2 SYNOPSIS

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Title of the study:
Randomized, double-blind, placebo-controlled multicentre study, with parallel groups, to determine the efficacy and safety of a new low-concentration estriol formulation (ITFE-2026 0.005%) for application by vaginal route in the treatment of postmenopausal vaginal atrophy

Investigators:
Coordinating Investigator: Prof. PPD
Principal investigators: Dr. PPD, Dr. PPD, Dr. PPD, Dr. PPD, Dr. PPD, Dr. PPD, Dr. PPD, Dr. PPD, Dr. PPD, Dr. PPD, Dr. PPD, Dr. PPD.

Study centre(s):
12 centres in Spain

Publication:
Not applicable

Study period:	Phase of Development: Phase:
January 2008 – February 2009	III

Objectives:
Primary objective:

- To evaluate the efficacy of 0.005% Estriol vaginal gel by evaluation of the change in the maturation value of the vaginal epithelium (MV) after 12 weeks of treatment.

Secondary objectives:

- To determine the variation of the vaginal pH, as well as symptoms and signs suggestive of vaginal atrophy after 12 weeks of treatment.
- To study the variation of the MV, pH and symptoms and signs suggestive of vaginal atrophy after an initial observation period of 3 weeks.
- To evaluate the safety of 0.005% Estriol vaginal gel
- To evaluate the acceptability of 0.005% Estriol vaginal gel

Methodology:
Eligible patients were randomised in a ratio of 2:1 to 0.005% Estriol vaginal gel : placebo. Each patient was treated for 12 weeks followed by a one-month observational period. The patients attended the study centre at baseline and at 3, 8 and 12 weeks after start of treatment. Vaginal cytology was performed at baseline and at weeks 3 and 12; the vaginal pH and the signs and symptoms of vaginal atrophy were recorded at baseline and after 3 and 12 weeks of treatment. Vital signs, gynaecological exploration and changes in health and concomitant medication were documented at each visit. Transvaginal ultrasound was performed at screening and week 12. The investigators telephoned the patient approximately one month after the final visit to check if the patient had experienced any adverse events since the final visit. Two independent cytopathologists assessed the maturation value of each cytology sample at the end of the study.

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Number of patients:
Planned: 165 in total, 110 in 0.005% Estriol group and 55 in placebo group.
Analysed: 167 in total, 114 in 0.005% Estriol group and 53 in placebo group.

Diagnosis and main criteria for inclusion:
Postmenopausal women with symptoms and signs suggestive of vaginal mucosa atrophy.
Main inclusion criteria:

- Menopause with amenorrhea time ≥ 2 years, either due to natural or surgical menopause (bilateral oophorectomy).
- Presence of symptoms and signs of atrophy of the vaginal mucosa including at minimum vaginal dryness as a symptom stated by the patient, together with at least one sign of the disease verified by the investigator.
  - As symptoms the patient could state vaginal dryness, pruritus, burning, dyspareunia, dysuria or any other symptom that the investigator considered related to the presence of vaginal atrophy.
  - As signs the investigator assessed in the gynaecological examination with a speculum, a thinned vaginal mucosa or with flattening of folds, a dry, fragile and pale vaginal mucosa, the presence of petechias or any other sign that the investigator considered indicative of the existence of vaginal atrophy
- Patients with mammography carried out in the period of one year prior to inclusion in the study.

