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<b>Study No.:</b> S3B10937	
<b>Title:</b> An open-label, single-dose, randomized, two-period, cross-over trial to evaluate the effect of alosetron (1 mg PO) on the pharmacokinetics of hydrocodone and acetaminophen (VICODIN 5 mg/ 500 mg PO) in healthy subjects.	
<b>Rationale:</b> Since hydrocodone/acetaminophen is a frequently prescribed medication in the female target therapeutic population, the potential for interaction with alosetron is of interest. Although <i>in vitro</i> data indicate that alosetron has no effect on cytochrome P450 (CYP) 2D6 metabolism, this study was conducted to confirm the lack of <i>in vivo</i> interaction. Additional <i>in vitro</i> and <i>in vivo</i> data indicate that alosetron has no effect on the CYP isoenzymes 1A2, 2E1, or 3A4. This study was also conducted to confirm the lack of interaction of alosetron with these CYP isoenzymes <i>in vivo</i> .	
<b>Phase:</b> I	
<b>Study Period:</b> 03 November 1999 – 23 November 1999.	
<b>Study Design:</b> An open-label, single-dose, randomized, two-period, crossover study.	
<b>Centres:</b> One centre in the United States.	
<b>Indication:</b> None.	
<b>Treatment:</b> Subjects were randomized to receive one oral (PO) tablet of hydrocodone 5 mg/acetaminophen 500 mg alone or in combination with one PO tablet of alosetron 1 mg. Following a washout period of 1 day (providing a 2-day interval between hydrocodone/acetaminophen doses), the subject received the alternate treatment.	
<b>Objectives:</b> To determine the effect of single-dose concomitant administration of alosetron 1 mg PO on the pharmacokinetics of acetaminophen and hydrocodone (and its active metabolite, hydromorphone) utilizing the combination tablet hydrocodone 5 mg/acetaminophen 500 mg.	
<b>Statistical Methods:</b> The following pharmacokinetic parameters were derived for hydrocodone (parent), hydromorphone (metabolite), and acetaminophen: area under the plasma concentration-time curve from time zero extrapolated to infinity ( $AUC_{\infty}$ ), area under the plasma concentration-time curve from time zero to the last quantifiable timepoint ( $AUC_{last}$ ), maximal observed plasma concentration ( $C_{max}$ ), time to $C_{max}$ ( $t_{max}$ ), terminal elimination half-life ( $t_{1/2}$ ) and terminal first-order elimination rate-constant ( $\lambda_z$ ). The sample size provided 80% power to detect a difference of 30% in acetaminophen $AUC$ and in hydrocodone $C_{max}$ . $\log_e$ -transformed pharmacokinetic endpoints were analysed by analysis of variance (ANOVA) allowing for subject, sequence, and treatment and period effects. Untransformed $t_{max}$ was analysed using the standard Koch procedure. The median difference in $t_{max}$ and associated 90% CI were calculated using standard non-parametric methods. The safety population was all subjects who received at least one dose of study drug. The pharmacokinetic population comprised all subjects dosed who provided evaluable data for both study periods.	
<b>Study Population:</b> Healthy, non-smoking male and female subjects, aged 18 to 50 years, with women using acceptable contraceptive methods. All subjects were extensive metabolisers of CYP2D6 substrates. Subjects with any predisposing condition that might interfere with the absorption, distribution, metabolism or excretion of drugs, or who had undergone gastrointestinal surgery, were excluded from study participation.	
<b>Number of Subjects:</b>	
Planned, N	12
Randomised, N	12
Completed, n (%)	12 (100)
Total Number Subjects Withdrawn, N (%)	0
Withdrawn due to Adverse Events n (%)	0
Withdrawn due to Lack of Efficacy n (%)	0
Withdrawn for other reasons n (%)	0
<b>Demographics</b>	<b>Total</b>
N (Safety)	12
Females: Males	8 : 4
Mean Age, years (SD)	34.7 (10.8)
Mean Weight, kg (SD)	74.17 (12.7)
White, n (%)	9 (75)

