Clinical Study Synopsis

This Clinical Study Synopsis is provided for patients and healthcare professionals to increase the transparency of Bayer's clinical research. This document is not intended to replace the advice of a healthcare professional and should not be considered as a recommendation. Patients should always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document or on the related website should not be considered as prescribing advice.
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:	11875	NCT00786253
Study Phase:	II	
Official Study Title:	A **r**andomized, **e**xplorative, double-blind, double-dummy, multi-center, parallel group **st**udy to assess sustainable efficacy of once daily vardenafil (10 mg) for 12 and 24 weeks versus vardenafil prn in men with mild **or** mild to moderate **e**rectile dysfunction (RESTORE)	
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:	10 mg vardenafil tablets, oral administration either once daily (od) at bedtime for 12 weeks followed by placebo od at bedtime for another 12 weeks ("vardenafil 12 weeks od") or vardenafil od at bedtime for 24 weeks ("vardenafil 24 weeks od") or vardenafil *pro re nata* (prn) for 24 weeks ("vardenafil 24 weeks prn") followed in all 3 groups by a 4-week single-blind placebo washout period.	
Reference Therapy/Placebo		
Reference Therapy:	Matching placebo tablets	
Dose and Mode of Administration:	Matching placebo tablets od at bedtime for 24 weeks in the vardenafil 24 weeks prn group, as prn doses in the 2 vardenafil od groups, and in all 3 groups during the 4-week single-blind placebo washout period which followed the 24-week double-blind treatment.	
Duration of Treatment:	28 weeks	
Studied period:	Date of first subjects' first visit:	12 OCT 2005
	Date of last subjects' last visit:	09 JAN 2007
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 16 AUG 2005) specified the following changes: • Added exclusion criterion "symptomatic angina pectoris". • Added exclusion of concomitant medications that might interact with vardenafil absorption. • Added exclusion of uncontrolled hypertension. • Added the withdrawal criterion in case of elevated transaminases. • Added new information on non-arteritic ischemic optic neuropathy (NAION), visual disturbance, and myocardial infarction to the "warnings/precautions" section. • Added physical examination at Visit 6 to the Study Flow Chart. Amendment no. 2 (dated 06 SEP 2005) specified the following changes:	

	• Added medical examination by an internist at Visit 1 (or between Visits 1 and 2) to confirm subject's eligibility. • The protocol and the statistical analysis plan described the application of a GL model for the analysis of the primary efficacy variable which included "TRUNIT" or center as an additional factor. Due to the low number of subjects recruited in several centers, the analysis resulted in non-estimable least square (LS)-means in some cases. Collapsing the centers with a small number of subjects (n<10) did not yield any significant effect of this factor. Also, the inclusion of "TRUNIT" did not change the conclusions to be drawn from the treatment factor. Therefore, it was decided to drop the "TRUNIT" factor from all analyses.
Study Centre(s):	The study was conducted in 19 active centers in Germany.
Methodology:	This multi-center, randomized, double-blind, double dummy, placebo-controlled, parallel group study consisted of a screening visit (Visit 1, about 4 weeks before randomization), 24-week randomized, double-blind treatment period (Visits 2 - 6), and a 4-week single-blind placebo (and no devices) washout period (in between Visits 6 and 7). Subjects were randomized at Visit 2 to any one of the three treatments: vardenafil for 12 weeks (i.e., vardenafil 10 mg for 12 weeks followed by double-blind placebo for another 12 weeks), or vardenafil for 24 weeks, or vardenafil prn in a 1:1:1 ratio. Following screening (Visit 1) and randomization (Visit 2), the visits were conducted at 4, 12, 16 weeks of randomized treatment (Visits 3, 4, 5) as well as at the end of the 24-week randomized treatment period (Visit 6) and at the end of the subsequent single-blind placebo-controlled washout period (final visit; Visit 7). The erectile function (EF) domain score of the International Index of Erectile Function (IIEF-EF) was assessed at all visits. The Treatment Satisfaction Scale (TSS) was administered at all visits with the exception of Visit 1 (unmedicated version at Visit 2; version designed for sequences of studies where the subjects were receiving the erectile dysfunction (ED) treatment at all subsequent visits). Data regarding the adverse events were collected at all visits after screening (or at the premature discontinuation visit).
Indication/ Main Inclusion Criteria:	Indication: Erectile dysfunction Inclusion criteria: 18- to 64-year old men with mild or mild to moderate ED (defined as 15 - 21 points according to the erectile function domain score of the International Index of Erectile Function [IIEF-EF] as assessed at Visit 2 [randomization]) and a history of at least 1 of the following conditions: diabetes mellitus type 2, hypertension, peripheral arterial occlusive disease.
Study Objectives:	<u>Primary:</u> To explore the prophylactic (prophylaxis of deterioration) or curative efficacy and safety of long-term (12 and 24 weeks) once-daily (od) administration of vardenafil therapy (administration at night) versus vardenafil as needed (prn) on ED in men with mild or mild to moderate, predominantly organic ED.

