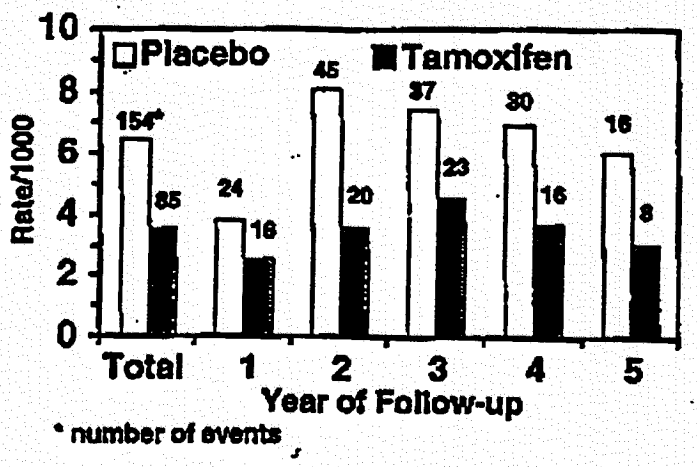
Figure 7. Breast cancer events over time (P-1 manuscript)



12. There are several cases considered by the FDA reviewers but not by the NSABP to represent invasive breast cancer. They are summarized below:

Placebo arm:

P47522CIN: 70 year old woman without other breast cancer risk factors, who began study drug 2/5/93. A screening mammogram 12/24/96 showed a new pleomorphic cluster of microcalcifications in the right lower inner quadrant. A stereotactic core biopsy performed 1/8/97 was read as predominantly ductal carcinoma in situ, and "An area of invasion is recognized." A biopsy was performed 2/6/97 and showed 1.8 cm of DCIS. No invasion was identified. According to the NSABP, cases of invasive breast cancer were identified according to an unequivocal statement by the local pathologist (Response to FDA Request for Information, 7/31/98). We therefore consider this case to represent invasive breast cancer.

The NSABP re-reviewed this case and does not consider the results from the stereotactic core biopsy to be valid. The FDA considers all biopsy specimens and continues to include this case as an invasive cancer.

P54804MON 61 year old woman with 2 first degree relatives with breast cancer who began study drug 7/14/92. In September 1996, a mass was found on physical examination; a mammogram was normal. A biopsy performed 11/14/96 demonstrated multifocal DCIS with lobular extension. The pathology report notes: "Un seul et unique foyer de micro-infiltration est observe."

The slides were sent to Edwin Fisher, M.D. for review. He interpreted the area as suspicious for invasion, but most consistent with in situ disease.

Because the NSABP relied on the local pathology reports for case assignment and did not utilize central review, we consider this case to represent invasive breast cancer. *The NSABP, in correspondence dated 9/23/98, agreed.*

Tamoxifen arm:

P45660LBM 56 year old woman at study entry, whose risk factor was a prior diagnosis of LCIS 10/28/93. She began therapy 3/21/94. On 2/1/94, prior to study entry, a mammogram was read as showing diffuse suspicious microcalcifications in the left breast. The mammographer recommended additional sampling despite the prior diagnosis of LCIS. A mammogram was performed the following year on 3/20/95, which demonstrated extensive microcalcifications. Sampling was again recommended despite the stability of the mammogram. Core biopsies of the breast were performed and did not show malignancy. A mammogram 9/19/95 was read as "mildly dense and unchanged since 3/20/95."

On 10/31/95, an abdominal ultrasound performed for abdominal discomfort showed hepatic metastases, which were biopsy-proven as adenocarcinoma. Sixty to seventy percent of the tumor cells stained 2+ positive for ER; a rare nucleus was positive for PgR. An MRI of the breast 11/8/95 showed an ill-defined 3 cm area in the right breast near the chest wall, not typical for carcinoma. No abnormalities were identified in the left breast. A supraclavicular node appeared and was biopsied. Pathologically, it was read as a poorly differentiated adenocarcinoma, identical in origin to the liver lesion in the opinion of the pathologist. The node, however, was negative on ERICA staining. The pathologist felt a GI source was most likely. A colonoscopy was negative, as were an IVP, cystoscopy, and pelvic ultrasound/endometrial biopsy. These studies were performed for clinical indications, not solely to evaluate a cancer of unknown primary work-up.

