Administration of Broad Consortium Microbiota-Based Live Biotherapeutic Suspension

Ferring Pharmaceuticals, Inc.

September 14, 2021

Helping people live better lives

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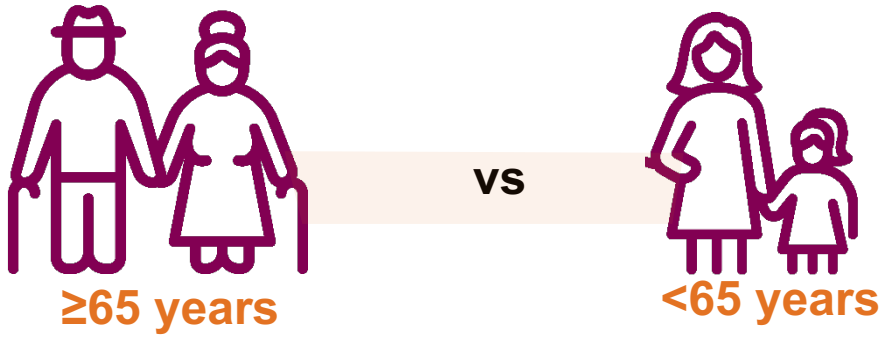
Clostridioides difficile (C. difficile) is a spore-forming, toxin-producing bacterium that is the most common healthcare-associated infection[1-9]

Responsible for an estimated 223,900 cases in hospitalized patients

12,800 estimated deaths annually

93% of deaths occur in patients over age 65



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2. Smits WK, Lyras D, Lacy DB, Wilcox MH, Kuijper EJ. Clostridium difficile infection. *Nat Rev Dis Primers*. 2016;2:16020.
3. Arbel LT, Hsu E, McNally K. Cost-effectiveness of fecal microbiota transplantation in the treatment of recurrent Clostridium difficile infection: a literature review. *Cureus*. 2017;9(8):e1599.
4. Reveles KR, Lee GC, Boyd NK, Frei CR. The rise in Clostridium difficile infection incidence among hospitalized adults in the United States: 2001-2010. *Am J Infect Control*. 2014;42(10):1028-1032.
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6. Yacyshyn B. Pathophysiology of Clostridium difficile–associated diarrhea. *Gastroenterol Hepatol (N Y)*. 2016;12(9):558-560.
7. Drekonja D, Reich J, Gezahegn S, et al. Fecal microbiota transplantation for Clostridium difficile infection: a systematic review. *Ann Intern Med*. 2015;162(9):630-638.
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A number of factors may increase the risk of *Clostridioides difficile* infection (CDI), resulting in a range of complications[1-11]

Risk factors

- Age (≥65 years)
- Antibiotic pharmacotherapy (standard of care)
- Healthcare exposure (hospitalization)
- Underlying chronic comorbidities
- Immunosuppressive medications

Complications

- Dehydration
- Electrolyte imbalance
- Toxic megacolon
- Sepsis
- Death

Recurrence

- 1 in 3 initially treated patients
- Nearly 2 in 3 patients with multiple prior occurrences

1. Smits WK, Lyras D, Lacy DB, Wilcox MH, Kuijper EJ. Clostridium difficile infection. *Nat Rev Dis Primers*. 2016;2:16020.
2. Arbel LT, Hsu E, McNally K. Cost-effectiveness of fecal microbiota transplantation in the treatment of recurrent Clostridium difficile infection: a literature review. *Cureus*. 2017;9(8):e1599.
3. Yacyshyn B. Pathophysiology of Clostridium difficile–associated diarrhea. *Gastroenterol Hepatol (N Y)*. 2016;12(9):558-560.
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5. Fernández-García L, Blasco L, López M, Tomás M. Clostridium difficile infection: pathogenesis, diagnosis, and treatment. In: Enany S, ed. Clostridium difficile – a comprehensive overview. InTech; 2017.
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10. Kelly CP. Can we identify patients at high risk of recurrent Clostridium difficile infection? *Clin Microbiol Infect*. 2012;18(Suppl 6):21-27.
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Disruption of the gut microbiome community may play a role in CDI and recurrent *Clostridioides difficile* infection (rCDI)[1]

HOMEOSTASIS

During homeostasis, the microbiota is composed of diverse organisms known to benefit host heath

USE OF ANTIMICROBIALS

STRESS

DIET

HYGIENE

DYSBIOSIS

Dysbiosis is the disruption of the composition and/or diversity of the gut microbiome

Pathobiont expansion

Reduced diversity

Loss of beneficial microbes

1. Petersen C, Round JL. Defining dysbiosis and its influence on host immunity and disease. *Cellular Microbiol*. 2014;16(7):1024-1033.

