U.S. FOOD & DRUG ADMINISTRATION

Vaccines and Related Biological Products Advisory Committee Meeting

FDA Review of Effectiveness and Safety Fecal Microbiota, Live (RBX2660)

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Outline

- **Overview of Clinical Studies**
- Effectiveness
- Safety
- Summary

Overview of Clinical Studies

Clinical Studies	Phase	RBX2660 Recipients	Placebo Recipients
2013-001: Efficacy and Safety, **Open-label**	2	34	N/A
2014-01: Efficacy and Safety, **Double-blinded**	2	108	20
2015-01: Efficacy and Safety, **Open-label**	2	149	Historical control used
2019-01:[a] Safety and Tolerability, **Open-label**	3	254	N/A
2017-01: Efficacy and Safety, **Double-blinded**	3	204	63
2019-02: Safety and Tolerability, **Retrospective** (RBX2660 under Enforcement Discretion)	N/A	94	N/A

[a]Additional safety update on 229 subjects exposed to ≥1 dose from study 2019-01 provided after initial BLA submission.

RBX2660: Double-Blinded Placebo-Controlled Studies

Study Design Feature	2014-01 (Phase 2)	2017-01 (Phase 3)
Treatment groups	Group A: 2 doses of RBX2660 Group B: 2 doses of placebo Group C: 1 dose of RBX2660/1 dose of placebo	1 dose of RBX2660 1 dose of placebo
Number of RBX2660 doses	1–2 (blinded) Up to 2 additional open-label doses	1 (blinded) Up to 1 additional open-label dose
Number of previous CDIs, including qualifying events	≥2 recurrences and ≥2 rounds of SOC oral antibiotic therapy or ≥2 severe CDI resulting in hospitalization	≥1 recurrence and ≥1 round of SOC oral antibiotic therapy or ≥2 severe CDI resulting in hospitalization
Dosage regimen	2 enemas, given 7±2 days apart	1 enema
Safety follow-up (months)	24	6

CDI, *Clostridioides difficile* infection; SOC, standard of care.

RBX2660: Open-Label Studies

Study	2013-001 (Phase 2)	2015-01 (Phase 2)	2019-01 (Phase 3)
Study Design	Open-label, uncontrolled	Open-label, historical control	Open-label, uncontrolled
Treatment received	1 dose of RBX2660	2 doses of RBX2660	1 dose of RBX2660
Number of RBX2660 doses	1–2	1–2	1–2
Optional second treatment course	Yes	No	Yes
Number of previous CDIs, including qualifying events	≥2 recurrences after a primary episode OR ≥2 severe CDAD resulting in hospitalization	≥2 recurrences after a primary episode OR ≥2 severe CDI resulting in hospitalization	rCDI not defined, relied on investigator opinion
Safety follow-up (months)	6	24	6

2019-02 is a retrospective safety and tolerability study of RBX2660 administration for prevention of recurrent CDI (rCDI) in subjects who received RBX2660 under enforcement discretion

CDAD, *Clostridioides difficile*-associated diarrhea; CDI, *Clostridioides difficile* infection; rCDI, recurrent *Clostridioides difficile* infection.

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Phase 2 Study 2014-01

- **Primary objective:** To assess the efficacy and safety of RBX2660 for the prevention of recurrent *Clostridioides difficile* infection (rCDI)

- **Study population:** ≥2 recurrences after a primary episode and had completed ≥2 rounds of SOC oral antibiotic therapy

- **Study groups:** Subjects were randomized 1:1:1 to one of the following groups:
  - **Group A**: 2 enemas of RBX2660
  - **Group B**: 2 enemas of placebo
  - **Group C**: 1 enema of RBX2660 and 1 enema of placebo

Study 2014-01: Efficacy Endpoint Analyses

- **Efficacy endpoint:** Treatment success, defined as the absence of *C. difficile*-associated diarrhea without need for retreatment with *C. difficile* anti-infective therapy or fecal transplant at 56 days after administration of the last assigned study enema

  - Primary: Group A (2 enemas of RBX2660) vs. Group B (2 enemas placebo)
  - Secondary: Group C (1 enema RBX2660 + 1 enema placebo) vs. Group B
  - Secondary: Group A vs. Group C

Study 2014-01: Efficacy Results

Analysis Parameter	ITT 2 Dose RBX2660 N=45	ITT 1 Dose RBX2660 N=44	ITT 2 Dose Placebo N=44	mITT 2 Dose RBX2660 N=40	mITT 1 Dose RBX2660 N=38	mITT 2 Dose Placebo N=43
Treatment success, n (%)	25 (55.6)	25 (56.8)	19 (43.2)	25 (62.5)	25 (65.8)	19 (44.2)
Difference (vs. placebo), % (95% CI)	12.4 (-8.2, 33.0)	13.6 (-7.1, 34.3)	--	18.3 (-2.8, 39.4)	21.6 (0.4, 42.8)	--
p-value	0.243	0.201	--	0.095	0.051	--

ITT, intention-to-treat; mITT, modified intention-to-treat.

