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:	12146	NCT00377793
Study Phase:	IV Interventional	
Official Study Title:	A randomized, double blind, parallel group study of vardenafil flexible dose versus placebo in males with erectile dysfunction and their female partners' sexual quality of life. PARTNER II	
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:	Dose: 5 mg, 10 mg, and 20 mg tablets There was one active treatment group, treated with the test drug on a flexible dose regimen. At Visit 3 (Month 1), Visit 4 (Month 12), and Visit 5 (Month 18), the dose could be increased to 20 mg, kept at 10 mg, or reduced to 5 mg, by the investigator. The maximal allowable daily *pro re nata* (PRN) dose was 20 mg. Mode of administration: oral	
Reference Therapy/Placebo		
Reference Therapy:	Matching placebo tablets	
Dose and Mode of Administration:	Matching placebo tablets were administered to the comparator group. Mode of administration: oral	
Duration of Treatment:	A total of 24 weeks (12-weeks on confirmatory phase, followed by a 12-weeks exploratory phase).	
Studied period:	Date of first subjects' first visit:	12 JUL 2006
	Date of last subjects' last visit:	12 AUG 2007
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 28 APR 2006) was approved prior to subject enrollment, and specified the following change: • The current validated version of the Partnership Questionnaire (PFB) was included. Amendment no. 2 (Dated 03 NOV 2006) specified the following changes: • Clarification of the warnings and precautions section regarding the timing of follow up tests for subjects who experienced	

	treatment-emergent liver transaminase elevations more than 1.8 times but less than 3 times the upper limit of normal from weekly retests to testing at the discretion of the principal investigator. • Improved consistency within the section for removal of subjects from the study by adding a new reason for removal; if the subject failed to complete a valid diary between Visit 1 and Visit 2.
Study Centre(s):	The study was conducted at 43 centers in 6 countries: Belgium (5), France (8), Germany (13), the Netherlands (4), South Africa (6), and Spain (7).
Methodology:	This randomized, double-blind, multi-center, flexible-dose, parallel group, and placebo controlled study had a duration for each subject participating in this study of 28 weeks comprising of the following assessment periods: Screening period (Visit 1, a 4-week, unmedicated period), a 4-week double-blind treatment period (Visit 2, Week 0), a subsequent 8-week double-blind treatment period (Visit 3), an exploratory phase of the study starting at Week 12 of the double-blind treatment (Visit 4 [Week 12], Visit 5 [Week 18], and Visit 6 [Week 24]), and a 24-hour follow-up period. At Visit 2 (Week 0), eligible subjects were randomly and equally assigned (using a 1:1 ratio) to receive either vardenafil 10 mg or placebo. The exploratory phase included two subsequent double-blind treatment periods of 6 weeks each, during which subjects stayed on flexible dose of either vardenafil or placebo. During this phase of the study, a subgroup of subjects/couples participating in approximately 50% of the sites (selected by randomization) received an educational program concerning ED, partnership and sex life which lasted until the end of the randomized treatment. Each subject visited the clinic on 6 occasions over a period of 7 months, and each partner visited the clinic on 4 occasions over a period of 7 months (Visits 1, 2, 4, and 6). The improvement in erection maintenance in subjects was assessed using the overall post randomization success rate after 12 weeks of randomized treatment from the Sexual Encounter Profile Question 3 (SEP3). The improvement in female partner's sexual quality of life was assessed using the change from baseline at last observation carried forward (LOCF) for the quality of life domain from the modified Sexual Life Quality Questionnaire (mSLQQ-QOL) after 12 weeks of randomized treatment. Secondary efficacy variables were measured at Weeks 4, 12, 18, and 24 of treatment compared to placebo. Safety variables were assessed from Week 4 - Week 24 (Visit 1 - Visit 6) or at premature discontinuation. Data regarding the adverse events (AEs) was collected at all visits after Visit 1 and, additionally, for serious adverse events (SAEs) during the 24-hour period after the last dose of the study medication.
Indication/ Main Inclusion Criteria:	Indication: Erectile dysfunction (ED) Main Inclusion criteria: Men 18 to 64 years of age with ED for more than 6 months in a stable, heterosexual relationship for at least 6 months and motivated female partners of these subjects. Their female partners were to be willing to participate in the study, to have at least approximately normal sexual functioning, and motivated to support the treatment for their male partner's ED.

