

Efficacy and Safety of a Combination of Sabal and Urtica Extract in Lower Urinary Tract Symptoms

A randomized, double-blind study versus tamsulosin

Udo Engelmann¹, Carola Walther², Boris Bondarenko¹, Petra Funk², and Sandra Schläfke²

¹ Department of Urology, University Clinics of Cologne, Cologne (Germany)

² Clinical Research Department, Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe (Germany)

Corresponding author: Prof. Dr. Udo Engelmann, Urologische Klinik der Universität Köln, Joseph-Stelzmann-Str. 9, 50924 Köln (Germany); fax: 0049 221 478 5198

Key words

- International Prostate Symptom Score
- Lower urinary tract symptoms
- Prostagutt[®] forte
- Sabal fruit extract, clinical trial, efficacy
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- Urtica root extract, clinical trial, efficacy
- WS[®] 1031
- WS[®] 1473

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Summary

The aim of this prospective, randomized, double-blind, double-dummy, multicenter clinical trial was to investigate the efficacy and safety of PRO 160/120 (Prostagutt[®] forte), a fixed combination preparation of 160 mg Sabal fruit extract WS[®] 1473 and 120 mg Urtica root extract WS[®] 1031 per capsule, in comparison to the α_1 -adrenoceptor antagonist tamsulosin (CAS 106463-17-6) in lower urinary tract symptoms (LUTS) caused by benign prostatic hyperplasia (BPH).

140 elderly out-patients suffering from LUTS caused by BPH, with an initial score ≥ 13 points in the International Prostate Symptom Score (I-PSS), received 2×1 capsule/d PRO 160/120 or 1×0.4 mg/d tamsulosin and were treated for 60 weeks with interim visits at weeks 8, 16, 24, 36, and 48.

The primary outcome measure for efficacy was the change in I-PSS total score, the percentage of patients with an I-PSS score ≤ 7 points at endpoint ('responders') was analyzed as well.

During 60 weeks of randomized treatment the I-PSS total score was reduced by a median of 9 points in both groups. In total, 32.4 % of the patients in the PRO 160/120 group and 27.9 % in the tamsulosin group were responders (test for non-inferiority of PRO 160/120: $p = 0.034$; non-inferiority margin 10 %). Both drugs were well tolerated, with one adverse event in 1514 treatment days for PRO 160/120 and one event in 1164 days for tamsulosin.

The study supports non-inferiority of PRO 160/120 in comparison to tamsulosin in the treatment of LUTS caused by BPH.

Zusammenfassung

Wirksamkeit und Verträglichkeit einer Kombination aus Sabal- und Urtica-Extrakt bei Patienten mit symptomatischer benigner Prostata-Hypertrophie / Eine randomisierte, doppelblinde Studie vs. Tamsulosin

Ziel dieser prospektiven, randomisierten, doppelblinden, multizentrischen Double-dummy-Studie war es, die Wirksamkeit und Verträglichkeit von PRO 160/120 (Prostagutt[®] forte), einer fixen Kombination aus 160 mg Sabalfrucht-

extrakt WS[®] 1473 und 120 mg Urticawurzelextrakt WS[®] 1031 pro Kapsel, im Vergleich zum α_1 -Adrenozeptor-Antagonist Tamsulosin (CAS 106463-17-6) bei durch eine benigne Prostata-Hyperplasie bedingter symptomatischer BPH (LUTS, lower urinary tract symptoms) zu untersuchen.

140 ältere Patienten, bei denen eine durch eine benigne Prostata-Hyperplasie bedingte symptomatische BPH vorlag und die einen Internationalen Prostata-Symptom-Score (I-PSS) von ≥ 13 Punkten aufwiesen, erhielten über 60 Wochen täglich 2×1 Kapsel PRO 160/120 oder täglich $1 \times 0,4$ mg Tamsulosin.

Als wirksamkeitsbeurteilende Zielgröße wurde die Veränderung des I-PSS-Gesamtscores herangezogen. Des Weiteren wurde der Anteil an Patienten bestimmt, die am Studienende einen I-PSS-Score ≤ 7 Punkte aufwiesen (Responder).

Nach der 60wöchigen Behandlungsphase war der I-PSS in beiden Behandlungsgruppen um 9 Punkte (Median) gesunken. Insgesamt waren 32,4 % der Patienten in der PRO-160/120-Gruppe und 27,9 % in der Tamsulosin-Gruppe Responder (Test auf Nichtunterlegenheit von PRO 160/120: $p = 0,034$, Schranke 10 %). Beide Präparate waren gut verträglich,

mit einem unerwünschten Ereignis in 1514 Behandlungstagen für PRO 160/120 und einem unerwünschten Ereignis in 1164 Tagen für Tamsulosin. Die Studienergebnisse belegen damit die Nicht-Unterlegenheit von PRO 160/120 im Vergleich zu Tamsulosin bei der Behandlung symptomatischer BPH (LUTS).

1. Introduction

Histological evidence of benign prostatic hyperplasia (BPH) can be found in more than 60 % of all males during the second half of their lives [1, 2]. BPH may lead to obstructive and irritative lower urinary tract symptoms (LUTS) like incomplete voiding, decreased uroflow and urinary stasis with associated nephrohydrosis, nocturia and pollakisuria.

