TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL

April 18, 2000

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

BS

RE: NDA 20-715
Trelstar® Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Response to request for additional information

Dear Dr. Allen:

Reference is made to Debio R.P. NDA 20-715 amendment submitted to FDA on December 16, 1999 and to the April 6, 2000 telephone contact of Dr. David Hoberman, reviewing statistician, during which he requested that additional data analysis be performed.

The following analyses were requested:

1. Do a "Worst Case" analysis. There are a lot of missing patients through 9 months. Reanalyze by counting those on Debio's product as failures at the time they are lost and those on the comparator as successes when the are lost.

2. Using only those subjects achieving castration at the end of the first month, calculate exact numbers of castration and confidence intervals on days 29 and 57.

3. Calculate successive life tables starting at month 1 =Time 0 using number of castrations at the end of the prior months in each treatment group as the denominator, repeat this for Month 2, Month 3, etc. In each case the denominator is the number of castrations at the end of the previous month, so each curve starts at 100% successes and drops from there.

In response to these requests, Target Research Associates is hereby submitting in duplicate, on behalf of Debio RP, the following tables in both paper and electronic format:

Table 1: Continued maintenance of castration levels, ITT Population

Table 2: Continued maintenance of castration levels, PP Population

Table 3: Continued maintenance of castration levels – Survival analysis ITT Population

Table 4: Continued maintenance of castration levels – Survival analysis PP Population

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Table 5: Castration levels on Day 29 and 57 for patients castrated after one month ITT Population

Table 6: Castration levels on Day 29 and 57 for patients castrated after one month PP Population

Table 7: Number of castrations as proportion of previous castrations ITT Population

Table 8: Number of castrations as proportion of previous castrations PP Population

Please contact me if you should have any questions regarding this submission.

Best regards,

Robert J. McCormack/mcj.

Robert J McCormack, Ph.D.
Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

April 18, 2000

ORIGINAL

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-715
Trelstar® Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Request for additional information

BB

Dear Dr. Allen:

Reference is made to Debio R.P. NDA 20-715 amendment submitted to FDA on December 16, 1999 and to the April 6, 2000 telephone contact of Jeanine Best in which she requested additional information on behalf of the biopharmaceutics reviewer.

Therefore, as requested on behalf of Debio RP, the following information is being submitted in duplicate in paper and electronic formats:

For studies DEB-96-TRI-01, DEB-96-TRI-02 and DEB-98-TRI-01

- Means and standard deviations for triptorelin and testosterone pharmacokinetic parameters at each sampling time point between day 0 and day 28

Please be advised that the data provided for study DEB-96-TRI-01 are from a subset of 30 patients in the first phase of the study only. There are no data to report from the second phase of the study.

Please contact me if you should have any questions regarding this submission.

Best regards,

Robert J McCormack, Ph.D.
Vice President, Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION
☐ LETTER ☐ MEMO
CSO INITIALS DATE

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TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL

April 17, 2000

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-715
Trelstar® Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Response to Biopharmaceutics reviewer request of April 13, 2000

BB

Dear Dr. Allen:

Reference is made to Debio R.P. NDA 20-715 amendment submitted to FDA on December 16, 1999. Reference is also made to a telephone call from Jeanine Best on April 13, 2000 during which time she requested, on behalf of the biopharmaceutics reviewer, that the locations of the triptorelin and testosterone assay validation information for studies 95-TRI-03, 96-TRI-01, 96-TRI-02, and 98-TRI-01 be provided. Attached is a table indicating where the triptorelin and testosterone assay validation information can be found.

Please contact me if you have any questions or need any additional information.

Best regards,

Robert J. McCormack/mg.

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL

April 5, 2000

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

RE: NDA 20-715
Trelstar® Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Request for additional information

Dear Dr. Allen:

Reference is made to Debio R.P. NDA 20-715 amendment submitted to FDA on December 16, 1999 and to the April 5, 2000 telephone contact of Jeanine Best in which she requested additional information on behalf of the medical reviewer.

The medical reviewer requested discontinuation and testosterone information for Patient 07209 from Study DEB-96-TRI-01 (2nd phase). Please be advised that this patient was not identified as being discontinued in the March 27, 2000 submission because he made all study visits. The patient died 9 days after the last study visit.

Therefore, as requested, Target Research Associates is hereby submitting in duplicate, on behalf of Debio RP, the information for patient 07209 which is summarized below:

Patient number	Reason for Discontinuation	Discontinuation Date	Last visit Name	Last visit date	Last testosterone level
07209	Did not discontinue	N/A	253	12/10/98	<0.2

Please contact me if you should have any questions regarding this submission.

Best regards,

Jill A Powers, RAC
Manager, Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

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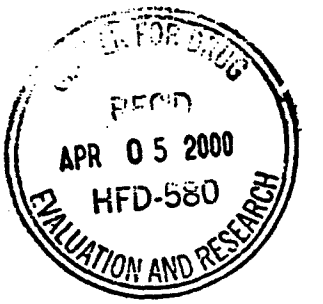
TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

April 4, 2000

ORIGINAL

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 20-715
Trelstar® Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Clarification of Trelstar® established name

NEW CORRESP [redacted]

NC

Dear Dr. Allen:

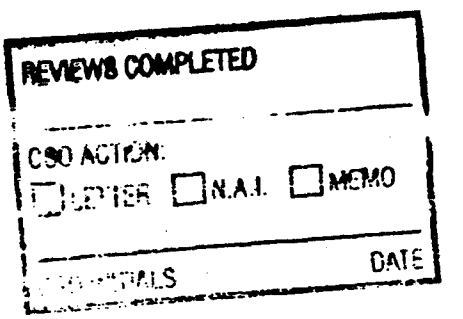
Reference is made to Debio R.P. NDA 20-715 amendment submitted to FDA on December 16, 1999, and to the April 3, 2000 telephone contact of Jeanine Best in which she requested clarification of the established name to be used for Trelstar®.

Therefore, as requested, Target Research Associates is hereby submitting in duplicate, on behalf of Debio RP, official notification that the established name for Trelstar® is triptorelin pamoate for injectable suspension.

Please contact me if you should have any questions regarding this submission.

Best regards,

Jill A Powers, RAC
Manager, Regulatory Affairs



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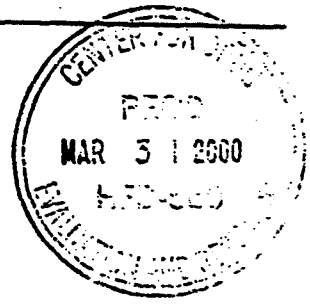
TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS



March 30, 2000

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

BB

RE: NDA 20-715
Trelstar® Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Response to biopharm reviewer request for information

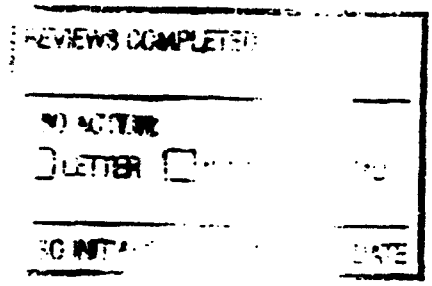
Dear Dr. Allen:

Reference is made to Debio R.P. NDA 20-715 amendment submitted to FDA on December 16, 1999, and to the March 27, 2000 telephone contact of Jeanine Best in which additional information was requested by the biopharm reviewer. Therefore, as requested, Target Research Associates is hereby submitting, on behalf of Debio RP, two diskettes (one archive copy and one review copy) containing full profile graphs including the mean and standard deviation for triptorelin, testosterone, LH and FSH concentrations. The graphs being provided are for studies 96-TRI-01 (first and second phase), 96-TRI-02 and 98-TRI-01.

Please contact me if you should have any questions regarding this submission.

Best regards,

Jill A Powers, RAC
Manager, Regulatory Affairs



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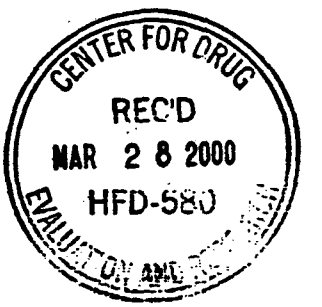
TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL

March 27, 2000



Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-715
Trelstar® Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Response to medical reviewer request for information

ORIG AMENDMENT
BM

Dear Dr. Allen:

Reference is made to Debio R.P, NDA 20-715 amendment submitted to FDA on December 16, 1999, and to the March 22, 2000 telephone contact of Jeanine Best in which additional information was requested by the medical reviewer.

