constipation is a desired therapeutic effect of alosetron. However, when this therapeutic effect is so extreme that demands drug discontinuation and exit of patients from an IBS trial, the extreme therapeutic effect becomes counterproductive and may be considered a treatment failure.

Overall, the imbalance in premature discontinuations due to adverse drug events (ADEs) was counterbalanced by an imbalance in a larger proportion of placebo events in another category, not lack of efficacy, but what the sponsor named *"consent withdrawn"*, e.g., lost to follow up (see table of patients disposition). It is unclear, at least to this reviewer, the reason for this imbalance in discontinuation for consent withdrawn in a randomized, multi center trial.

1.6 PIVOTAL TRIAL SB3A3002.

1.6.1 Protocol.

- The study **protocol for this pivotal trial A3002 is identical** to the protocol designed for the pivotal trial A3001. The reader is referred to section 1.4.1 of my review for protocol details.

1.7 Descriptive of Trial S3BA3002.

1.7.1 Patient Disposition.

Pivotal trial A3002 started on September 15, 1997, and was completed on October 14, 1998. GW enlisted 125 centers in the US; **113 centers enrolled subjects.**

GW reports that ***one thousand four hundred sixty-three (1463) subjects were screened for participation in the study. Fifty-six percent (56%, 816/1463) of these subjects were not randomized to treatment.*** The major reason for screening failure, 84%, was failure to meet screening criteria, e.g., failure to meet stool consistency or abdominal pain requirements.

Forty-four percent (44%, 647/1463) of screened subjects were randomized to treatment; 50% (323/647) to placebo BID, and 50% (324/647) to alosetron1 mg b.i.d. The **percentage of randomized subjects who completed the study was** 80% (515/647); **84% (270/323) in the placebo group and 76% (245/324) in the alosetron** group.

Twenty percent (132/647) of randomized subjects withdrew from the study during the treatment or follow-up phases; 16% (53/323) in placebo and 24% (79/324) in alosetron.

The majority of subjects who withdrew from the study in the alosetron group did so due to an adverse event. The adverse event driving this result was constipation. The major reason for placebo premature discontinuation was lack of efficacy. All reasons are shown in the next table.

Premature Study Withdrawals by Reason:
Intent-to-Treat Population

	Placebo BID n (%)	Alosetron 1mg BID n (%)	Total n (%)
Number of subjects withdrawing prematurely	53 (16)	79 (24)	132 (20)
Adverse event	14 (26)	49 (62)	63 (48)
Consent withdrawn	8 (15)	10 (13)	18 (14)
Lost to follow-up	11 (21)	11 (14)	22 (17)
Protocol violation	2 (4)	1 (1)	3 (2)
Lack of efficacy	14 (26)	6 (8)	20 (15)
Other*	4[1-4] (8)	2[5,6] (3)	6 (5)

Source data: Table T-6.1
* Subjects 6383[1], 6384[2], and 6553[5] rolled into a 1-year safety study, S3BA3003, at Week 12; Subject 7936[6] took a prohibited drug; Subject 8778[3] became pregnant; and Subject 8854[4] was non-compliant.

In a **post-hoc**, unblinded look of the efficacy results, the sponsor found higher efficacy of alosetron treatment in patients enrolled as IBS diarrhea-predominant subtype (treatment-by-subtype interaction). Investigators enrolled **458 (71% of 647) of diarrhea-predominant IBS patients, and 180 (28% of 647) with the alternating constipation/diarrhea IBS subtype.**

The next two tables show patient disposition of the two major subtypes of IBS patients.

Premature Study Withdrawals by Reason:
Subjects with Diarrhea-predominant IBS

	Placebo BID n (%)	Alosetron 1mg BID n (%)	Total n (%)
Number of subjects withdrawing prematurely	42 (19)	52 (22)	94 (21)
Adverse event	10 (24)	29 (56)	39 (41)
Consent withdrawn	5 (12)	8 (15)	13 (14)
Lost to follow-up	9 (21)	9 (17)	18 (19)
Protocol violation	2 (5)	0	2 (2)
Lack of efficacy	13 (31)	4 (8)	17 (18)
Other*	3[1,2,4] (7)	2[5,6] (4)	5 (5)

Source data: Table D-6.1
* Subjects 6383[1], 6384[2], and 6553[5] rolled into S3BA3003 at Week 12; Subject 7936[6] took a prohibited drug; and Subject 8854[4] was non-compliant.

