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CDB-2914 for Uterine Leiomyomata Treatment:

A Randomized Controlled Trial

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Abstract

OBJECTIVE—To evaluate whether 3-month administration of CDB-2914, a selective progesterone receptor modulator, reduces leiomyoma size and symptoms.

METHODS—Premenopausal women with symptomatic uterine leiomyomata were randomly assigned to CDB-2914 at 10 mg (T1) or 20 mg (T2) daily or to placebo (PLC) for 3 cycles or 90–102 days if no menses occurred. The primary outcome was leiomyoma volume change determined by magnetic resonance imaging at study entry and within 2 weeks of hysterectomy. Secondary outcomes included the proportion of amenorrhea, change in hemoglobin and hematocrit, ovulation inhibition, and quality-of-life assessment.

RESULTS—Twenty-two patients were allocated, and 18 completed the trial. Age and body mass index were similar among groups. Leiomyoma volume was significantly reduced with CDB-2914 administration (PLC 6%; CDB-2914 –29%; $P=.01$), decreasing 36% and 21% in the T1 and T2 groups, respectively. During treatment, hemoglobin was unchanged, and the median estradiol was greater than 50 pg/mL in all groups. CDB-2914 eliminated menstrual bleeding and inhibited ovulation (% ovulatory cycles: CDB-2914, 20%; PLC, 83%; $P=.001$). CDB-2914 improved the concern scores of the uterine leiomyoma symptom quality-of-life subscale ($P=.04$). One CDB-2914 woman developed endometrial cystic hyperplasia without evidence of atypia. No serious adverse events were reported.

CONCLUSION—Compared with PLC, CDB-2914 significantly reduced leiomyoma volume after three cycles, or 90–102 days. CDB-2914 treatment resulted in improvements in the concern subscale of the Uterine Fibroid Symptom Quality of Life assessment. In this small study, CDB-2914 was well-tolerated without serious adverse events. Thus, there may be a role for CDB-2914 in the treatment of leiomyomata.

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Uterine leiomyomata are the most common benign soft tissue tumors in women and frequently cause excessive uterine bleeding, chronic pelvic pain/pressure, and dyspareunia.¹ Hysterectomy remains the major therapeutic option for leiomyomata, resulting in more than 200,000 cases per year.² Despite the increasing use of uterus-preserving procedures,³ the overall invasive procedure rate for leiomyomata is unchanged, highlighting the paucity of effective, longterm medical therapies.

Because gonadal hormones induce or maintain leiomyoma growth,^{4,5} selective progesterone receptor modulators have been evaluated as therapeutic agents. When given for 3–6 months, mifepristone reduced leiomyoma size and symptoms and induced amenorrhea in 63–100% of women.⁶ However, there was a 28% incidence of simple endometrial hyperplasia, and potential for antiglucocorticoid activity has been a concern.⁷

CDB-2914 (17 α -acetoxy-11 β -[4-N,N-dimethylaminophenyl]-19-norpregna-4,9-diene-3,20-dione) is a relatively pure progesterone antagonist (selective progesterone receptor modulator) without agonist activity. It binds the human progesterone but not the estrogen receptor.^{7,8} Although structurally similar to mifepristone, CDB-2914 has less antiglucocorticoid activity, providing a potential advantage for long-term use. The goal of this study was to evaluate whether chronic daily administration of CDB-2914 at 10 mg or 20 mg is an effective treatment for women with uterine leiomyomata.

MATERIALS AND METHODS

Women aged 33–50 years with regular menses and one or more leiomyomata more than 2 cm in diameter were considered for enrollment. Eligible subjects were healthy, nonpregnant, and desired hysterectomy for symptomatic leiomyomata as defined by the American College of Obstetricians and Gynecologists Practice Bulletin.⁹ Additional inclusion criteria were a hemoglobin more than 10 g/dL, ovulatory cycles every 24–35 days, and the current use of nonhormonal contraception. In this study, we limited our subjects to a body mass index less than 33 kg/m² to reduce surgical risk. Exclusion criteria were an inability to complete the study requirements, prior uterine artery embolization, menopausal status (follicle-stimulating hormone [FSH] more than 20 milli-International Units/mL), cervical dysplasia, adnexal mass, genetic cause or rapid growth of leiomyomata (doubled size within 6 months), unexplained vaginal bleeding, and the use of glucocorticoids, progestins, or agents (prescribed or herbal) that alter ovarian or hepatic function.

