SYNOPSIS

UV-2007/01

Name of Company:	OM Pharma SA
Name of Finished Product:	OM-89
Name of Active Ingredients:	Bacterial extract of 18 strains of *Escherichia coli*

Title:	Multicentre, double-blind, placebo-controlled, randomised clinical study of Uro-Vaxom® in female subjects suffering from uncomplicated recurrent urinary tract infections
Short Title:	OM-89 in female subjects with recurrent UTI
Indication:	Recurrent uncomplicated urinary tract infections (rUTIs; recurrent cystitis)
Phase:	III
Study Code:	UV-2007/01
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:	83 European sites of which 53 were active, located in 3 countries: • Austria: 6 sites (6 inactive sites), • Germany: 72 sites (50 active sites), • Slovakia: 5 sites (3 active sites).
Objectives:	Primary Objective: • To confirm the efficacy and safety of OM-89 when compared with placebo in female subjects suffering from uncomplicated recurrent urinary tract infections within 6 months after enrolment. Secondary Objective: • To compare the efficacy and safety of OM-89 *vs.* standard prophylaxis (Nitrofurantoin) within 6 months (Months 7-12).
Design:	Multicentre, double-blind, placebo-controlled, randomised clinical study with one planned interim analysis.
Treatment:	Treatment period: 2 periods Period I: • 3-month treatment period (OM-89 or placebo daily) • Followed by a 3-month non-treatment period Period II: • 3-month double-blind treatment period (OM-89 and placebo or Nitrofurantoin daily) • Followed by a 3-month non-treatment follow-up period. The boxes for the double-blind treatment phase were carrying a randomisation number. In order to ensure random allocation, each new consecutive subject randomised had to be given the box bearing the lowest available randomisation number.

Name of Company:	OM Pharma SA
Name of Finished Product:	OM-89
Name of Active Ingredients:	Bacterial extract of 18 strains of *Escherichia coli*
	The dosage regimen of study medication was: • 1 capsule of OM-89 (containing 6 mg of lyophilised bacterial lysate extract from *Escherichia coli*) or placebo daily in the morning during or after meal between V2 and V4 (90 days). • No treatment between V4 and V5 (90 days). • 1 capsule of OM-89 (first 10 days/month) and placebo (last 20 days/month) or Nitrofurantoin (30 days/month) daily in the morning during or after meal between V5 and V6 (90 days). • No treatment between V6 and V7 (90 days).
Inclusion Criteria:	1. Female subjects aged between 18 and 73 years. 2. History of recurrent UTI (at least 3 documented UTIs in the previous year). 3. Women suffering from an acute uncomplicated UTI at the screening visit (V1) with clinical symptoms of dysuria (burning pain at micturition), pollakisuria (frequency) and urgency to urinate* and without symptoms at the enrolment visit (V2). **At least two clinical symptoms and the positive bacteriuria test have to be present in order to fulfil the definition of an acute UTI.* 4. Positive results of microbiological urine analysis ($\geq 10^5$ cfu/mL) and identification of bacteria at the screening visit (V1) and $< 10^2$ cfu/mL after antimicrobial treatment of the acute UTI episode at the enrolment visit (V2). 5. The beginning of this infection should not exceed 7 days prior to the screening visit. 6. Having given the written informed consent.
Exclusion Criteria:	1. Known complicated urinary tract infections (functional and structural abnormalities within the urinary tract), renal disease, pyelonephritis or obstructive morphological changes. 2. Acute UTI at Visit 2 (Enrolment Visit) 3. Persistent urinary tract infections ($\geq$ 14 days). 4. Indwelling urinary catheter. 5. Paraplegic subjects with known neurogenic bladder dysfunction. 6. Fever > 38.0°C at the enrolment visit. 7. Known allergy to the study medications (including antibiotics, Nitrofurantoin or derivative) 8. Severe cardiovascular disease (e.g. left ventricular failure, stroke). 9. Known significant liver insufficiency (*i.e.* ALAT and ASAT > two times the upper limit of reference range). 10. Known significant renal insufficiency (*i.e.* serum creatinine > 150 µmol/L and 1.5 mg/dL, respectively). 11. Malignant diseases under treatment. 12. Auto-immune disease and other systemic diseases related to immune system disorders (including diabetes mellitus). 13. Diseases of the gastrointestinal tract, which would impair

