# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 17-970/S-039 & S-040

## MEDICAL REVIEW(S)

**Medical Officer sNDA Review:** Nolvadex® (tamoxifen citrate)
**Primary Medical Officer:** Susan Flamm Honig, M.D.
**Secondary Medical Officers:**
Breast cancer case report form review: Karen Johnson, M.D.
Stroke case report form review: Donna Griebel, M.D.
Endometrial cancer case report form review: Alison Martin, M.D.
**Team Leader:** Julie Beitz, M.D.
**Biometrics Reviewer:** Tony Koutsoukos, Ph.D.
**Biometrics Team Leader:** Gang Chen, Ph.D.

October 21, 1998

Italicized sections of text reflect data submitted after the ODAC meeting of September 2, 1998.

## 1.0 General Information

### 1.1 NDA Information

**1.1.1 NDA number** NDA 17-970/SE1-40
**1.1.2 Submission date:** April 30, 1998
**1.1.3 Completion Date:** August 18, 1998 (ODAC draft)
September 16, 1998 (addenda to the draft are in italics and/or Appendices)

### 1.2 Drug Name

**1.2.1 Generic Name:** Tamoxifen citrate; ICI 46, 474
**1.2.2 Trade Name:** Nolvadex®
**1.2.3 Chemical Name:** (Z)-2-[-4-[p-(1,2-diphenyl-1-butenyl) phenoxy]-N,N-dimethylethylamine citrate (1:1)

**1.3 Sponsor:** Zeneca Pharmaceuticals

**1.4 Pharmacologic Category:** Antiestrogen

**1.5 Proposed Indication:** Breast cancer prevention in women at high risk

**1.6 Dosage Form and Route of Administration:** 10 mg tablets; oral

**1.7 NDA Drug Classification:** Priority

**1.8 Related INDs and NDAs:** NDA 17-970
IND IND

**1.9 Foreign Marketing:** Not applicable

## 2.0 Table of Contents

## 3.0 Material reviewed/Clinical data sources/Administrative review

### 3.1 Source

#### 3.1.1 Supplemental NDA submission

The *supplemental New Drug Application* for tamoxifen, sNDA 17-970/SE1-40, contains 4 volumes. To facilitate NDA preparation, FDA agreed to accept the ERSMAC and BCPT technical reports in lieu of a formal study report, Integrated Summary of Safety, and Integrated Summary of Efficacy, elements traditionally submitted with an sNDA. This review is derived from information contained in volume 1, which includes the cover letter and draft labeling, and volume 3, which contains the Endpoint Review, Safety Monitoring and Advisory Committee (ERSMAC) report, the BCPT technical report, and a copy of the protocol. The ERSMAC report was presented to the committee March 24, 1998 and is based on analysis of data through January 1, 1998. It consists of 7 pages of text in summary form with 27 pages of summarized data in tabular format. The technical report is a 3-page document that reiterates material in the ERSMAC report, accompanied by copies of 13 slides. Volume 2 contains the Environmental Assessment (sponsor requested exemption); volume 4 is identical to volume 3.

The database originally submitted with the sNDA consisted of 2 tables, one with efficacy endpoints and one containing safety endpoints. Each table had 1 entry per patient; all 13,388 patients were included in the efficacy table and 13,118 patients were included in the safety table. The tables as originally submitted did not contain adequate data with which to evaluate the reported results. The limitations of the original submitted database are listed below:

- Primary data were not included in the datasets. For example, WBC tabulations consisted of a grade presumably assigned by the NSABP; the worst grade over the course of the study was listed for each patient. No actual WBC value was provided, and only 1 grade per patient was available, without the date of occurrence.
- Although only 13, 118 patients were included in the safety table, suggesting that some patients were not included because of lack of data, there were additional entries coded as "no form received."
- Primary endpoints, such as the occurrence of invasive breast cancer, were coded as "yes/no" without dates of occurrence.
- The database originally submitted with the NDA did not include the participating centers, the principal investigator at each site (in order to assess conflict of interest issues for the ODAC meeting), the number of patients accrued per site (necessary for determining sites for audit), or date of randomization. No information was available about successive drop-out of patients at each of these stages prior to randomization. This information was received 7/1/98 in response to an FDA Request for Information.
- No information about the date study drug was started, the date study drug was stopped, the reason for stopping study drug, or drug holidays was provided
- The original database did not contain information about the patient's risk factors at entry, with the exception of the presence or absence of LCIS, a limited assessment of

family history (number of first-degree relatives, categorized as none, one, or two or more), and patient age. Information on the incidence of atypical hyperplasia was available only from copies of the ASCO/NSABP slides. Risk-related information was received, after multiple requests, on July 23, 1998.

