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Human Medicines Development and Evaluation

Assessment report

Conbriza

bazedoxifene

Procedure No.: EMEA/H/C/000913/II/0010

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Scientific discussion

Introduction

Conbriza contains the active substance bazedoxifene and was authorised in the EU on 17 April 2009. Bazedoxifene belongs to a class of compounds known as selective estrogen receptor modulators (SERMs). Bazedoxifene acts as both an oestrogen-receptor agonist and/or antagonist, depending upon the cell and tissue type and target genes. Bazedoxifene decreases bone resorption and reduces biochemical markers of bone turnover to the premenopausal range. These effects on bone remodeling lead to an increase in bone mineral density (BMD), which in turn contributes to a reduction in the risk of fractures. Bazedoxifene functions primarily as an oestrogen-receptor antagonist in uterine and breast tissues.

Conbriza is indicated for the treatment of postmenopausal osteoporosis in women at increased risk of fracture. A significant reduction in the incidence of vertebral fractures has been demonstrated; efficacy on hip fractures has not been established.

When determining the choice of Conbriza or other therapies, including oestrogens, for an individual postmenopausal woman, consideration should be given to menopausal symptoms, effects on uterine and breast tissues, and cardiovascular risks and benefits.

This type II variation concerns an update of sections 4.2, 4.4, 4.8 and 5.1 of the SPC to add safety and efficacy information after long-term treatment for up to 5-years from an extension of the pivotal Study 301-WW, submitted as part of the initial marketing authorisation application. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update Annex II with the standard DDPS wording, to update the annexes in line with the current QRD template, version 7.3.1 and the Guideline on Summary of Product Characteristics, revision 2, and to update the list of local representatives in the Package Leaflet.

Clinical aspects

Extension I (60 months) of pivotal study 301-WW

Osteoporosis treatment trial 301-WW is an ongoing, multicentre, double-blind, randomized, active controlled, phase 3 study, designed as a 3-year core study with two 2-year double-blind, placebo-controlled extensions; the core study was pivotal for the granting of the marketing authorisation for Conbriza. Originally the trial examined 4 groups, bazedoxifene 20 mg, bazedoxifene 40 mg, raloxifene 60 mg, and placebo. All participants were to be supplemented with 1000 mg to 1200 mg of calcium carbonate and 400 to 800 IU of vitamin D according to local standards. The study continues to be double-blind and placebo-controlled. During Extension I, month 36 through month 60, subjects from the raloxifene group were withdrawn after the last subject had completed the core study, and the database for the 36-month analysis was finalised. In addition, all subjects in the bazedoxifene 40 mg group were given the option to either switch to bazedoxifene 20 mg or to withdraw from the study at their first visit after all subjects had completed 4 years of treatment (bazedoxifene 40/20 mg).

Extension I did not include raloxifene, but to maintain the blind for the core study, subjects in the raloxifene 60 mg group were to participate in Extension I until the last subject had completed the core study and the database for the 3-year core study analysis had been finalized. After it had been determined that the marketed dose of bazedoxifene was to be 20 mg, the dose in the bazedoxifene 40 mg group was reduced to 20 mg daily. Before dose reduction, all subjects remaining in the study, regardless of treatment, were informed in a blinded manner of the impending dose change and

required to sign a new ICF; patients unwilling to sign the new ICF were withdrawn from the study. The study is continuing for an additional 2 years in study Extension II from the end of year 5 until the end of year 7. The 3-year core study was conducted at 206 investigative sites in Canada, United States, and countries in Asia-Pacific, Europe, Latin America, and South Africa.

Analyses of data after 60 months of treatment (Extension I) have been submitted for this variation.

Methods

The primary objectives of Extension I were to evaluate the efficacy of bazedoxifene 20 mg and bazedoxifene 40/20 mg in comparison with placebo in reducing the incidence of new vertebral fractures in postmenopausal women with osteoporosis after 5-years of therapy and to compare the safety profile of bazedoxifene with placebo over 5 years of treatment.

The primary efficacy endpoint was the cumulative incidence of new radiographically confirmed vertebral fractures (thoracic and lumbar spine, T4-L4) for bazedoxifene and placebo from baseline to 60 months of therapy, expressed as Kaplan-Meier rates. All radiographs were evaluated centrally.

Secondary objectives were to compare data on the incidence of breast cancer, clinical vertebral fractures, worsening vertebral fractures, non-vertebral fractures (NVF), height changes, BMD of the lumbar spine and hip, effects on the endometrium (endometrial sub-study only), serum bone markers (long-term bone markers sub-study only), and bone histomorphometry (histomorphometry sub-study II only).

Safety was monitored by means of physical examinations, gynaecologic examinations, mammography, cervical cytology smears, clinical laboratory determinations, vertebral radiographic assessments, and recording of AEs. For subjects enrolled in the endometrial safety substudy, and for subjects in the safety population when clinically indicated, endometrial thickness, ovarian volume, and presence and size of ovarian cysts were determined by transvaginal ultrasonography (TVU), and endometrial histology was used for the diagnosis of endometrial hyperplasia, malignancy, and polyps. NVFs, breast cancer, cerebrovascular events (CVEs), and venous thromboembolic events (VTEs) were assessed by independent blinded adjudication boards.

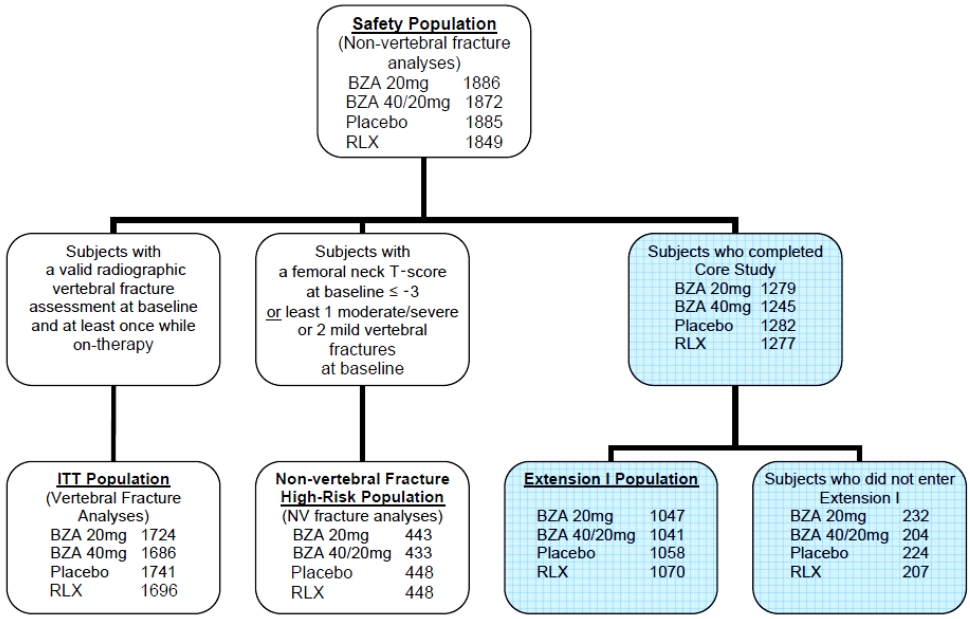
The analysis method for the primary efficacy endpoint was similar to the core study, utilizing Kaplan-Meier estimates for cumulative rate estimation, stratified log-rank test for between groups comparisons, and Cox proportional hazard regression for hazard ratio estimation. Subgroup analysis was performed for subjects with and without vertebral fractures present at baseline. Kaplan-Meier estimates of NVF cumulative incidence and between-group comparisons using the log-rank test were produced for 6, 12, 24, 36, 48, and 60 months of treatment. The incidence of breast cancer over 5 years between the combined bazedoxifene treatment groups and the placebo group was compared by means of logistic regression. Relative risk and excess risk compared with the placebo group was provided together with 95% CIs. The percent change from baseline of BMD was analyzed at months 6, 12, 18, 24, 36, 48, and 60 by analysis of covariance on the percent change from baseline. Prevalent vertebral status fracture and geographical region were included as factors in the model and baseline BMD as a covariate. The ranked percent change of s-CTx and serum osteocalcin from baseline to 3, 6, 12, 36, and 60 months was analyzed using an analysis of covariance with terms for treatment, and baseline as covariate.

