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·Original Article·

Efficacy and safety of oral SK3530 for the treatment of erectile dysfunction in Korean men: a multicenter, randomized, double-blind, placebo-controlled, fixed dose, parallel group clinical trial

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Abstract

Aim: To evaluate the efficacy and safety of SK3530, a newly developed type 5 phosphodiesterase inhibitor (PDE5I), in Korean men with erectile dysfunction (ED). **Methods:** A total of 119 patients were randomized at 10 centers in Korea to receive either SK3530 (50, 100, or 150 mg; $n = 89$) or placebo ($n = 30$) taken l h before anticipated sexual activity for an 8-week period. The patients were evaluated at baseline and 4 and 8 weeks after beginning therapy. Efficacy was assessed using the International Index of Erectile Function (IIEF), Sexual Encounter Profile (SEP), and the Global Assessment Question (GAQ). Safety was analyzed by adverse events, laboratory values and vital signs. **Results:** At the end of the study, all the primary and secondary efficacy end-points were statistically significantly improved by SK3530 compared with placebo ($P < 0.05$). Of the 89 patients in the treatment arm, 36 (42.3 %) achieved normal erectile function after treatment, including six patients with severe ED. Treatment-related adverse events occurred in 32 patients. The most common adverse events were flushing, headache, dizziness and eye redness (10.9%, 7.6%, 2.5% and 2.5%, respectively), and most were mild. Only two patients discontinued treatment during the study period because of adverse events. **Conclusion:** The results of our phase II study have confirmed the efficacy and safety of SK3530 in a broad population of men with ED of various etiologies and severity. The optimal doses in terms of efficacy and safety were determined to be 50 mg and 100 mg, respectively. *(Asian J Androl 2008 Sep; 10: 791–798)*

Keywords: erectile dysfunction; phosphodiesterase; sildenafil citrate

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1 Introduction

Erectile dysfunction (ED) is highly prevalent in Asian men [1], and can be distressing because of its effect on self-esteem, quality of life and interpersonal relationships [2, 3]. Three major type 5 phosphodiesterase (PDE5) inhibitors (PDE5Is), sildenafil, tadalafil and vardenafil, have been shown to be effective in treating ED of varying functional severity and etiology [4–6]. However, a substantial number of patients are believed to discontinue treatment in the long term [7–9]. The main reason for the poor compliance rate proved to be the lowered efficacy that did not meet patients' expectations [9]. If one PDE5I does not satisfy a patient's expectations, the availability of another PDE5I might provide a better opportunity to find the suitable agent that meets their needs.

SK3530 (2-(5-(4-(2-hydroxyethyl) piperazin-1-ylsulfonyl)-2-n-propoxyphenyl)-5-ethyl-7-n-propyl-3,5-dihydro-4H-pyrrolo[3,2-d]pyrimidin-4-one dihydrochloride) is a novel pyrrolopyrimidinone compound and a potent and reversible PDE5I [10–11]. Several key clinical pharmacokinetic and pharmacodynamic data have revealed that SK3530 has acceptable pharmacologic properties (Table 1). In particular, the selectivity ratios, which express the x-fold differences in inhibitory activity for a specific PDE compared with PDE5, has revealed comparable selectivity of SK3530 with other conventional PDE5Is. A previous preclinical study revealed that the IC_{50} of PDE5 for SK3530 is 10-fold lower than that of sildenafil, a protodrug of PDE5I [10]. In contrast, its inhibitory effects on other phosphodiesterases, such as PDE1 and PDE11, are much lower than those of sildenafil (Table 1) [12]. Moreover, a phase I study revealed that SK3530 is well tolerated at daily doses of up to 200 mg in healthy volunteers (COVANCE, unpublished data, 2003). Thus, the aim of the present trial was to evaluate the effect of on-demand SK3530 therapy at fixed doses (50, 100 and 150 mg) in Korean men with a broad range of ED severity, and to determine the optimal dose with respect to effectiveness and patient tolerance.

