

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

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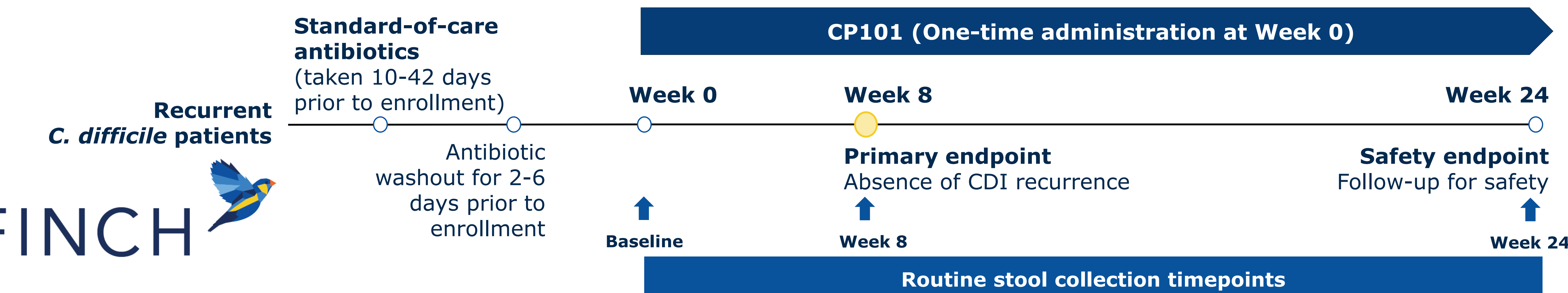
Background

- 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 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



PRISM-EXT enrolled PRISM3 rollovers and direct entry participants

	PRISM-EXT			Total N=132
	PRISM3 CP101 in PRISM3 N=20	Rollover Placebo in PRISM3 N=30	Direct Entry N=82	
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%)

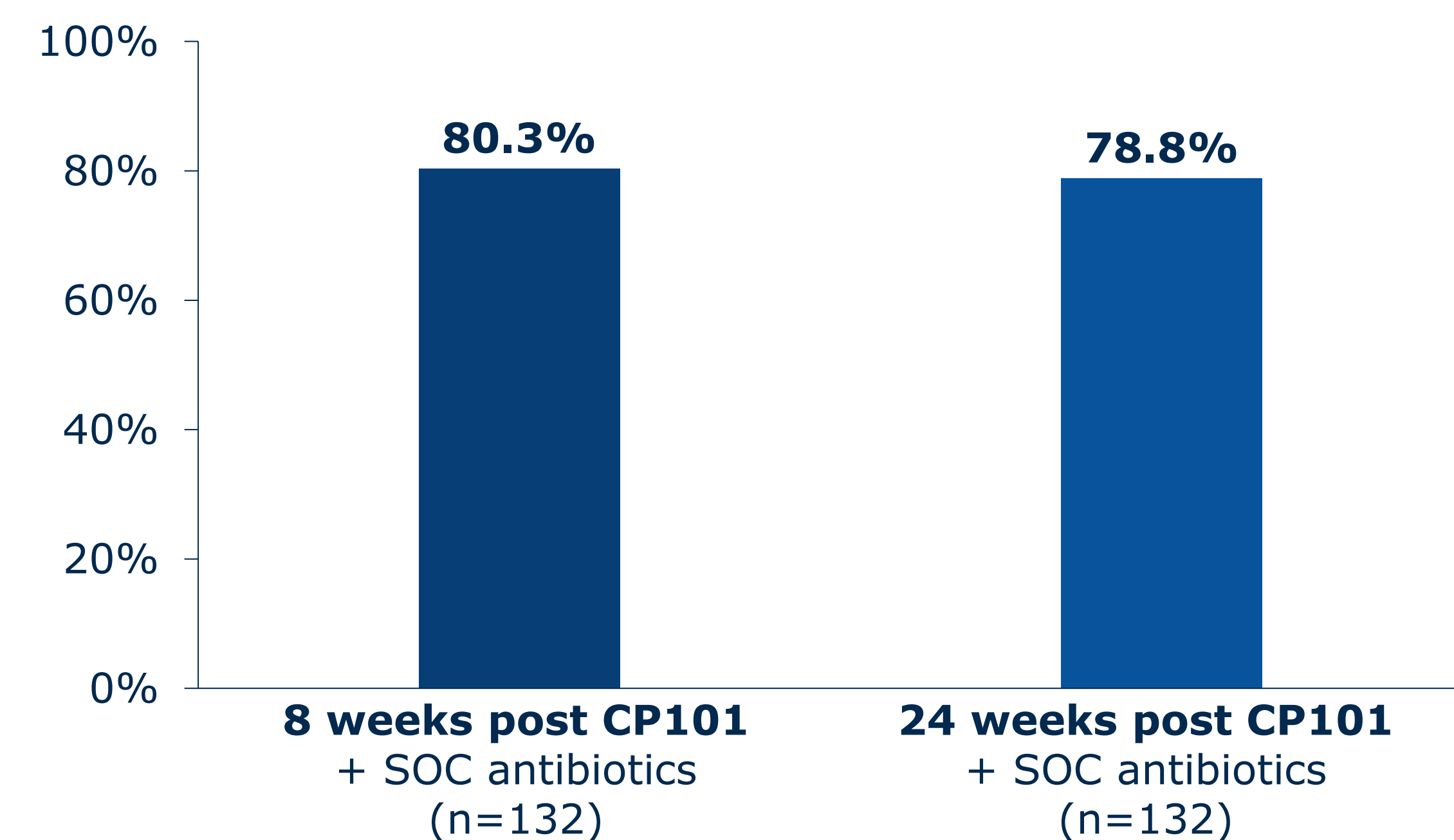
Abbreviations: SD = standard deviation; CDI = *C. difficile* infection; PCR = polymerase chain reaction; EIA = enzyme immunoassay; GDH = glutamate dehydrogenase

