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:	12049	NCT00666809
Study Phase:	IIb	
Official Study Title:	Evaluation of vardenafil for the treatment of subjective tinnitus: A controlled pilot study	
Therapeutic Area:	Primary Care	
Test Product		
Name of Test Product:	Vardenafil (Levitra, BAY38-9456)	
Name of Active Ingredient:	Vardenafil Hydrochloride (HCl)	
Dose and Mode of Administration:	Vardenafil 10 mg tablets were given as a fixed dose regimen of 10 mg twice a day (bid) at 12 hourly intervals (morning and evening), with total daily dose 20 mg orally.	
Reference Therapy/Placebo		
Reference Therapy:	Matching placebo	
Dose and Mode of Administration:	Matching placebo tablets were given bid at 12 hourly intervals orally.	
Duration of Treatment:	12 weeks in total	
Studied period:	**Date of first subjects' first visit:**	20 OCT 2006
	Date of last subjects' last visit:	25 MAY 2007
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 27 JUN 2006) specified the following changes: • Exclusion criterion concerning underlying cardiovascular conditions was modified. • Exclusion criterion concerning women of child-bearing potential was modified. • Exclusion of subjects committed to an institution due to an official or judicial directive.	
Study Centre(s):	The study was conducted at a single center in Germany.	
Methodology:	This was a monocentric, prospective, randomized, double-blind, placebo controlled parallel group study with adaptive design. Subjects were randomized (Visit 2) to the vardenafil or placebo group. Subjects received treatment with study medication from Visit 2 to Visit 4, i.e., over a period of 12 weeks. Subsequently, they went into follow-up for a further 4 weeks, until Visit 5. The Tinnitus Questionnaire (TQ) and SF-36 questionnaire were administered at baseline (Visit 2), during treatment (Visit 3), and after treatment (Visits 4 and 5) with study medication. Audiometric measurements were also performed from Visits 2 to 5.	

Indication/ Main Inclusion Criteria:	Indication: Tinnitus Main Inclusion Criteria: Male and female subjects between 18 and 64 years of age, with subjective tinnitus of duration >3 months. Only subjects without tinnitus treatment within the last 4 weeks were included.
Study Objectives:	**Overall:** • To evaluate improvement of tinnitus with vardenafil treatment. • To show superior efficacy of vardenafil over placebo in the treatment of chronic tinnitus. **Primary:** Not applicable **Secondary:** Not applicable
Evaluation Criteria:	**Efficacy (Primary):** • Total score of the Tinnitus Questionnaire **Efficacy (Secondary):** • Audiometric measurements (mode, frequency, loudness of tinnitus, pure tone audiogram, and speech audiogram) • Quality of life questionnaire (SF-36: Fragebogen zum Gesundheitszustand [Short-Form 36 Health Survey]) **Safety:** Treatment groups were compared with respect to incidence rates of premature termination, treatment-emergent adverse events (TEAEs), laboratory abnormalities, and electrocardiogram (ECG) abnormalities.
	Pharmacokinetics: Not applicable **Other:** Not applicable
Statistical Methods:	**Efficacy (Primary):** The primary efficacy analysis was based on the total score of the Tinnitus Questionnaire in the intent-to-treat (ITT) sample. The statistical analysis was based on an analysis of covariance (ANCOVA) with baseline as covariate and the last observation carried forward (LOCF) value as dependent variable. Factor was "treatment". The homogeneity of regression slopes was tested. This analysis was repeated for the valid for efficacy (VfE) sample. **Efficacy (Secondary):** Audiometric measurements (mode, frequency and loudness, pure tone audiogram) as well as quality of life (SF-36) were also analyzed via the aforementioned ANCOVA model. The appropriateness of the model was not tested. P values are exploratory and were not adjusted for

	multiplicity. **Safety:** Incidence rates of TEAEs by body system were analyzed using the Preferred Term of Medical Dictionary for Regulatory Activities (MedDRA) (version 10.0). Descriptive statistics was used for the analysis of clinical laboratory evaluations.
	Pharmacokinetics: Not applicable **Other:** Not applicable
Number of Subjects:	Overall, 43 subjects were randomized, 21 to vardenafil 10 mg and 22 to placebo (1 randomized to placebo invalid for safety analysis). Both the safety sample and the ITT sample included 21 subjects of each treatment group. The per-protocol (valid for efficacy) sample consisted of 16 subjects receiving vardenafil and 19 subjects receiving placebo.

