

Effects of a New Progesterone Receptor Modulator, CDB-4124, on Fibroid Size and Uterine Bleeding

a report by

Ronald D Wiehle, MD, PhD,¹ Jay Goldberg, MD, MSCP,² Teresa Brodniewicz, MD,³
Katarzyna Jarus-Dziedzic, MD, PhD³ and Zoulikha Jabiry-Zieniewicz, MD, PhD³

1. Repros Therapeutics, Inc.; 2. Jefferson Medical College, Philadelphia; 3. MTZ Clinical Research Ltd, Warsaw

Currently available medical treatments for symptomatic fibroids are limited, and include non-steroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, and gonadotropin-releasing hormone (GnRH) agonists. While both NSAIDs and oral contraceptives may provide some relief of fibroid-related menorrhagia and dysmenorrhea, they do not reduce bulk symptoms. GnRH agonists are effective in temporarily reducing bleeding and bulk symptoms. GnRH agonists suppress the pituitary-ovarian axis, reducing the amount of estrogen produced and causing systemic menopausal side effects, including hot flashes, vaginal dryness, mood swings, and a decrease in bone density. GnRH agonist treatment is generally used only for short-term treatment, with fibroids regrowing after cessation.¹

Steroid hormones are involved in the development and growth of fibroids. Fibroids express both estrogen and progesterone receptors, and demonstrate the greatest mitotic activity in the luteal phase during a peak in progesterone levels.² Previously thought to be mainly responsive to estrogen, it is now recognized that fibroids are similarly responsive to progesterone.³ Some of this response can be inferred by progesterone action and by the high progesterone receptor levels in these cells. Progesterone receptor modulators (PRMs) are receptor ligands that have tissue-selective progesterone agonist, antagonist, partial, or mixed effects.⁴ A new compound, 17 α -acetoxy-21-methoxy-11 β -[4-N,N-dimethylaminophenyl]-19-norpregna-4,9-diene-3,20-dione (CDB-4124), exhibits strong progesterone antagonist activities in receptor binding, *in vitro* activity, and uterine selectivity.⁵ The current study is the first human trial of CDB-4124.

Materials and Methods

Trial Design

The study was approved by the Institutional Review Board of the Klinika Pozocnictawa i Ginokologii Akamij Medycznej w Warszawie. This was a phase I/II study, with single-dose pharmacokinetic (PK) sampling conducted in subjects randomized to the CDB-4124 arm and a second PK investigation after one month to collect steady-state data. Following the initial PK visit, a randomized, double-blind, controlled safety trial of three doses of CDB-4124 (12.5mg [CDB-12.5], 25mg [CDB-25], or 50mg [CDB-50]) compared with placebo (PLA) and Lucron (Lupron Depot leuprolide acetate, 3.75mg intramuscularly monthly) was initiated in 30 females with symptomatic uterine fibroids that were measured by transvaginal ultrasound. The treatment lasted for three months.

Eligibility Criteria

All women were pre-menopausal and aged between 18 and 50 years. Surgical interventions for uterine fibroids were neither planned nor

anticipated during the 4.5-month study period. At least one fibroid was identifiable and measurable by transvaginal ultrasound. Women of child-bearing potential had to be willing to use effective non-hormonal contraception during the study period and for a minimum of 30 days after discontinuation of the study drug. Subjects had a negative pregnancy test at screen and baseline visits. All women had a regular or steady menstrual cycle lasting for 24–36 days. No patient with endometriosis, moderate to severe varicose veins, any significant cardiovascular, renal, or hepatic disease, past or present history of thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or known or suspected carcinoma of the breast or reproductive organs was allowed to enroll. The body mass index (BMI) of the women had to be between 18 and 35. All subjects gave their informed consent to participate.

