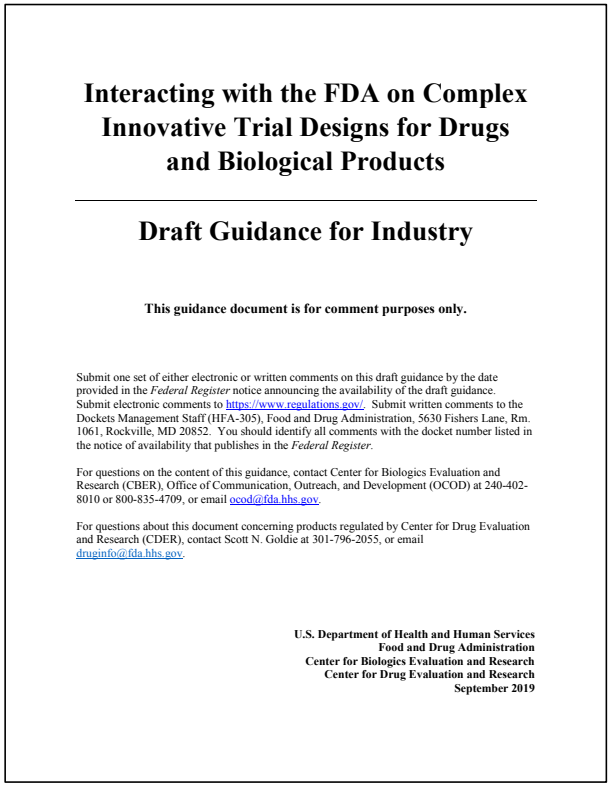
CID from pilot program, to program, to common submission

Scott Berry
Berry Consultants

December 16, 2022

Complex Innovative Designs

"For the purposes of this guidance, CID includes trial designs that have rarely or never been used to date to provide substantial evidence of effectiveness in new drug applications or biologics license applications. A common feature of many CIDs is the need for simulations rather than mathematical formulae to estimate trial operating characteristics (Section III of this guidance)."



Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products

Draft Guidance for Industry

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov/. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on the content of this guidance, contact Center for Biologics Evaluation and Research (CBER), Office of Communication, Outreach, and Development (OCOD) at 240-402-8010 or 800-835-4709, or email ocod@fda.hhs.gov.

For questions about this document concerning products regulated by Center for Drug Evaluation and Research (CDER), contact Scott N. Goldie at 301-796-2055, or email druginfo@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
September 2019

Complex Innovative Designs

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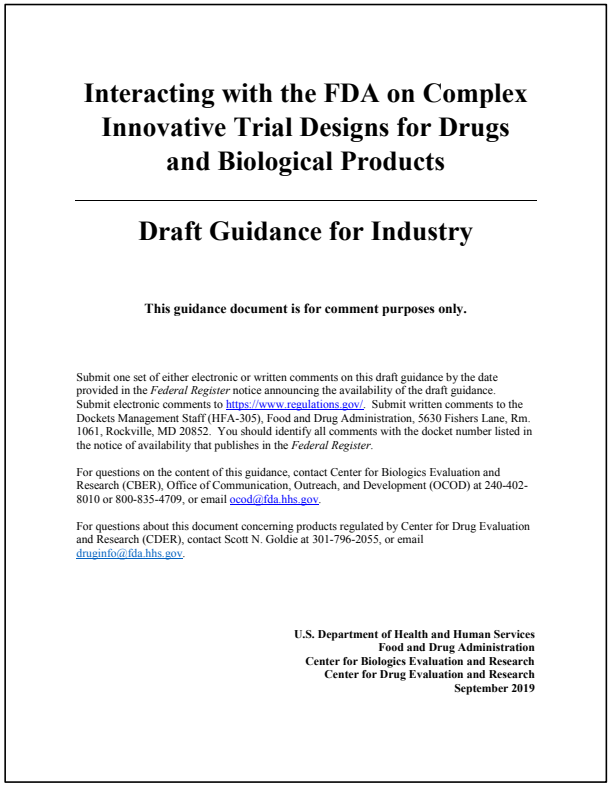

