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Alosetron use demonstrated improvement in numerous bowel functions in female subjects which was sustained throughout treatment. Specifically, subjects treated with alosetron experienced a decrease in the number of stools produced per day, had firmer stools (a desirable effect since subjects in the study presented with firm or loose/watery stools) and experienced a reduction in the incidence of incomplete stool evacuation and urgency. Also, the incidence of straining increased in alosetron-treated women. This effect is probably due to the production of firmer stools (Tables 15.7 through 15.13).

1.9.5 Reviewer Comments.

1. This reviewer concurs with the sponsor that alosetron 1 mg b.i.d. dose provided the greater therapeutic gain against placebo, particularly females, in the post-hoc comparison between treatments in the adequate relief abdominal pain/discomfort. It should be pointed out that among female completers, alosetron 2 mg b.i.d. provided similar therapeutic benefit than 1 mg b.i.d. (see above figure of adequate relief in female completers).

2. This reviewer also concurs with the sponsor in that the greatest therapeutic benefit with alosetron therapy was observed in IBS women. However, the male population enrolled in this dose-ranging study was too small to observe any significant treatment difference or draw any definite conclusions, i.e., there were a total of 19 men randomized to alosetron 1 mg b.i.d.

4. Reviewer Summary on Alosetron Efficacy in IBS Trials.

1.10 Pivotal Clinical Trial A3001 and A3002.

1.10.1 . Intention-to-Treat

- The sponsor submitted two pivotal clinical trials to support the claim, included in the proposed label, that alosetron 1 mg b.i.d. is superior to placebo in the treatment of women with diarrhea-predominant IBS . Both pivotal trials were conducted in the U.S., were multi center, randomized, double-blind, placebo-controlled and had the aim to show safety and efficacy in non-constipated women with IBS. Other than exclusion of constipated women, there was no prospective stratification in IBS subtypes, i.e., diarrhea-predominant IBS, or alternating constipation/diarrhea IBS. Both pivotal trials had identical prospective study design. IBS women were treated for a period of 3 months, and there was a follow-up period of 1 month without treatment. The primary efficacy endpoint was the adequate relief of IBS abdominal pain/discomfort. Relevant secondary efficacy endpoints were lower bowel functions such as improvement in stool consistency, stool frequency and stool urgency.

These **two pivotal trials randomized** to treatments a **total of 1273 IBS women**; 626 IBS women in A3001 and 647 IBS women in A3002. Most of the women were white and had experienced IBS symptoms for approximately 10 years. At screening, **IBS diagnosis followed the Rome Criteria** guidelines.

The Intention-to-Treat comparison of Primary Efficacy Endpoint results revealed similar results for both trials, with the highest significance in alosetron patients who responded to treatment all three months of the study. The summary results are shown below:

Reviewer Table 7

Overall Summary Primary Efficacy Results in Pivotal Trials A3001 and A3002
Responders to Alosetron Treatment in All 3 Months

A3001. Placebo = 26% versus Alosetron = 41% [15% Therapeutic Gain; *p<0.001*]
A3002 . Placebo = 29% versus Alosetron = 41% [12% Therapeutic Gain; *p=0.012*]

- The only duration of treatment that showed significant efficacy of alosetron over placebo in the adequate relief of abdominal pain/discomfort was the combined three month treatment. Partial 2 months or 1 month treatments did not reveal any differences between treatments.

- For the purposes of the presented pivotal clinical trials with alosetron the reviewer acknowledges and accepts the prospectively defined primary efficacy outcome. There is , however, a need to capture in the primary efficacy endpoint lower bowel functions by using a more encompassing IBS definition, e.g., adequate relief of IBS symptoms.

- There were no differences between alosetron and placebo in the proportion of pain-free days experienced by patients. The overall intensity of abdominal pain decreased from moderate at baseline (1.9) to mild (1) by the end of the three month treatment.

- Overall, alosetron treatment significantly superior to placebo in improving relevant IBS bowel abnormalities, such as stool consistency, stool frequency and stool urgency.

- In trial A3001, women with menses (app 40-45%) showed greater response to alosetron in the adequate relief of abdominal pain/discomfort than women without menses. This treatment by menses interaction was not observed in trial A3002.

