I. BACKGROUND/INTRODUCTION:

The 5-HT_3 subtype receptors have been implicated in the mechanisms controlling gastrointestinal function especially motility and sensation[3]. The drug which is the subject of the present multidisciplinary review is alosetron (also known as GR68755), proposed brand name LOTRONEX™. Alosetron belongs to a class of compounds known as 5-hydroxy-tryptamine type 3 (5-HT_3) receptor antagonists (5-HT_3RAnt). Three drugs of this type (ondansetron, granisetron and dolasetron) have been approved for the prevention of nausea or vomiting induced by either cancer chemotherapy or surgical anesthesia and operative procedures[4]. In addition, the 5-HT_3 receptors on visceral afferent neurons are thought to be implicated in the underlying pathophysiology of irritable bowel syndrome (IBS)[5] and other gastrointestinal disorders such as functional dyspepsia and non-cardiac chest pain. For example, ondansetron has been shown to delay colonic transit in healthy volunteers [S. Gore et al. Aliment. Pharmacol. Ther. 4: 139-144 (1990); N.J. Talley et al. Dig. Dis. Sci. 35: 477-480 (1990)] while granisetron has been shown to increase the volume threshold for perception of pain during rectal distention [A. Prior, N.W. Read Aliment. Pharmacol. Ther. 7: 175-180 (1993)]. 5-HT_3 receptors are also involved in the mediation of cutaneous vasodilatation with subsequent erythema and flare in response to intradermal 5-HT and several 5-HT_3 antagonists have been shown to inhibit this response[6]. Because of these and other properties, the 5-HT_3 RAnt have been anticipated to be of benefit in the treatment of non-constipated IBS patients[7].

IBS is the most common functional gastrointestinal disorder seen by general physicians. IBS is characterized by a number of clinical features and probably comprises a cluster of different conditions. Although the most frequent symptom reported by IBS patients is abdominal pain, for a number of patients, bowel disturbances are the most prominent symptoms[8]. During the last 12 years, epidemiological, physiological, and psychological data have emerged to improve our understanding of this disorder, which is now believed to result from dysregulation of intestinal motor, sensory, and CNS function (brain-gut dysfunction)[9]. IBS has been defined using symptom-based criteria (the Manning criteria, the Rome criteria) as "a combination of chronic or

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[3] [N.J. Tally 5-Hydroxytryptamine agonists and antagonists in the modulation of gastrointestinal motility and sensation. Aliment. Pharmacol. Ther. 6: 273-289 (1990)].

[4] The brand names of the approved drugs are ZOFRAN® (GlaxoWellcome), KYTRIL® (SmithKline Beecham) and ANZEMET® (Merrell Dow), respectively.

[5] [E.A. Mayer, H.E. Raybould. Role of visceral afferent mechanisms in functional bowel disorders. Gastroenterology 99: 1688-1704 (1990)].

[6] [J.R. Fozard, Neuropharma 23: 1473 (1984)]
[N.A. Minton. Br. J. Clin. Pharmacol. 37: 525-530 (1994)]
[J. M. Orwin, J.R. Fozard. Eur. J. Clin. Pharmacol. 20: 209-212 (1986)]

[7] [American Gastroenterological Association Medical Position Statement: Irritable Bowel Syndrome. Gastroenterology 112: 2118-2119 (1997)]

[8] [M. Delvaux, J. Frexinos. A European Approach to Irritable Bowel Syndrome Management. Can. J. Gastroenterol. 13 Suppl. A:85A-88A (1999)]

[9] [Irritable Bowel Syndrome: A Technical Review for Practice Guideline Development, AGA Patient Care Committee Bowel Syndrome: A Technical Review for Practice Guideline Development, AGA Patient Care Committee, Gastroenterology 112: 2120-2137 (1997)]
[D.A. Drossman Review article: an integrated approach to the irritable bowel syndrome. Aliment. Pharmacol. Ther. 13 Suppl.2:3-14 (1999)]

