

1.5 Descriptive of Trial S3BA3001

- In this section, I will include a summary of patient disposition and demographics, and of efficacy results submitted in the Glaxo Wellcome report of trial S3BA3001 (Vols. 139-141).

Note from the Reviewer. The reviewer's descriptive of pivotal clinical trials is a summary of results presented as closely as possible to the information submitted by the sponsor. I will not include comments in this descriptive, but subsequent to the completion of the trial's descriptive. Some tables and figures in descriptive sections were scanned from submitted reports.

1.5.1 Patient Disposition.

Pivotal trial S3BA3001 (3001), was started on September 18, 1997, and completed on December 18, 1998. Glaxo enlisted 115 US centers for the study; 104 centers enrolled patients.

The 104 US centers screened 1417 IBS women for participation in the study. There were 791 IBS women (56%) who, after the 2-week run-in period were not considered eligible for randomization to either of the two experimental treatments. The major reason for exclusion from the study was failure to meet the screening criteria to enter the randomization phase of the study (81%). The type of IBS in patients who failed the screening is summarized in the following paragraph:

The group of subjects who failed screening consisted of a lower proportion of diarrhea-predominant subjects (53%, 415/791) compared with the Intent-to-Treat Population (71%, 446/626). The screen failure group also had a higher proportion of alternating constipation/diarrhea subjects (38%, 301/791) compared with the Intent-to-Treat Population (27%, 169/626) and a higher proportion of constipation-predominant (9%, 74/791) subjects compared with the Intent-to-Treat Population (2%, 11/626). Other IBS-related characteristics were similar between screen failures and the subjects who were randomized

From the 1147 IBS women screened, 626 (44%) were eligible for randomization; of these 626, 317 were randomized to placebo and 309 to alosetron 1 mg bid.

In each of the treatment arms, there was a high proportion of patients discontinued prematurely from the trial, 22% (71 patients) in the placebo group, 23% (72 patients) in the alosetron group. Reasons for discontinuation are presented in the following table (*scanned from Glaxo submission*).

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

| | Placebo BID n (%) | Alosetron 1mg BID n (%) | Total n (%) |
|--|-----------------------|----------------------------|----------------|
| Number of subjects withdrawing prematurely | 71 (22) | 72 (23) | 143 (23) |
| Adverse event | 21 (30) | 48 (67) | 69 (48) |
| Consent withdrawn | 25 (35) | 6 (8) | 31 (22) |
| Lost to follow-up | 11 (15) | 6 (8) | 17 (12) |
| Protocol violation | 0 | 1 (1) | 1 (<1) |
| Lack of efficacy | 7 (10) | 7 (10) | 14 (10) |
| Other* | 7 ¹⁻⁷ (10) | 4 ⁸⁻¹¹ (6) | 11 (8) |

Source data: Table T-6.1

* Subject 4323¹ was non-compliant; Subjects 4507² and 4506⁸ were discontinued by the sponsor; Subject 4730³ had microscopic colitis on biopsy; Subjects 5279⁴ and 15739⁵ took or wanted to take prohibited medications; Subject 5141⁶ became pregnant; Subject 5926⁷ was improperly randomized; Subject 5111⁹ had an abnormal TSH level; Subject 4163¹⁰ discontinued birth control; and Subject 5488¹¹ cited insufficient time for making entries into the electronic touch-tone telephone data entry system.

The sponsor noted that *based on the significant treatment-by-IBS interaction in a replicate confirmatory trial, S3BA3002, post hoc analyses were also performed on the Diarrhea-predominant and Alternating populations in this study to facilitate comparison between the two trials.* Hence, the following table shows that majority of premature discontinuations were in the group of IBSD patients characterized by the sponsor as diarrhea predominant (*scanned from Glaxo submission*).

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

| | Placebo BID n (%) | Alosetron 1mg BID n (%) | Total n (%) |
|--|----------------------|----------------------------|----------------|
| Number of subjects withdrawing prematurely | 54 (24) | 55 (25) | 109 (24) |
| Adverse event | 19 (35) | 38 (69) | 57 (52) |
| Consent withdrawn | 17 (31) | 4 (7) | 21 (19) |
| Lost to follow-up | 8 (15) | 4 (7) | 12 (11) |
| Protocol violation | 0 | 1 (2) | 1 (<1) |
| Lack of efficacy | 5 (9) | 6 (11) | 11 (10) |
| Other* | 5 ¹⁻⁵ (9) | 2 ^{8,9} (4) | 7 (6) |

Source Data: Table D-6.1

* Subject 4323¹ was non-compliant; Subjects 4507² and 4506⁸ were discontinued by the sponsor; Subject 4730³ had microscopic colitis on biopsy; Subjects 5279⁴ and 15739⁵ took or wanted to take prohibited medications; and Subject 5111⁹ had an abnormal TSH level.

