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**Efficacy of bezlotoxumab in preventing recurrence of *Clostridioides difficile* infection:
an Italian multicenter cohort study**

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Abstract

Objectives: Bezlotoxumab (BEZ) is a promising tool for preventing recurrence of *Clostridioides difficile* infection (rCDI). The aim of the study was to emulate, in a real-world setting, the MODIFY trials in a cohort of participants with multiple risk factors for rCDI treated with BEZ in addition to standard of care (SoC) vs. SoC alone.

Methods: A multicenter cohort study was conducted including 442 patients with CDI from 2018 to 2022 collected from 18 Italian centers. The main outcome was the 30-days occurrence of rCDI. Secondary outcomes were: (i) all-cause mortality at 30 days (ii) composite outcome (30-day recurrence and/or all-cause death).

Results: rCDI at day 30 occurred in 54 (12%): 11 in the BEZ+SoC group and 43 treated with SoC alone (8% vs. 14%, OR=0.58, 95%CI:0.31-1.09, p=0.09). The difference between BEZ+SoC vs. SoC was statistically significant after controlling for confounding factors (aOR=0.40, 95%CI:0.18-0.88, p=0.02) and even more using the composite outcome (aOR=0.35, 95%CI:0.17-0.73, p=0.005).

Conclusion: Our study confirms the efficacy of BEZ+SoC for the prevention of rCDI and death in a real-world setting. BEZ should be routinely considered among participants at high risk of rCDI regardless of age, type of CDI therapy (vancomycin vs. fidaxomicin) and number of risk factors.

Keywords: *Clostridioides difficile* infection, recurrence, bezlotoxumab

1 **Introduction**

2 *Clostridioides difficile* (CD) is the main pathogen responsible for community and healthcare-
3 associated bacterial infectious colitis and hospital outbreaks worldwide[1]. In Europe, *Clostridioides*
4 *difficile* infection (CDI) accounts for 4% of care-related infections with an incidence rate of 4 per
5 10,000 patient-days and mortality ranging from 8 to 31% [2,3]. The same results were confirmed in
6 the FADOI-PRACTICE observational study involving more than 40 different Italian Internal
7 Medicine Units, reporting an overall CDI incidence rate of 5.3 per 10,000 patient-days over a 4-
8 month period from October 2013 to January 2014 [4]. The clinical manifestations of CDI are
9 extremely variable, ranging from mild symptoms such as simple enteritis to potentially lethal forms
10 such as toxic megacolon, shock and intestinal perforation. Complications mainly occur in elderly,
11 immunocompromised individuals and in the context of infection with epidemic ribotypes such as 027
12 [5]. Among these specific populations at risk, together with appropriate antimicrobial therapy
13 tailored to the severity of the disease, preventing recurrence of CDI (rCDI) is becoming increasingly
14 crucial. Indeed, the reported recurrence rate of CDI varies from 10 to 25% in the first episode and
15 increase from 30 to 65% in cases of subsequent recurrences (up to 50% over the age of 65 years)
16 [6,7]. A recent prospective study enrolled 309 hospitalized participants from 15 Italian hospitals
17 showed that rCDI occurred in 21% of participants with an incidence rate of 72/10,000 patient-days
18 and an all-cause mortality rate of 10.7%[8]. Moreover, rCDI is associated with a higher risk of death,
19 decrease quality of life and higher hospitalization costs and hospital readmissions [9,10]. In this
20 ever-increasing scenario, the prevention of rCDI represents the main challenge in the clinical
21 management of participants with CDI. Bezlotoxumab (BEZ), a novel fully humanized monoclonal
22 antibody directed against the binding domains of Toxin B produced by CD, that is given as a one-
23 time infusion in addition to a standard of care (SoC) antimicrobial, fits in as a promising tool at our
24 disposal to breaking the cycle of recurrence [11]. The main advantage of this innovative strategy is
25 that it does not affect the effectiveness of the antibacterial agents used to treat CDI and, on the

26 contrary, could reduce the need for them, thus minimizing further intestinal micro-perturbation that
27 predisposes to subsequent recurrences.

28 Two randomized, placebo-controlled, phase 3 trials, the MODIFY I and MODIFY II studies, showed
29 a substantial lower rate of recurrent infection than placebo with a comparable safety profile [12].

30 One limitation of these trials was the fact that the target population was a selected sample of
31 participants with low prevalence of multiple risk factors for recurrence and that several of these
32 factors, including immunodeficiency, have been loosely defined on clinical criteria.

33 Nevertheless, similar results were observed in a number of more recent observational studies of real-
34 world populations conducted in Europe as well as in the USA [13–15]. The majority of these were
35 retrospective cohorts including only participants treated with BEZ with no control group. The most
36 recent study conducted in Colorado was a standard of care (SoC)-controlled trial emulation which
37 also confirmed the difference in risk seen in the trials and extended these findings to a population
38 enriched with participants with multiple risk factors [16]. These studies led to update in 2021 the
39 most recent European and American guidelines, that recommend the use of Bezlotoxumab in
40 addition to SoC in case of: (i) a first CDI episode with high risk of recurrence; (ii) a first CDI
41 recurrence when fidaxomicin was used to manage the initial CDI episode; (iii) second or multiple
42 CDI recurrences [7,17].

