

NM14185/10156/1B/003

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Patient 10156/436 (120mg tid), a 46-year-old obese white woman weighing 120.2 kg (BMI=41.6) at screening, was diagnosis after 37 days of double-blind treatment with breast cancer. (preferred term = neoplasm breast female)

The patient has a significant past medical history of fibrocystic breast disease. Six weeks prior to screening for this study the patient had a mammography which revealed a cyst. This history was not provided to the study site and the patient otherwise met entry criteria and was entered into the study. The patient thought the cyst was getting larger. On study day 41, the patient had a breast biopsy and it was found to be positive for a malignancy. Forty-six days after the start of double-blind treatment, a mastectomy was performed. The patient was to receive chemotherapy. The patient was discontinued from the study. The double-blind code was not broken.

The investigator considered this adverse event severe in intensity and unrelated to study drug administration.

Sponsor's Opinion:

BEST POSSIBLE

The diagnosis of breast cancer after only 37 days of study drug administration in a patient with a pre-existing breast mass is thought to be unrelated to study drug administration.

withdrawal at 46 days. Weight change = -3.5 kg.
diagnosis at 41 days. Biopsy of symptomatic mass.
treatment = mastectomy.

APPEARS THIS WAY ON ORIGINAL

NM14302/12894 [REDACTED] 1B/426

Patient 12894 [REDACTED] (120mg tid), a 51-year-old white female weighing 84.5 kg (BMI = 29.9) at screening, was diagnosed with infiltrating lobular carcinoma of the right breast on day 80 of double-blind treatment and subsequently discontinued double-blind treatment on day 92. (preferred term=neoplasm breast female)

At screening the patient presented with secondary diagnoses of arthralgia, treated with Motrin 800 mg as needed, migraine headaches, and allergies treated with Beconase as needed. There was no significant past medical history. The patient's weight at initiation of double-blind treatment was 77.7 kg (BMI = 27.5).

Three years prior to initiation of double-blind treatment, the patient had an abnormal mammogram which revealed fibrocystic breasts. She underwent gynecological exams at 18 months, which was normal and at 49 days prior to initiation of double-blind treatment which revealed the right breast to be abnormal and indicating changes consistent with fibrocystic breast disease. A routine mammogram 45 days prior to initiation of double-blind treatment confirmed fibrocystic changes, however, on day 55, of double-blind treatment new nodules were noted in the right breast, and on day 76 the patient underwent a right breast biopsy. On day 80 of double-blind treatment the patient was diagnosed with an infiltrating lobular carcinoma with perineural involvement. Study medication was discontinued on day 92 of double-blind treatment. Twenty-two days after discontinuing the study the patient underwent a right mastectomy and subsequent reconstructive surgery. Pathology confirmed the diagnosis of metastatic infiltrating lobular carcinoma of the breast with lymph node (greater than ten) involvement. On day 170 after discontinuing the study the patient completed her sixth cycle of chemotherapy (Adriamycin, cyclophosphamide). Future plans were for the patient to receive high dose cyclophosphamide and Thiotepa, with a subsequent peripheral blood stem cell transplantation. The patient was discontinued from the study.

The investigator considered this adverse event severe in intensity and unrelated to study drug administration.

Sponsor's Opinion:

[REDACTED] BEST POSSIBLE

Since this obese patient with a history of fibrocystic breast disease had taken randomized medication for 55 days prior to finding palpable nodules, the diagnosis of breast cancer is considered remotely related to study medication.

withdrewal at 92 days. weight change = +1.4 kg.
diagnosis at 80 days. biopsy of symptomatic mass.
treatment = mastectomy.

NM14302/12895 [REDACTED] 1B/440

Patient 12895 [REDACTED] (120mg tid), a 57-year-old obese white female weighing 86.7 kg (BMI=30.7) at screening was diagnosed with carcinoma in situ in the left breast after 189 days of double-blind treatment, (preferred term = breast carcinoma).