The Institutional Review Board of the National Institute of Child Health and Human Development approved this protocol (02-CH-0287). After obtaining informed oral and written consent, eligible women underwent a history, physical examination, pelvic imaging, and routine laboratory analysis. Potential subjects were instructed to detect their luteinizing hormone (LH) surge using a home urinary kit (Ovuquick; Quidel, San Diego, CA) and to document vaginal bleeding or spotting and any constitutional symptoms on a menstrual calendar.

The Pharmaceutical Development Service at the National Institutes of Health Clinical Center randomly assigned subjects to computer-generated blocks of six to receive CDB-2914 at a dose of 10 (T1) or 20 mg (T2) or placebo (PLC). Allocation concealment was assured by this Service. The intended target enrollment was 36 subjects. However, due to slow subject recruitment, the study was terminated after 22 subjects were enrolled. The blocks were adjusted for two dropouts occurring within 1 month of study drug initiation. HRA Pharma (Paris, France) supplied CDB-2914 as a micronized crystalline powder. To blind both patients and health-care providers, gelatin capsules containing either CDB-2914 in doses of 10 mg and 20 mg or inert material (PLC) were prepared as previously reported.¹⁰

Subjects had a progesterone (P₄) level drawn 1 week after a documented LH surge to confirm ovulation. Women not exhibiting an LH surge or luteal phase P₄ were excluded. Blood was obtained for complete blood count, electrolytes, blood urea nitrogen, creatinine, liver function, thyroid-stimulating hormone, free T₄, follicle-stimulating hormone (FSH), and β-hCG. Partway through the study, baseline serum prolactin was obtained after some subjects were found to have elevated values during treatment. Subjects with hemoglobin less than 10 g/dL received iron supplementation until it exceeded that threshold. To determine leiomyoma number, location and size, eligible subjects underwent noncontrast enhanced pelvic T1- and T2-weighted spin echo magnetic resonance (MR) with images at a slice thickness of 6 mm (Achieva 1.5; Philips Medical Systems, Bothell, WA; or Signa HD 1.5, GE Healthcare, Buckinghamshire, UK).

On day 1 or 2 of menstrual bleeding, subjects underwent a urine pregnancy test before initiating the study agent. If negative, the subject began the study agent once daily while fasting and continued for three menstrual cycles or the equivalent (90–102 days), if amenorrheic. Subjects returned every 2–4 weeks during treatment to undergo endocrine evaluation, including measurements of adrenocorticotrophic hormone (ACTH), cortisol, prolactin, LH, FSH, P₄, and E₂. At roughly 30-day intervals, safety monitoring blood work, including a complete blood count, hepatic panel, electrolytes, blood urea nitrogen, creatinine, and glucose, was obtained. Subjects provided 24-hour urine specimens for cortisol and creatinine measurements at three intervals throughout the treatment period (days 20–30, days 50–60, and days 80–90). Pelvic MR imaging was repeated within 2 weeks of surgery to document leiomyoma size, location, and number.

Patients were admitted for hysterectomy after the LH surge in the third treatment cycle or in the follicular phase of the fourth cycle; if anovulatory, hysterectomy was performed at 90–102 days of treatment. Patients returned the menstrual cycle charts and symptom records upon admission for surgery and completed a second Uterine Fibroid Symptom (UFS) and/or Short Form-36 (SF-36) quality-of-life questionnaire. The study drug was discontinued immediately before surgery. An endometrial biopsy was obtained at surgery and a hysterectomy was performed; salpingo-oophorectomy was performed if indicated. To assess endometrial pathology, both the biopsy and hysterectomy specimens were evaluated.

Subjects returned for a postoperative evaluation at 4–6 weeks, and those undergoing salpingo-oophorectomy were offered hormone therapy. Subjects with intact ovaries who were anovulatory during treatment were monitored for a urinary LH surge and returned 5–7 days later for a serum P₄ value to document normal corpus luteum function. Subjects not demonstrating an LH surge during the posttreatment period were monitored until a luteal phase progesterone was documented or another reason for anovulation was determined.

