

# Efficacy and tolerability of *Roystonea regia* lipid extract (D-004) and terazosin in men with symptomatic benign prostatic hyperplasia: a 6-month study

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## Abstract

**Background:** Benign prostatic hyperplasia (BPH), a common urological disease in aging men, frequently produces lower urinary tract symptoms (LUTS). Clinical studies have shown that terazosin relaxes the smooth muscle of the prostate and bladder, facilitates bladder emptying, improves LUTS, increases maximum urinary flow, and reduces the residual volume of urine. D-004, a lipid extract of the fruit of the Cuban royal palm (*Roystonea regia*), presents a similar efficacy to Saw palmetto. Clinical studies have demonstrated its efficacy and safety in short- and medium-term trials in patients with BPH. The objective of this study was to compare the efficacy and tolerability of D-004 with terazosin for 6 months on LUTS in patients with BPH.

**Methods:** The present phase III study had an open, randomized, comparative design, with two parallel groups who received D-004 (320 mg/day) or terazosin (5 mg/day) for 6 months. The study included men at least 50 years of age, with evidence of the LUTS of moderate intensity according to the International Symptoms of the Prostate (IPSS). The effects on the IPSS Scale was the primary efficacy variable. The effects on the size of the prostate and the residual volume were secondary variables. The subjective self-perception of symptom relief at trial completion was a collateral outcome. Analysis was done by intention-to-treat.

**Results:** The study included 100 men with a diagnosis of BPH, confirmed by digital rectal examination and ultrasonography, and moderate LUTS (IPSS score  $>7$ ,  $<19$ ). Baseline characteristics were similar in both groups. Nine patients did not continue the study: one from group D-004 (due to protocol violation) and eight from the terazosin group (six due to adverse events and two due to protocol violation;  $p < 0.01$ ). D-004 and terazosin significantly reduced the IPSS scores at the end of the 6 months of therapy by 74.2% and 66.1%, respectively, with respect to baseline values. Comparisons between groups performed showed that, at the end of the treatment, D-004 was more effective ( $p < 0.05$ ) than terazosin in reducing the IPSS score. Although the average size of the prostate was reduced in both groups, this reduction reached statistical significance only for D-004. On the other hand, postvoid residual volume was significantly and similarly reduced in both groups. Both treatments were safe, while D-004 was better tolerated than terazosin.

**Conclusions:** D-004 administered at a dose of 320 mg/day for 6 months showed comparable efficacy with terazosin (5 mg/day) in reducing the LUTS (IPSS score), producing a significant decrease in prostate volume and postvoid residual volume. Both treatments were safe, with better tolerability for D-004 as compared with terazosin.

**Keywords:** benign prostate hyperplasia, D-004, IPSS, LUTS, terazosin

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## Introduction

Benign prostatic hyperplasia (BPH) is a disease that mainly affects men aged 50 years or older; disease frequency increases with age.<sup>1-3</sup> BPH consists of a benign growth of the prostate (stromal and glandular elements) due to excessive and uncontrolled cellular growth. Owing to the location of the gland, its growth can cause obstruction and promote the development of the lower urinary tract symptoms (LUTS), such as decreased urine volume and urination pressure, urinary retention, and nocturia.<sup>1-5</sup>

Inhibitors of prostatic 5 $\alpha$ -reductase<sup>6,7</sup> and  $\alpha$ 1-adrenoceptors (ADR- $\alpha$ 1) blockers,<sup>8,9</sup> are the main pharmacological therapy of BPH, and the combination therapy with both is recommended in severe or refractory BPH.<sup>10,11</sup>

The inhibitors of prostatic 5 $\alpha$ -reductase prevent the progression of BPH, producing a moderate reduction of prostate volume during a period ranging from 6 months to 1 year, and not always associated with an improvement in symptoms.<sup>6,7</sup> Adverse events (AEs) associated with its use include decreased libido, impotence, and ejaculation disorders.<sup>12</sup>

