Erste Veröffentlichung von Ergebnissen der Phase-III-Leitstudie mit Vardenafil:

Bis zu 85 Prozent der Männer erreichten signifikant verbesserte Erektionen

Weitere Phase-III-Daten zeigen erhebliche Verbesserung bei Männern mit Diabetes und erektiler Dysfunktion (ED)

Leverkusen – Die ersten Ergebnisse der Phase-III-Leitstudie von Vardenafil, dem neuen, selektiven PDE-5 Inhibitor von Bayer zeigen eine statistisch signifikante Verbesserungen der erektilen Funktion und eine zuverlässige Wirksamkeit bei bis zu 85 Prozent der behandelten Männer dieser breit angelegten Studienpopulation. Die Daten werden morgen auf der Jahrestagung der „Sexual Medicine Society of North America“ (SMSNA) in Charleston, South Carolina (USA) zum erstenmal präsentiert.

„Die wichtigen Kenndaten der Phase-III-Leitstudie zeigen, dass Vardenafil über das gesamte Patientenspektrum wirkt: Es erzielt zuverlässig sehr positive Ergebnisse bei einer breiten Auswahl von Männern mit erektiler Dysfunktion, unabhängig von der Ursache und dem Schweregrad der Beeinträchtigung“, erklärte Wayne J.G. Hellstrom, M.D., führender Spezialist für die Behandlung von erektiler Dysfunktion und Unfruchtbarkeit an der Tulane University School of Medicine, New Orleans, und leitender Prüfarzt der Studie.

Vielfältige Verbesserungen bei allen Patienten

An der Studie nahmen 736 Männer mit unterschiedlichen Schweregraden (leicht bis schwer) und Ursachen (organisch bis psychogen) der ED teil. Zu den organischen Ursachen gehören u. a. ED-fördernde Erkrankungen wie Hypertonie, Diabetes und gutartige Prostatavergrößerung.

Die Studie ergab bei 85 Prozent der mit 20 mg Vardenafil behandelten Männer verbesserte Erektionen, gegenüber 28 Prozent bei der Placebo-Gruppe. Hierbei zeigte die breit gefächerte Studienpopulation zudem eine gegenüber dem Placebo signifikante Verbesserung der Häufigkeit, mit der die Männer in der Lage waren, ihre Erektion während des Geschlechtsverkehrs aufrecht zu erhalten. Beide Werte sind Kenngrößen des Internationalen Index der Erektilen Funktion (IIEF).

Phase-III-Ergebnisse bei Männern mit Diabetes und ED

Vardenafil verbesserte auch die Erektionen bei bis zu 72 Prozent der Diabetiker mit ED, einer der am schwierigsten zu behandelnden Patientengruppen. Demgegenüber trat bei nur 13 Prozent, die das Placebo nahmen, eine Verbesserung ein. Darüber hinaus ergibt sich aus den beim Symposium vorgelegten Daten, dass Vardenafil bei dieser Patientengruppe auch andere Parameter verbessert. Eine von Dr. Irwin Goldstein, Boston University School of Medicine, vorgestellte Untersuchung belegt, dass Männer mit Diabetes bei den Kenngrößen für die sexuelle Erlebnisfähigkeit ebenfalls signifikante Verbesserungen gegenüber der Placebo-Gruppe erreichten. Außerdem zeigt die Untersuchung, dass die Männer in der Lage waren, diese Verbesserungen über die 12-wöchige Behandlungsdauer hinweg zuverlässig aufrecht zu erhalten oder sogar noch zu steigern.

„Nach diesen Daten hat Vardenafil bei Diabetikern nicht nur die erektile Funktion positiv beeinflusst, sondern auch deren sexuelle Erlebnisfähigkeit während des Untersuchungszeitraums verbessert“, erklärte Dr. Goldstein.

