2. SYNOPSIS

Name of Company: Futura Medical Development Ltd

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Name of Finished Product: MED2005

Page:

Name of Active Ingredient(s): Glyceryl trinitrate

Title of Study: A Phase III, dose-ranging, multi-centre, randomised, double-blind, placebo-controlled, home use, parallel group clinical trial of topically-applied glyceryl trinitrate (GTN) for the treatment of erectile dysfunction (ED), with an open label extension

Protocol Number: FM57

Study Period:

Study Phase: 3

Date of first patient, first visit: 05 Dec 2018

Date of last patient, last visit (Double-blind phase): 27 Oct 2019

NOTE: Only the results for the Double-blind Phase are presented in this report.

Principal Investigator: Dr Andrzej - Robert Depko

Study Centres:

This study took place in approximately 60 centres in 9 countries including Poland, Hungary, Czech Republic, Slovakia, Georgia, Russia, Ukraine, Bulgaria and Latvia

Publication(s):

None to date.

Objectives: The primary objective of this study was to demonstrate the efficacy of MED2005 versus placebo in male subjects clinically diagnosed with ED using the EF domain of the IIEF, the Sexual Encounter Profile (SEP) Question 2 and the SEP Question 3.

The primary objective was assessed via the change compared to baseline in the IIEF-EF domain, of the IIEF, the ability to achieve vaginal penetration (SEP Question 2) and the ability to have successful intercourse (SEP Question 3) over 12 weeks of treatment. in all subjects who met the study inclusion/exclusion criteria and who were randomised and attempted intercourse post-randomisation at least once.

The secondary objectives of this study were to evaluate:

- The efficacy of MED2005 in male subjects using the Self-Esteem And Relationship (SEAR) questionnaire for men, the Global Assessment Questionnaire (GAQ), the additional domains of the IIEF, the Patient Global Impression of Severity (PGI-S), the Patient Global Impression of Change (PGI-C) as well as subjective measures of the time of onset and duration of action (erection) and erection hardness and questions on usage and application of MED2005
- The long-term (up to 12 months) safety and efficacy of MED2005
- The safety of MED2005 using AEs and standard physico-chemical assessments

Study Design:

NOTE: Only the results for the Double-blind Phase are presented in this report.

Screening Period: Subjects were screened for eligibility during a screening period of 4 to 6 weeks between Day −43 and Day −1. The IIEF questionnaire was completed by the male subjects at the start of the screening period at the first site visit (Visit 1) and the EF domain of the IIEF (IIEF-EF; i.e. Questions 1−5 and 15) was used to determine eligibility. A score of ≤ 25 was acceptable for inclusion in the screening period of the study.

Baseline IIEF-EF, SEP Question 2 (the ability to achieve vaginal penetration), and SEP Question 3 (the ability to have successful intercourse) were assessed during the screening period. During the screening period, at home and after refraining from using other ED treatments for a period of at least 14 days, subjects and their partners were required to make a minimum of 4 attempts at sexual intercourse, at their convenience but within a 4-week period (without treatment). The subjects and their partners completed questionnaires to record their experiences after each sexual intercourse attempt (using the SEP questionnaire at home [male subjects and their female partners]) and at the end of the 4-week period at Visit 2 (using the IIEF, PGI-S, and SEAR questionnaires [male subjects only]). The IIEF-EF completed at the end of the screening period was used to confirm eligibility for randomisation.

Double-blind Phase: A total of 1000 subjects were planned to be randomised and treated in the double-blind phase of the study.

During the double-blind phase, treatment involved topical self- or partner-administration of a gel to the glans penis for 15 seconds prior to attempting sexual intercourse. Subjects were randomised to receive 1 of the following gel treatments in a 1:1:1:1 ratio:

- MED2005 0.2% (w/w) GTN gel to deliver a 0.6 mg dose of GTN
- MED2005 0.4% (w/w) GTN gel to deliver a 1.2 mg dose of GTN
- MED2005 0.6% (w/w) GTN gel to deliver a 1.8 mg dose of GTN
- Placebo vehicle (Dermasys)
  NOTE: The base formulation was consistent for all treatment types (given the proprietary name Dermasys), the only difference being the inclusion of GTN in 3 of the treatment arms, i.e., 0.2% , 0.4 and 0.6% (w/w).

Eligible subjects participated in the double-blind phase, comprising a 12-week treatment period (Visits 2, 3, 4 and 5) and a 1-week follow-up visit (Visit 6). At home, subjects or their partners applied the dispensed gel immediately prior to sexual intercourse and were to make at least 4 intercourse attempts in each of the three 4-weekly periods during treatment (Weeks 1−4, 5−8 and 9−12). Subjects and their partners completed questionnaires using electronic patient-reported outcomes (ePRO) to record their experiences after each sexual intercourse attempt (using the SEP questionnaire and the onset and duration of action [erection] and erection hardness questions at home [male subjects and their female partners]), and at the end of each of the three 4-week periods during treatment (using the IIEF, PGI-S, PGI-C and SEAR questionnaires [male subjects only], and GAQ questionnaires [male subjects and their female partners]; to be completed at site visits for subjects and at home for their partners if preferred).

Open-label Extension: After completing the final follow-up visit (Visit 6) in the double-blind phase, subjects and their female partners were invited to take part in an open-label extension phase comprised of up to 12-months treatment for eligible subjects, with visits every 3 months. Participation in the extension phase was at the discretion of the individual subject and his partner. Recruitment continued until approximately 450 subjects and their female partners consented. The remaining subjects were discharged from the study.

It was planned to include a total of 450 male subjects and their female partners to participate in the first 6 months. A total of 150 male subjects and their female partners were then to continue in the last 6 months, and once this total was reached the remaining subjects were to be discharged from the study after completion of the first 6 months.

During the open-label extension phase, all subjects received MED2005 0.6% (w/w) GTN gel to deliver a 1.8 mg dose of GTN in the Dermasys vehicle.

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Male subjects completed the SEP questionnaire to record their experiences after each sexual intercourse attempt as and when they occurred. At each site visit male subjects completed the IIEF questionnaire to cover the previous 1 month.