- The original database did not include demographic information.
- The original database did not include a list of protocol violations.
- The original database did not contain a list of concomitant illnesses or concomitant medications at baseline. This information was received 7/31/98.
- The database did not include invasive breast cancer characteristics, such as tumor size, nodal status, and receptor status.
- The database did not contain any information about eye problems, other than the presence or absence of cataracts and the need for surgery. Additional information was received 8/4/98.
- The database did not contain the results of endometrial sampling or of other gynecologic diagnoses made during the course of the study (such as endometrial polyps). Sampling information, coded as negative/atypia/cancer, was received in electronic format 7/29/98.

*Case report forms* (CRF) for deaths, for the efficacy endpoints of breast cancer and non-invasive breast cancer, and for selected toxicity endpoints (endometrial cancer, pulmonary embolus (PE), deep vein thrombosis (DVT), and stroke) were submitted at the FDA's request in a pre-NDA meeting. A total of approximately 864 CRFs were requested, or a non-random sample of 6% of the study population. These CRFs were submitted on a rolling basis and comprised submission 111. They were received from May 7, 1998 through June 24, 1998. Volumes 1 through 47 consisted of deaths; volumes 48-66 contained most of the invasive and non-invasive breast cancers; and volumes 67-256 contained the rest of the breast cancers, endometrial cancer, DVT, PE, and stroke, in random order.

Four medical officers reviewed the CRFs. The following comments are general observations about the CRFs based on the review:

- The participant number was entered at the site on the first page of each form, but entry of the identification number on subsequent pages of the Toxicity Report Form and the Compliance form was not consistent. When outside materials were obtained, the participant number was not entered on these documents.
- Different identification numbers were used in the screening process and during the study, making it difficult to ensure that the entry/eligibility data and the on-study data were derived from the same participant.
- The case report forms that were reviewed do not contain most of the mandated on-study evaluations. For example, although the Entry/Eligibility forms were in the CRFs, the detailed history and physical examination notes were not present in the majority of reviewed CRFs. Frequently the breast examination was also not included. Similarly, follow-up documentation included only the preprinted forms. Primary source materials were provided for events, but not for routine follow-up

examinations. It is therefore difficult to assess whether significant events were omitted from the database.

- Certain pieces of data, specified in the protocol, were consistently missing from the CRFs, such as the mammogram reports. Review of the requested case report forms by the medical reviewers demonstrated that mammogram reports were included in the CRFs about 25% of the time, and usually only 1 report per participant was provided. It was usually a mammogram report that prompted a biopsy or additional follow-up. Baseline mammograms were uncommonly included in the CRFs.
- It was discovered during a teleconference on July 15 that Zeneca chose not to send the demographic and lifestyle questionnaire, the quality of life questionnaire, the household demographic questionnaire, and the follow-up lifestyle questionnaire. The demographic and lifestyle questionnaires contain information pertinent to an efficacy and safety review, including smoking history and a detailed family history of cardiovascular disease. Quality of life information was not included in the CRFs or in the database as agreed upon at a pre-NDA meeting. However, these forms also included demographic information and patient symptoms; these sections were not submitted. Depression scores were sent at FDA request 7/29/98.
- In several cases it appeared that inadequate baseline screening for either pre-existing cancers or symptoms of other serious systemic disease was performed. In other words, it appeared that care providers did not always correlate the patient's self-reported symptoms or medication history with the medical history noted on the forms or with a directed physical examination. It did not appear that care providers addressed the "Special note" section of the Report of Eligibility Review; this section warned that the participant's depression score exceeded the normal range, for example.
- Every reviewed CRF contained a multi-page consent form with addenda, signed by the participant (name blacked out).
- In nearly all cases, the patient's self-reported risk questionnaire was present in the CRF, and these risks matched those entered into the computer program for calculation of breast cancer risk. The computer generated risk curve was also present in all but one of the reviewed CRFs. The curve was at or above the designated level of risk for study entry.
- Documentation of death was extensive. The investigators obtained death certificates and discharge summaries (hospital or hospice)/provider notes in nearly all cases. Completion of these tasks required considerable effort, which was well-documented in the CRFs.
- Documents obtained from participants in Quebec were frequently in French. Translations were provided about half the time. These translations were hand-written; they captured the main points but were not word-for-word translations; and the translations were not signed. The status and background of the translator is unknown.
- Lipid profiles were not submitted in the sNDA.
- The reviewed CRFs contained all relevant pathology reports, including reports of benign procedures. In most cases, tumor blocks or slides were submitted.

