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Serenoa repens + selenium + lycopene vs tadalafil 5 mg for the treatment of lower urinary tract symptoms secondary to benign prostatic obstruction: a Phase IV, non-inferiority, open-label, clinical study (SPRITE study)

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Objective

To compare in a randomised, open-label, non-inferiority clinical study, the efficacy and tolerability of *Serenoa repens* (SeR) + selenium (Se) + lycopene (Ly) (SeR-Se-Ly) therapy vs tadalafil 5 mg in men with lower urinary tract symptoms (LUTS).

Patients and methods

From May 2015 to January 2017, 427 patients were enrolled in 21 different centres (International Standard Randomised Controlled Trial Number Register [ISRCTN] 73316039). Inclusion criteria included: age between 50 and 80 years, International Prostate Symptom Score (IPSS) ≥12, maximum urinary flow rate (Q_{max}) ≤ 15 mL/s, and post-void residual (PVR) <100 mL. Patients were randomised into two groups in a 2:1 ratio: Group A (SeR-Se-Ly, 1 tablet daily for 6 months) and Group B (tadalafil 5 mg, 1 tablet daily for 6 months). The primary endpoint of the study was the non-inferior variation in the IPSS and Q_{max} in Group A vs Group B after 6 months of treatment.

Results

In all, 404 patients completed the full protocol. When comparing both therapies, Group A was statistically not inferior to Group B considering the median change in IPSS (−3.0 vs −3.0; $P < 0.01$), IPSS quality of life (−2.0 vs −2.0; $P < 0.05$), and Q_{max} (2.0 vs 2.0 mL/s; $P < 0.01$). We found statistically significant differences in the increase of at least 3 points in Q_{max} (38.2% vs 28.1%; $P = 0.04$) and of at least 30% of Q_{max} (39.2% vs 27.3%; $P < 0.01$) in Group A compared to Group B. The percentage of patients with an increase of at least 3 points in the IPSS and a decrease of at least 25% of the IPSS was not statistically different between the two groups. For adverse events, four patients in Group A (1.44%) and 10 in Group B (7.81%) ($P < 0.05$) reported side-effects.

Conclusion

We have shown that treatment with SeR-Se-Ly was not inferior to tadalafil 5 mg for improving IPSS and Q_{max} in men with LUTS.

Keywords

benign prostatic enlargement, LUTS, *Serenoa repens*, tadalafil, prostate

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Introduction

Medical treatment for LUTS secondary to benign prostatic obstruction (BPO) has consistently changed in recent years, with new indications and drugs. In fact, medical therapy may be tailored with α-blockers, 5α-reductase inhibitors (5ARIs), phosphodiesterase type 5 (PDE5) inhibitors, and phytotherapy on the basis of their different mechanisms of action [1,2].

However, LUTS may not only be a consequence of prostate enlargement, but also several complex mechanisms, which can play a significant role [3]. In this regard, new evidence has suggested that the nitric oxide/cyclic guanosine monophosphate (NO/cGMP) signalling pathway can influence the onset of symptoms of LUTS [4,5] and also chronic inflammation could be associated with the severity and progression of the disease [6,7].

Notwithstanding this evidence, tadalafil 5 mg once daily has been officially licensed for the treatment of male LUTS with or without erectile dysfunction (ED; Level of Evidence 1a), as reported by the European Association of Urology (EAU) [8], due to the reduction in smooth muscle tone of the detrusor, prostate and urethra and the increase of blood perfusion and oxygenation in the LUT [9]. However, a meta-analysis by Dahm et al. [10] reported that none of the drugs or drug combinations newly used to treat LUTS attributed to BPH were more effective compared with older α-blockers.

More recently, the benefit of α-blockers in combination with *Serenoa repens* (SeR) + selenium (Se) + lycopene (Ly) (SeR-Se-Ly) vs single monotherapies for the treatment of LUTS/BPO has been demonstrated by the PROCOMB (*Serenoa repens*, lycopene and selenium vs tamsulosin for the treatment of [LUTS]/[BPH]: An Italian multicenter comparative randomized study between single or combination therapy) study (International Standard Randomised Controlled Trial Number Register [ISRCTN] 78639965) [11]. The mechanism of action of the lipid extract of SeR has been established previously and consists of the inhibition of 5α-reductase and the antagonisms of the α_1-adrenergic receptor. In addition, SeR has been shown to promote apoptosis in BPH by reducing survivin and neuronal apoptosis inhibitory protein expression, which are involved in stimulating prostate growth [12,13]. Furthermore, Ly and Se act through some seleno-proteins by promoting an optimal balance between oxidants/antioxidants, with significant beneficial effects on LUTS/BPO [14].

