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# Efficacy and tolerability of CDB-2914 treatment for symptomatic uterine fibroids: a randomized, double-blind, placebo-controlled, phase IIb study

**Lynnette K. Nieman, M.D.**[a], **Wendy Blocker, R.N.**[a], **Tonja Nansel, Ph.D.**[b], **Sheila Mahoney, M.S., C.N.M., M.P.H.**[a], **James Reynolds, M.D.**[c], **Diana Blithe, Ph.D.**[d], **Robert Wesley, Ph.D.**[e], and **Alicia Armstrong, M.D.**[a]

[a]Program in Reproductive and Adult Endocrinology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, Maryland [b]Division of Epidemiology, Statistics and Population Research, National Institute of Child Health and Human Development, Bethesda, Maryland [c]Department of Radiology, The Mark O. Hatfield Clinical Research Center, Bethesda, Maryland [d]Contraception and Reproductive Health Branch, National Institute of Child Health and Human Development, Bethesda, Maryland [e]Biostatistics and Clinical Epidemiology Service, Warren Grant Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland

## Abstract

**Objective—**To evaluate the efficacy and tolerability of the P receptor modulator CDB-2914 (Ulipristal, CDB).

**Design—**Randomized, placebo-controlled double-blind clinical trial.

**Setting—**Clinical research center.

**Patient(s)—**Premenopausal women with symptomatic uterine fibroids.

**Intervention(s)—**Once-daily oral CDB (10 or 20 mg) or placebo (PLC) for 12 weeks (treatment 1). A second 3-month treatment with CDB (treatment 2) was offered. A computer-generated blocked randomization was used.

**Main Outcome Measure(s)—**Magnetic resonance imaging (MRI)-determined total fibroid volume (TFV) change was the primary outcome; amenorrhea and quality of life (QOL) were secondary end points.

**Result(s)—**Treatment 1 TFV increased 7% in the PLC group, but decreased 17% and 24% in the CDB10 and CDB20 groups. The TFV decreased further in treatment 2 (-11%). Amenorrhea occurred in 20/26 women taking CDB and none on PLC. Ovulation resumed after CDB. Hemoglobin improved only with CDB (11.9 ± 1.5 to 12.9 ± 1.0 g/dL) as did the Fibroid QOL



Reprint requests: Lynnette K. Nieman, M.D., Building 10, CRC, 1 East, Room 1-3140, 10 Center Drive, MSC 1109, Bethesda MD 20892-1109 (NiemanL@nih.gov).

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Questionnaire symptom severity, energy/mood, and concern subscores, and overall QOL scores. The CDB was well tolerated, with no serious adverse events. Adverse events were unchanged during treatments.

**Conclusion(s)—**Administration of CDB-2914 for 3–6 months controls bleeding, reduces fibroid size, and improves QOL.

### Keywords

Selective progestin receptor modulator; ulipristal acetate; fibroids; UFS-QOL

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Uterine fibroids convey significant morbidity, including menses-related anemia, pelvic pain and pressure and dysmenorrhea, reduced quality of life, and infertility (1–5). These problems lead many women to seek treatment. Because there are no safe and effective long-term medical therapies, surgical extirpation remains the major therapeutic option.

A well-tolerated nonsurgical alternative for treatment of fibroids is needed. Because fibroids increase in size during the reproductive years, one possibility would be to block gonadal steroid action. CDB-2914* [17a-acetoxy-11b-(4-*N*,*N*-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20 dione] binds to human progestin, gluco-corticoid, and androgen, but not estrogen (E) or mineralocorticoid receptors (*The modified International Non Proprietary Name (INN) for CDB-2914 is Ulipristal acetate; CDB 2914 has also been named HRP 2000, *RTI* 3021-012, VA2914 and PGL4001). It is a selective P receptor modulator (SPRM) with minimal in vivo antiglucocorticoid activity compared with its antiprogestin effect (6). The National Institute of Child Health and Human Development (NICHD) supported preclinical and phase 1- 2 studies of CDB-2914 to develop it as a therapeutic agent.

We previously reported that CDB-2914 treatment decreased fibroid volume in 12 women (7). The current study was designed to confirm and extend those findings.

## Materials and Methods

### Subjects

We enrolled women with symptomatic (anemia, pelvic pressure, chronic lower abdominal pain, bladder pressure with increased urinary frequency, or menorrhagia) uterine fibroids more than 2 cm in diameter (8). For other enrollment criteria, see Supplemental Materials (available online).

The NICHD Institutional Review Board approved this study. After giving consent, women were examined at the National Institutes of Health Clinical Center.

