Gastrointestinal Drugs Advisory Committee Meeting

Design of Clinical Trials to Evaluate the Safety, Efficacy, and Durability of Response with Repeat Treatment cycles of XIFAXAN® (rifaximin) for Irritable Bowel Syndrome with Diarrhea

November 16, 2011

Andrew E Mulberg, MD, FAAP
Division of Gastroenterology and Inborn Errors Products
CDER/FDA

Xifaxan® (rifaximin)

- Nonaminoglycoside, semisynthetic antibiotic derived from rifamycin that has antimicrobial activity of varying levels against Gram-positive, Gram-negative, aerobic, and anaerobic enteric bacteria similar to its parent compound (rifampin)
- Poorly absorbed, low systemic exposures in healthy population

Proposed Indication

- Treatment of Non-constipation Irritable Bowel Syndrome (IBS), and IBS related bloating in patients ≥18 years of age

Regulatory History

- NDA approval for traveler's diarrhea on May 2004
  - 200 mg three times a day for 3 days
- NDA approval for Hepatic Encephalopathy on March 2010
  - 550 mg twice daily
- NDA Submitted for IBS on June 2010
  - 550 mg three times a day for 14 days

Basis for Complete Response Letter Issued March 7, 2011

- Lack of durability of response of rifaximin
- Lack of demonstration of efficacy for retreatment
- Lack of definition of the effective frequency for retreatment or prevention of recurrence
- Lack of adequate definition of the patient population who would benefit from rifaximin
- Concern with development of bacterial resistance (*Clostridium difficile, Staphylococcus aureus)* and potential for serious enteric infections
- This is not sufficient for product labeling in a chronic disease as IBS

Additional comments Complete Response Letter Issued March 7, 2011

- Because the trials conducted included only patients with IBS-D, the submitted data do not support a general indication to include non-C IBS
- Patient population in clinical trials excluded patients with severe symptoms

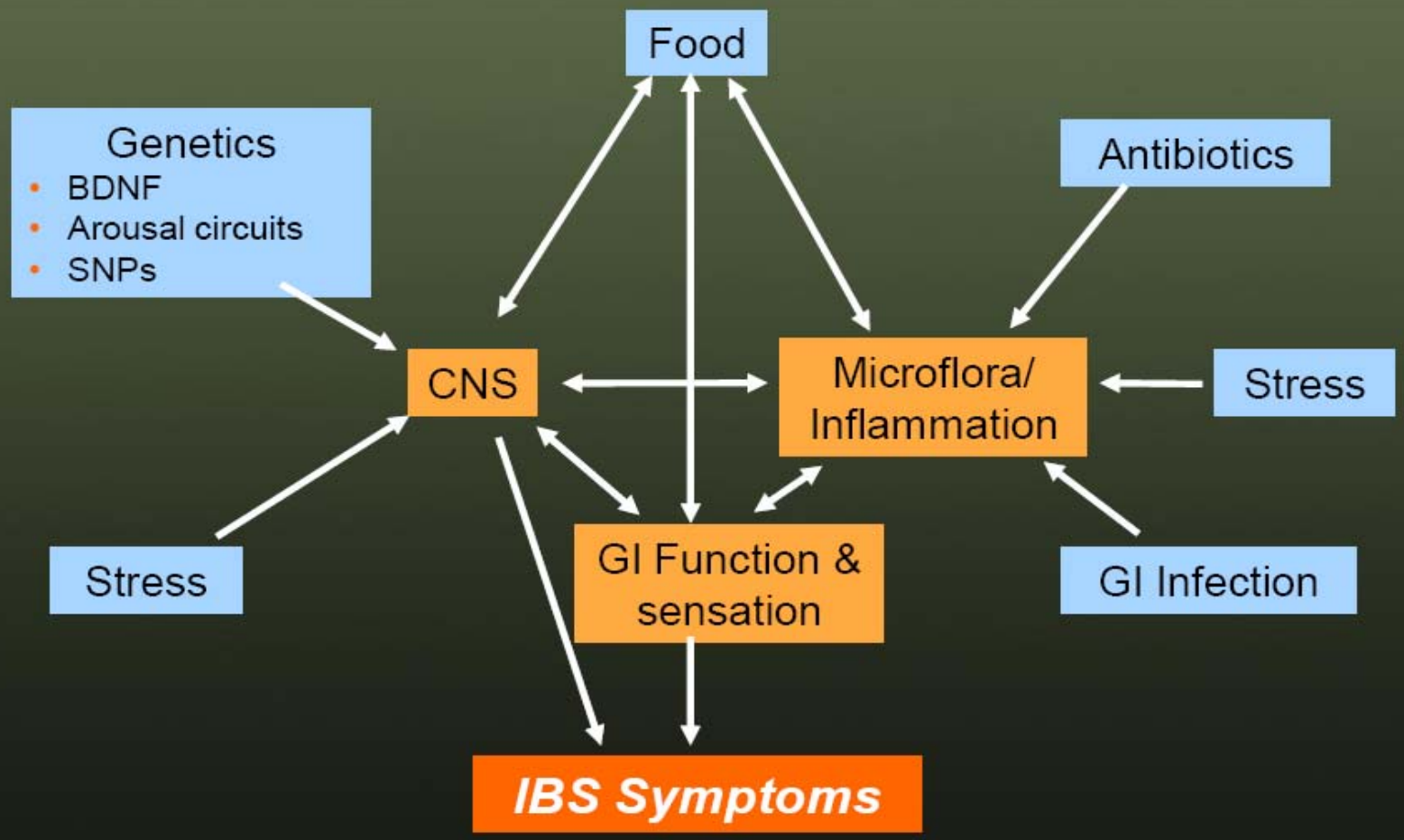
EMA Position

- "Points To Consider on the Evaluation of Medicinal Products for the Treatment of Irritable Bowel Syndrome (IBS)"
  - short term and long term continuous treatment programs
  - "demonstration of efficacy with repeated use would also be required for a short term indication and a minimum of two cycles would be needed as the use of the medication will be used chronically."

Reference

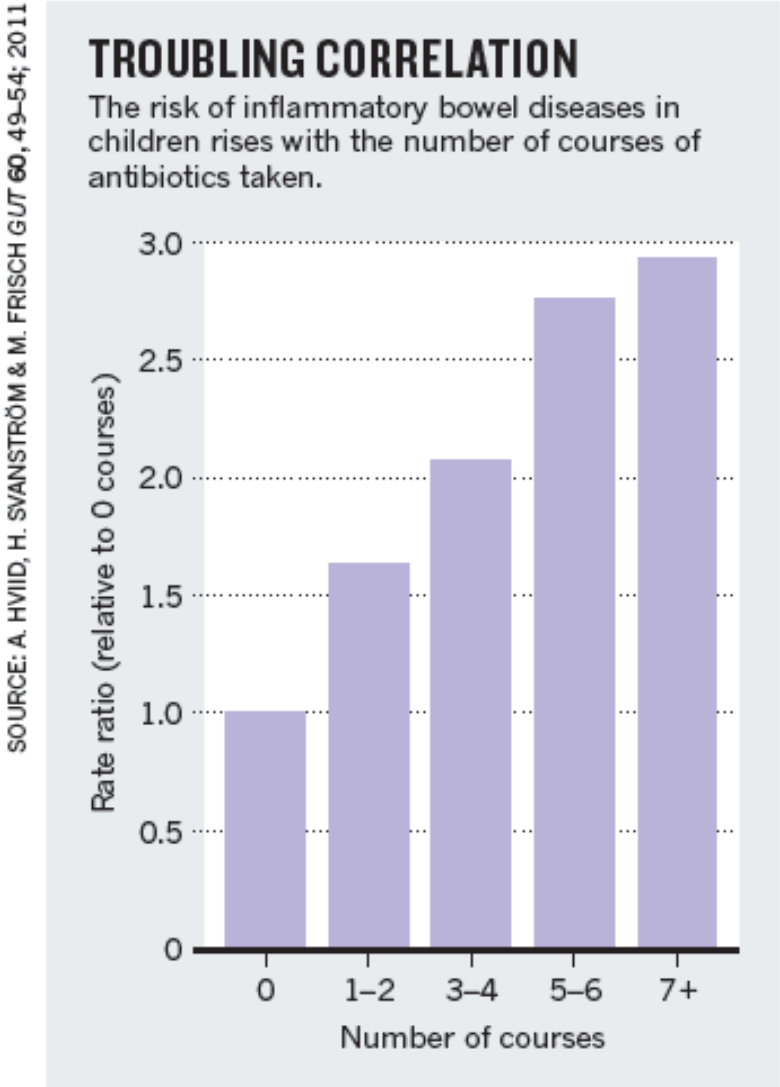
Points to Consider on the Evaluation of Medicinal Products for the Treatment of Irritable Bowel Syndrome
http://www.tga.gov.au/docs/pdf/euguide/ewp/078597en.pdf

