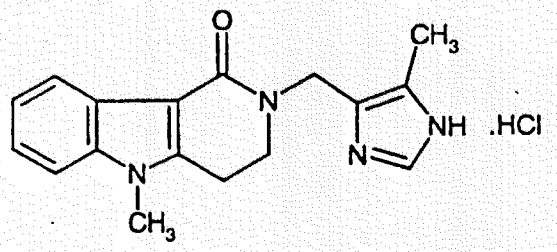
III. CHEMISTRY

A. Structure

Alosetron has two major ring systems, an indole ring and an imidazole ring. As will be discussed later these ring systems allow prediction of expected metabolic pathways as well as metabolic induction and inhibition.



Indole Imidazole

B. Molecular Formula

$C_{17}H_{18}N_4O \bullet HCl$

C. Molecular Weight

330.8

D. Isomerism and Stereoisomerism

Alosetron has no asymmetric centers and no potential for stereoisomerism.

E. pKa, Partition Coefficient (Log P), and pH

pKa 6.95
Log P 1.89
pH 3.3 (saturated solution)

F. Solid State Forms

According to the chemistry review, 'There is no evidence for polymorphism, hydration or solvation.'

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G. Solubility

Table 1 Solubility of Alosetron HCl at 21 °C

Solvent	Solubility (mg/ml)	Final Solution pH
Distilled Water	61	3.3
Saline	28	3.8
0.1 M HCl	42	1.1
pH 2 Chloride Buffer	50	1.8
0.01 M NaOH	13	4.5
pH 4 Phosphate Buffer	5	3.8
pH 6 Phosphate Buffer	0.3	5.9
pH 8 Phosphate Buffer	Less than 0.1	8.0
pH 10 Phosphate Buffer	Less than 0.1	10.3
0.1 M NaOH	Less than 0.1	12.5

H. Tablet Formulations

1. Composition

As shown in Table 2 and Table 3 the composition of the various table: strengths used in the pharmacokinetic studies do not differ markedly from the to-be-marketed formulation, (formulation E). The major differences in the various formulations are:

a) Some formulations used a mg total tablet weight, whereas the to-be-marketed formulation (Formulation E) used a mg compression weight. Excipients were scaled proportionately

b) Within the mg or mg tablet weight groups, the primary difference between different strength tablets was the amount of active ingredient and the amount of lactose

Table 2 Composition of Tablet Formulations used in Pharmacokinetic Studies

		H	F	C	D	E
	Ingredient (mg/tablet)	4mg Tablet	2mg Tablet	1mg Tablet[a]	1mg Tablet	1mg Tablet[b]
Tablet Core	Alosetron hydrochloride[c]	4.496	2.248	1.124	1.124	1.124
	Lactose (anhydrous) NF					
	Microcrystalline Cellulose NF					
	Pregelatinized Starch NF					
	Magnesium Stearate NF					
	Target compression weight					
Film Coat						

a
b Market-image formulation (identical to commercial image except not engraved)
c Equivalent to 4mg, 2mg, 1mg, 1mg, and 1mg alosetron base, respectively, assuming 100% purity
d

The composition of the tablets used in the Phase II dose ranging studies were direct dose multiples of the to be marketed 1 mg formulation.

Table 3 Composition of Tablet Formulations used in Phase II Dose Ranging Studies

		A	B	D[c]	G	I	J
	Ingredient (mg/tablet)	0.05mg Tablet	0.25mg Tablet	1mg Tablet	2mg Tablet	4mg Tablet	8mg Tablet
Tablet Core	Alosetron hydrochloride[a]	0.056	0.281	1.124	2.248	4.496	8.992
	Lactose (anhydrous) NF						
	Microcrystalline Cellulose NF						
	Pregelatinized Starch NF						
	Magnesium Stearate BP/NF						
	Target compression weight						
Film Coat							

a Equivalent nominal tablet strength in mg of alosetron base, assuming 100% purity
b
c Similar to commercial image (E - See Table 2) except for pigment in film coat and engraving

2. Formulations Used in Pharmacokinetic Studies

The total weight tablet formulation (Formulation C) was only used in a single multiple dose pharmacokinetic study. All other 1 mg formulations including the to-be-marketed formulation only differ with respect to the colorant used in the film coating.

