Clinical Study Synopsis

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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.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare AG	
Study Number:	11863	NCT00657839
Study Phase:	IIb	
Official Study Title:	A randomized, double-blind, placebo-controlled, multicenter, parallel group study to assess the efficacy of vardenafil in the treatment of symptomatic benign prostatic hyperplasia	
Therapeutic Area:	Men' s Health	
Test Product		
Name of Test Product:	Vardenafil (Levitra, BAY38-9456)	
Name of Active Ingredient:	Vardenafil	
Dose and Mode of Administration:	10 mg vardenafil tablets twice daily at 12-hour intervals	
Reference Therapy/Placebo		
Reference Therapy:	Placebo	
Dose and Mode of Administration:	Matching placebo tablets twice daily at 12-hour intervals	
Duration of Treatment:	Eight weeks	
Studied period:	Date of first subjects' first visit:	24 OCT 2005
	Date of last subjects' last visit:	19 JUN 2006
Premature Study Suspension / Termination:	None	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 22 SEP 2005) changed "serum creatinine ≥3.0 mg/dL" to "creatinine clearance <30 mL/min" in the exclusion criterion. Amendment no. 2 (dated 05 OCT 2005) specified the following changes: • Exclusion criterion "residual urine volume ≥150 mL" was changed to "residual urine volume >100 mL". • Exclusion criterion "previous episode of non-arteritic ischemic optic neuropathy (NAION)" was added. • Validity criterion "requirement for validity of measurement: minimal volume voided 120 mL" was added to the measurement of maximum urinary flow $Q_{max.}$ Amendment no. 3 (dated 14 NOV 2005) specified the optional collection of two additional blood samples at Visit 3 (interim) for assessment of pharmacokinetics and population pharmacokinetics.	
Study Centre(s):	The study was conducted at 16 active centers in Germany.	

Methodology:	This randomized, double-blind placebo controlled, multicenter, parallel group study consisted of a run-in phase, a treatment phase, and a follow-up visit (24 - 72 hours after the last intake of the study medication). The run-in phase comprised of the period between the screening visit (Visit 1) and the randomization visit (Visit 2). Subjects were randomized in block of 4 subjects at Visit 2. Subjects were assigned to 1 of the 2 treatment groups using a 1:1 ratio. Treatment was administered for 8 weeks, between Visit 2 and 4 (with Visit 2 considered as Day 1 of the treatment phase and Visit 4 considered as the first day after the treatment phase). International Prostate Symptoms Score (IPSS), maximum urinary flow (Q_{max}), and post-void residual urine volume (PVR) were assessed at Visits 1, 2, 3, 4, and at the premature discontinuation visit. Benign prostatic hyperplasia (BPH) Quality of Life Questionnaire 9 (QoL-9) was administered at Visits 2, 4, and at the premature discontinuation visit. International Index of Erectile Function (IIEF-EF) domain questionnaire was administered at Visits 2, 3, 4, and at the premature discontinuation visit. Data regarding adverse events were collected at all visits after Visit 1 (screening).
Indication Main Inclusion Criteria:	Indication: Benign prostatic hyperplasia (BPH) Inclusion criteria: Males aged 45 - 64 years with symptomatic BPH for at least 6 months and IPSS ≥12 at Visit 2 (randomization).
Study Objectives:	<u>Overall:</u> To assess the efficacy, tolerability, and safety of vardenafil (10 mg twice daily) versus placebo in the 2-month treatment of men with symptomatic benign prostatic hyperplasia.
Evaluation Criteria:	<u>Efficacy (Primary):</u> The primary efficacy variables included: • International Prostate Symptom Score • Maximal urinary flow <u>Efficacy (Secondary):</u> The secondary efficacy variables included: • Post-void residual urine volume (PVR) • Benign Prostatic Hyperplasia Quality of Life Questionnaire 9 (Urolife™) • Erectile function (EF) domain score of the International Index of Erectile Function • IPSS subscores-"obstruction" and "irritation" <u>Safety:</u> Treatment groups were compared with respect to the incidence rates of premature termination, adverse events, laboratory and electrocardiogram (ECG) abnormalities, and concomitant medication use emerging during the double-blind treatment period.

