Maturitas 133 (2020) 1–6

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Evaluation of Femaxeen® for control of urinary incontinence in women: A randomized, double-blind, placebo-controlled study

Santiago Palacios[a,*], Marieta Ramirez[a], Mariella Lilue[a], Barbara Vega[b]

[a] Palacios Institute of Women's Health, Madrid, Spain
[b] Medical Department, Sérélys Pharma, Fontvieille, Monaco

ARTICLE INFO

Keywords:
Urinary incontinence
Femaxeen
Cytoplasmic extracts of pollen
Pumpkin seed extract
Vitamin E

ABSTRACT

Background and aims: Urinary incontinence (UI) is common in women, with up to 50 % experiencing involuntary loss of urine at some point. Femaxeen®, a formulation containing purified and specific cytoplasmic extracts of pollen, pumpkin seed extract and vitamin E (referred to hereafter as Femaxeen), is indicated for control of UI in women. This study investigated the efficacy and safety of Femaxeen for the prevention and treatment of UI symptoms in women.

Methods: In this randomized, double-blind, placebo-controlled trial, 81 women with moderate, severe, or very severe urge (43.4 %), stress (31.6 %) or mixed (25.0 %) UI were allocated to receive Femaxeen or placebo once daily for 90 days. Treatment efficacy was assessed using three validated questionnaires.

Findings: Thirty-eight patients per group were analyzed. Femaxeen produced statistically significant improvements from baseline to Day 90 ($p < 0.001$ for all comparisons) in scores on the International Consultation on Incontinence Questionnaire–Short Form (ICIQ-SF), Measurement of Urinary Handicap (MHU) questionnaire, and Sandvik Incontinence Severity Index. Reduction from baseline in ICIQ-SF and MHU scores at Day 60 and Day 90 was significantly greater with Femaxeen than placebo ($p < 0.05$ for all comparisons). Femaxeen significantly reduced ICIQ-SF and MHU scores from baseline to Day 60 and Day 90 in all UI types ($p < 0.05$ for all comparisons except ICIQ-SF scores for stress UI). Femaxeen and placebo were well tolerated. Associated adverse events were few and mild in intensity.

Conclusions: Femaxeen is effective for treating UI, and has a safety profile comparable to that of placebo.

1. Introduction

Urinary incontinence (UI) is defined as an involuntary or uncontrollable loss of urine. Causes of UI include detrusor instability, failure of the sphincter mechanism, or dysfunction of a complex neural system involving neurotransmitters which co-ordinates bladder function to control urine voiding and storage [1]. UI is classified according to its presentation and underlying cause. Urge UI describes a sudden and strong need to urinate caused by an unstable or overactive bladder or detrusor instability. Stress UI describes an involuntary loss of urine during physical movement or activity (e.g. coughing, sneezing, laughing, standing up or running, heavy lifting) caused by insufficient urethral closure due to urethral hypermobility, intrinsic urethral sphincter weakness, or urethral atrophy secondary to postmenopausal hypoestrogenism. The term mixed UI describes involuntary leakage associated with a combination of urge and stress UI [2,3].

The most common risk factors for UI in women are age, ethnicity, obesity, pregnancy, childbirth, menopause, hysterectomy and functional or cognitive impairment [4–7]. For many women with UI, symptoms are highly distressing, often leading to avoidance of physical and social activity and impacting negatively on their health-related quality of life [8]. Moreover, the embarrassment and social stigma associated with UI frequently delay or even prevent women from seeking treatment [9].

Treatment options for UI include behavior and lifestyle modification, pelvic floor muscle exercise, medications (particularly for urge UI), and surgical procedures (particularly for stress UI) [10–12]. Anticholinergic agents are commonly used for second-line treatment of urge UI but are associated with adverse effects which vary depending on the muscarinic receptor specificity of the drug [11,12]. As some women with UI may have contraindications for medical or surgical treatment (e.g. receiving anticoagulants, desire for future pregnancy), or may prefer to use less intensive options including natural products, effective alternatives are required.

* Corresponding author at: Instituto Palacios de Salud y Medicina de la Mujer, Calle de Antonio Acuña 9, 28009, Madrid, Spain.
E-mail address: spalacios@institutopalacios.com (S. Palacios).

https://doi.org/10.1016/j.maturitas.2019.12.008
Received 12 July 2019; Received in revised form 25 November 2019; Accepted 10 December 2019

Phytotherapy based on plant extracts is an alternative approach to treat UI. In men, pollen extract preparations have been shown to be effective in alleviating lower urinary tract symptoms associated with benign prostatic hyperplasia [13–15]. To date, the effectiveness of pollen extract preparations has not been demonstrated in women. Femaxeen®, a formulation containing purified and specific cytoplasmic extracts of pollen (PSCEP; 160 mg), pumpkin seed extract (300 mg) and vitamin E (10 mg), and referred to hereafter as Femaxeen, is indicated for control of UI in women.

