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GENERIC DRUG NAME / COMPOUND NUMBER: Bazedoxifene acetate / PF-05208749 (WAY-140424)

PROTOCOL NO.: 3068A1-301-WW (B1781001)

PROTOCOL TITLE: Fracture Incidence Reduction and Safety of TSE-424 (Bazedoxifene Acetate) Compared to Placebo and Raloxifene in Osteoporotic Postmenopausal Women

Study Centers: A total of 206 sites participated in the core study; 151 sites participated in study Extension I; 92 sites participated in study Extension II. The study was conducted at 252 centers: US (128 centers); Canada (15 centers); Russian Federation (10 centers); Poland (8 centers); Bulgaria (7 centers); Australia, Brazil, Croatia, South Africa (6 centers each); Finland, Spain, Netherlands (5 centers each); Norway, Belgium, Romania (4 centers each); New Zealand, Denmark, Mexico, Italy, Slovak Republic, Hungary, France (3 centers each); Estonia, Lithuania, Germany (2 centers each); Hong Kong, Argentina, Chile, Austria, and Greece (1 centers each).

Study Initiation and Final Completion Dates: 09 October 2001 to 30 September 2010

Phase of Development: Phase 3

Study Objectives:

Primary Objectives:

- To evaluate the efficacy of bazedoxifene acetate 20 mg and bazedoxifene acetate 40 mg in comparison to placebo in reduction of new vertebral fractures in osteoporotic postmenopausal women after 36 months, after 60 months of therapy and after 84 months of therapy.

- To compare the safety profile of bazedoxifene acetate to placebo.

Secondary Objectives:

- For the Core Study: To compare bazedoxifene acetate to placebo and raloxifene after 36 months of therapy on breast cancer incidence, clinical vertebral fractures, worsening vertebral fractures, non-vertebral fractures, height changes, bone mineral density (BMD) of lumbar spine and hip, serum bone markers, the impact on lipid parameters and quality of life, endometrial assessment, bone histomorphometry and the effect on cardiac repolarization.

- A comparison of raloxifene 60 mg to placebo in reducing the incidence of new vertebral fractures and other fractures after 36 months of treatment was also conducted.

- For the Study Extensions I and II: To compare bazedoxifene acetate to placebo after 60 and 84 months of therapy on breast cancer incidence, clinical vertebral fractures, worsening vertebral fractures, nonvertebral fractures, height changes, BMD of lumbar spine and hip, endometrial assessment, serum bone markers (long term bone markers substudy only) and bone histomorphometry (bone histomorphometry substudy II only). Comparisons of bazedoxifene acetate to raloxifene were to be explored at month 48, provided that data for a satisfactory number of subjects in raloxifene arm was available at that time point.

METHODS

Study Design: This was a 4-arm, outpatient, multicenter, double-blind, randomized, placebo- and raloxifene-controlled Phase 3 trial of postmenopausal women with osteoporosis, conducted globally.

The core study was conducted from enrollment to the end of Year 3; study Extension I was a 2-year extension of the core study, from the end of Year 3 until the end of Year 5; the results of the core study and study Extension I are presented elsewhere. Extension II was an additional 2-year extension of the study, from the end of Year 5 (Month 60) until the end of Year 7 (Month 84).

Subjects who were eligible and willing to participate in Extension II signed a new informed consent form (ICF) and continued to receive bazedoxifene (or placebo) at the same dose they received in Extension I. Because the subjects randomized to the bazedoxifene 40 mg treatment group had their bazedoxifene dose reduced to 20 mg during the course of the Extension I, the proportion of subjects was approximately 2:1 in the active (bazedoxifene 20 mg) and placebo groups, respectively, in Extension II of the study.

In addition, an observational substudy (OSS) was conducted to compare changes in BMD values after discontinuation of therapy with BMD values observed on therapy. A total of 200 subjects who discontinued the test article and did not meet the visit window for Visit 13 (Month 60) specified for Extension II signed a new ICF and participated in the OSS. These subjects were to be followed on the normal visit schedule of Extension II but were not dispensed test article. Subjects in the OSS of Extension II continued to receive the same amount of calcium/vitamin D supplements as those subjects also receiving test article (bazedoxifene or placebo). The subject flowcharts are summarized in Table 1, Table 2 and Table 3.

Table 1. Subject Flowchart (Core Study)

General Study VisitNumber Bone Substudy/Endometrial Safety	**Screening**	**Baseline**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Posttherapy**[a]
Study schedule visit[b,c] **Month**			**0**	**3**	**6**	**9**	**12**	**18**	**24**	**30**	**36**	**(15 Days)**
Interval flexibility for visits in days				**±13**	**±13**	**±13**	**±13**	**±13**	**±13**	**±13**	**-28**	
Signed and dated informed consent	X											
Medical history and gynecologic history	X											
Assessment of prior medication	X[d]	X										
Height[e]	XXX						XXX		XXX		XXX	
Weight[f], blood pressure[g], pulse rate	X		X	X	X	X	X	X	X	X	X	
Physical examination	X[h]	X[h]		X	X	X	X	X	X	X	X	
Gynecological/pelvic/breast examination		X					X		X		X	
ECG		X										
Assessments by central laboratories[c]												
Biochemical bone markers[i]		X		X	X		X					
Additional serum markers[j]		X		X	X		X	X	X	X	X	
DXA of lumbar spine and total hip[k]	XX				X		X	X	XX			
Vertebral radiography[l]	X				X		X		X		X	
EMB (End Substudy only)		X							X			
Lipids[m]		X			X		X		X		X	
Coagulation parameters (Canada only)		X										
25-hydroxyvitamin D, PTH		X					X		X		X	
Laboratory safety screen		X		X	X		X	X	X	X	X	
Cervical cytology smear[n]		X							X			
ECG (ECG Substudy only)[o]							X.....	……	……..	……..	X	
Bone biopsy (Bone Substudy only)[p]									X[q]	X[q]	X[q]	
Assessments by local laboratories[c]												

Table 1. Subject Flowchart (Core Study)

General Study VisitNumber Bone Substudy/Endometrial Safety	Screening	Baseline	1	2	3	4	5	6	7	8	9	Posttherapy[a]
Mammography[r]		X					X		X		X	
TVU (End Substudy only)		X					X		X			
Urine dipstick		X		X	X		X	X	X	X	X	
Quality of life questionnaires[s]		X					X		X			
Dispense diary card			X	X	X	X	X	X	X	X		
Review diary card				X	X	X	X	X	X	X	X	
Adverse event reporting		X	X	X	X	X	X	X	X	X	X	X
Concomitant medication assessment			X	X	X	X	X	X	X	X	X	
Telephone call follow-up												X
Dispense test article			X	X	X	X	X	X	X	X		
Collect and inspect test article				X	X	X	X	X	X	X	X	
Treatment period			X	X	X	X	X	X	X	X	X	
Follow-up period												X

BMI = basal metabolic index; BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry ECG = electrocardiogram; EMB = endometrial biopsy; EuroQoL = European Quality of Life; EU = European Union; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; PTH = parathyroid hormone; QUALEFFO = Quality of Life Questionnaire of the European Foundation for Osteoporosis; SERMS = selective estrogen receptor modulator; TVU = transvaginal ultrasonography; TC = total cholesterol; TG = total cholesterol; US = United States; WHQ = Women's Health Questionnaire.

a. Hot flushes were included as adverse events. All adverse events that occurred after signing the informed consent form must be recorded.
b. For completers or subjects withdrawn from the study, a posttherapy follow-up phone call were made 15 days following the last dose of test article (whenever that occurs for a given subject) to document and follow-up on any adverse event that persisted or began during the 15-day follow-up period.
c. For subjects who withdraw from the study, please refer to the section entitled Safety Evaluation for timing of various exams and procedures.
d. Subjects had not used any of the following drugs within 6 months of screening: estrogen, progestin or androgen-containing medications, calcitonin, bisphosphonate, parathyroid hormone, SERMs, cholecalciferol and antiseizure drugs. Also subjects must had not used systemic fluoride (other than topical dental) for longer than 1 month within 6 months before screening, systemic corticosteroids at doses ≥ 10 mg of prednisone, for periods longer than 10 days within 6 months before screening or any other investigational drug or participation in any other clinical research study during screening.
e. Three measurements were performed at each specified visit using standardized Harpenden stadiometer. Height was based on middle stadiometer reading.
f. Subjects must had a BMI ≤ 35 (weight [kg]/[height {m}]2) using the Nomograph for BMI.
g. Blood pressure was taken after the subject had been in the sitting position for 5 minutes. At Screening, the blood pressure should not be equal or greater than 180 mm Hg systolic or 90 mm Hg diastolic.
h. If necessary for scheduling, the screening physical examination was performed at the Baseline visit.
i. These were collected at Baseline and at Months 3, 6, and 12, or when subjects withdraw before 12 months and >3 months had elapsed since the last assessment.
j. In EU and South Africa only, an additional blood sample was also collected in case of necessity for future analysis of new parameters.

Table 1. Subject Flowchart (Core Study)

General Study VisitNumber Bone Substudy/Endometrial Safety	Screening	Baseline	1	2	3	4	5	6	7	8	9	Posttherapy[a]

k. In US only, Subjects must had a BMD T-score at the femoral neck or lumbar spine between ‑2.5 and ‑4.0 (inclusive) without the presence of a vertebral fracture or lumbar spine and femoral neck BMD T-score no worse than -4.0 and 1 mild asymptomatic vertebral fracture for inclusion. In non-US countries, Subjects must had a BMD T-score at the femoral neck or lumbar spine of ‑2.5 or worse without the presence of a vertebral fracture or lumbar spine and femoral neck BMD T-score no worse than -3.5 along with 1-5 mild to moderate asymptomatic vertebral fractures for inclusion. A central laboratory evaluated BMD and vertebral radiography assessments to determine which subjects meet these eligibility criteria. Two (2) DXA measurements were performed at both the lumbar spine and hip at Screening, and 24 months, or when a subject withdraws before 24 months and > 6 months had elapsed since the last measurement. When 2 scans were performed, the subject must be removed completely from the table and repositioned before the second scan was done. Diskettes for prior DXA scans performed within approximately 75 days of screening had to be submitted to the central radiology laboratory for assessment of eligibility, provided they contain all necessary assessments and were performed by the same central laboratory-certified technician using the same DXA machine at the DXA facility. Reports alone were not accepted for eligibility consideration.

l. At Screening both anteroposterior and lateral radiographs of the thoracic and lumbar spine were done; other radiographs were lateral. Radiographs were performed at Screening and at 6, 12, 24 and 36 months, or if a subject withdraws and > 6 months had elapsed since the last radiograph.
Prior vertebral x-rays performed with approximately 75 days of screening may be submitted to the central radiographic laboratory for assessment of eligibility, provided the films contain all necessary assessments as outlined within the protocol. Reports alone were not to be accepted for eligibility consideration.

m. The following lipid assessments were made: TC, LDL-C, HDL-C, HDL2-C, HDL3-C, and TG. An 8-hour fast was required prior to collection of blood for lipid assessment. These were collected at Baseline, 6, 12, 24 and 36 months, or if subjects withdraw and > 3 months had elapsed in Year 1, or 6 months had elapsed since the last assessment in Years 2 or 3.

n. A cervical cytology smear was done on non-hysterectomized subjects only.

o. For subjects in Electrocardiogram substudy, Subjects had signed the Electrocardiogram Substudy informed consent form. At any 1 visit, a 1 time single set of 3 standardized 12-lead serial ECGs were be obtained at 2 minute intervals including rhythm strips from lead II. Subjects must be compliant for 5 of 7 days prior to obtaining the serial ECG; verified by test article diary card. Test article must have been taken with food no sooner than 1 but no more than 4 hours prior to ECG testing. The baseline and on-therapy ECGs were processed and analyzed by a centralized ECG laboratory. Readers of ECGs were blinded to treatment.

p. Only for subjects who did not participate in the Study Extension.

q. Bone biopsy had been done at Visit 7; however, it is considered acceptable to have the bone biopsy done at Visit 8 or exceptionally at Visit 9.

r. Mammograms were obtained at 12, 24 and 36 months or if a subject withdraws and > 9 months have elapsed since the last assessment.

s. Three (3) questionnaires were administered including the WHQ, QUALEFFO, and EuroQoL.

Table 2. Subject Flowchart (Study Extension I)

Study Procedures	**Month 36**	**Month 42**	**Month 48**	**Month 54**	**Month 60**	**Month 60.5**
Study Interval	**Core Study**	**Study Extension I**				**Follow-Up**
Visit Number	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**PostTherapy**
Interval Flexibility for Visits in Days	**-28**	**±13**	**±13**	**±13**	**-28**	
Signed and dated informed consent	X					
Height[a]	XXX		XXX		XXX	
Weight, blood pressure[b], pulse rate	X	X	X	X	X	
Physical examination	X		X		X	
Gynecological/pelvic/breast examination	X		X		X	
Assessments by central laboratories						
Serum Bone Markers[c] (Substudy only)	X				X	
DXA of lumbar spine and total hip[d]	X		X		X	
Vertebral radiography[e]	X		X		X	
Laboratory safety screen	X		X		X	
EMB (End of Substudy only)					X	
Bone biopsy (Bone Substudy II only)					X	
Cervical cytology smear[f]			X			
Assessments by local laboratories						
Mammography[g]			X			
TVU (End of Substudy only)					X	
Urine dipstick	X		X		X	
Dispense diary card	X	X	X	X		
Review diary card	X	X	X	X	X	
Adverse event reporting[h]	X	X	X	X	X	X
Concomitant medication assessment	X	X	X	X	X	
Telephone call follow-up[i]						X
Dispense test article	X	X	X	X		
Prescribe additional treatment if needed[j]	X	X	X	X		
Collect and inspect test article	X	X	X	X	X	

BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; EMB = endometrial substudy; TVU = transvaginal ultrasonography.

a. Three measurements were performed at each specified visit using standardized Harpenden stadiometer. Height was based on middle stadiometer reading.
b. Blood pressure was taken after the subject had been in the sitting position for 5 minutes.
c. These were collected at Months 36 and 60, or when a subject withdraws and > 12 months have elapsed since the last measurement, in a subset of 600 randomly allocated subjects.

Table 2. Subject Flowchart (Study Extension I)

Study Procedures	Month 36	Month 42	Month 48	Month 54	Month 60	Month 60.5
Study Interval	Core Study	Study Extension I				Follow-Up
Visit Number	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	PostTherapy
Interval Flexibility for Visits in Days	-28	±13	±13	±13	-28	

d. A central laboratory had evaluated BMD assessments. The DXA measurements were performed at both the lumbar spine and hip at 36, 48 and 60 months, or when a subject withdraws and > 9 months had elapsed since the last measurement.
e. A central laboratory had evaluated BMD and vertebral radiography assessments. Lateral radiographs of the thoracic and lumbar spine were taken at 36, 48, and 60 months, or if a subject withdraws and > 9 months had elapsed since the last radiograph.
f. A cervical cytology smear was done on non-hysterectomized subjects only.
g. Mammograms were obtained at 36, 48 and 60 months or if a subject withdraws and more than 9 months had elapsed since the last assessment.
h. Hot flushes were included as adverse events.
i. For completers or subjects withdrawn from the study, a posttherapy follow-up phone had been made approximately 15 days following the last dose of test article (whenever that occurs for a given subject) to document and follow-up on any study event that persisted or began during the 15-day follow-up period.
j. In case at least one osteoporosis related fracture was reported during the Core Study, a bisphosphonate was prescribed at Visit 9 (or calcitonin in case of known poor tolerance to bisphosphonates). In case of 7% or greater decrease in BMD at any skeletal site compared to baseline of the Core Study, confirmed by a second DXA of the same skeletal site performed within 3 months (mean BMD loss of 7% or greater), and/or at least one osteoporosis related fracture during the Study Extension, additional treatment was prescribed with a bisphosphonate. Calcitonin was prescribed as an alternative in case of poor tolerance to bisphosphonates.

Table 3. Subject Flowchart (Study Extension II)

Study Procedures	**Month 60**	**Month 66**	**Month 72**	**Month 78**	**Month 84**	**Month 84.5**
Study Interval	**Study Extension I**	**Study Extension II**				**Follow-Up**
Visit Number	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**	**Visit 17**	**Post-Therapy**
Interval Flexibility for Visits in Days	**±13**	**±13**	**±13**	**±13**	**-28**	
Signed and dated informed consent	X					
Height[a]	XXX		XXX		XXX	
Weight, blood pressure[b], pulse rate	X	X	X	X	X	
Physical examination	X		X		X	
Gynecological/pelvic/breast examination	X		X		X	
Assessments by central laboratories						
Serum Bone Markers[c] (Substudy only)	X		X		X	
PTH and 25 Hydroxy-Vitamin D (long term bone marker substudy only)	X		X		X	
Lipids (TC, LDL, HDL, TG)	X				X	
DXA of lumbar spine and total hip[d]	X	X[e]	X		X	
Vertebral radiography[f]	X		X		X	
Laboratory safety screen	X		X		X	
Cervical cytology smear[g]			X			
Assessments by local laboratories						
Mammography[h]	X		X		X	
TVU (End of Substudy only)	X				X	
Urine dipstick	X		X		X	
Dispense diary card	X	X	X	X		
Review diary card	X	X	X	X	X	
Adverse event reporting[i]	X[j]	X	X	X	X	X
Concomitant medication assessment	X[j]	X	X	X	X	
Telephone call follow-up[k]						X
Dispense test article[l]	X	X	X	X		
Prescribe/dispense calcium and vit D supplementation	X	X	X	X		
Prescribe additional treatment, if needed[m]	X	X	X	X		
Collect and inspect test article	X	X	X	X	X	

BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; HDL = high density lipoprotein; LDL = low density lipoprotein cholesterol; PTH =

Table 3. Subject Flowchart (Study Extension II)

Study Procedures	Month 60	Month 66	Month 72	Month 78	Month 84	Month 84.5
Study Interval	Study Extension I	Study Extension II				Follow-Up
Visit Number	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Post-Therapy
Interval Flexibility for Visits in Days	±13	±13	±13	±13	-28	

parathyroid hormone; TVU = transvaginal ultrasonography; TC = total cholesterol; TG = total cholesterol; Vit = vitamin.

a. Three measurements were performed at each specified visit using standardized Harpenden stadiometer. Height was based on middle stadiometer reading.
b. Blood pressure was taken after the subject had been in the sitting position for 5 minutes.
c. These were collected at Month 84, or when a subject withdraws and > 12 months had elapsed since the last measurement, in a subset of long term bone marker substudy.
d. A central laboratory had evaluated BMD assessments. The DXA measurements were performed at both the lumbar spine and hip at 72 and 84 months, or when a subject withdraws and > 9 months had elapsed since the last measurement.
e. For subjects in the observational substudy, a DXA was performed if > 3 months had elapsed from visit 13.
f. A central laboratory had evaluated BMD and vertebral radiography assessments. Lateral radiographs of the thoracic and lumbar spine were taken at 72, and 84 months, or if a subject withdraws and > 9 months had elapsed since the last radiograph.
g. A cervical cytology smear was done on non-hysterectomized subjects only.
h. Mammograms was obtained at 72 and 84 months or if a subject withdraws and > 9 months had elapsed since the last assessment.
i. Hot flushes were included as adverse events.
j. For subjects in the observational substudy, adverse events and concomitant medications were continued to be collected until the subject signs the consent for the substudy.
k. For completers or subjects withdrawn from the study, a posttherapy follow-up phone call was made approximately 15 days following the last dose of test article (whenever that occurs for a given subject) to document and follow-up on any study event that persisted or began during the 15-day follow-up period.
l. Subjects in the observational substudy did not have test article dispensed.
m. In case at least one osteoporosis related fracture was reported during the Extension Study I, a bisphosphonate was prescribed at Visit 13 (or calcitonin in case of known poor tolerance to bisphosphonates). In case of 7% or greater decrease in BMD at any skeletal site compared to baseline of the Extension Study I, confirmed by a second DXA of the same skeletal site performed within 3 months (mean BMD loss of 7% or greater), and/or at least one osteoporosis related fracture during the Study Extension II, additional treatment was prescribed with a bisphosphonate. Calcitonin was prescribed as an alternative in case of poor tolerance to bisphosphonates.

Number of Subjects (Planned and Analyzed): It was planned to enroll approximately 6,600 subjects (1,650 subjects per arm) over 18 months in approximately 206 centers. A total of 26,749 subjects were screened for enrollment in the core study; 19,140 subjects did not meet the inclusion and exclusion requirements at the Screening assessment. The remaining 7609 subjects were randomly assigned to 4 treatment groups at the beginning of the core study: bazedoxifene 20 mg, bazedoxifene 40 mg, raloxifene 60 mg, and placebo. A total of 117 randomized subjects never received test article, mostly because they withdrew consent, and thus were not included in any analyses. Therefore, a total of 7492 subjects formed the basis of the efficacy and safety analysis populations of the core study. These 7492 subjects were randomized as follows: 1886 in the bazedoxifene 20 mg treatment group, 1872 in the bazedoxifene 40 mg treatment group, 1885 in the placebo group, and 1849 subjects in the raloxifene 60 mg group. The raloxifene subjects were withdrawn from the study after the last subject had completed the core study and the database for the 3-year analysis was finalized.

During study Extension I, the subjects in the bazedoxifene 40 mg treatment group had their bazedoxifene dose reduced to bazedoxifene 20 mg, and this was subsequently called the bazedoxifene 40/20 mg treatment group. Upon entry into Extension II, all these subjects were receiving bazedoxifene 20 mg. Therefore, comparisons in Extension II were made between bazedoxifene 20 mg (subjects randomized to bazedoxifene 20 mg at the beginning of the study) and placebo, as well as the bazedoxifene 20 mg and the bazedoxifene 40/20 mg treatments (all subjects who received bazedoxifene combined) and placebo.

A total of 1732/5643 (30.7%) subjects continued in Extension II, and of these, 1530 (27.1%) received at least 1 dose of test article: 499/1886 (26.5%) subjects in the bazedoxifene 20 mg treatment group, 512/1872 (27.4%) in the bazedoxifene 40/20 mg treatment group (for a total of 1011/3758 [26.9%] subjects in the bazedoxifene combined group [all bazedoxifene-treated subjects], and 519/1885 (27.5%) in the placebo group.

