



Developing Novel Solutions for
Women's Health and Cancer Therapy

Clinically Meaningful Efficacy of a Non-Estrogen Agent, MF101, for Postmenopausal Vasomotor Symptoms

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Introduction

- MF101 is seeking approval for the treatment of postmenopausal vasomotor symptoms
- 80% of menopausal women turn to botanical dietary supplements to abate their symptoms
- MF101 is an Estrogen Receptor β Agonist
- The purpose of this study was to determine a clinically meaningful improvement in menopausal hot flushes of a non-estrogen treatment

Selecting Better/Safer Estrogens

THE IDEAL SERM:

	Bone +	Breast +	Uterus +	Brain +	Liver +	CV +
	Prevents Osteoporosis	Prevents Breast Cancer	No Endometrial Cancer	Prevents Hot flushes	No Clotting	No Stroke, CHD
Estradiol	+	-	-	+	-	-
Raloxifene	+	+	+	-	-	-
Tamoxifen	+	+	-	-	-	-

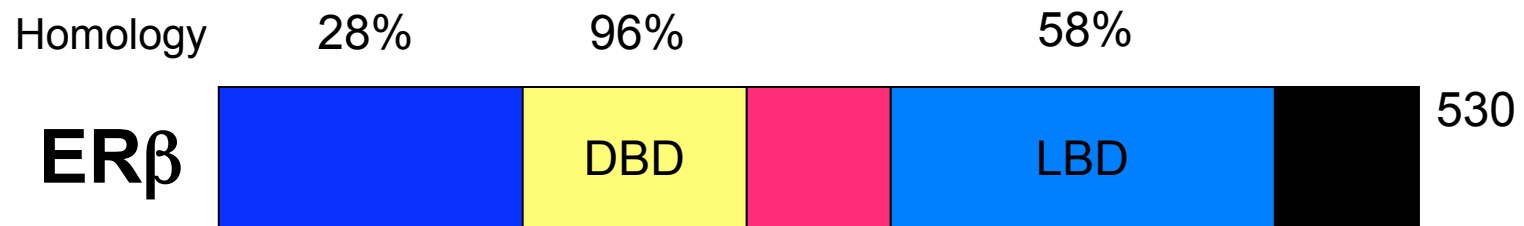
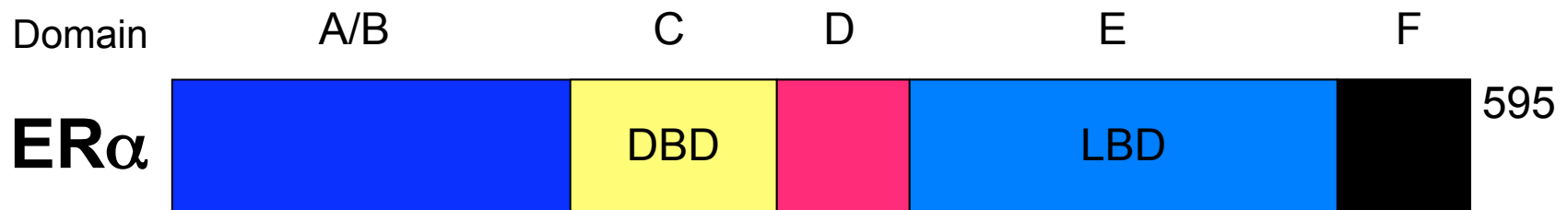
+ Positive Effect