### Study Procedures

Women underwent pelvic T1- and T2-weighted spin echo magnetic resonance imaging (MRI) before and at the end of treatment, and bone densitometry before and after 6 months of therapy.

### Treatment 1

For treatment1 (TX1), after a negative pregnancy test, subjects were randomized and began treatment on menstrual cycle day 1 or 2. Treatment administration continued for three menstrual cycles (90–102 days in amenorrheic women).

The FSH, ACTH, cortisol, PRL, LH, P, and $E_2$ levels were measured about every 2 weeks without considering the menstrual cycle. Cell blood count, liver function tests, and acute care panel were obtained monthly. Urine cortisol and creatinine excretion were measured three times (days 20–30, 50–60, and 80–90).

Women recorded vaginal bleeding on a daily calendar that included rows to document specific symptoms (Table 1) with blank rows for other symptoms. Subjects completed the short form-36 (SF-36) and uterine fibroid symptom (UFS) quality-of-life questionnaires initially and after 3 months of treatment (9, 10).

### Treatment Options After TX1

After initial treatment, women could elect hysterectomy, myomectomy, or 3 months of treatment with CDB-2914 (termed treatment 2, TX2). Surgery occurred after ovulation in the third month, in the follicular phase of the fourth month, or after 90-102 days of treatment. An endometrial biopsy obtained before completing treatment was dated according to the criteria of Noyes and Rock (11).

In TX2, women received their earlier CDB dose or were randomized to 10 or 20 mg if they had received placebo. Study procedures were identical to TX1.

### Extension Study

Women who did not undergo surgery or underwent myomectomy were invited to continue under an “extension” study during which they underwent pelvic MRI and health-related quality-of-life (HRQL) questionnaires at 3, 6, and 12 months after stopping taking the study drug.

### Data Capture and Analysis

Fibroids more than 2 cm were mapped and measured in three dimensions. The primary outcome, fibroid volume, was calculated by an ellipsoid formula ($\pi/6 \times d1 \times d2 \times d3$). Individual volumes were summed to assess total fibroid volume for each woman, which were log-transformed before analysis. Women with paired MRI results were included in this intent-to-treat analysis, even if they did not take all study medication. Fibroids were included if they were seen on both studies.

Data from a previously published study with an identical treatment design were combined to analyze a larger group for total fibroid volume and dose response (7). Results from the two CDB dose groups did not differ. They were combined into a single group and compared with the placebo (PLC) group, using analysis of variance (ANOVA) or the Jonckheere-Terpstra non-parametric tests for trend. Nonparametric variables were analyzed using the exact Kruskal-Wallis test or Wilcoxon signed rank test. *t*-Tests were used for paired data.

Exact two-tailed *P* values are reported; a *P* value ≤ .05 was considered significant. Prespecified secondary outcomes included HRQL scores, menstrual function, and adverse events.

The SF-36 and UFS questionnaires were scored using previously published methods (10, 12). A composite "bleeding" score was constructed as the mean of all UFS questions related to bleeding. Change from baseline was evaluated using univariate ANOVA on the difference between pretreatment and treatment scores.

## Results

Figure 1 shows the study participant flow diagram. Two women withdrew within 2 weeks of initiating study drug (see Supplemental Material). The baseline characteristics of the treatment groups were similar (Supplemental Table 1, Supplemental Material).

During TX1, the total fibroid volume increased by 7% in the PLC group, but decreased 17% and 24% in the CDB10 and CDB20 groups (CDB10 vs. CDB20 delta difference, *P*=.43; all CDB vs. PLC, *P*=.003). Total fibroid volume decreased in 10/13 (77%, range + 16% to -58%) CDB10-treated and 11/13 (85%, range +22% to −68%) CDB20-treated women. Fibroid volume increased in 9/12 (75%) of placebo-treated patients (range, +71% to −29%). When individual fibroids larger than 3 cm in diameter at baseline were considered, 83% (65/79) of fibroids in CDB treatment groups decreased ≥ 10% in volume, whereas 42% (9/19) in the PLC group decreased.

Eight women who received CDB for 6 months had MRI data. Overall fibroid volume continued to decrease (TX1: −21%, TX2: −11%, *P*=.014).

Eight women had myomectomy before the extension study. Final imaging 6 (n = 1) or 12 (n = 7) months later showed smaller total fibroid volume in women treated with CDB (0.4–11.9 cm) compared with the placebo group (6.2,20.9, and 21.7 $cm^3$). Among four women from all treatment groups without prior surgery, three had increased fibroid volume (changes of 3.8 $cm^3$ [CDB10], 8.1 $cm^3$ [PLC], and 16.3 $cm^3$ [CDB20], and two had decreases of 107.7 $cm^3$ and 0.6 $cm^3$ [both CDB20]). No statistical tests were applied because of the small number of patients.