Demonstration of Effectiveness: Approach

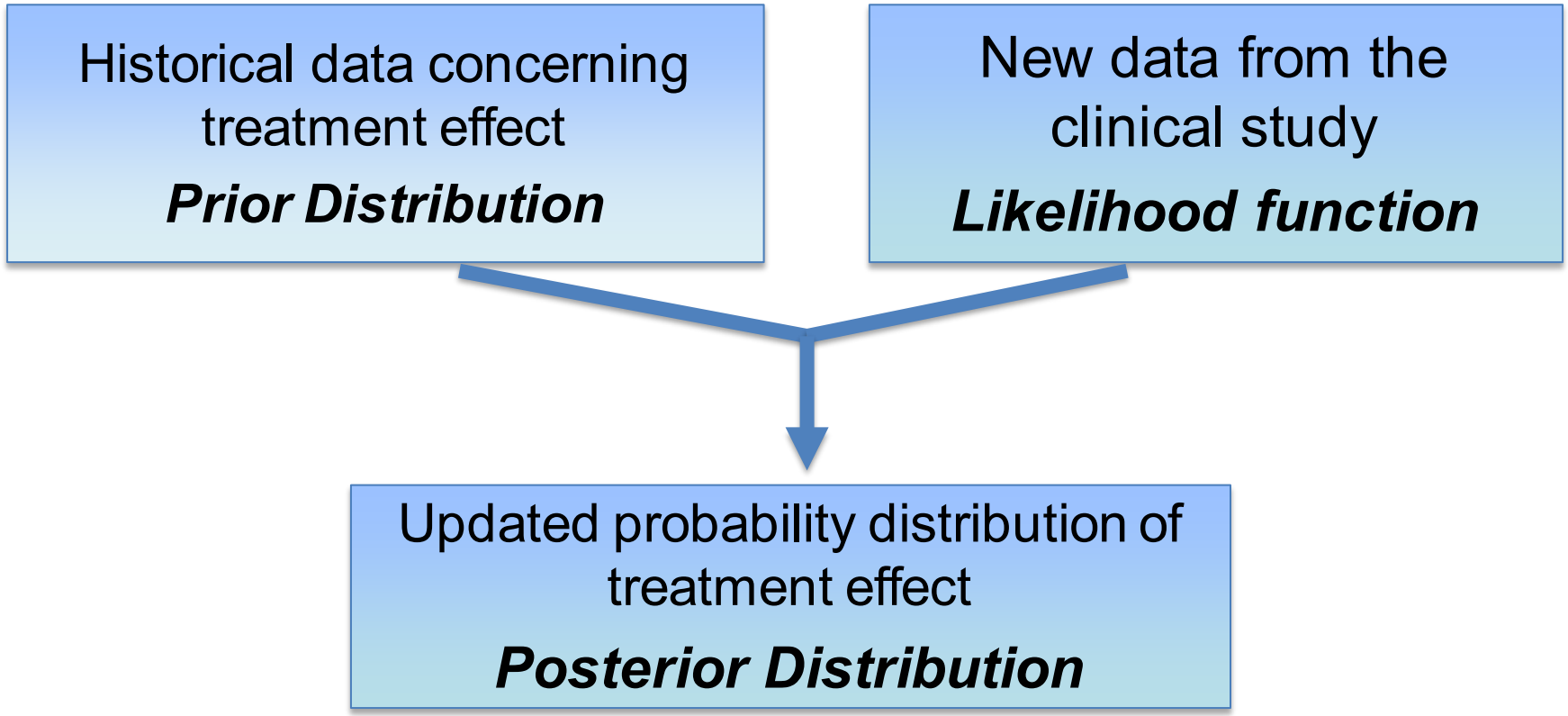
- Because Study 2014-01 did not demonstrate definitive evidence of effectiveness for a single dose of RBX2660, Rebiotix initially planned **two independent Phase 3 studies** to provide substantial evidence of effectiveness
  - Planned sample size ~300 subjects/each study, total ~600 subjects for two studies
- Study 2017-01 was one of the two planned Phase 3 studies
  - **Primary Efficacy Objective:** To confirm efficacy of RBX2660 compared to placebo in preventing recurrent episodes of CDI through 8 weeks
  - **Secondary Efficacy Objective**: To evaluate the sustained clinical response rate of RBX2660 as compared to placebo after blinded treatment
- In consideration of recruitment difficulties, CBER and Rebiotix agreed to modify the design of Study 2017-01 to a Bayesian adaptive study with data borrowing from Study 2014-01

Primary Efficacy Endpoint Analysis

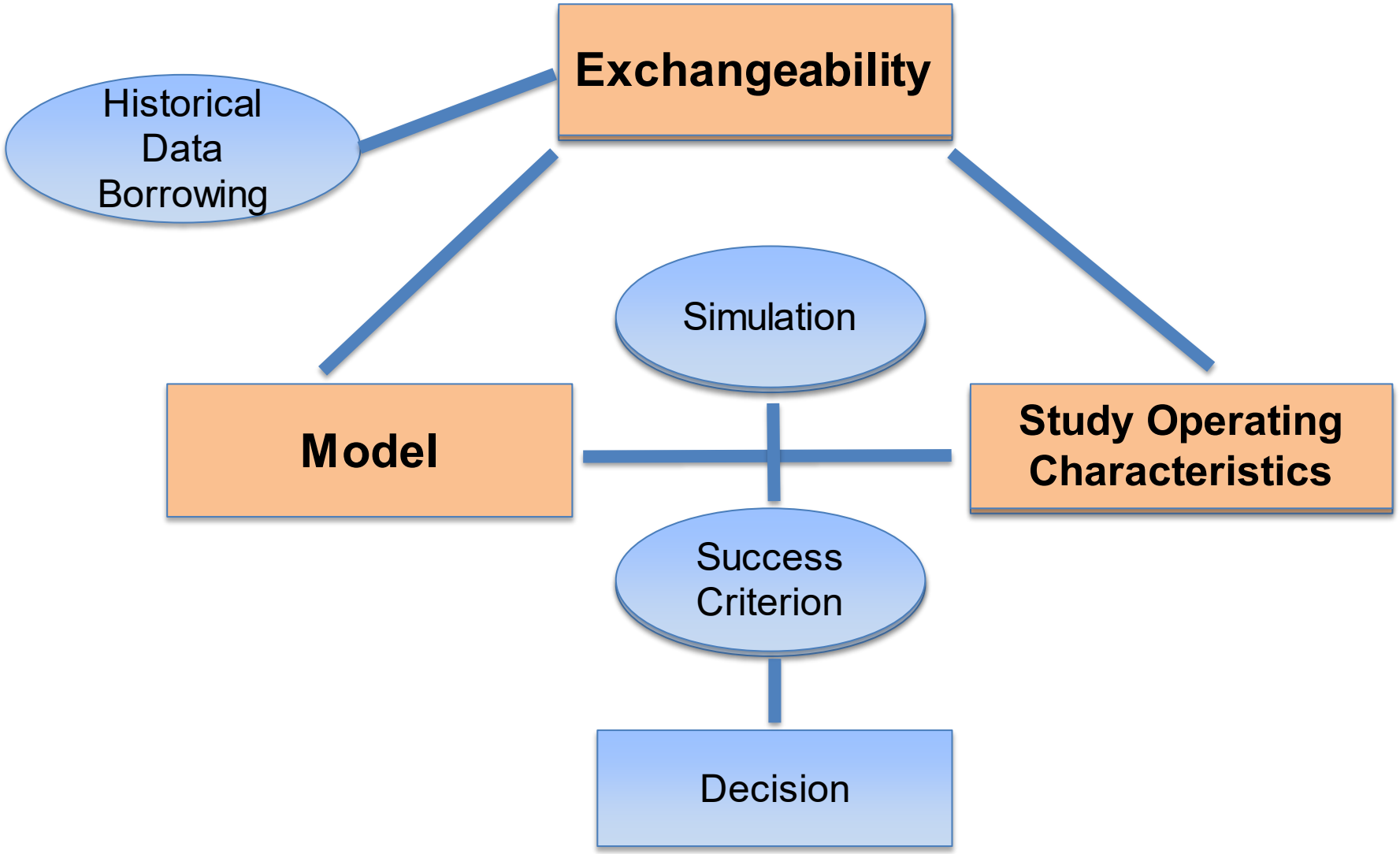
- **Treatment success**: The absence of CDI diarrhea through 8 weeks after the blinded study treatment
- **Study population**: ≥1 recurrence of CDI and ≥1 round of SOC oral antibiotic therapy for enrollment
- **Analysis population definitions**:
  - **Intention-to-Treat Population (ITT):** All randomized patients, analyzed as randomized, excluding subjects who exited prior to receiving blinded treatment
  - **Modified Intention-to-Treat Population (mITT):** ITT population, excluding subjects in whom treatment was attempted but not completed and subjects who discontinued from the study prior to evaluation of treatment failure or success if the reason for exit was not related to CDI symptoms
- **Analysis method:** Bayesian hierarchical model formally integrating treatment success rates from study 2014-01 into study 2017-01