Evolving Conceptual Model of IBS



Gut Microbiome and IBS: 2011

- **Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve.** Javier A. Bravo, Paul Forsythe, Marianne V. Chew, et al. **PNAS**
- **Global and Deep Molecular Analysis of Microbiota Signatures in Fecal Samples From Patients With Irritable Bowel Syndrome.** M Rajilic´–Stojanovic´ E Biagi, H.G.H.J. Heilig, et al. **Gastroenterology**
- **Gastrointestinal Microbiome Signatures of Pediatric Patients With Irritable Bowel Syndrome.** DM Aaulnier, K Riehle, T Mistretta et al. **Gastroenterology**



"Overuse of antibiotics could be fuelling the dramatic increase in conditions such as obesity, type 1 diabetes, inflammatory bowel disease, allergies and asthma, which have more than doubled in many populations"

Martin Blaser, MD
Nature 2011;476: 393-395

The Microbiome and Pathogenic Bacteria

- One of the important roles of an intact microbial ecosystem is to resist intrusions by pathogenic organisms.

- Changes in our microbiome may even be fueling the transmission of deadly organisms such as *Clostridium difficile* (*Nature* 2011;476: 393-395)

Next Steps in Rifaximin Development in IBS

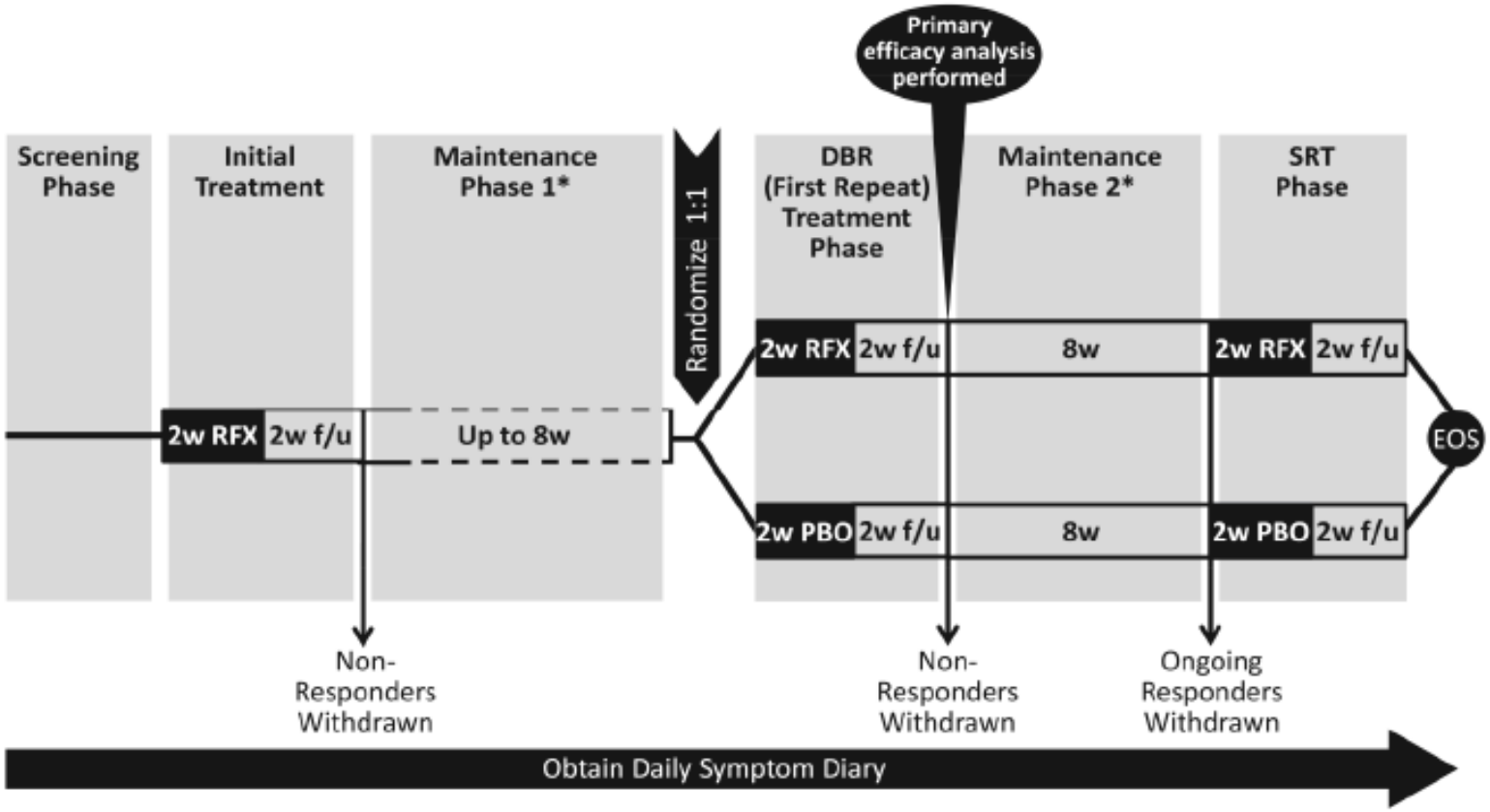
- Two single cycle rifaximin trials provide evidence of efficacy, but not durability
- What trial design(s) are necessary to adequately define the ongoing treatment regimen for rifaximin in IBS?
- Reasonable information that bacteria may have a role in IBS, at least in a subset of patients.
  - Should we better identify that subset?
  - If so, how?

POINTS TO CONSIDER WHEN EVALUATING FUTURE DEVELOPMENT PLAN

What is the major goal of Rifaximin treatment of IBS?

- How does the lack of understanding the natural history of IBS impact trial design for Rifaximin?
- What is the goal of treatment of the IBS population in general?
  - Short term treatment of acute exacerbations?
    - Proposed current trial design
  - Prevention of recurrent symptoms?
  - Induction of ‘cure’ or ‘long term remission’?
  - Are there subpopulations of IBS-D that require a different approach?

Figure 3 Proposed Repeat Treatment Study Design



Abbreviations: RFX = rifaximin; PBO = placebo; f/u = follow-up; DBR = Double-Blind, Randomized; SRT = Second Repeat Treatment; and EOS = end of study.

*During the Maintenance Phases subjects with recurrence enter the Repeat Treatment Phases:

- Maintenance Phase 1: Subjects who do not meet recurrence criteria by the end of the 8 week Maintenance Phase will be allowed to continue up to an additional 12 weeks until they experience recurrence; or until enrollment is met in DBR (Repeat Treatment) Phase.
- Maintenance Phase 2: Subjects who do not meet recurrence criteria by the end of 8 weeks will be withdrawn from the study.

Gastrointestinal Drugs Advisory Committee Meeting

NDA 21-361
Rifaximin for Treatment
of IBS-D
November 16th, 2011
Lara Dimick-Santos, MD, FACS

Dose Selection?

- Goal of treatment?
- How should rifaximin be dosed?
- How was current dose selected?

Insook Kim, PhD

Clinical Pharmacology Reviewer

Division of Clinical Pharmacology 3

Antibiotic Resistance Issues

- Susceptibility of rifaximin to induce resistance?
  - Effect of intermittent dosing?
  - Long term public health impact?
- Long term impact on GI flora?

Anne Purfield, PhD

Clinical Microbiology Reviewer

Division of Anti-Infective Products

Population Selection?

