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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Efficacy of two formulations of *Sabal serrulata*; a double-blind, randomized, placebo-controlled phase III study;
The "BASTA" Study

Trial information

Full title of the study:	Efficacy of two formulations of *Sabal serrulata*; a double-blind, randomized, placebo-controlled phase III study The "BASTA" Study
Study identifier:	EudraCT number: 2006-003532-30 Sponsor Protocol Code: BCSK/05/Pro-BPH/001
Sponsor details:	Berlin-Chemie AG; Glienicker Weg 125, 12489 Berlin, Germany
Scientific contact point:	Michela Falciani, M.D.; Berlin-Chemie AG; Tel.: +49 (39) 6707 2252; email: mfalciani@berlin-chemie.de
Result analysis stage:	Global end of trial reached; Date of integrated study report: 12. MARCH 2010
Main objectives:	Demonstrate equi-efficacy of an Ethanol extract and a Hexane extract of *Sabal serrulata (Saw palmetto fruit)*. For showing internal evidence of assay sensitivity of the selected primary clinical endpoint (change in IPSS), a placebo group was included additionally.
Date of start of recruitment	28-NOV-2006
Date of first subject in	28-DEC-2006
Date of last subject out	27-NOV-2008
Follow up duration	4-week placebo-controlled run in phase followed by 12 months of active treatment; randomization and start of active treatment at visit 2 (V2).
Experimental products used	1. Ethanol extract of *Sabal serrulata (Saw palmetto fruit)* (Prostamol® uno once daily, Berlin-Chemie AG) 1x320 mg p.o. as the investigational drug, 2. placebo as the control group.
Active comparator(s)	Hexane extract of *Sabal serrulata (Saw palmetto fruit)* (Permixon® twice daily, Pierre Fabre) 2x160 mg p.o. as the comparator drug,
Background therapy	None
Number of subjects in each country	59 centers in six countries: Germany (DE), Lithuania (LT), Romania (RO), Slovak Republic (SK), Poland (PL), Russia (RU): DE 128; LT 142; RO 405; SK 48; PL 131; RU 265; total 1119.
Age	Males: mean age of 64.76 years; minimum age: 48.3 years, maximum age 87.3 years; Median: 65.20 years.
Gender	Males of Caucasian race

Subject disposition

Blinding	Double blind, double dummy
Allocation method	Randomized, controlled
Arm title and description 1: Number of subjects	Ethanol extract of *Sabal serratula* berries *(Saw palmetto fruit)*; One capsule (320 mg) per day, p.o., 12 months. 334
Arm title and description 2: Number of subjects	Hexane extract of *Sabal serratula* berries *(Saw palmetto fruit*; two capsules per day (160 mg), p.o., 12 months. 330 (PP)
Arm title and description 3: Number of subjects	Placebo: Placebo, One capsule per day resembling the capsule of the investigational drug. 126
Number of subjects Completed	Planned (needed for analysis): 732 patients; Screened: 1119 patients Run in phase: 1109 patients Randomized: 1011 patients Analyzed: - Safety population: 1011 patients: - Intention to treat (ITT) population: 924 patients - Per protocol (PP) population: 790 patients
Number of subjects Not completed Reasons	ITT/PP: 88/6 subjects: 39/5 subjects Arm 1; 37/1 subjects Arm 2; 12/0 subject Arm 3; Protocol violation (incl./excl. criteria not met) (ITT 64), consent withdrawal (ITT 30)

Subject analysis set

Types, description and number of subjects	Safety population: all patients, safety set included all randomized patients for whom it cannot be ruled out that they took the study medication at least once (1011 subjects)
	Intent-to-treat population (ITT): all patients with at least one study medication and/or at least one study measure (924 subjects)
	Per protocol population (PP): patients, who were compliant with the clinical study protocol. Also patients who terminated the study prematurely because of an event related to the study medication were included in the per protocol set (790 subjects)

Baseline characteristics (PP set)