The purpose of the current study was to investigate the efficacy and safety of Femaxeen for prevention and treatment of UI symptoms in women.

2. Methods

This was a randomized, double-blind, placebo-controlled trial of Femaxeen in women with UI conducted at a single center in Madrid, Spain. Participants were enrolled during an inclusion period from October 2017 to January 2018.

2.1. Inclusion/exclusion criteria

Eligible patients were women aged 18–75 years, with moderate, severe, or very severe UI according to the Sandvik severity index [16]. All subjects provided written informed consent to participate.

Women were required to be postmenopausal, or surgically oophorectomized, or using a medically accepted contraceptive (oral contraceptives, implants, barrier method with spermicide, abstinence) at least 3 months before inclusion; have normal cervical smear cytology (Papanicolau test) during the last year and normal urological culture at the time of inclusion; have an external vaginal area (vestibule and introitus) free of wounds or bleeding; have a normal vaginal canal with no evidence of dysplasia and/or occult or active infection.

Major exclusion criteria were: pregnancy or breastfeeding; previous preventative surgery for UI; use of systemic or local hormone replacement therapy within 6 months of inclusion; use of vaginal lubricants or local vaginal preparations within 30 days of inclusion; history of herpes or candida infection in the last 3 months, or acute or recurrent genital (herpes or candida) or urinary tract infections; significant alterations or inflammatory lesions such as lacerations, abrasions or ulcers in the areas under treatment; history of neoplasia in the last 5 years; dysplastic nevus in the treatment area; history of keloids or abnormal scarring; prolapse degree II classified by the International Continence Society Pelvic Organ Prolapse Quantification System; an implanted pacemaker or internal defibrillator; concomitant disease e.g. cardiac disorder, uncontrolled type I or II diabetes, lupus porphyria, or relevant neurological disorders; anticoagulant or thromboembolic disorder or use of anticoagulant medications within one week of treatment or during treatment; history of immunosuppression or immunodeficiency (including HIV/AIDS) or use of immunosuppressive medications; uncontrolled hormonal imbalance, related to the thyroid, hypophysis or androgen; history of a lymphatic drainage problem or history of cancer requiring lymph node biopsy or dissection; history of epidermal or dermal alterations (particularly involving collagen or the microvasculature); participation in a clinical study of a device or drug within 6 months of study inclusion.

2.2. Treatment

Using a computer-generated list, patients were randomized in a 1:1 ratio to receive Femaxeen or placebo, administered orally once daily in the evening for 90 days. To maintain double-blinding, medication was provided as identical tablets in closed containers. Adherence was ensured by pill counts at clinic visits.

2.3. Outcomes

Treatment efficacy was assessed using three validated questionnaires. The primary outcome was treatment efficacy at Day 60 and Day 90 using the Spanish version of the International Consultation on Incontinence Questionnaire–Short Form (ICIQ-SF), which is a patient-reported subjective measure of urine loss severity and its impact on quality of life (maximum score 21, with higher scores indicating greater severity) [17]. Additional efficacy measures were the Mesure du Handicap Urinaire (MHU; Measurement of Urinary Handicap) questionnaire, which provides a quantitative measure of urinary symptoms (maximum score 28, with higher scores indicating greater severity) [18]; and the Sandvik incontinence severity index, which is a simple measure of urinary incontinence in women (maximum score 12, with higher scores indicating greater severity) [16]. Efficacy was assessed by the percentage change in scores for symptoms or urinary handicap from baseline to Day 60 and Day 90, and by the differences between Femaxeen and placebo in the percentage change in scores for symptoms or urinary handicap from baseline to Day 60 and Day 90.

Secondary outcomes were safety and tolerability.

2.4. Assessments

Participating patients underwent three visits within the study framework. The baseline assessment (Day 0) involved a medical examination, urological culture, completion of questionnaires, and enquiry about concomitant medication. Patients were issued with diaries to record relevant information. At each of Visits 2 (Day 60) and 3 (Day 90), patients again completed the questionnaires, diaries were reviewed (and collected on Day 90), and patients were asked about adverse events (AEs) and concomitant medication. AEs were described according to their duration (start and end dates), degree of severity (mild, moderate, severe), relation to study medication (suspected, not suspected), and any action(s) taken to resolve the event.

2.5. Statistical analysis

Statistical analyses were performed using SAS software version 9.3 (SAS Institute Inc. Cary, North Carolina, USA). Quantitative variables are described by mean and standard deviation (SD), and qualitative variables by frequency and percentage. Analysis of variance was used to compare the percentage change in scores for symptoms or urinary handicap from baseline to Day 60 and Day 90 in each treatment group, using a 5 % level to indicate statistical significance.

Based on previous research using pollen extract [19], it was calculated that 25 participants per group were required to detect a mean change of 3.0 points in the ICIQ-SF score from baseline to the end of the study, with a two-tailed alpha of 0.05 and a power of 80 %. To account for potential drop-outs and variations in presenting symptoms, 40 patients per group were recruited.