Premature Study Withdrawals by Reason:
Subjects with Alternating Constipation/Diarrhea IBS

	Placebo BID n (%)	Alosetron 1mg BID n (%)	Total n (%)
Number of subjects withdrawing prematurely	9 (9)	27 (32)	36 (20)
Adverse event	4 (44)	20 (74)	24 (67)
Consent withdrawn	1 (11)	2 (7)	3 (8)
Lost to follow-up	2 (22)	2 (7)	4 (11)
Protocol violation	0	1 (4)	1 (3)
Lack of efficacy	1 (11)	2 (7)	3 (8)
Other*	1[3] (11)	0	1 (3)

Source data: Table A-6.1
* Subject 8778[3] became pregnant.

Ninety one percent of premature discontinuations, i.e., 120 patients, occurred during the treatment phase. During the first month of treatment there were 62% (P) to 73% (A) premature withdrawals; during the second month 88% (P) to 94 (A) were premature withdrawals.

1.7.2 Demographics

The enrolled IBS women ranged in age from 19 to 83 years (mean ± 46); 93% of women were white. Thirty-two percent (32%, 210/647) of subjects were able to conceive children, **40% (262/647) reported menstruating during the study**.

Mean time since onset of IBS symptoms, 10.3 years, was comparable between treatment groups.

Likewise, treatment groups were generally similar with regard to symptoms associated with abdominal pain and discomfort over the previous 6 months.

As stated, 71% of the women were characterized by the investigator as suffering from the diarrhea-predominant IBS subtype, whereas 28% were characterized by alternating constipation/diarrhea; 1% of IBS women had constipation-predominant IBS,

Slightly less than half (45%) of all-IBS-women-randomized-treated supplemented their diets with fiber to improve bowel habits.

1.7.3 Primary Efficacy Results.

i. Monthly Adequate Relief. The sponsor reports that *alosetron treated subjects showed a significantly greater number of months with adequate relief of IBS abdominal pain and discomfort than placebo treated subjects (p=0.012)*. Thus, **41%** of patients in **the alosetron group** versus **29%** in the placebo group reported adequate relief of IBS pain and discomfort for at for **the combined 3 months** of treatment. Similar to the previous trial A3001, there were no differences between treatments after 1 month or a combined 2 months treatment. The results are shown in the next table (obtained from Glaxo Table T-7.1, Vol. 167). The number of patients in each treatment are **All 647 Randomized-Treated (Intention-to-Treat)**.

Primary Efficacy Results. Trial A3002

Number of Months with Adequate relief of Abdominal Pain/Discomfort [Patients Discontinued Prematurely With Missing Data Were Included With LOCF]

Number of Months Patient has Adequate Relief (Responder)	**Placebo** (N=323)	**Alosetron** (N=324)	Statistical Significance
0	129 (40%)	108 (33%)	
1	42 (13%)	37 (11%)	
2	58 (18%)	46 (14%)	
3	***94 (29%)***	***133 (41%)***	***0.012***

Next, GW noted the following

- *"The above findings indicate that alosetron treatment had a positive effect on the overall study population. However, during routine analysis of subgroup effects using a proportional odds model for the number of months with adequate relief, a significant treatment-by-IBS subtype interaction was found with adequate relief, a significant treatment-by-IBS subtype interaction was found. The results from the proportional odds model showed that for the diarrhea-predominant IBS subgroup, subjects treated with alosetron 1mg BID had more months with adequate relief than subjects in the placebo group; however for the alternating IBS subgroup, subjects in the placebo group had more months with adequate relief than subjects in the alosetron 1mg BID group".*

Treatment **responders for all 3 months** of the study in the diarrhea-predominant IBS subtype, a total of 458 patients, are shown in the next table *(scanned from Vol. 168)*.

Population: ITT (Diarrhea-Predominant)

Appendix Table D-7.1
Number of Months with Adequate Relief of IBS Pain/Discomfort: LOCF

Measurement	Statistic	Placebo (N=221)	Alosetron 1 mg BID (N=237)	p-value
Number of Months Subject is an Adequate Relief Responder	n (%)			<0.001**
0		90 (41%)	67 (28%)	
1		31 (14%)	26 (11%)	
2		38 (17%)	34 (14%)	
3		62 (28%)	110 (46%)	

Efficacy with either treatment in the adequate relief of abdominal pain/discomfort **at** month 1, **at** month 2, or **at** month 3 (point-prevalence) revealed superiority of alosetron at months 1 and 3, but not at month 2.

ii. Impact of Premature Discontinuations.

