

# XIFAXAN® (rifaximin) Tablets for Irritable Bowel Syndrome

United States Food and Drug Administration  
Gastrointestinal Drugs Advisory Committee  
November 16, 2011

CC-1

# Opening Comments

**William P. Forbes, PharmD**  
Executive Vice President,  
Medical and Research and Development  
Salix Pharmaceuticals, Inc.

CC-2

## Rifaximin Product Characteristics

- **Semisynthetic analog of rifamycin**
- **Gut targeted**
- **Minimal systemic absorption**
- **Binds to  $\beta$ -subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of RNA synthesis**

CC-3

## Rifaximin Experience

- **Available since 1987**
- **Approved in 36 countries**
- **Well-characterized safety profile**
  - Side effects mild and similar to placebo
  - No regulatory withdrawal
- **Well reported in the medical and scientific literature**
- **~5,000 subjects in controlled clinical trials**
- **7 years US post-marketing experience**

CC-4

## Rifaximin Development Programs

Use	Clinical Program	Filing Status
Irritable Bowel Syndrome	TARGET 1 & TARGET 2	Filed / CRL
Hepatic Encephalopathy*	RFHE3001 & RFHE3002	Filed and approved
Treatment of Travelers' Diarrhea	RFID9601, RFID9701, RFID9801 & RFID3001	Filed and approved
Crohn's Disease	RETIC/03/06	Not filed
Prophylaxis of Travelers' Diarrhea	RFID3003, RFID3004 & RFID3005	Not filed
Clostridium difficile	RFCL3001	Not filed

\* Reduction in risk of overt hepatic encephalopathy recurrence

CC-5

## Treatment of Travelers' Diarrhea Clinical Response

	XIFAXAN (n=125)	Placebo (n=129)	Estimate (97.5 % CI)	P-Value
Median Time to last unformed stool (hours)	32.5	58.6	1.78 <sup>a</sup> (1.26, 2.50)	0.0002
Clinical cure, n (%)	99 (79.2)	78 (60.5)	18.7 <sup>b</sup> (5.3, 32.1)	0.001

<sup>a</sup> Hazard Ratio

<sup>b</sup> Difference in rates

“Even though XIFAXAN had microbiologic activity similar to placebo, it demonstrated a clinically significant reduction in duration of diarrhea and a higher clinical cure rate than placebo. Therefore, patients should be managed based on clinical response to therapy rather than microbiologic response”

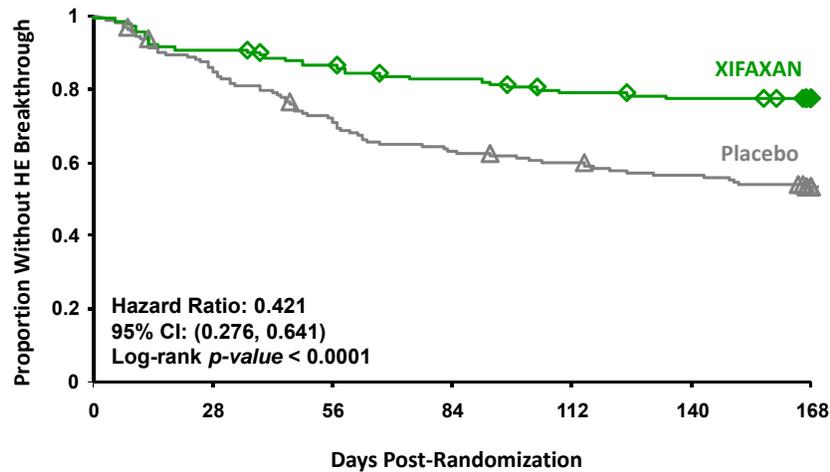
### Microbiologic Eradication Rates in Subjects with Baseline Pathogen

	XIFAXAN	Placebo
Overall	48/70 (68.6)	41/61 (67.2)
<i>E. coli</i>	38/53 (71.7)	40/54 (74.1)

Xifaxan® Prescribing Information 2010

CC-6

## Recurrence of Overt Hepatic Encephalopathy Kaplan-Meier Event-Free Curves

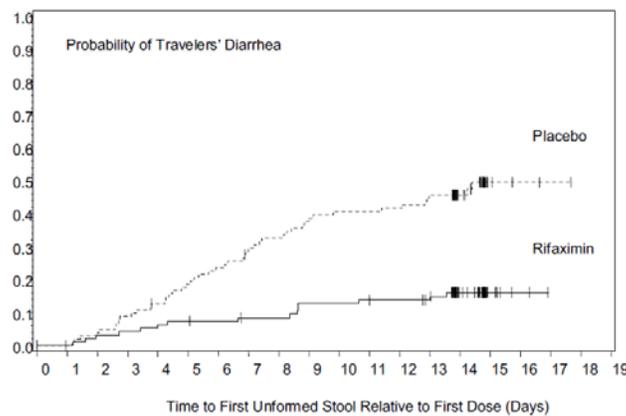


Time to First Breakthrough-HE Episode up to 6 Months of Treatment (ITT Population)  
Xifaxan® Prescribing Information 2010

CC-7

## Prophylaxis of Travelers' Diarrhea

Subjects treated prophylactically with rifaximin 600 mg QD had a significantly lower risk of developing TD compared with those treated prophylactically with placebo ( $p < 0.0001$ ).



Martinez-Sandoval F, et al. J Travel Med, 2010.

CC-8

## Rifaximin Clinical Program Crohn's Disease

**Objective:** To compare the efficacy, safety and tolerability of three doses of Rifaximin-EIR tablet (800 mg, 1,600 mg, 2,400 mg per day) vs. placebo in the treatment of active moderate Crohn's disease.

**1° Endpoint:** Clinical remission rate, defined as a CDAI < 150 at the end of treatment

	Placebo % (n)	RFX-EIR 400 mg bid % (n)	RFX-EIR 800 mg bid % (n)	RFX-EIR 1200 mg bid % (n)	All RFX-EIR doses % (n)
ITT population	42.6% (43/101)	53.8% (56/104)	62.2% (61/ 98)	47.5% (47/ 99)	54.5% (164/301)
P value vs placebo [95% CI]		0.106	0.005	0.486	0.038
OR [CI]		1.57 [0.91, 2.73]	2.22 [1.26, 3.92]	1.22 [0.70, 2.13]	n.d.

CC-9

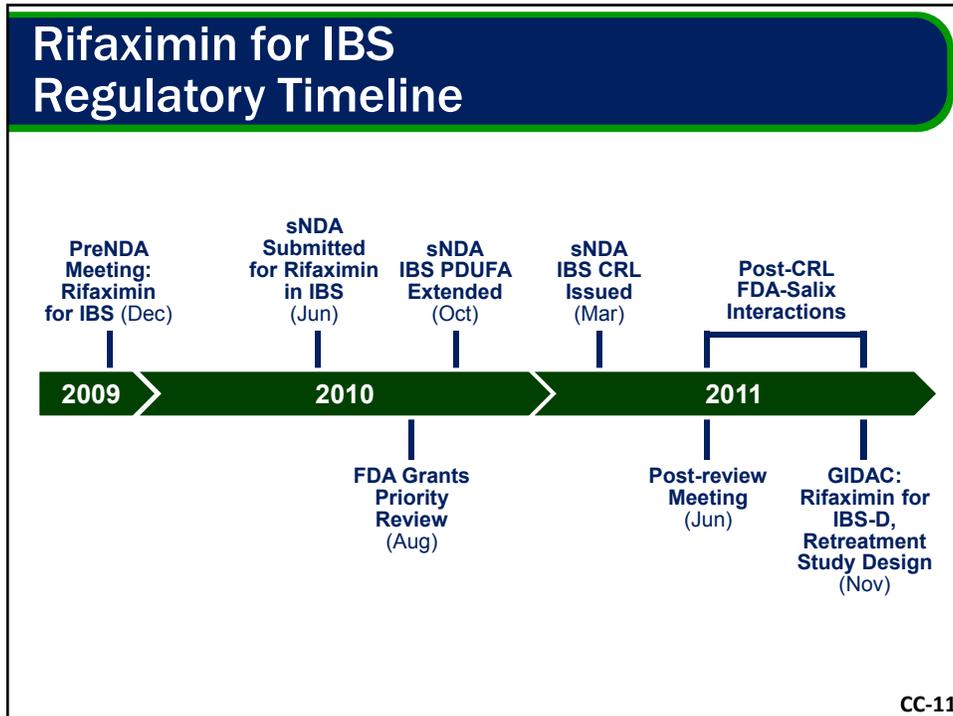
## Rifaximin Clinical Program for *Clostridium difficile*

**Study Design:** Double-blind, randomized, 10-day treatment of rifaximin 400 mg TID vs. Vancomycin 125 mg QID, non-inferiority trial for treatment of C. Diff

**1° Endpoint:** Proportion of subjects achieving clinical success defined as absence of severe abdominal pain at Test of Cure(TOC), absence of fever at TOC; <3 unformed stools at TOC

	Response	Rifaximin (N=117)	Vancomycin (N=115)	Treatment Difference (95% CI)
Clinical Success	Yes	67 (57%)	73 (64%)	-6.2%
	No	50 (43%)	42 (37%)	(-18.8%, 6.4%)
Severe Abdominal Pain/Discomfort	No	80 (74%)	95 (86%)	-11.5%
	Yes	28 (26%)	16 (14%)	(-22.1%, -0.98%)
Fever	No	98 (91%)	109 (98%)	-7.5%
	Yes	10 (9%)	2 (2%)	(-13.5%, -1.5%)
Diarrhea	No	86 (80%)	90 (81%)	-1.5%
	Yes	22 (20%)	21 (19%)	(-12.0%, 9.1%)

CC-10



## Need for Effective and Safe Therapies

**Current treatments require chronic dosing**

<p><b>Approved Since 2000</b></p> <p><u>IBS-D</u></p> <ul style="list-style-type: none"> <li>• Alosetron (Lotronex®) <ul style="list-style-type: none"> <li>• Approved Feb 2000 (withdrawn Nov 2000)</li> <li>• Re-launched and restricted to women with severe IBS</li> </ul> </li> </ul> <p><u>IBS-C</u></p> <ul style="list-style-type: none"> <li>• Tegaserod (Zelnorm®) <ul style="list-style-type: none"> <li>• Approved 2002 (withdrawn 2007)</li> </ul> </li> <li>• Lubiprostone (Amitiza®) <ul style="list-style-type: none"> <li>• Approved 2006</li> </ul> </li> </ul>	<p><b>DESI* (before 1962)</b></p> <ul style="list-style-type: none"> <li>• Antispasmodics</li> <li>• Anticholinergics</li> <li>• Benzodiazepines</li> </ul>
<p>* Pre 1962 "grandfathered" drugs</p>	<p><b>OTC</b></p> <ul style="list-style-type: none"> <li>• Bulking agents</li> <li>• Antidiarrheals</li> <li>• Probiotics</li> </ul>

CC-12

## ACG Evidence-based Review Grade of Recommendation for Rifaximin (2009)

- **A short- term course of a nonabsorbable antibiotic is more effective than placebo for global improvement of IBS and for bloating **Grade 1B****

Grade of Recommendation/ Description	Benefit vs. Risk and Burdens	Implications
1B. Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Strong recommendation, can apply to most patients in most circumstances. Higher quality evidence may well change our confidence in the estimate of effect

- **There are no data available to support the long-term safety and effectiveness of nonabsorbable antibiotics for the management of IBS symptoms**

ACG Task Force on IBS. *Am J Gastroenterol*. 2009.