Therefore, as requested, Target Research Associates is hereby submitting in duplicate, on behalf of Debio RP, information regarding individual testosterone levels for patients who dropped out of Study DEB-96-TRI-01 first and second phases. The individual patient data listings for the requested information can be found in the following locations of NDA 20-715 amendment:

Data	Study report patient data listing section	NDA 20715 Amendment Vol./Page
DEB-96-TRI-01, 1st phase		
Dropout	16.2.1	2.28 / 478-479
Visit dates	16.2.5.1	2.30 / 081-129
Testosterone levels	16.2.6.2.1	2.30 / 311-385
DEB-96-TRI-01, 2nd phase		
Dropout	16.2.1	2.39 / 002
Visit dates	16.2.5.1	2.39 / 280-320
Testosterone levels	16.2.6.2.1	2.40 / 041-140

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For ease of review, the requested data have been summarized in the attached tables.

Please contact me if you should have any questions regarding this submission.

Best regards,

Jill A Powers, RAC
Manager, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

March 15, 2000

ORIGINAL

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT
BM

RE: NDA 20-715
Trelstar® Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Response to medical reviewer request for information

Dear Dr. Allen:

Reference is made to Debio R.P. NDA 20-715 amendment submitted to FDA on December 16, 1999, and to the March 14, 2000 telephone contact of Jeanine Best in which additional information was requested by the medical reviewer.

Therefore, as requested, Target Research Associates is hereby submitting in duplicate, on behalf of Debio RP, the attached pages from study reports DEB-96-TRI-01 (first and second phases). These pages contain a line listing by patient # of study dropouts and the reason for dropout for patients in the 1 month triptorelin arm of the above mentioned study. Please be advised that this information can also be found in volume 2.28, pages 478-479 and volume 2.39, page 002 of the NDA 20-715 amendment.

Please contact me if you should have any questions regarding this submission.

Best regards,

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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ORIGINAL

TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

February 22, 2000

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

BC

RE: NDA 20-715
Trelstar® Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Submission of revised/updated DMF authorization letter

Dear Dr. Allen:

Reference is made to Debio R.P. NDA 20-715 amendment submitted to FDA on December 16, 1999, to point #2 cited in the Chemistry, Manufacturing and Controls section of the deficiency letter dated October 29, 1999 from Dr. Houns for NDA [redacted] regarding the [redacted] and to the deficiency response submitted in the December 16, 1999 amendment (Vol. 2 of 103/ page 001).

Target Research Associates is hereby submitting in duplicate, on behalf of Debio RP, an updated DMF authorization letter for [redacted]

Please contact me if you should have any questions regarding this submission.

Best regards,

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

REVIEWS COMPLETED

☐ MEMO

DATE

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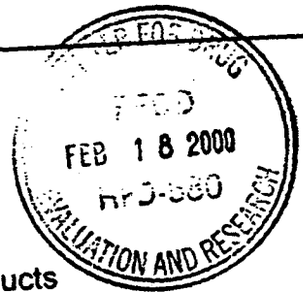
TARGET RESEARCH ASSOCIATES
CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL



February 17, 2000

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

AMENDMENT

BM

RE: NDA 20-715
Trelstar® Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Response to FDA request of February 10, 2000

Dear Dr. Allen:

Reference is made to Debio R.P. NDA 20-715 amendment submitted to FDA on December 16, 1999 and to a FDA telephone contact on February 10, 2000, during which the following information related to the complete response was requested:

1. Copies of the narrative portions of the ISE and ISS
2. Electronic copy of the annotated package insert
3. A written statement from Debio confirming that the patients who participated in the second phase of the pivotal study were naïve patients.

On behalf of Debio R.P., Target Research is hereby submitting the above mentioned items in duplicate to the NDA. If you should have any questions regarding this submission please feel free to contact the undersigned.

Best regards,

Robert J. McCormack/m.g.

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

COMPLETED
ACTION:
☐ LETTER ☐ MEMO
CSO _____ DATE

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TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL

February 14, 2000

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT
BC

RE: Debio, RP
NDA 20-715
Trelstar® Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Response to FDA request of February 1, 2000

Dear Dr. Allen:

Reference is made to the NDA 20-715 amendment submitted to FDA on December 16, 1999 and to the telephone conversation with Jeanine Best and Dr. David Lin on February 1, 2000. Dr. David Lin requested information on the role of Pharmacia and Upjohn in the packaging procedure of Trelstar®. On behalf of Debio, RP we are submitting in duplicate the following response to Dr. Lin's question:

- Trelstar® vials which have been tested and released by Debio are shipped with certificates of analysis to Pharmacia & Upjohn's Kalamazoo, Michigan facility.

- Pharmacia & Upjohn is responsible for primary labeling of the vial and individually packaging vials into single use cartons for marketing.

Please let me know if you have any questions or require additional information.

Best regards,

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION

☐ LETTER ☐ [illegible] ☐ MEMO

CSO INITIALS DATE

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TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

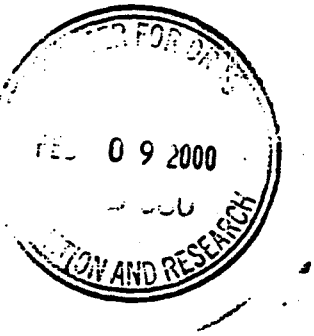
ORIGINAL

ORIG AMENDMENT

February 8, 2000

BZ

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 20-715
Trelstar® Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Response to FDA request of January 19, 2000

Dear Dr. Allen:

Reference is made to Debio R.P. NDA 20-715 amendment submitted to FDA on December 16, 1999 and to a FDA telefax of January 19, 2000 requesting additional information. On behalf of Debio R.P., Target Research is submitting the following information in duplicate:

- a table of in vitro dissolution studies, which includes results and a description of where the individual values for each lot number can be located in the NDA submission
- an electronic copy of the pharmacokinetic / bioavailabilility summary that was submitted in the NDA, which contains a synopsis of the new PK studies, a summary of bioavailability and PK studies and tables of the formulation compositions used in the PK and clinical studies
- copies of graphs and tables for all new pharmacokinetic studies and an electronic copy of the raw data (in excel format) for the PK studies

Please be advised that this submission completes the items that were requested in the January 19, 2000 correspondence. Please contact me if you have any questions regarding this information.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ [illegible] ☐ MEMO

CSO INITIALS DATE

554 Central Avenue • New Providence, NJ 07974 USA • 908/464-7500 • FAX: 908/464-7515

Best regards,

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

RESEARCH ASSOCIATES
CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL

February 1, 2000

ORIG AMENDMENT

BZ

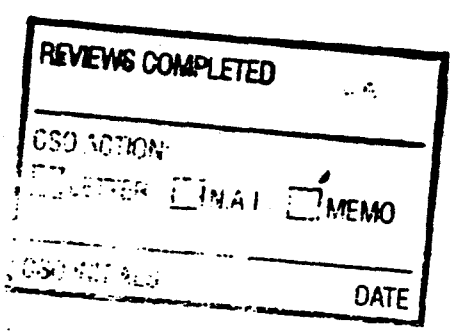
Jeanine A. Best, MSN, RN
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Parklawn Building, Room 17B-45
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-715
Trelstar® Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Partial response to FDA request of January 19, 2000

Dear Ms. Best:

Reference is made to Debio R.P. NDA 20-715 amendment submitted to FDA on December 16, 1999 and to your telefax of January 19, 2000 requesting additional information. On behalf of Debio R.P., Target Research is submitting the following information: Volume 2.2 (Chemistry, Manufacturing and Controls) of the December 16, 1999 submission (NDA 20-715 amendment) and volume 1 of 2 of the February 11, 1999 submission (response to CMC, Biopharmaceutics, and Microbiology deficiencies) for the Microbiology reviewer. Please be advised that the remaining items listed in the January 19, 2000 correspondence will be submitted to FDA in the near future.

Please contact me if you have any questions.



Best regards,

Robert J. McCormack, M.D.