Weitere positive Wirkungen

In einer zweiten, ebenfalls von Dr. Goldstein vorgestellten Studie berichteten Patienten, die mit Dosierungen von 20 und 10 mg behandelt wurden, über eine befriedigendere Sexualität. Die Patienten gaben außerdem statistisch signifikante Verbesserungen (gegenüber dem Placebo) hinsichtlich der Zufriedenheit in ihren Beziehungen und in ihrem Leben insgesamt an. Die Untersuchungen ergaben eine gute Verträglichkeit von Vardenafil bei leichten bis mittelschweren Nebenwirkungen, die nur vorübergehend auftraten.

„Vardenafil ist eines der wichtigsten Produkte in der Bayer-Pipeline. Sowohl von Ärzten als auch von Patienten wissen wir, dass der starke Wunsch nach mehr Behandlungsmöglichkeiten für ED besteht“, sagte Dr. David R. Ebsworth, Leiter des Geschäftsbereichs Pharma der Bayer AG.

Das neue Präparat ist ein hochselektiver Phosphodiesterase-5-Hemmer, der von Bayer entwickelt wird. Das Unternehmen hat im September 2001 in den USA und Mexiko die Zulassung von Vardenafil beantragt. Danach folgten Kanada, Südafrika und Japan. Mit der Erteilung der ersten Zulassung für Vardenafil ist in der zweiten Hälfte 2002 zu rechnen. Erst kürzlich haben Bayer und GlaxoSmithKline plc (GSK) den Abschluss eines weltweiten (außer Japan) Co-Promotion-Abkommens für Vardenafil bekannt gegeben.

Mehr als die Hälfte aller Männer über 40 erleben ein gewisses Nachlassen der erektilen Funktion[1]. Bei Männern mit Diabetes ist die Wahrscheinlichkeit, dass ED auftritt, wegen der mit ihrer Krankheit verbundenen Komplikationen dreimal höher als bei anderen Männern. Zudem hat sich gezeigt, dass sie weniger gut auf verfügbare ED-Therapien ansprechen. Die Häufigkeit von ED bei über 50-jährigen Männern mit Diabetes wird sogar mit 50 bis 60 Prozent angegeben.[2]

Beigefügt finden Sie die Vardenafil-Abstracts des Annual Meeting of the Sexual Medicine Society of North America (SMSNA)

Quellenangaben

1. Glasser D, Sweeney M. The prevalence of erectile dysfunction in four countries: Italy, Brazil, Malaysia, and Japan. Bei der 1st International Consultation on Erectile Dysfunction in Paris 1999 präsentiertes Poster.
2. Website der American Diabetes Association (www.diabetes.org).

Leverkusen, 2001-12-07

VARDENAFIL IMPROVED ERECTILE FUNCTION IN MEN WITH A BROAD RANGE OF ERECTILE DYSFUNCTION ETIOLOGIES AND SEVERITIES: A PHASE III TRIAL.

Wayne J.G. Hellstrom MD, New Orleans, LA; Marc C. Gittelman MD FACS, Aventura, FL; JoAnn Shapiro MS., Marc Thibonnier MD, and Thomas Segerson MD, West Haven, CT. *(Presentation by Wayne J.G. Hellstrom MD).* Funded by Bayer AG.

The efficacy and safety of vardenafil, a potent and selective PDE5 inhibitor, were investigated in a pivotal trial in men with erectile dysfunction (ED). This randomized, double-blind, placebo-controlled, parallel-group trial included men with ED of varied etiologies and severities. After a four-week baseline period, patients were randomized to either placebo or to 20 mg, 10 mg or 5 mg of vardenafil, taken orally as needed. Efficacy was assessed with secondary variables questions 3 (Q3, penetration) and 4 (Q4, maintenance) of the International Index of Erectile Function and the General Assessment Question (GAQ) regarding improvement in erections. Statistical comparisons were made for the Intent-to-treat population (26-week LOCF, n=736) for mean responses to Q3 and Q4 between treatment and placebo using the ANCOVA. GAQ was analyzed using a logistic regression model for those completing the 26 weeks of treatment. Improved erections were noted by 85%, 80%, and 65% of men treated with 20 mg, 10 mg and 5 mg vardenafil, respectively; all greater than the 28% for placebo ($p<0.0001$). Mean baseline score for the frequency of attaining an erection sufficient for penetration (Q3) ranged between 2.3 and 2.5 on a scale of 1 – 5. After treatment, mean value for placebo was 2.7 in contrast to 3.8, 3.7 and 3.2 for the 20 mg, 10 mg and 5 mg vardenafil, respectively; all greater than placebo ($p<0.01$). Mean baseline score for the frequency of maintaining erections during intercourse (Q4) ranged between 1.8 and 1.9. After treatment, mean score for placebo was 2.4 in contrast to 3.5, 3.6 and 2.9 for the 20 mg, 10 mg and 5 mg, respectively; all greater than placebo ($p<0.01$). Adverse events were mild to moderate with headache, rhinitis, vasodilation, and dyspepsia as the most frequent complaints. In conclusion, vardenafil significantly improved penetration and maintenance of erections in a broad population of patients. Treatment was generally well tolerated and vardenafil improved erections in up to 85% of men.