The primary outcome was leiomyoma volume as determined by MR imaging. After both baseline and presurgical MR imaging was performed, a senior radiologist (A.P.), unaware of treatment allocation, identified and mapped the leiomyomata seen at baseline assessment, noting the location and three-dimensional diameters. Preoperative images were compared with baseline in order to correlate with leiomyoma location. Once the corresponding leiomyomata were identified, three-dimensional diameters of all leiomyomata were recorded. To calculate the volume of each leiomyoma, the formula for an ellipsoid was employed ($\pi/6 \times d1 \times d2 \times d3$) using the three-dimensional measurements. To avoid multiple observations from individual subjects and to assess the overall leiomyoma burden, the calculated leiomyoma volumes were summed to yield a total leiomyoma volume for each subject.

Secondary outcomes included assessment of treatment-dependent inhibition of ovulation, alteration in menstrual function, and change in leiomyoma-related symptoms. Presumptive

evidence of an ovulatory event was a serum progesterone concentration more than 3 ng/mL. Menstrual data collected during each of the three treatment cycles were scored as 0 if there was no menses and 1 if some menstrual bleeding was present during the cycle. For amenorrheic subjects, treatment cycles were assigned by 30-day intervals. Hemoglobin and hematocrit changes over the course of therapy were analyzed.

Symptom scores were calculated based on calendar logs for headache, joint, calf, breast, abdominal, and pelvic pain, fatigue, appetite changes, nausea, vomiting, diarrhea, and skin reaction; symptom intensity in each cycle was determined by the following algorithm: symptom intensity equals the number of days the symptom was experienced during the cycle divided by the number of days in the cycle. The adjusted intensity equals (treatment symptom intensity minus baseline symptom intensity) times 100. The adjusted symptom intensity was used to evaluate treatment-related effects on symptoms.

All serum assays were performed in the Clinical Center Department of Laboratory Medicine using commercially available assays (LH, FSH, and prolactin: Abbott Diagnostics, Abbott Park, IL; E₂, P₄, and cortisol: Beckman-Coulter, Fullerton, CA; ACTH: Nichols Institute Diagnostics, San Clemente, CA). The urinary cortisol assessments were performed using Liquid Chromatography-Tandem Mass Spectrometry with an intraassay variation of less than 5% and an interassay variation of less than 10% (Mayo Medical Labs, Rochester, MN).

We quantified subjective symptoms by previously validated quality-of-life measurement instruments: the SF-36 version 2 for general quality-of-life measures and the leiomyoma-specific UFS questionnaire.^{11,12} The SF-36 was incorporated from the study onset; however, the UFS questionnaire was incorporated mid way through the study recruitment when it became available. Both quality-of-life questionnaires were administered before study drug start and upon completion of the trial before surgery.

The SF-36 scores range from 0–100 (higher scores reflect higher functioning) and have been used previously to examine quality of life in women with leiomyomata.^{13,14} It has eight subscales compiled to global scores for mental and physical well-being. The UFS score also ranges from 0–100 and includes eight leiomyoma-specific quality-of-life subscales (symptom severity, concern, activities, energy and mood, control, self-consciousness, sexual functioning) compiled into an overall health-related quality-of-life score.¹¹ The symptom severity subscale contains questions related to leiomyoma-associated bulk symptoms. The concern subscale focuses largely on concern surrounding the inconvenience of carrying sanitary protection, soiling garments, and anxiety about the unpredictability of menses. The activities subscale focuses on the effect of leiomyomata on the subject's ability to travel, exercise, and plan and carrying out typical daily activities. Energy and mood subscale assesses the effect of fatigue on activity and mood-related symptoms. The control subscale assesses emotions related to future uncertainty and control over one's health. The self-consciousness subscale assesses the effect of leiomyomata on physical appearance, including stomach appearance and bloating. Finally, the sexual functioning subscale addresses attractiveness and whether one avoids sexual relations due to leiomyomata. For the UFS, higher health-related quality-of-life scores reflect superior quality of life, whereas higher scores in the subscales reflect increasing intensity of the respective index.

Data entry and data management were performed using the Clinical Trials Database at the National Institute of Child Health and Human Development. Imaging and hormonal data were analyzed using Stata 10.0 (Stata; College Station, TX) and StatXact 8 (Cytel Software Corp., Cambridge, MA). The variables determining the primary endpoint, total leiomyoma volume at baseline and presurgery, were analyzed by the Shapiro-Wilk test for normality. Because of severe nonnormality they were log-transformed. Other variables not expected to meet

parametric distributional assumptions, such as those on an ordinal scale, were analyzed using exact Kruskal-Wallis nonparametric statistical methods. Descriptive statistics, including means, standard deviations, medians, frequencies, and proportions, were determined.