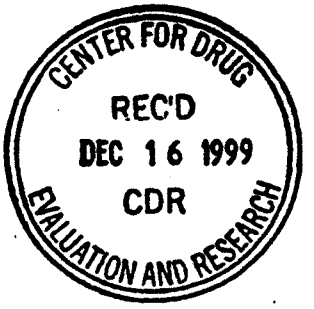
Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

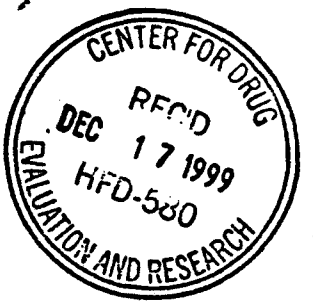
554 Central Avenue • New Providence, NJ 07974 USA • 908/464-7500 • FAX: 908/464-7515

TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL





December 16, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852-1833

Attn: Lisa Rarick, MD
Director
Division of Reproductive and Urologic Drug Products

ORIG AMENDMENT

RE: Debio Recherche Pharmaceutique S.A.
New Drug Application #20-715
Trelstar® Depot 3.75 mg (triptorelin pamoate for depot suspension)
Indication: Treatment of advanced prostate cancer
Submission of complete response to NDA non-approvable letter dated June 26,1997

AZ

Dear Dr. Rarick,

Reference is made to the non-approvable letter from the Agency dated June 26, 1997, which outlined the deficiencies in NDA 20-715. The issues presented in the letter were primarily related to the quality of the clinical data submitted in the application and to additional Chemistry, Manufacturing and Controls (CMC) information needed for the triptorelin pamoate active ingredient and Debioject delivery system. In order to address the clinical deficiencies, Debio conducted a Phase III study which evaluated the to-be-marketed Trelstar® Depot (triptorelin pamoate depot, 3.75 mg) with Lupron® Depot (leuprolide acetate depot, 7.5 mg) in patients with advanced prostate cancer. The protocol for the Phase III study was reviewed and approved by FDA prior to study initiation. Additionally, in a meeting held with the Agency on June 8, 1999, Division personnel agreed that the clinical trial results were adequate for inclusion in the complete response submission.

The Chemistry, Manufacturing and Control issues related to the Debioject delivery system are no longer relevant to the complete response since FDA has allowed the to-be-marketed product to be changed from the Debioject to the vial alone packaging configuration (see enclosed letter dated October 1, 1999). A formal letter officially withdrawing the Debioject delivery system and replacing it

with the vial alone packaging configuration is enclosed in this submission. All technical information requested by FDA regarding the vial alone packaging configuration in the October 1, 1999 letter has been included in the CMC section of the complete response. Additionally, responses to the CMC deficiencies outlined in two separate letters from the Agency dated October 29, 1999 (enclosed) related to NDA [redacted] have also been included. These CMC issues have been addressed as part of the complete response for prostate cancer since the CMC comments for NDA [redacted] would also be applicable to the approvability of NDA 20-715. All remaining relevant CMC, Biopharmaceutic and Microbiology issues raised in the June 26, 1997 non-approvable letter have been addressed in this submission or previous submissions.

At the beginning of each technical data section you will find an Introduction section which in part presents the relevant issues raised in the June 26, 1997 non-approvable letter with a cross-reference to where the information can be located. A completed form FDA 356h is enclosed. This application consists of 103 volumes which are numbered consecutively, individually paginated and organized in accordance with 21 CFR 314.50. We have provided both a complete archival copy (blue binders) and a review copy of the volumes. We have also provided ten additional copies of the Application Summary (Vol. 2.1) so that it can be supplied to reviewer and supervisory personnel as required. The organization and locations of the various sections of the complete response are listed in Volume 2.1. All CRFs and case report form tabulations have been supplied on CD-ROM in accordance with FDA guidelines and are located in Volumes 2.96-2.103 of the archival copy of the NDA.

We trust that the information provided has adequately addressed the issues raised in the June 26, 1997 non-approvable letter, the CMC issues resulting from FDA review of NDA [redacted] and the information FDA requested on the vial alone packaging configuration.

Please let me know if you have any questions regarding the enclosed information.

Sincerely,

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

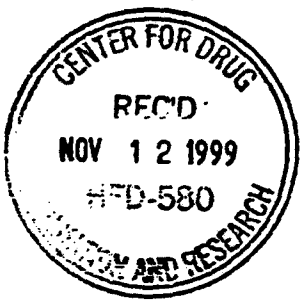
ORIGINAL

NEW CORRESP
NC

RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

November 10, 1999



Kim Colangelo
Program Manager
Food and Drug Administration
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research
HFD-580
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: Debio Recherche Pharmaceutique S.A.
NDA 20-715
Decapeptyl®(triptorelin pamoate for depot suspension) 3.75 mg
Indication: Prostate Cancer
Location change for Target Research Associates

Dear Ms. Colangelo,

Please note that as of November 15, 1999, Target Research Associates will be located at a new facility. The following is the information needed to update your records:

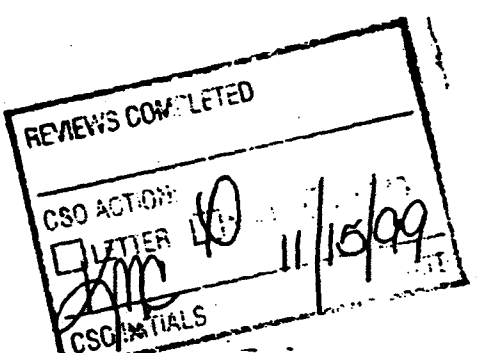
Target Research Associates, Inc.
554 Central Avenue
New Providence, NJ 07974
Main Phone – (908) 464-7500
Regulatory Fax – (908) 464-3529

Please direct all correspondence to Target to the new address and phone/fax as of November 15, 1999.

Sincerely,

Robert J. McCormack

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs



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ORIGINAL

ORIG AMENDMENT

52.

TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and
Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

NSay 9/24/99

CENTER FOR DRUG EVALUATION AND RESEARCH RECD SEP 22 1999 HFD-580

Noted see Chemistry memo. JTL 9/24/99

Noted for 9/24/99

September 21, 1999

Ref.: Debio Recherche Pharmaceutique S.A.
NDA 20-715 / Decapeptyl® (triptorelin pamoate for depot suspension) 3.75mg
Indication: Prostate Cancer
Rationale for withdrawal of the Decapeptyl® Debioject® and Debioclip® delivery systems and replacement with the vial alone package configuration

Dear Dr. Rarick,

The enclosed later dated July 16, 1999 which, describes the rationale for withdrawal of the Debioject® and Debioclip® was faxed to the Division on July 16, however it was never submitted to NDA 20-715. Therefore, on behalf of Debio RP, we are officially submitting in duplicate, the July 16, 1999 letter to NDA 20-715. Please note that the 356h form is dated September 21, 1999 while the enclosed letter retains its original date of July 16, 1999.

Please let me know if you have any questions or need additional information.

Sincerely,

Robert J McCormack /qp

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

REVIEWS COMPLETED
GC sent 10/1/99
CSO ACTION:
☒ LETTER ☐ N.A.I. ☐ MEMO
AMC 10/1/99
INITIALS DATE

1801 East Second Street • Scotch Plains, NJ 07076 USA • 908/322-2402 • FAX: 908/322-5277

ORIGINAL

NEW CORRESP
NC

TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

May 26, 1999

Kim Colangelo
Program Manager
Food and Drug Administration
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-715
Decapeptyl®(triptorelin pamoate for depot suspension) 3.75 mg
Submission of missing page for the meeting package for the June 8 meeting to discuss the complete response to NDA Non-Approvable Letter

Dear Ms. Colangelo:

Reference is made to NDA 20-715 for Decapeptyl®(triptorelin pamoate for depot suspension) 3.75 mg in the treatment of prostate cancer and to the June 8, 1999 meeting package submitted to the agency on May 11, 1999. On behalf of Debio RP, we are submitting one archive and 17 desk copies of page 09A, which was inadvertently omitted when the package was originally submitted.

I apologize for any inconvenience this may have caused.

If you have any questions or need any additional information please do not hesitate to contact me.

Best regards,

Jill A. Powers, RAC
Manager, Regulatory Affairs

Pages distributed to attendees

REVIEWS COMPLETED
Meeting held 6/8/99
CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
RMC 6/20/99
CSO INITIALS DATE

1801 East Second Street • Scotch Plains, NJ 07076 USA • 908/322-2402 • FAX: 908/322-5277

TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL

ORIG AMENDMENT

10 May 1999

Kim Colangelo
Program Manager
Food and Drug Administration
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-715
Decapeptyl®(triptorelin pamoate for depot suspension) 3.75 mg
Submission of meeting package to discuss complete response to NDA Non-Approvable Letter

Dear Ms. Colangelo:

In a letter dated June 26, 1997, the Agency notified Debio RP that NDA 20-715 was not approvable based on the inadequacy of clinical data submitted. In the non-approvable letter FDA also delineated additional information that would need to be provided in the biopharmaceutics, manufacturing/quality control, and microbiology areas before the NDA could receive final approval. Within the next six months, Debio plans to submit additional data to resolve the outstanding deficiencies outlined in the non-approvable letter. In a meeting with the Agency scheduled for 1 pm on June 8, 1999, we wish to discuss the questions included in the enclosed meeting package in order to ensure the adequacy of the content and format of Debio's complete response to the non-approvable letter of June 26, 1997. Please be advised that the clinical summary information provided in Appendix A, concerning the results of the 3 month formulation of Decapeptyl are presented for informational background purposes. The results of the Decapeptyl one month vs. three month formulation have been presented first since the protocol was originally designed to evaluate the one month vs. three month formulation and later the was amended to a Decapeptyl 1 month formulation vs 1 month Lupron study.

