Table 49. Cardiac risk factors among BCPT participants

RISK FACTORS	PLACEBO		TAMOXIFEN	
	Number	Percent	Number	Percent
Diabetes:				
No	6443	96%	6402	96%
Yes	264	4%	279	4%
Hypertension:				
No	5219	78%	5204	78%
Yes	1488	22%	1477	22%
Use of cholesterol-lowering drugs:				
No	6152	92%	6143	92%
Yes	555	8%	538	8%
Family history of MI*:				
No	3552	53%	3611	54%
Yes	3155	47%	3070	46%
Ever smoked:				
No	3499	52%	3378	51%
Yes	3208	48%	3303	49%
Current smoker:				
No	5867	87%	5821	87%
Yes	840	13%	860	13%
Amount smoked:				
≤ 1 ppd	611	73%#	665	77%#
1-2 ppd	212	25%#	173	20%#
2-3 ppd	16	2%#	21	2%#
3-4 ppd	1	0.1%#	1	0.1%#

*First-degree relatives only
Of current smokers

Twenty-two percent of participants on each arm had a baseline diagnosis of hypertension. Four percent of the population on each arm had a diagnosis of diabetes mellitus, and 8% required medication to lower their cholesterol. While half the women in the trial had smoked in the past, only 13% were current smokers. The amount smoked per day was balanced between treatment arms.

When history of diabetes, hypertension, cholesterol-lowering agents, current tobacco use, and MI in a first degree relative were combined, 4360 (65%) of the women on placebo and 4294 of women on tamoxifen (64%) had at least one risk factor for a cardiovascular event. This high percentage may be misleading, as family history of MI in a first-degree relative is probably the contributing factor to the total. No information was obtained about the first-degree relative's age at MI; the family history is significant only in young first-degree relatives (less than age 50 or 55). If one excludes family history

from the risk assessment, 38% of the population and on each study arm had a cardiac risk factor.

3. Risk factors in participants with ischemic heart disease events:

a. History of prior events

Table 50. Ischemic heart events prior to study entry in participants with cardiac events on study

Prior event	Placebo	Tamoxifen	Total
Hx angina	14	17	31
Hx MI	7	9	16
Hx CHF	3	1	4
Hx heart murmur	5	4	9
Hx hypertension	31	35	66
Hx diabetes mellitus	12	17	29
Hx TIA	3	2	5
Hx CVA	0	2	2
Hx vascular problems	7	7	14

Ninety-one of the 120 participants with a cardiac event had a prior history of one of the above events (75%).

b. History of risk factors

The electronic database was queried regarding baseline risk factors in women with myocardial infarction, angina, acute ischemic syndrome, and other cardiovascular death. These queries are not shown, but 75-85% of women with these syndromes had existing risk factors for cardiovascular disease at entry.

c. Overall, a high proportion of women with a cardiac event had a history of prior cardiac events or cardiac risk factors. The factors were balanced between treatment arms.

4. Another category of "other vascular death" was listed by the sponsor. Deaths in nine participants, 4 on placebo and 5 on tamoxifen, were included. These deaths consisted of complications from cardiomyopathy and sudden death.

5. The cardiac events of MI, angina, acute ischemic syndrome, and other cardiovascular death were analyzed by age at randomization:

Table 51. BCPT Cardiac events by age

Age	Placebo	Tamoxifen	Total
≤ 49	5	9	14
50-59	15	15	30
≥ 60	43	42	85
Total	63	66	129

While there appear to be more events in women under age 50 on tamoxifen compared to placebo, there are few events in this age category and the difference is not significantly different (p-value 0.60 for the overall distribution; p-value 0.40 for women ≤ 49 specifically). There is no significant difference between treatment arms for women aged 50 or more, or within the prospectively defined age groups of 50-59 and 60+. Younger women, as expected, had fewer events than older women.