Demographic variables

Demographic variable		Overall (N = 790)			
		Ethanol extract (N=334)	**Hexane extract (N=330)**	**Placebo (N=126)**	**All (N=790)**
Age [years], mean (SD)		65.14 (7.665)	64.61 (7.535)	64.14 (7.692)	64.76 (7.615)
Height [cm], mean (SD)		173.8 (5.90)	173.7 (6.07)	173.8 (6.19)	173.8 (6.01)
Weight [kg], mean (SD)		79.8 (10.65)	80.5 (11.10)	80.4 (12.09)	80.2 (11.06)
BMI [kg/m²], mean (SD)		26.40 (3.097)	26.65 (3.214)	26.58 (3.370)	26.53 (3.189)
Race [N], (%)	Caucasian	334 (100.0)	328 (99.4)	126 (100.0)	788 (99.7)
(Missing=1)	African	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Other	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Smoking [N] (%)	Non-smoker	269 (80.5)	260 (78.8)	87 (69.0)	616 (78.0)
	Occasional	30 (9.0)	29 (8.8)	12 (9.5)	71 (9.0)
	Regular	35 (10.5)	41 (12.4)	27 (21.4)	103 (13.0)
Alcohol [N] (%)	Never	84 (25.1)	85 (25.8)	28 (22.2)	197 (24.9)
	Occasional	247 (74.0)	244 (73.9)	97 (77.0)	588 (74.4)
	Daily	3 (0.9)	1 (0.3)	1 (0.8)	5 (0.6)

N = number of patients, Missing = number of missing values, SD = standard deviation, BMI = Body Mass Index

Vital signs (Safety set, N=1011)

Treatment	**Parameter**		
	Systolic blood pressure Mean (SD)	**Diastolic blood pressure Mean (SD)**	**Heart Rate Mean (SD)**
Ethanol extract (N=424)	134.1 (12.24)	79.9 (7.64)	71.7 (6.86)
Hexane extract (N=422)	134.9 (12.31)	80.6 (7.79)	72.2 (6.71)
Placebo (N=165)	133.4 (11.67)	81.2 (7.62)	72.1 (6.68)

N = number of patients, SD = standard deviation

Medical history (Most frequent previous and concomitant diseases by preferred term (occurrence in ≥ 2% of all patients, safety [run-in phase] set, N = 1109)

Preferred Term	**N_1**	**%**	**N_2**
Any disease	699	63.0	1689
Hypertension	350	31.6	350
Myocardial ischemia	122	11.0	122
Hypercholesterolemia	66	6.0	66
Hematuria	55	5.0	55
Crystalluria	43	3.9	43
Myocardial fibrosis	40	3.6	40
Coronary artery disease	31	2.8	31
Dyslipidemia	31	2.8	31
Gastritis	29	2.6	29
Appendectomy	26	2.3	26
Duodenal ulcer	25	2.3	25
Nephrolithiasis	24	2.2	24

N1 = number of patients with at least 1 disease, N2 = number of diseases; calculation of percentages based on N=1109

Endpoints and statistical analysis of endpoints

Primary Endpoint

Title	Response rate according to the International Prostate Symptom Score (IPSS) based on the comparison of the results of the Baseline Visit (V2) and after 12 months (V7). Response was defined as an improvement of at least 5 points according to the IPSS or 38.5% in relation to the baseline value of IPSS.
Statistical analysis type	Primary analysis type: non-inferiority of Ethanol extract over Hexane extract; primary population for analysis: PP set. Secondary analysis type: superiority of Ethanol extract in comparison to Placebo as well as non-inferiority in comparison to Hexane extract.
Subject analysis sets	PP: 5:5:2 randomization for Ethanol extract, Hexane extract and placebo, respectively.
Statistical analysis description	For the comparison with Hexane extract a non-inferiority margin of 15% was assumed. Point estimations for the responder rates according to the binomial distribution and the 95% confidence intervals were determined. The difference in responder rates (Ethanol extract – Hexane extract) and the respective exact one-sided 97.5% confidence interval according to the binomial distribution were calculated. Non-inferiority was concluded, if the value –0.15 was below this interval. For the comparison with Placebo for the difference in response rates according to the IPSS , point estimations according to the binomial distribution and the 95%-confidence intervals were calculated.For the difference in responder rates (Ethanol extract - Placebo) the point estimator was determined and the respective exact one-sided 97.5% confidence interval was calculated. Superiority was concluded, if the value 0 lay below this interval.
Sample size	Based on Fischers exact test and a = 0.05 305 patients in the Ethanol extract group and 122 patients in the placebo group were necessary to show superiority with a power of 90%. For Hexane extract non inferiority test of Ethanol to Hexane extract would have a power of 95% with a non-inferiority margin of 15% if both active groups had 305 patients, each.
Statistical hypothesis	Non-inferiority of Ethanol over Hexane extract of *Sabal Serrulata (Saw palmetto fruit)*; Superiority of Ethanol extract over placebo.

