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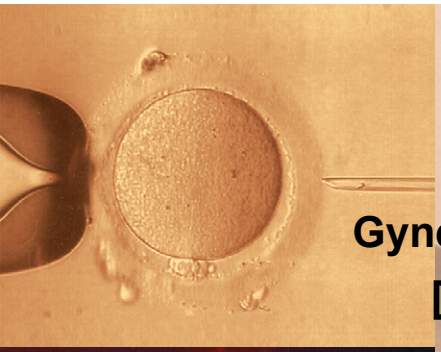

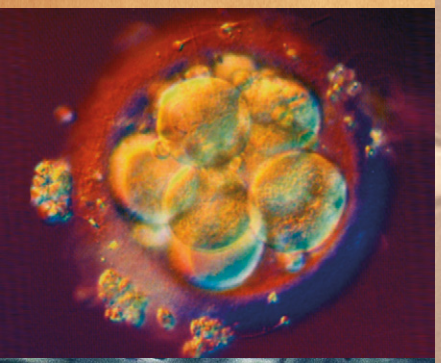

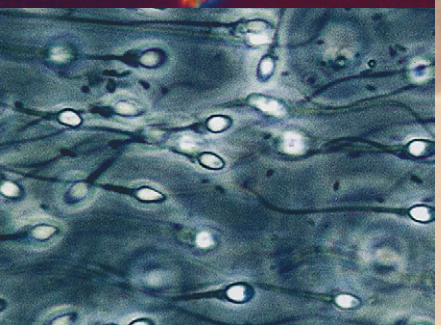

Selective Estrogen Receptor Modulators – an Update (Joint Statement by the German Society for Gynecological Endocrinology and Reproductive Medicine [DGGEF] and the German Professional Association of Gynecologists [BVF])

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Selective Estrogen Receptor Modulators – an Update*

Joint Statement by the German Society for Gynecological Endocrinology and Reproductive Medicine (DGGEF) and the German Professional Association of Gynecologists (BVF)

T. Rabe[1], N. Bruyniks[2], E. Merkle[3], B. Damann-Hanser[1], P. Hadji[4], H. Kuhl[5]
and the study group "Selective Estrogen Receptor Modulators (SERMs)" (in alphabetical order):
H.-J. Ahrendt[6], C. Albring[7], J. Bitzer[8], C. Egarter[9], L. Kiesel[10], K. König[11], G. Merki-Feld[12], A. O. Mueck[13], N. Sänger[14], E. Windler[15]

Selective estrogen receptor modulators (SERMs) are a heterogeneous group of non-steroidal substances with both estrogenic and anti-estrogenic properties.
Mode of action: Competitive binding to estrogen receptors (ER) with conformational changes of the receptor and involvement of tissue-specific co-activators and co-repressors, resulting in tissue-dependent, anti-estrogenic or estrogenic effects. Apart from the genomic activity via estrogen receptors in the nucleus, non-genomic effects via membrane-bound estrogen receptors have also been described.
Indications: The indications are substance-specific and include the treatment of breast cancer (tamoxifene) osteoporosis (raloxifene, bazedoxifene), infertility (clomifene), vaginal dryness (ospemifene), dysfunctional uterine bleeding (ormeloxifene) as well as hormone replacement therapy (bazedoxifene in combination with conjugated estrogens) and contraception (ormeloxifene). In addition, tamoxifene and raloxifene have marketing authorization is some countries for prevention of breast cancer in women at increased risk of breast cancer.
"Ideal SERM": substance showing desired estrogenic and anti-estrogen effects, yet without its drawbacks.

Characteristics of SERMs (in alphabetical order):
Compounds with marketing authorization:
Bazedoxifene (Indole derivative): Bazedoxifene has been approved in Europe as a stand-alone treatment for the treatment of osteoporosis (brand name Conbriza®). It has not been approved in the US as a stand-alone treatment.
"Tissue Selective Estrogen Complex (TSEC)": Combination with conjugated estrogens: Bazedoxifene plus conjugated estrogens is indicated in the US (tradename Duavee®) for the treatment of moderate to severe vasomotor symptoms associated with menopause and the prevention of postmenopausal osteoporosis. In Europe (where the tradename is Duavive®), the approved indication is the treatment of estrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate.
Clomifene (Triphenylethylene derivative): Treatment of ovarian dysfunction (infertility).
Ospemifene: FDA registration for treatment of moderate or severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause; EU-registration for moderate or severe symptoms of vulvo-vaginal atrophy.
Ormeloxifene used in India for contraception and treatment of dysfunctional uterine bleeding.
Raloxifene (Benzothiophene derivative) used for treatment and prevention of osteoporosis in postmenopausal women and in some countries (including the USA) for breast cancer prevention in high risk women. Raloxifene has no marketing authorization for this indication in Europe. The VTE risk is increased, similar to HRT. Death due to stroke was increased in the RUTH study (secondary prevention study), but not in the MORE or CORE studies (osteoporosis treatment and extension studies).
Tamoxifene (triphenylethylene derivative) is licensed for adjuvant use in women with primary or metastasized breast cancer and in some countries for the primary prevention of breast cancer. Tamoxifene is an antiestrogen, used (20 mg/day) in women who have estrogen receptor-positive (ER+) breast cancer. Unfortunately, resistance to tamoxifene is common in women with metastatic disease. Possible side effects include an increased risk of endometrial cancer and, like with all SERMs, an increased risk of VTE. An increased risk of stroke has been observed in the NSABP-1 study (RR1.42), but this was not statistically significant. Some antidepressants (SSRIs) abolish the effect of tamoxifene.
Toremifene (citrate) (also a triphenylethylene derivative) has EU marketing authorization for first line endocrine treatment of hormone-dependent metastatic breast cancer in postmenopausal patients. Fareston is not recommended for patients with estrogen receptor negative tumors. According to the US license, Fareston is indicated for the treatment of metastatic breast cancer in postmenopausal women with estrogen receptor positive or unknown tumors.

Compounds whose development has been suspended:
Arzoxifene: Development for use in osteoporosis and breast cancer prevention suspended
Droloxifene: Development suspended
EM 800: Development suspended
Lasofoxifene (= desmethyl dihydro analogue of nafoxidine): FDA registration for osteoporosis refused in 2005. In 2009 EU marketing authorization for the treatment of osteoporosis. Marketing authorization is no longer valid as a result of the "Sunset Clause". The rights to lasofoxifene have recently been acquired by Sermonix Pharmaceuticals LLC with a view to restarting the development.
Idoxifene: Development suspended ►

* Translated version from: Rabe T (ed). Seminar in Gynäkologischer Endokrinologie – Band 2. Heidelberg, 2013; 513–8. All links last seen: February 17th, 2015

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Levormeloxifene: Development suspended
Pipendoxifene: Development for the treatment of postmenopausal women with metastatic breast cancer has been suspended

Compounds in development:
Afimoxifene: Studies are being conducted in mastalgia and breast cancer.

Future aspects:
– Further research on active metabolites of above mentioned SERMs
– New indications for the use of SERMs: e.g. osteoarthritis, schizophrenia, postmenopausal vascular disease, increased lipid levels, virus infections (ebola), cryptococcal infections.
– New types of application may be vaginal ring, intrauterine devices, vaginal tablets.
– Selective estrogen receptor downregulators: Alternative choice to SERMs. These pure estrogen antagonists lead to a down-regulation of the estrogen receptors. An already registered product is fulvestrant (Faslodex®) which is indicated for the treatment of postmenopausal women with estrogen receptor positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant anti-estrogen therapy, or disease progression on therapy with an anti-estrogen (like tamoxifene).
– Multiple metabolites of tamoxifene as norendoxifen, 4,4'-dihydroxy-tamoxifene, endoxifene, N-desmethyl-tamoxifene, N-desmethyl-4'-hydroxy-tamoxifene, tamoxifene-N-oxide, 4'-hydroxy-tamoxifene, N-desmethyl-droloxifene, 4-hydroxy-tamoxifene can be used in women with breast cancer, based on their aromatase inhibition activity. Most of all, norendoxifene may be able to serve as a potent and selective lead compound in the development of improved therapeutic agents. **J Reproduktionsmed Endokrinol_Online 2015; 12 (4): 287–317.**

Key words: selective estrogen receptor modulators, SERMs, mode of action, indications, bazedoxifene, clomifene, ospemifene, ormeloxifene, raloxifene, tamoxifene, toremifene (citrate)

1. Introduction

The search for the ideal substance for the treatment of estrogen deficiency symptoms and diseases is not new (Fig. 1). As early in the 1930s, the first selective estrogen receptor modulators (SERMs) were developed, that possessed the desired estrogen effects, but not the undesired ones. This applies both estrogenic and antiestrogenic effects of SERMs. The potential of therapeutic applications are wideranging, from the treatment of breast cancer, osteoporosis, vulvo-vaginal atrophy, heavy menstrual bleeding to contraception and fertility treatment.

2. Mechanism of Action of Estrogens

Estrogens exert their biological function via the estrogen receptor (ER) alpha (α) and beta (β). Once estrogen binds to the ER, the estrogen-estrogen receptor complex forms dimers, either homodimers (ERα/ERα or ERβ/ERβ) or heterodimers (ERα/ERβ). These bind to specific estrogen response elements (ERE)-containing DNA segments or monomers (ER[ERα/ERβ], ERβ) on elements of AP1-controlled gene segments and activate transcription of the same. The classical ER-mediated genomic regulatory mechanism is not the opposite: here the transcription of certain gene segments without DNA binding of the ER is activated indirectly [1].

SERMs are compounds with competitive binding to the ER and exert tissue-dependent estrogenic or anti-estrogenic effects [2]. The exact mechanism has not been fully explained yet. It is probable that due to the binding of the SERMs to the ER certain co-factors are activated which, either as co-activators or as co-repressors, lead to different gene activations and deactivations in target tissues. Alternative explanations relate to a different affinity to ERα and ERβ or activation of ERα and ERβ, respectively [3] (Fig. 2, 3).

In addition to the genomic pathway of estrogen action, several non-genomic effects of estrogen have been described (Fig. 4), influencing regulatory proteins without action mediated via DNA. Such pathways are important both for estrogen and SERM action at the target cells (see section 2.3).

In the following chapter the estrogen receptor and its interaction with the so-called SERMs will be discussed in more depth.

2.1. Estrogen Receptor

The estrogen receptor belongs to the large family of transcription factors, together with more than 150 other molecules. It is important for the signal trans-

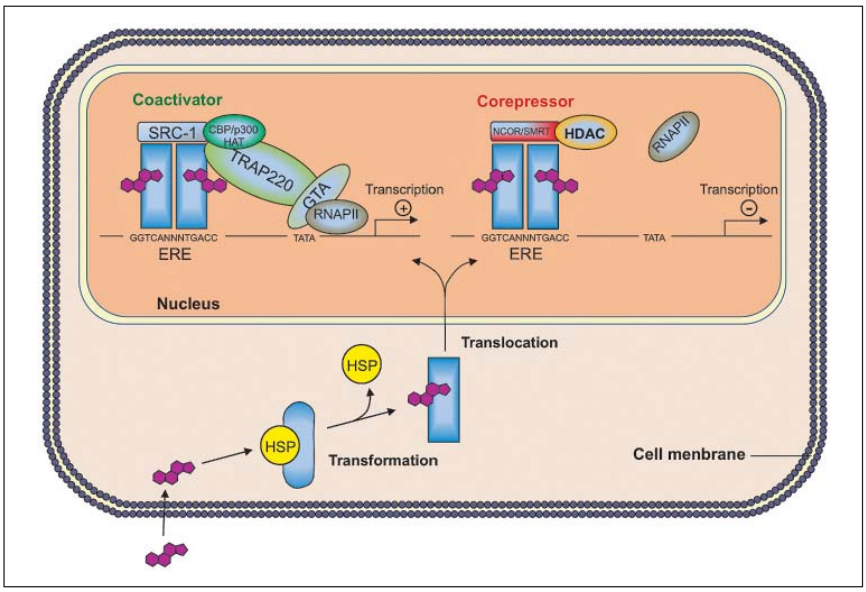

Figure 1. Genomic mode of estrogen action. © Thomas Rabe

mission of the steroid hormone from the cytoplasm into the nucleus.

In humans, 2 forms of the estrogen receptor are encoded by different genes, ESR1 (α) and ESR2 (β) to the 6th and 14th chromosome (6q25.1 and 14q23.2) respectively.

Receptor Distribution
Both ERs are expressed in various tissue types, but there are some notable differences in their expression pattern [4]:
– ERα: endometrium, breast cancer cells, stromal cells of the ovary and hypothalamus [5]
– ERβ: kidney, brain, bone, heart, lung, intestinal mucosa, prostate, and endothelial cells [6]

Polymorphism: Various polymorphisms of ERα- and ERβ-gene have been described.

Various ligands differ in their affinity for the alpha and beta isoforms of the estrogen receptor:
– 17β-estradiol binds equally well to both receptors
– Estrone and raloxifene preferentially bind to the receptor alpha (ERα)
– Estriol and genistein preferentially bind to the beta receptor (ERβ)

SERMs and their Interaction with the Estrogen Receptor Subtypes ERα and ERβ
Selective estrogen receptor modulators preferably bind to the α- or β-subtype of the receptor. In addition, the different estrogen receptor combinations can react differently to the different ligands, thus tissue-specific agonist and antagonist effects arise [7]. The ratio of the concentration of α- to β-subtype plays a role in certain diseases [8].

The concept of selective estrogen receptor modulators is based on the ability to influence the interaction with other ER proteins such as transcriptional co-activators or co-repressors, based on the conformational changes in the ligand-receptor complex which is different between SERMs and estrogen and also different for different SERMs. Since the ratio of co-activators and co-repressors is different in various tissues [9], the same ligand may act as an agonist in one tissue (provided that the co-activators predominate) and as an antagonist in other tissues

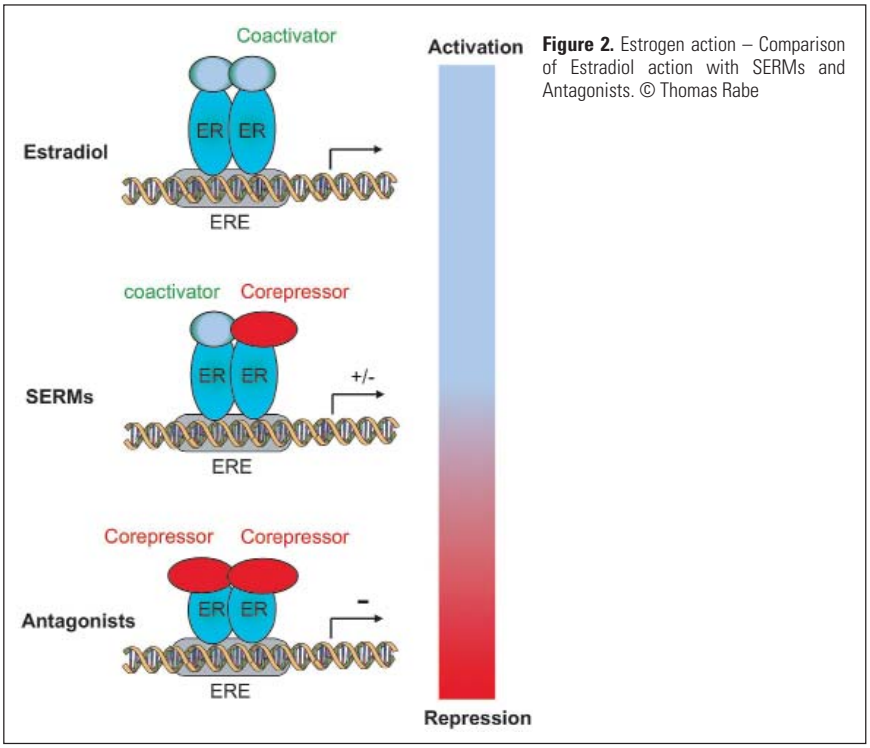

Figure 2. Estrogen action – Comparison of Estradiol action with SERMs and Antagonists. © Thomas Rabe

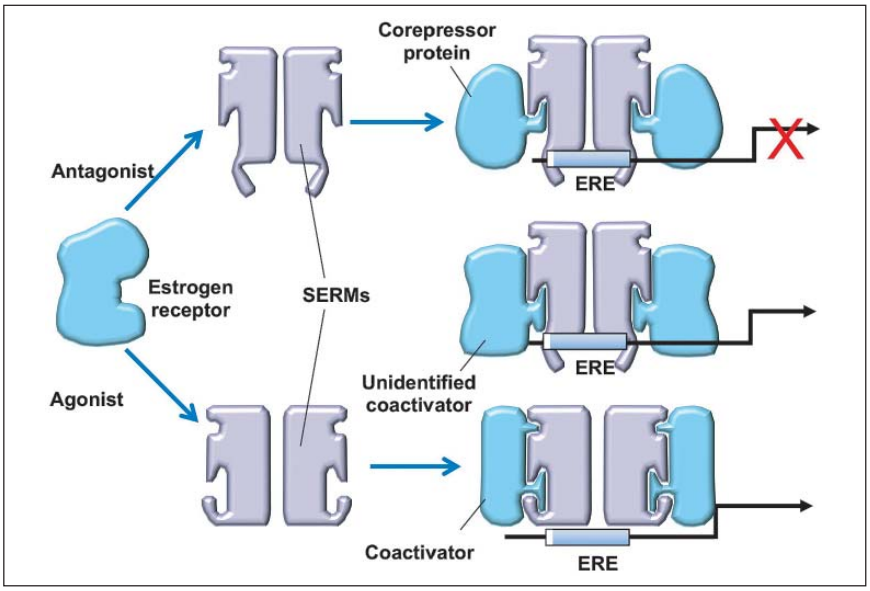

Figure 3. SERM action on Estrogen receptor: After binding of the ligand (agonist oder antagonist) at the estrogen receptor (α- or β-isoform), there is a change in conformation leading to a dimerisation of the receptor complex and binding to the estrogen-responsive element at the DNA at specific target organs. Estrogen-receptor activation depends on the presence of coactivators. During activation of the estrogen-receptor by an antagonist a coactivator protein is involved. SERM binding to the estrogen receptor lead to different conformational changes, as seen by classical agonists or antagonists. Different SERM activity in various target tissues depend on the varying expression of cofactors (corepressors or coactivators). Mod. from [2]. © Thomas Rabe

(where co-repressors dominate). Tamoxifene, for example, is an estrogen antagonist in the breast, and therefore suitable to treat breast cancer [10], while it acts as a partial agonist on bone and the endometrium (thereby creating a risk for endometrial cancer development). Bazedoxifene on the other hand also acts as an agonist on bone [11, 12], but as an antagonist on the endometrium [13].

2.2. Estrogen Action via Genomic Pathway

2.2.1. Most Pharmacological Effects of SERMs Can be Explained by One or More of the Following Three Mechanisms [14]
– Different tissue-specific expression of estrogen receptors
– Different changes in estrogen receptor conformation after ligand binding

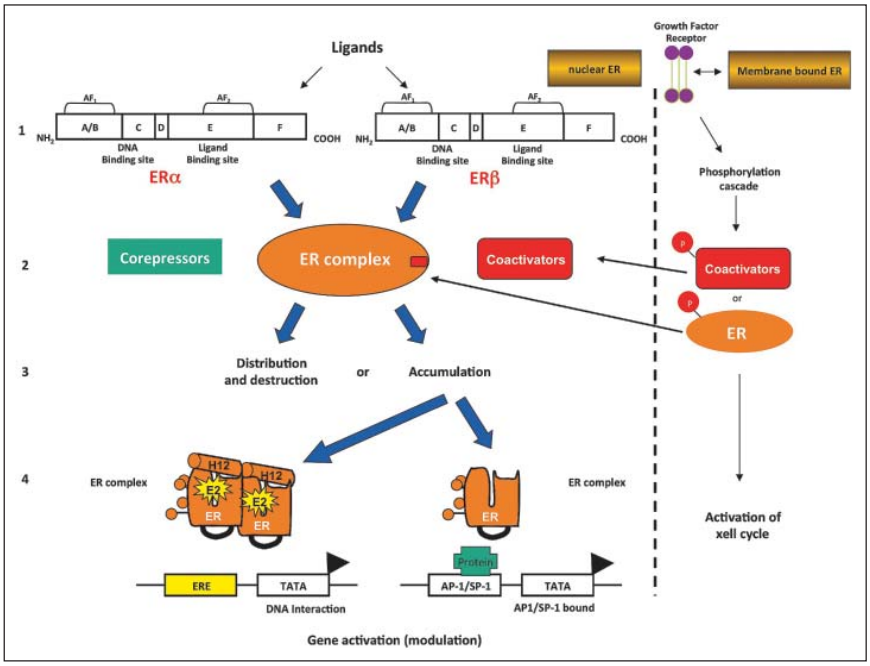

Figure 4. SERMs: Mode of action. The ligands of estrogen or SERM first bind either bind to the nuclear estrogen receptor (ER) alpha (α) or beta (β) or to the membrane-bound ER **(step 1)**. The following receptor-specific or non-specific binding to the ligand binding site (Region E) leads to a ligand specific conformational change of the receptor complex. This allows the complex to bind either co-activators or repressors to the surface **(step 2)**. The interactive proteins to the ER complex transform it into an active or inactive state. Besides the known coregulators other interactive proteins could play a role via an effect on gene transcription by phosphorylation. This can be initiated rapidly through the ER membrane-bound growth factor receptors or the cell surface. In the **third step**, the cofactors or the ER complex are ubiquitously distributed and possibly destroyed or accumulated to change into different estrogen-like complexes. In the following **step (4)** pathways are activated, depending on the binding ER, the binding ligand, the presence of an estrogen-response element or an interaction with the proteins of the AP-1 or SP-1 sites, causing as result a positive or negative gene regulation. Mod. from [Jordan VC. Selective estrogen receptor modulation: concept and consequences in cancer. Cancer Cell 2004; 5: 207–13]. © Thomas Rabe

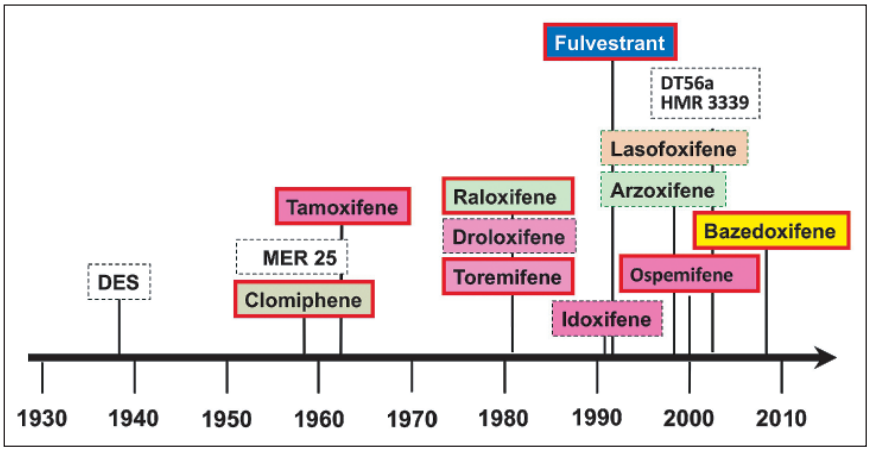

Figure 5. Development of SERMs.
red margin: products on the market; broken lines: substances are not developed anymore; DES: Diethylstilbestrol; MER-25: antiestrogen ethamoxytriphetol; HMR 3339: SERM; DT56a: Femarelle (DT56a) is as a selective estrogen receptor modulator (SERM) for the treatment of menopause and bone health. Femarelle contains approximately 322 mg DT56a (a tofu extract) and 108 mg flaxseed powder; Ospemifen: new SERM for treatment of dyspareunia (US-approval) and vaginal dryness (EU-approval 15.1.2015); Fulvestrant: selective estrogenreceptor-down-regulator; used for treatment of metastazing breast cancer; On the market: clomifene, tamoxifene, raloxifene, femarelle (US etc.), bazedoxifene (some countries), ospemifene (US, EU). © Thomas Rabe

– Differential expression and binding of the estrogen receptor to co-regulator proteins (Fig. 3–5)

For the estrogen effect, target cells contain different tissue-specific concentrations of

– Homodimers of either or both types of estrogen receptors (estrogen receptor α and estrogen receptor β).
– Heterodimers of estrogen receptor α with estrogen receptor β.
– Estrogen receptor α always acts as an activator.