If you have any questions or need any additional information please do not hesitate to contact me.

Best regards,

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

REVIEWS COMPLETED
Meeting held 6/8/99
CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
KM 6/20/99
CSO INITIALS DATE

attachments:
Appendix A: Summary of preliminary results of study DEB-96-TRI-01(first and second phase)
Appendix B: Decapeptyl packaging configurations and labeling
Appendix C: Stability protocols for pre-filled syringes and Debioclips
Appendix D: Certificate of Analysis for endotoxin-free lyophilizaton stoppers

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TARGET RESEARCH ASSOCIATES
CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL
NEW CORRESP
NC

Submitted to LNC on 4/29/99 DR 4/29/99

WT
/S/
4/21/99

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
APR 15 1999
HFD-580

Noted ER 4/29/99

April 13, 1999

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: Debio Recherche Pharmaceutique S.A.
NDA # 20-715
Decapeptyl® Depot, 3.75mg (triptorelin pamoate for depot suspension)
Indication: Prostate Cancer
Request for a change to the approved trade name for Decapeptyl® Depot

Dear Dr. Rarick:

Reference is made to NDA #20-715 for Decapeptyl Depot in the treatment of prostate cancer. Once approved, Decapeptyl® Depot will be packaged and distributed in the U.S. by Pharmacia & Upjohn, Co. FDA notified Target by telephone on January 21, 1999 stating that the nomenclature committee had approved [redacted] the proposed trade name for Decapeptyl® Depot.

Please be advised that Pharmacia & Upjohn would like to change the trade name of Decapeptyl® Depot from [redacted] to Trelstar®. Therefore, on behalf of Debio RP and Pharmacia & Upjohn, Co., we are submitting to NDA 20-715 an official request for approval to change the trade name of Decapeptyl® Depot from [redacted] to Trelstar®.

Please let me know if you need additional information.

Sincerely,

Robert J. McCormack /pp
Robert J. McCormack
Vice President, Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO
CSO INITIALS 4/30/99 DATE

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TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

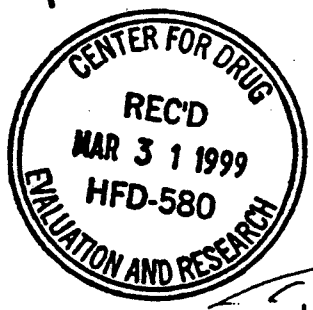
Meeting scheduled for 6/8/99. KMC 4/29/99

ORIGINAL

NEW CORRESP

noted DTC 4/13/99

DFS NOTED 4/2/99



noted KMC 4/13/99

March 30, 1999

Lisa Rarick, MD
Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: Debio Recherche Pharmaceutique SA
NDA 20-715/Decapeptyl Depot, 3.75mg
Indication: Prostate Cancer
Meeting Request to Discuss Complete Response to NDA Non-Approvable Letter

Dear Dr. Rarick:

Reference is made to NDA #20-715 for Decapeptyl Depot in the treatment of prostate cancer and to the letter dated June 26, 1997 from the agency which notified Debio that the NDA was not approvable based on the quality of the clinical data submitted in the NDA. FDA also delineated in the non-approvable letter additional information that would need to be provided in the CMC, biopharmaceutics and microbiology areas before the NDA could receive final approval.

Debio RP plans, in the third quarter of 1999, to submit clinical trial data from a new pivotal study (DEB-96-TRI-01) in order to address the clinical deficiencies outlined in the non-approvable letter. Therefore, on behalf of Debio RP, we are requesting a meeting with the agency for sometime early June to discuss the submission of the clinical data for DEB-96-TRI-01. We also wish to discuss information submitted to the agency on February 11, 1999 in response to the CMC, biopharmaceutics and microbiology issues raised in the non-approvable letter. Debio RP would also like to briefly discuss the timing of the submission for the NDA for the 3 month formulation of Decapeptyl Depot (11.25 mg) in the treatment of prostate cancer. The following information is being provided in this meeting request:

Purpose of Meeting:

To discuss the content and format of Debio's complete response to the non-approvable letter dated June 26, 1997.

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Meeting Objectives

1. To confirm the format and content of the clinical portion of Debio's complete response in terms of the DEB 96-TRI-01 Study Report, ISE and ISS.

2. To determine the electronic submission requirements of the clinical data for DEB-96-TRI-01.

3. To confirm the adequacy of the CMC, biopharmaceutics and microbiology response submitted to the agency on February 11, 1999.

4. To determine when, in relation to the filing of the complete response for the 1-month formulation, can the NDA for the 3-month Decapeptyl formulation be submitted to the agency.

Meeting Agenda

1. Presentation of background information concerning study DEB 96-TRI-01 **(10 min.)**

2. Discussion of the list of questions **(50-60 min.)**

Sponsor Attendees

Piero Orsolini, PhD	President and CEO, Debio RP
Hervé Porchet, MD	Director, Clinical Pharmacology
Pierre Grosgurin, MSc	Manager of Clinical Research, Biostatistics and Clinical Data

[ ]

Robert McCormack, PhD (Target Research Associates)

FDA Attendees Requested

1. Dr. Rarick, Division Director

2. Clinical, Statistical, Biopharmaceutics, CMC and Microbiology reviewers and/or supervisory personnel as required.

3. Randy Olmstead, Project Manager

Meeting Package

A meeting package including a detailed list of questions Debio RP would like answered during the meeting will be submitted to the agency at least 3 weeks in advance of the scheduled meeting.

We look forward to hearing from you regarding a date for the meeting which we hope could take place sometime in early June. Please let me know if you have any questions or need further information.

Sincerely,

Robert J. McCormack, PhD
Vice President, Regulatory Affairs

TARGET RESEARCH ASSOCIATES

NICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

DUPLICATE

February 11, 1999

Lisa Rarick, MD
Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: Debio Recherche Pharmaceutique SA
NDA 20-715/Decapeptyl Depot, 3.75mg
Indication: Prostate Cancer
Submission of partial response to FDA non-approvable letter dated June 26, 1997

Dear Dr. Rarick:

Reference is made to NDA #20-715 for Decapeptyl Depot in the treatment of prostate cancer and to the letter dated June 26, 1997 from the agency which notified Debio that the NDA was not approvable based on the currently available data.

The purpose of this submission is to provide complete responses and supporting information to address the biopharmaceutics, manufacturing/quality controls and microbiology issues outlined in the non-approvable letter. The clinical issues outlined in the non-approvable letter still remain outstanding. However, Debio expects to submit the results of their ongoing clinical trial with the to-be-marketed formulation of Decapeptyl Depot in prostate cancer patients by September 30, 1999. The submission of the clinical trial data in September 1999 will constitute a complete response to all of the issues outlined in the FDA non-approvable letter.

Information in this NDA amendment is being provided in an archival copy and one copy each for biopharmaceutics, manufacturing/quality controls and microbiology personnel.

Please let me know if you have any questions.

Sincerely,

Robert J. McCormack /gp

Robert J. McCormack
Vice President, Regulatory Affairs

01 East Second Street • Scotch Plains, NJ 07076 USA • 908/322-2402 • FAX: 908/322-5277

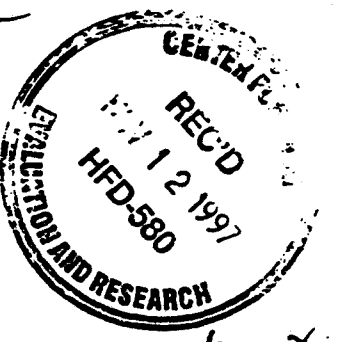
ORIGINAL

DEBIO RECHERCHE PHARMACEUTIQUE S.A

NEW CORRESP

November 10, 1997

Alvis Dunson, Jr.
Consumer Safety Officer
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. FOOD AND DRUG ADMINISTRATION
5600 Parklawn Drive
Rockville, MD 20657



Re: NDA 20-715
Decapeptyl® (triptorelin pamoate for depot suspension) Depot
Minutes of FDA Meeting held on September 9, 1997

Dear Mr. Dunson,

Enclosed is a copy of the Minutes of the FDA meeting which took place on September 9, 1997 where Clinical Deficiencies and CMC Issues listed in the Not Approvable letter of June 26, 1997 where discussed.