Bayesian Approach Overview

The Bayesian approach synthesizes prior information with new information to update knowledge about treatment effect

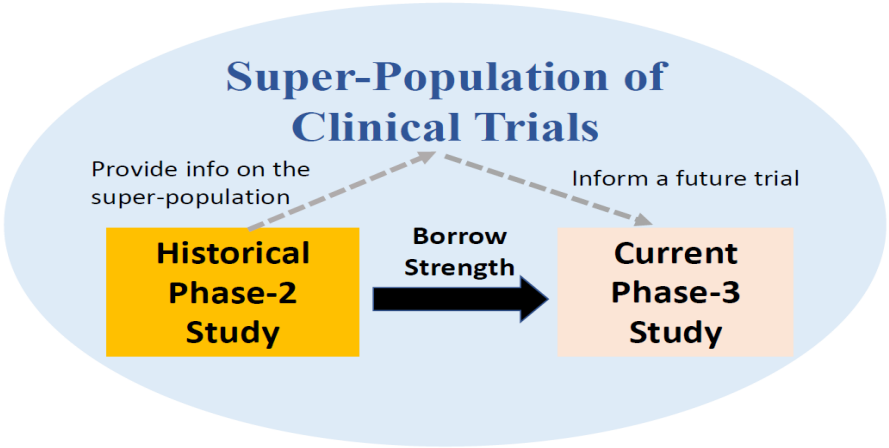


Process for Bayesian Study Design



Exchangeability of Studies

- Clinical outcomes in future studies tend to be similar to those in previous studies
- Exchangeable studies can be thought of as a representative sample of some ***super-population of clinical studies***



- Enables the current study to "***borrow strength***" from the previous study
- Acknowledge that the studies are ***not identical*** in all aspects
  - Bayesian hierarchical model
  - Dynamic borrowing: borrowing strength dependent on the similarity of effect of interest between historical and target studies

Bayesian Design of Study 2017-01

Exchangeability considerations:
- **Same product in dosage, route, and formulation (for a single dose)**
- **Generally similar in study design and study population**

Historical Data Borrowing: Phase 2 study 2014-01 (group C and B)

Bayesian hierarchical model

Phase 3 study 2017-01

Posterior prob threshold for success: 0.99943

Posterior prob threshold for success: 0.99943

Final posterior prob threshold for success: 1st: 0.99933 2nd: 0.97503

Recruitment difficulties / Bayesian design with historical data borrowing

Interim analysis **1** Planned: 160 Actual: 178

Interim analysis **2** Planned: 220 Actual: 214

Final analysis Planned: 270 Actual: 262

Study Success Criteria

- The statistical evidence for the treatment effect was evaluated based on the posterior probability of superiority for the RBX2660 group vs. the placebo group
- The success thresholds were selected as analogues to frequentist one-sided type 1 error rates of 0.00125 and 0.025 without borrowing, utilizing the Bayesian posterior probabilities of superiority.

Evaluation	Regulatory Implication	Type-I Error Control	Success Threshold
First (higher) study success threshold	**Statistical evidence that could potentially substitute for two adequate and well-controlled Phase 3 studies**	0.00125 (one-sided)	0.99933
Second study success threshold	**Evidence to declare success of the Phase 3 study 2017-01**	0.025 (one-sided)	0.97503

Further Considerations in Borrowing Study 2014-01 Data in Study 2017-01 Primary Efficacy Analysis

- Two studies were generally similar
- Some differences between the two studies
  - Analysis population definitions
  - Treatment success definition
  - Primary endpoint assessment period
- Refined analysis aligning above elements between studies
  - Improve exchangeability between Studies 2014-01 and 2017-01
  - Provide more interpretable information for regulatory decision making,

Study 2014-01 Data after Alignment to Study 2017-01 Definitions

Analysis Parameter	mITT Group C 1-Dose RBX2660 1-Dose Placebo	mITT Group B 2-Dose Placebo	ITT Group C 1-Dose RBX2660 1-Dose Placebo	ITT Group B 2-Dose Placebo
Number of subjects, (N)	39	43	43	44
Treatment success, n (%)	25 (64.1)	19 (44.2)	25 (58.1)	19 (43.2)

ITT, intention-to-treat; mITT, modified intention-to-treat.

Efficacy Data from Study 2017-01 Only

Analysis Parameter	mITT Placebo N=85 n (%)	mITT RBX2660 N=177 n (%)	ITT Placebo N=87 n (%)	ITT RBX2660 N=180 n (%)
Treatment success	53 (62.4)	126 (71.2)	53 (60.9)	126 (70.0)
Treatment failure	32 (37.6)	49 (27.7)	32 (36.8)	49 (27.2)
Indeterminate	0 (0.0)	2 (1.1)	2 (2.3)	5 (2.8)
Imputed as failures[a]	0 (0.0)	2 (1.1)	0 (0.0)	2 (1.1)

ITT, intention-to-treat; mITT, modified intention-to-treat.

