Efficacy and Safety of MED2005, a Topical Glyceryl Trinitrate Formulation, in the Treatment of Erectile Dysfunction: A Randomized Crossover Study

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ABSTRACT

Background: Current treatments for erectile dysfunction (ED) have some limitations.

Aim: This study evaluated the efficacy and tolerability of MED2005, a 0.2% glyceryl trinitrate topical gel, formulated into an enhanced absorption topical delivery system (DermaSys), administered on demand, in the treatment of ED.

Methods: This randomized, double-blinded, placebo-controlled, phase II crossover trial involved 232 men with ED (231 treated, 230 assessed for efficacy) and their partners. After a 4-week run-in period, patients were randomized to 1 of 2 treatment sequences, MED2005-placebo or placebo-MED2005. Each treatment was given for 4 weeks, separated by a 1-week washout interval. Efficacy was assessed by the International Index of Erectile Function (IIEF), the Sexual Encounter Profile, a Global Assessment Questionnaire (GAQ), and specific questions about the onset and offset of action and treatment preferences (patients and partners).

Outcomes: The primary outcome measure was the IIEF erectile function domain (IIEF-EF) score. Other efficacy assessments were secondary outcomes.

Results: The mean baseline IIEF-EF score was 17.1 (SD = 5.7), and this increased to 19.6 (SD = 7.5) after MED2005 treatment and 18.5 (SD = 6.7) after placebo (P = .0132). Overall, 23.1% of patients showed a clinically relevant ($\geq$4-point) increase in IIEF-EF scores after treatment with MED2005 only compared with 14.5% who responded after MED2005 and placebo, 14.0% who responded after placebo only, and 48.4% who did not respond after either treatment (P = .0272). MED2005 also was associated with significant improvements compared with placebo in the other IIEF domains, and this was consistent with patients' and partners' responses to the GAQ. For all assessments, significant effects of MED2005 were seen primarily in patients with mild ED. The start of erection was noticed within 5 and 10 minutes in 44.2% and 69.5%, respectively, of all intercourse attempts with MED2005. Patients and partners showed significant preferences for MED2005 over placebo. The most commonly reported adverse events during MED2005 treatment were headache (patients, n = 18 [7.9%]; partners, n = 3 [1.3%]) and nasopharyngitis (patients, n = 13 [5.7%]; partners, n = 2 [0.9%]).

Clinical Implications: These findings suggest that topical glyceryl trinitrate could be a useful treatment option in ED.

Strengths and Limitations: Strengths of this study include the use of a validated outcome measure. Limitations include the use of only 1 dosage.

Conclusion: Further studies are warranted to investigate the efficacy of topical glyceryl trinitrate to include higher doses, thereby improving clinical significance, especially in cases of moderate and severe ED. **Ralph DJ, Eardley I, Taubel J, et al. Efficacy and Safety of MED2005, a Topical Glyceryl Trinitrate Formulation, in the Treatment of Erectile Dysfunction: A Randomized Crossover Study. J Sex Med 2017;XX:XXX–XXX.**

INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to initiate and/or maintain an erection that is satisfactory for sexual intercourse.[1,2] ED, which increases with age, has a significant impact on quality of life for the man and his partner.[3–7]

Phosphodiesterase type 5 (PDE5) inhibitors have revolutionized the management of ED for some men but have certain limitations. They have to be taken daily or sufficiently in advance of sexual intercourse to allow effective circulating drug concentrations to be attained, thus hindering spontaneity. PDE5 inhibitors have a relatively long half-life that vastly exceeds the usual duration of sexual intercourse. They also are associated with adverse effects such as headache, back pain, and visual disturbances,[1,8] which can lead to discontinuation. Moreover, pre-existing comorbidities, such as unstable angina, and use of nitrates are contraindicated. Other non-oral local treatment strategies, such as intracavernosal injections, penile implants, or vacuum erection devices, also have significant limitations.[1,8] Topical therapy offers potential advantages for the treatment of ED, including non-invasiveness, the potential for a fast onset of action, ease of use, a lack of interaction with food or moderate alcohol intake, and good tolerability. Their use could be incorporated into sexual foreplay, increasing the level of intimacy between couples.

