SYNOPSIS

UV-2005/01

Name of Company:	OM Pharma SA
Name of Finished Product:	Uro-Vaxom®
Name of Active Ingredients:	Lysates of 18 strains of *E. coli*

Title:	Multicentre, randomised, double-blind, placebo-controlled clinical study to assess the efficacy and safety of Uro-Vaxom® in Chronic Prostatitis and Chronic Pelvic Pain Syndrom (CP/CPPS)
Short Title:	Uro-Vaxom® in patients with chronic prostatitis and chronic pelvic pain
Indication:	Chronic Prostatitis and Chronic Pelvic Pain Syndrom (CP/CPPS)
Phase:	III
Study Code:	UV-2005/01
Study Director	Prof. Dr. Kurt G. Naber Karl-Bickleder-Str. 44C - 94315 - Straubing - Germany
Co-ordinating Investigator:	Dr. med. Florian M. E. Wagenlehner Universitätsklinikum Giessen und Marburg - 35385 - Giessen - Germany
Study Centres:	55 European sites of which 32 were active, located in 4 countries: • Austria: 7 sites (4 inactive sites), • Germany: 41 sites (17 inactive sites), • Poland: 6 sites (1 inactive site), • Portugal: 1 site (inactive).
Objectives:	Primary Objective: • To assess the percentage of responder patients, *i.e.* presenting a reduction in the total NIH-Chronic Prostatitis Symptom Index (CPSI) score ≥6 at the end of the treatment phase compared to baseline. Secondary Objectives: To analyse: • The patients presenting a reduction in NIH-CPSI score ≥6 at the end of the follow-up period compared to baseline. • The patients presenting a reduction in NIH-CPSI score ≥6 at the end of the first treatment period compared to baseline. • The change in NIH-CPSI total score and subscales scores (pain, urinary symptoms, quality of life (QoL) impact) at each post baseline visit compared to baseline.

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	• The patients presenting a difference of at least 3 points from baseline in NIH-CPSI at each post baseline visit. • The intake of specific treatments during study period (antibiotics, quercetin, analgesics, relaxants, sedatives, α-blockers, etc…). • The global assessments of efficacy and tolerability by patients and investigators. • The primary efficacy variable by subgroups (type of prostatitis, such as II, IIIA and IIIB, and intake of α-blockers). • The safety laboratory variables. • The occurrence of Adverse Events (AEs) and Serious Adverse Events (SAEs).
Design:	Multicentre, randomised, double-blind, parallel, placebo-controlled study
Treatment:	Subjects were allocated to one of the following treatments: Uro-Vaxom® capsules or placebo. The randomization allocation ratio was 1:1 using a blocked scheme. Uro-Vaxom® arm (94 subjects): one capsule of lyophilised powder containing 6 mg of bacterial lysates. Placebo arm (91 subjects): one capsule containing matched powder. Treatment period: 1 capsule/day for 3 months, then 3 months without treatment, followed by 1 capsule/day for 10 days per month during 3 months. Follow-up period without treatment: 3 months. Mode of administration: oral route, to be taken in the morning on an empty stomach with some fluid.
Inclusion Criteria:	1. Males aged 30 to ≤60 years. 2. Presenting CP/CPPS (type II or type III): pain or discomfort in the pelvic region for at least 3 months in the previous 6 months. Corresponding symptoms could be perineal, lower abdominal, testicular and/or penile, rectal and lower back, or suprapubic, and might be associated with ejaculatory discomfort or voiding (associated voiding symptoms are irritative or obstructive in nature, similar to symptoms associated with benign prostatic hyperplasia). 3. With a NIH-CPSI ≥15. 4. Having signed a written informed consent.
Exclusion Criteria:	1. Any prostate, bladder, or urethral cancer, seizure disorder. 2. Presence of a concurrent inflammatory bowel disease, disorder affecting the bladder, liver disease.