Table 1. Relative binding affinities of various ligands to the estrogen receptor (ER) α and β. Mod. from [18] and [Gruber CJ, Tschugguel W, Schneeberger C, Huber JC. Production and actions of estrogens. N Engl J Med 2002; 346: 340–52]. © Thomas Rabe

Ligand	ER-alpha	ER-beta
17alpha-Estradiol	100	100
17beta-Estradiol	58	11
Estriol	14	21
Estrone	60	37
4-Hydroxyestradiol	13	7
2-Hydroxyestrone	2	0,2
Tamoxifene	4	3
Raloxifene	69	16
Genisteine	4	87
Coumestrol	20	140

– Estrogen receptor β inhibits the action of the estrogen receptor α by forming a heterodimer, there is a further inhibition of at least 240 estrogen-dependent genes by 46% [15].

The expression of these 2 receptor isoforms influences the cellular response of the target tissue to estrogen [16] and SERMs [17].

The relative binding affinity of different ligands to the ER α and β is shown in Table 1 [18]. Raloxifene and tamoxifene bind to both isoforms, which affect cellular responsiveness. SERMs act as pure antagonists if their effect on the genes occurs only via the estrogen receptor-β, or as (partial) agonists, when they act on the estrogen receptor α [17].

2.2.2. Change of Conformation of the Estrogen Receptor Following Ligand Binding

SERM Effects

The effect of the binding of estradiol, tamoxifene, raloxifene, and the pure estrogen antagonist ICI 164.384 depends on the respective ligand [19–22] ranging between pure agonistic effects after binding of estrogens and pure antagonistic effects after binding of anti-estrogens. The SERMs take an intermediate position according to the conformational changes of the receptor complex caused by a particular SERM.

2.2.3. Co-regulator Proteins

Currently more than 20 co-regulator proteins are known that bind to estrogen receptor complexes as either positive or

negative transcriptional regulators (as co-activators or co-repressors) [23–27]. Some 285 nuclear cofactors for receptors have been reported, though not specific for the estrogen receptor.

The relative and absolute level of expression of these co-regulator proteins in the various target cells is different [23, 28]. The ligand specific conformational changes of the SERM/ER complex determine the binding affinity for specific co-activators or co-repressors and thus its final activity [9].

SERM Effects

Tamoxifene induces the recruitment of co-repressors to target gene promoters in mammary cells. In endometrial cells, tamoxifene, in contrast to raloxifene, acts like an estrogen by stimulating the recruitment of co-activators to a subset of genes.

The estrogen-like activity of tamoxifene in the uterus requires a high level of steroid receptor co-activator 1 (SRC-1) expression. Thus cell type- and promoter-specific differences in co-regulator recruitment determine the cellular response to SERMs.

Raloxifene induces the recruitment of co-repressors to target gene promoters in mammary cells [9].

2.3. Estrogen Action via Non-Genomic Pathway

Novel non-transcriptional mechanisms of signal transduction through steroid hormone receptors have been identified [29]. These so-called "non-genomic" effects are independent of gene transcription or protein synthesis and involve steroid-induced modulation of cytoplasmic or cell membrane-bound regulatory proteins. Relevant biological actions of steroids have been associated with this signaling in different tissues. Ubiquitous regulatory cascades such as mitogen-activated protein kinases (MAPK), the phosphatidylinositol 3-OH kinase (PI3K) and tyrosine kinases are modulated through non-transcriptional mechanisms by steroid hormones. Furthermore, steroid hormone receptor modulation of cell membrane-associated molecules such as ion channels and G-protein-coupled receptors has been shown in various tissues. The vascular wall is a site where non-genomic steroid hormone actions are particularly prominent. For instance, estrogens trigger rapid vasodilatation due to rapid induction of nitric oxide synthesis in endothelial cells via the estrogen receptor-dependent activation of MAPK and PI3K, leading to relevant pathophysiological consequences, *in vitro* and *in vivo*.

SERMs

Acolbifene: Non-genomic effects of estrogens have been described by Simoncini et al [29] for the novel SERM acolbifene, which has estrogen-like activities on the vascular wall, directly increasing NO production through genomic and nongenomic mechanisms *in vitro* and *in vivo*.

Raloxifene: Non-genomic mechanisms of endothelial nitric oxide synthase activation by the selective estrogen receptor modulator raloxifene have been found by Simoncini et al (2002) [29]. This pathway might be important to understand the different effects of SERMs on the cardiovascular system.

Tamoxifene: E2-independent effects on the uterine epithelium [30].

3. Overview of SERMs

SERMs are subdivided according to their chemical structure into the following subgroups: triphenylethylenes (e.g. clomifene, tamoxifene, toremifene, ospemifene), benzothiophenes (e.g. raloxifene) benzopyrans (e.g. ormeloxifene), indoles (e.g. bazedoxifene), and naphthalenes (e.g. lasofoxifene) (Tab. 2, Fig. 6).

Table 2. Classification of SERMs according to the chemical structure. © Thomas Rabe

Substance group	Substance	Field of application
1. Triphenylethylene	Chlomifene	Ovarian dysfunction
	Tamoxifene and Toremifene	Breast cancer
	Ospemifene	Vulvovaginal atrophy FDA approval: moderate to severe dysparaneunie based on a vulvo-vaginal postmenopausal atrophy
	Droloxifene	No further development
	Idoxifene	No further development
2. Benzothiophenes	Raloxifene	Osteoporosis, breast cancer prevention (US only)
	Arzoxifene	No further development
3. Benzopyranes	Ormeloxifene	Contraception, DUB (India)
	Levormeloxifene	No further development
	EM-800	No further development (inferior to anastrozole)
4. Indoles	Pipendoxifene	Development (breast cancer)
	Bazedoxifene	Osteoporosis
5. Naphtalenes	Lasofoxifene	Osteoporosis

The historical development of the SERMs is demonstrated in Figure 5 and 7.

In the following section, some SERMs, which are often used in clinical practice, are described in detail. In addition, some of the SERMs the clinical development of which has been stopped (e.g. lasofoxifene, droloxifene (inferior to tamoxifene), levormeloxifene (endometrial safety, prolaps), idoxifene (endometrial safety, prolaps) [31] are also described.

The properties of the ideal SERM are shown in Figure 8. The ideal SERM would be a substance that could be used in the postmenopause for treatment of the estrogen deficiency symptoms (i.e. climacteric symptoms), and in addition would prevent breast cancer, osteopenia and osteoporosis. Furthermore, it would have to exert a favourable effect on the vaginal epithelium to prevent vaginal dryness and dyspareunia.

The different binding affinities of estrogens and selected SERMs on selected estrogen α- and β-receptor are shown in Table 1.

3.1. Clomifene

Substance

Triphenylethylene derivative (Fig. 9).

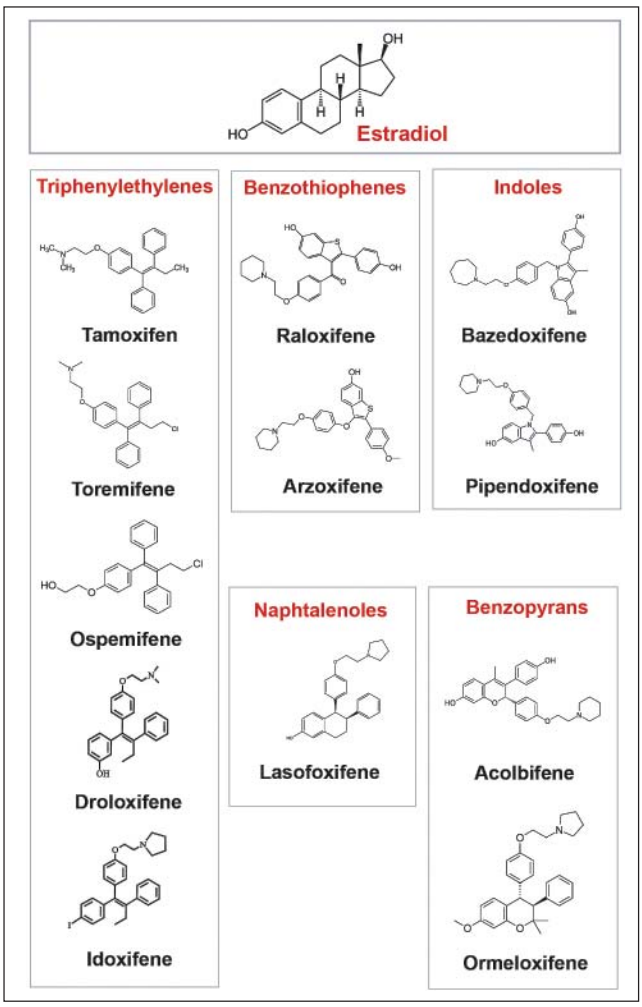

Figure 6. Chemical structure of selected SERMs. © Thomas Rabe

Clomifene citrate consists of two stereoisomers (Z- and E-isomer) has been used in fertility therapy for over 40 years.

Indication

– Treatment of anovulatory infertility in women (EU)
– Induction of ovulation in patients with persistent ovulatory dysfunction (US)

Mode of Action

Clomifene binds to the hypothalamic estrogen receptors and inhibit the negative feedback of endogenous estradiol, resulting in an increase of GnRH release and, hence, the secretion of the gonadotropins FSH and LH which stimulate ovarian follicular development. Clomifene has an estrogen antagonistic effect on the uterus, cervix and vagina.

Applications

The therapeutic indications include functional female sterility as a result of hypothalamic-pituitary dysfunction in normoprolactinemic women (anovulation with detectable endogenous estrogen production and normal to low serum FSH), idiopathic sterility (empirical approach) and controlled superovulation in combination with IVF. Most clomifene initiated conceptions occur in the first six ovulatory cycles. Approximately 50% of conceptions are achieved with the starting dose of 50 mg clomifene, 20–25% with 100 mg and 10% with the maximum dose of

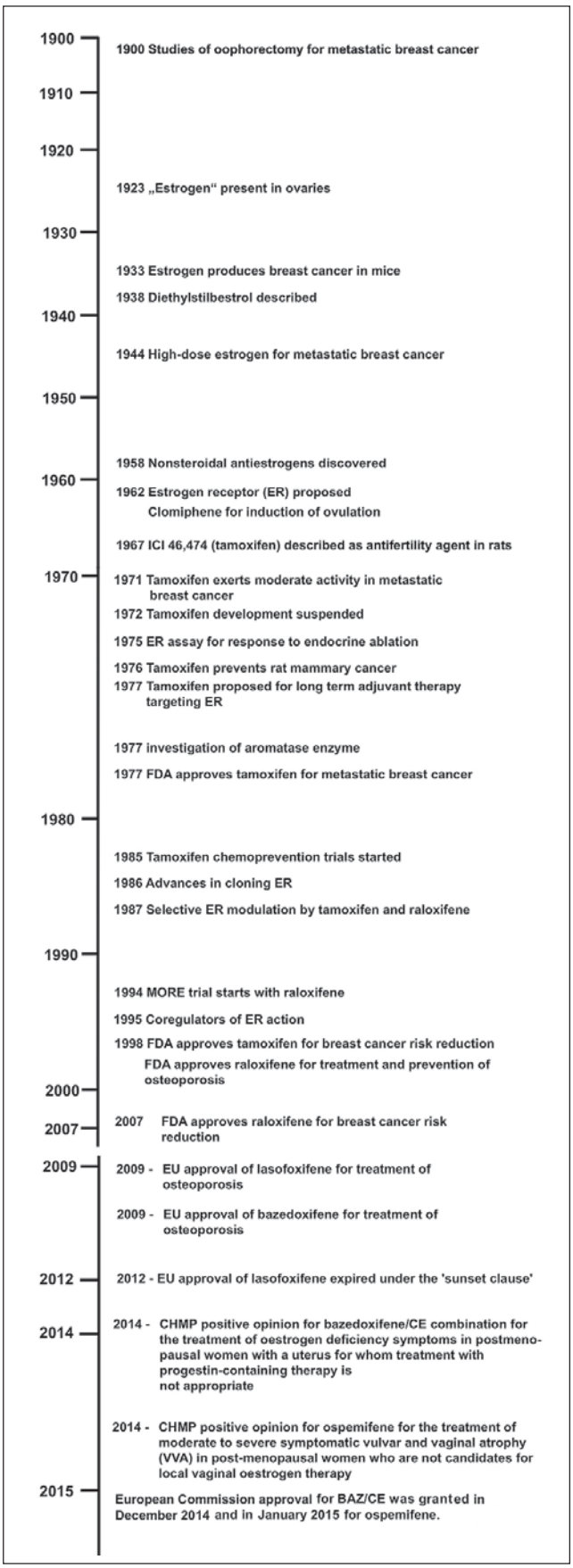

Figure 7. Historical development of estrogens, estrogen action, antiestrogens, selective estrogen receptor modulators (SERMs) for treatment and prevention of breast cancer and osteoporosis and in the last years for treatment of dyspareunia and vaginal dryness. Mod. from [48]. © Thomas Rabe

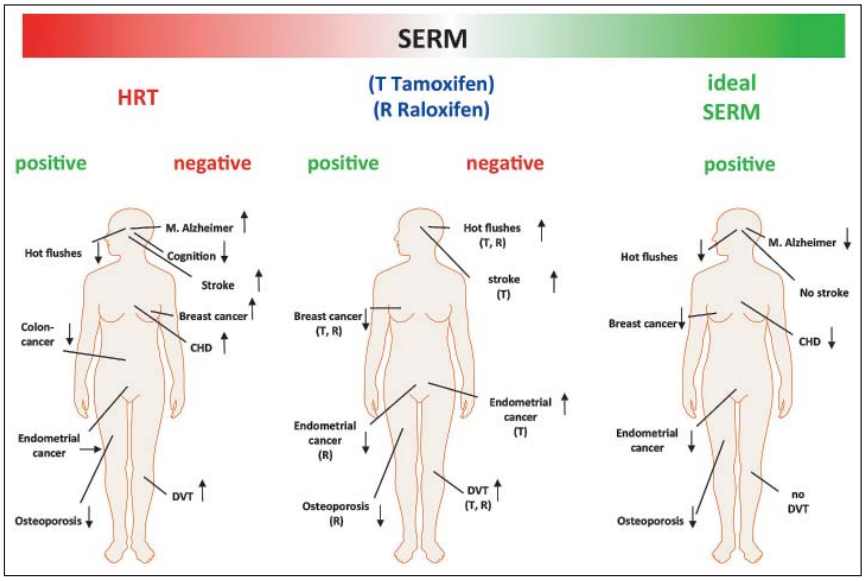

Figure 8. Development of an "ideal" SERM. CHD: coronary heart disease; DVT: deep vein thrombosis. Mod. from [48]. © Thomas Rabe

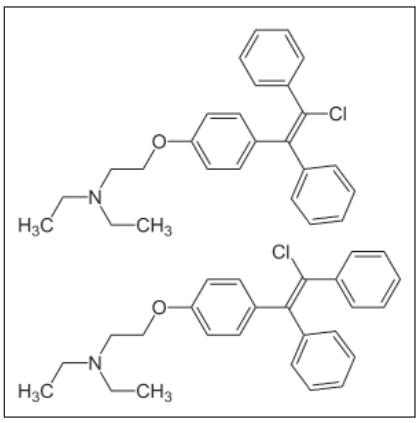

Figure 9. Clomifene is a mixture of (E)- and of (Z)-isomers (cis-trans-isomer). Clinical relevant is the antiestrogen action of the (E)-isomer (E-clomifene), with only a weak estrogenic action. The (Z)-isomer (Z-clomifene) possesses only an estrogen activity. © Thomas Rabe

150 mg [32]. In a review of 5.000 women, the ovulation rate for various indications of clomifene citrate was 73% and the pregnancy rate 36% [33]. Clomifene was not associated with an increased risk of spontaneous abortion or fetal malformations [34].

Side Effects
Reversible side effects include hot flushes (10–20%), abdominal pain (5.5%), nausea and vomiting (2.2%), breast discomfort (2%) and ocular disturbances (1–2%). Since an increased risk for (invasive and borderline) ovarian tumors has been described in a group of women treated with clomifene for more than 12 cycles [35], clomifene should only be used during a limited period of time (< 12 cycles). The effect of clomifene on the breast and endometrial cancer is not fully understood.

3.2. Ormeloxifene

Substance
Benzopyran derivative (also known as centchroman)

Indication
Contraception and dysfunctional uterine bleeding (India only)

Contraception
Ormeloxifene is used primarily as a contraceptive. It has both estrogenic and antiestrogenic activity. Unlike the combined oral contraceptive pill, it does not interfere with ovulation, but inhibits a fertilized ovum from implantation. It is licensed in India for contraception as a 30 mg tablet, twice weekly for 3 months followed by once weekly [36] (tradenames Saheli, Novex and Centron). The failure rate is 1–2% [37]. As a 60 mg twice weekly tablet it is also licensed for the treatment of dysfunctional uterine bleeding and menorrhagia [38] (tradenames Sevista and Noves-DS).

Breast Disease
It has also been investigated for for the treatment of mastalgia and fibroadenoma [39], breast cancer [40] and other cancers [41]. Gara et al [41] published new data on the anti-cancer potential of ormeloxifene.

Bone Health
Narayana Murthy et al [42] described how ormeloxifene was superior to raloxifene on ovariectomy-induced bone resorption, osteoclast differentiation and apoptosis and TGF-β-3-expression.

Mechanism of Action
Ormeloxifene is a SERM, which has an estrogenic effect in some parts of the body (e. g. bones) and an anti-estrogenic effect in other parts of the body (e.g., uterus, breast) [43, 44].

Unwanted Side Effect
Delay in menstruation [31].

3.3. Ospemifene

Substance
Triphenylethylene (metabolite of toremifene) (Fig. 9).

Indication
The treatment of vulvar and vaginal atrophy.

Application Instructions
- Dose: 60 mg/day
- Drug interactions: Ospemifene is primarily metabolized by CYP3A4 and CYP2C9. It should not be used concomitantly with estrogens and estrogen agonists/antagonists. The safety of concomitant use of ospemifene with estrogens and other SERMs has not been studied. Interaction has been described with fluconazole, rifampicin and ketoconazole. (Osphena® Prescribing Information).

Treatment Duration
There is no formal restriction on duration of use in Europe.

Mode of Action (according to [45])
Ospemifene binds to the human estrogen receptor (ERα and ERβ) [47]. It shows a higher specificity for the estrogen receptors for the vaginal epithelium than other commercially available SERMs (e.g. tamoxifene, raloxifene). Agonistic effects at these receptors lead to a positive effect on the vaginal mucosa [48]. Effects observed in other tissues include minimal effects on the endometrium, with a slight increase in mean endometrial thickness without concomitant cellular proliferation [49]. Ospemifene acts antagonistically on breast tissue and leads to a reduction in bone turnover makers [50, 51].

Pharmacokinetics
Maximum blood concentrations are measured 1 and 8 hours after oral admin-

istration of ospemifene. Steady-state was reached after nine days of ospemifene administration [46] (Micromedex® Healthcare Series, (electronic version). Thompson Micromedex, Greenwood Village, Colorado, USA. Available at: http://www.thomsonhc.com). Concomitant food intake can increase the drug concentration of ospemifene. In blood, more than 99% of ospemifene is bound to serum proteins [46]. The major metabolite is 4-hydroxyospemifene which is formed by the hepatic CYP enzymes 3A4, 2C9, and 2C19. Ospemifene itself is a weak inhibitor of CYP enzymes 2B6, 2C19, 2C8, 2D6 and 3A4. Elimination occurs primarily via the feces, and in small quantities in the urine [46].

Licensing

– USA: The FDA has approved ospemifene as new SERM in a dosage of 60 mg daily for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause [46].
– Europe: Ospemifene has been approved for the "treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women" who are not candidates for local estrogen therapy.

Clinical Trials

In a double blind randomized phase III study reported by Bachmann and Komi [52] 826 postmenopausal women were treated with daily doses of either 30 mg ospemifene, 60 mg ospemifene or a placebo over a period of 12 weeks. The primary inclusion criteria were: Having 5% or less superficial cells on the vaginal smear (maturation index), vaginal pH greater than 5.0 and at least one moderate or severe symptom of vulvovaginal atrophy. The four co-primary endpoints were the change from baseline to 12 weeks in the percentage of superficial and parabasal cells on the vaginal smear, change in vaginal pH, and change in severity of most bothersome symptom (vaginal dryness or dyspareunia) compared with placebo. All participants were given a nonhormonal vaginal lubricant for use as needed.

Ospemifene was statistically significantly superior to placebo in each of the co-primary endpoints at the 60-mg dose. Statistically significant results were achieved for all coprimary endpoints with the 30-mg dose except for dyspareunia. Ospemifene was well tolerated at both doses and demonstrated a favorable safety profile.

Ospemifene was shown to be effective and well tolerated for the treatment of the symptoms of vaginal dryness and dyspareunia associated with vulvovaginal atrophy over and above the use of provided lubricants.

In a second 12-week phase III randomized, double blind, parallel-group trial the effect of 60 mg ospemifene was compared to placebo. The inclusion criteria were similar to the first study, but the participants were stratified at randomization based on their most bothersome symptoms. The results for the dyspareunia stratum are reported by Portman et al [53], and for the vaginal dryness stratum by Portman et al [54]: A total of 605 women aged 40 to 80 years with VVA who reported dyspareunia as their most bothersome symptom were randomized to take a once-daily dose of ospemifene (n = 303) or placebo (n = 302) for 12 weeks and a total of 314 women whose most bothersome symptom was vaginal dryness were randomised to once-daily ospemifene 60 mg/day (n = 160) or placebo (n = 154).

Analysis of the intent-to-treat population for both strata found the efficacy of ospemifene to be significantly greater than that of placebo at 12 weeks for each of the following co-primary endpoints: percentages of parabasal and superficial cells and vaginal pH ($p < 0.0001$). In the dyspareunia stratum, there was a statistically significant improvement in the severity of dyspareunia ($p = 0.0001$). Among the randomized women, 186 (61.4%) in the ospemifene group and 154 (51.0%) in the placebo group reported at least one treatment-emergent adverse event. Hot flushes were the most frequently reported treatment-related adverse event (ospemifene 6.6% vs placebo 3.6%); only one participant discontinued in each group. As determined by the investigators, no serious adverse events related to the study drug were reported. Once-daily oral ospemifene 60 mg was effective for the treatment of vulvar and vaginal atrophy in postmenopausal women with dyspareunia.

In the vaginal dryness stratum, the mean change from baseline in severity score of vaginal dryness reported by women receiving ospemifene compared with those receiving placebo approached statistical significance in the ITT population ($p = 0.080$) and was statistically significant in the PP population ($p = 0.014$). The majority of treatment-emergent adverse events were considered mild to moderate in severity. Once-daily oral ospemifene 60mg was effective for the treatment of VVA in postmenopausal women with vaginal dryness.

Goldstein et al [55] summarized the 12-month efficay and safety of ospemifene in postmenopausal women with vulvar and vaginal atrophy.

Methods

In this 52-week, randomized, double blind, placebo controlled, parallel-group study, women 40–80 years with VVA and an intact uterus were randomized 6:1 to ospemifene 60 mg/day or placebo (363 ospemifene, 69 placebo). The primary objective was 12-month safety, particularly endometrial; 12-week efficacy was assessed. Safety assessments included endometrial histology and thickness and breast and gynecological examinations. Efficacy evaluations included changes from baseline to week 12 and 52 in percentage of superficial and parabasal cells and vaginal pH.

Results

Of 426 randomized subjects, 81.9% (n = 349) completed the study with adverse events the most common reason for discontinuation (ospemifene 9.5%; placebo 3.9%). Most (88%) treatment-emergent adverse events with ospemifene were considered mild or moderate. Three cases (1.0%) of active proliferation were observed in the ospemifene group. For one, active proliferation was seen at end of study, and diagnosed as simple hyperplasia without atypia on follow-up biopsy 3 months after the last dose. This subsequently resolved with progestogen treatment. In six subjects (five ospemifene (1.4%), one placebo (1.6%) endometrial polyps were found, however, only one (ospemifene) was confirmed as a true polyp during additional expert review. Endometrial histology showed no evidence of carcinoma. Statistically significant improvements were seen for all primary efficacy parameters and were sustained through week 52 with ospemifene vs. placebo.

Conclusions
The findings of this 52-week study confirm the tolerance and efficacy of oral ospemifene previously reported in short- and long-term studies.