3. Results

3.1. Study participants

The study took place at the Palacios Institute of Women's Health in Madrid, Spain, between December 2017 and November 2018. A total of 81 patients were allocated to treatment with Femaxeen (n = 41) or placebo (n = 40). Patient disposition is shown in Fig. 1. Three patients allocated to Femaxeen were not included in the final analysis due to loss to follow-up (n = 2) or treatment discontinuation (because of nervousness and anxiety; n = 1). Two patients allocated to placebo were not analyzed because treatment was not initiated (patient did not return to collect treatment; n = 1) or treatment was discontinued (due to headache; n = 1). Thirty-eight patients per group were included in the efficacy and safety analyses.

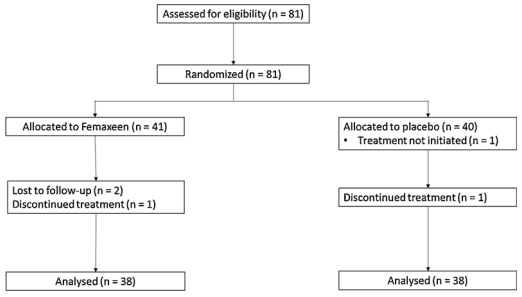

Fig. 1. Patient disposition.

Table 1
Baseline characteristics of patients with urinary incontinence (UI) treated with Femaxeen or placebo.

	Femaxeen (n = 38)	Placebo (n = 38)
Age, years: mean (SD)	61.1 (3.4)	60.3 (3.8)
Mean BMI, kg/m^2	26.4	27.1
Menopause, n (%)	33 (86.8)	32 (84.2)
UI type, n (%)		
Stress	12 (31.6)	12 (31.6)
Urge	17 (44.7)	16 (42.1)
Mixed	9 (23.7)	10 (26.3)
ICIQ-SF (maximum score 21)	9.76 (4.56)	9.71 (3.14)
MHU (maximum score 28)	9.76 (4.04)	8.13 (3.48)
Sandvik severity index (maximum score 12)	6.08 (2.32)	5.91 (2.14)

BMI: body mass index; Femaxeen: purified and specific cytoplasmic extracts of pollen (160 mg), pumpkin seed extract (300 mg) and vitamin E (10 mg); ICIQ-SF: International Consultation on Incontinence Questionnaire–Short Form; MHU: Mesure du Handicap Urinaire (Measurement of Urinary Handicap); UI: urinary incontinence.

Baseline demographic and clinical characteristics are summarized in Table 1. Mean age (SD) in each group was 61.1 (3.4) and 60.3 (3.8) years, respectively. Mean body mass index was 26.4 and 27.1 kg/m^2, respectively. The majority of patients were menopausal (85.5 % of the overall population) and the most common UI type was urge (43.4 % of the overall population). Treatment groups were well matched with respect to baseline clinical characteristics including ICIQ-SF scores, MHU scores, and Sandvik severity index values.

3.2. Efficacy

Femaxeen produced a statistically significantly reduction from baseline in ICIQ-SF scores at Day 90 ($p < 0.001$) and, compared with placebo, significantly reduced ICIQ-SF scores at Day 60 and Day 90 ($p < 0.05$ for both comparisons) (Fig. 2). Femaxeen and placebo reduced baseline ICIQ-SF scores by 59.8 % and 26.6 %, respectively, on Day 60, and by 64.1 % and 32.7 %, respectively, on Day 90.

Femaxeen produced a statistically significant reduction from baseline in MHU scores at Day 90 ($p < 0.001$) and, compared with placebo, significantly reduced MHU scores at Day 60 and Day 90 ($p < 0.05$ for both comparisons) (Fig. 3). Femaxeen and placebo reduced baseline MHU scores by 68.1 % and 34.3 %%, respectively, on Day 60, and by 74.9 % and 52.8 %, respectively, on Day 90.

Femaxeen produced a statistically significant improvement from baseline in incontinence severity at Days 60 and 90 ($p < 0.001$ at both time points; Fig. 4). At baseline, patients in the Femaxeen group were classified as having moderate (60.5 %), severe (36.8 %) or very severe (2.6 %) UI. At 60 days, there was a decrease in the proportion of patients with moderate (33.3 %) or severe (4.2 %) UI and a corresponding increase in the proportion of patients with mild UI (54.2 %) or no symptoms (4.2 %). On Day 90, there was a further decrease in the proportion of patients with moderate UI (25.0 %), and an accompanying increase in the proportion of patients with no symptoms (20.8 %).

For each UI type (urge, stress, mixed), Femaxeen produced statistically significant reductions from baseline in ICIQ-SF scores (Fig. 5A) and MHU scores (Fig. 5B) at Day 60 and Day 90 ($p < 0.05$ for all comparisons except ICIQ-SF scores for stress UI). The absolute changes in ICIQ-SF scores and MHU scores from baseline to Day 60 and Day 90 during treatment with Femaxeen are shown in Table 2.