However, we would point out that the mechanism of action of both drugs are not attributable to prostate size reduction or the inhibition of the release of noradrenaline in smooth muscle cells in the prostate [8]. In fact, α-blockers or PDE5 inhibitors have little effect on urodynamically determined bladder outlet resistance [15,16].

More recently, a systematic review and meta-analysis of 12 randomised controlled trials showed that SeR was significantly more effective than placebo in reducing the number of nocturnal voids (weighted mean difference [WMD] 0.31; $P = 0.03$) and increasing maximum urinary flow rate (Q_{max}; WMD 3.37; $P < 0.001$), and it was as effective as tamsulosin monotherapy and short-term therapy with finasteride in improving the IPSS (WMD 1.15, 95% CI 1.11–3.40; $P = 0.32$) and Q_{max} (WMD 0.16, 95% CI 0.60–0.28; $P = 0.48$) [17].

However, to date, there has been no comparison between SeR and tadalafil 5 mg for the treatment of LUTS/BPO. Therefore, in the present study using a randomised, open-label, non-inferiority design, we aimed to compare the effectiveness and tolerability of SeR-Ly-Se therapy vs tadalafil 5 mg in patients with LUTS/BPO.

Patients and Methods

From May 2015 to January 2017, 427 patients were enrolled at 21 different centres in this randomised, open-label, non-inferiority clinical study. Figure 1 shows the Consolidated Standards of Reporting Trials (CONSORT) flow chart of all enrolled patients.

The following trial was conducted in accordance with the ethical principles described in the Helsinki Declaration and it was approved by the Local Ethics Committee and further registered at the ISRCTN (ISRCTN73316039).

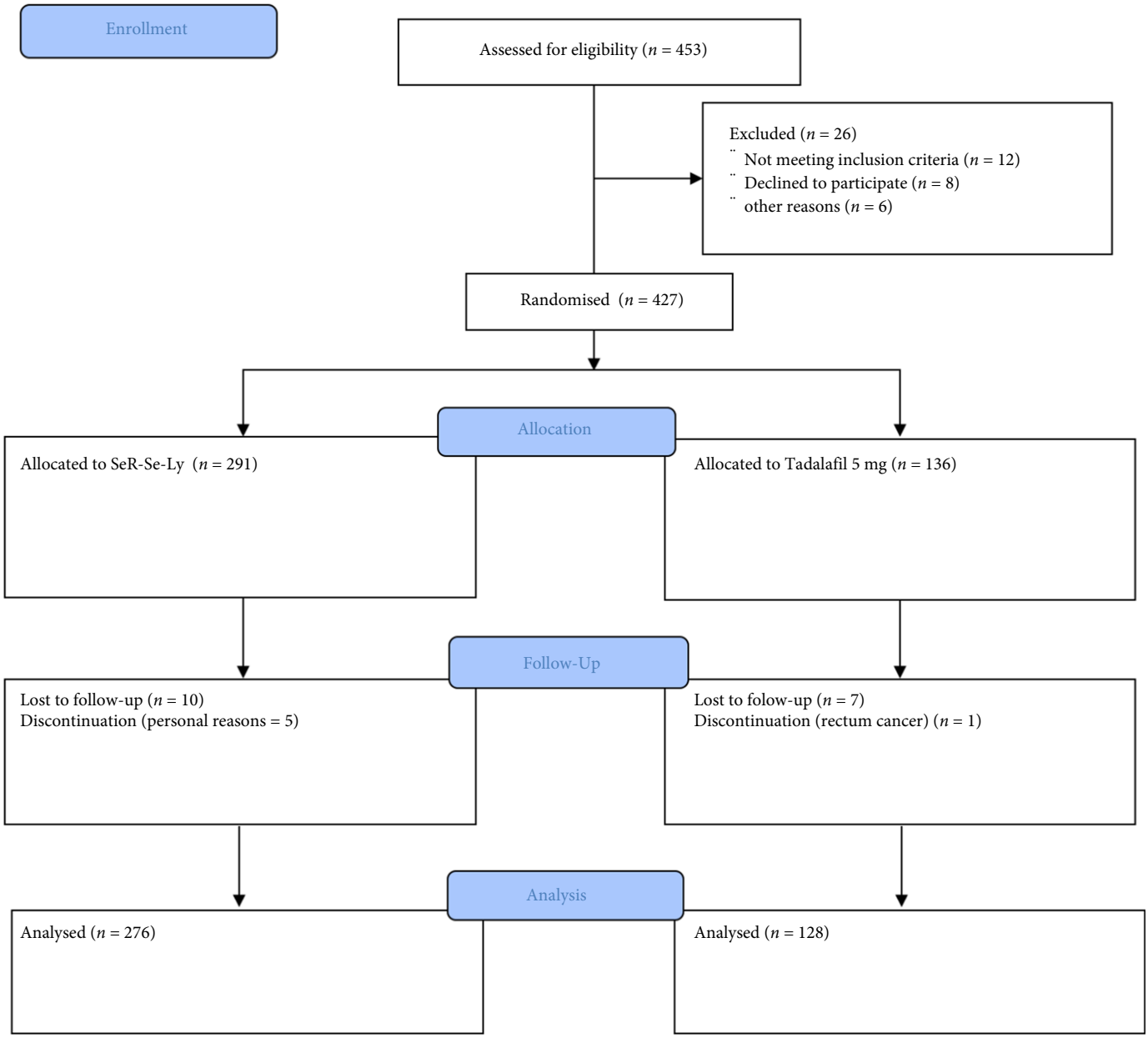
Inclusion criteria were: age between 50 and 80 years, negative DRE for prostate cancer, PSA level of <4 ng/mL, IPSS ≥ 12, $Q_{max} \leq 15$ mL/s, and post-void residual (PVR) <100 mL.