At screening the patient presented with a past medical history of a benign fatty tumor removed from her shoulder 11 years prior to study entry. Concomitant medications included Cardizem CD 30mg/day, and diazide 25mg taken every other day for hypertension. The patient had been postmenopausal for one year and was on hormone replacement therapy. She did not recall any known familial history of breast cancer. Her mammograms had always been negative for suspicious lesions until this occurrence. The patient's weight at initiation of double-blind treatment was 71 kg (BMI=25.2)

On approximately day 170 of double-blind treatment, a routine mammogram was performed and revealed a nodule in the left breast. At that time, the patient weighed 73.3 kg (BMI=26). On day 178 of double-blind treatment, a biopsy and excision of the left breast nodule and surrounding tissue was successfully done. The left breast nodule was diagnosed as a fibroadenoma, and the surrounding tissue showed microscopic foci of lobular carcinoma in situ in a background of proliferative fibrocystic changes with atypical lobular hyperplasia, duct hyperplasia, and adenosis. Microcalcifications were also detected. The tumor size was 2mm aggregated. The investigator was not informed of the malignancy prior to his receiving the biopsy report on day 356 of double-blind treatment. The patient's private physician did not consider this to be a serious event. Follow-up will consist of annual mammograms. The patient was discharged asymptomatic. The patient completed the study.

The investigator considered this adverse event to be moderate in intensity and unrelated to study drug administration.

Sponsor's Opinion:

The diagnosis of carcinoma in-situ in the left breast in a 57 year old obese female is not unexpected. Therefore, this event is considered remotely related to study medication.

withdrawal at 178 days. weight change = + 2.9 kg.
diagnosis at 178 days. routine mammogram
treatment = excisional biopsy.

94-01-75148-001 - DROP OUT - (Status report: FINAL)

507 (F)

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Patient 12671/1007 (120 mg tid), a 53-year-old obese white female weighing 75 kg (BMI = 30.9) at screening prematurely withdrew from the study on day 191 of double-blind treatment due to an adverse event lobular breast carcinoma (*preferred term: neoplasm breast female*).

At screening the patient presented with a past history of depression and ongoing fibrocystic mastopathy. Mammography and fine needle aspiration performed four months prior to screening did not show any significant lesion. A routine physical examination performed about two months after randomization (exact date not specified) indicated some changes which led to echography on day 196. The diagnosis of mastopathy with significant lesion was confirmed. Mammography and fine needle aspiration of the left breast were done. The results indicated a worsening of pre-existing fibrocystic mastopathy and a mastectomy was performed on day 198. Histopathological evaluations confirmed lobular breast carcinoma with metastases in 22 of the 23 axillary lymph nodes removed. The patient discontinued trial medication on day 191 with a body weight of 71.7 kg.

The investigator judged this adverse event severe in intensity and unrelated to trial treatment.

Sponsor's Opinion: Obese postmenopausal females over 50 with a history of fibrocystic breast disease have increased risk for developing breast cancer. This event is considered remotely related to test drug administration.

withdrawn at 191 days, weight change = -10.7 kg.
diagnosis at 198 days, routine physical exam.
treatment = mastectomy.

APPEARS THIS WAY ON ORIGINAL

94-01-75227-001 - DROP OUT - (Status report: FINAL) # 548 (F)

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Patient 12816 (120 mg tid), a 58-year-old obese white female weighing 92.8 kg (BMI = 34.1) at screening was hospitalized and discontinued test treatment on day 356 of double-blind treatment due to a malignant breast tumor diagnosed during routine mammography (preferred term: neoplasm breast female).