recurrent g.i. symptoms not explained by structural or biochemical abnormalities", which is "attributed to the intestines and associated with symptoms of pain and disturbed defecation and/or symptoms of bloated and distension". IBS affects 14% to 24% of women and 5% to 19% of men. For more than half of IBS patients the first presentation of symptoms to a physician is between the ages of 30 and 50 years[10] and prevalence decreases beyond age 60[11]. The symptoms of IBS wax and wane. Although the duration of exacerbations and remissions has not been adequately studied; instead of, **randomized clinical trials of 12-week duration** are usually recommended. Although consensus has not been reached, research to date indicates that symptoms of IBS are generated by quantitative differences in motor reactivity of the gut and increased sensitivity to stimuli (distension) or spontaneous contractions. However, the types of motility patterns seen in the colon and small intestine in patients with IBS are qualitatively similar to the contractions seen in healthy controls and there is no consensus on the patterns of motility responsible for diarrhea or constipation. In patients with IBS, factors such as meals, balloon inflation, cholecystokinin and psychological stress, lead to an exaggerated intestinal motor response[12]. There is increased sensitivity to painful distentions in the small bowel and colon. There is also increased sensitivity to normal intestinal function (e.g. spontaneous migrating motor complexes); as well as an increased or unusual area of somatic referral of visceral pain. Because the mechanisms of central interpretation of afferent signals are not known, it is also not known whether psychological or neurophysiological mechanisms work singly or together in the perception of incoming signals.

Other factors such as inflammation and motor activity play an important role in the development of IBS but the role of autonomic dysfunction in IBS requires further evaluation. An evolving theory is that chronic GI symptoms result from an alteration of the integration of intestinal motor, sensory, autonomic, and CNS activity, These domains interact through circuits at all levels of the brain-gut axis[13], which provide the linkage between visceral afferent sensation and intestinal motor function, and both can be modified by higher cortical centers. The numerous neurotransmitters found in brain and gut are the messengers that regulate these activities. The enkephalins, substance P, calcitonin gene-related polypeptide, nitric oxide, **5-HT**, cholecystokinin, and others have varied and integrated effects on pain control, GI motility, emotional behavior, and immunity[14].

The diagnosis of IBS is a **diagnosis of exclusion**. Now a days, the preferred approach is identification of IBS using positive symptom criteria (ex. the Rome criteria) and a limited diagnostic screen[15]. Additional diagnostic studies depend on the predominant symptom subgroup, namely constipation, diarrhea, alternating diarrhea/constipation, or pain/gas/bloating.

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[10] [R.F. Harvey, et al. Prognosis in the irritable bowel syndrome: a five-year prospective study Lancet i:963-965 (1987)]
[11] [L. Kay J. Intern. Med. 236: 23-30 (1994)]
[12] [D. Kumar, D.L. Wingate. Lancet 2: 973-977 (1985)]
[J.E. Kellow et al. Gut 29: (1236-1243 (1988)]
[J.E. Kellow et al. Gastroenterology 98: 1208-1218 (1990)]
[13] [E.A. Mayer, H.E. Raybould Gastroenterology 99: 1688-1704 (1990)]
[14] [E.A. Mayer, G.F. Gebhart. Basic and clinical aspects of visceral hyperalgesia. Gastroenterology 107: 271-293 (1994)]
[15] [D.A. Drossman. Diagnosing and treating patients with refractory gastrointestinal disorders. Ann. Intern. Med. 123: 688-697 (1995)]

In this era of managed care, a minimal evaluation and a therapeutic trial, rather than extensive investigation, is preferred[16].

The specific indication for which Glaxo Wellcome is seeking approval is:

> "LOTRONEX™ is indicated for the treatment of Irritable Bowel Syndrome (IBS) in female patients whose predominant bowel symptom is diarrhea,

II. SUMMARY OF THE EVIDENCE PRESENTED BY THE SPONSOR

In support of their request for the approval of the marketing of LOTRONEX™, Glaxo Wellcome has submitted information on chemistry, pharmacology/toxicology, pharmacokinetics/pharmacodynamics and clinical/statistics. A succinct appraisal of these materials follows.

Non-clinical findings and relevance to clinical studies

- Mutagenicity and carcinogenicity studies in mice and rats revealed no evidence of genotoxicity or neoplasia following 2-year exposure to alosetron.

- In animal studies, transient decreases in hearing acuity were observed in RH rats and beagle dogs after 12-month oral administration of high dose (ca. 1000-fold the recommended dose) alosetron. These changes were not permanent and reversed within one month of cessation of alosetron treatment. No effect on hearing was noted after 102-week administration of alosetron to Wistar rats.

