Tadalafil for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a review of clinical data in Asian men and an update on the mechanism of action

Osamu Yokoyama, Yasuhiko Igawa, Masayuki Takeda, Takafumi Yamaguchi, Masahiro Murakami and Lars Viktrup

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Abstract: Tadalafil, a phosphodiesterase type 5 (PDE5) inhibitor, is approved worldwide for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia (BPH-LUTS). The purpose of this narrative review is to summarize the clinical data on tadalafil 5 mg once-daily, primarily focusing on Asian men with BPH-LUTS, and to update the current understanding of the mechanism of action underlying PDE5 inhibition. Findings from studies have demonstrated that PDE5 is highly expressed in the lower urinary tract and supporting vasculature, and that PDE5 inhibition potentially decreases smooth muscle cell proliferation in the prostate, relaxes smooth muscle in the prostate, bladder neck and supporting vasculature, increases blood perfusion to the lower urinary tract, and modulates bladder afferent nerve activity. A total of 11 larger, 12-week, double-blind, randomized, placebo-controlled studies of tadalafil, including four Asian studies, have been conducted globally, enrolling >3000 men with BPH-LUTS. In addition, two long-term (42- and 52-week) studies enrolled 394 Japanese and 428 North American men, respectively, with BPH-LUTS. Overall, tadalafil 5 mg once-daily resulted in significant improvements in the change from baseline to endpoint in total International Prostate Symptom Scores (IPSS), IPSS storage and voiding subscores, and IPSS quality of life index compared with placebo. Tadalafil was well tolerated and had a favorable safety profile. These findings support tadalafil 5 mg once-daily for treating men, including Asian men, with BPH-LUTS.

Keywords: Asia, benign prostatic hyperplasia, lower urinary tract symptoms, mechanism of action, tadalafil

Introduction

Benign prostatic hyperplasia (BPH) is a histological diagnosis characterized by nonmalignant hyperplasia of prostatic tissue that is caused by smooth muscle and epithelial cell proliferation in the prostate transition zone [Roehrborn, 2008; Oelke *et al.* 2013]. This hyperplasia results in prostate enlargement [Roehrborn, 2008; Oelke *et al.* 2013], which can in turn lead to the development of lower urinary tract symptoms (LUTS) such as storage, voiding and postmicturition symptoms [Abrams *et al.* 2003; Homma *et al.* 2011]. An increased smooth muscle tone in the prostate or the vasculature supporting the lower

urinary tract may play a contributing role [Homma *et al.* 2011]. LUTS secondary to BPH (BPH-LUTS) are common in aging men worldwide [Verhamme *et al.* 2002; Irwin *et al.* 2006; Coyne *et al.* 2009], including Asia [Tsukamoto *et al.* 1995; Lee *et al.* 1998; Li *et al.* 2005; Kang *et al.* 2011]. In the US, approximately 75% of men aged 60–69 years and 83% of men aged 70 years or older are estimated to have BPH-LUTS [Wei *et al.* 2008]. In Japan, an estimated 1.98 million men were projected to require treatment for BPH-LUTS in 2010, a number that is expected to increase to 2.19 million by 2030 [Terai *et al.* 2000]. Given that BPH-LUTS often interferes

Correspondence to:
Osamu Yokoyama, MD, PhD
Department of Urology,
Faculty of Medical Science,
University of Fukui, 23-3
Matsuokashimoaizuki,
Eiheiji-cho, Yoshida-gun,
Fukui 910-1193, Japan
oyokof@u-fukui.ac.jp

Yasuhiko Igawa, MD, PhD
Department of Continence
Medicine, The University of
Tokyo Graduate School of
Medicine, Tokyo, Japan

Masayuki Takeda, MD, PhD
Department of Urology,
Interdisciplinary Graduate
School of Medicine and
Engineering, University of
Yamanashi, Yamanashi,
Japan

Takafumi Yamaguchi, MS
Masahiro Murakami, MD, PhD
Lilly Research
Laboratories Japan, Eli
Lilly Japan K.K., Hyogo,
Japan

Lars Viktrup, MD, PhD
Lilly Research
Laboratories, Eli Lilly and
Co., Indianapolis, Indiana,
USA

with activities of daily living [Rosen *et al.* 2003], many men with BPH-LUTS seek treatment to improve their quality of life (QoL) [Jacobsen *et al.* 1993].

Pharmacological treatment for men with BPH-LUTS typically begins with an α -adrenergic blocker (α -blocker), with the addition of a 5- α -reductase inhibitor (5ARI) in men with verified prostate enlargement. Of these treatments, α -blockers may reduce LUTS within weeks, whereas 5ARIs have a slower onset of action (within 6–12 months) [Homma *et al.* 2011; Oelke *et al.* 2013]. Long-term treatment with 5ARIs may also reduce the risk of urinary retention and surgical intervention [American Urological Association Practice Guidelines Committee, 2010; Oelke *et al.* 2013]. Although these treatments may be effective, individually or in combination, some men do not respond or experience side effects such as sexual dysfunction, including ejaculatory disorders (α -blockers and 5ARIs), orthostatic hypotension (α -blockers) and intraoperative floppy iris syndrome during cataract surgery (α -blockers) [Homma *et al.* 2011]. Further, persistent adverse effects on sexual function, including erectile dysfunction (ED) and decreased libido, have been reported in a subset of patients with BPH-LUTS treated with 5ARIs [Traish *et al.* 2011].