Exclusion criteria were: diagnosis of prostate cancer; previous bladder cancer; diabetes mellitus; neurological disease; severe liver disease; history of orthostatic hypotension or syncope; symptomatic UTI; treatment with anti-androgens, antidepressants, neuroleptics or anticholinergics; previous surgical treatment for LUTS/BPO; episode of acute urinary retention in the last 4 weeks; and previous treatment with 5ARIs, PDE5 inhibitors or anti-muscarinics. Patients with previous medical therapy with α-blockers were included in the study after a 1-month pharmacological washout.

After screening, the patients were randomised using a computer-generated sequence into two groups in a 2:1 ratio: Group A (SeR-Ly-Se, 1 tablet daily for 6 months) and Group B (tadalafil 5 mg, 1 tablet daily for 6 months).

The effectiveness variables included the IPSS and five-item version of the International Index of Erectile Function (IIEF-5), IPSS quality-of-life (QoL) score, Q_{max} measured at uroflowmetry, and PVR. Assessments were carried out at baseline (Visit 0), 1 month (Visit 1), 3 months (Visit 2), and 6 months (Visit 3). Uroflowmetry was performed using

Fig. 1 Flowchart of the study according to the CONSORT statement.



standard equipment and a valid Q_{max} measurement required a bladder fill measurement at ultrasonography of ≥150 and ≤550 mL and a drained volume ≥125 mL.

Treatment-emergent adverse events (TEAEs) were considered as self-reported AEs after randomisation.

The primary endpoint of the study was the non-inferior variation of the IPSS and Q_{max} in Group A with respect to Group B. Secondary endpoints of the study were considered to be the variation in prostate volume, PSA level, IPSS-QoL, and PVR.

One tablet of of SerR-Se-Ly (Profluss®; Ayanda AS, Tromsø, Norway) consisted of 320 mg of supercritical CO_2 lipidic extract SeR containing 85% of fatty acids sterols, Se (50 µg) and Ly (5 mg) and it is distributed by Konpharma SRL (Rome, Italy).

Statistical Analysis

A sample size of 390 patients with a 2:1 randomisation was considered sufficient to demonstrate that the IPSS variation in Group A was not inferior to Group B. For this purpose, we

used an equivalence margin of 0.5 for the IPSS and of 0.8 for the Q_{max} with a power of 95%. The study sample was increased to 450 to allow for a discontinuation rate of 15%. The results of the study are presented using a 'per protocol analysis'. The effectiveness variables were tested as a variation from Visit 0 to Visit 3 by the use of the Mann–Whitney *U*-test or Student's *t*-test according to the normal distribution of variables (tested with the Kruskal–Wallis *H*-test). Quantitative variables were tested by the chi-squared test or Fisher's exact test. In all the tests a $P < 0.05$ was considered statistically significant.