	Secondary: • To assess descriptively whether this estimated treatment effect depended upon the duration of daily dosing of the phosphodiesterase (PDE)-5 inhibitor. • To assess descriptively whether or not the immediate and the possible sustainable effect on ED corresponded with an effect on subjects' satisfaction by using a validated ED-specific questionnaire (TSS).
Evaluation Criteria:	Efficacy (Primary): Change from baseline in IIEF-EF score as observed in Weeks 24 - 28 (vardenafil 24 weeks od), Weeks 12 - 16 (vardenafil 12 weeks od), and Weeks 24 - 28 (vardenafil 24 weeks, prn) Efficacy (Secondary): The secondary efficacy variables included: • Domain changes from treatment phase to washout (placebo) phase. • Success rates of items #2 (penetration), #3 (maintenance), and #5 (success) of the subject diary as observed in the final placebo phases. • Individual diary success rates (items #2, #3, #5) were analyzed as changes from those rates observed in the treatment phase. • Number of subjects per treatment group with a minimum of 5 points improvement on the IIEF-EF from baseline to treatment phase and without any deterioration exceeding a 2-point change from treatment phase in the washout period ("cure rate"). • Number of subjects per treatment group with no deterioration exceeding 10% of their sexual encounter profile (SEP) #2 success rates in the washout phase when compared to their performance in the treatment period. • Number of subjects per treatment group with no deterioration exceeding 10% of their SEP#3 success rates in the washout phase when compared to their performance in the treatment period. • Number of subjects per treatment group with no deterioration exceeding 10% of their SEP#5 success rates in the washout phase when compared to their performance in the treatment period. • TSS for subject assessments, and where adequate, changes from the baseline per visit, item, and treatment group. Safety: 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 28-week treatment period.
Statistical Methods:	Efficacy (Primary): The primary efficacy analysis was based on the IIEF-EF last-observation carried forward (LOCF) scores of the intent-to-treat (ITT) sample adjusted for baseline (Visit 2). The Blinded Review Meeting (BRM) on 12 MAR 2007 decided to base the primary efficacy analysis on the modified ITT (mITT) sample. Adjustment of baseline was done with an analysis of covariance

	(ANCOVA) using baseline as covariate and the LOCF value as dependent variable. Treatment was considered as a factor. The variable "center" was included as an additional factor in the model if there were significant differences between the centers or an interaction effect between "treatment" and "center". Centers were pooled with regard to regional conditions and in order to achieve balanced sample sizes. This analysis was repeated for the PP sample. The analysis first included all treatment groups. If the overall F-test showed significance ($P<0.05$), all pairwise comparisons were conducted without any α adjustments. Curative efficacy was assumed if the comparison of the treatment group "vardenafil 24 od" showed superiority over "vardenafil 24 weeks prn". Efficacy (Secondary): For the secondary efficacy analysis, only the ITT sample was considered. The IIEF-EF LOCF scores under treatment were used as "baseline" covariate while the placebo washout phase scores remained as dependent variable in the model. This procedure excluded all subjects who dropped out of the treatment prior to the placebo washout. Diaries were available from the regular baseline phase. They were analyzed in 2 versions: • An analysis of variance (ANOVA) was conducted using the success rates of all sexual encounter profile (SEP) variables observed in the placebo phase in all the treatment groups. • An ANCOVA was conducted using the success rates of all SEP variables observed in the placebo phase adjusted for those scores reported as LOCF values in the prior drug treatment phase (covariate). The number of responders ("cure rate") in each od treatment group was compared with the prn group by using the Cochran-Mantel-Haenszel test with the adjustment for centers. The TSS was analyzed on an item basis using an ANOVA and, where adequate, an ANCOVA with baseline as covariate. This was because not all items used in the treatment phase had respective baseline assessments. All inferential statistics were conducted on an exploratory level without any adjustment for multiple testing. Nominal P value was $P<0.05$. Safety: Treatment groups were compared with respect to the incidence rates of premature termination, adverse events, laboratory abnormalities, ECG abnormalities, and concomitant medication use emerging during the double-blind treatment period, during single-blind placebo washout, and during the prn period. Measurements and changes from

