Preventing recurrence of Clostridium difficile infection: bezlotoxumab

Evidence summary
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Key points

The content of this evidence summary was up-to-date in June 2017. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Regulatory status: Bezlotoxumab (Zinplava, Merck Sharp & Dohme Limited) is a human monoclonal antitoxin antibody that binds with high affinity to Clostridium difficile toxin B and neutralises its activity. It received a marketing authorisation in January 2017 and is expected to be launched in June 2017 (source: Merck Sharp & Dohme Limited, May 2017). Bezlotoxumab is indicated for preventing future episodes of diarrhoea in people who are taking antibiotics to treat their C difficile infection and who are at high risk of the infection coming back. It is administered as a single one-off intravenous infusion during a course of antibacterial therapy for C difficile infection (summary of product characteristics).

Overview

This evidence summary discusses 2 similar randomised controlled trials (RCTs; MODIFY I [n=1,396] and MODIFY II [n=1,163]) that compared the efficacy and safety of a single dose of bezlotoxumab 10 mg/kg with placebo for preventing the recurrence of C difficile infection in people taking usual standard-of-care antibiotics (usually metronidazole or vancomycin) (Wilcox MH et al. 2017).
In a pooled analysis of MODIFY I and MODIFY II, at the 12-week follow-up, 17% of participants given bezlotoxumab had recurrent *C. difficile* infection compared with 27% of those given placebo (statistically significant difference). The European public assessment report highlights concerns over the population used to assess this primary endpoint and notes that the secondary endpoint of sustained clinical cure (initial clinical cure of the baseline infection and no recurrence for 12 weeks) is more relevant to clinical practice.

For sustained clinical cure, there was a statistically significant difference between bezlotoxumab and placebo in MODIFY II but not in MODIFY I. When data from these 2 trials were pooled, the difference was statistically significant (64% with bezlotoxumab compared with 54% with placebo).

Recurrence of *C. difficile* infection and sustained clinical cure were each improved by about 10% in absolute terms with bezlotoxumab compared with placebo at 12 weeks (giving a number needed to treat of around 10). However, almost three quarters of participants given placebo did not have recurrent infection by week 12 (73% compared with 83% given bezlotoxumab), and around half had sustained cure (54% compared with 64% with bezlotoxumab). Nevertheless, recurrent *C. difficile* infection is difficult to treat and is associated with more hospitalisations, severe outcomes, and higher costs than initial episodes (European public assessment report). The European public assessment report states that experts concluded that meaningful clinical relevant results were obtained in the pivotal trials, although the extent of actual benefit will only be established once the medicine has been used more widely. Only 4% of participants were taking fidaxomicin in the trials, so it is unclear what benefits bezlotoxumab has in people given this medicine to treat *C. difficile*.

Bezlotoxumab is the first medicine that is indicated for preventing the recurrence of *C. difficile* in adults who are at high risk of developing this infection again; however, its place in therapy is currently unclear. The benefits and risks of bezlotoxumab should be discussed with people considering treatment. Although bezlotoxumab was generally well-tolerated in the trials and had a similar adverse effect profile to placebo, given an explanation of the size of the potential benefits, some people may prefer not to have an intravenous infusion, particularly if they have very few risk factors for recurrent *C. difficile* infection. The European public assessment report lists age over 65 years, history of previous *C. difficile* infection, being immunocompromised, and having severe infection or infection with a hypervirulent strain as risk factors. However, the trials found no statistically significant difference in recurrence of infection between bezlotoxumab and placebo in participants with a hypervirulent strain of *C. difficile* (027, 048 or 244 combined and 027 alone).

A summary to inform local decision-making is shown in table 1.
Table 1 Summary of the evidence on effectiveness, safety, patient factors and resource implications

**Effectiveness**
- In the pooled dataset for MODIFY I and II (Wilcox MH et al. 2017), 16.5% of those given bezlotoxumab had recurrent *C difficile* infection compared with 26.6% of those given placebo (adjusted difference 10.0%, 95% confidence interval [CI] 6.0% to 14.0%, \( p<0.0001 \)).
- In the pooled dataset, in the subgroup of participants who had initial clinical cure (no diarrhoea for 2 consecutive days after completion of standard-of-care antibiotic therapy), recurrent infection was seen in 20.6% of people given bezlotoxumab compared with 33.2% given placebo (adjusted difference 12.2%, 95% CI 7.4% to 17.1%, \( p<0.0001 \)).
- In the pooled dataset, a statistically significant difference was also seen between the groups for sustained clinical cure (bezlotoxumab 63.5% compared with placebo 53.7%; adjusted difference 9.7%, 95% CI 4.8% to 14.5%, \( p=0.0001 \)).

**Safety**
- 60.5% of participants in the trials reported 1 or more adverse events, but the incidence was similar across the groups.
- Infusion-specific reactions within 24 hours were reported by 10.3% of participants receiving bezlotoxumab.
- Common adverse effects of bezlotoxumab (in more than 4 in 100 participants) included abdominal pain, diarrhoea, nausea, pyrexia, urinary tract infection and headache.
- The European public assessment report states that a robust conclusion on safety is hampered by the small population and the underlying morbidity and co-morbidity of the participants. However, the safety profile is considered 'sufficiently reassuring'.
Patient factors

- It is expected that bezlotoxumab will be used in people in hospital, under the guidance of a consultant in infectious disease. Bezlotoxumab is administered as a single, one-off intravenous infusion given over 60 minutes. It is administered alongside an antibiotic for treating the current episode of *C difficile* infection.

- After initial treatment and resolution of diarrhoea, 15% to 35% of people with *C difficile* infection experience recurrence.

- Recurrent infection is more difficult to treat and is associated with more hospitalisations, severe outcomes, and higher costs than initial episodes.

- No medicines are currently licensed for preventing first episodes of *C difficile* infection. Only bezlotoxumab is licensed for preventing the recurrence of *C difficile* infection (in adults who are at high risk of developing this infection again).

Resource implications

- The cost of 1 vial of bezlotoxumab 1,000 mg is £2,470.00 (source: Merck Sharp & Dohme Limited, May 2017).

- The dose of bezlotoxumab is 10 mg/kg; therefore, more than 1 vial will be needed to treat people weighing more than 100 kg.

- This cost is for the medicine only and does not include VAT, any local procurement discounts or other costs incurred, such as administration.

Introduction and current guidance

*Clostridium difficile* are bacteria that exist in the environment and can become established in the colon of healthy people (up to 3% of adults and 66% of babies). *C difficile* infection occurs when the other harmless bacteria in the colon are disrupted (for example, by taking antibiotics) or when the immune system is compromised, allowing the numbers of *C difficile* bacteria to increase to high levels. Certain strains of *C difficile* produce toxins (principally A and B) that damage the lining of the colon, causing symptoms ranging from mild, self-limiting diarrhoea to pseudomembranous colitis, toxic megacolon, perforation of the colon, sepsis and death. Type 027 is a strain that produces more toxins than most other types of *C difficile*. It causes a greater proportion of severe disease and appears to have a higher mortality (NICE clinical knowledge summary: diarrhoea – antibiotic associated; Public Health England, *Clostridium difficile*; guidance, data and analysis; Public Health England, *Clostridium difficile* infection: how to deal with the problem).
As well as broad-spectrum antibiotics, other factors increase the risk of *C difficile* infection. These include advanced age, underlying morbidity, hospitalisation, exposure to other people with the infection, long duration of antibiotic treatment, taking multiple antibiotics concurrently or taking multiple antibiotic courses, and inflammatory bowel disease. In hospitalised people, the rate of recurrence is around 20% after a first episode and 45–60% after a second episode of *C difficile* infection. The mortality rate of *C difficile* infection can be up to 25% in frail, elderly people in hospitals (NICE clinical knowledge summary: diarrhoea – antibiotic associated).