This patient was considered clinically by her treating physician to have metastatic breast cancer and was treated as such. She developed bony metastases and died of her disease 3/23/96. The death certificate recorded the cause of death as metastatic breast cancer. The NSABP coded it as unknown primary after several reviews, *and confirmed that classification in correspondence dated 9/23/98.* The reviewer considers this case to be consistent with metastatic breast cancer based on the mammogram reports, the prior diagnosis of LCIS, the receptor staining, and the judgement of the managing physician. (This case is also discussed in Section 10.1, Deaths on Study).

Overall, this review adds 2 cases to the placebo arm and adds 1 case to the tamoxifen arm. The reassignments do not change the previously described study results. The reassignments change disease-specific mortality figures to 5 deaths on placebo and 4 on tamoxifen, still not a statistically significant difference.

13. During the review of the CRFs, Dr. Martin identified several cases of breast cancer or suspicious for breast cancer that were not reported, because they occurred after the patient was removed from study.

Tamoxifen:

P34985FXC This 51 year old woman was randomized to tamoxifen 10/8/92. She was removed from study 4/23/96 for a diagnosis of endometrial cancer. On 1/7/97, she had a lumpectomy and radiation therapy for breast cancer. This breast cancer was not reported in the database.

In correspondence dated 9/23/98, the NSABP stated that they could not find supporting documentation for a diagnosis of breast cancer. On re-review, Dr. Martin noted that the breast cancer documentation, although included in the CRF for P34985FXC, actually belonged to a different participant.

P54910MON This 70 year old woman was randomized to tamoxifen 7/29/92 and was taken off study 4/27/95 for a diagnosis of endometrial cancer. The last follow-up form in the CRF, dated 1/6/98, codes a bilateral mammogram performed 12/29/97 as "suspicious". No information about a biopsy was provided. [The sponsor has been asked to supply additional documentation for this case. *Sponsor's reply 8/19/98: The dataset was frozen as of January 1, 1998. Information about this participant was received subsequent to this timepoint and was forwarded to FDA as part of the reply. The participant had a biopsy, which showed fibrocystic disease, microcalcifications, and no evidence of malignancy.*

14. As a result of the ODAC meeting, the sponsor was asked to provide information on the number of recurrences among women diagnosed with invasive breast cancer on the trial. This information was provided 9/25/98. Sites were not required to provide information on breast cancers after the date of occurrence; this information is therefore incomplete.

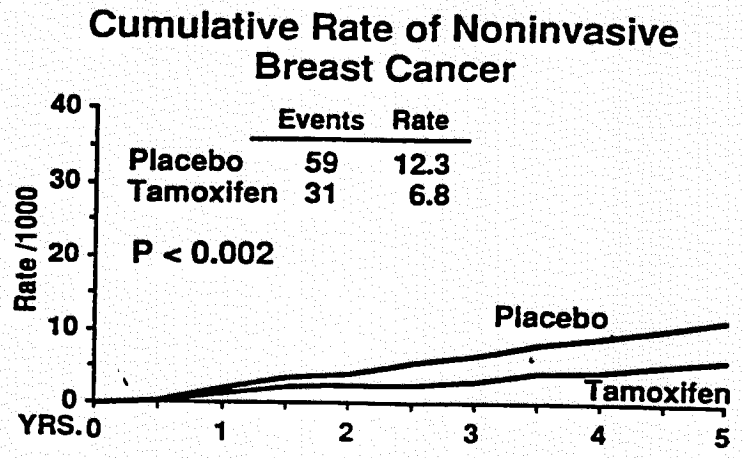
Information was provided on 20 of the 239 participants diagnosed with invasive breast cancer. Eleven women on placebo and 9 on tamoxifen recurred. One of the recurrences on the placebo arm was a contralateral breast primary. Six new deaths were reported, 3 on placebo and 3 on tamoxifen. There was 1 breast cancer-related death on placebo and 3 on tamoxifen. One woman on placebo died without information about recurrence; another died due to metastatic kidney cancer.

