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# Novel Anti-Infectives Update

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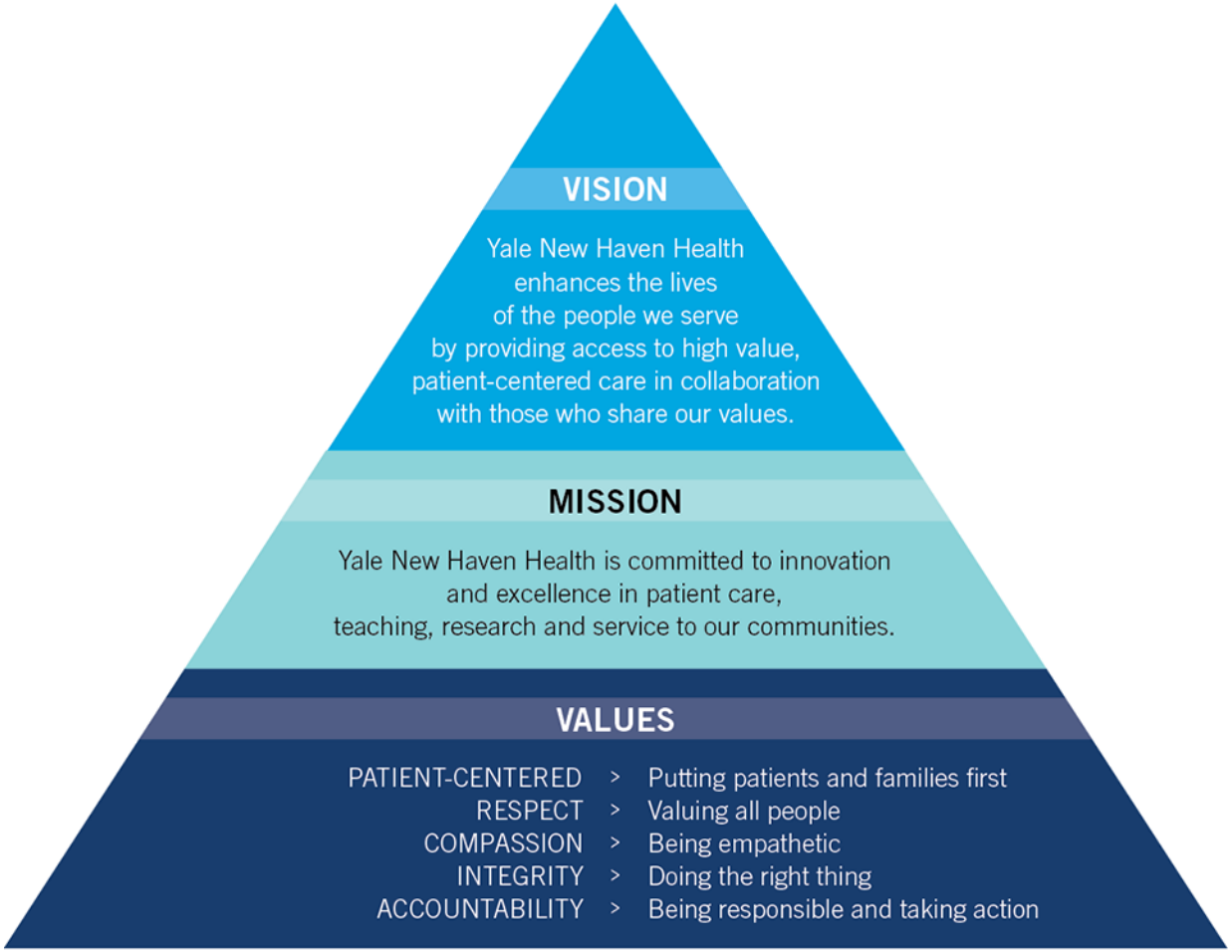
# VISION, MISSION AND VALUES

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Bridgeport Hospital | Greenwich Hospital | Lawrence + Memorial Hospital | Westerly Hospital | Yale New Haven Hospital | Northeast Medical Group

# Disclosures

- I have nothing to disclose

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# Objectives

- Review recently FDA-approved novel microbiota-based live biotherapeutics for prevention of recurrence of *Clostridioides difficile* infection (CDI)

- Discuss the newly FDA-approved, novel echinocandin antifungal, rezafungin for treatment of candidemia and invasive candidiasis

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# Slow Advances in Anti-Infective Therapy Approvals

