Using Testosterone in women

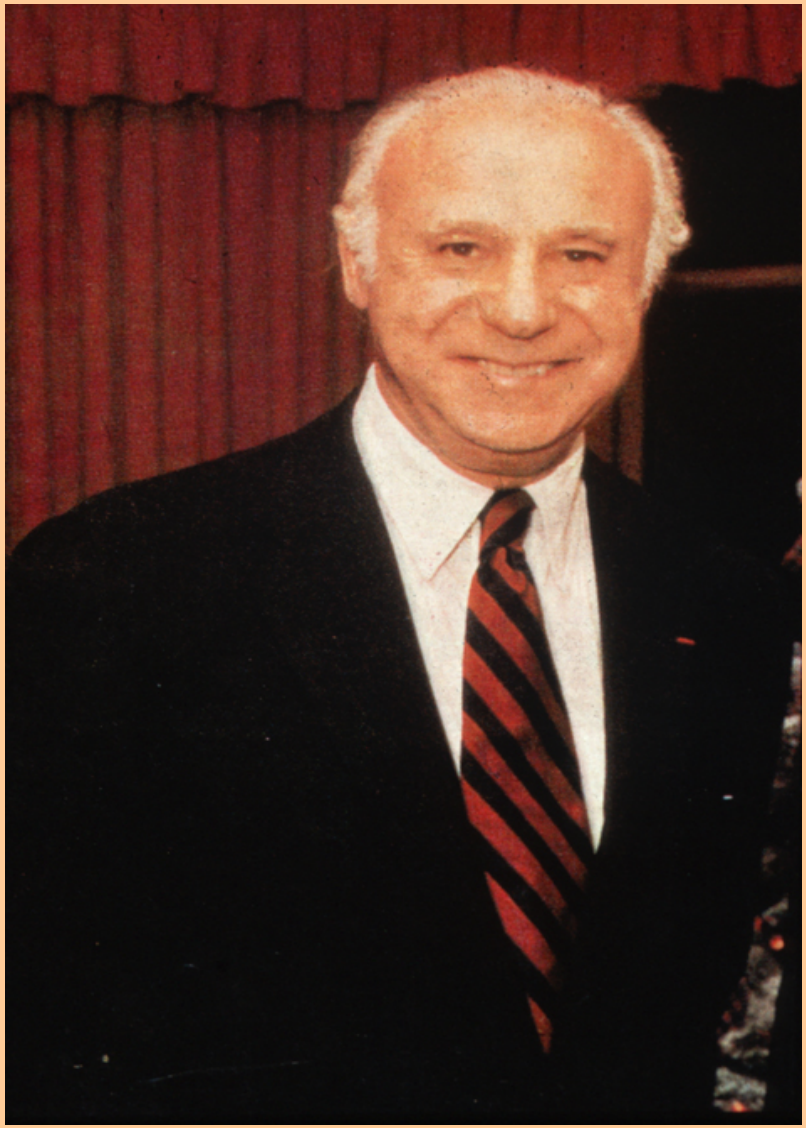
Nick Panay BSc MRCOG MFFP

West London Menopause & PMS Centre

Queen Charlotte's & Chelsea and Chelsea & Westminster Hospital

Androgenic Options

- Implants – only licensed option until recently
- Oral – ? Liver effects
- Livial (tibolone)
- DHEA – weakly androgenic
- Injections – sustanon
- Gel – useful but not licensed
- Transdermal



Greenblatt

Robert Greenblatt
Am. J. Obstet & Gynecol 1949

Indications for the use of Testosterone implants

- Persistent menopausal symptoms in women receiving ERT
- In the woman who is not psychologically frigid and in whom increased libido is desired

Postmenopausal Woman - Libido

Studd 1977 (BJOG)

Uncontrolled study of 76 patients with psychosexual problems

- E50mg - effective for dyspareunia and improved libido in 80% patients
- Additional T100mg significantly improved libido in 12 out of 15 patients who had not responded to estradiol alone

Effects of testosterone

- 2-year single-blind, randomised trial in 34 women

- E50 vs E50 / T50 3-monthly

- E/T group significant ↑ in:
  - sexual activity
  - satisfaction
  - pleasure
  - orgasm

Davis et al; Maturitas, 1995

Questionnaire of sexual and general health response in women receiving estradiol and testosterone implants

Hawkins A & Studd J 2004

What was the importance of loss of libido to you?

- **Sexual component**

  “made relationship difficult as not interested in sex” “libido almost zero” “inability to orgasm and feel satisfied” “no desire dead meat”

- **non sexual component**

  “ I felt my age”

  “lost self confidence – poor communication”

  “felt less capable”

  “others noticed that I had lost the “it” factor”

  “no creative drive”

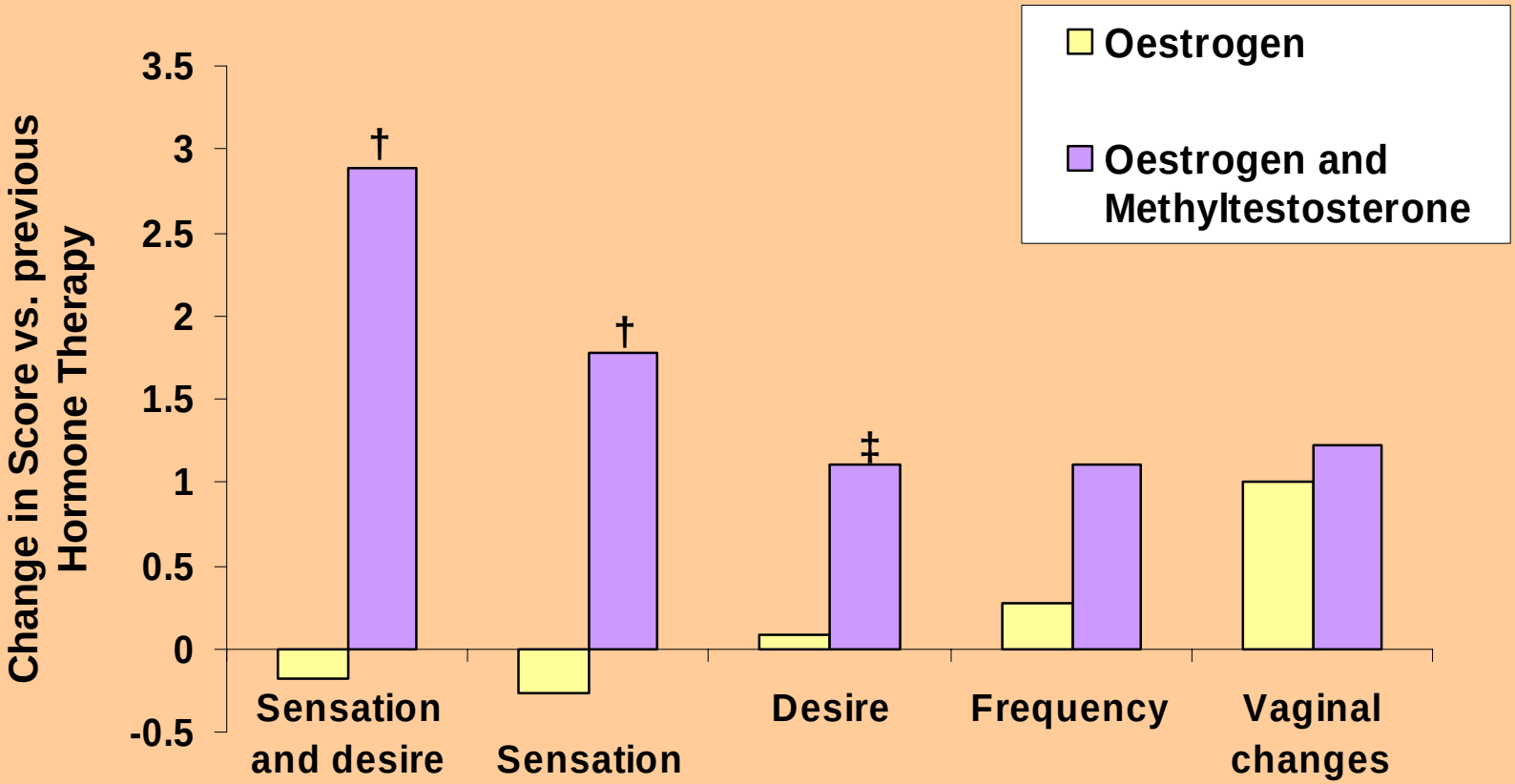
  “I hated myself”

In what way has the treatment improved your sexual response?

