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 Pharmaceuticals Inc.	
Study Number:	12392	NCT00478881
Study Phase:	II	
Official Study Title:	Randomized, double-blind, placebo-controlled, parallel group study of vardenafil 10 mg twice daily to assess the effect on urodynamics in patients with Overactive Bladder (detrusor overactivity)	
Therapeutic Area:	Urology	
Test Product		
Name of Test Product:	Vardenafil Hydrochloride (HCl) (Levitra, BAY38-9456)	
Name of Active Ingredient:	Vardenafil HCl	
Dose and Mode of Administration:	10 mg film-coated tablets, twice daily (BID) taken with water, with dose referring to vardenafil base. Mode of administration: oral	
Reference Therapy/Placebo		
Reference Therapy:	Matching placebo	
Dose and Mode of Administration:	Matching placebo tablets, BID Mode of administration: oral	
Duration of Treatment:	A total of 6 weeks	
Studied period:	Date of first subjects' first visit:	31 AUG 2007
	Date of last subjects' last visit:	13 NOV 2008
Premature Study Suspension / Termination:	None	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 07 MAR 2007) was approved prior to subject enrollment and specified the following change: • The medication regimen was changed from vardenafil 20 mg od (extended release) to vardenafil 10 mg BID (immediate release). Amendment no. 2 (dated 18 APR 2007) was approved prior to subject enrollment and was limited to Belgium and Israel. It specified the following change: • The requirement of filling in the OAB-q (overactive bladder questionnaire) during Visits 2 and 4 (and also PT) was removed. Amendment no. 3 (dated 25 JUN 2007) was approved prior to subject enrollment and was limited to Spain. It specified the following changes: • Five exclusion criteria (concomitant medication; previous or	

	current medical conditions) were added, as requested by the national regulatory authority. • Procedure for removal of subjects from the study was added, as requested by the national regulatory authority. Amendment no. 6 (dated 09 AUG 2007) was approved after subject enrollment had started and it specified the following change: • Androgens were added to concomitant medications prohibited during the study. Amendment no. 7 (dated 19 NOV 2007) was limited to Italy and approved after subject enrollment had started in Italy. It specified the following change: • A exclusion criterion was added, as requested by the Italian Independent Ethics Committee (IEC): Subjects with significantly abnormal findings (e.g., ST-depression, ventricular ectopic beats, arrhythmia) determined by an exercise elctrocardiogram (ECG)(stress test) according to the opinion of local internist/cardiologist. Amendment no. 8 (dated 15 JAN 2008) was approved after subject enrollment had started and it specified the following change: • The procedures in subjects with invalid urodynamic measurement at baseline (Visit 2) was changed from complete removal from the study to omission of urodynamic measurement at Visit 4. Amendment no. 9 (dated 08 SEP 2008) was approved after subject enrollment had started and it specified the following change: • A modified intent-to-treat population, for the purpose of a medically sound analysis of urodynamic data, and a modified per-protocol population was additionally defined.
Study Centre(s):	The study was conducted in 45 centers in Europe (Belgium 1, Czech Republic 3, France 2, Germany 13, Hungary 2, The Netherlands 6, Poland 6, Portugal 5, Spain 6, Switzerland 1), 4 centers in Canada, 4 centers in Russia, and 3 centers in Israel.
Methodology:	This study comprised of a 2- to 4-week untreated run-in period, a 6-week randomized, double-blind treatment period with vardenafil 10 mg (immediate release form) od versus placebo od, and a 24-hour follow-up period to assess any new occurrence of serious adverse events. The study consisted of 4 visits, i.e., Visit 1: Screening visit, Visit 2: Randomization visit-urodynamic measurements (filling cystometry and pressure flow investigations), ECG and safety laboratory, Visit 3: Safety visit after 2 to 3 weeks of randomized treatment, and Visit 4: Final visit-urodynamic measurements (filling cystometry and pressure flow investigations), ECG, safety laboratory and residual urine (by ultrasonography). Efficacy assessments were based on the data collected during urodynamic examinations (filling cystometry and pressure flow) as well as in a micturition diary. The micturition diary was examined at all the visits. Safety and tolerability were monitored throughout the trial. Plasma samples for the determination of vardenafil were taken at Visit 4 immediately before