3.3. Safety

Three AEs were recorded during the study. In the Femaxeen group, one patient experienced elevated transaminases (50 % higher than baseline but within the normal range), and another patient experienced increased cholesterol levels. One episode of headache was reported in the placebo group which led to treatment discontinuation. AEs were all mild in intensity, and a causal relationship with study medication could not be ruled out.

4. Discussion

The efficacy and safety of Femaxeen, a product containing ingredients of natural origin for control of UI symptoms, were demonstrated in this randomized, double-blind placebo-controlled trial. Patients with urge, stress or mixed UI received oral Femaxeen or placebo once daily for 90 days. Compared with baseline, Femaxeen significantly improved patients' perception of UI severity and its impact on quality of life (ICIQ-SF), alleviated UI symptoms (MHU), and reduced

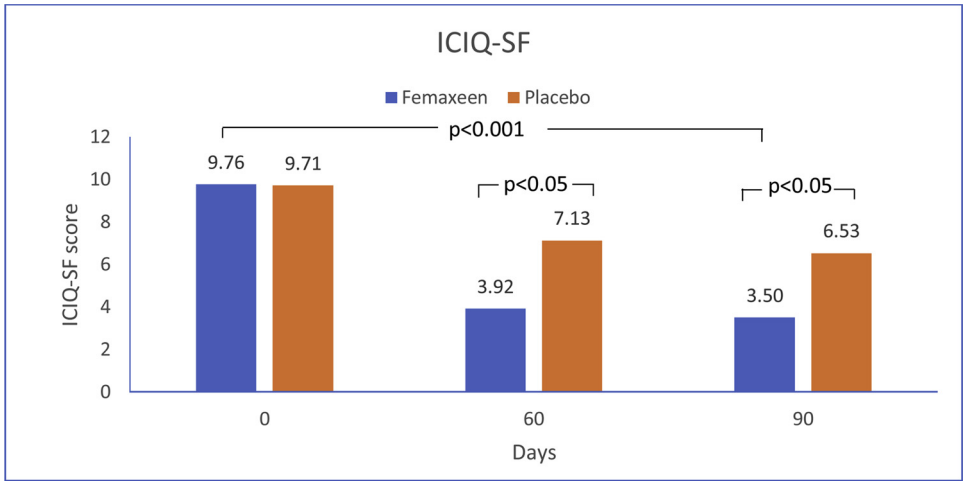

Fig. 2. Evolution of ICIQ-SF scores according to treatment with Femaxeen or placebo. P-values are shown for the change from baseline in ICIQ-SF scores with Femaxeen, and for the differences between Femaxeen and placebo in the change from baseline in ICIQ-SF scores, at Days 60 and 90. Femaxeen: purified and specific cytoplasmic extracts of pollen (160 mg), pumpkin seed extract (300 mg) and vitamin E (10 mg); ICIQ-SF: International Consultation on Incontinence Questionnaire–Short Form.

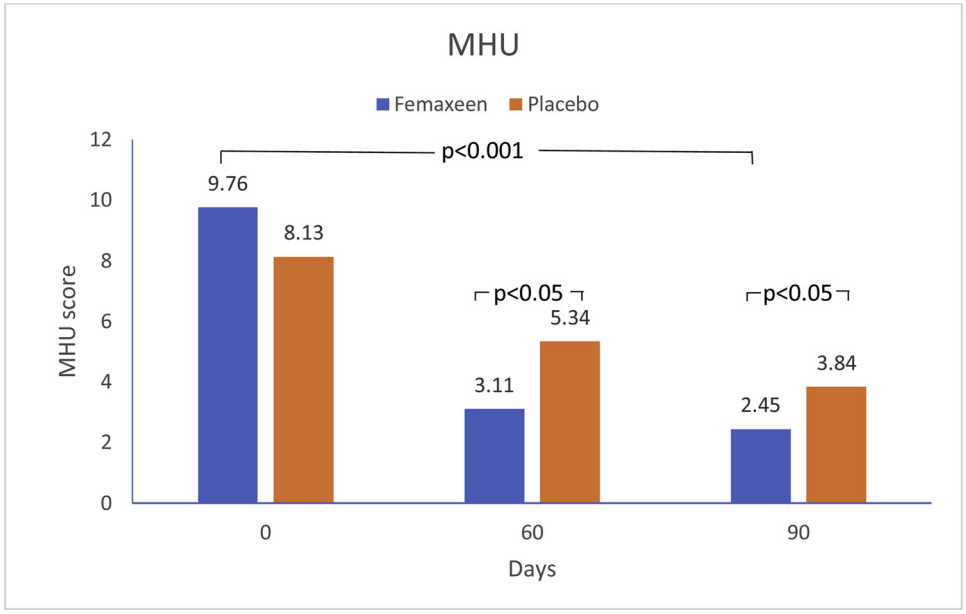

Fig. 3. Evolution of MHU scores according to treatment with Femaxeen or placebo. P-values are shown for the change from baseline in MHU scores with Femaxeen, and for the differences between Femaxeen and placebo in the change from baseline in MHU scores, at Days 60 and 90. Femaxeen: purified and specific cytoplasmic extracts of pollen (160 mg), pumpkin seed extract (300 mg) and vitamin E (10 mg); MHU: Mesure du Handicap Urinaire (Measurement of Urinary Handicap).