Results

A total of 7492 subjects (including subjects in the raloxifene-treated arm) were included in the analysis of efficacy and safety of the core study; 3140 withdrew from the study in months 0 to 60 (1053

(55.8%) bazedoxifene 20 mg, 1032 (55.1%) bazedoxifene 40/20 mg, 1055 (56.0%) placebo). 1837 (32.8%) discontinued during the core study. 660 (11.7%) completed the core study but did not enter study Extension I (232 [12.3%] bazedoxifene 20 mg, 204 [10.9%] bazedoxifene 40/20 mg, and 224 [11.9%] placebo). 643 (20.4%) discontinued from the study during study Extension I (214 [11.3%] bazedoxifene 20 mg, 201 [10.7%] bazedoxifene 40/20 mg, and 228 [12.1%] placebo). Details for the analysis population and discontinuations are given in Figure 1 and Tables 1 and 2.

Figure 1: Analysis Populations and Disposition



ITT = intent-to-treat; NV = non-vertebral;

Table 1: Number (%) of Subjects Who Completed the Core Study and Who Did Not Enter Study Extension I, Safety Population

Conclusion Status Reason[a]	Overall p-Value	Treatment BZA 20 mg n=1886	BZA 40/20 mg n=1872	Placebo n=1885	Total n=5643
Discontinued	0.389	232 (12.3)	204 (10.9)	224 (11.9)	660 (11.7)
Other event[b]	0.843	52 (2.8)	46 (2.5)	50 (2.7)	148 (2.6)
Patient request unrelated to study[c]	0.479	180 (9.5)	158 (8.4)	174 (9.2)	512 (9.1)

a. Total discontinued is the sum of individual reasons because they are mutually exclusive by subject.
b. Subjects who were ineligible for study Extension I or whose study site was not participating in study Extension I.
c. Subjects who completed the core study but elected not to participate in study Extension I.
Overall p-value: refers to number of subjects' data; p-value for Chi-Square.

Table 2: Number (%) of Subjects Who Discontinued From the Study by Primary Reason, Months 36 to 60, Extension I Subjects

Conclusion Status Reason[a]	Overall p-Value	Treatment BZA 20 mg n=1047	BZA 40/20 mg n=1041	Placebo n=1058	Total n=3146
Discontinued	0.445	214 (20.4)	201 (19.3)	228 (21.6)	643 (20.4)
Adverse event	0.949	57 (5.4)	58 (5.6)	61 (5.8)	176 (5.6)
Death	0.194	5 (0.5)	2 (0.2)	1 (0.1)	8 (0.3)
Failed to return	0.788	15 (1.4)	13 (1.2)	17 (1.6)	45 (1.4)
Other event[b]	0.793	34 (3.2)	29 (2.8)	34 (3.2)	97 (3.1)
Patient request unrelated to study[c]	0.507	99 (9.5)	89 (8.5)	106 (10.0)	294 (9.3)
Protocol violation	0.449	4 (0.4)	8 (0.8)	8 (0.8)	20 (0.6)
Unsatisfactory response - efficacy	0.364	0	2 (0.2)	1 (0.1)	3 (0.1)

a. Total discontinued is the sum of individual reasons because they are mutually exclusive by subject.
b. Includes subjects who were ineligible for study Extension I or whose study site was not participating in study Extension I.
c. Includes subjects who completed the core study but elected not to participate in study Extension I.
Overall p-value: refers to number of subjects' data; p-value for Chi-Square.

Analysis of the incidence of vertebral fractures was carried out using the ITT population, which included all randomized subjects who had taken at least 1 dose of test article, and for whom a valid vertebral fracture radiographic assessment was done at baseline and at least once while on therapy. Details are given in Table 3.

Table 3: Number (%) of Subjects in the Intent-to-Treat Population for Vertebral Fracture Data

	Treatment Group		
Criteria description	**BZA 20 mg n=1886**	**BZA 40 mg n=1872**	**Placebo n=1885**
Subjects included in ITT population	1724 (91)	1686 (90)	1741 (92)
Subjects excluded from ITT population	162 (9)	186 (10)	144 (8)
No valid screening assessment	0	0	1 (<1)
No valid on-therapy assessment	162 (9)	186 (10)	143 (8)

ITT = intent-to-treat.
n represents the number of subjects in each therapy group included or excluded, and number excluded for each criteria. A subject may have been excluded for more than 1 reason.

Demographics and baseline characteristics of subjects participating in Extension I were comparable to that of the core study and there were no significant differences between groups in Extension I regarding baseline characteristics. Baseline BMD T-scores for the lumbar spine in the ITT population of study 301-WW were approximately -2.4 for each group (range -2.38 to -2.40). In the ITT population approximately 56% per group (range 55.87% to 56.35%) had a prevalent vertebral fracture, the majority of which had 1 mild fracture.

Compliance with the assigned regimen was measured as the percentage of scheduled test article capsules and calcium supplement tablets consumed. Details are given in the following table.

Table 4: Number (%) of Subjects with Treatment Compliance ≥ 80%, Months 0 to 60

	Treatment		
Characteristic	**BZA 20 mg (n=1886)**	**BZA 40/20 mg (n=1872)**	**Placebo (n=1885)**
Treatment compliance			
Compliance < 80%	108 (5.73)	129 (6.89)	115 (6.10)
Compliance ≥ 80%	1778 (94.27)	1743 (93.11)	1770 (93.90)

Compliance % is calculated as number of capsules taken divided by the scheduled number of capsules during duration of therapy.

