Tissue-Selective Estrogen Complex (TSEC)

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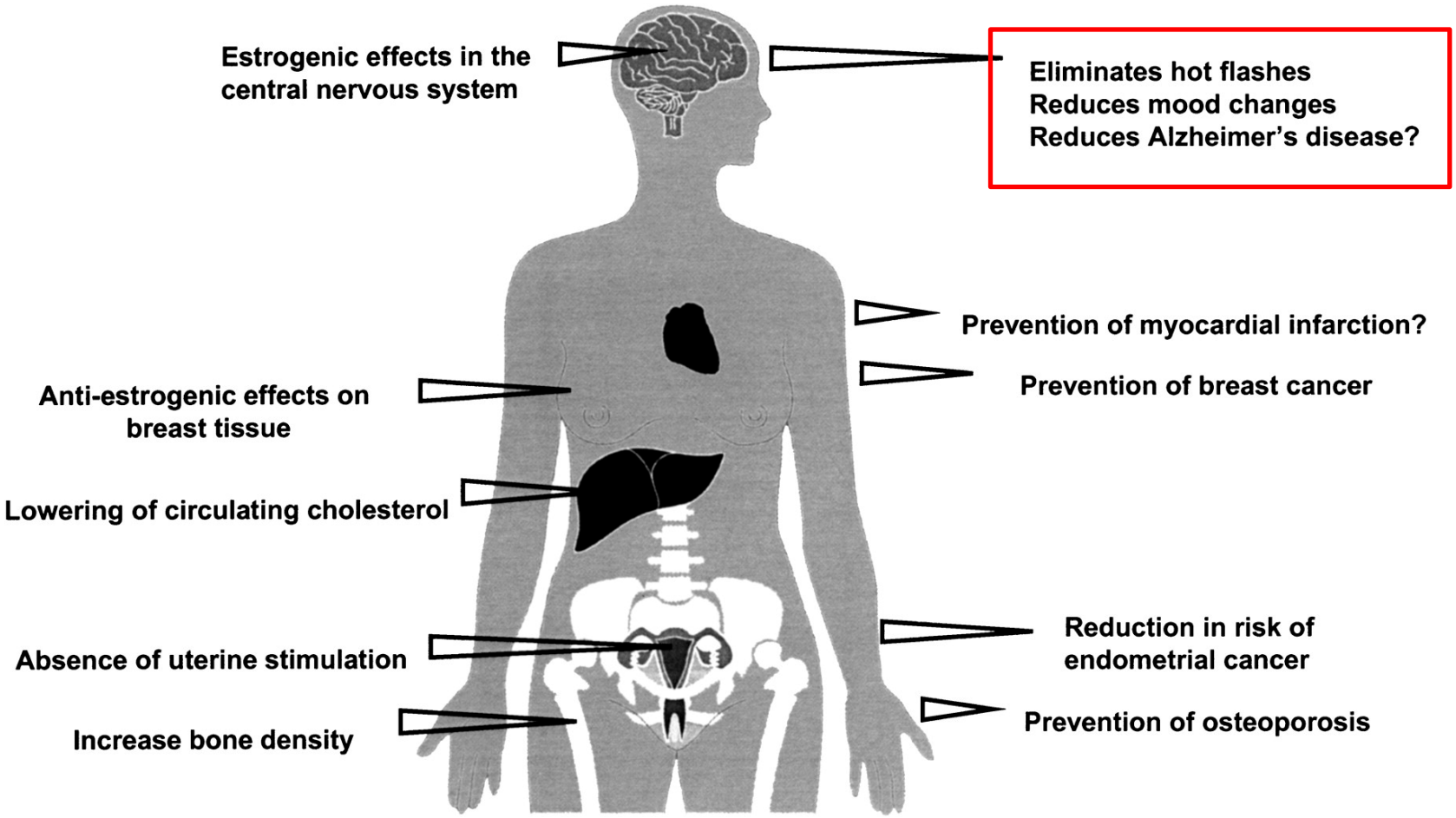
Ideal SERM



Jordan V C et al. JNCI J Natl Cancer Inst 2001;93:1449-1457

Old paradigm

- Unopposed estrogens increase the risk of endometrial cancer
- Estrogens are to be combined with progestins

- May increase the risk of breast cancer
- May increase the risk of CHD

New Paradigm

- A therapy that will maintained the benefits of CE, without the side effects of a progestin
- Compounds with antiestrogenic properties in the endometrium might be the solution
- These compounds should not antagonized the benefits of CE in the target tissues

TSEC

(Tissue selective estrogen complex)

Estrogen

postmenopausal Sx ↓

SERM

Protective effect on breast & EM

- Reduce hot flush
- Treat vulvar and vaginal atrophy
- Protect against bone loss
- Without stimulation breast
- Protect EM

Development of TSEC

- To achieve a balance of ER agonist & antagonist activity by blending the effects of estrogens with the tissue selective activity of SERM

- TSECs partnering CE with Raloxifene, Lasofoxifene, and Bazedoxifene have been evaluated in preclinical studies, with Bazedoxifene showing the most promising effects in both in vitro & in vivo models

Raloxifene + estrogen

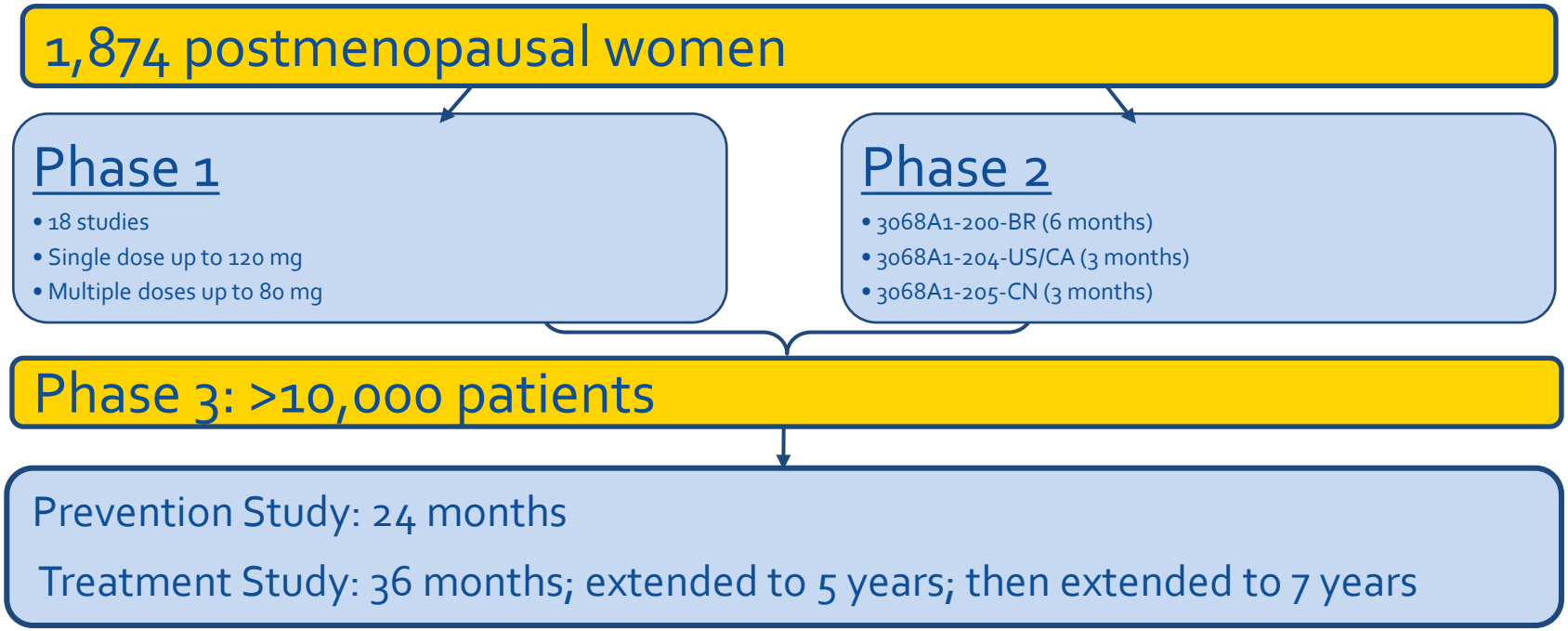
- Raloxifene (60mg/day) combined with oral 17β-estradiol (1mg/day) effectively relieved hot flushes, but did not fully protect against estrogenic stimulation of the endometrium *(Stovall et al., 2007)*