The total number of breast cancer-related deaths is therefore 6 on placebo and 7 on tamoxifen. Within the context of the short follow-up time in this trial, there are no data that suggest that cancers that develop on tamoxifen are more likely to recur than those that develop on placebo.

9.2 Non-invasive breast cancers

Ninety cases of non-invasive breast cancer were reported by the NSABP, 59 on placebo and 31 on tamoxifen. The p-value for this difference is 0.002. The following curve shows the cumulative rate of non-invasive breast cancer:

Figure 8. From NSABP slide, ASCO 1998



Reviewer Comment:

1. Karen Johnson, M.D., reviewed the CRFs on the participants with non-invasive breast cancer. There were 28 cases for which LCIS without any component of DCIS was reported, and 2 cases of atypical hyperplasia. These cases are summarized in the following table:

Table 29. Cases of LCIS and AH included among the non-invasive breast cancer cases

LCIS		Atypical Hyperplasia	
Placebo (n=21)	**Tamoxifen (n=7)**	**Placebo (n=1)**	**Tamoxifen (n=1)**
P00675QUE	P02405DAN*	P29144NEO	P59062UNC
P02829HOG*	P04401FXC*		
P07293DAN*	P10113RCH*		
P07461STA	P27564GLE*		
P12202BAS*	P49876CLR*		
P14125CIL*	P53400IOW#		
P16285MSK*	P53736MIA*		
P18798CAR			
P21056SCC*			
P28278EIN			
P28736STR*			
P35971ATL			
P37037EIN*			
P37099MIC*			
P43623MIA*			
P43969WVA			
P45786KAN*			
P46389NYC			
P54353OSU*			
P57062OKB			
P58638MSU			

*Participants with a diagnosis of LCIS at baseline
#Participants with a diagnosis of AH at baseline

Eighty-five percent (6/7) of participants who developed LCIS on tamoxifen had LCIS as part of their baseline entry criteria. The seventh participant randomized to tamoxifen who developed LCIS had a baseline diagnosis of AH. This participant's CRF was reviewed:

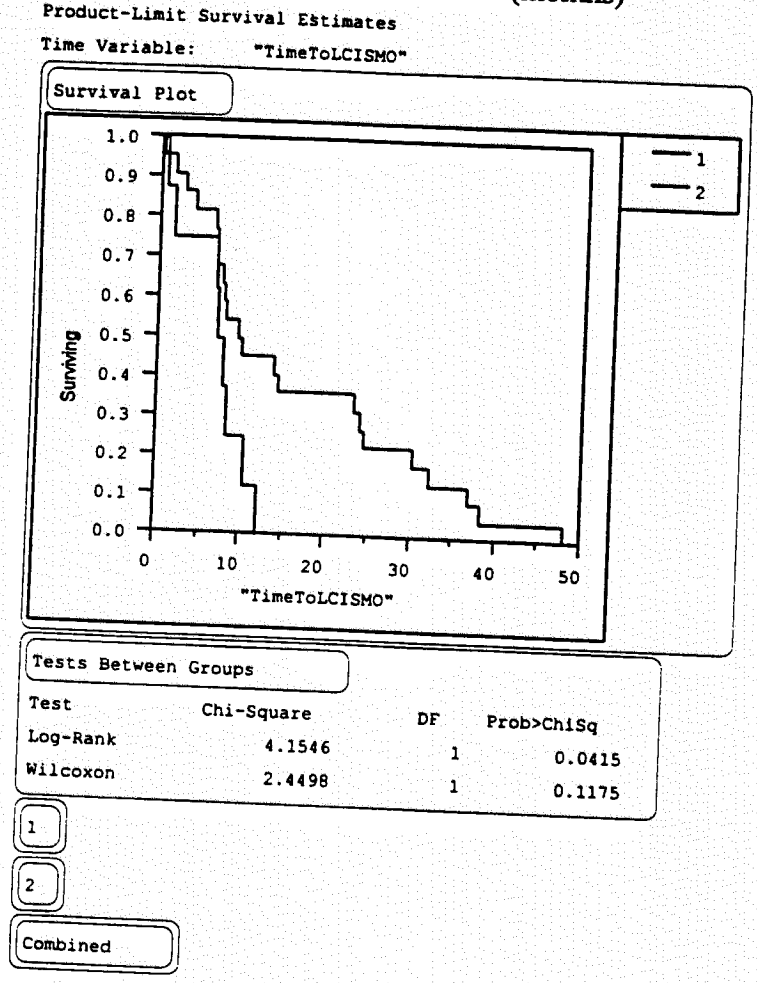
P53400IOW This 50 year old woman with a prior history of a biopsy that demonstrated AH was randomized to tamoxifen and began study drug 1/18/94. On 2/24/94, she had a biopsy performed. The slides from the 1994 biopsy were read in conjunction with the slides from the previous biopsy at the University of Iowa. The pathology report states that both samples represent LCIS.

It is likely, therefore, that all women randomized to tamoxifen who developed LCIS on study had this entity as part of their eligibility criteria.

Among women randomized to placebo who subsequently developed LCIS, 57% (12/21) had pre-existing LCIS at baseline.

The women with pre-existing disease can be considered to have had confirmation of their original pathology, as LCIS is commonly multicentric and multifocal. The time to the diagnosis of LCIS is shown below:

Figure 9. Time to diagnosis of LCIS (months)



Arm 1: Placebo
Arm 2: Tamoxifen

While there are few cases overall, the cases of LCIS diagnosed on the tamoxifen arm were identified sooner than were those on the placebo arm. All except one on the tamoxifen arm were diagnosed within 1 year of study entry; the 7th was diagnosed at 12.25 months after study entry. The shortened time to diagnosis again supports the concept of confirmation of pre-existing risk rather than a preventive effect.

These cases were sent to the NSABP for comment. In a response dated 7/31/98, the NSABP stated that LCIS was included as a non-invasive breast cancer endpoint for several reasons:

- If LCIS is a precursor lesion, then a decrease in the occurrence of LCIS may lead to a future reduction in the number of invasive breast cancers
- A decrease in the occurrence of LCIS will avoid the surgical treatment of the disease, including bilateral mastectomy
- A reduction in the occurrence of LCIS would result in fewer women "being labeled as cancer victims

The DODP disagrees with the inclusion of both pathologic entities under the blanket term "non-invasive breast cancer" for the following reasons:

- LCIS is considered a marker lesion, not a precursor lesion: it conveys a bilateral increased risk of breast cancer, and when breast cancer occurs, it is most commonly infiltrating ductal, not infiltrating lobular carcinoma
- LCIS has a high incidence of multifocality and multicentricity. Sequential diagnoses of LCIS do not change the level of risk conveyed by the initial LCIS diagnosis
- While bilateral prophylactic mastectomy is an appropriate treatment option, LCIS is most commonly managed by physicians and women with watchful waiting; the results of the P-1 study validate the use of tamoxifen as an additional therapeutic option to lower the subsequent risk of breast cancer

2. An additional 2 cases of DCIS with foci of microinvasion (described in Reviewer Comment 10 above) were re-classified by the DODP as invasive. The records for P54804MON, after a question sent to the sponsor, are under re-review by the NSABP for possible reassignment. No specific comments regarding participant P47522CIN were provided by the NSABP.

