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# RBX2660 for Reduction of Recurrence of *Clostridioides difficile* Infection

**September 22, 2022**

Rebiotix Inc., a Ferring Company

Vaccines and Related Biological Products Advisory Committee

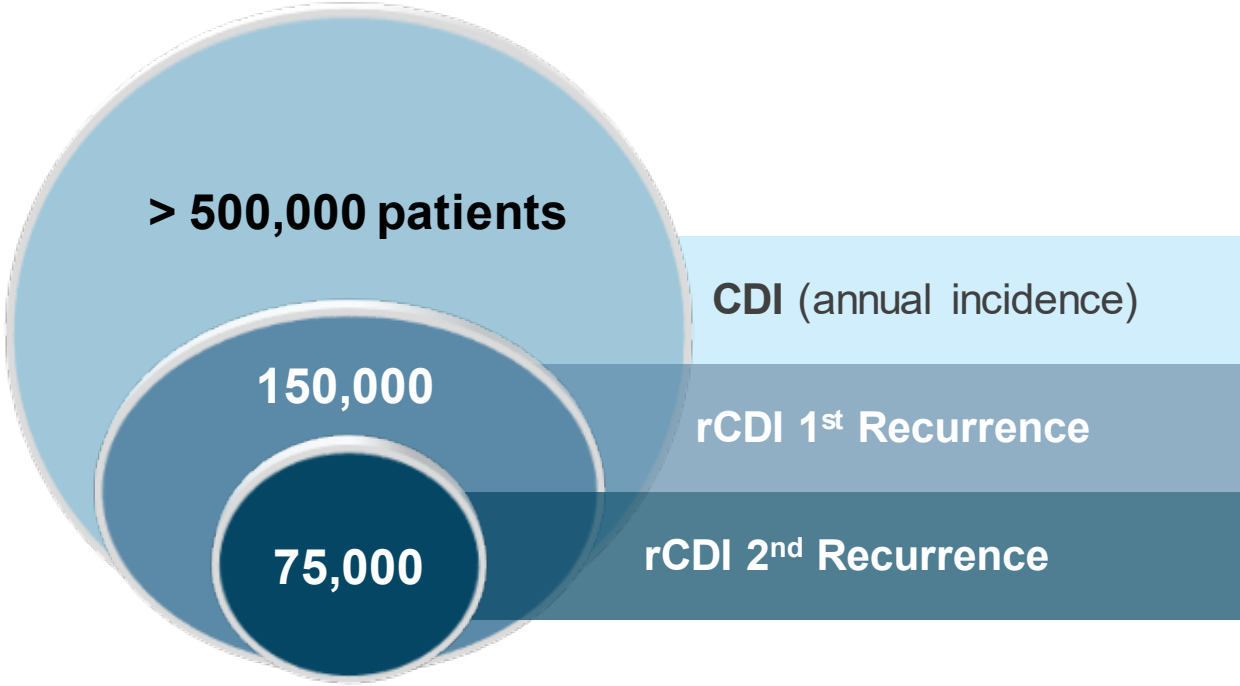
# Introduction

**Lee Jones**

Founder, Past President, and CEO
Rebiotix Inc, a Ferring Company

# Recurrent *Clostridioides difficile* Infection (rCDI): Rare, Serious, and Potentially Life-Threatening Infection

- *C. difficile* infection (CDI)
  - Declared urgent antibiotic resistant threat by CDC[1]
  - Most common cause of healthcare-associated infections[1]
  - Results in severe diarrhea, colitis, and potentially sepsis
- Antibiotics SOC for CDI and rCDI
  - 30% 1st recurrence[2]
    - 50% 2nd recurrence[3]
- Antibiotics contribute to ongoing gut microbiota disruption (dysbiosis)




1. CDC 2019; 2. Hopkins et al., 2018; 3. D. Riddle et al., 2009; SOC = standard of care

# Microbiota Restoration is a Well Recognized Platform

- Unapproved fecal microbiota transplantation (FMT) often used to treat rCDI due to patient need for effective therapy
  - No FDA-approved microbiome restoration therapies
  - Access to FMT remains limited
  - Variable donor screening and product manufacturing demonstrated risks
- Need a scalable, accessible, regulated product to solve unmet need

RBX2660 developed to standardize microbiota restoration

# RBX2660: Intestinal Fecal Microbiota Suspension that is Standardized, Stabilized, and Quality Controlled

- Standardized for potency with controlled formula
- Stabilized for extended shelf life
- Pre-packaged single-dose: 150 mL microbiota suspension from individual human stool donation

Fast Track, Breakthrough, Orphan Drug designations

# RBX2660: Oversight Throughout Product Lifecycle

## Manufacturing and Quality Controls

Donor screened → Stool collected at site and tested → Validated quality control and manufacturing processes → Drug product packaged and frozen → Shipped in validated conditions

## Administration and Surveillance

Physician prescribes RBX2660 → Product received ultra cold / thawed onsite → Administered rectally → Pharmacovigilance

# RBX2660 Standardization is Achieved through Stringent Donor Screening and Controlled Manufacturing Processes

**Donor Screening**

Initial and ongoing blood screening every 6-8 weeks

Initial COVID and ongoing screening every 14 days

**Health Questionnaire**

Initial health and behavior questionnaire

Questionnaire completion at every donation

**Donation Testing**

29 stool pathogens testing every donation

**Manufacturing and Quality Controls**

**Provides safe product with no reports of disease transmission**

# RBX2660 Clinical Development Program

| | |
|---|---|
| **Phase 2 (Open-Label)** | **Study 2013-001** (1 or 2 doses) |
| **Phase 2 (RCT)** | **Study 2014-01** (1 or 2 doses) |
| **Phase 2 (Open-Label)** | **Study 2015-01** (2 doses) |
| **Pivotal Phase 3 (RCT)** | **Study 2017-01** (1 dose) |
| **Phase 3 (Open-Label)** | **Study 2019-01** (1 dose) |
| **Retrospective** | **Study 2019-02** (1 or 2 doses) |

# RBX2660 Proposed Indication

To reduce the recurrence of *Clostridioides difficile* infection (CDI) in adults following antibiotic treatment for recurrent *Clostridioides difficile* infection

# Agenda

| | |
|---|---|
| **Unmet Need** | **Sahil Khanna, MBBS, MS**<br>Professor of Medicine, Division of Gastroenterology and Hepatology<br>Mayo Clinic |
| **Efficacy** | **Lindy Bancke, PharmD**<br>Head of Clinical Development<br>Rebiotix Inc., a Ferring Company |
| **Safety** | **Jonas Pettersson, MD, PhD**<br>Senior Medical Director<br>Ferring Pharmaceuticals |
| **Clinical Perspective** | **Colleen Kraft, MD, MSC, FIDSA**<br>Professor, Medicine/Division of Infectious Diseases<br>Associate Chief Medical Officer<br>Emory University |

# Additional Experts

**Scott Berry, PhD**
President, Senior Statistical Scientist
Berry Consultants

**Greg Fluet**
Chief Operating Officer and Site Head
Rebiotix Inc., a Ferring Company

**Ken Blount, PhD**
Chief Scientific Officer
Rebiotix Inc., a Ferring Company

**Karen Kuphal, PhD, MBA, PMP**
Head of Regulatory Affairs
Rebiotix Inc., a Ferring Company

# Effective Management of *C. difficile* An Unmet Clinical Need

**Sahil Khanna, MBBS, MS**

Professor of Medicine

Division of Gastroenterology and Hepatology

*C. difficile* Clinic and Microbiome Restoration Program

Mayo Clinic

Rochester, MN

# *Clostridioides difficile:* A Serious Infection

## ~ 500,000 people with CDI in US each year

- ~ 30,000 deaths annually

## Risk factors for CDI

- Antibiotics
- Proton pump inhibitors
- Previous *C. difficile*
- Healthcare exposure
- Age > 65 years
- Comorbidities: Immunosuppressed state, malignancy, kidney disease, inflammatory bowel disease

1. Lessa et al., 2015; 2. Guh et al., 2020; 3. Khanna, 2021

# *C. difficile*: A Serious Infection with High Morbidity

- Debilitating diarrhea
- Severe abdominal pain
- Weight loss
- Hospitalization
- Anxiety
- Social isolation

1. Guh et al., 2020; 2. Khanna, 2021

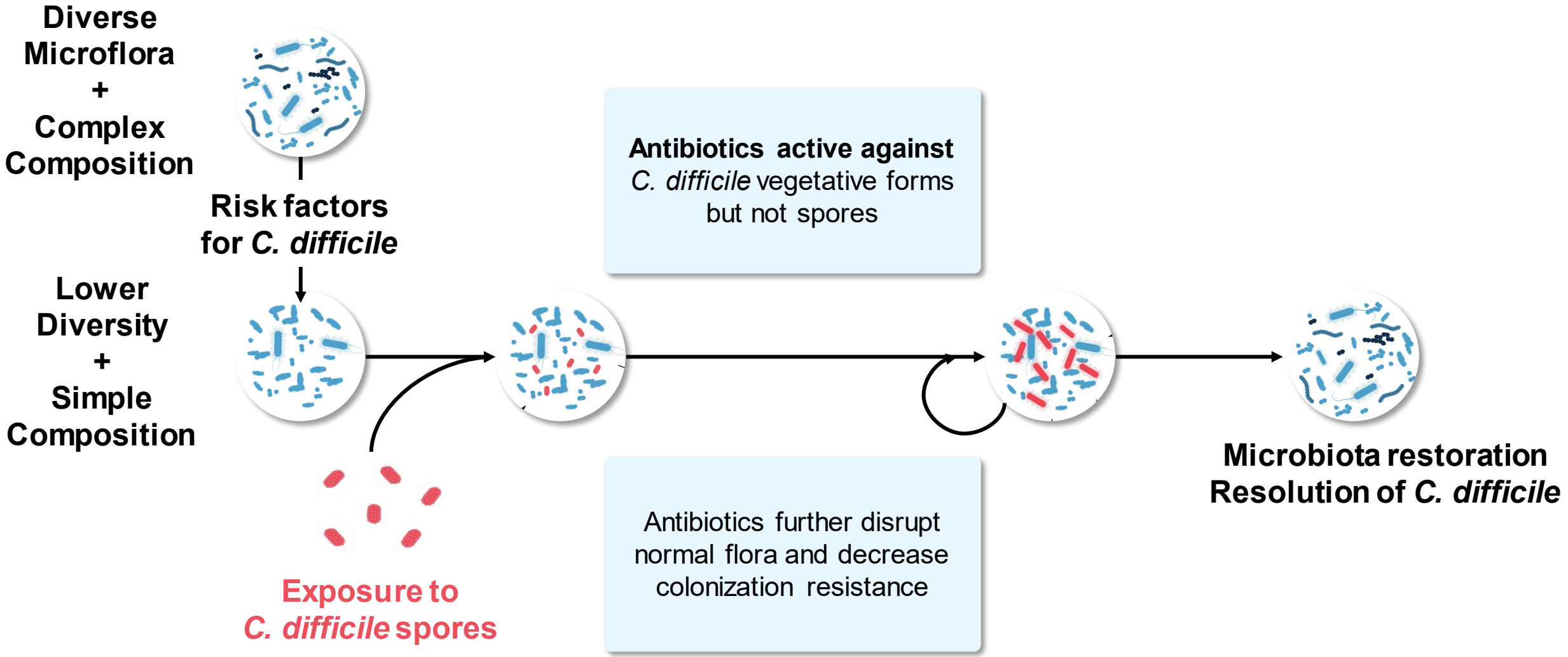
# Current Treatment Landscape of *C. difficile*

| Recurrence rates after antibiotic use | 20 - 30% recurrence | 40% - 50% recurrence | ~ 60% recurrence |
|---|---|---|---|

| First episode | Second episode (first recurrence) | Third episode (second recurrence) |
|---|---|---|
| **Vancomycin** | **Vancomycin taper-pulse** | **Antibiotic → Microbiota restoration** |
| Fidaxomicin | Fidaxomicin | Fidaxomicin extend |
| Vanco or Fidaxo + bezlotoxumab | Vancomycin taper-pulse + bezlotoxumab | Vancomycin taper-pulse |

