



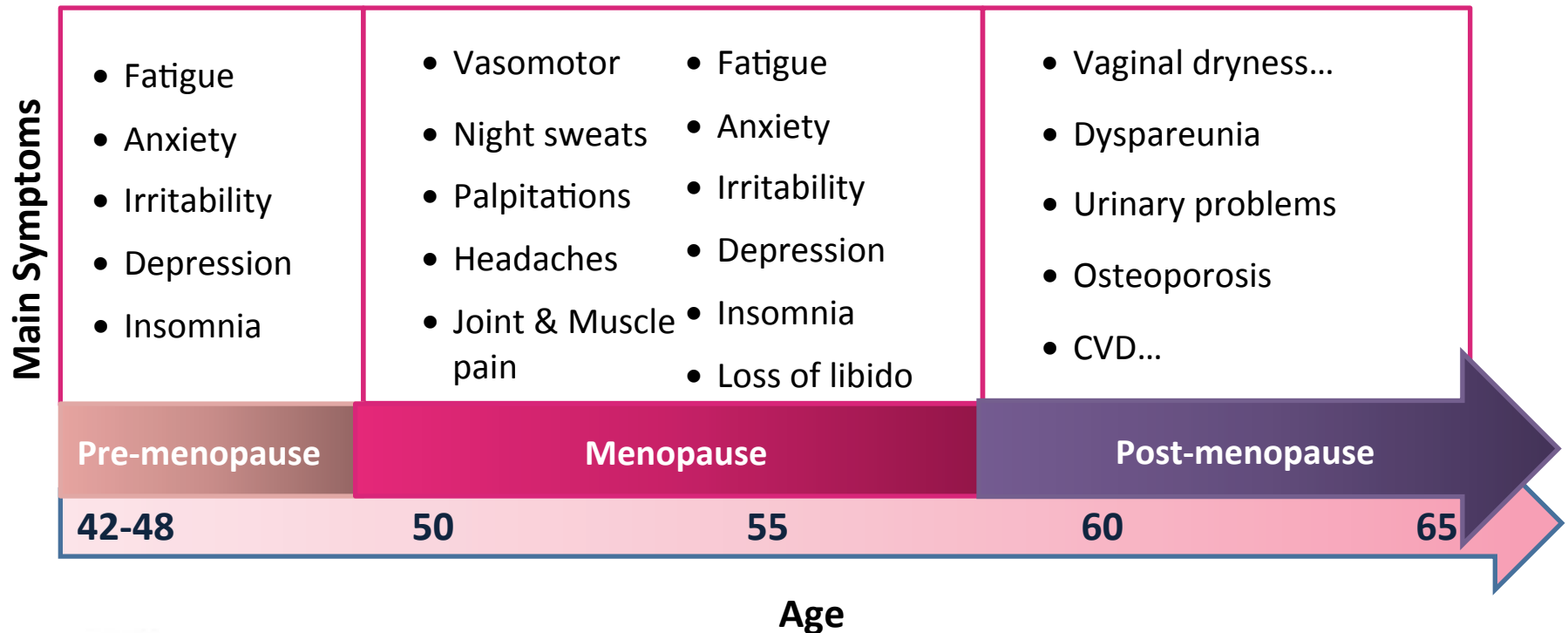
# Femarelle® a Treatment Option for Menopausal Patients



Marina Šprem Goldštajn  
Medical School University of  
Zagreb

# The Need Symptoms/Time Line

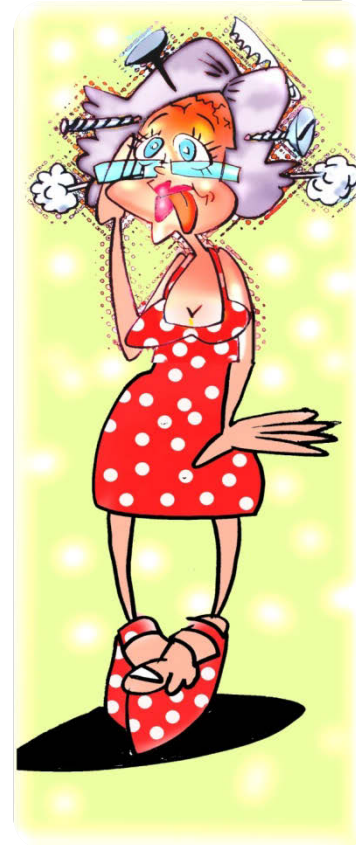
The decline in estrogen levels accompany women from pre-menopause onward



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## Menopause and its Symptoms

- Age ~ 50
- Decline in estrogen levels
- About 80% of women, at the peak of life
- Several to many years
- Main Symptoms:
  - Hot flashes
  - Vaginal dryness
  - Mood Disorders
  - Sleep disturbances
  - Loss of libido
  - Cognitive decline



Reduced Q O L ↓ ↓ ↓



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# Life Expectancy & Menopause

- Life expectancy of women in: Croatia- 80.3
- The average age for menopause is around 50
- Women are living at least one third of their lives after menopause
- The decrease in estrogen levels leads to:
  - Menopausal symptoms short & long term
  - Post-menopausal diseases (osteoporosis, CVD)



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# Osteoporosis Facts

- Women and men alike begin to lose bone in their mid-30s; as they approach menopause, women lose bone at a greater rate, from 2-3 per cent per year.
- Based on data collected in 2010, 22 million women and 5.5 million men in the EU27 have osteoporosis;
- 3.5 million new fragility fractures are sustained annually, comprising 610,000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures and 1,800,000 other fractures;
- The annual direct economic burden of new and prior fragility fractures is € 37 billion;
- The costs of fragility fractures are expected to increase by 25% from 2010 to 2025;



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## Osteoporosis in Croatia

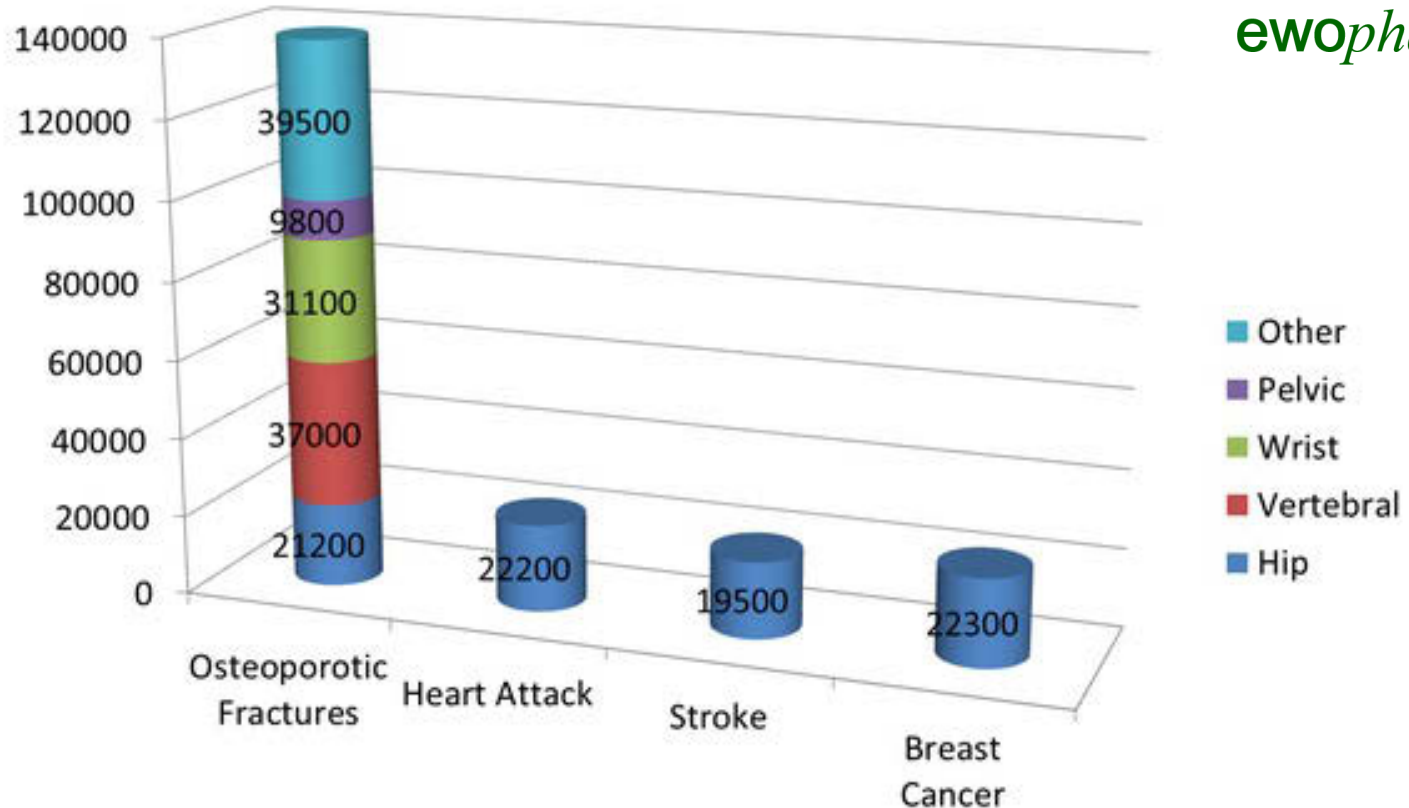
- Epidemiological data show that the prevalence of osteoporosis in Croatia is similar to other European countries
- While the prevalence and incidence of osteoporotic fractures is somewhat higher.
- In 2004, 0.70 % of all registered diseases in Croatia referred to osteoporosis and osteomalacia.
- The most important risk factors for osteoporosis are age, heredity, lifestyle, chronic diseases, hormonal abnormalities and physical characteristics of bone.
- Like in other chronic diseases, **prevention measures are most important for disease control.**



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# Annual Incidence of Common Diseases

*ewopharma*



- Fractures from osteoporosis are more common than heart attack, stroke and breast cancer combined.
- Osteoporotic hip fractures consume more hospital bed days than stroke, diabetes, or heart attack.

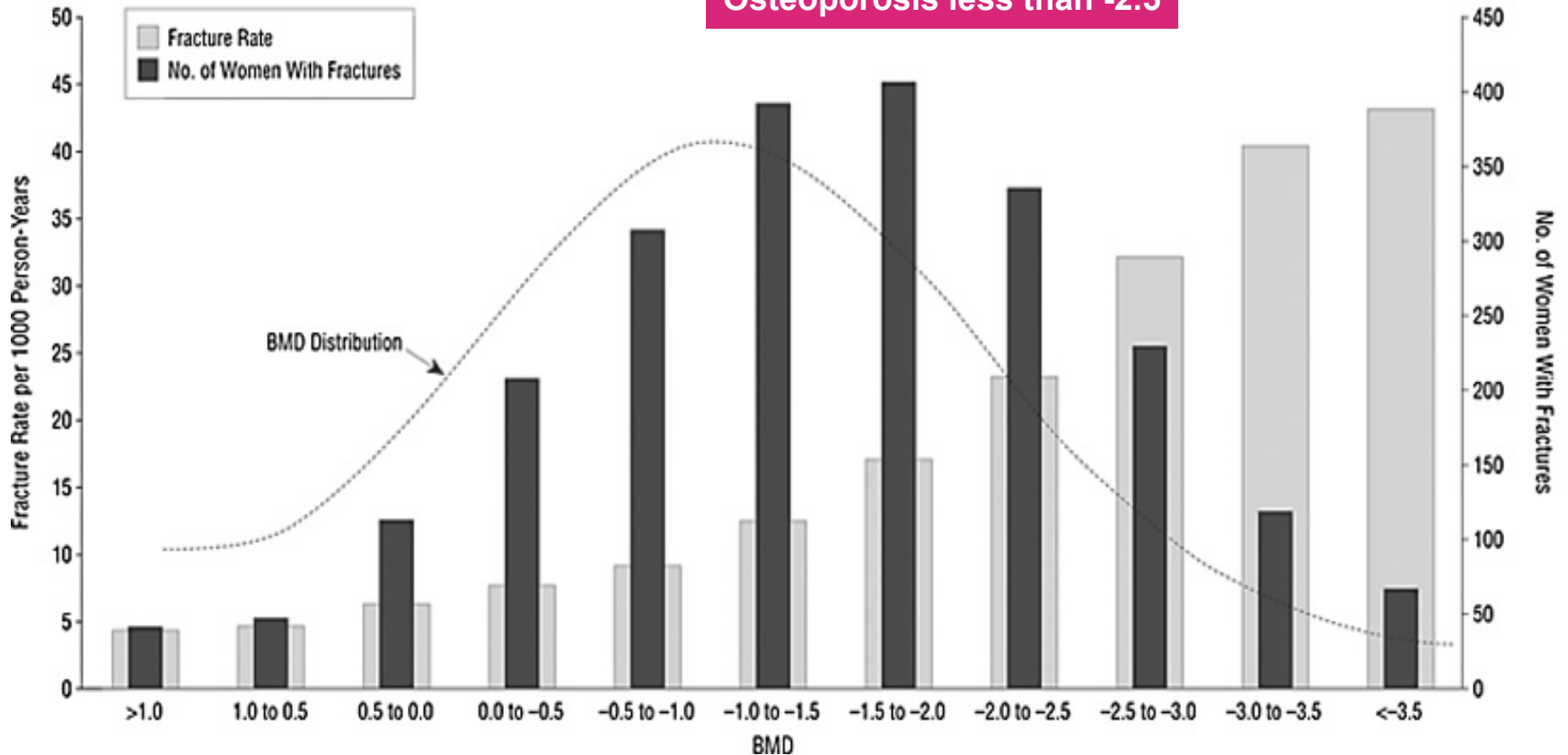


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<http://www.osteoporosis.ca>