Table 4 List of Pharmacokinetic Studies and Formulations Used

Protocol	Report	Title	Formulation	Strength	Tablet Code
GHP:89:44	GPK/91/005	A Pilot Study to Investigate the Absolute Bioavailability of GR68755 from an Aqueous Solution	Soln		—
GHP:90:13	GPK/91/007	A Study to Investigate the Absolute Bioavailability of GR68755	Soln Tab	— 4 mg	— H
GHP:89:38	GMH/90/004	Initial Safety and Tolerability Study with Oral Doses of GR68755 in Human Volunteers	Soln Soln	0.1 1.0	—
GHP:90:21	GMH/91/002	A Study to Investigate the Disposition of 14C-GR68755 in Man Following Single Oral Dose Administration as the Hydrochloride Salt at a Nominal Dose of 4 mg Base	Soln		—
C92-087	GCP/92/087	A Study to Evaluate an Improved Assay Methodology for Alosetron (GR68755 base) in Human Urine and Saliva, after Administration of a Single 1 mg PO Dose to Healthy Male Subjects	Tab	1 mg	D
AS-01	JJD/94/001	Phase I Single Dose Study in Healthy Volunteers	Tab	1 mg	D
S3B-101	UCP/91/014	A Placebo-controlled, Ascending-dose, Safety and Pharmacokinetic Evaluation of and Oral B.I.D. Dose Regimen of GR68755-C in Healthy, Adult Male Volunteers	Tab	1 mg 4 mg	C H
GPK:90:02	GPK/90/008	The Pharmacokinetics, Safety and Tolerability of GR68755 following 9½ Days Twice Daily Oral Dosing with 4 mg in Healthy Volunteers	Tab	4 mg	H
S3BB1011	NN1998/000 03/00	The Pharmacokinetics of Alosetron 1mg BID Oral Administration for 29 Days in Healthy Subjects	Tab	1 mg	E
AS-02	JJD/94/002	Alosetron (GR68755) Phase I Multiple Dose Study in Healthy Volunteers	Tab	1 mg	D
S3B-102	UCP/92/019	A Placebo-controlled, Double-blind, Safety and Tolerability Evaluation of GR68755C in Healthy, Adult and Elderly Volunteers	Tab	2 mg	F

