

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JANUARY 26, 2017

VOL. 376 NO. 4

Bezlotoxumab for Prevention of Recurrent *Clostridium difficile* Infection

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ABSTRACT

BACKGROUND

Clostridium difficile is the most common cause of infectious diarrhea in hospitalized patients. Recurrences are common after antibiotic therapy. Actoxumab and bezlotoxumab are human monoclonal antibodies against *C. difficile* toxins A and B, respectively.

METHODS

We conducted two double-blind, randomized, placebo-controlled, phase 3 trials, MODIFY I and MODIFY II, involving 2655 adults receiving oral standard-of-care antibiotics for primary or recurrent *C. difficile* infection. Participants received an infusion of bezlotoxumab (10 mg per kilogram of body weight), actoxumab plus bezlotoxumab (10 mg per kilogram each), or placebo; actoxumab alone (10 mg per kilogram) was given in MODIFY I but discontinued after a planned interim analysis. The primary end point was recurrent infection (new episode after initial clinical cure) within 12 weeks after infusion in the modified intention-to-treat population.

RESULTS

In both trials, the rate of recurrent *C. difficile* infection was significantly lower with bezlotoxumab alone than with placebo (MODIFY I: 17% [67 of 386] vs. 28% [109 of 395]; adjusted difference, -10.1 percentage points; 95% confidence interval [CI], -15.9 to -4.3; $P < 0.001$; MODIFY II: 16% [62 of 395] vs. 26% [97 of 378]; adjusted difference, -9.9 percentage points; 95% CI, -15.5 to -4.3; $P < 0.001$) and was significantly lower with actoxumab plus bezlotoxumab than with placebo (MODIFY I: 16% [61 of 383] vs. 28% [109 of 395]; adjusted difference, -11.6 percentage points; 95% CI, -17.4 to -5.9; $P < 0.001$; MODIFY II: 15% [58 of 390] vs. 26% [97 of 378]; adjusted difference, -10.7 percentage points; 95% CI, -16.4 to -5.1; $P < 0.001$). In prespecified subgroup analyses (combined data set), rates of recurrent infection were lower in both groups that received bezlotoxumab than in the placebo group in subpopulations at high risk for recurrent infection or for an adverse outcome. The rates of initial clinical cure were 80% with bezlotoxumab alone, 73% with actoxumab plus bezlotoxumab, and 80% with placebo; the rates of sustained cure (initial clinical cure without recurrent infection in 12 weeks) were 64%, 58%, and 54%, respectively. The rates of adverse events were similar among these groups; the most common events were diarrhea and nausea.

CONCLUSIONS

Among participants receiving antibiotic treatment for primary or recurrent *C. difficile* infection, bezlotoxumab was associated with a substantially lower rate of recurrent infection than placebo and had a safety profile similar to that of placebo. The addition of actoxumab did not improve efficacy. (Funded by Merck; MODIFY I and MODIFY II ClinicalTrials.gov numbers, NCT01241552 and NCT01513239.)

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*A complete list of investigators in the MODIFY I and MODIFY II trials is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2017;376:305-17.

DOI: 10.1056/NEJMoa1602615

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IN HIGH-INCOME COUNTRIES, *CLOSTRIDIUM difficile* is the most common cause of infectious diarrhea in hospitalized patients.^{1,2} After completing initial antibiotic therapy, up to 35% of patients have recurrent *C. difficile* infection,^{3,4} which is more difficult to treat and is associated with more hospitalizations, more severe outcomes, and higher costs than the first infection and a 50 to 60% chance of repeat recurrent infections.^{5,6} Currently, no therapy has been approved to prevent recurrent *C. difficile* infection.

Passive or active immunization against *C. difficile* toxins A and B is protective in animals that are challenged with toxigenic *C. difficile*,⁷⁻⁹ which underscores the key importance of the toxins in causing the symptoms of *C. difficile* infection. The relative biologic importance of toxins A and B in *C. difficile* infection is controversial, but it may be host species-dependent.¹⁰⁻¹² Neutralization of both toxins appears to be necessary for maximal protection in rodents, but neutralization of toxin B alone appears to be sufficient in piglets.¹³ In humans, the level of circulating antibodies against toxin A^{14,15} or toxin B¹⁶ has been correlated with protection against primary and recurrent *C. difficile* infection.

A new approach to the prevention of recurrent *C. difficile* infection is the administration of monoclonal antibodies against *C. difficile* toxins (in addition to antibiotic therapy) as a form of passive immunity. Actoxumab (MK-3415/GS-CDA1/CDA1) and bezlotoxumab (MK-6072/MDX-1388/CDB1) are fully human monoclonal antibodies that bind and neutralize *C. difficile* toxins A and B, respectively. In patients who were receiving metronidazole or vancomycin for *C. difficile* infection, a single intravenous infusion of actoxumab-bezlotoxumab was found to be associated with a significantly lower rate of recurrent infection than placebo (7% [7 of 101] vs. 25% [25 of 99], $P < 0.001$),¹⁷ whereas adjunctive treatment with actoxumab alone was not.¹⁶ In two global, phase 3 trials, we examined the safety and efficacy of bezlotoxumab, both alone and combined with actoxumab, for the prevention of recurrent *C. difficile* infection.

METHODS

TRIAL OVERSIGHT

MODIFY I and MODIFY II were randomized, double-blind, placebo-controlled trials conducted at 322 sites in 30 countries from November 1,

2011, through May 22, 2015. Both trials were conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. The protocols and amendments were approved by the institutional review board or independent ethics committee at each study site. Written informed consent was obtained from all participants before the trial began. The MODIFY I and MODIFY II trials were designed by representatives of Merck and by academic advisors. All the data were collected by investigators and associated site personnel, analyzed by Merck statisticians, and interpreted by the authors. The first, second, and last authors wrote the first draft of the manuscript with the assistance of a medical writer who is an employee of Merck. All the authors participated in reviewing and editing the manuscript, approved the submitted versions, had full access to the data (under confidentiality agreements), and vouch for the accuracy and completeness of the data and for the fidelity of the trials to the protocols, which are available with the full text of this article at NEJM.org.

PARTICIPANTS AND PROCEDURES

The participants were adults with primary or recurrent *C. difficile* infection who were receiving oral standard-of-care antibiotics (metronidazole, vancomycin, or fidaxomicin, chosen by the treating physician) for 10 to 14 days. Participants who were receiving oral vancomycin or fidaxomicin could also receive intravenous metronidazole. *C. difficile* infection was defined as diarrhea (≥ 3 unformed bowel movements [types 5 to 7 on the Bristol stool scale¹⁸] in 24 hours) with a stool test result that was positive for toxigenic *C. difficile*. The diagnostic methods included cytotoxicity assays, culture with toxin detection or strain typing, and commercial assays that detect (at least) toxin B or its gene (see the Supplementary Appendix, available at NEJM.org). Microbiologic assessments were performed at R.M. Alden Research Laboratory. Polymerase-chain-reaction ribotyping of *C. difficile* cultures was completed at Leeds Teaching Hospitals.¹⁹ Detailed inclusion and exclusion criteria are provided in the trial protocols.

