2. SYNOPSIS

Name of Company: Futura Medical Developments Ltd	**Volume:**	(For national authority use only)
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:

(Open-label Phase): 14 March 2019

Date of last patient, last visit 20 January 2020

NOTE: Only the results for the subjects who entered the open-label extension are presented in this report.

Principal Investigator: Dr Andrzej - Robert Depko

Study Centres:

This open-label extension part of the study took place in 34 centres in 8 countries including Poland, Hungary, Czech Republic, Georgia, Russia, Ukraine, Bulgaria and Latvia

Publication(s):

None to date.

Objectives:

For the open-label phase:

- To evaluate the long-term (up to 12 months) efficacy of MED2005
- To evaluate the safety of MED2005 using adverse events (AEs)

Study Design:

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.

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.

Name of Company: Futura Medical Developments Ltd	**Volume:**	(For national authority use only)
Name of Finished Product: MED2005	**Page:**	
Name of Active Ingredient(s): Glyceryl trinitrate		

The decision was made to stop the open-label extension prematurely because, despite all treatment groups showing an improvement in the patients' ED, it was not possible to differentiate between the efficacy between the MED2005 doses and the placebo (Dermasys) group in the double-blind phase.

Number of Patients (planned and analysed):

Planned: 450 for first 6 months of the open-label extension and 150 for next 6 months of the open-label extension

Analysed: 443 started first 6 months of the open-label extension and 75 started next 6 months of the open-label extension

Diagnosis and Main Criteria for Inclusion:

Subjects who completed the double-blind phase, were compliant to study procedures and who consented to the open-label extension phase. Exclusion criteria included:

1. Subsequent to recruitment into the double-blind phase of the study, had developed any significant or serious cardiovascular, pulmonary, hepatic, renal, gastrointestinal, haematological, endocrinological, metabolic, neurological, or psychiatric disease which, in the opinion of the investigator, rendered the subject unfit to continue in the open-label extension phase of the study
2. Used any medication that, in the opinion of the investigator, was likely to affect the subject's ability to complete or participate in the open-label phase of the study

   NB: The concomitant medications listed as exclusion criteria for the study applied to the open-label extension phase. Certain concomitant medications; e.g., other vasodilators, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, beta blockers, diuretics, anti-hypertensives, tricyclic antidepressants and major tranquillisers, as well as the consumption of alcohol, may potentiate the blood pressure lowering effects of MED2005; therefore, the investigator was to consider this carefully and include subjects at their discretion
3. Had the presence of any symptomatic, active urinary tract infection diagnosed by the investigator or their delegate at the start of the open-label extension phase
4. Subsequent to recruitment into the double-blind phase of the study, had developed postural hypotension, hypotension or uncontrolled hypovolaemia, increased intracranial pressure or inadequate cerebral circulation, any clinically significant vital signs or other safety findings as determined by medical history, physical examination or other evaluations conducted at Visit 6 prior to recruitment to the open-label phase

Test Product, Dose and Mode of Administration, and Lot Number(s): During the open-label phase all subjects received MED2005 0.6% GTN gel (Lot numbers 223955-0, 227608-0, and 230896-0).

Reference Therapy, Dose and Mode of Administration, and Lot Number(s): Not applicable to the open-label extension phase

Duration of Treatment:

Open-label Phase: planned to be 6 to 12 months

Criteria for Evaluation:

Safety:

Name of Company:	**Volume:**	(For national authority use only)
Futura Medical Developments Ltd		
Name of Finished Product: MED2005	**Page:**	
Name of Active Ingredient(s): Glyceryl trinitrate		

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.

Efficacy:

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

Statistical Methods:

Safety:

Safety analyses were conducted using 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):

Treatment-emergent AEs (TEAE) were defined as any adverse event with the onset date on or after the start date of the open-label phase. Adverse events were coded using version 21.1 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 TEAEs 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

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 ($\leq$ 1 day; > 1 to $\leq$ 3 days; > 3 to $\leq$ 7 days; > 7 days).

Physical Examination:

All physical examination findings are presented in a data listing.

Electrocardiogram:

The actual value and change from baseline (Visit 2 in the double-blind phase) in ECG parameters (ventricular rate, PR interval, QRS duration, QT interval corrected using Bazett's formula [QTcB] interval) were summarised descriptively. by time point (Day 270 and Day 450) for subjects who continued 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 Day 270 and Day 450.

