A Therapeutic Confirmatory Study to Assess the Safety and Efficacy of Zydena® (Udenafil) for the Treatment of Erectile Dysfunction in Male Patients with Diabetes Mellitus

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ABSTRACT

Introduction. Patients with diabetes mellitus (DM) are reported to experience more severe erectile dysfunction (ED) symptoms and respond less to ED treatments compared with patients with ED of other etiologies.
Aim. This study was undertaken to evaluate the safety and efficacy of udenafil for the treatment of ED in a larger number of patients with DM.
Methods. A placebo-controlled, randomized, double-blind, double-dummy, parallel-group design multicenter study, fixed-dose trial was conducted. The trial involved seven study sites in Korea, with 174 ED patients with DM. The subjects, treated with placebo, 100 mg, or 200 mg of udenafil for 12 weeks, were asked to complete the International Index of Erectile Function (IIEF), the Sexual Encounter Profile (SEP) diary, and the Global Assessment Question (GAQ) during the study period.
Main Outcome Measures. The primary efficacy parameter was the change in the erectile function domain (EFD) score of IIEF from baseline. Secondary parameters were IIEF questions 3 (Q3) and Q4, SEP Q2 and Q3, rate of achieving normal erectile function (EFD ≥ 26), and the response to GAQ.
Results. Compared with the placebo, patients receiving both doses of udenafil showed statistically significant improvements in the IIEF-EFD score, respectively. However, statistically significant difference was not observed between the udenafil 100 mg and the udenafil 200 mg groups. Similar results were observed in the comparison of Q3 and Q4 of IIEF, SEP diary, and GAQ. The percentages of subjects experiencing at least one adverse event related to the study drugs were 3.6%, 15.8%, and 22.4% for the placebo, udenafil 100 mg, and udenafil 200 mg groups, respectively. However, these events were all mild in severity. Major adverse events were flushing, headache, nausea, and conjunctival hyperemia.
Conclusion. Udenafil was significantly effective for the treatment of ED, demonstrating statistically significant improvement in erectile function in patients with DM. The incidence of adverse events was relatively low and well tolerated in patients with DM. **Moon DG, Yang DY, Lee CH, Ahn TY, Min KS, Park K, Park CK, and Kim JJ. A therapeutic confirmatory study to assess the safety and efficacy of Zydena® (udenafil) for the treatment of erectile dysfunction in male patients with diabetes mellitus. J Sex Med 2011;8:2048–2061.**

Key Words. Erectile Dysfunction; Udenafil; Diabetes Mellitus; Pharmacotherapy for Erectile Dysfunction in Men With Diabetes

Introduction

Erectile dysfunction (ED) is defined as the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual intercourse. ED is reported to affect as many as 152 million men worldwide [1] with an overall prevalence of 13.4% among Korean middle-aged men [2]. ED is a common complication of diabetes mellitus (DM), affecting about 35–75% of men diagnosed with DM [3–6]. In patients with DM, ED is caused by various etiologies, including vascular, neurogenic, drug-induced, and psychogenic. In addition, other organs are also affected in patients with DM, often resulting in serious cardiovascular, neurologic, and renal complications. Therefore, male patients with DM are reported to experience more severe ED symptoms and respond less to ED treatments compared with patients with ED of other etiologies [7].

Currently, oral ED agents are the most widely prescribed for pharmacotherapy of ED because of their convenience of use and good efficacy. Udenafil is a novel pyrazolopyrimidinone compound developed by Dong-A Pharmaceutical Co., Ltd (Seoul, South Korea) for the treatment of ED, which shares the same mechanism of action with sildenafil [8]. In previous studies of udenafil with doses of 100 mg and 200 mg, taken as needed 30 minutes to 12 hours before the sexual intercourse, the good efficacy of udenafil was demonstrated for the treatment of ED of various etiologies, as well as excellent safety and tolerability [9]. However, the present phase III study was undertaken to evaluate the safety and efficacy of udenafil for the treatment of ED in a larger number of patients with DM.

Methods

Study Population

One hundred and seventy-four ED patients were enrolled and randomized. The enrollment took place at seven institutions in Korea, all of which received the approval by the institutional review board and the local ethical committee (Korean Food and Drug Administration) to carry out the study. The inclusion criteria were male patients 19 years of age and older with type 1 or type 2 DM and with a diagnosis of ED for at least 6 months and those who had a stable sexual relationship with a female partner and could fully understand the study and give a written informed consent voluntarily prior to the participation in the study. We excluded patients with a history of stroke, myocardial infarction or coronary artery bypass graft, cardiac failure, unstable angina or life-threatening arrhythmia, serious hypoglycemia within the last 6 months, and diabetic ketoacidosis within the last 3 years. Also excluded were patients with current poorly controlled DM (glycosylated hemoglobin [HbA_{1C}] > 12%), proliferative diabetic retinopathy, hepatic or renal dysfunction, retinitis pigmentosa, resting hypotension (diastolic/systolic blood pressure [DBP/SBP] < 50/90 mm Hg) or uncontrolled hypertension (DBP/SBP > 100/170 mm Hg), anatomical deformities of the penis (e.g., severe cavernosal fibrosis, Peyronie's disease), and conditions accompanied by hyperprolactinemia or hypotestosteronemia. Also excluded were patients with a history of DM secondary to pancreatic injury, Cushing's disease or acromegaly, spinal cord injury, radical prostatectomy or radical pelvic surgery, and hematological (pancytopenia, multiple myeloma, and leukemia) or bleeding disorders that may predispose to priapism or serious gastrointestinal bleeding (e.g., active peptic ulceration) within the previous 12 months. Significant psychiatric disorders or drug abuse considered by the investigator inappropriate to participate in the study; current anticancer chemotherapy; use of anticoagulants; intake of drug or food known to inhibit the major cytochrome P450 enzymes in human liver microsomes; use of androgens (e.g., testosterone) or antiandrogens; use of trazodone; use of ED treatments within the last 2 weeks including phosphodiesterase type 5 inhibitors (PDE5Is) (such as Viagra®, Levitra®, or Cialis®), intracavernous self-injection of local vasodilator, and other ED treatments, were additional reasons for exclusion. All patients provided written informed consent before participation.

Patient Disposition

A total of 225 patients gave written informed consent to participate in this study and underwent screening examinations (Figure 1). Of these, 51 patients were excluded. Among 174 subjects who were found eligible and who enrolled in the study, four subjects discontinued the study before the administration of the study drug because of withdrawal of consent. Thus, a total of 170 subjects took at least one dose of the double-blind treatment randomized to each subject.

