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Study No.: S3B10948	
Title: An open-label, Within-Subject Study to Compare the Pharmacodynamics and Pharmacokinetics of an Oral Contraceptive Containing Levonorgestrel 100µg and Ethinyl Estradiol 20µg in Healthy Female Subjects When Administered Alone and Following Co-Administration of Alosetron 1mg BID Orally for 28 Days	
Rationale: A significant number of the target population for the treatment of Irritable Bowel Syndrome (IBS) in females whose predominant bowel symptom was diarrhea, would be females of childbearing age, many of whom would be taking concomitant oral contraceptives (OC). Several studies have suggested a dose-response relationship between the estrogen content of OC and the risk of both venous thrombosis and arterial disease, when estrogen doses were higher than 50µg. However, there is no clear epidemiological evidence for a decrease in thrombotic risk with formulations containing less than 50µg estrogen. This study investigated coagulation variables in users of OC containing 20µg ethinyl estradiol (EE) when taken alone and concomitantly with alosetron.	
Phase: I	
Study Period: 11 Jul 2000 to 22 Nov 2000	
Study Design: An open-label, within-subject, 28-day study in healthy female subjects.	
Centres: This study was conducted in 1 center in the US.	
Indication: None	
Treatment: Alosetron 1mg oral tablets (containing GR68755C as the hydrochloride salt); OC tablets (levonorgestrel [LN] 100µg and EE 20µg). Screening occurred within 28 days prior to Period 1 Treatment, during which time, subjects were switched to an OC if not already on a monophasic OC containing LN 100µg and EE 20µg. In Period 1, each subject received OC, daily from Day 1 to Day 21. In Treatment Period 2, the subjects received Alosetron 1mg bid from Days 1 to 7, and in Treatment Period 3, OC daily plus Alosetron 1mg bid from Days 1 to 21. There was no washout period between Treatments. Subjects completed a Post-Study Visit at least 30 hours after the last dose of Alosetron	
Objectives: The primary objective of this study was to determine the effect of alosetron when co-administered with an OC on pharmacodynamic (PD) surrogate markers of contraceptive efficacy.	
Statistical Methods: The sample size calculation was based on the paired t-test. The estimate of the within-subject standard deviation (SD) of the log(e) of the maximum luteinising hormone (LH) concentration observed over Days 5 through 9, and Days 33 through 37 from a previous study calculated from an analysis of variance (ANOVA) model was 0.6512. It was estimated that 15 subjects would provide 80% power to detect a difference of 0.72mIU/mL on the log(e) scale, at $\alpha=0.05$. Twelve subjects would provide 80% power to detect a difference of 0.82mIU/mL on the log(e) scale, at $\alpha=0.05$.	
The primary PD comparison was the maximum LH concentration on Days 5 through 9 in Period 1 (OC alone) compared to the maximum LH concentration on Days 5 through 9 in Period 3 (OC+alosectron). The maximum LH and follicle stimulating hormone (FSH) concentrations on Days 5 through 9, in Periods 1 and 3 were identified for each subject and were analyzed using the ANOVA model. The progesterone concentrations on Day 14 in each pill cycle were also analyzed using the ANOVA model. The frequency of the occurrence of breakthrough bleeding and the number of subjects experiencing breakthrough bleeding in each pill cycle were summarized for both treatments. Ovarian activity (based on follicle size, 17β estradiol and progesterone levels) was graded for each pill cycle.	
The safety population included all subjects who received at least 1 dose of any study drug. This population was used for summarizing background, demographic, and safety information. The PD population consisted of all subjects who received study drug and provided LH values or FSH values or progesterone or 17β estradiol values or ultrasound data during both Treatment Periods 1 and 3. This population was used in the PD data analysis. In the analysis of LH or FSH data, only those subjects who provided LH and FSH values on Days 5 through 9 (Treatment Periods 1 and 3), and Day 21 (Treatment Periods 1 and 3) were included. In analysis of progesterone data, only those who provided progesterone values on Day 14 for Treatment Periods 1 and 3 were included.	
Study Population: Healthy, non-smoking, pre-menopausal females, aged 18 to 45 years who were stabilized for 3 months on an OC-containing LN and EE and on a monophasic OC containing 150µg of LN and 20µg of EE for at least the OC pill cycle prior to Day 1 of Period 1.	
Number of Subjects:	Total

Planned, N	15
Dosed, N	18
Completed, n (%)	17 (94)
Total Number of Subjects Withdrawn, n (%)	1 (6)
Withdrawn Due to Adverse Events (AEs), n (%)	0
Withdrawn Due to Lack of Efficacy, n (%)	0
Withdrawn for Other Reasons, n (%)	1 (6)
Demographics:	Total
N (Safety)	18
Females:Males, n:n	18:0
Mean Age, years (SD)	28.2 (5.5)
Mean Weight, kg (SD)	65.41 (9.21)
Caucasian, n (%)	13 (72)

PD Endpoints:

Summary of LH Serum Levels (mIU/mL)