Procedures

All subjects participated in a screen visit. The screen visit was planned for completion at least 14 days prior to PK sampling (visit 1) and prior to study enrollment and randomization. Subjects randomized to the CDB-4124 arm returned to the facilities for the PK sampling (visit 1) on days one to four of their menstrual cycle. Subjects randomized to the Lupron and PLA groups did not participate in the PK sampling (visit 1). At



Ronald D Wiehle, MD, PhD, is Vice President of Research and Development at Repros Therapeutics, Inc. He has over 25 years of experience in biomedical sciences, including projects involving male and female reproductive biology, cancer biology, virology, and cell biology. He is member of the Endocrine Society, the American Society for Reproductive Medicine (ASRM), and the American Society of Andrology (ASA), among others. Dr Wiehle has held faculty positions at the James Graham Brown Cancer Center/University of Louisville and the

Department of Obstetrics and Gynecology at the Baylor College of Medicine, and has been awarded research grants by the National Institutes of Health (NIH) and the National Cancer Institute (NCI). His post-doctoral work at Phillips University in Marburg, Germany used recombinant retroviral vectors to transform mammalian cells. Dr Wiehle holds a BSc in chemistry from the University of Illinois at Chicago and a PhD in biochemistry from the University of Louisville School of Medicine/Health Science

E: rwiehle@reprosr.com



Jay Goldberg, MD, MSCP, is Director of the Division of General Obstetrics and Gynecology and Director of the Jefferson Fibroid Center at Jefferson Medical College in Philadelphia. He completed medical school at the University of Pennsylvania and a residency at Magee Womens Hospital, University of Pittsburgh.

Menstrual and Uterine Disorders

visit 1, samples were collected for cortisol/adrenocorticotrophic hormone (ACTH) and pregnancy testing. The subjects were then given one packet of randomized drug consisting of four oral capsules followed by blood collected at 0, 0.5, one, two, three, four, six, eight 12, 16, and 24 hours. The serum was maintained at -20°C until shipped to ABC Laboratories (Columbia, MO) for CDB-4124 analysis. Within seven days and following a safety review of the PK and laboratory results by an investigator, the subject was able to enter the treatment phase of the study. For all subjects, the treatment period lasted three months, with study visits at one-month intervals.

At visit 2 (baseline), subjects were instructed in the use of the daily patient diary and issued cards for a 28-day period. Subjects enrolled in the CDB-4124 arm were dispensed a one-month supply of the double-blind study drug and were instructed in its proper use. Subjects enrolled in the Lupron arm received their first 3.75mg intramuscular injection. Subjects in the CDB arms returned after four weeks of treatment for their second session of PK testing (visit 3). At visits 3, 4, and 5, the daily patient diary cards of subjects from the preceding month were assessed and sufficient blank diary cards issued for the next 30-day period. Subjects were dispensed another one-month supply of the double-blind study drug or received their Lupron injection. Visit 5 marked the end of drug treatment. Transvaginal ultrasounds were required at screen and visits 1, 2, 3, 4, and 5. Study drug compliance was assessed for all subjects in the CDB-4124 arm at each on-treatment visit. Subjects returned after 30 days off study medication for their final follow-up evaluation (visit 6).

Assays

ABC Laboratories in Columbia, MO conducted the CDB-4124 analysis of plasma samples. Validated methods for CDB-4124 and primary metabolite were developed prior to serum sample arrival at the laboratory. Assays of serum hematology, hormones, bone resorption test (c-telopeptide [CTX]), bone formation test (n-mid-osteocalcin), and clinical chemistry were performed locally in Warsaw. Assays included white blood cell (WBC), red blood cell (RBC), hybrid capture tube (HCT), hemoglobin (HGB), melanin-concentrating hormone (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), differential, platelets, prothrombin time (PT), sodium (Na), potassium (K), chlorine (Cl), carbon dioxide (CO₂)/bicarbonate (HCO₃), glucose, phosphorous, uric acid, creatinine, blood urea nitrogen (BUN), total protein, albumin, cholesterol, triglycerides, aspartate aminotransferase (SGOT), serum glutamic pyruvate transaminase (SGPT), alkaline phosphatase, total/direct bilirubin, lactate dehydrogenase (LDH), and routine urinalysis with microscopic exam.