- The prospective protocol and CRF's did not include baseline assessment of painful co-morbid diseases such as fibromyalgia. Alcohol use was not included in demographics.

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1.10.2. IBS Subtypes

Pivotal trial A3001 and A3002 were started on the same time-period, September 15-18, 1997. Pivotal trial A3002 was completed a few months earlier than trial A3001. In a ***post-hoc***, unblinded look of primary efficacy results, the sponsor noted a greater efficacy performance in the subset of women who at screening, were considered by investigators to have diarrhea-predominant IBS subtype. The sponsor then did a ***post-hoc*** analysis of IBS subtypes in A3001 and found that the difference favorable to alosetron in the Intention-To-Treat was similarly observed in the subset of diarrhea-predominant IBS subtype. The proposed label-indication reflects the sponsor ***post-hoc*** comparisons.

Examination of the submitted data led this reviewer to conclude that the use of subsets, i.e., IBS subtypes, for the purposes of ***post-hoc*** analyses and subsequent proposed indication do not meet customary clinical and statistical standards. My review allowed me to determine the following:

1. IBS diarrhea is defined in the Rome Criteria Guidelines as a form of IBS manifested by loose and/or watery stools + more than 3 bowel movements/day. Patients enrolled in these two trials as having diarrhea-predominant IBS subtype had a mean baseline stool consistency scores **below** 4 (4=loose, 5=watery), and a stool frequency ≤3/day.

2. Patients enrolled as having alternating the constipation/diarrhea subtype constituted 20% to 30% of the total sample size, too small to show any statistical superiority. Yet, in pivotal trial A3001, patients in this group on alosetron had consistent numerical superiority than patients on placebo in the adequate relief of abdominal pain/discomfort. In trial A3002, patients in this alternating/ constipation/diarrhea group **had statistically significant** superiority over placebo in improving stool consistency and stool frequency.

3. The value of a ***post-hoc***, unblinded, comparison on efficacy in a small subset of patients is controversial.

5. Recommendations For Regulatory Actions.

Based on my review of the efficacy results submitted in the two pivotal clinical trials, I recommend the following:

1. Approve oral alosetron tablets given at the dose of 1 mg b.i.d. for the treatment of non-constipated women with IBS.

2. Include in the label the subset of alternating constipation/diarrhea subtype, removing thus, the specific indication for *"diarrhea-predominant"* IBS subtype.

3. Include in the label duration of alosetron treatment.

4. The following are my recommended changes in the wording of the proposed label:

CLINICAL TRIALS SECTION	
Proposed by the Sponsor	**Recommended Changes**
(Lines 142, 149, 155, 158-159) IBS abdominal pain ~~and~~ discomfort	IBS pain/discomfort.
INDICATIONS AND USAGE	
Proposed by the Sponsor	**Recommended Changes**
LOTRONEX is indicated for the treatment of irritable bowel syndrome (IBS) in female patients	LOTRONEX is indicated for treatment of irritable bowel syndrome (IBS) in **non-constipated** female patients. **Treatment should be continued for a period of LOTRONEX has shown efficacy only in patients who respond to all treatment.**

/S/ November 4, 1999
Robert Prizont, M.D.

cc:
NDA 21-107
HFD-180
HFD-180/LTalaric
HFD-180/SAurecchia
HFD-180/HGallo-Torres
HFD-180/RPrizont
HFD-181/PLevine
HFD-180/JChoudary
HFD-180/LZhou
f/t 11/4/99 jgw
N/21107911.0RP

/S/ 11-4-99 Concur. November 4, 1999
/S/ Gallo-Torres, M.D., Ph.D.

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APPENDIX 1

Trial A3001. List of Prohibited Concurrent Medications

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Amended content:

Section 4.4.1. Assignment of subject number and treatment number, page 27

Treatments will be randomly assigned to consecutive subjects using an allocation ratio of (1:1) for the two treatment groups 1mg BID and placebo BID.

8. Content of previous version of protocol:

In Section 6.3. Package Inserts, page 41

Amended content:

***Delete:* Section 6.3. Package inserts, page 41**

9. Content of previous version of protocol:

Appendix 1. Prohibited Concurrent Medications, pages 56 and 57

Subjects must not have taken prohibited medications at least 7 days prior to entering the screening phase and remain off these medications for the duration of the study.