6. These data do not support a cardioprotective effect of tamoxifen. However, the statistical section of the protocol noted that the statistical power to detect a benefit of tamoxifen would depend on the age of the participants. Ten thousand postmenopausal women were mentioned as the target accrual to demonstrate this benefit; fewer than this target goal were accrued. While this trial does not demonstrate a cardiovascular benefit from tamoxifen, the trial may be underpowered to show a difference.

7. Considering the risk factors present in the overall study population, it was not possible to predict who would develop future cardiac events.

10.4.2 Stroke and transient ischemic attacks

Women who experienced both a TIA and a stroke were categorized as the more severe event, i.e. CVA. The number of strokes was increased on the tamoxifen arm, although not significantly so:

Table 52. Stroke and TIA on NSABP P-1

Event	Placebo	Tamoxifen	Total
Fatal stroke	3	4	7
Non-fatal stroke	21	30	51
TIA	21	18	39
Total	45	52	97

In the NSABP P-1 manuscript, the authors presented the annual hazard rate for these events in the total population and by age:

Table 53. Average annual hazard rates of vascular-related events by age at entry (NSABP P-1 manuscript, Table 8).

Event	Number of Events		Rate/1000 Women		Risk Ratio	95% CI
	Placebo	Tamoxifen	Placebo	Tamoxifen		
Stroke	24*	34#	1.00	1.43	1.42	0.82-2.51
≤ 49	4	3	0.42	0.32	0.76	0.11-4.49
≥ 50	20	31	1.38	2.13	1.55	0.86-2.87
TIA:	21	18	0.88	0.75	0.86	0.43-1.70
≤ 49	4	3	0.43	0.32	0.76	0.11-4.49
≥ 50	17	15	1.17	1.03	0.88	0.41-1.88

*3 fatal
#4 fatal

Six of the 24 strokes in the placebo group were considered hemorrhagic in origin and 10 of the 34 strokes in the tamoxifen group were categorized as hemorrhagic. Seventeen of the 34 strokes on the tamoxifen arm were considered occlusive and 7 were considered to be of unknown etiology. Fourteen of the 24 strokes on the placebo arm were reported as occlusive and 4 of unknown etiology.

The authors concluded that there was no difference in the incidence of TIAs between the 2 treatment arms, either for the entire population or by age. The number of strokes was increased, although not significantly so, in women over age 50.

Reviewer Comment:

1. Case report forms for stroke were reviewed by Donna Griebel, M.D., who wrote the following analysis .

2. Fatal stroke:

An Access Query of the database yielded 7 participants whose deaths were attributed to CVA. The death of one participant on that list, **P16874 UCL** (Tamoxifen), was attributed to CVA on the death certificate, but the reviewers believe her death was due to pancreatic cancer. Participant **P56876 MSU** (Tamoxifen) was not included in the Access Query list, and the reviewers believe that her death was due to CVA and not to metastatic lung cancer. These cases were discussed in section 10.1, Deaths. These changes do not change the total number of fatal strokes reported on each arm.

3. Hemorrhagic stroke:

The reviewer's totals of hemorrhagic events on each arm differed slightly, based on review of the case report forms. The reviewer noted 11 events on the tamoxifen arm that could be attributed to intracranial hemorrhage. The additional participant on the reviewer list **may** be **P31396 HAW** who was found to have evidence "thought to represent subacute subarrachnoid hemorrhage" on MRI and MRA performed for work-up of new onset headaches. The abnormal areas were noted in the right subfrontal cistern, two segments of interhemispheric cistern, and right middle cerebral artery cistern.

The reviewer noted 7 events in the placebo group that could be considered hemorrhagic. The additional event on the reviewer's list **may** be **P14725 NSU**. This participant had two events on study, but was only counted as one event. The first, 6/23/95, was an MRI read as probable petechial hemorrhage in the right posterior parietal region and 5 mm lacunar infarct in the left thalamus. The exam was ordered to investigate abnormal findings on a bone scan performed for multiple joint pain. The participant was otherwise asymptomatic at the time. The second event on 1/9/96 was a right corona radiata infarct without evidence of hemorrhage. The participant presented with new onset left sided weakness, facial droop, and slurred speech during an admission for malignant hypertension.

