

Table 42 Cisapride Pharmacokinetic Metrics in Presence and Absence of Alosetron¹

Parameter	Geometric LS Mean		Ratio (90% CI) p-value
	Cisapride 20mg QID + Placebo BID x 4 days	Cisapride 20mg QID + 1mg Alosetron BID x 4 days	
Cisapride			
C_{max} (ng/mL)	95.8	100.9	1.05 (0.98, 1.13) NS
t_{max} (h)	1.3	1.3	0.0 ^a (-0.25, 0.25)
AUC₀₋₆ (ng·h/mL)	454	473	1.04 (1.00, 1.08) p = 0.072
t_{1/2} (h)	9.7	10.1	1.03 (0.92, 1.16) NS
A₀₋₂₄ (mcg)	53.9	71.0	1.32 (1.14, 1.52) p = 0.006
Norcisapride			
A₀₋₂₄ (mcg)	10.2	10.4	0.98 (0.92, 1.04) NS

^a difference

There was no indication of any changes in the cardiac pharmacodynamics of cisapride in the presence of alosetron.

f) Cortisol Production

Two studies indicate that alosetron decreases cortisol production and based upon what is known about other imidizoles there is may be an effect on the production of other steroid hormones.

Cortisol is formed in the adrenal cortex from 11-deoxycortisol by mitochondrial CYP-21A1 and is under the control of several peptide hormones, including ACTH, LH, FSH and HCG. Ketoconazole and ondansetron (another 5HT₃ antagonist) both decrease cortisol. Ketoconazole is known to inhibit a number of different pathways involved in steroid hormone genesis (See APPENDIX 4). Consequently, these drugs could result in a shunting in the production of various steroid hormones. There are several observations that suggest that this could be involved in the mechanism of action. Specifically, cortisol production continues to decrease for at least 1 month and clinical efficacy increases over the first two weeks and doesn't become significantly different from placebo until after 4-5 weeks of treatment. In addition, the mean time for onset of constipation is 3 weeks. Finally, there is a gender effect in the incidence of the disease. There are also obviously gender differences in steroid hormones, as well as with the effect of alosetron on cortisol production.

Study S3B-102

¹ Values came from tables of individual parameters whenever possible. There were minor discrepancies between the values reported in these tables, the values reported in the summary table and the values reported in the abstract. In no case are differences of sufficient magnitude to be clinically significant.

Study S3B-102 was a randomized, double-blind, placebo controlled study in healthy volunteers. There was a total of 48 subjects, 24 young males (19 - 40 years of age), 12 elderly males (65 - 82 yo) and 12 elderly females (65 - 78 yo). Subjects received alosetron 2 mg or placebo bid for 27½ days.

There was a decreasing trend in 6-β-OH-cortisol excretion over the course of the study in all groups (See APPENDIX 4), although the variability was quite high (See Table 43).

In young males urinary 6-β-OH-cortisol decreased 52% over the course of the study. This was associated with a 62% increase in alosetron AUC₁₂ and a trend toward increasing 2 hour alosetron concentrations.

In elderly males and females there were trends toward decreasing urinary 6-β-OH-cortisol associated with a trend toward increasing alosetron AUC₁₂ over the course of the study. Although none of the changes are as pronounced as in young males.

Table 43 12 Hour Urinary 6β-Hydroxycortisol Excretion (mcgs)^a

Day	Young Males		Elderly Males		Elderly Females	
	Alosetron	PBO	Alosetron	PBO	Alosetron	PBO
	n = 10	n = 3	n = 7	n = 2	n = 5	n = 3
1 (pre-alosetron)	206 ± 78	116 ± 1	96 ± 78	88	111 ± 59	40 ± 15
2	133 ± 63	144 ± 25	89 ± 66	71	77 ± 28	57 ± 28
8	99 ± 72	78 ± 21	76 ± 34	49	81 ± 66	58 ± 66
29	96 ± 80	100 ± 56	60 ± 13	88	60 ± 24	65 ± 24
31 (post-alosetron)	146 ± 147	144 ± 55	46 ± 56	63	53 ± 15	46 ± 15

^a - values are mean ± SD

6β-hydrocortisol is formed by CYP3A4 and has been proposed as a marker for CYP3A4 activity. However, the lack of measurement of the cortisol, the precursor to 6β-hydrocortisol, precludes any conclusion regarding the effect of alosetron on CYP3A4 activity from this study.

