Table 2

UPA	patient	Age (yrs)	Visit	A(SF-MPQ)		B(VAS)		PBAC		Uterine Volume (cm3)	% Change in Uterine Volume
				Score +	CFB +	Score	CFB+	Score	CFB+		
5mg	210/5252	37	Baseline	12		43		225		236.1	
			Week 5	14	-2	64	21	375	150		
			week 9	11	-1	57	14	283	58		
			Week 13	9	-3	37	-6	124	-101	251.7	6.6
			Week 17					NA			
			Week 26	8	-4	67	24	755	530		
			Week 38	9	-3	70	27	271	46		
Myomectomy by laparotomy after Week 13 visit											
5mg	281/5214	49	Baseline	4		20		220		131.1	
			Week 5	1	-3	3	-17	46	-174		
			week 9	0	-4	0	-20	0	-220		
			Week 13	0	-4	0	-20	0	-220	159.1	21.3
			Week 17					NA		147.7	12.6
			Week 26			73	53	52	-168	102.2	-21.2
			Week 38	0	-4	0	-20	571	351	98.9	-24.6
No Surgery											
10mg	210/5095	49	Baseline	14		88		860		368.5	
			Week 5	0	14	0	-88	328	-532		
			week 9	0	14	0	-88	0	-860		
			Week 13	0	-14	0	-88	0	-860	284.7	-33.8
			Week 17	0	-14			NA			
			Week 26	0	-14	0	-88	0			
			Week 38	0	-14	0	-88				

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Table 2 (*cont'd*)

UPA	patient	Age (yrs)	Visit	A(SF-MPQ)		B(VAS)		PBAC		Uterine Volume (cm3)	% Change in Uterine Volume
				Score +	CFB +	Score	CFB+	Score	CFB+		
5mg	210/5252	37	Baseline	12		43		225		236.1	
			Week 5	14	-2	64	21	375	150		
			week 9	11	-1	57	14	283	58		
			Week 13	9	-3	37	-6	124	-101	251.7	6.6
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			Week 5	0	14	0	-88	328	-532		
			week 9	0	14	0	-88	0	-860		
			Week 13	0	-14	0	-88	0	-860	284.7	-33.8
			Week 17	0	-14			NA			
			Week 26	0	-14	0	-88	0			
			Week 38	0	-14	0	-88				

2.1 All four ulipristal treated patients (281/5214, 210/5095, 210/5308, 250/5090) showed an improvement in pain at week 5, 9, 13th compared to baseline. Data obtained for patient 210/5095 are particularly relevant: starting from 5th week the patient experienced no pain anymore and starting from week 9, she even did not bleed anymore.

This is the demonstration of ulipristal efficacy in pain and bleeding reduction in patient suffering from adenomyosis and uterine fibroids with results comparable to surgery.

2.2 All 3 patients (281/5214, 210/5095, 250/5090) treated with 5mg or 10mg of ulipristal had PBAC score of 0 (amenorrhea) at the end of treatment (week 13), whereas the placebo (example 1) treated patient had an increase in menstrual blood loss at week 13 (change +87). Patient 210/5308, had a PBAC value of 55 at week 13 which is considered as normal menstrual bleeding (normal menstrual bleeding PBAC is <75).

2.3 Among the 4 patients, 3 patients (210/5095, 210/5308, 250/5090) had a decrease in uterine volume at week 13 compared to baseline.

Example 3

Ulipristal liver toxicity analysis.

1. Clinical study

A double-blinded, randomized, study evaluating the effect of long term oral administration of 5mg or 10mg ulipristal in patients with heavy menstrual bleeding and pain.

A Hepatobiliary Disorders and Liver Safety analysis was carried out for all patients.
A summary of out of range values for biochemistry parameters is provided in table 4.
This summary table illustrates the increased number of subjects from the 3 treatment groups who had increased levels of AST, ALT and total bilirubin during the study.

