

Bionovo, Inc.
Initiation of Coverage

Bionovo is developing *Menerba* (MF101) for menopausal hot flashes. Phase II results indicate that the drug is effective at reducing vasomotor symptoms associated with menopause and has a very strong safety profile. After recent successful financing activity, a pivotal Phase III program is expected to begin in mid-2011.

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FDA has Approved Bionovo's CMC Plan for the Development of *Menerba*. Bionovo is developing a non-hormonal therapy for the treatment of vasomotor symptoms related to menopause. The drug, *Menerba*, is selective for estrogen receptor beta (ER- β) and is comprised of compounds purified from 22 botanical species used in traditional Chinese medicine. *Menerba* has an excellent safety profile, especially when compared to currently available therapies and other drugs in development. Because of the drug's botanical composition, which falls under relatively new and untested regulatory guidelines, Bionovo had to undergo a precedent setting, in-depth Chemistry, Manufacturing and Controls (CMC) review with the FDA. Successful completion of the CMC plan has set the stage for Phase III trials.

***Menerba* is Entering Pivotal Trials for the Treatment of Menopausal Hot Flashes.** Bionovo has advanced *Menerba* through Phase II clinical testing. During the Phase II trial, Bionovo identified a dose of *Menerba* that was statistically superior to placebo and extremely well tolerated. There was a clear dose response trend. Although the level of efficacy demonstrated by *Menerba* was in the target range for FDA approval of a non-estrogen agent, higher doses will be evaluated in the Phase III program to reach levels of efficacy similar to standard doses of hormone replacement therapy (HRT). The FDA has asked Bionovo to evaluate the tolerability and safety of 2 higher doses of *Menerba* over 28 days of treatment in a small Phase I trial (n = 40) to ensure the safety of the higher dose, and that trial has begun. The completion of this small trial will set the stage for identifying the two doses to be evaluated in the pivotal Phase III trial scheduled to commence in mid-2011. The double-blind, placebo-controlled Phase III trial will enroll 1200 patients. Patients will be randomized to receive one of two doses of *Menerba* or placebo for 12 weeks. The primary endpoint of the trial is change in frequency of moderate to severe hot flashes. A second Phase III trial of 680 patients will be required to

Ticker	BNVI
Price	\$0.59
Market Cap (M)	\$32.2
EV (M)	\$3.0
Shares Outstanding (M)	54.6
Avg. Daily Vol.	456,676
52-week Range:	\$0.52-\$3.15
Cash (M)	\$30.6
Net Cash/Share	\$0.54
Debt (M)	\$1.4
Annualized Cash Burn (M)	\$18.2
Years of Cash Left	1.7
Short Interest (M)	0.511
Short Interest (% of Float)	1.0%

	FY Dec	2009A	2010A	2011
EPS:	Q1	(\$0.24)A	(\$0.20)A	N/A
(GAAP)	Q2	(\$0.25)A	(\$0.20)A	N/A
	Q3	(\$0.24)A	(\$0.21)A	N/A
	Q4	(\$0.18)A	(\$0.18)A	N/A
	FY	(\$0.98)A	(\$0.80)A	N/A

assess the long term safety profile for *Menerba*. The two Phase III trials could proceed in parallel if the company secures adequate funding through a partnership or other means.

The *Menerba* Clinical Development Program is Supported by Strong Phase II Data. Bionovo completed a Phase II trial of *Menerba* for the treatment of menopausal hot flashes. The results were published in the *Journal of the North American Menopause Society*. The trial enrolled 217 women who were randomized to receive one of two doses of *Menerba* (5 g or 10 g) or placebo. In the 12 week trial, there was a statistically significant reduction in the frequency of all hot flashes in patients taking the higher dose of *Menerba* compared to placebo. Treated patients were 2.3 times more likely to have a 50% reduction in all hot flashes compared to those on placebo. *Menerba* treated patients also experienced an improvement in night time awakenings from hot flashes and some weight loss. The only (minor) adverse event reported in the trial was transient loose stools, which resolved without intervention. This problem will likely be mitigated with the new *Menerba* formulation.

Significant Market Opportunity for *Menerba*. There is a significant unmet need for safe, effective treatments for menopausal hot flashes. HRT, previously the standard of care, was revealed by the Women's Health Initiative (WHI) study in 2002 to increase the risks of cancer, cardiovascular disease, stroke, thromboembolic events and dementia. Before the study results were published, Wyeth's reported sales for their HRT franchise was \$2.1 billion and over 90 million prescriptions for HRT were written annually in the US. Following the results of the WHI study, and due to the multiple safety concerns it revealed, HRT use dropped precipitously so that now fewer than half as many prescriptions are written than before the study. The large number of discontinuations after the study and the fact that women are unwilling to initiate HRT therapy demonstrates the unmet need. Today, there are 40 million women in the US transitioning through menopause and up to 80% of them will experience hot flashes for an average of 4 years.¹ These symptoms are very debilitating, and there are no other FDA approved therapies for this indication. So, even though all HRT products have 7 black box warnings, some patients continue to take HRT despite the risks. A novel treatment that is not associated with serious side effects has blockbuster potential, even with a relatively small market share.

***Menerba* is a Selective Agonist of Estrogen Receptor β .** There are two distinct estrogen receptors (ERs), known as ER α and ER β . ER α has been shown to be involved in the proliferation of cancer cells and is often expressed in breast tumors. Activation of ER β has been shown in pre-clinical studies to inhibit the proliferation of breast cancer cells. Hormones such as estrogen are not selective ER agonists, and are associated with an increased cancer risk. A selective ER agonist such as *Menerba* has the potential to regulate hot flashes associated with menopause without the increased cancer risk associated with hormone replacement therapy.

***Menerba* Compares very favorably to Other Drugs in Development and on the Market.** There are currently two other non-hormonal drugs in development for the treatment of menopausal hot flashes. Depomed is developing *Serada* and Pfizer is developing *Pristiq*. In trials to date *Menerba* has demonstrated efficacy that is comparable to these drugs, and similar to low doses of estrogen, with a vastly favorable safety profile. Minor gastrointestinal side effects were the only AE experienced by *Menerba* patients. Patients treated with *Pristiq* experienced significant nausea and insomnia while *Serada* patients experienced dizziness and somnolence, two side effects that make driving difficult. In contrast to the trend with other drugs in development, patients taking *Menerba* experienced moderate weight loss. *Menerba* is the only drug in development to significantly improve night time awakenings

¹ Kronenberg, F; Hot flashes: epidemiology and physiology. *Ann N Y Acad Sci*. 1990; 592:52-86; discussion 123-133.

due to hot flashes. Finally, the strong safety profile of *Menerba* will allow for the testing of higher doses, which may improve the efficacy well beyond that of the non-hormonal competitors and similar to standard doses of estrogen.

Bionovo Possesses a Strong Pipeline of Drugs for Women's Health. In addition to *Menerba* for menopausal hot flashes, Bionovo is developing a variety of other therapies targeting unmet medical needs in women's health and cancer. *Bezielle* is ready to enter Phase II trials for the treatment of advanced breast cancer, and is also being studied in pancreatic cancer. *Seala* is a non-hormonal treatment for postmenopausal vaginal atrophy and dryness. The *Seala* program is ready to enter Phase I/II testing. In addition to these programs, the company is conducting clinical and preclinical testing of other promising cancer treatments. All of the drugs in Bionovo's pipeline are derived from botanical species used in traditional Chinese medicine, have novel mechanisms of action for important unmet medical needs, and exhibit strong safety profiles.

Recent Financing Activity/Cash. In February of this year Bionovo completed an underwritten public offering of 30,031,200 units at a price per unit of \$1.00. Each unit consisted of one share of common stock and a warrant to purchase one half of one share of stock at an exercise price of \$1.30 per share. The warrants may be exercised any time after closing and will expire after five years. The net proceeds of this offering were approximately \$28 million. In addition to the stock offering, Bionovo also received grants totaling approximately \$498,000 in November 2010 from the Qualifying Therapeutic Discovery Project Credit (QTDP) program. The grants, created to provide incentive to smaller companies focusing on innovative therapies, are intended to fund the *Menerba* and *Bezielle* programs for menopausal symptom alleviation and treatment of advanced breast cancer, respectively. The company finished 2010 with cash and cash equivalents of approximately \$2.6 million, which was before the financing activity in the first quarter.

YoY Financials. Bionovo reported a 2010 net loss of \$17.7 million or \$0.80 per share and revenues of \$0.6 million. This compared to a net loss in 2009 of \$16.4 million or \$0.98/share and revenues of about \$0.3 million. In both years, the revenues were realized from government grants. Expenses incurred supporting the *Menerba* manufacturing development process were the primary driver of the increased loss in 2010. Bionovo ended the year with cash and cash equivalents totaling about \$2.6 million.

Financial Outlook. After the recently completed round of financing, in which Bionovo raised about \$28 million, the company is on solid financial footing for the foreseeable future. Research and development costs will increase in 2011 as the company incurs increasing clinical costs due to the pivotal trials of *Menerba* for the treatment of menopausal hot flashes. Bionovo has estimated that the total cost of first Phase III trial will be \$25 million and results are expected in Q4 2012. The possibility exists for the Company to find a partner to help fund the second Phase III trial of *Menerba* and to help with commercialization and launch.

Expected Upcoming Milestones

- Q2 2011: Conduct a 40-patient Phase I trial testing the tolerability of two higher doses of *Menerba*.
- Q2 2011: Initiate non-clinical toxicity studies in two animal species.
- Q2 2011: Manufacture of *Menerba* for Phase III studies using FDA-approved process.
- Q2 2011: Complete contracts, training and IRB approval at US Phase III clinical sites.
- Q3 2011: Initiation of Phase III trial of *Menerba* for hot flashes in post-menopausal women.
- Q4 2011: First of five DSMB reviews of the ongoing Phase III trial.
- Q2 2012: Completion of patient enrollment for the Phase III trial.
- Q4 2012: Expected top-line data from the Phase III trial.

Company Description

Based in Emeryville, California, Bionovo, Inc. is a clinical stage drug discovery and development company focused on safe and effective treatments for women's health and cancer. All drug candidates address markets with significant unmet needs and billions of dollars in potential annual revenue. The company applies its expertise in the biology of menopause and cancer to design new drugs with novel mechanisms of action. The company's drug development process utilizes botanical sources known from traditional Chinese medicine (TCM). The company is integrating state of the art bio-pharmaceutical sciences with the age old empirical knowledge of Chinese medicine, which served the medical needs of Far Asian civilization for centuries. Rather than looking for designed compounds that only ensure intellectual property, Bionovo focuses on systems biology. Striving to understand the indications for its drugs, the company hopes to find therapies that are more likely to emulate nature. To this end, the company applies scientific rigor by purifying and studying the pharmaceutically active compounds in the botanical extracts. Identification of the relevant biologically active compounds leads to an understanding of mechanism of action, strengthens patent protection and opens the door to designing synthetic drugs in the future. Based on the results of early and mid-stage clinical trials, Bionovo believes they possess new classes of drug candidates within their rich discovery pipeline with the potential to be leaders in their respective markets.

Menerba (MF-101): Treatment for Menopausal Hot Flashes

Bionovo's lead development candidate *Menerba* (also known as MF101), which is being tested for the relief of menopausal hot flashes, is a new type of Selective Estrogen Receptor Modulator (SERM). *Menerba* is manufactured from botanical raw materials that have been safely used in humans for centuries. Bionovo's goal in developing this drug is to offer a safe, efficacious alternative to hormone replacement therapy (HRT) for the reduction of menopausal hot flashes. HRT, which has long been used for this indication, has been found to lead to a variety of unintended consequences, including increased risk for breast and uterine cancer, thromboembolism, stroke, cardiovascular disease and dementia. These therapies now carry strong safety warnings and their use has decreased due to these concerns. In clinical trials that have been completed to date, *Menerba* has exhibited a superior safety profile to HRT and all drugs in clinical development for this indication. Moreover, a strong expertise in the underlying biology of menopause has allowed Bionovo to develop this drug to potentially reduce the risks associated with HRT.

Patients take *Menerba* orally twice a day, and the drug itself consists of the purified small molecules from the aqueous extract from a group of 22 different botanical raw materials, each of which is

known in traditional Chinese medicine and contains ER β selective compounds.² The exact composition of the botanicals that are used in the treatment is detailed in **Figure 1** below. The selection of these particular materials was inspired by a historical understanding of their efficacy, a large number anecdotal success stories, and their ER β selective biological activity. The botanical raw material is carefully selected from specific sites in China and the plants are shipped to Bionovo's facility where the drug is made. The first step in ensuring a high-quality product is to verify the sourcing of all botanical materials. In addition to written certifications of authenticity from suppliers, a variety of multidisciplinary chemical and biological tests allow Bionovo to control the quality of each lot of plant material before it is introduced to the manufacturing process. Bionovo uses its proprietary extraction and purification technology to derive the biological drug substance. Finally, drug substance is formulated with taste enhancing excipients to yield the deliverable drug product.