Protocol	Report	Title	Formulation	Strength	Tablet Code
GPK:90:01	GPK/90/006	Comparative Pharmacokinetic Study of GR68755C in the Young and Elderly	Tab	4 mg	H
C92-058	GCP/92/058	A Investigation of the Gender Differences in the Pharmacokinetics of GR68755C	Tab	2 mg	F
S3BB1010	PM1999/00001/00	A Study to Compare the Pharmacokinetics of, and Tolerability to, a Single, Oral, 1mg Dose of Alosetron in Healthy Volunteers and Patients with Renal Impairment nor Requiring Dialysis	Tab	1 mg	E
S3BA2001	GM1997/00189/00	A 12 Week Dose-ranging, Double-blind, Placebo-controlled Study of Alosetron (GR68755) in Subjects with Irritable Bowel Syndrome: Population Pharmacokinetic Analysis	Tab	1 mg 2 mg 4 mg 8 mg	D G I J
S3BB1004	NN1996/00003/00	A study to Determine the Effects of Food on the Pharmacokinetics of Oral Alosetron in Healthy Volunteers	Tab	4 mg	I
A.S-03	JJD/94/003	Alosetron (GR98755) Phase I Study to Evaluate the Effect of Food	Tab	1 mg	D
S3B-201	UCP/93/009	A Randomized, Double-blind, Placebo-controlled, Crossover Evaluation of the Effect of GR68755 on Plasma Levels of Haloperidol in Patients with a Diagnosis of Schizophrenia	Tab	1 mg	D
S3BA1001	NN1999/00011/00	A Randomized, Placebo-controlled, Repeat-dose, Double-blind, Two-period, Crossover Study to Compare ECG Changes and Pharmacokinetics of Cisapride Following 4 days of Dosing with Cisapride 20mg QID with Placebo and with Alosetron 1 mg BID in Healthy Male and Female Volunteers	Tab	1 mg	E
S3BA1002	NN1999/00032/00	An Open-label, Non-randomized, Two-period, Crossover, Drug-drug Interaction Study to Compare the Pharmacokinetics of Min-Ovral® (150 µg Levonorgestrel and 30 µg Ethinyl Estradiol) in Healthy Female Subjects when Administered Alone for 21 days, and following Co-administration of Alosetron 1 mg BID Orally for 21 days	Tab	1mg	E
S3BA1004	NN1999/00025/00	A Randomized Double-blind, Placebo-controlled, Repeat-dose, Two-period, Crossover Study to Evaluate the Effect of Alosetron (1mg PO BID) on Theophylline (Theo-Dur® 200 mg PO BID) Pharmacokinetics in Healthy Females Volunteers	Tab	1 mg	E
GHP:89:23	GMH/89/024	Initial Safety and Tolerability Study with Intravenous GR68755 in Human Volunteers	Soln	0.01 0.1 1.0	—
GHP:90:05	GMH/90/012	To Investigate the Possible Cardiovascular Effects of GR68755 in a Healthy Volunteer	Soln	1 mg/ml	—
GHP:90:16	GMH/91/007	A Study to Investigate the Effect of Intravenous GR68755 on Intradermal 5-Hydroxytryptamine Induced Flare-Response in Volunteers	Soln	0.1 0.25	—
GHP:90:27	GMH/91/015	A Study to Investigate the Duration of Effect of Oral GR68755 on Intradermal 5-HT Induced Flare-Response in Volunteers	Soln	0.01 0.25	—
S3BB1007	GM1997/00311/00	A Study to Investigate the Effect of Alosetron 4 mg, BID, for 7 Days on 24-hour Colonic Motility in Healthy Volunteers and Patients with Irritable Bowel Syndrome (IBS)	Tab	4 mg	I

I. Dissolution

Table 5 Proposed Dissolution Method and Specification for Lotronex® (alosetron) 1 mg Tablets

Apparatus
Media
Volume
Speed of Rotation
Sampling Time(s)
Analytical Method
Proposed Specification

Thirty minute single point dissolution data was presented for 27 batches.

It's claimed that two of the 4 mg batches complied at the level of S2, whereas all other batches comply at the level of S1. However, this doesn't make sense since the lowest end of any range for percent dissolved for these two batches is 98%. Consequently, an explanation was requested. The sponsor subsequently provided the data in Table 6.

Table 6 Alosetron 1 mg Tablet Dissolution Data

Site	Lot Number	Batch Size (Kg)	Purpose	Percent Released @ 10 minutes		Percent Released @ 20 minutes		Percent Released @ 30 minutes	
				Mean	Range	Mean	Range	Mean	Range
?	F97/034B	150	Used in Clinical Studies	94		98		98	
	WNT521001	150	Primary NDA Stability Batch	88		97		98	
	WNT521002	150	Primary NDA Stability Batch	89		96		97	
	WNT521004	150	Primary NDA Stability Batch	88		98		100	
	WNT620001	?	Site Specific Stability Batch	83		94		97	
	WNT522003	?	Process Qualification Batch	87		95		96	
	WNT522004	?	Process Qualification Batch	85		96		98	
	WNT522005	?	Process Qualification Batch	80		94		96	
	9ZM0590	400	Suppl. Site Specific Batch	82		87		90	
	9ZM0873	400	Suppl. Site Specific Batch	86		91		93	

As can be seen, there is a decrease in percent released going from a clinical trial batch, through various batches produced at with the lowest release with produced batches.

