2. S024 Synopsis
Clinical Study Report Synopsis: Study H6D-CR-S024

Title of Study: A Comparison of Psychosocial Outcomes following Tadalafil Once a Day or PDE5 Inhibitor As Needed in Men with Erectile Dysfunction

Number of Investigators: This multicenter study included 34 principal investigators.

Study Centers: This study was conducted at 34 study centers in 7 countries.

Publications Based on the Study:

- Rubio-Aurioles E, Porst H, Stuckey B, Martin Morales A, Kim ED, Hackett G, F Montorsi, Lenero E, Büttner H, Huynh NN, Pinton P. Sexual Self-Confidence following tadalafil once-a-day versus sildenafil citrate as needed in the treatment of men with erectile dysfunction. *European Urology Supplement*. 2010; 9(2):122-123. Abstract #306.
- Rubio-Aurioles E, Porst H, Stuckey B, Martin Morales A, Hackett G, Kim ED, Montorsi F, Kopernicky V, Burns P, West TM. Psychosocial, efficacy and satisfaction outcomes following tadalafil once daily versus sildenafil citrate as need treatment in men with erectile dysfunction. *Canadian Urological Association Journal*. 2010; 4(3, Suppl 1):S82-S83. Abstract #UP100.

Length of Study:	**Phase of Development:** 3/4
Date of first patient enrolled: 04 September 2008 Date of last patient completed: 21 September 2009	

Objectives: The primary objective of this study was to test the hypothesis that tadalafil, given orally at 5 mg or 2.5 mg once a day for 8 weeks, achieved superior psychosocial outcomes to sildenafil citrate, given orally at 100 mg or 50 mg as needed (PRN) for 8 weeks, in the treatment of men with erectile dysfunction (ED), as measured by the change from baseline in the Sexual Self-Confidence domain of the Psychological and Interpersonal Relationship Scales (PAIRS).

The secondary objectives of the study were to compare tadalafil 5 mg or 2.5 mg once a day with sildenafil citrate 100 mg or 50 mg PRN, and tadalafil 5 mg or 2.5 mg once a day with tadalafil 20 mg or 10 mg PRN, at 8 weeks with respect to:

- Psychosocial outcomes, as measured by Sexual Self-Confidence, Spontaneity, and Time Concerns domains of PAIRS; the Self-Esteem And Relationship (SEAR) questionnaire; and Questions 1 to 4 of the Patient Perception and Feelings Questions (PPF-Q).
- Efficacy, as measured by the Erectile Function domain (sum of Items 1 through 5 and Item 15) of the International Index of Erectile Function (IIEF) and the frequency of morning erection.
- Sexual satisfaction, as measured by the Intercourse Satisfaction and Overall Satisfaction domains of the IIEF.
- Treatment satisfaction, as measured by the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS).
- Safety and tolerability.

Study Design: This was a multicenter, randomized, open-label, crossover, active comparator-controlled study that assessed psychosocial outcomes following 8 weeks of tadalafil once a day or PDE5 inhibitor as needed in men with erectile dysfunction.

Number of Patients:

Planned: 360
Randomized: 378
Treated (at least 1 dose): 378
Completed: 360 tadalafil OaD, 364 tadalafil PRN, 358 sildenafil PRN

Diagnosis and Main Criteria for Inclusion: Male participants at least 18 years of age with a history of ED, defined by a consistent change in the quality of erection that adversely affects the subject's satisfaction with sexual intercourse. Subjects with any severity of ED (mild, moderate, and severe) and with any etiological classification (psychogenic, organic, or mixed) are eligible for enrollment.

Tadalafil OaD Dose, and Mode of Administration: tadalafil 5 (or 2.5) mg/day, given orally once a day as one tablet.

Tadalafil PRN Dose, and Mode of Administration: tadalafil 20 (or 10) mg/day, given orally as needed as one tablet.

Sildenafil PRN Dose, and Mode of Administration: sildenafil citrate 100 (or 50) mg/day, given orally as needed as one tablet.

Duration of Treatment: tadalafil OaD Frequency: 8 weeks; tadalafil PRN Frequency: 8 weeks; sildenafil PRN Frequency: 8 weeks.

Variables:

Primary Measure: Psychological and Interpersonal Relationship Scales (PAIRS) Sexual Self-Confidence domain. The PAIRS is a self-administered 29-item scale containing 4 domains: Sexual Self-Confidence, Time Concerns, Spontaneity and Sexual Miscommunication. But, the items regarding the Sexual Miscommunication is not a validated domain of PAIRS, only 3 PAIRS domains are reported in the study results.

