



Conservative Treatment of Benign Prostatic Hyperplasia (BPH) with Cernilton N – Results of a placebo-controlled double-blind study

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Summary

The efficacy and tolerability of the pollen-extract preparation, Cernilton N*1, were investigated in a double-blind, placebo-controlled study carried out over a treatment period of 12 weeks in 6 urological practices, in a total of 103 patients suffering from benign prostatic hyperplasia (BPH) in Stages II and III. The investigational parameters were the disturbances of micturition classified according to the FDA recommendation, residual urine volume, palpation findings and uroflow index, as well as the global assessment of the therapy by the doctor and by the patient. Under the pollen-extract nocturia, the principal sign of BPH, improved in 68.8% of the cases, compared with 37.2% under the placebo medication ($P < 0.005$). Notable differences were observed in day time frequency and in sensation of residual urine, which were statistically significant as regards absence of these symptoms after the treatment, between the treatment (AT) and placebo (PI) ($P = 0.010$ and $P = 0.016$, respectively). Observation of the course of the symptoms after 6 weeks and 12 weeks showed higher rates of improvement under the active treatment, for all the individual symptoms. In case of the urodynamic study parameters similar changes were observed in the findings for all uroflow parameters, whereby the differences between the comparative groups were unremarkable.

At the control examination after 6 weeks a continuous increase in the maximum urine flow was observed, averaging 3.3 ml/sec under placebo ($P = 0.060$). The difference in the average decrease in the residual urine volume in the course of the treatment was statistically significant (AT/PI: 24.3 ml/3.7 ml ; $P = 0.006$). The pollen-extract led to a continuous reduction, whereas in the placebo-group the residual urine after 12 weeks had increased in comparison with

the value recorded after 6 weeks. Significant differences in the residual urine volumes before and after the treatment, in favour of the pollen-extract, were observed also in the patients in BPH Stage III ($P = 0.042$).

Prostate size and congestion showed higher response rates, in the sense of reduction in size and decongestion, as detected by palpation, under the active treatment, with a marked trend (AT/PI : 88.5% / 69.0%; $P = 0.155$). Nausea was recorded under active treatment in one case. In accordance with their positive experiences with the treatment the investigating physicians and the patients assessed the therapeutic result under the pollen-extract as very good or good significantly more often than that obtained under placebo ($P = 0.001$). The results of the study prove the efficacy of the pollen-extract in patients with BPH in Stages II and III, in regard to the clinical symptomatology, urodynamics and the global assessment, and demonstrate the good tolerability of the global assessment, and demonstrate the good tolerability of the drug, which permits long-term therapy with little risk of side effects.

Introduction

In view of the changing age structure and the rising average life expectancy of the male population the phytotherapeutic treatment of benign prostatic hyperplasia (BPH) will become increasingly more relevant. The justification and the need for such a drug therapy can be estimated on the basis of the available epidemiological data: the probability for a 40-year-old man to be operated for a BPH at the age of eighty is $P = 0.292$, and for him to develop the clinical symptoms of the disease it is $P = 0.777$ [4]. Consequently, for the treatment of BPH patients a symptomatically oriented medication

has priority. However, continuous observation of the course of the treatment must ensure that surgical measures are taken whenever they are indicated.

On the basis of our own positive experiences with the standardized pollen-extract preparation (trade-name Cernilton N) in the treatment of BPH, a placebo-controlled, double-blind study of the efficacy and tolerability of this drug was initiated and carried out in collaboration with six practicing urologists.

An effect on the congestion of the prostate and on the chronic inflammatory changes occurring in the framework of BPH is to be suggested as the pharmacodynamic mechanism of action for the symptomatic therapeutic effectiveness of pollen-extract preparation, as clinically a normalization of the pathological parameters of inflammation has been demonstrated in the EPS-expressed prostatic secretion (leucocytosis, raised pH value) [2].