- “can have easy orgasms and feel satisfied”
- “now feel like sex is part of my life again”
- “orgasms on train journey”
- “returned to normal”
- “like in my 20s with a bigger appetite –it’s wonderful”
- “initiate sex more orgasms”

Oral Testosterone

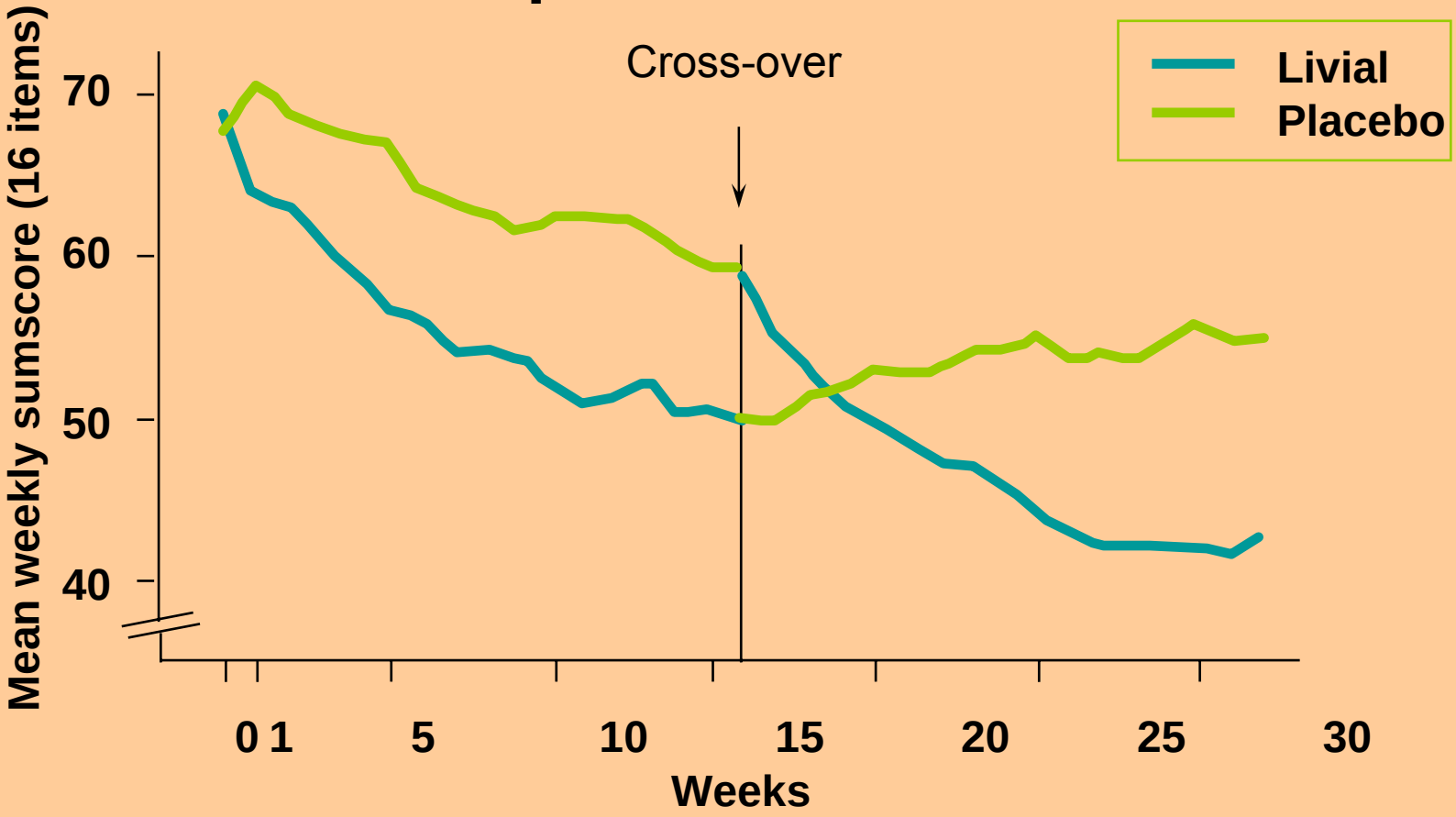
Oestrogen may not address all aspects of sexual function



Sexuality, Activity and Libido Scale assessed in menopausal women (n=20)
† $p<0.01$; ‡ $p \leq 0.05$

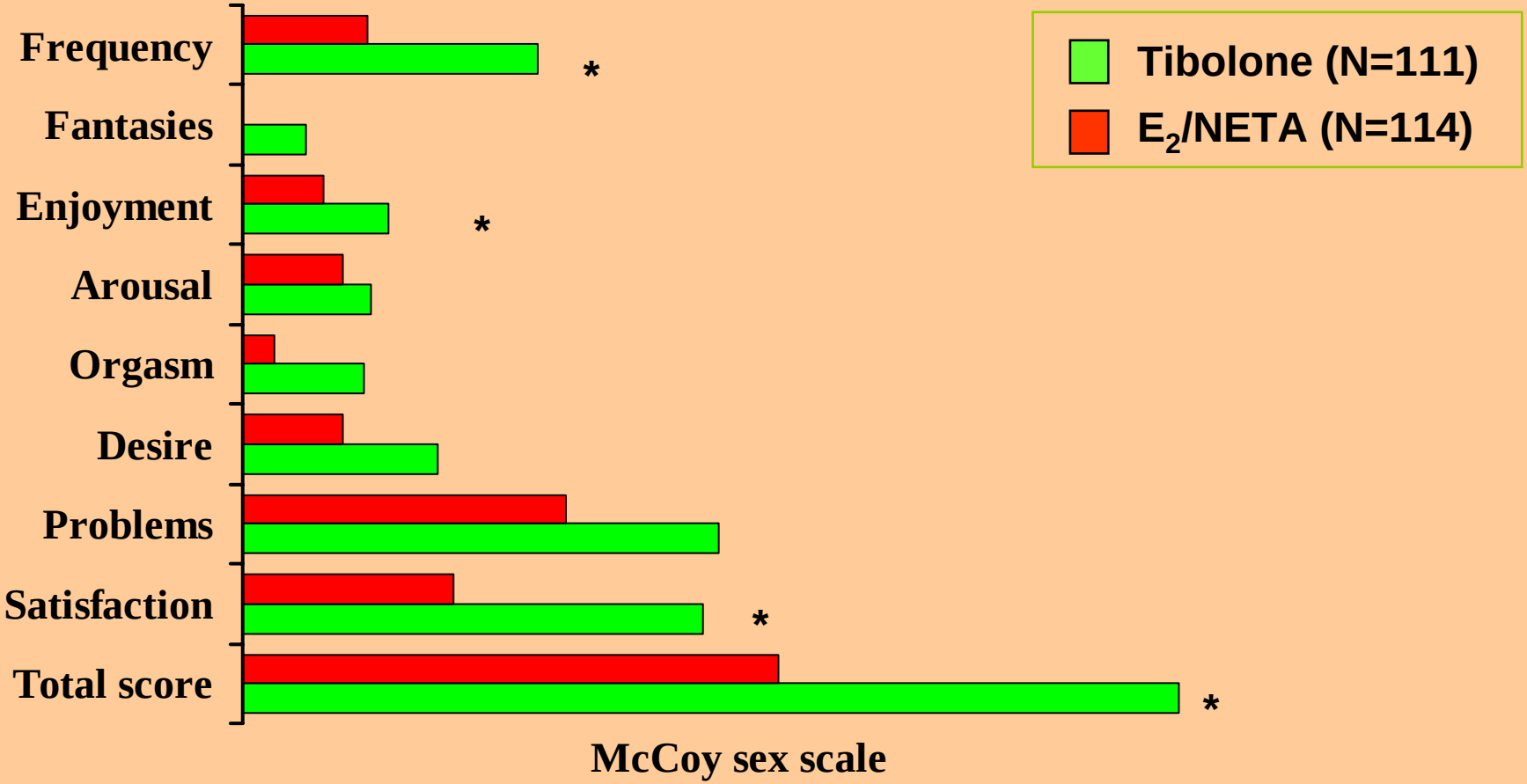
Sarrel PM, et al. (1998) *Journal of Reproductive Medicine*; 43: 10:847-856

Effect on mood: Livial® versus placebo



Tax *et al*., *Maturitas*

Effect on sexuality: Tibolone versus continuous combined HRT

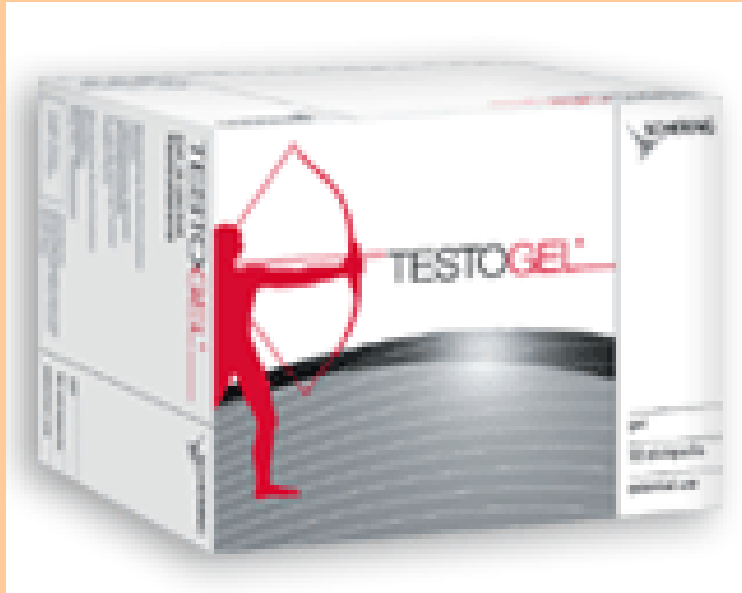


E_2/NETA, 17β-estradiol (2 mg/day)/norethisterone acetate (1 mg/day)
*$p < 0.05$ between groups

Nathorst-Böös *et al.*, *Maturitas* 1997

Testosterone gel

- Unlicensed for women
- 5ml gel 50mg sachet
- 0.5 – 1.0ml / day
- Abdo / inner thighs
- FAI up to 6.5%



Daily Mail

THURSDAY, OCTOBER 21, 2004 www.dailymail.co.uk 40p

Now, the love patch

A 'Viagra' to restore ladies' joie de vivre

WOMEN could be wearing stick-on patches to boost their sex drive within months, say researchers.

The patches release the male sex hormone testosterone to help women overcome a loss of desire.

Some experts claim it will be the female version of Viagra, with the latest research showing it can enhance libido and increase the amount of sexual activity enjoyed by women.

Men suffering impotence can already put on a testosterone patch. Manufacturers Procter & Gamble say that their Intrinsa patch for women will be available in the U.S. in three months, and in Britain later next year.