3. These changes in assignment result in the following table:

Table 30. DCIS in the P-1 trial

	Placebo	Tamoxifen	Reduction in Breast Cancer risk
DCIS	35	23	34%

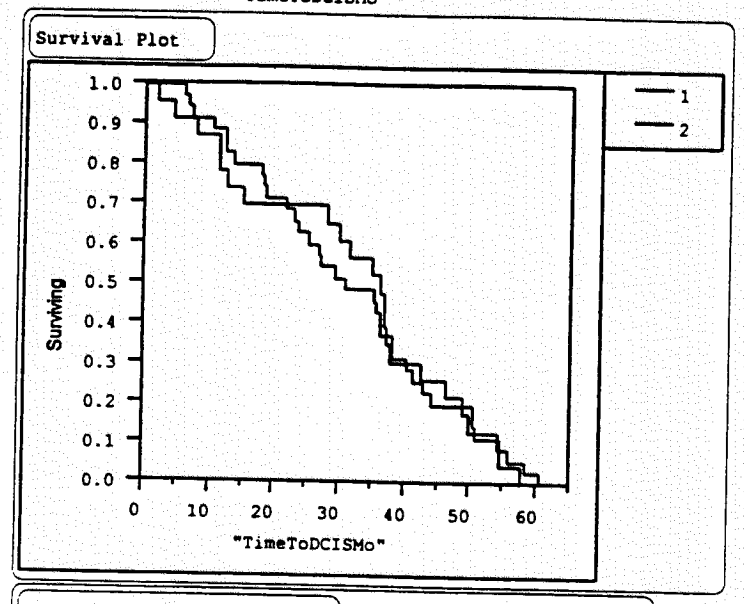
3a. Of the women diagnosed with DCIS, 16 on placebo and 11 on tamoxifen were removed from study (stopped study drug), and 9 on placebo and 7 on tamoxifen were unblinded. The 9 women on placebo were unblinded because of the diagnosis of non-invasive breast cancer (7 also stopped study drug). Of the 7 women on tamoxifen who were unblinded, 4 were unblinded because of the diagnosis of non-invasive breast cancer, 2 because of the participant's insistence, and 1 at physician request for another medical condition (all stopped study drug). It is therefore not possible to draw any conclusions about the effect of tamoxifen on DCIS from this trial.

4. If time to DCIS is calculated, using DCIS cases as per DODP, the following curve is generated:

Figure 10. Time to diagnosis of DCIS (DODP case assignment)

Product-Limit Survival Estimates

Time Variable: "TimeToDCISMo"



Tests Between Groups

Test	Chi-Square	DF	Prob>ChiSq
Log-Rank	0.0330	1	0.8557
Wilcoxon	0.0106	1	0.9179

1

2

Combined

Arm 1: Placebo
Arm 2: Tamoxifen

Although there were fewer events noted on the tamoxifen arm, they occurred at the same time points as on the placebo arm, suggesting a true preventive effect.

5. In summary, tamoxifen significantly decreased the incidence of DCIS, although the risk reduction was less than that observed for invasive breast cancer.

6. Dr. Martin also found an unreported case of DCIS in her review of CRFs for endometrial cancer:

Placebo:

P46348BOS This 51 year old woman with a prior history of LCIS was randomized to placebo 7/6/92. She was removed from study 2/11/97 because of a diagnosis of endometrial cancer. Follow-up forms indicated that an abnormal mammogram led to a biopsy, which documented DCIS, LCIS, and atypical hyperplasia.

Reviewer Note: This point is an error. This participant was included in the non-invasive breast cancer dataset.

9.3 Fractures

The protocol was designed to collect information on fractures at all sites, and to consider hip and spine fractures as primary endpoints. In the ERSMAC report and in the NSABP P-1 manuscript, spine fractures were added as an endpoint.

