



**Joint Advisory Committee Meeting**

**April 23, 2002**

**Lotronex<sup>®</sup>**

**(alosetron hydrochloride) Tablets**

**Introduction**

**James Palmer, M.D.**

**Senior Vice President  
New Product Development  
GlaxoSmithKline**

# Key Events in the History of Lotronex

- June 29, 1999
  - Original NDA submitted
  - Priority review granted
- November 16, 1999
  - GI Drugs Advisory Committee
  - Unanimous approval recommendation
- December 2, 1999 – FDA extends review clock to further review 4 cases of ischemic colitis

# Key Events in the History of Lotronex

- February 9, 2000 – Original NDA approved
  - Indication:  
*...for the treatment of irritable bowel syndrome in women whose predominant bowel symptom is diarrhea...*
  - Product labeling warnings:
    - Constipation:
      - Frequent and dose-related side-effect
      - Resulted in study withdrawal in approximately 10% of patients
    - Ischemic colitis:
      - Infrequently (1/100 to 1/1000) reported in clinical trials
      - Causal relationship between treatment with Lotronex and ischemic colitis not established
      - Risk factors not identified

# Key Events in the History of Lotronex

- March 13, 2000 – Lotronex launched in US
  - Rapid product uptake (130,000 Rx by June, 2000)
- May 11, 2000 – FDA requests Risk Management Plan following new ischemic colitis reports
- June 1, 2000 – FDA/Sponsor review of post-launch serious adverse event reports
  - Ischemic colitis (3 clinical trial, 5 spontaneous)
  - Complications of constipation (2 clinical trial, 4 spontaneous) including one colectomy

# Key Events in the History of Lotronex

- June 27, 2000 – GI Drugs Advisory Committee
  - Primary issues: ischemic colitis, complications of constipation
  - Proposed Risk Management Plan generally accepted by the Committee with inclusion of Medication Guide
- July – October 2000
  - Dear Physician and Dear Pharmacist Letters
  - Labeling changes and Medication Guide introduced
  - Elements of the Risk Management Plan in various stages of implementation
  - Additional serious adverse event reports including those with fatal outcome

# Key Events in the History of Lotronex

## November, 2000

- Multiple discussions with FDA to explore risk management options ranging from restriction of use to product withdrawal
- Uncertainty regarding etiology of serious adverse events
- Concerns centered on benefit:risk ratio and utility of possible risk management strategies
- Unable to reach agreement on a viable risk management plan
- Product withdrawn 28 November

# Key Events in the History of Lotronex

- **Following product withdrawal**
  - Thousands of patients and numerous physicians express significant need for Lotronex to GSK and FDA
  - Increased appreciation of the significance of IBS
- **January 2001**
  - FDA/GSK initiated discussions intended to explore options that might allow market reintroduction
- **December 7, 2001 – Supplemental NDA submission**
  - Seeks market reintroduction of Lotronex under restricted access



# Potential Product Reintroduction

## What has changed?

A substantial body of new data are available

- Better understanding of IBS severity and impact
- Sustainability of beneficial effects
- Beneficial effect across a spectrum of severity of IBS symptoms
- Beneficial effect on quality of life and productivity
- Relative incidence and nature of ischemic colitis from clinical trials consistent since initial product approval
- Increasing clarity that ischemic colitis and constipation are two separate entities

# Potential Product Reintroduction

## What has changed?

- A proposed risk management framework has been developed based on a comprehensive evaluation of all data
  - Use restricted to women with diarrhea-predominant IBS who have failed to respond to conventional therapy
  - Patient/Physician agreement process reinforces appropriate patient selection and informed patient use
  - Mandatory prescription sticker/no refill provision increases patient/physician interaction
  - Mitigate serious outcomes for constipation and ischemic colitis through patient/physician education and ongoing program evaluation

# GlaxoSmithKline Presentation

- Burden of Illness & Efficacy of Alosetron Peter Traber, M.D.
- Safety Assessment & Benefit Risk Overview Eric Carter, M.D., Ph.D.
- Proposed Risk Management Plan David Wheadon, M.D.
- Clinician's Perspective Robert Sandler, M.D.
- Summary and Conclusions James B.D. Palmer, M.D.



# **Irritable Bowel Syndrome: Burden of Illness & Efficacy of Alosetron**

**Peter G. Traber, M.D.**

Senior Vice President  
Clinical Development & Medical Affairs  
Chief Medical Officer  
GlaxoSmithKline

# Irritable Bowel Syndrome

"A functional bowel disorder in which abdominal pain is associated with defecation or a change in bowel habits, with features of disordered defecation and distension."

ROME II: A multinational consensus document on functional gastrointestinal disorders.

# Hallmark Symptoms of IBS

- Chronic or recurrent GI symptoms
  - Lower abdominal pain/discomfort
  - Altered bowel function (urgency, altered stool consistency, altered stool frequency, incomplete evacuation)
  - Bloating
- Not explained by identifiable anatomical or biochemical abnormalities

# Diagnosis of IBS

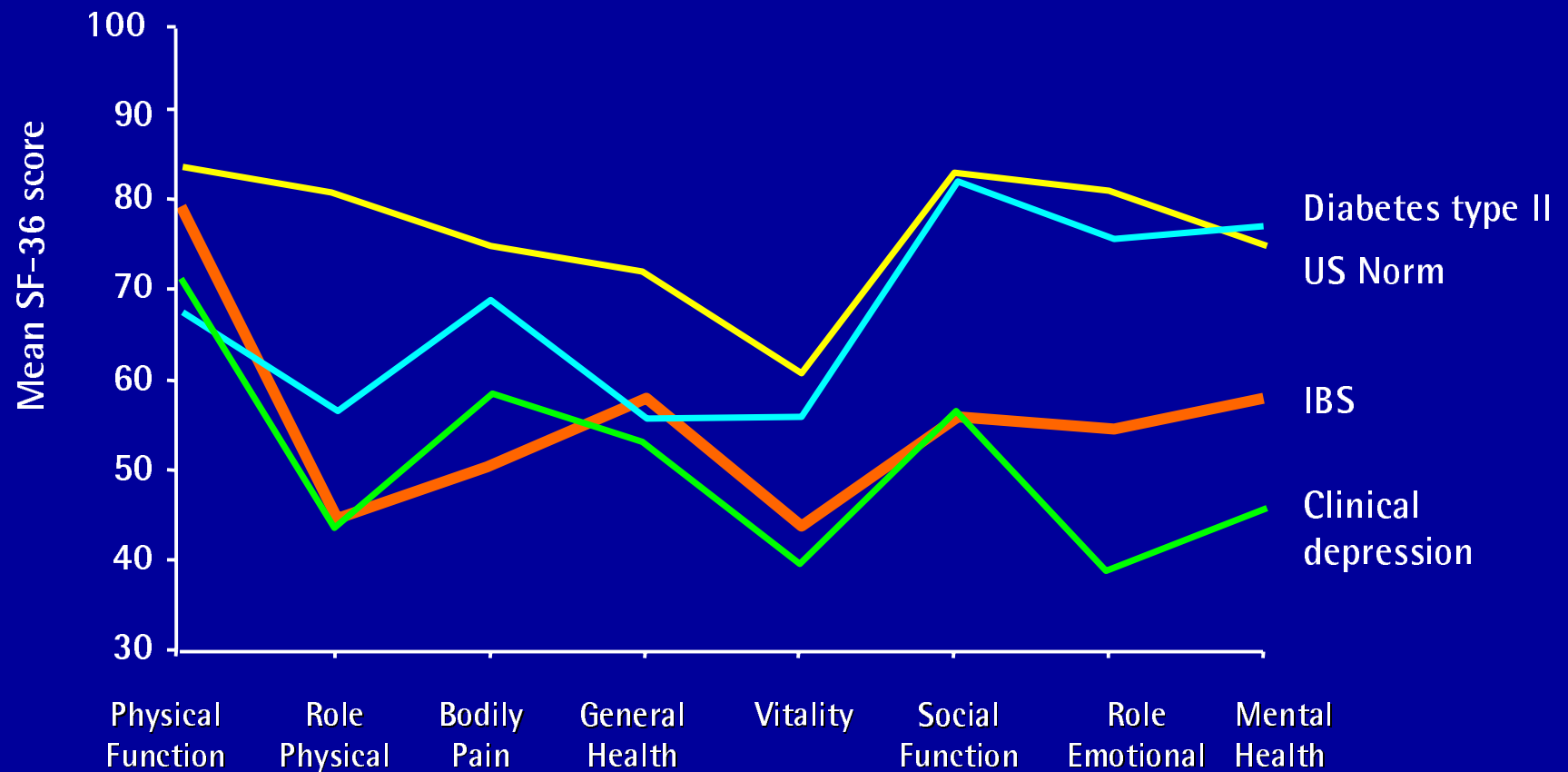
- AGA Practice Guidelines
  - Symptom-based diagnostic criteria (Rome) with careful history & physical exam
  - Search for organic diseases (clinical laboratory tests, stool O & P, flexible sigmoidoscopy + BE or colonoscopy)
- Diagnosis of IBS with initial evaluation rarely associated with missed diagnosis and once made, it is usually persistent.



# Population Statistics

- IBS Up to 20%
- Diarrhea-predominant 5-10%
- Female:Male 80:20
- Symptom severity
  - Mild 70%
  - Moderate 25%
  - Severe 5%

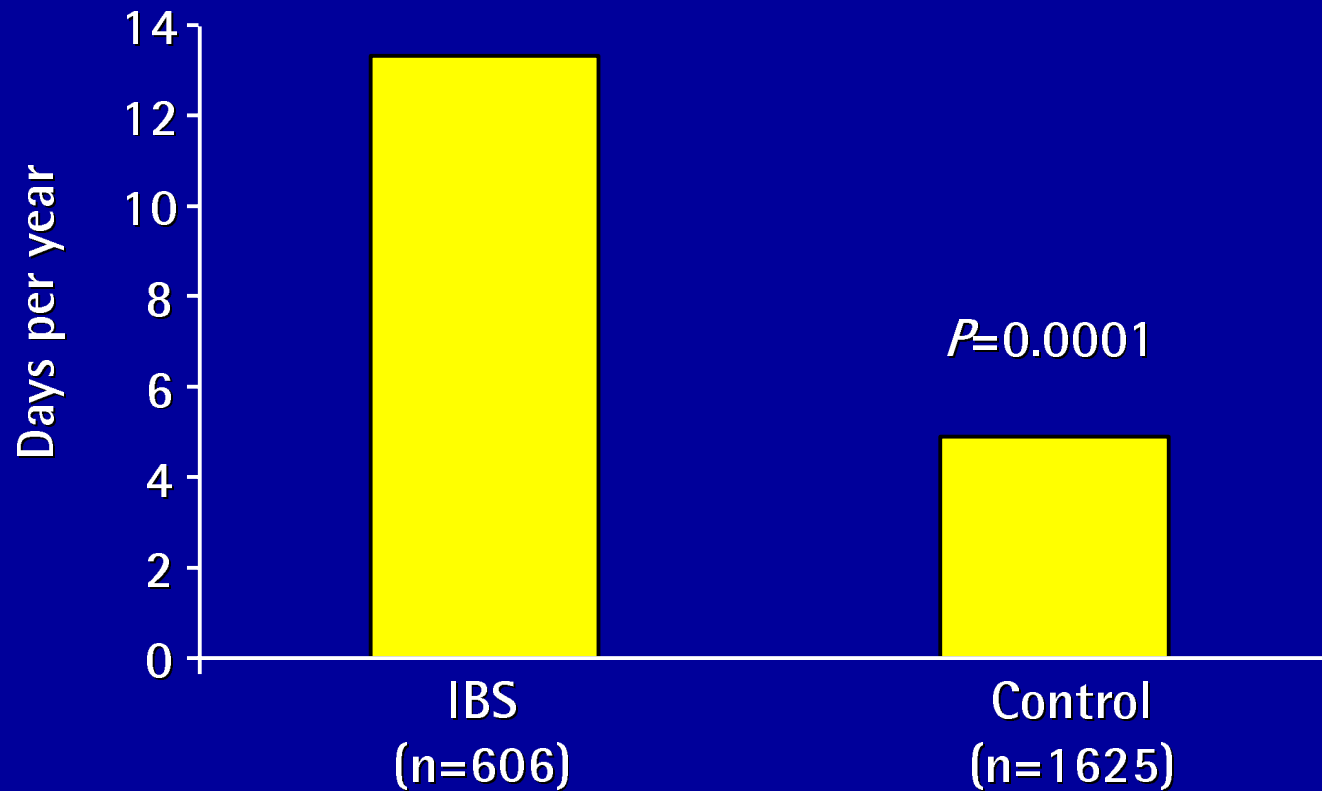
# Impact of IBS on Quality of Life Compared with Other Medical Conditions



Adapted from Wells et al. *Aliment Pharmacol Ther.* 1997;11:1019-1030.

# Productivity Burden in US

Absenteeism from work or school  
during the last 12 months



Drossman et al. *Dig Dis Sci*. September 1993;38:1569-1580.