	baseline in vital signs (blood pressure and heart rate), continuous laboratory variables, and ECG parameters were summarized using descriptive statistics by treatment group and visit. Statistical tests were not planned for the safety variables. The presentation of all the safety variables was done with regard to the treatment group.
Number of Subjects:	A total of 279 subjects were enrolled and screened in this study, out of which 43 subjects were not randomized because they did not fulfill the inclusion or met the exclusion criteria. Of the total screened subjects, 236 subjects were randomized to the study drug treatment (81 to vardenafil 24 weeks od, 78 to vardenafil 12 weeks od, and 77 to vardenafil 24 weeks prn group). Two subjects in both the vardenafil 24 weeks od and vardenafil 12 weeks od groups were assessed to be invalid because they were randomized but did not have any post-baseline safety evaluation or other measurements. Thus, the safety population consisted of 232 subjects.

Study Results

Results Summary — Subject Disposition and Baseline

The mITT sample on which the primary efficacy analysis was based according to the BRM of 12 MAR 2007 included all subjects who had Visit 4 (Week 12) and Visit 5 (Week 16) assessments or, depending on their treatment duration, Visit 6 (Week 24) and Visit 7 (Week 28) assessments in the primary efficacy variable (i.e., IIEF-EF). A total of 206 subjects fulfilled the criteria for the mITT sample, i.e., approximately 87% of all randomized subjects were included in the primary efficacy sample.

Of the 232 subjects valid for safety analysis, a total of 230 subjects were White and 2 subjects were Asian. The mean age of subjects was 54.5 years (range: 26 - 65 years) and mean body mass index (BMI) was reported as 28.6 kg/m^2 (range: 20.0 - 43.7 kg/m^2).

Results Summary — Efficacy

Primary efficacy analysis:

The primary efficacy analysis was based on the erectile function domain score of the IIEF-EF, baseline-adjusted change score at the end of the 4-week placebo washout period.

Table 1 summarizes the statistics for the change from baseline to Week 16 or Week 28 in IIEF-EF. Table 2 summarizes the ANCOVA results for the change from baseline to Week 16 or Week 28 in IIEF-EF.

Table 1: Summary statistics for change from baseline to Week 16 or Week 28 in IIEF-EF (mITT population)

	Mean ± SD		
Time	Vardenafil 24 weeks od n=69	Vardenafil 12 weeks od n=71	Vardenafil 24 weeks prn n=66
Baseline (Week 0)	17.8 ± 1.86	17.9 ± 2.10	18.0 ± 1.77
Washout (Week 16 or Week 28)	20.1 ± 7.59	19.9 ± 8.28	20.7 ± 7.78
Change from baseline	2.2 ± 7.47	2.0 ± 8.44	2.7 ± 7.53

Table 2: ANCOVA results for change from baseline to Week 16 or Week 28 in IIEF-EF (mITT population)

Time	LS-mean Vardenafil 24 weeks od n=69	LS-mean Vardenafil 12 weeks od n=71	LS-mean Vardenafil 24 weeks prn n=66
Baseline (Week 0)	17.83	17.86	17.96
Washout (Week 16 or Week 28)	20.11	19.88	20.58
Change from baseline	2.29	2.02	2.63
P (F-test "treatment")		0.4369	

It was expected that daily vardenafil treatment at bedtime might have an enduring effect even in the washout phase when compared to the traditional prn treatment. It was also suspected that treatment duration might moderate such an enduring effect.

The study results did not support this hypothesis. The F-test of the ANCOVA was insignificant and did not support the expected differences between od and prn dosing of vardenafil or any influence of different treatment durations.