A total of 533 fractures occurred in women on placebo and 518 fractures occurred in women on tamoxifen. Fractures at the sites designated as primary fracture endpoints were observed, but the majority of fractures occurred in other sites.

The fracture incidence as originally reported is listed below:

Table 31. Fractures among BCPT participants (sponsor table 15, ERSMAC report, volume 3, page 26)

Site of Fracture	Placebo	Tamoxifen	Total
Fracture endpoints	**71**	**47**	**118**
Hip	20#	9##	29
Colles'	12	7	19
Spine	39	31	70
Other	**462**	**471**	**933**
Skull	13	7	20
Trunk, except spine*	37	55	92
Clavicle	11	3	14
Scapula	2	5	7
Humerus	36	24	60
Radius/ulna**	84	78	162
Hand/wrist	56	69	125
Femur***	3	2	5
Patella	7	12	19
Tibia/fibula	22	28	50
Ankle/foot	190	188	378
Unspecified	1	0	1
TOTAL	**533**	**518**	**1051**

* Ribs, sternum, larynx, and trachea
** Except Colles'
*** Except hip
#One woman also had a Colles' fracture
One woman also had a Colles' fracture and one woman also had a spine fracture

In the NSABP P-1 manuscript, the number of spine fractures was changed to 30 on the placebo arm and 19 on the tamoxifen arm. The total number of fractures was the same as in the ERSMAC report.

The hazard rates were reported as follows:

Table 32. Average annual hazard rates for fracture events among participants (NSABP P-1 manuscript, Table 7)

Fracture site	Number of events		Rate/1000 women		Risk ratio	95% CI
	Placebo	Tamoxifen	Placebo	Tamoxifen		
Hip	20*	9#	0.84	0.38	0.45	0.18-1.04
Colles'	12	7	0.50	0.29	0.59	0.20-1.61
Spine	30	19	1.25	0.80	0.64	0.34-1.17
Total events	61	33	2.56	1.39	0.54	.0.34-0.84
≤ 49	10	2	1.06	0.22	0.20	0.02-0.95
≥ 50	51	31	3.53	2.13	0.61	0.37-0.97

* One woman also had a Colles' fracture

One woman also had a Colles' fracture and one woman also had a spine fracture

The sponsor concluded that tamoxifen significantly reduced fractures at the 3 designated endpoints.

Reviewer Comment:

1. For other events and AEs, only the first event per patient was entered in the database. For the fracture endpoint, however, the NSABP counted all fractures rather than the first fracture per patient.

2. Some of the fractures in the above table occurred 1-4 years after discontinuing study drug. Only the dates for hip, Colles', and spine fractures were provided; the timing of other fractures cannot be evaluated. These fractures are summarized below:

Table 33. Fractures that occurred after study drug was stopped

Fracture site	Placebo	Tamoxifen	Total
Hip	3	2	5
Colles	2	4	6
Spine	12	3	15

If these fractures are removed from the totals in Tables 31 and 32, the same relationships between the two treatment arms exist, although the absolute number of events changes. It is appropriate to count all fractures during follow-up, as tamoxifen might be expected to have long-term effects on bone, and because beneficial effects of tamoxifen might not be detectable for several years because of the slow growth and remodeling of bone.

2. The protocol stated that information on vertebral fractures will be collected, but they will not be included as events because there is no agreed-upon definition of a vertebral fracture, many vertebral fractures are unknown to the patient, and methods for determining vertebral fractures are costly and/or are not reproducible. We agree, after review of other applications that involve fracture endpoints, with these points. While information on spinal fractures is of interest, it should be considered as a "soft" endpoint.

3. In the NSABP P-1 manuscript, 9 vertebral fractures on the placebo arm and 12 on the tamoxifen arm were determined to involve bones other than vertebral bodies. These fractures were included in the totals, but re-assignment was not provided. This reassignment changed the outcome from no difference in spinal fracture rate between placebo and tamoxifen to a 36% reduction from tamoxifen therapy. The sponsor has been asked to provide the documentation for these decisions.

