# 2 Synopsis

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| **Trial Registration ID-number**<br>NCT00431132 | **IND Number –** Not applicable<br>**EudraCT number –** 2006-001629-24 |
| **Title of Trial**<br>A 12-month open label multicentre trial to investigate the endometrial safety of Vagifem Low Dose (10 µg 17beta-estradiol vaginal tablet) in postmenopausal women with atrophic vaginitis symptoms | |
| **Investigator(s)**<br>The Signatory Investigator for this study is [redacted], M.D. | |
| **Trial Site(s)**<br>There were 40 sites initiated in the following countries: Czech Republic, Denmark, Finland, France, Hungary, Norway, and Sweden. | |
| **Publications**<br>None | |
| **Trial Period**<br>05 January 2007 - 12 November 2008 | **Development Phase**<br>Phase 3a |
| **Objectives**<br>**Primary Objective:**<br>• To evaluate the endometrial safety of Vagifem 10 µg in the treatment of postmenopausal atrophic vaginitis symptoms.<br><br>**Secondary Objectives:**<br>• To evaluate the other safety endpoints which included: vital signs, laboratory tests, physical examination, gynaecological examination, Papanicolaou cervical smear, transvaginal ultrasound, local tolerability of Vagifem 10 µg, mammogram, and adverse events. | |
| **Methodology**<br>The trial was an open label, multi-centre trial to assess the endometrial safety of Vagifem (10 µg 17β-estradiol vaginal tablet). All subjects received active treatment. Using the supplied applicator, each enrolled subject inserted one Vagifem 10 µg vaginal tablet once daily during the first two weeks of treatment. Subjects then inserted the tablets twice weekly during the remainder of the trial (maintenance treatment duration was 50 weeks). The primary safety endpoint was the hyperplasia rate at the end of the study (Week 52). Endometrial biopsies were to be histologically analysed at the beginning and end of the study. Other safety endpoints included: vital signs, laboratory tests, physical examination, gynaecological examination, Papanicolaou cervical smear, transvaginal ultrasound, local tolerability of Vagifem 10 µg, mammogram, and adverse events. | |
| **Number of Subjects Planned and Analysed**<br>Of the 586 subjects that were screened, 336 subjects were enrolled and 292 (86.9%) completed the 52-week study. The endometrial safety data of 336 subjects enrolled in this trial were to be pooled with the data from the Vagifem 10 µg- treated subjects from the VAG-2195 study to provide in total at least 300 subjects treated with Vagifem 10 µg for 52 weeks, which is required by EMEA. A total of 336 subjects received an endometrial biopsy at baseline, and 284 subjects received the same procedure at Week 52. One subject out of the 284 discontinued due to an adverse event on day [redacted], and had a biopsy taken at Week [redacted]. Therefore, the number of completers who had biopsy results at Week 52 was 283. The total number of subjects who received end-of-treatment endometrial biopsies (including premature discontinuation) was 297. Of the 283 completers, 261 subjects had interpretable results for the evaluation of hyperplasia rate at Week 52. Among the 22 subjects who were excluded from this analysis, 21 did not have tissue available and one subject had "insufficient tissue for diagnosis" [redacted] this result did not fulfill the criteria for evaluable biopsy as defined in the protocol. | |

**Diagnosis and Main Criteria for Inclusion**

Healthy non-hysterectomised post-menopausal women (≥ 2 years after last menstruation or bilateral oophorectomy) ≥ 45 years of age, with serum FSH levels > 40 mIU/ml and estradiol < 20 pg/ml, at least one urogenital symptom of moderate to severe intensity as identified by the subject (vaginal dryness, vaginal and/or vulvar irritation/itching, vaginal soreness, dysuria, dyspareunia and vaginal bleeding associated with sexual activity), ≤ 5% superficial cells, vaginal pH ≥ 5, endometrial thickness < 4.0 mm, and normal mammograms.

**Test Product, Dose and Mode of Administration, Batch Number**

Vagifem vaginal tablets (17β-estradiol), 10 µg for vaginal use, batch number SBBE044.

**Duration of Treatment**

Screening: 2-4 weeks

Treatment: 52 weeks

**Reference Therapy, Dose and Mode of Administration, Batch Number**

All subjects received active treatment.

**Criteria for Evaluation – Efficacy**

- No efficacy evaluation was performed in this trial.

**Criteria for Evaluation – Safety**

- The primary safety endpoint was the hyperplasia rate at end-of-study (Week 52).
- Other safety assessments included vital signs, laboratory tests (biochemisty and haematology), physical exam, gynaecological exam, Papanicolaou cervical smear, transvaginal ultrasound, local tolerability of Vagifem 10 µg, mammogram, and adverse events.

**Statistical Methods**

The endometrial hyperplasia rate was calculated based on the number of subjects with endometrial hyperplasia/endometrial carcinoma divided by the total number of subjects with interpretable biopsies at Week 52. For the purpose of the study, an interpretable biopsy was defined as "endometrial tissue sufficient for diagnosis". The 95% confidence interval for endometrial hyperplasia will be calculated for the combined VAG-1748 and VAG-2195 population.

**Demography of Trial Population**

The subjects enrolled in this study were predominantly White (88.1%) and had a mean (±SD) age of 59.5 (±6.16) years. Enrolled subjects had a mean (±SD) BMI value of 24.6 (± 3.4) kg/m$^2$, and were on average 9.4 (± 5.9) years from last menses.

**Efficacy Results**

- No efficacy evaluation was performed in this trial.

**Safety Results**

- Of the 336 subjects enrolled in the study, 186 (55.4%) reported a total of 442 treatment emergent adverse events.
- A total of 44 (13.1 %) subjects were discontinued from the trial due to adverse events (18 subjects, 5.4%), non-compliance (7 subjects, 2.1%), ineffective therapy (6 subjects, 1.8%), or other reasons (13 subjects, 3.9%). The most commonly occurring adverse events considered related to the study drug were headache (10 subjects, 3.0%) and vulvovaginal discomfort (5 subjects, 1.5%). The proportion of subjects experiencing serious adverse events was 4.2% (14 subjects, 15 events). There was no relationship between the reported serious adverse events with the study drug. One subject ( ) experienced a serious adverse event with fatal outcome which was judged to be unrelated to the trial drug.
- A total of 336 subjects received an endometrial biopsy at baseline, and 284 subjects received the same procedure at Week 52. One subject (Subject ) out of the 284 discontinued due to an adverse event on day ; therefore, the number of completers who had a biopsy taken at Week 52 was 283. The total number of subjects who received an end-of–treatment endometrial biopsy (including premature discontinuation) was 297.
  At screening, in total 325 out of 336 subjects had biopsy results that were categorised as "atrophic" or "inactive" endometrium, which represents the expected endometrial status in the study population of postmenopausal women. Four subjects had "no tissue" results, 2 were categorized as "weakly proliferative", 3 had a diagnosis of polyps, and 2 were categorized as "other". At Week 52, overall 258 out of the 283 completers were in the category of "atrophic" or "inactive" endometrium, while 21 had a "no tissue" result, in several cases despite repeated biopsy attempts of obtaining endometrial tissue, being indicative of atrophic endometrium; 1 was categorised as "weakly proliferative" and 2 had a diagnosis of polyps. The results of the endometrial biopsies after 52 weeks of treatment support that Vagifem 10 µg has no proliferative effect on the endometrium.
- Subject was reported with a diagnosis of endometrial hyperplasia at biopsy that was, , endometrial thickness as measured by TVU, further clinical investigation and fractionated abrasion of the endometrium, not confirmed and therefore considered a false positive diagnosis.
- Of the 283 completers, 261 subjects had interpretable results available for the evaluation of hyperplasia rate at Week 52. There were no confirmed cases of hyperplasia/carcinoma reported; therefore, the incidence rate was 0 out of 261 subjects.

**Conclusions**

After 12 months of treatment with Vagifem 10 µg, there were no endometrial hyperplasia or cancer cases reported. Overall, treatment with Vagifem 10 µg was well tolerated and the adverse events were not unusual in women of postmenopausal age. No serious adverse events were judged to be related to the study drug. This study supports that Vagifem 10 µg is a locally acting estrogen therapy with no proliferative effect on the endometrium, and that treatment for one year does not pose an increased risk of endometrial hyperplasia in postmenopausal women. Therefore, Vagifem 10 µg should be considered a safe treatment option for estrogen deficiency-induced vaginal atrophy.

*The trial was conducted in accordance with the Declaration of Helsinki (*59th WMA General Assembly, Seoul 2008. Last amended with Note of Clarification on Paragraph 29 by the WMA General Assembly, Washington 2002, and Note of Clarification on Paragraph 30 by the WMA General assembly, Tokyo 2004) *and ICH Good Clinical Practice (July 2002)*.

The results presented reflect data available in the clinical database as of 12 February 2009.