Statistical and Analytical Plans

After the single oral dose of CDB-4124, the following PK parameters were calculated from the individual concentration-versus-time profiles: maximum concentration (C_{max}), time to C_{max} (T_{max}), area under the curve of concentration versus time (AUC)₍₀₋₂₄₎, lambda (λ), T_{1/2} and AUC_(0-∞). C_{max} and T_{max} were directly obtained from the experimental measurements without interpolation; AUC₍₀₋₂₄₎ was computed using the linear trapezoidal rule. The value for λ, the apparent elimination rate constant, was estimated by log linear regression over the last points of the descending part of the plasma-versus-time curves and the apparent elimination. The area extrapolated to infinite time AUC_(0-∞) was determined according to the standard formula:

$AUC_{0-\infty} = AUC_{(0-24)} + Ct/\lambda$. Half-life T_{1/2} was computed as $\ln(2)/\lambda$. At steady state, the following PK parameters were calculated from the individual concentration-versus-time profiles: C_{min}, C_{max}, AUC₍₀₋₂₄₎, and T_{max}. All calculations were performed using validated SAS procedures. Descriptive statistics are presented for all analyzed variables. Continuous variables were described by their mean, standard deviation, and range. Fibroid size and mean difference change from screening were summarized by descriptive statistics. Elliptical size and mean diameter were determined. The number of days that the studied subjects reported each of the possible categories was summarized with descriptive statistics by cycle and treatment group.

Role of the Funding Source

The study drug, CDB-4124, was provided by Repros Therapeutics, Inc. The final formulation into 12.5mg tablets used active agent obtained from the National Institute of Child Health and Human Development (NICHD). The study was conducted at the clinical site of MTZ Clinical Research Sp. z o.o with the assistance of Pharm-Olam International of Houston.

Results

Demographics

The populations studied were between 40 and 49 years of age, were 162–166cm in height, and had a BMI of 23–29. There were two differences worth highlighting: CDB-25 subjects were slightly older and heavier than the rest of the treatment groups. There were no clinically meaningful differences between treatment groups with respect to the menstrual histories of subjects. Fibroids were predominantly intramural in all treatment groups except CDB-12.5, in which subserosal fibroids predominated.

