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<b>Study No.:</b> S3B10947				
<b>Title:</b> An Open-Label, Non-Randomized, Mass Balance Study to Characterize the Metabolism of Isotopically Labeled Alosetron After a Single 4mg Oral Dose of [13C, 14C]-Alosetron in Healthy Subjects				
<b>Rationale:</b> The principal route of alosetron elimination is metabolic biotransformation. At least 13 metabolites have been detected in urine and nine of these were also present in feces extract. Unchanged drug represents approximately 6% and 1% of the dose in urine and feces, respectively. The two predominant products in urine are the 6-hydroxy metabolite (15% of the dose) present as a glucuronide, and a bis-oxidized metabolite (14% of the dose). No other urinary metabolite accounts for more than 4% of the dose. This study is being conducted to clarify the metabolism and disposition of alosetron in vivo, including formation of N-desmethyl-alosetron in Asians, and identification of circulating metabolites not characterized in a previous mass balance study.				
<b>Phase:</b> I				
<b>Study Period:</b> 06 Jul 2000 to 30 Aug 2000				
<b>Study Design:</b> This was an open-label, single-dose, mass balance study. The total duration of the study was up to 4½ weeks.				
<b>Centres:</b> This study was conducted at 1 center in the United States (US):				
<b>Indication:</b> None				
<b>Treatment:</b> . After an overnight fast of at least 12 hours, 4mg of [13C,14C]-alosetron (containing 25µCi of [14C]-radioactivity equivalent to 1.36mSv) was administered as an oral solution.				
<b>Objectives:</b> The objectives of the study were as follows: Confirm serum profiles and urinary and fecal recoveries of alosetron, total radioactivity, and previously identified relevant metabolites after a single, oral dose of [13C, 14C]-alosetron in healthy subjects Identify and quantify additional relevant metabolites of alosetron, including N-desmethyl-alosetron, in serum, urine, and feces following a single, oral dose of [13C, 14C]-alosetron in healthy subjects				
<b>Statistical Methods:</b> A total of 9 subjects were to be enrolled in the study as 3 groups of 3 subjects. The sample size was selected to provide sufficient data for this observational study while limiting the number of subjects exposed to radioactivity. However, only 7 subjects enrolled and completed the study (3 Caucasian males; 3 Caucasian females and 1 Asian [Korean] male); the study was terminated prior to enrolling the last 2 Asian subjects. All 7 subjects were included in the safety (All subjects who received a dose of study medication) and pharmacokinetic (all subjects who received a dose of study medication and provided evaluable PK data) populations.  There were no formal statistical analyses conducted for PK endpoints.  Descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum) were presented by subgroup (Caucasian males, Caucasian females, Asian male) for serum total radioactivity concentrations, serum total radioactivity PK parameters, urinary recovery of total radioactivity, urinary recovery of alosetron, urinary recovery of relevant metabolites, and fecal recovery of total radioactivity. Serum concentrations of alosetron and relevant metabolites, and fecal recovery of alosetron and relevant metabolites were presented by subject.  Descriptive statistics were calculated for adverse events (AEs) and clinical laboratory evaluations and were sub-grouped by subject group.				
<b>Study Population:</b> Healthy male and female subjects, aged 18 to 50 years (inclusive); Asian males had to have 2 biological parents of Asian origin; subjects of Chinese and/or Japanese origin were preferable.				
<b>Number of Subjects:</b>		<b>Alosetron</b>		
Planned, N		9		
Dosed, N		7		
Completed, n (%)		7 (100)		
Total Number of 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>Caucasian Females</b>	<b>Caucasian Males</b>	<b>Asian Male</b>	<b>Total</b>

N (Safety)	3	3	1	7
Females:Males, n:n	3:0	0:3	0:1	3:4
Mean Age, Years (SD)	38.0 (9.0)	36.7 (10.2)	24.0	35.4 (9.4)
Mean Weight, kg (SD)	60.80 (8.75)	81.13 (9.38)	78.80	72.09 (12.92)

#### Pharmacokinetic Results

Recovery of total radioactivity in urine accounted for 74-76% of the dose in Caucasian males, 73-79% in Caucasian females, and 64% in the Asian male. Recovery of total radioactivity in feces added 12-16%, 4-11%, and 12% in these groups, respectively. Recovery of total radioactivity in urine and feces together accounted for 76-91% of the dose across all subjects.

Serum concentrations (mean AUC) of total radioactivity in Caucasian males and females were similar (356 and 373 ng-equivalents•h/mL, respectively), but lower in the Asian male (266 ng-equivalents•h/mL). Radiochromatographic isolation of individual metabolites in serum indicated that none amounted to more than 15% of unmetabolized alosetron concentration in either Caucasian males or females, or the Asian male. Measurable metabolites in serum included the O-glucuronide and O-sulphate conjugates of the 6-hydroxy metabolite GR96105, the mono- and bis-oxygenated metabolites GR168355 and GR153732, and the hydroxymethyl metabolite GR169307.

Urinary recovery of radiolabeled unmetabolized alosetron was higher in Caucasian females (18% of the dose) than in Caucasian males (11% of the dose) or the Asian male (4% of the dose). The major radiolabeled metabolite detected in urine was the GR96105-O-glucuronide (14-19% of the dose). The next most abundant radiolabeled metabolites were the bis- and mono-oxygenated products GR153732 (13-15% of the dose) and GR168355 (4-7% of the dose). No substantial differences in urinary recovery of radiolabeled metabolites were observed between Caucasian males and females, although minor quantitative differences were observed in the Asian male.

The N-desmethyl metabolite, GR87620, which has not been detected previously in Caucasians, was previously reported to have been detected in the serum of Japanese males (Studies AS-01, AS-02, and AS-03). This metabolite was not detected in either serum or urine from the Asian and Caucasian males in this study, although similar amounts (<3% of the dose) were detected in the feces of most subjects.

**Safety Results:** An on therapy AE was defined as an AE with onset on or after the start date of study medication and during the study period. An on therapy serious adverse event (SAE) was defined as a SAE with onset on or after the start date of study medication and up to 30 days after the last dose of medication.

Adverse Events:	Caucasian Females	Caucasian Males	Asian Male	Total
	n (%)	n (%)	n (%)	n (%)
N (Safety)	3	3	1	7
Subjects With AEs	2 (67)	1 (33)	0	3 (43)
Musculoskeletal Pain	2 (67)	0	0	2 (29)
Serious Adverse Events:	Caucasian Females	Caucasian Males	Asian Male	Total
	n (%) [n]	n (%) [n]	n (%) [n]	n (%) [n]
Subjects With non-fatal SAEs	0	0	0	0
Subjects With non-fatal SAEs	0	0	0	0

#### Publications:

No Publication

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