CC-13

## TARGET 1 and TARGET 2

- **Pivotal trials for IBS-D and IBS-related bloating**
- **Primary endpoint met**
  - Rapid onset of relief
  - Persistence of efficacy
- **Key secondary endpoint met**
- **Adverse event profile similar to placebo**

CC-14

## Important Points

- Rifaximin is safe and effective for initial treatment for IBS-D
- Clinical efficacy unrelated to microbiologic findings
- Robust clinical development program
- Salix is committed to developing safe and effective therapies
- Repeat treatment study is final step

CC-15

## Presentations and Speakers

---

### Overview of IBS, Clinical Background and Biomarkers

**Anthony Lembo, MD**  
Associate Professor, Medicine  
Harvard Medical Faculty Physicians at Beth Israel  
Deaconess Medical Center, Boston, MA

---

### IBS and GI Microbiome

**Stephen M. Collins MBBS, FRCPC**  
Professor of Medicine & GSK Chair in Gastroenterology, Associate  
Dean, Research, McMaster University  
Hamilton, Ontario, Canada

---

### Rifaximin Clinical Pharmacology

**Pamela L. Golden, PhD**  
Executive Director, Nonclinical & Clinical Pharmacology  
Salix Pharmaceuticals, Inc.

---

### Clinical Development Program Clinical Efficacy and Safety Proposed Repeat Treatment Study Design

**Craig Paterson, MD**  
Vice President  
Medical & Clinical Development  
Salix Pharmaceuticals, Inc.

---

CC-16

## Experts Available to the Advisory Committee

**Ian Carroll, PhD**

Assistant Professor  
Dept. of Medicine  
University of North Carolina, Chapel Hill  
Chapel Hill, NC

**Naga Chalasani, MD**

Professor and Director  
Indiana University School of Medicine  
Division of Gastroenterology-Hepatology  
Indianapolis, IN

**Herbert L. DuPont, MD**

Clinical Professor of Medicine  
Vice Chair, Dept. of Medicine  
Chief of Medicine, St. Luke's Episcopal Hospital  
Director, Center for Infectious Diseases  
The University of Texas Health Science Center  
at Houston, School of Public Health  
Houston, TX

**Gary G. Koch, PhD**

Professor, Department of Biostatistics  
School of Public Health  
University of North Carolina, Chapel Hill  
Chapel Hill, NC

**Mark Pimentel, MD, FRCPC**

Director, Gastrointestinal Motility Program  
Director, GI Motility Laboratory  
Cedars-Sinai Medical Center  
Los Angeles, CA

**Philip Schoenfeld, MD, FRCPC, FRCG**

Associate Professor, Dept. of Internal Medicine  
Director, Training Program in GI Epidemiology  
University of Michigan,  
Ann Arbor, MI

CC-17

## Overview of IBS, Clinical Background, and Biomarkers



**Anthony Lembo, M.D.**  
Associate Professor of Medicine  
Harvard Medical School  
Director, GI Motility Center  
Beth Israel Deaconess Medical Center  
Boston, MA



CC-18

## Overview

- IBS is a common condition characterized by recurrent abdominal pain associated with altered bowel habits
- Significant negative impact on QOL
- No clinically useful biomarkers
  - Multi-factorial etiology
  - Diagnosis is symptom based
- There is an unmet need for safe and effective therapies in IBS

CC-19

## IBS Symptoms and Diagnosis

- IBS is a heterogeneous disorder associated with recurrent GI symptoms
  - Abdominal pain/discomfort
  - Bloating
  - Altered bowel habits (diarrhea, constipation, both)
- Diagnosis of IBS is symptom-based
  - Rome Criteria (I, II or III)

CC-20

## Rome II Criteria for IBS

At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two out of three features:

Relieved with defecation

Onset associated with a change in frequency of stool

Onset associated with a change in form (appearance) of stool

Thompson WG. et al Gut 1999

CC-21

## Rome ~~II~~ III Criteria for IBS

**At least 3 days/month**

~~At least 12 weeks~~, which need **3** not be consecutive, in the preceding ~~12~~ months of **recurrent** abdominal discomfort or pain that has two out of three features:

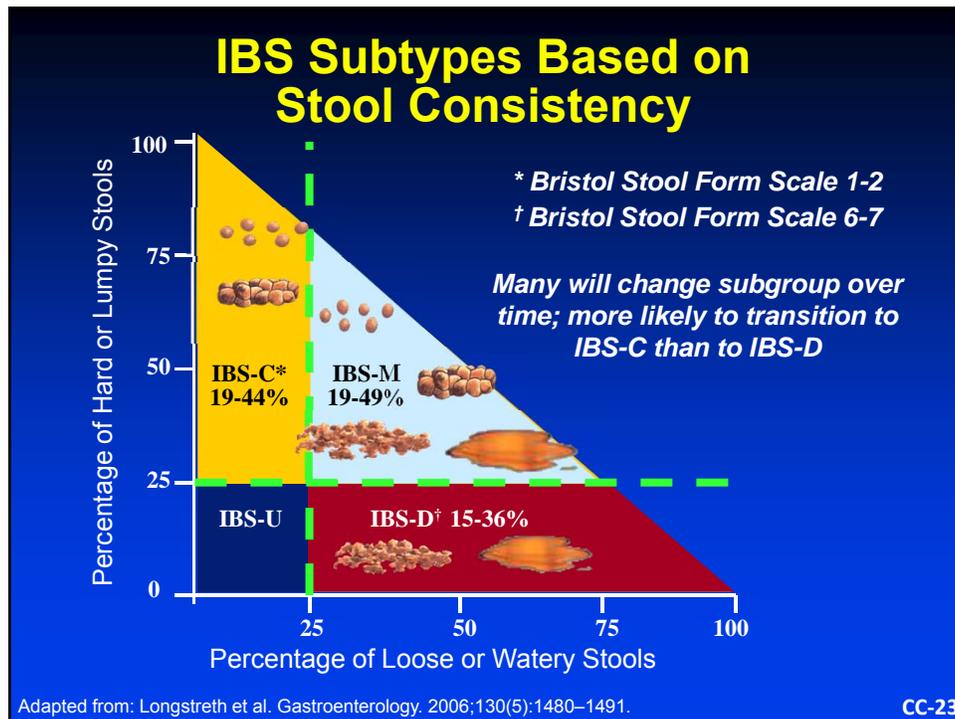
**Improvement**  
~~Relieved~~  
with defecation

Onset associated with a change in frequency of stool

Onset associated with a change in form (appearance) of stool

Adapted from: Longstreth et al. Gastroenterology. 2006;130(5):1480-1491.

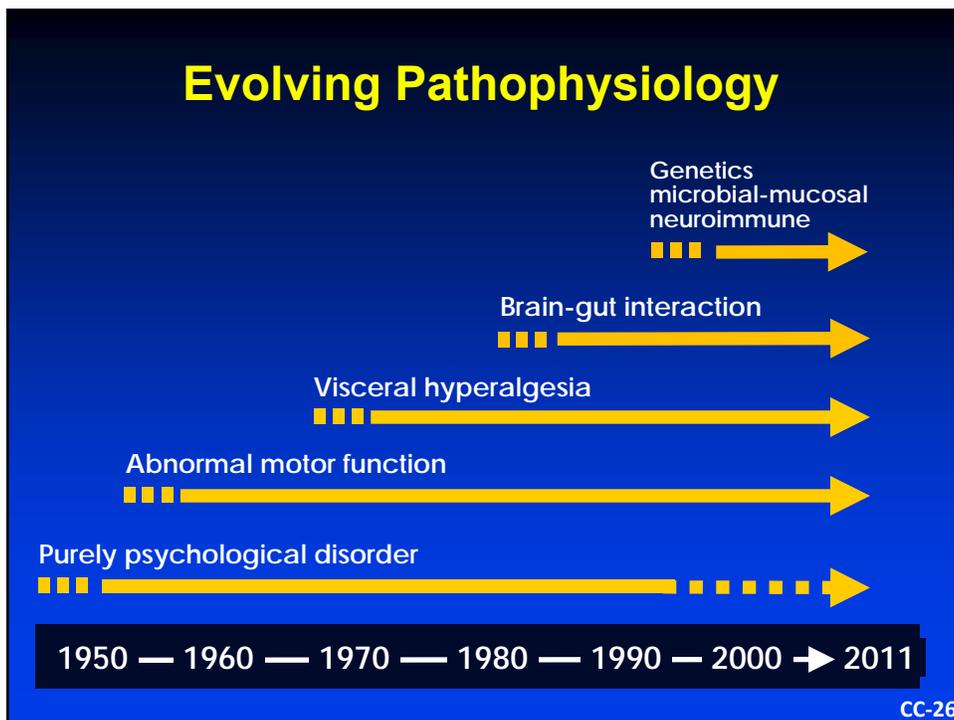
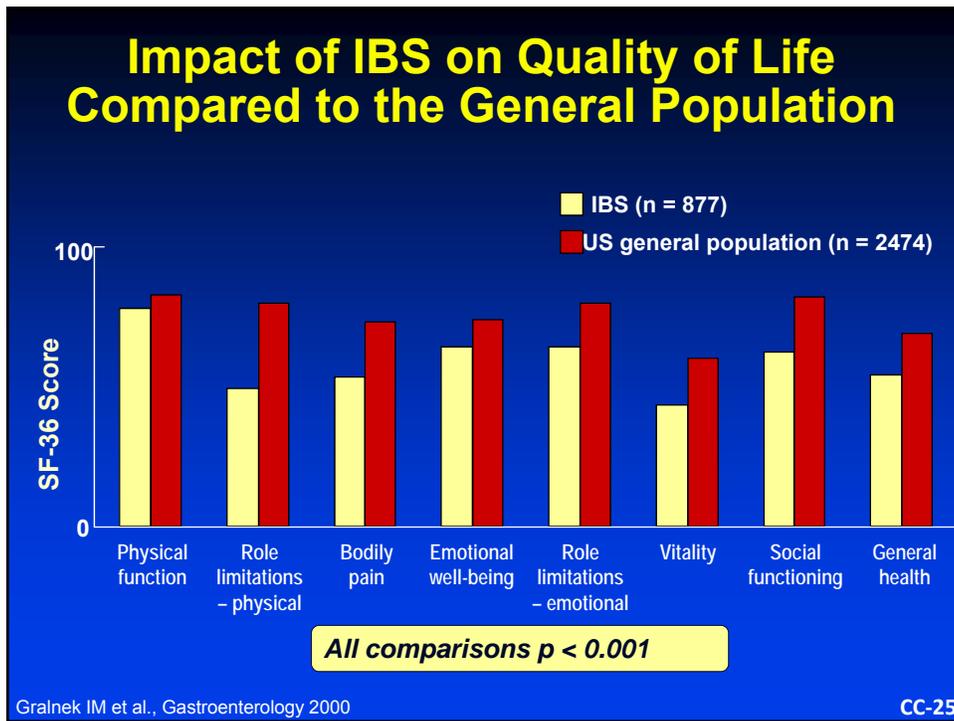
CC-22



## IBS Burden and Patient Experience

- 10-15% of the general population in Western countries have IBS symptoms<sup>1,2</sup>
  - Only 25% ever seek medical care for their IBS
- “Patients with IBS visit the doctor more frequently, use more diagnostic tests, consume more medications, miss more workdays, have lower work productivity, are hospitalized more frequently, and consume more overall direct costs than patients without IBS.”<sup>3</sup>

1. Talley, 2006 Intern. Med. J., 2004; 2 Spiegel, Curr Gastroenterol, Rep2009;  
3. Brandt LJ, et al. Am J Gastroenterol. 2009;104(Suppl):S1.