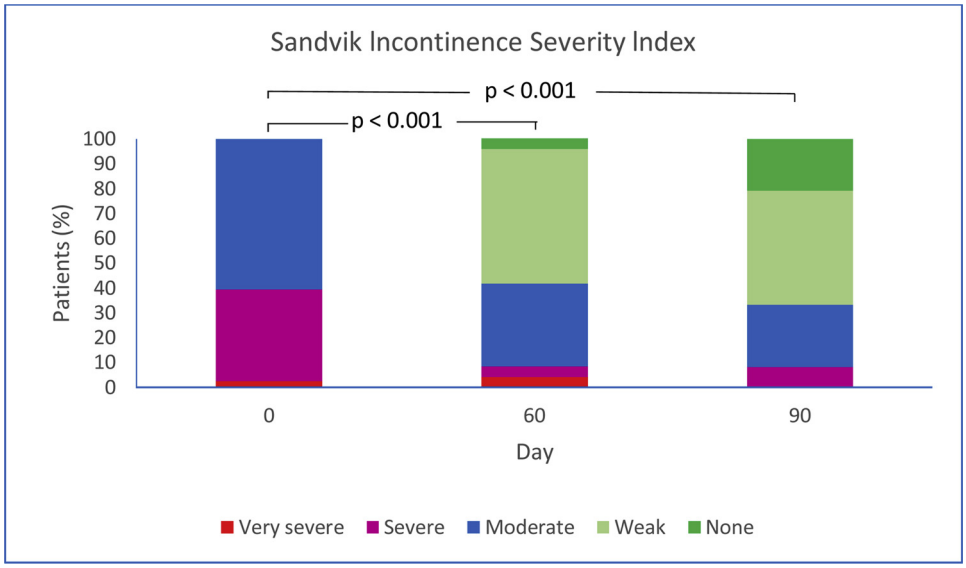

Fig. 4. Evolution in incontinence severity (proportion of patients in each category on the Sandvik incontinence severity index) at baseline (Day 0) and on Day 60 and Day 90 in patients treated with Femaxeen. Femaxeen: purified and specific cytoplasmic extracts of pollen (160 mg), pumpkin seed extract (300 mg) and vitamin E (10 mg).

UI severity (Sanvik severity index) at Days 60 and 90 ($p < 0.001$ for all comparisons). The reduction from baseline in ICIQ-SF and MHU scores at Days 60 and 90 was approximately 2-fold greater with Femaxeen than placebo ($p < 0.05$ for all comparisons). Femaxeen improved ICIQ-SF and MHU scores from baseline to Days 60 and 90 across all UI types ($p < 0.05$ for all comparisons except ICIQ-SF scores for stress IU). ICIQ-SF and MHU scores from baseline to Day 60 and Day 90 were also reduced with placebo, although the differences were not statistically significant. Femaxeen and placebo were both well tolerated; any associated AEs were few and mild in severity.

An understanding of the mode of action of the constituents of Femaxeen is beginning to emerge. A genomic study showed that PSCEP modulates acetylcholinesterase mRNA expression in a human cholinergic neuron cell line [20]. This activity may induce a neuron resting state controlling acetylcholine release, thereby diminishing bladder muscle contraction and controlling involuntary urine loss caused by an overactive bladder [21,22]. Elsewhere, similar purified specific cytoplasm pollen extracts were shown to inhibit re-uptake of [^{3}H]-serotonin into rat cortical synaptosomes in a dose-dependent manner [20]. This activity may increase urethral contraction with sustained sphincter tone during the storage phase, an action similar to that of the serotonin and noradrenaline reuptake inhibitor, duloxetine, the first drug approved for medical treatment of stress UI [23,24]. A second component of Femaxeen, pumpkin seed extract, inhibits 5-alpha-reductase, the enzyme responsible for metabolizing testosterone to dihydrotesterone [25,26]. In women, higher testosterone levels may increase both the size and strength of pelvic muscles including the skeletal, external sphincter muscle [27]. Inhibiting 5-alpha-reductase may contribute towards strengthening the pelvic floor and reducing stress UI. However, as evidence is preliminary, further studies are needed to clarify the mechanism of action of Femaxeen in controlling the symptoms of UI.