On the other hand, ADR- $\alpha$ 1 blockers usually induce rapid relief of symptoms, requiring medium- and long-term use.<sup>8,9</sup> Among its main AEs are those derived from its effects on  $\alpha$ 1 vascular adrenergic receptors, e.g., orthostatic hypotension.<sup>13</sup>

Terazosin is a selective antagonist of ADR- $\alpha$ 1, since it blocks only  $\alpha$ 1A receptors, which mediate the contractile function of prostatic smooth muscle and bladder neck. Comparative and placebo-controlled clinical trials have shown that terazosin relaxes the smooth muscle of the prostate and bladder, facilitates bladder emptying, improves LUTS, increases maximum urinary flow, and reduces the residual volume of urine, the effects being dose-dependent. This therapy is indicated in all patients with symptoms associated with BPH, regardless of the growth of the prostate gland.<sup>8,9</sup>

BPH is a pathology frequently treated with phytotherapeutic alternatives, among which the extracts of Saw palmetto (*Serenoa repens* B) constitute the most documented.<sup>14-17</sup>

D-004, a lipid extract of the fruit of the Cuban royal palm (*Roystonea regia*), has been effective in

experimental models of prostate hyperplasia,<sup>18-20</sup> with an efficacy similar to Saw palmetto based on a mechanism that involves two basic components: inhibition of prostatic 5 $\alpha$ -reductase,<sup>21</sup> a fact that supports its effects on the mechanical component of the disease; and antagonism of responses mediated by ADR- $\alpha$ 1, demonstrated *in vitro* and *in vivo*,<sup>22,23</sup> which supports its experimental efficacy on the dynamic component of the disease.

In addition, the multifactorial mechanism underlying the efficacy of D-004 involves anti-inflammatory and antioxidant effects in rat prostate tissue and on plasma oxidative variables in healthy and BPH men.<sup>22-27</sup>

D-004 has not shown an estrogenic or anti-estrogenic effect in animal experiments,<sup>28</sup> nor does it modify sexual activity in the male rat,<sup>29</sup> or various behavioral patterns in rodents.<sup>30</sup> Experimental toxicology studies have not found toxicity associated with the treatment.<sup>31-36</sup>

Single and repeated doses of D-004 (320-960 mg/day) administered to healthy volunteers for 21 days were well tolerated.<sup>37</sup> Thus supports a wide margin of safety with respect to the dose evaluated.

On the other hand, two other clinical studies showed that D-004 administered at a dose of 320 mg/day for 4 and 6 months, respectively, was as effective as Saw palmetto in reducing LUTS, as evaluated by reduction in IPSS score and decrease in postvoid residual volume. However, treatment with D-004, not with Saw palmetto, also produced a significant and moderate decrease in the size of the prostate. Both treatments were safe and well tolerated, with discrete advantages for treatment with D-004 in the AEs report when compared with Saw palmetto.<sup>38,39</sup>

In light of these issues, this study was undertaken to compare the effects of D-004 (320 mg/day) and Terazosin (5 mg/day), administered for 6 months on LUTS in BPH patients.

## Patients and methods

### Study design

This open, randomized, comparative study was conducted in accordance with the Declaration of Helsinki.<sup>40</sup> The study protocol and procedures were approved by the Institutional Committee for

Clinical Research of the Salvador Allende Hospital and the Cuban State Drug Control Centre (Havana, Cuba). This study was included in the Cuban Registry of Clinical Trials (RPCEC0000217).

All participants provided written informed consent at enrolment. Men aged 50 years or older and previously diagnosed with BPH were recruited. Enrolled participants underwent clinical history, IPSS questionnaires, and physical examination for screening their eligibility for randomization (visit 1).

