height, weight, childbearing potential, menstruation, or use of estrogens between study groups. The study was carried out at 113 U.S. centers, from 15 September 1997 to 14 October 1998.

Disposition of Patients Randomized into Study S3BA3002

	Placebo BID	A 1 mg BID	Total
Patients randomized men/women	323 0/323	324 0/324	647 0/647
Sub-type of IBS diarrheal alternating constipative	 221 (68.4%) 95 (29.4%) 7 (2.2%)	 237 (73.1%) 85 (26.2%) 2 (0.6%)	 458 (70.8%) 180 (27.8%) 9 (1.4%)
Withdrawn prematurely	**-53 (16.4%)**	**-79 (24.4%)**	**-132 (20.4%)**
adverse event	**-14 (4.3%)**	**-49 (15.1%)**	**-63 (9.7%)**
lack of efficacy	-14 (4.3%)	-6 (1.9%)	-20 (3.1%)
withdrew consent	-8 (2.5%)	-10 (3.1%)	-18 (2.8%)
lost to follow-up	-11 (3.4%)	-11 (3.4%)	-22 (3.4%)
other	-4 (1.2%)	-2 (0.6%)	-6 (0.9%)
protocol violation	2 (0.6%)	1 (0.3%)	1 (0.2%)
pregnancy	1 (0.3%)	0	1 (0.2%)
death	0	0	0
Completed study	270 (83.6%)	245 (75.6%)	515 (79.6%)

Note: A, alosetron; BID, twice daily, before breakfast and supper.

Comment: It is noteworthy again that there were significantly ($p < 0.02$) more patients who were withdrawn prematurely, and particularly ($p < 0.0001$) because of adverse events, but in this study no significant difference was seen in the proportions who withdrew consent or were lost to follow-up. The dropout rate of 20% was as predicted in the estimated study size calculation, and consistent with the rates of 24% in S3BA2001 and 23% in S3BA3001. It is noted that a few patients with constipation-predominant IBS again did slip through the screening process, 9 of the 649 randomized patients (1.4%), despite the exclusion of disproportionately larger fractions of constipation-prone and alternately types of IBS in the group of 816 excluded during screening (9% constipation-predominant, 40% alternating IBS), as listed in Table S-6.9, Volume 167, page 146. Significantly ($p < 0.015$) fewer patients on alosetron completed the study.

When the effect of the preceding perceived type of IBS was considered, comparisons of withdrawals from study of the three subsets showed (Volume 167, pages 71-2) again that there were too few patients in the constipation-predominant group to draw any conclusions. It was also apparent that withdrawals because of adverse events were significantly more frequent in the group treated with alosetron in both the diarrhea-prone ($p < 0.005$) and the alternating type of IBS ($p < 0.0002$), which made the total number of withdrawal significant ($p < 0.0002$) in the alternating group.

Comment: The pattern of increased withdrawals for adverse events in alosetron-treated patients is a recurring theme in these studies, the principal adverse effect being constipation.

Withdrawals from Study S3BA3002, by IBS Sub-type

Reasons for Premature Withdrawal from Study	Placebo BID n = 323	Alosetron 1 mg BID n = 324	Total n = 647
Diarrhea-predominant IBS	221 (68.4%)	237 (73.1%)	458 (70.8%)
All withdrawals	42	52	94
Adverse events	**10**	**29**	**39**
Consent withdrawn	5	8	13
Lost to follow-up	9	9	18
Lack of efficacy	13	4	17
Protocol violation	2	0	2
Other reason	3	2	5
Alternating type of IBS	95 (29.4%)	85 (26.2%)	180 (27.8 %)
All withdrawals	**9**	**27**	**36**
Adverse events	**4**	**20**	**24**
Consent withdrawn	1	2	3
Lost to follow-up	2	2	4
Lack of efficacy	1	2	3
Protocol violation	0	1	1
Other reason	1	0	1
Constipation-predominant IBS	7 (2.2%)	2 (0.6%)	9 (1.4%)
All withdrawals	2	0	2
Adverse events	**0**	**0**	**0**
Consent withdrawn	2	0	2
Lost to follow-up	0	0	0
Lack of efficacy	0	0	0
Protocol violation	0	0	0
Other reason	0	0	0

Deaths and Serious Adverse Events

There were no deaths during the course of this study, including the screening period, drug administration and follow-up periods.