VARDENAFIL IMPROVED ERECTILE FUNCTION IN DIABETIC MEN WITH ERECTILE DYSFUNCTION.

Irwin Goldstein, MD, Boston, MA; Jay M. Young, MD, Laguna Hills, CA; Jerome Fischer, MD, San Antonio, TX; Thomas Yuran, PharmD, West Haven, CT; Terry Taylor, MD, West Haven, CT; and the Vardenafil Diabetes Phase III study Group (Presentation by Irwin Goldstein, Funded by Bayer Corp.)

Patients with diabetes have a higher incidence of erectile dysfunction (ED), but have been shown to be less responsive to available oral ED therapies. A multicenter, randomised, double-blind, placebo-controlled trial determined the efficacy, safety and tolerability of vardenafil, a new oral agent, in patients with diabetes mellitus and ED. Type 1 (n=54) or 2 (n=398) patients with erectile dysfunction lasting > 6 months were randomised to placebo, 10 mg or 20 mg of vardenafil, as needed. Patients were evaluated after a 4-week baseline period and at 12 weeks. Primary efficacy variables were the Erectile Function (EF) Domain of the IIEF and the per patient success rates both for vaginal penetration and maintaining erections to complete intercourse by event diary. Responder rates for improved erection were derived from the Global Assessment Question (GAQ). The Fugl-Meyer Questionnaire was used to evaluate aspects of life satisfaction. For the GAQ, the responder rates were 72% and 57% for 20 mg and 10 mg, respectively, in contrast to 13% for placebo ($p<0.0001$). For the EF Domain, the final scores for the 20 mg and 10 mg dose were 19.0 and 17.1 compared to 12.6 for placebo ($p<0.0001$). Both the penetration and maintenance diary questions had statistically significantly greater responses than placebo for both vardenafil doses ($p<0.0001$). Patients reported improved satisfaction in their sexual life for the 10 mg and 20 mg groups compared to placebo ($p<0.0001$). Patients on 20 mg therapy reported statistically significant improvements over placebo for satisfaction with partner relationship ($p<0.01$) and life as a whole ($p<0.01$). Treatment-related adverse events were primarily headache, flushing and rhinitis. Vardenafil therefore improved erectile function and was generally well tolerated in these diabetic patients with ED. Improved satisfaction with partner relationship was also noted in this study.

VARDENAFIL, A NEW SELECTIVE PDE5 INHIBITOR, SIGNIFICANTLY IMPROVED ALL IIEF DOMAINS AND SHOWED A FAVORABLE SAFETY PROFILE IN PATIENTS WITH IMPAIRED ERECTILE FUNCTION AND DIABETES MELLITUS.

Irwin Goldstein, MD, Boston, MA; Jay M. Young, MD, Laguna Hills, CA; Jerome Fischer, MD, San Antonio, TX; Martin Mollen, MD, Phoenix AZ; Franklin Chu, MD; San Bernadino, CA; JoAnn Shapiro, MS, Thomas Segerson, MD, and Terry Taylor, MD, West Haven, CT (*Presentation by Dr. Goldstein.)* Funding provided by Bayer Corp.