- Negative Effect

MF101, an Estrogen Receptor β Agonist, may fit the Ideal Profile

Biological Effects of Estrogens Are Mediated by ER α and β

Six Functional Regions

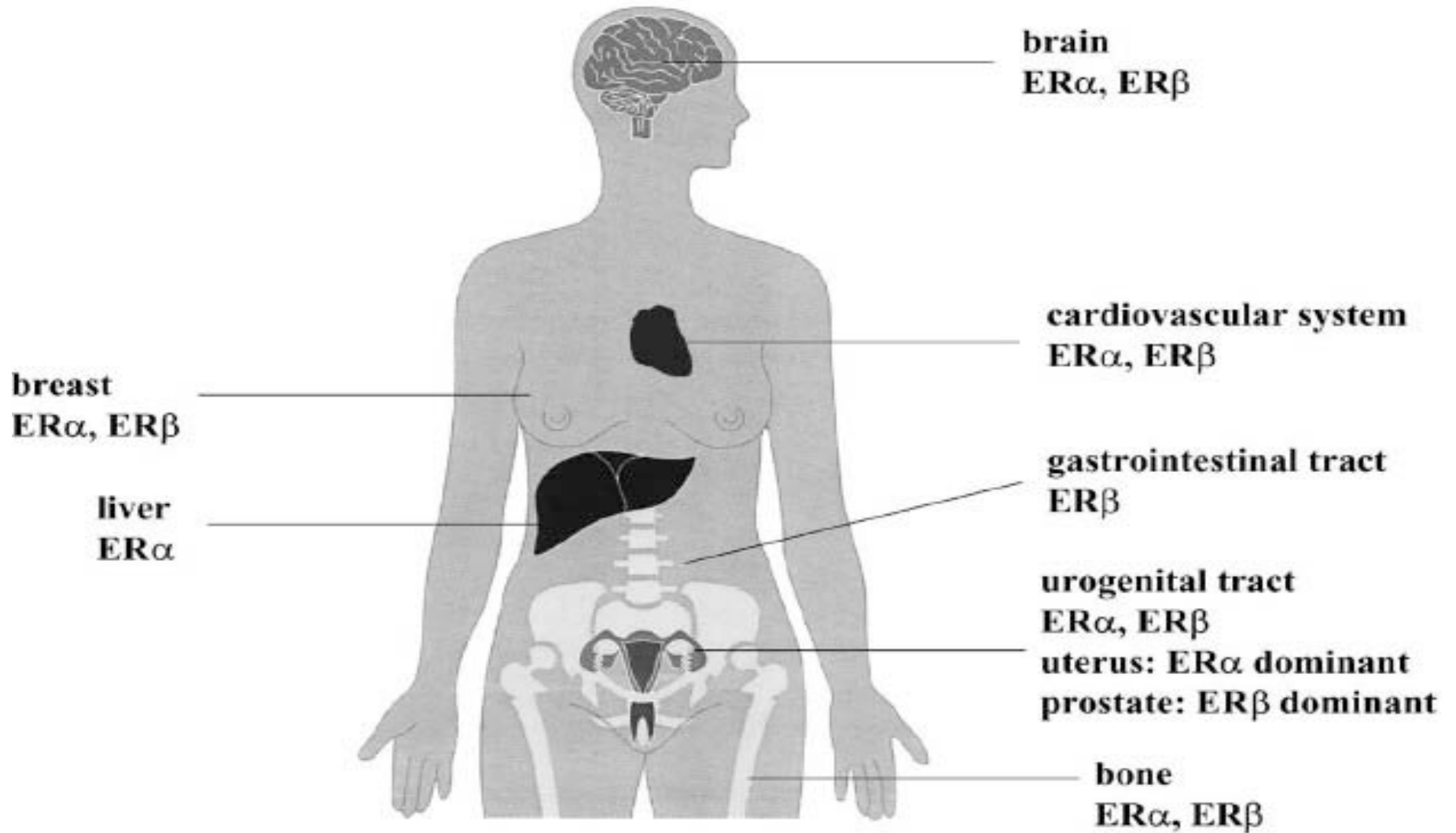


**Activation
Function 1**

**Binds
DNA**

**•Activation Function 2
•Binds ligand
•Recruits coactivators**

Tissue Distribution of ER α and ER β



Current & Potential Therapies for Vasomotor Symptoms

	Hormone Therapy	Pristiq	Gabapentin	MF101
Efficacy	60-90%	64%	67%	62%
Side Effects	breast cancer uterine cancer stroke cardiovascular disease thrombotic disease dementia	nausea (38%) body aches constipation dizziness insomnia somnolence 2 MIs and 3 coronary artery occlusions	headache (32%) somnolence dizziness weight gain jitteriness	loose stools (12%)
Dropout Rate On Drug Arms	20%	40-53%	16%*	1%
FDA approved for HF	Yes	No	No	No
Cost/ month	\$30/month	\$150/month	\$150/month	\$150/month

*Breeze 1 trial only reported the withdraws due to adverse events

The Aftermath of the WHI

- Due to risks associated with menopausal hormone therapy (MHT) that continue to be unmasked by ongoing findings from the WHI study, and given the media's widespread coverage of those risks, many women have become fearful to start or continue MHT.
- Prior to the initial publication of the WHI results, there were over 90 million prescriptions written for MHT^a and today usage has decreased by 52%^b.
- Even though MHT is very effective at preventing hot flashes, fewer women are willing to use MHT^b.
- Our previous study with MF101 showed that it had moderate efficacy for hot flush prevention, but that it was very safe^c.
- A major issue confronting postmenopausal women after the results of the WHI is whether they are willing to take alternative treatments, such as MF101, that are less effective than standard doses of MHT, but potentially safer

a. Nelson HD. Postmenopausal estrogen for treatment of hot flashes: clinical applications. *JAMA*. 2004;291(13):1621-1625.

b. Tsai SA, Stefanick ML, Stafford RS. Trends in menopausal hormone therapy use of US office-based physicians, 2000-2009. *Menopause*. 2010;18(4):000-000. DOI: 10.1097/gme.0b013e3181f43404 .

c. Grady D, Sawaya GF, Johnson KC, et al. MF101, a selective estrogen receptor beta modulator for the treatment of menopausal hot flashes: a phase II clinical trial. *Menopause*. 2009;16(3):458-465.

Pristiq (Desvenlafaxine) Received an FDA Approvable Letter

- A randomized, double-blind, placebo-controlled trial enrolled 707 healthy, postmenopausal women to one of 4 doses of Pristiq or placebo. Trial duration was 52 weeks. Primary outcomes were change from baseline in average daily number of moderate-to-severe hot flushes and in daily hot flush severity score at weeks 4 and 12.
- Desvenlafaxine 100 mg/d achieved a significantly greater reduction compared with placebo in average daily number of hot flushes at weeks 4 ($P.013$) and 12 ($P.005$), reaching a 64% decrease from baseline at week 12. Average daily severity of hot flushes was significantly lower in the desvenlafaxine 100-mg group compared with placebo at week 12 ($P.020$).
- On July 24, 2007 Wyeth received an approvable letter from the U.S. Food and Drug Administration (FDA) for Pristiq as a treatment for moderate-to-severe vasomotor symptoms.
- In its letter, the FDA said that before the application could be approved, it would be necessary for Wyeth to provide additional data regarding the potential for serious adverse cardiovascular and hepatic effects associated with the use of Pristiq in this indication. The Agency requested that these data come from a randomized, placebo-controlled clinical trial of a duration of one year or more conducted in postmenopausal women. The Agency also requested that Wyeth address certain CMC deficiencies prior to approval.
- There was no mention of any FDA concerns regarding efficacy, which set a precedence that a 64% decrease in average daily hot flushes at week 12 is clinically meaningful and adequate for FDA approval.

