Safety and Efficacy of Fecal Microbiota, Live-jslm in Reducing Recurrent *Clostridioides difficile* Infection in Immunocompromised Participants

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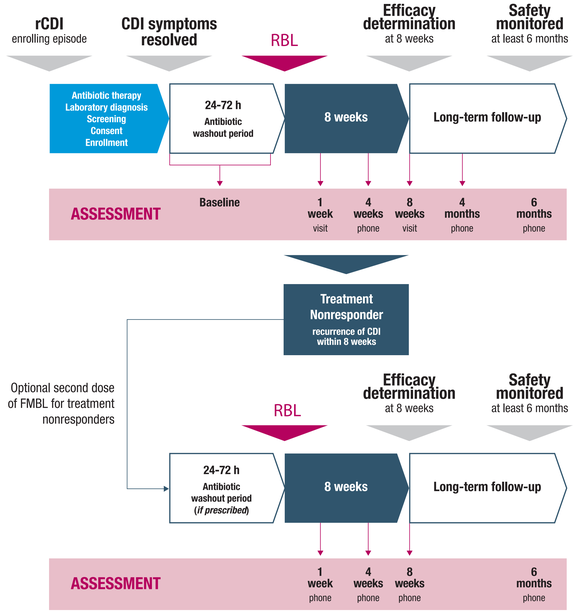
BACKGROUND

- *Clostridioides difficile* is an opportunistic pathogen that causes an estimated 500,000 infections and 29,300 deaths in the United States annually[1]
- Patients who are immunocompromised are at increased risk for primary and recurrent *C. difficile* infection (rCDI)[2]
- There are additional concerns that patients with immunocompromising conditions may be at increased risk for adverse events (AEs) related to fecal microbiota transplant (FMT), such as systemic infection[3]
- Fecal microbiota, live-jslm (RBL; REBYOTA™) is the first US Food and Drug Administration–approved, single-dose, rectally-administered, microbiota-based live biotherapeutic product indicated for the prevention of rCDI in adults, following antibiotic treatment for rCDI[4]
- The safety and efficacy of RBL in participants with immunocompromising conditions with rCDI are reported from an ad hoc analysis of PUNCH CD3-OLS (NCT03931941), an ongoing open-label, single-arm, phase 3 trial

METHODS

- Participants enrolled were ≥18 years old with medically documented rCDI, including first recurrence, as determined by the treating physician or had at least 2 episodes of severe CDI resulting in hospitalisation
- Notable exclusion criteria were CD4 cell count <200 cells/mm^3 or absolute neutrophil count <1000 cells/mm^3 at the time of screening, receipt of FMT within the past 6 months, and treatment with bezlotoxumab within the past year
- Participants with immunocompromising conditions were identified based on concomitant medication use (**Supplementary Table 1**) and medical history (**Supplementary Methods**)
- Participants received a single 150-mL dose of RBL via rectal administration without bowel preparation
- Treatment success was defined as the absence of rCDI through 8 weeks after treatment
- Participants were monitored for at least 6 months after treatment

Figure 1. PUNCH CD3-OLS Trial Design



CDI, *Clostridioides difficile* infection; RBL, fecal microbiota, live-jslm; rCDI, recurrent CDI.

KEY TAKEAWAYS

1. **No major safety signals were found in PUNCH CD3-OLS; RBL showed sustained efficacy through 6 months in immunocompromised participants**
2. **8-week treatment success and 6-month sustained response rates were comparable in participants with and without immunocompromising conditions**
3. **Efficacy outcomes are consistent with results of the pivotal phase 3 randomized controlled trial, PUNCH CD3 (70.6% treatment success at 8 weeks and 92.1% sustained response at 6 months in RBL participants)[6]**
4. **The safety and efficacy outcomes of RBL in this ad hoc analysis agree with previous FMT studies in immunocompromised patients with recurrent, refractory, or severe CDI[3,7]**
5. **There were no reported instances of bacteraemia or fungaemia related to RBL in these high-risk participants**

RESULTS

Table 1. Demographics and Baseline Characteristics (safety population)

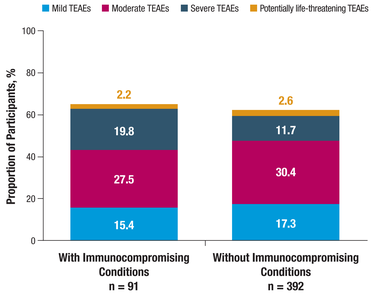
Demographic/Baseline Characteristic	PUNCH CD3-OLS Safety Population N = 483
Age, mean (SD), years	60.4 (17.4)
Female, n (%)	337 (69.8)
White, n (%)	453 (93.8)
No. of prior CDI episodes, n (%)	
Not available[a]	6 (1.2)
1	3 (0.6)
2	138 (28.6)
3	187 (38.7)
>3	149 (30.8)
Concomitant immunocompromising medications, n (%)[b]	
Corticosteroids	13 (2.7)
Noncorticosteroids[c]	61 (12.6)
Immunocompromising conditions, medical history, n (%)[a,b]	
Malignant tumours	24 (5.0)
End-stage renal disease	6 (1.2)
Immunodeficiency syndromes[d]	5 (1.0)
HIV	2 (0.4)
Congenital haemoglobinopathies	1 (0.2)

