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:	13171	NCT00738400
Study Phase:	IV Interventional	
Official Study Title:	Double-blind, Placebo Controlled, Randomized Study of Vardenafil to Determine Efficacy on Erectile Dysfunction (ED) in Men With ED and Metabolic Syndrome (ED-METABOLIC)	
Therapeutic Area:	Men' s Health	
Test Product		
Name of Test Product:	Vardenafil (Levitra, BAY38-9456)	
Name of Active Ingredient:	Vardenafil HCl	
Dose and Mode of Administration:	Vardenafil 10 mg tablets were administered orally *pro re nata* (PRN) (as needed) over a period of 4 weeks. After 4 weeks, at Visit 3, individual doses were titrated up to 20 mg or down titrated to 5 mg. Up-titration was not permitted if a subject had documented change in the International Index of Erectile Function - Erectile Function Domain (IIEF-EF) domain at Visit 3 (relative to Visit 2) by ≥+6 score points provided that he declared that he was then satisfied with his erectile function (subjective perception) or if normal erectile function (defined as IIEF-EF score ≥26) had been accomplished under randomized treatment.	
Reference Therapy/Placebo		
Reference Therapy:	Vardenafil-matching placebo tablets	
Dose and Mode of Administration:	Placebo tablets were administered orally PRN (as needed) over a period of 4 weeks. After 4 weeks, at Visit 3, individual doses were up or down titrated to 20 mg or 5 mg respectively. Up-titration was not permitted if a subject had documented change in the IIEF-EF domain at Visit 3 (relative to Visit 2) by ≥+6 score points provided that he declared that he was then satisfied with his erectile function (subjective perception) or if normal erectile function (defined as IIEF-EF score ≥26) had been accomplished under randomized treatment.	
Duration of Treatment:	A total of 8 weeks of treatment with study medication following a 4-week unmedicated run-in phase (without medication or devices).	
Studied period:	Date of first subjects' first visit:	19 NOV 2008
	Date of last subjects' last visit:	08 OCT 2009
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	None	
Study Centre(s):	The study was conducted at 14 sites in Germany.	

Methodology:	This randomized, placebo-controlled, prospective, parallel group, dose-titration, multicentric study comprised of 2 assessments periods (run-in period and treatment period) and 4 visits (Visits 1, 2, 3, and 4). After a 4-week run-in period (Visit 1), the subjects were randomized (Visit 2) in a 1:1 ratio to either vardenafil 10 mg PRN or placebo. The randomized subjects continued to receive the study drug or placebo, during the 8-week treatment period (Visits 3 and 4). At Visit 3, the subject did not received a higher dose of vardenafil (20 mg PRN) if there was a documented change in the IIEF-EF (International Index of Erectile Function - Erectile Function) domain at Visit 3 (relative to Visit 2) by ≥+6 score points and the subject declared that he was satisfied with his erectile function (subjective perception) or normal erectile function (defined as IIEF-EF score ≥26) had been achieved under randomized treatment. If a subject presented himself with normal erectile function, no uptitration to 20 mg PRN occurred. Depending on the tolerability of the previous dosage, the dose was decreased to 5 mg PRN. Dosing was on a demand basis; however, no more than one dose of study drug was allowed per day. The review of subject's diary and administration of the IIEF-EF domain questionnaire was done on Visit 2, 3, 4, and Premature Discontinuation Visit. The primary efficacy variables were the changes in the SEP2 (Sexual Encounter Profile Question 2) and SEP3 (Sexual Encounter Profile Question 3) success rates reported over the entire treatment course (cumulated attempts Visits 2 - 4; i.e., Week 0-8). The IIEF-EF score at Week 8 or the last observation carried forward (LOCF) was compared to the baseline.
Indication/ Main Inclusion Criteria:	Indication: Erectile dysfunction (ED) Main inclusion criteria: Men with a history of ED for at least 6 months, IIEF-EF entry score (at Visit 2) ≤21 points, documented metabolic syndrome according to International Diabetes Federation (IDF), living in a stable heterosexual relationship and motivated for ED treatment. Documented metabolic syndrome according to the definition of the International Diabetes Foundation (IDF) [8]: Waist circumference (to be measured at the umbilicus), >94 cm in European, Sub-Saharan Africans, Eastern Mediterranean and Middle East (Arab) populations, >90 cm in ethnic South Asian, Chinese, ethnic South and Central Americans, >85 cm in Japanese, or South and Central American men. In addition, at least two of the following criteria must be met: raised triglyceride (TG) level ☐150 mg/dL, or specific treatment for this abnormality, reduced high-density lipoprotein (HDL) cholesterol <40 mg/dL, or specific treatment for this abnormality, raised blood pressure (BP) systolic blood pressure (BP) >130 mmHg and/or diastolic BP ≥85 mmHg, or treatment of previously diagnosed hypertension, raised fasting plasma glucose blood glucose (FPG) ≥100 mg/dL or previously diagnosed type2 diabetes. The subjects not eligible were those who had any underlying