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BSWG KOL Series…

- I see “Bayesian Designs”, “Bayesian Analyses”, “Adaptive Bayesian”
- Are they different, are they complex? are they innovative?
- An adaptive design could use Bayesian to collect data (stop, start, RAR, enrich, expand, etc) but then analyze the data using a frequentist method – is that Bayesian? Is it Frequentist? Dopes it matter?
- Is a fixed design with a Bayesian analysis at the end a Bayesian Design? Is it Complex?
- Could do both…

Complex/Bayesian

- A Bayesian analysis converts a prior distribution into a posterior based on data:

$$\pi(\theta|X) \propto L(X|\theta)\pi(\theta)$$

- The probability of a hypothesis (the drug is effective) can be directly calculated
- A Bayesian Final Analysis: If the probability that drug A is better than PBO given the data is greater than 99% then we will claim trial success and Drug A is effective
- Is this complex?

Complex/Bayesian

- What is the type I error of that design (analysis)?
- If Drug A and PBO are identical in the trial, what is the chance of meeting that rule?
  - It isn't part of the Bayesian analysis
- If Drug A is better than PBO by delta what is the chance of meeting that success rule?
  - It isn't part of the Bayesian analysis
- In some cases we can calculate the probability that data meets that condition (approximations), in many we can't…
- Usually Bayesian is selected when there are 'reasons' to pick it beyond a "simple" frequentist procedure … which makes most uses complex and given the rarity makes them innovative

Why Bayesian?

- The data or analysis requires an analysis that brings more inferential strength than a naïve analysis
- The trial adaptive design has moving parts that make it difficult or impossible to calculate “frequentist” based tools – Bayesian provides appropriate characterization of uncertainty
- Using data from outside the trial final unit – borrowing – very natural to use Bayesian syntheses methods

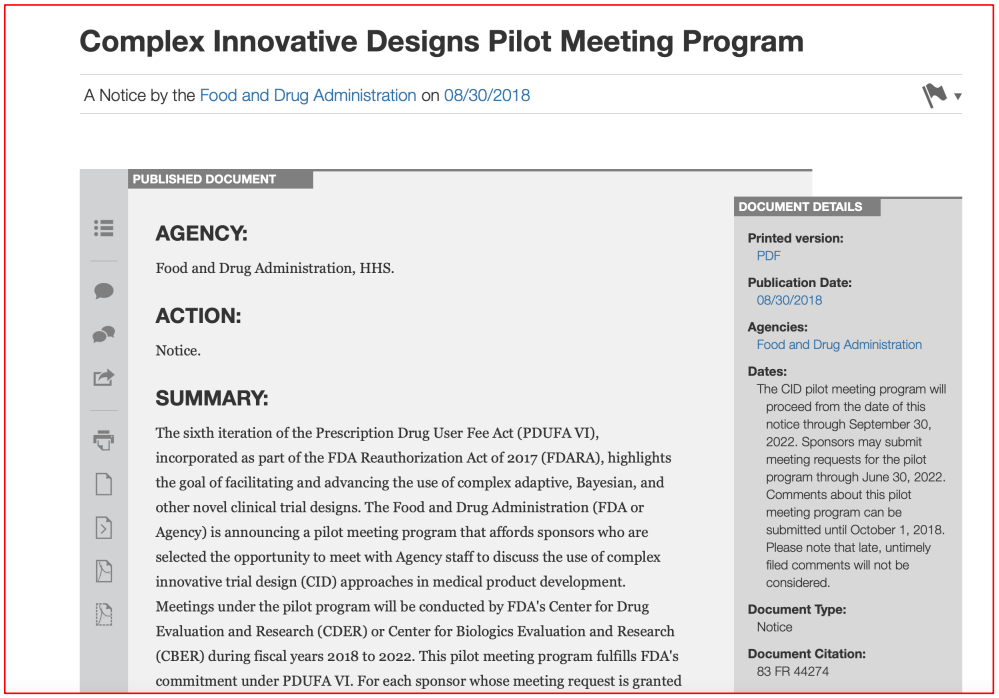
Why Bayesian?

- Using data from outside the trial final unit – very natural to use Bayesian syntheses
  - Adult → Pediatric
  - Subpopulation → Subpopulation
  - Stages → Stages
  - Trial → Trials (Control/Active/Both)
  - Arm → Arm
  - Drug → Drug
  - Disease → Disease

$$\pi(\theta|X) \propto L(X|\theta)\pi(\theta)$$

- A *strict* view of T1E in the "trial unit" would show inflation!