Study S3BA1001

In the cisapride interaction study (Study S3BA1001) there was significantly lower 12 hour urinary elimination of 6β-hydrocortisol in the alosetron arm. However, the 12 hour urinary 6β-hydrocortisol/cortisol ratio and the 12 hour urinary elimination of norcisapride are unchanged in the presence of alosetron (See Table 4A). This indicates no change in 3A4 activity by alosetron and a possible effect by alosetron on cortisol production or other elimination pathways.

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Table 44 Urinary 12 Hour 6β-Hydroxycortisol Excretion - Study S3BA1001*

	Placebo	Alosetron	Ratio Alosetron:Placebo ^a
A ₀₋₁₂ 6β-Hydroxycortisol (mcg)	125.2 (112.0-139.9)	110.0 (98.4-122.9)	0.88 (0.81, 0.95) p = 0.016
A ₀₋₁₂ 6β-OH-Cortisol/Cortisol Ratio	7.52 (6.19, 9.13)	7.68 (6.32, 9.32)	1.02 (0.95, 1.09) NS

* Cisapride Interaction Study; Values are least square geometric means and (95% CI), a - 90% CI.

3. Effect of Inhibitors on Alosetron Pharmacokinetics

The effect of P450 inhibitors on alosetron pharmacokinetics was not studied.

The sponsor proposes that since alosetron is metabolized by multiple pathways and no single metabolite accounts for more than 15% of the dose it's unlikely that inhibition of any one pathway would effect alosetron clearance, and consequently exposure. Since shunting to other metabolic pathways would occur.

As mentioned previously when secondary metabolism is accounted for, the two major metabolic pathways *in vivo* account for at least 35% and 26% of total body clearance respectively. Assuming one of these pathways were inhibited, total alosetron concentrations would likely rise slightly and some shunting would occur. However, saturation of alternative pathways would be unlikely to occur since enzyme saturation seen with ethanol, phenytoin, and salicylate occur at plasma concentrations at least 1000 fold higher than the concentrations seen with alosetron (See APPENDIX 1).

It should be noted that shunting to other pathways will increase the metabolite formation by these alternative pathways. Consequently, even if the contribution of an alternative pathway goes from 1 to 2% of the total clearance, this still results in a doubling of exposure to the metabolites formed via this alternative pathway. For a highly toxic or highly active metabolite, the clinical consequences can be quite significant. For alosetron, shunting to 6-OH alosetron could have quite a significant clinical effect on efficacy since it's approximately twice as potent as alosetron. For example, since 35% of alosetron is metabolized to 6-OH-alosetron, if the second most important pathway is totally inhibited 47% of the dose will be metabolized to 6-OH-alosetron.

4. Effect of Inducers on Alosetron Pharmacokinetics

The effect of inducers on alosetron pharmacokinetics was not studied.

Due to the extensive oxidative metabolism of alosetron, non-specific inducers of P450 might be expected to decrease alosetron exposure and increase exposure to some metabolites. Thus, activity and toxicity could either decrease, or increase if there's active metabolites.

In addition to general inducers of P450, specific isozyme inducers need to be considered. Proton pump inhibitors (benzimidazoles) are known to be potent inducers of CYP1A2 and could result in a decrease in alosetron exposure and possibly an increase in exposure to 6-OH alosetron, or other metabolites with activity, or toxic effects. Since, alosetron has a pKa of 6.95 an increase in gastric pH due to a proton pump inhibitor could also decrease the dissolution. This could result in a decreased absorption and possibly a slower absorption with a resulting increase in first pass effect. Since alosetron is being considered for psychiatric indications, the induction of CYP1A2 by phenothiazines needs to be kept in mind. There are also a number of dietary factors, as well as environmental factors (e.g. smoking), that

induce CYP1A2. These are addressed in more detail in these sections of the review. Glucocorticoids that may also be used for IBS, might also induce alosetron metabolism via CYP3A4.