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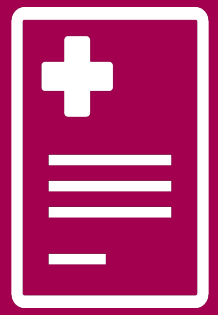
Fecal microbiota transplant (FMT) attempts to treat dysbiosis but has safety and consistency limitations[1-5]

FMT is not approved by the Food and Drug Administration (FDA)



Most studies assessing the benefits of FMT are retrospective case series or systematic reviews with limited safety data

Use of currently available modalities of FMT for rCDI may be suboptimal (eg, product is heterogenous)

3 safety alerts have been issued regarding FMT: 2 focused on the transmission of enteropathogens, and the most recent focused on potential COVID-19 transmission through stool

1. Drekonja D, et al. Fecal microbiota transplantation for Clostridium difficile infection: a systematic review. *Ann Intern Med*. 2015;162:630-638.
2. Leffler DA, Lamont JT. Clostridium difficile infection. *N Engl J Med*. 2015;372(16):1539-1548.
3. Wilcox MH, Gerding DN, Poxton IR, et al; for the MODIFY I and MODIFY II investigators. Bezlotoxumab for prevention of recurrent Clostridium difficile infection. *N Engl J Med*. 2017;376(4):305-317.
4. Gerding DN, Kelly CP, Rahav G, et al. Bezlotoxumab for prevention of recurrent Clostridium difficile infection in patients at increased risk for recurrence. *Clin Infect Dis*. 2018;67(5):649-656.
5. Tariq R, Pardi SD, Bartlett MG, Khanna S. Low cure rates in controlled trials of fecal microbiota transplantation for recurrent Clostridium difficile infection: a systematic review and meta-analysis. *Clin Infect Dis*. 2019;68(8):1351-1358.

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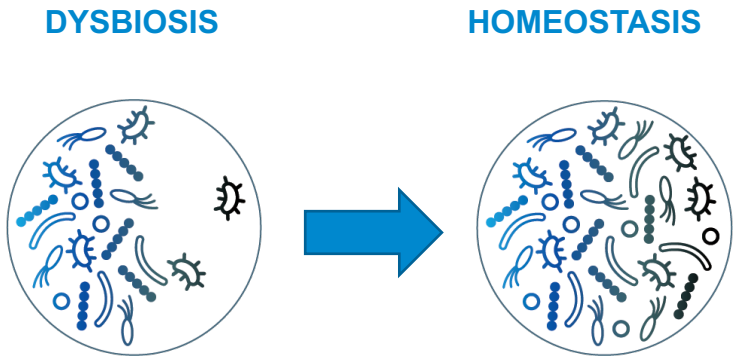
RBX2660 is a microbiota-based live biotherapeutic currently being studied for the treatment of rCDI[1]

RBX2660 leverages pharmaceutical GMP, standardized health screening, and pathogen testing to ensure patient safety

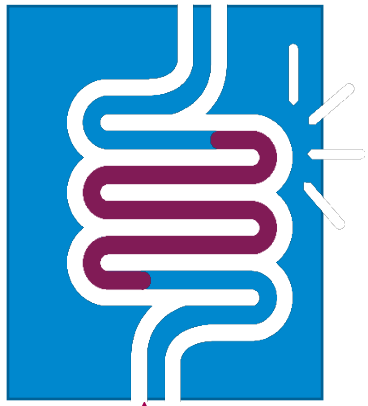
- Testing and screening protocols developed with guidance from the CDC and Minnesota Department of Health
  - Strict standards for donor acceptance and comprehensive evaluation, pathogenic blood testing, and ongoing monitoring
  - Tested for viruses, toxins, parasites, pathogens, and multidrug-resistant organisms
- Standardized, consistent pharmaceutical drug manufacturing process

Treatment with RBX2660 is associated with a change in the gut microbiome from dysbiosis to a composition and diversity similar to that of healthy individuals[a]



[a] **The exact mechanism of action of RBX2660 is unknown.**

Treatment administration



Single-dose microbiota suspension administered rectally by a healthcare provider[b]

[b] **24 to 72 hours after the last dose of antibiotics.**

RBX2660 received Fast Track and Breakthrough Therapy designations, demonstrating the unmet need in rCDI

CDC – Centers for Disease Control and Prevention; GMP – good manufacturing practice.

