Time to Onset of Clinically Meaningful Improvement with Tadalafil 5 mg Once Daily for Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: Analysis of Data Pooled from 4 Pivotal, Double-Blind, Placebo Controlled Studies

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Purpose: Tadalafil once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia consistently shows statistically significant I-PSS improvements. However, physicians and patients wish to know whether tadalafil provides rapid, clinically meaningful improvement in lower urinary tract symptoms. In this post hoc analysis we integrated results from 4 placebo controlled studies to determine the duration of tadalafil once daily required to achieve clinically meaningful improvement.

Materials and Methods: We performed post hoc analysis of data integrated from 4 double-blind studies of tadalafil 5 mg and placebo once daily in 742 and 735 men, respectively, 45 years old or older with total I-PSS 13 or greater. Two clinically meaningful improvement categories were assessed, including 1) 3-point or greater baseline to end point total I-PSS improvement and 2) 25% or greater baseline to end point total I-PSS improvement. I-PSS was assessed at weeks 4, 8 and 12 in all studies, week 1 in 2 and week 2 in 1. Results in men treated with tadalafil who showed clinically meaningful improvement (responders) were further examined to determine the earliest time to clinically meaningful improvement.

Results: Of 742 tadalafil treated patients 513 (69.1%) and 444 (59.8%) demonstrated category 1 and 2 clinically meaningful improvement, respectively, at the study end point. Of 234 category 1 responders with week 1 assessments 140 (59.8%) achieved clinically meaningful improvement by week 1 and 407 of the total of 513 category 1 responders (79.3%) showed it by week 4. Of the 205 category 2 responders with week 1 assessments 103 (50.2%) achieved clinically meaningful improvement by week 1 while 322 of the 444 category 2 responders (72.5%) did so by week 4.

Conclusions: Tadalafil 5 mg once daily led to clinically meaningful improvement in approximately two-thirds of men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. More than half of this group of tadalafil treated responders achieved clinically meaningful improvement after 1 week of therapy and more than 70% did so within 4 weeks.

Key Words: prostate, lower urinary tract symptoms, tadalafil, treatment outcome, questionnaires

Abbreviations and Acronyms

BII = BPH Impact Index

BPH = benign prostatic hyperplasia

CMI = clinically meaningful improvement

I-PSS = International Prostate Symptom Score

LS = least squares

LUTS = lower urinary tract symptoms

LUTS/BPH = LUTS secondary to BPH

PGI-I = Patient Global Impression of Improvement

QOL = quality of life

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BPH is a disorder that may result in LUTS, including storage symptoms such as increased urgency/frequency and incontinence, and voiding symptoms such as slow/intermittent urine stream and straining.[1–3] Moderate to severe LUTS/BPH is estimated to affect up to 25% of the adult male population worldwide, representing up to 900 million men.[4–7] According to the manufacturer tadalafil is currently the only phosphodiesterase type 5 inhibitor for daily use that is approved to treat BPH signs and symptoms.

According to LUTS/BPH studies[8,9] and the manufacturer tadalafil 5 mg once daily leads to statistically significant improvements vs placebo in total I-PSS as early as 1 to 2 weeks after initiation. However, limited information is available to physicians and patients on whether tadalafil results in CMI in men with LUTS/BPH, that is improvements in voiding/storage symptoms that are perceptible to patients.[10]

Treatment persistence (maintaining long-term medical therapy) and adherence (following long-term treatment instructions) are crucial concepts in managing chronic disorders such as LUTS/BPH. Persistence/adherence studies of other drugs show that patients withdraw from medication or deviate from dosing instructions for various reasons,[11–15] including a perceived lack of efficacy within a period deemed acceptable by the patient, typically within weeks of initiation. Thus, in LUTS/BPH management it is useful to know how quickly tadalafil once daily is likely to result in CMI to help set patient expectations and allow for an adequate trial of therapy.

In post hoc integrated analysis we determined how soon after the initiation of tadalafil 5 mg once daily therapy men with LUTS/BPH were likely to experience CMI using 2 CMI classifications/categories.

MATERIALS AND METHODS

In this post hoc analysis we used data integrated from 4 double-blind, placebo controlled studies of tadalafil 5 mg once daily for 12 weeks in men with LUTS/BPH of which the methodology, populations and results were previously described.[8–10,16–18] All 4 individual studies, designated as studies 1,[16] 2,[17] 3[8] and 4,[9] included men 45 years old or older with LUTS/BPH greater than 6 months in duration. Patients were also required to have a total I-PSS of 13 or greater, a maximum urinary flow rate of 4 or greater but 15 ml per second or less and postvoid residual urine volume 300 ml or less at baseline. Currently tadalafil 5 mg once daily is indicated for LUTS/BPH. Therefore, this post hoc analysis only included data on patients randomized to treatment with tadalafil 5 mg or placebo. Additionally, because the focus of this analysis was to provide physicians with information on the earliest time to CMI with tadalafil 5 mg therapy in men with LUTS/BPH, only results in the tadalafil 5 mg group are presented for those assessments.

I-PSS was the primary instrument in this post hoc analysis.[19] Patients in all 4 studies completed I-PSS at baseline (week 0), and weeks 4, 8 and 12 of double-blind treatment.[8,9,16,17] Additionally, an I-PSS version modified to enable assessments at 1 or 2 weeks was administered at week 1 to patients in studies 2[17] and 4,[9] and at week 2 in study 3.[8] The secondary efficacy instruments were I-PSS QOL,[19] BII[20,21] and PGI-I.[22]

Clinically meaningful improvement in LUTS/BPH was assessed by total I-PSS, that is the sum of the scores of all 7 I-PSS questions with a total score range of 0 to 35 points. Higher total I-PSS indicates LUTS of greater severity while decreases in total I-PSS with time represent LUTS improvement. In this post hoc analysis we used 2 classifications/categories of CMI, also referred to as a response with patients who achieved CMI designated as responders. The first CMI category was defined as a decrease in total I-PSS from baseline of 3 or more points. This was first described by Barry et al as a reliable measure of CMI in LUTS[21] and is accepted as a standard measure by the AUA (American Urological Association).[2] The second CMI category was defined as a decrease in total I-PSS of 25% or greater from baseline. This classification was applied in previous studies as a reliable measure of CMI in LUTS.[23–25] Its proportional nature accounts for the fact that men with higher total I-PSS (ie greater LUTS severity) likely require greater decreases in this score before experiencing perceptible LUTS improvement.

Calculations to determine time to onset of efficacy in tadalafil treated patients in each study and in the integrated analysis population were performed by first determining the number of patients in each of these groups who achieved a category 1 CMI (3-point or greater total I-PSS decrease) or a category 2 CMI (25% or greater total I-PSS decrease) by the study end point. Calculations were then performed to determine the number of patients who achieved a category 1 or 2 CMI after 1 week of treatment (data obtained and integrated from studies 2[17] and 4[9]), after 2 weeks (from study 3[8]), and after 4, 8 and 12 weeks (individual and integrated data obtained from all 4 studies).[8,9,16,17]

Other widely used measures of LUTS/BPH were examined to determine whether associations exist between CMI and improvements in these measures. Examinations included baseline to end point changes in I-PSS QOL and BII scores as well as end point responses to PGI-I by placebo and tadalafil treated patients who did or did not achieve a category 1 or 2 CMI.

Post hoc analyses were done of data on patients who were randomized to study treatment, received 1 or more doses of double-blind study drug and had 1 or more post-baseline I-PSS assessment. Baseline scores were defined as those obtained before randomization. End point scores were considered those obtained at the last nonmissing post-baseline study visit. For patients who withdrew or were discontinued before completing 12 weeks of treatment end point scores may have been obtained at week 1, 2, 4 or 8, or at the patient discontinuation visit.