43 However, despite this growing data evidence supporting the use of BEZ to prevent rCDI, its use in
44 Italy, as in many other European Countries, is still limited and restricted to participants who
45 experienced previous relapses. This might be mainly explained by direct drug cost of BEZ which is
46 higher than available standard of care treatments.

47 Here we aimed to emulate, in a real-world setting, the MODIFY trials in a multi-center cohort of
48 participants treated with BEZ in addition to SoC vs. SoC alone seen for care in several tertiary care
49 hospitals across Italy.

50

51 **Material and methods**

52 Study design and clinical definitions

53 Our study design is that of a multicentre cohort enrolling participants from 18 Italian hospitals,
54 including academic or tertiary referral hospitals (see full detailed list in Supplementary Table S1).

55 All adult participants (age > 18 years) admitted to these participating sites over the period January
56 2018 to January 2022 had at least an episode of CDI and i) ≥ 1 risk factor for rCDI, ii) at least ≥ 30
57 days of documented follow-up after the end of antimicrobial treatment for CDI episode in question
58 (baseline), and iii) were treated with either BEZ+SoC or only SoC.

59 The SoC cohort was an historical comparator group of participants included in the ReCloDi
60 (Recurrence of *Clostridioides difficile* Infection) Study Group cohort, over the period from January
61 2018 to March 2020 [8]. The BEZ cohort was a newly recruited group from a subset of the sites
62 participating in ReCloDi and three others sites over the more contemporary period of September
63 2018 to January 2022.

64 An incident CDI episode was defined on the basis of the new onset of the following conditions: a
65 clinically significant diarrhea (≥ 3 stools of Bristol type 5, 6, or 7 in a 24-hour period) accompanied
66 by a positive diagnostic test result (e.g. toxin enzyme immunoassay (EIA) and nucleic acid
67 amplification test (NAAT)). A Zar-Score ≥ 2 was used to define a severe CDI episode [18].

68 In all participants the CDI was successfully treated until resolution of all CDI-defining conditions
69 described above and they were followed-up until the development of the primary outcome of a CDI
70 recurrence (rCDI) or at least 30 days from baseline.

71 rCDI was defined as the reappearance of the CDI-defining conditions within 30 days from baseline,
72 which resulted again in pharmaceutical intervention, with or without positive stool test for toxigenic
73 CD [7,19]. rCDI was assessed by physician follow-up visit, patient records or telephone interview
74 with the patient or caregiver who were not blind to treatment allocation.

75 Data collection

76 Data collection from medical records included patient demographics, inpatient departments, prior
77 hospitalization, and origin from long-term care facilities within 12 weeks of the current CDI episode,
78 comorbidity burden assessed using Charlson Comorbidity Index (CCI), history of previous CDIs,
79 risk factors for rCDI, severity of the current episode and CDI treatment and duration.

80 Risk factors for rCDI were considered as age > 65 years, compromised immunity (defined as use of
81 immune-suppressive medication and/or presence of underlying disease such as onco-haematological
82 conditions, solid organ transplant, chemotherapy), renal impairment, hepatic impairment,
83 inflammatory bowel disease, HIV infection, use of pump proton inhibitors (PPI), concomitant
84 antibiotic treatment at the CDI diagnosis and previous antibiotic exposure within 12 weeks and
85 previous CDI episodes, according to the current literature [11,20].

86 SoC included vancomycin (VAN) alone or in association with iv metronidazole, fidaxomicin (FDX),
87 iv metronidazole in monotherapy. VAN was prescribed at the standard fixed dosage or in taper
88 regimes[21]. BEZ (10 mg/ kg) was administered as a single intravenous infusion over 60 minutes
89 during or at the end of CDI treatment with SoC [12].

90 The investigation was conducted in accordance with Good Clinical Practice guidelines and the
91 provisions of the Declaration of Helsinki. The study was approved by the Clinical Research Ethics
92 Committee from the coordinating center (reference number CE n. 86/2021/OSS/AOUMO). Written
93 informed consent was provided by all participants.

94 Outcome

95 The main outcome was the binary outcome indicating the occurrence of a rCDI at 30 days after the
96 completion of CDI treatment [7,19].

97 Secondary outcomes were the alternative binary outcomes: (i) all-cause mortality at 30 days (ii)
98 composite outcome (30-day recurrence or all-cause death).

99 Infusion-related adverse reactions and serious adverse events (SAE) that could potentially be related
100 to BEZ were also assessed.

101 Statistical analysis

102 Descriptive statistics of the main characteristics of participants at study entry have been calculated.

103 The χ^2 and Fisher exact tests were utilized to compare categorical variables by treatment group,
104 whereas continuous variables were analysed via Wilcoxon rank sum test as appropriate.