- Raloxifene (60mg/day) with transdermal 17β-estradiol (25mg/day) increased endometrial thickness *(Davis et al., 2004)*

- Raloxifene (60mg/day) combined with conjugated estrogens (0.3mg/day) alleviated hot flushes and vaginal dryness, but significantly increased endometrial thickness from baseline *(Carranza-Lira et al., 2007)*

Bazedoxifene Clinical Development

- Clinical profile of bazedoxifene was studied in 2 large, multicenter, double-blind, randomized, placebo- and active-controlled studies
  - Treatment Study: Study 301
  - Prevention Study: Study 300



Prevention Study: Conclusions

- In healthy, early postmenopausal women
  - Treatment with BZA demonstrated prevention of bone loss
  - BZA 20 mg was similar to RLX
- Overall, BZA was generally well tolerated
  - Similar VTE incidence as placebo
  - Similar CVD incidence as placebo
  - Excellent endometrial safety profile
  - Favorable/neutral lipid profile
  - Higher incidence of hot flushes than placebo

Treatment Study (Efficacy) : Conclusions

At 7 years:

- Significant and clinically meaningful reduction in the incidence of new vertebral fracture with BZA 20 mg and BZA combined groups: 30% and 36%, respectively

- No significant effect on non-vertebral fractures overall and in the high risk subgroup

Treatment Study (Efficacy) : Conclusions

At 7 years:

- BMD improved significantly relative to placebo at all hip sites but not lumbar spine

- Bone markers decreased significantly with BZA and placebo; no significant difference from placebo

Treatment Study (Safety) : Conclusions

At 7 years:

- BZA demonstrated a good safety and tolerability profile comparable to 3 and 5 year analyses
- Increased incidence of VTE; absolute risk is small and risk does not increase with time
- Increased risk of hot flushes and leg cramps and does not increase over time
- No increased CV or CVA risk
- No treatment effect on breast cancer

Uterine Effects of Bazedoxifene

- Bazedoxifene and placebo groups had similar incidences of endometrial hyperplasia and polyps[1-4]

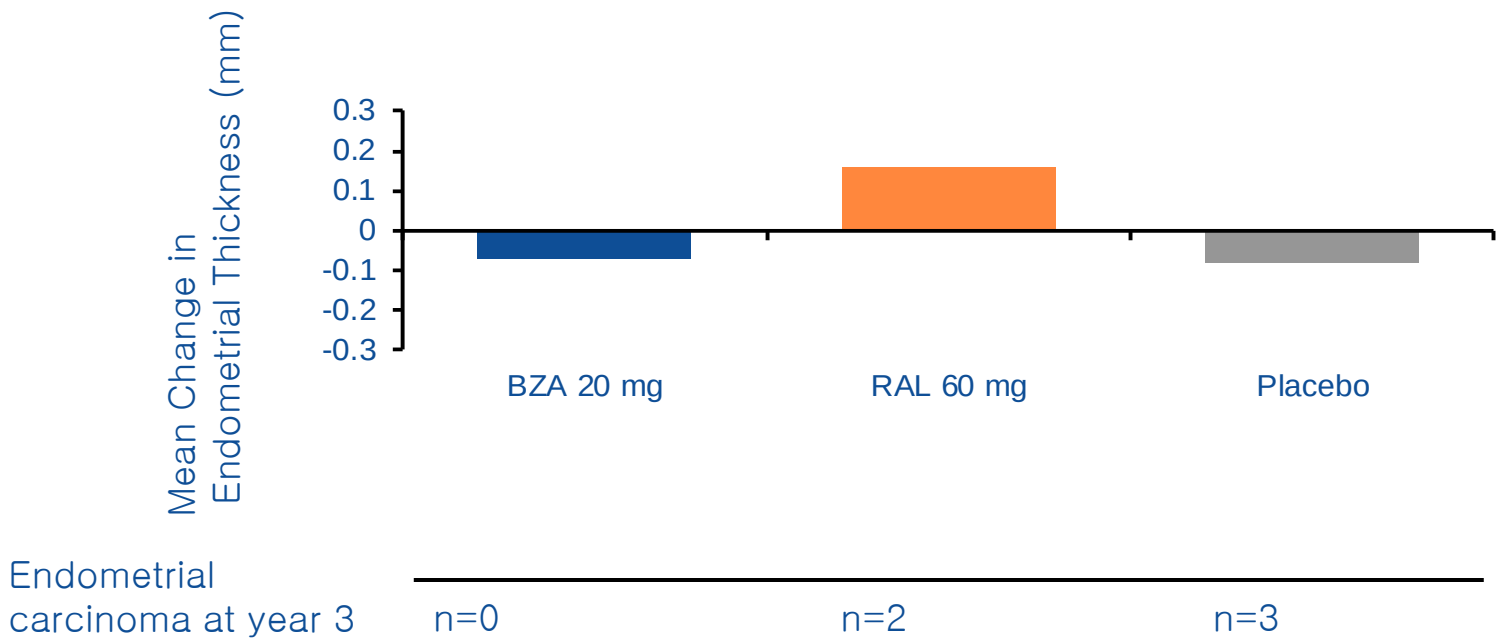
Incidence, n (%)	BZA 20 mg (n=1,886)	RAL 60 mg (n=1,849)	PBO (n=1,885)
Endometrial carcinoma	0 (0)	2 (0.1)	3 (0.2)
Endometrial hyperplasia	1 (0.1)	1 (0.1)	1 (0.1)
Endometrial neoplasia (polyps)	9 (0.5)	12 (0.6)	10 (0.5)

- No cases of endometrial malignancy were reported with bazedoxifene 20 mg[1-4]
- The incidence of uterine and vaginal bleeding was low and similar between groups[3,4]

1. Archer DF, et al. *Menopause*. 2009;16:1109–1115. 2. Pinkerton JV, et al. *Menopause*. 2009;16:1102–1108.
3. Christiansen C, et al. *BMC Musculoskelet Disord.* 2010;11:130. 4. de Villiers TJ, et al. *Osteoporos Int*. 2011;22:567–576.