# IBS Costs Estimated in 1998

- 4 million physician visits
- 2 million prescriptions, countless OTC drug purchases
- \$2 billion in national medical costs
- \$20 billion of direct and indirect costs related to absenteeism and lost productivity

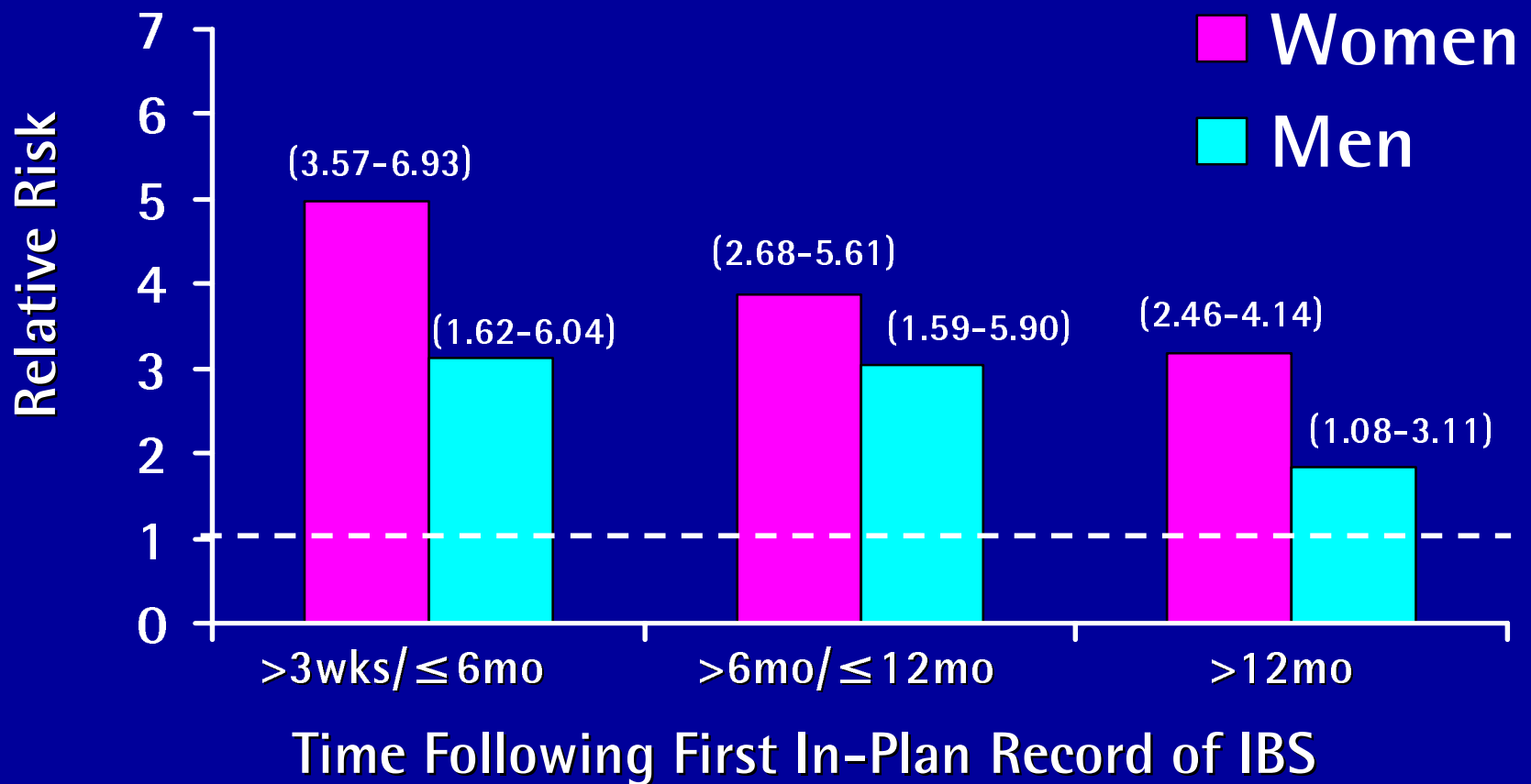


# UHC Epidemiology Study Approach

- Retrospective cohort study using United Healthcare Research Database
- 5,402,500 UHC members
  - IBS: 87, 449 (1.6%)
  - Complications of constipation: 2,661 (0.05%)
  - Ischemic colitis: 740 (0.01%)

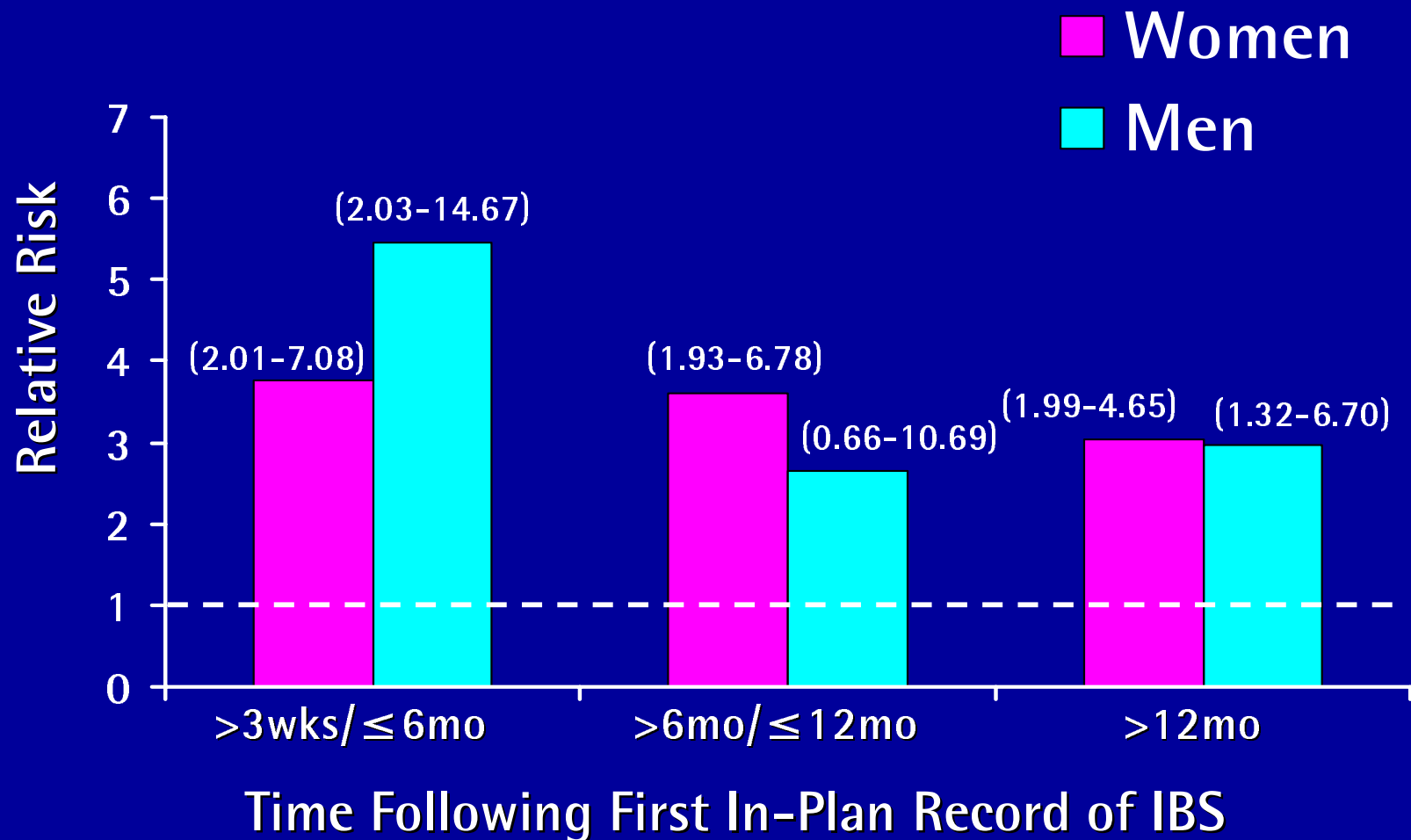
# UHC Epidemiology Data

## Relative Risk of Complications of Constipation (reference is non-IBS group)



# UHC Epidemiology Data

## Relative Risk of Ischemic Colitis (reference is non-IBS group)





# Treatment of IBS Symptoms

- Education & Reassurance
- Dietary Modification
- Symptom-Targeted Pharmacotherapy
  - Pain & bloating – antispasmodics\*
  - Diarrhea & Urgency – antidiarrheals\*
- Failure of these traditional/conventional therapies may lead physicians and patients to try other approaches
  - Psychotropics & Alternative Approaches

\* Most therapies are not approved for the treatment of IBS or as adjunctive therapy in the treatment of IBS. No therapy available that is directed against the multiple symptoms of IBS.

# Traditional/Conventional Therapy

S3B30020 IBS Therapy Used by >5% of Subjects Randomized to Traditional Therapy

## Treatment

N=727

- Antispasmodics 488 (67%)
- Antidiarrheals 237 (33%)
- Bulking agents 181 (25%)
- Tricyclic antidepressants 40 (6%)

# Alosetron (LOTRONEX)

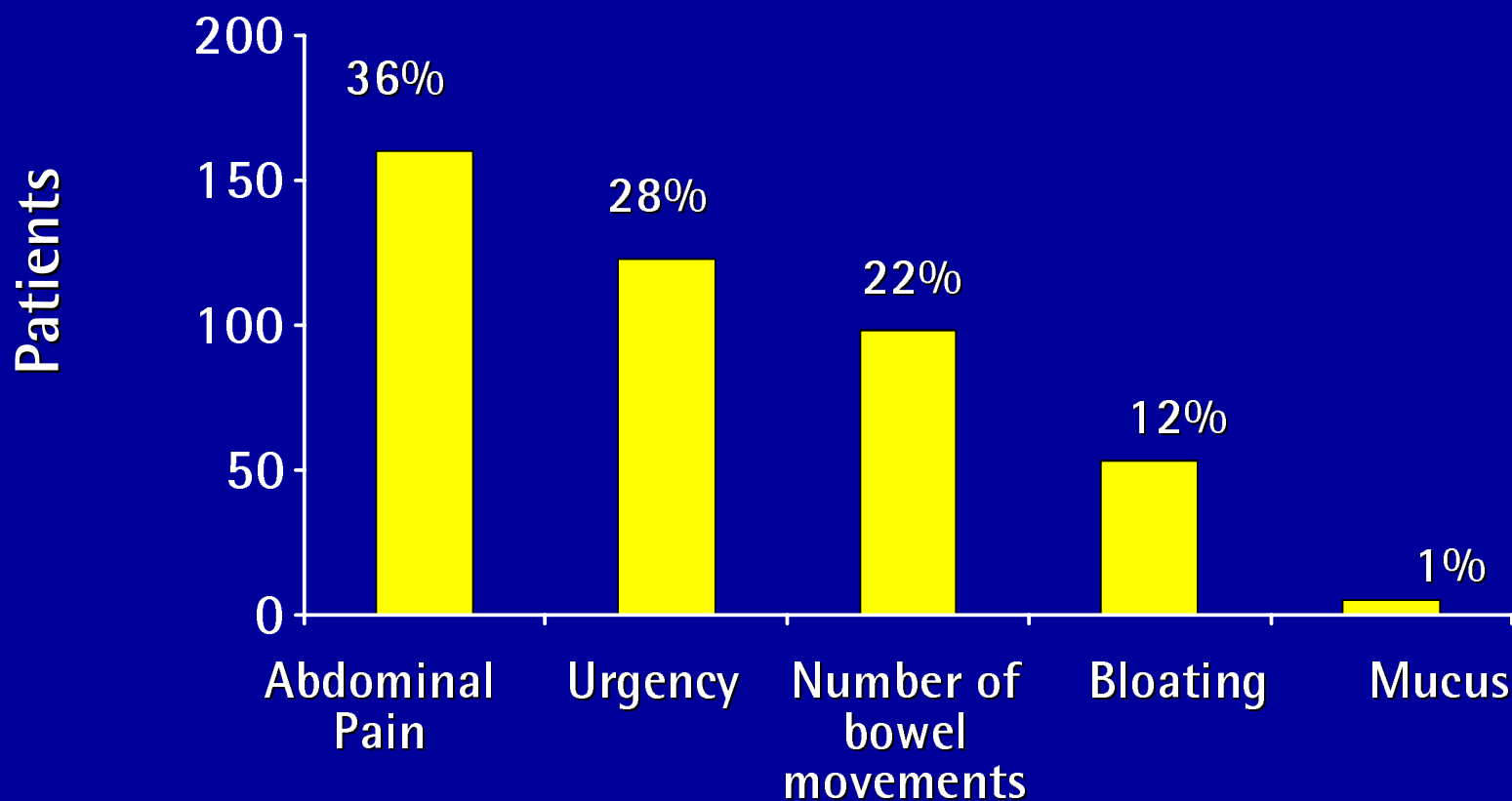
- Serotonin type 3 (5-HT<sub>3</sub>) Receptor Antagonist
- 5-HT<sub>3</sub> receptors are on sensory neurons of the gut and mediate gastrointestinal reflexes that control motility, secretion, and perception of pain.
- In patients with IBS, 5HT<sub>3</sub> receptor antagonists increase colonic compliance, slow colonic transit and improve stool consistency.

# Extent of Alosetron Exposure in Clinical Trials

	NDA	sNDA
Completed Studies	53	93*
Repeat dose - IBS	5	24*
Alosetron-treated	3000	11,874
Placebo-treated	1403	3500
Comparator agents	0	1661