Secondary Measures:

- PAIRS Time Concerns domain.
- PAIRS Spontaneity domain.
- The SEAR questionnaire: This was a subject-reported measure of psychosocial outcomes in men with ED consisting of 14 items assessing two domains: Sexual Relationship (Items 1 through 8) and Confidence (Items 9 through 14). The Confidence domain is comprised of 2 subscales: Self-Esteem (Items 9 through 12) and Overall Relationship (Items 13 and 14).
- The PPF-Q: This was a novel series of 4 questions that measured subject-reported psychosocial outcomes following treatment for ED. The questions captured the subject's consciousness of ED and perception of sexual health, sense of control over sexual lifestyle, and feelings of masculinity. Subjects were asked to agree with statements using a five-point scale from 0, "not at all" to 4, "extremely".
- Morning Erection Frequency was calculated using data from the Morning Erection and Sexual Attempt Diary. The frequency of morning erection was calculated as a proportion of 'yes' responses to the question "Did you experience an erection when you woke up this morning?" during a particular study phase.
- Erectile Function, Intercourse Satisfaction, and Overall Satisfaction domains of IIEF: The IIEF was a validated, multidimensional, self-administered questionnaire commonly employed to assess therapeutic efficacy of ED therapy. The questionnaire contains 5 domains, 3 of which were measured: Erectile Function (sum of Items 1 through 5 and Item 15), Intercourse Satisfaction (sum of Items 6 through 8), and Overall Satisfaction (sum of Items 13 and 14). The change from baseline to endpoint for each domain was assessed.
- Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS). The EDITS was a reliable and validated questionnaire used to assess satisfaction with the subjects' ED treatment.

Safety: Adverse events will be summarized by MedDRA preferred terms for severity and relationship to study drug.

Statistical Evaluation Methods: Primary and secondary analyses was conducted on the full analysis set (FAS) with a modified intention-to-treat (ITT) approach. For this population, subjects were analyzed according to the therapy to which they were randomly assigned. The FAS population for efficacy analyses included all subjects randomized to treatment with both baseline and at least one postbaseline data measurement. The FAS population for safety analyses included all randomized subjects who took at least one dose of the study drug. All tests of treatment effects were conducted at a 2-sided alpha level of 0.05. The primary and secondary outcomes were analyzed with a mixed effects model for crossover design, which included treatment, period, sequence, prior PDE5 inhibitor (tadalafil /sildenafil citrate/vardenafil HCl) and country as fixed effects, baseline Sexual Self-Confidence domain of PAIRS score as a covariate, and patient within treatment sequence as a random effect.

Primary Outcome: All mean scores from the PAIRS questionnaire scales and subscales were derived from applicable individual questions. For an individual PAIRS domain at any visit, if 50% or less of the applicable individual questions comprising that domain were missing then the mean score for that domain was imputed with the mean of the nonmissing questions in that domain for that subject at that visit. If more than 50% of applicable individual questions comprising that domain were missing at any visit, then the domain was considered missing for that subject at that visit.

Sample size calculations: Approximately 450 subjects were to be screened for enrollment in this study. Enrollment ended when approximately 360 subjects were randomized to treatment. Subjects were randomized to one of 6 treatment sequences in a 1:1:1:1:1:1 ratio. A 3x3 crossover design with 300 subjects completing (50 in each sequence) will have >90% power to detect a difference of 0.17 in the Sexual Self-Confidence domain change scores between tadalafil once a day and sildenafil citrate PRN, assuming a treatment difference standard deviation of 0.6 units, a between-subject standard deviation of 0.474, and a correlation between observations on the same subject under 2 different treatments of 0.2.

Secondary Outcomes: The total, domain, and subscale scores of the SEAR questionnaire were computed by summing their respective items and transforming them onto a 0-100 scale using the following equation: Transformed score = 100 x [(actual raw score – lowest possible raw score)/possible raw score range]. All total scores from IIEF domains were derived from individual items. The EDITS and PPF-Q did not have a baseline assessment therefore the primary outcome variables were actual scores (rather than change from baseline scores) and a baseline term in the mixed model was not included. All questions of the PPF-Q were analyzed individually.

Safety: The analysis of safety included all enrolled subjects. Safety was assessed by evaluating all reported adverse events. Adverse events (AEs) and serious adverse events (SAEs) were summarized by MedDRA preferred terms for severity and relationship to study drug. Treatment-emergent adverse events (TEAEs) are defined as events that first occurred or worsened after baseline.