	3. Prior 12 months diagnosed with or treated for symptomatic genital herpes. 4. Prior 3 months Urinary Tract Infection, with a urine culture value of >100,000 CFU/mL; clinical evidence of urethritis, sexually transmitted diseases, symptoms of acute or chronic epididymitis. 5. Any pelvic radiation, systemic chemotherapy; intravesical chemotherapy; intravesical BCG, TURP, TUIP, TUIBN, TUMT, TUNA, any other prostate surgery or treatment such as cryotherapy or thermal therapy; prior treatment for orchialgia without pelvic symptoms to treatment. 6. Prior 3 months prostate biopsy. 7. Treatment by the following concomitant medication: immunosuppressive medication, *e.g.* systemic corticosteroids (>15 mg prednisolone); methotrexate; any other immunostimulant medication or live vaccine. 8. Prior 6-month treatment by the following medication: initiated or stopped finasteride or other androgen hormone inhibitors. 9. Prior 4-week treatment by the following medication: immunosuppressive medication or immunostimulant medication or live vaccine; antimicrobial agents (oral or parenteral); started, stopped, or changed dose level of any prostatitis-specific medications. 10. Prior 2-week treatment by bioflavonoid agents, zinc or iron supplements. 11. Inability to comply with the requirements of the protocol (*e.g.* psychiatric problems; knowledge of language, unable to complete a patient diary, etc...). 12. Known allergy or previous intolerance or known hypersensitivity to the trial drug. 13. Participation in another clinical trial and/or treatment with an experimental drug within 3 months before study start and during the present trial.
Primary and Secondary Endpoints:	<u>Primary Endpoint</u>: • Reduction in NIH-CPSI score ≥ 6 at the end of the treatment phase (Visit 6) compared to baseline. <u>Secondary Endpoints</u>: • Reduction in NIH-CPSI score ≥ 6 at the end of the first treatment period (Visit 4) compared to baseline. • Reduction in NIH-CPSI score ≥ 6 at the end of the follow-up period (Visit 7) compared to baseline.

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	• Change in NIH-CPSI score at the end of the first treatment period (Visit 4) compared to baseline.
	• Change in NIH-CPSI score at the end of follow-up period (Visit 7) compared to baseline.
	• Change in NIH-CPSI score at each other post baseline visit.
	• Difference of at least 3 points from baseline in NIH-CPSI at each post baseline visit.
	• Evaluation of the subscales of the NIH-CPSI to analyse changes in individual domains:
	  o Pain: total of items 1a, 1b, 1c, 1d, 2a, 2b, 3 & 4.
	  o Urinary symptoms: total of items 5 & 6.
	  o QoL impact: total of items 7, 8 & 9.
	• Intake of specific treatments during study period (antibiotics, quercetin, analgesics, relaxants, sedatives, α-blockers).
	• Global assessments of efficacy and tolerability by patients and investigators.
	• Primary efficacy variable analysis by subgroups (type of prostatitis and intake of α-blockers).
	• Safety laboratory variables.
	• AEs and SAEs.

Procedures:	Twelve-month study divided in 4 periods: • A 3-month treatment period, between Visit 2 (randomisation) and Visit 4, • A 3-month period without treatment from Month 4 to Month 6, between Visit 4 and Visit 5, • A 3-month treatment period for the first 10 days of Month 7, Month 8 and Month 9, between Visit 5 and Visit 6, • A 3-month follow-up period without treatment from Month 10 to Month 12, between Visit 6 and Visit 7. During the screening period, between Visit 1 and Visit 2, an additional visit could be performed, *i.e.* Visit 1a, in case a demonstrable bacteriuria was present in midstream urine at Visit 1. Indeed, eligible subjects had to present no bacteriuria in midstream urine at Visit 2 to be randomised. Unscheduled visits could also be performed in case of acute pain in the pelvic region or any other medical event potentially related to the study medication.

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Sample Size:	200 subjects planned (80 patients per treatment arm, plus 25% drop rate), number based on a treatment effect of at least 18.7%, with a level of significance of $\alpha = 5$ % (two-tailed) and a power of 80 %. 203 subjects screened of which 185 were randomised.
Statistical Methods:	The main statistical analyses were to test the following six hypotheses, *i.e.* H01 for primary endpoint and H02 to H06 for the first two secondary endpoints: • H01: the percentage of patients with a reduction in NIH-CPSI score ≥ 6 at the end of the treatment phase (Visit 6) compared to baseline is the same in the Uro-Vaxom® and placebo treatment groups • H02: the percentage of patients with a reduction in NIH-CPSI score ≥ 6 at the end of follow-up period (Visit 7) compared to baseline is the same in the Uro-Vaxom® and placebo treatment groups. • H03: the percentage of patients with a reduction in NIH-CPSI score ≥ 6 at the end of the first treatment period (Visit 4) compared to baseline is the same in the Uro-Vaxom® and placebo treatment groups. • H04: the mean change in NIH-CPSI score from baseline to the end of the treatment phase (Visit 6) is the same for the Uro-Vaxom® and placebo treatment groups. • H05: the mean change in NIH-CPSI score from baseline to the end of follow-up period (Visit 7) is the same for the Uro-Vaxom® and placebo treatment groups. • H06: the mean change in NIH-CPSI score from baseline to the end of the first treatment period (Visit 4) is the same for the Uro-Vaxom® and placebo treatment groups. The hypotheses H01, H02 and H03 were tested using a logistic regression with the treatment group and the baseline NIH-CPSI score as covariates. The hypotheses H04, H05 and H06 were tested using a repeated measures analysis of covariance to handle potential missing visits.
Results:	A total of 203 patients were screened from July 09th, 2008, to December 16th, 2010, of whom 185 (91.1%) were randomized into the study; 94 patients (50.8%) in the Uro-Vaxom® treatment arm and 91 patients (49.2%) in the Placebo arm. All patients received at least one dose of study medication and were thus included in the Safety Set (SS). Four subjects did not perform a post baseline visit and were excluded from the Full Analysis Set (FAS). A total of 26 additional subjects were excluded from the Per Protocol Set (PPS) analysis due to Visit 6 not performed (n=14) or major protocol violations (n=12).