Nitric oxide (NO) plays a key role in initiating and maintaining penile erection, because it relaxes cavernosal smooth muscle, thereby compressing the penile veins and preventing local venous return.[8,9] Therefore, NO donors, such as glyceryl trinitrate (GTN), could be effective in the treatment of ED.

MED2005 is a topical gel containing 0.2% (w/w) GTN, which is under development for the treatment of ED. This product uses the MED2002 topical gel formulation and incorporates DermaSys (Futura Medical plc, Guildford, UK) technology to facilitate rapid absorption (to minimize any potential partner transference) and effective delivery of GTN across the skin.[10] Pharmacokinetic and pharmacodynamic studies with this preparation suggest that a GTN dose of 0.6 mg (0.2%, w/w) produces changes in penile blood flow consistent with erection, with a relatively short half-life. This creates the ideal profile needed for spontaneous sexual intercourse, which generally lasts for several minutes rather than hours. This also suggests a favorable safety profile (unpublished data). This article reports on a randomized phase II trial evaluating the efficacy and safety of MED2005 (0.2%, w/w) in men with ED.

METHODS

The trial was a randomized, double-blinded, placebo controlled, crossover study performed at 1 site in the United Kingdom and 3 sites in Poland. It was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Council for Harmonization guidelines for Good Clinical Practice. The protocol was approved by independent ethics committees at all participating centers. The study is registered with ClinicalTrials.gov (NCT02495467).

The primary objective of the study was to evaluate the efficacy of MED2005 vs placebo in men with a confirmed diagnosis of ED according to the International Index for Erectile Function erectile function domain (IIEF-EF).[11,12] Secondary objectives were to evaluate the efficacy of MED2005 using other IIEF domains and other questionnaires, in addition to subjective measures of onset and offset of action, and to assess the safety and tolerability of MED2005 in patients and their partners.

Patients

Men 18 to 70 years old were eligible for inclusion in the study if they had a confirmed diagnosis of ED (defined as the inability to achieve and/or maintain a penile erection sufficient for satisfactory sexual performance[13]) for at least 3 months and a score no higher than 25 points on IIEF questions 1 to 5 and question 15 (IIEF-EF). In addition, they were required to have been in a continuous heterosexual relationship for at least 6 months before screening and to have had residual erectile function, as assessed by the IIEF, during the previous 3 months. Adequate contraception was to be used throughout the study period if the patient's female partner was of childbearing potential.

Patients were excluded if they had significant medical or psychiatric conditions or if they had active and symptomatic urinary tract infection at screening. Other exclusion criteria included anatomic abnormalities that could significantly impair erectile function; primary hypoactive sexual desire or a history of hypogonadism; previous radical prostatectomy or surgery for Peyronie disease; concurrent treatment with PDE5 inhibitors or NO donors such as GTN, isosorbide dinitrate, or amyl or butyl nitrite; hypotension; migraine or a history of recurrent headache; evidence of alcoholism or drug abuse within the previous 12 months; or confirmed positive results from a urine drugs-of-abuse screen.

Written informed consent was obtained from all patients and their partners before inclusion in the study.

Study Procedures

Eligible patients entered a 4-week baseline run-in period, during which they refrained from using any ED therapy, and were required to attempt sexual intercourse on at least 4 occasions. On completion of this period, eligible patients were randomized 1:1 to 1 of 2 treatment sequences, MED2005-

placebo or placebo-MED2005. Randomization numbers were allocated sequentially according to a computer-generated randomization list. The 2 treatments were given for 4 weeks, separated by a 1-week treatment-free period. To maintain blinding, MED2005 and placebo gels were identical in appearance and were supplied in identical packaging.

During each treatment period, patients and their partners were required to attempt sexual intercourse, using their study medication, on at least 4 occasions. The study medication was administered by massaging a pea-size amount [containing 0.2% (w/w) GTN] into the glans of the penis using a finger for at least 15 seconds immediately before intercourse; this could be done by the patient or partner (with no requirement to remove any residual gel or wait for any period before sexual intercourse), and all patients and partners were shown how to apply the gel. Concomitant treatment with other ED therapies, androgens, or NO donors was prohibited throughout the study. However, there were no restrictions on food or alcohol intake during the study.