Recently, the phosphodiesterase type 5 (PDE5) inhibitor tadalafil, widely approved as once-daily and/or on-demand treatment for ED, has been approved (5 mg once-daily) for the treatment of BPH-LUTS worldwide, including in several Asian countries, the US and the European Union. Like α -blockers, tadalafil has an onset of action that occurs within weeks [Egerdie *et al.* 2012; Oelke *et al.* 2012; Yokoyama *et al.* 2013]. The efficacy of PDE5 inhibitors, with a focus on tadalafil clinical data, was acknowledged in the recent guidelines published by the Japanese Urological Association (JUA) [Homma *et al.* 2011] and the European Association of Urology (EAU) [Oelke *et al.* 2013], both of which state that there is Level 1 evidence (i.e. from multiple, large-scale, randomized, controlled trials, the majority involving tadalafil) supporting the efficacy of PDE5 inhibitors for the treatment of BPH-LUTS.

The purpose of this narrative review, focusing on Asian men with BPH-LUTS, is to summarize the clinical data on tadalafil 5 mg once-daily as monotherapy or in combination with α -blockers or 5ARIs, and to update the current understanding

of the mechanism of action underlying PDE5 inhibition. The review of clinical data was focused on published findings from key randomized, placebo-controlled studies examining the efficacy of tadalafil 5 mg once-daily in men ($n \geq 50$ in the tadalafil treatment arm) with BPH-LUTS.

Potential pathology

Pathophysiological changes underlying the development of BPH-LUTS are multifaceted and may include reduced pelvic nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) signaling, overactivity of the autonomic nervous system, atherosclerosis, pelvic ischemia, increased Rho-kinase activity (which mediates smooth muscle contraction by modulating the activity of myosin phosphatase), an altered androgen environment and tissue inflammation [Andersson *et al.* 2011]. These changes may mediate increased smooth muscle cell (SMC) proliferation, SMC tone and bladder afferent nerve activity [Andersson *et al.* 2011; Giuliano *et al.* 2013]. The resultant structural and functional changes in the bladder, prostate, supporting vasculature and nerve innervation can affect bladder function [Andersson *et al.* 2011]. Metabolic syndrome may be independently associated with BPH-LUTS [Moul and McVary, 2010]. Although a direct causal link has not been identified, several of the characteristic changes associated with metabolic syndrome, including insulin resistance, hormonal changes, pelvic atherosclerosis and inflammation, seem to contribute to the development of LUTS [De Nunzio *et al.* 2012]. The results of a recently published systematic review and meta-analysis have also demonstrated a link between metabolic syndrome, in particular dyslipidemia and central obesity, and prostate enlargement [Gacci *et al.* 2015].

Location of PDE5 isoenzymes

To date, PDE5 isoenzymes have been identified in the SMCs of the corpus cavernosum [Taher *et al.* 1997], vascular and visceral smooth muscle [Rybalkin *et al.* 1999; Watkins *et al.* 2000], skeletal muscle [Loughney *et al.* 1998], platelets [Haslam *et al.* 1999], kidney [Kotera *et al.* 2000], lung [Cortijo *et al.* 1998], spinal cord [Fullhase *et al.* 2013], cerebellum [Kotera *et al.* 2000] and pancreas [Loughney *et al.* 1998]. In the lower urinary tract, PDE5 isoenzymes have been identified in the prostate [Uckert *et al.* 2001; Filippi *et al.* 2007; Waldkirch *et al.* 2007; Fibbi *et al.* 2010; Morelli *et al.* 2011a], urethra [Werkstrom *et al.*

Figure 1. Location of phosphodiesterase type 5 (PDE5) isoenzymes in the lower urinary tract.

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2006; Fibbi *et al.* 2010; Morelli *et al.* 2011a] and bladder [Filippi *et al.* 2007; Fibbi *et al.* 2010; Morelli *et al.* 2011a] (Figure 1).

PDE5 inhibition

In NO/cGMP signaling, PDE5 isoenzymes catalyze cGMP hydrolysis, thereby regulating the activity of cGMP-dependent protein kinases (PKGs) [Francis *et al.* 2010]. The proteins modified by PKGs play a role in regulating cellular calcium homeostasis [Francis *et al.* 2010]. The inhibition of PDE5 in SMCs potentiates the action of NO by increasing cGMP concentrations which, in turn, lead to calcium efflux and SMC relaxation. The inhibition of PDE5 isoenzymes in the lower urinary tract mediates a number of processes that may help relieve BPH-LUTS.

Smooth muscle relaxation

Organ bath studies of human prostate and bladder tissue have shown that PDE5 inhibitors induce smooth muscle relaxation. Specifically, a study of human prostate tissue, obtained from patients with BPH who underwent suprapubic adenectomy or from organ donors free from urologic disease, demonstrated that tadalafil potentiated sodium nitroprusside (SNP) induced relaxation in muscle strips and enhanced cGMP accumulation in homogenized tissue [Angulo *et al.* 2012]. Other studies demonstrated that PDE5 inhibitors

attenuated α -adrenergic-induced contractions [Uckert *et al.* 2001; Uckert *et al.* 2008], including in a concentration-dependent manner [Uckert *et al.* 2008], or electrical field-induced contractions [Takeda *et al.* 1995] in isolated human prostate strips obtained from nonmalignant tissue from men who had undergone surgery for localized prostate or urinary bladder cancer. Studies have also demonstrated that vardenafil potentiated SNP-induced relaxation [Filippi *et al.* 2007], and that sildenafil citrate induced relaxation [Bittencourt *et al.* 2009], of precontracted human bladder neck strips obtained from men undergoing transvesical prostate adenectomy, radical cystectomy or radical prostatectomy.