Please let me know if you have any questions.

Sincerely,

Piero Orsolini, Ph.D.
President Debio R.P.

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
CSO INITIALS AD DATE 11/21/97

Encl. : ment.

Administration: CH-1000 Lausanne 9, rue des Terreaux 17, case postale 211, téléphone +41/21 321 01 11, fax +41/21 321 01 69
Laboratoire: CH-1920 Martigny, route du Levant 146, case postale 348, téléphone +41/27 722 33 83, fax +41/27 722 33 85

DEBIO RECHERCHE PHARMACEUTIQUE S.A

ORIGINAL

July 3, 1997

7/11/97 DMS noted

NEW CORRESP

Alvis Dunson
Consumer Safety Officer
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
FOOD & DRUG ADMINISTRATION
5600 Fishers Lane
Rockville, MD 20855
USA

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL - 7 1997
HFD-580

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
AD 7/15/97
CSO INITIALS DATE

7/10/97

7/14/97

Re : **NDA # 20-715**
Decapeptyl® (triptorelin pamoate for depot suspension) Depot
Response to FDA letter dated June 26, 1997

Dear Mr. Dunson,

In response to the action letter received on June 26, 1997, we are writing to notify you of our intent to file amendments to correct the deficiencies listed, consistent with our options under 21 CRF 314.120(a).

To respond to the clinical deficiencies, we intend to provide new clinical data from the lyophilized pamoate microgranule 1-month depot formulation arms from two recent cGCP clinical studies. One of the studies (DEB-96-TRI-02) is an open, non-comparative pharmacology study in which 30 patients with advanced prostate cancer were administered two sequential doses of the 1-month depot formulation.

The other study (DEB-96-TRI-01) is an ongoing multicenter, randomized study comparing Decapeptyl Depot 1-month and 3-month formulations in patients with advanced prostate cancer. The protocol of this study was submitted to the IND [redacted] in the amendment 68, on October 21, 1996. Following analysis of DEB-96-TRI-02 and interim analysis of the 1-month arm only of the DEB-96-TRI-01 study, we will have data demonstrating :

(1) Achievement of castrate levels of testosterone within one month following administration of the proposed commercial 1-month depot formulation to patients with advanced prostate cancer. Samples are being analyzed in a central laboratory using a validated test method.

Administration: CH-1000 Lausanne 9, rue des Terreaux 17, case postale 211, téléphone +41/21 321 01 11, fax +41/21 321 01 69
Laboratoire: CH-1920 Martigny, route du Levant 146, case postale 348, téléphone +41/27 722 33 83, fax +41/27 722 33 85

(2) Absence of stimulation of FSH and LH following the second injection (DEB-96-TRI-02) fourth and seventh injections (DEB-96-TRI-01) of the proposed commercial 1-month depot formulation in patients with advanced prostate cancer. Samples are being analyzed in a central laboratory using a validated test method.

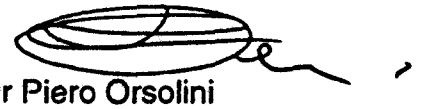
(3) Maintenance of castrate levels of testosterone in patients with advanced prostate cancer treated with the proposed commercial 1-month depot formulation for at least six months. In the DEB-96-TRI-01 study, testosterone values are being monitored before each monthly administration. Samples are being analyzed in a central laboratory using a validated test method.

These clinical results will demonstrate that the proposed commercial 1-month depot formulation has the biological effects expected for an agent in this class.

In order to understand whether these data will be sufficient to resolve the clinical deficiencies listed in the action letter, we hereby request, under 21 CRF 314.102(d), a meeting at the beginning of September. We have no questions regarding the provision of additional information to address the manufacturing/quality control, microbiology, and biopharmaceutics issues raised in the action letter.

We look forward to learning of the meeting date at your earliest convenience.

Sincerely,



Dr Piero Orsolini
President &CEO

Administration: CH-1000 Lausanne 9, rue des Terreaux 17, case postale 211, téléphone +41/21 321 01 11, fax +41/21 321 01 69
Laboratoire: CH-1920 Martigny, route du Levant 146, case postale 348, téléphone +41/27 722 33 83, fax +41/27 722 33 85

DEBIO RECHERCHE PHARMACEUTIQUE S.A

May 2, 1997

ORIGINAL

NEW CORRESP

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
5600 Fishers Lane
HFD 580, Room 17B20
Rockville, Maryland 20857
USA

CENTER FOR DRUG
REC'D
MAY 0 5 1997
HFD-580
EVALUATION AND RESEARCH

Attn :
Lisa Rarick, MD
Director Division of Reproductive
& Urologic Drug Products

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO

CSO INITIALS 5/27/97 DATE

RE : New Drug Application 20-715
Decapeptyl® (triptorelin pamoate for depot suspension)

Dear Dr Rarick,

In our NDA 20-715 cover letter dated June 24, 1997, we mentioned that the product, once approved, will be package and distributed in the US by Pharmacia & Upjohn, Co (Kalamazoo, MI) under a tradename different than Decapeptyl® Depot.

Pharmacia & Upjohn have designated the relevant name and request that [redacted] be the triptorelin trademark in USA.

Sincerely,

Piero Orsolini
President & CEO

Administration: CH-1000 Lausanne 9, rue des Terreaux 17, case postale 211, téléphone +41/21 321 01 11, fax +41/21 321 01 69
Laboratoire: CH-1920 Martigny, route du Levant 146, case postale 348, téléphone +41/27 722 33 83, fax +41/27 722 33 85

KOSTOPULOS & ASSOCIATES
A PROFESSIONAL CORPORATION
205 S. WHITING STREET, SUITE 201
ALEXANDRIA, VIRGINIA 22304

TELEPHONE (703) 751-7777
TELECOPIER (703) 751-2807

ORIGINAL

ORIG AMENDMENT

DC OFFICE
1912 SUNDERLAND PLACE, N.W.
WASHINGTON, D.C. 20036-1608
TELEPHONE (202) 296-4444
TELECOPIER (202) 296-7623

March 27, 1997

Lisa Rarick, MD, Director
Food and Drug Administration
Division of Reproductive & Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B20
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

RE: **New Drug Application 20-715**
Decapeptyl® (triptorelin pamoate for depot suspension)
Submission of SAS Data Sets for the Parmar, Botto and De Sy Clinical Studies

Dear Dr. Rarick:

Reference is made to the meeting held between Debio personnel and members of the Division of Reproductive and Urologic Drug Products on February 4, 1997, in which the FDA statisticians requested SAS data sets for the Parmar, Botto, and De Sy studies in a simplified format. In response to this request, I am hereby submitting on behalf of Debio R.P. a diskette containing demographic, efficacy and safety data for the three studies mentioned above. The databases were created using PC SAS Version 6.11.

Also, provided in this submission is documentation which describes the variables and their values in the SAS data sets. This coding information has been provided in duplicate. A single diskette has been provided containing the SAS data sets and can be located on the inside cover of the designated copy of the SAS data set documentation.

Please feel free to call Robert J. McCormack, Ph.D., at Oxford Research, at (201) 777-2800, should you have any questions regarding the enclosed information.

Sincerely,

N. Peter Kostopulos

N. Peter Kostopulos

3/27/97
C:\DEBIO\KOSTOP\lr-sas data set.doc

DUPLICATE

ORIG AMENDMENT

March 26, 1997

Alvis Dunson, B.S.
Consumer Safety Officer
Division of Reproductive and Urologic Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. FOOD AND DRUG ADMINISTRATION
5600 Parklawn Drive
Rockville, MD 20657

Re: NDA 20-715
Decapeptyl® Depot 3.75 mg (triptorelin pamoate)
Modification of *In-Vitro* Dissolution Test Method and Specifications

Dear Mr. Dunson:

This letter provides the following modifications and additional information regarding the *in-vitro* dissolution test for Drug Product (triptorelin pamoate microgranules):

Method Modification

- The [redacted] method used to assess the peptide concentration in the supernatant from the dissolution tank has been modified in that the sample concentration is determined using [redacted] response factor (R_f) instead of using the linear regression curve defined by two standard solutions at high and medium concentration [redacted] respectively). This modification achieves better linearity at low concentrations, but results in lower calculated values for percent peptide released at [redacted] hours. Two updated versions of the [redacted] method C-02-06-0365 are provided in Appendix A: version 3R which has been used to recalculate previously obtained [redacted] *in-vitro* dissolution data, and version 4 which has been used to calculate more recently obtained data in which the concentration of the reference standard has been calculated by [redacted]

- The validation reports for the *in-vitro* dissolution test (G-04-05-0065) and associated [redacted] method (G-04-05-0066) have been reissued following recalculation of the results using the revised [redacted] method C-02-06-0365 version 3R. Copies of the revised validation reports are provided in Appendix B.