Study Objectives:	Primary: The primary objective of this study was to compare the efficacy of vardenafil flexible dose after 12 weeks of treatment versus placebo in terms of: • Success of maintenance of erection in men with ED. • Improvement of their female partner's sexual quality of life. Secondary: The major secondary objective was to explore the effect of an educational program on the endpoints of this study.
Evaluation Criteria:	Efficacy (Primary): Primary efficacy measures: • Maintenance of erection in men with ED • Improvement of their female partners sexual quality of life The Sexual Encounter Profile Question 3 (SEP3) was used to assess the success of maintenance of erection in men with ED. Quality of life domain (10 items) from the mSLQQ-QOL was used to assess the improvement of their female partner's sexual quality of life. Efficacy (Secondary): Secondary efficacy measures for subjects: • SEP3 at Weeks 4, 12, 18, and 24 of treatment compared to placebo. • Additional subject diary questions at weeks 4, 12, 18, and 24, LOCF, and over entire treatment period compared to placebo. • Global confidence question (GCQ) at Weeks 12, and 14 of treatment compared to placebo. • The score for the IIEF questionnaire EF domain (IIEF-EF) at Weeks 12 and 24, and LOCF of treatment compared to placebo. • Scores from the Treatment Satisfaction Scale (TSS) -- Subject Active Medication module at Weeks 12, 24, and LOCF of treatment compared to placebo. • Scores from the mSLQQ-QOL at Weeks 12, 24, and LOCF of treatment compared to placebo. • Percentage of subjects achieving back to normal rates of erectile functioning (IIEF-EF >25) at Weeks 12, and 24 of treatment compared to placebo. • Partnership questionnaire (PFB) at Weeks 12, 24 and LOCF of treatment compared to placebo. Secondary efficacy measures for partners: • Partner's scores from the Female Sexual Function Index (FSFI) at Week 24 and LOCF of treatment compared to placebo. • Scores from the mSLQQ-QOL for partners at Week 24 of treatment compared to placebo. • Scores from the TSS, Partner Active Medication module, at Week 24 and LOCF of treatment compared to placebo. • PFB at Weeks 12, 24 and LOCF of treatment compared to placebo. The PFB was replaced by a validated version as part of Amendment 1.

	Safety: • Treatment-emergent adverse events (TEAEs) • Blood chemistry • 12-lead electrocardiogram (ECG) • Vital signs
Statistical Methods:	Efficacy (Primary): Primary efficacy variables: SEP3 ("maintenance of erection") and mSLQQ-QOL (female partner) as a step-down decision procedure. Analysis: The change from baseline for both the primary variables was analyzed using analysis of covariance (ANCOVA) with baseline as covariate, treatment and country as independent variables, cumulated success rate (SEP3) and mSLQQ-QOL up to and at Week 12, respectively, as dependent variables. Efficacy (Secondary): Secondary analyses: ANCOVAs and Cochran-Mantel-Haenszel statistic method were used for the responder analysis. Analysis of educational material (Weeks 12 - 24): 2 x 2 factorial ANCOVAs with interaction effect was used. Safety: Treatment groups were compared using incidence rates and descriptive statistics. Statistical tests were not planned for safety variables.
Number of Subjects:	A total of 352 subjects were randomized, 175 to vardenafil and 177 to placebo. The safety population consisted of 347 subjects. A total of 168 (vardenafil) and 175 (placebo) subjects were classified as members of the intent-to-treat (ITT) sample. A total of 148 (vardenafil) and 130 (placebo) subjects were classified as per-protocol ("valid for efficacy") subjects.

Study Results

Results Summary — Subject Disposition and Baseline

A total of our 473 subjects were enrolled and 352 (74%) subjects were randomized. In the vardenafil treatment group, 3 subjects were dispensed study medication at Visit 2. However, because there was no further information available about them, these subjects were excluded from the safety sample. Two additional subjects; one belonging to vardenafil, the other to placebo group returned all the dispensed drugs which suggested no study medication intake. Thus, the Blind Review Meeting conducted on 26 OCT 2007 decided not to include these subjects in the safety sample.

A total of 4 subjects did not fulfill the ITT criteria because they had no baseline- or follow-up efficacy assessment (3 subjects were lost in the vardenafil group and 1 subject in the placebo group). Therefore, 96% (vardenafil) and 99% (placebo) of the randomized subjects were included in the primary efficacy analysis.