For each assessment, the treatment groups were compared first to each other to establish whether these groups behaved similarly. If similar behavior was demonstrated, the treatment groups were collapsed into a single group and compared with the PLC group. Confirmatory analyses compared the primary outcome in the three groups using the Jonckheere-Terpstra nonparametric test for trend.¹⁵ Exact two-tailed *P* values were reported and $\alpha = 0.05$ was considered significant. The SF-36 and UFS questionnaires were scored according to previously published and validated methods.^{11,12} Changes in the quality-of-life scores were evaluated using the Wilcoxon rank sum test on the difference between pretreatment and posttreatment scores for each woman as determined by SPSS 13.0 for Windows (SPSS; Chicago, IL). Dropouts were excluded from the primary analysis; however, a secondary analysis was performed to evaluate whether significant differences between dropouts and completers were present.

RESULTS

Subjects were enrolled from March 2003 to August 2006. The last study subject completed medication and underwent surgery in November 2006. The study participant flow diagram is presented in Figure 1. There were four dropouts after randomization; two subjects in T1 group completed treatment but declined to undergo hysterectomy. One subject receiving PLC was unable to comply with follow-up visits completing a single cycle of treatment; another dropout in the PLC group presented with pelvic pain at baseline that continued during the first study cycle, dropping out before its completion and electing for surgical intervention.

Among completers, baseline characteristics were compared between groups (Table 1). There were no significant differences in baseline symptoms or the baseline SF-36 and UFS scores between groups (data not shown). The primary outcome was the overall change in leiomyoma volume based on MR imaging. During the 3-month study interval, the total leiomyoma volume increased by 6% in those receiving PLC; whereas those receiving T1 and T2 demonstrated a 36% and 21% reduction in leiomyoma volume, respectively. There was no significant difference in the response of the two treatment groups ($P=.59$). Additionally, there was insufficient evidence of a trend in leiomyoma volume reduction with increasing CDB-2914 dosage (Jonckheere-Terpstra trend test; $P=.06$). Thus, the CDB-2914 groups were collapsed and subsequently compared with PLC. When comparing CDB-2914 to PLC, there was a significant reduction in total leiomyoma volume after 3 months of therapy (PLC 6%, CDB-2914 -29%; $P=.01$).

Short Form-36 data were available for all completers ($n = 18$) and revealed no changes in either physical or mental quality-of-life scores. The uterine leiomyoma symptom quality-of-life assessments were completed by 12 subjects (PLC = 4, CDB-2914 = 8), including the two T1 dropouts. Although the sample size was sufficient to detect statistical significance only among the concern subscale (PLC, -20.0; CDB-2914, 31.3; $P=.04$), overall the CDB-2914 group improved on all UFS subscales and had improved symptom severity (PLC 3.9 ± 9.0 ; CDB-2914 -25.4 ± 32.1 ; $P=.11$).

Secondary analyses evaluated treatment-related differences in menstrual function. Subjects receiving PLC had monthly menses throughout the study interval. On the contrary, there was only a single menstrual bleeding episode that occurred in a subject receiving T1; no subject receiving T2 had any bleeding. When compared with PLC, CDB-2914 was associated with a significant reduction in menses, with evidence of a dose-dependent effect ($P<.001$). Three

subjects assigned to CDB-2914 and one in the PLC group received iron supplementation before study entry. Although there was evidence of profound menses suppression with CDB-2914, hemoglobin remained unchanged during the study interval (PLC -0.9 g/dL; CDB-2914 -0.3 g/dL; $P=.77$). Hematocrit values followed a similar trend (data not shown).

CDB-2914 altered the observed ovulatory rate. The PLC group had 83% ovulatory menstrual cycles, whereas those receiving CDB-2914 had lower ovulatory rates based on 30-day cycle intervals (T1 17%, T2 22%; $P=.92$; CDB-2914 compared with PLC $P=.001$). Of the 14 subjects receiving CDB-2914 who completed the trial, eight (57%) were anovulatory throughout the 3-month study interval; none receiving PLC were anovulatory. Of those receiving CDB-2914 not undergoing oophorectomy ($n=14$), 11 (79%) documented ovulatory events occurred during the menstrual cycle after surgery, in the second postoperative cycle ($n=1$) and the third cycle ($n=1$). One patient did not return. Despite the inhibition of ovulation by CDB-2914, the median serum E2 level was sufficient to support bone health (median 63 pg/mL; first to third quartiles 46–110 pg/mL), but was significantly lower than in the PLC group (median 105 pg/mL; first to third quartiles 64–171 pg/mL; $P=.003$). Within the CDB-2914 group there was no evidence of a dosage effect on serum E2 levels (1 subject receiving the 20 mg dose had an E2 more than 400 pg/mL) and no differences in median E2 during anovulatory or ovulatory intervals.

