Budget impact analysis of REBYOTA™ (fecal microbiota, live-jslm [FMBL]) for preventing recurrent *Clostridioides difficile* infection in the US

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ABSTRACT

Introduction: Patients with *Clostridioides difficile* infection (CDI) often experience recurrences (rCDI), which are associated with high morbidity, mortality, and healthcare expenditures. REBYOTA™ (fecal microbiota, live-jslm [FMBL]) is a microbiota-based live biotherapeutic approved for the prevention of rCDI following antibiotic treatment for rCDI. We quantified the budget impact of FMBL during the first 3 years following introduction from a third-party US payer perspective.

Methods: A decision-tree model was used to estimate the budget impact of one-course FMBL by comparing costs under the scenario with FMBL to the scenario without FMBL (standard of care) in patients with one or more (≥1) recurrences after a primary episode of CDI and had completed ≥1 round of antibiotic treatments. Drug costs, rCDI-related medical costs and budget impact over 1-3 years, were estimated in 2022 US dollars. One-way sensitivity analyses were performed.

Results: For an insurance plan with a population size of 1,000,000, 468 patients per year were estimated to have ≥1 rCDI. The budget impact of one-course FMBL at $9,000/course was cost-saving at an average of -$0.0039 on a per-member-per-month (PMPM) basis, an average of -$8.30 on a per-treated-member-per-month (PTMPM) basis and a total of -$139,865 on a plan level assuming 5%, 15% and 20% of patients receive FMBL over 1-3 years, respectively. The scenario with FMBL entry was associated with higher drug costs (difference at $0.0474 PMPM; $101.26 PTMPM; $1,706,445 total plan) and lower rCDI-related medical costs (difference at -$0.0513 PMPM; -$109.56 PTMPM; -$1,846,309 total plan). The budget impact of FMBL in

patients at first rCDI was cost-saving at -$0.0139 PMPM, -$84.78 PTMPM, corresponding to an annual savings of $500,022.

Conclusions: FMBL has a cost-saving budget impact for a US payer, with higher initial drug costs being offset by savings in rCDI-related medical costs. Greater cost saving was found in patients at first recurrence.

Keywords: Recurrent Clostridioides difficile infection, FMBL, budget impact, economic modeling

SUMMARY POINTS

Why carry out this study?

- *Clostridioides difficile* infection (CDI) is an urgent public health threat in the United States (US) and is associated with significant economic and clinical burden. Many patients with CDI experience high rates of CDI recurrence (rCDI).
- Treatments for active CDI include oral antibiotics vancomycin or fidaxomicin. The purpose of this study is to evaluate the budget impact of REBYOTA™ (fecal microbiota, live-jslm [FMBL]) for the prevention of rCDI after receipt of oral antibiotic treatment.

What was learned from this study?

- FMBL introduction results in a cost-saving budget impact compared to no FMBL from a US third-party payer perspective (an average saving of $0.0039 on a per member per month basis over three years).
- The higher initial drug costs associated with FMBL were fully offset by savings in medical costs through lowering recurrence and healthcare resource utilization.

INTRODUCTION

Clostridioides difficile infection (CDI) represents an urgent health threat in the United States (US), as identified in the 2019 Antibiotic Resistance Threat Report by the Centers for Disease Control and Prevention (1). CDI is caused by *C. difficile,* an anaerobic gram-positive, spore-forming, toxin-producing bacterium. *C. difficile* is most often found in health care facilities and is also found in the environment (2, 3), and is transmissible through the fecal-oral route. CDI is the most commonly isolated pathogen of antibiotic- and healthcare-associated infection in the US (4). Recurrent CDI (rCDI) is commonplace among patients with CDI.

Treatments for primary CDI and rCDI typically involve oral antibiotics vancomycin or fidaxomicin (5). A 2021 real-world US claims study found that vancomycin was the most commonly used antibiotic for CDI and rCDI, with 55% of patients receiving vancomycin for their first recurrence, 56% for second recurrence, and 60% for third recurrence (6). Despite current treatment options, patients with CDI experience high rates of rCDI. Up to 35% of patients with a primary CDI episode experience recurrence(s) and up to 65% who develop rCDI go on to have more recurrences (7-9).

REBYOTA™ (fecal microbiota, live-jslm [FMBL]) is a rectally administered suspension and is the first microbiota-based live biotherapeutic for the prevention of rCDI following antibiotic treatment for rCDI recently approved by the US Food and Drug Administration (FDA) (10). Given the novelty of FMBL, a careful evaluation of the economic implications is needed. This study estimated the budget impact of FMBL from a US third-party payer perspective.

METHODS

Model Overview

The model assessed the budget impact of FMBL during the first 3 years following the approval and introduction of FMBL for preventing rCDI. The budget impact was estimated by comparing the total budget with FMBL (a market basket of FMBL and standard of care [SOC]) to without FMBL (SOC only). One course of FMBL in the scenario with FMBL was considered. SOC for the prevention of rCDI, proxied by the placebo arm of the FMBL phase 3 clinical trial (PUNCH CD3, NCT03244644) (10), was defined as no treatment to prevent recurrence following antibiotic treatment for rCDI (i.e., rCDI diarrhea being under control). Model outputs included estimates of budget impact of FMBL and the total cost per year without FMBL and with FMBL, from the overall US health plan perspective, on a per member per month (PMPM) basis, and on a per treated member per month (PTMPM) basis. PTMPM cost was calculated as the total costs divided by the total number of patients treated with either FMBL or SOC. The drug cost with FMBL was calculated as the drug costs of FMBL per course multiplied by the number of patients received FMBL per market share of FMBL in respective years and then divided by the total number of patients treated with either FMBL or SOC. The average budget impact on a PMPM and on a PTMPM and the total budget impact on a plan level over three years were estimated.

