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Finished product(s): **MUSE® 250 mcg, Viagra® 50 mg, Viagra® 100 mg**			

SYNOPSIS

Study No.: RP-01 **Report No.: X-03012 / 9359000001**
Eudra-CT No.: 2005-003971-19

Title of the study:

Clinical study to evaluate the ability of MUSE® to increase erectile function in post-radical prostatectomy patients.
Randomised, controlled, open study with two parallel groups comparing MUSE® 250 mcg to Viagra® 50 mg over a treatment period of 9 months.

Principal investigators:

Germany: [redacted]

UK: [redacted]

Study centres:

Two centres planned, one in Germany (active) and one in the UK (no patients enrolled):

Germany: Urological department of the University Hospital Munich-Groβhadern Marchioninistr. 15, 81377 Munich

UK: The Archway Sexual Health Clinic, Clerkenwell Building, Archway Campus, Whitington Hospital, Highgate Hill, London N19 5NF

Publication (reference): Not available

First visit of first patient: 13 Nov 2006 **Clinical phase:** IV
Last visit of last patient: 05 Dec 2007 **Type of study:** interventional
Last telephone contact: 08 Jan 2008

Duration of treatment per subject:

Ten months (nine months MUSE® 250 mcg or Viagra® 50 plus Viagra®100 mg, and one month Viagra® 100 mg only)

Objectives:

The primary objective of the study was to evaluate if early introduction of MUSE® 250 mcg after nerve-sparing radical prostatectomy [RP] increases erectile function measured by completion of the International Index of Erectile Function [IIEF] questionnaire.

The secondary objective was to evaluate if early introduction of MUSE® 250 mcg after nerve-sparing RP

- increases the frequency of successful sexual intercourses
- affects answers in the Erectile Dysfunction Inventory of Treatment Satisfaction [EDITS] questionnaires.

The tertiary objective was to evaluate if early introduction of MUSE® 250 mcg after nerve-sparing RP improves

- patient global assessment.
- patient stretched penile length measurement.

Methodology (according to the fourth amended version of the protocol of 18 Apr 2006):

The study was conducted in male patients who were screened at the study site (urological department of the hospital) before bilateral nerve-sparing RP for prostate cancer. The individual study duration of maximum 13 months was divided in five periods with a total of eight visits (V1-V8) to the investigator and a patient diary from V2-V8. Acceptable deviation from intended time distances between visits was ± 2 weeks.

Study period	*Duration*	*Time points of investigational assessment*
Screening	1-30 days before surgery	V1 → informed consent/study start
Surgery (nerve-sparing RP) and recovery	1 month	-
Randomised treatment (ratio 2:1) with MUSE® 250 mcg or Viagra® 50 mg three times a week plus Viagra® 100 mg only* at two different occasions within two weeks before V4, V5 and V6	9 months	V2 (1 month post surgery) → randomisation (ratio 2:1), treatment start V3 (1 month after V2) V4 (3 months after V2) V5 (6 months after V2) V6 (9 months after V2)
No treatment	1 month	V7 (1 month after V6) → end of treatment-free period
Viagra® 100 mg only at six different occasions	1 month	V8 (1 month after V7) → study end

* without concomitant use of randomised study medication

Evaluation of efficacy and tolerability (case record form, diary and questionnaires)

Efficacy and tolerability of the investigational drugs were monitored clinically by using a diary and two questionnaires (IIEF and EDITS).
Measurements, assessments, score calculation (IIEF questionnaire) and diary checks made by the investigator were documented on the case record form [CRF] at study visits as requested by protocol.

The following variables were recorded by the patient in his diary (V2-V8):

- Intake/application of allocated study medication
- Start (date; time) and outcome (successful: yes; no) of sexual intercourse
- Date and time of last medication of MUSE® or Viagra® (50 or 100 mg) before sexual intercourse
- Additional medication or treatments
- Disorders/diseases.

The following variables were recorded in the CRF by the investigator:

AT BASELINE ONLY (V1 or V2):

- Date of patient's signature on informed consent (V1)
- Demographic data (V1)
- Diagnosis of prostatic cancer: date of histological diagnosis, PSA (V1)
- Gleason score before (V1) and after (V2) radical prostatectomy (RP)
- Medical history and previous/concomitant treatments (V1)
- Physical examination (V1, V2)
- 12-lead electrocardiogram [ECG] (V1)
- Relevant haematological and clinical chemistry findings (V1)

- Date of prostatectomy (V2)
- Inclusion/exclusion criteria (V1,V2)
- Partner's fertility status and adequate contraception (if applicable)

DURING THE STUDY:

- Vital signs (V1-V8)
- Change in concomitant diseases (V2-V8)
- Change in concomitant treatments (V2-V8)
- Adverse events (V2-V8)
- Treatment compliance (V3-V6, V8)
- Patient's stretched penile length (V1-V8)
- IIEF score (V1-V6 and V8)
- Patient's global assessment of erections compared to last visit (V3-V8)

AT END OF STUDY:

- Vital signs
- EDITS questionnaire
- Reason for premature discontinuation (if applicable)
- Date of final contact

Number of subjects planned:

It was planned to screen approximately 100 males 1-30 days before surgery (RP). Of these, maximal 60 males were to be randomised to MUSE® 250 mcg or Viagra® 50 mg at a ratio of 2:1 (40 vs. 20 patients, respectively) in two study sites (30 patients per site) in order to have a total of 39 (26 vs. 13 patients, respectively evaluable patients per protocol (assumed dropout rate: 30 %).

Diagnosis and main selection criteria:

Diagnosis

Prostate cancer and a bilateral nerve-sparing radical retropubic prostatectomy between Visit 1 and Visit 2.

Inclusion criteria

To be eligible for this study the patient had to:

1. be an adult male less than 70 years of age*;
2. have a normal erectile function, defined by a pre surgery score on the IIEF erectile function domain of ≥ 26 prior to surgery*;
3. have a bilateral nerve-sparing radical retropubic prostatectomy for prostate cancer**;
4. have a post surgery ED, as determined by an IIEF score of < 26**;
5. be willing and able to self-administer MUSE® or Viagra® three times a week for 9 months or until there was evidence of spontaneous erectile function;
6. be in a stable, monogamous heterosexual relationship;
7. provide written informed consent*;
8. be willing and able to comply with all study requirements, visit schedules and procedures.

*at Visit 1; ** at Visit 2

Exclusion criteria

The patient was excluded if he

1. had a tumour Gleason score equal to or greater than 8 or a prostate specific antigen [PSA] score equal to or greater than 20 ng/ml;
2. required post surgical radiation therapy or androgen ablation;
3. had a known allergy to alprostadil or any of the components of the formulation or to Viagra® or any of the components of the formulation;
4. had used an investigational drug within the past 30 days or previously been enrolled in this study;
5. had participated in another trial within the past 6 weeks or currently participated in another trial;
6. required nitrates, or had a history of cardiac failure or coronary artery disease causing unstable angina or congestive heart failure that had required medical intervention and treatment;
7. had a history of chronic blood pressure less than 90/50 or greater than 170/100 mmHg;
8. was taking alpha blockers as antihypertensive medication;
9. had a concomitant treatment with CYP3A4-inhibitory drugs;
10. had been treated with locally administered alprostadil (e.g. MUSE®) or phosphodiesterase inhibitors (e.g. Viagra®) within 30 days before study start or was going to be concomitantly treated with other locally administered alprostadil or phosphodiesterase inhibitors besides study medication;
11. had had a stroke, myocardial infarction or life-threatening arrhythmia within the past six months;
12. had hepatic or severe renal failure;
13. had retinitis pigmentosum;
14. had abnormal penile anatomy (stenosis of the distal urethra, severe hypospadia or severe curvature), balanitis, acute or chronic urethritis;
15. had conditions with an increased risk of priapism (sickle cell anaemia or trait, thrombocythaemia, polycythaemia, multiple myeloma, predisposition to venous thrombosis), or a history of recurrent priapism;
16. had a significant medical problem such as an unstable cardiovascular or cerebrovascular condition which, in the opinion of the investigator, precluded the administration of study medications, interfered with study evaluations, limited study participation, or otherwise contraindicated sexual activity;
17. had an abnormal electrocardiogram [ECG] that the investigator deemed to be clinically significant. The ECG had to be maximum three months old.

Study medication, dose and mode of administration, batch number:

Investigational product:	MUSE® 250 mcg
Active ingredient:	alprostadil
Formulation:	urethral stick
Active dose per form:	250 mcg
Mode of administration:	transurethral
Batch numbers:	Germany: 32-027-6V; 33-034-6V; 35-079-6V; 42-034-6V; 49-021-6V
	UK (planned): 35-076-6V; 35-076-6V

Reference product:	Viagra® 50 mg and 100 mg
Active ingredient:	sildenafil
Formulation:	tablet
Active dose per form:	50 mg or 100 mg
Mode of administration:	peroral [p.o.]
Batch numbers:	Viagra® 50 mg
	Germany: 5148409D; 5129517D; 5107510D
	UK (planned): 5114810U; 5114811U
	Viagra® 100 mg
	Germany: 5164803 D
	UK (planned): 5151303U; 5165003U

Timing of doses for each patient

MUSE® 250 mcg (1 urethral stick) or Viagra® 50 mg (1 tablet peroral [p.o.]) had to be administered three times a week in the evening irrespectively of sexual activity with at least one calendar day break between two administrations. If possible, the drugs had to be taken before initiating sexual activity (MUSE® 250 mcg 5–10 minutes and Viagra® 50 mg 1 hour before sexual intercourse).
Viagra® 100 mg (1 tablet to be taken p.o. 1 hour before sexual intercourse) was used as a test drug to ascertain whether the long term treatment with MUSE® 250 mcg or Viagra® 50 mg had improved respectively accelerated the ability for erection.