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

Although these results suggest that the initial phase of dissolution may be more important in man than *in vitro*, the difference might be explained by the high variability of initial values in man, [redacted], different distribution volumes among patients, and differences in peptide microenvironment.

- Analysis of Molecular Weight of Residual Polymer
  To verify that the microgranules in the dissolution medium were slowly releasing peptide rather than simply dissolving in the dissolution medium, the filtered microgranules from each dissolution sampling of clinical lots DLGSD 95-71 and D3312 5086 were analyzed for the molecular weight of the residual polymer. As described in the report provided in Appendix D, the average molecular weight decreased gradually over the 35 day period, from [redacted] at baseline to [redacted] after 7 days, and reaching [redacted] at 35 days.

Should you have any additional questions regarding the in vitro dissolution test used to assess Decapeptyl Depot 3.75 mg, please do not hesitate to contact me.

Sincerely,

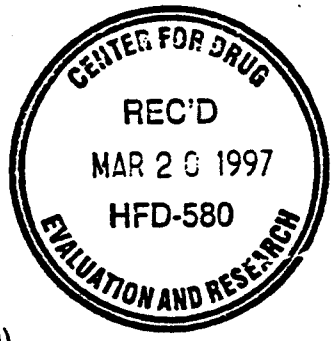
N. Peter Kostopulos, Esq.
U.S. Agent for Debio RP

Appendices:
A. Revised [redacted] test methods
B. Revised validation reports
C. Report: *In vitro/in vivo* correlation study
D. Report: Analysis of residual polymer molecular weight

DEBIO RECHERCHE PHARMACEUTIQUE S.A

ORIG AMENDMENT

DUPLICATE



March 19, 1997

Lisa Rarick, MD, Director
Food and Drug Administration
Division of Reproductive & Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Document Control Room 14B20
5600 Fishers Lane
Rockville, MD 20857

RE : New Drug Application 20-715
Decapeptyl® (triptorelin pamoate for depot suspension)

Dear Dr Rarick,

Enclosed as required by 21 CFR 314.50(d)(5)(vi)(b) we are hereby submitting in duplicate a periodic safety update report to NDA 20-715. This safety report covers the period July 1, 1995 through December 31, 1996, and includes adverse experiences from clinical studies as well as post-marketing adverse events. No new animal safety studies have been conducted with Decapeptyl®, therefore, the enclosed report presents only safety information from humans.

Additionally, no participants in any of the Decapeptyl® clinical trials sponsored by Debio R.P. during the period covered by this report died or dropped out of a study due to adverse events related to the study drug, therefore, no case report forms have been included in this submission.

If you have any questions about the enclosed information, please do not hesitate to contact Robert J. McCormack, Ph.D. at Oxford Research Int'l., (201) 777-2800 or by facsimile at (201) 777 1279.

Sincerely,

Piero Orsolini
President & CEO

Administration: CH-1000 Lausanne 9, rue des Terreaux 17, case postale 211, téléphone +41/21 321 01 11, fax +41/21 321 01 69
Laboratoire: CH-1920 Martigny, route du Levant 146, case postale 348, téléphone +41/27 722 33 83, fax +41/27 722 33 85

Oxford
Research
International Corp.

AN AFFILIATE OF
OXFORD PHARMACEUTICAL SERVICES, INC.

1425 BROAD STREET
CLIFTON, NEW JERSEY 07013-4221
(201) 777-2800

March 19, 1997

Alvis Dunson, Jr.
Consumer Safety Officer
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-715
Decapeptyl® Depot 3.75 mg (triptorelin pamoate)
Response to Clinical Clarifications Requested 1/29/97

Dear Mr. Dunson:

Enclosed is a copy of Debio's response to the clinical clarifications presented in FDA's letter dated January 29, 1997. All requested clarifications have been addressed and we are submitting hard copies with attachments in duplicate via Federal Express for delivery to FDA on Thursday, March 20, 1997. Please note that this information is being submitted as per FDA's request prior to March 24, 1997, so as to avoid a 90-day extension for the review of the Decapeptyl® NDA.

Please let me know if you have any questions.

Sincerely,

Robert McCormack / cc

Robert McCormack, Ph.D.
Vice President, Regulatory Affairs

RMC/cc

FAX: (201) 777-1279
FAX: (201) 777-9847

ORIGINAL

DEBIO RECHERCHE PHARMACEUTIQUE S.A.

ORIG AMENDMENT

Lisa Rarick, MD, Director
Food and Drug Administration
Division of Reproductive &
Urologic Drug Products
(HFD-580)
Office of Drug Evaluation II
Document Control Room 14B20
5600 Fishers Lane
Rockville, MD 20857

Martigny, le 14 mars 1997

RE : New Drug Application 20-715
Decapeptyl® (triptorelin pamoate for depot suspension)

Dear Dr. Rarick ,

Reference is made to the Agency's letter dated January 29, 1997, which requested clarifications on the data from the Parmar, Botto and De Sy clinical studies submitted in the Decapeptyl® prostate cancer NDA. Enclosed in duplicate on behalf of Debio R.P., we are hereby submitting responses to each of the points raised in the FDA letter.

We trust that the information provided herein satisfactorily addresses each of the issues related to the clinical trials conducted by Parmar, Botto and De Sy.

If you should have any questions or require additional information, please contact Robert J. Mc Cormack, Ph.D. at Oxford Reseach Int'1., (201) 777-2800 or by facsimile at (201) 777-1279.

Sincerely,

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Dr. Piero Orsolini
President & CEO

DEBIO R P. S.A. route du Levant 146. C.P. 368. CH-1920 MARTIGNY - Tel 027/722 33 83 - Fax 027/722 33 85
Groupe DEBIO. rue des Terreaux 17. C.P. CH-1000 LAUSANNE 9 - Tel 021/311 21 60 - Fax 021/311 21 69

LAW OFFICES
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205 S. WHITING STREET, SUITE 201
ALEXANDRIA, VIRGINIA 22304

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ORIGINAL

NC

February 7, 1997

DC OFFICE
1912 SUNDERLAND PLACE, N.W.
WASHINGTON, D.C. 20036-1608
TELEPHONE (202) 296-4444
TELECOPIER (202) 296-7622

Lisa Rarick, M.D.
Acting Division Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Document Control Room 17B-20, HFD 580
5600 Fishers Lane
Rockville, MD 20857

2/13/97

4/15/97

Re: NDA 20-715, Decapeptyl (triptorelin pamoate)

Dear Dr. Rarick:

Please be advised that, with respect to the above-referenced NDA, the following communication protocol is requested:

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
AT 2/19/97
CSO INITIALS DATE

1. All written communications form the FDA to the Sponsor, Debio R.P., will be directed to:

   N. Peter Kostopulos
   Kostopulos & Associates
   205 S. Whiting St., Suite 205
   Alexandria, VA 22304.

   Debio R.P. assures the FDA that Mr. Kostopulos will direct all such written communications immediately to the appropriate party to insure prompt response to FDA queries.

2. All oral communications between the FDA and the sponsor should be directed to

   Dr. Robert McCormack, Ph.D.
   Oxford Research International, Inc.
   1425 Broad Street
   Clifton, NJ 07013-4221
   tel: (201) 777-2800

   Dr. McCormack is expressly authorized to contact the FDA and respond to inquiries at any time.

2/12/97

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 10 1997
HFD-580

We have established this system to insure that the written record is maintained by our U.S. Agent, Mr. Kostopulos, and that all oral communications are handled by our technical person, Dr. McCormack.

Please call me if you have any questions.