A decision-tree model was used to estimate the total costs with and without FMBL as a treatment for preventing rCDI (see **Figure 1**). There were 3 decision points: initial treatment choice, 8-week response status, and 6-month response status. Per the endpoints in the PUNCH CD3 trial, patients could have an initial 8-week treatment success, defined as the absence of CDI

diarrhea within 8 weeks of administration of FMBL or treatment failure (10). After the 8-week period, patients could have sustained clinical response, defined as treatment success of the presenting CDI recurrence and no more CDI episodes for greater than 8 weeks through 6 months after administration of FMBL, or could experience more CDI episodes within this time period. Patients would continue the same response status for the remaining six months through the end of the year. The clinical inputs that informed response status at 8 weeks and 6 months are presented in **Table 1**.

Target Population

Calculation of the target population used an incidence-based approach to estimate the total number of patients in the plan, assuming a 1,000,000-person population size, eligible to be treated with FMBL for rCDI prevention within the year. Patients who have at least 1 recurrence after a primary episode of CDI and have completed at least one round of oral antibiotic therapy would be eligible (10).

It was further assumed that 25.3% of the total plan population had Medicare coverage, with a CDI incidence of 627.7 per 100,000 patients, while the remaining 74.7% had commercial coverage, with a CDI incidence of 97.8 per 100,000 patients (7). The relative percentages of Medicare and commercial coverage were based on health insurance coverage information collected in the Current Population Survey Annual Social and Economic Supplement released by US Census Bureau from the general US population. This model assumed that the distribution would be similar for the rCDI population (11). The primary CDI recurrence rate was 20.2% and the subsequent recurrence rate was 65.0% (7, 12, 13) (**Table 2**).

The main analysis included all patients who had ≥1 rCDI episode. The treatment effect of FMBL in reducing rCDI was also demonstrated as early as the first recurrence. Therefore, a subgroup analysis of patients who had their first recurrence was conducted to assess the economic implications of an early treatment with FMBL.

Market Shares

The assumption on market shares of FMBL and SOC are presented in **Figure 2** for three years based on data from market research. Specifically, the market shares were assumed to be 5% FMBL and 95% SOC in year 1, 15% FMBL and 85% SOC in year 2, and 20% FMBL and 80% SOC in year 3 under the scenario with FMBL. Under the scenario without FMBL, the market share is 100% SOC.

Cost Inputs

The base-case model considered drug costs for the initial treatment with FMBL and rCDI-related medical costs, subsequent treatment costs were not considered in the base-case model (**Table 1**). The drug costs of the initial antibiotic treatment were not considered because all patients (including patients who received FMBL or SOC) would have completed the initial antibiotic treatment before entering the model and drug costs of the antibiotic treatment before the model entry were assumed to be the same.

All costs were estimated in or inflated to 2022 US dollars (USD) using the Personal Consumption Expenditure (PCE) Index for health care services from the US Bureau of Economic Analysis (14). The price of FMBL was set at $9,000. The FMBL administration cost was based on the 2022 Centers for Medicare and Medicaid Services (CMS) physician fee schedule (15). In a sensitivity analysis considering subsequent antibiotic treatment (a composite

of oral vancomycin taper-pulse and fidaxomicin), the drug cost of subsequent antibiotic treatment was estimated to be $2,342 per treatment regimen based on the average wholesale acquisition cost (WAC) prices for oral antibiotics taken from IBM Micromedex Red Book® and dosing schedules taken from the Infectious Diseases Society of America (IDSA) 2021 guidelines (10, 16) (**Appendix Table A1**).

Healthcare resource utilization (HRU) directly attributable to rCDI was included as medical cost. Annual rates of rCDI-related HRU were extracted from Rodrigues et al. 2017 (17) as it provided recent real-world data of rCDI-related HRU among patients with rCDI. Other publications reporting all-cause HRU were not applicable for this study because the model considered rCDI-related HRU. rCDI-related HRU included hospitalizations, intensive care unit (ICU), post-acute care (defined as a stay in a skilled nursing facility, inpatient rehabilitation facility, or long-term acute care hospital or services provided by a home health agency), colectomy, ileostomy reversal, stool tests, outpatient visits, emergency department (ED) visits, and terminal care. A one-time terminal care cost was applied upon death, and it was assumed that death occurred at the end of the year. Unit costs for each rCDI-related HRU category were obtained from the literature (12, 17-20), the Optum360 National Fee Analyzer (21), and the Healthcare Cost and Utilization Project (HCUP) (22). Total annual r-CDI related medical costs were estimated at $77,861.23 per patient as the sum of the unit costs multiplied by the annual HRU rates across care settings. Costs of adverse events (AEs) were not considered in our study given their minimal, if any, impact on the model results. The proportion of patients experiencing moderate and severe AEs were similar between the FMBL and SOC treatment arms, although

patients experiencing a higher incidence of mild gastrointestinal events in the FMBL vs. SOC arm.

Patients with treatment failure at 8 weeks were assumed to recur at the end of the first week based on the median time to recurrence reported in the PUNCH CD3 trial (10) and thus were assumed to incur rCDI-related medical cost for 51 weeks out of the total 52 weeks in the year annually (i.e., $76,363.90). Patients with treatment success at 8 weeks but having new CDI episodes within 6 months were assumed to have new CDI episodes at the end of 12 weeks based on the median time to recurrence reported in the PUNCH CD3 trial, and thus were assumed to incur rCDI-related medical cost for 40 weeks out of the total 52 weeks in the year annually (i.e., $59,893.25). Patients with treatment success at 8 weeks who did not have no CDI episodes within 6 months were assumed to incur no rCDI-related medical costs.

In the subgroup of patients who had their first recurrence, data on treatment success were derived from an adjusted analysis of the PUNCH CD3 trial data. In a post hoc analysis of the modified intention-to-treat (mITT) population enrolled after 1 CDI recurrence (86/262 patients [32.8%]), FMBL demonstrated a 21% absolute risk reduction and a 52.5% relative risk reduction of recurrence in comparison to placebo by week 8. Treatment success was achieved by 81% of FMBL-treated patients compared to 60% of placebo-treated patients at week 8. This analysis adjusted for differences in known risk factors for recurrence, including age, gender, antibiotics use, and proton pump inhibitor (PPI) use between the FMBL and placebo arms (23).