All tests were completed using the Statistical Package for the Social Sciences (SPSS®) version 19 software (SPSS Inc., IBM Corp, Somers, NY, USA).

Results

Of all randomised patients, 404 patients completed 6 months of treatment (Fig. 1). In the whole population, the median (SD) age was 63 (6.5) years, PSA level was 2.0 (1.0) ng/mL, Q_{max} was 12.0 (2.1) mL/s, prostate volume was 46.0 (13.0) mL, IPSS was 18 (4.4), and the PVR was 40 (33.4) mL. Table 1 shows the baseline characteristics in the two groups.

Table 1 Baseline characteristics of the patients.

Variable	Group A SeR-Se-Ly	Group B Tadalafil 5 mg
Number of patients	276	128
Median (SD)		
Age, years	64.0 (6.3)	63 (6.9)
PSA level, ng/mL	1.8 (1.0)	1.9 (1.1)
Prostate volume, mL	45.0 (13.1)	45.0 (13.0)
Q_{max}, mL/s	12.0 (2.2)	12.0 (2.0)
PVR, mL	40.0 (33.5)	40.0 (33.2)
IPSS	17.0 (4.6)	18.0 (4.0)
IIEF-5	18.0 (4.7)	17.5 (4.7)
IPSS-QoL	3.0 (1.0)	3.0 (0.8)

There were significant differences in the IPSS ($P < 0.01$), Q_{max} ($P < 0.01$) and PVR ($P < 0.01$) in Group A between baseline and the last follow-up. In Group B, there were significant differences in the IPSS ($P < 0.01$), Q_{max} ($P < 0.01$), PVR ($P < 0.01$) and IIEF-5 ($P < 0.01$) between baseline and the last follow-up.

Table 2 shows the primary and secondary outcomes after 6 months of treatment in both groups. When comparing both therapies, Group A was statistically not inferior to Group B with respect to IPSS (−3.0, 95% CI: −5.0 to −2.0 vs −3.0, 95% CI: −4.0 to −1.0; $P < 0.01$) (Fig. 2), IPSS-QoL (−2.0, 95% CI: −3.0 to 0.0 vs −2.0 95% CI: −3.0 to −0.25; $P < 0.05$), and Q_{max} (2.0, 95% CI: 1.0 to 3.4 vs 2.0, 95% CI: −3.0 to −0.25; $P < 0.01$) (Fig. 3). No differences were found with respect to the PVR (Fig. 4).

The percentage of patients with an increase of ≥3 points in the IPSS and a decrease of ≥25% in the IPSS was not statistically different between the two groups.

We found statistically significant differences in the increase of ≥3 points in the Q_{max} (38.2% vs 28.1%; $P = 0.04$) and ≥30% in the Q_{max} (39.2% vs 27.3%; $P < 0.01$) in Group A compared to Group B (Fig. 5). Finally, we found significant differences in the increase of IIEF-5 in Group B compared to Group A (4.0 vs 1.0; $P < 0.01$) (Fig. 6).

During the entire study, we did not observe significant variations between groups for the other variables in question, i.e. PSA level and prostatic volume.

Regarding TEAEs, four patients in Group A (1.44%) and 10 in Group B (7.81%) ($P < 0.05$) reported side-effects (Table 3).

Discussion

Currently, medical therapy with tadalafil 5 mg has been officially introduced for the treatment of men with LUTS,

Table 2 Median change of primary and secondary outcomes from baseline to 6 months.