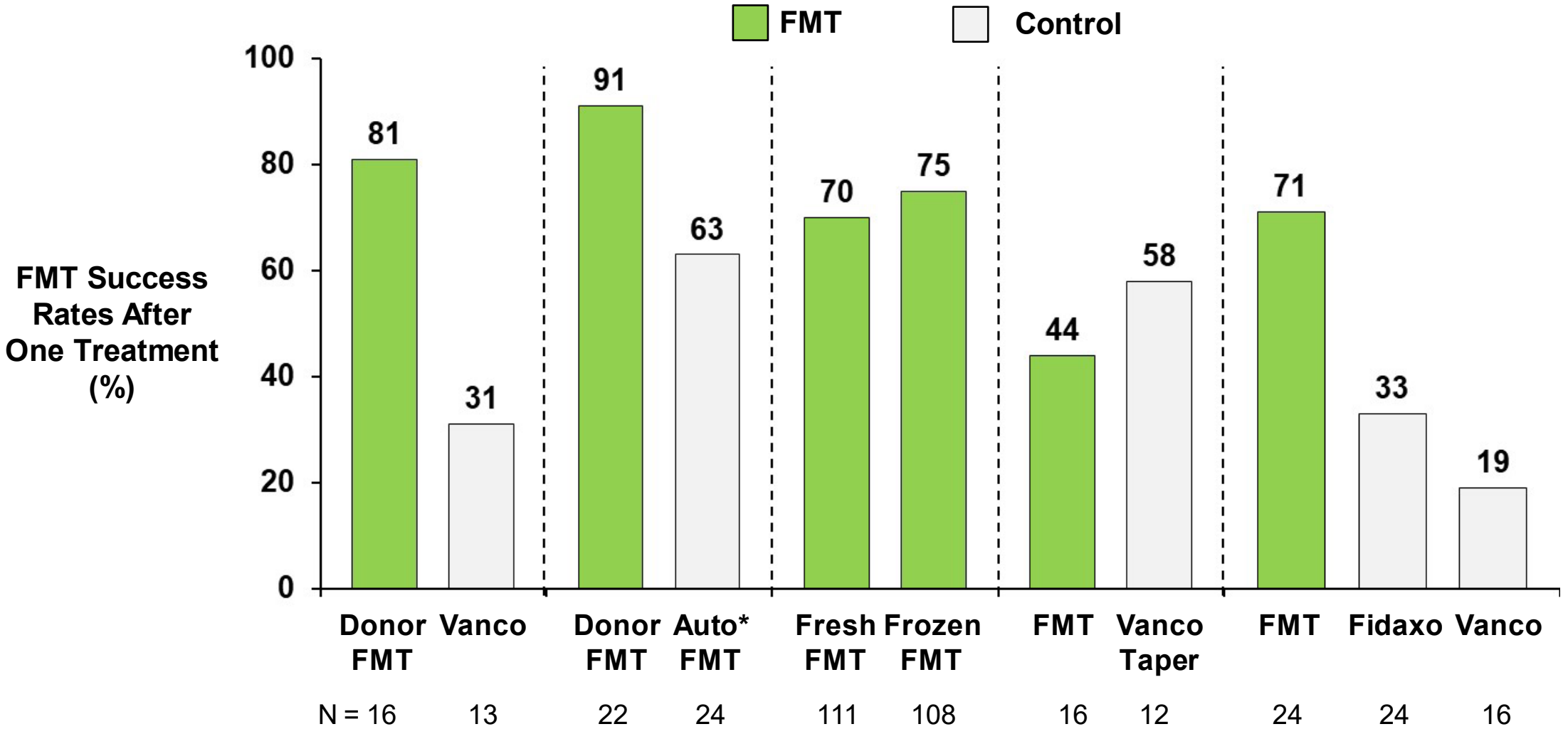
1. Johnson et al., 2021; 2. Kelly et al., 2021; 3. Hopkins and Wilson, 2018.

# Prevent Recurrences: Restore the Microbiome




Adapted from Khanna, 2021

# Demand for FMT Increasing Due to Success Rates Observed in Mostly Small Randomized Control Trials

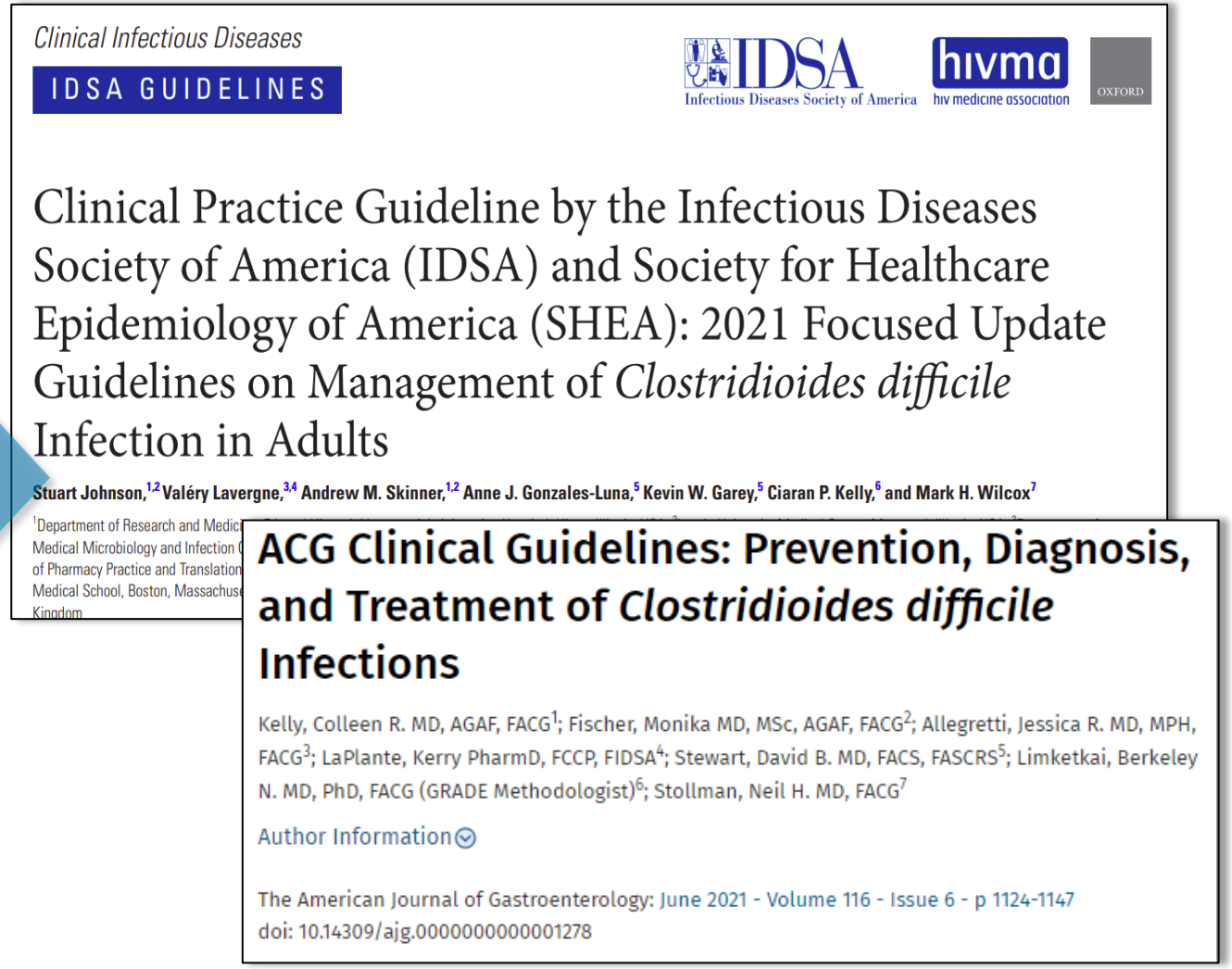



*Autologous

1. Van Nood et al., 2013; 2. Kelly et al., 2016; 3. Lee et al., 2016; 4. Hota et al., 2017; 5. Hvas et al., 2019

# Clinical Practice Guidelines Recommend FMT for Patients with rCDI

*As a reminder,* ***FMT is recommended only for patients with multiple recurrences of CDI*** *who have failed appropriate antibiotic treatments and where appropriate screening of donor and donor fecal specimens has been performed, in accordance with these newer FDA recommendations.*



*Clinical Infectious Diseases*

IDSA GUIDELINES

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of *Clostridioides difficile* Infection in Adults

Stuart Johnson,[1,2] Valéry Lavergne,[3,4] Andrew M. Skinner,[1,2] Anne J. Gonzales-Luna,[5] Kevin W. Garey,[5] Ciaran P. Kelly,[6] and Mark H. Wilcox[7]

[1]Department of Research and Medic
Medical Microbiology and Infection
of Pharmacy Practice and Translation
Medical School, Boston, Massachus
Kingdom

**ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of *Clostridioides difficile* Infections**

Kelly, Colleen R. MD, AGAF, FACG[1]; Fischer, Monika MD, MSc, AGAF, FACG[2]; Allegretti, Jessica R. MD, MPH, FACG[3]; LaPlante, Kerry PharmD, FCCP, FIDSA[4]; Stewart, David B. MD, FACS, FASCRS[5]; Limketkai, Berkeley N. MD, PhD, FACG (GRADE Methodologist)[6]; Stollman, Neil H. MD, FACG[7]

Author Information

The American Journal of Gastroenterology: June 2021 - Volume 116 - Issue 6 - p 1124-1147
doi: 10.14309/ajg.0000000000001278

**FDA 2013 Guidance for Industry Enforcement Policy Regarding IND Requirements for Use of FMT to Treat CDI Not Responsive to Standard Therapies**

# Unapproved FMT Comes with Safety Concerns Due to Lack of Standardization and Regulation



## Consistent Screening Needed

**Health and infection screening**

**Stool tests for donors**
- Enteric pathogens, viruses, parasites
- Multi-drug resistant organisms

**Blood tests for transmissible infections**
- HIV, viral Hepatitis, syphilis, others

**Emerging pathogens**
- SARS-CoV-2

**FDA Alerts**

**Multidrug resistant organism transmission**
- ESBL-producing *E. coli*

**SAEs due to transmission of infectious agents from asymptomatic donors**
- *EPEC and STEC*

**COVID-19**

**Monkeypox**

1. Khanna, 2021; 2. Khanna et al., 2020; 3. Khanna and Kraft, 2021

EPEC = enteropathogenic *Escherichia coli*; STEC = Shiga toxin-producing *E. coli*; ESBL = extended-spectrum beta-lactamase

# Clear Benefits of A Regulated, FDA Approved Microbiome Restoration Therapy

**Well-studied, consistent process to product**

**Established, positive benefit-risk profile**

**Approval of a standardized product**

- Reduce variability and heterogeneity of the processes and preparation
- Uniform and iterative donor screening to improve safety outcomes
- Improve access for patients

**Address the cycle of CDI recurrence**

# Efficacy

**Lindy Bancke, PharmD**

Head of Clinical Development

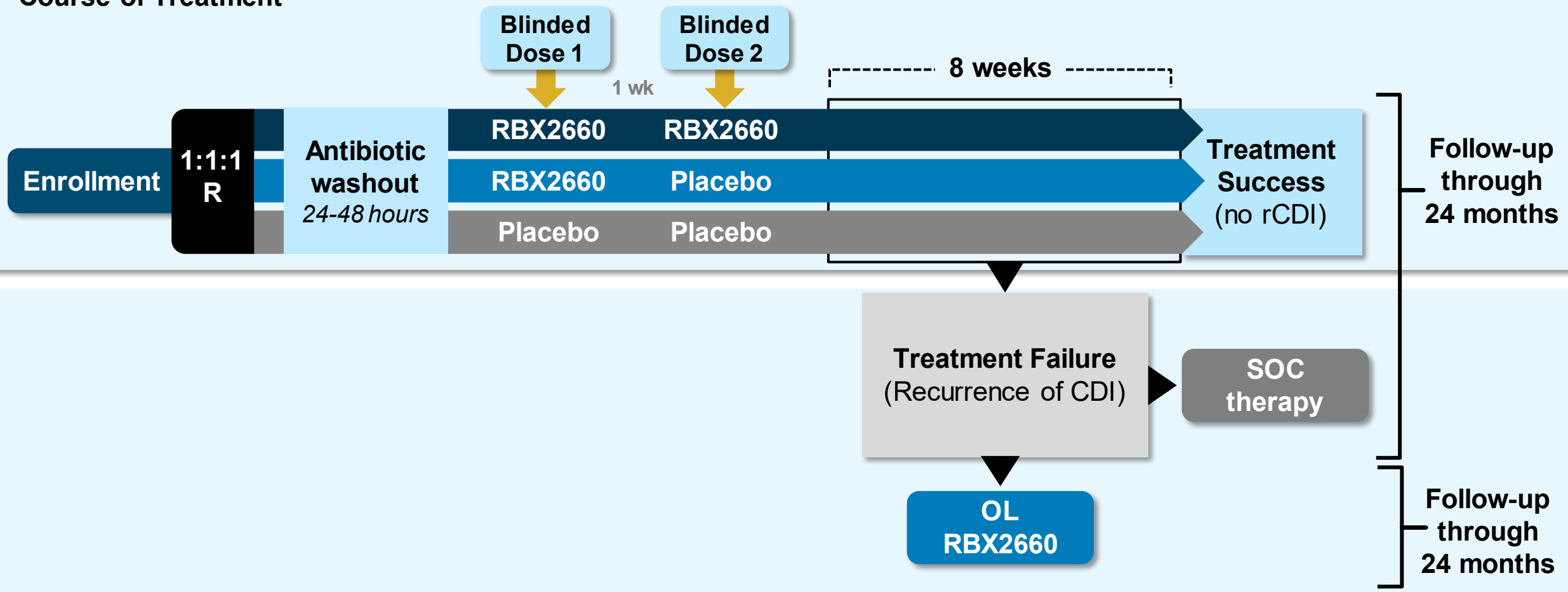
Rebiotix Inc, a Ferring Company

# RBX2660 Clinical Development Program

| | | |
|---|---|---|
| **Phase 2 (Open-Label)** | Feasibility and safety | **Study 2013-001** (1 or 2 doses) N = 32 |
| **Phase 2 (RCT)** | Identify treatment regimen for Phase 3 RCT | **Study 2014-01** (1 or 2 doses) N = 133 |
| **Phase 2 (Open-Label)** | Supportive evidence of efficacy and safety | **Study 2015-01** (2 doses) N = 142 |
| **Pivotal Phase 3 (RCT)** | Demonstrate substantial evidence of effectiveness | **Study 2017-01** (1 dose) N = 262 |
| **Phase 3 (Open-Label)** | Supportive evidence of efficacy and safety | **Study 2019-01** (1 dose) N = 402 |
| **Retrospective** | Supportive evidence of efficacy and safety | **Study 2019-02** (1 or 2 doses) N = 64 |