PAIRS Spontaneity domain

The LS means difference in the Spontaneity domain score was statistically significantly higher for tadalafil OaD compared to sildenafil PRN treatment (0.15 ± 0.03; 95% CI: 0.10, 0.20; p<.001) and for tadalafil PRN compared to sildenafil PRN treatment (0.13 ± 0.03; 95% CI: 0.08, 0.18; p<.001). There were no statistically significant differences in Spontaneity LS means between tadalafil OaD and tadalafil PRN (0.02 ± 0.03; 95% CI: -0.03, 0.07; p = 0.395).

SEAR-Sexual Relationship domain

The change in the transformed SEAR-Sexual Relationship scales increased following all 3 treatments from baseline to endpoint (LS mean ± SE = 25.40 ± 1.36, 25.56 ± 1.36, and 26.92 ± 1.35 for sildenafil PRN, tadalafil OaD, and tadalafil PRN, respectively) with no statistically significant differences between treatments.

SEAR-Confidence domain

The change in the transformed SEAR Confidence scales increased following all 3 treatments from baseline to endpoint (LS mean ± SE = 19.50 ± 1.31, 19.40 ± 1.31, and 20.42 ± 1.30 for sildenafil PRN, tadalafil OaD, and tadalafil PRN, respectively) with no statistical significant differences between treatments.

SEAR-Total score

The change in the transformed SEAR total scores also increased following all 3 treatments from baseline to endpoint (LS mean ± SE = 22.87 ± 1.29, 22.94 ± 1.29, and 24.39 ± 1.29 for sildenafil PRN, tadalafil OaD, and tadalafil PRN, respectively) with no statistical significant differences between treatments.

PPF-Q

There were no statistically significant differences for Question 1, “I felt as if I did not have ED” between any of the 3 treatment comparisons. However, for Question 2, “I felt in control of my sex life” there was a statistically significant difference between tadalafil OaD vs sildenafil PRN (difference of LS mean ± SE = 0.20 ± 0.06, 95% CI: 0.07, 0.32; p = .002) and tadalafil PRN vs sildenafil PRN (difference of LS mean ± SE = 0.22 ± 0.06, 95% CI: 0.09, 0.34; p<.001). There was no difference in whether patients felt in control of their sex life according to the responses to PPF-Q Question 2 between tadalafil OaD and tadalafil PRN treatment (difference of LS mean ± SE = -0.02 ± 0.06, 95% CI: -0.15, 0.10; p = .722). There were statistically significant differences for Question 3 of the PPF-Q where patients indicated whether they felt that the drug was in control of their erection between tadalafil OaD vs sildenafil PRN (-0.51 ± 0.07, 95% CI: - 0.65, -0.37; p<.001), tadalafil OaD vs tadalafil PRN (-0.21 ± 0.07, 95% CI: -0.35, -0.08; p = .002) and tadalafil PRN vs sildenafil PRN (-0.21 ± 0.07, 95% CI: -0.35, -0.08; p = .002). There was a statistical significant difference for Question 4, “I felt like a whole man”, of the PPF-Q comparisons between tadalafil PRN vs sildenafil PRN (0.13 ± 0.06, 95% CI: 0.02, 0.25; p = .022) but not for either tadalafil OaD vs sildenafil PRN (0.11 ± 0.06, 95% CI: -0.01, 0.22; p = .070) or tadalafil OaD vs tadalafil PRN treatment (-0.03 ± 0.06, 95% CI: -0.14, 0.09; p = .637)

Summary:

Patients:

There were 418 patients assessed for study entry eligibility, 40 patients were excluded prior to randomization (22 did not meet the inclusion criteria, 11 declined to participate and 7 were excluded for other reasons). A total of 378 patients were randomized (62 allocated to sequence 1, 63 to each sequence from 2 to 5 and 64 to sequence 6). Forty-four patients discontinued from the study (of these 14 patients were lost to follow-up). For analysis, there were 371 patients with one baseline and at least one post-baseline efficacy measurement, 7 patients were excluded from analysis of the primary endpoint due to missing post-baseline assessment.

The mean (standard deviation [SD]) age of all randomized men was 56.2 (11.0) years and their mean (SD) body mass index was 28.2 (3.9) kg/m^2; 255 (67.5%) were Caucasian, 105 (27.8%) were Hispanic, 12 (3.2%) were African and 6 (1.6%) were of other ethic origin. There were 146 (38.6%) patients with mixed ED etiology and 163 (43.1%) with organic ED etiology. The majority of patients (356 [94.2%]) had an ED diagnosis of ≥1 year. There were no clinically important differences between the sequence groups in baseline and demography measures.