A recent Phase III study demonstrated significant improvement in erectile function in diabetics, a difficult to treat population. This report further evaluates the changes in all domains of the International Index of Erectile Function (IIEF) and the adverse events (AE) that occurred over time. In a double-blind, placebo-controlled study, 452 adult males with impaired erectile function and diabetes mellitus (type 1 or 2) were randomized to take oral doses of placebo or 10 mg or 20 mg of vardenafil. Efficacy, which was measured by the IIEF domain scores and AE rates were calculated at 4-week intervals. Mean baseline scores for erectile function ranged from 11.1 to 12.5. By 4 weeks, the placebo mean score increased only to 12.7 while mean scores for 10 mg and 20 mg increased to 17.5 and 18.3 (vs. placebo $p < 0.0001$). Significant improvement after 4 weeks of treatment was also observed for orgasmic function, intercourse satisfaction and overall satisfaction domains. By the end of the 12-week study, mean vardenafil scores were maintained or increased compared to those at 4 weeks. A small increase in sexual desire, which was not clinically meaningful, was noted. The most common treatment related AEs were headache, flushing and rhinitis. AEs were either highest in the first 4 weeks or were relatively stable throughout the 12 weeks.

Conclusion: In this diabetic study population, vardenafil was generally well tolerated and provided both early and sustained improvement in impaired erectile function and other measures of sexual experience.

VARDENAFIL IMPROVED ERECTILE FUNCTION REGARDLESS OF BASELINE SEVERITY, ETIOLOGY AND HYPERTENSIVE MEDICATIONS IN PHASE II TRIAL.

Hartmut Porst MD, Hamburg, Germany, AC Schmidt MD, Tygerberg, South Africa and The Vardenafil Study Group *(Presentation by Harmut Porst, Funded by Bayer)*

Vardenafil hydrochloride, a highly selective PDE5 inhibitor, was significantly better than placebo in improving erectile function in a Phase IIb study. Additional subanalyses were carried out to evaluate whether key factors may influence the efficacy of vardenafil such as baseline severity, etiology of erectile dysfunction (ED) or concurrent use of antihypertensive medications. A total of 601 men with ED for at least 6 months were randomized to placebo, 5 mg, 10 mg or 20 mg vardenafil for 12 weeks. Efficacy was assessed by IIEF Erectile Function domains (EF) after 12 weeks. Those starting with severe ED (EF<11) improved to 18.4, 18.6 and 20.1 for 5 mg, 10 mg and 20 mg, respectively compared to 11.5 for placebo. For those starting with mild ED (EF 17 to 25), the mean values after treatment were 22.5, 26.0 and 25.6 for 5 mg, 10 mg and 20 mg, respectively compared to 19 for placebo. Moderate ED had intermediate values. The change from baseline for those with organic etiology (1.7, 7.0, 8.7 and 8.8 for placebo, 5 mg, 10 mg and 20 mg, respectively) were similar to those with psychogenic etiology (1.3, 7.2, 7.3, 8.4 for placebo, 5 mg, 10 mg and 20 mg, respectively). For those on antihypertensives, the vardenafil-treated patients had final EF scores from 19.2 to 23.7 compared to 21.4 to 23.8 for those who were not on antihypertensives. This compared to placebo final scores of 13.9 for patients on antihypertensives compared to 16.1 who were not. The adverse events over the three months were low with headache occurring in 7 % to 15 %, flushing in 10 % to 11 %, and dyspepsia and rhinitis up to 7 % of patients, depending on the dose.

Mean Erectile Function domain scores of patients treated with vardenafil were similar among patients with mild, moderate or severe baseline severity, whether the etiology was organic or psychogenic and whether or not patients were taking antihypertensive medications.

VARDENAFIL DEMONSTRATED SIMILAR EFFICACY AND TOLERABILITY AMONG OLDER AND YOUNGER PATIENTS WITH MARGINAL DIFFERENCES IN PK CHARACTERISTICS BETWEEN AGE GROUPS.