Eligible patients were randomized to D-004 (soft gel capsules 320 mg) or terazosin (tablets 5 mg) once daily for 6 months, and were advised to continue on their usual dietary habits. Further visits were done after completing 2, 4, and 6 months on therapy (visits 3–5). Subjects underwent physical examination and IPSS interview at each visit. Treatment compliance and AEs were controlled from visits 3 to 5. Laboratory tests and ultrasound evaluation were conducted at baseline and at study completion.

#### *Study participants*

Patients aged 50 years or older with moderate BPH as confirmed by both digital examination and ultrasound/LUTS (IPSS  $\geq 7$ ,  $< 19$ ), and not showing exclusion criteria were enrolled in the trial to be randomized.

Patients with any major prostate disease except BPH, or those who had had urogenital surgery, urinary retention, neurogenic bladder, or prostate-specific antigen (PSA) level  $> 5.0$  ng/dL were excluded. Others exclusion criteria were to have arterial pressure  $> 180/110$  mmHg, psychiatry problems that limited proper answers to the IPSS questionnaire, chronic renal failure, diagnosed neoplasias, serious events (acute coronary syndromes, stroke, transient ischemic attacks, or major surgery) during the preceding 6 months or consumption of  $5\alpha$ -reductase inhibitors,  $\alpha 1$ -ADR blockers, phytotherapy for BPH/LUTS, steroids, androgens, antiandrogens, or cholinergic or anticholinergic drugs.

Causes of premature withdrawal were to suffer any AE justifying such a decision, unwillingness to continue on the study, and major violations (failure to take study treatments for 15 days or

more or taking supplements or medicines with known effects on BPH/LUTS).

#### *Treatments*

Taking into account the results of the studies in patients with BPH, the use of a dose of 320 mg/day was estimated for the D-004 group, while, for the terazosin group, a dose of 5 mg/day was estimated: the recommended dose in clinical practice in Cuba for the management of these patients.

D-004 capsule and terazosin tablets were given to the patients according to their serial progressive inclusion. Randomization was computer generated using balanced blocks and with an allocation ratio of 1:1, without stratification. Study treatments were dispensed in bottles (provided by the manufacturer) according to the randomization sequence. Study patients and the personnel distributing the treatments, assessing the outcomes, or performing data analysis were blind to treatment allocation.

Patients were advised to take the capsules or tablets once a day before bedtime for 6 months, and to bring unused capsules or tablets to each visit. Treatment compliance was estimated by capsule or tablet counts at each visit and by interviews with the subjects, and was considered good and very good if patients took at least 80% or more than 90%, respectively, of the capsules or tablets scheduled from the previous visit.

Medications or supplements with known effects on BPH/LUTS or/and urination were not allowed. Patients who were taking some of these were eligible for randomization only if they ceased consumption for at least 6 months prior to the trial.

#### *Efficacy variables*

The primary outcome measure was a reduction in IPSS from baseline to 6 months. Secondary analyses on the IPSS were a comparison of the proportion of participants achieving a 3-point score decrease *versus* baseline, suggested as clinically meaningful. Efficacy should be comparable if the treatments reached statistically similar final IPSS values and net changes. IPSS was assessed using a standard questionnaire form with seven questions, each measured on a scale to which patients respond from 0 (best) to 5 (worst).<sup>17</sup>

Secondary efficacy outcomes included prostate size and residual volume after voiding, measured by ultrasonography. Treatments were considered similarly effective if no significant differences between groups were found.

The subjective self-perception of symptom relief at trial completion was a collateral outcome. This matter was assessed according to four options: very good (complete symptoms relief), good (remarkable symptom relief, but some symptoms still remaining), fair (modest symptom relief), and poor (no symptom relief, or worsening of symptoms).

#### *Safety and tolerability*

Included data from physical examination (body weight, pulse rate, blood arterial pressure), hematological indicators (hemoglobin, hematocrit, platelets, red cell, and white cell counts), blood indicators [PSA levels, alanine amino transferase (ALT), aspartate amino transferase (AST), glucose, creatinine, and C-reactive protein] and AE report.