The following GW table displays the proportion of responders and non-responders among those discontinued prematurely from the trial. **Noteworthy, patients on alosetron discontinued prematurely from the trial exhibited lower primary efficacy to the experimental drug, only 15% responders, than those who completed the trial.**

Intent-to-Treat

Appendix Table T-7.5
Number of Months with Adequate Relief of IBS Pain/Discomfort for Subjects who Discontinued the Study Prematurely: LOCF

Measurement	Statistic	Placebo (N=323)	Alosetron 1 mg BID (N=324)	p-value
Number of Subjects who Discontinued the Study Prematurely	n	53	79	
Number of Months Subjects who Discontinued the Study Prematurely are Adequate Relief Responders	n (%)			0.462
0		35 (66%)	55 (70%)	
1		2 (4%)	6 (8%)	
2		5 (9%)	6 (8%)	
3		11 (21%)	12 (15%)	

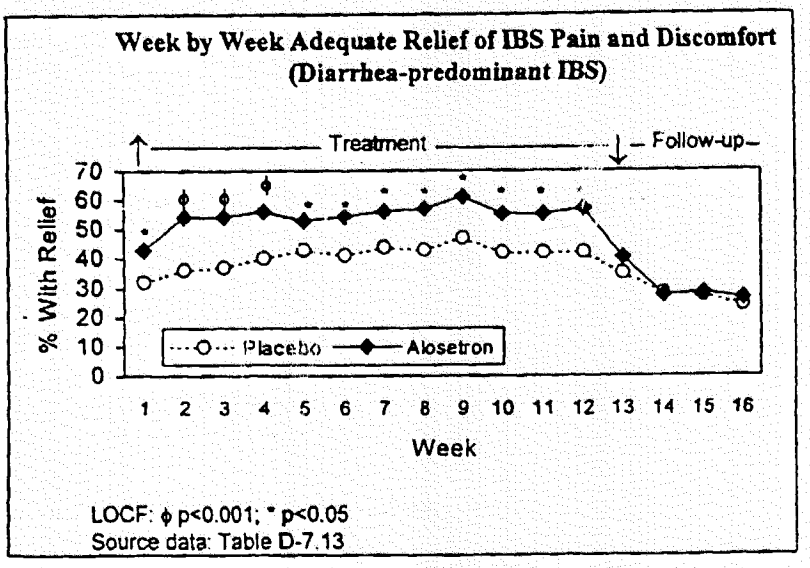
iii. Women with Menses versus Women without Menses.

In this trial, there was no correlation between menses and relief or exacerbation of IBS abdominal pain/discomfort.

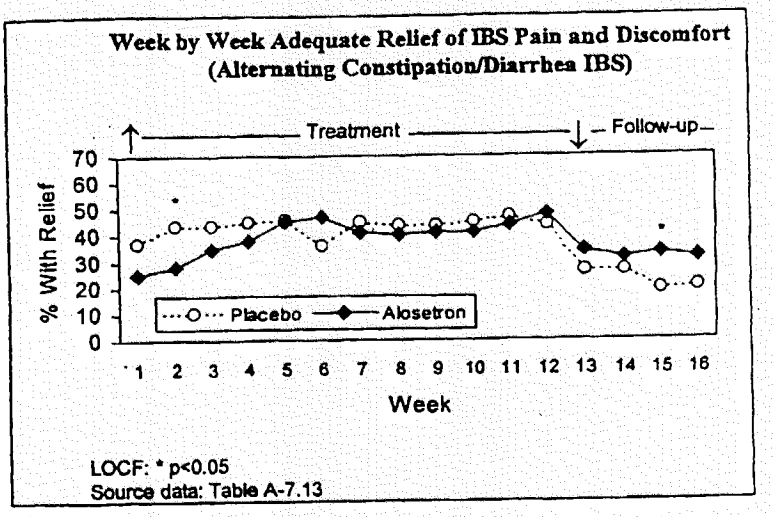
iv. Weekly Relief.

Glaxo-Wellcome reported that in the all Randomized-Treated population, alosetron administration resulted in significantly superior adequate relief of IBS abdominal pain/discomfort on every week of the 12-week study period, except the first (p=0.012).

The following GW figures represent the weekly adequate relief of IBS abdominal pain/discomfort in the subsets of Diarrhea-Predominant and alternating Constipation/Diarrhea IBS subtypes. In the first figure, the group of IBS women with the diarrhea-predominant subtype who were treated with alosetron showed significantly superiority to placebo in the weekly relief of IBS abdominal pain/discomfort.