There were 16 adverse events classified as serious that occurred during or shortly after the 12-week treatment phase, 4 of which caused withdrawal* from the study. In addition, one patient, #8778, a 23-year-old Caucasian woman, became pregnant after 2 months on placebo, was withdrawn from the study, and then delivered a healthy baby boy at full term. Additional cases of serious AEs involving the biliary tract occurred in four patients during the screening period before initiation of study drug treatment, they were excluded, not randomized, and the biliary disorders in them could not be alosetron-related. Two patients #7956 and 8712 were randomized to placebo, and one, #6085, to alosetron, but never took any study drug and were not included in the safety analyses. Another, listed under serious AEs below, #6451, also withdrew before taking study drug. The safety set was therefore 321 placebo, 322 alosetron. Narrative summaries were provided by the applicant for the cases with SAEs in Volume 167, pages 115-23.

Serious Adverse Events, Study S3BA3002 *(Vol. 167, pages 101-2, 115-23)*

Dose, mg b.i.d.	*Patient no. & age/sex/race*	*Clinical Problem After __ time on study drug*	*Investigator's Opinion*
Placebo	6462 40Fc	Bleeding gastric ulcer @ 4 weeks	unrelated
	6585 31Fc	Endometriosis, obstruction @ 2 weeks*	unrelated
	6703 58Fb	Bleeding colon polypectomy site @ 4 weeks	unrelated
	7100 22Fc	Cephalexin gastritis @ 5 weeks	unrelated
	7388 49Fb	Colonic polypoid adenocarcinoma @ 1 day*	unrelated
	7932 68Fb	Back pain @ 4 weeks	unrelated
	7937 68F	Non-cardiac chest pain @ 12 weeks	unrelated
Alosetron 1 mg	6333 65Fc	Transient ischemic attack @ 11 weeks	unrelated
	6451 54F	Otitis, bronchitis @ Day 0	unrelated
	6641 53Fc	Upper respiratory infection @ 12 days*	unrelated
	7002 44Fc	Overdose, constipation @ 6 weeks	related
	7104 34Fc	Peptic ulcer pain @ 5 weeks	unrelated
	7195 48Fc	***Ischemic colitis @ 3 weeks****	unrelated *(!?)*
	7228 53Fb	Gastroenteritis flare @ 6 weeks	unrelated
	7809 28Fc	Osteoarthritis of ankle @ 11 weeks*	unrelated
	7900 49F	Bronchopneumonia @ 14 weeks (after study)	unrelated

Comment: There was no significant difference in the proportions of patients with SAEs between the two treatment groups: 7/323 (2.2 %) on placebo and 9/324 (2.3 %) on alosetron ($p > 0.4$). Copies of case reports as .pdf files were provided for only 5 (patients # 6585, 6641, 7195, 7388, and 7809) of the 16 patients who had SAEs listed above. Missing from the tape provided were the patients with SAEs who were not withdrawn because of the SAEs: patients #6333, 6451, 6462, 6703, 7002, 7100, 7104, 7228, 7900, 7932, and 7937.

From examination of the CRFs and narrative provided in the submission, one of the alosetron patients deserves further comment and discussion:

Patient #7195, a 48-year-old Caucasian woman, overweight (body mass index 34.5 kg/m^2) but not diabetic, not on estrogenic hormones, and with normal screening laboratory values and colonoscopy two years before randomization, called her local doctor on the 39th day of treatment with alosetron 1 mg b.i.d to report rectal bleeding and crampy abdominal pain. She did not respond to fluid and fiber treatment and was hospitalized for investigation at 3 a.m. the next day. Colitis was seen by colonoscopy the following day, thought to be due to ischemic colitis. There had been no prior suggestion of atherosclerotic vascular disease nor a precipitating circulatory event of hypotension or reduced cardiac output. Laboratory tests done a week later showed mild leukocytosis of 12,100/μL, ALT increased from 22 to 93 U/L, AST from 15 to 32 U/L, alkaline phosphatase from 58 to 156 U/L, without rise in serum bilirubin. These changes were attributed to the ischemic colitis episode, from symptoms of which she recovered within a week of the onset. Alosetron was not restarted, but the physician was reported to have felt the episode was not caused by study drug.