Of note, two of the hemorrhagic strokes on the tamoxifen arm were post-traumatic subdural hematomas. One of the hemorrhagic strokes on the placebo arm was a subdural hematoma, subacute to chronic, with no history given of trauma.

4. Occlusive stroke:

It is unclear what criteria were used to designate a stroke occlusive vs. of unknown origin in the study, and the reviewer's tabulation of each subtype does not match that in the study report. In addition, there were participants with multiple events that were only counted as a single stroke. **P14725 NSU** (Placebo) was considered by the reviewer as having had two CNS events – one hemorrhagic as noted above. **P13809 SIO** (Tamoxifen) was considered to have had at least two CNS events. **P17878 MID** (Tamoxifen) had two events – one occurred approximately 5 months after stopping study medication.

5. Risk factors for occlusive stroke

The majority of participants on each arm of the study who had CNS events (stroke) considered non-hemorrhagic were found by the reviewer to have had at least one risk factor for occlusive stroke, based on medical history data available in the case report forms in the form of self report, medical records from hospitalizations, or deduced from medication lists. Two participants on the placebo arm and 5 participants on the tamoxifen arm had no discernible risk factor other than age. The placebo participants without other risk factors were 63 and 60 years of age. Those on the tamoxifen arm were 76, 75, 69, 60, and 50 years of age. Risk factors noted included hypertension, diabetes, hyperlipidemia, atrial fibrillation/flutter, tobacco use, coagulopathy, prior history of TIA, symptomatic coronary artery disease, and documented significant carotid atheromatous plaques. Eleven of the tamoxifen and 4 of the placebo group had only one discernible risk factor beyond age. Nine of the tamoxifen and 4 of the placebo group had 2 risk factors. Four in each group had 3 risk factors, and 2 in the tamoxifen group had 4 risk factors.

When the documented hemorrhagic CNS events were excluded, the reviewer found 23 participants with 25 events on the tamoxifen arm, and 18 participants with 18 events on the placebo arm who had not had documented hemorrhagic events. One of the tamoxifen participants (P16874 UCL) had had no imaging performed and, conceivably, could have had a hemorrhagic event. She had metastatic pancreatic carcinoma and died

before imaging studies could be performed to diagnose the etiology of her neurologic symptoms.

If it is assumed that the tamoxifen participant without radiographic documentation did not have a hemorrhagic event, the relative risk of an occlusive/ischemic CNS event on tamoxifen/placebo = 1.39, slightly less than the overall relative risk for all types of CNS events reported for the study. If she is not counted, the relative risk is lower still - 1.33.

Treatment with tamoxifen has previously been reported to be associated with increased risk for arterial thrombotic events. Saphner, et al (*Journal of Clinical Oncology, vol. 9, No 2, 1991: pp. 286-294*) reported in their review of the records of 2673 patients who had participated in seven ECOG studies of adjuvant breast cancer therapy, that premenopausal patients treated with a combination of adjuvant chemotherapy and tamoxifen had a significantly higher incidence of arterial thrombosis than those who were treated with chemotherapy alone (1.6% vs. 0.0%, p=0.004). Postmenopausal patients in these studies, however, did not demonstrate a significantly increased risk with the addition of tamoxifen to adjuvant chemotherapy. The incidence of arterial thrombosis in postmenopausal patients on adjuvant chemotherapy combined with tamoxifen was 1.0% compared to 1.7% in an observation group, (p=0.31). The incidence of arterial thrombosis in postmenopausal patients on tamoxifen alone in this study was 1.2%. The arterial thrombotic events that did occur associated with tamoxifen in this analysis were observed while on therapy, not after stopping therapy, and they tended to occur during early cycles of therapy. The time to both venous and arterial thrombotic events with tamoxifen in this analysis was found to be 1-11 months. Of 22 total arterial events, only 10 were cerebral vascular accidents. Eleven were embolic events involving an extremity and one was a mesenteric artery thrombosis.