Approximately 60% of premature discontinuations occurred during the first month of the study; ±95 % by the second month.

1.5.2 Demographics.

The 626 women randomized to experimental treatments ranged in age between 18 to 83 years, 88% of the women were white; 42% of randomized women reported menstruating during the study; 33% were potentially able to conceive, and 55% used hormones for contraception or replacement therapy..

Mean time of onset of IBS was comparable in both treatment groups, i.e., mean of 11.6 years, with a median of 9 years in the alosetron group and 7 years in the placebo group. **Only 2% of the randomized women were considered by the investigator as constipated whereas 98% were considered not constipated.** Of the 309 placebo and 306 alosetron IBS patients who were considered not constipated, 71% were characterized by the investigator as suffering from diarrhea-predominant IBS, and 21% were characterized as alternating constipation with diarrhea. Less than 40% of the randomized IBS women were ingesting an average of 2 days per week (high) fiber diet to improve the bowel habits.

The majority of the IBS women enrolled, i.e., ±73%, were taking concurrent medication drugs prescribed for the nervous system. A similar proportion of patients, i.e., ±68%, were on endocrine/metabolic drugs; 47% of the patients were on concurrent G.I. drugs.

1.5.3 Primary Efficacy Results.

i. Monthly Adequate Relief. Results presented in the next table show that a statistically significantly higher proportion of IBS women treated with alosetron had adequate relief of the abdominal discomfort (41%) than patients treated with placebo (26%) for the **combined three months** of the study (patients needed to show relief for at least 2 weeks/month). There was no difference in the proportion of alosetron and placebo patients who responded to a combined 2 months of treatment (P=15%, A=15%), or to only 1 month of treatment. There were **significantly more placebo patients who did not respond to the combined three months treatment, i.e., the table shows "0 number of months" as P=43%, A=32%.** The results in the table were obtained from Glaxo Table T-7.1. Number of patients in each treatment are **All Randomized-Treated (Intention-to-Treat).**

Primary Efficacy Results. Trial A3001

Number of Months with Adequate Relief of Abdominal Pain/Discomfort [Patients Discontinued Prematurely With Missing Data Were Included With The Last Observation Carried Forward (LOCF)].

| Number of Months Patient has Adequate Relief (Responder) | Placebo (N=317) | Alosetron (N=309) | Statistical Significance |
|--|-----------------|-------------------|--------------------------|
| 0 | 135 (43%) | 100 (32%) | |
| 1 | 53 (17%) | 36 (12%) | |
| 2 | 47 (15%) | 46 (15%) | |
| 3 | 82 (26%) | 127 (41%) | <0.001 (A>P) |

- Similar to the comparison of All Randomized-Treated IBS patients (Intention-To-Treat), **comparison of adequate relief of abdominal pain/discomfort in women with the diarrhea-predominant IBS revealed a statistical superiority of alosetron.** There were a **total of 446 women enrolled with this IBS subtype (Placebo=222, Alosetron=224).** Comparison of primary efficacy revealed a significantly larger proportion of patients on alosetron reporting adequate relief of abdominal pain/discomfort. Similar to the results observed in the study total patient population, comparison of primary efficacy in this subset of diarrhea-predominant IBS women showed that alosetron superiority was **only present in patients treated for the combined three months, i.e. A=43% (96/224) vs. P=26% (58/222),** statistical significance favors alosetron with a $p < 0.001$. Treatments for a period of 1 month or a combined 2 months revealed no differences in efficacy between alosetron and placebo.
 - As stated in the Disposition of Patients subsection, **a total of 169 patients were enrolled with the diagnosis of alternating/constipation IBS subtype (Placebo=87, Alosetron=82).** In this small subset of IBS patients, comparison between alosetron and placebo in the proportion of IBS women with adequate relief of abdominal pain/discomfort revealed superiority of alosetron over placebo, but the difference in favor of alosetron was only numerical and did not reach statistical significance. Thus, for the combined three months of treatment, **35% of alosetron patients versus 26% of placebo patients with this IBS subtype of alternating constipation/diarrhea reported adequate relief of abdominal pain/discomfort [p-value=0.133].**
 - The sponsor did additional analyses to show superiority of alosetron over placebo in the adequate relief of abdominal pain/discomfort. One of them was determining primary efficacy **at a particular point (day) of the month (point-prevalence).** In this analysis which included all 626 Randomized-Treated women (Intention-to-Treat), alosetron exhibited superiority over placebo **at month 1 (50% of alosetron versus 40% placebo), at month 2 (57% of alosetron versus 43% placebo), or at month 3 (58% alosetron versus 41% placebo).** Statistics showed significant superiority of alosetron over placebo ($p \leq 0.01$).
- ii. *Impact of Premature Discontinuations.* In order to assess the impact of the Last Observation Carried Forward (LOCF) imputation on monthly responders, ***“the number of months with adequate relief was compared among subjects on placebo or alosetron who discontinued from the study prematurely”***. The next Glaxo table shows that there were no differences between treatments in the proportion of monthly responders among those discontinued prematurely from the trial. This lack of difference between treatments was observed in all IBS subtypes.