NOTE: Only the results for the Double-blind Phase are presented in this report.

Number of Patients (planned and analysed):

Planned: 1000

Analysed: 1003

Diagnosis and Main Criteria for Inclusion: Males aged between 18 and 70 years, inclusive who had confirmed clinical diagnosis of ED for more than 3 months according to the NIGH Consensus Statement ('the inability to achieve or maintain penile erection sufficient for satisfactory sexual performance at least once') and answered yes to the question regarding the presence of residual EF over the past 3 months ('At home of the past 3 months, have you experienced at least some growth in your penis in response to [1]) mechanical stimulation by yourself or your partner or [2] visual stimulation?') were eligible to participate in this study. Additionally, they must have been involved in a continuous heterosexual relationship for at least 6 months prior to screening.

Test Product, Dose and Mode of Administration, and Lot Number(s): During the double-blind phase, 3 strengths of MED2005 were used in this study: 0.2% GTN gel (Lot number: 214068-0), 0.4% GTN gel (Lot number: 214069-0), and 0.6% GTN gel (Lot number 214071-0) all formulated into the Dermasys vehicle.

During the open-label phase all subjects received MED2005 0.6% GTN gel. **NOTE: Only the results for the Double-blind Phase are presented in this report.**

Reference Therapy, Dose and Mode of Administration, and Lot Number(s): During the double-blind phase, the matching placebo (Lot number: 214067-0) used was the Dermasys gel containing no active ingredients.

Duration of Treatment:

Double-blind Phase: 12 weeks (± 1 week)

Open-label Phase: 6 to 12 months

Criteria for Evaluation:

NOTE: Only the results for the Double-blind Phase are presented in this report.

Efficacy:

Double-blind Phase: Efficacy was evaluated using questionnaires (IIEF, SEP, SEAR, GAQ, PGI-S, PG-C) as well as subjective measures of time of onset and duration of action (erection) and erection hardness. Information on usage and application of the gels was evaluated.

Open-label Phase: Efficacy was evaluated using the SEP and IIEF questionnaires.

Safety:

Double-blind Phase: Safety was evaluated throughout the double-blind phase using standard assessments including physical examinations and visual examination of the penis, vital signs (BP, heart rate [HR], body temperature), standard clinical laboratory testing (haematology, biochemistry, urinalysis), 12-lead ECGs, pregnancy testing (females of childbearing potential only) and recording of AEs and concomitant medication with paper diaries (potential partner AEs were captured at site visits or by telephone).

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Open-label Phase: Safety was evaluated throughout the open-label extension phase by monitoring of AEs and concomitant medication with paper diaries (potential partner AEs were captured at site visits or via telephone call), monitoring of vital signs, ECGs, and visual examination of the penis.

Statistical Methods:

NOTE: Only the results for the Double-blind Phase are presented in this report.

Efficacy:

Double-blind Phase:

Primary Analyses:

The co-primary endpoints, assessed in the male subjects, were:

1. The change from baseline of the average of the Week 4, Week 8, and Week 12 IIEF-EF domain scores
2. The change in percentage of sexual intercourse attempts in which subjects were able to insert their penis into their partner's vagina (SEP Question 2) between baseline and the 12-week treatment period
3. The change in percentage of sexual intercourse attempts in which subjects were able to maintain an erection of sufficient duration to have successful intercourse (SEP Question 3) between baseline and the 12-week treatment period

For each of the 15 questions from IIEF, the number and percentage of subjects were summarised at each 4-week visit and by treatment group.

Absolute and change from baseline in the IIEF-EF, SEP questions 2 and 3 were summarised by treatment group at each 4-week visit and during the 12-week treatment period.

The statistical model for the primary analysis of the IIEF-EF was an analysis of covariance (ANCOVA) including terms for treatment group, country and baseline (as a continuous variable). Baseline ED severity, used as part of the randomisation scheme, was a categorical grouping of the baseline IIEF-EF and as such was not included in the primary analysis of the IIEF-EF as it already appeared in the model as a continuous variable.

The statistical model for the primary analyses of SEP Question 2 and SEP Question 3 was an ANCOVA including terms for treatment group, country, baseline (as a continuous variable) and baseline ED severity (categorical variable).

In addition, a dose response/trend test using a CONTRAST statement with dose as a categorical variable was performed (coefficients were Placebo = -3, MED2005 0.6 = -1, MED2005 1.2 = 1, MED2005 1.8 = 3).

Secondary Analyses:

- The analysis of the 3 co-primary endpoints (ANCOVA and trend test) was repeated in the 3 pre-specified subgroups of ED severity: mild, moderate and severe. The estimated mean change from baseline and its Bonferroni corrected 95% CI coming from the ANCOVA is displayed graphically for the 12-week treatment period and by treatment group for the Full Analysis Set.
- The change from baseline in the IIEF-EF domain, SEP Question 2 and SEP Question 3 were analysed using the same approach as for the primary endpoints (ANCOVA) at each 4-week visit. The estimated mean change from baseline and its Bonferroni corrected 95% CI coming from the

ANCOVA is displayed graphically by 4-week visit and by treatment group for the Full Analysis Set.