Diagnosis and Main Criteria for Inclusion: Subjects were generally healthy, postmenopausal women with osteoporosis from 55 to 85 years of age (non-USA countries) or from 55 to 80 years of age (USA only) that were at least 2 years postmenopausal (≥2 years since last menopause, >60 years old, or surgically sterile.) Osteoporotic subjects without vertebral fracture who met BMD criteria or osteoporotic subjects with vertebral fracture were included in the study. Subjects with vasomotor symptoms that required treatment and who had a history or suspected cancer of the breast or active or past history of venous thromboembolic events were excluded from the study.

Study Treatment:

Core Study/Extension I: Bazedoxifene 20 mg capsules, bazedoxifene 40 mg capsules, or placebo capsules to be taken orally once daily. During the core study, subjects randomized to the raloxifene arm took oral capsules containing raloxifene 60 mg in the same manner as bazedoxifene. In addition, each subject was prescribed 1000 to 1200 mg of calcium and 400 to 800 IU of vitamin D daily to be sourced locally. During Extension I, the subjects in the bazedoxifene 40 mg treatment group had their bazedoxifene dose reduced to bazedoxifene 20 mg.

Extension II: Bazedoxifene 20 mg capsules or placebo capsules to be taken orally once daily; prescribed 1000 to 1200 mg of calcium and 400 to 800 IU of vitamin D daily.

OSS: No test article (bazedoxifene or placebo) was used during Years 6 and 7 for subjects in the OSS; prescribed 1000 to 1200 mg of calcium and 400 to 800 IU of vitamin D daily.

Efficacy Endpoints:

Primary Endpoint:

- The incidence of new radiographically confirmed vertebral fractures

Secondary Endpoints:

- Incidence of new breast cancer
- Number of non-verebral fractures
- Incidence of clinical and worsening vertebral fractures
- Percentage changes from baseline in BMD of the lumbar spine, total hip, femoral neck, and femoral trochanter
- Changes from baseline in height
- Changes from baseline in serum bone markers C-telopeptide (CTx) and osteocalcin (long-term bone markers substudy).

Safety Evaluations: Safety was monitored by means of physical examinations (including blood pressure, pulse, body weight, and assessment of the skin, head, eyes, ears, nose, throat, mouth, neck, chest, heart, lungs, abdomen, extremities, and nervous system), gynecologic examinations (including pelvic and breast examinations), mammography, cervical cytology smears (from non-hysterectomized women), clinical laboratory determinations, vertebral radiographic assessments, and recording of adverse events. In addition, for subjects enrolled in the endometrial safety substudy, and for subjects in the safety population when clinically indicated, transvaginal ultrasonography (TVU) to determine endometrial thickness, ovarian volume, and presence and size of ovarian cysts and endometrial biopsies were performed. For more accurate assessment of the nature and proper classification of non-vertebral fractures, breast cancer, cerebrovascular events (CVEs), and venous thromboembolic events (VTEs), independent blinded adjudication boards were formed. The primary objective of these adjudication boards was to ensure a consistent, accurate, and unbiased assessment of clinically important events. The adjudication boards continued through Extension II for breast cancer, CVEs, and VTEs. Non-vertebral fractures were not adjudicated during Extension II.

Statistical Methods: The modified ITT population of SP1 for each efficacy scale includes the subpopulation of SP1 consisting of subjects with a baseline and at least 1 postbaseline assessment. Similarly the modified ITT subpopulation of SP2 consists of subjects having a

baseline assessment and at least 1 assessment during Extension II. Efficacy data measured after Year 5 for the subjects who entered the OSS were excluded. Three safety populations were defined as follows:

- Safety Population 1 (SP1): All subjects randomized to the bazedoxifene treatment or placebo groups and who received at least 1 dose of study medication. Safety variables measured after Month 60 for the subjects who entered the OSS were excluded from the analyses.

- Safety Population 2 (SP2): All subjects in SP1 who signed the ICF to participate and enroll in Extension II and who received at least 1 dose of blinded test article in Extension II. Subjects from the OSS did not receive test article and are therefore not included in this safety population.

- Observational Substudy Safety (OSS): All subjects in SP1 who signed the ICF to enter the OSS after Year 5. Note that no test article (bazedoxifene or placebo) was administered during Years 6 and 7 for subjects in the OSS. Efficacy data measured after Year 5 for the subjects who entered the OSS were excluded from all of the above populations.

All statistical testing was done at the alpha =0.05, without any adjustment for multiple comparisons.

Efficacy Analysis:

New Incident Vertebral Fracture Assessment

The assessment of incidence of new vertebral fracture was based on the radiographically confirmed fractures. For new vertebral fractures, the primary population for analysis was a subpopulation of SP1 consisting of subjects with a baseline and at least 1 postbaseline assessment. It is referred to as the modified intent-to-treat (mITT) population of SP1. The cumulative incidence of new vertebral fractures ([Thoracic4] T4 to [Lumbar4] L4) between Baseline and Month 84 utilized Kaplan-Meier estimates and 95% confidence intervals (CIs). Between-group comparisons were made using the stratified log-rank test, and hazard ratio (HR) estimates were made using the Cox proportional hazard regression. All analyses of the incidence of new vertebral fracture were repeated, censoring subjects at the time of the first use of bone active agents. Of note, the comparison of study arms by the stratified log-rank test was a comparison of survival experience, stratified by Baseline fracture status, and was not be construed as a direct comparison of the (unstratified) Kaplan-Meier estimates.

Non-vertebral Fractures

Non-vertebral fractures were analyzed in the SP1 population and in a high-risk population (all randomized subjects having a femoral neck T-score ≤-3 at Baseline or the presence of at least 1 moderate vertebral fracture or multiple vertebral fractures at Baseline); this population was defined based on exploratory analysis in the 3-year core study. The analysis included all on-therapy (postbaseline and within 60 days of last medication intake) osteoporosis related non-vertebral fractures (ie, all non-vertebral fractures excluding pathologic and any fractures of the face, skull, toes, fingers, and elbow) as well as fractures of the hip and wrist.

Kaplan-Meier estimates and 95% CIs of the incidence of non-vertebral fractures through 84 months were calculated for the bazedoxifene 20 mg and bazedoxifene combined treatment groups and the placebo group, censored by early discontinuation and the switch to the OSS. Cox regression was utilized to estimate HRs and 95% CIs at each indicated time point. The bazedoxifene treatment groups were compared with the placebo group using the log-rank test.

Clinical and Worsening Vertebral Fractures

A clinical vertebral fracture was defined as any new or worsening vertebral fracture presenting because of back pain suggestive of fracture. Clinical vertebral fractures were to have been verified with radiographic assessment using both the semiquantitative and quantitative morphometric assessment approaches. Kaplan-Meier estimates and 95% CIs of the incidence of clinical vertebral fractures through 84 months were calculated for the bazedoxifene 20 mg and bazedoxifene combined treatment groups and the placebo group.

An unadjusted for exposure incidence was also provided. Between-group comparisons were performed using the log-rank test. The percentage of clinical vertebral fractures by Baseline status fracture and treatment arm was also provided. A worsening vertebral fracture was defined as a decrease in anterior, middle, or posterior vertebral height of ≥20% and ≥4 mm as evaluated by quantitative morphometric assessment or an increase in grade of at least 1 as rated by a radiologist using the semiquantitative rating in a vertebra that was already fractured at baseline. Worsening vertebral fractures were presented by number and percentage by year.

Bone Mineral Density Measurement

For BMD and serum bone markers, the primary population for analysis was a subpopulation of SP2 that consisted of subjects who had a valid BMD evaluation at Baseline and at least 1 valid on-therapy BMD evaluation during Extension II (referred to as the mITT population of SP2). The percent change from baseline of BMD was analyzed by analysis of covariance (ANCOVA). Treatment, prevalent vertebral status fracture, and geographical region were included as factors in the model and Baseline BMD was a covariate. The ANCOVA model was also utilized for study completers only (the subset of the population for the BMD analysis having a valid Month 84 assessment); the same analysis was repeated, deleting the observations after the first intake of bone active agent.

Subject Height

Change in height from Baseline through Month 84 was analyzed by ANCOVA. Treatment, baseline height, and geographical region were included in the ANCOVA model. The ANCOVA model was repeated for study completers.

Serum Bone Marker

The metabolic bone markers serum osteocalcin and serum type I collagen CTx were assessed (along with 25-hydroxyvitamin D and parathyroid hormone for subjects participating in the long-term bone marker substudy, which included all subjects who participated in Extension II

and had a serum bone marker assessment at Month 60 and at another time point in Extension II. The ranked percent change from Baseline of serum CTx and serum osteocalcin was analyzed using an ANCOVA on ranked data, with the ranked percentage change from Baseline as dependent variable, treatment as factor and baseline as covariate. Within group comparisons were based on the ranked percent change from Baseline by applying the Wilcoxon signed rank test. The ANCOVA model was repeated for study completers only (sub-set of the bone marker population analysis having a valid Month 84 assessment). The same ANCOVA model also was repeated deleting any BMD assessments after first intake of the bone active agent.

Breast Cancer:

The incidence of breast cancer was defined as the number of subjects with breast cancer diagnosis during active therapy or in the posttherapy phase, divided by the number of subjects in the SP1 population, and was calculated for the bazedoxifene 20 mg and bazedoxifene combined treatment groups and the placebo group after 7 years of therapy. The reported rate was re-scaled to reflect cases per 1000 woman-years of follow-up. Relative risk and excess risk compared with the placebo group were provided together with 95% CIs.

Safety Analyses

Analyses of safety data were carried out using the safety populations SP1 and SP2. For adverse events, 1 set of adverse event reports in SP1 was generated which provided cumulative 7-year data but excluding years 6 and 7 data in the OSS population. For SP2, 2 sets of adverse event reports were generated: cumulative 7 year data and data for Extension II (Years 6 and 7). The adjudicated VTE and CVEs, as well as deaths, were analyzed on SP1. For the purpose of these summaries, exposure was defined as the number of days from first test article taken to the last dose of study medication. A modified definition of exposure was also employed for the death analysis. Exposure was defined from the first test article intake to study termination for all subjects. This definition allowed for all reported cases to be included in the numerator. Events observed during Years 6 and 7 in the OSS population were included in these summaries. Estimated rates per 1000 woman-years and 95% CIs were provided for each treatment group for selected time intervals: cumulative rates over the periods 0 to 3 years, 0 to 5 years, and 0 to 7 years as well as by year through Year 7. Relative risk (ratio) and excess risk (difference) estimates and 95% CI comparing each bazedoxifene group with the placebo group were also provided. Between-group comparisons of event first occurrence utilized the log-rank test. The 95% CI for the rate per 1000 woman-years was obtained using the exact Poisson method, 95% CI for relative risk was obtained using Wilson's formula, and the 95% CI for excess risk was obtained using Wald's formula.

Laboratory Evaluation and Vital Signs

For continuous laboratory tests, vital signs, and electrocardiogram parameters, ANCOVA models with a baseline value as covariate were used to evaluate the change from Baseline values for each study time point. Only subjects with observations at both baseline and any given time point were included in these analyses (ie, missing data were not imputed). Both within-group and between-group comparisons were conducted. P-values and basic summary statistics (eg, number of subjects, (n), raw mean and standard deviation, adjusted mean and

standard error, median, minimum, maximum) are reported for signal detection purposes only because control for multiplicity was not applied. For categorical laboratory tests, summary statistics (n, percentage, total) in each category were reported by study time point. The Chi-square test was used to obtain all p-values of pairwise comparisons. The overall p-values for comparisons among treatment groups were reported using Chi-square test.

Substudies

For subjects participating in the endometrial substudy, TVU of the uterus and ovaries was performed at Baseline, at Months 12, 24, and 60 in study Extension I, and at Month 84 in Extension II. Endometrial thickness, ovarian volume, and the existence of ovarian cysts were included as a part of endometrial assessment. For endometrial thickness, the following were presented:

- Descriptive statistics for the observed values and change from Baseline to Month 12, 24, 60, and 84 for total double-wall thickness (mm).
- An ANCOVA on the change from Baseline with treatment as factor and baseline evaluation as a covariate to compare the endometrial thickness across treatment groups.
- The number and percentage of subjects with a thickness from 0 to 5 mm and <5 mm on therapy, a thickness <8 mm at Screening, and a change from Baseline <3 mm and <5 mm at Months 12, 24, 60, and 84.
- Fisher's exact test was used for comparisons between treatment arms at each time point for each category.

All ovarian volume summaries and analyses were performed separately for left and right ovary. For ovarian volume, the following were presented:

- Descriptive statistics for the actual values, change from Baseline, and percentage change from Baseline to Months 12, 24, 60, and 84 for each treatment group.
- An ANCOVA on change from Baseline with treatment as factor and baseline evaluation as a covariate to compare the ovarian volume between treatment groups. Pairwise treatment comparisons were also performed.
- The number and percentage of subjects with an increase in ovarian volume ≤ 2 cm^3 from Baseline by treatment group.

For ovarian cysts, the following were presented:

- The number and percentage of subjects having ovarian cysts by treatment group, by the number of cysts visualized and size.
- A listing of subjects with a cyst ≤20 mm.

- The number and percentage of subjects with a cyst ≤20 mm by treatment group.
- A listing of subjects with an increase in the number of cysts from Baseline to Months 12, 24, 60, and 84.

All summaries and analyses for the OSS were performed on the OSS population. Although subjects in the OSS were no longer on blinded treatment, reported results were based upon the treatment arms randomized at the beginning of the study with the bazedoxifene dose switch in study Extension I. Efficacy evaluation for the OSS included vertebral and non-vertebral fracture assessments, BMD and bone marker assessment (based on the available data). Safety analyses included adverse events and serious adverse events, summarized throughout 84 months with baseline as the starting reference point by treatment groups, and for Months 60 to 84 with Month 60 as the starting reference point. No other safety endpoints were to be reported for the OSS.

RESULTS

Subject Disposition and Demography: Subject disposition is provided in Table 4. A total of 4146 of the 5643 (73.5%) subjects who received bazedoxifene or placebo withdrew from the study in Months 0 to 84. Of the subjects who discontinued from the study over 84 months, 45.5% of subjects did so because they were ineligible to enter Extension II, their site was not participating in Extension II, or they chose not to enter Extension II for personal reasons. Overall, there were no statistically significant differences in the proportion of subjects withdrawn. The only significant difference among the groups was the greater percentage of subjects withdrawn for unsatisfactory response-efficacy in the placebo group compared to the bazedoxifene 20 mg group (p=0.040) and the bazedoxifene combined group (p=0.026).

Overall, the baseline characteristics of the bazedoxifene and placebo groups were similar. In the bazedoxifene treatment groups, all subjects were postmenopausal women with a mean age at enrollment of 66.4 years. The mean time since the last menstrual period was 19.5 years. Approximately 22.2% of subjects had had a hysterectomy. The mean body mass index was 26.5 kg/m^2.

Table 4. Subject Disposition

Study Status	BZA 20 mg	BZA 40 mg	BZA Combined	Placebo	RLX 60 mg	Total
Core						
Enrolled	1907	1904	3811	1914	1884	7609
Safety (SP1)	1886	1872	3758	1885	1849	7492
mITT of SP1 – vertebral fractures	1724	1686	3410	1741	1696	6847
Completed Core study	1279	1245	2524	1282	1277	5083
Extension I						
Enrolled	1047	1041	2088	1058	1070	4216
Completed Extension I	833	840	1673	830		2503
Extension II						
Enrolled	560		1142	590	-	1732
Safety (SP2)[a]	499		1011	519	-	1530
Completed Extension II (SP2)[a]	421		860	441	-	1301

BZA = bazedoxifene; mITT = modified intent-to-treat; OSS = observational substudy only; RLX = raloxifene; SP1 = safety population 1; SP2 = safety population 2.
a. Excludes OSS subjects.

Efficacy Results:

Primary Endpoint:

The efficacy evaluation of main interest was the comparison of the incidence of new vertebral fractures among the bazedoxifene 20 mg, bazedoxifene combined, and placebo groups after 84 months of study therapy. The incidence of non-vertebral fractures after 84 months of study therapy was a secondary endpoint. Evaluations over 84 months of study therapy were also conducted for clinical and worsening vertebral fractures; changes in BMD, subject height, and serum bone markers; and incidence of breast cancer.

Since the subjects enrolled in the study Extensions I and II on a self-selected basis, the randomization at the Baseline of the core study may no longer be in operation to draw valid inference based on treatment comparisons. It was possible that there were differences in the profiles of subjects who enrolled in the core study compared with those who enrolled in Extensions I and II of the study. These potential differences limit the interpretation of these comparisons and the generalizability of the findings to the population randomized at Baseline.

In the core study, statistically significant and clinically meaningful reductions compared with placebo in the incidence of new radiographically confirmed vertebral fractures (the primary efficacy endpoint) were observed in the active treatment groups at 36 months. All active treatment groups demonstrated significantly greater ($p<0.05$) reduction relative to the placebo group in incidence of vertebral fracture at 36 months of study treatment. There were no significant differences in fracture rates between the active treatment groups.

The 7-year analyses show that the cumulative incidence of new vertebral fractures was significantly lower in the bazedoxifene treatment groups compared with the placebo group at 84 months (Table 5 and Figure 1). At Month 84, the relative risk reduction (RRR = 1.000 - hazard ratio) in the cumulative vertebral fracture incidence for the

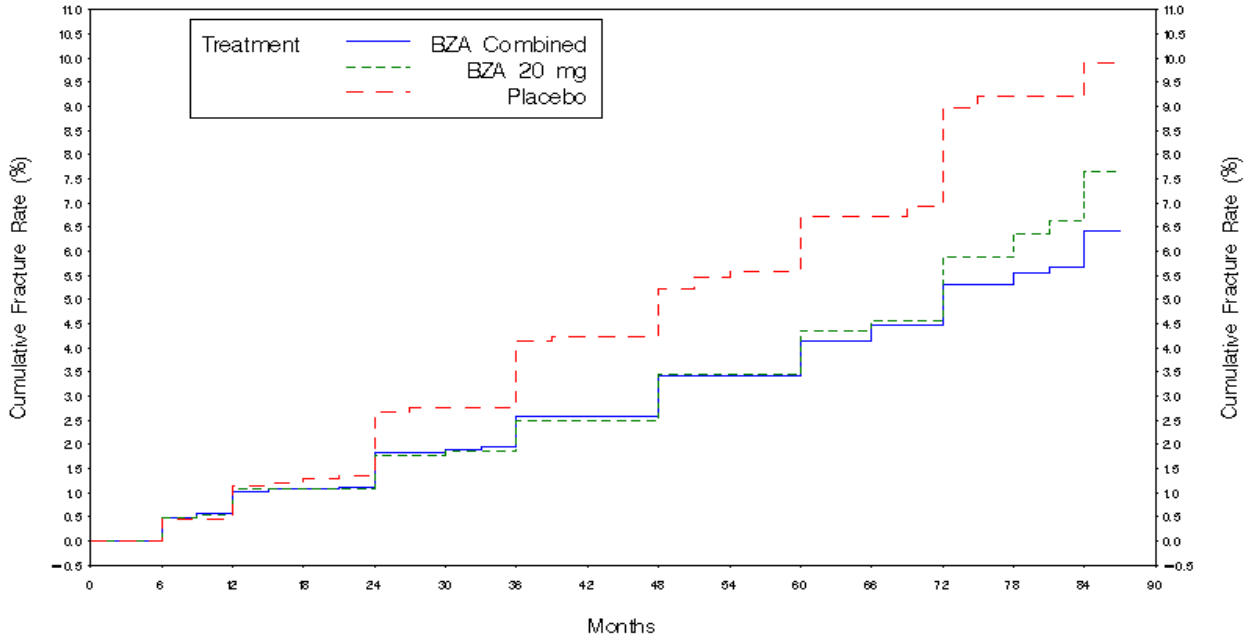
bazedoxifene 20 mg treatment group and bazedoxifene combined treatment group compared with placebo was 30% and 36%, respectively (Table 6).

Table 5. Summary Tabulation of New Vertebral Fracture Incidence, Kaplan-Meier Estimates of Vertebral Fracture Cumulative Rate, Months 0 to 84, mITT Population of SP1

	Number of Subjects With New Fractures	Number of Subjects	Unadjusted Fracture Rate (%)	Kaplan-Meier Rate Estimate (%)	LL 95% CI	UP 95% CI
Months 0-36						
Bazedoxifene 20 mg	35	1724	2.03	2.34	1.68	3.25
Bazedoxifene 40 mg	36	1686	2.14	2.51	1.81	3.47
Raloxifene 60 mg	34	1696	2.00	2.34	1.67	3.26
Placebo	59	1741	3.39	4.07	3.16	5.23
Months 0-60						
Bazedoxifene 20 mg	53	1724	3.07	4.36	3.31	5.74
Bazedoxifene Combined	102	3410	2.99	4.14	3.39	5.04
Placebo	82	1741	4.71	6.73	5.40	8.36
Months 0-72						
Bazedoxifene 20 mg	60	1724	3.48	5.87	4.44	7.72
Bazedoxifene Combined	113	3410	3.31	5.30	4.34	6.47
Placebo	93	1741	5.34	8.98	7.22	11.13
Months 0-84						
Bazedoxifene 20 mg	67	1724	3.89	7.64	5.83	9.98
Bazedoxifene Combined	122	3410	3.58	6.42	5.26	7.82
Placebo	97	1741	5.57	9.90	7.98	12.26

CI = confidence interval; LL = lower limit; mITT = modified intent-to-treat; SP1 = safety population 1; UP = upper limit.
First New Vertebral Fractures Were Included in the Summary.

Figure 1. Kaplan-Meier Estimates of New Vertebral Fracture Cumulative Rate, Months 0 to 84, mITT Population of SP1



This is a Kaplan-Meier plot based on a hypothetical standard month. Most incident fractures were detected at the scheduled radiographic study visits given in months.
BZA = Bazedoxifene; mITT = modified intent-to-treat; SP1 = Safety Population 1.