Table 2 shows the proportion of days during baseline and treatment in which subjects reported symptoms and the assessment of subjects with new or increased symptoms. Most symptoms occurred less than 5 d/mo and improved during the study interval. Analysis of the adjusted symptom intensity scores did not find differential adverse effects between groups. One subject (No. 5) complained of multiple symptoms, including headache, loss of appetite, nausea, vomiting, and diarrhea, both at baseline and during treatment. These signs were suggestive of adrenal insufficiency; however, there was no biochemical evidence of adrenal blockade in any study subject, because cortisol and ACTH levels were normal throughout the study interval.

Serum prolactin levels were transiently elevated in some subjects, in both the PLC and CDB-2914 groups (Table 2). In the PLC arm, two women had transient increases during treatment, with normal macroprolactin results, and normalization before the end of treatment. Eight women receiving CDB-2914 had increased prolactin levels. Of the four with increased baseline values, two had normalization during the study interval; the other two subjects, with maximal values of 61 and 67 ng/mL, were found to have pituitary microadenomas on MR imaging. The remaining four subjects had transient elevations in prolactin during the study interval (maximal values of 12–37 ng/mL), which normalized before surgery.

At baseline, one subject (T1) had transiently elevated hepatic transaminases, which were normal during treatment, and another subject (T2) had a single transient elevation in hepatic transaminases during treatment. One subject had a mild decrease in white blood cells and platelets during treatment that resolved and was thought to be spurious by the hematology consultant. The remaining safety blood analyses identified no additional adverse events.

Evaluation of endometrial histology demonstrated a single case of cystic glandular hyperplasia in a patient receiving the 10 mg CDB-2914 dose who was amenorrheic throughout treatment. This histologic subtype has been associated with antiprogestational agents, and the significance of such a finding has not been well-established.¹⁶ There were no other identified complications or untoward effects of CDB-2914 administration.

A secondary analysis of the dropouts showed no difference between these subjects and the completers in any baseline characteristics or symptoms. The subjects in the T1 group who dropped out were amenorrheic throughout treatment and had no adverse events.

DISCUSSION

In this randomized, placebo-controlled clinical trial, total uterine leiomyoma volume decreased significantly after three consecutive treatment cycles with 10-mg or 20-mg dosages of CDB-2914. The total leiomyoma volume reduction was similar at each CDB-2914 dose and was similar to that seen with other medical therapies, including gonadotropin-releasing hormone (GnRH) agonists and mifepristone.^{6,17} Unlike GnRH agonists, CDB-2914 was not associated with a hypoestrogenic environment and as a result would be unlikely to affect bone mineralization.

Short Form-36 quality-of-life surveys did not demonstrate a treatment difference in physical and mental quality-of-life assessments. This was not altogether surprising given the general nature of the questions and the small sample size. However, the uterine leiomyoma symptom quality-of-life assessment yielded interesting results. There was significant improvement in the concern subscale and the potential remains that a larger sample size may yield improvements in both health-related quality of life and symptom severity. Nevertheless, these preliminary results are encouraging.

In the present study there was no evidence of antiglucocorticoid effects during CDB-2914 administration. Treatment-associated hyperprolactinemia occurred in both the PLC (n=2) and CDB-2914 (n=8) arms of the study. Most women (7 of 10) had maximal values less than 50 ng/mL that were transient, consistent with venipuncture-induced stress. Of the three women with maximal levels up to 77 ng/mL, two had documented microadenomas, presumably a preexisting condition. Four subjects with hyperprolactinemia did not have baseline determinations. It is known that leiomyomata secrete prolactin and that it may be a growth factor for these tumors.¹⁸ However, it is unclear whether CDB-2914 has a potential role in this observation, and because of the small sample size in our study, further data are needed to evaluate fully the safety profile of this drug.