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Protocol: S3BA3001
Population: 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=317) | Alosetron 1 mg BID (N=309) | p-value |
|---|-----------|--------------------|----------------------------------|---------|
| Number of Subjects who Discontinued the Study Prematurely | n | 71 | 72 | |
| Number of Months Subjects who Discontinued the Study Prematurely are Adequate Relief Responders | n (%) | | | 0.445 |
| 0 | | 58 (79%) | 53 (74%) | |
| 1 | | 6 (8%) | 7 (10%) | |
| 2 | | 2 (3%) | 3 (4%) | |
| 3 | | 7 (10%) | 9 (13%) | |

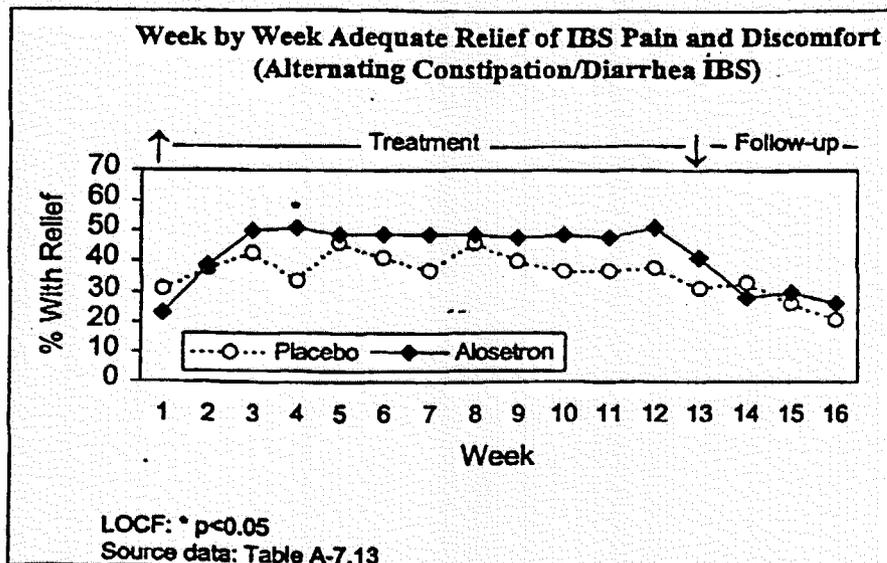
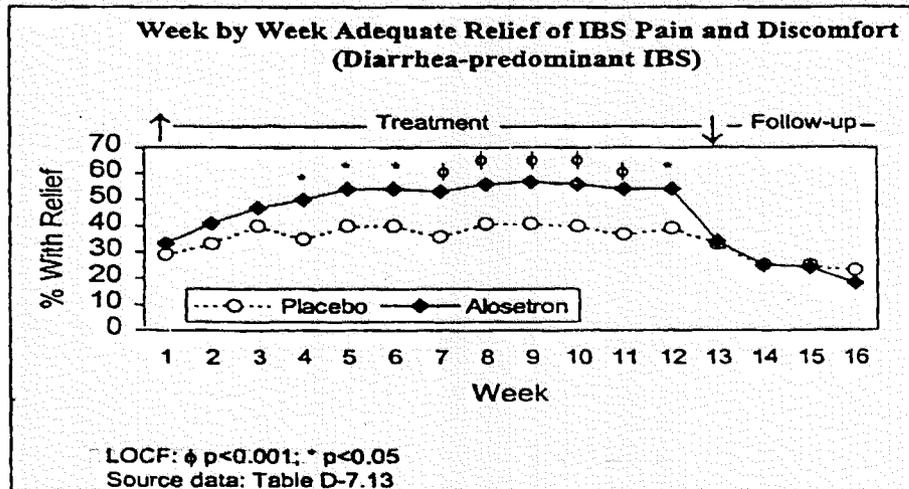
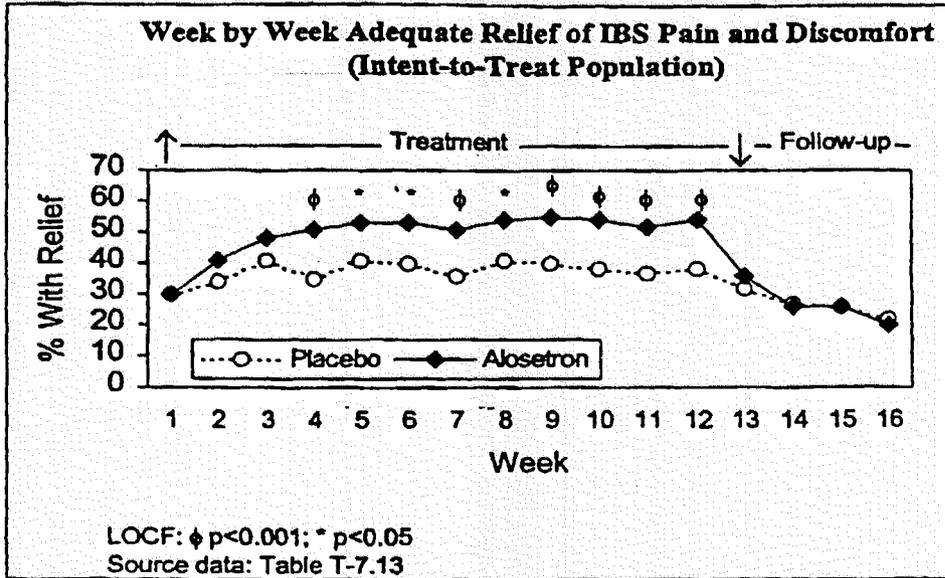
iii. *Women with Menses versus Women without Menses.* In its report of the primary efficacy results, the sponsor states that in the comparison of subsets it noted a significant treatment-by-menstruation interaction. Namely, among all IBS women who reported menses, 50% (65/130) of alosetron-treated had adequate relief of abdominal pain/discomfort vs 28% (37/131) in placebo, whereas among IBS women without menses, only 34% (59/172) of alosetron-treated experienced adequate relief of abdominal pain/discomfort in all three months vs 25% (42/170) in the placebo group (Appendix Table T 7.66). The sponsor states that "findings similar to the Intent-to-Treat population were observed in the diarrhea-predominant IBS subtype (Appendix Table D 7.66), and among subjects with alternating constipation/diarrhea IBS (Appendix Table A 7.66)".