	and approximately 60 minutes after intake of study medication in order to describe the plasma exposure of vardenafil and correlate estimates of exposure vs therapeutic effect as determined by urodynamics.
Indication/ Main Inclusion Criteria:	Indication: Overactive bladder (OAB) Main inclusion criteria: Subjects who had an overactive bladder (with and without urge incontinence) for at least 6 months prior to allocation to this study; male subjects aged ≥18 years and female postmenopausal subjects aged ≥55 years. Sites aimed at recruting at least 40% of male subjects.
Study Objectives:	Overall: To determine the therapeutic effect of vardenafil 10 mg BID on overactive bladder (OAB). Primary: Not applicable Secondary: Not applicable
Evaluation Criteria:	Efficacy (Primary): Primary variables of efficacy included: • Primary: To determine the therapeutic effect of vardenafil 10 mg BID on volume at first detrusor contraction. • Co-primary: Change in the number of daily micturitions as reported in the subject diaries. Efficacy (Secondary): • Detrusor pressure at first contraction • Cystometric bladder compliance • Volume at first detectable leakage • Maximum cystometric bladder capacity • Volume at first desire to void • Number of micturitions per day • Number of urgency episodes per day • Number of incontinence episodes per day • In men aged 50 years and older: Peak urinary flow • OverActive Bladder questionnaire (OAB-q) • Volume at 40 cm H_2O detrusor pressure (added per Statistical Analysis Plan) • Cystometric bladder compliance • Post-Void Residual urinary volume (PVR)) Safety: Incidence rates of premature termination, adverse events, and laboratory abnormalities; vital signs and electrocardiogram (ECG) abnormalities.

	Pharmacokinetics: Vardenafil plasma concentrations at the time of trough and peak, the area under the plasma concentration vs time curve from zero to 1 h [AUC(0-1)], and correlation with urodynamic parameters.
Statistical Methods:	Efficacy (Primary): The primary efficacy variable was the change from baseline in bladder volume (mL) at first detrusor contraction at Week 6. If significant, the change in the average number of daily micturitions (co-primary variable) was tested using the same significance level ($P<0.05$). Countries were pooled into 2 country clusters, which allowed for testing of treatment by center interactions. Testing for homogenous slopes was also done. After applying the algorithm specified in the Statistical Analysis Plan, an analysis of covariance (ANCOVA) including baseline (Visit 2) as a covariate with main effects for treatment and country was used to test treatment differences for the primary variable and co-primary variable. The modified intent-to-treat (mITT) population was the primary population for the volume at first detrusor contraction. The ITT population was the primary population for the average number of daily micturitions. Efficacy (Secondary): ANCOVA models used for the secondary efficacy variables were the models determined for the primary efficacy variable or co-primary efficacy variable depending on the type of variable. P-values were reported as nominal values and without any adjustments for multiplicity. Safety: Treatment groups were compared with respect to the incidence rates of premature termination, adverse events coded by Medical Dictionary for Regulatory Activities (MedDRA), laboratory abnormalities, ECG abnormalities, and treatment-emergent concomitant medication use coded by the Anatomic Therapeutic Chemical (ATC) classification system. For tables summarizing the treatment-emergent adverse events, only treatment-emergent adverse events which occurred up to 1 day after the last dose of study medication were included. Measurements and changes from baseline in vital signs (blood pressure and pulse rate), continuous laboratory variables, and ECG parameters were summarized using descriptive statistics (i.e., n, mean, standard deviation, minimum, median, maximum) by treatment group and visit.
	Pharmacokinetics: Descriptive summary statistics were used to summarize plasma concentrations of vardenafil and its metabolite BAY 44-5576 per sampling time. The area under the plasma concentration vs time curve from zero to 1 hour after single (first) dose [AUC(0-1)] was calculated by the linear trapezoidal rule. Trough and peak concentrations, were plotted vs the relative time of sample collection. Correlation plots of trough concentrations vs urodynamic data, peak concentrations vs urodynamic data, and AUC(0-1) vs urodynamic data were constructed. Bravais-Pearson correlation coefficients were calculated to explore the linear dependencies.

Number of Subjects:	A total of 635 subjects were screened and enrolled, out of these 396 subjects were actually analysed and evaluated.