2 Materials and methods

2.1 Study design

This phase II, multicenter, randomized, double-blind, placebo-controlled, four-arm, parallel group, fixed dose comparison of 50, 100 and 150 mg SK3530 *vs.* placebo consisted of three parts: 1) a 4-week run-in period without any ED treatment; 2) randomization to 8 weeks of treatment with SK3530 or placebo; and 3) a 1-week follow-up period for continued adverse event monitoring. The eligible patients were men aged 19–70 years with ED, defined as an inability to achieve or maintain a penile erection sufficient for satisfactory sexual intercourse, evident for a period longer than 6 months. To be enrolled in the treatment phase of the study, the patients were required to have experienced a 50% or greater failure rate in maintaining an erection sufficient to complete intercourse on at least four separate attempts during the 4-week treatment-free baseline period. The patients were excluded from eligibility if they were determined by an investigator to have experienced a serious cardiovascular condition within the previous 6 months (e.g., myocardial infarction, unstable angina, a significant electrocardiograph conduction defect, congestive heart failure of New York Heart Association class 2 or greater, or a

Table 1. Comparative key clinical pharmacokinetic and pharmacodynamic data of phosphodiesterase (PDE) inhibitors. AUC, area under curve; C_{max}, maximal drug concentration; IC_{50}, concentration that inhibits 50% of phosphodiesterase; PDE, phosphodiesterase; $T_{1/2}$, half life; T_{max}, time of maximal concentration.

Parameter	SK3530	Sildenafil [12]	Vardenafil [12]	Tadalafil [12]
T_{max} (range, h)	1.4 (0.8–2.0)	1 (0.5–2.0)	0.7 (0.25–3.0)	2 (0.5–6.0)
C_{max} (μg/L) (tested dose)	298.9 (100 mg)	560 (100 mg)	20.9 (20 mg)	378 (20 mg)
AUC (h·μg/L) (dose)	790.7 (100 mg)	1 685 (100 mg)	74.5 (20 mg)	8 066 (20 mg)
$T_{1/2}$ (h)	2.5	3–5	4–5	17.5
IC_{50} for PDE5 (nmol/L)	0.3	3.5–8.5	0.1–0.7	0.94–6.4
IC_{50} for PDE1 (nmol/L)	16 400	41	136	> 1 000
IC_{50} for PDE3 (nmol/L)	86 500	> 1 000	> 1 000	> 1 000
IC_{50} for PDE6 (nmol/L)	10.2	7.4	15	780
IC_{50} for PDE11 (nmol/L)	3750	203	346	7.1

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stroke), or a systolic blood pressure > 170 mmHg or < 90 mmHg, or a diastolic blood pressure > 100 mmHg or < 50 mmHg, or if they were being treated with nitrates. Other exclusion criteria included anatomic abnormalities of the penis that could impair sexual intercourse, hypoactive sexual desire, a history of radical prostatectomy, ED after spinal cord injury, retinitis pigmentosa, chronic liver disease, major hematologic disorder, poorly controlled diabetes (hemoglobin A1c greater than 12 %), or a history of peptic ulcer disease within 1 year. Any patients who had experienced previous ineffective treatment with sildenafil, vardenafil, or tadalafil were also excluded. During the treatment period, the use of anti-androgens, anticoagulants, androgens, drugs affecting cytochrome P450 3A4 (CYP3A4) metabolism, or trazodone hydrochloride were not allowed. The study was conducted at 10 tertiary-care, academically affiliated investigative sites in Korea. The first patient was enrolled in October 2004, and the study was completed in June 2005. The ethics committees of the participating institutions approved the final protocol, amendments, and the informed consent document.

2.2 Treatment

Medical history, a physical examination, laboratory safety tests and an electrocardiogram were carried out during each screening visit. Patients who met all enrolment criteria were randomly allocated to 8 weeks of on-demand treatment. The patients were instructed to take the study medication approximately 1 h before intended sexual intercourse. It was recommended that the drug should be taken at least 1 h after a meal. Medication use was monitored using patient medication/outcome diaries, and the study personnel counted the number of used pills during the assessment visits.