## No Proven Biomarkers Currently Exist for IBS

- **Criteria for a potential biomarker in clinical trials**
  - Objectively defines a disorder and defines a patient subgroup within a disorder
  - Demonstrates low inter-subject variability (reduces the number needed to test)
  - Predicts treatment response (surrogate endpoint)
  - Meets criteria for reproducibility
  - Correlates with symptoms and/or severity
  - Practical with regard to cost, availability and ease of use

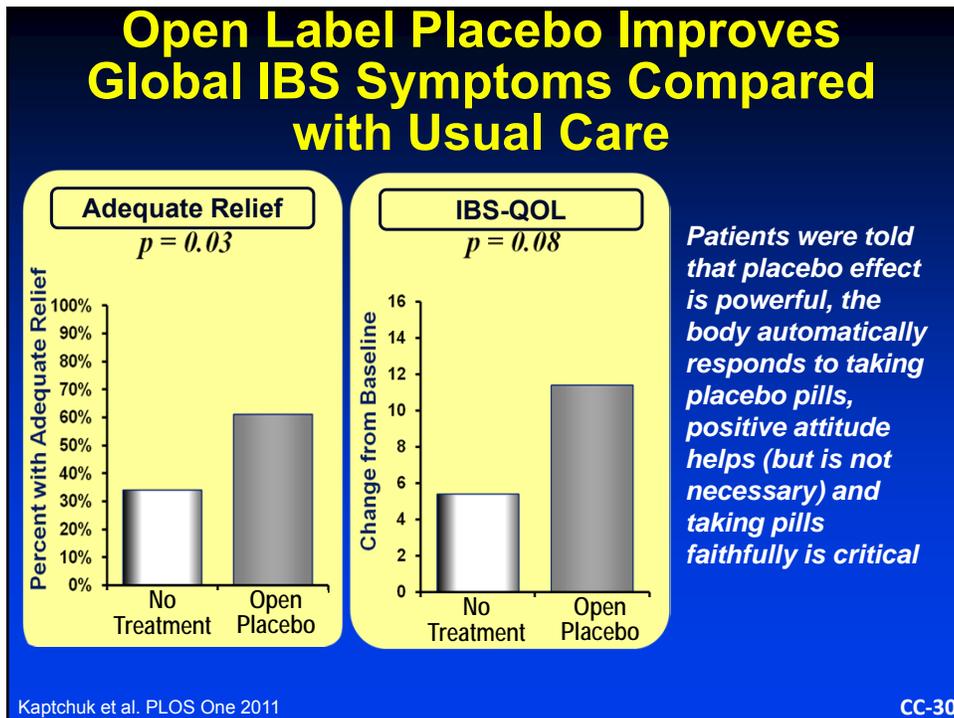
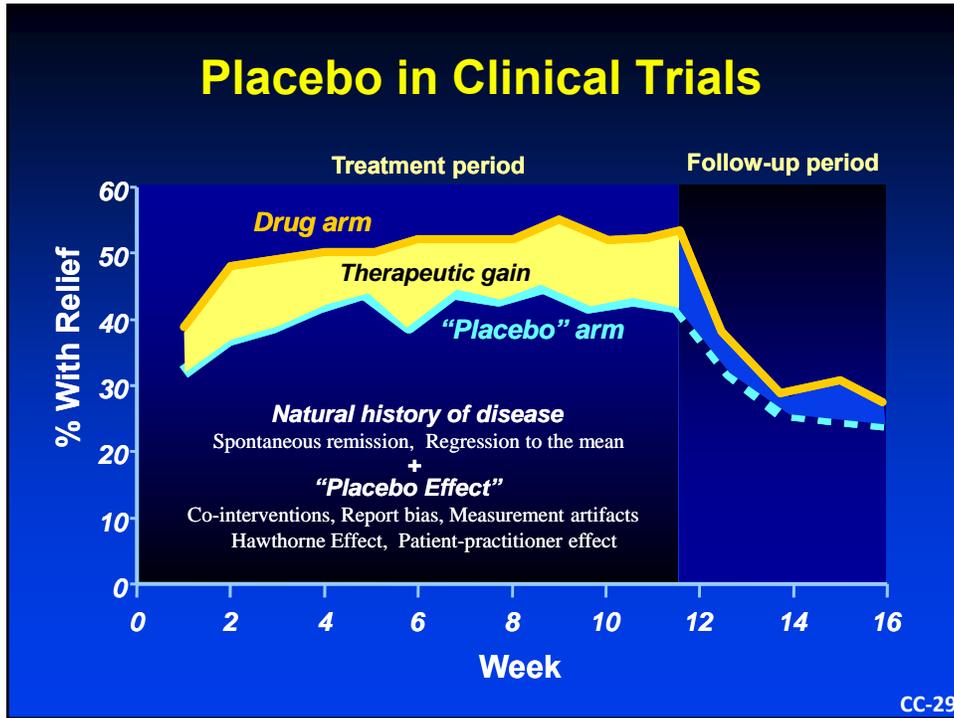
Biomarkers obtained from blood, urine, or stool may be the most practical surrogate endpoints in large clinical trials

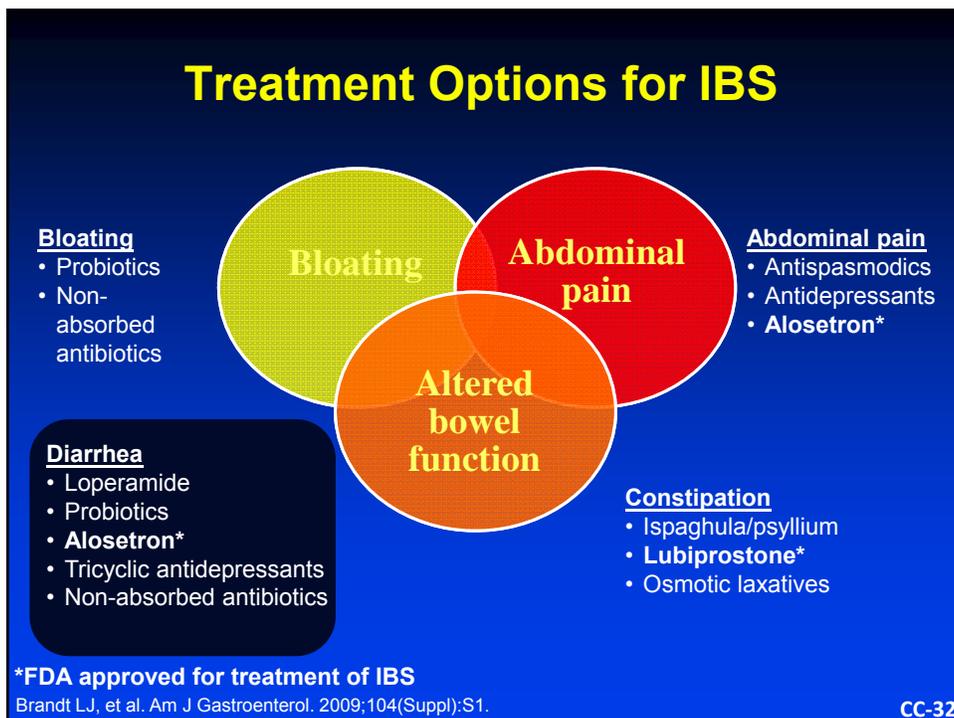
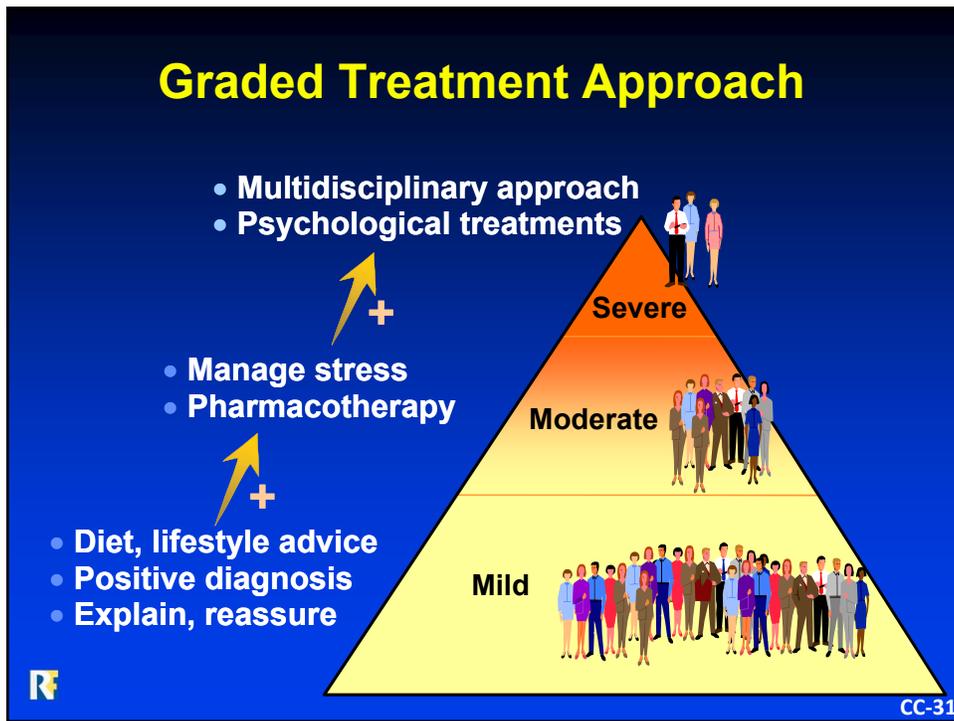
Spiller, Gastroenterol Clin N Am, 2011; Cheng L, FDA AMNS Joint Biomarker Qualification Workshop 2010 **CC-27**

## Other Challenges to IBS Study Design

- Heterogeneity, fluctuation and subjectivity of symptoms
- Multiple potential pathophysiological mechanisms
- Study methodology issues (eg, maintaining blinding, study duration)
- Contamination by parallel interventions
- High placebo response rate

CC-28





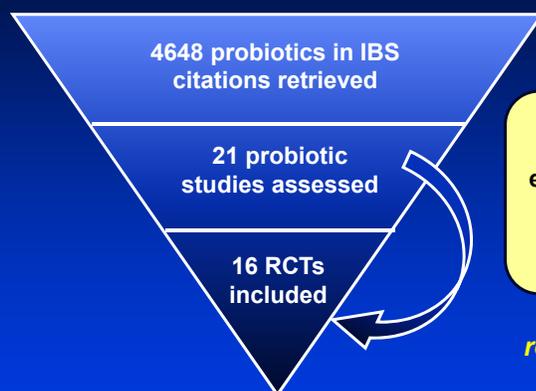
## Loperamide in IBS

- Decrease intestinal motility by activating the  $\mu$ -opioid receptor
- Two RCTs (n = 42 patients) of low-intermediate quality that showed improvement in stool consistency and frequency but not global improvement or improvement in pain
  - **Grade 2C: weak recommendation based on low-quality evidence**

Brandt LJ, et al. Am J Gastroenterol. 2009;104(Suppl):S1.

CC-33

## Probiotics for IBS: Few Appropriately Designed Randomized Clinical Trials



In single organism studies, *lactobacilli* do not appear effective for patients with IBS; *bifidobacteria* and certain combinations of probiotics demonstrate some efficacy.

**Grade 2C: weak recommendation based on low-quality evidence**

*B infantis* 35624 demonstrated efficacy in 2 appropriately designed RCTs

Brenner DM et al. Am J Gastroenterol. 2009;104:1033-1049.

CC-34

## Efficacy of Alosetron in IBS-D: Meta-analysis

### Global IBS Symptoms or Abdominal Pain

Study (Year)	Treatment n/N	Control n/N	RR (Random) 95% CI	RR (Random) 95% CI
Camilleri (1999)	179/290	54/80	0.91	[0.77, 1.09]
Bardhan (2000)	166/345	57/117	0.99	[0.80, 1.23]
Camilleri (2000)	191/324	229/323	0.83	[0.74, 0.93]
Camilleri (2001)	182/309	235/317	0.79	[0.71, 0.89]
Lembo (2001)	144/532	156/269	0.47	[0.39, 0.55]
Chey (2004)	167/351	197/363	0.88	[0.76, 1.01]
Chang (2005)	268/534	77/128	0.83	[0.71, 0.98]
Krause (2007)	279/529	122/176	0.76	[0.67, 0.86]
<b>Subtotal (95% CI)</b>	<b>3,214</b>	<b>1,773</b>	<b>0.79</b>	<b>[0.69, 0.90]</b>

0.1 0.2 0.5 1 2 5 10  
Favors Treatment Favors Control

NNT = 8; (95% CI 5-17)

#### ACG Task Force Recommendation

Grade 2A (women): weak recommendation, high quality evidence, benefits closely balance with risks and burden

Ford AC, et al. Am J Gastroenterol. 2009;104:1831-1843. Brandt LJ, et al. Am J Gastroenterol. 2009;104(Suppl 6):S5

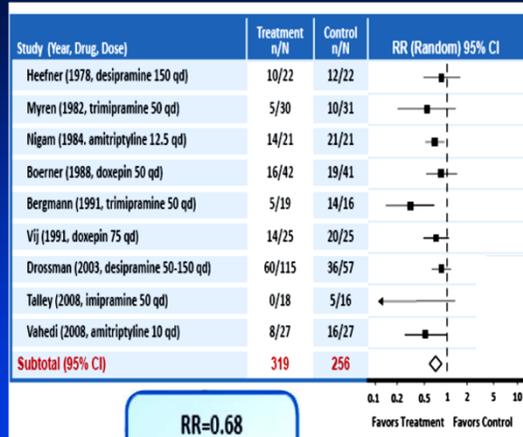
## Alosetron Use Restricted in IBS

- Indicated for women with chronic, severe IBS-D who have not responded adequately to conventional therapy<sup>1</sup>
- Alosetron use limited by risk of rare but SAEs
  - Ischemic colitis 0.95/1000 patient-years<sup>2</sup>
  - Serious complications of constipation per 0.36/1000 patient-years<sup>2</sup>
- Use regulated by prescribing program designed with FDA
  - Patient required to sign Attestation Form

1 Physicians' Desk Reference. 64th ed. Montvale, NJ: Thompson Reuters;2010. 2 Chang L, et al. Am J Gastroenterol. 2010;105:866-875.