- [During the review of the safety data from clinical studies, special attention was put on the occurrence of hearing-related adverse events that may have been noted during alosetron treatment; see review of the 120 day SU of NDA 21-107].

- High dose alosetron administered in studies of rats and rabbits did no seem to produce significant adverse effects on reproductive function, fertility, or embryofetal toxicity. [However, the available clinical information on the use of this drug in pregnancy in IBS patients is minimal].

Human Pharmacokinetic/Phamacodynamic Data

This information appears incomplete.

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[16] [M. Camilleri, C.M. Prather. The irritable bowel syndrome: mechanisms and a practical approach to management. Ann. Intern. Med. 116: 1001-1008 (1992)]
[D.A. Drossman, W.G. Thompson. The irritable bowel syndrome: review and a graduated, multicompoaint treatment approach. Ann. Intern. Med. 116: 1009-1016 (1992)]

- Because alosetron is metabolized by a variety of liver enzymes, the sponsor proposes (and this seems reasonable) that alosetron metabolism is unlikely to be significantly affected by inhibition or induction of any one enzyme. Alosetron does not appear to induce the cytochrome P_{450} metabolizing enzyme system of the liver to a great extent. *In vitro* and *in vivo* drug-drug interaction studies appear to indicate little potential for clinically significant drug interactions by alosetron.
  [Alosetron interaction studies were conducted with cisapride, theophylline and oral contraceptives. These evaluations revealed no evidence of interaction. Assessment of EKG changes during alosetron treatment and concomitantly with cisapride also revealed no significant effects].

Clinical/Statistical Data

The efficacy and safety of alosetron has been evaluated in 3,670 patients and healthy volunteers enrolled in a total of 52 completed studies worldwide. This includes 1810 patients with IBS who received alosetron monotherapy. In the main, the clinical/statistical data consist of the following.

a) Two Phase II dose-ranging trials: S3BP12 [n=467; conducted in Europe and Canada] and S3BA2001 [n=370; conducted in the US (n=315) and Europe and Canada (n=55)]. In essence, data from these two trials showed:

   - Efficacy was preferentially observed in females, as compared to males. This differential gender effect was not readily explained by PK differences.

   - 1 mg BID is the optimal clinical dose.

At an end-of-phase II meeting with members of the Division, two options for Phase III trial designs (both testing 1 mg BID in studies of 12-week duration) were discussed.

i) inclusion of both men and women with stratified analysis by gender
or
ii) inclusion of women only.

Since female patients comprise the largest subgroup of IBS sufferers and Phase II results had demonstrated efficacy and an optimal clinical dose in this population, the sponsor made the decision to pursue the option of progressing to Phase III trials enrolling females only.

b) Two critical Phase III trials: S3BA3001 (n=626) and S3BA3002 (n=647)
   [It is important to note that studies to further explore possible physiologic mechanisms responsible for the observed differences in gender effect are underway. Also initiated is an additional, large dose-ranging efficacy trial in males (study S3B20023)].

- Both critical studies used an identical protocol, with a very useful design and were 2-arm, multicenter, double-blind, randomized (4 patients per permuted block), US trials. The treatment groups consisted of either alosetron (1 mg BID) or placebo BID. A 2-week

screening phase was followed by a 12-week double-blind treatment period and a 4-week post-treatment follow-up period for a total duration of 18 weeks.

- Key inclusion criteria were:

  i) an average abdominal pain/discomfort score between 1.0 and 3.3 during the screening phase[17] and

  ii) an average stool consistency score of at least 2.5[18].

- The **primary clinical endpoint** was the patient's weekly response in a diary to the question: "In the past 7 days, have you had adequate relief of your Irritable Bowel Syndrome pain and discomfort (YES/NO)?" The primary analysis[19] compared the number of **"monthly responders"** (patients who indicated "adequate relief" for at least 2 weeks out of the month). Thus a patient could be a responder for any of months 1, 2, or 3.

- In one of the Phase III trials **(3002)**, Glaxo Wellcome concluded that efficacy on the primary endpoint was demonstrated only in the subgroup of women with the diarrhea-predominant type "(D-IBS)" but not in the alternating diarrhea/ constipation "(A-IBS)" or the constipation-predominant types of IBS "(C-IBS)". The sponsor subsequently performed post hoc analyses (not formulated before unbinding the data) on the D-IBS and A-IBS subgroups in the other critical study **(3001)**.