Public Health England's guidance on managing common infections in primary care recommends metronidazole (400 mg or 500 mg 3 times daily for 10–14 days) first-line for treating first episodes of mild to moderate *C difficile* infection. Vancomycin (125 mg 4 times daily for 10–14 days) is an option for second episodes, or if the infection is severe (raised temperature or white cell count, rising creatinine, or signs or symptoms of severe colitis) or caused by the type 027 strain of *C difficile*. If infection recurs, vancomycin or fidaxomicin (200 mg twice daily for 10 days) may be used.

This is based on Public Health England's updated guidance on the management and treatment of *C difficile* infection, which includes more information on the assessment and treatment of *C difficile* infection, including a summary of the evidence base and 2 treatment algorithms. It also gives more detail on managing recurrent infection, advising that fidaxomicin should be preferred for people with recurrent *C difficile* infection, but that the efficacy of fidaxomicin in people with multiple *C difficile* infection recurrences is unclear. Depending on local cost-effectiveness based decision making, oral vancomycin is an alternative.

This evidence summary considers the evidence to support the use of a new medicine, bezlotoxumab, which is the first medicine that is indicated for preventing the recurrence of *C difficile*, rather than treating the infection.

**Product overview**

**Mode of action**

Bezlotoxumab is a human monoclonal antitoxin antibody that binds with high affinity to *Clostridium difficile* toxin B and neutralises its activity. Bezlotoxumab prevents recurrence of *C difficile* infection by providing passive immunity against toxins produced by the outgrowth of persistent or newly acquired *C difficile* spores (summary of product characteristics).
Regulatory status

Bezlotoxumab (Zinplava, Merck Sharp & Dohme Limited) received a marketing authorisation in January 2017 and is expected to be launched in June 2017 (source: Merck Sharp & Dohme Limited, May 2017). It is indicated for preventing the recurrence of *C difficile* infection in adults who are at high risk of developing this infection again (summary of product characteristics).

Bezlotoxumab is not a treatment for *C difficile* infection and has no effect on the current episode of *C difficile* (summary of product characteristics).

Dosing information

Bezlotoxumab is administered as a single one-off intravenous infusion of 10 mg/kg over 60 minutes. It is given during a course of antibacterial therapy for *C difficile* infection (summary of product characteristics). There is no experience of repeat administration of bezlotoxumab.

Cost

The cost of 1 vial of bezlotoxumab 1,000 mg (25 mg/ml × 40 ml) is £2,470.00 (source: Merck Sharp & Dohme Limited, May 2017). This cost is for the medicine only and does not include VAT, any local procurement discounts or other costs incurred, such as administration.

Evidence review

A literature search was conducted which identified 6 references (see search strategy for full details). These references were screened using their titles and abstracts and 1 reference was obtained and assessed for relevance.

The paper identified (Wilcox MH et al. 2017) included 2 similar multicentre, randomised, placebo-controlled, double-blind trials that examined the safety and efficacy of bezlotoxumab, alone and combined with another monoclonal antibody (actoxumab, to act against *Clostridium difficile* toxin A), for preventing the recurrence of *C difficile* infection in people taking usual standard-of-care antibiotics (MODIFY I and MODIFY II). A summary of the included trials is shown in table 2 (see the evidence tables for full details).

Table 2 Summary of included studies
### Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention and comparison</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>MODIFY I RCT (n=1,452) NCT01241552</td>
<td>Adults with confirmed primary or recurrent <em>Clostridium difficile</em> infection who were receiving oral standard-of-care antibiotics (metronidazole, vancomycin or fidaxomicin)</td>
<td>A single infusion of: • bezlotoxumab 10 mg/kg (total n=810) • actoxumab 10 mg/kg (n=242)(^a) • actoxumab 10 mg/kg plus bezlotoxumab 10 mg/kg (total n=800) or • placebo (total n=803)</td>
<td>Recurrent <em>Clostridium difficile</em> infection within 12 weeks of the trial infusion</td>
</tr>
<tr>
<td>MODIFY II RCT (n=1,203) NCT01513239</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** *C difficile*, *Clostridium difficile*; RCT, randomised controlled trial.

\(^a\) MODIFY I included an actoxumab alone arm. However, enrolment into this group was stopped following an interim analysis, which found that the rate of recurrent infection was higher in the actoxumab group than in the actoxumab plus bezlotoxumab group, and more deaths and serious adverse events occurred in the actoxumab group than in the placebo group. Actoxumab alone was not studied in MODIFY II.

No references were excluded.

### Clinical effectiveness

An overview of the results for clinical effectiveness can be found in the results tables. The efficacy results for MODIFY I and MODIFY II (Wilcox MH et al. 2017) are presented separately in the tables for the bezlotoxumab, actoxumab plus bezlotoxumab and placebo groups. Actoxumab is not currently available and results for actoxumab alone are not shown. A pre-planned pooled analysis
of MODIFY I and MODIFY II was undertaken and where outcomes in the individual trials were similar, results for bezlotoxumab from the pooled dataset are presented in this section.

Recurrent *C difficile* infection

The proportion of participants with recurrent *C difficile* infection by week 12 (the primary outcome) was lower with bezlotoxumab compared with placebo in MODIFY I (n=1,396), MODIFY II (n=1,163) and the pooled dataset (all differences were statistically significant). For example, in the pooled dataset, 16.5% of participants had recurrent infection with bezlotoxumab compared with 26.6% with placebo (adjusted difference 10.0%, 95% confidence interval [CI] 6.0% to 14.0%, \( p < 0.0001 \)). Most recurrences of *C difficile* infection (71%) occurred within 4 weeks of the trial infusion.

In the subgroup of participants who had initial clinical cure (no diarrhoea for 2 consecutive days after completion of standard-of-care antibiotic therapy), the differences in the proportions of participants with recurrent infection by week 12 were slightly higher than those found in the overall trial population in MODIFY I, MODIFY II and the pooled dataset (for example, in the pooled dataset, bezlotoxumab 20.6% compared with placebo 33.2%; adjusted difference 12.2%, 95% CI 7.4% to 17.1%, \( p < 0.0001 \)).

The results were analysed in prespecified subgroups of participants who were at high risk of recurrent *C difficile* infection or for adverse outcomes related to *C difficile* infection (including age 65 years or older, history of *C difficile* infection, compromised immunity, clinically severe *C difficile* infection, and infection with a strain associated with poor outcomes). In the subgroups, the rates of recurrent infection were lower in the bezlotoxumab group than in the placebo group, both in the individual trials and the pooled data set. However, the difference between the groups was not statistically significant for strains associated with poor outcomes (027, 048 or 244 combined and 027 alone). Also, according to the summary of product characteristics, the results did not point towards a benefit of bezlotoxumab in participants with no known risk factors for recurrent *C difficile* infection (and it is not licensed for use in this population).

When participants were analysed according to their hospitalisation status (inpatient or outpatient), standard-of-care antibiotic treatment (metronidazole, vancomycin or fidaxomicin) or geographic region, the rates of recurrent infection were consistent with those seen in the overall trial population.

The European public assessment report raises concerns over this primary endpoint. (See evidence strengths and limitations for more information.)
Initial clinical cure

There was no statistically significant difference between bezlotoxumab and placebo in initial clinical cure (an exploratory endpoint) in MODIFY I, MODIFY II or the pooled dataset. However, in MODIFY I the cure rate was higher with placebo (82.8% compared with 77.5%; adjusted difference 5.3%, 95% CI −0.3 to 10.9, p=0.0643), whereas in MODIFY II the cure rate was higher with bezlotoxumab (82.5% compared with 77.8% with placebo; adjusted difference 4.8%, 95% CI −10.4% to 0.9%, p=0.0962).

Note that bezlotoxumab is indicated for preventing recurrence of *Clostridium difficile* infection, not treating infection.