Name of Company:	OM Pharma SA
Name of Finished Product:	OM-89
Name of Active Ingredients:	Bacterial extract of 18 strains of *Escherichia coli*
	absorption of the study medication. 14. Any medication which is not allowed during the course of the study. 15. Pregnant subjects, lactating, or of child-bearing potential and not protected from pregnancy by a sufficiently reliable method (Oral Contraceptive, Intra Uterine Device, Abstinence, Sterilisation). 16. Unreliable or non-compliant subjects including non-compliant subjects, subjects with known alcoholism, drug abuse or with a history of serious psychiatric disorder as well as subjects unwilling to give the written informed consent or to abide by the requirements of the protocol, *i.e.* unable to complete a subject diary. 17. Major surgical procedure within the last 3 months prior to study start. 18. Participation in another clinical study within the last 3 months prior to study start and during the present study. 19. Previous (during the past 3 months before study start) and/or concomitant immuno-stimulating or immuno-suppressive therapy. 20. Subject with antibiotic therapy/ prophylaxis in the last 4 weeks prior to the screening visit.
Primary and Secondary Endpoints:	<u>Primary Endpoint</u>: • Mean rate of events of acute uncomplicated UTIs within 6 months after enrolment (Months 1 to 6), *i.e.* mean of the total number of UTIs per subject. <u>Secondary Endpoints</u>: • Rate of events of acute uncomplicated UTIs (Month 7 to 12) • Severity of symptoms (absent, mild, moderate, severe). • Type and duration of prescribed concomitant treatment(s). • Duration of absenteeism from work. • Vaginitis occurrence (clinical symptoms and high number of Candida). • Time to event of next symptomatic UTI. • Episodes of asymptomatic bacteriuria (ASB). • Global assessment of efficacy by subject and investigator (V4, V6, V7). The mean value of creatinine, sIgA and IgM levels between V1 and V4 have been added to the post protocol analyses.
Procedures:	Twelve-month study divided in 2 periods: • Period I: double-blind treatment period (OM-89 / Placebo) of 6 months from Visit 2 (randomisation) to Visit 4 • Period II: double-blind treatment period (OM-89 and Placebo / Nitrofurantoin) of 6 months from Visit 5 to Visit 7 Unscheduled visits (Visit A, B, C etc.) could be performed in case of

Name of Company:	OM Pharma SA
Name of Finished Product:	OM-89
Name of Active Ingredients:	Bacterial extract of 18 strains of *Escherichia coli*
	occurring acute UTIs.
Sample Size:	446 randomised subjects planned (including dropouts).
Statistical Methods:	A null and an alternative hypotheses were stipulated for the confirmatory part of the statistical analysis: H_0: The mean rates of UTI of OM-89 and placebo within the Study Period I (Months 1 to 6) are equal. $\mu_U = \mu_P$. H_1: The mean rates of UTI of OM-89 and placebo within the study period Study Period I (Months 1 to 6) is not equal. $\mu_U \neq \mu_P$. This was analysed by means of an analysis of covariance (ANCOVA) with adjustment for the baseline rate of UTI and the stratification factors centre, hormonal replacement therapy and menopausal status. The treatment effect was estimated by means of the mean difference between OM-89 and placebo with regard to the primary variable. Moreover, corresponding repeated 95% confidence intervals were calculated. All other efficacy variables were analysed by means of descriptive and exploratory statistical methods. For quantitative variables the usual parameters of location and dispersion (means, standard deviations, quartiles, and extremes) were calculated. For qualitative variables the corresponding absolute and relative frequencies were determined. The analysis of data from Study Period II was analysed descriptively. For quantitative variables, the usual parameters of location and dispersion (means, standard deviations, quartiles, and extremes) were calculated. For qualitative variables, the corresponding absolute and relative frequencies were determined. The treatment effects were estimated by mean differences between the treatment groups. Additionally, 95% confidence intervals were determined. Survival methods (Kaplan-Meier estimators, log-rank test) were used for the analysis of the variable time to event of UTI.
Results:	An interim analysis was initially planned to be carried out after the first 180 subjects were enrolled into the study. However due to quality assurance issues and change in the CRO in charge of the data management and analysis of the data during the conduct of the study, the interim analysis was cancelled as per sponsor decision and amendments Germany n°5 and Slovakia n°6. Only one final and confirmatory analysis was performed at the end of the study. From July 2008 to March 2011, a total of 451 subjects were randomized in the study (220 subjects in the OM-89/placebo treatment group (Verum group) and 231 subjects in the placebo/Nitrofurantoin treatment group (Control group). Of these 451 subjects, 344 (76,3%) completed the study as per protocol (168 subjects in the Verum group and 176 subjects in the Control group). All randomized subjects received at least one study medication and

were evaluable for the safety analysis. A total of 188 subjects (42%) presented with at least one major protocol violation (88 subjects in the Verum group and 100 subjects in the Control group) and were therefore excluded from the per protocol analysis (PPS).

