weight (Unit kg)

Height (Unit cm)

RACE

DPOUT - Y if patient dropped out of the study; N otherwise.

STUDYL - Time length for the patient participating in the study, calculated from the baseline date (Unit Day).

HIPA - Y if Heparin-Induced Platelet Aaggregation was positive; N otherwise.

SRA - Y if Serotonin Release Assay was positive; N otherwise.

CIRSYSD - Y if patient had baseline circulatory system disease defined/generated in the

sponsor's History data set; N otherwise.

ENMD – Y if patient had endocrine, nutritional and metabolic disease defined/generated in the sponsor's History data set; N otherwise.

INJPD – Y if patient had injury and poisoning disease defined/generated in the sponsor's History data set; N otherwise.

RESPSD – Y if patient had respiratory system disease defined/ generated in the sponsor's History data set; N otherwise.

DIGSD – Y if patient had digestive system disease defined/generated in the sponsor's History data set; N otherwise.

GENSD – Y if patient had genitourinary system disease defined/ generated in the sponsor's History data set; N otherwise.

MSCTD – Y if patient had musculoskeletal system and connective tissue disease defined/ generated in the sponsor's History data set; N otherwise.

MENTDD – Y if patient had mental disorder disease defined/ generated in the sponsor's History data set; N otherwise.

AMPUT – Y if patient had all-cause amputation event within 37 days from baseline date; N otherwise.

DAETH – Y if patient had all-cause death within 37 days from baseline date; N otherwise.

THROMB – Y if patient developed new thrombosis within 37 days from baseline date; N otherwise.

PRIENDE – First occurrence event (composite event) of all-cause amputation, all- cause death, and the development of a new thrombosis within 37 days from baseline date

TAMPUT – Time to the all-cause amputation event, calculated form the baseline date.

TDEATH – Time to the all-cause death, calculated form the baseline date .

TTHROMB – Time to new developed thrombosis, calculated from the baseline date.

DIFF – Time to the first occurrence event (composite endpoint) of all-cause amputation, all- cause death, and the development of a new thrombosis within 37 days from baseline date.

Please add any other efficacy related variables which the sponsor utilized to carry out their efficacy analyses.

Leave one space between two adjacent variables.

II. Please provide the SAS programs used to perform the statistical efficacy analyses, for the data sets from the three types of populations (ITT, EVALU, and TESTP), described in the sections 9.7.1.3, 9.7.1.4, and 9.7.1.5. The above SAS programs should be modified to read data from the file requested in I.

III. A diskette with data set defined in request I and the sponsor's SAS programs specified in request II should be submitted to the agency.

/S/
Wen-Jen Chen Ph.D.,
Mathematical Statistician

cc: Original NDA 20-883

HFD-180/Dr. Farrell

HFD-715/Dr. Alesh

HFD-715/Dr. Chen

HFD-715/File Copy

CSO/DuBeau

NDA 20-883

Texas Biotechnology Corporation
Attention: John McMurdo, M.D.
7000 Fannin Street, Suite 1920
Houston, Texas 77030

MAR 24 1999

Dear Dr. McMurdo:

We acknowledge receipt on March 19, 1999, of your March 17, 1999, resubmission to your new drug application (NDA) for Novastan® (argatroban) Injection.

This resubmission contains additional clinical, statistical, and biopharmaceutics information submitted in response to our May 8, 1998, action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is September 19, 1999.

If you have any questions, contact me at (301) 827-7310.

Sincerely,

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-883
HFD-180/Div. Files
HFD-180/J.DuBeau
HFD-180/Farrell
HFD-180/W.J.Chen
HFD-870/D.Lee
DISTRICT OFFICE
JD/March 24, 1999 (drafted)
JD/3/24/99/

3/24/99
/S/

CLASS 2 RESUBMISSION ACKNOWLEDGEMENT (AC)

CSC/DuBau

NDA 20-883

Texas Biotechnology Corporation
Attention: Gary D. Knappenberger
7000 Fannin, Suite 1920
Houston, TX 77030

OCT 30 1998

Dear Mr. Knappenberger:

Please refer to your pending August 11, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Novastan® (argatroban) Injection.

We also refer to your submissions dated July 8 and July 20, 1998, in response to our May 5, 1998, letter requesting additional chemistry, manufacturing, and controls (CMC) information. These requests were also referenced in our May 8, 1998, Not Approvable letter.

We have completed our review of your submissions and have the following information requests:

1. Regarding your response to Item IIA (Drug Product Impurities) of the May 5, 1998, letter:
 - a. Please justify your proposed specifications _____ for individual and total impurities and degradation products, given that information in the application would appear to support specifications of less than 0.1%.
 - b. Please provide the number of each batch/lot and date of manufacturing for the pivotal clinical, toxicological, and stability batches.
2. Regarding your response to Items IIIB and IIIC (Drug Product Manufacturing and Testing) of the May 5, 1998, letter, provide a detailed description of the "ANSI-ASQC Z1.4" sampling plan.

Please note that sufficient stability data has been submitted to support an expiry of 12 months. In addition, we have completed our review of Drug Master File (DMF) _____ (titled "MCI-9038") and found it acceptable.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely,

/S/

T 10/29/98

Eric P. Duffy, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug
Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:

Archival NDA 20-883

HFD-180/Div. Files

HFD-180/J.DuBeau

HFD-820/DNDC Division Director (only for CMC related issues)

DISTRICT OFFICE

r/d Init: Johnson 10/28/98

r/d Init: Duffy 10/29/98

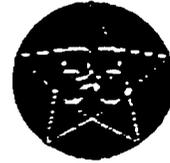
JD/October 27, 1998 (drafted)

JD/10/29/98. _____

/S/ 10/29/98

INFORMATION REQUEST (IR)

September 14, 1998



Lilia Talarico, M.D.
Director, Division of Gastrointestinal
And Coagulation Drug Products (HFD-180)
CDER
Document Control Room 6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Texas Biotechnology
Corporation

7000 Fannin
Houston, TX 77030
Telephone 713-796-8822
Fax 713-796-8232

RE: New Drug Application 20,883
NOVASTAN[®] (argatroban) Injection Concentrate
Volume 5.7
Re: Request for teleconference

Dear Dr. Talarico:

This letter serves as a written request for a teleconference with you regarding the ARG-911 clinical study as well as to provide background information with the regard to the topic for discussion. Argatroban is the subject of NDA 20, 883.