Previous site specific batches produced at had even worse release characteristics. This was found to be at least partially due to an increase in tablet hardness, consequently the compression pressure was reduced and the above data was obtained. Other possible factors that have been suggested to effect dissolution at the site include lactose source, and differences in the thickness of the film coating.

Based upon the above data, a specification of Q = would be achieved at the S1 or S2 levels in the same batches whether determined at 20 or 30 minutes. Since, the 20 minute time point would likely have greater discriminatory power if the process were to become out of control there is no good justification for a 30 minute time point.

In addition, since the drug is highly soluble in water (61 mg /ml) but much less so in basic media (<0.1 mg/ml), additional media should have been examined to see if there is greater discriminatory power.

Although dissolution is rapid, the significance of the slower dissolution compared to the clinical trial batches is unclear to this reviewer. A consult and possibly additional data from the sponsor will need to be obtained, before the dissolution specifications can be set.

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J. *Bioanalytic Assay Validation*

Numerous different assays were used throughout the development program (See Table 7 and Table 8). This reviewer has examined each validation report in depth and finds all assays sensitive and specific; and to have acceptable levels of bias and precision.

Since, each assay validation critique takes several pages, they will not be included in this review in order to save space. Specific assay related issues are addressed with individual study critiques.

1. Alosetron Assays

The degree of sensitivity, bias and precision tends to be excellent for all of the alosetron assays.

Alosetron in human serum is stable through 3 freeze/thaw cycles, and is stable for 72 hours at room temperature. It is also stable at - 20 °C for 26 months at - 30 °C for 41 months.

Table 7 Alosetron Assays

Method Validation Number	Type of Assay	Matrix	Title
WBP/90/036		Plasma	An Analytical Procedure with Validation for the Determination of GR 68755 Base in Human Plasma (2-50 ng/ml) by
UCP/90/037		Serum	Determination of GR68755 in Human Serum: Method and Validation
UCP/92/014		Serum	Determination of GR68755 in Human Serum: Method and Validation (Improved)
WBP/92/036		Plasma	Validation of a Method (AM/WBP/1041/01) for the Determination of GR68755 in Human Plasma
UCP/93/008		Plasma	Method and Validation for the Robotic Assay of GR68755 in Human Plasma
RD1996/00116/00		Serum	Determination of GR68755 (Alosetron) in Human Serum by and Method and Validation (96/BA/0002)
RD1999/00659/00		Serum	Method Validation of a Low Range Assay for Alosetron (GR68755) in Human Serum by and

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2. Assays of Other Compounds

Validation reports were also provided for seven assays measuring 18 different compounds in two different matrices (See Table 8).

Table 8 Assays for Drugs Used for *In Vivo* Drug Interaction Studies

Method Validation Number	Title
WD1998/00383/00	The Validation of a Method for the Determination of Caffeine, Dapsone, Chlorzoxazone and their Respective Metabolites, Paraxanthine, Monoacetyldapsone and 6-Hydroxy- Chlorzoxazone in Human Plasma
WD1998/00382/00	The Validation of a Methods and for the Determination of Dapsone, Racemic Mephenytoin and their Respective Metabolites, Dapsone Hydroxylamine and 4-Hydroxymephenytoin in Human Urine
RD1999/00356/00	Validation of an for the Determination of Cisapride in Human Plasma (EDTA)
RD1999/00881/00	Validation of an Method for the Determination of Cisapride and Norcisapride in Human Urine (contract study:
RD1999/00355/00	Method Analysis of 17α-Ethinyl Estradiol and Norgestrel in Human Plasma
RD1999/00973/00	Analysis of Theophylline in Caffeine-free Human Plasma (contract study:
RD1999/00988/00	Analysis of Theophylline and Metabolites in Human Urine (contract study:

Cisapride - Assay RD1999/00356/00 - There is a high level of positive bias and precision at lower level of quantitation, but still within acceptable limits.