Main exclusion criteria:

- Patients with contraindications for hormone therapy with estrogens because they had a history of:
  - Malignant or premalignant lesions of the breasts or endometrium.
  - Pathology of malignant colon tumour.
  - Malignant melanoma
  - Hepatic tumour pathology
  - Venous thromboembolic conditions (deep vein thrombosis, pulmonary embolism) or arterial thromboembolic conditions (angor pectoris, myocardial infarction, cerebrovascular accident), peripheral arterial disease, mesenteric artery thrombosis, renal artery thrombosis
  - Coagulopathies
  - Vaginal bleeding of unknown etiology
- Patients with signs and symptoms suggestive of infection of the genital or urinary tract at the start of the study.
- Patients with endometrial thickness equal to or greater than 4 mm measured by transvaginal ultrasound.
- Patients with grade II or higher uterovaginal prolapse.
- Patients who had received any type of vulvovaginal treatment in the 15 days prior to the start of the study.
- Patients who had received phytoestrogens in the period of one month prior to the start of the study, including administration by vaginal route.
- Patients who had received hormone therapy in the period of 3 months prior to the start of the study, including the administration of estrogens by vaginal route.

Test product, dose and mode of administration, batch number:
0.005% Estriol (50 µg/g) gel for vaginal administration.
Batch No.: PPD

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Duration of treatment:
12 weeks

Reference therapy, dose and mode of administration, batch number:
Placebo gel for vaginal administration.
Batch No.: PPD

Criteria for evaluation:
Efficacy:
Primary variable:
- The change in maturation value (MV), a cytologic parameter indicative of the degree of atrophy of the vaginal mucosa, after 12 weeks of treatment with respect to the baseline value.

Secondary efficacy variables:
- Variation of the vaginal pH after the 12-week observation period with respect to the baseline value.
- Variation of the individual signs and symptoms of vaginal atrophy after the 12-week observation period with respect to the baseline value
- Change in the maturation value (MV) after 3 weeks of treatment with respect to the baseline value.
- Variation in the vaginal pH after the 3-week observation period with respect to the baseline value.
- Variation of the individual signs and symptoms of vaginal atrophy after the 3-week observation period with respect to the baseline value.

Safety and tolerability:
- Adverse events
- Physical examination
- Gynaecological examination
- Haematology and urine tests
- Changes in concomitant treatment

Treatment acceptability

Statistical methods:
Raw data listings, summary tables, graphs and statistical tests were generated by means of the program SAS Vers. 9.1. Special non-parametric tests were done with Proc-StatXact 9® from ©Cytel Software. The significance level of all statistical tests was established at 0.05.
The efficacy analysis was carried out on the *Intention-to-treat* population and additionally on the *Per Protocol* population. The safety analysis was carried out on the *Intention-to-treat* population.
The averages of the differences between the baseline MV and the final MV of the 0.005% Estriol vaginal gel and placebo groups were compared by means of a Wilcoxon rank test, to determine the possible superiority of the 0.005% Estriol vaginal gel treatment compared with placebo administration.
The continuous variables were described by the number of patients with valid values (n), average, standard deviation (SD), median, minimum and maximum in both groups.
The variables with asymmetric frequency distributions were described using the medians and their percentiles 25-75. All efficacy and safety variables were analysed based on the 'valid case' approach, i.e. missing data (e.g. for drop-outs) was not replaced.
The baseline characteristics of each group were summarized descriptively.

SUMMARY - CONCLUSIONS
EFFICACY RESULTS:
0.005% Estriol vaginal gel produced a significant improvement in the maturation value of the

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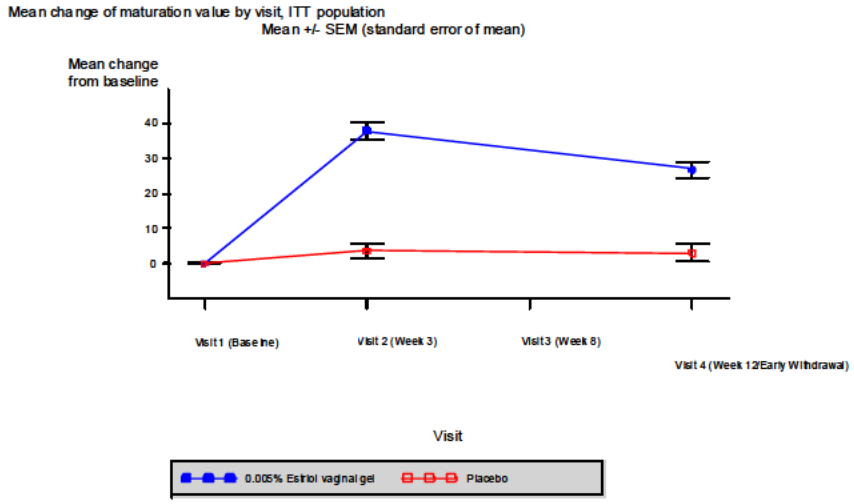
vaginal mucosa after 3 and 12 weeks of treatment. After 12 weeks of treatment the mean maturation value was significantly higher in the Estriol group compared to placebo (65.4 and 41.9, respectively, p<0.001). The maturation value after 3 weeks of treatment was also significantly improved in the Estriol group compared to placebo (76.4 and 41.6 respectively, p<0.001).