Side Effects
- Minor side effects: Hot flushes represent 7.5% and are the most common side effect [46]
- Major side effects:
  - Endometrial safety: Endometrial proliferation only occurred in 1% of subjects in the 1-year study [49]. There were no cases of endometrial cancer. In another prospective study of 180 women for 1 year no endometrial changes were diagnosed [56]. Compared with placebo, there were no significant estrogen-related or clinically important adverse effects on the endometrium at a dose of 60 mg ospemifene over a 1-year duration of treatment.
  - Venous thromboembolism: FDA-black box warning: *"Estrogen-alone therapy has an increased risk of stroke and deep vein thrombosis (DVT). For deep vein thrombosis, the incidence rate for OSPHENA 60 mg is 1.45 per thousand women vs. 1.04 per thousand women in placebo [see Warnings and Precautions (5.1)]."* (http://www.shionogi.com/pdf/PI/Osphena-PI.pdf; 30.3.2014; http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203505s000lbl.pdf; 30.3.2014). When corrected for exposure, the Incidence Rate Ratio (or Relative Risk) of VTE for ospemifene compared to placebo is 1.0 (95-%-CI: 0.052–58.783), see Table 3.
  - Cerebrovascular insults: FDA-black box warning: *"OSPHENA 60 mg had cerebral thromboembolic and hemorrhagic stroke incidence rates of 0.72 and 1.45 per thousand women, respectively vs. 1.04 and 0 per thousand women, respectively in placebo."* When corrected for exposure, the Incidence Rate Ratio (or Relative Risk) of CVA for ospemifene compared to placebo is 0.498 (95-%-CI: 0.006–39.102).

Contra Indications
(US Prescribing Information: http://www.shionogi.com/pdf/PI/Osphena-PI.pdf http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203505s000lbl.pdf)
- Undiagnosed abnormal genital bleeding
- Known or suspected estrogen-dependent neoplasia
- Active DVT, pulmonary embolism (PE), or a history of these conditions
- Active arterial thromboembolic disease [for example, stroke and myocardial infarctions (MI)], or a history of these conditions
- Women who are or may become pregnant.

Further Investigations
The positive effects on breast and bone need to be confirmed in clinical trials.

Although more data on drug safety during long-term use are required, ospemifene provides a promising alternative to local estrogen therapy for the treatment of vulvovaginal atrophy.

3.4. Raloxifene

Substance
Benzothiophene derivative

Indication
- Treatment and prevention of osteoporosis in postmenopausal women (EU, US)
- Reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis (US)
- Reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer (US).

Fields of Application
Raloxifene (60 mg/day) is used for treating and preventing osteoporosis in postmenopausal women. In 2007, the US FDA extended the indication to the reduction in risk of breast cancer in postmenopausal women with osteoporosis and at high risk for invasive breast cancer.

Breast Cancer Prevention
The breast cancer prevention indication granted by the FDA was based on the results of the STAR trial [57] which compared the relative effects and safety of raloxifene and tamoxifene on the risk of developing invasive breast cancer and other disease outcomes. In this study, raloxifene is as effective as tamoxifene in reducing the risk of invasive breast cancer (risk ratio [RR], 1.02; 95-%-CI: 0.82–1.28) and has a lower risk of thromboembolic events (RR, 0.70; 95-%- CI: 0.54–0.91) and cataracts (RR, 0.79; 95-%-CI: 0.68–0.92) but a nonstatistically significant higher risk of noninvasive breast cancer (RR, 1.40; 95-%-CI: 0.98–2.00). The risk of other cancers, fractures, ischemic heart disease, and stroke is similar for both drugs.

Bone Health
Raloxifene significantly reduced the risk of vertebral fractures (OR 0.6, 95-%-CI: 0.5–0.7) [58]. The cumulative risk of one or more vertebral fractures after 4 years of raloxifene compared to placebo is 0.64 (95-%-CI: 0.53–0.76) [59]. The evidence of efficacy with respect to a risk reduction of non-vertebral fractures is based only in the post-hoc analyses, especially in the subgroup of women with vertebral fractures [59]. For raloxifene there are efficacy and safety data available for an observation period of eight years [60].

After discontinuation of raloxifene however, there is a significant decrease in bone mineral density at the lumbar spine and femoral neck within one year [61].

Side Effects
Typical side effects of raloxifene include hot flushes (especially in the first six months), leg cramps, and pollakisuria. The risk of endometrial hyperplasia or carcinoma, post-menopausal bleeding disorders, ovarian cancer and vulvovaginal discomfort is not increased. The risk of venous thromboembolism (VTE) is approximately doubled by raloxifene similarly by a conventional oral hormonal replacement therapy or tamoxifene [62]. Thus, raloxifene is contraindicated in current VTE and in patients with a history of VTE. The overall risk of stroke is not increased, but rather the risk of fatal stroke [62] especially in women who are already at a high risk of stroke at baseline [63]. The risk of coronary events, however, is not increased in women with preexisting cardiovascular disease [63].

A post-hoc analysis of the three major studies Multiple Outcomes of Raloxifene Evaluation (MORE), Continuing Outcomes Relevant to Evista (CORE) and Raloxifene Use for the Heart (RUTH) showed a decrease in overall mortality among raloxifene users [64].

Table 3. Cardiovascular safety profiles of SERMs in Phase-III treatment studies: Venous thromboembolism. © Thomas Rabe

	Mean age (yrs)	Duration	Incidence Proportion/ 1000 patients (n/N)		Incidence Proportion Ratio (95% CI)	Incidence Rate/ 1000 patients (95% CI)		Incidence Rate Ratio (95% CI)	References
Bazedoxifene			**BAZ 20 mg**	**Placebo**		**BAZ 20 mg**	**Placebo**		
Osteoporosis prevention study	58	2 yrs	6 (2/322)	3 (1/310)	1.9	NA	NA	NA	Miller et al [189]
Osteoporosis treatment study	66	1st yr (a)	4.2 (8/1886)	1.6 (3/1885)	2.6	4.6 (e) (2.00–9.14)	1.7 (e) (0.36–5.05)	2.69 (e) (0.64–15.70	Christiansen et al [190] (a) Silverman et al [12] (b)
		2nd yr (a)	2.1 (4/1886)	1.1 (2/1885)	1.9	2.7 (0.73 - 6.83)	1.3 (0.16 - 4.82)	2.1 (0.3 - 22.96)	Conbriza® EPAR (c) Conbriza® updated EPAR (d)
		3rd yr (a)	0.5 (1/1886)	1.6 (3/1885)	0.3	0.7 (0.02–3.94)	2.1 (0.44–6.20)	0.3 (0.01–4.15)	Conbriza® SmPC (e) De Villiers [192] (f)
		3 yrs	6.9 (13/1886)	4.2 (8/1885)	1.6	2.86 (e) (1.49–4.79)	1.76 (e) (0.74–3.39)	1.63 (e) (0.68–3.94)	
		5 yrs	8 (15/1886) (b, f)	5.3 (10/1885) (b, f)	1.5 (0.68; 3.35) (f)	2.34 (e) (1.3–3.9) (f)	1.56 (e) (0.8–2.9) (f)	1.5 (e) (0.68–3.35) (f)	
		7 yrs (e)	NA	NA	NA	2.06	1.36	1.51	
Raloxifene			**RAL 60 mg**	**Placebo**		**RAL 60 mg**	**Placebo**		
Osteoporosis prevention trials	54	3 yrs	3.5 (1/286)	0 (0/286)	–	NA	NA	NA	Johnston et al [156]
Osteoporosis	66.5		**RAL 60/120**	**Placebo**		**RAL 60/120**	**Placebo**		
treatment studies		1st yr	4.7 24/5129	0.7 2/2576	6.45	5.1	0.8	6 (1.4–25.5)	
		2nd yr	2.5 13/5129	0.4 1/2576	6.99	3	0.5	6.6 (0.9–50.4)	
		3rd yr	2.5 13/5129	2.5 7/2576	1	3.2	3.6	0.9 (0.4–2.3)	
		4th yr	1.8 9/5129	1.5 4/2576	1.21	2.4	2.2	1.1 (0.3–3.5)	
			RAL 60 mg	**Placebo**		**RAL 60 mg**	**Placebo**		
		3 yrs (a)	11 (28/2557)	3.1 (8/2576)	3.8	NA	NA	2.4 (g) (1.2–4.5)	Cummings [157] (a) Delmas [59] (b)
		4 yrs (b)	12.9 (33/2557)	6.6 (17/2576)	1.96	NA	NA	NA	Grady et al [188] (c) Martino [117, 191] (c, e)
		8 yrs (c)	17.3 (47/2725)	10.1 (13/1286)	1.7	2.2	1.3	1.7 (0.93–3.14)	Evista SmPC (d) Evista USPI (g)
		All DBPC studies (d)	8	NA	NA	3.22	NA	1.6 (0.95–2.71)	
RUTH-Study	67.5	5 yrs	20.4 (103/5044)	14 (71/5057)	1.5	3.9	2.7	1.44 (1.06–1.95)	Barrett-Connor et al [63]
STAR-Study	58.5		**RAL 60 mg**	**TAM 20 mg**		**RAL 60 mg**	**TAM 20 mg**		
		4 yrs (a)	10.3 (100/9745)	14.5 (141/9726)	0.71	2.61	3.71	0.7 (0.54–0.91)	Vogel [57, 132] (a, b)
		81 months (b)	15.8 154/9745	20.8 202/9726	0.76	2.47	3.3	0.75 (0.60–0.93)	
Tamoxifene (Breast cancer prevention only)			**TAM 20 mg**	**Placebo**		**TAM 20 mg**	**Placebo**		
NSABP-P1-Study	≤ 49 yrs	4 yrs (a)	5 (13/2581)	3.5 (9/2596)	1.43	1.28	0.88	1.45	Fisher et al [133] (a)
	> 50 yrs		10.5 (40/3795)	4.7 (19/4003)	2.21	2.51	1.19	2.11	
	≤ 49 yrs	7 yrs (b)	7.7 (20/2599)	5.4 (14/2600)	1.43	1.26	0.89	1.42	Fisher et al [137] (b) (DVT + PE)
	> 50 yrs		14.2 (57/4008)	8.2 (33/4010)	1.73	2.29	1.33	1.72	
IBIS-Study	50.8	Median: 50 months	12 (43/3573)	4.8 (17/3566)	2.52 (1.5–4.4)	2.87	1.14	2.52	IBIS Investigators [136]
Royal Marsden-Study	Median age: 47 yrs	8 yrs	6.5 (8/1238)	2.4 (3/1233)	2.66	NA	NA	NA	Powles et al [139]
Ospemifene			**OSP 60 mg**	**Placebo**		**OSP 60 mg**	**Placebo**		
Ospemifene DBPC Phase 2/3 studies	59.1	6 weeks–1 yr	1.6 (2/1241)	1 (1/958)	1.54 (0.14–17.0)	3.65 (0.44–13.19)	3.66 (0.09–20.41)	1 (0.052–58.783)	EPAR Senshio

CI: confidence interval; NA: not available

3.5. Tamoxifene

Substance

Triphenylethylene derivative (Fig. 9)

Field of Applications

Tamoxifene is approved for:

- Adjuvant treatment of estrogen-receptor positive early, locally advanced or metastatic breast cancer (EU/US)
- In women with DCIS, following breast surgery and radiation, tamoxifene citrate is indicated to reduce the risk of invasive breast cancer (US only)
- Tamoxifene citrate is indicated to reduce the incidence of breast cancer in women at high risk for breast cancer (US only)

Off-label use of tamoxifene includes ovulation induction as well as prevention and treatment of precocious puberty.

In addition, it is also used off-label in men to treat or prevent side effects like breast tenderness and swelling in some men with prostate cancer treatment, to treat gynaecomastia in men or by ste-

roid-taking, weight-training athletes to prevent the undesirable effects of anabolic steroids [65].

Mechanism of Action
Tamoxifene is a prodrug with a relatively low affinity to the estrogen receptor. In the liver, tamoxifene is metabolised by CYP2D6 and CYP 3A4 into active metabolites, e.g. 4-hydroxytamoxifene (afimoxifene) and 4-hydroxy-*N*-desmethyl tamoxifene (endoxifene) which both have a high affinity for the estrogen receptors and a 30- to 100-fold higher potency than tamoxifene in suppressing estrogen-dependent cell proliferation through competitive binding (vs. estrogen) to the estrogen receptor [66].

In breast tissue, 4-hydroxy-tamoxifene works as an estrogen antagonist by inhibiting the transcription of estrogen-regulated genes [67].

The effect of tamoxifene is regulated via different factors, a.o. growth factors like EGFR and IGF [68]. The tamoxifene-ER complexes directly repress ErbB2 transcription via a cis-regulatory element within the ErbB2 gene. This effect is dependent on the Paired Box 2 gene product (Pax2), and results in inhibition of the ErbB2/HER-2 pathway. Pax2 and the ER coactivator AIB-1/SRC-3 compete for binding and regulation of ErbB2 transcription. Enhanced AIB-1 expression leads to an increase in ErbB2 transcription and an increase in cell proliferation in the presence of tamoxifene [69]. High levels of AIB-1 are commonly found in tamoxifene resistant tumors [70].

Breast Cancer Studies
In a meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) a 5-year tamoxifene therapy versus no endocrine therapy in both pre- and postmenopausal women with breast cancer, showed a significant reduction of the risk of recurrence (RR 0.61; 95 % CI: 0.57–0.65) and breast cancer mortality (RR 0.70; 95% CI: 0.64–0.75) at a follow-up period of 15 years [71].

Recurrence Rates
In estrogen receptor- (ER) positive disease (n = 10,645), allocation to about 5 years of tamoxifene substantially reduced recurrence rates throughout the first 10 years (RR 0.53 [SE 0.03] during years 0–4 and RR 0.68 [0.06] during years 5–9 [both 2 $p < 0.00001$] but RR 0.97 [0.10] during years 10–14, suggesting no further gain or loss after year 10). Even in marginally ER-positive disease (10–19 fmol/mg cytosol protein) the recurrence reduction was substantial (RR 0·67 [0·08]). In ER-positive disease, the RR was independent of progesterone receptor status (or level), age, nodal status, or use of chemotherapy.

Breast Cancer Mortality
It was reduced by about a third throughout the first 15 years; during years 0-4: RR 0.71 [0.05], during years 5–9: 0.66 [0.05], during years 10–14: 0.68 [0.08]; $p < 0.0001$ for extra mortality reduction during each separate time period. Overall non-breast-cancer mortality was little affected, despite small absolute increases in thromboembolic and uterine cancer mortality (both only in women older than 55 years), so all-cause mortality was substantially reduced. In ER-negative disease, tamoxifene had little or no effect on breast cancer recurrence or mortality.

Five years of adjuvant tamoxifene safely reduces 15-year risks of breast cancer recurrence and death. ER status was the most important important factor which was predictive of the proportional reductions.

Receptor Status
It is well known that ER pos/PR pos breast cancer responds better to endocrine therapy than ER pos/PR neg [72], possibly as a result of "cross-talk" and because ER pos/PR neg tunours express higher levels of HER-1 and HER-2 and display more aggressive features than ER pos /PR pos tumors [73]. During tamoxifene treatment, the PR pos status is lost quicker than the ER pos. status [74].

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [71] has demonstrated that, for the efficacy of tamoxifene, the ER status is the single most important predictor, independent from progesterone receptor status (or levels), age, lymph node status or chemotherapy. In ER neg breast cancer tamoxifene has little or no effect on breast cancer recurrence or mortality.

Treatment Resistance
Breast cancer cells can develop resistance to tamoxifene. A distinction is made between intrinsic (de novo) and acquired resistance. Almost all patients with metastases and 40% of patients on adjuvant therapy have a relapse and die eventually from their disease [75].

Various mechanisms have been discussed including a variable ERα or ERβ expression, an interaction with co-activators or repressors and certain CYP2D6 genotypes (Fig. 10, Tab. 4).

CYP2D6 is important for the metabolism of tamoxifene to endoxifene. A congenital lack of this enzyme, or inhibition through inhibitors leads to a reduction in this active metabolite of tamoxifene. In women who use tamoxifene for metastatic breast cancer, overall survival was significantly shorter in patients with a CYP2D6 poor metabolizer phenotype, compared with extensive metabolizers (HR 2.09; $p = 0.034$) and co-administration of CYP2D6 inhibitors alone was also associated with a worse overall survival (HR 3.55; $p = 0.002$) or time to breast cancer progression (HR 2.97; $p = 0.008$) compared with patients without CYP2D6 inhibitors [76].

Acquired tamoxifene resistance might be due to changes in signaling pathways of growth factors, by which the typical estrogen-receptor meditated pathway is bypassed or the activity of the ER can be changed so that an initially ER + tumor becomes hormone-independent.

Patients with different cytochrome CYP2D6 genotypes, resulting in CYP2D6 poor metabolizer phenotype, have low levels of the metabolite 4-hydroxy-*N*-desmethyl tamoxifene (endoxifene) and receive less benefit from tamoxifene therapy with higher risk of disease relapses [77, 78]. On October 18, 2006, the Clinical Pharmacology Subcommittee of the FDA Advisory Committee for Pharmaceutical Science held a meeting to answer specific questions regarding the evidence and recommendations for a tamoxifene label update. While the committee members recommended including information on CYP2D6 genotyping tests, they did not reach a consensus as to whether it should be recommended or optional (FDA 2006; http://www.fda.gov/ohrms/dockets/ac/06/minutes/2006-4248m1.pdf. However, the current US labels for tamoxifene citrate does not contain any information on genotype testing.

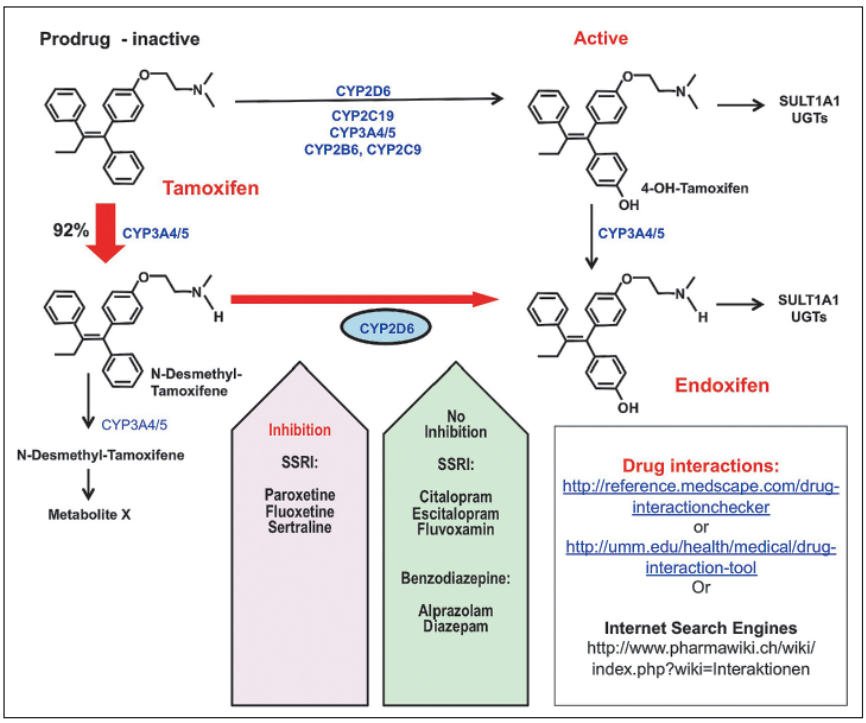

Figure 10. Metabolisation of tamoxifene and formation of its active metabolite endoxifene with examples of inhibition of CYP2D6 (selection of several substances as examples, see also Table 5). Mod. from [Irvin WJ Jr. Genotype-guided tamoxifene dosing increases active metabolite exposure in women with reduced CYP2D6 metabolism: a multicenter study. J Clin Oncol 2011; 29: 3232–9]. © Thomas Rabe

Since certain CYP 2D6 genotypes in breast cancer patients lead to a worse prognosis with tamoxifene treatment [79], genotyping offers the opportunity to identify the women whose CYP 2D6 phenotype will lead to poor treatment outcome with tamoxifene.

Bone Health

In postmenopausal women with breast cancer tamoxifene provides some protection from bone loss. In premenopausal women, however, tamoxifene leads to a decrease in bone density. Tamoxifene is not indicated for fracture protection in women with osteoporosis due to its inferiority to estrogens and bisphosphonates.

Drug-Drug Interactions

Concomitant use of antidepressants of the Selective Serotonin Re-uptake Inhibitor (SSRI) family like paroxetine, fluoxetine and sertraline can reduce the efficacy of tamoxifene since these drugs inhibit CYP 2D6 which is essential to metabolize tamoxifene to its active metabolite endoxifene [80]. Recent research into the effect of SSRIs on the efficacy of tamoxifene have yielded conflicting results. A US-based study, presented at the 2009 American Society for Clinical Oncology meeting, demonstrated 7.5% recurrence rate on tamoxifene alone, but a 13.9% recurrence rate on tamoxifene in combination with moderate/strong 2D6 inhibitors, including SSRIs [81]. Presented at the same meeting was a study by a Dutch group which showed no effect on breast cancer event-free time of CYP2D6 inhibitors, but demonstrated that poor compliance to tamoxifene treatment was associated with a poorer outcome [82]. However, the latter study was much smaller than the US study. In a recent study in Canada, the authors found an increased risk of death due to breast cancer in patients on tamoxifene related to the concomitant use of paroxetine, varying from 24% for patients who used both drugs for 25% of the time to 91% for patients who used both drugs for 75% of the time. No such increase was found with other antidepressants (fluoxetine, sertraline, fluvoxamine, citalopram and venlafaxine) [83]. All 3 studies are retrospective database studies and a prospective randomizsed trial is anxiously awaited.

Side Effects

The side effects and risks of tamoxifene include hot flushes, vaginal discharge, sexual dysfunction, abnormal uterine bleeding, venous thromboembolism (factor of 2–3) and cataract (rare). For women over 55 years, the risk of endometrial cancer increased [71].

Black box warning (http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/17970s37s44s49lbl.pdf): In 2012 the U.S. Food and Drug Administration (FDA) mandated a change in all labels for tamoxifene citrate, specifically aimed at women with Ductal Carcinoma in Situ (DCIS) and women at high risk for breast cancer (so-called "black box" warning), including a warning of serious or life-threatening side effects as uterine malignancies, including sarcoma and adenocarcinoma, stroke, and pulmonary embolism.

In an overview of the breast cancer prevention trials (including 28,419 patients), Cuzick [84] reported a 38% (95-%- CI: 28–46; $p < 0.001$) reduction in breast cancer incidence with tamoxifene use in the preventative setting with an increase in endometrial cancer (relative risk 2.4; 95-%-CI: 1.4–4.0; $p = 0.00050$) and venous thromboembolic events (relative risk 1.9; 95-%-CI: 1,4–2,6; $p < 0.0001$).

Despite the increased risk of endometrial cancer in women using tamoxifene there is no satisfactory screening method for the early discovery of these cancers. Both the American College of Obstetricians and Gynecologists (ACOG 2014: ACOG Committee Opinion Number 601, June 2014; Tamoxifene and uterine cancer; accessed November 20, 2014) as well as the German Society of Gynaecology and Obstetrics [85] do not recommend routine ultrasound screening due to the rather low specificity and sensitivity.

The clinical results of different endometrial findings are shown in Figures 11 and 12 [86]. The effect of tamoxifene on endometrial thickness is demonstrated in Figure 13 [87].

Duration of Treatment

Patients with breast cancer (adjuvant therapy)/prevention of breast cancer in high risk patients: 20 mg/day TAM over 5 years (or switch to aromatase inhibitors after 2 years). Therapy in metastatic breast cancer possibly until progression.

3.6. Bazedoxifene

Substance

Indole derivative

Indications

Treatment of postmenopausal osteoporosis in women at increased risk of fracture

Table 4. Results of large placebo controlled clinical trials with tamoxifene in relation to the prevention of breast cancer. Mod. from [14]. © Thomas Rabe

Variable	NSABP P-1 Study [133]	Royal Marsden Hospital Trial [134]	Italian Trial [135]	IBIS-I* [136]
Primary outcome	Breast cancer	Breast cancer	Breast cancer	Breast cancer
Secondary outcome	Bone, cardiovascular	–	Cardiovascular, psychometrics	Thromboembolic, cardiovascular, endometrial cancer
Eligibility	Age ≥ 60 yr, or 35–59 yr with a 5-yr predicted risk of ≥ 1.66%, lobular carcinoma *in situ*	Age 30–70 with a family history	Age 35–70 yr after hysterectomy	Age 35–70 yr with a family history, lobular carcinoma *in situ* or atypia
No. of women	13.388	2471	5408	7152
Study drugs	Tamoxifene (n = 6681) vs. Placebo (n = 6707)	Tamoxifene vs. Placebo	Tamoxifene vs. Placebo	Tamoxifene vs. Placebo
Age distribution (%)				
< 50 yr	39	61	38	–†
50–60 yr	31	39	50	
> 60 yr	30		12	
Family history of breast cancer (%)	77	96	18	97
Mean follow-up (months)	57.6	171.6	139.6	96
Cases with invasive breast cancer				
Placebo	248	96	45	85
Tamoxifene	130	113	34	64
HR (95% CI)	0.52 (0.42–0.64)	0.84 (0.64–1.10)	0.83 (0.58–1.19)	0.72 (0.58–0.90

* IBIS-I denotes International Breast Cancer Intervention Study I, and NSABP National Surgical Adjuvant Breast and Bowel Project; † the median age in the trial was 51 years.