The efficacy of MED2005 was assessed by the IIEF at the end of the run-in period and each treatment period and by the Sexual Encounter Profile (SEP) after each intercourse attempt during run-in and treatment. Only patients completed the IIEF, whereas separate SEPs were completed by patients and their partners. In addition, patients and their partners completed a Global Assessment Questionnaire (GAQ) at the end of each treatment period. Specific questions on the onset and offset of action of treatment were asked in conjunction with the SEP after each intercourse attempt, and overall treatment preference was assessed at the end of the study. The primary efficacy end point was the IIEF-EF score. Secondary end points were other IIEF domain scores, SEP questions, onset-offset questions, GAQ assessments, and overall treatment preference.

Safety and tolerability were assessed by monitoring adverse events throughout the study and by physical examination, measurement of vital signs, and clinical laboratory investigations at various times during the study.

Statistical Methods

Efficacy analyses were performed on the full analysis set, consisting of randomized patients who had at least 1 efficacy assessment in a treatment period during which an intercourse attempt was reported. Analyses were performed using linear mixed models, which assumed that missing values were randomly distributed, and were complemented using a last-observation-carried-forward strategy. Safety analyses were based on the safety set, consisting of all randomized patients who used their medication at least once.

The primary efficacy end point and other IIEF domains were analyzed using a linear mixed model with treatment, period, and sequence as fixed effects, patient as a random effect, and baseline (run-in) value as a covariate. In addition, the proportion of patients showing a minimally clinically important difference ($\geq$4-point increase defined by Rosen et al[11]) in IIEF-EF score was

analyzed using the Prescott test. For each SEP question, a generalized linear model was fitted to the number of "yes" responses using a log-link function and a negative binomial distribution, with the log-transformed number of intercourse attempts as an offset. Onset-offset questions were analyzed by Wilcoxon ranks for each intercourse attempt, averaged across each treatment period for each patient. The averaged ranked data were analyzed using a linear mixed model. Responses to the individual GAQ questions were analyzed by the Prescott test, and the question on treatment preference was analyzed using a 2-sided binomial test comparing to a proportion of 0.5.

Prespecified subgroup analyses were performed in patients with mild (IIEF-EF score = 17−25), moderate (IIEF-EF score = 11−16), or severe (IIEF score $\leq$ 10) ED and in the combined mild and moderate ED subgroups (IIEF-EF score = 11−25).

All statistical analyses were carried out using SAS 9.3 (SAS Institute, Cary, NC, USA), with no adjustments for multiplicity. P values less than .05 were considered significant.

The sample size calculation was based on previous studies with topical alprostadil, in which the mean changes from baseline in IIEF-EF scores compared with placebo were 2.4 to 8.4.[14] Assuming a mean difference in IIEF-EF scores between MED2005 and placebo of 2.5 (SD = 7.5), a sample size of 192 patients would provide 90% power with a 2-sided type I error rate of 0.05.

RESULTS

Of 392 patients screened, 232 were randomized; of these, 114 were randomized to the placebo-MED2005 treatment sequence and 118 to the MED2005-placebo sequence (Figure 1). The safety set consisted of 231 patients who used the medication at least once. An additional patient was excluded from the full analysis set because of no on-treatment efficacy assessments. 2 patients in each sequence withdrew their consent before the 2nd treatment period and 3 patients (MED2005-placebo) were not treated in period 2; overall, 225 patients completed the study.

Baseline demographic and clinical characteristics of the patients are presented in Table 1. The mean age of the patients was 43 years (range = 19−70), and the mean IIEF-EF score was 17.1 (SD = 5.7).

The total number of intercourse attempts with MED2005 and placebo was 1,003 and 984, respectively. The mean number of intercourse attempts during each treatment period and with the 2 treatments was 4.4.