The size of the CDB treatment effect was similar in the current and earlier study (*P*=.945). When the studies were combined, the magnitude of CDB10 and CDB20 effects were similar (*P*=.865) and effects on total fibroid volume remained (PLC +7% ± 0.1% vs. CDB -23% ± 0.1%, *P*=.0002).

Paired SF-36 and UFS data were available for nearly all women (Supplemental Table 2, Supplemental Materials). Age-adjusted SF-36 results for role-physical and role-mental components improved significantly in the CDB group but decreased in the PLC group. Compared with PLC, the CDB group had significant improvements in the UFS symptom severity score, overall HRQL scores, the concern, activities, and energy/mood subscales, and the bleeding score. These scores were similar at the end of 3 and 6 months of treatment in those who received CDB.

CDB-2914 prevented menses (Fig. 2). In TX1, eight women in the CDB10 group were amenorrheic, three had interval spotting without menses, and two had either one or two menses. In the CDB20 group, 12 women were amenorrheic and one had monthly menses. One woman in the PLC group missed one cycle (PLC vs. CDB, $P<.001$). No TX2 woman had menses; one CDB20-treated woman had vaginal spotting (PLC vs. CDB both phases, $P<.0001$).

Among women taking CDB who were not simultaneously taking iron, 3 months of treatment was associated with a significant increase in hemoglobin (11.9 ± 1.5 g/dL to 12.9 ± 1.0 g/dL, $P=.027$) and hematocrit (36.5% ± 4.2% to 38.9% ± 2.7%, $P=.039$). No additional improvement was observed in TX2. Women taking PLC had no change in either hemoglobin (12.3 ± 1.4 g/dL vs. 12.2 ± 1.1 g/dL, $P=.82$) or hematocrit (36.9% ± 3.6% vs. 36.7% ± 2.6%, $P=.82$). Treatment assignment did not influence the postoperative change in hematocrit or hemoglobin.

The CDB treatment suppressed ovulation. Consistent ovulatory P values were observed in 13 menstruating PLC women (including one late dropout), and 1 with menses taking CDB20. Another four women with menses or spotting and five who were amenorrheic on CDB had only one ovulatory value. All values were <3 ng/mL in 11 other women taking CDB who were amenorrheic (n = 10) or who had spotting. Twenty-seven women had surgery, of which three had oophorectomy (2 PLC, 1 CDB10). Among the remainder, 18 had ovulatory *P* values at the postoperative visit (7 PLC; 11 CDB) or a documented postoperative LH surge (5 CDB). One patient declined evaluation.

Mean $E_2$ levels were not affected by TX1 CDB (PLC 117.5 ng/mL vs. CDB 117.2 ng/mL, $P=.36$), but decreased in TX2 (mean TX1 103.7 ± 62 ng/mL vs. TX2 74.4 ± 35.2 ng/mL, delta change $P=.008$). Median values for CDB groups in TX1 and TX2 were 84.0 ng/mL and 76.1 ng/mL, respectively, with interquartile ranges of 75.7−100.4 ng/mL and 48.2–74.5 ng/mL, respectively. Serum LH and FSH were occasionally elevated in all groups, but with no consistent pattern.

At baseline, the number of different adverse events and the percentage of days with adverse events were similar among the treatment groups (Table 1). Most symptoms occurred less than 3 days each month. There was a trend to fewer summed adverse events in the CDB20 group, but a direct comparison between CDB10 and CDB20 was not statistically significant (CDB10 delta: 15.6 ± 68.8 vs. CDB20 delta: −19.8 ± 34.1, $P=.11$). When adverse events from the earlier and current 3-month studies were combined (n = 57), there was no statistical difference between the three treatments. Although the median change improved more in the CDB20 group than the others (CDB20 = −23.9, CDB10 = −7.1, PLC = 3.8), this trend was not significant ($P=.53$) and there was no difference between the two CDB groups ($P=.25$).

Serum PRL was elevated during treatment (>25 but < 90 ng/mL) in 17 women from all groups; most elevations were transient and mild. Two had elevated baseline values. Of these, one (CDB20) had galactorrhea and pituitary microadenoma with five of seven values increased during and after treatment. Another (CDB10) had no galactorrhea; all eight values were abnormal. The macroprolactin and pituitary MRI were normal.

Either alanine aminotransferase and/or aspartate aminotransferase were abnormal in nine women (all received CDB) (PLC vs. CDB, *P*=.0346); six had a single abnormal result (Fig. 3). All values were less than 2.1 times the upper reference range and all bilirubin results were normal.