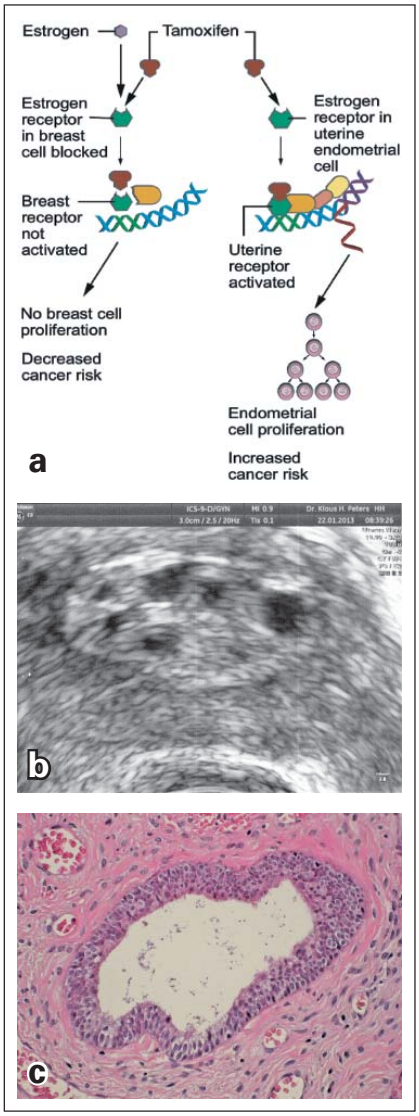

Figure 11. Tamoxifene: Induction of endometrial cancer. **(a):** Flow sheet. Mod. from National Cancer Institute. © Thomas Rabe; **(b):** Endometrial changes by tamoxifene shown by ultrasound (Peters, Hamburg, reprint with permission); **(c):** Hyperplasia of the endometrial cells in fibrous stroma under tamoxifene therapy (62 years, 12981/2014 HE 20×). © Thomas Rabe.

(EU only). (Note: In Switzerland, bazedoxifene monotherapy is also approved for the prevention of postmenopausal osteoporosis, however, based on the CHMP Guideline on the Evaluation of Medicinal Products in the Treatment of Primary Osteoporosis, revised in 2007 (CPMP/EWP/552/95 Rev. 2, effective since May 31, 2007) the indication 'prevention of osteoporosis' is no longer recognized as a separate indication in the EU.)

Tissue Selective Estrogen Complex

The combination of bazedoxifene with conjugated estrogens has been named as a "Tissue Selective Estrogen Complex" (TSEC).

Approval Status

– US: Bazedoxifene plus CE (Duavee®, an alternative to Prempro for women who want to use estrogen for menopausal symptoms but need an alternative to a progestin) has been approved in October 2013 in the US for:

a.) Treatment of moderate to severe vasomotor symptoms associated with menopause
b.) Prevention of postmenopausal osteoporosis

From the conditions associated particularly with the latter indication it is clear that the approval was based on the CE component: *"Use DUAVEE for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary"*

AND

"When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis, and non-estrogen medication should be carefully considered."

Both are standard HRT warnings in the US, not SERM warnings.

– EU: Bazedoxifene plus CE has been approved for the treatment of estrogen deficiency symptoms in postmenopausal women with an uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate (http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002314/WC500176326.pdf).

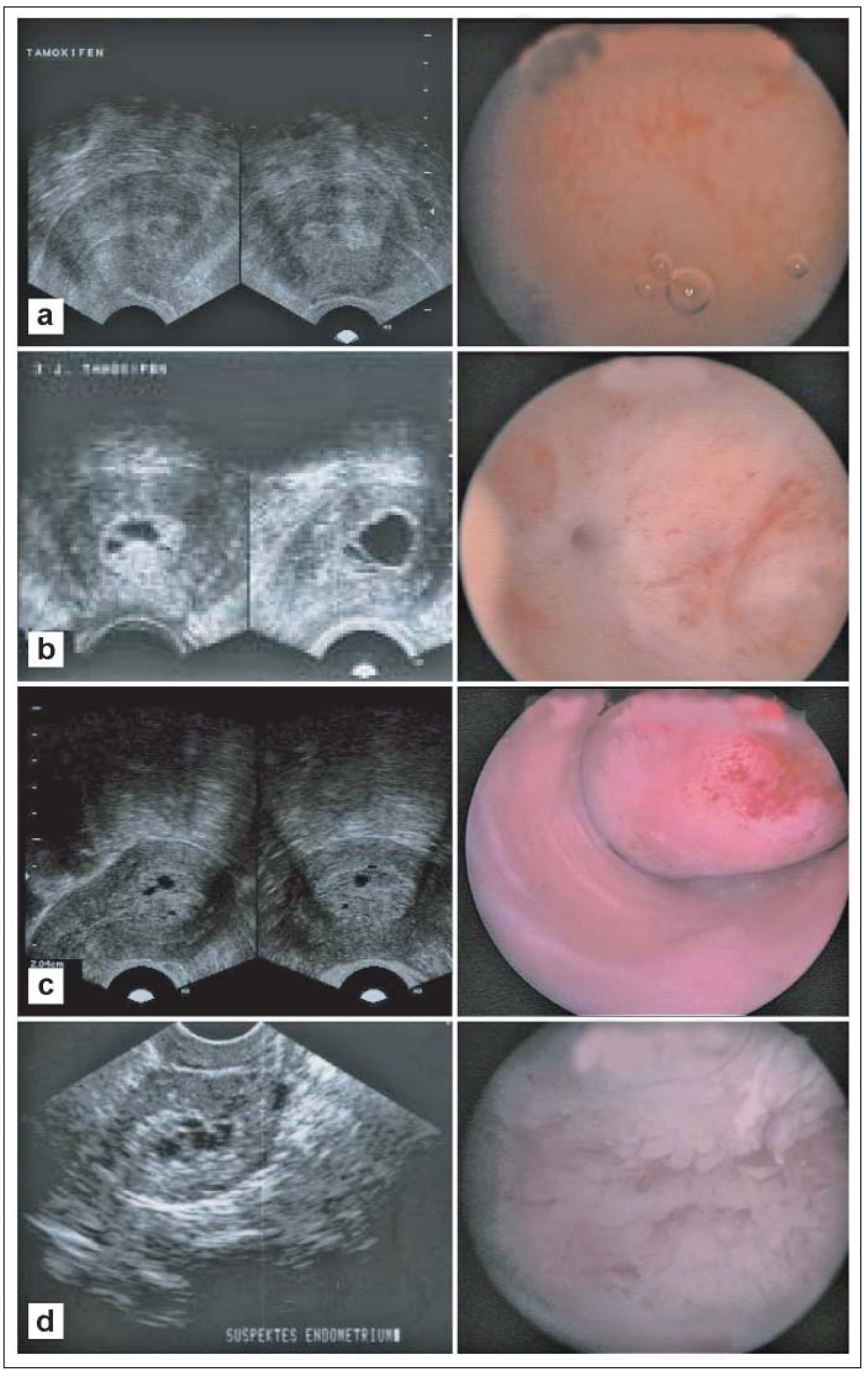

Figure 12. Endometrial changes: Horizontal ultrasonography and hysteroscopic pictures. **(a):** Endometrial thickness: 10.5 mm, histology: (glandulozystic) atrophy; **(b)** Endometrial thickness: 10.9 mm, histology: Atrophy with serometra; **(c)** Endometrial thickness: 20.4 mm, histology: Polyp of corpus uteri; **(d):** Endometrial thickness: 18.0 mm, histology: Hyperplasia. Reprint from [86] with kind permission by © *Frauenarzt*.

Fields of Application

Bazedoxifene in combination with conjugated estrogens is licensed for the treatment of postmenopausal symptoms (including the prevention of postmenopausal osteoporosis). The drug is further investigated in regard to a possible use in treatment of dyspareunia and breast cancer (http://medicalxpress.com/news/2013-06-osteoporosis-drug-growth-breast-cancer.html).

Clinical Trials

– Osteoporosis: Similar to raloxifene it reduces in postmenopausal women with osteoporosis, the risk of vertebral, but not non-vertebral fractures [11]. The side effects and risks are similar to those of raloxifene [11, 88].

– Hormone replacement therapy: With this new combination of a SERM (bazedoxifene) and conjugated estrogens a progestogen-free hormone replacement therapy seems possible. The dosage for bazedoxifene is 20 mg in combination with 0.45 mg conjugated estrogen. This so-called TSEC (tissue selective estrogen complex) has been investigated in several studies (SMART Selective estrogens, Menopause And Response to Therapy) [89–91] and has demonstrated a significant reduction of menopausal symptoms compared to placebo. There is also a beneficial effect on bone metabolism [92]. No stimulatory effect on the endometrium has been described [93]. Longitudinal data e. g. for the risk of breast cancer, are not yet available.

3.7. Toremifene

Substance

Triphenylethylene

Indication

Treatment of metastatic breast cancer in postmenopausal women with estrogen-receptor positive or unknown tumors (US). First line hormone treatment of hormone-dependent metastatic breast cancer in postmenopausal patients. Fareston is not recommended for patients with estrogen receptor negative tumors (EU)

Fields of Application

FDA-approved 60 mg toremifene oral once daily in the United States under the brand name Fareston for use in advanced (metastatic) breast cancer. An 80 mg dose has also been under development for the prevention of bone fractures in men with prostate cancer on androgen deprivation therapy (ADT). Under the brand name Acapodene by US company GTx (GTx Inc 2009; http://phx.corporate-ir.net/phoenix.zhtml?c=148196&p=irol-newsArticle&ID=1257471&highlight). In 2012, GTx sold the rights to Fareston and all toremifene based products to ProStrakan, a subsidiary of Kyowa Hakko Kirin Co. Ltd (ProStrakan 2012; http://www.prostrakan.com/perch/resources/ukprostrakanfarestonpressrelease1stoct2012.pdf). EU marketing authorization of Fareston is for first line hormone treatment of hormone-dependent metastatic breast cancer in postmenopausal patients. Fareston is not recommended for patients with estrogen receptor negative tumors.

Clinical Trials

Three prospective, randomized, controlled clinical studies (North American,

Eastern European, and Nordic) were conducted to evaluate the efficacy of FARESTON for the treatment of breast cancer in postmenopausal women. The patients were randomized to parallel groups receiving FARESTON 60 mg (FAR60) or tamoxifen 20 mg (TAM20) in the North American Study or tamoxifene 40 mg (TAM40) in the Eastern European and Nordic studies. The studies included postmenopausal patients with estrogen-receptor (ER) positive or estrogen-receptor (ER) unknown metastatic breast cancer. Two of the three studies showed similar results for all effectiveness endpoints. However, the Nordic Study showed a longer time to progression for tamoxifene (Fareston USPI; http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020497s006lbl.pdf).

Side Effects

Most common adverse reactions are hot flushes, sweating, nausea and vaginal discharge. Endometrial hypertrophy may develop during the treatment due to the partial estrogenic effect of toremifene. There is a risk of increased endometrial changes including hyperplasia, polyps and cancer. This may be due to the underlying mechanism/estrogenic stimulation.

The FDA has included a "Black Box" Warning: *"FARESTON has been shown to prolong the QTc interval in a dose- and concentration-related manner. Prolongation of the QT interval can result in a type of ventricular tachycardia called Torsade de pointes, which may result in syncope, seizure, and/or death. Toremifene should not be prescribed to patients with congenital/acquired QT prolongation, uncorrected hypokalemia or uncorrected hypomagnesemia. Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided."* (http://www.nlm.nih.gov/medlineplus/druginfo/meds/a608003.html).

Phytoestrogens

Phytoestrogens are secondary plant chemicals, which include isoflavones and lignans. They are no estrogens in a chemical sense, but have only some structural similarity to estrogens and a mechanism of action similar to that of SERMs. This similarity allows binding to estrogen receptors, exerting either an estrogenic or antiestrogenic effect. The most known phytoestrogens are isoflavones genistein, daidzein (Fig. 14) and coumestrol.

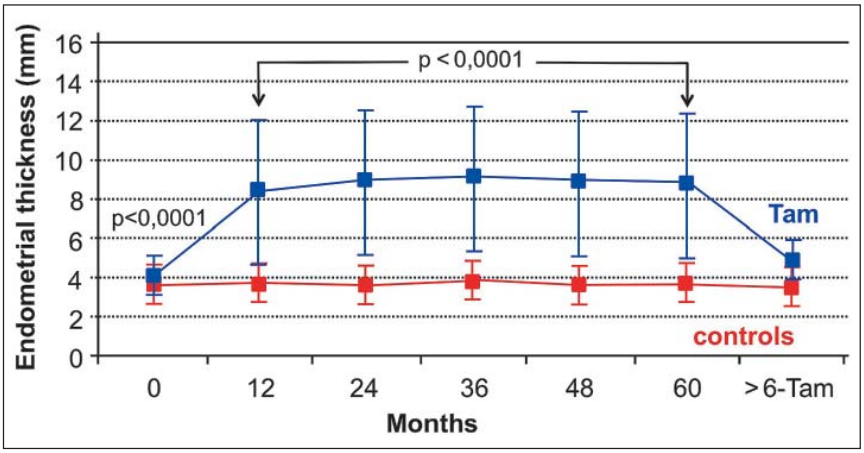

Figure 13. Endometrial thickness measured by sonography in patients with breast cancer during tamoxifene therapy compared to untreated controls. Reprint from [86] with kind permission by © *Frauenarzt.*

3.8. Femarelle®

Femarelle® (DT56a) seems to act like a Selective Estrogen Receptor Modulator (SERM) [94] for the treatment of climacteric symptoms and for bone health. Femarelle contains approximately 322 mg DT56a (a tofu extract) and 108 mg flaxseed powder (Maneesh Pharmaceuticals Product Femarelle®; http://www.maneeshpharma.com/products/Ace_Femarelle.html).

Mechanism of Action

In animal models, Femarelle® has an agonistic activity on the estrogen receptors in brain and bone [95]. It was shown that Femarelle® alleviates menopausal symptoms such as hot flushes [96] and increases bone mineral density (BMD) [97]. It does not have a proliferative effect on MCF-7 breast cancer cell lines [98] or on the uterus of rats [95, 99].

Femarelle® increases the activity of the osteoblasts in bone [100], which is the basis for its use in postmenopausal bone loss. Although Femarelle® stimulates the estrogen receptors, it does not lead to changes in blood hormone profile [96]. Both healthy women as well as women with thrombophilia showed no change in coagulation [101].

Quality and Regulatory Issues

Femarelle is not a standardized drug. The European Food Safety Authority considered that Femarelle® has not been sufficiently characterised and that that a cause and effect relationship has not been established between the consumption of Femarelle® and increased BMD, increased bone formation, or decreased risk of osteoporosis or other bone disorders in post-menopausal women (EFSA 2008; Femarelle® and bone mineral density – Scientific substantiation of a health claim related to "Femarelle®" and *"induces bone formation and increases bone mineral density reducing the risk for osteoporosis and other bone disorders"* pursuant to Article 14 of the Regulation (EC) No 1924/2006[1] – Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies).

Marketing

Certain countries in Europe, Israel, Mexico, USA and others.

Compounds whose development has been suspended

3.9. Arzoxifene

Arzoxifene is a benzothiophene derivative [102]. It is a potent antagonist of estrogen in breast and uterine tissue while acting as an estrogen agonist in bone with respect to the maintenance of bone density. Furthermore, it leads to a reduction of serum cholesterol. Arzoxifene is a very effective measure for the prevention of breast cancer in the rat, which is inducible by the carcinogen nitrosomethylurea, and acts much stronger than raloxifene in this regard.

Arzoxifene shows no uterotrophic effect, suggesting that, in contrast to tamoxifene, arzoxifene does not increase the risk of endometrial cancer.

Clinical Trials

In a Phase 3 clinical trial in postmenopausal women it has been shown that

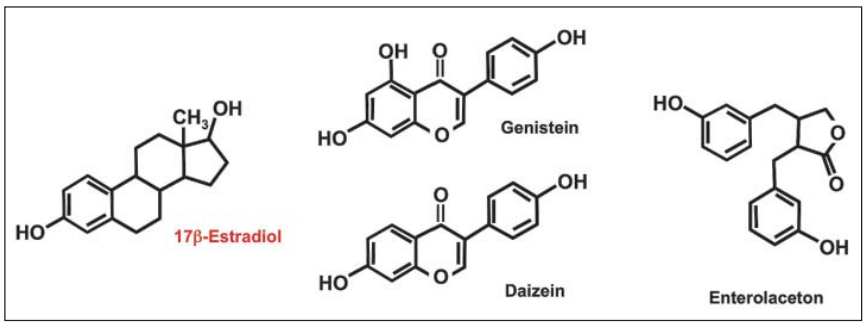

Figure 14. Phytoestrogens (selection) structural comparison to natural 17β-Estradiol. © Thomas Rabe

arzoxifene increases bone mineral density in the spine and hip, but has no effect on the uterus and the endometrium [103].

In a pivotal, five-year, phase III trial, arzoxifene met its primary endpoints of significantly reducing the risk of vertebral fracture and invasive breast cancer in postmenopausal women. However, the study failed to demonstrate a statistically significant difference in key secondary efficacy endpoints, such as non-vertebral fractures, clinical vertebral fractures, cardiovascular events and cognitive function, compared to placebo. In addition, certain adverse events, including venous thromboembolic events, hot flushes and gynecological-related events, were reported more frequently in the arzoxifene group compared with placebo. Based on these results further development of the drug has been suspended [104].

Burke and Walker [113] tested arzoxifene as therapy for endometrial cancer and found in a substantial number of women a stabilization of metastatic or recurrent endometrial cancer.

3.10. Droloxifene

Substance

Triphenylethylene derivative, 3-OH-Tamoxifene.

Licensed from Klinge Pharma GmbH in Germany, Ligand Pharmaceuticals Inc and Pfizer co-developed droloxifene initially for the treatment of advanced (metastatic) estrogen-receptor-positive breast cancer. However, when it was shown that at the dose studied, droloxifene which is the active 3-OH derivative of tamoxifene, offers no benefit beyond the current therapy, further development focussed on osteoporosis. In December 1999, Pfizer decided not to continue with the development of droloxifene (http://www.secinfo.com/dR1Cs.5d.htm, page 9) due to its adverse effect on the endometrium [105]

3.11. Lasofoxifene

Substance

Naphtalene derivative, a desmethyl dihydro analogue of nafoxidine [106].

Indications

There are currently no approved indications for lasofoxifene.

Fields of application

Lasofoxifene has been developed by Pfizer for the treatment and prevention of osteoporosis and for the treatment of vaginal atrophy [107].

Approval Status

In 2005, the FDA refused the approval of lasofoxifene (trade name Oporia) for the prevention of osteoporosis. In 2008 the FDA issued a "not approvable letter" based on a theoretical risk of endometrial cancer and concerns for a possible increase in the risk of blood clots and stroke. On February 24, 2009 Lasofoxifene received EU approval for the treatment of postmenopausal osteoporosis (trade name: Fablyn).

Although marketing authorization was obtained in Europe in 2009, this was withdrawn on February 27, 2012 as a result of the "Sunset Clause". Development of the product has recently been restarted (http://uk.reuters.com/article/2015/02/03/caligand-pharmaceutical-idUSnBw035264a+100+BW20150203).

Clinical Trials

The Pearl-Study [108] was a 5-year double blind randomized placebo controlled trial of postmenopausal women aged between 50 and 80 years with osteoporosis. The subjects were to receive once-daily lasofoxifene (at a dose of either 0.25 mg [n = 2852] or 0.5 mg [n = 2852]) or placebo (n = 2852). Vertebral fracture was the primary end-point for the first three years of the trial, and non-vertebral fracture and ER-positive breast cancer were co-primary end-points through five years. A statistically significant reduction was reached in risk of new/worsening radiographic vertebral fractures through years 3 and 5 in postmenopausal women with osteoporosis. The risk for a new/worsening radiographic vertebral fracture was reduced by 31% and 42% in the lasofoxifene 0.25 mg and 0.5 mg groups, respectively, compared with placebo through 3 and 5 years. Analysis of the time to first non-vertebral fracture (hip, pelvis, femur, knee, lower leg, ankle, calcaneus, foot, shoulder, humerus, elbow, forearm, wrist, scapula, clavicle, rib, sternum, non-thoracic/non-lumbar spine) revealed a significant effect compared to placebo for the 0.5 mg dose, but not for the 0.25 mg dose both through years 3 and 5. However, the reduction in non-vertebral fractures was mainly due to an effect on wrist and forearm fractures. The effect on hip fractures was modest at best and did not reach statistical significance for either dose of lasofoxifene. In the high dose group, lasofoxifene reduced the risk of invasive breast cancer by 85% ($p < 0.001$). A 21% reduction in the lower dose group did not reach statistical significance.

Side Effects

Lasofoxifene increased the incidence of VTE (not including stroke) and endometrial hypertrophy, uterine polyps and fibroids but had no effect on endometrial cancer or endometrial hyperplasia.

CHD

In postmenopausal women with osteoporosis, lasofoxifene 0.5 mg/d for 5 years reduced the risk of CHD events, regardless of the presence or absence of risk factors for cardiovascular disease. The significant reduction in risk of CHD events with lasofoxifene 0.5 mg/d was due primarily to lower risks of coronary revascularization procedures, hospitalization for unstable angina, and diagnosis of new ischemic heart disease [109].

3.12. Pipendoxifene

Pipendoxifene, an indole derivative, chemical substance 2-(4-Hydroxyphenyl)-3-methyl-1-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-1H-indol-5-ol, is also

known as pipindoxifene or ERA-923. In the rest of the text the name pipendoxifene will be used.

Patent Situation
Since 2006, Wyeth (now: Pfizer) has held a patent (WO2006/017639 A2) which included the use of pipendoxifene for (a) treating a disease or syndrome associated with estrogen deficiency or excess of estrogen, (b) treating a disease or disorder associated with proliferation or abnormal development of mammary tissues, (c) lowering cholesterol, (d) inhibiting bone loss, (e) treating breast cancer or (f) treating a postmenopausal woman for one or more vasomotor disturbances (World International Property Organization 2006; http://patentscope.wipo.int/search/docservicepdf_pct/id00000002465807.pdf?download).

Pre-Clinical Studies
In pre-clinical studies with ERα positive human MCF-7 breast carcinoma cells, pipendoxifene inhibits estrogen-stimulated growth (IC50, 0.2 nM) and even an MCF-7 variant with inherent resistance to tamoxifene (10-fold) or 4-OH tamoxifene (> 1000-fold) retained complete sensitivity to ERA-923. Partial sensitivity to pipendoxifene exists in MCF-7 variants that have acquired profound tamoxifene resistance.

MCF-7 Cells and Xenograft Model
In 2006, Sadler reported on the combined use of pipendoxifene and temsirolimus on MCF-7 cells *in vitro* and in a xenograft model. Combination of noninhibitory doses of temsirolimus with suboptimal doses of pipendoxifene synergistically inhibited the growth of MCF-7 cells. Synergism was found across a wide range of doses and could also be achieved by combining temsirolimus with other antiestrogens such as raloxifene and 4-hydroxy-tamoxifene. In the xenograft model, combination of temsirolimus and pipendoxifene at certain doses and schedules completely inhibited tumor growth, while individual agents were only partially effective. The combination of temsirolimus and a pure antiestrogen has excellent anticancer activity in preclinical models and, therefore, might be clinically useful for treatment of hormone-dependent tumors [110].

In tumor-bearing animals, pipendoxifene (10 mg/kg/day given p. o.) inhibits 17-α-estradiol-stimulated growth of human tumors derived from MCF-7, EnCa-101 endometrial, or BG-1 ovarian carcinoma cells, including a MCF-7 variant that is inherently resistant to tamoxifene. Unlike tamoxifene, droloxifene, or raloxifene, pipendoxifene is not uterotropic in immature rats or ovariectomized mice [111].