Cisapride - Assay RD1999/00881/00 - The mobile phase was modified in the middle of the validation. Cisapride is unstable on the autosampler at 22 °C for 49.5 hours.

Norcisapride - Assay RD1999/00881/00 - The mobile phase was modified in the middle of the validation. There were interfering substances in 2 of 10 urine sources. Bias and precision data indicate the lower limit of quantitation should be raised to ng/ml from ng/ml. Norcisapride was unstable at -22 °C for 42 days and on the autosampler at 22 °C for 49.5 hours.

Theophylline and Metabolites - Assay RD1999/00988/00 - Caffeine an interfering substance can be found in a variety of sources including: prescription medications, OTC Medications, herbal medications, dietary substances and illicit drugs. Consequently, obtaining a clean blank urine from each subject is important. For M2 (1-methyluric acid) there's a large bias and imprecision at the lower end of the standard range but it falls just within recommended acceptance criteria (± 20%).

Assays WD1998/00382/00 and WD1998/00383/00 - Only intra-assay variability was determined. Interassay variation was not determined for any compound.

Mephenytoin, 4-OH-Mephenytoin and Dapsone Hydroxylamine - Assay WD1998/00382/00 - Data points were excluded. It's impossible to tell how this would effect the assay validation data.

Monoacetyl-Dapsone - Assay WD1998/00382/00 - There was a large negative bias at the lower limit of the assay range and a large positive bias at the upper limit of the assay range. This combined with exclusion of data from both of these points suggests the assay may not be valid, and may have structural model misspecification.

IV. PHARMACOKINETICS / PHARMACODYNAMICS

A. Linearity with Dose

1. Oral Administration

Alosetron appears to exhibit linear kinetics up through doses of at least 8 mg when orally administered as tablets, 4 mg when administered as an oral solution, and 4 mg when administered intravenously. It's questionable if there's nonlinearity or not at oral doses of 16 mg. Concentrations at 16 mg are several thousand fold less than concentrations normally required to see saturable enzyme kinetics (See APPENDIX 1). There could be auto-inhibition at these concentrations but alosetron or it's metabolites would have to be several fold more potent as an inhibitor of P450's than ketoconazole, unless there was auto-inhibition of intestinal first pass.

There were two single rising oral dose studies to assess the pharmacokinetic linearity of alosetron, studies GHP:89:38 and AS-01. Both studies were performed in young healthy males utilizing alosetron solutions. Study GHP:89:38 administered alosetron in grapefruit juice and study AS-01 was performed in a Japanese population. Dose linearity was also examined study S3B-101, a multiple rising dose study utilizing 1 and 4 mg tablets and in the population pharmacokinetic analysis.

Study GHP:89:38

Study GHP:89:38 showed that alosetron concentrations increased in a generally proportional manner with increasing dose, up to 16 mg with similar half-lives across the range of doses.

Plots of median AUC_∞ vs. dose suggest possible nonlinearity (not shown). This apparent nonlinearity may be spurious and due to a number of factors. Including the small number of subjects at the 1, 2, and 16 mg doses, and the larger percentage of the AUC that is extrapolated at the lowest doses. Mean values of Cmax and AUC_∞ shown in Table 9 suggest that this apparent nonlinearity might be due to simple variability in the data. Inspection of individual data and comparing the concentrations and AUC's across two dose levels in individual subjects does not provide a clear resolution of the issue. The more than proportionate higher peak concentrations at the higher doses may be partly due to more rapid absorption. Co-administration with grapefruit juice may result in a more than proportionate increase in AUC and Cmax with dose and the shorter Tmax, if sufficient drug is metabolized via CYP3A4 or if pGP slows absorption. Such an effect would be more pronounced with higher concentrations. Alternatively, concentrations may become high enough that autoinhibition by alosetron on metabolites become apparent.