- Antimicrobial resistance is one of the leading causes of death globally

- The clinical pipeline of new antimicrobials has been dry

- Slow FDA approval on anti-infectives in the pipeline for the past few years
  - **2022 FDA approvals**
    - fecal microbiota, live – jslm (Rebyota) for prevention of recurrence of *Clostridioides difficile* infection (CDI)
    - lenacapavir (Sunleca) for HIV treatment
    - vonoprazan, amoxicillin, and clarithromycin (Voquenza) for *H. pylori* infection treatment
  - **2023 FDA approvals**
    - rezafungin (Rezzayo) for treatment of candidemia and invasive candidiasis
    - fecal microbiota spores, live-brpk (Vowst) for prevention of recurrence of *Clostridioides difficile* infection (CDI)

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# *Clostridioides difficile* Infection Microbiome - Based Novel Agents

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# Mechanism – Restoring the Microbiome

Patients in a healthy state have a diverse microbiome with a complex composition of bacteria
- Firmicutes phylum
- Bacteroidetes phylum

↓

Exposure to *C. difficile* infection and risk factors ↓ the diversity and composition of the microbiome, leading to dysbiosis and ↑ levels of primary bile acids

↓

↑ in primary bile acids can trigger *C. difficile* spores to germinate into vegetative forms that produce toxins

→

Microbiome restoration re-establishes wide variety of commensal organisms that directly and indirectly antagonize *C. difficile:*
- ↑ secondary bile acids that suppress germination of *C. difficile* spores
- Reconstitute barrier integrity

↑

*Current C. difficile treatments:*
- Do not repair disrupted microbiome
- *Target vegetative forms only,* ***not spores***

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# Fecal microbiota, live – jslm (**Rebyota**)

- First FDA-approved microbiota-based live biotherapeutic against *C. difficile:*
  - Standardized for potency with controlled formula
  - Quality control → stringent and uniform donor screening and controlled manufacturing process
  - Stabilized for extended shelf life

- **Approved Indication:** prevention of recurrence *C. difficile* infection (CDI) in individuals
  - 18 years of age and older
  - following antibiotic treatment for recurrent CDI
  - not indicated for treatment of CDI


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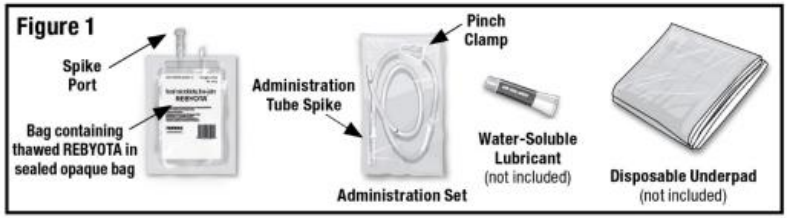
# Fecal microbiota, live – jslm (**Rebyota**) Dosage and Administration

- **Dosage**: pre-packaged single dose of 150 mL fecal microbiota suspension (enema) in a solution of polyethylene glycol (PEG 3350) and saline
  - Containing $1x10^8$ to $5x10^{10}$ colony forming units (CFUs)/mL of fecal microbes derived from qualified donors
    - Composed of *Bacteriodia* and *Clostridia* classes
      - $>1x10^5$ CFU/mL of *Bacteroides*




- **Route of Administration:** rectal (given as enema)

- **Special Instructions:**
  - Thaw product by placing in refrigerator (36°F to 46°F), for approximately 24 hours prior to use

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# Efficacy – PUNCH CD3 Trial

| | |
|---|---|
| **Study Type** | Phase 3, randomized, double-blind, placebo-controlled trial, with a Bayesian primary analysis integrating previous phase IIb study (PUNCH CD2) |
| **Design** | **Inclusion:**<br>• ≥ 18 years of age<br>• ≥ 1 episode of recurrent *C. difficile* infection (CDI) after primary CDI and ≥ 1 round of SOC antibiotic<br>OR<br>≥2 episodes of severe CDI resulting in hospitalization<br><br>Randomized 2:1 to receive a blinded single dose enema of RBX2660 or placebo |
| **Primary and Secondary Efficacy Endpoints** | **Primary:** Treatment success → absence of CDI diarrhea within 8 weeks of study treatment<br><br>**Secondary:** Sustained Clinical Response → treatment success of the presenting CDI recurrence and no new CDI episodes for > 8 weeks though 6 months after completing study treatment |

