Cadazolid for treatment of Clostridium difficile-associated diarrhoea

LAY SUMMARY

Clostridium difficile is a bacterium that infects the gut and causes diarrhoea. It usually affects people who have recently taken antibiotics and it can cause serious bowel problems if left untreated. The bacterium is easily spread by direct contact with infected people or surfaces.

Cadazolid is a new antibiotic that is taken by mouth as a liquid. Some studies have suggested that this drug can help to treat Clostridium difficile-associated diarrhoea, and more studies are trying to show how well cadazolid works. If cadazolid is licensed for use in the UK, it could offer a new treatment option for this patient group.

NIHR HSRIC ID: 10123
TARGET GROUP

- Clostridium difficile-associated diarrhoea – treatment of first occurrence and recurrence.

TECHNOLOGY

DESCRIPTION

Cadazolid (ACT-179811) is a fluoroquinolone-oxazolidinone, non-absorbable antibiotic that inhibits Clostridium difficile protein synthesis, and leads to suppression of toxin and spore formation. In a phase III clinical trial, patients with C. difficile-associated diarrhoea (CDAD) are administered cadazolid 250mg oral twice daily for 10 days.

Cadazolid does not currently have a Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, cadazolid will offer an additional treatment option for this patient group following first occurrence or recurrence.

DEVELOPER

Actelion.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

C. difficile is a commensal bacterium that lives harmlessly in the gut of approximately 5% of healthy people. However, wide-spread antibiotic use and immunosuppressive agents change the gut flora, resulting in C. difficile overgrowth. C. difficile is the most commonly identified infectious cause of antibiotic-associated diarrhoea. C. difficile produces toxins A and B, which are the main virulence factors. Infection and exotoxin production leads to purulent watery diarrhoea, abdominal cramps, nausea and dehydration. In severe cases, it can also cause bloody diarrhoea and fever, and may be complicated by pseudomembranous colitis, sepsis, toxic megacolon, colonic rupture and death. The frequency and severity of C. difficile infections has risen over many years, with increased morbidity and mortality particularly among the elderly.

CLINICAL NEED and BURDEN OF DISEASE

Between April 2014 and March 2015, 14,165 cases of CDAD were reported in England, representing an infection rate of 24.8 per 100,000 population, an increase of 6% compared to 2013-14.
Recurrence occurs in about 20% of patients treated initially with metronidazole or vancomycin\(^5\). Between 20-50% are thought to be reinfections rather than relapse due to the same strain. Relapses tend to occur in the first two weeks after treatment cessation\(^5\). After a first reoccurrence, the risk of reinfections increases to 45-60%\(^5\).

In 2014-15, there were 4,335 admissions for enterocolitis due to \textit{C. difficile} (ICD-10 A04.7) in England, resulting in 100,166 bed days and 10,609 finished consultant episodes\(^6\). In 2014, there were 522 deaths registered in England and Wales from enterocolitis due to \textit{C. difficile}\(^7\).

### PATIENT PATHWAY

### RELEVANT GUIDANCE

#### NICE Guidance

- NICE guidelines. Antimicrobial stewardship: systems and processed for effective antimicrobial medicine use (NG15). August 2015.

#### Other Guidance

- Public Health England. Updated guidance on the management and treatment of \textit{Clostridium difficile} infection. May 2013\(^6\).
- American College of Gastroenterology. Guidelines for Diagnosis, Treatment, and Prevention of \textit{Clostridium difficile} Infections. February 2013\(^8\).