² Cvoro, A., et. al; Selective Activation of Estrogen Receptor β Transcriptional Pathways by an Herbal Extract. *Endocrinology*. Vol. 148, No. 2 538-547.

Figure 1: Botanical Composition of *Menerba*

Botanical Name	Family	Pre-Extraction Percentage ¹
<i>Scutellaria barbata</i> D. Don	Lamiaceae	11.2%
<i>Sophorae Subprostratae</i> or <i>Tokinensis</i> Gapnep	Leguminosae	5.6%
<i>Anemarrhenae asphoeloides</i> Bunge	Liliaceae	4.5%
<i>Glycine soja</i> Sieb. Et Zucc.	Leguminosae	7.5%
<i>Glycyrrhizae uralensis</i> Fisch.	Leguminosae	3%
<i>Rheum palmatum</i> L.	Polygonaceae	3%
<i>Triticum sativum</i> L.	Gramineae	5.6%
<i>Astragalus membranaceus</i> Fisch. Bge. Var. <i>mongolicus</i> Bge.	Leguminosae	4.5%
<i>Rehmannia glutinosa</i> Libosch.	Scropuhulariaceae	4.5%
<i>Ligustrum lucidum</i> Ait.	Oleaceae	5.6%
<i>Ziziphus jujuba</i> Mill. Var <i>spinosa</i> Bunge Hu ex H.F. Chou	Rhamnaceae	3.7%
<i>Nelumbo nucifera</i> Gaertner	Nymphaeaceae	3.7%
<i>Poria cocos</i> Schw. Wolf	Polyporaceae	3.7%
<i>Alisma orientalis</i> Sam. Juzep.	Alismataceae	3.7%
<i>Paeonia suffruticosa</i> Andr.	Ranunculaceae	3%
<i>Cornus officinalis</i> Sieb. Et Zucc.	Cornaceae	3.7%
<i>Achyranthes bidentata</i> Bl.	Amarathaceae	3.7%
<i>Ostrea gigas</i> Thunberg	Osteridae	4.5%
<i>Asparagus cochinchinensis</i> Lour. Merr.	Liliaceae	4.5%
<i>Pueraria lobata</i> Willd. Ohwi	Leguminosae	3.7%
<i>Atractylodes macrocephala</i> Koidz	Compositae	3.7%
<i>Epimedium brevicornum</i> Maxim.	Berberidaceae	3%
<i>Total</i>		<i>100%</i>

¹ Percentage of total weight for each dry plant in the mixture before extraction.

Source: Grady et. al.³

Recently, Bionovo added an extra filtration step to remove soluble fiber that is not an active ingredient. As a result, the actual amount of material distributed for a given dose in future clinical trials will be reduced by 50%. It is suspected that the exclusion of the soluble fiber will also decrease the incidence of loose stool, the only minor side effect associated with *Menerba*. As part of the change in manufacturing, it is important to remember that the **doses listed in ongoing clinical trials are twice as potent as the doses used in previous trials**. So, for example, a Phase II dose of 10 g/day is equivalent to a 5 g/day dose in the Phase III trial.

³ Grady, D., et al.; Menopause: The Journal of The North American Menopause Society. May-Jun 2009, 16(3); 458-465.

The second important step for the company is to ensure the safety and quality of the delivered product. Before releasing each batch of drug, it is submitted to rigorous spectroscopic examination and biological tests such as estrogen receptor beta bioassays for dose and consistency determination. Spectroscopically, each batch must match a specific profile, or fingerprint, with a high level of consistency. The innovative nature of the manufacturing process, which adheres to new FDA regulatory guidance that has never before been applied to an oral botanical agent, caused some delays for the Company as they pursued a Chemistry, Manufacturing and Controls (CMC) plan. Whereas the FDA is accustomed to working with drugs such as small molecules, which have a very specific chemical profile, the use of a mixture in this case mandated some new protocols. However, scrutiny of the manufacturing process has led to a very strong, precedent setting plan that ensures consistency and reproducibility of *Menerba* for on-going clinical trials and eventually marketing.

The drug product is delivered to patients as a powdered sachet. Patients dissolve the contents in water and drink it. Flavoring and sweeteners are used to mask the bitter flavor of the plant compounds. In the ongoing clinical trials, the same flavorings and sweeteners are mixed with maltodextrin to create the placebo. The final, marketed form of the drug will likely be very similar to that used in the trials. Using currently identified sources of botanical materials, Bionovo has the capacity to make up to 1 million doses/year. If *Menerba* is very successful the company may have to develop independent sources of some of the active ingredients, although that possibility is many years off at this point. Regardless, the Company has embarked on agricultural R&D for some of the botanicals that require longer lead time.

A BACKGROUND ON MENOPAUSE

Derived from the Greek words *men-* (month) and *pausis* (cessation), menopause refers to the programmed termination of the primary functioning of the ovaries, including the menstrual cycle, that occurs only in human females and a few other primates.⁴ Although menopause is sometimes medically induced for various reasons, the usual cause is the natural slowing and loss of ovarian follicular function due to aging. Every woman who reaches middle age will undergo this change. According to the North American Menopause Society (NAMS), menopause begins at age 51 on average, but this number is highly misleading since natural variation leads to a wide range in the onset of menopause, from approximately 40-58 years. Menopause itself is recognized as having “occurred after 12 months of amenorrhea with no obvious pathological cause.”⁵ It is worth mentioning that there are specific, clinically-defined stages of menopause, however here the term ‘menopausal’ is used loosely to refer to women experiencing symptoms, such as hot flashes, known to be associated with the transition.

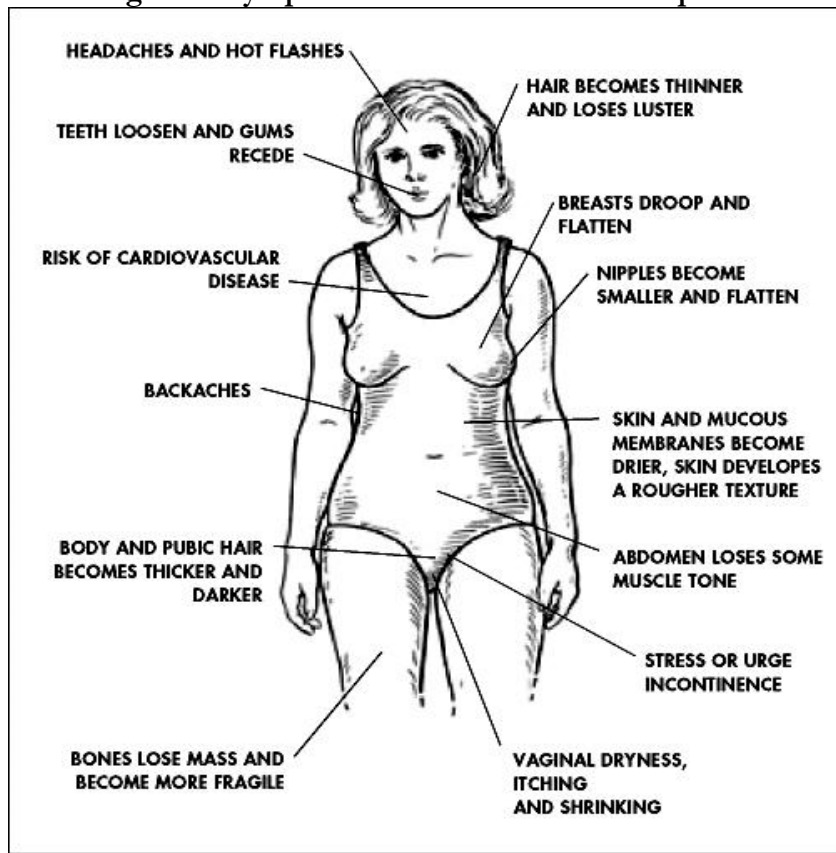
The menopausal transition is not clearly defined and the symptoms and timing of the changes manifest differently in each individual. The transition is brought on as the ovaries stop making the hormones estradiol and progesterone. **Figure 2** outlines some of the major symptoms and changes that are sometimes associated with menopause. One important change not detailed in the figure is central abdominal fat accumulation and weight gain after menopause, the risks of atherosclerosis and cardiovascular disease increase. The bones can begin to weaken due to osteoporosis and metabolism shifts, sometimes leading to metabolic syndrome and diabetes. There is also an increased

⁴ Walker, M.L. and Herndon, J.G. *Menopause in nonhuman primates?*. *Biology of Reproduction*. 2008, 79(3): 398–406.

⁵ *Menopause Practice: A Clinician's Guide*, 3rd Ed. 2007. North American Menopause Society.

risk of cancer, especially uterine and breast cancers. It is important to note that two thirds of dementia and Alzheimer’s disease cases occur in aging women and most autoimmune disorders are experienced by menopausal women. Urogenital changes, commonly known as vaginal atrophy, can begin, including thinning and loss of elasticity in tissues, itching, dryness, bleeding, inflammation and urinary symptoms. A number of psychological and sexual changes have been associated with menopause, and these vary most widely. Many of the changes associated with menopause continue through life, but some cause significant symptoms during the transition. Notable among these are vasomotor symptoms such as hot flashes, night sweats and occasionally cold sweats, all of which can significantly affect quality of life. Any new treatment for these latter symptoms must not exacerbate the long-term effects of menopause, and ideally the therapy will actually have positive effects in these other areas. It has been established that hot flashes are an important predictor to many of the menopausal associated disorders such as breast cancer, osteoporosis and cardiovascular disease. It is therefore becoming medically important to treat menopausal hot flashes as part of an effort to prevent the later consequences of the menopausal transition, rather than thinking of hot flashes as quality of life nuisance.

Figure 2. Symptoms Associated with Menopause



Source: premenopausal-symptoms.com.

The menstrual cycle is governed by the hormones follicle stimulating hormone (FSH), luteinizing hormone (LH), and estrogen. The ovaries produce estradiol, testosterone and progesterone in a cyclical pattern in response to the action of the other two hormones, originating in the pituitary gland. The menstrual cycle is one of monthly stimulation of growth and differentiation (which continues if a woman becomes pregnant) followed by degradation and eventually replacement of the tissue. During menopause, women may experience very high variation in FSH and estradiol levels, often accompanied by dramatic swings. Therefore, measuring hormone levels is not an effective test for menopause. Eventually, the ovaries stop making estradiol and progesterone, and it is the conspicuous drop in blood estradiol levels that leads to menopause-associated symptoms and diseases in other tissues. Menopause leads to a major remodeling of many different tissues, and the lack of estradiol is the main driver of this process.

HRT and the Women's Health Initiative

Considering that menopause is characterized by a loss of estrogen, it seems natural that replacing the hormone would be a good treatment for the symptoms of menopause. The notion of hormone replacement was supported by the dramatic therapeutic benefits noted in the early 1900s when young patients with type I diabetes were treated with insulin. To this end, the first estrogen extract supplementation, derived from pregnant mare's urine, was approved by the FDA in 1942 for the treatment of menopausal hot flashes. Hormone replacement therapy (HRT), as estrogen use is known, slowly grew, eventually becoming very popular throughout most of the last century. The first cause for concern about the use of HRT came in 1975 when a study published in the *New England Journal of Medicine* suggested a link between estrogen only HRT and endometrial cancer.⁶ This specific side effect was eventually mitigated by the use of estrogen plus progesterone combination HRT in women with an intact uterus. In the following decades, a number of other studies raised the possibility that HRT in all forms increased numerous health risks, however the therapy remained popular due to its ability to decrease hot flashes, reduce osteoporosis and a purported long term benefit to decrease cardiovascular disease. The suspected cardio-protective benefit of HRT led the NIH to fund an \$800 million study called the Women's Health Initiative (WHI), to evaluate not only the health risks and benefits of HRT but also low fat dietary patterns and vitamin D and calcium use. The study consisted of four randomized interventional studies, including two that looked at the use of HRT. The first of these two trials compared the long-term effects of a mixture of estrogen and progestin vs. placebo in women with an intact uterus while the second looked at estrogen-only vs. placebo in women with no uterus. The goal of these two studies was to discover the differences in important indications such as cardiovascular disease, osteoporosis and cancer between the placebo and HRT groups. The trials began enrolling patients in 1993 and were scheduled to last 8.5 years but the trials were stopped early due to clearly identified risks that were predetermined in the study design.

Estrogen plus Progestin in Healthy Postmenopausal Women. The estrogen plus progestin portion of the Women's Health Initiative was designed to assess the risks and benefits of the hormone preparation used most commonly in the US. 16,608 study participants were randomized to receive either conjugated equine estrogens (0.625 mg/d) plus medroxyprogesterone acetate (2.5 mg/day) or placebo. The primary outcome of the trial was coronary heart disease and invasive breast cancer was the primary adverse outcome. The balance of risks and benefits was also examined for stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture and death. Although the trial was planned for a longer duration, it was stopped in 2002 after a mean follow-up time of

⁶ Ziel, H.K.; Increased risk of endometrial carcinoma among users of conjugated estrogens. *NEJM*, 1975, 293(23):1167.