Consultations were requested from the Division of Metabolic and Endocrine Drug Products, the Division of Reproductive and Urologic Drugs, the Division of Hematologic Drug Products, and the Division of Ophthalmologic Drug Products.

### 3.1.2 Submissions to the IND for tamoxifen chemoprevention

Some data was submitted directly by the NSABP; this information was submitted to the IND:

*Submission to IND*

This submission contained a Letter of Authorization from Zeneca Pharmaceuticals to allow cross-reference between NDA 17-970 (S-040) and this IND. In addition, it contained the originally submitted electronic data sets for the NSABP P-1 trial and descriptions of the files.

*Submission to IND*

The NSABP submitted a copy of the ASCO abstract for NSABP P-1 and a copy of the final manuscript, "Long-term tamoxifen citrate use and potential ocular toxicity", derived from the NSABP B-14 study, published in the April 1998 issue of the American Journal of Ophthalmology.

*Submission to IND*

This submission amended the P-1B trial, which was designed to evaluate the effect of tamoxifen on bone mineral density and serum markers of bone turnover. Data was to be collected at baseline and after 1, 2, and 5 years on study. Because of the unblinding of P-1, this amendment outlines the data collection required of each participant to close the study.

### 3.1.3 Administrative correspondence

This section summarizes questions sent to the sponsor, responses to FDA requests for information, additional materials, and minutes of teleconferences and meetings during the course of the sNDA review. The content of the sponsor's replies is addressed in the sNDA review in the relevant sections. The section documents the lack of a complete set of primary data for review until August 4, 1998, despite an initial agreement to provide the data and repeated requests for submission. Data submission was not complete until August 4, 1998, 1.5 weeks before the deadline for review submission to ODAC. Until July 16, 1998, response times to FDA Requests for Information ranged from 2 weeks to one month, representing significant delays in the highly compressed timeframe of the review of this application.

*Notification of Significant Efficacy Results, April 2, 1998*

On April 2, 1998, the NSABP submitted a technical report to the FDA, written for the ERSMAC, that demonstrated a statistically significant reduction in the number of invasive breast cancers in the tamoxifen-treated group of the NSABP P-1 trial. The

ERSMAC recommended that the trial be unblinded. The NSABP met with officials at the National Cancer Institute and planned a press conference for April 8, 1998. The NSABP indicated that further discussions with the FDA would be forthcoming.

*Teleconference April 23, 1998*

A briefing package was sent to the FDA 4/16/98. The purpose of the teleconference was to determine the format and content of the sNDA submission and resolve technical issues regarding coordination of the submission between the NSABP (the holder of the IND under which the study was conducted), the NCI (the oversight body for the study), Zeneca Pharmaceuticals (the drug manufacturer), and the FDA. It was agreed at this meeting that "...the data [would be submitted] in an electronic format acceptable to the Agency..." (Zeneca's written proposal).

*Teleconference April 29, 1998*

A second teleconference was held to identify CRFs for FDA review. The Division asked that a draft copy of the manuscript describing the NSABP P-1 trial be submitted. It was agreed that the NSABP would send a near-final draft when available.

*sNDA Submission April 30, 1998*

The sNDA was formally submitted on this date. A six month user fee goal date (10/30/98) was calculated from this time point.

*FDA Request for Information 6/3/98*

The following requests for information were sent:

1. The full text of all protocol amendments made to the P-1 study with dates.
2. A list of accrual sites and the number of patients accrued at each site.
3. A list of P-1 substudies, the number of patients on each study, and the sites at which these studies were conducted.
4. Please update us on whether or not the NSABP is working to verify the data that could not be quality-assured in time for the sNDA submission. If the NSABP is working on this now, when will they notify us of any major discrepancies in the data that they have already submitted?