2.3 Measures

Erectile function was measured using the International Index of Erectile Function (IIEF) and the Sexual Encounter Profile (SEP) patient diary. Patients completed the IIEF at the end of the run-in period and at the end of each 4-week treatment period. The erectile function (EF) domain scores at the start of the run-in period were used to determine the baseline ED severity. Patients recorded every sexual attempt in an SEP diary. Global assessment question (GAQ) scores were also assessed.

The primary efficacy measures were changed in the response to IIEF question 3 (Q3: Freguency of penetration) and question 4 (Q4: Freguency of maintained erection). The secondary efficacy end-points were changed between baseline and week 8 in the IIEF EF domain scores, the percentage of "yes" responses to SEP Q2 (penetration), SEP Q3 (successful intercourse) and the GAQ score.

At each patient visit, a safety assessment was carried out that included the recording of adverse events and vital signs. A physical examination with routine laboratory testing was carried out at randomization and at every treatment visit.

2.4 Statistical analysis

An intent-to-treat analysis of each of the efficacy variables included all patients with a baseline and at least one post-baseline observation. The last-observation-carried-forward imputation method was used for missing data. Only variable age was significantly different between the placebo group and each of the SK3530 groups. Therefore, the ANCOVA method, using age and baseline as covariates, was used to evaluate the primary efficacy end-points and all secondary end-points, except for the GAQ.

The GAQ was assessed using the χ^2-test. The testing of the hypotheses included comparisons of each SK3530 dosage group with placebo; therefore, Bonferroni's adjustment was used. Statistical significance was accepted at the $P < 0.05$ level.

The number of patients needed for this study was determined by both primary efficacy variables, IIEF Q3 and Q4. The sample size calculations assumed a standard deviation of 1.06 for Q3 and 1.22 for Q4, as indicated in a previous Korean study on sildenafil [13]. Treatment differences considered to be clinically significant were awarded 1.6 and 1.7 points for each question.

With approximately 23 valid patients per group, this study had the power of approximately 90% for the two questions. Allowance for a 20% withdrawal rate required a total of 116 randomized patients for efficacy analysis, with 29 per group. The safety analysis included all patients who had taken the drug at least once. Changes from baseline in the continuous safety variables (laboratory analysis and vital signs) were evaluated by ANOVA. Between groups, comparisons of treatment-emergent adverse event frequencies were conducted using the χ^2-test. Baseline demographics in the SK3530 and placebo groups were compared using ANOVA for continuous

variables and the χ^2-test for categorical variables.

3 Results

3.1 Patient population and demographics

A total of 119 men at 10 study centers completed the baseline evaluations and were randomized for treatment with placebo (n = 30) or SK3530 at 50 mg (n = 30), 100 mg (n = 30), or 150 mg (n = 29). During the 8 weeks of therapy, five men (4.2%) withdrew from the study: three men (one each in the placebo, 100 mg and 150 mg groups) committed a protocol violation and were excluded; and two men (one each in the 50 mg and 100 mg groups) withdrew because of adverse events. A total of 119 and 116 men were valid for the safety and intent-to-treat analyses, respectively (Figure 1).

At baseline, no clinically or statistically meaningful differences were found among the treatment groups with respect to any demographic or clinical variables except age (P = 0.02). The mean age of the placebo group was lower than that of the SK3530 groups. However, there were no significant differences in age distribution as a categorical variable (P = 0.46; Table 2).

Overall, patients were diagnosed as having ED for a mean of 50.9 months before screening. Of the 119 study subjects, 46 (38.7%) had had previous experience with a PDE5I. However, no significant difference was found among the study groups in this respect. In addition, the distribution of comorbid diseases was not statistically different between treatment groups (P = 0.46 by Fisher's exact test; Table 2).