In the second figure, it is noted that women with the alternating constipation/diarrhea IBS subtype did not show response to alosetron treatment during the 12-week study treatment. Noteworthy, during the third week of post-treatment follow-up, the group of women with the constipation/diarrhea IBS subtype, who had been treated with alosetron, revealed superior relief of IBS abdominal pain/discomfort than placebo patients.



1.7.4 Secondary Efficacy Results

v. Monthly Pain-Free. At baseline, the mean percentage of pain/discomfort-free days in the total population was 14 % in the alosetron group and 15 % in the placebo group.

GW reports that ***in the total population there was no significant difference between treatments in the number of months subjects were monthly responders for pain/discomfort-free days (i.e., reported ≥50% days free from pain out of at least 14 days)***. GW noted the following:

- *Analyses of subgroup effects revealed a significant interaction for treatment-by-IBS subtype and a significant main effect for childbearing status. The results from the proportional odds model showed that for the diarrhea-predominant subgroup, subjects treated with alosetron had more months as pain/discomfort-free days responders than subjects in the placebo group; however for the alternating IBS subgroup, subjects in the placebo group had more months as pain/discomfort-free days responders than subjects in the alosetron. In addition, sterile and post-menopausal subjects had more months as pain/discomfort-free days responders than subjects who were potentially able to conceive.*

The proportion of monthly responders for pain/discomfort-free days in the diarrhea-predominant IBS subgroup, was **numerically** greater in the alosetron group compared with the placebo group at Month 1, Month 2, and Month 3. Hence, **the proportion of subjects with diarrhea-predominant IBS who were monthly responders increased over time but only borderline statistical significance between treatment groups was seen at Month 3 (p=0.085).**

Among subjects with alternating constipation/diarrhea IBS, the proportion of monthly pain/discomfort-free responders was lower in the alosetron group than in the placebo group.

vi. Patient Rating of Abdominal Pain/Discomfort. The sponsor reports that at baseline mean **monthly abdominal pain and discomfort scores in the total population were 1.95 in the alosetron group and 1.90 in the placebo group.**

GW noted that ***abdominal pain and discomfort severity scores in the Intent-to-Treat Population decreased over time, with subjects in the alosetron reporting a significantly greater change than subjects in the placebo group at Months 2 and 3. Mean changes from baseline in abdominal pain and discomfort severity scores in the alosetron and placebo groups were -0.83 versus -0.72, respectively (p=0.020) at Month 2, and -0.87 versus -0.73, respectively (p=0.036) at Month 3*** (Tables T-7.34 and T-7.35).

Tables T-34, T-35 and D-35, Pages 200-201, 206-207, Vol. 167, are included as Appendix 6 of this review.

vii. Stool Consistency. In the **total population, mean stool consistency at baseline was 3.42 in the alosetron group and 3.40 in the placebo group.** Women with diarrhea-predominant IBS, had mean **stool consistency at baseline of 3.55 in the alosetron group and 3.57 in the placebo** group. GW notes that subjects with alternating constipation/diarrhea IBS had more formed stools; baseline stool consistency was 3.08 in the alosetron group and 3.05 in the placebo group.

During the three month treatment and in the all-randomized-treated patient population, **alosetron was significantly superior to placebo in increasing monthly stool consistency.**

Women with diarrhea-predominant and alternating constipation/diarrhea IBS subtypes developed significantly firmer stools with alosetron treatment than with placebo treatment.

Tables D-7.42, A-7.42, D.7-43, A-7.43, Pages 2-3 and 5-6, Vol. 168, which show stool consistency in IBS subtypes are included as Appendix 7 of this review.

viii. Stool Frequency. At baseline and in the total population, women reported passing stool an average of 2.7 times per day in the alosetron group and 2.8 times per day in the placebo group. At the same **baseline, women with diarrhea-predominant IBS passed stool slightly more frequently, i.e., 2.9 times per day in the alosetron group and 3.0 times per day in the placebo group, than women in the alternating constipation/diarrhea IBS group, i.e., 2.2 times per day in the alosetron group and 2.8 times per day in the placebo group.**

In the total population, and in all treatment months, **alosetron was significantly superior to placebo** in decreasing stool frequency.

Regarding treatment effectiveness on stool frequency in the two IBS subtypes, GW notes that subjects with diarrhea-predominant or **alternating constipation/diarrhea IBS who were treated with alosetron experienced a significant decrease in the number of times per day stool was passed** compared with subjects who were treated with placebo.