Comment: Despite the investigator's impression that this was not related to study drug, he was not aware of the similar cases that had occurred in studies S3BA2001 and S3BA3001. Ischemic colitis is generally thought of as a disease of the elderly, especially if predisposing vascular disease is present, or there was a precipitating episode of hypotension or low cardiac output.

This was not the case in patient #7195, nor was in patient #15687 of S3BA3001 or patient #2829 of S3BA2001. Drug-induced ischemic colitis has been reported in patients taking cocaine, anti-migraine drugs such as ergotamine or sumatriptan (a selective 5-HT$_1$-receptor antagonist), pseudoephedrine, estrogens, interferon, NSAIDs, neuroleptic or psychotropic agents, amphetamines, hyperosmotic laxatives, and occasionally others.

The lesion is generally benign and heals after removal of the offending agent, unless the colitis is of a gangrenous form, when the mortality is considerable and surgical intervention is required. It is now known that ischemic colitis is not restricted to elderly persons, that about a third of the cases occur in people under 50 years of age, and that a predisposing cause cannot always be identified. Procedures, especially aortic aneurysm repair, are often considered the precipitating cause, but even colonoscopy may trigger ischemic colitis. Clearly, vascular diseases such as systemic scleroderma, polyarteritis, atherosclerosis, Wegener's granulomatosis, Takayasu's disease, diabetes mellitus, and others may predispose. Acute pancreatitis and colon carcinoma have also been associated, as have disorders such as polycythemia and sickle cell disease. Even constipation has been reported to be associated with ischemic colitis.

With three cases, one in each of the three studies of approximately 300 patients on alosetron (S3BA2001: 1/286; S3BA3001: 1/316; S3BA3002: 1/322), it will be particularly important to be alert for additional cases in the long-term studies, in the safety update due to be submitted at the end of September 1999, and in future use of the drug. If the true incidence of this lesion is about 1/100, series of 300 patients would have 95% probability of showing at least one case.

Adverse events for which patients were withdrawn are listed in Volume 168, pages 145-7, and individual patients are listed in Table T-9.6, Volume 168, pages 147-61.

Adverse Events Causing Premature Withdrawal, S3BA3002

patients	Placebo BID n = 321	A 1 mg BID n = 322	Difference p-value
Withdrawn prematurely	53 (16.5%)	79 (24.5%)	**0.013**
Any adverse event	**14 (6.7%)**	**49 (15.2%)**	**< 0.0001**
Gastrointestinal event	**11 (3.4%)**	**43 (13.4%)**	**<<0.0001**
constipation	**1 (0.3%)**	**33 (10.2%)**	**<<0.0001**
all other gi events*	16 (5.0%)	18 (5.6%0	N.S.
Neurological event	1 (0.3%)	1 (0.3%)	N.S.
headache	0 (0.3%)	1 (0.3%)	N.S.
Cardiovascular event	0	0	N.S.
arrhythmias	0	0	N.S.
Malaise or fatigue	0 (0.6%)	1 (0.3%)	N.S.
All other system AEs*	3 (0.9%)	9 (2.8%)	N.S.

*Note: BID, twice daily; A, alosetron; *, some patients had more than one AE.*

Comment: Very significant differences were found between treatment groups in the relative numbers of patients withdrawn from study because of adverse events, due almost entirely to gastrointestinal events and particularly if not entirely to constipation (including the patient with ischemic colitis, who had complained of constipation two days after starting alosetron. These findings reconfirmed the findings made repeatedly before in the previous studies.

Adverse Events, General

Considering all AEs, regardless of whether they were serious or caused withdrawal (Table T-9.2, Volume 168, pages 134-41):

