## **Menopause Classification**



#### Premature Menopause

- About 8% Women (US) stops having period before age 40
- Same symptoms as Menopause

### Peri-menopause

- Average women go through this phase age 45~49
- Wildly fluctuating Estrogen Level
- Same symptoms as Menopause

#### Menopause

- Estradiol level<50 pg/mL; FSH>50 mIU/mg; no period for >1 yr\*
- Average age for onset of menopause is 52 in US
- Symptoms last 2~8 years, many more than 5 years

### Surgical Menopause

After Hysterectomy/Bilateral surgery



<sup>\*</sup> Definition: Dr. Joel Harglove, MD, Chairman, Vanderbilt Menopause Center, Nashville, TN

# Black Cohosh & Isoflavone (Soy)



#### Black Cohosh

- First developed in Germany, it has been prescription medication in EU
- Numerous clinical studies showed strong as well as mixed efficacy, until recently, it is claimed to cause liver damage (Natural Products Insider, July 30, 2007) and last 360-subject NIH sponsored clinical trial showed no efficacy (Natural Products Insider, Jan. 15, 2007)

## Isoflavone (Genistein)

- Mixed Reviews on Efficacy: Asian diets are rich in isoflavone (miso soup, tofu, soy bean paste, bean sprouts), but symptoms manifest at the same rate as in Western countries
- The key compound, Genistein, has been shown to bind to estrogen receptors alpha & beta and thus may be carcinogenic (National Toxicology Program TR 545, NIH)



## Truth of Isoflavone



#### **Clinical Research on Isoflavones**

#### **Effective Dose**

As Isoflavone Aglycones, the Symptoms Improved w/ Daily Intake of 70 ~ 100mg, but...

#### **Limitation of Dose**

Upper Limit of the Daily Intake of Isoflavone Aglycone is 30mg.

– Food Safety Commission (Japanese Government)

	Daily Intake	Researcher	Research Result	Published	
	Soy Isoflavone 34 mg	Washburn	No effect	1999	
	Soy Isoflavone 36 mg	Penotti	No effect	2003	
	Soy Isoflavone 60 mg	Duffy	No effect	2003	
	Genistein 54 mg (Isoflavone 77mg)	Crisafulli	Significant Improve	2004	
	Genistein & Daidzein 70mg (Isoflavone 79mg)	Fauer	Significant Improve	2002	
	Isoflavone 100 mg	Han	Significant Improve	2002	

## Is Isoflavone Carcinogenic?!!





## SUMMARY

In none of the three studies were there any increased rates of cancer in male rats. In female rats exposed to genistein from conception and throughout two years, the rates of admorna or adenosarcinoma of the mammary gland and pituritary gland adenoma or carcinoma were increased. In female rats exposed to genistein for 20 weeks following birth, the rates of pituritary gland adenoma or carcinoma were slightly increased, and in female rats exposed to genistein just from conception through weaning, the rates of mammary gland adenoma or adenocarcinoma were slightly increased.

#### Conclusions

Regults

We conclude that exposure to genise in for two years caused tumors of the mammary gland and pituitary gland in female rats. Exposure to genise in for shorter durations following birth was also possibly associated with increased rates of pitritury gland and mammary gland tumors.

Genistein (a major isoflavone aglycone) May Cause Cancers (NIH & FDA – National Toxicology Program, Genistein Final, Jan, 2008)

- ✓ Exposure to Genistein for 2 years caused mammary gland / pituitary gland adenoma in female rats.
- ✓ Exposure to Genistein for shorter duration following birth was also possibly associated with increased rates of pituitary gland and mammary gland tumors.