Clinical Trials
Phase I: A multiple dose phase I study (once-daily oral pipendoxifene (10–200 mg) for 28 days in healthy postmenopausal females) was performed and reported by Wyeth-Ayerst in 2002 [112]. Pipendoxifene was well tolerated, and adverse events were mild and reversible. No clinically significant changes in laboratory values were found with pipendoxifene versus placebo. Pipendoxifene appeared to undergo extensive metabolism and enterohepatic recirculation. In addition, pharmacokinetic analysis showed that a high-fat breakfast increased the extent of absorption. Pipendoxifene-dosed subjects had no uterine or ovarian changes when evaluated with transvaginal ultrasound and compared to placebo subjects. Overall, pipendoxifene was safe and well tolerated in postmenopausal women dosed for 28 days.

Phase II: On October 4, 2000, the H. Lee Moffitt Cancer Centre and Research Institute submitted a protocol for a A Phase II, Randomized, Double-Masked, Multicenter Study of Two Dose Levels of pipendoxifene for the Treatment of Metastatic Breast Cancer in Postmenopausal Women Who Have Failed Tamoxifene Therapy (NCT00006369). The objectives of this study were to compare the efficacy of 2 dose levels of ERA-923 in postmenopausal patients with metastatic breast cancer refractory to tamoxifene, to determine the safety and plasma levels of this drug in these patients and to determine the impact on quality of life of these patients by this drug. Patients were to be randomized to one of two treatment arms receiving different doses of ERA-923. Patients were to receive oral ERA-923 daily for 48 weeks in the absence of disease progression or unacceptable toxicity. Quality of life was to be assessed at baseline; at weeks 4, 8, 16, 24, 32, 40, and 48; and then at 4 weeks after last dose. Patients were to be followed at 4 weeks and then every 3 months thereafter. It was planned that a total of 36–100 patients (18–50 per arm) will be accrued for this study within 1 year. The study chair was Susan E Minton (https://clinicaltrials.gov/ct2/show/NCT00006369?term=era-923&_rank=1). At the last update on 5 November 2013, the trial was reported as active, no longer recruiting (http://clinicaltrials.gov/archive/NCT00006369/ 2013_11_05).

Since the phase I pharmacokinetic data, no clinical trial results have been published on pipendoxifene. In the latest update of their pipeline, Pfizer, which acquired Wyeth in 2009, does not show pipendoxifene to be an active development compound (http://www.pfizer.com/sites/default/files/product-pipeline/May%208%2C%202014%20Pipeline%20Update_Final_to%20BT.pdf).

4. Health Benefits

4.1. Study Overview
The main clinical studies on the preventive effects of tamoxifene and raloxifene in view to breast cancer are ATLAS, ATTOM [114], IBIS2 [115], STAR [116], CORE [117] und RUTH [118] (Tab. 5).

4.2. Breast Cancer Prevention
Breast cancer is the most frequent cancer among women with about 1.38 million new cases worldwide every year. Most of these patients are postmenopausal and suffer from hormone receptor positive breast tumors [119].

Estrogen receptors are overexpressed in approximately 70 % of cases of breast cancer, called “ER-positive” tumors, which can be detected by means of immunohistochemistry on tumor tissue.

The effect of postmenopausal hormone replacement has been recently reanalysed by Beral et al [120] with special view to the breast cancer risk in relation to the interval between menopause and starting hormone therapy. A total of 1,129,025 postmenopausal UK women provided prospective information on hormonal therapy use and other factors relevant for breast cancer risk. There was substantial heterogeneity in breast cancer risk among current users of hormonal therapy. Risks were greater among users of estrogen-progestin than estrogen-only formulations and if hormonal therapy started at around the time of menopause than later.

Table 5. Large clinical trials with SERMs. Mod. from [14]. © Thomas Rabe

Study	Aim and design of the study	
ATLAS	Adjuvant Tamoxifene Longer Against Shorter trial	Assessment of optimal duration of tamoxifene adjuvant therapy Accrual goal is 20,000 pre- and postmenopausal patients with breast cancer who are receiving adjuvant tamoxifene Therapy: tamoxifene for 5 yr vs. 10 yr (or longer)
ATTOM	Adjuvant Tamoxifene Treatment Offers MORE trial	Assessment of optimal duration of tamoxifene adjuvant therapy Accrual goal is 8000–20,000 pre- and postmenopausal patients with breast cancer who are receiving adjuvant tamoxifene Therapy: tamoxifene for 2 yr (group 1) vs. 7 yr (group 2)
IBIS2	International Breast cancer Intervention Study 2	Primary prevention of breast cancer Accrual goal is 16,000 women at high risk for breast cancer (age 35–70 yr) Therapy: anastrozole vs. placebo
STAR	Study of Tamoxifene And Raloxifene	Primary prevention of breast cancer Accrual goal is 22,000 postmenopausal women at high risk for breast cancer Therapy: 20 mg tamoxifene per day vs. 60 mg of raloxifene per day for 5 yr
CORE	Continuing Outcomes Relevant to Evista	4000 postmenopausal women who were previous participants in the MORE (Multiple Outcomes of Raloxifene Evaluation) trial with raloxifene 60 or 120 mg/day receiving in the CORE trial raloxifene (60 mg/day) or placebo for an additional 4 yr, primary end point is breast-cancer prevention; secondary end points are nonvertebral fractures and uterine safety Therapy: Raloxifene (60 mg/day) or placebo
RUTH	Raloxifene Use in The Heart	Effect of raloxifene vs. that of placebo in prevention of coronary events and death from coronary causes 10,000 postmenopausal women at risk for coronary disease Duration of 7.5 yr Therapy: Raloxifene (60 mg/day) or placebo

Hormonal Replacement Therapy
In the Women's Health Initiative (WHI) randomized trial, estrogen plus progestin increased both breast cancer incidence and mortality. In contrast, most observational studies associate estrogen plus progestin with favourable prognosis breast cancers.

Chlebowski et al [121] published data about estrogen plus progestin and breast cancer incidence and mortality in the Women's Health Initiative Observational Study. Consistent with WHI randomized trial findings, estrogen plus progestin use is associated with increased breast cancer incidence. Because prognosis after diagnosis on combined hormone therapy is similar to that of nonusers, increased breast cancer mortality can be expected.

There are several hypotheses to tumor formation and probably the following two mechanisms are involved:

– First, the binding of estrogen to the ER stimulates proliferation of mammary cells and the resulting increase in cell division and DNA replication leads to mutations.
– Second, the formation of genotoxic waste products is caused by the estrogen metabolism.

The result of the two processes is a disturbance of the cell cycle, apoptosis, and DNA repair and, therefore, leads to tumor formation. ERα is associated with more differentiated tumors, while the role of ERβ in tumorigenesis is controversial. Various forms of the ESR1 gene (single nucleotide polymorphisms) result in a different risk for the development of breast cancer [122].

In the U.S., there is the possibility of endocrine prevention of breast cancer in women at increased risk of breast cancer since both raloxifene and tamoxifene have this indication included in their approved label [123].

Bazedoxifene
Reduction of ER-positive breast cancer [124].

Palacios et al [125] evaluated the clinical safety of bazedoxifene on the reproductive tract in postmenopausal women with osteoporosis over 7 years. Rates of breast-related and other gynecologic AEs (ovarian cancer, benign ovarian cysts, uterine or vaginal hemorrhoage, vaginitis) were similar among groups.

A further analysis based upon the same study by Pinkerton et al [126] confirmed that bazedoxifene 20 mg and conjugated estrogens 0.45 and 0.625 mg did not increase mammographic breast density or breast tenderness over the course of 1 year with a favorable breast-related safety profile.

Clomifene
A risk analysis is difficult, due to combined use of antifertility drugs [127].

Lasofoxifene
Decreased risk of estrogen-positive breast cancer is similar to that seen with raloxifene in the MORE study [108] (Tab. 6).

Ormeloxifene
Studies are ongoing [128]. In a recent publication from Tejwani, ormeloxifene was more effective in pain score reduction at 24 weeks as compared to Danazol ($p = 0.019$) [129].

Ospemifene
In a review Wurz et al [130] focused on data demonstrating the antiestrogenic activity of ospemifene in several breast cancer animal models, and the implications for utilizing ospemifene in patients with breast cancer suffering from vulvovaginal atrophy (VVA). Additional clinical research addressing the expanded use of ospemifene in breast cancer patients is necessary [131].

Raloxifene
The chemopreventive effect is greater for tamoxifene than for raloxifene. However, tamoxifene when compared with raloxifene led to a higher risk of VTE, endometrial cancer and cataracts. Both SERMs reduce the risk of fracture. If serious positive events were weighed

Table 6. Incidence of breast-related adverse events in phase-III treatment studies of SERMs. © Thomas Rabe

	Raloxifene (MORE; n = 7705)[1] (CORE; n = 4011) [191]		**Lasofoxifene** (PEARL; n = 8556) [108][2, 3]		**Bazedoxifene** (n = 7492 and n = 4216) [190, 192]		**Ospemifene** Phase 2 & 3 trials (n = 1476) Placebo (n = 958)	
	60 mg	120 mg	0.25 mg	0.5 mg	20 mg	40 mg	0	60 mg
Overall incidence of breast cancer†								
1 year							1+	0
3 years	RR vs. Placebo 0.35* (95% CI: 0.21–0.58) for pooled RLX 60/120 mg		–	–	0.3%	0.2%		
5 years	–	–	0.73% (HR vs. Placebo 0.82; 95% CI: 0.45–1.49)	0.18% (HR vs. Placebo 0.21*; 95% CI: 0.08–0.55)	0.5%**	–		
Incidence of ER-positive breast cancer#								
1 year							n.a.	n.a.
3 years	0.08% (RR vs. Placebo 0.10; 95% CI: 0.04–0.24 for pooled RLX 60/120 mg)		–	–	–	–		
5 years	–	–	0.40% (HR vs. Placebo 0.52; 95% CI: 0.25–1.08)	0.15% (HR vs. Placebo 0.19*; 95% CI: 0.07–0.56)	–	–		
Incidence of invasive breast cancer#								
1 year							0	0
3 years	0.25% (RR vs. Placebo 0.24; 95% CI: 0.13–0.44 for pooled RLX 60/120 mg)		–	–	–	–		
5 years	–	–	0.59% (HR vs. Placebo 0.79; 95% CI: 0.41–1.52)	0.11% (HR vs. Placebo 0.15*; 95% CI: 0.04–0.50)	0.5%	–		

MORE: Multiple Outcomes of Raloxifene Evaluation; CORE: Continuing Outcomes Relevant to Evista; PEARL: Postmenopausal Evaluation And Risk-reduction with Lasofoxifene; RLX: raloxifene; RR: relative risk; CI: confidence interval; HR: hazard ratio; ER: estrogen receptor; n.a. = not available

* $p \leq 0.001$ vs. placebo; ** $p < 0.01$ vs. placebo; † $p < 0.05$ vs. placebo; # RR und HR vs. placebo; + one case with lobular carcinoma *in situ*

[1] Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA 1999; 281: 2189–97.

[2] Goldstein SR, Neven P, Cummings S, et al. Postmenopausal evaluation and risk reduction with lasofoxifene trial: 5-year gynecological outcomes. Menopause 2010; 18: 17–22.

[3] LaCroix AZ, Powles T, Osborne CK, et al. Breast cancer incidence in the randomized PEARL trial of lasofoxifene in postmenopausal osteoporotic women. J Natl Cancer Inst 2010; 102: 1706–15.

against serious negative events, the benefit-risk ratio for tamoxifene is 7:1 and 13:1 for raloxifene [132].

Tamoxifene

Approval 1998 by the FDA for the prevention of primary breast cancer. Tamoxifene is approved for breast cancer prevention in pre-and postmenopause; raloxifene for the prevention of postmenopausal breast cancer.

Results of clinical trials analysing the protective effect of tamoxifene for breast cancer are summarized in Table 4 including the following trials: NSABP P-1 Study [133], Royal Marsden Hospital Trial [134], Italian Trial [135], IBIS-I [136].

The following criteria of patient selection, which are also used in practice, were selected in the appropriate clinical trials [137–140]:

1) age > 60 years,
2) age > 35 years plus LCIS, DCIS, or atypical lobular or ductal hyperplasia,
3) age 35-59 years plus 5-year risk of breast cancer ≥ 1.66% according the GAIL model (http://www.cancer.gov/bcrisktool/) and
4) women with known BRCA1 or BRCA2 mutation who do not wish prophylactic mastectomy.

In a recent meta-analysis of seven placebo controlled studies in mainly postmenopausal women, the U.S. Preventive Services Task Force (USPSTF) made the following conclusion [141]: A 5-year use of both tamoxifene and raloxifene reduced the risk of invasive breast cancer at 7–9 cases per 1000 women. The risk reduction is most pronounced for women with a 5-year risk of breast cancer (GAIL model) > 5%. Neither the risk of non-invasive breast cancers nor the total or breast cancer mortality can be significantly reduced.

Toremifene

No data available in PubMed.

A comparision of the protective effect of different SERMs with regard to breast cancer is shown in Table 6.

4.3. Bone Health

Estrogens act upon bone cells, which carry both isoforms of estrogen receptors [142, 143]. The number of ER-beta in cancellous bone is higher while the concentration of ER-alpha is higher in the cortical bone [144].

Estrogen deficiency is the main cause of postmenopausal osteoporosis [142]. A low level of estrogen increases bone turnover leading to bone loss. By taking HRT in the early and the late stages of the postmenopause, this process can be stopped or even reversed [142]. Even though this has been demonstrated by many observational studies, the Women's Health Initiative Study, was the first large scale placebo controlled randomized study that showed that hormone replacement therapy reduces osteoporotic fractures, leading to a 34-percent reduction of vertebral and hip fractures [145]. This risk reduction occurred despite the study participants having a low risk for fractures.

Bazedoxifene

According to Reginster et al [146] bazedoxifene may be appropriate for postmenopausal women seeking a tolerable, safe, effective, and cost-effective long-term osteoporosis treatment. In a 3 year, global, phase 3 study, bazedoxifene significantly reduced the risk of new vertebral fractures and nonvertebral fractures in women with higher baseline fracture risk compared with placebo. In two extensions of this study, the efficacy of bazedoxifene in reducing vertebral fracture risk was sustained over seven years. Bazedoxifene improved lumbar spine and total hip bone mineral density compared with placebo at years 3 and 5, and demonstrated a favorable safety/tolerability profile, with no endometrial or breast stimulation.

An indirect comparison with bisphosphonates has been described by Ellis et al [147], which demonstrated that bazedoxifene was comparable to bisphosphonates in preventing vertebral fractures in postmenopausal osteoporotic women and at least as effective in preventing vertebral fractures among higher risk postmenopausal osteoporotic patients.

Clomifene

Due to short term intermitted use as fertility drug no negative effect on bone health is expected. No relevant data in PubMed.

Lasofoxifene

In postmenopausal women with osteoporosis, lasofoxifene at a dose of 0.5 mg per day was associated with a reduced risk of nonvertebral and vertebral fractures, ER-positive breast cancer, coronary heart disease, and stroke but an increased risk of venous thromboembolic events [108].

Ormeloxifene

Despite promising early pre-clinical data of the effect of ormeloxifene in bone tissue [148, 149], there are no data in humans.

Ospemifene

In estrogen-deficient rats Kangas et al [150] could demonstrate antiresorptive, selective agonist effects of ospemifene on bone that appear similar to the effect of raloxifene. Two small phase 2 studies have examined the effect of ospemifene on markers of bone metabolism compared to placebo [151] or raloxifene [152]. The results show that ospemifene is effective in reducing bone turnover in postmenopausal women and that the bone-restoring activity of ospemifene, is comparable to that of raloxifene.

Raloxifene

The effects of raloxifene on bone are well established. In postmenopausal women with osteoporosis treated with raloxifene the markers of bone turnover decreased by 30–40% after one year and bone mineral density increased at various sites by about 2–3% after 3 years [153–156] (Tab. 7). Raloxifene decreased in a dose-dependent way the incidence of vertebral fractures by 30–50%, but not the incidence of hip fractures and other non-vertebral fractures [155].

Although bisphosphonate (alendronate or risedronate) therapy reduces the risk of vertebral fractures, the reduction in vertebral fractures by about 50 percent is only slightly higher than during raloxifene therapy [157, 158] despite the fact that bone mineral density increased to a much greater extent with bisphosphonates (4–9% measured at the same sites) [159, 160].

There are no data showing a significant reduction in the incidence of hip fractures by lasofoxifene or raloxifene.

Tamoxifene

The influence of tamoxifene (20–30 mg/day) and raloxifene on bone density is summarized in Table 7 [161].

Although early studies have shown that tamoxifene acts as estrogen antagonist at the breast, subsequent animal experiments and clinical trials [162–165] showed that it acts on the bone as a weak estrogen agonist. In postmenopausal women, however, there is only a small gain in bone density after two years of tamoxifene therapy (Tab. 7), and half of this short-term increase is lost during continued treatment over 5 years [165].

Tamoxifene led to an increase [166] or decrease [167] of hip fractures.

Toremifene

There is a lack of data. Toremifene seems to be a weaker agonist on bone than tamoxifene [168].

4.4. Vaginal Dryness and Dyspareunia

Vaginal dryness is a problem in postmenopausal women without HRT. In case of patients with HRT, the increased risk of breast cancer should be considered.

Hormone therapy for sexual function in perimenopausal and postmenopausal women has been reviewed in a cochrane analysis by Nastri et al [169]. More studies evaluating the effect of synthetic steroids, SERMs and the association of SERM + estrogens would improve the quality of evidence for the effect of these treatments on sexual function in perimenopausal and postmenopausal women. Future studies should also evaluate the effect of HRT solely among women with sexual complaints.

4.4.1. Vaginal Dryness in Breast Cancer Patients

Breast cancer is the most frequent cancer among women with about 1.38 million new cases worldwide every year. Most of these patients are postmenopausal and suffer from hormone receptor positive breast tumors. About 50% of postmenopausal women between 50 and 60 years and 72% of women over 70 years suffer from vulvovaginal athrophy (VVA) [119].

Table 7. Results of major randomized clinical trials of SERMs with regard to bone mineral density. (There are no data for Ospemifene). Mod. from [187] and [Riggs BL, Hartmann LC. Selective estrogen-receptor modulators -- mechanisms of action and application to clinical practice. N Engl J Med 2003; 348: 618–29]. © Thomas Rabe

Trial	Study Subjects	Duration (months)	Change in Bone Mineral Density as Compared with Placebo Group (%)		
			Total-body Bone Mineral	Lumbar Spine	Proximal Femur
Tamoxifene (20–30 mg/day)					
Love et al. (1992) [165]	140 postmenopausal women with breast cancer	24	–	1.6*	1.6*
Grey et al. (1995)[1]	57 normal late-postmenopausal women	24	0.5†	2.1†	0.6
Powles et al. (1996)[2]	179 healthy women in chemoprevention trial for breast cancer				
	54 postmenopausal women	36	–	4.7*	3.6†
	125 premenopausal women	36	–	–2.6*	–4.3†
Raloxifene (60 mg/day)					
Delmas et al. (1997) [153]	302 normal postmenopausal women	24	2.0*	2.4*	2.4*
Lufkin et al. (1998) [154]	143 postmenopausal women with osteoporosis and vertebral fractures	12	–0.1	1.8†	1.0†
Ettinger et al (1999) [155]	5140 postmenopausal women with osteoporosis	36	–	2.6*	2.1*
Johnston et al. (2000) [156]	576 healthy early-postmenopausal women	36	1.7*	2.6*	2.5*
Bazedoxifene (20 mg/day) in combination with CEE					
Pinkerton et al. (2014) [90]	Daily oral BZA 20 mg/CE 0.45 or 0.625 mg, BZA 20 mg, CE 0.45 mg/medroxyprogesterone acetate (MPA) 1.5 mg, or PBO	1 year	The BZA/CE group showed significantly greater increases in lumbar spine and total hip BMD vs decreases with PBO ($p < 0.001$); the CE/MPA group had increased lumbar spine BMD compared with that in the BZA/CE group.		
Reginster et al. (2014) [146	Review	3 yrs 7 yrs	In a 3 year, global, phase 3 study, BZA significantly reduced the risk of new vertebral fractures and nonvertebral fractures in women with higher baseline fracture risk compared with placebo. In two extensions of this study, the efficacy of BZA in reducing vertebral fracture risk was sustained over 7 years. BZA improved lumbar spine and total hip bone mineral density compared with placebo at 3 and 5 years.		
Lasofoxifene (0.5 mg/day)					
Cummings et al. (2010) [108]	8556 women who were between the ages of 59 and 80 years and had a bone mineral density T score of –2.5 or less at the femoral neck or spine; Randomization: 0.25 versus 0.5 mg/day vs. placebo	60	Reduced risks of vertebral fracture (13.1 cases vs. 22.4 cases per 1000 person-years; HR 0.58; 95% CI: 0.47–0.70), nonvertebral fracture (18.7 vs. 24.5 cases per 1000 person-years; HR 0.76; 95% CI: 0.64–0.91)		

HR: hazard ratio; CI: confidence interval
* $p < 0.05$ for the comparison with placebo; † $p < 0.005$ for the comparison with placebo
[1] Grey AB, Stapleton JP, Evans MC, Tatnell MA, Ames RW, Reid IR. The effect of the antiestrogen tamoxifene on bone mineral density in normal late postmenopausal women. Am J Med 1995; 99: 636–41.
[2] Powles TJ, Hickish T, Kanis JA, Tidy A, Ashley S. Effect of tamoxifene on bone mineral density measured by dual-energy x-ray absorptiometry in healthy premenopausal and postmenopausal women. J Clin Oncol 1996; 14: 78–84.

Low Dose Estrogens

In a retrosepctive nested case-control study of Le Ray et al [170], a total of 13,479 women were included of which 2,673 received aromatase inhibitors, 10,806 received tamoxifene, and 271 received Low Hormone Therapy (LHT). Mean (SD) age at cohort entry was 63.7 (14.1) years, and mean follow-up was 3.5 (2.6) years. The crude recurrence rate was 25.9 per 1,000 per year. Overall, the use of LHT was not associated with an increased risk of recurrence (RR: 0.78; 95-%-CI: 0.48–1.25) compared with non-use. In stratified analyses, LHT did not increase the risk of recurrence among tamoxifene-treated patients (RR: 0.83; 95-%-CI: 0.51–1.34), while the risk could not be estimated among aromatase inhibitor treated patients since no patients receiving a local hormonal therapy experienced a recurrence. The use of LHT is not associated with an increase in breast cancer recurrence among women receiving hormone therapy.

The combination of raloxifene with low dose estrogens must be further evaluated (semisystematic review by Cameiro et al [171].

In patients treated with aromatase inhibitors (AI) vaginal administration of estradiol is a well known alternative to systemic estrogen therapy, but studies demonstrated significant increases in plasma concentrations of estradiol. Further studies are needed to explore the risk of breast cancer recurrence after vaginal estrogen application for patients on adjuvant endocrine therapy with AI [119].

Table 8. Incidence of endometrial-related adverse events in phase-III treatment studies of SERMs. © Thomas Rabe

	Raloxifene (MORE; n = 7705)[1] (CORE; n = 4011) [191]		Lasofoxifene (PEARL; n = 8556) [108][2, 3]		Bazedoxifene (n = 7492 and n = 4216) [190, 192]		Ospemifene[++] (n = 317)[4]	
	60 mg	120 mg	0,25 mg	0,5 mg	20 mg	40 mg		60 mg
Incidence of endometrial hyperplasia								
1 year								0.32% (95% CI: 0.01–1.74%) 1[+]
3 years	0.05% (pooled RLX) 60/120 mg)		–	–	0.1%	0.1%		
5 years	–	–	0.11%	0.07%	0.1%	–		
Incidence of endometrial cancer								
1 year								0
3 years	0.2%	< 0.1%	–	–	0	0.1%		
5 years	–	–	0.07%	0.07%	0	–		
Incidence of endometrial neoplasia (polyps)								
1 year							1 Polyps 0.2%[++]	5 Polyps 0.6%[++]
3 years	–	–	–	–	0.5%	0.6%		
5 years	–	–	3.8%*	4.0%*	0.7%	–		
8 years	3.2%[†]							
Change from baseline in endometrial thickness (mm)								
1 year							n.a.	0.81[+++]
2 years			–	–	0.07 ± 0.11	0.10 ± 0.12		
3 years	0.01** (pooled RLX) (60/120 mg)		–	–	–	–		
5 years				1.19*	1.43*	0.05 ± 0.13	–	

MORE: Multiple Outcomes of Raloxifene Evaluation; CORE: Continuing Outcomes Relevant to Evista; PEARL: Postmenopausal Evaluation And Risk-reduction with Lasofoxifene; RLX: raloxifene; RR: relative risk; CI: confidence interval; HR: hazard ratio; ER: estrogen receptor; n.a. = not available

* $p \leq 0.001$ vs. placebo; ** $p < 0.01$ vs. placebo; [†] $p < 0.05$ vs. placebo; [#] RR and HR vs. placebo; [+] diagnosed 88 days after the subject was discontinued from the study (her endometrial biopsy at study termination showed active proliferation and the TVUS was 11.12 mm); [++] In the double blind placebo controlled Phase 2/3 study database, there are 5 cases of endometrial polyps in the 60 mg ospemifene population (n = 851; 0.6%) and 1 case in the placebo population (n = 570; 0.2%); [+++] In the double blind placebo controlled Phase 2/3 study database, a mean increase in endometrial thickness is seen in the 60 mg ospemifene population at 12 weeks of 0.507 mm (SD 1.5406) (n = 640), at 6 months of 0.561 mm (SD 1.6092) (n = 370) and at 12 months of 0.814 mm (SD 1.5405) (n = 344). The medians (min, max) for these time-points are 0.30 (–3.93; 9.94), 0.54 (–3.84; 10.79) and 0.60 (–2.92; 8.79), respectively.

