**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 older  Heavy menstrual bleeding  Two 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 phase  Willing to use barrier method of contraception  Normal endometrial biopsy result or mild, simple endometrial hyperplasia 6 months prior to study entry  **Exclusion criteria:**  Abnormal transvaginal ultrasound  Abnormal lab values which were clinically significant  History of endometrial ablation  Dilatation and curettage 2 months preceding the study  Bleeding due to organic pathology determined during 90 day run-in phase including chronic endometriosis, adenomyosis, endometriosis, endometrial polyps, leiomyomas or uterine malignancy  Unwilling to discontinue tranexamic acid or NSAIDs during menses  BMI >32 kg/m2  Women 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:** 0  Heavy 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 + 391.2  Bleeding and spotting days, 90-day run-in phase, mean:  **G1:** 23.0  **G2:** 21.0  Bleeding only days, 90-day run-in phase, mean ± SD:  **G1:** 17.3 ± 6.7  **G2:** 16.6 ± 6.7  Spotting only days, 90-day run-in phase, mean ± SD:  **G1:** 5.7 ± 5.6  **G2:** 4.4 ± 5.1  Bleeding episodes, 90-day run-in phase, mean ± SD:  **G1:** 3.5 ± 0.6  **G2:** 3.4 ± 0.7  Sanitary protection items, 90-day run-in phase, mean ± SD:  **G1:** 81.6 ± 32.7  **G2:** 82.0 ± 39.3  Hemoglobin, mean g/dl ± SD:  **G1:** 12.1 ± 1.2  **G2:** 12.1 ± 1.4  Hematocrit, mean % ± SD:  **G1:** 39.7 ± 3.7  **G2:** 39.8 ± 4.2  Ferritin, 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<0.0001  MBL < 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:** -1.9  Bleeding only days, 90-day efficacy phase, mean ± SD:  **G1:** 13.7 ± 7.0  **G2:** 14.9 ± 5.7  Bleeding only days, mean changed ± SD:  **G1:** -3.7 ± 8.4  **G2:** -2.1 ± 7.2  **G1 vs. G2:** p=0.0186  Spotting only days, 90-day efficacy phase, mean ± SD:  **G1:** 7.6 ± 7.8  **G2:** 4.2 ± 5.5  Spotting only days, mean changed ± SD:  **G1:** 2.1 ± 8.2  **G2:** -0.2 ± 6.0  Bleeding 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=0.5095  Sanitary protection items, 90-day efficacy phase, mean ± SD:  **G1:** 43.3 ± 31.7  **G2:** 64.8 ± 26.3  Sanitary protection items, mean changed ± SD:  **G1:** -38.4 ± 30.0  **G2:** -16.5 ± 32.2  **G1 vs. G2**: p<0.0001  Reduction 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:** 0  Hemoglobin, 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<0.0049  Ferritin, adjusted change from baseline, mean ng/ml:  **G1:** +8.6  **G2:** +0.4  **G1 vs. G2**: p<0.0017  Patient reported improvement in bleeding symptoms, %:  **G1:** 77.9  **G2:** 45.1  **G1 vs. G2:** p<0.0001  Responder 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:  Low  Allocation concealment:  Low  Selective reporting:  Unclear  Blinding patients/personnel:  Low  Blinding outcome assessment:  Low  Incomplete outcome reporting:  Low  Other:  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).