- **Secondary endpoints** included a daily pain severity score,[20] proportion of pain-free days,[21] and evaluations of Lower GI functions such as number of times stool passed/ day and stool consistency using the scale mentioned above in connection with the inclusion criteria. Sense of urgency, bloating, and sense of incomplete evacuation were also evaluated using daily reports of 'Yes/No' to the presence of each symptom. Sponsor's **Amendment 2** contained a "step-down" (closed testing) plan for secondary endpoints where the order of endpoints to be tested would be 1) stool consistency, 2) sense of urgency, 3) stool frequency, 4) sense of incomplete evacuation, and 5) bloating, in that order. **The primary time point for these analyses was to be the change from baseline at month 1, "and if significance is demonstrated for this interval, change from baseline will then be interpreted for each week in the interval..." As mentioned in the FDA statistical**

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[17] where 1= mild, 2=moderate, 3=intense, and 4=severe

[18] where 1=very hard, 2=hard, 3=formed, 4=loose, and 5=watery

[19] For the **primary analysis**, Last Observation Carried Forward **(LOCF)** was used whereby months with all missing weeks of adequate relief were replaced by the number of weeks with relief in the previous non-missing month. Since there were 3 months of evaluation, the sponsor proposed a multiple endpoint adjustment using O'Brien's global testing approach. If the global test was significant at the 0.05 level, Koch and Gansky's strategy was used: viz., each month was analyzed separately for treatment effect at the 0.05 level using the CMH test using geographic clusters as strata. In addition to monthly responders, a full trial responder was defined as anyone who completed the study and reported adequate relief for at least 6 of the study's 12 weeks.

[20] Where 0=no pain, 1=mild, 2=moderate, 3=intense, and 4=severe.

[21] **Pain-free Days** would be analyzed by defining a "monthly responder to be one who reported at least 50% pain/discomfort-free days in a month with a least 14 daily pain assessments".

review, the protocol did not specify how comparisons of pain scores would control Type I error.

- The protocols (n=300 patients per group) predicated a 15% therapeutic gain of alosetron (55% responders) over placebo (40% responders), resulting in 90% power at the 0.05 level.

c) One long-term safety study: S3BA3003 (n=859, 637 women and 222 men). This study was begun on 30 September 1997; enrollment was completed in November, 1999. This trial was designed to extend the period of treatment and observation of alosetron 1 mg b.i.d. and placebo from 12 weeks to an additional 12 months, in about 600 females and 160 males with non-constipation-predominant IBS at 250 centers, derived mainly from patients who had completed pivotal studies S3BA3001 and S3BA3002. The protocol called for gender-stratified re-randomization in 3:1 ratio to alosetron:placebo. Thus, 450 women and 120 men would be studied on a dose of alosetron 1 mg b.i.d. for up to about 15 months, compared to 150 women and 40 men on placebo, depending on randomization. At the time this study was designed, the principal safety concerns[22] were reflected in the special measurements to be made of EKGs, pure tone audiograms (PTAs), and certain laboratory tests [blood cell counts; serum electrolytes, liver enzymes (alanine and aspartate aminotransferase, alkaline phosphatase), total bilirubin, protein, albumin, calcium, phosphorus, creatinine, urea nitrogen], in addition to adverse events in general. Also planned were evaluations of changes in quality-of-life (by questionnaires) and secondarily for resource utilization (questionnaire).

III. JUSTIFICATION FOR ACCELERATED REVIEW

Glaxo Wellcome requested and was granted, accelerated review of NDA 21-107. In granting this request, the Division considered that, in comparison to existing therapies, alosetron represents a significant therapeutic advance (with an apparently acceptable safety profile) as a first line monotherapy for the significant population of female patients with non-constipating IBS.