1. Data on File. TPP. Ferring Pharmaceuticals Inc.

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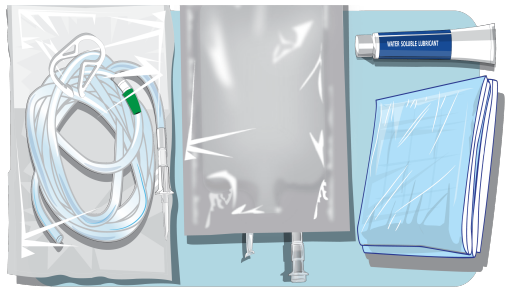
Patients should be administered RBX2660 24 to 72 hours after completing a course of antibiotics[1]

RBX2660 has no requirements for bowel preparation, colonoscopy, or conscious sedation

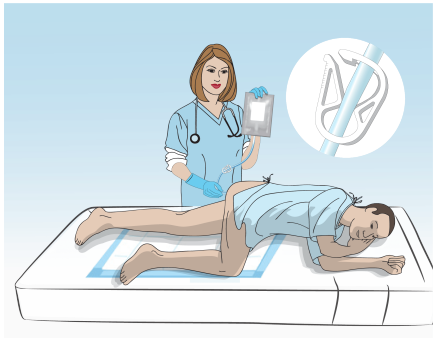
Steps for product administration:



The product is shipped frozen to the clinical site in a kit containing 1 bag of frozen RBX2660 and components for administration

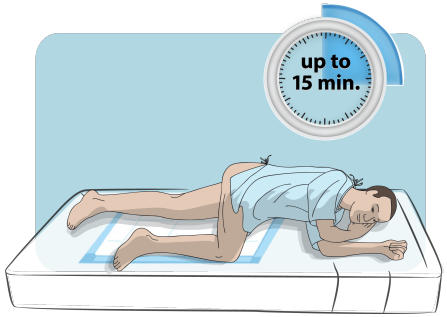
RBX2660 must be thawed completely prior to use

The patient will be asked to empty their bladder/ bowels, if possible



The patient will be positioned lying on left-side or knee-chest position

To administer, the healthcare provider must insert a lubricated tube into the patient's rectum about 12 cm (5 inches)



Once the product is fully instilled, the assembly should be removed

The patient should remain in the administration position for up to 15 minutes

The administration procedure will be detailed in a separate operative report that will become part of the patient's medical record

1. Ferring Pharmaceuticals Inc. Data on File.

RBX2660 can be used in both inpatient and outpatient settings[1]

Up to 85% of patients with rCDI are hospitalized[2] and, among Medicare beneficiaries, the average length of stay is ~18 days[3]

Similar to FMT, RBX2660 is administered after antibiotic treatment for reduction of rCDI

While FMT is not FDA approved and lacks standardized manufacturing and treatment protocols, it is used up to 17% of the time in the inpatient setting[4]

Certain patients who currently receive FMT in either inpatient or outpatient settings would be candidates for RBX2660 in the same care settings, according to market research and advisory boards with clinicians

1. Ferring Pharmaceuticals Inc. Data on File.
2. Rodrigues R, Barber GE, Ananthakrishnan AN. A comprehensive study of costs associated with recurrent Clostridium difficile infection. *Infect Control Hosp Epidemiol.* 2017;38(2):196-202.
3. Nelson WW, Scott TA, Boules M, et al. Health care resource utilization and costs of recurrent Clostridium difficile infection in the elderly: a real-world claims analysis. *J Manag Care Spec Pharm.* 2021;27(7):828-838.
4. Fischer M, Kao D, Mehta SR, et al. Predictors of early failure after fecal microbiota transplantation for the therapy of Clostridium difficile infection: a multicenter study. *Am J Gastroentrol.* 2016;111:1024-1031.