Populations of analyses were as follows:

- SS=451 (220 subjects in the Verum group and 231 in the Control group)
- FAS=451 (220 subjects in the Verum group and 231 in the Control group)
- PPS=263 (132 subjects in the Verum group and 131 in the Control group)

Baseline demographics and other relevant baseline characteristics:

The mean age of the study population was 43.9 ± 17.3 years (range, 18 to 80). The majority of the subjects (60.2%) were pre-menopausal (60.2%), and 19.7% were undergoing an adjuvant hormonal therapy. Other baseline characteristics (including physical examination) were well balanced between the two treatment groups.

Prior to the screening visit (V1), 88.2% of the subjects had received antibacterial treatment for previous UTIs, which consisted mainly in ciprofloxacin (51.7%), levofloxacin (16.0%), fosfomycin (12.6%) and sulfamethoxazole trimethoprim (11.1%).

The percentage of subjects having received these medications was higher among subjects randomised in the OM-89 group (92.3%), as compared to the placebo group (88.7%).

A very small percentage of subjects had taken Nitrofurantoin for previous UTIs (2.7% in the OM-89 group *vs.* 1.3% in the placebo group).

No relevant prior or concomitant medical conditions were reported.

Compliance and treatment exposure:

For the whole duration of the study, mean exposure to treatment was 240 ± 76.96 days, 234. 71 ± 76.18 days in the Verum group and 241.71 ± 77.90 in the Control group.

Mean dose received was 31 ± 4 during the period between V2 and V3 (Month 1 of study treatment), 61 ± 7 during the period between V3 and V4 (Months 2 and 3) and 86.98 ± 7.28 during the period between V5 and V6 (Months 7, 8 and 9).

Overall, compliance to study treatment was good (> 80% of the study medications taken) in both treatment groups and whatever the study treatment period.

Concomitant medications during the treatment period:

More than half of the subjects (57.6%) took at least one concomitant medication for UTIs during the study. The most frequently reported ones were antibacterials for systemic use (56.8% of subjects, mainly ciprofloxacin, levofloxacin, fosfomycin and sulfamethoxazole

Name of Company:	OM Pharma SA
Name of Finished Product:	OM-89
Name of Active Ingredients:	Bacterial extract of 18 strains of *Escherichia coli*
	trimethoprim), with no difference in the distribution of these medications between the two treatment groups. Efficacy results: *Primary efficacy endpoint (mean rate of acute UTIs up to the end of the first treatment period (between V2 and V5):* In the FAS, no difference in the mean total number of UTIs was observed between the OM-89 group and the placebo group at the end of the first period (Month 1 to 6). Mean number of UTIs was 0.66 ± 0.93 in the OM-89 group *vs.* 0.63 ± 0.86 in the placebo group (p-value=0.95). The mean rate of UTIs per year (calculated as the number of UTIs occurring until Visit 5 / premature discontinuation, divided by the time until Visit 5 / premature discontinuation), was similar between the OM-89 and the placebo groups (1.5 ± 2.1 *vs.* 1.6 ± 4.0, respectively, p-value=0.83). In the multivariate analyses including either treatment, countries adjuvant hormonal status or menopausal status as a covariates, no difference were also observed between the two treatment groups, except a trend for a lower rate of UTIs in favour of OM-89 in Slovakia (n=14), although not statistically significant (0.7 ± 1.1 *vs.* 1.3 ± 1.4, p=0.15). The sensitivity analyses performed on the PPS and on only documented UTIs, did not translate in positive results in favour of OM-89. No difference in the primary efficacy endpoint was observed between the two treatment groups for both analyses. However, it is to note that the rate of documented UTIs in the PPS was lower in the OM-89 group as compared to the placebo group (38.6% *vs.* 45.8). *Secondary efficacy endpoints:* As exploratory data, analyses of secondary efficacy endpoints have shown - A lower number of UTIs occurring during the second period of the study (V5 to V7) in subjects treated with Nitrofurantoin as compared to those treated with OM-89. Mean number of UTIs was 0.53 ± 1.0 *vs.* 0.36 ± 0.6, but this difference was not statistically significant (p=0.40). This trend in favour of the Nitrofurantoin group was confirmed in the multivariate analysis taking into account the treatment and countries as covariates (HR=1.50; IC 95%: 1.05- 2.24; p=0.02). - No statistically significant difference in the mean scores of severity of symptoms of UTIs occurring during the study between the two treatment groups, either during Period I or Period II. - No difference in the type and scores of concomitant medications, in particular those of interest (fosfomycin, trometamol, mecillinam and fluoroquinolone) between both treatment groups whatever the study period, with half of the subjects in both treatment groups having a score of 0 (no medications taken). - Absenteeism from work concerned only a small percentage of

subjects during Period I (n=45) and during Period II (n=20).