- Should antibiotics be given to entire IBS-D population?
- Can the population be targeted?
- Is it possible to develop H_2 breath testing as a predictive biomarker?
  - Diagnosing SIBO versus predicting response to rifaximin

Courtney Lias, PhD

Director

Division of Chemistry and Toxicology Devices

Recognition

Andrew Mulberg, MD, FAAP, CPI, Deputy Director DGIEP

Milton Fan, PhD & Mike Welch, PhD - Biometrics

Insook Kim, PhD & DiLara Jappar, PhD & Sue Chih Lee, PhD – Clinical Pharmacology

Tamal Chakraborti, PhD & Sushanta Chakder, PhD Toxicology

Jeff Medwid, PhD & Marie Kowblansky, PhD - CMC

Diane Munroe, RN, MBA & Brian Strongin, RPh, MBA - RPM

Recognition

Anne Purfield, PhD & Shukal Bala, PhD– Clinical Microbiology DSPTP

Elizabeth O'Shaughnessy, M.D. & Joette Meyer, Pharm.D. – Clinical DSPTP

Khairy Malek, M.D - DSI

Alyson Karesh, MD & Hari Sachs, MD – PMHS

Miskala, Paivi Miskala, PhD, MSPH - SEALD

David Shih, MD, MS & Patty Greeen, Pharm D & Anne Corken Mackey, RPh, MPH - OSE

Thank you

Rifaximin for IBS-D Clinical Pharmacology

Gastrointestinal Drugs Advisory Committee Meeting
November 16, 2011

Insook Kim, Ph.D.
Office of Clinical Pharmacology
CDER/FDA

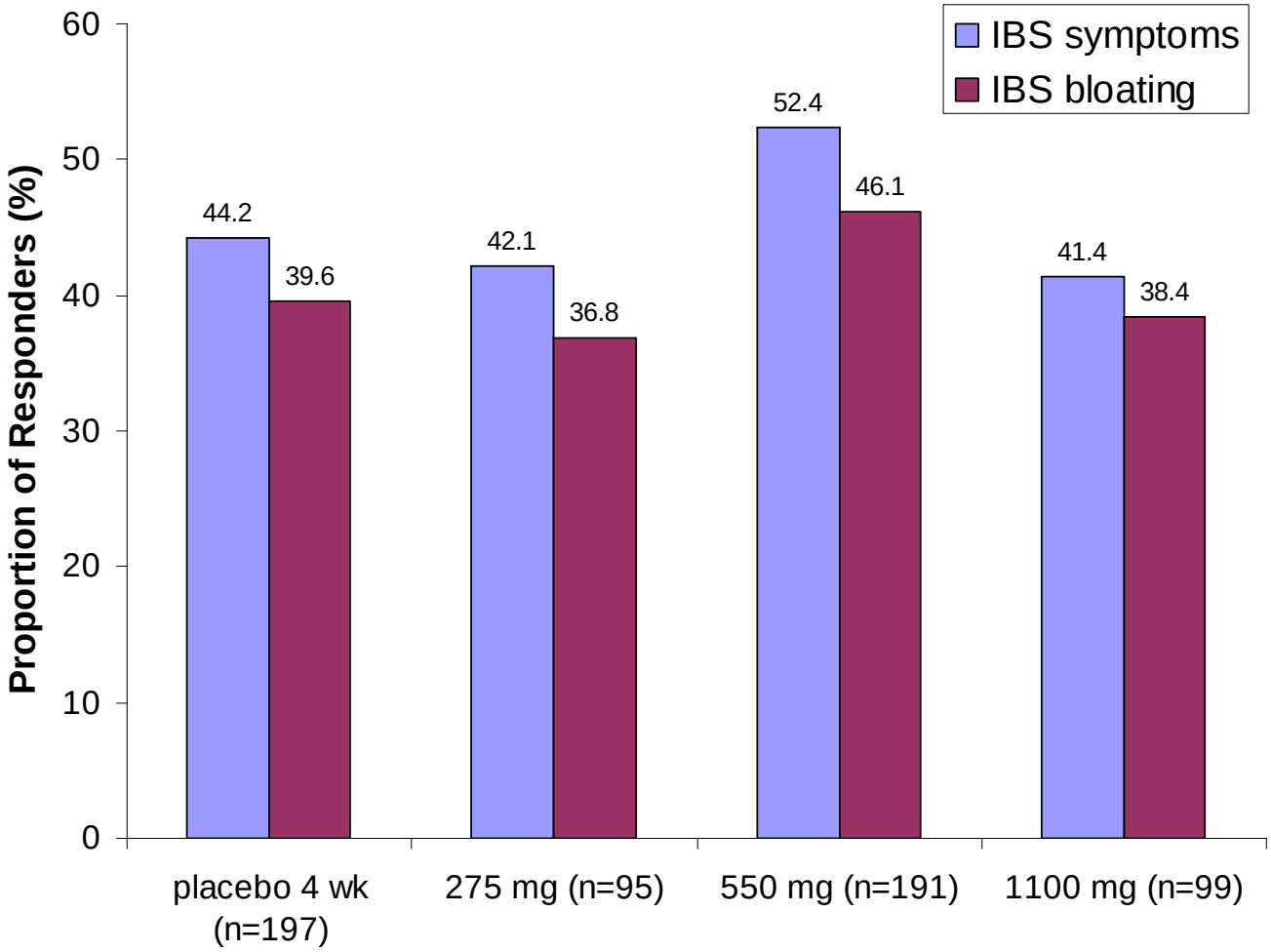
Rifaximin

- Practically insoluble in water
  - Solubility increases in presence of surfactant
- Limited oral bioavailability
  - < 1% of the oral dose is absorbed
  - Extensively metabolized, mainly by CYP3A4
  - PK in IBS patients similar to healthy volunteers
  - Mean Cmax : ~4 ng/ml at steady-state in IBS patients
  - Cmax in patients w/ hepatic impairment: up to 52.2 ng/ml (dosed 550 mg bid)
  - Mean Cmax of rifampin: 7 mcg/ml after single dose of 600 mg
- Not suitable for treating systemic bacterial infections because of low oral systemic availability (Xifaxan® Labeling)

Phase 2 study

- Multicenter, randomized, double-blind, placebo-controlled
- Patients: IBS-D by Rome II
- Treatment:
  - Rifaximin 2 week treatment followed by 2 weeks of placebo
    - 275 mg, 550 mg and 1100 mg **Twice daily**
  - Rifaximin 4 week treatment
    - 550 mg BID **Twice daily**
  - Placebo 4 week treatment
- Two co-primary efficacy endpoints at the end of the 4-week treatment phase (for at least 2 of the final 3 weeks)
  - Adequate relief of global IBS symptoms
  - Adequate relief of IBS bloating

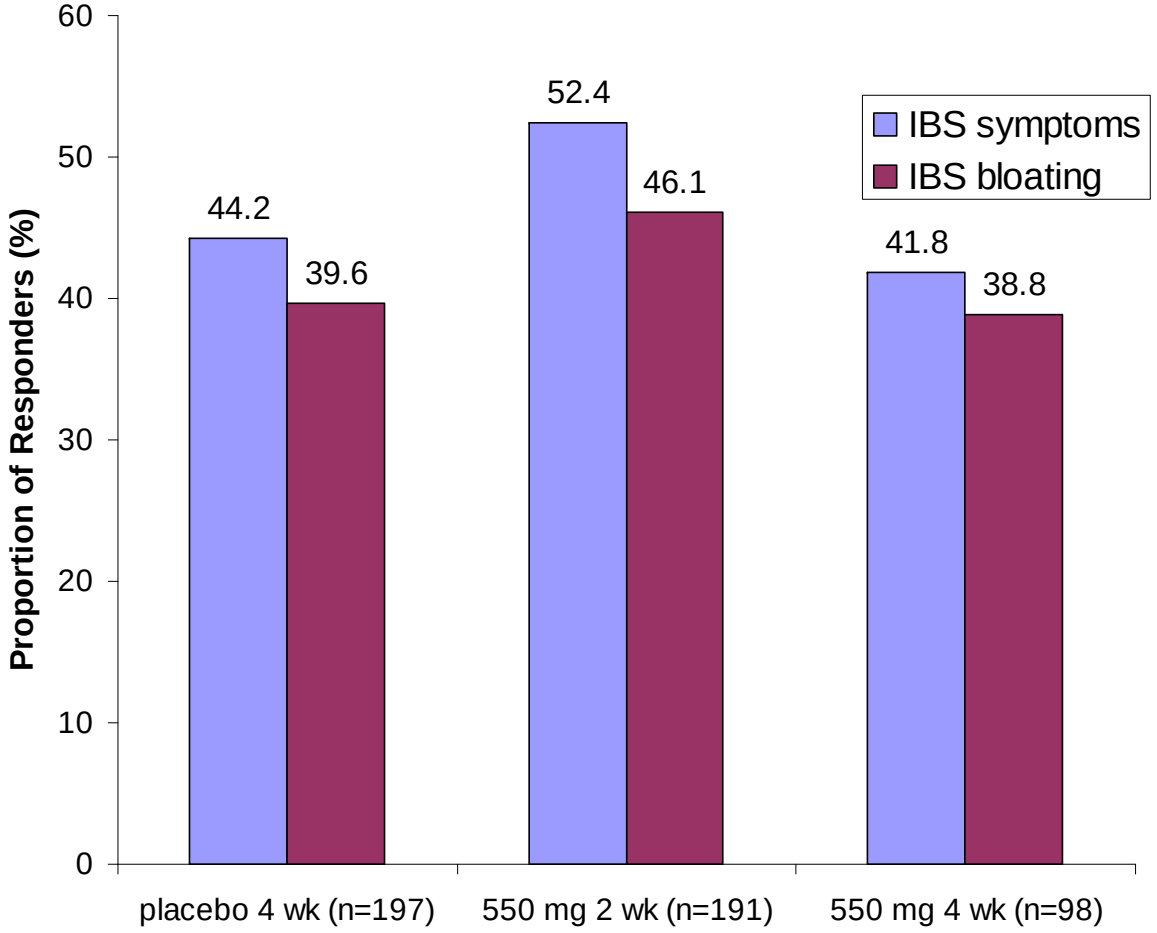
Adequate relief of IBS symptoms and bloating
2 week treatment with 275, 550, and 1100 mg **BID**