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Table 9 Pharmacokinetic Metrics After a Single Rising Oral Dose of Alosetron Solution in Grapefruit Juice

Dose (mg)	n	Cmax (ng/ml)	Tmax (hr)	t1/2 (hours)	$AUC_{0-\infty}$	% AUC extrapolated
1	3	4.04 ± 1.46	1 ± 0.0	1.7 [a]	15 [a]	36.06 [a]
2	5	6.66 ± 5.32	1.5 ± 1	1.4 ± 0.14 [b]	25.8 ± 4.53 [b]	22.27 ± 0.13 [b]
4	5	20.84 ± 8.49	1.8 ± 0.84	1.72 ± 0.19	75.46 ± 31.25	7.4 ± 3.83
8	6	58.37± 19.5	1.5 ± 0.55	1.67 ± 0.4	202.5 ± 93.45	4.26 ± 3.18
16	3	106.9 ± 51.55	0.83 ± 0.28	1.93 ± 0.78	400.93 ± 254.78	5.41 ± 4.94

All values are reported as mean ± SD (range)
a n = 1
b n = 2
* reported as such, must consider typographical error

Study S3B-101

This was a randomized, double-blind, parallel, placebo controlled, multiple, rising oral dose study in 48 healthy male volunteers 19 - 40 years of age. Doses ranged from 1 to 16 mg bid for 3½ days. Formulations used included a 1 mg and a 4 mg tablet.

The results showed dose-proportionality up to 8mg, but a greater than proportional increase in plasma concentrations at the 16mg dose. (See Table 10).

Concentration vs. time profiles from many subjects showed a double peak, usually within the first two hours or so. This was the only study that this was seen in and since this was the only study that used formulation C, this may be a formulation effect.

Table 10 Dose Normalized Pharmacokinetic Metrics after the First Dose - Protocol S3B-101

Dose (mg)	*Dose Normalized* Cmax (ng/ml)	Tmax (hours)	*Dose Normalized* AUC (ng*hr/ml)	Half-Life (hours)	Mean Residence Time (hours)
1	3.6 ± 1.8	1.5 ± 0.45	9.9 ± 4.8	1.43 ± 0.42	3.16 ± 1.07
4	7.2 ± 3.0	1.17 ± 0.28	21.1 ± 9.5	1.30 ± 0.19	2.64 ± 0.23
8	7.6 ± 2.3	1.19 ± 0.33	25.2 ± 11.4	1.42 ± 0.24	2.95 ± 0.30
16	9.1 ± 2.0	1.50 ± 0.60	37.7 ± 13.1	1.73 ± 0.38	3.41 ± 0.59

Values are mean ± SD

Protocol AS-01 (Japan)

In the Japanese study AS-01, alosetron was administered as a solution. Geometric mean Cmax and AUC increased roughly linearly with dose. Due to infrequent early sampling (i.e. hourly sampling until 4 hours) the Cmax, tmax, and AUC are less accurate than they could be. Visual inspection of the plots of the mean concentrations vs. time and individual subject concentration vs. time data supports a conclusion of linear pharmacokinetics up to 4 mg po. The percent of the dose eliminated in the urine as unchanged parent drug (Ae) is relatively consistent regardless of dose. This also supports a conclusion of linear kinetics (See Table 11).

Table 11 Pharmacokinetic Metrics After a Single Rising Oral Dose in Japanese Males

Dose	n	C_{max} (ng/mL)	t_{max} (h)	AUC_∞ (ng•h/mL)	$t_{½}$ (h)	A_e (% of dose)
0.5mg	3	2.22 ± 0.42	1.12 ± 0.27	6.33 ± 2.07	1.51 ± 0.20	7.47 ± 2.19
1mg	6	5.08 ± 1.75	1.43 ± 0.43	15.72 ± 5.55	1.33 ± 0.20	5.61 ± 2.06
2mg	6	11.38 ± 4.21	1.04 ± 0.20	36.62 ± 16.38	1.52 ± 0.26	4.91 ± 2.39
4mg	6	29.11 ± 11.07	1.39 ± 0.36	93.10 ± 39.16	1.42 ± 0.24	9.07 ± 3.05

Values are mean ± SD

2. Intravenous Administration

In addition to the oral dose studies, there were two studies with intravenous dosing that give supportive evidence of dose linearity up through doses of 4 mg IV.