Criteria for evaluation (according to protocol):

EFFICACY

PRIMARY ENDPOINT:

a. Erectile function (IIEF questionnaire)

SECONDARY ENDPOINTS:

b. Successful sexual intercourses (Diary)
c. Treatment satisfaction at study end (EDITS questionnaire)

TERTIARY ENDPOINTS:

d. Patient's global assessment of erections (CRF)
e. Patient's stretched penile length (CRF)

TOLERABILITY

a. Adverse events (Diary/CRF)
b. Vital signs (CRF)

The IIEF score was calculated by the investigator based on patient's ratings related to questions 1-5 and 15.

Statistical methods:

Due to the premature study discontinuation of all patients and the reduced sample size, the confirmatory analysis was not performed and descriptive statistics were provided only.
Mean, standard deviation [SD], minimum [Min], median and maximum [Max] were calculated for continuous data. Otherwise frequency tables were used.

Primary efficacy endpoint

The IIEF score was tabulated by time point using descriptive statistics.

Secondary efficacy endpoints

- Successful and not successful sexual intercourses were listed by patient and time point.
- EDITS score and subscores frequencies were tabulated.

Tertiary efficacy endpoints

- Patient global assessment frequencies were tabulated by time point.
- Stretched penile length was tabulated by time point with descriptive statistics.

Tolerability endpoints

- AE rates were compared between both treatment groups. AEs (coded by Medical Dictionary for Regulatory Activities [MedDRA]) were classified and tabulated into the defined categories of severity and investigator's causality assessments. Additionally, AEs were classified by pattern of occurrence, duration, intensity, impact on study treatment, actions taken because of AE(s) and outcome. As no SAEs occurred, no table was prepared for seriousness.
- Descriptive statistics of vital signs were tabulated by visit for both treatment groups.

Results - background:

The British study site had been prematurely set on hold on 22 Mar 2007 and was closed on 18 Aug 2008 because no eligible patients could be included within a period of approximately half a year. Most of the screened patients with prostate cancer were treated by high intensity focussed ultrasound [HIFU], which was not adequate and acceptable according to the study protocol.

The German site randomised the first patient on 13 Nov 2006. Due to deficiencies in the GCP-conform conduct of the study and safety concerns, the sponsor prematurely stopped recruitment on 14 Sep 2007 after inclusion of 12 patients. To ensure a proper site closure, a study termination visit, which either was the next regular visit or an additional study visit, was performed for the 11 patients still under treatment at that time. One patient had been taken off the study earlier on request of the sponsor because of suspected violation of exclusion criterion no. 6. The principle investigator had been asked to recommend an appropriate therapy of the patients' erectile dysfunction on an individual basis. As with a regular study termination, adverse events were followed-up by a telephone contact between the investigator and patient until four weeks after the study termination visit. The last telephone contact between the investigator and a study patient took place on 08 Jan 2008. As a result, the number of patients treated and analysed was lower than planned.

Patient disposition:

	MUSE® 250 mcg + Viagra® 100 mg	Viagra® 50 mg + Viagra® 100 mg	Total
Patients	N	N	N
randomised	8	4	12
prematurely discontinued (dropouts)	8	4	12
completed (V1-V8)	0	0	0

Patients analysed:

	MUSE® 250 mcg + Viagra® 100 mg	Viagra® 50 mg + Viagra® 100 mg	Total
Patients included in the	N	N	N
Safety Population [SAF]	8	4	12
Full Analysis Set [FAS]	8	4	12

Results - efficacy:

Primary efficacy endpoint

Erectile function (IIEF score)

Treatment with MUSE® 250 mcg or Viagra® 100 mg (both drugs combined with Viagra® 100 mg) resulted in a continuous improvement in erectile function in both treatment groups. At Visit 6 (last evaluated time point), the number of patients available for analysis was low in both groups (N=4 vs. N=2).