[1] Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA 1999; 281: 2189–97.

[2] Goldstein SR, Neven P, Cummings S, et al. Postmenopausal evaluation and risk reduction with lasofoxifene trial: 5-year gynecological outcomes. Menopause 2010; 18: 17–22.

[3] LaCroix AZ, Powles T, Osborne CK, et al. Breast cancer incidence in the randomized PEARL trial of lasofoxifene in postmenopausal osteoporotic women. J Natl Cancer Inst 2010; 102: 1706–15.

[4] Shionogi file 2014.

4.4.2. Vaginal Dryness in Postmenopausal Women without Breast Cancer

Bazedoxifene

In a phase 3, multicenter, double blind, randomized, placebo controlled, and active comparator-controlled study by Kagan et al [172]. BAZ 20 mg/CE 0.625 or CE 0.45 mg significantly ($p < 0.01$) increased superficial cells and decreased parabasal cells compared with placebo. Vaginal pH and most bothersome symptom significantly improved with BAZ 20 mg/CE 0.625 mg compared with placebo ($p < 0.05$). Improvements in vaginal dryness, but not in dyspareunia were also observed with both BAZ/CE doses ($p < 0.05$). Bazedoxifene alone has no, or even a negative effect, on VVA [172].

The QoL data from the same study are reported by Bachmann [173] who shows that the improvement in QoL with bazedoxifene is restricted to the group that used conjugated estrogens whilst the placebo group shows better QoL improvements than the BAZ only group, with e.g. ease of orgasm (in the Arizona Sexual Experience Score), vasomotor function (in the Menopause-Specific Quality of Life score) and Interest in sex (in the Menopause Symptoms-Treatment Satisfaction Questionnaire) showing statistically significant worsening over 12 weeks for the bazedoxifene only group compared to placebo. What these publications from this study show, is that the beneficial effects one would expect from CE on VVA are not negated by BAZ. However, since there is no CE only control group in this study it cannot be excluded that BAZ does not attenuate the effect of (oral) conjugated estrogens.

Table 9. Incidence of stroke in phase-III treatment studies of SERMs. © Thomas Rabe

	Raloxifene (MORE; n = 7705)[1] (RUTH; n = 10101) [63]		Lasofoxifene (PEARL; n = 8556) [109]		Bazedoxifene (n = 7492 and n = 4216) [190, 191]		Ospemifene Source[2]	
	60 mg	120 mg	0.25 mg	0.5 mg	20 mg	40 mg	0	60
Incidence of total stroke								
1 year							1	1
3 years	–	–	–	–	HR 0.9 (95% CI: 0.40–1.86)	HR 1.0 (95% CI: 0.49–2.17)	HR 0.498 (95% CI: 0.006–39.102)	
5 years	HR 1.10 (95% CI: 0.92–1.32)	–	HR 0.61 (95% CI: 0.39–0.96)	HR 0.64 (95% CI: 0.41–0.99)	HR 0.8 (95% CI: 0.43–1.63)	–	–	–

MORE: Multiple Outcomes of Raloxifene Evaluation; RUTH: Raloxifene Use for The Heart (phase-3 cardiovascular effects study); PEARL: Postmenopausal Evaluation And Risk-reduction with Lasofoxifene; CI: confidence interval; HR: hazard ratio
[1] Cummings S R, Eckert S, K rueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA 1999; 281: 2189-97
[2] Shionogi file 2014.

Clomifene
Although there are very limited data about Clomiphene and vaginal dryness, the US Package Insert mentions vaginal dryness as being reported in fewer than 1% of patients in clinical trials (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/016131s026lbl.pdf).

Lasofoxifene
A positive effect of lasofoxifene on symptoms of VVA has been reported for a phase 2 study in 387 women by Gass for physiological signs [174], by Bachmann for symptoms [175] and by Simon in a 12-week phase-III-study with 445 postmenopausal women [176].

Ormeloxifene
No data in PubMed.

Ospemifene
Ospemifene is the only SERM specifically developed for the treatment of vulvo-vaginal atrophy. Two pivotal 12-week efficacy studies have confirmed its efficacy [53, 54, 173] on physiological signs and symptoms and a 52 week study confirmed that the beneficial effects on physiology, seen in the 12-week efficacy trials, was maintained during the 52 week treament in this study [55]. In the US, ospemifene is registered under the tradename Osphena and in Europe under the trade name Senshio.

Raloxifene
Glusman et al [177] did not see differences between raloxifene and placebo in integrated data from five randomized, placebo controlled studies involving 1,165 healthy, postmenopausal women, with up to 30 months of study drug exposure. The effect of raloxifene on vaginal physiology has been described as positive [178], negative [179] or neutral [180]. However, in neither of these publications the administration of raloxifene caused any change of symptoms of vulvo-vaginal atrophy. In a randomized placebo controlled study of 187 postmenopausal women with pre-existing and untreated vaginal atrophy, which were treated with either a cream containing conjugated estrogens (0.5 g) or an applicator of non-hormonal moisturizer (open label), raloxifene administration had no negative effects on sexual function in postmenopausal women with vaginal atrophy who were treated concomitantly with vaginal estrogen cream and Raloxifene [181] did not diminish the magnitude of improvement in signs and symptoms of vaginal atrophy when administered with either vaginal preparation [182].

Tamoxifene
Several authors have reviewed the available evidence of the effect of tamoxifene on the vagina. Despite an effect on physiology that seems to indicate an estrogenic effect on the vagina of postmenopausal women, e.g., an increase in maturation value, karyopyknotic index and recurrent vulvovaginal candidiasis which normally occurs only in glycogen rich, estrogen stimulated vaginal epithelium, tamoxifene increases vaginal dryness and dyspareunia and, paradoxically, also leucorrhea. Particularly in the presence of estrogen (either exogenous, administered to treat severe vasomotor symptoms in a clinical trial setting, or endogenous as in pre-menopausal women), tamoxifene appears to exert a strong antiestrogenic effect, both on physiology (i.e. a decrease in maturation value) as well as on symptoms, expressed as a worsening of vaginal atrophy and concomitant sexual sequelae [183–185].

Toremifene
There are few data about the vaginal effects of toremifene. According to the US Package Insert, vaginal discharge is one of the most common side effects reported in the North American Study (13%). In a study by Marttunen which compared the gynaecological effects of tamoxifene with toremifene, vaginal symptoms (dryness, irritation, discharge) increased during the use of antiestrogen in both groups [186].

5. Drug Safety

5.1. Breast Cancer
Data on the SERM effect in the breast are summarized in section 4.2 in view to breast cancer prevention.

5.2. Endometrial Safety
See review of Hadji [187] and Table 8.

Bazedoxifene
Palacios et al [125] evaluated the clinical safety of bazedoxifene on the reproductive tract in postmenopausal women with osteoporosis over 7 years. At 7 years, the adjusted mean (± standard error) change in endometrial thickness was similar with bazedoxifene and placebo (–0.11 ± 0.21 and 0.07 ± 0.32 mm, respectively). The incidence of endometrial hyperplasia was low (0.1% for both groups). Bazedoxifene showed a significantly lower incidence of endometrial carcinoma than placebo (0.1% vs. 0.4%; p = 0.020).

Clomifene
The US Package Insert mentions reports of new cases of endometriosis and exacerbation of pre-existing endometriosis during clomifene therapy as well as reduced endometrial thickness as adverse events. Long-term data on clomifene use are sparse since it is only given for 5 days early in the cycle and long-term cyclic therapy, i.e. beyond a total of about six cycles (including three ovulatory cycles), is not recommended, based on epidemiological data which suggest that prolonged use of ospemifene may increase the risk of ovarian cancer (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/016131s026lbl.pdf).

Lasofoxifene
Lasofoxifene has been associated with benign endometrial effects. These included, in some subjects, a small excess in the incidence of vaginal bleeding as well as cystic endometrial changes (by ultrasound examination) and histological benign cystic atrophy (a variant of atrophic endometrium). Placebo-treated women had a 1.9% incidence of cystic changes at 3 years, whereas the lasofoxifene treated women had a 20.4% incidence. All histology findings were benign. Placebo-treated women had a 0.7 mm mean decrease from baseline in endometrial thickness over 3 years, whereas the lasofoxifene-treated women had a 1.4 mm mean increase. The increase was observed at 12 months, and did not significantly increase through 3 years. In all women with a uterus at baseline, histological benign endometrial polyps were reported in 34 of 2,302 (1.5%) of lasofoxifene treated women versus 18 of 2,309 (0.8%) placebo-treated women (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000977/WC500020092.pdf). Five years of treatment with lasofoxifene did not increase the risk of endometrial cancer or endometrial hyperplasia [108].

Ormeloxifene
According to a recent publication, there are no reports of endometrial carcinoma with the long-term use of ormeloxifene [129].

Ospemifene
In a 12-months study reported by Simon, mean endometrial thickness increased slightly in the 60 mg ospemifene (n = 53) treated population compared to the placebo (n = 30) population (1.14 mm vs. –0.04 mm respectively) [56]. Another study, reported by Goldstein, showed similar changes in mean endometrial thickness after 12 months (0.75 ± 1.5 mm for 60 mg ospemifene [n = 294] vs. 0.17 ± 1.3 mm for placebo [n = 55]) There have been no reports on endometrial cancer with ospemifene. There was one case of simple endometrial hyperplasia without atypia found in a patient who had a follow-up biopsy three months after the last dose of ospemifene [55].

Raloxifene
In a study of 444 women over two years, Delmas reported no increase in endometrial thickness in the four treatment groups (placebo, 30, 60 and 150 mg raloxifene) in this study [153]. In the MORE study of 7705 postmenopausal women with osteoporosis, 5957 women had an intact uterus at study entry. Of those, 1781 had a baseline TVUS and at least one follow-up test. Endometrial thickness increased by an average of 0.01 mm in the raloxifene group and decreased 0.27 mm in the placebo group after three years of follow-up ($p < 0.01$) [157]. In this study raloxifene was not associated with an increased risk for endometrial hyperplasia (RR 1.3; 95-%-CI: 0.4–5.1), or endometrial cancer (RR 0.9; 95-%-CI: 0.3–2.7) compared to placebo [188]. Martinho describes the four-year follow-up study to the MORE study and reports that for the 3193 subjects with an intact uterus who continued for eight years (raloxifene n = 2167, placebo n = 1026), there was no increase in uterine cancer (4 subjects (0.39%) in the placebo group and 7 subjects (0.32%) in the raloxifene group, $p = 0.75$) or endometrial hyperplasia (3 subjects (0.29%) in the placebo group and 8 (0.37%) in the raloxifene group, $p > 0.99$) in the raloxifene group.

Tamoxifene
A number of benign (endometrial polyps, endometrial hypertrophy and endometrial hyperplasia) changes have been described with tamoxifene as well as an increased risk of uterine cancer risk. They have recently been summarized by Polin. The incidence of endometrial polyps in women treated with tamoxifene is between 8 and 36% versus 0–10% in untreated women. Tamoxifene-related polyps are usually larger than polyps found in the general population and are reported to have an increased rate of malignant change ranging from 3–10.7% compared with 0.48%. The incidence of endometrial hyperplasia is increased in breast cancer patients. The incidence is 1.3–20% in these patients, compared to the 0-10% incidence in postmenopausal breast cancer patients who are not receiving tamoxifene [185].

The risk of endometrial cancer is increased 1.3- to 7.5-fold, indicating tamoxifene use results in an approximately two-fold increase in the incidence rate of endometrial cancer for both patients who use tamoxifene as adjuvant treatment for breast cancer as well as patients who take tamoxifene to prevent breast cancer. In the large Breast Cancer Prevention Trial (P-1) of the National Surgical Adjuvant Breast and Bowel Project (n = 13388), the rate of endometrial cancer was increased in the tamoxifene group (RR 2.53; 95-%-CI: 1.35–4.97); this increased risk occurred predominantly in women aged 50 years or older [133].

Toremifene
Since most toremifene trials have been conducted in patients with metastatic disease, adequate data on the potential endometrial tumorigenicity of long-term treatment with toremifene are not available. Endometrial hyperplasia has been reported. Some patients treated with toremifene have developed endometrial cancer, but circumstances (short duration of treatment or prior antiestrogen treatment or premalignant conditions) make it difficult to establish the role of toremifene (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020497s006lbl.pdf). In the relatively small 3-year study by Marttunen, comparing 20 mg/day tamoxifen (n = 84) with 40 mg/day toremifene (n = 83), there was no difference in endometrial thickening between the two drugs, but the incidence of proliferative endometrium and endometrial polyps was slightly higher in the tamoxifene group [186].

5.3. Cardiovascular Disease
The risk of stroke associated with different SERMs is summarized in Table 9.

5.4. Venous Thromboembolism
The risk of VTE among different SERMs is summarized in Table 3 (data summa-

rized from Miller et al [189], Christiansen et al [190], Silverman et al [12], Johnston et al [156], Cummings [157], Delmas et al [59], Martino et al [191], Barrett-Connor et al [63], Vogel et al [57, 132], Fisher et al [133, 137], IBIS investigators [136], Powles et al [139], de Villiers et al [192], Grady et al [188].

Regulatory information: Conbriza EPAR, Conbriza updated EPAR, Conbriza SmPC, Evista SmPC, EPAR Senshio. See also review by Hadji [193].

Bazedoxifene
Reduction of non-vertebral and vertebral fractures, ER-positive breast cancer, coronary heart disease and stroke but an increased risk of venous thromboembolic events [125].

Clomifene
No clinical data available in PubMed. No VTE according SMPC. Circulatory and visual problems described.

Lasofoxifene
Increased the incidence of VTE (but not stroke) [108]. The risk of major coronary events was reduced with lasofoxifene 0.5 mg/day, and lasofoxifene 0.5 and 0.25 mg/day were associated with less frequent hypertension and hyperlipidaemia. See review Hadji [187].

Ormeloxifene
No data found in PubMed.

Ospemifene
In the Phase 2 and 3 double blind placebo controlled studies, a total of 2 VTE cases were reported in women using ospemifene (n = 1242, 547.89 WY) and one in the placebo group (n = 958, 272.95 WY). The incidence rate for VTE is therefore 3.65/1,000 women years for 60 mg ospemifene (95-%-CI: 0.44–13.19) and 3.66/1,000 women years for placebo (95-%-CI: 0.09–20.41). The Incidence Rate Ratio (IRR) is 0.996 (95-%-CI: 0.052–58.783), i.e. there is no signal in the Phase 2 and 3 double blind placebo controlled studies of an increased risk of VTE with 60 mg ospemifene, but the confidence intervals are very wide. Based on the FDA methodology, which includes all phase 2/3 studies, the incidence rate would be 2.53/1,000 women years (95-%-CI: 0.31–9.15) for 60 mg ospemifene and the IRR would be 0.692 (95-%-CI: 0.063–40.802).

Raloxifene
RUTH-trial (secondary prevention study): Barrett-Connor et al [63]: There was no significant difference in the rates of death from any cause or total stroke according to group assignment, but raloxifene (vs placebo) was associated with an increased risk of fatal stroke (59 vs. 39 events ; hazard ratio, 1.49; 95-%-CI: 1.00–2.24; absolute risk increase, 0.7 per 1000 woman-years) and venous thromboembolism (103 vs 71 events; hazard ratio, 1.44; 95-%-CI: 1.06–1.95; absolute risk increase, 1.2 per 1000 woman-years).

MORE-trial: see Table 3.

Tamoxifene
Tamoxifene is associated when compared with raloxifene with a higher risk of VTE [132].

Toremifene
No published information about VTE risk.

6. Summary

Estrogens and SERMs
Selective estrogen receptor modulators (SERMs) are a class of compounds that act via the estrogen receptor. A characteristic that distinguishes these substances from pure receptor agonists and antagonists is that their action is different in different tissues, opening the possibility to selectively inhibit or stimulate estrogen-like action in various tissues. Phytoserms are SERMs from a botanical source.

Mechanism of Action
Genomic, estrogen-receptor mediated pathways (Fig. 15).

Most pharmacologic effects of SERMs can be explained through three mechanisms [14] (Fig. 16).

Target cells contain different tissue-specific concentrations of homodimers of either or both of two types of estrogen receptors. Expression of these two receptor isoforms affect the cellular response of the target tissue to estrogen.

A change in conformation of the estrogen receptor during ligand binding.

Co-regulator Proteins
A large number of co-regulator proteins are currently known which bind to estrogen receptors. Their function is defined as either a positive (co-activator) or a negative transcriptional regulator (as co-repressor). The relative and absolute level of expression of these co-regulator proteins is different in various target cells.

Non Genomic Pathways
influence on regulatory proteins without action mediated via DNA. Important both for estrogen and SERM action at target cells.

Mode of action as shown in Figures 15 and 16 [194].

Estrogen Action (Fig. 15)
- Estradiol (E) binds with high affinity to estrogen receptor (ER) and dissociates heat shock protein 90 (HSP90)
- E-ER complex homodimerizes and localizes preferentially in the cell nucleus
- E-ER homodimer binds DNA sequence at palindromic estrogen response element (ERE) in the promotor region of estrogen-sensitive genes
- Activation of transcription by ER involves interaction of the transcription activation functions of ER, AF1 and AF2 with transcriptional co-activators to stimulate the activity of RNA polymerase II (RNA POL II)

Tamoxifene Action (Fig. 11b)
- Tamoxifene (T) binds to ER with low affinity compared with estradiol (E) (Breast cancer update:
- http://www.breastcancerupdate.com/breast_cancer_symposium/posters_files/rationale_nsabp.html) and dissociates heat shock protein 90 (HSP90)
- T-ER complex homodimerizes and translocates to the cell nucleus, and activation function (AF1) (but not AF2) is active
- T-ER homodimer binds to the DNA of the palindromic ERE in the promotor region of estrogen-sensitive genes
- Transcription of E-responsive genes(s) is attenuated because AF2 is inactive, and co-activator binding is attenuated by the T-ER complex; partial agonist activity results from AF1, which remains active in the T-ER complex.

Estrogenic Compounds Span a Spectrum of Activity Ranging from:
- full agonists (agonistic in all tissues) such as the natural endogenous hormone estrogen

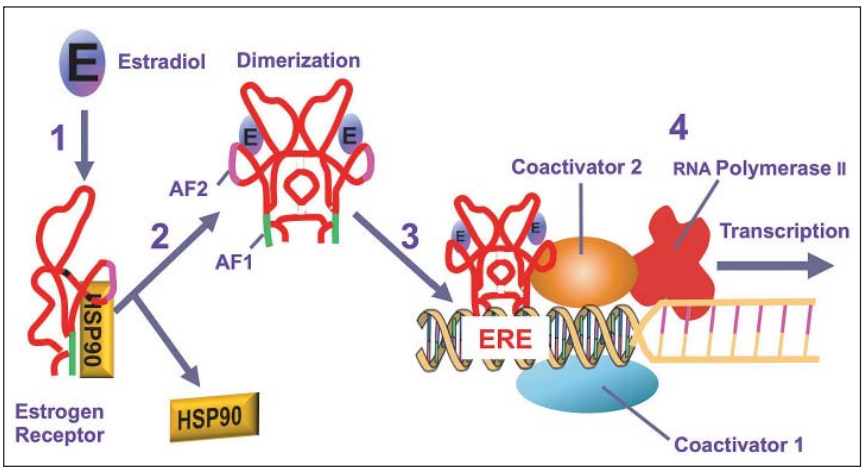

Figure 15. Molecular action of estradiol. Mod. from [Howell A, et al. ICI 182,780 (Faslodex): development of a novel, "pure" antiestrogen. Cancer 2000; 89: 819] and according to Prof. SN Panda, Berhampur, India. © Thomas Rabe

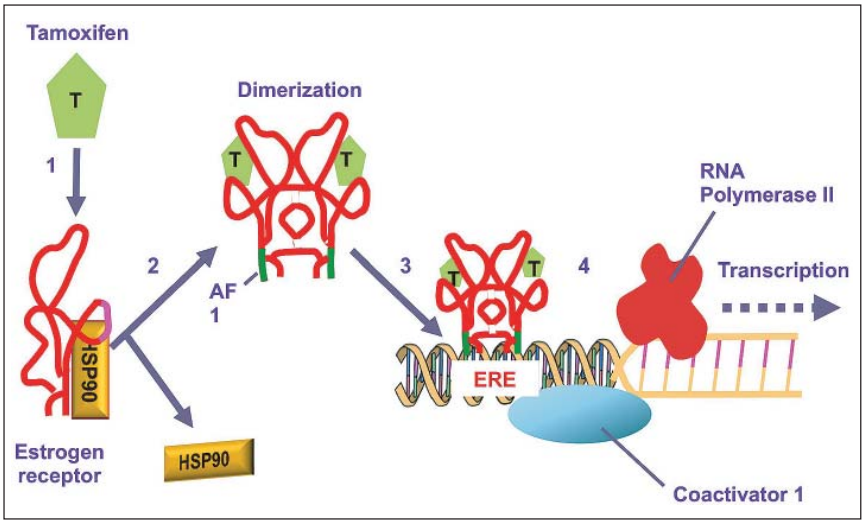

Figure 16. Molecular action of SERMs: tamoxifene. After binding to the estrogenreceptor there is a conformation change. Mod. from [Howell A, et al. ICI 182,780 (Faslodex): development of a novel, "pure" antiestrogen. Cancer 2000; 89: 819] and according to Prof. SN Panda, Berhampur, India. © Thomas Rabe

– mixed agonists/antagonistics (agonistic in some tissues while antagonist in others) such as tamoxifene (a SERM)
– pure antagonists (antagonistic in all tissues) such as fulvestrant (ICI-182780).

Actions

The actions of SERMs on various tissues:

– Bone turnover and postmenopausal osteoporosis respond favourably to most SERMs, although premenopausal women may experience bone loss with some SERMs including tamoxifene.
– Breast: All SERMs decrease breast cancer risk, and tamoxifene is mainly used for its ability to inhibit growth in estrogen receptor-positive breast cancer.
– Lipids: Cholesterol- and triglyceride-levels respond favorably to SERMs.
– Deep vein thrombosis: The risk may be elevated with some SERMs.
– Hot flushes are increased by most SERMs.
– Pituitary gland: Clomifene blocks estrogen action, thus leading to an increase of follicle-stimulating hormone and luteinizing hormone.
– Uterus: Tamoxifene may increase endometrial carcinoma risk, but raloxifene and femarelle do not. Data on toremifene and clomifene is insufficient.

Compounds Currently Used in Clinical Practice (in Alphabetical Order)

– Bazedoxifene: Licensed in Europe as mono-therapy under the trade name Conbriza® for the treatment of postmenopasusal osteoporosis. Licensed in the US in combination with conjugated estrogens under the trade name Duavee® for the treatment of moderate to severe vasomotor symptoms associated with menopause and prevention of postmenopausal osteoporosis. The same combination, under the trade name Duavive®, received marketing authorisation in December 2014 for the treatment of estrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate.
– Clomifene: Has become the most widely prescribed drug for ovulation induction to reverse anovulation or oligoovulation.
– Ospemifene: SERM acting similarly to an estrogen on the vaginal epithelium, building vaginal wall thickness which in turn reduces the pain associated with dyspareunia.
– Ormeloxifene: Best known as a non-hormonal, non-steroidal oral contraceptive which is taken once per week. In India, ormeloxifene has been available as birth control since the early 1990s.
– Tamoxifene (triphenylethylene): The archetypal SERM. It is an antagonist of the estrogen receptor in breast tissue via its active metabolite, 4-hydroxytamoxifene. In other tissues such as the endometrium, it behaves as an agonist, and thus may be characterized as a mixed agonist/antagonist. It is used in women who have estrogen receptor (ER)-positive breast cancer in pre-menopausal women, and is also the standard in post-menopausal women, although aromatase inhibitors are also frequently used in that setting.