Medications:

A concomitant medication is defined as any medication used on or after start date and time of open-label phase. 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

Name of Company: Futura Medical Developments Ltd	**Volume:**	(For national authority use only)
Name of Finished Product: MED2005	**Page:**	
Name of Active Ingredient(s): Glyceryl trinitrate		

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.

Efficacy:

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 used were the same ones as for 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. Summary statistics were produced based on observed values only.

Efficacy Results:

- Four hundred and fifty subjects were to be assessed for 6 months, of which 150 subjects were to be assessed for an additional 6 months. Overall, a total of 443 couples entered the open-label extension phase. However, this phase was discontinued early once the results of the double-blind phase showed no evidence of a difference between the different doses of the study drug and placebo. Because of the discontinuation, some study visits (especially those later in the study [i.e., Day 360 and Day 450]) had fewer than half of the planned number of subjects.
- Responder Analyses Based on Rosen (IIEF-EF)
    - Overall, during the 12-week double-blind period, 68.6% (304) of the 443 male subjects who went into the open-label extension phase met the definition of responders. At Day 180, the proportion of responders increased to 90.2% (377 out of the 418 subjects with non-missing values). At Day 270, the proportion of responders increased to 91.9% (262 out of the 285 subjects with non-missing values). At Day 360, the proportion of responders continued to increase, though there are fewer male subjects with data. No data are available for Day 450.
    - During the 12-week double-blind period, 63.1%, 68.5%, and 86.7% of male subjects with mild, moderate, or severe ED, respectively, who went into the open-label extension phase met the definition of responders. At Day 180, the proportion of responders increased to 87.3% in male subjects with mild ED, 90.7% in subjects with moderate ED, and 98.6% in subjects with severe ED. At Day 270, the proportion of responders was 89.9%, 92.5%, and 96.5% in subjects with mild, moderate, or severe ED, respectively. At Day 360, the proportion of responders continued to increase, though with fewer male subjects with data. No data are available for Day 450.
    - When analysed by treatment sequence, the percentages of responders were similar regardless of the treatment received in the double-blind phase.
- Responder Analyses Based on Araujo (SEP Questions 2 and 3)
    - SEP Question 2
        - Overall, during the 12-week double-blind period, 78.7% (348) of the 442 male subjects with available data who went into the open-label extension phase met the definition of responders. At Day 180, the proportion of responders increased to 86.3% (346 out of the 401 subjects with non-missing values). After Day 180, the proportion of responders continued to increase (except for Day 360), though there are fewer subjects with data.
        - During the 12-week double-blind period, 83.3%, 72.4%, and 74.7% of male subjects with mild, moderate, or severe ED, respectively, who went into the open-label extension phase met the definition of responders. At Day 180, the proportion of

Name of Company: Futura Medical Developments Ltd	**Volume:**	(For national authority use only)
Name of Finished Product: MED2005	**Page:**	
Name of Active Ingredient(s): Glyceryl trinitrate		

responders had increased across all groups to 90.3% in subjects with mild ED, 79.6% in subjects with moderate ED, and 83.9% in subjects with severe ED. At Day 270, the proportion of responders had again increased across all groups to 94.2% in male subjects with mild ED, 86.3% in subjects with moderate ED, and 89.7% in subjects with severe ED. At Day 360, the proportion of responders was 100.0% in subjects with mild ED, 82.6% in subjects with moderate ED, and 90.0% in subjects with severe ED. For subjects with mild and moderate ED, the proportion increased at Day 450, though there are fewer male subjects with data. No data are available at Day 450 for subjects with severe ED.

- When analysed by treatment sequence, the percentages of responders were similar regardless of the treatment received in the double-blind phase.

- SEP Question 3
  - Overall, during the 12-week double-blind period, 68.8% (304) of the 439 male subjects with available data who went into the open-label extension phase met the definition of responders. At Day 180, the proportion of responders had increased to 86.0% (345 out of the 401 subjects with non-missing values). After Day 180, the proportion of responders stayed around the same level, though there are fewer male subjects with data.
  - During the 12-week double-blind period, 70.8%, 63.8%, and 70.7% of male subjects with mild, moderate, or severe ED, respectively, who went into the open-label extension phase met the definition of responders. At Day 180, the proportion of responders had increased across all groups to 85.8% in subjects with mild ED, 83.2% in subjects with moderate ED, and 91.9% in subjects with severe ED. At Day 270, the proportion of responders stayed around the same level in all ED severity groups.
  - When analysed by treatment sequence, the percentages of responders were similar regardless of the treatment received in the double-blind phase.