## Tricyclic Antidepressants in IBS

- Reduces pain/global symptoms (Grade 1B)
- May be more effective in IBS-D due to anti-cholinergic properties
- Desipramine 50-150mg/d is best studied dose
- Poorly tolerated due to frequent side effects
- Discontinuation due to AEs is > 20%



RR=0.68  
(95% CI=0.56-0.83)  
NNT=4

1 Lesbros-Pankoflickova Et al. *APT*, 20:1253 2004. 2 Ford AC, et al. *Gut* (58), 2009.  
3. Drossman DA et al., *Gastroenterology*, 2003:125:19-31.

CC-37

## Summary

- IBS is characterized by recurrent abdominal pain associated with altered bowel habits
- IBS can have a significant negative impact on QOL and creates a substantial economic burden for patients and society
- IBS symptoms reflect a multi-factorial etiology
- No clinically useful biomarkers have been established and IBS diagnosis is symptom based
- There is an unmet need for safe and effective therapies for patients suffering from IBS

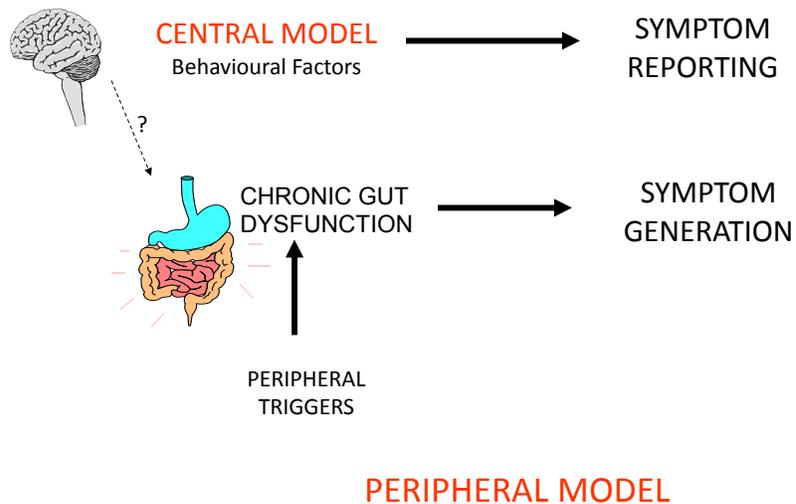
CC-38

## THE ROLE OF THE MICROBIOME IN IBS

Stephen M Collins MB.BS., FRCPC  
Professor of Medicine & GSK Chair in  
Gastroenterology, Associate Dean, Research,  
McMaster University  
Hamilton, Ontario, Canada.

CC-39

## CONCEPTUAL MODELS OF IBS



CC-40

## ACUTE ENTERIC INFECTION & IBS (POST-INFECTIOUS IBS)

- Suspected for over 50 years on basis of clinical observation and retrospective studies.
- Cohort and epidemiological studies following large scale outbreaks of food and water poisoning have now established acute enteric infection as the strongest risk factor for the development of IBS (RR>10)
- Supported by proof-of-concept from animal models studies
- Prompted acceptance of a “Peripheral Model” of IBS
- Associated with low grade inflammation and increased intestinal permeability.

CC-41

## LINES OF EVIDENCE OF LOW GRADE INFLAMMATION IN IBS PATIENTS

- INCREASED CELLULARITY IN GUT WALL
- GENETICALLY DETERMINED PREDISPOSITION TO PRO-INFLAMMATORY CYTOKINE SECRETION IN IBS PATIENTS
- ABNORMAL MEDIATOR RELEASE FROM INFLAMMATORY CELLS.
- NOT RESTRICTED TO POST-INFECTIOUS IBS.

CC-42

## WHAT MAINTAINS LOW GRADE INFLAMMATION IN IBS PATIENTS?

### THE INTESTINAL MICROBIOTA ?

CC-43

## LINES OF EVIDENCE IMPLICATING THE MICROBIOTA IN THE PATHOPHYSIOLOGY OF IBS

- **FACTORS THAT TRIGGER IBS ALSO INFLUENCE THE MICROBIAL COMPOSITION OF THE GUT.**

- Acute Enteric Infection (Marshall 2010; Garcia-Rodriguez 1999)
- Antibiotic Usage (Mendall 1998)

- **SYMPTOMATIC IMPROVEMENT SEEN IN IBS PATIENTS FOLLOWING THERAPIES THAT MODULATE INTESTINAL MICROBIAL COMPOSITION/ACTIVITY**

- Probiotics
  - Prebiotics
  - Antibiotics
- (Moayyedi 2010; Parkes 2010; Whelan 2011; Pimentel & Lexcano 2007)

- **ALTERATIONS IN THE MICROBIAL COMPOSITION/ACTIVITY IN IBS PATIENTS** (for review see Salonen A et al 2010)

CC-44

## MICROBIAL COMPOSITION IN IBS

- No uniform alterations in composition of the microbiota seen in IBS compared to healthy controls (for review see Salonen 2010).
- Sub-group analyses indicate that IBS-D exhibits the greatest deviation from healthy controls (Lyra 2009; Rajilic-Stojanovic 2007).
- Greater temporal instability of microbiota over time in IBS compared to healthy controls (Matto et al 2005).
- Disruption of biofilm may restrict access of certain counter-inflammatory bacteria (*F.prausnitzii*) to host tissue (Swidswinski 2008)

CC-45

## MICROBIAL ACTIVITY IN IBS

- Abnormal excretion profiles of hydrogen & methane in IBS patients; correlation of methane production & IBS-C. (Kunkel et al 2011)
- Increased fecal organic acid levels in IBS; correlation with abdominal pain & bloating (Tana et al 2010)
- No metabolomic data currently available.

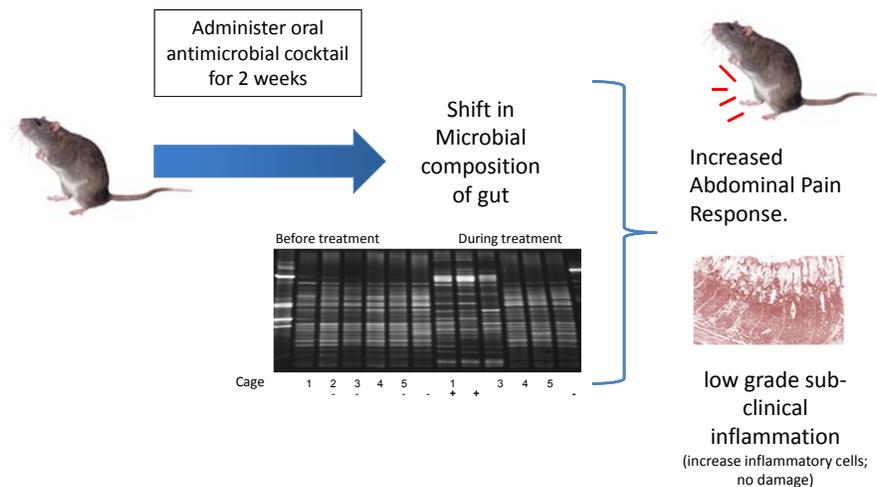
CC-46

## GUT RESPONSE TO CHANGES IN THE MICROBIOTA

Does perturbation of the microbiota induce low grade inflammation & alter gut function?

CC-47

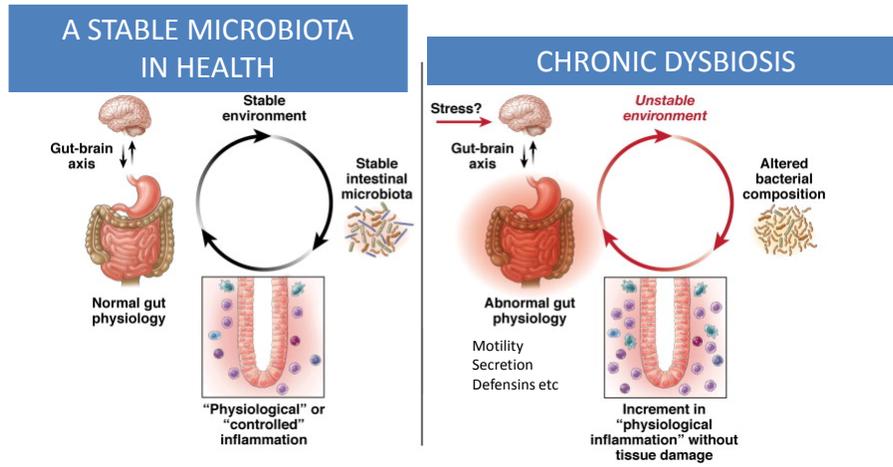
## PROOF OF CONCEPT FROM ANIMAL STUDIES



Verdú E F et al. Gut 2006;55:182-190

CC-48

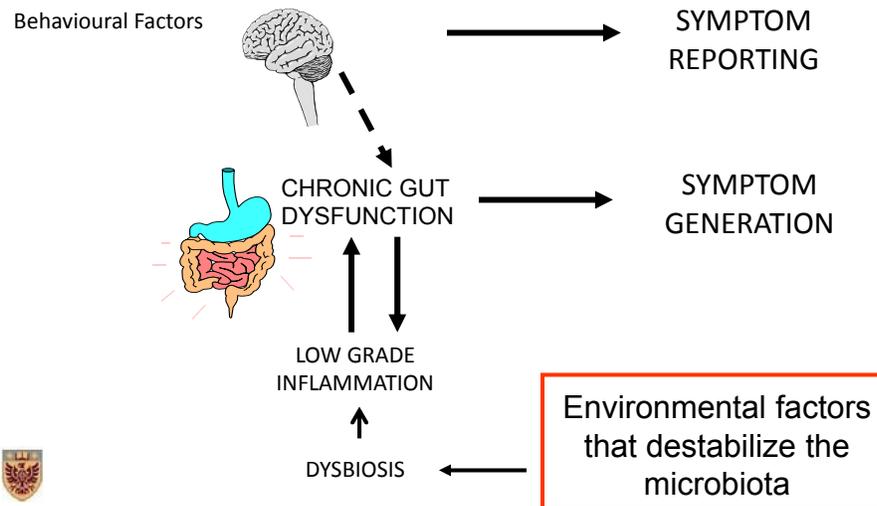
## HOW IS INSTABILITY OF THE MICROBIOTA MAINTAINED IN IBS ?



Collins SM & Bercik P Gastroenterology 2009 May;136(6):2003-14.

CC-49

## A MICROBIOME-CENTRIC MODEL OF IBS



CC-50

## CONCLUSIONS

- Changes in the intestinal microbiota exist in IBS patients.
- Alterations in the microbiota may drive low grade inflammation & gut dysfunction in IBS.
- Therapies directed at the microbiota constitute a novel & rational approach to the treatment of IBS.

CC-51

## Clinical Pharmacology

**Pamela L Golden, PhD**

Executive Director, Nonclinical & Clinical Pharmacology  
Salix Pharmaceuticals, Inc.

