The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No: S3B10946		
Title: An open-label parallel-group, pharmacokinetics and tolerability study of a single 1mg oral dose of alosetron in hepatically impaired subjects and in healthy control subjects.		
Rationale: Alosetron is predominantly eliminated through metabolism by a variety of hepatic microsomal cytochrome P450 (CYP) enzymes. Due to the importance of hepatic metabolism in the elimination of alosetron, this study aimed to compare the pharmacokinetics (PK) of alosetron and its 6-hydroxy, N-desmethyl, hydroxymethyl- and imidazole metabolites and tolerability in subjects with hepatic impairment compared with healthy subjects.		
Phase: I		
Study Period: 21st May 2003 - 24th April 2004		
Study Design: This study was an open-label, parallel-group design in which subjects with varying degrees of hepatic impairment received a single oral dose of 1mg alosetron.		
Centres: 2 centres in the USA.		
Indication: None		
Treatment: The study treatment comprised a single 1mg oral dose of alosetron.		
Objectives: The primary objective of this study was to compare alosetron pharmacokinetics following a single 1mg oral dose in subjects with hepatic impairment (mild, moderate, and severe) versus healthy control subjects. The secondary objectives were to evaluate the tolerability of alosetron in subjects with hepatic impairment and to evaluate the pharmacokinetics of alosetron metabolites in subjects with hepatic impairment.		
Statistical Methods: The protocol detailed analysis of variance models for the area under the concentration-time curve from zero (pre-dose) extrapolated to infinite time (AUC(0-∞)), maximum observed concentration (Cmax) and terminal half-life (t½) and a non-parametric analysis for the first time of occurrence of Cmax (tmax), to compare the hepatic impairment groups to the healthy subject group. However, as the study was terminated early, and no healthy subject group was recruited, no formal analysis was conducted. Pharmacokinetic and safety parameters were summarized descriptively for all subjects.		
Study Population: Thirty-two evaluable subjects were planned, with 8 subjects in each of 4 hepatic function groups (mild, moderate and severe hepatic impairment and normal healthy subjects). Nine subjects were recruited (6 in the moderate and 3 in the severe hepatic impairment group). Subjects were excluded from the study if they had any other underlying condition that could interfere with the results of the study or constituted an unacceptable risk to the subject, they were receiving any concurrent prohibited medications, had a history of drug or alcohol abuse, had given a blood donation within the previous 6 weeks, were a pregnant or lactating female subject, or were hypersensitive to any component of the study treatments.		
Number of Subjects:	Moderate impairment	Severe impairment
Dosed N	6	3
Completed n (%)	6	3
Total Number Subjects Withdrawn N (%)	0	0
Withdrawn due to Adverse Events, n (%)	0	0
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable
Withdrawn for Other Reasons, n (%)	0	0
Demographics		
N (ITT)	6	3
Females: Males	1:5	1:2
Mean Age in Years (sd)	51 (4.5)	52 (6.6)
Mean Weight in Kg (sd)	89.0 (9.70)	87.8 (12.82)
White n (%)	6 (100)	2 (67)

Pharmacokinetics (PK) results:
Summary of Selected Plasma Alosetron and its Hydroxy-imidazole and Mono-oxo-imidazole Metabolites Pharmacokinetic Parameters[1]

Analyte	Group[3]	Gender	AUC(0-∞) (ng.h/mL)	AUC(0-t) (ng.h/mL)	Cmax (ng/mL)	tmax[2] (h)	t½ (h)
Alosetron	Moderate	Male (n=5)	40.8 (60.7)	37.8 (58.6)	8.06 (21.5)	0.520 (0.500-1.50)	3.78 (52.5)
		Female (n=1)	73.2 (NC)	69.2 (NC)	19.9 (NC)	0.500	5.77 (NC)
	Severe	Male (n=2)	68.9 (11.2)	62.7 (11.2)	9.98 (13.8)	1.00 (1.00-1.00)	7.35 (1.06)
		Female (n=1)	226 (NC)	160 (NC)	13.1 (NC)	1.00	13.0 (NC)
Hydroxy-methyl-imidazole	Moderate	Male (n=3)	NC	2.19 (33.4)	0.600 (27.9)	2.00 (1.00-3.00)	NC
		Female (n=1)	NC	1.41 (NC)	0.471 (NC)	2.00	NC
	Severe	Male (n=2)	NC	0.667 (27.9)	0.353 (11.4)	2.25 (1.50-3.00)	NC
		Female (n=1)	NC	2.09 (NC)	0.423 (NC)	2.00	NC
Mono-oxo-imidazole	Moderate	Male (n=4)	NC	0.896 (279)	0.673 (42.5)	1.50 (1.00-2.00)	NC
		Female (n=1)	NC	2.83 (NC)	0.747 (NC)	1.00	NC
	Severe	Male (n=2)	NC	1.68 (15.7)	0.573 (23.4)	2.00 (1.00-3.00)	NC
		Female (n=1)	NC	7.64 (NC)	1.04 (NC)	2.00	NC

1 = geometric mean (CVb%)
2 = median (range) where applicable
3 = moderate hepatic impaired (score 7-9) and severe hepatic impaired (score >9)
NC = Not Calculable

Safety results:
Adverse events (AEs) were assessed during the Screening, Treatment and Post-Study phases of the study. All AEs and serious adverse events (SAEs) were assessed and recorded in source documents throughout the study. During the Screening phase, prior to receipt of study drug, only AEs that meet the definition of serious and that, in the investigator's opinion, are related to study procedures were recorded in the Case Report Form (CRF). During the Treatment and Post-Study phases, all AEs and SAEs were recorded in the CRF.

Adverse Events:	Moderate impairment N=6	Severe impairment N=3
Number of subjects with AEs, n (%)	1 (17)	1 (33)
Serious Adverse Events		
Number of subjects with SAEs, n (%) - includes fatal and non-fatal events	0	0

Publications:
No Publication

Date Updated: 08-Aug-2005