The valid-for-efficacy sample which had to fulfill a more comprehensive set of inclusion criteria was smaller and was reduced to 148 (85%; vardenafil), and 130 (73%; placebo) subjects.

The mean age of subjects was 52.6 years (range: 23 - 67 years) and mean body mass index (BMI) was 27.5 kg/m^2 (range: 16.7 - 43.2 kg/m^2). A total of 220 subjects were White, 14 were Black, 22 were Asian, and for 91 subjects the race was not reported (in France it is not allowed to report race).

Results Summary — Efficacy

As for the primary efficacy criterion, maintenance of erection in men with ED, a significant ($P<0.0001$) difference was observed between vardenafil and placebo in the overall (i.e., total) SEP3 success rates up to and at Week 12/LOCF compared to baseline.

While there was an arithmetic mean change of approximately 13% success rate increase in the placebo group, vardenafil treated subjects improved by approximately 57% (Table 1).

Table 1: Summary statistics for change from baseline to Week 12 (Overall) for SEP3 success rates (ITT)

'Success rates' (%)		
Time	Vardenafil Mean ± SD	Placebo Mean ± SD
	N=165	N=172
Baseline (Visit 2)	9.5 ± 16.06	12.4 ± 17.39
Week 12 (Overall)	66.2 ± 33.45	25.2 ± 30.51
Change from baseline	56.7 ± 32.18	12.8 ± 28.43

SEP3: Sexual Encounter Profile Question 3, ITT: intent-to-treat, SD: standard deviation

The estimated least squares mean (LS-mean) increases (from baseline) of success rates were 58% for vardenafil and 12% for placebo, which corresponds to an estimated difference between groups of approximately 43% in favor of vardenafil.

The first primary criterion being significant, a subsequent test was conducted for the mSLQQ-QOL total scores, which was derived from 10 items of the modified rating scale to assess the female partner's sexual quality of life (Table 2).

Table 2: Summary statistics for change from baseline to Week 12 (LOCF) for the partners' mSLQQ-QOL (ITT)

Total score		
Time	Vardenafil Mean ± SD	Placebo Mean ± SD
Baseline (Visit 2)	28.8 ± 20.5	24.6 ± 15.9
Week 12	69.0 ± 24.1	43.2 ± 25.2
Change from baseline	40.3 ± 28.3	18.3 ± 27.5

mSLQQ-QOL: Quality of life domain (10 items) from the modified Sexual Life Quality Questionnaire,
LOCF: last observation carried forward, ITT: intent-to-treat, SD: standard deviation

Vardenafil was significantly effective in the treatment of ED according to the subject's self-assessment and as reported by the female partner. Educational material about sexual relationship (video- or DVD-based) introduced after 12 weeks of treatment did not have any "add-on" effect (SEP1, SEP2, SEP3, and TSS).

Results Summary — Safety

In the safety population, the mean (median) exposure time was 150 (165) days for the vardenafil group and 131 (158) days for the placebo group. A total of 128 subjects (75%) of the vardenafil group and 103 subjects (58.5%) of the placebo group had been treated for more than 22 weeks.

The treatment-emergent AEs were more common in the vardenafil group (42%) than in the placebo group (26%) and were considered to be drug-related in more subjects receiving vardenafil (26%) than placebo (4%) (Table 3).

The major contributors to these events were headache (vardenafil 16%; placebo 2%), flushing (vardenafil 6%; placebo 0%), and nasal congestion (vardenafil 5%; placebo <1%).

Table 3: Incidence rates of AEs (Safety)

Subjects with respective events (N (%))	Vardenafil (N=171)	Placebo (N=176)
Treatment emergent adverse events (TEEs)	72 (42.1)	46 (26.1)
Drug-related TEEs	44 (25.7)	7 (4.0)
TEEs leading to discontinuation	2 (1.2)	0
Serious adverse events [a]	5 (2.9)	2 (1.1)
Serious adverse events with outcome death	0)	0
a: In the vardenafil group, 3 subjects (1.8%) had treatment emergent serious adverse events		

There were few cardiac AEs: 3 vardenafil subjects (<2%: angina pectoris, supraventricular systoles, and right atrial dilatation, respectively) and 1 placebo subject (<1%: palpitations).