# The number of fractures is highest in women with Osteopenia

Normal bone -1 to +1  
 Osteopenia -1.0 to -2.5  
 Osteoporosis less than -2.5



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Siris ES, et al. Arch Intern Med 164:1108-1112 (based on National Osteoporosis Risk Assessment study- JAMA 2001;286:2815-2822)

## Hormone Therapy Dilemma

- Main reason to search for treatment - Hot flushes
  - Occurs in 60%-80% of women during menopause
  - May occur dozens of times per day
  - 20% of women rate their flushes as being very severe and causing significant impairment
  - Most hot flushes will subside in 3 to 5 years, but in 10% of women they persist for 15 years or more
- Prolonged treatment crucial for the prevention of chronic conditions
  - Bone loss which leads to osteopenia & osteoporosis
  - Vagina dryness (atrophy)
  - Urinary problems based on change of pH levels

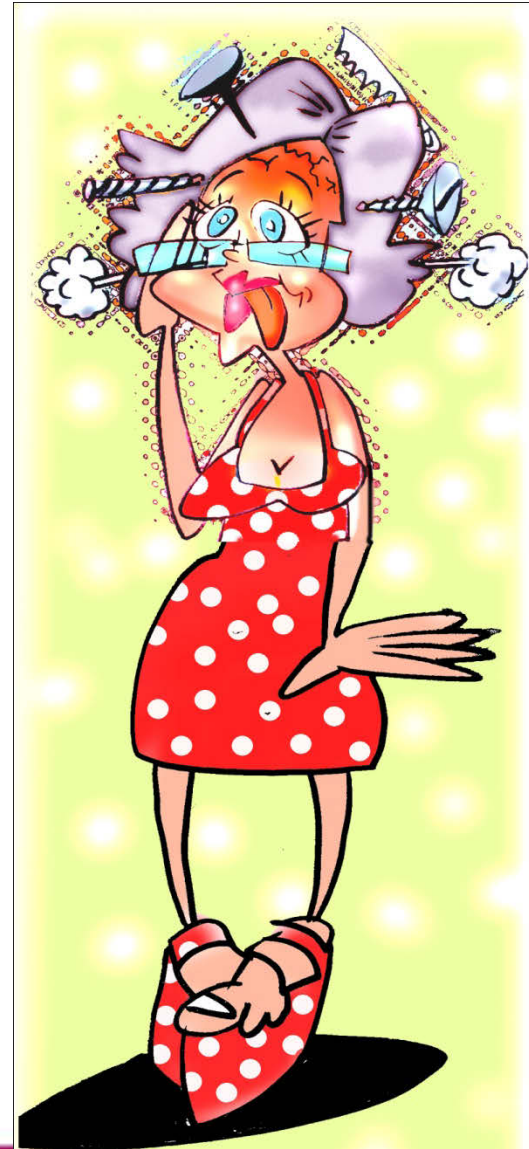


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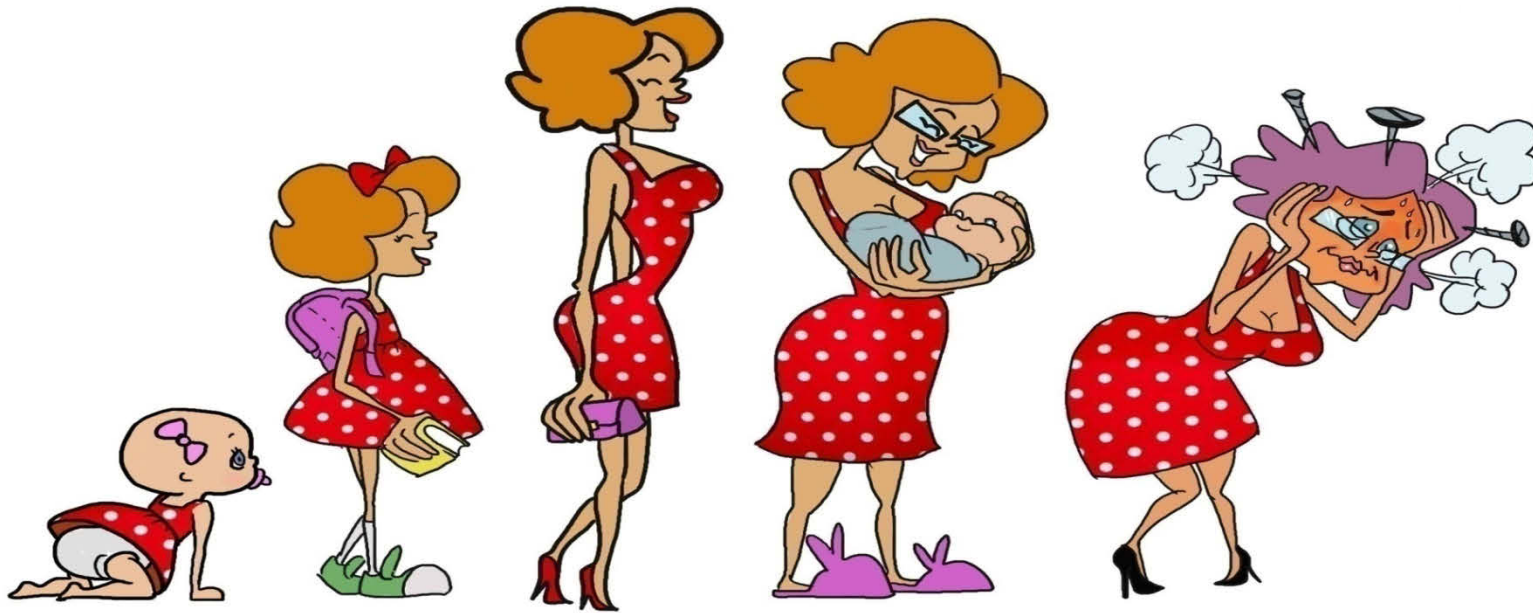
# The Menopause Market Today

## The Women's Perspective

- Media has brought a lot of confusion with the publication of the WHI data in 2002
- Basically the decision is led by her concern over the risks of the treatment
- Creating a most dominant category where the patient = consumer, plays a most dominant role in the decision making process

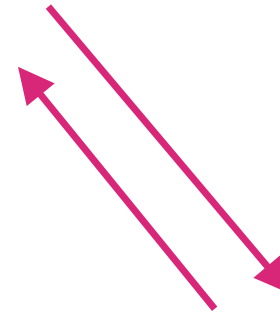
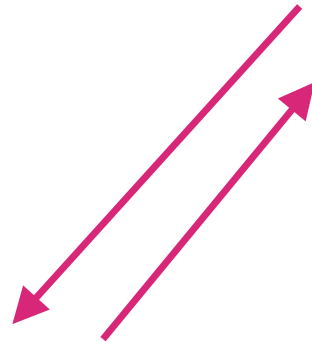


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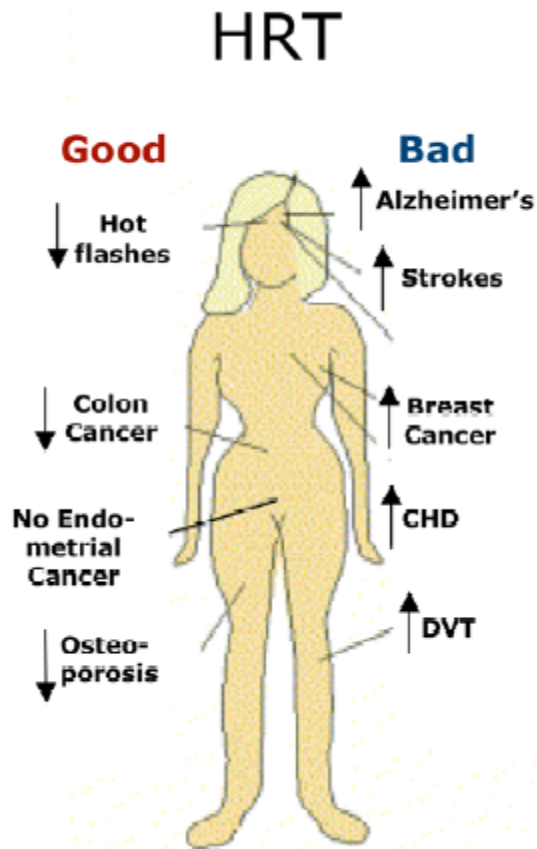
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# Triangle Approach



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# Ideal Therapy Paradigm



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# Femarelle® (DT56a) a SERM for the Management of Menopause

- Femarelle is a standardized substance from Botanical origin
- Scientifically proven through pharmaceutical accepted standards.
- Extensive research leading to the “ideal” solution- SERM properties.
- A comprehensive treatment rather than a focused one.
- Produced under strict pharmaceutical conditions
- Marketed as food supplement for more than 10 years in about 15 countries, registered in Canada as a Natural Health Product (NHP)
- With more than 3.5 M. months of treatment rare and non-significant side effects reported.



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## Efficacy of Femarelle® Agonistic Effect

- Relieves Hot Flashes/VSM symp.
- Elevates  $\beta$ -Endorphine & allopregnanolone levels

- effective for vaginal dryness

- Significant Elevation of BMD
- Bone regeneration mechanism of osteoblast activation



## Safety of Femarelle® Antagonistic Effect

- No Estrogen Receptor (ER) activation in the Breast

- No ER activation in the uterus- does not cause proliferation of cells in the vagina or uterus

- No effect on clotting (even in thrombophilic women)

- Does not change hormonal blood profile- not recognized by the body as hormones



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# Femarelle® & Menopausal Symptoms



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# Effect of Femarelle<sup>®</sup> on Menopausal Symptoms Clinical Study

- 80 healthy postmenopausal women ( $55 \pm 5$ )
  - Study Group: Femarelle<sup>®</sup> - 644 mg/d DT56a (n=38)
  - Low Dose Group: 344 mg/d DT56a + calcium (n=42)
- Assessment of menopausal symptoms through Kupperman Index, vaginal ultrasound and blood tests were done at baseline and after 3, 6, 9 and 12 months.



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n=80  
p<0.01

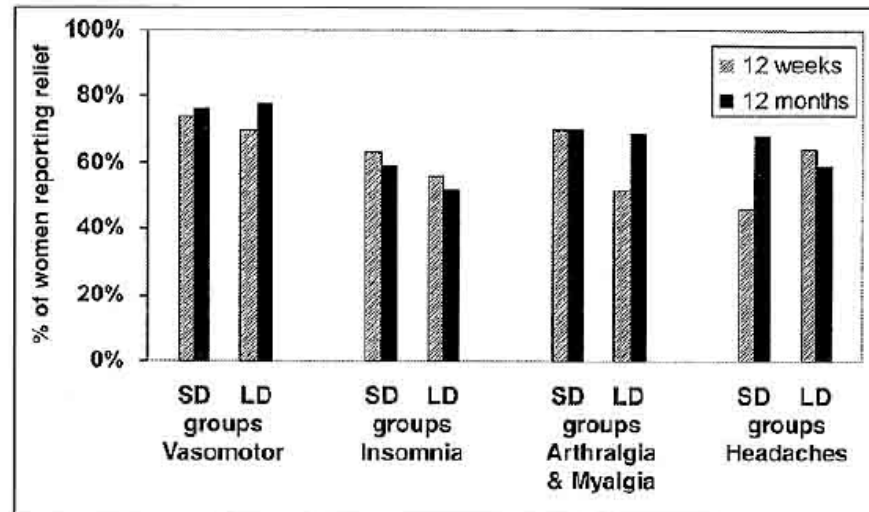
# Effect of Femarelle® on Menopausal Symptoms

## Clinical Study

### Results Efficacy 12 weeks/12 months:

Stat. Significant alleviation of symptoms in 3 out of 4 women

- 76% hot flashes relief
- 70% joint and muscle pain relief
- 68% Headache relief
- The results were maintained throughout the 12 months of the study



n=80  
p<0.01

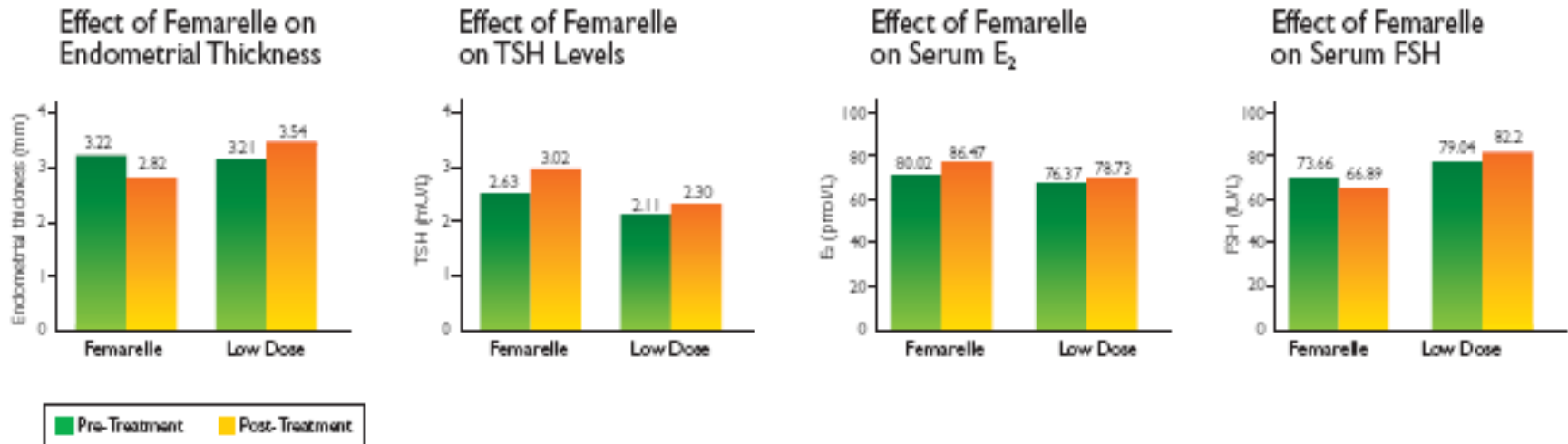


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# Effect of Femarelle® on Menopausal Symptoms

## Clinical Study

### Results Safety 12 months:



- No changes seen in the endometrial thickness, the breast tissue, TSH levels and in the hormonal blood profile
- No monthly bleeding
- There were no reported side effects.