The primary reasons for excluding 51 volunteers from participating in this study were as follows: subject's withdrawal of consent, ineligibility determined at screening tests, hyperpro-
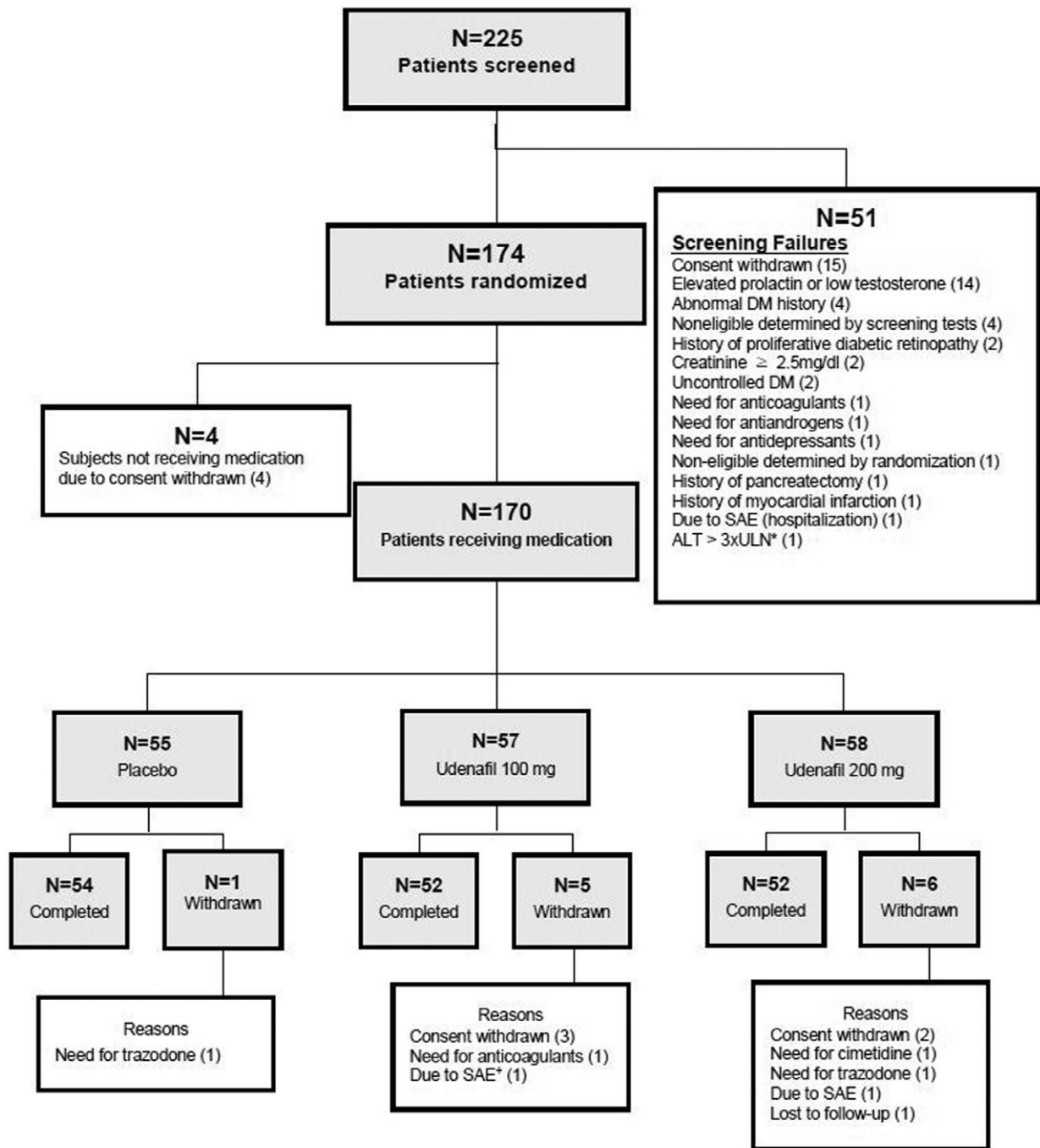
Figure 1 Disposition of patients.

lactinemia and hypotestosteronemia, incompatibility with the diabetes criteria, history of proliferative diabetic retinopathy, and serum creatinine ≥ 2.5 mg/dL.

Among a total of 174 subjects enrolled in the study, with the exception of the four subjects who withdrew consent for the study before the administration of study drug, 170 subjects were treated

with placebo, udenafil 100 mg, or udenafil 200 mg. Of these 170 subjects, 12 subjects discontinued the study and 158 subjects completed the study. The number of completed subjects for each group was 54, 52, and 52 for the placebo, udenafil 100 mg, and udenafil 200 mg groups, respectively. The number of subjects who discontinued the study was one, five, and six for the placebo, udenafil 100 mg, and udenafil 200 mg groups, respectively. Primary reasons for 12 cases of study discontinuation were withdrawal of consent not due to adverse events (five subjects), serious adverse events definitely not related to investigational products (one subject as adjustment disorder caused by psychological stress due to personal circumstance and one subject as angina pectoris occurred during exercise after about 102 hours postdose; total of two subjects), use of prohibited medications (anticoagulant, cimetidine, and trazodone; four subjects), and failure to return (one subject).

Patient Demographics and Characteristics

As shown in Table 1, there were no significant differences among the three treatment groups with respect to demographic data and baseline characteristics. The treatment groups were well balanced in terms of age (range 34–73 years), height (158 –185 cm), and weight (49–109 kg). They showed no significant intergroup differences. With respect to baseline interview, a history of ED and HbA_{1C} level, significant difference was not observed between treatment groups.

Statistically significant differences were observed between the study sites with respect to smoking history, duration of ED, etiology of ED, and prior use of PDE5Is. Thus, the adjustments for these intersite differences at baseline were considered for efficacy analysis.

Regarding current comorbid conditions, patients with genitourinary disorders occupied the highest proportion (17.0%). No subject had any history of allergy and two (3.6%) subjects of the placebo group had a history of drug hypersensitivity.

Study Design

This was a placebo-controlled, randomized, double-blind, double-dummy, parallel-group design, multicenter study, fixed-dose trial of

Table 1 Demographics and baseline characteristics of study subjects

	Placebo (N = 57)		Udenafil 100 mg (N = 58)		200 mg (N = 59)		Total (N = 174)		P value[a]
Demographics	Mean ± SD, min, and max								
Age (year)	54.89 ± 8.18		55.47 ± 8.54		54.44 ± 7.92		54.93 ± 8.18		0.7961
Height (cm)	168.95 ± 4.33		169.84 ± 5.23		169.41 ± 4.96		169.40 ± 4.84		0.6129
Weight (kg)	70.29 ± 8.03		72.52 ± 11.13		70.68 ± 9.29		71.16 ± 9.57		0.4113
Baseline interview									
Smoking history—no. (%)									
Current smoker	16	(28.1)	21	(36.2)	17	(28.8)	54	(31.0)	0.5140
None	22	(38.6)	16	(27.6)	16	(27.1)	54	(31.0)	
Past smoker	19	(33.3)	21	(36.2)	26	(44.1)	66	(37.9)	
Current alcohol consumption—no. (%)									
Yes	35	(61.4)	36	(62.1)	42	(71.2)	113	(64.9)	0.4643
No	22	(38.6)	22	(37.9)	17	(28.8)	61	(35.1)	
ED history									
ED duration (year)	3.67 ± 2.93		3.48 ± 2.47		3.22 ± 2.83		3.45 ± 2.74		0.6800
ED etiology—no. (%)									
Organic	42	(73.7)	43	(74.1)	43	(72.9)	128	(73.6)	0.9879
Psychogenic	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	
Mixed	15	(26.3)	15	(25.9)	16	(27.1)	46	(26.4)	
Baseline severity (Erectile function domain score)—no. (%)									
Severe (≤10)	16	(28.1)	18	(31.0)	16	(27.1)	50	(28.7)	0.3543
Moderate (11–16)	31	(54.4)	22	(37.9)	27	(45.8)	80	(46.0)	
Mild-Moderate (17–21)	9	(15.8)	17	(29.3)	12	(20.3)	38	(21.8)	
Mild (22–25)	1	(1.8)	1	(1.7)	4	(6.8)	6	(3.5)	
Prior use of other PDE5 inhibitors—no. (%)	33	(57.9)	33	(56.9)	35	(59.3)	101	(58.1)	0.9649
Diabetes test									
HbA_{1C}									
<7.0%	23	(40.4)	30	(51.7)	26	(44.1)	79	(45.4)	0.5048
7.0% to 9.5%	28	(49.1)	20	(34.5)	28	(47.5)	76	(43.7)	
9.5% to 12.0%	6	(10.5)	8	(13.8)	5	(8.5)	19	(10.9)	

[a]*P* values were calculated using chi-square or Fisher's exact tests for comparison of subject numbers and ANOVA for comparison of mean values.
ED = erectile dysfunction; HbA_{1C} = glycosylated hemoglobin; PDE5 = phosphodiesterase type 5.

Table 2 Evaluation and visit schedule

	Run-in period						
Study period	Screening	Baseline	Treatment period			Follow-up call	
Visit number	1	2	3	4	5	(6–7 days	Premature
Week	−4	0	4	8	12	after treatment)	discontinuation
Inclusion/exclusion criteria	•						
Medical history	•						
Body weight	•				•		•
Randomization		•					
Dispense study medication*		•	•	•			
Vital signs†	•	•	•	•	•		•
Physical examination	•						
Laboratory evaluation‡	•				•		•
Diabetes test (HbA$_{1C}$)§	•				•		•
Serology¶	•						
Hormone assay**	•						
ECG††	•				•		•
IIEF questionnaire‡‡		•	•	•	•		•
Life satisfaction§§		•			•		•
GAQ¶¶					•		•
Handout of patient diary cards	•	•	•	•			
Collection of patient diary cards		•	•	•	•		•
Adverse events		•	•	•	•	•	•

*Subjects were instructed to take study medication 30 minutes to 12 hours before intended sexual intercourse.
†Blood pressure and pulse rate were measured at screening and weeks 0, 4, 8, and 12 visits.
‡Included hematology/blood coagulation, blood chemistry, and urinalysis. Laboratory evaluations were done at screening and week 12 visits.
§HbA$_{1C}$ was measured at screening and week 12 visits.
¶Serological tests (for human immunodeficiency virus and hepatitis B/C) were done only at screening visit.
**Serum concentrations of prolactin and total testosterone were measured only at screening.
††ECGs were measured at screening and week 12 visits.
‡‡Performed at week 0 for establishment of baseline values and at each visit during the treatment period (weeks 4, 8 and 12).
§§Performed at week 0 and at the end of the treatment period (week 12).
¶¶Performed at the end of the treatment period (week 12).
ECG =electrocardiogram; GAQ = Global Assesment Question; HbA$_{1C}$ = glycosylated hemoglobin; IIEF = International Index of Erectile Function.

udenafil in male patients with ED and DM. At the end of a 4-week treatment-free run-in period, patients who were found eligible at screening were randomized to one of three treatments (placebo, udenafil 100 mg, and udenafil 200 mg) using a double-blinded method. The evaluation and visit schedule of this study are detailed in Table 2. Study subjects were instructed to visit the study site every 4 weeks during the 12-week treatment period. One follow-up telephone call was scheduled 6–7 days after the completion of the treatment period. To be eligible for randomization at visit 2 (week 0) following the completion of the run-in period, all patients had to meet the following conditions: (i) patients had attempted sexual intercourse at least four times on four separate days during the 4 weeks of the run-in period, experiencing a failure rate of ≥50%; and (ii) erectile function domain (EFD) score was ≤25, according to the International Index of Erectile Function (IIEF) evaluation administered at visit 2 (week 0). Each subject was required to return to the study site every 4 weeks during the 12-week treatment period. Afterwards, a poststudy call was scheduled 6–7 days after completing the treatment period.

Main Outcome Measures

Efficacy

For efficacy assessment, all subjects were required to provide answers to 15 questions of IIEF questionnaire at visits 2, 3, 4, and 5, respectively. At each visit, the study subject was asked to submit the patient diary card, which contained information about the intake of the study medications and the attempts for sexual intercourse for the past 4 weeks to the investigator. After each sexual attempt, subjects were required to answer five questions of Sexual Encounter Profile (SEP) on the patient diary card dispensed at each visit (visits 1 to 4). The primary efficacy parameter was the 12-week change from baseline for an IIEF EFD score calculated as the sum of the scores from Q1 to Q5 and Q15. The secondary efficacy parameters were the 12-week change from baseline in the IIEF Q3 and Q4, and the mean per-patient percentage of "yes" responses to Q2 and Q3 of SEP diary asking, "Were you able to insert your penis into your partner's vagina?" (SEP Q2) and "Did your erection last long enough for you to have a successful intercourse?" (SEP Q3). The

additional secondary efficacy parameters included the response to the Global Assessment Question (GAQ), "Has the treatment you have taken over the past 4 weeks improved your erection?" (The answer to which was "yes" or "no") and the percentage of patients reaching EFD score consistent with normal erectile function (EF $\geq$ 26).

Safety

After obtaining written informed consent, adverse events experienced by the study subjects were evaluated by the investigator at each visit during the study. Any changes in the subjects' conditions and all cases of adverse events occurring during study period were recorded in detail. In addition to the subjects' voluntary reports, the occurrence of adverse events were sought by the investigator's nondirective questioning of the patient at each visit and detected through vital signs (sitting/standing blood pressure and pulse rate), physical examination, laboratory test (hematology, blood chemistry, and urinalysis), 12-lead electrocardiograms or other assessments. All information about each adverse event, including signs and symptoms, duration, severity grade, causal relationship to the study drug, actions taken, and the outcome were described in detail in adverse event section of the case report form.

Statistical Analysis

Data analysis of this study was done using two different methods: an intention-to-treat (ITT) analysis and a per-protocol (PP) analysis. Among all the subjects enrolled in the study, the ITT analysis was performed for the subjects with adequate data for efficacy evaluation. For PP analysis, data obtained from those who were included in the ITT analysis and completed the study without any major protocol deviation were used.

When a missing value occurred for an efficacy variable or a subject withdrew prematurely before the completion of the study, the last observation carried forward method, in which a missing value was replaced by the most recent postbaseline measurement was used. As the purpose of this study was to demonstrate the superior efficacy of udenafil compared with placebo, the ITT analysis was adopted as the primary statistical analysis.

For analysis of intragroup changes between visits and intergroup differences, repeated measures analysis of variance (RM ANOVA) and ANOVA were used, respectively. For multiple comparisons, Duncan's multiple range test was used. The differ-

ences between the groups in the assessment of GAQ and the proportion of achieving normal EF were compared using the chi-square test. All tests of statistical significance were two-tailed at the 0.05 significant level ($\alpha = 0.05$) and all statistical analyses were carried out using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA).

Additionally, subgroup analysis was planned to investigate significantly effective covariates on the primary efficacy variable. Thus, analysis of covariance (ANCOVA) was used for each covariate (the presence of hypertension, duration of ED, prior use of PDE5Is, HbA_{1C} 3 level), which was expected to have effect on the primary efficacy variable of changes from baseline for EFD score. Classification of each subgroup was defined appropriately by considering the actual distribution of study data.