Genistein The Risks of Causing Cancer: 3 out of 4 Post Menopausal Cases of Intake of the Isoflavone – AFSSA (French Food Commission)

## Why Is GenisteinToxic?



## Cancer Causing Risks

- Isoflavone could be toxic because its high level of hormone-like action.
- It could be Hormone Dependent Cancer Causing Material due to its High Binding Affinity to Estrogen Receptor  $\alpha$ , and  $\beta$

	Relative Binding Affinity			
	α	β		
Estradiol	100	100		
Coumestrol	20	140		
Genistein	4	87		

## Isoflavone from Sources other than Soybean

- Chinese Scholar Tree (*Sophora japonica*): Isoflavone Contents 5 to 6 times Higher than Soybean

- Red Clover has also Higher Isoflavone Contents than Soybean

# **New Product Innovation:** FeminaPlus®



#### Femina Plus<sup>®</sup> has 3 herbal extracts

- Phlomis umbrosa: Shanzhiside methyl ester
- Cynanchum wilfordii: Cinnamic acid (wilfosides)
- Angelica gigas Nakai: decursin / nodakenin









## Science of EstroG-100<sup>®</sup>



- Herbal extracts screened out of 71 herbal extracts via non-reproductive tract target tissue response (E-screen test)
  - 3 herbal extracts were chosen:

Cynanchum wilfordii, Phlomis umbrosa, and Angelica gigas Nakai

- Proven Safety
  - About 400 years of documented use in Korea and China as folk medicine
  - Registered as safe food ingredient in Korea Food Codex and in China
  - No increase of uterus weight in ovariectomized rat tests
  - Inhibition of proliferation of human breast cancer cell (MCF-7)
  - No binding Affinity to both Estrogen Receptor α and β, cancer-inhibitory
  - Safe: Acute & Multi-dose toxicity tests , Genetic toxicity tests
- Proven Efficacy in vitro, in vivo, and 2 published human (Asian and non-Asian) clinical studies (one in Korea, one in USA)
- US FDA's full Acknowledgement as New Dietary Ingredient (FDA Docket No. 1995-S-0039 Report 668)
- Health Canada's Approval (Product License Issuance NPN 80026169)

# Clinical study II (Non-Asian)

## - Protocol



Randomized Double-blind, Placebo-controlled study				
	(CA, USA)			
Test material	EstroG-100			
Dosing period	3 months (2009-2010)			
Method	Double-blind			
Evaluation style	Long Term Safety Evaluation			
Patients (n=61)	32 subjects in placebo group & 29 active group			
Inclusion Criteria	Age>42 years old & Diagnosis of menopausal syndromes (average age=53)			

## Clinical Study II - Efficacy



- Report (Kupperman Menopause Index & scores of vaginal dryness )
  - Stearling IRB
- The mean KMI scores were significantly reduced in FeminaPlus group from 29.45±7.39 at baseline to 13.62±7.61 at week 6 after and to 11.31±5.78 at week 12 while those were from 29.16±6.55 at baseline to 23.31±8.96 at week 6 after and to 23.66±7.98 at week 12 in the placebo group. The improvement was statistically significant in comparison with the two groups (p<0.01, t-test).

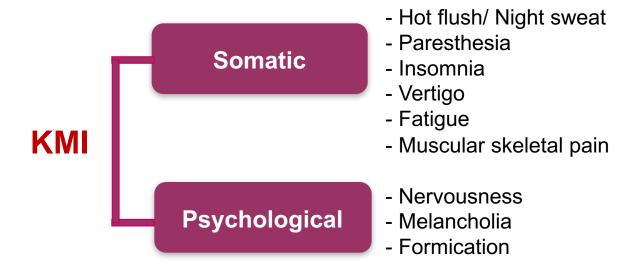


## Results



Kupperman Menopause Index and Vaginal Dryness (Difficulties in Sexual Intercourse) Improved Significantly

**Vaginal Dryness (Difficulties in Sexual Intercourse)** 

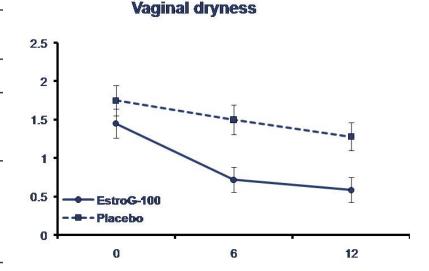


Femina Plus® was confirmed to improve both somatic and physiological symptoms with statistical significance.

