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:	14694	NCT01168817 EudraCT: 2010-020122-18
Study Phase:	II	
Official Study Title:	A prospective, randomized, double-blind, double-dummy, placebo- and active controlled, multicenter study assessing the efficacy and safety of the combination BAY 60 4552 / vardenafil compared to vardenafil (20 mg) for the treatment of erectile dysfunction not sufficiently responsive to standard therapy with PDE5 inhibitors	
Therapeutic Area:	Men's Health	
Test Product		
Name of Test Product:	BAY98-7081	
Name of Active Ingredient:	BAY 60-4552 and vardenafil	
Dose and Mode of Administration:	1 mg BAY 60-4552 plus 10 mg vardenafil once daily (od), orally	
Reference Therapy/Placebo		
Reference Therapy:	Reference drug 1 **Vardenafil** Reference drug 2 **Placebo**	
Dose and Mode of Administration:	**Vardenafil** once daily (od)**:** 20 mg given orally as needed (prn) (open-label run-in period) 20 mg given orally od (double-blind treatment period) **Placebo** od	
Duration of Treatment:	**BAY 60-4552 and vardenafil:** 4 weeks (double-blind treatment period) **Vardenafil (**Reference drug 1)**:** 4 weeks (open-label run-in period) 4 weeks (double-blind treatment period) **Placebo (**Reference drug) 4 weeks (double-blind treatment period)	
Studied period:	Date of first subjects' first visit:	19 AUG 2010
	Date of last subjects' last visit:	04 MAY 2011

Premature Study Suspension / Termination:	Not applicable
Substantial Study Protocol Amendments:	During this study there was one protocol amendment dated 3 Nov 2012. Additional exclusion criteria were added for history of pelvic radiotherapy and pulmonary venous occlusive disease. Exclusion criteria for the double-blind period of the study regarding specific ECG and laboratory results were removed from this section and included as criteria for withdrawal from the study because it was judged that these results would not be available by the start of the double blind period at Visit 4. Text was added stating that ECG and laboratory results would be reviewed immediately to check whether a patient was to be withdrawn from the study.
Study Center(s):	31 active study centers screened subjects in the following countries: in Finland (n=3), France (n=6), Germany (n=5), Italy (n=4), Spain (5), Sweden (n=5), and The Netherlands (n=3)
Methodology:	The study was conducted using a multicenter, randomized, double-blind, double-dummy, placebo- and active controlled, parallel-group design. All subjects eligible for the 28 day (±2 days) open-label run-in phase received 20 mg vardenafil tablets to be taken as needed (prn) but not more often than od. After 7±2 days, an interim visit took place to assess safety and tolerability of the 20 mg vardenafil prn treatment. Subjects eligible for the 28 day (±2 days) double-blind treatment phase were randomized 1:1:1 to receive 1 of the following 3 study treatments (3 tablets per day in each treatment group): 1) **1 mg BAY 60 4552 plus 10 mg vardenafil**, corresponding to 1 tablet of 1 mg BAY 60 4552 plus 1 tablet of 10 mg vardenafil plus 1 placebo tablet identical in appearance to the 20 mg vardenafil tablet 2) **20 mg vardenafil**, corresponding to 1 placebo tablet identical in appearance to the 1 mg BAY 60 4552 tablet plus 1 placebo tablet identical in appearance to the 10 mg vardenafil tablet plus 1 tablet of 20 mg vardenafil 3) **Placebo**, corresponding to 1 placebo tablet identical in appearance to the 1 mg BAY 60 4552 tablet plus 1 placebo tablet identical in appearance to the 10 mg vardenafil tablet plus 1 placebo tablet identical in appearance to the 20 mg vardenafil tablet
Indication/ Main Inclusion Criteria:	Erectile dysfunction At the end of the 28 day (±2 days) open-label run-in phase, subject eligibility was assessed for the 28 day (±2 days) randomized, double-blind, double-dummy treatment phase of the study. Only men with an insufficient response to 20 mg vardenafil prn during the open-label run in phase were eligible and randomized. Insufficient response was defined as follows: • International Index of Erectile Function (IIEF) Erectile Function domain (IIEF EF) score (i.e. the sum of the scores of questions 1-5 and 15) <17 and • At least 50% of attempts at sexual intercourse during the open-label run-in phase had been unsuccessful, i.e. the following question in the