Primary Endpoint

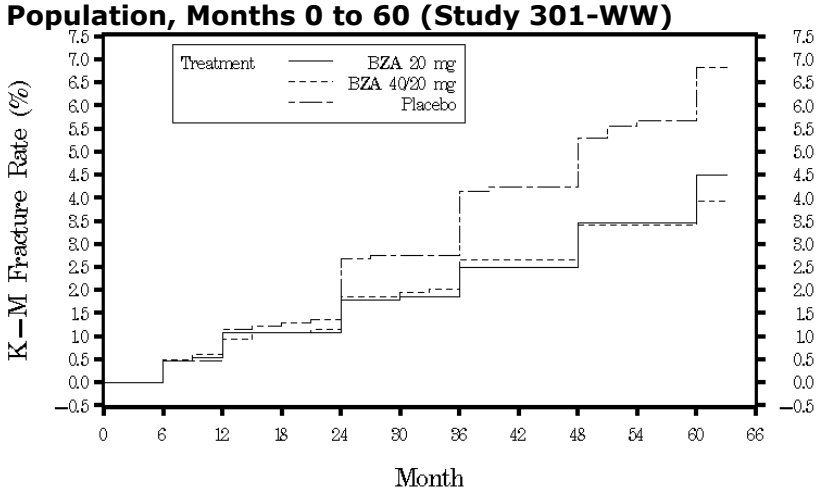
Compared to placebo treatment with bazedoxifene resulted in a lower cumulative rate of vertebral fractures and a corresponding reduction in risk of vertebral fracture regardless of baseline vertebral fracture status. The effect was apparent for all active treatment groups at 24 months, reaching statistical significance by 36 months. For the month 0 to 36 interval, the Kaplan-Meier rate estimates of cumulative fracture incidence for the bazedoxifene 20 and 40 mg and the raloxifene 60 mg groups were 2.34%, 2.51%, and 2.34%, respectively; they were significantly ($p < 0.05$) lower than that seen in the placebo group (4.07%). Kaplan-Meier estimates of the cumulative incidence of radiographically confirmed new vertebral fractures for months 0 to 36, 0 to 48, and 0 to 60 in the ITT population are presented in Table 5 and Figure 2. The treatment effect was sustained through 60 months of treatment. From month 0 to 60, vertebral fracture incidence rates were 6.82%, 4.49%, and 3.92% for placebo, bazedoxifene 20 mg, and bazedoxifene 40/20 mg, respectively.

Table 5: Summary Tabulation of New Vertebral Fracture Incidence, Intent-to-Treat Population, Kaplan-Meier Estimates of Vertebral Fracture Rate (Study 301-WW)

	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	37	1724	2.15	2.49	1.80	3.42
Bazedoxifene 40/20 mg	38	1686	2.25	2.66	1.94	3.64
Placebo	60	1741	3.45	4.13	3.21	5.29
Months 0-48						
Bazedoxifene 20 mg	46	1724	2.67	3.44	2.57	4.61
Bazedoxifene 40/20 mg	45	1686	2.67	3.40	2.54	4.56
Placebo	71	1741	4.08	5.29	4.20	6.67
Months 0-60						
Bazedoxifene 20 mg	54	1724	3.13	4.49	3.42	5.90
Bazedoxifene 40/20 mg	49	1686	2.91	3.92	2.95	5.21
Placebo	83	1741	4.77	6.82	5.49	8.47

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

Figure 2: Kaplan-Meier Estimates of Incident Vertebral Fractures, Intent-to-Treat Population, Months 0 to 60 (Study 301-WW)



At 36 months, estimates of the relative risk reduction (RRR) of vertebral fracture compared with placebo were 42% for bazedoxifene 20 mg, 37% for bazedoxifene 40 mg, and 42% for raloxifene 60 mg; at 60 months, the RRR were 35% for bazedoxifene 20 mg and 40% for bazedoxifene 40/20 mg; the difference between the 2 bazedoxifene groups was not statistically significant ($p = 0.69$). The treatment effect was also observed at 48 months. Analysis by strata of subjects with and without prevalent vertebral fracture did not show differences in the effect between strata. For subjects with no radiographically confirmed vertebral fracture at baseline, the RRR was 35%. For subjects with at least 1 prevalent vertebral fracture at baseline, the RRR was 45% for the bazedoxifene 20 mg and 38% for the bazedoxifene 40 mg group. Similar results were seen after 60 months of treatment (see Table 6). Analysis of the interaction of treatment group and study phase (core study vs. Extension I) did not show a significant interaction ($p > 0.6$), indicating that the treatment effect was maintained during Extension I.

Table 6: Summary Tabulation of New Vertebral Fracture Incidence, ITT Population, by Baseline Fracture Status, Hazard Ratio Estimates, Months 0 to 60 (Study 301-WW)

Treatment	Comparator	Hazard Ratio	Lower 95% Limit	Upper 95% Limit	p-Value Between Group
Overall					
Bazedoxifene 20 mg	Placebo	0.645	0.457	0.910	0.014
Bazedoxifene 40/20 mg	Placebo	0.599	0.421	0.853	0.005
No prevalent Fractures					
Bazedoxifene 20 mg	Placebo	0.610	0.339	1.099	0.097
Bazedoxifene 40/20 mg	Placebo	0.645	0.361	1.151	0.15
≥ 1 Prevalent Fracture					
Bazedoxifene 20 mg	Placebo	0.666	0.435	1.019	0.067
Bazedoxifene 40/20 mg	Placebo	0.573	0.367	0.896	0.014

BMD = bone mineral density; ITT = intent-to-treat.
First new vertebral fractures were included in the summary.
Hazard ratio estimation based on Cox proportional hazard regression, adjusted for baseline BMD T-score.
Between group p-value based on the log-rank test.

Secondary Endpoints

The principal investigator evaluated each NVF and classified it as osteoporotic or traumatic. Traumatic or pathologic fractures and fractures of body locations face, skull, toes, fingers, and elbow were excluded from the NVF analysis. The incidence of NVF, including hip and wrist fractures, was relatively low and there were no significant differences between groups. Kaplan-Meier estimates of non-adjudicated osteoporosis-related NVF for months 0 to 36, 0 to 48, and 0 to 60 are presented in Table 7. These data do not indicate significant differences between treatment groups in NVF rates over 36, 48, and 60 months. There was no evidence of treatment effect on the incidence of NV, hip, or wrist fractures with bazedoxifene treatment relative to placebo through 36 or 60 months of treatment.