Sensitivity Analyses

One-way deterministic sensitivity analyses (DSAs) were conducted to examine varying inputs and assumptions one at a time (**Figure 3**). Parameters such as efficacy, drug acquisition

and administration costs, annual HRU and unit costs were varied. Specifically, the 95% confidence interval of efficacy inputs and +/-25% of the cost inputs (in absence of data on variability) were used to inform the low and high values in the DSA. Scenario analyses including varying assumptions on the market uptake of FMBL and the inclusion of a second course of FMBL or oral antibiotics (composite treatment of 93% vancomycin taper-pulse and 7% fidaxomicin informed by antibiotics use at screening in the PUNCH CD3 trial) as subsequent treatment.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Base Case Results

Model Population

The budget impact associated with one-course FMBL was modeled over three years using an incidence-based approach in a hypothetical plan population of 1,000,000 covered lives. Calculated using primary CDI and subsequent CDI recurrence rates, 468 of the 1,000,000 covered lives were estimated to have ≥1 rCDI episode. Among the 468 patients with ≥1 rCDI each year, the number of patients receiving FMBL increased from 23 in year 1 to 70 in year 2 and 94 in year 3 after FMBL introduction(**Table 2**). A total of 164 patients were estimated to have their first rCDI episode (i.e., no subsequent recurrences). Among the 164 (35%) patients at first rCDI each year, the number of patients receiving FMBL increased from 8 in year 1 to 25 in year 2 and 33 in year 3 after FMBL introduction (**Table 2**).

Budget impact among patients with ≥1 rCDI

In the population with 468 patients with ≥1 rCDI, on a PMPM basis, the average total cost over three years was $1.3955 without FMBL versus $1.3916 with FMBL, corresponding to a cost saving of $0.0039 PMPM. The average drug costs over three years was $0 versus $0.0474 without versus with FMBL, respectively, corresponding to a drug cost difference of $0.0474 PMPM. The average medical costs over three years was $1.3955 versus $1.3442 without versus with FMBL, respectively, corresponding to medical cost savings of 0.0513 PMPM (**Table 3**).

On a PTMPM basis, the average total cost over three years was $2,981.15 without FMBL versus $2,972.85 with FMBL, corresponding to a cost saving of $8.30 PTMPM. The average drug costs over three years was $0 versus $101.26 without versus with FMBL, respectively, corresponding to a drug cost difference of $101.26 PTMPM. The average medical costs over three years was $2,981.15 versus $2,871.59 without versus with FMBL, respectively, corresponding to medical cost savings of 109.56 PTMPM (**Table 3**).

On a plan level, the total cost over three years was $50,236,719 without FMBL versus $50,096,855 with FMBL, corresponding to a cost saving of $139,865. The total drug costs over three years was $0 versus $1,706,445 without versus with FMBL, respectively, corresponding to a drug cost difference of $1,706,445 at the plan level. The total medical costs over three years was $50,236,719 versus $48,390,410 without versus with FMBL, respectively, corresponding to a medical cost saving of $1,846,309 at the plan level (**Table 3**).

Budget impact among patient at first rCDI

In the population with 164 patients at first rCDI, on a PMPM basis, the average total costs over three years without and with FMBL corresponded to a cost saving of $0.0139 PMPM. On a PTMPM level, without and with FMBL average total costs corresponded to a cost saving of $84.78. On a plan level, the total costs of without and with FMBL corresponded to a cost saving of $500,022 over three years (**Table 4**).

Deterministic Sensitivity Analyses Results

The results of the DSA among patients with ≥1 rCDI are shown on a PMPM basis in **Figure 3**. The tornado diagram presents the results of sensitivity analyses from the most to the least influence on budget impact. Across the sensitivity analyses, the budget impact of FMBL relative to no FMBL ranged from -$0.0517 to $0.0357 PMPM. The most influential model drivers included treatment success rates of SOC and FMBL at 8 weeks and the inclusion of a second course of FMBL or antibiotic treatment. With a higher treatment success rate for SOC, the budget impact is $0.0357 PMPM and with a lower treatment success rate for SOC, the budget impact is cost saving by $0.0376 PMPM. With a higher treatment success rate for FMBL, the budget impact is cost saving by $0.0271 PMPM and with a lower treatment success rate for FMBL, the budget impact is $0.0219 PMPM. Including a second course of FMBL in the FMBL arm led to a cost saving of $0.0517 PMPM (**Appendix Table A2**). With a second course of FMBL in the FMBL arm and a second course of antibiotic treatment in the SOC arm, the budget impact is $0.0333 PMPM. With a second course of antibiotic treatment in both arms, the budget impact is $0.0223 PMPM.

DISCUSSION

Primary CDI and rCDI are associated with a large economic burden due to an increased use of in healthcare resources, which could include hospitalizations, post-acute care stays, and surgical interventions for severe patients (12, 24, 25). Despite current treatment with antibiotics, patients with rCDI are at a higher risk for recurrence and may experience substantially worse outcomes compared to those without a recurrence, resulting in detrimental health-related quality of life and possibly higher mortality (26). This study evaluated the budget impact of FMBL, the first in class microbiota-based live biotherapeutic, for rCDI prevention. Over a 3-year time horizon with market shares of FMBL increased from 5% in year 1 to 15% in year 2 and 20% in year 3, the market introduction of FMBL for preventing rCDI was estimated to have a cost-saving budget impact among patients with ≥1 rCDI from a US third-party payer perspective (an average of $0.0039 PMPM, an average of $8.30 PTMPM, a total of $139,865 on a plan level over three years in a hypothetical plan with 1 million covered lives). The cost-saving of FMBL was due in part to the small size of the target population and the improved efficacy of FMBL over SOC to prevent rCDI and thus the associated reduction in HRU, including hospitalizations. The lower medical costs, attributed to its treatment efficacy, offset the drug acquisition and administration costs of FMBL. Most notably, treatment of first rCDI with FMBL was also cost saving by an average of $0.0139 PMPM, by an average of $84.78 PTMPM and by a total of $500,022 on a plan level over three years. The first rCDI subgroup had greater cost saving than the overall population with ≥1 rCDI due to the greater treatment effect of FMBL vs. SOC in preventing rCDI and subsequently rCDI-related medical costs.

