Synopsis

Name of Sponsor:	Dr. Kade Pharmazeutische Fabrik GmbH Rigistraße 2 D-12277 Berlin Germany	
Name of Finished Product:	Pessaries with 0.2 mg and pessaries with 0.03 mg estriol	
Name of Active Substance(s):	Estriol	

Title:	Double-blind trial investigating the efficacy of pessaries with 0.2 mg and 0.03 mg estriol compared with placebo in vaginal atrophy	
Investigators:	Dr. med. Stefan Skonietzki, Andreasstr. 51, 10243 Berlin, Germany, et. al. A listing of all investigators is provided in Appendix.	
Study centre(s):	59 study centres in Germany.	
Publication (reference)	None as of date of report.	
Studied period:		Clinical Phase:
(date of first enrolment)	22 Oct 2008	III
(date of last completed)	14 Jan 2011	
Objectives:	To confirm superior efficacy of pessaries with 0.2 mg and/or 0.03 mg estriol compared with pessaries without an active substance (placebo) in treatment of vaginal atrophy.	
Study design:	Prospective, multicentre, randomised, placebo-controlled, double-blind.	
Study population:	Postmenopausal women with vaginal atrophy	
Diagnosis and criteria for inclusion:	Postmenopausal women ≥ 18 years with a clinical diagnosis of vaginal atrophy, a vaginal maturation index (VMI) < 40% and a vaginal pH > 5 were eligible for inclusion. At least one symptom of vaginal atrophy (dryness, pain/burning sensation, pruritus, discharge, cohabitation problems) had to be rated ≥ 65 on the visual analogue scale (VAS) = “most bothersome symptom (MBS)”. Subjects with hormone replacement or phyto-oestrogen therapy during the preceding 12 weeks, a current or suspected oestrogen-dependent malignant tumour, a Pap smear ≥ III, endometrial thickness > 5 mm, current or suspected vaginal infection, current symptomatic urinary tract infection, active or previous breast cancer or suspicion thereof, undiagnosed bleeding in	

	the genital area, current venous thromboembolic disease or known severe renal insufficiency were not eligible for inclusion.
Test product, dose, batch number:	Pessary containing 0.2 mg estriol, batch no.: 0408(53) or pessary containing 0.03 mg estriol, batch no.: 0408(52) During the first 3 weeks, 1 pessary was to be inserted deep into the vagina once daily in the evening, thereafter 1 pessary twice weekly as maintenance dose
Reference therapy, dose, batch number:	Pessaries without active substance, batch no.: 0408(51) During the first 3 weeks, 1 pessary was to be inserted deep into the vagina once daily in the evening, thereafter 1 pessary twice weekly as maintenance dose
Duration of treatment:	12 weeks
Criteria of evaluation:	
Efficacy	Primary efficacy endpoints: • Rise (increase) in the vaginal maturation index (VMI) • Normalisation (decrease) of the vaginal pH value • Improvement (decrease) in the subjective most bothersome symptom (MBS) of vaginal atrophy Secondary efficacy variables: • Course of VMI, vaginal pH and MBS • Physician's evaluation of efficacy • Responder rates
Safety	Safety was assessed on the basis of incidence of adverse events (AEs), sonographic evaluation of endometrial thickness and gynaecological examination. Furthermore, a subject-based evaluation of tolerability was performed.
Statistical methods:	For numerical data sample statistics were calculated, for categorical data frequency tables. Primary analysis The 3 primary endpoints 1. Increase in VMI: difference $VMI_{T3} - VMI_{T-1}$ 2. Decrease in vaginal pH: difference $pH_{T-1} - pH_{T3}$ 3. Decrease in the subjective most bothersome symptom (MBS) of vaginal atrophy: difference $VAS_{T-1} - VAS_{T3}$ *with T_{-1}=Screening and T_3=12 weeks after Baseline* were to be tested individually for superiority using the univariate Wilcoxon-Mann-Whitney U test in the above mentioned order, with the null and alternative hypothesis

	H0: $MW_{TR} \leq 0.5$ and H1: $MW_{TR} > 0.5$. The single primary endpoints were to be tested first for 0.2 mg estriol versus placebo. Only if all three single tests showed a significant superiority, the superiority of 0.03 mg estriol versus placebo was to be tested in the same manner. In addition to the precise p value, the MW statistic with confidence interval was to be given as the effect size. The significance level was defined as α=2.5% (1-sided). Through the a priori arranged tests, no further alpha adjustment was necessary for the testing of the two verum groups against the placebo group. The primary analysis was to be performed with the ITT population.