Table 7: NVF Rate (Osteoporosis-Related), All Data Included (Study 301-WW)

Month	Treatment	Subjects With New Fractures	Subjects	Unadjusted Fracture Rate (%)	KM Rate Estimate (%)	95 (%) CI
0-36	BZA 20 mg	91	1886	4.83	5.83	(4.76, 7.12)
	BZA 40/20 mg	88	1872	4.70	5.83	(4.75, 7.15)
	Placebo	100	1885	5.31	6.35	(5.24, 7.68)
0-48	BZA 20 mg	114	1886	6.04	8.12	(6.77, 9.73)
	BZA 40/20 mg	96	1872	5.13	6.68	(5.48, 8.13)
	Placebo	115	1885	6.10	7.88	(6.58, 9.44)
0-60	BZA 20 mg	126	1886	6.68	9.47	(7.96, 11.25)
	BZA 40/20 mg	104	1872	5.56	7.59	(6.27, 9.18)
	Placebo	125	1885	6.63	9.03	(7.58, 10.74)

CI = confidence interval; KM = Kaplan-Meier.
Pathologic NVFs are excluded. Summary based on principal investigator's data.

The applicant has also performed a post-hoc analysis of NVF for a high fracture risk subgroup defined as subjects with a femoral neck T-score of ≤ -3, or the presence of at least 1 moderate vertebral fracture, or multiple vertebral fractures at baseline based on core study data. Comparisons between groups based on HR estimates and by stratified log-rank test are presented in Table 8. Statistically significant reductions were observed in the bazedoxifene 20 mg group at months 36 and 48, with a similar trend noted at 60 months. These analyses suggest that bazedoxifene might be beneficial in a subgroup of subjects at high risk for NVF when the risk for fractures is primarily due to a compromised skeleton (low BMD or prevalent fractures). As in the 36-month core study the incidence of NVF in this post-hoc subgroup was significantly lower in the bazedoxifene 20 mg group than in the placebo group

at 48 months, and showed a similar, but not statistically significant, trend at 60 months; there was no significant reduction in the bazedoxifene 40/20 mg treatment group.

Table 8: Hazard Ratio Estimates of On-Therapy NVFs (Osteoporosis-Related), Posthoc High-Risk Subgroup, All Data Included (Study 301-WW)

Month	Treatment	Comparator	Hazard Ratio	95 (%) CI	p-Value
0-36	BZA 20 mg	Placebo	0.531	(0.298, 0.947)	0.029
	BZA 40/20 mg	Placebo	0.727	(0.425, 1.244)	0.271
	BZA 20 mg	BZA 40/20 mg	0.725	(0.391, 1.345)	0.295
0-48	BZA 20 mg	Placebo	0.584	(0.347, 0.982)	0.040
	BZA 40/20 mg	Placebo	0.651	(0.389, 1.089)	0.116
	BZA 20 mg	BZA 40/20 mg	0.895	(0.505, 1.587)	0.672
0-60	BZA 20 mg	Placebo	0.625	(0.380, 1.027)	0.060
	BZA 40/20 mg	Placebo	0.691	(0.423, 1.130)	0.161
	BZA 20 mg	BZA 40/20 mg	0.909	(0.530, 1.559)	0.674

CI = confidence interval.
Pathologic non-vertebral fractures are excluded. Summary based on principal investigator's data.
The model is: time-to-fracture=treatment +baseline vertebral status fracture + femoral neck T-score. p-Value is based on the log-rank test.

Data were also analysed using the FRAX tool to estimate the 10-year fracture probability in subjects treated with bazedoxifene and the treatment effect as a function of fracture risk. Interaction between treatment of combined bazedoxifene 20 and 40 mg versus placebo and the 10-year probability of osteoporotic fracture was examined with and without inclusion of baseline BMD. The relationship between treatment effect over 36 months and baseline fracture risk based on FRAX was estimated. The population enrolled in study 301-WW had a mean 10 year fracture probability of 10.5%. HRs decreased with increasing fracture probability. A similar effect was observed for NVF. Using 10-year fracture probability as a baseline risk, a significant reduction in all clinical and all NVF was observed with bazedoxifene. In addition, a significant reduction in morphometric vertebral fractures was observed using the WHO fracture assessment tool, supporting the bazedoxifene treatment effect. The fracture benefit increased with increasing fracture probabilities. The treatment effect was evident at or above a fracture probability of 16%, 21%, and 6.9% for all clinical, NVF, and morphometric vertebral fractures, respectively.

BMD was assessed at baseline and at months 6, 12, 18, 24, 36, 48, and 60 at anatomic sites lumbar spine, total hip, femoral neck, and femoral trochanter. Populations of interest for BMD 5-year analyses were anatomic site-specific MITT populations including subjects who took at least 1 dose of test article, and who had a BMD evaluation at the site of interest at baseline and at least once during Extension I. Statistically significant ($p < 0.001$) increases from baseline in BMD of the lumbar spine were seen in both bazedoxifene treatment groups beginning at month 6; the mean percent change from baseline reached maximum between months 12 and 18 and was sustained through month 60. Smaller, statistically significant ($p < 0.001$) increases from baseline in BMD were also noted for the placebo group. After reaching a maximum at month 12, the BMD in the placebo group showed further small increases at months 36, 48, and 60. The increases from baseline in lumbar spine BMD in both bazedoxifene treatment groups were statistically significantly greater than the increases in the placebo group at all time points. The mean percentage changes from baseline in BMD of the total hip were significantly different from that in the placebo group. In the bazedoxifene groups, the BMD of the total hip at 60 months compared to baseline was maintained, while a significant bone loss was observed in the placebo groups. However, all groups showed a decline in total hip BMD from about 12 month onward. In summary over 60 months, the changes from baseline in BMD in both bazedoxifene groups were statistically significantly greater than in the placebo group for all time points at all 4 skeletal sites.

Figure 3: Percentage Change from Baseline in BMD of the Lumbar Spine, MITT Population, Months 0 to 60