Bazedoxifene: Effects on Endometrial Thickness

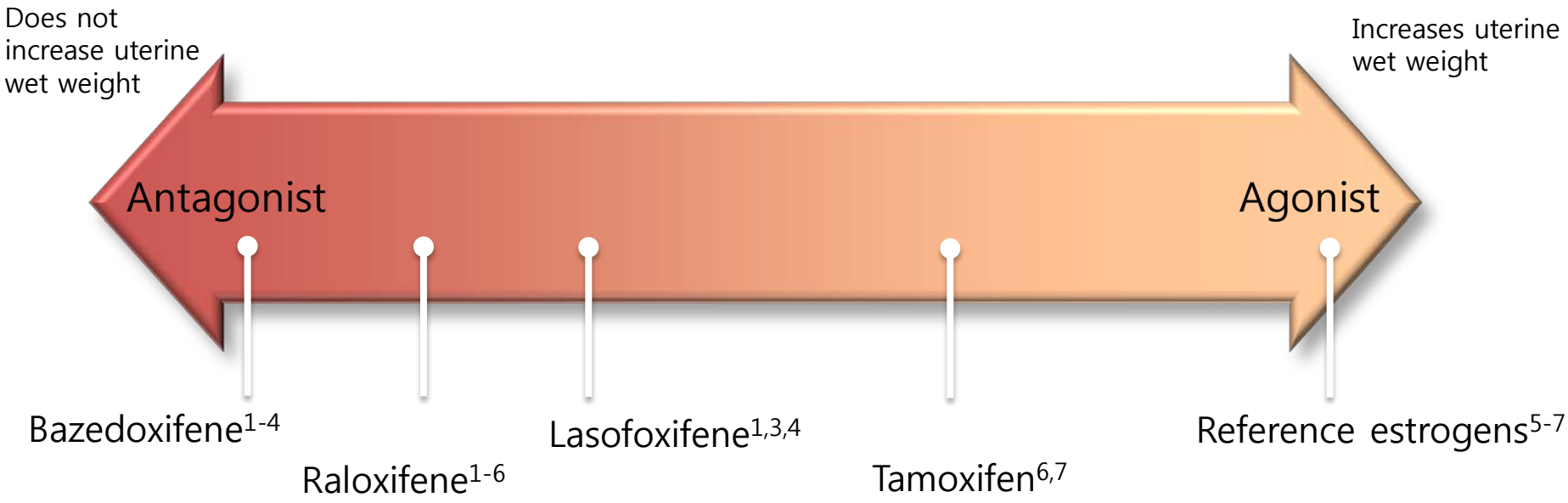
Change in Endometrial Thickness After 2 Years[1]*



*Transvaginal ultrasound data from a safety analysis of the phase 3 fracture prevention trial for bazedoxifene reported by Silverman et al in 753 subjects at year 2.[1,2]

1. Christiansen C, et al. *BMC Musculoskelet Disord.* 2010;11:130. 2. Silverman SL, et al. *J Bone Miner Res.* 2008;23:1923–1934.

Endometrial Tissue Selectivity of Estrogens and SERMs: Based on In Vivo Studies



1. Komm BS, et al. *Ann N Y Acad Sci*. 2001;949:317–326. 2. Komm BS, et al. *Endocrinology*. 2005;146:3999–4008.
3. Crabtree JS, et al. *Mol Cell Endocrinol.* 2008;287:40–46. 4. Peano BJ, et al. *Endocrinology.* 2009;150:1897–1903.
5. Qu Q, et al. *Endocrinology*.2000;141:809–820. 6. Stygar D, et al. *Reprod Biol Endocrinol*. 2003;1:40.
7. Carthew P, et al. *Toxicol Sci*. 1999;48:197–205.

Effects of Bazedoxifene on the Breast

- The incidence of breast-related adverse events with bazedoxifene was similar to that with placebo[1-4]

Incidence, n (%)	BZA 20 mg (n=1,886)	RAL 60 mg (n=1,849)	PBO (n=1,885)
Breast carcinoma	6 (0.3)	7 (0.4)	8 (0.4)
Breast neoplasm (benign)	12 (0.6)	11 (0.6)	22 (1.2)
Breast cyst	8 (0.4)	17 (0.9)	11 (0.6)
Fibrocystic breast disease*	6 (0.3)	15 (0.8)	9 (0.5)
Breast pain	53 (2.8)	56 (3.0)	48 (2.5)

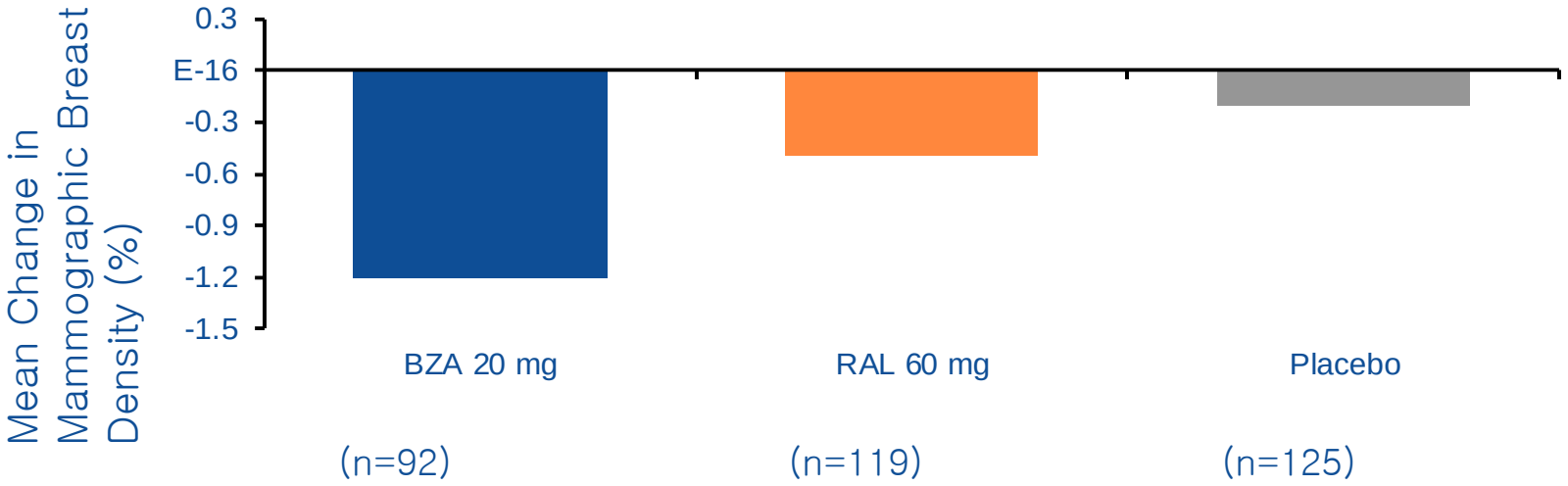
*$P<0.05$ overall between groups; $P=0.050$ for bazedoxifene vs. raloxifene

- Fibrocystic breast disease incidence was lower with bazedoxifene than with raloxifene or placebo[3,4]
- Breast cyst incidence was numerically lower with bazedoxifene (P=NS) than with raloxifene or placebo[3,4]

1. Archer DF, et al. *Menopause*. 2009;16:1109–1115. 2. Pinkerton JV, et al. *Menopause*. 2009;16:1102–1108.
3. Christiansen C, et al. *BMC Musculoskelet Disord.* 2010;11:130. 4. de Villiers TJ, et al. *Osteoporos Int*. 2011:22:567–76.