In this study, the change in the vaginal maturation value at week 12 of treatment was studied as primary end-point. Other indicators of vaginal status were also evaluated; the change in maturation value at week 3, the change in vaginal pH at week 3 and week 12 and the change in the different symptoms and signs of vaginal atrophy at week 3 and week 12 were studied as secondary end-points.

The results for the primary end-point, the change in maturation value from baseline to week 12 show a highly significant superiority of Estriol compared to placebo, as the mean change from baseline was 26.9 in the Estriol group and 3.2 in the placebo (p<0.001). The mean change from baseline after 3 weeks of daily administration was also significantly greater in the Estriol group (37.9) compared to placebo (3.6), (p<0.001).



The vaginal administration of Estriol vaginal gel significantly improves the pH value of the vaginal mucosa. The mean change from baseline to week 12 was significantly greater in the Estriol group compared to that observed in the placebo (mean change -1.2 and -0.4 respectively; p<0.001). The mean change from baseline to week 3 was also significantly superior in the Estriol group compared to that observed in the placebo (mean changes -1.4 and -0.3 respectively, p<0.001).

For the evaluation of variation in symptoms and signs, responders were defined as patients who had an improvement or cured of a symptom or a sign that was present at baseline. Improvement was defined as changing from severe to moderate or to mild intensity, or changing from moderate to mild intensity. Cure was defined as changing from severe, moderate or mild intensity to absence of the symptom or the sign.

Evaluation of the patient's symptoms showed a mean improvement in all studied symptoms in both groups. However, a higher proportion of patients in the Estriol group experienced an improvement in all symptoms and to a higher extent as compared to placebo. There were also more responders in the Estriol group for most of the signs of vaginal atrophy and both times of evaluation, week 3 and week 12.

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There were more responders for vaginal dryness in the Estriol group at week 12, as 88.2% of patients were responders as compared to 66.7% in the placebo group (p=0.001). At week 3, 82.9% of patients were responders in the Estriol group and 70.6% in the placebo group. Though the comparison between groups did not reach the statistical significance at week 3, a trend for superiority was observed for Estriol (p=0.078).

It was demonstrated that the vaginal treatment with Estriol improved the dyspareunia. The response was evident at week 3 and was maintained throughout the study. The superiority of Estriol over placebo was demonstrated after three weeks of daily treatment, as 87.6% of patients in the Estriol group and 68.9% in the placebo group responded to dyspareunia at week 3 (p=0.009), while a trend for superiority was found at week 12 (86.5% and 75% of responders for Estriol and placebo respectively, p=0.095).

Regarding pruritus, 88% of patients responded in the Estriol group and 64.3% in the placebo group at week 3 (p=0.013), while no significant differences between groups were found at week 12 (83% and 82.1% of responders, respectively).

The most bothering symptom reported by patients in both groups was vaginal dryness, followed by dyspareunia. A trend for superiority of Estriol as compared to placebo was shown in the evaluation of the response to the most bothering symptom at week 3 (p=0.10) and at week 12 (p=0.09).