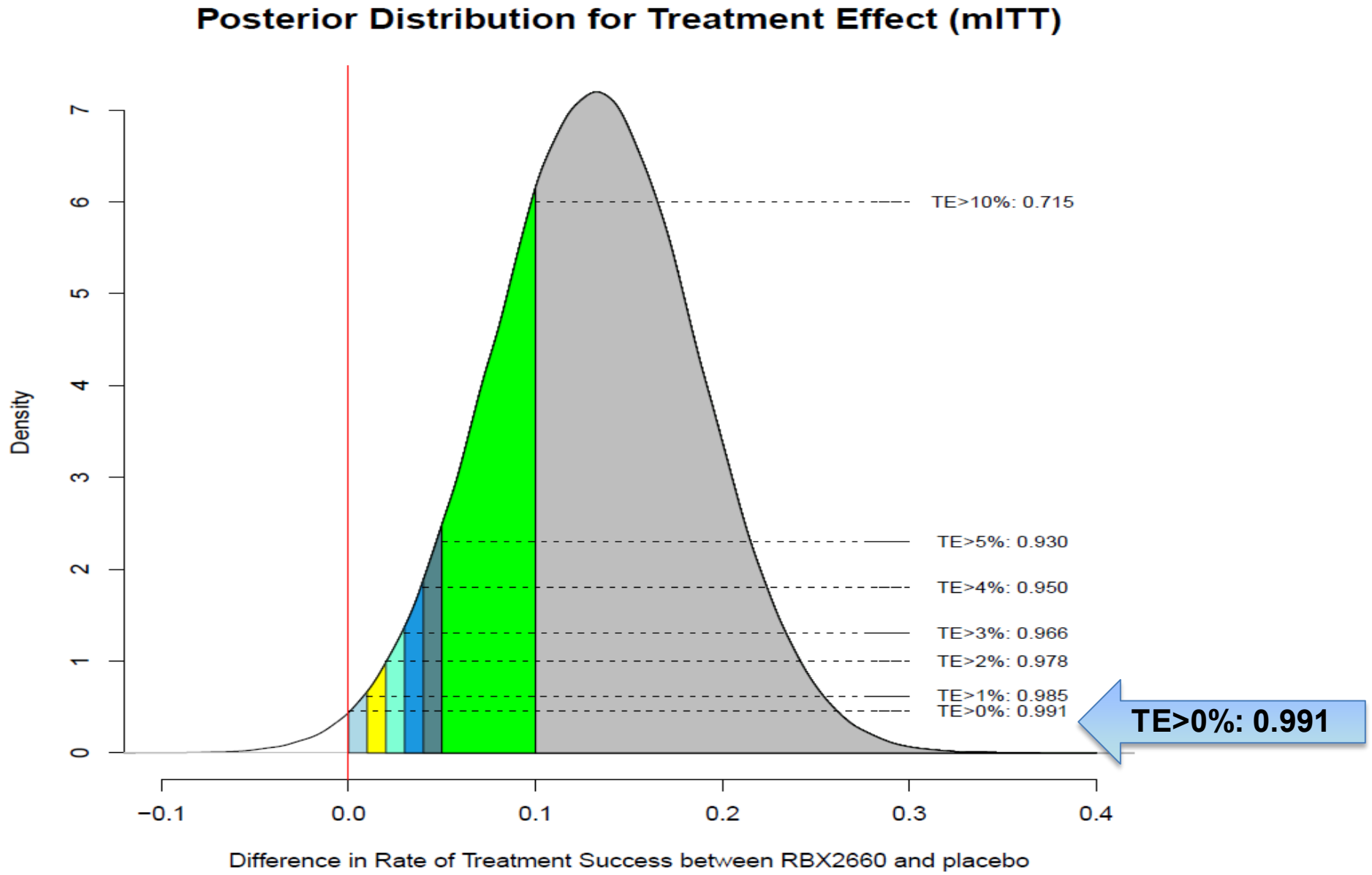
[a]Subjects that exited the study prior to 8 weeks due to CDI-related symptoms are imputed as failure

Posterior Estimates from the Bayesian Hierarchical Model (mITT and ITT)

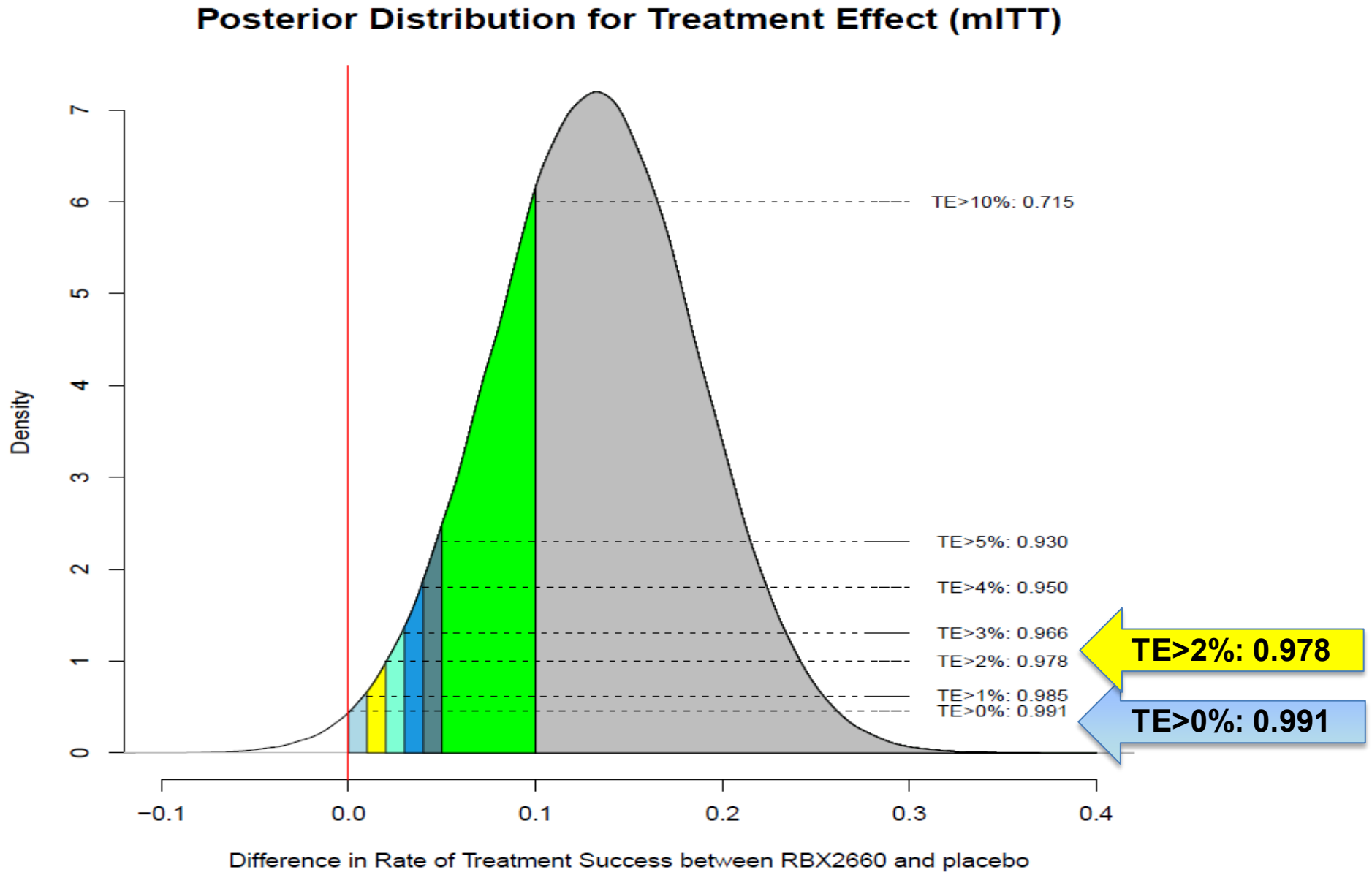
Population	Placebo Success Rate (%)	RBX2660 Success Rate (%)	Treatment Effect (%) (95% Credible Interval)	Posterior Probability	Met the first threshold (0.9993)?	Met the second threshold (0.9750)?
mITT	57.5	70.6	13.1 (2.3, 24.0)	0.991	**No**	**Yes**
ITT	56.9	69.1	12.2 (1.4, 23.0)	0.986	**No**	**Yes**

ITT, intention-to-treat; mITT, modified intention-to-treat.