Sustained clinical cure

The results of MODIFY I and MODIFY II also differed for sustained clinical cure (initial clinical cure of the baseline infection and no recurrence for 12 weeks). There was no statistically significant difference between bezlotoxumab and placebo in MODIFY I (60.1% compared with 55.2% respectively; adjusted difference 4.8%, 95% CI −11.7% to 2.1%, p=0.1722), whereas a statistically significant difference was seen between the groups in MODIFY II (66.8% compared with 52.1% respectively; adjusted difference 14.6%, 95% CI 7.7% to 21.4%, p<0.0001). When the data from these 2 trials were pooled the difference was statistically significant (63.5% with bezlotoxumab compared with 53.7% with placebo; adjusted difference 9.7%, 95% CI 4.8% to 14.5%, p=0.0001).

According to the [European public assessment report](https://www.nice.org.uk), this outcome is more relevant to clinical practice than the primary outcome. (See [evidence strengths and limitations](https://www.nice.org.uk) for more information.)

Safety and tolerability

An overview of the results for safety and tolerability can be found in the [results tables](#). The results of MODIFY I and MODIFY II have been pooled (Wilcox MH et al. 2017).

In the trials, during the 4 weeks after the infusion, the proportions of treatment-related adverse events (bezlotoxumab 7.5% [59/786], bezlotoxumab plus actoxumab 6.4% [50/777], placebo 5.9% [46/781]) and serious treatment-related adverse events (bezlotoxumab 0.5% [4/786], actoxumab plus bezlotoxumab 0.6% [5/777], placebo 0.3% [2/781]) were similar across the groups (no statistical analyses). The adverse events reported by 4% or more of participants in the bezlotoxumab alone group in MODIFY I and MODIFY II were abdominal pain, diarrhoea, nausea, pyrexia, urinary tract infection and headache.
Four weeks after infusion, 32 people (4.1%) in the bezlotoxumab group, 28 people (3.6%) in the combination treatment group and 32 people (4.1%) in the placebo group had died. The most common fatal adverse events were related to infections and infestations, which occurred in 11 participants (1%) in the combination treatment group, 11 participants (1%) in the bezlotoxumab group and 25 participants (3%) in the placebo group. The next most common type of fatal adverse events were cardiac disorders, which occurred in 8 (1%), 14 (2%), and 12 (2%) participants respectively.

Infusion-specific reactions within 24 hours were reported by 10.3% of participants receiving bezlotoxumab alone. The most frequent reactions in the trials were nausea (2%), headache (2%), dizziness (1%), fatigue (1%), and pyrexia (1%), with similar rates across the trial groups.

The summary on the safety of bezlotoxumab in the European public assessment report concludes that the majority of participants in the trials (60.5% across all groups) reported 1 or more adverse events, but that the incidence was similar across the groups and bezlotoxumab was well-tolerated. The proportion of participants reporting 1 or more adverse event was slightly higher in people aged 65 years or more compared with those aged less than 65 years across all treatment groups.

The proportion of participants with a serious adverse event was lower in the active treatment groups compared with placebo. Similarly, the proportion of fatal adverse events was comparable in all groups and consistent with age and comorbidity, with more serious adverse events and deaths seen in the older age group. The European public assessment report found some imbalances in adverse events between the bezlotoxumab and placebo groups in people with congestive heart failure at baseline; however, it concludes that the safety data at present suggests that there is no clear evidence that bezlotoxumab is associated with a negative effect on cardiac function.

See the summary of product characteristics for more information on adverse effects, precautions and contraindications.

**Evidence strengths and limitations**

MODIFY I and MODIFY II were well-conducted randomised, controlled trials with a low risk of bias (see evidence tables). Overall, the participants are representative of people with *C difficile* infection in the UK, and baseline characteristics of the treatment groups were generally well-matched. According to the European public assessment report, the Bristol stool scale is widely used to diagnose *C difficile* infection, and the Zar score is suitable for measuring severity, although it is not universally used in Europe. Recall bias was minimised, diarrhoea reporting was appropriate, and less than 1% of participants had missing data.
The standard-of-care antibiotics used in the trials were oral metronidazole (47%), vancomycin (48%) and fidaxomicin (with or without intravenous metronidazole, 4%) for a mean duration of 14 days. Use of these antibiotics is in line with Public Health England’s updated guidance on the management and treatment of C difficile infection; however, specialists involved in producing this evidence summary have advised that the proportions of use of these medicines is changing, with use of fidaxomicin increasing for treating recurrent C difficile infection. From the trials, it is unclear what benefits bezlotoxumab will have in terms of reducing recurrence in people with C difficile infection treated with fidaxomicin because only 4% of participants were taking this medicine. Also, although it is not specifically licensed for this indication, there is some evidence that fidaxomicin reduces recurrence of C difficile infection compared with vancomycin (see the updated guidance on the management and treatment of C difficile infection), and it is not known whether bezlotoxumab offers any benefits over fidaxomicin alone.

The trial has some limitations that affect its application to clinical practice. The European public assessment report notes that the primary endpoint of the trials (recurrence of C difficile infection) is limited because participants whose initial episode of infection was not cured were considered as not having recurrent infection and were evaluated as though treatment was successful, not as non-responders. The report states that a more appropriate approach would have been to randomise participants after the initial episode of C difficile infection was cured, and notes that the secondary endpoint of sustained clinical cure at week 12 is more relevant. However, the European public assessment report also notes that some degree of injury to the gut lining must be present in order for bezlotoxumab to act, which may mean that it is less effective if it is administered after C difficile infection has been cured.

For sustained clinical cure, there was a statistically significant difference between bezlotoxumab and placebo in MODIFY II but not in MODIFY I. When the data from the 2 trials were pooled the difference was statistically significant. In spite of the difference between the trials, the European public assessment report states that, although there is a concern regarding the chosen primary endpoint, additional analyses are reassuring (concordant with the result of the primary analysis), and support the claimed efficacy of bezlotoxumab. However, the report also notes that the extent of actual benefit will only be established once the medicine has been used more widely.

Many participants in the trials did not have severe C difficile infection, or risk factors for developing severe or recurrent infection. For example, about 65% did not have a previous history of C difficile infection, about 70% of participants were aged less than 75 years, and about 80% of the participants had a Zar score below 2, indicating less severe infection. Low numbers of people with immunosuppression, elevated temperature or white blood cell count, impaired renal or hepatic function or other serious conditions, (such as pseudomembranous colitis or toxic megacolon) were
included, and most people had not been diagnosed with a hypervirulent strain of \textit{C difficile} infection (European public assessment report). Wilcox et al. (2017) considered that the proportion of participants with a severe baseline episode of \textit{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.

The \textit{summary of product characteristics} notes that the efficacy results of MODIFY I and MODIFY II did not point towards a benefit of bezlotoxumab in people with no known risk factors for recurrent \textit{C difficile} infection, and the European public assessment report states that no effect of bezlotoxumab was seen in participants with 'no risk' or 'unknown risk' of developing severe infection. This supports the use of bezlotoxumab for preventing the recurrence of \textit{C difficile} infection in adults who are at high risk of developing this infection again, according to the marketing authorisation. However, there were no statistically significant differences between bezlotoxumab and placebo for participants with strains associated with poor outcomes (027, 048 or 244 combined and 027 alone), 1 of the populations considered to be high risk of recurrence according to the European public assessment report. Specialists involved in producing this evidence summary noted that this may have been due to limited numbers of people in the subgroups, or another effect that was not investigated such as production of binary toxin, which tends to be produced by more virulent strains of \textit{C difficile}. The effect of bezlotoxumab on binary toxin was not assessed in the trials.

The European public assessment report states that a robust conclusion on safety is hampered by the small population and the underlying morbidity and co-morbidity of the participants. However, the safety profile is considered 'sufficiently reassuring'.

