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.

1. Study synopsis NCT00667966

Title of the study:	Double-blind, cross-over, placebo controlled pilot study to characterize the profile of those patients with spinal cord injury diagnosed by electrophysiological, urodynamic and clinical (ASIA group) assessment who may respond to vardenafil treatment. (**LEMDE**)
Investigators:	Dr. Joan Vidal Samsó. Instituto Guttmann. Hospital de Neurorehabilitación. Badalona, Spain. See Section 16.1.4 for the list of investigators.
Study centers:	2 centers in Spain.
Publications (references):	Not available.
Period of study:	19 Jul 2005 to 13 Feb 2007
Clinical phase:	Phase IV.
Objectives:	To characterize patients with erectile dysfunction secondary to a traumatic spinal cord injury lasting more than 6 months who respond to therapy with vardenafil in terms electrophysiological, urodynamic and clinical (ASIA group) tests. Responders are defined as patients with rigidity ≥ 60% in the base measured with RigiScan during at least 5 minutes after withdrawing the vibrator and/or finishing manual stimulation. To study whether or not there is a difference between in the erection duration with rigidity ≥ 60 % in the base between placebo and 10 mg dose of vardenafil and between 10 mg and 20 mg doses of vardenafil.
Methodology (design of study):	Randomised, double-blinded, cross-over, placebo controlled, pilot study of 10 mg and 20 mg doses of vardenafil on patients with spinal cord injury classified on the 4 ASIA groups of International Scale (A,B,C,D), carried out in two sites in Spain.
Number of patients:	51 subjects enrolled, 45 subjects were randomised. - Per protocol population: 39. - Evaluable for Safety: 45.

	- Evaluable for Efficacy: 45 for intent to treat (ITT).
Diagnosis and main criteria for inclusion:	Men between 18 and 64 years old with stable cord injury (more than 6 months) who had erectile dysfunction according to the National Institutes if Health (NIH) after their traumatic spinal cord injury.
Test product, dose and mode of administration, batch number:	BAY 38-9456 was supplied as 10 mg, and 20 mg oral tablets. The batch number was BX01XGG.
Duration of treatment:	Each subject received the treatment 4 days during the study. The treatment started with the 10 mg dose at Visits 2 and 4 (Days 1 and 3 of treatment), followed by the 20 mg dose administered at Visit 3 and 5 (Days 2 and 4 of treatment).
Reference therapy, dose and mode of administration, batch number:	Placebo tablets, identical in appearance to each dosage of the active treatment, were also provided. The batch number is BX01XGG
Criteria of evaluation:	Efficacy: Primary efficacy assessment: Characteristics of responders and non responder with respect to the electrophysiological (skin sympathetic response, bulbocavernosus reflex and somatosensory and pudendal evoked potential), urodynamical and clinical (ASIA group) tests of each patient at starting of the trial. Secondary efficacy assessment: - Duration of an erection ≥ de 60%in the base induced by an erectogenic stimulus (vibrator and/or manual) in each patient after administering a 10 mg dose of vardenafil. - Duration of an erection ≥ de 60%in the base induced by an erectogenic stimulus (vibrator and/or

	manual) in each patient after administering a 20 mg dose of vardenafil. Safety: A laboratory evaluation (hematology, blood chemistry), was performed at the start of the study (between Visits 1 and 2) and at the last visit (Visit 5) or at premature discontinuation. A complete physical examination was performed at selection and at the end of the study or premature discontinuation. Arterial blood pressure and heart rate was measured at all Visits. Adverse Events was recorded at all Visits.
Statistical methods:	Efficacy: The main assessment described the electrophysiologic, urodynamic and clinical (ASIA group) characteristics of each patient, which were grouped in two categories: responders and non responders. Responder patients are defined as those that achieve a rigidity greater than 60% measured in the base with RigiScan during at least 5 minutes after removing the vibrator and/or finishing manual stimulation. The analysis of the secondary efficacy variables was based on the data of the patients of per protocol population (PP). The ITT analysis included all the randomised patients that have taken at least one tablet of each treatment period. Secondary assessment compared the erection duration with 10 mg of vardenafil with respect to placebo and the erection duration with 20 mg of vardenafil with respect to 10 mg of vardenafil.