Increased blood perfusion

Animal and human studies have shown that PDE5 inhibitors can increase prostate and/or bladder blood perfusion. In spontaneously hypertensive rats (SHR), which exhibit prostate hyperplasia, bladder overactivity, and an increased density of hypoxic cells in prostate and bladder tissue, 7 days of tadalafil administration normalized the density of hypoxic cells in prostate tissue slices [Morelli *et al.* 2011a]. Likewise, in a similar SHR study, vardenafil, administered 90 minutes before sacrifice, normalized the density of hypoxic cells in bladder tissue slices [Morelli *et al.* 2010]. In a clinical study, an increase in prostate microcirculation was demonstrated, using power Doppler ultrasound,

60 minutes after vardenafil 20 mg administration in men ($n = 9$) who were prostate biopsy naïve and had a prostate-specific antigen concentration >4 ng/ml at first diagnosis with negative digital rectal and transrectal ultrasound examinations [Morelli *et al.* 2011b]. In another study, an increase in prostate blood flow was demonstrated, using transrectal contrast-enhanced ultrasound, 90 minutes after tadalafil 20 mg administration in men ($n = 12$) with BPH awaiting benign prostate surgery [Bertolotto *et al.* 2009]. Furthermore, in a case report of a man with a normal prostate, an approximate 75% increase in prostate blood flow was detected using dynamic contrast enhanced magnetic resonance imaging 60 minutes after administration of sildenafil citrate 25 mg [Haaga *et al.* 2007].

Encouraged by these results, a double-blind, randomized, placebo-controlled study of 97 men with BPH-LUTS was carried out to assess the arterial resistive index in the prostate transition zone and other flow measures in the prostate peripheral zone and bladder neck *via* transrectal ultrasonography after 8 weeks of tadalafil 5 mg once-daily therapy compared with placebo [Pinggera *et al.* 2014]. However, no detectable improvements were observed across several parameters. One potential explanation for the lack of improvement is that the prostatic arterial resistive index observed at baseline was less severe than reported in previous studies [Kojima *et al.* 1997; Tsuru *et al.* 2002; Berger *et al.* 2005; Ozden *et al.* 2010; Abdelwahab *et al.* 2012; Zhang *et al.* 2012], leaving less room for improvement. Other explanations include potential insufficient sensitivity of the novel techniques used, methodological variability across study sites, or PDE5 inhibition having an inconsistent impact on prostate blood perfusion [Pinggera *et al.* 2014].

Inhibition of PDE5 may also affect vascular reactivity *via* mediators of endothelial function. Specifically, sildenafil citrate has been demonstrated to enhance epithelial NO synthase (eNOS) expression in the sickle cell mouse penis [Musicki *et al.* 2014] and to restore eNOS activation in human umbilical vein endothelial cells cultured under conditions designed to mimic insulin resistance [Mammi *et al.* 2011]. Moreover, a study of 32 men with increased cardiovascular risk demonstrated that 4 weeks of treatment with tadalafil 20 mg resulted in improved brachial artery flow-mediated dilation and decreased plasma

concentrations of endothelin-1, a vasoconstrictor produced by the vascular endothelium [Rosano *et al.* 2005].

Decreased afferent nerve activity

Animal studies involving models of bladder distension, spinal cord injury and bladder outlet obstruction have shown that PDE5 inhibition modulates bladder afferent nerve activity. Specifically, tadalafil significantly decreased the single bladder afferent (afferents were identified by electrical stimulation of the pelvic nerve and bladder distension) activity of both A δ - and C-fibers induced by bladder distension or acrolein instillation in rats [Minagawa *et al.* 2012]. In another study, vardenafil decreased both bladder afferent (afferents were identified as described above) nerve firing during filling and the amplitude of nonvoiding contractions in rats with spinal cord injury [Behr-Roussel *et al.* 2011]. In a study of bladder outlet obstruction through partial urethral ligation in rats, vardenafil decreased nonvoiding contractions [Filippi *et al.* 2007].

In addition to the effects on afferent nerves in the bladder, a study of bladder overactivity *via* partial urethral obstruction in rats demonstrated that intrathecal sildenafil citrate administered at the level of the sacral spinal cord decreased both the frequency of micturition and bladder pressure [Fullhase *et al.* 2013].

Decreased SMC proliferation

The findings from several *in vitro* studies indicate that PDE5 inhibitors exert antiproliferative effects on human SMCs. Specifically, in a study of human prostatic SMCs obtained from men with BPH, PDE5 inhibition was demonstrated to inhibit lysophosphatidic acid induced increases in DNA replication by nearly 100% [Adolfsson *et al.* 2002]. More recently, a study of human bladder, prostatic and urethral SMCs, obtained from men who underwent suprapubic adenectomy for BPH, demonstrated that vardenafil significantly increased the antiproliferative effect (determined by cell counting) of the NO donor SNP [Fibbi *et al.* 2010].

In addition to these effects on SMCs, a study of human prostatic stromal cells demonstrated that vardenafil significantly attenuated transforming growth factor β 1-induced fibroblast-to-myofibroblast transdifferentiation (determined by assessing SMC actin and insulin-like growth factor

binding protein 3 mRNA and protein levels), an important underlying change in BPH [Zenzmaier *et al.* 2012]. Furthermore, the fibroblast-like morphology in transdifferentiated myofibroblasts was restored [Zenzmaier *et al.* 2012].

Summary

Several different pathophysiological changes in the bladder, prostate, supporting vasculature and nerve supply may lead to LUTS in men with BPH. The abundance of PDE5 isoenzymes in the lower urinary tract and the inhibition of PDE5 in these tissues, leading to increased cGMP, have been demonstrated to reduce SMC proliferation, relax SMCs, increase tissue oxygenation and modulate afferent nerve activity. The improvement of symptoms in patients with BPH-LUTS treated with tadalafil is most likely mediated by a combination of these effects.