Dilated cystic glandular endometrial hyperplasia has been an uncommon but consistent finding among women receiving chronic progesterone antagonists.¹⁹ The mechanism(s) by which this occurs with use of selective progesterone receptor modulators is unknown. In our study, this treatment-related effect occurred in one patient receiving the 10-mg CDB-2914 dose. Although the incidence of this pattern of hyperplasia was lower (8%; 95% confidence interval 1–35%) than that reported for mifepristone (28% of patients), the confidence intervals of the two studies overlap.⁶ With mifepristone, a smaller daily dose of 2–5 mg was associated with a lower risk of hyperplasia during chronic administration. A lower CDB-2914 dose (eg, 5 mg) may eliminate this adverse effect while effectively reducing leiomyoma volume. We previously examined the effect of a single mid follicular dose of CDB-2914 (PLC, 10, 50, or 100 mg) on folliculogenesis and endometrial maturation in normally cycling, healthy women.¹⁰ CDB-2914 suppressed lead follicle growth, resulting in a dose-dependent delay in folliculogenesis. In some women, a second lead follicle was recruited before ovulation occurred. In the current study, 3-month administration of CDB-2914 significantly reduced ovulation, as judged by serum progesterone, to 20% of treated cycles compared with 83% among PLC, without evidence for a dose effect ($P=.001$). Although women receiving CDB-2914 had lower serum E2 levels, adequate concentrations above 50 pg/mL were maintained. Chabbert-Buffet et al²⁰ reported similar findings based on 46 women who received CDB-2914 (2.5 mg, 5 mg, or 10 mg daily) for 84 days. In that study, approximately 80% of women in the 5-mg and 10-mg dose group were anovulatory, with amenorrhea rates of 81% and 90%, respectively, and physiologic follicular phase E2 levels.

All women receiving CDB-2914 were amenorrheic, and hemoglobin levels increased, but did not improve significantly, during the study interval. It is possible that the inclusion criteria

requiring a hemoglobin level more than 10 g/dL obscured a potential effect. A meta-analysis of GnRH agonist use for the treatment of leiomyomata found that the mean difference with PLC treatment women was small (1.0 g/dL; 95% confidence interval 0.7–1.2).¹⁷ Because this falls within the range seen in this study, perhaps with a larger sample size, a similar difference would be detected with CDB-2914 treatment.

In summary, this study reports the use of the selective progesterone receptor modulator, CDB-2914, for the treatment of uterine leiomyomata. CDB-2914 at 10 mg and 20 mg reduced leiomyoma volume and improved one leiomyoma-specific quality-of-life measure over 3 months. Although a single subject developed dilated cystic hyperplasia, a known effect of long-term progesterone antagonist administration, CDB-2914 did not seem to have significant adverse events or antiglucocorticoid effects. Thus, this small study suggests that CDB-2914 holds promise for the treatment of uterine leiomyomata. Further investigation is needed to establish whether longer therapy provides additional leiomyoma reduction and whether a lower dose (eg, 5 mg) might be effective.

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Fig. 1.
Patient enrollment, randomization, and outcomes.
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Table 1
Baseline Patient Characteristics by Treatment Group

	Placebo (n = 6)	T1 (n = 6)	T2 (n = 6)	P
Age	45.1 (±5.1)	42.6 (±4.8)	44.3 (±4.2)	.66
BMI (kg/m ²)	27.7 (±2.4)	26.3 (3.0)	29.3 (2.1)	.15
Gravidity	2.2	2.7	1.7	.88
Parity	1	1.2	0.3	.17
Ethnicity (%)				
White	17	33	33	1.00
African American	83	67	67	
Other	0	0	0	
Hematocrit (%)	37.2 (±3.9)	36.9 (±5.1)	37.5 (±2.3)	.41
Baseline total leiomyoma volume (cm ³)	290 (12-4,112)	116 (20-963)	411 (102-1,343)	.42

T1, CDB-2914 at 10 mg; T2, CDB-2914 at 20 mg; BMI, body mass index.

Data are mean (±standard deviation) or median (range) unless otherwise specified.

