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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 (≥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.**

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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-