As previously mentioned, one of the major obstacles to demonstrate drug efficacy in IBS is the **high placebo response rate** in these patients. This placebo response could be as high as 60%[23] or even higher. [30% to 88%, according to the AGA (Gastroenterology 112: 2120-2137 (1997)]. Strictly speaking, only a few agents in the US are labeled for the treatment of IBS or symptoms of IBS. Most are described as **"adjunctive treatment"** while others, such as LIBRAX (a combination of the antidepressant Librium with the anticholinergic clidinium bromide) have the qualifier that they are **"possibly effective."** This reflects the market introduction of these products prior to establishment of the current regulatory standards for providing substantial evidence of effectiveness. Among the approved drugs is LOPERAMIDE (IMODIUM; and

[22] The reasons cited for special concerns about EKGs and PTAs were the history of EKG QT prolongation by certain agents affecting serotonin receptors (especially cisapride, a 5-HT_4 agonist) and the above mentioned findings in rats of decreased ear twitch reflex response to noise (Preyer test) and in dogs (BAER test).

[23] [G.F. Longstreth et al. Ann. Intern. Med. 95: 53 (1981)]
[R.F. Harvey et al. 1: 1278 (1973)]

probably other opioid agonists), belladona alkaloids and synthetic substitutes. An example of this type of drug is DONNATAL, a drug combination that provides natural belladona alkaloids in a specific fixed ratio, combined with phenobarbital to provide peripheral anticholinergic/antispasmodic action and mild sedation. This combination is classified as "possibly effective". Another example is the long line of LEVSIN products (Tablets, Elixir, Drops, Injection, LEBSID Extended-release Tablets, LEVSINEX TIMECAPS). One of the difficulties when using IBS drugs that contain an anticholinergic agent as one of the primary active ingredients is the numerous adverse events that are associated with their use. These evens include constipation, bloating, abdominal pain, and numerous CNS-related adverse events.

In literature reviews dealing with the subject of therapy of IBS, the use of fiber (12g per day in patients with constipation-predominant IBS) is always mentioned. Then drugs, both approved and those not yet approved for this indication by the FDA, are usually listed according to their pharmacologic effect (anticholinergics, drugs that inhibit contractile colonic motor activity, those that modulate g.i. transit and visceral perception, psychotropic substances and psychological treatment)[24]. In his recent review article, M. Camilleri [25] concludes that current therapies targeted on the predominant symptoms of IBS (meaning diarrhea, constipation or abdominal pain/bloating) are "moderately successful". Marvin M. Schuster[26] states: **"given the many visceral afferent innervations-and the even greater complexity introduced by the dynamic interaction of these factors (both of which remain poorly understood)- it is easy to see why no effective treatment for IBS has yet evolved."**

It was therefore concluded that, in spite of IBS being an important clinical entity (see Section I of this review), there is no "gold standard" treatment for this condition. No commercially available agent in the United States has been shown to have proven efficacy in the treatment of IBS. Specifically, in non-constipated female IBS patients, no agent has been shown to be of proven benefit in the treatment of the patient's most bothersome symptoms of abdominal pain, urgency and increased stool frequency. Alosetron appears to be suitable to meet this need.

In summary, antidiarrheals are effective in increasing stool firmness and decreasing stool frequency but do not have a significant effect on a) relieving abdominal pain; b) pain thresholds nor c) decrease rectal pain sensitivity[27]. The neuromodulatory and analgesic properties of antidepressants may aid in the relief of IBS symptoms; but only a few trials have specifically evaluated the efficacy of tricyclic antidepressants in IBS. According to Francis and Whorwell[28] tricyclic antidepressants have not demonstrated consistent improvement in abdominal pain, bowel functions or other IBS symptoms. In addition, tricyclic antidepressants are frequently poorly tolerated, causing weight gain, dry mouth, constipation, sexual disfunction and cognitive

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[24] [F. Pace et al. Therapy of Irritable Bowel syndrome-An Overview. Digestion 56: 433-442 (1995)]
[25] [M. Camilleri. Review article: clinical evidence to support current therapies of irritable bowel syndrome. Aliment. Pharmacol. Ther. 13 Suppl. 2: 48-53 (1999)].
[26] [M.M. Schuster. Chapter 13. Pharmacologic Therapy of Irritable Bowel Syndrome. Gastroint. Pharmacol. Ther. G. Friedmant et al. (eds.). Lippincott-Raven Publishers, Philadelphia pp. 127-131 (1997)]
[27] [W.E. Whitehead. Effects of Loperamide on Pain Thresholds in Healthy Subjects. Gastroenterology 116:A1102 (1999)]
[28] [Brain and Irritable Bowel Syndrome:Time for Reappraisal. Lancet 344: 39-40 (1994)]

impairment[29]. Recent evaluations reveal that the antidepressant amitriptyline[30] improves somatic pain while it does not significantly change visceral noniception.