Study Results

Results Summary — Subject Disposition and Baseline

In this study, 635 subjects were screened and enrolled. A total of 238 subjects were not randomized because they did not fulfill the inclusion/exclusion criteria. Thus, 397 subjects were randomized to receive placebo (198 subjects) or vardenafil 10 mg BID (199 subjects). As one subject did not take any study drug, the safety population included 396 subjects: placebo 198, vardenafil 198. The mITT population, i.e., the primary analysis set, comprised of 261 subjects: placebo 136, vardenafil 125.

In the safety population, the mean age was 56.9 years (range: 18 - 89 years) and mean body mass index (BMI) was 27.8 kg/m^2 (range: 16.4 - 53.5 kg/m^2). Nearly all subjects were Whites except for 2 Blacks, 1 Asian and 1 Hispanic; race was not recorded for 9 subjects.

Results Summary — Efficacy

The primary efficacy results based on the change of bladder volume at first detrusor contraction at Week 6 LOCF are given in Table 1. The co-primary efficacy results based on change in the average number of daily micturitions at Week 6 are presented in Table 2.

No statistically significant differences were observed between placebo and vardenafil 10 mg BID in either the change from baseline in bladder volume (mL) at first detrusor contraction or the change in the average number of daily micturitions.

Table 1: ANCOVA results for Volume (mL) at First Detrusor Contraction (subjects valid for mITT)

	Week 6 LOCF	
	Placebo (N=136)	Vardenafil 10 mg BID (N=122)
Baseline LSmean	156.01	153.29
LSmean of change from baseline ± SE	36.95 ± 8.78	44.99 ± 9.28
Placebo – Vardenafil 10 mg bid [a]	-8.05	
95% confidence interval	[-33.19,17.10]	
P value (t-test)	0.5293	

a LSmean Difference between treatment groups in change from baseline: Negative values indicate a larger increase from baseline in volume for vardenafil compared to placebo, which indicates a numerical improvement for vardenafil.

Abbreviations: ANCOVA: analysis of covariance, LOCF: last observation carried forward, LSmean: least squares mean, SE: standard error

Table 2: ANCOVA results for average number of daily micturitions (subjects valid for ITT)

	Week 6 LOCF	
	Placebo (N=178)	Vardenafil 10 mg BID (N=163)
Baseline LSmean	13.2	12.9
LSmean of change from baseline ± SE	-1.6 ± 0.2	-2.2 ± 0.3
Placebo – Vardenafil 10 mg bid [a]	0.7	
95% confidence interval	[-0.0,1.4]	
P value (t-test)	0.0575	

a LSmean Difference between treatment groups in change from baseline: Positive values indicate that vardenafil numerically reduced (ie, improved) the number of micturitions/day more than placebo.

Abbreviations: ANCOVA: analysis of covariance, LOCF: last observation carried forward, LSmean: least squares mean, SE: standard error

None of the secondary endpoints showed nominally statistically significant or clinically meaningful differences.

Results Summary — Safety

Extent of exposure:

In the safety population, mean (SD) treatment duration was 40.4 (12.4) days, 42.1 (9.7) in the placebo group and 38.7 (14.5) in the vardenafil group. Treatment duration was considered insufficient in more subjects randomized to vardenafil (39, 20%) than in those randomized to placebo (20, 10%).

Adverse events:

A brief summary of treatment-emergent adverse events is given in Table 3.

Table 3: Incidence rates of treatment-emergent adverse events (Safety population)

Incidence rate	Placebo (N=198)	Vardenafil 10 mg BID (N=198)	Total (N=396)
Adverse events	71 (35.9%)	97 (49.0%)	168 (42.4%)
Drug-related adverse events	39 (19.7%)	76 (38.4%)	115 (29.0%)
Adverse events leading to discontinuation of study drug	12 (6.1%)	31 (15.7%)	43 (10.9%)
Serious adverse events	4 (2.0%)	4 (2.0%)	8 (2.0%)
Drug-related serious adverse events	0 (0.0%)	1 (0.5%)	1 (0.3%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)

Treatment-emergent: adverse events which occurred up to 1 day after the last dose of study medication. Each of these categories of events also includes serious adverse events.