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RBX2660 has a robust clinical trial program across 1,000+ patients[1,2]

Study Design Criteria	PUNCH™ CD (Phase 2)	PUNCH™ CD2 (Phase 2b)	PUNCH™ Open-Label (Phase 2)	PUNCH™ CD3 (Phase 3)	PUNCH™ CD3-OLS (Phase 3)	Retrospective AAT Study
Patient population: Recurrent CDI	✓	✓	✓	✓	✓	✓
Efficacy endpoint: Preventing recurrent CDI	✓	✓	✓	✓	✓	✓
Consistent product: Same manufacturing process and release criteria	✓	✓	✓	✓	✓	✓
Controlled trial	Open-label	Yes	Open-label	Yes	Open-label	Open-label
Total subjects (active + control)	N=40	N=150	N=272	N=320	Up to N=200	N=94
Study duration	6 months	24 months	24 months	6 months	6 months	6 months
Current status	Complete	Complete	24-month safety follow-up	Complete	Ongoing	Ongoing

1. Ferring Pharmaceuticals Inc. Data on file: investigator's brochure RBX2660.
2. Rebiotix Inc. Microbiota restoration therapy for recurrent Clostridium difficile infection (PUNCHCD3). Accessed June 20, 2021. https://clinicaltrials.gov/ct2/show/NCT03244644.

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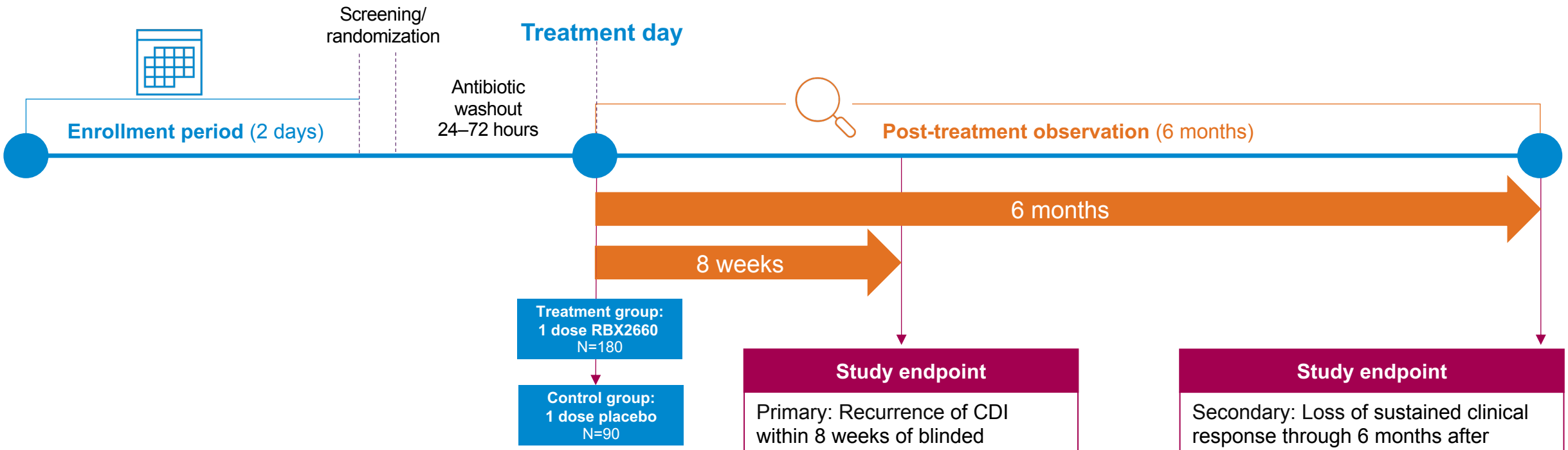
The PUNCH-CD3 study primary endpoint was designed to show reduction of rCDI within 8 weeks[1]

Inclusion criteria:
- Adult patients with ≥1 recurrence of CDI after primary episode **and**
- Completion of 1 round of standard of care oral antibiotic therapy **or**
- ≥2 rounds of severe CDI resulting in hospitalization within the last year