\*Completed and terminated

# "When Your Irritable Bowel Syndrome is Active, Which of the Following Symptoms Bothers You the Most?"



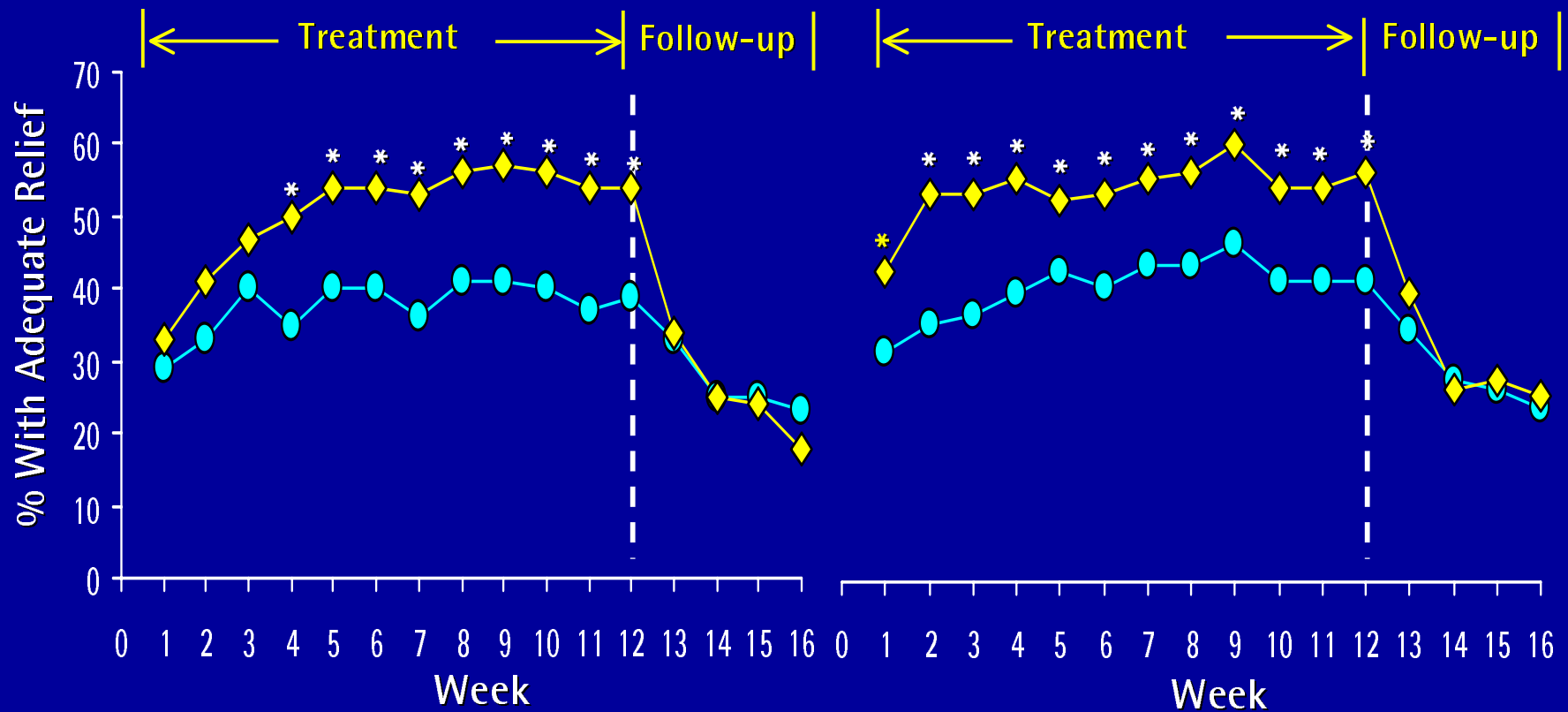
S3BA3001  
S3BA3002

# Pivotal Phase III Trials for NDA

## (Diarrhea-Predominant IBS in Women)

S3BA3001

S3BA3002



\*p<0.05

LOCF

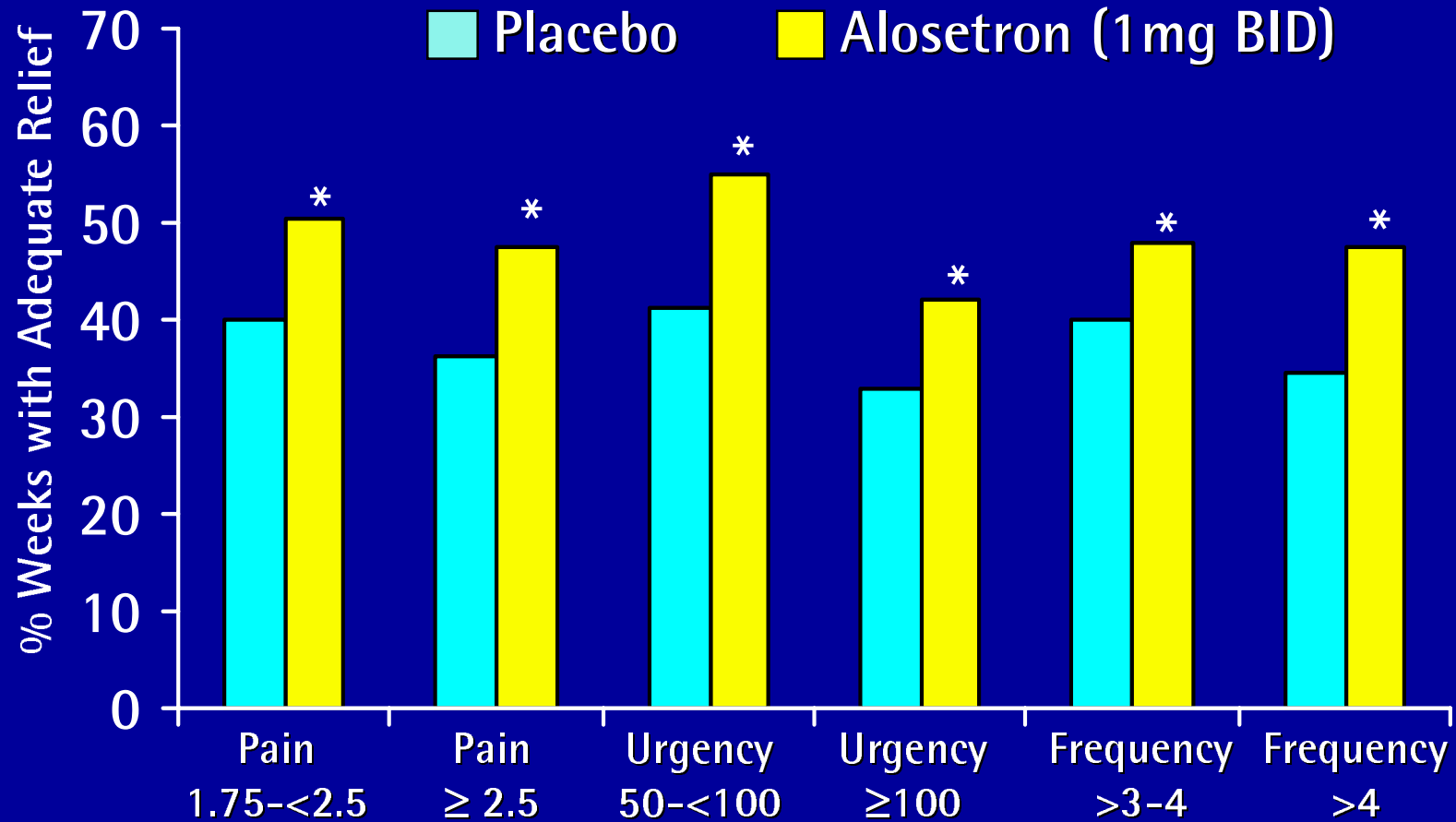
—●— Placebo

—◆— Alosetron (1 mg BID)

# Efficacy Update in sNDA

- Durability of effect
- Efficacy in patients with severe symptoms
- Global improvement of IBS symptoms
- Improvement in productivity measures
- Improvement in quality of life measures

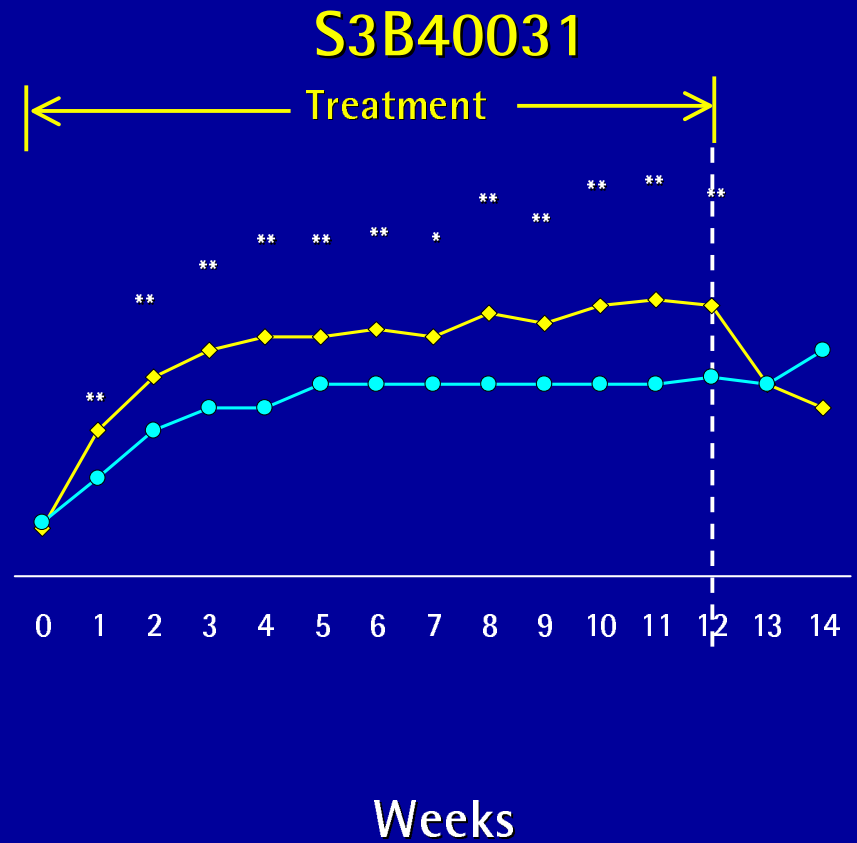
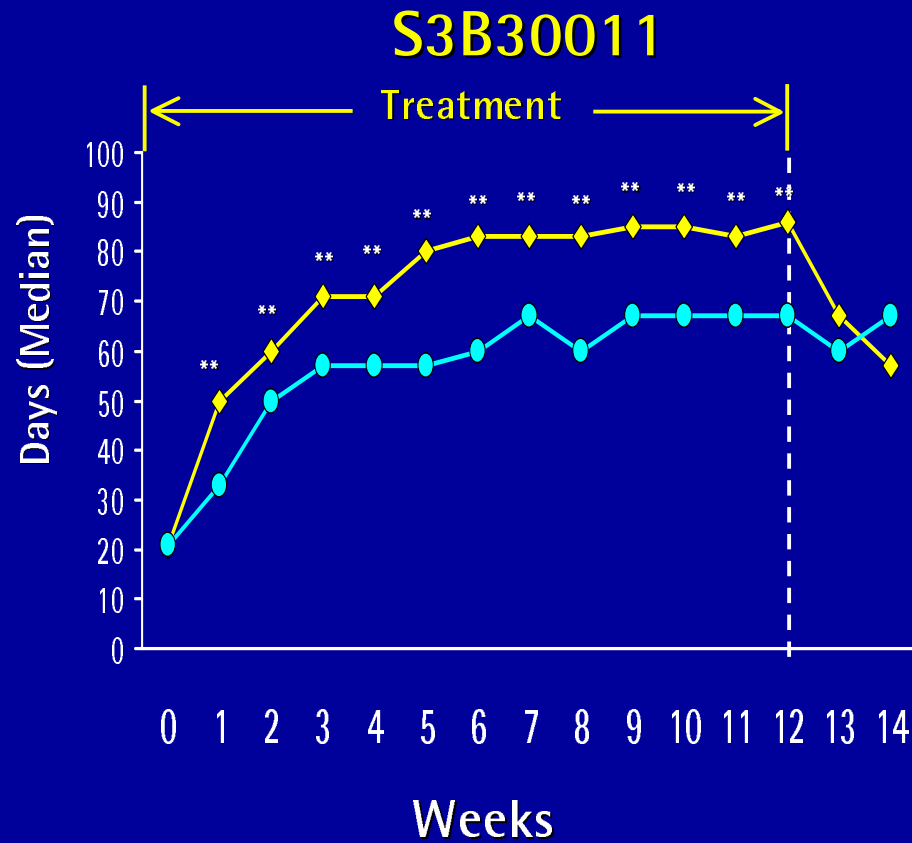
# 12-Week Adequate Relief Rates by Baseline Pain, Urgency, and Frequency



\*p < 0.05



# Percentage of Days Patients Report Satisfactory Control of Bowel Urgency



\*\*  $p \leq 0.001$

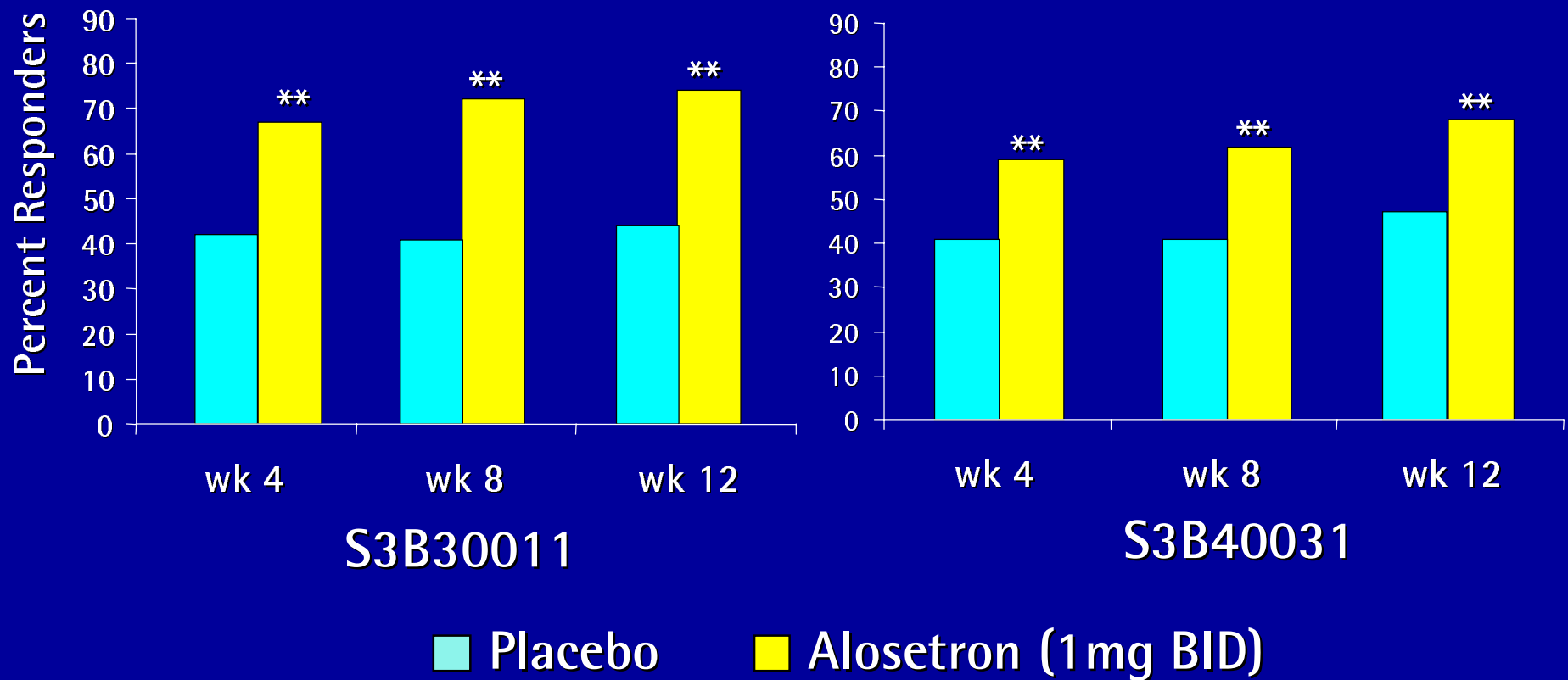
\*  $p < 0.05$

● Placebo

◆ Alosetron

# Improvement of Global IBS Symptoms

Responders were defined as those substantially or moderately improved on a 7-point Likert scale