Sincerely,

N. Peter Kostopulos

N. Peter Kostopulos
U.S. Agent

DEBIO RECHERCHE PHARMACEUTIQUE

NEW CORRESP ORIGINAL

February 7, 1997

Alvis Dunson, Jr.
Consumer Safety Officer
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. FOOD AND DRUG ADMINISTRATION
5600 Parklawn Drive
Rockville, MD 20657

see the notes /S/ 2/18/97

Re NDA 20-715
Decapeptyl® Depot 3.75 mg (triptorelin pamoate)
Minutes of pre-NDA meeting on February 4, 1997

noted /S/ 2/19/97

Dear Mr. Dunson:

Attached are three copies of Debio's minutes of the pre-NDA meeting held on February 4, 1997, copies of the overheads presented at the meeting are appended to the minutes Unless we receive a contradictory written notice from you, we will assume that these minutes are an accurate recording of the meeting.

Please note that Debio's minutes indicate that [redacted]

Should the Division decide that previous understandings no longer apply, it will be necessary for Debio to meet with the Division to negotiate new understandings and provide appropriate amendments to the NDA prior to the March 27, 1997 deadline.

Please note that Debio intends to submit responses to the clinical clarification letter, complete documentation and appropriate SAS datasets replacing those previously provided to FDA, and updated stability information for the Decapeptyl Debiojects prior to the March 27, 1997 deadline. Although Debio has not yet received FDA requests for clarification of CMC or biopharmaceutics data, we request that any such requests be submitted to Debio no later than Friday, February 22, to provide Debio sufficient time to submit responses by the March 27th deadline

Sincerely,

2/13/97

Piero Orsolini, PhD

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO

AI 2/18/97
CSO INITIALS DATE

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 11 1997
HFD-580

205 S. WHITING STREET, SUITE 201
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ORIGINAL

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1912 SUNDERLAND PLACE, N.W.
WASHINGTON, D.C. 20036-1605
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TELECOPIER (202) 296-7623

BEST POSSIBLE COPY

January 31, 1997

Alvis Dunson, Jr.
Consumer Safety Officer
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. FOOD AND DRUG ADMINISTRATION
5600 Parklawn Drive
Rockville, MD 20657

Should be sent for consult review by a microbiologist.
MPiller 2/18/97

Re: NDA 20-715
Decapeptyl® Depot 3.75 mg (triptorelin pamoate)
Response to Deficiencies in Microbiology Section

Dear Mr. Dunson:

In a letter dated November 15, 1996, we responded to most of the questions raised in the FDA letter dated October 9, 1996, regarding deficiencies in the Microbiology section of the above-referenced NDA. In this letter, we are responding to the two questions, restated below, regarding microbiological monitoring of the environment.

Microbiological Monitoring of the Environment

1. ***Please clarify the labeling and symbols used in the diagrams on pages 8 to 10. Where are the [redacted] ? A key to the numerical representation in these diagrams will be helpful.***
2. ***The number of plates used for each type of monitoring during [redacted] operation and product assembly should be indicated.***

The sampling points for environmental monitoring, type of sampling and sampling frequency are given in the chart on the following pages. Sampling points and equipment locations [redacted] used for production of Decapeptyl Debiojects [redacted] as well as ancillary production areas are indicated in the room diagrams following each sampling chart.

Please let me know if you have additional questions regarding Debio RP's microbiological monitoring program.

2/10/97

Sincerely,

N. Peter Kostopulos

N. Peter Kostopulos
U.S. agent for Debio R.P.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 03 1997
HFD-580

Oxford Research International Corp.

AN AFFILIATE OF
OXFORD PHARMACEUTICAL SERVICES, INC.

1425 BROAD STREET
CLIFTON, NEW JERSEY 07013-4221
(201) 777-2800

January 29, 1997

Lisa Rarick, MD, Director
Food and Drug Administration
Division of Reproductive & Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Document Control Room 14B20
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
CSO INITIALS 2/3/97 DATE

RE: New Drug Application 20-715
Decapeptyl® (triptorelin pamoate for depot suspension)

Dear Dr. Rarick:

Reference is made to the telephone conversation on January 17, 1997 between Dr. Robert McCormack of Oxford Research and individuals from the Division of Reproductive and Urologic Drug Products. During the telephone conversation the Agency requested among other things, that the individual patient testosterone data be sorted by study center and submitted to the FDA in an ASCII file.

Contained in this submission is a diskette containing the individual patient testosterone data in an ASCII file. We have also provided a duplicate copy of the transmittal letter for the official NDA file. In the ASCII file the 20 study centers comprising the Botto trial are identified using the last name of the investigator. The investigators in the Parmar and De Sy studies are identified with a numeric code. This numeric code with the corresponding investigator are presented below:

Parmar Study

Code Number	Investigator
W60	Harsukh Parmar, M.B., Ch.B.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 31 1997
HFD-580

FAX: (201) 777-1279
FAX: (201) 777-9847

De Sy Study

Code Number	Investigator
B04	Prof. W.A. De Sy

Attached to this letter is a two page document which describes the codes used for the variables presented in the ASCII testosterone database. Please note that the numeric codes with the corresponding time the study visits took place are presented in the attachment for the Parmar and Botto studies. Numeric study visit codes are not contained in the attachment for the De Sy study as study visits are presented in the database in three columns entitled, *datex, lag and c_visit*. A description of these variables are supplied in the attachment. Additionally, although not specified in the database, the units for testosterone are expressed in nmol/l.

We trust that the data provided will be adequate to allow the continued review of the Decapeptyl® NDA for the treatment of prostate cancer.

Please let me know if you have any additional questions.

Sincerely,

Robert McCormack, Ph.D.
Vice President, Regulatory Affairs

RMC/cc

u:\debio\letters\ir-asc files doc

KOSTOPULOS & ASSOCIATES
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ORIGINAL

January 27, 1997

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TELECOPIER (202) 296-7623

ORIG AMENDMENT

Alvis Dunson, Jr.
Consumer Safety Officer
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. FOOD AND DRUG ADMINISTRATION
5600 Parklawn Drive
Rockville, MD 20657

BEST POSSIBLE COPY

Re: NDA 20-715
Decapeptyl® Depot 3.75 mg (triptorelin pamoate)
Response to Deficiencies in Environmental Assessment

Dear Mr. Dunson:

Attached is a revised Environmental Assessment which includes the following corrections to the deficiencies identified in the FDA letter dated January 10, 1997:

Section 4c: Description of Proposed Action, Production Locations

If no proprietary intermediates are used in the manufacture of the drug substance, the EA should so state. If proprietary intermediates are used that are manufactured at a facility other than those identified for production of the drug substance and finished products, the EA should identify the location and provide a brief description of the surrounding environment. Any additional production facilities would also have to be addressed under format item 6.

Please note that no proprietary intermediates are used in the manufacture of the drug substance, and all intermediate peptides are manufactured by [redacted] at the facility indicated. This has been indicated in the revised EA, attached.

Section 5: Identification of Chemical Substances Subject to the Proposed Action

The molecular formula should be corrected (H82 rather than H84).

The molecular formula has been corrected in the revised EA, attached.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.L. ☐ MEMO

CSO INITIALS DATE

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 31 1997
HFD-580

Section 8: Environmental Effects of Released Substances

The information regarding the microbial inhibition studies should be deleted unless the studies are provided so that we can independently evaluate the information in accordance with 40 CFR 1506.5.

The reference to microbial inhibition studies has been deleted in the revised EA, attached.

Should you have any additional questions regarding the EA, please do not hesitate to contact me.

Sincerely,

N. Peter Kostopulos

N. Peter Kostopulos
U.S. Agent for Debio R.P.

ORIGINAL

DEBIO RECHERCHE PHARMACEUTIQUE, S.A.
CH-1920 Martigny, route du Levant 146, case postale 348, telephone +41/26.22.33.83, fax +41/26.22.33.85

January 23, 1997

NEW CORRESP

Lisa Rarick, M.D.
Acting Director
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Document Control Room 17B-20
FOOD AND DRUG ADMINISTRATION
5600 Fishers Lane
Rockville, MD 20857
USA

Re: New Drug Application #20-715
Decapeptyl® (triptorelin pamoate for depot suspension)

Dear Dr. Rarick,

Reference is made to the telephone conversation on January 17, 1997 between Dr. Robert McCormack of Oxford Research and individuals from the Division of Reproductive and Urologic Drug Products. During the telephone conversation, the agency requested among other things, that an outline of the companies involved with the Decapeptyl® NDA (No. 20-715) with a description of each company's responsibilities be prepared and submitted to FDA.

In reference to this request listed below is a brief description of the organization and activities of the Debio Group companies followed by a list of organizations involved with the Debio NDA with a description of their primary responsibilities.