There was no evidence for adrenal blockade in women taking CDB. Endometrial histology was unremarkable in the nine women in the PLC group who did not elect TX2. Of 21 women who received CDB and had adequate biopsies, one showed cystic glandular hyperplasia (CDB10), two had PAEC changes (P receptor modulator-associated endometrial changes) (13) without atypia (both CDB20; hysterectomy) and another had cystic glandular changes. There was no endometrial intraepithelial neoplasia (14) (additional details as Supplemental Material). There were no other symptoms or untoward effects of CDB administration and no serious adverse events.

## Discussion

This study confirms and extends our previous report that a 3-month treatment with the SPRM CDB-2914 controlled bleeding, reduced fibroid size, and improved quality of life in women with symptomatic uterine fibroids (7). This study further demonstrated improvements in the UFS questionnaire. New but preliminary findings emerged from the eight women who took the agent for an additional 3 months, during which there was more decrease in total fibroid volume and improvement in quality of life, but amenorrhea continued. In a small cohort followed after myomectomy, there was less re-growth of fibroids at 6–12 months after surgery in the CDB group. When data from our earlier smaller study were pooled with this study (n = 56), the CDB effect persisted, with a 23% decrease in total fibroid compared with a 7% increase in those who received placebo.

Ideally, nonsurgical alternatives for the treatment of fibroids would improve symptoms, quality of life, anemia, and fibroid size, without affecting future fertility or causing adverse events. The GnRH agonists cause amenorrhea or decreased menstrual bleeding, decrease fibroid size, and allow for subsequent fertility (15). However, they are associated with hypoestrogenism and hot flashes (16), and use is limited to 6 months because of potential bone loss (17). In contrast, SPRMs usually maintain $E_2$ levels (18, 19). In this study, nearly all $E_2$ levels were more than 50 pg/mL, suggesting no adverse effect on bone health. Six-month CDB treatment did not decrease bone mineral density or increase hot flashes, suggesting that the $E_2$ levels were adequate.

Another SPRM, mifepristone, reduced uterine and/or fibroid volume, as assessed by ultrasound, at daily doses of 2.5–50 mg, during 3–6 months (20–27). Although less expensive than MRI, ultrasound has less reproducible results, which may introduce variability (28). In placebo-controlled trials, mifepristone, 5 mg/d to 50 mg every other day, decreased the size end point by 28%–47% (21, 22, 29). An open label trial using 2.5 mg/d decreased uterine volume by 11%, suggesting a possible dose effect (20). Reduced bleeding and amenorrhea occur more often at higher doses.

The CDB group had amenorrhea or fewer days of bleeding, and hematocrit and hemoglobin levels improved. These changes, and possible attendant unblinding, may have contributed to improved HRQL.

Neither the cause(s) of fibroids nor the mechanism by which CDB reduces fibroid size is fully understood. The catechol-O-methyl transferase (COMT) polymorphisms and increased aromatase expression, which might increase local E levels are more common in black than in white women (30, 31). Fibroid micro-RNA distribution also differs by race (31). Thus, it is possible that CDB treatment might be more effective in certain women. The current study could not address that question because of its size and the large proportion of black participants.

The CDB was well tolerated, with a nonsignificant trend to greater improvement of symptoms in women receiving CDB20. One woman dropped out due to a severe headache. Seven women taking CDB had one or two increases in alanine aminotransferase and/or aspartate aminotransferase; two had about 40% abnormal results. All values were below 2.1 times the upper normal value and bilirubin was not elevated. Previous studies noted mildly increased liver function tests in up to 10% of women receiving mifepristone and asoprisnil; development of onapristone was stopped because of this (32). Larger studies are needed to evaluate the benefits and risks of CDB-2914.

All SPRMs have been associated with endometrial histology termed glandular, cystic, or simple hyperplasia in the current nomenclature (13). A consensus conference identified biopsies with cystically dilated glands and a mixture of estrogenic (mitotic) and progestogenic (secretory) features. The panel designated these as PAEC and recommended additional studies to define their natural history. The incidence of PAEC is unclear; studies evaluating 5 and 10 mg of mifepristone treatment for 3 months found endometrial hyperplasia in 2% and 63% of subjects (22, 23). This may reflect differences in pathologic interpretation or study populations. In our studies, 4 of 33 women who received CDB had cystic glandular dilatation, simple hyperplasia, or complex hyperplasia without cellular atypia or endometrial intraepithelial neoplasia.