**Pharmacokinetic Endpoints:** Geometric means and 95% CI for pharmacokinetic parameters are presented below.

	Parameter	Hydrocodone/acetaminophen 5 mg/500 mg		Hydrocodone/acetaminophen 5 mg/500 mg + alosetron 1 mg	
<b>Hydrocodone</b>	AUC <sub>∞</sub> (ng.h/mL)	93.73	(80.23, 109.51)	97.49	(84.40, 112.61)
	AUC <sub>clast</sub> (ng.h/mL)	80.30	(69.69, 92.52)	83.47	(73.79, 94.41)
	C <sub>max</sub> (ng/mL)	16.41	(13.44, 20.04)	15.70	(13.54, 18.21)
	t <sub>1/2</sub> (h)	4.20	(3.80, 4.65)	4.13	(3.72, 4.59)
	λ <sub>z</sub> (1/h)	0.17	(0.15, 0.18)	0.17	(0.15, 0.19)
	t <sub>max</sub> (h) <sup>a</sup>	1.50	[0.50 – 4.00]	1.00	[0.50 – 2.02]
<b>Hydromorphone</b>	AUC <sub>∞</sub> (pg.h/mL)	1338.6	(991.8, 1806.8)	1352.9	(1044.8, 1751.9)
	AUC <sub>∞</sub> ratio <sup>b</sup>	0.0143	(0.0101, 0.0202)	0.0139	(0.0105, 0.0183)
	AUC <sub>clast</sub> (pg.h/mL)	662.75	(599.27, 732.96)	721.66	(642.41, 811.12)
	C <sub>max</sub> (pg/mL)	138.2	(116.4, 164.1)	138.1	(114.3, 166.8)
	t <sub>1/2</sub> (h)	12.0	(8.18, 17.7)	10.9	(7.57, 15.8)
	λ <sub>z</sub> (1/h)	0.06	(0.04, 0.08)	0.06	(0.04, 0.09)
t <sub>max</sub> (h) <sup>a</sup>	1.00	[0.50 – 2.00]	0.50	[0.50 – 1.50]	
<b>Acetaminophen</b>	AUC <sub>∞</sub> (ng.h/mL)	21795	(17542, 27078)	23543	(19568, 28326)
	AUC <sub>clast</sub> (ng.h/mL)	20373	(16476, 25193)	22363	(18693, 26753)
	C <sub>max</sub> (ng/mL)	6110	(4662, 8009)	7476	(6472, 8635)
	t <sub>1/2</sub> (h)	3.39	(2.60, 4.41)	2.95	(2.73, 3.19)
	λ <sub>z</sub> (1/h)	0.20	(0.16, 0.27)	0.23	(0.22, 0.25)
	t <sub>max</sub> (h) <sup>a</sup>	0.50	[0.50 – 4.00]	0.50	[0.50 – 1.50]

t<sub>max</sub> was analyzed by non-parametric methods with median and [range] presented.

AUC<sub>∞</sub> ratio: hydromorphone AUC<sub>∞</sub>/hydrocodone AUC<sub>∞</sub>.

A summary of the log<sub>e</sub>-transformed pharmacokinetic analysis for assessment of drug interaction is presented below.

	Hydrocodone		Hydromorphone		Acetaminophen	
	TRT Ratio <sup>a</sup>	90%CI	TRT Ratio <sup>a</sup>	90%CI	TRT Ratio <sup>a</sup>	90%CI
<b>AUC<sub>∞</sub></b>	1.04	(0.99, 1.09)	1.01	(0.87, 1.17)	1.08	(1.01, 1.16)
<b>AUC<sub>clast</sub></b>	1.04	(0.99, 1.09)	1.09	(1.01, 1.17)	1.10	(1.03, 1.17)
<b>AUC<sub>∞</sub> ratio<sup>b</sup></b>	NA	NA	0.97	(0.85, 1.11)	NA	NA
<b>C<sub>max</sub></b>	0.96	(0.84, 1.09)	1.00	(0.84, 1.19)	1.22	(0.97, 1.54)
<b>t<sub>1/2</sub></b>	0.98	(0.93, 1.04)	0.91	(0.74, 1.11)	0.87	(0.71, 1.07)
<b>λ<sub>z</sub></b>	1.02	(0.96, 1.08)	1.10	(0.90, 1.35)	1.15	(0.94, 1.40)
<b>t<sub>max</sub><sup>c</sup></b>	0.00	(-0.50, 0.25)	-0.25	(-0.50, 0.00)	-0.25	(-0.75, 0.00)

TRT Ratio: treatment ratio of hydrocodone/acetaminophen plus alosetron vs. hydrocodone/acetaminophen alone.

AUC<sub>∞</sub> ratio: hydromorphone AUC<sub>∞</sub>/hydrocodone AUC<sub>∞</sub>.

The analysis of t<sub>max</sub> was based on non-parametric methods.

**Safety Results:** Adverse events were monitored from the time consent was signed until final discharge. Only drug-related SAEs were to be collected between screening and first dose. All AEs irrespective of causality occurring after the first dose of study medication were documented.

Adverse Events	Hydrocodone/acetaminophen 5 mg/500 mg	Hydrocodone/acetaminophen 5 mg/500 mg + alosetron 1 mg
No. of subjects, N	12	12
Subjects with any AE(s), n(%)	1 (8)	2 (17)
Headache	0	2 (17)
<b>Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:</b>		
<b>Serious Adverse Events – On-Therapy</b>		
No. subjects with SAEs n (%) -includes fatal and nonfatal SAEs	0	0

**Publications:**

No publication

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