CID Pilot Program @ FDA



Complex Innovative Designs Pilot Meeting Program

A Notice by the Food and Drug Administration on 08/30/2018

PUBLISHED DOCUMENT

AGENCY:

Food and Drug Administration, HHS.

ACTION:

Notice.

SUMMARY:

The sixth iteration of the Prescription Drug User Fee Act (PDUFA VI), incorporated as part of the FDA Reauthorization Act of 2017 (FDARA), highlights the goal of facilitating and advancing the use of complex adaptive, Bayesian, and other novel clinical trial designs. The Food and Drug Administration (FDA or Agency) is announcing a pilot meeting program that affords sponsors who are selected the opportunity to meet with Agency staff to discuss the use of complex innovative trial design (CID) approaches in medical product development. Meetings under the pilot program will be conducted by FDA's Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER) during fiscal years 2018 to 2022. This pilot meeting program fulfills FDA's commitment under PDUFA VI. For each sponsor whose meeting request is granted

DOCUMENT DETAILS

Printed version: PDF

Publication Date: 08/30/2018

Agencies: Food and Drug Administration

Dates: The CID pilot meeting program will proceed from the date of this notice through September 30, 2022. Sponsors may submit meeting requests for the pilot program through June 30, 2022. Comments about this pilot meeting program can be submitted until October 1, 2018. Please note that late, untimely filed comments will not be considered.

Document Type: Notice

Document Citation: 83 FR 44274

In my words:

- For FDA and industry to learn best practices in submission and review of CID trials
- For FDA to be able to publicly disclose details of CID projects to accomplish the above

Why?

“However, we anticipate that the process of XX and the Agency reaching agreement (including, but not limited to, the iterative process of XX conducting extensive simulations and the Agency reviewing the corresponding simulation reports) will be very time-consuming. Given the urgent nature of the COVID-19 pandemic, we are concerned that any anticipated gain via the use of the complex and innovative elements of your proposed study design may not outweigh this loss of efficiency. You may consider modifying the study design to be analytically tractable, such that the use of simulations is not necessary."

CID Program @ FDA

Complex Innovative Trial Design Meeting Program

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On this page

Content current as of:
10/27/2022

Regulated Product(s)
Drugs

As displayed in the Federal Register notice on October 20, 2022, FDA is continuing the Complex Innovative Trial Design (CID) Paired Meeting Program, originally established under PDUFA VI, to support the goal of facilitating and advancing the use of complex adaptive, Bayesian, and other novel clinical trial designs. The CID Paired Meeting Program fulfills a performance goal agreed to by the Prescription Drug User Fee Act (PDUFA) reauthorization for fiscal years (FYs) 2023-2027, known as PDUFA VII.

This paired meeting program offers sponsors whose meeting requests are granted the opportunity for increased interaction with FDA staff to discuss their proposed CID approach.

Meetings will be conducted by FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) during fiscal years 2023 to 2027. To promote innovation in this area, trial designs developed through the meeting program may be presented by FDA (e.g., in a guidance or public workshop) as case studies, including trial designs for medical products that have not yet been approved by FDA.

Goals of the CID Paired Meeting Program

The CID Paired Meeting Program is designed to:

- Facilitate the use of CID approaches with emphasis in late-stage drug development.
- Promote innovation by allowing FDA to publicly discuss the trial designs accepted by the paired meeting program, including trial designs for medical products that have not yet been approved by FDA.

My advice for sponsors on CID Program

- I am a huge fan of the program
- Okay with the disclosure and the timing of the program
- Have your design ready to go and the simulations done when you apply (more on this later)
  - Meeting 1 – submit 30 days later is challenge
  - Meeting 2 – have 90 days to review
  - Lot of work
- I think you will get a very thorough review that gives better chance of a better design
- It's not a way to lower the bar

What is missing …?