This study is the first to demonstrate the efficacy and safety of a pollen extract preparation in women with UI, as previously shown in men with lower urinary tract symptoms associated with benign prostatic hyperplasia [13–15]. Supporting our findings are studies which showed that pumpkin seed oil preparations significantly reduced symptom scores at 6 and 12 weeks in men and women with overactive bladder [28] and significantly reduced the frequency of UI episodes, and daytime and nocturnal urinary frequency, at 6 and 12 weeks in women with stress UI [29]. A subgroup analysis of the stress UI group

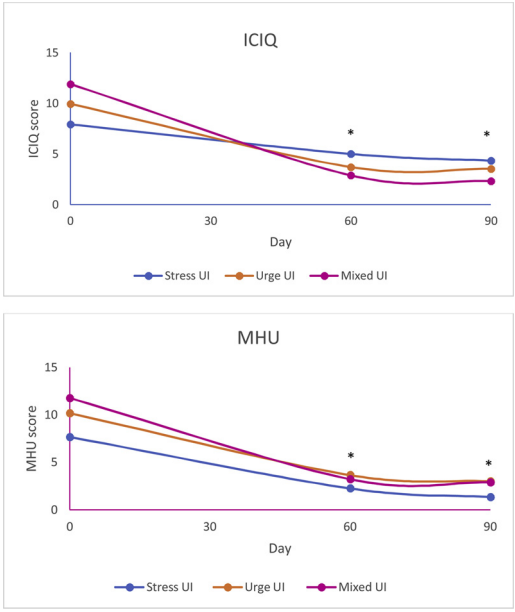

Fig. 5. A. Effect of Femaxeen on ICIQ-SF scores by type of urinary incontinence. * $p < 0.05$ for change from baseline in scores for urge and mixed (not stress) UI. Femaxeen: purified and specific cytoplasmic extracts of pollen (160 mg), pumpkin seed extract (300 mg) and vitamin E (10 mg); ICIQ-SF: International Consultation on Incontinence Questionnaire–Short Form (maximum score 21). B. Effect of Femaxeen on MHU scores by type of urinary incontinence. * $p < 0.05$ for change from baseline in scores for stress, urge, and mixed UI. Femaxeen: purified and specific cytoplasmic extracts of pollen (160 mg), pumpkin seed extract (300 mg) and vitamin E (10 mg); MHU: Mesure du Handicap Urinaire (Measurement of Urinary Handicap; maximum score 28).

Table 2
Change from baseline to Day 60 and Day 90 in ICIQ-SF and MHU scores during treatment with Femaxeen according to UI type.

UI type	Day 60	Day 90
ICIQ-SF		
Stress	−2.92	−3.58
Urge	−6.24*	−6.41*
Mixed	−9.00*	−9.56*
MHU		
Stress	−5.42*	−6.33*
Urge	−6.53*	−7.18*
Mixed	−8.56*	−8.89*

ICIQ-SF: International Consultation on Incontinence Questionnaire–Short Form; MHU: Mesure du Handicap Urinaire (Measurement of Urinary Handicap); UI: urinary incontinence.
* $p < 0.05$ for change from baseline.

(n = 24) from the current study presented at the European Congress of Menopause and Andropause in 2019 indicated significant improvement in ICIQ-SF scores (p = 0.048) and MHU scores (p = 0.021) with Femaxeen relative to placebo after 90 days' treatment [30]. Combining pollen and pumpkin seed extracts in a single preparation such as Femaxeen appears to be a rational approach to the management of UI.

A large systematic review to assess cure rates in UI found that, apart from surgical interventions for stress UI and mixed UI (median cure rates for women of 84.4 % and 82.3 %, respectively), other interventions were associated with lower cure rates [31]. Urge UI was managed mainly with medications and, median cure rates varied by agent and duration of follow-up (49 % for antimuscarinics) [31]. However, before progressing to pharmacological therapy and ultimately surgery to manage UI, European Association of Urology (EAU) guidelines recommend a conservative approach that incorporates lifestyle interventions, and physical and behavioural therapies [1]. Within the framework of conservative management, and as the results of the current study suggest, a product of natural origin such as Femaxeen that reduces the perception of symptom severity and is well tolerated may have a role in early intervention for women with UI, although this remains to be demonstrated in larger studies of longer duration.

The main limitations of the study are the modest sample size, single-center design, and relatively short follow-up which limits the generalizability of the results across the broader population with UI. In particular, because subgroup analyses by UI type involved small patient numbers, further larger studies are required to draw firm conclusions about the efficacy of Femaxeen by UI type. Conversely, the single-center design is also a strength as it reduces investigator variability. The findings were also strengthened by employing multiple efficacy measures, which captured objective and subjective information across a range of associated UI symptoms and their impact on patients' health-related quality of life.

5. Conclusions

Analysis of the evolution in UI symptom severity using validated questionnaires (ICIQ-SF, MHU, Sandvik severity index) showed that Femaxeen provided effective control of all UI types (urge, stress, mixed), although the data are preliminary and must be replicated in further studies. Femaxeen was well tolerated with a safety profile similar to that of placebo. An effective agent such as Femaxeen with better tolerability than muscarinic receptor antagonists would be valuable addition to the therapeutic armamentarium for treating UI in women.