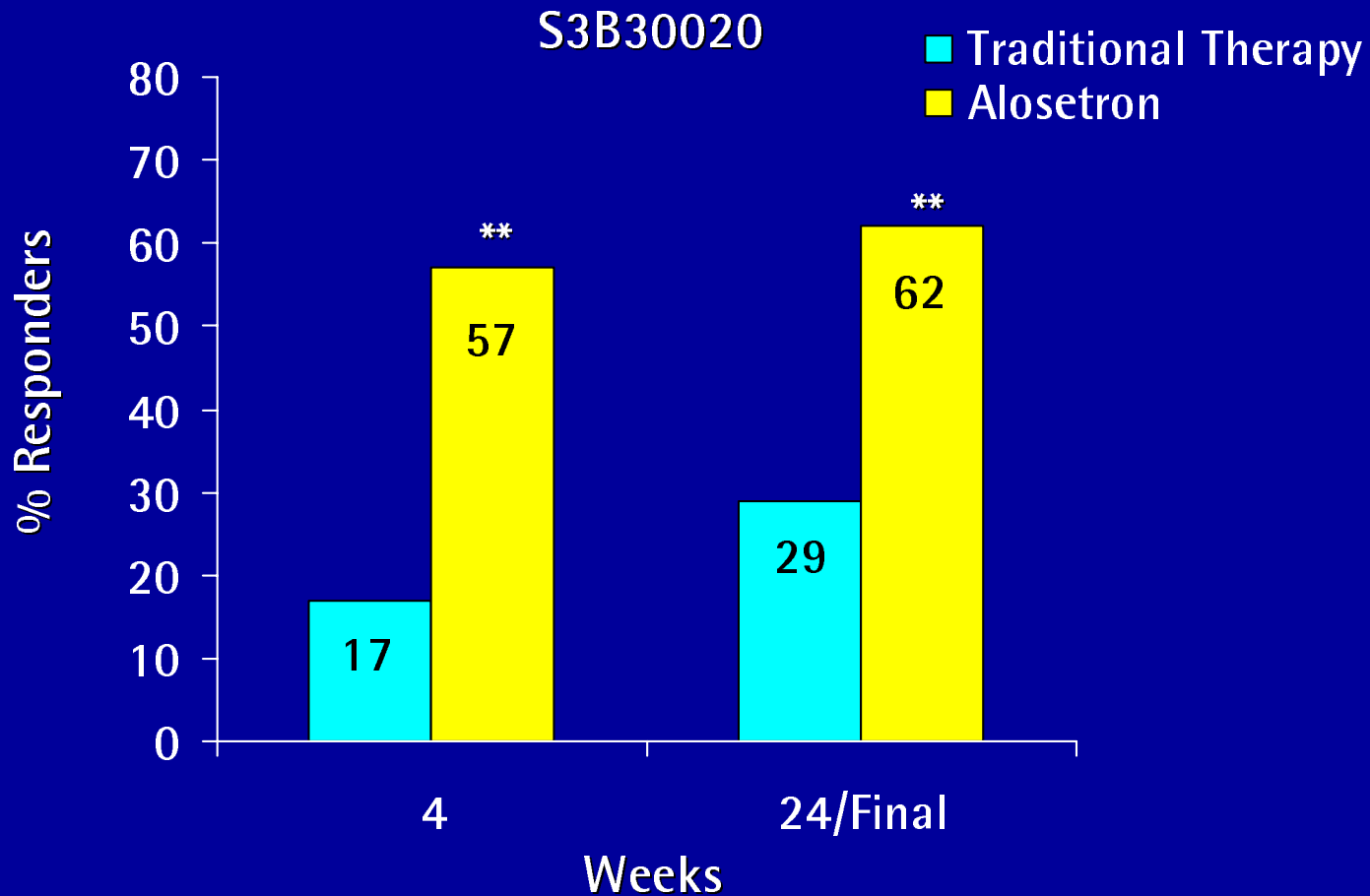


\*\*p<0.001

# Improvement of Global IBS Symptoms

Week 4 and Week 24 or Final Visit

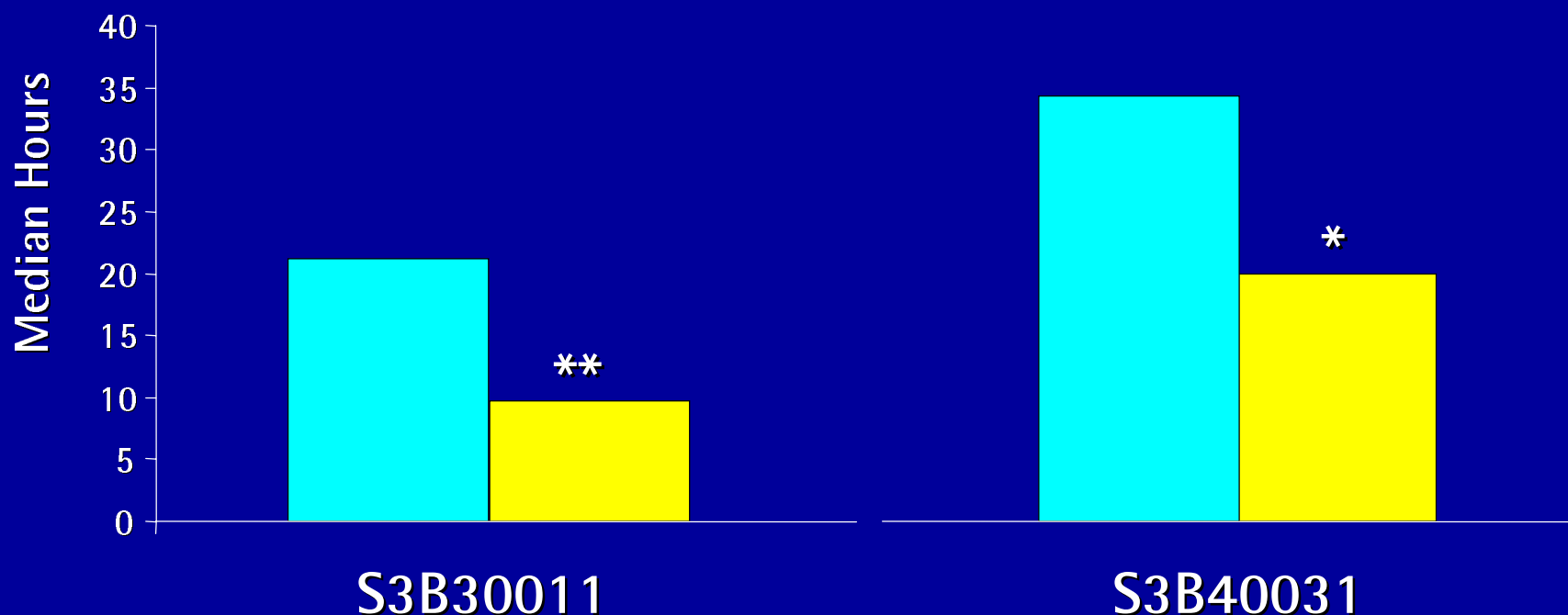
Responders were defined as those substantially or moderately improved on a 7-point Likert scale



\*\*p<0.001

# Median Hours of Lost Workplace Productivity Over The Last 12 Weeks

Patients Working Full- or Part-Time at Baseline



\*\*  $p < 0.001$

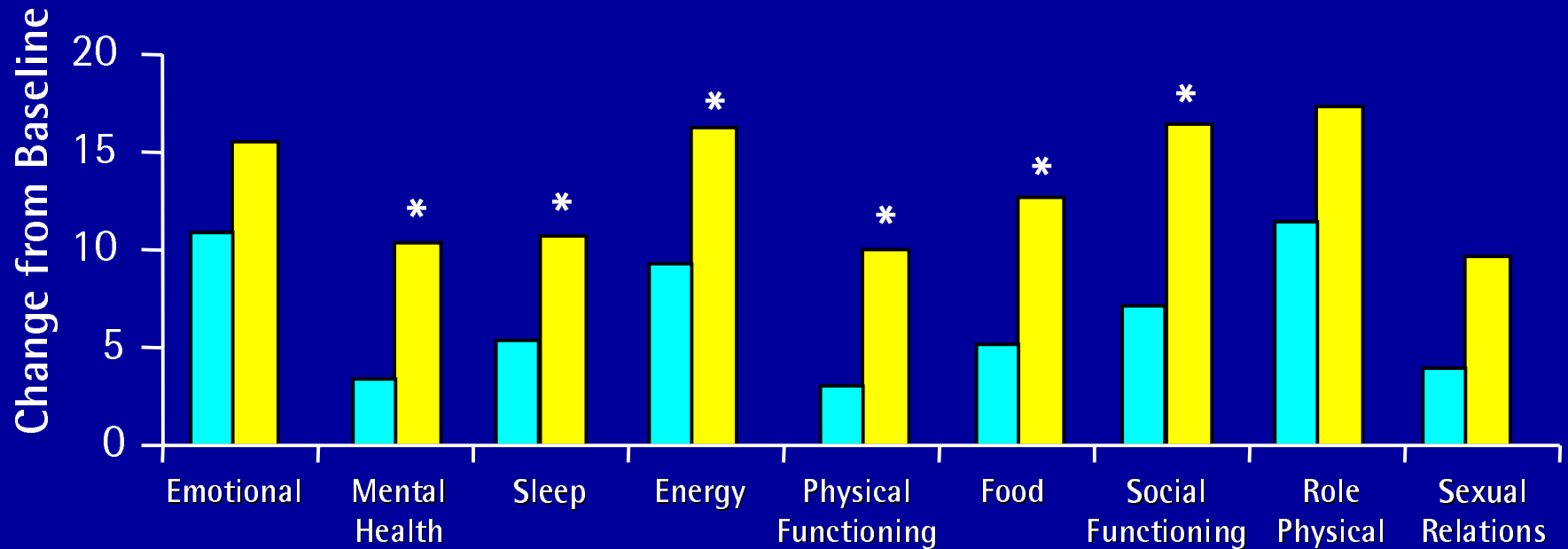
\*  $p < 0.05$

■ Placebo

■ Alosetron (1mg BID)

# IBS Quality of Life Alosetron Compared to Placebo

Change from Baseline to Month 12  
(Diarrhea-Predominant IBS in Women)



S3B3003

\*p<0.05

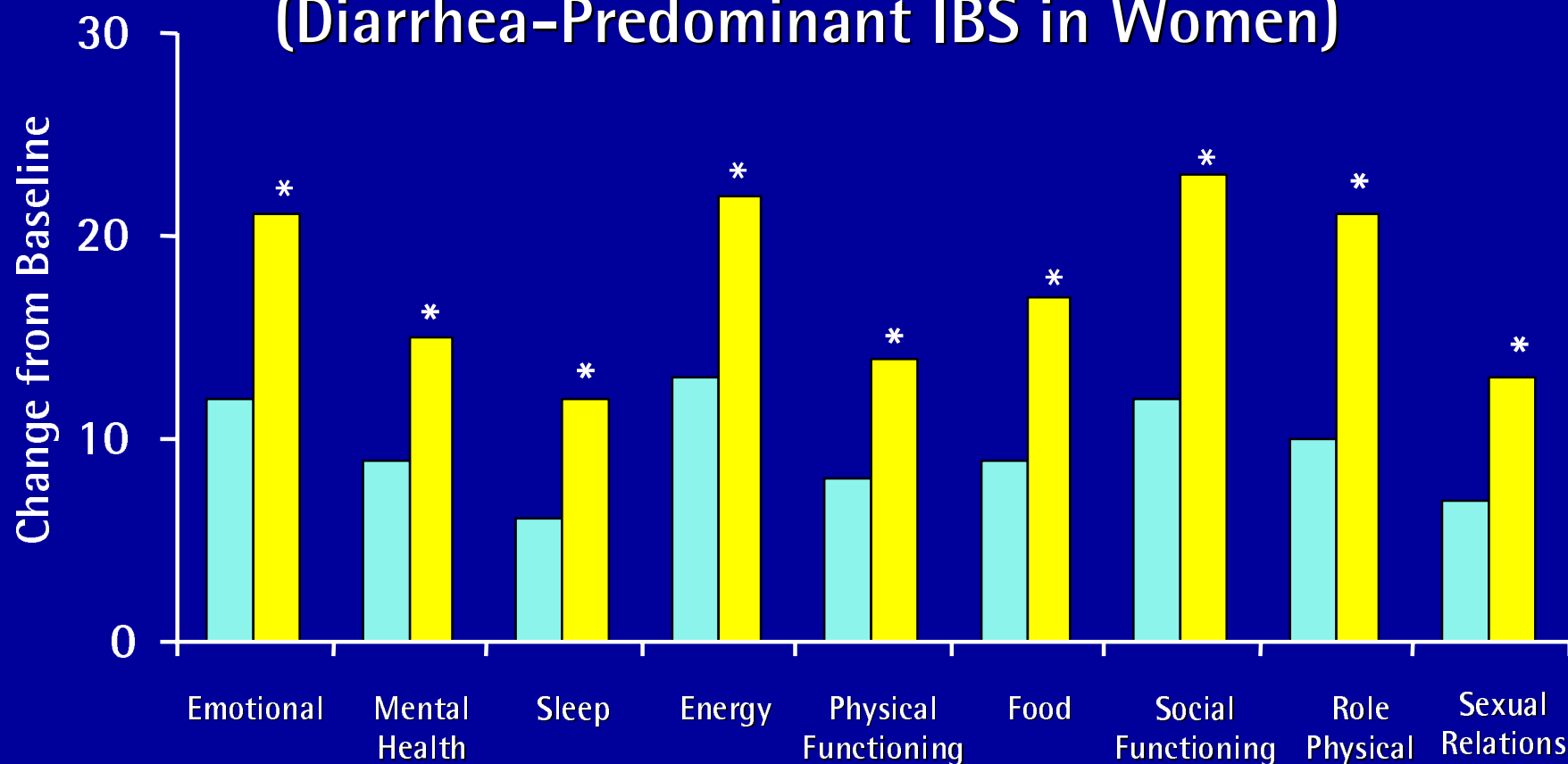
■ Placebo

■ Alosetron (1mg BID)

# IBS Quality of Life

## Alosetron Compared to Conventional/Traditional Therapy

Change from Baseline to Week 24 or Final Visit  
(Diarrhea-Predominant IBS in Women)



S3B30020

\*p < 0.001

■ Traditional Therapy ■ Alosetron (1 mg BID)

# Conclusions

- IBS is a well-defined functional bowel disorder which has a large impact on patients, health care, and society.
- In women with diarrhea-predominant IBS and moderate or severe symptoms, alosetron produces robust and consistent improvement on:
  - Multiple symptom-based endpoints
  - Important function-based endpoints





# **Safety Assessment & Benefit-Risk Overview**

**Eric Carter, Ph.D., M.D.**

Vice President, Gastroenterology  
Clinical Development & Medical Affairs  
GlaxoSmithKline

# Safety Assessment

Focus on events of special interest:

- Constipation
- Ischemic colitis

And related outcomes:

- Hospitalization
- Surgery
- Death

# Safety Assessment Approach (CIOMS IV)

- Weight of Evidence for Dominant Risks
  - Complications of constipation; Ischemic colitis
  - Outcomes of special interest; Hospitalization, Surgery, Death
  - Databases:
    - Clinical trials – most complete and reliable. Basis for generating risk estimates.
    - Post-marketing – useful for identifying rare events of medical importance. Often incomplete and imprecise.
    - Epidemiology – Background rates and risk factors in disease population. Provides context.