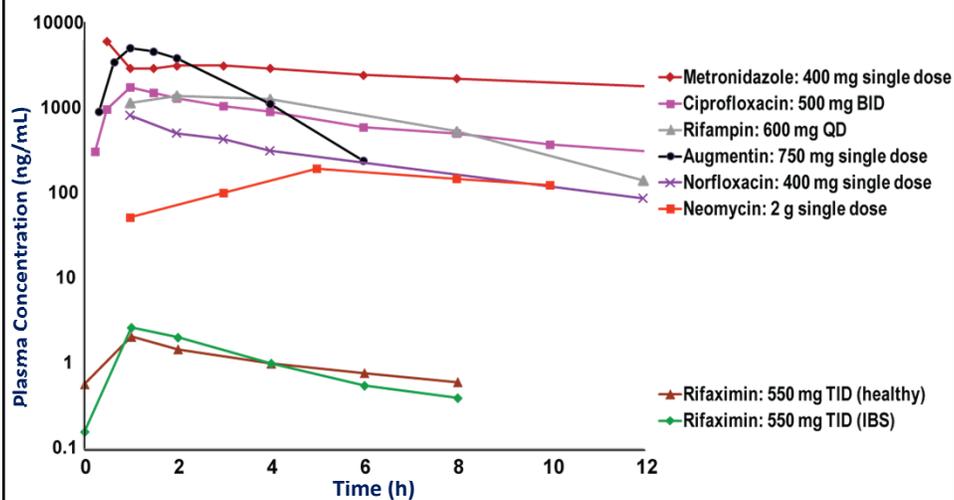
CC-52

## Rifaximin Pharmacology Summary

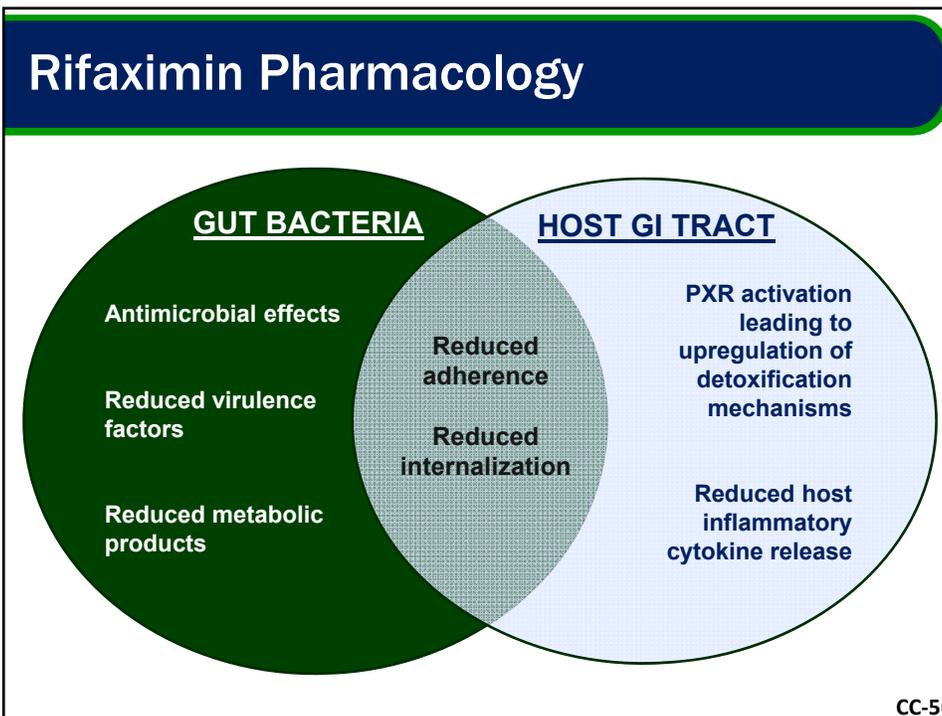
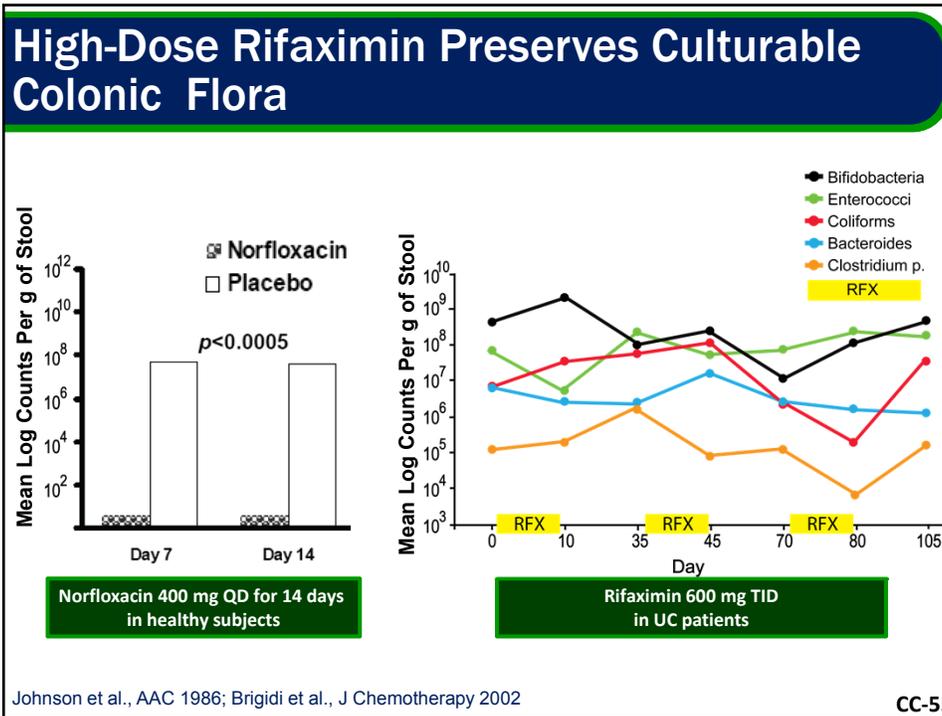
- **Poorly absorbed (< 0.4%)**
  - Low solubility and permeability
  - P-glycoprotein efflux
  - > 99% excreted unchanged in feces
- **Multiple sites of action in the gut lumen**
  - Bacterial
  - Bacteria-epithelium interface
  - Host defense mechanisms

CC-53

## Rifaximin Systemic Exposure is Significantly Lower than Other Antibiotics Used in IBS/SIBO



CC-54



## Rifaximin Modulation of Intestinal Microbiota: Lessons from IBD

### In vivo in ulcerative colitis patients

- **Repeated high dose rifaximin treatment courses**
  - Overall microbiota equilibrium not affected
  - Beneficial species not disrupted

### Ex vivo human gut model

- **High dose rifaximin in fecal incubations from Crohn's patients**
  - Total bacterial counts and biodiversity remain stable
  - Significant increases in *Bifidobacterium*, *Atopobium*, *F. prausnitzii*
  - Altered bacterial metabolism
  - Protection from geno- and cytotoxicity

Brigidi P et al., J Chemotherapy 2002; Maccaferri S et al., J Antimicrob Chemother 2010

CC-57

## Rifaximin Alters Bacterial Behavior

- **In vitro: effects at sub-MIC levels**
  - Cures host cells of plasmids and reduces plasmid transfer
  - Reduces virulence of enteric bacteria
  - Inhibits bacterial adherence and internalization
- **In vivo**
  - In hepatic encephalopathy patients, significant reductions ( $p = 0.0391$ ) in venous ammonia with rifaximin compared with placebo

Debbia EA, et al., J Chemotherapy 2008; Jiang ZD, et al., Int J Antimicrob Agents 2009; Brown EL, et al., Antimicrob Agents Chemo 2010; Bass NM, et al., N Engl J Med 2010

CC-58

## Pregnane X Receptor Activation Linked to Reduced Inflammation in IBD

**PXR:** nuclear receptor responsible for regulating expression of genes associated with host defense mechanisms

- **Rifaximin induces PXR in vitro and in vivo**
  - Evidence from UC colon biopsies, cell models, mouse models, and clinical studies
  - ~10% reduction in PXR-activated substrates in DDI studies
- **Rifaximin causes intestinal, but not liver, PXR activation**
- **Decreased PXR and target gene expression have been linked to IBD**

**Inflammation-linked etiology suggests that rifaximin-mediated PXR activation may play a role in treatment of IBS**

Shah et al., Am J Physiol Gastrointest Liver Physiol, 2007; Dring MM et al., Gastroenterology 2004; Langmann T et al., Gastroenterology 2004; Wallace et al., J Steroid Biochem Molec Biol, 2010; Panwala et al., J Immunol, 1998; Schwab et al., Gastroenterology, 2003; Sonoda et al., Proc Natl Acad Sci USA, 2002. Ma X et al., J Pharmacol Exp Ther 2007; Cheng J et al., J Pharmacol Exp Ther 2010; Mencarelli A et al., Eur J Pharmacol 2011; Salix studies RFD11009, RFDI 1001

CC-59

## Rationale for IBS Dose Selection

### Primary considerations

- **Total daily dose and treatment duration**
  - Results from Salix Phase 2 IBS trial
    - Significant improvement in IBS symptom scales at 550 mg BID
    - Significant improvement in abdominal pain at 2200 mg/day
    - 14-day duration resulted in significant efficacy
- **Dosing frequency**
  - Findings from Salix scintigraphy study
    - Mean intestinal transit time indicated TID dosing
    - Frequency chosen to maximize GI lumen exposure to rifaximin

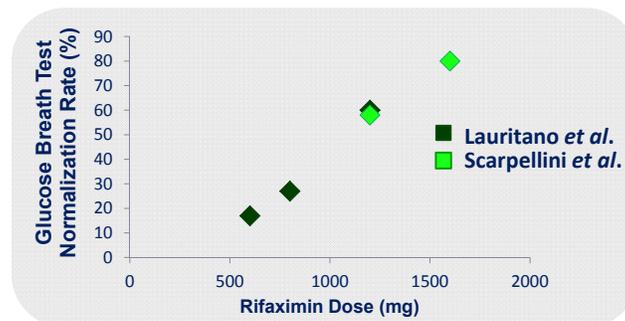
**1650 mg/day (550 mg TID) for 14 days**

Salix studies RFIB2001, RFPK1002

CC-60

## Positive Dose-Response Relationship for Rifaximin in SIBO

- Response to rifaximin measured by glucose breath test normalization
- Strong dose-response relationship for rifaximin
- Maximum response achieved at 1600 mg daily dose with TID administration



Lauritano et al., Aliment Pharmacol Ther 2005; Scarpellini et al., Aliment Pharmacol Ther 2007

CC-61

## Rifaximin Clinical Pharmacology

- High local GI lumen concentrations
- Extremely low systemic exposure
- Mechanisms of action address GI dysbiosis and/or host response to dysbiosis
  - Gut-targeted PXR activation
  - Beneficial effects on bacterial virulence and metabolism
  - May shift bacterial subpopulations beneficially
- Efficacy in multiple disease states associated with GI dysbiosis
- Resistance surveillance from clinical data

CC-62

## No Evidence of Therapeutic Resistance

- **Hepatic encephalopathy**
  - No efficacy loss with ongoing treatment
  - Efficacy resumes after treatment restarts
- **Crohn's disease**
  - Efficacy maintained during 12 weeks treatment and 12 weeks follow-up
- **Irritable bowel syndrome**
  - Retrospective studies report efficacy of rifaximin with up to 6 treatment cycles

Bass et al., NEJM, 2010; Mullen et al., EASL 2011; Lochs et al., DDW annual meeting, 2011; Pimentel et al., Dig Dis Sci 2011; Weinstock, Dig Dis Sci 2011; Jolley, Clin Exp Gastro 2011; Yang et al., Dig Dis Sci 2008.