- Responder Analysis Based on Responder Thresholds
  - IIEF-EF
    - Overall, during the 12-week double-blind period, 55.1% (244) of the 443 male subjects with data available who went into the open-label extension phase met the definition of responders. At Day 180, the proportion of responders had increased to 80.1% (335 out of the 418 subjects with non-missing values). At Day 270, the proportion of responders had again increased to 83.9% (239 out of the 285 subjects with non-missing values). At Day 360, the proportion of responders decreased slightly to 83.3% (15 out of the 18 subjects with non-missing values. No data are available for Day 450.
    - During the 12-week double-blind period, 49.0%, 51.2%, and 81.3% of male subjects with mild, moderate, or severe ED, respectively, who went into the open-label extension phase met the definition of responders. At Day 180, the proportion of responders increased to 71.1% in male subjects with mild ED, 86.4% in subjects with moderate ED, and 98.6% in subjects with severe ED. At Day 270, the proportion of responders increased in subjects with mild ED (77.0%) and moderate ED (87.5%). After Day 270, the proportion of responders continued to increase in subjects with mild ED and moderate ED, though there are fewer male subjects with data; no data are available for subjects with severe ED at Day 360. No data are available for Day 450.

Name of Company: Futura Medical Developments Ltd	**Volume:**	(For national authority use only)
Name of Finished Product: MED2005	**Page:**	
Name of Active Ingredient(s): Glyceryl trinitrate		

- When analysed by treatment sequence, the percentages of responders were similar regardless of the treatment received in the double-blind phase.

- SEP Question 2
  - Overall, during the 12-week double-blind period, 49.5% (219) of the 442 male subjects with data available who went into the open-label extension phase met the definition of responders. At Day 180, the proportion of responders had increased to 54.9% (220 out of the 401 subjects with non-missing values). At Day 270, the proportion of responders had increased again to 60.2% (207 out of 344 subjects with non-missing values). At Day 360, the proportion of responders was 69.1% (38 out of 55 subjects with non-missing values). At Day 450, the proportion had decreased, though there are fewer male subjects with data.
  - During the 12-week double-blind period, 34.6%, 64.6%, and 72.0% of male subjects with mild, moderate, or severe ED, respectively, who went into the open-label extension phase met the definition of responders. At Day 180, the percentages of responders increased to 41.2% in subjects with mild ED, 68.1% in subjects with moderate ED, and 80.6% in subjects with severe ED. At Day 270, the proportion of responders was 45.5% in male subjects with mild ED, 73.7% in subjects with moderate ED, and 86.2% in subjects with severe ED. At Day 360, the proportion of responders increased in the subjects with mild ED only (63.6%). At Day 450, the proportion of subjects increased in subjects with mild ED only (75.0%), though there are fewer male subjects with data; no data are available for subjects with severe ED.
  - When analysed by treatment sequence, the percentages of responders were similar regardless of the treatment received in the double-blind phase.
- SEP Question 3
  - Overall, during the 12-week double-blind period, 55.0% (243) of 442 subjects with available data) of male subjects who went into the open-label extension phase met the definition of responders. At Day 180, the proportion had increased to 73.6% (295 out of the 401 subjects with non-missing values). At Day 270, the proportion of responders was 75.3% (259 out of the 344 subjects with non-missing values). After Day 270, the proportion of responders continued to increase but at Day 450, the proportion decreased, though there are fewer male subjects with data.
  - During the 12-week double-blind period, 50.0%, 58.3%, and 65.3% of male subjects with mild, moderate, or severe ED, respectively, who went into the open-label extension phase met the definition of responders. At Day 180, the proportion of responders was 65.5% in subjects with mild ED, 79.6% in subjects with moderate ED, and 91.9% in subjects with severe ED. At Day 270, the proportion of responders was 66.5% in subjects with mild ED, 82.1% in subjects with moderate ED, and 93.1% in subjects with severe ED. At Day 360, the proportion of responders increased in subjects with mild (90.9%) and moderate ED (82.6%). At Day 450, the proportion of responders increased in subjects with mild ED only; no data are available for subjects with severe ED.
  - When analysed by treatment sequence, the percentages of responders were similar regardless of the treatment received in the double-blind phase.