- The big hole – perhaps the misunderstanding about “role of simulation” in CID is the creation of the design
- An iterative process guided by simulations that explores different aspects of the design and analysis to optimize the design – “in silico design”
- Adaptive designs don’t “fall off the tree” ready to simulate final OCs
- The final step is “calculation”
- The design process is critically important, part science, part art, visualization, programming skill, problem solving, operationalizing goals, teamwork

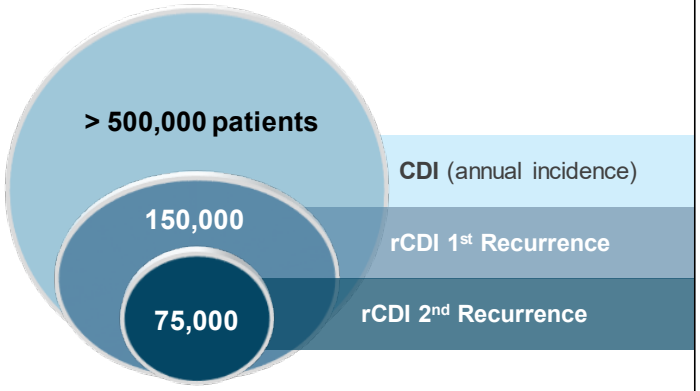
The goal for the program is to not need the program

Rebyota

CO-3

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

https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-september-22-2022-meeting-announcement

Rebyota

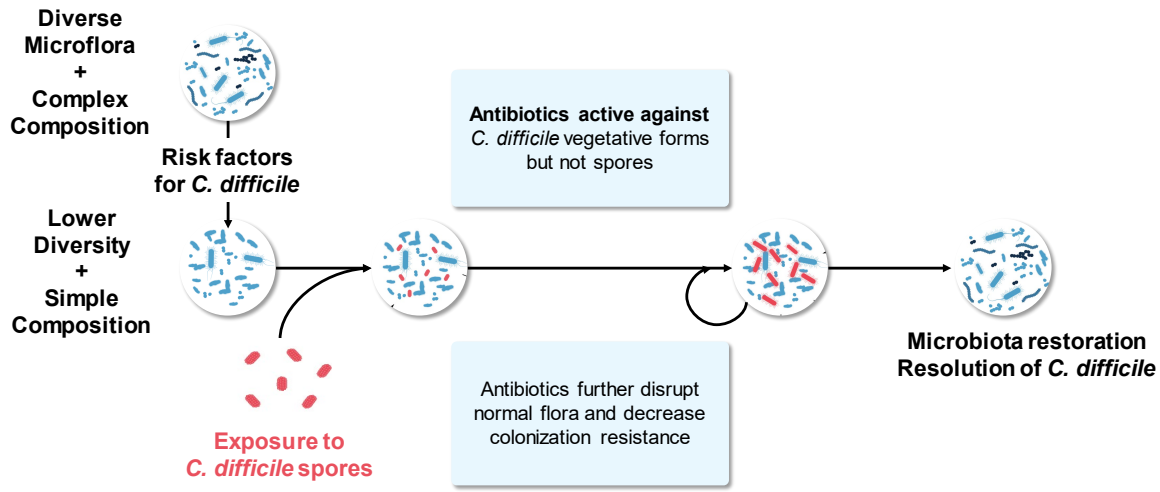
CO-12

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

CO-16

Prevent Recurrences: Restore the Microbiome



Adapted from Khanna, 2021

Rebyota

RBX2660: Intestinal Fecal Microbiota Suspension that is Standardized, Stabilized, and Quality Controlled [CO-5]

- 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

Rebyota

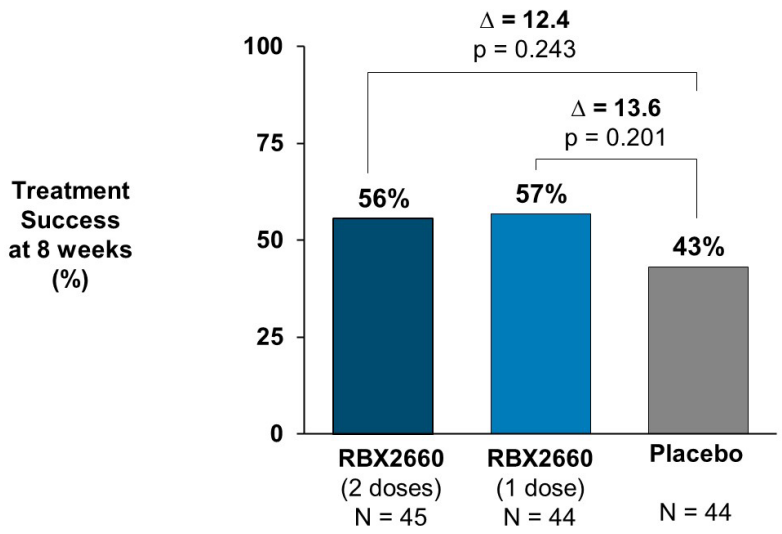
- Phase 3 Trial of RBX2660, randomized 2:1 ~ 300 patients
- Primary endpoint is “no recurrence of CDI by 8 weeks”
- Planning second phase 3 trial of similar size
- Trial enrollment for phase 3 trial becomes very challenging, in part because of the “use of FMT” (guidelines suggest FMT for recurrent CDIFF)
- Discussion with FDA leads to an analysis of the phase 3 using Bayesian borrowing from the one phase 2 trial of RBX2660
  - Added during Phase 3 before any unblinding