Primary outcomes:

The difference in least square (LS) means ± standard error (SE) between tadalafil OaD and sildenafil PRN was 0.12 ± 0.04 (95% CI: 0.04, 0.19; p = .001), showing statistical significance in favor of tadalafil OaD for the primary efficacy measure Sexual Self-Confidence.

Secondary outcomes:

PAIRS Sexual Self-Confidence domain

The improvement between baseline and endpoint (change in PAIRS $Score_{endpoint-baseline}$) in the Sexual Self-Confidence domain in terms of the difference in LS means between tadalafil PRN and Sildenafil PRN was 0.11 ± 0.04 (95% confidence interval [CI]: 0.04, 0.19; p = .002). There was no statistically significant difference in Sexual Self-Confidence LS means between tadalafil OaD and tadalafil PRN (p = .872).

PAIRS Time Concerns domain

The LS means difference in the Time Concerns domain score was statistically significantly lower for tadalafil OaD compared to sildenafil PRN treatment (-0.31 ± 0.03; 95% CI: -0.36, -0.25; p<.001), for tadalafil OaD compared to tadalafil PRN treatment (-0.14 ± 0.03; 95% CI: -0.20, -0.08; p<.001), as well as for tadalafil PRN compared to sildenafil PRN treatment (-0.17 ± 0.03; 95% CI: -0.22, -0.11; p<.001).

IIEF Erectile Function domain

The difference in LS means (±SE) between tadalafil OaD and sildenafil PRN was -0.85 ± 0.30 (CI: -1.43, 0.27; p = .004) in favor of sildenafil PRN. Similarly the difference in LS means between tadalafil OaD and tadalafil PRN was -0.80 ± 0.29 (CI: -1.37, -0.22; p = .007) in favor of tadalafil PRN. There was no statistically significant difference in the IIEF-EF domain score between sildenafil PRN and tadalafil PRN.

IIEF Overall Satisfaction domain

There was no statistical significant difference in the LS means (±SE) of the IIEF Overall Satisfaction for either tadalafil OaD vs sildenafil PRN (-0.22 ± 0.11; 95% CI: -0.44, 0.00; p = .055) or tadalafil PRN vs sildenafil PRN (0.01 ± 0.11; 95% CI: -0.21, 0.23; p = .947). Comparisons between tadalafil OaD vs tadalafil PRN, however, were statistically different for the IIEF overall satisfaction domain in favor of tadalafil PRN (-0.22 ± 0.11; 95% CI: -0.44, 0.00; p = .046).

Proportion of days with Morning Erection

At baseline, the mean (±SD) proportion of days with reported morning erections experienced over the 4-week run-in period was 0.28 ± 0.27. The LS mean (±SE) proportion of days with Morning erection increased following 3 treatments 0.11 ± 0.02, 0.26 ± 0.02, and 0.20 ± 0.02 for sildenafil PRN, tadalafil OaD, and tadalafil PRN, respectively. The LS means difference ± SE was statistically significantly greater for tadalafil OaD compared to sildenafil PRN (0.15 ± 0.01, 95% CI: 0.12, 0.18; p<.001), for tadalafil PRN compared to sildenafil PRN (0.09 ± 0.01, 95% CI: 0.06, 0.12; p<.001), and for tadalafil OaD compared to tadalafil PRN (0.06 ± 0.01, 95% CI: 0.03, 0.09; p<.001).

EDITS

The EDITS score for sildenafil PRN LS mean (±SE) was 75.68 ± 1.32, for tadalafil OaD it was 75.81 ± 1.31, and it was highest with tadalafil PRN 79.50 ± 1.31. There were no statistically significant differences of LS means between sildenafil PRN and tadalafil OaD (p = .926). However, the LS means difference in the EDITS score was statistically significantly greater for tadalafil PRN compared to sildenafil PRN (LS means difference = 3.66; p = .004) and lower for tadalafil OaD compared to tadalafil PRN (LS means difference = -3.55; p = .006).