From **Jenny Hope**
Medical Correspondent, in Philadelphia

found in menopausal women who had been diagnosed with hypoactive sexual desire disorder (HSDD), in which libido and sexual activity is reduced, leading to psychological distress.

Altogether 550 women took part in a six-month study, with half unaware they had been given a dummy patch.

As well as boosting the amount of satisfying sex they had – making love four times more every two months than those wearing a dummy patch – it also increased desire.

How coming off the Pill can boost women's sex drive

COMING off the Pill can boost women's sex drive, according to researchers.

Taking the hormonal contraceptive causes a loss in sexual desire in one in six women, scientists claimed yesterday.

Four weeks after abandoning the Pill, women who had complained of a lack of desire found their appetite for sex returned.

They had increases in libido, arousal and orgasm, according to a report at the American Society for Reproductive Medicine conference in Philadelphia.

Not taking the Pill led to rising levels of the sex hormone testosterone and a fall in a hormone that can suppress desire.

Experts also believe that the loss of sexual appetite experienced by some women on the Pill may be triggered by the elimination of ovulation – nature's way of telling women to have sex.

Researcher Dr Susan Sarajari, of the University of California, Los Angeles, said: 'Discontinuing hormonal contraception should be considered a first-line treatment for women complaining of sexual dysfunction.'

Around 15 per cent of women taking the Pill, injectables or using a hormonal patch have symptoms of sexual dysfunction such as sexual distress, low libido and vaginal dryness, she said.

In a pilot study, 20 women aged around 34 stopped taking the Pill after six months. Their sex life improved significantly, with increases in sexual appetite and orgasms, and a cut in sexual distress.

A larger study involving 200 women is now under way.

Dr Marian Damewood, president of ASRM, said: 'This study presents evidence for an effect many women are familiar with. When a healthy pre-menopausal woman experiences decreased sexual function, hormonal contraception could be considered as a possible cause and may be discontinued to determine whether it is indeed a factor.'

But Dr Anne Szarewski, author of Contraception: A User's Guide, said it was difficult to prove that a loss of libido is directly attributable to the Pill. 'There can be many factors that affect sexual desire, including stress, lifestyle and bereavement,' she said.

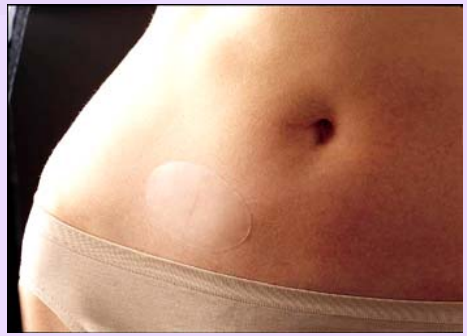
Intrinsa

(testosterone transdermal patch)

A new treatment option for surgically menopausal women with Hypoactive Sexual Desire Disorder (HSDD) on concomitant oestrogen (not CEE)

Two studies in over 1000 surgically menopausal women

Safety and efficacy of a 300 mcg/day testosterone transdermal patch (TTP) in surgically menopausal (SM) women with hypoactive sexual desire disorder (HSDD) on concomitant oestrogen



- **Thin, clear, oval transdermal patch**
- **Twice-a-week application to abdomen**

- 1,095 women in 2 Phase III Trials (INTIMATE SM 1 and INTIMATE SM 2)
- 24-weeks of treatment

- Women aged 20 – 70 years with bilateral oophorectomy & hysterectomy
- Women receiving concomitant oestrogen

Simon JA, et al. *Journal of Clinical Endocrinology & Metabolism* 2005;90(9):5226-33, Buster J. et al., *Obstetrics & Gynecology* 2005;105;944-52

HSDD key parameters: desire, distress, sexual activity

Primary Endpoint:

- Change in frequency of total satisfying sexual activity from the Sexual Activity Log (SAL©)

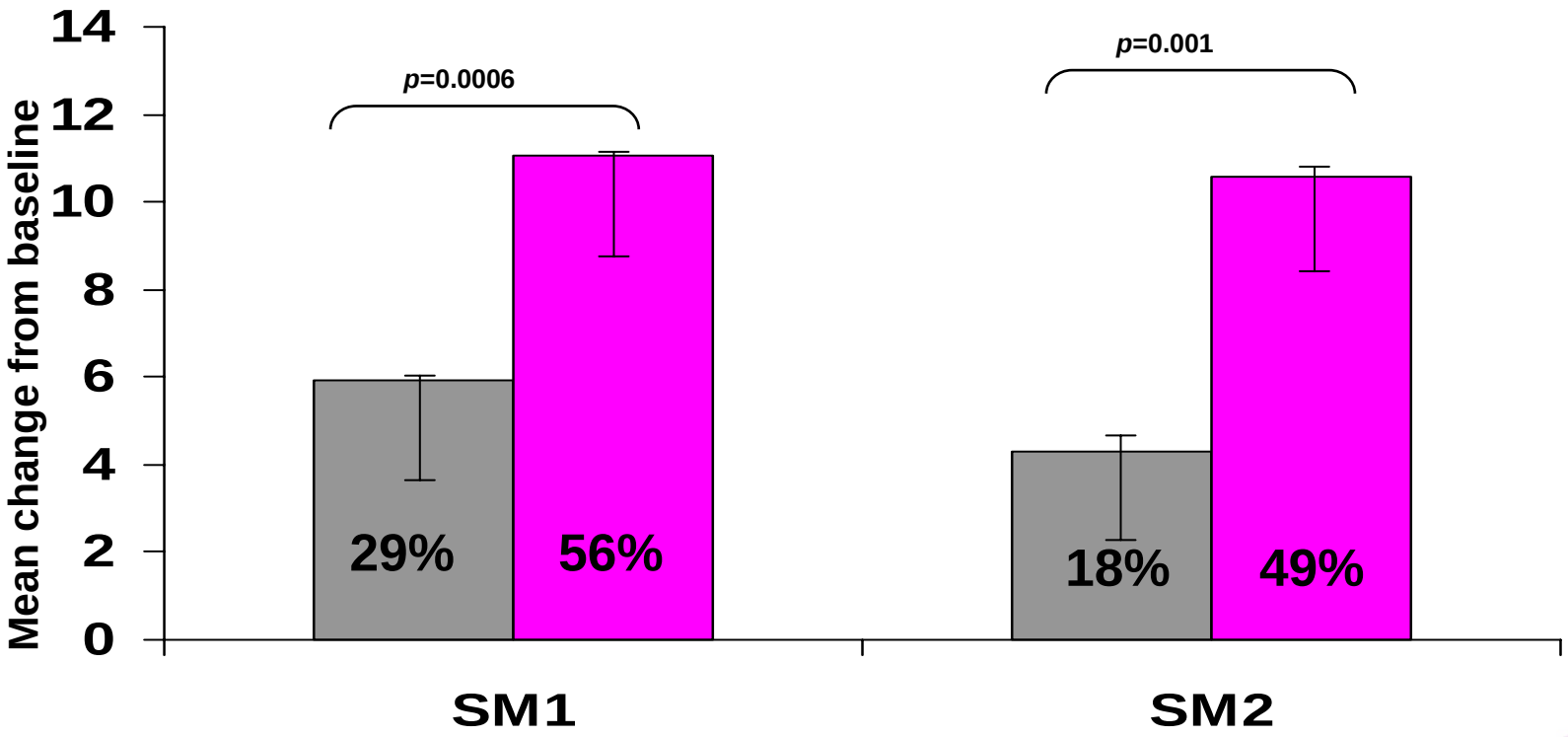
Secondary Endpoints Included:

- Change in the Seven (7) Domains from the Profile of Female Sexual Function (PFSF©)
  - Desire
  - Arousal
  - Orgasm
  - Pleasure
  - Concerns
  - Responsiveness
  - Self-Image
- Change in distress with the Personal Distress Scale (PDS©)
- AEs and clinical labs

Simon JA, et al. *Journal of Clinical Endocrinology & Metabolism* 2005;90(9):5226-33
Buster J. et al., *Obstetrics & Gynecology* 2005;105;944-52

Significantly increased sexual desire

In surgically menopausal women with Hypoactive Sexual Desire Disorder (HSDD) on concomitant oestrogen:



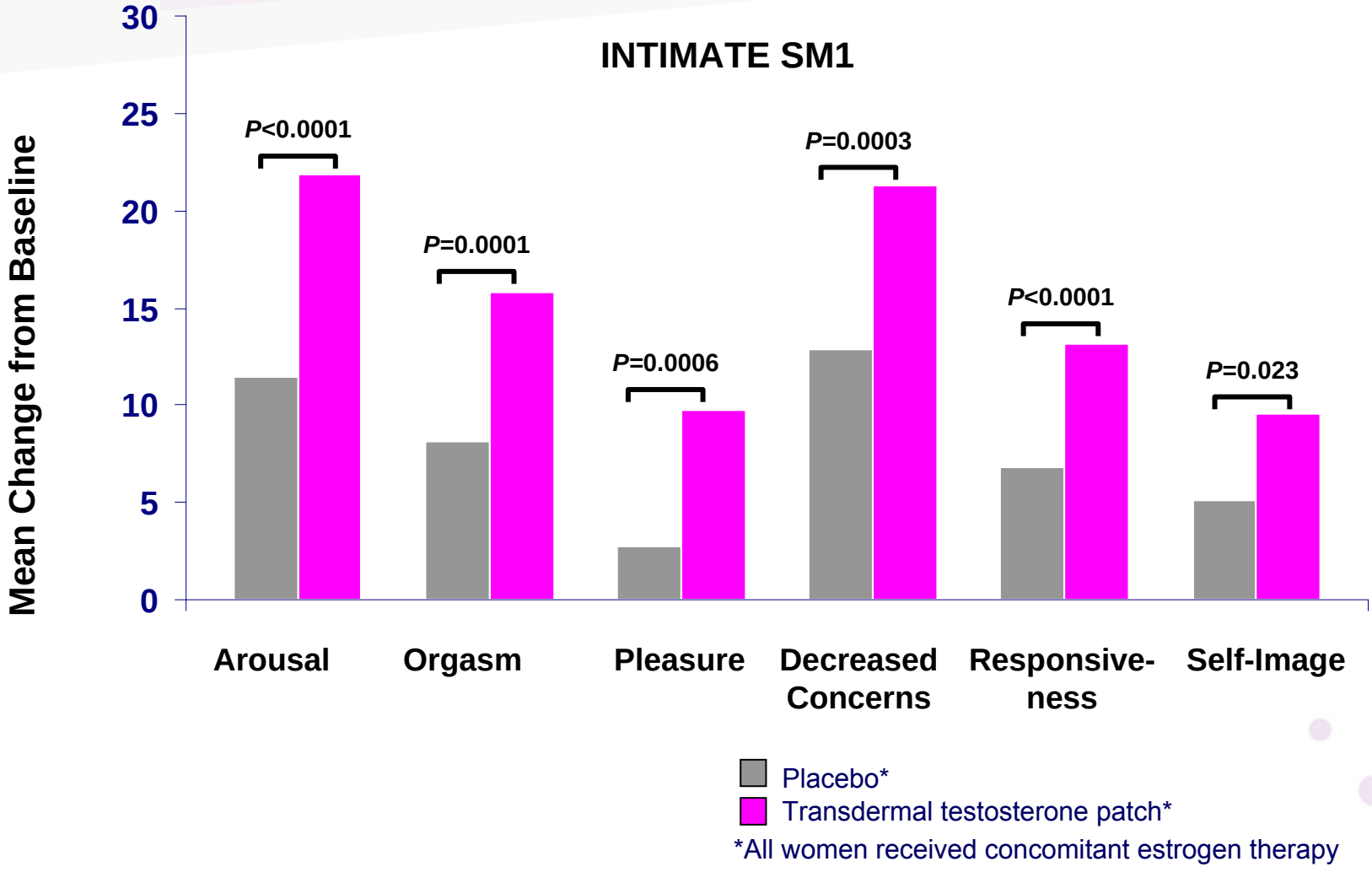
% Increase From Baseline

Placebo* Transdermal testosterone patch*

*All women received concomitant estrogen therapy

Simon JA, et al. *Journal of Clin Endo & Metab* 2005;90(9):5226-33
Buster J. et al., *Obstetrics & Gynecology* 2005;105;944-52

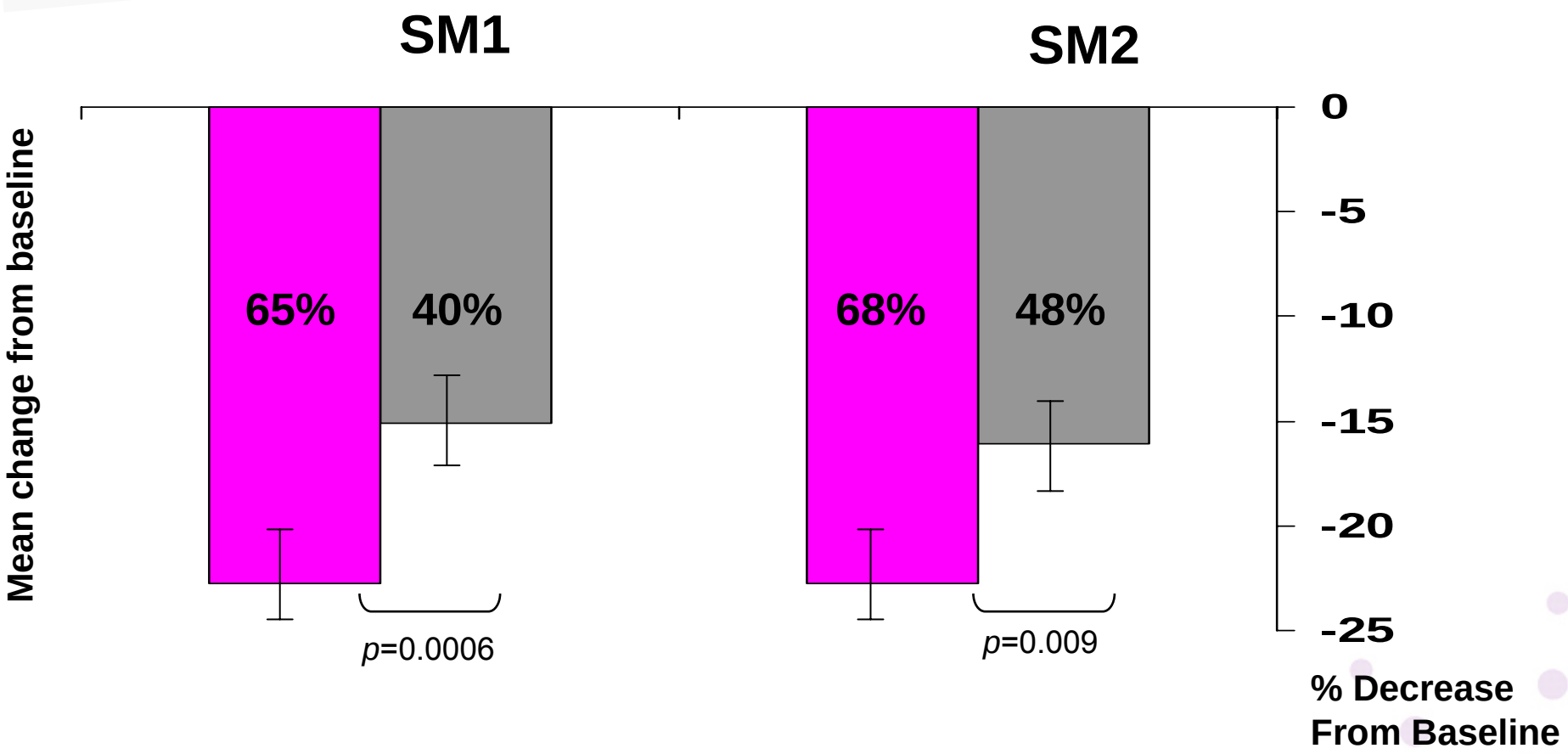
Intrinsa improves all domains of Profile of Female Sexual Function (PFSF)



Adapted from Simon JA, et al. *Journal of Clin Endo & Metab* 2005;90(9):5226-33

Significantly reduced distress due to low sexual desire

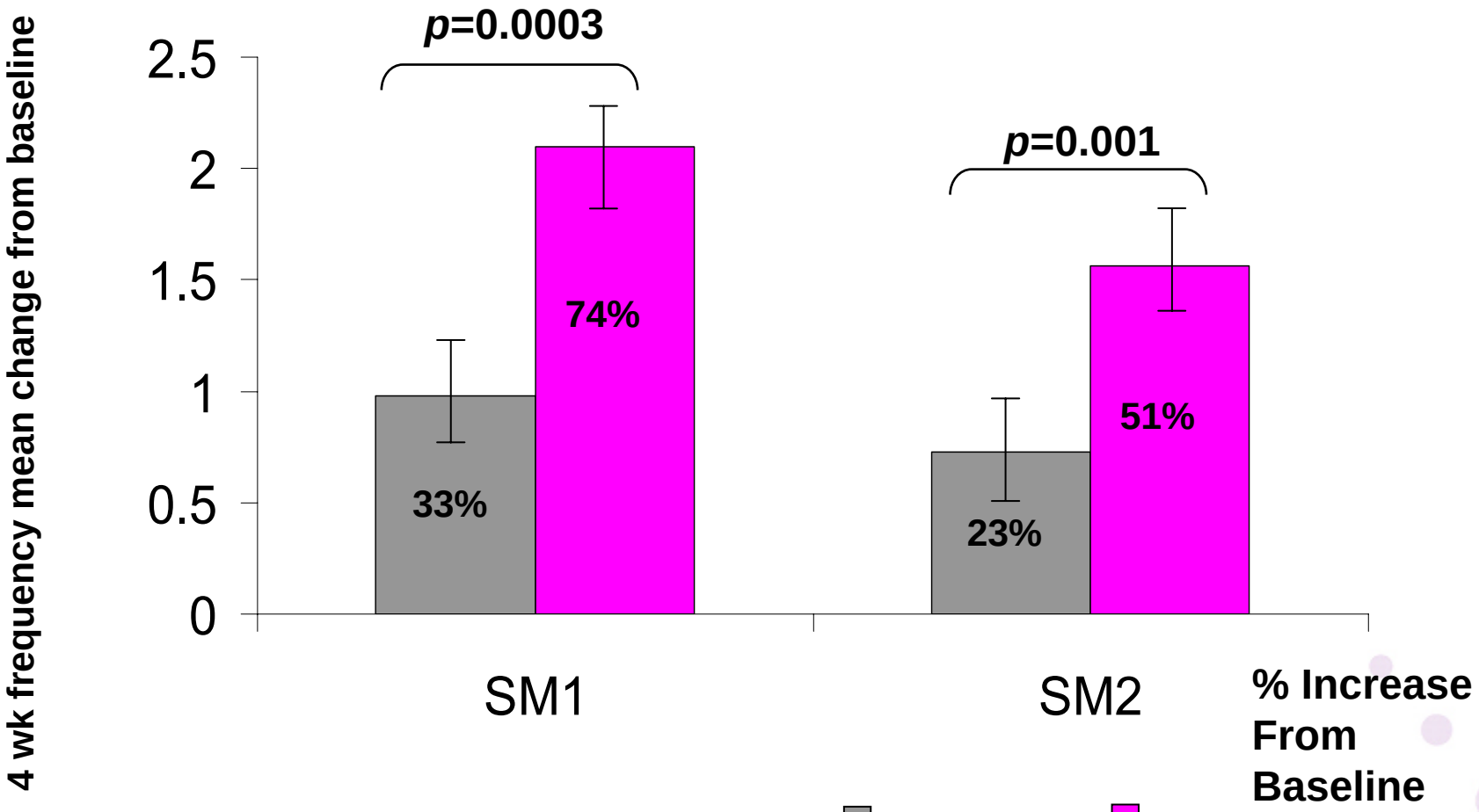
In surgically menopausal women with Hypoactive Sexual Desire Disorder (HSDD) on concomitant oestrogen:



Simon JA, et al. *Journal of Clin Endo & Metab* 2005;90(9):5226-33
Buster J. et al., *Obstetrics & Gynecology* 2005;105;944-52

Significantly increased satisfying sexual activity

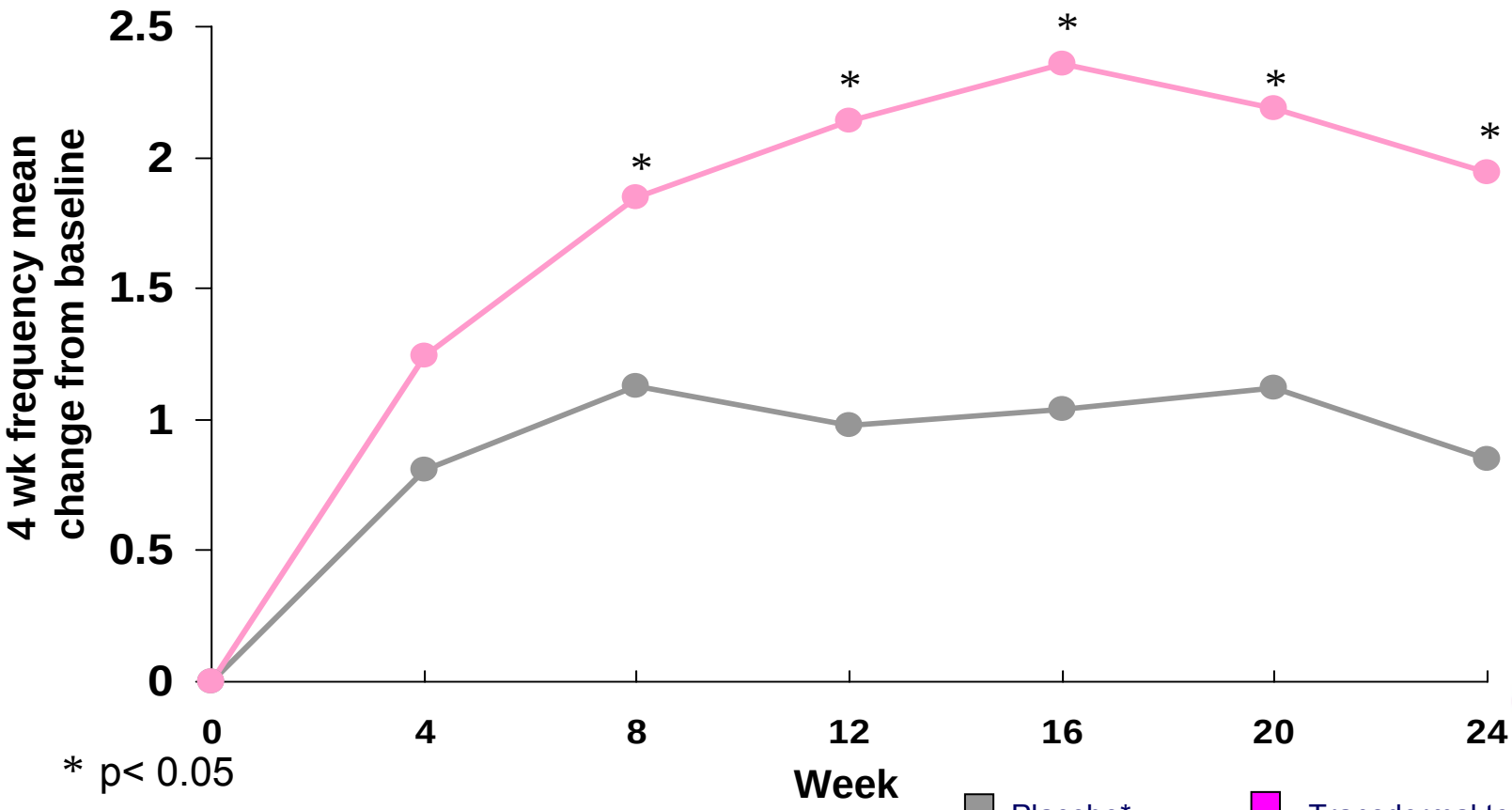
In surgically menopausal women with Hypoactive Sexual Desire Disorder (HSDD) on concomitant oestrogen:



Simon JA, et al. *Journal of Clin Endo & Metab* 2005;90(9):5226-33
Buster J. et al., *Obstetrics & Gynecology* 2005;105;944-52

Continuous treatment for at least 3 months for maximal benefit – total satisfying activity§

In surgically menopausal women with Hypoactive Sexual Desire Disorder (HSDD) on concomitant oestrogen:



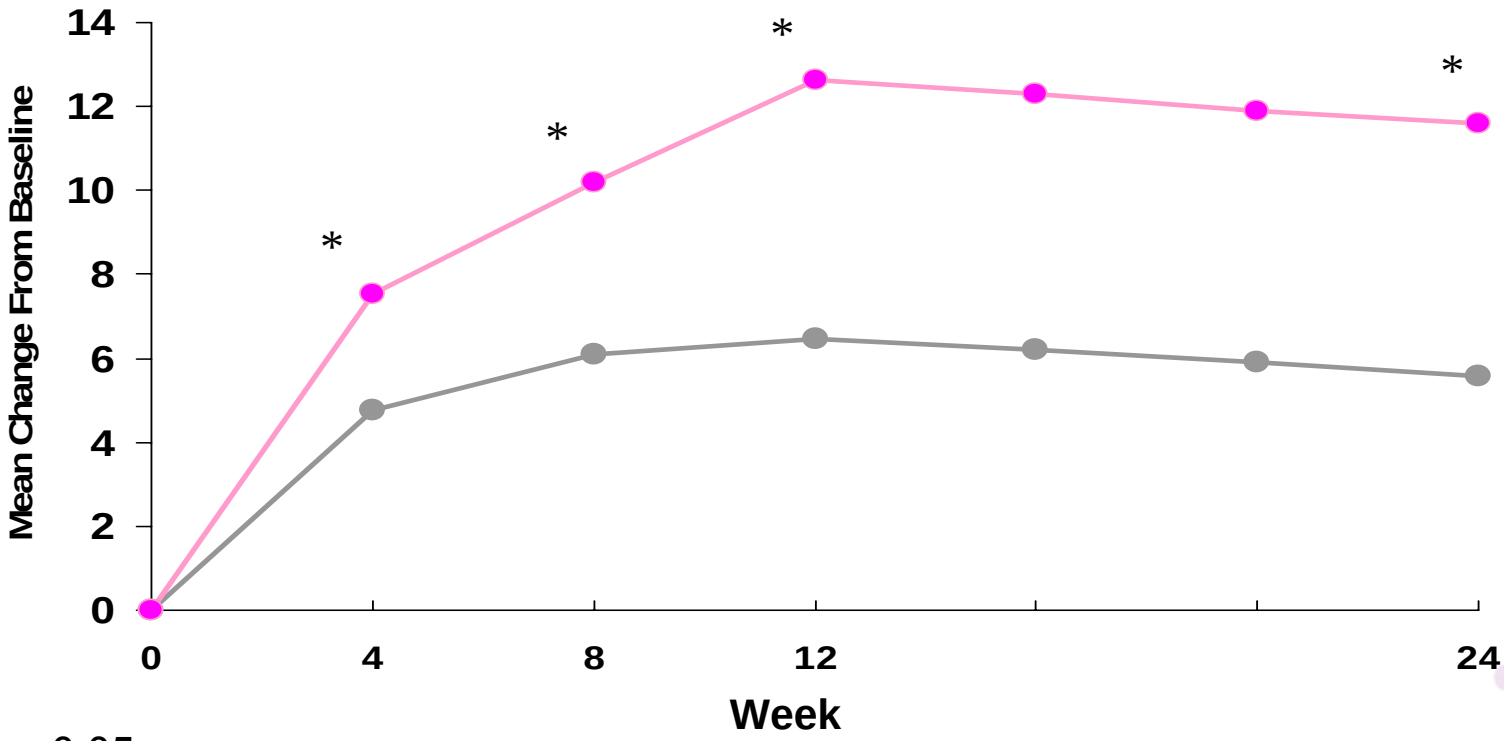
§Analysis combined Intimate SM1 & SM2

*All women received concomitant estrogen therapy

Kingsberg S et al. ***Poster presentation at the Annual Meeting of the American Obstetrics and Gynecology Society*****, May 2005**

Continuous treatment for at least 3 months for maximal benefit – sexual desire§

In surgically menopausal women with Hypoactive Sexual Desire Disorder (HSDD) on concomitant oestrogen:



* p< 0.05

§Analysis combined Intimate SM1 & SM2

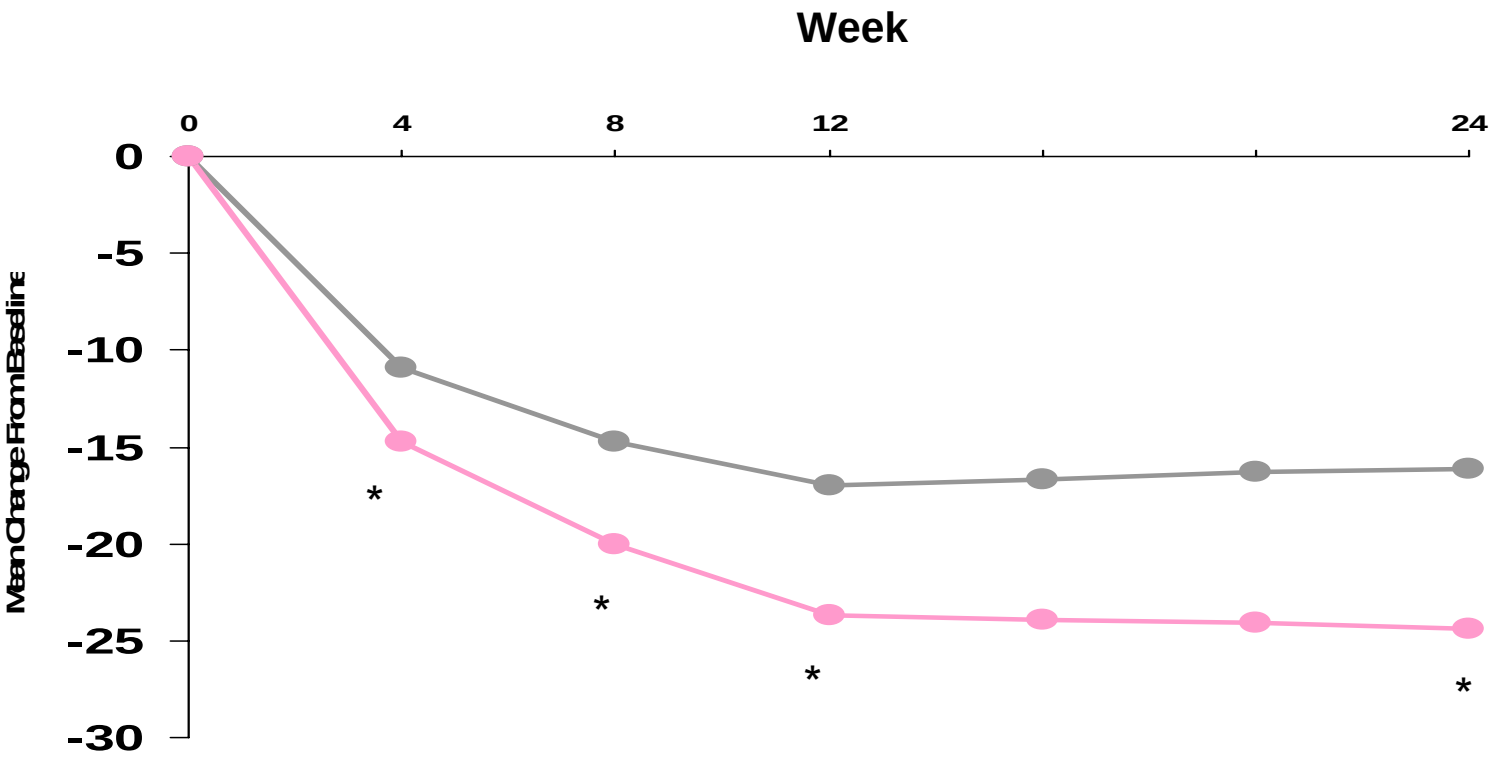
Placebo* Transdermal testosterone patch*

*All women received concomitant estrogen therapy

Kingsberg S et al. ***Poster presentation at the Annual Meeting of the American Obstetrics and Gynecology Society*****, May 2005**

Continuous treatment for at least 3 months for maximal benefit – sexual distress§

In surgically menopausal women with Hypoactive Sexual Desire Disorder (HSDD) on concomitant oestrogen:



* p< 0.05

§Analysis combined Intimate SM1 & SM2

Placebo*

Transdermal testosterone patch*

*All women received concomitant estrogen therapy

Kingsberg S et al. ***Poster presentation at the Annual Meeting of the American Obstetrics and Gynecology Society*****, May 2005**

Testosterone patch clinical trials: Focus on relevant safety areas

In addition to adverse event reporting, the following parameters were assessed :

- Androgenic effects
  - Acne, Hirsutism, Alopecia, Voice Deepening
- Weight
- Blood Pressure
- Liver Function
- Haematology
- Lipids
- Carbohydrate Metabolism
- Cardiovascular Disease
- Breast Cancer
- Application Site Reactions

Simon JA, et al. *Journal of Clinical Endocrinology & Metabolism* 2005;90(9):5226-33
Buster J. et al., *Obstetrics & Gynecology* 2005;105;944-52
P&GP Data on file - ES02-2005

Overall Adverse Events (AE) profile

Adverse Event (%)	INTIMATE SM1		INTIMATE SM2	
	Placebo (N = 279)	TTP (N = 283)	Placebo (N = 266)	TTP (N = 266)
Patients with AEs	79.6	77.7	74.1	74.4
Serious AEs	2.5	2.5	2.3	1.9
Withdrawal due to AEs	6.8	8.5	8.3	8.3
Most Common AEs				
Application Site Reaction	39.1	31.1	28.9	29.7
Upper Respiratory Infection	24.4	21.9	19.9	21.4
Unwanted Hair Growth	6.5	5.7	5.3	9.0

Simon JA, et al. *Journal of Clinical Endocrinology & Metabolism* 2005;90(9):5226-33
Buster J. et al., *Obstetrics & Gynecology* 2005;105;944-52
P&GP Data on file - ES02-2005

Safety focus: Androgenic AEs

Androgenic AE (%)	INTIMATE SM1		INTIMATE SM2	
	Placebo (N = 279)	TTP (N = 283)	Placebo (N = 266)	TTP (N = 266)
Acne	6.1	6.0	4.1	7.5
Alopecia	3.2	3.2	2.6	5.3
Unwanted Hair Growth	6.5	5.7	5.3	9.0
Voice Deepening	2.9	2.5	1.5	3.0
Withdrawal due to Androgenic AE	0.4	1.1	0.8	2.3

Simon JA, et al. *Journal of Clinical Endocrinology & Metabolism* 2005;90(9):5226-33
Buster J. et al., *Obstetrics & Gynecology* 2005;105;944-52
P&GP Data on file - ES02-2005

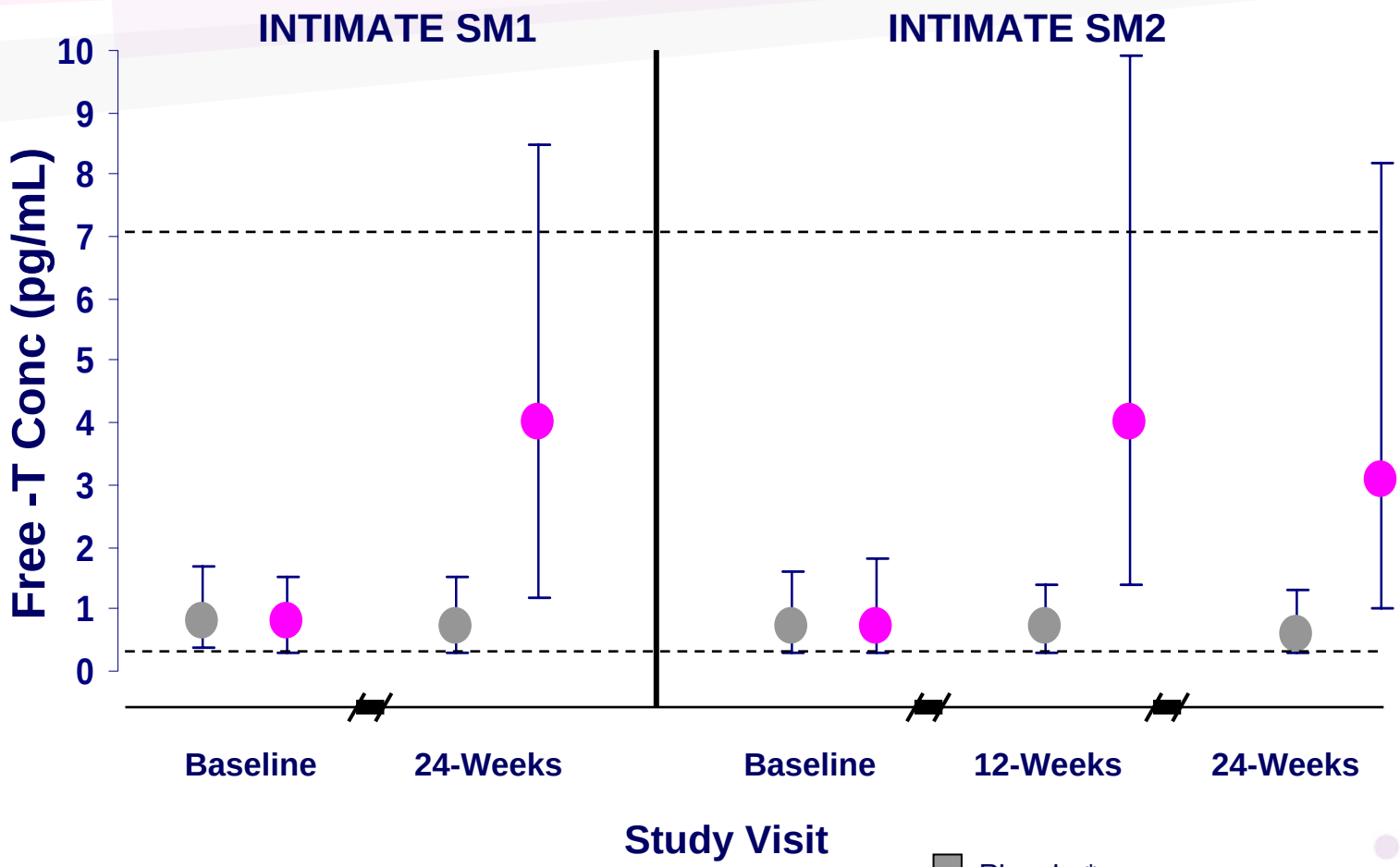
Safety focus: Androgenic AEs

Androgenic AE (%)	Combined INTIMATE SM1 & SM 2	
	Placebo (N = 545)	TTP (N = 549)
Acne	5.1	6.7
Alopecia	2.9	4.2
Unwanted Hair Growth	5.9	7.3
Voice Deepening	2.2	2.7
Withdrawal due to Androgenic AE	0.6	1.6

Simon JA, et al. *Journal of Clinical Endocrinology & Metabolism* 2005;90(9):5226-33
Buster J. et al., *Obstetrics & Gynecology* 2005;105;944-52
P&GP Data on file - ES02-2005

"What makes you think the hormone replacement therapy is having side effects, Mrs Brown?"