105 To control for potential confounding bias while aiming to emulate a randomised controlled trial, we
106 fitted a marginal structural logistic regression model by means of inverse probability of treatment
107 weighting (IPTW) of potential confounding factors. Our assumptions regarding underlying causal
108 structure of the data is described in Supplementary Figure S1 through the visual aid of a direct
109 acyclic graph (DAG). According to our assumptions, controlling for age, Zar-score, immuno-
110 suppression, ≥ 1 CDI episodes within 8 weeks (all fitted as time-fixed covariates) is sufficient to
111 block all backdoor confounding pathways from treatment to outcomes. In an alternative adjustment
112 we have used the number of previous CDI episodes fitted as continuous instead of the indicator for
113 ≥ 1 CDI episodes within 8 weeks. In order to assess the robustness of the results against potential
114 unmeasured confounding bias, the e-value was calculated on the basis of the predictor showing the
115 strongest association with the outcome [22]. We performed another adjusted analysis not considering
116 patients treated with metronidazole iv alone, that is not considered anymore as optimal choice in CDI
117 treatment among standard of care regimens[7].

118 Because of the larger number of events observed when using the composite outcome, to maximise
119 the statistical power, subgroup analysis was planned for this secondary outcome by stratification by a
120 number of *a priori* identified predictors: age (binary with a threshold of 70 years), type of CDI
121 therapy (VAN vs. FDX) and the number of risk factors for rCDI (binary with threshold of 5 risk
122 factors). Formal interaction test was performed to evaluate whether the difference in risk of
123 outcomes might vary by strata.

124 Given the small number of participants and events, a couple of unadjusted sensitivity analyses were
125 conducted: the first after restricting the analysis to the 3 clinical sites contributing data to both

126 treatment groups (Modena, Palermo and Genova); the second after restricting to the participants who
127 never experienced previous CDI episodes.

128 The level of statistical significance was generally set at 0.05 or 0.05/3 for the interactions test to
129 correct for inflation of type I error (Bonferroni correction). All analyses were conducted using SAS
130 version 9.4 (Carey North Carolina USA).

132 Results

133 Overall, 442 participants with CDI were included in this analysis: 135 (31%) were treated with BEZ
134 in combination with standard of care (SoC) therapy, 307 (69%) were treated with SoC alone.
135 Demographic, clinical characteristics and treatments of the study participants are shown in Tables 1-
136 3. The median age of patients was 73 (IQR 61, 81), 210 (48%) were female and the median Charlson
137 score at time of treatment initiation was 5 (IQR 4, 7). BEZ was infused in the outpatient setting only
138 in 10 (2%) participants, during or at the end of the treatment with SoC antibiotics.

139 Patients treated with SoC alone were all at their first CDI episode, while more than two third (n=95,
140 71%) of participants who received BEZ+SoC had experienced ≥ 1 previous CDI episodes; in
141 particular, 56 (42%) and 39 (29%) were at the second or later episode, respectively. Sixty-five (48%)
142 of these 95 participants treated with BEZ+SoC had a previous episode which occurred within 8
143 weeks of the date of treatment initiation, then treated for a recurrence.

144 The CDI episode was severe (Zar-score ≥ 2) in 152 (34%) individuals and there was little evidence
145 for a difference by treatment group (BEZ+SoC vs. SoC alone, 39% vs. 32%, $p=0.153$).

146 Overall, the study population included patients at high risk of recurrence, however those in the
147 BEZ+SoC group had a slightly higher number of risk factors for rCDI than those in SoC alone group
148 ($p=0.005$) and were more likely to have ≥ 2 risk factors (99.3% vs. 95.7%, $p=0.05$). Regarding
149 comorbidities, intestinal bowel disease was more frequent in individuals treated with BEZ+SoC (4%

150 vs. 0.3%, $p=0.005$); participants in BEZ+SoC group were also more likely to have in general an
151 immunocompromising condition (58% vs. 39%, $p<0.001$).

152 There was no evidence for a difference by treatment group in previous antibiotic use, while
153 concomitant antibiotic use was higher in the SoC alone group (62% vs. 47%, $p=0.003$) with similar
154 data regardless of specific antibiotic class.

155 With regard to CDI therapy, vancomycin was the most frequently used drug, adopted in fixed dose
156 (65%), in tapered regimen (4%) and in association with metronidazole (9%). As expected, the
157 tapered regimen was mostly used in participants treated with BEZ+SoC (11% vs. 1%, $p>0.001$).
158 Fidaxomicin was used mostly in participants of the BEZ+SoC group than in those treated with SoC
159 alone (25% vs. 5%, $p<0.001$).

160 BEZ was well tolerated in all participants. No adverse events were reported even mild
161 hypersensitivity reactions due to infusion.

162 Cure was obtained in 94% of participants, without any difference by treatment group (BEZ+SoC
163 91% vs. SoC alone 96%).

164 rCDI at day 30 occurred in 54 (12%) participants while all-cause death at 30 days occurred in 16
165 (3.6%) patients (Supplementary Table S2). Unadjusted and adjusted 30-day effectiveness outcomes
166 are shown in Table 4. Among 54 participants who experienced rCDI, 11 were in the BEZ+SoC
167 group and 43 were treated with SoC alone (8.1% vs. 14.0%, $OR=0.58$, 95% $CI:0.31-1.09$, $p=0.09$).

168 This difference was more marked and statistically significant after controlling for confounding
169 factors ($aOR=0.40$, 95% $CI:0.18-0.88$, $p=0.02$). Results were similar after controlling for total
170 number of previous CDI episodes (fitted as a continuous covariate, Supplementary Table S3). Of
171 note, with an observed odds ratio of 0.40 and an incidence of outcome of $<15\%$, an unmeasured
172 confounder that was associated with both the outcome and the treatment by a $RR=4.4$ -fold each
173 could explain away the estimate, but weaker confounding could not. Similarly, to move the
174 confidence interval to include the null, an unmeasured confounder that was associated with the

175 outcome and the treatment by a risk ratio of 1.53-fold each could do so, but weaker confounding
176 could not.

177 All-cause mortality within 30 days occurred less frequently in participants treated with BEZ+SoC
178 than in those treated with SoC alone (0.7% vs. 4.9%, $p=0.03$). Using the composite outcome
179 (recurrence and/or all-cause death at 30 days) there was even greater evidence for a benefit for
180 participants treated with BEZ+SoC vs. SoC alone (aOR=0.35, 95% CI:0.17, 0.73, $p=0.005$) (Table
181 4). The benefit of BEZ+SoC vs SoC alone was strongly confirmed also in another supplemental
182 analysis performed excluding patients treated with metronidazole intravenously and belonging only
183 to SoC group (Table S4).

184 In the sensitivity analyses (unadjusted estimates only) results were also similar to those of the main
185 analysis. After restricting to 141 participants enrolled in sites contributing both BEZ+SoC and SoC
186 alone treated patients, the risk of rCDI was 5/72 (7%) in participants treated with BEZ+SoC vs.
187 11/69 (16%) in those treated with SoC alone (unadjusted OR 0.39, 95% CI: 0.10-1.32, $p=0.09$).
188 Similarly, after restricting the analysis to 347 participants who were at their first CDI episode, 1/40
189 (3%) in the BEZ+SoC vs. 43/307 (14%) experienced a rCDI (unadjusted OR 0.16, 95% CI: 0.004-
190 .99, $p=0.04$).

191 Finally, the forest plot in Figure 1 shows the estimated aOR in subsets of the study population for the
192 secondary outcome of rCDI and/or death at day 30. Overall, there was no evidence for effect
193 measure modification considering age, type of CDI therapy and number of risk factors. In particular,
194 the aOR was similar regardless of the number of risk factors and similar to that of the main analysis
195 (68-70% reduction in risk, $p=0.79$). Although not reaching statistical significance, the benefit of
196 BEZ+SoC on the composite outcome appeared to be attenuated in participants aged under 70 years
197 ($p=0.61$) and in those who received fidaxomicin ($p=0.71$). Follow-up up to 90 days was available for
198 127 of the 135 participants treated with BEZ+SoC (95%) and, among these, only one experienced a
199 recurrence in the window 31-90 days from end of CDI treatment; therefore, the estimated 90-day risk

of rCDI in the BEZ+SoC group was 9.4% (Supplementary Table S5). No infusion-related reactions or SAE have been observed in the BEZ+SoC treated subset.

Discussion

To our knowledge, ours is the analysis of the largest real-world dataset to date, comparing BEZ plus SoC to SoC alone for prevention of rCDI. Our results are consistent with those of randomised trials showing a marked efficacy of BEZ when used in combination with SoC in rCDI prevention, reducing the risk of recurrence by 60% in the multiplicative scale (and 6% using the risk difference as the estimand) after controlling for key confounding factors. Importantly, we showed an even more significant reduction in the risk of developing a composite outcome (30-day recurrence and death) associated with the administration of BEZ+SoC.

Another recent trial emulation using observational study has been conducted in the USA showing similar results, although suggesting an even large effect of BEZ vs. SoC for the risk of rCDI (86% risk reduction by 90 days) [16]. In this study 53 participants also received BEZ between 2015 and 2019, in addition to SoC, were compared to 53 historical controls, receiving SoC alone, in the 2 years immediately prior to BEZ use [16]. As compared to the USA setting, access to care in Italy is universal and therefore it is important to show reproducibility (direct and conceptual) of these previous findings in a distinct geographical area with a national health system. In addition, although follow-up was shorter, sample size of our cohort is 4-fold bigger than the recent trial emulation conducted in the USA and the cohort of unexposed participants treated with SOC alone is a more contemporary group seen for care over 2018-2020 (vs. 2015-2016 in the study by Johnson et al), thus reducing one possible source of confounding [16].

The largest randomized studies comparing these same strategies are the MODIFY trials which also found similar efficacy of BEZ showing a risk difference vs. placebo for rCDI ranging between 10% and 16%, again slightly larger than the magnitude that we found, although the timing of the endpoint

225 was also 90 days [12]. Importantly, compared to these trials and more recent real-world European
226 cohorts treated with BEZ, our study population has a larger proportion of hospitalized participants,
227 more immunocompromised and a higher proportion with multiple rCDI risk factors (Supplementary
228 Table S5) [8,12–16]. Indeed, when restricting to the subset of participants who received BEZ, most
229 of our participants (71%) had ≥ 1 previous CDI episode pre-BEZ, 95% of participants had ≥ 2 risk
230 factors for rCDI, and 63% an age > 65 years. In addition, multiple comorbidities were present at
231 baseline, as shown by a mean CCI of 4.6. Despite these differences at baseline in comparison to
232 other studies, the CDI recurrence rate of 8.1% in our participants who received BEZ+SoC by day 30
233 is entirely consistent with those reported by others (Supplementary Table S5). If anything, our risk of
234 rCDI was slightly higher, possibly reflecting the fact that ours was a more difficult to treat
235 population and/or because of other potential effect modifiers.