Primary Endpoint estimates (results)

The difference in estimated response rates between Ethanol extract and Hexane extract was 0.014 with the 97.5% confidence interval [-0.061; 1]. As the predetermined non-inferiority margin of –0.15 lies below the confidence interval, non-inferiority of Ethanol extract can be concluded.
The difference in estimated response rates between Ethanol extract and placebo was -0.081 with the 97.5% confidence interval [-0.181; 1]. As 0 does not lie below the confidence interval, superiority of Ethanol extract cannot be concluded.
Since non-inferiority of Ethanol and Hexane extract and no superiority of Ethanol extract over placebo were shown, it can be concluded that responder rates following treatment with Hexane extract were also not superior over placebo.
As this study was conducted in six different countries, a test for country effects was performed using Cochran-Mantel-Haenszel statistics. The test for general association resulted in a test value of 3.3051 with a p-value of 0.1916, i.e. there were no significant country effects, which might have biased the results.

Secondary Endpoints

Statistical analyses for all secondary endpoints

Statistical analysis type	Descriptive
Subject analysis set	PP: 5:5:2 randomization for Ethanol extract, Hexane extract and placebo, respectively
Statistical analysis description	All parameters were analyzed using descriptive methods. Comparison between treatment groups was done using the Wilcoxon rank-sum test for continuous data and Fisher's exact test for categorical data. All obtained p-values were only interpreted in an exploratory manner.
Point estimate	N.A.

Secondary end point # 1	Change in IPSS from baseline at Randomization Visit (V2) to the end of treatment after 12 months at Visit 7, Development of IPSS over time

Results: No significant differences between treatment groups were found.

Secondary end point # 2	Development of IPSS over time

Results: The IPSS sum scores decreased constantly in all treatment groups during the course of the study. No significant differences between Ethanol extract and Hexane extract treatments were observed at any visit, but the p-values for Visits 3 and 4 were close to significance ($p = 0.0565$ and $p = 0.0616$, respectively). In contrast, the differences between the placebo and Ethanol extract groups were significant for Visits, 1, 2, 3, and 5 (0.0236, 0.0363, 0.0404, and 0.0371, respectively). The differences of placebo and Hexane extract treatments were significant only for Visit 7 with $p = 0.0450$.

Secondary end point # 3	Development of irritative and obstructive symptoms over time

Results: A steady decline of scores could be observed for irritative symptoms. No significant difference in treatment effects occurred after randomization.
A steady decrease in scores over time was observed for the obstructive symptoms subscale. In the placebo group a steeper decrease than in the other groups occurred. No significance was found at any point of time.

Secondary end point # 4	Changes of urodynamical examinations by measuring maximum urinary flow (Q_{max})
Secondary end point # 5	Changes of urodynamical examinations by measuring residual urinary volume (RUV)

Results: The change in Q_{max} did not show consistent patterns between treatment groups. A negative pre-post difference in RUV from respective visits to baseline indicate an improvement. For voided volume, improvement can be concluded by a pattern of pre-post differences contrary to residual volume: the higher the change, the more volume could be voided at the respective visit. The comparison of treatments using the Wilcoxon two-sample test resulted in no significant differences between treatments except for the comparison of residual volume between Hexane extract and both Ethanol extract and placebo at Visit 4 ($p = 0.0479$ for Hexane extract - Ethanol extract and 0.0471 for Hexane extract - placebo).