At the time of screening the patient presented with secondary diagnoses of hematuria and low back pain. According to the country specific medical procedure the patient had routine mammography on day 342 and a biopsy was performed which confirmed the diagnosis of breast cancer with malignant epithelia cells identified. No symptoms had been reported before or after the mammography. On day 357 the patient was admitted to the hospital and underwent partial breast reduction surgery with an excision of axillary lymphoid nodes on day 358. The histopathological diagnosis indicated low differentiated ductal breast cancer with no metastases observed in the lymph nodes. On day 359 the patient was discharged from the hospital with the perspective of radiation therapy. She discontinued test treatment on day 356. Her body weight at the time of the event was 79.9 kg.

The investigator considered this adverse event severe in intensity and unrelated to study drug administration.

Sponsor's Opinion: Obese postmenopausal females over age 50 have increased risk for developing breast cancer. This event is considered remotely related to study drug administration.

BEST POSSIBLE

withdrawal at 356 days. weight change = -12.6 kg.
diagnosis at 358 days. routine mammogram.
treatment = breast surgery + radiotherapy.

APPEARS THIS WAY ON ORIGINAL

NM14185/10160 [REDACTED] 1B/038 [REDACTED]

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Patient 10160/924 (120mg tid/60mg tid), a 61-year-old obese white female weighing 115.5 kg (BMI = 42.9) at screening, was diagnosed with breast cancer after 436 days of double-blind treatment. (preferred term = neoplasm breast female)

At the time of screening, the patient had a history of hypertension for 18 years prior to screening and for which she was taking lisinopril 20 mg for 1.5 years prior to screen. The patient also had arthritis for 2 years prior to screening and is taking oxaprozin 1200 mg which she started 161 days after the start of double-blind treatment. On study day 428, the patient had a routine mammogram which revealed a mass in her breast. On study day 436, a biopsy was performed and the mass was found to be malignant. The patient weighed 112.3 kg at this time. After 450 days since the start of double-blind treatment, the patient withdrew from the study. The double-blind code was not broken.

The investigator considered this adverse event severe in intensity and unrelated to study drug administration.

Sponsor's Opinion:

[REDACTED] BEST POSSIBLE [REDACTED]

It is not unexpected that a woman in her sixties would be diagnosed with breast cancer. Therefore, this adverse event is remotely related to study medication.

Withdrawal at 450 days. Weight change = -3.8 kg.
diagnosis at 436 days. routine mammogram.
treatment = unknown.

[REDACTED] APPEARS THIS WAY ON ORIGINAL [REDACTED]

0010

95-01-75233-001- DROP-OUT - (Status report: FINAL) # 554 (F)

Patient 12622 (120 mg tid), a 55-year-old obese white female weighing 118.1 kg (BMI = 39.9) at screening, prematurely withdrew from the study on day 461 of double-blind treatment due to a breast cancer (preferred term: neoplasm breast female).

At the time of screening the patient's relevant medical history included breast reduction surgery, a hysterectomy and abdominal wall fat reduction surgery. No secondary diagnosis was mentioned. Physical examinations at screening, baseline and day 370 showed no abnormalities other than scars from previous surgeries.

After about one year of randomized treatment the patient felt a small tumor on her right breast. Physical examination at that time indicated a small mass of one centimeter diameter which had been diagnosed as a lipoma. On day 460 she felt slight pain in her right breast and went to see her doctor. On day 461 a fine needle biopsy was performed and tissue was sent for pathological evaluation. On day 469 the results were positive and confirmed that the patient had developed breast cancer. At that time her body weight was 114.4 kg. She discontinued trial medication on day 461 and withdrew from the study. On day 475 a breast preserving operation was performed with lymphatic nodes resection. Histology indicated a malignant, not well differentiated, ductal breast carcinoma with a diameter of 2.5 cm and metastases were found in three nodes. The patient was prescribed radiotherapy for seven weeks as well as tamoxifen treatment.

The investigator considered this adverse event severe in intensity and unrelated to study medication.

Sponsor's Opinion: Obese postmenopausal females over the age of 50 have increased risk of breast cancer. The development of this event during the study is considered remotely related to study drug administration.

withdrew at 461 days. weight change = -2.6 kg.
diagnosis at 475 days. biopsy of symptomatic mass.
treatment = breast surgery + radiotherapy + tamoxifen.