# Efficacy – PUNCH CD3 Trial

| | |
|---|---|
| **Results (Primary Outcome)** | **Treatment Success (absence of CDI within 8 weeks)**<br><br>• 262 patients included (n = 177 RBX2660; n = 85 placebo)<br>• Bayesian Hierarchical Model Estimates:<br>  • Model-estimated treatment success rate was 70.6% with RBX2660 versus 57.5% with placebo<br>  • Estimated treatment effect of 13.1% and a posterior probability of superiority of 0.991 |
| **Results (Secondary Outcome)** | **Sustained Clinical Response (at 6 months)**<br><br>Proportion of participants with treatment success at 8 weeks remained free of CDI recurrence at 6 months:<br>• Approximately ~90% for both treatment groups across analysis populations |

# Fecal microbiota, live – jslm (**Rebyota**) Contraindications, Warnings, and Adverse Effects

| Contraindications |
| --- |
| Allergy to any of the known product components (ex. PEG 3350) |

| Warnings |
| --- |
| May contain food allergens |
| May carry a risk of transmitting infectious agents |

| Adverse Reactions |
| --- |
| Abdominal pain (8.9%) |
| Diarrhea (7.2%) |
| Abdominal Distension (3.9%) |
| Flatulence (3.3%) |
| Nausea (3.3%) |

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# Fecal microbiota spores, live-brpk **(Vowst)**

- First FDA-approved **<u>orally administered</u>** microbiota-based live biotherapeutic against *C. difficile*

- Approved indication → prevent the recurrence of CDI
  - 18 years of age and older
  - Following antibacterial treatment for recurrent CDI
  - <u>Not</u> indicated for the treatment of CDI


- Donor derived consortium of *Firmicutes* spores
  - Approximately between $1x10^6$ to $3x10^7$ spore colony forming units of firmicute spores
  - Spore suspension treated with ethanol to kill organisms that are not spores

- Stringent screening and manufacturing process

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# Fecal microbiota spores, live-brpk **(Vowst)** Dosage and Administration

- **Formulation** = capsules
  - Resistant to gastric acid, allowing formulation into oral capsules

- **Dosage** → 4 capsules given once daily x 3 consecutive days
  - Take on empty stomach prior to first meal of the day

- **Following are required prior to initiating treatment:**
  - Need to have completed antibacterial treatment for recurrent CDI 2 to 4 days before taking first dose
  - Drink 296 mL (10 oz) of magnesium citrate on the day before and at least 8 hours prior to taking the first dose

# Efficacy - ECOSPOR III Trial (NEJM)

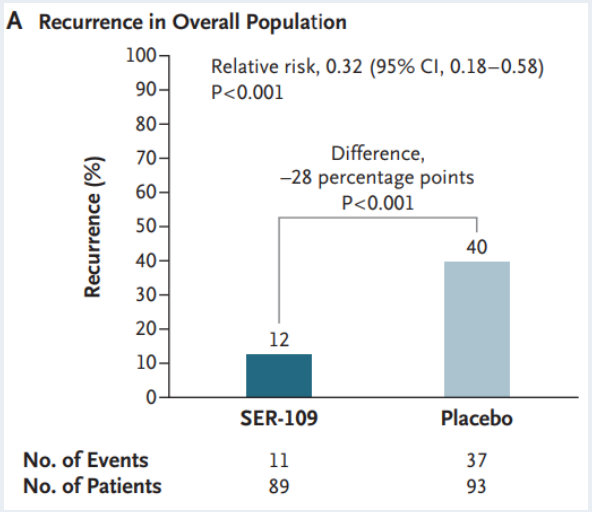
| | |
|---|---|
| **Study Type** | Phase 3, randomized, double-blind- placebo-controlled trial |
| **Design** | **Inclusion:**<br>• ≥ 18 years of age<br>• ≥ 3 episodes of C. difficile infection within 12 months, inclusive of the qualifying acute episode<br>• Resolution of symptoms while receiving 10 to 21 days of standard of care antibiotic therapy<br><br>Randomized 1:1 to SER 109 vs placebo |
| **Primary and Secondary Efficacy Endpoints** | **Primary:**<br>• Recurrence of CDI via toxin assay up to 8 weeks after treatment initiation<br><br>**Secondary:**<br>• Engraftment of SER-109 Dose Species<br>• Concentration of Secondary Bile Acids |