Patients Showing Adverse Events, Study S3BA3002

Patients Showing, During 12-week treatment	Placebo BID n = 321	A 1 mg BID N = 322	Difference p-value
Any adverse event	**210 (65.4%)**	**233 (73.4%)**	N.S.
Gastrointestinal event	**97 (30.2%)**	**156 (48.4%)**	**< 0.001**
Constipation	**10 (3.1%)**	**96 (29.8%)**	**<< 0.0001**
GI or Abdominal pain	23 (7.2%)	35 (10.9%)	N.S.
Nausea or vomiting	31 (9.7%)	28 (8.7%)	N.S.
Neurological event	62 (19.3%)	45 (14.0%)	N.S.
Headaches	34 (10.6%)	27(8.4%)	N.S.
Cardiovascular event	15 (4.7%)	8 (2.5%)	N.S.
Arrhythmias	1 (0.3%)	1 (0.3%)	N.S.
Malaise or fatigue	14 (4.4%)	1 (0.3%)	p < 0.001
Psychiatric event	9 (2.8%)	13 (4.2%)	N.S.
Musculoskeletal event	34 (10.6%)	26 (8.1%)	N.S.
Pain or discomfort	18 (5.6%)	10 (3.1%)	N.S.
Lower respiratory	35	33	N.S.
Endocrine/Metabolic	11	7	N.S.
Hepatobiliary/pancreatic	5	0	p = 0.0305
Blood & Lymphatic	3	1	N.S.
Urologic	12	7	N.S.
Reproductive	8	10	N.S.
Skin	15	12	N.S.
Eye	5	7	N.S.
Ear, Nose & Throat	58	66	N.S.
Non-Site Specific	45	20	p <0.001
Trauma/Overdose	15	13	N.S.

Note: BID, bis in die, twice daily; A, alosetron

Comment: The significant increase in adverse events in patients taking alosetron was due almost entirely to constipation, with no other adverse event showing any significant increase in alosetron-associated differences between treatment groups, although the placebo-treated group showed significantly more malaise/fatigue, hepatobiliary/pancreatic, and unspecific events . No significant reductions in these three clusters of symptoms were noted in the other studies, and they are not likely to be of any clinical consequence.

The applicant company, in planning these pivotal trials, had become fully aware of the problem of alosetron-induced constipation, particularly in patients with IBS not of the frankly diarrheal type. To reduce problems in the study patients, both protocols included provisions for study drug interruption for 4 days if the patient had no stools for 4 consecutive days; if stools returned at or within the 4 days of drug interruption, blinded treatment could resume after the 4-day interruption, but if not and the person had no stool for 8 days, the drug was to be stopped and the participant withdrawn from study because of constipation. This interruptive cycle could be

repeated if necessary, and study participation continued. When results off this procedure were analyzed (Tables T-9.7, D-9.7, A-9.7, Volume 168, pages 162-4):

Interruption of Study Drug Because of Constipation, Study S3BA3002

	Placebo BID	A 1 mg BID	Total	Difference p-value
All participants	*n = 323*	*n = 324*	*n = 647*	
at least 4 days without stool	10	43	53	*p < 0.0001*
1 cycle	7	30	37	
2 cycles	1	8	9	
>2 cycles	2	3	5	
8 days without stool	0	2	2	
Diarrhea-predominant	*n = 221*	*n = 237*	*n = 458*	
at least 4 days without stool	8	25	33	*p < 0.005*
1 cycle	5	19	24	
2 cycles	1	3	4	
>2 cycles	2	2	4	
8 days without stool	0	1	1	
Alternating type of IBS	*n = 95*	*n = 85*	*n = 180*	
at least 4 days without stool	2	18	20	*p < 0.0001*
1 cycle	2	11	13	
2 cycles	0	5	5	
>2 cycles	0	1	1	
8 days without stool	0	1	1	
Constipation-predominant	*n = 7*	*n = 2*	*n = 9*	
at least 4 days without stool	0	0	0	*N.S.*
1 cycle	0	0	0	
2 cycles	0	0	0	
>2 cycles	0	0	0	
8 days without stool	0	0	0	

Comment: Again, significantly greater proportions of patients on alosetron showed need for interruption of treatment because of constipation (no stool for 4 consecutive days) than did patients on placebo, overall and in the subgroups with either diarrhea-predominant or alternating type of IBS. There were too few patients with pre-randomization constipation-predominant IBS to draw any conclusions.

Because of the case of apparent alosetron-induced hepatotoxicity in which both serum aminotransferases and total bilirubin were elevated in patient #4595 (described in Study S3BA3001), search was made for any other cases in this study in which the combination occurred. Listing 28 (Volume 188, pages 305-9, 311-5) shows 5 patients on placebo (of 321) who had transient elevations of ALT, 3 of which were abnormal before the study, and only 1 was more than 3x the upper limit of the normal range (ULN). None were associated with serum total bilirubin elevations, although there were 2 other women who had mild bilirubin elevations without increased aminotransferases. Among the 322 who took alosetron, there were 3 who showed elevated ALT values, all appearing while on drug but none over 3x ULN nor associated with bilirubin rises. One woman on alosetron had a slight, transient, isolated bilirubin rise to more than 31 μM, the threshold level at 1.5x ULN.