For the AEs considered to be related to the study drug, the most common events were headache (vardenafil 15%; placebo 2%), followed by flushing (vardenafil 6%; placebo 0%) and nasal congestion (vardenafil 5%; placebo <1%).

Serious AEs were reported for 5 subjects randomized to vardenafil and 2 subjects randomized to placebo. There were 3 subjects (1.8%) receiving vardenafil and 2 subjects (1.1%) receiving placebo who reported serious AEs after initiation of study drug and within 30 days after the last drug intake (i.e., TEAEs).

In the vardenafil group, TEAEs were reported for 3 subjects; one subject reported iliac artery occlusion, aortic aneurysm, and peripheral artery aneurysm (the first event starting on the day of first dose); another subject reported angina pectoris (starting 3 months after first intake of the study drug), followed by angina unstable; and the third subject reported intervertebral disc protrusion (9 days after first intake of the study drug). Except for angina pectoris in the second subject, none of these SAEs were related to the treatment with study drug.

There were no clinically important differences between the treatment groups for the change from baseline in mean values for vital signs and laboratory parameters at any time point. In addition, no clinically relevant safety findings were determined by ECG and the assessments of AEs and SAEs.

Conclusion(s)

From this study it was concluded that oral vardenafil at a flexible dose regimen (5, 10, and 20 mg) improves erectile function significantly (Week 12) according to the overall reported success rate (SEP3) and as reported by the female partners assessment on the sexual quality of life. Sexual quality of life improved accordingly in males. Additional educational material about sexual relationship which was introduced after Week 12 did not further increase the treatment responses.

The AE profile based on this study was consistent with the safety profile in vardenafil studies as presented in Development Core Safety Information. There were no clinically important differences between treatment groups for the change from baseline in mean values for vital signs and laboratory parameters at any time-point. In addition, no safety relevant findings were determined by the ECG and the assessment of SAEs and AEs.

Publication(s):	None		
Date Created or Date Last Updated:	31 AUG 2012	Date of Clinical Study Report:	23 APR 2008

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	CHU de Liège	Hôpital du Sart Tilman Service Cardiologie Domaine Universitaire du Sart Tilman Bâtiment B35	4000	LIEGE	BELGIUM
2	Clinique Saint-Jean/Kliniek Sint Jan	Boulevard du Jardin Botanique 32 Kruidtuinlaan	1000	BRUXELLES - BRUSSEL	BELGIUM
3	Dr Bongaerts - Dr Denier	Huisartsenpraktijk Heeldstraat 58	3600	GENK	BELGIUM
4	Dr Van Der Mullen	Huisartsenpraktijk Van 't Sestichstraat 8	3000	LEUVEN	BELGIUM
5	H.-Hartziekenhuis Roeselare-Menen	Campus Wilgenstraat Dienst Endocrinologie - Andrologie Wilgenstraat 2	8800	ROESELAERE	BELGIUM
6	Cabinet Médical - 32 Leclerc - La Rochelle	Cabinet Médical 32 avenue du Général leclerc	17000	LA ROCHELLE	FRANCE
7	Cabinet Médical - 45 Maubeuge - Paris	Cabinet Médical 45 rue de Maubeuge	75009	PARIS	FRANCE

8	Cabinet Médical - Gambetta - Lyon	Cabinet Médical 68, cours Gambetta	69000	LYON	FRANCE
9	Cabinet Médical - Martinon - Mont de Marsan	Cabinet Médical 26 rue Martinon	40000	MONT-DE-MARSAN	FRANCE
10	Cabinet Médical - Morgiou - Marseille	Cabinet Médical 2, chemin de Morgiou	13009	MARSEILLE	FRANCE
11	Cabinet Médical - Romiguières - Toulouse	Cabinet Médical 7 rue Romiguières	31000	TOULOUSE	FRANCE
12	CETPARP - Carolus - Lille	Centre d'Etude et de Traitement de la pathologie de l'appareil reproducteur et de la psychosomatique Résidence de l'Ile au Bois Le Grand Hunier 3. allée Carolus	59000	LILLE	FRANCE
13	Hôpital Sainte Marguerite - Marseille	Assistance Publique - Hopitaux Sud Hôpital Sainte Marguerite Service de Psychiatrie 270, boulevard Sainte Marguerite	13275	MARSEILLE	FRANCE
14	Kliniken der Medizinischen Hochschule Hannover	Abt. Klinische Psychiatrie und Psychotherapie Klinische Psychologie Carl-Neuberg-Str. 1	30625	Hannover	GERMANY
15	Praxis Dr. S. Szymula	Urologische Praxis Nordplatz 1	04105	Leipzig	GERMANY
16	Praxis Drs. Tim Schneider /B. Schneider	Praxisklinik Urologie Rhein/Ruhr Schulstr. 11	45468	Mülheim	GERMANY
17	Praxis Fr. Dr. W. Pohl	Bautzner Str. 62	01099	Dresden	GERMANY
18	Praxis Hr. Dr. D. Hennig	Dresdner Str. 42-44	01662	Meißen	GERMANY