The \textit{summary of product characteristics} notes that the experience with bezlotoxumab is limited to a single episode of \textit{C difficile} infection and a single administration. Bezlotoxumab is not a treatment for \textit{C difficile} infection and has no effect on the current episode, and it should be administered during a course of antibacterial therapy for \textit{C difficile} infection. During the trials, bezlotoxumab was administered after a median of 3 days of standard-of-care antibiotic therapy (European public assessment report). There is no data regarding the efficacy of bezlotoxumab if it is given after the initial 10–14 days of antibacterial therapy for \textit{C difficile} infection.

An overview of the quality assessment of each included trial can be found in \textit{evidence tables}. 

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Estimated impact for the NHS

Other treatments

No medicines are currently licensed for preventing first episodes of \( \textit{C} \textit{difficile} \) infection. Only bezlotoxumab is licensed for preventing the recurrence of \( \textit{Clostridium difficile} \) infection (in adults who are at high risk of developing this infection again).

There is some evidence that \textit{fidaxomicin} reduces the recurrence of \( \textit{C} \textit{difficile} \) infection compared with vancomycin, and it is the preferred antibiotic for treating people with recurrent infection (see the updated guidance on the management and treatment of \( \textit{C} \textit{difficile} \) infection). However, fidaxomicin is not specifically licensed for preventing recurrence of \( \textit{C} \textit{difficile} \). Public Health England guidance notes that there is no evidence of a benefit of using metronidazole or vancomycin to prevent \( \textit{C} \textit{difficile} \) infection (in people receiving antibiotic therapy), and that this approach may actually increase risk. Probiotics and \textit{Saccharomyces boulardii} (not available as a licensed product in the UK) are also not recommended by Public Health England based on the evidence available when the guidance was produced (2013).

\textit{NICE} guidance on faecal microbiota transplant for recurrent \( \textit{Clostridium difficile} \) infection advises that current evidence on the efficacy and safety of faecal microbiota transplant for recurrent \( \textit{C} \textit{difficile} \) infection is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit. The procedure should only be considered for people with recurrent \( \textit{C} \textit{difficile} \) infections that have failed to respond to antibiotics and other treatments.

Costs of other treatments

No other medicines are currently licensed for preventing recurrence of \( \textit{C} \textit{difficile} \) infection.

It is expected that bezlotoxumab will be used in people in hospital, under the guidance of a consultant in infectious disease. Bezlotoxumab is administered as a single, one-off intravenous infusion given over 60 minutes. It is administered alongside an antibiotic for treating the current episode of \( \textit{C} \textit{difficile} \) infection.

The cost of 1 vial of bezlotoxumab 1,000 mg is £2,470.00 (source: Merck Sharp & Dohme Limited, May 2017). The dose of bezlotoxumab is 10 mg/kg; therefore, more than 1 vial will be needed to treat people weighing more than 100 kg.
This cost is for the medicine only and does not include VAT, any local procurement discounts or other costs incurred, such as administration.

**Current or estimated usage**

The manufacturer (Merck Sharp & Dohme Limited) anticipates that bezlotoxumab will be used according to the licensed indication under the guidance of a microbiologist or infectious disease specialist, following the principles of good antimicrobial stewardship. Merck Sharp & Dohme Limited anticipates that usage will be appropriately low, with an estimated peak of 700 eligible people being treated with bezlotoxumab in a 12-month period after 5 years. This reflects the indication in adults at high-risk of recurrence of *C* difficle infection, in line with local unmet need. This figure represents an estimation based on current epidemiology; a significant increase in *C* difficle infection or recurrence would have a large impact on these figures (source: Merck Sharp & Dohme Limited, March 2017).

**Likely place in therapy**

Local decision makers need to take safety, efficacy, cost and patient factors into account when considering the likely place in therapy of bezlotoxumab for preventing the recurrence of *C* difficle infection in adults who are at high risk of developing this infection again. The summary of product characteristics does not define high risk within the therapeutic indication, but the European public assessment report considered the following to be risk factors, based on European guidance and the population studied in the trials:

- age over 65 years
- history of previous *C* difficle infection
- being immunocompromised
- having infection with hypervirulent strain, including ribotype 027
- having severe *C* difficle infection.

In pooled analyses of MODIFY I and MODIFY II, at 12 weeks, recurrence of *C* difficle infection and sustained clinical cure were each improved by about 10% in absolute terms with a single infusion of bezlotoxumab 10 mg/kg compared with placebo in adults with confirmed primary or recurrent *C* difficle infection who were receiving oral standard-of-care antibiotics (both statistically significant: numbers needed to treat [NNT] 10 and 11 respectively). However, almost three quarters of people given placebo did not have recurrent infection by week 12 (73% compared with
83% with bezlotoxumab), and around half had sustained cure (54% compared with 64% with bezlotoxumab). Conversely, almost a fifth of people given bezlotoxumab had recurrent infection and more than a third did not have sustained cure (17% and 36% respectively compared with 27% and 46% respectively with placebo).

Compared with the total trial population, the NNTs for preventing recurrent infection at 12 weeks were lower in people aged 65 years or more, with previous C. difficile infection in the last 6 months, who were immunocompromised, or who had severe infection (NNTs 7, 7, 8 and 9 respectively), reflecting the licensed indication, which specifies use in high risk subgroups. This was not the case for people with hypervirulent strains, in whom no significant difference was seen compared with placebo.

After initial treatment and resolution of diarrhoea, 15% to 35% of people with C. difficile infection experience recurrence. Recurrent infection is more difficult to treat and is associated with more hospitalisations, severe outcomes, and higher costs than initial episodes. (European public assessment report). The benefits and risks of bezlotoxumab should be discussed with people considering treatment. Although bezlotoxumab was generally well-tolerated in the trials and had a similar adverse effect profile to placebo, given an explanation of the size of the potential benefits, some people may prefer not to have an intravenous infusion, particularly if they have very few risk factors for recurrent C. difficile infection. Common adverse effects seen in the bezlotoxumab group in the trials (in more than 4 in 100 participants) included abdominal pain, diarrhoea, nausea, pyrexia, urinary tract infection and headache.

No other medicines are currently licensed for preventing recurrence of C. difficile infection.

The cost of 1 vial of bezlotoxumab 1,000 mg administered as a one-off intravenous infusion in a person weighing 100 kg or less is £2,470.00 (source: Merck Sharp & Dohme Limited, May 2017). This cost is for the medicine only and does not include VAT, any local procurement discounts or other costs incurred, such as administration.

**Information for the public about medicines**

Evidence summaries provide an overview of the best evidence that is available about specific medicines. They also give general information about the condition that the medicine might be prescribed for, how the medicine is used, how it works, and what the aim of treatment is.

Evidence summaries aim to help healthcare professionals and patients decide whether medicines are safe to use and if they are likely to work well, especially when there isn't another suitable
medicine that has a licence for the condition. They don't contain recommendations from NICE on whether the medicine should be used.

**Information about licensing of medicines**

In the UK, medicines need to have a licence before they can be widely used. To get a licence, the manufacturer of the medicine has to provide evidence that shows that the medicine works well enough and is safe enough to be used for a specific condition and for a specific group of patients, and that they can manufacture the medicine to the required quality. Evidence summaries explain whether a medicine has a licence, and if it does what the licence covers.

There is more information about licensing of medicines on [NHS Choices](https://www.nhs.org.uk).

Medicines can be prescribed if they don't have a licence (unlicensed) or for 'off-label' use. Off-label means that the person prescribing the medicine wants to use it in a different way than that stated in its licence. This could mean using the medicine for a different condition or a different group of patients, or it could mean a change in the dose or that the medicine is taken in a different way. If a healthcare professional wants to prescribe an unlicensed medicine, or a licensed medicine off-label, they must follow their professional guide, for example for doctors the General Medical Council's [good practice guidelines](https://www.gmc-uk.org). These include giving information about the treatment and discussing the possible benefits and harms so that the person has enough information to decide whether or not to have the treatment. This is called giving informed consent.