Phase 2 Trial

- Randomized trial 1:1:1

CO-27

Study 2014-01: Primary and Secondary Efficacy Results
ITT Population



Selected 1-dose For Phase 3

Bayesian Model

Does not use 2-dose from P2

$$X_{k,s} \sim \text{Binomial}\left(N_{k,s}, p_{k,s}\right)$$

K = arm, s=study

$$\log\left(\frac{p_{0,s}}{1-p_{0,s}}\right) = \alpha_s$$

$$\alpha_S \sim N(\mu_\alpha, \tau_\alpha^2)$$

$$\mu_\alpha \sim N(0, 10^2)$$

$$\tau_\alpha^2 \sim IG(0.001, 0.01)$$

$$\log\left(\frac{p_{1,s}}{1-p_{1,s}}\right) = \alpha_s + \theta_s$$

$$\theta_S \sim N(\mu_\theta, \tau_\theta^2)$$

$$\mu_\theta \sim N(0, 10^2)$$

$$\tau_\theta^2 \sim IG(0.01, 0.01)$$

- Primary analysis of Phase 3 is based on the estimated effect, θ_2

Primary Analysis

- Interim analysis @160 and @220, final analysis @270
- If Pr($\theta_2 > 0$) $> 1 - 0.00125^*$ stop @ interim
  - * adjusted for two interim analyses
  - Is PP(Success by 270) < 0.01 then stop for futility
- At final analysis, label a success at a threshold of “0.025” (1 trial) if