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IV. Integrated Summary of Efficacy

Note: The clinical efficacy review of this submission was done by Dr. Robert Prizont (q.v.), of the Division of Gastrointestinal and Coagulation Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration HFD-180. The document should be consulted for details and critical interpretive commentary. This brief summary is taken from the applicant's submitted comments, and is not critically reviewed here.

The applicant has summarized the clinical effectiveness of alosetron tablets 1 mg twice daily in Volume 208. Following two 12-week, dose-ranging studies (S3BP12 and S3BA2001) in 238 men and 593 women (about 71%), done in Europe and North America, it was observed that the women but not the men showed a greater proportion of patients with decreased abdominal pain or discomfort, reduced urgency of stooling, increased percentage of pain-free days, and patients' impression of adequate relief. The range of doses explored in S3BP12 was 0.1, 0.5, and 2.0 mg of alosetron b.i.d., compared to placebo; in S3BA2001 the range of doses was 1, 2, 4, and 8 mg of alosetron b.i.d., compared to placebo. The best dose appeared to be 1 mg of alosetron taken twice daily. The drug was significantly more constipating than placebo, and led to significantly more voluntary discontinuation of treatment in both men and women taking alosetron than taking placebo.

Therefore, Phase III clinical trials (S3BA3001 and S3BA3002) were designed to be carried out in women only, seeking to avoid any who had the constipation-predominant form of IBS, using the patients' weekly retrospective assessment of the "adequate relief" of IBS pain/discomfort as the primary outcome measure. Results of surveys (Volume 208, pages 16-17) of women with non-constipation-predominant IBS from 678 patients from those trials revealed that the symptom that bothered them most were abdominal pain or discomfort (35-36%), urgency of bowel movements (26-28%), excessive numbers of bowel movements (22-23%), and bloating (12-14%). Relatively few were most-bothered by mucus in stools (1-2%). The survey results were interpreted to indicate that patients most desired a therapeutic agent that would reduce or relieve abdominal pain or discomfort associated with stool frequency and urgency.

Data on daily pain and stool scores were collected each day by telephone calls from participating patients, according to a standardized question-and-scoring system, using a special software program developed and implemented by a consulting contract research organization [redacted] for Glaxo Wellcome. Patients were asked to report each day by touch-tone telephone entry system whether they had pain that day, and if so, how severe was the maximally severe pain on a scale of 0 to 4 (0, none; 1, mild; 2, moderate; 3, intense; 4, severe). They also were asked how many stools they had that day, and the consistency of the stool(s) on a scale of 0 to 5 (0, no stool; 1, very hard; 2, hard; 3, formed; 4, loose; 5, watery). Finally, they were asked whether or not they had a sense of urgency with the stooling, whether or not they felt a sense of incomplete evacuation, and whether or not they had a feeling of bloating that day. The date and time of the call were recorded by the telephone data entry system. In addition, once each week they were asked "In the past seven days, have you had had adequate relief of your irritable bowel syndrome-pain or discomfort?" Results of the daily reports averaged over the 12-14 days of the screening period were used to establish eligibility for entry into the study, which for the principal clinical trials S3BA3001 and S3BA3002 required average maximum daily pain score of 1.0 to 3.3 and

average daily stool consistency score of at least 2.5 (Volume 158, pages 20, 27-8 for S3BA3001; the same criteria were used for S3BA3002). The primary outcome measure was weekly adequate relief, and "responders" were defined as patients who reported adequate monthly response rates. An adjustment was made to compensate for the statistical significance of analytical multiplicity of three monthly response rates (See statistical review by Dr. D. Hoberman, FDA statistician).

Comment: The entry criterion of average stool consistency of 2.5 or more would hardly justify the characterization of patients at the lower bound of the range from 2.5 to 5.0 as having "diarrhea," since a score of 2.5 would describe stools a semi-hard-formed, and not until scores between 4 and 5 were reached would they be diarrheal in consistency. Actually the characterization of the patients into diarrhea-predominant, alternating, or constipation-predominant IBS was done by the investigators independently of the scoring system and was based on the medical history rather than by collected and analyzed data. This led, as might be expected, to inconsistencies between the averaged scores from daily telephone reports and categorization based on recollections. With respect to the range of average daily pain scores to establish eligibility, the very mild or minimal and very severely afflicted patients were excluded for the study, which will need to be reflected as appropriate in the labeling. It is unclear how patients could distinguish between "intense" and "severe" pain to choose whether to enter a 4 or a 5 into the telephone data collection system.