Antibiotics (more than a 14-day course of therapy)
- EXCEPTION: The macrolide antibiotics are prohibited for any duration of dosing.

Anticholinergics
- Dicyclomine
- Hyoscyamine
- Physostigmine
- Pyridostigmine
- Tacrine

Cholestyramine
Cholinomimetic agents (bethanechol, propantheline, anticholinergics [see above])
Codeine and codeine containing analgesics
Colchicine
Docusate
Enemas (including corticosteroids, 5-ASA preparations)
Gastrointestinal preparations
- Antacids which contain aluminum and/or magnesium
- Antidiarrheal agents
- Antinausea agents (benzquinamide, trimethobenzamide, prochlorperazine, promethazine, hydroxyzine)
- Antispasmodic agents (e.g. Donnatal®, Librax®, dicyclomine, propantheline)
- 5-ASA preparations

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- Bismuth compounds
- Laxatives (see below)
- Prokinetic agents (cisapride, metoclopramide)
- Stool softeners (see below)
- Sulfasalazine

Iron supplements

Laxatives (Laxatives that need to be given as a preparation for the required flexible sigmoidoscopy, colonoscopy or flexible sigmoidoscopy plus barium enema will not be excluded as a preparation for these tests.)

- Docusate
- Enemas
- Stimulant laxatives (including phenopthlalein, bisacodyl, milk of magnesia, mineral oil, magnesium citrate)
- All other laxatives if used more than once per week

Morphine and morphine containing analgesics

All other narcotics

Tramadol

Nonsteroidal anti-inflammatory drugs (if used more than 3 days per week)

- Note: Aspirin ≤ 325mg per day is allowed

All other analgesics (if used more than 3 days per week)

Anti-Parkinson agents (e.g. levodopa, deprenyl)

Antipsychotics

Isoniazid

Rifampicin

Anticonvulsants

Peppermint oil

Leuprolide

Stimulants and amphetamine-like drugs

Amended content:

Appendix 1. Prohibited Concurrent Medications, pages 56 and 57

Subjects must not have taken prohibited medications at least 7 days prior to entering the screening phase and remain off these medications for the duration of the study.

Antibiotics (more than a 14-day course of therapy)

- EXCEPTION: The macrolide antibiotics are prohibited for any duration of dosing.

Anticholinergics

- Dicyclomine
- Hyoscyamine
- Physostigmine

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- Pyridostigmine
- Tacrine

Cholestyramine
Cholinomimetic agents (bethanechol, propantheline, anticholinergics [see above])
Codeine and codeine containing analgesics
Colchicine
Docusate
Enemas (including corticosteroids, 5-ASA preparations)
Gastrointestinal preparations

- Antacids which contain aluminum and/or magnesium
- Antidiarrheal agents
- Antinausea agents (benzquinamide, trimethobenzamide, prochlorperazine, promethazine, hydroxyzine)
- Antispasmodic agents (e.g. Donnatal®, Librax®, dicyclomine, propantheline)
- 5-ASA preparations
- Bismuth compounds
- Laxatives (see below)
- Prokinetic agents (cisapride, metoclopramide)
- Stool softeners (see below)
- Sulfasalazine

Iron supplements
Laxatives (Laxatives that need to be given as a preparation for the required flexible sigmoidoscopy, colonoscopy or flexible sigmoidoscopy plus barium enema will not be excluded as a preparation for these tests.)

- Docusate
- Enemas
- Stimulant laxatives (including phenopthlalein, bisacodyl, milk of magnesia, mineral oil, magnesium citrate)
- All other laxatives if used more than once per week

Morphine and morphine containing analgesics
All other narcotics
Tramadol
Nonsteroidal anti-inflammatory drugs (if used more than 3 days per week)

- Note: Aspirin ≤ 325mg per day is allowed

All other analgesics (if used more than 3 days per week)

- **Note: Acetaminophen if used more than 3 days per week is allowed**

Anti-Parkinson agents (e.g. levodopa, deprenyl)
Antipsychotics
Isoniazid
Rifampicin
Anticonvulsants used for a seizure disorder
Peppermint oil
Lesmolide