Participants were randomly assigned in a 1:1:1:1 ratio to receive a single dose of bezlotoxumab (10 mg per kilogram of body weight), actoxumab plus bezlotoxumab (10 mg per kilogram each), placebo (0.9% saline), or, in MODIFY I



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only, actoxumab alone (10 mg per kilogram); actoxumab was not evaluated alone in MODIFY II because earlier results suggested a lack of efficacy for this antibody.¹⁶ The use of a single dose was supported by the long half-life of the monoclonal antibodies (approximately 19 days). Randomization was stratified according to oral standard-of-care antibiotic and hospitalization status (inpatient or outpatient). The participants, investigators, study-center personnel (except the pharmacist preparing the infusion), and sponsor personnel were unaware of the study-group assignments until the trial was completed and the database was locked.

Participants who underwent randomization received a single, 60-minute intravenous infusion of the assigned monoclonal antibody or placebo (study day 1) while they were receiving standard-of-care antibiotic therapy (in three cases, standard-of-care therapy was initiated on the day after the infusion). Participants recorded unformed bowel movements daily until day 80 to 90 after the infusion; new episodes of diarrhea were monitored through telephone contact between visits. Safety assessments included preinfusion and postinfusion electrocardiography, monitoring for reactions for 24 hours after infusion, recording of all adverse events and results of laboratory tests through week 4, and recording of serious adverse events (including deaths) through week 12.

Both trials had a planned sample size of 400 participants per group. Efficacy was assessed in a modified intention-to-treat population, which included all randomly assigned participants who received the study infusion, had a baseline stool test that was positive for toxigenic *C. difficile*, and began receiving standard-of-care therapy before or within 1 day after receiving the monoclonal antibodies. Safety was assessed in the as-treated population, which included all randomly assigned participants who received the study infusion, analyzed according to the actual treatment received.

PRESPECIFIED END POINTS

The primary end point was the proportion of participants with recurrent *C. difficile* infection (defined as a new episode of *C. difficile* infection after initial clinical cure of the baseline episode) during 12 weeks of follow-up in the modified intention-to-treat population (for the rationale for using this end point, see the Statistical Analysis Methods section in the Supplementary

Appendix). Initial clinical cure (defined as no diarrhea for 2 consecutive days after completion of standard-of-care antibiotic therapy administered for ≤ 16 days) was an exploratory end point. Secondary analyses included the rate of recurrent *C. difficile* infection in the subgroup of participants in the modified intention-to-treat population who had an initial clinical cure, as well as in prespecified subgroups of participants with risk factors for recurrent *C. difficile* infection or for adverse outcomes related to *C. difficile* infection: an age of 65 years or older,^{20,21} a history of *C. difficile* infection,^{3,4} compromised immunity,^{22,23} clinically severe *C. difficile* infection (defined as a Zar score ≥ 2 ; scores range from 1 to 8, with higher scores indicating more severe infection),²⁴ and infection with a strain associated with poor outcomes (strain 027,^{20,25-27} 078,²⁸ or 244^{29,30}). A secondary end point was the rate of sustained cure (i.e., initial clinical cure of the baseline episode of *C. difficile* infection and no recurrent infection through 12 weeks), also known as global cure or sustained clinical response. The time to recurrent infection and the rate of recurrence of diarrhea (defined as a new diarrheal episode, regardless of whether it was associated with toxigenic *C. difficile*) were exploratory end points. The prespecified and post hoc efficacy end points are listed in Table S1 in the Supplementary Appendix.

STATISTICAL ANALYSIS

MODIFY I and MODIFY II were independent and nearly identical trials, each of which was powered to determine the efficacy of bezlotoxumab alone or in combination with actoxumab for prevention of recurrent *C. difficile* infection. MODIFY I had an adaptive design in which discontinuation of enrollment in the actoxumab group, bezlotoxumab group, or both was allowed if a significant difference in the rate of recurrent infection between either of these groups and the actoxumab–bezlotoxumab group was found in an interim analysis. In the interim analysis, which was prepared and reviewed by an independent data and safety monitoring committee and included 632 participants in the modified intention-to-treat population (39.5% of the 1600 planned), the rate of recurrent infection was found to be significantly higher in the actoxumab group than in the actoxumab–bezlotoxumab group ($P=0.02$), and more deaths and serious adverse events were found to have occurred in the actoxumab group

than in the placebo group. Enrollment in the actoxumab group was therefore stopped.

The protocols of both trials were designed to strongly limit the study-wise type I error rate to 5% for the primary end point. The multiplicity strategy addressed multiple comparisons among the study groups in both trials and multiple analysis times in MODIFY I (see the protocols). Comparisons between treatment and placebo with regard to the primary end point were performed at a two-sided alpha level of 0.025 in MODIFY I (because of the more complex multiplicity strategy) and at a two-sided alpha level of 0.050 in MODIFY II. Both trials had more than 90% power to detect a difference of 9 to 10 percentage points in the rate of recurrent infection, under the assumption of a rate of 20% in the placebo group.

A planned analysis of pooled data from the two trials was documented in an integrated statistical analysis plan (see the protocol). Pooling the data also facilitated the analysis of treatment effects in important prespecified subgroups of participants who were at high risk for recurrent *C. difficile* infection or for adverse outcomes related to *C. difficile* infection. Additional details regarding statistical methods, including sensitivity analyses and approaches to handling missing data, are provided in the Supplementary Appendix.

RESULTS

STUDY POPULATION

Of the 2655 participants who underwent randomization in the trials, 2580 (97%) were treated and 2559 (96%) were included in the modified intention-to-treat population (Fig. S2 in the Supplementary Appendix). In the modified intention-to-treat population, 2174 participants (85%) completed the trial through 12 weeks. The most common reasons for early discontinuation (death, 7% [182 of 2559]; withdrawal of consent, 4% [106 of 2559]; and loss to follow-up, 3% [71 of 2559]) were consistent among the study groups, with the exception of death, which was more common in the actoxumab group (11% [26 of 232]) than in the other groups.

The median age of participants in the modified intention-to-treat population was 66 years (range, 18 to 100); 86% were white, and 56% were women. Key baseline characteristics were balanced among the study groups (Table 1, and

Tables S2 and S3 in the Supplementary Appendix). Most participants were inpatients (68%), and most received either metronidazole (47%) or vancomycin (48%) as the oral standard-of-care antibiotic; only 4% received fidaxomicin. In 94% of the participants, the study agent was infused within 6 days after initiation of standard-of-care antibiotic treatment (median, 3 days in all groups) (Table S4 in the Supplementary Appendix).

INITIAL CLINICAL CURE

In the MODIFY I trial, initial clinical cure was achieved in 77% of the participants in the bezlotoxumab group (299 of 386) and in 83% of those in the placebo group (327 of 395) (adjusted difference, -5.3 percentage points; 95% confidence interval [CI], -10.9 to 0.3). In the MODIFY II trial, initial clinical cure was achieved in 83% of the participants in the bezlotoxumab group (326 of 395) and in 78% of those in the placebo group (294 of 378) (adjusted difference, 4.8 percentage points; 95% CI, -0.9 to 10.4). In the pooled data set, the rate of initial clinical cure was 80% (625 of 781) in the bezlotoxumab group and 80% (621 of 773) in the placebo group. Among participants who received actoxumab-bezlotoxumab, initial clinical cure was achieved in 75% (286 of 383) of those in MODIFY I, in 72% (282 of 390) of those in MODIFY II, and in 73% (568 of 773) of those in the pooled data set (Table S5 in the Supplementary Appendix).