Statistical Methods:	Efficacy (Primary): The primary efficacy analysis was based on an analysis of covariance (ANCOVA) with baseline values as covariate and the last observation carried forward (LOCF) as dependent variable. Factors were "treatment" (i.e., placebo vs vardenafil) and "center". The analysis included an interaction term (treatment by center), if it appears to be statistically meaningful ($P<0.10$). The homogeneity of regression slopes was tested in order to investigate the appropriateness of the ANCOVA model. The IPSS was tested first, and if the result was found to be significant ($P<0.05$), Q_{max} was tested via the same model and with the same α (step-down procedure). The efficacy analyses of the primary efficacy variables were conducted for the intention-to-treat (ITT) and per-protocol (PP) samples. Efficacy was stated if the difference in the IPSS between the 2 treatment groups was significantly in favor of vardenafil in both the samples (ITT and PP). Efficacy (Secondary): The secondary efficacy analyses were applied on the ITT sample only. All analyses were descriptive. PVR, IIEF-EF, and QoL-9 were also analyzed using the same ANCOVA as outlined for the primary efficacy variables. Baseline values corresponded to the assessments done at Visit 2 (randomization). Subgroup analyses using pre-defined classifications were conducted for descriptive purposes. Furthermore, the correlation structure including factor analyses of all clinical variables was examined at baseline and LOCF. Stepwise discriminant analysis was employed to separate treatment groups on the basis of weighted clinical outcome variables. Psychometric properties of the IPSS were analyzed describing the factorial structure, reliability coefficients, and validity coefficients in relation to included rating scales and urodynamic variables. Safety: Statistical tests were not planned for safety variables. All safety variables were presented with regard to the treatment group. Adverse events were included if reported up to 30 days after study endpoint. Adverse events were considered treatment-emergent if they occurred after randomization or not later than 24 hours after last dose of the study treatment and the study endpoint. Adverse events were tabulated and classified according to the following definitions: • Treatment-emergent adverse events: all adverse events occurring the first time after randomization or pre-existing adverse events deteriorating after randomization. • Treatment-emergent, drug-related adverse events: all treatment-emergent adverse events being documented as "drug related" by the investigator, provided they occurred after randomization. • Serious adverse events: all adverse events classified to be "serious" and occurring at any time after the subject signed the informed consent.

	• Serious drug-related adverse events: all serious adverse events being documented as "drug related" by the investigator, provided they occurred after randomization. Measurements and changes from baseline in vital signs (blood pressure and pulse rate), continuous laboratory variables, and ECG parameters were summarized using descriptive statistics by treatment group and visit.
Number of Subjects:	A total of 247 subjects were enrolled and 222 were randomized to the study treatment (109 to vardenafil and 113 to placebo group). A total of 221 subjects (108 on vardenafil and 113 on placebo) were used for safety analysis. A total of 215 subjects (105 on vardenafil and 110 on placebo) were used for ITT analysis.

Study Results

Results Summary — Subject Disposition and Baseline

Of the 247 subjects enrolled into the study, one subject randomized to receive vardenafil did not take any study medication and, therefore, was considered invalid for any kind of analysis. Thus, the safety population consisted of 221 subjects. Six subjects of the safety population did not have any post-treatment efficacy data and were invalid for the ITT analysis. Thus, the ITT population consisted of 215 subjects.

A total of 18 subjects did not complete the study and had at least 1 required post-baseline efficacy measurement missing. Two subjects completed the study but had at least 1 required post-baseline efficacy measurement missing. Four subjects completed the study, had all IPSS and Q_{max} measurements documented, but had a change in IPSS total score by >7 points during the run-in phase, i.e., from screening (Visit 1) to baseline (Visit 2), which was considered a significant deterioration. One subject had an IPSS total score of 10 at baseline (Visit 2), whereas an IPSS ≥12 was required. All these 25 subjects were invalid for the PP analysis. Thus, the PP population consisted of 190 subjects (94 on vardenafil and 96 on placebo).

Demographic data and baseline characteristics of the safety population are summarized in Table 1.

Table 1: Demographic data and baseline characteristics (safety population)

Parameter		Vardenafil 10 mg (N=108)	Placebo (N=113)
Race [n (%)]	White	108 (100)	111 (98.2)
	Black	0 (0.0)	1 (0.9)
	Asian	0 (0.0)	1 (0.9)
Age (years)	Mean ± SD	56.5 ± 5.4	55.4 ± 5.7
Weight (kg)	Mean ± SD	88.3 ± 13.3	85.9 ± 11.3
Height (cm)	Mean ± SD	178.4 ± 6.9	178.5 ± 6.6
Body mass index (kg/m^2)	Mean ± SD	27.7 ± 3.9	27.0 ± 3.5

Abbreviations: N = number (entire population under study); n = number (sample of population under study) ; SD = standard deviation

Nearly all subjects had symptomatic BPH classified as "genital urinary tract disorders" and/or "prostatic neoplasms and hypertrophy". More than 60% of the subjects had erectile or ejaculation disorders. No differences in medical history findings were observed between the

two treatment groups. No differences in concomitant medications were observed between the two treatment groups.