5.2 years. At that time, the data safety monitoring board (DSMB) for the trial concluded that the statistical test for invasive breast cancer had exceeded the stopping boundary and the global index statistic supported risks exceeding benefits.⁷

When the trial was stopped and the initial results were released, it created a media frenzy and intense public discussion. The fear of side effects from HRT drove patients away from this treatment en masse. According to Datamonitor, sales of estrogen only HRT products fell from 2.1 billion units in 2003 to 1.1 billion units in 2007. For estrogen plus progestin the corresponding fall was from 1.1 billion units in 2003 to 599 million units in 2007. During the same period, US sales of HRT products fell from \$1.46 billion to \$1.33 billion, but this included significant price increases over the period from companies trying to make up for lost sales. Investigators in the estrogen plus progesterone trial report that compared to placebo, women taking HRT experienced:

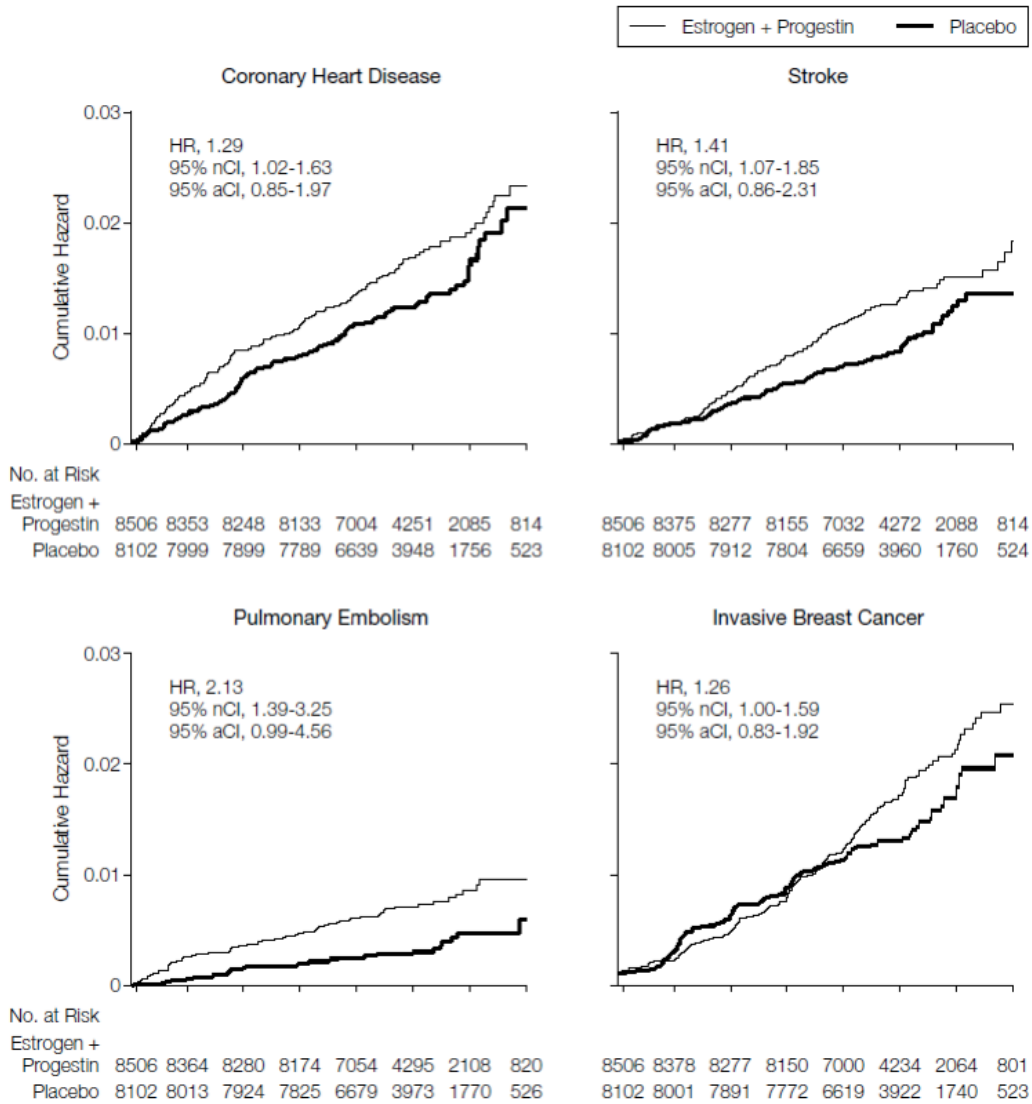
- Increased risk of breast cancer
- Increased risk of heart attack
- Increased risk of stroke
- Increased risk of blood clots
- Increased risk for dementia
- Reduced risk of colorectal cancer
- Reduced risk of bone fractures

The increased risks for breast cancer and cardiovascular disease led to an immediate and sustained reduction in the number of women taking HRT for menopausal symptoms. Although participants in the active intervention arm experienced a reduction in colorectal cancers and fractures, these were more than offset by the increased risks for serious side effects. **Figure 3** shows the Kaplan-Meier estimates of the cumulative hazards for selected indications in the active and control arms of the study. Although the cause-effect relationship has not been established conclusively, there was a reduction in the number of breast cancer cases in the US after release of the WHI results. More recent research has confirmed the breast cancer risk, with more women in the hormone-arm eventually developing breast cancer, and it appears that HRT may hinder the detection of breast cancer.⁸

⁷ 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(3): 321–333.

⁸ Chlebowski, R.T. et. al.; Breast Cancer after Use of Estrogen plus Progestin in Postmenopausal Women. *NEJM*. 2009, 260:573-587. And references therein.

Figure 3. Relative Hazards for Select Indications in the WHI



Source: JAMA 2002, 288(3):321-333.

Conjugated Equine Estrogen in Postmenopausal Women with Hysterectomy. The estrogen only component of the WHI was designed to assess the effects of estrogen on major disease incidence rates in women with prior hysterectomy. 10,739 study participants were randomized to receive either conjugated equine estrogens (0.625 mg/d) or placebo. The primary outcome of the trial was incidence of coronary heart disease and invasive breast cancer was the primary safety outcome. The overall risks and benefits were also examined by looking at stroke, pulmonary embolism, colorectal cancer, hip fracture and death. The trial was stopped after a mean follow-up time of 6.8 years due to safety concerns for increased risk of stroke. The results of the estrogen-only arm were not as stark as those from the previous trial, but they nonetheless point away from

HRT use.⁹ In summary, the trial found that when compared to those taking placebo, women in the estrogen arm experienced:

- Increased risk of stroke
- Increased risk of blood clots
- Uncertain effect for breast cancer
- No difference in risk for heart attack
- No difference in risk for colorectal cancer
- Reduced risk of fracture

Based on the aggregate results from both WHI trials, the FDA immediately placed 7 black box warnings on all HRT products and advised all physicians to prescribe HRT at the lowest effective dose and for the shortest possible period of time. The guidelines do not specify what the lowest effective dose should be or a specific time period, but rather urges women to consult their doctors with the guidelines in mind.¹⁰

In the intervening decade since the initial publication of WHI results pointing to the frightening effects of using estrogen plus progestin, a debate has smoldered as to the validity of the results. Some doctors still believe strongly in the use of HRT for treating the symptoms of menopause. They point to design flaws of the WHI trials, such as enrolling women who are older than early menopausal symptomatic women, raise problems with the statistical analysis, and point to a host of other problems, including conflicting study results.^{11,12} On the other hand, the so-called Million Women Study in the UK concluded that the use of HRT increases the risk of ovarian cancer.¹³ To help navigate the issue, NAMS issues regularly-updated guidelines suggesting who should and should not use HRT.¹⁴ Regardless of an individual's feeling about this issue, though, most agree that alternatives to HRT are needed. The best way to end the debate would be to develop new interventions for the treatment of menopausal hot flashes that avoid the problems associated with HRT. To address this area of high unmet need, Bionovo has capitalized on its in-depth understanding of estrogen receptor biology to develop *Menerba*, a more selective SERM, designed to result in higher safety and tolerability in humans.

Estrogen Receptor Biology

An estrogen receptor (ER) is any of a group of receptors that are activated by estrogens. Estrogen receptors act as DNA-binding transcription factors to regulate gene expression, however they also have other, independent functions. Estrogen receptors are activated differently by different combinations of agonists and a particular type of activation can lead to different actions in different types of tissues. The role of ERs in the body is complicated, to say the least. Although ERs were first discovered in the 1970s, a much better understanding of ERs has been gained since the

⁹ The Women's Health Initiative Steering Committee. Effects of Conjugated Equine Estrogen in Postmenopausal Women With Hysterectomy: The Women's Health Initiative Randomized Controlled Trial. *JAMA*. 2004, 291(14): 1701–1712.

¹⁰ US Food and Drug Administration: *For Consumers: Menopause and Hormones*. <http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118624.htm>. Accessed 4/8/2011.

¹¹ Harman, S.M., et. al.; *Annals of the New York Academy of Sciences*. 2005, 1052:43-56.

¹² Michels, K.B.; *Int. J. Epidemiol.* 2006, 35(4):814-816.

¹³ Beral, V.; Ovarian cancer and hormone replacement therapy in the Million Women Study. *The Lancet*. 2007, DOI: 10.1016/S0140-6736(07)60534-0.

¹⁴ The North American Menopause Society; *Menopause*. 2010, 17(2):242-255.

mid-1990s, when estrogen receptor β (ER β) was first discovered – revealing that there is more than one ER.¹⁵ Since that time, many of the roles of the individual receptors (ER α and ER β) in various diseases and conditions have been elucidated.¹⁶ While both ERs are expressed in a wide variety of tissues, ER α is specifically found in the endometrium, breast cancer cells, ovarian stroma cells and the hypothalamus.¹⁷ Similarly, ER β has been detected in the kidneys, lungs, heart, bones, brain, intestinal mucosa, prostate and endothelial cells.¹⁸

Simply elucidating the mechanism of action of ERs in a single instance is very difficult since they affect change in a variety of ways. For example, in a typical cascade the ER would be activated by an estrogen forming a complex that can bind DNA sequences directly or with the assistance of activator proteins. The activator proteins may involve co-regulatory activators and repressors into the process and may also affect the expression of mRNA in the cell.¹⁹ At the same time, the ERs may enter into this process without being activated by any ligand.²⁰ The presence of various co-promoters and helper proteins in different cells has a strong effect on the activity of ERs in particular tissues. Despite this complexity, the roles of the two ERs in different tissues and diseases have been illuminated to some extent. For example, ER α is known to be active in breast tumor cells and has become a target of chemotherapy drugs used against breast cancer. These drugs, known as selective estrogen receptor modulators (SERMs), agonize the estrogen receptors, but their action is different and distinguishable in various tissues. On the flip-side, ER β has been shown in pre-clinical studies to inhibit the proliferation of breast cancer cells.^{21,22}

Considering the recent nature of the discovery of ER β , it is clear that our understanding of the role of the different ERs is just in the fledgling stage. However, research like that which Bionovo and affiliated researchers are conducting into the differentiation of the two ER pathways is helping to bring a new understanding to this area. While the role of ERs in disease proliferation is intricate, the complexity actually creates opportunity. By understanding the roles of various estrogen agonists and co-activators, it should be possible to tailor medical interventions to specific diseases.²³ Creation of ER agonists that lead to specific tissue responses would allow researchers to take advantage of the healthy aspects of a particular ER while avoiding dangerous outcomes. In addition to the anti-proliferative effects associated with ER β , for example, it has been shown that selective activation of this ER can also lead to anti-inflammatory actions.²⁴

OTHER DRUGS ON THE MARKET

The leading therapy used to treat menopausal hot flashes is hormone replacement therapy. Even after almost 70 years on the market, the leading estrogen sold for use as HRT is Pfizer's (formerly Wyeth) *Premarin*, which is a mixture of conjugated estrogens obtained from pregnant mare's urine

¹⁵ Gustafsson J.A. et. al; Cloning of a novel receptor expressed in rat prostate and ovary. *Proc. Natl. Acad. Sci. U.S.A.* 1996, 93(12):5925–30.

¹⁶ Gustafsson J.A. et. al; Reflections on the Discovery and Significance of Estrogen Receptor β . *Endocrine Reviews*. 2005, 26(3):465-478.

¹⁷ Timiras P.S., et. al.; *Neuro Endocrinol. Lett.* 2005, 26(3):197–203.

¹⁸ Babiker, F.A., et. al.; *Cardiovasc. Res.* 2002, 53(3):709–19.

¹⁹ Deroo, B.J. and Korach, K.S.; *The Journal of Clinical Investigation*. 2006, 116(3):561-570.

²⁰ Leitman, D.C., et. al.; *Molecular Cell*. February 17, 2006, 21:555-564.

²¹ Gustafsson, J.A., et. al.; *Proc. Natl. Acad. Sci. USA*. 2004, 100:1566-1571.

²² Leitman, D.C., et. al.; *Cancer Research*, 2004, 64:423.