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+)

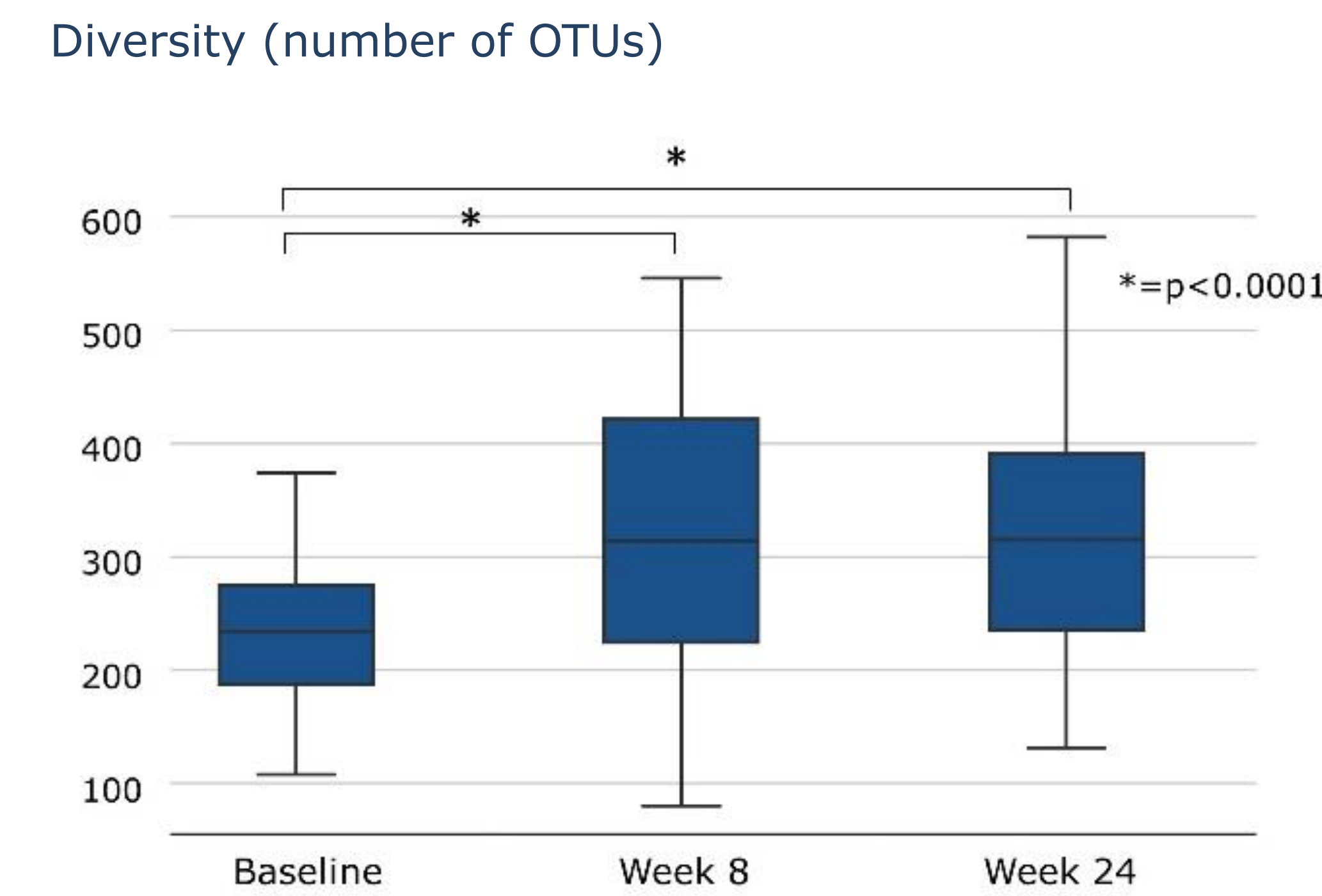
~80% of participants were without CDI recurrence at Week 8 and Week 24 in PRISM-EXT