6. Time to event

In light of this prior analysis, the reviewer examined the non-hemorrhagic strokes reported in this study from the standpoint of whether the event occurred while on active treatment with study drug, and, if that was so, whether the event occurred early during the course of treatment. For this exploratory analysis the reviewer selected the time frame of $\leq$ 1 year from start of therapy as the definition of "early". This time was based on the cited reference, which found the majority of vascular events associated with tamoxifen as having occurred $\leq$ 11 months on treatment.

Eighteen events in 17 participants occurred before stopping tamoxifen treatment on study. Thus 72% of the events (in 74% of the patients with these events) on the tamoxifen arm occurred while on active treatment. Conversely, 28% of the events (in 26% of the patients with such events) on the tamoxifen arm occurred after having stopped treatment. Six of the seven post-treatment events occurred less than 12 months after stopping tamoxifen, and one occurred at 2 years. The tamoxifen post-treatment events are summarized in the table below.

Table 54. Non-hemorrhagic Events Which Occurred **After** End of Therapy – Tamoxifen Arm

Participant	**Time After Stop**	**Time on Treatment**	**Age at Study Entry**	**Approximate Age at Event**
P31095 RCH	25	27	69	73
**P16874 UCL – undocumented (pancreatic ca)	6	12	66	67
P56876 MSU	4	27	60	62
*P25300 BOS	11	24	57	59
*P32029 NVM	10	4	56	57
P31828 DEL	2	60	50	55
P17878 MID (undocumented, second event)	5	43	50	54

* = *CT findings normal or with evidence of multiple old lacunar infarcts concurrent with clinical findings consistent with a lacunar infarct. No evidence of hemorrhage*

** = *No radiographic imaging performed to determine the etiology*

The median time to event after stopping tamoxifen was 6 months. The median duration of therapy prior to event for these participants was 27 months. One of the participants, **P16874 UCL**, had metastatic pancreatic cancer and no imaging performed to confirm CVA as opposed to brain metastasis as the etiology of her symptoms before her death. When this participant was excluded, the median time to CNS event after stopping tamoxifen increased slightly to 7.5 months, but the median duration of therapy before event did not change. On the placebo arm 17 events in 17 participants occurred before stopping treatment on study. Only one participant had a non-hemorrhagic CNS event after stopping therapy, and that occurred 1 year after stopping treatment. That participant is summarized in tabular form below.

Table 55. Non-hemorrhagic Event Which Occurred **After** End of Therapy– Placebo

Participant	**Time After Stop (months)**	**Time on Treatment (months)**	**Age at Study Entry**	**Approximate Age at Event**
*P26783 MAR	12	22	63	65

* = *CT findings normal or with evidence of multiple old lacunar infarcts concurrent with clinical findings consistent with a lacunar infarct. No evidence of hemorrhage*

Tables 56 and 57 summarize events that occurred on study treatment. Seven of the 18 events that occurred before stopping treatment on the tamoxifen arm were observed at ≤ 12 months after starting therapy, 39%. Three of the 17 such events on the placebo arm occurred ≤ 12 months after starting therapy, 18%. The median time to first

event occurring prior to discontinuing treatment on the tamoxifen arm was 15 months. The median time to first such event on the placebo arm was longer, 34 months. The median age at study entry of those participants who experienced a non-hemorrhagic stroke before stopping therapy on the tamoxifen arm was 69 years (71 yo at time of event), and 68 years on the placebo arm (71 yo at time of event). Nine of the 17 participants on the tamoxifen arm had treatment on study stopped related to the CNS event (53%), while 7/17 participants (41%) on the placebo arm had treatment on study stopped because of the event.