$$\Pr(\theta_2 > 0) > 1 - 0.025^*$$

- At final analysis, label a success at a threshold of “0.00125” (2 trials) if

$$\Pr(\theta_2 > 0) > 1 - 0.00125^*$$

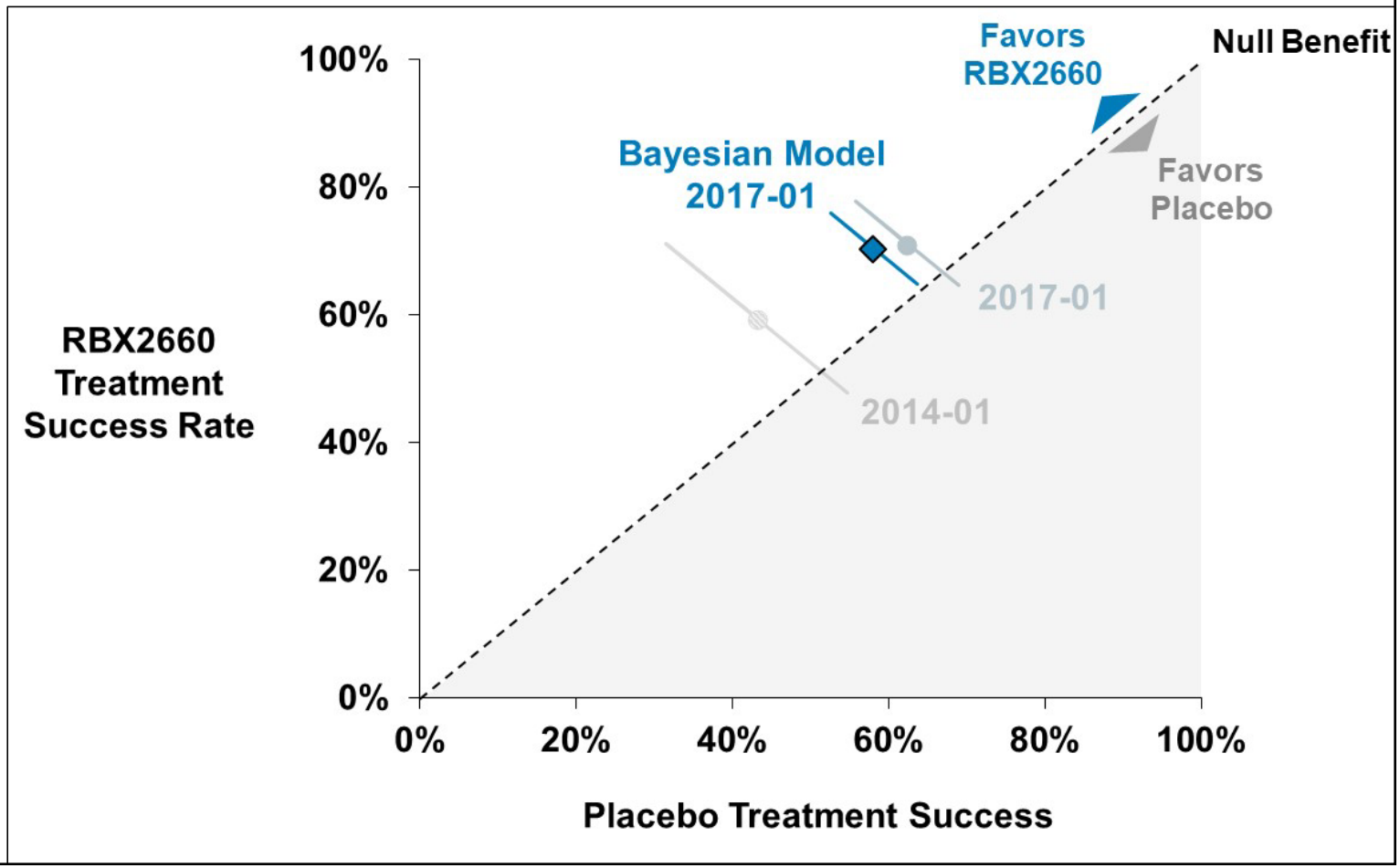
Submission

- Full adaptive design report has been made public
  - Advisory committee website
- Simulate power, T1E, effective sample size, sample size, multiple levels of success, …
- Full simulation for design approval
- Full FDA review and approval