A total of 4 subjects (2.0%) in the placebo group and 4 subjects (2.0%) in the vardenafil group experienced treatment-emergent serious adverse events. There were no deaths. Most common were cardiac disorders (placebo 1.0%, vardenafil 0.0%) and nervous system disorders (placebo 0.0%, vardenafil 1.0%). All serious adverse events were considered to be not related to the study medication, except for one vardenafil-treated subject who experienced mild blurred vision and moderate headache.

Laboratory, vital signs, and ECG:

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. No relevant safety findings were determined by the ECG and the assessment of serious adverse events, and adverse events.

Results Summary — Pharmacokinetics

The peak and trough plasma exposure of vardenafil in this study was in accordance with the expectations of a 10 mg vardenafil BID regimen. The observed vardenafil concentrations (geometric mean) were 0.57 µg/L (trough) and 5.2 - 6.3 µg/L (peak). PK/PD analyses were conducted between trough, peak concentration, and AUC(0-1) of vardenafil (PK), respectively, and a number of selected urodynamic parameters (PD). The regression analyses in scatter-plots of PK vs PD indicated a weak association between vardenafil plasma exposure and PD effect with marked variability and the slope of regression lines appeared to be driven primarily by a few individual subjects rather than the data points as a whole.

Conclusion(s)

In this study, the objective was to determine the therapeutic effect of vardenafil 10 mg BID versus placebo on OAB using urodynamic measurements. The estimated (LS-mean) change from baseline in bladder volume at first detrusor contraction at Week 6 LOCF was 37.0 mL for placebo and 45.0 mL for vardenafil, which was not a statistically significant difference in the primary variable. The estimated change from baseline in the number of daily micturitions at Week 6 LOCF was -1.6 for placebo and -2.2 for vardenafil (nominal P=0.0575).

The adverse event profile based on this study was consistent with the safety profile as presented in the Development Core Safety Information. 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 safety relevant findings were determined by the ECG and the assessment of serious adverse events, and adverse events.

Publication(s):	None		
Date Created or Date Last Updated:	24 APR 2012	Date of Clinical Study Report:	06 OCT 2009

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	CU Saint-Luc/UZ St-Luc	Service Urologie/Dienst Urologie Avenue Hippocrate 10 Hippocrateslaan	1200	BRUXELLES - BRUSSEL	BELGIUM
2	Brantford Urology Research	Medical Arts Building 353 St. Paul Avenue	N3R 4N3	Brantford	CANADA
3	Dr. Steinhoff Clinical Research	1121 Yates Street Suite 201	V8V 3N1	Victoria	CANADA
4	Sir Mortimer B. Davis Jewish General Hospital	Urology Department Room E-941 3755 Cote Ste. Catherine	H3T 1E2	Montreal	CANADA
5	Urology Associates	450 Westheights Drive Unit 18	N2N 2B9	Kitchener	CANADA
6	Androgeos - private center of urology and andrology	Na Valech 4/289	160 00	Praha 6	CZECH REPUBLIC

7	Fakultni Thomayerova Nemocnice	Department of Urology Videnska 800	140 59	Praha 4	CZECH REPUBLIC
8	Vseobecna Fakultni Nemocnice Olomouc	Clinic of Urology I.P. Pavlova 6	775 20	Olomouc	CZECH REPUBLIC
9	Hôpital Tenon - Paris	Hopital Tenon Service de Chirurgie Urologique 4 rue de la Chine	75970	PARIS CEDEX 20	FRANCE
10	ROTHSCHILD-PARIS	Service de Rééducation Neurologique & Exploration Perinéale 33 boulevard de Picpus	75571	PARIS CEDEX 12	FRANCE
11	Asklepios Klinikum Uckermark	Urologische Klinik Auguststraße 23	16303	Schwedt	GERMANY
12	Kliniken Maria Hilf GmbH	Krankenhaus St. Franziskus Klinik für Urologie Viersener Straße 450	41063	Mönchengladbach	GERMANY
13	Kliniken Nordoberpfalz AG - Klinikum Weiden	Klinik für Urologie und Kinderurologie Söllnerstr. 16	92637	Weiden	GERMANY
14	Klinikum der Ernst-Moritz-Arndt-Universität	Klinik und Poliklinik für Urologie Fleischmannstr. 42-44	17475	Greifswald	GERMANY
15	Praxis Drs. Roth / Wins	Urologische Gemeinschaftspraxis Morianstr. 10	42103	Wuppertal	GERMANY
16	Praxis Dr. Stefan Carl & Dr. Achim Forth	Karl-Friedrich-Str. 55	79312	Emmendingen	GERMANY
17	Praxis Fr. Dr. E. Heßdörfer	Reinickendorfer Str. 15	13347	Berlin	GERMANY
18	Praxis Hr. Dr. K.-U. Laval	MVZ Hans-Günther-Sohl-Str. 12	40235	Düsseldorf	GERMANY

