Evaluation of Engraftment and Diversity Following Open-Label Administration of CP101, an Investigational Oral Microbiome Therapeutic for the Prevention of Recurrent *C. Difficile* Infection, in the PRISM-EXT Trial

Jessica R. Allegretti, Colleen Kelly, Monika Fischer, Ylaine Gerardin, Josh Silva, Jennifer Lau, Bharat Misra, Nick Van Hise, Thomas Louie, Thomas J. Borody, Shrish Budree, Sahil Khanna, PRISM Investigator Group

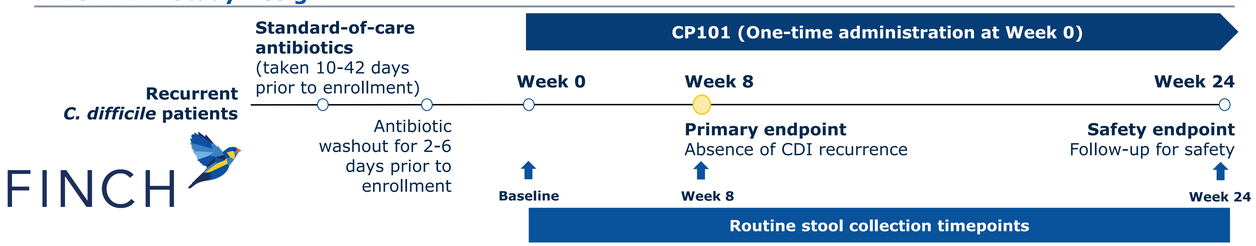
Background

- Disruption of the microbiome is key to the pathogenesis of recurrent *Clostridioides difficile* infection (CDI).
- CP101 is an investigational orally administered microbiome therapeutic designed to restore microbiome diversity and potentially enable early intervention in the management of recurrent CDI.
- Engraftment of drug-specific microbes and changes to the microbiome are important pharmacokinetic and pharmacodynamic markers of microbiome therapeutics.
- Overall, the pharmacology data and its connection to the mechanism of action for investigational microbiome therapies remains limited.

Methods

- PRISM-EXT was an open-label study of CP101 that enrolled adults with 1 or more CDI recurrences across 51 sites in the U.S. and Canada.
- The qualifying CDI episode was diagnosed by guideline-recommended testing (PCR or toxin EIA) and clinical symptoms.
- Following standard-of-care (SOC) antibiotics, participants received a one-time oral administration of CP101 without bowel preparation.
- PRISM-EXT comprised: 1) participants who rolled over from PRISM3, a Phase 2 randomized double-blind placebo-controlled trial, following an on-study CDI recurrence and 2) direct entry participants with recurrent CDI who were not previously enrolled in PRISM3.
- The primary efficacy endpoint was the proportion of participants without CDI recurrence through Week 8.
- Exploratory microbiome endpoints were measured at baseline following SOC antibiotics, Week 8 and 24 using 16S rRNA gene amplicon sequencing.
- Engraftment of CP101-associated taxa was determined by identification of CP101-associated operational taxonomic units (OTUs) in participants' post-treatment samples which were absent at baseline.
- Alpha diversity was measured using ecological richness, i.e., the number of OTUs per sample.
- Non-parametric tests (Wilcoxon/Mann-Whitney) were used to determine statistical significance.

PRISM-EXT Study Design



Results

PRISM-EXT enrolled PRISM3 rollovers and direct entry participants

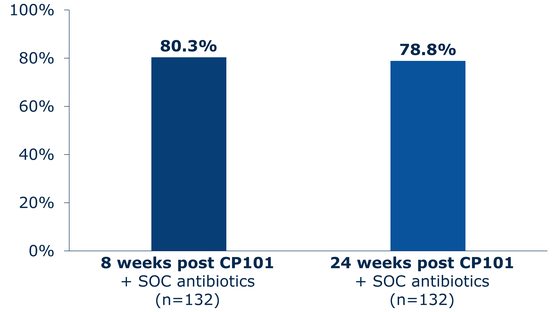
	PRISM-EXT			
	PRISM3 Rollover		Direct Entry N=82	Total N=132
	CP101 in PRISM3 N=20	Placebo in PRISM3 N=30		
Age in years - median (range)	76.5 (63-94)	71.0 (30-94)	67.0 (18-95)	69.5 (18-95)
Female sex - n (%)	17 (85%)	22 (73%)	60 (73%)	99 (75%)
Charlson comorbidity index - mean (SD)	5.3 (2.5)	3.6 (2.6)	3.0 (2.2)	3.5 (2.5)
Number of CDI episodes within the previous 6 months - n (%)				
≤ 2	1 (5%)	2 (7%)	43 (52%)	46 (35%)
≥ 3	19 (95%)	28 (93%)	39 (48%)	86 (65%)
Positive CDI laboratory test at study entry - n (%)				
PCR-based testing (alone or in combination)[1]	1 (5%)	0	39 (48%)	40 (30%)
Toxin EIA-based testing (alone or in combination)[2]	19 (95%)	30 (100%)	39 (48%)	88 (67%)
Not reported	0	0	4 (4%)	4 (3%)
Standard-of-care CDI antibiotic at study entry – n (%)				
Oral vancomycin (alone or in combination)	19 (95%)	25 (83%)	73 (89%)	117 (89%)
Oral fidaxomicin (alone or in combination)	2 (10%)	6 (20%)	16 (20%)	24 (18%)
Oral metronidazole (alone or in combination)	0	0	1 (1%)	1 (0.8%)