19	Praxis Hr. Dr. E. U. Krohn	Hellbrookkamp 31-33	22177	Hamburg	GERMANY
20	Praxis Hr. Dr. F. Matthes	Markt 3	04703	Leisnig	GERMANY
21	Praxis Hr. Dr. G. Korda	Mühlenstr. 14	50321	Brühl	GERMANY
22	Praxis Hr. Dr. J. Gleißner	Hofaue 91-93	42103	Wuppertal	GERMANY
23	Praxis Hr. Dr. M. Orlowski	Ostlandstr. 8	23812	Wahlstedt	GERMANY
24	Praxis Hr. Prof. Dr. H. Porst	Facharzt für Urologie & Andrologie Neuer Jungfernstieg 6a	20354	Hamburg	GERMANY
25	Universitätsklinikum Hamburg Eppendorf (UKE)	Institut für Männergesundheit Gebäude W38 Martinistr. 52	20246	Hamburg	GERMANY
26	Urologische Praxis Dr. D. Müller	Dr. Ernst-Mucke-Str. 6	02625	Bautzen	GERMANY
27	Andros Mannenkliniek Arnhem	Mr.E.N. van Kleffensstraat 5	6836 BH	ARNHEM	NETHERLANDS
28	Deventer Ziekenhuis	Van Oldenielstraat 12	7415 EH	DEVENTER	NETHERLANDS
29	Huisartsenmaatschap L.S.V.	Nijkerkendijk 38-01	7442 LS	NIJVERDAL	NETHERLANDS
30	Medisch Spectrum Twente, Locatie Ariensplein	Afdeling gynaecologie, Ariënsplein 1	7511 JX	ENSCHEDE	NETHERLANDS
31	Disa Clinic	15 Lebenstraum Place Hurlingham Manor Sandton	2090	Johannesburg	SOUTH AFRICA
32	Josha Research	Rubins Building 28 East Burger Street	9324	Bloemfontein	SOUTH AFRICA
33	Newkwa Medical Centre	909 - 913 Inanda Road Newlands	4037	Durban	SOUTH AFRICA

34	Parklands Medical Centre - Durban	Parklands Medical Centre 75 Hopelands Road Overport	4091	Durban	SOUTH AFRICA
35	Private Practice Dr MK Dhanjee	75 Montague Street	2940	Newcastle	SOUTH AFRICA
36	Randles Road Medical Centre	468 Randles Road Syndenham	4091	Durban	SOUTH AFRICA
37	CAP Dr. Vicenç Papaceit - ABS La Roca del Vallès	Plaça de l'Era s/n	08430	La Roca del Vallès	SPAIN
38	CAP Sarrià	c/Bonaplata, 54-58	08034	Barcelona	SPAIN
39	Hospital Clínico Universitario de Valencia	Servicio de Urología Consultas Externas. Ed. Materno Infantil. Pl. 1ª Avda. Blasco Ibáñez, 17	46010	Valencia	SPAIN
40	Hospital Fundació Puigvert	Servicio de Andrología Cartagena, 340-350	08025	Barcelona	SPAIN
41	Hospital General Universitario de Alicante	Servicio de Urología c/ Pintor Baeza, s/n	03010	Alicante	SPAIN
42	Hospital Policlínico de Vigo - Clínica Povisa	Servicio de Urología Salamanca, 5	36211	Vigo	SPAIN
43	Hospital Universitario de Canarias	Servicio de Urología c/ Ofra, s/n	38320	La Laguna	SPAIN

.

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