Table 2
Abnormalities Occurring by Subjects Completing the 3-Month Trial Stratified by Treatment Group

Grp	Pain					Symptom Experienced				Laboratory Abnormalities				
	Abd	Pelvic	Breast	Joint	Calf	Headache	Chg Appetite	N/V	D	Fatigue	Skin Rash	Other	Prolactin	AST/ALT (2× nl)
PL	1	0/6	16/7	-	0/1	-	4/0	-	0/1	0/2	0/1	20/18	↑ ^{a,b,c}	-
	2	100/16	0/7	-	-	-	-	-	-	-	-	-	-	-
	3	0/1	-	0/6	-	4/3	-	0/1	-	0/13 ^{d,e}	8/0	0/1	-	-
	4	-	-	-	-	-	-	-	-	-	-	-	-	-
	5	-	10/0	-	-	10/0	-	-	-	10/0	-	0/44 ^{d,e,f}	-	-
	6	-	-	-	-	-	-	0/1	-	0/4	-	13/14	↑ ^{a,b,c,g}	-
T1	1	11/6	36/23	4/16	0/3	4/71 ^{d,h}	-	-	-	-	0/2	0/3	↑ ^{a,b}	-
	2	-	-	7/0	-	-	-	-	-	-	-	-	↑ ^{a,b}	-
	3	12/2	12/8	8/2	100/91	12/11	-	0/2	-	100/91	-	-	-	-
	4	-	30/31	-	-	-	-	-	-	-	-	80/0	-	-
	5	13/47	17/12	9/4	0/8	22/22	13/16	9/15	0/30 ^{e,h,i}	-	-	-	↑ ^{a,b,j}	-
	6	7/2	-	19/14	7/2	-	-	-	7/2	11/10	-	0/12 ^{d,h}	-	-
	7	4/4	4/0	-	23/11	0/10 ^{e,k}	8/14	4/22 ^{e,l}	0/8	35/0	-	12/0	↑ ^{a,j,m}	-
	8	8/0	-	8/6	0/1	4/0	-	-	-	0/2	-	-	-	-
T2	-	-	-	-	-	-	-	-	-	-	-	-	-	↑ ^{a,b}
	1	0/3	-	0/4	0/4	0/71 ^{h,n}	-	-	-	100/81	-	-	↑ ^{a,b}	↑ ^{a,b}
	2	-	-	-	-	-	-	-	-	-	-	0/18 ^{e,o}	-	-
	3	11/4	15/3	48/20	11/42 ^{d,e}	-	11/0	-	4/0	11/5	0/11 ^{d,e}	-	-	-
	4	4/0	-	4/0	-	-	-	-	-	-	-	0/16 ^{d,e,p}	↑ ^{a,b}	↑ ^{b,j}
	5	-	-	-	100/64	100/64	-	0/1	-	100/64	-	0/12 ^{d,e,q}	↑ ^{a,c,i,m}	-
	6	-	-	4/6	-	-	-	-	-	-	-	-	↑ ^{a,b,c,g,j}	-

Grp, treatment group; Abd, abdominal; Chg, change in; N/V, nausea and vomiting; D, diarrhea; AST/ALT (2× nl), aspartate transaminase/alanine transaminase (indicates highest liver function test that exceeded two times the upper normal range); PL, placebo; T1, CDB 10 mg; T2, CDB 20 mg; -, no abnormalities or symptoms noted during the baseline cycle or treatment period.

Data are % days (baseline/treatment).

- ^aElevated during treatment.
- ^bReturned to normal.
- ^cMacroprolactin negative.
- ^dNot reported to team for evaluation.
- ^eResolved before end of treatment.
- ^fSymptoms were back pain and menstrual flooding.
- ^gNormal pituitary magnetic resonance imaging.
- ^hDid not resolve before end of treatment.
- ⁱDiarrhea not reported to team; seen in clinic for dizziness/dehydration; improved with oral hydration and antiemetics; hematology consulted for isolated mild leukopenia/thrombocytopenia; results suggested spurious values.
- ^jElevated at baseline.
- ^kSubject had a broken molar.
- ^lSubject diagnosed with gastroesophageal reflux disease, and symptoms improved with proton pump inhibitor treatment.
- ^mPituitary microadenoma.
- ⁿReported lower extremity edema, associated calf pain and chest pain; no evidence of edema or tenderness to palpation identified on examination; systolic ejection murmur present; cardiac evaluation with stress thallium scan revealed no abnormality.
- ^oBack pain relieved with nonsteroidal antiinflammatory drugs.
- ^pHot flashes; single follicle-stimulating hormone values at that time=73 milli-International Units/mL, all other follicle-stimulating hormone values were less than 10 milli-International Units/mL; subsequently ovulated after study ended.
- ^qNonspecific complaints of itching.