Table 6. Summary of Incidence of New Vertebral Fractures, Hazard Ratio Estimates, Months 0 to 84, mITT Population of SP1

Treatment	Comparator	Hazard Ratio	Lower 95% Limit	Upper 95% Limit	p-Value Between Group
Months 0-36					
Bazedoxifene 20 mg	Placebo	0.584	0.383	0.891	0.015
Bazedoxifene 40 mg	Placebo	0.634	0.419	0.960	0.031
Raloxifene 60 mg	Placebo	0.581	0.381	0.887	0.012
Months 0-60					
Bazedoxifene 20 mg	Placebo	0.646	0.456	0.915	0.013
Bazedoxifene Combined	Placebo	629	0.469	0.842	0.002
Months 0-72					
Bazedoxifene 20 mg	Placebo	0.647	0.467	0.897	0.008
Bazedoxifene Combined	Placebo	0.613	0.465	0.808	<0.001
Months 0-84					
Bazedoxifene 20 mg	Placebo	0.696	0.509	0.952	0.022
Bazedoxifene Combined	Placebo	0.635	0.486	0.831	<0.001

First new vertebral fractures were included in the summary Hazard ratio estimation based on Cox Proportional Hazard Regression, adjusted for prevalent vertebral status fracture and Baseline BMD T-score.
Between Group p-Value Based on Stratified Log Rank Test (by fracture status prevalent).
BMD = bone mineral density; mITT = modified intent-to-treat; SP1 = Safety Population 1.

While the incidence of vertebral fractures was higher in subjects with a prevalent fracture at Baseline, the RRR of vertebral fracture in the bazedoxifene treatment groups was similar in both baseline vertebral fracture status strata. The treatment effect (based on cumulative vertebral fracture incidence) of bazedoxifene over 7 years appears to be similar to that over 5 years.

Secondary Endpoints:

As was seen after 3 years in the core study, after 7 years there was no demonstrable effect relative to placebo on non-vertebral fractures. In the subgroup of high-risk subjects, the incidence of non-vertebral fracture was numerically lower in the bazedoxifene 20 mg and bazedoxifene combined treatment groups than in the placebo group, but this difference was not statistically significant at 7 years (Table 7 and Table 8).

Table 7. Non-Vertebral (Osteoporosis-Related) Cumulative Rate of New Fractures, Months 0 to 84, High-Risk Sub-Population of SP1

Treatment	Number of Subjects With New Fractures	Number of Subjects	Unadjusted Fracture Rate (%)	Kaplan-Meier Rate Estimate (%)	95% CI
Months 0-60					
Bazedoxifene 20 mg	26	443	5.87	9.17	(6.22, 13.40)
Bazedoxifene Combined	53	876	6.05	9.11	(6.95, 11.91)
Placebo	39	448	8.71	12.73	(9.30, 17.29)
Months 0-72					
Bazedoxifene 20 mg	27	443	6.09	10.35	(6.89, 15.39)
Bazedoxifene Combined	55	876	6.28	10.26	(7.72, 13.56)
Placebo	39	448	8.71	12.73	(9.30, 17.29)
Months 0-84					
Bazedoxifene 20 mg	29	443	6.55	12.84	(8.45, 19.24)
Bazedoxifene Combined	59	876	6.74	12.84	(9.55, 17.15)
Placebo	40	448	8.93	13.99	(10.03, 19.35)

CI = confidence interval; SP = safety population.
Pathologic Non-Vertebral Fractures are Excluded. Summary Based on Principal Investigator's Data
First New Vertebral Fractures Were Included in the Summary.

Table 8. Hazard Ratio Estimates of On-Therapy Non-Vertebral (Osteoporosis-Related) Fractures, Months 0 to 84, High-Risk Sub-Population of SP1

Treatment	Comparator	Hazard Ratio	95 (%) CI	p-Value
Months 0-60				
Bazedoxifene 20 mg	Placebo	0.63	(0.38, 1.03)	0.064
Bazedoxifene Combined	Placebo	0.66	(0.43, 0.99)	0.047
Months 0-72				
Bazedoxifene 20 mg	Placebo	0.65	(0.40, 1.06)	0.086
Bazedoxifene Combined	Placebo	0.68	(0.45, 1.03)	0.069
Months 0-84				
Bazedoxifene 20 mg	Placebo	0.68	(0.42, 1.10)	0.12
Bazedoxifene Combined	Placebo	0.72	(0.48, 1.07)	0.10

Pathologic Non-Vertebral fractures were excluded. Summary based on Principal Investigator Data.
CI = confidence interval; SP1 = Safety Population 1.

After 7 years of treatment, there were 49 subjects with new clinical vertebral fractures (Table 9) and 8 subjects with worsening vertebral fractures across the bazedoxifene treatment and placebo groups. There were no significant differences among the incidence rates of new clinical vertebral fractures in the bazedoxifene treatment and placebo groups at Month 84

(Table 10). The numbers of subjects with worsening vertebral fractures were insufficient for any meaningful statistical comparisons (Table 11).

Table 9. Summary Tabulation of New Clinical Vertebral Fracture Cumulative Rate Months 0 to 84, mITT Population of SP1

	Number of Subjects With New Fractures	Number of Subjects	Unadjusted Fracture Rate	Kaplan-Meier Rate Estimate (%)	LL 95% CI	UP 95% CI
Bazedoxifene 20 mg	15	1724	0.87	1.52	0.82	2.81
Bazedoxifene Combined	28	3410	0.82	1.28	0.82	1.97
Placebo	21	1741	1.21	1.92	1.20	3.08

CI = confidence interval; LL = lower limit; UP = upper limit.
First new vertebral fractures were included in the summary.

Table 10. Summary Tabulation of New Clinical Vertebral Fracture Cumulative Rate Between-Group Comparisons - Stratified Log-Rank Test, Months 0 to 84, mITT Population of SP1

Treatment Group	Comparator	p-Value
Bazedoxifene 20 mg	Placebo	0.34
Bazedoxifene Combined	Placebo	0.18

mITT = modified intent-to-treat; SP1 = Safety Population 1.

Table 11. Summary Tabulation of Worsening Vertebral Fracture Rate, Months 0 to 84, mITT Population of SP 1

Treatment Group	Number of Subjects With Worsening Fracture (%)	Total
Bazedoxifene 20 mg	5 (0.29%)	1724
Bazedoxifene Combined	7 (0.21%)	3410
Placebo	1 (0.06%)	1741

mITT = modified intent to treat; SP1 = Safety Population 1.

Through 84 months, the increases from Baseline in lumbar spine BMD in the bazedoxifene 20 mg treatment and bazedoxifene combined treatment groups were greater than the placebo group at all scheduled evaluations and were statistically significantly different (Table 12).

Table 12. Summary Tabulation of Lumbar Spine Bone Mineral Density, Analysis of Percentage Change From Baseline, Between- and Within-Group Comparisons, Months 0 to 84, Lumbar Spine mITT of SP2

Visit	N	Adjusted %Change-Mean (SE)	Within Group p-Value	Adjusted % Change From Placebo	
				Mean (LCB95, UCB95)	p-Value
Bazedoxifene 20 mg					
Months 60	445	2.26 (0.39)	<0.001	0.56 (-0.11, 1.23)	0.10
Months 72	434	1.92 (0.41)	<0.001	0.12 (-0.60, 0.84)	0.74
Months 84	393	2.73 (0.51)	<0.001	0.53 (-0.32, 1.39)	0.22
Bazedoxifene combined					
Months 60	906	2.31 (0.30)	<0.001	0.52 (-0.06, 1.10)	0.078
Months 72	888	2.24 (0.31)	<0.001	0.30 (-0.32, 0.93)	0.34
Months 84	800	2.95 (0.39)	<0.001	0.54 (-0.20, 1.28)	0.15
Placebo					
Months 60	468	1.70 (0.38)	<0.001		
Months 72	457	1.80 (0.40)	<0.001		
Months 84	417	2.19 (0.49)	<0.001		

Adjusted %changes, within and between group p-values are based on the model: % changes from Baseline = treatment + baseline BMD + geographic region + baseline vertebral status fracture category.
BMD = bone mineral density; LCB = lower confidence bound; mITT = modified intent-to-treat; SE = standard error; SP2 = safety population 2; UCB = upper confidence bound.

At the other 3 skeletal sites, BMD decreased from Baseline over the course of 7 years, with significantly greater decreases in placebo than in the bazedoxifene treatment groups (Table 13, Table 14, Table 15). Results of analyses by age group, in study completers, and up to the first use of bone-active agents were consistent with the results in the mITT populations of SP2. Results in the bazedoxifene combined treatment group were similar.

Table 13. Summary Tabulation of Total Hip Bone Mineral Density, Analysis of Percentage Change From Baseline, Between- and Within-Group Comparisons, Months 0 to 84, Total Hip mITT of SP2

Visit	N	Adjusted %Change-Mean (SE)	Within Group p-Value	Adjusted % Change From Placebo	
				Mean (LCB95, UCB95)	p-Value
Bazedoxifene 20 mg					
Months 60	444	-0.32 (0.31)	0.31	1.11 (0.58, 1.65)	<0.001
Months 72	424	-0.84 (0.34)	0.013	1.12 (0.53, 1.71)	<0.001
Months 84	386	-1.19 (0.39)	0.002	1.34 (0.67, 2.00)	<0.001
Bazedoxifene combined					
Months 60	902	-0.22 (0.25)	0.37	1.09 (0.63, 1.56)	<0.001
Months 72	871	-0.85 (0.25)	<0.001	0.97 (0.47, 1.46)	<0.001
Months 84	787	-1.15 (0.30)	<0.001	1.16 (0.59, 1.74)	<0.001
Placebo					
Months 60	451	-1.43 (0.31)	<0.001		
Months 72	448	-1.96 (0.33)	<0.001		
Months 84	405	-2.53 (0.38)	<0.001		

Adjusted % changes, within and between group p-values are based on the model: % changes from Baseline = treatment + baseline BMD + geographic region + baseline vertebral status fracture category.
BMD = bone mineral density; LCB = lower confidence bound; SP2 = safety population 2; SE = standard error; UCB = upper confidence bound.

Table 14. Summary Tabulation of Femoral Neck Bone Mineral Density, Analysis of Percentage Change From Baseline, Between- and Within-Group Comparisons, Months 0 to 84, Femoral Neck mITT of SP2

Visit	N	Adjusted% Change-Mean (SE)	Within Group p-Value	Adjusted % Change From Placebo	
				Mean (LCB95, UCB95)	p-Value
Bazedoxifene 20 mg					
Months 60	444	-0.14 (0.36)	0.69	1.59 (0.98, 2.21)	<0.001
Months 72	424	-0.64 (0.40)	0.11	1.49 (0.79, 2.18)	<0.001
Months 84	386	-0.97 (0.45)	0.031	1.38 (0.61, 2.14)	<0.001
Bazedoxifene combined					
Months 60	902	0.10 (0.29)	0.73	1.79 (1.24, 2.33)	<0.001
Months 72	871	-0.60 (0.30)	0.044	1.45 (0.87, 2.03)	<0.001
Months 84	787	-0.80 (0.35)	0.022	1.32 (0.65, 1.98)	<0.001
Placebo					
Months 60	451	-1.74 (0.36)	<0.001		
Months 72	448	-2.12 (0.39)	<0.001		
Months 84	405	-2.35 (0.43)	<0.001		

Adjusted %changes, within and between group p-values are based on the model: % changes from Baseline = treatment + baseline BMD + geographic region + baseline vertebral status fracture category.
BMD = bone mineral density; LCB = lower confidence bound; SP2 = safety population 2; SE = standard error; UCB = upper confidence bound

Table 15. Summary Tabulation of Femoral Trochanter Bone Mineral Density, Analysis of Percentage Change From Baseline, Between- and Within-Group Comparisons, Months 0 to 84, Femoral Trochanter mITT of SP2

Visit	N	Adjusted % Change-Mean (SE)	Within Group p-Value	Adjusted % Change From Placebo	
				Mean (LCB95, UCB95)	p-Value
Bazedoxifene 20 mg					
Months 60	444	0.27 (0.43)	0.52	1.17 (0.45, 1.90)	0.002
Months 72	424	-0.25 (0.45)	0.58	1.18 (0.40, 1.97)	0.003
Months 84	386	-1.37 (0.49)	0.006	1.35 (0.51, 2.19)	0.002
Bazedoxifene combined					
Months 60	902	0.22 (0.33)	0.51	1.04 (0.41, 1.68)	0.001
Months 72	871	-0.31 (0.34)	0.36	1.02 (0.36, 1.69)	0.003
Months 84	787	-1.41 (0.38)	<0.001	1.10 (0.39, 1.82)	0.002
Placebo					
Months 60	451	-0.90 (0.42)	0.034		
Months 72	448	-1.43 (0.44)	0.001		
Months 84	405	-2.72 (0.47)	<0.001		

Adjusted %changes, within and between group p-values are based on the model: %changes from Baseline = treatment + baseline BMD + geographic region + baseline vertebral status fracture category.
BMD = bone mineral density; LCB = lower confidence bound; SE = standard error; UCB = upper confidence bound.

No effect on loss of height was seen with bazedoxifene treatment compared with placebo (Table 16 and Table 17).

Table 16. Summary Tabulation of Height, Analysis of Change From Baseline, Between- and Within-Group Comparisons, Months 60 to 84, Height SP1

		Baseline (cm)	Observed (cm)	Adjusted Change (cm)		Adjusted Difference From Placebo (cm)	
Visit	**N**	**Mean (SD)**	**Mean (SD)**	**Mean (SE)**	**p-Value Within Group**	**Mean (LCB95, UCB95)**	**p-Value**
Bazedoxifene 20 mg							
Months 60	740	156.56 (7.24)	156.16 (6.94)	-0.52 (0.06)	<0.001	-0.09 (-0.21, 0.03)	0.12
Months 72	438	155.81 (7.34)	155.42 (7.03)	-0.59 (0.10)	<0.001	-0.11 (-0.28, 0.07)	0.22
Months 84	364	156.03 (7.17)	155.40 (6.88)	-0.85 (0.11)	<0.001	-0.16 (-0.36, 0.03)	0.092
Bazedoxifene combined							
Months 60	1478	156.41 (7.26)	156.07 (6.96)	-0.46 (0.05)	<0.001	-0.05 (-0.15, 0.05)	0.36
Months 72	898	155.58 (7.42)	155.23 (7.10)	-0.54 (0.07)	<0.001	-0.08 (-0.23, 0.06)	0.26
Months 84	736	155.96 (7.29)	155.41 (7.01)	-0.73 (0.08)	<0.001	-0.09 (-0.25, 0.07)	0.26
Placebo							
Months 60	744	156.46 (6.76)	156.17 (6.59)	-0.43 (0.06)	<0.001	-	-
Months 72	459	156.04 (6.84)	155.75 (6.57)	-0.48 (0.10)	<0.001	-	-
Months 84	407	156.09 (6.82)	155.61 (6.54)	-0.68 (0.10)	<0.001	-	-

Adjusted %changes, within and between group p-values are based on the model: changes from Baseline = treatment + baseline Height + geographic region.
BMD = bone mineral density; LCB = lower confidence bound; SP1 = safety population 1; SE = standard error; UCB = upper confidence bound.

Table 17. Summary Tabulation of Height, Analysis of Change From Baseline, Between- and Within-Group Comparisons, Months 60 to 84, Height SP2

		Baseline (cm)	Observed (cm)	Adjusted Change (cm)		Adjusted Difference From Placebo (cm)	
Visit	**N**	**Mean (SD)**	**Mean (SD)**	**Mean (SE)**	**p-Value Within Group**	**Mean (LCB95, UCB95)**	**p-Value**
Bazedoxifene 20 mg							
Month 60	502	155.72 (7.30)	155.43 (6.99)	-0.44 (0.09)	<0.001	-0.10 (-0.25, 0.06)	0.22
Month 72	438	155.81 (7.34)	155.42 (7.03)	-0.59 (0.10)	<0.001	-0.11 (-0.28, 0.07)	0.22
Month 84	364	156.03 (7.17)	155.40 (6.88)	-0.85 (0.11)	<0.001	-0.16 (-0.36, 0.03)	0.092
Bazedoxifene combined							
Month 60	1015	155.48 (7.35)	155.26 (7.04)	-0.36 (0.07)	<0.001	-0.04 (-0.17, 0.10)	0.60
Month 72	898	155.58 (7.42)	155.23 (7.10)	-0.54 (0.07)	<0.001	-0.08 (-0.23, 0.06)	0.26
Month 84	736	155.96 (7.29)	155.41 (7.01)	-0.73 (0.08)	<0.001	-0.09 (-0.25, 0.07)	0.26
Placebo							
Month 60	526	155.79 (6.84)	155.60 (6.62)	-0.34 (0.09)	<0.001	-	-
Month 72	459	156.04 (6.84)	155.75 (6.57)	-0.48 (0.10)	<0.001	-	-
Month 84	407	156.09 (6.82)	155.61 (6.54)	-0.68 (0.10)	<0.001	-	-

Adjusted % changes, within and between group p-values are based on the model: changes from Baseline = treatment + Baseline Height + geographic region.
BMD = bone mineral density; LCB = lower confidence bound; SP2 = safety population 2; SE = standard error; UCB = upper confidence bound.

Significant within-group decreases from Baseline in serum osteocalcin (Table 18) and CTx levels (Table 19) were seen in all treatment groups at 84 months.

Table 18. Summary Tabulation of Serum Osteocalcin, Analysis of Percentage Change From Baseline Within Groups, Nonparametric Analysis, Months 60 to 84, SP2

		Baseline			Observed			% Change From Baseline			p-Values	
Visit	**N**	**Lower Q**	**Median**	**Upper Q**	**Lower Q**	**Median**	**Upper Q**	**Lower Q**	**Median**	**Upper Q**	**Within-Group**	**Vs Placebo**
Osteocalcin (mcg/L)												
Bazedoxifene 20 mg												
Months 60	91	22.69	28.81	36.49	15.62	19.73	25.25	-44.25	-31.56	-14.88	<0.001	0.005
Months 72	82	23.00	29.37	36.49	14.75	18.80	25.83	-47.71	-27.28	-10.35	<0.001	0.19
Months 84	70	22.71	28.78	37.09	15.96	18.80	23.63	-46.56	-31.12	-18.83	<0.001	0.13
Bazedoxifene combined												
Months 60	192	22.93	30.73	38.16	15.58	20.73	25.13	-45.71	-33.77	-17.91	<0.001	<0.001
Months 72	170	24.51	31.45	38.37	14.75	20.48	26.09	-49.30	-33.76	-13.30	<0.001	0.037
Months 84	147	23.91	31.58	38.91	16.20	19.94	27.23	-51.48	-32.25	-13.60	<0.001	0.16
Placebo												
Months 60	105	25.14	31.51	43.46	18.24	24.27	30.90	-37.55	-22.96	-8.16	<0.001	
Months 72	97	24.93	31.70	43.77	17.57	23.81	28.97	-43.48	-26.72	-9.53	<0.001	
Months 84	84	25.04	31.02	43.62	18.31	23.22	28.00	-42.38	-29.50	-12.01	<0.001	

Between group comparisons are based on model: Ranked % change from Baseline = treatment + Baseline
Q = quartile; SP2 = safety population 2; Vs = versus..

Table 19. Summary Tabulation of Serum C-Telopeptide, Analysis of Percentage Change From Baseline Within Groups, Nonparametric Analysis, Months 60 to 84, SP2

		Baseline			Observed			% Change From Baseline			p-Values	
Visit	**N**	**Lower Q**	**Median**	**Upper Q**	**Lower Q**	**Median**	**Upper Q**	**Lower Q**	**Median**	**Upper Q**	**Within-Group**	**Vs Placebo**
C-telopeptide (pmol/L)												
Bazedoxifene 20 mg												
Months 60	91	2839.00	3816.50	4828.00	2074.00	2958.00	4326.50	-42.52	-21.83	11.11	0.002	0.093
Months 72	82	2864.50	3863.25	4828.00	1623.50	2388.50	3400.00	-58.21	-32.67	-7.20	<0.001	0.072
Months 84	70	2694.50	3765.50	4828.00	2235.50	2779.50	4165.00	-44.19	-17.32	5.06	0.001	0.93
Bazedoxifene combined												
Months 60	192	2932.50	4058.75	5478.25	2031.50	3051.50	4284.00	-47.22	-26.31	7.81	<0.001	0.032
Months 72	170	3043.00	4190.50	5482.50	1632.00	2567.00	3774.00	-59.11	-37.41	-11.36	<0.001	0.034
Months 84	147	2992.00	4063.00	5516.50	2142.00	2949.50	4165.00	-48.02	-28.17	1.70	<0.001	0.77
Placebo												
Months 60	105	3332.00	4692.00	5873.50	2541.50	3680.50	4828.00	-42.38	-11.86	17.82	0.002	
Months 72	97	3332.00	4624.00	5873.50	1997.50	3128.00	4326.50	-49.83	-29.44	4.04	<0.001	
Months 84	84	3162.00	4462.50	5801.25	2329.00	3327.75	4228.75	-49.04	-28.61	3.92	<0.001	

Between group comparisons are based on model: Ranked % change from Baseline = treatment + Baseline.
Q = quartile; SP2 = safety population 2; Vs = versus.

Over the 7-year duration of the study, the overall incidence of breast cancer was similar in the bazedoxifene and placebo groups. Rates per 1000 woman-years (95% CI) for the bazedoxifene 20 mg, bazedoxifene combined, and placebo groups were 1.78 (0.95,3.05), 1.52 (0.95,2.30), and 1.50 (0.75,2.69), respectively (Table 20 and Table 21).

Table 20. Number of Subjects and Rate per 1000 Woman-Years of Breast Carcinoma, Study Period Interval, Based on Principal Investigator Data, Months 0 to 84, SP1.

	n			Rate per 1000 Woman-Year of Breast Carcinoma (95% CI)		
Month	Placebo	Bazedoxifene 20 mg	Bazedoxifene Combined	Placebo	Bazedoxifene 20 mg	Bazedoxifene Combined
0-84	11	13	22	1.50 (0.75,2.69)	1.78 (0.95,3.05)	1.52 (0.95,2.30)

CI = confidence interval; n = number of subjects; SP1 = safety population 1.

Table 21. Number of Subjects and Rate per 1000 Woman-Years of Breast Carcinoma, Study Period Interval, Based on Principal Investigator Data, Months 0 to 84, SP1

	Relative Risk to Placebo (95% CI)		Excess AE Rate (95% CI)	
Month	Bazedoxifene 20 mg	Bazedoxifene Combined	Bazedoxifene 20 mg	Bazedoxifene Combined
0-84	1.19 (0.54,2.6)	1.01 (0.5,2.06)	0.28 (-1.03,1.59)	0.02 (-1.07,1.11)

AE = adverse event; CI = confidence interval; SP1 = safety population 1.