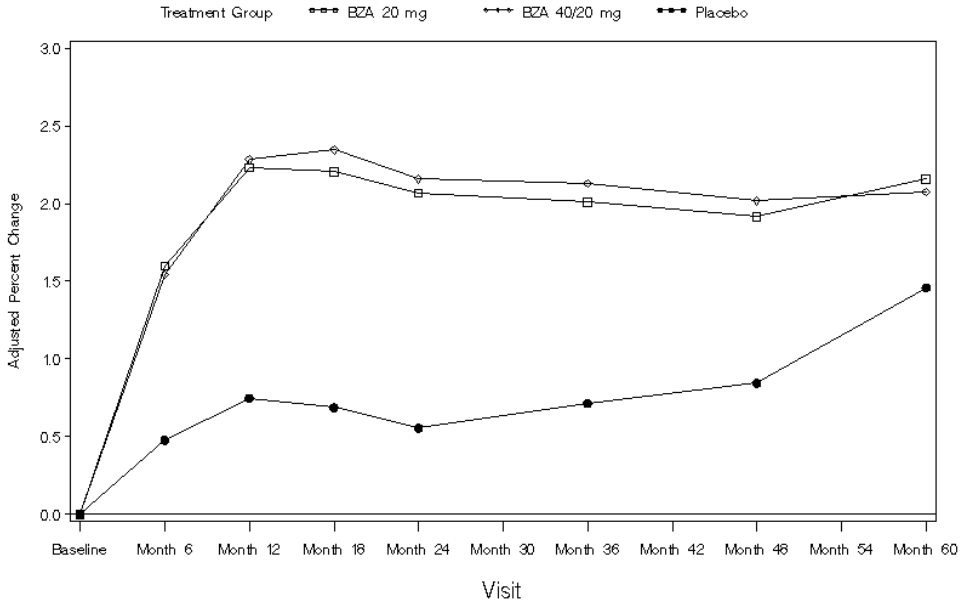
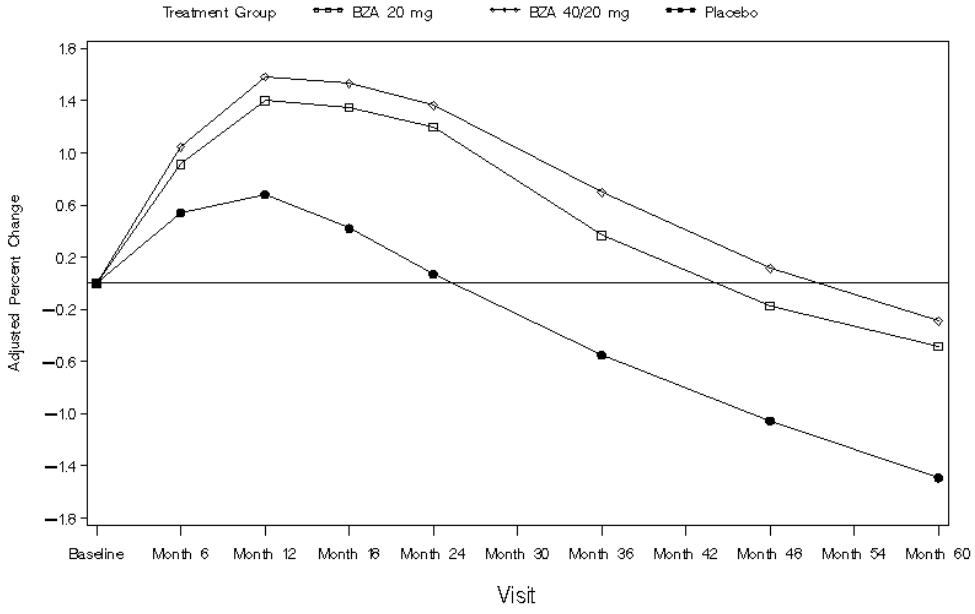


Figure 4: Percentage Change from Baseline in BMD of the Total Hip, MITT Population, Months 0 to 60



No effect on loss of height was seen with bazedoxifene treatment. This was most likely the result of a relatively low-risk population affected by osteoporosis who experienced a relatively small number of new vertebral fractures, especially severe vertebral fractures, making detection of changes in height more difficult.

Biochemical markers of bone metabolism serum osteocalcin and sCTx were assessed in study 301-WW at months 3, 6, and 12 for all subjects, and at months 36 and 60 for a subset. In the bazedoxifene groups, serum osteocalcin level decreased from baseline at all time points evaluated. In study 301-WW, percentage decreases from baseline were significantly ($p \leq 0.001$) greater for all bazedoxifene groups compared to placebo at each time point evaluated. Serum CTx levels decreased from baseline in the bazedoxifene groups at all time points evaluated. Decreases were significantly ($p \leq 0.05$) greater for all bazedoxifene groups compared to placebo at all time points evaluated. These

effects were sustained through month 60. There was little difference between the 2 bazedoxifene groups in the magnitude of the changes.

Regarding the lipid profile, overall, bazedoxifene 20 or 40 mg resulted in an increased HDL-C, decreased LDL-C and TC, and neutral effects on TG levels compared with placebo; these effects were maintained through 60 months of treatment. The clinical relevance of the observed changes in lipid profile remains to be determined.

After 36 months of exposure to bazedoxifene the number of subjects diagnosed with breast cancer was numerically, but not statistically significant, lower in the bazedoxifene groups compared to placebo. However, after 60 months of treatment, the overall incidence of breast cancer was not different between groups; the 28 cases included in the analysis were similarly distributed among treatment groups, 9 in each of the 2 bazedoxifene groups and 10 in the placebo group.

Clinical safety

Patient exposure

In study 301 overall 7609 subjects have been enrolled; the safety population of the 3 year core study includes 7492 women, of whom 3758 have been treated with bazedoxifene. The 24-month Extension I includes 3146 subjects, of whom 2088 have been treated with bazedoxifene.

Adverse events

A total of 5359 (95.0%) subjects reported at least 1 treatment emergent adverse event (TEAE) and in study Extension I 3075 (97.7%) subjects reported at least 1 TEAE. Abdominal pain, accidental injury, arthralgia, back pain, flu syndrome, headache, hypertension, infection, and pain were reported since the start of the study by ≥ 20% of subjects in at least 1 of the bazedoxifene or placebo groups. The incidences of vasodilatation, leg cramps, and depression were significantly different among bazedoxifene and placebo groups with the lowest rates occurring in the placebo group. The incidences of accidental injury, hypercholesterolaemia, anxiety, pharyngitis, and vaginitis were significantly different among these groups with the highest rates occurring in the placebo group.

In general, the common and non-serious adverse events reported during the 60 months of Extension 1 are consistent with the results of the 36-month core study and do not raise new safety concerns for the use of bazedoxifene.

Serious adverse events and deaths

Deaths

A total of 81 subjects died on therapy or had their deaths reported to the sponsor after conclusion of study participation, 24 (1.3%) in the bazedoxifene 20 mg, 18 (1.0%) in the bazedoxifene 40/20 mg, 13 (0.7%) in the placebo, and 26 (1.4 %) in the raloxifene 60 mg group. Overall, there were fewer deaths with placebo relative to bazedoxifene and raloxifene groups. The number of deaths due to CV aetiologies was similar between bazedoxifene and placebo. Compared to placebo, there were more deaths due to cancer in the bazedoxifene 20 mg, but not the bazedoxifene 40/20 mg group. The cancer deaths were not noted in any specific organ system and were not consistent with known estrogen dependent cancers. In addition, there were more deaths in the "other" category, which included a variety of conditions, in the bazedoxifene treatment groups compared to placebo. Table 9 summarises the deaths reported to the sponsor by category.