Secondary end point # 6	Frequency of Acute Urinary Retention (AUR)

Results: Symptoms of AUR occurred rarely among study patients. Because of the rare occurrence of AUR symptoms, only few comparisons between treatments using Fisher's exact test could be performed, none of which revealed a significant difference in frequencies of AUR symptoms between groups.

Secondary end point # 7	Change in Quality of Life (QoL)

Results: In all three treatment groups the pre-post differences of QoL scores decreased constantly from Visit 2 to Visit 7. A pairwise comparison of treatments using the Wilcoxon two-sample test resulted in no significant values with the exception of Ethanol extract and Hexane extract for the change between Visit 3 and Visit 2 with a p-value of 0.0443.

Secondary end point # 8	Change in prostatic volume

Results: The prostate volumes decreased in all three treatment groups. Despite the obvious differences between groups regarding volume changes, no significance could be detected.

Post-hoc subgroup analyses

As it is possible that superiority of Ethanol extract over placebo was obscured because the patients had little potential for improvement, the following patient subgroups were analyzed post-hoc:

1. Subgroup analysis: IPSS Sum Scores at Baseline

Analysis of the primary variable was also performed for patients with baseline IPSS of ≥ 20, ≥ 19 and ≥ 18. The analyses were based on the safety (study medication) set, because IPSS scores of 20 or more were a criterion for exclusion; thus, the patients considered were not part of the ITT and PP populations.
It could be shown for these subgroups that Ethanol extract is superior to placebo treatment if the definition of response was adapted in each subgroup. For the subgroup of patients with an IPSS of ≥ 20 at baseline, Ethanol extract was superior if response was defined as an improvement of at least 5 points. For the subgroup with a baseline IPSS of at ≥ 19 points, superiority could be concluded if response was defined as an improvement of at least 8 points. Finally, for a subgroup of patients with a baseline IPSS of ≥ 18 points, superiority could be concluded if response was defined as an improvement of at least 13 points. In other words, the lower the IPSS at baseline, the more distinct a response is required to detect superiority.

2. Subgroup analysis: Residual Volume and Maximum Urinary Flow (Q_{max})

Patients with RUV ≥ 15 ml and Q_{max} ≤ 11 ml/s at Baseline (PP set, N = 330)
In this subgroup of patients, response was defined as an improvement of at least 10 points according to the IPSS scale. Superiority of Ethanol extract over placebo could be concluded for this subgroup of patients when response was defined as an improvement of at least 10 IPSS points. Also, non-inferiority of Ethanol extract to Hexane extract could be concluded for this subgroup.

Patients with RUV > 50 ml at Baseline (PP set, N = 169)
In this subgroup of patients response was defined as an improvement of at least 9 points according to the IPSS scale. Superiority of Ethanol extract over placebo could be concluded for this subgroup of patients when response was defined as an improvement of at least 9 IPSS points. Also, non-inferiority of Ethanol extract to Hexane extract could be concluded for this subgroup.

Patients with RUV ≥ 50 ml and Q_{max} ≤ 12 ml/s at Baseline (PP set, N = 158)
In addition to the criterion of an RUV of at least 50 ml at Baseline, only patients with a Q_{max} of not more than 12 ml/s at baseline were specifically included in this subgroup. Again, response was defined as an improvement of at least 9 points according to the IPSS scale. Superiority of Ethanol extract over placebo could not be concluded for this subgroup of patients and with response defined as an improvement of at least 9 IPSS points, but the proof of superiority was missed narrowly. This may be concerned with the low number of patients in this subgroup. However, non-inferiority of Ethanol extract to Hexane extract could be concluded for this subgroup.

3. Influence of Smoking Behavior

In order to find factors that might have influenced the distribution of responders and non-responders in the total IPSS score, we investigated the influence of smoking behavior by means of a discriminant analysis. A placebo effect among regular and occasional smokers emerged. Analysis of response in non-smokers resulted in responder rates of 56.1% (Ethanol extract), 53.1% (Hexane extract) and 54% (placebo) after 12 months. That is, the placebo effect does not occur in non-smokers. An ANOVA analysis showed that there was significant interaction between treatment and smoking behavior ($p = 0.0174$).