²³ Leitman, D.C., et. al; *Current Opinion in Pharmacology*. 2010, 10(6):639-636.

²⁴ Leitman, D.C., et. al; *The Journal of Immunology*. 2008, 180:630-636.

(hence the name). Despite the prominence of *Premarin*, though, there are dozens of other HRT drugs approved to treat hot flashes. Some of the other forms of estrogen that are used include estradiol, 17 β -estradiol, and other estradiol derivatives. Progestins (i.e. progesterone) are almost always included along with estrogen in the HRT formulations for women with an intact uterus to prevent uterine cancer (approximately 65-70% of the menopausal population). In addition to the number of hormones available, therapies come in a wide range of doses and myriad forms of delivery vehicles. HRT can be delivered orally, subcutaneously, using a suppository, or transdermally using patches, gels and creams.

Hormone replacement therapies are the best yet discovered to relieve the vasomotor symptoms of menopause. They all also carry seven black box warnings from the FDA concerning the serious health risks related to HRT, which were mostly identified through the WHI. A black box warning is the FDA's strongest warning, used when medical studies indicate a significant risk of adverse events related to the drug. For estrogen HRT, all approved drugs carry warnings concerning an increased risk of breast cancer, uterine cancer, cardiovascular disease, deep vein thrombosis, pulmonary embolism, stroke, and dementia. There is clinical evidence of an increased risk related to HRT for each of these indications. The release of data from WHI and the FDA's subsequent introduction in 2003 of the boxed warnings significantly curtailed HRT use in the US.

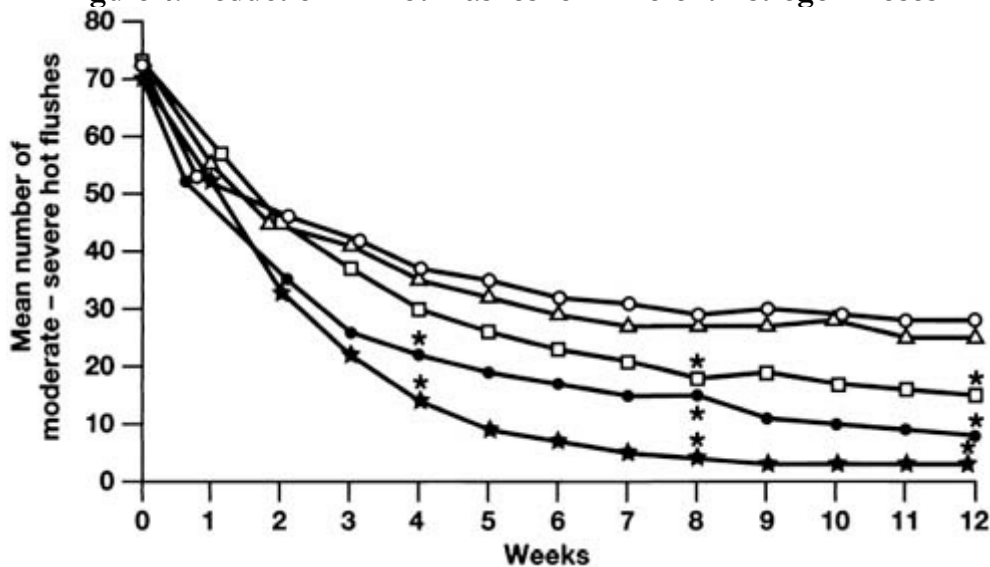
Another result of the WHI results is that the FDA now recommends that patients taking HRT for menopausal symptoms or other uses take the absolute lowest effective dose. Using one of the many doses and formulations available, many women can find a workable dose. There is a clear dose response for estrogen in treating hot flashes, so lower doses are not as effective. Wide variation generally exists in clinical trial data about estrogen for the treatment of hot flashes.²⁵ This variation is due mostly to differences in study design rather than efficacy. There is also variation in the placebo response. For various reasons, there is usually a large placebo response in clinical trials treating hot flashes. A common range for placebo response is about 45-55%.

A study in the late 1990s established the dose response for estrogen in the treatment of hot flashes. In the double-blind, placebo-controlled trial, 333 menopausal women were randomized to receive one of four doses (0.25 mg, 0.5 mg, 1 mg, 2 mg) of oral estrogen or placebo once a day. The specific form of estrogen was micronized 17 β -estradiol. Patients reported the number and severity of hot flashes in a daily diary. **Figure 4** below shows the reduction in hot flashes in each of the dose groups over the course of the study. There is a clear trend of increasing efficacy with increased dose. After 4 weeks there was a statistically significant improvement ($p < 0.05$) for the 1 mg and 2 mg doses groups compared to placebo. By week 12, all except the lowest dose had statistically significant improvement over placebo ($p < 0.001$). In the figure, open circles represent placebo; open triangles, 0.25 mg; open squares, 0.5 mg; solid circles, 1 mg; and asterisks, 2 mg 17 β -estradiol. The stars represent statistical significance when compared to placebo.²⁶

²⁵ Nelson, H.D.; *JAMA*. 2004, 291(13):1610-1620.

²⁶ Notelovitz, M., et. al.; *Obstetrics & Gynecology*. May 2000, 95(5):726-731.

Figure 4. Reduction in Hot Flashes for Different Estrogen Doses



Source: Notelovitz et. al.

Results such as these can help doctors and patients decide on the proper course of action if HRT is the chosen treatment. This also gives us an idea of the minimum standard that any new therapy would have to overcome to receive FDA approval. In order to attain approval, a drug should be at least as effective as the lowest effective doses of estrogen, and safe.

Off-Label Hot Flash Treatments. Although there are no effective non-hormonal therapies approved to treat menopausal hot flashes, there are a number of drugs approved for other indications that are prescribed. The most commonly prescribed drugs outside of HRT include certain antidepressants, gabapentin, and clonidine.²⁷ The antidepressants that are commonly used for this indication are certain selective serotonin reuptake inhibitors (SSRIs) such as *Paxil* and *Prozac* and selective serotonin and norepinephrine inhibitors (SNRIs) such as *Effexor* and *Pristiq*. While these medications have been found to moderately relieve hot flashes, they are usually accompanied by harsh side effects. Some of the side effects of antidepressant use include nausea, dizziness, weight gain and sexual dysfunction. Moreover, many doctors and patients are unwilling to use what are viewed as very powerful drugs for this particular indication.

Gabapentin, approved under various brand names including *Neurontin*, is approved for the treatment of epilepsy and neuropathic pain. Like the SSRIs and SNRIs, gabapentin also carries the risk of substantial side effects. The AEs associated with gabapentin use can include dizziness, severe drowsiness and lack of energy, making it hard for some who take this drug to carry out every day tasks. Clonidine (*Catapres*) was originally a drug to treat hypertension, but is now approved for a wide variety of uses ranging from neuropathic pain to opioid detoxification. In addition to hot flashes, it is prescribed off label to treat insomnia. Clonidine use is limited by disorienting side effects, dry mouth and constipation. Two of the drugs mentioned, the SSRI *Pristiq* (Pfizer) and gabapentin (Depomed as *Serada*), are being tested in clinical trials to treat hot flashes. They are discussed in more detail below.

²⁷ Mayo Clinic Staff; <http://www.mayoclinic.com/health/hot-flashes/DS01143>

EPIDEMIOLOGY

Eventually, every woman will be affected by menopause. NAMS estimates that in the US about 6,000 women reach menopause each day, more than 2 million/year.²⁸ Datamonitor estimates that in 2008 there were about 22 million perimenopausal women (aged 45-54 years) in the US and another 39 million 55 years or above. The corresponding numbers for the European Union were 22 million/50 million and for Japan 8 million/25 million.²⁹ Of those who are experiencing menopause, not all experience vasomotor symptoms and not all seek treatment. In one study in the US, 60% of women reported seeking healthcare for menopausal symptoms, most commonly for vasomotor symptoms.³⁰

HRT Market Information

Despite warnings and years of negative press, hormone replacement therapies remain popular with doctors and patients for treating menopausal hot flashes. The fact that so many women will take a dangerous therapy illustrates the debilitating nature of the symptoms, and accentuates the need for a safe, effective treatment. As many countries experience aging populations – including the arrival of the baby-boom generation in the US – the number of women seeking treatment for menopause related symptoms will increase. A good starting point for the potential size of the market for an effective non-hormonal treatment for hot flashes is the HRT market. In 2007, the market for HRT in the US, EU and Japan was approximately \$1.6 billion. That was down from almost \$2 billion in 2003, largely due to the WHI results. The US makes up the large majority of this market; during the same period, US sales of HRT products fell from \$1.46 billion to \$1.33 billion. It must also be noted that manufacturers have increased prices to make up for lost sales, so the number of prescriptions is still below 2003 levels. This shows that there is a huge untapped market for non-hormonal therapies, one that has clearly grown.

The introduction of a safe, effective treatment should easily double the size of the market, in addition to the many women who are currently taking or contemplating HRT who would likely use the new drug instead. The sales figures for HRT are based on a \$30/month pricing schedule. *Menerba* is expected to cost approximately \$150/month, so the gross revenue potential is immediately 5x that of HRT. If *Menerba* receives marketing approval from the FDA it could quickly become a multi-billion dollar drug. In order to be approved, *Menerba* must be shown in clinical trials to be at least as effective as low-dose estrogen. If the drug can treat hot flashes with the same effectiveness but without the worry of side effects then the market will materialize.

Pre-Clinical Discussion and Mechanism of Action (MoA)

One of the most intriguing aspects of *Menerba* as a drug development candidate is its constitution, since unlike most drugs it is made up of a mixture of extracted plant compounds. Typically, companies identify a pharmaceutically active molecule – either a small molecule or large biological molecule – and specifically test the action of that molecule against known biological targets. After identifying the various botanical ingredients that might be useful for treating the symptoms of menopause, Bionovo scientists began testing the combined compounds. However, at the same time they engaged in the usual discovery process, rigorously isolating and testing compounds. Of about

²⁸ Menopause Practice: A Clinician's Guide, 3rd Ed. 2007. North American Menopause Society.

²⁹ Datamonitor: Commercial and Pipeline Insight: HRT for Menopausal Symptoms, 2008.

³⁰ Williams, R.E., et. al; Health care seeking and treatment for menopausal symptoms in the United States. 2007, *Maturitas*, 58, 348–358.

90 compounds that were characterized, more than 40 were found to be selective for estrogen receptor β . However, none of the individual components correlated with the activity of the mixture.³¹ A deeper understanding of the role and activity of different estrogen receptors has since shed some light on why this is so, validating Bionovo's multi-component approach.

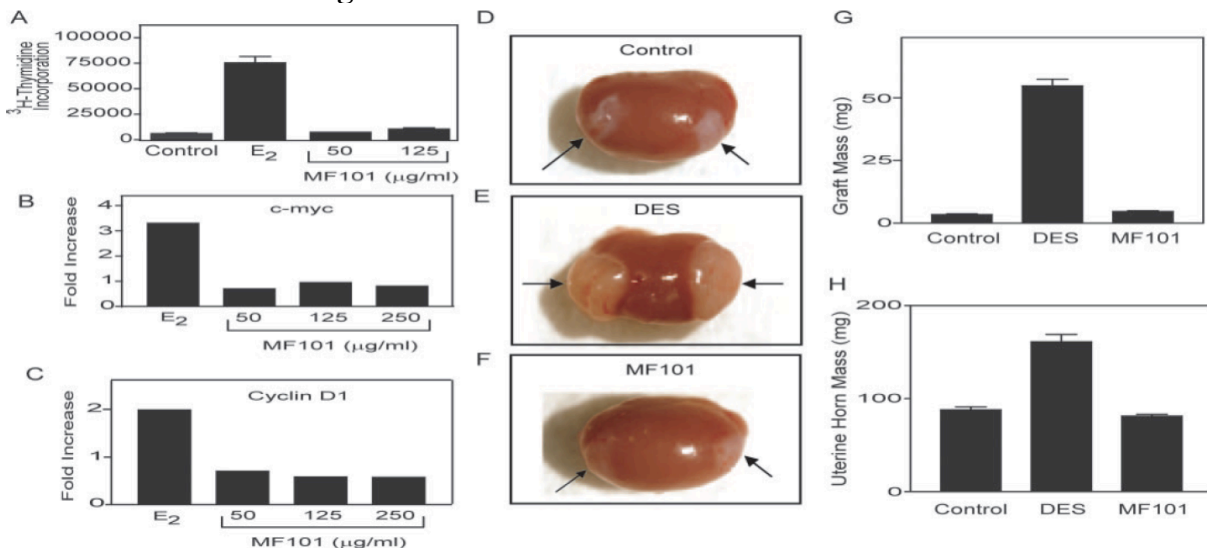
As was discussed above, the role of ER agonists and the participation of co-promoters is very complex. The result of this complexity is that activation of ERs by specific ligands should lead to a specific response. Selective estrogen receptor modulators (SERMs) are drugs that act on ERs throughout the body. This class of drugs includes tamoxifen, used to treat breast cancer, and raloxifene, used to treat osteoporosis and for the primary prevention of breast cancer. Unfortunately, these drugs also cause hot flashes. *Menerba* is not a classic SERM, but is more accurately characterized as an estrogen receptor subtype agonist (ERSA), because it selectively activates ER β . The selective nature of these compounds means they have the possibility to provide the benefits of estrogen replacement (reduction of hot flashes) without the problems (increase in cancer). Pre-clinical studies conducted by Bionovo indicated that *Menerba* does not stimulate the proliferation of human breast cancer cells nor does it stimulate growth of the uterus in mice, like estrogen does.