	cardiovascular condition, including unstable angina pectoris that would preclude sexual activity according to the NIH (National Institute of Health) consensus report; a history of myocardial infarction, stroke or life treating arrhythmias within 6 months prior to screening; uncontrolled atrial fibrillation/flutter (ventricular response rate>100 bpm) or any other additional exclusion criteria.
Study Objectives:	Overall: • To determine efficacy, tolerability, and safety of vardenafil on ED in men with ED and Metabolic Syndrome. • To explore the rate of subjects who require the highest dosage based upon the expectation that most men can stay on 10 mg PRN according to pre-defined criteria for dose titration (secondary variable).
Evaluation Criteria:]	Efficacy (Primary): • IIEF-EF score at Week 8 or LOCF compared with baseline • SEP2: successful penetration overall • SEP3: maintenance of erection overall Efficacy (Secondary): • Percentage of subjects achieving "back to normal" erectile function (IIEF-EF≥26) at Week 8 or LOCF. • All diary questions other than SEP2 and SEP3 concerning erectile function that were assessed over the entire treatment period. • Percentage of subjects who stayed on the initially provided dosage of vardenafil (10 mg PRN) according to the following criteria not permitting up-titration of the dose at Visit 3: ▪ A subject had a documented change in the IIEF-EF domain at Visit 3 (relative to Visit 2) by ≥+6 score points provided he declared that he was then satisfied with his erectile function (subjective perception), or ▪ Normal erectile function (defined as IIEF-EF score ≥26) was achieved under randomized treatment. Safety: • Vital signs: supine and standing heart rate and blood pressure measured at all visits; body weight measured at the first and the final visit. • Physical examinations were done at all visits. • Data regarding (serious) adverse events were collected at all visits after Visit 1. • Concomitant medications were collected from Visit 1 onwards.
Statistical Methods:	Efficacy (Primary): All quantitative clinical variables were tabulated as descriptive statistics using sample sizes, means, standard deviations, minimum and maximum, and the median per item, domain, visit, LOCF, and the treatment group. For the primary and co-primary variables tables were generated for two samples: Intent-to-treat (ITT) population and Per-protocol (PP). Categorical variables were

	presented as frequency counts and percentages. The statistical analysis of the IIEF-EF, SEP2, and SEP3 was conducted via an analysis of covariance (ANCOVA) with baseline as covariate, and with treatment and center as factors. The ANCOVA was conducted in 3 versions: (1) main effects (treatment and center) plus baseline as a covariate plus baseline by treatment interaction; (2) main effects (treatment and center) plus baseline as covariate; (3) main effects (treatment and center) plus baseline as covariate plus center by treatment interaction. The appropriate statistical general linear model (GLM) was selected for each variable. The selected models were applied for both, the ITT and the PP population. Efficacy (Secondary): The statistical analysis of the secondary efficacy variables was provided only for the ITT sample. The statistical model selected for the primary efficacy analyses was also applied for the secondary efficacy variables which, in this case, were the remaining SEP item success rates. P-values of <0.05 was referred to as "nominally" significant values. Safety: Treatment groups were compared with respect to the incidence rates of premature termination, adverse events (classified and summarized according to the current classification system: Medical Dictionary for Regulatory Activities [MedDRA], and the current globally harmonized summary procedure), and the use of concomitant medication. Measurements and changes from baseline in vital signs (blood pressure and pulse rate), and continuous laboratory variables were summarized using descriptive statistics (i.e., n, mean, standard deviation, minimum, median, maximum) by treatment group and visit.
Number of Subjects:	In this study, 180 subjects were planned to be screened. A total of 165 subjects were enrolled and of these, 150 subjects were randomized (76 to vardenafil and 74 to placebo. As 3 subjects randomized did not take study drug, the safety population included 75 subjects (vardenafil) and 72 subjects (placebo).