Contributor

Santiago Palacios conceived of and led the study, contributed to data collection and analysis, and contributed to revision of the manuscript.

Marieta Ramirez contributed to data collection and analysis, and revision of the manuscript.

Mariella Lilue contributed to data collection and analysis, and revision of the manuscript.

Barbara Vega contributed to revision of the manuscript.

All authors read and approved the final version of the manuscript.

Conflict of interest

Santiago Palacios is a symposium speaker or advisory board member on menopausal hormone therapy and tibolone, raloxifene and biphosphonates for Bayer Schering, Daiichi Sankyo, Eli Lilly, Exeltis, Gedeon Richter, MSD, Novo Nordisk, Procter & Gamble, Sanofi, Sérélys Pharma, Servier, and Teva; and has received research grants and/or consulting fees from Amgen, Arkochim, Bayer Schering, Daiichi Sankyo, Eli Lilly, Exeltis, Gedeon Richter, Pfizer, Sérélys Pharma, and Servier.

Marieta Ramirez has received research grants from Gedeon Richter and Sérélys Pharma.

Mariella Lilue is a symposium speaker for Shionogi and has received grants from Sérélys Pharma.

Barbara Vega is an employee of Sérélys Pharma.

Funding

The study was funded by Sérélys Pharma, Monaco. Sérélys Pharma was not involved in the study in other respects.

Ethics

Approval was granted by the Ethics Committee of the Princess Hospital, Madrid, Spain. The study was conducted in accordance with

ICH Guidelines for Good Clinical Practice. All patients provided written informed consent prior to participating in the study.

Data sharing and collaboration

There are no linked research data sets for this paper. Data will be made available on request.

Provenance and peer review

This article has undergone peer review.

Acknowledgements

The authors wish to thank Eva Soler for her contribution to protocol elaboration and data collection and analysis; and Philippe Diaz for his contribution to analysis of genomic data.

Medical writing assistance was provided by Robert Furlong and Kerry Dechant on behalf of Content Ed Net (Madrid, Spain), with funding from Sérélys Pharma, Monaco.

References

[1] A.K. Nambiar, R. Bosch, F. Cruz, G.E. Lemack, N. Thiruchelvam, A. Tubaro, D.A. Bedretdinova, D. Ambühl, F. Farag, R. Lombardo, M.P. Schneider, F.C. Burkhard, EAU guidelines on assessment and nonsurgical management of urinary incontinence, Eur. Urol. 73 (2018) 596–609.

[2] E.F. DeMarco, Urinary tract disorders in perimenopausal and postmenopausal women, in: R.A. Lobo (Ed.), Treatment of the Postmenopausal Woman: Basic and Clinical Aspects, 2nd ed., Lippincott, Williams & Wilkins, Philadelphia, PA, 1999, pp. 213–227.

[3] V.A. Minassian, T. Bazi, W.F. Stewart, Clinical epidemiological insights into urinary incontinence, Int. Urogynecol. J. 28 (2017) 687–696.

[4] V.A. Minassian, W.F. Stewart, G.C. Wood, Urinary incontinence in women: variation in prevalence estimates and risk factors, Obstet. Gynecol. 111 (2 Pt. 1) (2008) 324–331.

[5] L. Peyrat, O. Haillot, F. Bruyere, J.M. Boutin, P. Bertrand, Y. Lanson, Prevalence and risk factors of urinary incontinence in young and middle-aged women, BJU Int. 89 (2002) 61–66.

[6] K.N. Danforth, M.K. Townsend, K. Lifford, G.C. Curhan, N.M. Resnick, F. Grodstein, Risk factors for urinary incontinence among middle-aged women, Am. J. Obstet. Gynecol. 194 (2006) 339–345.

[7] R. Botlero, S.R. Davis, D.M. Urquhart, S. Shortreed, R.J. Bell, Age-specific prevalence of, and factors associated with, different types of urinary incontinence in community-dwelling Australian women assessed with a validated questionnaire, Maturitas 62 (2009) 134–139.

[8] C. Bradway, K.S. Coyne, D. Irwin, Z. Kopp, Lower urinary tract symptoms in women-a common but neglected problem, J. Am. Acad. Nurse Pract. 20 (2008) 311–318.

[9] I. Milsom, P. Abrams, L. Cardozo, R.G. Roberts, J. Thüroff, A.J. Wein, How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study, BJU Int. 87 (2001) 760–766.

[10] F.C. Burkhard, J.L.H.R. Bosch, F. Cruz, G.E. Lemack, A.K. Nambiar, N. Thiruchelvam, A. Tubaro, EAU Guidelines on Urinary Incontinence in Adults, EAU Guidelines Office, Arnhem, The Netherlands, 2018 Available online at: https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Urinary-Incontinence-2018-large-text.pdf (Accessed June 2019).

