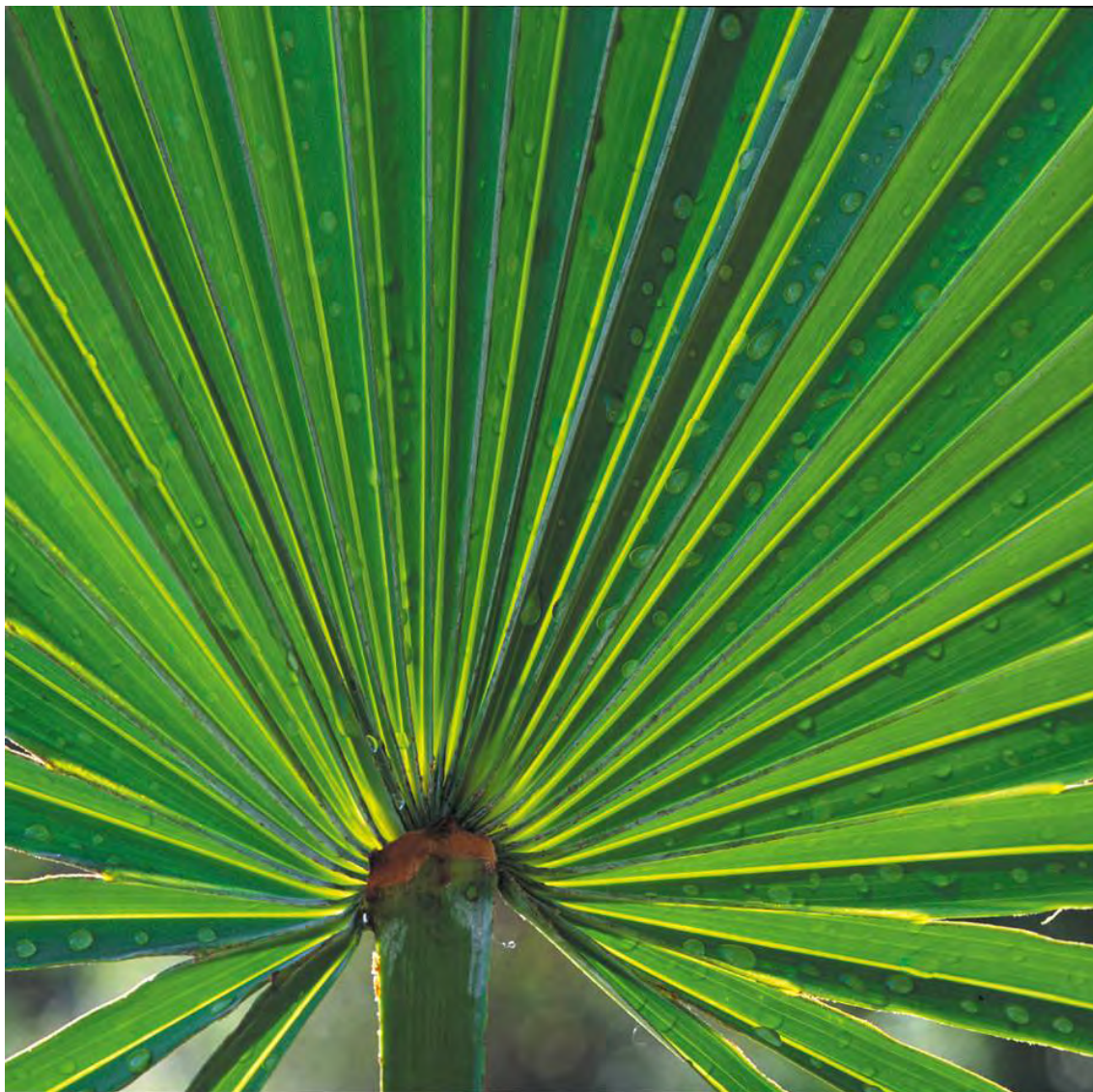




# Saw palmetto

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# Study Summary

## What can we learn from this study?

- An enlarged prostate does not only give rise to urinary symptoms (poor urine stream, frequency of urination and dribbling)
- Sexual symptoms such as difficulty obtaining an erection and loss of libido are also frequently seen in men with an enlarged prostate
- This study is the first to show that Saw palmetto not only helps with urinary symptoms, but also symptoms of sexual dysfunction associated with an enlarged prostate

## Background

The enlarged prostate (benign prostatic hyperplasia, BPH) is a very common problem in the older man. It is estimated that 50% of men over the age of 50 and nearly all men at the age of 80 suffer from an enlarged prostate to a greater or lesser extent. <sup>(1)</sup>

Sexual problems can also be seen in the older man. Causes include poor arterial blood flow, underlying illnesses such as diabetes and prescribed medication. However, what is now known is that the most common cause of sexual dysfunction in this age group is the presence of an enlarged prostate. For instance, men are nearly 4 times more likely to develop erection problems 2 years after first noticing symptoms of an enlarged prostate. <sup>(2)</sup>

In addition to this, it is well known that medicines which may be prescribed for BPH can give rise to sexual dysfunction as side effects – 38% of men using 5-alpha-reductase inhibitors (eg. finasteride) experience erectile dysfunction and up to 30% of long-term users of alpha-blockers (eg. tamsulosin) complain of retrograde ejaculation. <sup>(3,4)</sup>

These side effects cause many men with BPH to stop using prescribed medication and use alternatives such as Saw palmetto.

## Study objective

To assess whether or not Saw palmetto can improve the sexual symptoms and urinary symptoms of men suffering from BPH.

## Study design

This was an open pilot study conducted to GCP (Good Clinical Practice) guidelines. A total of 69 men, average age 57 years, were recruited into the trial. They complained of urinary symptoms of BPH as well as having symptoms indicating sexual dysfunction, for more than 2 months.