- **91 (18.8%) of 483 participants had immunocompromising conditions—mostly secondary to concomitant medication use (81.3% [n = 74/91])**

CDI, *Clostridioides difficile* infection; EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; LAMP, loop-mediated isothermal amplification; PCR, polymerase chain reaction.

[a]Data for these participants were not available at the time of this analysis because of the ongoing nature of PUNCH CD3-OLS.
[b]Participants can be included in more than 1 immunocompromising category and on multiple medications.
[c]Noncorticosteroids medications are summarized in **Supplementary Table 1**
[d]Hypogammaglobulinemia, IgA deficiency (n = 2), immune system deficiency, and medication-related immunosuppression.

Figure 2. TEAEs Through 6 Months (safety population)



- **TEAEs were reported in a similar proportion of participants with and without immunocompromising conditions (64.8% and 62.0%, respectively)**
- **Most participants with and without immunocompromising conditions experienced TEAEs that were of mild or moderate severity (42.9% and 47.7%, respectively)**

TEAEs, treatment-emergent adverse events.

Percentage of participants with TEAEs by maximum severity; severity was determined by the site investigator. Participants with multiple events were counted according to the event with the maximum severity.

Table 2. Serious TEAEs Through 6 Months (safety population)

n (%)	With Immunocompromising Conditions n = 91	Without Immunocompromising Conditions n = 392
Any serious TEAE	18 (19.8)	33 (8.4)
Serious TEAEs by relatedness[a]		
RBL	1 (1.1)[b]	1 (0.3)[c]
Administration procedure	0	1 (0.3)
CDI	6 (6.6)	12 (3.1)
Pre-existing condition	10 (11.0)	25 (6.4)
Discontinued because of TEAEs	1 (1.1)	2 (0.5)
TEAEs leading to death	1 (1.1)[d]	2 (0.5)[e]

CDI, *Clostridioides difficile* infection; RBL, fecal microbiota, live-jslm; TEAEs, treatment-emergent adverse events.

[a]TEAEs were categorised by relatedness by the site investigator; an event could be related to any of the parameters (one or multiple).
[b]Due to CDI.
[c]Due to ulcerative colitis flare in a participant with pre-existing ulcerative colitis. Assessed as possibly related to RBL and definitely related to pre-existing conditions.
[d]Due to cardiac arrest unrelated to RBL and administration procedure but related to pre-existing conditions.
[e]Due to pulmonary sepsis unrelated to RBL and administration procedure but related to pre-existing conditions (n = 1); complications of spina bifida unrelated to RBL and administration procedure, probably related to CDI, and possibly related to pre-existing conditions (n = 1).

- **Most serious TEAEs were related to CDI or pre-existing conditions**
- **Serious TEAEs occurred across different system organ classes, with most occurring in less than 1% of participants, without clustering or trends**

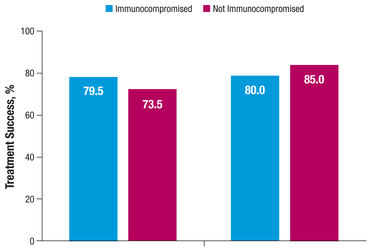
Table 3. TEAEs in ≥5% of Participants (safety population)

System Organ Class/Preferred Term, n (%)	With Immunocompromising Conditions n = 91	Without Immunocompromising Conditions n = 392
GI disorders	36 (39.6)	168 (42.9)
Diarrhoea	19 (20.9)	82 (20.9)
Abdominal pain	11 (12.1)	55 (14.0)
Nausea	8 (8.8)	37 (9.4)
Abdominal distension	4 (4.4)	28 (7.1)
Flatulence	5 (5.5)	24 (6.1)
Constipation	5 (5.5)	17 (4.3)
General disorders and administration site conditions	11 (12.1)	35 (8.9)
Pyrexia	5 (5.5)	7 (1.8)
Infections and infestations	25 (27.5)	80 (20.4)
UTI	4 (4.4)	23 (5.9)
Musculoskeletal and connective tissue disorders	7 (7.7)	31 (7.9)
Nervous system disorders	7 (7.7)	38 (9.7)

GI, gastrointestinal; TEAEs, treatment-emergent adverse events; UTI, urinary tract infection.