- IIEF

Name of Company: Futura Medical Developments Ltd	**Volume:**	(For national authority use only)
Name of Finished Product: MED2005	**Page:**	
Name of Active Ingredient(s): Glyceryl trinitrate		

- IIEF-EF
  - The mean at IIEF-EF at baseline was 16.26. The mean change from baseline for the 12-week double-blind period in male subjects who went into the open-label extension phase was an increase of 5.66. At Day 180 and Day 270, the mean changes from baseline continued to increase to 8.99 and 9.86 respectively. At Day 360, the mean change from baseline decreased, though there are fewer male subjects with data.
  - When analysed by treatment sequence, the percentages of responders were similar regardless of the treatment received in the double-blind phase.
  - When analysed by treatment sequence and country (with at least 80 patients in the open-label extension phase), means at baseline showed that subjects with more severe ED were enrolled in Bulgaria compared with the Russian Federation. Mean changes from baseline were larger in subjects from Bulgaria.
- IIEF-IS: The mean IIEF-IS at baseline was 7.80. The mean change from baseline for the 12-week double-blind period in male subjects who went into the open-label extension phase was an increase of 1.77. At Day 180, the mean change from baseline increased to 3.34. At Day 270 and Day 360, the mean change from baseline decreased, though there are fewer male subjects with data.
- IIEF-OF: The mean IIEF-OF at baseline was 5.78. The mean change from baseline for the 12-week double-blind period in male subjects who went into the open-label extension phase was an increase of 1.59. At Day 180 and Day 270, the mean changes from baseline continued to increase to 2.80 and 2.98, respectively. At Day 360, the mean change from baseline decreased, though there are fewer male subjects with data.
- IIEF-OS: The mean at IIEF-OS baseline was 4.84. The mean change from baseline for the 12-week double-blind period in male subjects who went into the open-label extension phase was an increase of 1.88. At Day 180 and Day 270, the mean changes from baseline continued to increase to 3.21 and 3.22 respectively. At Day 360, the mean change from baseline decreased, though there are fewer male subjects with data.
- IIEF-SD: The mean IIEF-SD at baseline was 6.06. The mean change from baseline for the 12-week double-blind period in male subjects who went into the open-label extension phase was an increase of 0.84. At Day 180 and Day 270, the mean changes from baseline continued to increase to 1.48 and 1.72 respectively. At Day 360, the mean change from baseline decreased, though there are fewer male subjects with data.

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

Safety Results:

- There were no deaths or other serious TEAEs and no subjects withdrew from the open-label extension phase of the study because of TEAEs.
- Overall, 3.8% (17/443) of male subjects who received MED2005 reported a TEAE during the open-label extension phase of the study. Treatment-emergent AEs considered related to the IMP were seen in 3.6% of subjects (16/443). The only TEAE occurring in ≥ 2.0% of subjects was headache (2.9%; 13/443 subjects).
- There were no deaths, serious TEAEs, or TEAEs leading to study withdrawal in female partners during the open-label extension phase of the study.

Name of Company: Futura Medical Developments Ltd	**Volume:**	(For national authority use only)
Name of Finished Product: MED2005	**Page:**	
Name of Active Ingredient(s): Glyceryl trinitrate		

- Overall, 0.9% (4/443) of female partners whose male subject received MED2005 reported a TEAE during the open-label extension phase of the study. No TEAEs were reported in ≥ 2.0% of female partners.
- No clinically meaningful changes in laboratory values, vital signs, or ECG results were noted during the open-label extension phase of the study

Conclusions:

- The open-label extension phase included subjects who volunteered to continue in the study. All subjects received the highest dose of MED2005.
- Four hundred and fifty subjects were to be assessed for 6 months, of which 150 subjects were to be assessed for an additional 6 months. Overall, a total of 443 couples entered the open-label extension phase. However, this phase was discontinued early once the results of the double-blind phase showed no evidence of a difference between the different doses of the study drug and placebo. Because of the discontinuation, some study visits (especially those later in the study [i.e., Day 360 and Day 450]) had fewer than half of the planned number of subjects enrolled.
- Large changes from the baseline scores continued to be observed during the open-label extension phase and in most instances, the changes from baseline scores were larger than those seen during the 12-week double-blind phase. These improvements were seen regardless of the treatment received in the double-blind phase.
- The application of MED2005 1.8 mg (0.6% w/w) was generally safe and well tolerated. The low incidences of TEAEs in female partners are indicative of lack of transference of MED2005 to the female partner during the open-label extension phase of the study.

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