Study GHP:89:23

Study GHP:89:23 was a single rising intravenous dose study that determined pharmacokinetic metrics and parameters after a 4 mg IV dose in 3 male subjects. Doses were administered as an ascending series of short, intermittent infusions (15 minutes every 2 hours), with the 10 mg nominal dose actually a cumulative dose (i.e. 1 + 2 + 3 + 4 mg = 10 mg).

Cmax and AUC after the 4 mg dose were corrected for superpositioning from the previous doses. The first blood sample was taken at 20 minutes, i.e. 5 minutes after a 15 minute infusion. The delay in sampling results in an underestimation of Cmax and AUC. The sponsor estimates Cmax is off by 20% and Vc can't be estimated. Other parameter estimates are also in error.

The resulting pharmacokinetic data are difficult to interpret. However, the observed plasma concentrations and AUC are similar to those seen in the po study (See Table 11 and Table 12).

Table 12 Pharmacokinetic Metrics After a 4 mg IV Dose - Protocol GHP:89:23

C_{max} (ng/mL)	AUC_∞ (ng•h/mL)	$t_{½}$ (h)	CL_p (mL/min)	Vdβ (L)
70.3	111.2	1.7	*600*	*600*

All values are shown as median (range)

It should be noted that Vdβ is reported. Consequently, Vdβ cannot be compared to the steady state volume of distribution estimates reported elsewhere, since its' calculation is dependent on clearance, whereas all true volumes are independent of clearance.

It was claimed that distribution was rapid. Inspection of concentration vs. time plots showed a rapid first phase over 5 - 10 minutes followed by a concentration plateau lasting until 0.5, 0.75 or 1.25 hrs post-dose respectively, followed by a second phase of concentration decline. The plateau might indicate enterohepatic recycling. Alternatively, since it consistently occurs at around 80 ng/ml, a concentration that tends to occur with doses greater than 8 mg, the possibility of a nonlinear process, possibly protein binding, or tissue binding, etc. needs to be considered. However, the low molar concentrations would argue against both of these mechanisms.

Study GHP:90:16

Study GHP:90:16 assessed the effect of various doses of alosetron on the flare response to intradermal 5-HT in males. Plasma concentrations were determined before dosing of alosetron and at 10, and 35 minutes after a 10 minute intravenous infusion of alosetron 0.1, 1, or 4 mg. The protocol was not designed to assess pharmacokinetics, and the limited plasma sampling precludes an in depth assessment.

Geometric mean concentrations at 10 and 35 minutes post infusion are shown in Table 13. By inspection, geometric mean concentrations appear to increase linearly with dose at both time points.

Table 13 Dose Linearity with Intravenous Administration

Dose (mg) n = 12	Geometric Mean Concentration (ng/ml) (Range)	
	10 minutes	35 minutes
0.1	2.5	0.8
1	28.1	8.6
4	136.1	42.0

B. Multiple Dose Pharmacokinetics - Time Invariance

The pharmacokinetics of alosetron appear to be time invariant. However, data is somewhat conflicting with indications of both auto-induction and auto-inhibition. Both are possible, with various effects due to metabolites and different dosages. However, changes observed in the drug exposure over time are more likely spurious.

Consistent with the short half-life there is no accumulation. Based upon the wide therapeutic margin with alosetron and the relatively small changes in exposure over time, there does not appear to be any reason to titrate the dose over time.

Study S3B-101

Study S3B-101 was a randomized, double-blind, parallel, placebo controlled, multiple, rising oral dose study in 48 healthy male volunteers 19 - 40 years of age. Doses ranged from 1 to 16 mg bid for 3 ½ days.

Formulations used included a 1 mg tablet and a 4 mg tablet both of which had a total tablet weight of mg. This was the only study that used the mg total tablet weight formulations.