In conclusion, CDB-2914 represents a new approach to symptomatic uterine fibroids. It shrinks total fibroid burden, improves quality of life, and anemia, and does not provoke bone loss or hot flashes. The CDB-associated anovulation is reversible, suggesting that it may be useful in women wishing to preserve fertility.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## References

1. Mauskopf J, Flynn M, Thieda P, Spalding J, Duchane J. The economic impact of uterine fibroids in the United States: a summary of published estimates. J Women's Health. 2005; 14:692–703. 2002.
2. Williams VS, Jones G, Mauskopf J, Spalding J, DuChane J. Uterine fibroids: a review of health-related quality of life assessment. J Women's Health. 2006; 15:818–29. 2002.
3. Bucek RA, Puchner S, Lammer J. Mid- and long-term quality-of-life assessment in patients undergoing uterine fibroid embolization. AJR. 2006; 186:877–82. [PubMed: 16498124]
4. Hartmann KE, Birnbaum H, Ben-Hamadi R, Wu EQ, Farrell MH, Spalding J, et al. Annual costs associated with diagnosis of uterine leiomyomata. Obstet Gynecol. 2006; 108:930–7. [PubMed: 17012456]
5. Lerner D, Mirza F, Chang H, Renzulli K, Perch K, Chelmow D. Impaired work performance among women with symptomatic uterine fibroids. J Occup Environ Med/Am Col Occup Environ Med. 2008; 50:1149–57.
6. Attardi BJ, Burgenson J, Hild SA, Reel JR. In vitro antiprogestational/antiglucocorticoid activity and progestin and glucocorticoid receptor binding of the putative metabolites and synthetic derivatives of CDB-2914, CDB-4124, and mifepristone. J Steroid Biochem Mol Biol. 2004; 88:277–88. [PubMed: 15120421]
7. Levens ED, Potlog-Nahari C, Armstrong AY, Wesley R, Premkumar A, Blithe DL, et al. CDB-2914 for uterine leiomyomata treatment: a randomized controlled trial. Obstet Gynecol. 2008; 111:1129–36. [PubMed: 18448745]
8. Bulletin AT. Uterine leiomyomata. ACOG technical bulletin. International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics. 1994; 46:73–82. Number 192— May 1994.
9. Ware JE Jr, Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) project. J Clin Epidemiol. 1998; 51:903–12. [PubMed: 9817107]
10. Spies JB, Coyne K, Guaou Guaou N, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. Obstet Gynecol. 2002; 99:290–300. [PubMed: 11814511]
11. Noyes RW, Rock J. Dating the endometrial biopsy. Fertil Steril. 1950; 1:3–25.
12. Ware, JE.; K, M.; Dewey, JE. How to score version two of the SF-36 Health Survey. Lincoln, RI: QualityMetric Incorporated; 2000.
13. Mutter GL, Bergeron C, Deligdisch L, Ferenczy A, Glant M, Merino M, et al. The spectrum of endometrial pathology induced by progesterone receptor modulators. Mod Pathol. 2008; 21:591–8. [PubMed: 18246050]
14. Lacey JV Jr, Mutter GL, Nucci MR, Ronnett BM, Ioffe OB, Rush BB, et al. Risk of subsequent endometrial carcinoma associated with endometrial intraepithelial neoplasia classification of endometrial biopsies. Cancer. 2008; 113:2073–81. [PubMed: 18720479]
15. Kessel B, Liu J, Mortola J, Berga S, Yen SS. Treatment of uterine fibroids with agonist analogs of gonadotropin-releasing hormone. Fertil Steril. 1988; 49:538–41. [PubMed: 3277869]
16. Palomba S, Pellicano M, Affinito P, Di Carlo C, Zullo F, Nappi C. Effectiveness of short-term administration of tibolone plus gonadotropin-releasing hormone analogue on the surgical outcome of laparoscopic myomectomy. Fertil Steril. 2001; 75:429–33. [PubMed: 11172852]
17. Bianchi G, Costantini S, Anserini P, Rovetta G, Monteforte P, Menada MV, et al. Effects of gonadotrophin-releasing hormone agonist on uterine fibroids and bone density. Maturitas. 1989; 11:179–85. [PubMed: 2512467]