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# Effect of Femarelle® vs. HT & Control on Menopausal Symptoms

## Method: Clinical Study

- 89 postmenopausal women were studied prospectively.
  - 27 women - Femarelle
  - 26 women- Actiwell, Novo-Nordisk
  - 36 symptomatic women not wishing to receive any treatment served as controls
- Menopausal symptoms as assessed through the Kupperman index, serum lipids and lipoproteins, calcium, as well as bone mineral density, endometrial thickness, and mammography were assessed at baseline and at 12 months.

## Results:

- Femarelle decreased menopausal symptoms significantly and in the same degree as Actiwell ( $p < 0.001$ )
- No significant change in lumbar spine BMD T- score in both treatment arms compared to the control group which was significantly lower
- No differences in endometrial thickness or mammography classification, serum lipids or lipoproteins



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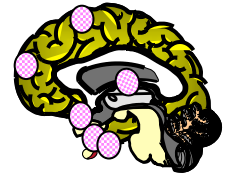
# Effect of Femarelle<sup>®</sup> on the Brain Related to Anxiolytic and Opioid Properties

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- It has been well established that certain neurotransmitters have a positive effect on various brain derived symptoms such as HF, sleep dist., mood disorders...
- This study evaluates whether Femarelle<sup>®</sup> has a similar effect on these neurotransmitters as estrogen.

## Method:

- Evaluation of brain content of:
  - **Allopregnanolone**- reduces anxiety, stress and has the ability to create calm.
  - **Beta-endorphin**- act as an analgesic in the body, it is involved in response to stress, emotional regulation, pain mechanism, and reward system, it increases relaxation and promotes overall well-being.



## Results:

- OVX induced an important and significant reduction of AP in all regions examined (except for the adrenal glands) and serum. Similarly,  $\beta$ -END was reduced in all brain areas



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Study headed by: Prof. Andrea Genazzani- President of the International Society of Gynecological Endocrinology- Pisa University, Italy

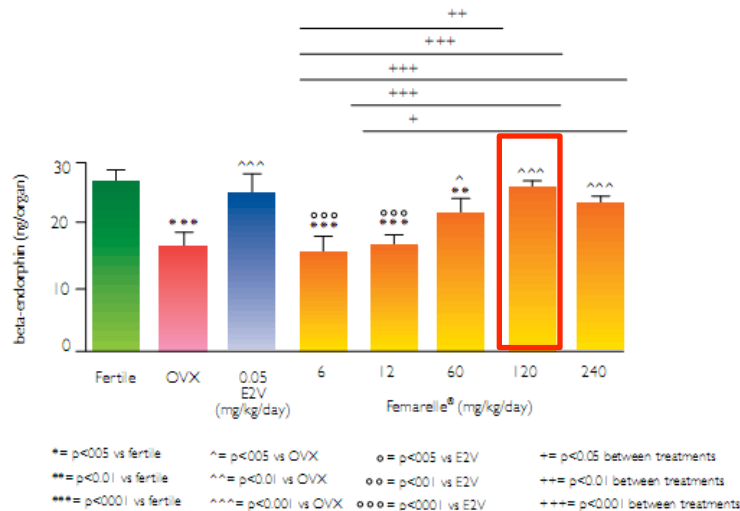
## Allopregnanolone and Beta-Endorphin

### Results:

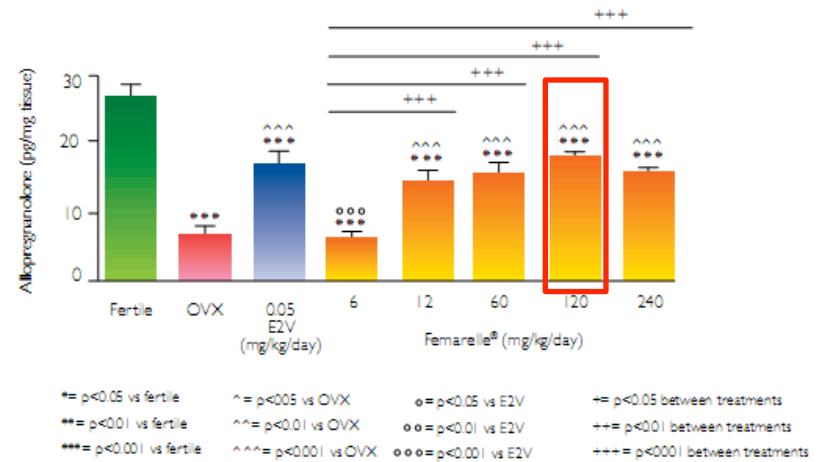
Femarelle exerts an estrogen-like effect on selective areas related to mood, cognition and homeostasis control.

- The activity of Femarelle was similar to the administration of E2V, consequently evidencing an estrogen-like profile of action on selective areas of the brain neurosteroidogenesis.
- These findings may, in part, explain the clinical effect of Femarelle on menopausal symptoms.

Beta-Endorphin Levels in the Hippocampus



Allopregnanolone Levels in the Anterior Pituitary



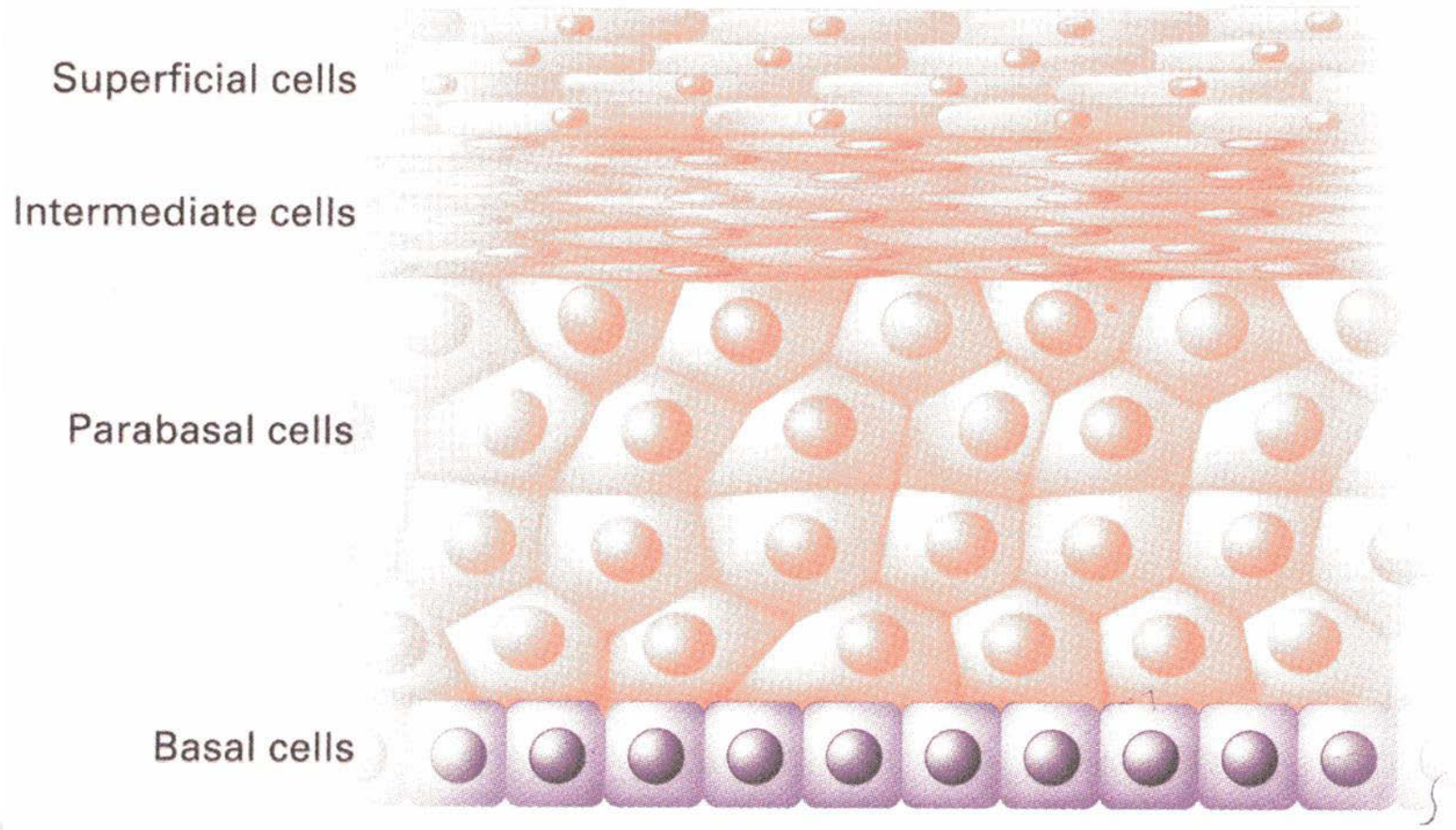
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# Femarelle® & Vaginal Atrophy



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# The Vaginal Histology



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## Femarelle® & Vaginal Atrophy

- 12 menopausal women with vaginal atrophy
- Open label, subject her own control
- Inclusion criteria-
  - bothersome atrophy symptom(s)
  - <5% superficial cells
- Exclusion criteria-
  - hormone therapy or significant soy in diet or supplement
- Femarelle given PO 2x/day (644 mg./day) for 12 weeks
- pH, cultures, Utian QOL and symptom questionnaires, every 4 weeks
- VMI, PE, pap smears, vaginal cultures, blood tests at baseline and 12 weeks



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# Femarelle® & Vaginal Atrophy

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## ***Most Bothersome Symptom reported:***

- Dyspareunia- 5, Vaginal soreness- 3 , Vaginal dryness- 2, Vaginal irritation- 1, Bleeding with coitus- 1.

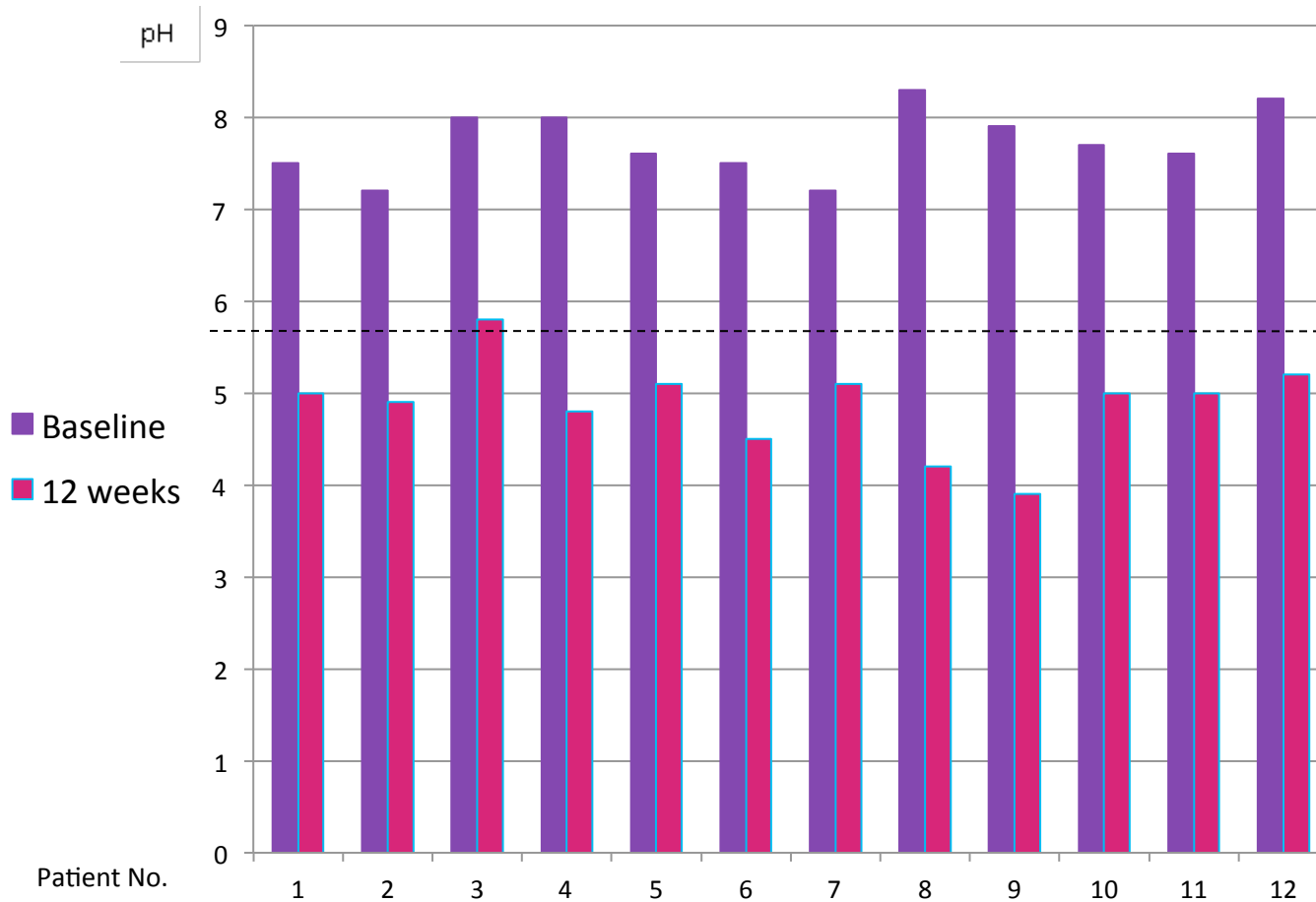
## ***Results:***

- All 12 women reported their most bothersome symptom improved
- Vaginal pH decreased in all subjects
- Significant improvement in MI
- Utian QoL scale improved
- Utian Sexual QoL improved
- No significant change in standard biochemical laboratory tests between baseline and 12 weeks
  - CBC, Chemistries, Lipid Profile, Estradiol and FSH