Table 56. Non-Hemorrhagic Events Which Occurred *Before* End of Therapy - Tamoxifen

Participant	TIME (months)	Age at Study Entry	Approximate Age at Event	Off Therapy for Event	Menopausal Status
	40	67	70	Yes	Post
	48	75	79	Yes	Unknown
	39	73	76		Post
	9	59	59		Post
	2	69	69	Yes	Post
	12 *31	72	73 74		Post
	48	75	79		Post
	15	52	53	Yes	Unknown
	43	76	79		Unknown
	54	75	79		Post
	9	68	68		Post
	10	56	56		Post
	2	68	68	Yes	Unknown
	12	63	64	Yes	Post
	15	76	77	Yes	Post
	56	57	61	? 2 months after event for toxicity?	Post
	43	50	53	Yes	Pre

* = *CT findings normal or with evidence of multiple old lacunar infarcts concurrent with clinical findings consistent with a lacunar infarct. No evidence of hemorrhage*

Table 57. Non-hemorrhagic Events Which Occurred *Before* End of Therapy - Placebo

Participant	Time (Months)	Age at Study Entry	Approximate Age at Event	Off Therapy for Event	Menopausal Status
	34	66	69	Yes	Unknown
	58	74	78		Unknown
	42	68	71	Yes	Post
	14	54	55	Death from CVA	Post
	7	60	60	Yes	Unknown
	21	71	72		Post
	29	72	74		Unknown
	51	69	73	Yes	Post
	42	77	80		Post
	33	50	52		Unknown
	41	51	54		Unknown
	36	77	80		Unknown
	3	63	63		Post
	46	72	75		Post
	38	47	50		Unknown
	22	73	74	Yes	Unknown
	6	47	47	Yes	Pre

* = *CT findings normal or with evidence of multiple old lacunar infarcts concurrent with clinical findings consistent with a lacunar infarct. No evidence of hemorrhage*

In this exploratory analysis, the median time to non-hemorrhagic stroke while on active treatment was shorter on the tamoxifen arm, and a higher percentage occurred within the first year of treatment. More events were noted after stopping study treatment on the tamoxifen arm.

The paper by Saphner, et al, noted the risk for arterial thrombotic events to be significantly increased in the premenopausal adjuvant population and not the postmenopausal population represented in the studies analyzed. In contrast, the majority of participants (12/17) on the tamoxifen arm in this prevention trial that had a non-hemorrhagic CNS event before end of therapy were postmenopausal - either reporting a date of menopause or date of bilateral oophorectomy. Only 1/17 reported premenopausal status at study entry. The remaining four gave a history of a total abdominal hysterectomy, but there was no definite menopausal status provided in the data set. The ages of these four patients – 75, 76, 68, and 52 – indicate that three were likely to have been postmenopausal. Of the participants on the placebo arm with a non-hemorrhagic stroke prior to stopping therapy, 7/17 reported a date of menopause or bilateral oophorectomy. Only one reported a premenopausal status, and the remaining 9 were of uncertain menopausal status, although four were ≤ 60 years of age – 50, 51, 47, and 60 yo. The authors of the referenced paper, however, expressed reservations regarding

drawing the conclusion that tamoxifen does not influence the incidence of arterial thrombotic events in the postmenopausal population, as the results of the analysis could have been influenced by the data from one of the studies included, EST 1178 (169 patients randomized between adjuvant treatment with tamoxifen or placebo). The incidence of arterial thrombotic events on the placebo arm in that study was much higher than expected, 4.8%. The incidence was higher not only than that observed on its tamoxifen arm (1.2%), but on all arms of the other studies examined in that analysis. The reason for the skewed incidence in the placebo arm of EST 1178 is unknown.

7. In conclusion, the reviewer confirmed a slightly higher risk of arterial thrombotic events on the tamoxifen arm compared to placebo in this prevention trial. Exploratory analyses suggested a trend for earlier thrombotic events on the tamoxifen arm when compared to the placebo arm as well. The overwhelming majority of patients with such events were postmenopausal and had significant underlying risk factors for developing thrombotic strokes. Most events occurred while on active treatment – on both the tamoxifen and placebo arms – but there were more post-treatment events in the tamoxifen group than the placebo group. Previous reports, however, have correlated arterial thrombotic events associated with tamoxifen with the active treatment phase, and not after treatment cessation.