Changes in IIEF-EF Scores

The mean IIEF-EF scores after treatment with MED2005 or placebo were 19.6 (SD = 7.5) and 18.5 (SD = 6.7), respectively, compared with a mean score during the run-in period of 17.1 (SD = 5.7). The least squares mean treatment difference
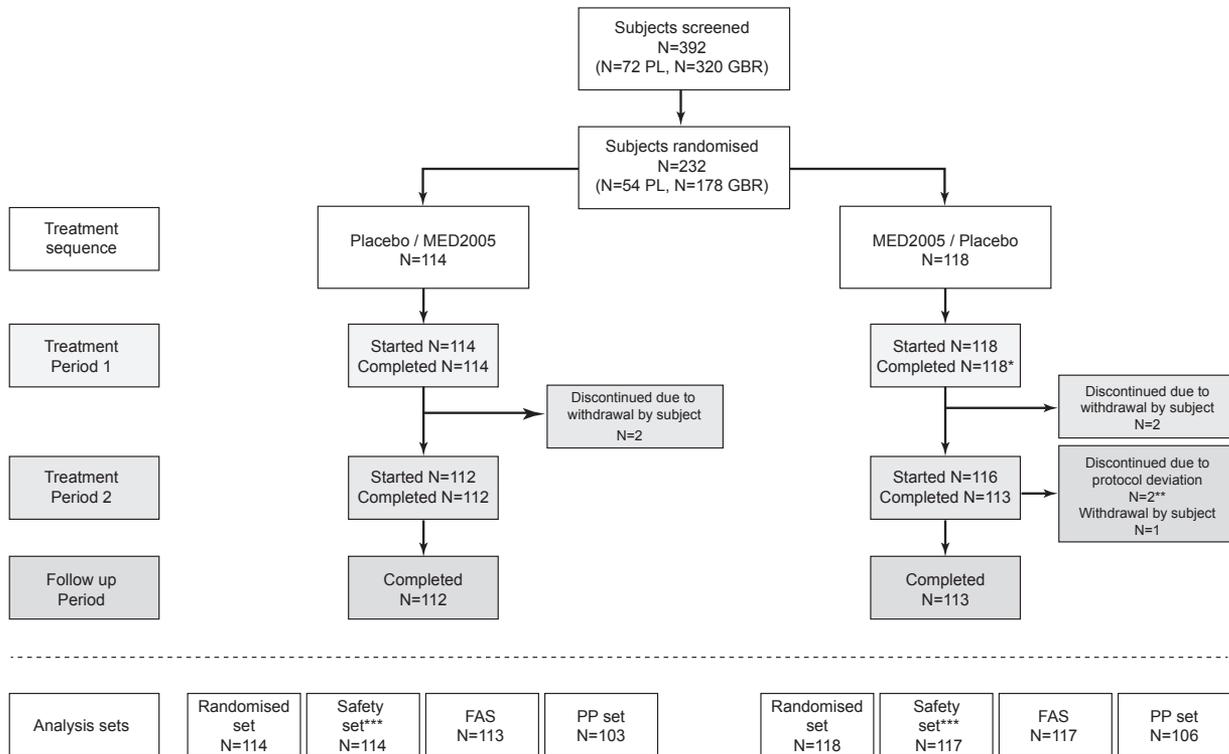
Figure 1. Patient disposition. *1 patient completed visits in treatment period 1 but never sent back the investigational medical product. The investigator's comment was, "Reviewing online questionnaire it would appear that the volunteer has never used the [investigational medical product]." Therefore, the subject was excluded from the safety set, FAS, and PP set. **Reasons leading to study discontinuation were positive results from drugs-of-abuse testing. ***Within the safety set, 227 subjects (114 + 113) received placebo and 229 subjects (117 + 112) received MED2005. FAS = full analysis set, GBR = Great Britain (United Kingdom); PL = Poland; PP = per protocol.

favoring MED2005 was 1.03 (95% CI = 0.22–1.84, P = .0132). MED2005 also was associated with significant improvements compared with placebo in IIEF-EF scores in the subgroup of patients with mild ED and in the combined subgroups of patients with mild and moderate ED (Table 2, Figure 2). No significant improvement was noted in the moderate and severe subgroups.

Overall, 51 of 221 patients (23.1%) showed an increase in IIEF-EF scores of at least 4 points after treatment with MED2005 only compared with 31 of 221 patients (14.0%) after placebo only; 32 of 221 patients (14.5%) showed this increase after the 2 treatments, and 107 of 221 (48.4%) did not show this increase after either treatment. The difference between treatments was statistically significant (P = .0272).

Other IIEF Domains

In the overall study population, there were significant treatment differences favoring MED2005 in all other domains of the IIEF (orgasmic function, P = .012; sexual desire, P < .0001; intercourse satisfaction, P = .0055; overall satisfaction, P = .001; Figure 2).