Qualitative results of the human breast cancer cell experiment can be seen in **Figure 5**. The first column shows the expression of particular cancer-related genes (oncogenes) in mice treated with both MF101 and estradiol (E₂). As you can see, these genes are down-regulated in *Menerba* treated animals. In second column, mouse kidneys were grafted with human MCF-7 breast cancer cells. In the top picture, the control, the mice were left untreated. In the second picture, the mice were treated with diethylstilbestrol (DES), a synthetic nonsteroidal estrogen, which led to rapid tumor growth. In the bottom picture, the mice were treated with *Menerba*, resulting in no increase in the size of the tumor graft over control. The third column shows a comparison in mass of the tumor grafts (top box) and uteri (lower box). The uterus was removed from the study animals and weighed, revealing that *Menerba* did not contribute to uterine growth. The results confirm the proliferative effects of ER α , and also reinforce the anti-inflammatory activity of ER β .³²

³¹ Leitman, D.C., et. al.; *Molecular and Cellular Endocrinology*. 2008, 283:49-57.

³² Cvorovic A., et. al.; *Endocrinology*. 2007, 148:538-547.

Figure 5. Anti-Proliferative Effects of *Menerba*



Source: Cvor, et. al.

Safety Profile. *Menerba's* safety profile is one of the strongest parts of the clinical package for the drug. First, the drug is made up of botanical ingredients that have been known and used as medicines for hundreds of years, so unexpected side effects are unlikely. Second, and more importantly, clinical trials to date have not revealed any significant safety issues. Participants in the Phase II trial of *Menerba* for the treatment of hot flashes experienced an increase over placebo in transient loose stools (not diarrhea) but still only a small portion of participants experienced the problem. Moreover, this side effect may be reduced due to an additional purification step, eliminating soluble fiber, believed to contribute to the transient loose stools. This step also removes some of the extra mass from the active material, lowering the overall amount of material ingested per dose. Bionovo is preparing to test a more potent dose of the drug in an attempt to increase efficacy, and will be monitoring new clinical data for any sign of an up-tick in adverse events.

It is worth commenting on data from the Phase II trial regarding endometrial thickening, since this can be an indicator of uterine hyperplasia, which can lead to uterine cancer. In the study, there was no difference between treatment and placebo groups regarding the change in endometrial thickness. There were more women in the treatment group (7/low dose, 11/high dose) than the placebo group (3) who were found to have a double-wall endometrial thickness of 5 mm or more or greater or to have an increase in endometrial thickness of 2 mm or greater from baseline. These arbitrary cut-off points were preset by the Company for requiring an endometrial biopsy while on the study since the Company had relied only on transvaginal ultrasound to determine endometrial safety at baseline and study termination, not the more invasive gold standard, endometrial biopsy. None of the double wall endometrial measurements on transvaginal ultrasound found during the trial were clinically worrisome for uterine cancer. This finding was confirmed by the definitive biopsy results which showed no cases of endometrial hyperplasia or cancer among any of the study subjects. While endometrial thickening may lead to hyperplasia, and endometrial hyperplasia can lead to uterine cancer, the vast majority of cases of endometrial thickening do not lead to cancer, especially at the measurements seen in the Company's Phase II study. So to date, there is no evidence that *Menerba* will increase the risk of uterine cancer. We will now move on to a discussion of the complete Phase II trial results.

Clinical Data Discussion: Menopausal Hot Flashes

Bionovo completed a Phase II trial of *Menerba* for the treatment of menopausal hot flashes in early 2007 and the results were initially presented at the annual meeting of the North American Menopause Society in Dallas in October of that year. Complete results of the trial were published in *Menopause: The Journal of The North American Menopause Society* in 2008.³³ After the company resolved issues with the chemistry, manufacture and control (CMC) procedures for *Menerba*, the FDA gave clearance for the commencement of the pivotal clinical trials in 2011. Since no safety issues were identified, and because maximum desired efficacy was not reached, Bionovo will test a higher dose of *Menerba* in one arm of the Phase III trial than was used in Phase II. Due to the dose increase planned in the Phase III trials, the FDA has asked Bionovo to complete a Phase I trial of higher doses before choosing one of the higher doses to evaluate in Phase III. The company will save time by conducting the small Phase I trial before Phase III rather than sub-dividing the Phase III patient population for the safety study.

Phase II Results Indicate Solid Efficacy and Safety

Study Design. Bionovo's Phase II trial of *Menerba* was officially titled "Clinical Trial Assessing Toxicity and Efficacy of MF101 for Hot Flashes," however it is also referred to as the Chinese Herbs in Menopausal Symptoms (CHIMES) study. The randomized, double-blind, placebo-controlled trial enrolled 217 female patients and dosing was initiated between February and October 2006. Patients were randomized in a 1:1:1 ratio to receive one of two doses of *Menerba* (5g or 10g/day) or placebo. The treatment was administered on a twice-daily (BID) schedule for 12 weeks. Otherwise-healthy postmenopausal women between 40 and 60 years old who reported at least 7 moderate to severe hot flashes per day or 50 per week were included in the trial. The average age of enrolled patients was 54 and 80% were white. The baseline mean (SD) frequency of hot flashes was 9.8 (3.7). The primary endpoint of the trial was a comparison of baseline to 4 and 12 weeks in frequency of hot flashes. The analysis included a breakdown of different types of hot flashes including mild, moderate and severe. The Phase III trial will look more specifically at changes in moderate to severe hot flashes. Change in a subjective measure of hot flash severity and safety measures were other endpoints for the study.

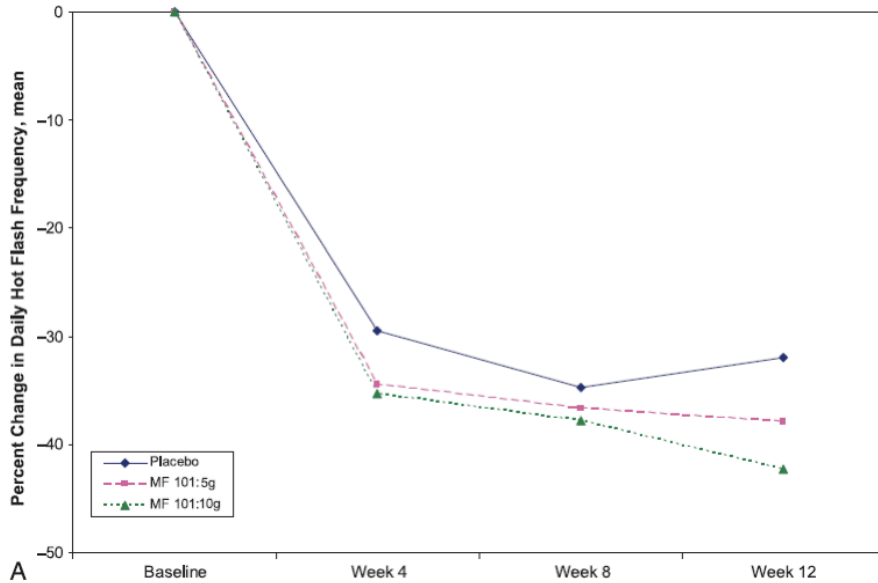
The primary reasons for exclusion from the trial were history of uterine, ovarian or breast cancers or melanoma, cardiovascular disease, and severe allergies to food or medicine. Patients with various other medical conditions and those already taking medications known to affect hot flashes were also excluded from the trial. Before randomization into this Phase II trial, patients received placebo medication and diaries for recording symptoms for 1 week. Patients who completed the diaries, took at least 80% of the placebo medication and remained otherwise eligible for the study were randomized. A data safety monitoring board (DSMB) met four times throughout the trial and each time recommended that the study proceed.

Efficacy and Safety Results. Out of the 217 patients who completed pre-trial screening and randomization, 98% completed the trial and 91% took at least 75% of the assigned study medication. There was no difference in adherence or completion between the treatment and placebo groups. Patients treated with *Menerba* experienced improvements in symptoms that were either statistically significant or had a positive trend when compared to placebo. Overall, after 12 weeks of treatment the mean decrease in frequency of all hot flashes was 9.7% ($p=0.29$) for the low dose

³³ Grady, D., et al.; *Menopause: The Journal of The North American Menopause Society*. May-Jun 2009, 16(3); 458-465.

group and 12.9% ($p=0.15$) for the higher dose of *Menerba*. **Figure 6** compares the overall reduction for each treatment group, indicating that efficacy continued to increase throughout the trial for both dose groups; no plateau was reached during the study period. For mild hot flashes, there was a 27% ($p=0.06$) greater decrease in the low dose group compared to placebo and a 33% ($p=0.02$) greater decrease in the high dose group. The high dose group also experienced a significant 48% ($p=0.05$) reduction in overall hot flashes per week compared to 36.7% with placebo.

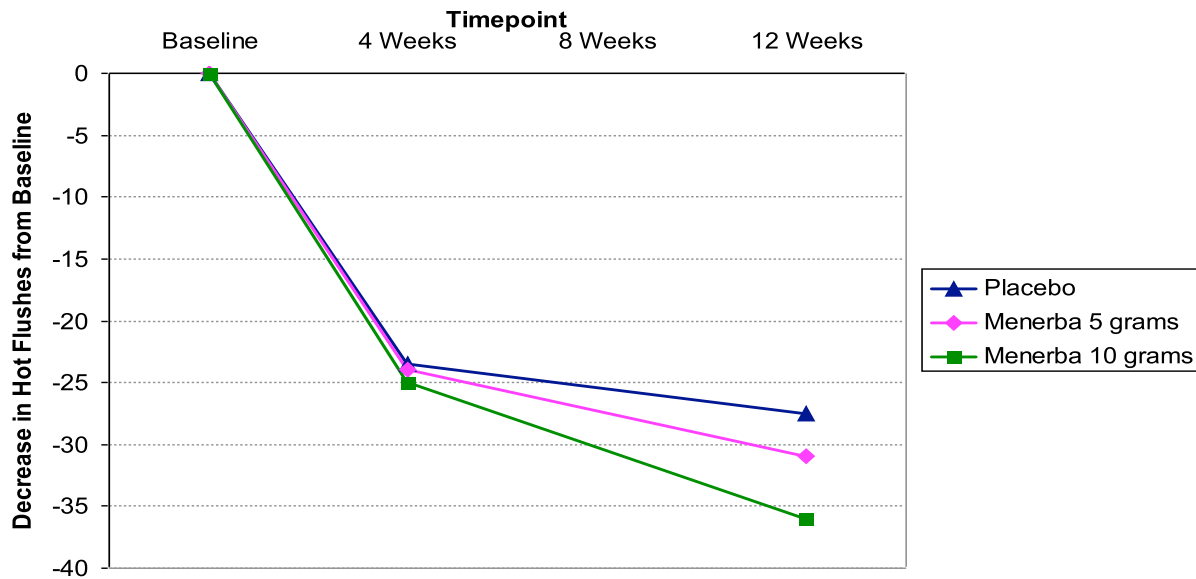
Figure 6. Reduction in Daily Hot Flash Frequency



Source: Grady, et. al.; Menopause. 16(3); 458-465.

The median reduction in the number of hot flashes per week from baseline to 12 weeks of treatment was as follows: 68 to 41 in the placebo group, 63 to 32 in the MF101 5g/day dose group and 67 to 31 in the MF101 10g/day dose group. The difference in the median reduction in hot flashes per week after 12 weeks of treatment in the MF101 high dose group compared to placebo was statistically significant ($p=0.04$). This data is summarized in Figure 7.

Figure 7. Change in Median Number of Hot Flashes.