  Unfortunately, resistance to tamoxifene is common in women with metastatic disease and serious side effects, including an increased risk of endometrial cancer, exist. It is used in patients for the primary treatment of breast cancer and in some countries for breast cancer prevention.

– Raloxifene: SERM that has estrogenic actions on bone and anti-estrogenic actions on the uterus and breast. It is used in the treatment and prevention of osteoporosis in postmenopausal women as well as for the primary prevention of breast cancer in women with osteoporosis and at increased risk (US).

– Toremifene: Licensed in the US and Europe under the brand name Fareston for use in advanced (metastatic) breast cancer. It is also being evaluated for prevention of prostate cancer under the brand name Acapodene.

  Warning: *"Toremifene may cause QT prolongation (an irregular heart rhythm that can lead to fainting, loss of consciousness, seizures, or sudden death)."*

Phytoserm without Regulatory Approval (Food Supplement)
– Femarelle (DT56a) is a SERM for the treatment of climacteric symptoms and bone health. Femarelle contains approximately 322 mg DT56a (a tofu extract) and 108 mg flaxseed powder. Since 2005 on the US market available.

Compounds for which the Development has been Suspended
– Arzoxifene: Suspended following the presentation of the GENERATION study by Lilly.
– Idoxifene: Derivative of tamoxifene; pyrrolidino-4-iodotamoxifene. The compound has a 2.5 fold higher affinity to the estrogen receptor than tamoxifen, but is significant less uterotropic and has a positive effect on the bone [195].
– Droloxifene: Active metabolite of tamoxifene: 3-OH-tamoxifene. Droloxifene in breast cancer patients has been described by Bruning [196]. Droloxifene has an anti-implantation effect in rats, and the effect appears to be not completely due to its anti-estrogenic activity [197].
– Lasofoxifene (Fablyn®): Received a marketing authorization in Europe, but was never commercialized. Under the "Sunset Clause" its marketing authorization was withdrawn.
– Pipendoxifene: Indole derivative, with lower affinity for the ERα receptor and tissue-specific activity for both ER-Subtypes.

Fields of Application
– Prevention and treatment of osteopenia and osteoporosis
– Reduction in breast cancer risk
– Treatment of menopausal symptoms
– Treatment of dyspareunia

Beneficial Effects (Compound Specific)
– Positive effect on bone health
– Positive effect on menopausal symptoms
– Positive effect on vaginal dryness and dyspareunia
– Protection from breast cancer

Side Effects
– The side effect profile of the individual compounds is different.
– Common side effects are hot flushes, vaginal discharge, muscle spasms and excessive sweating.
– Serious side effects include the risk of endometrial cancer, stroke and venous thromboembolism.

New SERMs on Market
– Ospemifene: In February 2013 ospemifene (60 mg/day) was approved by the FDA and in January 2015 by the EMA. Safety data did not show clinical relevant endometrial changes after 12 months. The bone metabolism is affected positively. During all clinical trials only two VTE cases occurred in the ospemifene group and one in the placebo group. Long-term data on breast safety, prevention or treatment of osteoporosis and VTE risk are still missing.

Outlook
SERMs are an exciting, diverse and versatile class of compounds. For nearly 80 years, SERMs are developed with different indications.

Estrogen/SERM-combinations (Progestin-Free Hormonal Replacement)
As a result of the Women's Health Initiative study and the resulting concerns regarding estrogen/progestin therapy, interest in the therapy with SERMs has increased because a lower side effect profile has been observed while the positive estrogen-like effects remained. This development continues. The combination of a SERM with estrogens may allow the omission of a progestin for endometrial protection in women with an intact uterus and may simultaneously lead to protection against breast cancer.

Clinical Trials are Necessary for Each Product and Indication
Current evidence indicates that each SERM has a unique spectrum of clinical effects. Differences in the patterns of action of SERMs suggest that each clinical endpoint must be evaluated individually, and conclusions about any particular SERM can only be established through appropriate clinical trials [31].

New SERMs in the Pipeline
– Afimoxifene: (4-hydroxytamoxifene) is a selective estrogen receptor modulator which is the active metabolite of tamoxifene [66]. Afimoxifene is a transdermal gel formulation and is being developed by Ascend Therapeutics, Inc. under the trademark TamoGel. Afimoxifene has completed a phase II clinical trial for the treatment of cyclical mastalgia [198].

Estrogen Receptor Downregulators
– Mechanism of action (Fig. 17) [194].
– Estrogen receptor downregulators, called ERDs for short, block the effects of estrogen in breast tissue. ERDs work in a similar way like SERMs, e.g., tamoxifene. ERDs occupy the estrogen receptors in breast cells. Binding of an ERD to the estrogen receptor prevents binding of an estrogen to this receptor. If estrogens cannot be bound, the breast cell cannot receive estrogenic signals for growth.
  ERDs also:
  ○ reduce the number of estrogen receptors
  ○ change the conformation of estrogen receptors in breast cells resulting in a blockade of their effects.
  ○ There is only one ERD available for treatment of hormone-receptor-positive breast cancer: Faslodex® (chemical name: fulvestrant).
– Further research on active metabolites of above mentioned SERMs

Metabolites of Tamoxifene
– Norendoxifen, 4,4'-dihydroxy-tamoxifene, endoxifene, N-desmethyl-tamoxifene, N-desmethyl-4'-hydroxy-tamoxifene, tamoxifene-N-oxide, 4'-hydroxy-tamoxifene, N-desmethyl-droloxifene, 4-hydroxy-tamoxifene may contribute to its action in the treatment of breast cancer via aromatase inhibition. Among these compounds, norendoxifen may serve as a potent and selective leading compound with respect to the development of improved therapeutic agents [199].
– New indications for the use of SERMs: e.g. osteoarthritis, schizophrenia, IGF1-in GH-deficient wom-

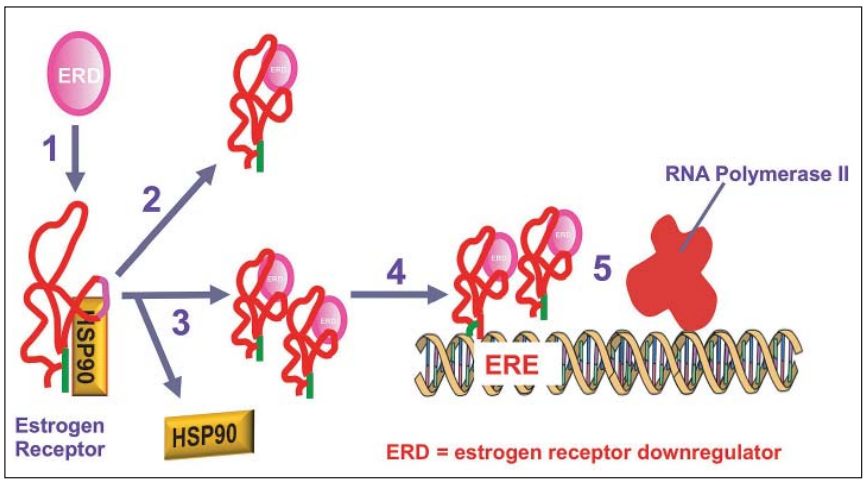

Figure 17. Molecular action of an estrogen receptor downregulator (future aspects). Mod. from [Howell A, et al. ICI 182,780 (Faslodex): development of a novel, "pure" antiestrogen. Cancer 2000; 89: 819] and according to Prof. SN Panda, Berhampur, India. © Thomas Rabe

en, postmenopausal vascular disease, lipid lowering effect, virus infections (ebola), anti-cryptococcal agents.
– New modes of delivery may include vaginal ring, intrauterine devices, vaginal tablets.

Internetlinks

– http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624793/#!po=12.0968
– http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624793/pdf/CCP-8-135.pdf
– http://www.osphena.com/

Conflict of Interest

No conflict of interest: H-J. Ahrendt, C. Albring, J. Bitzer, B. Damann-Hanser, K. König, H. Kuhl, N. Sänger.

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References:

1. Rollerova E, Urbancikova M. Intracellular estrogen receptors, their characterization and function (Review). Endocr Regul 2000; 34: 203–18.

2. McDonnell DP. The molecular pharmacology of estrogen receptor modulators: implications for the treatment of breast cancer. Clin Cancer Res 2005; 11: 871s–877s.

3. McInerney EM, Weis KE, Sun J, Mosselman S, Katzenellenbogen BS. Transcription activation by the human estrogen receptor subtype beta (ER beta) studied with ER beta and ER alpha receptor chimeras. Endocrinology 1998; 139: 4513–22.

4. Couse JF, Lindzey J, Grandien K, Gustafsson JA, Korach KS. Tissue distribution and quantitative analysis of estrogen receptoralpha (ERalpha) and estrogen receptor-beta (ERbeta) messenger ribonucleic acid in the wildtype and ERalpha-knockout mouse. Endocrinology 1997; 138: 4613–21.

5. Yaghmaie F, Saeed O, Garan SA, Freitag W, Timiras PS, Sternberg H. Caloric restriction reduces cell loss and maintains estrogen receptoralpha immunoreactivity in the pre-optic hypothalamus of female B6D2F1 mice. Neuro Endocrinol Lett 2005; 26: 197–203.

6. Babiker FA, De Windt LJ, van Eickels M, Grohe C, Meyer R, Doevendans PA. Estrogenic hormone action in the heart: regulatory network and function. Cardiovasc Res 2002; 53: 709–19.

7. Kansra S, Yamagata S, Sneade L, Foster L, Ben-Jonathan N. Differential effects of estrogen receptor antagonists on pituitary lactotroph proliferation and prolactin release. Mol Cell 2005; (1–2): 27–36.

8. Bakas P, Liapis A, Vlahopoulos S, Giner M, Logotheti S, et al. Estrogen receptor alpha and beta in uterine fibroids: a basis for altered estrogen responsiveness. Fertil Steril 2006; 5: 1878–85.

9. Shang Y, Brown M. Molecular determinants for the tissue specificity of SERMs. Science 2002: 95: 2465–8.

10. Deroo BJ, Korach KS. Estrogen receptors and human disease. J Clin Invest 2006; 116: 561–7.

11. Silverman SL, Christiansen C, Genant HK, Vukicevic S, Zanchetta JR, et al. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. Bone Miner Res 2008; 23: 1923–34.

12. Silverman SL, Chines AA, Kendler DL, Kung AW, Teglbjærg CS, et al. Bazedoxifene Study Group. Sustained efficacy and safety of bazedoxifene in preventing fractures in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled study. Osteoporos Int 2012; 23: 351–63.

13. Pickar JH, Yeh IT, Bachmann G, Speroff L. Endometrial effects of a tissue selective estrogen complex containing bazedoxifene/conjugated estrogens as a menopausal therapy. Fertil Steril 2009; 92: 1018–24.

14. Riggs BL, Hartmann LC. Selective estrogenreceptor modulators – mechanisms of action and application to clinical practice. N Engl J Med 2003; 348: 618–29.

15. Lindberg MK, Movérare S, Skrtic S, Gao H, Dahlman-Wright K, et al. Estrogen receptor (ER)-beta reduces ERalpharegulated gene transcription, supporting a "ying yang" relationship between ERalpha and ERbeta in mice. Mol Endocrinol 2003; 17: 203–8.

16. Pettersson K, Delaunay F, Gustafsson J-Å. Estrogen receptor b acts as a dominant regulator of estrogen signaling. Oncogene 2000; 19: 4970–8.

17. Hall JM, McDonnell DP. The estrogen receptor bisoform (ERb) of the human estrogen receptor modulates ERa transcriptional activity and is a key regulator of the cellular response to estrogens and antiestrogens. Endocrinology 1999; 140: 5566–78.

18. Kuiper GGJM, Carlsson B, Grandien K, Enmark E, Häggblad J, et al. Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. Endocrinology 1997; 138: 863–70.

19. Shiau AK, Barstad D, Loria PM, et al. The structural basis of estrogen receptor/ co-activator recognition and the antagonism of this interaction by tamoxifen. Cell 1998; 95: 927–37.

20. Brzozowski AM, Pike AC, Dauter Z, et al. Molecular basis of agonism and antagonism in the oestrogen receptor. Nature 1997; 389: 753–8.

21. Paige LA, Christensen DJ, Grøn H, et al. Estrogen receptor (ER) modulators each induce distinct conformational changes in ERa and ERb. Proc Natl Acad Sci U S A 1999; 96: 3999–4004.

22. Pike ACW, Brzozowski AM, Walton J, et al. Structural insights into the mode of actio of a pure antiestrogen. Structure (Camb) 2001; 9: 145–53.

23. McKenna NJ, Lanz RB, O'Malley BW. Nuclear receptor coregulators: cellular and molecular biology. Endocr Rev 1999; 20: 321–44.

24. Smith CL, Nawaz Z, O'Malley BW. Co-activator and co-repressor regulation of the agonist/antagonist activity of the mixed antiestrogen, 4-hydroxytamoxifen. Mol Endocrinol 1997; 11: 657–66.

25. Norris JD, Paige LA, Christensen DJ, et al. Peptide antagonists of the human estrogen receptor. Science 1999; 285: 744–6.

26. Jepsen K, Hermanson O, Onami TM, et al. Combinatorial roles of the nuclear receptor corepressor in transcription and development. Cell 2000; 102: 753–63.

27. McCafferty MP, McNeill RE, Miller N, Kerin MJ. Interactions between the estrogen receptor, its cofactors and microRNAs in breast cancer. Breast Cancer Res Treat 2009; 116: 425–32.

28. McKenna NJ, Xu J, Nawaz Z, Tsai SY, Tsai MJ, O'Malley BW. Nuclear receptor co-activators: multiple enzymes, multiple complexes, multiple functions. J Steroid Biochem Mol Biol 1999; 69: 3–12.

29. Simoncini T, Mannella P, Fornari L, Caruso A, Varone G, Genazzani AR. Genomic and nongenomic effects of estrogens on endothelial cells. Steroids 2004; 69: 537–42.

30. Johnson SM, Maleki-Dizaji M, Styles JA, White IN. Ishikawa cells exhibit differential gene expression profiles in response to oestradiol or 4-hydroxytamoxifen. Endocr Relat Cancer 2007; 14: 337–50.

31. Shelly W, Draper MW, Krishnan V, Wong M, Jaffe RB. Selective estrogen receptor modulators: an update on recent clinical findings. Obstet Gynecol Surv 2008; 63: 163–81

32. Gorlitsky GA, Kase NG, Speroff L. Ovulation and pregnancy rates with clomiphene citrate. Obstet Gynecol 1978; 51: 265–9.

33. Homburg R. Clomiphene citrate – end of an era? A mini-review. Hum Reprod 2005; 20: 2043–-51.

34. Kurachi K, Aono T, Minagawa J, Miyake A. Congenital malformations of newborn infants after clomiphene-induced ovulation. Fertil Steril 1983; 40: 187–9.

35. Rossing MA, Daling JR, Weiss NS, Moore DE, Self SG. Ovarian tumours in a cohort of infertile women. N Engl J Med 1994; 331: 771–6.

36. Lal J. Clinical pharmacokinetics and interaction of centchroman – a mini review. Contraception 2010; 81: 275–80.

37. Singh MM. Centchroman, a selective estrogen receptor modulator, as a contraceptive and for the management of hormone-related clinical disorders. Med Res Rev 2001; 21: 302–47.

38. Kriplani A, Kulshrestha V, Agarwal N. Efficacy and safety of ormeloxifene in management of menorrhagia: a pilot study. J Obstet Gynaecol 2009; 35: 746–52.

39. Dhar A, Srivastava A. Role of centchroman in regression of mastalgia and fibroadenoma. World J Surg 2007; 31: 1180–6.

40. Misra NC, Nigam PK, Gupta R, Agarwal Ak and Kamboj VP. Centchroman – a non-steroidal anti-cancer agent for advanced breast cancer: Phase-II study. Int J Canc 1989; 43: 781–3.

41. Gara RK, Sundram V, Chauhan SC, Jaggi M. Anti-Cancer Potential of a Novel SERM Ormeloxifene. Curr Med Chem 2013; 20: 4177–84.

42. Narayana Murthy PS, Sengupta S, Sharma S, Singh MM. Effect of ormeloxifene on ovariectomyinduced bone resorption, osteoclast differentiation and apoptosis and TGF beta-3 expression. J Steroid Biochem Mol Biol 2006; 100: 117–28.

43. Kumar GR, Rituraj K, Hemant BK, Singh MM. In vitro anticancer breast activity of ormeloxifene is mediated via induction of apoptosis and autophagy. 37th annual conference of the endocrine society of India. November 30th–December 2nd, 2007. Abstract p35.

44. Nigam M, Ranjan V, Srivastava S, Sharma R, Balapure AK. Centchroman induces G0/G1 arrest and Caspase-dependent Apoptosis involving Mitochondrial Membrane Depolarization in MCF-7 and MDA MB-231 Human Breast Cancer Cells. Life Sci 2008; 82: 577–90.

45. Wu F. Ospemifene (Osphena®): A New Treatment for Dyspareunia and Vaginal Atrophy. Materia Medica 2013; 2: 5.

46. Product Information: OSPHENA® oral tablets, ospemifene. Shionogi Inc. (per manufacturer), Florham Park, NJ, USA, 2013.

47. Qu G, et al. Selective estrogenic effects of a novel triphenylethylene compound, FC1271a, on bone, cholesterol level, and reproductive tissues in intact and ovariectomized rats. Endocrinology 2000; 141: 809–20.

48. Maximov PY, Lee TM, Jordan VC. The discovery and development of selective estrogen receptor modulators (SERMs) for clinical practice. Curr Clin Pharmacol 2013; 8: 135–55.

49. Goldstein SR, Archer DF, Simon JA, Constantine G. Endometrial safety of ospemifene and the ability of transvaginal ultrasonography to detect small changes in endometrial thickness. Obstet Gynecol 2014; 123 (Suppl 1): 96S–97S.

50. Komi J, Heikkinen J, Rutanen EM, et al. Effects of ospemifene, a novel SERM, on biochemical markers of bone turnover in healthy postmenopausal women. Gynecol Endocrinol 2004; 18: 152–8.

51. Taras TL, Wurz GT, DeGregorio MW. In vitro and in vivo biologic effects of Ospemifene (FC-1271a) in breast cancer. J Steroid Biochem Mol Biol 2001; 77: 271–9.

52. Bachmann GA, Komi JO. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. Menopause 2010; 17: 480–6.

53. Portman DJ, Bachmann GA, Simon JA, et al. Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. Menopause 2013; 20: 623–30.

54. Portman D, Palacios S, Nappi RE, Mueck AO. Ospemifene, a non-oestrogen selective oestrogen receptor modulator for the treatment of vaginal dryness associated with postmenopausal vulvar and vaginal atrophy: A randomised, placebocontrolled, phase III trial. Maturitas 2014; 78: 91–8.

55. Goldstein SR, Bachmann GA, Koninckx PR, Lin VH, Portman DJ, et al. Ospemifene 12-month safety and efficacy in postmenopausal women with vulvar and vaginal atrophy. Climacteric 2014; 17: 173–82.

56. Simon JA, Lin VH, Radovich C et al. One year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus. Menopause 2013; 20: 418–27.

57. Vogel VG, Constantino JP, Wickerham DL, Cronin WM, Cecchini RS, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial. JAMA 2006; 295: 2727–41.

58. Seeman E, Crans GG, Diez-Perez A, Pinette KV, Delmas PD. Anti-vertebral fracture efficacy of raloxifene: a meta-analysis. Osteoporos Int 2006; 17: 313–6.

59. Delmas PD, Ensrud KE, Adachi JD, Harper KD, Sarkar S, et al. Mulitple Outcomes of Raloxifene Evaluation I. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. J Clin Endocrinol Metab 2002; 87: 3609–17.

60. Siris ES, Harris ST, Eastell R, Zanchetta JR, Goemaere S, et al. Continuing Outcomes Relevant to Evista I. Skeletal effects of raloxifene after 8 years: results from the continuing outcomes relevant to Evista (CORE) Study. J Bone Miner Res 2005; 20: 1514–24.

61. Neele SJ, Evertz R, De Valk-De Roo G, Roos JC, Netelenbos JC. Effect of 1 year of discontinuation of raloxifene or estrogen therapy on bone mineral density after 5 years of treatment in healthy postmenopausal women. Bone 2002; 30: 599–603.

62. Adomaityte J, Farooq M, Qayyum R. Effect of raloxifene therapy on venous thromboembolism in postmenopausal women. A meta-analysis. Thromb Haemost 2008; 99: 338–42.

63. Barrett-Connor E, Cox DA, Song J, Mitlak B, Mosca L, Grady D. Raloxifene and risk for stroke based on the framingham stroke risk score. Am J Med 2009; 122: 754–61.

64. Grady D, Cauley JA, Stock JL, Cox DA, Mitlak BH, Song J, Cummings SR. Effect of Raloxifene on all-cause mortality. Am J Med 2010; 123: 469 e1–7.

65. Brown M, et al. Is the breast cancer drug tamoxifen being sold as a bodybuilding dietary supplement? BMJ 2014; 348: g1476.

66. Desta Z, Ward BA, Soukhova NV, Flockhart DA. Comprehensive evaluation of tamoxifen sequential biotransformation by the human cytochrome P450 system in vitro: prominent roles for CYP3A and CYP2D6. J Pharmacol Exp Ther 2004; 310: 1062–75.

67. Wang DY, Fulthorpe R, Liss SN, Edwards EA. Identification of estrogen-responsive genes by complementary deoxyribonucleic acid microarray and characterization of a novel early estrogen-induced gene: EEIG1. Mol Endocrinol 2004; 18: 402–11.

68. Massarweh S, Osborne CK, Creighton CJ, Qin L, Tsimelzon A. Tamoxifen resistance in breast tumours is driven by growth factor receptor signalling with repression of classic estrogen receptor genomic function. Cancer Res 2008; 68: 826–33.

69. Hurtado A, Holmes KA, Geistlinger TR, Hutcheson IR, Nicholson RI, et al. Regulation of ERBB2 by oestrogen receptor-PAX2 determines response to tamoxifen. Nature 2008; 456: 663–6.

70. Osborne CK, Bardou V, Hopp TA, Chamness GC, Hilsenbeck SG, et al. Role of the estrogen receptor coactivator AIB1 (SRC-3) and HER-2/neu in tamoxifen resistance in breast cancer. J Natl Cancer Inst 2003; 95: 353–61.

71. Early Breast Cancer Trialists' Collaborative, Davies C, Godwin J, Gray R, Clarke M, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011; 378: 771–84.

72. Bardou VJ, Arpino G, Elledge RM, Osborne CK, Clark GM. Progesterone receptor status significantly improves outcome prediction over estrogen receptor status alone for adjuvant endocrine therapy in two large breast cancer databases. J Clin Oncol 2003; 15: 1973–9.

73. Arpino G, Weiss H, Lee AV, Schiff R, De Placido S, et al. Estrogen receptor-positive, progesterone receptor-negative breast cancer: association with growth factor receptor expression and tamoxifen resistance. J Natl Cancer Inst 2005; 97: 1254–61.

74. Gross GE, Clark GM, Chamness GC, McGuire WL. Multiple progesterone receptor assays in human breast cancer. Cancer Res 1984; 44: 836–40.

75. Ring A, Dowsett M. Mechanisms of tamoxifen resistance. Endocr Relat Cancer 2004; 11: 643–58.

76. Lammers LA, Mathijssen RH, van Gelder T, Bijl MJ, de Graan AJ, et al. The impact of CYP2D6-predicted phenotype on tamoxifen treatment outcome in patients with metastatic breast cancer. Br J Cancer 2010; 103: 765–71.

77. Goetz MP, Rae JM, Suman VJ, Safgren SL, Ames MM, et al. Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. J Clin Oncol 2005; 23: 9312–8.

78. Beverage JN, Sissung TM, Sion AM, Danesi R, Figg WD. CYP2D6 polymorphisms and the impact on tamoxifen therapy. J Pharm Sci 2007; 96: 2224–31.

79. Schroth W, Goetz MP, Hamann U, Fasching PA, Schmidt M, et al. Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. JAMA 2009; 302: 1429–36.

80. Jin Y, Desta Z, Stearns V, Ward B, Ho H, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst 1997; 97: 30–9.

81. Aubert RE, StanekEJ, Yao J, Teagarden JR, Subar M, et al. Risk of breast cancer recurrence in women initiating tamoxifen with CYP2D6 inhibitors. J Clin Oncol 2009; 27: 18 (suppl; abstr CRA508).