Patients and Methods

For this randomized, placebo-controlled, double-blind study in BPH patients in Stages II and III according to Vahlensieck [12] a total of 103 patients could be included by six practicing urologists. Due to carcinoma in 1 case and antibiotic therapy for a concomitant urinary tract infection in 6 cases, a total of 96 patients were eligible for the statistical analysis.

Further specific criteria for exclusion from the study were: suspected carcinoma of the prostate, residual urine volume more than 150 ml, neurogenic disturbances of micturition, acute and/or chronic prostatitis/ prostatic vesiculitis, malformation or post-operative status in the urogenital area with obstruction of the efferent urinary tract, bladder stones. Previously treated BPH patients were subjected to a four-week wash-out phase. All the patients received identical trial packs containing active drug or placebo capsules also of identical outward appearance. The treatment lasted 12 weeks, with control examinations of weeks 0, 6 and 12. The examination time 2 weeks after the start of the treatment, which was originally planned, proved to be impracticable. The dosage was 2 capsules t.i.d.

The control parameters investigated were: disturbances of micturition, nocturia, sensation of residual urine, dysuria, urge to urinate, discomfort in the inguinal, peritoneal and genital areas, palpation findings (enlargement, congestion of the prostate) uroflow index, residual urine volume determined by ultrasound, and the global assessment of the therapy by the doctor and by the patient.

In the laboratory examinations, SGOT, SGPT, PAP and creatinine in the serum were determined, as well as leucocytes, erythrocytes and germ count (if possible with identification of pathogens) in the sediment or in the urine culture. Besides descriptive-statistical methods the following analytical procedures were used: chi-square test (with Yates' correction for 2 x 2-field tables) for testing the homogeneity of qualitative parameters, comparison of the changes in the clinical symptoms at the end of the treatment versus the baseline findings, and for the comparison of the assessments of tolerability, the incidence of side effects and the global assessments by the doctor and by the patients, in both trial-groups; the t-test for

independent random tests in the homogeneity testing for age, height, body weight and urodynamic and quantitative laboratory parameters; the U-test in the homogeneity testing for the length of previous treatment of the BPH; variance analysis for the split-plot design for the evaluation of the course of the quantitative parameters. On account of the findings, the different levels of attendance at the appointed examination times and the practicability of the study, parameter specific sample sizes were achieved which, in the evaluations of courses, are documented in the form of a reduced number of patients.

In accordance with the FDA recommendations, the disturbances of micturition were classified according to their intensity [1]. The statistical comparison was based on the changes observed under the treatment, which were recorded as 'symptom-free', 'improved', 'unchanged', or 'worsened'. In patients with symptoms at the start of the study, response to the treatment is defined as a 'symptom-free' or 'improved' status of the therapy. Quantitative parameters were evaluated for the course and the pre-treatment/post-treatment comparison. The parallelism of the mean levels of intensity was also tested. The uroflow findings were

based on the secondary parameter, uroflow index (10).

Results

As regards medication and stage of the BPH, randomization gave a practically evenly distributed study population, with homogeneous baseline status in the two comparative groups. The age of the patients ranged from 42 to 85 years with a medium duration of the disease of 10 months; the BPH had been treated previously in 40.6 % of the cases (Table 1).

The initial clinical examination showed nocturia to be the leading symptom, occurring as a disturbance of micturition in 96.9 % of the patients (Figure 1). In the total study population examination by palpation showed enlargement of the prostate, with retained sulcus in 35.8 %, with obliterated sulcus in 55.8 % and with undefinable laterallobes in 8.4 % of the patients. On admission to the study, congestion of the prostate was palpable in 61.5 % of the cases, being classified as slight in 33.0 %, moderate in 17.5 % and severe in 11.0 %. The urodynamic status on admission to the study also showed homogeneous baseline data in the two comparative groups, whereby the uroflow parameters are presented also according to the uroflow index (Table 2).