CC-63

## Infections in HE Patients Treated Long-term RFHE3001 and RFHE3002

Infection of special interest, % (rate*)	RCT Study Population		All Rifaximin
	Placebo (n=159)	Rifaximin (n=140)	All Rifaximin Patients (n=392)
	PEY=46.0	PEY=50.0	PEY=510.5
<b>Any Infection</b>	49 (1.326)	46 (1.119)	214 (0.729)
<b>Cellulitis</b>	3 (0.066)	3 (0.006)	34 (0.071)
<b>C. difficile infection†</b>	0	2 (0.040)	6 (0.012)
<b>Peritonitis</b>	6 (0.131)	3 (0.060)	22 (0.044)
<b>Pneumonia</b>	1 (0.022)	4 (0.080)	42 (0.084)
<b>Sepsis / septic shock</b>	5 (0.109)	2 (0.040)	31 (0.062)
<b>Urinary tract / kidney</b>	14 (0.320)	9 (0.187)	83 (0.193)

\* Rate is calculated as number of subjects /PY.

\*\* Infections of special interest include infections that commonly occur among patients with cirrhosis

†Subjects who experienced had recent clinical histories that included several risk factors for infection: hepatic cirrhosis, advanced age, hepatitis C, numerous hospitalizations, multiple courses of antibiotics and concurrent use of proton pump inhibitors

CC-64

## Infection Incidence Decreased in Rifaximin-treated Patients (AASLD 2011)

- ***C. difficile* incidence**
  - Incidence of *C. difficile* infection significantly lower in rifaximin-treated versus lactulose-treated HE patients ( $p < 0.007$ )
- **Antibiotic-resistant infections**
  - Rates of antibiotic-resistant infection in hospitalized cirrhotic patients:

<u>In prior 30 days</u>	<u>Odds Ratio (95% CI)</u>
No antibiotic exposure	1
Systemic antibiotic exposure	4.8 (1.5 – 15.4)
Nonsystemic antibiotic exposure	0.48 (0.12 – 2.01)

Zuchelli et al., AASLD annual meeting, 2011; Tandon et al., AASLD annual meeting, 2011

CC-65

## Monitoring in Upcoming HE Trials

- **An FDA-approved method will be used to detect *C. difficile* toxin in patients prior to randomization**
- **Methods for stool specimen collection, specimen identification, shipping and processing will be submitted for review prior to study initiation**
- **Stools will be cultured to allow for isolation of *C. difficile* and detection of overgrowth of bacteria and yeast**
- **Information on methods for culture, identification, and susceptibility testing of antimicrobial agents, including rifaximin and rifampin, will be submitted for review**
- **Monitoring of resistance and overall effects on gut flora will be discussed today for upcoming IBS retreatment trial**

CC-66

## Clinical Development Program

**Craig Paterson, MD**

Vice President, Medical and Clinical Development  
Salix Pharmaceuticals, Inc.

CC-67

## Adequate Relief as Primary Endpoint in IBS Trials

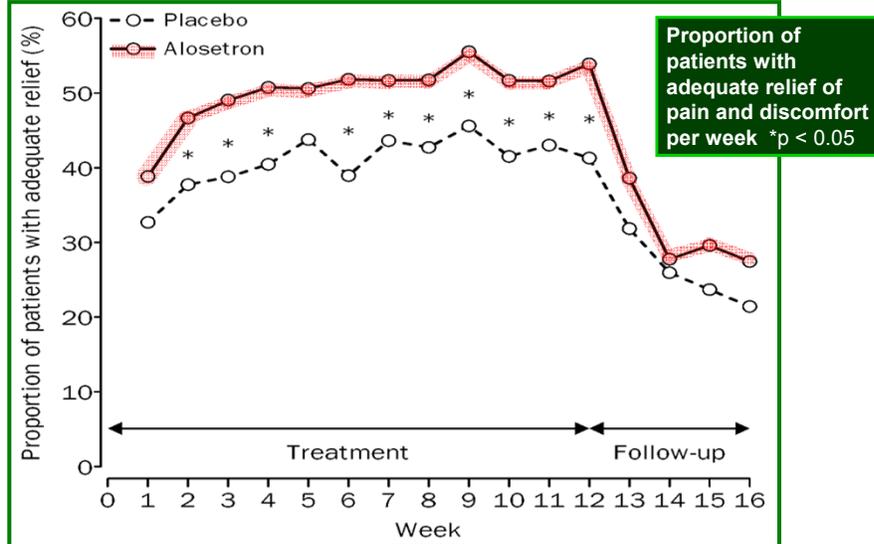
### Rome Working Group Report

- Evaluated patient reported outcomes (PROs) in irritable bowel syndrome (IBS)
- Traditional binary and 50% improvement endpoints are equivalent in psychometric properties
- No impact of baseline severity, and both demonstrate excellent construct validity
- Optimized for IBS-D population, but also appear valid in IBS-C

Spiegel, B et al Gastroenterology, 2009.

CC-68

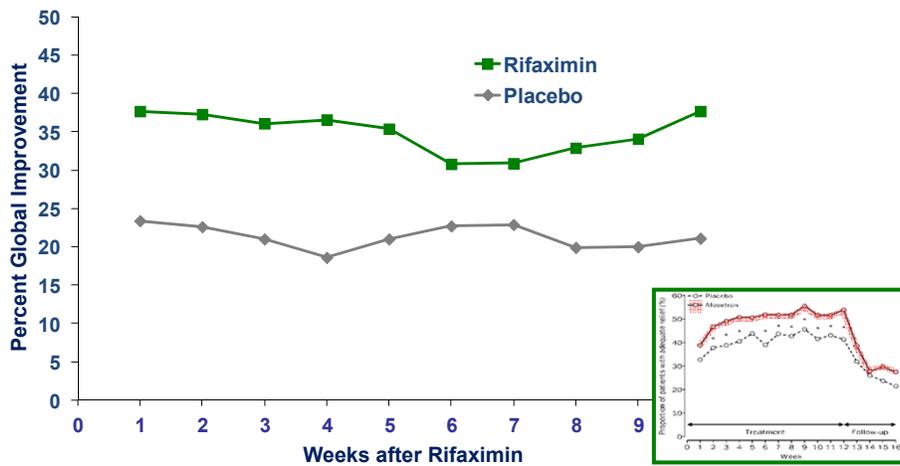
## Alosetron Return to Baseline at Treatment Cessation



Camilleri, et al., Lancet 2000.

CC-69

## Rifaximin for IBS



Pimentel, et al, Ann Intern Med, 2006.

CC-70

## Rifaximin Studies in the Literature

Author	Dose	Efficacy Results
<b>Pimentel</b> 2006	1200 mg/d	Rifaximin improved IBS symptoms (p = 0.02)
<b>Sharara</b> 2006	800 mg/d	Rifaximin improved global symptom relief at the end of treatment (p = 0.04) and follow-up (p = 0.05)
<b>Scarpellini</b> 2007	1200 mg/d & 1600 mg/d	Glucose breath test normalization: 80% at rifaximin 1600 mg vs. 58% at rifaximin 1200 mg group (p < 0.05)
<b>Yang</b> 2008	1200 mg/d	Clinical response: rifaximin 1200 mg 69% vs. 38% with neomycin (p < 0.01) and 44% with all rifaximin antibiotics (p < 0.01)
<b>Peralta</b> 2009	1200 mg/d	Treatment with rifaximin resulted in normalization of lactulose breath tests in about 50% of patients and significantly reduced symptoms

Pimentel M et al. Ann Intern Med, 2006; Sharara AI et al. Am J Gastroenterol, 2006; Scarpellini E et al. Aliment Pharmacol Ther, 2007; Yang J et al. Dis Sci, 2008; Peralta S, et al. World J Gastroenterol, 2009.

CC-71

## Rifaximin Phase 2 IBS Study RFIB2001

- **Replicated effects reported in the literature**
- **Efficacy in co-primary endpoints with 550 mg BID dosing vs placebo after 14 days of rifaximin treatment:**
  - improvement in IBS symptoms and
  - improvement in IBS bloating
- **Secondary analyses of IBS daily symptoms also suggested superiority**
- **Safe and well tolerated with daily doses ranging from 550 mg to 2200 mg for 2 to 4 weeks**

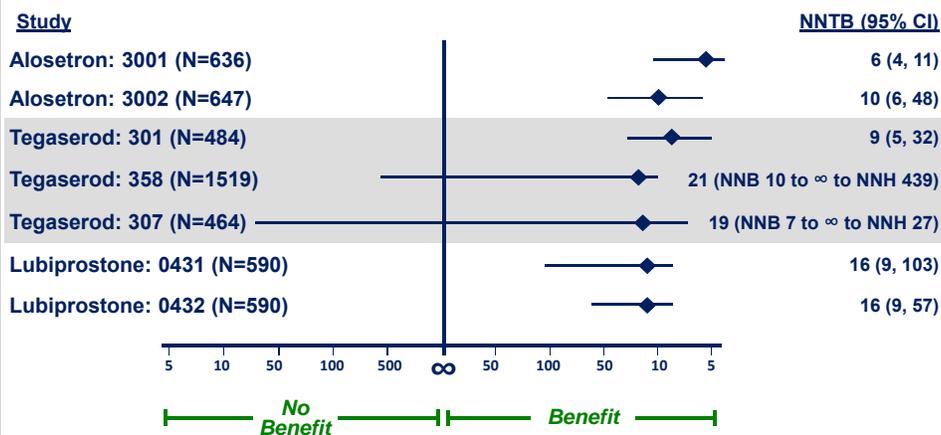
CC-72

## Clinical Development Program Rifaximin for IBS-D

Study	Study Design	Duration	Subject Population
TARGET 1	Double-blind, placebo-controlled, phase 3 study <ul style="list-style-type: none"> <li>Rifaximin 550 mg TID</li> <li>Placebo TID</li> </ul>	14 d treatment; 10 weeks of follow-up	IBS-D, confirmed using Rome II
TARGET 2	Double-blind, placebo-controlled, phase 3 study <ul style="list-style-type: none"> <li>Rifaximin 550 mg TID</li> <li>Placebo TID</li> </ul>	14 d treatment; 10 weeks of follow-up	IBS-D, confirmed using Rome II
RFIB2001	Double-blind, placebo-controlled, phase 2b study <ul style="list-style-type: none"> <li>Rifaximin 275 mg BID</li> <li>Rifaximin 550 mg BID for 2 wks</li> <li>Rifaximin 550 mg BID for 4 wks</li> <li>Rifaximin 1100 mg BID for 2 wks</li> <li>Placebo BID</li> </ul>	14-28 d treatment; 12 weeks of follow-up	IBS-D, confirmed using Rome II

CC-73

## Relative Comparison of NNT



Alosetron (Lotronex) data from Summary Basis of Approval (SBA) NDA 21-107, tegaserod (Zelnorm) data from SBA NDA 21-200, lubiprostone (Amitiza) data from SBA for NDA 21-908 S005.