All undesirable events that newly appeared to a subject during the trial, disregarding the cause, were considered as AEs. In accordance with their intensity, AEs were classified as mild, moderate, or serious, as follows: mild AEs did not require suspension of study capsules or specific treatment of the AE; moderate AEs required stopping therapy or specific treatment of the AE; serious AEs led to hospitalization or death.<sup>41</sup>

#### *Laboratory variables*

Blood venous samples were drawn after an overnight fast of 8–10 h. Hematological indicators were determined automatically using Hematological Complex equipment. Blood biochemistry indicators were assessed using reagent kits (Roche, Basel, Switzerland) in a Hitachi 912 autoanalyzer (Tokyo, Japan). PSA levels were determined by immunoenzymatic enzyme-linked immunosorbent assay (ELISA; UMELISA PSA kit, Immunoassay Center, Havana, Cuba).

#### *Statistical analysis*

Data was analyzed according to intention-to-treat, including all randomized patients, regardless of study treatment compliance, and data imputation was performed by the drag method.

The study should detect a 10% between-group difference in mean change from baseline in IPSS ( $\beta = 0.8$ ,  $\alpha = 0.05$ ), for which a sample size of 50 patients/treatment group (100 randomized patients) was estimated. Assuming that 10% of randomized patients could be dropouts, at least 110 subjects should be enrolled. No interim analyses were planned or performed.

Comparisons of continuous variables were performed using Student's *t* test for paired (within-group comparisons) and independent samples (between-group comparisons). Categorical variables were compared with a chi-square test. A value of  $\alpha = 0.05$  was assumed for statistical significance. Comparisons were made with the SPSS 21 system on Windows 10 (Microsoft, Seattle, WA, USA).

## **Results**

#### *Baseline characteristics of study patients*

A total of 125 patients were recruited, of whom 100 were included in the treatment phase. The causes of noninclusion were PSA > 5 ng/ml (16 patients), chronic renal failure (3 patients), failure to perform the tests and analyses indicated (3 patients), and no attendance of the inclusion consultation (3 patients).

Nine patients withdrew from the study: one from the group treated with D-004 for protocol violation (no desire to continue) and eight from the group treated with terazosin ( $p < 0.01$ ): six due to AEs and two due to the violation protocol (no desire to continue).

Both groups were well balanced at baseline (Table 1). The average age of the study population was 66 years and the patients included had other pathological backgrounds, in addition to BPH, such as hypertension (55%), overweight (46%), obesity ( $\text{kg/m}^2 \geq 30$ ) (21%), smoking habit (14%), diabetes (11%), coronary disease (10%), and dyslipidemia (2%).

The frequency of consumption of concomitant therapy was high (71%), similar in both groups, and in correspondence with their clinical history, highlighting the consumption of antihypertensive drugs (angiotensin-converting enzyme inhibitors, diuretics, calcium channel blockers, and  $\beta$ -blockers), followed by platelet antiplatelet, oral hypoglycemic agents, vasodilators, antiasthma, and lipid-lowering drugs.