Clinical symptomatology

As regards the clinical symptomatology, the pre-treatment/post-treatment comparison shows clear differences between the treatment groups: Under the pollen-extract the nocturia improved significantly, in 68.8% of the patients compared with 37.2% under the placebo medication. Freedom from the symptoms daytime frequency and sensation of residual urine is found significantly more frequently under the active treatment (table 3). For all the individual symptoms the examinations of the courses after 6 weeks and after 12 weeks of the study show higher rates of improvement or positive response course under the active treatment, with no change or deterioration under placebo. In the case of nocturia, day time frequency and sensation of residual urine these differences are particularly pronounced (Figure 2).

Enlargement and congestion of the prostate show higher response rates, in the sense of decrease in size and decongestion, under the active treatment (AT), whereby a striking trend is to be observed in comparison with placebo (PI) (Table 3). In contrast to the course in regard to the enlargement of the prostate, where the response rate remained constant in both groups, in the case of the congestion the improvement rate after 12 weeks, at 86.7%, was 20% higher than that recorded after 6 weeks' treatment, under the active preparation. In comparison, the response under placebo at these two examination times was 70.8% and 70.9%, respectively.

Urodynamics

Significant differences in favour of the pollen-extract are also to be seen in regard to the urodynamic test parameters. For all the uroflow parameters the changes in the findings were similar in both treatment groups, whereby the differences before and after the treatment are not statistically significant. Taking into account the examination after 6 weeks, a continuous increase of the initially pathological uroflow index is to be observed, by an average of 0.18, under the pollen-extract. In the placebo group ($x = +0.10$ after 12 weeks) the uroflow decreased in the second half of the study (Table 4, Figure 3).

The peak urine flow rate increase by an average of 3.3 ml/sec in the pollen extract group and by 0.9 ml / sec in the placebo group.

The difference in the reduction of the residual urine volume in the course of the study was statistically significant (AT 24.3 ml / PL 3.7 ml; $P = 0.006$). The pollen-extract leads to a continuous reduction, whereas in the placebo group there is a decrease after 6 weeks, compared with an increase in the residual urine volume after 12 weeks (Figure 3). When BPH stage III is considered separately there is an average decrease of 36.9 ml under the active treatment, compared with 7.2 ml under placebo, whereby an increase in the residual urine volume is to be observed in the second of the two 6-week study periods in the placebo group (Figure 4).

Global Assessment

The laboratory parameters show no noteworthy changes. Unwanted drug effects in the form of slight nausea are recorded in one case under the

active treatment. The good tolerability of the treatment is documented in 95.8% of the patients. With regard to the therapeutic efficacy, both investigator and patient assessed the result of the treatment as 'very good' or 'good' significantly more frequently under the pollen- extract (Figure 5). A statistically significant difference of the assessments by the investigator and by the patient was observed in the patients with an initially pathological uroflow index (Table 5).

Discussion

The results of this study demonstrate the good efficacy of the pollen-extract preparation in benign prostatic hyperplasia (BPH) in stages II and III. The superiority of the active therapy is documented in the symptomatology, the results of the urodynamic investigations and by the global evaluation of the therapy by both doctor and patient.

The course of the characteristic disturbances of micturition is an important parameter for the assessment of therapeutic efficacy. Under the pollen-extract the nocturia improved in the course of the 12-week study period in 68.8 % of the patients. In the placebo group, on the other hand, regression was observed in only 37.2 %. In the pre-treatment/post-treatment comparison this leading symptom of BPH showed a significant difference, which increased progressively in the course of the study, in favor of the active trial therapy. While under placebo the response rate remained practically constant, under the pollen-extract medication, regression of the symptoms was observed in a further 21.3% of the patients after the second 6-week period of the study. For the symptoms of daytime frequency and sensation of residual urine there are also clear differences in favour of the active treatment, whereby the differences as regards symptom-free status are statistically significant. For dysuria, urge to urinate and discomfort no statistically significant differences are recorded on account of the high placebo-response rates. The irritative symptoms, which are predominant in BPH, showed a particularly positive response to the active treatment. The obstructive components of the general disturbance of micturition were investigated on the basis of the urodynamic parameters, so that here an evaluation based on the symptoms themselves was not necessary.