Results Summary — Efficacy

The primary efficacy analysis was based on 2 variables: IPSS total score and maximum flow rate (Q_{max}). Analyses for 2 populations were conducted: ITT and PP populations.

The descriptive statistics for IPSS total score is summarized in Table 2 and the ANCOVA results for IPSS total score are summarized in Table 3.

Treatment efficacy with regard to the primary efficacy variables was demonstrated for the IPSS total score. The difference of 2.3 points between treatment groups was in the range of the differences found for alpha-adrenergic blockers (0.7 - 4.1 points).

Table 2: Summary statistics for change from baseline to Week 8 (LOCF) for the total scores of the IPSS questionnaire (ITT population)

'Total' (Q1-Q7) 'mild': 0-7; 'moderate': 8-19; 'severe': 20-35 Time	Vardenafil 10 mg (N=104) Mean ± SD (points)	Placebo (N=110) Mean ± SD (points)
Baseline (Visit 2)	16.7 ± 4.7	16.7 ± 4.4
Week 8 (LOCF)	10.3 ± 5.7	12.7 ± 7.2
Change from baseline	-6.4 ± 5.4	-4.1 ± 5.3

Abbreviations: IPSS = International Prostate Symptom Score; ITT = intent-to-treat; LOCF = last observation carried forward; N = number (entire population under study); SD = standard deviation

Table 3: ANCOVA results for change from baseline to Week 8 (LOCF) for the total scores of the IPSS questionnaire (ITT population)

'Total' (Q1-Q7) ('mild': 0-7; 'moderate': 8-19; 'severe': 20-35) Time	Vardenafil 10 mg (N=104) LS-mean (points)	Placebo (N=110) LS-mean (points)
Baseline (Visit 2)	16.8	16.8
Week 8 (LOCF)	11.0	13.2
Change from baseline	-5.9	-3.6
Difference between LS-means	2.3	
95% confidence interval	0.90 – 3.64	
P (F-test)	0.0013	

Abbreviations: ANCOVA = analysis of covariance; IPSS = International Prostate Symptom Score; ITT = intent-to-treat; LOCF = last observation carried forward; LS-mean = least square mean; N = number (entire population under study)

The descriptive statistics for Q_{max} is summarized in Table 4 and the ANCOVA results for Q_{max} are summarized in Table 5.

Table 4: Summary statistics for change from baseline to Week 8 (LOCF) for Q_{max} (ITT population)

Time	Vardenafil 10 mg (N=104)	Placebo (N=107)
	Mean ± SD (mL/s)	
Baseline (Visit 2)	15.6 ± 6.8	15.6 ± 7.9
Week 8 (LOCF)	18.2 ± 8.0	17.5 ± 10.0
Change from baseline	2.6 ± 7.6	1.9 ± 8.7

Abbreviations: ITT = intent-to-treat; LOCF = last observation carried forward; LS-mean = least square mean; N = number (entire population under study); Q_{max} = maximal urinary flow SD = standard deviation

Table 5: ANCOVA results for change from baseline to Week 8 (LOCF) for Q_{max} (ITT population)

Time	Vardenafil 10 mg (N=104)	Placebo (N=110)
	LS-mean (mL/s)	
Baseline (Visit 2)	15.9	15.9
Week 8 (LOCF)	17.5	16.9
Change from baseline	1.6	1.0
Difference between LS-means	-0.6	
95% confidence interval	-2.62 – 1.43	
P (F-test)	0.5614	

Abbreviations: ANCOVA = analysis of covariance; ITT = intent-to-treat; LOCF = last observation carried forward; LS-mean = least square mean; N = number (entire population under study); Q_{max} = maximal urinary flow

The maximum flow velocity (Q_{max}) exhibited a small improvement of 1.6 mL/s (vardenafil) versus 1.0 mL/s (placebo). This difference was too small for reaching a statistical significance. The Q_{max} standard deviation used for sample size estimation was 3.5 mL/s. The actual scatter as derived from the ANCOVA mean square error was about 6.8 - 9.0 mL/s and the baseline values were generally approximately 5 mL/s higher than reported in other studies on BPH.

It was therefore assumed that the failure to show efficacy of vardenafil in this variable was predominantly caused by 2 factors: inconsistent Q_{max} measurements, which is a common phenomenon and method-related, and normal range baseline unlikely to improve significantly under treatment.

