1950. Prevention of Recurrent *Clostridium difficile* at Six Months Following Treatment With Microbiota-Based Therapy RBX2660: Durability Results From a Phase 2 Open-Label Study

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Background. Numerous microbiota-based therapies are being evaluated for prevention of *C. difficile* infection (rCDI), a public health threat with high recurrence rates associated with the current standard of care. RBX2660, a standardized microbiota-based drug, was efficacious for preventing rCDI in a double-blinded Phase 2b clinical study (PUNCH CD 2). Herein we report the durability of RBX2660 beyond the initial primary clinical end-point of a subsequent Phase 2 open-label study, demonstrating rCDI prevention at 6 months post-treatment.

Methods. This prospective, multi-center, open-label Phase 2 study enrolled subjects who had experienced either ≥2 recurrences of CDI following standard-of-care antibiotic therapy or ≥2 episodes of severe CDI requiring hospitalization. Participants received up to two doses of RBX2660 delivered via enema with doses 7 days apart. The primary endpoint of the open-label clinical study defined efficacy as absence of CDI at 8 weeks from the last dose. Safety follow-ups and durability assessments occurred via telephone at 3, 6, 12, and 24 months. The study is ongoing, and not all subjects have completed their assessments.

Results. This study included 149 RBX2660-treated subjects and 110 historical control subjects from 31 and 4 centers, respectively, in the United States and Canada. At 8-weeks post-treatment, RBX2660's efficacy in preventing rCDI (79.9%; 119/149) was higher than CDI-free rates in the historical control group (51.8%, 57/110; $P < 0.001$). Of the 119 subjects who were determined to be treatment success at 8 weeks, 117 have data through 6 months, of which 8 were exited for non-CDI reasons. Of those 109 subjects through the 6-month follow-up, 3 (2.8%) had a new CDI beyond 8 weeks after enema. The 6-month long-term CDI-free rate was 97.2% (106/109) (median follow-up: 182 days; mean: 177 days).

Conclusion. RBX2660, a microbiota-based drug, was efficacious for the prevention of recurrent CDI with long-term durability at 6-months post-treatment; a result consistent with 6-month rCDI prevention reported for the Phase 2b PUNCH CD 2 trial. Long-term follow-up of RBX2660 safety and efficacy 24 months is ongoing.

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1951. Nephrotoxicity Associated With Imipenem/Cilastatin/Relebactam (IMI/REL) vs. Imipenem/Cilastatin Plus Colistin (IMI+CST) in Patients With Imipenem-Nonsusceptible (NS) Bacterial Infections

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Background. Nephrotoxicity is a common complication of CST-based therapy, limiting its use to treat carbapenem-resistant bacterial infections. REL is a novel β-lactamase inhibitor that restores imipenem activity against many imipenem-NS strains of Gram-negative pathogens. IMI/REL was shown to be as effective but better tolerated than IMI+CST in the phase 3 RESTORE-IMI 1 study (NCT02452047), including a lower incidence of treatment-emergent nephrotoxicity (prespecified secondary endpoint). Here we present additional renal safety data from that trial.

Methods. Randomized, active-controlled, double-blind, phase 3 trial in adults with infections caused by ≥1 imipenem-NS (but CST- and IMI/REL-susceptible) pathogen. Treatment (2:1) was IMI/REL or IMI+CST for 5–21 days in complicated intra-abdominal infection and complicated urinary tract infection and 7–21 days in hospital-acquired/ventilator-associated bacterial pneumonia. For baseline serum creatinine (Cr) <1.2 mg/dL, nephrotoxicity was defined as a doubling of serum Cr to >1.2 mg/dL OR decrease in Cr clearance [CrCl] ≥50%; for Cr ≥1.2 mg/dL, nephrotoxicity was defined as an increase in serum Cr ≥1 mg/dL OR decrease from baseline in CrCl ≥20% OR need for renal replacement therapy. KDIGO and RIFLE criteria of acute kidney injury (AKI) were applied to the data; renal-related adverse events (AEs) were analyzed.