The sponsor replied August 19, 1998. Documentation was provided that the fractures in questions did not involve the spine. Most were stress fractures of the feet.

4. In reviewing the case report forms, we identified additional fractures that were not included above:

Placebo:

P20088SML 74 year old woman randomized to placebo 11/13/92; took study drug until 11/20/97. She had a T2 fracture following a fall 9/25/94. She is listed as having a fracture of the "trunk" rather than as a spine fracture.

P19634HOG Randomized to placebo; sustained a hip fracture 12/3/96

Tamoxifen:

P02753MAR Randomized to tamoxifen 7/31/92; sustained a fracture 3/10/97 reported in the CRF as a Colles' fracture. In the NSABP database, this fracture was listed as a radial head fracture.

P47230SCC Age 53 at study entry; randomized 11/16/92 to tamoxifen; off study 1/5/96 because of a diagnosis of invasive breast cancer. Sustained a fracture of the proximal phalanx of the foot 9/5/93.

P17878MID Randomized to tamoxifen; had an arm/wrist fracture 10/20/97

The final FDA assessment of the number of spine and Colles' fractures is pending review of full documentation for these events.

The sponsor agreed August 19, 1998 that P02753MAR had a Colles' fracture. This participant was added to the database. A review of all radial head fractures was begun to ensure correct coding of Colles' fractures.

The sponsor agreed August 20, 1998 that P20088SML sustained a spine fracture; she was added to the database.

The sponsor reported 9/23/98 that no documentation of a foot fracture could be found in the CRF for P47230SCC. This fracture was reported by Dr. Johnson, who subsequently left FDA. Dr. Honig could not find the documentation for this event. The sponsor agreed with the FDA assessments for P19634HOG and for P17878MID.

4a. Four participants had bone fractures that occurred after a diagnosis of cancer metastatic to bone. These fractures were not included in the database, appropriately in the opinion of the reviewer. However, P47330THM, who had cancer of unknown primary metastatic to bone with an L-spine compression fracture, was listed in the database. The NSABP agreed that all these fractures should be excluded, and removed the fracture listed for P47330THM.

5. Overall, review of the electronic database demonstrated a total of 1051 fractures (533 on placebo, 518 on tamoxifen) in 960 participants (490 on placebo, 470 on tamoxifen). The numbers of fractures per participant is summarized below:

Table 34. Number of fractures per participant, NSABP P-1

Number of fractures per participant	Placebo (# of participants)	Tamoxifen (# of participants)	Total (# of participants)
1	454	428	882
2	29	36	65
3	7	6	13

Seventy-eight participants experienced more than one fracture, 36 on placebo and 42 on tamoxifen. For participants with one fracture, the events were balanced between treatment arms.

The following table summarizes the number of women with fractures, rather than the number of fracture events, by age, using the original attributions for spine fractures and correcting the table for a spine fracture based on comment 3.

Table 35. Number of Participants with fractures by age

Age/Fracture site	Placebo (#)	Tamoxifen (#)	Total (#)
≤ 49:			
Hip	4	0	4
Colles	3	0	3
Spine	5	8	13
All sites*	132	145	277
≥ 50:			
Hip	16	9	25
Colles'	9	7	16
Spine	35	23	58
All sites*	358	325	683

*Including hip, Colles', spine

The following table summarizes the number of fractures, rather than the number of participants with fractures, by age, including the fracture described in comment 3 that was not in the database:

Table 36. Number of fractures by age

Age	Placebo (#)	Tamoxifen (#)	Total (#)
≤ 49	144	159	303
≥ 50	389	360	749

The total number of fractures and the number of women with fractures were not significantly different between the two arms of the study. If the major fracture endpoints are evaluated, tamoxifen decreased the number of observed hip and Colles' fractures. It is unclear whether it had an effect on spine fractures. The definition of a vertebral fracture is controversial, and spinal fractures may be difficult to identify conclusively.