Clinical efficacy and safety data

More than 3000 men with BPH-LUTS have participated in 11 large, randomized, placebo-controlled studies of tadalafil carried out globally [McVary *et al.* 2007; Roehrborn *et al.* 2008; Dmochowski *et al.* 2010; Kim *et al.* 2011; Porst *et al.* 2011; Egerdie *et al.* 2012; Goldfischer *et al.* 2012; Oelke *et al.* 2012; Takeda *et al.* 2012, 2014; Yokoyama *et al.* 2013]. Two long-term, open-label studies enrolled 394 Japanese [Takeda *et al.* 2012] and 428 North American [Donatucci *et al.* 2011] men. In addition, two large, randomized, placebo-controlled studies of tadalafil combination therapy with finasteride [Casabe *et al.* 2014] or α -blockers [Goldfischer *et al.* 2012] enrolled 346 and 158 men, respectively. Studies enrolling fewer than 50 patients to the tadalafil treatment arm are not included in this review.

Efficacy

To date, three 12-week, randomized, controlled studies [Takeda *et al.* 2012; Yokoyama *et al.* 2013; Takeda *et al.* 2014], a 12-week, randomized, controlled pilot study [Kim *et al.* 2011], and a 42-week, open-label, extension study [Takeda *et al.* 2012] have investigated the efficacy of tadalafil 5 mg once-daily as a treatment for BPH-LUTS in men from Asian countries. Four 12-week, randomized, controlled studies [Roehrborn *et al.* 2008; Porst *et al.* 2011; Egerdie *et al.* 2012; Oelke *et al.* 2012] and a 1-year, open-label, extension study [Donatucci *et al.* 2011] have investigated the

efficacy of tadalafil 5 mg once-daily in men from non-Asian countries. These studies included men aged ≥ 45 years with a 6-month history of BPH-LUTS, a total International Prostate Symptom Score (IPSS) ≥ 13 and intermediate voiding obstruction as defined by maximum urinary flow ($Q_{\max}$) of 4–15 ml/s. In all of these studies, the primary or coprimary outcome was the change from baseline to endpoint in total IPSS for tadalafil 5 mg compared with placebo. The IPSS [Barry *et al.* 1992; Homma *et al.* 2002] is widely accepted and recommended as the standard instrument for assessing BPH-LUTS worldwide [Homma *et al.* 2011; Oelke *et al.* 2013].

Asian studies. The 12-week, double-blind, randomized, placebo-controlled studies of tadalafil 5 mg once-daily in Japanese men [Takeda *et al.* 2012], Japanese, Korean and Taiwanese men [Yokoyama *et al.* 2013], and Japanese and Korean men [Takeda *et al.* 2014] consistently demonstrated greater improvement in the change from baseline to endpoint in total IPSS for tadalafil 5 mg compared with placebo (Figure 2A). The improvement was significantly greater ($p < 0.05$) in two of these studies [Yokoyama *et al.* 2013; Takeda *et al.* 2014], whereas in the third smaller study [Takeda *et al.* 2012], the magnitude of symptom improvement (IPSS) was numerically greater ($p = 0.062$) on primary analysis (analysis of covariance) and significantly greater ($p < 0.05$) on secondary analysis (mixed-effects models repeated measures). Of note, integrated analysis of data from these three studies demonstrated significantly greater improvement in total IPSS for tadalafil 5 mg compared with placebo (mean change from baseline to endpoint: placebo = -3.8 , tadalafil = -5.3 ; $p < 0.001$ [Nishizawa *et al.* 2015]).

The randomized, controlled Asian studies also consistently demonstrated greater improvement in secondary efficacy measures, including the change from baseline to endpoint in IPSS storage and voiding subscores and IPSS QoL index, for tadalafil 5 mg compared with placebo (Table 1). The magnitude of improvement in the IPSS storage subscore was significantly greater ($p < 0.05$) in two studies [Yokoyama *et al.* 2013; Takeda *et al.* 2014] and numerically greater in one study [Takeda *et al.* 2012], whereas the magnitude of improvement in the IPSS voiding subscore and IPSS QoL index was significantly greater ($p < 0.05$) in all three studies [Takeda *et al.* 2012, 2014; Yokoyama *et al.* 2013].

Figure 2. Change from baseline to endpoint in total IPSS after 12 weeks of treatment with placebo or tadalafil 5 mg in (A) Asian and (B) non-Asian randomized, controlled studies of men with lower urinary tract symptoms secondary to benign prostatic hyperplasia; *p* values represent the tadalafil *versus* placebo comparison in each study.

^aFull study.

^bPilot study.

IPSS, International Prostate Symptom Score; *n* = number of randomized participants.

In the two randomized, controlled Asian studies in which assessments were made [Yokoyama *et al.* 2013; Takeda *et al.* 2014], a greater proportion of participants treated with tadalafil had better or improved urinary symptoms compared with those treated with placebo, as assessed by both the Patient and Clinician Global Impression of Improvement instruments.

In all three randomized, controlled Asian studies [Takeda *et al.* 2012; Yokoyama *et al.* 2013; Takeda

et al. 2014], changes from baseline in Q_{max} were not significantly different for tadalafil 5 mg compared with placebo (Table 1).

The findings of the initial 12-week, double-blind, randomized, placebo-controlled, small pilot study of tadalafil 5 mg once-daily in Korean men [Kim *et al.* 2011] are consistent with those of the other Asian studies, demonstrating numerically greater improvements in the change from baseline to endpoint in total IPSS, IPSS subscores and IPSS

Table 1. Mean changes from baseline to endpoint in IPSS storage and voiding subscores, IPSS quality of life index, and maximum urinary flow rate in 12-week, double-blind, randomized, placebo-controlled clinical studies of tadalafil 5 mg in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia.