The men were treated using a Saw palmetto extract (320mg lipophilic acids) for 8 weeks and symptoms were assessed using:

- International Prostate Symptoms Score (IPSS) to measure their BPH symptoms
- Brief Sexual Function inventory (bSFI)
- Urolife BPH Quality of Life (QoL) questionnaire

## Results

During the 8 week period, the IPSS reduced by 51% - from 14.4 to 6.9. This level of improvement is consistent with previously published research on Saw palmetto.

Sexual function also improved, with the men's ability to achieve and maintain an erection improving by 64% and a 54% improvement in drive. The bSFI improved by 40% (from 22.4 to 31.4) and the Urolife QoL-9 total score improved by 55% (from 162.7 to 105.0 – lower scores are better).

This is a pilot study and it is clear that more research is needed. However, it is also clear from the results that Saw palmetto can help, not only with the urinary symptoms of BPH, but in the symptoms of sexual dysfunction seen in BPH.

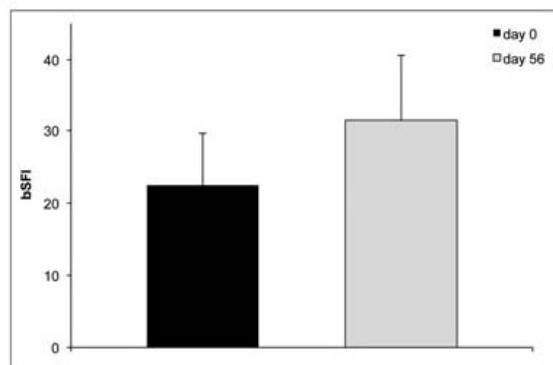


Figure 2. Improvement of brief Sexual Function Inventory (bSFI) at the start and the end of therapy (per protocol population,  $n = 69$ ;  $p < 0.0001$ ).

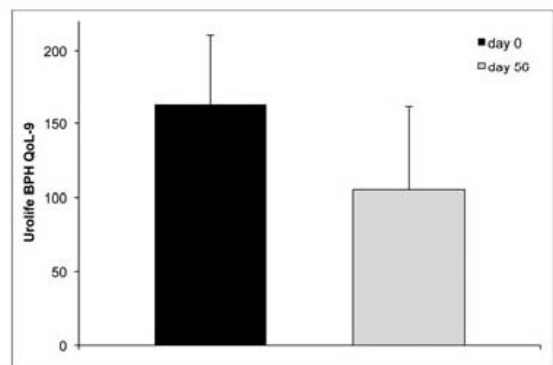


Figure 3. Improvement of the Urolife benign prostatic hyperplasia (BPH) quality of life-9 (QoL-9) total score between the start and the end of therapy (per protocol population,  $n = 69$ ;  $p < 0.0001$ ).

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# Improving BPH symptoms and sexual dysfunctions with a saw palmetto preparation? Results from a pilot trial

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**In elderly men, benign prostatic hyperplasia (BPH) is a major risk factor for sexual dysfunctions (SDys). Additionally, the standard treatments for BPH symptoms, alpha blockers and 5-alpha-reductase inhibitors, cause SDys themselves. Preparations from saw palmetto berries are an efficacious and well-tolerated symptomatic treatment for mild to moderate BPH and have traditionally been used to treat SDys. We conducted an open multicentric clinical pilot trial to investigate whether the saw palmetto berry preparation Prostan® influenced BPH symptoms and SDys. Eighty-two patients participated in the 8-week trial, taking one capsule of 320 mg saw palmetto extract daily. At the end of the treatment, the International Prostate Symptom Score was reduced from  $14.4 \pm 4.7$  to  $6.9 \pm 5.2$  ( $p < 0.0001$ ); SDys measured with the brief Sexual Function Inventory improved from  $22.4 \pm 7.2$  to  $31.4 \pm 9.2$  ( $p < 0.0001$ ), and the Urolife BPH QoL-9 total improved from  $162.7 \pm 47.9$  to  $105.0 \pm 56.3$  ( $p < 0.0001$ ). Investigators' and patients' assessments confirmed the good efficacy, and treatment was very well tolerated and accepted by the patients. Correlation analyses confirmed the relationship between improved BPH symptoms and reduced SDys. This was the first trial with saw palmetto to show improvement in BPH symptoms and SDys as well. Copyright © 2012 John Wiley & Sons, Ltd.**

*Keywords:* benign prostatic hyperplasia; sexual dysfunctions; clinical trial; saw palmetto; *Serenoa repens*.

## INTRODUCTION

The prostate is a fibromuscular glandular organ that lies between the urinary bladder and the pelvic floor and surrounds the prostatic urethra (Dixon, 2005). Starting around the age of 40, the prostatic tissue enclosing the urethra starts growing; this nonmalignant growth is known as benign prostatic hyperplasia (BPH) (Isaacs and Coffey, 1989). It leads to constriction of the urethra and gives rise to associated lower urinary tract symptoms (LUTS), such as urgency, frequency, nocturia, incomplete bladder emptying and weak urine stream. LUTS occur in about one third of all men in their 60s and half of men older than 80 (McVary, 2006), even though the histological presence of BPH is observed in more than 90% of men in this age group (Berry *et al.*, 1984).

In addition to obstructive and irritative symptoms, BPH also negatively influences sexual functions (Gur *et al.*, 2008). Epidemiological studies show that, along with the general ageing process, BPH-related LUTS are a key factor in development of erectile dysfunctions and ejaculatory disorders (Braun *et al.*, 2003; Boyle *et al.*, 2004), representing a stronger risk factor than diabetes, hypertension, heart disease or hyperlipidemia (Rosen *et al.*, 2003). Overall, there appears to be a clear

and clinically significant association between LUTS and various types of sexual dysfunctions in ageing men worldwide. From epidemiological data, Rosen *et al.* (2005) concluded that, compared with patients without BPH-symptoms, patients with BPH-symptoms were at a 3.7-fold higher risk of developing erectile dysfunction during the 2-year period following the onset of BPH-symptoms. Additionally, the severity of the LUTS symptoms was correlated with more frequent and more severe occurrence of erectile and ejaculatory dysfunctions (Rosen *et al.*, 2005).