RECURRENCE OF *C. DIFFICILE* INFECTION

In both trials, the percentage of participants in the modified intention-to-treat population who had recurrent infection (Fig. 1) was significantly lower in the bezlotoxumab group than in the placebo group (MODIFY I: 17% [67 of 386] vs. 28% [109 of 395]; adjusted difference, -10.1 percentage points; 95% CI, -15.9 to -4.3; $P < 0.001$; MODIFY II: 16% [62 of 395] vs. 26% [97 of 378]; adjusted difference, -9.9 percentage points; 95% CI, -15.5 to -4.3; $P < 0.001$) and was significantly lower in the actoxumab-bezlotoxumab group than in the placebo group (MODIFY I: 16% [61 of 383] vs. 28% [109 of 395]; adjusted difference, -11.6 percentage points; 95% CI, -17.4 to -5.9; MODIFY II: 15% [58 of 390] vs. 26% [97 of 378]; adjusted difference, -10.7 percentage points; 95% CI, -16.4 to -5.1; both $P < 0.001$). All P values were below the threshold determined by the multiplicity strategy. In contrast, the rate of recurrent infection did not differ significantly be-

Table 1. Clinical and Demographic Characteristics of Participants in the Modified Intention-to-Treat Population in Both Trials.

Characteristic	Actoxumab plus Bezlotoxumab (N = 773)	Bezlotoxumab (N = 781)	Actoxumab (N = 232)	Placebo (N = 773)	All Participants (N = 2559)
	number of participants (percent)				
Standard-of-care antibiotic					
Metronidazole	366 (47.3)	365 (46.7)	112 (48.3)	353 (45.7)	1196 (46.7)
Vancomycin	366 (47.3)	370 (47.4)	113 (48.7)	372 (48.1)	1221 (47.7)
Fidaxomicin	25 (3.2)	30 (3.8)	7 (3.0)	30 (3.9)	92 (3.6)
Inpatient	523 (67.7)	530 (67.9)	158 (68.1)	520 (67.3)	1731 (67.6)
Female sex	423 (54.7)	442 (56.6)	130 (56.0)	449 (58.1)	1444 (56.4)
Age ≥65 years	441 (57.1)	390 (49.9)	122 (52.6)	405 (52.4)	1358 (53.1)
≥1 Episodes of <i>C. difficile</i> infection in previous 6 mo	200 (25.9)	216 (27.7)	69 (29.7)	219 (28.3)	704 (27.5)
≥2 Previous <i>C. difficile</i> infection episodes ever	103 (13.3)	100 (12.8)	34 (14.7)	126 (16.3)	363 (14.2)
Severe <i>C. difficile</i> infection*	142 (18.4)	122 (15.6)	31 (13.4)	125 (16.2)	420 (16.4)
Immunocompromised†	163 (21.1)	178 (22.8)	55 (23.7)	153 (19.8)	549 (21.5)
Other antibiotic use during standard-of-care therapy‡	333 (43.1)	292 (37.4)	86 (37.1)	317 (41.0)	1028 (40.2)
Other antibiotic use after standard-of-care therapy‡	274 (35.4)	273 (35.0)	83 (35.8)	275 (35.6)	908 (35.5)
Renal impairment§	96 (12.4)	123 (15.7)	37 (15.9)	110 (14.2)	366 (14.3)
Hepatic impairment¶	56 (7.2)	49 (6.3)	14 (6.0)	44 (5.7)	163 (6.4)
Region of enrollment					
Africa	2 (0.3)	5 (0.6)	1 (0.4)	2 (0.3)	10 (0.4)
Asia–Pacific	80 (10.3)	79 (10.1)	10 (4.3)	77 (10.0)	246 (9.6)
Latin America	37 (4.8)	30 (3.8)	9 (3.9)	35 (4.5)	111 (4.3)
Europe	292 (37.8)	313 (40.1)	80 (34.5)	293 (37.9)	978 (38.2)
North America	362 (46.8)	354 (45.3)	132 (56.9)	366 (47.3)	1214 (47.4)
PCR ribotype					
Participants with positive culture	477 (61.7)	490 (62.7)	144 (62.1)	486 (62.9)	1597 (62.4)
Most common strains**††	222 (46.5)	210 (42.9)	57 (39.6)	233 (47.9)	722 (45.2)
027, 078, or 244 strain††	90 (18.9)	102 (20.8)	30 (20.8)	115 (23.7)	337 (21.1)
027 strain††	76 (15.9)	89 (18.2)	24 (16.7)	100 (20.6)	289 (18.1)

* Severe infection was defined as a Zar score of 2 or higher. The Zar score ranges from 1 to 8 and is based on the following factors: age greater than 60 years (1 point), body temperature higher than 38.3°C (100°F) (1 point), albumin level lower than 2.5 g per deciliter (1 point), peripheral white-cell count higher than 15,000 per cubic millimeter within 48 hours (1 point), endoscopic evidence of pseudomembranous colitis (2 points), and treatment in an intensive care unit (2 points).

† The determination of whether a participant was immunocompromised was made on the basis of medical history or use of immunosuppressive therapy.

‡ Included are systemic antibiotics other than the standard-of-care antibiotic that was given to treat *C. difficile* infection.

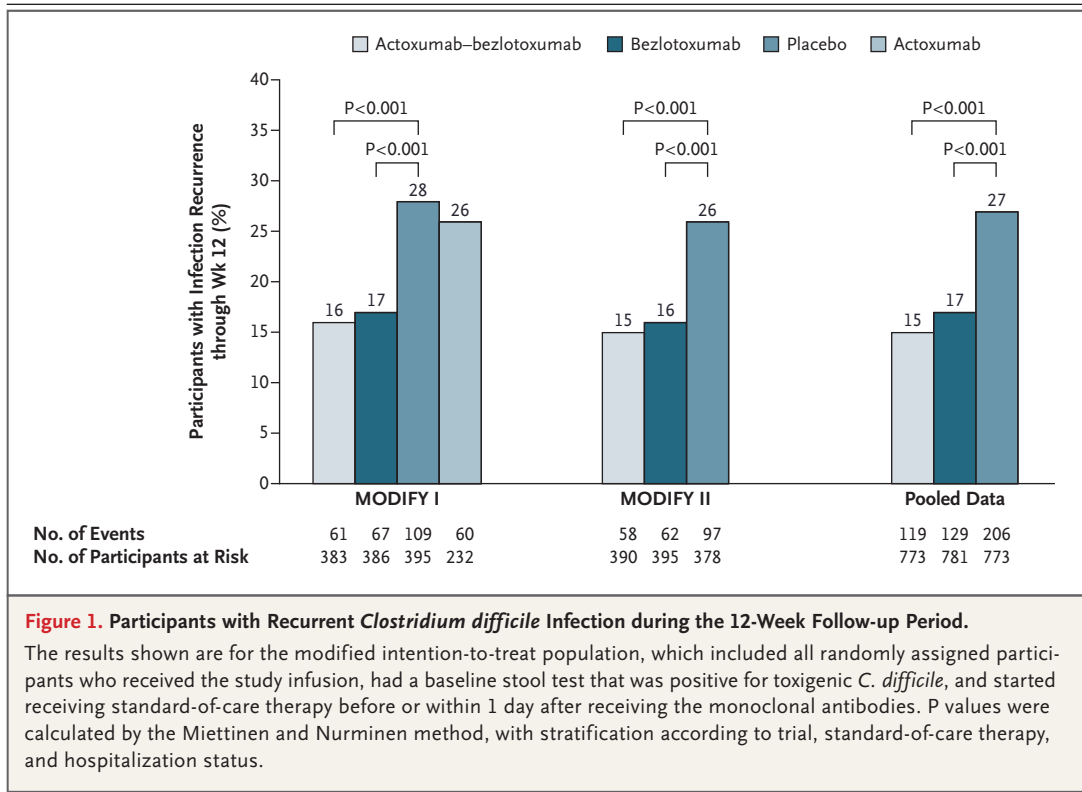
§ Renal impairment was defined as a serum creatinine level of 1.5 mg per deciliter (133 μmol per liter) or higher.