Bazedoxifene: Effects on Mammographic Breast Density

Change in Mammographic Breast Density



Of the mammograms from 1,243 women who were ≤62 years of age, had completed 24 months of the study, were >85% compliant, and had undergone mammography at baseline and at month 24, 442 mammograms were technically acceptable and had adequate penetration for analysis.

Harvey JA, et al. *Menopause*. 2009;16:1193–1196.

SMART-1

- ✓ PostMP women aged 40–75 years with acceptable EM biopsy results at screening(N = 3397), 2yrs
- ✓ BZA 10, 20, 40mg/CE 0.45,0.625mg vs RLX 60mg vs PBO
- ✓ Primary endpoint; incidence of EM hyperplasia
- ✓ Secondary endpoint;
  L spine & total hip BMD , BTM markers
  Frequency & severity of hot flush
  Change of atrophic vagina
  Incidence of DUB,breast pain /Breast density change
  Assessment of AEs

SMART-1

TABLE 4

Differences in the incidence of endometrial hyperplasia at months 12 and 24 (efficacy evaluable population).

		CE (0.625 mg)			CE (0.45 mg)		
	Time (mo)	BZA (10 mg)	BZA (20 mg)	BZA (40 mg)	BZA (10 mg)	BZA (20 mg)	BZA (40 mg)
Difference from placebo	12	n = 341	n = 314	n = 311	n = 320	n = 336	n = 309
Rate (%) ± SE		3.81 ± 1.04[a]	0.32 ± 0.32	0.00 ± 0.00	0.94 ± 0.54	0.00 ± 0.00	0.00 ± 0.00
95% CI		1.78–5.85[a]	−0.31–0.94	0.00–0.00	−0.12–2.00	0.00–0.00	0.00–0.00
	24	n = 294	n = 271	n = 267	n = 277	n = 293	n = 268
Rate (%) ± SE		7.14 ± 1.50[a]	0.74 ± 0.52	0.00 ± 0.00	2.53 ± 0.94[a]	0.34 ± 0.34	0.00 ± 0.00
95% CI		4.19–10.09[a]	−0.28–1.76	0.00–0.00	0.68–4.38[a]	−0.33–1.01	0.00–0.00
Difference from raloxifene	12	n = 341	n = 314	n = 311	n = 320	n = 336	n = 309
Rate (%) ± SE		3.81 ± 1.04[a]	0.32 ± 0.32	0.00 ± 0.00	0.94 ± 0.54	0.00 ± 0.00	0.00 ± 0.00
95% CI		1.78–5.85[a]	−0.31–0.94	0.00–0.00	−0.12–2.00	0.00–0.00	0.00–0.00
	24	n = 294	n = 271	n = 267	n = 277	n = 293	n = 268
Rate (%) ± SE		7.14 ± 1.50[a]	0.74 ± 0.52	0.00 ± 0.00	2.53 ± 0.94[a]	0.34 ± 0.34	0.00 ± 0.00
95% CI		4.19–10.09[a]	−0.28–1.76	0.00–0.00	0.68–4.38[a]	−0.33–1.01	0.00–0.00

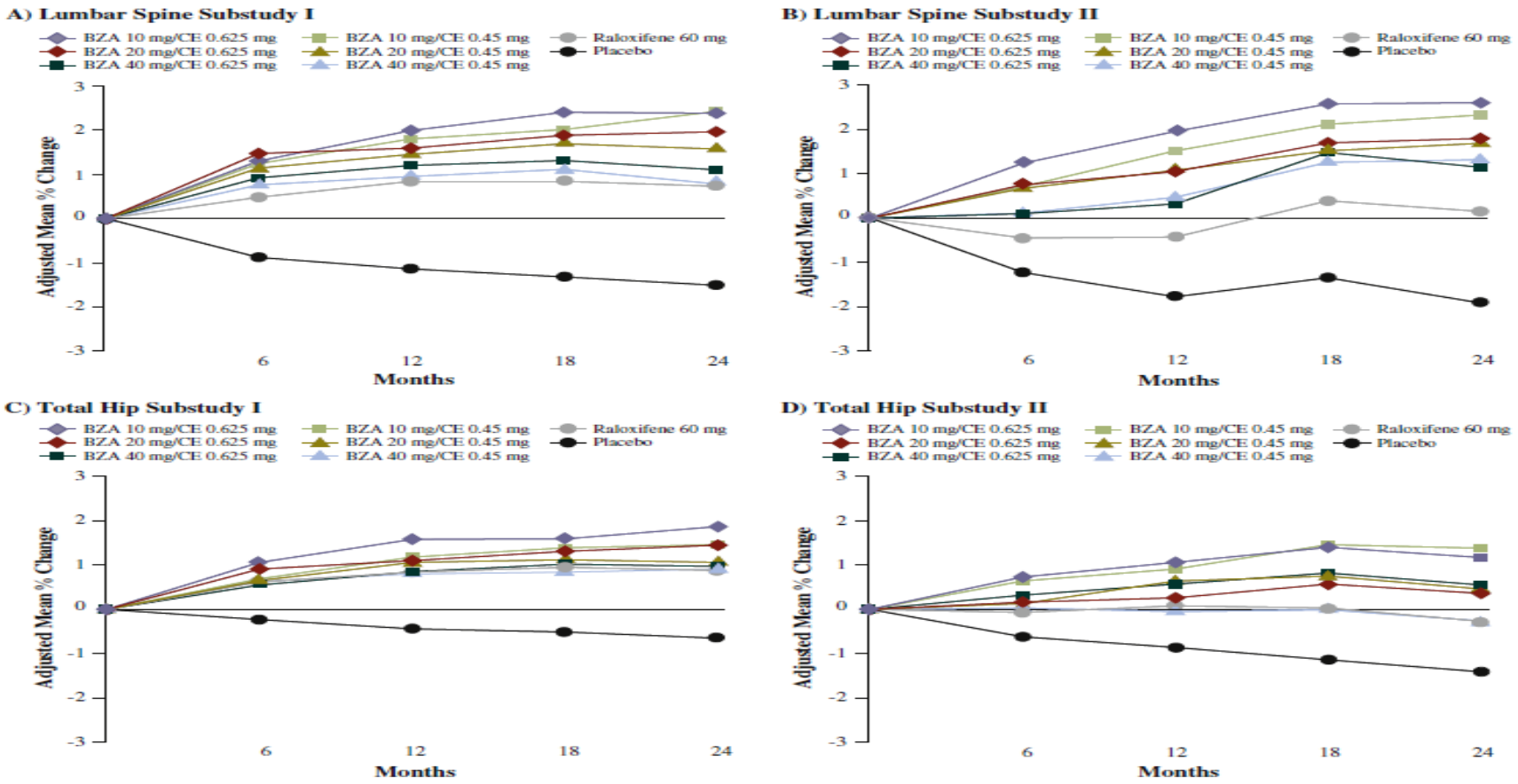
[a] Differences are statistically significant (95% CIs do not include 0.00).

Pickar. Effects of BZA/CE on the endometrium. Fertil Steril 2009.

Combined with either CE (0.625 or 0.45 mg),
BZA (20 mg) was the lowest effective dose that prevented EM hyperplasia

➔Suggesting alternative to the addition of a progestin to estrogens for EM protection

SMART-1



BMD significantly increased at all doses of BZD/CE compared with placebo at L-spine and total hip, for most BZA/CE doses compared with raloxifen at L-spine (BZA 10mg>20mg>40mg)

SMART-1

TABLE 3

Median percent changes in serum osteocalcin and serum C-telopeptide from baseline for women between 1 and 5 years postmenopause.