# Efficacy - ECOSPOR III Trial (NEJM)

**Results (Primary Outcome)**

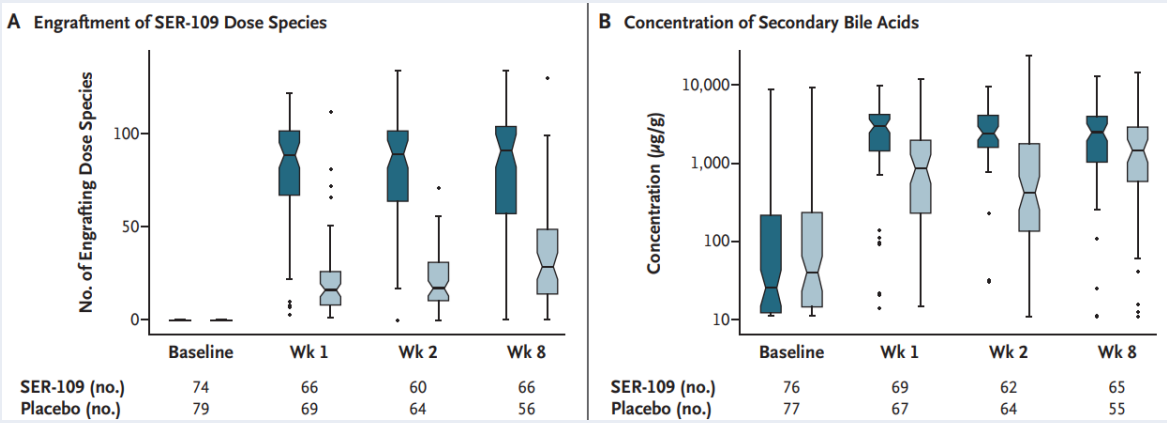
**Recurrence of CDI at 8 weeks:**

SER-109 found to be superior to placebo in reducing risk of CDI recurrence




**Results (Secondary comes)**

**Engraftment of SER-109 Dose Species and Concentration of Secondary Bile Acids: →**




**Additional Notes**

- Additional data presented after publication showed durably reduced recurrent CDI rates through week 24

# Fecal microbiota spores, live-brpk **(Vowst)** Contraindications, Warnings, and Adverse Effects

| Contraindications |
| --- |
| None |

| Warnings |
| --- |
| May contain food allergens |
| May carry a risk of transmitting infectious agents |

| Adverse Reactions |
| --- |
| Abdominal distension (31%) |
| Fatigue (22%) |
| Constipation (14%) |
| Chills (11%) |
| Diarrhea (10%) |

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# New FDA Approved Novel Antifungal - rezafungin

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# Rezafungin (Rezzayo)

- Novel semisynthetic echinocandin
  - Inhibit 1,3–D-glucan synthase enzyme complex in fungal cell walls
  - Activity observed against *Candida sp, Aspergillus sp.,* and *Pneumocystis jirovecii*

- FDA Approved Indication
  - Treatment of candidemia and invasive candidiasis in those who have limited or no alternative options **(limited use indication)**
  - ≥18 years of age
  - *Has not been studied for infective endocarditis, osteomyelitis or meningitis due to Candida sp.*

- Currently in Phase 3 trials for prevention of Invasive Fungal Disease in Blood & Marrow Transplant Patients

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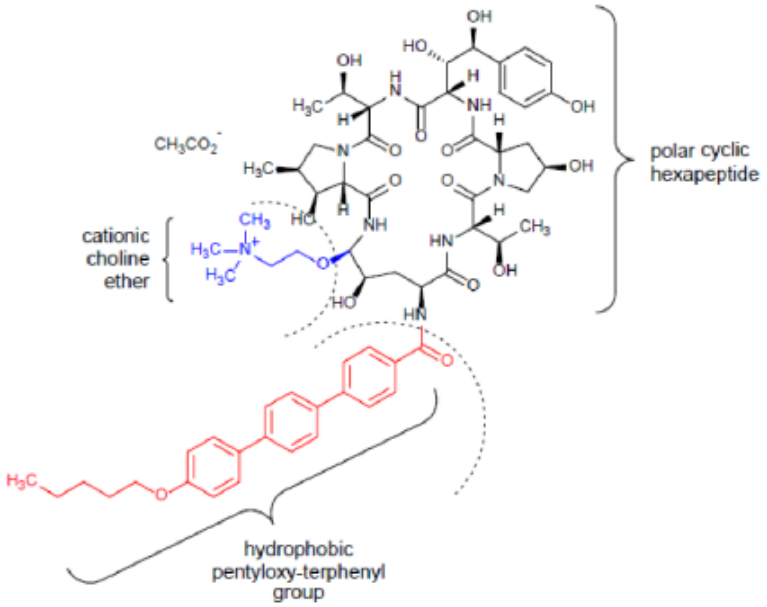
# Rezafungin (Rezzayo) Structure