Speroff L, Gass M, Constantine G, Oliver S. Efficacy and tolerability of desvenlafaxine succinate treatment for menopausal vasomotor symptoms: a randomized controlled trial. *Obstet Gynecol.* 2008 Jan;111(1):77-87.

Oral 17 β Estradiol (0.25, 0.5, 1, 2 mg and placebo)

Efficacy data for 333 postmenopausal women, aged 40-60, ≥ 56 hot flushes/week

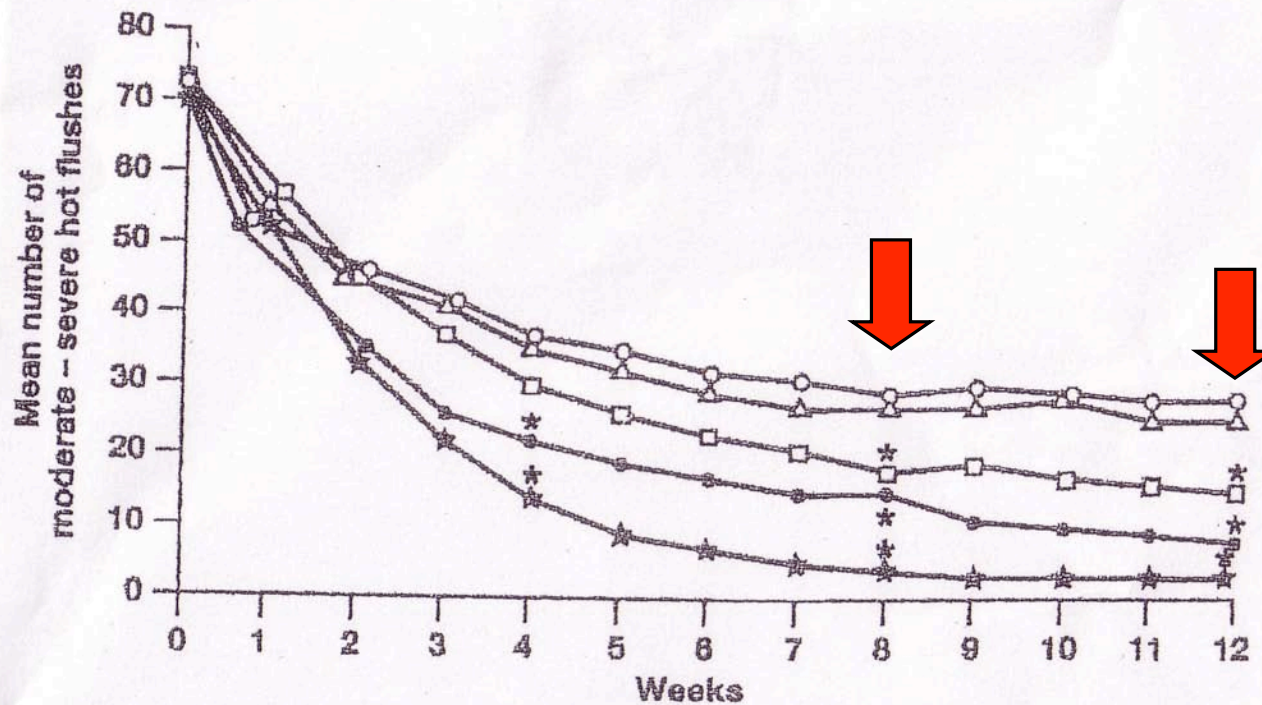


Figure 1. Mean number of moderate to severe hot flushes during 12 weeks of treatment with placebo (open circles) or 0.25 mg (open triangles), 0.5 mg (open squares), 1 mg (solid circles), or 2 mg (asterisks) 17 β -estradiol. Stars indicate statistically significant difference versus placebo.

Notelovitz et al. *Obstetrics and Gynecology*. Vol 95, No 5, Part 1, May 2000.

Hot Flush Drugs That Did Not Meet the 4 Co-Primary Endpoints

Drug and Dose	4 Week Frequency	4 Week Severity	12 Week Frequency	12 Week Frequency
Cenestin (0.45mg)	Yes	No	Yes	Yes
Elestrin (0.87g)	No	No	Yes	Yes
Enjuvia (0.3mg)	No ^a	No ^a	Yes	Yes
Divigel (0.25g)	No	No	Yes	Yes
Evamist (1-spray)	Yes	No	Yes	Yes
Femtrace (0.45mg)	Yes	No	Yes	Yes
femHRT (0.5/2.5mg)	Yes	No	Yes	Yes
Serada ^b				
1200mg (BREEZE1)	Yes	Yes	No	No
1200mg (BREEZE2)	Yes	No	Yes	No
1800mg (BREEZE1)	Yes	Yes	No	No
1800mg (BREEZE2)	Yes	Yes	No	Yes
Pristiq ^b				
50mg	No	No	No	No
100mg	Yes	No	Yes	Yes
150mg	No	No	Yes	No
200mg	No	No	No	Yes

^adid not reach statistical significance originally and was given a "no approvable letter" (May 21, 2003). In re-analysis of the data on June 29, 2004 using rank-based procedure it was statistically significant, the FDA reviewer re-analyzed the data with a Wilcoxon test, stating the preferred method, and it did reach statistical significance in all 4 co-primary endpoints.