CC-74

## Efficacy and Safety TARGET 1 and TARGET 2

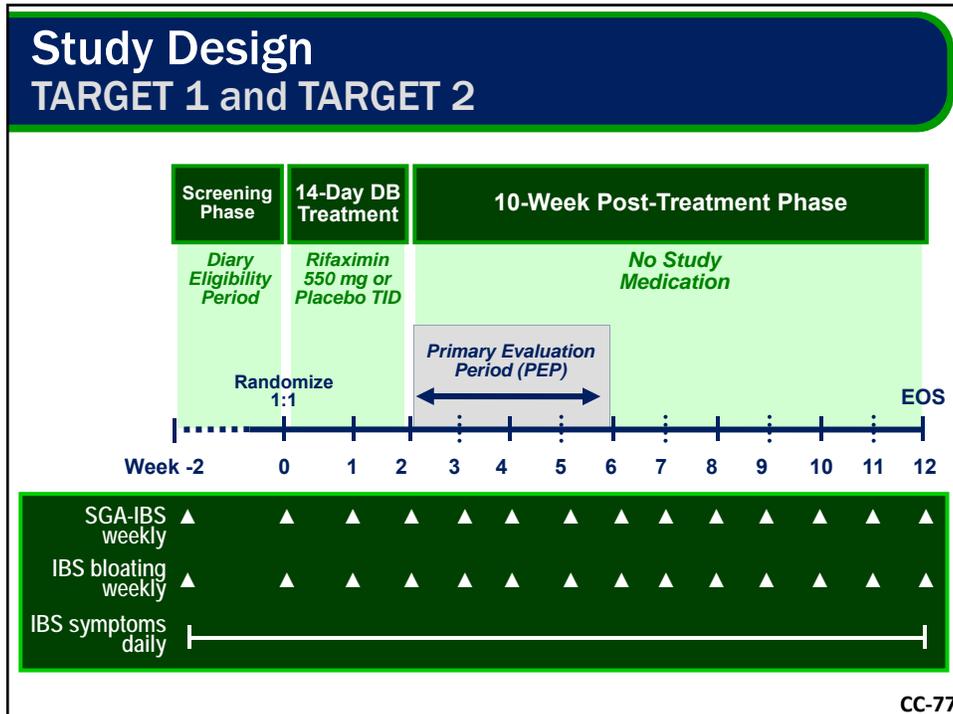
CC-75

## TARGET 1 and TARGET 2

- **Two large scale, identically designed, randomized, double-blind, placebo-controlled trials**
- **Conducted in parallel in the U.S. and Canada**
  - TARGET 1: 95 centers (Start 06/04/08; End 08/17/09)
  - TARGET 2: 84 centers (Start 06/26/08; End 08/11/09)
  - Site participation unique to either TARGET 1 or 2
- **To study rifaximin 550 mg or placebo TID for 14 days in IBS-D**
- **1260 patients randomized**

Pimentel M, et al. NEJM, 2011

CC-76



## Definition of Responder Basis of Efficacy

- 1. Weekly Question**
  - Subject's Global Assessment of IBS (yes/no)
  - IBS-Related Bloating (yes/no)
- 2. Daily Questions (IBS, IBS-Related Bloating, Abdominal Pain)**
  - Weekly responder: rated symptoms (7-point scale) as either
    - 0 (not at all) or 1 (hardly) ≥ 50% of days in a given week
    - OR
    - 0 (not at all), 1 (hardly) or 2 (somewhat) 100% of days in a given week
- 3. FDA Draft Guidance Endpoint (exploratory)**
  - Using daily question for weekly response: both abdominal pain and stool consistency
    - ≥ 30% decrease in mean abdominal pain score from baseline and a weekly mean stool consistency score of < 4 (5-point scale) in a given week

Efficacy is defined over 4 consecutive 1-week periods with criteria for a responder being met for ≥ 2 out of those 4 weeks

CC-78

## Primary and Key Secondary Efficacy Endpoints Weekly Questions

### Primary Endpoint

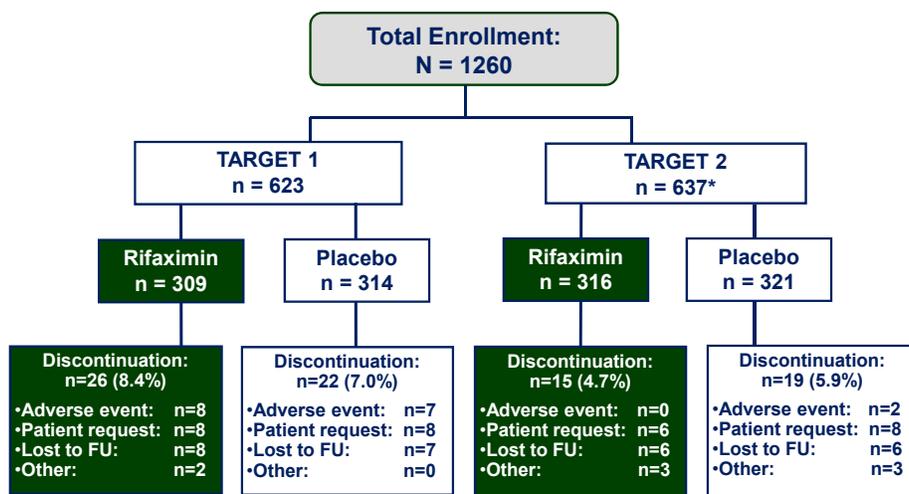
- Proportion of patients who indicated adequate relief of *global IBS symptoms* in 2 out of 4 weeks during the PEP compared to baseline

### Key Secondary Endpoint

- Proportion of patients who indicated adequate relief of *IBS-related bloating* in 2 out of 4 weeks during the PEP compared to baseline

CC-79

## Patient Disposition – TARGET 1 and 2 Intent-to-Treat Population



\*2 patients did not receive study medication (1 per treatment arm) and were not included in the analysis

CC-80

## Demographic Characteristics Intent-to-Treat Population

Characteristic	TARGET 1		TARGET 2	
	Rifaximin (n = 309)	Placebo (n = 314)	Rifaximin (n = 315)	Placebo (n = 320)
Mean age, y (SD)	46 (15)	46 (15)	46 (14)	46 (15)
Age group, n (%)	< 65 years	275 (89)	276 (88)	285 (90)
	≥ 65 years	34 (11)	38 (12)	30 (10)
Gender, n (%)	Male	74 (24)	92 (29)	88 (28)
	Female	235 (76)	222 (71)	227 (72)
Race, n (%)	White	281 (91)	280 (89)	282 (90)
	Non-White	28 (9)	34 (11)	33 (10)
Ethnicity, n (%)	Hispanic or Latino	12 (4)	22 (7)	29 (9)
	Not Hispanic or Latino	297 (96)	292 (93)	286 (91)

Groups and studies were comparable

CC-81

## Baseline IBS Characteristics Intent-to-Treat Population

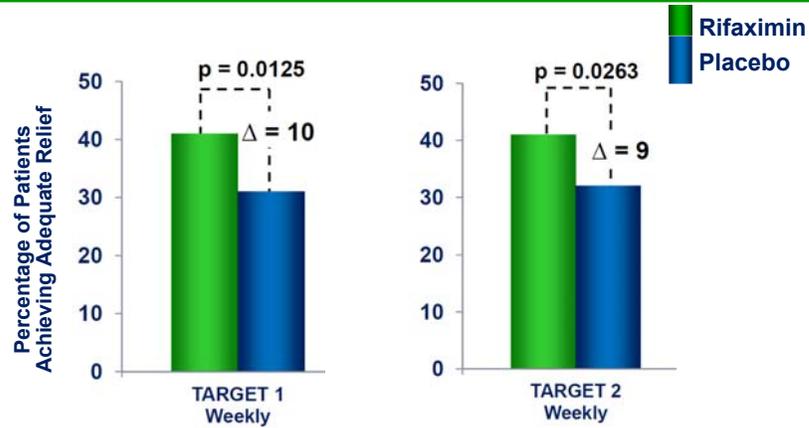
Characteristic	TARGET 1		TARGET 2	
	Rifaximin (n = 309)	Placebo (n = 314)	Rifaximin (n = 315)	Placebo (n = 320)
Duration of IBS symptoms, yr (SD)	11.9 (10.5)	11.4 (11.9)	10.8 (10.2)	11.8 (10.4)
Average daily scores, mean (SD)	IBS symptoms	3.4 (0.7)	3.4 (0.7)	3.4 (0.7)
	Ab pain & discomfort	3.3 (0.7)	3.2 (0.7)	3.3 (0.7)
	Bloating	3.3 (0.8)	3.3 (0.7)	3.2 (0.7)
	Stool consistency	3.9 (0.3)	3.9 (0.3)	3.9 (0.3)
Average daily bowel movements, mean (SD)	2.9 (1.3)	3.0 (1.4)	3.0 (1.6)	3.0 (1.5)
Percentage of days with sense of urgency, mean (SD)	81.8 (22.3)	82.9 (22.3)	81.3 (22.8)	82.2 (22.5)
IBS Severity,* n (%)	Non-severe	227 (73.5)	222 (70.7)	222 (70.5)
	Severe	81 (26.2)	92 (29.3)	91 (28.9)

Groups and studies were comparable

\*IBS Severity categorized as severe and non-severe (IBS-QOL ≤40 and > 40, respectively) based on a recently published international survey of IBS patients (Drossman DA et al., J Clin Gastroenterol, 2009.)

CC-82

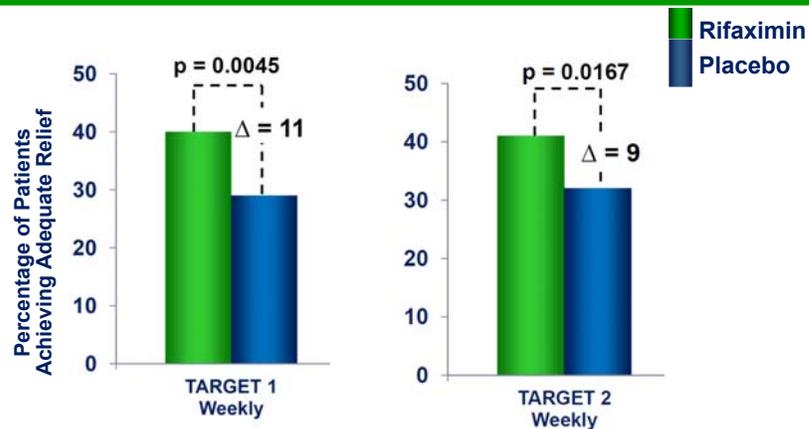
## SGA-IBS at PEP Weekly (ITT Population)



**Responder:** Patient who answered 'yes' to adequate relief to SGA-IBS question "In regards to your IBS symptoms, compared to the way you felt before you started study medication, have you, in the past 7 days, had adequate relief of your IBS symptoms?"

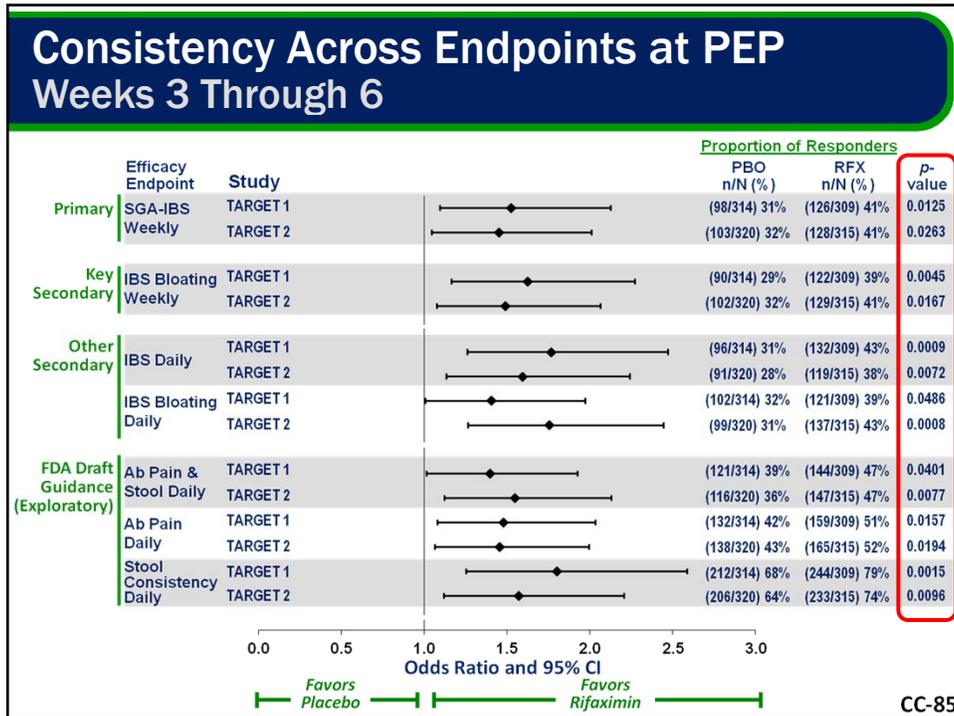
CC-83

## IBS-Related Bloating at PEP Weekly (ITT Population)



**Responder:** Patients who answered 'yes' to adequate relief of IBS-bloating question "In regards to your IBS symptom of bloating, compared to the way you felt before you started study medication, have you, in the past 7 days, had adequate relief of your IBS symptom of bloating?"