10.4.3 Thromboembolic Events

The following thromboembolic events were reported by the NSABP:

Table 58. Thromboembolic events in NSABP P-1

Type of events	Placebo	Tamoxifen	Total
Fatal PE	0	2	2
Non-fatal PE	6	15	21
Deep vein thrombosis w/o hospitalization	3	3	6
Deep vein thrombosis w/hospitalization	16	27	43

The NSABP reported 49 women with DVT on the trial, 19 on placebo compared with 30 on tamoxifen. The investigators distinguished events requiring hospitalization from those managed as an outpatient. However, only 3 women on each arm were not hospitalized for the event; most were admitted.

Seventeen women in the trial were originally reported with a pulmonary embolus, 6 on placebo and 17 on tamoxifen. Originally, 2 of these events, both on the tamoxifen arm, were reported as fatal (see reviewer comment below).

Thirty women on tamoxifen were diagnosed with DVT compared to 19 women on placebo.

The following hazard ratios for these events were reported in the NSABP P-1 manuscript:

Table 59. Average annual hazard rates of vascular-related events by age at entry (from Table 8, NSABP P-1 manuscript)

Event	Number of Events		Rate/1000 Women		Risk Ratio	95% CI
	Placebo	Tamoxifen	Placebo	Tamoxifen		
PE:	6	18*	0.25	0.75	3.01	1.15-9.27
≤49	1	2	0.11	0.21	2.02	0.18-22.32
≥50	5	16	0.34	1.10	3.20	1.12-11.17
DVT**:	19	30	0.79	1.26	1.59	0.86-2.98
≤49	8	10	0.85	1.08	1.27	0.45-3.69
≥50	11	20	0.76	1.38	1.82	0.83-4.20

*3 fatal

**All but 3 cases in each arm required hospitalization

The sponsor concluded that there were an excess number of events on the tamoxifen arm, concentrated in women age 50 or more.

Reviewer Comments: Deep vein thrombosis

1. In the grading of DVT severity, grade 1 was defined as thrombophlebitis, grade 2 as DVT not requiring hospitalization, grade 3 as DVT requiring hospitalization, and grade 4 as pulmonary embolism. The revised CTC criteria for thrombosis/embolism are as follows:

Event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Thrombosis/ embolism	None	-	deep vein thrombosis, not requiring anticoagulant	deep vein thrombosis, requiring anticoagulant therapy	embolic event including pulmonary embolism

These criteria were recently published and were not available when the study was designed. They are more in keeping with clinical practice, as they distinguish between events which do and do not require therapeutic intervention. The distinction between grade 2 and grade 3 events, as defined in the trial, is not clinically meaningful. Therefore, the total number of deep vein thromboses should be considered in the risk-benefit assessment of the trial.

2. An additional case was identified during review of case report forms. was randomized to tamoxifen 9/8/92; the risk assessment forms were not present in her CRF. She was diagnosed with cancer of unknown primary at age 62 on 4/12/96. She discontinued study drug 4/23/94 due to the adverse publicity about the P-1 trial. A CT scan 4/17/96 demonstrated subclavian vein thrombosis.

In the reviewer's opinion, although the participant was randomized to tamoxifen, it is unlikely that this event is related to study drug given the timing of its occurrence.

3. Some of the DVTs listed in Tables 58 and 59 occurred after study drug was discontinued:

Table 60. DVTs that occurred after study drug was discontinued:

	Placebo	Tamoxifen	Total
DVT	10	3	13

The ten events on the placebo arm occurred from 2 months to 3 years after stopping study drug. On tamoxifen, the 3 events that occurred after study drug occurred within 19 to 33 days of discontinuing study drug, at a time when tamoxifen blood levels are still detectable. If one excludes events on placebo that occurred after study drug was stopped, the comparison is between 9 DVTs on placebo and 30 on tamoxifen, a more striking difference.