- Responder analyses assessing the proportion of subjects with a specific increase in the IIEF-EF domain from baseline as per the published minimally clinically important differences (MCIDs) according to Rosen 2011 were conducted. A subject was considered as responder with an increase of ≥ 2, ≥ 5 and ≥ 7 for the mild, moderate and severe baseline ED respectively. These analyses were done the same as the responder analyses for IIEF-EF, and SEP Questions 2 and 3. This analysis was repeated in the 3 pre-specified subgroups of ED severity: mild, moderate, and severe.
- Responder analyses for SEP Questions 2 and 3 for males only were conducted in the same way as for the IIEF-EF. A responder was defined as having an increase of –1.3%, 16.7% and 27.3% for SEP Question 2 and 5.0%, 23.3% and 17.0% for SEP Question 3 for subjects with mild, moderate, and severe baseline ED, respectively as per the published MCID according to Araujo 2012. The same methodology and analysis as the one used previously for IIEF-EF was applied for SEP Questions 2 and 3. This analysis was repeated in the 3 pre-specified subgroups of ED severity: mild, moderate, and severe.
- Responder analyses assessing the proportion of subjects with a specific increase in the IIEF-EF, SEP Questions 2 and 3 domains from baseline, using a different responder definition defined separately for each baseline severity group, were conducted. The thresholds were defined using a set of data from this study prior to study unblinding. A responder was defined as having an increase of ≥ 3.3, ≥ 6.7 and ≥ 9.4 on IIEF-EF for the mild, moderate and severe baseline ED respectively. A responder was defined as having an increase of ≥ 3.7%, ≥ 30.2% and ≥ 34.3% on SEP Question 2 and ≥ 27.4%, ≥ 31.6% and ≥ 27.6% on SEP Question 3 for subjects with mild, moderate and severe baseline ED, respectively. The proportion of responders was summarised at each 4-week visit, and on the 12-week treatment period. The 12-week treatment period response was analysed using a logistic regression, with fixed effects for treatment group, country and baseline ED severity (categorical variable). The analyses were repeated in the three pre-specified subgroups of ED severity: mild, moderate and severe.
- The GAQ allows the subject to rate (yes or no) the improvement in EF. Subjects completed GAQ Question 1 ‘Has the treatment you have been taking improved your erectile function?’ and if necessary Question 2 ‘If yes, has the treatment improved your ability to engage in sexual activity?’. If a subject answered No at Question 1, then his Question 2 answer was set as No. The number and percentage of subjects answering Yes or No to both questions was summarised at each 4-week visit and by treatment group. Each 4-week visit response was analysed using a logistic regression. The model was implemented in SAS using the LOGISTIC procedure using the same methodology as the one described for the responder analysis for IIEF-EF, and SEP Questions 2 and 3. The same analysis was repeated on assessments provided by female partners.
- The 4 other domains from IIEF are: orgasmic function (2 questions), sexual desire, (2 questions), intercourse satisfaction (3 questions) and overall satisfaction (2 questions). Absolute and changes from baseline were summarised by treatment group and 4-week visit and the average during the 12-week treatment period for the 4 domains. In addition, the other IIEF domains were analysed using an ANCOVA including terms for treatment group, country, baseline (as a continuous variable) and baseline ED severity (categorical variable) to provide estimates of the change from baseline to each 4-week visit and during the 12-week treatment period.
- The change in the other SEP questions (Questions 1, 4, and 5) was summarized and analysed using the same methodology (ANCOVA) as the one described for change from baseline in the SEP

Question 2 and SEP Question 3 at each 4-week visit and during the 12-week treatment period. The same analysis was repeated on the 5 SEP questions completed by female partners.

- For each of the 14 items from SEAR, the number and percentage of subjects were summarised at each 4-week visit and by treatment group. Absolute and changes from baseline were summarised by treatment group and 4-week visit and during the 12-week treatment period for both domains, both subscales and the overall score. In addition, both domains and the overall score were analysed using an ANCOVA including terms for treatment group, country, baseline (as a continuous variable) and baseline ED severity (categorical variable) to provide estimates of the change from baseline to each 4-week visit and during the 12-week treatment period. The 12-week treatment period was defined as the average of the Week 4, Week 8 and Week 12 scores.
- For PGI-S actual and changes from baseline (as continuous variables), as well as actual (as categorical variable) were summarised by treatment group and 4-week visit and during the 12-week treatment period. The 12-week treatment period value was the average of Week 4, Week 8, and Week 12 assessments. In addition, PGI-S was analysed using an ANCOVA including terms for treatment group, country, baseline (as a continuous variable) and baseline ED severity (categorical variable) to provide estimates of the change from baseline to each 4-week visit and during the 12-week treatment period.
- For PGI-C, actual values (as continuous as well as categorical variable) were summarised by treatment group and 4-week visit and during the 12-week treatment period. The 12-week treatment period value was the actual score at Week 12. In addition, PGI-C was analysed using an ANCOVA including terms for treatment group, country and baseline ED severity (categorical variable) to provide estimates of the value at each 4-week visit and during the 12-week treatment period
- The subjects and their partners were asked 4 questions about the onset and duration of their/their partner's erection and erection hardness in conjunction with the SEP after each sexual intercourse attempt during each of the three 4-weekly periods during treatment in the double-blind phase (i.e., Weeks 1 through 4, 5 through 8, and 9 through 12). For each of the 4 questions, the number and percentage of records within each category were summarised by treatment group. Similarly, a cumulative summary within each category was provided. For each of the 4 questions, averaged rank values were summarised by treatment group and 4-week visit and during the 12-week treatment period and analysed using an ANCOVA including terms for treatment group, country and baseline ED severity (categorical variable) to provide estimates of the value at each 4-week visit and during the 12-week treatment period. The 12-week treatment period was defined as the average of the Week 1 through 4, Week 5 through 8 and Week 9 through 12 scores. The same analysis was repeated on assessments provided by female partners.
- Questions on the usage and application of the gel were completed once by the subject at the end of the treatment period in the double-blind phase (Visit 5). Responses were summarised by treatment group.

Efficacy analyses were to be conducted using the Full Analysis Set (all randomised subjects who made use of the medication at least once). The co-primary efficacy endpoints were, additionally, analysed using the PP Analysis Set (all subjects in the Full Analysis Set who completed the 12-week treatment period without protocol deviations that were deemed to have a major impact on the co-primary efficacy endpoints and who had valid IIEF at Week 12 (Visit 5) and valid SEP Question 2 and SEP Question 3 assessments leading up Week 12 (Visit 5).

Formal statistical hypothesis testing was performed on the primary and secondary efficacy endpoints with all tests conducted at the 2-sided, 5% level of significance. A Bonferroni correction was used to take into account that there were three active versus placebo comparisons. All p-values resulting from comparing the three different MED2005 doses versus placebo were multiplied by three and statistical significance was then declared if $p < 0.05$. Corresponding Bonferroni corrected 95% confidence intervals (CI) were produced. The objective for the double-blind phase was for all co-primary endpoints to show superiority of MED2005 to placebo in order to conclude a significant result of the study. For this objective, no additional adjustment for multiplicity of the error probability for the individual co-primary endpoints was required.