Secondary efficacy analysis

All applied treatment schedules in this study resulted in consistent efficacy assessments: no differences at baseline, under treatment, or after washout were observed.

Poor performance at baseline (as requested), comparable clinically relevant improvement under all treatments, and a sharp decline of all performance measures to a level slightly better than observed at baseline after withdrawal of the active treatment were observed. This was consistently found in all the clinical variables: IIEF-EF, subject diary success rates, and treatment satisfaction scale domains.

Summarizing, there were no statistically significant differences between vardenafil treatment schedules after washout. Especially, vardenafil od was not superior to vardenafil prn.

Results Summary — Safety

Vardenafil was generally safe and well tolerated. About 49%, 42%, and 44% of subjects in the vardenafil 24 weeks od, 12 weeks od, and 24 weeks prn treatment groups reported at least 1 treatment-emergent adverse event, respectively (Table 3). A total of 26% of subjects (vardenafil 24 weeks prn) had drug-related, treatment-emergent adverse events. Treatment-emergent adverse events led to premature discontinuation in 1% of the subjects for all the 3 treatment groups (Table 3).

The most frequent treatment-emergent adverse events were headache, flushing, and dyspepsia (Table 4). Headache and flushing could be attributed to the mechanism of action of PDE-5 inhibitors.

Most treatment-emergent adverse events were of mild or moderate severity. The 8 severe adverse events reported in the 7 subjects of the vardenafil 12 weeks od treatment groups were cardiac failure, erosive gastritis, pneumonia, tibia fracture, musculoskeletal pain, carotid artery stenosis, paresthesia, and neurodermatitis. An additional severe adverse event was actually an outcome of an adverse event, i.e., sudden cardiac death. The only severe adverse event reported in the vardenafil 24 weeks od treatment group was epididymitis. No severe treatment-emergent adverse event was reported in the vardenafil 24 weeks prn group.

Table 3: Incidence rates of adverse events (safety population) [n(%)]

Adverse event type	Vardenafil 24 weeks od N=79	Vardenafil 12 weeks od N=76	Vardenafil 24 weeks prn N=77
Treatment-emergent AEs	39 (49.4)	32 (42.1)	34 (44.2)
Drug-related treatment-emergent AEs	14 (17.7)	9 (11.8)	20 (26.0)
TEEs leading to discontinuation	1 (1.3)	1 (1.3)	1 (1.3)
Serious adverse events	4 (5.1)	9 (11.8)	1 (1.3)
Treatment-emergent serious adverse events	4 (5.1)	9 (11.8)	1 (1.3)
Serious adverse events with outcome death	1 (1.3)	2 (2.6)	0 (0.0)

Table 4: Incidence rates of predominant/common treatment-emergent adverse events (safety population) [n(%)]

Treatment-emergent adverse event (MedDRA Preferred Term)	Vardenafil 24 weeks od N=79	Vardenafil 12 weeks od N=76	Vardenafil 24 weeks prn N=77
Headache	3 (3.8)	6 (7.9)	9 (11.7)
Dyspepsia	5 (6.3)	5 (6.6)	2 (2.6)
Flushing	4 (5.1)	1 (1.3)	8 (10.4)
Back pain	3 (3.8)	1 (1.3)	2 (2.6)
Nasal congestion	2 (2.5)	1 (1.3)	2 (2.6)

About 5%, 12%, and 1% of subjects in the vardenafil 24 weeks od, 12 weeks od, and 24 weeks prn treatment groups, respectively, reported at least 1 treatment-emergent serious adverse event. None of the serious adverse events was considered related to the study drug.

A total of 3 subjects died during the study (as summarized in Table 5): Subject 11875-117-006 of the vardenafil 24 weeks od treatment group died from myocardial infarction. For Subject 11875-120-014 of the vardenafil 12 weeks od treatment group, sudden death was reported. In addition, for Subject 11875-106-003, sudden cardiac death was reported on Day 109 after the start of study drug treatment. Since this subject was randomized to receive a 12-week vardenafil od treatment, the subject had already received placebo for at least 3 weeks by the time of death.