^bNot yet FDA-approved for the treatment of vasomotor symptoms

Approved Drugs that Didn't Have a Difference in 2 Hot Flushes/Day

Drug	Difference in at least 2 Hot Flushes/Day at 4 Weeks?	Difference in at least 2 Hot Flushes/Day at 12 Weeks?
Cenestin (0.45mg)	No: 1.97	Yes
Alora (0.05mg)	No: 1.71	Yes
Elestrin (0.87g)	No: 1.4	Yes
Climara (0.025mg)	No: 1.34	No: 1.58
Enjuvia (0.3mg)	No: 1.8	Yes
Divigel (0.25g)	No: 1.37	Yes
Estrogel (1.25g)	No: 0.85	No: 1.71
Femtrace (0.45mg)	No: 1.1	No: 1.39
Serada^a		
1200mg (BREEZE1)	No: 0.9	No: 1.8
1200mg (BREEZE2)	No: 0.5	No: 1.9
1800mg (BREEZE1)	No: 1.4	No: 0.4
1800mg (BREEZE2)	No: 1.6	No: 1.3
Pristiq^a		
50mg	Not Reported	No: 0.6
100mg	Not Reported	No: 1.73
150mg	Not Reported	No: 1.44
200mg	Not Reported	No: 0.96

a. Not yet FDA-approved for the treatment of vasomotor symptoms

Independent Survey of Physicians' Opinions of VMS Treatment

- Two in-depth, structured, online, qualitative and quantitative survey approaches were used to elicit physicians' practicing patterns about HT and attitudes about MF101 as a new treatment for VMS.
- The first part of the survey dealt with the physicians' feelings regarding current therapies for VMS. The second part of the survey required physicians to read a product profile of MF101 (which was referred to as Product X) and provide professional opinions regarding MF101 as a potential treatment option for VMS.
- In order to be eligible for the panel, physicians had to meet the following criteria:
 - board certified medical doctor in internal medicine (PCP) or obstetrics and gynecology (OB/GYN),
 - 2-30 years of clinical experience,
 - currently practicing medicine in the United States,
 - >75% of professional time spent in clinical care,
 - treat a minimum number of VMS patients per month:
 - 50 patients per month for OB/GYNs
 - 10 patients per month for PCPs, and
 - no conflict of interest with the sponsor of the study based on disclosures of past and current consulting relationships.
- Twelve physicians board certified in internal medicine and eleven physicians board certified in obstetrics and gynecology participated in the web-based qualitative survey. Fifty physicians board certified in internal medicine and 51 physicians board certified obstetrics and gynecology participated in the web-based quantitative survey.
- The average number of years in clinical practice for the 23 participating physicians in the qualitative study was 15 years (range 5-27) and the average number of patients treated for VMS per month was 77 (range 20-225).
- In the quantitative study, the average number of years in clinical practice for the 101 participating physicians was 15 years (range 3-30) and the average number of patients treated for VMS per month was 64 (range 10-200).

Independent Survey of Physicians' Opinions of VMS Treatment, Cont.

- Physicians in the survey reported that 35% of their patients going through menopause are prescribed HT.
- The most commonly recommended treatments for VMS for patients who refuse to use HT were over-the-counter herbal supplements. SSRIs were also cited as alternative treatments for VMS.
- The overwhelming majority of physicians reported the greatest unmet need is for a safe therapy that would not lead to abnormal uterine bleeding or cause increased risks for breast cancer, cardiovascular disease or thromboembolic events.
- For a new therapy to treat VMS, physicians want a drug that can reduce the number of hot flushes by 63%-65%. Physicians would be satisfied with a new therapeutic agent for VMS with a side effects profile that caused untoward effects in 14%-19% of patients.
- **If available, MF101 would be used as a first-line therapy by 78% of physicians for the treatment of VMS. In addition, 92% of the physicians stated they would prescribe MF101 prior to prescribing either an SSRI or SNRI.**

Previous Publications- Butt et al

- Butt et al^a reported data on an important research question: to determine the minimal important difference in the frequency and severity of hot flashes that postmenopausal women desire from a nonhormonal agent.
- Seventeen postmenopausal women complaining of troublesome hot flashes and asking for a nonhormonal treatment for the relief of their symptoms were asked to evaluate during 1 week their hot flashes. The authors asked each woman to indicate at the end of the week the minimal percent reduction in hot flashes that she would find acceptable from a nonhormonal agent.
- Approximately 69% of the postmenopausal women who reported their hot flashes as moderate to severe responded that they wanted a nonhormonal agent that provided at least a 50% mean reduction in the frequency of hot flashes (95% CI, 32% to 66%).
- This study paved the way for future trials to evaluate this important question of women's expectations and degree of satisfaction with specific therapeutic agents.

a. Butt DA, Deng LY, Lewis JE, Lock M. Minimal decrease in hot flashes desired by postmenopausal women in family practice. *Menopause*. 2007;14:203-207.