Results from the DSA demonstrated the robustness of the model, supporting the base case

findings. As expected, the budget impact was most sensitive to variations in efficacy of FMBL and SOC at the first 8 weeks. The model was also sensitive to the inclusion of a second course of FMBL and/or antibiotics. While the addition of a second course FMBL increased the budget impact due to a higher drug cost associated with FMBL, the budget impact remained minimal at $0.0333 PMPM in the analysis of having a second course of FMBL for patients treated with FMBL and a second course of antibiotics for patients treated with SOC, respectively.

Prior studies have evaluated the budget impact of oral antibiotics entering the market for rCDI (27). In Watt (2016), the 1-year budget impact associated with fidaxomicin per patient was $635.77 in Germany (converted to 2022 USD from €461 2016 Euros using historical exchange rates and consumer price indices) for patients with at least 1 recurrence (28). Given the differences in healthcare systems, it is difficult to compare the per patient cost in Germany for fidaxomicin to the PMPM cost of FMBL in the US; however, both models showed that higher drug costs were offset by the reduction in medical costs associated with rCDI. A recent US model by Jiang et al. (29) was developed from a hospital perspective, and demonstrated a minimal budget impact of fidaxomicin in the US. In addition, two prior studies evaluated the budget impact of bezlotoxumab plus antibiotics compared to antibiotics alone in patients for the prevention of recurrence from a hospital perspective in Germany and the US, respectively (30, 31). Both studies found that bezlotoxumab plus antibiotics was cost-saving with the higher treatment costs of bezlotoxumab being offset by the lower rCDI rate and lower hospitalization costs among patients treated with bezlotoxumab, which correlates with our study finding that FMBL was cost-saving given its high efficacy in preventing rCDI and subsequently low rCDI-related medical cost, thus may offer additional advantages to a US health plan.

A few limitations of the model should be noted. Our model considered FMBL vs. SOC only as proxied by the placebo arm of the PUNCH CD3 trial following a course of antibiotic treatment. In clinical practice, incremental antibiotics or other therapeutic options could have been considered and used sooner, which may result in treatment effectiveness rates different from the SOC efficacy rates in the PUNCH CD3 trial (and may also have a subsequent impact on drug costs). Sensitivity analyses by varying efficacy rates of FMBL and SOC allowed us to test the robustness of the model findings. Even with an assumed higher efficacy rate for SOC (i.e., the upper bound of the 95% confidence interval), the budget impact of FMBL is expected to be small (0.0357 PMPM). Further research may consider using real-world efficacy data to confirm the model findings when such data are available. Our model also assumed a 3-node decision tree with critical time points at week 8 and month 6 to reflect the clinical trial design and thus data availability from the trial. In practice, physicians could evaluate treatment success or failure at different times and hence deviate the HRU and costs for rCDI from our model estimates. The model was developed from a US third-party payer perspective and the findings may not be generalizable to specific payers. For example, their patient population (e.g., age distribution) and market shares might differ from the model assumptions. The medical costs considered in this model came from the literature, including the unit prices for medical services. The actual values could differ for a specific payer. For example, WAC prices were used to calculate drug acquisition costs. Such prices may not reflect the actual costs borne by the payer. Future studies should evaluate the budget impact of FMBL among different types of payers. Additionally, the distribution of vancomycin use vs. fidaxomicin use as the subsequent antibiotic treatment was assumed to be constant over 3 years after FMBL introduction and assumptions on the projected

market uptake of FMBL are yet to be tested when more data from the real world become available. Lastly, treatments that are not approved by the FDA or have limited use in real-world practice (e.g., fecal microbiota transplant [FMT], bezlotoxumab) were not considered in our study (6, 32). FMT is not FDA-approved for rCDI prevention while bezlotoxumab is indicated for use in conjunction with antibiotic therapy to reduce rCDI, rather than after antibiotic therapy, and for patients with congestive heart failure, bezlotoxumab can only be used when benefit outweighs the risks. Both treatments have limited use in real-world practice. For example, a recent study found that only 8.5% of episodes were treated using bezlotoxumab or FMT and bezlotoxumab was used mostly in immunosuppressed patients (32). It is anticipated that other FDA-approved rCDI treatments will become available in future years and the budget impact model of FMBL suspension will need to be revisited when these new live biotherapeutic products become available.

CONCLUSION

FMBL, a novel microbiota-based live biotherapeutic, for prevention of rCDI was demonstrated to be cost saving from a US third-party payer perspective, attributable to reductions in direct medical costs through recurrence prevention and associated reduction in HRU, including hospitalizations. Given its high efficacy, FMBL showed further cost savings among patients at first recurrence, suggesting additional benefits of FMBL with early initiation of the therapy.

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All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article. All authors have contributed significantly and are in agreement with the content of the manuscript.

Author contributions:

Model conceptualization and idea for this study: Amy Guo, Min Yang, Erin E. Cook, Wei Song, Thomas Lodise, and Markian Bochan; Model input collection and development: Amy Guo, Min Yang, Erin Cook, Wei Song, Danni Yang, Qingyuan Wang, and Angela Zhao; Model review: Amy Guo, Thomas Lodise, Markian Bochan; All authors contributed to the writing and reviewing of the manuscript and have approved the final manuscript.