Populations of analysis were as follows:

- SS = 185 subjects (94 in the Uro-Vaxom® group and 91 in placebo group).
- FAS = 181 subjects; 97.8% (91 in the Uro-Vaxom® group and 90 in the placebo group).
- PPS = 155 subjects; 83.8% (77 in the Uro-Vaxom® group and 78 in the placebo group).

Baseline demographics and other relevant baseline characteristics:

At study entry the two treatment groups were comparable with regard to the baseline and demographic characteristics, except for total NIH-CPSI; the mean baseline NIH-CPSI score was slightly higher in the Placebo group (23.0 ± 5.7, range 15 to 38) than in the Uro-Vaxom® group (21.8 ± 3.8, range 15 to 30). Mean age of study population was 47.8 ± 8.4 years old (range 29 to 62). The majority of subjects (90.1%) had type IIIb prostatitis. Pain and discomfort in pelvic region and associated CP/CPPS symptoms were comparable between the two treatment groups. A proportion of 18.4% of subjects had at least one prior medication; the most frequently reported ones were anti-bacterials for systemic use (10.8% of subjects; mainly ciprofloxacin, enoxacin and levofloxacin) and urologicals (5.4% of subjects; mainly tamsulosin).

Compliance and treatment exposure:

Overall, compliance to study treatments was good in both treatment arms. At the end of the first treatment period (between Visit 2 and Visit 4), the majority of subjects (100.0% in the Uro-Vaxom® group and 98.8% in the Placebo group) had a good compliance (>80 % of capsules taken). On the second treatment period (between Visit 5 and Visit 6), the mean number of capsules intake was 30 ± 2 (range, 20 to 40).

Concomitant medications during the treatment period:

During study treatment period, treatments defined as specific in the framework of the protocol (antibiotics, analgesics, relaxants, sedatives or alpha-blockers) were comparable between the two treatments arms among subjects included in the FAS, except for antibiotics intake that was slightly more frequent in the Placebo group than in the Uro-Vaxom® group (39.6% *vs.* 28.7% of subjects respectively).

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Efficacy results:

Primary efficacy endpoint: percentage of responders at the end of the treatment period, i.e. percentage of subjects with a reduction of at least 6 points in the NIH-CPSI questionnaire score.

In the FAS (n=185 subjects), the percentage of responders at the end of treatment period (Month 9-Visit 6) was 67.0% in the Uro-Vaxom® group *versus* 64.0% in the Placebo group, with a mean relative decrease in score of 40.5% and 43.4%, respectively.

When adjusted on the baseline NIH-CPSI total score, subjects treated by Uro-Vaxom® were more likely to be responders than those treated by placebo (OR =1.20, 95% CI: 0.65-2.24), but this result was not statistically significant (p-value = 0.563).

In the sensitive analysis on the PPS (N=155), a better effect was observed for patients treated in the Uro-Vaxom® group, with 72.7% of responders versus 64.1% for the placebo group. However these results were not statistically significant (OR of 1.62, 95% CI: 0.81-3.25, p-value = 0.173).

No difference on the primary efficacy endpoint could be evidenced at Visit 6 between Uro-Vaxom® and Placebo on either the FAS or PPS. Therefore the hypothesis of equality between the two treatment groups could not be rejected.