The main medical treatments for BPH symptoms include alpha blockers such as tamsulosin, doxazosin and alfuzosin (Novara *et al.*, 2006) that provide fast relief of the LUTS symptoms (Kaplan, 2004) or the 5-alpha-reductase-inhibitors finasteride and dutasteride, which lead to symptom relief after 6–9 months and are most favourable in patients with large prostates (Dull *et al.*, 2002). Both treatment options show beneficial effects on the BPH symptoms; however, they also each have a significant negative impact on sexual functions.

The main sexual dysfunction reported under alpha blocker therapy is retrograde or abnormal ejaculation, which occurs in 4–18% of patients taking tamsulosin, with rise to 30% during long-term use (Carbone and Hodges, 2003). Studies on 5-alpha-reductase inhibitors report sexual dysfunctions with a frequency of 2.1–38%, with erectile dysfunctions being most prominent, followed by decreased libido and ejaculatory disorders (Erdemir *et al.*, 2008). Sexual dysfunctions are the most often reported adverse events under 5-alpha-reductase-

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inhibition, with similar frequencies reported for finasteride and dutasteride (Naslund and Miner, 2007).

Preparations made from the berries of saw palmetto *Serenoa repens* (W. Bartram) Small (synonym *Sabal serrulata* (Michx.) Schult.f.) have a long standing use in the treatment of mild to moderate BPH symptoms. The plant, which is indigenous to Florida, was first used by white settlers in the United States not only for treatment of LUTS but, interestingly, also as a treatment for erectile dysfunctions, to improve testicular atrophy and sperm production, and as a genitourinary and sexual stimulant (Bennett and Hicklin, 1998). More than 30 controlled clinical trials have been conducted to investigate BPH treatment with saw palmetto preparations, which generally consist of 320 mg lipophilic berry extract per day (Ulbricht *et al.*, 2006). Compared with placebo, the studies demonstrate good efficacy of long-term saw palmetto use to treat BPH symptoms; the results are similar to finasteride (Carraro *et al.*, 1996) and tamsulosin (Debruyne *et al.*, 2004), but saw palmetto has a much better safety profile than these substances particularly in regards to sexual dysfunctions (Wilt *et al.*, 2002). As modes of action, *in vitro* and *in vivo* inhibition of both isoforms of the 5-alpha-reductase (Habib *et al.*, 2005; Abe *et al.*, 2009) and anti-inflammatory activities (Breu *et al.*, 1992; Iglesias-Gato *et al.*, 2011) have been reported, as well as inhibition of autonomous receptors in the lower urinary tract (Suzuki *et al.*, 2007).

It is very desirable to find a treatment that not only improves the symptoms of BPH but also has no negative or possibly even a beneficial impact on sexual dysfunctions (Skolarus and Wei, 2009). With this as a goal, we carried out a clinical pilot trial investigating whether a standardized saw palmetto product influenced sexual dysfunctions in patients with mild to moderate BPH.

## PATIENTS AND METHODS

### Patients

The study was carried out between June 2009 and October 2010 in two urological and four general practices in Switzerland, in patients with at least moderate BPH symptoms and sexual dysfunctions, such as erectile dysfunctions or lack of drive. The trial was approved by the relevant cantonal ethical committees and was carried out in accordance with the provisions of good clinical practice and the ethical obligations of the Declaration of Helsinki. The Swiss regulatory authority Swissmedic notified the study that is registered in the international clinical trial registry ClinicalTrials.gov, identifier number NCT01021267.

Inclusion criteria were as follows: male patients between 18–80 years of age with International Prostate Symptom Score (IPSS) >7, presence of BPH symptoms for at least 2 months, patients suffering from sexual dysfunction (erectile dysfunction and/or decrease of libido) for at least 2 months, sexual drive component of the brief Sexual Function Inventory (bSFI) <5, desire and possibility of sexual activity (masturbation, sexual partnership), no organic impairment preventing sexual practice (physical or vascular impairment, etc.),

willingness to honestly answer questions on sexuality and written informed consent given by the patient.

Exclusion criteria included lack of libido because of a psychiatric disease or a depressive mood, occurrence of lack of libido in the judgement of the investigator within the last 2 months, patients with severe vascular disorders (microangiopathies), severe diabetes mellitus, patients with hypertension who were on a stable antihypertensive medication for less than 2 months, known neuropathies, known poor compliance of the patient, participation in a clinical trial within the last 2 months prior to the study start, alcohol and drug abuse and planned surgeries within the observation period. The participants were prohibited from regular application (>1 unit/2 weeks) of phosphodiesterase-5-phosphodiesterase-5-inhibitors (PDE) inhibitors and intake of PDE-5-inhibitors less than 4 days prior to the first study visit. If not taken continuously for 3 months as stable medication, the following concomitant medications were also not allowed: 5-alpha-reductase inhibitors, alpha-antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs) (synthetics and phytochemicals), paracetamol and synthetic antidepressive agents.

### Test medication and study conduct

This was an open clinical trial with total study duration of 9 weeks per patient, which consisted of a 1-week untreated run-in phase and a subsequent treatment period of 8 weeks. At each visit, efficacy parameters were recorded as detailed in the succeeding text. The run-in phase was carried out to observe if BPH symptoms and sexual dysfunctions remained stable. The test medication was a lipophilic saw palmetto berry extract with a daily dosage of one capsule, containing 320 mg extract (Prostasan<sup>®</sup>, batch nr. 025070, drug extractant ratio 9–12:1, extractant ethanol 96% V/V; manufactured by A. Vogel Bioforce AG, Roggwil, Switzerland. The berries are from A. Vogel Bioforce's own organic certified cultivation in Florida, USA.) The extract complied with the provisions of the European Pharmacopoeia for saw palmetto fruit. One capsule of this batch contained 275 mg fatty acids, which comprised of 29.5% lauric acid, 39.2% oleic and linoleic acid, 13.5% myristic acid and 10% palmitic acid.

At the second visit, each patient received one bottle with 90 capsules and compliance was checked by counting the remaining tablets at the final study visit.