	Subject Diary had to be answered with "No": • "Did your erection last long enough for you to have successful intercourse?" (SEP 3: success in maintenance of erection)
Study Objectives:	**Primary:** The primary objective of this study was to: Investigate the efficacy of a combination of BAY 60 4552 and vardenafil in men with ED and insufficient response to standard therapy with 20 mg vardenafil taken as needed (prn) during the 4 week open-label run in phase **Secondary:** The secondary objectives of this study were to assess the: Safety and tolerability of the combination when given od for 4 weeks Pharmacokinetics of vardenafil, its metabolite M 1 (BAY 44 5576), and BAY 60 4552 based on a 0 4 hour profile at Visit 4 and concentration values at approximately 12 hours post-administration at Visit 5 (interim visit) and Visit 7 (end-of-treatment visit)
Evaluation Criteria:	Efficacy (Primary) Primary efficacy variable of this study was the International Index of Erectile Function – Erectile Function subscale (IIEF EF). The International Index of Erectile Function (IIEF) is a 15 item self-report instrument assessing male sexual function. The Erectile Function (EF) domain, comprised of items 1 to 5 and 15 from the IIEF, was used in this study. Efficacy (Secondary) Secondary efficacy variables of this study were the following 6 items of the Sexual Encounter Profile (SEP): • SEP 1 'Enlargement' (Were you able to achieve at least some erection?) • SEP 2 'Penetration' (Were you able to insert your penis into your partner's vagina?) • SEP 3: 'Maintenance' (Did your erection last long enough to have sexual intercourse?) • SEP 4 'Hardness' (Overall were you satisfied with the hardness of your erection?) • SEP 5 'Satisfaction' (Overall were you satisfied with this sexual experience?) • SEP 6 'Ejaculation' (Did you ejaculate?) Safety: Adverse events, safety laboratory parameters (hematology, blood chemistry, and urinalysis), vital signs, and electrocardiogram (ECG) Pharamacokinetics: Pharmacokinetics were assessed in all subjects at Visit 4 (start of double-blind treatment), and a single blood sample was taken about 12 hours post dosing at Visit 5 and Visit 7 (end of treatment). Plasma concentrations of vardenafil, M 1 (vardenafil metabolite BAY 44 5576), and BAY 60 4552 were determined.
Statistical Methods:	The statistical analysis of the IIEF EF, SEP 2, and SEP 3 was conducted via an ANCOVA with baseline as covariate, and with treatment and center as factors.

	The ANCOVA for the primary efficacy analysis 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 GLM (generalized linear model) was selected for each variable. The primary analysis was based on the ITT sample. However, this analysis was repeated for the PP population. The statistical analysis of the secondary efficacy variables was only provided for the ITT sample.
Number of Subjects:	**Planned:** 42 subjects were to be randomized per treatment group **Analyzed:** 43 subjects were randomized to receive the combination treatment of 1 mg BAY 60-4552 plus 10 mg vardenafil od, 51 to receive 20 mg vardenafil od, and 46 to receive placebo od

Study Results

Results Summary — Subject Disposition and Baseline

Altogether 288 subjects were enrolled in 31 active study centers in Finland, France, Germany, Italy, Spain, Sweden, and The Netherlands. Of these, 240 subjects entered the open-label run-in period to select non-responders to 20 mg vardenafil prn treatment. Of the 140 subjects who completed the open-label run-in period, 43 were randomized to receive the combination treatment of 1 mg BAY 60 4552 plus 10 mg vardenafil od, 51 to receive 20 mg vardenafil od, and 46 to receive placebo od. 1 subject randomized to receive the combination treatment of 1 mg BAY 60 4552 plus 10 mg vardenafil od did not receive any study drug. 35, 40, and 40 subjects completed the study in the 1 mg BAY 60 4552 plus 10 mg vardenafil od, 20 mg vardenafil od, and placebo od treatment groups.

The 139 non-responders to 20 mg vardenafil prn treatment who received double-blind treatment were 26 to 64 years old (mean age: 55.1 years). There were no clinically relevant differences in age, weight, height, or BMI between these 139 subjects and the 97 subjects not randomized to double-blind treatment nor between the 3 subgroups of subjects randomized to the 3 different double-blind treatment.