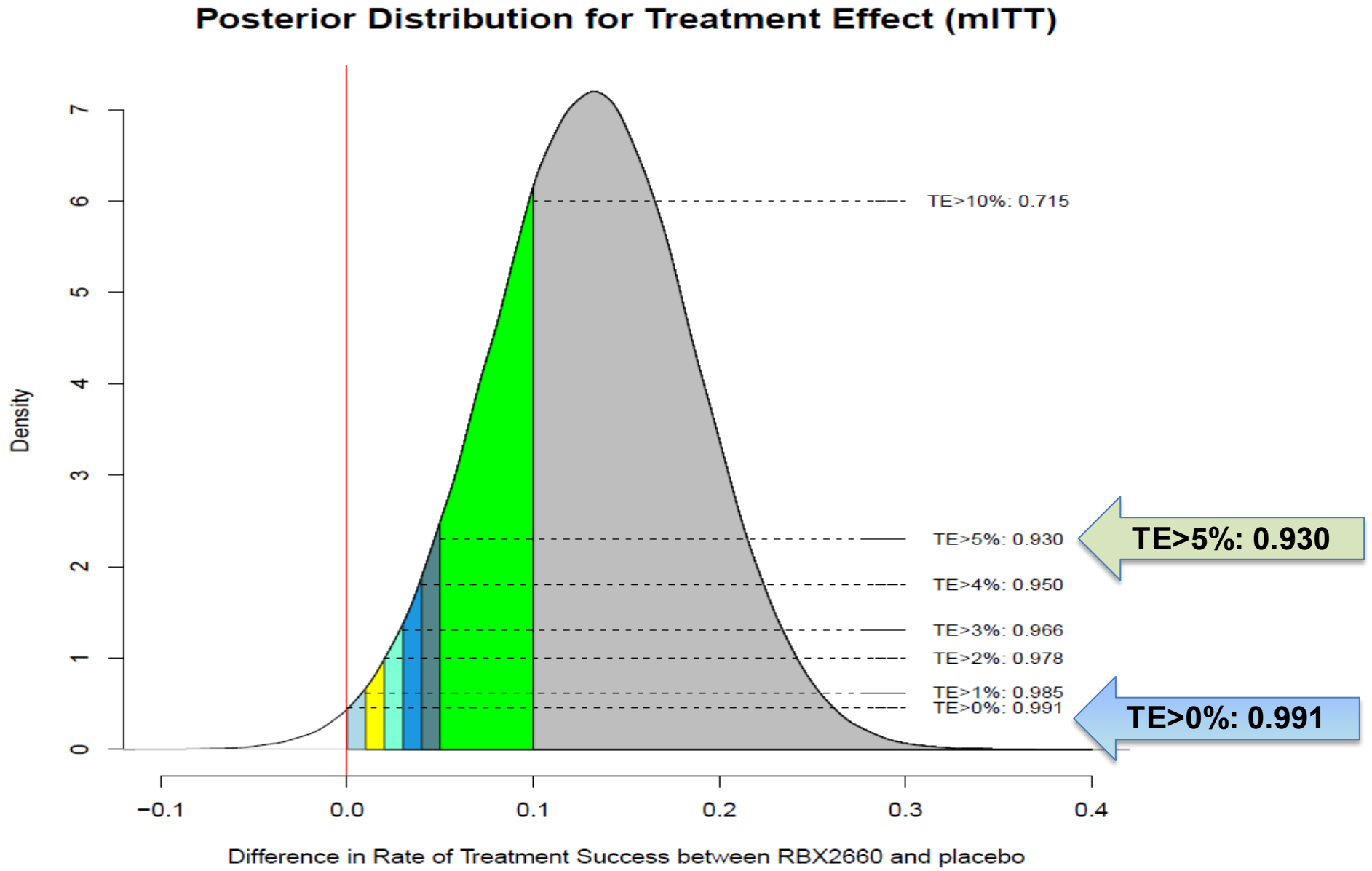
Posterior Probability for Different Treatment Effect Levels



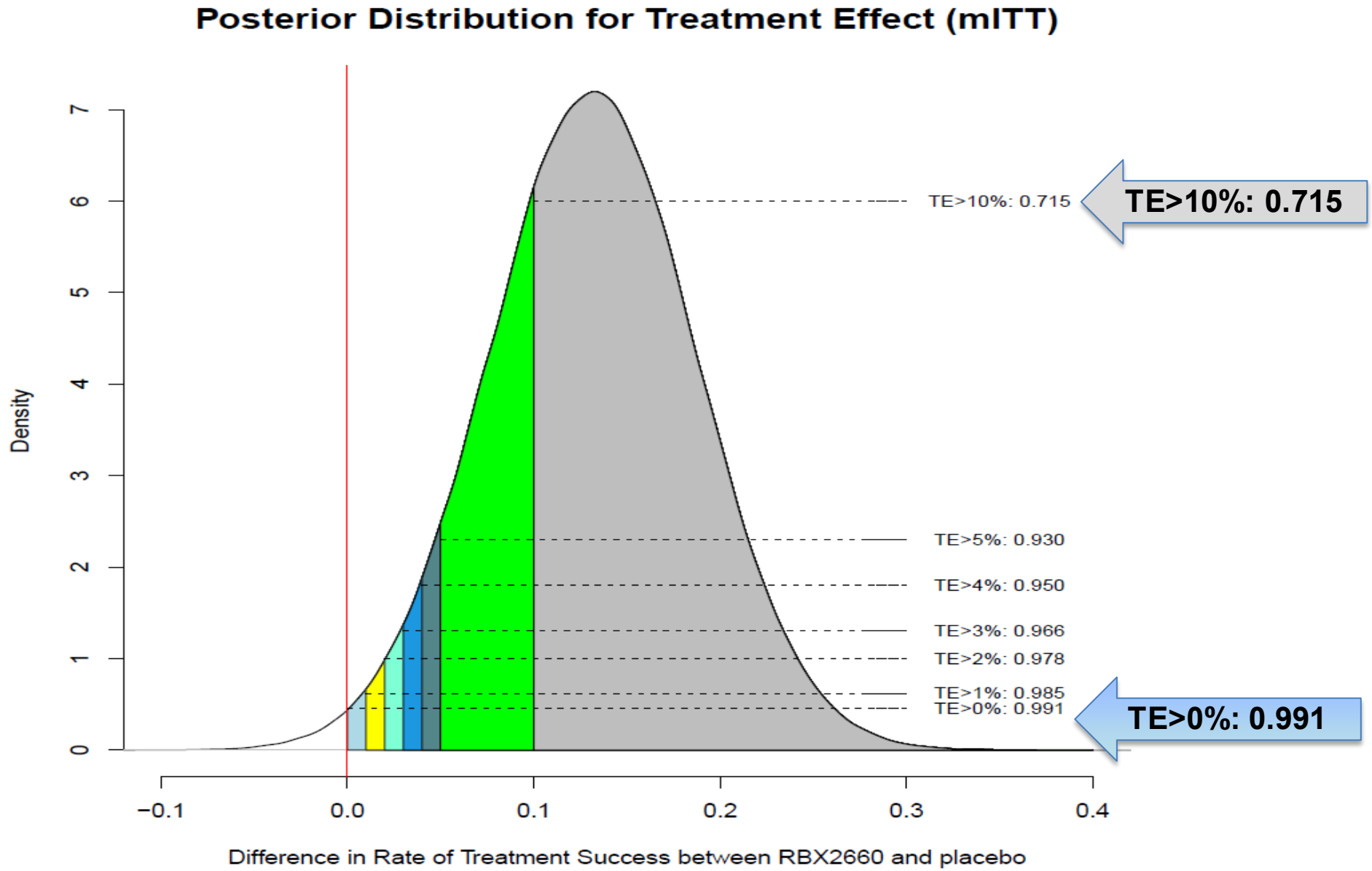
Posterior Probability for Different Treatment Effect Levels