18. Batista MC, Cartledge TP, Zellmer AW, Merino MJ, Axiotis C, Loriaux DL, et al. Delayed endometrial maturation induced by daily administration of the antiprogestin RU 486: a potential new contraceptive strategy. Am J Obstet Gynecol. 1992; 167:60–5. [PubMed: 1442957]
19. Chabbert-Buffet N, Pintiaux-Kairis A, Bouchard P. Effects of the progesterone receptor modulator VA2914 in a continuous low dose on the hypothalamic-pituitary-ovarian axis and endometrium in normal women: a prospective, randomized, placebo-controlled trial. J Clin Endocrinol Metab. 2007; 92:3582–9. [PubMed: 17579200]
20. Eisinger SH, Fiscella J, Bonfiglio T, Meldrum S, Fiscella K. Open-label study of ultra low-dose mifepristone for the treatment of uterine leiomyomata. Eur J Obstet Gynecol Reprod Biol. 2009; 146:215–8. [PubMed: 19586708]
21. Engman, M.; Granberg, S.; Williams, AR.; Meng, CX.; Lalitkumar, PG.; Gemzell-Danielsson, K. Hum Reprod. Vol. 24. Oxford; England: 2009. Mifepristone for treatment of uterine leiomyoma. A prospective randomized placebo controlled trial; p. 1870-9.
22. Bagaria M, Suneja A, Vaid NB, Guleria K, Mishra K. Low-dose mifepristone in treatment of uterine leiomyoma: a randomised double-blind placebo-controlled clinical trial. Aust N Z J Obstet Gynaecol. 2009; 49:77–83. [PubMed: 19281585]
23. Carbonell Esteve JL, Acosta R, Heredia B, Perez Y, Castaneda MC, Hernandez AV. Mifepristone for the treatment of uterine leiomyomas: a randomized controlled trial. Obstet Gynecol. 2008; 112:1029–36. [PubMed: 18978102]
24. Fiscella K, Eisinger SH, Meldrum S, Feng C, Fisher SG, Guzick DS. Effect of mifepristone for symptomatic leiomyomata on quality of life and uterine size: a randomized controlled trial. Obstet Gynecol. 2006; 108:1381–7. [PubMed: 17138770]
25. Eisinger SH, Bonfiglio T, Fiscella K, Meldrum S, Guzick DS. Twelve-month safety and efficacy of low-dose mifepristone for uterine myomas. J Min Invas Gynecol. 2005; 12:227–33.
26. Murphy AA, Morales AJ, Kettel LM, Yen SS. Regression of uterine leiomyomata to the antiprogesterone RU486: dose-response effect. Fertil Steril. 1995; 64:187–90. [PubMed: 7789557]
27. Zeng C, Gu M, Huang H. A clinical control study on the treatment of uterine leiomyoma with gonadotrophin releasing hormone agonist or mifepristone. Zhonghua fu chan ke za zhi. 1998; 33:490–2. [PubMed: 10806751]
28. Dueholm M, Lundorf E, Hansen ES, Ledertoug S, Olesen F. Accuracy of magnetic resonance imaging and transvaginal ultrasonography in the diagnosis, mapping, and measurement of uterine myomas. Am J Obst Gynecol. 2002; 186:409–15. [PubMed: 11904599]
29. Fiscella K, Eisinger S. CDB-2914 for uterine leiomyomata treatment: a randomized controlled trial. Obstet Gynecol. 2008; 112:707. author reply: 707–8. [PubMed: 18757682]
30. Ishikawa H, Reierstad S, Demura M, Rademaker AW, Kasai T, Inoue M, et al. High aromatase expression in uterine leiomyoma tissues of African-American women. J Clin Endocrinol Metab. 2009; 94:1752–6. [PubMed: 19240151]
31. Othman EE, Al-Hendy A. Molecular genetics and racial disparities of uterine leiomyomas. Best Pract Res Clin Obstet Gynaecol. 2008; 22:589–601. [PubMed: 18373954]
32. Spitz IM. Progesterone antagonists and progesterone receptor modulators: an overview. Steroids. 2003; 68:981–93. [PubMed: 14667991]