# Safety Assessment Approach

- Analysis to quantify risks
- Context and interpretation
- Risk factors
- Steps to mitigate risk
- Steps to mitigate severe outcomes
- Benefit–risk balance

# Summary of Events of Special Interest and Related Outcomes

---

	Approval (Feb 2000)	<u>Advisory Committee</u> Clinical Trial	Spontaneous
Patients	3000	11,874	~275,000
<b>Events</b>			
Ischemic Colitis	4	17	80
Serious Complications of Constipation	1	11	100
<b>Outcomes</b>			
Hospitalization	5	19	122
Surgery	1	2	30
Death	0	0	2

---

# Summary of Events of Special Interest and Related Outcomes

	Approval	<u>Advisory Committee</u>	
	(Feb 2000)	Clinical Trial	Spontaneous
Patients	3000	11,874	~275,000
<b>Events</b>			
Ischemic Colitis	4	17	80
Serious Complications of Constipation	1	11	100
<b>Outcomes</b>			
Hospitalization	5	19	122
Surgery	1	2	30
Death	0	0	2

## Summary of Events of Special Interest and Related Outcomes

	Approval (Feb 2000)	<u>Advisory Committee</u> Clinical Trial	Spontaneous
Patients	3000	11,874	~275,000
<b>Events</b>			
Ischemic Colitis	4	17	80
Serious Complications of Constipation	1	11	100
<b>Outcomes</b>			
Hospitalization	5	19	122
Surgery	1	2	30
Death	0	0	2

# Constipation



# Constipation Definitions

## Clinical Trials

- Constipation Adverse Event
  - Patient report or 4 consecutive days without stool
- Serious Adverse Event of Constipation
  - Regulatory definition
- Complications of Constipation
  - Bowel obstruction, ileus, toxic megacolon, perforation
  - Impaction (if serious event)

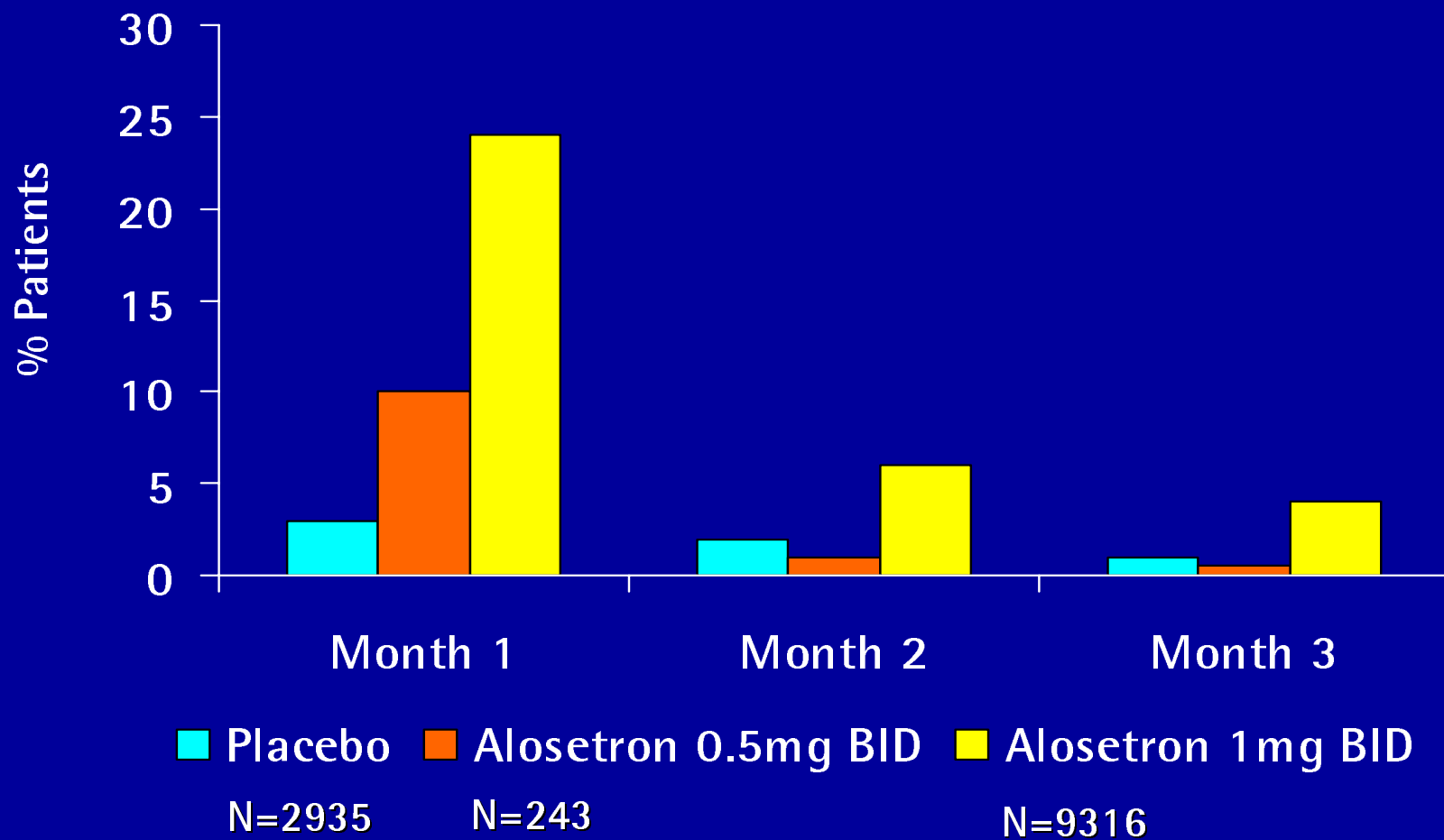
# Constipation – Clinical Trials

---

	Placebo	Alosetron 0.5 mg BID	Alosetron 1 mg BID
Patients	2935	243	9316
Female:Male	2697:238	85:158	8980:336
Patients (%)	6	11	29
Duration (median days)	5	8.5	6
Patient Withdrawal (%)	0.9	4	11

---

# Constipation - Clinical Trials



# Serious Complications of Constipation Clinical Trials

---

	Alosetron	Placebo	Mebeverine
N	10,805	2,935	390
Reports	11 (0.10%)	3 (0.10%)	1 (0.26%)
Onset (days)	7-128	3-43	20

---

## Outcome

Withdrawn	9	2	1
Hospitalization	10	3	1
Ileus/Obstruction/Impaction	8	3	0
Surgery	2	1	0
Death	0	0	0

---

# Risk Estimates for Serious Complications of Constipation - 24 IBS Clinical Trials

---

	Alosetron	Placebo
Reports	11/10805	3/2935
Cumulative risk (event/10,000 pts)	10.2	10.2
Incidence rate (month 1) (event/1000 pt-years)	4.9	4.3
Incidence rate (month 12) (event/1000 pt-years)	3.9	3.3

---

# Constipation Conclusions

## Clinical Trials

- Most frequent adverse event reported
- Dose dependent; (0.5 mg BID=11% v. 1mg BID=29%)
- Occurs mostly in the first month
- Occurs mostly once
- Managed by withdrawing alosetron therapy and routine clinical care
- Rare reports of serious constipation: rate same for both treatment groups

# Constipation Definitions

## Post Marketing Experience

- Constipation: Defined by the *reporter* (patient, family member, physician, pharmacist, etc.)
- Serious Constipation: Cases assessed as "serious" where a reported event of constipation led to the assessment of "serious"
- Complications of Constipation: Cases of serious constipation with
  - Intestinal perforation
  - Toxic megacolon
  - Intestinal obstruction/ileus
  - Fecal impaction

# Serious Constipation and Complications Post Marketing Experience (~ 275,000 patients)

- Serious constipation N=100
  - Age 20–80 (median 49)
  - Onset from 3 days to several months
  - 67% in 1st month
- Serious constipation associated with complications N= 58
  - Fecal impaction 17
  - Intestinal obstruction/ileus 30
  - Toxic megacolon 2
  - Intestinal perforation 9



# Outcomes of Serious Constipation Post Marketing Experience

N=100

- Death 2
- Intestinal surgery 15
- Anorectal surgery 7
- Hospitalization 54
- ER visit 10
- Out-patient disimpaction 3
- None of the above 9

Outcomes listed in order of severity.

Each case included once, in most severe category.

# Constipation Conclusions

## Post Marketing Experience

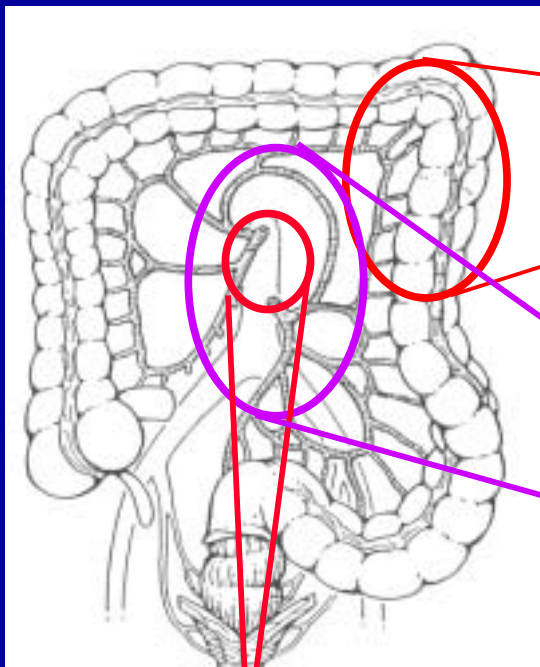
- Typically reported in the first month of therapy
- Managed with withdrawal of therapy and routine clinical care
- Cases of impaction, obstruction, megacolon, and perforation reported
- Outcomes included surgery, hospitalization, disimpaction
- 2 deaths

# Constipation Risk Considerations

- Background disease-related risk
- Constipation; pharmacologic side-effect
- Constipation dose dependent
- Increases with age
- Current or pre-existing constipation
- Predisposing co-morbidities
- Concomitant use of constipating drugs

# Ischemic Colitis

# Intestinal Ischemia – Clinical Features



## Ischemic Colitis

- Typically self-limited, without sequelae
- Mild/moderate pain (>80%)
- Diarrhea (50%)
- Hematochezia (87%)

## Chronic Mesenteric Ischemia

- Insidious
- Post-prandial pain
- Weight loss

## Acute Mesenteric Ischemia

- Severe abdominal pain
- Significant morbidity/mortality
- Hx CVD/emboli/CHF
- Hx cardiac surgery

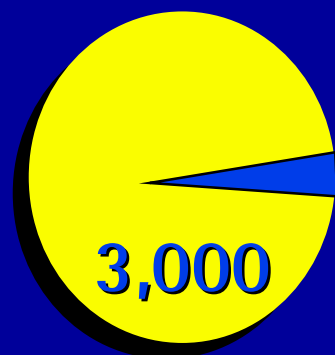
Brandt L, Boley SJ. AGA Technical Review *Gastroenterology* 2000;118:954-968

Cohn SM, Birnbaum EH In: Yamada TY, AlpersDH, Laine L. Textbook of *Gastroenterology* 3rd Ed 1999:1767

# Ischemic Colitis - Clinical Trials

Frequency

1:1000

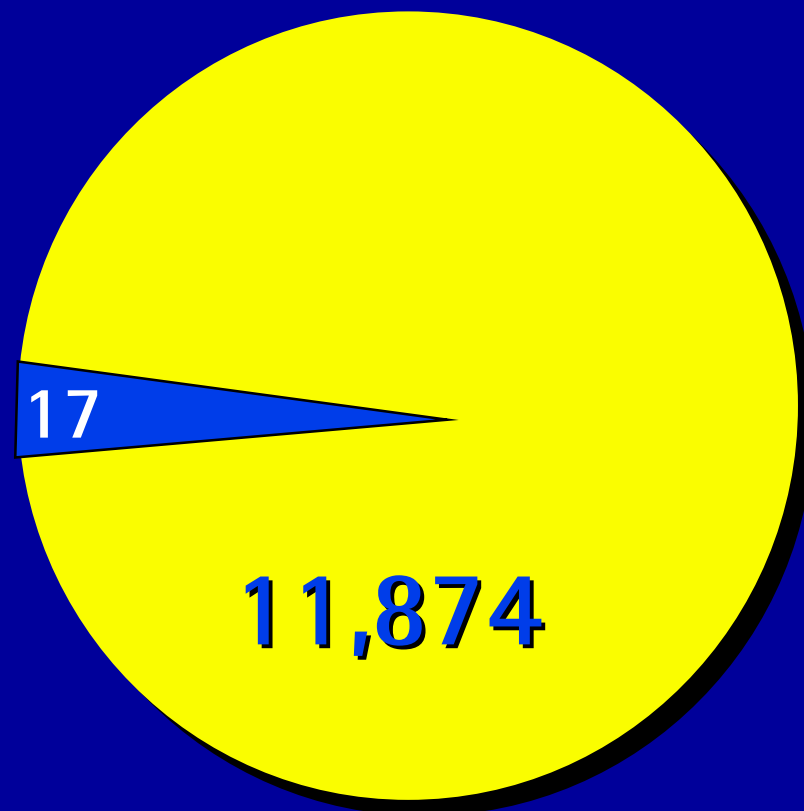


NDA Approval  
February 2000

4 } 1:750

1:698 {

17



sNDA  
Dec 2001

1:100

# Ischemic Colitis (N=17) - Clinical Trials

- Female/Male 16 /1
- Serious (regulatory definition) 12
- Age range (median) 20-75 (51)
- Age >65 1
- Age <50 9

<u>Dose (mg BID)</u>	<u>Total Subjects</u>	<u>Reports</u>
1	9763	15
0.5	243	1
2	563	1

- Onset within first month 11
- Time to onset 2-162 days
- Withdrawn from trials 16

# Ischemic Colitis (N=17)

## Clinical Trials

### Clinical Presentation

- Acute, mild-moderate pain and hematochezia
- In-patient management in 53% (9/17) cases
- Hospital duration, range 1-7 days (median 3)
- Conservative treatment
- Constipation in 18% (3/17) cases
- Estrogen use in 50% (8/16 females) cases



# Risk Estimates of Ischemic Colitis Clinical Trials

---

	Alosetron	Placebo
Reports	17	1
Cumulative risk (event/10,000 pts)	14.3	2.86
Incidence rate (month 1) (event/1000 pt-years)	12.9	0
Incidence rate (month 12) (event/1000 pt-years)	5.9	1.1

---

# Ischemic Colitis

## Post Marketing Experience

- Approximately 275,000 patients
- Number of reports 80
  - Classification
  - Probable (clinical + endoscopic and/or Bx) 44
  - Possible (clinical + X-ray and/or endoscopic) 14
  - Insufficient evidence 22