3.2 Efficacy and treatment satisfaction

At baseline, the mean EF domain scores ranged from

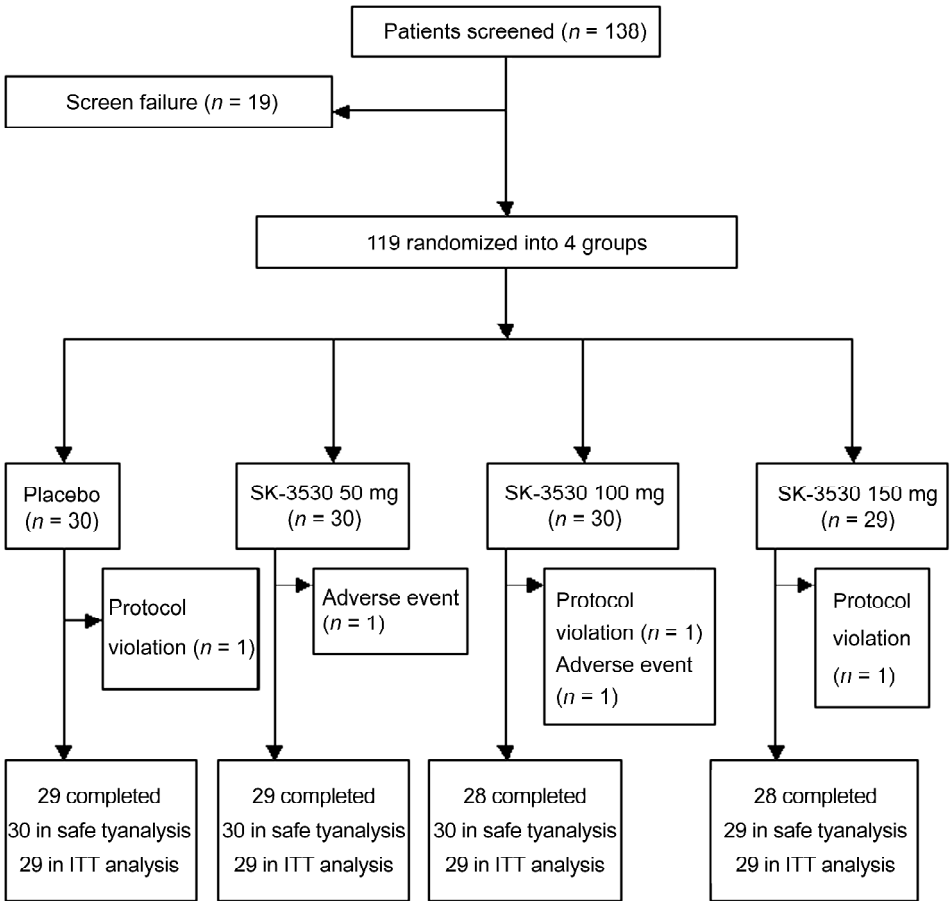

Figure 1. Progress of patients through study to evaluate the efficacy and safety of SK3530, a newly developed type 5 phosphodiesterase inhibitor (PDE5I), in Korean men with erectile dysfunction (ED). ITT, intent-to-treat.

Table 2. Demographics and clinical characteristics of the study group of Korean men with erectile dysfunction (ED) who participated in a phase II trial of SK3530, a newly developed type 5 phosphodiesterase inhibitor (PDE5I). †Data in parentheses indicate percentage. IIEF-EFD, erectile function domain in International Index of Erectile Function.

	Placebo (n = 30)	SK3530		
		50 mg (n = 30)	100 mg (n = 30)	150 mg (n = 29)
Mean age at enrolment (years)	49.7	54.2	55.4	53.6
Median interval since first noticed ED (months)	36.5	37.5	36.0	60.0
Severity of ED (n) stratified by IIEF-EFD†				
Severe (≤ 10)	4 (13.3)	9 (30.0)	6 (20.0)	6 (20.7)
Moderate (11–16)	15 (50.0)	15 (50.0)	16 (53.3)	9(31.0)
Mild (17–25)	11 (36.7)	6 (20.0)	8 (26.7)	14 (48.3)
Etiology (n)†				
Organic	18 (60.0)	18 (60.0)	14 (46.7)	15 (51.7)
Psychogenic	2 (6.7)	3 (10.0)	4 (13.3)	2 (6.9)
Mixed	10 (33.3)	9 (30.0)	12 (40.0)	12 (41.4)
Current alcohol consumption (% Yes)	83	60	70	76
Smoking history (% Yes)	60	67	50	59
Previous experience with PDE5I (n)†	12 (40.0)	13 (43.3)	9 (30.3)	12 (30.0)
Medical history (n)†				
Hypertension	8 (26.7)	11 (36.7)	7 (23.3)	9 (31.0)
Hyperlipidemia	1 (3.3)	2 (6.6)	0 (0.0)	1 (3.3)
Type 2 diabetes	7 (23.3)	4 (13.3)	6 (20.0)	6 (20.7)
Prostatic hyperplasia	3 (10.0)	4 (13.3)	3 (10.0)	5 (17.2)