ITT

RFIB2001

Adequate relief of IBS symptoms and bloating
2 or 4 week treatment with **550 mg <u>BID</u>**



ITT

RFIB2001

Findings of the dose-ranging study

- High placebo response:~ 40%
- 550 mg BID for 2 wks resulted in higher proportion of responders than placebo and other doses
- No dose-response relationship among 275 mg, 550 mg, and 1100 mg BID
  - No treatment effect with the highest dose studied (1100 mg BID)
- No benefit with a longer treatment duration
  - 550 mg BID for 4 wks: no treatment effect

Dosage for phase 3 trials

- 550 mg **TID** (1650 mg daily) for 2 weeks
- More frequent dosing
  - To maintain higher intestinal concentration of rifaximin based on the initial small intestinal transit time in healthy subjects (3.8 to 6.3 hr)
- Higher daily dose of 1650 mg[1]
  - Breath Test normalization rate was significantly higher in 1600 mg/day group than in 1200 mg/day group
  - **<u>7 day course</u>**

[1]Scarpellini et al. (2007) Aliment Pharmacol Ther 25, 781-786

Rifaximin Dosage Regimen for IBS-d - Summary

- Unknown if the proposed dosage regimen (550 mg TID) is optimal
  - Only one dose level with TID was studied in phase 3 trials
  - Different dosing frequency i.e. BID was studied in the phase 2 trial
  - Treatment duration shorter than 2 weeks was not explored
  - Effect of rifaximin of different doses and treatment durations on gut flora was not assessed during development

Thank you

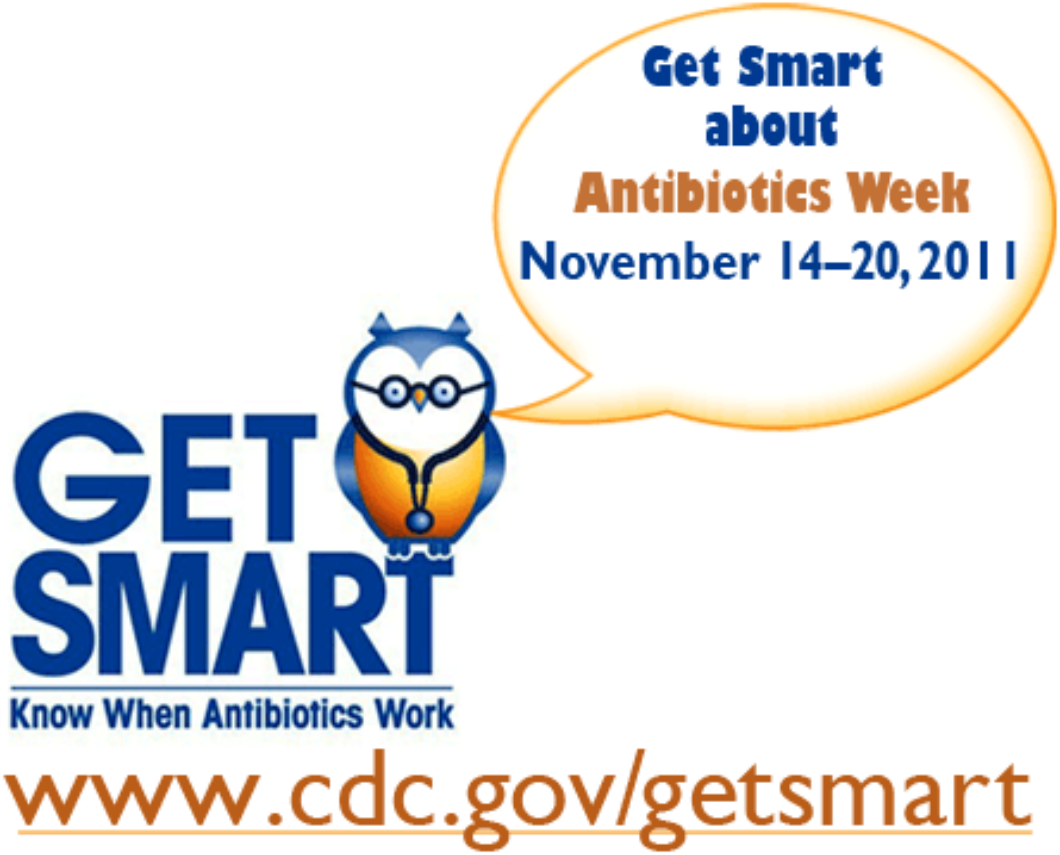
Clinical Microbiology Perspective

NDA 21-361 Rifaximin

November 16, 2011

Anne E. Purfield, PhD
Division of Anti-Infective Products

Happy Get Smart About Antibiotics Week



Rifaximin

- Inhibits DNA-dependent RNA polymerase activity in bacteria
  - Prevents protein synthesis
- Approved for traveler's diarrhea (*E. coli*)
  - 200 mg, three times daily for 3 days
  - Applicant proposes 550 mg, three times a day for 14 days for IBS-D

Rifaximin in vitro Susceptibility

- Incidence of spontaneously resistant mutants is higher than fluoroquinolones against enteric pathogens[1,8]
  - Resulting mutants were stable, with single-step chromosomal mutation[8]
- Mechanism of resistance is unknown, but likely due to mutations in target, RNA polymerase subunit B (rpoB)[2]
- Cross resistance with rifamycins is likely[2,6,7,8]

Rifaximin Clinical Susceptibility

- No breakpoints for in vitro susceptibility of any pathogen to rifaximin
  - Established based on correlation between clinical outcome and in vitro susceptibility
- No evidence of increase in minimum inhibitory concentration (MIC) in clinical isolates since FDA approval (2004)
- Subset of *C. difficile* isolates have higher relative MIC (>32 mcg/mL)[2,3,4,5]
  - Prevalence differs by study/geography
  - ~5-10% in USA

Rifaximin Antibacterial Activity-- Limitations

- Limited clinical data based on single course, short term treatment and/or non-IBS population
  - Quantitative effect on fecal flora[9]
  - Effect on gut microbiome diversity[9, 11]
  - Effect on bacterial in vitro susceptibility[10]

Rifaximin Antibacterial Activity-- Unknowns

- Effects of intermittent, repeated use are not known
  - Heteroresistance (polyclonal populations)
  - Changes in gut flora (diversity)
  - Gram negative “carriers” (Salmonella)
  - *C. difficile* susceptibility

Summary

- Selective pressure applied to microorganisms by the use of antimicrobial agents results in the development of resistance over time
- Rate at which this occurs varies by organism and antimicrobial agent
- For rifaximin, we don't have data at this time to predict how the proposed use of rifaximin in the IBS population will affect the emergence of rifaximin resistance, however the development of some resistance is probable

Points to Consider for Future Clinical Trials

- Determine if relapse diarrhea is due to pathogen or IBS-related
  - Culture and identify pathogens
- *C. difficile* toxin positive patients should be excluded and subjects should be monitored for *C. difficile* toxin throughout trial
- Measure in vitro susceptibility for *C. difficile* or any isolated pathogen

Acknowledgements

Andrew Mulberg
Lara Dimick
John Farley
Janice Pohlman
Frederick Marsik
Elizabeth O'Shaughnnessey
Hala Shamsuddin

References

1 Marchese et al., Chemotherapy 2000
2 Miller et al., JCM 2011
3 Huang et al., Anaerobe 2010
4 Ouyang-Latimer et al., AAC 2010
5 Mille et al., JCM 2011
6 Valentin et al., J Infection 2011
7 O'Connor et al., AAC 2008
8 Ruiz et al., JAC 2008
9 Brigidi et al., J Chemotherapy 2002
10 DuPont et al., CID 2001
11 DuPont et al., Ann Intern Med 2005

Development of Biomarkers

Gastrointestinal Drugs Advisory Committee Meeting
November 16, 2011

Courtney H. Lias, PhD
Director, Division of Chemistry and Toxicology Devices
Center for Devices and Radiological Health

Biomarker:

a characteristic that is an objective indicator of normal biologic processes, pathogenic processes, or biological responses to a therapeutic intervention.