19	Reha-Zentrum Passauer Wolf	Urologie Thermalbadstrasse 20	94086	Bad Greisbach-Therme	GERMANY
20	Städtisches Klinikum Neunkirchen gemeinnützige GmbH	Brunnenstraße 20	66538	Neunkirchen	GERMANY
21	St. Hedwig Krankenhaus	Urologie Große Hamburger Str. 5-11	10115	Berlin	GERMANY
22	Universitätsklinikum Essen	Urologie/Andrologie Hufelandstr. 55	45147	Essen	GERMANY
23	Universitätsklinikum Leipzig AöR	Klinik und Poliklinik für Urologie Liebigstr. 20	04103	Leipzig	GERMANY
24	Budai Egeszsegkozpont Kft	Kiralyhago u. 1-3	1126	Budapest	HUNGARY
25	University of Semmelweis	Urology Clinic of SOTE Ulloi ut 78/b	1082	Budapest	HUNGARY
26	Rabin Medical Center	Jabotinsky St.		Petach Tikva	ISRAEL
27	Rambam Medical Center	8, Haaliya Hashniya St. Bat Galim	31096	Haifa	ISRAEL
28	Shaare Zedek Medical Center	P.O.B. 3235	91031	Jerusalem	ISRAEL
29	Academisch Medisch Centrum Universiteit van Amsterdam	Meibergdreef 9	1105 AZ	AMSTERDAM	NETHERLANDS
30	Academisch Ziekenhuis Maastricht	Afd. Urologie - P. Debyelaan 25	6229 HX	MAASTRICHT	NETHERLANDS
31	Catharina	Afd. Urologie Michelangelolaan 2	5623 EJ	EINDHOVEN	NETHERLANDS
32	Erasmus Medisch Centrum	Dr. Molewaterplein 40	3015 GD	ROTTERDAM	NETHERLANDS

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34	Vrije Universiteit Medisch Centrum	De Boelelaan 1117	1081 HV	AMSTERDAM	NETHERLANDS
35	Centrum Leczenia Chorób Cywilizacyjnych	ul. Komisji Edykacji Narodowej 98/U18	02-777	Warszawa	POLAND
36	NZOZ Centrum Medyczne Wola	ul. Ciolka	01-432	Warszawa	POLAND
37	NZOZ Urolog - Poradnia Urologiczna	ul. Ujejskiego 75	85-168	Bydgoszcz	POLAND
38	Slaskie Centrum Urologii "Urovita"	ul. Strzelcow Bytomskich 11	41-500	Chorzow	POLAND
39	Szpital Kliniczny Dzieciatka Jezus -Centrum Leczenia Obrazen	Katedra i Klinika Urologii AM ul. Lindleya 4	02-005	Warszawa	POLAND
40	Uroprojekt s.c. - Gabinet urologiczny	ul. Mieszka I 24	08-110	Siedlce	POLAND
41	Hospital Santo António Oporto	Largo Prof. Abel Salazar	4099-001	Porto	PORTUGAL
42	H. Militar Reg. Nº1 - Pedro V	Serviço Urologia Av. da Boavista	4050-013	Porto	PORTUGAL
43	H. Fernando Fonseca	Serviço Urologia IC 19	2720-276	Amadora	PORTUGAL
44	H.Curry Cabral	Serviço Urologia R. da Beneficência Nº 8	1069-166	Lisboa	PORTUGAL
45	C H Coimbra	Serviço Urologia Quinta dos Vales	3046-853	S. Martinho do Bispo	PORTUGAL
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55	Hospital Universitario Virgen de las Nieves	Servicio de Urología Avda. de las Fuerzas Armadas, 2	18014	Granada	SPAIN
56	Universitätsspital Basel	Urologische Klinik Spitalstrasse 21	4031	Basel	SWITZERLAND

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