Changes in BPH symptoms were evaluated using the IPSS, sexual dysfunctions with the bSFI and the Urolife BPH Quality of Life-9 (Urolife QoL-9) questionnaire. The bSFI is a validated instrument with two questions about sexual drive, three on erections, two on ejaculation, four on problem assessment and one question on the overall satisfaction. Each question is rated on a corresponding scale from 0 (most severe problem) to 4 (no problem) (O'Leary *et al.*, 1995). The Urolife QoL-9 questionnaire is also a validated score with one question each on desire, erection and satisfaction; each is rated on a 100 mm visual analogue scale, ranging from 0 (most severe problem) to 100 (no problem at all) (Lukacs *et al.*, 1997). Two questionnaires were used instead of only one to achieve a better validity of changes in sexual dysfunctions. No validated German version was available for either questionnaire, and thus they were first translated to German by two independent translators.

From these two translated versions, one German version was compiled, which was then re-translated to English by two other translators, to be compared with the original version. The German version was then corrected and used by a German speaking doctor in his daily practice. Based on his experiences, further corrections were made, and final versions of the German scores were completed. At end of the treatment, global assessment of efficacy by the patient and the investigator was given on a 4-point scale (very good, good, moderate or bad). Safety parameters included the occurrence of adverse events and the global assessment of safety by the patient and the investigator at the end of the treatment as very good, good, moderate or poor. Additionally, questions were asked about the patients' daily routines. The patients were asked if they would take the medication again, how important it was for them to use herbal treatment, and whether they would prefer a herbal remedy over a synthetic compound. Investigators were asked if they would use the test medication again and were asked to provide reasons if they answered affirmatively.

### Statistical analysis

As this was an open clinical pilot trial, descriptive statistics were used using Excel (Microsoft Corporation, Redmond, Washington, USA) and SAS Version 9.2 (SAS Institute, Enhanced Logging Facilities, Cary, NC, USA). For the outcome measures, IPSS, bSFI and Urolife QoL, within group comparisons of changes from visit 1 to visit 2, from visit 1 to visit 3, and from visit 2 to visit 3, were performed using the Wilcoxon test for paired differences. Correlations between changes in IPSS and bSFI, IPSS and Urolife QoL-9, and bSFI and Urolife QoL-9 were analysed by calculating Pearson's coefficient of correlation.

## RESULTS

### Patients

A total of 82 patients were recruited, forming the intention-to-treat population. Thirteen patients had at least one major protocol deviation and were excluded from the per protocol population, which was used for final analysis. Deviations included one patient with IPSS <7 at inclusion, one with sexual drive component of bSFI >5 at inclusion, four patients with disallowed concomitant medication and seven patients who did not return to the participating practice after the first visit. Reasons for discontinuation of treatment included one instance of the death of a patient's wife, two adverse events (nausea that was seen as related to the study medication and an unrelated transient ischemic attack) and in four cases the patients did not show up at all to the follow-up visits. The patients were  $57.3 \pm 11.1$  years old and baseline characteristics as well as the age distribution in the population were without pathological findings. Details are shown in Table 1.

One centre recruited the majority of the patients ( $n=54$ ), and the other five centres the remaining 15 patients. The baseline characteristics of the patients from this one centre did not differ significantly from those that form the other centres. Compliance

**Table 1. Demographic baseline characteristics of the per protocol population at inclusion ( $n = 69$ )**

Number of patients	69
Age (mean $\pm$ SD)	$57.3 \pm 11.1$ years
Age (median)	60.0 years
Body weight (mean $\pm$ SD)	$80.3 \pm 13.0$ kg
Systolic blood pressure (mean $\pm$ SD)	$132.5 \pm 14.8$ mmHg
Diastolic blood pressure (mean $\pm$ SD)	$84.3 \pm 8.3$ mmHg
Heart rate (mean $\pm$ SD)	$71.4 \pm 11.2$ bpm
Age distribution ( <i>N</i> )	
Age 31–40 years	5 (7.2%)
Age 41–50 years	16 (23.2%)
Age 51–60 years	19 (27.5%)
Age 61–70 years	22 (31.9%)
Age 71–80 years	7 (10.1%)

during the treatment period was assessed as good when 80–120% of the test medication was taken; 78.6% of the patients fulfilled this criterion, only 7.1% of the patients took less than 80% of the medication.

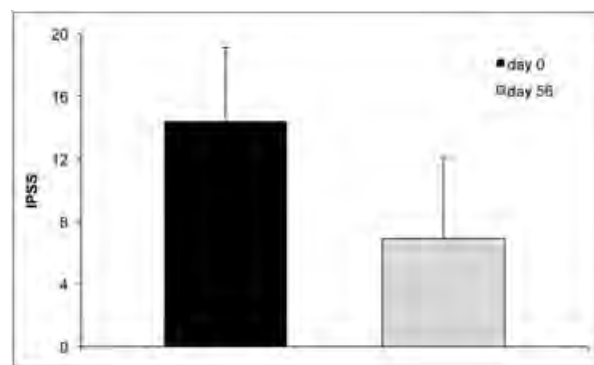
### Efficacy

There were no significant differences between the intention to treat population and the per protocol population in all parameters; therefore, the results of per protocol population will be shown. There were also no statistical changes in the efficacy parameters during the time period without treatment (between visit 1 and visit 2), showing that the symptoms were stable and did not alter within a short time frame; thus, only results from visit 2 (the start of treatment) and visit 3 (the end of treatment) will be presented.

### International prostate symptom score

The IPSS was reduced by 51%, from  $14.4 \pm 4.7$  to  $6.9 \pm 5.2$ , after 8 weeks of treatment ( $p < 0.0001$ ) (Fig. 1).