**Efficacy Evaluable Population**

# Study 2014-01: Design



# Study 2014-01: Key Inclusion and Exclusion Criteria

## Inclusion criteria

- ≥ 18 years old
- ≥ 2 episodes of recurrent CDI after primary CDI and ≥ 2 rounds SOC antibiotics

  OR

  ≥ 2 episodes of severe CDI resulting in hospitalization

## Exclusion criteria

- History of IBD (ulcerative colitis, Crohn's disease, microscopic colitis), IBS, chronic diarrhea, celiac disease
- Previous fecal transplant

IBD = inflammatory bowel disease; IBS = irritable bowel syndrome (by Rome III criteria)

# Study 2014-01: Primary Endpoint Selection

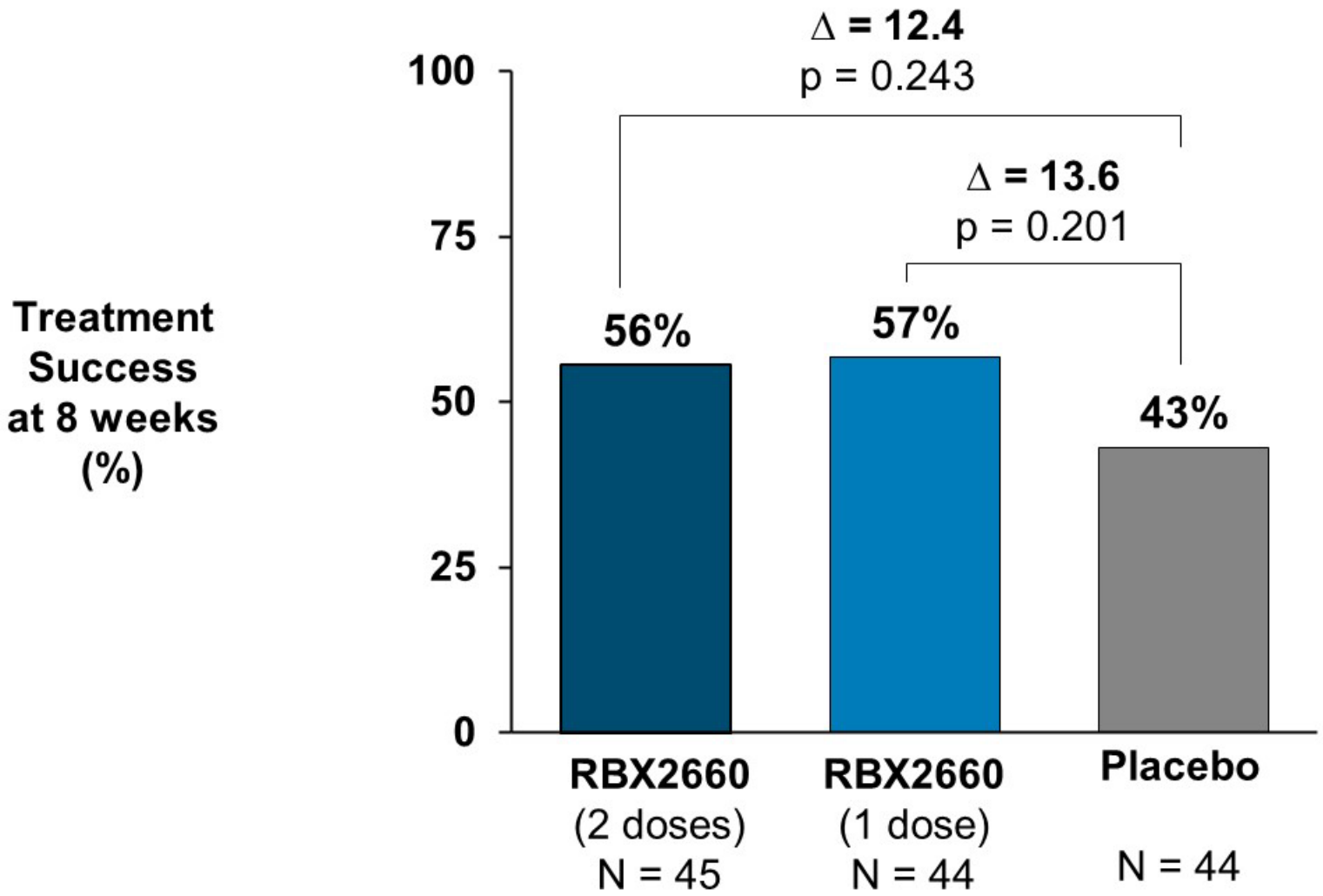
| | Description |
|---|---|
| **Primary Endpoint** | |
| **Treatment Success** | Absence of CDI diarrhea for 8 weeks after study treatment |
| **Primary Analysis Population** | |
| | **All randomized patients** |
| **Intent-to-treat (ITT)** | ▪ Discontinuations prior to 8 weeks were considered failures |

# Study 2014-01: Baseline Demographics and Medical Characteristics Balanced (ITT)

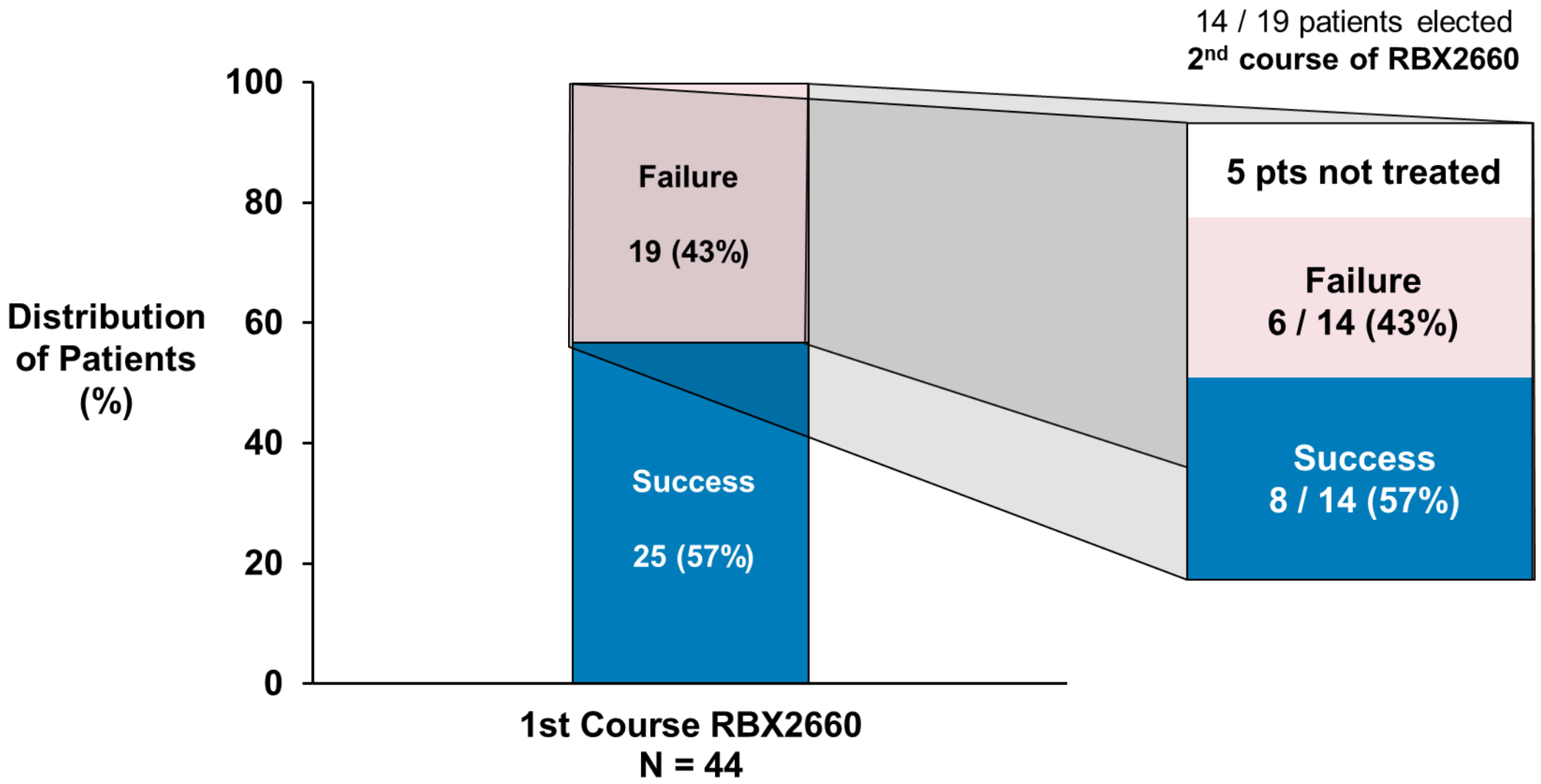
| | **RBX2660** (2 doses) N = 45 | **RBX2660** (1 dose) N = 44 | **Placebo** N = 44 |
|---|---|---|---|
| **Age (years), mean** (SD)<br>Min, max | **63.6** (19.2)<br>(24 – 89) | **61.0** (19.7)<br>(18 – 88) | **58.8** (19.2)<br>(19 – 92) |
| **Female** | **58%** | **57%** | **68%** |
| **White** | **98%** | **96%** | **98%** |
| **Duration of CDI (days), mean** (SD) | **19** (13) | **17** (11) | **20** (18) |
| **Previous episodes of CDI, mean** | **4.3** | **4.1** | **3.8** |
| **Hospitalization** | | | |
| **Due to CDI episode** | **58%** | **43%** | **57%** |
| **Duration (days), median** (IQR) | **9.5** (15.0) | **7.0** (6.0) | **5.0** (3.5) |
| **Vancomycin during screening** | **91%** | **86%** | **91%** |