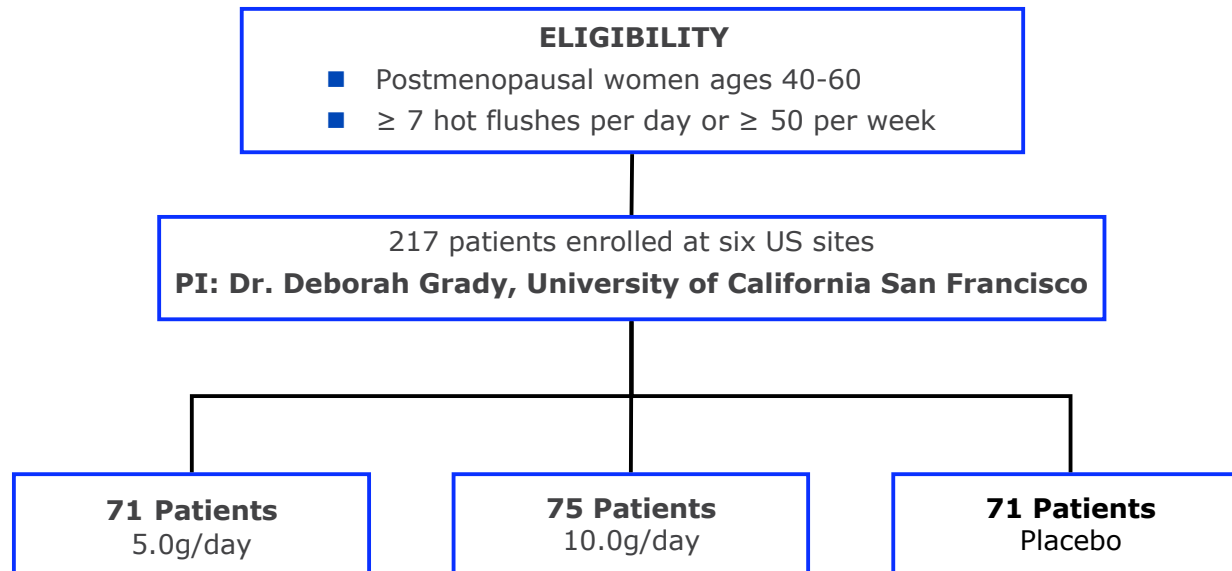
Previous Publication- Wyrwich et al

- Wyrwich et al^a reported data on treatment satisfaction thresholds for interpreting treatment-related changes in vasomotor symptoms.
- 620 postmenopausal women with moderate to severe vasomotor symptoms participated in a double-blind, placebo-controlled trial and were randomly assigned to placebo or 50, 100, 150, or 200 mg desvenlafaxine. At week 12, responses to the Menopause Symptoms Treatment Satisfaction Questionnaire were compared with efficacy results.
- Among the 620 postmenopausal women with moderate to severe vasomotor symptoms, the treatment satisfaction thresholds that were meaningful to participants were 1.64 fewer moderate to severe hot flushes per day and 0.42 fewer nighttime awakenings per night.

a. Wyrwich KW, Spratt DI, Gass M, Yu H, Bobula JD. Identifying meaningful differences in vasomotor symptoms among menopausal women. *Menopause*. 2008;15:698-705.

Completed Phase 2 Clinical Trial Design

Positive Safety, Efficacy and Tolerability Data from Completed Phase 2 Trial Per FDA Guidance of 217 Postmenopausal Women with Moderate to Severe Hot Flushes



PRIMARY ENDPOINTS

(Assessed at baseline, week 4, week 12)