Results

Efficacy

Following adjustments for the significant intersite differences in the demographic data and baseline characteristics, statistically significant differences in the primary efficacy values were not observed between study sites ($P = 0.0527$). This indicated that although all covariates are not well balanced among study sites, the imbalance between sites is not large enough to interfere with the evaluation of primary efficacy variable. Accordingly, the efficacy analyses were done without adjusting for the intersite differences.

With respect to the primary efficacy endpoint (mean change from baseline for EFD score), both ITT and PP analyses using ANOVA model indicated significant differences in mean change from baseline for EFD score at week 12 visit across all treatment groups ($P < 0.0001$) (Figure 2). Duncan's multiple range test also indicated statistically significant improvements in both udenafil 100 mg and 200 mg groups vs. the placebo group (ITT and PP analyses, $P < 0.001$), but no significant dose-related difference between the udenafil 100 mg and 200 mg groups (ITT analysis, $P = 0.6335$; PP analysis, $P = 0.6850$) For both ITT and PP populations, intragroup analysis of the differences between visits indicated that statistically significant improvements in EFD scores were observed in patients on udenafil 100 mg and 200 mg, but not in patients on placebo. That is, significant change from baseline for EFD score was observed at weeks 4, 8, and 12 of treatment in the udenafil 100 mg and 200 mg groups (ITT and
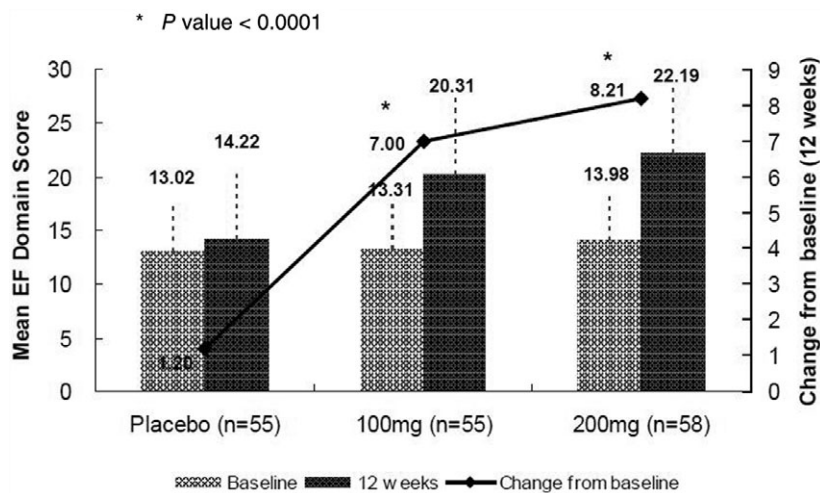
Figure 2 Primary efficacy endpoints: erectile function domain scores at baseline and week 12. There were statistically significant improvements in both udenafil 100 mg and 200 mg groups vs. the placebo group, but no significant dose-related difference between the udenafil 100 mg and 200 mg groups.

PP analyses, $P < 0.0001$), but not in the placebo group (ITT analysis, $P = 0.1655$; PP analysis, $P = 0.4620$).

With respect to the secondary efficacy endpoints (mean changes from baseline for IIEF Q3 and Q4, each domain of other IIEF questions, SEP Q2 and Q3, GAQ, and percentage of patients achieving normal EF [EFD score ≥ 26]), statistically significant improvements were observed in the udenafil 100 mg and 200 mg groups, compared with the placebo group by both ITT and PP analyses.

Intergroup comparison of mean changes from baseline for responses to IIEF Q3 and Q4 indicated statistically significant differences in patients on udenafil 100 mg and 200 mg, compared with patients on placebo (ITT analysis, $P < 0.0001$ for

Q3 and Q4; PP analysis, $P = 0.0003$ for Q3, $P < 0.0001$ for Q4). Intragroup comparison of changes of responses to IIEF Q3 and Q4 between visits indicated statistically significant improvements for both udenafil 100 mg and 200 mg groups, but not for the placebo group (ITT and PP analyses, $P < 0.0001$ for Q3 and Q4) (Figures 3 and 4).

Changes from baseline at week 12 for responses to other questions of IIEF questionnaire (intercourse satisfaction [IS], orgasmic function [OF], sexual desire [SD], and overall satisfaction [OS]) were compared between treatment groups using ANOVA, and intragroup changes between visits were analyzed using RM ANOVA. Intergroup comparisons in both ITT and PP populations indicated
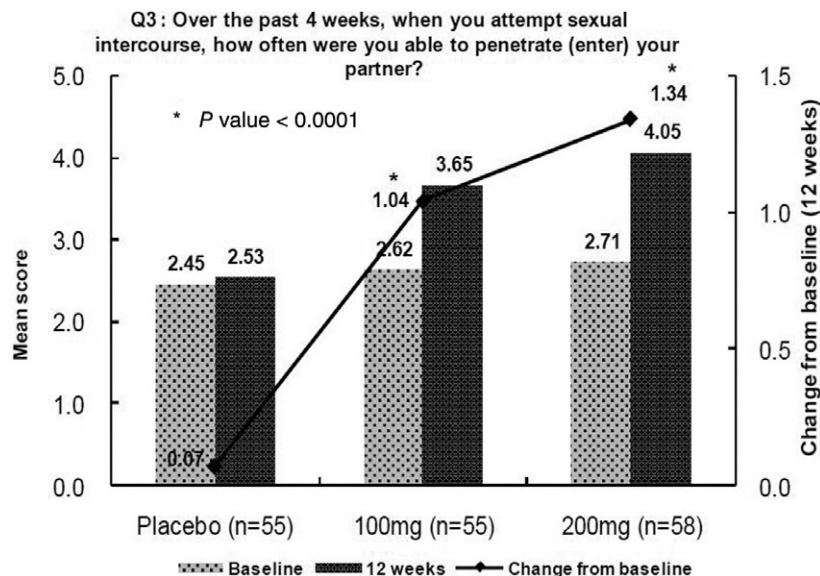

Figure 3 Secondary efficacy endpoints: mean change from baseline for response to International Index of Erectile Function (IIEF) question 3 (Q3). Intergroup comparison of mean changes from baseline for responses to IIEF Q3 indicated statistically significant differences in patients on udenafil 100 mg and 200 mg, compared with patients on placebo (ITT analysis, $P < 0.0001$).

Figure 4 Secondary efficacy endpoints: mean change from baseline for responses to International Index of Erectile Function (IIEF) question 4 (Q4). Intergroup comparison of mean changes from baseline for responses to IIEF Q4 indicated statistically significant differences in patients on udenafil 100 mg and 200 mg, compared with patients on placebo (ITT analysis, $P < 0.0001$).
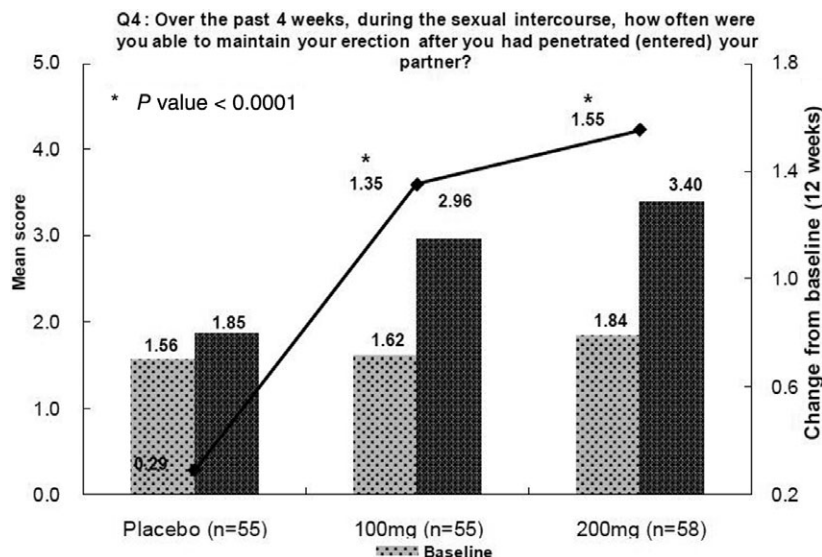
statistically significant changes for all domains of IIEF across all treatment groups: IS domain (ITT and PP analyses, $P < 0.0001$), OF domain (ITT analysis, $P = 0.0003$; PP analysis, $P = 0.0004$), SD domain (ITT analysis, $P = 0.0327$; PP analysis, $P = 0.0048$), and OS domain (ITT and PP analyses, $P < 0.0001$). Duncan's multiple range tests also showed significant improvements in all domains of IIEF questionnaire for both udenafil 100 mg and 200 mg groups compared with the placebo group. However, significant dose-related differences were not observed between the udenafil 100 mg and 200 mg groups (Figure 5).

The rates of "yes" responses to Q2 and Q3 of the SEP diary (i.e., success rates) were compared within and between treatment groups and the results are presented in Figures 6 and 7. At baseline, 49.53% of placebo group, 53.04% and 55.60% of the treatment groups answered "yes" to the SEP Q2, and there was no significant difference among the three groups ($P > 0.05$) (Figure 6). In the case of SEP Q3, 7.5% of the placebo group, 7.16% and 7.44% of the men in the treatment groups could maintain erection long enough to complete intercourse with ejaculation at baseline (Figure 7). Intergroup comparison by ANOVA indicated statistically significant differences (ITT and PP analyses, $P < 0.0001$). Duncan's multiple range tests also indicated significant improvements in the udenafil 100 mg and 200 mg groups compared
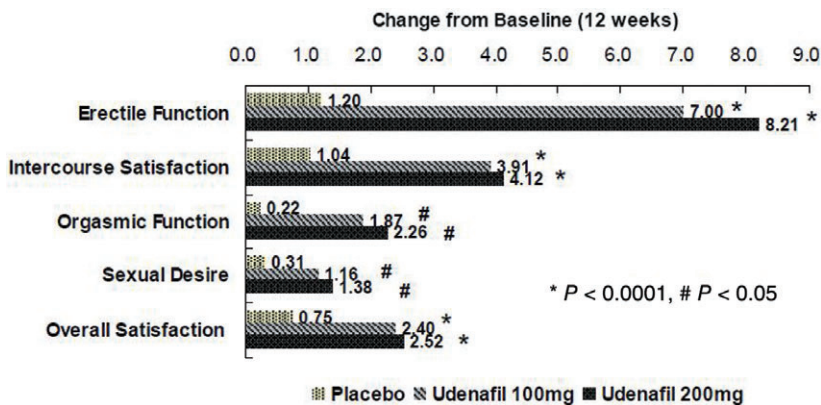

Figure 5 Secondary efficacy endpoints: mean change from baseline for each domain of IIEF There were statistically significant changes for all domains of International Index of Erectile Function (IIEF) across all treatment groups: intercourse satisfaction domain ($P < 0.0001$), orgasmic function domain ($P = 0.0003$), sexual desire domain ($P = 0.0327$), and overall satisfaction domain ($P < 0.0001$). Duncan's multiple range tests also showed significant improvements in all domains of IIEF questionnaire for both udenafil 100 mg and 200 mg groups compared with the placebo group. However, significant dose-related differences were not observed between the udenafil 100 mg and 200 mg groups.
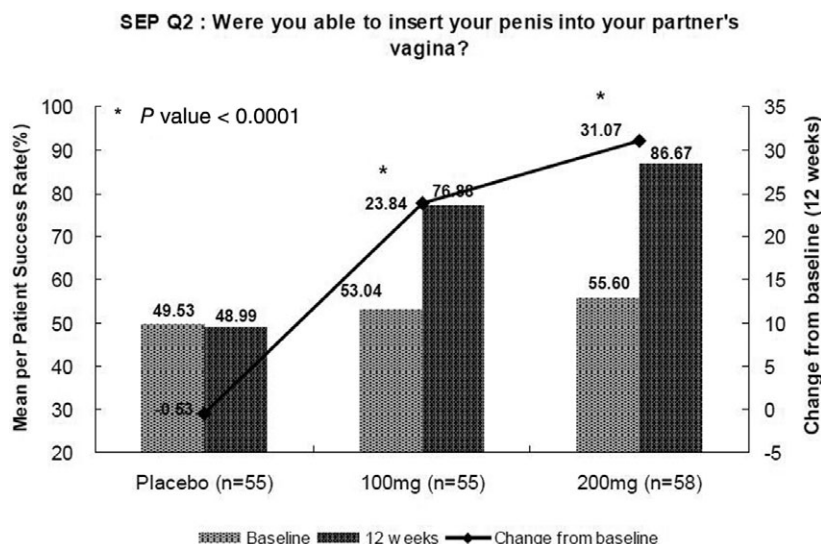
SEP Q2 : Were you able to insert your penis into your partner's vagina?

Figure 6 Secondary efficacy endpoints: response to Sexual Encounter Profile (SEP) question 2 (Q2; penetration rate). The change from baseline at week 12 revealed statistically significant changes for SEP Q2 in the udenafil 100 mg and 200 mg groups, compared with the placebo group ($P < 0.0001$).

with the placebo group. Intragroup paired *t*-test of the change from baseline at week 12 revealed statistically significant changes for SEP Q2 and Q3 in the udenafil 100 mg and 200 mg groups, compared with the placebo group (ITT and PP analyses, $P < 0.0001$).

The proportion of subjects who answered "yes" to the GAQ at week 12, which measured the improvement of erections for the past 4 weeks of treatment in response to a global question, was compared between treatment groups using chi-square test. The results are presented in Figure 8. Significant intergroup differences were observed among treatment groups (ITT and PP analyses, $P < 0.0001$). The proportion of responders who affirmatively answered the GAQ was significantly greater for patients on udenafil (100 mg and 200 mg groups combined) than for those on placebo (ITT and PP analyses, $P < 0.0001$).

The percentage of patients reaching postbaseline EFD scores consistent with normal EF (≥ 26) from the baseline scores ≤ 25 was compared between treatment groups using chi-square tests. The results are presented in Figure 9. Significant differences were observed among treatment groups (ITT and PP analyses, $P < 0.0001$), indicating significantly higher percentage of patients achieving normal function for patients on udenafil (100 mg and 200 mg groups combined) than for those on placebo (ITT and PP analyses, $P < 0.0001$). The percentage of patients achieving normal EF at week 12 was higher for patients on udenafil 200 mg than for patients on 100 mg, but the difference was not statistically significant.