In summary, the results of the efficacy analyses from this study showed a protective effect on the skeleton with respect to a reduction in the incidence of new vertebral fractures, reduced decline in BMD relative to placebo, and a reduced rate of serum bone turnover markers with bazedoxifene treatment. Taken together, these findings provide evidence of sustained efficacy of bazedoxifene relative to placebo over 7 years.

Observational Substudy Safety Substudy: The OSS was intended to assess the residual effect of bazedoxifene after discontinuation of treatment. Significant increases in BMD were observed in all treatment groups at the lumbar spine and femoral neck while the femoral trochanter showed a significant reduction in BMD of a magnitude similar to increases observed in the lumbar spine. These findings were in contradiction what 1 would expect after bazedoxifene was discontinued: BMD was expected to decrease but not to increase. In addition, changes in the lumbar spine usually go in the same direction with changes in femoral trochanter. Thus these findings were difficult to interpret. Markers of bone turnover decreased by similar magnitudes from Months 60 to 84 in all treatment groups which is an unexpected result. Interpretation of results in the OSS was limited in that only 1 site participated in the OSS, and subjects were not randomized into the study but were self-selected, and therefore these results cannot be generalized to the general study population.

Safety Results:

Safety Population 1 (SP1): In the bazedoxifene 20 mg treatment and placebo groups, TEAEs were reported for 95.5% and 95.1% of subjects, respectively. The most frequently (≥5% of subjects in at least 1 group) reported TEAEs during the study are presented in Table 22 for bazedoxifene 20 mg treatment group compared with placebo. A total of 95.2% (3577 of 3758) of subjects in the bazedoxifene combined treatment group and 95.1% (1793 of 1885) of subjects in the placebo group reported at least 1 TEAE (Table 40).

Table 22. Number (%) of Subjects With Treatment-Emergent Adverse Events With an Incidence of ≥5% in at Least 1 Group, Bazedoxifene 20 mg Versus Placebo, Months 0 to 84, SP1

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=1886)	Placebo (n=1885)
Any adverse event	1802 (95.5)	1793 (95.1)
Body as a whole		
Abdominal pain	446 (23.6)	496 (26.3)
Accidental injury	499 (26.5)	518 (27.5)
Asthenia	224 (11.9)	215 (11.4)
Back pain	638 (33.8)	631 (33.5)
Chest pain	173 (9.2)	156 (8.3)
Flu syndrome	506 (26.8)	543 (28.8)
Headache	440 (23.3)	437 (23.2)
Infection	496 (26.3)	491 (26.0)
Neck pain	161 (8.5)	177 (9.4)
Pain	609 (32.3)	644 (34.2)
Cardiovascular system		
Hypertension	461 (24.4)	444 (23.6)
Vasodilatation	241 (12.8)	123 (6.5)
Digestive system		
Constipation	369 (19.6)	338 (17.9)
Diarrhea	187 (9.9)	207 (11.0)
Dyspepsia	205 (10.9)	213 (11.3)
Gastritis	112 (5.9)	86 (4.6)
Nausea	169 (9.0)	169 (9.0)
Vomiting	113 (6.0)	134 (7.1)
Metabolic and nutritional		
Hypercholesteremia	137 (7.3)	174 (9.2)
Hyperglycemia	94 (5.0)	121 (6.4)
Hyperlipidaemia	106 (5.6)	107 (5.7)
Peripheral edema	229 (12.1)	179 (9.5)
Musculoskeletal system		
Arthralgia	652 (34.6)	634 (33.6)
Arthrosis	190 (10.1)	194 (10.3)
Leg cramps	260 (13.8)	197 (10.5)
Myalgia	99 (5.2)	109 (5.8)
Nervous system		
Anxiety	95 (5.0)	128 (6.8)
Depression	128 (6.8)	122 (6.5)
Dizziness	217 (11.5)	207 (11.0)
Insomnia	174 (9.2)	188 (10.0)
Paresthesia	100 (5.3)	101 (5.4)
Vertigo	162 (8.6)	159 (8.4)
Respiratory system		
Bronchitis	202 (10.7)	178 (9.4)
Cough increased	241 (12.8)	220 (11.7)
Pharyngitis	155 (8.2)	205 (10.9)
Pneumonia	95 (5.0)	107 (5.7)
Sinusitis	121 (6.4)	100 (5.3)
Upper respiratory infection	155 (8.2)	143 (7.6)

Table 22. Number (%) of Subjects With Treatment-Emergent Adverse Events With an Incidence of ≥5% in at Least 1 Group, Bazedoxifene 20 mg Versus Placebo, Months 0 to 84, SP1

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=1886)	Placebo (n=1885)
Skin and appendages		
Pruritus	132 (7.0)	135 (7.2)
Special senses	456 (24.2)	480 (25.5)
Cataract specified	113 (6.0)	118 (6.3)
Urogenital system		
Breast disorder	126 (6.7)	142 (7.5)
Cervix disorder	118 (6.3)	138 (7.3)
Cystitis	105 (5.6)	90 (4.8)
Urinary tract infection	207 (11.0)	200 (10.6)
Vaginitis	94 (5.0)	121 (6.4)

AEs and SAEs are not separated out.
AE = adverse events; n = number of subjects in each treatment group; SAE = serious adverse event; SP1 = safety population 1.
a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system.

Table 23. Number (%) of Subjects With Treatment-Emergent Adverse Events With an Incidence of ≥5% in at Least 1 Group, Bazedoxifene Combined Versus Placebo, Months 0 to 84, SP1

Body System[a] Adverse Event	Bazedoxifene Combined (n=3758)	Placebo (n=1885)
Any adverse event	3577 (95.2)	1793 (95.1)
Body as a whole		
Abdominal pain	889 (23.7)	496 (26.3)
Accidental injury	945 (25.1)	518 (27.5)
Asthenia	440 (11.7)	215 (11.4)
Back pain	1244 (33.1)	631 (33.5)
Chest pain	341 (9.1)	156 (8.3)
Flu syndrome	1015 (27.0)	543 (28.8)
Headache	861 (22.9)	437 (23.2)
Infection	983 (26.2)	491 (26.0)
Neck pain	322 (8.6)	177 (9.4)
Pain	1201 (32.0)	644 (34.2)
Cardiovascular system		
Hypertension	897 (23.9)	444 (23.6)
Vasodilatation	485 (12.9)	123 (6.5)
Digestive system		
Constipation	725 (19.3)	338 (17.9)
Diarrhea	408 (10.9)	207 (11.0)
Dyspepsia	392 (10.4)	213 (11.3)
Gastritis	211 (5.6)	86 (4.6)
Gastroenteritis	189 (5.0)	94 (5.0)
Nausea	339 (9.0)	169 (9.0)
Vomiting	230 (6.1)	134 (7.1)
Metabolic and nutritional		
Hypercholesteremia	251 (6.7)	174 (9.2)
Hyperglycemia	183 (4.9)	121 (6.4)
Hyperlipemia	212 (5.6)	107 (5.7)
Peripheral edema	435 (11.6)	179 (9.5)
Musculoskeletal system		
Arthralgia	1271 (33.8)	634 (33.6)
Arthrosis	386 (10.3)	194 (10.3)
Leg cramps	520 (13.8)	197 (10.5)
Myalgia	182 (4.8)	109 (5.8)
Nervous system		
Anxiety	191 (5.1)	128 (6.8)
Depression	276 (7.3)	122 (6.5)
Dizziness	404 (10.8)	207 (11.0)
Insomnia	336 (8.9)	188 (10.0)
Paresthesia	207 (5.5)	101 (5.4)
Vertigo	295 (7.8)	159 (8.4)
Respiratory system		
Bronchitis	403 (10.7)	178 (9.4)
Cough increased	461 (12.3)	220 (11.7)
Pharyngitis	332 (8.8)	205 (10.9)
Pneumonia	188 (5.0)	107 (5.7)
Sinusitis	230 (6.1)	100 (5.3)

Table 23. Number (%) of Subjects With Treatment-Emergent Adverse Events With an Incidence of ≥5% in at Least 1 Group, Bazedoxifene Combined Versus Placebo, Months 0 to 84, SP1

Body System[a] Adverse Event	Bazedoxifene Combined (n=3758)	Placebo (n=1885)
Upper respiratory infection	302 (8.0)	143 (7.6)
Skin and appendages		
Pruritus	265 (7.1)	135 (7.2)
Special senses		
Cataract specified	227 (6.0)	118 (6.3)
Urogenital system		
Breast disorder	247 (6.6)	142 (7.5)
Cervix disorder	262 (7.0)	138 (7.3)
Cystitis	220 (5.9)	90 (4.8)
Urinary tract infection	405 (10.8)	200 (10.6)
Vaginitis	180 (4.8)	121 (6.4)

AEs and SAEs are not separated out.
AE = adverse event; n = number of subjects in each treatment group; SAE = serious adverse event; SP1 = safety population 1.
a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system.

Extension II population (SP2): The distribution of all TEAEs reported since the start of study participation for the bazedoxifene 20 mg Extension II population is presented in Table 24 and the distribution of all TEAEs, according to body system, reported since the start of study participation for subjects entering Extension II in the bazedoxifene combined treatment group compared with placebo is presented in Table 25.

Table 24. Number (%) of Subjects With Treatment-Emergent Adverse Events With an Incidence of ≥5% in at Least 1 Group, Bazedoxifene 20 mg Versus Placebo, Subjects Who Entered Extension II (SP2) Months 0 to 84

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=499)	Placebo (n=519)
Any adverse event	495 (99.2)	515 (99.2)
Body as a whole	441 (88.4)	472 (90.9)
Abdominal pain	151 (30.3)	161 (31.0)
Accidental injury	176 (35.3)	180 (34.7)
Asthenia	75 (15.0)	70 (13.5)
Back pain	231 (46.3)	220 (42.4)
Chest pain	59 (11.8)	63 (12.1)
Flu syndrome	169 (33.9)	219 (42.2)
Headache	149 (29.9)	147 (28.3)
Infection	167 (33.5)	186 (35.8)
Neck pain	52 (10.4)	59 (11.4)
Neoplasm	27 (5.4)	22 (4.2)
Pain	223 (44.7)	227 (43.7)
Cardiovascular system	286 (57.3)	283 (54.5)
Hypertension	188 (37.7)	181 (34.9)
Tachycardia	13 (2.6)	27 (5.2)
Varicose vein	23 (4.6)	30 (5.8)
Vasodilatation	63 (12.6)	39 (7.5)
Digestive system	305 (61.1)	324 (62.4)
Abdominal distension	18 (3.6)	28 (5.4)
Anorexia	25 (5.0)	35 (6.7)
Constipation	118 (23.6)	94 (18.1)
Diarrhea	64 (12.8)	75 (14.5)
Dyspepsia	61 (12.2)	62 (11.9)
Gastritis	44 (8.8)	41 (7.9)
Gastroenteritis	35 (7.0)	40 (7.7)
Nausea	38 (7.6)	44 (8.5)
Rectal disorder	36 (7.2)	27 (5.2)
Vomiting	24 (4.8)	38 (7.3)
Endocrine system	59 (11.8)	67 (12.9)
Diabetes mellitus	26 (5.2)	23 (4.4)
Hemic and lymphatic system	80 (16.0)	94 (18.1)
Anemia	25 (5.0)	31 (6.0)
Metabolic and nutritional	257 (51.5)	270 (52.0)
Hypercholesteremia	70 (14.0)	72 (13.9)
Hyperglycemia	48 (9.6)	65 (12.5)
Hyperlipidaemia	43 (8.6)	50 (9.6)
Peripheral edema	89 (17.8)	62 (11.9)
Weight gain	46 (9.2)	46 (8.9)
Weight loss	34 (6.8)	25 (4.8)

Table 24. Number (%) of Subjects With Treatment-Emergent Adverse Events With an Incidence of ≥5% in at Least 1 Group, Bazedoxifene 20 mg Versus Placebo, Subjects Who Entered Extension II (SP2) Months 0 to 84

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=499)	Placebo (n=519)
Musculoskeletal system	331 (66.3)	335 (64.5)
Arthralgia	228 (45.7)	235 (45.3)
Arthrosis	77 (15.4)	84 (16.2)
Leg cramps	83 (16.6)	71 (13.7)
Myalgia	34 (6.8)	36 (6.9)
Tenosynovitis	21 (4.2)	28 (5.4)
Nervous system	253 (50.7)	276 (53.2)
Anxiety	33 (6.6)	47 (9.1)
Depression	41 (8.2)	45 (8.7)
Dizziness	69 (13.8)	61 (11.8)
Insomnia	54 (10.8)	70 (13.5)
Memory impairment	28 (5.6)	22 (4.2)
Neuralgia	33 (6.6)	26 (5.0)
Paresthesia	38 (7.6)	35 (6.7)
Vertigo	66 (13.2)	58 (11.2)
Respiratory system	262 (52.5)	260 (50.1)
Bronchitis	64 (12.8)	61 (11.8)
Cough increased	91 (18.2)	85 (16.4)
Dyspnea	21 (4.2)	28 (5.4)
Pharyngitis	52 (10.4)	71 (13.7)
Pneumonia	36 (7.2)	55 (10.6)
Rhinitis	26 (5.2)	26 (5.0)
Sinusitis	39 (7.8)	34 (6.6)
Upper respiratory infection	53 (10.6)	41 (7.9)
Skin and appendages	187 (37.5)	204 (39.3)
Fungal dermatitis	30 (6.0)	25 (4.8)
Pruritus	53 (10.6)	57 (11.0)
Rash	23 (4.6)	32 (6.2)
Special senses	185 (37.1)	179 (34.5)
Cataract specified	53 (10.6)	50 (9.6)
Conjunctivitis	18 (3.6)	27 (5.2)
Tinnitus	25 (5.0)	23 (4.4)
Urogenital system	293 (58.7)	312 (60.1)
Breast disorder	51 (10.2)	53 (10.2)
Cervix disorder	52 (10.4)	59 (11.4)
Cystitis	35 (7.0)	32 (6.2)
Dysuria	35 (7.0)	36 (6.9)
Urinary tract infection	70 (14.0)	86 (16.6)
Vaginitis	46 (9.2)	53 (10.2)

Table 24. Number (%) of Subjects With Treatment-Emergent Adverse Events With an Incidence of ≥5% in at Least 1 Group, Bazedoxifene 20 mg Versus Placebo, Subjects Who Entered Extension II (SP2) Months 0 to 84

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=499)	Placebo (n=519)
Adverse event associated with miscellaneous factors	29 (5.8)	35 (6.7)

AEs and SAEs are not separated out.
AE = adverse event; n = number of subjects in each treatment group;SAE = serious adverse event; SP2 = safety population 2.
a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system.

Table 25. Number (%) of Subjects With Treatment-Emergent Adverse Events With an Incidence of ≥5% in at Least 1 Group, Bazedoxifene Combined Versus Placebo, Subjects Who Entered Extension II (SP2) Months 0 to 84

Body System[a] Adverse Event	Bazedoxifene Combined (n=1011)	Placebo (n=519)
Any adverse event	999 (98.8)	515 (99.2)
Body as a whole	898 (88.8)	472 (90.9)
Abdominal pain	295 (29.2)	161 (31.0)
Accidental injury	347 (34.3)	180 (34.7)
Asthenia	150 (14.8)	70 (13.5)
Back pain	442 (43.7)	220 (42.4)
Chest pain	113 (11.2)	63 (12.1)
Fever	32 (3.2)	32 (6.2)
Flu syndrome	367 (36.3)	219 (42.2)
Headache	296 (29.3)	147 (28.3)
Infection	349 (34.5)	186 (35.8)
Neck pain	116 (11.5)	59 (11.4)
Pain	450 (44.5)	227 (43.7)
Cardiovascular system	583 (57.7)	283 (54.5)
Hypertension	381 (37.7)	181 (34.9)
Tachycardia	37 (3.7)	27 (5.2)
Varicose vein	44 (4.4)	30 (5.8)
Vasodilatation	126 (12.5)	39 (7.5)
Digestive system	624 (61.7)	324 (62.4)
Abdominal distension	32 (3.2)	28 (5.4)
Anorexia	42 (4.2)	35 (6.7)
Constipation	235 (23.2)	94 (18.1)
Diarrhea	132 (13.1)	75 (14.5)
Dyspepsia	126 (12.5)	62 (11.9)
Gastritis	82 (8.1)	41 (7.9)
Gastroenteritis	80 (7.9)	40 (7.7)
Nausea	84 (8.3)	44 (8.5)
Rectal disorder	64 (6.3)	27 (5.2)
Vomiting	56 (5.5)	38 (7.3)
Hemic and lymphatic system	169 (16.7)	94 (18.1)
Anemia	56 (5.5)	31 (6.0)
Metabolic and nutritional	521 (51.5)	270 (52.0)
Hypercholesteremia	122 (12.1)	72 (13.9)
Hyperglycemia	90 (8.9)	65 (12.5)
Hyperlipidaemia	95 (9.4)	50 (9.6)
Peripheral edema	166 (16.4)	62 (11.9)
Weight gain	82 (8.1)	46 (8.9)
Weight loss	65 (6.4)	25 (4.8)
Musculoskeletal system	672 (66.5)	335 (64.5)
Arthralgia	464 (45.9)	235 (45.3)
Arthritis	52 (5.1)	14 (2.7)

Table 25. Number (%) of Subjects With Treatment-Emergent Adverse Events With an Incidence of ≥5% in at Least 1 Group, Bazedoxifene Combined Versus Placebo, Subjects Who Entered Extension II (SP2) Months 0 to 84

Body System[a] Adverse Event	Bazedoxifene Combined (n=1011)	Placebo (n=519)
Arthrosis	144 (14.2)	84 (16.2)
Leg cramps	173 (17.1)	71 (13.7)
Myalgia	54 (5.3)	36 (6.9)
Tenosynovitis	40 (4.0)	28 (5.4)
Nervous system	514 (50.8)	276 (53.2)
Anxiety	70 (6.9)	47 (9.1)
Depression	93 (9.2)	45 (8.7)
Dizziness	128 (12.7)	61 (11.8)
Insomnia	124 (12.3)	70 (13.5)
Memory impairment	67 (6.6)	22 (4.2)
Neuralgia	58 (5.7)	26 (5.0)
Paresthesia	70 (6.9)	35 (6.7)
Vertigo	133 (13.2)	58 (11.2)
Respiratory system	536 (53.0)	260 (50.1)
Bronchitis	137 (13.6)	61 (11.8)
Cough increased	186 (18.4)	85 (16.4)
Dyspnea	54 (5.3)	28 (5.4)
Pharyngitis	115 (11.4)	71 (13.7)
Pneumonia	69 (6.8)	55 (10.6)
Rhinitis	55 (5.4)	26 (5.0)
Sinusitis	73 (7.2)	34 (6.6)
Upper respiratory infection	103 (10.2)	41 (7.9)
Skin and appendages	363 (35.9)	204 (39.3)
Fungal dermatitis	64 (6.3)	25 (4.8)
Pruritus	108 (10.7)	57 (11.0)
Rash	52 (5.1)	32 (6.2)
Special senses	379 (37.5)	179 (34.5)
Cataract specified	113 (11.2)	50 (9.6)
Conjunctivitis	38 (3.8)	27 (5.2)
Tinnitus	51 (5.0)	23 (4.4)
Urogenital system	600 (59.3)	312 (60.1)
Breast disorder	106 (10.5)	53 (10.2)
Cervix disorder	118 (11.7)	59 (11.4)
Cystitis	71 (7.0)	32 (6.2)
Dysuria	78 (7.7)	36 (6.9)
Urinary tract infection	141 (13.9)	86 (16.6)
Vaginitis	86 (8.5)	53 (10.2)
Adverse event associated with miscellaneous factors	51 (5.0)	35 (6.7)

Table 25. Number (%) of Subjects With Treatment-Emergent Adverse Events With an Incidence of ≥5% in at Least 1 Group, Bazedoxifene Combined Versus Placebo, Subjects Who Entered Extension II (SP2) Months 0 to 84

Body System[a] Adverse Event	Bazedoxifene Combined (n=1011)	Placebo (n=519)

AEs and SAEs are not separated out.
AEs = adverse events; n = number of subjects in each treatment group; SAE = serious adverse event; SP2 = safety population 2.
a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system.

Treatment-Related Adverse Events: The overall distribution of TEAEs is summarized on the basis of their relatedness and severity in Table 26 for the bazedoxifene 20 mg treatment group compared with placebo. The overall distribution of TEAEs is summarized on the basis of their relatedness and severity in Table 27 for the bazedoxifene combined treatment group compared with placebo.