APPENDIX 2

Trial A3001. Women with Menses versus Women without Menses

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Protocol: S3BA3001
Population: Intent-to-Treat

Appendix Table T-7.66
Number of Months with Adequate Relief of IBS Pain/Discomfort
By Menstruation Category

Measurement	Statistic	Placebo (N=317)	Alosetron 1 mg BID (N=309)
Menstruation Category: Not Menstruating	n	16	7
Number of Months Subject is an Adequate Relief Responder	n (%)		
0		6 (38%)	3 (43%)
1		3 (19%)	0
2		4 (25%)	1 (14%)
3		3 (19%)	3 (43%)
Menstruation Category: Menstruating	n	131	130
Number of Months Subject is an Adequate Relief Responder	n (%)		
0		58 (44%)	31 (24%)
1		24 (18%)	16 (12%)
2		12 (9%)	18 (14%)
3		37 (28%)	65 (50%)
Menstruation Category: Not Applicable	n	170	172
Number of Months Subject is an Adequate Relief Responder	n (%)		
0		71 (42%)	66 (38%)
1		26 (15%)	20 (12%)
2		31 (18%)	27 (16%)
3		42 (25%)	59 (34%)

Note: Percentages are based on the number of subjects in each menstruation category.
Note: A subject is defined as a responder if they report adequate relief of abdominal pain/discomfort for at least two of the four weeks during a month.

Source: ALOS0500EV:[S3BA3001.TABLELIB]ITT_ADEQRELF_MENSTR.SAS/QUINTILES (US)/18APR99/16:51

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Protocol: S38A3001
Population: ITT (Diarrhea-Predominant)

Appendix Table D-7.66
Number of Months with Adequate Relief of IBS Pain/Discomfort
By Menstruation Category

Measurement	Statistic	Placebo (N=222)	Alosetron 1 mg BID (N=224)
Menstruation Category: Not Menstruating	n	7	5
Number of Months Subject is an Adequate Relief Responder	n (%)		
0		2 (29%)	3 (60%)
1		2 (29%)	0
2		1 (14%)	0
3		2 (29%)	2 (40%)
Menstruation Category: Menstruating	n	98	89
Number of Months Subject is an Adequate Relief Responder	n (%)		
0		43 (44%)	18 (20%)
1		18 (18%)	10 (11%)
2		8 (8%)	12 (13%)
3		29 (30%)	49 (55%)
Menstruation Category: Not Applicable	n	117	130
Number of Months Subject is an Adequate Relief Responder	n (%)		
0		50 (43%)	50 (38%)
1		17 (15%)	16 (12%)
2		23 (20%)	19 (15%)
3		27 (23%)	45 (35%)

Note: Percentages are based on the number of subjects in each menstruation category.
Note: A subject is defined as a responder if they report adequate relief of abdominal pain/discomfort for at least two of the four weeks during a month.

Source: ALOS050DEV:[S38A3001.TABLEL18.IBSDP]DP_ITT_ADEQRELF_MEN.SAS/QUINTILES (US)/18APR99/17:37

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Protocol: [illegible]
Population: ITT (Alternating)

Appendix Table A-7.88
Number of Months with Adequate Relief of IBS Pain/Discomfort
By Menstruation Category

Measurement	Statistic	Placebo (N=87)	Alosetron 1 mg BID (N=82)
Menstruation Category: Not Menstruating	n	7	2
Number of Months Subject is an Adequate Relief Responder	n (%)		
0		3 (43%)	0
1		1 (14%)	0
2		2 (29%)	1 (50%)
3		1 (14%)	1 (50%)
Menstruation Category: Menstruating	n	32	40
Number of Months Subject is an Adequate Relief Responder	n (%)		
0		15 (47%)	13 (33%)
1		6 (19%)	6 (15%)
2		3 (9%)	6 (15%)
3		8 (25%)	15 (38%)
Menstruation Category: Not Applicable	n	48	40
Number of Months Subject is an Adequate Relief Responder	n (%)		
0		17 (35%)	15 (38%)
1		9 (19%)	4 (10%)
2		8 (17%)	8 (20%)
3		14 (29%)	13 (33%)

Note: Percentages are based on the number of subjects in each menstruation category.
Note: A subject is defined as a responder if they report adequate relief of abdominal pain/discomfort for at least two of the four weeks during a month.