Appendices Tables T 7.66, D 7.66 and A 7.66, Pages 173, 174, 175, Vol. 139 are included as Appendix 2 of this review.

The sponsor states that *none of the other factors examined was significantly associated with adequate relief of IBS pain/discomfort.*

iv. *Weekly Relief.* Similar to the monthly responders, there was a significantly higher proportion of IBS women on alosetron who reported weekly adequate relief of pain. This treatment differences in weekly responders was observed in the Intention-to-Treat group and in the subset of diarrhea predominant IBS women. This point was shown by Glaxo in the next two figures. The third figure shows the trend of weekly alosetron superiority in adequate relief of pain in the IBS women with alternating constipation/diarrhea; in this small subset, the observed difference was mostly numerical and not statistically significant (with exception of week 4).

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Tables T 7.13, D 7.13, and A 7.13, Pages 162, 163, 164, Vol. 138, with data on weekly relief of abdominal pain/discomfort, are included as Appendix 3 of this review.

1.5.4 Secondary Efficacy Results.

v. *Monthly Pain-Free.* The comparison between treatments in the proportion of monthly responders for abdominal pain/discomfort-free days revealed no significant differences. As seen in the next figure, after the three months treatment, only 21% in each treatment group reported $\geq 50\%$ of pain-free days.

Table 7-7.18
Number of Months with Pain/Discomfort-free Days: LOCF

| Measurement | Statistic | Placebo (N=317) | Alosetron 1 mg BID (N=309) | p-value |
|---|-----------|--------------------|----------------------------------|---------|
| Number of Months Subject is a Pain/Discomfort-free Days Responder | n (%) | | | 0.587 |
| 0 | | 164 (52%) | 148 (47%) | |
| 1 | | 35 (11%) | 44 (14%) | |
| 2 | | 50 (16%) | 55 (18%) | |
| 3 | | 68 (21%) | 84 (21%) | |

The sponsor points out that the comparison of pain-free days at a given month revealed that patients on alosetron had significantly more pain-free days at the third month of the study (Alo=46%, 143/309 versus Pl=38%, 120/317, $p=0.031$). There was no difference between placebo and alosetron in the pain-free days reported at the first or at the second month.

vi. Patient Rating of Abdominal Pain/Discomfort.

