European Journal of Obstetrics & Gynecology and Reproductive Biology 159 (2011) 457–460

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

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

The efficacy and safety of PSD503 (phenylephrine 20%, w/w) for topical application in women with stress urinary incontinence. A phase II, multicentre, double-blind, placebo controlled, 2-way cross over study

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ARTICLE INFO

Article history:
Received 11 April 2011
Received in revised form 7 July 2011
Accepted 14 July 2011

Keywords:
Phenylephrine
Stress incontinence
Women

ABSTRACT

Objective: PSD503 is a topical gel containing phenylephrine 20% weight/weight (w/w) intended for vaginal application close to the area of the urethral sphincter in women with SUI and has been used in patients with faecal incontinence. The primary objective of this proof of concept study was to evaluate the efficacy of PSD503 in women with SUI as measured by the change in pad weight following an exercise stress pad test. The secondary objectives were to evaluate plasma concentrations of PSD503, BP changes and pulse rate over 3 h following administration and to assess safety and tolerability.
Study design: This was a phase II multi-centre, double-blind, placebo-controlled, 2 way cross-over study. Women were assessed objectively pre and post PSD503 administration using a standardised exercise stress pad test. Safety was assessed by monitoring pulse, BP and plasma levels of PSD503 over 3 h following administration. A power calculation suggested a >80% power to demonstrate (at the 5% level of significance) a difference between treatments of 10–20 g with a sample size of 30 patients.
Results: 14 patients were screened and 12 patients randomised over 20 months. Projections indicated the study would not attain its full quota within 1 year and it was terminated early. Treatment with PSD503 resulted in a greater reduction in pad weight gain than placebo, when expressed as both a percentage change (median % change: placebo – 38.00%, PSD503 – 54.33%) and absolute change (median absolute change: placebo – 10.0 g, 20% (w/w) PSD503 – 22.0 g) from pre-dose leakage. PSD503 was absorbed into the blood within 1 h (median concentration 1.490 ng/ml). Plasma concentrations at 3 h (median 1.305 ng/ml) were less than that at 1 h and lower than plasma concentrations seen following phenylephrine-containing cold remedies. There were no withdrawals, serious adverse events and it was well tolerated overall.
Conclusion: This is the first proof of concept study to demonstrate that a topical α adrenergic agonist gel is rapidly and consistently absorbed vaginally and may have a role in the management of female SUI. However, since recruitment was difficult this may indicate that whilst objectively effective, acceptability in clinical practice may be poor.

1. Introduction

The symptom of Stress Urinary Incontinence (SUI), the 'involuntary leakage of urine on effort or exertion, or on sneezing or coughing', is the most commonly reported type of urinary incontinence in women [1].

Whilst a conservative approach is generally indicated initially many women will benefit from continence surgery and drug therapy has a minor role. Whilst oral α adrenergic agonists, such as phenylpropanolamine and phenylephrine, have been used there is little evidence to support their efficacy [2] and the risk of systemic sympathetic side effects limits their safety and usefulness [3]. Duloxetine, a balanced Serotonin (5-Hydroxytryptamine) and Noradrenaline Reuptake Inhibitor (SNRI) which enhances urethral striated sphincter activity via a centrally mediated pathway [4], is currently the only drug licensed for the treatment of SUI. Despite large phase II [5] and III [6] clinical studies demonstrating significant efficacy compliance and persistence rates are low [7]

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0301-2115/$ – see front matter © 2011 Published by Elsevier Ireland Ltd.
doi:10.1016/j.ejogrb.2011.07.030

and nausea is a significant adverse effect [8]. Consequently there remains a need for an effective well tolerated medical therapy.

PSD503 is a gel containing phenylephrine 20% weight/weight (w/w) intended for topical application close to the area of the urethral sphincter and urethra in women with SUI. A double-blind, placebo-controlled, two way crossover pilot study of 0.5 ml 20% (w/w) (100 mg) phenylephrine gel has been reported in 11 women complaining of mild to moderate SUI [9]. Whilst there was no significant effect on mean arterial blood pressure equally, in this small study, there was also no consistent effect on urethral closure pressure. In addition phenylephrine gel in doses of 0.5 ml of concentrations ranging from 10% to 40% w/w (50–200 mg) have been applied to the anal area in volunteers and patients with faecal incontinence with no cardiovascular side effects [10].

The primary objective of this proof of concept study was to evaluate the efficacy of treatment with vaginally applied PSD503, compared to placebo, in women with SUI as measured by the change in pad weight gain following an exercise stress pad test. The secondary objectives were to evaluate plasma concentrations of PSD503, to evaluate changes in blood pressure and pulse rate over 3 h following administration, and to evaluate the safety and tolerability.