Table 26. Number (%) of Subjects With Drug Related Treatment Emergent Adverse Events, Bazedoxifene 20 mg Versus Placebo, Months 0 to 84, SP1

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=1886)	Placebo (n=1885)
Any adverse event	66 (3.5)	72 (3.8)
Body as a whole		
Abdominal pain	4 (0.2)	5 (0.3)
Accidental injury	0	1 (0.1)
Asthenia	1 (0.1)	0
Back pain	2 (0.1)	2 (0.1)
Chest pain	2 (0.1)	0
Chest pain substernal	0	1 (0.1)
Headache	5 (0.3)	3 (0.2)
Overdose	0	1 (0.1)
Pain	4 (0.2)	1 (0.1)
Cardiovascular system		
Angina pectoris	1 (0.1)	1 (0.1)
Arteriosclerosis	0	1 (0.1)
Atrial fibrillation	0	1 (0.1)
Cerebral ischemia	0	1 (0.1)
Cerebrovascular accident	2 (0.1)	2 (0.1)
Coronary artery disorder	1 (0.1)	0
Deep vein thrombosis	3 (0.2)	0
Extrasystoles	1 (0.1)	0
Hypertension	0	1 (0.1)
Migraine	0	3 (0.2)
Myocardial infarct	0	2 (0.1)
Occlusion	0	1 (0.1)
Palpitation	1 (0.1)	1 (0.1)
Pulmonary embolus	4 (0.2)	1 (0.1)
Qt interval prolonged	1 (0.1)	0
Retinal artery occlusion	1 (0.1)	0
Retinal vein thrombosis	0	1 (0.1)
Thrombophlebitis superficial	2 (0.1)	1 (0.1)
Varicose vein	4 (0.2)	0
Vasodilatation	6 (0.3)	1 (0.1)
Digestive system		
Constipation	1 (0.1)	4 (0.2)
Flatulence	0	1 (0.1)
Gastritis	1 (0.1)	4 (0.2)
Gastroesophageal reflux disease	1 (0.1)	0
Intestinal ulcer	0	1 (0.1)
Jaundice	0	1 (0.1)
Liver function tests abnormal	1 (0.1)	1 (0.1)
Nausea	1 (0.1)	2 (0.1)
Vomiting	0	1 (0.1)

Table 26. Number (%) of Subjects With Drug Related Treatment Emergent Adverse Events, Bazedoxifene 20 mg Versus Placebo, Months 0 to 84, SP1

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=1886)	Placebo (n=1885)
Hemic and lymphatic system		
Anemia	0	1 (0.1)
Metabolic and nutritional		
Alkaline phosphatase increased	0	1 (0.1)
Avitaminosis	0	1 (0.1)
Edema	0	1 (0.1)
Peripheral edema	0	1 (0.1)
SGOT increased	1 (0.1)	0
SGPT increased	1 (0.1)	0
Weight gain	0	2 (0.1)
Musculoskeletal system		
Arthralgia	1 (0.1)	5 (0.3)
Arthritis	0	1 (0.1)
Leg cramps	10 (0.5)	6 (0.3)
Muscle cramp	1 (0.1)	1 (0.1)
Myalgia	0	1 (0.1)
Osteoporosis	0	2 (0.1)
Nervous system		
Depression	1 (0.1)	2 (0.1)
Hypertonia	1 (0.1)	0
Hypesthesia	0	1 (0.1)
Nervousness	0	1 (0.1)
Restless legs syndrome	0	1 (0.1)
Vertigo	1 (0.1)	0
Respiratory system		
Cough increased	0	1 (0.1)
Pneumonia	0	1 (0.1)
Skin and appendages		
Alopecia	1 (0.1)	0
Lichenoid dermatitis	1 (0.1)	0
Pruritus	1 (0.1)	1 (0.1)
Rash	1 (0.1)	0
Special senses		
Abnormal vision	0	1 (0.1)
Urogenital system		
Breast carcinoma	0	1 (0.1)
Breast disorder	7 (0.4)	6 (0.3)
Endometrial carcinoma	0	1 (0.1)
Ovarian carcinoma	1 (0.1)	0
Vaginal dryness	0	1 (0.1)

Table 26. Number (%) of Subjects With Drug Related Treatment Emergent Adverse Events, Bazedoxifene 20 mg Versus Placebo, Months 0 to 84, SP1

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=1886)	Placebo (n=1885)

n = number of subjects in each treatment group; SGOT = serum glutamate oxaloacetate transaminase; SGPT = serum glutamate pyruvate transaminase; SP1 = safety population 1.

a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system.

Table 27. Number (%) of Subjects With Drug Related Treatment Emergent Adverse Events, Bazedoxifene Combined Versus Placebo, Months 0 to 84, SP1

Body System[a] Adverse Event	Bazedoxifene Combined (n=3758)	Placebo (n=1885)
Any adverse event	138 (3.7)	72 (3.8)
Body as a whole		
Abdominal pain	6 (0.2)	5 (0.3)
Accidental injury	0	1 (0.1)
Asthenia	4 (0.1)	0
Back pain	6 (0.2)	2 (0.1)
Chest pain	3 (0.1)	0
Chest pain substernal	0	1 (0.1)
Headache	11 (0.3)	3 (0.2)
Overdose	0	1 (0.1)
Pain	6 (0.2)	1 (0.1)
Cardiovascular system		
Angina pectoris	1 (0.0)	1 (0.1)
Arteriosclerosis	0	1 (0.1)
Atrial fibrillation	0	1 (0.1)
Cerebral ischemia	0	1 (0.1)
Cerebrovascular accident	4 (0.1)	2 (0.1)
Coronary artery disorder	1 (0.0)	0
Deep vein thrombosis	7 (0.2)	0
Extrasystoles	1 (0.0)	0
Hypertension	0	1 (0.1)
Migraine	0	3 (0.2)
Myocardial infarct	0	2 (0.1)
Occlusion	0	1 (0.1)
Palpitation	2 (0.1)	1 (0.1)
Pulmonary embolus	5 (0.1)	1 (0.1)
QT interval prolonged	1 (0.0)	0
Retinal artery occlusion	1 (0.0)	0
Retinal vein thrombosis	0	1 (0.1)
Syncope	1 (0.0)	0
Thrombophlebitis superficial	2 (0.1)	1 (0.1)
Varicose vein	4 (0.1)	0
Vasodilatation	14 (0.4)	1 (0.1)
Digestive system		
Abdominal distension	1 (0.0)	0
Constipation	10 (0.3)	4 (0.2)
Diarrhea	3 (0.1)	0
Dyspepsia	1 (0.0)	0
Flatulence	0	1 (0.1)
Gastritis	2 (0.1)	4 (0.2)
Gastroesophageal reflux disease	1 (0.0)	0
Intestinal ulcer	0	1 (0.1)

Table 27. Number (%) of Subjects With Drug Related Treatment Emergent Adverse Events, Bazedoxifene Combined Versus Placebo, Months 0 to 84, SP1

Body System[a] Adverse Event	Bazedoxifene Combined (n=3758)	Placebo (n=1885)
Jaundice	0	1 (0.1)
Liver function tests abnormal	1 (0.0)	1 (0.1)
Nausea	2 (0.1)	2 (0.1)
Stomach ulcer	1 (0.0)	0
Vomiting	0	1 (0.1)
Endocrine system		
Diabetes mellitus	1 (0.0)	0
Hemic and lymphatic system		
Anemia	0	1 (0.1)
Metabolic and nutritional		
Alkaline phosphatase increased	0	1 (0.1)
Avitaminosis	0	1 (0.1)
Edema	0	1 (0.1)
Hyperlipemia	1 (0.0)	0
Peripheral edema	0	1 (0.1)
SGOT increased	1 (0.0)	0
SGPT increased	1 (0.0)	0
Weight gain	0	2 (0.1)
Weight loss	1 (0.0)	0
Musculoskeletal system		
Arthralgia	2 (0.1)	5 (0.3)
Arthritis	0	1 (0.1)
Bone pain	1 (0.0)	0
Leg cramps	22 (0.6)	6 (0.3)
Muscle cramp	1 (0.0)	1 (0.1)
Muscle spasms	1 (0.0)	0
Myalgia	0	1 (0.1)
Myasthenia	1 (0.0)	0
Osteoporosis	0	2 (0.1)
Nervous system		
Abnormal dreams	1 (0.0)	0
Depression	1 (0.0)	2 (0.1)
Hypertonia	1 (0.0)	0
Hypesthesia	1 (0.0)	1 (0.1)
Insomnia	1 (0.0)	0
Libido decreased	1 (0.0)	0
Nervousness	0	1 (0.1)
Restless legs syndrome	0	1 (0.1)
Vertigo	1 (0.0)	0
Respiratory system		
Cough increased	0	1 (0.1)
Pneumonia	0	1 (0.1)

Table 27. Number (%) of Subjects With Drug Related Treatment Emergent Adverse Events, Bazedoxifene Combined Versus Placebo, Months 0 to 84, SP1

Body System[a] Adverse Event	Bazedoxifene Combined (n=3758)	Placebo (n=1885)
Skin and appendages		
Alopecia	2 (0.1)	0
Lichenoid dermatitis	1 (0.0)	0
Pruritus	1 (0.0)	1 (0.1)
Rash	1 (0.0)	0
Urticaria	1 (0.0)	0
Special senses		
Abnormal vision	0	1 (0.1)
Deafness	1 (0.0)	0
Vestibular disorder	1 (0.0)	0
Urogenital system		
Bladder neoplasm	1 (0.0)	0
Breast carcinoma	1 (0.0)	1 (0.1)
Breast disorder	12 (0.3)	6 (0.3)
Endometrial carcinoma	0	1 (0.1)
Endometrial neoplasia	1 (0.0)	0
Ovarian carcinoma	1 (0.0)	0
Vaginal dryness	0	1 (0.1)

n = number of subjects in each treatment group; SGOT = serum glutamate oxaloacetate transaminase; SGPT = serum glutamate pyruvate transaminase; SP1 = safety population 1.

a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system.

Serious Adverse Events: Overall, there was no significant difference in the percentage of subjects with SAEs between the bazedoxifene 20 mg treatment (26.9%) and placebo (25.4%) groups (Table 28). A total of 1454 (25.8%) subjects in the bazedoxifene combined treatment and placebo groups reported SAEs during the study (Table 29).

The distribution of all SAEs reported since the start of study participation for the bazedoxifene 20 mg Extension II population is presented in Table 30. A summary of SAEs that occurred in the Extension II bazedoxifene combined treatment and placebo groups during Months 0 to 84 is presented in Table 31.

In the opinion of the investigators, 33 (1.7%) subjects in the bazedoxifene 20 mg treatment group and 31 (1.6%) subjects in the placebo group had at least 1 SAE that was considered at least possibly related to test article Table 32. In the opinion of the investigators, 71 (1.9%) subjects in the bazedoxifene combined treatment group and 31 (1.6%) subjects in the placebo group had at least 1 SAE that was considered at least possibly related to test article (Table 33). Subjects in bazedoxifene 20 mg treatment group who participated in Extension II and had at least 1 SAE that was considered at least possibly related to test article are presented in Table 34. A summary of drug related SAEs that occurred in the bazedoxifene combined treatment and placebo groups during Months 0 to 84 is presented in Table 35.

Table 28. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene 20 mg Versus Placebo, SP1

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=1886)	Placebo (n=1885)
Any adverse event	507 (26.9)	479 (25.4)
Body as a whole	152 (8.1)	150 (8.0)
Abdominal pain	7 (0.4)	8 (0.4)
Abdominal syndrome acute	4 (0.2)	5 (0.3)
Abscess	8 (0.4)	3 (0.2)
Accidental injury	65 (3.4)	61 (3.2)
Accidental overdose	4 (0.2)	3 (0.2)
Adenoma	1 (0.1)	2 (0.1)
Allergic reaction	0	1 (0.1)
Anaphylactoid reaction	0	1 (0.1)
Asthenia	1 (0.1)	3 (0.2)
Back pain	9 (0.5)	4 (0.2)
Carcinoma	6 (0.3)	2 (0.1)
Cellulitis	1 (0.1)	0
Chest pain	6 (0.3)	12 (0.6)
Chest pain substernal	3 (0.2)	3 (0.2)
Collagen disorder	1 (0.1)	0
Cyst	6 (0.3)	0
Death	0	1 (0.1)
Fever	2 (0.1)	4 (0.2)
Fibrosis	0	1 (0.1)
Headache	0	1 (0.1)
Hernia	9 (0.5)	12 (0.6)
HIV test positive	1 (0.1)	1 (0.1)
Hormone level altered	0	1 (0.1)
Hydrocephalus	0	1 (0.1)
Hyperplasia	0	1 (0.1)
Infection	6 (0.3)	10 (0.5)
Lab test abnormal	1 (0.1)	0
Malaise	1 (0.1)	0
Neck pain	2 (0.1)	0
Neoplasm	8 (0.4)	9 (0.5)
Non-specified drug reaction	1 (0.1)	0
Overdose	10 (0.5)	10 (0.5)
Pain	2 (0.1)	2 (0.1)
Peritonitis	3 (0.2)	2 (0.1)
Sarcoma	0	1 (0.1)
Sepsis	3 (0.2)	3 (0.2)
Septic shock	4 (0.2)	1 (0.1)
Cardiovascular system	128 (6.8)	110 (5.8)
Angina pectoris	13 (0.7)	9 (0.5)
Aortic stenosis	3 (0.2)	2 (0.1)
Arrhythmia	4 (0.2)	0

Table 28. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene 20 mg Versus Placebo, SP1

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=1886)	Placebo (n=1885)
Arterial anomaly	1 (0.1)	2 (0.1)
Arterial thrombosis	1 (0.1)	0
Arteriosclerosis	1 (0.1)	2 (0.1)
Atrial fibrillation	9 (0.5)	6 (0.3)
Atrial flutter	2 (0.1)	0
Av block	1 (0.1)	0
Av block complete	0	1 (0.1)
Av block second degree	1 (0.1)	0
Bradycardia	0	2 (0.1)
Cardiac tamponade	1 (0.1)	0
Cardiovascular disorder	1 (0.1)	1 (0.1)
Carotid occlusion	0	1 (0.1)
Cerebral hemorrhage	1 (0.1)	2 (0.1)
Cerebral infarct	0	2 (0.1)
Cerebral ischemia	6 (0.3)	7 (0.4)
Cerebral thrombosis	0	1 (0.1)
Cerebrovascular accident	14 (0.7)	18 (1.0)
Cerebrovascular disorder	1 (0.1)	1 (0.1)
Congestive heart failure	3 (0.2)	2 (0.1)
Coronary artery disorder	9 (0.5)	3 (0.2)
Coronary occlusion	1 (0.1)	1 (0.1)
Deep vein thrombosis	8 (0.4)	3 (0.2)
Embolus lower extremity	1 (0.1)	0
Heart arrest	0	4 (0.2)
Heart failure	3 (0.2)	1 (0.1)
Hypertension	13 (0.7)	17 (0.9)
Intracranial hemorrhage	0	1 (0.1)
Migraine	1 (0.1)	0
Myocardial infarct	9 (0.5)	11 (0.6)
Myocardial ischemia	6 (0.3)	1 (0.1)
Palpitation	2 (0.1)	1 (0.1)
Pericarditis	1 (0.1)	0
Peripheral vascular disorder	3 (0.2)	0
Phlebitis	0	1 (0.1)
Pulmonary embolus	7 (0.4)	4 (0.2)
Pulmonary hypertension	0	1 (0.1)
Retinal artery occlusion	1 (0.1)	1 (0.1)
Retinal vein thrombosis	0	2 (0.1)

Table 28. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene 20 mg Versus Placebo, SP1

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=1886)	Placebo (n=1885)
Shock	3 (0.2)	1 (0.1)
Sick sinus syndrome	1 (0.1)	1 (0.1)
Subarachnoid hemorrhage	0	1 (0.1)
Supraventricular tachycardia	3 (0.2)	2 (0.1)
Syncope	8 (0.4)	6 (0.3)
Tachycardia	0	1 (0.1)
Thrombophlebitis superficial	4 (0.2)	0
Thrombosis	1 (0.1)	0
Valvular heart disease	3 (0.2)	0
Varicose vein	8 (0.4)	5 (0.3)
Vascular disorder	1 (0.1)	0
Vascular purpura	1 (0.1)	0
Vasculitis	1 (0.1)	0
Ventricular arrhythmia	0	1 (0.1)
Ventricular extrasystoles	0	1 (0.1)
Ventricular fibrillation	1 (0.1)	0
Digestive system	103 (5.5)	108 (5.7)
Abdominal distension	1 (0.1)	1 (0.1)
Biliary pain	2 (0.1)	1 (0.1)
Blood in stool	1 (0.1)	0
Carcinoma of mouth	0	1 (0.1)
Cholangitis	1 (0.1)	2 (0.1)
Cholecystitis	12 (0.6)	11 (0.6)
Cholelithiasis	21 (1.1)	31 (1.6)
Colitis	5 (0.3)	6 (0.3)
Constipation	6 (0.3)	1 (0.1)
Diarrhea	1 (0.1)	2 (0.1)
Duodenal ulcer	2 (0.1)	3 (0.2)
Enteritis	1 (0.1)	0
Enterocolitis	3 (0.2)	0
Esophageal stenosis	0	1 (0.1)
Fecal impaction	1 (0.1)	2 (0.1)
Fecal incontinence	0	1 (0.1)
Gastritis	4 (0.2)	2 (0.1)
Gastroenteritis	2 (0.1)	4 (0.2)
Gastroesophageal reflux disease	1 (0.1)	4 (0.2)
Gastrointestinal carcinoma	15 (0.8)	17 (0.9)
Gastrointestinal disorder	5 (0.3)	1 (0.1)
Gastrointestinal hemorrhage	3 (0.2)	3 (0.2)

Table 28. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene 20 mg Versus Placebo, SP1

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=1886)	Placebo (n=1885)
GI neoplasia	4 (0.2)	0
Hemorrhage of colon	1 (0.1)	0
Hepatitis	0	1 (0.1)
Hepatomegaly	1 (0.1)	0
Hiatal hernia	3 (0.2)	2 (0.1)
Ileus	1 (0.1)	3 (0.2)
Intestinal obstruction	4 (0.2)	4 (0.2)
Intestinal perforation	1 (0.1)	1 (0.1)
Jaundice	3 (0.2)	0
Large intestine perforation	2 (0.1)	0
Liver function tests abnormal	3 (0.2)	7 (0.4)
Malabsorption syndrome	1 (0.1)	0
Megacolon	0	2 (0.1)
Nausea	1 (0.1)	3 (0.2)
Pancreas disorder	1 (0.1)	1 (0.1)
Pancreatitis	1 (0.1)	1 (0.1)
Rectal disorder	11 (0.6)	7 (0.4)
Rectal hemorrhage	1 (0.1)	0
Stomach ulcer	0	5 (0.3)
Stomach ulcer hemorrhage	1 (0.1)	0
Vomiting	2 (0.1)	7 (0.4)
Endocrine system	16 (0.8)	7 (0.4)
ADH inappropriate	1 (0.1)	0
Diabetes mellitus	2 (0.1)	1 (0.1)
Goiter	4 (0.2)	0
Parathyroid disorder	1 (0.1)	4 (0.2)
Thyroid adenoma	2 (0.1)	0
Thyroid carcinoma	5 (0.3)	1 (0.1)
Thyroid disorder	0	1 (0.1)
Thyroiditis	1 (0.1)	0
Hemic and lymphatic system	8 (0.4)	13 (0.7)
Anemia	0	4 (0.2)
Chronic lymphocytic leukemia	2 (0.1)	1 (0.1)
Ecchymosis	1 (0.1)	0
Iron deficiency anemia	1 (0.1)	1 (0.1)
Leukocytosis	1 (0.1)	1 (0.1)
Leukopenia	1 (0.1)	1 (0.1)
Lymphocytosis	0	2 (0.1)
Lymphoma	1 (0.1)	4 (0.2)
Neutropenia	1 (0.1)	0

Table 28. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene 20 mg Versus Placebo, SP1

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=1886)	Placebo (n=1885)
Petechiae	0	1 (0.1)
Thrombocytopenia	1 (0.1)	1 (0.1)
Metabolic and nutritional	12 (0.6)	19 (1.0)
Acidosis	0	1 (0.1)
Alkaline phosphatase increased	0	4 (0.2)
Bilirubinemia	0	1 (0.1)
Cachexia	0	1 (0.1)
Dehydration	2 (0.1)	5 (0.3)
Edema	0	1 (0.1)
Electrolyte abnormality	0	1 (0.1)
Healing abnormal	3 (0.2)	1 (0.1)
Hypokalemia	0	2 (0.1)
Hyponatremia	0	1 (0.1)
Obesity	1 (0.1)	0
Peripheral edema	3 (0.2)	0
SGOT increased	1 (0.1)	5 (0.3)
SGPT increased	2 (0.1)	7 (0.4)
Weight gain	0	1 (0.1)
Weight loss	1 (0.1)	1 (0.1)
Musculoskeletal system	48 (2.5)	50 (2.7)
Arthralgia	5 (0.3)	9 (0.5)
Arthritis	7 (0.4)	4 (0.2)
Arthrosis	26 (1.4)	23 (1.2)
Bone disorder	1 (0.1)	1 (0.1)
Bursitis	1 (0.1)	1 (0.1)
Chondrodystrophy	0	1 (0.1)
Intervertebral disc protrusion	0	3 (0.2)
Joint disorder	0	1 (0.1)
Leg cramps	2 (0.1)	0
Meniscus lesion	1 (0.1)	1 (0.1)
Muscle spasms	0	1 (0.1)
Musculoskeletal anomaly	3 (0.2)	4 (0.2)
Myalgia	0	2 (0.1)
Myasthenia	1 (0.1)	1 (0.1)
Myopathy	0	1 (0.1)
Rheumatoid arthritis	1 (0.1)	0
Spinal fracture	1 (0.1)	0
Tendinous contracture	1 (0.1)	0
Tendon rupture	1 (0.1)	1 (0.1)
Tenosynovitis	0	1 (0.1)

Table 28. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene 20 mg Versus Placebo, SP1

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=1886)	Placebo (n=1885)
Nervous system	23 (1.2)	24 (1.3)
Addiction	1 (0.1)	0
Amnesia	3 (0.2)	0
Anxiety	1 (0.1)	3 (0.2)
Apathy	0	1 (0.1)
Aphasia	0	1 (0.1)
CNS neoplasia	0	1 (0.1)
Dementia	0	1 (0.1)
Depression	3 (0.2)	3 (0.2)
Dizziness	1 (0.1)	5 (0.3)
Emotional lability	1 (0.1)	0
Facial paralysis	1 (0.1)	0
Hemiplegia	0	1 (0.1)
Memory impairment	1 (0.1)	0
Nerve compression	1 (0.1)	2 (0.1)
Neuralgia	2 (0.1)	0
Neuritis	1 (0.1)	0
Paresis	3 (0.2)	1 (0.1)
Paresthesia	0	1 (0.1)
Radiculopathy nos	1 (0.1)	0
Somnolence	0	1 (0.1)
Speech disorder	0	1 (0.1)
Suicidal ideation	1 (0.1)	0
Tremor	0	1 (0.1)
Vertebrobasilar insufficiency	4 (0.2)	2 (0.1)
Vertigo	1 (0.1)	4 (0.2)
Respiratory system	48 (2.5)	47 (2.5)
Asthma	3 (0.2)	3 (0.2)
Atelectasis	2 (0.1)	1 (0.1)
Bronchitis	5 (0.3)	3 (0.2)
Carcinoma of lung	4 (0.2)	5 (0.3)
Chronic obstructive airways disease	6 (0.3)	7 (0.4)
Cough increased	0	2 (0.1)
Dyspnea	1 (0.1)	1 (0.1)
Emphysema	0	1 (0.1)
Epistaxis	0	1 (0.1)
Hemoptysis	0	1 (0.1)
Hemothorax	1 (0.1)	0
Laryngeal neoplasia	1 (0.1)	0

Table 28. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene 20 mg Versus Placebo, SP1