5. Other Mechanisms

Since, alosetron has a pKa of 6.95 alterations in gastrointestinal pH by antacids, laxatives containing magnesium, H₂ antagonists or proton pump inhibitors might effect absorption. This has been shown for other imidazoles, e.g. ketoconazole. Alosetron causes a number of gastrointestinal symptoms including a high incidence of dose dependent constipation (28% at 1 mg bid) for which laxative use is recommended. Consequently, self-medication is expected and drug interaction studies need to be performed.

K. Special Populations

1. Special Population - Elderly

There is an effect of age on the plasma concentrations and pharmacokinetics of alosetron. Plasma concentrations tend to be elevated in the elderly. However, current information does not indicate that dosing needs to be adjusted with age. This is due to the large variability in observed concentrations, the wide therapeutic index, and the short half-life relative to the dosage interval.

With age, decreases in clearance are variously observed, whether or not clearance is normalized. However, it appears that clearance does decrease with age. This may be due to a combination of a decrease in metabolic capacity and a decrease in hepatic blood flow with age. There is also an associated increase in bioavailability with the decrease in clearance.

Total volume of distribution also decreases with age. The decrease in total volume of distribution appears to be largely attributable to differences in body weight as it is negated by normalization to body weight. However, even with normalization there is still a consistent trend toward decreasing weight-normalized volume of distribution with increasing age, although the differences are not statistically significant. This may be associated with changes in body composition with aging.

There is a dose related increase in constipation in the dose ranging studies. Consequently the incidence of constipation needs to be evaluated in the elderly where concentrations are higher.

Study S3B-102

Study S3B-102 was conducted to examine the safety and pharmacokinetics of alosetron in young males, elderly males, and elderly females following twice daily 2mg oral doses for 27½ days. According to the sponsor, *the results showed that repeated twice-daily dosing did not result in appreciable accumulation. Serum concentrations were higher (≈50%) in elderly females compared to elderly males. Apart from a slightly (30%) longer half-life in the elderly males, no effect of age was observed (in males) in this study.*

Study S3B-102 was a randomized, double-blind, placebo controlled study in healthy volunteers. There was a total of 48 subjects, 24 young males (19 - 40 years of age), 12 elderly males (65 - 82 yo) and 12 elderly females (65 - 78 yo). Subjects received alosetron 2 mg or placebo bid for 27½ days. One quarter of the subjects in each group received placebo. All doses were taken 1.5 hours after food and no food was to be eaten for 2 hours following dosing.

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Table 45 Pharmacokinetic Metrics in Young and Elderly with Multiple Dosing

Dose		C _{max} (ng/mL)	t _{max} (h)	AUC ₁₂ (ng·h/mL)	t _{1/2} (h)
2mg alosetron BID x 27½ days					
Young Males:	Day 2:	8.64 ± 4.96	1.75 ± 0.43	26.6 ± 14.8	1.40 ± 0.22
	Day 29:	12.38 ± 6.74	1.71 ± 0.57	39.4 ± 22.9	1.44 ± 0.22
Elderly Males:	Day 2:	11.59 ± 4.15	1.56 ± 0.71	39.1 ± 18.2	1.78 ± 0.43
	Day 29:	13.02 ± 5.07	2.11 ± 0.90	47.4 ± 19.9	1.82 ± 0.30
Elderly Females:	Day 2:	18.72 ± 5.71	1.83 ± 0.61	62.4 ± 23.7	1.64 ± 0.31
	Day 29:	18.85 ± 5.64	1.63 ± 0.63	66.9 ± 22.9	1.68 ± 0.29

All values of C_{max}, t_{max}, AUC, and t_{1/2} are shown as geometric LS mean (95% confidence interval) or arithmetic mean ± standard deviation

Except for young males no time invariance was observed in this study (See Table 46).

Table 46 p-Values 1st Dose Metrics vs. Day 28 Metrics

Parameter	Young Males	Elderly Males	Elderly Females
AUC ₁₂	0.0003	NS	NS
C _{max}	0.0004	NS	NS
T _{max}	NS	NS	NS
t _{1/2}	NS	NS	NS

NS - not significant

In all three groups there was a trend toward increasing AUC over the course of the study. This was associated with a trend towards decreasing urinary 6-β-OH-cortisol over time, suggesting inhibition of CYP3A4. However, an additional studies indicate that CYP3A4 is not induced. This effect on 6-β-OH-cortisol was most pronounced in young males, less pronounced in elderly males, and even less pronounced in elderly females (See Page 49).