Secondary efficacy endpoints:

Secondary endpoints were analysed in an exploratory way. The results are summarized below:

- A higher rate of responders at Visit 7 (end of the follow-up period) compared to Visit 6, particularly for subjects treated by Uro-Vaxom® (75.3% of the subjects with NIH-CPSI total score decrease of at least 6 points in comparison to 65.4% of subjects in the placebo group). This difference was however statistically not significant in the adjusted model on the baseline score (OR of 1.66, 95% CI: 0.83-3.31, p-value of 0.154).
- A similar rate of responders at Visit 4 (end of the first treatment period) between the two treatment groups (*i.e.* 66.7%; OR: 0.99, 95% CI: 0.52-1.89, p-value of 0.985).
- A visit effect was detected on the mean change in NIH-CPSI score from baseline in the repeated mixed model analysis ($p < 0.0001$) at Visits 3 and 4, but the interaction between the treatment and visit was not statistically significant ($p = 0.92$).
- The proportion of subjects with a reduction in NIH-CPSI ≥3 increased for the Uro-Vaxom® group from Visit 3 (63.2%) to Visit 6 (89.3%) then slightly decreased at Visit 7 (85.2%), whereas in the Placebo group, the proportion of subjects with a reduction in NIH-CPSI score ≥3 increased from 70.6% at Visit 3 to 79.5% at Visit 7.

- Mean NIH-CPSI subscales scores (pain, urinary symptoms and quality of life) were lower in the Uro-Vaxom® group than in the Placebo group at all visits, with greater differences observed starting from Visit 4 especially in the pain and quality of life subscales. At Visit 6 mean subscale scores were of 4.8 ± 3.8 *vs*. 5.9 ± 4.7 for pain, 2.6 ± 2.1 *vs*. 3.0 ± 3.0 for urinary symptoms and 4.4 ± 2.6 *vs*. 4.9 ± 3.2 for quality of life.
- No difference was reported between the Uro-Vaxom® group and the placebo group in the assessment of efficacy by investigators at Visits 4, 6 or 7.
- Approximately two third of the subjects declared an improvement in their medical status regardless of treatment groups.

Safety analysis:

Overall the safety profile of Uro-Vaxom® was good and in accordance with the Investigator's Brochure.

Of the 185 subjects included in the SS analysis, 58.5% of the subjects in Uro-Vaxom® group and 59.3% of subjects in Placebo group experienced at least one Treatment-Emergent Adverse Event (TEAE) with 614 TEAEs reported in total (286 for Uro-Vaxom® group and 328 for Placebo group).

The most frequently reported TEAEs were headache (20.2% of Uro-Vaxom® group and 17.6% of Placebo group), influenza (6.4% of the Uro-Vaxom® group and 9.9% of the Placebo group) and nasopharyngitis (9.6% of the Uro-Vaxom® group and 6.6% of the Placebo group).

In the Uro-Vaxom® group, one subject experienced 3 TEAEs leading to permanent discontinuation and another subject experienced 4 TEAEs leading to temporary discontinuation during the first period of treatment (between Visit 2 and Visit 4). None of these AEs was related to the study product.

The incidence of severe TEAEs was low and similar between the two treatment groups (13.2 % in the Uro-Vaxom® group and 16.7% in the placebo group) and consisted mainly in gastrointestinal disorders for subjects treated by Uro-Vaxom® (6.6%; mainly diarrhoea) and musculoskeletal and connective tissue disorders for subjects randomised to placebo (4.3%; mainly back pain).

The proportion of subjects with at least one treatment-related TEAE was low in both treatment groups (8.5% for the Uro-Vaxom® group and 5.5% for the Placebo group) and consisted mainly in diarrhoea for patients under Uro-Vaxom® and nausea for patients under Placebo.

The proportion of subjects who experienced Treatment-Emergent Serious Adverse Events (TESAEs) was higher in the Placebo group than in the Uro-Vaxom® group (8 subjects with 14 TESAEs *versus* 2 subjects with 2 TESAEs, respectively), but none was related to study drug.

	One death occurred during study treatment in the placebo group. The event was not related to study medication (road traffic accident).
Conclusion	This phase III randomised study was designed to investigate the efficacy of Uro-Vaxom® in a male population with CP/CPPS as a possible new indication. The rationale was based on the known preventive effects of Uro-Vaxom® in recurrent Urinary Tract Infections and on the anti-inflammatory properties of Uro-Vaxom®. Demographic data showed that less than 10% of the included patients were belonging to CP/CPPS type II (bacterial) and type IIIa (non bacterial, inflammatory), whereas the majority of the patients had a type IIIb (non bacterial, non inflammatory) CP/CPPS. The study has shown that oral Uro-Vaxom® resulted in a decrease in the total baseline NIH-CPSI scores as demonstrated by the significant rate of responders at the end of the treatment period and over time, and CP/CPPS symptoms related improvement, although no statistically significant difference with the placebo group could be evidenced on the primary efficacy endpoint in a population with type IIIb CP/CPPS. The study demonstrated that Uro-Vaxom® was well tolerated and safe in this population of patients with standard therapies for CP/CPPS.