IV. REVIEW PLAN

On the basis of considerations discussed in detail under Section III. above, the GlaxoWellcome application on alosetron (NDA 21-107) **received a priority review classification**. A 6-month Review Plan was instituted (Appendix 1). The reviewers and the dates of reviews are listed in Table 1.

TABLE 1
NDA 21-107: Reviewers

Discipline	Reviewer
Chemistry	Dr. M. Ysern (November 18, 1999)
Pharmacology/Toxicology	Dr. Ke Zhang (November 4, 1999)
Pharmacokinetics/Pharmacodynamics	Dr. R. Kavanagh (December 3 , 1999
Efficacy	Dr. R. Prizont (November 4, 1999)
Safety	Dr. J. Senior (October 25, 1999)
Review of ➡ Safety Update	Dr. J. Senior (December , 1999)
Secondary (Multidisciplinary) Review	Dr. H. Gallo-Torres (This memorandum)

Throughout the NDA evaluation, contemporaneous communication to sponsor and prompt reply by GlaxoWellcome of reviewer questions (Appendix 2), mainly related to safety concerns have been place. This interaction has greatly facilitated timely completion of reviews and adequate preparation for presentations to the Gastrointestinal Advisory Committee Meeting scheduled for November 16, 1999.

[29] [AGA Medical Position Statement: Irritable Bowel Syndrome. Gastroenterology 112: 2119 (1997)]
[30] [A.B. Gorelick et al. Differential Effects of Amitriptyline on Perception of Somatic and Visceral stimulation in Healthy Humans. Amer. J. Physiol. 275: G460-G466 (1998)].

V. SUMMARY REVIEW OF THE EVIDENCE

A. Efficacy (Studies 3001 and 3002)

1. Baseline Characteristics (Table 2)

- There were no imbalances in important baseline characteristics between alosetron (ALOS) and placebo (PL).

- In all 4 randomixed groups (between the 2 trials), the mean baseline parameters of evaluation were:

Pain score	2.0
Stool consistency	3.4
Stool frequency	2.7/day
Sense of urgency	69% days/week
Abdominal bloating	77% days/week
Incomplete evacuation	70% days/week

Thus the study population did not have diarrhea at randomization, either by definition of stool consistency (diarrhea would be 4=loose stools, 5=watery stools) or frequency (diarrhea would be ≥3 bowel movements per day).

2. Number of Patients in Analyzed Study Populations

Study Population	3001		3002	
	PL	ALOS 1 mg BID	PL	ALOS 1 mg BID
ITT	317	309	323	324
"Diarrhea Predominant"	222	224	221	237
Alternating Pattern	87	82	95	85

Source: Tables 3 and 4, Statistical Review and Evaluation by Dr. D. Hoberman

TABLE 2

Patient Baseline Characteristics in Principal Clinical Trials

I. Demographics				
	3001		3002	
	PL [n=317]	ALOS [n=309]	PL [n=323	ALOS [n=324]
Age (Mean)	45.3	46.5	45/7	46.5
Race				
- White	87%	88%	03%	92%
Mensturation				
- Yes	41%	42%	40%	41%
Fiber Use				
- Yes	46%	45%	46%	44%
- No	54%	55%	54%	57%
II. IBS				
Time since onset of symptoms (mean years)	10.7	12.4	9.6	11.1
IBS subtype "Diarrhea-Predominant"	70%	72%	68%	73%
Alternating	27%	27%	29%	26%
Pain/Discomfort score	1.97	1.93	1.90	1.95
% Pain/Discomfort free days	12.7	13.0	14.8	14.3
% Days urgency	69.3	69.8	69.3	67.0
Stool frequency	2.71	2.75	2.77	2.71
Stool consistency	3.46	3.42	3.40	3.42

3. Dropouts (Table 3)

- Both trials suffered from a substantial number of patients who exited prematurely, ca. 25% in each trial. The FDA statistician carried out a detailed examination of the numbers and timing of dropouts in each study arm. According to the FDA statistician, this approach is expected to help in the assessment of constraints in drawing conclusions about efficacy.