[11] G.A. Demaagd, T.C. Davenport, Management of urinary incontinence, P&T 37 (2012) 345–361H.

[12] E.S. Lukacz, Y. Santiago-Lastra, M.E. Albo, L. Brubaker, Urinary incontinence in women: a review, JAMA 318 (2017) 1592–1604.

[13] T. Wilt, R. Mac Donald, A. Ishani, I. Rutks, G. Stark, Cernilton for benign prostatic hyperplasia, Cochrane Database Syst. Rev. (2) (2002) CD001042.

[14] H.G. Preuss, D. Bagchi, W.G. Chambliss, A critical review of Cernitin™ for symptomatic relief of lower urinary tract symptoms (LUTS) in men, Res. Comm. Pharmacol. Toxicol. 8 (2003) 2–10.

[15] J. Elist, Effects of pollen extract preparation Prostat/Poltit on lower urinary tract symptoms in patients with chronic nonbacterial prostatitis/chronic pelvic pain syndrome: a randomized, double-blind, placebo-controlled study, Urology 67 (2006) 60–63.

[16] H. Sandvik, A. Seim, A. Vanvik, S. Hunskaar, A severity index for epidemiological surveys of female urinary incontinence: comparison with 48-hour pad-weighing tests, Neurourol. Urodyn. 19 (2000) 137–145.

[17] K. Avery, J. Donovan, T.J. Peters, C. Shaw, M. Gotoh, P. Abrams, ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence, Neurourol. Urodyn. 23 (2004) 322–330.

[18] G. Amarenco, J. Kerdraon, M. Perrigot, Evaluation scale of the pelvic handicap: measurement of the urinary handicap (MHU), in: J. Pelissier, P. Costa, S. Lopez, P. Mares (Eds.), Rééducation vésico-sphinctérienne et ano-rectale, Masson, Paris, 2007, pp. 498–504.

[19] A.C. Buck, R.W. Rees, L. Ebeling, Treatment of chronic prostatitis and prostatodynia with pollen extract, Br. J. Urol. 64 (1989) 496–499.

[20] Internal report. Sérélys Pharma, Monaco.

[21] A.F. Brading, Acetylcholine and the overactive bladder, Eur. Urol. 51 (2007) 881–883.

[22] C.J. Fowler, D. Griffiths, W.C. de Groat, The neural control of micturition, Nat. Rev. Neurosci. 9 (2008) 453–466.

[23] N.R. Zinner, Duloxetine: a serotonin-noradrenaline re-uptake inhibitor for the treatment of stress urinary incontinence, Expert Opin. Invest. Drugs 12 (2003) 1559–1566.

[24] W.H. Jost, P. Marsalek, Duloxetine in the treatment of stress urinary incontinence, Ther. Clin. Risk Manag. 1 (2005) 259–264.

[25] M. Gossell-Williams, A. Davis, N. O'Connor, Inhibition of testosterone-induced hyperplasia of the prostate of Sprague-Dawley rats by pumpkin seed oil, J. Med. Food 9 (2006) 284–286.

[26] Y.S. Tsai, Y.C. Tong, J.T. Cheng, C.H. Lee, F.S. Yang, H.Y. Lee, Pumpkin seed oil and phytosterol-F can block testosterone/prazosin-induced prostate growth in rats, Urol. Int. 77 (2006) 269–274.

[27] M.H. Ho, N.N. Bhatia, S. Bhasin, Anabolic effects of androgens on muscles of female pelvic floor and lower urinary tract, Curr. Opin. Obstet. Gynecol. 16 (2004) 405–409.

[28] M. Nishimura, T. Ohkawara, H. Sato, H. Takeda, J. Nishihira, Pumpkin seed oil extracted from Cucurbita maxima improves urinary disorder in human overactive bladder, J. Tradit. Complement. Med. 4 (2014) 72–74.

[29] A. Gažová, S. Valášková, V. Žufková, A.M. Castejon, J. Kyselovič, Clinical study of effectiveness and safety of CELcomplex® containing Cucurbita Pepo Seed extract and Flax and Casuarina on stress urinary incontinence in women, J. Tradit. Complement. Med. 9 (2019) 138–142.

[30] S. Palacios, M. Ramirez, M. Lilue, A randomized, double-blind, placebo-controlled clinical trial: evaluating safety and efficacy of a composition of purified and specific cytoplasm extracts of pollen (PSCEP), pumpkin seed extract and vitamin E (Femaxeen®) in women with stress urinary incontinence, Presented at: 12th European Congress on Menopause and Andropause, 15–17 May 2019, Berlin, Germany, 2019.

[31] R. Riemsma, S. Hagen, R. Kirschner-Hermanns, C. Norton, H. Wijk, K.E. Andersson, C. Chapple, J. Spinks, A. Wagg, E. Hutt, K. Misso, S. Deshpande, J. Kleijnen, I. Milsom, Can incontinence be cured? A systematic review of cure rates, BMC Med. 15 (2017) 63.