For the analysis of primary and secondary endpoints, multiple imputation (MI) was used to handle missing values. The imputation method of choice depended on the pattern of missingness in the data. Any missing values in efficacy questionnaire data that occurred during the treatment period and was then followed by observed data was treated as missing at random. Remaining missing values for the endpoints for subjects who left the study and provided no further questionnaire data were handled using a control-based multiple imputation approach. The imputation model for the missing observations in both the MED2005 and placebo (control) groups was constructed from the control group only. This assumes that efficacy results post withdrawal, for subjects who withdraw, would have mirrored those seen in the placebo group and thus lose any potential MED2005 treatment benefit.

Open-label Phase:

- For the 5 IIEF domains and the 5 SEP Questions, absolute and changes from baseline were summarised by treatment group and 3-month visit on the Open-label Analysis Set. The baseline assessments were the ones prior to the double-blind phase. There was no formal comparison between treatment groups; that is, no statistical hypothesis testing. Summaries of responders at each visit were given using the same responder definitions (per published MCID and thresholds determined using a suitable set of data from this study, prior to study unblinding) for IIEF-EF, SEP Questions 2 and 3.

Safety:

Safety analyses were conducted using the Safety Analysis Set (all randomised subjects who made use of the medication at least once) for double-blind phase and the Open-Label Analysis Set (all subjects who made use of medication at least once during the open-label extension phase) for the open-label phase.

Adverse Events (AEs):

Adverse events were coded using the current version of the Medical Dictionary for Regulatory activities (MedDRA) and displayed in tables and listings using System Organ Class (SOC) and Preferred Term (PT). An overview of AEs is presented and includes the number and percentage of subjects with at least one:

- Treatment-emergent AE (TEAE)
- TEAE related to the study drug
- Serious TEAEs
- TEAE leading to treatment discontinuation
- TEAE leading to study discontinuation
- TEAE leading to death

This overview AEs table was to be repeated by nitrate users.

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The number of TEAEs and number (%) of subjects with TEAEs were summarised by SOC and PT. The same summary was provided for all serious TEAEs.

In addition, the TEAEs were summarized by SOC, by PT and by severity, by relationship to study treatment and by duration (≤ 1 day; > 1 to ≤ 3 days; > 3 to ≤ 7 days; > 7 days).

Clinical Laboratory Assessment:

Laboratory data were only collected during double-blind phase. Laboratory parameters (haematology, biochemistry and urinalysis) were summarised over the scheduled visits by treatment group. The actual value and change from baseline were summarised for the haematology and biochemistry parameters based on central laboratory measurements.

Urinalysis categorical parameters were summarised using the number and percentage of subjects within each category.

In addition, for haematology and biochemistry parameters, number of subjects in each low/normal/high category based on laboratory reference ranges were provided at baseline and each post-baseline visit.

All laboratory data were provided in data listings. Laboratory values outside the reference range were flagged in the subject listings.

A subset listing is presented for all laboratory values with an overall abnormal clinically significant assessment.

Physical Examination:

All physical examination findings are presented in a data listing.

Electrocardiogram:

The actual value and change from baseline in ECG parameters (ventricular rate, PR interval, QRS duration, QT interval corrected using Bazett's formula [QTcB] interval) were summarised descriptively by treatment group and time point (week 12 for the double-blind phase and at month 12 or month 6 for subjects who did not continue in the last 6 months of the study for open-label phase).

ECG Overall Interpretation (normal, abnormal clinically and not clinically significant results) was summarized at baseline and each study visit.

Medications:

Prior and concomitant medications were coded using the World Health Organization (WHO) Drug Dictionary. Number and percentages of subjects with at least 1 medication were tabulated by Anatomic Therapeutic Chemical class (ATC level 2) and PT. ATC classes were sorted by descending order of frequency in the total column and the same rule applied for PTs within each ATC class. Previous therapies and concomitant therapies were summarized separately. Data for males and data for females were summarized separately in a same output. Prior and concomitant medications were also summarized by nitrate users.

Efficacy Results:

- The primary objective was assessed via the change compared to baseline in the IIEF–EF domain of the IIEF-EF the ability to achieve vaginal penetration (SEP Question 2) and the ability to have successful intercourse (SEP Question 3) over 12 weeks of treatment. This was to demonstrate the efficacy of MED2005 versus placebo in male subjects clinically diagnosed with ED using the EF domain of the IIEF, the SEP Question 2, and the SEP Question 3. For all 3 of these assessments, all 4 treatment groups saw mean improvements from baseline to the 12-week period. These mean improvements were similar amongst all 4 the treatment groups and achieved $p < 0.001$.

- Mean changes in the IIEF-EF from baseline to the 12-week period for observed values were also similar among the treatment groups and ranged from an improvement of 4.82 in the 1.2 mg group to 5.22 in the 1.8 mg group. The mean change from baseline to the 12-week period for observed values for the placebo group was 5.10. The LS mean change from baseline values from the ANCOVA were also similar among the treatment groups and ranged from an improvement of 3.41 in the 0.6 mg group to 3.67 in the 1.8 mg group. The LS mean change from baseline for the placebo group was 3.61. The mean IIEF-EF values at baseline for the Full Analysis Set were similar among the treatment groups and ranged from 16.51 in the 0.6 mg group to 16.78 in the 1.2 mg group; the mean was 16.58 in the placebo group. The median IIEF-EF values at baseline were 18.00 for all treatment groups. There was no evidence of differences between any MED2005 dose and placebo regardless of the severity of ED.
- Mean changes in SEP Question 2 from baseline to the 12-week period were also similar among the treatment groups and ranged from 18.65 in the 0.6 mg group to 24.26 in the placebo group. The LS mean change from baseline values from the ANCOVA were also similar among the treatment groups and ranged from an improvement of 9.04 in the 0.6 mg group to 13.82 in the placebo group. The p-values for the within-group change from baseline (testing the null hypothesis of no change) were < 0.001 for all groups including placebo. The mean SEP Question 2 values at baseline for the Full Analysis Set were similar among the treatment groups and ranged from 61.80 in the placebo group to 65.27 in the 1.8 mg group. There was no evidence of differences between any MED2005 dose and placebo.
- Mean SEP Question 3 changes from baseline to the 12-week period were similar among the treatment groups and ranged from 34.80 in the 0.6 mg group to 37.14 in the placebo group. The LS mean change from baseline values from the ANCOVA were also similar among the treatment groups and ranged from an improvement of 20.81 in the 0.6 mg group to 23.33 in the 1.8 mg group; the value for the placebo group was 23.18. The p-values for the within-group change from baseline (testing the null hypothesis of no change) were < 0.001 for all groups including placebo. The mean SEP Question 3 values at baseline for the Full Analysis Set were similar among the treatment groups and ranged from 21.45 in the placebo group to 25.06 in the 1.8 mg group There was no evidence of differences between any MED2005 dose and placebo.