The critical data, on daily pain/discomfort-urgency/bloating/straining-number and consistency of stools, were captured by an innovative touch-tone telephone diary system (Harding, et al., 1997) developed by Glaxo Welcome and their consultants. The system was introduced for S3BA2001, and participants were asked both daily and weekly questions. The responses were made by number entries on touch-tone telephones, in response to recorded questions, and were captured in a computerized central database, including date and time of responses and subject identification. The system was available to participants for 8040 of 8135 hours (99%), and a subsequent survey revealed that patients found the system satisfactory or very satisfactory to use. Compliance for data entry was about 82%, and there was assurance that the data were entered at the prescribed times, as well as assuring the reliability and security of the data. Because of the success in using this innovative method, it was used again during principal efficacy trials S3BA3001 and –3002.

Comment: This novel method of data collection overcame some major objections to diary data. In use of paper diaries, collected at visit intervals, there has not been any reliable assurance that the patients wrote in their symptom scores on the day associated, for there was no way to prevent or detect entry of data just prior to the visit and reliance on recollections of data. Another problem that the system overcame was transcription error, from diaries to case report forms to electronic databases for analysis. On the other hand, in these studies there were some drawbacks that were not addressed or solved: 1) the data for the screening periods were not made available either to the investigator or study site, so that average pain and stool consistency scores could not be correlated with patient histories categorizing their IBS subtype as diarrhea-predominant, alternating, or constipation-predominant, leading to some question as to the validity of the categorization; and 2) the data for individual patients were not linked to the case report forms (CRFs), so that evaluation of any adverse events or problems from CRFs provided for review lacked any of the critical data on daily IBS pain scores and stool characteristics. This should be remedied in future studies. Also, data summaries should be printed from the databases for inclusion with each CRF.

The principal support for the claim of alosetron efficacy rests on the analyses of results from the two large clinical trial S3BA3001 and S3BA3002 in 1273 women with IBS of mild-to-moderate average severity and not showing stools that were hard or very hard during the two-week screening period. The two studies used identical protocols, and were conducted at about the same time, although S3BA3002 was completed two months earlier (14 October 1998) than S3BA3001 (18 December 1998) despite both being started at about mid-September 1997.

Comment: The difference in completion time was not entirely inconsequential, since some findings and analyses from –3002 were used to influence interpretations of data from –3001, as is discussed in much more detail in the clinical efficacy review by Dr. Robert Prizont (q.v.).

In these two 12-week studies, the eligible women were randomized to receive either placebo or alosetron 1 mg twice daily:

Treatment Randomization of Women Participating in Pivotal Clinical Trials

	placebo	alosetron	total
Study S3BA3001	317	309	626
Study S3BA3002	323	324	647
both	640	633	1273

The results summarized from these two trials (Volume 208, page 25) were as follows:

Monthly Responders for Adequate Relief of IBS Discomfort in Women with Diarrhea-Predominant IBS Patterns in Pivotal Clinical Trials

Study S3BA3001	MONTH 1	MONTH 2	MONTH 3
alosetron	112/224 (50%)	129/224 (58%)	135/224 (60%)
placebo	87/222 (39%)	96/222 (43%)	92/222 (41%)
p-value	0.022	0.003	<0.001
Study S3BA3002	MONTH 1	MONTH 2	MONTH 3
alosetron	139/237 (59%)	140/237 (59%)	145/237 (61%)
placebo	89/221 (40%)	104/221 (47%)	100/221 (45%)
p-value	<0.001	0.013	<0.001

Also highly significant ($p < 0.001$) were reductions in the number of days on which stool urgency was reported, number of stools per day, and firmer stools in those months among study participants taking alosetron, compared to those on placebo. These results were seen at all three months in both studies.