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# Reduction of Vaginal pH Following 12 weeks of Femarelle Treatment

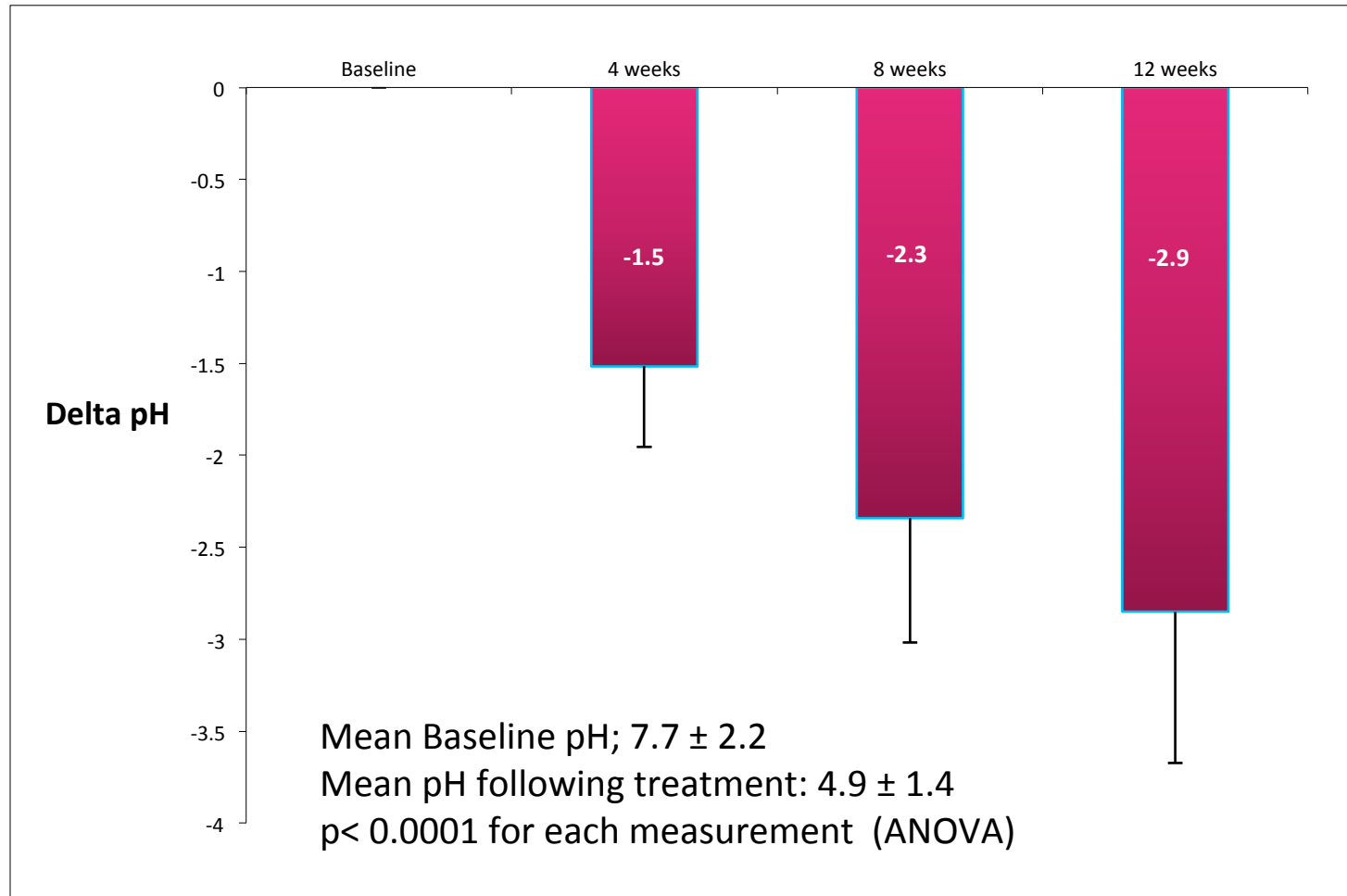


Pt No.	Baseline pH	12 weeks- pH
1	7.5	5
2	7.2	4.9
3	8	5.8
4	8	4.8
5	7.6	5.1
6	7.5	4.5
7	7.2	5.1
8	8.3	4.2
9	7.9	3.9
10	7.7	5
11	7.6	5
12	8.2	5.2



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## Reduction of Vaginal pH Following Treatment



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# Maturation index

## % of Parabasal Cells

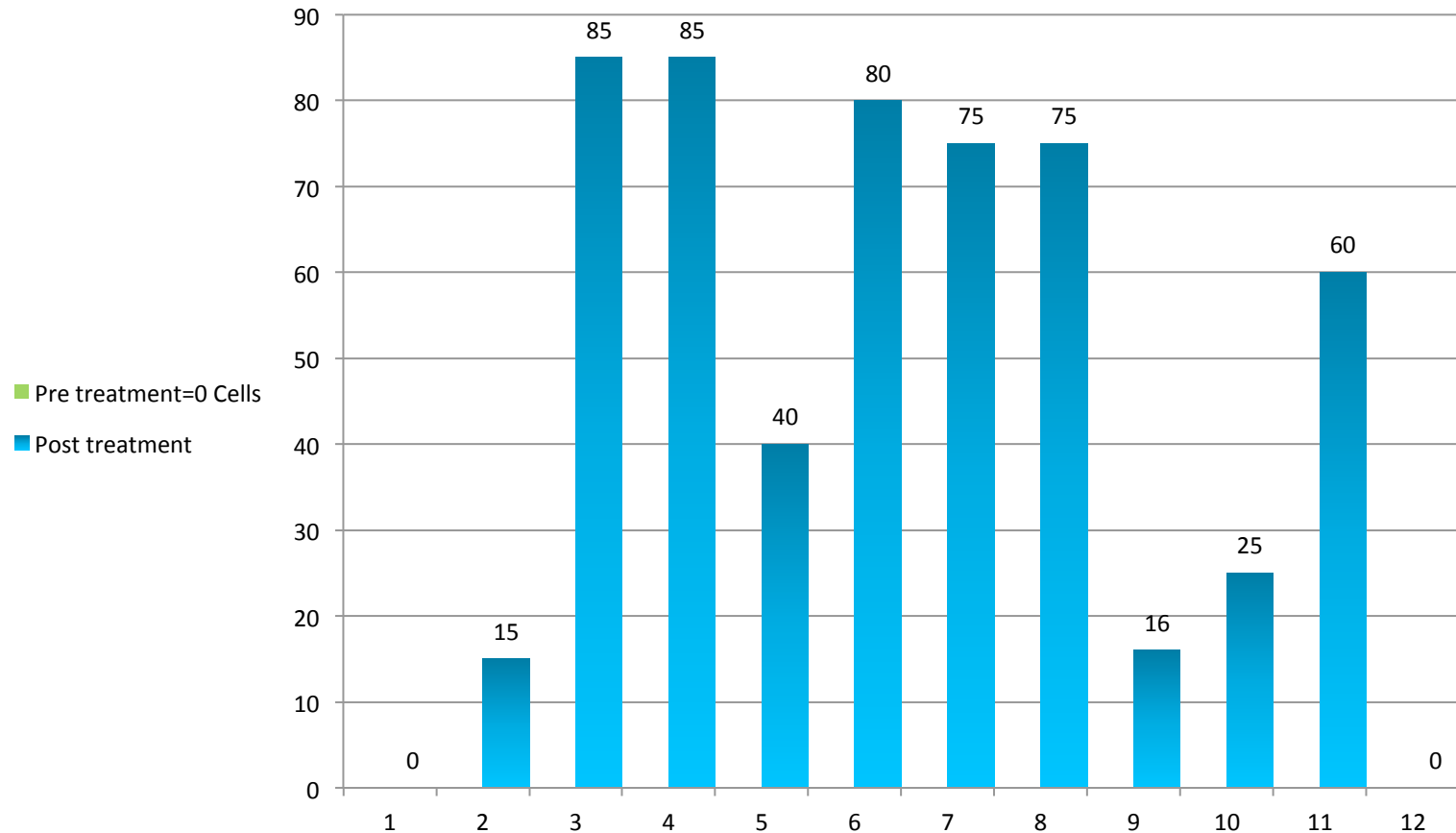


**Femarelle®**

Nachtigall M. et al. A Prospective Study of DT56a (Femarelle) for the Treatment of Postmenopausal Vaginal Atrophy. Menopause book of abstract of the NAMS 22<sup>nd</sup> Annual Meeting, Sept, 2011, p. 55