With respect to life satisfaction, ITT and PP analyses indicated that the response to "sexual life" was significantly improved in the udenafil 100 mg and 200 mg groups, compared with the placebo
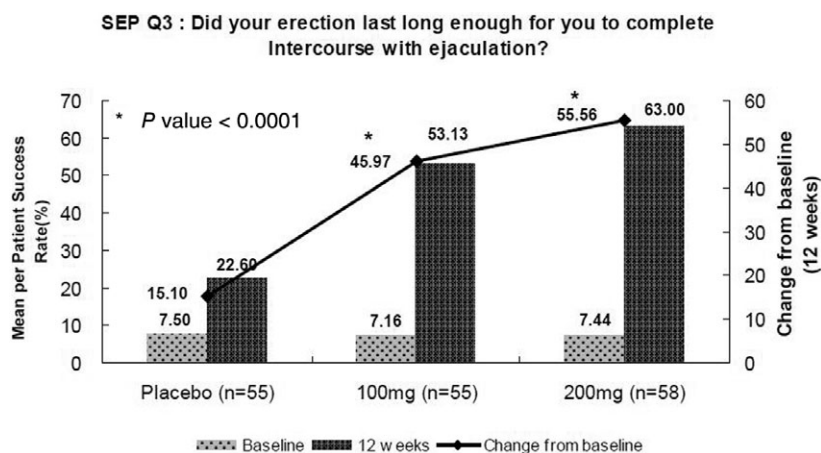
SEP Q3 : Did your erection last long enough for you to complete Intercourse with ejaculation?

Figure 7 Secondary efficacy endpoints: response to Sexual Encounter Profile (SEP) question 3 (Q3; intercourse success rate). The change from baseline at week 12 revealed statistically significant changes for SEP Q3 in the udenafil 100 mg and 200 mg groups, compared with the placebo group ($P < 0.0001$).

Figure 8 Secondary efficacy endpoints: Global Assessment Question (GAQ; satisfaction with erection quality) at week 12. Significant intergroup differences were observed among treatment groups (*P* < 0.0001). The proportion of responders who affirmatively answered the GAQ was significantly greater for patients on udenafil (100 mg and 200 mg groups combined) than for those on placebo (*P* < 0.0001).

GAQ : Has the treatment you have been taking over the past 4 weeks improved your erection?
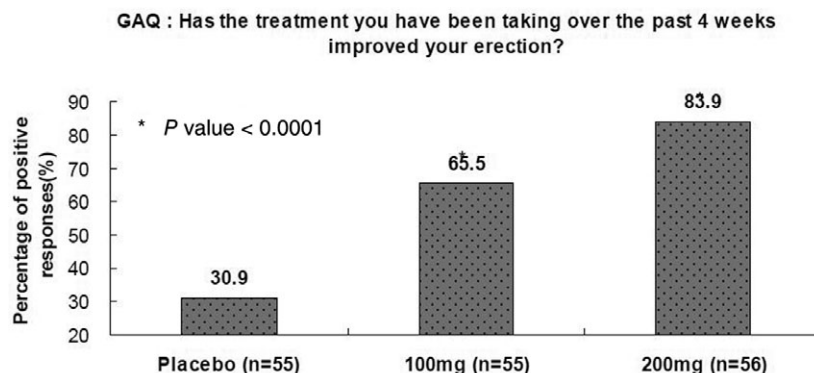
group, but there were no dose-related differences between the udenafil 100 mg and 200 mg groups (Figure 10). With respect to the presence of hypertension, at week 12, significant differences in changes from baseline for EFD scores were not observed according to the history of hypertension (ITT analysis, *P* = 0.8090; PP analysis, *P* = 0.4076). With respect to the duration of ED, at week 12, significant differences in changes from baseline for EFD scores were not observed according to the duration of ED (ITT analysis, *P* = 0.4020; PP analysis, *P* = 0.4157). Also, with

Figure 9 Secondary efficacy endpoints: percentage of patients achieving normal erectile function (EF; erectile function domain score ≥26) at week 12. Significant differences were observed among treatment groups (*P* < 0.0001), indicating significantly higher percentage of patients achieving normal function for patients on udenafil (100 mg and 200 mg groups combined) than for those on placebo (*P* < 0.0001). The percentage of patients achieving normal EF at week 12 was higher for patients on udenafil 200 mg than for patients on 100 mg, but the difference was not statistically significant.
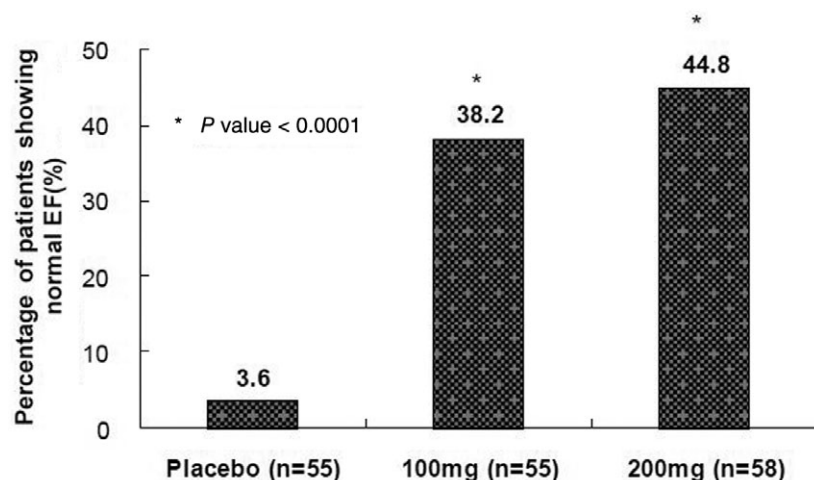

Figure 10 Secondary efficacy endpoints: life satisfaction. With respect to "sexual life", significant improvements were observed for both udenafil 100 mg and 200 mg groups, compared with the placebo group (*P* < 0.0001). With respect to "contacts with friends and acquaintance," significant difference was not observed between visits in the placebo and udenafil 100 mg groups, while significant increase was observed in the udenafil 200 mg group in ITT populations (*P* = 0.0301).
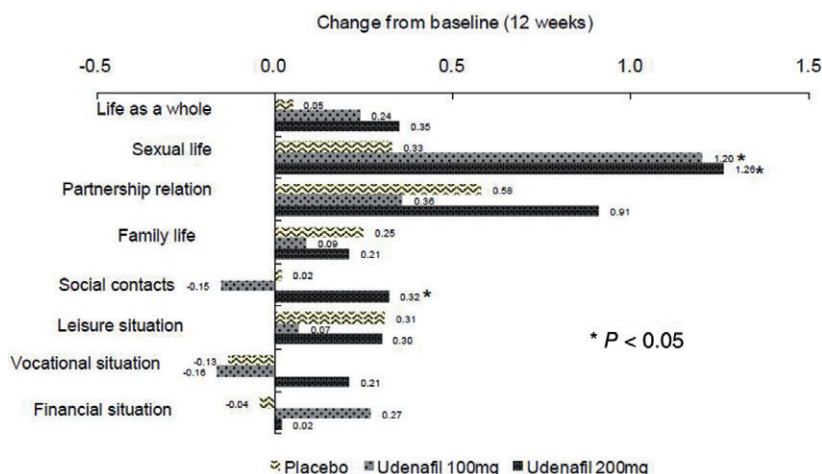
respect to the prior use of PDE5Is, at week 12, significant differences in changes from baseline for EFD scores were not observed irrespective of prior use of PDE5Is (ITT analysis, $P = 0.16$; PP analysis, $P = 0.4247$). In the case of HbA_{1C} level, the HbA_{1C} value at screening test was divided into three categories: $<7.0\%$, $7.0–9.5\%$, and $\geq9.5\%$. At week 12, significant differences in changes from baseline for EFD scores were not observed according to the HbA_{1C} levels (ITT analysis, $P = 0.6089$; PP analysis, $P = 0.8930$). In conclusion, subgroup analysis would not be shown in this paper because no covariate (the presence of hypertension, duration of ED, prior use of PDE5I, HbA_{1C} 3 level) indicated significant effect on the primary efficacy variables.