As was to be expected, the size of the prostate, as determined by palpation, showed a low response rate, which remained constant in the course of the study.

Particularly striking is the change in the findings in regard to congestion of the prostate, which showed improvement in 69.0 % of the patients under placebo. Because of this high placebo-response rate, the response rate of 88.5 % under the active treatment is not statistically significant.

The differences in the response rates observed in the course of the study, between the active treatment and placebo, in the clinical symptomatology and in the congestion of the prostate demonstrate the sustained therapeutic effect of the pollen extract on the intensity of the disturbance of micturition.

Because of the relation of the peak urine flow on the volume voided (3,10), the uroflow index was chosen for the evaluation of these parameters. An increase in this index is to be observed in both comparative groups, whereby the difference is not statistically significant. In the assessment over the course of the study a continuous increase is seen in the active- treatment group, while under placebo the index decreases in the second half of the study.

The proportion of 35%, compared with 20% in the placebo group of initially pathological uroflow index values getting borderline or normal after treatment, is to be evaluated as a trend in favour of the active treatment. Clear differences are recorded in regard to the decrease in residual urine volume.

Under both trial preparations a reduction is to be observed in the first 6 weeks, which in the active treatment group becomes even more pronounced in the second half of the study, whereas under placebo there is a deterioration of the value recorded after the first 6 weeks.

As the separate evaluations according to the stage of the BPH demonstrate, the pollen extract leads to a more pronounced mean reduction in those cases with an initially high residual urine volume. The reduction in the residual urine volume in the patients with stage III BPH was 54.7 % under the active treatment and 12.5 % under placebo.

As a reflection of the therapeutic efficacy of the pollen-extract there are clear differences between the active treatment and placebo in the global assessments of the therapy by the doctors and by the patients. Particularly also in regard to the patient group with an initially pathological uroflow index, where the assessment of efficacy by the urologists as "poor" was documented in 41.9 % of the patients under placebo.

The fact that in 55.2 % of these patients the result of the treatment under the pollen extract was evaluated as "very good" or "good" is possibly an indication that the uroflow index is a relatively inaccurate parameter for detecting the more subtle urodynamic changes.

In order to obtain a representative patient population for the investigation of the efficacy of a drug therapy, this study was carried out in collaboration with six practicing urologists. The consistency of the data confirms our view that in the case of conservative therapeutic measures which are used mainly on an ambulant basis, the involvement of the preclinical aspects in the clinical research is both desirable and possible. However, the possible disadvantage that the number of patients attending the different control examinations can vary has to be taken into account.

The mechanism of action of the pollen-extract can be suggested as being its effect on the congestive and inflammatory changes occurring in BPH. Too little attention has been paid to the possible clinical relevance particularly of the chronic inflammatory changes (9, 11), the incidence of which, in BPH, is given as up to 98.1 % (5-8). In the long term, changes can develop in the connective tissue, which then become pathological in the form of fibrosis and sclerosis. The congestion of the prostate caused by stasis of secretions or the formation of

interstitial edema also has to be considered as a pathophysiological substrate of the disturbances of micturition occurring in BPH. It is to be

assumed that these concomitant changes lead to alterations in the nerve supply in the prostate and this influence the clinical symptomatology and urodynamics.

The documented normalization of the parameters of inflammation in the EPS with the pollen-extract in patients with chronic prostatitis (2), can explain the therapeutic efficacy of this preparation, in the sense of its antiedematous and anti-inflammatory action, also in patients with BPH. In view of the antisclerotic properties of the pollen-extract, with continuous application a long-term pharmacological effect on the clinical symptomatology and urodynamics is conceivable, so that surgical intervention, at least in certain cases, is not necessary (9).

Conclusion

The results of this study demonstrate the efficacy of the pollen-extract preparation in BPH patients in stages II and III, in regard to the clinical symptomatology, urodynamics, and global assessment. The pollen-extract preparation is well tolerated and makes long-term treatment possible with a low risk of side effects. The use of Cernilton N is recommended for the treatment of BPH stages II and III.