Efficacy Results:

A total of 739 subjects entered the study; 301 subjects were screening failures leading to 438 subjects who were randomised to one of the study treatments. Except for 2 subjects in the 0.2 mg estriol group all of the randomised subjects took study medication. A total of 91.1% of the treated subjects completed the study with no relevant differences between the treatment groups (p=0.977; Fisher's exact test). Both the safety population and the ITT population consisted of 142 subjects in the 0.2 mg estriol group, 147 subjects in the 0.03 mg estriol group and 147 subjects in the placebo group. The per protocol (PP) population comprised 105 subjects in the 0.2 mg estriol group, 102 subjects in the 0.03 mg estriol group and 110 subjects in the placebo group. The study was conducted at 59 study centres.

On average, the subjects were 65.0 ± 7.7 years old. The symptom most frequently selected as MBS was "dryness" (60.8% of subjects, ITT population). With regard to demographic and further baseline characteristics including the primary efficacy variables there were no relevant differences between the 3 treatment groups.

The primary efficacy results are summarised in Table A (0.2 mg estriol) and Table B (0.03 mg estriol). In a first step it was shown that subjects treated with 0.2 mg estriol pessaries and in a second step that subjects treated with 0.03 mg estriol pessaries showed statistically significantly greater improvement in the 3 efficacy variables (VMI, vaginal pH and MBS) than those using pessaries with no active substance (placebo) after 12 weeks of treatment (p-value <0.001 for all 3 parameters and for both dose groups; Wilcoxon-Mann-Whitney U test; ITT population). Sensitivity analyses in the PP population and analyses employing best case / worst case scenarios for the imputation of missing values confirmed the results of the primary analysis.

Table A: Primary efficacy results (0.2 mg estriol; ITT population; Wilcoxon-Mann-Whitney U T.)

		0.2 mg Estriol Median (Q_1; Q_3)	**Placebo** Median (Q_1; Q_3)	Effect size [LCL; UCL]	p-value
VMI, %	T_{-1}	N=142	N=146		
		5.0 (1.0; 14.0)	6.9 (1.5; 21.0)		
	T_3	N=128	N=131		
		55.0 (51.3; 60.6)	40.0 (21.0; 50.0)		
	ΔT_3-T_{-1}	48.5 (37.5; 56.6)	24.0 (9.0; 40.0)	0.243 [0.185; 0.300]	<0.001
Vaginal pH	T_{-1}	N=142	N=147		
		6.8 (6.1; 7.0)	6.6 (6.0; 7.0)		
	T_3	N=129	N=132		
		5.0 (4.5; 5.0)	5.8 (5.2; 6.8)		
	ΔT_{-1}-T_3	-1.7 (-2.3; -1.0)	-0.3 (-1.1; 0.0)	0.252 [0.194; 0.310]	<0.001
MBS, VAS	T_{-1}	N=142	N=147		
		75.0 (71.0; 90.0)	75.0 (70.0; 85.0)		
	T_3	N=130	N=130		
		25.5 (10.0; 40.0)	50.0 (26.0; 67.0)		
	ΔT_{-1}-T_3	-55.0 (-70.0; -35.0)	-27.0 (-51.0; -7.0)	0.307 [0.246; 0.369]	<0.001

LCL/UCL = Lower/upper confidence limit
MBS = Most bothersome symptom
Q = Quartile
VMI = Vaginal maturation index
T_{-1}=Screening and T_3=12 weeks after Baseline (+ 2–3 days without treatment)

Table B: Primary efficacy results (0.03 mg estriol; ITT population; Wilcoxon-Mann-Whitney U T.)

		0.03 mg Estriol Median (Q_1; Q_3)	**Placebo** Median (Q_1; Q_3)	Effect size [LCL; UCL]	p-value
VMI, %	T_{-1}	N=147	N=146		
		5.3 (1.5; 20.0)	6.9 (1.5; 21.0)		
	T_3	N=133	N=131		
		52.5 (50.0; 57.0)	40.0 (21.0; 50.0)		
	ΔT_3-T_{-1}	43.8 (26.0; 51.0)	24.0 (9.0; 40.0)	0.322 [0.260; 0.383]	<0.001
Vaginal pH	T_{-1}	N=147	N=147		
		6.8 (6.0; 7.0)	6.6 (6.0; 7.0)		
	T_3	N=135	N=132		
		5.0 (4.5; 5.3)	5.8 (5.2; 6.8)		
	ΔT_{-1}-T_3	-1.5 (-2.1; -0.8)	-0.3 (-1.1; 0.0)	0.276 [0.217; 0.335]	<0.001
MBS, VAS	T_{-1}	N=147	N=147		
		75.0 (71.0; 85.0)	75.0 (70.0; 85.0)		
	T_3	N=135	N=130		
		30.0 (10.0; 49.0)	50.0 (26.0; 67.0)		
	ΔT_{-1}-T_3	-50.0 (-69.0; -30.0)	-27.0 (-51.0; -7.0)	0.344 [0.282; 0.407]	<0.001

LCL/UCL = Lower/upper confidence limit
MBS = Most bothersome symptom
Q = Quartile
VMI = Vaginal maturation index
VAS = Visual analogue scale
T_{-1}=Screening and T_3=12 weeks after Baseline (+ 2–3 days without treatment)

Whereas results in the verum groups were comparable with regard to changes in vaginal pH and MBS at T_3 (p=0.109 and p=0.039, respectively), improvement in VMI was greater under 0.2 mg estriol than under 0.03 mg estriol (p<0.001; post hoc analysis; Wilcoxon-Mann-Whitney U test; ITT population).