Table 5: Deaths recorded during the study

Subject ID	Age (years)	Reason of death	Treatment arm	Treatment administered	Relatedness (Investigator's assessment)
11875-106-003	46	Sudden cardiac death	Vardenafil 12 weeks od[a]	Test drug for 12 weeks followed by placebo for 12 weeks + placebo prn	Not related
11875-117-006	50	Myocardial infarction	Vardenafil 24 weeks od[b]	Test drug for 24 weeks + placebo prn	Not related
11875-120-014	51	Sudden death	Vardenafil 12 weeks od[a]	Test drug for 12 weeks followed by placebo for 12 weeks + placebo prn	Not related

[a]Vardenafil 10 mg od at bedtime for 12 weeks, subsequently matching placebo tablets od at bedtime for the remaining 12 weeks + matching placebo tablets prn

[b]Vardenafil 10 mg od at bedtime for 24 weeks + vardenafil matching placebo tablets prn

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

There were no clinically relevant changes in heart rate, blood pressure, or any mean ECG parameter during the course of the study.

Conclusion(s)

In this study, vardenafil od for 24 or 12 weeks did not prove to be superior to vardenafil prn for 24 weeks for the treatment of mild to moderate ED at the end of a subsequent 4-week placebo washout period.

Vardenafil was safe and well tolerated in subjects with mild to moderate ED.

Publication(s):	None		
Date Created or Date Last Updated:	03 APR 2012	Date of Clinical Study Report:	30 NOV 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	Charité Campus Benjamin Franklin	Klinik und Poliklinik für Urologie des Universitätsklinikums Benjamin Franklin Hindenburgdamm 30	12200	Berlin	GERMANY
2	Diabetes-Forschungs-Institut	Diabetologie Auf'm Hennekamp 65	40225	Düsseldorf	GERMANY
3	Kliniken der Medizinischen Hochschule Hannover	Abt. Klinische Psychiatrie und Psychotherapie Klinische Psychologie Carl-Neuberg-Str. 1	30625	Hannover	GERMANY

Appendix to Clinical Study Synopsis for study11875

4	Kliniken Nordoberpfalz AG - Klinikum Weiden	Klinik für Urologie und Kinderurologie Söllnerstr. 16	92637	Weiden	GERMANY
5	Klinikum der Eberhard-Karls-Universität Tübingen	Universitätsklinik für Urologie Hoppe-Seyler-Str. 3	72076	Tübingen	GERMANY
6	Klinikum Leverkusen gGmbH	Klinik für Urologie Dhünnberg 60	51375	Leverkusen	GERMANY
7	Klinikum Osnabrück GmbH	Urologie Am Finkenhügel 1	49076	Osnabrück	GERMANY
8	Med. Fakultät der Martin-Luther-Universität Halle-Wittenberg	Klinikum der Med. Fakultät Univ.-Klinik und Poliklinik für Urologie Magdeburger Str. 16	06097	Halle	GERMANY
9	Praxis Drs. F. Merfort / M. Stammen / S. van Haag	Königstr. 90	41515	Grevenbroich	GERMANY
10	Praxis Fr. Dr. H. Täschner	Gerhard-Ellrodt-Straße 19	04249	Leipzig	GERMANY
11	Praxis Hr. Dr. A. von Keitz	Am Krummbogen 15	35039	Marburg	GERMANY
12	Praxis Hr. Dr. D. Hennig	Dresdner Str. 42-44	01662	Meißen	GERMANY
13	Praxis Hr. Dr. K. Sperling	Sierichstr. 140	22299	Hamburg	GERMANY
14	Praxis Hr. Dr. W. Grohmann	Urologie Daphnestr. 4	81925	München	GERMANY
15	Praxis Hr. Dr. W. Warnack	Poststr. 25	19230	Hagenow	GERMANY

16	Praxis Hr. Prof. Dr. H. Porst	Facharzt für Urologie & Andrologie Neuer Jungfernstieg 6a	20354	Hamburg	GERMANY
17	Universitätsklinikum Hamburg Eppendorf (UKE)	Klinik und Poliklinik für Urologie Martinistr. 52	20246	Hamburg	GERMANY
18	Universitätsklinikum Münster	Klinik und Poliklinik für Urologie der Westf. Wilhelms-Universität Albert-Schweitzer-Str.33	48149	Münster	GERMANY
19	Universitätsklinikum Regensburg	Klinik und Poliklinik für Urologie Caritas-Krankenhaus St. Josef Landshuter Str. 65	93053	Regensburg	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