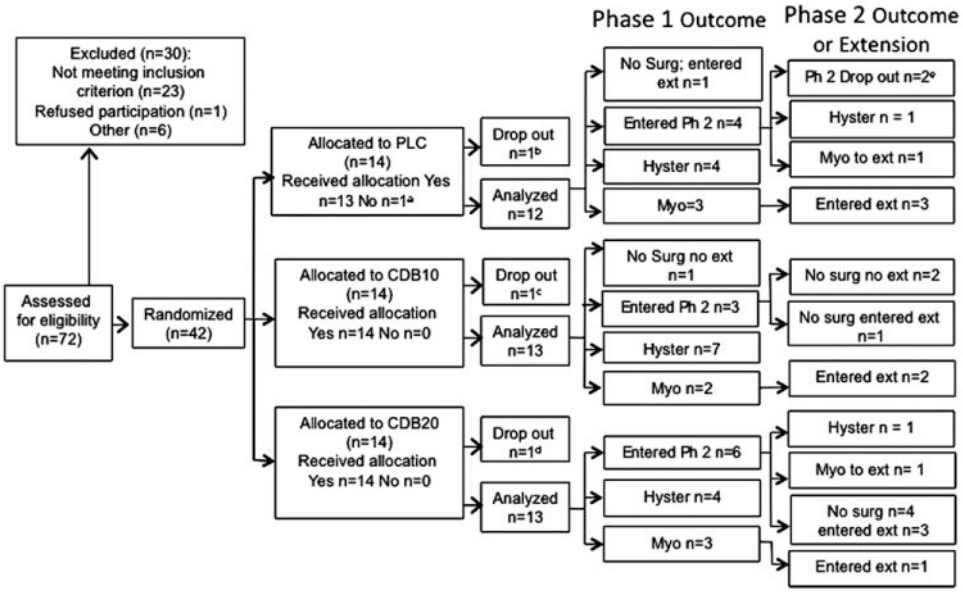


**Figure 1.**

Patient flow through the protocol. Women were enrolled beginning on 3/16/2006. The final magnetic resonance imaging (MRI) of the extension study was obtained on 6/8/09. Ph 2 = treatment 2, Surg = surgery, Myo = myomectomy, Hyster = hysterectomy, Ext = extension study. Reasons for dropping out are provided by superscripts: [a]did not pick up medication; [b]did not want to have second MRI; [c]had severe headache; [d]had an out-of-body experience; [e]study was inconvenient.