Posterior Probability for Different Treatment Effect Levels



Posterior Probability for Different Treatment Effect Levels



Applicant's Initial Analysis: Primary Efficacy Endpoint

- The Applicant used non-final ITT data from Study 2014-01 as historical data because these data were used for evaluation of study operating characteristics at the design stage
- The analyses led to the same conclusion for efficacy

Population	Placebo Success Rate (%)	RBX2660 Success Rate (%)	Treatment Effect (%) (95% Credible Interval)	Posterior Probability	Met the first threshold (0.9993)?	Met the second threshold (0.9750)?
mITT	58.1	70.4	12.3 (1.4, 23.3)	**0.986**	**No**	**Yes**
ITT	56.7	69.1	12.5 (1.6, 23.3)	**0.987**	**No**	**Yes**

ITT, intention-to-treat; mITT, modified intention-to-treat.

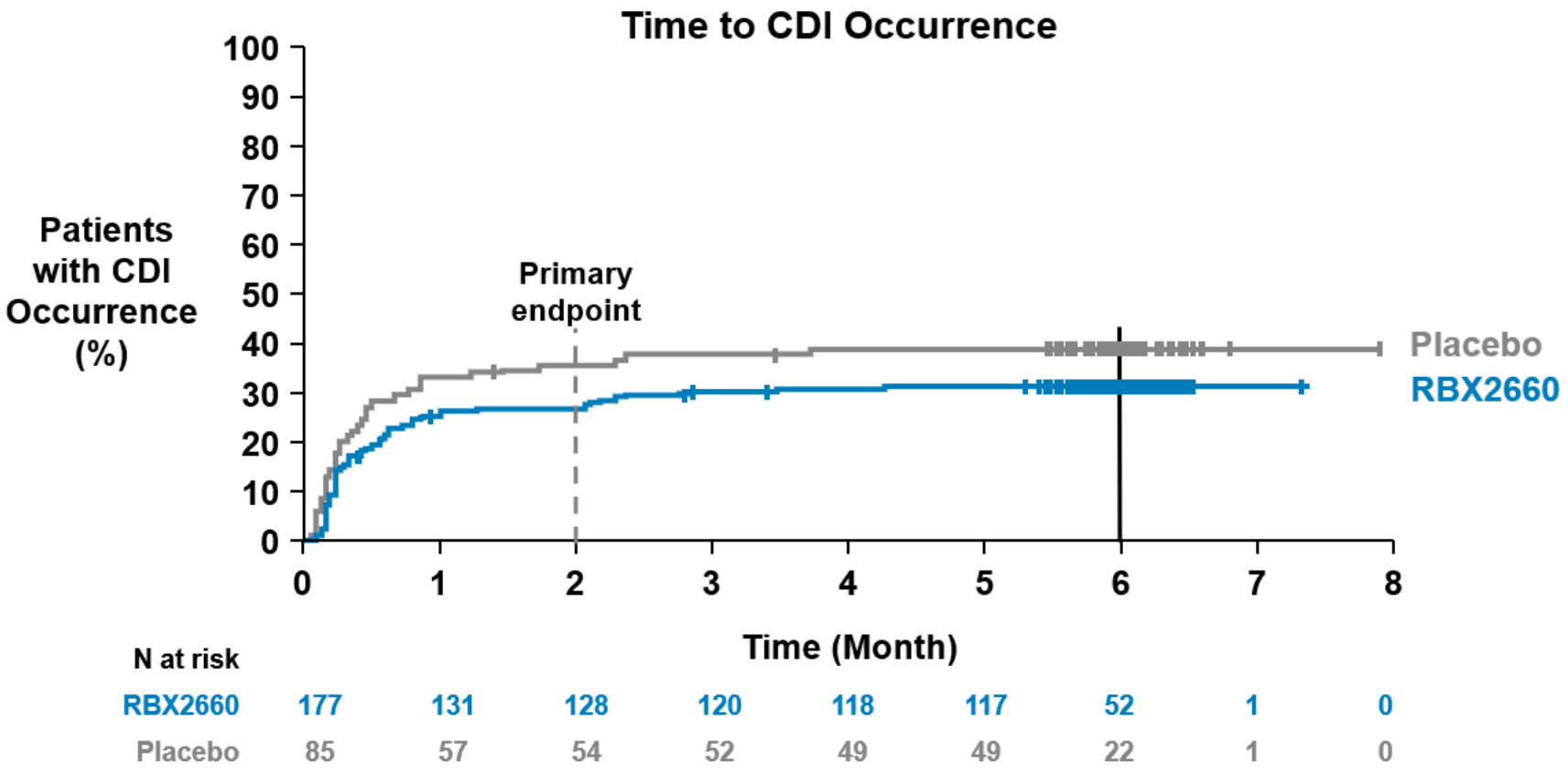
Secondary Endpoint Analysis: Sustained Clinical Response
Study 2017-01 Data Only

- Definition: Treatment success for the presenting CDI recurrence at 8 weeks and no new CDI episodes during the 6 months of follow-up

Analysis Parameter	ITT RBX2660 N=180	ITT Placebo N=87	mITT RBX2660 N=177	mITT Placebo N=85
Sustained Clinical Response, n (%)	116 (64.4)	48 (55.2)	116 (65.5)	48 (56.5)
Difference (%)	9.3	--	9.1	--
95% CI	-3.3, 21.9	--	-3.6, 21.7	--
p-value	0.145	--	0.156	--

ITT, intention-to-treat; mITT, modified intention-to-treat.