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SYMPTOM	CLINICAL STATUS ON ADMISSION	% OF PATIENTS
Nocturia	XXXXXXXXXXXXXXXXXXXXXXXXXXXX	96,9%
Daytime frequency	XXXXXXXXXXXXXXXXXXXXXXXXXXXX	89,1%
Urge to urinate	XXXXXXXXXXXXXXXXXXXXXXXXXXXX	87,9%
Sensation of residual urine	XXXXXXXXXXXXXXXXXXXX	66,3%
Discomfort	XXXXXXXXXXXX	62,4%
Dysuria	XXXXXXXXXX	47,3%

Figure 1: Clinical status on admission into the study: incidence of the different symptoms in the total study population (n = 96)

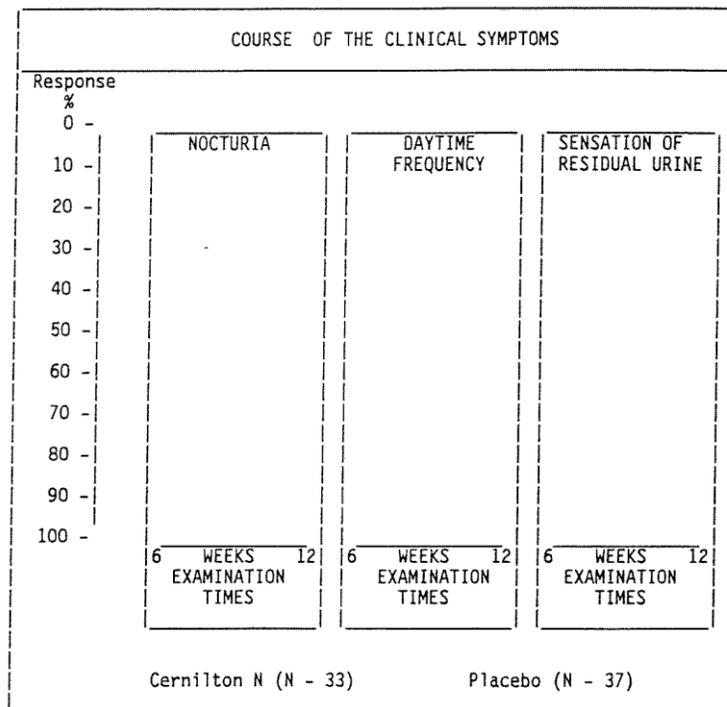


Figure 2: Response rate for the symptoms nocturia, daytime frequency and sensation of residual urine at the examinations after 6 weeks and 12 weeks, under the pollen-extract and placebo.

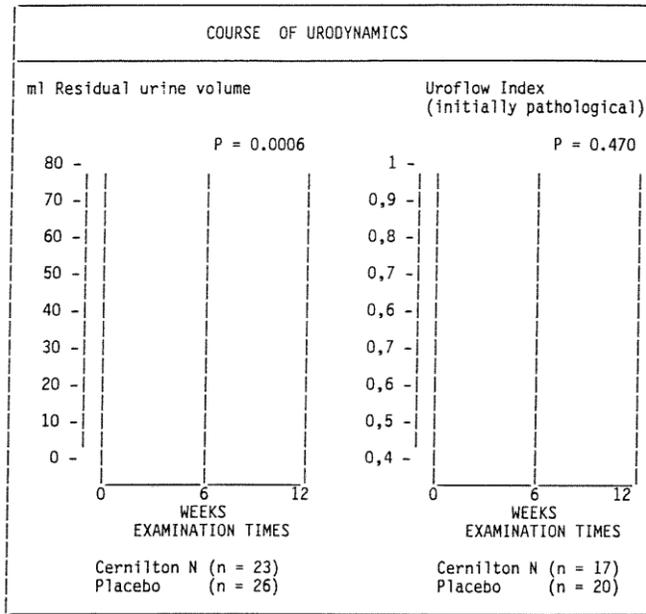


Figure 3: Course of the residual urine volume (ml) and the uroflow index (initially pathological) in the comparative groups. Continuous reduction resp. increase of the two parameters, under the pollen-extract. Unfavourable response of both parameters after 6 weeks under placebo.