236 Unfortunately, although our study population included a large proportion of participants treated with
237 fidaxomicin as part of SoC, was not powered to evaluate whether the benefit of BEZ might vary
238 according to fidaxomicin use. Interestingly, subgroup analysis from MODIFY I/II showed effect
239 measure modification by fidaxomicin use which, however, was not confirmed by our analysis and by
240 others in the observational setting [23]. Although without reaching statistical significance, our results
241 however indicate that the efficacy of BEZ+SoC in preventing recurrences might be even greater in
242 participants aged 70+ and in those treated with vancomycin as SoC. These results are important to
243 identify participants who are at risk for recurrent CDI and may best benefit from receiving this new
244 promising therapeutic strategy in addition to SoC.

245 In addition, our results for the first time show a larger beneficial effect of BEZ+SoC in preventing
246 not only rCDI but also death. Indeed, although Spanish colleagues in their study including only
247 patients treated with BEZ with no control group have shown that death is not directly related to CDI,
248 it has been equally demonstrated how rCDI is independently associated with further nosocomial
249 bloodstream infections (BSIs) and these increased significantly mortality attributable to primary BSI.

250 Moreover, innovative strategies to restore microbiome such as fecal microbiota transplantation
251 increase overall survival by 30% [24]. The protective role of BEZ towards death could justify the
252 reason why the 2021 ESCMID guidelines placed greater emphasis on the importance of preventing
253 rCDI despite the higher costs of these innovative therapeutic strategies.

254 Our study has several limitations. First, the design of the study has potential pitfalls as it includes an
255 historical control with only a few clinical sites contributing data for both strategies and none of the
256 participants who received SoC alone had previously experienced ≥ 1 episode. However, the latter is a
257 potential conservative bias and results were similar in sensitivity analyses after restricting to more
258 comparable populations. Second, it is not a randomized study and although the analysis was
259 conducted under transparent assumptions regarding the underlying causal structure of the data,
260 unmeasured confounding cannot be ruled out (e.g. the exact clostridium ribotype). Data on CD strain
261 type was also missing in Johnson's study; however previous studies suggested BEZ efficacy is not
262 impacted by ribotype [25]. Nevertheless, several important confounders have been accounted for and
263 our sensitivity analysis (e-values) shows that results are very robust to potential unmeasured
264 confounding bias. Moreover, the presence of patients treated with suboptimal metronidazole iv only
265 in the SoC group could influence the occurrence of the outcome in favor of SoC+BEZ group;
266 however, the supplemental analysis conducted excluding those patients confirmed the benefit of the
267 use of BEZ together with SoC in preventing rCDI.

268 In addition, most of the other studies reported the incidence of rCDI at day 90 while our follow-up
269 ends at day 30 and therefore the overall incidence rates are difficult to compare. However, for the
270 participants treated with BEZ+SoC alone we also provided the risk of rCDI by 90 days and our
271 estimate is similar to that of other real-words studies of similar populations treated with BEZ
272 ($<10\%$). Moreover, the 30 day-period after the end of anti-CDI treatment corresponds to the time
273 frame in which most of the rCDIs tend to occur ($<30\%$ of participants in MODIFY and $<1\%$ in our
274 study experienced the event beyond 4 weeks of observation) and by extending the follow-up to 90

275 days, re-infections can also be included which complicates the interpretation. Finally, although the
276 target population is likely to be representative of the Italian population, our results may not be
277 applicable to other epidemiological contexts.

278 In conclusion, our results show a higher efficacy of BEZ+SoC vs. SoC alone for the prevention of
279 rCDI confirming those seen in randomized studies and a similar previous trial emulation performed
280 using observational data. A benefit of using BEZ+SoC vs. SoC alone was seen regardless of age,
281 concomitant use of vancomycin vs. fidaxomicin and number of risk factors. Overall, these results
282 support the updated clinical practice guidelines indicating that BEZ effectively and safely prevents
283 rCDI and should be routinely considered among participants at high risk of rCDI regardless of their
284 age and concomitant use of other CDI drugs.

285 Further studies are needed to assess the potential benefit associated with the use of fidaxomicin
286 treatment concomitantly with BEZ. One of the main obstacles to more universal use of BEZ in
287 routine practice is its high cost. A more precise selection of CDI treatments, based on independent
288 cost-benefit analysis of health-economic studies in different settings and populations, is also
289 required.

Transparency declaration**Conflict of interest**

All authors declare no competing interests.

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Author contributions

MMes, CM and AC-L conceptualised and designed the study. AC, AC-L, MMes, CR and GG wrote and revised the manuscript. AC-L, Mmes, GG, and NP supervised the final version of the manuscript. AC-L did the statistical analysis. MMen and all the author participants contributed to data collection, clinical management of the patients and data interpretation. MMes is also the author responsible for the overall content as the guarantor.