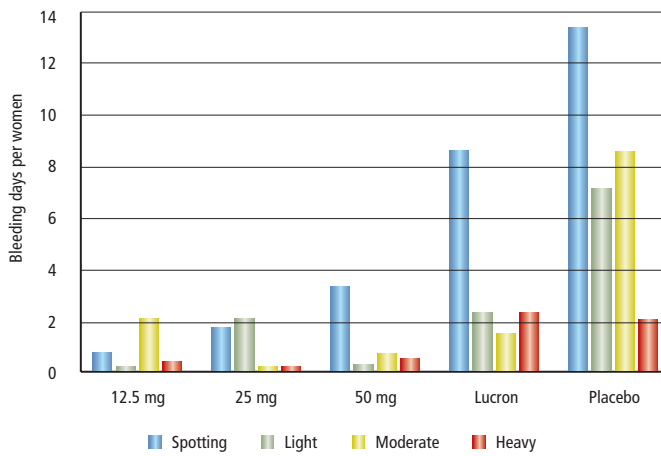
Pharmacokinetics

Individual plasma concentration profiles showed a biphasic decay pattern for all subjects. CDB-4124 was rapidly absorbed, reaching peak plasma levels in 0.5 to two hours. Mean C_{max} yielded the lowest values at 12.5mg, and increased at 25 and 50mg. The mean apparent half-life values of CDB-4124 were 18.8, 13.3, and 8.3 hours after the administration of 12.5, 25, and 50mg, respectively. No statistically significant differences were found between the 12.5 and 25mg doses, but a significant difference was seen with the 50mg dose. Dose proportionality was compared after the normalization of PK parameters by dose and logarithmic transformation. Under steady-state conditions CDB-4124 was rapidly absorbed and T_{max} was observed at 0.8–1.1 hours. The pharmacokinetics of CDB-4124 appeared to be influenced by repeated administration. The C_{max} ratios of last dose versus first dose averaged 159, 130, and 108%, while the AUC ratios (AUC₅₅/AUC₀₋₂₄) reached 185, 206, and 168% for the three escalating doses.

Uterine Bleeding

Based on subject diary information of the first four cycles, PLA subjects most frequently reported uterine/vaginal bleeding, with heavy bleeding for one to three days during each of the four four-week cycles. For the CDB-4124 subjects, uterine/vaginal bleeding was practically non-existent during cycles 1 and 2. For bleeding during cycles 3 and 4, the three CDB-4124 groups were similar to the Lupron group. A comparison of differences from cycle 1 to 4 between each CDB-4124 dose group and Lupron found no pair-wise statistically significant differences for any of the uterine/vaginal bleeding

Figure 1: Total Bleeding Days During Four Menstrual Cycles on CDB-4124, Lupron, or Placebo



categories. PLA subjects had the highest mean number of bleeding days, with about half of these classified as spotting days. The number and intensity of uterine bleeding days are shown in *Figure 1*.

Fibroid Size

Effects on fibroid size are given in *Table 1*. The CDB-50 subjects had the greatest reduction in global tumor size compared with the baseline; CDB-25 subjects experienced the second largest reduction in mean global tumor size, followed by Lupron subjects. For both elliptical area and mean diameter of fibroids (data not shown), the mean baseline value was largest among the CDB-50 subjects and smallest among the CDB-25 subjects. When mean change from baseline was evaluated at different time-points, there was an overall statistically significant difference between treatment groups ($p=0.05$). Statistically significant pair-wise comparisons ($p=0.05$) favored the CDB-50 group over the CDB-12.5, CDB-25, Lupron, and PLA groups based on elliptical area analysis. Within treatment groups, there was a statistically significant mean reduction in tumor size at visit 5 and follow-up compared with baseline among CDB-25, CD-50, and Lupron subjects ($p=0.05$). Significantly, the CDB-50 group demonstrated a significant change in size ($p=0.018$) after one month of treatment compared with PLA.

Safety and Adverse Events

After three months of treatment, the overall incidence rate of treatment-emergent adverse events was lower among the CDB-4124 subjects compared with Lupron and PLA subjects (83.3 versus 100%, respectively). The Lupron subjects had the highest incidence of headache and vaginitis, the largest increase in cholesterol, and the only statistically significant mean change in bone resorption CTX.

The mean change in cholesterol from baseline to visit 5 for the Lupron subjects was 13.1 compared with 5.3 for CDB-12.5, -7.1 for CDB-25, -1.4 for CDB-50, and -7.2 for PLA subjects. Liver panel tests showed two subjects with increased SGPT and SGOT levels at the end of treatment; one patient from the CDB-25 group and the other from the CDB-50 group. In both cases, these values returned to normal. All mean hematology parameters at baseline and at the end of treatment were within the normal ranges, as were mean values for systolic blood