Table 9: Deaths Reported to the Sponsor by Category, Cumulative, Years 0 to 5

	Treatment				
Category	BZA 20 mg n=1886	BZA 40/20 mg n=1872	Placebo n=1885	Raloxifene 60 mg n=1849	Total n=5643
All deaths	24	18	13	26	81
Cardiovascular[a]	7	5	6	9	27
Oncology	9	4	5	7	25
Other[b]	6	5	1	7	19
Unknown	2	4	1	3	10

a. Cardiovascular includes coronary, stroke, other vascular, and pulmonary embolism.
b. Other includes infection, trauma, upper gastrointestinal bleed, chronic obstructive pulmonary disease, suicide, subdural hematoma, myeloproliferative disease, aspiration, and postoperative complication.

The mortality rates per 1000 women-years for all AEs and for subjects who died within 15 days after study discontinuation are shown in the following tables.

Table 10: Mortality Rate per 1000 Women-Years, All AE, Years 0 to 5

	----- n -----				-Rate Per 1000 Women-Years (95% CI)-			
Year	PBO	BZA20	BZA 40/20	RLX	PBO[a]	BZA20[a]	BZA40/20[a]	RLX60[a]
Death (all)								
0-5	13	24	18	26	1.96 (1.04,3.35)	3.62 (2.32,5.38)	2.78 (1.64,4.39)	4.71 (3.08,6.90)
Death (cardiovascular disease)								
0-5	6	7	5	9	0.90 (0.33,1.97)	1.06 (0.42,2.17)	0.77 (0.25,1.80)	1.63 (0.75,3.09)
Death (oncology)								
0-5	5	9	4	7	0.75 (0.24,1.76)	1.36 (0.62,2.57)	0.62 (0.17,1.58)	1.27 (0.51,2.61)
Death (other)								
0-5	1	6	5	7	0.15 (0.00,0.84)	0.90 (0.33,1.97)	0.77 (0.25,1.80)	1.27 (0.51,2.61)
Death (unknown)								
0-5	1	2	4	3	0.15 (0.00,0.84)	0.30 (0.04,1.09)	0.62 (0.17,1.58)	0.54 (0.11,1.59)

CI = confidence interval.
a. Denominator = patient-years on therapy.

Table 11: Mortality Rate per 1000 Women-Years within 15 Days of Termination From Study

	----- n -----				-Rate Per 1000 Women-Years (95% CI)-			
Year	PBO	BZA20	BZA 40/20	RLX	PBO[a]	BZA20[a]	BZA40/20[a]	RLX60[a]
Death (all)								
0-5	10	18	13	24	1.51 (0.72,2.77)	2.71 (1.61,4.29)	2.01 (1.07,3.43)	4.35 (2.79,6.47)
Death (cardiovascular disease)								
0-5	6	7	5	9	0.90 (0.33,1.97)	1.06 (0.42,2.17)	0.77 (0.25,1.80)	1.63 (0.75,3.09)
Death (oncology)								
0-5	2	4	2	6	0.30 (0.04,1.09)	0.60 (0.16,1.54)	0.31 (0.04,1.11)	1.09 (0.40,2.36)
Death (other)								
0-5	1	5	3	6	0.15 (0.00,0.84)	0.75 (0.24,1.76)	0.46 (0.10,1.35)	1.09 (0.40,2.36)
Death (unknown)								
0-5	1	2	3	3	0.15 (0.00,0.84)	0.30 (0.04,1.09)	0.46 (0.10,1.35)	0.54 (0.11,1.59)
4-5	0	0	0	0	0.00 (0.00,3.10)	0.00 (0.00,3.07)	0.00 (0.00,3.07)	0.00 (0.00,52.06)

CI = confidence interval.
a. Denominator = patient-years on therapy.

Serious Adverse Events

Regarding SAEs, the results observed during Extension I were similar to those observed in the core study. A total of 1345 (23.8%) subjects reported at least 1 SAE and for 99 (1.8%), these events were considered by the investigator to be at least possibly drug related. Overall, the number of subjects with at least 1 SAE was similar among bazedoxifene and placebo groups (p = 0.508). No significant differences were observed for the SAEs of special interest cerebrovascular accidents, myocardial infarct and myocardial ischemia, endometrial neoplasia (endometrial polyps), and breast carcinoma. There was a significant difference among the 3 groups for DVT, with more cases reported for the bazedoxifene groups compared to placebo (p=0.042).

Adverse Events of Special Interest

Particular attention was paid to the AEs VTEs, selected cardiovascular events including CVEs, vasodilatation, reproductive disorders, including breast disorders, and leg cramps. All AEs were defined as events reported during therapy and after therapy (after the last dose of test article).

VTE events were defined in the bazedoxifene clinical trials as any acute DVT, any acute PE, or any RVT. These events were adjudicated by experts in order to provide accurate and unbiased assessment of these events. Adjudicated data were similar to the unadjudicated clinical database results. Table 12 summarises all AEs and TEAEs for VTEs by group for the safety population in the 5-year database, based on verbatim descriptions. Overall, a small number of VTE events were observed, with a higher but not statistically significant (p = 0.359) incidence with bazedoxifene compared to placebo. The higher incidence was a result of an increased incidence of DVT; the significant increase in DVT was observed in the bazedoxifene groups compared with placebo. Superficial thrombophlebitis was also reported with a higher incidence in the bazedoxifene groups compared with placebo. The incidence of PE and RVT was comparable among all 3 groups. Based on the adjudicated data, the RR for the bazedoxifene 20 mg group relative to placebo was 1.63 at 36 months and remained similar after 60 months (RR = 1.5). The RR was similar between the 2 dose groups.

Table 12: Number (%) of Subjects Reporting Venous Thromboembolic AEs and Superficial Thrombophlebitis Based on Principal Investigator Data, Years 0 to 5

		Treatment			
Adverse Event	**Overall p-Value**	**BZA 20 mg n=1886**	**BZA 40/20 mg n=1872**	**Placebo n=1885**	**Total n=5643**
Any adverse event	0.359	16 (0.8)	17 (0.9)	10 (0.5)	43 (0.8)
Deep vein thrombosis	0.042*	8 (0.4)	13 (0.7)	3 (0.2)	24 (0.4)
Pulmonary embolus	0.589	6 (0.3)	3 (0.2)	4 (0.2)	13 (0.2)
Retinal vein thrombosis	0.869	2 (0.1)	2 (0.1)	3 (0.2)	7 (0.1)
Superficial thrombophlebitis	0.285	20 (1.1)	22 (1.2)	13 (0.7)	55 (1.0)
Treatment-emergent adverse events	0.339	12 (0.6)	11 (0.6)	6 (0.3)	29 (0.5)
Deep vein thrombosis	0.029*	7 (0.4)	10 (0.5)	1 (0.1)	18 (0.3)
Pulmonary embolus	0.869	3 (0.2)	2 (0.1)	2 (0.1)	7 (0.1)
Retinal vein thrombosis	0.248	2 (0.1)	0	3 (0.2)	5 (0.1)
Superficial thrombophlebitis	0.296	17 (0.9)	22 (1.2)	13 (0.7)	52 (0.9)

Overall p-value: refers to number of subjects' data; p-value for Chi-Square.
Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.