Tables D-7.47 and A-7.47, Pages 38 and 39, Vol. 168, with stool frequency results in IBS subtypes, are included as Appendix 8 of this review.

ix. Stool Urgency, Incomplete Evacuation. Both of these secondary endpoints were improved during the trial, with alosetron demonstrating significant superiority over placebo.

x. Bloating and Psychological Scores. There were no significant improvement in any of the two treatment for any of these two secondary outcome measures.

1.7.5 Reviewer Comments.

1. My review of the primary efficacy results of this pivotal multi center trial A3002 revealed that, a larger proportion of IBS women administered oral alosetron in the dose of 1 mg b.i.d. for a three month period experienced adequate relief of abdominal pain/discomfort than patients given placebo tablets. The therapeutic gain achieved with administration of alosetron, 15%, was highly significant (p=0.012). Hence, and as previously stated in my initial comments of pivotal trial A3001, I concur with the sponsor that the prospectively established primary efficacy outcome, adequate relief of IBS abdominal pain/discomfort, has been successfully met .

2. The primary efficacy results of this trial A3002 confirm my conclusion on the primary efficacy of trial A3001, that is, the alosetron significant superiority in primary efficacy is only observed in IBS women who respond to alosetron treatment for ***all*** 3 months of study treatment. As mentioned, the statistician reviewer, Dr. David Hoberman, estimated 8 possible outcomes of adequate relief response to alosetron treatment. The next two tables illustrate this point. The first table is a schematic representation of the 8 possible outcomes *(already explained in detail in my comments of trial A3001)*. The second table includes the percentage of responders in each of the 8 possible outcomes. Alosetron revealed significant superiority **only** in scenario 8 **(responders to a combined 3 month therapy)**. *In this Intention-To-Treat analysis, the statistician reviewer included (imputed) patients with missing data as non-responders.*

Reviewer Table 5

Possible Patterns of Adequate Relief for IBS Women Enrolled in Pivotal Trial 3002

	Month1	Month2	Month3
(1)	NR	NR	NR
(2)	R	NR	NR
(3)	NR	R	NR
(4)	NR	NR	R
(5)	R	R	NR
(6)	R	NR	R
(7)	NR	R	R
(8)	R	R	R

Reviewer Table 6

Trial 3002: Percentage of Responders to Alosetron During the 3-Month Study Period

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
(P)	40	6	4	5	6	4	8	27
(D)	33	6	5	3	2	5	6	39

3. The results of this pivotal trial A3002 further draws attention to the need to examine the claim that alosetron therapeutic effectiveness is greater in the diarrhea-predominant subtype, and its benefit is low or non-existent upon another IBS subtype, i.e., alternating constipation/diarrhea. In the particular instance of this latter IBS subtype, the therapeutic benefit of alosetron should be considered not only on the basis of the primary efficacy endpoint, but rather, on the basis of the entire clinical IBS spectrum (primary + secondary efficacy outcomes), which is the basis of the Rome Criteria diagnostic guidelines. The following are my comments on this issue:

i. As in protocol A3001, the protocol design for A3002 did not include any prospective definition for the diarrhea-predominant IBS subtype. Patients considered by investigators to fit the diarrhea-predominant subtype had at baseline, stool consistency values ranging between 3.55 and 3.57, that is, **stool consistency values that were neither** loose nor watery, i.e., 4 to 5. Further, the stool frequency in this diarrhea-predominant group was not greater than 3 times a day (>3 times a day is the number included in the Rome Criteria to define the diarrhea subtype). Hence, the baseline stool characteristics of women with the diarrhea-predominant IBS subtype who were enrolled in this pivotal trial A3002, does not meet a definition of diarrhea.

ii. Alosetron treatment was not superior to placebo in the adequate relief of abdominal pain/discomfort in patients affected by the alternating constipation/diarrhea IBS subtype. Noteworthy, in this group of patients, alosetron was significantly superior to placebo in the improvement of ***all*** lower functions, relevant symptomatology in the IBS diagnosis, i.e., patients with alternating constipation/diarrhea IBS subtype revealed **significantly** superior improvements in stool consistency, stool frequency and stool urgency than patients on placebo control. Hence, the possibility exist of missing efficacy in relevant IBS outcomes, if, as is this case, because the primary efficacy endpoint did not encompass all relevant symptoms included in the Rome Criteria guidelines.