*Sponsor response:*

June 18, 1998 Protocol and amendments submitted (question 1)

July 1, 1998 Question 2 was answered. In response to question 4, Zeneca stated that the NSABP was working to verify the data sent to the Agency and thus far, had found "no major discrepancies." If discrepancies are found, the Agency will be notified. Question 3 answered as "P1B, P1U, P1E, and P1G". [Reviewer's comment: this question was resubmitted to the sponsor and was answered in full on July 16, 1998.]

*NSABP response to FDA request, June 5, 1998*

E-mail response by Joseph Costantino, NSABP, to Tony Koutsoukos, Ph.D., Biostatistical Reviewer, outlining the statistical methods used for analysis.

*FDA request for Information 6/15/98*

The following requests for information were sent:

Minutes of the March 24 ERSMAC meeting and a list of the ERSMAC committee members.

A copy of the slides used in the ASCO plenary session, the June NSABP group meeting, and the July NCI-sponsored BCPT workshop

A copy of the CES-D depression scale

Information on the number of pregnancies that occurred during the trial, including treatment arm, time on study drug, and pregnancy outcome

A timetable for the submission of the CRFs for patients with adverse events

A copy of the P-1 manuscript that will be submitted for publication

Any new data or analyses that have become available since the original ERSMAC report was written in March.

*Sponsor reply, June 25, 1998*

Addressed all points; stated that no new data or analyses had been performed. Stated that the manuscript would be provided as soon as it was ready.

*Reviewer's note:* Slides presented at ASCO and the NSABP meeting presented analyses not included in the ERSMAC report and were based on data not submitted to the Agency (for example, smoking history by treatment arm; quality of life).

*FDA Request for Information, June 18, 1998*

The submitted database contains derived data elements. Please submit the entire electronic database with primary data as soon as possible.

*Submission 115, June 24, 1998*

The sponsor provided additional CRFs for 2 participants who experienced a pulmonary embolism and invasive breast cancer, and a list of cases by category. A master table of contents, organized by volume but not by patient number or by category, was provided.

*FDA Request for Information, July 2, 1998*

The following information was requested from the sponsor:

1. Provide the final autopsy report on participant P51364KEN.

2. List the number of women on each arm with hypertension, elevated cholesterol, and diabetes mellitus at entry.

3. List all treatment unblindings by treatment arm with reasons.

4. Provide a list of the single institution studies that were performed in conjunction with P-1.

5. Provide a master table of contents by category of event. [This point was further clarified in a telephone call.]

6. When will the full electronic database be provided?

7. On 6/3/98, we requested information on the P-1 substudies. Please provide the full names of the studies, their objectives, and the data collected.

8. Provide the baseline mammogram reports on the attached list of selected breast cancer cases.

[*Reviewer's note:* In the 4/29/98 teleconference, the Agency specifically requested that all mammogram reports, which were required elements per protocol, be submitted. The NSABP at that meeting stated that these reports were part of the CRFs.]

*Sponsor reply July 16, 1998*

Questions 2, 3, 4, and 7 answered fully.

Questions 1 and 5 pending.

Question 6: The sponsor referred to the July 14 and 15 teleconferences (see below) and agreed that "...all efforts would be employed to expedite the request and submission of the electronic data elements."

*Sponsor reply July 17, 1998*

Questions 1 and 5 were answered.

Question 8 was partially answered; 89 of the 126 requested reports were submitted. Additional reports were to be submitted on a rolling basis.

*Sponsor reply July 21, 1998*

An additional 21 mammogram reports were submitted.

*Sponsor reply July 31, 1998*

An additional 8 mammogram reports were submitted.

*Sponsor Reply August 12, 1998*

An additional 2 mammogram reports were submitted.

*Sponsor Reply August 19, 1998*

Three additional reports were submitted. Stanford University notified NSABP that it did not have a copy of a baseline mammogram report on P32308STA. An additional 2 reports were outstanding.

*Sponsor Reply August 27, 1998*

The final 2 mammogram reports were submitted.

*Sponsor communication July 7, 1998*

Zeneca called to say that NSABP was not willing to submit the entire database to the Agency. They will, however, supply specific data elements on request.

The Agency responded by scheduling a teleconference for July 15, 1998 to discuss this pivotal issue, and prepared a letter to the NSABP.

*FDA Request for Information July 10, 1998*

1. Identify the CRF volume for a specified participant
2. Provide lists of participants, organized by ID number, with MI, TIA, fracture
3. Provide information on how the toxicity forms were completed
4. Provide a list of all worldwide breast cancer tamoxifen prevention studies and results
5. Please explain why duplicate CRFs submitted for P21876UPA (one for death and one for PE) were not identical.