During our meeting on July 14th, a proposal with regard to the selection of a new historical control group was discussed. The proposal described a process whereby potential historical control candidates would be identified by investigators, screened by Texas Biotechnology Corporation monitors and then submitted to an Independent Medical Review Panel (IMRP) together with prospectively enrolled treated patients in a blinded fashion. The IMRP was to review the summarized information and provide the following assessments:

- 1) To determine eligibility for inclusion
- 2) To classify eligible patients as either HIT or HITTS
- 3) To determine outcome with regard to the development of new thrombosis, amputation, death and attribution of death as to whether due to HIT/HITTS or underlying diseases.

The IMRP members were to make their assessment based on information provided from medical summaries and Case Record Tabulations which were created by the Sponsor from case report forms completed by the investigators and their study personnel.

The prospectively treated group was included in this process for the purpose of blinding the IMRP with respect to treatment, so that active and historical control patients would be evaluated by the same panel. The primary efficacy analysis in the prospectively treated group as reflected in the initial submission was not subject to change by the IMRP and this process was to be conducted solely for the purpose of selecting and classifying an appropriately matched historical control group.

During the process of preparing the medical summaries and CRTs, it became evident that blinding with respect to treatment group could not be preserved. Attempts to blind the summaries, results in the masking of information, which would be critical to the IMRP for the purpose of classification and assessing outcome.

As a result of the difficulties encountered we would like to offer an alternative proposal which we believe will maintain center diversity, provide less bias, greater standardization and a ultimately a more accurately matched historical control group.

This proposal would allow the investigators to select the historical control group, classify patients as HIT or HITTS and to determine outcome with regard to the development of new thrombosis, amputation and death. We believe that the investigator has access to all the required information including the original hospital records, in order to make an accurate determination. The investigator's assessment would be reviewed by Texas Biotechnology Corporation's medical monitor. Any disagreement by the medical monitor and the investigators would then be submitted to the IMRP in an unblinded fashion for arbitration.

We wish to determine whether this proposal will be acceptable to FDA in light of the practical difficulties that we have encountered.

Sincerely,



Gary D. Knappenberger,
Senior Director, Clinical Development and Regulatory Affairs

Texas Biotechnology Corporation Participants:

Philip Jochelson, M.D., Vice President, Clinical Development & Regulatory Affairs
Gary D. Knappenberger, Senior Director, Clinical Development & Regulatory Affairs

SmithKline Beecham Participants:

Sunita Sheth, M.D., Associate Director, Clinical Pharmacology
Bernie Ilson, M.D., Director, Clinical Research and Development
Tina Blumhardt, Ph.D., Vice President, Regulatory Affairs

Requested Participants from FDA:

Dr. Talarico, Director, Division of Gastrointestinal and Coagulation Drug Products
Julie Ann DuBeau, Consumer Safety Officer, Division of GI and Coagulation Drug Products
Dr. Kathy Robie-Suh, Medical Reviewer, Division of GI and Coagulation Drug Products
Dr. Hugo Gallo-Torres, Medical Supervisor, Division of GI and Coagulation Drug Products
Dr. A.J. Sankoh, Statistical Reviewer, Division of GI and Coagulation Drug Products

GDK:jw

180/DuBeau

NDA 20-883

AUG 11 1998

Texas Biotechnology Corporation
Attention: Gary D. Knappenberger
7000 Fannin, Suite 1920
Houston, TX 77030

Dear Mr. Knappenberger:

Please refer to the meeting between representatives of your firm and FDA on July 14, 1998.

As requested, a copy of our minutes of that meeting is enclosed. Please notify us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely,

/S/ 8-11-98

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

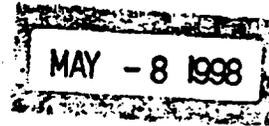
Enclosure

cc:
Archival NDA 20-883
HFD-180/Div. Files
HFD-180/J.DuBeau
JD/August 11, 1998 (drafted)
JD/8/11/98/

/S/ 8/11/98

GENERAL CORRESPONDENCE (MINUTES SENT)

NDA 20-883



Texas Biotechnology Corporation
Attention: Gary D. Knappenberger
7000 Fannin, Suite 1920
Houston, TX 77030

Dear Mr. Knappenberger:

Please refer to your new drug application dated August 11, 1997, received August 15, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Novastan® (argatroban) Injection.

We acknowledge receipt of your submissions dated October 30, November 14, 18, and 20, December 10, 15, and 18, 1997, and January 26, February 6, and March 27, 1998. The original User Fee goal date for this application was February 15, 1998. Your submission of December 18, 1997, extended the User Fee goal date to May 15, 1998.

We also refer to your submissions dated April 9 and 14, 1998, received on April 10 and 15, 1998, respectively. These submissions will be evaluated during the next review cycle.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

Study ARG-911 was a multicenter, open-label, historically controlled, prospective study of 304 patients with HIT (heparin-induced thrombocytopenia)/HITTS (heparin-induced thrombocytopenia and thrombosis syndrome) treated with argatroban. The primary efficacy outcome was a composite of death, amputation, or development of a new thrombosis for HIT patients, and death or amputation for HITTS patients. Study ARG-915 was an open-label (compassionate-use) extension study of ARG-911, designed to collect additional safety information. Study ARG-915 enrolled 271 HIT/HITTS patients, and employed the same historical control as Study ARG-911.