Secondary efficacy results:

Clear improvements in the 3 primary efficacy variables were already observed after 20 days of treatment (at T_1). VMI showed an increase compared to Screening by (mean ± SD) 51.3 ± 20.1% under 0.2 mg estriol, by 43.8 ± 20.8% under 0.03 mg estriol and by 26.0 ± 19.6% under placebo. Vaginal pH had improved by -1.5 ± 0.9 under 0.2 mg estriol, by -1.4 ± 0.8 under 0.03 mg estriol and by -0.7 ± 0.8 under placebo. MBS severity (VAS) had decreased by -36.5 ± 24.6 under 0.2 mg estriol, by -31.2 ± 21.9 under 0.03 mg estriol and by -22.3 ± 22.3 under placebo (ITT population).

The results of the primary analysis were supported by the results of the physician's evaluation of efficacy. In 85.4% of subjects in the 0.2 mg estriol group, in 80.0% of subjects in the 0.03 mg estriol group and in 44.7% of subjects in the placebo group the efficacy of the study treatment was assessed to be very good or good after 12 weeks of treatment (ITT population).

The rate of responders (meeting the criteria of VMI ≥ 55%, vaginal pH value ≤ 5 and

MBS intensity ≤ 35 on the VAS) was considerably higher in the verum groups compared to the placebo group both after 20 days and after 12 weeks of treatment ($p<0.001$ for comparison of 0.2 mg estriol or 0.03 mg estriol versus placebo at both points in time; Chi-square test). Response rates after 12 weeks of treatment were 33.1% for 0.2 mg estriol, 18.5% for 0.03 mg estriol and 3.4% for placebo.

Safety Results:

The study treatment was safe and well tolerated and no new or unexpected safety signals were observed.

AE incidences were 23.9% in the 0.2 mg estriol group, 21.8% in the 0.03 mg estriol group and 25.9% in the placebo group. The most frequent AEs were a vulvovaginal burning sensation (7.1% of subjects in total group), application site pain (2.8% of subjects in total group) and vulvovaginal pruritus (2.1% of subjects in total group) occurring at similar rates in all treatment groups.

Severe AEs were overall rare (4.6% of subjects in total group); the most frequent severe AE (1.1% of subjects in total group) was a vulvovaginal burning sensation reported exclusively in the placebo group.

"Vulvovaginal burning sensation" was also the most frequent drug-related AE (6.7% of subjects in total group) recorded with similar frequency in all treatment groups. Apart from application site pain (2.8%), vulvovaginal pruritus (1.8%) and vaginal discharge (1.6%; 5 subjects in the placebo group and each 1 subject in the verum groups) all further drug-related AEs occurred at rates of less than 1.0%.

No subject died and only 5 subjects suffered SAEs (3 subjects in the 0.03 mg estriol group: ankle fracture / chronic obstructive pulmonary disease and pneumonia / breast cancer; 2 subjects in the placebo group: anal cancer stage 0 / haemorrhoids); none of the events was considered by the investigators to be drug-related.

AEs leading to discontinuation of study treatment were reported in 5.7% of subjects in the total group with no relevant differences between the treatment groups. Most common was a vulvovaginal burning sensation (2.1% of subjects in total group).

Clear indications for changes under treatment were neither observed for endometrial thickness evaluated via sonography nor in the gynaecological examination.

Tolerability of study treatment was mainly assessed by the subjects to be very good or good and showed a trend towards improvement with longer duration of usage. The proportions of subjects stating very good or good tolerability after 12 weeks of treatment were 94.6% under 0.2 mg estriol, 88.9% under 0.03 mg estriol and 80.5% under placebo.

Conclusion

In conclusion, in a stepwise procedure superiority of estriol over placebo in the local treatment of postmenopausal vaginal atrophy was shown for 0.2 mg estriol and also for 0.03 mg estriol. Although there were indications of slightly better effectiveness in the higher dose group, the low dose formulation was sufficient to achieve significant improvement in objective parameters (vaginal maturation index, vaginal pH) as well as a considerable alleviation of subjective symptoms in the presence of good tolerability.

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