Adverse Event Information

Secondary end point # 9	Adverse events (AE)
Serious Adverse Events (SAE)	During the run-in phase, 5 SAE symptoms in 4 patients were reported. These SAE symptoms were assessed as "unrelated" to the intake of study medication. 6 patients prematurely withdrew from the study during the run-in phase because of Treatment Emergent Adverse Events (TEAEs), one of which was assessed as "possibly" related and the others were assessed as "unrelated" to the study medication by the investigator. After randomization, 19 patients had SAEs until the end of the study, 5 of them discontinued prematurely due to SAEs. The causality assessment of all SAEs was "unrelated" or "unlikely". Statistical analysis revealed that the 3 groups were homogenous with respect to numbers of patients who had TESAEs and to numbers of patients who had TEAEs that led to premature study discontinuation.

Results: Serious AEs (safety [study medication] set, N = 1011)

Patient-Number	SAE (MedDRA preferred term)	Severity	Causal relationship to study drug	Final outcome
Ethanol extract:				
368	Cerebral ischemia	Moderate	Unrelated	Resolved with sequelae
825	Cholelithtotomy	Mild	Unrelated	Resolved
910	Urinary retention*	Moderate	Unrelated	Resolved
1223	Arrhythmia	Moderate	Unrelated	Resolved
1223	Myocardial infarction	Moderate	Unrelated	Fatal
1322	Colon cancer*	Severe	Unrelated	Not resolved
1382	Lactose intolerance	Moderate	Unrelated	Resolved
1384	Meniscus operation	Moderate	Unrelated	Resolved
1426	Gastrointestinal hemorrage	Severe	Unrelated	Resolved
1444	Vertrebrobasilar insufficiency	Moderate	Unrelated	Unknown
1476	Phimosis	Mild	Unrelated	Resolved
Hexane extract:				
242	Coronary artery stenosis	Moderate	Unrelated	Resolved
287	Goiter	Moderate	Unrelated	Not resolved

Patient-Number	SAE (MedDRA preferred term)	Severity	Causal relationship to study drug	Final outcome
357	Cerebral infarction*	Moderate	Unlikely	Not resolved
433	Urinary retention*	Severe	Unrelated	Resolved
478	Vertebrobasilar insufficiency*	Mild	Unrelated	Resolving
634	Chronic Lympholytic leukemia	Mild	Unrelated	Not resolved
891	Lower limb fracture	Moderate	Unrelated	Resolved
1035	Myocardial ischemia	Severe	Unrelated	Resolved
Placebo:				
347	Cholelithiasis	Moderate	Unrelated	Resolved
347	Thrombophlebitis	Mild	Unrelated	Resolved
347	Abdominal hernia	Moderate	Unrelated	Resolved
347	Deep vein thrombosis	Mild	Unrelated	Resolved
401	Syncope	Mild	Unrelated	Resolved

* = SAE symptoms leading to premature discontinuation

Non-serious adverse event	During the run-in phase, 4 AEs (3 reports of diarrhea, 1 gastrointestinal disorder) with a "possible" or "probable" relation to treatment were documented in 3 patients. After randomization, AEs with a "possible" or "probable" relation to treatment were diagnosed only in the Ethanol extract and the Hexane extract treatment groups, but not in the placebo group. Statistical analysis revealed that there were no differences between treatment groups with respect to AEs.

Results: Treatment emergent adverse event symptoms assessed as "possible" or "probable" (safety [study medication] set, N=1011)

Treatment group Patient number	Episode number	Symptom (as coded by MedDRA)	Assessment
Ethanol extract			
65	1	Lower limb fracture	Possible
133	1	Hyperhidrosis	Possible
279	2	Urinary retention	Possible
Hexane extract			
308	1	Dyspepsia	Possible
629	1	Constipation	Possible
710	1	Diarrhea	Probable
823	1	Pain in extremity	Possible
921	1	Polyuria	Possible
1011	1	Hepatic pain	Possible
Placebo			
No AEs assessed as 'possible' or 'probable'			

Secondary end point # 10	Premature study withdrawals

Six patients discontinued the study because of AEs during the run-in phase. One of these AEs was considered to have a "possible" relation to study medication. After randomization, 17 patients discontinued the study due to AEs. In the Ethanol extract group, 6 patients had AEs that led to premature discontinuation, one of which was assessed to be "possibly" related to study medication. In the Hexane extract group, 10 patients had AEs that led to premature discontinuation, one of which was assessed to be "possibly" related to study medication. In the placebo group, 1 patient had an AE that led to premature discontinuation ("prostate cancer"), which was assessed as to be "unrelated" to study medication.