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=1886)	Placebo (n=1885)
Laryngitis	0	1 (0.1)
Lung disorder	2 (0.1)	2 (0.1)
Lung edema	3 (0.2)	2 (0.1)
Pharyngitis	1 (0.1)	0
Pleural effusion	0	1 (0.1)
Pneumonia	21 (1.1)	23 (1.2)
Pneumonitis	1 (0.1)	1 (0.1)
Pneumothorax	1 (0.1)	0
Respiratory failure	2 (0.1)	2 (0.1)
Sinusitis	1 (0.1)	1 (0.1)
Upper respiratory infection	0	1 (0.1)
Skin and appendages	25 (1.3)	33 (1.8)
Dermatitis allergic	0	1 (0.1)
Pruritus	1 (0.1)	1 (0.1)
Psoriasis	0	1 (0.1)
Rash	0	1 (0.1)
Skin benign neoplasm	0	1 (0.1)
Skin carcinoma	18 (1.0)	23 (1.2)
Skin melanoma	3 (0.2)	3 (0.2)
Skin necrosis	1 (0.1)	0
Skin ulcer	1 (0.1)	1 (0.1)
Subcutaneous nodule	0	1 (0.1)
Sweating	1 (0.1)	1 (0.1)
Urticaria	1 (0.1)	0
Special senses	15 (0.8)	6 (0.3)
Abnormal vision	1 (0.1)	1 (0.1)
Blindness transient	1 (0.1)	0
Cataract specified	7 (0.4)	1 (0.1)
Ear disorder	0	2 (0.1)
Eye hemorrhage	1 (0.1)	0
Glaucoma	2 (0.1)	0
Ophthalmitis	1 (0.1)	0
Optic neuritis	1 (0.1)	0
Retinal degeneration	0	2 (0.1)
Retinal detachment	1 (0.1)	0
Retinal disorder	2 (0.1)	1 (0.1)
Vitreous disorder	0	1 (0.1)
Urogenital system	75 (4.0)	76 (4.0)
Acute kidney failure	1 (0.1)	1 (0.1)

Table 28. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene 20 mg Versus Placebo, SP1

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=1886)	Placebo (n=1885)
Anuria	1 (0.1)	0
Bladder carcinoma	2 (0.1)	1 (0.1)
Bladder neoplasm	0	1 (0.1)
Breast carcinoma	14 (0.7)	11 (0.6)
Breast cyst	1 (0.1)	0
Breast disorder	1 (0.1)	0
Breast neoplasm	1 (0.1)	2 (0.1)
Cervix carcinoma in situ	2 (0.1)	0
Cervix disorder	1 (0.1)	2 (0.1)
Cervix neoplasm	2 (0.1)	3 (0.2)
Cystitis	0	2 (0.1)
Dysuria	0	1 (0.1)
Endometrial carcinoma	0	7 (0.4)
Endometrial disorder	2 (0.1)	1 (0.1)
Endometrial neoplasia	5 (0.3)	6 (0.3)
Genital leukoplakia	1 (0.1)	0
Hematuria	1 (0.1)	1 (0.1)
Hydronephrosis	1 (0.1)	0
Kidney calculus	4 (0.2)	2 (0.1)
Kidney failure	1 (0.1)	0
Kidney function abnormal	1 (0.1)	1 (0.1)
Ovarian carcinoma	5 (0.3)	0
Ovarian cyst	4 (0.2)	5 (0.3)
Ovarian disorder	3 (0.2)	1 (0.1)
Pyelonephritis	7 (0.4)	3 (0.2)
Urinary incontinence	6 (0.3)	9 (0.5)
Urinary retention	0	1 (0.1)
Urinary tract disorder	9 (0.5)	8 (0.4)
Urinary tract infection	6 (0.3)	3 (0.2)
Urination impaired	1 (0.1)	0
Urogenital anomaly	0	1 (0.1)
Urogenital disorder	1 (0.1)	1 (0.1)
Urolithiasis	1 (0.1)	0
Uterine disorder	7 (0.4)	9 (0.5)
Uterine fibroids enlarged	1 (0.1)	2 (0.1)
Vulvovaginal disorder	2 (0.1)	5 (0.3)
Adverse event associated with miscellaneous factors	6 (0.3)	5 (0.3)
Local reaction to procedure	5 (0.3)	3 (0.2)
Surgical procedure	1 (0.1)	2 (0.1)

Table 28. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene 20 mg Versus Placebo, SP1

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=1886)	Placebo (n=1885)

ADH = anti-diuretic hormone; Av = atrio-ventricular; GI = gastrointestinal; HIV = human immunodeficiency virus; n = number of subjects in each treatment group; SGOT = serum glutamate oxaloacetate transaminase; SGPT = serum glutamate pyruvate transaminase; SP1 = safety population 1.

a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system.

Table 29. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene Combined Versus Placebo, SP1

Body System[a] Adverse Event	Bazedoxifene Combined (n=3758)	Placebo (n=1885)
Any adverse event	975 (25.9)	479 (25.4)
Body as a whole	288 (7.7)	150 (8.0)
Abdominal pain	13 (0.3)	8 (0.4)
Abdominal syndrome acute	13 (0.3)	5 (0.3)
Abscess	10 (0.3)	3 (0.2)
Accidental injury	115 (3.1)	61 (3.2)
Accidental overdose	8 (0.2)	3 (0.2)
Adenoma	3 (0.1)	2 (0.1)
Allergic reaction	2 (0.1)	1 (0.1)
Anaphylactoid reaction	0	1 (0.1)
Asthenia	3 (0.1)	3 (0.2)
Back pain	13 (0.3)	4 (0.2)
Carcinoma	11 (0.3)	2 (0.1)
Cellulitis	1 (0.0)	0
Chest pain	15 (0.4)	12 (0.6)
Chest pain substernal	7 (0.2)	3 (0.2)
Collagen disorder	1 (0.0)	0
Cyst	6 (0.2)	0
Death	3 (0.1)	1 (0.1)
Fever	3 (0.1)	4 (0.2)
Fibrosis	0	1 (0.1)
General physical health deterioration	1 (0.0)	0
Headache	0	1 (0.1)
Hernia	15 (0.4)	12 (0.6)
HIV test positive	1 (0.0)	1 (0.1)
Hormone level altered	0	1 (0.1)
Hydrocephalus	0	1 (0.1)
Hyperplasia	0	1 (0.1)
Infection	16 (0.4)	10 (0.5)
Lab test abnormal	1 (0.0)	0
Malaise	2 (0.1)	0
Neck pain	3 (0.1)	0
Neoplasm	14 (0.4)	9 (0.5)
Non-specified drug reaction	1 (0.0)	0
Overdose	18 (0.5)	10 (0.5)
Pain	5 (0.1)	2 (0.1)
Peritonitis	4 (0.1)	2 (0.1)
Sarcoma	2 (0.1)	1 (0.1)
Sepsis	4 (0.1)	3 (0.2)
Septic shock	4 (0.1)	1 (0.1)
Suicide attempt	1 (0.0)	0
Cardiovascular system	252 (6.7)	110 (5.8)

Table 29. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene Combined Versus Placebo, SP1

Body System[a] Adverse Event	Bazedoxifene Combined (n=3758)	Placebo (n=1885)
Aneurysm	2 (0.1)	0
Angina pectoris	19 (0.5)	9 (0.5)
Aortic stenosis	7 (0.2)	2 (0.1)
Arrhythmia	5 (0.1)	0
Arterial anomaly	2 (0.1)	2 (0.1)
Arterial thrombosis	2 (0.1)	0
Arteriosclerosis	3 (0.1)	2 (0.1)
Atrial fibrillation	19 (0.5)	6 (0.3)
Atrial flutter	3 (0.1)	0
Av block	2 (0.1)	0
Av block complete	0	1 (0.1)
Av block second degree	1 (0.0)	0
Bradycardia	0	2 (0.1)
Cardiac tamponade	1 (0.0)	0
Cardiomyopathy	2 (0.1)	0
Cardiovascular disorder	3 (0.1)	1 (0.1)
Carotid occlusion	0	1 (0.1)
Carotid thrombosis	1 (0.0)	0
Cerebral hemorrhage	2 (0.1)	2 (0.1)
Cerebral infarct	4 (0.1)	2 (0.1)
Cerebral ischemia	16 (0.4)	7 (0.4)
Cerebral thrombosis	0	1 (0.1)
Cerebrovascular accident	31 (0.8)	18 (1.0)
Cerebrovascular disorder	1 (0.0)	1 (0.1)
Congestive heart failure	7 (0.2)	2 (0.1)
Coronary artery disorder	17 (0.5)	3 (0.2)
Coronary occlusion	2 (0.1)	1 (0.1)
Deep vein thrombosis	21 (0.6)	3 (0.2)
Embolus lower extremity	1 (0.0)	0
Extrasystoles	1 (0.0)	0
Heart arrest	0	4 (0.2)
Heart failure	8 (0.2)	1 (0.1)
Hypertension	21 (0.6)	17 (0.9)
Intracranial aneurysm	1 (0.0)	0
Intracranial hemorrhage	1 (0.0)	1 (0.1)
Migraine	1 (0.0)	0
Myocardial infarct	19 (0.5)	11 (0.6)
Myocardial ischemia	7 (0.2)	1 (0.1)
Palpitation	3 (0.1)	1 (0.1)
Pericarditis	2 (0.1)	0
Peripheral gangrene	1 (0.0)	0

Table 29. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene Combined Versus Placebo, SP1

Body System[a] Adverse Event	Bazedoxifene Combined (n=3758)	Placebo (n=1885)
Peripheral vascular disorder	4 (0.1)	0
Phlebitis	0	1 (0.1)
Pulmonary embolus	10 (0.3)	4 (0.2)
Pulmonary hypertension	0	1 (0.1)
Retinal artery occlusion	1 (0.0)	1 (0.1)
Retinal vein thrombosis	2 (0.1)	2 (0.1)
Shock	6 (0.2)	1 (0.1)
Sick sinus syndrome	3 (0.1)	1 (0.1)
Subarachnoid hemorrhage	2 (0.1)	1 (0.1)
Supraventricular tachycardia	4 (0.1)	2 (0.1)
Syncope	17 (0.5)	6 (0.3)
Tachycardia	0	1 (0.1)
Thrombophlebitis superficial	10 (0.3)	0
Thrombosis	1 (0.0)	0
Valvular heart disease	4 (0.1)	0
Varicose vein	10 (0.3)	5 (0.3)
Vascular disorder	1 (0.0)	0
Vascular purpura	1 (0.0)	0
Vasculitis	1 (0.0)	0
Ventricular arrhythmia	0	1 (0.1)
Ventricular extrasystoles	1 (0.0)	1 (0.1)
Ventricular fibrillation	1 (0.0)	0
Digestive system	195 (5.2)	108 (5.7)
Abdominal distension	1 (0.0)	1 (0.1)
Anorexia	1 (0.0)	0
Biliary pain	4 (0.1)	1 (0.1)
Blood in stool	1 (0.0)	0
Carcinoma of mouth	0	1 (0.1)
Cholangitis	2 (0.1)	2 (0.1)
Cholecystitis	24 (0.6)	11 (0.6)
Cholelithiasis	44 (1.2)	31 (1.6)
Cholestatic jaundice	1 (0.0)	0
Colitis	14 (0.4)	6 (0.3)
Constipation	10 (0.3)	1 (0.1)
Diarrhea	2 (0.1)	2 (0.1)
Duodenal ulcer	2 (0.1)	3 (0.2)
Duodenal ulcer perforation	1 (0.0)	0
Duodenitis	2 (0.1)	0
Dysphagia	1 (0.0)	0
Enteritis	1 (0.0)	0
Enterocolitis	4 (0.1)	0
Esophageal stenosis	1 (0.0)	1 (0.1)

Table 29. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene Combined Versus Placebo, SP1

Body System[a] Adverse Event	Bazedoxifene Combined (n=3758)	Placebo (n=1885)
Fecal impaction	1 (0.0)	2 (0.1)
Fecal incontinence	0	1 (0.1)
Gastritis	5 (0.1)	2 (0.1)
Gastroenteritis	3 (0.1)	4 (0.2)
Gastroesophageal reflux disease	1 (0.0)	4 (0.2)
Gastrointestinal carcinoma	28 (0.7)	17 (0.9)
Gastrointestinal disorder	7 (0.2)	1 (0.1)
Gastrointestinal hemorrhage	4 (0.1)	3 (0.2)
GI neoplasia	4 (0.1)	0
Hemorrhage of colon	1 (0.0)	0
Hemorrhagic gastritis	1 (0.0)	0
Hemorrhagic pancreatitis	1 (0.0)	0
Hepatic neoplasia	3 (0.1)	0
Hepatitis	0	1 (0.1)
Hepatomegaly	1 (0.0)	0
Hiatal hernia	5 (0.1)	2 (0.1)
Ileus	4 (0.1)	3 (0.2)
Intestinal obstruction	5 (0.1)	4 (0.2)
Intestinal perforation	1 (0.0)	1 (0.1)
Jaundice	4 (0.1)	0
Large intestine perforation	2 (0.1)	0
Liver function tests abnormal	6 (0.2)	7 (0.4)
Malabsorption syndrome	1 (0.0)	0
Megacolon	0	2 (0.1)
Nausea	3 (0.1)	3 (0.2)
Pancreas disorder	1 (0.0)	1 (0.1)
Pancreatitis	3 (0.1)	1 (0.1)
Periodontitis	1 (0.0)	0
Pyloric stenosis	1 (0.0)	0
Rectal disorder	18 (0.5)	7 (0.4)
Rectal hemorrhage	2 (0.1)	0
Stomach ulcer	0	5 (0.3)
Stomach ulcer hemorrhage	2 (0.1)	0
Ulcerative colitis	1 (0.0)	0
Vomiting	5 (0.1)	7 (0.4)
Endocrine system	31 (0.8)	7 (0.4)
ADH inappropriate	1 (0.0)	0
Diabetes mellitus	7 (0.2)	1 (0.1)
Goiter	9 (0.2)	0
Hyperthyroidism	1 (0.0)	0
Parathyroid disorder	1 (0.0)	4 (0.2)

Table 29. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene Combined Versus Placebo, SP1

Body System[a] Adverse Event	Bazedoxifene Combined (n=3758)	Placebo (n=1885)
Thyroid adenoma	3 (0.1)	0
Thyroid carcinoma	5 (0.1)	1 (0.1)
Thyroid disorder	3 (0.1)	1 (0.1)
Thyroid neoplasia	1 (0.0)	0
Thyroiditis	1 (0.0)	0
Hemic and lymphatic system	14 (0.4)	13 (0.7)
Anemia	2 (0.1)	4 (0.2)
Chronic lymphocytic leukemia	2 (0.1)	1 (0.1)
Ecchymosis	1 (0.0)	0
Iron deficiency anemia	2 (0.1)	1 (0.1)
Leukocytosis	1 (0.0)	1 (0.1)
Leukopenia	1 (0.0)	1 (0.1)
Lymphadenopathy	1 (0.0)	0
Lymphocytosis	1 (0.0)	2 (0.1)
Lymphoma	2 (0.1)	4 (0.2)
Neutropenia	1 (0.0)	0
Petechiae	0	1 (0.1)
Thrombocytopenia	1 (0.0)	1 (0.1)
Metabolic and nutritional	20 (0.5)	19 (1.0)
Acidosis	1 (0.0)	1 (0.1)
Alkaline phosphatase increased	1 (0.0)	4 (0.2)
Bilirubinemia	0	1 (0.1)
Cachexia	1 (0.0)	1 (0.1)
Dehydration	3 (0.1)	5 (0.3)
Edema	0	1 (0.1)
Electrolyte abnormality	0	1 (0.1)
Healing abnormal	3 (0.1)	1 (0.1)
Hyperlipemia	1 (0.0)	0
Hypoglycemia	1 (0.0)	0
Hypokalemia	1 (0.0)	2 (0.1)
Hyponatremia	2 (0.1)	1 (0.1)
Obesity	1 (0.0)	0
Peripheral edema	3 (0.1)	0
SGOT increased	2 (0.1)	5 (0.3)
SGPT increased	3 (0.1)	7 (0.4)
Weight gain	0	1 (0.1)
Weight loss	1 (0.0)	1 (0.1)
Musculoskeletal system	91 (2.4)	50 (2.7)
Arthralgia	8 (0.2)	9 (0.5)

Table 29. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene Combined Versus Placebo, SP1

Body System[a] Adverse Event	Bazedoxifene Combined (n=3758)	Placebo (n=1885)
Arthritis Arthrosis	11 (0.3)	4 (0.2)
Bone disorder	1 (0.0)	1 (0.1)
Bursitis	1 (0.0)	1 (0.1)
Chondrodystrophy	0	1 (0.1)
Intervertebral disc protrusion	2 (0.1)	3 (0.2)
Joint disorder	2 (0.1)	1 (0.1)
Leg cramps	2 (0.1)	0
Meniscus lesion	1 (0.0)	1 (0.1)
Muscle spasms	0	1 (0.1)
Musculoskeletal anomaly	12 (0.3)	4 (0.2)
Myalgia	0	2 (0.1)
Myasthenia	2 (0.1)	1 (0.1)
Myopathy	0	1 (0.1)
Rheumatoid arthritis	1 (0.0)	0
Spinal fracture	2 (0.1)	0
Tendinous contracture	1 (0.0)	0
Tendon rupture	1 (0.0)	1 (0.1)
Tenosynovitis	0	1 (0.1)
Nervous system	46 (1.2)	24 (1.3)
Addiction	1 (0.0)	0
Amnesia	4 (0.1)	0
Anxiety	1 (0.0)	3 (0.2)
Apathy	0	1 (0.1)
Aphasia	0	1 (0.1)
CNS neoplasia	2 (0.1)	1 (0.1)
Confusion	2 (0.1)	0
Convulsion	1 (0.0)	0
Dementia	0	1 (0.1)
Depression	6 (0.2)	3 (0.2)
Dizziness	2 (0.1)	5 (0.3)
Emotional lability	1 (0.0)	0
Facial paralysis	1 (0.0)	0
Hallucinations	1 (0.0)	0
Hemiplegia	1 (0.0)	1 (0.1)
Manic depressive reaction	1 (0.0)	0
Memory impairment	1 (0.0)	0
Nerve compression	1 (0.0)	2 (0.1)
Neuralgia	2 (0.1)	0
Neuritis	1 (0.0)	0
Neuropathy	1 (0.0)	0

Table 29. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene Combined Versus Placebo, SP1

Body System[a] Adverse Event	Bazedoxifene Combined (n=3758)	Placebo (n=1885)
Paralysis	1 (0.0)	0
Paresis	4 (0.1)	1 (0.1)
Paresthesia	0	1 (0.1)
Parkinson's disease	1 (0.0)	0
Personality disorder	1 (0.0)	0
Radiculopathy nos	2 (0.1)	0
Somnolence	0	1 (0.1)
Speech disorder	1 (0.0)	1 (0.1)
Subdural hematoma	1 (0.0)	0
Suicidal ideation	1 (0.0)	0
Suicide	1 (0.0)	0
Tremor	0	1 (0.1)
Vertebrobasilar insufficiency	5 (0.1)	2 (0.1)
Vertigo	3 (0.1)	4 (0.2)
Respiratory system	90 (2.4)	47 (2.5)
Asthma	6 (0.2)	3 (0.2)
Atelectasis	2 (0.1)	1 (0.1)
Bronchiectasis	1 (0.0)	0
Bronchitis	8 (0.2)	3 (0.2)
Carcinoma of lung	7 (0.2)	5 (0.3)
Chronic obstructive airways disease	14 (0.4)	7 (0.4)
Cough increased	1 (0.0)	2 (0.1)
Dyspnea	2 (0.1)	1 (0.1)
Emphysema	0	1 (0.1)
Epistaxis	1 (0.0)	1 (0.1)
Hemoptysis	0	1 (0.1)
Hemothorax	1 (0.0)	0
Laryngeal neoplasia	1 (0.0)	0
Laryngitis	0	1 (0.1)
Lung disorder	6 (0.2)	2 (0.1)
Lung edema	3 (0.1)	2 (0.1)
Pharyngitis	1 (0.0)	0
Pleural disorder	1 (0.0)	0
Pleural effusion	0	1 (0.1)
Pleuritic pain	0	1 (0.0)
Pneumonia	40 (1.1)	1 (0.0)
Pneumonitis	1 (0.0)	1 (0.1)
Pneumothorax	2 (0.1)	0
Respiratory disorder	1 (0.0)	0
Respiratory distress syndrome	1 (0.0)	0
Respiratory failure	5 (0.1)	2 (0.1)

Table 29. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene Combined Versus Placebo, SP1

Body System[a] Adverse Event	Bazedoxifene Combined (n=3758)	Placebo (n=1885)
Sinusitis	1 (0.0)	1 (0.1)
Upper respiratory infection	0	1 (0.1)
Skin and appendages	63 (1.7)	33 (1.8)
Dermatitis allergic	0	1 (0.1)
Pruritus	2 (0.1)	1 (0.1)
Psoriasis	0	1 (0.1)
Rash	0	1 (0.1)
Skin benign neoplasm	0	1 (0.1)
Skin carcinoma	51 (1.4)	23 (1.2)
Skin disorder	2 (0.1)	0
Skin melanoma	6 (0.2)	3 (0.2)
Skin necrosis	1 (0.0)	0
Skin ulcer	1 (0.0)	1 (0.1)
Subcutaneous nodule	0	1 (0.1)
Sweating	1 (0.0)	1 (0.1)
Urticaria	1 (0.0)	0
Special senses	30 (0.8)	6 (0.3)
Abnormal vision	1 (0.0)	1 (0.1)
Blindness transient	3 (0.1)	0
Cataract specified	9 (0.2)	1 (0.1)
Deafness	1 (0.0)	0
Ear disorder	0	2 (0.1)
Eye disorder	2 (0.1)	0
Eye hemorrhage	1 (0.0)	0
Glaucoma	3 (0.1)	0
Keratitis	1 (0.0)	0
Ophthalmitis	1 (0.0)	0
Optic neuritis	1 (0.0)	0
Otitis media	1 (0.0)	0
Retinal degeneration	1 (0.0)	2 (0.1)
Retinal detachment	2 (0.1)	0
Retinal disorder	3 (0.1)	1 (0.1)
Tinnitus	1 (0.0)	0
Vestibular disorder	1 (0.0)	0
Vitreous disorder	0	1 (0.1)
Urogenital system	137 (3.6)	76 (4.0)
Acute kidney failure	1 (0.0)	1 (0.1)
Anuria	1 (0.0)	0
Bladder carcinoma	4 (0.1)	1 (0.1)
Bladder neoplasm	1 (0.0)	1 (0.1)
Breast carcinoma	23 (0.6)	11 (0.6)
Breast cyst	1 (0.0)	0

Table 29. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene Combined Versus Placebo, SP1

Body System[a] Adverse Event	Bazedoxifene Combined (n=3758)	Placebo (n=1885)
Breast disorder	4 (0.1)	0
Breast neoplasm	6 (0.2)	2 (0.1)
Cervix carcinoma	1 (0.0)	0
Cervix carcinoma in situ	2 (0.1)	0
Cervix disorder	2 (0.1)	2 (0.1)
Cervix neoplasm	3 (0.1)	3 (0.2)
Cystitis	4 (0.1)	2 (0.1)
Dysuria	1 (0.0)	1 (0.1)
Endometrial carcinoma	3 (0.1)	7 (0.4)
Endometrial disorder	3 (0.1)	1 (0.1)
Endometrial neoplasia	9 (0.2)	6 (0.3)
Genital leukoplakia	1 (0.0)	0
Hematuria	1 (0.0)	1 (0.1)
Hydronephrosis	4 (0.1)	0
Kidney calculus	5 (0.1)	2 (0.1)
Kidney failure	1 (0.0)	0
Kidney function abnormal	2 (0.1)	1 (0.1)
Ovarian carcinoma	6 (0.2)	0
Ovarian cyst	5 (0.1)	5 (0.3)
Ovarian disorder	4 (0.1)	1 (0.1)
Pyelonephritis	10 (0.3)	3 (0.2)
Urinary incontinence	10 (0.3)	9 (0.5)
Urinary retention	0	1 (0.1)
Urinary tract disorder	18 (0.5)	8 (0.4)
Urinary tract infection	8 (0.2)	3 (0.2)
Urination impaired	1 (0.0)	0
Urogenital anomaly	0	1 (0.1)
Urogenital disorder	1 (0.0)	1 (0.1)
Urolithiasis	1 (0.0)	0
Uterine disorder	17 (0.5)	9 (0.5)
Uterine fibroids enlarged	1 (0.0)	2 (0.1)
Vaginitis	1 (0.0)	0
Vulvovaginal disorder	3 (0.1)	5 (0.3)
Adverse event associated with miscellaneous factors	10 (0.3)	5 (0.3)
Local reaction to procedure	8 (0.2)	3 (0.2)
Surgical procedure	2 (0.1)	2 (0.1)

ADH = anti-diuretic hormone; Av = atrio-ventricular; GI = gastrointestinal; HIV = human immunodeficiency virus; n = number of subjects in each treatment group; SGOT = serum glutamate oxaloacetate transaminase; SGPT = serum glutamate pyruvate transaminase; SP1 = safety population 1.