Safety

In this study, the safety of the study drug was analyzed using data obtained from all subjects who were enrolled and randomized to one of three study groups and treated with at least one dose of the study drug after randomization. Of 174 subjects randomized to treatment groups (57, 58, and 59 subjects for placebo, udenafil 100 mg and udenafil 200 mg groups, respectively), 170 subjects were included in the safety analysis (55, 57, and 58 subjects for placebo, udenafil 100 mg and udenafil 200 mg groups, respectively), excluding four subjects who did not take study drug at all (two, one, and one subjects for placebo, udenafil 100 mg and udenafil 200 mg groups, respectively).

The number of adverse events considered to have causal relationship to the study drug was 3, 11, and 25 events occurring in two (3.6%), nine (15.8%), and 13 (22.4%) subjects treated with placebo, udenafil100 mg, and udenafil 200 mg, respectively. All of these, 39 adverse events were mild in intensity and did not need any specific action. Compared with the placebo group, the udenafil treatment groups showed significantly higher incidences of adverse events, but there were no significant differences between the udenafil 100 mg and 200 mg groups. The most frequent drug-related adverse events were flushing and headache with incidences of 10% and 5% for each treatment group, respectively.

Discussion

DM is commonly associated with several conditions, such as hypertension, hyperlipidemia, and the metabolic syndrome, which are all markedly more common in diabetic patients than in nondia-

betic subjects and are recognized independent risk factors of ED [10]. Several studies regarding the efficacy of other PDE5Is on ED patients with DM have been published. However, there has been no attempt to evaluate the safety and efficacy of udenafil for the treatment of ED in a larger number of patients with DM especially in Korean populations. Udenafil is a PDE5I developed for the treatment of ED. In preclinical studies of udenafil, inhibitory concentration of 50% for PDE5 was 5 nM, indicating an excellent inhibitory effect on PDE5 [8]. Additionally, it was shown that udenafil is a highly selective PDE5I, based on its low inhibitory effects on other isozymes of phosphodiesterase. Its pharmacokinetic profile includes relatively rapid absorption after oral administration with a time to reach a peak plasma concentration of 1–2 hours [11]. Regardless of the dose, the elimination half-life ($t_{1/2}$) was approximately 10 hours (7–12 and 11–15 hours in Koreans and Caucasians, respectively), which was longer compared with sildenafil (3–5 hours) [12]. Further, in patients with ED of mild to moderate severity, single oral dosing of 100–200 mg udenafil significantly improved the EF in terms of the hardness and duration of erections, and the quality of life, including satisfaction and enjoyment of intercourse, compared with the treatment with placebo [9]. In recent experimental research, it also showed that chronic inhibition of PDE5 with udenafil is a useful therapeutic strategy to prevent the progression of diabetic ED by enhancing cNOS gene and protein expression levels in diabetic corpus cavernosum [13].

This multicenter study involving seven study sites in Korea was conducted to evaluate the safety and efficacy of 100 mg and 200 mg doses of udenafil (Zydena®; a PDE5I developed and marketed by Dong-A Pharmaceutical Co., Ltd) for the treatment of ED in male patients with DM. For the primary efficacy variable (change from baseline for the EFD score at week 12), statistically significant improvements were observed in patients on udenafil 100 mg and 200 mg, respectively, compared with patients on placebo. For secondary efficacy variables, statistically significant intergroup differences were also observed in patients on udenafil, compared with patients on placebo. For IIEF EFD score, udenafil 100 mg and 200 mg treatments showed improvements by ≥7 and ≥8 points on average (a total of 30 points) at week 12, compared with the placebo group. For IIEF Q3 and Q4, improvement by ≥1 point (a total of 5 points) on average was observed. With respect to

SEP Q2 and Q3 based on the results of SEP diary, statistically significant improvements were observed at Week 12 following udenafil 100 and 200 mg treatments, compared with baseline values. Furthermore, statistically significant intergroup differences were also observed between the udenafil and placebo groups. With respect to GAQ, by which the assessment of overall treatment effect on erection was surveyed for each subject, the proportion of subjects who answered "yes" to the question was 65.5% and 83.9% in the udenafil 100 mg and 200 mg groups, respectively, compared with 30.9% in the placebo group, and these increases were statistically significant.

There have been other studies regarding the efficacy of PDE5Is on DM patients. Those studies only used different primary efficacy parameters or described the post-treatment data only. Therefore, direct comparison is difficult. However, the results of those studies also showed the efficacy and safety of those PDE5Is in DM patients. In a sildenafil study, for an IIEF EFD score, significant improvements were demonstrated at week 12, compared with the initial EFD score [14]. In comparison of the EF domain, Q3 and Q4 before and after sildenafil administration in patients with DM also showed significant improvements' at week 12 [14]. With respect to the global efficacy question, the proportion of subjects who answered "yes" to the question at week 12 was 73.6%. Therapy with tadalafil (particularly at 20 mg) significantly enhanced EF across all three efficacy outcome variables: IIEF EFD, SEP Q2 and Q3 [15]. The proportions of positive responses to the GAQ in the tadalafil 10 mg and 20 mg groups were 56% and 64%, respectively, compared with 25% in the control group (both $P < 0.001$) [15]. In a study of vardenafil treatments, vardenafil significantly improved mean success rates for SEP Q2 and Q3 compared with baseline and placebo at week 12 ($P < 0.0001$) and treatment also significantly improved the EFD score ($P < 0.0001$) of the IIEF compared with placebo, in addition to scores for the other individual domains of the IIEF [16].

In the present study, subgroup analysis was planned to investigate significantly effective covariates on the primary efficacy variable. Thus, ANCOVA was used for each covariate (the presence of hypertension, duration of ED, prior use of PDE5I, HbA_{1C} 3 level), which was expected to have effects on the primary efficacy variable of changes from baseline for EFD score. Classification of each subgroup was defined appropriately by considering the actual distribution of study data.

In a tadalafil study [15], men taking concomitant antihypertensive medications had greater improvements in EF with tadalafil 20 mg than those not taking antihypertensives. However, significant differences in changes from baseline for EFD scores were not observed according to the history of hypertension in the present study. In the subgroup analysis according to the duration of ED, the mean duration of ED was 3.45 years in the present study. To examine the difference in the primary efficacy variable according to the duration of ED, the durations of ED were divided into three categories: <1.725 years, 1.725–3.45 years, and ≥3.45 years. At week 12, significant differences in changes from baseline for EFD scores were not observed according to the duration of ED. Also with respect to the prior use of PDE5I, significant differences in changes from baseline for EFD scores were not observed irrespective of any prior use of PDE5I at week 12. In the case of HbA_{1C} levels, significant differences in changes from baseline for EFD scores were not observed according to the HbA_{1C} levels at week 12. However, in a sildenafil study [14], there were significant differences in the mean of EFD, Q3 and Q4 in presildenafil administration regarding metabolic control, DM duration, and DM-related complications. As subgroup analyses of this study were not sufficiently powered to provide reliable tests, the results of subgroup analyses should be interpreted cautiously and further studies are required to confirm any difference in efficacy results according to subgroups. It can be considered as the limitations of present study.