4. The CRFs of the participants who experienced DVT were reviewed. Predisposing factors are summarized as follows:

Table 61. Predisposing factors in women with DVT

Factor	Placebo (n=19)	Tamoxifen (n=30)	Total (n=49)
Weight:			
<155 lbs	3 (16%)	6 (20%)	9 (18%)
156-175 lbs	5 (26%)	7 (23%)	12 (24%)
> 175 lbs	11 (58%)	17 (57%)	28 (57%)
Tobacco:			
Past/current tob	11 (58%)	13 (43%)	24 (49%)
Current tobacco	5 (26%)	3 (10%)	8 (16%)
Precipitating event:			
Surgery/general anesthesia	6 (32%)	10 (33%)	16 (33%)
Long trips	2 (11%)	2 (7%)	4 (8%)
Trauma	2 (11%)	1 (3%)	3 (6%)
Underlying predisposing medical disorder:			
Malignancy	5* (26%)	1 (3%)	6 (12%)
Subclavian catheter	1 (5%)	0	1 (3%)
Thoracic outlet syndrome	1 (5%)	0	1 (3%)
Open-label tamoxifen	1 (5%)	0	1 (3%)
Protein S/protein C deficiency	1 (5%)	1 (3%)	1 (3%)
Enlarged uterus	0	1 (3%)	1 (3%)

*Includes 2 breast cancer patients who are also listed under "open-label tamoxifen" and "subclavian catheter" and 1 glioma patient included under "surgery"

Approximately 80% of the women in each group were above the population median for weight; 58% of women on each arm weighed over 175 pounds. Fifty-eight percent of women with DVT on placebo had a past or current history of smoking compared to 43% of women with DVT on tamoxifen; fewer women on tamoxifen with a DVT had a current smoking history.

Predisposing events or medical conditions are discussed by arm.

Placebo:

Ten of the 19 women on placebo had a predisposing event, such as surgery, trauma, or a long trip prior to the development of clot. Six participants had medical conditions that increased the likelihood of clotting. These conditions are detailed below:

- A participant on the placebo arm was diagnosed with invasive breast cancer. Her therapy was unblinded and she was placed on open-label tamoxifen. Her deep vein

thrombosis occurred while on tamoxifen. She is included on the placebo arm in an intent-to-treat analysis, but had a tamoxifen-related event.

- Two women experienced subclavian vein thromboses, included in the count of DVT. One woman had documented pressure from the first rib, requiring a rib resection. The second developed a clot in her indwelling catheter while receiving chemotherapy for invasive breast cancer.
- Two participants were diagnosed with cancer without other events (pancreatic cancer with liver metastases diagnosed 2 months prior to the DVT; 1 woman diagnosed with T2N0M0 invasive breast cancer approximately 1 year prior to the DVT with no antineoplastic therapy documented in the CRF).
- One participant experienced 3 separate clotting events and was found to have protein S and protein C deficiency.

Overall, 16 of the 19 participants on placebo who experienced a DVT (84% of this group) had an associated event known to increase clotting risk.

Tamoxifen:

On the tamoxifen arm, 17 of the 30 participants with a DVT (57%) had a predisposing event, including surgery with general anesthesia, prolonged immobility associated with travel, and trauma. Other medical events included:

- Two women had a diagnosis of malignancy
- One woman was described in the CRF as having protein C deficiency, although protein C levels were measured while anticoagulated. It is unlikely that she has a true deficiency.
- One woman had a pelvic ultrasound performed at the time of her clot which demonstrated a 10-cm uterus and a 5.5-cm right ovarian cyst. The study was performed because she presented with a right-sided clot that extended from the calf through the thigh and into the pelvis.

Nineteen of the 30 participants (63%) with a DVT on tamoxifen had a predisposing event.

5. Overall, tamoxifen increased the risk of DVT compared to placebo. If the two subclavian clots are removed from the placebo group (related to extrinsic compression and a foreign body) and the clot that occurred on open-label tamoxifen is attributed to the tamoxifen arm, the numbers are 16 on placebo and 31 on tamoxifen. There is almost a doubling of risk with tamoxifen, even though women on placebo were more likely to have a predisposing factor for DVT.

6. The NSABP presented DVT by age of randomization (Table 59). The following table summarizes age at the time of event with annual hazard rates. Joseph Costantino, Ph.D., NSABP statistician, ran this analysis at our request: