Week 24 Efficacy and Safety Data from PRISM3: A Randomized, Placebo-Controlled Trial Evaluating CP101, an Investigational Orally Administered Microbiome Therapeutic for the Prevention of Recurrent *C. difficile* Infection

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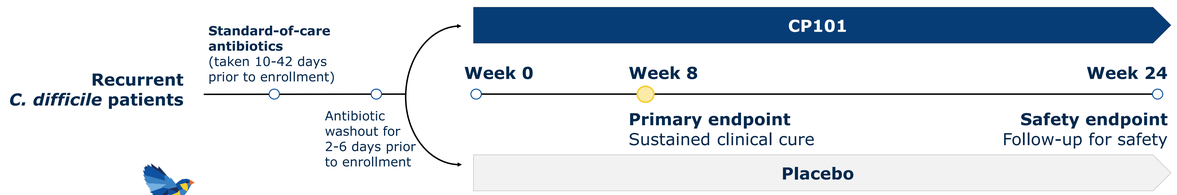
Background

- Disruption of the microbiome is key to the pathogenesis of recurrent *Clostridioides difficile* infection (CDI).
- Placebo-controlled trials assessing microbiome therapeutics have demonstrated efficacy in recurrent CDI; however, there is a paucity of data on response durability and long-term safety.
- CP101 is an investigational orally-administered microbiome therapeutic designed to restore microbiome diversity and enable early intervention in the management of recurrent CDI.
- Given its complete consortia composition, CP101 is hypothesized to have a durable effect.

Methods

- We conducted a double-blind, randomized, placebo-controlled trial (PRISM3) enrolling adults who received standard-of-care antibiotics for recurrent CDI.
- Patients with first CDI recurrence at high-risk for further recurrence (≥65 years), or those with two or more recurrences were eligible.
- The qualifying CDI episode was diagnosed prior to study entry by guideline recommended testing (PCR-based or toxin EIA-based).
- Following CDI antibiotics, eligible participants were randomized 1:1 to receive one-time oral administration of CP101 or placebo without bowel preparation.
- The primary efficacy endpoint was sustained clinical cure, defined as an absence of CDI recurrence through Week 8 following dosing.
- Secondary endpoints of efficacy and safety were evaluated through Week 24.

PRISM3 Study Design



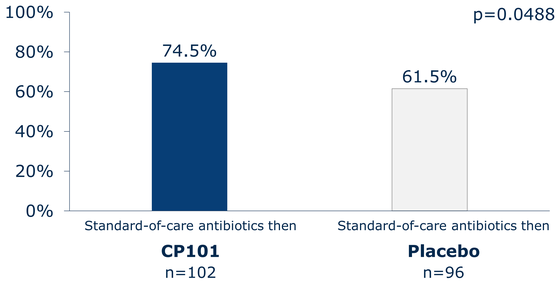
Results

Baseline characteristics were similar between treatment groups

Characteristics	CP101 (n=102)	Placebo (n=96)	Total (n=198)
Age in years - mean (SD)	65.9 (17.3)	66.5 (14.3)	66.2 (15.8)
Female sex - n (%)	69 (67.6)	65 (67.7)	134 (67.7)
Charlson comorbidity index - mean (SD)	3.9 (2.9)	3.8 (2.7)	3.9 (2.8)
Number of CDI recurrences - n (%)			
First recurrence	28 (27.5)	29 (30.2)	57 (28.8)
Second or further recurrence	73 (71.6)	67 (69.8)	140 (70.7)
NR	1 (1.0)	0 (0.0)	1 (0.5)
CDI laboratory test at study entry - n (%)			
PCR-based testing (alone or in combination)	64 (62.7)	57 (59.4)	121 (61.1)
Toxin EIA-based testing (alone or in combination)	36 (35.3)	38 (39.6)	74 (37.4)
NR	2 (2.0)	1 (1.0)	3 (1.5)