The prior assumption is partially supported by findings in the individual centers. There were no interaction effects (center by treatment) but in some centers, there were generally deteriorations while others reported slight but global improvements (LS-means). Moreover, the mean Q_{max} levels were different, which did not have any negative impact on the analysis. However, since Q_{max} measurements were influenced by the actual urinary volume voided, this could be an indicator of insufficient procedural standardization. Serial flows with a minimum volume of 150 mL were to be conducted and the investigator had to exclude artifacts.

Similarly, the PVR measurements did not show any drug effect. However, subjects with a high PVR (≥100 mL) were excluded according to the protocol. The average baseline PVR (29 - 31 mL) in this study was lower than a PVR >50 mL recommended in similar studies. Therefore, substantial changes in PVR due to treatment could not be expected with these baseline values. In agreement with these findings, the EAU Guidelines state that PVR has a

high test-retest variability and there is a lack of outcome studies useful as reference.

Nominal significant differences were observed in both IPSS subscores ("obstruction" and "irritation"), which were in line with differences found in studies on alpha-adrenergic blockers. The compound score "irritation" was derived from the factor analysis which showed consistent results although nothing can be said so far about its actual usefulness. However, the compound score "irritation" includes 3 additional items and should therefore provide a better reliability. Although frequently cited as typical overactive bladder marker, the "nocturia" item did not prove to be especially important in this cluster.

According to the publication ("Construction and validation of a short-form benign prostatic hypertrophy health-related quality-of-life questionnaire"), it has been shown that the BPH QoL-9 global score (range 0 - 90) of subjects with BPH had a mean total score of 45.8 points while subjects without BPH had a mean total score of 57.2 points. These subjects were about 10 years older than the ITT population of this study. It remains dubious whether a quality of life scale should be used as diagnostic tool to assess the efficacy of drug treatment.

As demonstrated in the factor analysis, there were some items (urgency, leisure pursuits) which were more generic, i.e., these items may be considered as constituents of malfunction or functional disorder. But the majority of the BPH QoL-9 items were related to social and other consequences of the underlying medical disorder.

Vardenafil is an established treatment for erectile dysfunction. Although erectile dysfunction was not an entry criterion in this study, more than 60% of the subjects reported ejaculation problems and erectile dysfunction in their medical history. Baseline scores of the IIEF-EF in this study were, however, better than those reported in erectile dysfunction studies of vardenafil. There was a nominally significant improvement in the vardenafil group, which nearly achieved a re-normalization of the IIEF-EF score with a mean of 23.1 at LOCF.

Results Summary — Safety

The incidence of treatment-emergent adverse events and drug-related treatment-emergent adverse events was higher in the vardenafil group, whereas serious adverse events occurred at virtually the same rates in both treatment groups (Table 6).

The 3 most frequent treatment-emergent adverse events in the vardenafil group were headache, dyspepsia, and flushing (Table 7). The pattern of drug-related events was very similar to that observed for treatment-emergent events.

There were 5 out of 108 subjects with treatment-emergent adverse events of severe intensity in the vardenafil treatment group compared to 3 out of 113 in the placebo treatment group.

There were no deaths while subjects were on study drug or within 24 hours after the last dose of study drug. Two subjects of the vardenafil treatment group had serious adverse events (one had myocardial infarction, chest pain, and cardiac rehabilitation therapy and the other had hypertensive crisis). All serious adverse events were assessed as not related to study medication.

Table 6: Incidence rates of adverse events (safety population)

Adverse event type	Vardenafil 10 mg (N=108) n (%)	Placebo (N=113)
Treatment-emergent adverse events (TEEs)	32 (29.6)	18 (15.9)
Drug-related TEEs	27 (25.0)	10 (8.8)
TEEs leading to discontinuation	9 (8.4)	2 (1.8)
Serious adverse events (SAEs)	2 (1.9)	3 (2.7)
Treatment-emergent SAEs	2 (1.9)	3 (2.7)
SAEs with outcome death	0 (0.0)	0 (0.0)

Table 7: Incidence rates of treatment-emergent events which occurred in >1% of the subjects (safety population)

MedDRA Primary System Organ Class Preferred Term	Vardenafil 10 mg (N=108) n (%)	Placebo (N=113)
Any system organ class		
Any event	32 (29.6)	18 (15.9)
Gastrointestinal disorders		
Dyspepsia	8 (7.4)	0 (0.0)
Diarrhea	5 (4.6)	1 (0.9)
Gastrointestinal reflux disease	3 (2.8)	0 (0.0)
Musculoskeletal and connective tissue disorders		
Back pain	3 (2.8)	0 (0.0)
Nervous system disorders		
Headache	14 (13.0)	2 (1.8)
Respiratory, thoracic, and mediastinal disorders		
Nasal congestion	2 (1.9)	0 (0.0)
Vascular disorders		
Flushing	7 (6.5)	1 (0.9)

There was no obvious relationship between any mean changes in laboratory values and study drug treatment for any of the laboratory parameters.