	CEs (0.625 mg)			CEs (0.45 mg)				
Time (mo)	BZA (10 mg)	BZA (20 mg)	BZA (40 mg)	BZA (10 mg)	BZA (20 mg)	BZA (40 mg)	Raloxifene (60 mg)	Placebo
Serum Osteocalcin								
6	−27.30[a,b]	−25.19[a,b]	−18.75[a]	−23.93[a,b]	−27.14[a,b]	−21.90[a,c]	−13.79	−4.13
12	−31.75[a,b]	−31.07[a,b]	−23.89[a,c]	−30.89[a,b]	−25.00[a,b]	−27.78[a,b]	−18.00	−0.59
18	−30.12[a,b]	−30.20[a,b]	−20.41[a,c]	−26.25[a,b]	−24.19[a,b]	−25.26[a,c]	−17.35	1.41
24	−20.34[a,b]	−28.05[a,b]	−19.78[a,b]	−22.65[a,b]	−23.09[a,b]	−20.51[a,b]	−10.43	3.08
Serum C-Telopeptide								
6	−46.84[a,b]	−44.77[a,b]	−37.47[a,b]	−45.73[a,b]	−40.56[a,b]	−38.45[a,b]	−25.06	−6.99
12	−56.42[a,b]	−55.64[a,b]	−40.96[a,b]	−52.19[a,b]	−48.35[a,b]	−43.76[a,b]	−33.18	−4.46
18	−58.77[a,b]	−58.85[a,b]	−49.84[a,b]	−55.16[a,b]	−51.67[a,b]	−47.26[a,b]	−39.75	−12.66
24	−53.40[a,b]	−53.35[a,b]	−44.49[a,d]	−45.66[a,c]	−47.78[a,c]	−42.72[a]	−35.59	−13.81

BTM marker significantly decreased with all BZA/CE doses vs placebo
Most BZA/CE doses vs raloxifene (BZA 10mg>20mg>40mg)

SMART-2

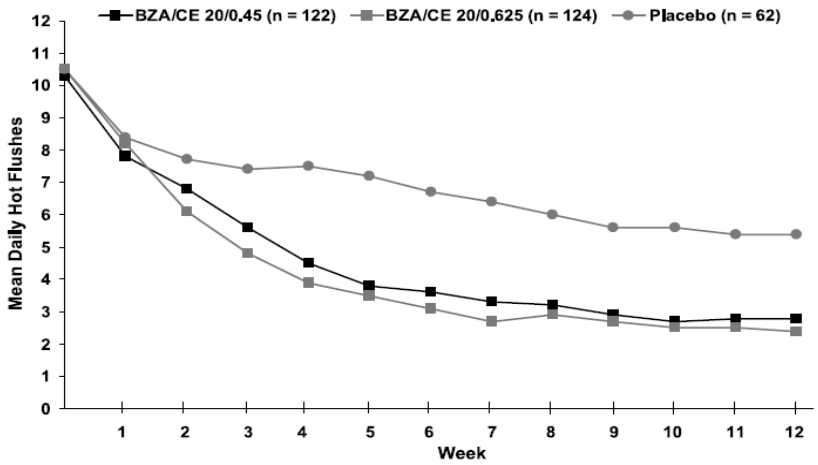
- Post MP women aged 40–65 years with ≥ 7 moderate-tosevere hot flushes/day and acceptable EM biopsy results at screening (n = 318) , 12wks

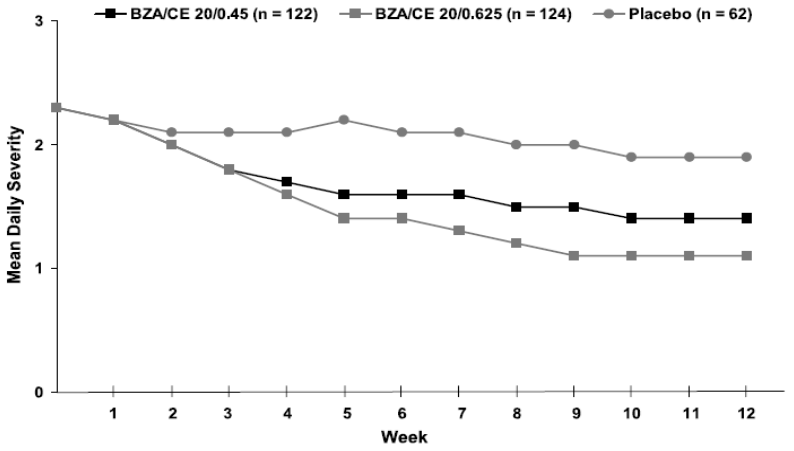
✓ BZA 20mg/CE 0.45, 0.625mg vs PBO

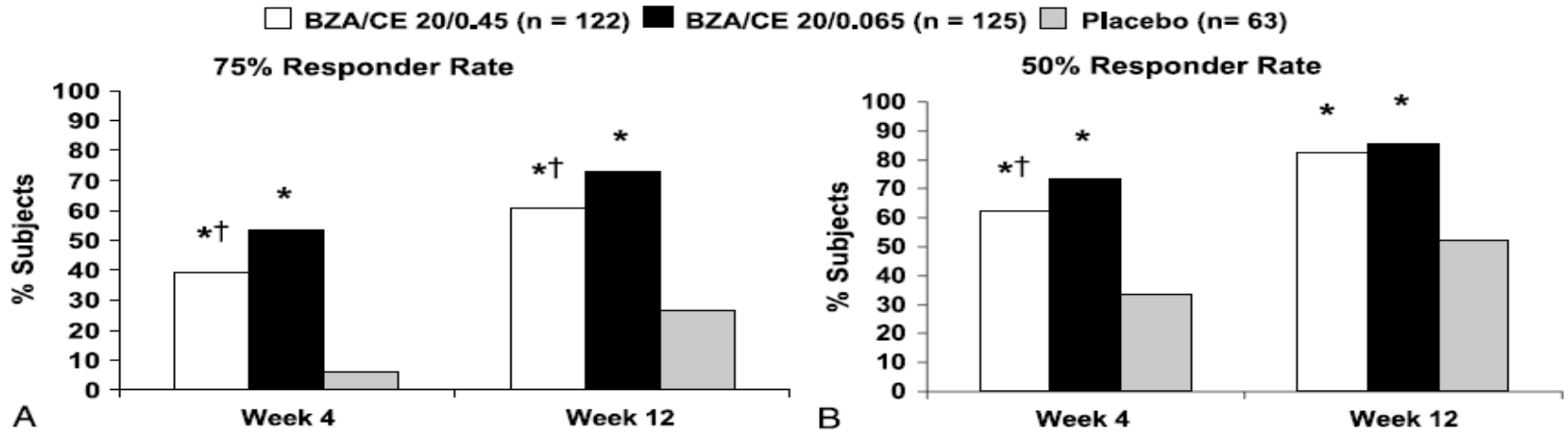
✓ Primary endpoint; Change in daily number and severity of hot flushes (at 4wks,12wks)

✓ Secondary endpoint;
Sleep parameters, QOL, Tx satisfaction, Incidence of breast pain
Assessment of AEs

SMART-2







BZA 20 mg /CE 0.45 or 0.625 mg is effective for treating vasomotor symptoms in postmenopausal women