- Among the 51.9% of the subjects who experienced at least one additional UTI during the study, the median time (Kaplan-Meier curves) to first occurrence of UTI was similar in both treatment groups (224 days IC95%: 164-352 in the Verum group and 237 days, IC95%: 131-161 in the Control group (HR=1.02, 95%CI: 0.79-1.33, p-value=0,85 log rank).
- During Period I, the rate of asymptomatic bacteriuria was 18.6% in the OM-89 group *vs.* 19.5% in the placebo group. During Period II, the frequency of asymptomatic bacteriuria decreased significantly in favour of the Nitrofurantoin group compared with the OM-89 + placebo group (8.4% *vs.* 12.4%, respectively, p-value=0.02)
- A small number of subjects experienced vaginitis (*i.e.*, 2% in Period I and 1.1% in Period II). There were fewer events of vaginitis among subjects treated in the OM-89 group (1.8% *vs.* 2.0% during Period I and 0% *vs.* 2.1% during Period II in the Nitrofurantoin group, p=0.051).
- According to subject's opinion, the treatment resulted in an improvement of their medical condition for more than 80% of them, without any difference between the two treatment groups at Visit 4, 6 and 7. Similar observations were recorded as regard to the investigator's efficacy assessment.
- The mean value of creatinin level increased slightly between V1 and V4 in the OM-89 group (from 0.96 ± 0.74 to 1.02 ± 0.66 g/L) and remained stable in the placebo group (0.91 ± 0.73 and 0.96 ± 0.68 g/L). The mean value of IgM level dropped in the OM-89 group (from 0.45 ± 1.66 to 0.16 ± 0.07 mg/L) and decreased in the placebo group (from 0.32 ± 0.62 to 0.16 ± 0.10 mg/L). The mean value of sIgA level decreased in both groups (from 2.78 ±3.24 to 2.63 ± 2.57 mg/L in the OM-89 group and from 2.96 ± 2.89 to 2.31 ± 2.10 mg/L in the placebo group).

<u>Safety analysis:</u>

A total of 451 subjects were included in the SS analysis, of whom 387 (85.8%) experienced at least one TEAE with 2924 TEAEs reported in total (*i.e*, 189 subjects with 1457 TEAEs in the Verum group and 198 subjects with 1467 TEAEs in the Control group).

Urinary tract infection was the most frequently reported TEAE that occurred with a similar incidence in the Verum group (52.7%) and the Control group (50.6%).

Most TEAEs were of mild or moderate intensity. The proportion of subjects who experienced at least one severe TEAE was comparable between the two treatment groups (15.5% in the Verum group *vs.* 16.5% in the Control group).

A higher incidence of nasopharyngitis (17.7% *vs.* 13.4%), influenza (6.4% *vs.* 3.9%), dysuria (23.2% *vs.* 20.8%), pollakisuria (23.2% *vs.* 19.9%), micturition urgency (20.0% *vs.* 14.3%), diarrhoea (8.2% *vs.* 5.2%), back pain (11.4% *vs.* 6.9%) and headache (27.7% *vs.* 22.5%) was reported in the Verum group as compared to the Control group.

	On the opposite nausea was most frequent in the Control group (6.1%) compared with the Verum group (3.6%), as well as abdominal pain (5.6% *vs.* 4.1%), toothache (5.2% *vs.* 3.6%), cough (6.9% *vs.* 5.0%) and oropharyngeal pain (5.6% *vs.* 4.1%). A total of 16 subjects experienced at least one TEAE leading to permanent discontinuation from the study (*i.e*, 7 subjects in the Verum group and 9 subjects in the Control group). A total of 102 TEAEs were considered by the investigators as related to the study medication (48 in the Verum group for 23 subjects and 54 in the Control group for 20 subjects). The most frequent being infestations and infections (3.6% in the Verum group and 2.6% in the Control group), gastrointestinal disorders (4.1% *vs.* 3.0%, respectively), renal and urinary disorders (2.3% *vs.* 0.4%, respectively), nervous system disorders (1.4% *vs.* 1.7%, respectively) musculoskeletal and connective tissue disorders (none for the Verum group and 1.3% in the Control group). Only one related SAE (a case of eczema) in the Control group was reported and no TEAE with outcome of death has been recorded during the study.
Conclusion	The study failed to demonstrate an effect of OM-89 compared with placebo in reducing the number of recurrent UTIs in female subjects with uncomplicated recurrent UTIs. Several confounding factors, might have an influence on the results of the trial: quality issues as expressed by the high number of exclusions from the per protocol analysis, the low observed rate of UTIs during the trial, potential impact of the modified manufacturing process on the clinical efficacy. The product proved to be safe and well tolerated when given on a long-term treatment period.