**Questions that might be useful to ask about medicines**

- Why am I being offered this medicine?
- Why am I being offered a medicine that is unlicensed or is being used off-label?
- What does the treatment involve?
- What are the benefits I might get?
- How good are my chances of getting those benefits?
- Could having the treatment make me feel worse?
- Are there other treatments I could try?
- What are the risks of the treatment?
• Are the risks minor or serious? How likely are they to happen?

• What could happen if I don’t have the treatment?

Relevance to other NICE programmes

NICE has been invited to consider a technology appraisal of bezlotoxumab for preventing recurrent Clostridium difficile infection (ID 1068). Should the appraisal be formally referred onto the NICE technology appraisal work programme, this evidence summary will be withdrawn when the technology appraisal guidance is published.

NICE has issued the following guidance relating to the management of C difficile infection:

• Faecal microbiota transplant for recurrent Clostridium difficile infection (2014) NICE interventional procedures guidance 485.

• Diarrhoea and vomiting caused by gastroenteritis in under 5s: diagnosis and management (2009) NICE guideline CG84.

NICE has produced several guidelines relating to healthcare-associated infections and antimicrobial stewardship:


• Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) NICE guideline NG15.

• Antimicrobial stewardship: changing risk-related behaviours in the general population (2017) NICE guideline NG63.

NICE pathways on prevention and control of health-care associated infections and antimicrobial stewardship are also available. See also the NICE quality standards on infection prevention and control and antimicrobial stewardship. NICE guidance on managing common infections is being developed.

As well as guidance, NICE produces advice publications which do not constitute formal NICE guidance but critically appraise the evidence to help decision-making. A Medicines and Prescribing Briefing examined the evidence for the risk of Clostridium difficile infection with broad-spectrum
antibiotics, and a NICE evidence summary: new medicine assessed fidaxomicin for Clostridium difficile infection when fidaxomicin was launched in 2012. Two NICE key therapeutic topics consider antibiotic prescribing, including antibiotic prescribing – especially broad spectrum antibiotics.

References


Evidence tables

Table 3 MODIFY I

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unique identifier</td>
<td>NCT01241552</td>
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<tr>
<td>Study type</td>
<td>Multicentre, randomised, placebo-controlled, double-blind trial</td>
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<tr>
<td>Aim of the study</td>
<td>To examine the safety and efficacy of bezlotoxumab, alone and combined with another monoclonal antibody (actoxumab), for preventing recurrent C difficile infection</td>
</tr>
<tr>
<td>Study dates</td>
<td>October 2011 to December 2014 (NCT01241552)</td>
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<tr>
<td>Setting</td>
<td>19 countries including the UK</td>
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<tr>
<td>Number of participants</td>
<td>1,452 randomised (modified ITT population(^a) n=1,396, 34% from Europe, 54% from North America)</td>
</tr>
<tr>
<td>Population</td>
<td>Adults with primary or recurrent C difficile infection (67% hospital inpatients, 51% aged at least 65 years, 27% at least 1 episode of C difficile in the last 6 months, 16% with severe infection(^b), 16% with strain 027, 22% immunocompromised)</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Participants had confirmed C difficile infection(^c) and were receiving oral standard-of-care antibiotics (metronidazole [49%], vancomycin [48%] or fidaxomicin [3%], chosen by the treating doctor) for 10–14 days(^d)</td>
</tr>
</tbody>
</table>
People with uncontrolled diarrhoeal illness or who planned to take medicines to decrease gastrointestinal peristalsis in the next 14 days were excluded, as were people planning to take the probiotic *Saccharomyces boulardii* or receive faecal transplant therapy, or any other therapies that have been demonstrated to decrease recurrences of *C difficile* infection. People who were expected to be treated with standard-of-care antibiotics for more than 14 days were also excluded (NCT01241552).

### Intervention(s)

Bezlotoxumab (10 mg/kg, n=386) as a single intravenous infusion

### Comparator(s)

Actoxumab\(^1\) (10 mg/kg, n=232), actoxumab plus bezlotoxumab (both 10 mg/kg, n=383) or placebo (0.9% saline, n=395) as a single intravenous infusion

### Length of follow-up

12 weeks

### Outcomes

**Primary outcome:**
- the proportion of participants with recurrent *C difficile* infection\(^{h,i}\)

**Exploratory outcome:**
- the proportion of participants with initial clinical cure\(^{i,j}\)

**Secondary outcomes:**
- the proportion of participants with recurrent *C difficile* infection in the subgroup of participants who had an initial clinical cure\(^{i,j}\)
- the proportion of participants with recurrent *C difficile* infection in the subgroup of participants who had an initial clinical cure\(^{i}\) in prespecified subgroups of participants with risk factors for recurrent *C difficile* infection or for adverse outcomes related to *C difficile* infection\(^{i,k}\)
- the proportion of participants with sustained clinical cure\(^{i,l}\)

**Safety outcomes:**
- infusion-related reactions
- all adverse events
- serious adverse events
- results of laboratory tests and electrocardiography
<table>
<thead>
<tr>
<th>Source of funding</th>
<th>Merck &amp; Co., Inc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall risk of bias/quality assessment (CASP RCT checklist)</td>
<td>Did the trial address a clearly focused issue?</td>
</tr>
<tr>
<td></td>
<td>Was the assignment of patients to treatments randomised?</td>
</tr>
<tr>
<td></td>
<td>Were patients, health workers and study personnel blinded?</td>
</tr>
<tr>
<td></td>
<td>Were the groups similar at the start of the trial?</td>
</tr>
<tr>
<td></td>
<td>Aside from the experimental intervention, were the groups treated equally?</td>
</tr>
<tr>
<td></td>
<td>Were all of the patients who entered the trial properly accounted for at its conclusion?</td>
</tr>
<tr>
<td></td>
<td>How large was the treatment effect?</td>
</tr>
<tr>
<td></td>
<td>How precise was the estimate of the treatment effect?</td>
</tr>
<tr>
<td></td>
<td>Can the results be applied in your context? (or to the local population)</td>
</tr>
<tr>
<td></td>
<td>Were all clinically important outcomes considered?</td>
</tr>
<tr>
<td></td>
<td>Are the benefits worth the harms and costs?</td>
</tr>
</tbody>
</table>
### Study limitations