13 to 15 and there were no significant differences in severity of ED among the groups. After 8 weeks of treatment, the primary efficacy measures, IIEF Q3 and Q4, indicated a significant positive effect for all SK3530 doses compared with placebo ($P < 0.01$; Figure 2). For those taking 100 mg SK3530, the mean Q3 score increased from 2.6 at baseline to 4.4 at week 8, and the mean Q4 score increased from 1.7 at baseline to 3.9 at the same time point.

Similar results were obtained for the secondary efficacy measures (Figure 3). The change from baseline to end-point on the IIEF EF domain (maximal score 30) was 8.4, 10.7 and 8.2 for the 50, 100 and 150 mg groups, respectively, compared with 2.3 for placebo ($P < 0.01$). In addition, SK3530 significantly improved the percentage of successful penetrations (SEP Q2) and successful intercourse completions (SEP Q3) compared with placebo. In the SK3530 treatment groups, the mean SEP Q2 score increase ranged from 28.4% to 37.9% compared with 8.3% in the placebo group ($P < 0.01$). The range of the SEP Q3 increases was 44.9% to 63.2%, significantly greater than that of placebo (18.6%, $P < 0.05$).

The superior efficacies of these doses were maintained during treatment. The beneficial effect of SK3530 was apparent by GAQ analysis (Figure 3). Of the intent-to-treat group, the proportion of affirmative responders to the GAQ was significantly greater for the three SK3530 groups than for the placebo group ($P < 0.01$). At the end of the study, 75.9% of the 50 mg group, 86.2% of the 100 mg group, and 82.1% of the 150 mg group described a positive response to the GAQ *vs*. 34.5% of the placebo group.

SK3530 was able to induce normal EF (EF domain score greater than 25), irrespective of baseline ED severity. After 8 weeks of treatment, 36 men (42.3%) in the treatment group (7 [24.1%] in the 50 mg group, 15 [51.7%] in the 100 mg group, and 14 [48.3%] in the 150 mg group) achieved normal EF compared with 5 men (17.2%) in the placebo group. For those who regained erectile function, 14 (50.0%), 16 (40%), and 6 (28.6%) had mild, moderate, and severe ED at baseline, respectively.

3.3 Safety

In general, SK3530 was well tolerated at all given

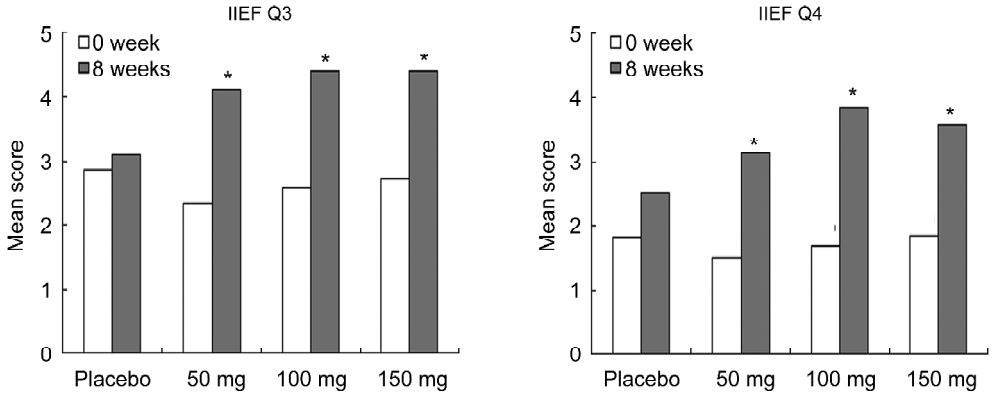

Figure 2. Comparison of primary efficacy variables (questions 3 [Q3] and 4 [Q4] of the International Index of Erectile Function [IIEF]). Compared to placebo, the treatment with SK3530 significantly improved all tested variables regardless of doses. Q3 of IIEF is, "When you attempted sexual intercourse, how often were you able to penetrate your partner?". Q4 is, "During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?". **P* < 0.05 *vs.* placebo.