Outcome

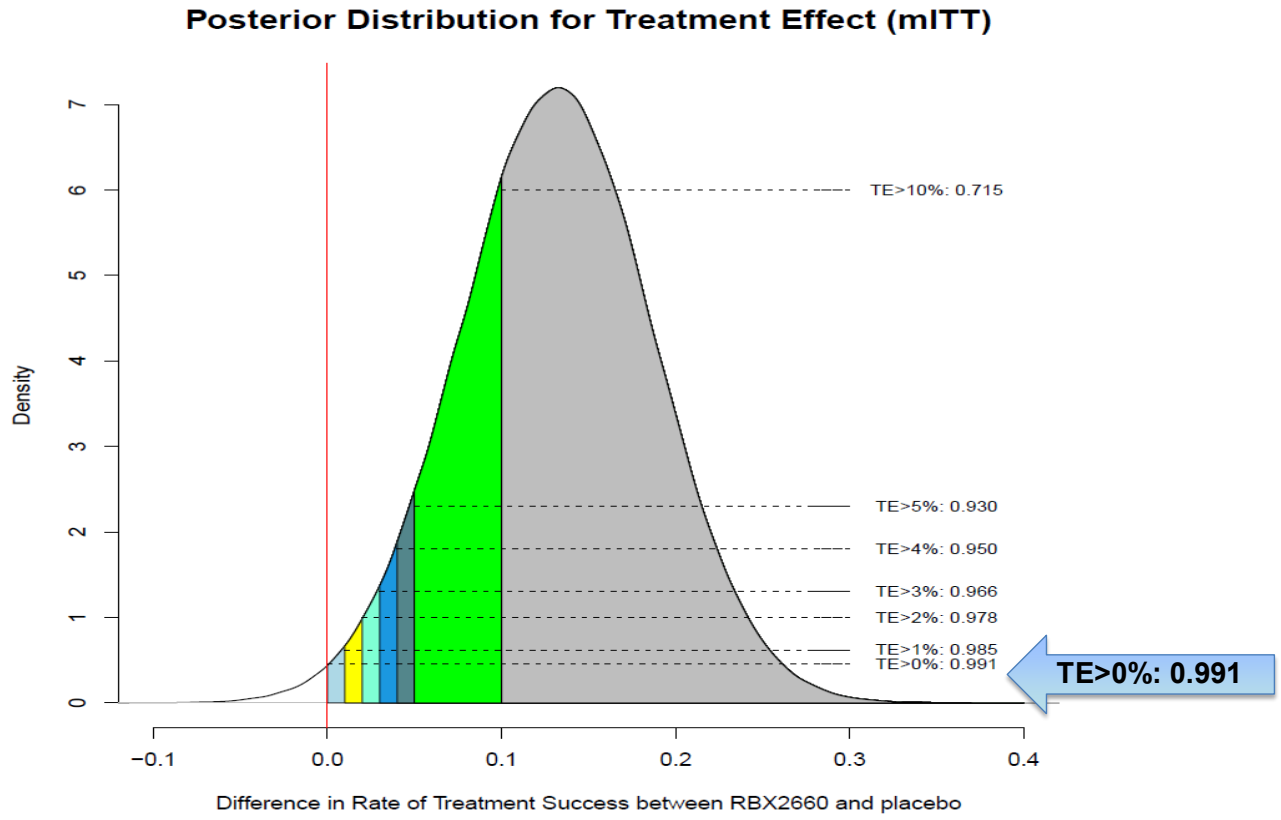
- PBO: 53/85 (62.4%)
- RBX2660: 126/177 (71.2%)