- Change in frequency of hot flushes
- Change in severity of hot flushes

Phase 2 Clinical Trial Results

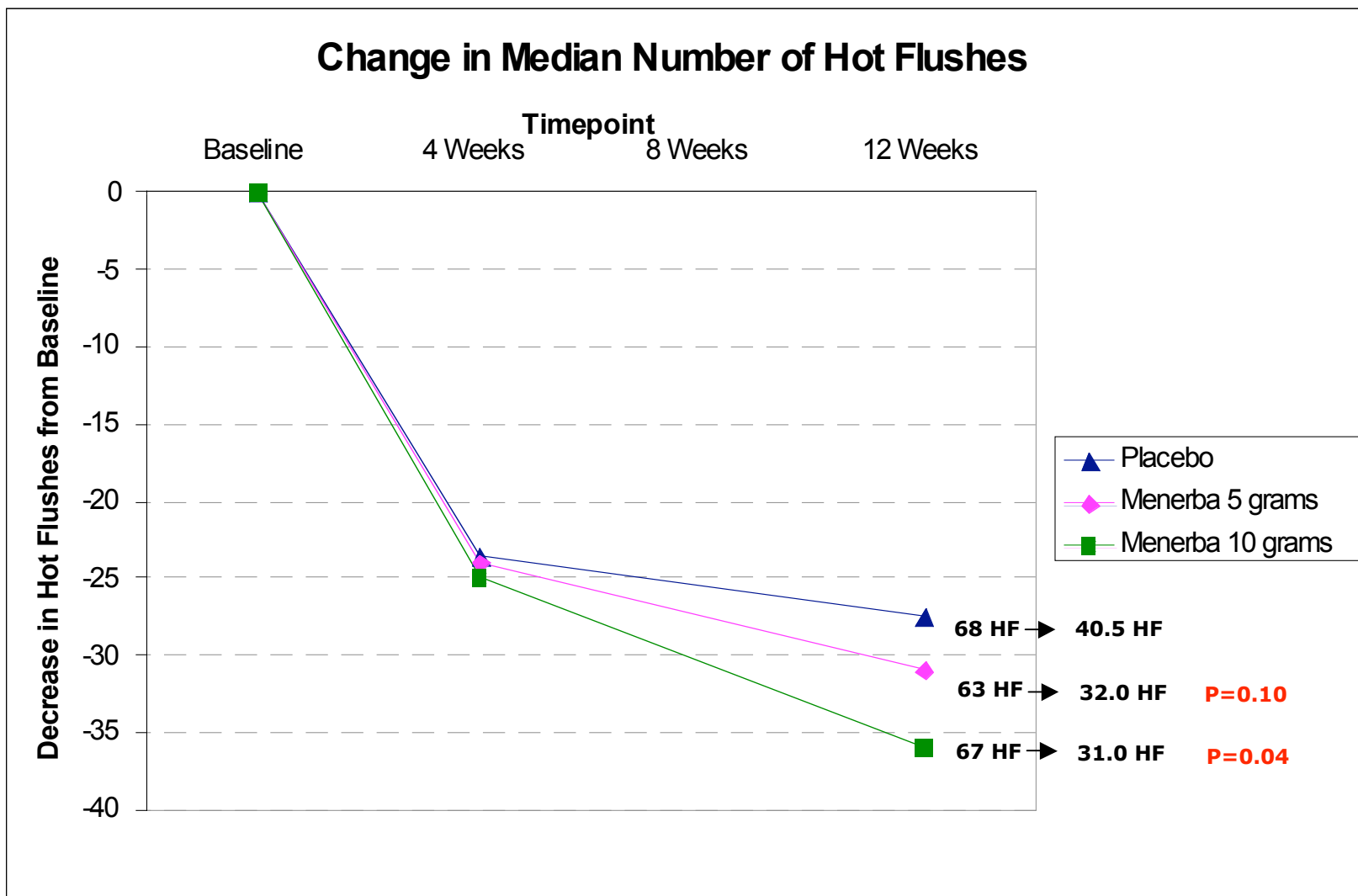
Efficacy

- MF101 demonstrated statistically significant ($p=0.04$) results in the high dose group
- 62% reduction in moderate to severe hot flushes
- Odds ratio of 60% reduction on MF101 vs. placebo was 2.4 ($p=0.02$)
- MF101 exhibits a clear dose response curve
- Higher dose (3x) to be included in Phase 3 trial

Safety

- No difference in the number of uterine bleeding episodes between treatment and placebo
- No cases of endometrial hyperplasia
- “Transient loose stools” was the only side effect (12.0% vs. 3.0% for placebo)
 - Benefit from reduced constipation on MF101 vs. placebo (1.3% vs. 4.0%)
- Statistically significant reduction in weight ($p=0.04$) and BMI ($p=0.05$) on MF101 versus placebo
- Trend toward reduction in blood pressure
- 91.0% of participants used greater than 75.0% of study medication during the 12 week period
 - Low drop out rate (2.0%)

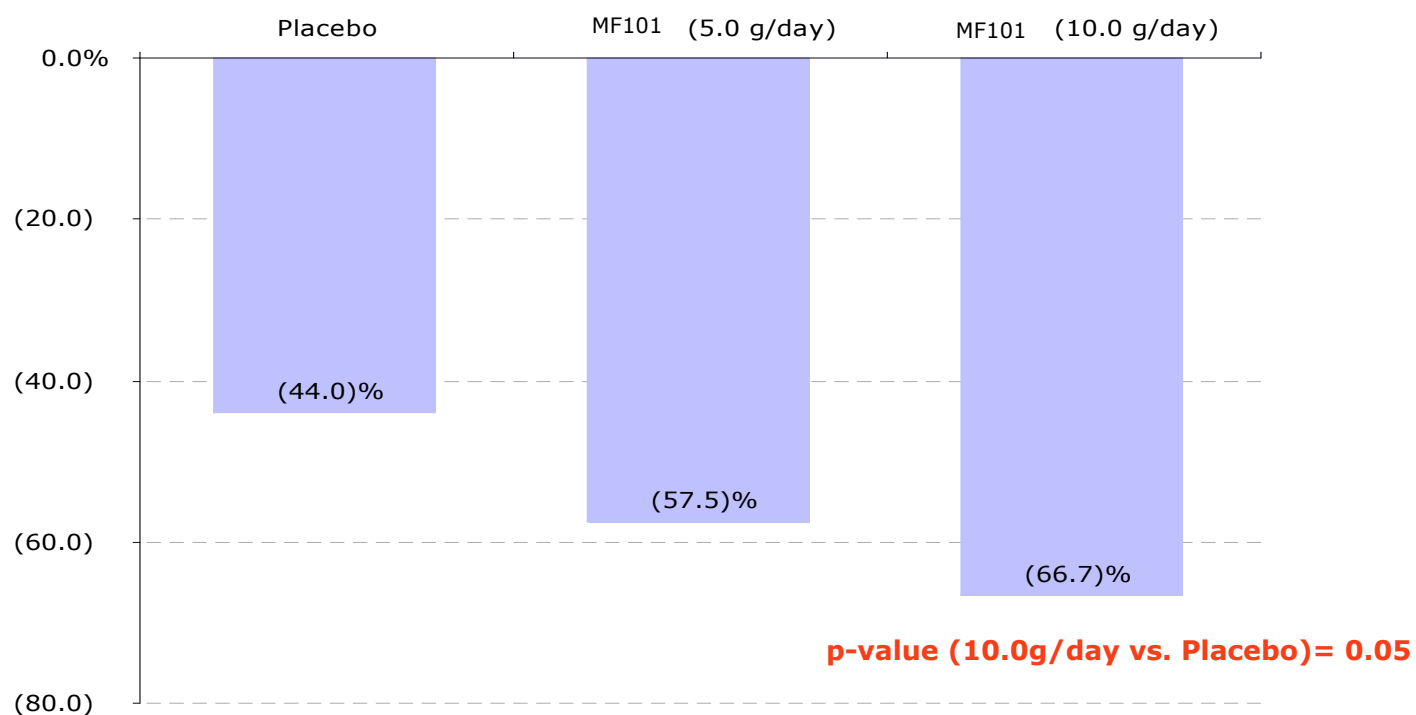
Phase 2 Efficacy Data



Reduction in Nighttime Awakenings

MF101 demonstrated a significant reduction in nighttime awakenings, a common issue with hot flushes compared to placebo group

(Median % Reduction at 12 Weeks)



Source: Data from Phase 2 clinical trial of MF101.