If one looks at fracture endpoints by age, younger women had fewer fractures than older women. Total number of fractures and number of participants with fractures by age were balanced between the arms. Women aged 49 or less had a reduction in hip and Colles' fractures; the spinal fractures are difficult to interpret. Women aged 50 or older had a reduction in hip fractures and minimal changes in the incidence of Colles' fractures. Spine fractures cannot be evaluated, as the majority of re-assigned cases were in this age group.

It should be noted that the confidence intervals for these assessment include 1.00, indicating that the differences are not statistically significantly different.

6. There were 84 and 78 radial head fractures, respectively, on the placebo and tamoxifen arms. It is possible that some of these fractures may represent overlooked Colles' fractures.

This point was discussed with the sponsor. The NSABP prospectively collected information on all fractures and required submission of the radiology reports, but not the films, for ascertainment. When the NSABP reviewed the reports for radial fractures, they could identify 12 Colles' fractures on the placebo arm and 7 on the tamoxifen arm with certainty. The reports for other lower radial fractures (62 on each arm) did not permit a definite assessment of a Colles' fracture versus other radial fracture.

Because the protocol prospectively specified "wrist fractures" and because it is likely that there are additional Colles' fractures included in the "other lower radial fracture" category, total wrist fractures will be used. The total numbers are 72 on placebo and 69 on tamoxifen.

7. Data was collected on baseline illnesses and medications relevant to the fracture endpoint:

Table 37. Baseline fracture and osteoporosis history and calcium use in P-1 participants

Baseline parameter	Placebo	Tamoxifen	Total
Hx prior fracture	2053	2046	4099
Hx osteoporosis	303	302	605
Hx fracture or osteoporosis	2194	2196	4390
Current calcium use	2093	2099	4192
Hx current or past calcium use	2598	2590	5188

Thirty-one percent of the study population had experienced a prior fracture; 4.5% of the population carried a diagnosis of osteoporosis at entry.

The following table summarizes baseline risks in women with fractures:

Table 38. Baseline fracture/osteoporosis history and calcium use in P-1 participants with bone fractures.

Baseline Parameter	Placebo	Tamoxifen	Total
Hx prior fracture	197	193	390
Hx osteoporosis	43	38	81
Current calcium use	91	94	185
Past calcium use	103	101	204

Most fractures occurred in women without a history of osteoporosis or prior fracture.

Information on concomitant use of aledronate, etidronate, or other medications for osteoporosis was not collected.

8. A consultation was requested from HFD-510, the Division of Metabolic and Endocrine Drug Products. The reviewer, Leo Lutwak, M.D., Ph.D., concluded that the data warranted a safety statement regarding bone fractures with tamoxifen. However, the data were not sufficiently robust to permit a labeling claim concerning the efficacy of tamoxifen in preventing fractures. The design limitations of the trial for evaluating reduction in fracture incidence include:

- *No baseline x-rays to determine prevalent fractures at baseline (influences the rate of subsequent fracture)*
- *X-rays were obtained after clinical suspicion of a fracture. Because of the large number of clinical sites and without standardized timepoints for interval radiographs, variations in clinical practice are expected.*
- *Amount of calcium intake was not reported; no dietary surveys were provided*
- *No data is available on dietary vitamin D and its biologically active forms*
- *No surrogate endpoint data, including bone mineral density and biochemical indices of bone formation and bone resorption, are available*

Thus, a separate efficacy claim for fracture reduction cannot be made.

10.0 Safety Review

10.1 Deaths

Overall, 118 deaths have been reported, 65 on placebo and 53 on tamoxifen. The sponsor reported no difference in cause of death between the two arms and noted that the death rates were comparable between the two arms. The following table represents the sponsor's assessment of cause of death.