# Maturation index

## % of Intermediate Cells

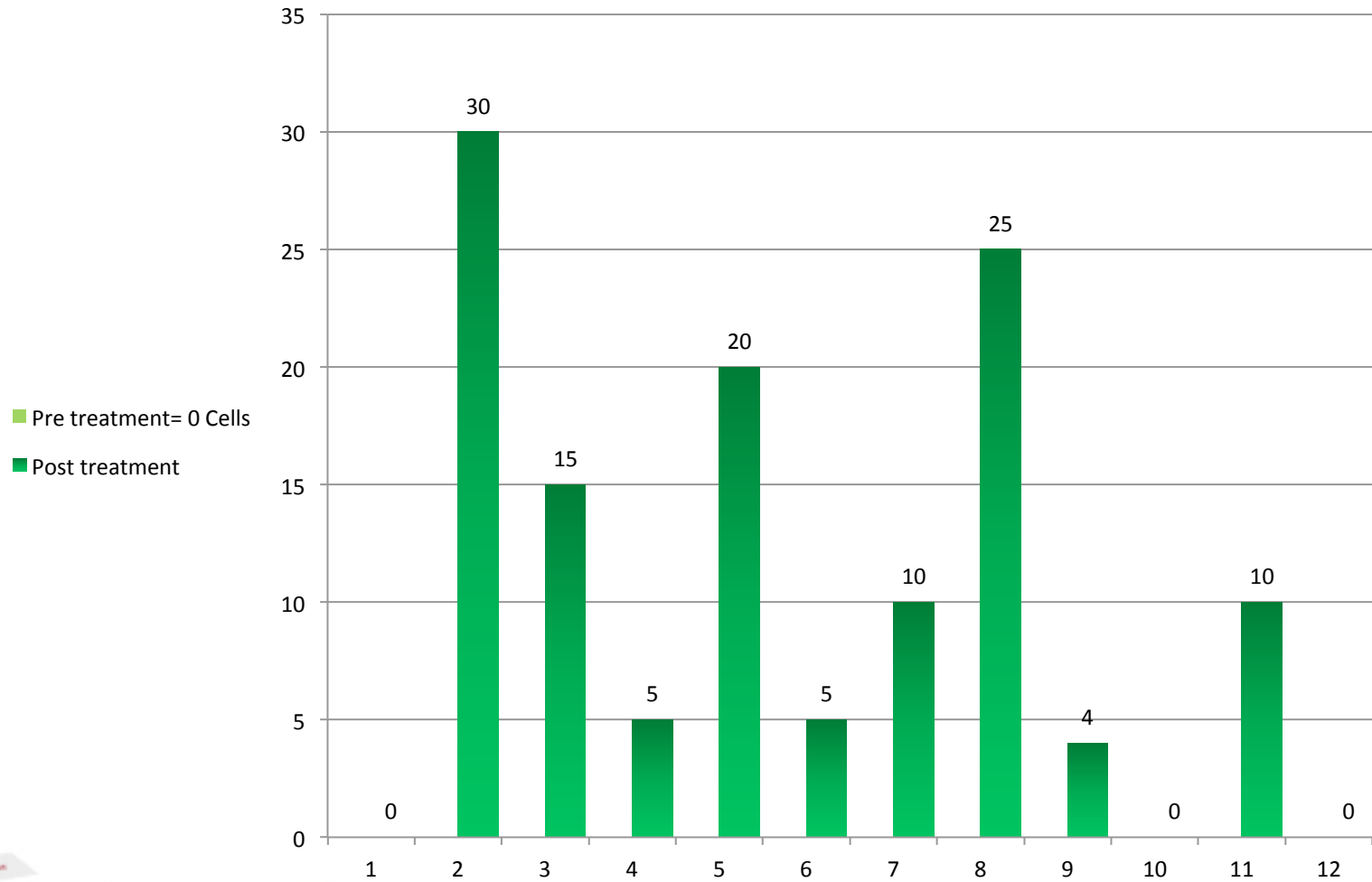


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# Maturation index

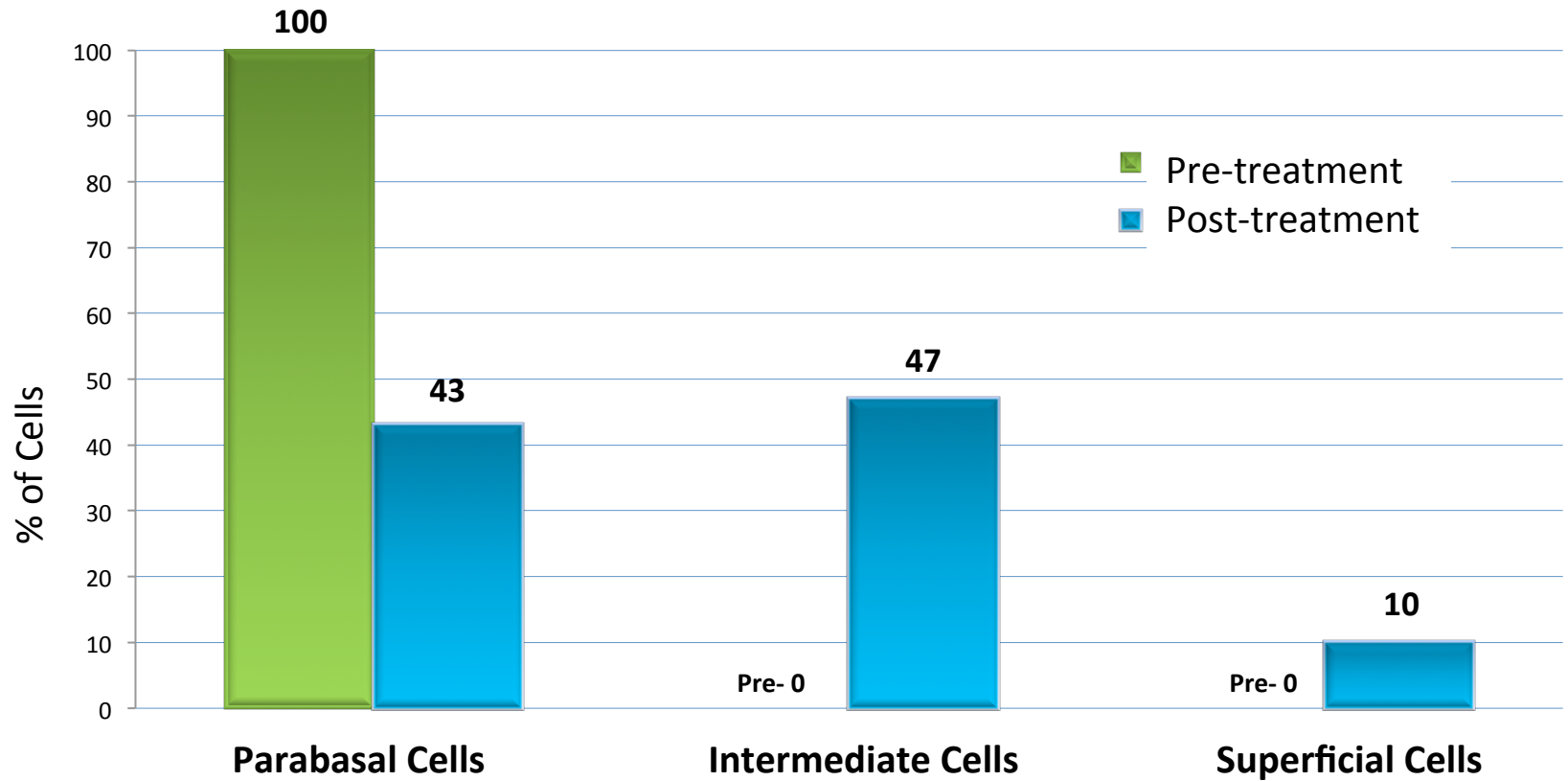
## % of Superficial Cells



# Femarelle®

Nachtigall M. et al. A Prospective Study of DT56a (Femarelle) for the Treatment of Postmenopausal Vaginal Atrophy. Menopause book of abstract of the NAMS 22<sup>nd</sup> Annual Meeting, Sept, 2011, p. 55

# Maturation Index Pre & Post DT56a Treatment



n=12  
p< 0.001



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# Utian Quality of Life Scale (UQOL)

Please rate the degree to which you agree with the following statements, as they apply to you *within the past month*. Be sure to *answer every question!* Please circle your answer using the following 5-point scale:

	1	2	3	4	5
	Not true of me		Moderately true of me		Very true of me
1. I am able to control things in my life that are important to me.	1	2	3	4	5
2. I feel challenged by my work.	1	2	3	4	5
3. I believe my work benefits society.	1	2	3	4	5
4. I am not content with my sexual life.	1	2	3	4	5
5. I am content with my romantic life.	1	2	3	4	5
6. I have gotten a lot of personal recognition in my community or at my job.	1	2	3	4	5
7. I am unhappy with my appearance.	1	2	3	4	5
8. My diet is not nutritionally sound.	1	2	3	4	5
9. I feel in control of my eating behavior.	1	2	3	4	5
10. Routinely, I engage in active exercise three or more times each week.	1	2	3	4	5
11. My mood is generally depressed.	1	2	3	4	5
12. I frequently experience anxiety.	1	2	3	4	5
13. Most things that happen to me are out of my control.	1	2	3	4	5
14. I am content with the frequency of my sexual interactions with a partner.	1	2	3	4	5
15. I currently experience physical discomfort or pain during sexual activity.	1	2	3	4	5
16. I believe I have no control over my physical health.	1	2	3	4	5
17. I am proud of my occupational accomplishments.	1	2	3	4	5
18. I consider my life stimulating.	1	2	3	4	5
19. I continue to set new personal goals for myself.	1	2	3	4	5
20. I expect that good things will happen in my life.	1	2	3	4	5
21. I feel physically well.	1	2	3	4	5
22. I feel physically fit.	1	2	3	4	5
23. I continue to set new professional goals for myself.	1	2	3	4	5

# Utian Quality of Life Scale (UQOL) Scoring Summary

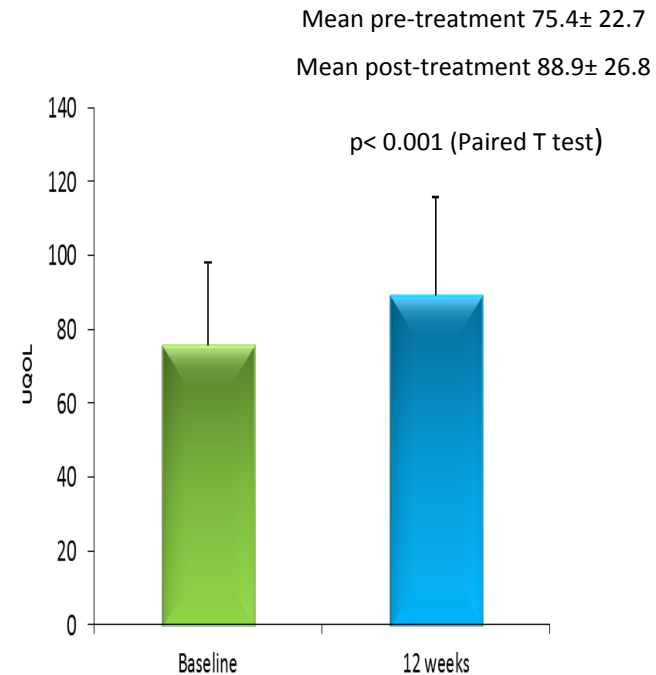
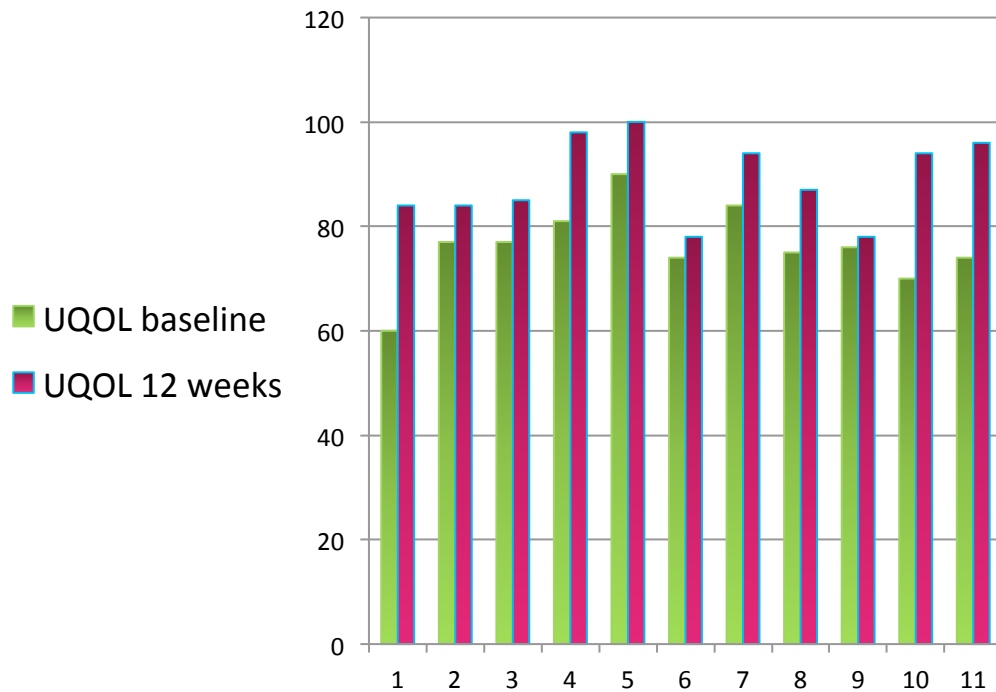
**Instructions:** Each of the four subscales of the UQOL is represented by a unique color, as shown below. Sum the circled responses by color and enter the sum in the scoring summary section at the bottom of the page.

1. I am able to control things in my life that are important to me.	1	2	3	4	5
2. I feel challenged by my work.	1	2	3	4	5
3. I believe my work benefits society.	1	2	3	4	5
4. I am not content with my sexual life.	5	4	3	2	1
5. I am content with my romantic life.	1	2	3	4	5
6. I have gotten a lot of personal recognition in my community or at my job.	1	2	3	4	5
7. I am unhappy with my appearance.	5	4	3	2	1
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21. I feel physically well.	1	2	3	4	5
22. I feel physically fit.	1	2	3	4	5
23. I continue to set new professional goals for myself.	1	2	3	4	5

## Scoring Summary

	Lower QoL	-2SD	-1SD	Mean	+1SD	+2SD	Higher QoL
Occupational QoL	13	19	25	31	35		
Health QoL	11	16	21	26	31		
Emotional QoL	12	16	20	24	28		
Sexual QoL	0	4	8	12	15		
Total QoL	4R	R1	24	R7	100		

# Improvement in Utian QOL questionnaire following 12 weeks of treatment with Femarelle

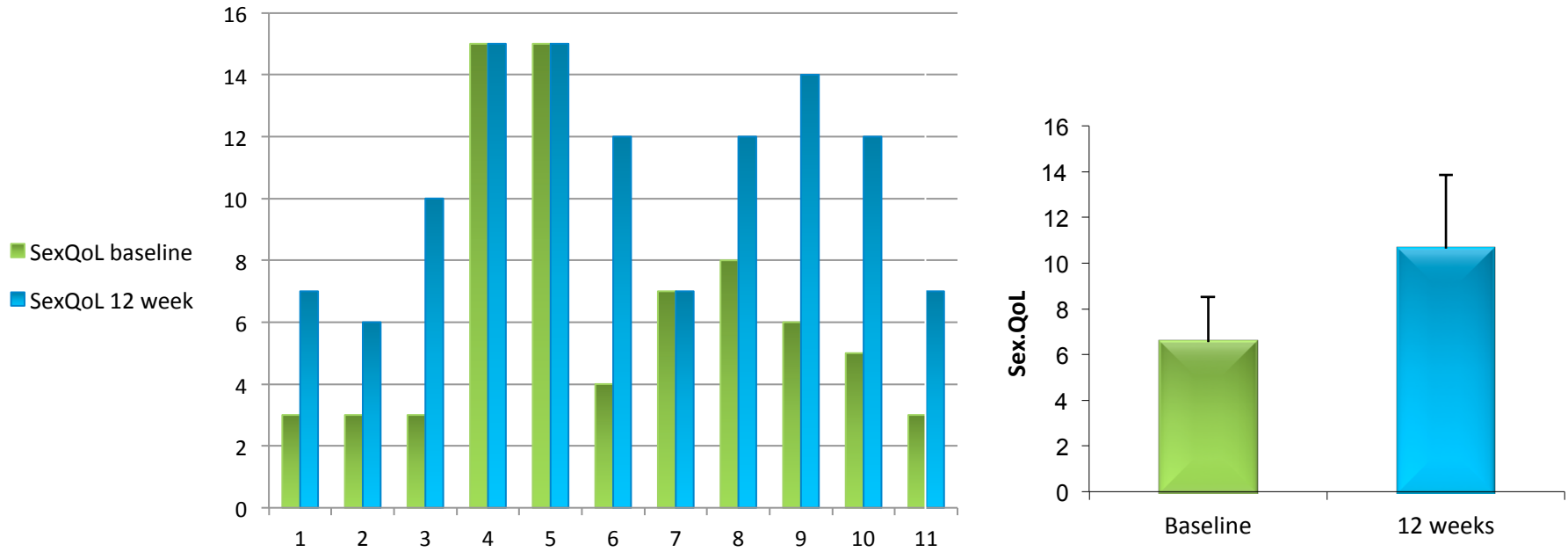


n=11



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# Improvement in Utian *Sexual QOL* questionnaire following 12 weeks of treatment with DT56a



Mean pre-treatment  $6.5 \pm 2$

Mean post-treatment  $10.6 \pm 3.2$

$p < 0.001$  (Paired T test)

n=11



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## Conclusions Femarelle® & Vaginal Atrophy

- Vaginal dryness significantly affects postmenopausal women
- Following 12 weeks of treatment with Femarelle®:
  - Most bothersome symptom was improved in all patients
  - Significant reduction in Vaginal pH in all patients
  - Significant improvement in Maturation Index
  - Significant improvement in sexual QOL questionnaire
  - Significant improvement in Utian QOL questionnaire
- No side effects detected in subjective or objective measurements.
- Femarelle seems to be effective for vulvovaginal atrophy



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# Femarelle® & Bone Health



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## Effect of Femarelle® on BMD

- 98 healthy postmenopausal women ( $55 \pm 5$ )
  - Study Group: 644 mg/d DT56a (n=39)
  - Low Dose Group: 344 mg/d DT56a + calcium (n=43)
- BMD test as was done through DEXA scan at time 0 and after 12 months of treatment.
- Vaginal ultrasound and blood tests were done at time 0 and after 12 months.