NM14185/12051- /1B/050

*follow-up to original (New event; same number)

Patient 12051/1858 (120mg tid/120mg tid), a 52-year-old white female weighing 97.6 kg (BMI=36.3) at screening, was diagnosed with intraductal lobular carcinoma of the left breast. (preferred term = neoplasm breast female)

At the time of screening, the patient had no significant secondary diagnoses, nor was she receiving any medications routinely. The patient had several risk factors for breast cancer- 1) her mother had breast cancer 6 years ago 2) the patient started post-menopausal hormone replacement therapy in January 1995 3) the patient had no children. After 308 days of double-blind treatment, the patient developed an adverse event of leiomyomata uteri (fibroids) which lasted approximately 154 days at which point she had a hysterectomy. The patient had a routine yearly mammogram done 665 days after the start of double-blind treatment which revealed a mass on her left breast. The patient had a breast biopsy and a lumpectomy, which was done on an outpatient basis. After 678 days of double-blind treatment, the patient was diagnosed with intraductal lobular carcinoma of the left breast. Given the size and histology of the tumor and the age of the patient, it was recommended that the patient undergo adjuvant CMF (Cyclophosphamide, Methotrexate, Fluorouracil) chemotherapy as well as radiotherapy. Subsequently, this patient prematurely terminated from the study after 693 days of double-blind treatment. The double-blind code was not broken.

The investigator considered this adverse event severe in intensity and remotely related to study drug administration.

Sponsor's Opinion:

Development of breast carcinoma in the face of known risk factors is not unexpected. This event is considered remotely related to study medication.

withdrew at 693 days. weight change = -16.4 kg.
diagnosis at 678 days. routine mammogram.
treatment = breast surgery + radiotherapy + chemotherapy.

NM14161/12672/ [REDACTED] 1B/258

Patient 12672/0617 (120 mg tid), a 55-year-old obese white female weighing 103.3 Kg (BMI = 34.5) at screening, was diagnosed with carcinoma of the right breast following a routine mammogram on day 689 of double-blind treatment. (preferred term = neoplasm breast female)

At screening, the patient had a history of mild fibrocystic breasts since 1991, hypercholesterolemia since 1992, fibromyalgia since 1994 treated with ibuprofen, and a history of sinusitis since 1986. The patient was using estrogen replacement therapy Premarin and Provera since 1993.

Mammograms done in March of 1993 and 1994 showed no evidence of malignancy. Nodularity of both breasts was noted during a study required physical exam which was performed on day 360 of double-blind treatment. A routine mammogram was performed on day 689 of randomized treatment which revealed fibroglandular tissue on both breasts. A 5 mm density in the upper outer right breast appeared to be present on the mammogram. A biopsy resection was done on day 709 of double-blind treatment which demonstrated a resected specimen measuring 9x3x3 cm. in size, containing a 7x3x3 mm. tumor. This was read as a small focus of poorly differentiated infiltrating ductal carcinoma. There was a separate foci of intraductal cancer. The infiltrating tumor was well within the biopsy resection, with the intraductal tumor near the biopsy line. A chest x-ray was negative and a chemistry profile demonstrated normal liver functions. The CBC showed adequate counts for radiation therapy. The breast was irradiated with 4,680 cGy to the entire breast and a 1400 cGy boost to the area of tumor bed using electron beam. A decision was made not to administer any adjuvant therapy as the tumor was less than 1cm. The patient was comfortable with this decision. The patient continued study participation and completed the study on day 717. The double-blind code was not broken.

The investigator considered the adverse event was moderate in intensity and was unrelated to study drug.