SEP Questionnaire

The proportions of patients answering "yes" to the 5 questions of the SEP are presented in Table 3. In the overall study

population, there were no significant treatment differences in patients' responses to SEP questions 1 to 3, but significant (P < .001) treatment differences favoring MED2005 were seen for question 4 ("Were you satisfied with the hardness of your erection?") and question 5 ("Were you satisfied overall with this sexual experience?").

Onset and Offset of Action

In the overall study population, the start of erection was noticed within 5, 10, and 20 minutes in 44.2%, 69.5%, and 75.5%, respectively, of all intercourse attempts with MED2005. The corresponding respective figures with placebo were 42.0%, 69.5%, and 75.5%.

In the overall study population, there was no significant treatment difference in the time to offset of erection. Partners' responses to the onset-offset questions were similar to the patients' responses.

Global Assessment Questionnaire

For GAQ question 1 ("Has the treatment you have been taking improved your erectile function?"), 58 of 216 (26.9%) answered "yes" for MED2005 only, 20 of 216 (9.3%) for placebo only, 36 of 216 (16.7%) for the 2 treatments, and 102 of 216 (47.2%) for neither treatment (P < .0001). For question 2 ("If yes, has the treatment improved your ability to engage in

Table 1. Baseline demographic and clinical characteristics (safety set)*

	Country		
	UK (n = 177)	Poland (n = 54)	Overall (N = 231)
Age (y)	43.6 (15.0)	40.9 (10.9)	43.0 (14.2)
Body mass index (kg/m^2)	26.7 (4.2)	26.3 (3.9)	26.6 (4.1)
Race			
White	140 (79.1%)	54 (100.0%)	194 (84.0%)
Black or African American	17 (9.6%)	0	17 (7.4%)
Asian	9 (5.1%)	0	9 (3.9%)
Other	11 (6.2%)	0	11 (4.8%)
IIEF-EF score	16.0 (5.7)	20.7 (4.1)	17.1 (5.7)
IIEF-EF score by severity[†]			
Mild ED (IIEF-EF score = 17−≤25)[‡]	90 (51.1%)	44 (81.5%)	134 (58.3%)
IIEF-EF score	20.7 (2.3)	22.4 (1.6)	21.3 (2.2)
Moderate ED (IIEF-EF score = 11−≤16)	46 (26.1%)	9 (16.7%)	55 (23.9%)
IIEF-EF score	14.2 (1.5)	13.9 (1.5)	14.1 (1.5)
Severe ED (IIEF-EF ≤ 10)	40 (22.7%)	1 (1.9%)	41 (17.8%)
IIEF-EF score	7.5 (1.7)	7.0	7.5 (1.7)
Mild and moderate ED (IIEF-EF score = 11−≤25)	136 (77.3%)	53 (98.1%)	189 (82.2%)
IIEF-EF score	18.5 (3.7)	21.0 (3.6)	19.2 (3.8)

ED = erectile dysfunction; IIEF-EF = International Index of Erectile Function erectile function domain.
*Results are presented as mean (SD) or number (percentage).
[†]Baseline ED categories are reported for the full analysis set (n = 230). 1 patient from the United Kingdom was excluded from the full analysis set; hence, the percentages of patients in each category are based on sample of 176.
[‡]Includes mild ED (IIEF-EF score = 22−25) and mild to moderate ED (IIEF-EF score = 17−21).

sexual activity?"), when patients answering "no" to question 1 were assumed to have also answered "no" to this question, 52 of 216 patients (24.1%) answered "yes" for MED2005 only, 21 of 216 (9.7%) for placebo only, 33 of 216 (15.3%) for the 2 treatments, and 110 of 216 (50.9%) for neither treatment (P = .0003 for difference between treatments). Partners' responses were consistent with those of the patients.

Overall Treatment Preference

Overall, 91 of 225 patients (40.4%) expressed a preference for MED2005, 50 of 225 (22.2%) for placebo, and 84 of 225 (37.3%) for neither (P = .0007). Corresponding figures for the partners were 38.0%, 22.2%, and 39.8%, respectively (P = .003).