Study Results

Results Summary — Subject Disposition and Baseline

The safety population in this study comprised of 147 subjects which were 98% of all randomized subjects. The ITT population lost 2 additional subjects in the placebo group because these subjects had no post-baseline efficacy measurements. This corresponded to about 97% of all randomized subjects. The PP population comprised of 98 subjects which were 65% of randomized subjects.

The average age of all safety subjects was 56.0 years (range: 36.0 to 65.0 years) which was in accordance with earlier studies. The calculated age at entry in the study ranged from 36 to 65 years. There was one subject who was 65 years of age. About 85% of all subjects were married, and all subjects were White/Caucasians with an average body mass index (BMI) of 30.4 kg/m^2 (range: 23.6 to 42.5 kg/m^2) indicating that the study sample was clearly overweight.

Results Summary — Efficacy

Primary variables:

In the ITT and PP populations, vardenafil 5, 10, or 20 mg PRN treatment was shown to be significantly superior ($p<0.0001$) to placebo with respect to the change from baseline to Week 8 in the IIEF-EF domain (LS [least square]-mean difference of -7 points [placebo-vardenafil, 95% confidence interval {CI}: -9.03 to -4.49]).

Similarly, vardenafil 5, 10, or 20 mg PRN treatment also showed significant superiority ($p<0.0001$) compared with placebo in the change from baseline to Week 8 in the diary item SEP2 (penetration) success rate (LS-mean difference of -21 percentage points [95% CI: -30.66 to -10.76]), and the diary item SEP3 (maintenance of erection) success rate (LS-mean difference of -26 percentage points [95% CI: -37.48 to -14.83]).

Secondary variables:

All secondary efficacy measures demonstrated nominally significant differences in favor of vardenafil 5, 10, or 20 mg PRN.

Vardenafil 5, 10, or 20 mg PRN treatment also showed nominally significant superiority (P-value [Mantel-Haenszel-test]: 0.0004) compared with placebo in the change from baseline to Week 8 with respect to "back to normal" response in the IIEF-EF responder analysis.

As for SEP2 and SEP3, vardenafil 5, 10, or 20 mg PRN treatment also showed significant superiority (p: 0.0003 and $p<0.0001$, respectively) compared with placebo in the change from baseline to Week 8 in the diary item SEP1 (enlargement) success rate (LS-mean difference of -16 percentage points [95% CI: -23.80 to -7.34]), and the diary item SEP6 (ejaculation) success rate (LS-mean difference of -27 percentage points [95% CI: -37.24 to -17.43]).

Overall, the majority of subjects (69%) reported a dose titration to 20 mg vardenafil at any time during treatment, whereas for about 30% no information on dose change was available.

Results Summary — Safety

The most common treatment-emergent adverse events recorded in the vardenafil group included headache (vardenafil 9.3%, placebo 1.4%), nasopharyngitis (vardenafil 4.0%, placebo 1.4%), and back pain (vardenafil 2.7%, placebo 0.0%). Table 1 summarizes incidence rates of treatment-emergent adverse events.

Table 1: Incidence rates of treatment-emergent adverse events occurring in at least two subjects in either treatment group (Safety population)

Number (%) of subjects with MedDRA preferred term	Vardenafil 5/10/20 mg (N=75)	Placebo (N=72)
Headache	7 (9.3%)	1 (1.4%)
Nasopharyngitis	3 (4.0%)	1 (1.4%)
Back pain	2 (2.7%)	0 (0.0%)
Nausea	0 (0.0%)	2 (2.8%)

In the vardenafil group, the treatment-emergent adverse events assessed as drug-related were headache (vardenafil 4.0%, placebo 0%), arrhythmia (vardenafil 1.3%, placebo 0%), reflux oesophagitis (vardenafil 1.3%, placebo 0%), pain in extremity (vardenafil 1.3%,

placebo 0%), and flushing (vardenafil 1.3%, placebo 0%).