# Ischemic Colitis (N=80)\*

## Post Marketing Experience

- Female/Male/Unknown 75/2/3
- Median age 55
- Median time to onset  
(range) 14 days  
(12h -6mos)
  
- Onset within first month 74%
- Age >65 23%
- Age <50 24%
- Hospitalization 60%
- Intestinal surgery 8% (n=6)

\*Data not reported in all cases

## Mesenteric Ischemia, Occlusion, or Infarction (N=12)\* Post Marketing Experience

• Female	12
• Time to onset (range)	(4h - 3mos)
• Median age	61
• Intestinal surgery	9
• Death	3

\*Data not reported in all cases

- Interpretation confounded by predisposing conditions (intestinal vascular insufficiency, hypercoagulable state, thrombotic disease)
- No meaningful signal can be derived

# Ischemic Colitis – Conclusions

## Presentation

- Generally occurs early in therapy
- Acute presentation without prodrome
- Occurred in subjects across a spectrum of baseline severity

## Management

- Managed with drug withdrawal and routine clinical care (40% as outpatients)

## Outcomes

- Almost all cases resolved without sequelae
- Post-approval reports of 6 surgeries; 3 with very limited information
- No deaths reported

# Ischemic Colitis

## Risk Factor Considerations

- Idiosyncratic – no mechanistic link elucidated
- Background disease-related risk
- Cumulative risk in clinical trials has remained constant over time
- 65% clinical trial and 74% spontaneous reports occurred in the first month
- Specific risk factors (including constipation, concomitant medications or co-morbid conditions) have not been identified

# Benefit–Risk Balance

## Unmet Need

- IBS is associated with a significant burden of illness
- Conventional therapy provides limited options and uncertain benefit–risk profiles
- IBS represents a significant unmet medical need

# Benefits of Alosetron

- Consistent benefits across multiple IBS symptoms
- Benefits persist over time
- Global improvement of symptoms
- Improvement in QoL over placebo and conventional therapy
- Improved productivity



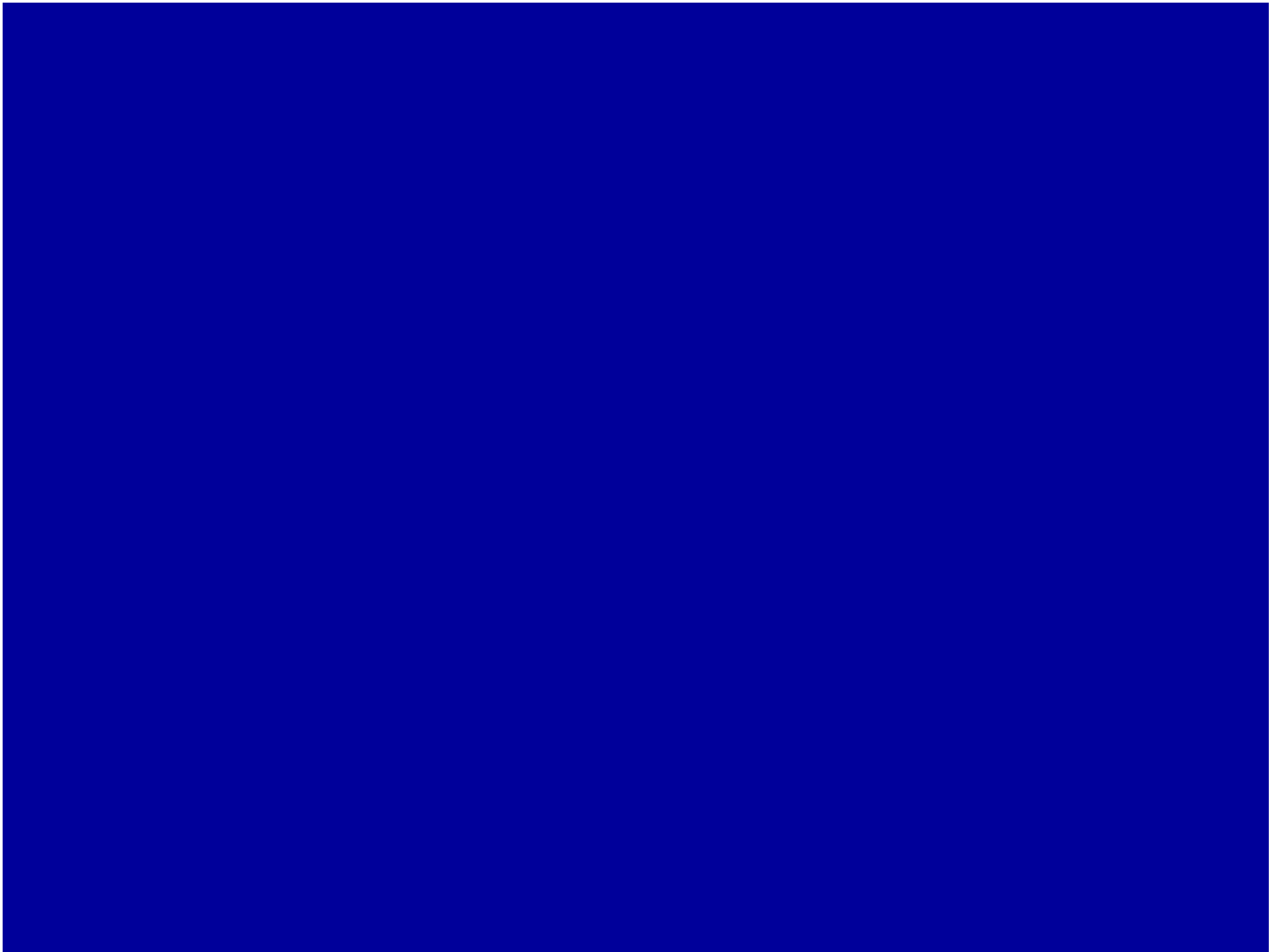
# Population for whom Benefit–Risk Balance Most Favorable

- Restriction to women with diarrhea-predominant IBS who have failed conventional therapy

# Benefit–Risk Balance for Alosetron

## Conclusions

- The alosetron benefit–risk balance is positive for diarrhea–predominant women with IBS who have failed conventional therapy
- Implementation of the Risk Management Plan including changes in prescribing information and the Medication Guide will focus on the population most in need and will mitigate risks



# **Lotronex Risk Management Plan**

**David Wheadon, M.D.**

Senior Vice President  
U.S. Regulatory Affairs  
GlaxoSmithKline

# Participants in Benefit vs Risk Decision

- **Sponsor and FDA**
  - Evaluate and communicate benefit vs risk for intended population
- **Prescriber**
  - Key in determining benefits and managing risks for individual patient
- **Patient**
  - Once informed, the ultimate decision maker concerning the balance



# Key Considerations IBS Burden of Illness

- Significant quality of life impact
- Reduced productivity
- Limited treatment options

# Key Considerations Benefits of Lotronex

- Improvement in:
  - Moderate and severe IBS symptoms
  - Global IBS symptoms
  - Quality of life
  - Productivity

# Key Considerations

## Dominant Risks

- Complications of constipation
  - Event is potentially avoidable
  - Severe outcomes can be mitigated by early recognition of signs and symptoms and timely intervention
- Ischemic colitis
  - Event is idiosyncratic
  - Careful monitoring of signs and symptoms is warranted with the goal of mitigating severe outcomes



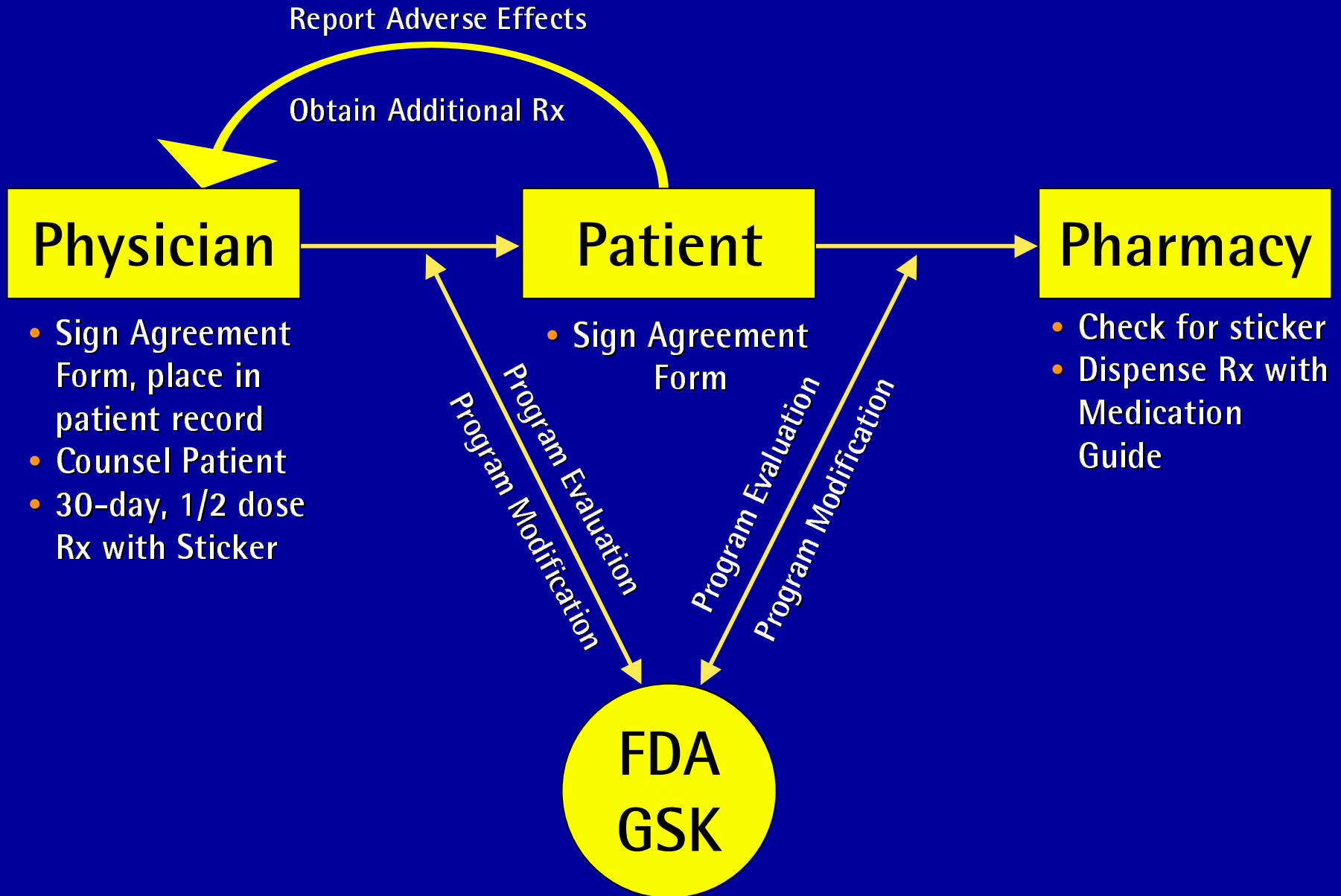
# Risk Management Plan Goals

- Restrict use to patients with the most favorable benefit–risk balance
  - Women with diarrhea–predominant IBS who have failed to respond to conventional therapy
- Informed patient use
- Mitigate serious outcomes of constipation
- Mitigate serious outcomes of ischemic colitis

# Risk Management Activities

- Evaluation of Benefits
- Assessment of Risk
- Balancing Benefits vs Risks
  - Identify appropriate target population
- Communication of Risks
- Managing Risks
- Safety Monitoring
- Program Evaluation

# Lotronex Risk Management Plan



# Joint Sponsor/FDA Responsibilities

- Revised Labeling
  - Concise boxed warning with key safety information and program restrictions
  - Indication: Reserved for women with diarrhea-predominant IBS symptoms who have failed conventional therapy
  - Modified to include a half-dose, 30-day initial treatment period
  - Medication Guide which reflects labeling modifications
- Regular (e.g., quarterly) meetings to review evolving safety information

# Joint Sponsor/FDA Responsibilities

- Revised Labeling

Con... governing with key safety

**WARNING: Serious gastrointestinal events, some fatal, have been reported in association with the use of LOTRONEX. These events, including ischemic colitis and serious complications of constipation, have resulted in hospitalization, blood transfusion, and/or surgery.**

- Only **physicians who are knowledgeable and experienced** in the diagnosis and treatment of irritable bowel syndrome (IBS), **able to diagnose and manage** ischemic colitis and complications of constipation, and who have signed a Patient-Physician Agreement for each patient, should prescribe LOTRONEX.
- LOTRONEX is **indicated only for women with diarrhea-predominant IBS who have failed to respond to conventional therapy**. Before receiving an initial prescription for LOTRONEX, the patient must read and understand the Medication Guide and must sign the Patient-Physician Agreement (see PRECAUTIONS: Information for Patients).
- LOTRONEX should be **discontinued immediately in patients who develop constipation or symptoms of ischemic colitis**. Physicians should instruct patients to immediately report constipation or symptoms of ischemic colitis. LOTRONEX should not be resumed in patients who develop ischemic colitis. Physicians should instruct patients who report constipation to immediately contact them if the constipation does not resolve after discontinuation of LOTRONEX. Patients with resolved constipation should resume LOTRONEX only on the advice of their treating physician.