4. This study A3002 did not show any difference in effectiveness in IBS with menses. The different in responses between trials A3001 and A3002 in women with and without menses is unclear to this reviewer As stated before, assessment of the response to treatment in IBS women with menses during menstrual periods is needed to arrive to more definitive conclusion on this issue.

References

1. Drossman DA, Whitehead WE, Camilleri M. Irritable Bowel Syndrome: a technical review for practice guideline development. Gastroenterology; 112:2120-2137, 1997.

2. Masand PS, Sousou AJ, Gupta S et al. Irritable bowel syndrome (IBS) and alcohol abuse or dependence. Am J Alcohol Abuse; 24:513-521, 1998.

3. Veale D, Kavanagh G, Fielding JF et al. Primary fibromyalgia and the irritable bowel syndrome: different expressions of a common pathogenic process. British J Rheumat; 30:220-222, 1991.

4. Chun A, Desaultels S, Silvka A et al. Visceral algesia in irritable bowel syndrome, fibromyalgia, and sphincter of oddi dysfunction, type III. Dig Dis Sci; 44:631-636, 1999.

5. Moore J, Barlow D, Jewell D et al. Do gastrointestinal symptoms vary with the menstrual cycle? British J Obste Gynecol; 105:1322-1325, 1998.

6. Prior A, Wilson K, Whorwell PJ et al. Irritable Bowel Syndrome in the Gynecological Clinic. Survey of 798 new referrals. Dig Dis Sci; 12:1820-1824, 1989.

1.8 Dose-Ranging Study S3B2001.

The sponsor conducted two **Phase II dose ranging studies** in patients with IBS, one foreign (S3B-P12), and one domestic conducted in the US and Canada (S3BA2001). These were not supportive pivotal studies, but were conducted to determine the optimal therapeutic alosetron dose. In this section I will **briefly** describe the protocol and the results of the domestic A2001.

1.8.1 Protocol.

The following are relevant sections not included in the protocol for pivotal trial A3001.

Design.

Type: Randomized, dose ranging, double-blind, placebo-controlled, parallel group, multi-center.

No. of Centers: Approximately 70

No. of Subjects: 350 subjects randomized.

Study Duration: 16 weeks

This is a 16-week study to assess alosetron therapy in subjects with irritable bowel syndrome (IBS). Subjects with symptoms fulfilling the Rome criteria for IBS for 6 months will be screened for 2 weeks to confirm active disease. At the end of the 2-week screening period, subjects reporting sufficient abdominal pain/discomfort symptoms and appropriate stool consistency scores will be randomized to treatment with either alosetron 1mg, 2mg, 4mg or 8mg BID or placebo BID for 12 weeks. Subjects will continue to record abdominal pain/discomfort and other lower GI symptoms for 12 weeks, at which time the subject has completed the study drug treatment. During the next 14 ± 2 days, subjects will continue to record their abdominal symptoms until they receive their follow-up telephone call. The follow-up telephone contact to assess adverse events will be made 14 ± 2 days after the 12 Week/Final Visit.

Setting:

The study will be conducted at approximately 70 ambulatory care centers/hospitals and private physician offices in the United States, Europe, and Canada. A follow-up telephone contact to assess adverse events will be made 14 ± 2 days after the Week 12/Final Visit.

Subjects:

Approximately 350 subjects will be randomized for treatment with study drug. Subjects may be enrolled in the study if they are men or women at least 18 years of age. Women of child-bearing potential must be surgically sterilized or using an acceptable means of contraception,

ii. Inclusion Criteria. **Identical to those described in protocol A3001.**

iii. Exclusion Criteria. **Identical to those described in protocol A3001.**

iv. Drug and Doses. The prospective protocol states the following:

Each subject will be allocated to receive one of the following treatment regimens according to a random code generated by the Department of Biostatistics at Glaxo Wellcome Inc. or designee:

1. alosetron 1mg BID
2. alosetron 2mg BID
3. alosetron 4mg BID
4. alosetron 8mg BID
5. Placebo BID

v. Primary Efficacy Endpoint. The section on statistical methods includes the following primary efficacy measures **(amended):**

The proportion of pain/discomfort-free days during the Week 8 to Week 12 interval is the primary efficacy parameter for this study.

vi. Secondary Efficacy Endpoints. The amended secondary efficacy measures were the following:

Key Secondary Efficacy Measures

Subject self rating of pain/discomfort and severity and adequate relief of pain/discomfort are the two key secondary efficacy parameters for this study. Changes in mean pain/discomfort score will indicate the therapeutic benefit of treatment, and reporting of adequate relief of pain/discomfort will indicate the clinical relevance of the observed changes in mean pain/discomfort score.