Study Results

Results Summary — Subject Disposition and Baseline

Out of 43 randomized subjects, 42 subjects completed the study as 1 subject did not receive the study drug. Demographic characteristics by treatment group are summarized in Table 1.

Table 1: Major demographic characteristics (Safety)

Parameter		Vardenafil 10 mg (N=21)	Placebo N=21)
Sex (%)	Male	14 (67)	16 (76)
	Female	7 (33)	5 (24)
Race n (%)	White/Caucasian	21 (100)	21 (100)
Age (years)	Mean±SD	51.3±10.0	46.7±10.2
Weight (kg)	Mean±SD	82.6±19.2	80.6±14.8
BMI (kg/m^2)	Mean±SD	27.1±4.2	25.9±3.5

Results Summary — Efficacy

During the ongoing study, i.e., before unblinding, it was decided not to conduct a sample size re-estimation for an adapted trial, as originally planned. Instead, it was decided to stop the trial after all recruited subjects had completed the study.

Primary efficacy analysis on the TQ total score did not result in rejection of the null hypothesis. Accordingly, this study did not show superior efficacy of vardenafil over placebo in the treatment of chronic tinnitus. Further, the secondary efficacy criteria did not support the impression that vardenafil might have had any influence on subjective reports or objective audiological investigations.

Significant or clinically apparent differences between active and placebo were not seen, neither for the primary efficacy variable (TQ) nor for any of the secondary variables such as audiometric measurements and quality of life (SF-36).

Results Summary — Safety

TEAEs were reported by 38% of vardenafil subjects and 14% of placebo subjects. The most common TEAEs were headache (vardenafil 5%; placebo 10%), diarrhea (vardenafil 10%; placebo 0%), and nasal congestion (vardenafil 10%; placebo 0%). A total of 29% of subjects in the vardenafil group and approximately 10% in the placebo group experienced TEAEs considered drug-related, and in about 19% and 5% of subjects drug treatment was discontinued due to these events.

No subjects died. Serious adverse events were not reported. Non-serious adverse events led to premature discontinuation in 4 vardenafil subjects (a woman with diarrhea, a woman with sensation of heat, a man with erection increased, and a man with flushed face and nasal mucosal swelling) and in 1 placebo subject (a man with dizziness, headache, and nausea). All these events were considered drug-related.

There were no clinically important differences between treatment groups determined neither for the change from baseline in mean values for vital signs or laboratory parameters at any timepoint, nor by the comparison of ECG findings, active vs placebo. The audiometric measurements (mode, frequency and loudness, pure tone audiogram) gave no hint for any deterioration under active treatment. This may be of relevance with respect to rare reports about hearing loss, which have been reported in the context of the use of phosphodiesterase-5 (PDE-5) inhibitors and the respective change in labeling for PDE-5 inhibitors.

Conclusion(s)

In subjects with chronic tinnitus, oral vardenafil 10 mg bid did not show any clinical benefit on symptoms of tinnitus in comparison with placebo. In this pilot study, the safety profile was favorable and in line with the labeling information.

Publication(s):	None		
Date Created or Date Last Updated:	20 APR 2012	**Date of Clinical Study Report:**	02 JUN 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	Universitätsklinikum Charite zu Berlin	Campus Charité Mitte Hals-, Nasen-, Ohrenklinik und Poliklinik Tinnituszentrum Schumannstr. 20/21	10117	Berlin	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