Study GPK:90:01

Study GPK:90:01 was a single dose, randomized, open label, cross-over study, in 16 young and 16 elderly healthy male volunteers. It compared the pharmacokinetics in each group after a 4 mg oral and a 4 mg IV dose of alosetron. Subject demographics are shown in Table 47.

Table 47 Subject Demographics In Study GPK:90:01

Treatment Dose(s)	Number for Each Treatment	Age Range In Years (mean ± SD)	M/F (B/W/O)
Alosetron 4mg PO	32	25-82	32/0
Alosetron 4mg IV	32	25-35 30.5 ± 3.9	(0/32/0)
		65-82 70.6 ± 6.1	

According to the sponsor the 'clearance was 21% lower and plasma AUC higher in the elderly males compared to the younger males. Absolute bioavailability was approximately 60% and volume of distribution was approximately 90L in both groups' and 'Absolute bioavailability and volume of distribution unaffected by age.' (See Table 48)

Table 48 Pharmacokinetic Metrics of Alosetron in Young and Elderly Males - Study GPK:90:01

Dose Route of Admin. Dosage Form	C _{max} (ng/mL)	t _{max} (h)	AUC _∞ (ng·h/mL)	t _{1/2} (h)	CL _p (mL/min)	V _{ss} (L)	F (%)
4mg alosetron PO Tablet Young:	17.2 (14.5-20.4)	1.50	47.8 (38.4-59.6)	1.5 (1.4-1.7)	—	—	55.1 (49.2-61.6)
Elderly:	20.5 (17.3-24.3)	1.00	66.7 (53.5-83.1)	1.8 (1.6-1.9)	—	—	60.9 (54.5-68.2)
Ratio Elderly:Young			1.40				1.10
4mg alosetron IV Young:	72.9 (61.9-85.9)	0.25	86.8 (74.9-100.7)	1.6 (1.5-1.7)	768 (662-891)	97.2 (87.0-108.6)	—
Elderly:	74.8 (63.5-88.1)	0.25	109.4 (94.3-126.9)	1.9 (1.5-2.0)	609 (525-707)	92.8 (83.1-103.7)	—
Ratio Elderly:Young			1.26		0.79	0.96	

All values of C_{max}, AUC_∞, CL_p, V_{ss}, A_s, and F are shown as geometric mean (95% confidence interval).
 t_{max} is shown as median (range) and t_{1/2} is shown as harmonic mean (95% confidence interval)

However, when volume is normalized to total body weight, there is a mean decrease of 13.3% in volume of distribution in the elderly, although the variability is quite large (See Table 49). Consequently, this difference is unlikely to be statistically significant. However, this is a consistent finding across studies and may be due to differences in body composition with age. The higher concentrations in the elderly are thus due to a lower total body clearance (~20%), which also accounts for a higher bioavailability (~8-10%). There are differences in volume but these were partially offset by weight differences.

Since this is a high intrinsic clearance drug, assuming 100% absorption, decreased hepatic blood flow in the elderly may be contributing to the decreased clearance.

Table 49 Normalized Alosetron Pharmacokinetic Metrics with Age - Protocol GPK:90:01

	Cl (ml/min)	Vdss (L)	Cl (ml/min/m ²)	Vdss (L/kg)	F
Young	790.9 ± 218.6 28	99.7 ± 25.2 25	418.3 ± 104.1 25	1.4 ± 0.4 26	0.57 ± 0.13 22.3
Elderly	636.7 ± 198.3 31	92.6 ± 19.7 21	334.3 ± 110.5 33	1.2 ± 0.4 31	0.612 ± 0.125 0.4
Ratio Elderly:Young	0.805	0.928	0.799	0.867	1.081

All parameter values are mean ± SD (CV)

Study C92-058

Study C92-058 was a single dose, randomized, open label, cross-over study, in young and elderly healthy male and female volunteers (n = 12/group). It was designed to compare alosetron pharmacokinetics in

each group after a 2 mg oral to a 2 mg IV dose. The age range was 19-78 years of age with a mean of 49 years.

According to the sponsor, there was both an age and a gender effect (See Table 50 and Table 51).