**Table 1.** Main baseline characteristics of the study.

Characteristics	D-004 (n = 50)		Terazosin (n = 50)		Total (n = 100)	
Age (years) (X ± SD)	66 ± 8		66 ± 8		66 ± 8	
Body mass index (kg/m <sup>2</sup> ) (X ± SD)	26.7 ± 4.0		26.6 ± 3.7		26.6 ± 3.6	
IPSS score (X ± SD)	12.8 ± 3.1		12.7 ± 2.7		12.8 ± 2.9	
Prostate size (cm <sup>3</sup> ) (X ± SD)	31.4 ± 23.2		29.7 ± 19.4		30.6 ± 21.3	
Residual post-voiding volume (cm <sup>3</sup> ) (X ± SD)	25.1 ± 23.0		22.6 ± 19.8		23.9 ± 21.4	
Personal history	n	%	n	%	n	%
Hypertension	27	54.0	28	56.0	55	55.0
Overweight (kg/m <sup>2</sup> ≥ 25, <30)	23	46.0	23	46.0	46	46.0
Obesity (kg/m <sup>2</sup> ≥ 30)	10	20.0	11	22.0	21	21.0
Smoking	6	12.0	8	16.0	14	14.0
Diabetes mellitus	5	10.0	6	12.0	11	11.0
Coronary disease	6	12.0	4	8.0	10	10.0
Dyslipidemia	1	2.0	1	2.0	2	2.0
Family history						
Prostate cancer	9	18.0	6	12.0	15	15.0
Concomitant therapy <sup>a</sup>						
Any concomitant drug	38	76.0	33	66.0	71	71.0
ACEI	16	32.0	18	36.0	34	34.0
Diuretics	11	22.0	12	24.0	23	23.0
Antiplatelet drugs	7	14.0	6	12.0	13	13.0
Calcium antagonists	6	12.0	5	10.0	11	11.0
Oral hypoglycemic drugs	5	10.0	5	10.0	10	10.0
β-blockers	8	16.0	2	4.0	10	10.0
Vasodilators	2	4.0	2	4.0	4	4.0
Antiasthma	2	4.0	2	4.0	4	4.0
Cholesterol-lowering drugs	1	2.0	1	2.0	2	2.0
X, mean; SD, standard deviation; IPSS, International Prostate Symptom Score; ACEI, angiotensin-converting enzyme inhibitors, all comparison were not significant: continuous variables (Student's <i>t</i> test for paired samples), categorical variables ( $\chi^2$ test).						
<sup>a</sup> Consumed by ≥2 patients						



**Table 2.** Effects on IPSS values in men with BPH (X±SD).

Treatment	Baseline	2 months	Changes (%)	4 months	Changes (%)	6 months	Changes (%)
D-004	12.8 ± 3.1	6.3 ± 1.8**	-50.8	4.2 ± 1.3**	-67.2	3.3 ± 1.3**+	-74.2
95% CI	(12.0–13.7)	(5.8–6.9)		(3.8–4.5)		(2.9–3.7)	
Terazosin	12.7 ± 2.7	7.0 ± 2.3**	-44.9	5.1 ± 2.3**	-59.8	4.3 ± 2.6**	-66.1
95% CI	(11.9–13.5)	(6.4–7.6)		(4.5–5.9)		(3.6–5.0)	

X, mean; SD, standard deviation.  
 \*\* $p < 0.001$ , Comparison with baseline (Student's  $t$  test for paired samples).  
 + $p < 0.05$ , Comparison between groups (Student's  $t$  test for independent samples).

With the exception of the nine patients who were discharged, the rest of the patients included consumed all the capsules programmed for each stage according to the count of remaining capsules or tablets and interrogation of the patients, which shows an excellent adherence to treatment, similar in both groups.

#### Effects on primary outcomes

At the end of the 2 months of treatment, both D-004 and terazosin significantly reduced the IPSS scores by 50.8% and 44.9%, respectively, with respect to the initial values ( $p < 0.001$ ) (Table 2). This effect was increased at the end of 4 and 6 months; thus, initial values of 12.8 (D-004) and 12.7 (terazosin), at the end of the study IPSS scores of 3.3 (D-004) and 4.3 (terazosin) were reached, which implied significant reductions of 74.2% (D-004) and 66.1% (terazosin), equivalent to average reductions of 9.5 and 8.4 points, respectively.

Comparisons between groups performed showed that at the end of the treatment, D-004 was more effective ( $p < 0.05$ ) than terazosin in reducing the IPSS score.

#### Effects on secondary and collateral outcomes

Although the average size of the prostate was reduced in both groups (10.8% D-004; 4.7% terazosin), this reduction reach statistical significance only in group D-004 ( $p < 0.01$ ) (Table 3). On the other hand, postvoid residual volume was also significantly reduced and similarly with both treatments (35.8%). However, comparison between groups at the end of treatment for both variables revealed that differences were not significant.