Time to CDI Occurrence through 6 Months
Study 2017-01 Data Only



Efficacy Summary

- Primary efficacy analysis of Study 2017-01 (integrated Bayesian analysis):
  - Treatment effect estimate: 13.1% (95% credible interval 2.3% to 24.0%)
  - Posterior probability of superiority: 0.991
    - Met threshold of posterior probability >0.9750
    - Did not meet threshold of posterior probability >0.9993

- Secondary efficacy endpoint analyses of Study 2017-01 data only yielded a similar trend with primary efficacy endpoint analysis
  - Treatment effect: ~9%
  - Not statistically significant at 0.05 level

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Definition of Adverse Events

	Events	Duration of collection
Solicited adverse event (AE)	Events collected via subject diary included: • Gas or flatulence; abdominal distension or bloating; rectal irritation or pain; chills/severe shivering; abdominal pain or cramping; increased diarrhea; constipation; rectal bleeding; nausea; vomiting; fever ≥38.0 °C	First 7 days after receiving assigned treatment
Treatment Emergent Adverse Event (TEAE)	Any unsolicited AE that occurred post RBX2660 exposure	Baseline through 6 months after last dose
Adverse Events of Special Interest (AESI)	AESIs retrospectively defined as terms identified using two Standardized MedDRA Queries (SMQs)[a] • Hyperglycemia/new onset diabetes mellitus • Immune-mediated/autoimmune disorders	Baseline through 6 months after last dose
Serious TEAE	Results in death; Is life-threatening; persistent or significant disability/incapacity; hospitalization ≥24 hours or prolongation of an existing hospitalization; congenital anomaly/birth defect; important medical event	Baseline through 6 months after last dose

[a]SMQs represent a variety of safety topics of regulatory interest and are standard sets of MedDRA terms used to support safety signal detection and monitoring

Safety Analysis Methodology

Safety analysis population included all subjects who received ≥1 dose of RBX2660

Double blinded placebo-controlled studies 2014-01 and 2017-01

Placebo only (N=83)
Received ≥1 dose of placebo (no open-label RBX2660)

Blinded RBX2660 (N=312)
Received ≥1 dose of RBX2660

Integrated Safety - All prospective studies 2013-001, 2014-01, 2015-01, 2017-01 and 2019-01

Any RBX2660 (N=749)
Received ≥1 blinded or open label dose of RBX2660

Single dose proposed for licensure

One dose RBX2660 (N=429)
Received only one blinded or open label dose of RBX2660

Safety Analysis Methodology (cont)

Double-blinded, placebo-controlled studies 2014-01 and 2017-01

Considerations in the interpretation of comparisons between the blinded placebo and RBX2660 groups include:

- Loss of randomization due to CDI recurrence
- Loss of Placebo group to cross-over open-label RBX2660

All prospective studies 2013-001, 2014-01, 2015-01, 2017-01 and 2019-01

Considerations in the interpretation of comparisons between the placebo and any RBX2660 groups include:

- The open-label nature of many of the RBX2660 doses
- Subjects crossed over to receive RBX2660 in an open-label fashion due to recurrence of CDI, which may reflect increased risk for AEs due to underlying risk factors that predispose to rCDI or morbidities attributable to the CDI
- Subjects were followed for 6 months after the last dose of study treatment, resulting in a longer duration of follow up for subjects who received multiple doses

Treatment Courses

Treatment course:

- Can include 1 or 2 doses of RBX2660
- Can be open label or blinded
- Maximum number of 1 to 2 treatment courses
- Maximum number of 1 to 4 doses

Exposure to placebo group accounted for in overall exposure data, some subjects in the RBX2660 only group also exposed to placebo

Treatment and Dose by Study: Safety Population

Study	Placebo Only 1–2 doses N=83 n (%)	Blinded RBX2660 1–2 doses N=193 n (%)	RBX2660 1 Dose N=429 n (%)	ANY RBX2660 1–4 doses N=749 n (%)
2013-001	0	0	19 (4.4)	34 (4.5)
2014-01	20 (24.1)	54 (28.0)	30 (7.0)	108 (14.4)
2015-01	0	0	6 (1.4)	149 (19.9)
2017-01	63 (75.9)	139 (72.0)	163 (38.0)	204 (27.2)
2019-01 (Ongoing)	0	0	211 (49.2)	254 (33.9)

Subject Disposition by Treatment and Dose: Safety Population

Category	Placebo Only 1–2 doses N=83 n (%)	Blinded RBX2660 1–2 doses N=193 n (%)	RBX2660 1 dose N=429 n (%)	Any RBX2660 1–4 doses N=749 n (%)
Completed				
8-wks follow-up	78 (94.0)	180 (93.3)	358 (83.4)	647 (86.4)
6-mo follow-up	75 (90.4)	173 (89.6)	292 (68.1)	557 (74.4)
Discontinued between treatment and 8-wk follow-up	5 (6.0)	13 (6.7)	37 (8.6)	64 (8.5)
Reasons for discontinuation				
Adverse event	0	1 (0.5)	1 (0.2)	2 (0.3)
Death	0	2 (1.0)	3 (0.7)	8 (1.1)
Failure to comply with study requirements	0	0	1 (0.2)	1 (0.1)
Investigator withdrawal	0	1 (0.5)	4 (0.9)	6 (0.8)
Lost to follow-up	0	4 (2.1)	6 (1.4)	11 (1.5)
Withdrawal by subject	5 (6.0)	4 (2.1)	19 (4.4)	31 (4.1)
Other	0	1 (0.5)	3 (0.7)	5 (0.7)
Discontinued between 8-wks and 6-mo follow-up	3 (3.6)	7 (3.6)	14 (3.3)	23 (3.1)
Reasons for discontinuation				
Death	0	2 (1.0)	2 (0.5)	6 (0.8)
Failure to comply with study requirements	0	0	1 (0.2)	1 (0.1)
Investigator withdrawal	0	1 (0.5)	1 (0.2)	3 (0.4)
Lost to follow-up	1 (1.2)	0	4 (0.9)	6 (0.8)
Withdrawal by subject	0	2 (1.0)	3 (0.7)	4 (0.5)
Other	2 (2.4)	2 (1.0)	3 (0.7)	3 (0.4)

Demographics by Treatment and Dose: Safety Population

Category	Placebo Only 1–2 doses N=83 n (%)	Blinded RBX2660 1–2 doses N=193 n (%)	RBX2660 1 dose N=429 n (%)	Any RBX2660 1–4 doses N=749 n (%)
Age (years)				
Mean	58.1	61.1	59.5	61.3
Min-Max	19.0 – 90.0	18.0 – 91.0	18.0 – 94.0	18.0 – 103.0
Age group (years)				
< 65	52 (62.7)	99 (51.3)	245 (57.1)	390 (52.1)
≥ 65	31 (37.3)	94 (48.7)	184 (42.9)	359 (47.9)
≥ 75	12 (14.5)	48 (24.9)	86 (20.0)	193 (25.8)
Sex				
Male	23 (27.7)	71 (36.8)	143 (33.3)	259 (34.6)
Female	60 (72.3)	122 (63.2)	286 (66.7)	490 (65.4)
Race				
White	75 (90.4)	180 (93.3)	401 (93.5)	701 (93.6)
Black or African American	6 (7.2)	8 (4.1)	13 (3.0)	27 (3.6)
American Indian or Alaskan native	0	2 (1.0)	4 (0.9)	4 (0.5)
Asian	0	1 (0.5)	3 (0.7)	6 (0.8)
Other/Multiple	2 (2.4)	1 (0.5)	9 (2.1)	12 (1.6)
Ethnicity				
Hispanic or Latino	3 (3.6)	3 (1.6)	12 (2.8)	19 (2.5)
Not Hispanic or Latino	79 (95.2)	183 (94.8)	407 (94.9)	712 (95.1)
Not reported	0	5 (2.6)	6 (1.4)	10 (1.3)
Unknown	1 (1.2)	2 (1.0)	4 (0.9)	8 (1.1)