Table 1: Fibroid Size Reduction on CDB-4124, Lupron, or Placebo

Mean	CDB-4124 12.5mg	CDB-4124 25mg	CDB-4124 50mg	Lupron (L)	Placebo (PLA)
Number of subjects	6	6	5	5	6
Number of tumors	8	12	7	9	11
Elliptical Area (mm ²)					
Mean values:					
Baseline	1104.3	477.5	1874.5	885.2	698.8
Visit 3	1098.5	392.4	1362.6	719.9	536.7
Visit 5	906.3	284.9	1119	596.6	624.6
Follow-up	419.5	348.5	982.6	500.5	647.1
Mean difference change:					
Visit 3–Baseline	-5.8	-85.1	-511.9	-165.3	-162.1
$p=0.0212^a$					
p -value within ^b					
p -value between ^c	0.9627	0.0963	0.0557	0.0171	0.0196
	P50 (0.0019)	P50 (0.0040)	L (0.0243)		PLA (0.0182)
Visit 5–Baseline	-198	-192.5	-755.6	-288.5	-74.2
$p=0.0024^a$					
p -value within ^b					
p -value between ^c	0.1548	0.0017	0.0324	0.0006	0.0996
	P50 (0.0024)	P50 (0.0010)	L (0.0081)		PLA (0.0001)
Follow-up–Baseline	-684.8	-129	-892	-384.7	-51.7
$p=0.0211^a$					
p -value within ^b	0.153	0.0063	L 0.0217	0.001	0.3338
p -value between ^c	P25 (0.0454)	P50 (0.0095)	PLA (0.0053)		
					PLA (0.0260)
Percent decrease in elliptical area from baseline to visit 5	17.9	40.3	40.3	32.6	10.6

a = p -value from general linear model with treatment as a factor; *b* = p -value from t -test within treatments; *c* = p -value from t -test between treatments (pair-wise presented only if statistically significant, $p=0.05$).

pressure (SBP), diastolic blood pressure (DBP), pulse, and temperature. One subject in the CDB-25 group and one in the PLA group experienced ACTH values that were higher than normal. The bone resorption CTX showed a significant change between baseline and three-month treatment among the Lupron subjects: CTX increased from 0.2 to 0.6ng/l ($p=0.0018$), indicating increases in bone breakdown.

There were two serious adverse events: both subjects were from the CDB-50 group and both underwent elective hysterectomy due to uterine bleeding. One subject received only one study drug dose (at her PK visit) and one month later underwent an elective hysterectomy. The second subject took all of the prescribed study drug doses, and two days after the end of treatment underwent an elective hysterectomy due to a cervical polyp. Neither hysterectomy was considered to be treatment-related.

Discussion

The results of the study show that following once-daily administration CDB-4124 is rapidly absorbed, with maximum plasma concentrations occurring at one hour. Plasma levels were slightly lower after the 50mg dose. This discrepancy may be explained by the high inter-individual variability. More studies are needed in order to determine whether there

Menstrual and Uterine Disorders

is proportionality between the doses. However, based on the PK studies shown here, a dose of 50mg per day appeared to be no higher than the 25mg per day dose in terms of $C_{max}/dose$, C_{min} , AUC, and T_{max} .

There were statistically significant differences in efficacy between and within treatment groups. Overall, findings favored the CDB-4124 treatments (in particular CDB-50) in pre-menopausal women with fibroids. Specifically, for elliptical area, statistically significant pair-wise comparisons favored CDB-50 over CDB-12.5, CDB-25, Lupron, and PLA. Within treatments, there was a statistically significant mean reduction in tumor size at visit 5 and follow-up compared with baseline for CDB-25, CDB-50, and Lupron subjects. With regard to uterine/vaginal bleeding, CDB-4124 subjects experienced the fewest bleeding days. As expected, PLA subjects had the smallest global tumor size reduction, most frequently reported uterine/vaginal bleeding, and used the most pain medication. A dose of 12.5–50mg per day appears to be appropriate for clinical studies and the higher dose was effective within one month.