# Study 2014-01: Primary and Secondary Efficacy Results

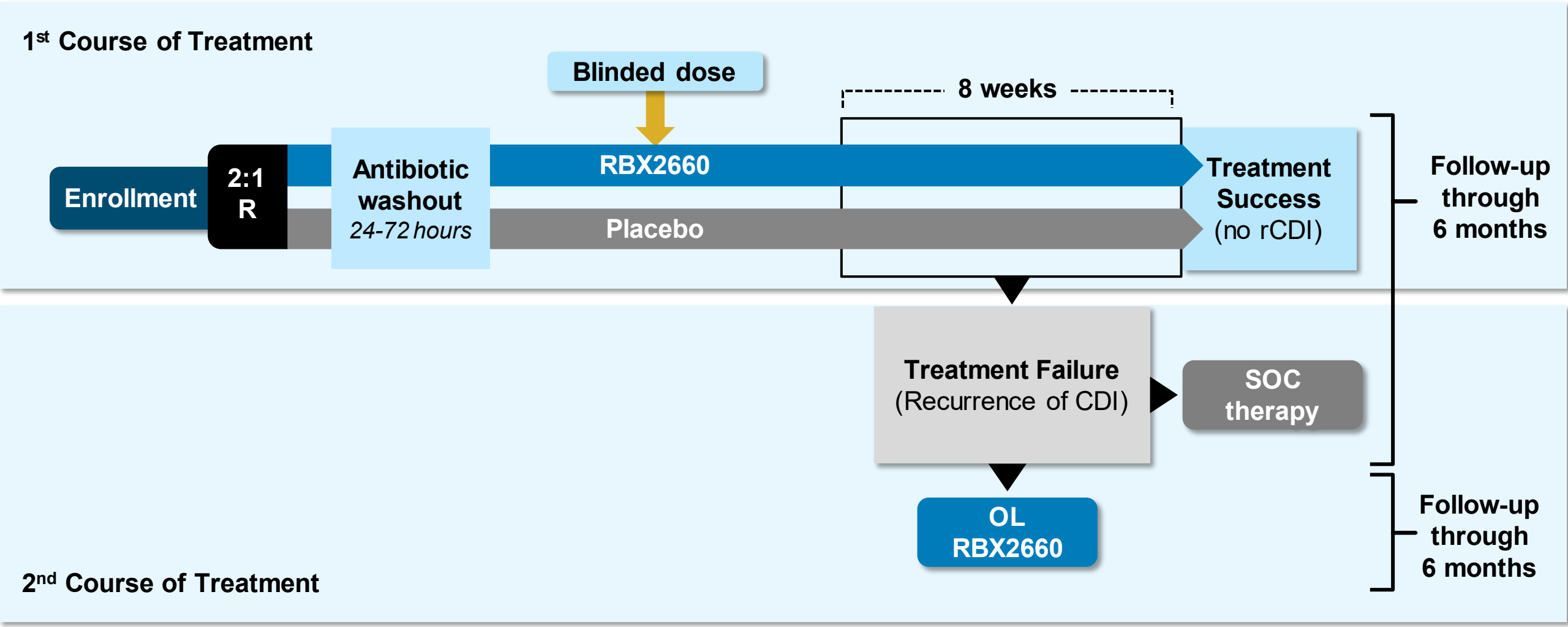
*ITT Population*



# Study 2014-01: Treatment Success After Second Course of RBX2660



# Study 2017-01: Design



# Study 2017-01: Key Inclusion and Exclusion Criteria

## Inclusion criteria

- ≥ 18 years old
- ≥ 1 episode of recurrent CDI after primary CDI and ≥ 1 round SOC antibiotics

  OR

  ≥ 2 episodes of severe CDI resulting in hospitalization

## Exclusion criteria

- History of IBD (ulcerative colitis, Crohn's disease, microscopic colitis), IBS, chronic diarrhea, celiac disease
- Previous fecal transplant, investigational CDI vaccine, CDI monoclonal antibodies

IBD = inflammatory bowel disease; IBS = irritable bowel syndrome (by Rome III criteria)

# Study 2017-01: Baseline Demographics and Medical Characteristics Well-Balanced (mITT)

| | RBX2660<br>N = 177 | Placebo<br>N = 85 |
|---|---|---|
| **Age (years), mean** (SD)<br>Min, max | **61.3** (16.8)<br>(19, 93) | **57.5** (15.9)<br>(26, 86) |
| **Female** | **69%** | **69%** |
| **White** | **93%** | **89%** |
| **Duration of CDI (days), mean** (SD) | **26.3** (14.8) | **25.3** (11.4) |
| **Previous episodes of CDI, mean** | **3** | **3** |
| **Hospitalization** | | |
| **Due to CDI episode** | **13%** | **12%** |
| **Duration (days), median** (IQR) | **5.0** (4.0) | **5.0** (4.0) |
| **Vancomycin during screening** | **87%** | **89%** |

# Additional Table for Slide 31

**Table 8 Demographic and Baseline Disease Characteristics (Primary Analysis Set or Full A**

| Characteristic | Randomized, Placebo-Controlled Studies | | | | |
|---|---|---|---|---|---|
| | 2014-01 | | | 2017-01 | |
| | RBX2660 (2 Doses) (N = 45) | Placebo (2 Doses) (N = 44) | RBX2660 (1 Dose) (N = 44) | RBX2660 (1 Dose) (N = 177) | Placebo (1 Dose) (N = 85) |
| Age, years | | | | | |
| Mean (SD) | 63.6 (19.2) | 58.8 (19.2) | 61.0 (19.7) | 61.3 (16.8) | 57.5 (15.9) |
| Median | 68.0 | 62.0 | 63.0 | 64.0 | 60.0 |
| Minimum, maximum | 24, 89 | 19, 92 | 18, 88 | 19, 93 | 26, 86 |
| Age group, n (%) | | | | | |
| <65 years | 19 (42.2) | 25 (56.8) | 26 (59.1) | 90 (50.8) | 53 (62.4) |
| ≥65 years | 26 (57.8) | 19 (43.2) | 18 (40.9) | 87 (49.2) | 32 (37.6) |
| Sex, n (%) | | | | | |
| Male | 19 (42.2) | 14 (31.8) | 19 (43.2) | 55 (31.1) | 26 (30.6) |
| Female | 26 (57.8) | 30 (68.2) | 25 (56.8) | 122 (68.9) | 59 (69.4) |
| Race, n (%) | | | | | |
| White | 44 (97.8) | 43 (97.7) | 42 (95.5) | 165 (93.2) | 76 (89.4) |
| Non-White | - | - | - | 12 (6.8) | 9 (10.6) |
| American Indian or Alaska Native | 0 | 0 | 0 | 2 (1.1) | 0 |
| Asian | 0 | 0 | 0 | 1 (0.6) | 0 |
| Black or African American | 0 | 1 (2.3) | 2 (4.5) | 8 (4.5) | 6 (7.1) |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 | 0 |
| Other | 1 (2.2) | 0 | 0 | 0 | 3 (3.5) |
| Multiple | 0 | 0 | 0 | 1 (0.6) | 0 |
| Ethnicity, n (%) | | | | | |
| Hispanic or Latino | 1 (2.2) | 2 (4.5) | 1 (2.3) | 2 (1.1) | 4 (4.7) |
| Not Hispanic or Latino | 43 (95.6) | 42 (95.5) | 42 (95.5) | 166 (93.8) | 78 (91.8) |
| Not reported | 1 (2.2) | 0 | 1 (2.3) | 4 (2.3) | 0 |
| Unknown | 0 | 0 | 0 | 5 (2.8) | 3 (3.5) |
| Site Geography, n (%) | | | | | |
| Canada | - | - | - | 51 (28.8) | 26 (30.6) |
| Eastern US | - | - | - | 23 (13.0) | 8 (9.4) |
| Southern US | - | - | - | 48 (27.1) | 27 (31.8) |
| Northern US | - | - | - | 29 (16.4) | 13 (15.3) |
| Western US | - | - | - | 26 (14.7) | 11 (12.9) |
| Duration of qualifying CDI episode, days | | | | | |
| Mean (SD) | 18.8 (13.4) | 19.8 (17.7) | 17.3 (11.4) | 26.3 (14.8) | 25.3 (11.4) |
| Median | 15.0 | 15.0 | 14.0 | 24.0 | 22.0 |
| Minimum, maximum | 1, 74 | 1, 98 | 1, 71 | 11, 163 | 11, 67 |

# Study 2017-01: Primary Endpoint Definition Consistent with 2014-01

| | Description |
|---|---|
| **Primary Endpoint** | |
| **Treatment Success** | Absence of CDI diarrhea for 8 weeks after study treatment |
| **Primary Analysis Population** | |
| **Modified Intent-to-treat (mITT)** | **All randomized who received blinded treatment**<br>▪ Excluded: discontinued prior to outcome evaluation if not related to CDI symptoms<br>▪ Discontinuations due to CDI symptoms were considered failures |
| **Secondary endpoint** | **Loss of sustained clinical response through 6 months** |

# Increased Availability of Unapproved FMT Resulted in Enrollment Difficulties

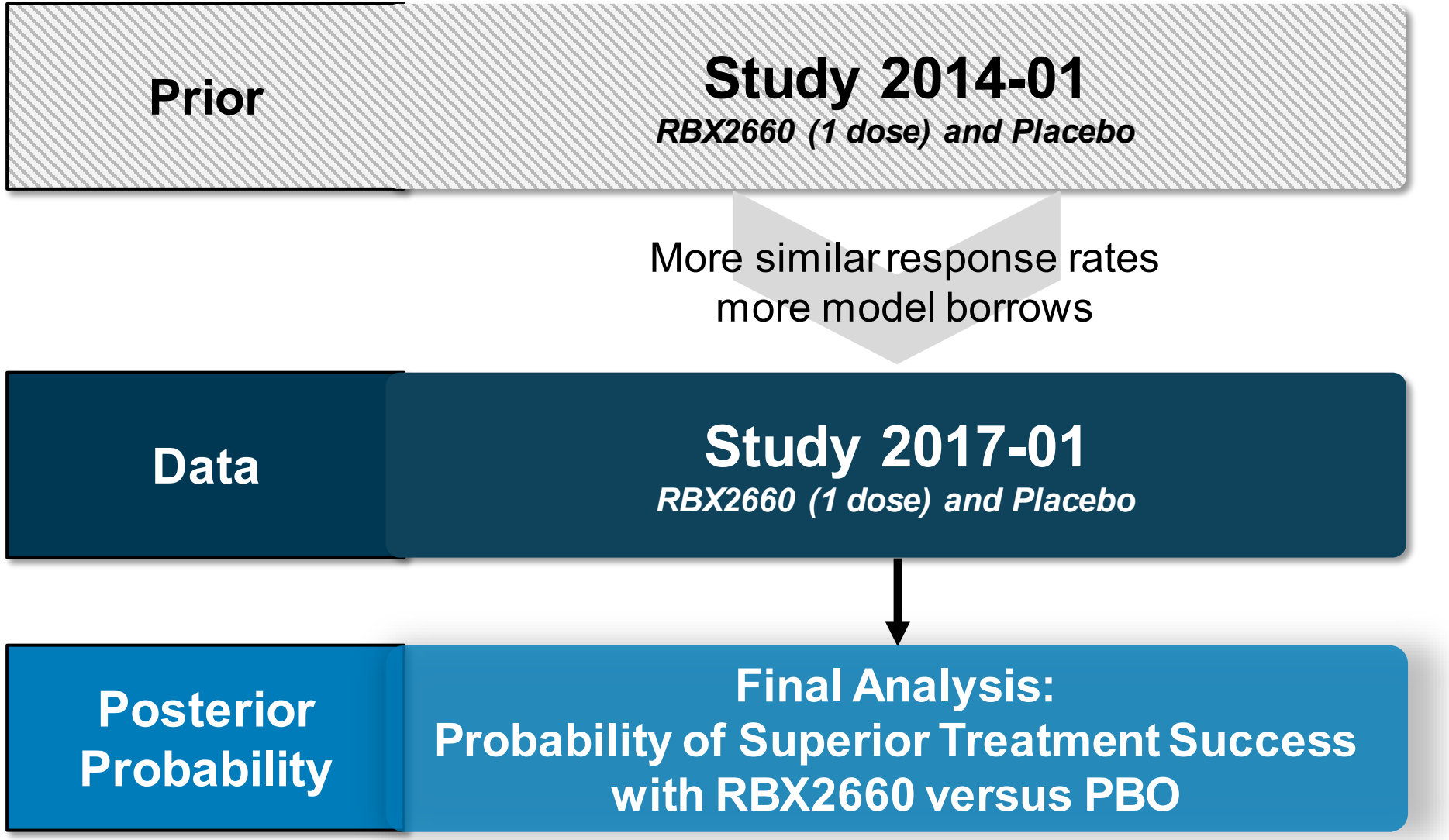
- Planned enrollment in two Phase 3 studies (N ≈ 300 each)
  - Expanded number of clinical sites
  - Accrual rates continued to be far less than anticipated
  - Delayed completion of pivotal Phase 3 study
- Conducting another placebo-controlled study would have been challenging
  - Would take ~ 6 additional years to complete

# Innovative Design Incorporated in Consultation with FDA Due to Enrollment Challenges

- Type C meeting with FDA to discuss recruitment difficulties
- FDA agreed with formal borrowing of 2014 data
  - Bayesian approach incorporated in statistical analysis plan prior to enrollment completion and before data unblinding or interim / final analyses
- Exceeded required number of patients for safety assessment (N = 600); robust for orphan designated population
- Confirmatory evidence of FMT success