Although the etiology of BPH has not yet been completely resolved, there are several ways to treat this disease. One group of drugs commonly used for the treatment of LUTS aims at a reduction of symptoms through 5α -reductase inhibition (e.g. finasteride), thus blocking the conversion of testosterone into dihydrotestosterone (DHT) that acts on the prostatic level [3]. A different mode of action is based on the high percentage of smooth muscle tissue in the enlarged prostate. Selective α_1 -adrenoceptor antagonists relax the smooth muscle of the bladder neck and prostatic urethra by blocking the post-synaptic α_1 -adrenergic receptors prevailing in the prostatic muscular tissue and cause fewer unwanted effects (e.g. hypotension) than non-selective α -blockers. Further improvements regarding tolerability have been achieved by the development of drugs that act selectively on specific α_1 subtypes [4, 5].

The efficacy of tamsulosin (CAS 106463-17-6), a selective α_{1A} -adrenoceptor antagonist, in LUTS has been demonstrated in numerous clinical trials with a follow-up duration of up to 6 years [6–11]. In placebo-controlled studies a beneficial effect of tamsulosin on subjective symptoms was usually observed within 2 weeks after the start of treatment and improvements on the International Prostate Symptom Score (I-PSS) [12], a self-rating questionnaire consisting of seven items of lower urinary tract symptoms, ranged between 20 % and 36 % versus baseline. Patients treated with 0.4 mg/d tamsulosin showed average improvements of the peak urinary flow rate between 1.1 and 3.6 ml/s, and residual urinary volume decreased by 21–43 % versus baseline. Symptom improvements were significant versus placebo

after 4 weeks of treatment and reached their maximum after 12–14 weeks.

In many European countries, plant extracts play a major role in the management of BPH and related LUTS. In Germany, 61.6 % of male LUTS patients participating in a survey conducted by Berges et al. [13] were treated with plant extracts, which thus are the most frequently used prescription drugs for male LUTS treatment in this country. The most frequently used herbal drugs in LUTS treatment are based on extracts from the fruits of saw palmetto (*Sabal serrulata*, or *Serenoa repens*) and the roots of stinging nettle (*Urtica dioica*) [14, 15]. Saw palmetto extract inhibits 5α -reductase without exhibiting any androgen binding activity [16, 17], and potently and non-competitively inhibits human α_1 -adrenoceptors in vitro [18]. Stinging nettle root extract causes an inhibition of the membrane Na^+, K^+ -ATPase activity of the prostate, which may limit prostate-cell metabolism and growth [19]. Furthermore, antiproliferative, antiphlogistic and antiedematous effects were observed for both drugs [20, 21].

For mono-preparations from Sabal fruit extract (SFE) and Urtica root extract (URE), efficacy in BPH related LUTS has been demonstrated in a number of randomized, double-blind clinical trials [22–25]. In a combination of both extracts a synergistic effect based on their mechanisms of action may be expected. PRO 160/120¹⁾ is a fixed combination of 160 mg SFE and 120 mg URE per capsule. Two prospective, randomized, placebo-controlled long-term trials with PRO 160/120 in patients with BPH not requiring surgery were performed by Metzker and colleagues [26] (40 patients, initial peak urinary flow rate < 20 ml/s) and by Lopatkin et al. [27] (257 patients, initial I-PSS ≥ 14 points, initial peak urinary flow rate < 15 ml/s). The trials featured 24

¹⁾ Marketed in Germany under the trade name Prostagutt[®] forte; Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe (Germany).

weeks of double-blind treatment with 2 × 1 capsule/d PRO 160/120 or placebo, after which all participants received PRO 160/120 (2 × 1 capsule/d) in an open 24-weeks control period (with Lopatkin et al. [27] this was followed by another 48 weeks of open-label follow-up with 2 × 1 capsule/d PRO 160/120). Both studies showed significant superiority of PRO 160/120 over placebo in improving LUTS as measured by I-PSS. PRO 160/120 was also superior to placebo regarding the improvement of urodynamic measures (notably peak urinary flow) [26]. In another double-blind, randomized trial Sökeland and colleagues [28] treated 543 patients with BPH (initial peak urinary flow rate < 20 ml/s) with 2 × 1 capsule/day PRO 160/120 or 5 mg/day finasteride for 48 weeks. For peak urinary flow, both treatments were equivalent assuming a maximum irrelevant difference of 1.5 ml/s, and the improvements observed in the I-PSS were also in a comparable range. Both drugs' treatment effects were unrelated to baseline prostatic volume [29].

In this study we compared the efficacy and tolerability of PRO 160/120 to the α_1 -adrenoceptor antagonist tamsulosin in patients with LUTS.

2. Patients and methods

In a prospective, randomized, double-blind, double-dummy, multicenter trial the efficacy and safety of PRO 160/120 in the treatment of LUTS caused by BPH were compared to tamsulosin. Tamsulosin was purchased from the domestic market as merchandise. PRO 160/120 is a fixed combination of 160 mg

Sabal fruit extract WS[®] 1473²⁾, drug-extract ratio 10.0–14.3 : 1; extraction agent: 90 % ethanol [m/m]) and 120 mg Urtica root dry extract WS[®] 1031²⁾ (8.3–12.5 : 1; 60 % ethanol [m/m]) per capsule. Tamsulosin was administered in slow-release capsules containing 0.4 mg of active ingredient. For both drugs placebo capsules were available which were indistinguishable from their pharmacologically active counterparts in all aspects of their outward appearance.

The trial was performed in accordance with the ICH Good Clinical Practice guidelines, the Declaration of Helsinki as well as with national regulatory and legal requirements, including approval of the protocol by an independent ethics committee. After complete description of the study, written informed consent was obtained from all participants. The subjects were outpatients suffering from BPH that did not require surgery. At study inclusion a maximum urinary flow rate \leq 12 ml/s at a urinary volume \geq 150 ml was required. Patients whose peak urinary flow rate changed by more than 3 ml/s during a 2-week placebo run-in phase were excluded. Eligible patients (50 years and older) also had to have an initial I-PSS total score \geq 13 points and \geq 3 points for the I-PSS quality of life (QoL) assessment. Patients with a residual urinary volume > 150 ml, congested urinary tract passages, an indication for BPH surgery, urinary tract infection, prostate carcinoma, diabetes, neurogenic or bladder dysfunction as well as patients previously treated with 5 α -reductase inhibitors were ineligible. During trial participation any concomitant medication which could interfere with the assessment of treatment efficacy was not al-

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Table 1: I-PSS self-rating questionnaire (modified according to [12]).

I-PSS							
Over the past 4 weeks, ...	Never	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	
1. ... how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
2. ... how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
3. ... how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. ... how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. ... how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. ... how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
7. ... how many times did you usually get up to urinate from the time you went to bed at night until the time you got up in the morning?	Never 0	1 time 1	2 times 2	3 times 3	4 times 4	5 times or more 5	
Single-Item Quality-of-life-Index							
If you were to spend the rest of your life with your prostate symptoms just as they are now, how would you feel about that?	Very good 0	Pleased 1	Mostly satisfied 2	Mixed (about equally satisfied and dissatisfied) 3	Mostly dissatisfied 4	Very unhappy 5	Very bad 6

lowed. Any such medication had to be washed out before the start of randomized treatment.

After a screening examination eligible patients entered a single-blind placebo run-in phase of two weeks. Patients who were still eligible were randomized at a ratio of 1 : 1 to 60 weeks of double-blind treatment with 2 × 1 capsule/day PRO 160/120 plus 1 × 1 capsule tamsulosin placebo, or 1 × 1 capsule/day tamsulosin plus 2 × 1 capsule PRO 160/120 placebo. Randomization was performed in balanced blocks, by means of a validated EDP random number generator program. To each trial center only complete random blocks were allocated. Within each center, the random numbers were assigned to the patients chronologically in ascending order. Visits were scheduled after 8, 16, 24, 36, 48 and 60 weeks of double-blind treatment.

Efficacy assessment was focused on the subjective symptoms caused by BPH which were assessed by means of the I-PSS [12] self-rating questionnaire (primary outcome measure) which was administered at each visit. This scale consists of an index with seven items describing the frequency of occurrence of specific urinary symptoms (incomplete emptying, intermittency, weak stream, hesitancy, micturition frequency, urgency, nycturia) during the past four weeks on a six-point scale ranging from 0 ('never') to 5 ('almost always'), resulting in a total score of 0 to 35 points (Table 1). The total I-PSS is complemented by a single-item quality-of-life index assessing a subject's condition on a seven-point scale ranging from 0 ('very good') to 6 ('very bad').

At screening and baseline as well as after 8, 24, 48 and 60 weeks the peak urinary flow rate was determined in the medical practice by means of an electronic uroflow recorder, when the patient felt the urge to urinate. The patient should be undisturbed and in his normal micturition position (sitting or standing). Other secondary objective outcome measures for efficacy were the average urinary flow rate, urinary output, duration of micturition and flow increase, residual urinary volume and size of prostate (both determined by ultrasound at pre-treatment and after 24 and 60 weeks), the Cologne Erectile Dysfunction Questionnaire (CEDQ) [30], administered at each visit, as well as clinical findings during rectal examinations. Safety measures included physical examinations and a digital-rectal examination of the prostate as well as safety laboratory monitoring (pre-treatment as well as weeks 24 and 60). In the physical examinations, the filling of the urinary bladder (exclusion of an extremely full bladder) and the sphincter tone ('moderate', 'normal', 'spastic') were examined, whereas in the digital-rectal examination the size ('highly enlarged', 'moderately enlarged', 'according to the age'), surface ('knotty', 'smooth'), sensitivity (yes/no) and consistency ('hardened', 'soft', 'normal') of the prostate were evaluated. In addition, the patients were thoroughly questioned for adverse events during all follow-up visits.

Compliance was monitored by study drug counting at each visit during randomized treatment. The observance of the protocol and the accuracy of the documentation were assured by regular, GCP-compliant monitoring visits at the study centers, which were held every 4 to 6 weeks.

The primary outcome measure for treatment efficacy was the change of the I-PSS total score between baseline and the end of the period of observation (week 60). The proportion of responders at the end of randomized treatment was analyzed as well. Responders were defined as patients who had an I-PSS total score ≤ 7 at endpoint, which was interpreted as an only very mild grade of symptoms, and who are not obliged to be

treated anymore. In patients terminating treatment prematurely the last valid value was carried forward starting at baseline. For the I-PSS, only patients with any valid data during randomized treatment were evaluated, since the use of baseline values for missing data imputation was considered anti-conservative in a test for non-inferiority. The primary analysis was based on the full analysis set (FAS) which included all patients who were randomized and received the investigational treatment at least once (intention to treat principle). The treatment groups' I-PSS total score changes versus baseline were compared by means of a two-sided Wilcoxon-Mann-Whitney U-test. The differences in responder rates were tested according to the procedure described by Farrington and Manning [31], using a non-inferiority margin of 10 %. An additional per protocol (PP) analysis was conducted for the primary outcome measure to assess the robustness of the results. All other outcome measures were analyzed descriptively using appropriate statistics and two-sided tests. Safety analyses were based on all patients who took at least one dose of the randomized study medication.

Between May 1999 and November 2000, 149 patients were included in 23 private urological practices and out-patient clinics in Germany. 140 patients were randomized; 71 received PRO 160/120 and 69 tamsulosin. 9 patients were excluded because of revoked informed consent (2 patients), adverse event during placebo run-in (2 patients) and not meeting selection criteria (5 patients). Patient accountability is summarized in Fig. 1 (see p. 226). All decisions regarding the analysis populations were made before code-breaking. All randomized patients took the trial medication at least once and were thus evaluable for efficacy (FAS) and safety. The percentages of patients evaluable per protocol were 78.9 % (56 of 71) for PRO 160/120 and 78.3 % (54 of 69) for tamsulosin.

Table 2: Demographic characteristics and outcome measures at baseline (full analysis set; mean ± SD; two-sided U-test p-value).

	PRO 160/120 (n = 71)	Tamsulosin (n = 69)	p-value
Age (years)	65 ± 8	65 ± 8	0.92
Time since diagnosis of BPH (years)	3.1 ± 3.4	3.6 ± 4.5	0.63
I-PSS total score	20 ± 4	21 ± 4	0.33
Quality of life	4 ± 1	4 ± 1	0.52
Erectile function score (CEDQ) ^{a)}	17 ± 7	18 ± 7	0.69
Uroflowmetry			
Maximum flow (ml/s)	9.6 ± 1.9	9.7 ± 2.2	0.86
Average flow (ml/s) ^{b)}	5.3 ± 2.0	5.4 ± 1.9	0.75
Urinary volume (ml)	224 ± 70	234 ± 77	0.52
Duration of micturition (s)	54 ± 29	51 ± 21	0.82
Duration of flow increase (s) ^{c)}	15 ± 18	14 ± 12	0.61
Ultrasound			
Residual urine (ml)	53 ± 38	55 ± 39	0.99
Prostate volume (cm ³) ^{d)}	38.5 ± 16.6	38.2 ± 18.5	0.77

^{a)} n = 69/67 (PRO 160/120 / tamsulosin). ^{b)} n = 70/68. ^{c)} n = 66/64.

^{d)} n = 55/56.

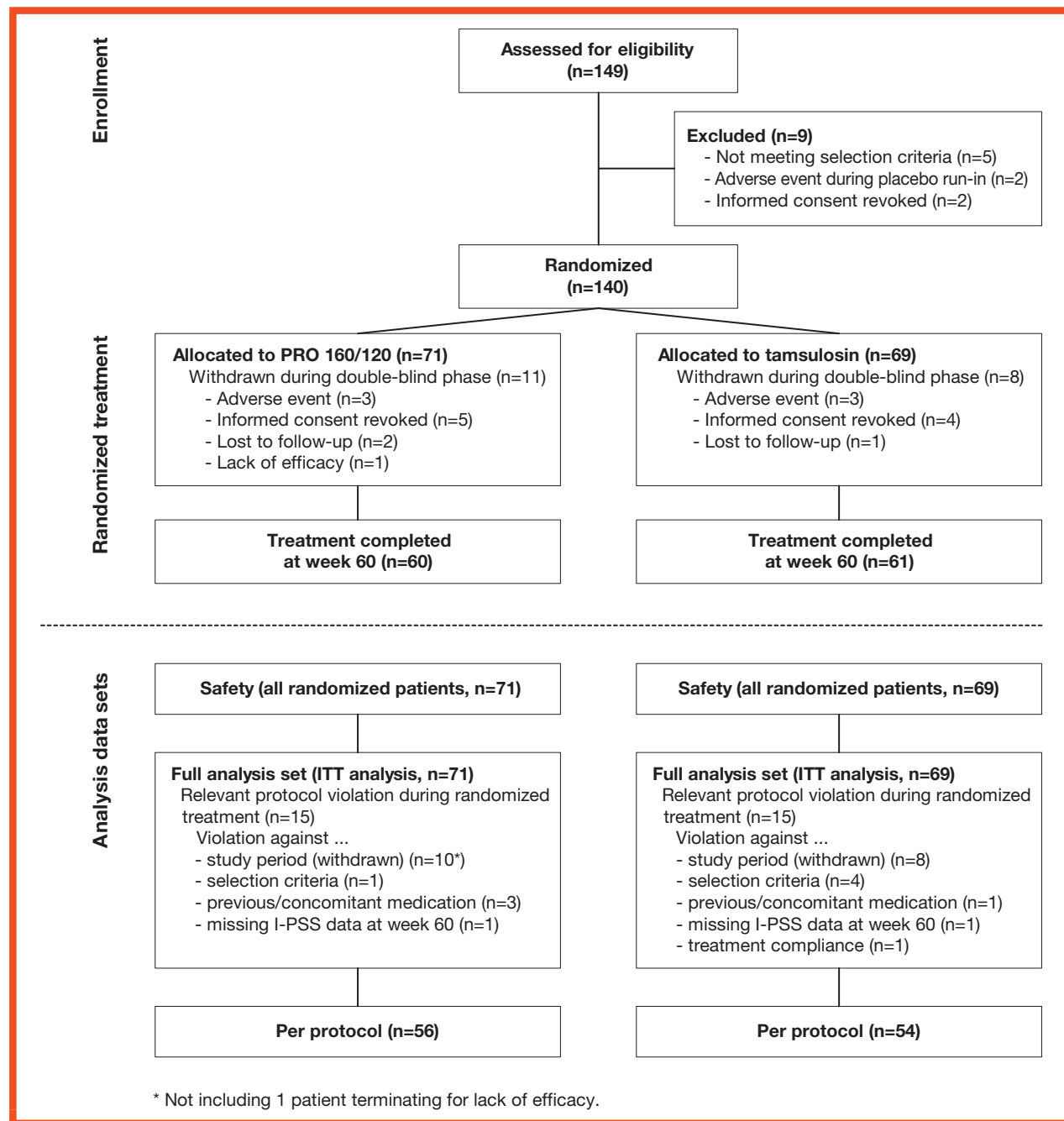


Fig. 1: Disposition of study participants / analysis populations.

Table 2 shows basic demographic data and pre-treatment values of efficacy outcome measures. At baseline the treatment groups were essentially comparable in all measures shown. With baseline I-PSS total scores ≥ 13 points, all study participants suffered from moderate or severe LUTS. According to the medication count, the average treatment compliance was $104\% \pm 17\%$ for PRO 160/120 and $103\% \pm 13\%$ for tamsulosin (mean \pm SD).

3. Results

In the FAS, the I-PSS total score decreased from a median of 20 points in both treatment groups (inter-quartile range [IQR] PRO 160/120 16–23; tamsulosin 18–23) at

baseline (week 0) to medians of 11 (IQR 7–17) and 10 (IQR 7–15) points for PRO 160/120 and tamsulosin, respectively, at week 60 or an earlier individual endpoint (last observation carried forward). Fig. 2 shows a similar time course of LUTS amelioration in both treatment groups. In the FAS the median intraindividual decrease of the I-PSS total score was 9 points in both groups (IQR PRO 160/120 2–12 points; tamsulosin 7–14 points; U-test for difference: $p = 0.25$, two-sided). Median intraindividual improvement in the PP analysis was comparable. In the FAS 32.4% of the patients in the PRO 160/120 group (22 of 68 patients with any efficacy data after day 0) and 27.9% of the patients in the tamsulosin

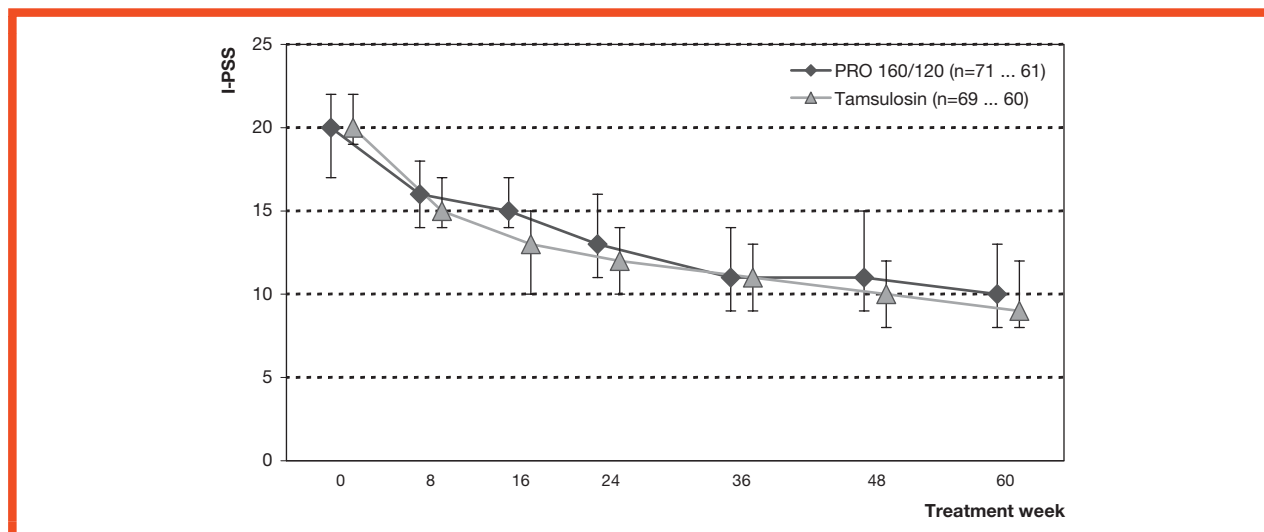


Fig. 2: I-PSS total score – time course during double-blind treatment (full analysis set, no missing data imputation; medians with 95 % confidence intervals).

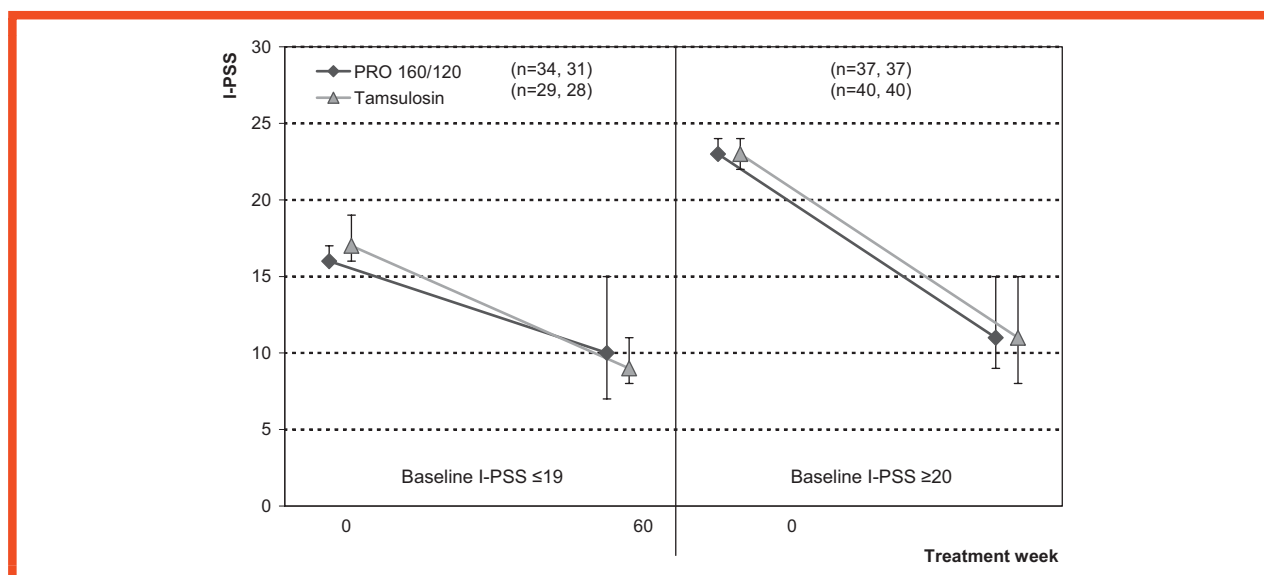


Fig. 3: I-PSS total score – change during double-blind treatment, by baseline I-PSS (full analysis set; medians with 95 % confidence intervals).

group (19 of 68) were responders (i.e. I-PSS \leq 7 at endpoint). Assuming a margin of 10 % for non-inferiority of PRO 160/120, a p-value of 0.034 was determined for the responder rates with the Farrington-Manning test. In the PP analysis the responder rates were 32.1 % (18 of 56) for PRO 160/120 and 29.6 % (18 of 54) for tamsulosin ($p = 0.074$ for non-inferiority).

In a subgroup analysis by baseline I-PSS, PRO 160/120 and tamsulosin were comparably effective in patients with an initial total score \leq 19 points, which means symptoms of moderate severity, as well as in those with a baseline score \geq 20 points, which are defined as patients with severe symptoms (Fig. 3). By the

end of the period of observation, the severely impaired patients in both treatment groups reached average I-PSS endpoint scores that were in a comparable range with those in patients who had suffered from moderate complaints at baseline. At week 60, descriptive Wilcoxon-Mann-Whitney U-tests for the differences between the treatment groups resulted in $p = 0.60$, two-sided, for patients with baseline I-PSS \leq 19 and $p = 0.65$, two-sided, for those with baseline I-PSS \geq 20 points.

In the assessment of LUTS-associated QoL (single item, range 0 [very good] – 6 [very bad]) the patients treated with PRO 160/120 improved by a median of 2

points (IQR 0–3) compared to 1 point (IQR 1–3) for tamsulosin (FAS, baseline versus treatment end). 36 patients in the PRO 160/120 group (50.7 % of 71) and 34 in the tamsulosin group (49.3 % of 69) showed QoL improvement by at least 2 points. With a margin of 13 % for non-inferiority of PRO 160/120, treatment with the herbal drug was significantly not inferior to treatment with tamsulosin ($p = 0.04$; Farrington-Manning test).

From the results of the CEDQ, neither of the investigational treatments had any measurable effect on the patients' sexual functioning. After baseline medians of 17 and 18 points for PRO 160/120 and tamsulosin, respectively, (according to the authors of the scale [30] 17 points are indicative of erectile dysfunction) the median score change until treatment end was 0 for both groups.

As regards the results of uroflowmetry and ultrasound measurement, both treatment groups showed considerable improvements regarding peak and mean urinary flow. Both treatments also decreased the duration of micturition and the amount of residual urine in a comparable manner, but had no systematic effect on urinary volume, flow increase and size of prostate.

During double-blind treatment with PRO 160/120, 15 patients (21.1 % of 71) reported 18 adverse events (AEs), compared to 23 events in 19 patients (27.5 % of 69) in the tamsulosin group. This corresponds to 1 AE in 1514 treatment days in the PRO 160/120 group and to 1 AE in 1164 days in the tamsulosin group. According to double-blind assessment 6 events in the PRO 160/120 group and 9 events in the tamsulosin group were classified to be drug-related.

4. Discussion

During recent years, it has been recognized that a patient's own perception of the frequency and intensity of urinary symptoms and their direct relationship to quality of life may have greater practical importance than changes in a so-called 'objective' but not very reliable measure, which are often hardly recognizable by the suffering patient subjectively. The focus of attention in BPH therapy research has therefore shifted from uroflowmetry and ultrasound assessment to the 'subjective' suffering of the patients from LUTS [32, 33].

For the amelioration of BPH-associated LUTS, this study supports non-inferiority of the Sabal fruit / Urtica root extract PRO 160/120 in comparison to the well investigated and widely used α_1 -adrenoceptor antagonist tamsulosin. Both drugs reduced the subjective symptoms of BPH to a comparable, clinically relevant extent that had a direct, beneficial influence on the patients' quality of life. This applied to patients with initially moderate LUTS as well as to those whose symptoms had been severe at baseline. The fact that patients with different baseline severities of LUTS achieved comparable scores at study exit can be interpreted as a 'floor effect', which could indicate that both drugs reduced

the subjective symptoms to the minimum attainable under the conditions of physiological obstruction caused by BPH. Notably, a larger percentage of patients in the PRO 160/120 group had only minimal symptoms (I-PSS ≤ 7 points) at treatment end. Also considering the results of a previous trial which showed comparability of PRO 160/120 and the 5α -reductase inhibitor finasteride [28, 29], recent research thus puts the efficacy of herbal combination in LUTS therapy into one line with leading synthetic drugs.

For PRO 160/120 the results of the uroflowmetry are consistent with previously published data with the same herbal combination [26] as well as with the improvements reported by Wilt and colleagues in their review of 18 randomized, controlled trials with Sabal fruit extract (as a mono-preparation or in combination with another herbal extract) [23]. In particular, the uroflow improvements observed for the herbal combination in this trial were clearly superior to those observed under placebo treatment in previous trials with a comparable patient population [26]. Although treatment with tamsulosin lead to somewhat larger improvements than PRO 160/120 regarding maximum and average urinary flow, both drugs showed a clinically relevant, beneficial long-term influence on the majority of the urodynamic parameters assessed in this trial, but did not lead to a reduction of prostatic volume.

The study was planned and conducted according to recent guidance [32, 33], used a reliable and internationally validated scale (I-PSS) for measuring LUTS, and included an observation period of more than one year. Some researchers criticized repeatedly that trials with herbal drugs in urology are often compared with reference formulations administered at a subtherapeutic dose [34]. Contrary to that, the reference drug tamsulosin was administered with the recommended, full therapeutic dose of 0.4 mg/d in the present investigation.

With fewer than 1 adverse event in 1000 treatment days over a period of 60 months, the tolerability of both drugs was excellent, albeit with a 30 % advantage regarding AE rates in favor of PRO 160/120.

References

- [1] Simpson, R. J., Fisher, W., Lee, A. J. et al., Benign prostatic hyperplasia in an unselected community-based population: a survey of urinary symptoms, bothersomeness and prostatic enlargement. *Br. J. Urol.* **77**, 186 (1996)
- [2] Berry, S. J., Coffey, D. S., Walsh, P. C. et al., The development of human benign prostatic hyperplasia with age. *J. Urol.* **132**, 474 (1984)
- [3] Isaacs, J. T., Brendler, C. B., Walsh, P. C., Changes in the metabolism of dihydrotestosterone in the hyperplastic human prostate. *J. Clin. Endocrinol. Metab.* **56**, 139 (1983)
- [4] Andersson, K.-E., Lepor, H., Wyllie, M. G., Prostatic α_1 -adrenoceptors and uroselectivity. *Prostate* **30**, 202 (1997)
- [5] Kirby, R., Andersson, K. E., Lepor, H. et al., α_1 -Adrenoceptor selectivity and the treatment of benign prostatic hyper-

plasia and lower urinary tract symptoms. *Prostate Cancer Prostatic Dis.* **3**, 76 (2000)

[6] Schulman, C. C., Cortvriend, J., Jonas, U. et al., Tamsulosin, the first prostate-selective α_{1A} -adrenoceptor antagonist. Analysis of a multinational, multicentre, open-label study assessing the long-term efficacy and safety in patients with benign prostatic obstruction (symptomatic BPH). European Tamsulosin Study Group. *Eur. Urol.* **29**, 145 (1996)

[7] Lee, M., Tamsulosin for the treatment of benign prostatic hypertrophy. *Ann. Pharmacother.* **34**, 188 (2000)

[8] Lyseng-Williamson, K. A., Jarvis, B., Wagstaff, A. J., Tamsulosin. An update of its role in the management of lower urinary tract symptoms. *Drugs* **62**, 135 (2002);

[9] Wilt, T. J., MacDonald, R., Nelson, D., Tamsulosin for treating lower urinary tract symptoms compatible with benign prostatic obstruction: a systematic review of efficacy and adverse effects. *J. Urol.* **167**, 177 (2002)

[10] Wilt, T. J., MacDonald, R., Rutks, I., Tamsulosin for benign prostatic hyperplasia. In: *The Cochrane Library*, Issue 4, 2003. John Wiley & Sons, Chichester, UK (2003)

[11] Narayan, P., Evans, C. P., Moon, T., Long-term safety and efficacy of tamsulosin for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia. *J. Urol.* **170**, 498 (2003)

[12] Barry, M. J., Fowler, F. J., Jr., O'Leary, M. P. et al., The American Urological Association symptom index for benign prostatic hyperplasia. *J. Urol.* **148**, 1549 (1992)

[13] Berges, R. R., Pientka, L., Höfner, K. et al., Male lower urinary tract symptoms and related health care seeking in Germany. *Eur. Urol.* **39**, 682 (2001)

[14] Koch, E., Extracts from fruits of saw palmetto (*Sabal serrulata*) and roots of stinging nettle (*Urtica dioica*): viable alternatives in the medical treatment of benign prostatic hyperplasia and associated lower urinary tracts symptoms. *Planta Med.* **67**, 489 (2001)

[15] Dvorkin, L., Song, K. Y., Herbs for benign prostatic hyperplasia. *Ann. Pharmacother.* **36**, 1443 (2002)

[16] Düker, E. M., Kopanski, L., Schweikert, H.-U., Inhibition of 5- α -reductase activity by extracts from *Sabal serrulata*. *Planta Med.* **55**, 587 (1989)

[17] Casarosa, C., Cosci di Coscio, M., Fratta, M., Lack of effects of a lyosterolic extract of *Serenoa repens* on plasma levels of testosterone, follicle-stimulating hormone, and luteinizing hormone. *Clin. Ther.* **10**, 585 (1988)

[18] Goepel, M., Hecker, U., Kregel, S. et al., Saw palmetto extracts potently and noncompetitively inhibit human α_1 -adrenoceptors in vitro. *Prostate* **38**, 208 (1999)

[19] Hirano, T., Homma, M., Oka, K., Effects of stinging nettle root extracts and their steroidal components on the Na⁺,K⁺-ATPase of the benign prostatic hyperplasia. *Planta Med.* **60**, 30 (1994)

[20] Koch, E., Biber, A., Pharmakologische Wirkungen von Sabal- und Urtikaextrakten als Grundlage für eine rationale medikamentöse Therapie der benignen Prostatahyperplasie. *Urologe B* **34**, 90 (1994)

[21] Lichius, J. J., Lenz, C., Lindemann, P. et al., Antiproliferative effect of a polysaccharide fraction of a 20 % methanolic extract of stinging nettle roots upon epithelial cells of the human prostate (LNCaP). *Pharmazie* **54**, 768 (1999)

[22] Wilt, T. J., Ishani, A., Rutks, I. et al., Phytotherapy for benign prostatic hyperplasia. *Public Health Nutr.* **3** (4A), 459 (2000)

[23] Wilt, T. J., Ishani, A., Stark, G. et al., Saw palmetto extracts for treatment of benign prostatic hyperplasia. A systematic review. *J. Am. Med. Assoc.* **280**, 1604 (1998)

[24] Dathe, G., Schmid, H., Phytotherapie der benignen Prostatahyperplasie (BPH). Doppelblindstudie mit Extractum Radicis urticae (ERU). *Urologe B* **27**, 223 (1987)

[25] Vontobel, H. P., Herzog, R., Rutishauser, G. et al., Results of a double-blind study on the efficacy of ERU capsules in the conservative treatment of benign prostatic hyperplasia [in German]. *Urologe A* **24**, 49 (1985)

[26] Metzker, H., Kieser, M., Hölscher, U., Wirksamkeit eines Sabal-Urtica-Kombinationspräparats bei der Behandlung der benignen Prostatahyperplasie (BPH). *Urologe B* **36**, 292 (1996)

[27] Lopatkin, N., Sivkov, A., Walther, C. et al., Long-term efficacy and safety of a combination of sabal and urtica extract for lower urinary tract symptoms – a placebo-controlled, double-blind, multicenter trial. *World J. Urol.* **23**, 139 (2005)

[28] Sökeland, J., Albrecht, J., Combined Sabal and Urtica extract vs finasteride in BPH (Alken stage I–II) [in German]. *Urologe A* **36**, 327 (1997)

[29] Sökeland, J., Combined sabal and urtica extract compared with finasteride in men with benign prostatic hyperplasia: analysis of prostate volume and therapeutic outcome. *Br. J. Urol. Int.* **86**, 439 (2000)

[30] Braun, M., Klotz, T., Reifenrath, B. et al., "KEED" - erster deutschsprachig validierter Fragebogen zur Erfassung der männlichen sexuellen Funktion. *Akt. Urol.* **29**, 300 (1998)

[31] Farrington, C. P., Manning, G., Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. *Stat. Med.* **9**, 1447 (1990)

[32] Denis, L., Mc Connell, J., Yoshida, O. et al., 4th International Consultation on BPH. Recommendations of the International Scientific Committee: The evaluation and treatment of lower urinary tract symptoms (LUTS) suggestive of benign prostatic obstruction. In: Denis, L., Griffiths, K., Khoury, S. et al., 4th International Consultation on Benign Prostatic Hyperplasia (BPH), Proceedings 4, 669–683. Plymbridge Distributors, Plymouth (1998)

[33] Roehrborn, C. G., Abbou, C. C., Akaza, H. et al., Clinical research criteria for studies of: lower urinary tract symptoms (LUTS), enlarged prostate gland (EPG), bladder outlet obstruction (BOO) and benign prostatic hyperplasia (BPH). In: Chatelain, C., Denis, L., Foo, K. T. et al., 5th International Consultation on Benign Prostatic Hyperplasia (BPH), 317–395. Plymbridge Distributors, Plymouth (2001)

[34] Lowe, F. C., Fagelman, E., Phytotherapy in the treatment of benign prostatic hyperplasia. *Curr. Opin. Urol.* **12**, 15 (2002)