- For the following, mean changes from baseline were generally similar among the treatment groups at all time points, with all 4 treatment groups showing improvements compared with baseline. The p-values for the within-group change from baseline (testing the null hypothesis of no change) were < 0.05 for most groups including placebo (with many having $p < 0.001$). There was no evidence of differences between any MED2005 dose and placebo.
  - Regardless of the severity of ED:
    - IIEF-EF: All treatment groups showed large mean changes from their respective baseline scores. The mean changes from baseline in IIEF-EF by severity ranged from 2.42 to 3.15, 5.84 to 7.13, and 10.51 to 13.92 for the subjects with mild, moderate, and severe ED, respectively. Mean baseline IIEF-EF score ranged from 19.85 to 20.23, 13.43 to 13.72, and 7.76 to 8.09. There was an increase in the IIEF-EF scores over the 12-week period compared with baseline for all treatment groups with the mean of the observed scores ranging from 22.26 to 23.08, 19.23 to 20.71, and 18.26 to 22.02 for the subjects with mild, moderate, and severe ED, respectively.

- SEP Question 2: All treatment groups showed large mean changes from their respective baseline scores. The mean changes from baseline in SEP Question 2 by severity ranged from 7.71 to 12.86, 25.67 to 31.73, and 42.51 to 64.40 for the subjects with mild, moderate, and severe ED, respectively. Mean baseline SEP Question 2 scores ranged from 76.99 to 79.77, 46.52 to 56.81, and 16.51 to 26.65 for the subjects with mild, moderate, and severe ED respectively. There was an increase the SEP Question 2 scores over the 12-week period compared with baseline for all treatment groups with the mean observed scores ranging from 86.60 to 90.60, 75.96 to 84.64, and 69.15 to 81.11 for the subjects with mild, moderate and severe ED respectively.
- SEP Question 3: All treatment groups showed large mean changes from their respective baseline scores. The mean changes from baseline in SEP Question 3 by severity ranged from 30.87 to 36.45, 33.33 to 39.51, and 39.40 to 49.07, for subjects with mild, moderate, and severe ED, respectively. Mean baseline SEP Question 3 scores ranged from 29.26 to 35.23, 7.79 to 14.77, and 2.19 to 5.30 for the subjects with mild, moderate, and severe ED respectively. There was an increase the SEP Question 3 scores over the 12-week period compared with baseline for all treatment groups with the mean observed scores ranging from 65.33 to 68.31, 46.24 to 53.84, and 44.71 to 51.88 for the subjects with mild, moderate and severe ED, respectively.

o IIEF-EF and SEP Questions 2 and 3 over time:

- At Week 4, the LS mean of the IIEF-EF was similar among the treatment groups and ranged from 2.65 in the 0.6 mg group to 3.00 in the 1.8 mg group; the LS mean for placebo was 2.97. The LS mean change from baseline increased at Week 8 compared with Week 4. The Week 8 results were also similar among the treatment groups and ranged from 3.52 in the 1.2 mg group to 3.92 in the placebo group. Week 12 LS means were similar to Week 8 and also among the treatment groups ranging from 3.70 in the 0.6 mg group to 4.30 in the 1.8 mg group; the LS mean for the placebo group was 3.93.
- At Week 4, the LS mean for SEP Question 2 was largest in the placebo group (12.61) followed by the 1.2 mg group (11.07), the 1.8 mg group (8.92), and the 0.6 mg group (6.77). At Week 8, the LS mean for SEP Question 2 was largest in the placebo group (14.91), followed by the 1.2 mg group (13.63), the 1.8 mg group (11.73), and the 0.6 mg group (9.04). At Week 12, the LS mean for SEP Question 2 was largest in the 1.2 mg group (15.44), followed by the placebo group (13.74), the 1.8 mg group (11.50) and the 0.6 mg group (11.30).
- At Week 4, the LS mean for SEP Question 3 was largest in the placebo group (19.15), followed by the 1.8 mg group (17.54), the 1.2 mg group (16.16), and the 0.6 mg group (14.67). The LS mean change from baseline increased at Week 8 compared with Week 4. At Week 8, the LS mean for SEP Question 3 was similar among the treatment groups and ranged from 22.26 for the 0.6 mg group to 25.09 in the 1.8 mg group. Week 12 LS mean results were similar among the treatment groups and ranged from 25.38 in the 0.6 mg group to 27.43 in the 1.8 mg group; the LS mean for the placebo group was 26.42. The LS means for Question 3 increased over time for all treatment groups.