The frequency of patients who evaluated an efficacy of 'very good' with respect to the relief of symptoms was higher in the D-004 group (34, 68%) with respect to the terazosin group (25, 50%), while efficacy was evaluated as 'good' by 16 patients (32%) in the D-004 group and 25 (50%) in the terazosin group. However, the frequency of patients who evaluated the efficacy as very good or good was similar in both groups (50, 100%), with no significant differences between the respective therapies.

#### Safety and tolerability

Both treatments were safe. In the analysis of the effects on physical indicators, no significant changes were obtained in any of the comparisons made. Nevertheless, in analysis of the effects on the laboratory indicators investigated, a significant decrease in the hematocrit values was observed only in the group treated with terazosin, as well as a reduction in the ALT values at the end of the treatment in both groups. However, there were no significant differences in the between-group comparisons performed (values not show for simplicity).

Eight patients reported AEs during the study, seven (14%) in the terazosin group and one (2%) in the D-004 group ( $p < 0.05$ ) (Table 4).

Three of the patients in the terazosin group who reported AEs presented only with postural hypotension, while the other four patients in this group, together with postural hypotension, presented a clinical picture accompanied by tachycardia, palpitations, blurred vision, fatigue, sweating, or dry mouth. These adverse experiences were classified as moderate in six patients due to discontinuation of the study medication, and, in one of the cases, it was classified as mild. However, all these AEs

**Table 3.** Effects on secondary outcomes in men with BPH (X ± SD).

Treatment	Baseline	6 months	Changes (%)
Prostate size (cm <sup>3</sup> )			
D-004	31.4 ± 23.2	28.0 ± 20.3**	-10.8
Terazosin	29.7 ± 19.4	28.3 ± 17.9	-4.7
Residual postvoiding volume (cm <sup>3</sup> )			
D-004	25.1 ± 23.0	14.2 ± 14.5**	-35.8
Terazosin	22.6 ± 19.8	14.5 ± 16.6***	-35.8

X, mean; SD, standard deviation.  
 \*\**p* < 0.01, \*\*\**p* < 0.001 Comparison with baseline (Student's *t* test for paired samples).  
 Comparison between group were not significant (Student's *t* test for independent samples).

**Table 4.** Adverse event reports during the study.

Adverse events	D-004 (n = 50)		Terazosin (n = 50)	
	n	%	n	%
Postural hypotension	0	0.0	7**	14.0
Tachycardia	0	0.0	1	2.0
Palpitations	0	0.0	1	2.0
Blurred vision	0	0.0	2	4.0
Sweating	0	0.0	1	2.0
Dry mouth	0	0.0	1	2.0
Fatigue	0	0.0	1	2.0
Urinary sepsis	1	2.0	0	0.0
Total adverse events	1	2.0	14***	28.0
Total number of patients with adverse events	1	2.0	7*	14.0

*n*, number of patients.  
 \* *p* < 0.05, \*\**p* < 0.01, \*\*\**p* < 0.001 Comparison between groups (χ<sup>2</sup> test).

were classified as definitely related to the reference treatment (terazosin).

Only one patient from group D-004 reported an AE during the study (urinary sepsis), an event classified as moderate due to requiring treatment with amikacin, but did not require stopping the therapy and was classified as doubtfully related to treatment.

The frequency of patients whose tolerance of the medication was evaluated as very good or good by

the doctor at the end of the study was significantly higher (*p* < 0.01) in group D-004 (48, 96%) than in the terazosin group (41, 82%).

## Discussion

### *Strengths of the study*

Both groups were homogeneous in basal conditions, as evidenced by the similarity of their demographic characteristics and the main response variables, which supports that the results

obtained are attributable to the investigated treatments and not to any disparity in the initial condition of the groups compared.