Table 29. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene Combined Versus Placebo, SP1

Body System[a] Adverse Event	Bazedoxifene Combined (n=3758)	Placebo (n=1885)

a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system.

Table 30. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene 20 mg, Subjects Who Entered Extension II (SP2), Month 0 to 84

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=499)	Placebo (n=519)
Any adverse event	146 (29.3)	151 (29.1)
Body as a whole	42 (8.4)	53 (10.2)
Abdominal pain	1 (0.2)	3 (0.6)
Abdominal syndrome acute	2 (0.4)	3 (0.6)
Abscess	3 (0.6)	1 (0.2)
Accidental injury	21 (4.2)	20 (3.9)
Accidental overdose	1 (0.2)	0
Adenoma	0	1 (0.2)
Allergic reaction	0	1 (0.2)
Anaphylactoid reaction	0	1 (0.2)
Asthenia	1 (0.2)	0
Back pain	1 (0.2)	2 (0.4)
Cellulitis	1 (0.2)	0
Chest pain	1 (0.2)	5 (1.0)
Cyst	2 (0.4)	0
Fever	0	2 (0.4)
Fibrosis	0	1 (0.2)
Hernia	2 (0.4)	8 (1.5)
Infection	1 (0.2)	4 (0.8)
Neoplasm	4 (0.8)	3 (0.6)
Non-specified drug reaction	1 (0.2)	0
Overdose	2 (0.4)	4 (0.8)
Peritonitis	0	1 (0.2)
Sepsis	0	1 (0.2)
Cardiovascular system	30 (6.0)	24 (4.6)
Angina pectoris	2 (0.4)	4 (0.8)
Aortic stenosis	1 (0.2)	0
Arrhythmia	1 (0.2)	0
Arterial anomaly	1 (0.2)	0
Atrial fibrillation	2 (0.4)	1 (0.2)
Av block second degree	1 (0.2)	0
Cardiovascular disorder	1 (0.2)	0
Cerebrovascular accident	4 (0.8)	1 (0.2)
Congestive heart failure	0	1 (0.2)
Coronary artery disorder	0	1 (0.2)
Embolus lower extremity	1 (0.2)	0
Heart failure	0	1 (0.2)
Hypertension	6 (1.2)	5 (1.0)
Migraine	1 (0.2)	0
Myocardial infarct	1 (0.2)	2 (0.4)
Myocardial ischemia	4 (0.8)	1 (0.2)
Palpitation	2 (0.4)	0

Table 30. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene 20 mg, Subjects Who Entered Extension II (SP2), Month 0 to 84

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=499)	Placebo (n=519)
Peripheral vascular disorder	1 (0.2)	0
Phlebitis	0	1 (0.2)
Pulmonary embolus	1 (0.2)	0
Retinal artery occlusion	0	1 (0.2)
Supraventricular tachycardia	2 (0.4)	0
Syncope	1 (0.2)	2 (0.4)
Thrombosis	1 (0.2)	0
Varicose vein	5 (1.0)	5 (1.0)
Vascular disorder	1 (0.2)	0
Vasculitis	1 (0.2)	0
Ventricular extrasystoles	0	1 (0.2)
Digestive system	33 (6.6)	38 (7.3)
Abdominal distension	0	1 (0.2)
Biliary pain	0	1 (0.2)
Cholangitis	0	1 (0.2)
Cholecystitis	4 (0.8)	4 (0.8)
Cholelithiasis	11 (2.2)	12 (2.3)
Colitis	0	3 (0.6)
Constipation	2 (0.4)	1 (0.2)
Duodenal ulcer	1 (0.2)	1 (0.2)
Enteritis	1 (0.2)	0
Enterocolitis	2 (0.4)	0
Fecal impaction	0	2 (0.4)
Fecal incontinence	0	1 (0.2)
Gastritis	1 (0.2)	0
Gastroenteritis	1 (0.2)	3 (0.6)
Gastroesophageal reflux disease	0	1 (0.2)
Gastrointestinal carcinoma	2 (0.4)	3 (0.6)
Gastrointestinal hemorrhage	1 (0.2)	0
GI neoplasia	1 (0.2)	0
Hiatal hernia	0	1 (0.2)
Ileus	1 (0.2)	1 (0.2)
Intestinal obstruction	2 (0.4)	1 (0.2)
Jaundice	1 (0.2)	0
Liver function tests abnormal	0	2 (0.4)
Malabsorption syndrome	1 (0.2)	0
Megacolon	0	1 (0.2)
Nausea	0	2 (0.4)
Pancreatitis	0	1 (0.2)
Rectal disorder	3 (0.6)	5 (1.0)
Rectal hemorrhage	1 (0.2)	0
Vomiting	0	1 (0.2)

Table 30. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene 20 mg, Subjects Who Entered Extension II (SP2), Month 0 to 84

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=499)	Placebo (n=519)
Endocrine system	6 (1.2)	1 (0.2)
Diabetes mellitus	0	1 (0.2)
Thyroid adenoma	2 (0.4)	0
Thyroid carcinoma	3 (0.6)	0
Thyroiditis	1 (0.2)	0
Hemic and lymphatic system	2 (0.4)	4 (0.8)
Anemia	0	3 (0.6)
Iron deficiency anemia	0	1 (0.2)
Lymphoma	1 (0.2)	1 (0.2)
Thrombocytopenia	1 (0.2)	0
Metabolic and nutritional	1 (0.2)	5 (1.0)
Alkaline phosphatase increased	0	1 (0.2)
Dehydration	0	2 (0.4)
Electrolyte abnormality	0	1 (0.2)
Healing abnormal	1 (0.2)	0
Hypokalemia	0	1 (0.2)
Hyponatremia	0	1 (0.2)
SGOT increased	0	2 (0.4)
SGPT increased	0	4 (0.8)
Musculoskeletal system	17 (3.4)	19 (3.7)
Arthralgia	1 (0.2)	3 (0.6)
Arthritis	1 (0.2)	1 (0.2)
Arthrosis	11 (2.2)	9 (1.7)
Bone disorder	1 (0.2)	1 (0.2)
Bursitis	0	1 (0.2)
Chondrodystrophy	0	1 (0.2)
Intervertebral disc protrusion	0	1 (0.2)
Leg cramps	1 (0.2)	0
Meniscus lesion	0	1 (0.2)
Muscle spasms	0	1 (0.2)
Musculoskeletal anomaly	1 (0.2)	1 (0.2)
Myalgia	0	1 (0.2)
Tendon rupture	1 (0.2)	1 (0.2)
Tenosynovitis	0	1 (0.2)
Nervous system	6 (1.2)	3 (0.6)
Anxiety	0	1 (0.2)
Depression	1 (0.2)	0
Dizziness	0	2 (0.4)
Emotional lability	1 (0.2)	0
Nerve compression	1 (0.2)	0
Neuralgia	1 (0.2)	0
Neuritis	1 (0.2)	0
Vertebrobasilar insufficiency	1 (0.2)	1 (0.2)

Table 30. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene 20 mg, Subjects Who Entered Extension II (SP2), Month 0 to 84

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=499)	Placebo (n=519)
Respiratory system	11 (2.2)	12 (2.3)
Asthma	0	1 (0.2)
Bronchitis	1 (0.2)	1 (0.2)
Carcinoma of lung	0	1 (0.2)
Chronic obstructive airways disease	1 (0.2)	4 (0.8)
Cough increased	0	2 (0.4)
Dyspnea	0	1 (0.2)
Laryngeal neoplasia	1 (0.2)	0
Lung edema	0	1 (0.2)
Pneumonia	8 (1.6)	7 (1.3)
Respiratory failure	0	1 (0.2)
Skin and appendages	7 (1.4)	15 (2.9)
Psoriasis	0	1 (0.2)
Rash	0	1 (0.2)
Skin carcinoma	5 (1.0)	12 (2.3)
Skin melanoma	0	1 (0.2)
Skin necrosis	1 (0.2)	0
Sweating	1 (0.2)	0
Special senses	4 (0.8)	3 (0.6)
Blindness transient	1 (0.2)	0
Cataract specified	3 (0.6)	1 (0.2)
Ear disorder	0	1 (0.2)
Eye hemorrhage	1 (0.2)	0
Retinal degeneration	0	1 (0.2)
Retinal disorder	0	1 (0.2)
Urogenital system	32 (6.4)	30 (5.8)
Acute kidney failure	1 (0.2)	1 (0.2)
Bladder carcinoma	1 (0.2)	1 (0.2)
Breast carcinoma	5 (1.0)	1 (0.2)
Breast neoplasm	1 (0.2)	0
Cervix carcinoma in situ	1 (0.2)	0
Cervix disorder	1 (0.2)	1 (0.2)
Cervix neoplasm	1 (0.2)	2 (0.4)
Cystitis	0	1 (0.2)
Endometrial carcinoma	0	2 (0.4)
Endometrial neoplasia	3 (0.6)	3 (0.6)
Genital leukoplakia	1 (0.2)	0
Kidney calculus	0	1 (0.2)
Ovarian cyst	1 (0.2)	1 (0.2)
Ovarian disorder	1 (0.2)	1 (0.2)
Pyelonephritis	4 (0.8)	2 (0.4)
Urinary incontinence	4 (0.8)	6 (1.2)

Table 30. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene 20 mg, Subjects Who Entered Extension II (SP2), Month 0 to 84

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=499)	Placebo (n=519)
Urinary tract disorder	5 (1.0)	3 (0.6)
Urinary tract infection	3 (0.6)	1 (0.2)
Urination impaired	1 (0.2)	0
Urogenital disorder	1 (0.2)	1 (0.2)
Uterine disorder	4 (0.8)	5 (1.0)
Uterine fibroids enlarged	0	1 (0.2)
Vulvovaginal disorder	1 (0.2)	3 (0.6)
Adverse event associated with miscellaneous factors	2 (0.4)	3 (0.6)
Local reaction to procedure	1 (0.2)	2 (0.4)
Surgical procedure	1 (0.2)	1 (0.2)

Av = atrio-ventricular; GI = gastrointestinal; n = number of subjects in each treatment group; SGOT = serum glutamate oxaloacetate transaminase; SGPT = serum glutamate pyruvate transaminase; SP2 = safety population 2.

a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system.

Table 31. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene Combined Versus Placebo, Subjects Who Entered Extension II (SP2), Month 0 to 84

Body System[a] Adverse Event	Bazedoxifene Combined (n=1011)	Placebo (n=1530)
Any adverse event	254 (24.2)	151 (29.1)
Body as a whole	75 (7.4)	53 (10.2)
Abdominal pain	4 (0.4)	3 (0.6)
Abdominal syndrome acute	4 (0.4)	3 (0.6)
Abscess	4 (0.4)	1 (0.2)
Accidental injury	39 (3.9)	20 (3.9)
Accidental overdose	4 (0.4)	0
Adenoma	0	1 (0.2)
Allergic reaction	0	1 (0.2)
Anaphylactoid reaction	0	1 (0.2)
Asthenia	1 (0.1)	0
Back pain	1 (0.1)	2 (0.4)
Cellulitis	1 (0.1)	0
Chest pain	2 (0.2)	5 (1.0)
Cyst	2 (0.2)	0
Fever	0	2 (0.4)
Fibrosis	0	1 (0.2)
Hernia	3 (0.3)	8 (1.5)
Infection	2 (0.2)	4 (0.8)
Neoplasm	5 (0.5)	3 (0.6)
Non-specified drug reaction	1 (0.1)	0
Overdose	4 (0.4)	4 (0.8)
Peritonitis	0	1 (0.2)
Sepsis	1 (0.1)	1 (0.2)
Cardiovascular system	50 (4.9)	24 (4.6)
Aneurysm	1 (0.1)	0
Angina pectoris	4 (0.4)	4 (0.8)
Aortic stenosis	1 (0.1)	0
Arrhythmia	1 (0.1)	0
Arterial anomaly	1 (0.1)	0
Atrial fibrillation	3 (0.3)	1 (0.2)
Av block second degree	1 (0.1)	0
Cardiovascular disorder	1 (0.1)	0
Cerebrovascular accident	5 (0.5)	1 (0.2)
Congestive heart failure	1 (0.1)	1 (0.2)
Coronary artery disorder	1 (0.1)	1 (0.2)
Coronary occlusion	1 (0.1)	0
Embolus lower extremity	1 (0.1)	0
Extrasystoles	1 (0.1)	0
Heart failure	0	1 (0.2)
Hypertension	7 (0.7)	5 (1.0)
Intracranial aneurysm	1 (0.1)	0

Table 31. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene Combined Versus Placebo, Subjects Who Entered Extension II (SP2), Month 0 to 84

Body System[a] Adverse Event	Bazedoxifene Combined (n=1011)	Placebo (n=1530)
Intracranial hemorrhage	1 (0.1)	0
Migraine	1 (0.1)	0
Myocardial infarct	3 (0.3)	2 (0.4)
Myocardial ischemia	4 (0.4)	1 (0.2)
Palpitation	2 (0.2)	0
Peripheral vascular disorder	1 (0.1)	0
Phlebitis	0	1 (0.2)
Pulmonary embolus	1 (0.1)	0
Retinal artery occlusion	0	1 (0.2)
Sick sinus syndrome	1 (0.1)	0
Subarachnoid hemorrhage	2 (0.2)	0
Supraventricular tachycardia	2 (0.2)	0
Syncope	5 (0.5)	2 (0.4)
Thrombosis	1 (0.1)	0
Varicose vein	7 (0.7)	5 (1.0)
Vascular disorder	1 (0.1)	0
Vasculitis	1 (0.1)	0
Ventricular extrasystoles	1 (0.1)	1 (0.2)
Digestive system	59 (5.8)	38 (7.3)
Abdominal distension	0	1 (0.2)
Biliary pain	0	1 (0.2)
Cholangitis	1 (0.1)	1 (0.2)
Cholecystitis	9 (0.9)	4 (0.8)
Cholelithiasis	23 (2.3)	12 (2.3)
Colitis	4 (0.4)	3 (0.6)
Constipation	2 (0.2)	1 (0.2)
Duodenal ulcer	1 (0.1)	1 (0.2)
Duodenal ulcer perforation	1 (0.1)	0
Duodenitis	1 (0.1)	0
Enteritis	1 (0.1)	0
Enterocolitis	3 (0.3)	0
Fecal impaction	0	2 (0.4)
Fecal incontinence	0	1 (0.2)
Gastritis	1 (0.1)	0
Gastroenteritis	2 (0.2)	3 (0.6)
Gastroesophageal reflux disease	0	1 (0.2)
Gastrointestinal carcinoma	3 (0.3)	3 (0.6)
Gastrointestinal hemorrhage	1 (0.1)	0
GI neoplasia	1 (0.1)	0
Hiatal hernia	0	1 (0.2)

Table 31. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene Combined Versus Placebo, Subjects Who Entered Extension II (SP2), Month 0 to 84

Body System[a] Adverse Event	Bazedoxifene Combined (n=1011)	Placebo (n=1530)
Ileus	1 (0.1)	1 (0.2)
Intestinal obstruction	2 (0.2)	1 (0.2)
Jaundice	1 (0.1)	0
Liver function tests abnormal	0	2 (0.4)
Malabsorption syndrome	1 (0.1)	0
Megacolon	0	1 (0.2)
Nausea	0	2 (0.4)
Pancreatitis	0	1 (0.2)
Periodontitis	1 (0.1)	0
Rectal disorder	5 (0.5)	5 (1.0)
Rectal hemorrhage	1 (0.1)	0
Stomach ulcer hemorrhage	1 (0.1)	0
Vomiting	0	1 (0.2)
Endocrine system	8 (0.8)	1 (0.2)
Diabetes mellitus	1 (0.1)	1 (0.2)
Thyroid adenoma	3 (0.3)	0
Thyroid carcinoma	3 (0.3)	0
Thyroiditis	1 (0.1)	0
Hemic and lymphatic system	2 (0.2)	4 (0.8)
Anemia	3 (0.6)	3 (0.2)
Iron deficiency anemia	0	1 (0.2)
Lymphoma	1 (0.1)	1 (0.2)
Thrombocytopenia	1 (0.1)	0
Metabolic and nutritional	2 (0.2)	5 (1.0)
Alkaline phosphatase increased	0	1 (0.2)
Cachexia	1 (0.1)	0
Dehydration	1 (0.1)	2 (0.4)
Electrolyte abnormality	0	1 (0.2)
Healing abnormal	1 (0.1)	0
Hypokalemia	0	1 (0.2)
Hyponatremia	0	1 (0.2)
SGOT increased	0	2 (0.4)
SGPT increased	0	4 (0.8)
Musculoskeletal system	27 (2.7)	19 (3.7)
Arthralgia	2 (0.2)	3 (0.6)
Arthritis	3 (0.3)	1 (0.2)
Arthrosis	16 (1.6)	9 (1.7)
Bone disorder	1 (0.1)	1 (0.2)
Bursitis	0	1 (0.2)
Chondrodystrophy	0	1 (0.2)
Intervertebral disc protrusion	0	1 (0.2)

Table 31. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene Combined Versus Placebo, Subjects Who Entered Extension II (SP2), Month 0 to 84

Body System[a] Adverse Event	Bazedoxifene Combined (n=1011)	Placebo (n=1530)
Leg cramps	1 (0.1)	0
Meniscus lesion	0	1 (0.2)
Muscle spasms	0	1 (0.2)
Musculoskeletal anomaly	3 (0.3)	1 (0.2)
Myalgia	0	1 (0.2)
Tendon rupture	1 (0.1)	1 (0.2)
Tenosynovitis	0	1 (0.2)
Nervous system	6 (0.6)	3 (0.6)
Anxiety	0	1 (0.2)
Depression	1 (0.1)	0
Dizziness	0	2 (0.4)
Emotional lability	1 (0.1)	0
Nerve compression	1 (0.1)	0
Neuralgia	1 (0.1)	0
Neuritis	1 (0.1)	0
Vertebrobasilar insufficiency	1 (0.1)	1 (0.2)
Respiratory system	17 (1.7)	12 (2.3)
Asthma	0	1 (0.2)
Bronchiectasis	1 (0.1)	0
Bronchitis	1 (0.1)	1 (0.2)
Carcinoma of lung	0	1 (0.2)
Chronic obstructive airways disease	3 (0.3)	4 (0.8)
Cough increased	0	2 (0.4)
Dyspnea	1 (0.1)	1 (0.2)
Laryngeal neoplasia	1 (0.1)	0
Lung edema	0	1 (0.2)
Pneumonia	12 (1.2)	7 (1.3)
Respiratory failure	0	1 (0.2)
Skin and appendages	17 (1.7)	15 (2.9)
Psoriasis	0	1 (0.2)
Rash	0	1 (0.2)
Skin carcinoma	14 (1.4)	12 (2.3)
Skin melanoma	1 (0.1)	1 (0.2)
Skin necrosis	1 (0.1)	0
Sweating	1 (0.1)	0
Special senses	7 (0.7)	3 (0.6)
Blindness transient	1 (0.1)	0
Cataract specified	3 (0.3)	1 (0.2)
Ear disorder	0	1 (0.2)
Eye disorder	1 (0.1)	0
Eye hemorrhage	1 (0.1)	0

Table 31. Number (%) of Subjects Reporting Serious Adverse Events, Bazedoxifene Combined Versus Placebo, Subjects Who Entered Extension II (SP2), Month 0 to 84

Body System[a] Adverse Event	Bazedoxifene Combined (n=1011)	Placebo (n=1530)
Otitis media	1 (0.1)	0
Retinal degeneration	0	1 (0.2)
Retinal disorder	0	1 (0.2)
Tinnitus	1 (0.1)	0
Urogenital system	50 (4.9)	30 (5.8)
Acute kidney failure	1 (0.1)	1 (0.2)
Bladder carcinoma	1 (0.1)	1 (0.2)
Breast carcinoma	6 (0.6)	1 (0.2)
Breast neoplasm	2 (0.2)	0
Cervix carcinoma in situ	1 (0.1)	0
Cervix disorder	1 (0.1)	1 (0.2)
Cervix neoplasm	1 (0.1)	2 (0.4)
Cystitis	3 (0.3)	1 (0.2)
Dysuria	1 (0.1)	0
Endometrial carcinoma	0	2 (0.4)
Endometrial neoplasia	3 (0.3)	3 (0.6)
Genital leukoplakia	1 (0.1)	0
Hydronephrosis	2 (0.2)	0
Kidney calculus	0	1 (0.2)
Ovarian cyst	1 (0.1)	1 (0.2)
Ovarian disorder	1 (0.1)	1 (0.2)
Pyelonephritis	6 (0.6)	2 (0.4)
Urinary incontinence	4 (0.4)	6 (1.2)
Urinary tract disorder	8 (0.8)	3 (0.6)
Urinary tract infection	4 (0.4)	1 (0.2)
Urination impaired	1 (0.1)	0
Urogenital disorder	1 (0.1)	1 (0.2)
Uterine disorder	10 (1.0)	5 (1.0)
Uterine fibroids enlarged	0	1 (0.2)
Vaginitis	1 (0.1)	0
Vulvovaginal disorder	2 (0.2)	3 (0.6)
Adverse event associated with miscellaneous factors	3 (0.3)	3 (0.6)
Local reaction to procedure	2 (0.2)	2 (0.4)
Surgical procedure	1 (0.1)	1 (0.2)

Av = atrio-ventricular; GI = gastrointestinal; n = number of subjects in each treatment group; SGOT = serum glutamate oxaloacetate transaminase; SGPT = serum glutamate pyruvate transaminase; SP2 = safety population

a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system.