'An effect of age on alosetron pharmacokinetics was also observed. Peak serum concentrations were 40% higher in elderly females compared to young females. No age-related differences were observed in males.'

'The results showed a gender difference in alosetron pharmacokinetics. Clearance was 30% lower and serum concentrations 40% higher in elderly females compared to elderly males. Similar tendencies in young subjects were not statistically significant. Volume of distribution was 20% lower in females (65L) than in males (80L) regardless of age.'

'Absolute bioavailability was approximately 50% in both young males and females.'

Table 50 Alosetron Pharmacokinetic Metrics with Age After Intravenous Dosing - Protocol C92-058

Dose	C _{max} (ng/mL)	t _{max} (h)	AUC _∞ (ng·h/mL)	t _{1/2} (h)	CL _R (mL/min)	V _{ss} (L)
2mg alosetron IV						
Young Males:	40.2	0.25	49.4	1.5	675	82
Elderly Males:	49.8	0.25	52.2	1.7	639	83
Young Females:	44.6	0.25	61.3	1.6	544	65
Elderly Females:	62.9	0.25	74.1	1.8	450	62

All values of C_{max}, AUC, t_{1/2}, CL_R, and V_{ss} is shown as geometric LS mean (range) or arithmetic mean ± standard deviation. Whereas t_{max} is shown as median (range)

Table 51 Alosetron Pharmacokinetic Metrics with Age After Oral Dosing - Protocol C92-058

Dose	C _{max} (ng/mL)	t _{max} (h)	AUC _∞ (ng·h/mL)	t _{1/2} (h)	F (%)
Alosetron 2 mg PO Tablet					
Young Males:	9.4	1.00	24.8	1.4	0.50
Elderly Males:	9.8	0.75	26.5	1.6	0.51
Young Females:	12.0	1.00	30.5	1.4	0.49
Elderly Females:	17.2	0.75	47.1	1.7	0.63

All values of C_{max}, AUC, t_{1/2}, and F are shown as geometric LS mean (range) or arithmetic mean ± standard deviation. Whereas t_{max} is shown as median (range)

As before, when parameters are normalized many of the differences largely disappear (See Table 52). However, there is still a clear decrease in clearance and the associated increase in bioavailability in elderly females. Part of the difference in clearance in elderly females may be due to a lack of tobacco use and differences in elimination via 3A4 due to sex hormones. Another factor contributing to the lack of difference in the elderly population, may be the relatively young elderly population in this study compared with other studies, as well as an older young population. In spite of a lack of difference in volume of

distribution with normalization there is still a trend for decreasing volume with age and with sex. This could be due to differences in body composition between groups.

Table 52 Normalized Alosetron Pharmacokinetic Metrics with Age - Protocol C92-058

	Age ^a	Cl ^a (ml/min/m ²)	Vd ^a (L/kg)	Smokers (N)	Smokers >1/2 ppd (N)
Young Males	27.4 ± 5.65 20.6	363.5 ± 83.5 23	1.2 ± 0.3 24	4	2
Young Females	29.67 ± 7.36 24.83	342.7 ± 139.8 40.8	1.1 ± 0.3 25.9	6	5
Elderly Males	69.83 ± 3.27 4.68	354.1 ± 79.6 22.5	1.1 ± 0.2 14.6	3	1
Elderly Females	70.25 ± 3.36 4.78	269.4 ± 71.5 27	1.0 ± 0.2 25	2	1

^a Mean ± SD, CV (range)

Study S3BB1010

Finally, in study S3BB1010 analysis of variance indicated that there were statistically significant effects of age on C_{max}, AUC, Cl/F, V/F, and t_{1/2}. It should be noted that for a high intrinsic clearance drug such as alosetron Cl/F is equivalent to intrinsic clearance. Study S3BB1010 examined the effects of renal insufficiency on alosetron pharmacokinetics.

2. Special Population - Pediatrics

Pediatric subjects were not studied, and an exemption has been requested. Due to the higher clearances seen in pediatric patients with theophylline, which is also metabolized by CYP1A2, greater clearances in children would not be surprising.