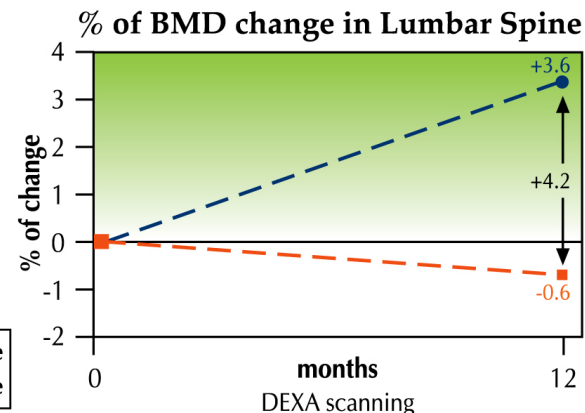
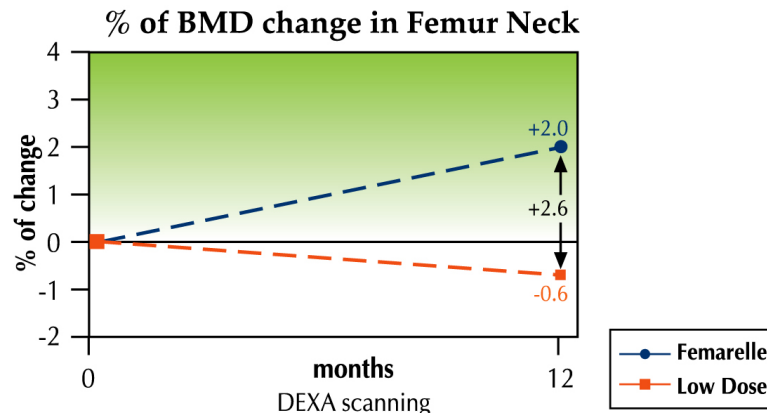
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# Effect of Femarelle® on BMD

## Clinical Study

Following 12 months of treatment:

- 3.6% increase of BMD in the spine.
- 2.0% increase of BMD in the hip.



- Neither group showed any change in endometrial thickness or in blood hormone levels
- There were no reported side effects



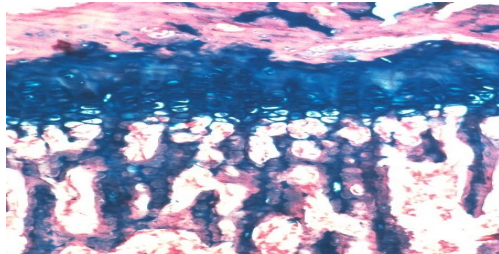
# Femarelle®

# Effect of Femarelle® on Skeletal Tissues

## Histology

- The dynamics of Femarelle® compared to E<sub>2</sub> and placebo on the rebuilding process in different parts of the bone.

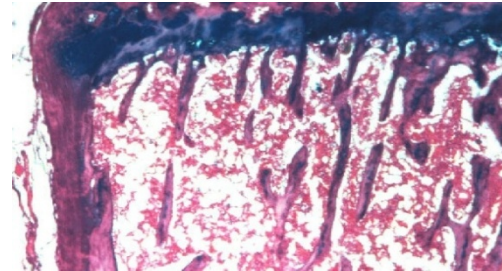
Young (intact) Rats  
Control



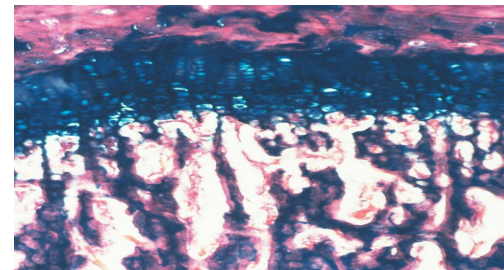
Cortical bone width

Trabecules

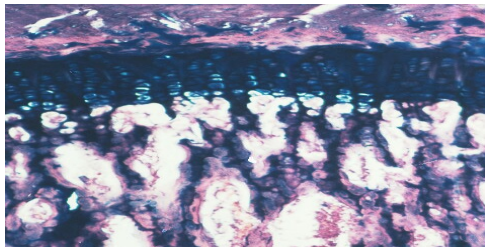
Ovx – Control  
after 2 months



Ovx – DT56a  
after 2 months



Ovx - E<sub>2</sub>  
after 2 months



Cortical bone width

Trabecules

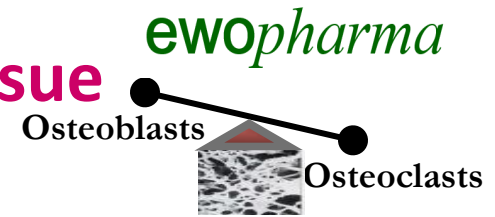
*microscopic structures through tissue slice examination under microscope*

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# Mechanism of Action in Skeletal Tissue

## Osteoblasts Activation



### Objective:

- New bone tissue, is formed through the stimulation of osteoblast activity.
- To investigate the mechanism of action of Femarelle<sup>®</sup> (vs. E<sub>2</sub>) in promoting bone mineral density, osteoblast activation was examined in human bone cultures of pre- and post menopause females by the use of three markers:
  - DNA synthesis: a marker of increased activity of osteoblasts through cell proliferation
  - Alkaline phosphatase (ALP): a marker of osteoblast activation
  - CK activity: a marker of ER activation, which induces osteoblast activity
- Raloxifene was added in order to allow examination of the effect of Femarelle<sup>®</sup> after blocking of the estrogen receptors.



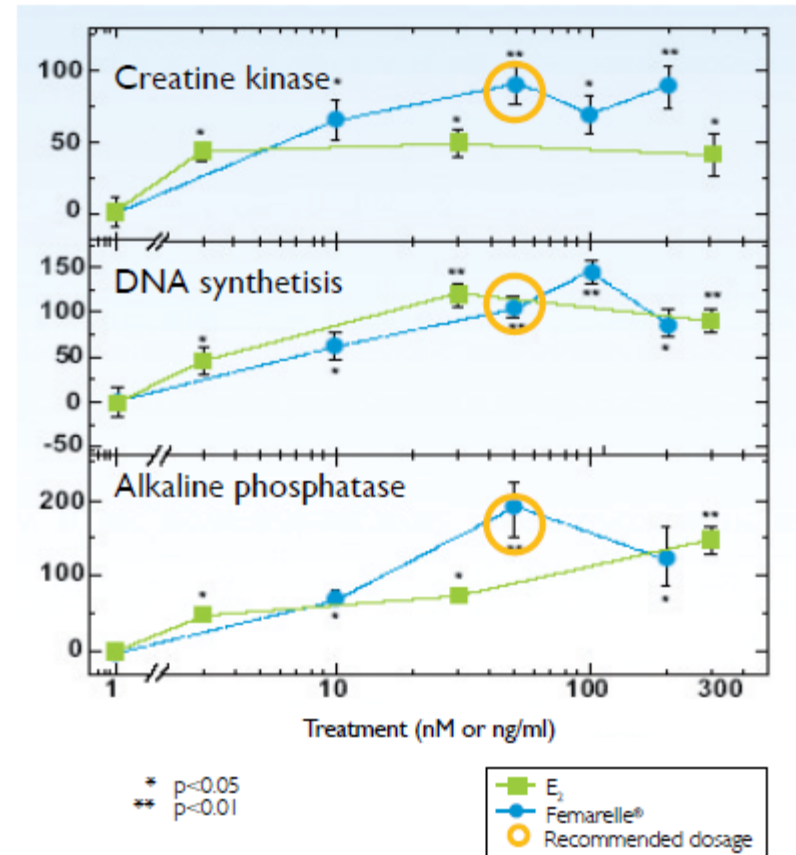
Femarelle<sup>®</sup>

# Mechanism of Action in Skeletal Tissue

## Osteoblasts Activation

### Results:

- Femarelle stimulates osteoblastic activity, showing its bone forming properties
- Raloxifene inhibited Femarelle's effect in both groups, proving that Femarelle works through estrogen receptors
- Femarelle is a unique agent for postmenopausal bone loss by its **bone-forming properties**



# Femarelle®

## Effect of Femarelle® and different compounds on Fat Volume in Bone Marrow

	Group	% of fat volume in bone marrow (% FV±SEM)
	Control (Intact)	0.28 ± 0.17
	OVX (Control)	27.10 ± 1.80**
<b>Estrogen:</b>	OVX + E2	0.03 ± 0.002**
<b>Femarelle:</b>	OVX + Femarelle (DT56a)	0.00-0.00**
<b>Raloxifene:</b>	OVX + RAL	0.20 ± 0.02**
<b>Isoflavones:</b>	OVX + Daidzein	5.37 ± 0.30*
	OVX + Genistein	23.00 ± 2.10

\*P<0.05, \*\*<0.01 from the corresponding mean values of OVX control rats

- Osteoporosis and age related osteopenia were shown to be associated with an increase in marrow fat tissue
- Osteoblasts negatively correlate with the numbers of adipocytes, suggesting that adipocytes are generated at the expense of osteoblasts
- Treatment with Femarelle® resulted in abolishment of fat cells content similar to E<sub>2</sub> and better than RAL and isoflavones



# Femarelle®

Somjen D. et al. The Effects of Native and Synthetic Estrogenic Compounds as well as Vitamin D Less-Calceemic Analogs on Adipocytes Content in Rat Bone Marrow. *J Endocrinol Invest.* 2011;34(2):106-10

# Femarelle®'s Mechanism of Action

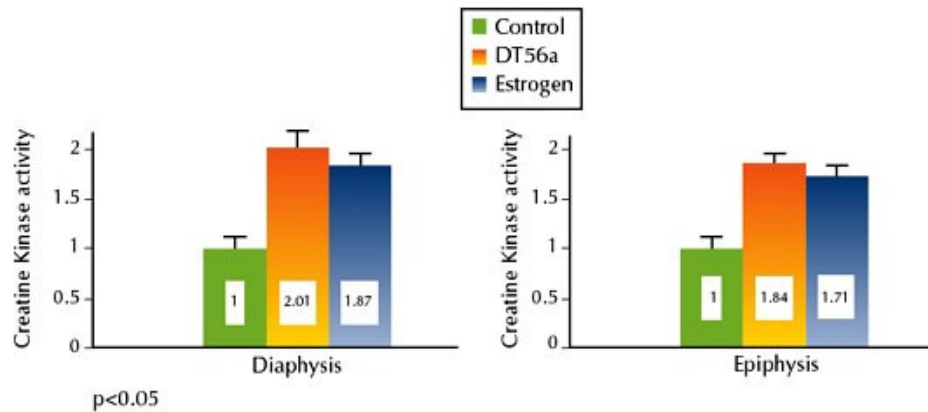


Femarelle®

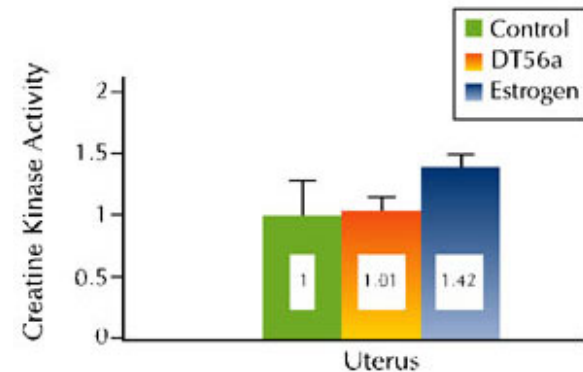
# Femarelle<sup>®</sup>'s Mechanism of Action as a SERM

## Results:

- Femarelle stimulates CK activity, a marker of ER activity (agonist), in the epiphyseal cartilage and diaphyseal bone



- Contrary to the estrogen group, there was no estrogenic effect on the uterus in the Femarelle group.