Safety:

No patient deaths were reported during this study. A total of 11 SAEs were reported in this study: 5 occurred during sildenafil PRN; 4 during tadalafil OaD; and 2 during tadalafil PRN treatment. There was one report of each of the following from patients on sildenafil PRN: coronary artery occlusion, elbow operation, gastric cancer, oesophageal carcinoma, and pneumonia. Patients on tadalafil OaD treatment reported: one fall, one retinal detachment, and two of pneumonia. While on tadalafil PRN treatment, there was one reported incidence each of myocardial infarction and of thyroid cancer. In total, 11 patients discontinued due to an AE, and 5 of those discontinuations were due to a SAE. Headaches were the most common TEAE in all

3 study treatments. The highest incidence (n[%]) of headaches possibly related to treatment was reported in sildenafil PRN (sildenafil PRN, tadalafil OaD, and tadalafil PRN = 12 [3.4%], 7 [1.9%], and 6 [1.6%], respectively). While on sildenafil PRN treatment, the second most common TEAEs were 7 incidences each of flushing and nasal-congestion, which was numerically higher than during both tadalafil OaD and tadalafil PRN treatments. The third most common TEAE across all 3 treatment groups was dyspepsia. There were 4 (1.1%), 5 (1.4%), and 3 (0.8%) incidences of dyspepsia that were possibly related to sildenafil PRN, tadalafil OaD, and tadalafil PRN treatment respectively. There were no incidences of myalgia possibly related to sildenafil PRN treatment, compared to 1.4% with tadalafil OaD treatment and 0.3% for tadalafil PRN. Similarly, the incidence of back pain 0.3% possibly related to sildenafil PRN treatment, compared to 0.6% and 1.1% with tadalafil OaD and tadalafil PRN, respectively. There were no clinically significant effects on vital signs.

Conclusions:

- We were able to demonstrate that tadalafil 5 mg OaD was superior to sildenafil 100 mg PRN in term of the Sexual Self-Confidence domain of the PAIRS thereby meeting our primary hypothesis.
- In terms of the secondary objectives, other outcomes and treatment comparison we found that:
    - Psychosocial outcomes differed with the tool used; there were significant differences seen in the treatment comparison for PAIRS and PPF-Q but not with SEAR. Specifically, Sexual Self-Confidence was also higher for tadalafil PRN vs sildenafil PRN. However there was no difference between tadalafil OaD and tadalafil PRN with respect to PAIRS Sexual Self-Confidence. Time Concerns however was significantly reduced following a tadalafil OaD treatment when compared to both tadalafil PRN and sildenafil PRN therapy. Time Concerns for tadalafil PRN was significantly lower than sildenafil PRN as well. There was an improvement in PAIRS Spontaneity following both tadalafil OaD and tadalafil PRN treatments which was significantly greater than with the sildenafil PRN treatment. However, there was no significant difference in PAIRS spontaneity between tadalafil OaD and tadalafil PRN. For the PPF-Q, we did not observe any differences as to whether men had felt like they had no ED following treatment. However, in the second question of the PPF-Q which asked whether men felt more in control of their sex lives, the results showed there was significantly higher score for this question following tadalafil OaD or tadalafil PRN treatment when compared to sildenafil PRN. There was no difference in Question 2 of PPF-Q between tadalafil OaD and tadalafil PRN. The PPF-Q score for Question 3 demonstrated that men felt that PDE5 inhibitor on-demand therapy was in greater control of their erection when either tadalafil PRN or sildenafil PRN was compared to tadalafil OaD. The PPF-Q score for Question 3 is higher following sildenafil PRN when compared to tadalafil PRN. The PPF-Q score for Question 4 ("I felt like a whole man") was not statistically significant between tadalafil OaD

vs sildenafil PRN or tadalafil OaD vs tadalafil PRN. However, the PPF-Q score was significantly better for tadalafil PRN when compared to sildenafil PRN.

- Efficacy as measured by IIEF-EF score was not in favor of tadalafil OaD when compared to sildenafil PRN and tadalafil PRN however, no differences were seen when tadalafil PRN was compared to sildenafil PRN.
- Morning erection frequency, as measured by proportion of days during treatment period, was highest following tadalafil OaD treatment, which was significantly better than both tadalafil PRN and sildenafil PRN.
- Overall sexual satisfaction as measured by the IIEF-OS score was not different between tadalafil OaD and sildenafil PRN or between tadalafil PRN with sildenafil PRN. Overall sexual satisfaction was higher with tadalafil PRN when compared with tadalafil OaD.
- Treatment satisfaction as measured by EDITS was highest for tadalafil PRN which was significantly better than either tadalafil OaD or sildenafil PRN. There was no statistically significant difference in treatment satisfaction between tadalafil OaD or sildenafil PRN.

- All 3 treatments, tadalafil OaD, tadalafil PRN, and sildenafil PRN were well tolerated by patients with no reports of death, and few SAEs and TEAEs were observed. Commonly observed TEAEs included flushing and nasal congestion for sildenafil PRN while headaches and dyspepsia were observed for all study treatments, consistent with other reports on the use of PDE5 inhibitors.