Outcome	Group A SeR-Se-Ly (*n* = 276)	Group B Tadalafil 5 mg (*n* = 128)	*P*
IPSS, median change from baseline (95% CI)	−3.0 (−5.0 to −2.0)	−3.0 (−4.0 to −1.0)	<0.01*
% change of IPSS, median change from baseline (95% CI)	−20.0 (−28.42 to −10.0)	−16.7 (−25.27 to −5.26)	0.03*
Decrease of 3 point of IPSS, *n* (%)	164 (59.4)	67 (52.3)	0.18†
Decrease of 25% of IPSS, *n* (%)	87 (31.5)	38 (29.7)	0.71†
Q_{max}, mL/s, median change from baseline (95% CI)	2.0 (1.0 to 3.4)	1.6 (0.60 to 3.0)	<0.01*
% change of Q_{max}, median change from baseline (95% CI)	18.2 (7.69 to 33.33)	14.25 (5.54 to 26.25)	0.02*
Increase of 3 point of Q_{max}, *n* (%)	104 (38.2)	36 (28.1)	0.04†
Increase of 30% of Q_{max}, *n* (%)	108 (39.6)	35 (27.3)	<0.01†
PVR, mL, median change from baseline (95% CI)	−15.0 (−30.0 to 0.0)	−13.5 (−30.0 to 0.0)	0.44‡
IIEF-5, median change from baseline (95% CI)	1.0 (0.0 to 2.0)	4.0 (2.0 to 6.0)	<0.01‡
Prostate volume, mL, median change from baseline (95% CI)	−2.0 (0.33)	0.0 (0.06)	0.30‡
PSA, ng/mL, median change from baseline (95% CI)	−0.1 (−0.3 to 0.09)	−0.06 (−0.28 to 0.10)	0.95‡
IPSS-QoL, median change from baseline (95% CI)	−2.0 (−3.0 to 0.0)	−2.0 (−3.0 to −0.25)	<0.05*

**Non-inferiority test; †Chi-squared test; ‡Superiority test.*

Fig. 2 Median change in the IPSS from baseline at each follow-up. *from baseline to 6 months (non-inferiority test).

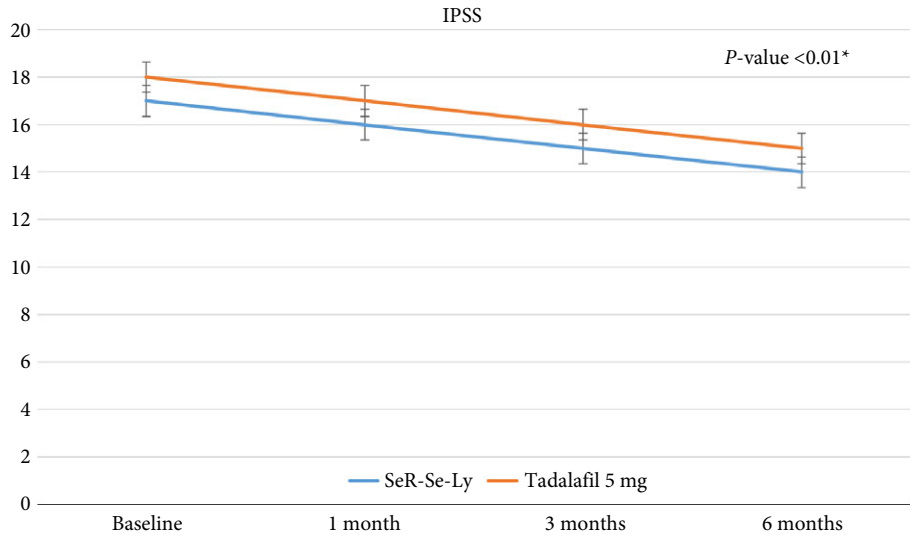
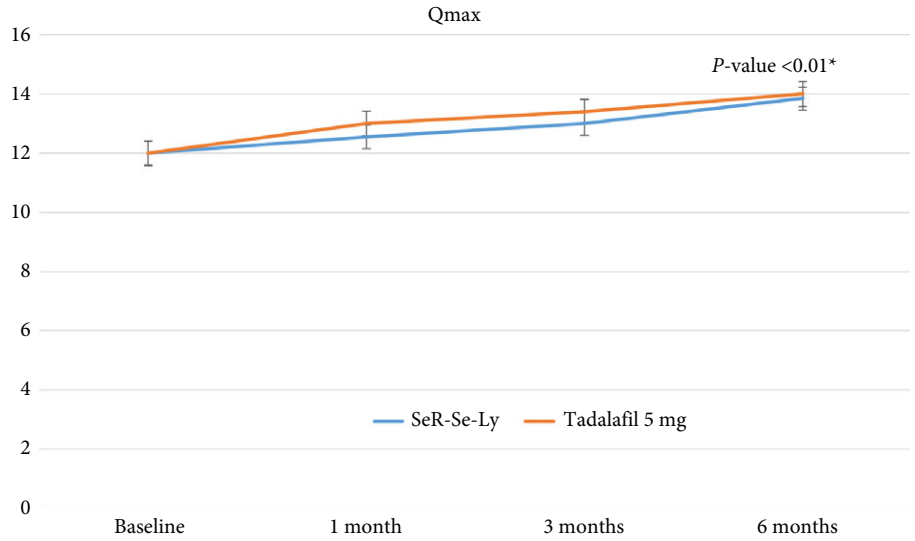