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This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data availability:

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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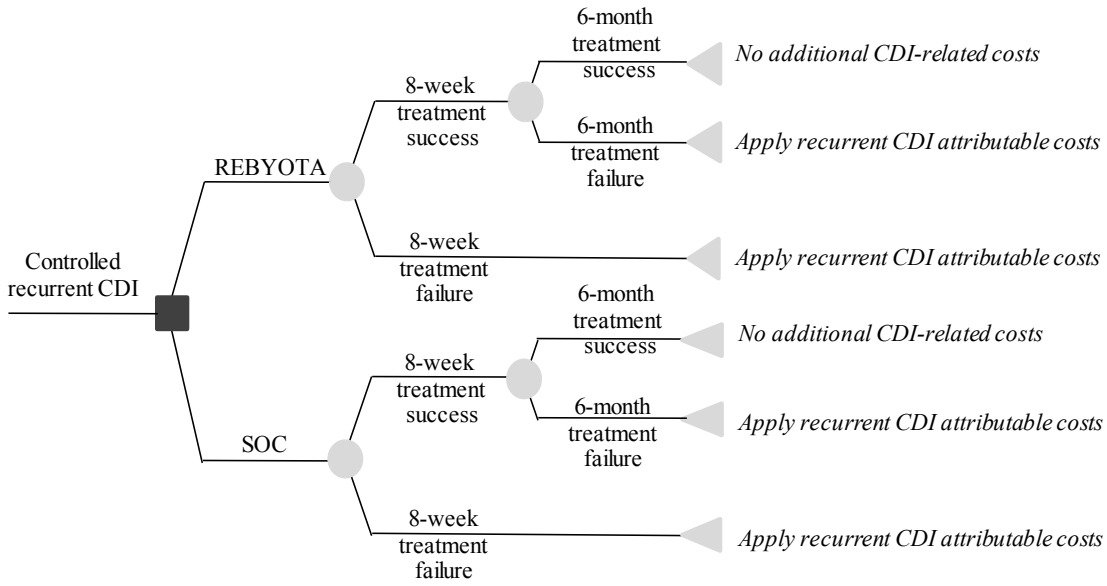
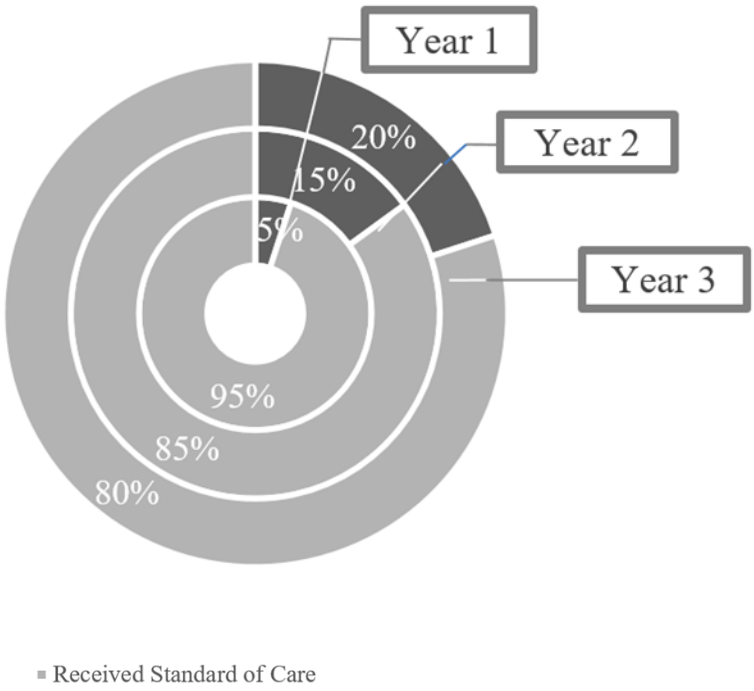
TABLES AND FIGURES

Figure 1. Model structure diagram



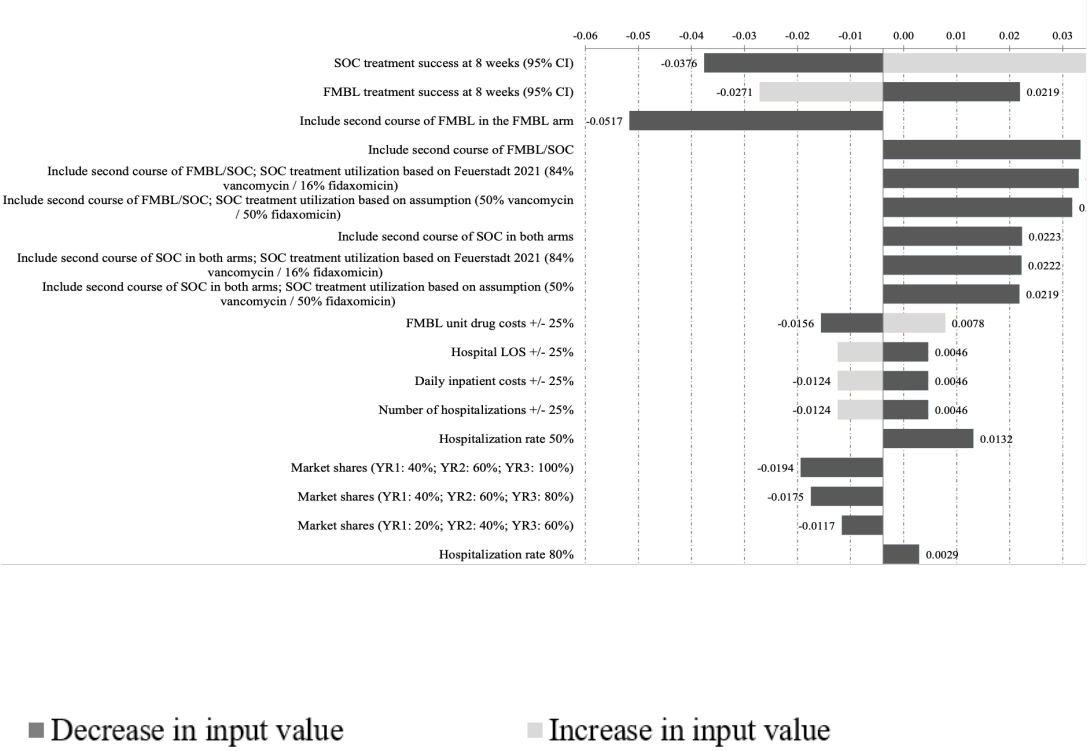
Abbreviations: CDI, C. difficile infection; FMBL, fecal microbiota, live-jslm; SOC, standard of care.