Table 32. Number (%) of Subjects Reporting Drug Related Serious Adverse Events, Bazedoxifene 20 mg Versus Placebo, Month 0 to 84 (SP1)

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=1886)	Placebo (n=1885)
Any adverse event	33 (1.7)	31 (1.6)
Body as a whole		
Accidental overdose	0	1 (0.1)
Cyst	1 (0.1)	0
Overdose	1 (0.1)	2 (0.1)
Septic shock	1 (0.1)	0
Cardiovascular system		
Angina pectoris	1 (0.1)	0
Arteriosclerosis	1 (0.1)	1 (0.1)
Atrial fibrillation	0	1 (0.1)
Cerebral ischemia	2 (0.1)	1 (0.1)
Cerebrovascular accident	1 (0.1)	2 (0.1)
Coronary artery disorder	1 (0.1)	0
Deep vein thrombosis	6 (0.3)	1 (0.1)
Hypertension	0	1 (0.1)
Myocardial infarct	1 (0.1)	2 (0.1)
Pulmonary embolus	7 (0.4)	3 (0.2)
Retinal artery occlusion	1 (0.1)	0
Retinal vein thrombosis	0	1 (0.1)
Thrombophlebitis superficial	3 (0.2)	0
Digestive system		
Gastritis	0	1 (0.1)
Liver function tests abnormal	0	2 (0.1)
Nausea	0	1 (0.1)
Endocrine system		
Parathyroid disorder	1 (0.1)	0
Hemic and lymphatic system	1 (0.1)	1 (0.1)
Ecchymosis	1 (0.1)	0
Petechiae	0	1 (0.1)
Metabolic and nutritional		
Alkaline phosphatase increased	0	2 (0.1)
Bilirubinemia	0	1 (0.1)
Edema	0	1 (0.1)
Obesity	1 (0.1)	0
SGOT increased	1 (0.1)	1 (0.1)
SGPT increased	1 (0.1)	1 (0.1)
Weight gain	0	1 (0.1)
Musculoskeletal system		
Leg cramps	1 (0.1)	0
Myasthenia	0	1 (0.1)
Nervous system		
Hemiplegia	0	1 (0.1)

Table 32. Number (%) of Subjects Reporting Drug Related Serious Adverse Events, Bazedoxifene 20 mg Versus Placebo, Month 0 to 84 (SP1)

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=1886)	Placebo (n=1885)
Respiratory system		
Pneumonia	1 (0.1)	1 (0.1)
Skin and appendages	2 (0.1)	0
Pruritus	1 (0.1)	0
Urticaria	1 (0.1)	0
Special senses		
Abnormal vision	1 (0.1)	0
Urogenital system		
Anuria	1 (0.1)	0
Breast carcinoma	0	1 (0.1)
Endometrial carcinoma	0	3 (0.2)
Endometrial disorder	1 (0.1)	1 (0.1)
Endometrial neoplasia	1 (0.1)	2 (0.1)
Ovarian carcinoma	1 (0.1)	0
Ovarian cyst	0	2 (0.1)

n = number of subjects in each treatment group; SGOT = serum glutamate oxaloacetate transaminase; SGPT = serum glutamate pyruvate transaminase; SP1 = safety population 1.

a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system.

Table 33. Number (%) of Subjects Reporting Drug Related Serious Adverse Events, Bazedoxifene Combined Versus Placebo, Month 0 to 84 (SP1)

Body System[a] Adverse Event	Bazedoxifene Combined (n=3758)	Placebo (n=1885)
Any adverse event	71 (1.9)	31 (1.6)
Body as a whole		
Accidental overdose	2 (0.1)	1 (0.1)
Cyst	1 (0.0)	0
Overdose	1 (0.0)	2 (0.1)
Septic shock	1 (0.0)	0
Cardiovascular system		
Angina pectoris	1 (0.0)	0
Arteriosclerosis	1 (0.0)	1 (0.1)
Atrial fibrillation	0	1 (0.1)
Cerebral ischemia	4 (0.1)	1 (0.1)
Cerebrovascular accident		
Coronary artery disorder	2 (0.1)	0
Deep vein thrombosis	16 (0.4)	1 (0.1)
Hypertension	0	1 (0.1)
Myocardial infarct	1 (0.0)	2 (0.1)
Pulmonary embolus	8 (0.2)	3 (0.2)
Retinal artery occlusion	1 (0.0)	0
Retinal vein thrombosis	2 (0.1)	1 (0.1)
Thrombophlebitis superficial	8 (0.2)	0
Digestive system		
Gastritis	0	1 (0.1)
Liver function tests abnormal	1 (0.0)	2 (0.1)
Nausea	0	1 (0.1)
Endocrine system		
Parathyroid disorder	1 (0.0)	0
Hemic and lymphatic system		
Ecchymosis	1 (0.0)	0
Petechiae	0	1 (0.1)
Metabolic and nutritional		
Alkaline phosphatase increased	0	2 (0.1)
Bilirubinemia	0	1 (0.1)
Edema	0	1 (0.1)
Obesity	1 (0.0)	0
SGOT increased	1 (0.0)	1 (0.1)
SGPT increased	1 (0.0)	1 (0.1)
Weight gain	0	1 (0.1)
Musculoskeletal system		
Leg cramps	1 (0.0)	0
Myasthenia	1 (0.0)	1 (0.1)
Nervous system		
Hemiplegia	1 (0.0)	1 (0.1)

Table 33. Number (%) of Subjects Reporting Drug Related Serious Adverse Events, Bazedoxifene Combined Versus Placebo, Month 0 to 84 (SP1)

Body System[a] Adverse Event	Bazedoxifene Combined (n=3758)	Placebo (n=1885)
Respiratory system		
Pneumonia	1 (0.0)	1 (0.1)
Skin and appendages	2 (0.1)	0
Pruritus	1 (0.0)	0
Urticaria	1 (0.0)	0
Special senses		
Abnormal vision	1 (0.0)	0
Blindness transient	1 (0.0)	0
Urogenital system		
Anuria	1 (0.0)	0
Bladder neoplasm	1 (0.0)	0
Breast carcinoma	1 (0.0)	1 (0.1)
Endometrial carcinoma	0	3 (0.2)
Endometrial disorder	2 (0.1)	1 (0.1)
Endometrial neoplasia	4 (0.1)	2 (0.1)
Ovarian carcinoma	1 (0.0)	0
Ovarian cyst	0	2 (0.1)

n = number of subjects in each treatment group; SGOT = serum glutamate oxaloacetate transaminase; SGPT = serum glutamate pyruvate transaminase; SP1 = safety population 1.

a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system.

Table 34. Number (%) of Subjects Reporting Drug Related Serious Adverse Events, Bazedoxifene 20 mg Versus Placebo, Month 0 to 84 (SP2)

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=499)	Placebo (n=519)
Any adverse event	3 (0.6)	1 (0.2)
Body as a whole	1 (0.2)	1 (0.2)
Overdose	1 (0.2)	1 (0.2)
Cardiovascular system	1 (0.2)	0
Pulmonary embolus	1 (0.2)	0
Urogenital system	1 (0.2)	0
Endometrial neoplasia	1 (0.2)	0

n = number of subjects in each treatment group; SP2 = safety population 2.

a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system

Table 35. Number (%) of Subjects Reporting Drug Related Serious Adverse Events, Bazedoxifene Combined Versus Placebo, Month 0 to 84 (SP2)

Body System[a] Adverse Event	Bazedoxifene Combined (n=1011)	Placebo (n=519)
Any adverse event	4 (0.4)	1 (0.2)
Body as a whole	2 (0.2)	1 (0.2)
Accidental overdose	1 (0.1)	0
Overdose	1 (0.1)	1 (0.2)
Cardiovascular system	1 (0.1)	0
Pulmonary embolus	1 (0.1)	0
Urogenital system	1 (0.1)	0
Endometrial neoplasia	1 (0.1)	0

n = number of subjects in each treatment group; SP2 = safety population 2.
a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system.

Discontinuations:

Safety Population 1: Overall, the percentage of subjects who had adverse events as the primary reason for withdrawal in the bazedoxifene 20 mg treatment (18.2%) and placebo (17.1%) groups was similar (Table 36). A total of 985 (17.5%) subjects in the bazedoxifene and placebo groups of the safety population had adverse events as the primary reason resulting in withdrawal from the study (Table 37).

Table 36. Adverse Events as the Primary Reason Resulting in Withdrawal From the Study That Were Significantly Different Among Groups, Number (%) of Subjects, Bazedoxifene 20 mg Versus Placebo, Months 0 to 84, SP1

Body System[a] Adverse Event	Overall p-Value	Bazedoxifene 20 mg (n=1886)	Placebo (n=1885)
Any Adverse Event	0.393	344 (18.2)	323 (17.1)
Vasodilatation	0.004†	16 (0.8)	3 (0.2)
Leg cramps	0.030*	14 (0.7)	4 (0.2)
Osteoporosis	0.031*	0	5 (0.3)
Endometrial carcinoma	0.016*	0	6 (0.3)

Overall p-value: Fisher's Exact Test (2-Tail).
p-Value <.05, .01, .001 levels is denoted by *, †, ‡ respectively.
n = number of subjects in each treatment group; SP1 = safety population 1.
a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system

Table 37. Adverse Events as the Primary Reason Resulting in Withdrawal From the Study That Were Significantly Different Among Groups, Number (%) of Subjects, Bazedoxifene Combined Versus Placebo, Months 0 to 84, SP1

Body System[a] Adverse Event	Overall p-Value	Bazedoxifene Combined (n=3758)	Placebo (n=1885)
Any Adverse Event	0.255	691 (18.4)	323 (17.1)
Deep vein thrombosis	0.017*	16 (0.4)	1 (0.1)
Heart arrest	0.037*	0	3 (0.2)
Vasodilatation	<0.001‡	36 (1.0)	3 (0.2)
Lymphoma	0.046*	1 (0.0)	4 (0.2)
Osteoporosis	0.004†	0	5 (0.3)

Overall p-value: Fisher's Exact Test (2-Tail).
p-Value < .05, .01, .001 levels is denoted by *, †, ‡ respectively.
n = number of subjects in each treatment group; SP1 = safety population 1.
a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system.

Extension II population: The distribution of all adverse events leading to withdrawal that were reported since the start of study participation for the Extension II population is presented in Table 38 for the bazedoxifene 20 mg treatment group compared with placebo and in Table 39 for the bazedoxifene combined treatment group compared with placebo.

Table 38. Number (%) of Subjects Reporting Adverse Events as the Primary Reason Resulting in Withdrawal From the Bazedoxifene Study 20 mg Versus Placebo, Subjects Who Entered Extension II (SP2), Months 0 to 84

Body System[a] Adverse Event	Bazedoxifene 20 mg (n=499)	Placebo (n=519)
Any adverse event	16 (3.2)	15 (2.9)
Body as a whole	1 (0.2)	3 (0.6)
Abdominal syndrome acute	0	1 (0.2)
Accidental injury	0	1 (0.2)
Adenoma	0	1 (0.2)
Neoplasm	1 (0.2)	0
Cardiovascular system	4 (0.8)	1 (0.2)
Cerebral ischemia	1 (0.2)	0
Cerebrovascular accident	2 (0.4)	1 (0.2)
Embolus lower extremity	1 (0.2)	0
Digestive system	2 (0.4)	1 (0.2)
Gastrointestinal carcinoma	2 (0.4)	1 (0.2)
Hemic and lymphatic system	0	1 (0.2)
Lymphoma	0	1 (0.2)
Metabolic and nutritional	1 (0.2)	0
SGOT increased	1 (0.2)	0
SGPT increased	1 (0.2)	0
Musculoskeletal system	0	1 (0.2)
Leg cramps	0	1 (0.2)
Nervous system	0	1 (0.2)
Depression	0	1 (0.2)
Respiratory system	0	2 (0.4)
Carcinoma of lung	0	1 (0.2)
Lung edema	0	1 (0.2)
Special senses	0	2 (0.4)
Eye disorder	0	1 (0.2)
Retinal degeneration	0	1 (0.2)
Retinal disorder	0	1 (0.2)
Urogenital system	8 (1.6)	3 (0.6)
Bladder carcinoma	1 (0.2)	1 (0.2)
Breast carcinoma	5 (1.0)	0
Cervix neoplasm	0	1 (0.2)
Endometrial carcinoma	0	1 (0.2)
Endometrial neoplasia	1 (0.2)	0
Ovarian cyst	1 (0.2)	0

n = number of subjects in each treatment group; SGOT = serum glutamate oxaloacetate transaminase; SGPT = serum glutamate pyruvate transaminase; SP2 = safety population 2.

a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system.

Table 39. Number (%) of Subjects Reporting Adverse Events as the Primary Reason Resulting in Withdrawal From the Study Bazedoxifene Combined Versus Placebo, Subjects Who Entered Extension II (SP2), Months 0 to 84

Body System[a] Adverse Event	Bazedoxifene Combined (n=1011)	Placebo (n=519)
Any adverse event	31 (3.1)	15 (2.9)
Body as a whole	3 (0.3)	3 (0.6)
Abdominal pain	1 (0.1)	0
Abdominal syndrome acute	0	1 (0.2)
Accidental injury	0	1 (0.2)
Adenoma	0	1 (0.2)
Neoplasm	2 (0.2)	0
Cardiovascular system	9 (0.9)	1 (0.2)
Cerebral ischemia	1 (0.1)	0
Cerebrovascular accident	3 (0.3)	1 (0.2)
Embolus lower extremity	1 (0.1)	0
Intracranial hemorrhage	1 (0.1)	0
Myocardial infarct	1 (0.1)	0
Thrombophlebitis superficial	1 (0.1)	0
Vasodilatation	1 (0.1)	0
Digestive system	5 (0.5)	1 (0.2)
Constipation	1 (0.1)	0
Dysphagia	1 (0.1)	0
Gastrointestinal carcinoma	3 (0.3)	1 (0.2)
Hemic and lymphatic system	0	1 (0.2)
Lymphoma	0	1 (0.2)
Metabolic and nutritional	1 (0.1)	0
SGOT increased	1 (0.1)	0
SGPT increased	1 (0.1)	0
Musculoskeletal system	0	1 (0.2)
Leg cramps	0	1 (0.2)
Nervous system	0	1 (0.2)
Depression	0	1 (0.2)
Respiratory system	1 (0.1)	2 (0.4)
Carcinoma of lung	0	1 (0.2)
Cough increased	1 (0.1)	0
Lung edema	0	1 (0.2)
Skin and appendages	1 (0.1)	0
Skin melanoma	1 (0.1)	0
Special senses	1 (0.1)	2 (0.4)
Cataract specified	1 (0.1)	0
Eye disorder	0	1 (0.2)
Retinal degeneration	0	1 (0.2)
Retinal disorder	0	1 (0.2)
Urogenital system	10 (1.0)	3 (0.6)
Bladder carcinoma	1 (0.1)	1 (0.2)
Breast carcinoma	6 (0.6)	0

Table 39. Number (%) of Subjects Reporting Adverse Events as the Primary Reason Resulting in Withdrawal From the Study Bazedoxifene Combined Versus Placebo, Subjects Who Entered Extension II (SP2), Months 0 to 84

Body System[a] Adverse Event	Bazedoxifene Combined (n=1011)	Placebo (n=519)
Cervix neoplasm	0	1 (0.2)
Endometrial carcinoma	0	1 (0.2)
Endometrial neoplasia	1 (0.1)	0
Ovarian cyst	1 (0.1)	0
Vulvovaginal disorder	1 (0.1)	0

n = number of subjects in each treatment group; SGOT = serum glutamate oxaloacetate transaminase; SGPT = serum glutamate pyruvate transaminase; SP2 = safety population 2.

a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system.

A total of 70 subjects either died while on therapy or had their deaths reported to the Sponsor after the conclusion of their study participation: 28 (1.5%) subjects who were randomized to the bazedoxifene 20 mg treatment group, 24 (1.3%) subjects randomized to the bazedoxifene 40 mg treatment group, and 18 (1.0%) subjects in the placebo group (Table 40). In addition, 26 (1.4%) subjects in the raloxifene 60 mg treatment group died during the study period or had their deaths reported to the Sponsor after the conclusion of their participation in the study. Although numerically there were more deaths in the bazedoxifene groups than the placebo group, no identifiable pattern of etiologies was noted. Hazard ratios (95% CIs) for all deaths, deaths within 15 days of study termination, and deaths on therapy were 1.57 (0.87, 2.84), 1.33 (0.69, 2.54), and 1.26 (0.66, 2.44), respectively, for the bazedoxifene 20 mg treatment group relative to placebo. HRs (95% CIs) in the bazedoxifene combined treatment group relative to placebo were 1.46 (0.85, 2.49), 1.21 (0.67, 2.16), and 1.14 (0.63, 2.06), respectively.

Table 40. Deaths Reported to the Sponsor by Category, Cumulative, Months 0 to 84, SP1

Category	BZA 20 mg	BZA Combined	Placebo	Total
	n=1886	n=3758	n=1885	n=5643
All deaths	28	52	18	70
Cardiovascular[a]	11	20	6	26
Oncology	9	14	5	19
Other[b]	6	12	3	15
Unknown	2	6	4	10

BZA = Bazedoxifene; COPD = Chronic obstructive pulmonary disease; n = Number of subjects; SP1 = Safety Population 1; UGI = Upper gastrointestinal.

a. Cardiovascular includes coronary, stroke, other vascular, and pulmonary embolism.

b. Other includes infection, trauma, UGI bleed, COPD, suicide, subdural hematoma, myeloproliferative disease, aspiration, postoperative complication, medullary aplasia.

The clinical laboratory profile, including serum chemistry, liver function tests, and hematology did not disclose any clinically meaningful differences among treatment groups.

The changes in the lipid profile were favorable, with reduction in low-density lipoprotein cholesterol levels and increases in high-density lipoprotein cholesterol levels in the bazedoxifene groups compared with placebo. The clinical relevance of these changes is as yet to be determined.

At the end of 7 years, there were no significant differences between treatment groups in the mean changes from Baseline in pulse, systolic and diastolic blood pressure, weight, and BMI.

Overall, the 7-year data revealed no new safety signals, and results were consistent with those at 3 and 5 years.

CONCLUSIONS:

- The 7-year analyses show that in post-menopausal women with osteoporosis, there was a significant reduction in the incidence of vertebral fractures in the bazedoxifene treatment groups compared with the placebo group.

- Overall, bazedoxifene was safe and generally well tolerated at oral doses of 20 mg daily during the 7-year observation period of this study.

- There were no significant differences between bazedoxifene treatment and placebo in the incidence of non-vertebral fractures at 84 months.

- Over the 7-year duration of the study, the incidence of breast cancer was similar in the bazedoxifene and placebo groups.

- There were no significant differences in the incidence rates of new clinical vertebral fractures between the bazedoxifene and placebo groups at 84 months.

- Overall, the numbers of subjects with worsening vertebral fractures were numerically higher in the bazedoxifene 20 mg treatment group, but the numbers were low and not sufficient for a meaningful statistical comparison.

- With regard to subject height, there were no statistically significant differences between either of the bazedoxifene treatment groups and the placebo group at any time point.

- The increases from Baseline in lumbar spine BMD in the bazedoxifene 20 mg and bazedoxifene combined treatment groups were greater than in the placebo group at all scheduled evaluations, but not significantly different at 84 months. At the other 3 skeletal sites, BMD initially increased from Baseline but over the course of 7 years decreased from Baseline, with significantly greater decreases noted in placebo than in the bazedoxifene treatment groups.

- Significant decreases from Baseline in serum osteocalcin and CTx levels were seen in all groups at 84 months.

- There is an increased risk of VTE in the bazedoxifene treatment groups compared with placebo.

- Overall, the incidence of adverse events related to the reproductive system in the bazedoxifene treatment groups was similar to that in the placebo group.

- The present study results demonstrate a protective effect on the skeleton with respect to a reduction in the incidence of new vertebral fractures, reduced decline in BMD relative to placebo, and a reduced rate of serum bone turnover markers with bazedoxifene treatment. Taken together, these findings provide evidence of sustained efficacy of bazedoxifene relative to placebo over 7 years. Overall, the 7-year data demonstrate that bazedoxifene is generally safe and well tolerated.