APPEARS THIS WAY ON ORIGINAL

Sponsor's Opinion:

BEST POSSIBLE

Development of breast carcinoma in a postmenopausal female on estrogen replacement therapy with pre-existing breast nodularity is not unexpected. This event was considered remotely related to study drug administration.

withdrawal at 717 days, weight change = -0.1 Kg.
diagnosis at 709 days, routine mammogram
treatment = breast surgery & radiotherapy.

94-01-75140-001 - DROP OUT - (Status Report: FINAL) # 502 (F)

Patient 12818 (60 mg tid), a 47-year-old obese white female patient weighing 90.2 kg (BMI = 37.2) at screening prematurely withdrew from the study after 36 days of double-blind treatment because of right breast cancer diagnosis (preferred term: neoplasm breast female).

At the time of screening the patient presented with breast hypertrophy for which breast reduction surgery had been planned. On day 36 of double-blind treatment she was hospitalized for this surgery and discontinued study medication. During pre-surgical examinations breast cancer was diagnosed and a mastectomy was performed the following day. The post-operative diagnosis was ductal invasive cancer (T1n0m0). No other treatment was given and no metastases were found. The patient left the hospital on day 42. Her last body weight on day 30 was 85.5 kg.

The investigator considered this adverse event severe in intensity and unrelated to study treatment.

Sponsor's Opinion: This event is considered unrelated to study drug administration.

BEST POSSIBLE

Withdrawal at 36 days. weight change = -3.0 kg.
diagnosis at 37 days pre-surgical exam for
treatment = mastectomy breast reduction.

APPEARS THIS WAY ON ORIGINAL

95-01-75267-001 - DROP OUT (Status report: FINAL) #582 (F)

Patient 12820 (placebo), a 53-year-old obese white female weighing 102.0 kg (BMI = 39.8) at screening prematurely withdrew from the study on day 568 of double-blind treatment because of intraductal carcinoma of left breast (preferred term: neoplasm breast female).

At the time of screening the patient reported a history record of right breast biopsy, hysterectomy, and laparoscopic biopsy of the right ovary several years prior. She also presented with secondary diagnoses of fibrous mastopathy on both breasts. The patient received Estradiol (0.5 mg/day) for prophylaxis during the study. On day 443 of double blind treatment a routine mammogram showed diffuse macrocalcification in the left breast, and it was biopsied. The biopsy showed intraductal carcinoma of the left breast. The patient was hospitalized for left breast mastectomy on day 557 and resection was done the day after. No metastases were reported. The patient was discharged from the hospital the following day with no further treatment indicated. She discontinued test drug treatment on day 568 when she attended her last visit with a weight of 98.3 kg. Her weight before surgery was 99.5 kg.

The investigator judged this adverse event severe in intensity and unrelated to study medication.

Sponsor's Opinion: This event is considered remotely related to study drug administration.

BEST POSSIBLE

withdrawal at 568 days, weight change = -0.8 kg;
diagnosis at 443 days, routine mammogram.
treatment = mastectomy.

APPEARS THIS WAY ON ORIGINAL

From Telephone Survey

Xenical® (orlistat)
Breast Cancer Survey Report



Resubmission of:
NDA 20-766 / Section 8/10
Clinical and Statistical

Appendix 5. Listing of New Cases of Breast Cancer

Protocol	Center	Patient Treatment	Cancer Type	Number of Days from Random to Diagnosis	Result	Mammogram Comment
BP04119C	B07571	CD17 120(2 years)	CARCINOMA OF BREAST	1462	abnormal	BREAST CARCINOMA
BP04185	10159 10163	AB06 120(year 1)/60(year 2) SP070 Placebo(2 years)	BREAST CANCER BREAST CA R	1520 412	abnormal normal	SPOT/BT/BIOPSY/CANCEROS

Completed 816 days
diagnosis at 1462 days
treatment = breast surgery
55 years old

Completed 707 days
diagnosis at 1520 days
treatment = breast surgery
51 years old

Withdrawn at 412 days
diagnosis at 292 days
treatment = surgery
59 years old

ATTACHMENT 1