The study population was representative of men with moderate BPH/LUTS, according to the IPSS score values used in the inclusion criteria. The average age (66 years) corresponded to the stratum of elderly included, so that 72 patients were between 61 and 80 years old, consistent with data from the literature.<sup>42–46</sup>

The distribution of other antecedents such as hypertension, overweight, obesity, smoking habit, diabetes, coronary heart disease, and dyslipidemia, also consistent with what has been described in other studies,<sup>42–46</sup> reveals the concurrence of factors that contribute negatively to progression of the illness.

The frequency of concomitant therapy consumption was high (71%) and in correspondence with the pathological antecedents, so that antihypertensive agents, antiplatelet and oral hypoglycemic drugs were consumed by more than 10% of the patients included in the study.

In this study, D-004 and terazosin showed a consistent safety and tolerability profile with data reported for both treatments.<sup>26,27,37–39,47–50</sup>

### Main results

Both treatments produced significant reductions in the primary and secondary efficacy variables preset in the study. The percentages of reduction of the total score of the IPSS scale reached in this trial by D-004 and terazosin are similar to those obtained in previous studies of similar duration (6 months) and corroborate the efficacy of both treatments in patients with HPB.<sup>10,13,39,49</sup>

The reductions obtained at the end of the study (74.2% with D-004 and 66.1% with terazosin after 6 months of therapy) also met this criterion, achieving marked reductions in the IPSS score. However, it should be noted that comparisons between groups showed that, at the end of the treatment, D-004 was more effective ( $p < 0.05$ ) than terazosin in reducing the IPSS score.

The analysis of efficacy according to the frequency of cases that achieved reductions of the IPSS score  $\geq 30\%$  showed that, in the group treated with D-004 (100%), the result was slightly

higher than in the group treated with terazosin (94%). Similarly, an analysis of the frequency of responders according to the percentage of cases that achieved net decreases of the IPSS score  $\geq 3$  points showed consistent results, since 50 (100%) and 47 (94%) of the patients treated with D-004 and terazosin, respectively, achieved such declines.

The frequency of patients who achieved decreases in the IPSS score  $\geq 50\%$  (clinically very relevant) was also higher in the group treated with D-004 (100%) than in the group treated with terazosin (86%), without differences between groups, and consistent with the frequency of cases that achieved final scores of the IPSS score  $< 7$ , which reflects their passage from the initial category of moderate LUTS to the final mild or asymptomatic: 50 (100%) with D-004 and 47 (94%) with terazosin.

However, there were no significant differences between groups in the comparisons made in the average decrease in score regarding the frequency of cases that achieved clinically relevant or very relevant responses (100%); they showed comparable efficacy.

The evaluation of LUTS with the IPSS not only allows the impression of the degree of severity or severity of the disease to be standardized, but also influences the final treatment decision, which usually depends on the patient's personal perception of their own symptoms, so that in cases with mild LUTS or without symptoms (IPSS  $< 7$ , not included in the study), the expectant attitude (watchful waiting) is usually chosen, even if they have an enlarged prostate. In contrast, in men with moderate LUTS (IPSS  $\geq 7$ ,  $< 19$ , all included in the study) the choice is more difficult, and generally depends on the patient's ability to tolerate LUTS or the doctor's impression about the progression of the disease, while cases with severe LUTS (IPSS  $\geq 19$ ) should always be treated.

Nevertheless, we cannot forget that, although IPSS is a validated and widely used scoring system, the subjective nature of the responses is inherent to any scale. Then, maybe the high motivation of study patients to adhere to the trial could have resulted in an overestimation of efficacy: a factor that may affect both groups similarly. Thus, the real magnitude of the effects of both treatments on symptoms could be lower than that found.



Taking the decreases described for the antagonists of ADR- $\alpha 1$ <sup>13,45,46</sup> as a reference, it is possible to infer that the efficacy of both treatments (terazosin and D-004) in relieving LUTSs is clinically relevant, although further long-term comparative studies should define the real scope of this extrapolation.