3. Gender Effects

There is an effect of gender on the plasma concentrations and pharmacokinetics of alosetron. Plasma concentrations tend to be higher in females than males. Due to the lack of efficacy in males in the pilot efficacy study, the sponsor only performed pivotal trials in women. Consequently, no dose adjustments need to be made based on gender.

The lack of efficacy in males, even with higher dosages, suggests that there might be gender based pharmacodynamic differences that are not explained by the gender-related differences in alosetron concentration. However, this study was underpowered to detect a difference in men. Plus, there is a gender difference in the prevalence of irritable bowel syndrome with the frequency in women higher than in men.

Gender based differences are also known to occur with chemotherapy induced emesis (CIE) and the efficacy of other 5HT₃ antagonists against CIE. As mentioned earlier, alosetron results in alterations in cortisol production. Cortisol production is under hormonal control and consequently gender plays a role.

There is a gender-based difference in total body clearance associated with a decrease in first pass and a slight increase in bioavailability. However, there is no change in T_{max}.

The total volume of distribution also decreases, this change in volume of distribution offsets the change in clearance, consequently, half-life does not change.

When volume is normalized to body weight and clearance is normalized to body surface area most of the differences in pharmacokinetic parameters disappear. However, there is still a clear decrease in clearance with an associated increase in bioavailability in elderly females. Part of the difference in clearance in elderly females may be due to a lack of tobacco use and differences in 3A4 mediated elimination due to sex hormones. In spite of a lack of difference in volume of distribution with normalization, there is still a trend for decreasing volume with age and with sex. This could be due to differences in body composition between groups.

Pharmacokinetic data in women was obtained in the studies in Table 53.

Table 53 Studies with Pharmacokinetic Data in Women

Study	Description	Dose	Duration	Number of Women	Comment
S3BB1011	Time Invariance Study	1 mg po BID	29.5 days	15	Data from women not separated out
C92-058	Gender & Age Effect	2 mg po	SD	12	Separate Subgroup
S3B-102	Gender & Age Effect	2 mg po	27.5 days	12	Separate Subgroup
S3BB10004	Food Effect	4 mg po	SD X 2	10	
S3BA1002	Theophylline Interaction Study	1 mg po BID	15.5 days	14	No Men Studied
S3BA1005	Min Ovril	1 mg po BID	21 days	16	No Men Studied
S3B-201	Haloperidol Interxn	1 mg po BID	2 weeks	2	Crossover
S3BA1001	Cisapride Interxn Study	1 mg po BID	4 days	6	Separate Subgroup
S3BB1010	Renal Insufficiency	1 mg po	SD	9	
S3BA2001	Population PK	1 mg po BID	12 weeks	44	
S3BA2002	Population PK	2 mg po BID	13 weeks	33	
S3BA2003	Population PK	4 mg po BID	14 weeks	45	
S3BA2004	Population PK	8 mg po BID	15 weeks	27	

Study S3BB1011

Study S3BB1011 was a multiple dose study to assess the time invariance of alosetron pharmacokinetics in male and female volunteers. Subjects were administered 57 doses of alosetron 1 mg orally bid for 28½ days.

Table 54 Pharmacokinetic Metrics in Male and Females after 57 Doses - Protocol S3BB1011

	Male	Female	Geometric Mean Ratio 90% CI	p-value
Cmax (ng/ml)	4.25 ± 2.28	8.46 ± 4.25	0.46 0.36, 0.60	<0.001
Tmax (hours)	1.13 ± 0.35	1.10 ± 0.21	1.0 0.86, 1.17	1.0
AUC ₁₂ (ng*hr/ml)	13.60 ± 7.8	25.98 ± 9.06	0.49 0.37, 0.65	<0.001
Half-Life (hours)	1.51 ± 0.29	1.55 ± 0.30	0.98 0.86, 1.10	0.737

Male to female AUC and C_{max} ratios of approximately 0.5 are present even when AUC's are normalized to total body weight or body surface area with a p value of < 0.005. By inspection of the data there does not appear to be a relationship to hispanic ethnicity, (there were 8 hispanics out of 15 females and 1 hispanic of 15 males). The higher C_{max}, same T_{max}, and no change in half-life, indicates a lower in total body clearance associated with a lower first pass. This is supported by the lack of difference in T_{max}. Since half-life does not differ, there must also be a proportionate difference in total volume of distribution.