SMART-3

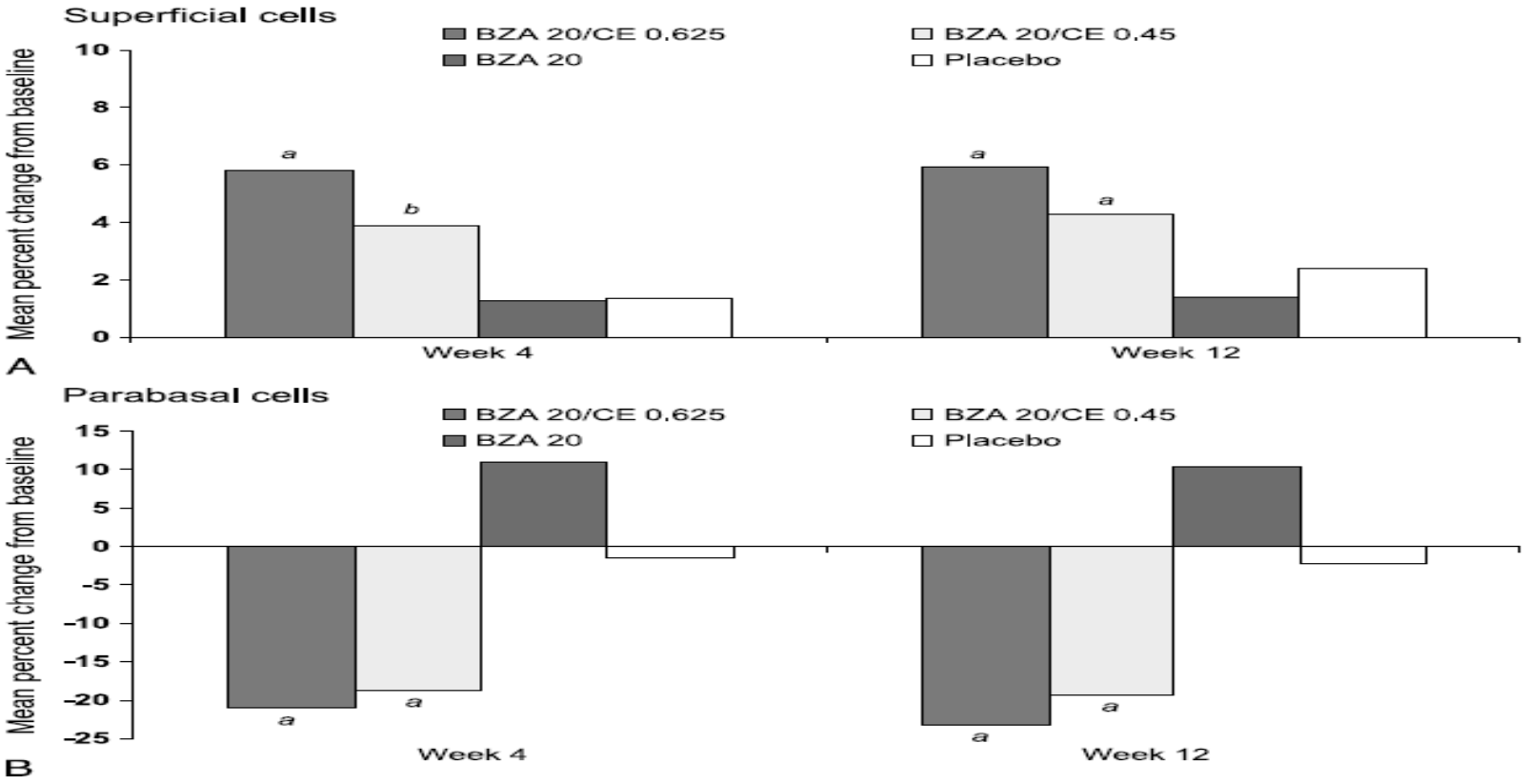
- Post MP women aged 40–65 years with ≥ 1 moderate-tosevere VVA sx and acceptable EM biopsy results at screening (n = 652) , 12wks

✓ BZA 20mg/CE 0.45, 0.625mg vs BZA 20mg vs PBO

✓ Primary endpoint; Change in superficial and parabasal cells, vaginal pH, and most bothersome VVA symptom at Weeks 4 and 12

✓ Secondary endpoint;
QOL, Treatment satisfaction, Incidence of breast pain
Assessment of AEs

SMART-3



Superficial cell ↑, Parabasal cell ↓ : BZA/CE is effective in treating moderate to severe VVA and vaginal symptoms

SMART-4

- Post MP women aged 40–65 years (N= 318) , 1yr

✓ BZA 20mg/CE 0.45, 0.625mg vs MPA 1.5mg/CE 0.45mg vs PBO

✓ Primary endpoint; Incidence of EM hyperplasia at 1yr, L-spine and total hip BMD change at 1y

✓ Secondary endpoint;
Incidence of breast pain and uterine bleeding/spotting

SMART-4

BMD

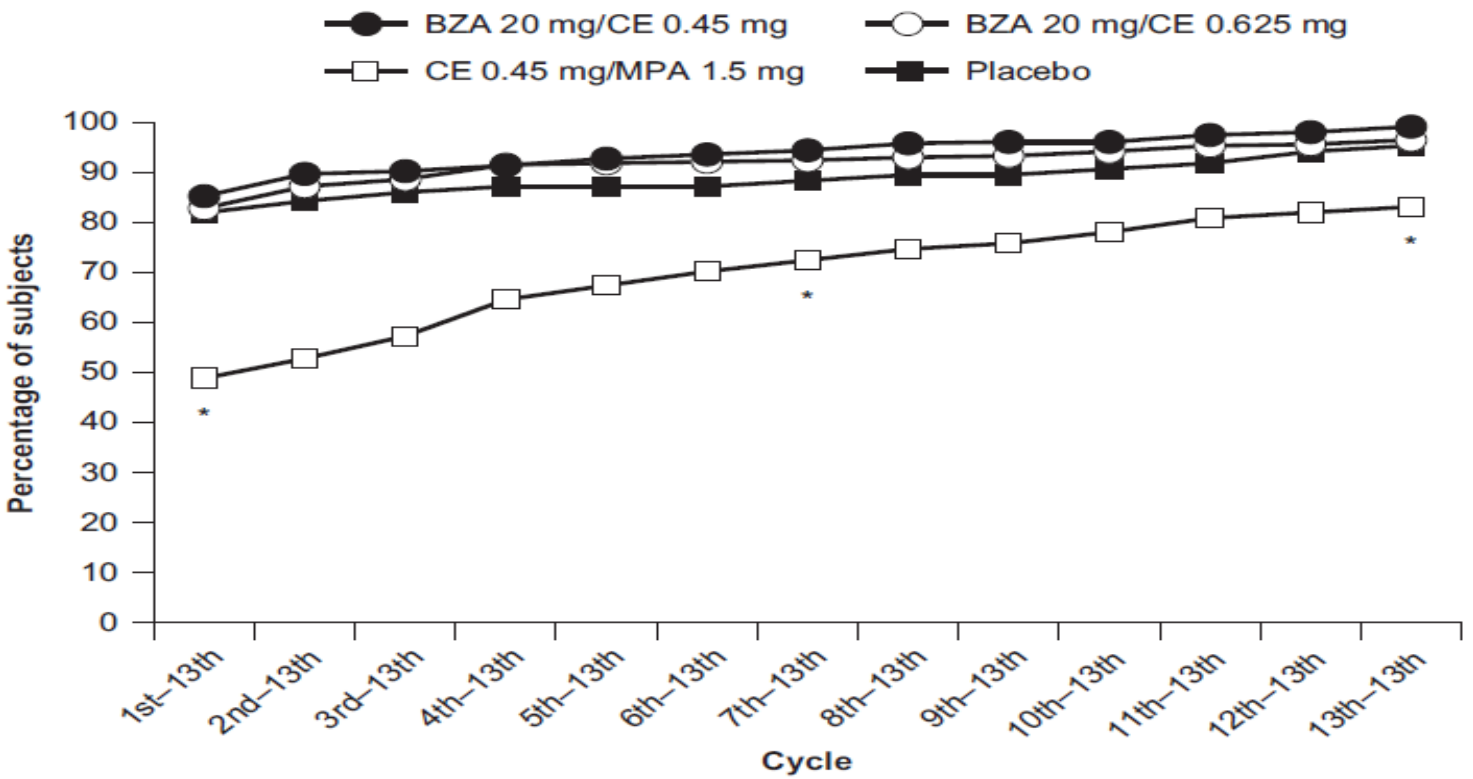
Parameter	*BZA 20 mg/ CE 0.45 mg*	*BZA 20 mg/ CE 0.625 mg*	*CE 0.45 mg/ MPA 1.5 mg*	*Placebo*
Lumbar spine				
*n**	146	144	60	65
Adjusted percent change	0.80 (0.24)†,‡,**	0.80 (0.24)†,‡,**	2.22 (0.37)†,‡	−1.56 (0.35)†
Total hip				
*n**	148	145	60	66
Adjusted percent change	0.62 (0.19)†,‡,**	0.84 (0.19)†,‡	1.47 (0.29)†,‡	−0.99 (0.27)†