Free Testosterone levels following 24 weeks of treatment



Whiskers describe the 10th and 90th percentiles; dots represent the median values
Dashed lines denote reference ranges in premenopausal women (0.9 – 7.3 pg/mL)

Simon JA, et al. ***Journal of Clin Endo & Metab*** **2005;90(9):5226-33**
Buster J. et al., ***Obstetrics & Gynecology*** **2005;105;944-52**

Conclusions from the testosterone patch phase III studies

In surgically menopausal women with Hypoactive Sexual Desire Disorder (HSDD) on concomitant oestrogen:

- The 300 mcg/day testosterone patch significantly improved desire and personal distress at 24 weeks
- The testosterone patch significantly increased satisfying sexual activity at 24 weeks
- The testosterone patch was generally well tolerated

Simon JA, et al. *Journal of Clinical Endocrinology & Metabolism* 2005;90(9):5226-33
Buster J. et al., *Obstetrics & Gynecology* 2005;105;944-52

Clinical Lab and Vital Signs Summary
(SM1&2 Months 6-36 Open Label)

- **No Significant effect on:**
  - Blood Pressure
  - Triglycerides
  - Total Cholesterol
  - Alkaline Phosphatase, Alanine Aminotransferase, Aspartate Aminotransferase or Total Bilirubin
- **Over 3 years, patients experienced a small weight gain of 1.7 kg ($p<0.05$)**

Nachtigall et al., NAMS, 2006

TTP Open Label Extension
Overall Conclusions Over 36 Months*

- Over 36 months in surgically menopausal women with hypoactive sexual desire disorder (HSDD)†, the 300 mcg/day testosterone transdermal patch:
  - Was well tolerated and
  - No clinically relevant safety concerns were detected

† receiving concomitant oestrogen

*** The absence of a parallel placebo treated control group limits our ability to draw definitive conclusions from these data**

Nachtigall et al., NAMS, 2006

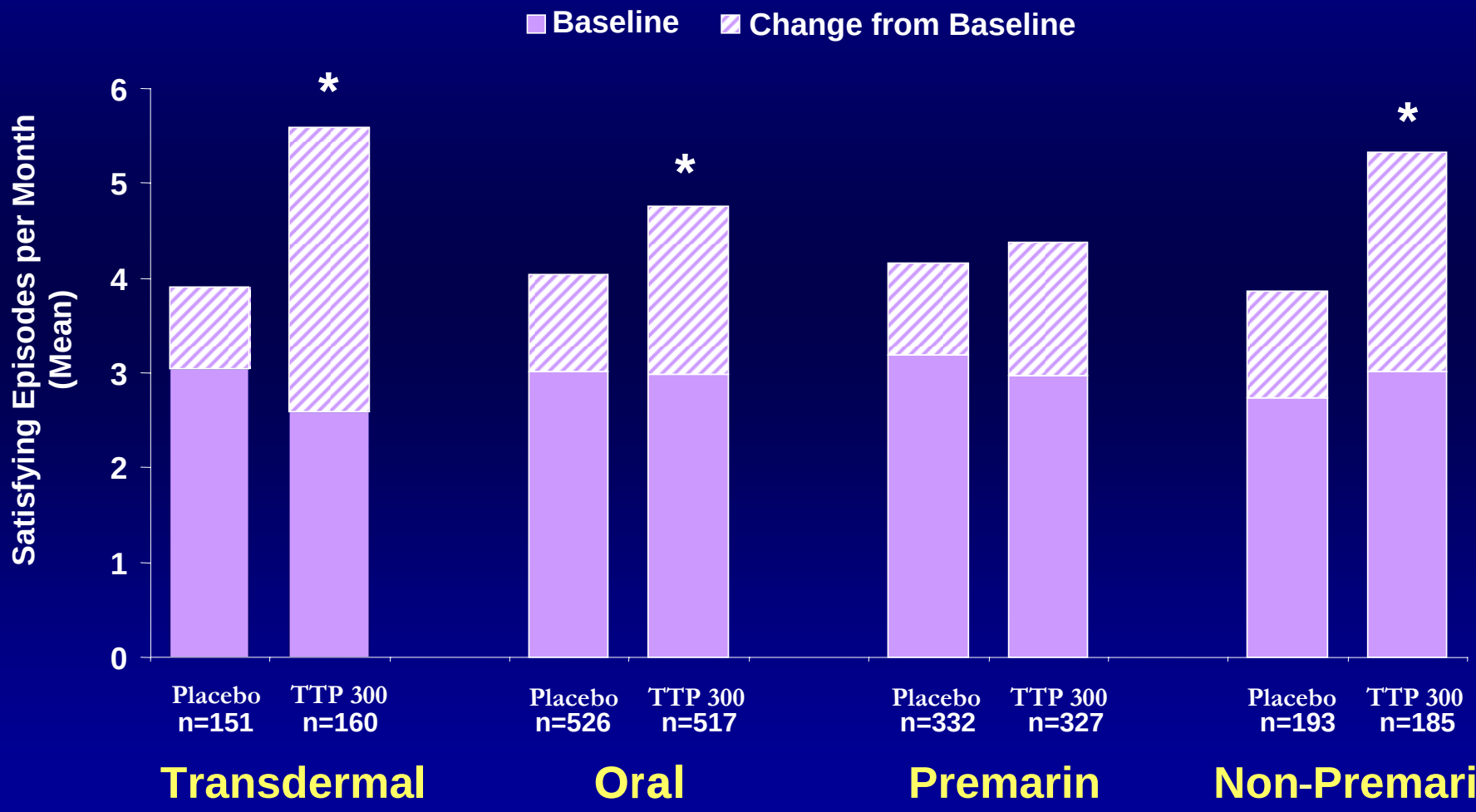
Considerations before use

In surgically menopausal women with Hypoactive Sexual Desire Disorder (HSDD) on concomitant oestrogen:

- Intrinsa is not recommended in women over 60
- The safety of Intrinsa has been demonstrated in randomised studies up to 1 year and open label up to 3 years
- ‘Continued use of Intrinsa is only recommended while concomitant use of oestrogen is appropriate‘
- Intrinsa treatment response should be evaluated within 3-6 months of initiation, to determine if continued therapy is appropriate
- Intrinsa should not be used in women on conjugated equine oestrogen (CEE), as the trial subgroup of patients receiving CEE did not demonstrate a sig. improvement in sexual function

Oestrogen Effect on Total Satisfying Sexual Activity at Week 24†

(SM1&2 Weeks 0-24 Double-blind)



†Combined SM Phase IIb, III Studies

*p<0.05

Testosterone Patch for the treatment of Hypoactive Sexual Desire Disorder (HSDD) in naturally menopausal women: results from the INTIMATE NM1 study

Menopause: The Journal of The North American Menopause Society
Vol. 13, No. 5, pp. 00-00
DOI: 10.1097/01.gme.0000243567.32828.99

Text printed on acid-free paper.

Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 Study

Jan L. Shifren, MD,[1] Susan R. Davis, MD,[2] Michele Moreau, MD,[3] Arthur Waldbaum, MD,[4] Celine Bouchard, MD,[5] Leonard DeRogatis, PhD,[6] Christine Derzko, MD,[7] Patricia Bearnson, MD,[8] Norman Kakos, MD,[9] Sheila O'Neill, MD,[10] Stephen Levine, MD,[11] Kathryn Wekselman, PhD,[12] Akshay Buch, PhD,[12] Cynthia Rodenberg, PhD,[12] and Robin Kroll, MD[13]

ABSTRACT

Objective: To evaluate the efficacy and safety of a testosterone patch for the treatment of women with hypoactive sexual desire disorder after natural menopause.