- Selection of standard-of-care antibiotics was not standardised
- The time interval between onset of symptoms and administration of the trial infusion was broad
- The proportion of participants with a severe *C difficile* infection at baseline is probably underestimated because more than 90% of participants were receiving standard-of-care antibiotics when the severity assessment was performed
- Use of other therapies for preventing recurrence of *C difficile* infection (for example, faecal microbiota transplant) was not allowed
- A relatively small number of patients received bezlotoxumab, making it difficult to detect rare adverse events
<table>
<thead>
<tr>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>a All randomly assigned participants who received the trial infusion, had a baseline stool test that was positive for toxigenic <em>C difficile</em>, and began receiving standard-of-care therapy before or within 1 day after receiving the monoclonal antibodies.</td>
</tr>
<tr>
<td>b Defined as a Zar score of 2 or more (scores range from 1 to 8, with higher scores indicating more severe infection).</td>
</tr>
<tr>
<td>c <em>C difficile</em> infection was defined as diarrhoea (3 or more unformed bowel movements [types 5 to 7 on the Bristol stool scale] in 24 hours) with a stool test result that was positive for toxin-producing <em>C difficile</em>.</td>
</tr>
<tr>
<td>d Participants who were receiving oral vancomycin or fidaxomicin could also receive intravenous metronidazole.</td>
</tr>
<tr>
<td>e The trial treatment was administered a median of 3 days after initiation of standard-of-care antibiotics across MODIFY I and MODIFY II.</td>
</tr>
<tr>
<td>f In the interim analysis, the rate of recurrent infection was found to be higher in the actoxumab group than in the actoxumab plus 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. Enrolment in the actoxumab group was therefore stopped. Actoxumab is not available; therefore, results for this group are of little relevance to this evidence summary and are not presented.</td>
</tr>
<tr>
<td>g Participants recorded unformed bowel movements daily until day 80 to 90 after the infusion. New episodes of diarrhoea were monitored through telephone contact between visits.</td>
</tr>
<tr>
<td>h Defined as a new episode of <em>C difficile</em> infection after initial clinical cure of the baseline episode.</td>
</tr>
<tr>
<td>i In the modified ITT population.</td>
</tr>
<tr>
<td>j Defined as no diarrhoea for 2 consecutive days after completion of standard-of-care antibiotic therapy administered for up to 16 days.</td>
</tr>
<tr>
<td>k Aged 65 years or older, a history of <em>C difficile</em> infection, compromised immunity, clinically severe <em>C difficile</em> infection and infection with a strain associated with poor outcomes (strain 027, 078 or 244). Results for individual subgroups are not reported in this evidence summary.</td>
</tr>
<tr>
<td>l Defined as initial clinical cure of the baseline episode of <em>C difficile</em> infection and no recurrent infection for 12 weeks, also known as global cure or sustained clinical response.</td>
</tr>
</tbody>
</table>
Safety was assessed in the as-treated population, which included all randomly assigned participants who received the trial infusion.

Randomisation was performed via an interactive voice response system (European Public Assessment Report). This method of randomisation suggests allocation was concealed.

**Abbreviations:** C *difficile*, *Clostridium difficile*; ITT, intention-to-treat; p, p-value

### Table 4 MODIFY II

<table>
<thead>
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<tr>
<td>Unique identifier</td>
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<tr>
<td>Study type</td>
<td>Multicentre, randomised, placebo-controlled, double-blind trial</td>
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<tr>
<td>Aim of the study</td>
<td>To examine the safety and efficacy of bezlotoxumab, alone and combined with another monoclonal antibody (actoxumab), for preventing recurrent <em>C difficile</em> infection</td>
</tr>
<tr>
<td>Study dates</td>
<td>February 2012 to May 2015 (NCT01513239)</td>
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<tr>
<td>Setting</td>
<td>17 countries not including the UK</td>
</tr>
<tr>
<td>Number of participants</td>
<td>1,203 randomised (modified ITT population(^a) n=1,163, 43% from Europe, 41% from North America)</td>
</tr>
<tr>
<td>Population</td>
<td>Adults with primary or recurrent <em>C difficile</em> infection (69% hospital inpatients, 56% aged at least 65 years, 28% at least 1 episode of <em>C difficile</em> in the last 6 months, 17% with severe infection(^b), 20% with strain 027, 20% immunocompromised)</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Participants had confirmed <em>C difficile</em> infection(^c) and were receiving oral standard-of-care antibiotics (metronidazole [48%], vancomycin [48%] or fidaxomicin [3%], chosen by the treating doctor) for 10–14 days(^d)</td>
</tr>
</tbody>
</table>
### Exclusion criteria
People with uncontrolled diarrhoeal illness or who planned to take medicines to decrease gastrointestinal peristalsis in the next 14 days were excluded, as were people planning to take the probiotic *Saccharomyces boulardii* or receive faecal transplant therapy, or any other therapies that have been demonstrated to decrease recurrences of *C difficile* infection. People who were expected to be treated with standard-of-care antibiotics for more than 14 days were also excluded (NCT01513239).

### Intervention(s)
Bezlotoxumab (10 mg/kg, n=395) as a single intravenous infusion

### Comparator(s)
Actoxumab plus bezlotoxumab (both 10 mg/kg, n=390) or placebo (0.9% saline, n=378) as a single intravenous infusion

### Length of follow-up
12 weeks

### Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
</tr>
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<tbody>
<tr>
<td><strong>Primary outcome:</strong></td>
<td>the proportion of participants with recurrent <em>C difficile</em> infection&lt;sup&gt;g,h&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Exploratory outcome:</strong></td>
<td>the proportion of participants with initial clinical cure&lt;sup&gt;h,i&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Secondary outcomes:</strong></td>
<td>the proportion of participants with recurrent <em>C difficile</em> infection in the subgroup of participants who had an initial clinical cure&lt;sup&gt;h,i&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>the proportion of participants with recurrent <em>C difficile</em> infection in the subgroup of participants who had an initial clinical cure&lt;sup&gt;h,i&lt;/sup&gt; in prespecified subgroups of participants with risk factors for recurrent <em>C difficile</em> infection or for adverse outcomes related to <em>C difficile</em> infection&lt;sup&gt;h,j&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>the proportion of participants with sustained clinical cure&lt;sup&gt;h,k&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Safety outcomes:</strong></td>
<td>infusion-related reactions</td>
</tr>
<tr>
<td></td>
<td>all adverse events</td>
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<tr>
<td></td>
<td>serious adverse events</td>
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<td>results of laboratory tests and electrocardiography</td>
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<tr>
<td>Source of funding</td>
<td>Merck &amp; Co. Inc.</td>
</tr>
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<td>Did the trial address a clearly focused issue?</td>
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<tr>
<td>Were all of the patients who entered the trial properly accounted for at its conclusion?</td>
<td>Yes</td>
</tr>
<tr>
<td>How large was the treatment effect?</td>
<td>See table 6</td>
</tr>
<tr>
<td>How precise was the estimate of the treatment effect?</td>
<td>See table 6</td>
</tr>
<tr>
<td>Can the results be applied in your context? (or to the local population)</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all clinically important outcomes considered?</td>
<td>Yes</td>
</tr>
<tr>
<td>Are the benefits worth the harms and costs?</td>
<td>See overview</td>
</tr>
</tbody>
</table>
### Study limitations

- Selection of standard-of-care antibiotics was not standardised
- The time interval between onset of symptoms and administration of the trial infusion was broad
- The proportion of participants with a severe *C difficile* infection at baseline is probably underestimated because more than 90% of participants were receiving standard-of-care antibiotics when the severity assessment was performed
- Use of other therapies for preventing recurrence of *C difficile* infection (for example, faecal microbiota transplant) was not allowed
- A relatively small number of patients received bezlotoxumab, making it difficult to detect rare adverse events
All randomly assigned participants who received the trial 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.

Defined as a Zar score of 2 or more (scores range from 1 to 8, with higher scores indicating more severe infection).

C. difficile infection was defined as diarrhoea (3 or more unformed bowel movements [types 5 to 7 on the Bristol stool scale] in 24 hours) with a stool test result that was positive for toxin-producing C. difficile.

Participants who were receiving oral vancomycin or fidaxomicin could also receive intravenous metronidazole.

The trial treatment was administered a median of 3 days after initiation of standard-of-care antibiotics across MODIFY I and MODIFY II.

Participants recorded unformed bowel movements daily until day 80 to 90 after the infusion. New episodes of diarrhoea were monitored through telephone contact between visits.

Defined as a new episode of C. difficile infection after initial clinical cure of the baseline episode.

In the modified ITT population.

Defined as no diarrhoea for 2 consecutive days after completion of standard-of-care antibiotic therapy administered for up to 16 days.

Aged 65 years or older, a history of C. difficile infection, compromised immunity, clinically severe C. difficile infection and infection with a strain associated with poor outcomes (strain 027, 078 or 244). Results for individual subgroups are not reported in this evidence summary.

Defined as initial clinical cure of the baseline episode of C. difficile infection and no recurrent infection for 12 weeks, also known as global cure or sustained clinical response.