✓ L- spine and total hip BMD significantly increased at BZA 20mg/CE 0.45 and 0.625mg vs PLB

✓ L- spine and total hip BMD at BZA 20mg/CE 0.45 and 0.625mg not statistically different from CE 0.45mg/MPA 1.5mg

SMART-4

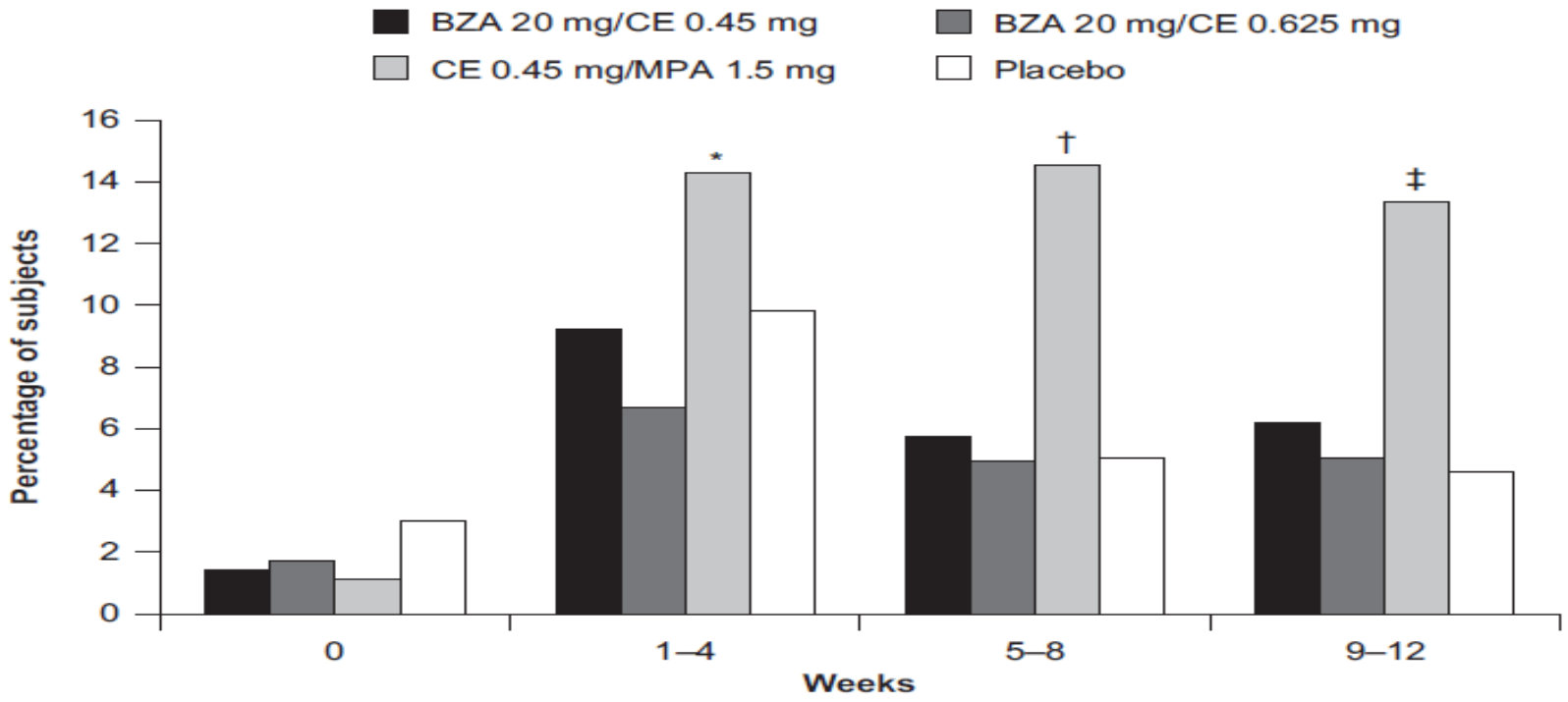
EM protection



Both BZA/CE groups showed high rates of cumulative amenorrhea over 1 year of treatment similar to placebo and higher than those for CE 0.45 mg/MPA 1.5 mg

SMART-4

Percentage of subjects reporting ≥ 1 day of breast pain over 3month



BZD/CE group :
Similar to that of placebo group
Significantly higher than those for CE0.45/MPA 1.5mg

SMART-4

Safety and tolerability

The most frequently reported adverse events
: nasopharyngitis, arthralgia, back pain, headache(10% in any group)

Incidences of abdominal pain, with higher rates observed in the three active treatment groups compared with placebo (overall p=0.009*)*

Metrorrhagia (overall p=0.001), Uterine hemorrhage (overall p= 0.001), Uterine spasm (overall p=0.02), Vaginal hemorrhage (overall p= 0.001) : with the highest rates observed in the CE 0.45-mg/MPA 1.5-mg group

Significantly higher percentages of subjects who discontinued the study d/t metrorrhagia, uterine hemorrhage, and vaginal hemorrhage in CE/MPA group (overall p =0.01 for all*).*