- Responders with an increase of ≥ 2, ≥ 5, ≥ 7 in IIEF-EF for mild, moderate, and severe ED respectively (based on Rosen): Overall, the estimated proportions of responders for the IIEF-EF over the 12-week period, as per logistic regression analysis, were 0.63 in the placebo group, 0.64 in the 0.6 mg group, 0.62 in the 1.2 mg group, and 0.70 in the 1.8 mg group. When analysed by ED severity, the subjects with mild ED had estimated proportions that were similar, ranging from 0.61 in the placebo and 0.6 mg groups to 0.63 in the 1.2 mg and 1.8 mg groups. For subjects with moderate ED, the estimated proportions of responders were 0.59, 0.60, 0.56, and 0.75 in the placebo, 0.6 mg, 1.2 mg, and 1.8 mg groups, respectively. As with the percentages of responders, the estimated proportion of responders was highest in subjects with severe ED, ranging from 0.72 in the 1.2 mg group to 0.88 in the 1.8 mg group; the estimated proportion of responders was 0.80 in the placebo group.
- Responder with an increase of –1.3%, 16.7% and 27.3% for SEP Question 2 or an increase of 5.0%, 23.3% and 17.0% for SEP Question 3 (based on Araujo):
  - SEP Question 2: Overall, the estimated proportions of responders for SEP Question 2 over the 12-week period, as per the logistic regression analysis, were 0.75 in the placebo group, 0.72 in the 0.6 mg group, 0.74 in the 1.2 mg group, and 0.73 in the 1.8 mg group. When analysed by ED severity, the subjects with mild ED had estimated proportions that were similar, ranging from 0.80 in the 0.6 mg group to 0.83 in the placebo and 1.2 mg groups. For subjects with moderate ED, the estimated proportions of responders were similar among the groups and ranged from 0.56 in the 0.6 mg group to 0.63 in the 1.2 mg group; the estimated proportion of responders was 0.57 in the placebo group. The estimated proportions of responders in subjects with severe ED were 0.77, 0.72, 0.58, and 0.69 in the placebo, 0.6 mg, 1.2 mg, and 1.8 mg groups, respectively.
  - SEP Question 3: Overall, the estimated proportions of responders for SEP Question 3 over the 12-week period, as per the logistic regression analysis, were 0.68 in the placebo group, 0.67 in the 0.6 mg group, 0.67 in the 1.2 mg group, and 0.70 in the 1.8 mg group. When analysed by ED severity, the subjects with mild ED had estimated proportions that were similar, ranging from 0.69 in the 0.6 mg group to 0.72 in the 1.8 mg group; the estimated proportion was 0.71 in the placebo group. For subjects with moderate ED, the estimated proportions of responders were similar among the groups and ranged from 0.59 in the 1.2 mg group to 0.63 in the 1.8 mg group. The estimated proportions of responders in subjects with severe ED were 0.71, 0.69, 0.64, and 0.75 in the placebo, 0.6 mg, 1.2 mg, and 1.8 mg groups, respectively.
- IIEF-EF and SEP Questions 2 and 3 responder analysis based on thresholds estimated using the blinded study data (based on Responder Thresholds Analyses):
  - For the IIEF-EF, a responder was defined as an increase of ≥ 3.3, ≥ 6.7 and ≥ 9.4 for the mild, moderate and severe ED, respectively. Overall, the estimated proportions of responders over the12-week period, as per the logistic regression analysis, were 0.51 in the placebo group, 0.54 in the 0.6 mg group, 0.49 in the 1.2 mg group, and 0.55 in the 1.8 mg group. When analysed by severity of ED, the estimated proportion of responders were similar for male subjects with mild ED (0.49, 0.50, 0.49, and 0.50 for the placebo, 0.6 mg, 1.2 mg, and 1.8 mg groups, respectively). For subjects with moderate ED, the estimated proportion of responders was smallest in the placebo group (0.44) and largest in the 1.8 mg group

(0.54). The highest estimated proportions of responders was seen in subjects with severe ED with 0.73, 0.83, 0.56, and 0.80 responders in the placebo, 0.6 mg, 1.2 mg, and 1.8 mg groups, respectively.

- For SEP Question 2, a responder was defined as an increase of ≥ 3.7%, ≥ 30.2% and ≥ 34.3% for mild, moderate and severe ED, respectively. Overall, the estimated proportions of responders for SEP Question 2 over the 12-week period, as per logistic regression analysis, were 0.45 in the placebo group, 0.40 in the 0.6 mg group, 0.48 in the 1.2 mg group, and 0.43 in the 1.8 mg group. When analysed by severity of ED, the estimated proportion of responders for male subjects with mild ED was smallest in the 0.6 mg group (0.32) and largest in the 1.2 mg group (0.42); the estimated proportion was 0.38 in the placebo group. For subjects with moderate ED the estimated proportion of responders was smallest in the 0.6 mg group (0.44) and largest in the 1.2 mg group (0.56); it was 0.47 in the placebo group. In subjects with severe ED, the estimated proportion of responders ranged from 0.57 in the 1.2 mg group to 0.73 in the placebo group.
- For SEP Question 3, a responder was defined as an increase of ≥ 27.4%, ≥ 31.6% and ≥ 27.6% for mild, moderate, and severe ED, respectively. Overall, the estimated proportions of responders for SEP Question 3 over the 12-week period, as per logistic regression analysis, were 0.53 in the placebo group, 0.52 in the 0.6 mg group, 0.52 in the 1.2 mg group, and 0.52 in the 1.8 mg group. When analysed by severity of ED, the estimated proportion of responders for male subjects with mild ED was similar among the treatment groups (0.52, 0.49, 0.51, and 0.48 in the placebo, 0.6 mg, 1.2 mg, and 1.8 mg groups, respectively). The estimated proportion of responders with moderate ED were similar to those with mild ED and similar among the treatment groups (0.49, 0.53, 0.49, and 0.54 in the placebo, 0.6 mg, 1.2 mg, and 1.8 mg groups, respectively). The highest estimated proportions of responders was seen in subjects with severe ED with values ranging from 0.60 in the 1.2 mg group to 0.69 in the 1.8 mg group.

o GAQ:

- For both male subjects and female partners, the answers to GAQ were found to be similar.

o IIEF other domains

- For the IIEF-IS, mean changes from baseline for the 12-week period were 1.70, 1.76, 1.55, and 1.57 in the placebo, 0.6 mg, 1.2 mg and 1.8 mg groups, respectively. The LS mean changes from baseline were similar among the treatment groups at all time points. The LS mean changes from baseline during the 12-week period ranged from 1.01 in the 1.8 mg group to 1.10 in the 1.2 mg group. The means at baseline ranged from 7.88 in the placebo and 0.6 mg groups to 8.12 in the 1.2 mg group.
- For the IIEF-OF, mean changes from baseline during the 12-week period were 1.25, 1.44, 1.20, and 1.40 in the placebo, 0.6 mg, 1.2 mg and 1.8 mg groups, respectively. The LS mean changes from baseline were similar among the treatment groups at all time points. The LS mean changes from baseline during the 12-week period ranged from 0.90 in the 1.2 mg group to 1.10 in the 1.8 mg group. The means at baseline ranged from 6.00 in the 0.6 mg group to 6.25 in the 1.2 mg group; the mean for the placebo group was 6.24.