Study	Treatment	n	Mean change from baseline			
			IPSS storage subscore	IPSS voiding subscore	IPSS QoL index	Q _{max} [†] ml/s
Asian studies						
Takeda <i>et al.</i> [2014]	Placebo	304	-1.4	-3.1	-0.9	0.6 [‡]
	Tadalafil	306	-2.0*	-4.0*	-1.1*	1.2 [‡]
Yokoyama <i>et al.</i> [2013] [§]	Placebo	154	-1.1	-1.9	-0.5	2.1
	Tadalafil	155	-1.7*	-3.0*	-0.8*	1.3
Takeda <i>et al.</i> [2012] [§]	Placebo	140	-1.4	-2.4	-0.4	1.4
	Tadalafil	140	-1.6	-3.3*	-0.7*	0.6
Kim <i>et al.</i> [2011]	Placebo	51	-1.5	-2.7	-0.9	2.3
	Tadalafil	51	-2.1	-3.7	-1.2	2.5
Non-Asian studies						
Roehrborn <i>et al.</i> [2008] [§]	Placebo	210	-1.0	-1.3	-0.5	1.2
	Tadalafil	212	-1.9*	-2.9*	-0.9*	1.6
Egerdie <i>et al.</i> [2012] [§]	Placebo	200	-1.6	-2.2	-0.8	1.2
	Tadalafil	208	-2.5*	-3.6*	-1.0	1.7
Oelke <i>et al.</i> [2012]	Placebo	172	-1.6	-2.6	-1.0	1.2
	Tadalafil	171	-2.2	-4.1*	-1.3*	2.4*
Porst <i>et al.</i> [2011]	Placebo	164	-1.3	-2.3	-0.7	1.1
	Tadalafil	161	-2.3*	-3.3*	-1.0*	1.6
* <i>p</i> < 0.05 versus placebo						
[§] Tadalafil 2.5 mg was also tested in this study.						
[‡] Median change from baseline to endpoint.						
[§] Tadalafil 2.5, 10., and 20 mg were also tested in this study.						
IPSS = International Prostate Symptom Score; <i>n</i> = number of randomized participants; Q _{max} = maximum urinary flow rate; QoL = quality of life.						

QoL index for tadalafil 5 mg compared with placebo (Figure 2; Table 1). As in the other Asian studies, the change from baseline in Q_{max} was small and not significantly different for tadalafil compared with placebo (Table 1). Integrated analysis of data from Korean men in the pilot study [Kim *et al.* 2011] and the two randomized, controlled trials [Yokoyama *et al.* 2013; Takeda *et al.* 2014] also demonstrated significantly greater improvements in the change from baseline to endpoint in total IPSS, IPSS subscores and IPSS QoL index for tadalafil 5 mg compared with placebo [Lee *et al.* 2014].

The open-label extension of the study of tadalafil 5 mg once-daily carried out in Japanese men ($n = 394$) [Takeda *et al.* 2012] demonstrated that improvements in total IPSS, IPSS subscores and IPSS QoL index at the end of the 12-week, double-blind, placebo-controlled phase were maintained with long-term treatment (for up to 42

weeks). Although the change in Q_{max} observed at the end of the double-blind phase was not significantly different for tadalafil 5 mg compared with placebo, Q_{max} persistently improved with long-term treatment.

To obtain further information on the efficacy of tadalafil in Asian men with BPH-LUTS (specifically, factors that may be considered when prescribing medication for BPH-LUTS in the clinical setting), subgroup analyses by age (<65 years or ≥65 years), severity of BPH-LUTS at baseline (mild-to-moderate or severe), previous α -blocker therapy within 12 months (yes or no) and prostate volume (<median or ≥median) were carried out. The three Asian studies [Takeda *et al.* 2012, 2014; Yokoyama *et al.* 2013] and the integrated analyses of data from these studies demonstrated numerically greater improvements in the change from baseline to endpoint in total IPSS for tadalafil 5

mg compared with placebo regardless of age, BPH-LUTS severity, previous α -blocker therapy or prostate volume grouping [Nishizawa *et al.* 2015].

The integrated analyses also demonstrated a number of within subgroup differences regarding total IPSS [Nishizawa *et al.* 2015]. Specifically, the magnitude of improvement was significantly greater for participants aged <65 years compared with participants aged ≥ 65 years, whereas symptom severity at the end of treatment was similar in both age categories. Participants who had severe BPH-LUTS at baseline demonstrated numerically greater improvement compared with participants who had mild-to-moderate BPH-LUTS at baseline. Participants who had not received previous α -blocker therapy within 12 months demonstrated numerically greater improvement compared with participants who had received previous α -blocker therapy. Finally, the magnitude of improvement in total IPSS was similar among participants, regardless of prostate volume.

Non-Asian studies. The efficacy findings of the randomized, controlled non-Asian studies are generally consistent with those of the randomized, controlled Asian studies (Figure 2a; Table 1). Integrated analysis of data from these non-Asian studies demonstrated significantly greater ($p < 0.001$) improvement in the change from baseline in total IPSS for tadalafil compared with placebo (placebo = -2.7, tadalafil = -5.0) [Porst *et al.* 2013]. Likewise, there was significantly greater ($p < 0.001$) improvement in the change from baseline in IPSS storage and voiding subscores and IPSS QoL index for tadalafil compared with placebo [Porst *et al.* 2013]. Interestingly, the integrated analysis also demonstrated a small, but significant ($p = 0.003$), improvement in the change from baseline in median $Q_{\max}$ for tadalafil compared with placebo [Roehrborn *et al.* 2014]. This significant improvement (*versus* lack of significance in most individual studies and the integrated analyses of Asian data) likely reflects greater statistical power ($n = 752$ in the non-Asian studies *versus* $n = 601$ in the Asian studies) to detect a small difference and is consistent with tadalafil exerting some effect on SMC relaxation in the prostate or bladder neck. The clinical relevance of such an effect on improvement in BPH-LUTS is unclear [Roehrborn *et al.* 2014].

Subgroup analysis of pooled data from the four non-Asian studies demonstrated significantly

greater ($p < 0.05$) improvement in the change from baseline in total IPSS for tadalafil compared with placebo regardless of baseline age (<65 years *versus* ≥ 65 years), severity of BPH-LUTS, previous α -blocker use within 12 months, or prostate-specific antigen-predicted prostate volume [Porst *et al.* 2013].