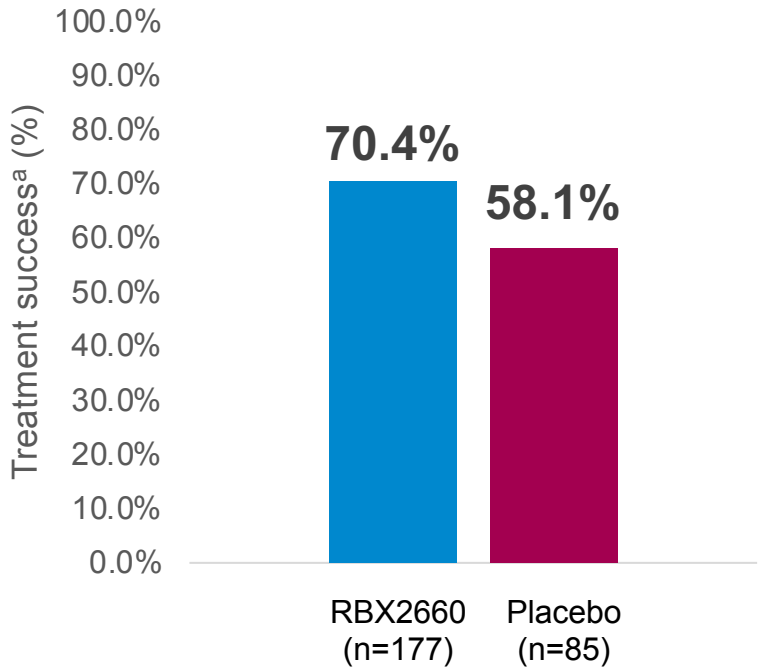
Key exclusion criteria:
- Has continued CDI diarrhea despite being on a course of antibiotics prescribed for CDI treatment
- Requires systemic antibiotic therapy for a condition other than CDI
- FMT within the past 6 months
- FMT with an associated serious adverse event (AE) related to the FMT product or procedure
- Bezlotoxumab (CDI monoclonal antibodies) if received within the last year



ClinicalTrials.gov Identifier: NCT03244644.

1. Ferring Pharmaceuticals Inc. Data on File. RBX2660 CSR.

RBX2660 demonstrated superior efficacy with a comparable safety profile to placebo[1-5]



98.6%

probability of RBX2660 treatment superiority[b]

Overall treatment-emergent AEs were similar to placebo, and the majority were mild to moderate in nature

- Most commonly reported AEs were gastrointestinal
- 2 (1.1%) participants treated with RBX2660 discontinued the study due to an AE (diarrhea)
- 2 deaths were reported; neither were related to RBX2660 or the product administration

[a] Treatment success is defined as the absence of *C difficile*-associated diarrhea (passage of 3 or more unformed stools, in 24 or fewer consecutive hours, for at least 2 consecutive days) at 56 days after the last treatment with RBX2660. Chart represents modified intent-to-treat population.

[b] The primary statistical analysis used a Bayesian hierarchical model, which formally incorporated data from a previous randomized phase 2B study (Protocol 2014-01) of RBX2660. Pre-defined threshold for superiority was 97.5%.

1. Data on File.
2. Orenstein R, Mische S, Blount D, et al. A long-time coming: final 2-year analysis of efficacy, durability, and microbiome changes in a controlled open-label trial of investigational microbiota-based drug RBX2660 for recurrent Clostridioides difficile infections. IDWeek 2019 late breaker oral abstract LB5. *Open Forum Infect Dis.* 2019;6(Suppl 2):S994-S995.
3. Garcia-Diaz J, Jones C, Karathia H, Fanelli B, Hasan NA, Blount K. Response to microbiota-base drug RBX2660 is associated with reduction in antimicrobial resistance genes in patients with recurrent Clostridioides difficile infections. Poster presented at ASM Microbe 2019; June 20-24, 2019; San Francisco, CA.
4. Jones C, Mische S, Blount K, Shannon B. Twelve-month durability of microbiota-based therapy RBX2660 for prevention of recurrent Clostridium difficile infection. IDWeek 2019 poster abstract 669. *Open Forum Infect Dis.* 2019;6(Suppl 2):S306.
5. Blount KF, Shannon WD, Deych E, Jones C. Restoration of bacterial microbiome composition and diversity among treatment responders in a phase 2 trial of RBX2660: an investigational microbiome restoration therapeutic. *Open Forum Infect Dis.* 2019;6(4):ofz095.

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