- For the IIEF-OS, mean changes from baseline during the 12-week period were 1.60, 1.82, 1.60, and 1.80 in the placebo, 0.6 mg, 1.2 mg and 1.8 mg groups, respectively. The LS mean changes from baseline were similar among the treatment groups at all time points. The LS mean changes from baseline during the 12-week period ranged from 0.97 in the placebo group to 1.14 in the 1.8 mg group. The means at baseline ranged from 4.97 in the 1.8 mg group to 5.18 in the 1.2 mg group; the mean was 4.98 in the placebo group.
- For the IIEF-SD, mean changes from baseline during the 12-week period were 0.64, 0.84, 0.57, and 0.68 in the placebo, 0.6 mg, 1.2 mg and 1.8 mg groups, respectively. The LS mean changes from baseline were similar among the treatment groups at all time points. The LS mean changes from baseline during the 12-week period ranged from 0.56 in the 1.8 mg group to 0.66 in the 0.6 mg group; the LS mean was 0.59 in the placebo group. The means at baseline ranged from 6.13. in the 0.6 mg group to 6.42 in the 1.2 mg group; the mean was 6.30 in the placebo group.

o SEP other questions

- For both male subjects and female partners, the answers to SEP Questions were found to be similar.

o SEAR questionnaire

- For the SEAR total score, mean changes from baseline during the 12-week period were 14.72, 16.56, 14.35, and 15.01 in the placebo, 0.6 mg, 1.2 mg, and 1.8 mg groups, respectively. LS means were similar among the treatment groups at all time points. The LS mean changes from baseline during the 12-week period ranged from 10.78 in the placebo group to 12.07 in the 0.6 mg group. The means at baseline ranged from 38.05 in the 0.6 mg group to 39.57 in the 1.2 mg group; the mean for the placebo group was 38.65.
- For the SEAR sexual relationship satisfaction domain, mean changes from baseline during the 12-week period were 15.58, 17.83, 15.90, and 15.70 in the placebo, 0.6 mg, 1.2 mg, and 1.8 mg groups, respectively. LS means were similar among the treatment groups at all time points. The LS mean changes from baseline during the 12-week period ranged from 11.60 in the placebo group to 13.04 in the 0.6 mg group. The means at baseline ranged from 37.21 in the 0.6 mg group to 38.68 in the 1.8 mg group; the mean was 38.10 in the placebo group.
- For the SEAR confidence domain, mean changes from baseline during the 12-week period were 13.58, 14.87, 12.28, and 14.09 in the placebo, 0.6 mg, 1.2 mg, and 1.8 mg groups, respectively. LS means were similar among the treatment groups at all time points. The LS mean changes from baseline during the 12-week period ranged from 9.59 in the placebo group to 10.70 in the 0.6 mg group. The means at baseline ranged from 39.17 in the 0.6 mg group to 41.17 in the 1.2 mg group; the mean was 39.38 in the placebo group.
- For the SEAR self-esteem subdomain, mean changes from baseline during the 12-week period were 11.80, 12.14, 10.15, and 10.09 in the placebo, 0.6 mg, 1.2 mg, and 1.8 mg groups, respectively. LS means were similar among the treatment groups at all time points. The LS mean changes from baseline during the 12-week period ranged from 7.34 in the 1.8 mg group to 8.20 in the 0.6 mg group; the LS

mean was 8.01 in the placebo group. The means at baseline ranged from 38.15 in the placebo group to 39.73 in the 1.2 mg group.

- For the SEAR overall relationship satisfaction subdomain, mean changes from baseline during the 12-week period were 17.14, 20.33, 16.54, and 22.10 in the placebo, 0.6 mg, 1.2 mg, and 1.8 mg groups, respectively. In general, LS means were similar among the treatment groups at all time points. The LS mean changes from baseline during the 12-week period ranged from 12.66 in the placebo group to 15.60 in the 0.6 mg group. The means at baseline ranged from 39.47 in the 1.8 mg group to 44.05 in the 1.2 mg group; the mean was 41.85 in the placebo group.

- Patient Global Impression scales
  - PGI-S: At baseline, the majority of subjects had ED that they considered to be moderate, severe, or very severe in each treatment groups (range: 88.8% in the placebo group to 92.1% in the 0.6 mg group). During the 12-week period, the majority of subjects had ED that they considered to be none, mild, or moderate (range: 84.4% in the placebo group to 87.4% in the 1.8 mg group).
  - PGI-C: For the PGI-C, means at Week 4 ranged from 2.9 in the 1.2 mg group to 3.1 in the placebo group. The 12-week period means were 2.9, 2.7, 2.7, and 2.6 for the placebo, 0.6 mg, 1.2 mg, and 1.8 mg groups, respectively. LS means were similar among the treatment groups at all time points. There was no evidence of differences between any MED2005 dose and placebo except for the 12-week period in the 1.8 mg group ($p = 0.050$). During the 12-week period, the majority of subjects (66.9% in the placebo group, 70.4% in the 0.6 mg group, 75.7% in the 1.2 mg group, and 77.4% in the 1.8 mg group) thought that their ED was very much better, moderately better or a little better

- Onset of action and hardness questions
  - For both male subjects and female partners, the answers to the onset of action and hardness questions were found to be similar.
  - With regards to the total number of intercourse attempts, cumulatively, in the placebo group subjects noted erections starting almost immediately (8.2%), under 5 minutes (32.1%) and under 10 minutes (60.1%) and were able to have penetrative sex almost immediately (6.3%), under 5 minutes (24.7%) and under 10 minutes (54.5%). Similar patterns were noted in the 3 active treatment groups.
- In all treatment groups, the majority of subjects applied the gel themselves (range: 67.6% in the 1.2 mg group to 72.3% in the 1.8 mg group; 70.6% in the placebo group), with a corresponding 27.7% to 32.4% being applied by the partner (29.4% in the placebo group). Additionally, the majority of subjects found the tube easy to use (range: 60.0% in the 1.2 mg group to 62.6% in the placebo group) and the gel easy to apply (range: 86.7% in the 1.2 mg group to 90.9% in the 0.6 mg group; 89.6% in the placebo group). The majority in all treatment groups did not prefer to use a different applicator (range: 76.4% in the 1.2 mg group to 86.8% in the 0.6 mg group; 84.4% in the placebo group). The gel was incorporated into foreplay in slightly more than 50% of subjects in each treatment group (range: 51.7% in the placebo group to 56.3% in the 1.8 mg group). The majority of subjects liked the gel a lot or mostly liked the gel (range: 53.8% in the 1.2 mg group to 63.9% in the 1.8 mg group; 58.3% in the placebo group).