Fig. 3 Median change in the Q_{max} from baseline at each follow-up. *from baseline to 6 months (non-inferiority test).



with and without ED [10]. The putative mechanisms involved in this clinical indication are the increase in cellular levels of cGMP resulting in reduced tone of the smooth muscle of the detrusor, prostate, and urethra. In addition, increased levels of NO may result in greater blood perfusion and oxygenation of the LUT [1,18,19]. Finally, a study by Vignozzi et al. [20] highlighted the possibility of tadalafil 5 mg reducing chronic inflammation in the prostate and bladder.

In a recent meta-analysis, Dahm et al. [10] evaluated the clinical effectiveness of tadalafil 5 mg vs tamsulosin or alfuzosin. The analysis of four clinical trials with a 3-month follow-up showed that tadalafil and tamsulosin similarly improved the IPSS (weighted mean difference [WMD] −0.07, 95% CI: −2.12 to 2.23; with a moderate strength of evidence [SOE]) and the IPSS-QoL (WMD −0.01, 95% CI: −0.75 to 0.73; low SOE). However, withdrawal from the study was a greater in the tadalafil (3%) and tamsulosin groups (1%). Although the authors concluded the lack of robustness of the included studies, we would point out that they had not been designed as non-inferiority trials. In fact, the calculation of the primary endpoint and sample size were made based on a comparison with placebo, rather than with tamsulosin or other α-blockers. It should be emphasised that when a treatment is compared with a standard drug, a non-inferiority study should be conducted. In fact, a non-inferiority clinical trial is designed to show that the experimental treatment is not clinically worse than the standard treatment [21].

Fig. 4 Median change in the PVR from baseline at each follow-up. *from baseline to 6 months (superiority test).

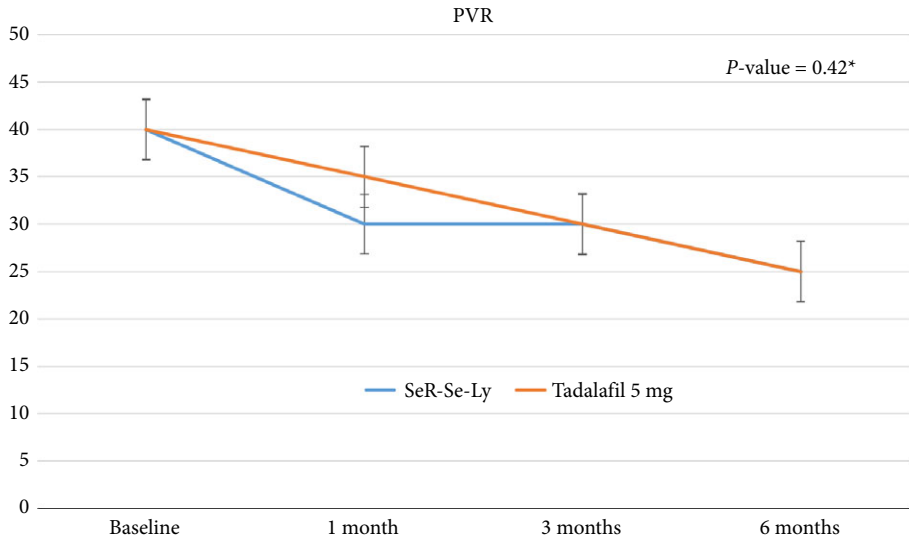
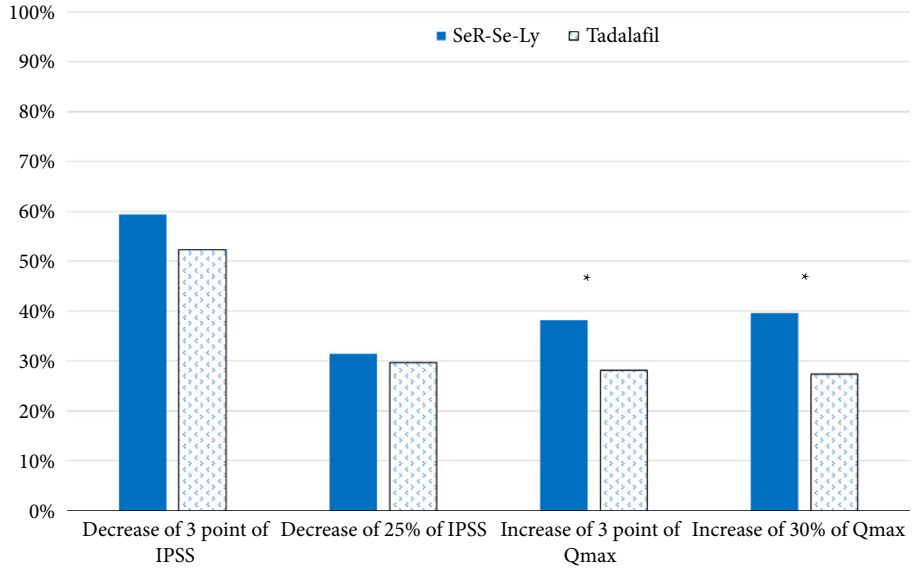