Debio Group Companies

Debio Recherche Pharmaceutique and Debiopharm are two sister companies of the private Swiss Debio group that were involved in the NDA for Decapeptyl® in the treatment of prostate cancer. The first company, Debio Recherche Pharmaceutique (Debio R.P.) is engaged in the conception, development and manufacture of sustained release, biodegradable copolymer

formulations for peptides and small proteins. In this respect, Debio R.P. has responsibility over chemistry manufacturing and controls for various drug products.

The complementary company Debiopharm is involved in pharmaceutical research and development. The aim of the company is to bring a university discovery to the stage of a marketable drug. The final mission of Debiopharm is to find marketing partners to commercialize the drug, in exchange for payment royalties, which are shared with the discovering university or individual. Triptorelin, Decapeptyl®, the subject of this NDA was one such product that was discovered by Prof. Andrew Schally (Nobel Prize winner of Tulane University, USA). The product was investigated by various companies before Debiopharm acquired world-wide rights. With reference to the current NDA (# 20-715) Debio R.P. is the sponsor.

Organizations involved with the NDA preparation :

Debio R.P., (located at Route du Levant 146, 1920 Martigny, Switzerland) is responsible for the chemistry, manufacturing and controls for the Decapeptyl® drug product. This company in conjunction with a consultant, [redacted] were responsible for the preparation of the Chemistry, Manufacturing and Controls technical data section as well as the CMC summary information.

Debiopharm, (located at Rue des Terreaux 17, 1000 Lausanne 9, Switzerland) personnel were primarily responsible for the preparation of the non-clinical (with a consultant [redacted] and biopharmaceutics NDA technical data section summaries and for reviewing the documents prepared by [redacted]

Oxford Research International Corporation
(located at 1425 Broad Street, Clifton, New Jersey, 07013) had the overall responsibility for formatting and compiling each of the technical data sections (except the CMC technical data section) for the NDA. Additionally [redacted] were responsible for the preparation of the following NDA documents :

1. Overall NDA Summary
2. Integrated Clinical reports for the Parmar, Botto, DeSy studies
3. ISE and ISS documents
4. Clinical Pharmacology Summary

DEBIO RECHERCHE PHARMACEUTIQUE, S.A.

Oxford Research, specifically, Robert McCormack, Ph. D., Vice President Regulatory Affairs, has been designated as the regulatory point of contact for Debio R.P. NDA (# 20-715)

US agent for Debio R.P. N.P. Kostopulos in Alexandria is the designed agent for Debio R.P. (205 S. Whiting St, Suite 201, Alexandria, Virgina 22304, USA).

We trust that the information provided clarifies the parties involved with the Decapeptyl® NDA. Should you have any questions or require additional information, please do not hesitate to contact Dr Robert McCormack at Oxford Research by telephone at 201-777-2800 or by fax at 201-777-1279.

Sincerely,

Dr Piero Orsolini
President

KOSTOPULOS & ASSOCIATES
A PROFESSIONAL CORPORATION
205 S. WHITING STREET, SUITE 201
ALEXANDRIA, VIRGINIA 22304

TELEPHONE (703) 751-7777
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January 21, 1996

DC OFFICE
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TELEPHONE (202) 296-4444
TELECOPIER (202) 296-7623

M E M O R A N D U M

To: Alvis Dunson, Jr., Consumer Safety Officer

From: N. Peter Kostopulos

Re: Meeting on February 4, 1997, DEBIO R.P.

Dear Mr. Dunson:

Thanks again for scheduling the meetings for the current NDA 20-715 for prostate cancer (Decapeptyl®). We understand that the meetings will begin at 1:00 pm and will proceed for up to two hours. We plan to use the first part of the meeting to discuss pre-NDA issues Enclosed are 10 copies of the pre-NDA package for which was submitted on December 2, 1996, and an agenda for the meeting.

We plan to use the remaining time to discuss the current NDA 20-715, including a review of the prior meetings, conclusions and agreements reached with the Metabolism and Endocrine Drug Products Division as well as topics raised by the Division in the teleconference with Bob McCormack on January 17, 1997. The enclosed agenda references the relevant meeting minutes and topics raised by the Division recently so as to facilitate the Division's review of this NDA.

Again, thank you for your assistance in making these arrangements. Please call me if you need anything further in advance of the meetings.

N. Peter Kostopulos

KOSTOPULOS & ASSOCIATES
A PROFESSIONAL CORPORATION
205 S. WHITING STREET, SUITE 201
ALEXANDRIA, VIRGINIA 22304

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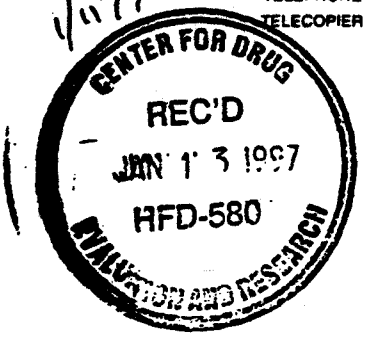
TELECOPIER (703) 751-2807

DC OFFICE
1912 SUNDERLAND PLACE, N.W.
WASHINGTON, D.C. 20036-1608
TELEPHONE (202) 296-4444
TELECOPIER (202) 296-7623

BS

January 10, 1997

1/11/97



Via Federal Express

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Drug Evaluation II
5600 Fishers Lane
HFD 580, Room 17B20
Rockville, MD 20857

Attn: Lisa Rarick, M.D., Acting Director
Division of Reproductive and Urologic Drug Products

Re: New Drug Application #20-715
Decapeptyl® (triptorelin pamoate for depot suspension)
Depot

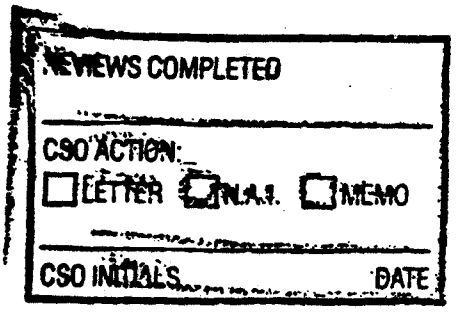
Dear Dr. Rarick:

In accordance with the agreement reached by telephone on 23 December 1996, between Mr. Baldeo Taneja, Ph.D., FDA Statistician, and Mr. Robert J. McCormack (Oxford Research Intl.), please find enclosed data sets and SAS programs reflecting:

1. Demographic and efficacy for each individual study i.e., Botto, De Sy and Parmar.

2. Combined demographic and efficacy for the pooled analysis that was presented in the Integrated Summary of Effectiveness.

This information is provided on 3 diskettes, and detailed in 2 tables of contents (see enclosures).



We trust this answers your request. Should you have any additional questions or need further clarification, please do not hesitate to contact our technical contact person, Mr. Robert J. McCormack at (201) 777-2800.

Sincerely,

N. Peter Kostopulos
U.S. Agent

Encls: 3 diskettes
2 tables of contents

LAW OFFICES
KOSTOPULOS & ASSOCIATES
A PROFESSIONAL CORPORATION
205 S WHITING STREET, SUITE 201
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TELECOPIER (202) 296-7823

January 8, 1997

M E M O R A N D U M

To: Alvis Dunson, Consumer Safety Officer

From: N. Peter Kostopulos

Re: NDA 20-715, Meeting Scheduled for January 16, 1997

Dear Alvis:

You have scheduled a teleconference for January 16, 1997, between the Sponsor, Debio R.P. and members of the Division regarding the pending NDA for triptorelin pamoate, No. 20-715. As you will recall, we asked for this meeting so that we could outline for the new members of the Division the understandings reached previously with the Division regarding the basis of support for the NDA.

We would like to request that this meeting be postponed until February 4, when we are scheduled for We understand that Drs. Rarick, Shames, and Jolson, as well as yourself and Lana Pauls, are scheduled to attend the February 4 meeting. We believe that our briefing of the new members of the Division will be much more effective and efficient if we can do it in person, rather than by telephone. The participants from our side are located in Europe and the U.S., and we want to avoid problems with phone lines that we have experienced previously. Several of these persons scheduled to participate on the teleconference are travelling from Switzerland for the meeting on February 4, so it would be a good opportunity for them to discuss these issues directly with your colleagues.

pending NDA

We suggest that we meet either before or after the other meeting. Please call me to discuss this request. Thank you.

maybe an hour

Peter Kostopulos

LAW OFFICES

KOSTOPULOS & ASSOCIATES

A PROFESSIONAL CORPORATION

205 S. WHITING STREET, SUITE 201

ALEXANDRIA, VIRGINIA 22304

TELEPHONE (703) 751-7777
TELECOPIER (703) 751-2807

WASHINGTON, D.C. OFFICE

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