# Study 2017-01: Bayesian Hierarchical Model

*Amended Primary Analysis*

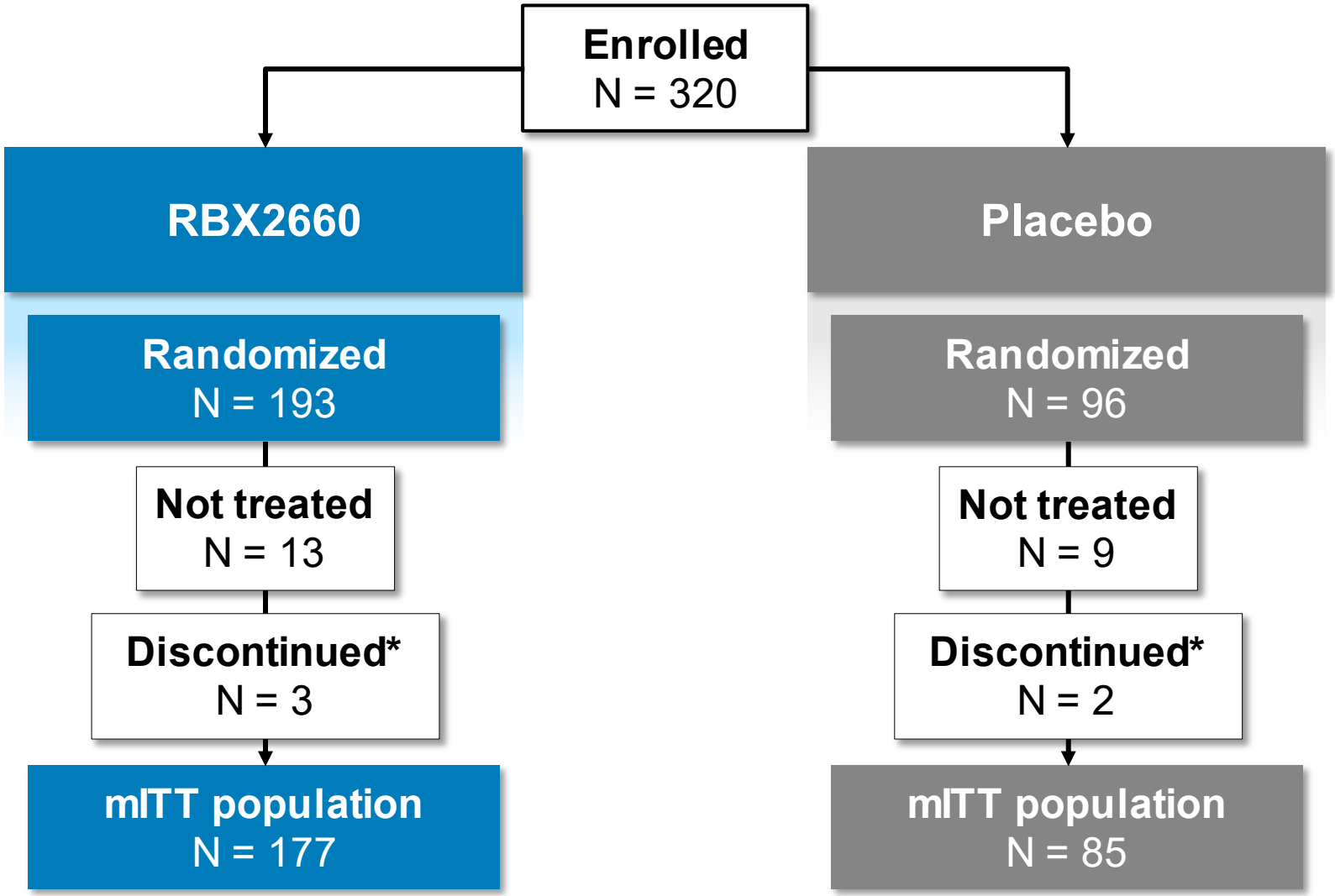


# Study 2017-01: FDA Regulatory Statistical Significance Thresholds

*Amended Primary Analysis*

| | Bayesian Posterior Probability Superiority |
|---|---|
| **Statistically significant** | **97.50%** |
| **Statistically very persuasive** | **99.93%** |

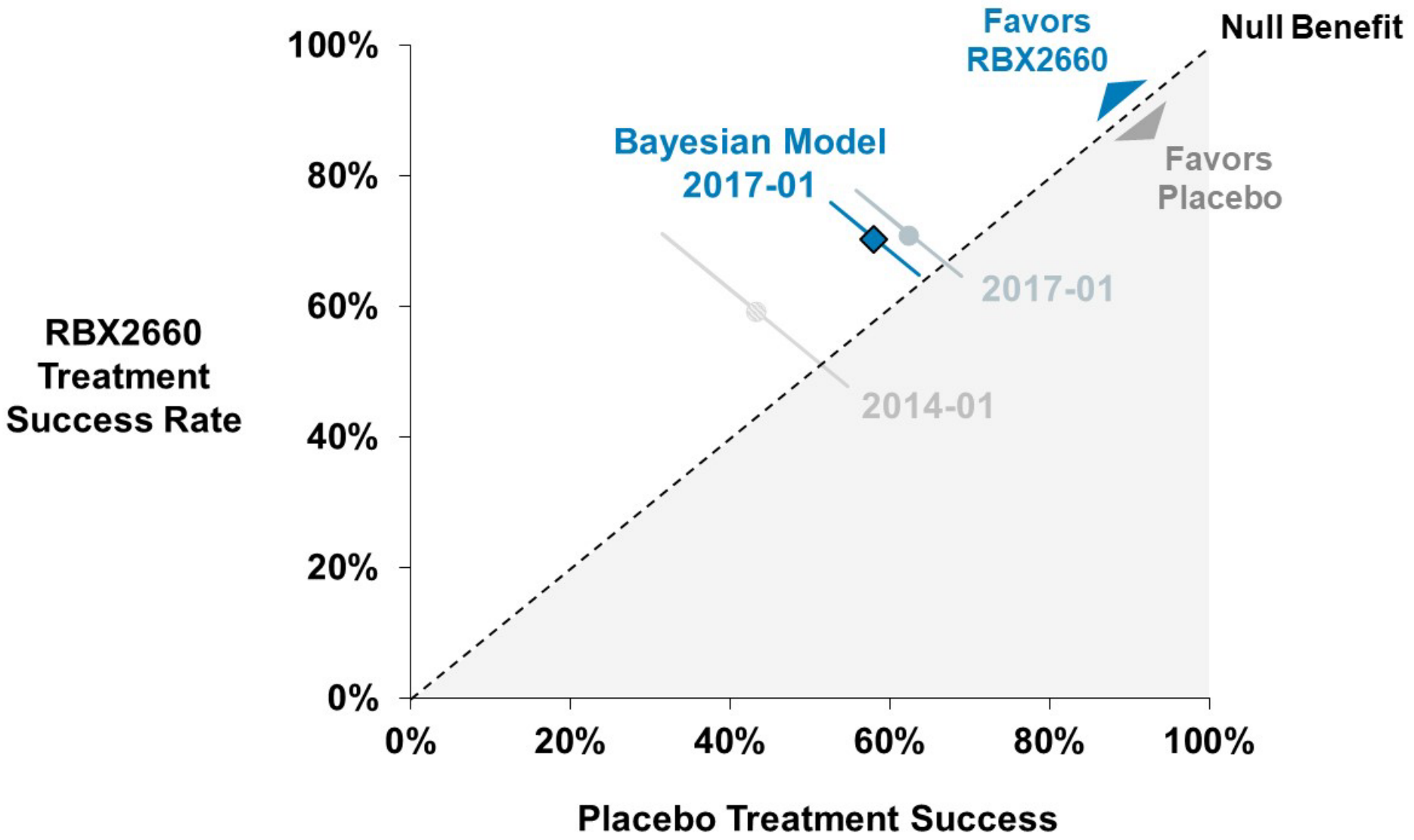
# Study 2017-01: Disposition of Patients in mITT Population




*Prior to 8-week efficacy analysis not due to CDI-related symptoms

# Study 2017-01: Bayesian Analysis Demonstrated Efficacy

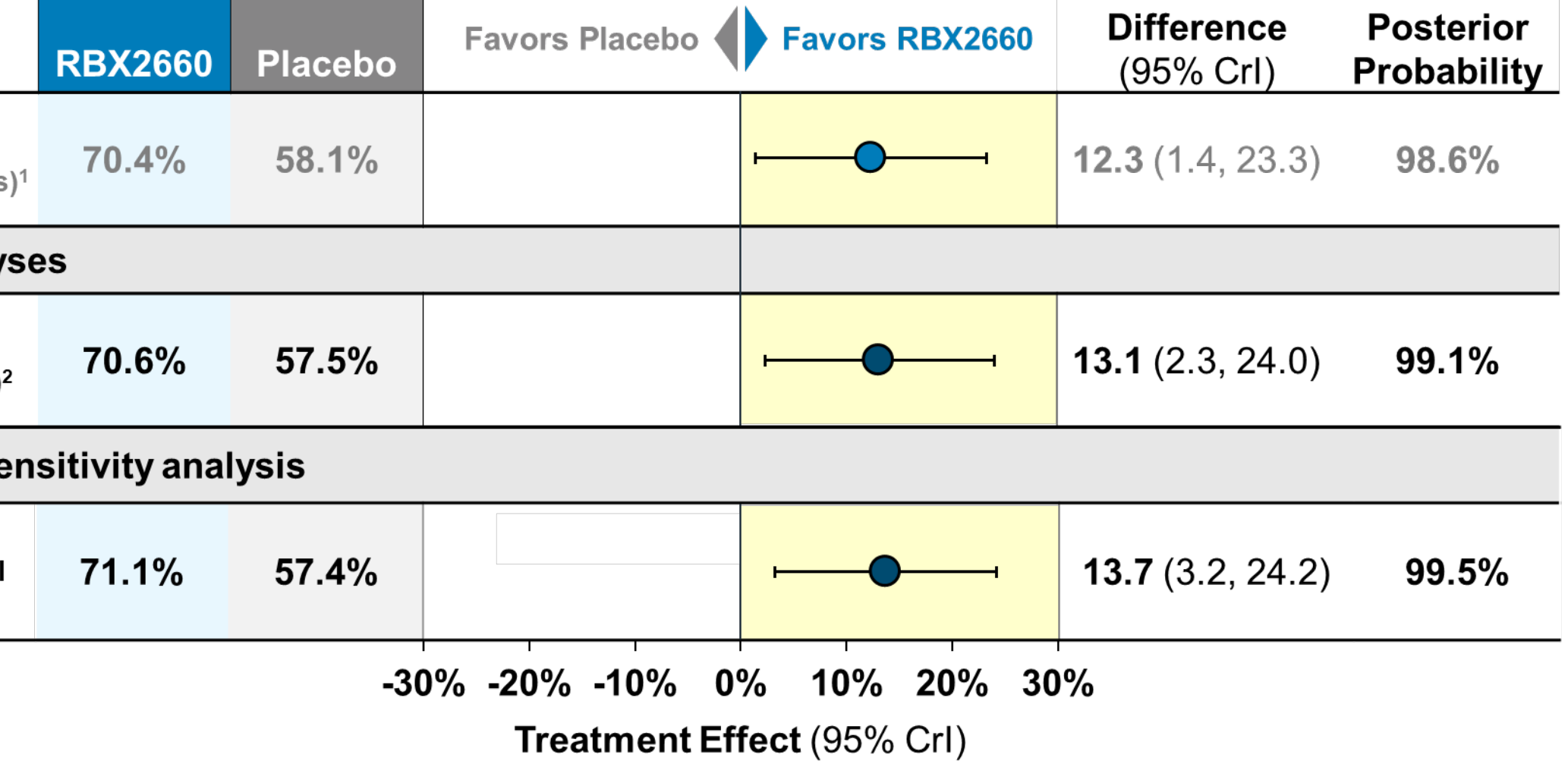
*2017-01 mITT Population and 2014-01 ITT Population*



# Study 2017-01: Primary Efficacy Analysis

*Bayesian Model*

| Population | RBX2660 | Placebo | Difference (95% CrI) | Posterior Probability |
|---|---|---|---|---|
| mITT (Initial primary analysis)[1] | 70.4% | 58.1% | **12.3** (1.4, 23.3) | 98.6% |
| **FDA-refined analyses** | | | | |
| **mITT (FDA primary analysis)[2]** | **70.6%** | **57.5%** | **13.1** (2.3, 24.0) | **99.1%** |
| **FDA-requested sensitivity analysis** | | | | |
| **mITT (Adjusted for prior CDI episodes)[2]** | **71.1%** | **57.4%** | **13.7** (3.2, 24.2) | **99.5%** |




1. Borrowed 2014 ITT to 2017 mITT;
2. Borrowed 2014 mITT to 2017 mITT, aligned analysis population definitions and endpoint assessment period

# Additional Information for Slide 40

### 3.3.1.1.1.2 Study 2017-01

### Analysis Populations

A sensitivity analysis of Treatment Success using the mITT, ITT, and PP analysis populations demonstrated that the Bayesian hierarchical model results were consistent across analysis populations (Table 11).