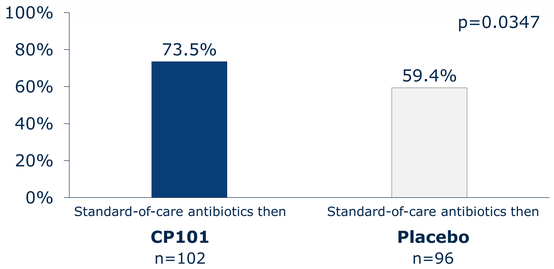
CP101 achieved 33.8% relative risk reduction for CDI recurrence

Primary efficacy analysis: Sustained clinical cure (absence of CDI recurrence) through Week 8



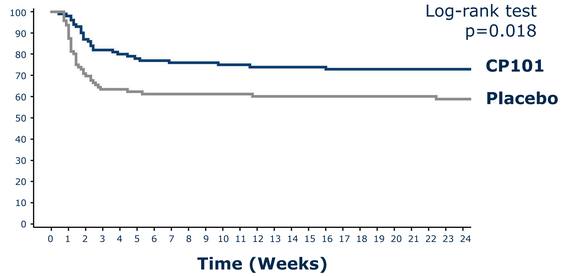
CP101 demonstrated durable efficacy for the prevention of recurrent CDI in PRISM3

Sustained clinical cure (absence of CDI recurrence) through Week 24



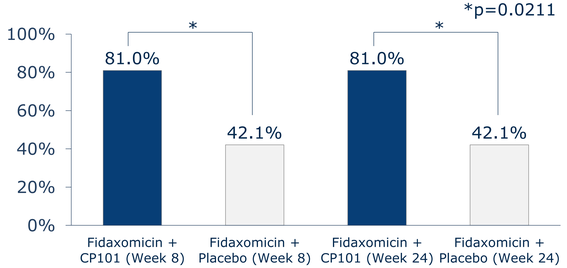
CP101 demonstrated a durable effect over time compared to placebo in PRISM3

Rate (%) of sustained clinical cure (absence of CDI recurrence) through Week 24



Significantly higher cure rate with targeted antibiotic fidaxomicin

Sustained clinical cure (absence of CDI recurrence through Week 8 and Week 24) in fidaxomicin subgroup (n=40)



*Fidaxomicin alone or in combination with vancomycin

CP101 exhibited favorable safety profile through Week 24

- In the safety population, adverse events and drug-related treatment emergent adverse events (TEAEs) were similar between treatment groups (CP101: n=17/104 [16.3%] vs Placebo: n=19/99 [19.2%]).
- In the CP101 arm, drug-related TEAEs were mild (Grade 1: 16/17) and moderate (Grade 2: 1/17), and primarily gastrointestinal in nature.
- No drug-related serious adverse events were reported in the CP101 arm.

Discussion

- CP101 is the first orally-administered investigational microbiome therapeutic to demonstrate durable efficacy and a favorable safety profile in a large RCT including patients with first CDI recurrence. Placebo-controlled trials in first recurrence are necessary to assess the clinical impact of microbiome therapeutics.
- CP101 demonstrated durable efficacy in a broad population including patients with PCR **or** Toxin EIA-based CDI testing at study entry. With ~83% of CDI diagnosed by PCR-based testing in the U.S., the trial results are generalizable to clinical practice[1].
- Persistence of residual colonic vancomycin due to a short washout period may have impacted CP101 efficacy, which is not expected with fidaxomicin, a targeted antibiotic. Future studies should aim to minimize the impact of residual antibiotic (e.g., extend washout).
- Early use of microbiome therapies such as CP101 may reduce the economic costs, morbidity, and mortality associated with recurrent CDI.

Conclusions

On long-term assessment, CP101 demonstrated durable efficacy for the prevention of recurrent CDI and a safety profile similar to placebo through Week 24.

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[1]Guh N Engl J Med 2020