- Derived from anidulafungin




- Cationic amphiphilic drug
  - Possesses a cationic polar head group (cyclic hexapeptide with choline ether) and hydrophobic tail (pentyloxy-terphenyl group)
    - ↑ stability of the drug in solutions
    - Drug's action in the body is prolonged
      - T ½ = 152 ± 29 hours

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# Rezafungin (Rezzayo) Dosing

- **Dosing**: loading dose of 400 mg intravenous (IV) in Week 1, followed by 200 mg IV once weekly thereafter
  - in 250 mL in 0.9% Sodium Chloride, 0.45% Sodium Chloride, or 5% Dextrose in Water
  - Given over 1 hour

- No dose adjustments required:
  - No clinically relevant effects noted:
    - Renal impairment
    - Hepatic impairment
    - Age
    - Weight

- No notable drug-drug interactions

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# Efficacy – ReSTORE Trial

| | |
|---|---|
| **Study Type** | Phase 3, randomized, double-blind- double-dummy, multi-center trial |
| **Design** | **Inclusion:**<br>• ≥ 18 years of age<br>• Systemic signs and mycological confirmation of candidemia or invasive candidiasis<br><br>Randomized 1:1 rezafungin or caspofungin (with optional step down to fluconazole at day 3 with caspofungin) |
| **Primary and Secondary Efficacy Endpoints** | **Primary:**<br>• Global cure (consisting of clinical cure, radiological cure, and mycological eradication) at day 14 for the European Medical Agency (EMA)<br>• 30-day all-cause mortality for the US Food and Drug Administration (FDA)<br>**Secondary:**<br>• Global cure, mycological cure, clinical cure, and radiological cure at day 5, day 30, and end of treatment |

# Efficacy – ReSTORE Trial

| | |
|---|---|
| **Results (Primary Outcome)** | **Global Cure at Day 14:**<br>• 55 (59%) of 93 patients in the rezafungin group and 57 (61%) of 94 patients in the caspofungin group<br>• Weighted treatment difference −1.1% [95% CI −14.9 to 12.7]<br><br>**30-Day All-Cause Mortality:**<br>• 22 (24%) of 93 patients in the rezafungin group and 20 (21%) of 94 patients in the caspofungin group died or had an unknown survival status at day 30<br>• Treatment difference 2.4% [95% CI −9.7 to 14.4]<br><br>***Of note: a 20% non-inferiority margin was used for the primary outcomes*** |
| **Results (Secondary comes)** | **Global cure, mycological cure, clinical cure, and radiological cure at day 5, day 30, and end of treatment:**<br>• No major differences noted between groups |

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# Rezafungin (Rezzayo) – Adverse Reactions, Warnings, and Contraindications

| Adverse Reactions |
| --- |
| Hypokalemia (15%) |
| Pyrexia (12%) |
| Diarrhea (11%) |
| Anemia (10%) |
| Nausea (9%) |
| Vomiting (9%) |
| Hypomagnesemia (8%) |
| Abdominal Pain (7%) |
| Constipation (5%) |
| Hypophosphatemia (5%) |

| Warnings |
| --- |
| Infusion Related Reactions |
| Photosensitivity |
| Hepatic Reactions |

| Contraindications |
| --- |
| Known hypersensitivity to rezafungin or echinocandins |

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# Rezafungin (Rezzayo) – Antifungal Activity

- Shown to be active in vitro **and** in clinical infections (seen in the Phase III trial):
  - *Candida albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis*

- Shown to be active in vitro, however clinical significance unknown (clinical studies needed):
  - *Candida krusei, Candida auris, Candida dubliniensis, Candida lusitaniae*, and other *Candida spp.*
    - Of note: CLSI has allowed a provisional breakpoint for *C. auris* of ≤ 0.5 µg/mL
  - *Aspergillus sp.,* and *Pneumocystis jirovecii*

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# Conclusion

- Newly approved live therapeutic biologic products focus on microbiome restoration through a regulated process, with the goal of reducing *Clostridioides difficile* infection recurrences

- Rezafungin is a novel echinocandin antifungal with unique pharmacokinetic properties that allows for once weekly dosing, and has a limited use indication for treatment of invasive candidiasis and candidemia

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# Questions?

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