**Table 11 Posterior Estimates from the Bayesian Hierarchical Model (ITT, mITT, and PP Analysis Populations)**

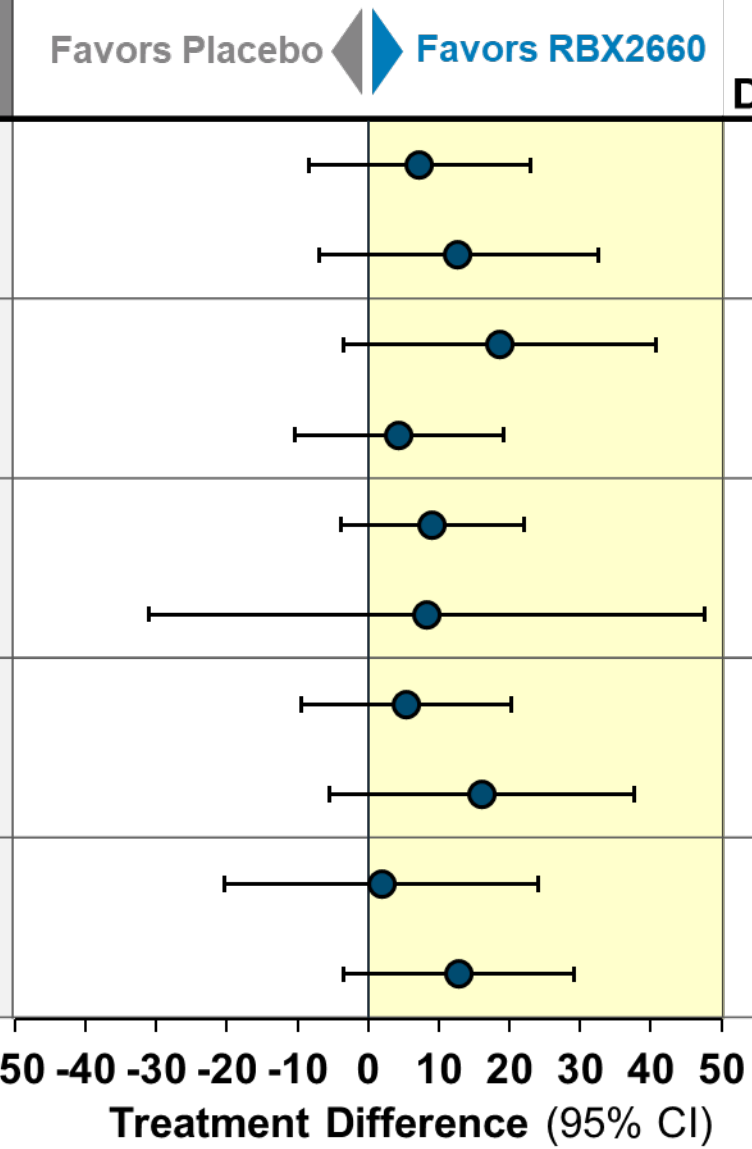
| Population<br>Statistic | RBX2660 (Blinded)<br>Success Rate | Placebo<br>Success Rate | Treatment Difference | Posterior Probability of Superiority |
|---|---|---|---|---|
| mITT | | | | |
| Mean (SD) | 0.704 (0.034) | 0.581 (0.051) | 0.123 (0.056) | 0.986 |
| 95% CI | 0.637, 0.768 | 0.484, 0.682 | 0.014, 0.233 | |
| ITT | | | | |
| Mean (SD) | 0.691 (0.033) | 0.567 (0.049) | 0.125 (0.056) | 0.987 |
| 95% CI | 0.625, 0.756 | 0.472, 0.665 | 0.016, 0.233 | |
| PP | | | | |
| Mean (SD) | 0.709 (0.034) | 0.572 (0.053) | 0.137 (0.058) | 0.991 |
| 95% CI | 0.640, 0.774 | 0.472, 0.677 | 0.024, 0.251 | |

CI = confidence interval; ITT = intent-to-treat; mITT = modified intent-to-treat; PP = per-protocol; SD = standard deviation.

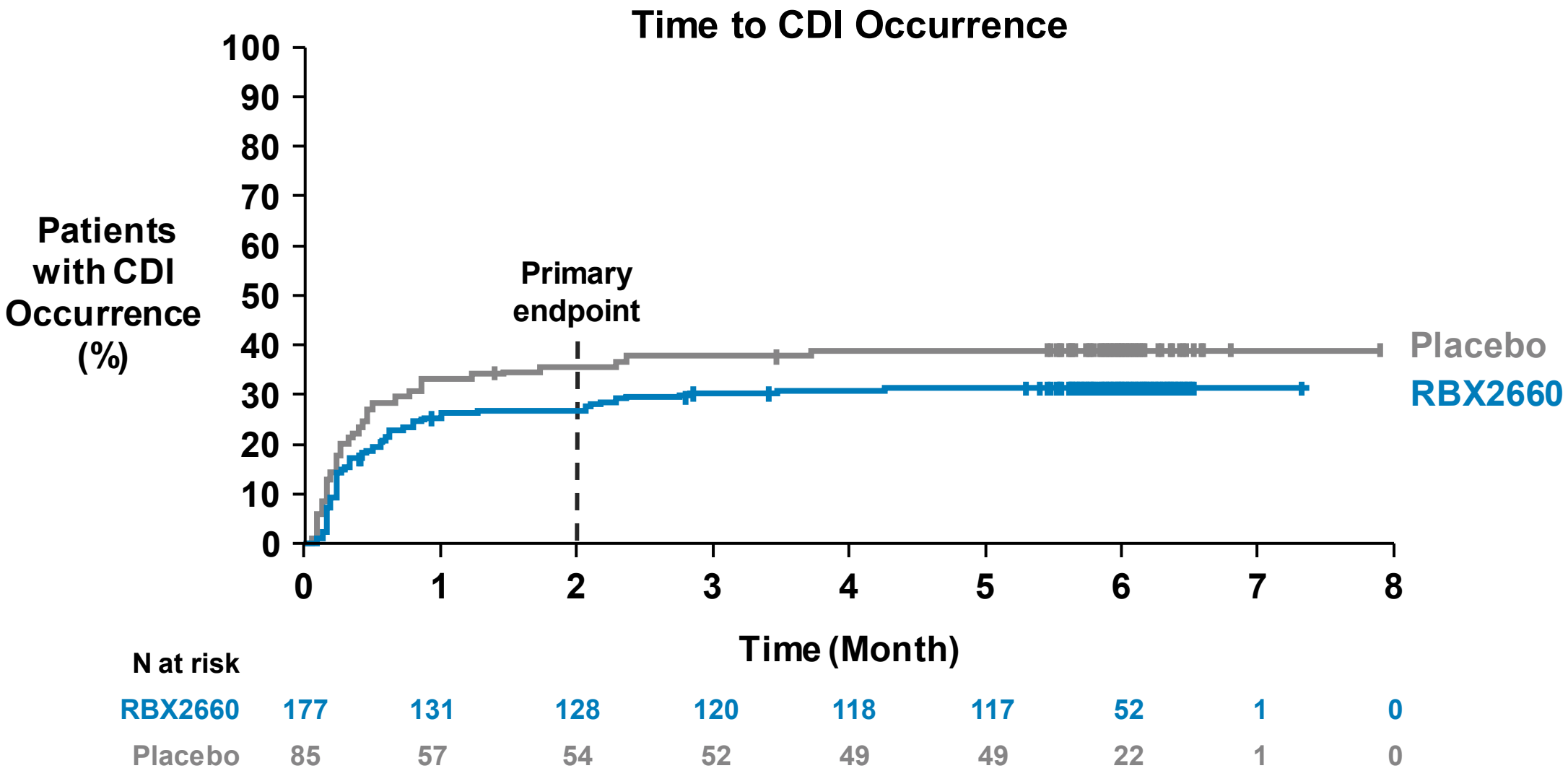
# Study 2017-01: Efficacy Consistent Across Subgroups

*Treatment Success at 8 Weeks (mITT)*

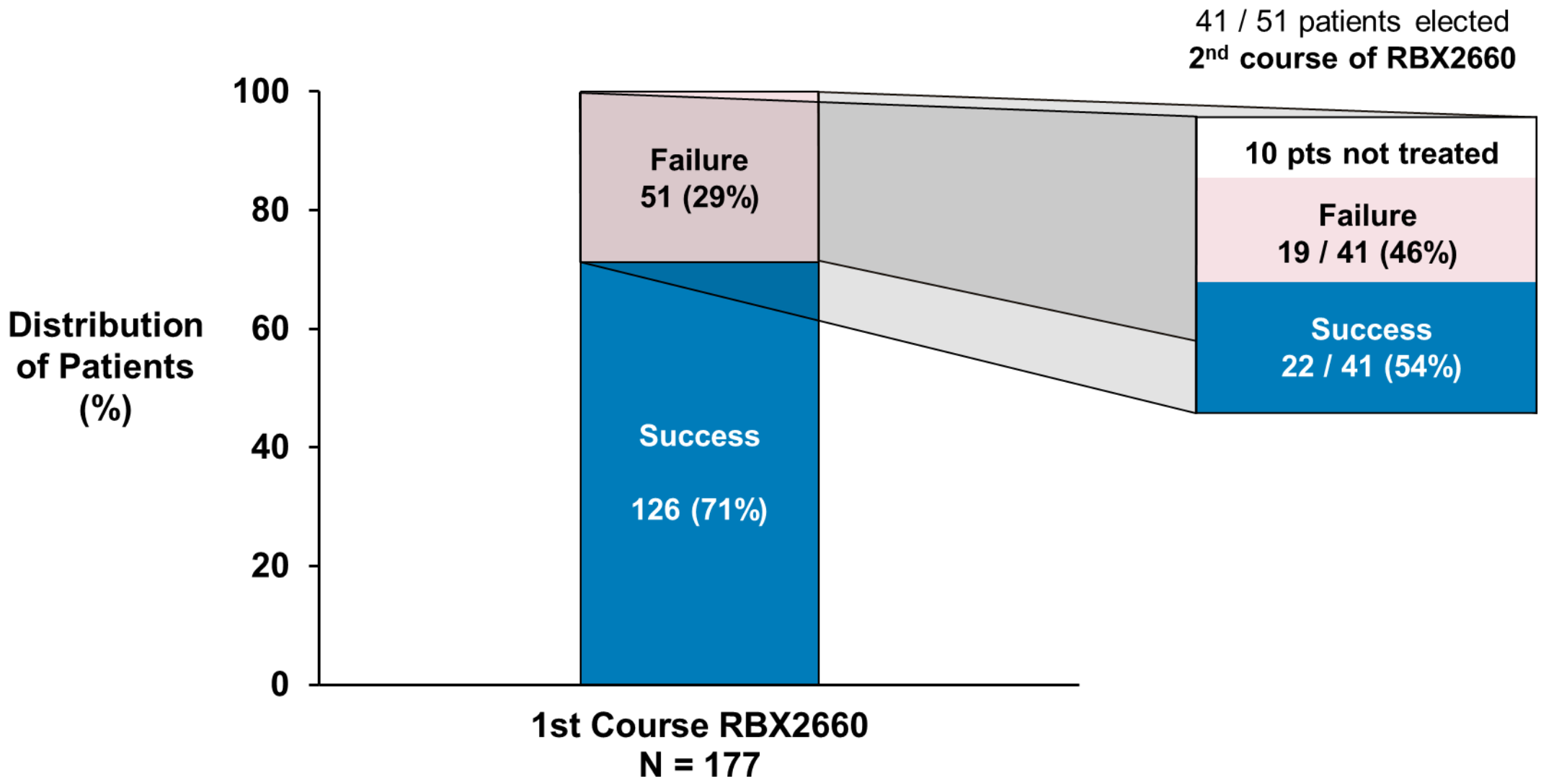
| Treatment Success Rate, % | | RBX2660 | Placebo | Difference (95% CI) |
|---|---|---|---|---|
| Age | < 65 years | 73.3 | 66.0 | **7.3** (-8.4, 23.0) |
| | ≥ 65 years | 69.0 | 56.3 | **12.7** (-7.0, 32.5) |
| Sex | Male | 76.4 | 57.7 | **18.7** (-3.4, 40.7) |
| | Female | 68.9 | 64.4 | **4.4** (-10.3, 19.2) |
| Race | White | 70.9 | 61.8 | **9.1** (-3.9, 22.0) |
| | Non-white | 75.0 | 66.7 | **8.3** (-31.0, 47.7) |
| Previous episodes of CDI | ≤ 3 | 72.1 | 66.7 | **5.4** (-9.4, 20.2) |
| | > 3 | 69.7 | 53.6 | **16.1** (-5.4, 37.7) |
| Duration of vancomycin use for qualifying CDI | ≤ 14 days | 71.1 | 69.2 | **1.9** (-20.3, 24.0) |
| | > 14 days | 68.8 | 56.0 | **12.8** (-3.5, 29.1) |