Glaxo reports that mean monthly abdominal pain/discomfort scores in the Intention-to-Treat population were 1.93 in the alosetron group and 1.97 in the placebo group (see study protocol for detailed description of abdominal scores, i.e., a score of 2= moderate IBS abdominal pain). **Glaxo reported that abdominal pain/discomfort scores in the Intention-To-Treat population decreased over time in the two experimental treatments, with the alosetron group showing a greater change than the placebo group. The sponsor notes that at Month 3 this difference was significant (Alosetron= -0.88 versus Placebo= -0.72, $p=0.014$).** Glaxo notes that in diarrhea-predominant IBS women, baseline abdominal pain/discomfort were significantly lower in the alosetron group compared to the placebo group (Alo=1.85 versus Pl=1.97, $p=0.028$). In IBS patients with the alternating constipation/diarrhea subtype, baseline abdominal pain scores were higher than in the previous subtype (Alosetron=2.13 versus Placebo=1.99).

Tables T.34 and T.35, D.34 D.35, A.34 and A.35, Pages 201 to 209, Vol. 138, which show the monthly decrease in abdominal pain/discomfort and the percentage of decrease from baseline, are included as Appendix 4 of this review.

vii. Stool Consistency.

The sponsor reports that mean stool consistency at baseline was 3.42 in the alosetron group and 3.46 in the placebo group. Patients with alternating constipation/diarrhea IBS had "slightly more formed stools on average than subjects with diarrhea-predominant IBS".

GW reported in the all Randomized-Treated patient population, ***alosetron patients developed significantly firmer stools with alosetron treatment than with placebo treatment.*** The significant superiority of alosetron was observed during all three months of treatment.

viii. *Stool Frequency.*

IBS patients randomized to alosetron had a mean stool frequency of 2.75/day; IBS patients randomized to placebo exhibited a comparable stool frequency of 2.71/day. The sponsor notes that IBS patients with the diarrhea-predominant IBS subtype had slightly higher average of stool frequency. ***In the Intention-to-Treat population and in the subset of diarrhea predominant subtype, patients on alosetron experienced a significantly larger decrease in the daily stool frequency than IBS patients treated with placebo.***

ix. *Sense of Urgency and of Incomplete Stool Evacuation.*

At baseline, IBS patients randomized to alosetron complained of the sensation of urgency to attend to bowel movements a mean of 70% of days per month whereas IBS randomized to placebo complained of urgency 69% of days per month. During the 3 month study, patients treated with alosetron had significantly greater reduction in the sensation of urgency than patients treated with placebo. The percentage of reduction in urgency ranged from 23%-30% in the alosetron group versus 15%-20% in the placebo group ($p < 0.001$).

Glaxo reports that the percentage of days in which subjects noted incomplete stool evacuation was 70% in the alosetron group and 73 % in the placebo group. During the second and third month of the study, patients treated with alosetron had a significantly greater decrease in the sensation of incomplete evacuation (23%-24%) than patients treated with placebo (16%-17%),

x. *Bloating.*

At baseline, all IBS patients randomized to alosetron and all IBS patients randomized to placebo reported a similar percentage of days per month with bloating=77%.. ***After one month of treatment, randomized patients to placebo reported a significantly lower percentage of days with bloating than randomized patients to alosetron ($p=0.04$).*** This superiority of placebo over alosetron in bloating during the first month of treatment was due to significant differences of placebo over alosetron at Weeks 1 and 2 of treatment, and was driven by placebo IBS subset of women with the diarrhea-predominant subtype.

xi. *Psychological Symptoms (SCL-90R).*

Glaxo reports that data on psychological symptoms revealed no differences between treatments.

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1.5.5 Reviewer Comments.

1. The efficacy results from this pivotal multi center trial A3001 revealed that a larger proportion of IBS women administered oral alosetron tablets 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 for alosetron in patients who exhibited adequate relief in all three months of treatment, 15% (41% vs 26%), was statistically very significant ($p < 0.005$).