Pharmacokinetic metrics showed no accumulation with repeated dosing, consistent with the short half-life. The results also showed dose-proportionality up to 8 mg, but a greater than proportional increase in plasma concentrations at the 16 mg dose. Disproportionality may be due to either saturable clearance, possibly due to autoinhibition, or enhanced bioavailability on first pass (See Table 14).

Concentration vs. time profiles from many subjects showed a double peak, usually within the first two hours or so. The reason for the double peak in this study, but not in other studies is not clear, but might indicate a formulation effect.

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Table 14 Multiple Dose Pharmacokinetic Metrics - 3.5 days

Dose (mg)	*Dose Normalized* Cmax (ng/ml)		Tmax (hours)		*Dose Normalized* AUC[a] (ng*hr/ml)		Half-Life (hours)		Mean Residence Time (hours)	
	Dose 1	Dose 7	Dose 1	Dose 7	Dose 1	Dose 7	Dose 1	Dose 7	Dose 1	Dose 7
1	3.6 ± 1.8	3.4 ± 1.4	1.5 ± 0.45	1.22 ± 0.40	9.9 ± 4.8	7.3 ± 3.3	1.43 ± 0.42	1.39 ± 0.37	3.16 ± 1.07	1.86 ± 0.22
4	7.2 ± 3.0	6.9 ± 2.5	1.17 ± 0.28	1.08 ± 0.28	21.1 ± 9.5	20.2 ± 8.5	1.30 ± 0.19	1.31 ± 0.18	2.64 ± 0.23	2.49 ± 0.30
8	7.6 ± 2.3	7.8 ± 2.0	1.19 ± 0.33	1.03 ± 0.23	25.2 ± 11.4	23.0 ± 8.1	1.42 ± 0.24	1.37 ± 0.19	2.95 ± 0.30	2.64 ± 0.29
16	9.1 ± 2.0	9.1 ± 2.7	1.50 ± 0.60	1.08 ± 0.40	37.7 ± 13.1	***32.1 ± 11.4****	1.73 ± 0.38	**1.48 ± 0.23***	3.41 ± 0.59	***2.95 ± 0.40****

a Dose 1 AUC_{∞} ; Dose 7 AUC_{12}
b $p < 0.05$ first vs. seventh dose.

Study AS-02 (Japan)

This was a multiple oral dose study in 6 healthy male Japanese volunteers, 26 - 30 years of age. The dose was 1 mg bid for 3½ days.

Data is only available from 3 to 5 time points per subject and only mean values are reported. Due to the small number of samples, firm conclusions cannot be reached. However, differences in Cmax, Tmax, and AUC's between the first and 13th doses are internally inconsistent (See Table 15), and is probably due to inaccurate estimates of pharmacokinetic metrics consequential to the limited sampling.

Table 15 Multiple Dose Pharmacokinetic Metrics in Japanese Males - 6.5 days

Dose (mg)	Cmax (ng/ml)		Tmax (hours)		AUC (ng*hr/ml)		Half-Life (hours)	
	Dose 1	Dose 13	Dose 1	Dose 13	Dose 1	Dose 13	Dose 1	Dose 13
1	3.36	3.04	1.94	1.64	11.85	13.64	0.96	1.32

Study GPK:90:02

Study GPK:90:02 was a randomized, double-blind, placebo controlled study that administered alosetron 4mg po bid for 9 ½ days to 16 healthy young male volunteers, 19 to 30 years of age.

Based upon mean data there is a decrease in exposure on day 10 (9.5 days of dosing; dose 19) compared to the first dose (See Table 16). However, when data from individual subjects are examined it's hard to tell if there's a consistent pattern. In addition, there was a mean assay bias of approximately 10–15 % with a large CV near 20% at the lower end of the assay range (i.e. < 5 ng/ml). A number of samples were in this range and could result in a bias and erroneous conclusions. However, many profiles had low concentrations throughout the dosage interval, thus it's difficult to tell if there was any spurious differences between dose 19 and dose 1 samples due to the assay bias.

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