Study S3B-102

A gender effect was also detected in study S3B-102. This protocol was designed to assess the effect of age on the pharmacokinetics of alosetron. However, a gender effect also was detected, with alosetron plasma concentrations approximately 45% in higher in elderly females compared with elderly males (See Table 55).

Table 55 Gender Effect on Alosetron Plasma Concentrations - Protocol S3B-102

		C _{max} (ng/mL)	t _{max} (h)	AUC ₁₂ (ng·h/mL)	t _{1/2} (h)
Alosetron 2 mg po BID (tablets) x 27½ days					
Young Males:	Day 2:	8.64 ± 4.96	1.75 ± 0.43	26.6 ± 14.8	1.40 ± 0.22
	Day 29:	12.38 ± 6.74	1.71 ± 0.57	39.4 ± 22.9	1.44 ± 0.22
Elderly Males:	Day 2:	11.59 ± 4.15	1.56 ± 0.71	39.1 ± 18.2	1.78 ± 0.43
	Day 29:	13.02 ± 5.07	2.11 ± 0.90	47.4 ± 19.9	1.82 ± 0.30
Elderly Females:	Day 2:	18.72 ± 5.71	1.83 ± 0.61	62.4 ± 23.7	1.64 ± 0.31
	Day 29:	18.85 ± 5.64	1.63 ± 0.63	66.9 ± 22.9	1.68 ± 0.29

All values of C_{max}, t_{max}, AUC, and t_{1/2} are shown as geometric LS mean (95% confidence interval) or arithmetic mean ± standard deviation

Study C92-058

A gender effect was also detected in protocol C92-058. This study was specifically designed to assess the influence of age and gender on the pharmacokinetics of alosetron. In this study a single 2 mg dose of alosetron was administered intravenously over 15 min as an oral solution in a crossover manner to 24 male and female subjects with a 7 day between treatment wash-out phase.

According to the sponsor, clearance was 30% lower and serum concentrations are 40% higher in elderly females vs. males. Also, the volume of distribution was 25% lower in females compared with males. There was also an age effect in females with the C_{max} 40% higher in elderly females compared with young females, whereas there was no age effect in males. (See Table 56)

Table 56 Gender Effects - Protocol C92-058

Dose	C _{max} (ng/mL)	t _{max} (h)	AUC _{0-∞} (ng·h/mL)	t _{1/2} (h)	CL _D (mL/min)	V _D (L)	F (%) Geo mean (Min - max)	
Alosetron 2 mg PO tablet	Young Males:	9.4	1.00	24.8	1.4	—	—	0.50
	Elderly Males:	9.8	0.75	26.5	1.6	—	—	0.51
	Young Females:	12.0	1.00	30.5	1.4	—	—	0.49
	Elderly Females:	17.2	0.75	47.1	1.7	—	—	0.63
Alosetron 2 mg IV solution	Young Males:	40.2	0.25	49.4	1.5	675	82	—
	Elderly Males:	49.8	0.25	52.2	1.7	639	83	—
	Young Females:	44.6	0.25	61.3	1.6	544	65	—
	Elderly Females:	62.9	0.25	74.1	1.8	450	62	—

All values of C_{max}, AUC, t_{1/2}, CL_D, V_D, A_s, and F are shown as geometric LS mean (range) or arithmetic mean ± standard deviation. T_{max} is shown as median (range)

However, when parameters are normalized many of the differences disappear (See Table 57). Yet, there is still a clear decrease in clearance with an associated increase in bioavailability in elderly females. Part of the difference in clearance in elderly females may be due to a lack of tobacco use and differences in 3A4 mediated elimination due to sex hormones. In spite of a lack of difference in volume of distribution with normalization, there is still a trend for decreasing volume with age and with sex. This could be due to differences in body composition with aging and gender. As mentioned previously this could indicate alosetron distribution and binding to skeletal muscle.

