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.: S3B40040

Title: A Double-Blind, Placebo-Controlled, Randomised, 2-Way Crossover Study to Evaluate the Potential Inhibition of Alosetron Metabolism by Ketoconazole in Healthy Female Subjects

Rationale: Alosetron is predominantly eliminated through metabolism by a variety of hepatic microsomal cytochrome P450 (CYP) enzymes, shown in vitro to involve: 2C9 (30%), 3A4 (18%), 1A2 (10%) and some non-CYP-mediated phase I metabolism (11%). Due to the importance of P450-mediated metabolism in the elimination of alosetron, the pharmacokinetics (PK) of alosetron and its 6-hydroxy, N-desmethyl, hydroxymethyl-imidazole and mono-oxo-imidazole metabolites were evaluated in this drug-interaction study with ketoconazole, a known inhibitor of CYP 3A4 and 2C19.

Phase: I

Study Period: 09 Jul 2003 to 03 Feb 2004

Study Design: A double-blind, placebo-controlled, randomised, 2-way crossover study in healthy female subjects.

Centres: A single center in Australia:

Indication: None

Treatment:
Single doses of oral alosetron 1mg and repeated doses of oral ketoconazole 200mg or placebo. Subjects were randomised to 1 of 2 treatment sequences, AB or BA, where: A=alosetron + ketoconazole and B=alosetron + placebo. Subjects were to be dosed twice daily (*bis in die* [BID]) for 7 days with 200mg ketoconazole or matching placebo. On Day 7 of each treatment period a single 1mg dose of alosetron was to be administered.

Objectives: The primary objective of the study was to determine whether ketoconazole significantly alters the PK of alosetron in healthy female subjects.

Statistical Methods: The area under the plasma-concentration-time curve extrapolated to infinity (AUC[0-∞]) and the area up to the last quantifiable time-point (AUC[last]), Cmax, and terminal plasma elimination half life (t½) of alosetron were analysed separately by analysis of variance (ANOVA), fitting terms for sequence, subject within sequence, treatment period, and regimen. Point estimates and corresponding 90% confidence intervals (CI) were determined for the difference between 'alosetron + ketoconazole - alosetron + placebo' using the residual error from the ANOVA (MSE). The point and interval estimates on the log(e) scale were then exponentially back-transformed to give estimates of the ratio and 90% CI for alosetron + ketoconazole : alosetron + placebo. Time of maximum observed plasma concentration (tmax) was analysed non-parametrically using the Wilcoxon Matched Pairs method. The point estimate and approximate 90% CI for the median difference of alosetron + ketoconazole and alosetron + placebo was calculated.
Subjects who contributed to the comparisons of interest were included in the pharmacokinetic analysis. All subjects who received at least one dose of study medication are included in the evaluation of clinical safety and tolerability.

Study Population: Healthy, non-smoking female volunteers aged 18 to 50 years.

Number of Subjects:	**Alosetron 1mg**
Planned, N	32
Dosed, N	38
Completed, n (%)	34 (89)
Total Number of Subjects Withdrawn, n (%)	4 (11)
Withdrawn Due to Adverse Events, n (%)	1 (3)
Withdrawn Due to Lack of Efficacy, n (%)	0
Withdrawn for Other Reasons, n (%)	3 (8)
Demographics:	**Alosetron 1mg**
N (Safety)	38
Females:Males, n:n	38:0
Mean Age, Years (SD)	25 (5.5)
Mean Weight, kg (SD)	62.3 (8.1)
Caucasian, n (%)	35 (92)

PK Endpoints:

Alosetron PK Parameters Following Treatment with Ketoconazole and Placebo

	Alosetron + Placebo	**Alosetron + Ketoconazole**	

Parameter (units)	**(Treatment B)[a]**	**(Treatment A)[a]**	**Treatment Comparison[b]**
n	34	34	
AUC∞ (ng*hr/mL)[c]	25.1 (22.2, 28.4)	32.5 (28.6, 36.8)	1.29 (1.14, 1.46)
AUClast (ng*hr/mL)	22.0 (18.8, 25.8)	29.3 (25.2, 34.2)	1.33 (1.15, 1.54)
Cmax (ng/mL)	7.14 (6.28, 8.12)	9.28 (8.07, 10.68)	1.30 (1.15, 1.46)
tmax (hr)	1.00 (0.50, 3.00)	1.00 (0.50, 3.00)	0.00 (-0.25, 0.25)
t1/2 (hr)[c]	1.69 (1.56, 1.83)	1.61 (1.52, 1.71)	0.95 (0.89, 1.02)
Hydroxymethyl-Imidazole Alosetron PK Parameters Following Treatment with Ketoconazole and Placebo			
Parameter (units)	**Alosetron + Placebo (Treatment B) [a]**	**Alosetron + Ketoconazole (Treatment A) [a]**	**Treatment Comparison[b]**
n	33	33	
AUClast (ng*hr/mL)	2.23 (2.00, 2.48)	1.78 (1.63, 1.94)	0.80 (0.75, 0.85)
Cmax (ng/mL)	0.86 (0.79, 0.92)	0.66 (0.63, 0.70)	0.77 (0.73, 0.82)
tmax (hr)	1.50 (1.00, 4.00)	1.00 (1.00, 3.00)	0.00 (-0.50, 0.24)
Mono-Oxo-Imidazole Metabolite PK Parameters Following Treatment with Ketoconazole and Placebo			
Parameter (units)	**Alosetron + Placebo (Treatment B) [a]**	**Alosetron + Ketoconazole (Treatment A) [a]**	**Treatment Comparison[b]**
n	32	32	
AUClast (ng*hr/mL)	2.60 (2.30, 2.93)	2.13 (1.90, 2.38)	0.81 (0.73, 0.91)
Cmax (ng/mL)	1.11 (1.03, 1.21)	0.86 (0.79, 0.93)	0.76 (0.72, 0.81)
tmax (hr)	1.02 (0.50, 3.00)	1.00 (0.50, 3.00)	0.00 (-0.25, 0.24)

a. Geometric mean (95% CI) is presented for AUClast, AUC∞, Cmax, and t1/2. Median (range) is presented for tmax.
b. Geometric least square (LS) mean ratio (90% CI) is presented for AUClast, AUC∞, Cmax, and t1/2. Median difference (90% CI) is presented for tmax.
c. n=31 for Treatment A and B.

Safety Results: Adverse events (AEs) and serious AEs (SAEs) were collected from screening through to the end of the follow-up visit. During the screening period, prior to receipt of any study drug, only AEs that met the definition of serious and that, in the investigator's opinion, were related to study procedures were recorded.

Adverse Events (Safety):	**Placebo N=36** **n (%)**	**Ketoconazole N=36** **n (%)**	**Alosetron + Placebo N=36** **n (%)**	**Alosetron + Ketoconazole N=35** **n (%)**
Subjects With AEs	23 (64)	21 (58)	14 (39)	26 (74)
Headache	15 (42)	18 (50)	11 (31)	22 (63)
Nausea	1 (3)	8 (22)	1 (3)	3 (9)
Constipation	1 (3)	2 (6)	1 (3)	5 (14)
Upper Abdominal Pain	1 (3)	3 (8)	1 (3)	1 (3)
Hyperhidrosis	0	2 (6)	0	2 (6)
Dizziness	0	1 (3)	0	2 (6)
Dyspepsia	0	2 (6)	0	0
Abdominal Pain	1 (3)	1 (3)	0	0
Diarrhoea	1 (3)	0	0	1(3)
Upper Rrespiratory Tract Infection	1 (3)	0	1 (3)	0
Dysmenorrhoea	0	0	1 (3)	1(3)
Agitation	1(3)	0	0	0
Dehydration	1(3)	0	0	0
Impetigo	1(3)	0	0	0
Lethargy	1(3)	0	0	0
Memory Impairment	1(3)	0	0	0
Nasal Congestion	1(3)	0	0	0
Pruritus	1(3)	0	0	0
Rhinitis Allergic	1(3)	0	0	0
Syncope Vasovagal	1(3)	0	0	0
Hyperventilation	0	0	1(3)	0

Pharynoglaryngeal Ppain	0	0	1(3)	0
vomiting	0	0	1(3)	0
Serious Adverse Events, n (%) [# considered by the investigator to be related, possibly related, or probably related to study medication]:				
	Placebo N=38	**Ketoconazole N=38**	**Alosetron + Placebo N=38**	**Alosetron + Ketoconazole N=38**
	n (%) [n]	**n (%) [n]**	**n (%) [n]**	**n (%) [n]**
Subjects With Non-fatal SAEs	0	0	0	0
Subjects With Fatal SAEs	0	0	0	0

Publications: No publication

Date Updated: 03-Jun-2005