CDI Characteristics at Baseline by Treatment and Dose: Safety Population

Category	Placebo Only 1–2 doses N=83 n (%)	Blinded RBX2660 1–2 doses N=193 n (%)	RBX2660 1 dose N=429 n (%)	ANY RBX2660 1–4 doses N=749 n (%)
Total number of CDAD/CDI episodes before first enema treatment, n (%)				
1	0	0	7 (1.6)	7 (0.9)
2	26 (31.3)	46 (23.8)	113 (26.3)	138 (18.4)
≥3	57 (68.7)	147 (76.2)	304 (70.9)	598 (79.8)
Duration of qualifying CDAD/CDI episodes, (d)				
Mean	24.3	23.5	30.2	28.2
Min – Max	3.0–85.0	3.0–65.0	3.0–278.0	1.0–278.0
Antibiotics administration for qualifying CDAD/CDI episode, n (%)				
Vancomycin alone	73 (88.0)	166 (86.0)	354 (82.5)	631 (84.2)
Vancomycin in combination	2 (2.4)	4 (2.1)	4 (0.9)	5 (0.7)
Fidaxomicin	5 (6.0)	13 (6.7)	26 (6.1)	40 (5.3)
Other	3 (3.6)	10 (5.2)	19 (4.4)	44 (5.9)

CDAD, Clostridioides difficile-associated diarrhea; CDI, *Clostridioides difficile* infection.

Adverse Events

Solicited Adverse Events

- Subjects with ≥1 solicited AE reported from day 1 through 7 after receipt of assigned treatment:
  - RBX2660: 170/180 (94.4%)
  - Placebo: 84/87 (96.6%)
- Most events were mild or moderate in severity
- Flatulence, abdominal distension/bloating and abdominal pain/cramping were the most frequently reported events
- Abdominal pain/cramping, increased diarrhea, and abdominal distension/bloating were the most frequently reported severe solicited AEs, all of which were more common in the placebo group compared to the RBX2660 group

Unsolicited TEAEs in ≥5% of Subjects in Any Group

MedDRA System Organ Class and Preferred Term	Placebo Only 1–2 doses N=83 n (%)	Blinded RBX2660 1–2 doses N=193 n (%)	RBX2660 1 dose N=429 n (%)	Any RBX2660 1–4 doses N=749 n (%)
Subjects with ≥1 TEAE	50 (60.2)	135 (69.9)	265 (61.8)	521 (69.9)
Gastrointestinal disorders				
Diarrhea	15 (18.1)	41 (21.2)	77 (17.9)	173 (23.1)
Abdominal pain	7 (8.4)	38 (19.7)	64 (14.9)	123 (16.4)
Nausea	3 (3.6)	21 (10.9)	43 (10.0)	70 (9.3)
Flatulence	1 (1.2)	14 (7.3)	36 (8.4)	60 (8.0)
Constipation	5 (6.0)	11 (5.7)	16 (3.7)	54 (7.2)
Abdominal distension	3 (3.6)	11 (5.7)	24 (5.6)	51 (6.8)
Infections and Infestations				
Urinary tract infection	4 (4.8)	6 (3.1)	17 (4.0)	50 (6.7)

TEAE, treatment emergent adverse event.

Adverse Events of Special Interest

No patterns or clusters observed

No safety signals identified

Serious TEAEs in ≥ 5 Subjects From Baseline to 6 Months Following RBX2660 Exposure

Preferred Term (PT)	Placebo only 1–2 doses N=83 n (%)	Blinded RBX2660 1–2 doses N=193 n (%)	RBX2660 1 dose N=429 n (%)	Any RBX2660 1–4 doses N=749 n (%)
Subjects with ≥1 serious TEAE	**6 (7.2)**	**20 (10.4)**	**36 (8.4)**	**106 (14.2)**
C. difficile infection[a]	0	2 (1.0)	9 (2.1)	16 (2.1)
Urinary tract infection	0	1 (0.5)	2 (0.5)	8 (1.1)
Cardiac failure congestive	0	1 (0.5)	2 (0.5)	7 (0.9)
Chronic obstructive pulmonary disease	0	2 (1.0)	3 (0.7)	7 (0.9)
C. difficile colitis	0	1 (0.5)	3 (0.7)	6 (0.8)
Pneumonia	0	0	2 (0.5)	6 (0.8)
Sepsis	1 (1.2)	0	1 (0.2)	5 (0.7)
Abdominal pain	0	2 (1.0)	2 (0.5)	5 (0.7)
Diarrhea	0	1 (0.5)	2 (0.5)	5 (0.7)

TEAE, treatment emergent adverse event.

[a]Recurrent CDI, (rCDI, recurrent *Clostridioides difficile* infection) reported as serious TEAE in subjects who require hospitalization for ≥24 hours because of the protocol definition of serious adverse event. All rCDI considered treatment failure within 8 weeks of treatment.

Serious Adverse Events

Serious Adverse Events Considered Related by Investigator	FDA Assessment Alternative Etiology
44 yo female with history of rCDI (4 episodes): Abdominal pain 10 days post RBX2660 exposure diagnosed with rCDI	rCDI
58 yo male with history of diabetes: rCDI on days 4, 31 and 64 post RBX2660 exposure and diarrhea on day 24 post RBX2660	rCDI
94 yo female with history of chronic kidney disease stage IV and rCDI (5 episodes): Ileus, leukocytosis, CDI and pyrexia on day 31 post RBX2660 exposure	rCDI
53 yo male with history of AML in remission: Relapsed AML on day 69 post RBX2660 exposure	Underlying AML
59 yo female with history of Parkinson's disease and chronic constipation: Worsening chronic constipation 45 days post RBX2660	Underlying Parkinson's disease and chronic constipation

AML, acute myeloid leukemia; CDI, *Clostridioides difficile* infection; rCDI, recurrent *Clostridioides difficile* infection; SOC, standard of care.

Deaths

18 total deaths, all of which were in RBX2660 recipients (18/749 [2.4%] versus 0/83 [0%] in placebo)

- None considered related to RBX2660 by the investigator or FDA
- Two of the deaths occurred within 30 days after last RBX2660 dose
  - 94 yo: rCDI on Day 14 and death Day 24 post last RBX2660 dose
  - 63 yo: Methicillin-resistant *Staphylococcus aureus* bacteremia on Day 25 and death Day 29 post last RBX2660 dose
- In-depth review of individual case reports and aggregate analyses did not reveal any patterns to suggest a causal relationship to RBX2660
- The increased death rates in the RBX2660 group may reflect both the small sample size of the placebo group comparator and the severity of the underlying CDI in the subjects who received multiple RBX2660 doses in the RBX2660 group


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