¶ Hepatic impairment was defined as having two or more of the following: an albumin level of 3.1 g per deciliter or lower, an alanine aminotransferase level at least 2 times the upper limit of the normal range, a total bilirubin level at least 1.3 times the upper limit of the normal range, or mild, moderate, or severe liver disease (as reported on the Charlson Index).

|| Africa includes South Africa; Asia–Pacific includes Australia, Japan, Korea, New Zealand, and Taiwan; Latin America includes Argentina, Brazil, Chile, Colombia, and Mexico; Europe includes Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Israel, Italy, Poland, Portugal, Russia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom; and North America includes Canada and the United States.

** The most common strains were ribotypes 027, 014, 002, 001, 106, and 020.

†† The denominators used to calculate percentages are the numbers of participants who had a positive culture.



tween the actoxumab group and the placebo group in MODIFY I (26% [60 of 232] and 28% [109 of 395], respectively; $P=0.64$). Bezlotoxumab and actoxumab-bezlotoxumab were similar in their effect on the rate of recurrent infection, with no significant difference found between these groups in either trial (Table S6 in the Supplementary Appendix).

In the subgroup of participants in the modified intention-to-treat population who had initial clinical cure, the differences in the rate of recurrent infection were similar to those found in the overall modified intention-to-treat population, both with respect to the rates in the bezlotoxumab group as compared with the placebo group (MODIFY I: 22% [67 of 299] vs. 33% [109 of 327]; adjusted difference, -10.8 percentage points; 95% CI, -17.7 to -3.8; $P=0.003$; MODIFY II: 19% [62 of 326] vs. 33% [97 of 294]; adjusted difference, -13.7 percentage points; 95% CI, -20.4 to -6.9; $P<0.001$) and with respect to the rates in the actoxumab-bezlotoxumab group as compared with the placebo group (MODIFY I: 21% [61 of 286] vs. 33% [109 of 327]; adjusted difference, -11.7 percentage points; 95% CI, -18.6 to -4.7; $P=0.001$; MODIFY II: 21% [58 of

282] vs. 33% [97 of 294]; adjusted difference, -11.9 percentage points; 95% CI, -19.0 to -4.7; $P=0.001$) (Table S7 in the Supplementary Appendix). Sensitivity analyses addressing the effect of the initial clinical cure rate and the effect of missing or incomplete data (including early discontinuations due to death or other reasons) on the rate of recurrent infection were consistent with the results of the primary analysis (see the Supplementary Appendix).

The distribution of the time to recurrent infection according to study group is shown in Figure 2. Most recurrences (71%) occurred within 4 weeks after study infusion. Differences in the rate of recurrent infection between either regimen that included bezlotoxumab and placebo were apparent as early as 2 weeks after infusion and were maintained through week 12. The absolute differences in the Kaplan-Meier rates of recurrent infection between the bezlotoxumab group and the placebo group were 12 percentage points at week 4, 12 percentage points at week 8, and 13 percentage points at week 12; the corresponding differences between the actoxumab-bezlotoxumab group and the placebo group were 11, 12, and 13 percentage points.

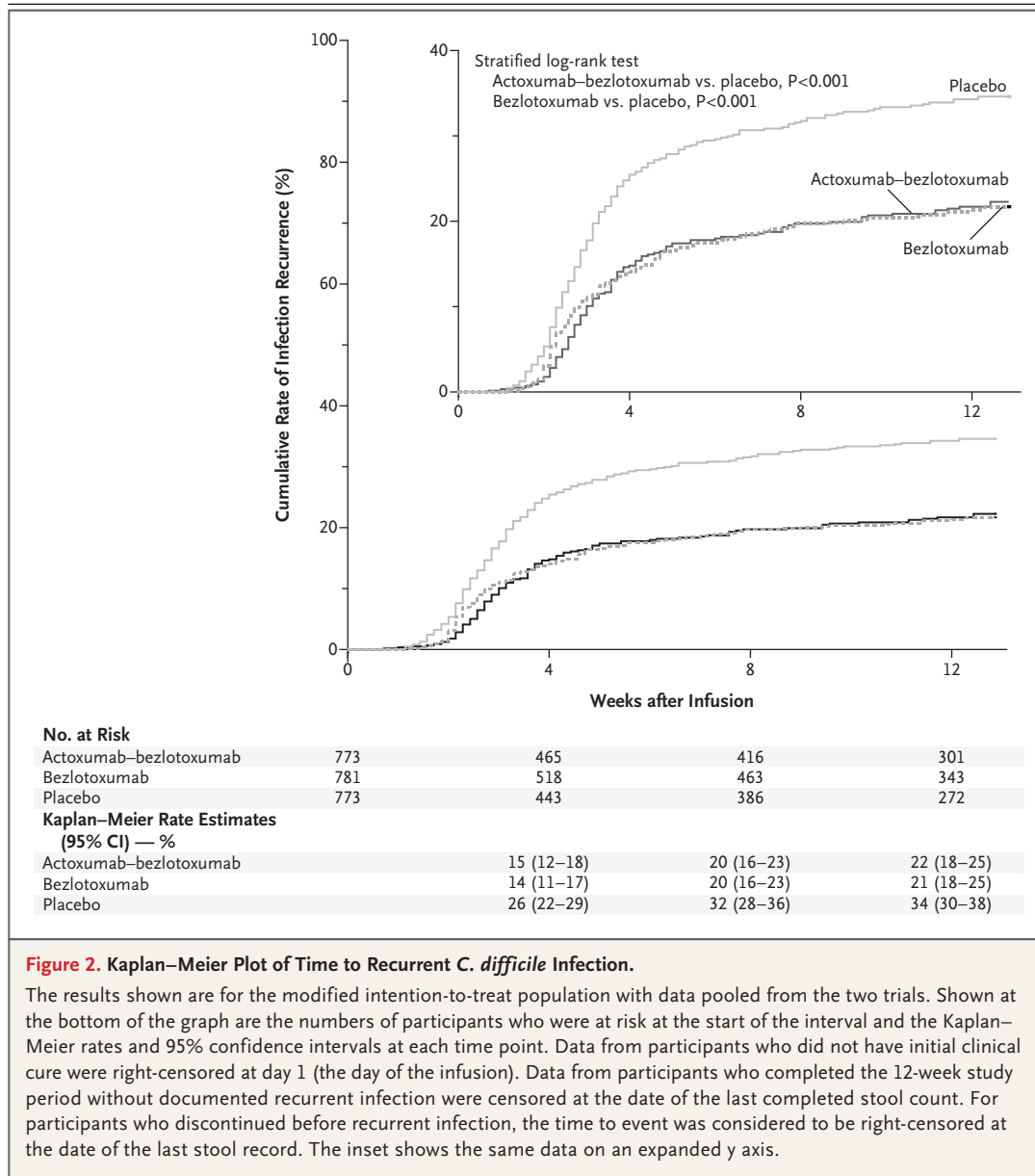
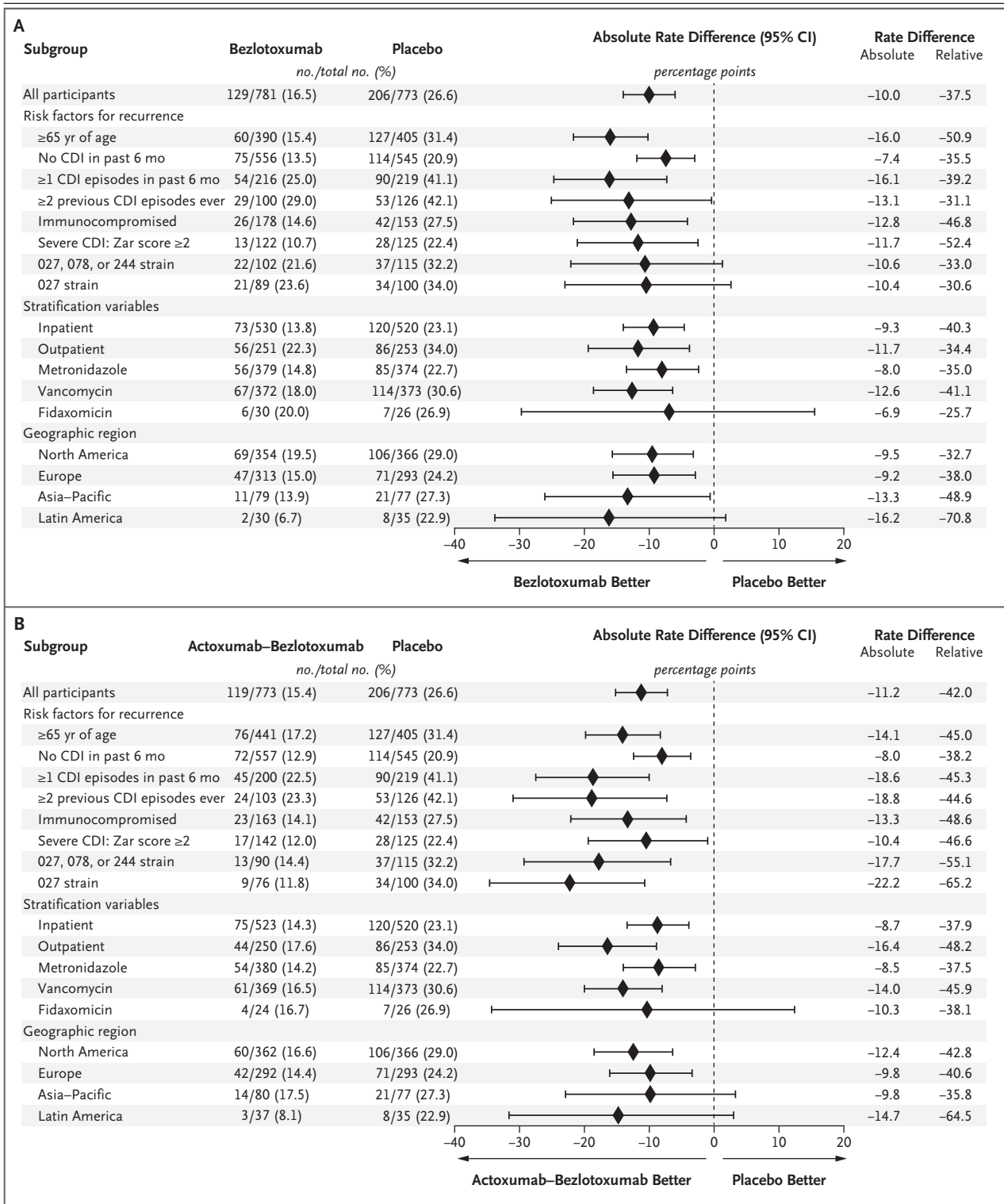


Figure 2. Kaplan-Meier Plot of Time to Recurrent *C. difficile* Infection.

The results shown are for the modified intention-to-treat population with data pooled from the two trials. Shown at the bottom of the graph are the numbers of participants who were at risk at the start of the interval and the Kaplan-Meier rates and 95% confidence intervals at each time point. Data from participants who did not have initial clinical cure were right-censored at day 1 (the day of the infusion). Data from participants who completed the 12-week study period without documented recurrent infection were censored at the date of the last completed stool count. For participants who discontinued before recurrent infection, the time to event was considered to be right-censored at the date of the last stool record. The inset shows the same data on an expanded y axis.

Across prespecified subpopulations of participants who were at high risk for recurrent *C. difficile* infection or for adverse outcomes related to *C. difficile* infection, the rates of recurrent infection were lower in the bezlotoxumab group and in the actoxumab-bezlotoxumab group than in the placebo group, both in the pooled data set (Fig. 3) and in the individual trials (Figs. S3 and S4 in the Supplementary Appendix). The observed effects on the rate of recurrent infection were similar with bezlotoxumab and actoxumab-bezlotoxumab in all subgroups except partici-

pants with infection caused by *C. difficile* strain 027 and participants with infection caused by strain 027, 078, or 244. Among participants with one or more risk factors (1964 of 2559, 77%), recurrent infection occurred in 17% of the participants (100 of 592) in the bezlotoxumab group, in 16% of the participants (99 of 606) in the actoxumab-bezlotoxumab group, and in 30% of the participants (174 of 583) in the placebo group (post hoc analysis). In a comparison of participants according to hospitalization status, standard-of-care antibiotic therapy, and geographic region,



the differences in the rates of recurrent infection were consistent with those seen overall (Fig. 3). Specifically, the choice of standard-of-care antibiotic (metronidazole, vancomycin, or fidaxomicin) had no discernible effect on the efficacy of bezlotoxumab (see the Supplementary Appendix).

Figure 3 (facing page). *C. difficile* Infection Recurrence According to Subgroup.

The results shown are for recurrence of *C. difficile* infection (CDI) in the modified intention-to-treat population, with data pooled from the two trials. Panel A shows the subgroup results for bezlotoxumab versus placebo; Panel B shows the subgroup results for actoxumab–bezlotoxumab versus placebo. The absolute differences between rates (expressed as percentage points) and 95% confidence intervals for active treatment versus placebo were calculated by the Miettinen and Nurminen method without stratification. The Zar score ranges from 1 to 8 and is based on the following factors: age greater than 60 years (1 point), body temperature higher than 38.3°C (100°F) (1 point), albumin level lower than 2.5 g per deciliter (1 point), peripheral white-cell count higher than 15,000 per cubic millimeter within 48 hours (1 point), endoscopic evidence of pseudomembranous colitis (2 points), and treatment in an intensive care unit (2 points).

SUSTAINED CURE AND RECURRENCE OF DIARRHEA

In MODIFY I, sustained cure was achieved in 60% of the participants (232 of 386) in the bezlotoxumab group and in 59% of the participants (225 of 383) in the actoxumab–bezlotoxumab group, as compared with 55% of the participants (218 of 395) in the placebo group (difference between bezlotoxumab and placebo, 4.8 percentage points; 95% CI, –2.1 to 11.7; difference between actoxumab–bezlotoxumab and placebo, 3.5 percentage points; 95% CI, –3.5 to 10.4). In MODIFY II, sustained cure was achieved in 67% (264 of 395) of bezlotoxumab recipients and in 57% (224 of 390) of actoxumab–bezlotoxumab recipients, as compared with 52% (197 of 378) of placebo recipients (difference between bezlotoxumab and placebo, 14.6 percentage points; 95% CI, 7.7 to 21.4; $P < 0.001$; difference between actoxumab–bezlotoxumab and placebo, 5.2 percentage points; 95% CI, –1.8 to 12.2). In the pooled data set, the rate of sustained cure was 64% (496 of 781) with bezlotoxumab, 58% (449 of 773) with actoxumab–bezlotoxumab, and 54% (415 of 773) with placebo (Fig. S5 and Table S8 in the Supplementary Appendix). Diarrhea recurrence, irrespective of an association with *C. difficile* infection, was an exploratory end point. As expected, the rates of diarrhea recurrence were higher than the rates of *C. difficile* infection recurrence; however, the treatment effects observed in association with each study agent with regard to the primary end point were maintained (Table S9 in the Supplementary Appendix).

SAFETY

Adverse events are summarized in Table 2. Infusion-specific reactions were reported by 9% of the participants; the most frequent reactions were nausea (2%), headache (2%), dizziness (1%), fatigue (1%), and pyrexia (1%), with similar rates across the study groups (Table S10 in the Supplementary Appendix). Infusion-specific reactions were rated as mild (76%) or moderate (22%) and resolved within 24 hours. Study infusion was discontinued because of an adverse event in 2 participants (1 in the bezlotoxumab group and 1 in the actoxumab group). During the 4 weeks after infusion, the overall rates of adverse events were similar with bezlotoxumab (62%), actoxumab–bezlotoxumab (59%), and placebo (61%) and were higher with actoxumab (67%). Rates of serious adverse events and deaths were also higher in the actoxumab group than in the other study groups. Drug-related adverse events occurred in 7% of the participants (172 of 2579), and serious drug-related adverse events in 1% (14 of 2579), and both occurred at similar rates across the study groups. The adverse events reported by 4% or more of participants in any study group were abdominal pain, diarrhea, nausea, vomiting, fatigue, pyrexia, *C. difficile* infection, urinary-tract infection, and headache. The most common fatal adverse events were related to infections and infestations, which occurred in 11 participants (1%) in the actoxumab–bezlotoxumab group, 11 participants (1%) in the bezlotoxumab group, 11 (5%) participants in the actoxumab group, and 25 participants (3%) in the placebo group; the next most common type of fatal adverse event was cardiac disorders, which occurred in 8 (1%), 14 (2%), 2 (1%), and 12 (2%) participants, respectively (Table S11 in the Supplementary Appendix). No binding or neutralizing antidrug antibodies to bezlotoxumab were detected after treatment with bezlotoxumab or actoxumab–bezlotoxumab (see the Supplementary Appendix).

DISCUSSION

The results of MODIFY I and MODIFY II, separately and combined, show that among participants receiving standard-of-care antibiotic therapy for primary or recurrent *C. difficile* infection, bezlotoxumab was associated with a significantly lower rate of recurrent infection than was placebo. Both the rates of recurrent infection

Table 2. Clinical Adverse Events in the As-Treated Population in Both Trials.

Time Period and Event	Actoxumab plus Bezlotoxumab (N = 777)	Bezlotoxumab (N = 786)	Actoxumab (N = 235)	Placebo (N = 781)
	number of participants (percent)			
During the 24 hours after infusion				
Infusion-specific reaction*	62 (8.0)	81 (10.3)	26 (11.1)	59 (7.6)
Treatment stopped because of an adverse event	0	1 (0.1)	1 (0.4)	0
During the 4 weeks after infusion				
One or more adverse events	455 (58.6)	485 (61.7)	158 (67.2)	478 (61.2)
Serious adverse event	123 (15.8)	156 (19.8)	65 (27.7)	167 (21.4)
Death	28 (3.6)	32 (4.1)	14 (6.0)	32 (4.1)
Drug-related adverse event†	50 (6.4)	59 (7.5)	17 (7.2)	46 (5.9)
Serious drug-related adverse event‡	5 (0.6)	4 (0.5)	3 (1.3)	2 (0.3)
Most common adverse events§				
Abdominal pain	32 (4.1)	34 (4.3)	15 (6.4)	34 (4.4)
Diarrhea	46 (5.9)	47 (6.0)	13 (5.5)	45 (5.8)
Nausea	47 (6.0)	52 (6.6)	28 (11.9)	39 (5.0)
Vomiting	24 (3.1)	31 (3.9)	10 (4.3)	21 (2.7)
Fatigue	21 (2.7)	18 (2.3)	11 (4.7)	12 (1.5)
Pyrexia	31 (4.0)	36 (4.6)	11 (4.7)	27 (3.5)
<i>C. difficile</i> infection¶	27 (3.5)	23 (2.9)	20 (8.5)	48 (6.1)
Urinary tract infection	24 (3.1)	32 (4.1)	13 (5.5)	35 (4.5)
Headache	33 (4.2)	35 (4.5)	14 (6.0)	24 (3.1)
During the 12 weeks after infusion				
Serious adverse event	212 (27.3)	231 (29.4)	104 (44.3)	255 (32.7)
Death	51 (6.6)	56 (7.1)	27 (11.5)	59 (7.6)

* The adverse events reported on the day of or day after infusion that might have been a sign of an acute hypersensitivity reaction were nausea, vomiting, chills, fatigue, feeling hot, infusion-site conditions, pyrexia, arthralgia, myalgia, dizziness, headache, dyspnea, nasal congestion, pruritus, rash, urticaria, flushing, hot flush, hypertension, and hypotension.

† Causality was assessed by the investigator, who was unaware of the study-group assignments.

‡ A list of serious drug-related events is provided in Table S12 in the Supplementary Appendix.

§ This category includes events with an incidence of at least 4% in at least one study group reported during the first 4 weeks after infusion.

¶ *C. difficile* infection (the primary efficacy end point) was to be reported as an adverse event only if it was serious.

|| A summary of serious adverse events is provided in Table S13 in the Supplementary Appendix.

and the absolute differences in the rates of recurrent infection among the study groups were consistent between the two trials. Bezlotoxumab was associated with a rate of recurrent infection that was 38% (10 percentage points) lower than that associated with standard-of-care therapy alone. Actoxumab was not efficacious when given alone and provided no additional benefit when given with bezlotoxumab. These observations are consistent with evidence indicating that

toxin B is the main determinant of virulence in recurrent *C. difficile* infection in humans,¹⁰⁻¹³ but they do not exclude the possibility that toxin A is also a contributing factor and that anti-toxin A antibodies are protective in human disease, as is suggested by seroepidemiologic data.^{14,15}

The effect of bezlotoxumab in preventing recurrent *C. difficile* infection was sustained throughout 12 weeks. We note that 29% of recurrent infections occurred beyond the conventional

4-week assessment period for treatment efficacy. The number needed to treat to prevent one episode of recurrent *C. difficile* infection was 10; it was 6 among participants 65 years of age or older and those with previous *C. difficile* infection.

Our trials included a substantial percentage of participants (77%) who had one or more risk factors for recurrent *C. difficile* infection or for adverse outcomes related to *C. difficile* infection; bezlotoxumab was consistently associated with rates of recurrent infection that were lower than those associated with placebo across these subgroups. In the largest subgroup (persons ≥ 65 years of age), bezlotoxumab was associated with a rate of recurrent infection that was 51% lower than that associated with placebo. Among participants who were infected with the 027 strain, actoxumab–bezlotoxumab was found to have a larger treatment effect than bezlotoxumab alone. However, given the relatively small number of participants, it is not clear whether this difference was due to a true advantage of actoxumab–bezlotoxumab over bezlotoxumab alone.

A single intravenous dose of bezlotoxumab at 10 mg per kilogram, given alone or in combination with actoxumab, had a generally favorable safety profile in adults who were receiving standard-of-care antibiotic therapy. The rates of adverse events were generally as expected, given the underlying disease severity, baseline coexisting conditions, and ages of the participants. The reasons that higher rates of death and serious adverse events were found in the actoxumab group are unclear. The conditions associated with death in this group (including sepsis, which was present in approximately 25% of those who died) also occurred in the other groups. The rates of death and serious adverse events in the actoxumab–bezlotoxumab group were similar to those in the placebo group and the bezlotoxumab group. In light of the advanced age and coexisting conditions of the participants who died, a causal association between actoxumab treatment and death could not be established or ruled out.

A lower rate of initial clinical cure in the bezlotoxumab group than in the placebo group was found in MODIFY I, but the reverse was found in MODIFY II (by a similar magnitude). The differences in the rate of initial clinical cure between these two groups in each trial were small and not clinically meaningful. Furthermore, the observed rate of initial clinical cure in the pooled

data from the two trials was the same (80%) for these two groups, a finding consistent with the a priori expectation that bezlotoxumab does not affect the efficacy of standard-of-care antibiotic treatment. Toxin B levels in stool are markedly reduced early after the start of standard-of-care antibiotic therapy; therefore, bezlotoxumab would not be expected to affect initial clinical cure, since most participants received the antitoxin 3 or more days after standard-of-care antibiotic therapy began.^{31,32}

The results from each trial regarding the rate of recurrent *C. difficile* infection significantly favored bezlotoxumab when either the modified intention-to-treat population or the subgroup with initial clinical cure was used as the denominator. The advantage in the rate of sustained cure associated with bezlotoxumab was smaller in MODIFY I than in MODIFY II and did not reach significance in MODIFY I because of the smaller difference in observed initial clinical cure rates between the bezlotoxumab group and the placebo group in that trial.

These trials had several limitations. First, the selection of standard-of-care antibiotic was not standardized but rather was at the discretion of the investigator. To control for this, the study groups were stratified according to the standard-of-care antibiotic and therefore were balanced with regard to that variable. Moreover, the efficacy of bezlotoxumab with regard to the rate of recurrent infection was not affected by the choice of standard-of-care antibiotic. Second, although the time of study infusion relative to the onset of symptoms was balanced across treatment groups, the time interval was broad; thus, an assessment of the effect of neutralization of toxin B or toxin A on the severity and duration of the baseline episode could not be performed. Third, the proportion of participants with a severe baseline episode of *C. difficile* infection is probably an underestimate, since more than 90% of participants were receiving standard-of-care antibiotics when the severity assessment was performed. Fourth, other therapies that are currently used for the prevention of recurrent *C. difficile* infection were not allowed; therefore, the combined effect of bezlotoxumab and other approaches (e.g., fecal microbiota transplantation) is not known. Finally, safety assessments were limited because of the relatively small number of patients who received bezlotoxumab, which makes

it difficult to detect potentially serious but low-frequency toxic effects.

In summary, a single intravenous dose of bezlotoxumab against *C. difficile* toxin B, when given with standard-of-care antibiotics, provided protection against recurrent *C. difficile* infection for up to 12 weeks that was superior to that provided by treatment with standard-of-care antibiotics alone. Bezlotoxumab has a novel mechanism of action that reduces the likelihood of recurrent *C. difficile* infection, most notably among patients who have an increased risk of this unfavorable outcome.

Supported by Merck.

Dr. Wilcox reports receiving consulting fees from Alere, Actelion Pharmaceuticals, Cubist Pharmaceuticals, Astellas, Optimer Pharmaceuticals, Sanofi Pasteur, Summit Pharmaceuticals, bioMérieux, Da Volterra, Qiagen, Cerexa, Abbott, AstraZeneca, Pfizer, Durata Therapeutics, Merck, Seres Therapeutics, Valneva, Nabriva Therapeutics, Roche, the Medicines Company, and Basilea Pharmaceutica, lecture fees from Actelion Pharmaceuticals, Cubist Pharmaceuticals, Astellas, Optimer Pharmaceuticals, Sanofi Pasteur, Summit Pharmaceuticals, bioMérieux, Da Volterra, Qiagen, AstraZeneca, and Pfizer, and grant support from Alere, Actelion Pharmaceuticals, Cubist Pharmaceuticals, Astellas, Optimer Pharmaceuticals, Sanofi Pasteur, Summit Pharmaceuticals, bioMérieux, Da Volterra, Qiagen, Cerexa, and Abbott; Dr. Gerding, receiving fees for serving on advisory boards from Actelion Pharmaceuticals, Rebiotix, and Summit Pharmaceuticals, consulting fees from Da Volterra, Pfizer, Cubist Pharmaceuticals, Sanofi Pasteur, Daiichi-Sankyo, and ViroPharma (now Shire), and a research grant from Seres Therapeutics, and holding patents related to the treatment and prevention

of *C. difficile* infection (US No. 6,635,260, EU No. 0952773, CAN No. 2,232,001); Dr. Poxton, receiving fees for serving on an advisory board from Merck; Dr. Kelly, receiving travel support and fees for serving on advisory boards from Seres Therapeutics, Summit Pharmaceuticals, and Synthetic Biologics, lecture fees from Seres Therapeutics, and grant support from Institut Mérieux, Entera Health, and Merck; Dr. Cornely, receiving consulting fees from Anacor Pharmaceuticals, Amplyx, Actelion Pharmaceuticals, Astellas, Basilea, Cidara Therapeutics, Da Volterra, F2G, Gilead, Janssen Pharmaceuticals, Matinas, Menarini Ricerche, Merck/Merck Sharp & Dohme, Paratek Pharmaceuticals, Scynexis, Seres, Summit, Vical, and Vifor Pharma, lecture fees from Astellas, Basilea, Gilead Sciences, and Merck Sharp & Dohme, and grant support from Actelion Pharmaceuticals, Aramis, Astellas, AstraZeneca, Basilea Pharmaceutica, Bayer, Cidara Therapeutics, F2G, Gilead, GlaxoSmithKline, MedPace, Melinta Therapeutics, Merck/Merck Sharp & Dohme, Miltenyi Biotec, Pfizer, Rempex, Roche, Sanofi Pasteur, Scynexis, Seres Therapeutics, and the Medicines Company; Dr. Rahav, receiving fees for lectures and serving on advisory boards from Pfizer and Merck Sharp & Dohme; Dr. Bouza, receiving fees for serving on advisory boards or payment for conferences from Merck Sharp & Dohme, Pfizer, Astellas, Sanofi Pasteur, Roche, and Basilea Pharmaceutica; Dr. Lee, receiving grant support from Rebiotix, Merck, and Actelion Pharmaceuticals and fees for serving on advisory boards from Rebiotix and Summit Pharmaceuticals; Dr. Yoshida, receiving clinical trial fees from Bayer, Astellas, Toyama Chemical Pharmaceuticals, and Sanofi; and Ms. Gabryelski, Dr. Pedley, Ms. Eves, Mr. Tipping, Dr. Guris, Dr. Kartsonis, and Dr. Dorr, being employees of and holding stock in Merck. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients and families whose participation enabled the successful conduct of the MODIFY studies, the study teams and study site personnel, Kim Strohmaier (Merck) for assistance with medical writing, and Carol Zecca (Merck) for editorial assistance.