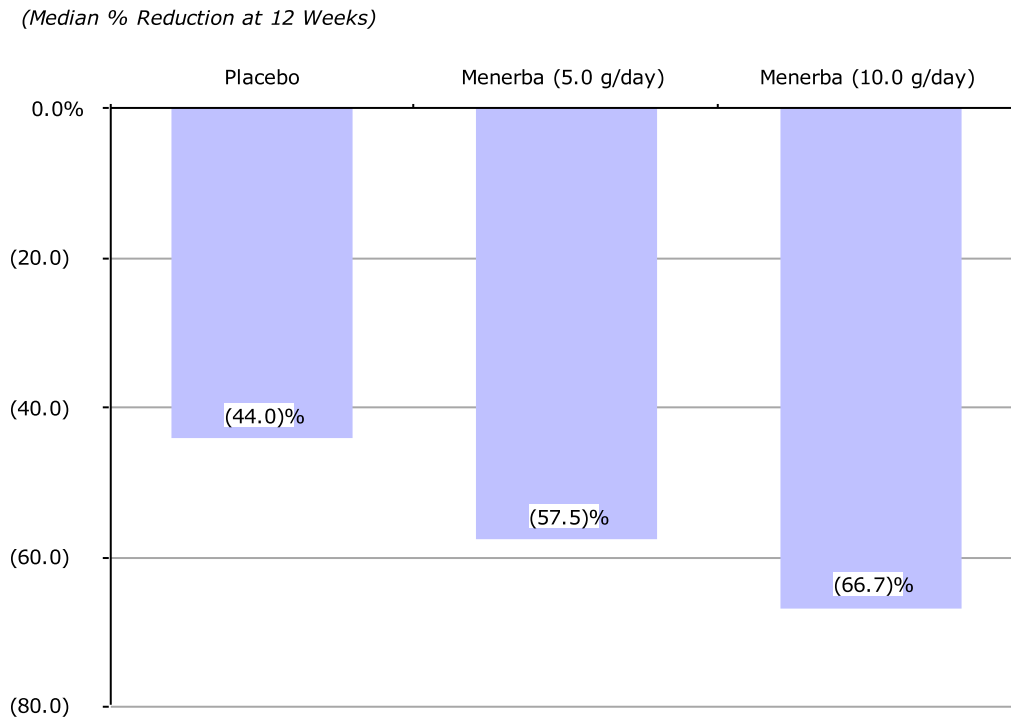
Source: Tagliaferri et. al.³⁴

In a responder analysis, compared to placebo, participants in the Menerba 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 flashes at 12 weeks of treatment (OR 2.3, $p=0.03$ or OR 2.4, $p=0.02$) respectively.

Another interesting efficacy result with the *Menerba* treatment groups was an effect on the number of hot flashes that woke study participants from sleep. The median percent reduction in the number of such events was 44% for placebo, 58% ($p=0.10$) for the low-dose group, and 67% ($p=0.05$) for the high-dose group (Figure 8 below). This is an important result because it distinguishes *Menerba* from competing therapies such as gabapentin, which have not yet been shown to affect night time awakenings from hot flashes. Finally, almost half – 47% ($p=0.03$) of patients in the 10g/day group, 39% ($p=0.29$) of patients in the 5g/day group and only 31% of patients in the placebo group achieved a 50% improvement in the frequency of hot flashes.

³⁴ Tagliaferri, M.A., Leitman, D., Olyaie, A., Caygill, K., Cohen, I.; *Menerba, A Novel Selective Estrogen Receptor-Beta Agonist for Climacteric Women*. 8th Congress of the European Society of Gynecology, Rome, September 12, 2009. <http://www.seg2009.com/pdf/seg-finalprog.pdf>

Figure 8. Median Percent Reduction in Night Time Awakenings Due to Hot Flashes



Source: Tagliaferri et. al.

Importantly, no cases of endometrial hyperplasia or uterine cancer were reported during the trial. There were no differences in incidents of vaginal bleeding between the treatment and placebo groups and no increase in blood estradiol levels was observed. The most prominent safety concern was transient loose stools, reported by 12% of *Menerba* treated patients, compared to 3% for placebo. The loose stool is most likely due to the presence of soluble fiber in the treatment. On the other side of the coin, there was a small improvement in the number of patients reporting constipation with *Menerba*, 1.3% vs. 4% for placebo. There was one serious AE, a case of pancreatitis, which was recorded as ‘possibly related to study medication’. There was a positive trend towards reduction in blood pressure in the treatment arm. Finally, there was a significant reduction in weight ($p=0.04$) and BMI ($p=0.05$) for *Menerba* treated patients compared to placebo. If confirmed in Phase III, this finding would definitely be a strong selling point to encourage patients to take this course of treatment. The finding also compares favorably to therapies in this space, such as the SNRIs, that usually cause patients to gain weight.

The Phase II trial was powered to look for a difference between *Menerba* and placebo in the ability to reduce all hot flashes. Despite that fact, the study was able to detect a reduction in moderate to severe hot flashes of 62% for *Menerba* versus 50% for placebo. The Phase III trial will be powered to address the FDA approved endpoint for efficacy, which is reduction in moderate to severe hot flashes. In addition, Bionovo will evaluate the effective dose from the Phase II trial as well as a higher dose in order to reach levels of efficacy that are not only equivalent to low doses of estrogen but also to higher doses of estrogen.

Ongoing Clinical Development Program for *Menerba*

As mentioned above, in clinical trials going forward Bionovo plans to use a slightly different formulation of *Menerba* that contains a stronger dose of active ingredients. Because of the increase in dose, the FDA has asked the company to conduct a new Phase I trial to test the dosing and toxicity of the new formulation. While Bionovo initially planned to incorporate this extra study into the Phase III trial, they determined that the pivotal program could move forward more quickly if a small, separate Phase I trial was completed beforehand.

Phase I Tolerability Trial. On March 28, Bionovo announced the commencement of enrollment of patients in a Phase I clinical trial assessing the safety of two doses of *Menerba* in postmenopausal women experiencing hot flashes.³⁵ The study will enroll 40 generally healthy, postmenopausal women ages 40-65 years at three clinical sites. The patients will be randomized to receive one of two doses of *Menerba* orally, twice-daily for 4 weeks. These doses are equivalent in potency to 2X and 3X of the efficacious dose from the Phase II study. At this point, we believe this trial is simply a formality that must be taken care of before moving on to pivotal trials. As an important note, the **doses used in this Phase I trial and in all trials going forward are effectively twice as concentrated as earlier studies.** Therefore, a Phase II dose of 10 g/day is equivalent to a Phase III dose of 5 g/day.

While this additional trial does add a new step for the Company, the overall timeline may be shortened. We are happy to see Bionovo undertake this Phase I trial for two reasons. First, despite our optimism, it is always possible that a safety issue could arise and we'd rather the Company catches that in a small Phase I study than in Phase III. New pre-clinical data suggests that the increase in dose will not be a problem. Second, we are happy to see Bionovo moving forward with a higher dose of *Menerba* that should lead to greater efficacy and demonstrate a wider therapeutic window.

Pivotal Phase III Clinical Program. In order to gain approval, Bionovo will have to run two Phase III trials treating patients experiencing menopausal hot flashes. In the US, a placebo-controlled trial is required while the EU requires an active comparator arm for long term safety assessment only, which in this case will be a combination HRT formulation of estrogen plus progestin. The first Phase III trial, which is expected to commence in the second half of this year, will have the same protocol in both the US and EU. The second Phase III trial will have a different structure in the US and EU due to the active comparator arm. The first Phase III trial will use 5 g/day (the efficacious dose from Phase II) and either a 10g/day or 15 g/day doses, administered twice-daily.³⁶

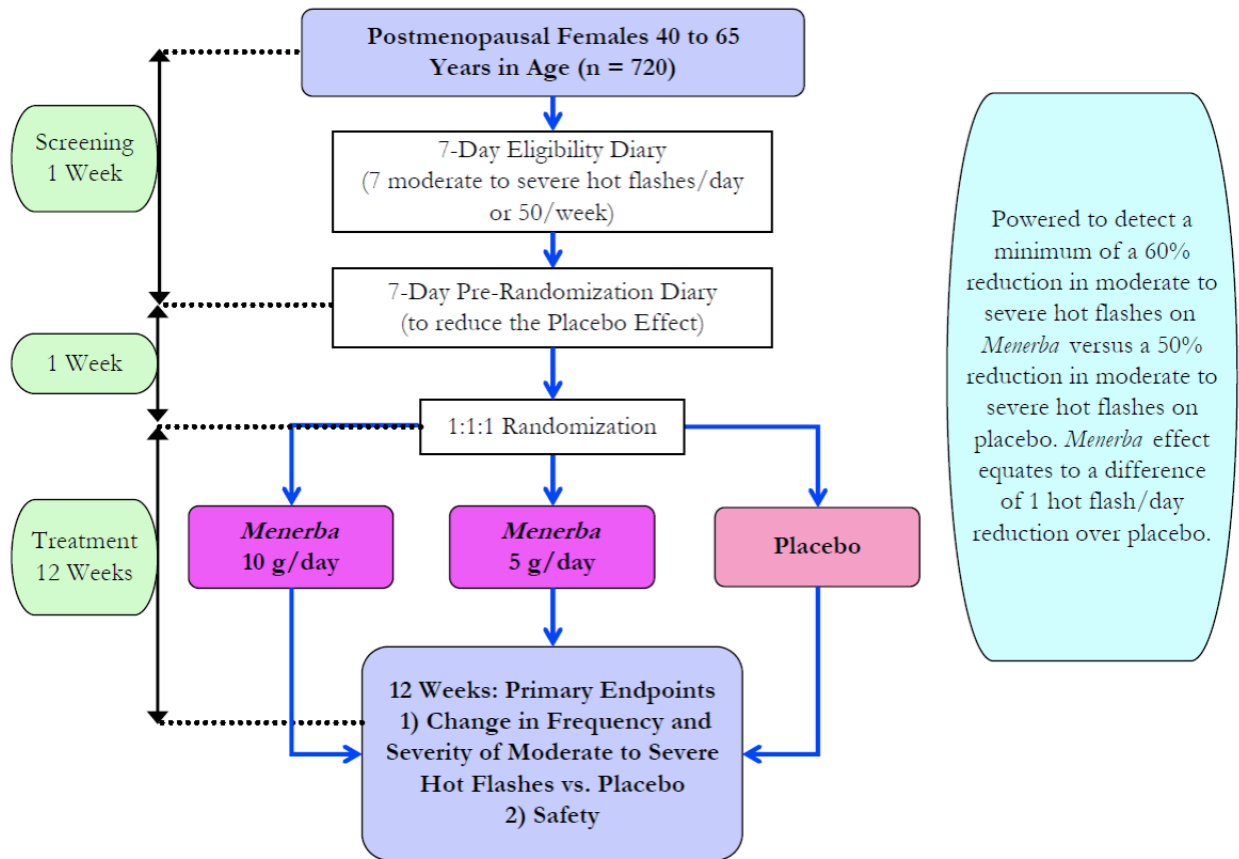
The official title of the first Phase III trial is "A Phase III, Double-blind, Placebo-Controlled, Randomized Clinical Trial, Assessing Safety and Efficacy of Menerba for Hot Flashes and Menopausal Symptoms in Postmenopausal Women". The trial is expected to enroll up to 1200 women aged 40-65 who are experiencing 7 moderate to severe hot flashes/day or 50 moderate to severe hot flashes/week. Patients will be randomized to receive one of two doses of *Menerba* or placebo. The primary endpoint is change in frequency of moderate to severe hot flashes. Keep in mind that one of the doses of *Menerba* that will be used in the Phase III trial will be either 2X or 3X as potent as the efficacious dose used in Phase II. Patients with a history of breast and uterine

³⁵ <http://www.clinicaltrials.gov/ct2/show/NCT01300078>

³⁶ <http://www.clinicaltrials.gov/ct2/show/NCT00906308>

cancers, deep vein thrombosis, and active liver or gall bladder disease are excluded. Patients already taking HRT or certain other medications are also excluded. The trial was designed based on the FDA Guidance for Industry in the areas of ‘Botanical Drug Products’ and ‘Estrogen and Estrogen/ Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation’. Figure 9 outlines the Phase III trial design.

Figure 9: Menerba Phase III Trial Design



Source: LifeSci Advisors

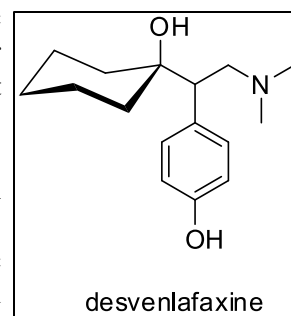
Although the FDA’s guidelines are very clear in certain areas, the level of efficacy needed for approval in this indication is not well defined. However, the absolute minimum hurdle that any new therapy must overcome is believed to be approximately 60% reduction in symptoms. This is based on the efficacy of low-dose HRT and on the efficacy of *Pristiq*, which received an approvable letter from the FDA for this indication. This is also the reported effect of Menerba in the Phase II trial. However, higher doses of HRT lead to a reduction in symptoms of up to 80%, and this type of reduction is the goal of Bionovo’s new higher-dose formulation. The Phase III trial is powered to show a statistically significant reduction in hot flashes at a minimum of 60%, assuming 50% efficacy rate in the placebo group. For multiple reasons, including the expectation of efficacy and typical fluctuations in hot flashes, historically there has been a very strong placebo effect in clinical trials for this indication. The company is taking multiple positive steps, including an extra baseline diary, to try to mitigate the placebo effect. Specifically, the company will administer the first baseline 7-day diary for eligibility. In the first diary, patients must report at least 7 moderate to severe hot flashes per day or at least 50 moderate to severe hot flashes per week to qualify for the trial. A second 7 day pre-randomization diary will be administered and no minimum number of moderate to severe hot

flashes will be required on the second diary. The objective of administering 2 diaries is to reach a regression to the mean and minimize the overall placebo effect prior to randomization. This trial should be able to deliver a significant result based on a reduction in the treatment vs. placebo groups of just one hot flash/day.