## Femarelle<sup>®</sup>

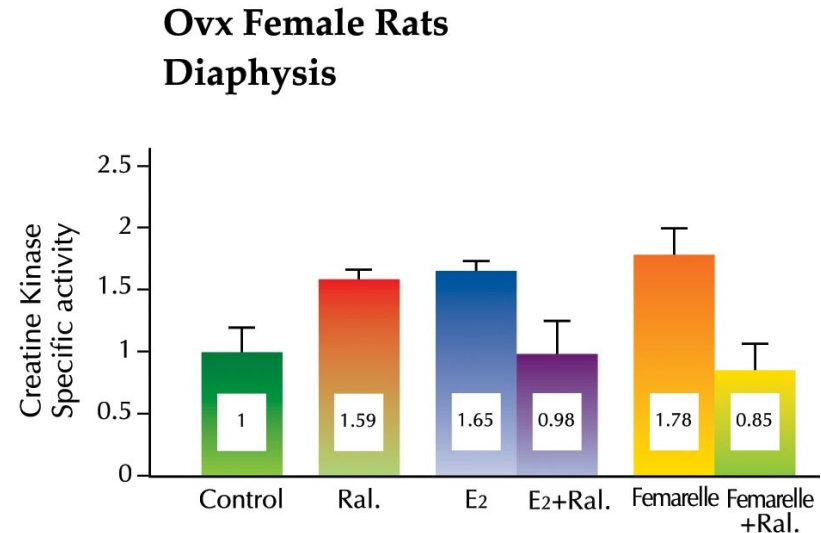
Somjen D, Yoles I. "DT56a (Tofupill/Femarelle), selectively stimulates creatine kinase specific activity in skeletal tissues of rats but not in the uterus" *J. of Steroid Biochemistry & Molecular Biology* 2003;86(1):93-98

# Femarelle<sup>®</sup>'s Mechanism of Action as a SERM (cont.)

## MoA - through ER

### Results cont.:

- The effect on bone growth was lost when the estrogen receptors were blocked with Raloxifene
- Identifying Femarelle as a SERM, capable of selectively activating bone formation via estrogen receptors without inducing any estrogenic activity in the uterus



## Femarelle<sup>®</sup>

Somjen D, Yoles I. "DT56a (Tofupill/Femarelle), selectively stimulates creatine kinase specific activity in skeletal tissues of rats but not in the uterus" *J. of Steroid Biochemistry & Molecular Biology* 2003;86(1):93-98

# Femarelle® & Clotting



Femarelle®

## Prevalence of Clotting Problems in the General Population

**TABLE 1. Occurrence of FV<sub>Leiden</sub> and Other Risk Factors for Venous Thrombosis and the Relative Risks (RR) They Contribute**

Risk Factor	Population Prevalence, %	Thrombosis Patients, %	RR
FV <sub>Leiden</sub>	2–15	20	6.6*
Protein S deficiency	0.03–0.13	1–2	0.7†
Protein C deficiency	0.2–0.4	3	6.5
Antithrombin deficiency	0.02	1	5.0
Prothrombin 20210A	2	6	2.8
High FVIII levels	11	25	4.8

\*Risk for heterozygous FV<sub>Leiden</sub> carriers, risk for homozygous carriers is approximately 80-fold.

†This low number is derived from case-control studies, which fail to identify protein S deficiency as a risk factor. However, family studies demonstrate that protein S deficiency carries similar risk for thrombosis as FV<sub>Leiden</sub> and protein C deficiency (reviewed by Zöller et al<sup>69</sup>).

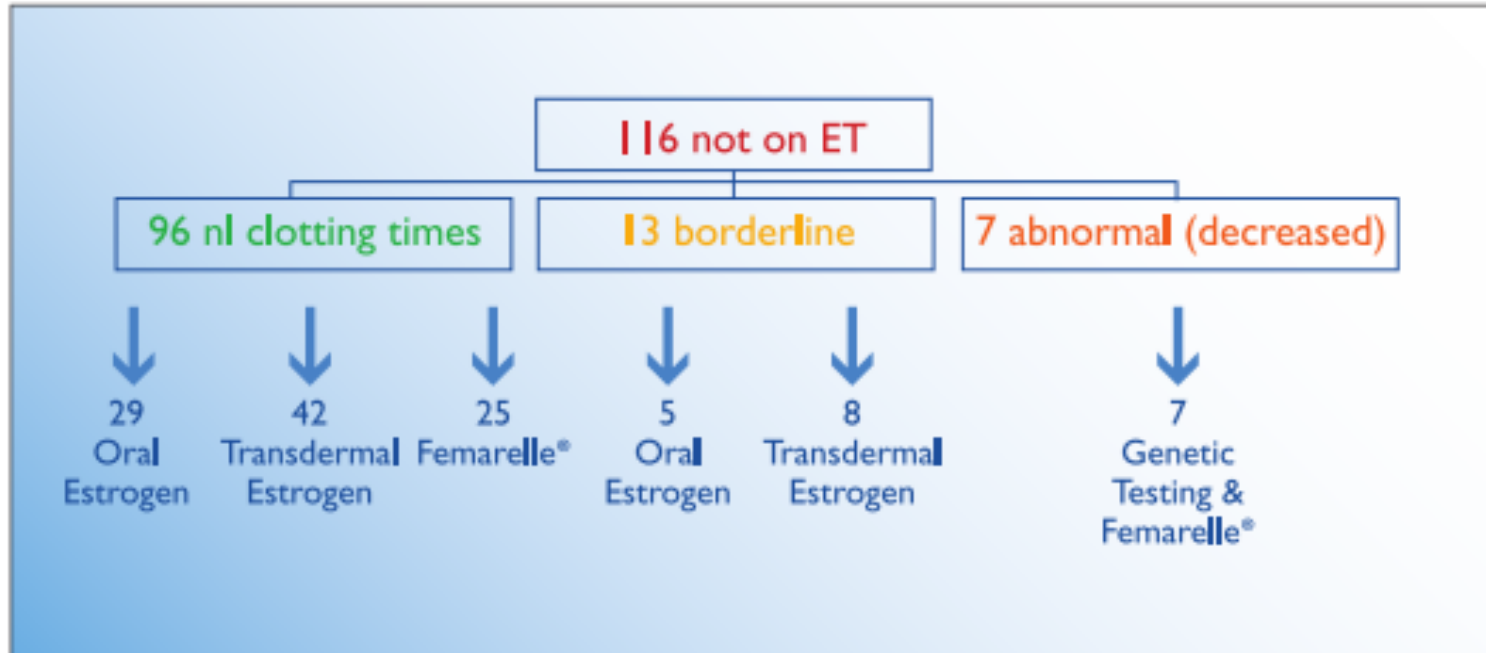
Data adapted from Martinelli,<sup>10</sup> Rees et al,<sup>49</sup> Rosendaal,<sup>62</sup> Rosendaal et al,<sup>70</sup> Koster et al,<sup>71</sup> and Dykes et al.<sup>72</sup>

- This population has a 5-21 fold greater risk to develop VTE = contraindication



Femarelle®

# Effect of Femarelle on Clotting Clinical Study

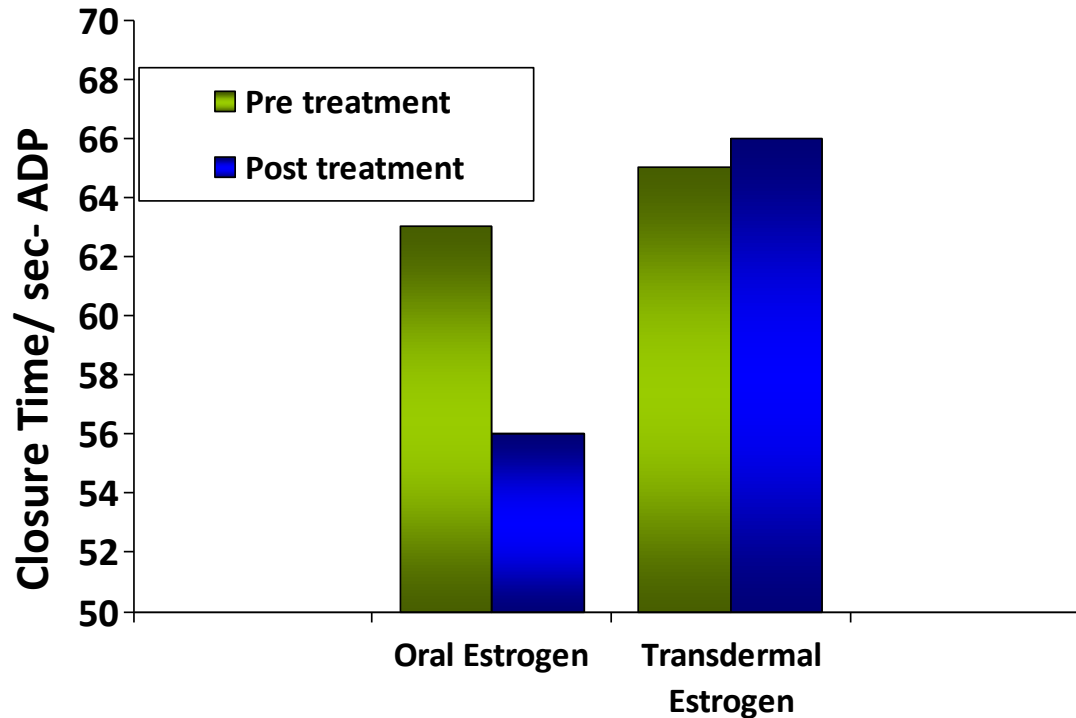


	CADP (sec)	CEPI (sec)
<b>Normal</b>	<b>71-118</b>	<b>85-165</b>
<b>Borderline</b>	<b>56-70</b>	<b>70-84</b>
<b>Pathological</b>	<b>&lt;56</b>	<b>&lt;70</b>



## Femarelle®

# Oral or Transdermal Estrogen in Women with Increased Clotting Risk ("Borderline")



Pre-and Post Treatment (8 wks) Closure Times with either Oral or Transdermal Estrogen in Women with Increased Clotting Risk

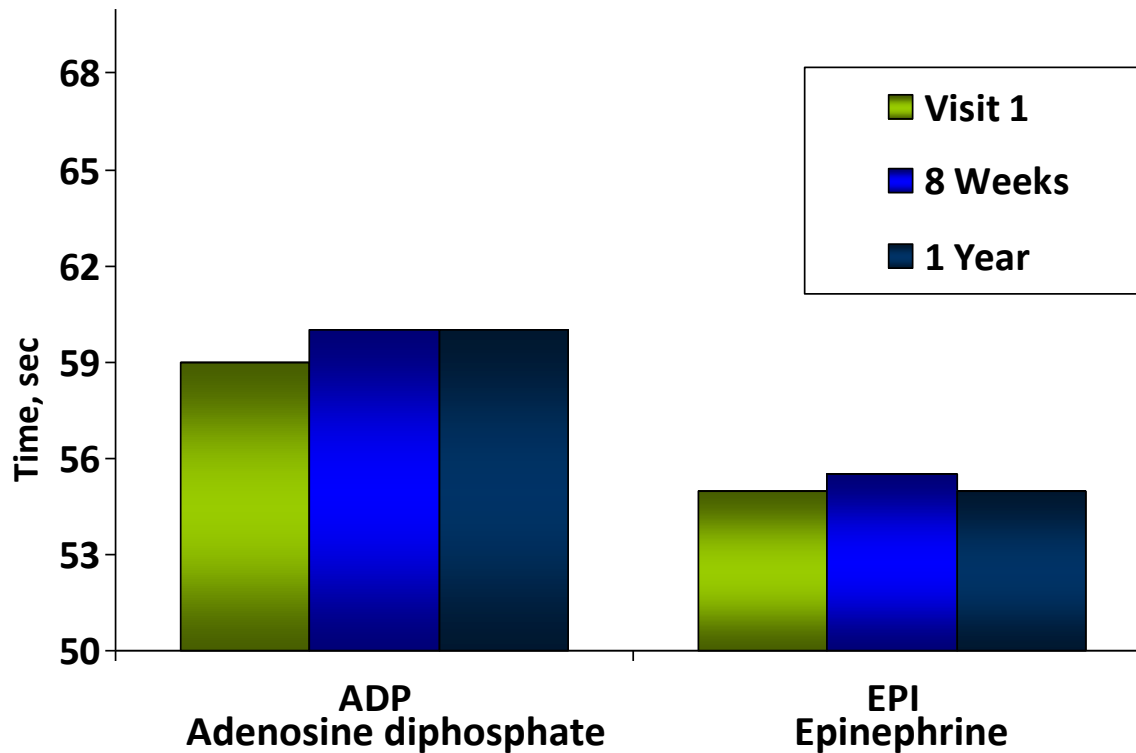
Borderline cADP: 56-70 / cEPI: 70-84



Femarelle®

Nachtigall L. et al. Association of oral but not transdermal estrogen therapy with enhanced platelet reactivity in a subset of postmenopausal women. *Menopause* 2009;16(2):407-12

## 7 Thrombophilic Women on Femarelle®



n=4	Factor V Leiden
n=1	Mutant Prothrombin
n=1	Protein S Deficiency
n=1	Elevated Anticardiolipins Antibodies

- Femarelle was shown to have no effect on the coagulation system in either normal or thrombophilic women.



# Femarelle®

# Femarelle® & Breast Cancer Tissue



Femarelle®

# Effect of Femarelle® on Breast Cancer Cells

## **Objective:**

Examine the effect of Femarelle® on MCF-7 breast cancer tissue culture  
–Estrogen dependent human breast cancer (70 % of all breast cancers)

## **Methods:**

Cells were seeded for 96 hrs. in estrogen-depleted medium, following addition of Femarelle or E<sub>2</sub> at various concentrations for additional 72 hrs.