The data are included in table 3 below:

Table 3

Summary of Biochemistry Out of Normal Range (Safety Population)

Laboratory Parameter	On-Treatment Status	Week	Ulipristal 5 mg (n=97)	Ulipristal 10 mg (n=103)	GnRH-agonist (N=101)
AST	Baseline (visit normal)		95 (97.9%)	100 (97.1%)	97 (96.0%)
	High not CS	5	6 (6.2%)	6 (5.8%)	2 (2.0%)
		9	3 (3.1%)	3 (2.9%)	9 (8.9%)
		13	2 (2.1%)	4 (3.9%)	3 (3.0%)
		17	3 (3.1%)	4 (3.9%)	3 (3.0%)
	Low not CS	5	0	0	0
		9	0	0	0
		13	0	0	0
		17	0	0	0
ALT	Baseline visit (normal)		94 (96.9%)	100 (97.1%)	98 (97.0%)
	High not CS	5	4 (4.1%)	6 (5.8%)	3 (3.0%)
		9	0	3 (2.9%)	5 (5.0%)
		13	1 (1.0%)	5 (4.9%)	6 (5.9%)
	High not CS	17	2 (2.1%)	4 (3.9%)	3 (3.0%)
	High CS	17	0	0	1 (1.0%)
	Low not CS	5	0	0	0
		9	0	0	0
		13	0	0	0
		17	0	0	0
Total bilirubin	Baseline visit (normal)		92 (94.8%)	102 99.0%)	98 (97.0%)
	High not CS	5	2 (2.1%)	3 (2.9%)	0
	High CS	5	0	0	1 (1.0%)
	High not CS	9	3 (3.1%)	4 (3.9%)	1 (1.0%)
		13	3 (3.1%)	6 (5.8%)	2 (2.0%)
		17	2 (2.1%)	2 (1.9%)	2 (2.0%)
	Low not CS	5	0	0	0
		9	0	0	0
		13	0	0	0
		17	0	0	0

AST – aspartate transaminase, ALT – alanine transaminase, CS – clinically significant.

2. Results

Mildly elevated transaminase levels, were reported for a few subjects from all 3 treatment groups; in general the elevations were less than 2 x upper limit of normal range (ULN) , transient and resolved under treatment. Elevated transaminase levels were not accompanied by increased bilirubin levels. Four subjects (1 subject from each of the Ulipristal 5 mg and GnRH-agonist groups and 2 subjects from the Ulipristal 10 mg group), had elevations of both AST and ALT above 2 x ULN, but <3 x ULN for consecutive samples during the study. One subject from the GnRH-agonist group had raised direct, indirect and total bilirubin levels throughout the study, which were not accompanied by raised transaminase levels.

In summary, there were no signals of any treatment related changes in liver function tests.

In addition, the Hepatobiliary Disorders and Liver Safety analysis revealed no evidence of liver toxicity based on the Treatment Emergent Adverse Events (TEAEs) reported in the clinical studies.

CLAIMS

1. Ulipristal, or any metabolite thereof, for use in the treatment of pain associated with dislocation of the endometrium, wherein said ulipristal, or said metabolite thereof, is administered at a daily dosage at a therapeutically effective amount of 5 to 12 mg.

2. The ulipristal, or any metabolite thereof, according to claim 1 wherein the dislocation of basal endometrium results in adenomyosis or in endometriosis.

3. The ulipristal, or any metabolite thereof, according to claim 1 or 2, wherein the pain is selected from the group comprising chronic pelvic pain, pain before and during periods, pain with intercourse, low back pain, painful bowel movements (especially during menstruation) and painful urination during menstruation.

4. The ulipristal, or any metabolite thereof, according to any one of the preceding claims, wherein the patient is administered with a tablet comprising ulipristal or any metabolite thereof.

5. The ulipristal, or any metabolite thereof, according to any one of the preceding claims, wherein the daily dosage of ulipristal, or any metabolite thereof, is about 5 mg.