82. Dezentje V, Van Blijderveen NJ, Gelderblom H, Putter H, Van Herk, et al. Concomitant CYP2D6 inhibitor use and tamoxifen adherence in early-stage breast cancer: A pharmacoepidemiologic study. J Clin Oncol 2009; 27: 18 (suppl; abstr CRA509).

83. Kelly CM, Juurlink DN, Gomes T, Duong-Hua M, Pritchard KI, et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. BMJ 2010; 8: 340.

84. Cuzick J, Powles T, Veronesi U. Overview of the main outcomes in breast-cancer prevention trials. Lancet 2003; 361: 296–300.

85. Steiner E, Juhasz-Bösz I, Emons G, Kölbl H, Kimmig R, Mallmann P, and fort the AGO Uterus of the DGGG. Transvaginal Ultrasound for Endometrial Carcinoma Screening – Current Evidence-based Data. Geburtshilfe Frauenheilkd 2012; 72: 1088–91.

86. Gerber B. Endometrium-Veränderungen unter Tamoxifen. Frauenarzt 2005; 46: 1054–8.

87. Gerber B, Krause A, Muller H, et al. Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective longterm study using transvaginal ultrasound. J Clin Oncol 2000; 18: 3464–70.

88. Archer DF, Pinkerton JV, Utian WH, Menegoci JC, de Villiers TJ, et al. Bazedoxifene, a selective estrogen receptor modulator: effects on the endometrium, ovaries, and breast from a randomized controlled trial in osteoporotic postmenopausal women. Menopause 2009; 16: 1109–15.

89. Lobo RA, Pinkerton JV, Gass ML, Dorin MH, Ronkin S, et al. Evaluation of bazedoxifene/conjugated estrogens for the treatment of menopausal symptoms and effects on metabolic parameters and overall safety profile. Fertil Steril 2009; 92: 1025–38.

90. Pinkerton JV, Harvey JA, Lindsay R, Pan K, Chines AA, et al, SMART-5 Investigators. Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: a randomized trial. J Clin Endocrinol Metab 2014; 99: E189–98.

91. Pinkerton JV, Abraham L, Bushmakin AG, Cappelleri JC, Racketa J, et al. Evaluation of the efficacy and safety of bazedoxifene/conjugated estrogens for secondary outcomes including vasomotor symptoms in postmenopausal women by years since menopause in the Selective estrogens, Menopause and Response to Therapy (SMART) trials. J Womens Health (Larchmt) 2014; 23: 18–28.

92 .Kagan R. The tissue selective estrogen complex: a novel approach to the treatment of menopausal symptoms. J Womens Health (Larchmt) 2013: 21: 975–81.

93. Mirkin S, Archer DF, Taylor HS, Pickar JH, Komm BS. Differential effects of menopausal therapies on the endometrium. Menopause 2014; 899–908.

94. Somjen D, Katzburg S, Knoll E, et al. DT56a (Femarelle®): a natural selective estrogen receptor modulator (SERM). J Steroid Biochem Mol Biol 2007; 104: 252–8.

95. Somjen D, Yoles I. DT56a stimulates creatine kinase specific activity in vascular tissues of rats. J Endocrinol Invest 2003; 26: 966–71.

96. Yoles I, Yogev Y, Frenkel Y, Hirsch M, Nahum R, Kaplan B. Efficacy and safety of standard versus low-dose Femarelle® (DT56a) for the treatment of menopausal symptoms. Clin Exp Obstet Gynecol 2004; 31: 123–6.

97. Yoles I, Yogev Y, Frenkel Y, Nahum R, Hirsch M, Kaplan B. Tofupill/Femarelle® (DT56a): a new phyto-selective estrogen receptor modulatorlike substance for the treatment of postmenopausal bone loss. Menopause 2003; 10: 522–5.

98. Yoles I, Lilling G. Pharmacological doses of the natural phyto-SERM DT56a (Femarelle®) have no effect on MCF-7 human breast cancer cell-line. Eur J Obstet Gynecol Reprod Biol 2007; 130: 140–1.

99. Oropeza MV, Orozco S, Ponce H, Campos MG. Tofupill lacks peripheral estrogen-like actions in the rat reproductive tract. Reprod Toxicol 2005; 20: 261–6.

100. Somjen D, Katzburg S, Lieberherr M, Hendel D, Yoles I. DT56a stimulates gender-specific human cultured bone cells in vitro. J Steroid Biochem Mol Biol 2006; 98: 90–6.

101. Nachtigall MJ, Jessel RH, Flaumenhaft R, Nachtigall R, Yoles I, et al. The selective estrogen receptor modulator DT56a (Femarelle®) does not affect platelet reactivity in normal or thrombophilic postmenopausal women. Menopause 2010; 18: 1–4.

102. Overk CR, Peng KW, Asghodom RT, et al. Structure-activity relationships for a family of benzothiophene selective estrogen receptor modulators including raloxifene and arzoxifene. Chem Med 2007; 2: 1520–6

103. Bolognese M, Krege JH, Utian WH, Feldman R, Broy S, et al. Effects of arzoxifene on bone mineral density and endometri-

um in postmenopausal women with normal or low bone mass. J Clin Endocrinol Metab 2009; 94: 2284–9.

104. https://investor.lilly.com/releasedetail.cfm?ReleaseID=403905

105. Hendrix SL, McNeeley SG. Effect of selective estrogen receptor modulators on reproductive tissues other than endometrium. Ann N Y Acad Sci 2001; 949: 243–50.

106. Lednicer D, Emmert DE, Lyster SC, Duncan GW. Mammalian antifertility agents. VI. A novel sequence for the preparation of 1,2-disubstituted 3,4-dihydronaphthalenes. J Med Chem 1969; 12: 881–5.

107. Gennari L, Merlotti D, Martini G, Nuti R. Lasofoxifene: a third-generation selective estrogen receptor modulator for the prevention and treatment of osteoporosis. Expert Opin Investig Drugs 2006; 15: 1091–3.

108. Cummings SR, Ensrud K, Delmas PD, LaCroix AZ, Vukicevic S, et al.; PEARL Study Investigators. Lasofoxifene in postmenopausal women with osteoporosis. N Engl J Med 2010; 362: 686–96.

109. Ensrud K, LaCroix A, Thompson JR, Thompson DD, Eastell R, et al. Lasofoxifene and cardiovascular events in postmenopausal women with osteoporosis: Five year results from the Postmenopausal Evaluation and Risk Reduction with Lasofoxifene. Circulation 2010; 122: 1716–24.

110. Sadler TM, Gavriil M, Annable T, Frost P, Greenberger LM, Zhang Y. Combination therapy for treating breast cancer using antiestrogen, ERA-923, and the mammalian target of rapamycin inhibitor, temsirolimus. Endocr Relat Cancer 2006; 13: 863–73.

111. Greenberger LM, Tami A, Collins KI, Komm BS, et al. A new antiestrogen, 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol hydrochloride (ERA-923), inhibits the growth of tamoxifen-sensitive and -resistant tumours and is devoid of uterotropic effects in mice and rats. Clin Cancer Res 2001; 7: 3166–77.

112. Cotreau MM, Stonis L, Dykstra KH, Gandhi T, Gutierrez M, et al. Multiple-dose, safety, pharmacokinetics, and pharmacodynamics of a new selective estrogen receptor modulator, ERA-923, in healthy postmenopausal women. J Clin Pharmacol 2002; 42: 157–65.

113. Burke TW, Walker CL. Arzoxifene as therapy for endometrial cancer. Gynecol Oncol 2003; 90: S40–S46.

114. Earl H, Gray R, Kerr D, Lee M. The optimal duration of adjuvant tamoxifen treatment for breast cancer remains uncertain: randomize into aTTom. Clin Oncol (R Coll Radiol) 1997; 9: 141–3.

115. Cuzick J. Chemoprevention of breast cancer with tamoxifen. In: Hakama M, Beral V, Buiatti E, Faivre J, Parkin DM (eds). Chemoprevention in cancer control. International Agency for Research on Cancer, Lyon, France; 1996: 95–109.

116. Wickerham DL, Tan-Chiu E. Breast cancer chemoprevention: current status and future directions. Semin Oncol 2001; 28: 253–9.

117. Martino S, Cauley JA, Barrett-Connor E, Powles TJ, Mershon J, et al. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. J Natl Cancer Inst 2004; 96: 1751–61.

118. Mosca L, Barrett-Connor E, Wenger NK, et al. Design and methods of the Raloxifene Use for the Heart (RUTH) study. Am J Cardiol 2001; 88: 392–5.

119. Moegele M, Buchholz S, Seitz S, Ortmann O. Vaginal estrogen therapy in postmenopausal breast cancer patients treated with aromatase inhibitors. Arch Gynecol Obstet 2012; 285: 1397–402.

120. Beral V, Reeves G, Bull D, Green J; Million Women Study Collaborators. Breast cancer risk in relation to the interval between menopause and starting hormone therapy. J Natl Cancer Inst 2011; 103: 296–305.

121. Chlebowski RT, Manson JE, Anderson GL, Cauley JA, Aragaki AK, et al. Estrogen plus progestin and breast cancer incidence and mortality in the Women's Health Initiative Observational Study. J Natl Cancer Inst 2013; 105: 526–35.

122. Deroo BJ, Korach KS. Estrogen receptors and human disease. J Clin Invest 2006; 116: 61–7.

123. Visvanathan K, Chlebowski RT, Hurley P, Col NF, Ropka M, et al. American society of clinical oncology clinical practice guideline update on the use of pharmacologic interventions including tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction. J Clin Oncol 2009; 27: 3235–58.

124. Gennari L, Merlotti D, Nuti R. Selective estrogen receptor modulator (SERM) for the treatment of osteoporosis in postmenopausal women: focus on lasofoxifene. Clin Interv Aging 2010; 5: 19–29.

125. Palacios S, de Villiers TJ, Nardone Fde C, Levine AB, Williams R, et al. Assessment of the safety of longterm bazedoxifene treatment on the reproductive tract in postmenopausal women with osteoporosis: results of a 7-year, randomized, placebo-controlled, phase 3 study. Maturitas 2013; 76: 81–7.

126. Pinkerton JV, Harvey JA, Pan K, Thompson JR, Ryan KA, et al. Breast effects of bazedoxifene-conjugated estrogens: a randomized controlled trial. Obstet Gynecol 2013; 121: 959–68.

127. Zreik TG, Mazloom A, Chen Y, Vannucci M, Pinnix CC, et al. Fertility drugs and the risk of breast cancer: a metaanalyses and review. Breast Cancer Res Treat 2010; 124: 13–26.

128. Gara RK, Sundram V, Chauhan SC, Jaggi M. Anticancer potential of a novel SERM ormeloxifene. Curr Med Chem 2013; 20: 4177–84.

129. Tejwani PL, Srivastava A, Nerkar H, Dhar A, Hari S, et al. Centchroman regresses mastalgia: a randomized comparison with danazol. Indian J Surg 2011; 73: 199–205.

130. Wurz GT, Soe LH, Degregorio MW. Ospemifene, vulvovaginal atrophy, and breast cancer. Maturitas 2013; 74: 220–5.

131. Berga SL. Profile of ospemifene in the breast. Reprod Sci 2013; 20: 1130–6.

132. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing breast cancer. Cancer Prev Res (Phila) 2010; 3: 696–706.

133. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998; 90: 1371–88.

134. Powles T, Eeles R, Ashley S, et al. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. Lancet 1998; 352: 98–101.

135. Veronesi U, Maisonneuve P, Costa A, et al. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women: Italian Tamoxifen Prevention Study. Lancet 1998; 352: 93–7.

136. IBIS Investigators. First results from the International Breast Cancer Intervention study (IBIS-I): a randomised prevention trial. Lancet 2002; 360: 817–24.

137. Fisher B, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 2005; 97: 1652–62.

138. Cuzick J, Forbes J, Edwards R, Baum M, Cawthorn S, et al. First results from the International Breast Cancer Intervention Study (IBIS-I): a randomised prevention trial. Lancet 2002; 360: 817–24.

139. Powles TJ, Ashley S, Tidy A, Smith IE, Dowsett M. Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. J Natl Cancer Inst 2007; 99: 283–90.

140. Veronesi U, Maisonneuve P, Rotmensz N, Bonanni B, Boyle P, et al. Tamoxifen for the prevention of breast cancer: late results of the Italian Randomized Tamoxifen Prevention Trial among women with hysterectomy. J Natl Cancer Inst 2007; 99: 727–37.

141. Nelson HD, Smith ME, Griffin JC, Fu R. Use of medications to reduce risk for primary breast cancer: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2013; 158: 604–14.

142. Riggs BL, Khosla S, Melton LJ III. Sex steroids and the construction and conservation of the adult skeleton. Endocr Rev 2002; 23: 279–302.

143. Gustafsson JA. Estrogen receptor β – a new dimension in estrogen mechanism of action. J Endocrinol 1999; 163: 379–83.

144. Bord S, Horner A, Beavan S, Compston J. Estrogen receptors a and b are differentially expressed in developing human bone. J Clin Endocrinol Metab 2001; 86: 2309–14.

145. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002; 288: 321–33.

146. Reginster JY, Ferrari S, Hadji P. Current challenges in the treatment of osteoporosis: an opportunity for bazedoxifene. Curr Med Res Opin 2014; 1165–76.

147. Ellis AG, Reginster JY, Luo X, Bushmakin A, Williams R, et al. Indirect comparison of bazedoxifene vs oral bisphosphonates for the prevention of vertebral fractures in postmenopausal osteoporotic women. Curr Med Res Opin 2014; 1617–26.

148. Narayana Murthy PS, Sengupta S, Sharma S, Singh MM. Effect of ormeloxifene on ovariectomy-induced bone resorption, osteoclast differentiation and apoptosis and TGF beta-3 expression. J Steroid Biochem Mol Biol 2006; 100: 117–28.

149. Kharkwal G, Chandra V, Fatima I and Dwivedi A. Ormeloxifene inhibits osteoclast differentiation in parallel to downregulating RANKL induced ROS generation and suppressing the activation of ERK and JNK in murine RAW264.7 cells. J Mol Endocrinol 2012; 48: 261–70.

150. Kangas L, Härkönen P, Väänänen K, Peng Z. Effects of the selective estrogen receptor modulator ospemifene on bone in rats. Horm Metab Res 2014; 46: 27–35.

151. Komi J, Heikkinen J, Rutanen EM, Halonen K, Lammintausta R, Ylikorkala O. Effects of ospemifene, a novel SERM, on biochemical markers of bone turnover in healthy postmenopausal women. Gynecol Endocrinol 2004; 18: 152–8.

152. Komi J, Lankinen KS, DeGregorio M, Heikkinen J, Saarikoski S, et al. Effects of ospemifene and raloxifene on biochemical markers of bone turnover in postmenopausal women. J Bone Miner Metab 2006; 24: 314–8.

153. Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. N Engl J Med 1997; 337: 1641–7.

154. Lufkin EG, Whitaker MD, Nickelsen T, et al. Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial. J Bone Miner Res 1998; 13: 1747–54.

155. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. JAMA 1999; 282: 637–45.

156. Johnston CC Jr, Bjarnason NH, Cohen FJ, et al. Long-term effects of raloxifene on bone mineral density, bone turnover, and serum lipid levels in early postmenopausal women: three-year data from 2 double-blind, randomized, placebo-controlled trials. Arch Intern Med 2000; 160: 3444–50.

157. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998; 280: 2077–82.

158. Reginster JY, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Osteoporos Int 2000; 11: 83–91.

159. Liberman UA, Weiss SR, Bröll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. N Engl J Med 1995; 333: 1437–43.

160. Fogelman I, Ribot C, Smith R, Ethgen D, Sod E, Reginster JY. Risedronate reverses bone loss in postmenopausal women with low bone mass: results from a multinational, double-blind, placebo-controlled trial. J Clin Endocrinol Metab 2000; 85: 1895–900.

161. Riggs BL, Hartmann LC. Selective estrogenreceptor modulators – mechanisms of action and application to clinical practice. N Engl J Med 2003; 348: 618–29.

162. Jordan VC, Phelps E, Lindgren JU. Effects of antiestrogens on bone in castrated and intact female rats. Breast Cancer Res Treat 1987; 10: 31–5.

163. Turner RT, Wakley GK, Hannon KS, Bell NH. Tamoxifen inhibits osteoclast-mediated resorption of trabecular bone in ovarian hormone- deficient rats. Endocrinology 1988; 122: 1146–50.

164. Turken S, Siris E, Seldin D, Flaster E, Hyman G, Lindsay R. Effects of tamoxifen on spinal bone density in women with breast cancer. J Natl Cancer Inst 1989; 81: 1086-8.

165. Love RR, Mazess RB, Barden HS, et al. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. N Engl J Med 1992; 326: 852–6.

166. Kristensen B, Ejlertsen B, Mouridsen HT, Andersen KW, Lauritzen JB. Femoral fractures in postmenopausal breast cancer patients treated with adjuvant tamoxifen. Breast Cancer Res Treat 1996; 39: 321–6.

167. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998; 90: 1371–88.

168. Marttunen MB, Hietanen P, Tiitinen A, Ylikorkala O. Comparison of effects of tamoxifen and toremifene on bone biochemistry and bone mineral density in postmenopausal breast cancer patients. J Clin Endocrinol Metab 1998; 83: 1158–62.

169. Nastri CO, Lara LA, Ferriani RA, Rosa-E-Silva AC, Figueiredo JB, Martins WP. Hormone therapy for sexual function in perimenopausal and postmenopausal women. Cochrane Database Syst Rev 2013; 6: CD009672.

170. Le Ray I, Dell'Aniello S, Bonnetain F, Azoulay L, Suissa S. Local estrogen therapy and risk of breast cancer recurrence among hormone-treated patients: a nested case-control study. Breast Cancer Res Treat 2012; 135: 603–9.

171. Carneiro AL, de Cassia de Maio Dardes R, Haidar MA. Estrogens plus raloxifene on endometrial safety and menopausal symptoms – semisystematic review. Menopause 2012; 19: 830–4.

172. Kagan R, Williams RS, Pan K, Mirkin S, Pickar JH. A randomized, placebo- and active-controlled trial of bazedoxifene/conjugated estrogens for treatment of moderate to severe vulvar/vaginal atrophy in postmenopausal women. Menopause 2010; 17: 281–9.

173. Bachmann G, Bobula J, Mirkin S. Effects of bazedoxifene/conjugated estrogens on quality of life in postmenopausal women with symptoms of vulvar/vaginal atrophy. Climacteric 2010; 13: 132–40.

174. Gass M, Portman D, Moffett A, Symons J. Clinical signs of vaginal strophy are improved by the SERM, lasofoxifene. Menopause 2004; 11: 670–7.

175. Bachmann G, Portman D, Bachmann G, Moffett A, Symons J. Lasofoxifene improves symptoms associated with vaginal atrophy. Menopause 2004; 116: 69–77.

176. Simon J, Gass M, Kagan R, Spino C, Nemeth MA. Lasofoxifene effectively treats dyspareunia in postmenopausal women with vaginal atrophy. Obstet Gynecol 2005; 105: 2–4.

177. Glusman JE, Huster WJ, Paul S. Raloxifene effects on vasomotor and other climacteric symptoms in postmenopausal women. Prim Care Update Ob Gyns 1998; 5: 166.

178. Zeyneloglu HB, Oktem M, Haberal NA, Esinler I, Kuscu E. The effect of raloxifene in association with vitamin D on vaginal maturation index and urogenital symptoms in postmenopausal osteoporotic women. Fertil Steril 2007; 88: 530–2.

179. Checa MA, Garrido A, Prat M, Conangla M, Rueda C, Carreras R. A comparison of raloxifene and calcium plus Vitamin D on vaginal atrophy after discontinuation of long-standing postmenopausal hormone therapy in osteoporotic women A randomized, masked-evaluator, one-year, prospective study. Maturitas 2005; 52: 70–7.

180. Delmanto A, Nahas-Neto J, Nahas EA, de Oliveira ML, Fernandes CE, Traiman P. Effect of raloxifene on the vaginal epithelium of postmenopausal women. Eur J Obstet Gynecol Reprod Biol 2008; 139: 187–92.

181. Kessel B, Nachtigall L, Plouffe L, Siddhanti S, Rosen A, Parsons A. Effect of raloxifene on sexual function in postmenopausal women. Climacteric 2003; 6: 248–56.

182. Parsons A, Merritt D, Rosen A, Heath H 3rd, Siddhanti S, Plouffe L. Effect of raloxifene on the response to conjugated estrogen vaginal cream or nonhormonal moisturizers in postmenopausal vaginal atrophy. Obstet Gynecol 2003; 101: 346–52.

183. Yldirim Y, Toz E. The effect of long-term tamoxifen usages on the lower part of the female genital tract in breast cancer survivors: a review. Marmara Med J 2001; 20: 196–201.

184. Mourits MJE, De Vries EGE, Willemse PHB, Ten Hoor KA, Hollema H, Van der Zee AGJ. Tamoxifen treatment and gynecologic side effects: A review. Obstet Gynecol 2001; 97: 855–66.

185. Polin SA, Ascher SM. The effect of tamoxifen on the genital tract. Cancer Imaging 2008; 8: 135–45.

186. Marttunen MB, Cacciatore B, Hietanen P, Pyrhönen S, Tiitinen A, et al. Prospective study on gynaecological effects of two antioestrogens tamoxifen and toremifene in postmenopausal women. Br J Cancer 2001; 84: 897–902.

187. Hadji P. The evolution of selective estrogen receptor modulators in osteoporosis therapy. Climacteric 2012; 15: 513–23.

188. Grady D, Ettinger B, Moscarelli E, Plouffe L Jr, Sarkar S, et al. Multiple Outcomes of Raloxifene Evaluation Investigators. Safety and adverse effects associated with raloxifene: multiple outcomes of raloxifene evaluation. Obstet Gynecol 2004; 104: 837–44.

189. Miller PD, Chines AA, Christiansen C, Hoeck HC, Kendler DL, et al. Effects of bazedoxifene on BMD and bone turnover in postmenopausal women: 2-year results of a randomized, double-blind, placebo-, and activecontrolled study. J Bone Miner Res 2008; 23: 525–35.

190. Christiansen C, Chesnut CH III, Adachi JD, et al. Safety of bazedoxifene in a randomized, double-blind, placebo- and activecontrolled phase 3 study of postmenopausal women with osteoporosis. BMC Musculoskelet Disord 2010; 11: 130.

191. Martino S, Disch D, Dowsett SA, Keech CA, Mershon JL. Safety assessment of raloxifene over eight years in a clinical trial setting. Curr Med Res Opin 2005; 21: 1441–52.

192. de Villiers TJ, Chines AA, Palacios S, et al. Safety and tolerability of bazedoxifene in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled phase 3 trial. Osteoporos Int 2011; 22: 567–76.

193. Hadji P. The evolution of selective estrogen receptor modulators in osteoporosis therapy. Climacteric 2012; 15: 513–23.

194. Panda SN. Selective estrogen receptor modulators. Lecture at the 45th All India Congress of Obstretrics and Gynecology, Bhubanseswar, India. January 9th, 2002. http://www.powershow.com/view/26505-MzU5M/SELECTIVE_ESTROGEN_RECEPTOR_MODULATORS_powerpoint_ppt_presentation

195. Badger AM, Blake SM, Dodds RA, Griswold DE, Swift BA, et al. Idoxifene, a novel selective estrogen receptor modulator, is effective in a rat model of adjuvant-induced arthritis. J Pharmacol Exp Ther 1999; 291: 1380–6.

196. Bruning PF. Droloxifene, a new anti-oestrogen in postmenopausal advanced breast cancer: preliminary results of a double-blind dose-finding phase II trial. Eur J Cancer 1992; 28A: 1404–7.

197. Huang Y, Shen Y, Feng Y, Cao L, Leng Y. Antiimplantation effect of droloxifene in rats and its relationship with anti-estrogenic activity. Acta Pharmacol Sin 2005; 26: 1243–7.

198. Mansel R, Goyal A, Nestour EL, Masini-Etévé V, O'Connell K. A phase II trial of Afimoxifene (4-hydroxytamoxifen gel) for cyclical mastalgia in premenopausal women. Breast Cancer Res Treat 2007; 106: 389–97.

199. Lu WJ, Xu C, Pei Z, Mayhoub AS, Cushman M, Flockhart DA. The tamoxifen metabolite norendoxifen is a potent and selective inhibitor of aromatase (CYP19) and a potential lead compound for novel therapeutic agents. Breast Cancer Res Treat 2012; 133: 99–109.

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