Fig. 5 Proportion of patients with improvement in the IPSS and Q_{max}. *$P < 0.05$ (chi-squared test).



Recently, two clinical trials have reported promising clinical efficacy of the SeR and tamsulosin in combination for the treatment of LUTS, as reported by the latest guidelines of the EAU [8]. Previously, the PROCOMB study showed that combined treatment with SeR-Se-Ly and tamsulosin was more effective than single monotherapy in improving the IPSS and Q_{max} after 12 months of follow-up [11]. In another study, Ryu et al. [22] reported that the combination of SeRs and tamsulosin (0.2 mg) was more effective than tamsulosin monotherapy in reducing storage symptoms.

In this regard, the anti-inflammatory effect of SeR has been previously reported by Navarrete et al. [23], who found a significant reduction in interleukin 1 and TNF-α levels after 3 months of SeR vs placebo. In addition, evidence has shown that SeR inhibits the expression of two inflammatory mediators, monocyte chemoattractant protein 1/chemokine (C-C motif) ligand 2 (MCP-1/CCL2) and vascular cell adhesion molecule 1 (VCAM-1) [24], and that the SeR-Se-Ly combination was more effective than individual therapies in reducing prostate inflammation, expression of growth factors and oxidative stress, via an increase in caspase-9 and a reduction in the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2) [25].

In the present study, with a non-inferiority design, we studied the clinical efficacy of SeR-Se-Ly vs tadalafil 5 mg for the

Fig. 6 Median change in the IIEF-5 from baseline at each follow-up. *from baseline to 6 months (superiority test).

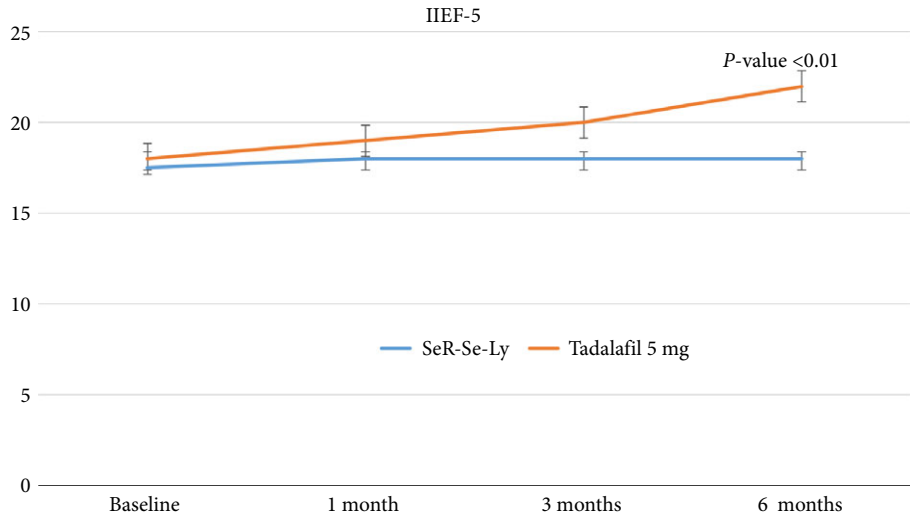


Table 3 Reported TEAE in the two groups.