Phase 2 Endometrial Safety

Endometrial Abnormality	Placebo N = 52	MF101 5g/d N=52	MF101 10g/d N = 60
Vaginal bleeding	6	5	8
Biopsy completed	4	4	7
Thickened endometrium	3	7	11*
Biopsy completed	3	4	10

Histology, N	Placebo (n=7)	MF101 5 g/d (n=6)	MF101 10g/d (n=12)
Insufficient tissue	1	0	1
Normal/benign	6	6	11
Inactive/atrophic	4	5	8
Proliferative	2	1	2
Secretory	0	0	1
Hyperplasia or cancer	0	0	0

- No difference in number of cases of vaginal bleeding at 12 weeks
- No difference in mean endometrial double wall thickness at 12 weeks
- No difference in mean estradiol levels at 12 weeks
- **No cases of endometrial hyperplasia or cancer**
- Statistically significant difference in number of women who met an arbitrary pre-set cutoff point for endometrial biopsy (>5mm in double wall thickness at study termination or >2mm increase in thickness over baseline).
- Endometrial safety will be carefully evaluated in both Phase 3 trials with endometrial biopsies.

Clinically Meaningful Efficacy of MF101

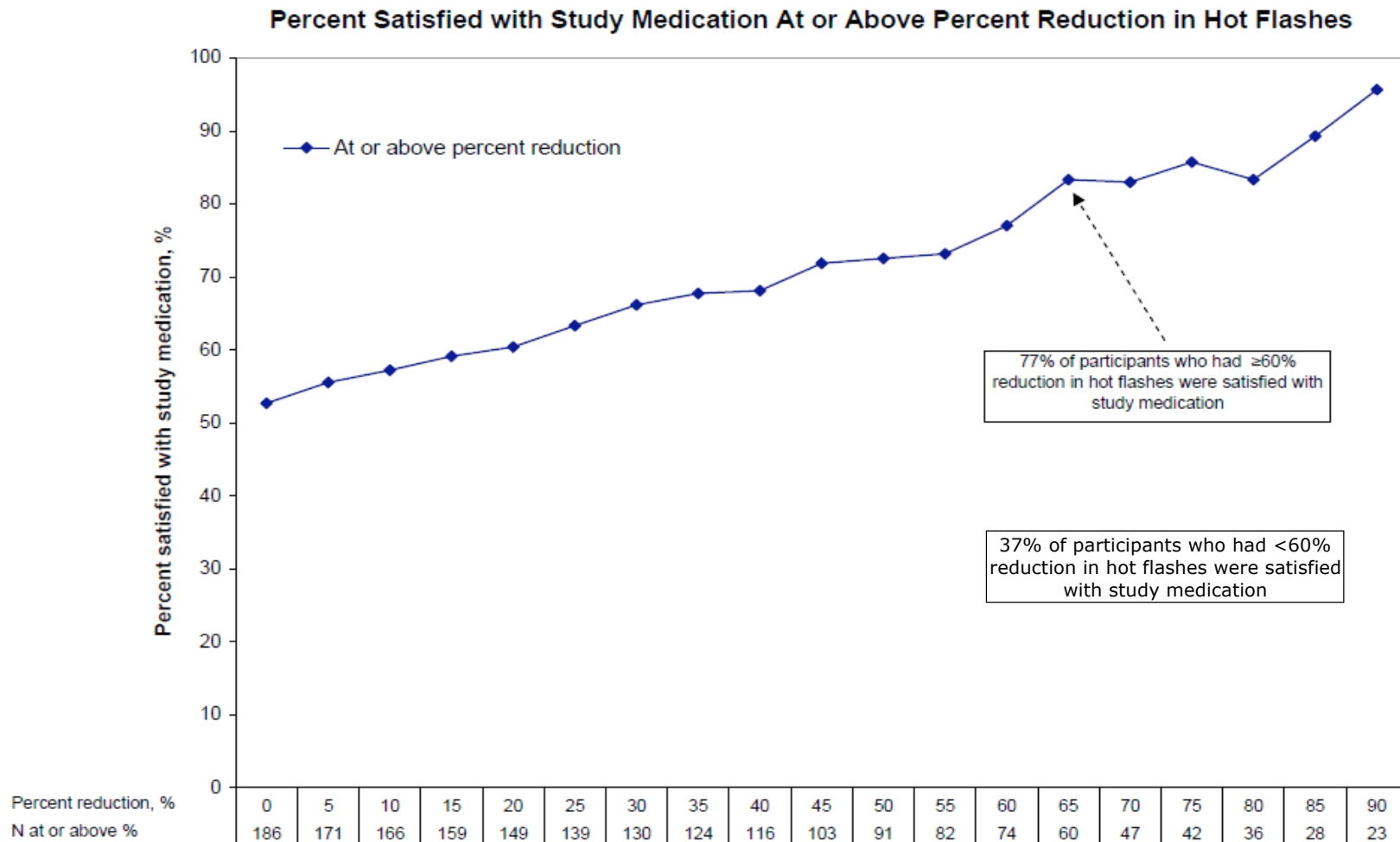
Methods

- We performed a re-analysis of data from a double-blinded, placebo-controlled trial of 217 postmenopausal women randomized to treatment with MF101 or placebo for 12 weeks to evaluate if the clinical efficacy of MF101 correlates with willingness of postmenopausal women to use MF101 for the treatment of hot flushes.
- Hot flush frequency was recorded on a diary modeled after a diary widely used in prior studies. The 7-day diary was completed prior to randomization and at 12 weeks on study medication.
- 12 weeks after treatment, prior to un-blinding, all participants were asked, “Were you satisfied enough with the study medication that you would like to continue taking it for hot flushes?” with possible responses of yes, no or don’t know/not sure.
- The current analyses include all participants in the trial, regardless of assignment to MF101 or placebo.
- We used separate logistic regression models to evaluate whether a 50% reduction or 60% reduction in hot flushes was associated with willingness to continue treatment.
- Differences in willingness to continue treatment by MF101 dose was estimated by including a treatment group hot flush reduction interaction term in the logistic regression model.

Results

- Participants averaged 54 years old and reported 9.8 (SD 3.7) hot flushes per day at baseline.
- The trial was completed by 98% of the participants.
- After 12 weeks of treatment, more women who had a 50% reduction in hot flushes were willing to continue treatment compared to women with less than a 50% reduction, 73% and 34%, respectively ($p < 0.001$).
- Similarly, 77% of women with at least a 60% reduction in hot flushes were willing to continue treatment compared to 37% of women with less than 60% reduction ($p < 0.001$).
- There was no linear relationship between more improvement and greater willingness to continue therapy from 60 to 80% reduction of hot flushes (test for linear trend $p = 0.51$).
- In addition, there was no difference in the willingness to continue treatment by dose of MF101, with 71% and 74% of women with at least a 50% reduction for the 5 gram and 10 gram dose, respectively ($p = 0.72$).

Proportion of Women Willing to Continue Treatment



Odds Ratio for Willingness to Continue Treatment