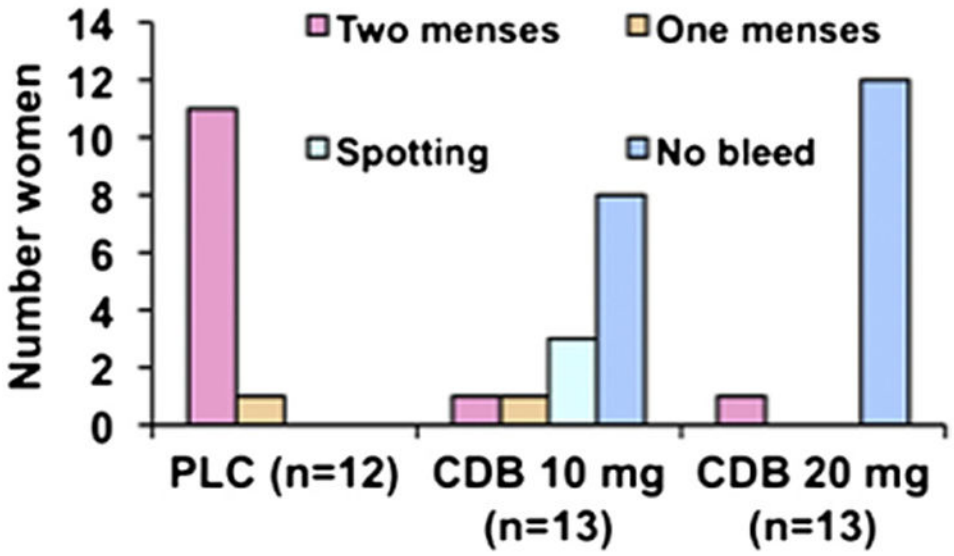


**Figure 2.**
Vaginal bleeding during treatment 1. PLC = placebo; CDB = P receptor modulator CDB-2914.

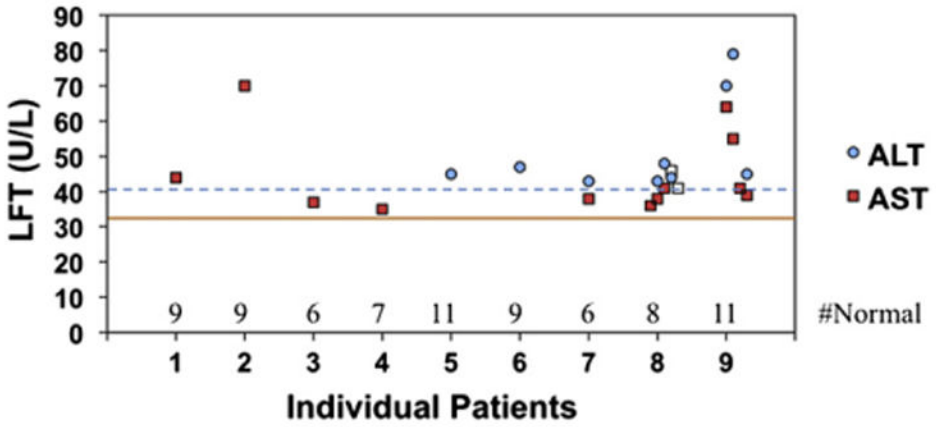


**Figure 3.**

Liver function abnormalities (LFT) in treatments 1 and 2. All abnormal aspartate aminotransferase (AST) (closed squares during treatment; open squares at baseline) and alanine aminotransferase (ALT) (closed circles) results are shown. All women with abnormal values received P receptor modulator CDB-2914. The solid line represents the upper limit of normal for aspartate aminotransferase and the dashed line shows the upper limit of normal for alanine aminotransferase. The number of normal results during the study for each patient is shown at the bottom of the graph. At the end of the study, patient 8 had normal values; patient 9 had values within 3 U/L of the upper limit of normal; all other patients had normal results except for the minor increase in alanine aminotransferase in patients 5 and 7.

**Table 1**

**Percentage of days that an adverse event was reported for baseline cycle and throughout treatment 1 in study completers (mean)**

| | Delta: Baseline to treatment 1 mean | | | | | | Baseline mean | | | Treatment 1 mean | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PLC | CDB10 | CDB20 | Mean CDB | ANOVA trend P value | t-test P value | PLC | CDB10 | CDB20 | PLC | CDB10 | CDB20 |
| Vaginal spotting | −1 | 3 | −1 | 1 | .904 | .356 | 2 | 6 | 1 | 1 | 9 | 0 |
| Vaginal discharge | 7 | 0 | −2 | −1 | .177 | .169 | 3 | 4 | 7 | 9 | 4 | 6 |
| Cramps[a] | −1 | 1 | −1 | 0 | .694 | .309 | 2 | 1 | 1 | 1 | 2 | 0 |
| Menses/clots | −1 | 0 | −2 | −1 | .373 | .962 | 2 | 0 | 2 | 1 | 0 | 0 |
| Mood changes[a] | 0 | 0 | 0 | 0 | .589 | .657 | 2 | 0 | 0 | 1 | 0 | 0 |
| Bloating[a] | 1 | 0 | 0 | 0 | .549 | .339 | 0 | 0 | 0 | 1 | 0 | 0 |
| Breast pain | 0 | 4 | −4 | 0 | .282 | .950 | 3 | 4 | 6 | 3 | 8 | 2 |
| Abdominal pain[b] | −1 | −6 | 1 | −2 | .655 | .738 | 8 | 8 | 8 | 7 | 3 | 10 |
| Pelvic pain[b] | −3 | −1 | −5 | −3 | .413 | .846 | 5 | 3 | 7 | 2 | 1 | 1 |
| Joint pain | 0 | 1 | −1 | 0 | .798 | .709 | 4 | 0 | 3 | 3 | 1 | 3 |
| Calf pain | 0 | 0 | 1 | 0 | .286 | .586 | 2 | 1 | 1 | 2 | 0 | 2 |
| Back pain[a] | −1 | −1 | −1 | −1 | .711 | .757 | 1 | 2 | 2 | 0 | 1 | 1 |
| Fatigue | −7 | −6 | −8 | −7 | .940 | .973 | 14 | 22 | 9 | 7 | 16 | 2 |
| Loss of appetite | −1 | 0 | 0 | 0 | .300 | .178 | 2 | 0 | 0 | 1 | 0 | 0 |
| Nausea/vomiting | 1 | 5 | 0 | 2 | .901 | .632 | 0 | 1 | 0 | 1 | 5 | 0 |
| Diarrhea | 1 | 1 | 0 | 0 | .493 | .752 | 0 | 1 | 1 | 1 | 1 | 0 |
| Headache[b] | 2 | 2 | 0 | 1 | .249 | .526 | 1 | 1 | 1 | 2 | 2 | 1 |
| Skin rash | −1 | 5 | 1 | 3 | .688 | .192 | 2 | 0 | 0 | 1 | 5 | 1 |
| Hot flashes[a] | 1 | 5 | 1 | 3 | .967 | .614 | 0 | 0 | 0 | 1 | 5 | 1 |
| Irregular heartbeat[a] | 0 | 0 | 0 | 0 | .194 | .126 | 0 | 0 | 0 | 0 | 0 | 0 |
| Other | 1 | 3 | 0 | 1 | .724 | .988 | 0 | 7 | 3 | 2 | 10 | 3 |

*Note:* The delta represents the difference of the phase 1 and baseline values.

[a]These symptoms were not prespecified on the daily calendar, but were added by the women.

[b]The most common symptoms or adverse events experienced by subjects who dropped out (headache).