A score from 0 to 7 is defined as mild, from 8 to 19 as moderate and from 20 to 35 as severe BPH symptoms. At the beginning of the treatment, 18.8% of all patients had severe and 78.3% had moderate symptoms; by the final visit, this shifted to 63.8% patients with mild, 31.9% with moderate, and only 4.3% with severe symptoms. Looking at the single items contributing to the score, they were all significantly improved to the same extent,



**Figure 1.** Change of International Prostate Symptom Score (IPSS) between the start and the end of treatment (per protocol population,  $n = 69$ ;  $p < 0.0001$ ).

and none was superior to another. The average nycturia score changed from  $1.7 \pm 1.1$  to  $1.0 \pm 0.8$ , the obstructive subscore from  $8.1 \pm 3.9$  to  $3.7 \pm 3.7$ , and the irritative subscore from  $6.3 \pm 2.6$  to  $3.2 \pm 2.3$ .

### Brief sexual function inventory

The total bSFI score improved from  $22.4 \pm 7.2$  to  $31.4 \pm 9.2$  ( $p < 0.0001$ ) (Fig. 2). The single item scores for sexual drive, erectile function, ejaculatory function, problem assessment and sexual satisfaction were each also significantly improved ( $p < 0.0001$ ) (Table 2). The biggest relative improvements in single questions were seen in the problem assessment domain, where 'getting and keeping an erection' improved by 64%, and 'having problems with lack of drive' and 'ejaculation' each improved by 54%. 'Feeling sexual drive within the last 30 days' improved by 47%, and 'having an erection firm enough to have sexual intercourse' was scored as 42% better, which, in absolute values, is a change from below 'fairly often' to 'usually'.

There was a centre effect, as mean values of the centre with the most patients exhibited a significant improvement, whereas the other 15 patients pooled together from the other centres only exhibited a trend ( $p = 0.12$ ). Of these 15 patients, eight saw an improvement, four no change and three a worsening of their state, whereas the vast majority of the patients from

the single centre experienced at least some improvement of their sexual dysfunctions.

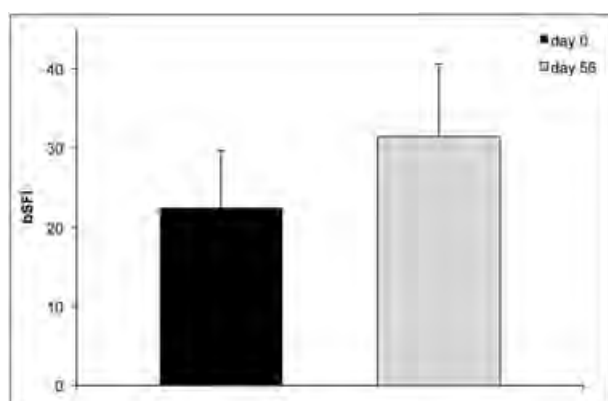
### Urolife BPH QoL-9

The Urolife QoL-9 total score saw an improvement from  $162.7 \pm 47.9$  to  $105.0 \pm 56.3$  ( $p < 0.0001$ ) (Fig. 3). Contrary to the bSFI, the improvements in QoL-9 were significant at all centres. All three single questions were also statistically significantly improved, as detailed in Table 2. (Fig. 4)

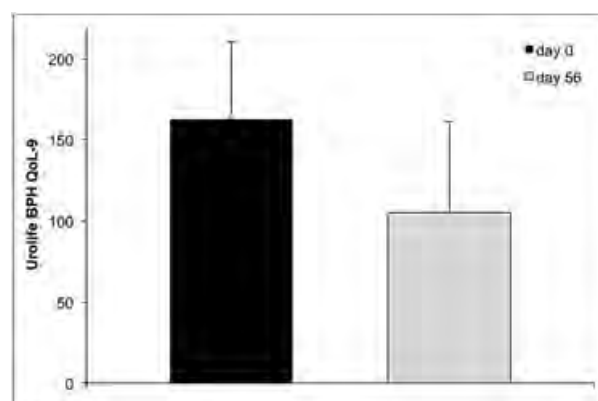
### Assessments by investigators and patients

The majority of the patients rated the efficacy as very good (22%) or good (54%) and only 15% saw a small effect. The investigators assessed efficacy more favourably, reporting 38% of the cases as being very good, 44% good and only 7% patients with unchanged condition. When asked on what parameters the study medication had the best effect, 8% of the patients indicated erectile function, 26% libido and 66% erectile function and libido together.

Of the total 82 patients, 62 patients would take the capsules again (data are missing from six patients); and in 91% of all cases, the investigators would use the medication again.



**Figure 2.** Improvement of brief Sexual Function Inventory (bSFI) at the start and the end of therapy (per protocol population,  $n = 69$ ;  $p < 0.0001$ ).



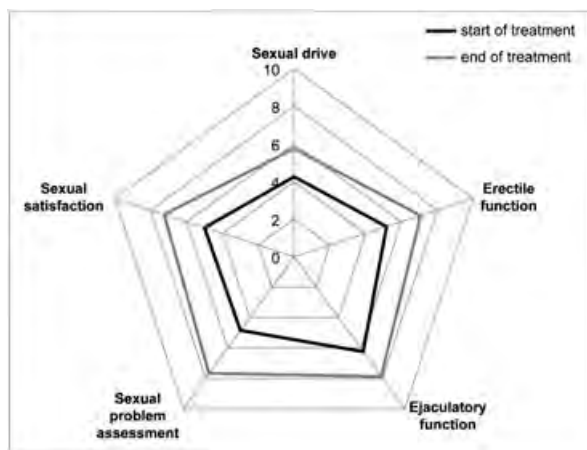
**Figure 3.** Improvement of the Urolife benign prostate hyperplasia (BPH) quality of life-9 (QoL-9) total score between the start and the end of therapy (per protocol population,  $n = 69$ ;  $p < 0.0001$ ).

**Table 2.** Single item scores of the bSFI and Urolife BPH QoL

Score item with range (min–max)	Start of treatment		<i>p</i> -value*
	day 0	day 56	
<b>bSFI</b>			
Sexual drive (0–8)	$3.4 \pm 1.1$	$4.6 \pm 1.4$	$< 0.0001$
Erectile function (0–12)	$6.2 \pm 3.0$	$8.5 \pm 3.5$	$< 0.0001$
Ejaculatory function (0–8)	$5.0 \pm 2.0$	$6.3 \pm 2.4$	$< 0.0001$
Sexual problem assessment (0–12)	$5.8 \pm 2.4$	$9.2 \pm 3.0$	$< 0.0001$
Sexual satisfaction (0–4)	$2.0 \pm 0.8$	$2.9 \pm 0.9$	$< 0.0001$
<b>Urolife BPH QoL-9</b>			
Sexual drive (0–100)	$51.3 \pm 20.6$	$33.9 \pm 20.0$	$< 0.0001$
Erections (0–100)	$55.0 \pm 21.0$	$34.8 \pm 24.2$	$< 0.0001$
Sexual satisfaction (0–100)	$56.4 \pm 19.7$	$36.3 \pm 22.4$	$< 0.0001$

BPH, benign prostate hyperplasia; bSFI, brief sexual function inventory.

\*Wilcoxon signed rank test.



**Figure 4.** Single item scores of the brief Sexual Function Inventory (bSFI) at the start and the end of treatment, normalized to a scale of 0–10 (0 = worst state, 10 = best) ( $n = 69$ ).

For 61% of the patients, it was very important that the medication was of herbal origin and 97% of them would, given the same efficacy and safety, prefer herbal to a synthetic drug. Investigators stated that the most important reason to apply this saw palmetto preparation was the good safety observed in 95% of all cases, followed by the efficacy observed in 93% of patients.

### Correlation analysis

We carried out correlation analyses to assess if changes in IPSS, bSFI and Urolife QoL-9 were associated. There was a negative correlation between changes in the IPSS score and the bSFI (Pearson's  $\rho = -0.366$ ;  $p = 0.002$ ) and a positive correlation between changes in the IPSS and the Urolife QoL-9 (Pearson's  $\rho = 0.365$ ;  $p = 0.002$ ), indicating that less urinary problems were associated with better assessment of sexual function. Furthermore, there was a high negative correlation between the bSFI and Urolife QoL-9, showing that both questionnaires were valid for evaluating sexual dysfunctions and consequently assessed changes to the same degree (Pearson's  $\rho = -0.607$ ;  $p < 0.0001$ ).

Subgroup analyses confirmed these findings, showing that patients with a higher IPSS at inclusion (IPSS 20–35) exhibited better improvements in their bSFI ( $p = 0.029$ ) and in their Urolife QoL-9 ( $p = 0.032$ ) values than did patients with lower IPSS (8–19). Comparing younger patients (21–50 years) to older patients (51–80 years) did not show a significant difference regarding changes of IPSS, bSFI and Urolife QoL-9, or did concomitant medication have an influence on these parameters.

### Safety

Five patients reported six adverse events, including nausea, eructation and acid regurgitation, all of which were mild in nature and seen as related to the study medication, and two incidents of a transient ischemic attack in the same patient and a mild pruritus, which were not related to the study medication. From the total 82 patients, data from six patients were missing on the safety assessment; from the remaining patients, 89.5% rated tolerability as very good and 6.6% as good.

Similarly, investigators regarded tolerability in 90.8% of the cases as very good and 5.3% as good.

## DISCUSSION

In this pilot trial, we wanted to assess if a saw palmetto berry preparation had an influence on both, prostate symptoms and sexual dysfunctions. We first examined the improvement in BPH symptoms as measured with the IPSS, which is the standard instrument to measure severity of BPH symptoms (Simpson, 1997). We observed a greater than 50% reduction, indicating a good treatment response that was in the efficacy range observed for saw palmetto treatments in other trials on BPH and larger than the effect of placebo. A survey of seven clinical trials for a lipophilic saw palmetto preparation describes the observation of a total of 2555 patients that were observed with average treatment duration of 300 days and a mean initial IPSS value of 14.72. At the end of the treatment, IPSS was reduced on average by 31.2% (Boyle *et al.*, 2004). In two other clinical trials, 320 mg lipophilic saw palmetto berry extract was used daily and, after 6 months, the IPSS was reduced by 26.3% (Gerber *et al.*, 2001) and 37% (Bauer *et al.*, 1999) with respective reductions under placebo of 13.9% and 13.6%.

Secondly and more importantly, we assessed whether the treatment had a positive influence on concomitant sexual dysfunctions. Four previous clinical trials of saw palmetto treatment for BPH also evaluated changes in sexual dysfunctions as a secondary parameter, with mixed results. However, the patients in these trials had mainly BPH symptoms, not necessarily sexual dysfunctions (SDys) as well. Using the International Index of Erectile Function (IIEF), Willetts *et al.* (2003) observed a trend of improvement, with an increase from 51.5 to 55.1 after 12 weeks of saw palmetto treatment compared with a small decrease from 49.4 to 48.7 with placebo (Willetts *et al.*, 2003), and Sinescu *et al.* (2011) reported a significant improvement of the IIEF from 44.4 to 50.8 after 24 months of treatment (Sinescu *et al.*, 2011). In the trial conducted by Gerber *et al.* (2001), the patients had to fill out a non-specified 'sexual function questionnaire'; results indicated no change with either placebo or saw palmetto treatment (Gerber *et al.*, 2001). In an open trial, Bauer *et al.* (1999) asked if the treatment had an influence on patients 'sexual activity'; responses indicated that it mostly remained unchanged with two patients reporting an increase (Bauer *et al.*, 1999). Taken together, data from these trials are insufficient to convincingly show that saw palmetto had a positive influence on BPH-related SDys.

To determine this, it was important to confirm at inclusion that the patients in our trial definitely suffered from SDys; all the patients in our trial had obvious SDys, based on comparisons of the initial values from the bSFI and the Urolife QoL-9 in our trial with epidemiological. O'Leary *et al.* (2003) observed an average total bSFI score of 27.7 in a population of 1883, >50-year-old men in the United States (O'Leary *et al.*, 2003), whereas in our study the same age group had a lower initial value of 20.1. In another study, the patients with ages of  $36.9 \pm 12.0$  years displayed an average total bSFI of  $33.5 \pm 2.2$  (Collins *et al.*, 2002)



compared with the total initial bSFI of  $26.3 \pm 6.6$  observed in our 21–50-year-old patients. A large study of 2829 LUTS patients with an average age of 65.9 years evaluated Urolife QoL-9 scores and found an initial total value of  $8.8 \pm 0.1$  (scale 0–30) (Lukacs *et al.*, 2000), whereas in our study an initial score of  $170.3 \pm 47.0$  (scale 0–300) was recorded for the 51–80 year patient group.

Saw palmetto showed a significant treatment success regarding improvement of SDys in this study population. Both scores for SDys changed significantly, the bSFI by 40.2% and the Urolife QoL-9 by 35.5%. Looking at the subscores, ‘sexual drive’ and ‘erectile function’, almost the same degree of improvement was seen for both scores, with 35.3% and 37% in the bSFI and 33.9% and 36.7% in the Urolife QoL-9, respectively. The major difference between these two scores is caused by the more weighted problem assessment domain of the bSFI. It has been shown that both questionnaires are equally sensitive in assessing sexual dysfunctions, which was also substantiated by the correlation analysis. Interestingly, we observed that it was almost impossible for patients to fill out the bSFI without doctor’s help, whereas the Urolife QoL-9 was quite easy for patients to fill out alone. In summary, we have shown for the first time that a saw palmetto intervention in patients with BPH and SDys had a beneficial influence on both BPH symptoms and on SDys.

Our efficacy results are of further importance when considering the other available options for simultaneous treatment of LUTS and SDys. It is currently debated whether alpha blockers or PDE inhibitors may be beneficial for treating symptoms of both disorders. Experimental models have shown that  $\alpha 1$ -adrenergic agents may improve erectile dysfunctions by influencing the balance between contraction and relaxation of the corpus cavernosum smooth muscle, of which, relaxation leads to an erection (Hellstrom and Kendirci, 2006). On the other hand, experimental data also indicates that NO synthase and NO could play important roles in tissue from the urethra, corpus cavernosum, prostate, vas deferens and bladder neck (Ehren *et al.*, 1994). Reduced concentrations of NOS/NO in the prostate and bladder increase smooth muscle tone and may improve prostatic cell proliferation (Mirone *et al.*, 2011), indicating that PDE-5-inhibitors, which increase the NO concentration, may have positive effects on LUTS.

Initial clinical trials have been carried out with alpha blockers or PDE-5-inhibitors (Kaminetsky, 2006). Clinical data with alpha blockers, however, has shown a good treatment effect on BPH symptoms but only a small positive influence on SDys. In a clinical trial where patients with moderate to severe BPH symptoms took 10 mg alfuzosin for 6 months, the IPSS decreased from 18.93 to 9.59 points, and the Male Sexual Health Questionnaire (MSHQ) ejaculation subscore improved from 23.09 to 21.54; this was statistically significant, but the clinical relevance remains doubtful with an improvement only of about 7%. The overall number of patients with moderate to severe erectile dysfunctions decreased from 35% to 22% (Leungwattanakij *et al.*, 2010). These results were not confirmed in another trial where patients with BPH symptoms took 10 mg alfuzosin daily for 12 weeks. Results of this trial showed that IPSS decreased significantly from 17.92 to 12.07, but the MSHQ ejaculatory subdomain worsened significantly

from 24.9 to 27.14, and subdomains for erection and satisfaction did not change significantly (Kim *et al.*, 2010). In a large open trial with 839 enrolled patients suffering from LUTS caused by BPH, 10 mg alfuzosin was taken daily for 2 years. The initial IPSS of 15.5 was reduced by 7 points, whereas the total initial bSFI value of 21.5 improved only slightly during the treatment period, leading to the assessment by the authors that the treatment at least ‘did not have any deleterious effect on sexual dysfunctions’ (Elhilali *et al.*, 2006). A further open clinical trial with 10 mg alfuzosin showed, besides a significant improvement of the IPSS after 1 year of treatment, a significant improvement of the bother score of the Danish Prostatic Symptom Score questionnaire for sexual dysfunction (van Moorselaar *et al.*, 2005) whereas a study comparing tamsulosin/solifenacin either alone or in combination in patients with LUTS also saw improved IPSS, but observed no significant changes in the IIEF (Seo *et al.*, 2011). The IPSS reductions of about 6 to 7 points found in these studies with alpha-blockers were similar to those observed in placebo-controlled trials (van Kerrebroeck *et al.*, 2000; Nordling, 2005), but were not superior to the improvements in IPSS seen in our study. This is in line with the trials of Debruyne *et al.* (2004) and Zlotta *et al.* (2005), which showed similar IPSS reductions following treatment with a saw palmetto preparation and tamsulosin (Debruyne *et al.*, 2004; Zlotta *et al.*, 2005). The main difference between our results and those of the cited studies on alpha blockers is that patients under saw palmetto treatment may experience an improvement in their SDys, whereas this effect cannot be expected from alpha-blocking medication.

It also remains doubtful whether PDE-5 inhibitors are a good treatment for both LUTS and SDys together. Clinical data for PDE-5 inhibitors has shown a good improvement on erectile dysfunctions, but a small effect on BPH symptoms. McVary *et al.* (2007) saw a significant improvement in the IPSS following 12 weeks of treatment with 100 mg sildenafil, with an IPSS change of  $-6.3$  versus  $-1.9$  with placebo, as well as a significant improvement of the IIEF erectile function domain (McVary *et al.*, 2007). In the trial of Roehrborn *et al.* (2008), the application of different dosages of tadalafil demonstrated that an increased dosage correlated with increased IPSS improvement, from  $+3.9$  at 2.5 mg to  $+5.2$  at 20 mg, with a dose of 5 mg showing the best benefit/risk ratio. After the treatment period of 12 weeks, improvement was also seen in the IIEF erectile function subdomain (Roehrborn *et al.*, 2008). Vardenafil (20 mg) taken twice daily for 8 weeks improved the IPSS by 5.9 points, compared with placebo with 3.6 points; significant changes were also seen in the IIEF erectile dysfunction (ED), and the Urolife QoL-9 improved by 27% compared with 7% under placebo (Stief *et al.*, 2008). Although IPSS was improved in these trials, interestingly, changes in flow rates were never reported. In total, clinical data for PDE-5-inhibitors show a smaller improvement in LUTS than that observed in our trial following saw palmetto treatment, and our trial demonstrates better effects on ED. Interestingly, when assessing a broader spectrum of SDys, as with the Urolife QoL-9 and not ED alone, the results of our trials are at least comparable with those of vardenafil.

One solution that has been discussed in the literature for concomitant reduction of BPH symptoms and ED is the combination of an alpha blocker with a PDE-5-inhibitor. Data from three such clinical studies are presently available. One small trial investigated alfuzosin, sildenafil or the combination on LUTS and EDs. After 12 weeks of treatment, initial values of IPSS, which were between 16.9 and 17.8, were reduced significantly in all treatment groups with the largest reduction (24.1%) in the combination group. The IIEF erectile function score was significantly improved by the combination and sildenafil, but not in the alfuzosin group (Kaplan *et al.*, 2007). Another combination trial with sildenafil or tamsulosin showed comparable results, with the largest IPSS improvement observed with the combination (-40.1%), followed by tamsulosin (-36.2%), and sildenafil (-28.2%); the IIEF improved significantly with sildenafil and the combination but not with tamsulosin (Tuncel *et al.*, 2010). In further trial, 100 mg udenafil was added to a stable alpha-blocking therapy in patients with BPH and ED for 8 weeks. The IPSS was reduced by 2.8 points, and the IIEF-5 improved by more than 5 points, indicating that a combination or add-on therapy of udenafil may be beneficial (Chung *et al.*, 2009). Comparing these data with the results of our trial, with an IPSS-reduction of 51% and improved SDys by 40.1% as measured with the bSFI, the saw palmetto treatment yielded efficacy results similar to the combination of an alpha blocker and a PDE-5-inhibitor.

Phosphodiesterase-5-inhibitors are expensive treatments; therefore, a cost-benefit assessment is warranted for further extensive PDE-prescription. In the USA, a single dose of 25 mg sildenafil costs about eight times as much as an alpha-blocking agent like 1 mg doxazosin (Stafford and Radley, 2002) or 30 times more than 0.4 mg tamsulosin in Germany (Schneider and Richling, 2008), whereas the cost for a daily dosage of Prostan is in the lower range of an alpha blocker. These differences in price, in addition to the only moderate efficacy, make it doubtful if PDE-5-inhibitors should be advocated as standard treatments for BPH symptoms.

When looking at safety and tolerability, our data were in accordance with the previous findings and indicated that saw palmetto was very well tolerated, in contrast to the standard treatments for LUTS. A major problem for patients taking an alpha blocker and/or a 5-alpha-reductase inhibitor is the occurrence of sexual adverse effects that cause many men to discontinue treatment (Roehrborn, 2004). Study data show that 2–16% of all patients under alpha reductase inhibitor therapy experience EDs, decreased libido and decreased volume of ejaculate (twice the frequency seen with placebo), whereas alpha-blocking agents, particularly tamsulosin, have been frequently linked with ejaculatory disorders in around 10% of all patients (Gacci *et al.*, 2011). In daily practice, the incidence rates may even be higher than in clinical trials. In a large epidemiological study carried out with urologists and internal medicine physicians in the United States, doctors estimated that 18–27% of the patients taking an alpha-blocking medication suffer from ejaculatory disorders and 16–22% of men taking a 5-alpha-reductase-inhibitor suffer from EDs (Seftel *et al.*, 2007). Nevertheless, the latest American Urology

Association guideline for treatment of BPH symptoms also advocates using a combination of alpha-blockers and 5-alpha-reductase inhibitors (McVary *et al.*, 2011), a protocol designed to achieve better efficacy, but without fully considering the additive side effect rates of these two drugs as shown in combination trials (Mirone *et al.*, 2011).

Our present trial has some limitations; it was designed as an uncontrolled pilot trial to elucidate if any effect of a saw palmetto treatment would be observed. Consequently, the size of the placebo effect can only be estimated. Furthermore, there was a strong centre effect, as one centre recruited substantially more patients than the others, and these other centres did have fewer responders than the main centre. Subgroup analysis did not unveil any significant differences in patient characteristics between these centres; however, these analyses were limited by the low number of patients in the other five centres together. A further placebo-controlled clinical trial with a more balanced patient distribution in the centres would be the next step to confirm our findings.

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## CONCLUSIONS

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This is the first trial ever to indicate that saw palmetto treatment had not only a good efficacy in reducing BPH symptoms but also a concomitant effect on SDys. We demonstrated that a saw palmetto treatment was as effective in reducing BPH symptoms as an alpha blocker or a 5-alpha-reductase inhibitor, but that, in contrast to those treatments, saw palmetto was associated with an improvement of SDys as measured with the bSFI and the Urolife QoL-9 score. Compared with PDE-5-inhibitors, the saw palmetto treatment did not have the same efficacy in improving ED, but did have the same treatment effect for overall change of SDys, with a better reduction in IPSS. The cost of daily treatment with saw palmetto is much cheaper than with many other medications, for example, in Switzerland, the cost would be 0.75 Swiss francs for saw palmetto versus 22.30 Swiss francs for 100 mg sildenafil (Stebler, 2009). In our trial, we observed the same efficacy results as have been seen for combination therapy with alpha blocker and PDE-5-inhibitor, but with much better tolerability of the saw palmetto treatment. Based on these promising results, which are also reflected by the good acceptance of patients and investigators, we consider saw palmetto to be the first line treatment for patients with mild and moderate BPH symptoms, as it may also improve concomitant SDys, while having a very good tolerability and cost effectiveness.

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## Conflict of Interest

The study was financed by A.Vogel Bioforce AG, where A. Suter is employed in medical research.

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