- The odds ratio for willingness to continue treatment with a $\geq 50\%$ or $\geq 60\%$ reduction in hot flushes after 12 weeks of treatment was 5.1 ($p < 0.001$) and 5.8 ($p < 0.001$), respectively.

Willingness to Continue Treatment after Hot Flush Reduction*	Odds Ratio (95% CI)	P-Value
50% or greater reduction in hot flushes vs < 50% reduction at 12 weeks	5.1 (2.8, 9.2)	<0.001
60% or greater reduction in hot flushes vs < 60% reduction at 12 weeks	5.8 (3.0, 11.1)	<0.001

*Odds ratios, 95% confidence intervals and p-values were calculated from logistic regression models.

Responder Analysis

- In the responder analysis, compared to placebo, participants in the MF101 10 grams/day group were 2.3 and 2.4 fold more likely to have at least a 50% or 60% reduction in all hot flushes at 12 weeks of treatment (OR 2.3, p=0.03 or OR 2.4, p=0.02) respectively.

MF101 10 grams/day Versus Placebo*	Odds Ratio (95% CI)	P-Value
50% reduction in hot flushes at 12 weeks	2.3 (1.1 – 4.7)	0.03
60% reduction in hot flushes at 12 weeks	2.4 (1.1 – 5.3)	0.02

*Odds ratios, 95% confidence intervals and p-values were calculated from logistic regression models

Conclusions

- In the Phase 2 trial with 217 postmenopausal women, who on average had 9.8 hot flushes per day, the majority of women wanted to continue treatment if they had on average a 50% reduction in hot flushes.
- Given there was no linear relationship between more improvement and greater willingness to continue therapy from 60 to 80% reduction of hot flushes, it may be that symptomatic menopausal women are equally satisfied with therapies that reduce hot flushes significantly and with non-estrogenic agents, such as MF101, that at the doses tested have more moderate efficacy.
- A prior study showed that postmenopausal women with moderate to severe hot flushes were willing to take a non-estrogen agent if it reduced the frequency of hot flushes by at least 50%^a.
- Our results showed that only 34% of the women with less than a 50% reduction were willing to continue treatment in contrast to 73% of the women with greater than 50% reduction (OR 5.1, $p < 0.001$).

a. Butt DA, Deng LY, Lewis JE, Lock M. Minimal decrease in hot flashes desired by postmenopausal women in family practice. *Menopause*. 2007;14:203-207.

Conclusions

- This study is the first prospective analysis from a randomized clinical trial that provides insight into the degree of efficacy that is clinically meaningful to women with menopausal hot flashes.
- This type of data can have important clinical implications when alternative drugs, such as MF101 are compared to current MHT regimens for safety and efficacy, because they indicate that many women are willing to take safe, alternative drugs that reach a degree of efficacy, even if it is less than MHT.
- To further evaluate this important question, we will conduct a large Phase 3 clinical trial with 1,200 postmenopausal women to assess the efficacy and safety of 2 doses of MF101 compared to placebo for the treatment of moderate to severe hot flashes.
- 50 clinical sites in the United States will participate in the Phase 3 trial and Dr. Wulf Utian will serve as the Principal Investigator.
- Enrollment to this study, allowing for more definitive data, is anticipated to begin later this year.

■ Thank you to all the patients who participated in the trial.

■ Thank you to all the authors of the abstract.

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