# Study 2017-01: Sustained Clinical Response Observed Through 6 Months (mITT)

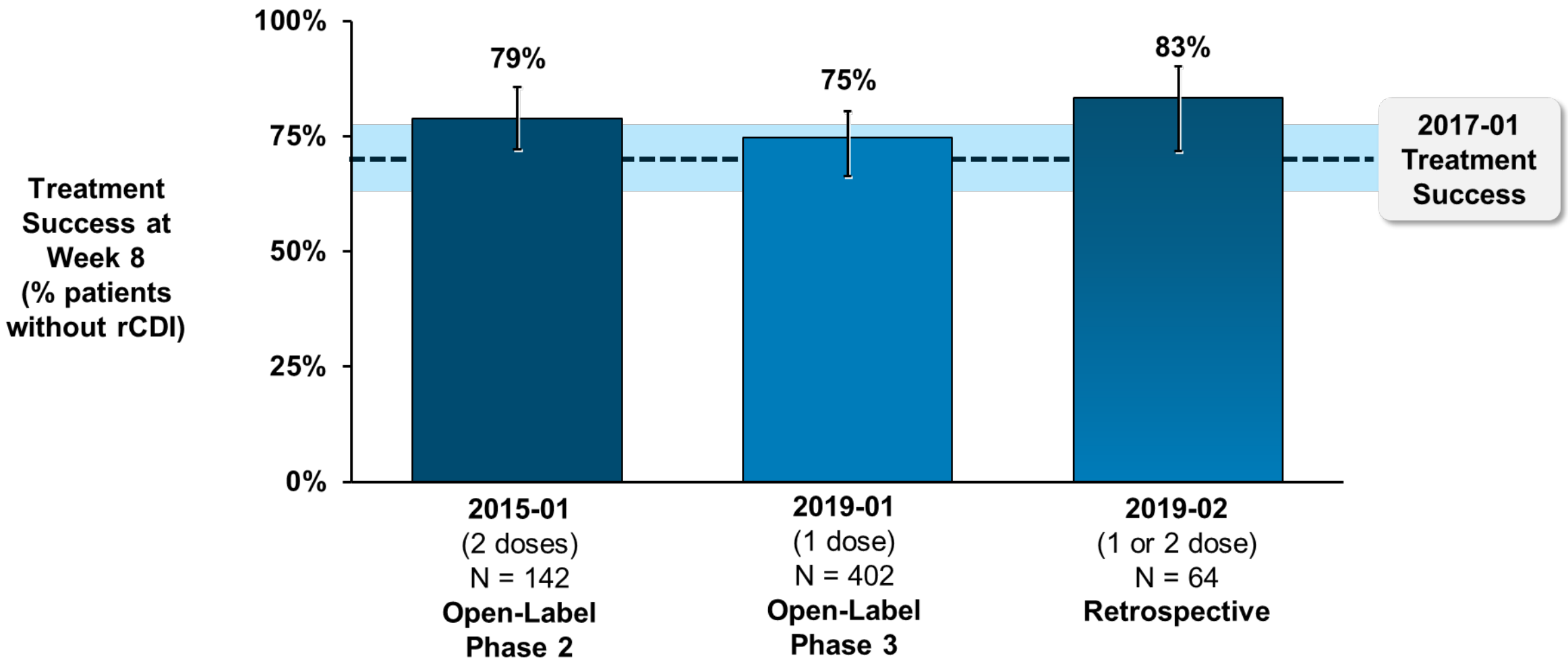


# Study 2017-01: Treatment Success After Second Course of RBX2660



# Evidence of RBX2660 Trials Demonstrating Consistent Treatment Success

*Open-Label, Nonrandomized*



# Evidence of Efficacy Supports RBX2660

- RBX2660 clinical evidence
  - Pivotal Study 2017 achieved statistical significance with 99.1% probability of superiority
  - Supported by consistently favorable results across clinical program
  - Serious, rare disease with orphan designation
- RBX2660 builds upon already used, unapproved FMT and provides larger well-controlled dataset
- RBX2660 standardized to provide consistent efficacy

# Safety

**Jonas Pettersson, MD, PhD**

Senior Medical Director

Ferring Pharmaceuticals

# Overall Safety Exposures

## Integrated Safety Population

| | | | | |
|---|---|---|---|---|
| N = 128 | Phase 2 (RCT) | **Study 2014-01*** (1 or 2 doses) | | |
| N = 267 | Pivotal Phase 3 (RCT) | **Study 2017-01** (1 dose) | | |
| N = 666 | Open-Label | **Study 2013-001** (1 or 2 doses) | **Study 2015-01*** (2 Doses) | **Study 2019-01** (1 dose) |
| N = 78 | Retrospective | **Study 2019-02** (1 or 2 doses) | | |

*Included 2 doses of Investigational Product within each course of treatment

# Study 2017-01 Safety Overview (8 Week Double-Blind Period)

*Treatment-Failures Censored at Time of CDI Recurrence*

| | Blinded RBX2660 N = 180 | Blinded Placebo N = 87 |
|---|---|---|
| AEs* | 48% | 39% |
| Mild | 22% | 15% |
| Moderate | 21% | 21% |
| Severe | 4% | 3% |
| Potentially life-threatening** | 1 (0.6%) | 0% |
| SAEs | 2% | 1% |
| AEs leading to discontinuation** | 1 (0.6%) | 0% |
| AEs leading to death** | 1 (0.6%) | 0% |

*AEs reported by maximum severity as assessed by investigator using CTCAE criteria
**Same patient represented in each category

# AEs in ≥ 5% of Patients (8 Week Double-Blind Period)

***Study 2017-01: Treatment- Failures Censored at Time of CDI Recurrence***

| System Organ Class<br>Preferred Term | Blinded RBX2660<br>N = 180 | Blinded Placebo<br>N = 87 |
|---|---|---|
| **AEs** | **48%** | **39%** |
| **Gastrointestinal disorder** | **29%** | **30%** |
| **Diarrhea** | **12%** | **13%** |
| **Abdominal pain** | **13%** | **10%** |
| **Nausea** | **8%** | **5%** |

- GI AEs typically occurred within first 7 days (median) after treatment
- GI AEs lasted median 2 days RBX2660, 4 days placebo

# SAEs Comparable Between Groups (8 Week Double-Blind Period)

*Study 2017-01: Treatment-Failures Censored at Time of CDI Recurrence*

| | Preferred Term | Blinded RBX2660 N = 180 | Blinded Placebo N = 87 |
|---|---|---|---|
| **SAEs** | | **4 (2%)** | **1 (1%)** |
| **Patient #1** | **Ileus** | **0.6%** | **0%** |
| | **Abdominal abscess** | **0.6%** | **0%** |
| **Patient #2** | **Asthenia** | **0.6%** | **0%** |
| | **Hand fracture** | **0.6%** | **0%** |
| **Patient #3** | **Abdominal pain** | **0.6%** | **0%** |
| **Patient #4** | **Cardio-respiratory arrest*** | **0.6%** | **0%** |
| **Patient #5** | **Cellulitis** | **0%** | **1%** |

*SAE leading to discontinuation and death

# Study 2017-01 Safety Overview (Through 6 Months)

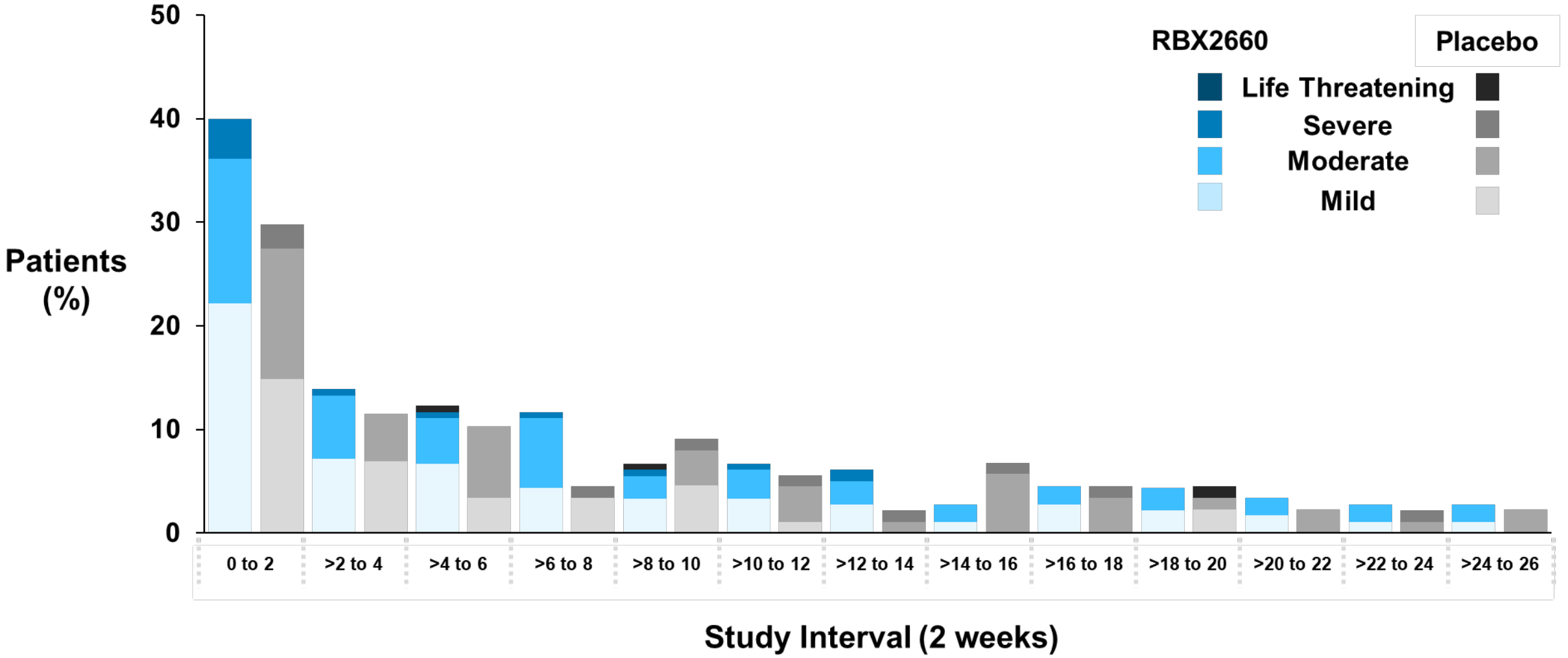
*Treatment-Failures Censored at Time of CDI Recurrence*

| | Blinded RBX2660 N = 180 | Blinded Placebo N = 87 |
|---|---|---|
| AEs* | 56% | 45% |
| Mild | 23% | 10% |
| Moderate | 26% | 29% |
| Severe | 6% | 6% |
| Potentially life-threatening** | 1 (0.6%) | 0% |
| SAEs | 4% | 2% |
| AEs leading to discontinuation** | 1 (0.6%) | 0% |
| AEs leading to death** | 1 (0.6%) | 0% |

*AEs reported by maximum severity as assessed by investigator using CTCAE criteria
**Same patient represented in each category

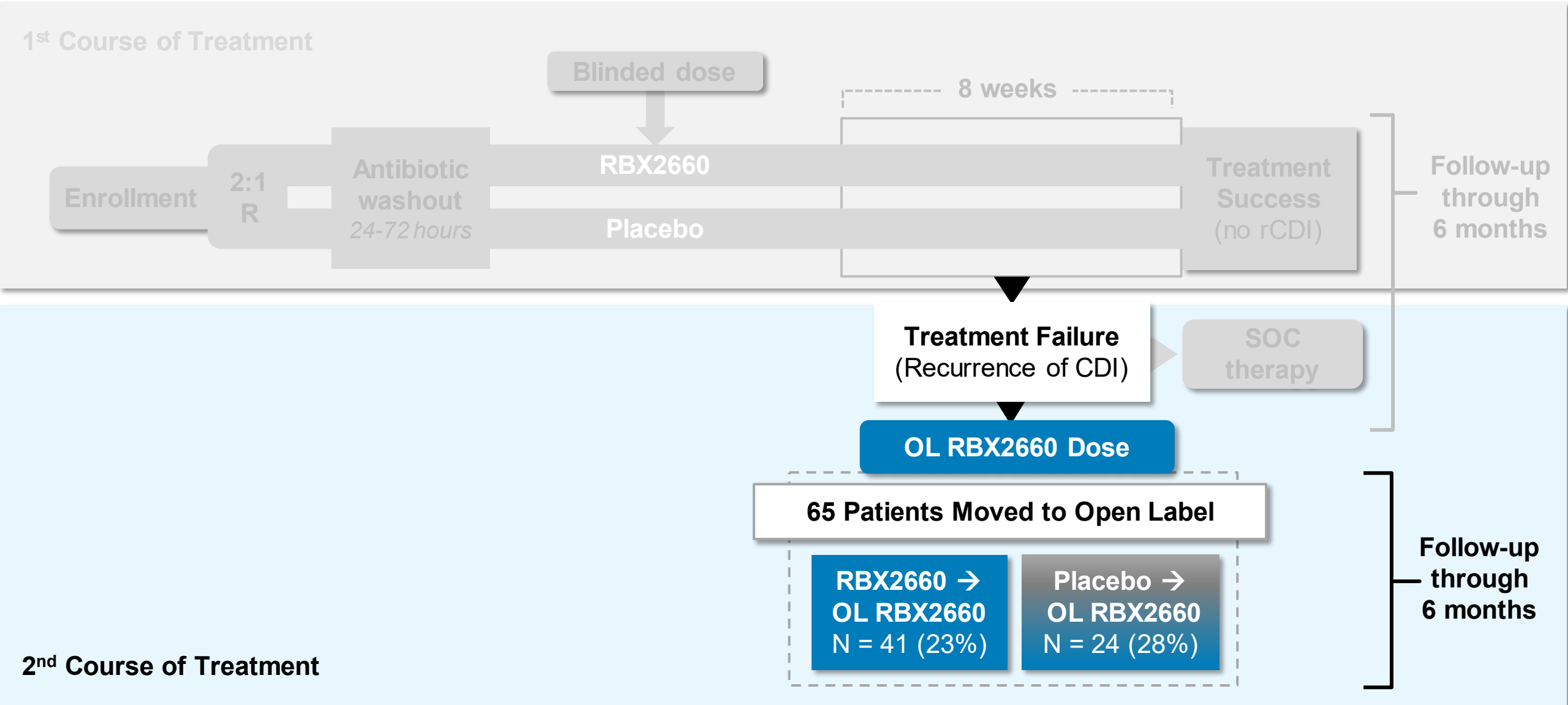
# Study 2017-01 (Through 6 Months): AEs Occur Early and Balanced Over Time