Biomarker Tests in Drug Development

- Discovery
  - Identify Drug Targets
- Pre-clinical Development
  - PK, PD
  - Toxicity
  - Effect
- Clinical Development
  - Classify disease
  - Stratify population
  - Select patients for therapy
  - **Identify responders/non-responders (Predictive Biomarker)**
  - Identify patients at high risk for adverse events
  - Select dose for safety/efficacy
  - Act as Surrogate endpoint

Biomarker ≠ Test

- Biomarker – A characteristic
  (e.g., H_2 production from bacterial overgrowth)
- Biomarker test – The method of detecting the characteristic.
  (e.g., can the breath test (BT) specifically detect bacterial overgrowth?)
- When biomarker tests are applied for a purpose, safety and effectiveness for that purpose (e.g., for clinical use, for drug development) must be evaluated
  (e.g., can the BT predict response to Rifaximin?)

Uses

- Risk estimation
- Screening
- Diagnosis
- Residual (refractory) disease
- Recurrent disease
- Monitoring
- Prognosis
- Therapeutic response prediction

Each context has its own requirements for studies or trials to demonstrate analytical and clinical validity of the test.

Test Effectiveness

Sensitivity

How likely is the test to detect the presence of a disease in someone with the disease?

Specificity

How likely is the test to detect the absence of a disease in someone without the disease?

Positive Predictive Value (PPV)

How likely is someone with a positive test result to actually have the disease?

Negative predictive value (NPV)

How likely is someone with a negative test result to actually not have the disease?

(PPV and NPV are highly dependent on prevalence)

Study Population Matters

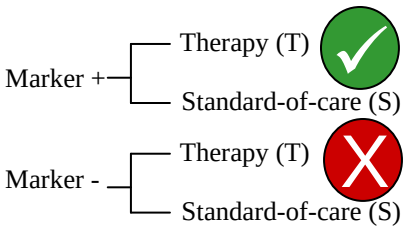
- To demonstrate the effectiveness of a biomarker test, it should be studied in the population in which the test will be used
- Test result is compared to "Truth" standard (clinical diagnosis, clinical endpoint, etc.)
  - e.g., BT+ group exhibits clinical response to Rifaximin, BT- group does not
- Studies in wrong population provide biased estimates of test performance

Trial Designs

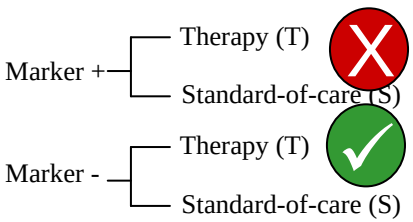
All subjects → All subjects' samples tested, randomization is not stratified by marker result
- Therapy (T)
- Standard-of-care (S)

All subjects → All subjects tested, randomization is stratified by marker result
- Marker +
  - Therapy (T)
  - Standard-of-care (S)
- Marker -
  - Therapy (T)
  - Standard-of-care (S)

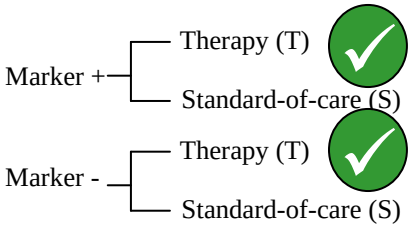
Trial Designs



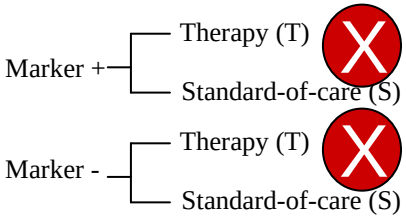
Rx effective in targeted population



Rx effective in targeted population

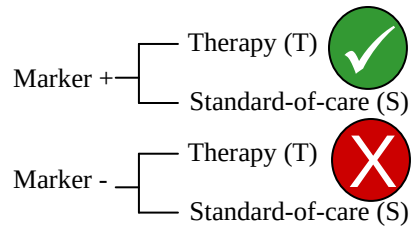


Rx effective,
Test not predictive



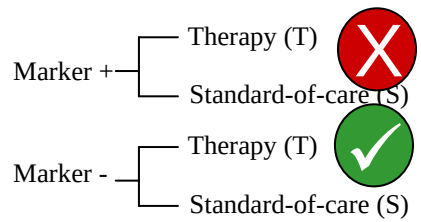
Rx not effective,
Test not predictive

Trial Designs

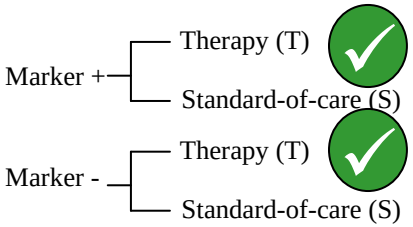


Rx effective in targeted population

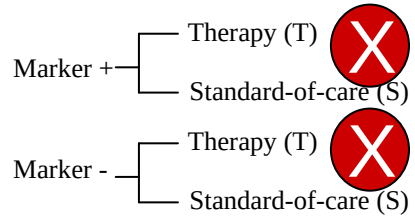
Note: This study does NOT demonstrate that the test is diagnostic of any particular disease subpopulation.



Rx effective in targeted population

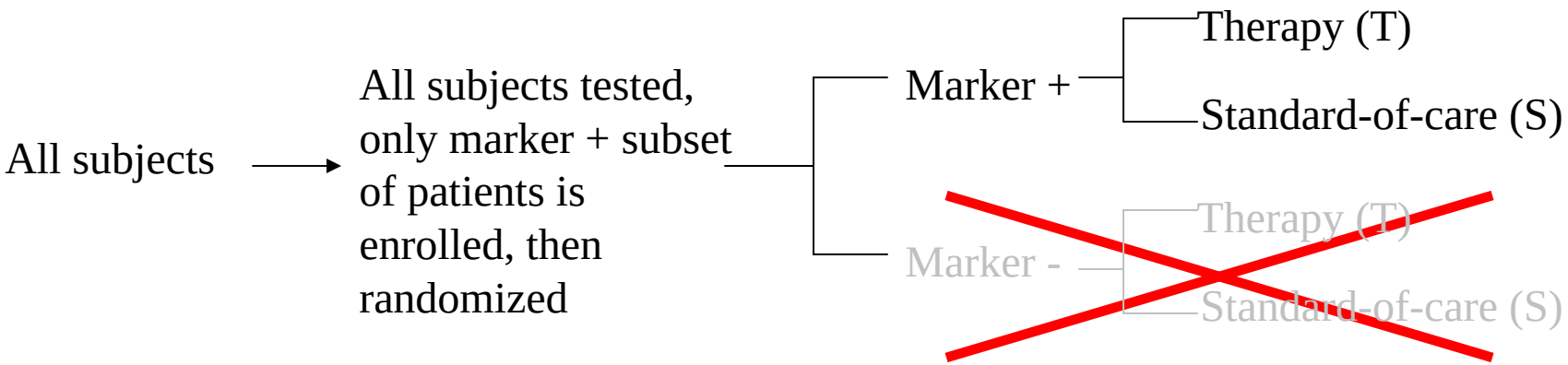


Rx effective,
Test not predictive



Rx not effective,
Test not predictive

However, often…



No information about:

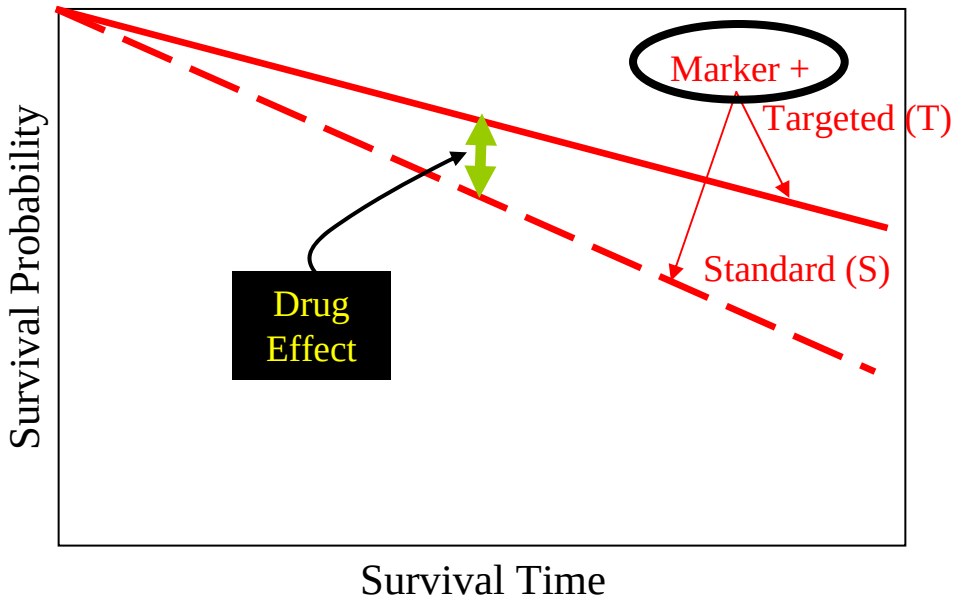
- Sensitivity (fraction of Rx responders who are marker+)
- Specificity (fraction of Rx non-responders who are marker-)
- NPV (fraction of marker- who do not respond to the therapeutic)

for the test.