Safety was assessed in the as-treated population, which included all randomly assigned participants who received the trial infusion.

Randomisation was performed via an interactive voice response system (European Public Assessment Report). This method of randomisation suggests allocation was concealed.

Abbreviations: C. difficile, Clostridium difficile; ITT, intention-to-treat; p, p-value
## Results tables

### Table 6 Efficacy results from MODIFY I ([Wilcox MH et al. 2017](#))

<table>
<thead>
<tr>
<th></th>
<th>Bezlotoxumab</th>
<th>Bezlotoxumab + actoxumab</th>
<th>Placebo</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>386</td>
<td>383</td>
<td>395</td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of participants</td>
<td>17.4% (67/</td>
<td>15.9% (61/</td>
<td>27.6%</td>
<td>Bezlotoxumab versus placebo: adjusted difference 10.1% (95% CI 4.3% to</td>
</tr>
<tr>
<td>with recurrent C difficile</td>
<td>386)</td>
<td>383)</td>
<td>(109/395)</td>
<td>15.9%), p=0.0007</td>
</tr>
<tr>
<td>infection^b</td>
<td></td>
<td></td>
<td></td>
<td>Combination versus placebo: adjusted difference 11.6% (95% CI 5.9% to</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17.4%), p&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bezlotoxumab versus combination: adjusted difference 1.4% (95% CI</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>-3.9% to 6.7%), p=0.5993 (NS)</td>
</tr>
<tr>
<td><strong>Exploratory outcome</strong></td>
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<td></td>
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<tr>
<td>Proportion of participants</td>
<td>77.5% (299/</td>
<td>74.7% (286/</td>
<td>82.8%</td>
<td>Bezlotoxumab versus placebo: adjusted difference 5.3% (95% CI -0.3% to</td>
</tr>
<tr>
<td>with initial clinical cure^c</td>
<td>386)</td>
<td>383)</td>
<td>(327/395)</td>
<td>10.9%), p=0.0643 (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Combination versus placebo: adjusted difference 8.2% (95% CI 2.4% to</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13.9%), p=0.0055</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bezlotoxumab versus combination: adjusted difference 2.8% (95% CI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-3.2% to 8.8%), p=0.3607 (NS)</td>
</tr>
</tbody>
</table>
### Selected secondary outcomes

<table>
<thead>
<tr>
<th></th>
<th>Bezlotoxumab versus placebo</th>
<th>Combination versus placebo</th>
<th>Bezlotoxumab versus combination</th>
</tr>
</thead>
</table>
| Proportion of participants with recurrent *C difficile* infection in the subgroup of participants who had an initial clinical cure<sup>c</sup> | 22.4% (67/299) | 21.3% (61/286) | 33.3% (109/327) | Bezlotoxumab versus placebo: adjusted difference 10.8% (95% CI 3.8% to 17.7%), p=0.0026  
Combination versus placebo: adjusted difference 11.7% (95% CI 4.7% to 18.6%), p=0.0012  
Bezlotoxumab versus combination: adjusted difference 1.0% (95% CI −5.8% to 7.7%), p=0.7812 (NS) |
| Proportion of participants with sustained clinical cure<sup>d</sup> | 60.1% (232/386) | 58.7% (225/383) | 55.2% (218/395) | Bezlotoxumab versus placebo: adjusted difference 4.8% (95% CI −11.7% to 2.1%), p=0.1722 (NS)  
Combination versus placebo: adjusted difference 3.5% (95% CI −10.4% to 3.5%), p=0.3292 (NS)  
Bezlotoxumab versus combination: adjusted difference 1.4% (95% CI −5.5% to 8.3%), p=0.6936 (NS) |

### Safety and tolerability outcomes

Safety outcomes are not reported for MODIFY I alone. Pooled results with MODIFY II are presented in table 7.
a Modified ITT population (all randomly assigned participants who received the trial infusion, had a baseline stool test that was positive for toxigenic \textit{C difficile}, and began receiving standard-of-care therapy before or within 1 day after receiving the monoclonal antibodies)

b Defined as a new episode of \textit{C difficile} infection after initial clinical cure\textsuperscript{c} of the baseline episode

c Defined as no diarrhoea for 2 consecutive days after completion of standard-of-care antibiotic therapy administered for up to 16 days

d Defined as initial clinical cure of the baseline episode of \textit{C difficile} infection and no recurrent infection for 12 weeks

\textbf{Abbreviations:} \textit{C difficile}, \textit{Clostridium difficile}; CI, confidence interval; ITT, intention-to-treat; NS, not statistically significant; \textit{p}, \textit{p}-value

\textbf{Table 6 Efficacy results from MODIFY II (Wilcox MH et al. 2017)}

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Bezlotoxumab</th>
<th>Bezlotoxumab + actoxumab</th>
<th>Placebo</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textbf{n}\textsuperscript{a}</td>
<td>395</td>
<td>390</td>
<td>378</td>
<td></td>
</tr>
<tr>
<td>\textbf{Primary outcome}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Proportion of participants with recurrent \textit{C difficile} infection\textsuperscript{b} | 15.7\% (62/395) | 14.9\% (58/390)          | 25.7\% (97/378) | Bezlotoxumab versus placebo: adjusted difference 9.9\% (95\% CI 4.3\% to 15.5\%), \textit{p}=0.0006  
Combination versus placebo: adjusted difference 10.7\% (95\% CI 5.1\% to 16.4\%), \textit{p}=0.0002  
Bezlotoxumab versus combination: adjusted difference 0.8\% (95\% CI -4.2\% to 5.9\%), \textit{p}=0.7435 (NS) |
| \textbf{Exploratory outcome}                  |              |                          |         |                                               |
### Proportion of participants with initial clinical cure

|                | Bezloxtumab | Placebo | Combination | Bezloxtumab versus placebo: adjusted difference 4.8% (95% CI –10.4% to 0.9%), p=0.0962 (NS)  
|----------------|------------|---------|-------------|------------------------------------------------------------------------------------------  
|                | 82.5% (326/395) | 72.3% (282/390) | 77.8% (294/378) |                                                                                          
|                | Bezlotoxumab versus combination: adjusted difference 10.3% (95% CI 4.4% to 16.1%), p=0.0006  
|                | 19.0% (62/326) | 20.6% (58/282) | 33.0% (97/294) |                                                                                          
|                | Bezlotoxumab versus placebo: adjusted difference 13.7% (95% CI 6.9% to 20.4%), p<0.0001  
|                | Combination versus placebo: adjusted difference 11.9% (95% CI 4.7% to 19.0%), p=0.0013  
|                | Bezloxtumab versus combination: adjusted difference 1.6% (95% CI –8.0% to 4.6%), p=0.6076 (NS)  

### Selected secondary outcomes

|                | Bezloxtumab | Placebo | Combination | Bezloxtumab versus placebo: adjusted difference 4.8% (95% CI –10.4% to 0.9%), p=0.0962 (NS)  
|----------------|------------|---------|-------------|------------------------------------------------------------------------------------------  
|                | 82.5% (326/395) | 72.3% (282/390) | 77.8% (294/378) |                                                                                          
|                | Bezlotoxumab versus combination: adjusted difference 10.3% (95% CI 4.4% to 16.1%), p=0.0006  
|                | 19.0% (62/326) | 20.6% (58/282) | 33.0% (97/294) |                                                                                          
|                | Bezlotoxumab versus placebo: adjusted difference 13.7% (95% CI 6.9% to 20.4%), p<0.0001  
|                | Combination versus placebo: adjusted difference 11.9% (95% CI 4.7% to 19.0%), p=0.0013  
|                | Bezloxtumab versus combination: adjusted difference 1.6% (95% CI –8.0% to 4.6%), p=0.6076 (NS)  

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Proportion of participants with sustained clinical cure:

<table>
<thead>
<tr>
<th></th>
<th>Bezlo</th>
<th>Bezlot + acto</th>
<th>Placebo</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>66.8% (264/395)</td>
<td>57.4% (224/390)</td>
<td>52.1% (197/378)</td>
<td>Bezlo vs placebo: adjusted difference 14.6% (95% CI 7.7% to 21.4%), p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Combination vs placebo: adjusted difference 5.2% (95% CI -1.8% to 12.2%), p=0.1444 (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bezlo vs combination: adjusted difference 9.4% (95% CI 2.7% to 16.1%), p=0.0063</td>
</tr>
</tbody>
</table>

Safety and tolerability outcomes:

Safety outcomes are not reported for MODIFY I alone. Pooled results with MODIFY II are presented in table 7.