# Joint Sponsor/FDA Responsibilities

- Revised Labeling
  - Concise boxed warning with key safety information and program restrictions
  - Indication: Reserved for women with diarrhea-predominant IBS symptoms who have failed conventional therapy
  - Modified to include a half-dose, 30-day initial treatment period
  - Medication Guide which reflects labeling modifications
- Regular (e.g., quarterly) meetings to review evolving safety information

# Sponsor Responsibilities

- Establish External Expert Medical Review Board to review events of special interest
- Voluntary expedited reporting of events of special interest
- Provide Dear Physician and Dear Pharmacist letters conveying key elements of the Risk Management Plan and labeling changes
- Provide Patient-Physician Agreement Kit
  - 1-800 number described in Dear Physician letter
  - Sales representative calls during introductory period

# Sponsor Responsibilities

- Provide Lotronex and IBS disease information to physicians via sales representatives
- Provide internet website



# Sponsor Responsibilities

## Program Evaluation

- Use in Proposed Target Patient Population
  - Utilization of Lotronex in the United Healthcare Research Database
    - 5 million covered lives
    - Assess appropriateness for therapy
      - Demographic characteristics
      - IBS history and other GI history
      - Drugs dispensed in 6 months prior to Lotronex and during Lotronex use

# Sponsor Responsibilities

## Program Evaluation

- Compliance with Risk Management Plan
  - Pharmacy-Based Post Marketing Study of Lotronex (Slone Epidemiology Unit, Boston University School of Medicine)
    - Conduct with large, national retail pharmacy chain; 2600 retail pharmacies will participate
    - Patient contact within 1 week of dispensing
      - Questionnaire: IBS history, receipt of counseling regarding Benefit and Risk, Agreement Form and Medication Guide
      - Follow-up 30-45 days after dispensing

# Sponsor Responsibilities

## Additional Safety Evaluation

- Lotronex Safety Study
  - Occurrence of events of special interest in relation to Lotronex use in the United Healthcare Research Database
    - 5 million covered lives
    - Incidence of these events in patients receiving Lotronex
    - Incidence of these events in IBS patients who do not receive Lotronex
    - Risk factors for these events
    - Target number of Lotronex users: 10,000

# Prescriber Responsibilities

- Appropriate patient selection
- Obtain Patient–Physician Agreement Kit
- Sign Agreement Form confirming appropriate experience/training
  - Knowledgeable and experienced in diagnosis and treatment of IBS
  - Able to diagnose and manage ischemic colitis and complications of constipation
- Counsel patient on benefits–risks

# Prescriber Responsibilities

- Appropriate patient selection
- Obtain Patient-Physician Agreement Kit

LOTRONEX is **contraindicated** in patients:

- With a **history of chronic or severe constipation** or with a history of sequelae from constipation.
- With a **history of intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions.**
- With a **history of ischemic colitis** or impaired intestinal circulation.
- With **current or a history of Crohn's Disease or ulcerative colitis.**
- With **active diverticulitis** or a **history of diverticulitis.**
- Who are **unable to understand or comply** with the Patient-Physician Agreement.
- With **known hypersensitivity** to any component of the product.

# Prescriber Responsibilities

- Appropriate patient selection
- Obtain Patient–Physician Agreement Kit
- Sign Agreement Form confirming appropriate experience/training
  - Knowledgeable and experienced in diagnosis and treatment of IBS
  - Able to diagnose and manage ischemic colitis and complications of constipation
- Counsel patient on benefits–risks

# Prescriber Responsibilities

- Educate patient on signs and symptoms that require prompt action
- Obtain patient signature on Agreement Form
- Provide copy of Agreement Form to patient and place a copy in the patient's medical record
- Affix special sticker to prescription
  - No verbal Rx orders or Rx orders by facsimile
  - No refills, every Rx will require a sticker
- Active patient follow-up

# Prescriber Responsibilities

## PHYSICIANS MUST:

- **Counsel the patient about the potential risks and benefits** of LOTRONEX given the patient's response to other treatments and how much IBS symptoms interfere with the patient's life.
- **Give the patient a copy of the Medication Guide**, which outlines the potential risks and benefits of LOTRONEX and instruct the patient to carefully read the Medication Guide. Answer all questions the patient may have about LOTRONEX. The complete text of the Medication Guide is printed at the end of this document.
- **Review the Patient-Physician Agreement with the patient**, answer all questions, and **confirm that the patient has signed the Agreement**.
- **Sign the Patient-Physician Agreement, give a copy of the signed Agreement to the patient**, and put the **original in the patient's medical record**.
- Provide each patient with appropriate instructions for taking LOTRONEX.
- Copies of the Patient-Physician Agreement and additional copies of the Medication Guide are available by contacting GlaxoSmithKline at 1-888-825-5249 or [www.LOTRONEX.com](http://www.LOTRONEX.com).



# Prescriber Responsibilities

- Educate patient on signs and symptoms that require prompt action
- Obtain patient signature on Agreement Form
- Provide copy of Agreement Form to patient and place a copy in the patient's medical record
- Affix special sticker to prescription
  - No verbal Rx orders or Rx orders by facsimile
  - No refills, every Rx will require a sticker
- Active patient follow-up

# Pharmacist Responsibilities

- Accept only written prescriptions with an affixed sticker
- Dispense Medication Guide
- Additional resource for product information

# Patient Responsibilities

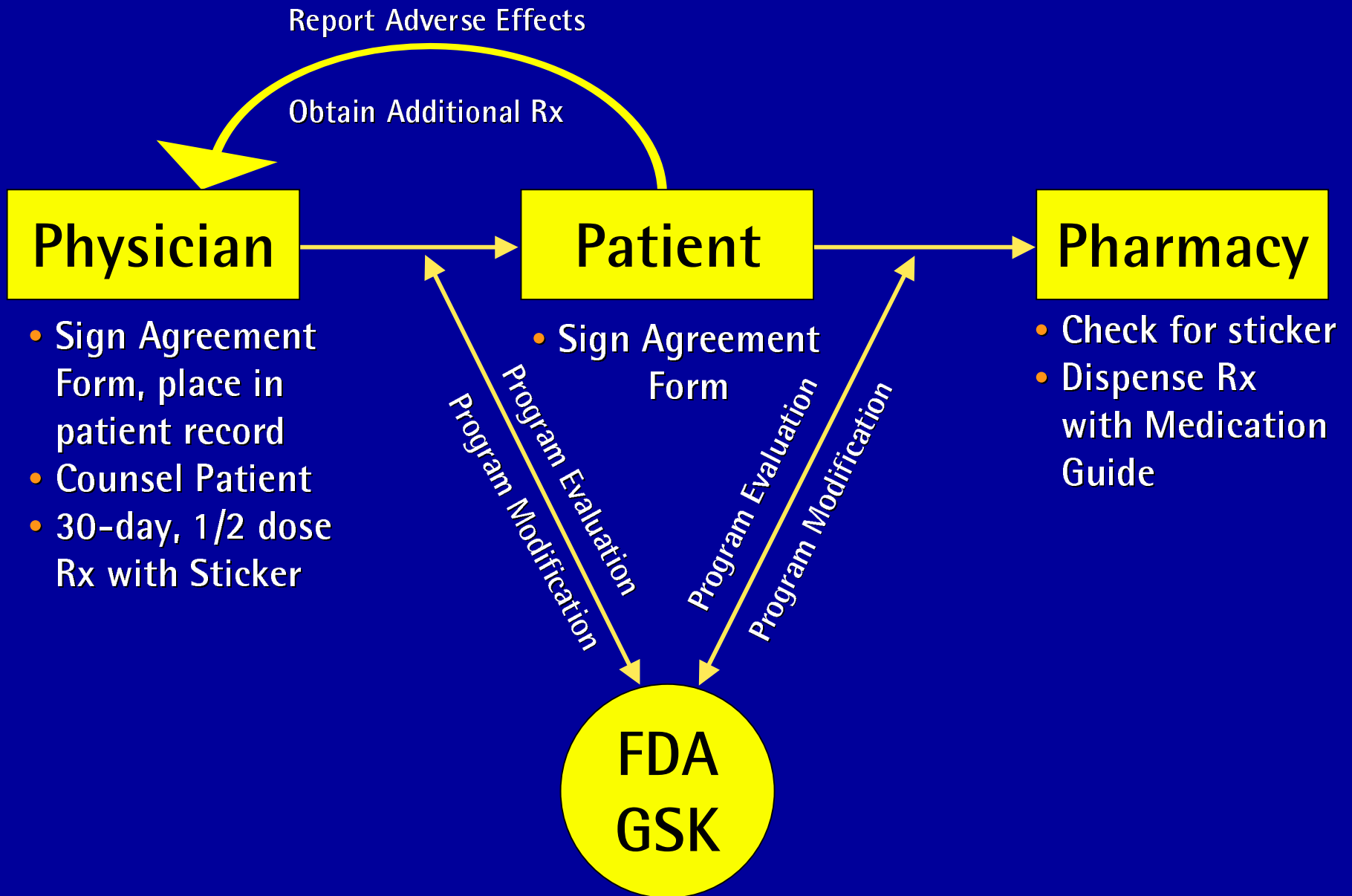
- Understand the benefits and risks
- Make an informed decision regarding treatment
- Sign the Agreement Form
- Follow physician and Medication Guide instructions
- Recognize important signs and symptoms
- Take prompt action
  - Discontinue treatment
  - Seek medical attention

# Patient Responsibilities

PATIENTS WHO ARE PRESCRIBED LOTRONEX SHOULD BE INSTRUCTED TO:

- **Read the Medication Guide** before starting LOTRONEX and each time they refill their prescription.
- **Not start taking LOTRONEX if they are constipated.**
- **Immediately discontinue LOTRONEX and contact their physician if they become constipated, or have symptoms of ischemic colitis such as new or worsening abdominal pain, bloody diarrhea, or blood in the stool.** Immediately contact their physician again if their constipation does not resolve after discontinuation of LOTRONEX. Resume LOTRONEX only if their constipation has resolved and after discussion with and the agreement of their treating physician.
- **Stop taking LOTRONEX and contact their physician if LOTRONEX does not adequately control IBS symptoms after 4 weeks of taking one tablet twice a day.**

# Lotronex Risk Management Plan



# Summary

## Risk Management Plan

- Designed to address benefit:risk of Lotronex
- Modified conditions of use: restricted access
- Communication plan includes messages to prescribers, pharmacists and patients
- Modified package insert and Medication Guide
- Patient-Physician Agreement process
- Real-time double check at pharmacy level
- Ongoing program evaluation

# Summary

## Risk Management Plan

- Informed patient use
- Reduce the occurrence of complications of constipation
- Mitigate serious outcomes associated with complications of constipation and ischemic colitis
- Strike a balance between mitigating risks without creating extraordinary barriers to patient access





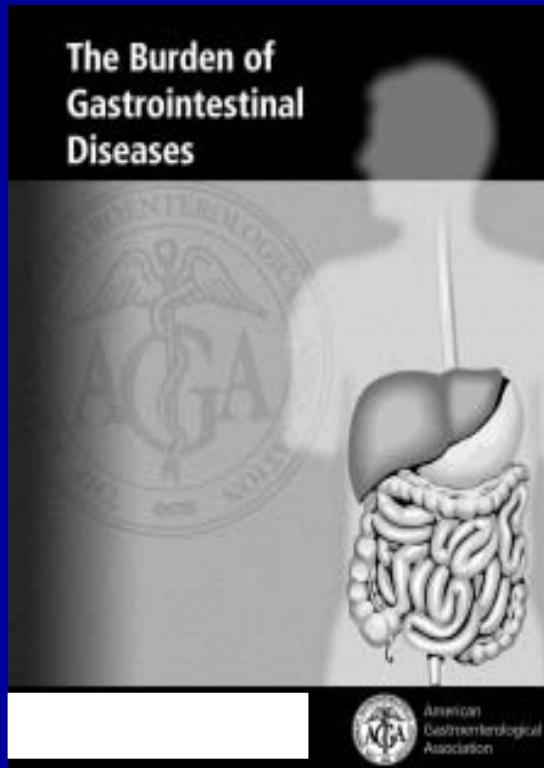
# Clinician's Perspective

Robert S. Sandler, M.D., M.P.H.  
Professor of Medicine and Epidemiology  
University of North Carolina at Chapel  
Hill  
Chapel Hill, North Carolina

# Topics

- Economic and social burden of IBS
- Treatment options
- Benefits
- Potential risks
- Risk management program

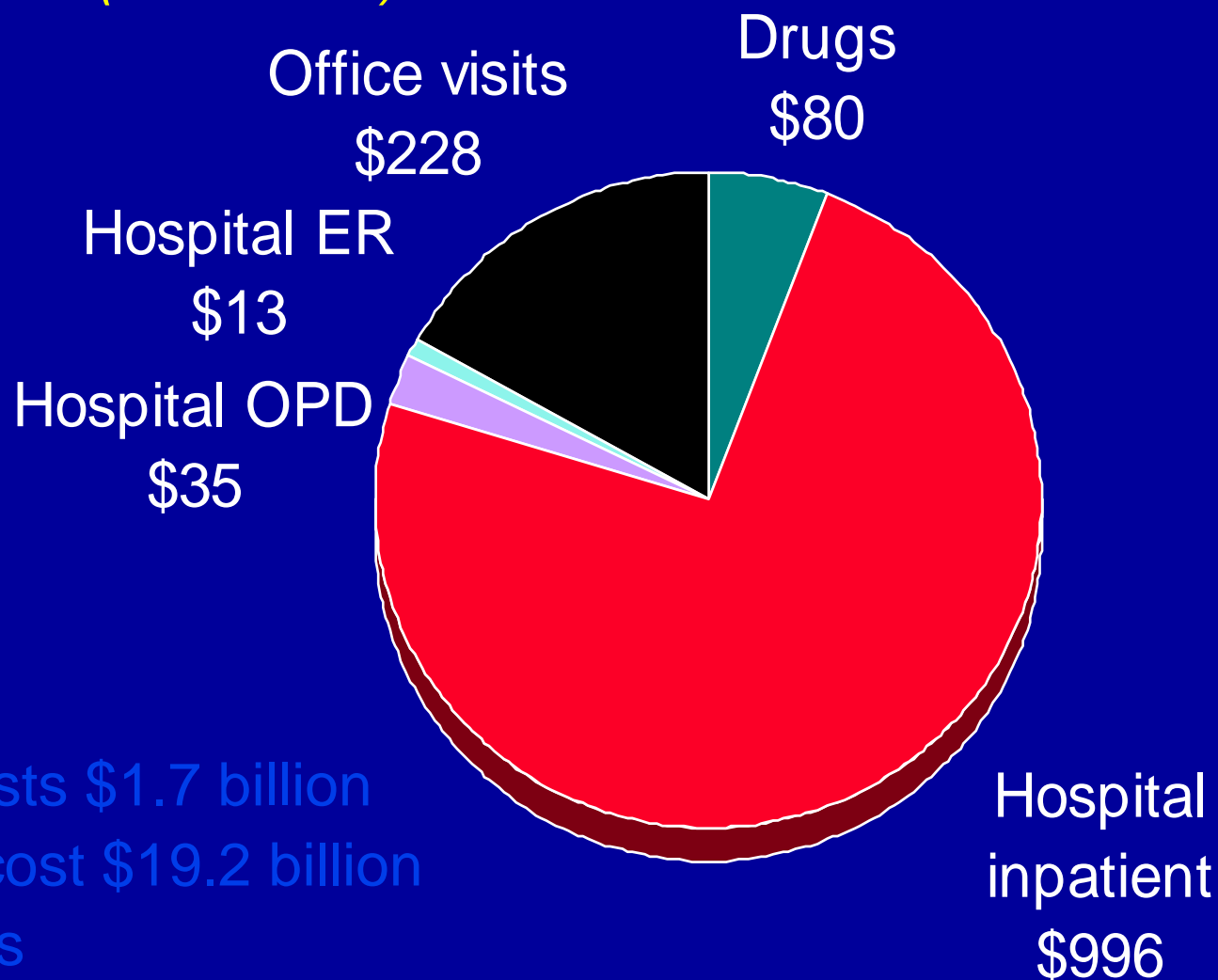
# Burden of IBS



- IBS is a common digestive complaint in US
  - 15.4 million prevalent cases
  - 3.6 million office visits
  - 150,000 hospital OPD visits
  - 87,000 ER visits

# Economic burden of IBS, 1998

*Direct cost of IBS (in millions)*



Total direct costs \$1.7 billion

Total indirect cost \$19.2 billion

Collateral costs

# Pain and suffering

- Economic analyses ignore social and emotional costs of IBS that are unmeasured & immeasurable.
- Physicians, policy-makers and critics typically pay insufficient attention to conditions that cause symptoms but are not fatal.
- Lack of appreciation for symptomatic conditions is insensitive and insulting to patients who are suffering.
- Given the high prevalence and high impact, we need therapeutic agents that are effective.