Regarding selected CVE after 60 months of treatment no increased incidence was observed for coronary occlusion, myocardial infarction, or myocardial ischemia in either of the bazedoxifene groups compared to placebo. The incidence of subjects with any ischaemic and hemorrhagic CV AE was similar and not significantly different among groups. No difference was observed in the overall incidence of CV AEs between active treatment groups and placebo. CVEs were also adjudicated by an independent Adjudication Board including identification of strokes and TIAs. Table 13 summarizes the results of the adjudication. Adjudicated data were similar to the unadjudicated clinical database results. Overall, small numbers of CVEs were observed and the incidence of all CVEs was similar and not statistically different among groups. The adjudicated data for total stroke or ischaemic stroke showed that there were no clinically or statistically significant differences. The adjudicated data for TIA showed numerically more cases of TIA in the bazedoxifene 40/20 mg group compared with the other groups. All subjects in this 40/20 mg treatment group had TIA prior to the switch to bazedoxifene 20 mg. The number of TIAs in the bazedoxifene 20 mg group was similar to placebo. The incidence of hemorrhagic strokes was higher in the placebo group. There were 7 fatal strokes through 60 months, 2 in the

bazedoxifene 20 mg, 1 in the bazedoxifene 40/20 mg group, 2 in the raloxifene 60 mg group, and 2 in the placebo group.

Table 13: Number (%) of Subjects with CV AEs Based on Adjudicated Data, Years 0 to 5

	Treatment			
Adverse Event	**BZA 20 mg n = 1886**	**BZA 40/20 mg n = 1872**	**PBO n = 1885**	**RLX 60 mg n = 1849**
Exposure (pt-years)	6425	6275	6428	5330
Any adverse event	55 (2.9)	65 (3.5)	66 (3.5)	46 (2.5)
Ischemic stroke	12 (0.6)	14 (0.7)	13 (0.7)	11 (0.6)
Hemorrhagic stroke	1 (0.1)	1 (0.1)	4 (0.2)	1 (0.1)
Stroke: unspecified	3 (0.2)	2 (0.1)	2 (0.1)	2 (0.1)
Transient ischemic attack	6 (0.3)	12 (0.6)	4 (0.2)	5 (0.3)
Symptom NCS stroke/TIA, normal head image finding	0	0	0	NA
Symptoms NCS stroke/TIA, head imaging not related	7 (0.4)	5 (0.3)	5 (0.3)	7 (0.4)
Nonvascular CNS diagnosis	4 (0.2)	8 (0.4)	9 (0.5)	4 (0.2)
Non CNS symptoms/diagnosis	5 (0.3)	14 (0.7)	22 (1.2)	13 (0.7)
Insufficient to determine diagnosis	9 (0.5)	13 (0.7)	11 (0.6)	8 (0.4)
Event is part of previously adjudicated event	8 (0.4)	3 (0.2)	6 (0.3)	8 (0.4)

CNS = central nervous system; NA = not available; NCS = not clinically suggestive; PBO = placebo; RLX = raloxifene; TIA = transient ischaemic attack.
Adverse event totals are not necessarily the sum of the individual adverse events because a subject may have been adjudicated for 2 or more different events.

The incidence rates for vasodilatation and leg cramps were significantly higher in the bazedoxifene groups compared with placebo, but were similar between the bazedoxifene groups.

Regarding the reproductive system bazedoxifene exhibited a neutral endometrial profile. TVU examinations of uterus and ovaries revealed no clinically relevant changes in endometrial thickness, ovarian volume, or ovarian cysts with bazedoxifene treatment. No increased incidence of endometrial neoplasm (polyps) or hyperplasia was observed in the bazedoxifene groups compared with placebo. There were fewer cases of endometrial carcinoma, at both 3 and 5 years, in the bazedoxifene groups compared with placebo, 0 subjects in the bazedoxifene 20 mg, 3 in the bazedoxifene 40/20 mg, 2 in the raloxifene 60 mg, and 6 in the placebo group for up to 60 months. Overall, the incidence of AEs related to the reproductive system was similar to that with placebo. Through 60 months, a total of 10 subjects were reported to have AEs coded to the preferred term ovarian carcinoma, 5 in the bazedoxifene 20 mg, 1 in the bazedoxifene 40/20 mg, 4 in the raloxifene 60 mg, and no subjects in the placebo group. Upon examination of the histopathological reports, 2 of the 5 cases in bazedoxifene 20 mg group were not confirmed as ovarian carcinoma. There was 1 case reported in the higher dose bazedoxifene 40 mg treatment group, suggesting that a causal relationship is unlikely.

The integrated safety database revealed that 510 subjects (5.8%) reported depression as an adverse event (AE). There was no statistically significant difference among treatment groups in the number of subjects reporting depression as an AE (bazedoxifene 20 mg n = 128 [5.8%], bazedoxifene 40 mg n = 142 [6.5%], raloxifene n = 128 [5.9%], and placebo n = 112 [5.1%], p = 0.278). Additionally, there were no clinically meaningful differences found between treatment groups. In each of the individual studies, there was no statistically significant difference among treatment groups in the number of subjects reporting depression as an AE.

There was a statistically significant difference among the 3 treatment groups (bazedoxifene 20 mg, bazedoxifene 40/20 mg, and placebo) participating in the extension to study 301 with regard to the number of subjects reporting depression as either a TEAE or an AE in the 5-year data from study 301.

However, pairwise comparisons between treatment groups demonstrated that the only statistically significant differences for the number of subjects reporting depression as an AE or as a TEAE were between the bazedoxifene 40/20 mg and placebo groups (p = 0.017; p = 0.016). There was no significant difference between the bazedoxifene 20 mg dose group (the 'approved' dose) and the placebo group (p = 0.470). Importantly, no clinically meaningful differences were found between either dose of bazedoxifene and placebo. In addition, the current EU SPC for raloxifene does not identify depression as an ADR; hence, depression does not appear to be a known class effect for SERMs.

With respect to these data there is currently no indication of a significant increase of depression for bazedoxifene 20 mg, which is the approved dose. However, there seems to be a dose dependency; a significant difference to placebo was seen in the 40/20 mg bazedoxifene group.

The MAH will include depression as a potential risk in the RMP and has committed to present a cumulative review of spontaneous reports and interim data from the ongoing study extension phase II as a follow-up measure. Currently no changes to the Product Information are considered necessary.