13.1% Mean Difference
57.5% vs 70.6%
(2.3%, 24%) 95% CrI

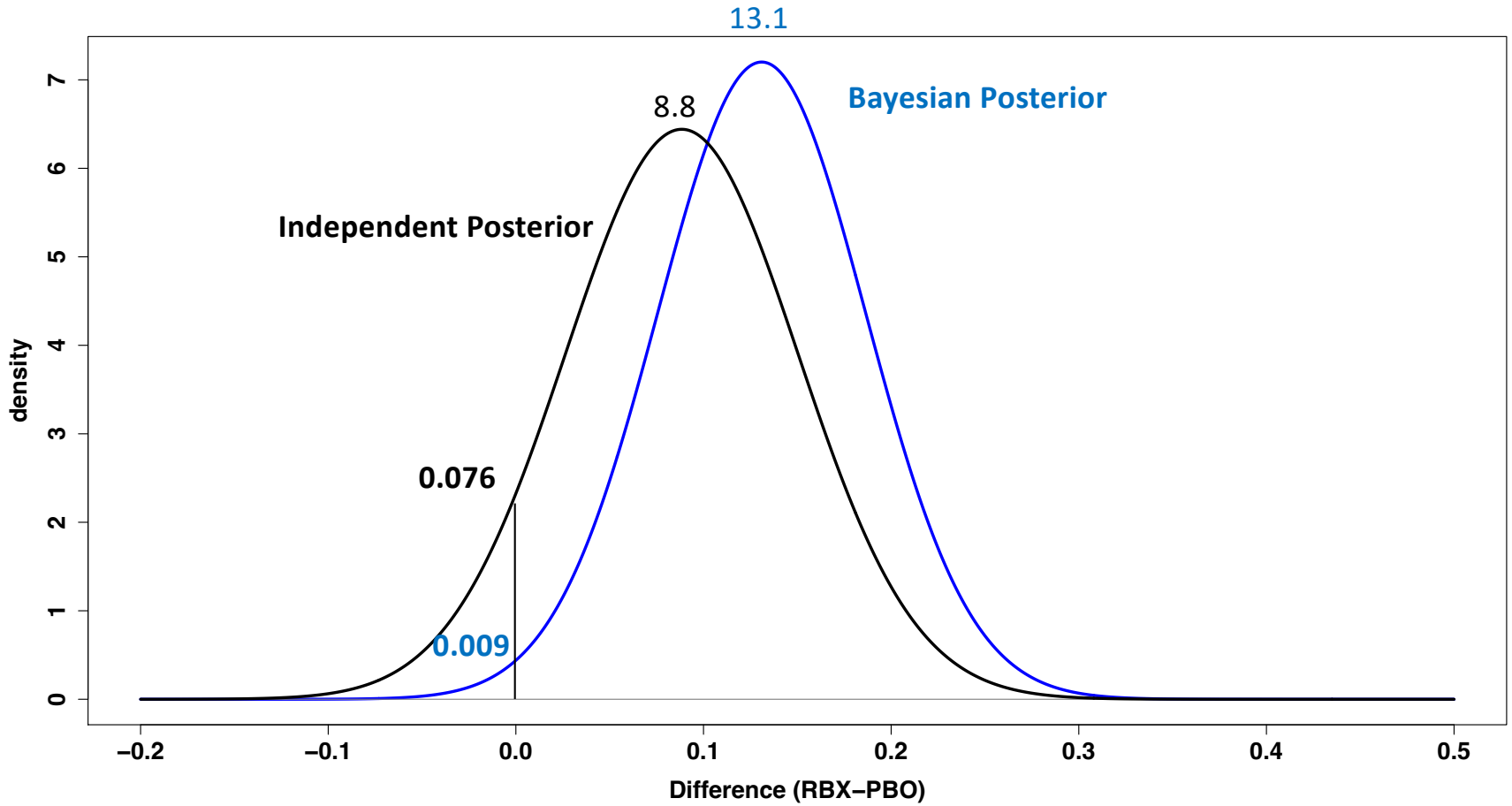


Outcome

Posterior Probability for Different Treatment Effect Levels



Outcome


13.1
8.8
Bayesian Posterior
Independent Posterior
0.076
0.009
density
0
1
2
3
4
5
6
7
−0.2
−0.1
0.0
0.1
0.2
0.3
0.4
0.5
Difference (RBX−PBO)

Statisticians

- We are so attuned to the biases that can happen when we borrow phase 2 (after the fact) to phase 3…
- Why? We are so use to the lack of predictability of 2 -> 3
- Multiplicities:
  - Selection of a subset of patients! … Here they slightly expanded
  - Selection of endpoint! … Here there is only 1 endpoint
  - Selection of dose/arm! … the two-arms couldn't be closer
  - Go/No-Go bias of phase 2 … extensive FMT knowledge scientific basis
- Analysis used every patient ever enrolled in the two-arms (mITT) in any trial
- If ever it was reasonable to do integrated analysis it is here (and used dynamic borrowing)

Panel Meeting, September 22, 2022

- Panel voted 13 to 4 that it demonstrated efficacy
- Panel voted 12 to 4 (1 abs) that it demonstrated safety

Adaptive Design Report

https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-september-22-2022-meeting-announcement

FDA Label (no p-values!)

Table 2: Efficacy Results: Treatment Success at 8 weeks Post-Treatment (mITT Population*)

Parameter	REBYOTA Mean (95% CrI)	Placebo Mean (95% CrI)	Treatment Effect (REBYOTA – Placebo) Mean (95% CrI)
Model-Estimated Treatment Success (%)	70.6 (64.1, 76.8)	57.5 (48.1, 67.1)	13.1 (2.3, 24.0)
Posterior Probability of Superiority	-	-	0.991[#]

CrI=credible interval
*mITT includes all randomized subjects excluding: 1) those who withdrew prior to treatment; 2) those in whom treatment was attempted but not completed; 3) those who discontinued from the study prior to evaluation of treatment outcome for the primary endpoint if the reason for exit was not related to CDI symptoms.
[#]Pre-defined threshold was 0.975

In the Bayesian analysis, the estimated rate of treatment success was significantly higher in the REBYOTA group (70.6%) than in the Placebo group (57.5%) through 8 weeks after completing blinded treatment, resulting in a difference of 13.1 percentage points (95% Credible Interval: 2.3, 24.0) which corresponds to a 99.1% posterior probability that REBYOTA is superior to Placebo (Table 2).

CID

- What is complex continues to evolve
- What is innovative continues to evolve
- The program is successful in removing the need for the program
- Review of simulation is normal
  - As most designs should be better understood by more rigorous understanding of the design