6. The ulipristal, or any metabolite thereof, according to any one of the preceding claims, wherein the daily dosage of ulipristal, or any metabolite thereof, is about 10 mg.

7 The ulipristal, or any metabolite thereof, according to any one of the preceding claims, wherein said ulipristal metabolite is selected from the group comprising CDB-3877, CDB-3963, CDB-3236, and CDB-4183.

8. The ulipristal, or any metabolite thereof, according to any one of the preceding claims, wherein ulipristal or a metabolite thereof is administered for a period of 1 to up to 120 days.

9. Ulipristal, or any metabolite thereof, for use in reducing or stopping bleeding in a patient afflicted with dislocation of the endometrium (endometriosis or adenomyosis) wherein said ulipristal, or said metabolite thereof, is administered a daily dosage of 5 to 12 mg.

10. Ulipristal, or any metabolite thereof, for use in preventing or treating anemia in a patient afflicted with dislocation of the endometrium (endometriosis or adenomyosis) wherein said ulipristal, or said metabolite thereof, is administered a daily dosage of 5 to 12 mg.

11. Ulipristal, or any metabolite thereof, for use in reducing uterine volume in a patient afflicted with dislocation of the endometrium (endometriosis or adenomyosis), comprising administering to said patient in need thereof, a daily dosage of 7 to 12 mg of ulipristal, or any metabolite thereof.

12. A kit for treating and/or preventing pain associated with dislocation of the endometrium, comprising ulipristal, or any metabolite thereof to be administered at a daily dosage at a therapeutically effective amount of 5 to 12 mg , optionally with reagents and/or instructions for use.

Table 2

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			Week 38	0	-14	0	-88				
Hysterectomy Laparoscopy after Week 13 visit											
10mg	210/5308		Week 13					55			decrease
Myomectomy Hysteroscopy after Week 13 visit. Myomectomy Laparoscopy; Hysteroscopy between Week 26 & 38 visits											
10mg	250/5090		Week 13					0			decrease
No Surgery											

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CLAIMS

1. The use of ulipristal, or any active metabolite thereof, in the manufacture of a medicament for the treatment of pain associated with dislocation of the endometrium, wherein said ulipristal, or said active metabolite thereof, is to be administered at a daily dosage at a therapeutically effective amount of 5 to 12 mg.

2. The use, according to claim 1, wherein the dislocation of basal endometrium results in adenomyosis or in endometriosis.

3. The use, according to claim 1 or 2, wherein the pain is selected from the group comprising chronic pelvic pain, pain before and during periods, pain with intercourse, low back pain, painful bowel movements (especially during menstruation) and painful urination during menstruation.

4. The use, according to any one of the preceding claims, wherein the patient is to be administered with a tablet comprising ulipristal or any active metabolite thereof.

5. The use, according to any one of the preceding claims, wherein the daily dosage of ulipristal, or any active metabolite thereof, is about 5 mg.

6. The use, according to any one of claims 1 - 4, wherein the daily dosage of ulipristal, or any active metabolite thereof, is about 10 mg.

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10. The use of ulipristal, or any active metabolite thereof, in the manufacture of a medicament for preventing or treating anemia arising from heavy menstrual bleeding wherein said

ulipristal, or said active metabolite thereof, is to be administered a daily dosage of 5 to 12 mg.

11. The use of ulipristal, or any active metabolite thereof, in the manufacture of a medicament for reducing uterine volume in a patient afflicted with dislocation of the endometrium, comprising the administration to said patient in need thereof, a daily dosage of 5 to 12 mg of ulipristal, or any active metabolite thereof.

12. A kit for treating and/or preventing pain associated with dislocation of the endometrium, comprising ulipristal, or any active metabolite thereof to be administered at a daily dosage at a therapeutically effective amount of 5 to 12 mg, with reagents and/or instructions for use.