OTHER DRUGS IN DEVELOPMENT FOR MENOPAUSAL HOT FLASHES

Not surprisingly, the large market potential for treating menopausal hot flashes and the problems with HRT that were revealed by the WHI have drawn other pharmaceutical companies into this space. In addition to *Menerba*, there are a number of other development candidates targeting this indication. The two products that are most advanced in clinical trials are medications that are actually already used off-label to treat menopausal vasomotor symptoms. *Pristiq* (desvenlafaxine) is an antidepressant originally developed and marketed by Wyeth. Pfizer is now seeking approval for the treatment of hot flashes. The drug has been in Phase III testing for more than 5 years. Gabapentin (*Serada*, a.k.a.: *Fanatrex*, *Gabarone*, *Gralise*, *Neurontin*) was originally developed as a treatment for epilepsy and is widely prescribed to treat neuropathic pain and major depressive disorder. Depomed is now developing the drug as a treatment for the symptoms of menopause. Phase III trial results were initially reported in late 2009.

Pristiq. Desvenlafaxine, trade name *Pristiq*, is a serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant that was originally approved for antidepressant use in the US in 2008. The drug was approved as a treatment for depression in 2009 but has not yet received any approvals in the EU. The most common side effect, experienced by 30-50% of patients (vs. ~10% on placebo) was nausea, and this led to a significant dropout rate in clinical trials. In March 2008 the European Medicines Agency (EMA) published a list of “Questions and Answers on the Withdrawal of the Marketing Application for Pristiq”.³⁷ In the document, the agency stated that Wyeth had withdrawn the marketing application for Pristiq to treat menopausal hot flashes in the EU. The withdrawal was in response to a withdrawal assessment that the agency had earlier sent to the company. The Q & A letter describes the drug and its submission and details some reasons for the application’s withdrawal. The agency had concerns that one of the three pivotal studies, conducted in Europe, did not confirm the benefits of the other two studies. There were also significant safety concerns. The EMA’s letter prompted Wyeth to withdraw the application, although it has since been re-submitted.



The table below (**Figure 10**) summarizes some of the key data from three Phase III trials that was presented by Wyeth at the 55th Annual Meeting of the American College of Obstetricians and Gynecologists (ACOG) in 2007. The efficacy is measured by the percentage change in moderate to severe hot flashes after 12 weeks. As you can see, the various doses of *Pristiq* helped patients achieve a reduction in the neighborhood of 60%, which is in line with what would be needed for approval. The adverse events, however, are a totally different story, with unacceptable numbers of patients experiencing most of AEs listed below.

³⁷ European Medicines Agency; [Questions and answers on the withdrawal of the marketing application for Pristiq](#). March 19, 2008; London.

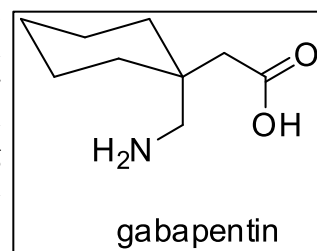
Figure 10. Summary of Data for Pristiq in Hot Flashes

	<i>Pristiq</i> (desvenlafaxine) dose				
	50 mg	100 mg	150 mg	200 mg	Placebo
# of Participants	154	157	163	155	178
Change from baseline in moderate to severe hot flashes (12 Weeks)	55%	64%	60%	60%	51%
Discontinued Treatment	61 (40%)	68 (43%)	81 (50%)	82 (53%)	29 (37%)
Adverse Events [# (%)]					
Hypertension	6 (4.0)	8 (5.2)	10 (6.4)	12 (7.9)	1 (1.3)
Anorexia	7 (4.7)	9 (5.8)	13 (8.3)	15 (9.9)	2 (2.6)
Constipation	16 (10.7)	27 (17.4)	25 (15.9)	27 (17.9)	8 (10.4)
Dry Mouth	18 (12.1)	33 (21.3)	31 (19.7)	35 (23.2)	3 (3.9)
Nausea	41 (27.5)	60 (38.7)	75 (47.8)	68 (45.0)	5 (6.5)
Weight Gain	4 (2.7)	9 (5.8)	12 (7.6)	5 (3.3)	3 (3.9)
Insomnia	23 (15.4)	27 (17.4)	43 (27.4)	39 (25.8)	8 (10.4)

Source: ACOG 2007.

In late 2007, before Wyeth had withdrawn its marketing application for *Pristiq* in this indication, the EMA issued a withdrawal assessment to Wyeth regarding the drug and its use in vasomotor symptoms.³⁸ In the report, the agency deeply details the problems that Wyeth/Pfizer will have to overcome before bringing the drug to market. Frankly, after reading the report we find it highly unlikely that this drug will ever be approved in this indication. Notably, the report mentioned that upon re-analysis, only the 100 mg dose group achieved a significant ($p=0.05$) reduction in hot flashes and no increase in effectiveness was seen with higher doses. And, even as effectiveness hit a plateau, AEs continued to increase. Regarding safety, the report flatly states, “Although these SNRI-like adverse events and the occurrence of withdrawal symptoms are consistent with the known AE profile of venlafaxine in the treatment of major depression disorders, it is doubtful if these bothersome adverse events could also be acceptable for an indication such as VMS.”

Serada. Gabapentin, which is being developed under the trade name *Serada* for the treatment of hot flashes, is a gamma-aminobutyric acid (GABA) analogue that is approved for the treatment of epilepsy, major depressive disorder and neuropathic pain. On rare occasion, it prescribed off-label for the treatment of menopausal symptoms. Indeed, the drug has been controversial over the years because of this type of use, with Pfizer paying out multiple settlements due to off-label marketing activity. The most common AEs associated with gabapentin use are dizziness, drowsiness and peripheral edema (swelling), and they increase with higher doses. The drug also has withdrawal symptoms that often continue despite a long tapering period.



³⁸ European Medicines Agency; [Withdrawal Assessment Report for Pristiq](#). November 15, 2007; London.

In October 2009, Depomed reported the results of 2 Phase III studies of *Serada* in hot flashes, the BREEZE 1 and BREEZE 2 Trials. Data from the BREEZE 1 Trial is summarized in **Figure 11** below, and is comparable to data collected in BREEZE 2. These trials were randomized, placebo-controlled studies with a primary endpoint being a statistically significant reduction in the frequency and severity of hot flashes at 4 and 12 weeks. After 12 weeks, patients taking both doses of *Serada* experienced a significant decrease in the number of hot flashes/day. However, the change from baseline in moderate to severe hot flashes did not reach statistical significance. One problem that both BREEZE trials suffered from was an extremely high placebo response. Conversely, the placebo response in the *Serada* Phase II was probably too low, at 28%. This definitely raises questions about the design and execution of the trial. Indeed, the FDA asked Depomed in late 2009 to run a third Phase III trial, with focus on placebo response. Typically in published trials concerning hot flashes the placebo response should be between 45-55%, but in the BREEZE trials the rate was 55-62%. This raises concerns about the viability of the early two previous trials. Depomed agreed to a Special Protocol Assessment (SPA) for the third trial, which began enrolling patients in April 2010 and completed enrollment in March 2011.

Figure 11. Summary of Data for *Serada* in BREEZE 1

	<i>Serada</i> (gabapentin) dose		
	1200 mg	1800 mg	Placebo
# of Participants	174	181	177
Mean frequency/day of moderate to severe hot flashes (12 weeks)	3.9 (p=.0024)	3.7 (p=.0028)	5.0
Change from baseline in moderate to severe hot flashes (12 Weeks)	67%	66%	62%
Discontinued Treatment	28 (16%)	20 (11%)	7 (4%)
Adverse Events [# (%)]			
Nausea	12 (6.9)	16 (8.8)	7 (4.0)
Flatulence	11 (6.3)	7 (3.9)	2 (1.1)
Dizziness	41 (23.6)	35 (19.3)	5 (2.8)
Headache	15 (8.6)	17 (19.4)	10 (5.6)
Somnolence	23 (13.2)	35 (19.3)	4 (2.3)
Weight Gain	5 (2.9)	9 (5.0)	4 (2.3)

Source: Depomed

The recently completed BREEZE III trial was a double-blind, placebo-controlled study of *Serada* that enrolled approximately 600 patients. Patients were randomized into one of two treatment arms, receiving either placebo or a total of 1800 mg of *Serada* dosed 600 mg in the morning and 1200 mg in the evening. The co-primary efficacy endpoints in the study are reductions in the mean frequency of moderate-to-severe hot flashes and the average severity of hot flashes, measured after four and 12 weeks of stable treatment.³⁹ As in the other BREEZE trials, patient follow-up continues to week 24 in order to satisfy the FDA requirement that drugs should continue to show statistically significant efficacy until that time.

According to Depomed, the differences in BREEZE III that will distinguish it from BREEZE I & II are as follows:⁴⁰

- 1) A single active arm rather than two arms, and therefore a required statistical p value of .05 rather than .025 to achieve statistical significance.
- 2) Up to 65% more patients in the active treatment arm than in the placebo arm
- 3) A two-week run in period to prior to randomization, rather than one week, which is designed to reduce the regression to the mean observed in Breeze I and II, resulting in a more stable baseline, and thereby potentially reducing the placebo effect.
- 4) An alternative statistical analysis method, known as a non-parametric analysis, that is designed to reduce the influence significant outliers can have on the achievement of efficacy endpoints.

Clinicians at Bionovo appear to have learned their lesson from the Depomed trials that failed win FDA approval for *Serada*. The *Menerba* trial will enroll more patients, 1200, than the total of BREEZE I & II combined. This will allow the company to achieve the desired level of statistical power. They have also integrated the extended run-in period prior to randomization to help control the placebo effect. During this time period, patients in the *Menerba* trial will complete extensive diaries to help researchers accurately determine eligibility and a stable baseline for analysis. Bionovo recognizes the presence of a strong placebo effect in this type of trial and has taken steps to both reduce this effect and give the trial adequate power to overcome the effect.

Considering the data for Depomed, it appears that *Serada* has a reasonable chance of achieving statistically meaningful reduction in menopausal hot flashes. One important note that can be seen in this data is that the drug was more effective at 4-weeks than at 12-weeks. This is in contrast to *Menerba*, which showed increasing efficacy throughout the 12-week trial. However, once again it is the safety and adverse event profile that is worrisome for this drug. First, similar to the *Pristiq* trial, there were an unacceptable number of drop-outs. Next, a very large portion of participants experienced either dizziness or sleepiness (somnolence), AEs that drastically impact quality of life. For example, patients experiencing these AEs often have trouble going to work and can not drive. Finally, there was a trend toward increasing weight in the treatment group vs. placebo, a side-effect that will, at the very least, damage the commercial potential of the drug.

³⁹ <http://www.clinicaltrials.gov/ct2/show/NCT01080300>

⁴⁰ Depomed Press Release, January 19, 2010.

HRT Competitive Landscape

There is a significant unmet need for a safe, effective, and non-hormonal therapy for the treatment of the vasomotor symptoms associated with menopause. In the US, approximately 60% of menopausal women seek healthcare for hot flashes. However, due to a paucity of treatments, only a small proportion of this population actually receives pharmaceutical intervention. Of those who do take medication, most take some form of estrogen replacement therapy. Many of those who do not take estrogen are seeking an effective medication but avoid HRT because of the associated health risks. In addition, many women who do take estrogens to treat menopausal symptoms would prefer to take a non-hormonal medication, but there are few reasonable options. Any new entrant into this market that fits the key criteria (safe, effective, non-hormonal) will not only gain market share from HRT products but will greatly expand the market into a currently un-treated population.

Currently, there are three leading contenders to enter the market as non-hormonal therapies for hot flashes. They are Bionovo's *Menerba*, Pfizer's *Pristiq*, and Depomed's *Serada*. Whichever of the three of these is first to market will no doubt try to use their period of exclusivity to establish themselves as the market leader. During this time that company will have exclusive access to this lucrative patient population. If the treatment proves to be safe and effective and is well received, it will be much more difficult for follow-on products to establish market share. We believe that *Menerba* is the most safe and effective treatment currently in development in this area. Furthermore, *Menerba* has a chance to be the first to market. If *Menerba* is approved, Bionovo may not have the resources to commercialized *Menerba* on its own. Moreover, Bionovo will have difficulty competing with the sales and marketing muscle of Pfizer or Depomed/Big Pharma, should Bionovo fail to find a Big Pharma partner for *Menerba*. We hope to see the Company establish a partnership with a large company that has solid footing in the women's health area. The combination of Bionovo's strong science and a proven marketing partner would give *Menerba* strong market potential.

In order to understand why we believe that *Menerba* has a competitive advantage when compared to other late-stage candidates, it is useful to examine the available clinical trial data. The table in **Figure 12** compares the most effective dose of each drug in recent clinical trials and includes some key safety measures. The dose included for *Serada* is the one that is being tested in ongoing Phase III trials. We must note that caution is necessary when comparing Phase II data to Phase III, especially concerning efficacy. All of the data shown here are from placebo-controlled, randomized trials. In this case, especially concerning safety, the differences are quite compelling.