The superiority of Estriol over placebo was well demonstrated for the improvement or cure of the signs: fragility of the mucosa at weeks 3 (p=0.002) and 12 (p=0.006); flattening of folds at weeks 3 (p<0.001) and 12 (p<0.001); dry mucosa at week 3 (p<0.001); and pallor of the mucosa at week 12 (p<0.001). A trend to statistical superiority of Estriol was also observed in the evaluation of the presence of pethechiae in the vaginal mucosa (p=0.08).

Overall 88% of the patients in the Estriol group and 84% of patient in the placebo group rated the ease of administration and cleanliness of product as excellent or good at the end of treatment. The patient's opinion of the effectiveness of the treatment was rated as excellent or good by 74% of patients in the Estriol group and 43% of patients in the placebo group (p<0.001).

SAFETY RESULTS:

43.7% of the patients experienced at least one adverse event. No significant differences were found in the incidence of AEs between the two groups. The majority of adverse events were of mild intensity. Only one serious adverse event (SAE) (crural hernia) was reported, and was not related to the study medication.

AEs suspected to be related to the study medication were experienced by 8.8% of patients (n=10) patients in the Estriol group and 13.2% (n=7) patients in the placebo group (p NS). All AEs suspected to be related to the study medication were of mild intensity except for two patients with moderate AEs in the placebo group and one patient with a severe AE in the Estriol group. The most frequent AE suspected to be related to treatment was pruritus, experienced in 7 patients in the Estriol group (2 vulvovaginal pruritus, 1 genital pruritus, 2 application site pruritus, 1 pruritus and 1 prurigo) and in 2 patients in the placebo group (1 generalized pruritus and 1 pruritus).

No marked changes were found in mean blood pressure, heart rate or body weight during the study. No clinically relevant changes in the laboratory parameters were observed throughout the study.

CONCLUSION:

The aim of this study was to evaluate the efficacy and safety of a new low concentration estriol

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formulation (0.005% Estriol vaginal gel) for the treatment of postmenopausal vaginal atrophy. This formulation delivers an ultra-low dose of estriol per application (50µg), which is ten times lower than the current dose of this hormone used in clinical practice for vaginal administration.

The results of this study have demonstrated that 0.005% Estriol vaginal gel is highly efficacious in the treatment of postmenopausal vaginal atrophy, inducing clinically relevant improvements in all variables studied.

It has been proven that the studied formulation provides substantially reduced amount of estriol without compromising the efficacy: while the efficacy is maintained the hormonal burden is drastically reduced.

The superiority over placebo has been clearly demonstrated on the reversion of the cytological vaginal atrophy after 12 weeks of therapy, which was the primary endpoint of the trial. In addition, the superiority of 0.005% Estriol vaginal gel over placebo has been demonstrated for the majority of the secondary endpoints, objective and subjective, studied.

The efficacy of 0.005% Estriol vaginal gel on vaginal dryness must be underlined. Vaginal dryness was referred as the most bothering symptom by the largest group of patients and was moderate to severe in almost all patients. In this demanding scenario the majority of the patients showed a clinical response and the superiority over placebo was highly significant at the end of the treatment.

Overall, the efficacy of the treatment with 0.005% Estriol vaginal gel was considered excellent or good by more than 75% of patients. In the evaluation of this variable it was found a highly significant difference over the placebo.

The 0.005% Estriol vaginal gel has shown a highly favorable safety profile based on the evaluation of adverse events laboratory parameters and vital signs. This is an expected conclusion as estriol is a well known molecule with a well established safety profile, currently used similar products for vaginal use containing estriol have demonstrated its endometrial safety in clinical practice over years and, importantly, Estriol 0.005% vaginal gel provides an ultra low dose per application 10 times lower than that provided by similar products marketed in Europe.

Based on the observations presented and discussed above, it can be concluded that the benefit risk ratio of 0.005% Estriol vaginal gel is highly favorable.

Date of the report: 23 July 2009