Results. A total of 47 patients were randomized, treated (31 IMI/REL, 16 IMI+CST), and included in this analysis. A significantly smaller percentage of patients in the IMI/REL than the IMI+CST group experienced protocol-defined nephrotoxicity (% difference: −45.9 [95% CI: −69.1, −18.4]; $P = 0.002$) during study treatment and the 14-day follow-up period (table). These results were confirmed by applying KDIGO and RIFLE criteria, with no patients in the IMI/REL group in stage 3 AKI or failure compared with 31.3% and 25.0%, respectively, in the IMI+CST group. Fewer renal AEs, including discontinuations due to renal events, were observed in the IMI/REL group.

Conclusion. IMI/REL demonstrates a more favorable renal safety profile compared with CST-based therapy, as demonstrated by a lower incidence of treatment-emergent nephrotoxicity and AKI with IMI/REL across several different analyses.

Table. Protocol-specified nephrotoxicity and renal AEs

	IMI/REL N=31		IMI+CST[a] N=16	
	n/m	% (95% CI)	n/m	% (95% CI)
Protocol-specified nephrotoxicity	3/29	10.3 (2.8, 27.2)	9/16	56.3 (33.2, 76.9)
AKI (KDIGO)	**n/m**	**%**	**n/m**	**%**
Stage 1	5/29	17.2	6/16	37.5
Stage 2	1/29	3.4	2/16	12.5
Stage 3	0/29	0	5/16	31.3
AKI (RIFLE)	**n/m**	**%**	**n/m**	**%**
Risk	3/29	10.3	6/16	37.5
Injury	1/29	3.4	2/16	12.5
Failure	0/29	0	4/16	25.0
Renal AEs[b]	**n/m**	**%**	**n/m**	**%**
Blood Cr increased	0/31	0	4/16	25.0
Blood urea increased	0/31	0	1/16	6.3
CrCl decreased	2/31	6.5	2/16	12.5
GFR decreased	0/31	0	1/16	6.3
Acute kidney injury	1/31	3.2	0/16	0
Renal failure	1/31	3.2	0/16	0
Drug-related renal AEs leading to discontinuation of treatment	**n/m**	**%**	**n/m**	**%**
Blood Cr increased	0/31	0	1/16	6.3
CrCl decreased	0/31	0	1/16	6.3

[a]Provided as colistimethate sodium. [b]Based on investigator assessment.
GFR, glomerular filtration rate; n/m, number of patients with event of interest/number of patients evaluable (for nephrotoxicity and AKI, those with a baseline Cr measurement and ≥1 Cr measurement following ≥1 dose of study therapy).
Two IMI/REL patients with missing Cr values were excluded from nephrotoxicity/AKI analyses.
Protocol-specified nephrotoxicity: CrCl was estimated by Cockcroft Gault equation (Cockcroft DW, Gault MH. *Nephron.* 1976;16[1]:31-41).
KDIGO (Kidney Disease: Improving Global Outcomes) Criteria: KDIGO Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl.* 2012 Mar;2(1):1-138.
RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) Criteria: GFR was estimated based on the Chronic Kidney Disease Epidemiology Collaboration equation (Levey AS, et al. *Ann Intern Med*. 2009;150[9]:604-612).

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1952. Evaluation of Relapse and Reinfection Using Whole-Genome Sequencing of *Clostridium difficile* Isolates From Elderly Patients With *C. difficile* Infection (CDI) in the EXTEND Randomized, Controlled, Comparative Study of Extended-Pulsed Fidaxomicin and Vancomycin for the Treatment of CDI

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Background. The EXTEND study demonstrated reduced 90-day recurrence rates for an extended-pulsed regimen of fidaxomicin (EPFX) vs. standard vancomycin (SV) in the treatment of *Clostridium difficile* infection (CDI): treatment difference −13%, $P = 0.00073$.[1] Whole-genome sequencing (WGS) is used to differentiate between