Ethical Considerations

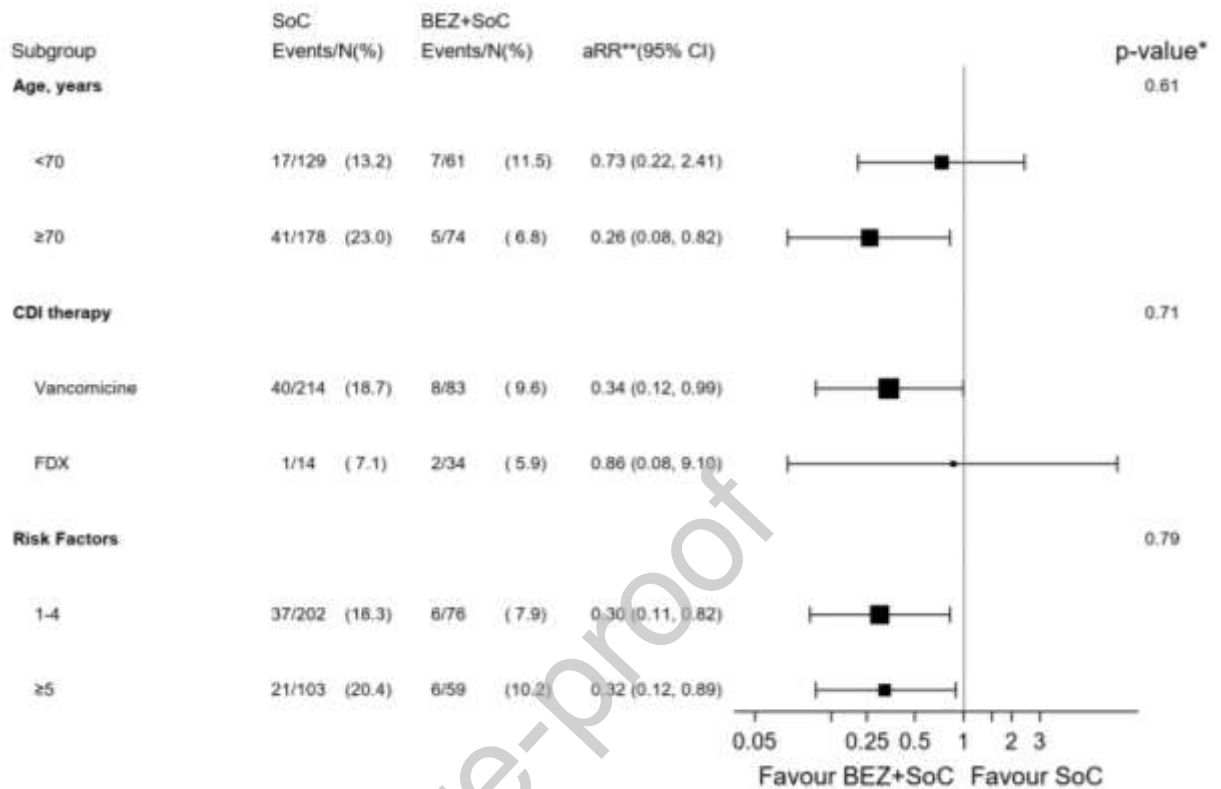
The study was approved by the local Institutional Review Board, that waived the need for the participants to sign the informed consent. The study was approved by Local ethical committee of University of Modena and Reggio Emilia. Reference number 0019510/21 of 06/23/2021.

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Figure 1. Forest plot of subsets analysis by secondary endpoint (CDI recurrence or death at day 30)

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Subgroup analysis was conducted for the secondary outcome (rCDI or death at day 30) by stratification by a number of *a priori* identified predictors: age (binary with a threshold of 70 years), risk factors). Formal interaction test was performed to evaluate whether the difference in risk of outcomes might vary by strata. type of CDI therapy (VAN vs. FDX) and the number of risk factors for rCDI (binary with threshold of 5

*p-value corresponds to the test for interaction between intervention (BEZ+SoC vs SoC alone) and each subgroup unadjusted for multiplicity; **aRR from fitting a standard logistic regression analysis adjusted for age, immunosuppression, zar score and previous CDI episode within 8 weeks.

Abbreviations: aRR, adjusted relative risk; BEZ, bezlotoxumab; CDI, *Clostridioides difficile* infection; CI, confidence interval; FDX, fidaxomicin; SoC, standard of care.

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Table 1. Key baseline factors by intervention: standard of care (SoC) treatment for *Clostridioides difficile* infections vs SoC + Bezlotoxumab

Characteristic	Intervention		p-value*	Total
	SoC + BEZ	SoC		
	N	N		N
	=	=		=
	1	3		4
	3	0		4
	5	7		2
			0	
			.	
Age, years			6	
			0	
			4	
	7	7		7
	2	3		3
Median (IQR)	(((
	6	6		6
	2	0		1
	,	,		,

	8	8	8
	0	2	1
)))
			0
<i>Gender</i>			.
<i>, n(%)</i>			8
			1
			4
		1	2
	6	4	1
	3	7	0
	(((
Female	4	4	4
	6	7	7
	.	.	.
	7	9	5
	%	%	%
)))
<i>Long</i>			
<i>term</i>			0
<i>facility</i>			.
<i>over</i>			5
<i>prior 3</i>			0
<i>months</i>			1
<i>, n(%)</i>			
	2	3	5
Yes	0	8	8

(((
1	1	1
4	2	3
.	.	.
8	5	2
%	%	%
)))

Hospita

lization

over

prior 3

months

, n(%)

<

.