Laboratory findings

The clinical laboratory analyses did not disclose any clinically meaningful difference between groups after 60 months of treatment. The mean changes from baseline of ALT and AST levels were similar among groups and no significant differences were observed in potentially clinically important laboratory test results for ALT and AST levels at any evaluation time point. However, there were significantly fewer subjects in the bazedoxifene groups, compared with placebo, who had an ALT or AST level ≥ 5 x ULN. There were small, statistically significant mean decreases from baseline in haemoglobin level, haematocrit level, and RBC count observed in the bazedoxifene and placebo groups; the decrease from baseline was greater in the bazedoxifene groups compared with placebo. These decreases did not appear to have clinical consequences. After both 36 and 60 months of treatment, there was no increased incidence of TEAEs of anaemia or withdrawals due to anaemia in the bazedoxifene groups compared with placebo. Bazedoxifene was associated with significant increases in HDL-C and significant decreases in LDL-C levels compared to placebo. At the end of 5 years there were no significant differences among the treatment groups in the mean changes from baseline in pulse, systolic and diastolic blood pressure, height, weight, and BMI. In the ECG substudy no safety signal was detected for QT interval prolongation with bazedoxifene use.

Discontinuation due to AES

A total of 971 (17.2%) subjects had AEs as the primary reason for withdrawal from study. Overall, no significant difference was observed among the 3 groups in the total number of AEs that were listed as the primary reason for withdrawal. Of the subjects in the bazedoxifene and placebo groups who participated in Extension I, 187 (5.9%) had AEs as the primary reason resulting in withdrawal from study, and there were no significant differences among the groups in either the total number of subjects who had an AE as primary reason for withdrawal or in the numbers withdrawing because of any specific AE. There were significant differences among groups in the number of subjects whose primary reason for withdrawal included the following events accidental injury, DVT, leg cramps, respiratory failure, and vasodilatation, which occurred more frequently in both bazedoxifene groups, and endometrial carcinoma and osteoporosis, which occurred more frequently in the placebo group. Overall, the AEs associated with withdrawal from the study noted after 60 months were consistent with those reported for the 36-month core study.

Changes to the Product Information

Following the assessment of the data from the extension phase I of the pivotal Study 301-WW, sections 4.2, 4.4, 4.8 and 5.1 of the SPC have been updated with further safety and efficacy information after long-term treatment for up to 5-years. The Package Leaflet has been updated accordingly.

In addition, the MAH took the opportunity to update Annex II with the standard DDPS wording, to update the annexes in line with the current QRD template, version 7.3.1 and the Guideline on Summary of Product Characteristics, revision 2, and to update the list of local representatives in the Package Leaflet.

All these changes to the product information are acceptable.

Follow-up Measures

Area	Description	Due Date
Pharmacovigilance	**RMP 025:** The MAH commits to include depression as a potential risk in the next update to the Risk Management Plan (RMP), which is due to be submitted at the same time as the next PSUR (PSUR No. 4, PSU 019).	17/06/2011
Pharmacovigilance	**PSU 019**: The MAH commits to present a cumulative review of spontaneous reports of depression and interim data regarding adverse event reports of depression from Extension II (7-year data) from bazedoxifene study 3068A1-301-WW within PSUR No. 4 (PSU 019), for the reporting period from 17 Oct 2010 to 16 April 2011.	17/06/2011

Benefit / Risk assessment

With reference to the primary endpoint 'subject incidence of new vertebral fractures' the treatment effect was sustained through 60 months of treatment and the difference in the incidence in new vertebral fractures remained significantly lower in the bazedoxifene treatment groups compared to placebo.

However, in contrast to the results of the core study bazedoxifene did not show even a numerical effect on the incidence of NVF compared to placebo. Also in the post-hoc analysis of NVF in a high risk subgroup defined as subjects with a femoral neck T-score of ≤ -3, or the presence of at least 1 moderate vertebral fracture, or multiple vertebral fractures at baseline, there was no statistically significant difference in the incidence of NVF at 60 months, compared to a statistically significant difference at 36 and 48 months of treatment.

Regarding BMD, statistically significant increases from baseline of the lumbar spine were seen in both bazedoxifene groups; the mean percent change from baseline reached a maximum between months 12 and 18 and was sustained through month 60. Increases from baseline in BMD were also noted for the placebo group; after reaching a first maximum at month 12, the BMD in the placebo group showed further increases at months 36, 48, and 60. Mean percentage changes from baseline in BMD of the total hip were different from that in the placebo group. However, all groups showed a decline in total hip BMD from about 12 month onward.

The effects on biochemical markers of bone metabolism serum osteocalcin and sCTx as well as the effects on the lipid profile were maintained throughout the trial extension.

While a numerically lower incidence of breast cancer with bazedoxifene compared to placebo was found at the end of the core study, this effect has not been seen during Extension I.

In summary, the efficacy results of Extension I are in line with those of the core study, with a reduction in the incidence of new vertebral fractures, an increased BMD relative to placebo, and a reduced rate of bone turnover with bazedoxifene treatment compared to placebo.

In terms of safety, 7609 subjects were enrolled in study 301 overall; the safety population of the 3 year core study included 7492 women, of whom 3758 were treated with bazedoxifene. The 24-month Extension I includes 3146 subjects, of whom 2088 were treated with bazedoxifene. It is agreed that the AEs reported during Extension I do not raise any new safety concerns and that the AE profile is comparable between the core study and extension I.

Regarding AE death and other SAEs, the safety results of extension I do not indicate new, currently unknown risks. There were more deaths in the bazedoxifene groups compared to placebo but the number of deaths was higher in the raloxifene group compared to either bazedoxifene group.

As in the core study the incidence of VTEs was higher in the bazedoxifene groups compared to placebo.

Regarding cardiovascular AEs no difference was observed in the overall incidence between bazedoxifene and placebo. Similar to the results of the core study the incidences of vasodilatation and leg cramps were significantly higher in the bazedoxifene groups compared to placebo. The analysis of AEs of the reproductive system, the analysis of laboratory AEs, and the analysis of discontinuations due to AEs did not reveal new safety findings.

The MAH has made a commitment to include depression as a potential risk in the RMP and has committed to present a cumulative review of spontaneous reports and interim data from the ongoing study extension phase II as a follow-up measure. Currently no changes to the Product Information in this regard are considered necessary.

In summary, the safety findings of Extension I are in line with the findings of the core study.

The overall benefit-risk balance is not altered by the results of Extension I of study 301-WW.

Conclusion

On 20 January 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.

Variation(s) requested		**Type**
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

This type II variation concerns an update of sections 4.2, 4.4, 4.8 and 5.1 of the SPC to add safety and efficacy information after long-term treatment for up to 5-years from an extension of the pivotal Study 301-WW. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update Annex II with the standard DDPS wording, to update the annexes in line with the current QRD template, version 7.3.1 and the Guideline on Summary of Product Characteristics, revision 2, and to update the list of local representatives in the Package Leaflet.