Primary efficacy endpoint: IIEF score (Visit 2 – Visit 6) [FAS: N=12]

Visit (treatment duration)	**Patients** MUSE®/Viagra®	**Treatment group** **MUSE® 250 mcg**	**Viagra® 50 mg**
Visit 2 (baseline)	8/4	5.9 ± 5.14	7.0 ± 3.16
Visit 3 (1 month)	8/4	9.9 ± 9.20	14.5 ± 6.81
Visit 4 (3 months)	8/3	12.0 ± 9.61	16.3 ± 13.01
Visit 5 (6 months)	8/3	14.6 ± 6.59	20.7 ± 8.33
Visit 6 (9 months)	4/2	18.8 ± 8.06	1.5 ± 17.68

Successful sexual intercourses

The mean frequency of successful sexual intercourses between Visit 2 and study end was slightly lower under MUSE® 250 mcg plus Viagra® 100 mg compared to Viagra® 50 mg plus Viagra® 100 mg with a high variance in both treatment groups (39.3 ± 36.4 % vs. 42.3 ± 39.6 %; FAS).

EDITS score

The analysis of the EDITS patient questionnaires completed at study end indicate that patients had less treatment satisfaction when using MUSE® 250 mcg urethral sticks before initiating sexual activities than patients taking Viagra® 50 mg tablets with a high variance in both treatment groups (mean EDITS score: 61.65 ± 22.68 points vs. 72.16 ± 28.77 points; FAS).

Patient's stretched penile length

Before RP (Visit 1), the mean stretched penile length of patients was 126.3 ± 31.6 mm in the MUSE® 250 mcg group compared to 147.5 ± 20.2 mm in the Viagra® 50 mg group.

One month after surgery (Visit 2/baseline), mean values were lower than before particularly in the MUSE® 250 mcg group (118.8 ± 33.0 mm vs. 146.3 ± 20.6 mm) and further decreased on average until study end (except for Visit 4 in the MUSE® 250 mcg group). The standard deviations were higher in the MUSE® group indicating a higher variance in measurements.

Global assessment of efficacy by patient

Overall, patients' global assessments of efficacy did not demonstrate a difference between treatment groups. At the four time points of assessment, the percentage of patients with an improvement in erections varied between 25.0% and 100.0% in the MUSE® 250 mcg group compared to 33.3% to 66.7% of patients in the Viagra® 50 mg group.

At Visit 4 and Visit 5, 12.5% of patients in the MUSE® 250 mcg group reported that erections had worsened compared to none in the Viagra® 50 mg group.

The remaining patients reported no change in the quality of erections for the respective interval.

Results - safety:

In the MUSE® 250 mcg (plus Viagra® 100 mg) group, 3/8 (37.5%) patients experienced nineteen AEs. None of these AEs was judged related to the study treatment. Headache was reported most commonly (nine unrelated mild episodes in one patient), followed by dysuria (two unrelated mild episodes in one patient).

In the Viagra® 50 mg (plus Viagra® 100 mg) group, 2/4 (50.0%) patients experienced ten AEs. Of these, eight AEs were classified as ADRs (investigator's causality assessment 'likely'). Headache was reported most commonly (four likely related mild episodes and one likely related moderate episode in the same patient), followed by nasal congestion (three likely related mild episodes in one patient).

In both treatment groups the majority of AEs was of mild intensity. Severe or serious AEs were not reported. All AEs were transient and had resolved by study end except for bladder pain for which the outcome was unknown (one patient affected).
No patient discontinued treatment due to an AE.

Conclusions:

Due to the small patient population, numerous protocol violations and the deficiencies in the GCP-compliant study conduct, the data recorded during this open, randomised, active controlled study do not contribute to the evaluation of effectiveness of MUSE® 250 mcg in the approved indication.
Safety data collected in 12 patients under intermittent use of MUSE® 250 mcg and Viagra® 50 mg during a mean duration of about eight and seven months respectively, contribute some evidence that both drugs (plus single doses of Viagra® 100 mg) were tolerated well by the majority of patients. Based upon the data from this study, headache and nasal congestion occurring in a few patients were considered as ADRs to Viagra®. All urinary disorders were unlikely related to study treatment.

Referring to Part	Vol:	Page:	
Not applicable	**Not applicable**	**Not applicable**	
Finished product(s): **MUSE® 250 mcg, Viagra® 50 mg, Viagra® 100 mg**			

SYNOPSIS

Study No.: RP-01 **Report No.: X-03012 / 9359000001**
Eudra-CT No.: 2005-003971-19

Sponsor:

Meda AB
Pipers väg 2A
SE - 170 09 Solna, Sweden

Substantial amendments (protocol amendments and premature interruption and/or discontinuation):

No.	Date issued	In force	Modifications
1	15 Dec 2005	Upon approval by EC / CA	Protocol Amendment 1 due to requirements of German central Ethics Committee
2	09 Jan 2006	Upon approval by EC / CA	Protocol Amendment 2 due to requirements of German Competent Authority
3	27 Feb 2006	Upon approval by EC / CA	Protocol Amendment 3 due to requirements of British Central Ethics Committee
4	18 Apr 2006	Upon approval by EC / CA	Protocol Amendment 4 due to administrative changes
5	14 Sep 2007	Immediately	Premature discontinuation