Results Summary — Efficacy

Primary efficacy variable

Baseline LS mean IIEF EF scores at Visit 4 were 11.4, 11.1, and 12.0 in the 1 mg BAY 60 4552 plus 10 mg vardenafil od, 20 mg vardenafil od, and placebo od treatment groups, respectively (ITT analysis set). At Visit 7, the LS mean IIEF EF scores were 17.1, 15.8, and 11.0 in the 1 mg BAY 60 4552 plus 10 mg vardenafil od, 20 mg vardenafil od, and placebo od treatment groups, respectively (ITT analysis set).

In the ITT analysis set, the combination treatment of 1 mg BAY 60 4552 plus 10 mg vardenafil od was significantly better than placebo od at Visit 7 (difference of LS means: 6.1; $P<0.0001$) and using the LOCF technique (difference of LS means: 5.9; $P<0.0001$). The same was true comparing 20 mg vardenafil od versus placebo od (differences of LS means: 4.8 and 4.1; $P=0.0005$ and $P=0.0011$). Comparing the 2 active treatments, 1 mg BAY 60 4552 plus 10 mg vardenafil od was not significantly superior to 20 mg vardenafil od at Visit 7 (difference of LS means: 1.3; $P=0.3541$) or using the LOCF technique (difference of LS means: 1.8; $P=0.1431$).

Results for IIEF EF were similar in the PP analysis set.

Secondary efficacy variables

For most secondary efficacy variables, the combination treatment of 1 mg BAY 60 4552 plus 10 mg vardenafil od was significantly better than placebo od at Visit 7 and / or using the LOCF technique and the same was true comparing 20 mg vardenafil od versus placebo od. Comparing the 2 active treatments, 1 mg BAY 60 4552 plus 10 mg vardenafil od was not significantly superior to 20 mg vardenafil od at Visit 7 or using the LOCF technique (P=0.2260). At single early time points, nominally significant superiority of the combination was determined, i.e. for SEP 3 'Maintenance', SEP 4 'Hardness', and SEP 5 'Satisfaction' at Visit 5.

Results Summary — Safety

No death occurred during this study. 2 subjects experienced serious adverse events during the open-label run-in period, i.e. on 20 mg vardenafil prn treatment, i.e. severe sciatica and spinal operation (not further specified). Both events were assessed as not related to study drug by the investigator. Both subjects discontinued study drug prematurely due to these events, which resolved by end of the study. Another 2 subjects experienced serious adverse events during the double-blind treatment period, i.e. severe biliary colics (20 mg vardenafil od) and knee arthroplasty (pre-planned surgery; placebo od). Both events were assessed as not related to study drug by the investigator. Both subjects discontinued study drug prematurely due to these events, which resolved by end of the study.

Another 8 subjects (including Subject 14694-22003-0006) discontinued study drug prematurely due to non-serious adverse events during the open-label run-in period. Another 7 subjects discontinued study drug prematurely due to non-serious adverse events during the double-blind treatment period. Most of these events were labeled adverse reaction of vardenafil such as flushing and headache.

During the open-label run-in period, i.e. on 20 mg vardenafil prn treatment, 77 of 236 subjects (32.6%) experienced any treatment-emergent adverse event. 43 of 139 non-responders to 20 mg vardenafil prn (30.9%) experienced any treatment-emergent adverse event during the open-label run-in period. 70 of 139 randomized subjects (50.4%) who received double-blind treatment experienced any treatment-emergent adverse event during the double-blind treatment period.

The incidence of subjects with drug-related adverse events was 45.2%, 37.3%, and 8.7% in the 1 mg BAY 60 4552 plus 10 mg vardenafil od, 20 mg vardenafil od, and placebo od treatment groups, respectively. Similar pattern of drug-related adverse events occurred with subjects experiencing moderate (n=10, 23.8%) and mild (n=9, 21.4%) events in the 1 mg BAY 60 4552 plus 10 mg vardenafil od treatment group. Subjects with drug-related adverse events in the 20 mg vardenafil od treatment group experienced predominantly mild events (n=14, 27.5%) and subjects with drug-related events were rare (n=4, 8.7%) in the placebo od treatment group.