Integrated analysis [Oelke *et al.* 2014] of data from the four non-Asian studies demonstrated a small but significant ($p = 0.002$) improvement in the change from baseline to endpoint in the severity of nocturia (IPSS question 7) for tadalafil 5 mg compared with placebo. However, the treatment difference (-0.2) was not considered to be clinically meaningful.

Integrated analyses [Brock *et al.* 2013, 2014] of data from non-Asian studies have also demonstrated that ED does not affect the LUTS treatment response to tadalafil in men with BPH-LUTS. The impact of ED on the efficacy and safety of tadalafil 5 mg was investigated in an integrated analysis [Brock *et al.* 2013] of data, which included men with BPH-LUTS who had ED and men with BPH-LUTS who did not have ED, from three of the non-Asian studies [Roehrborn *et al.* 2008; Porst *et al.* 2011; Oelke *et al.* 2012]. Significantly greater ($p < 0.05$) improvements in the change from baseline in total IPSS, IPSS subscores and IPSS QoL index for tadalafil compared with placebo were found, regardless of ED status (treatment-by-ED-status interaction: all $p \geq 0.687$).

More recently, an integrated analysis [Brock *et al.* 2014] of data from all four non-Asian studies [Roehrborn *et al.* 2008; Porst *et al.* 2011; Egerdie *et al.* 2012; Oelke *et al.* 2012] assessed whether the effects of treatment with tadalafil 5 mg for BPH-LUTS were independent of improvements in ED. A weak correlation ($r^2 = 0.08$) between the change from baseline in total IPSS and the change from baseline in the International Index of Erectile Function-Erectile Function (IIEF-EF) domain score was detected. Further, unidirectional path analysis revealed that 70% of the improvement in total IPSS was due to a direct effect of tadalafil, whereas 30% of the improvement in total IPSS was due to an indirect effect of tadalafil *via* improvement in IIEF-EF ($p < 0.001$). Bidirectional path analysis revealed that 92.5% of the improvement in total IPSS was due to a direct effect of tadalafil, whereas 7.5% of the improvement in total IPSS was due to an indirect effect of tadalafil *via* improvement in IIEF-EF ($p < 0.001$).

Table 2. Mean changes from baseline to end point in total IPSS, IPSS subscores, IPSS quality of life index, and maximum flow rate in 12-week, double-blind, randomized, placebo-controlled clinical studies of tamsulosin in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia.

Study	Treatment	n	Mean change from baseline				
			Total IPSS	IPSS storage subscore	IPSS voiding subscore	IPSS QoL index	Q _{max} , ml/s
Asian studies ^{\$}							
Yokoyama <i>et al.</i> [2013]	Placebo	154	-3.0	-1.1	-1.9	-0.5	2.1
	Tadalafil 5 mg	155	-4.7*	-1.7*	-3.0*	-0.8*	1.3
	Tamsulosin 0.2 mg	152	-5.5	-1.7	-3.8	-1.1	2.1
Kawabe <i>et al.</i> [2006]	Placebo	89	-5.3	-1.5	-3.8	-1.1	0.3
	Tamsulosin 0.2 mg	192	-6.8	-2.1	-4.8	-1.4	2.6
Kim <i>et al.</i> [2011]	Placebo	51	-4.2	-1.5	-2.7	-0.9	2.3
	Tadalafil 5 mg	51	-5.8	-2.1	-3.7	-1.2	2.5
	Tamsulosin 0.2 mg	49	-5.4	-1.8	-3.6	-1.0	2.1
Non-Asian study							
Oelke <i>et al.</i> [2012]	Placebo	172	-4.2	-1.6	-2.6	-1.0	1.2
	Tadalafil 5 mg	171	-6.3*	-2.2	-4.1*	-1.3*	2.4*
	Tamsulosin 0.4 mg	168	-5.7*	-2.2	-3.5*	-1.1	2.2*

* $p < 0.05$ versus placebo.

^{\$}Tamsulosin versus placebo statistical comparisons were not made in the studies reported by Kawabe *et al.* [2006] and Yokoyama *et al.* [2013]. IPSS, International Prostate Symptom Score; n, number of randomized participants; Q_{max}, maximum urinary flow rate; QoL, quality of life.

These findings indicate that tadalafil exerts independent effects on BPH-LUTS and ED.

Comparison of efficacy with tamsulosin. There are very limited publically available data from 12-week, double-blind, randomized, placebo-controlled studies of tamsulosin in Asian men with BPH-LUTS (Table 2). The available data, mostly from clinical tadalafil studies [Kim *et al.* 2011; Yokoyama *et al.* 2013], demonstrate placebo-adjusted improvement in the change from baseline in total IPSS after treatment with tamsulosin 0.2 mg once-daily ranging from -1.2 to -2.5. In comparison, the placebo-adjusted improvement with tadalafil 5 mg once-daily ranged from -1.1 to -1.7 in the Asian studies [Kim *et al.* 2011; Takeda *et al.* 2012; Yokoyama *et al.* 2013; Takeda *et al.* 2014] (and from -1.9 to -2.6 in the non-Asian studies [Roehrborn *et al.* 2008; Porst *et al.* 2011; Egerdie *et al.* 2012; Oelke *et al.* 2012]). Placebo-adjusted improvements in IPSS subscores and IPSS QoL index were also generally similar for tamsulosin 0.2 mg and tadalafil 5 mg in the Asian studies. Changes from baseline in Q_{max} were generally small in the placebo-controlled studies of tamsulosin and the Asian studies of tadalafil. Although Q_{max} has historically been a commonly reported measure in studies examining medical

therapies for BPH-LUTS, it is worth noting that both the American Urological Association guideline for the management of BPH and the JUA BPH guidelines indicate that increases in Q_{max} are poorly correlated with symptomatic improvement [American Urological Association Practice Guidelines Committee, 2010; Homma *et al.* 2011]

The available data from Asian studies of men with BPH-LUTS suggest that tadalafil 5 mg once-daily for 12 weeks results in improvements in total IPSS, IPSS subscores and IPSS QoL index that are generally similar to those observed with tamsulosin 0.2 mg once-daily. In comparison, a 12-week, double-blind, randomized, placebo-controlled, non-Asian study of tadalafil 5 mg or tamsulosin 0.4 mg once-daily in men with BPH-LUTS [Oelke *et al.* 2012] demonstrated a placebo-adjusted improvement in the change from baseline in total IPSS of -2.1 for tadalafil 5 mg and -1.5 for tamsulosin 0.4 mg (Table 2).