APPENDIX

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REFERENCES

- Rupnik M, Wilcox MH, Gerding DN. *Clostridium difficile* infection: new developments in epidemiology and pathogenesis. *Nat Rev Microbiol* 2009;7:526-36.
- Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med* 2014;370:1198-208.
- Cornely OA, Miller MA, Louie TJ, Crook DW, Gorbach SL. Treatment of first recurrence of *Clostridium difficile* infection: fidaxomicin versus vancomycin. *Clin Infect Dis* 2012;55:Suppl 2:S154-S161.
- Kelly CP, LaMont JT. *Clostridium difficile* — more difficult than ever. *N Engl J Med* 2008;359:1932-40.
- McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent *Clostridium difficile* disease. *Am J Gastroenterol* 2002; 97:1769-75.
- Shields K, Araujo-Castillo RV, Theethira TG, Alonso CD, Kelly CP. Recurrent *Clostridium difficile* infection: from colonization to cure. *Anaerobe* 2015;34:59-73.
- Torres JF, Lyerly DM, Hill JE, Monath TP. Evaluation of formalin-inactivated *Clostridium difficile* vaccines administered by parenteral and mucosal routes of immunization in hamsters. *Infect Immun* 1995;63:4619-27.
- Kink JA, Williams JA. Antibodies to recombinant *Clostridium difficile* toxins A

- and B are an effective treatment and prevent relapse of *C. difficile*-associated disease in a hamster model of infection. *Infect Immun* 1998;66:2018-25.
9. Babcock GJ, Broering TJ, Hernandez HJ, et al. Human monoclonal antibodies directed against toxins A and B prevent *Clostridium difficile*-induced mortality in hamsters. *Infect Immun* 2006;74:6339-47.
 10. Kuehne SA, Cartman ST, Heap JT, Kelly ML, Cockayne A, Minton NP. The role of toxin A and toxin B in *Clostridium difficile* infection. *Nature* 2010;467:711-3.
 11. Lyras D, O'Connor JR, Howarth PM, et al. Toxin B is essential for virulence of *Clostridium difficile*. *Nature* 2009;458:1176-9.
 12. Carter GP, Chakravorty A, Pham Nguyen TA, et al. Defining the roles of TcdA and TcdB in localized gastrointestinal disease, systemic organ damage, and the host response during *Clostridium difficile* infections. *MBio* 2015;6(3):e00551.
 13. Steele J, Mukherjee J, Parry N, Tzipori S. Antibody against TcdB, but not TcdA, prevents development of gastrointestinal and systemic *Clostridium difficile* disease. *J Infect Dis* 2013;207:323-30.
 14. Kyne L, Warny M, Qamar A, Kelly CP. Association between antibody response to toxin A and protection against recurrent *Clostridium difficile* diarrhoea. *Lancet* 2001;357:189-93.
 15. Kyne L, Warny M, Qamar A, Kelly CP. Asymptomatic carriage of *Clostridium difficile* and serum levels of IgG antibody against toxin A. *N Engl J Med* 2000;342:390-7.
 16. Leav BA, Blair B, Leney M, et al. Serum anti-toxin B antibody correlates with protection from recurrent *Clostridium difficile* infection (CDI). *Vaccine* 2010;28:965-9.
 17. Lowy I, Molrine DC, Leav BA, et al. Treatment with monoclonal antibodies against *Clostridium difficile* toxins. *N Engl J Med* 2010;362:197-205.
 18. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol* 1997;32:920-4.
 19. Fawley WN, Knetsch CW, MacCannell DR, et al. Development and validation of an internationally-standardized, high-resolution capillary gel-based electrophoresis PCR-ribotyping protocol for *Clostridium difficile*. *PLoS One* 2015;10(2):e0118150.
 20. Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. *N Engl J Med* 2015;372:825-34.
 21. Bauer MP, Notermans DW, van Benthem BHB, et al. *Clostridium difficile* infection in Europe: a hospital-based survey. *Lancet* 2011;377:63-73.
 22. Morrison RH, Hall NS, Said M, et al. Risk factors associated with complications and mortality in patients with *Clostridium difficile* infection. *Clin Infect Dis* 2011;53:1173-8.
 23. See I, Mu Y, Cohen J, et al. NAP1 strain type predicts outcomes from *Clostridium difficile* infection. *Clin Infect Dis* 2014;58:1394-400.
 24. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. *Clin Infect Dis* 2007;45:302-7.
 25. Abou Chakra CN, Pepin J, Valiquette L. Prediction tools for unfavourable outcomes in *Clostridium difficile* infection: a systematic review. *PLoS One* 2012;7(1):e30258.
 26. Inns T, Gorton R, Berrington A, et al. Effect of ribotype on all-cause mortality following *Clostridium difficile* infection. *J Hosp Infect* 2013;84:235-41.
 27. Rao K, Micic D, Natarajan M, et al. *Clostridium difficile* ribotype 027: relationship to age, detectability of toxins A or B in stool with rapid testing, severe infection, and mortality. *Clin Infect Dis* 2015;61:233-41.
 28. Walker AS, Eyre DW, Wyllie DH, et al. Relationship between bacterial strain type, host biomarkers, and mortality in *Clostridium difficile* infection. *Clin Infect Dis* 2013;56:1589-600.
 29. Lim SK, Stuart RL, Mackin KE, et al. Emergence of a ribotype 244 strain of *Clostridium difficile* associated with severe disease and related to the epidemic ribotype 027 strain. *Clin Infect Dis* 2014;58:1723-30.
 30. De Almeida MN, Heffernan H, Dervan A, et al. Severe *Clostridium difficile* infection in New Zealand associated with an emerging strain, PCR-ribotype 244. *N Z Med J* 2013;126:9-14.
 31. Louie TJ, Cannon K, Byrne B, et al. Fidaxomicin preserves the intestinal microbiome during and after treatment of *Clostridium difficile* infection (CDI) and reduces both toxin reexpression and recurrence of CDI. *Clin Infect Dis* 2012;55:Suppl 2:S132-S142.
 32. Thabit AK, Alam MJ, Khaleduzzaman M, Garey KW, Nicolau DP. A pilot study to assess bacterial and toxin reduction in patients with *Clostridium difficile* infection given fidaxomicin or vancomycin. *Ann Clin Microbiol Antimicrob* 2016;15:22.

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