0

0

1

1	1	2
0	7	8
7	8	5
(((
7	5	6
9	8	4
.	.	.
3	0	5
%	%	%
)))

Yes

<

.

0

0

1

Admissi

on

ward,

n(%)

	1	2	3
	1	3	5
	5	6	1
Medical	(((
area	8	7	8
	7	6	0
	.	.	.
	1	9	0
	%	%	%
)))
		4	5
	9	3	2
Surgica	(((
l area	6	1	1
	.	4	1
	8	.	.
	%	0	8
)	%	%
))
		1	1
	0	0	0
Outpati	(((
ent	0	3	2
	.	.	.
	0	3	3
	%	%	%
)))

	0	1	1
		8	8
	(((
Emergence	0	5	4
	.	.	.
	0	9	1
	%	%	%
)))
	8	0	8
	(((
ICU	6	0	1
	.	.	.
	1	0	8
	%	%	%
)))
<i>Previous CDI episode</i>			<
<i>s, n(%)</i>			.
			0
			0
			1
	9	0	9
	5		5
		(
Yes	(0	(
	7	.	2
	0	0	1
	.	%	.
	9)	5

	%		%
))
<hr/>			
<i>CDI</i>			<
<i>episode</i>			.
<i>s over</i>			0
<i>prior 8</i>			0
<i>weeks,</i>			1
<i>n(%)</i>			
<hr/>			
	6		6
	5	0	5
	(((
Yes	4	0	1
	8	.	4
	.	0	.
	1	%	7
	%)	%
))
<hr/>			
			<
<i>Year of</i>			.
<i>starting</i>			0
			0
			1
<hr/>			
	2	2	2
	0	0	0
Median	2	1	1
(IQR)	0	9	9
	(((

	2	2	2
	0	0	0
	1	1	1
	9	8	8
	,	,	,
	2	2	2
	0	0	0
	2	1	2
	1	9	0
)))
<i>Duratio</i>			0
<i>n of</i>			.
<i>treatme</i>			8
<i>nt, days</i>			2
			5
	1	1	1
	0	2	1
	(((
Median	1	1	1
(IQR)	0	0	0
	,	,	,
	1	1	1
	4	5	4
)))

*Chi-square or Mann-Whitney test as appropriate

406

407

Abbreviations: BEZ, bezlotoxumab; CDI, *Clostridioides difficile* infection; ICU, intensive care unit; IQR,

408

interquartile range; SoC, standard of care.

409

Median	4	4	4
(IQR)	(4, 5)	(3, , 5)	(3, 5)
<i>FDR=1,</i>	1	1	1
<i>n(%)</i>	(0.7 %)	3 (4 .2 %)	4 (3. 2 %)
<i>FDR=2,</i>	8	4	4
<i>n(%)</i>	(5.9 %)	0 (1 3 .0 %)	8 (1 0. 9 %)
<i>FDR=3,</i>	23	5	8
<i>n(%)</i>	(17. 0%)	7 (1 8 .6	0 (1 8. 1 %

		%)
)	
FDR=4,	44	9	1
n(%)	(32.	2	3
	6%	(6
)	3	(
		0	3
		.	0.
		0	8
		%	%
))
FDR>=5,	59	1	1
n(%)	(43.	0	6
	7%	3	2
)	((
		3	3
		3	6.
		.	7
		6	%
		%)
)	
Zar Score	53	9	0
>=2, n(%)	(39.	9	.
	3%	(1
)	3	5
		2	3
		.	4.
		2	4
		%	%
))

<i>Comorbidities, n(%)</i>				
Chronic kidney disease	26 (19.3%)	6 (19.9%)	0 (0%)	8 (20.5%)
Cirrhosis/hepatopathy	11 (8.1%)	2 (9.9%)	0 (6.9%)	4 (9.9%)
IBD	5 (3.7%)	1 (0%)	0 (0%)	6 (4.5%)
HIV	1 (0.7%)	1 (0%)	0 (0%)	2 (5%)

		3	0	%
		%)
)		
Immunosup	78	1	<	1
pression	(57.	2	.	9
	8%	1	0	9
)	(0	(
		3	1	4
		9		5.
		.		0
		4		%
		%)
)		
Solid organ	11	.		1
transplant	(8.1	(.		1
	%)	%		(
)		8.
				1
				%
)
Haematolog	18	2	0	4
ical disease	(13.	4	.	2
	3%	(0	(
)	7	6	9.
		.	9	5
		8		%
		%)
)		
Chemothera	3	.		3
py	(2.2	(.		(

%)	%	2.
)	2
		%
)

*Chi-square or Mann-Whitney test as appropriate

413

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Abbreviations: BEZ, bezlotoxumab; CDI, *Clostridioides difficile* infection; FDR, risk factor; HIV,

415

human immunodeficiency virus, IBD, intestinal bowel disease; IQR, interquartile range; SoC,

416

standard of care.