Tolerability

Overall, 80 adverse events occurred in 55 of 229 patients (24.0%) during treatment with MED2005, and 50 occurred in 42 of 227 patients (18.5%) receiving placebo gel (Table 4). Among partners, 7 adverse events occurred in 7 of 229 women (3.1%) with MED2005 and 3 occurred in 3 of 227 women (1.3%) with placebo. Of the adverse events considered related to treatment, 34 occurred in 24 of 229 patients (10.5%) and 4 occurred in 4 of 229 partners (1.7%) during MED2005 treatment compared with 9 occurring in 8 of 227 (3.5%) and 1 occurring in 1 of 227 (0.4%), respectively, during placebo treatment. In patients and partners, the most commonly reported adverse events during MED2005 treatment were headache (patients, n = 18 of 229 [7.9%]; partners, n = 3 of 229 [1.3%]) and nasopharyngitis (patients, n = 13 of 229 [5.7%]; partners, n = 2 of 229 [0.9%]). No other adverse event occurred in more than 5 patients or more than 1 partner. No cases of priapism were reported during the study. All except 2 adverse events, which occurred during MED2005 treatment, were mild or moderate in severity; the 2 severe adverse events (gastroenteritis

Table 2. Mean (SD) IIEF-EF scores (full analysis set)

	Run-in period	MED2005	Placebo	LS mean difference (95% CI)	P value
All patients (n = 230)	17.1 (5.7)	19.6 (7.5)	18.5 (6.7)	1.03 (0.22−1.84)	.0132
Mild ED (n = 134)*	21.3 (2.2)	23.1 (5.4)	21.3 (5.0)	1.81 (0.93−2.68)	<.0001
Moderate ED (n = 55)	14.1 (1.5)	16.7 (6.4)	17.1 (5.3)	−0.099 (−1.89 to 1.69)	.91
Severe ED (n = 41)	7.5 (1.7)	11.7 (7.6)	11.3 (7.5)	0.057 (−2.58 to 2.70)	.97
Mild and moderate ED (n = 189)	19.2 (3.8)	21.2 (6.4)	20.1 (5.4)	1.18 (0.38−1.99)	.0043

ED = erectile dysfunction; IIEF-EF = International Index of Erectile Function erectile function domain; LS = least squares.
*Includes mild ED (IIEF-EF score = 22−25) and mild to moderate ED (IIEF-EF score = 17−21).
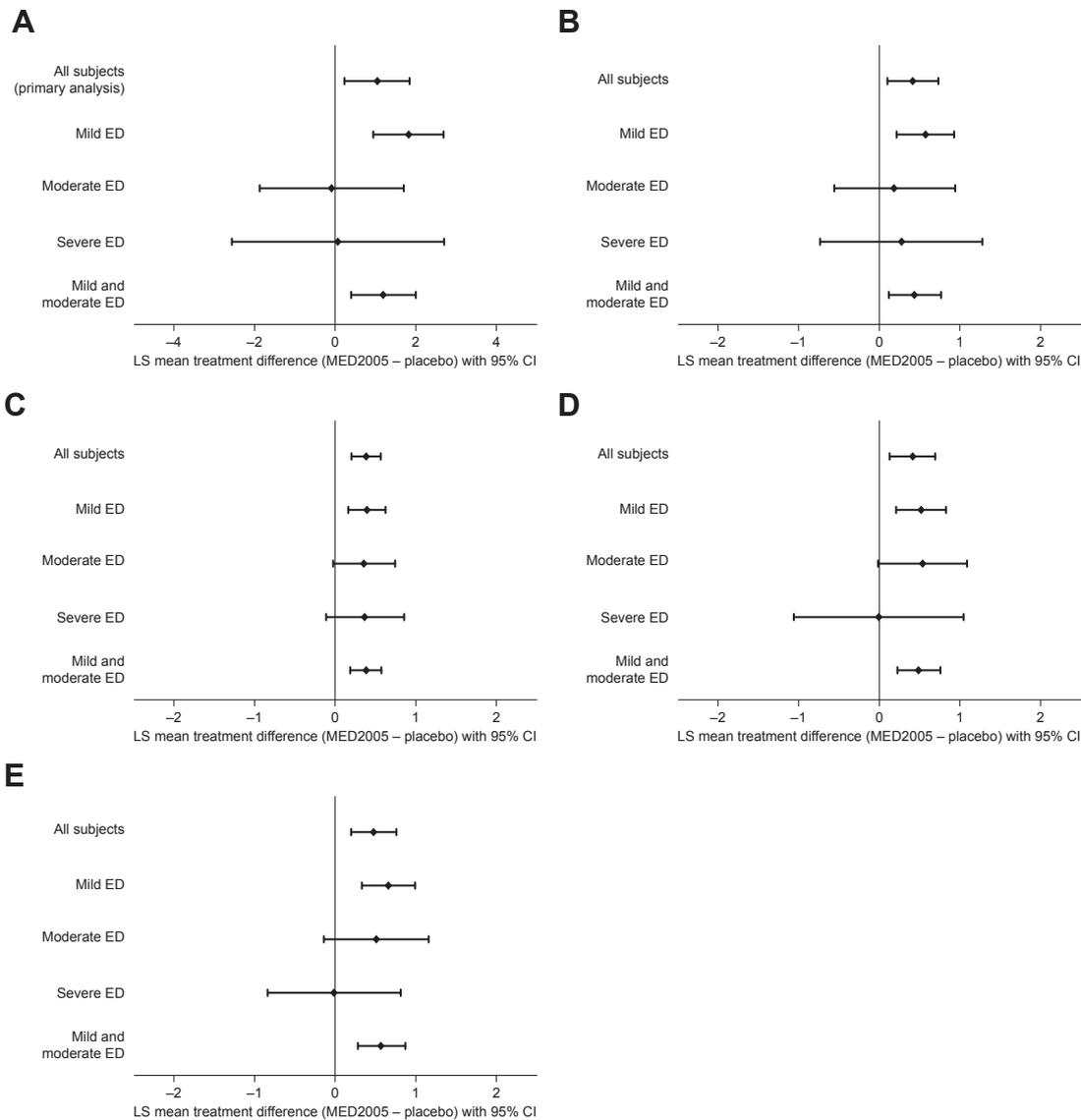
Figure 2. Panels A to E show forest plots of LS mean treatment differences (MED2005 vs placebo) in erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction domains, respectively, of the International Index of Erectile Function. Horizontal lines indicate 95% CI. International Index of Erectile Function erectile function domain scores are 17 to 25 for mild ED, 11 to 16 for moderate ED, no higher than 10 for severe ED, and 11 to 25 for mild and moderate ED. ED = erectile dysfunction; LS = least squares.