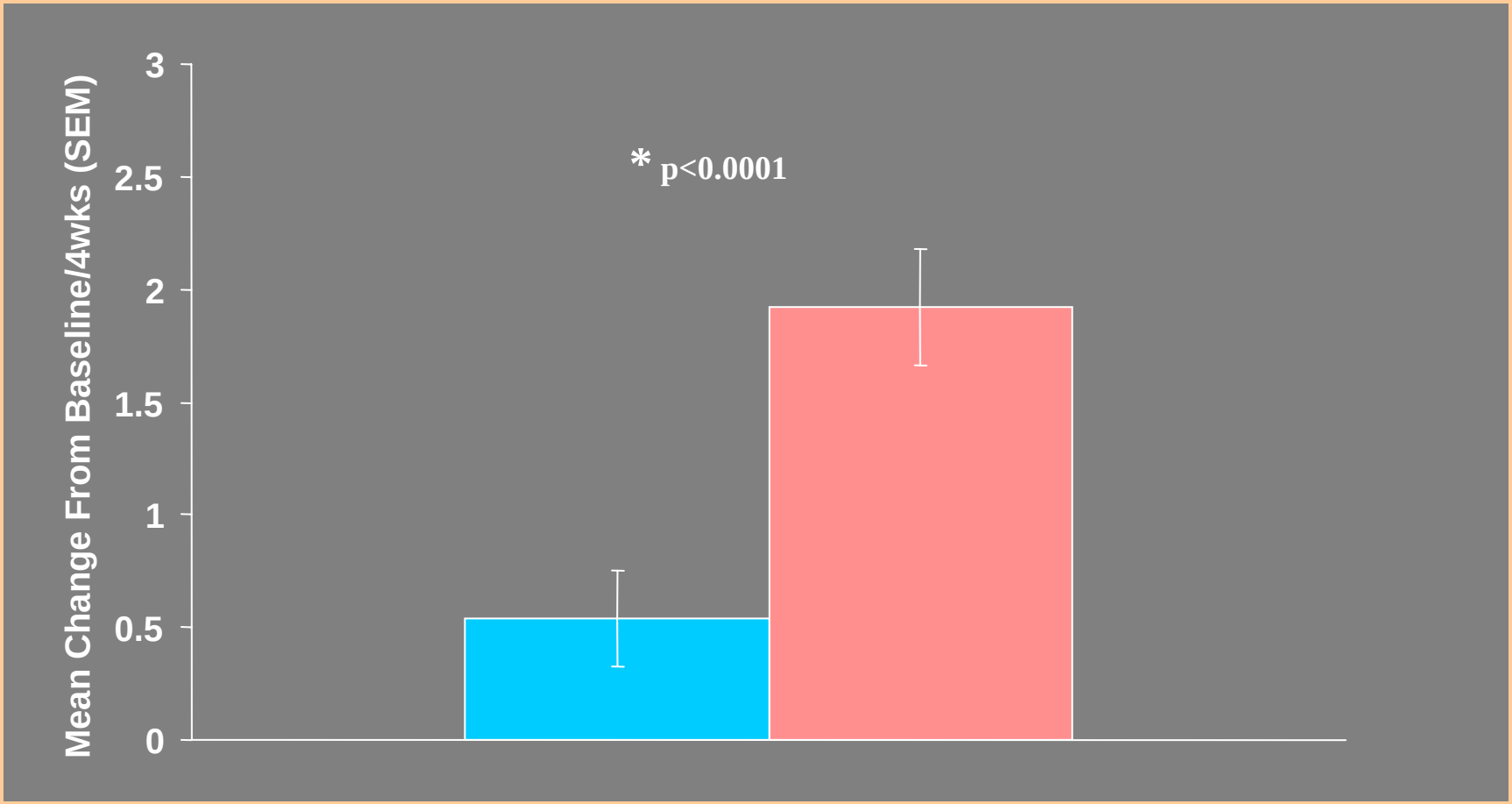
Design: A multicenter, randomized, double-blind, placebo-controlled, parallel-group trial was conducted in naturally menopausal women with hypoactive sexual desire disorder receiving a stable dose of oral estrogen with or without progestin (N = 549). Women were randomized to receive testosterone 300 μg/day or placebo patches twice weekly for 24 weeks. The primary efficacy measure was change from baseline in frequency of total satisfying sexual activity over a 4-week period (weeks 21-24).

Results: A total of 483 women (88%) were included in the primary analysis population (those with baseline sex hormone binding globulin levels ≤160 nmol/L). The change from baseline in number of total satisfying sexual episodes was significantly greater for testosterone compared with placebo (participants with baseline sex hormone binding globulin levels ≤160 nmol/L, mean change of 2.1 ± 0.28 versus 0.5 ± 0.23 episodes/4 weeks; $P < 0.0001$; intent-to-treat population, mean change from baseline of 1.9 ± 0.26 versus 0.5 ± 0.21 episodes/4 weeks, $P < 0.0001$). Testosterone also produced statistically significant improvements compared with placebo in all secondary efficacy measures, including sexual desire and personal distress. The testosterone patch was well tolerated.

Conclusions: Testosterone patch treatment increased the frequency of satisfying sexual activity and sexual desire, decreased personal distress, and was well tolerated in naturally menopausal women with hypoactive sexual desire disorder.

Key Words: Transdermal testosterone – Hypoactive sexual desire – Natural menopause – Postmenopausal women – Libido.

Increased Total Satisfying Sexual Activity at 24 Weeks



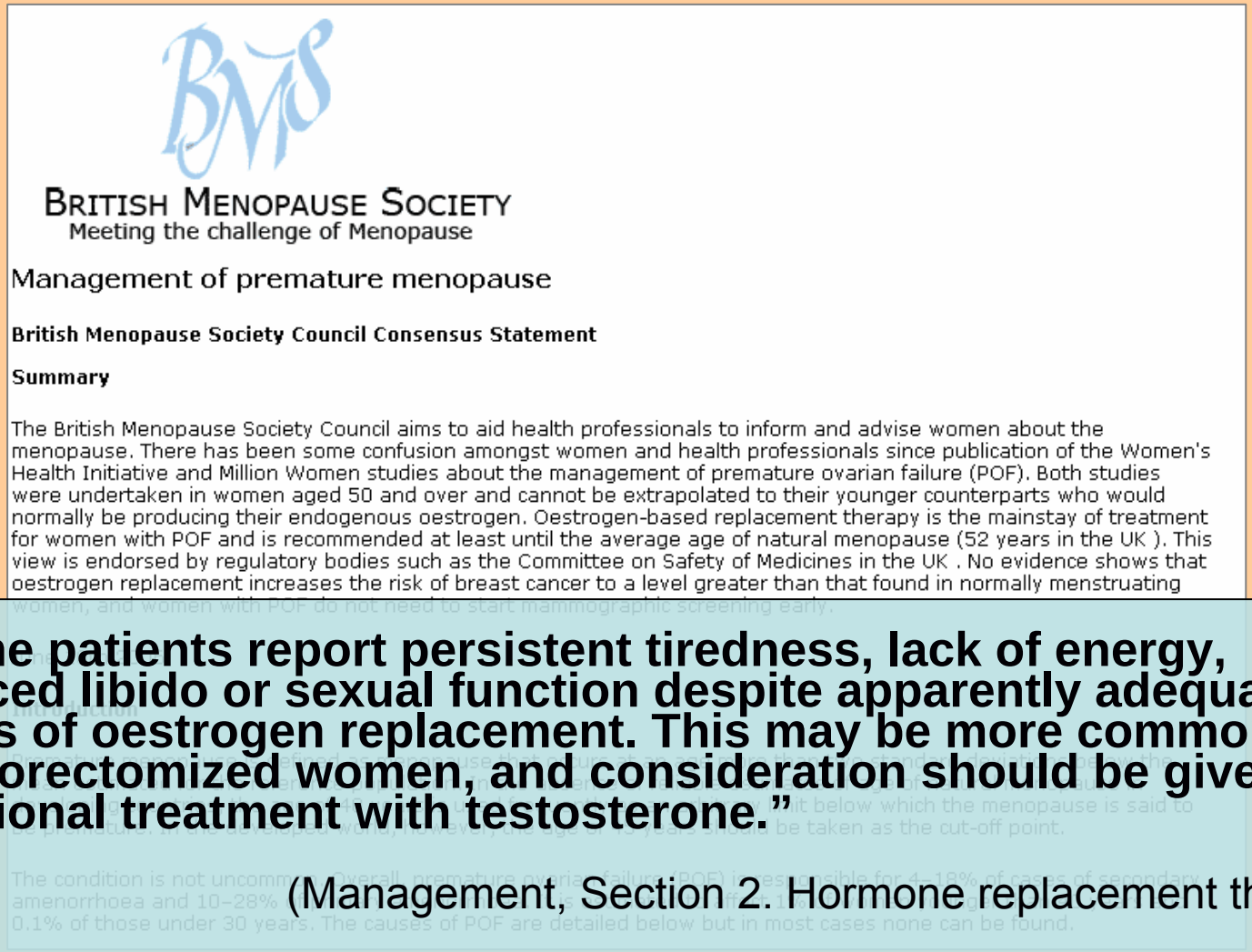
% Increase From Baseline **19%** **73%**

*** Testosterone compared to placebo**

Conclusions

- Evidence for benefits of testosterone in oestrogen replete women in both SM and NM women
- Initially only testosterone pellets available …
- Now, transdermal testosterone licensed in surgically menopaused women with HSDD using concomittant oestrogen.
- Published data exist for the effect of transdermal testosterone in naturally menopausal women
- Off label use of product should be confined to specialists at present

British Menopause Society Council Consensus Statement



BRITISH MENOPAUSE SOCIETY
Meeting the challenge of Menopause

Management of premature menopause

British Menopause Society Council Consensus Statement

Summary

The British Menopause Society Council aims to aid health professionals to inform and advise women about the menopause. There has been some confusion amongst women and health professionals since publication of the Women's Health Initiative and Million Women studies about the management of premature ovarian failure (POF). Both studies were undertaken in women aged 50 and over and cannot be extrapolated to their younger counterparts who would normally be producing their endogenous oestrogen. Oestrogen-based replacement therapy is the mainstay of treatment for women with POF and is recommended at least until the average age of natural menopause (52 years in the UK). This view is endorsed by regulatory bodies such as the Committee on Safety of Medicines in the UK . No evidence shows that oestrogen replacement increases the risk of breast cancer to a level greater than that found in normally menstruating

"Some patients report persistent tiredness, lack of energy, reduced libido or sexual function despite apparently adequate doses of oestrogen replacement. This may be more common in oophorectomized women, and consideration should be given to additional treatment with testosterone."

(Management, Section 2. Hormone replacement therapy)