- **GI events like diarrhea and nausea were most frequently reported TEAEs in participants with and without immunocompromising conditions**
- **No participant with immunocompromising conditions was reported to experience bacteraemia or fungaemia**

Figure 3. 8-Week Treatment Success and 6-Month Sustained Response (mITT population)



Treatment Success, % (n/N)[a]	
Immuno-compromised	Not Immuno-compromised
79.5 (62/78)	73.5 (238/324)

Sustained Response Through 6 Months, % (n/N)[b]	
Immuno-compromised	Not Immuno-compromised
80.0 (44/55)	85.0 (176/207)

- **Treatment success was comparable in participants with and without immunocompromising conditions (79.5% and 73.5%, respectively)**
- **Sustained clinical response through 6 months was maintained in 80.0% and 85.0% of RBL responders with and without immunocompromising conditions, respectively**

mITT, modified intent-to-treat.

[a]Only participants with adjudicated treatment outcomes are included.
[b]Number of participants with treatment outcome adjudications by the Endpoint Adjudication Committee and completed 6-month follow-up or discontinued from the study.

References

1. Guh AY, et al. *N Engl J Med.* 2020;382:1320-1330.
2. DePestel DD, et al. *J Pharm Pract.* 2013;26:464-475.
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4. REBYOTA™ (fecal microbiota, live-jslm). Prescribing information. Ferring Pharmaceuticals Inc. November 2022.
5. Centers for Disease Control and Prevention. Accessed March 2, 2023. https://www.cdc.gov/vaccines/vpd/pneumo/hcp/recommendations.html.
6. Khanna S, et al. *Drugs.* 2022;82(15):1527-1538.
7. Cheng YW, et al. *Am J Transplant.* 2019;19(2):501-511.

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Contact Information

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Disclosures

ED: Serves on the Rebiotix Physician Advisory Board, received research grants from Synthetic Biologics and consulting fees from Pfizer, Merck, Seres, and Abbott

MF: Serves on the DSMB for Rebiotix, advisory board member for Ferring Pharmaceuticals and Seres Pharmaceuticals

GT: Consultant for Ferring Pharmaceuticals, Dynavax Therapeutics, and Spero Pharmaceuticals

MB and FH: Employees of Ferring Pharmaceuticals

BG: Employee of Rebiotix Inc., a Ferring Company

CA: Received prior research funding from Merck (paid to her institution) and served in an advisory role to Cidara Therapeutics, AiCuris, and Merck

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SUPPLEMENTAL INFORMATION

Supplementary Methods

- Systemically administered concomitant medications (**Table S1**) were identified based on the Anatomical Therapeutic Chemical classification during the period between 2 weeks before RBL administration to 8 weeks after RBL administration
- Corticosteroids (≥20 mg prednisone/day or prednisone equivalent doses) were considered to be immunocompromising
- Immunocompromising conditions were identified based on standardised Medical Dictionary for Regulatory Activities queries for malignant tumours and the following conditions based on the Centers for Disease Control and Prevention (CDC) guidelines for immunocompromised conditions listed under CDC pneumococcal vaccine recommendations: end-stage renal disease/renal failure, asplenia, HIV infection, congenital haemoglobinopathies, and immunodeficiency syndromes[5]

Table S1. List of Concomitant Noncorticosteroids Taken by PUNCH CD3-OLS Participants (safety population)

Medication Class	Standardized Medication Name	Number of Participants, n
Disease-modifying antirheumatic drugs	Hydroxychloroquine	8
	Methotrexate	5
	Azathioprine	3
	Leflunomide	3
Biologics	Vedolizumab	10
	Ustekinumab	4
	Rituximab	2
	Ixekizumab	1
	Trastuzumab emtansine	1
TNF-α inhibitors	Infliximab	10
	Adalimumab	3
Antineoplastic agents	Mercaptopurine	2
	Daunorubicin	1
	Etoposide	1
	Lenalidomide	1
	Hydroxycarbamide	1
	Oxaliplatin	1
	Vincristine	1
	Cyclophosphamide	1
	Fluorouracil	2
	Ifosfamide	1
Calcineurin inhibitors	Tacrolimus	6
	Cyclosporine	1
Protein kinase inhibitors	Dasatinib	1
	Imatinib	1
	Osimertinib	1
Interferons	Interferon β-1A	1
Other immunosuppressants	Mycophenolate mofetil/ sodium	4
	Tofacitinib	2
	Sirolimus	1

TNF, tumour necrosis factor.

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1. Guh AY, et al. *N Engl J Med.* 2020;382:1320-1330.
2. DePestel DD, et al. *J Pharm Pract.* 2013;26:464-475.
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