Figure 2. Market share for the scenario with FMBL market entry over three years



Abbreviations: FMBL, fecal microbiota, live-jslm

Figure 3. Tornado Diagram based on DSAs/scenario analyses (PMPM) among patients with ≥1 rCDI1



[1]The budget impact is presented in 2022 USD on a PMPM basis.

Abbreviations: CDI, C. difficile infection; DSA, deterministic sensitivity analyses; FMBL, fecal microbiota, live-jslm; LOS, length of stay; PMPM, per member per month; rCDI, recurrent C. difficile infection; SOC, standard of care; YR, year; USD, US Dollar

Table 1. Clinical and cost inputs

Variable	Base case value	Sensitivity low[3]	Sensitivity high[3]	Sources
Clinical inputs				
8-week treatment success				
Among patients with ≥1 rCDI				
FMBL	70.6%	63.7%	76.8%	PUNCH CD3 (10)
SOC	57.5%	48.4%	68.2%	PUNCH CD3 (10)
Among patients at first rCDI				
FMBL	81.0%	N/A	N/A	PUNCH CD3 (23)
SOC	60.0%	N/A	N/A	PUNCH CD3 (23)
6-month treatment failure (among patients with 8-week treatment success)				
Among patients with ≥1 rCDI				
FMBL	7.9%	N/A	N/A	PUNCH CD3 (10)
SOC	9.4%	N/A	N/A	PUNCH CD3 (10)
Among patients at first rCDI				
FMBL	9.5%	N/A	N/A	PUNCH CD3 (23)
SOC	15.0%	N/A	N/A	PUNCH CD3 (23)
FMBL drug and administration cost[1]				
Drug cost	$9,000	$6,750	$11,250	Redbook (33)
Administration Cost	$113.75	$85.31	$142.19	CMS physician fee schedule (15)
Unit cost of rCDI-related medical care				
Daily inpatient cost	$2039.06	$1529.30	$2548.83	HCUPnet (22)
Daily ICU cost	$5,232.00	$3924.00	$6540.00	Halpern 2016 (18)
Post-acute care cost	$562.12	$421.59	$702.65	Nelson 2021 (12)
Colectomy	$54,421.37	$ 40,816.02	$68,026.71	Rodrigues et al, 2017 (17)
Ileostomy reversal	$46,297.54	$ 34,723.16	$57,871.93	Wilson 2013 (19)
Stool Tests	$58.35	$43.76	$72.94	Rodrigues, 2017 (17)
Outpatient visits	$208.67	$156.50	$260.84	Optum360 National Fee Analyzer (21)
ED visits	$1,003.73	$752.80	$1,254.66	Nelson 2021 (12)

Terminal care	$53,332.75	$39,999.56	$66,665.94	Byhoff 2017 (34)
Annual rCDI-related HRU				
Percent hospitalized	100%	50%	80%	Assumption
Hospitalization rate	1.60	1.20	2.00	Rodrigues, 2017 (17)
Hospital LOS (days)	15.80	11.85	19.75	Rodrigues, 2017 (17)
ICU days	0.18	0.14	0.23	Rodrigues, 2017 (17)
Post-acute care (days)	21.08	15.81	26.36	Nelson, 2021 (12); Rodrigues, 2017 (17)
Percent of patients needing colectomy	7.30%	5.48%	9.13%	Feuerstadt 2020 (25)
Outpatient visit rate	2.20	1.65	2.75	Rodrigues, 2017 (17)
Stool test rate	4.40	3.30	5.50	Rodrigues, 2017 (17)
ED visit rate	0.12	0.09	0.15	Rodrigues, 2017 (17)
Percent of patients with ileostomy reversal	7.05%	5.29%	8.81%	Feuerstadt 2020 (25); Neal 2011 (35)
rCDI-related mortality rate	10.90%	4.00%	19.00%	Olsen 2020 (36)
Total annual rCDI-related medical costs[2]	$77,861.23	N/A	N/A	Calculated

Notes:

[1]Subsequent antibiotic treatment for rCDI after the initial treatments with FMBL or SOC was not considered in the base case but were considered in the sensitivity analysis. Cost inputs for subsequent antibiotic treatment are presented in Appendix Table A1.

[2]The total annual rCDI-related medical costs were calculated as the sum of the annual rCDI-related HRU multiplied by the unit cost for each medical cost component

[3] Parameters were varied based on 95% confidence intervals in the case of efficacy inputs and by +/- 25% for costs in the sensitivity analysis. The low and high inputs for rCDI-related mortality rate were based on the range of mortality rates reported in literature.

Costs are in 2022 USD.

Abbreviations: CMS, Centers for Medicare & Medicaid Services; CPT, current procedural terminology; ED, emergency department; ICD-10, International Classification of Diseases, Tenth Revision; FMBL, fecal microbiota, live-jslm; ICU, intensive care unit; LOS, length of stay; N/A, not applicable; rCDI, recurrent C. difficile infection; SOC, standard of care; USD, US Dollar.

Table 2. Model population

	Year 1	Year 2	Year 3	Average of Years 1-3	Sources
Total plan size	1,000,000	1,000,000	1,000,000	1,000,000	Assumption
% Medicare population	25.0%	25.0%	25.0%	25.0%	US Census
CDI incidence (per 100,000)[1]	231.73	231.73	231.73	231.73	Calculation
Medicare population	627.70	627.70	627.70	627.70	Lessa 2015 (7)
Commercial population	97.80	97.80	97.80	97.80	Lessa 2015 (7)
Primary CDI recurrence rate	20.2%	20.2%	20.2%	20.2%	Finn 2021 (37)
CDI subsequent recurrence rate	65.0%	65.0%	65.0%	65.0%	Nelson 2021 (12)
Patients with ≥1 rCDI (n)[2]	468	468	468	468	
With FMBL[3]					
Patients treated with FMBL	23	70	94	62	
Patients treated with SOC	445	398	374	406	Calculation
Without FMBL					
Patients treated with FMBL	0	0	0	0	
Patients treated with SOC	468	468	468	468	
Patients with at first rCDI (n)[4]	164	164	164	164	
With FMBL[3]					
Patients treated with FMBL	8	25	33	22	
Patients treated with SOC	156	139	131	142	Calculation
Without FMBL					
Patients treated with FMBL	0	0	0	0	
Patients treated with SOC	164	164	164	164	

[1]CDI incidence among the overall population was calculated as the weighted average of CDI incidence rates among the Medicare and commercial population.

[2] Number of patients with ≥1 rCDI was estimated as the multiplication of the total plan size, CDI incidence rate and primary CDI recurrence rate.

[3]Number of patients treated with FMBL vs. SOC with FMBL introduction was estimated as the number of patients multiplied of the market shares in respective years.

[4]Number of patients at first rCDI was estimated as the multiplication of the total plan size, CDI incidence rate, primary CDI recurrence rate and (1- CDI subsequent recurrence rate).

Abbreviations: CDI, C. difficile infection; FMBL, fecal microbiota, live-jslm; N/A, not applicable; SOC, standard of care.

Table 3. Budget impact results among patients with ≥1 rCDI (drug costs of initial antibiotic treatment before model entry were not included)

Per member per month	Year 1	Year 2	Year 3	Average of Years 1-3
Budget impact (with FMBL – without FMBL)	**-$0.0015**	**-$0.0044**	**-$0.0048**	**-$0.0039**
Drug costs	$0.0178	$0.0533	$0.0711	$0.0474
Medical costs	-$0.0192	-$0.0577	-$0.0769	-$0.0513
Total cost per year (without FMBL)	$1.3955	$1.3955	$1.3955	$1.3955
Drug costs	$0.0000	$0.0000	$0.0000	$0.0000
Medical costs	$1.3955	$1.3955	$1.3955	$1.3955
Total cost per year (with FMBL)	$1.3940	$1.3911	$1.3896	$1.3916
Drug costs	$0.0178	$0.0533	$0.0711	$0.0474
Medical costs	$1.3762	$1.3378	$1.3185	$1.3442

Per treated member per month	Year 1	Year 2	Year 3	Average of Years 1-3
Budget impact (with FMBL – without FMBL)	**-$3.11**	**-$9.34**	**-$12.45**	**-$8.30**
Drug costs	$37.97	$113.92	$151.90	$101.26
Medical costs	-$41.09	-$123.26	-$164.35	-$109.56
Total cost per year (without FMBL)	$2,981.15	$2,981.15	$2,981.15	$2,981.15
Drug costs	$0.00	$0.00	$0.00	$0.00
Medical costs	$2,981.15	$2,981.15	$2,981.15	$2,981.15
Total cost per year (with FMBL)	$2,978.04	$2,971.81	$2,968.70	$2,972.85
Drug costs	$37.97	$113.92	$151.90	$101.26
Medical costs	$2,940.06	$2,857.89	$2,816.80	$2,871.59

Plan	Year 1	Year 2	Year 3	Total of Years 1-3
Budget impact (with FMBL – without)	**-$17,483**	**-$52,449**	**-$69,932**	**-$139,864**
Drug costs	$213,306	$639,917	$853,222	$1,706,444
Medical costs	-$230,788	-$692,366	-$923,154	-$1,846,309
Total cost per year (without FMBL)	$16,745,573.12	$16,745,573.12	$16,745,573.12	$50,236,719
Drug costs	$0	$0	$0	$0
Medical costs	$16,745,573.12	$16,745,573.12	$16,745,573.12	$50,236,719

Total cost per year (with FMBL)	$16,728,090	$16,693,123	$16,675,640	$50,096,854
Drug costs	$213,306	$639,917	$853,222	$1,706,444
Medical costs	$16,514,784	$16,053,207	$15,822,418	$48,390,410

[1]Drug costs with FMBL introduction only included drug costs of the initial treatment with FMBL among patients receiving FMBL per market share of FMBL in perspective years. Drug costs of the initial antibiotic treatment were not considered in the model given all patients would have completed the initial antibiotic treatment before entering the model and the antibiotic drug costs before the model entry were assumed to be the same.

[2]Drug cost per treated member with FMBL market entry was calculated as the drug acquisition and administration costs of FMBL per course multiplied by the number of patients received FMBL per market share of FMBL in respective years of market entry and then divided by the total number of patients treated with either FMBL or SOC.

Costs are in 2022 USD.

Abbreviations: FMBL, fecal microbiota, live-jslm; SOC, standard of care; USD, US Dollar.

Table 4. Budget impact results among patients at first rCDI (drug costs of initial antibiotic treatment before model entry were not included)

Per member per month	Year 1	Year 2	Year 3	Average of Years 1-3
Budget impact (with FMBL – without FMBL)	**-$0.0052**	**-$0.0156**	**-$0.0208**	**-$0.0139**
Drug costs	$0.0062	$0.0187	$0.0249	$0.0166
Medical costs	-$0.0114	-$0.0343	-$0.0457	-$0.0305
Total cost per year (without FMBL)	$0.4910	$0.4910	$0.4910	$0.4910
Drug costs	$0.0000	$0.0000	$0.0000	$0.0000
Medical costs	$0.4910	$0.4910	$0.4910	$0.4910
Total cost per year (with FMBL)	$0.4858	$0.4754	$0.4701	$0.4771
Drug costs[1]	$0.0062	$0.0187	$0.0249	$0.0166
Medical costs	$0.4795	$0.4567	$0.4453	$0.4605

Per treated member per month	Year 1	Year 2	Year 3	Average of Years 1-3
Budget impact (with FMBL – without FMBL)	**-$31.79**	**-$95.38**	**-$127.17**	**-$84.78**
Drug costs	$37.97	$113.92	$151.90	$101.26
Medical costs	-$69.77	-$209.30	-$279.06	-$186.04
Total cost per year (without FMBL)	$2,996.80	$2,996.80	$2,996.80	$2,996.80
Drug costs	$0.00	$0.00	$0.00	$0.00
Medical costs	$2,996.80	$2,996.80	$2,996.80	$2,996.80
Total cost per year (with FMBL)	$2,965.01	$2,901.42	$2,869.63	$2,912.02
Drug costs[1,2]	$37.97	$113.92	$151.90	$101.26
Medical costs	$2,927.03	$2,787.50	$2,717.73	$2,810.76

Plan	Year 1	Year 2	Year 3	Total of Years 1-3
Budget impact (with FMBL – without FMBL)	**-$62,503**	**-$187,508**	**-$250,011**	**-$500,022**
Drug costs	$74,657	$223,971	$298,628	$597,256
Medical costs	-$137,160	-$411,479	-$548,639	-$1,097,278
Total cost per year (without FMBL)	$5,891,716	$5,891,716	$5,891,716	$17,675,148

Drug costs	$0	$0	$0	$0
Medical costs	$5,891,716	$5,891,716	$5,891,716	$17,675,148
Total cost per year (with FMBL)	$5,829,213	$5,704,208	$5,641,705	$17,175,126
Drug costs[1]	$74,657	$223,971	$298,628	$597,256
Medical costs	$5,754,556	$5,480,237	$5,343,077	$16,577,870

[1]Drug costs with FMBL introduction only included drug costs of the initial treatment with FMBL among patients receiving FMBL per market share of FMBL in perspective years. Drug cost of the initial antibiotic treatment was not considered given all patients would have completed the initial antibiotic treatment before entering the model and the antibiotic drug costs before the model entry were assumed to be the same.

[2] Drug cost per treated member with FMBL introduction was calculated as the drug acquisition and administration costs of FMBL per course multiplied by the number of patients received FMBLper market share of FMBL in respective years and then divided by the total number of patients treated with either FMBL or SOC.

Costs are in 2022 USD.

Abbreviations: FMBL, fecal microbiota, live-jslm; SOC, standard of care; USD, US Dollar.

Appendix

Table A1. Subsequent antibiotic treatment costs in the sensitivity analysis

Treatment	Vancomycin taper-pulse	Fidaxomicin	Source
Dosing schedule	125 mg orally four times daily for 14 days, followed by 125 mg orally twice daily for 7 days, followed by 125 mg orally once daily for 7 days, followed by 125 mg orally every other day for 7 days 125mg orally every third day for 7 days	200 mg twice a day for 10 days	The Infectious Diseases Society of America (IDSA) 2021 guidelines (16)
Strength per unit (mg)	125	200	RedBook
Cost per unit	$26.85	$194.14	
Total units required per regimen	83	20	Calculation
Treatment utilization (%)	93%	7%	PUNCH CD3 (10)
Total costs per regimen	$2,342.36		Calculation

Table A2. Budget impact of including a second course of FMBL in the FMBL arm among patients with ≥1 rCDI

Per member per month	Year 1	Year 2	Year 3	Average of Years 1-3
Budget impact (with FMBL – without FMBL)	**-$0.0194**	**-$0.0582**	**-$0.0776**	**-$0.0517**
Drug costs	$0.0230	$0.0690	$0.0920	$0.0613
Medical costs	-$0.0424	-$0.1272	-$0.1696	-$0.1131
Total cost per year (without FMBL)	$1.3955	$1.3955	$1.3955	$1.3955
Drug costs	$0.0000	$0.0000	$0.0000	$0.0000
Medical costs	$1.3955	$1.3955	$1.3955	$1.3955
Total cost per year (with FMBL)	$1.3761	$1.3373	$1.3179	$1.3437
Drug costs[1]	$0.0230	$0.0690	$0.0920	$0.0613
Medical costs	$1.3531	$1.2683	$1.2259	$1.2824
Per treated member per month	**Year 1**	**Year 2**	**Year 3**	**Average of Years 1-3**
Budget impact (with FMBL – without FMBL)	**-$41.43**	**-$124.29**	**-$165.72**	**-$110.48**
Drug costs	$49.14	$147.41	$196.55	$131.04
Medical costs	-$90.57	-$271.70	-$362.27	-$241.51
Total cost per year (without FMBL)	$2,981.15	$2,981.15	$2,981.15	$2,981.15
Drug costs	$0.00	$0.00	$0.00	$0.00
Medical costs	$2,981.15	$2,981.15	$2,981.15	$2,981.15
Total cost per year (with FMBL)	$2,939.72	$2,856.86	$2,815.43	$2,870.67
Drug costs[1,2]	$49.14	$147.41	$196.55	$131.04
Medical costs	$2,890.58	$2,709.45	$2,618.88	$2,739.64
Plan	**Year 1**	**Year 2**	**Year 3**	**Total of Years 1-3**
Budget impact (with FMBL – without FMBL)	**-$232,715**	**-$698,145**	**-$930,860**	**-$1,861,721**
Drug costs	$276,017	$828,052	$1,104,070	$2,208,139

Medical costs	-$508,732	-$1,526,197	-$2,034,930	-$4,069,860
Total cost per year (without FMBL)	$16,745,573	$16,745,573	$16,745,573	$50,236,719
Drug costs	$0	$0	$0	$0
Medical costs	$16,745,573	$16,745,573	$16,745,573	$50,236,719
Total cost per year (with FMBL)	$16,512,858	$16,047,428	$15,814,713	$48,374,999
Drug costs[1]	$276,017	$828,052	$1,104,070	$2,208,139
Medical costs	$16,236,841	$15,219,376	$14,710,643	$46,166,859

[1]Drug costs with FMBL introduction included drug costs of the initial treatment with FMBL among patients receiving FMBL per market share of FMBL in respective years and drug costs of a second course of FMBL among patients who did not respond to the initial treatment with FMBL. Drug cost of the initial antibiotic treatment was not considered given all patients would have completed the initial antibiotic treatment before entering the model and the antibiotic drug costs before the model entry were assumed to be the same.

[2] Drug cost per treated member with FMBL introduction was calculated as the drug acquisition and administration costs of FMBL per course multiplied by the number of patients received FMBLper market share of FMBL in respective years and then divided by the total number of patients treated with either FMBL or SOC.

Costs are in 2022 USD.

Abbreviations: FMBL, fecal microbiota, live-jslm; SOC, standard of care; USD, US Dollar.