Other secondary efficacy endpoints were rating of the lower bowel functions, i.e., stool consistency, stool frequency.

Score rating of abdominal pain intensity and lower bowel functions were the same as those included in protocol A3001.

1.9 Descriptive of Trial SB3A2001.

1.9.1 Disposition of Patients.

Eight hundred thirty-five (835) subjects were screened for participation in the study. Of these, 465 (56%) subjects, comprising the Screen Failure Population, were not randomized

Three hundred seventy (370/835, 44%) subjects were randomized to treatment, constituting the Intent-to-Treat of Total Population: (80/370, 22% in the placebo BID group, 72/370 (19%) in the alosetron 1mg BID group, 74/370 (20%) in the alosetron 2mg BID group, 76/370 (21%) in the alosetron 4mg BID group, and 68/370 (18%) in the alosetron 8mg BID group)

The following GW table displays the disposition of randomized patients

TABLE 1.1

SUBJECT RANDOMIZATION
INTENT-TO-TREAT POPULATION

Status	Statistic	(A) Placebo	(B) Alosetron 1mg BID	(C) Alosetron 2mg BID	(D) Alosetron 4mg BID	(E) Alosetron 8mg BID	Total
Total Number of Subjects Randomized	n	80	72	74	76	68	370
Number of Subjects Completing Study	n (%)	68 (85%)	57 (79%)	52 (70%)	56 (74%)	48 (71%)	281 (76%)
Number of Subjects Withdrawing Prematurely	n (%)	12 (15%)	15 (21%)	22 (30%)	20 (26%)	20 (29%)	89 (24%)

Note: Subject 2325 was a screen failure, but was randomized via the telephone system in error. The subject was not dispensed medication and did not have a treatment case report form.
Note: Percentages for the number of subjects completing study and the number of subjects withdrawing prematurely are based on the number of subjects randomized.

The next table shows reasons for withdrawals. There was a significant difference in the withdrawals for adverse reactions between alosetron 2 mg b.i.d. and placebo ($p<0.005$), and between 8 mg b.i.d. and placebo ($p<0.03$).

Premature Study Withdrawals by Reason

n (%)

	Placebo BID	Alosetron 1mg BID	Alosetron 2mg BID	Alosetron 4mg BID	Alosetron 8mg BID	Total
Number of subjects withdrawing prematurely	12	15	22	20	20	89
Lack of efficacy	2 (17)	2 (13)	0	4 (20)	2 (10)	10 (11)
7-Day absence of stool	0	4 (27)	1 (5)	1 (5)	4 (20)	10 (11)
Adverse event	5 (42)	4 (27)	17 (77)	10 (50)	13 (65)	49 (55)
Failed to return	1 (8)	2 (13)	3 (14)	0	0	6 (7)
Consent withdrawn	3 (25)	1 (7)	0	1 (5)	1 (5)	6 (7)
Other	1 (8)	2 (13)	1 (5)	4 (20)	0	8 (9)

1.9.2 Demographics

The sponsor states the following on patient demographics:

The Total Population ranged in age from 18 to 94 years (mean±standard deviation was 45.1 ±14.8 years across groups), and was predominantly composed of White females. Treatment groups were similar with regard to sex, race, age, height, weight, childbearing potential among females, and tobacco and alcohol use (Table 5.0).

1.9.3 Primary Efficacy Results.

The sponsor reports that due to the *"subject perception in determining pain relief"*, the primary efficacy endpoint was changed **post-hoc** from the proportion and number of pain-free days, to *the adequate relief of abdominal pain/discomfort.*

GW notes that in the Intention-to-Treat population, there was a larger proportion of alosetron responders, but that sample size limitations (groups randomized to 5 treatments) prevented to reach statistical significance. The next table displays the post-hoc primary efficacy results.