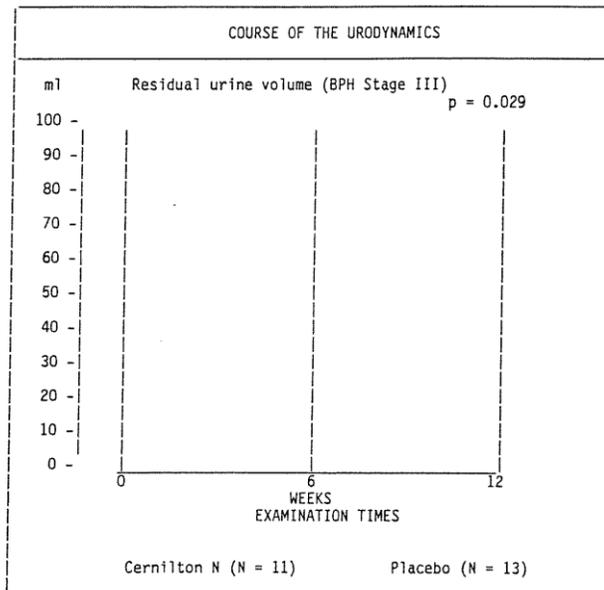


Figure 4: Course of the residual urine volume (ml) in BPH stage III. Significantly different and continuous reduction of the residual urine volume under the pollen-extract. Increase of the residual urine volume in the second half of the study period under placebo.

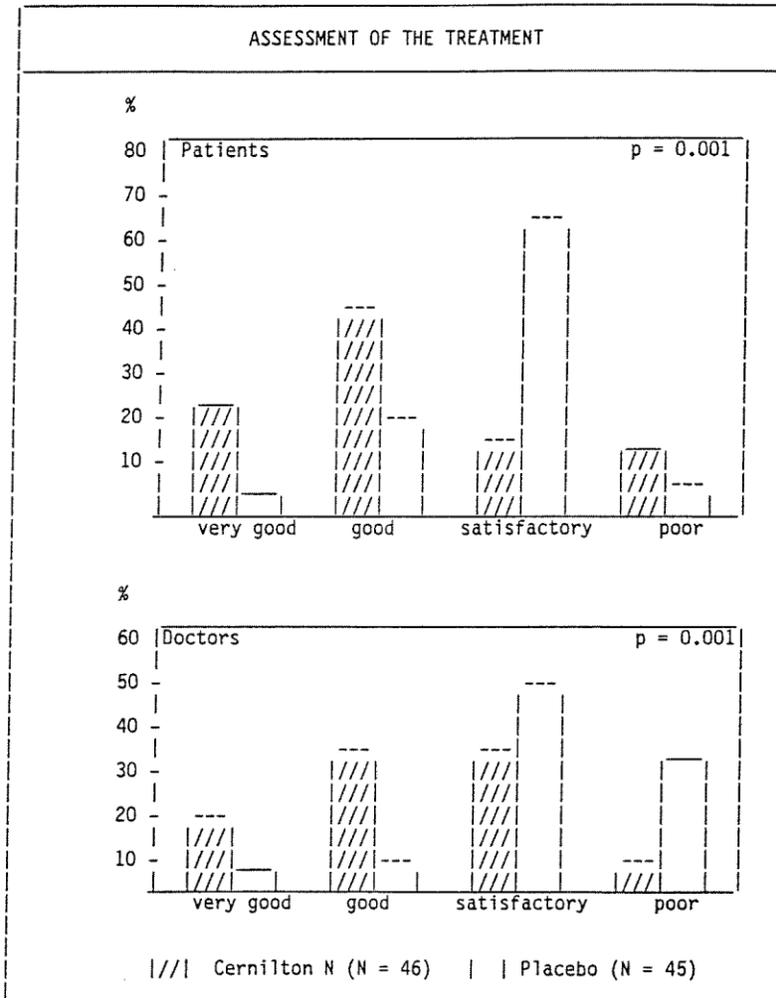


Figure 5: Significantly better assessment of the treatment by both doctors and patients in the pollen-extract group.