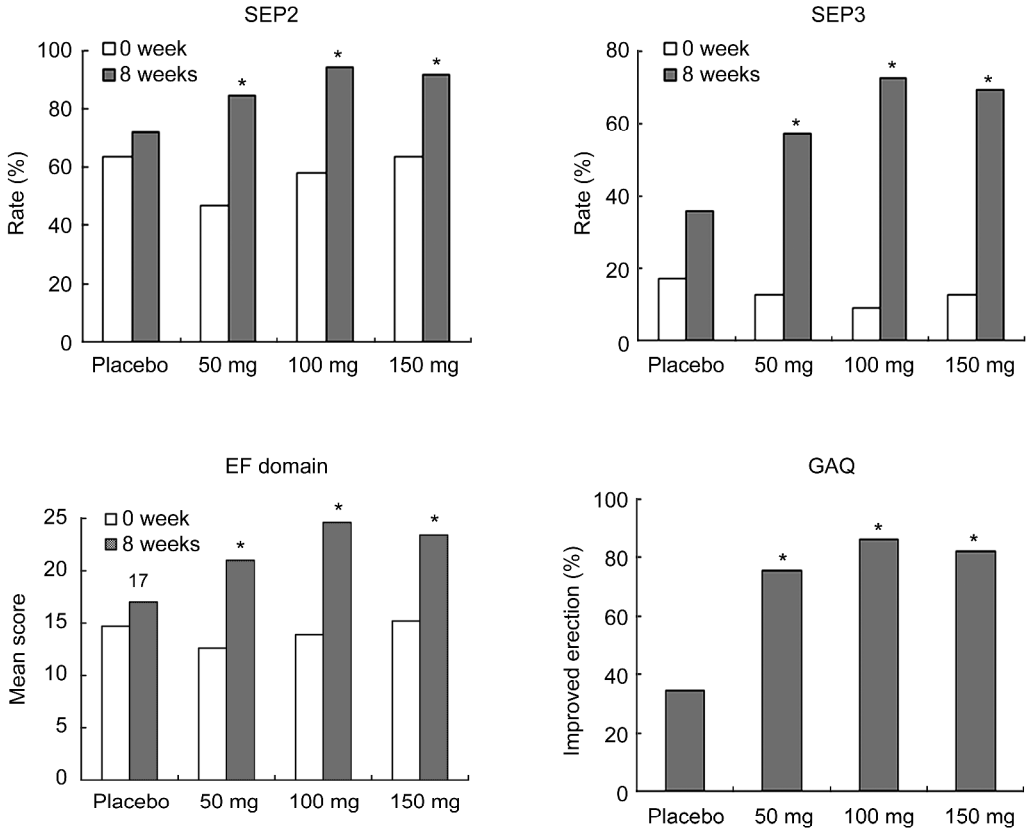

Figure 3. Comparison of secondary efficacy variables (Sexual Encounter Profile [SEP] questions 2 [penetration] and 3 [successful intercourse], erectile function [EF] domain of the International Index of Erectile Function [IIEF], and Global Assessment Question [GAQ]) between placebo and various treatment groups. Three SK3530 groups showed significantly superior improvement in various aspects of EF to placebo following 8 weeks of treatment. **P* < 0.05 *vs.* placebo.

Table 3. Summary of treatment-related adverse events in study group of Korean men with erectile dysfunction who participated in a phase II trial of SK3530, a newly developed type 5 phosphodiesterase inhibitor (PDE5I). $^{*}P < 0.05$ *vs.* placebo.