Results: Treatment emergent AEs leading to premature discontinuation of the study (safety [run-in phase] set, N = 1109)

Patient number	**AE (MedDRA preferred term)**	**Severity**	**Causal relationship to study drug**	**Final outcome**
241	Prostate cancer	Moderate	Unrelated	Unknown
341	Ischemic stroke	Severe	Unrelated	Resolving
899	Mental disorder	Severe	Unrelated	Resolved with sequelae
900	Gastrointestinal disorder	Moderate	Possible	Resolved
949	Back pain	Mild	Unrelated	Unknown
949	Chest pain	Mild	Unrelated	Unknown
1467	Abdominal pain upper	Mild	Unrelated	Resolved

Results: Treatment emergent AEs leading to premature discontinuation of the study (safety [study medication] set, N = 1011)

Patient number	**AE (MedDRA preferred term)**	**Severity**	**Causal relationship to study drug**	**Final outcome**
Ethanol extract:				
133	Hyperhidrosis	Moderate	Possible	Resolved
852	Hyperkalemia	Moderate	Unrelated	Resolving
910	Urinary retention	Moderate	Unrelated	Resolved
1065	Gastric ulcer	Moderate	Unlikely	Resolving
1248	Erythema	Mild	Unlikely	Resolved
1248	Pruritus	Mild	Unlikely	Resolved
1322	Colon cancer	Severe	Unrelated	Not resolved
Hexane extract:				
37	Anuria	Mild	Unrelated	Resolved
308	Dyspepsia	Moderate	Possible	Not resolved
357	Cerebral infarction	Moderate	Unrelated	Not resolved
403	Weight increased	Moderate	Unrelated	Not resolved
433	Urinary retention	Severe	Unrelated	Resolved
478	Vertebrobasilar insufficiency	Mild	Unrelated	Resolving
851	Abdominal pain lower	Moderate	Unrelated	Resolved with sequelae

Patient number	AE (MedDRA preferred term)	Severity	Causal relationship to study drug	Final outcome
968	Diabetes mellitus	Mild	Unrelated	Not resolved
1011	PSA increased	Severe	Unlikely	Resolved
1017	PSA increased	Mild	Unrelated	Not resolved
Placebo:				
370	Prostate cancer	Moderate	Unrelated	Not resolved

More Information

Global Substantial Amendments	There was one country-specific substantial amendment in Russia. The amendment of the study protocol became necessary after discussion with Berlin-Chemie and the investigators at the investigator meetings for the study. With references to "Guidelines on Benign Prostate Hyperplasia" 2002 and to "5th International Consultation of Benign Prostate Hyperplasia (BPH) in Paris June 25 - 28, 2000 changes and explanations were required.
Global Interruptions and re-starts	The study was not interrupted.
Limitations & Caveats	This double-blind, double-dummy clinical study was conducted upon request of the national competent authority in EU with whom study design and endpoint parameters were agreed upon before study start. In their detailed assessment of the results national competent authority in EU emphasized that the study design was compliant with medical and scientific knowledge at the time of study conduct. IPSS as primary endpoint, especially in the lower measuring range (i.e. in less severe BPH symptoms) was not sensitive enough, a possible reason for the failure to proof efficacy. For any new clinical study to be conducted, it is recommended 1. the patient cohort to be selected more stringently (i.e.percentage of patients with higher severity of symptoms to be balanced in all study arms) 2. alternative to the IPSS as primary endpoint should be justified sufficiently Since non-inferiority of Ethanol and Hexane extract and no superiority of Ethanol extract over placebo was shown, it can be concluded that responder rates following treatment with Hexane extract were also not superior over placebo.