Original Article
Male sexual health and dysfunction

The World Journal of
MEN's HEALTH

Check for updates

Efficacy and Safety of Mirodenafil Oro-Dispersible Film in Korean Patients with Erectile Dysfunction: A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter, Phase IV Study

Sung Won Lee[1], Hwancheol Son[2,3], Seung Wook Lee[4], Kang Su Cho[5], Du Geon Moon[6], Dae Yul Yang[7], Woo Sik Chung[8], Jun-Kyu Suh[9], Hyun Jun Park[10,11], Kweonsik Min[12], Ki Hak Moon[13], Kwangsung Park[14], Jong Kwan Park[15], Jae Seog Hyun[16], Sang-Kuk Yang[17]

[1]Department of Urology, Samsung Medical Center, Samsung Biomedical Research Institute, Sungkyunkwan University School of Medicine, [2]Department of Urology, Seoul National University College of Medicine, [3]Department of Urology, SMG-SNU Boramae Medical Center, [4]Department of Urology, Hanyang University College of Medicine, [5]Department of Urology, Gangnam Severance Hospital, Urological Science Institute, Yonsei University College of Medicine, [6]Department of Urology, Korea University College of Medicine, [7]Department of Urology, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, [8]Department of Urology, Ewha Womans University School of Medicine, Seoul, [9]National Research Center for Sexual Medicine and Department of Urology, Inha University School of Medicine, Incheon, [10]Department of Urology, Pusan National University School of Medicine, [11]Medical Research Institute of Pusan National University Hospital, [12]Department of Urology, Busan Paik Hospital, Inje University College of Medicine, Busan, [13]Department of Urology, Yeungnam University College of Medicine, Daegu, [14]Department of Urology, Chonnam National University Medical School, Gwangju, [15]Department of Urology, Jeonbuk National University Medical School, Research Institute of Clinical Medicine of Jeonbuk National University – Biomedical Research Institute and Clinical Trial Center of Medical Device, Jeonbuk National University Hospital, Jeonju, [16]Department of Urology, Gyeongsang National University Hospital, Gyeongsang National University School of Medicine, Jinju, [17]Department of Urology, Konkuk University Chungju Hospital, Konkuk University School of Medicine, Chungju, Korea

Purpose: To investigate the efficacy, safety, and tolerability of oro-dispersible film (ODF) formulation of mirodenafil 50 mg and 100 mg for the treatment of patients with erectile dysfunction (ED) in Korea.

Materials and Methods: A multicenter, randomized, double-blind, placebo-controlled, parallel-group study of 129 subjects was performed. Subjects were randomized to either placebo or mirodenafil ODF 50 mg or 100 mg to be taken in an "on demand" manner for 8 weeks. The primary efficacy variable was the International Index of Erectile Dysfunction (IIEF)-5 questionnaire. The secondary efficacy variables comprised Sexual Encounter Profile questions 2 and 3 (SEP2 and SEP3), the Global Assessment Question (GAQ), and the Life Satisfaction Checklist (LSC).

Results: IIEF-5 was significantly increased in all groups after treatment. However, compared to the placebo group, only the mirodenafil ODF 100 mg group showed a significant difference. SEP2 and SEP3 were increased in both mirodenafil groups; however, the increase was not statistically significant for SEP2. In terms of GAQ and LSC, the mirodenafil ODF groups showed significant increases compared with the baseline. Most treatment-associated adverse events were mild and resolved spontaneously.

Conclusions: Mirodenafil ODF is an effective and well-tolerated agent for the treatment of patients with ED in Korea.

Keywords: Erectile dysfunction; Mirodenafil; Orally disintegrating formulations; Oro-dispersible film; Phosphodiesterase 5 inhibitors

INTRODUCTION

Phosphodiesterase type 5 (PDE5) inhibitors dilate the corpora cavernosa of the penis, facilitating erection upon sexual stimulation, and are used in the treatment of erectile dysfunction (ED). PDE5 inhibitors prolong the action of cyclic guanosine monophosphateby inhibiting its degradation by the enzyme PDE5 [1].

The currently approved PDE5 inhibitors in South Korea include sildenafil, vardenafil, tadalafil, udenafil, avanafil, and mirodenafil. These PDE5 inhibitors have slight differences in efficacy, which are attributed to their individual characteristics, but are generally excellent therapies for ED [2]. Therefore, PDE5 inhibition has been established as first-line therapy for ED in the European Association of Urology and American Urological Association guidelines [3,4].

Mirodenafil (Mvix; SK Chemicals Life Science, Seongnam, Korea), developed in 2007 in Korea, is a second-generation PDE5 inhibitor. So far, it has been approved for use only in the Korean market. The pharmacokinetic profile of mirodenafil is similar to that of sildenafil, but its selectivity for PDE5 is 10 times stronger than that of sildenafil [5]. To date, mirodenafil has shown excellent efficacy and safety in the clinical studies, regardless of the etiology or severity of ED [5-9].

Although PDE5 inhibitors are the most effective and widely used ED therapeutics, dropout rates are reported to be between 11% and 57% [10]. The reasons for dropout include: abstinence for a long period of time before treatment, concerns about side effects, comorbidities with ED, drug cost, loss of sexual interest on the part of the patient or partner, and inconvenience or rejection of planned sexual activity.

Orally disintegrating formulations have been developed with the aim of improving adherence to treatment with PDE5 inhibitors by providing a more convenient form of administration. An orally disintegrating formulation is defined as a single layer or multilayer sheet of suitable materials. When administered, the patient does not need to drink water; with a little saliva, the formulation melts within a few minutes on the tongue [11].

Orally disintegrating formulations can make PDE5 inhibitors available to patients who have difficulty with fluid intake owing to medical problems, such as renal impairment and congestive heart failure, or patients who have difficulty swallowing conventional tablet dosage forms owing to dysphagia. In South Korea, sildenafil, vardenafil, and tadalafil were developed as orally disintegrating formulations in the form of oro-dispersible film (ODF) or oro-dispersible tablet (ODT). The ODF formulation of mirodenafil was developed in December 2011 and is currently in clinically use.

In this clinical trial, we investigated the efficacy, safety, and tolerability of mirodenafil ODF 50 mg and 100 mg for the treatment of patients with ED in Korea.

MATERIALS AND METHODS

1. Ethics statement and description of study design

This double-blind, randomized, placebo-controlled, parallel-group, multicenter, phase IV study was conducted at 16 centers in Korea in accordance with Good Clinical Practice and was consistent with the ethical principles of the Declaration of Helsinki (2013). Written informed consent was obtained from each patient before enrolment in the study. All forms of the documents related to this clinical study, *i.e.*, the protocol and the informed consent form, were approved by the relevant institutional review board of the Pusan National University Hospital (IRB No. 1210-010-012).

Initially, eligible patients had a 4-week, treatment-free run-in period during which the patients were required to have attempted intercourse on at least four separate days and have been unsuccessful in at least half of these attempts. Subsequently, the patients were randomly assigned to receive mirodenafil ODF 50 mg or 100 mg or placebo.

In this clinical study, block randomization was performed in a manner that the proportion of subjects between the dosing groups was set to 1:1:1 for placebo: mirodenafil ODF 50 mg: mirodenafil ODF 100 mg in consideration of the appropriate block size. Subjects assigned to each administration group received the clinical trial drug for 8 weeks and were instructed to visit the hospital after administration of the study drug for 4 and 8 weeks (Fig. 1A).

2. Investigational drugs

The mirodenafil ODF contained 50 mg or 100 mg of mirodenafil in one sheet and was a white translucent rectangle. The placebo was a white translucent square film that did not contain mirodenafil but was other-

wise indistinguishable from the mirodenafil ODF. The patients were instructed to take the investigational drug for 8 weeks in an 'on demand' or 'as needed' manner, ~30 minutes before sexual intercourse, and to not exceed one dose per day during the trial.

3. Subjects

The inclusion criteria were as follows: men with a history of ED for at least 6 months according to the National Institutes of Health (NIH) Consensus Statement (inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance); over 20 years of age; in a stable, monogamous relationship with a female sexual partner; and had failed >50% of at least four sexual attempts during the run-in period.

Men with the following conditions were excluded from the study: penile anatomical defects, spinal cord injury, radical prostatectomy, and radical pelvic surgery; a primary diagnosis of another sexual disorder; retinitis pigmentosa; uncontrolled diabetes mellitus (HbA1C >12%); proliferative diabetic retinopathy; serum total testosterone level <2.5 ng/mL; serum prolactin level >55 ng/mL; serum creatinine >2.5 mg/dL; major uncontrolled psychiatric disorder; history of major hematological, renal, or hepatic abnormalities; recent (within the previous 6 months) history of cardiovascular disease, stroke, or myocardial infarction, cardiac failure, unstable angina, life-threatening arrhythmia; and a history of alcoholism or substance abuse. In addition, patients were ineligible if they had been receiving regular treatment with nitrates, anticoagulants (except for low-dose aspirin), androgens, anti-androgens, cytochrome P450 3A4 inhibitors, anticancer chemotherapy, or trazodone. Patients with a history of anaphylactic reaction to PDE5 inhibitors or unsuccessful use of sildenafil, vardenafil, tadalafil, udenafil, and avanafil or those who had taken other agents in a clinical trial within the previous month were excluded from the study. The concomitant use of any ED treatment was prohibited.

4. Outcome measures

The primary efficacy variable was a change in the score of the International Index of Erectile Dysfunction (IIEF)-5 questionnaire from the baseline. Secondary efficacy variables included changes in question 2 and 3 of the Sexual Encounter Profile (SEP2: Were you able to insert your penis into your partner's vagina? SEP3: Did your erection last long enough for you to have successful intercourse?) from baseline and patient responses to the Global Assessment Question (GAQ: Has the treatment you have been taking during the last 4 weeks improved your erections?) and Life Satisfaction Checklist (LSC) [12]. The safety assessments included laboratory tests (hematology, clinical biochemistry, blood coagulation test, and urinalysis), vital signs (blood pressure and heart rate), physical examination, 12-lead electrocardiogram recordings, and patients' reporting of adverse events.

5. Statistical analysis

Efficacy analysis was performed on the full analysis set (FAS) population. The last-observation-carried-forward imputation method was used for missing data. The repeated measures analysis of covariance (ANCOVA) method, using baseline characteristics as covariates, was used to evaluate the primary efficacy endpoints and all secondary endpoints, except for GAQ. Efficacy was calculated in comparison with the placebo group after assessment of the change from baseline at given points, including the end of treatment. Within each group, the changes from baseline in the primary efficacy endpoints and all secondary endpoints at a given point were assessed by repeated measures analysis of variance (ANOVA), except for GAQ and LSC. Inter-group differences in the GAQ response rate were analyzed using a χ^2 test or Fisher's exact test. Statistical significance was accepted at the $p<0.05$ level.

In this clinical trial, the number of subjects was calculated through the analysis of phase II and III clinical trials of 50 mg or 100 mg mirodenafil tablet. The analysis of the scores of the IIEF-5 domain, the primary efficacy endpoint of this clinical trial, using weighted averages and weighted variances, revealed that the mean±standard deviation was 8.67±6.43 in patients receiving mirodenafil tablet and 2.26±6.11 in patients receiving placebo [5,6]. With approximately 33 avaluable patients per group, this study had a power of approximately 90% at a significance level of 0.05. Allowance for a 30% withdrawal rate required a total of 144 randomized patients for the efficacy analysis, with 48 patients per group. Statistical analyses were performed using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The patients' demographic variables and the efficiency data were analyzed in the FAS. All subjects who received any amount of study drug and had at least one post-baseline safety assessment were included in the safety set, and the safety evaluation was performed on this set.

In total, 137 subjects were screened after they provided written consent to participate in the study. Eight subjects failed the screening procedures; consequently, 129 subjects were randomized to receive 50 mg mirodenafil ODF, 100 mg mirodenafil ODF, or placebo (all n= 43).

Of the 129 randomly assigned subjects, 127 subjects were administered the investigational drugs (safety set: 43 in the 50 mg mirodenafil group, 43 in the 100 mg mirodenafil group, and 41 in the placebo group), and 120 of these completed the trial (40 subjects in each of the 50 mg mirodenafil, 100 mg mirodenafil, and placebo groups). During the 8 weeks of therapy, 9 (7.0%) patients withdrew from the study: five subjects withdrew their consent (two in the 50 mg mirodenafil group, two in the 100 mg mirodenafil group, and one in the placebo group); three subjects committed a protocol violation (one subject each in the 50 mg mirodenafil, 100 mg mirodenafil, and placebo groups) and were excluded; and one subject in the placebo group withdrew for unknown reasons (Fig. 1B).

1. Demographics

The demographic information and baseline characteristics of the 126 subjects included in the FAS group are summarized in Table 1.

The mean age of the patients was 59.92±8.46 years, and the mean duration of ED was 4.26±3.56 years. At baseline, no clinically or statistically meaningful differences were found between the treatment groups with regard to demographic or clinical variables.
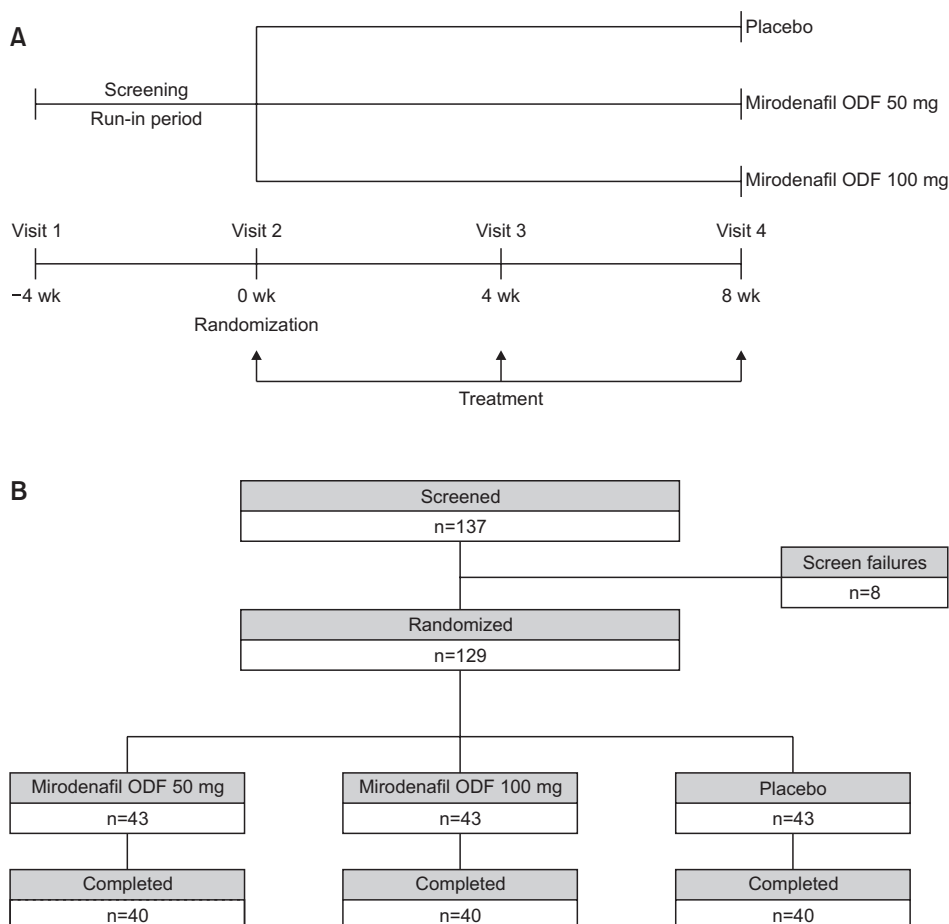

Fig. 1. Study schedule (A) and patient disposition (B). ODF: oro-dispersible film.

Table 1. Demographic and baseline characteristics of patients (full analysis set)

Variable	Mirodenafil ODF 50 mg (n=43)	Mirodenafil ODF 100 mg (n=42)	Placebo (n=41)	Total (n=126)
Age (y)				
Patient (n)	43	42	41	126
Mean (SD)	61.47 (6.86)	59.17 (9.40)	59.07 (8.93)	59.92 (8.46)
Median	61.00	61.00	61.00	61.00
Min, Max	45.00, 75.00	39.00, 73.00	35.00, 75.00	35.00, 75.00
p-value[a]				0.3392
Height (cm)				
Patient (n)	42	42	41	125
Mean (SD)	169.41 (5.54)	171.22 (6.17)	169.53 (4.56)	170.06 (5.49)
Median	169.00	170.00	169.00	169.80
Min, Max	156.20, 180.00	161.20, 189.00	161.00, 180.00	156.20, 189.00
p-value[a]				0.2429
Weight (kg)				
Patient (n)	42	42	41	125
Mean (SD)	70.20 (7.99)	71.30 (7.44)	70.45 (8.69)	70.65 (8.00)
Median	70.00	70.00	71.00	70.00
Min, Max	56.00, 90.30	56.70, 86.00	51.00, 96.20	51.00, 96.20
p-value[a]				0.8085
History of ED (y)[b]				
Patient (n)	43	42	41	126
Mean (SD)	5.07 (4.58)	3.90 (2.65)	3.78 (3.03)	4.26 (3.56)
Median	3.00	3.00	3.00	3.00
Min, Max	1.00, 24.00	1.00, 11.00	1.00, 15.00	1.00, 24.00
p-value[a]				0.1839
Severity of ED (IIEF-5 score)				
Paitient (n)	43	42	41	126
Mean (SD)	10.95 (3.80)	9.24 (4.22)	9.88 (4.13)	10.03 (4.08)
Median	11.00	10.00	11.00	11.00
Min, Max	1.00, 17.00	1.00, 17.00	1.00, 19.00	1.00, 19.00
p-value[a]				0.1470
Severity of ED, n (%)				
Severe (IIEF-5 score <11)	15 (34.88)	24 (57.14)	20 (48.78)	59 (46.83)
Moderate (IIEF-5 score 11–16)	26 (60.47)	16 (38.10)	19 (46.34)	61 (48.41)
Mild to moderate (IIEF-5 score 17–21)	2 (4.65)	2 (4.76)	2 (4.88)	6 (4.76)
p-value[c]				0.3044

ODF: oro-dispersible film, SD: standard deviation, Min: minimum, Max: maximum, ED: erectile dysfunction, IIEF-5: International Index of Erectile Function-5.
[a]Difference between the treatment groups (ANOVA). [b]History of ED (year)=year of diagnosis-year of consent+1. [c]Difference between the treatment groups (Fisher's exact test).

2. Efficacy outcome variables

1) International Index of Erectile Dysfunction-5

IIEF-5 increased significantly in all groups after treatment (p<0.0001 at both mirodenafil doses, p=0.0437 in the placebo group). However, compared with the placebo group, only the 100 mg mirodenafil ODF group showed a significant difference (p=0.0256) (Fig. 2).

2) Sexual Encounter Profile 2 (Were you able to insert your penis into your partner's vagina?)

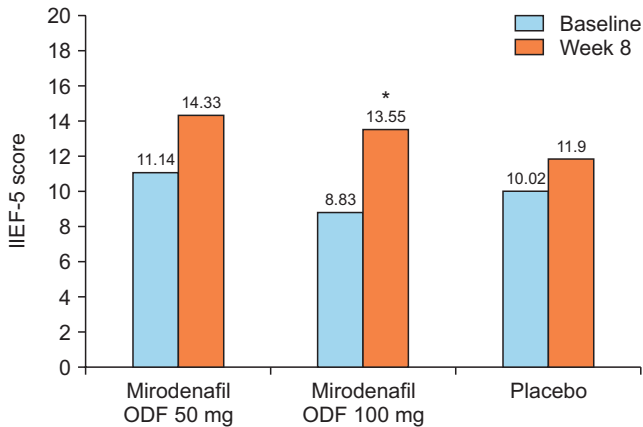SEP2 increased significantly in all groups after

Fig. 2. Effects of mirodenafil on the IIEF-5 score at 8 weeks after the start of treatment. ODF: oro-dispersible film, IIEF-5: International Index of Erectile Function-5. *p=0.0256 *vs*. placebo.

treatment. However, there was no statistically significant difference at either mirodenafil dose compared with the placebo group (Table 2).

3) Sexual Encounter Profile 3 (Did your erection last long enough for you to have successful intercourse?)

SEP3 increased significantly in all groups after treatment. On comparing these changes with the placebo group, the differences in the mirodenafil ODF 50 mg and 100 mg groups were statistically significant (p=0.0056, p=0.0432) (Table 2).

4) Global Assessment Question (Has the treatment you have been taking during the last 4 weeks improved your erections?)

When the proportion of patients who responded positively to GAQ after treatment was compared with that in the placebo group, the differences in the mirodenafil ODF 50 mg and 100 mg groups were statistically significant (p=0.0063, p=0.0018) (Table 2).

5) Life Satisfaction Checklist

After treatment, both the mirodenafil 50 mg and 100 mg groups showed significant increases compared with the baseline (p=0.0036, p<0.0001). However, compared with the placebo group, these changes were not statistically significant (Table 2).

3. Safety results

Safety was analyzed in 127 patients who received the trial drug (the safety set). The number of treatment-

emergent adverse events (TEAEs) was 7/43 (16.28%) in the 50 mg mirodenafil ODF group, 10/43 (23.26%) in the 100 mg mirodenafil ODF group, and 5/41 (12.20%) in the placebo group. However, no serious adverse events occurred. The difference in the incidence of TEAEs among the groups during the clinical trial period was not statistically significant (Table 3).

DISCUSSION

The pharmacokinetic profile of mirodenafil is described by a time to peak serum concentration (Tmax) of 1.25 hours, a half-life (T1/2) of 2.5 hours, and a half-maximal inhibitory concentration (IC50) for PDE5 of 0.34 nmoL/L; thus, it has a relatively high affinity (potency) for PDE5 [5,13].

In phase II and III studies, treatment with mirodenafil 50 mg and 100 mg resulted in an increase of 5.3–8.4 and 7.6–11.6 points in IIEF-5 or IIEF-EF, respectively.

The results for SEP2 showed an increase of 27.72%–43.4% and 37.3%–38.98% after treatment, respectively, and SEP3 showed an increase of 28.6%–44.9% and 63.2%–67.33%, respectively. After treatment, the proportion of patients who moved to the category of normal erectile function, as indicated by IIEF, was 17.3%–24.1% and 51.7%–62.2% in the mirodenafil 50 mg and 100 mg treatment groups, respectively [5-8,14]. The results of clinical studies conducted on patients with ED and specific concurrent diseases have also been reported. Mirodenafil 100 mg increased IIEF-EF by 9.35 and 9.3 points, respectively, in clinical trials conducted in patients with ED and hypertension or diabetes, respectively. In these studies, SEP2 increased by 30.2% and 36.1%, respectively, and SEP3 increased by 55.3% and 61.8%, respectively. In the classification by IIEF-EF score, 40.7% and 32.7% of patients, respectively, moved to the category of normal erectile function after treatment [7,8].

The main purpose of this phase IV study was to investigate the efficacy and safety of mirodenafil ODF in general patients with ED. The study utilized a double-blind, randomized, placebo-controlled, parallel-group, multicenter design.

Orally disintegrating formulations, considered innovative drug delivery systems, can increase patient convenience, thereby increasing drug compliance and reducing dropout rates.

Table 2. Summary of primary and secondary outcomes before and after treatment

Variable	Mirodenafil ODF 50 mg (n=43)	Mirodenafil ODF 100 mg (n=42)	Placebo (n=41)
IIEF-5 (full analysis set)			
Baseline	11.14±3.97	8.83±3.95	10.02±3.95
Week 8	14.33±5.19	13.55±5.79	11.90±4.99
Change	3.19±4.86	4.71±4.58	1.88±4.60
p-value (RM ANOVA)	<0.0001	<0.0001	0.0437
Difference *vs.* placebo p-value (RM ANCOVA)	0.0869	0.0256	
SEP2 (full analysis set)			
Baseline	47.92±44.88	41.63±44.07	37.36±43.34
Week 8	77.91±36.27	75.99±36.40	62.80±42.78
Change	29.99±45.93	34.36±45.09	25.45±58.18
p-value (RM ANOVA)	<0.0001	<0.0001	0.0002
Difference *vs.* placebo p-value (RM ANCOVA)	0.0902	0.0783	
SEP3 (full analysis set)			
Baseline	6.35±14.06	8.39±20.21	7.59±22.51
Week 8	49.81±41.80	49.60±39.77	31.71±39.54
Change	43.46±38.25	41.22±41.63	24.12±48.42
p-value (RM ANOVA)	<0.0001	<0.0001	0.0003
Difference *vs.* placebo p-value (RM ANCOVA)	0.0056	0.0432	
	Mirodenafil ODF 50 mg (n=40)	**Mirodenafil ODF 100 mg (n=37)**	**Placebo (n=38)**
GAQ (per-protocol set)			
Response rate	25 (62.50)	25 (67.57)	12 (31.58)
Compare with placebo p-value (chi-square test)	0.0063	0.0018	
	Mirodenafil ODF 50 mg (n=43)	**Mirodenafil ODF 100 mg (n=42)**	**Placebo (n=41)**
LSC (full analysis set)			
Baseline	31.77±4.92	28.93±6.16	30.24±5.92
Week 8	33.88±4.40	32.08±7.15	31.34±6.46
Change	2.14±4.50	3.15±4.59	1.10±3.74
p-value (paired t-test)	0.0036	<0.0001	0.0676
Difference *vs.* Placebo p-value (ANCOVA)	0.1060	0.0608	

Values are presented as mean±standard deviation or number (%).
ODF: oro-dispersible film, IIEF-5: International Index of Erectile Dysfunction-5, RM ANOVA: repeated measures analysis of variance, RM ANCOVA: repeated measures analysis of covariance, SEP: Sexual Encounter Profile, GAQ: Global Assessment Question, LSC: Life Satisfaction Checklist.

Table 3. Brief summary of TEAEs (safety analysis set)

Variable	Mirodenafil ODF 50 mg (n=43)	Mirodenafil ODF 100 mg (n=43)	Placebo (n=41)	Total (n=127)
Number of subjects with TEAEs	7 (16.28)	10 (23.26)	5 (12.20)	22 (17.32)
95% confidence interval	5.24–27.31	10.63–35.88	2.18–22.21	10.74–23.90
p-value (chi-square test)				0.3981
Number of TEAEs				
Mild	22	29	10	61
Moderate	0	1	0	1
Severe	0	0	0	0

Values are presented as number (%) or number only.
TEAEs: treatment-emergent adverse events, ODF: oro-dispersible film.

Studies on orally disintegrating formulations of sildenafil have been published. In the bioequivalence study of a sildenafil 100 mg ODF compared with the conventional film-coated 100 mg tablet administered to healthy male volunteers, the pharmacokinetic profiles were not significantly different and the incidence of adverse events was similar [11]. In the study conducted by Cocci et al [15], a sildenafil ODF had equivalent safety and effectiveness to the film-coated tablets but had better results in terms of overall satisfaction. These results suggest that the ODF can be used interchangeably with conventional film-coated formulations.

Orally disintegrating formulations provide an opportunity for ED treatment in patients who find it difficult to take conventional PDE5 tablets owing to specific diseases or condition. ED tends to coexist with chronic diseases, and patients with ED are often elderly individuals who need to take various concomitant medications. Therefore, for patients with diseases such as renal impairment, congestive heart failure, nocturia, and dysphasia, a drug that does not require water provides the convenience of discreet administration [16-18].

A rapidly disintegrating ODT formulation of vardenafil 10 mg was developed and is being marketed in South Korea, Europe, the United States, and other countries. Vardenafil 10 mg ODT has a pharmacokinetic profile similar to that of vardenafil film-coated tablets; however, it has greater bioavailability owing to significant drug absorption through the oral mucosa [19]. Although they are similar to orally disintegrating formulations, ODFs offer several advantages over ODTs. ODTs have problems related to hardness and friability during the processes of manufacture, storage, handling, and administration, and there is also a risk of choking [16]. ODFs are thin and flexible, can be manufactured in a range of sizes and shapes, and are easily transported and stored. Owing to these advantages, it was reported that four out of five patients prefer orally disintegrating dosage forms over conventional solid oral dosage forms [18].

In South Korea, ODFs of mirodenafil, tadalafil, and sildenafil are already used widely and are the primary treatment for patients with ED. However, no clinical studies on these ODFs have been published.

We believe this study is significant as it is the first report of a clinical trial on a mirodenafil ODF. In this study, the mean IIEF-5 scores were increased by 3.19 and 4.71 in the mirodenafil ODF 50 mg and 100 mg treatment groups, respectively, after 8 weeks of treatment. These increases were slightly lower than those reported in a previous study of mirodenafil conventional tablets.

With regard to SEP2, the 50 mg and 100 mg mirodenafil ODF groups showed increases in the mean response rate of 29.99% and 34.36%, respectively, after treatment. This was similar to the results of previous studies on mirodenafil conventional tablets [5-8]. With regard to SEP3, the 50 mg and 100 mg mirodenafil ODF groups showed increases in the mean response rate of 43.46% and 41.22%, respectively, after treatment. Compared with the results of previous studies on conventional tablets, the results of mirodenafil ODF 50 mg were similar, whereas ODF 100 mg showed a slightly smaller increase [5-8].

In this study, the mirodenafil ODF was shown to have slightly lower efficacy than conventional tablets in terms of IIEF-5 and SEP3 improvement. One of the reasons for this finding could be that the proportion of individuals with moderate to severe ED in our study was relatively higher than that in previous mirodenafil trials [5-8]. However, unlike the present study, a study investigating a sildenafil ODF and conventional tablets showed similar efficacy and safety for both agents [15].

Some limitations of the present study should be noted.

First, although this study is the first on a mirodenafil ODF formulation, it is not a direct comparison with conventional tablets. Therefore, it was not possible to perform a direct comparison of the differences in efficacy, safety, and satisfaction between the two formulations.

Second, with regard to the changes in IIEF-5 (the primary efficacy variable), the mirodenafil 50 mg treatment group showed a greater improvement than the placebo group, but the changes were not statistically significant. This was considered to be attributed to the high participation rate of patients with severe ED, who did not improve sufficiently with the lower dose of mirodenafil.

Third, a relatively short study treatment period of 8 weeks was used. Fourth, owing to sociocultural differences among various populations of different ethnic origins, the efficacy and safety profile of mirodenafil observed in this study, which included Korean patients only, may not be similar to that in other ethnic groups.

CONCLUSIONS

Mirodenafil ODF 50 mg and 100 mg, taken as needed before sexual activity during an 8-week study period, resulted in significant improvements in erectile function, as measured by the IIEF-5, SEP, GAQ, and LSC scores in patients with ED. Moreover, the frequency and severity of adverse events were low, indicating that the mirodenafil ODF was safe and well tolerated. The mirodenafil ODF may be a good choice to complement conventional tablets and increase the therapeutic compliance of patients taking PDE5 inhibitors.

ACKNOWLEDGEMENTS

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: SWL, HJP. Data curation: SWL, HJP. Formal analysis: SWL, HJP. Funding acquisition: SWL, HJP. Investigation: All authors. Methodology: SWL, HJP. Project administration: SWL, HJP. Resources Software: SWL, HJP. Supervision: SWL, HJP. Validation Visualization: SWL, HJP. Writing – original draft: All authors. Writing – review & editing: SWL, HJP.

REFERENCES

1. Carrier S. Pharmacology of phosphodiesterase 5 inhibitors. Can J Urol 2003;10 Suppl 1:12-6.

2. Moon du G. Evolution of phosphodiesterase-5 inhibitors. World J Mens Health 2015;33:123-4.

3. Burnett AL, Nehra A, Breau RH, Culkin DJ, Faraday MM, Hakim LS, et al. Erectile dysfunction: AUA guideline. J Urol 2018;200:633-41.

4. Hatzimouratidis K, Amar E, Eardley I, Giuliano F, Hatzichristou D, Montorsi F, et al.; European Association of Urology. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. Eur Urol 2010;57:804-14.

5. Paick JS, Ahn TY, Choi HK, Chung WS, Kim JJ, Kim SC, et al. Efficacy and safety of mirodenafil, a new oral phosphodiesterase type 5 inhibitor, for treatment of erectile dysfunction. J Sex Med 2008;5:2672-80.

6. Paick JS, Choi HK, Kim SC, Ahn TY, Kim JJ, Park JK, et al. 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. Asian J Androl 2008;10:791-8.

7. Paick JS, Kim JJ, Kim SC, Moon KH, Min KS, Park K, et al. Efficacy and safety of mirodenafil in men taking antihypertensive medications. J Sex Med 2010;7:3143-52.

8. Park HJ, Choi HK, Ahn TY, Park JK, Chung WS, Lee SW, et al. Efficacy and safety of oral mirodenafil in the treatment of erectile dysfunction in diabetic men in Korea: a multicenter, randomized, double-blind, placebo-controlled clinical trial. J Sex Med 2010;7:2842-50.

9. Chung JH, Kang DH, Oh CY, Chung JM, Lee KS, Kim TH, et al. Safety and efficacy of once daily administration of 50 mg mirodenafil in patients with erectile dysfunction: a multicenter, double-blind, placebo controlled trial. J Urol 2013;189:1006-13.

10. Al-Shaiji TF, Brock GB. Phosphodiesterase type 5 inhibitors for the management of erectile dysfunction: preference and adherence to treatment. Curr Pharm Des 2009;15:3486-95.

11. Radicioni M, Castiglioni C, Giori A, Cupone I, Frangione V, Rovati S. Bioequivalence study of a new sildenafil 100 mg orodispersible film compared to the conventional film-coated 100 mg tablet administered to healthy male volunteers. Drug Des Devel Ther 2017;11:1183-92.

12. Fugl-Meyer AR, Lodnert G, Bränholm IB, Fugl-Meyer KS. On life satisfaction in male erectile dysfunction. Int J Impot Res 1997;9:141-8.

13. Palit V, Eardley I. An update on new oral PDE5 inhibitors for the treatment of erectile dysfunction. Nat Rev Urol 2010;7:603-9.

14. Cho MC, Paick JS. A review of the efficacy and safety of mirodenafil in the management of erectile dysfunction. Ther Adv Urol 2016;8:100-17.

15. Cocci A, Capece M, Cito G, Russo GI, Falcone M, Timpano M, et al. Effectiveness and safety of oro-dispersible sildenafil in a new film formulation for the treatment of erectile dysfunction: comparison between sildenafil 100-mg film-coated tablet and 75-mg oro-dispersible film. J Sex Med 2017;14:1606-11.

16. Hoffmann EM, Breitenbach A, Breitkreutz J. Advances in orodispersible films for drug delivery. Expert Opin Drug Deliv 2011;8:299-316.

17. Irfan M, Rabel S, Bukhtar Q, Qadir MI, Jabeen F, Khan A. Orally disintegrating films: a modern expansion in drug de-

livery system. Saudi Pharm J 2016;24:537-46.

18. Kathpalia H, Gupte A. An introduction to fast dissolving oral thin film drug delivery systems: a review. Curr Drug Deliv 2013;10:667-84.

19. Heinig R, Weimann B, Dietrich H, Böttcher MF. Pharmacokinetics of a new orodispersible tablet formulation of vardenafil: results of three clinical trials. Clin Drug Investig 2011;31:27-41.