### CURRENT TREATMENT OPTIONS

The specific treatment of patients with CDAD depends on the severity of disease: mild disease may not require specific antibiotic treatment, although oral metronidazole is recommended for mild to moderate disease\(^4,5,8\). Guidelines indicate that severe disease warrants the use of oral vancomycin, and fidaxomicin should also be considered in patients susceptible to recurrence. Surgery (colectomy) may be necessary in severe, worsening cases and to manage serious complications\(^4,5,8\). Treatment of recurrent CDAD may require vancomycin tapering/pulse therapy, IV immunoglobulin, or donor stool transplant\(^4,5,8\).
# EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Design</th>
<th>Participants</th>
<th>Schedule</th>
<th>Follow-up</th>
<th>Primary outcome/s</th>
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<tbody>
<tr>
<td>NCT01987895, AC-061A301; cadazolid vs vancomycin; phase III.</td>
<td>Actelion.</td>
<td>Ongoing.</td>
<td>Trial registry², manufacturer.</td>
<td>EU (not UK), USA, Canada, Australia, Brazil and Peru.</td>
<td>Randomised, active-controlled.</td>
<td>n=640 (planned); aged ≥18 years; mild, moderate or severe CDAD (first occurrence or first recurrence within 3 months) defined as a change in bowel habit with &gt;3 liquid or unformed bowel movements (UBM) within 24 hours prior to randomisation, and a positive <em>C. difficile</em> toxin test on a stool sample produced within 72 hours prior to randomisation; no more than 1 previous episode of CDAD in the previous 3-mths; no evidence of life-threatening or fulminant CDAD; no likelihood of death within 72 hrs from any cause; no antimicrobial treatment active against CDAD administered for &gt;24 hrs except metronidazole for treatment failure; no history of inflammatory colitides, chronic abdominal pain or chronic diarrhoea.</td>
<td>Randomised to cadazolid 250mg oral suspension twice daily or vancomycin 125mg oral capsules four times daily.</td>
<td>Active treatment for 10 days, follow-up for up to 32 days.</td>
<td>Clinical cure, defined as resolution of diarrhoea on study treatment that is Clinical cure.</td>
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<tr>
<td>NCT01983683, AC-061A302; cadazolid vs vancomycin; phase III.</td>
<td>Actelion.</td>
<td>Ongoing.</td>
<td>Trial registry², manufacturer.</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
<td>Randomised, active-controlled.</td>
<td>n=640 (planned); aged ≥18 years; mild, moderate or severe CDAD (first occurrence or first recurrence within 3 months) defined as: a change in bowel habits with &gt;3 liquid or UBM within 24 hours prior to randomisation, and a positive <em>C. difficile</em> toxin test on a stool sample produced within 72 hours prior to randomisation; no more than 1 previous episode of CDAD in the previous 3-mths before study; no evidence of life-threatening or fulminant CDAD; no likelihood of death within 72 hrs from any cause; no antimicrobial treatment active against CDAD administered for &gt;24 hrs except metronidazole for treatment failure; no history of inflammatory colitides, chronic abdominal pain or chronic diarrhoea.</td>
<td>Randomised to cadazolid 250mg oral suspension twice daily or vancomycin 125mg oral capsules four times daily.</td>
<td>Active treatment for 10 days, follow-up for up to 32 days.</td>
<td>Clinical cure.</td>
</tr>
<tr>
<td>NCT01222702, AC-061A201; cadazolid vs vancomycin; phase II.</td>
<td>Actelion.</td>
<td>Published.</td>
<td>Published⁴, trial registry¹⁰.</td>
<td>EU (incl UK), USA and Canada.</td>
<td>Randomised, active-controlled.</td>
<td>n=81; aged ≥18 years; CDAD (first occurrence or first recurrence); no concomitant antimicrobial treatment for CDAD.</td>
<td>Randomised to cadazolid 250mg oral, twice daily; cadazolid 500mg oral, twice daily; cadazolid 1,000mg oral, twice daily or vancomycin 125mg oral, four times daily.</td>
<td>Active treatment for 10 days, follow-up for up to 4 weeks.</td>
<td>Clinical cure.</td>
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maintained for 2 days after end of treatment with no addition treatment against CDAD, including faecal microbiota treatment between first dose of cadazolid and 2 days after end of treatment.

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<tr>
<th>Secondary outcome/s</th>
<th>Sustained cure; time to resolution of diarrhoea; absolute change from baseline in CDAD DaySyms patient reported outcomes (PRO) daily score.</th>
<th>Sustained cure; time to resolution of diarrhoea; absolute change from baseline in CDAD DaySyms PRO daily score.</th>
<th>Disease recurrence rate.</th>
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<tbody>
<tr>
<td>Key results</td>
<td>-</td>
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<td>For cadazolid 250mg, 500mg, 1,000mg and vancomycin groups, respectively: primary endpoint achieved in 76.5% (80% CI, 58.4, 89.3), 80.0% (63.9, 91.0), 68.4% (51.1, 82.5) and 68.2% (52.3, 81.3). For combined cadazolid vs vancomycin groups, respectively: recurrence rate, 18.2 to 25.0% vs 50%; clinical response rates, 46.7 to 60.0% vs 33.3%. Times to diarrhoea resolution were reportedly similar for cadazolid and vancomycin.</td>
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<td>Adverse effects (AEs)</td>
<td>-</td>
<td>-</td>
<td>The majority of AEs were of mild or moderate intensity. Overall, treatment emergent AEs were experienced by 30%, 23%, 30% and 46% of pts receiving 250, 500, or 1,000mg cadazolid, and 125mg vancomycin, respectively. Two pts discontinued cadazolid and one pt discontinued vancomycin. Eight serious AEs were reported across all groups, none were considered to be related to the study treatment. Two deaths occurred after drug treatment ceased, neither considered to be related to the study treatment.</td>
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<td>Expected reporting date</td>
<td>Study completion date reported as July 2016.</td>
<td>Study completion date reported as July 2016.</td>
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## ESTIMATED COST and IMPACT

### COST

The cost of cadazolid is not yet known. One vial of vancomycin (as vancomycin hydrochloride) 500mg starts at £6.25 while a pack of 20 x 200mg fidaxomicin tablets costs £1,350\(^1\).

### IMPACT - SPECULATIVE

#### Impact on Patients and Carers

- Reduced mortality/increased length of survival
- Other: potential for reduced length of hospital stay if recurrence rates are reduced.
- Reduced symptoms or disability
- No impact identified

#### Impact on Health and Social Care Services

- Increased use of existing services
- Decreased use of existing services: potential for reduced length of hospital stay if recurrence rates are reduced.
- Re-organisation of existing services
- Need for new services
- Other
- None identified

#### Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
- Other reduction in costs:
- Other: uncertain unit cost compared to existing alternative treatment options.
- None identified

#### Other Issues

- Clinical uncertainty or other research question identified
- None identified

### REFERENCES