Christopher Steidle, MD, Fort Wayne, IN; Hartmut Porst, MD, Hamburg, Germany; Alan Hollister, MD, West Haven, CT; and Thomas Segerson, MD, West Haven, CT *(Presentation by Christopher Steidle, MD)* Funding from Bayer Corp.

Erectile dysfunction (ED) affects all age groups but especially the older population. Vardenafil was evaluated in a Phase II at-home study which was analyzed according to age group. A separate Phase I study compared pharmacokinetic (PK) data in older and younger men. In the Phase II study, men with mild to severe ED for >6 months were randomized to placebo or 5 mg, 10 mg or 20 mg vardenafil, on-demand, and efficacy was evaluated by the International Index of Erectile Function (IIEF). The responses of patients aged <45 (n=134) were compared with those aged >65 (n=65). In the Phase I study, healthy male volunteers aged 18 to 45 (n= 9) and aged >65 (n=9) were given a single oral dose of 40 mg vardenafil and safety, tolerability and PK parameters were determined. For the Phase II study, the mean Erectile Function domain score increased for all vardenafil groups. The mean changes from baseline for subjects <45 yo were 1.1, 7.9, 8.4 and 8.1 for placebo, 5 mg, 10 mg and 20 mg respectively. For patients >65 yo, the corresponding increases from baseline were 0.5, 2.5, 7.8, and 10.3. Adverse events (AEs) >5% were headache, flushing, dyspepsia with no consistent differences between age groups. For the phase I study, Cmax and AUC_{0-tn} were 134% and 152%, for the older men compared to the younger. AEs were primarily headache, rhinitis, nausea, dyspepsia and flushing with no clear differences between age groups. These studies show that older men had comparable improvements in IIEF scores to younger men with slightly higher plasma levels.

VARDENAFIL, A NEW SELECTIVE PDE-5 INHIBITOR, INTERACTS MINIMALLY WITH NITROGLYCERIN IN HEALTHY MIDDLE-AGED MALE SUBJECTS

Arthur L Mazzu, PhD, West Haven, CT; Andrew J. Nicholls, MD, PhD, West Haven, CT and Miguel Zinny, MD, Boston, MA (Presentation by Dr. Mazzu) Funded by Bayer Corp.

The combination of the phosphodiesterase-5 (PDE-5) inhibitor sildenafil and an organic nitrate may produce significant hypotension. The population likely to be prescribed a PDE-5 inhibitor for erectile dysfunction (ED) is also at risk of coronary ischemia. The current study was undertaken to evaluate the interaction between nitroglycerin and vardenafil, a selective PDE-5 inhibitor under development. This was a randomized, placebo-controlled cross-over study of vardenafil in healthy males (n=18, age 40-65). The hypotensive effect of single doses of sublingual nitroglycerin (NTG, 400 µg) was assessed 24, 8, 4 and 1 hour (approximately tmax) after a series of oral doses of vardenafil 10 mg or matching placebo. Subjects' blood pressure (BP) and heart rate (HR) were measured when seated. Immediately prior to NTG administration, BP and HR were comparable following treatment with vardenafil and placebo. BP and HR data over the 90 minutes following NTG for the treatment day in which vardenafil or placebo was administered 1 hour before NTG are provided in the Table. NTG administration 1 hour after vardenafil caused changes in blood pressure and heart rate comparable with those observed following NTG and placebo. Similar data were obtained for larger intervals between vardenafil and NTG dosing. In all cases the combination of agents was well tolerated.

The apparent lack of an interaction between NTG and vardenafil observed in this study should be evaluated in the target patient population.

Table: Mean maximum changes (min, max) in BP and HR following NTG (400 µg) administered one hour after oral vardenafil (n=18).

	Vardenafil10 mg	Placebo
Change in syst. BP (mm Hg)	-19.2 (-3 to -42)	-20.9 (-9 to -37)
Change in diast. BP (mm Hg)	-20.1 (-9 to -32)	-17.9 (-9 to -33)
Increase in HR (bpm)	13.9 (1 to 27)	15.6 (6 to 27)