Table 57 Normalized Alosetron Pharmacokinetic Metrics with Age - Protocol C92-058

	Age ^a	Cl ^a (ml/min/m ²)	Vd ^a (L/kg)	Smokers	Smokers >1/2 ppd
Young Males	27.4 ± 5.65 20.6 19 - 39	363.5 ± 83.5 23	1.2 ± 0.3 24	4	2
Young Females	29.67 ± 7.36 24.83 19 - 39	342.7 ± 139.8 40.8	1.1 ± 0.3 25.9	6	5
Elderly Males	69.83 ± 3.27 4.68 66 - 78	354.1 ± 79.6 22.5	1.1 ± 0.2 14.6	3	1
Elderly Females	70.25 ± 3.36 4.78 66 - 75	269.4 ± 71.5 27	1.0 ± 0.2 25	2	1

^a Mean ± SD, CV and range

4. Race & Ethnicity

Ethnicity has not been shown to influence alosetron pharmacokinetics. However, this has not been sufficiently studied to draw any firm conclusions. Due to the large variability in alosetron pharmacokinetics it may be difficult to show an effect of ethnicity. Differences in metabolism however may be present. N-desmethyl-alosetron accounted for up to 30% of the dose in Japanese, but was not detected in the two caucasian males studied.

Nine of thirty subjects in protocol S3BB1011 were Hispanic. This was a multiple dose study to assess the time invariance of alosetron pharmacokinetics in male and female volunteers. Subjects were administered 57 doses of alosetron 1 mg orally bid for 28 ½ days. By inspection of the data there does not appear to be a relationship to hispanic ethnicity, (there were 8 hispanics out of 15 females and 1 hispanic out of 15 males).

In addition, the population pharmacokinetic study found no suggestion that race influences the clearance. This is not surprising due to the small numbers of non-white subjects (n = 12).

N-desmethyl-alosetron (GR87620) was not detected in the mass balance study. However, there were measurable plasma concentrations in all three Japanese studies with mean concentrations in males after a 1 mg dose in the range of 2 ng/ml. In the Japanese food effect study it accounted for 6.69 ± 4.41 % of a 1 mg dose under fasted conditions and 9.15 ± 9.07 % of the dose when administered with food. In one subject it accounted for as much as 30.54% of the dose.

5. Renal Insufficiency

The effects of renal insufficiency on alosetron pharmacokinetics is unclear and additional study is needed to clarify there is an effect of renal disease on alosetron pharmacokinetics, and if dosing needs to be adjusted in renal insufficiency.

The effect of renal insufficiency was examined in protocol S3BB1010. This was a parallel design 1 mg single oral dose study in male and female volunteers with varying degrees of renal function. Subjects were categorized as healthy (Clcr > 60 ml/min), moderately (Clcr 30 - 59 ml/min), or severely renally impaired (Clcr <30 ml/min but not requiring dialysis), n = 8 per group. Subjects with moderate renal insufficiency were matched for age (± 5 years)², weight (± 5 kg), and sex to healthy controls. Subject demographics are shown in Table 58. All subjects claimed to smoke less than 10 cigarettes per day.

The sample size was calculated to provide an 80% power for a one-sided α of 0.05 to detect a 97% increase in AUC_∞. Due to the dose dependent increase in constipation, this might be larger than we desire.

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² One subject in the moderately impaired group was not matched due to a typographical error, and was 33 years older than the subject that he/she was paired to in the control group.

Table 58 Subject Demographics in Alosetron Renal Impairment Study

	Controls	Moderate Renal Impairment	Severe Renal Impairment
	Clcr > 60 ml/min	Clcr 30 - 59 ml/min	Clcr < 30 ml/min
Sex			
Male	6	6	3
Female	2	2	5
Race			
White	8	5	8
Black	0	3	0
Age (years)			
Mean ± SD	42.6 ± 16.2	47.5 ± 14.8	68.3 ± 12.5
(Range)	23 - 73	27 - 75	45 - 84
Height (cm)			
Mean ± SD	168.6 ± 6.8	165.8 ± 7.8	168.5 ± 9.1
Weight (kg)			
Mean ± SD	67 ± 7.75	69.05 ± 8.25	74.55 ± 9.69
(Range)	59 - 79	58 - 80	59.8 - 89.6

The conclusion of no effect of renal insufficiency is based on an examination of the geometric means of pharmacokinetic parameters (See Table 59). In addition, median concentration vs. time profiles for the healthy and moderate groups were virtually superimposable. It should be noted that examination of median values is only useful with normally distributed data, which is not true for alosetron pharmacokinetic parameters.

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