SMART-4

Safety and tolerability

	BZA 20 mg/ CE 0.45 mg (*n* = 361)	*BZA 20 mg/ CE 0.625 mg* (*n* = 349)	*CE 0.45 mg/ MPA 1.5 mg* (*n* = 179)	*Placebo* (*n* = 172)
Any AE	308 (85.3)	299 (85.7)	160 (89.4)	147 (85.5)
Any treatment-emergent AE	298 (82.5)	281 (80.5)	151 (84.4)	139 (80.8)
Any serious AE	15 (4.2)	11 (3.2)	4 (2.2)	5 (2.9)
Discontinuations due to AEs	30 (8.3)	25 (7.2)	23 (12.8)	14 (8.1)
Death	0	0	1 (0.6)	0
Selected AEs				
Venous thromboembolism	2 (0.6)	0	0	0
Angina pectoris	1 (0.3)	0	1 (0.6)	0
Coronary artery disease	0	1 (0.3)	0	0
Cerebrovascular events	1 (0.3)	0	0	0
Breast cyst	1 (0.3)	0	1 (0.6)	2 (1.2)
Fibrocystic breast disease	2 (0.6)	1 (0.3)	0	0
Uterine polyp	1 (0.3)	1 (0.3)	1 (0.6)	0
Ovarian cyst	1 (0.3)	1 (0.3)	1 (0.6)	0

Overall, no differences among treatment groups in the incidences of adverse events of special interest, including selected cardiac events, CVA, and reproductive tract and breast-related adverse events

SMART-5

- Post MP women aged 40-65 years with acceptable EM biopsy results at screening and seeking treatment for menopausal symptoms (N = 1848), 1yr

✓ BZA 20mg/CE 0.45, 0.625mg vs BZA 20mg
vs MPA 1.5mg/CE 0.45mg vs PBO

✓ Primary endpoint; Incidence of EM hyperplasia at 1yr
L-spine BMD change at 1yr

✓ Secondary endpoint;
L spine & total hip BMD , BTM markers
Incidence of DUB,breast pain, Sleep parameters and QOL
Change in percent breast density, Assessment of AEs

SMART-5

EM hyperplasia substudy

The incidence of EM hyperplasia with BZA 20 mg/CE 0.45 and 0.625mg was low (< 1%) and similar to that observed with PBO, BZA 20 mg and MPA 1.5mg/CE 0.45mg

Osteoporosis substudy

All treatment group were all associated with significantly greater improvement in L- spine, total hip, femoral neck, and femoral trochanter BMD at 1 year compared with PBO

All active treatment groups showed significantly reduced levels of BTM markers in the serum compared with PBO

SMART-5

Sleep substudy

BZA 20mg/CE 0.45 and 0.625mg and MPA 1.5mg/CE 0.45mg were associated with significantly greater improvements in sleep disturbance and time to fall asleep ($p < 0.05$ for all), as well as in vasomotor function and total MENQOL scores ($p < 0.05$ for all), compared with PBO

Breast density substudy

BZA 20 mg/CE 0.45 and 0.625mg demonstrated noninferiority compared with PBO in terms of percent change from baseline in breast density at 1 year

MPA 1.5mg/CE 0.45mg showed a significantly greater increase compared with PBO ($p < 0.001$)

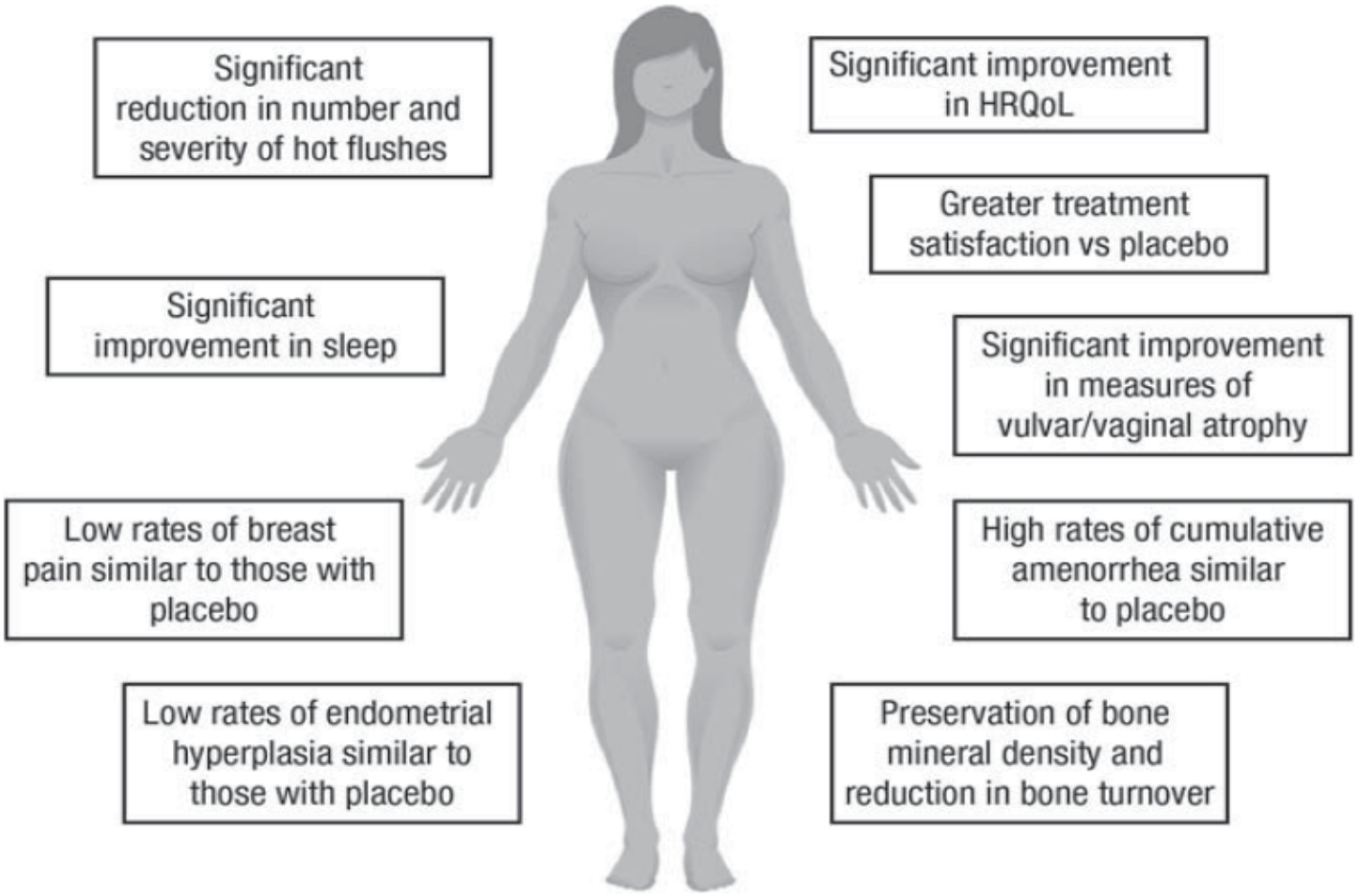
SMART-5

Assessment of AE

BZA/CE-treated groups showed high rates of cumulative amenorrhea, low rates of bleeding and spotting, a low incidence of breast tenderness, similar to those observed with PBO.

Women treated with MPA 1.5mg/CE 0.45 mg had a significantly higher incidence of bleeding and breast tenderness compared with either dose of BZA/CE or PBO ($p < 0.01$)

Benefits of TSEC



Conclusion

- TSEC is a novel approach to developing a therapy that can provide comprehensive relief of **MP symptoms and prevention of osteoporosis**

- The combination of BZA with CE has a unique clinical profile and has been shown to **effectively treat VMS and VVA symptoms and prevent bone loss** while ensuring **endometrial and breast safety**

- BZA/CE is a **promising alternative to conventional EPT** for nonhysterectomized postMP women