417

Journal Pre-proof

418

419 **Table 3. Antibiotic therapies by intervention: standard of care (SoC) treatment for *Clostridioides difficile***

420 **infections vs SoC + Bezlotoxumab**

Therapies	Intervention			
	SoC	SoC + Bezlotoxumab	p-value	Total
	N=135	N=135		N=270
		3		4
		0		4
		6		1
Antibiotic use	99	2	0	3
within 3	(73	1	.	1
months	.3	8	6	7
	%)		5	
		(3	(
		7		7
		1		1
		.		.
		2		9
		%		%
))

Penicillines	53	1	0	1
	(39	0	.	6
	.3	8	5	1
	%)		4	
		(8	(
		3		3
		6		7
		.		.
		2		2
		%		%
))
Cephalosporin	45	8	0	1
es	(33	1	.	2
	.3		1	6
	%)	(9	
		2	2	(
		7		2
		.		9
		2		.
		%		1
)		%
)
Fluoroquinolo	16	5	0	6
nes	(11	1	.	7
	.9		1	
	%)	(6	(
		1	1	1
		7		5
		.		.
		1		5

		%		%
))
<i>Concomitant</i>	63	1	0	2
<i>use of</i>	(47	9	.	5
<i>antibiotic</i>	.0	0	0	3
	%)		0	
		(3	(
		6		5
		2		7
		.		.
		1		5
		%		%
))
Penicillines	30	6	0	9
	(22	5	.	5
	.4		8	
	%)	(0	(
		2	1	2
		1		1
		.		.
		3		6
		%		%
))
Cephalosporin	14	5	0	6
es	(10	2	.	6
	.4		0	
	%)	(7	(
		1	5	1
		7		5
		.		.

		0		0
		%		%
))
Fluoroquinolones	5 (3.7%)	2 0	0 .	2 5
		(4	(
		6	0	5
		.		.
		6		7
		%		%
))
Carbapenems	8 (6.0%)	3 4	0 .	4 2
		(9	(
		1	0	9
		1		.
		.		6
		1		%
		%)
))
Glycopeptides	4 (3.0%)	1 5	0 .	1 9
		(6	(
		4	0	4
		.		.
		9		3
		%		%

))		
<i>Use of PPI</i>	1	2	0	3
	0	1	.	2
	8	4	0	2
	(1	
	8	(6	(
	0.	6		7
	6	9		3
	%	.		.
)	7		0
		%		%
))
<i>CDI treatment</i>				
Vancomycin	7	2	0	2
	6	1	.	8
		0	0	6
	(1	
	5	(6	(
	7	6		6
	.	9		5
	1	.		.
	%	1		4
)	%		%
))
Vancomycin	1	4	<	1
tapered	5		.	9
		(0	
	(1	0	(
	1	.	1	4
	1	3		.

	.	%		4
	4)		%
	%)
)			
Fidaxomicin	3	1	<	4
	4	4	.	8
			0	
	((0	(
	2	4	1	1
	5	.		1
	.	6		.
	6	%		0
	%)		%
))
Metronidazole	0	3	<	3
		7	.	7
	(0	
	0	(0	(
	.	1	1	8
	0	2		.
	%	.		5
)	2		%
		%)
)		
Vancomycin+	8	3	0	4
Metronidazole		9	.	7
	(0	
	6	(3	(
	.	1	5	1
	0	2		0

%	.	.
)	8	8
	%	%
))

*Chi-square or Mann-Whitney test as appropriate

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Abbreviations: BEZ, bezlotoxumab; CDI, *Clostridioides difficile* infection; PPI, pump

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proton inhibitor; SoC, standard of care.

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Table 4. Effectiveness of Bezlotoxumab (BEZ) associated with standard of care (SoC) versus SOC alone by primary (recurrence of CDI) and secondary (rCDI or death) endpoint at 30 days of follow-up.

Unweighted and weighted marginal relative risk				
	Unweighted RR (95% CI)	p-value	Weighted RR (95% CI)	p-value
All patients				
Primary endpoint (rCDI at day 30)				
SoC	1.00		1.00	
SoC+ BEZ	0.58 (0.31, 1.09)	0.09	0.40 (0.18, 0.88)	0.03

Seco	ndar	y	endp	oint	(rCD	I or	deat	h at	day	30)
SoC	1.00			1.00						
		0		0.35		0				
SoC+	0.47	.		(0.1		.				
BEZ	(0.26,	0		7,		0				
	0.85)	1		0.73		0				
		2)		5				

*adjusted for age, Zar Score, immuno-suppression, CDI episodes within 8 weeks using IPW

Abbreviations: BEZ, bezlotoxumab; CDI, *Clostridioides difficile* infection; CI, confidence interval; IPW, inverse probability weighting; rCDI, *Clostridioides difficile* infection recurrence; RR, relative risk; SoC, standard of care.

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Declaration of interests

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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