in 1 patient and nasopharyngitis in 1 partner) were considered unrelated to study treatment. There were no partner side effects from direct contact with MED2005 with respect to pain or burning on urination. No serious adverse events were reported during the study, and there were no withdrawals from the study because of adverse events. There were no clinically significant changes in blood pressure or electrocardiogram during the study.

DISCUSSION

ED can markedly affect quality of life and psychological well-being[2,5,15,16] and can adversely affect female partners.[17] Because there is evidence that the condition is often

underdiagnosed and undertreated,[18,19] there is a clear unmet need for new treatment strategies.[6] The results of this phase II study suggest that topical GTN formulated into a rapid and efficient delivery system (DermaSys) could offer a new option for the treatment of ED.

Compared with placebo, MED2005 was associated with significantly greater increases in IIEF-EF score, which has been shown to be a valid measure of ED severity.[12] Furthermore, the proportion of patients showing a clinically relevant increase in IIEF-EF scores (≥4 points[11]) was significantly larger with MED2005 than with placebo. MED2005 also was associated with significant improvements in scores for the other IIEF domains compared with placebo. These overall improvements were

Table 3. Summary of patients' responses* to SEP questions (full analysis set)

	Percentage of "yes" responses[†]			LS mean ratio (95% CI)	P value
	Run-in	MED2005	Placebo		
SEP question 1: "able to achieve at least some erection" (n = 229)	91.6 (18.5)	87.2 (26.5)	86.9 (26.2)	0.995 (0.96–1.03)	.80[‡]
SEP question 2: "able to insert penis" (n = 229)	74.9 (31.8)	75.5 (36.5)	75.4 (34.9)	0.99 (0.94–1.04)	.67
SEP question 3: "erection lasts long enough" (n = 229)	39.1 (34.0)	57.3 (39.4)	52.6 (38.8)	1.08 (0.99–1.17)	.10[‡]
SEP question 4: "satisfied with hardness of erection" (n = 229)	17.1 (24.7)	42.9 (41.0)	29.0 (33.1)	1.52 (1.27–1.83)	<.001
SEP question 5: "satisfied overall with this sexual experience" (n = 229)	27.0 (31.8)	48.2 (40.9)	36.9 (37.0)	1.32 (1.13–1.55)	<.001

LS = least squares; SEP = Sexual Encounter Profile.
*Partners' responses were generally consistent with those of patients.
[†]Mean (SD).
[‡]Convergence of statistical model questionable.

driven by the patient subgroups with mild ED; no significant effect of MED2005 was seen in patients with moderate or severe ED, although the study was not powered to detect a difference in these subgroups. This could suggest that the GTN dose used in this study, based on findings from a previous phase I pharmacokinetic study (unpublished data), was a minimally effective dose.