Drug-related adverse event	Placebo	SK3530 50 mg	SK3530 100 mg	SK3530 150 mg
Flushing	0	5	2	6
Headache	0	1	2	6
Eye redness	0	1	1	1
Dizziness	1	0	1	1
Nasal congestion	0	0	1	1
Epigastric soreness	0	0	1	1
Other	0	2	3	4
Total	1	9*	11*	20*

doses. Although the 150 mg group experienced significantly more treatment-emergent adverse events, all adverse events were mild or moderate in intensity (Table 3). The most common treatment-emergent adverse events were 13 cases (10.9%) of facial flushing, 9 (7.6%) of headache, and 3 (2.5%) of dizziness and eye redness.

Two men withdrew from the study because of adverse events (one in the 50 mg group and one in the 100 mg group). No clinically significant changes in the laboratory parameters or vital signs occurred.

4 Discussion

The results of this study indicated that SK3530 dosages of 50, 100 and 150 mg are significantly superior to placebo for the treatment of ED, as determined by the primary study end-points of IIEF Q3 and Q4. In both questions, the mean increases from baseline ranged from 1.6 to 2.2, significantly greater than that for placebo (range, 0.2–0.7). Also, all doses of SK3530 were significantly superior to placebo for the various secondary study end-points (EF domain score, diary-recorded success rates for penetration and maintenance of erection during intercourse, and the GAQ).

The results are quite comparable to those of a previous phase III trial of sildenafil in a similar population. Choi *et al*. [13] reported results after 8 weeks of sildenafil treatment with a flexible dosing regimen. The changes in IIEF Q3 and Q4 from baseline were 1.6 and 1.9, respectively. Treatment-related adverse events were observed in 56% of the sildenafil arm. Our study adopted a fixed dose regimen and included 39% of patients who had experienced other PDE5Is. Comparison with the results from the previous Korean study supports the belief that SK3530 might be at least as efficacious as sildenafil.

One of the interesting findings was that SK3530 enabled approximately 42% of patients to achieve normal EF; 50% of patients with mild ED and up to 29% of patients with severe ED who received SK3530 achieved normal EF (as determined from EF domain scores greater than 25). As was stressed by Mulhall [14], the percentage of those regaining normal EF can be clinically meaningful when comparing the efficacy of the drug evaluated. Despite the difference in dosing design and treatment duration, our results were comparable with previous trials of vardenafil and tadalafil [15, 16]. SK3530 was well tolerated. The adverse events often noted with its use, flushing, headache, dizziness, and eye redness, were expected from the pharmacology of PDE5Is [17] and the results from clinical trials of other PDE5Is [15, 16]. All of the adverse events recorded for patients in the present trial were mild or moderate in severity and typically resolved with continued use of the drug. Only two patients discontinued during the study period because of adverse events. Given the nature of fixed dosing, which disallowed dose reductions resulting from poor tolerability, this finding might be additional evidence of the safety of SK3530.

Concerns might be raised regarding the benefit of a new PDE5I with similar efficacy and safety to pre-existing ones. However, a number of studies have indicated that preference for a medication depends on factors other than efficacy, safety and tolerability [12, 18]. Besides efficacy and safety, preference could be determined by factors such as mode of action, duration, food interaction, and cost. Therefore, we believe that the addition of a new PDE5I that has a unique pharmacologic profile would benefit someone that was not satisfied with their current medication.

Concurrent medical diseases such as hypertension and diabetes could affect the response to PDE5Is. Therefore, the number of patients with various comorbidities should be equally distributed between the tested groups. This is not always the case, especially in a trial with a small number of patients. Fortunately, each group in this study was balanced in terms of the number of patients with comorbidities. If there is any concern about unequal distribution between groups regarding the number or severity of comorbidities, the use of validated

comorbidity indices, such as the Charlson comorbidity index [19], might be of help .

Another important aim of this phase II study was to determine the optimal dosage of SK3530. The efficacy and safety results showed that 100 mg and 50 mg were associated with the greatest efficacy and lowest adverse events, respectively. Thus, it would be rational to examine the efficacy and safety of 50 mg and 100 mg dosing in a future phase III study.

This multicenter, randomized, double-blind, placebo-controlled phase II trial showed that SK3530 safely improved all efficacy parameters of erection in a broad population of men with ED of varying etiologies and severity. The most efficacious and safest doses were determined to be 100 mg and 50 mg, respectively.

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