During the open-label run-in period, i.e. on 20 mg vardenafil prn treatment, the highest incidence of subjects (non-responder subgroup) with treatment-emergent, drug-related adverse events were reported for flushing (n=13, 9.4%), headache (n=9, 6.5%), and dyspepsia (n=6, 4.3%), i.e. adverse events well-known to be associated with the use of PDE5 inhibitors such as vardenafil.

The highest incidence of subjects in the 2 active treatment groups with treatment-emergent, drug-related adverse events were reported for flushing (n=7, 16.7%, and n=5, 9.8%, in the 1 mg BAY 60 4552 plus 10 mg vardenafil od and 20 mg vardenafil od treatment groups, respectively), headache (n=4, 9.5%, and n=6, 11.8%), i.e. adverse events well-known to be associated with the use of PDE5 inhibitors such as vardenafil and other vasodilators such as BAY 60 4552. Gastrointestinal disorders such as nausea and dyspepsia were predominantly reported by subjects in the 1 mg BAY 60 4552 plus 10 mg vardenafil od treatment group

(n=3, 7.1% each). Adverse events associated with vasodilation were considerably less frequently reported in the placebo group (flushing: n=2, 4.3%; headache: n=1, 2.2%).

Overall, there were no signals for unexpected high or low laboratory abnormalities during the open-label run-in period or on active treatment as compared to placebo during the double-blind treatment period.

Overall, there were no clinically relevant changes from baseline in mean vital signs values detected at any time during the study.

Overall, there were no signals for any untoward influence of any of the active treatment components on any ECG parameter as compared to results in the placebo od treatment group.

Results Summary-Pharamacokinetics

Vardenafil

Vardenafil was rapidly absorbed with median tmax of 1.0 hour after 20 mg vardenafil alone and 10 mg vardenafil in combination with 1 mg BAY 60 4552. Geometric mean Cmax and AUC(0 tlast) values for vardenafil were approximately 2.3 times and 2.2 times higher after 20 mg vardenafil alone (25.0 □g/L and 50.6 □g*h/L) compared to values after 10 mg vardenafil in combination with 1 mg BAY 60 4552 (10.7 □g/L and 23.3 □g*h/L). Interindividual variability of Cmax (CV: 76.5% and 74.8%) and AUC(0 tlast) (CV: 82.2% and 75.5%) of vardenafil was high after 20 mg vardenafil alone and 10 mg vardenafil in combination with 1 mg BAY 60 4552.

BAY 44 5576

Vardenafil was rapidly metabolized to BAY 44 5576 with median tmax of 1.0 hour after 20 mg vardenafil alone and 10 mg vardenafil in combination with 1 mg BAY 60 4552. Geometric mean Cmax and AUC(0 tlast) values for BAY 44 5576 were approximately 1.8 times and 1.5 times higher after 20 mg vardenafil alone (22.6 □g/L and 36.3 □g*h/L) compared to values after 10 mg vardenafil in combination with 1 mg BAY 60 4552 (12.6 □g/L and 23.8 □g*h/L). Interindividual variability of Cmax (CV: 78.6% and 72.9%) and AUC(0 tlast) (CV: 87.4% and 73.9%) of BAY 44 5576 was high after 20 mg vardenafil alone and 10 mg vardenafil in combination with 1 mg BAY 60 4552.

BAY 60 4552

BAY 60 4552 was rapidly absorbed with median tmax of 1.5 hour after 1 mg BAY 60 4552 in combination with 10 mg vardenafil. Interindividual variability of Cmax (CV: 41.6%) and AUC(0 tlast) (CV: 52.2%) of BAY 60 4552 was moderate.

Conclusion(s)

- The study failed to demonstrate superior efficacy of the combination treatment of 1 mg BAY 60 4552 plus 10 mg vardenafil od versus 20 mg vardenafil od considering the primary efficacy variable and secondary efficacy variables.
- Both active treatments demonstrated superior efficacy versus placebo.
- Overall, the safety and tolerability of 20 mg vardenafil od and the combination treatment of 1 mg BAY 60 4552 plus 10 mg vardenafil od were similar with a tendency of more frequent gastrointestinal adverse events in the combination treatment group.

Publication(s):	Not applicable		
Date Created or Date Last Updated:	14 Dec Nov 2012	Date of Clinical Study Report:	14 Dec 2012

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