# Vaginal Dryness (Difficulties in Sexual Intercourse)



	FGF-271	Placebo
	Mean±SD	Mean±SD
Week0 (Baseline)	1.45±1.02	1.75±1.11
Week6	0.72±0.88	1.50±1.11
Change from baseline	-0.72±0.84 ** <sup>##</sup>	-0.25±0.57#
Week12	0.59±0.87	1.28±1.02
Change from baseline	-0.86±0.88*##	-0.47±0.72##
		p=0.0536



\*; p-<0.05 compared between groups, \*\*; p<0.01 compared between groups by t -test ††; p<0.01 compared between groups by Wilcoxon rank sum test #; p-<0.05 compared to baseline, ##; p<0.01 compared to baseline by paired t-test

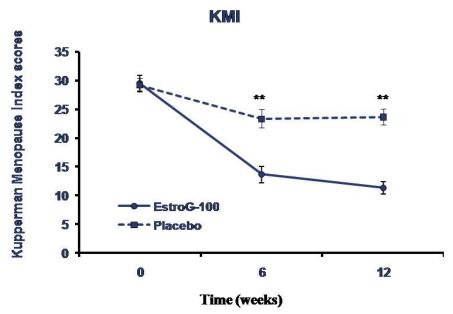
Vaginal Dryness Improved Unlike Black cohosh and Isoflavone



## **Kupperman Index**



	FGF271	Placebo
	Mean±SD	Mean±SD
Week 0 (Baseline)	29.45±7.39	29.16±6.55
Week 6	13.62±7.61	23.31±8.96
Change from baseline	-15.83±9.10 ** <sup>##</sup>	-5.84±6.15##
Week 12	11.31±5.78	23.66±7.68
Change from baseline	-18.14±8.46 ** <sup>##</sup>	-5.50±5.34##



\*\*; p<0.01 compared between groups by t -test

††; p<0.01 compared between groups by Wilcoxon rank sum test

##; p<0.01 compared to baseline by paired t-test

**Kupperman Index for Moderate to Severe Menopausal Symptoms Improved** 



## **2nd Clinical- Symptoms Analysis**



Summa to me	Femina Plus (n=29)		Placebo (n=32)			
Symptom	Week 0	Week 6	Week 12	Week 0	Week 6	Week 12
Vasomotor	2.24±0.69	1.03±0.82**††##	0.79±0.73**††##	2.22±0.66	1.78±0.75##	2.06±0.76
Paresthesia	1.31±0.85	0.59±0.78*†##	0.55±0.74*†##	1.41±0.91	1.13±0.94#	1.09±0.96##
Insomnia	2.28±0.84	1.28±0.96**†##	0.97±0.82**††##	2.03±0.86	1.63±1.01#	1.63±0.87#
Nervousness	1.72±0.88	0.76±0.69**††##	0.66±0.67**††##	1.56±0.84	1.22±0.83	1.34±0.75
Melancholia	1.93±0.88	1.03±0.68**††##	0.83±0.71**††##	1.59±0.95	1.31±0.93	1.31±0.74
Dizziness	0.97±0.82	0.21±0.49**††##	0.21±0.41**††##	0.75±0.72	0.72±0.77	0.59±0.80
Fatigue	2.21±0.77	0.90±0.77**††##	0.72±0.70**††##	2.00±0.88	1.69±0.90#	1.59±0.80#
Arthritic Pain	1.59±1.02	0.79±0.94**†##	0.55±0.78*†##	1.84±0.95	1.63±0.83	1.47±0.88
Headache	1.34±1.04	0.69±0.76##	0.66±0.77##	1.53±0.95	1.13±0.91#	0.84±0.72##
Palpitation	1.00±0.96	0.48±0.69#	0.55±0.63#	1.31±0.93	0.91±0.82##	0.75±0.84##
Formication	0.83±0.85	0.14±0.44* ##	0.28±0.45##	1.25±1.05	0.88±1.01##	0.72±0.96##

\*; *p*-<0.05 compared between groups, \*\*; p<0.01 compared between groups by t –test †; *p*-<0.05 compared between groups, ††; p<0.01 compared between groups by Wilcoxon rank sum test, #; *p*-<0.05 compared to baseline, ##; p<0.01 compared to

baseline by paired t-test