MED2005 had a rapid onset of action in this study, with the start of erection within 5 minutes in 44% of patients and within 10 minutes in almost 70%. This is in marked contrast to oral PDE5 inhibitors, which typically have an onset of action of 0.5 to 1.0 hour, and peak circulating drug concentrations are attained only 1 to 2 hours after administration.[1,2] There was no significant difference in onset time between MED2005 and placebo gel, probably because the gel in the 2 treatments was massaged onto the glans penis for 15 seconds, causing sexual stimulation. Importantly, no restrictions on food or alcohol intake were imposed during this study. Hence, the finding that an effect of MED2005 was observed within 5 to 10 minutes in

most patients suggests that food or alcohol intake has no impact on the effectiveness of MED2005. By contrast, the efficacy of some oral PDE5 inhibitors, notably sildenafil and vardenafil, is decreased after ingestion of fatty meals because of delays in drug absorption from the gut.[1,8,20,21]

MED2005 was well tolerated compared with other topically applied gels or PDE5 inhibitors. Adverse event rates of up to 78% have been reported in clinical trials with topical alprostadil cream,[22] and a meta-analysis of trials with PDE5 inhibitors reported rates of 8.6% to 25.1%, depending on agent and dose.[23] Most adverse events were mild or moderate, and there were no serious adverse events during the study; indeed, no patient discontinued treatment because of adverse events. The most common adverse event, headache, occurred in only 18 patients during treatment with MED2005 in 1,003 intercourse attempts and was considered related to treatment in 14. There were only isolated cases of vasodilator adverse events (mild tachycardia or dizziness) and application site reactions, such as coldness or irritation, and no cases of priapism. The incidence of adverse

Table 4. Summary of adverse events (safety set)

	Male patients		Female partners	
	MED2005 (n = 229)	Placebo (n = 227)	MED2005 (n = 229)	Placebo (n = 227)
Any adverse event	55 (24.0%)	42 (18.5%)	7 (3.1%)	3 (1.3%)
Serious adverse events	0	0	0	0
Adverse events leading to withdrawal	0	0	0	0
Mild adverse events	51 (22.3%)	39 (17.2%)	6 (2.6%)	3 (1.3%)
Related	24 (10.5%)	8 (3.5%)	4 (1.7%)	1 (0.4%)
Unrelated	32 (14.0%)	32 (14.1%)	2 (0.9%)	2 (0.9%)
Moderate adverse events	5 (2.2%)	4 (1.8%)	0	0
Related	0	1 (0.4%)	0	0
Unrelated	5 (2.2%)	3 (1.3%)	0	0
Severe adverse events	1 (0.4%)	0	1 (0.4%)	0
Related	0	0	0	0
Unrelated	1 (0.4%)	0	1 (0.4%)	0

events in female partners was extremely low (4 treatment-related mild adverse events, including 2 mild headaches, in 1,003 intercourse attempts), indicating that there is little or no transference of GTN to the female partner during intercourse or during application of the gel by the female partner. Indeed, more than 300 applications of MED2005 were performed by the patient's partner. There were no treatment-related partner side effects such as pain or burning on urination.

In conclusion, the results of this phase II study suggest that MED2005 is a potentially effective treatment for ED. Further studies including higher doses of MED2005 are warranted to improve clinical significance, especially in cases of moderate and severe ED.

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Conflicts of Interest: David J. Ralph is a consultant to Coloplast, Boston Scientific, Sobi, and Futura Medical. Ian Eardley is a consultant to Futura Medical and Pfizer. Jorg Taubel is an employee of Richmond Pharmacology Ltd. Tim Holland is an employee of Futura Medical Developments Ltd and holds stock options in the company. Paul Terrill provides consultancy services to Futura Medical Developments Ltd and was a statistical consultant for CROS NT Ltd during his contributions to this work.

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