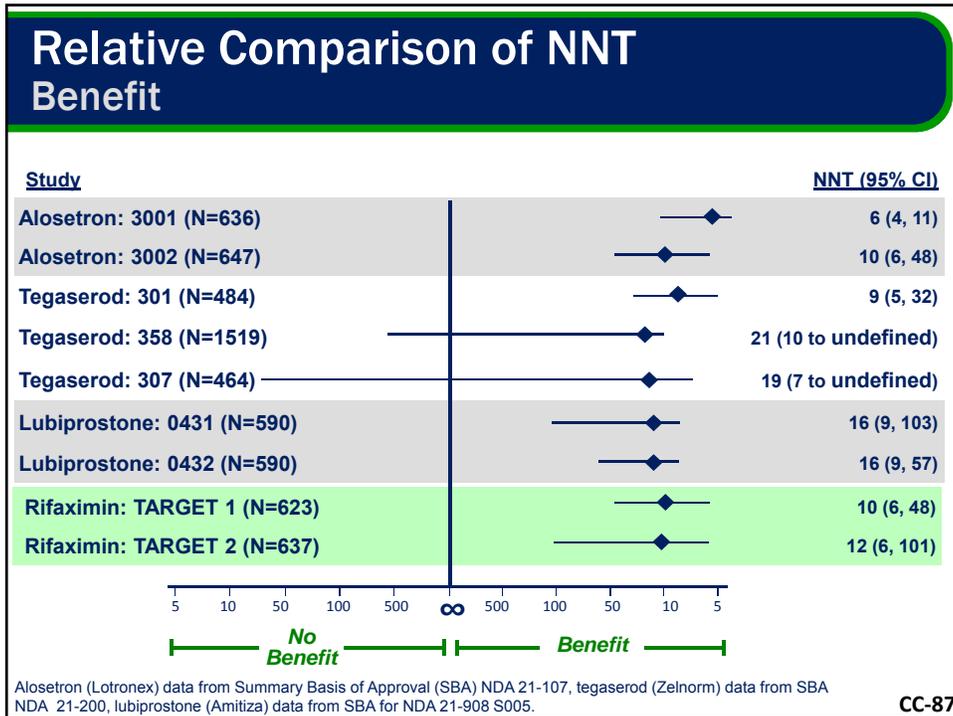
CC-84



### Assessment of Durability Discussions between Salix and FDA

- Sponsor approach**
  - Monthly efficacy defined as positive response for  $\geq 2$  of 4 weeks
  - Durability tested by number of responders for 0 through 3 months
  - Demonstrated statistical superiority for responders in all 3 months
  - Details in Sponsor Briefing Document
- FDA approach**
  - Monthly efficacy defined as positive response for  $\geq 2$  of 4 weeks
  - Durability tested by the number of responders in 2 out of 3 months
  - Demonstrated numerical, not statistical, superiority
  - Details in FDA Briefing Document
- Discussion on proposed repeat treatment study design**

CC-86



CC-87

### Safety Profile of Rifaximin

**Combined Data from TARGET 1 and TARGET 2**

	Rifaximin (n = 624) n (%)	Placebo (n = 634) n (%)
<b>Any AEs</b>	178 (28.5)	188 (29.7)
<b>SAEs</b>	2 (0.3)	8 (0.8)
<b>AEs resulting in discontinuation</b>	6 (1.0)	6 (0.9)
<b>Deaths</b>	0	0

- Most AEs were mild or moderate in intensity
- No AEs of *C. difficile* associated diarrhea or ischemic colitis

CC-88

## Rifaximin for IBS-D Repeat Treatment Study Design

CC-89

## Clinical Experience with Repeat Rifaximin Treatment

Study (Duration) Population	Number of Repeat Treatments	Results
<b>Pimentel, et al. (&gt; 6 yr)</b> 169 Non-C IBS Patients (Rome III)	<b>1 to 6</b>	<ul style="list-style-type: none"> <li>- Initial treatment response: 75% (111/148)</li> <li>- Re-treatment response (at least 1): &gt; 75%</li> <li>- First: 54/65 Second 38/40: Third: 17/18</li> <li>- Duration of benefit ~4 m</li> </ul>
<b>Weinstock (&gt; 6 yr)</b> 99 Non-C IBS Patients (Rome II)	<b>1 to 5</b>	<ul style="list-style-type: none"> <li>- Initial treatment response: 75% (74/99)</li> <li>- 27% did not require re-treatment</li> <li>- 41% maintained response for mean 1.6 yr</li> <li>- 51% only 1-2 retreatment in 2 yr</li> </ul>
<b>Yang, et al. (1.25 yr)</b> 84 IBS Patients (Rome I)	<b>Up to 2</b>	<ul style="list-style-type: none"> <li>- Initial treatment response: 69% (58/84)</li> <li>- Re-treatment response (at least 1): 100%</li> <li>- First: 16/16, Second: 4/4</li> </ul>

Pimentel M, et al. Dig Dis Sci. 2011; Weinstock LB. Dig Dis Sci. 2011; Yang J, et al. Dig Dis Sci. 2008.

CC-90

## Development of Proposed Study Design

- Iterative process with GI Division at FDA as well as further assistance from thought leaders
- Multiple design options considered
- Final efficacy analysis on the primary endpoint following the 1st repeat treatment
- Proposed design is a representation of the collaborative efforts of FDA and Salix
- Feedback from November 16 GIDAC meeting

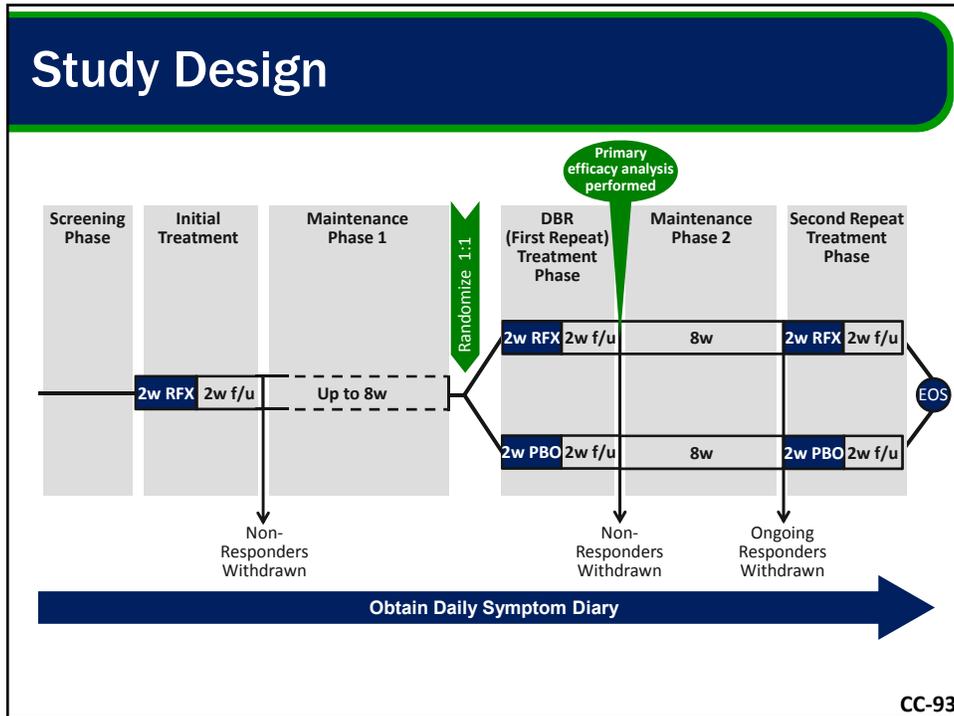
CC-91

## Rationale for Proposed Study Design

- Initial treatment efficacy and safety demonstrated (TARGET 1 and 2)
- Only responders continue (early escape)
  - Represents clinical practice
- Repeat treatment efficacy and durability of effect in a single study
- Utilizes available recommendations from current FDA draft guidance

Temple R. Commun. Statist – Theory Meth. 1994; Dunger-Buldouf C, Drug Info J, 2006.

CC-92



## Repeat Treatment Study Objectives

**Primary Objective**

- To evaluate the efficacy of repeat treatment with rifaximin 550 mg TID in patients with IBS-D

**Secondary Objective**

- To evaluate the safety of rifaximin 550 mg TID in patients with IBS-D

CC-94

## Key Entry Criteria

### Inclusion

- **IBS-D confirmed by Rome III criteria and symptom of bloating**
- **Baseline Enrollment Criteria**
  - Pain Severity
    - Weekly average “worst pain in past 24 hours” score  $\geq$  3.0 on a 0 to 10 point scale
  - Stool Consistency
    - $\geq$  2 days per week with at least one stool which has a consistency of Type 6 or 7 Bristol Stool Score (BSS)

CC-95

## Key Exclusion Criteria

### Exclusion

- **History consistent with constipation predominant IBS**
- **History of IBD, diabetes, unstable thyroid disease, previous abdominal surgery, HIV, renal or hepatic disease**
- **Current use of alosetron, tegaserod, lubiprostone, antipsychotics, antispasmodics, antidepressants (except stable dose TCA or SSRI), warfarin, antidiarrheals, probiotics, narcotics; antibiotics within 14 days, rifaximin within 60 days**

CC-96

## Primary Endpoint

- **Proportion of patients who are responders to repeat treatment in IBS-related abdominal pain and stool consistency during the first repeat treatment phase**
- **Weekly response for the primary endpoint is based on daily IBS symptom-related questions**

- Decrease in weekly average of “worst pain in past 24 hours” score  $\geq 30\%$  compared with baseline
- Patient who experiences a  $\geq 50\%$  reduction in the number of days per week with at least one stool which has a consistency of  $\geq$  type 6 BSS compared with baseline

BSS = Bristol Stool Scale

CC-97

## Secondary Endpoints

- **Proportion of patients who are responders for the following:**
  - IBS-related abdominal pain
  - Stool consistency
  - IBS-related bloating
  - IBS symptoms
- **Change from baseline to each week for the following:**
  - IBS-related abdominal pain
  - Stool consistency
  - IBS-related bloating
  - IBS symptoms
  - Sense of urgency
- **Durability**

CC-98

## Other Endpoints for Consideration

- **Salix is committed to help advance the science and our understanding of IBS**
- **No readily available or validated biomarker**
- **Characterization of flora and resistance to antibiotics in stool samples**
- **Exploration of other biomarkers**

CC-99

## Breath Testing as Exploratory Endpoint

- **Prevalence of abdominal bloating ranges from 16% in normal population to 90% in IBS-D patients**
- **Lactulose hydrogen breath testing (LHBT) proposed as less invasive surrogate for diagnosing small intestinal bacterial overgrowth (SIBO)**
- **Glucose hydrogen breath testing (GHBT) may better reflect proximal SIBO but not sensitive for distal SB or colonic overgrowth**
- **LHBT ± scintigraphy remain controversial**

Posserud I, et al. Gut 2007; Yamini D, Pimentel M. J Clin Gastroenterol. 2010; Khan S, Chang L. Nat Rev Gastroenterol Hepatol. 2010; Yu D, et al. Gut. 2011.

CC-100

## Breath Testing

- **Errors in interpretation of LHBT**
- **The contribution of SIBO in IBS remains inconclusive**
  - Test endpoints and interpretation
  - Correlation with Orocecal Transit Time (OCTT)
  - Variability in test procedures and patient compliance
- **Interpretation of LHBT results as relative over-production of total gas by hydrogen producing bacteria**
  - Small intestine & colon
  - Relative comparison of AUC

Collins BS, et al. J Pediatr Gastroenterol Nutr 2011; Yu D, et al. Gut. 2011; Scarpellini E, et al. Gut 2010; Ford AC, et al. CGH 2009

CC-101

## Definitions Responder and Recurrence

Patients are responders in a given month if they have a positive response during  $\geq 2$  out of 4 weeks

**Based on composite endpoint**

- Using daily question for weekly response: abdominal pain and stool consistency

Patients will be considered to have recurrence when criteria for response are absent for at least 3 weeks during a 4-week assessment period

CC-102

## Durability Analysis

- **Endpoint**
  - Rates of responding patients without recurrence and exposure time
- **Assessment period**
  - 4-week first repeat treatment phase plus subsequent 8-week maintenance phase
- **Analysis conducted at the end of study**

CC-103