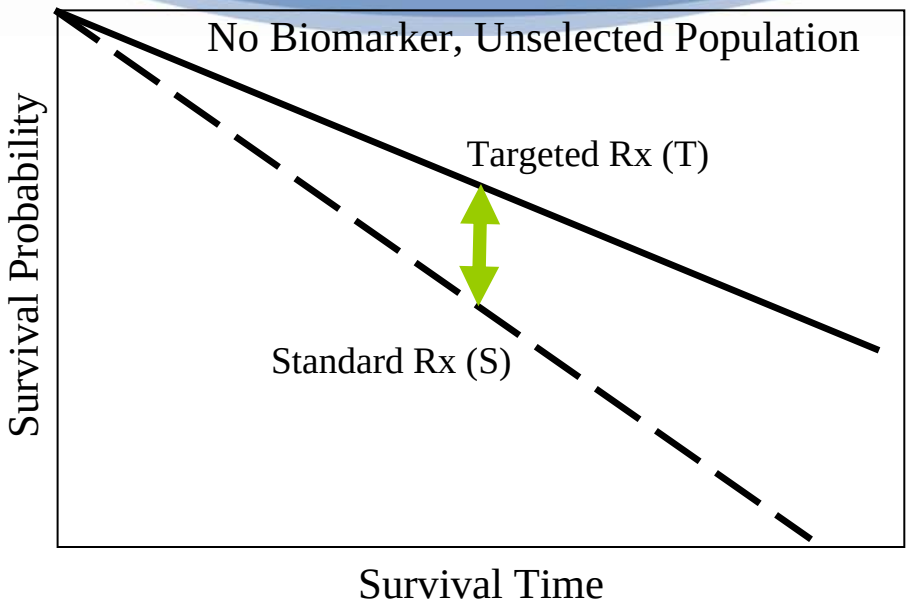
Pre-supposition: BT + patients are "enriched" for responders. (i.e., you believe the BT identifies responders, so BT- subjects are not enrolled)

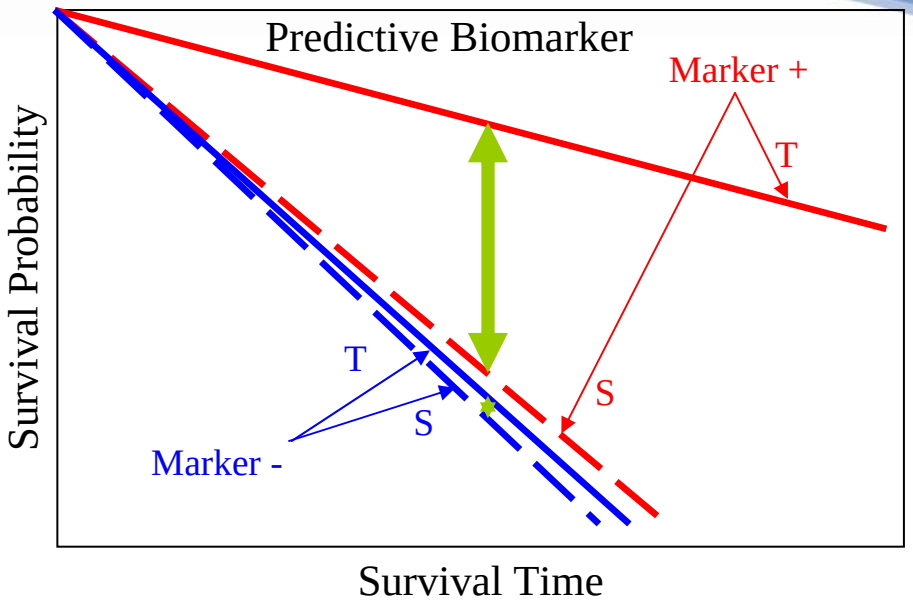
Can we study the marker-positive population alone?

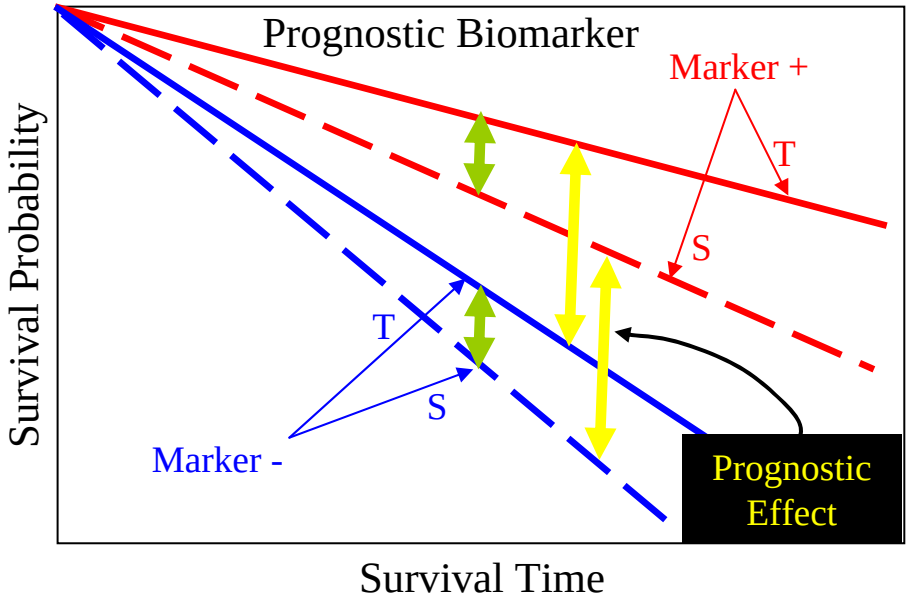
Marker-Positive Drug Trial

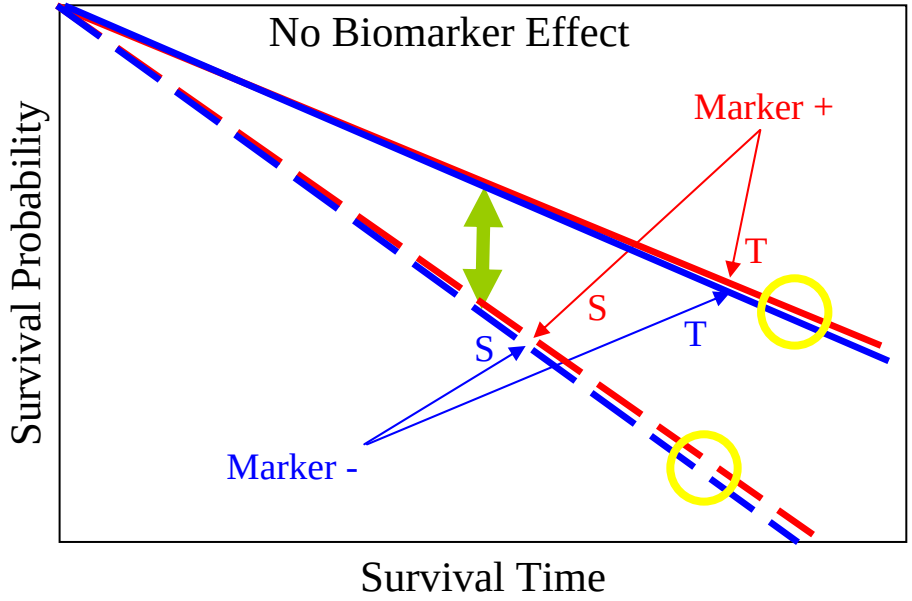


Yes, but the picture is incomplete.