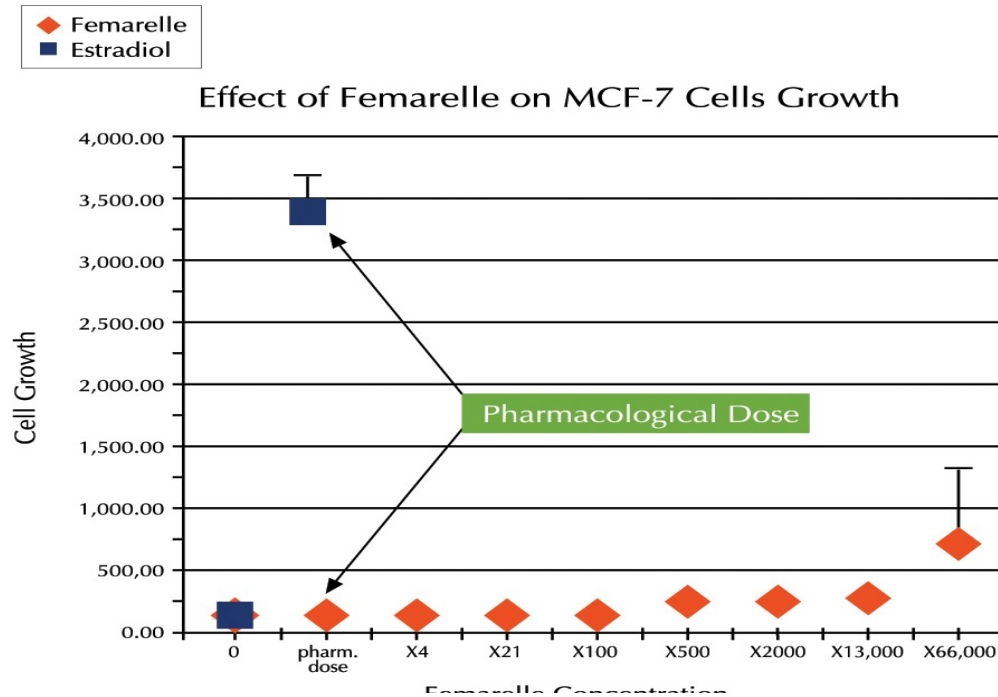
- *Estrogen dose:* pharmacological dose
- *Femarelle dose:* incremental dosage- pharmacological dose (PD)-66,000 times PD



Femarelle®

# Effect of Femarelle® on MCF-7 Breast Cancer Cells

## Results:



- Femarelle® does not trigger breast cancer cell growth.
- This finding further supports the accumulating data verifying the activity of Femarelle® as a SERM.



## Femarelle®

Yoles I., and Lilling G. Pharmacological Doses of the Natural phyto-SERM DT56a (Femarelle) Have no Effect on MCF-7 Breast Cancer Cell-Line. *European J. of Obstetrics & Gynecology and Reproductive Biology* 2007;130(1):140-141

## Toxicology Study - Femarelle®

### *O b j e c t i v e s :*

- Evaluate the secondary estrogenic effects of Femarelle® on the estrogen-dependent characteristics of the female reproductive tract in a post-menopausal model of OVX rats.

### *Methods:*

- Ovariectomized female rats were treated with a low dose and high dose of estrogen, Femarelle, and a vehicle, for a period of 14 days.
- Three estrogenic characteristics of female reproductive tracts were examined:
  - *Uterine weight*
  - *Keratinization of the vaginal lining*
  - *Sensitivity of uterine smooth muscle to serotonin*

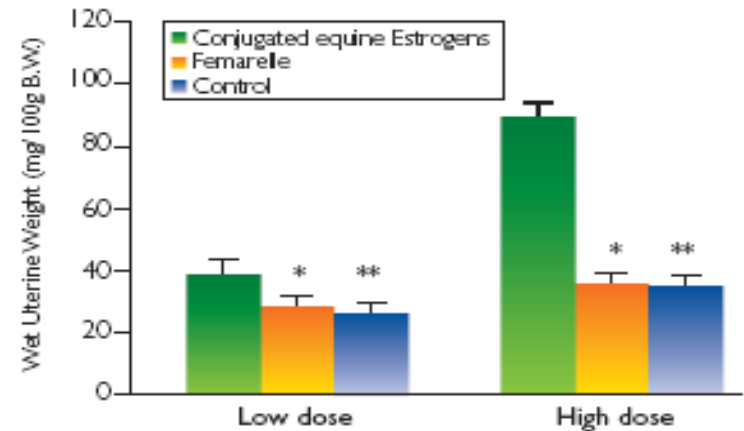


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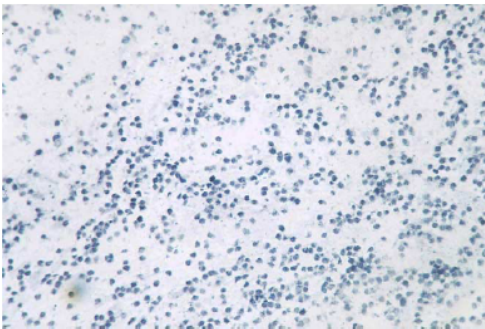
# Toxicology Study - Femarelle®

## Results:

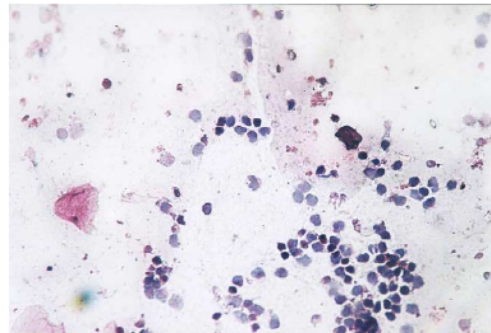
Contrary to the effect of estrogen, Femarelle did not display any estrogenic effect on the uterine weight vaginal epithelium or serotonin-induced contractile activity of rat uterus.



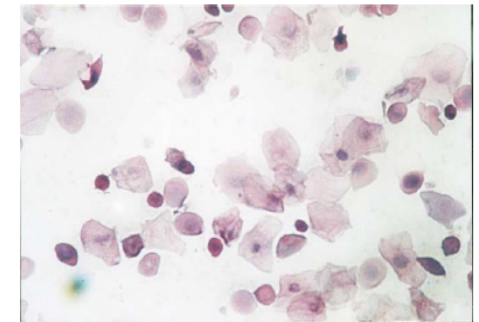
OVX with Placebo



OVX with Femarelle



OVX with E<sub>2</sub>



Femarelle induced the presence of small-nucleated cells in the vaginal epithelium (showing its promise to treat vaginal dryness )



**Femarelle®**

# Femarelle® Scientific Summary to Date

## *Efficacy*

- Femarelle was shown to ***significantly relieve menopausal symptoms***- from mild to severe symptoms
- The ***Efficacy of Femarelle is similar to the efficacy of HT*** (Activelle- Novo-Nordisk)
- Femarelle was shown to be effective for ***vulvo-vaginal atrophy*** (NYU)
- Femarelle was shown to ***increase BMD***
- Femarelle was shown to have a ***unique bone regeneration mechanism***, through osteoblast activation
- Femarelle was shown to have an ***agonistic activity in selective areas in the brain, the skeletal tissue, and on the lower genital track***



Femarelle®

## Safety

- Femarelle was shown to have an ***antagonistic effect on estrogen receptors in the breast and the uterus***
- Femarelle was shown ***not to affect clotting*** parameters even in thrombophilic patients (NYU)
- Femarelle does ***not change the hormonal blood profile***, TSH levels, liver and kidney functions, and endometrial thickness nor does it cause bleeding
- Femarelle was shown to have a high safety profile; having no estrogenic effect on the uterus and breast cancer tissue (MCF-7)
- With more than 3.5 Million months of treatment, rare and transient side effects (n=34) were reported:
  - Bloating, nausea, breast tenderness
  - No serious adverse events were reported to date.



Femarelle®

# The Medical Value of Femarelle Pre-Menopause

The decline in estrogen levels in the pre-menopausal stage leads to an overall reduction in QoL without knowing the cause of it

- **Fatigue**
- Anxiety
- Irritability
- **Depression**
- **Insomnia**

- Femarelle targets pre-menopause stage assisting with the overall feeling of loss of energy and improvement in QoS



Pre-menopause

42-48

50

55

60

65

Age



Femarelle®

# The Medical Value of Femarelle Menopause

*ewopharma*

The decline in estrogen levels lead to very recognizable & “telling” symptoms



- Vasomotor
- Night sweats
- Palpitations
- Headaches
- Joint & Muscle pain
- Fatigue
- Anxiety
- Irritability
- Depression
- Insomnia
- Loss of libido

- Femarelle provides the same relief as HT reducing vasomotor symptoms, alleviating mood related symptoms, QoS and improves libido

Menopause

42-48

50

55

60

65

Age



Femarelle®

# The Medical Value of Femarelle *ewopharma*

## Post-Menopause

Prolonged estrogen deprivation leads to disease and great reduction in QoL



- Femarelle assists with VVA, and decreases pH levels in the vagina.
- Femarelle increases BMD through osteoblast activity.

- Vaginal dryness...
- Dyspareunia
- Urinary problems
- Osteoporosis
- CVD...

Post-menopause

42-48

50

55

60

65

Age



Femarelle®

## Femarelle® Scientific Advisory Board

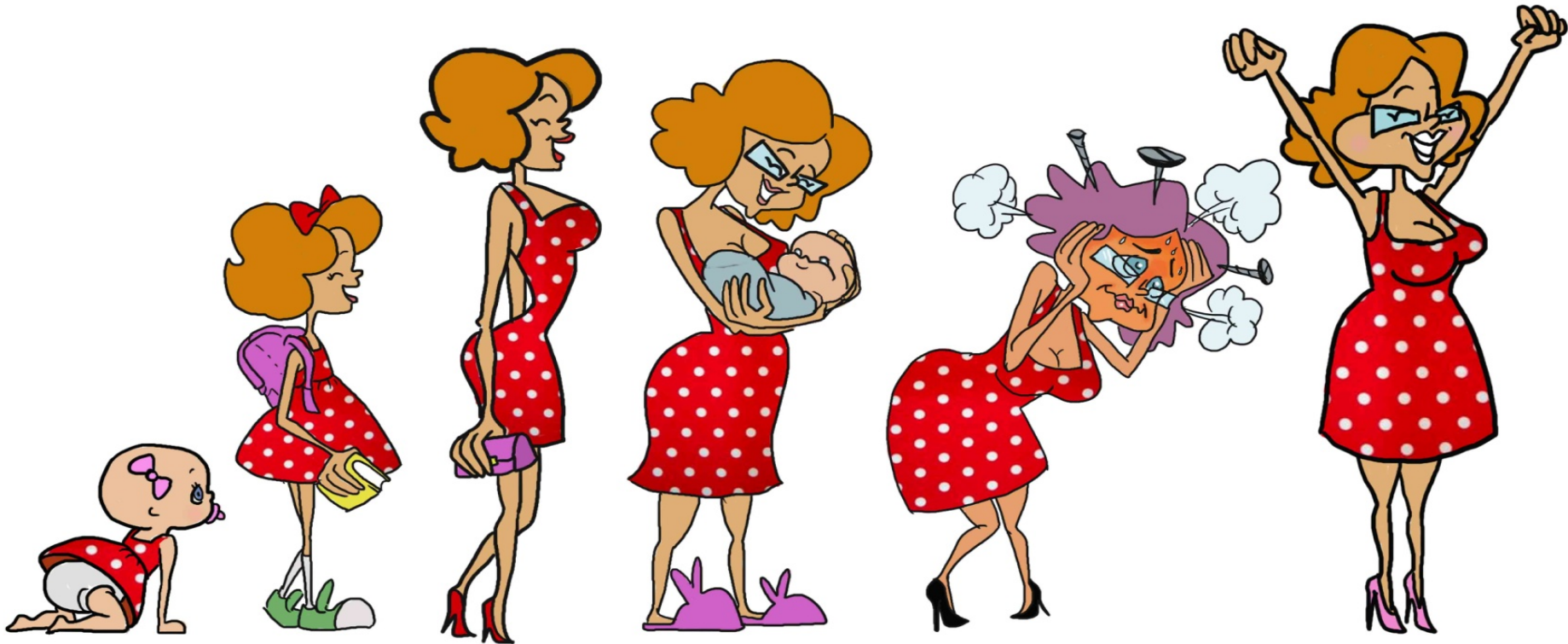
- Femarelle has a strong Scientific Advisory Board made up of Key Opinion Leaders in Women's Health

Dr. Lila Nachtigall, MD	USA	Prof. of OBGYN at NYU School of Medicine, Former president of NAMS
Dr. Frederick Naftolin, MD, PhD	USA	Prof. of OBGYN at NYU School of Medicine, Former president of NAMS
Dr. Richard Nachtigall, MD, PhD	USA	Professor Clinical Medicine, NYU School of Medicine, Senior VP PEPSICO Intl.
Dr. Nick Panay, MD	UK	Chief editor 'Climacteric', Gynecologist, Queen Charlotte's & Chelsea Hospital, former president of the British Menopause Society, 2014-5 President Obstetrics & Gynaecology Section, Royal Society of Medicine
Dr. Andrea Genazzani, MD, PhD	Italy	President of Intl. Society of Gynecological Endocrinology, former president International Menopause Society, Dir. Dept. of OBGYN, University of Pisa
Dr. Rafael Sanchez Borrego, MD	Spain	President of the Spanish Menopause Society



Femarelle®

## Evolution?



*Menopause?  
Not for me...*



**Femarelle®**