Although significant reductions in the incidence of new thrombotic events were observed for HIT and HITTS patients in both studies, the overall composite endpoint (of death, amputation, or new thrombosis) in Study ARG-911 was not statistically significant in the HIT group, and only trending in the HITTS group. When Study ARG-915 was analyzed post-hoc, there was no statistically significant difference in the overall composite endpoint in the HIT group; however, there was a statistically significant difference in the HITTS group compared to the historical control.

Your secondary analysis of the deaths attributed to thrombosis or underlying disease appeared to show that argatroban reduced mortality due to thrombosis. However, when the deaths were reclassified by the medical reviewer based on data in the Case Report Forms, there was no difference in thrombotic deaths between the treatment and historical control groups. Based on the above information, it appears that the statistically significant reduction in new thrombotic events did not result in a mortality benefit.

With respect to safety, numerical trends of greater all-cause mortality were observed in Studies ARG-911 and ARG-915 in the argatroban-treated patients. In Study ARG-911, these trends in mortality were attributed to significant imbalances in patient characteristics, with argatroban-treated patients being more compromised at baseline. However, our statistical analyses, adjusting for this imbalance, did not support this conclusion. In addition, there was a greater incidence of all-cause mortality in argatroban-treated HIT and HITTS patients observed in Study ARG-915 where patient baseline characteristics of treatment and historical control groups were similar.

To clearly demonstrate safety and efficacy, we suggest that you 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.

In addition, you must adequately address the chemistry, manufacturing, and controls (CMC) deficiencies with regard to drug substance as well as drug product sterility, impurities, manufacturing, testing, and stability. The specific deficiencies were described in our Information Request letter dated May 5, 1998.

Labeling comments will be forthcoming once the application is otherwise approvable.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

If you have any questions, please contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely yours,

/S/
Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

- Original NDA 20-883
- HFD-180/Div. files
- HFD-002/ORM
- HFD-103/Office Director
- HFD-101/L.Carter
- HFD-820/ONDC Division Director
- DISTRICT OFFICE
- HFD-92/DDM-DIAB
- HFD-180/J.DuBeau
- HFD-180/Talarico
- HFD-180/Sizer
- HFD-720/Sankoh
- HFD-180/Choudary
- HFD-180/Antonipillai
- HFD-870/Gary Barnette
- HFD-870/Mike Fossler
- HFD-180/Duffy
- HFD-180/Al-Hakin.
- HFD-805/Cooney
- HFD-805/Uratani
- HFD-344/Robert Young
- HFD-355/Skelly
- r/d Init: Johnson 4/13/98, 5/5/98
- r/d Init: Sankoh 4/14/98, 5/4/98
- r/d Init: Sizer 5/4/98
- r/d Init: Duffy 4/14/98
- r/d Init: Talarico 5/5/98
- JD/April 13, 1998 (drafted)
- JD/5/8/98, _____
- NOT APPROVABLE (NA)

/S/ 5-8-98

/S/ 5/8/98

/S/ 5/8/98
/S/ 5/8/98

MAY - 5 1998

Texas Biotechnology Corporation
Attention: Gary D. Knappenberger
7000 Fannin, Suite 1920
Houston, TX 77030

Dear Mr. Knappenberger:

Please refer to your new drug application dated August 11, 1997, received August 15, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Novastan® (argatroban) Injection.

We also refer to your amendments dated October 30, November 14, 1997, and January 26, 1998.

We have completed our review of the chemistry, manufacturing, and controls (CMC) section of your submission and have identified the following deficiencies:

I. Drug Substance

Drug Master File (DMF) — held by Mitsubishi Chemical Corporation for argatroban, has been reviewed as authorized and has been found deficient. The DMF holder will be notified of the specific deficiencies.

II. Drug Product Impurities

A. Justify the proposed specifications for the impurities and degradation products based upon the data from the studies listed below. Provide a table containing a listing of the batch numbers for the pivotal clinical, toxicological, and stability batches. In addition, provide impurities information which includes the following:

1. quantitation of identified impurities and degradation products (individual and total),
2. quantitation of unidentified impurities and degradation products (individual and total),
3. number of each batch/lot, and
4. date of manufacturing.

B. Regarding validation of the — assay for degradation products, provide information (tabulated) about the quantitation of the individual impurities. In

addition, provide a chromatogram showing the synthesis related impurity, another chromatogram which shows both the synthesis related and the forced degradation impurities, and explain how impurities and degradation products were observed below the limit of detection

III. Drug Product Manufacturing and Testing

- A. Provide reprocessing operations information.
- B. Regarding the sampling plan for the drug product, provide further information about the sampling method, and justify the proposed sample o. vials/batch.
- C. Provide information regarding the sampling plan used for container/closure acceptance testing.
- D. Regarding the method for assay of Type I and Type II stereoisomers, provide details about the quantitation of the two isomers and how peak overlap was handled.

IV. Drug Product Stability

- A. Define symbols contained in the stability tables (e.g. A, AS, AMSP).
- B. Indicate whether photo-stability testing was performed per ICH conditions.
- C. Include an oxidation test for Novastan® in the validation of the stability indicating assay.
- D. Regarding the stability studies of the diluted drug product, indicate whether you are going to confirm that the impurities referred to are from the solvent system, and not from any other source.

V. Microbiology

- A. Filter validation

Contamination of non-indicator organisms in all three runs of the filter validation suggests inadequate aseptic technique. The inability to control flow rate raises the question of whether the validation parameters simulated production runs. Please explain.