2. Materials and methods

This was a phase II multi-centre, double-blind, placebo-controlled, 2 way cross-over study to evaluate the efficacy, plasma concentrations and safety of 0.25 ml 20% (w/w) PSD503 for topical application in women complaining of SUI (Fig. 1).

Women aged 18–75 with symptomatic SUI who had a positive cough stress test and USI diagnosed by urodynamic evaluation within 36 months of screening were recruited. All had a SUI episode frequency $\geq$7 and $\leq$21 per week confirmed by a frequency volume chart. Exclusion criteria included women with predominant symptoms suggestive of overactive bladder (OAB), a urodynamic diagnosis of detrusor overactivity (DO) or a post void residual >150 mls. In addition those patients with a history of cardiac disease, hypertension, stroke, diabetes mellitus, recurrent urinary tract infection, significant (>grade 1) cystocele and previous pelvic surgery were excluded. The study was conducted in six study sites within the UK between January 2006 and October 2007 although patients were only recruited in five.

After obtaining written consent a physical examination, urinalysis and baseline electrocardiogram (ECG) were performed at a screening visit (visit 1).

Patients then attended for treatment day 1 (visit 2) within 14 days and were randomised to a treatment sequence and allocated a sequential randomisation number.

Prior to drug administration subjects were asked to void to completion and immediately drink 500 mls of water over a 15 min period whilst sitting. An exercise stress pad test, lasting 1 h, with a standardised protocol was then performed with a pre-weighed pad. If the pre administration pad test loss was 0 g then the patient was withdrawn from the study.

Drug administration was performed by the investigator. 20% (w/w) PD503 and matching placebo were supplied in tubes containing 7 g of gel. A single use Metricap facilitating delivery of a dose of 0.25 ml of gel was used for drug administration. The gel was evenly applied to the anterior vaginal wall at the level of the urethral sphincter (3.5 cm proximal to the external urethral meatus) using a gloved finger.

After administration the subject was monitored for 3 h with vital signs being recorded at 30, 60, 90 and 180 min. At 60 min a blood sample was performed to measure the plasma concentration of PSD503 prior to starting the post treatment standardised exercise stress pad test.

Following completion of treatment day 1 (visit 2) subjects were asked to return within 3–10 days for treatment day 2 (visit 3). The procedure at this visit was identical to that described for day 1.

Study subjects attended for a post treatment follow up visit 3–10 days following treatment day 2 (visit 3). History and physical examination were repeated in addition to urinalysis. In the absence of any on going adverse events the subject was the discharged from the study.

2.1. Randomisation and blinding

Randomisation and blinding were maintained throughout. The allocation to treatment sequence was random and based on a pre-defined randomisation code generated by the sponsor and stratified by study site. All supplies were pre-packaged and provided to each site according to the sequence code. On treatment days (visit 2 and 3) subjects received study treatment according to the computer generated randomisation code. The study was of cross-over design and therefore each subject received each treatment once during the study period. Subjects were randomised to a treatment sequence following an eligibility check at treatment day 1 (visit 2) and allocated the next site specific sequential randomisation number.

2.2. Sample size estimation

The study was designed as a 2-treatment, 2-period cross over design. Each subject received each treatment once in one of the two treatment periods in an order dependent on the randomisation, and consequently comparisons were made within-subject.

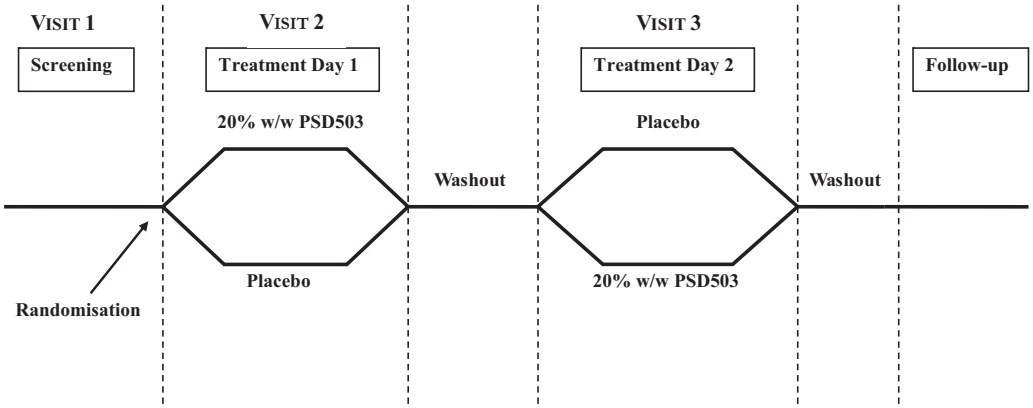

Fig. 1. Study design.