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Safety Results:

- There were no deaths in male subjects during the study and of the 3 serious TEAEs reported during the study (all unrelated to IMP) only 3 subjects (all in the 0.6 mg group) reported serious TEAEs: 1 subject reported moderate pneumonia, 1 subject reported severe acute myocardial infarction, and a third subject reported mild arthralgia.
- Overall, 22.7% (171/753) of male subjects who received MED2005 reported a TEAE during the study compared with 8.4% (21/250) of subjects who received placebo. The incidences of TEAEs were similar among the MED2005 treatment groups (21.5%, 20.9%, and 25.7% in the 0.6 mg, 1.2 mg, and 1.8 mg groups, respectively).
- TEAEs occurring in ≥ 2.0% of male subjects in any treatment group were increased blood pressure (2.0% in the 1.2 mg group compared with 0% in the placebo and 1.8 mg groups and 0.8% in the 0.6 mg group), headache (2.8%, 10.8%, 9.5%, and 17.3% in the placebo, 0.6 mg, 1.2 mg, and 1.8 mg groups, respectively), and penile burning sensation (1.2%, 1.2%, 2.0%, and 6.0% in the placebo, 0.6 mg, 1.2 mg, and 1.8 mg groups, respectively).
- More male subjects who received MED2005 (12.5%) reported headache than did subjects who received placebo (2.8%). The incidences of headache were similar in the 0.6 mg and 1.2 mg groups (10.8% and 9.5%, respectively) while the incidence in the 1.8 mg group was higher (17.3%). The incidences of penile burning sensation were similar among the placebo (1.2%), 0.6 mg (1.2%), and 1.2 mg (2.0%) groups. Overall, 6.0% of subjects in the 1.8 mg group reported a penile burning sensation.
- Two male subjects reported TEAEs that led to study withdrawal: the serious TEAE of arthralgia in a subject in the 0.6 mg group and a TEAE of presyncope in a subject in the 1.8 mg group.
- There were no deaths, serious TEAEs, or TEAEs leading to study withdrawal in female partners during the study. Overall, 2.7% (20/753) of female partners whose male subject received MED2005 reported a TEAE during the study compared with 0.8% (2/250) of female partners whose subjects received placebo. The 3 TEAEs in 2 female partners whose male subject received placebo were headache and rhinitis in 1 female partner and vulvovaginal burning sensation in 1 female partner. The incidences of TEAEs were similar among the MED2005 treatment groups (2.4%, 2.0%, and 3.6% in the 0.6 mg, 1.2 mg, and 1.8 mg groups, respectively).
- The incidences of headache in female partners were similar among the treatment groups and ranged from 0.4% in the placebo group to 2.4% in the 1.8 mg group. Vulvovaginal burning sensation was reported in 3 female partners: 1 whose male subject received placebo and 2 whose male subjects received 1.8 mg.
- No clinically meaningful changes in laboratory values, vital signs, or ECG results were noted

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Conclusions:

It was not possible to differentiate the efficacy of the different dose strengths of MED2005 from the placebo vehicle gel (Dermasys) (except for the GAQ Question 1 in female partners and the PGI-C which did differentiate from placebo).

Large changes from the baseline scores were observed in each of the treatment groups. The subjects who received placebo and those who received MED2005 had similar clinically relevant responses. The estimated proportions of responders for the IIEF-EF over the 12-week period, as per logistic regression analysis, ranged from 0.62 in the 1.2 mg group to 0.70 in the 1.8 mg group. When analysed by ED severity, the subjects with mild and moderate ED had estimated proportions that were similar (0.61 in the placebo and 0.6 mg groups to 0.63 in the 1.8 mg group for mild ED and 0.59 in the placebo group to 0.75 in the 1.8 mg group). The estimated proportion of responders was highest in subjects with severe ED, ranging from 0.72 in the 1.2 mg group to 0.88 in the 1.8 mg group; the estimated proportion of responders was 0.80 in the placebo group.

For all treatment groups, a response within 10 minutes of application was seen in the majority of intercourse attempts. In all treatment groups, the majority of subjects applied the gel themselves (range: 67.6% in the 1.2 mg group to 72.3% in the 1.8 mg group; 70.6% in the placebo group), with a corresponding 27.7% to 32.4% being applied by the partner (29.4% in the placebo group). The majority of subjects in each treatment group reported that they found the gel easy to apply.

The application of MED2005 0.6 mg (0.2% w/w), 1.2 mg (0.4% w/w), or 1.8 mg (0.6% w/w) or placebo was generally safe and well tolerated. There were no treatment related SAEs reported during the study The low incidences of TEAEs in female partners are indicative of lack of transference of MED2005 or placebo to the female partner.

Following the outcome of the study Futura would be interested in pursuing the placebo gel (Dermasys) as a treatment for ED because of the following:

- The placebo gel was highly effective and performed equally as well in terms of efficacy as the MED2005 gel and was found to be safe (there were no serious TEAEs in male subjects who received placebo gel). No events of penile dryness were reported.
- 60% of intercourse attempts had an onset of erection using the placebo gel within 10 minutes, which is much faster than published figures for PDE5s
- There was no evidence of a drop off in efficacy over time, indeed efficacy appeared to improve over time
- The placebo gel (Dermasys) would likely have no drug interactions with other medical treatments-and could be used in combination therapy

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