*Sponsor reply, July 16, 1998*

Question 2 was answered for MI and TIA.

Questions 1 and 3 were fully addressed.

The sponsor indicated that question 5 was under evaluation, and question 4 will be answered in a separate communication.

*Sponsor reply July 17, 1998*

Question 2 was answered for hip and Colles' fractures.

*Sponsor reply July 27, 1998*

The sponsor replied to question 5. Parts of the CRFs were inadvertently not copied for the participant in question. Because of this finding, all CRFs submitted in duplicate were reviewed and were intact except for P48542MDA. CRFs for these 2 subjects were re-submitted with a complete set of clinical data.

*Sponsor communication July 10, 1998*

Zeneca called to say NSABP agreed to submit the database but because it is in VAX, it will not be compatible with FDA systems. The project manager asked them to translate the database into ASCII; they replied that it was too large to do so.

*FDA Request for Information July 13, 1998*

Volume 111.180 cannot be located. Please resubmit this volume.

*Sponsor reply:*

Submission 118 contained the missing volume; dated 7/16/98

*Teleconference with Zeneca, July 14, 1998*

The Agency and the sponsor discussed certain technical problems with the database submission, the delayed response times to Agency requests, and the results of the Italian and Royal Marsden tamoxifen chemoprevention studies published in the Lancet. Action items for Zeneca:

- Ask the NSABP for a data dictionary in order to target essential data elements for translation into ASCII
- Ask the NSABP to explore remote access to their database
- Submit the Lancet publications, the protocols from the Italian and IBIS studies, and the protocol from the Royal Marsden trial if available
- Provide a written report discussing the potential impact of the Lancet publications on the sNDA.

*Sponsor communication, July 14, 1998*

The NSABP does not have a data dictionary, but has a complete set of blank forms from which all data were derived.

*Teleconference with the sponsor and NSABP, July 15, 1998*

The importance of database submission was stressed. The NSABP stated that requested data elements would be provided; submission time could range from several days to several weeks depending on the number of elements requested. The Agency stressed the short amount of time remaining before the ODAC meeting. The NSABP did not feel comfortable allowing remote access to their database for security reasons. They would not consider creating a copy of the database for FDA use via remote access. They offered to have an FDA representative come to Pittsburgh and work with the data on site

through an NSABP representative. The Agency indicated that we do not have the resources to send a reviewer to the site for an extended time period for review.

Action items for FDA: The medical reviewer will send a preliminary list of required data elements today by facsimile (done, by the project manager). The final list will depend on review of the full set of blank data forms.

Action items for Zeneca: Provide a comprehensive table of contents, organized by category and alphabetically by participant number, as soon as possible. See action items from July 14, 1998 teleconference.

*Sponsor reply:*

The blank NSABP data forms were submitted July 16—see below.

The breast cancer chemoprevention articles and commentary were submitted July 16, 1998.

*Sponsor Communication, July 16, 1998*

The blank NSABP data forms were submitted. The FDA request for data elements was sent July 23, 1998 directly to the NSABP.

*FDA Request for Information, July 20, 1998*

The NSABP was asked to comment on diagnostic assessments of breast cancer cases, both invasive and non-invasive.

*Sponsor Reply, July 31, 1998*

Discussed in Section 9.2, Non-invasive breast cancer

*Sponsor communication, July 20, 1998; Submission 7/21/98*

The NSABP, after quality assurance of their data, amended the number of spine fractures. The final number of fractures with a participant ID list was submitted.

*Teleconference July 23, 1998*

This teleconference was held specifically to discuss submission of the electronic data. The NSABP, represented by Joe Costantino and Sam Wieand, indicated that they had spent the last week preparing elements of the data list for submission. At this meeting, the NSABP and FDA prioritized the requested data elements; the NSABP supplied a timeline for submission. The FDA also asked for a copy of the Quality of Life analyses and all participant eye findings.

The first set of data elements was received by e-mail the evening of July 23.

July 28, 1998: 3 additional data sets

July 29, 1998: 3 data sets

July 31, 1998: 3 data sets

August 4, 1998: 1 data set

All requested electronic data elements were submitted by August 4, 1998. These data sets were sent by e-mail as ASCII files and were translated into Access by Gary Gensinger, B.S., M.B.A., Computer Specialist.