Source: ALOSOSOODEV:[538A3001.TABLELIB.IBSACD]ACD_ITT_ADEQRELF_MN.SAS/QUINTILES (US)/18APR99/18:06

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APPENDIX 3

Trial A3001. Weekly Relief of Abdominal Pain/Discomfort

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Population: Intent-to-Treat

Table T-7.13
Weekly Adequate Relief of IBS Pain/Discomfort: LOCF

Measurement	Statistic	Placebo (N=317)	Alosetron 1 mg BID (N=309)	p-value
Number of Subjects with Adequate Relief During the Treatment Phase	nn/n (%)			
Week 1		94/317 (30%)	94/309 (30%)	0.843
Week 2		108/317 (34%)	126/309 (41%)	0.075
Week 3		129/317 (41%)	147/309 (48%)	0.079
Week 4		110/317 (35%)	157/309 (51%)	<0.001**
Week 5		130/317 (41%)	163/309 (53%)	0.003**
Week 6		127/317 (40%)	163/309 (53%)	0.001**
Week 7		115/317 (36%)	159/309 (51%)	<0.001**
Week 8		131/317 (41%)	168/309 (54%)	0.001**
Week 9		127/317 (40%)	169/309 (55%)	<0.001**
Week 10		122/317 (38%)	168/309 (54%)	<0.001**
Week 11		116/317 (37%)	162/309 (52%)	<0.001**
Week 12		122/317 (38%)	166/309 (54%)	<0.001**
Number of Subjects with Adequate Relief During the Follow-up Phase	nn/n (%)			
Week 1		102/317 (32%)	112/309 (36%)	0.278
Week 2		86/317 (27%)	79/309 (26%)	0.855
Week 3		81/317 (26%)	80/309 (26%)	0.823
Week 4		70/317 (22%)	63/309 (20%)	0.605

* Significant at the 0.050 level; ** significant at the 0.010 level.
Note: LOCF = last observation carried forward.
Note: P-values are the result of a Mantel-Haenszel test with stratification for cluster.

Source: ALOS050DEV:[S3BA3001.TABLELIB]ITT_ADEQRELF_WKLY_LOCF.SAS/QUINTILES (US)/15APR99/10:23

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Protocol: S3BA3001
Population: ITT (Diarrhea-Predominant)

Table 0-7.13
Weekly Adequate Relief of IBS Pain/Discomfort: LOCF

Measurement	Statistic	Placebo (N=222)	Alosetron 1 mg BID (N=224)	p-value
Number of Subjects with Adequate Relief During the Treatment Phase	nn/n (%)			
Week 1		64/222 (29%)	75/224 (33%)	0.324
Week 2		73/222 (33%)	92/224 (41%)	0.072
Week 3		89/222 (40%)	105/224 (47%)	0.147
Week 4		78/222 (35%)	113/224 (50%)	0.001**
Week 5		88/222 (40%)	121/224 (54%)	0.003**
Week 6		88/222 (40%)	122/224 (54%)	0.002**
Week 7		80/222 (36%)	118/224 (53%)	≤0.001**
Week 8		90/222 (41%)	126/224 (56%)	≤0.001**
Week 9		90/222 (41%)	128/224 (57%)	≤0.001**
Week 10		88/222 (40%)	126/224 (56%)	≤0.001**
Week 11		82/222 (37%)	121/224 (54%)	≤0.001**
Week 12		87/222 (39%)	122/224 (54%)	0.001**
Number of Subjects with Adequate Relief During the Follow-up Phase	nn/n (%)			
Week 1		73/222 (33%)	76/224 (34%)	0.823
Week 2		55/222 (25%)	55/224 (25%)	0.933
Week 3		56/222 (25%)	54/224 (24%)	0.774
Week 4		50/222 (23%)	41/224 (18%)	0.261

* Significant at the 0.050 level; ** significant at the 0.010 level.
Note: LOCF = last observation carried forward.
Note: P-values are the result of a Mantel-Haenszel test with stratification for cluster.