# Current therapy for IBS

- There are currently no FDA-approved drugs for IBS that have been proven to be effective in randomized placebo-controlled trials.
- Commonly used drugs include:
  - Fiber
  - Smooth muscle relaxants
  - Anti-depressants
  - Anxiolytics

# Current therapy for IBS

REVIEW

## Pharmacologic Treatment of the Irritable Bowel Syndrome: A Systematic Review of Randomized, Controlled Trials

Jeegar Jailwala, MD; Thomas F. Imperiale, MD; and Kurt Kroenke, MD

**Purpose:** To evaluate the efficacy of pharmacologic agents for the irritable bowel syndrome.

**Data Sources:** Electronic literature search of MEDLINE (1966 to 1999), EMBASE (1980 to 1999), PsycINFO (1967 to 1999), and the Cochrane controlled trials registry and a manual search of references from bibliographies of identified articles.

**Study Selection:** Randomized, double-blind, placebo-controlled, parallel, or crossover trials of a pharmacologic intervention for adult patients that reported outcomes of improvement in global or irritable bowel-specific symptoms.

**Data Extraction:** Qualitative and quantitative data reported on study groups, interventions, treatment outcomes, and trial methodologic characteristics.

**Data Synthesis:** 70 studies met the inclusion criteria. The most common medication classes were smooth-muscle relaxants (16 trials), bulking agents (13 trials), prokinetic agents (6 trials), psychotropic agents (7 trials), and loperamide (4 trials). The strongest

evidence for efficacy was shown for smooth-muscle relaxants in patients with abdominal pain as the predominant symptom. Loperamide seems to reduce diarrhea but does not relieve abdominal pain. Although psychotropic agents were shown to produce global improvement, the evidence is based on a small number of studies of suboptimal quality. Psychotropic drugs, 5-hydroxytryptamine (5-HT)-receptor antagonists, peppermint oil, and Chinese herbal medicine require further study.

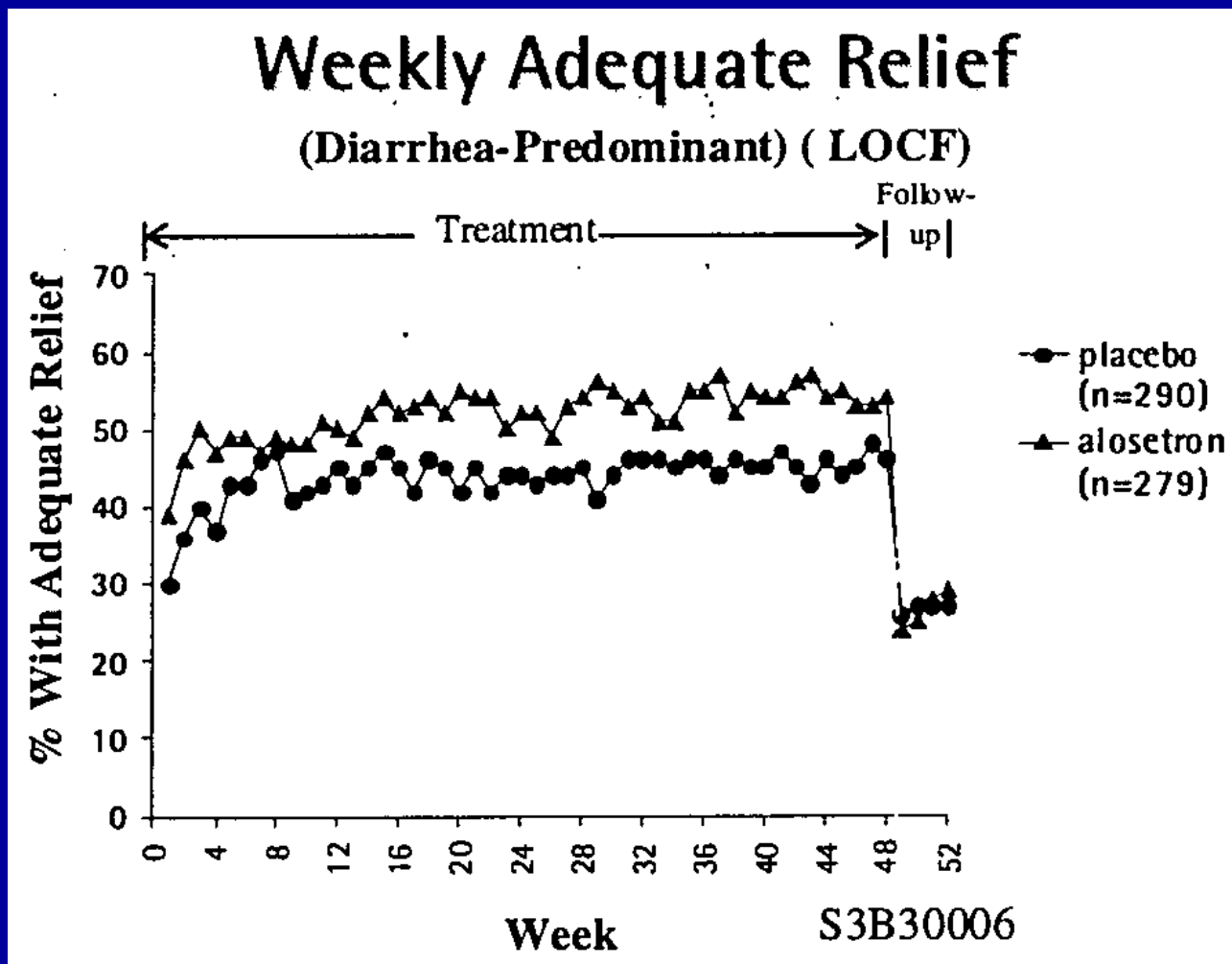
**Conclusions:** Smooth-muscle relaxants are beneficial when abdominal pain is the predominant symptom. In contrast, the efficacy of bulking agents has not been established. Loperamide is effective for diarrhea. Evidence for use of psychotropic agents is inconclusive; more high-quality trials of longer duration are needed. Evidence for the efficacy of 5-HT-receptor antagonists seems favorable, although more studies are needed.

*Ann Intern Med.* 2000;133:136-147.

For author affiliations and current addresses, see end of text.

*Ann Intern Med* 2000;133:136-147

# Benefits





# Benefits

- In placebo- and active-controlled comparator studies, alosetron provided significant improvement for a range of symptoms including:
  - Pain and discomfort
  - Bowel urgency
  - Stool frequency and consistency
  - Global IBS symptoms
  - Quality of life
  - Dietary limitations, social functioning, ability to carry out work or main activity

# Risks

- Information about risks come from
  - Controlled clinical trials – best evidence
  - Spontaneous reports
    - Factually uncertain, incomplete, imprecise
    - Unable to account for cases not related to drug (background)
    - Provide signal for rare events
  - Epidemiological studies
    - Susceptible to problems of misclassification of disease and exposure
    - Large size and population base provide insight into background rates in the general population

# Risks

- Constipation

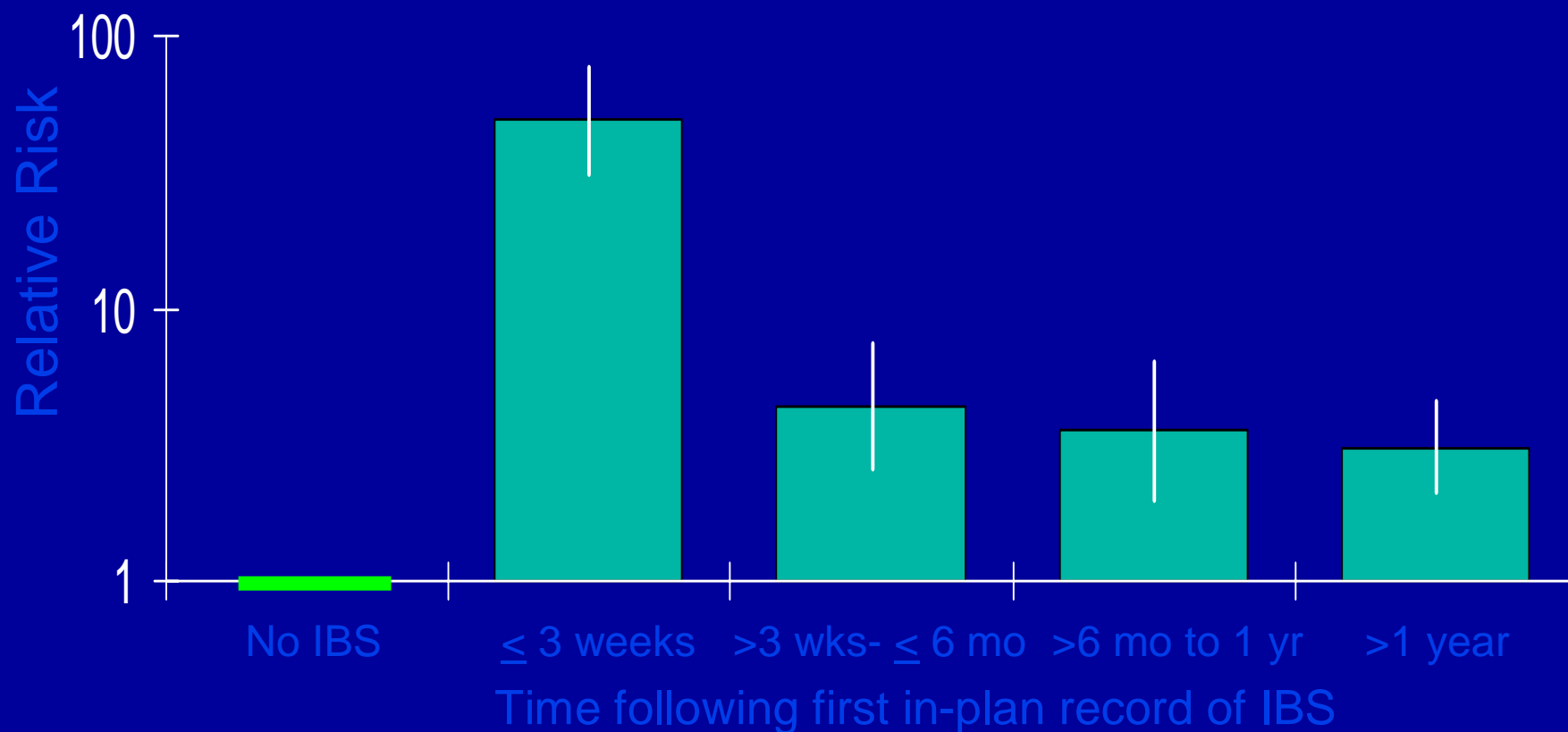
- Predictable based on pharmacological effects of 5-HT<sub>3</sub> antagonists
- Dose dependent (29% 1 mg BID; 11% 0.5 mg BID)
- In randomized trials with nearly 12,000 patients complications of constipation not more frequent in alosetron than placebo
- Epidemiology study shows IBS patients are more than twice as likely to be hospitalized with constipation complications than non-IBS patients

# Risks

- Ischemic colitis
  - 5–6–fold increase in risk with alosetron in randomized trials
  - All cases from clinical trials were self-limited and did not result in sequelae
  - In epidemiological study there was about a 4–fold increase in colonic ischemia in IBS patients compared to non-IBS patients

# Colonic ischemia

Adjusted Relative Risk (95% CI) of colonic ischemia in 5,402,500 UHC members



# Risks

## Conclusions about risk

### Constipation

- Should be straightforward to manage
- Complications of constipation not more common than placebo in randomized trials
- May be less frequent with lower starting dose

### Ischemic colitis

- Heightened awareness provides early detection
- Colonic ischemia is self-limited
- Relative risk 5.4 (95% CI 0.9-229)
- Etiologic fraction – questionable assumptions
- Attributable risk is 3.9 cases per thousand per year (excess risk from drug)

# Risk management program

- Risk management program
  - Appropriate patients – women with diarrhea predominant IBS who failed traditional therapy
  - Appropriate providers
    - Experienced, knowledgeable providers
    - Agreement Form
    - Counseling benefits, risks, safety monitoring
    - Signed agreement in medical record
    - Sticker on prescription
  - Phase IV studies

ROBERT S. SANDLER, M.D., M.P.H.  
DIV. OF DIGESTIVE DISEASES & NUTRITION  
UNIVERSITY OF NORTH CAROLINA  
228 106, THURMONT ACADEMIC BUILDING  
CHAPEL HILL, NC 27599-1066

STUDY NUMBER: \_\_\_\_\_ CDA # AB01074

NAME: \_\_\_\_\_ AGE: \_\_\_\_\_  
ADDRESS: \_\_\_\_\_ DATE: \_\_\_\_\_  
BY SIGNING, I AGREE TO THE SAFETY OF MY BACKGROUND

B

Sticker

Name: \_\_\_\_\_ State: \_\_\_\_\_

PRODUCT SELECTION PERMITTED      RESPOND AS WRITTEN  
©      10A015475

# Risk management program

## Impact of risk management program

- Discourage casual use – might prevent some deserving patients from getting the drug
- Alert physicians and patients to potential side effects
- Lead to early termination and evaluation for adverse events

*Physicians deal with risk-benefit issues every day –  
steroids, NSAIDs, immunosuppressives, biologics*



# Conclusions

- IBS is a significant economic and social problem
- Therapeutic options are limited
- Alosetron has demonstrated consistent benefits in rigorous studies and offers advantages to selected patients (women/diarrhea) with IBS
- The risk management program would limit use to knowledgeable MD's and appropriate patients
- Physicians and patients want the option to use an effective drug



**Lotronex<sup>®</sup>**  
**(alosetron hydrochloride) Tablets**

**Summary and Conclusions**

**James Palmer, M.D.**

Senior Vice President  
New Product Development  
GlaxoSmithKline

# Conclusions

- Reintroduction of Lotronex to patients without suitable therapeutic alternatives is supported by a substantial body of new data
- The proposed Risk Management Plan strikes an appropriate balance between the need to mitigate risks without creating extraordinary barriers to product access
- GlaxoSmithKline expectations