Phase [Normal Range Without OC]	OC Alone N=18	OC+Alosetron N=18
Follicular Phase [1.00-18.0] Mean SD (CV%) Min-Max 95% CI	Day 1 (Period 1) 5.697 2.883 (50.6) 0.73-10.17 4.26, 7.13	Day 1 (Period 3) 5.652 2.867 (50.7) 0.69-10.41 4.23, 7.08
Mid-Cycle Phase [24.0-105] Mean SD (CV%) Min-Max 95% CI	Max Day 5-9 (Period 1) 9.102 4.954 (54.4) 0.50-18.05 6.64, 11.57	Max Day 5-9 (Period 3) 9.862 4.669 (47.3) 0.50-19.12 7.54, 12.18
Least Squares Mean (LSM)	9.102	9.862
LSM Ratio (90% Confidence Interval)	1.08 (0.93, 1.24)	
P-value	0.359	
Luteal Phase [0.40-20.0] Mean SD (CV%) Min-Max 95% CI	Day 21 (Period 1) 2.659 1.849 (69.5) 0.50-5.89 1.74, 3.58	Day 21 (Period 3) 3.087 2.115 (68.5) 0.50-6.53 2.04, 4.14

Summary of FSH Serum Levels (mIU/mL)

Phase [Normal Range Without OC]	OC Alone N=18	OC+Alosetron N=18
Follicular Phase [4.00-13.0] Mean SD (CV%) Min-Max 95% CI	Day 1 (Period 1) 6.082 2.375 (39.1) 3.74-14.09 4.90, 7.26	Day 1 (Period 3) 6.007 1.085 (18.1) 3.50-7.90 5.47, 6.55
Mid-Cycle Phase [15.0-22.0] Mean SD (CV%) Min-Max 95% CI	Max Day 5-9 (Period 1) 4.988 2.396 (48.0) 0.55-8.78 3.80, 6.18	Max Day 5-9 (Period 3) 5.172 2.126 (41.1) 1.22-9.01 4.11, 6.23
Luteal Phase [2.00-13.0] Mean SD (CV%) Min-Max 95% CI	Day 21 (Period 1) 2.668 1.604 (60.1) 0.40-5.74 1.87, 3.47	Day 21 (Period 3) 2.607 1.618 (62.1) 0.40-5.16 1.80, 3.41

Summary of Progesterone Serum Levels (ng/mL)

	OC Alone	OC+Alosetron
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Phase [Normal Range Without OC]	N=18	N=18	
Mid-Luteal Phase [6.00-30.0] Mean SD (CV%) Min-Max 95% CI	Day 14 (Period 1) 0.717 0.287 (40.0) 0.25-1.43 0.57, 0.86	Day 14 (Period 3) 0.688 0.304 (44.2) 0.25-1.31 0.54, 0.84	
Summary of SHBG Levels (mmoles/L)	OC Alone N=18	OC+Alosetron N=18	
Mean SD Min-Max	Day 1 (Period 1) 85.150 32.155 32.29-140.64	Day 1 (Period 3) 87.711 30.539 33.48-145.80	
Mean SD Min-Max	Day 8 (Period 1) 108.540 36.696 44.37-165.65	Day 8 (Period 3) 110.970 32.568 58.34-173.52	
Summary Breakthrough Bleeding			
	OC Alone Treatment Period 1 N=18 n=24 Episodes	OC+Alosetron Treatment Period 3 N=18 n=25 Episodes	
At Least 1 Episode, n Subjects (%)	5 (28)	7 (39)	
Flow			
Light, n Episodes (%)	20 (83)	23 (92)	
Moderate, n Episodes (%)	4 (17)	2 (8)	
Heavy, n Episodes (%)	0	0	
Frequency			
Intermittent, n Episodes (%)	20 (83)	23 (92)	
Continuous, n Episodes (%)	4 (17)	2 (8)	
Summary of Ovarian Activity			
	OC Alone N=18 n (%)	OC+Alosetron N=18 n (%)	
Grade^a			
Grade 1	11 (61)	9 (50)	
Grade 2	1 (6)	1 (6)	
Grade 3	3 (17)	3 (17)	
Grade 4	3 (17)	5 (28)	
Grade 5	0	0	
Grade 6	0	0	
Grade 1=no activity; Grade 2=potential activity; Grade 3=non-active follicle-like structure (FLS); Grade 4=active FLS; Grade 5=luteinized unruptured follicle; Grade 6=ovulation			
Safety Results: All AEs that occurred from the time of first dosing with study medication until completion of the study were recorded regardless of causality.			
Adverse Events:	OC	Alosetron	OC+Alosetron
N (Safety)	18	18	18
Subjects with Any AEs, n (%)	9 (50)	11 (61)	16 (89)
Most Frequent AEs, n (%)			
Constipation	0	7 (39)	4 (22)
Gastrointestinal Discomfort & Pain	0	3 (17)	4 (22)
Nausea	2 (11)	0	2 (11)
Vomiting	2 (11)	0	2 (11)
Diarrhea	1 (6)	0	2 (11)
Abdominal Discomfort & Pain	1 (6)	1 (6)	2 (11)
Headache	3 (17)	2 (11)	5 (28)
Nasal Signs and Symptoms	2 (11)	0	0
Faintness	2 (11)	0	0

Serious Adverse Events (SAEs), n (%) [n (%) considered by the investigator to be related, possibly related, or probably related to study medication]:			
Serious Adverse Events:	OC	Alosetron	OC+Alosetron
Subjects with SAEs, n (%)	0	0	0
Subjects with Fatal SAEs, n (%)	0	0	0
Conclusion: See publication below.			
Publications: Pharmacodynamics and Pharmacokinetics of Oral Contraceptives Co-administered with Alosetron, Koch K, Campenella C, C Baidoo, Manzo J, Ameen V, Kersey K, Dig Dis Sci,49(7-8);1244-1249,2004			

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