Source: ALOS050DEV:[S3BA3001.TABLELIB.IBSDP]DP_ITT_ADEQRELF_WL.SAS/QUINTILES (US)/16APR99/10:27

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Protocol: S3BA3001
Population: ITT (Alternating)

Table A-7.13
Weekly Adequate Relief of IBS Pain/Discomfort: LOCF

Measurement	Statistic	Placebo (N=87)		Alosetron 1 mg BID (N=82)		p-value
Number of Subjects with Adequate Relief During the Treatment Phase	nn/n (%)					
Week 1		27/87	(31%)	19/82	(23%)	0.312
Week 2		33/87	(38%)	32/82	(39%)	0.801
Week 3		37/87	(43%)	41/82	(50%)	0.339
Week 4		30/87	(34%)	42/82	(51%)	0.018*
Week 5		40/87	(46%)	40/82	(49%)	0.652
Week 6		36/87	(41%)	40/82	(49%)	0.291
Week 7		32/87	(37%)	40/82	(49%)	0.104
Week 8		40/87	(46%)	40/82	(49%)	0.652
Week 9		35/87	(40%)	38/82	(46%)	0.293
Week 10		32/87	(37%)	40/82	(49%)	0.098
Week 11		32/87	(37%)	38/82	(46%)	0.131
Week 12		33/87	(38%)	42/82	(51%)	0.066
Number of Subjects with Adequate Relief During the Follow-up Phase	nn/n (%)					
Week 1		27/87	(31%)	34/82	(41%)	0.167
Week 2		29/87	(33%)	23/82	(28%)	0.486
Week 3		23/87	(26%)	25/82	(30%)	0.620
Week 4		18/87	(21%)	21/82	(26%)	0.476

* Significant at the 0.050 level; ** significant at the 0.010 level.
Note: LOCF = last observation carried forward.
Note: P-values are the result of a Mantel-Haenszel test with stratification for cluster.

Source: ALOSOSODEV:[S3BA3001.TABLELIB.IBSACD]ACD_ITT_ADEQRELF_WL.SAS/QUINTILES (US)/18APR99/17:06

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APPENDIX 4

Trial A3001. Patient Rating of Abdominal Pain/discomfort

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Protocol: S3BA3001
Population: Intent-to-Treat

Table 7-7.34
Monthly Abdominal Pain/Discomfort Scores
LOCF

Measurement	Statistic	Placebo (N=317)	Alosetron 1 mg BID (N=309)
Pain/Discomfort Score Month 3	n	317	309
	Mean	1.25	1.05
	SD	0.83	0.81
	Median	1.11	0.92
	Min.		
	Max.		

Note: Low scores are favored for abdominal pain/discomfort: 0 = none, 1 = mild, 2 = moderate, 3 = intense, 4 = severe pain/discomfort.
Note: LOCF = last observation carried forward.

Source: ALOSOSOOEV:[S3BA3001.TABLE1(B)]ITT_ABDPAIN_MNTHLY.SAS/QUINTILES (US)/20APR99/15:13

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Protocol: S3BA3001
Population: Intent-to-Treat

Table T-7.34
Monthly Abdominal Pain/Discomfort Scores
LOCF

Measurement	Statistic	Placebo (N=317)	Alosetron 1 mg BID (N=309)
Pain/Discomfort Score Baseline	n	317	308
	Mean	1.87	1.93
	SD	0.61	0.58
	Median	1.93	1.86
	Min.		
	Max.		
Month 1	n	317	309
	Mean	1.43	1.40
	SD	0.74	0.70
	Median	1.33	1.36
	Min.		
	Max.		
Month 2	n	317	309
	Mean	1.27	1.14
	SD	0.81	0.77
	Median	1.14	1.00
	Min.		
	Max.		

Note: Low scores are favored for abdominal pain/discomfort; 0 = none, 1 = mild, 2 = moderate, 3 = intense, 4 = severe pain/discomfort.
Note: LOCF = last observation carried forward.

Source: ALOS0500DEV:[S3BA3001.TABLELIB]ITT_ABDPAIN_MNTHLY.SAS/QUINTILES (US)/20APR99/15:13