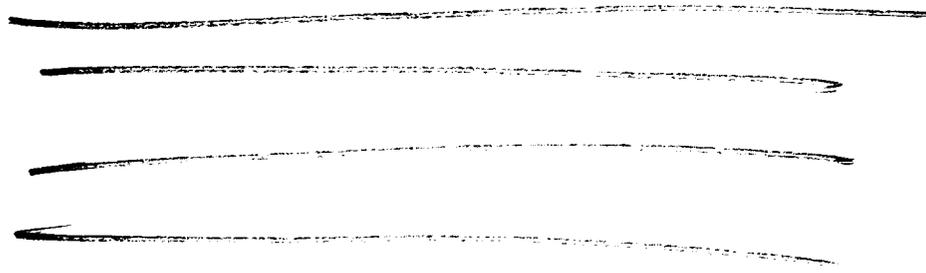
B. Depyrogenation/sterilization of vials

1. 
2. Submit information on the biological indicator (BI) challenge including the type of BI, the amount inoculated on each vial (spores/vial), and the resistance.
3. Provide details and an explanation for the insufficient BI inoculum in Run # 0273-96-720.

C. Sterilization of container/closure system

1. Submit information on the endotoxin challenge including the amount of bacterial endotoxin spiked onto each stopper (EU/stopper) and the efficiency of endotoxin recovery from unprocessed controls.
2. Provide details of the quality control testing (tests and specifications) which are performed on the terminally sterilized vials.

D. Terminal sterilization of the drug product



E. Bacterial endotoxin test

1. Submit data for endotoxin determination by the kinetic method.
2. Include endotoxin data from recent lots to ensure there is no lot to lot variation.
3. Specify which endotoxin method, gel-clot or kinetic, will be used for lot release.



LOYOLA
UNIVERSITY
MEDICAL CENTER

2160 South First Avenue
Maywood, Illinois 60153
Telephone: (708) 216-9000

Loyola University Chicago

April 9, 1998

Lilia Talarico, M.D.
Director, Division of Gastrointestinal
And Coagulation Drug Products (HFD-180)
CDER
Document Control Room 6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Re: Original New Drug Application 20 883
NOVASTAN® (argatroban) Injection Concentrate

Dear Dr. Talarico:

I have again reviewed the data from 911 with specific attention to the historic control population at our institution. The methodology for gathering historic control data involved a retrospective approach which produced 32 cases at our institution. My review of our 911 historic control patients revealed this: only one patient died, three patients required amputation, and two patients developed new thrombosis (mortality 3%, amputation 9%, new thrombosis 6.2%). Our local prospective HIT registry which was conducted over a similar time period, identified 114 patients. In the prospective Loyola HIT registry 39 patients died, eight patients required amputation, and 32 patients developed a new thrombosis (mortality 34%, amputation 6%, new thrombosis 28%). In the Loyola 911 argatroban treated experience (44 patients) six died, two required amputations, and three developed new thrombosis.

Comparison of the historic control population contributed by Loyola to 911 and our prospective registry which was collected over a simultaneous time period can be summarized as follows:

		Death	Amputation	New Thrombosis
*Loyola Historical Controls in 911 (**93-94)	32	3%	9%	6%
Loyola HIT Registry (92-96)	114	34%	6%	28%
*Loyola ARG 911 Patients (95-96)	44	14%	5%	7%

- Data in NDA 20,883
- Time frame of data collection

136-16-98

The Loyola registry represents our universe of patients for comparison to treated 911 patients. A selection bias appears to be effecting our local 911 historic control database. Reasons for the selection bias on the 911 historic control patients identified at our local institution include:

1. A discharge diagnosis of thrombocytopenia was used to identify potential historic control patients. However, No ICD-9 code exists for Heparin-Induced Thrombocytopenia. The discharge diagnosis of thrombocytopenia is not frequently listed and, therefore, registry HIT patients were not captured for inclusion in 911 historic controls.
2. Charts of catastrophic HIT registry patients were unavailable for review secondary to ongoing medical - legal issues.
3. The retrospective application of exclusion criteria means that patients who were on the oncology service or had serious organ system failure (e.g.: renal failure, respiratory failure, hepatic failure, sepsis) were excluded from analysis, however, prospective treated patients could be included after "clinically controlled" state was achieved (e.g.: cardiogenic shock controlled with artificial heart or assist device could be included in the treatment arm of 911, but would be excluded from the historic control arm).
4. The elimination of the platelet function laboratory as a means of identifying patients in the historic control population meant that our best mechanism for HIT patient identification was ignored. Both our prospective HIT registry and our treated 911 patients utilized the platelet function lab for identifying HIT patients.

The biggest concern prior to creation of the historic control population in 911 was creation of a historic control population that was "sicker" than our treated population. The very strict interpretation of the historic control methodology instead created a very "healthy" group of HIT patients at our center. This selection bias, therefore, created a very atypical group of control HIT patients.

A second bias operative of our institution was the nature of our tertiary referral network. The availability of an agent to treat HIT was well known in the medical community surrounding our university hospital. Physicians in the community would seek therapy for their very ill HIT patients and transfer these patients for argatroban therapy; conversely those patients who remained free of both HIT and non-HIT complications, would remain in their local hospital. The strategy adopted by the referring physician is quite logical and does help to explain our outcomes listed in the enclosed table.

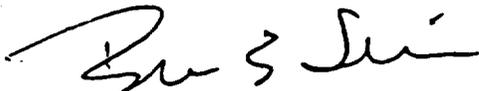
Lilia Talarico, M.D.
Food and Drug Administration

April 9, 1998
Page Three

My interpretation of our local experience is that argatroban produces a very positive effect on the clinical outcomes in our patient population. The compound is easy to use and provides us with a marvelous therapeutic alternative in this very ill group of patients.

Thank you for the commitment demonstrated by both you and the administration to development of therapeutic strategies for the catastrophic process of HIT.

Sincerely,



Bruce E. Lewis, M.D.
Associate Professor of Medicine
Division of Cardiology
Loyola University Medical Center
and
Chief, Section of Cardiology
Catholic Health Partners

BEL:ln

HFD-180/NDA 20883

Food and Drug Administration
Rockville MD 20857

MAR 19 1998

TRANSMITTED BY FACSIMILE

Mr. Gary D. Knappenberger
Senior Director, Clinical Development and Regulatory Affairs
Texas Biotechnology Corporation
7000 Fannin, Suite 1920
Houston, TX 77030



Re: **NDA 20-883**
Novastan (argatroban) Injection
MACMIS ID #6407

Dear Mr. Knappenberger:

This letter is in response to Texas Biotechnology Corporation's (TBC) letter dated March 10, 1998, requesting comments on proposed introductory "coming soon" advertisement for Novastan (argatroban) Injection. The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the "coming soon" advertisement submitted and has no objections to the proposed material submitted.

If TBC has any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm-17B-20, 5600 Fishers Lane, Rockville, MD, 20857. DDMAC reminds TBC that only written communications are considered official.

In all future correspondence regarding this matter, please refer to both the NDA number and the MACMIS ID # 6407.

Sincerely,

/S/

Stephen W. Sherman, JD, MBA
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

/S/ 2-23-98

Mr. Gary Knappenber
Texas Biotechnology Corporation
NDA 20-883

Page 2

Novastan.317

draft: SSherman 3/17/98
concur: TAbrams 3/18/98

cc:
HFD-40/NDA 20-883
HFD-40/chron/sherman/abrams
~~HFD-180/NDA-20-883~~
HFD-180/Talarico

MACMIS type code: lett
MACMIS content code: advp

MACMIS File ID # 6407

close-out: yes

FOI Status: NONRELEASEABLE - launch

Handwritten signature

NDA 20-883

JAN 15 1998

Texas Biotechnology Corporation
Attention: Gary D. Knappenberger
7000 Fannin, Suite 1920
Houston, TX 77030

Dear Mr. Knappenberger:

Please refer to your pending August 11, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Novastan® (argatroban) Injection.

We also refer to your amendment dated December 18, 1997, which includes safety and efficacy information for 174 patients enrolled in Study ARG-915 entitled, "An Open-Label Clinical Study of NOVASTAN® in Patients with Heparin-Induced Thrombocytopenia (HIT)/Heparin-Induced Thrombocytopenia and Thrombosis Syndrome (HITTS)."

To complete our review of your submission, we request the following tabulations for Study ARG-915. Please note that the left side of the table below is the specific tabulation, and the right side is the comparable tabulation(s) provided for Study ARG-911. Compare the historical control and argatroban-treated patients, and present separately for HIT and HITTS patients.

1. Patient disposition	Table 1, Appendix 16.2.1, vol. 128, p.2
2. Patients who prematurely discontinued argatroban and reasons why	Table 4, vol. 105, p. 87 Appendix 16.4.1, vol. 129, p. 3-29
3. Patient demographics	Table 5, vol. 105, p. 89
4. Mean dosage, duration, and delay in initiation of argatroban therapy	Table 6, vol. 105, p. 90
5. Patient baseline characteristics	Table 2S, vol. 105, p. 304
6. Concomitant medications; antithrombotic concomitant medications	Table 13, vol. 105, pp. 101-2 Vol. 4.6, p. 9
7. Efficacy outcome tables and individual patient listings for patients positive for ANY HIT antibody test (SRA, HIPA, or H-PF4 ELISA)	Appendix 16.4.15, vol. 4.1, p. 193FF
8. Adverse events leading to study withdrawal	Table 38, vol. 105, p. 192

9. Serious adverse events tabulated for historical control compared to argatroban-treated patients	(Please tabulate)
10. Major and minor bleeding events	Table 47, vol. 105, p. 220 Table 49, vol. 105, pp. 223-25 Tables 52 and 53, vol. 105, pp. 236-40 Vol. 4.5, p. 4
11. Case report forms for all deaths	
12. Summary of efficacy analysis results (by primary/secondary endpoints, center, subgroup analyses, and primary/secondary analyses)	
13. Efficacy data in SAS.SD2 format on 3.5 floppy diskette as well as all programs used to generate the efficacy results	
14. The original ARG-915 protocol and all amendments if different from the ARG-911 protocol.	

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely yours,

/s/ 1-15-92
Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Original NDA 20-883

HFD-180/Div. Files

HFD-180/CSO/J.DuBeau

HFD-180/Talarico

HFD-180/Sizer

HFD-720/Sankoh

r/d Init: Sizer 1/3/98

r/d Init: Talarico 1/13/98

JD/December 31, 1997 (drafted)

JD/1/15/98/

/S/

1/15/98

INFORMATION REQUEST (IR)

NDA 20-883

DEC 23 1997

Texas Biotechnology Corporation
Attention: Gary D. Knappenberger
7000 Fannin, Suite 1920
Houston, TX 77030

Dear Mr. Knappenberger:

We acknowledge receipt on December 19, 1997, of your December 18, 1997, amendment to your new drug application for Novastan® (argatroban) Injection.

This amendment includes safety and efficacy information for 174 patients enrolled in Study ARG-915 entitled, "An Open-Label Clinical Study of NOVASTAN® in Patients with Heparin-Induced Thrombocytopenia (HIT)/Heparin-Induced Thrombocytopenia and Thrombosis Syndrome (HITTS)." Study ARG-915 is the open-label continuation of the pivotal study ARG-911. The amendment includes the following: a brief summary of the safety data; separate patient data listings for demographics, baseline characteristics, concomitant medications, etc.; and a set of MedWatch forms for serious adverse events. Under 21 CFR 314.60, this is a major amendment received by the agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is May 15, 1998.

If you have any questions, please contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely yours,

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Original NDA 20-883

HFD-180/Div. Files

HFD-180/J. DuBeau

HFD-180/Sizer

DISTRICT OFFICE

r/d Init: L. Talarico 12/22/97

JD/December 19, 1997 (drafted)

JD/12/23/97.

/S/

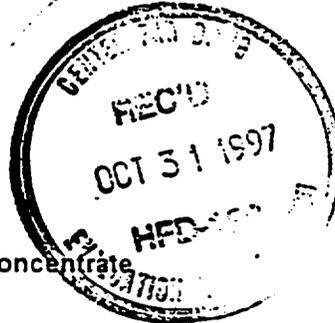
12/23/97

REVIEW EXTENSION

October 30, 1997

Lilia Talarico, M.D.
Acting Director, Division of Gastrointestinal
and Coagulation Drug Products (HFD-180)
CDER
Documentation Control Room 6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIGINAL
AZ



RE: NDA 20,883
NOVASTAN® (argatroban) Injection Concentrate
Response to Questions
Volumes 4.1

Dear Dr. Talarico:

On October 9, 1997 Texas Biotechnology received a set of questions and requests for additional information relative to NDA 20,883 for NOVASTAN® (argatroban) Injection Concentrate which was filed August 15, 1997. In reference to your requests of October 9, 1997, Texas Biotechnology Corporation has the following responses.

A. Administrative

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

The proposed Labeling is on diskette #1 which has been formatted into WordPerfect 6.1 using a three column format. In addition, as requested by the Biopharmacology reviewers, diskette #2 contains the same document in single column format.

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

A Revised Table of Contents for the Overall NDA and especially the Clinical Table of Contents is after Tab 1 in the general information.

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

Upon follow-up discussion with Ms. DuBeau, this request originated with the statistical reviewer. All referenced textbook chapters for Study ARG-911 are included volumes 2.126 - 2.127. A copy of these volumes is included for the statistician.

4. A revised 356h form which references _____ in the "Cross References" section.

A revised 356h form which references _____ in the cross reference section is attached.

B. Chemistry, Manufacturing and Controls (CMC)

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.

Stability data in the three diluents have been provided to the Agency in the following Information Amendments to _____. To facilitate the ongoing review, we are submitting the information previously submitted as part of the IND.

1. In the Information Amendment to the CMC Section (Serial No. 036) submitted on December 22, 1994, a compatibility study was conducted in room light and at room temperature up to 48 hours. NOVASTAN[®] was diluted with Dextrose Injection, USP, in iv bags. For the convenience of the Reviewer, a copy of Section 6.2.6, Compatibility Studies, pages 21 - 25, of the Information Amendment is provided in Tab 4.
 2. In the Information Amendment to the CMC Section (Serial No. 064) submitted on November 9, 1995, a compatibility study was conducted in room light and at room temperature up to 72 hours. NOVASTAN[®] was diluted with Sodium Chloride Injection, USP, and Lactated Ringer's Injection, USP, and placed in iv bags. For the convenience of the Reviewer, a copy of the Information Amendment is provided in Tab 5.
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)].

The Sponsor is withdrawing the Environmental Impact Assessment which was included in the NDA presubmission of June 27, 1997. Included in Tab 6 is the revised Volume 1.5, Section A.3, Environmental Impact Assessment, with the request for categorical exclusion.

3. Stability data on diskette in SAS data set format (See the following INTERNET site: [gopher://cdvs2.cder.fda.gov:70/11GOPHER_ROOT%3A%5Bstab5D](http://cdvs2.cder.fda.gov:70/11GOPHER_ROOT%3A%5Bstab5D)).

The potency assay stability data through 12 months of storage at 25 °C/ _____ for the five registration lots are currently being statistically analyzed for the expiration date estimation using the SAS/PC (Version 6.12) program system STAB prepared, by Moh-Jee Ng (March 23, 1992) of the Division of Biometrics, Center for Drug Evaluation and Research. The results of the statistical analyses along with a diskette containing the potency assay stability data will be submitted in the Amendment of the CMC Section of NDA 20,883 in early November 1997.

C. Pharmacology/Toxicology

1. List of all pharmacology and toxicology studies that were not previously submitted to _____

Tab 7 contains the list of all toxicology studies not submitted to the IND. In addition, all pharmacology reports not previously submitted are flagged (*) in the Table of Contents. (Tab 1). In addition, a summary of the toxicology studies which was inadvertently omitted from from Vol. 1.10 is attached.

D. Biopharmacology

1. Biopharmacological information and study summaries on diskette in ASCII file format.

Tab 8 contains a listing of diskettes containing Biopharmacological information and study reports. Each diskette contains a different clinical study and has data in SAS formatted files.

E. Statistical

1. Efficacy data on diskette in SAS data set forth.

SAS data sets for all efficacy data from ARG-911 and safety data from all studies are on diskettes numbered 7 (see Tab 8)

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

The two-sample normalization test was not performed, rather logistic regression was performed to allow for modeling for the treatment effect and for estimating the treatment odds ratio. Results from both the one-sample Normalization test and the logistic regression (called "2-sample test based on logistic regression") appear in Tables 15 and 16, pp. 107 and 108, Vol. 105. Because the two-sample normalization test does not allow for treatment effect, it was not used.

3. Any unpublished programs used to generate the efficacy results.

Unpublished programs used to generate the efficacy results are on diskette 7 (see Tab 8)

F. Clinical

1. Plans for studying NOVASTAN[®] (argatroban Injection in the pediatric population.

Because of the very small number of pediatric patients under age 12 with Heparin Induced Thrombocytopenia, there are no plans to study this indication in a pediatric population. Dosing in patients between the age of 12 and 18 should be similar to dosing in adults.

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

Section 8A has been restated to include specific page numbers for both study reports and location of patient data. This is included as Tab 9.

G. Clinical Statistical

The following requests pertain to the pivotal clinical study 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)".

For the following requests, note that "Endpoint" refers to new thrombosis, all-death, thrombotic death, and all-amputation, as well as the overall composite, and thrombotic composite endpoints. In addition to the three copies required to be submitted under 21CFR 314.50, please provide a statistical technical copy and diskettes as appropriate.

1. Provide the following information pertaining to the submitted historical control:

- a. State whether the historical control received any therapy for HIT/HITTS (e.g. Coumadin, Ancrod, Dextran, plasmapheresis, other agents). If so, please describe. In addition, conduct an endpoint analysis for historical control patients who received no antithrombotic treatment (except Coumadin), and for historical control patients who receive Ancrod (or other antithrombotic) therapy. Divide into the first 14 days post discontinuation of heparin, and the period following the first 14 days until the end of the following-up period.

Historical Control patients received a alternative therapy for HIT/HITTS (Dextron, plasmapheresis, other agents and Coumadin) Tab 10 contains the listing of alternative therapies.

The endpoint analysis of historical patients will be submitted within the next three weeks as part of our follow up submission.

- b. Define the duration of the "observation period" of emergent events for the historical control population as stated in the safety section of the study. In addition, conduct an analysis of the "delay in follow-up after discontinuation of heparin in the historical control group versus endpoint development."

This question was dropped following discussions with Ms. Julie DuBeau on October 16, 1997.

- c. With regards to Table 6 (vol. 105, p.90), define time-to-follow-up after this discontinuation of heparin in the historical control patients.

The time to follow-up after discontinuation of heparin in the historical controls (Table 6, p. 90; Vol. 105) refers to the time between cessation of heparin and attainment of a platelet count that met entry criteria.

- d. State the platelet count recovery time for historical control patients.

The platelet count recovery time is being determined and will be submitted as part of our follow-up submission.

- e. Divide the occurrence of the historical control endpoints into the first 14 days post discontinuation of heparin, and the period following the first 14 days until the end of the follow-up period.

Tab 11 contains the occurrence of historical control endpoints into the first 14 days post discontinuation of heparin, and the period following the first 14 days.

- f. Account for all patients screened for inclusion in the historical control and provide specific reasons for those not included.

This list of all patients screened for historical control and reasons for those not included will be submitted as part of our follow-up.

2. Regarding the SRA-positive populations:

- a. State whether the SRA test was the only test used to detect the HIT antibody. If not, please provide a list of all patients in whom other diagnostic tests for HIT were employed (e.g. HIPA).

Three tests were used to detect the HIT antibody. These include the Serotonin Release Assay, HIPA, H-PF₄ Elisa. Tab 11 contains the individual results for each test. An Abstract of a presentation at American Heart Association, November 10, 1997, on this item is attached.

- b. Analyze separately the safety and efficacy results for the patient population with a documented history of a positive laboratory test for heparin-dependent antibody.

Tab 12 contains the results of the separate analysis of patients enrolled into the study based on a history of positive laboratory test results.

3. Regarding the reporting of Adverse Events:

- a. Provide the bleeding rates for the first 14 days following the discontinuation of heparin for major, minor, and ALL (including insignificant) bleeding for HIT and HITTS, historical control (if possible), and argatroban-treated patients.

Bleeding rates will be provided as part of our follow-up submission.

- b. Define the types of MINOR BLEEDS.

- c. Provide a listing of ALL Serious Adverse Events divided into body system and component adverse events for historical control and argatroban-treated HIT and HITTS patients which occurred during the argatroban infusion period versus the remainder of the study period.

This listing of Serious Adverse Events will be provided as part of our follow-up submission.

- d. Explain the discrepancy between the data regarding patient withdrawal due to adverse events. Specifically, according to Table 38 (Vol. 105, p. 192) and Appendix 19.1.56 (Vol. 151A, p. 486 in the Integrated Summary of Safety), 22 argatroban-treated patients withdrew due to adverse events. In contrast,

according to the Case Report Form listings (Vol. 1, pp. 58-60), 90 argatroban-treated and 9 historical patients withdrew.

This discrepancy will be explained in our follow-up submission.

4. Provide the location of the following:

- a. The dosing guidelines for patients with underlying liver or renal disease in the study protocol.

In the ARG-911 protocol, the dosing guidelines were the same for all patients, including those with underlying liver or renal disease. Specifically, argatroban was to be started at 2 mcg/kg/min and adjusted as necessary (not to exceed 10 mcg/kg/min) to achieve an aPTT between 1.5-3 times the patient baseline (not to exceed 100 s). However, in correspondence dated 6/20/96 to all investigators, Dr. J.C. Becker (Senior Director, Medical Department) recommended caution in dosing hepatic or renally impaired patients due to higher risk of bleeding.

In addition, a Phase I study (ARG-103) completed after initiation of ARG-911 demonstrated that renal dysfunction did not alter the disposition of argatroban; these results were incorporated into the revised Investigator's Brochure of June, 1996. Another Phase I study (ARG-106) completed after ARG-911 enrollment was essentially completed demonstrated that hepatic impairment significantly decreased argatroban's clearance. An abstract of that study was sent to all investigators participating in the follow-up study (ARG-915) on 12/20/96 and has been included with each Investigator Brochure sent out 12/20/96 and has been included with each investigator Brochure sent out since. Based on that study, the recommendation for dosing hepatically impaired patients with a Child's score >6 is to start at no greater than 0.5mcg/kg/min. Since the Child's score of an hepatically impaired patient may not be known when initiating argatroban, additional caution in dosing, including starting as low as 0.2 mcg/kg/min. may be prudent.

- b. The urinalysis data for patients included in the Integrated Summary of Safety.

The ISS currently states that the general clinical impression is that argatroban has no clinically significant effects or urinary analyses. Reference is made to an appendix (19.6.2) which has full listings of chemistry and hematology values, but only shift tables on urinalysis. The detailed listing of urinalysis data follow Tab 13.

5. State whether there were any patients lost-to-follow-up.

No patients were lost to follow-up in the ARG-911 pivotal study.

6. State whether patients listed for individual investigators were seen and treated by that investigator, or were provided from a registry. (See vol. 70, Section 8A). Specifically, state the site(s) of the historical control patients.

Argatroban treated patients were all seen and treated by the individual investigators at the sites listed in Section 8A. Historical Control patients were obtained from hospital records at those sites with active investigators but may not

have been treated by the investigator themselves. Dr. Warkentin, had established a registry of patients with heparin-induced thrombocytopenia treated primarily at one of four hospitals in the Hamilton, Ontario area.