Primary efficacy analysis: Proportion without CDI recurrence

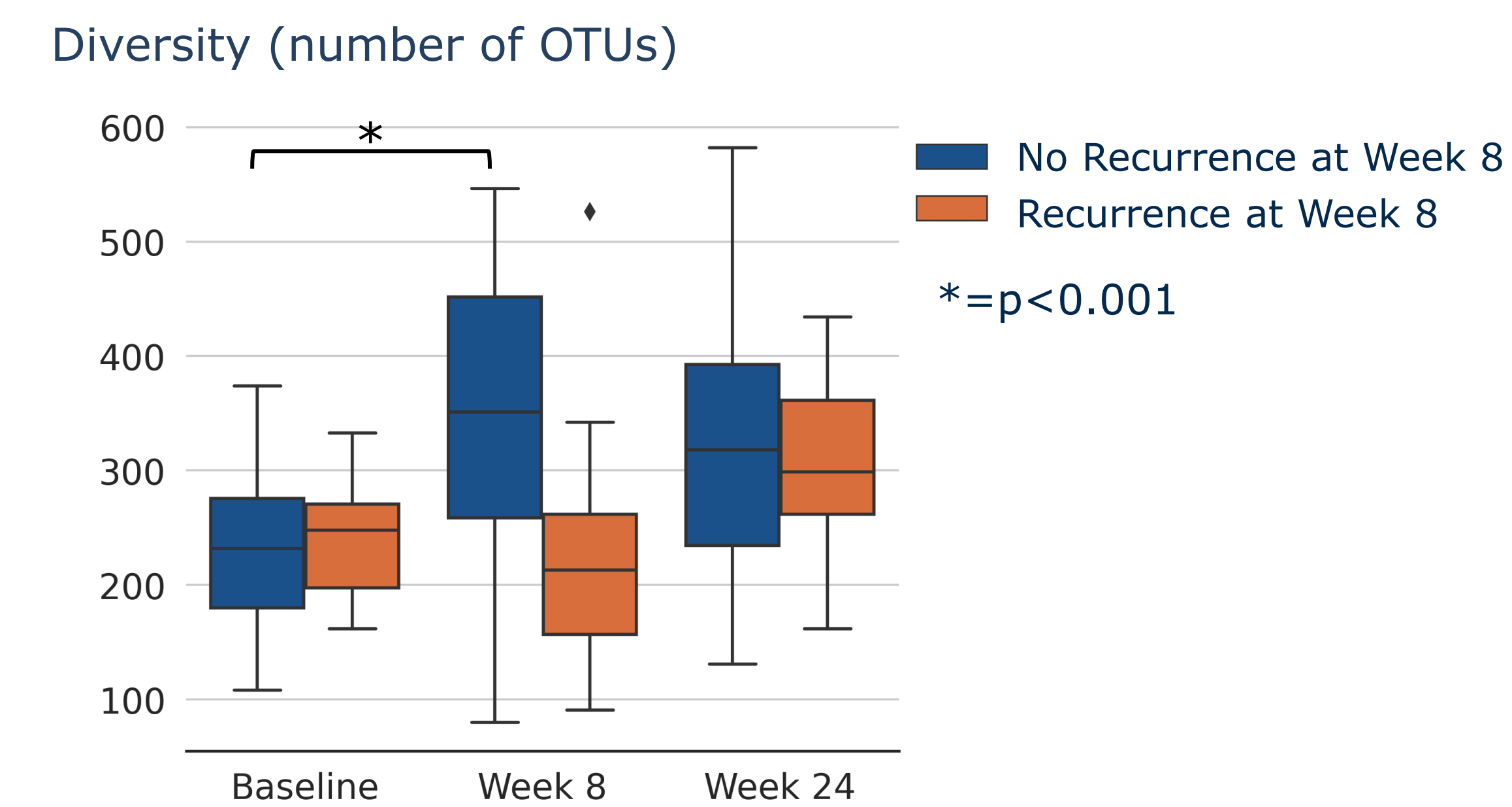


Results

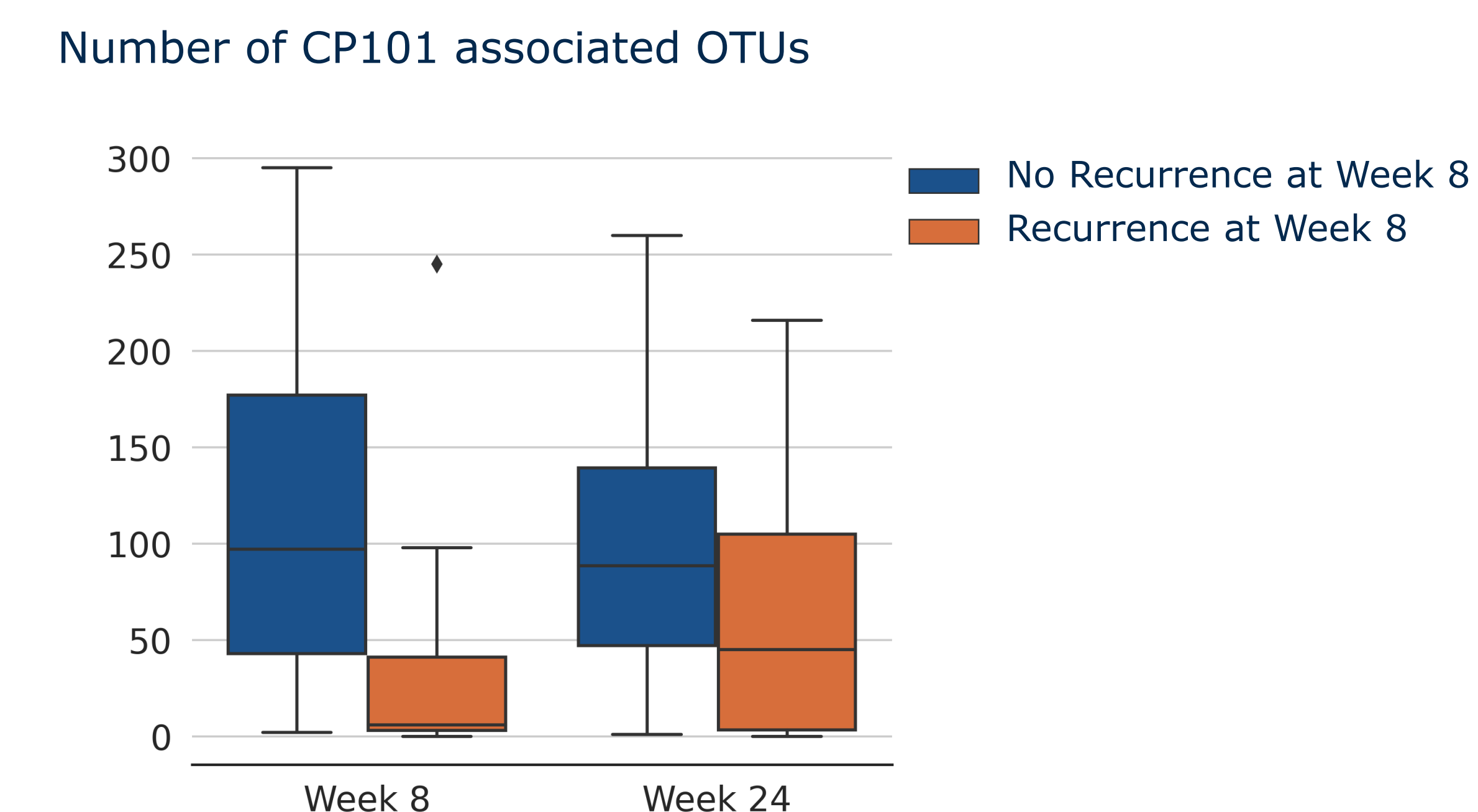
Increase in microbiome diversity following CP101 administration



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



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



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.