- Modified ITT population (all randomly assigned participants who received the trial 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)
- Defined as a new episode of *C. difficile* infection after initial clinical cure of the baseline episode
- Defined as no diarrhoea for 2 consecutive days after completion of standard-of-care antibiotic therapy administered for up to 16 days
- Defined as initial clinical cure of the baseline episode of *C. difficile* infection and no recurrent infection for 12 weeks

**Abbreviations:** *C. difficile*, Clostridium difficile; CI, confidence interval; ITT, intention-to-treat; NS, not statistically significant; p, p-value

**Table 7 Pooled safety results from MODIFY I and MODIFY II (Wilcox MH et al. 2017)**

<table>
<thead>
<tr>
<th></th>
<th>Bezlo</th>
<th>Bezlo + acto</th>
<th>Placebo</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety and tolerability outcomes*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>786</td>
<td>777</td>
<td>781</td>
<td></td>
</tr>
</tbody>
</table>
Infusion-related adverse reactions in the 24 hours after infusion

<table>
<thead>
<tr>
<th></th>
<th>10.3% (81/786)</th>
<th>8.0% (62/777)</th>
<th>7.6% (59/781)</th>
<th>Statistical analysis not reported</th>
</tr>
</thead>
</table>

1 or more adverse events in the 4 weeks after infusion

<table>
<thead>
<tr>
<th></th>
<th>61.7% (485/786)</th>
<th>58.6% (455/777)</th>
<th>61.2% (478/781)</th>
<th>Statistical analysis not reported</th>
</tr>
</thead>
</table>

Treatment-related adverse events in the 4 weeks after infusion

<table>
<thead>
<tr>
<th></th>
<th>7.5% (59/786)</th>
<th>6.4% (50/777)</th>
<th>5.9% (46/781)</th>
<th>Statistical analysis not reported</th>
</tr>
</thead>
</table>

Serious adverse events in the 12 weeks after infusion

<table>
<thead>
<tr>
<th></th>
<th>29.4% (231/786)</th>
<th>27.3% (212/777)</th>
<th>32.7% (255/781)</th>
<th>Statistical analysis not reported</th>
</tr>
</thead>
</table>

Deaths in the 12 weeks after infusion

<table>
<thead>
<tr>
<th></th>
<th>7.1% (56/786)</th>
<th>6.6% (51/777)</th>
<th>7.6% (59/781)</th>
<th>Statistical analysis not reported</th>
</tr>
</thead>
</table>

* Safety was assessed in the as-treated population, which included all randomly assigned participants who received the trial infusion

**Excluded studies**

No references were excluded.

**Terms used in this evidence summary**

**Recurrent Clostridium difficile infection** is defined as a new episode of *C difficile* infection after initial clinical cure of the baseline episode.

**Initial clinical cure** is defined as no diarrhoea for 2 consecutive days after completion of standard-of-care antibiotic therapy administered for up to 16 days.

**Sustained clinical cure** is defined as initial clinical cure of the baseline episode of *C difficile* infection and no recurrent infection for 12 weeks.

**Search strategy**

Database: Medline
Preventing recurrence of Clostridium difficile infection: bezlotoxumab (ES13)

Platform: Ovid

Version: 1946 to February wk 3 2017

Search date: 27/02/2017

Number of results retrieved: 11

Search strategy:

Database: Ovid MEDLINE(R) <1946 to February Week 3 2017>

Search Strategy:

--------------------------------------------------------------------------------

1 (bezlotoxumab or bezlo or zinplava or MK-6072 or MK 6072 or MK6072).tw. (11)

Database: Medline in-process

Platform: Ovid

Version: February 24 2017

Search date: 27/02/2017

Number of results retrieved: 9

Search strategy:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <February 24, 2017>

Search Strategy:

--------------------------------------------------------------------------------

1 (bezlotoxumab or bezlo or zinplava or MK-6072 or MK 6072 or MK6072).tw. (9)
Preventing recurrence of Clostridium difficile infection: bezlotoxumab (ES13)

Database: Medline epubs ahead of print

Platform: Ovid

Version: February 24 2017

Search date: 27/02/2017

Number of results retrieved: 0

Search strategy:

As above 0 results

Database: Embase

Platform: Ovid

Version: 1974 to 2017 February 22

Search date: 27/02/2017

Number of results retrieved: 48

Search strategy:

Database: Embase <1974 to 2017 February 22>

Search Strategy:

Database: Embase <1974 to 2017 February 24>

Search Strategy:

--------------------------------------------------------------------------------

1 bezlotoxumab/ (44)
Preventing recurrence of Clostridium difficile infection: bezlotoxumab (ES13)

2 (bezlotoxumab or bezlo or zinplava or MK-6072 or MK 6072 or MK6072).tw. (27)

3 1 or 2 (48)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED

Platform: Wiley

Version:

CDSR – 2 of 12 February 2017

DARE – 2 of 4, April 2015 (legacy database)

CENTRAL – 1 of 12 January 2017

HTA – 4 of 4 October 2016

NHS EED – 2 of 4, April 2015 (legacy database)

Search date: 27/02/2017

Number of results retrieved: CDSR 0 ; DARE 0 ; CENTRAL 0; HTA 1 ; NHS EED 0.

Search strategy:

Search Name:

Date Run: 27/02/17 11:04:10.21

Description:

ID Search Hits

#1 bezlotoxumab or bezlo or zinplava or MK-6072 or MK 6072 or MK6072:ti,ab,kw (Word variations have been searched) 1
Development of this evidence summary

The evidence summaries: process guide (2017) sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

Expert advisers

Dr Philippa Moore, Consultant Microbiologist, Gloucestershire Hospitals NHS Foundation Trust.

Neil Powell, Consultant Antimicrobial Pharmacist, Royal Cornwall Hospitals NHS Trust.

Paul Wade, Consultant Pharmacist Infectious Diseases, Guy’s and St. Thomas’ NHS Foundation Trust.

Declarations of interest

Dr Philippa Moore received sponsorship from Merck for attending ECCMID 2016 and is a Director of Clinical Microbiology Consultancy Ltd. She contributed to the Expert Group for EU guidelines on the prudent use of antimicrobials in human medicine.

Neil Powell has received educational sponsorship for venue hire and refreshments from MSD, Pfizer, Cardiome, and diagnostics companies; Nanoporetech, Alere and Radiometer.

Paul Wade has received lecture fees, consultancy fees, advisory board fees and conference attendance support from Astellas, AstraZeneca, Basilea, Baxter, Cardiome, Clinigen, Cubist, Durata, Eumedica, Gilead, ICNet, Merck and Pfizer. He has published papers, spoken at conferences and meetings, and presented posters concerning management of Clostridium difficile infection, including use of pharmacological treatments for C difficile infection.

About this evidence summary

Evidence summaries provide a summary of the best available published evidence for selected new medicines, unlicensed medicines or off-label use of licensed medicines.

The summaries assess the strengths and weaknesses of the best available evidence to inform health professionals and commissioners' decision-making.

This summary is not NICE guidance.