The shrinkage in the size of the fibroids observed here is consistent with other studies of progesterone antagonists. RU 486, an antiprogestin, has achieved modest success in the treatment of symptomatic fibroids, but its use has been restricted due to its antigluocorticoid effects and the political backlash to its use as an abortifacient. Kettel et al. reported that an oral 50mg daily dose of RU 486 administered for three months yielded

a 49% reduction in uterine fibroids.⁶ Recently, Asoprisnil, an agent with mixed agonist/antagonist properties, was shown to be effective in shrinking fibroid tumors to 36% of their original volume.⁷ In comparison, the GnRH agonists have been shown to decrease fibroid size by 40–46%^{1,8} and uterine volume by 36–57%.⁹ Uterine fibroid embolization can reduce uterine size by 35–69%.^{10,11}

Although this was a phase III trial in which PK and safety were the primary objectives, the encouraging safety and efficacy results in this first human trial of CDB-4124 as a treatment for symptomatic uterine fibroids provide evidence of its potential. These results support further evaluation of CDB-4124 in future clinical trials. ■

Acknowledgments

The authors would like to thank Dr Richard Blye and Dr HK Kim of the NICDH, who provided CDB-4124. We would like to recognize Rebeca Ponce de Leon, MD, and Claudia Lara, MSc, of Kendle, Mexico City, who contributed to the data analysis. The authors would also like to thank Fred Lowrey of Pharm-Olam International for his assistance. Dr Goldberg assisted in writing and editing the manuscript.

Reprint Citation: Wiehle RD, Goldberg J, Brodniewicz T, et al., Effects of a New Progesterone Receptor Modulator, CDB-4124, on Fibroid Size and Uterine Bleeding, *US Obstetrics and Gynaecology*, in press

1. Friedman AJ, Harrison-Atlas D, Barbieri RL, et al., A randomized, placebo-controlled, double-blind study evaluating the efficacy of leuprolide acetate in the treatment of uterine leiomyomata, *Fertil Steril*, 1989;51:251–6.
2. Kawaguchi K, Fujii S, Konishi I, et al., Mitotic activity in uterine leiomyomas during the menstrual cycle, *Am J Obstet Gynecol*, 1989;160:637–41.
3. Rein MS, Advances in uterine leiomyoma research: the progesterone hypothesis, *Environ Health Perspect*, 2000;108 (Suppl. 5):791–3.
4. Chwalisz K, Perez MC, Demanno D, et al., Selective progesterone receptor modulator development and use in the treatment of leiomyomata and endometriosis, *Endocr Rev*, 2005;26:423–38.
5. Attardi BJ, Burgenson J, Hild SA, et al., CDB-4124 and its putative monodemethylated metabolite, CDB-4453, are potent antiprogestins with reduced antigluocorticoid activity: *in vitro* comparison to mifepristone and CDB-2914, *Molec Cell Endocrinol*, 2002;188:111–23.
6. Kettel M, Murphy A, Morales A, Yen SSC, Clinical efficacy of the antiprogestone RU486 in the treatment of endometriosis and uterine fibroids, *Human Rep*, 1994;9:116–20.
7. Chwalisz K, Larsen L, Mattia-Goldberg C, et al., A randomized, controlled trial of Asoprisnil, a novel selective progesterone receptor modulator, in women with uterine leiomyomata, *Fertil Steril*, 2007;87:1399–1412.
8. Andreyko JL, Blumenfeld Z, Marshall LA, Use of an agonistic analog of gonadotropin-releasing hormone Nafarelin to treat leiomyomas; assessment by magnetic resonance imaging, *Am J Obstet Gynecol*, 1988;158:903–10.
9. Friedman AJ, Hoffman DI, Comite F, et al., Treatment of leiomyomata uteri with leuprolide acetate depot: a double-blind, placebo-controlled, multicenter study. The Leuprolide Study Group, *Obstet Gynecol*, 1991;77:720–25.
10. Hurst BS, Stackhouse DJ, Matthews ML, Marshburn PB, Uterine artery embolization for symptomatic uterine myomas, *Fertil Steril*, 2000;74:855–69.
11. Goldberg J, Current thinking on the role of interventional radiology in women's health, *Expert Opin Gyn Obstet*, 2007;2: 621–9.