7. Provide a copy of "European Public Assessment Report of Lepirudin (1997)".

A copy of the European Public Assessment Report for Lepirudin (1997) was submitted as part of the references on ARG-911 Vol. 1.127. It is included here in its entirety. In addition to the requested data, a copy of the translated Japanese labeling, which was sent to Dr. Sizer by fax, is included as Tab 15.

Should you have additional questions, please feel free to contact me.

Sincerely,



Gary D. Knappenberger,
Senior Director, Clinical Development and Regulatory Affairs

GDK:jcw
attachment

as Biotechnology
poration

Submit

NDA 20-883

Texas Biotechnology Corporation
Attention: Gary D. Knappenberger
7000 Fannin, Suite 1920
Houston, TX 77030

OCT - 9 1997

Dear Mr. Knappenberger:

Please refer to your pending August 11, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Novastan® (argatroban) Injection.

To complete our review of your submission, we request that you submit the following:

A. Administrative

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. Copy of all chapters from textbooks referenced in the application.
4. A revised 356h form which references in the "Cross References" section.

B. Chemistry, Manufacturing, and Controls (CMC)

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)].
3. Stability data on diskette in SAS data set format (See the following INTERNET site: gopher://cdvs2.cder.fda.gov:70/11GOPHER_ROOT%3A%5Bstab%5D).

C. Pharmacology/Toxicology

1. List of all pharmacology and toxicology studies that were not previously submitted to

D. Biopharmacology

1. Biopharmacological information and study summaries on diskette in ASCII file format.

E. Statistical

1. Efficacy data on diskette in SAS data set format.
2. Efficacy results of the Two-sample Normalization Test.
3. Any unpublished programs used to generate the efficacy results.

F. Clinical

1. Plans for studying Novastan® (argatroban) Injection in the pediatric population.
2. Revised "Location of Study Report" and "Location of Patient Data" sections of investigator tables to reference specific page numbers.

G. Clinical/Statistical

The following requests pertain to the pivotal clinical study 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)".

For the following requests, note that "Endpoint" refers to new thrombosis, all-death, thrombotic death, and all-amputation, as well as the overall composite, and thrombotic composite endpoints. In addition to the three copies required to be submitted under 21 CFR 314.50, please provide a statistical technical copy and diskettes as appropriate.

1. Provide the following information pertaining to the submitted historical control:
 - a. State whether the historical control received any therapy for HIT/HITTS (e.g. Coumadin, Ancrod, Dextran, plasmapheresis, other agents). If so, please describe. In addition, conduct an endpoint analysis for historical control patients who received no antithrombotic treatment (except Coumadin), and for historical control patients who received Ancrod (or other antithrombotic) therapy. Divide into the first 14 days post discontinuation of heparin, and the period following the first 14 days

until the end of the follow-up period.

- b. Define the duration of the "observation period" of emergent events for the historical control population as stated in the safety section of the study. In addition, conduct an analysis of the "delay in follow-up after discontinuation of heparin in the historical control group versus endpoint development."
 - c. With regard to Table 6 (vol. 105, p. 90), define time-to-follow-up after the discontinuation of heparin in the historical control patients.
 - d. State the platelet count recovery time for historical control patients
 - e. Divide the occurrence of historical control endpoints into the first 14 days post discontinuation of heparin, and the period following the first 14 days until the end of the follow-up period.
 - f. Account for all patients screened for inclusion in the historical control and provide specific reasons for those not included.
2. Regarding the SRA-positive population:
- a. State whether the SRA test was the only test used to detect the HIT antibody. If not, please provide a list of all patients in whom other diagnostic tests for HIT were employed (e.g. HIPA).
 - b. Analyze separately the safety and efficacy results for the patient population with a documented history of a positive laboratory test for heparin-dependent antibody.
3. Regarding the reporting of Adverse Events:
- a. Provide bleeding rates for the first 14 days following the discontinuation of heparin for major, minor, and ALL (including insignificant) bleeding for HIT and HITTS, historical control (if possible), and argatroban-treated patients.
 - b. Define the types of MINOR BLEEDS.
 - c. Provide a listing of ALL Serious Adverse Events divided into body system and component adverse events for historical control and

argatroban-treated HIT and HITTS patients which occurred during the argatroban infusion period versus the remainder of the study period.

- d. Explain the discrepancy between the data regarding patient withdrawal due to adverse events. Specifically, according to Table 38 (vol. 105, p. 192) and Appendix 19.1.56 (vol. 151A, p. 486 in the Integrated Summary of Safety), 22 argatroban-treated patients withdrew due to adverse events. In contrast, according to the Case Report Form listings (vol. 1, pp. 58-60), 90 argatroban-treated and 9 historical control patients withdrew.
4. Provide the location of the following:
 - a. The dosing guidelines for patients with underlying liver or renal disease in the study protocol.
 - b. The urinalysis data for patients included in the Integrated Summary of Safety.
 5. State whether there were any patients lost-to-follow-up.
 6. State whether patients listed for individual investigators were seen and treated by that investigator, or were provided from a registry. (See vol. 70, Section 8A). Specifically, state the site(s) of the historical control patients.
 7. Provide a copy of "European Public Assessment Report for Lefirudin (1997)".

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely yours,

LS/ 10-9-99

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA 20-883

Texas Biotechnology Corporation
Attention: Gary D. Knappenberger
7000 Fannin, Suite 1920
Houston, TX 77030

JuBeau
AUG 20 1997

Dear Mr. Knappenberger:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Novastan® (argatroban) Injection

Therapeutic Classification: Priority

Date of Application: August 11, 1997

Date of Receipt: August 15, 1997

Our Reference Number: NDA 20-883

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 14, 1997, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact me at (301) 443-0487.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Original NDA 20-883

HFD-180/Div. Files

HFD-180/CSO/J.DuBeau

HFD-180/Talarico

DISTRICT OFFICE

JD/August 20, 1997 (drafted)

JD/8/20/97, _____

/S/8/20/97

ACKNOWLEDGEMENT (AC)