**Table (Reference ID #1349)**

| **Study Description** | **Intervention(s)/ Comparator(s)** | **Patient Population** | **Baseline Measure(s)** | **Outcome Measure(s)** | **Overall Quality****Risk of Bias** |
| --- | --- | --- | --- | --- | --- |
| **Author:**Fraser et al., 2011**Country:**Australia, Europe**Enrollment** **period:** February 2006 to May 2008**Intervention** **setting:** 34 centers **Funding:**Bayer Health Care Pharmaceuticals**Author industry relationship disclosures:**7/7**Study Design:** RCT**Blinding:** Patients, investigators | **Intervention:**Estradiol valerate/ dienogest, oral 7 consecutive treatment cycles of 28 days each (estradiol valerate 3 mg on days 1-2, estradiol valerate 2 mg /dienogest 2 mg on days 3-7, estradiol valerate 2 mg/ dienogest 3 mgs on days 8-24, estradiol valerate 1 mg on days 25-26, placebo on days 27-28)**Comparator:**Placebo**Groups:****G1:** Estradiol valerate/dienogest**G2:** Placebo**Followup:**8 months | **Inclusion criteriaa:**Aged 18 or olderHeavy menstrual bleedingTwo or more menstrual bleeding episodes with a MBL of >80 ml, prolonged menstrual bleeding (≥8 days) and/or frequent menstrual bleeding (>5 episodes with a minimum of 20 bleeding days overall) during the 90 day run-in phaseWilling to use barrier method of contraceptionNormal endometrial biopsy result or mild, simple endometrial hyperplasia 6 months prior to study entry**Exclusion criteria:** Abnormal transvaginal ultrasoundAbnormal lab values which were clinically significantHistory of endometrial ablationDilatation and curettage 2 months preceding the studyBleeding due to organic pathology determined during 90 day run-in phase including chronic endometriosis, adenomyosis, endometriosis, endometrial polyps, leiomyomas or uterine malignancyUnwilling to discontinue tranexamic acid or NSAIDs during mensesBMI >32 kg/m2Women aged 35 or older who smoked more than 10 cigarettes per day (or any number of cigarettes in Australia and the UK)Contraindications to the use of combined oral contraceptives**N at enrollment:** **G1:** 149**G2:** 82**N at followup:** **G1:** 109**G2:** 62**Age, mean years ± SD:****G1:** 39.5 ± 6.6**G2:** 38.5 ± 7.5**BMI, mean kg/m2 ± SD:****G1:** 24.6 ± 3.5**G2:** 25.7 ± 3.0**Weight, mean kg ± SD:****G1:** 69.8 ± 11.8**G2:** 71.6 ± 10.2**Parity:**NR**Race/ethnicity, n (%):**Caucasian:**G1:** 144 (96.6)**G2:** 80 (97.6)Black:**G1:** 1 (0.7)**G2:** 0 (0)Asian:**G1:** 2 (1.3)**G2:** 1 (1.2)Other:**G1:** 2 (1.3)**G2:** 1 (1.2)**Bleeding symptoms,b n (%):**Prolonged bleeding:**G1:** 20 (13.4)**G2:** 10 (12.2)Frequent bleeding:**G1:** 0**G2:** 0Heavy bleeding:**G1:** 136 (91.3)**G2:** 76 (92.7) | **Bleeding:**MBL measured by the alkaline hematin method, mean ml ± SD:**G1:** 639.4 + 513.5 **G2:** 645.1 + 391.2Bleeding and spotting days, 90-day run-in phase, mean:**G1:** 23.0**G2:** 21.0Bleeding only days, 90-day run-in phase, mean ± SD:**G1:** 17.3 ± 6.7**G2:** 16.6 ± 6.7Spotting only days, 90-day run-in phase, mean ± SD:**G1:** 5.7 ± 5.6**G2:** 4.4 ± 5.1Bleeding episodes, 90-day run-in phase, mean ± SD:**G1:** 3.5 ± 0.6 **G2:** 3.4 ± 0.7Sanitary protection items, 90-day run-in phase, mean ± SD:**G1:** 81.6 ± 32.7**G2:** 82.0 ± 39.3Hemoglobin, mean g/dl ± SD:**G1:** 12.1 ± 1.2**G2:** 12.1 ± 1.4Hematocrit, mean % ± SD:**G1:** 39.7 ± 3.7**G2:** 39.8 ± 4.2Ferritin, mean ng/ml ± SD:**G1:** 13.6 ± 13.6**G2:** 13.9 ± 14.5 | **Bleeding:**MBL measured by the alkaline hematin method, mean ml ± SD:**G1:** 175.8 ± 200.8 **G2:** 553.6 + 308.0 MBL measured by the alkaline hematin method, mean changed ml ± SD:**G1:** -485 ± 409.6 **G2:** -93.2 ± 268.0 **G1 vs. G2:** p<0.0001MBL < 80 ml for each episode, n (%):**G1:** 86/136 (63.2)**G2:** 11/76 (14.5)Bleeding and spotting days, 90-day efficacy phase, mean:**G1:** 21.3**G2:** 19.1 Bleeding and spotting days, mean changed:**G1:** -1.6**G2:** -1.9Bleeding only days, 90-day efficacy phase, mean ± SD:**G1:** 13.7 ± 7.0**G2:** 14.9 ± 5.7Bleeding only days, mean changed ± SD:**G1:** -3.7 ± 8.4**G2:** -2.1 ± 7.2**G1 vs. G2:** p=0.0186Spotting only days, 90-day efficacy phase, mean ± SD:**G1:** 7.6 ± 7.8**G2:** 4.2 ± 5.5Spotting only days, mean changed ± SD:**G1:** 2.1 ± 8.2**G2:** -0.2 ± 6.0Bleeding episodes, 90-day efficacy phase, mean ± SD:**G1:** 3.1 ± 0.9 **G2:** 3.1 ± 0.6 Bleeding episodes, mean changed ± SD:**G1:** -0.4 ± 1.1**G2:** -0.4 ± 0.7**G1 vs. G2**: p=0.5095Sanitary protection items, 90-day efficacy phase, mean ± SD:**G1:** 43.3 ± 31.7 **G2:** 64.8 ± 26.3Sanitary protection items, mean changed ± SD:**G1:** -38.4 ± 30.0**G2:** -16.5 ± 32.2**G1 vs. G2**: p<0.0001Reduction in MBL volume, mean % (median):**G1:** 69.4 (79.2)**G2:** 5.8 (7.4)**G1 vs. G2:** p<0.0001≥20% reduction in MBL,%:**G1:** 94**G2:** 40≥50% reduction in MBL,%:**G1:** 84**G2:** 12≥80% reduction in MBL,%:**G1:** 50**G2:** 0Hemoglobin, adjusted change from baseline, mean g/dl:**G1:** +0.70**G2:** +0.05**G1 vs. G2:** p<0.0001 Hematocrit, adjusted change from baseline, mean %:**G1:** +1.5**G2:** -0.05**G1 vs. G2**: p<0.0049Ferritin, adjusted change from baseline, mean ng/ml: **G1:** +8.6**G2:** +0.4**G1 vs. G2**: p<0.0017Patient reported improvement in bleeding symptoms, %:**G1:** 77.9**G2:** 45.1**G1 vs. G2:** p<0.0001Responder status,c n (%):Complete:**G1:** 44 (29.5)**G2:** 1 (1.2)Partial or non-respondere:**G1:** 64 (43.0)**G2:** 61 (74.4)Missing data:**G1:** 41 (27.5)**G2:** 20 (24.4)Complete response rate (excluding patients with missing data), % (95% CI):**G1:** 40.7 (31.4, 50.6)**G2:** 1.6 (0.0, 8.7)**Quality of life:**NR**Pain:**NR**Sexual function:**NR**Patient satisfaction:**NR**Fertility:**NR**Time to conception:**NR**Additional interventions:**Concomitant use of iron, n (%):**G1:** 28/149 (18.8)**G2:** 27/82 (32.9) | **Overall quality:**Good**Risk of bias:** Randomization: LowAllocation concealment:LowSelective reporting:UnclearBlinding patients/personnel:LowBlinding outcome assessment:LowIncomplete outcome reporting:LowOther:Low |

**Table Notes:** See #1365 Jensen et al same study protocol used in United States and Canada; a Use of medications to relieve women of heavy menstrual bleeding (sex steroids, NSAIDS, tranexamic acid) was not allowed during study period; b Some women presented with multiple symptoms. c Complete response to treatment defined as composite of following components: no bleeding episodes lasting more than 7 days, no more than 4 bleeding episodes overall, no bleeding episodes with blood loss volume ≥80 ml, no more than one bleeding episode increase from baseline, no more than 24 days of bleeding overall and no increase from baseline in total number of bleeding days. In addition patients recruited because of presence of prolonged bleeding were required to demonstrate a decrease of at least 2 days in maximum duration of a bleeding cycle. Patients recruited because of heavy bleeding, the blood loss volume had to <80 ml and had to represent a decrease of at least 50% relative to average blood loss volume per episode during the study recruitment phase; d Change from 90 day run-in phase to 90-day efficacy phase; e Detail on criteria not achieved in partial or non-responders presented in Table 2 of manuscript (pg. 2702).