On the other hand, both treatments were effective in reducing the size of the prostate, as well as in significantly reducing postvoid residual volume, and secondary efficacy variables, which agrees with results of previous studies for both treatments.<sup>13,38,39,49</sup>

Although the average size of the prostate was reduced in both groups, these reductions reached statistical significance only in the D-004 group. On the other hand, postvoid residual volume was significantly reduced, similarly with both treatments.

Nine patients were discharge from the study: one treated with D-004 for protocol violation and eight treated with terazosin: six for AEs and two for protocol violation ( $p < 0.01$ ). Therefore, 91% included patients completed the study, a very satisfactory figure since in studies in patients with BPH/LUTS very variable dropout rates have been obtained.<sup>47,48</sup> Adding that all the patients who completed the study properly consumed their medication further reinforces the validity of the efficacy and safety data obtained.

The treatments did not lead to any modification of the physical examination indicators; despite this, the laboratory variables investigated revealed a significant decrease in hematocrit values in the group treated with terazosin, as well as a reduction in ALT values at the end of the treatment in both groups. There were no significant differences in the between-group comparisons performed and values were within the ranges considered normal for these variables.

The tolerability of D-004 was very good, since only one patient reported an AE (urinary sepsis), classified as moderate for requiring treatment but considered to be dubiously related to treatment, while in the terazosin group, seven patients (14%) experienced AEs during the study, six of which were classified as moderate, due to discontinuing the study medication, and one as mild, in addition to being classified as definitely related to the reference treatment (terazosin).

The frequency of patients whose tolerance of the medication at the end of the study was evaluated as very good or good by the doctor was significantly higher in the D-004 group (48, 96%) than in the terazosin group (41, 82%) ( $p < 0.01$ ), which reveals that D-004 was better tolerated than terazosin by the patients included in the study.

#### *Limitations of the trial*

First, the assignment of treatments was open, not blind, which cannot exclude the presence of subjective biases from patients and doctors: a matter of more relevance when the nature of the response is subjective, as the answers to the questionnaire validated. Second, the effects of treatment on the maximal urinary flow, a relevant urological outcome, was not investigated.

The use of a placebo group was not considered appropriate because the efficacy of terazosin (the comparator) is considered as well established and the treatment is in widespread use. In addition, both treatment groups have already demonstrated superiority *versus* placebo in randomized controlled trials.<sup>26,37,45,49</sup>

The present data merit the conduct of new studies on the effects of D-004 in patients with BHP/LUTS, including larger sizes, longer treatment, and evaluation of the effects on urinary flow.

The study population was representative of men with moderate BPH/LUTS according to the IPSS score values used in the exclusion criteria. The average age corresponded with the stratum reported in the literature for the studied pathology. The distribution of other clinical antecedents such as hypertension, overweight, obesity, smoking habits, diabetes, coronary heart disease, and dislipidemia, as well as drug consumption, were comparably distributed between both groups, and is consistent with those described in other studies.<sup>42-46</sup> In this way the homogeneity of basal conditions supports that results obtained are attributable only to the investigated treatments and not to disparity in the initial conditions of the group compared. Finally, the present study was preceded by others that supports the beneficial effects of D-004 on BTH treatment. On the other hand, terazosin used as reference is a recognized drug used extensively to treat BPH.

## Conclusion

D-004 administered at a dose of 320 mg/day for 6 months showed comparable efficacy with terazosin (5 mg/day) in reducing the LUTS evaluated by reducing the IPSS score, also producing a significant decrease in prostate volume and post-void residual volume. Both treatments were safe, with better tolerability for D-004 compared with terazosin.

## Authorship declaration

The authors have been involved in the conception and design of the work, or in the collection of data, or in the analysis and interpretation of the data, as well as in the writing of the article or in its critical review and in the approval of the final version for publication.

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## Conflict of interest statement

The authors declare that there is no conflict of interest.

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