- A substantial number of dropouts occurred within the first 4 weeks (Table 3). Patients who were assigned to ALOS felt they could not continue in the trial due to AEs (partly constipation); it is to be noted what PL patients left for a variety of reasons. Dropouts tended to taper off after 4 weeks. The reason for the substantial number of "Withdrawn Consents" in the PL group in study 3001 has not been determined. To assess the extent to which dropouts contributed to the achievement of adequate relief response, Dr. Hoberman tabulated the number of dropouts achieving adequate relief in each group:

In Study 3001, there were a total of 40 dropouts who happen to be monthly responders for adequate relief for at least one month during the trial, 18 (PL) and 22 (ALOS). Of the 22 (ALOS) dropouts, 9 did so due to AEs.

In Study 3002, there were a total of 38 dropouts who happen to be monthly responders for adequate relief for at least one month during the trial, 16 (PL) and 22 (ALOS). Of the 22 (ALOS) dropouts, 7 did so due to AEs.

TABLE 3
NDA 21-107

DROPOUTS IN PRINCIPAL CLINICAL TRIALS

		3001 [n=616]			3002 [n=647]		
		Week			Week		
		4[a]	8	11	4	8	11
Adverse Event	PL	8	7	6	10	2	1
	ALOS	36	11	1	36	10	3
Consent Withdrawn	PL	16	8	1	6	1	0
	ALOS	4	1	1	7	0	0
Lack of Efficacy	PL	3	4	0	8	5	1
	ALOS	4	2	1	4	1	1
Lost to Follow-up	PL	4	4	2	5	1	1
	ALOS	4	1	0	6	1	2
Protocol Violation	PL	0	0	0	0	1	1
	ALOS	0	1	0	1	0	0
Other	PL	5	0	1	1	0	1
	ALOS	1	1	2	0	1	0
Misc[b]	PL	0	0	6	0	1	13
	ALOS	1	0	10	2	0	14
Total		**86**	**40**	**31**	**86**	**24**	**38**

Source: Statistical Review, pages 3 and 4.
a) These columns (W4, W8, etc.) refer to separate epochs during which patients dropped out.
This "miscellaneous" category is Dr. Hoberman's. It accounts for patients that were not evaluated for the primary efficacy endpoint but were not accounted for by the sponsor.

- The FDA statistician noted that of all the reasons for withdrawal, the only one which is specific enough to likely affect the comparison of the two arms is "adverse events" dropouts which are not random. Dr. Haberman showed that patients who dropped out on ALOS did not contribute more adequate relief responses than PL dropouts. As already mentioned, the bulk of non-random dropouts occurred within the first 4 weeks of the trial,

thus leaving the remaining cohort relatively free of non-random dropouts. Since there were non-random dropouts, it is not possible to estimate a "true" treatment difference at any particular time. However, using all the data in the trial, one can ask the global question; "Is there convincing evidence that the distribution of responses on the drug is different from that on PL, given the pattern of dropouts?" Dr. Hoberman further noted that if the pattern and number of dropouts is judged not to have overwhelmingly determined the result of the treatment comparison, then a statistical analysis is often reasonable. Similar results of analyses using the 75% of the initial cohorts who completed the trial are useful as a way to check that the dropouts did not unduly affect the evidence which will lead to an inference concerning the activity of the drug. In summary, **dropouts did not seem to influence efficacy results.**

4. Electronic Data Capturing (EDC)

Using the EDC method the patients phoned in daily to a central database and responded to automated questions by pressing appropriate keys on a touch phone pad. The symptom data entered by patients was time and date stamped. Once the patient data had been entered, the database was secured and not accessible to modification. The patients were asked questions about pain and discomfort and bowel function.

This EDC approach, used in the gathering of Phase II and III data, represents a significant advantage over the traditional paper diary cards. Inherent problems with the latter included uncertainty about when the data were recorded by the patient and the possibility of retrospective changes (recall bias).

The usefulness of the EDC can be summarized as follows:

	Phase II Results	**Phase III** Results
Time system was operational	98%	>99%
Phone calls completed by patients	82%	85%

5. Results of Primary Efficacy Analyses (Tables 4 and 5)

The primary efficacy endpoint was adequate relief of IBS pain and discomfort, captured when the following question was asked of patients.