No Biomarker, Unselected Population
Targeted Rx (T)
Standard Rx (S)
Survival Probability
Survival Time


Predictive Biomarker
Marker +
T
S
T
S
Marker -
Survival Probability
Survival Time


Prognostic Biomarker
Marker +
T
S
T
S
Marker -
Prognostic Effect
Survival Probability
Survival Time


No Biomarker Effect
Marker +
T
S
S
T
Marker -
Survival Probability
Survival Time

Predictive Biomarkers

- Assuming that a biomarker is predictive can be misleading – complete data is necessary to distinguish a prognostic effect from a predictive effect
- The most useful study design to demonstrate that a test is predictive includes both test+ and test- subjects
- If a test is required for safe and effective use of the drug, it must be cleared or approved for that purpose along with the drug

Summary

- What is the value of exploring H_2 breath testing to enrich the population?
- Proper validation of a biomarker for a particular purpose is critical
- Study design matters – need unbiased estimates of predictive value
- Biomarkers must be carefully measured by accurate and reliable tests

Questions?

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Gastrointestinal Drugs Advisory Committee Meeting

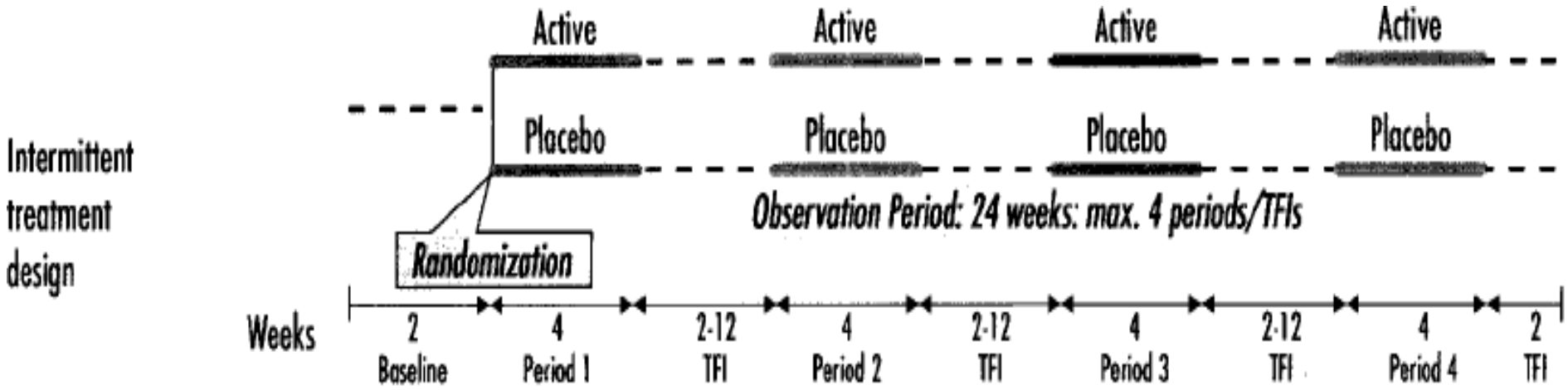
NDA 21-361 Rifaximin

Comments on Study Design and Charge to Committee

November 16, 2011

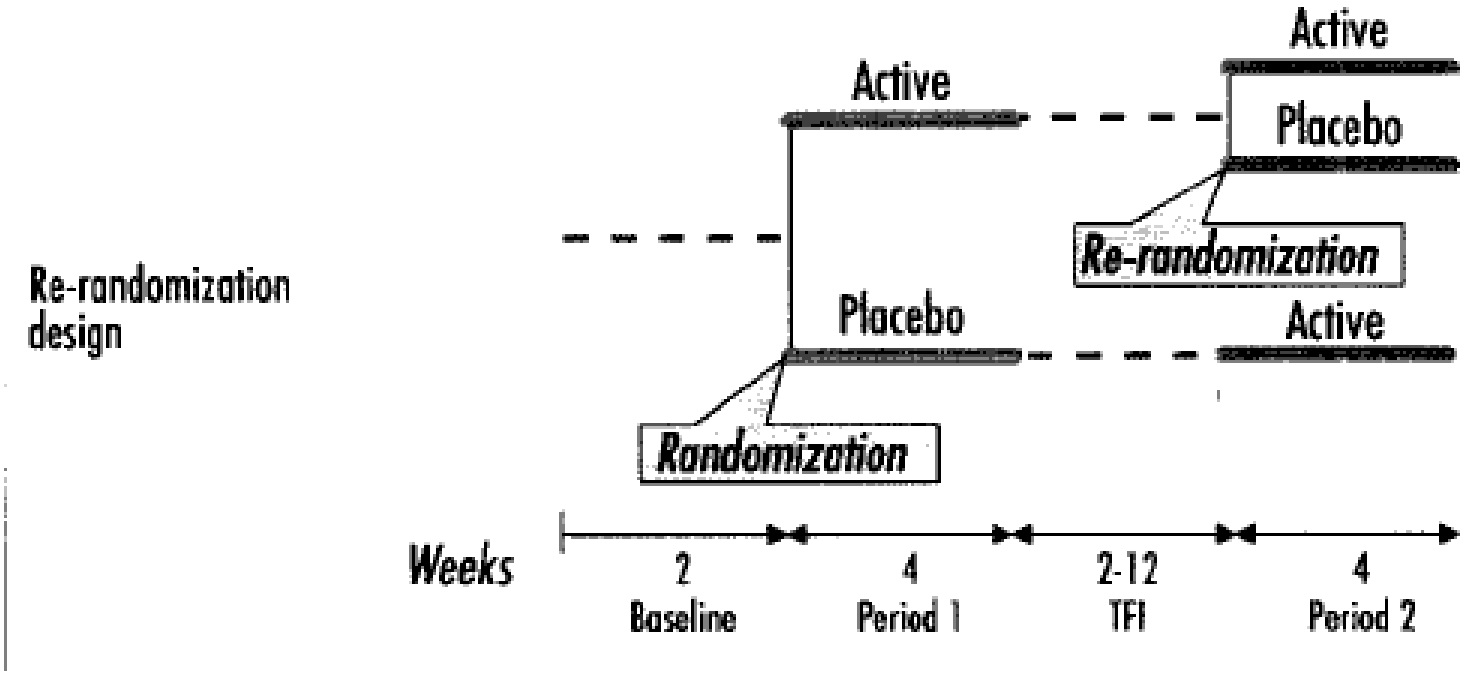
Andrew E Mulberg, MD, FAAP
Division of Gastroenterology and Inborn Errors Products
CDER/FDA