Summary. The 12-week Asian studies demonstrated consistently greater improvements in the change from baseline in total IPSS, IPSS subscores and IPSS QoL index for tadalafil 5 mg compared with placebo in men with BPH-LUTS. The improvements at 12 weeks were maintained

Table 3. Treatment-emergent adverse events reported by $\geq 2\%$ of participants in 12-week, double-blind, randomized, placebo-controlled clinical studies of tadalafil in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia.

Common TEAEs	Asian studies*		Non-Asian studies [§]	
	Placebo (n = 598)	Tadalafil 5 mg (n = 601)	Placebo (n = 748)	Tadalafil 5 mg (n = 752)
Dyspepsia	0.3%	3.0%	0.1%	2.4%
Headache	1.7%	2.5%	2.0%	3.9%
Nasopharyngitis	5.4%	4.8%	2.3%	2.3%

*Safety dataset pooled from all participants in the Asian studies [Takeda *et al.* 2012, 2014; Yokoyama *et al.* 2013].
[§]Safety dataset pooled from all participants in the non-Asian studies [Roehrborn *et al.* 2008; Porst *et al.* 2011; Egerdie *et al.* 2012; Oelke *et al.* 2012].
n, number of randomized participants; TEAEs, treatment-emergent adverse events.

for 42 weeks, demonstrating the long-term efficacy of tadalafil 5 mg. Furthermore, the greater improvements were apparent regardless of age, severity of BPH-LUTS, previous α -blocker therapy, or prostate volume subgroupings. These findings are consistent with the efficacy findings from the non-Asian studies of tadalafil 5 mg once-daily in men BPH-LUTS and demonstrate that tadalafil 5 mg once-daily is an efficacious treatment for Asian men with BPH-LUTS.

Safety

To date, three randomized, controlled studies [Takeda *et al.* 2012, 2014; Yokoyama *et al.* 2013], a randomized, controlled pilot study [Kim *et al.* 2011, and an open-label extension study [Takeda *et al.* 2012] have investigated the safety and tolerability of tadalafil 5 mg once-daily as a treatment for BPH-LUTS in men from Asian countries, whereas four randomized, controlled studies have investigated the safety and tolerability of tadalafil 5 mg in men from non-Asian countries [Roehrborn *et al.* 2008; Porst *et al.* 2011; Egerdie *et al.* 2012; Oelke *et al.* 2012]. A randomized, controlled study has also investigated the urodynamic safety of tadalafil 20 mg once-daily in men from non-Asian countries [Dmochowski *et al.* 2010].

Asian studies. Tadalafil 5 mg was well tolerated in the randomized, controlled Asian studies [Takeda *et al.* 2012, 2014; Yokoyama *et al.* 2013] and had a safety profile consistent with the known safety profile of tadalafil as per the current package insert for tadalafil (Cialis) 5 mg to 20 mg as needed for ED [Eli Lilly Japan, 2012]. Integrated analysis of safety data from these studies demonstrated that the most common

treatment-emergent adverse events (TEAEs) were nasopharyngitis, dyspepsia and headache (Table 3). Few participants experienced serious adverse events (placebo = 0.5%, tadalafil = 0.7%; none were considered to be treatment-related) or TEAEs leading to discontinuation (placebo = 2.7%, tadalafil = 1.8%).

The type and frequency of individual TEAEs in the pilot study [Kim *et al.* 2011] were similar to those reported in the randomized, controlled Asian studies. No new or unexpected safety findings were observed with longer term treatment [Takeda *et al.* 2012].

Subgroup analysis of data from the three randomized, controlled Asian studies demonstrated that there were no meaningful differences in safety findings by age, ethnicity, pre-existing disease, renal function, or previous α -blocker therapy [unpublished data].

Non-Asian studies. The safety and tolerability findings of the non-Asian studies are consistent with those of the Asian studies. Integrated analysis of data from the non-Asian studies of tadalafil 5 mg demonstrated that the most common TEAEs were headache, back pain (placebo = 1.2%, tadalafil = 2.4%), dyspepsia and nasopharyngitis (Table 3). As in the Asian studies, few participants experienced serious adverse events (placebo = 0.7%, tadalafil = 0.8%) or TEAEs leading to discontinuation (placebo = 1.5%, tadalafil = 3.1%).

The findings from the double-blind, placebo-controlled, 12-week, invasive/noninvasive urodynamic study [Dmochowski *et al.* 2010] of tadalafil

20 mg in men with BPH-LUTS (with and without bladder outlet obstruction) indicate that tadalafil has no negative effects on bladder function. In this study, there were no statistically significant or clinically adverse differences between tadalafil and placebo in change in detrusor pressure at Q_{max} , mean urine flow, voided volume, maximum detrusor pressure during voiding, postvoid residual volume, total bladder capacity, bladder voiding efficiency, bladder contractility index, bladder outlet obstruction index, presence of involuntary detrusor contractions during bladder filling, or bladder volume at first involuntary detrusor contraction. As participants with detrusor overactivity were not excluded or proactively enrolled and the frequency or amplitude of detrusor contractions were not assessed, no conclusions can be made from the results of this study regarding the effects of tadalafil on detrusor overactivity.