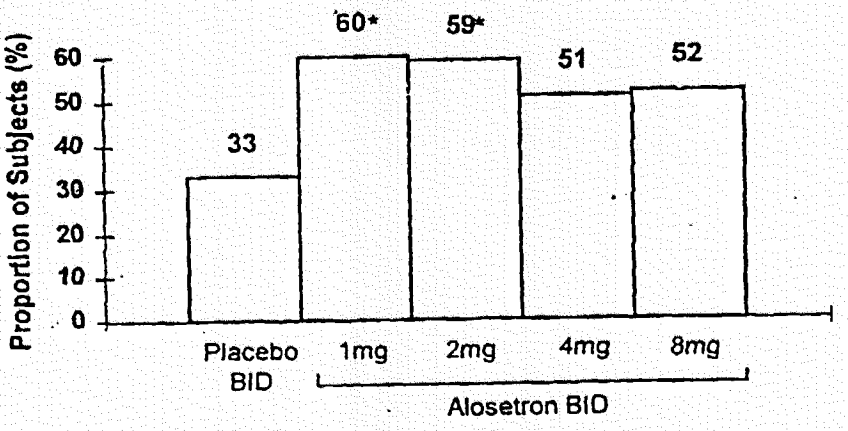
TABLE 12.0

ADEQUATE RELIEF OF IBS PAIN/DISCOMFORT
RESPONDERS AT WEEK 12
INTENT-TO-TREAT POPULATION

	Statistic	(A) Placebo	(B) Alosetron 1mg BID	(C) Alosetron 2mg BID	(D) Alosetron 4mg BID	(E) Alosetron 8mg BID	P-values ABCDE	AvsB	AvsC	AvsD	AvsE
Total Number of Subjects	n	80	72	74	76	68					
Adequate Relief for at Least Half the Weeks	n	80	70	72	72	64	0.965	0.661	0.460	0.691	0.608
Responder	n (%)	35 (44%)	34 (49%)	36 (50%)	34 (47%)	31 (48%)					
Non-Responder	n (%)	45 (56%)	36 (51%)	36 (50%)	38 (53%)	33 (52%)					
Adequate Relief for at Least Six Weeks	n	68	57	52	56	48	0.374	0.236	0.072	0.146	0.172
Responder	n (%)	26 (38%)	28 (49%)	29 (56%)	29 (52%)	25 (52%)					
Non-Responder	n (%)	42 (62%)	29 (51%)	23 (44%)	27 (48%)	23 (48%)					

Alosetron showed superiority in the subset of female completers with IBS at the 1 mg and 2 mg b.i.d. dose, but did not show any difference with placebo in the male population. The results in females are shown in the next figure.

Proportion of IBS Pain/Discomfort Responders by Group Among Females (Adequate Relief for 6 of 12 Weeks Among Completers)



* Statistically different from placebo BID ($p<0.05$)

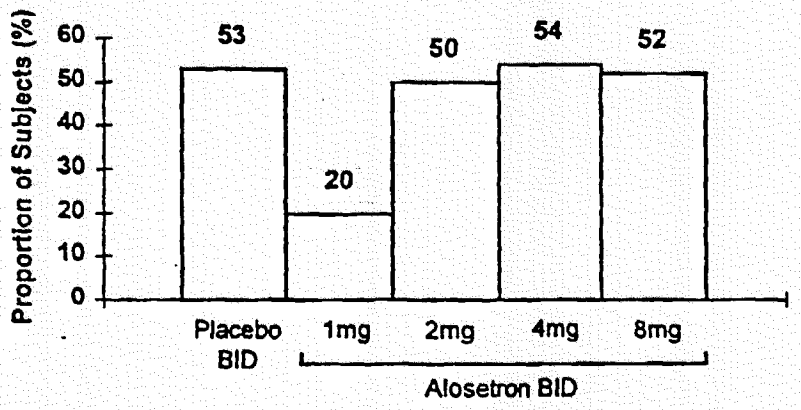
The following table shows the monthly response in the female Intention-to-Treat population. As seen, alosetron 1 mg b.i.d. was significantly superior to placebo in each of the three months.

Female Subjects: Monthly Responders for Adequate Relief of IBS Pain/Discomfort

	Month 1	Month 2	Month 3
alosetron 1mg BID	28/53, 53%	33/53, 62%	32/53, 60%
placebo BID	19/59, 32%	25/59, 42%	21/59, 36%
p-value	0.038	0.050	0.013

The next figure shows the post-hoc comparison of adequate relief of abdominal pain/discomfort among alosetron male completers and placebo male completers. As noticeable, there are no significant differences between treatments.

Proportion of IBS Pain/Discomfort Responders by Group Among Males (Adequate Relief for 6 of 12 Weeks Among Completers)



1.9.4 Secondary Efficacy Parameters

For the purposes of this review, the only secondary efficacy parameters of significance are the lower bowel functions. The sponsor summarizes bowel results in IBS females as follows: