CP101 Engraftment Drives Efficacy: Results from a Randomized, Placebo-Controlled Trial Evaluating CP101, an Investigational Orally Administered Microbiome Therapeutic for Prevention of Recurrent *C. difficile* Infection

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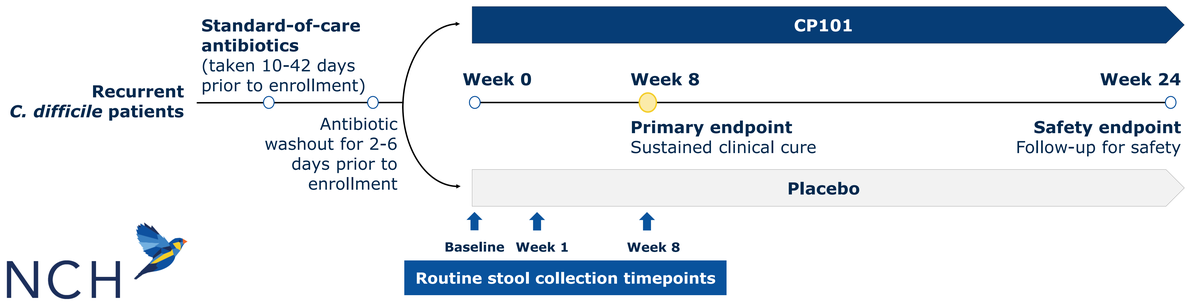
Background

- Disruption of the microbiome is key to the pathogenesis of recurrent *Clostridioides difficile* infection (CDI).
- CP101 is an investigational orally administered microbiome therapeutic designed to restore microbiome diversity and enable early intervention in the management of recurrent CDI.
- Engraftment, defined as the presence of product-specific microbes that colonize the gastrointestinal tract, is a key pharmacokinetic marker of microbiome therapeutics.
- There is a paucity of data on the impact of engraftment on clinical efficacy of microbiome therapeutics in patients with recurrent CDI.

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.
- Engraftment of CP101 was measured using 16S ribosomal RNA gene amplicon sequencing.
- Engraftment of CP101-associated taxa was determined by the identification of CP101-associated operational taxonomic units (OTUs) in participants' post-treatment samples which were absent at baseline.

PRISM3 Study Design



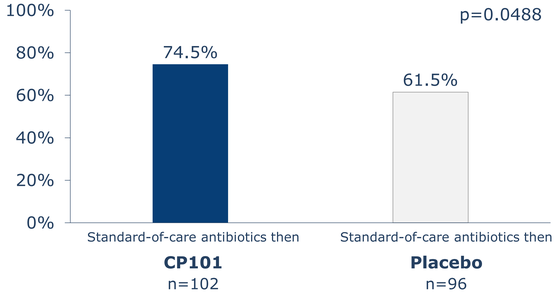
Results

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)

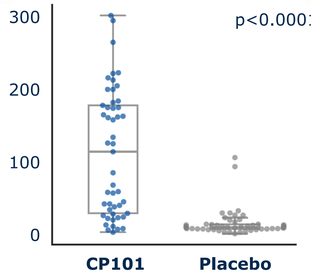
CP101 achieved 33.8% relative risk reduction for CDI recurrence

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



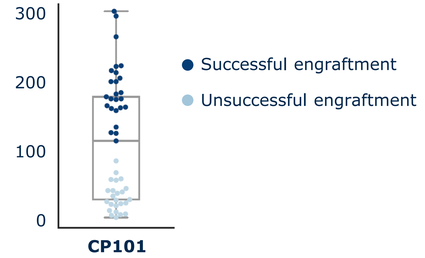
CP101 showed significant engraftment in PRISM3

Number of engrafted CP101-associated taxa at Week 1



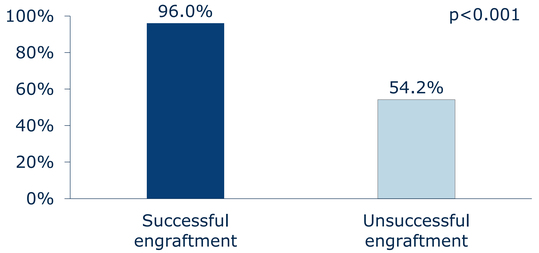
CP101 engraftment showed a bimodal distribution in PRISM3

Number of engrafted CP101-associated taxa at Week 1



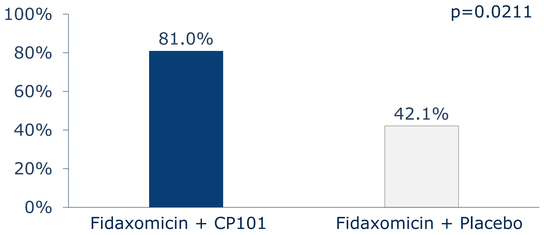
CP101 engraftment strongly associated with sustained clinical cure in PRISM3

Sustained clinical cure (absence of CDI recurrence through Week 8) by engraftment group



Significantly higher sustained clinical cure rate with targeted antibiotic fidaxomicin

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



*Fidaxomicin alone or in combination with vancomycin

Discussion

- We observed a strong relationship between engraftment and clinical outcomes in PRISM3.
- Engraftment of CP101 microbes may have been impacted by the persistence of residual broad-spectrum vancomycin, despite participants completing a minimum two-day washout period to ensure antibiotic clearance from the colon.
- Data suggest that a two-day washout period may be insufficient to clear residual vancomycin[1].
- In contrast to vancomycin, residual fidaxomicin, a targeted antibiotic with expected limited activity against CP101 microbes, should not impact CP101 activity.
- In a pre-specified subgroup analysis, we observed a 38.8% difference in the rate of sustained clinical cure between CP101 and placebo among those treated with fidaxomicin (p=0.0211).

Conclusions

- **These data suggest that successful CP101 engraftment drives high rates of sustained clinical cure in recurrent CDI.**
- **Future trials will deploy strategies to optimize engraftment by further minimizing the effect of residual CDI antibiotics.**

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[1]Abujamel PLoS One 2013