Abbreviations: SD = standard deviation; CDI = C. difficile infection; PCR = polymerase chain reaction; EIA = enzyme immunoassay; GDH = glutamate dehydrogenase

1. *PCR based testing includes: PCR positive alone or in combination (e.g. GDH+/PCR+; GDH+/toxin EIA-/PCR+; PCR+/Toxin EIA-/without toxigenic culture)*
2. *Toxin EIA based testing includes: Toxin EIA positive alone or in combination (e.g. GDH+/Toxin EIA+; PCR+/Toxin EIA+; GDH+/PCR+/Toxin EIA+; PCR+/Toxin EIA-/toxigenic culture+)*

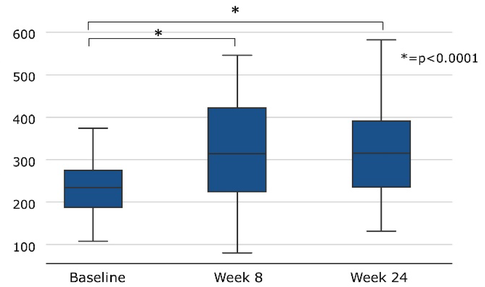
~80% of participants were without CDI recurrence at Week 8 and Week 24 in PRISM-EXT

Primary efficacy analysis: Proportion without CDI recurrence



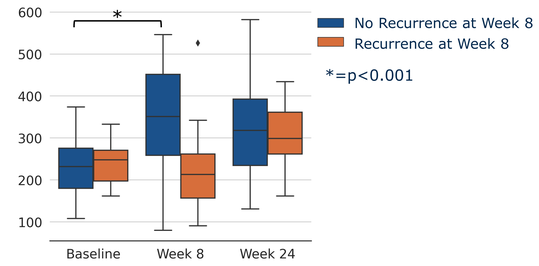
Increase in microbiome diversity following CP101 administration

Diversity (number of OTUs)



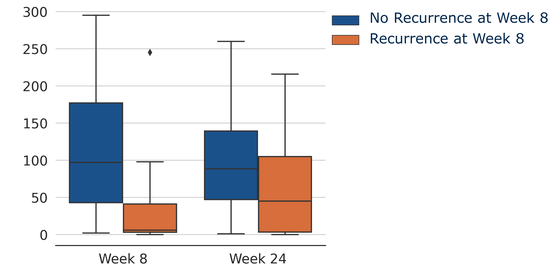
Increase in microbiome diversity at week 8 following CP101 is associated with no CDI recurrence at week 8

Diversity (number of OTUs)



Higher CP101 engraftment at week 8 and 24 is associated with no CDI recurrence at week 8

Number of CP101 associated OTUs



CP101 safety results from PRISM-EXT (n=132) are consistent with previously reported results

- No treatment-related serious adverse events (SAEs) or deaths.
- 9.8% of participants experienced a treatment related adverse event.
- Most frequent treatment-related adverse events were gastrointestinal symptoms (mild-moderate in severity).
- Participants that received a first dose of CP101 in PRISM3 and a second dose in PRISM-EXT exhibited a similar safety profile to those that received a single dose.
- No adverse events of special interest (e.g., bacteremia/sepsis or newly diagnosed autoimmune disease).

Discussion

- PRISM-EXT enrolled patients with one or more CDI recurrences and any guideline approved CDI diagnostic method in keeping with clinical practice.
- Approximately 80% of participants had no CDI recurrence through Week 8 following administration of SOC antibiotics and CP101 in PRISM-EXT.
- PRISM-EXT safety and efficacy results are consistent with the CP101 arm in PRISM3, a positive Phase 2 placebo-controlled trial of CP101 for the prevention of recurrent CDI.
- Following administration of CP101, there was a significant increase in microbiome diversity from baseline through Week 8 and 24.
- Higher engraftment of CP101-associated taxa and improvement in diversity were both associated with prevention of CDI recurrence at Week 8.
- Engraftment and diversity at Week 8 and 24 in participants with an on-study recurrence may have been affected by SOC-antibiotic exposure after CP101 dosing.

Conclusions

- **These data suggest that successful CP101 engraftment and increase in microbiome diversity are associated with the prevention of CDI recurrence.**
- **Strategies focused on optimizing engraftment of microbiome therapies may enhance clinical efficacy.**