The increase of EFD score in IIEF and SEP Q2 and Q3 after PDE5I treatment is an important factor in evaluating the efficacy of PDE5Is; however, the increase of the score does not indicate successful intercourse or normal sexual life. It just illustrates the improvement of sexual function quantitatively. Therefore, knowing or evaluating the percentage of subjects experiencing an improvement in EF to normal level is very important. The other previous studies about the efficacy of PDE5I on EF of DM patients did not consider this aspect. Therefore, the results of the present study are very valuable and meaningful in interpreting the real efficacy of udenafil on EF in DM patients. The percentage of subjects experiencing an improvement in EF to normal level at week 12 (IIEF EFD score ≥ 26) were 38.2% and 44.8% in the udenafil 100 mg and 200 mg groups, respectively, compared with 3.6% in the placebo group, indicating statistically significant improvements following the udenafil treatment.

The evaluation of change in life satisfaction is also a great tool for estimating the real efficacy of udenafil in ED patients with DM. However, the consideration of life satisfaction was lacking in most of the other studies. Therefore, the results of our study were important and meaningful in interpreting the efficacy of udenafil in ED patients with DM. With respect to life satisfaction categories, statistically significant improvements in "sexual life" and "contacts with friends and acquaintance" were observed in the udenafil 100 mg and 200 mg groups, respectively, compared with the placebo group. This result is meaningful not only because of the category of "sexual life", but also that of "social contacts" were significantly improved after udenafil treatment.

Major adverse events in our study were flushing, headache, nausea, and conjunctival hyperemia, and the incidence of them were 3.6%, 15.8%, and 22.4% for the placebo, 100 mg, and 200 mg groups, respectively. In a sildenafil study [14], the incidence of drug-related adverse events was not evaluated concretely such as in the present study; therefore, we could not estimate the safety of udenafil in DM subjects effectively. However, compared with the incidence of adverse events of the tadalafil study [15]; 31%, 39.7%, and 44.4% in either the placebo, tadalafil 10 mg, and 20 mg groups, our study showed that udenafil had less incidence of adverse events. From that, we could estimate that udenafil had well tolerated in patients with ED and DM. The most common drug-related adverse events in our study were flushing and headache, which is also different from the results of the tadalafil study [15] where the most common adverse event was dyspepsia. However, all adverse events in the present study were mild in severity and resolved spontaneously without specific action taken. With respect to laboratory tests and vital signs, neither statistically significant intergroup differences nor clinically meaningful changes from baseline were observed, indicating an adequate safety and tolerability of 100 mg and 200 mg doses of udenafil.

According to Malavige et al. [17], ED in diabetes patients is strongly associated with premature ejaculation and reduced libido. Therefore, they insisted that DM patients presenting with one of these three conditions should be screened for the other two [17]. However, hypotestosteronemia, which is known to be related to reduced libido, was excluded at the enrollment step of this study, and we did not consider the effects of premature ejaculation on EF of DM patients. Therefore, the lack of evaluations about the symptom of premature ejaculation and libido was one of the limitations of the present study.

Conclusion

Overall, the results of this study indicated that in patients with DM, oral dosing of udenafil tablets (100 mg and 200 mg doses) was effective for the treatment of erectile dysfunction, demonstrating statistically significant improvement in EF as measured by IIEF, SEP, and GAQ evaluations. The incidence of adverse events was low, indicating that udenafil is safe and well tolerated in patients with DM.

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References

1 Oh TY, Kang KK, Ahn BO, Yoo M, Kim WB. Erectogenic effect of the selective phosphodiesterase type 5 inhibitor, DA-8159. Arch Pharm Res 2000;23:471–6.
2 Ahn TY, Park JK, Lee SW, Hong JH, Park NC, Kim JJ, Park K, Park H, Hyun JS. Prevalence and risk factors for erectile dysfunction in Korean men: Results of an epidemiological study. J Sex Med 2007;4:1269–76.

3 McCulloch DK, Campbell IW, Wu FC, Prescott RJ, Clarke BF. The prevalence of diabetic impotence. Diabetologia 1980;18:279–83.

4 Rundles RW. Diabetic neuropathy. Bull N Y Acad Med 1950;26:598–616.

5 Rubin A, Babbott D. Impotence and diabetes mellitus. J Am Med Assoc 1958;168:498–500.

6 Zemel P. Sexual dysfunction in the diabetic patient with hypertension. Am J Cardiol 1988;61:27H–33H.

7 Korean Andrological Society. Text book of andrology. Korean Andrological Society: Seoul, Korea; 2010.

8 Doh H, Shin CY, Son M, Ko JI, Yoo M, Kim SH, Kim WB. Mechanism of erectogenic effect of the selective phosphodiesterase type 5 inhibitor, DA-8159. Arch Pharm Res 2002;25:873–8.

9 Paick JS, Kim SW, Yang DY, Kim JJ, Lee SW, Ahn TY, Choi HK, Suh JK, Kim SC. The efficacy and safety of udenafil, a new selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction. J Sex Med 2008;5:946–53.

10 Malavige LS, Levy JC. Erectile dysfunction in diabetes mellitus. J Sex Med 2009;6:1232–47.

11 Paick JS, Kim SW, Park YK, Hyun JS, Park NC, Lee SW, Park K, Moon KH, Chung WS. The efficacy and safety of Udenafil [zydena] for the treatment of erectile dysfunction in hypertensive men taking concomitant antihypertensive agents. J Sex Med 2009;6:3166–76.

12 Salem EA, Kendirci M, Hellstrom WJ. Udenafil, a long-acting PDE5 inhibitor for erectile dysfunction. Curr Opin Investig Drugs 2006;7:661–9.

13 Ahn GJ, Chung HK, Lee CH, Kang KK, Ahn BO. Increased expression of the nitric oxide synthase gene and protein in corpus cavernosum by repeated dosing of udenafil in a rat model of chemical diabetogenesis. Asian J Androl 2009;11:435–42.

14 El-Sakka AI. Efficacy of sildenafil citrate in treatment of erectile dysfunction: Effect of type 2 diabetes. Eur Urol 2004;46: 503–9.

15 Saenz de Tejada I, Anglin G, Knight JR, Emmick JT. Effects of tadalafil on erectile dysfunction in men with diabetes. Diabetes Care 2002;25:2159–64.

16 Ziegler D, Merfort F, van Ahlen H, Yassin A, Reblin T, Neureither M. Efficacy and safety of flexible-dose vardenafil in men with type 1 diabetes and erectile dysfunction. J Sex Med 2006;3:883–91.

17 Malavige LS, Jayaratne SD, Kathriarachchi ST, Sivayogan S, Fernando DJ, Levy JC. Erectile dysfunction among men with diabetes is strongly associated with premature ejaculation and reduced libido. J Sex Med 2008;5:2125–34.