TEAE	Group A SeR-Se-Ly (*n* = 276)	Group B Tadalafil 5 mg (*n* = 128)	*P*
Total, *n* (%)	4 (1.44)	10 (7.81)	<0.01
Hypotension, *n*	1	1	
Headache, *n*	–	2	
Lumbar pain, *n*	–	2	
Asthenia, *n*	–	5	
Dysuria, *n*	3	–	

treatment of men with LUTS. By analysing the two primary endpoints, it emerged that for the IPSS and Q_{max}, the SeR-Se-Ly combination was not worse than tadalafil 5 mg, using an equivalence margin of 0.5 for the IPSS and 0.8 for the Q_{max}.

Yoshida et al. [26] compared treatment with silodosin vs tadalafil and showed that α-blockers therapy appeared to be better in terms of the IPSS and with a tendency to significance for the Q_{max}. Similarly, Oelke et al. [27] in a comparative study comparing tamsulosin vs tadalafil 5 mg showed similar improvement in LUTS after 12 weeks of therapy between both therapies. However, as reported within the limits of the study, the design of the work was lacking sample-size calculation in terms of non-inferiority.

Regarding the present results, this is the first study investigating the clinical efficacy of tadalafil 5 mg compared to another treatment for LUTS through a sample size calculation based on an equivalence margin. We may suppose that our present results can be attributed to a different mechanism of action by both molecules, but that may result in a similar improvement in LUTS.

Regarding AEs, a meta-analysis by Gacci et al. [28] reported a rate of ~16% for AEs in patients treated with PDE5 inhibitors vs 6% for the placebo group. However, in studies comparing the effects of combined therapy with PDE5 inhibitors and α-blockers vs α-blockers alone, 6.8% of AEs were reported compared to 5.1% respectively. In our present study, we found a greater rate of AEs in the tadalafil 5 mg group (8.8%) compared to the SeR-Se-Ly group (1%) ($P < 0.05$). Although there were no discontinuations in therapy due to the occurrence of AEs, the reduced percentage of side-effects in the SeR-Se-Ly treated group can be seen as an advantage.

However, it is appropriate to consider some limitations of the present study before concluding. Firstly, the lack of a placebo group may represent a possible bias. Secondly, we did not evaluate clinical efficacy for >6 months. Finally, the impact of medical therapy in terms of variations in molecular markers was not analysed. On the contrary, strengths of the present study include the non-inferiority design and a follow-up that exceeded 12 weeks, which is commonly reported in other published studies.

Conclusion

In this randomised, open label, non-inferiority clinical study, we have shown that treatment with SeR-Se-Ly is not significantly worse than tadalafil 5 mg in terms of improving the IPSS and Q_{max}. The side-effects reported in the study were low, but clinically less in the SeR-Se-Ly group. These results should be considered in the treatment of moderate LUTS/BPO.

Conflict of Interest

Each author discloses no conflict of interest. This study has been designed and conducted independently. Data collection

and management and all statistical analyses were performed and retained by data manager. The corresponding author and other co-authors interpreted the data and participated in the preparation, review and approval of the manuscript. Giuseppe Morgia, Giuseppe Vespasiani, Rosaria Maria Pareo, Salvatore Voce, Massimo Madonia, Marco Carini, Antonio Ingrassia, Carlo Terrone, Marcello Gentile, Maurizio Carrino, Antonella Giannantoni, Franco Blefari, Salvatore Arnone, Giorgio Santelli, Giorgio Ivan Russo received travel grant from Konpharma SRL.

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The study was funded by Konpharma SRL and designed by Prof Giuseppe Morgia. Konpharma SRL had a role in drugs costs, conducting the study, monitoring, data management and analysis.

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Appendix 1

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Abbreviations: (TE)AE, (treatment-emergent) adverse events; BPO, benign prostatic obstruction; cGMP, cyclic guanosine monophosphate; CONSORT, Consolidated Standards of Reporting Trials; EAU, European Association of Urology; ED, erectile dysfunction; IIEF-5, five-item version of the International Index of Erectile Function; ISRCTN, International Standard Randomised Controlled Trial Number Register; Ly, lycopene; NO, nitric oxide; PVR, post-void residual; Q_{max}, maximum urinary flow rate; QoL, quality of life; SeR, *Serenoa repens*; Se, selenium; SOE, strength of evidence.