Comment: The results tabulated above, as taken from the applicant's table (Volume 208, page 25) in the submitted integrated summary of efficacy, must be interpreted as a subset of all patients treated, which in turn is a subset of women with IBS, and of all persons with IBS symptoms. Only 998 of the 1273 patients randomized completed the study, and only 904 were included in the data tabulated above, not all of whom completed the study. There were 169 women with self-classified "alternating" and 11 with constipation-predominant IBS in S3BA3001, and 180 alternating and 9 constipation-predominant IBS in S3BA3002, who are not considered in the above results. More detailed review and commentary are in Dr. Prizont's clinical efficacy review (q.v.).

V. Integrated Summary of Safety

The integrated safety summary, provided in the applicant's submission Volume 209 and supplemented by listings in Volumes 210-215, and briefly summarized in Volume 1, mainly repeats and recapitulates results from the individual studies. The major studies for safety data are the two 12-week dose-ranging studies in 228 men and 593 women, and the two principal efficacy studies done in 1273 women only. This group is referred to as the "primary safety database" that is analyzed to support the claim for a dose of 1 mg of alosetron twice daily for treatment of women with a subset of IBS symptoms. Most of the data are for the 1 mg b.i.d. dose, and for women with self-characterized diarrhea-predominant forms of IBS, but there are some data for a total of 184 men on alosetron (and 54 on placebo) at doses from 0.1 to 16 mg alosetron b.i.d. and for 395 women at alosetron doses other than 1 mg b.i.d.

12-Week, Placebo-Controlled Alosetron Studies (Primary Safety Database)

Study started-ended	Sites	P M/F	A 0.1 M/F	A 0.5 M/F	A 1.0 M/F	A 2.0 M/F	A 4.0 M/F	A 8.0 M/F	*Total M/F*	Duration
S3B-P12 Jul'93-Sep'94	43 Eur	33/84	38/77	31/85		25/89			127/ 335	12 weeks
S3BA2001 Oct'95-Dec'96	71 U.S.	21/59			18/54	23/51	21/54	28/40	111/ 258	12 weeks
S3BA3001 Sep'97-Dec'98	112 U.S.	0/317			0/309				0/626	12 weeks
S3BA3002 Sep'97-Oct'98	120 U.S.	0/323			0/324				0/647	12 weeks

Note: Doses b.i.d.: P, placebo; A 0.1 to 8.0, alosetron 0.1 to 8.0 mg. M/F, males, females.
S3BA3003, partial report as of 26 Feb '99 on 728 of 859 patients entered by 225 Sep '98.*

The "primary safety database" identified by the applicant comprised 1263 patients (184 men, 1079 women) who received alosetron, and 834 (54 men, 780 women) who received placebo for up to 12 weeks in the four clinical studies listed above. Studies S3BP12 and S3BA2001, were dose-ranging studies (from 0.1 to 8.0 mg b.i.d.) that included some men; studies (S3BA3001 and S3BA3002) were done in women only, comparing alosetron 1 mg to placebo b.i.d.

Table 8.10: Demographic Characteristics of Patients in the Primary Safety Database (Studies S3BP12, S3BA2001, S3BA3001 and S3BA3002) ***[Vol. 1, page 402]***

	Placebo n = 834	A 0.1 n = 115	A 0.5 n = 116	A 1.0 n = 702	A 2.0 n = 187	A 4.0 n = 75	A 8.0 n = 68	Total A n= 1263
Gender: M/F % M/F	54/780 6/94%	38/77 3/67%	31/85 27/73%	18/684 3/97%	48/139 26/74%	21/54 28/72%	28/40 41/59%	184/1079 15/85%
Age: m ± sd (range)	45 ± 0.5 (18-63)	42 ± 1.2 (18-70)	45 ± 1.3 (18-74)	46 ± 0.5 (18-82)	44 ± 1.0 (18-77)	44 ± 1.4 (20-71)	45 ± 1.4 (20-93)	45 ± 1.1 (18-93)
Race: w/b/o % w/b/o	763/51/20 91/6/2%	112/2/1 97/2/1%	113/2/1 97/2/1%	635/28/39 90/28/39%	177/6/4 95/3/2%	72/2/1 97/2/1%	63/0/5 99/0/7%	1172/40/51 93/3/4%

Note: Note: Doses b.i.d.: Placebo; A 0.1 to 8.0, alosetron 0.1 to 8.0 mg; M/F, males, females; m ± sd, mean ± standard deviation; w/b/o, white/black/other.