"In the past seven days have you had adequate relief of your irritable bowel syndrome pain and discomfort?"

In both the ITT and "Diarrhea Predominant" (but not in the Alternating Pattern) study populations, patients on ALOS treatment reported significantly more months with adequate relief

in IBS pain and discomfort[31] as compared to patients receiving PL, in both 3001 and 3002. In Study 3002, the difference at Month 2 in the ITT population was N.S.

- On page 5 of Dr. Hoberman's review, he points out that the sponsor's LOCF strategy for filling in data on 'adequate relief' monthly responders for the purpose of an all patients-randomized analysis could be misleading because it reports percentages of patients who were responders at month 3 who were not in the trial at that time. As an alternative, he analyzed the *patterns* of response over the 3 months. Like the sponsor' LOCF analysis, this approach incorporates all patients, but **does not carry forward the last response evaluation of a dropout**. The CMH test using modified ridit scores (essentially a Wilcoxon Rank Sum test) yielded a p-value of <0.001 in 3001 and 0.008 in 3002. This indicated that the ALOS groups had a more favorable adequate relief profile than the PL groups. Dr. Hoberman further notes that the difference between the two distributions appears to be due to the fact that more patients were ***never*** responders in the PL group, while more patients responded at all 3 months in the ALOS group. Using Dr. Hoberman's approach, there was no statistical evidence of interaction between treatment and either baseline pain, pre-study symptom duration, or geographical cluster. The results for the "Diarrhea Predominant" IBS subgroup were similar.

[31] Definition of Primary Endpoint
- ≥2 weeks/month with adequate relief
- For months with incomplete data, missing weeks were imputed as no relief
- LOCF for months with all weeks missing

TABLE 4
NDA 21-107

Study 3001: Monthly Relief of IBS Pain/Discomfort: LOCF

Measurement (Month)	Statistic	PL [n=317]	ALOS 1 mg BID [n=309]	Therapeutic Gain[a]	p-value[b]
I. ITT Population					
1	n (%) (95% CI)	126 (40%) (34.4%, 45.1%)	154 (50%) (44.3%, 55.4%)	10.1% (2.3%, 17.8%)	0.010
2	n (%) (95% CI)	137 (43%) (37.8%, 48.7%)	176 (57%) (51.4%, 62.5%)	13.7% (6.0%, 21.5%)	<0.001
3	n (%) (95% CI)	130 (41%) (35.6%, 46.4%)	179 (58%) (52.4%, 63.4%)	16.9% (9.2%, 24.6%)	<0.001
II. "Diarrhea Predominant" Population					
		[n=222]	[n=224]		
1	n (%) (95% CI)	87 (39%) (32.8%, 45.6%)	112 (50%) (43.5%, 56.5%)	10.8% (1.6%, 20.0%)	0.022
2	n (%) (95% CI)	96 (43%) (36.7%, 49.8%)	129 (58%) (51.1%, 64.1%)	14.3% (5.2%, 23.5%)	0.003
3	n (%) (95% CI)	92 (41%) (35.0%, 47.9%)	135 (60%) (53.9%, 66.7%)	18.8% (9.7%, 27.9%)	<0.001
III. Alternating Pattern Population					
		[n=87]	[n=82]		
1	n (%) (95% CI)	35 (41%) (31.0%, 51.7%)	40 (49%) (38.0%, 59.6%)	7.4% (-7.6%, 22.4%)	N.S.
2	n (%) (95% CI)	38 (44%) (33.3%, 54.1%)	45 (55%) (44.1%, 65.6%)	11.2% (-3.8%, 26.2%)	N.S.
3	n (%) (95% CI)	37 (43%) (32.1%, 52.9%)	42 (51%) (40.4%, 62.0%)	8.7% (-6.3%, 23.7%)	N.S.

Source: Table 3a, 3b and 3c in Dr. Hoberman's Statistical Review and Evaluation, with major modifications.

NOTE: A subject was defined as a responder if she reported adequate relief of abdominal pain/discomfort for at least two of the four weeks during a month.

a) ALOS > PL
b) Mantel-Haenszel test with stratification for cluster