Summary. Tadalafil was well tolerated and no new safety concerns were identified in any of the Asian studies. The safety findings from the non-Asian studies of tadalafil 5 mg once-daily in men with BPH-LUTS are consistent with the corresponding findings from the Asian studies.

Tadalafil combination therapy

Tadalafil/ α -blocker combination therapy

No large, double-blind, placebo-controlled study has assessed the efficacy of tadalafil/ α -blocker combination therapy. However, several small clinical studies have reported that tadalafil/ α -blocker combination therapy may provide greater improvement in the change from baseline in total IPSS than α -blocker therapy alone [Bechara *et al.* 2008; Liguori *et al.* 2009] or tadalafil therapy alone [Liguori *et al.* 2009; Singh *et al.* 2014] in men with BPH-LUTS. However, these studies either included a small number of participants, involved tadalafil doses >5 mg once-daily, and/or were not placebo controlled.

The safety of tadalafil 5 mg in combination with α -blockers (alfuzosin, silodosin, tamsulosin, doxazosin or terazosin) was investigated in a US double-blind, randomized, placebo-controlled trial of men with BPH-LUTS (tadalafil/ α -blocker, $n = 158$; placebo, $n = 160$) [Goldfischer *et al.* 2012]. This study was not designed to assess efficacy. No new safety concerns were identified for tadalafil/ α -blocker combination therapy in this

study. Furthermore, the proportion of participants reporting treatment-emergent dizziness or with a positive orthostatic test was similar between the tadalafil/ α -blocker combination therapy group and the placebo/ α -blocker combination therapy group.

Note that combining doxazosin with tadalafil is not recommended (per the package inserts for Cialis and Zoladex) as tadalafil may potentiate the hypotensive effects of this non-uroselective α -blocker [Kloner *et al.* 2004; Guillaume *et al.* 2007; Eli Lilly Japan, 2014].

Tadalafil/5ARI combination therapy

Several clinical studies have examined the efficacy and safety of tadalafil/5ARI combination therapy, with simultaneous initiation, in men with an enlarged prostate and BPH-LUTS. In a multinational, randomized, double-blind, 26-week study of finasteride 5 mg/tadalafil 5 mg ($n = 346$) compared with finasteride 5 mg/placebo ($n = 350$) [Roehrborn *et al.* 2015; Casabe *et al.* 2014; Glina *et al.* 2014], there was significantly greater ($p < 0.05$) improvement in the change from baseline in total IPSS for finasteride/tadalafil compared with finasteride/placebo at weeks 4, 12 and 26 [Casabe *et al.* 2014]. There were also significant treatment differences in secondary outcomes assessed, including the change from baseline in the IPSS voiding subscore for finasteride/tadalafil compared with finasteride/placebo at weeks 4, 12, and 26, the IPSS storage subscore at weeks 4 and 12 and IPSS QoL index at week 4. Furthermore, participants who received finasteride/tadalafil were significantly more satisfied with their treatment (Treatment Satisfaction Scale-BPH) at week 26 than participants who received finasteride/placebo [Roehrborn *et al.* 2015]. In a small, 12-week, Korean, randomized study, a similar magnitude of improvement in the change from baseline in total IPSS at week 12 was found for tadalafil 5 mg/dutasteride 0.5 mg (-2.3 , $n = 86$) compared with tamsulosin 0.2 mg/dutasteride 0.5 mg (-2.5 , $n = 82$) [Park and Park, 2013].

No new safety concerns were identified for tadalafil/5ARI combination therapy in either of these studies [Park and Park, 2013; Casabe *et al.* 2014]. In the 26-week study, a lower proportion of participants who received finasteride/tadalafil discontinued compared with participants who received finasteride/placebo [Casabe *et al.* 2014]. Few

participants in either group reported adverse events related to sexual dysfunction [Glina *et al.* 2014].

The findings from these studies suggest that tadalafil/5ARI combination therapy may result in earlier and greater improvement in BPH-LUTS compared with 5ARI therapy alone [Casabe *et al.* 2014] and that tadalafil/dutasteride combination therapy may result in similar improvements in BPH-LUTS compared with tamsulosin/dutasteride combination therapy [Park and Park, 2013].

Summary

The available data from large, well-controlled studies suggest that tadalafil/5ARI combination therapy provides added benefit in the treatment of BPH-LUTS compared with 5ARI monotherapy and that both tadalafil/ α -blocker and tadalafil/5ARI combination therapy have favorable safety profiles.

Conclusion

Studies have shown that the inhibition of PDE5 isoenzymes relaxes smooth muscle in the prostate and bladder neck (*via* cGMP), increases blood perfusion to the prostate and bladder, and decreases bladder afferent nerve activity. These underlying effects of tadalafil are in keeping with the findings from clinical studies, which have demonstrated that tadalafil relieves BPH-LUTS. Specifically, clinical studies carried out in Asian and non-Asian countries have demonstrated that tadalafil 5 mg once-daily is an efficacious treatment for men with BPH-LUTS and has a safety profile consistent with the known safety profile of tadalafil for ED. These findings support tadalafil monotherapy for men, including Asian men, with BPH-LUTS. Clinical studies also suggest that tadalafil/5ARI combination therapy may be more efficacious than 5ARI monotherapy, and that tadalafil/5ARI and tadalafil/urol selective α -blocker combination therapy have favorable safety profiles.

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Conflict of interest statement

T.Y. and M.M. are employees of Eli Lilly Japan K.K. L.V. is an employee of Eli Lilly and Company. O.Y., Y.I. and M.T. have been advisory board members for Eli Lilly Japan K.K. M.M. and L.V. are stockholders of Eli Lilly and Company.

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