Table 1: Age distribution, BPH stage, duration of symptoms and previous treatment in the comparative groups. The BPH Stages are according to the classification of W. Vahlensieck.

Age Distribution and baseline status				
Parameter	Value/Code	Cernilton	N	Placebo
Age (years)	Minimum	42		45
	Maximum	83		85
	Median	65		67
	Mean value	66.0		67.1
	Standard deviation	9.7		10.1
BPH Stage	II	23		22
	III	25		26
Duration of Symptoms (months)	Minimum	1		1
	Maximum	48		48
	Median	11.4		8.3
	Missing data	4		3
Previous Treatment	No	29		28
	Yes	19		20

Table 2: Baseline urodynamic status: residual urine volume (ml) and uroflow index in the comparative groups. Homogeneous baseline status in both parameters (n = 96 and 86, respectively).

Urodynamic status at baseline						
Parameter	Value/Code	Cernilton	N	Placebo	Total	Homogeneity P-value
Residual urine volume (ml)	Minimum	0		0	0	
	Maximum	100		120	120	
	Mean value	45.6		47.8	46.7	0.735
	Standard deviation	30.6		31.5	31.5	
Uroflow Index	Minimum	0.21		0.27	0.21	
	Maximum	1.43		1.76	1.76	
	Mean value	0.73		0.71	0.72	0.843
	Standard deviation	0.26		0.33	0.29	

Table 3: Statistically significant differences in favour of the active treatment, in the symptoms nocturia, daytime frequency and sensation of residual volume. The congestion of the prostate improved significantly more frequently under the pollen-extract.

Pre-/Post-treatment comparison of clinical symptomatology				
Symptom	Cernilton	N	Placebo	Significance P-value
Response				
Nocturia	68.8 %		37.2 %	0.005
Daytime frequency	65.8 %		43.9 %	0.076
Sensation of residual urine	71.4 %		48.1 %	0.109
Freedom from symptoms				
Nocturia	25.0 %		16.3 %	0.445
Daytime frequency	48.8 %		19.5 %	0.010
Sensation of residual urine	37.1 %		7.7 %	0.016
Palpation	Cernilton	N	Placebo	Significance P-value
Enlargement of the prostate	17.4 %		10.6 %	0.522
Congestion of the prostate	88.5 %		69.0 %	0.155

Table 4: Residual urine volume (ml) and uroflow index before and after treatment in the two comparative groups. Statistically significantly greater reduction of the residual urine volume under the pollen extract.

Pre-/Post-treatment comparison of the urodynamic findings						
Parameter	Time of the control	Cernilton		Placebo		Variance analysis P-value
		\bar{x}	s	\bar{x}	s	
Residual urine volume (ml)	n	48		48		
	Before treatment	45.6	30.4	47.8	32.8	
	After treatment	22.5	20.9	37.0	28.9	0.032
Uroflow Index	n	40		40		
	Before treatment	0.74	0.27	0.72	0.34	
	After treatment	0.86	0.25	0.82	0.31	0.747

Table 5: Significant better assessment of the treatment by Investigator in favour of pollen-extract in patients with initially pathological uroflow-index ($p < 0,001$)

ASSESSMENT OF TREATMENT (INVESTIGATOR) ON PATIENTS WITH INITIALLY PATHOLOGICAL UROFLOW-INDEX		
	Cernilton N (n = 29)	Placebo (n = 31)
Very good	17,3 %	6,5 %
Good	37,9 %	6,5 %
Satisfactory	41,4 %	45,1 %
Poor	3,4 %	41,9 %

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