Table 2 summarizes incidence rates of drug-related treatment-emergent adverse events.

Table 2: Incidence rates of drug-related treatment-emergent adverse events (Safety population)

Number (%) of subjects with preferred term	Vardenafil 5/10/20 mg (N=75)	Placebo (N=72)
Any event	6 (8.0%)	0 (0.0%)
Arrhythmia	1 (1.3%)	0 (0.0%)
Reflux oesophagitis	1 (1.3%)	0 (0.0%)
Pain in extremity	1 (1.3%)	0 (0.0%)
Headache	3 (4.0%)	0 (0.0%)
Flushing	1 (1.3%)	0 (0.0%)

Treatment-emergent serious adverse events were reported for one subject. The subject receiving placebo was diagnosed with bladder cancer 22 days after the last intake of study drug. This cancer was considered not related to the study drug.

One subject was prematurely discontinued from the treatment with study drug due to an adverse event: The subject receiving vardenafil experienced an adverse event of moderate headache which, in the investigator's and sponsor's opinion, was not related to study drug.

There were no clinically relevant differences between vardenafil and placebo with regard to vital signs.

Conclusion(s)

In this study of 147 subjects, Vardenafil HCl 5 - 20 mg PRN was tested in men with ED and metabolic syndrome. Primary analysis of efficacy based on IIEF-EF, SEP2 ("penetration") and SEP3 ("maintenance") demonstrated that vardenafil was significantly ($P<0.05$) superior to placebo. All secondary efficacy measures showed nominally significant differences in favor of vardenafil.

It was stated that the baseline mean IIEF-EF score in ED subjects with metabolic syndrome was fairly low (11.9 + 4.95) compared to ED subjects, also with underlying conditions like hypertension or diabetes (maximum mean baseline score 15).

Treatment of ED with vardenafil was shown to be safe and well tolerated. The safety profile obtained in this trial was consistent with that presented in the Development Core Safety Information.

Publication(s):	Schneider T, Gleissner J, Merfort F, Hermanns M, Beneke M, Ulbrich E. Efficacy and safety of vardenafil for the treatment of erectile dysfunction in men with metabolic syndrome: results of a randomized, placebo-controlled trial. J Sex Med. 2011 Oct;8(10):2904-11.		
Date Created or Date Last Updated:	24 APR 2012	Date of Clinical Study Report:	12 OCT 2010

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	Gemeinschaftspraxis Dres. M. Brandl, M. Fichtlscherer,	H. Weidacher Schulstraße 1	93413	Cham	GERMANY
2	Praxis Drs. F. Merfort / M. Stammen / S. van Haag	Königstr. 90	41515	Grevenbroich	GERMANY
3	Praxis Drs. Netzer/Sachse	Talstr. 51	66424	Homburg	GERMANY
4	Praxis Drs. Popp/Hanika	Donaueinkaufszentrum Weichser Weg 5	93055	Regensburg	GERMANY
5	Praxis Drs. Tim Schneider /B. Schneider	Praxisklinik Urologie Rhein/Ruhr Schulstr. 11	45468	Mülheim	GERMANY
6	Praxisgemeinschaft Stuhr-Brinkum	Melcherstätte 7	28816	Stuhr	GERMANY
7	Praxis Hr. Dr. A. Rollenhagen	Albulaweg 27	12107	Berlin	GERMANY

8	Praxis Hr. Dr. A. von Keitz	Am Krummbogen 15	35039	Marburg	GERMANY
9	Praxis Hr. Dr. H.-P. Fischer	Löhrstr. 66c	56068	Koblenz	GERMANY
10	Praxis Hr. Dr. J. Gleißner	Hofaue 91-93	42103	Wuppertal	GERMANY
11	Praxis Hr. Dr. J. Willgerodt	Käthe-Kollwitz Strasse 9	04109	Leipzig	GERMANY
12	Praxis Hr. Dr. M. Indig	Kutzbachstr. 7	54290	Trier	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

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