There were 4 subjects who had signs of "myocardial infarction of indeterminate age" detected through routine ECG findings during the course of the study [Subject IDS: 11863-10007-0011 (placebo group), 11863-10008-0010 (vardenafil group), 11863-10008-0032 (placebo group), and 11863-10013-007 (placebo group)]. All these subjects had an ECG finding of "possible" myocardial infarction. In addition, 1 subject in the vardenafil treatment group (Subject 11863-10015-0024) who had an ECG finding of "myocardial infarction, indeterminate" 29 days before the start of treatment with the study drug, had a "possible" myocardial infarction ECG finding during the study.

Conclusion(s)

In this study, the treatment efficacy with regard to the primary efficacy variables was demonstrated for the IPSS total score but not for Q_{max}. The latter may be due to almost normal baseline values of Q_{max}. Vardenafil was safe and well tolerated in subjects with BPH. The study population may rather have had overactive bladder (hard to distinguish from lower urinary tract symptoms) than BPH, if urinary outflow obstruction is considered an obligatory symptom of BPH.

Publication(s):	None		
Date Created or Date Last Updated:	23 APR 2012	Date of Clinical Study Report:	30 MAR 2007

Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer Pharma AG
Postal Address	D-13342 Berlin Deutschland
Sponsor in Germany	
Legal Entity Name	Bayer HealthCare AG
Postal Address	D-51368 Leverkusen, Germany

List of Investigational Sites

No	Facility Name	Street	ZIP Code	City	Country
1	Kliniken Nordoberpfalz AG - Klinikum Weiden	Klinik für Urologie und Kinderurologie Söllnerstr. 16	92637	Weiden	GERMANY
2	Klinikum der Christian-Albrechts-Universität	Klinik für Urologie Arnold-Heller-Str. 7	24105	Kiel	GERMANY
3	Klinikum Osnabrück GmbH	Urologie Am Finkenhügel 1	49076	Osnabrück	GERMANY
4	Praxis Dr. S. Szymula	Urologische Praxis Nordplatz 1	04105	Leipzig	GERMANY
5	Praxis Dr. S. Szymula	Urologische Praxis Nordplatz 1	04105	Leipzig	GERMANY
6	Praxis Drs. Tim Schneider /B. Schneider	Praxisklinik Urologie Rhein/Ruhr Schulstr. 11	45468	Mülheim	GERMANY
7	Praxis Hr. Dr. A. von Keitz	Am Krummbogen 15	35039	Marburg	GERMANY
8	Praxis Hr. Dr. Dierkopf	Gautinger Str. 9	82319	Starnberg	GERMANY
9	Praxis Hr. Dr. J. Franz	Unter den Linden 26a	21255	Tostedt	GERMANY

Appendix to Clinical Study Synopsis for study 11863

10	Praxis Hr. Dr. P. Gratzke	Salinstr. 11 a	83022	Rosenheim	GERMANY
11	Praxis Hr. Dr. W. Grohmann	Urologie Daphnestr. 4	81925	München	GERMANY
12	Praxis Hr. Dr. W. te Breuil	Karlstr. 17-19	40210	Düsseldorf	GERMANY
13	Praxis Hr. Prof. Dr. H. Porst	Facharzt für Urologie & Andrologie Neuer Jungfernstieg 6a	20354	Hamburg	GERMANY
14	Praxis Klunder/Stephan-Odenthal	Friedrich-Ebert-Platz 17	51373	Leverkusen	GERMANY
15	Universitätsklinikum Hamburg Eppendorf (UKE)	Klinik und Poliklinik für Urologie Martinistr. 52	20246	Hamburg	GERMANY
16	Urologische Praxis Hr. Dr. H.-J. Compter	Zeppelinring 7	88400	Biberach	GERMANY

Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Levitra, STAXYN
Brand/Trade Name(s) ex-US	Levitra, Vivanza, Yaila, Levitra 10mg orodispersible tablets, STAXYN, Vivanza 10mg orodispersible tablets
Generic Name	Vardenafil
Main Product Company Code	BAY38-9456
Other Company Code(s)	
Chemical Description	Vardenafil: 1-[[3-(3,4-Dihydro-5-methyl-4-oxo-7propylimidazo[5,1-f]-as-triazin-2-yl)-4-ethoxyphenyl]sulfony]-4-ethylpiperazine
Other Product Aliases	

Date of last Update/Change: 18 March 2014