Intermittent Treatment Design



Drug Information Journal 2006;40:209-217

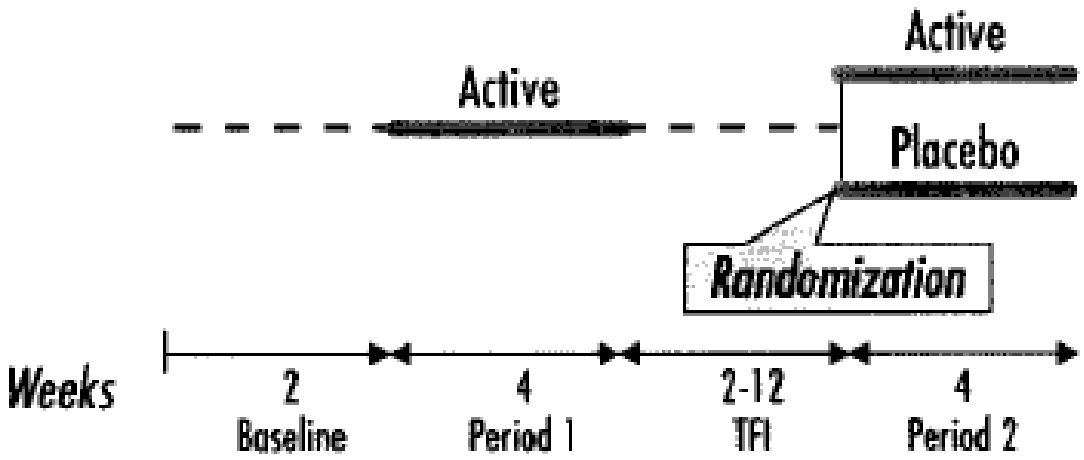
Re-randomization Design



Drug Information Journal 2006;40:209-217

Randomization of Partial Responders: Withdrawal Design

Randomization of partial responders design

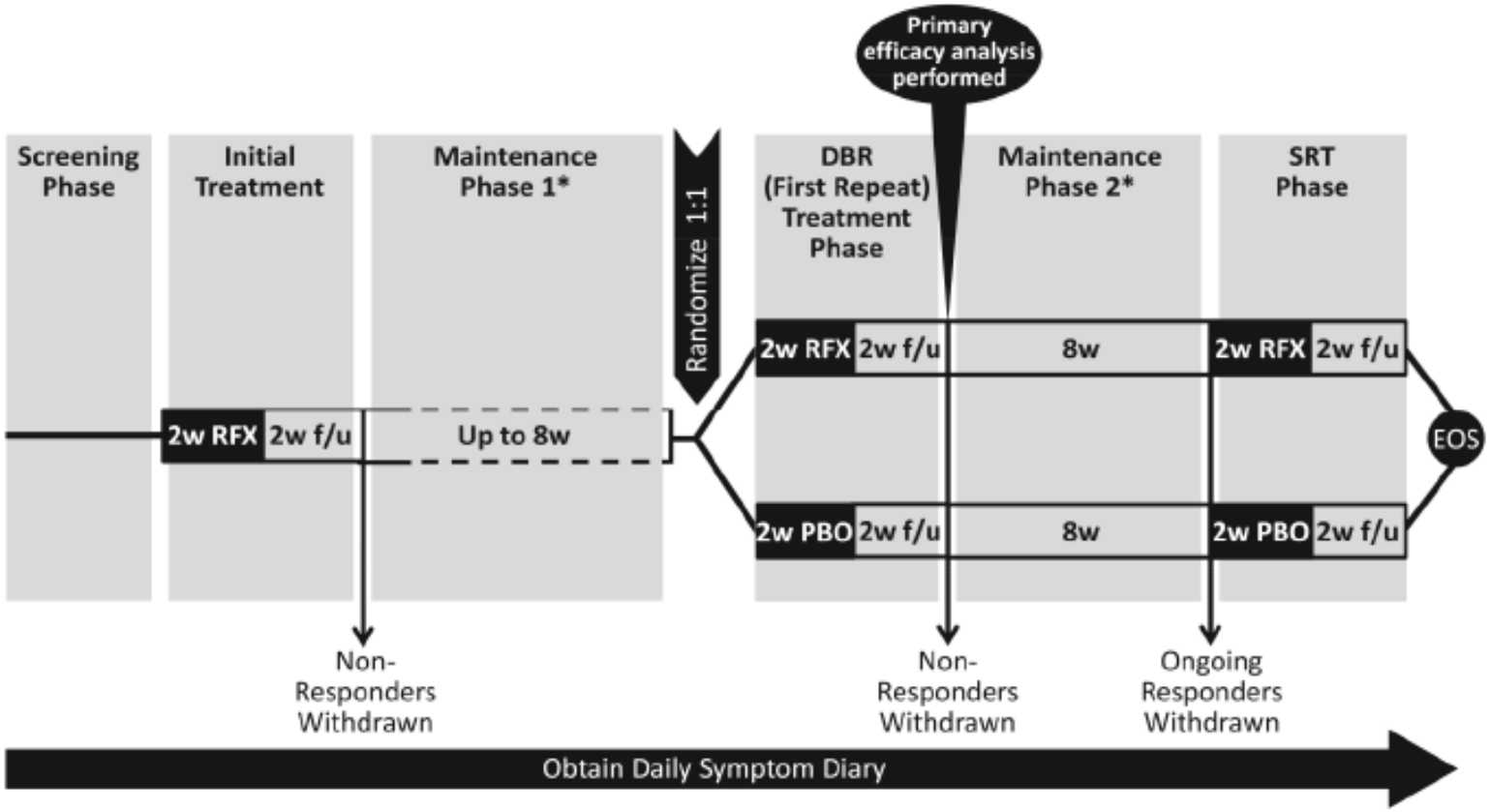


Drug Information Journal 2006;40:209-217

Advantage	Disadvantage
Intermittent treatment design A	
Low sample size	Prolonged placebo treatment
Close to clinical practice	Baseline conditions for repeated treatment might differ between treatments and might introduce bias for treatment comparison
Initial treatment comparison can be performed	The number of successful weeks might be difficult to interpret because they are the same for very different outcome profiles over the 24 weeks
Patients initially not at least partially responding get a second chance	
Randomization of partial responders B and re-randomization design C	
Repeated treatment comparison can be performed	Large sample size
Initial treatment comparison can be performed (C only)	Randomization to re-treatment does not reflect clinical practice
Preference of the CPMP guideline	
≤4 weeks of placebo treatment	

Drug Information Journal 2006;40:209-217

Figure 3 Proposed Repeat Treatment Study Design



Abbreviations: RFX = rifaximin; PBO = placebo; f/u = follow-up; DBR = Double-Blind, Randomized; SRT = Second Repeat Treatment; and EOS = end of study.

*During the Maintenance Phases subjects with recurrence enter the Repeat Treatment Phases:

- Maintenance Phase 1: Subjects who do not meet recurrence criteria by the end of the 8 week Maintenance Phase will be allowed to continue up to an additional 12 weeks until they experience recurrence; or until enrollment is met in DBR (Repeat Treatment) Phase.
- Maintenance Phase 2: Subjects who do not meet recurrence criteria by the end of 8 weeks will be withdrawn from the study.

Strengths of Proposed Trial Design

- Assesses durability of response to rifaximin
  - to a maximum of 20 weeks in “phase 1”
  - to a maximum of 8 weeks in “phase 2”
- Assesses effect of retreatment after recurrence of symptoms
  - to a maximum of 3 cycles
- Time to retreatment is individualized based on symptom recurrence.
  - Assumes that time to recurrence will vary
- Studies the impact of retreatment on intestinal flora

Weaknesses of Proposed Trial Design

- Does not address prevention of symptom recurrence
- Does not address targeting “cure” or more durable “remission” with a different dosing strategy
- One dose level assessed
- Is it possible that subsequent cycles should require a different dose?
- Phase 2 eight week treatment-free period may not be long enough to allow symptom recurrence

Weaknesses of Proposed Trial Design

- Is the population adequately defined?
  - Are clinical criteria sufficient to identify an IBS population for whom an antibiotic is appropriate treatment of IBS symptoms?
  - Is there a way to define better the target population than a trial course of rifaximin?
    - Is there a potential role of a Predictive biomarker?
    - Is there a truth standard to rely on?
- Potential operational constraints on sample size

Questions to the Advisory Committee

1. **Vote**:

   Which of the following goals for rifaximin treatment of IBS should be pursued in its development to support product labeling?

   a. Prevention of recurrent symptoms (e.g., starting treatment before symptoms occur and/or continuing rifaximin on a chronic basis as a “maintenance regimen”)?

   b. Acute short-term treatment of symptomatic recurrence?

   c. Induction of “cure” or “long term remission”?

Questions to the Advisory Committee

2. Vote:

The study design presented in this meeting addresses acute short-term treatment of symptomatic recurrence. Is the proposed study design acceptable to address this issue? If not, please explain.

Questions to the Advisory Committee

3. **Discuss:**

   If you believe that a different treatment paradigm than acute treatment of symptomatic recurrence is relevant for rifaximin treatment for IBS-D, please discuss the clinical trial designs that will best meet those objectives.

Questions to the Advisory Committee

4. **Vote**:

   The applicant is proposing to study rifaximin at a dose of 550 mg three times a day for two weeks, repeated as needed based on symptom recurrence. Should other dose levels and regimens be explored in future clinical trials? If so, describe what other regimens should be explored.

Questions to the Advisory Committee

5. **Vote**:

   For product labeling for a chronically administered antibiotic, is it acceptable to define the target population of IBS-D patients for long term treatment based on whether they respond to therapy in the first cycle of treatment? If not, how do you suggest defining the appropriate population?

Questions to the Advisory Committee

6. **Vote:**

   Identifying a more targeted patient population of rifaximin responders for treatment of IBS-D would limit exposure of this drug more conservatively than the larger at risk population with IBS-D. Do you believe that there is a potential role of a predictive biomarker, i.e. breath hydrogen testing to achieve this goal? If so, please describe your perspectives.

Questions to the Advisory Committee

7. **Discuss:**

   Please discuss your concerns regarding the potential for future development of antibiotic resistance due to chronic use of rifaximin. How can your concerns be addressed in the clinical development program for rifaximin in the IBS-D population?

Questions to the Advisory Committee

8. **Vote**:

   Are you concerned that chronic use of rifaximin could cause changes in the GI microbiome that would result in an adverse effect on patient health? If so, what are your concerns and how should they be addressed in the clinical development program?