*Treatment-Failures Censored at CDI recurrence – AE Onset in Different Intervals*




Maximum severity per patient for each 2-week interval; patient may be represented > 1 interval

# Study 2017-01: Safety in Retreated Patients Through 6 Months



# Study 2017-01: Safety Overview Through 6 Months After Open-Label RBX2660 Treatment

| | Blinded RBX2660 → OL RBX2660 N = 41 | Placebo → OL RBX2660 N = 24 |
|---|---|---|
| AEs* | 59% | 58% |
| Mild | 20% | 25% |
| Moderate | 24% | 25% |
| Severe | 12% | 4% |
| Potentially life-threatening | 2% | 4% |
| SAEs | 12% | 4% |
| AE leading to discontinuation | 5% | 0 |
| AEs leading to deaths | 1 (2%) | 0 |

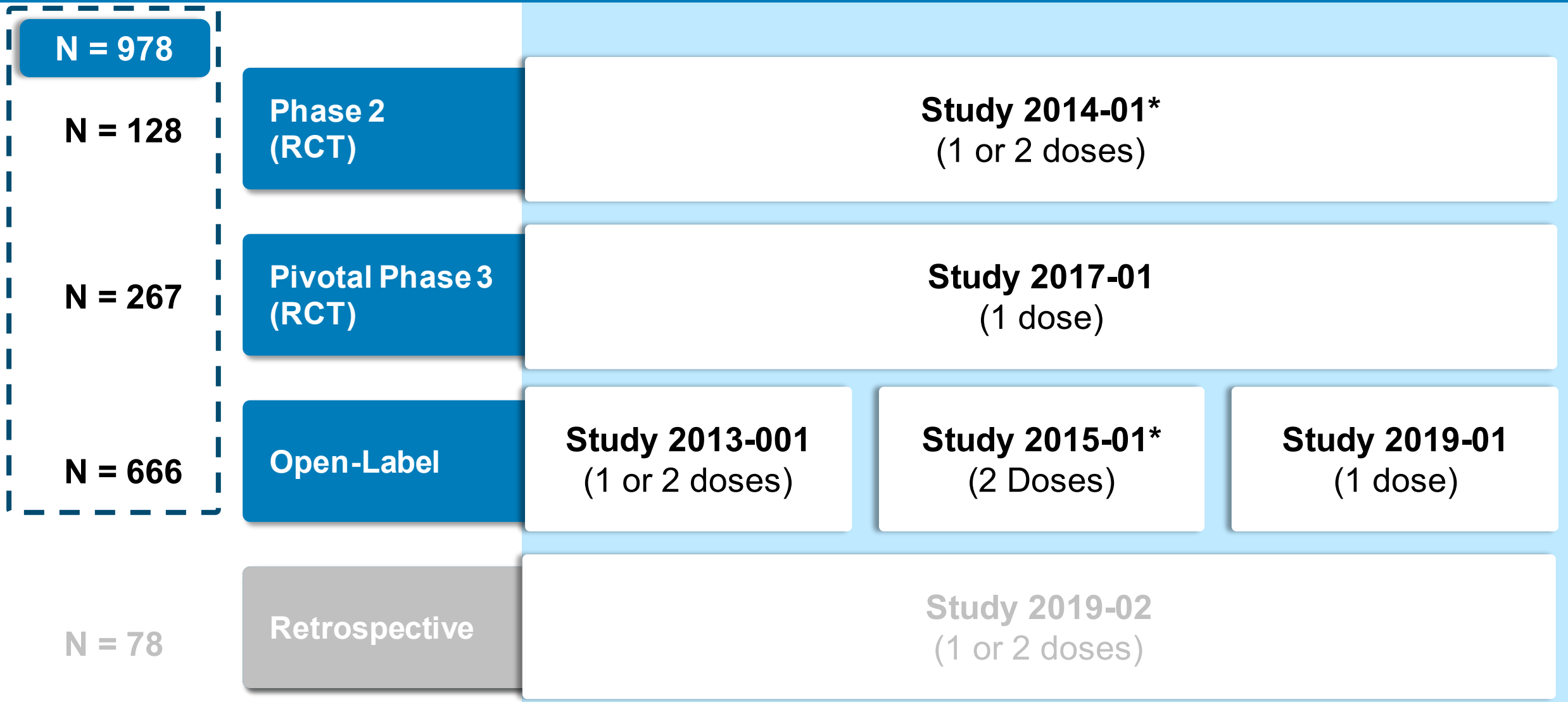
*AEs reported by maximum severity as assessed by investigator using CTCAE criteria

# Study 2017-01: Deaths Deemed Not Related to RBX2660 or Procedure by Investigator and DSMB

| Age / Sex | Treatment Details | Cause of Death (Day of Death from Last Dose) | Key Medical History / Comorbidities | Related to Study Drug (Y / N)* |
|---|---|---|---|---|
| **75 / M** | Blinded RBX2660 | Cardio-respiratory arrest (Day 37) | CABG x 4, hyperlipidemia, A-Fib, cerebrovascular accident, tachycardia, epilepsy, Parkinson's disease, dementia | N |
| **79 / F** | Blinded RBX2660 / OL RBX2660 | Multimorbidity (Day 151) | Congestive heart failure, hyperlipidemia, diabetes mellitus, chronic kidney disease, cerebrovascular disease, anemia, chronic urinary tract infections | N |

*Relatedness determined by Investigator, also DSMB reviewed

# Prospective Studies: RBX2660 Safety Exposures from Integrated Safety Population




*Included 2 doses of Investigational Product within each course of treatment

# Overall Safety Profile: Blinded ISS Through 6 Months (Study 2014-01 and 2017-01)

| | Blinded RBX2660 Only (1 or 2 doses) N = 193 | Blinded Placebo Only (1 or 2 doses) N = 83 |
|---|---|---|
| AEs* | 70% | 60% |
| Mild | 29% | 16% |
| Moderate | 28% | 35% |
| Severe | 10% | 8% |
| Potentially life-threatening | 3% | 1% |
| SAEs | 10% | 7% |
| AE leading to discontinuation** | 1 (0.5%) | 0 |
| AEs leading to deaths | 5 (3%) | 0 |

*AEs reported by maximum severity as assessed by investigator using CTCAE criteria
**AEs leading to discontinuation only collected in 2017-01, which includes deaths

# Overall Safety Profile: Integrated Safety Population

| Through 6 months post last dose | All RBX2660* (1 to 4 Doses) N = 978 | RBX2660 1 Dose Only N = 595 | Placebo Only N = 83 |
|---|---|---|---|
| **AEs**** | 69% | 64% | 60% |
| Mild | 23% | 21% | 16% |
| Moderate | 30% | 30% | 35% |
| Severe | 13% | 11% | 8% |
| Potentially life-threatening | 3% | 2% | 1% |
| **SAEs** | 14% | 10% | 7% |
| **AEs leading to discontinuation***** | 0.8% | 5 (0.8%) | 0% |
| **AEs leading to death** | 18 (1.8%) | 5 (0.8%) | 0% |

*Includes those who failed on placebo and crossed over to RBX
**AEs reported by maximum severity as assessed by investigator using CTCAE criteria
***AEs leading to discontinuation only collected in 2017-01 and 2019-01, which includes deaths

# AEs Leading to Death: Integrated Safety Population

| | All RBX2660* (1 to 4 Doses) N = 978 | Placebo Only N = 83 |
|---|---|---|
| **AEs occurring within 6 months leading to death** | **18 (1.8%)** | **0%** |
| **Observation time (patient-years)*** | **404** | **42** |
| *Observation time through 6 months (404 / 446 total time: 91% on RBX2660) | | |
| **Date of death (from last dose)** | | |
| **1 – 30 days** | **2** | **0** |
| **> 30 – 60 days** | **5** | **0** |
| **> 60 – 6 months** | **8** | **0** |
| **> 6 months – 2 years** | **3** | **0** |

- Broad diversity of causes, spanning across system organ classes

***Includes those who failed on placebo and crossed over to RBX**

# No Infection Transferred During Clinical Program; Rigorous Screening and Pharmacovigilance Will Continue to Mitigate Risks

| | |
|---|---|
| Screen | Screen donor and stool for pathogens |
| Standardize | Standardize manufacturing and administration |
| Adapt | Adapt screening processes for emerging pathogens |
| Follow-up | Follow-up pharmacovigilance surveillance |

# Safety Conclusion: RBX2660 is Well-Tolerated in Extensive Safety Dataset

- Favorable safety profile
- AEs mostly mild to moderate
  - Mostly gastrointestinal-related, as expected
- SAEs and deaths not plausibly related to RBX2660, most cases related to underlying CDI and comorbidities
- Rigorous donor screening program successfully mitigated risks
  - No infections transferred
  - Stringent controls will continue post-approval

# Clinical Perspective

**Colleen Kraft, MD, MSc, FIDSA**

Associate Chief Medical Officer

Professor, Pathology and Laboratory Medicine

Professor, Medicine/Division of Infectious Diseases

Emory University

# Unmet Need for Effective Treatment to Address Cycle of Recurrent CDI

**Treats the CDI but destroys natural gut microbiome**

CDI / rCDI

Vancomycin, fidaxomicin, with / without bezlotoxumab

**Restoration of microbiome reduces recurrence of infection**

FMT (unapproved)

RBX2660 (well tested, well-characterized)

# Clinically Meaningful Benefits of RBX2660

- Study 2017-01 results clinically meaningful
  - 71% treatment success with 1 course of treatment
    - NNT = 8
- Additional clinical study data supportive

# Practical Benefits of RBX2660

In office procedure

Delivered by enema

Simple pre-packaged, pre-mixed

Consistent, rigorous donor screening

Approval to provide greater access to those in need

**RBX2660**

# RBX2660 Safety in Context: Expected and Manageable Safety Profile for a Microbiota Restorative Treatment

- Safety aligns with expectations
  - Events mostly mild to moderate and manageable
  - Long-term safety appears unchanged
  - Safety of second course consistent to first, without accumulated risk
  - 30-day all-cause mortality
    - Background rate 1.3-9.3%[1]
- RBX2660 minimizes risk of transmissible pathogens

1. Johnson et al., 2021

# Treatment Considerations in Context

| | Efficacy and Safety Data | Benefit-Risk from Well-Controlled RCTs | Scalable Product | GMP / Standardized Process | Evolving Screening and Safety Surveillance |
|---|---|---|---|---|---|
| RBX2660 | ✓ | ✓ | ✓ | ✓ | ✓ |
| FMT | ✓ | ✗ | ✗ | ✗ | ✗ |

# RBX2660: Positive Benefit-Risk Profile

- Pivotal prospective data outcomes that align with goal of treatment - to prevent recurrent infection
- Acceptable safety profile with strict donor screening
- Approval of RBX2660, an important step towards meeting unmet medical need of our patients

# RBX2660 for Reduction of Recurrence of *Clostridioides difficile* Infection

**September 22, 2022**

Rebiotix Inc., a Ferring Company

Vaccines and Related Biological Products Advisory Committee