In addition, Study S3BA3003 was a year-long, placebo-controlled observation of 637 women and 222 men with IBS randomized (or rerandomized) to either placebo or 1 mg alosetron b.i.d. The

patients on placebo with spontaneously occurring constipation, onset was later at a mean of 37 days and duration was shorter at about 9 days. The applicant summarizes these findings as indicating that alosetron was associated with "" greater severity, as well as slightly earlier onset, of constipation," and that this "may have contributed to patients withdrawing from the studies secondary to constipation." In concluding statements (Volume 1, page 421) the applicant states that "constipation is a class effect following treatment with 5HT3 receptor antagonists . ." and also that ". . . the majority of patients who developed constipation during treatment with 1 mg b.i.d. alosetron did not withdraw from the study secondary to the AE."

The proposed labeling mentions that constipation was reported in 28% of patients treated with LOTRONEX® (compared to 5% on placebo, in the table) in the section on Adverse Reactions .It is further stated that "However, only 10% of patients treated with LOTRONEX® withdrew from studies due to constipation." And "Most occurrences of constipation were mild to moderate in intensity, transient, and resolved with continued treatment or were managed with a brief interruption of drug therapy."

Comment: There is no mention in the proposed labeling of how prescribing physicians should adjust the regimen of alosetron administration, take precautions not to give the drug to patients who are constipated, what to do if they become constipated. The conclusions of the study seriously underplay the problem of alosetron-induced constipation, and the proposed labeling does not address this important adverse effect of alosetron that commonly (more than 25% of patients) affects patients taking the drug.

The applicant mentions in the concluding part of the section on Adverse Reactions (Volume 1, page 37) that adverse events reported during treatment with LOTRONEX were not necessarily caused by it, classifies adverse events as infrequent if their incidence is 1/100 to 1/1000, and rare if the incidence is less than 1/1000 patients. For the systemic listing, they propose:

Gastrointestinal –Infrequent: Abnormal stools. ***Rare:*** Ischemic colitis and perianal abscess.

Comment: This is inappropriate. Constipation was NOT infrequent, but occurred in more than a quarter of the patients; it was COMMON, and almost to be expected. The incidence of the much more serious lesion of ischemic colitis is "buried in the fine print" and minimized by being termed rare. By their own definition it was not rare, but probably infrequent. This review disclosed one case of diagnosed ischemic colitis in each of three separate studies (S3BA2001: 1 in 290 (91 men, 199 women) exposed to alosetron, from 1 to 8 mg b.i.d.; S3BA3001, 1 in 309 women exposed to 1 mg alosetron b.i.d., and S3BA3002, 1 in 322 women exposed to 1 mg alosetron b.i.d.). This represents a combined incidence of 3/921, or 1/307, and may be considered uncommon or infrequent but not rare. A request has been sent to the epidemiology branch to make an estimate of the 95% confidence limits for the probable true incidence of ischemic colitis based on these findings in the controlled studies. It is suggested that this finding represents a signal of a potentially serious problem that should be anticipated, perhaps even more severely expressed, if the drug is approved for clinical use in hundreds of thousands of women with IBS. No cases of occlusive or infarcting ischemic colitis were observed as yet in the controlled trials, but it may be possible that predisposed patients with extensive mesenteric atherosclerotic disease, coagulation disorders, or circulatory disturbances may show infarction of bowel, perforation,

and life-threatening forms of ischemic colitis. This possibility is sufficiently great to justify consideration of a required prospective clinical trial after approval for prescription and marketing to establish more precisely the true incidence of the problem, and to define better which patients may be at increased risk.

Another item in the systemic listing is:

Hepatobiliary Tract and Pancreas – Infrequent: Abnormal bilirubin levels.

Comment: Again, the applicant downplays an important problem. The patient who had the serious adverse event of pulmonary edema after an endoscopic retrograde pancreatocholangiography (ERCP) procedure under anesthesia had shown an apparently alosetron-induced hepatotoxicity that was the reason for the ERCP to be done. It has been the experience of several decades that other drugs which cause both ALT and bilirubin elevations, indicating both hepatocellular injury and loss of overall liver function, may show idiosyncratic rates of hepatic failure in 10% or more of patients treated long-term with the drug after marketing and use in large numbers of patients under less well controlled conditions. It is premature to conclude that this will be the case with this drug, but is grounds for some caution and another reason to carry out a prospective study after marketing.