Secondary variables were analyzed using an analysis of variance (ANOVA) following the cross-over study model. In addition to the treatment effect (vardenafil vs placebo), the subject effect that was nested inside the order of sequence or treatment order (vardenafil/placebo or placebo/vardenafil sequences), the interaction of sequence effect or treatment order and the effect of treatment period were considered. Since we wanted our inference to include individuals not included in the trial, the individual effect was considered a random effect. An estimate of the direct effect of treatment was included in this analysis. To perform the analysis, the assumptions of normality, homogeneity of variances and homogeneity of the regression slopes were verified.

All the secondary variables were summarized using descriptive statistic.

In the analyses by subgroups it was considered, whenever appropriate, the age, and the various groups based on the main comorbidity parameters (hypertension, diabetes, depression, hypercholesterolemia...). These analyses only considered the demographic variables and secondary efficacy variables considered to be of interest.

Safety: Those patients that have taken at least one dose of the product were considered for the safety population. All the adverse effects appearing for each treatment were classified by body system, specifying their relationship with the medicinal product, as well as the causes of early withdrawals. When possible, their exploratory statistical significance was assessed by the Chi-square test or alternative method.

The incidence of disorders in the physical examination has been described.

The laboratory parameters were quantified by Visit and treatment and descriptive statistics of them was performed.

Summary and conclusions:	
Summary of efficacy:	This was an exploratory study without formal sample size calculation investigating vardenafil effects on a pharmacodynamic variable (rigidity). The primary efficacy variable is the number of responders observed under each treatment condition. Responders are defined as subjects achieving a rigidity of at least 60% over a period of at least 5 minutes under an experimental session i.e., each subject could be maximally 4 times a responder depending upon his response after each drug application. As expected the percentage of responders observed in the vardenafil group is superior to that one observed under placebo: 55% vs 30%. This difference is nominally significant and the odds ratio is about 2.8 (CI 1.59-5.03). Simultaneously, the difference between 10 mg and 20 mg is also significant ($P<0.05$). However, this time 10 mg seems to be superior to 20 mg: 49% vs 35% (OR=1.83; CI 1.06-3.15). Here, it has to be taken into consideration that doses had to be estimated irrespective of the drugs so that these effects are confounded. Second, uncontrolled factors may have biased the results: in the treatment sequence A-B-C-D the responder rate under 10 mg placebo – although starting in period 3 – is as high as under vardenafil 10 mg, and under both treatments (vardenafil, placebo) the subsequent higher dose (20 mg) yields inferior results when compared to the lower dose. In the sequence C-D-A-

	B vardenafil 20 mg is also inferior to 10 mg but under placebo there is a negligible improvement under 20 mg when compared to 10 mg placebo. Although vardenafil 20 mg had shown in some studies only a moderate superiority when compared to 10mg the present results are surprising and may be related to some non specific experimental factors, e.g. patient instructions which are nevertheless unknown.
Summary of safety:	Adverse events: Vardenafil was well tolerated. The serious adverse events were not related with the treatment. The most frequent reported adverse events had all an incidence of 2% in each treatment group. Most of them related to the basic condition of the patients: spinal cord injury. Serious Adverse Events: There was one case of increase of spasticity resolved with remedial drug therapy and not related to the study drug. And one case of intrathecal catheter infection resolved with remedial drug therapy and the replacement of the catheter. It was also not related to the study drug.
Summary of pharmacokinetics:	Not applicable
Conclusions:	This randomized, double-blind, crossing over study was conducted to characterise responders of spinal cord injury's patients to vardenafil and to determine whether or not there are significant differences in the duration of the erection with the increase of the

	vardenafil dose from 10 to 20 mg. The percentage of responders observed in the vardenafil group is superior to placebo: 55% vs 30%.. The difference between 10 mg and 20 mg is also significant (P<0.05). However, 10 mg seems to be superior to 20 mg: 49% vs 35% (OR=1.83; CI 1.06-3.15).These results may be related to some non specific experimental factors, e.g. patient instructions. The rigidity times as summarized in Table 11-4.1 of the text show a clear dose-response relationship under vardenafil treatment with longer rigidity times, under 20 mg, but a reversed picture under placebo. These data were in accordance with other clinical trials. ASIA categories C and D responded better than A and B (23% vs 15-8%). Vardenafil was generally well tolerated in this population with spinal cord injury.

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	

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