Figure 12. Comparison of *Menerba*, *Pristiq*, & *Serada*

	<i>Menerba</i> 10 g Phase II		<i>Serada</i> 1800 mg Phase III		<i>Pristiq</i> 100 mg Phase III	
Intervention	10 g	Placebo	1800 mg	Placebo	100 mg	Placebo
# of Participants	75	71	181	177	157	78
Change from baseline in moderate to severe hot flashes (12 Weeks)	62%	50%	66%	62%	64%	51%
Discontinued Treatment	1	2	20	7	68	29
Adverse Events (% of Participants)						
Nausea	6.7%	9.9%	8.8%	4.0%	38.7%	6.5%
Diarrhea	12%	2.8%	n/a	n/a	7.7%	7.8%
Anorexia	1.3%	0	n/a	n/a	5.8%	2.6%
Somnolence	1.3%	0	19.3%	2.3%	15.5%	3.9%
Dizziness	5.3%	0	19.3%	2.8%	19.4%	7.8%
Weight Gain	<i>Weight Loss!</i>		5.0%	2.3%	5.8%	3.9%
Hypertension	1.3%	0	n/a	n/a	5.2%	1.3%

Source: LifeSci Advisors

A few conclusions can immediately be drawn from the data. From what we know so far, these drugs are essentially equally effective, although a problem with trial design casts doubt on *Serada's* efficacy. From a safety point of view, though, it is no contest. Regarding nausea, fewer *Menerba* patients had the experience than those on placebo, where as almost 2 in 5 *Pristiq* patients reported the AE. The only other blip for *Menerba* concerns transient loose stools, but as was discussed above we believe that problem is not only minor, but may have been solved. Below are some other key points of comparison between these drug candidates:

- *Pristiq* and *Serada* showed no (or negative) dose response whereas the maximum effective dose of *Menerba* has not yet been reached in the clinic.
- *Serada* causes significant cases of sleepiness and dizziness - patients can't drive.
- *Serada* and *Pristiq* both caused some weight gain compared to placebo, whereas *Menerba* patients lost weight overall.
- Botanically derived *Menerba* is, from all appearances, quite safe.

As a final comparison of these three drugs, it is worth noting that all three have really been seen as 'on the cusp' of approval for a number of years. *Pristiq* Phase III trials in hot flashes were conducted in 2005. *Serada* and *Menerba* both once had aspirations of making it to market by late 2009. The reasons for the delays, however, are quite different. In the case of *Serada*, poor Phase III trial design and a possible lack of efficacy led the FDA to insist on further trials. In the case of *Menerba*, the main problem was related to manufacturing. This is not surprising given the FDA's inexperience with this type of drug and a mutual desire between Bionovo and the Agency to get the CMC plan straight. The delay was also related to discovering the proper dose for *Menerba*, which will be positive in the long term if a more effective dose is found. Plus, as a smaller company, Bionovo is always fighting for the resources necessary to move clinical programs forward.

Finally, concerning *Pristiq*, the most succinct way to summarize the development program is to say that it's very likely dead. We have included the candidate in this analysis because Pfizer still lists the drug as a promising piece of its development pipeline. However, in addition to the problems already outlined there is an addendum. A class action lawsuit against Wyeth (now Pfizer) alleges that company executives knowingly misled menopausal hot flash clinical study participants (and investors) regarding the dangers of *Pristiq*. In addition to the AEs discussed above, three study participants suffered coronary occlusions and there were two heart attacks. There were 27 total AEs in the treatment arm vs. zero on placebo. On September 29, 2010, a judge for the United States District Court for the Southern District of NY ruled that the case had merit to go to trial.⁴¹ The next most likely step is for Pfizer to settle the case, but regardless of what happens, *Pristiq* will almost certainly not be approved in this indication.

Intellectual Property

Menerba (MF-101) & *Bezielle* (BZL101)

Bionovo has been very aggressive in patenting their discoveries, with 126 patent applications currently pending with the USPTO and in other jurisdictions. The patent estate surrounding *Menerba* as a treatment for menopausal hot flashes is quite strong. Bionovo holds a composition of matter patent on the formulation, entitled "Composition for Treatment of Menopause" that was issued on March 29, 2006 and gives the product market exclusivity until 2026. The company filed 37 other patents related to *Menerba*, including composition of matter, structure-function and methods of treatment. For *Bezielle*, the company filed 6 patents including one entitled "*Scutellaria barbata* Extract for the Treatment of Cancer". The patent, issued on April 20, 2010, covers the method and use of the drug as a monotherapy for breast cancer, and also expires in 2026. Beyond the intellectual property estate, Bionovo has a large amount of institutional knowledge to protect their assets. For example, it is hard to imagine another company would have the expertise to source and qualify botanicals only to face an uncertain FDA approval, since no rules exist regarding generics in this area.

Financial Discussion

Bionovo reported a 2010 net loss of \$17.7 million or \$0.80 per share and revenues of \$0.6 million. This compared to a net loss in 2009 of \$16.4 million or \$0.98/share and revenues of about \$0.3 million. In both years the revenues were realized from government grants. Expenses incurred supporting the *Menerba* manufacturing development process were the primary driver of the increased loss in 2010. Bionovo ended the year with cash and cash equivalents totaling about \$2.6 million.

In October 2010, the company completed a small, direct offering of common stock and warrants which raised approximately \$3.0 million. The offering consisted of 2,727,270 shares at a price of \$1.10 per share and 2,045,451 warrants to purchase shares. The warrants are exercisable six months after issuance at \$1.64 per share and will expire five years from the date of issuance. More recently, in February of this year the company completed an underwritten public offering of 30,031,200 units at a price per unit of \$1.00. Each unit consisted of one share of common stock and a warrant to

⁴¹ United States District Court Southern District of New York; [City of Livonia Employees' Retirement System, on Behalf of Itself and All Others Similarly Situated](#). No. 07 Civ. 10329 (RJS)

purchase one half of one share of stock at an exercise price of \$1.30 per share. The warrants may be exercised any time after closing and will expire after five years. The net proceeds of this offering were approximately \$28 million.

In addition to the stock offering, Bionovo also received grants totaling approximately \$498,000 in November 2010 from the Qualifying Therapeutic Discovery Project Credit (QTDP) program. The grants, created to provide incentive to smaller companies focusing on innovative therapies, are intended to fund the *Menerba* and *Bezielle* programs for menopausal symptom alleviation and treatment of advanced breast cancer, respectively.

After the recently completed round of financing, in which Bionovo raised about \$28 million, the company is on solid financial footing for the foreseeable future. Research and development costs will increase in 2011 as the company incurs increasing clinical costs due to the pivotal trials of *Menerba* for the treatment of menopausal hot flashes. Bionovo has estimated that the total cost of two Phase III studies will be \$25 million and results are expected in Q4 2012. We hope to see the Company find a partner to help fund the final development of *Menerba* and help with commercialization.

Management Team

Isaac Cohen, O.M.D., L.Ac.

Chairman of the Board and Chief Executive Officer

Dr. Cohen was a co-founder of Bionovo, Inc., served as its Chairman, Chief Executive Officer and Chief Scientific Officer, and has been a Director since February 2002. He became the Chairman, Chief Executive Officer and Chief Scientific Officer and a Director of the public company Bionovo Pharmaceuticals, Inc. in April 2005. Dr. Cohen has been a Guest Scientist at the University of California, San Francisco (UCSF) Cancer Research Center and UCSF Center for Reproductive Endocrinology since 1996. Dr. Cohen was in private practice at The American Acupuncture Center, located in Berkeley, California, from 1989-2005.

Mary Tagliaferri, M.D., L.Ac.

President, Chief Medical Officer, Chief Regulatory Officer

Dr. Tagliaferri was a co-founder of Bionovo, Inc., and served as its Chief Regulatory Officer, Chief Medical Officer, Secretary and Treasurer and as a Director since February 2002. She became Vice President, Chief Medical Officer, Chief Regulatory Officer, Secretary and Treasurer of the public company Bionovo Pharmaceuticals, Inc. in April 2005, and a Director effective May 2005. She became President of Bionovo Pharmaceuticals, Inc. in May 2007, in addition to continuing her functions as the Company's Chief Medical Officer, Secretary, Treasurer and a Director. Dr. Tagliaferri conducted translational research at the University of California, San Francisco from 1996-2002.

Thomas C. Chesterman

Senior Vice President and Chief Financial Officer

Mr. Chesterman has served as Bionovo's Senior Vice President, Chief Financial Officer and Assistant Secretary since July 2007. From January 2002 to June 2007, Mr. Chesterman was Sr. Vice President and Chief Financial Officer at Aradigm Corporation, a drug development company. From

March 1996 to December 2001, Mr. Chesterman was Vice President and Chief Financial Officer at Bio-Rad Laboratories, Inc., a life-science research products and clinical diagnostics company. From 1993 to 1996, Mr. Chesterman was Vice President of Strategy and Chief Financial Officer of Europolitan AB, a telecommunications company.

Risk to an Investment

At this time we consider an investment in Bionovo, Inc. to be a high-risk investment. The Company does not yet have any marketed products and is pursuing the clinical development and marketing approval of a botanical product to treat hot flashes associated with menopause. The Company is in relatively new territory with the FDA, which does not routinely oversee this type of drug. The Company is also developing a similar treatment for use in breast cancer patients. The advancement of these developmental stage programs is the primary factor contributing to Bionovo's value. Factors affecting the chances of these programs achieving regulatory approval by the FDA, EMEA, or other regulatory bodies, include lack of efficacy, problems with manufacturing or material supply, and as-yet unknown safety problems. Failure to obtain marketing approval, or to achieve commercial success once approved, could have a significant, negative impact on Bionovo's stock price. Finally, as a development-stage biotechnology company, Bionovo is not profitable and may not have sufficient funds to complete the development and commercialization of their products. Failure to obtain a partner for product development and commercialization is a risk, and future financing activity may cause dilution of existing shareholders.

DISCLOSURES

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Bionovo
4/7/711

Numbers in Thousands

	FY07A	FY08A	1Q09A	2Q09A	3Q09A	4Q09A	FY09A	1Q10A	2Q10A	3Q10A	4Q10A	FY10A
Revenues												
All Revenue	582	233	-	7	155	126	288	-	14	68	531	613
Total Revenues	582	233	-	7	155	126	288	-	14	68	531	613
Operating Expenses												
Research and Development	9,938	11,416	3,601	2,954	2,938	3,006	12,499	3,806	3,328	3,673	3,835	14,642
General and Administrative	4,284	6,097	1,009	1,175	926	943	4,053	852	788	987	899	3,526
Total Operating Expense	14,222	17,513	4,610	4,129	3,864	3,949	16,552	4,658	4,116	4,660	4,734	18,168
Operating Loss	(13,640)	(17,280)	(4,610)	(4,122)	(3,709)	(3,823)	(16,264)	(4,658)	(4,102)	(4,592)	(4,203)	(17,555)
Change in Fair Value of Warrant Liability	-	-	-	-	-	-	-	-	-	-	-	(94)
Interest Income	850	730	54	16	5	9	84	8	6	2	2	18
Interest Expense	(87)	(129)	(33)	(22)	(22)	(18)	(95)	(14)	(10)	(9)	(28)	(61)
Other Income (Expense), net	(21)	(17)	(77)	(6)	-	(5)	(88)	3	(14)	(28)	(1)	(39)
Total Other Income (expense)	742	584	(56)	(12)	(17)	(14)	(99)	(3)	(18)	(35)	(121)	(176)
Loss Before Income Tax	(12,898)	(16,696)	(4,666)	(4,134)	(3,726)	(3,837)	(16,363)	(4,661)	(4,120)	(4,627)	(4,324)	(17,731)
Income Tax Provision	(3)	(4)	(2)	-	-	1	(1)	(1)	-	-	-	(1)
Net Income (loss)	\$ (12,901.0)	\$ (16,700.0)	\$ (4,668.0)	\$ (4,134.0)	\$ (3,726.0)	\$ (3,836.0)	\$ (16,364.0)	\$ (4,662.0)	\$ (4,120.0)	\$ (4,627.0)	\$ (4,324.0)	\$ (17,732.0)
EPS - Basic	\$ (0.98)	\$ (1.09)	\$ (0.31)	\$ (0.27)	\$ (0.24)	\$ (0.18)	\$ (0.98)	\$ (0.22)	\$ (0.19)	\$ (0.21)	\$ (0.18)	\$ (0.80)
EPS - Diluted	\$ (0.98)	\$ (1.09)	\$ (0.31)	\$ (0.27)	\$ (0.24)	\$ (0.18)	\$ (0.98)	\$ (0.22)	\$ (0.19)	\$ (0.21)	\$ (0.18)	\$ (0.80)
Shares Out - Basic & Diluted	13,153	15,271	15,273	15,273	15,274	21,101	16,725	21,508	21,524	21,785	24,352	22,299