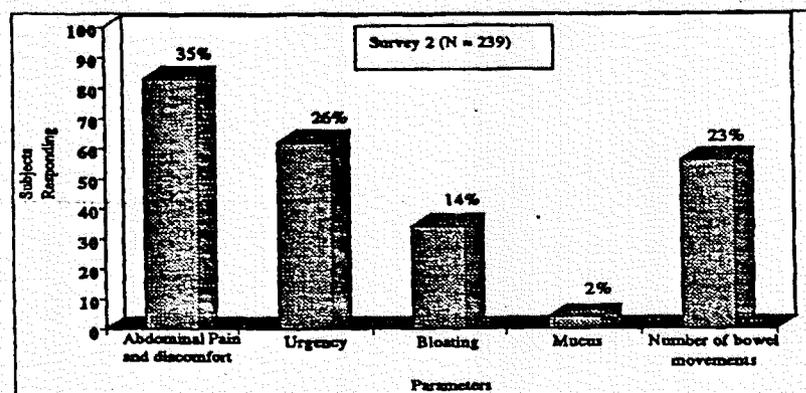
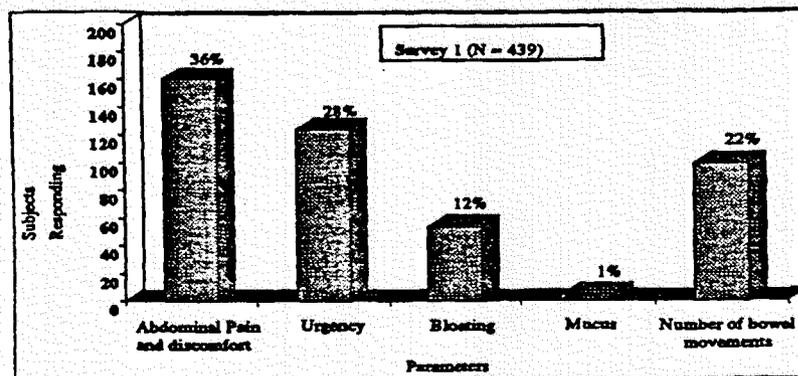
Adequate relief of abdominal pain/discomfort was the primary efficacy outcome prospectively established in the protocol. **Hence, this medical reviewer concurs that the prospectively established primary efficacy outcome was successfully met in this pivotal IBS trial.**

2 Although the primary efficacy outcome superiority shown by alosetron is acceptable, the sole use of *adequate relief of IBS abdominal pain/discomfort* to measure IBS primary outcome may be incomplete to assess other relevant IBS symptoms. In this definition of efficacy outcome, only one relevant IBS symptom, i.e., abdominal pain/discomfort, is specified. It may be argued that the first part of the question used to assess the primary outcome, i.e. *have you had adequate relief of your IBS.....* carries implicitly the understanding of the rest of the relevant symptoms. It might have been so **only if** the second part of the question would have incorporated general IBS symptoms, e.g., *have you had adequate relief of your IBS...symptoms*. As worded in the study protocol, it **specifically and explicitly** points to one single symptom: *IBS abdominal pain/discomfort*, and, implicitly excludes other relevant IBS symptoms, i.e., lower bowel disturbances. Bowel disturbances were described as major symptom-components in the Rome definition of IBS, i.e., abdominal pain/discomfort *relieved by (or related to)* lower bowel disturbances (constipation, diarrhea, alternating constipation/diarrhea, urgency to evacuate the bowel, or incomplete bowel evacuation). The lack of capturing lower bowel functions by the primary efficacy endpoint definition was exemplified by the inclusion of lower bowel functions as secondary efficacy outcomes.

Two surveys among IBS patients, conducted by GW during the pivotal trials indicate the importance placed by IBS patients to lower bowel abnormalities. Patients were asked the following question: *When your irritable bowel syndrome is active, which of the following symptoms bother the most?* Possible answers were "*abdominal pain and discomfort, urgency, bloating, mucus, and number of bowel movements*". Though a higher proportion of patients (36%) considered abdominal pain/discomfort, urgency to evacuate came a close second in the largest first survey (28%) and the **sum** of urgency + number of bowel movements was, actually, more bothersome than abdominal pain/discomfort (taken from Page 17, Vol. 208).

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In the strict context of the used outcome measure, alosetron may have demonstrated to be *primarily* effective in the relief of abdominal pain/discomfort.

3. The primary efficacy results indicate that alosetron was *significantly* better than placebo in IBS women who responded to alosetron treatment to the **combined 3 months** of study treatment. The sponsor reported that the alosetron was **not** better than placebo in the adequate relief of abdominal pain/discomfort if we compare the proportion of patients who responded to treatment to a **combined 2 months** of treatment, or to a 1 month treatment (see *Descriptive*, Table T-7.1). Possible combination of outcomes were further expanded by the statistician reviewer, Dr. David Hoberman. According to his analysis, there were 8 possible outcomes of *adequate relief* response to alosetron treatment or placebo. His first scenario, (1), is similar to "0 number of months" depicted in the sponsor table T-7.1, i.e., all **non-responders** in the combined 3 months of treatment (in this comparison, alosetron had significantly lower proportion of non-responders than placebo). His last scenario of possible outcomes, (8), is also similar to the sponsor's comparison of **responders to the combined 3 months treatment** i.e., alosetron had significantly higher proportion of responders. In between these two extremes, the reviewer considered 6 other possible month combinations, e.g., combination of responders to month 1 but not to month 2, combination of responders to month 2 + 3, combination of responders to month 2 but not to months 1 + 3, combination of responders to month 3 but not to month 1, and so on. The following tables exemplify the possible combinations and actual outcomes.

Reviewer Table 1

Possible Patterns of Adequate Relief for IBS Women Enrolled in Pivotal Trial 3001.
(NR=Non Responder to Alosetron Therapy; R=Responder to Alosetron Therapy)

| | 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 2

Trial 3001: 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 |

(D)=Alosetron; (P)=Placebo. ITT analysis, patients with missing data were considered non-responders

i. Observations. The results of the above eight possible outcomes reveal the following: alosetron is superior to placebo treatment in adequate relief of abdominal pain/discomfort **only** if IBS women are treated with alosetron for a combined and consecutive 3 months. Any other treatment plausible combination of partial treatments for 1 or 2 month periods would fail to show any alosetron efficacy. Clinically, it means an *all or nothing* approach to duration of alosetron treatment for IBS women.

4. The design of this multi center trial **excluded** women who, at screening, complained of IBS abdominal pain of severe intensity. Women eligible to treatment experienced abdominal pain/discomfort of **MILD to MODERATE intensity** (MILD=1; MODERATE=2), i.e., Baseline Alosetron Mean Score=1.93; Baseline Placebo Mean Score=1.97.

This reviewer agrees that the majority of IBS patients seen by physicians complain of mild to moderate abdominal pain, and **this population relate symptoms with stronger bowel components**, as exemplified in this next table, cited from the AGA Patient Care Committee publication on IBS¹.

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Table 7. Spectrum of Clinical Features Among Patients With IBS⁹⁹

| Clinical features | Mild | Moderate | Severe |
|---------------------------------|---------|-----------|----------|
| Estimated prevalence | 70% | 25% | 5% |
| Practice type | Primary | Specialty | Referral |
| Correlation with gut physiology | +++ | ++ | + |
| Symptoms constant | 0 | + | +++ |
| Psychosocial difficulties | 0 | + | +++ |
| Health care use | + | ++ | +++ |

0, generally absent; +, mild; ++, moderate; +++, marked.

My following observations relate to the intensity of abdominal pain relieved by alosetron in this pivotal multi center trial.

- i. **Only a small proportion of IBS women, 21%, reported to be free of pain during all three months of treatment, and the proportion of patients experiencing complete relief of abdominal pain was the same in both treatments, alosetron and placebo.**
- ii. As noticeable in table T-7.35 (*Appendix 4 of this review*), the **decrease in abdominal pain intensity** experienced by patients was from moderate, before experimental treatment, to mild after treatment (it did not reach a mean level below mild). The relief of degree in pain intensity was essentially similar in IBS women treated with either alosetron or placebo [Noteworthy, there was superiority of alosetron over placebo in the decrease of abdominal pain intensity at the third month of the study (time-comparison), but this decrease was driven by a significant decrease in the intensity of abdominal pain observed in the group of patients with the **alternating constipation/diarrhea IBS subtype**. As noticeable in the proposed label, women with alternating constipation/diarrhea IBS are excluded from the *indication* of alosetron therapy].
- iii. **The monthly decrease in the intensity of abdominal pain in the subset of women with diarrhea-predominant-IBS revealed no difference between alosetron and placebo.** The diarrhea-predominant IBS subtype was labeled for alosetron therapy.

The next table summarizes my comments in ii, iii, iv.

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following table, the mean baseline scores of the All-Randomized and Treated (Intention-To-Treat) population or the so-named diarrhea predominance subset of patients, did not reach the scores of 4 (loose stools) or 5 (watery stools).

Reviewer Table 4

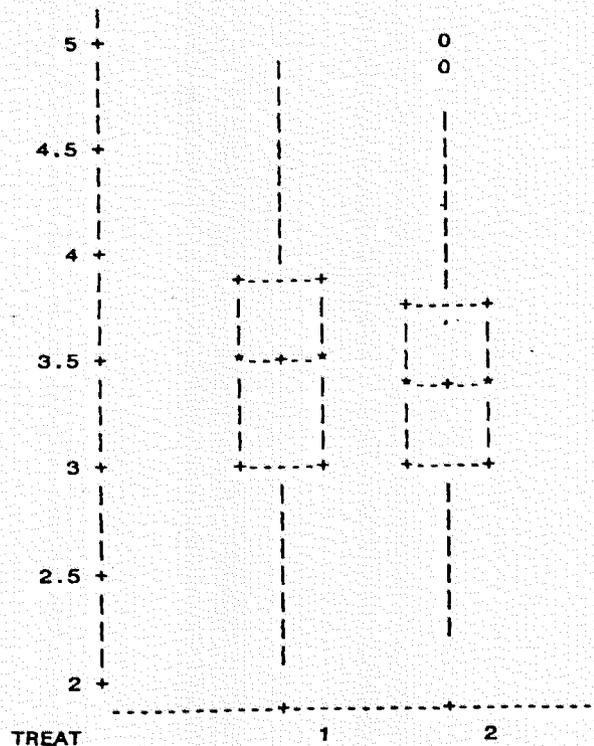
Study 3001. Stool Consistency Scores at Baseline

| Patient Population | Placebo | Alosetron | Statistical Median |
|--------------------------|---------|-----------|--------------------|
| All-Randomized (N=626) | 3.40 | 3.42 | P=3.44; A=3.43 |
| Diarrhea Predom. (N=446) | 3.58 | 3.50 | P=3.54, A=3.50 |
| Constip/Diarrhea (N=169) | 3.19 | 3.21 | P=3.12; A=3.19 |

As noticeable in the table, baseline stool consistency in the diarrhea-predominant patient population was only 3% higher than stool consistency in the Intention-to-Treat (ITT) population (*excluded in this ITT were 11 IBS patients enrolled with diagnosis of constipation*), and only 10% higher than stool consistency in the alternating constipation/diarrhea population. The next figure shows the statistical distribution of baseline stool consistency in IBS women randomized to either placebo or alosetron (*as calculated by the statistician reviewer, Dr. David Hoberman, SAS system, representing Placebo as Treat=1 and Alosetron as Treat=2*).

Univariate Procedure
Schematic Plots

Mean Stool Consistency at Baseline (Obs)



This reviewer acknowledges that during the screening phase the Case Report Form (CRF) had a provision (box) for investigators to state their clinical impression of IBS subtypes based on symptoms, i.e., diarrhea-predominant, alternating constipation/diarrhea, constipation. However, there was no definition of diarrhea-predominance in the prospective study protocol other than the Rome Criteria guidelines for IBS diagnosis. In the screening phase of the protocol (*see Protocol, this review*) the Rome Criteria guidelines required **>3 bowel movements per day and loose or watery stool to establish the diagnosis of a IBS diarrhea** (*The Rome Criteria does not use the terminology of diarrhea-predominant*). As shown in Table T-7.48 (*see my Descriptive section*), IBS women enrolled in this pivotal study revealed **baseline daily stool frequencies of 2.75 for Alosetron patients and 2.75 for Placebo patients.**

In summary, based on the submitted data, **IBS patients enrolled in this study did not meet the definition of diarrhea, either by applying the stool consistency scores developed by the sponsor, or by applying the diagnostic Rome Criteria for IBS diarrhea (>3 bowel movements per day in frequency + loose/watery stools).**

6. IBS patients with a history of alcohol abuse were excluded from the two pivotal multi center trials. Alcohol use was not captured by the CRF and was not included in patient demographics. In a recent study² conducted at a department of psychiatry, the prevalence of IBS was compared in 31 ambulatory patients seeking treatment for alcohol abuse or dependence; this group was sex-matched to a control group of 40 patients seeking treatment in a general physician's office for other medical illnesses. Thirteen (42%) patients with alcohol dependence met the criteria for IBS compared to 1 (2.5%) patient in the control group. There are a few co-morbid painful disorders that have been, rather consistently, associated to a high incidence of IBS^{3,4}. The classical example is fibromyalgia. History of fibromyalgia or other painful co-morbid disorders was not a part of the CRF questionnaire. At the request of this reviewer, GW retrospectively tabulated the efficacy of alosetron in a small subset of IBS women with associated fibromyalgia. The results of IBS + fibromyalgia are included as *Appendix 5 of this review*.

7. The sponsor reports significant interaction between the experimental drug and women with menses, i.e., women with menses have higher response to alosetron than do women without menses. This issue is of some relevance^{5,6} because alosetron therapy for IBS is targeted to provide adequate relief of IBS abdominal pain/discomfort. During and just prior to the menstrual period, some women may experience abdominal pain/discomfort, sometimes severe. If women with menses happen to respond better to alosetron than women without menses, menstrual abdominal pain/discomfort may become a confounding variable in the alosetron therapy of IBS women. The sponsor was requested to provide specific information on alosetron response in women with menses during the menstrual period. At this present time, the sponsor is reviewing the data and is expected to provide its response on this issue in the forthcoming days.

8. As shown in the *Descriptive (Patient Disposition section)*, 22%-23% of all enrolled IBS patients were discontinued prematurely from the trial. Of the 72 patients treated with alosetron that were removed prematurely 48 were removed due to an adverse event, most of them for resistant and severe constipation (48/309=16%). Only 21 placebo patients, out of 71 discontinuations, were removed because of an adverse event (21/317=7%). The difference between alosetron vs. placebo was significant ($p=0.01$). An argument could be made that