

Cadazolid: A new hope in the treatment of *Clostridium difficile* infection

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REVIEW

Please cite this paper as: Kali A, Charles MVP, Srirangaraj S. Cadazolid: A new hope in the treatment of *Clostridium difficile* infection. AMJ 2015;8(8):253–262. <http://doi.org/10.21767/AMJ.2015.2441>

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ABSTRACT

Clostridium difficile infection (CDI) is a potential life-threatening consequence of antibiotic therapy. Although the risk increases with duration of treatment, it can also occur after a short treatment course. In addition to broad-spectrum antibiotics, anti-neoplastic agents, proton pump inhibitors, H₂ blockers, and several other drugs have been reported to induce intestinal dysbiosis, which is central to the pathogenesis of CDI. There is an increase in incidence and mortality attributed to CDI globally. Moreover, the epidemiology of *C. difficile*-associated diseases has changed significantly with an increasing occurrence of community-acquired CDI. Metronidazole and oral vancomycin are the first-line antibiotics used to treat CDI. However, metronidazole has limited effectiveness in severe cases and vancomycin use is associated with increasing risk of vancomycin resistance among *Enterococcus spp.* Cadazolid, a novel oxazolidinone antibiotic, has recently shown potent antimicrobial activity against *C. difficile* and has a lower propensity to induce resistance. The implications of its use in treating CDI have been reviewed based on current evidence.

Key Words

Cadazolid, oxazolidinone, *Clostridium difficile* infection

What this review adds:

1. What is known about this subject?

Clostridium difficile has been increasingly reported worldwide as a cause of infectious diarrhoea in patients with prolonged hospital stay. Metronidazole and oral vancomycin are the most widely used antibiotics for its treatment.

2. What new information is offered in this review?

Research evidence suggests cadazolid, a novel oxazolidinone antibiotic, is effective against *C. difficile* both in-vivo and in-vitro, with a lower risk of development of resistance and alteration of intestinal microbiota.

3. What are the implications for research, policy, or practice?

Cadazolid has shown promising results. It may emerge as a first-line therapeutic choice for both primary and recurrent *C. difficile* infections.

Introduction

Clostridium difficile is an anaerobic spore forming gram-positive bacillus. It constitutes part of normal intestinal flora in 1–3 per cent of adults and 15–20 per cent of infants.¹ It is known to cause potentially lethal infections in both hospitalised and community patients, especially those receiving broad-spectrum antimicrobials. The incidence of *C. difficile* infection (CDI) varies from 45.7 to 155.9/100,000 in healthcare facilities.² Evidences suggest the epidemiology of CDI has changed significantly over decades.¹ Until recently, it was primarily nosocomial in nature. However, several community-acquired cases have been recently reported. The incidence of community-acquired CDI (CA-CDI) has shown an increasing trend, accounting for about 32 per cent of CDI cases in the United States.² Furthermore, occurrence of CDI has become frequent among low-risk groups (i.e., children and peripartum women).^{1,3} The worldwide increase in the incidence of CDI in recent years is attributed to excessive usage of antibiotics and proton pump inhibitors, increased incidence of inflammatory bowel disease, and growing numbers of elderly people in assisted

living facilities and nursing homes. Pseudomembranous colitis, fulminant colitis, toxic megacolon and bowel infarction are the common complications.¹ Bacterial translocation associated with bowel inflammation, infarction, and perforation often results in sepsis, systemic inflammatory response syndrome, hypotension, and renal failure.¹

Antibiotics are the mainstay of non-surgical treatment for primary and recurrent CDI. The emergence of hypervirulent strains and the risk of drug resistance among *C. difficile* is now a growing concern among clinicians.¹ Resistance to metronidazole and reduced susceptibility to vancomycin have been reported.⁴ Also, antibiotic selection is further complicated by the risk of dissemination of vancomycin resistance among *Enterococcus spp.*^{1,5} There is an increasing need and interest to counter these by developing novel therapeutic modalities. Among the newer drugs under development, cadazolid has shown initial promising results. Here, cadazolid as a prospective medical therapy for CDI is discussed in light of current clinical and experimental evidence.

***Clostridium difficile* infections**

CDI is acquired either as an endogenous (caused by carrier strains) or exogenous infection (from nosocomial sources). The ingested spores of *C. difficile* survive in gastric acid and germinate in the intestine. Altered intestinal microflora associated with medical therapy promote its colonisation, proliferation, and toxin production resulting in a carrier state, diarrhoea (*C. difficile*-associated diarrhoea), or colitis (*C. difficile*-associated colitis, pseudomembranous colitis, fulminant colitis).¹

Two major toxins (toxin A and toxin B) along with several other virulence factors (i.e., binary toxin, fimbriae, fibronectin-binding protein, Cwp84 cysteine protease, and SlpA S-layer) are implicated in the pathogenesis of CDI.

Males over 65 years, prolonged hospitalisation, and treatment with antibiotics are the major risk factors. Comorbidities like inflammatory bowel disease, immunodeficiency, diabetes, malnutrition, cancer, cystic fibrosis, and hypoalbuminaemia also contribute to disease causation.^{1,5}

Existing treatment and pitfalls

Clinical presentation of CDI varies from asymptomatic carriage or mild diarrhoea to acute abdomen with life-threatening complications. While the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) 2014

guidelines are mainly based on clinical criteria,⁶ white blood cell (WBC) count and serum creatinine levels are taken into consideration by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) Guidelines of 2010.⁷ According to it, mild to moderate CDI is defined as WBC count less than 15,000 cells per μL and a serum creatinine value less than 1.5 times the pre-morbid level, while patients with severe CDI have WBC count of 15,000 cells per μL or more with serum creatinine 1.5 times or greater in comparison to the pre-morbid level.⁷ Presence of at least one feature of severe or complicated course (i.e., shock or hypotension, ileus, megacolon) in conjunction with diarrhoea and colitis indicate severe complicated disease.⁷

The treatment depends on the severity of CDI. While metronidazole, 500mg three times daily per oral for 10–14 days is recommended for mild to moderate disease; in cases of severe CDI 125mg vancomycin should be given four times per day orally for 10–14 days.^{7,8} The dosage of vancomycin may be increased up to 500mg four times per day along with intravenous metronidazole, 500mg every eight hours in severe complicated infections. The benefits of medical therapy are often limited by antibiotic resistance and frequent relapses and recurrences. Patients with CDI who suffer from multiple relapses usually do so within two weeks of completing treatment, especially in the presence of risk factors.⁸ Although metronidazole is recommended for mild to moderate initial episodes and first recurrence of CDI, low antibiotic concentrations are achieved in the faeces. Both vancomycin and metronidazole are ineffective orally in the presence of ileus, requiring intravenous metronidazole or retrograde vancomycin therapy (rectal enema).^{7,8} Metronidazole resistance is not uncommon. An increase in metronidazole MIC in comparison to historical isolates has been reported from Spain and the United Kingdom.^{4,9}

C. difficile ribotype 001 recent isolates from the United Kingdom were found to have relatively higher metronidazole resistance (mean MIC of 5.94 mg/L) in comparison to historic isolates.⁹ Recently, heteroresistance to metronidazole has been described, which may explain its incomplete therapeutic response in CDI cases.¹⁰ Although the MICs for vancomycin in most studies were in the sensitive range, *C. difficile* isolates with reduced susceptibility to vancomycin have also been reported.⁴ Oral (or rectal enema) vancomycin using a tapered or pulse regimen is preferred in severe or recurrent CDI. Owing to the high concentration achieved in faeces with enteral vancomycin therapy, resistance development is unlikely to

be a concern. However, it is more likely to disseminate vancomycin resistance among *Enterococcus spp.*⁵

Antibiotics in *Clostridium difficile* infections

Currently, oral vancomycin and metronidazole are the drugs of choice.⁷ Fusidic acid, teicoplanin, tigecycline, rifaximin, and ramoplanin are the other agents proposed to treat CDI.¹¹ As per the SHEA-IDSA guidelines of 2010, metronidazole is not recommended in severe CDI and beyond first recurrence.⁷ There is risk of cumulative neurotoxicity with chronic use of metronidazole. Although the primary infection is often amenable to vancomycin or metronidazole, the recurrence of CDI is exceedingly high (20–30 per cent).¹² Consequently, newer therapeutic modalities like novel antibiotics, intravenous immunoglobulins, probiotics, and faecal microflora transplantation have been introduced.¹¹ Fidaxomicin, a new macrocyclic antibiotic, is recently approved for treatment of an initial episode of severe CDI as well as for recurrences. It binds to bacterial DNA-dependent RNA polymerase resulting in inhibition of RNA synthesis.¹³ Oral fidaxomicin, 200mg twice daily for 10 days, was found to be effective in reducing relapses and is crucial in treating patients with multiple risk factors, recurrent CDI and intolerance to oral vancomycin. However, it showed limited therapeutic efficacy for the ribotype 027 epidemic strain.⁸

Cadazolid molecular structure

Oxazolidinone antibiotics characteristically contain 2-oxazolidone, an organic heterocyclic compound possessing a 5-membered ring.¹⁴ Although cycloserine was the first member of this class, it has limited utility as an antibiotic (except for tuberculosis). In contrast, linezolid rapidly emerged as a popular oxazolidinone antibiotic, effective against multi-resistant, gram-positive bacteria. Cadazolid, eperezolid, tedizolid, radezolid, and posizolid are other members of this class.¹⁴ The chemical structure of cadazolid [(R)-1-cyclopropyl-6-fluoro-7-{4-[2-fluoro-4-(5-hydroxymethyl-2-oxo-oxazolidin-3-yl)-phenoxy-methyl]-4-hydroxy-piperidin-1-yl}-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid] indicates that it is a hybrid antibiotic containing a quinolone pharmacophore incorporated in an oxazolidinone ring.¹⁵ It has a 6-fluoro group in the heterobicyclic quinolone nucleus similar to that of fluoroquinolone derivatives. The quinolone pharmacophore of cadazolid contributes to bacterial DNA synthesis inhibition.^{14,15} Cadazolid is acidic and lipophilic in nature with poor solubility in aqueous solutions.¹⁶ Consequently, its systemic bioavailability is negligible, as the absorption from intestine following oral administration is minimal.

History of development

The preclinical and clinical development of cadazolid as an antibiotic for treating CDI was sponsored by Actelion Ltd.¹⁷ It has been evaluated for tolerability, safety, and pharmacokinetic profile in clinical trials. Of the six clinical trials for cadazolid in Actelion's trial registry, two multicentric, randomised, double-blind clinical trials are in phase III.¹⁸ These two studies are the essential components of the International Multi-Center Program Assessing Cadazolid Treatment (IMPACT) in *Clostridium difficile*-associated diarrhoea (CDAD). It has recently received Qualified Infectious Disease Product (QIDP) and Fast Track development designations from the United States Food and Drug Administration (FDA).¹⁷ The promising results of phase I and phase II studies support its priority on development.

Mechanisms of action

Protein synthesis inhibition is the main antibacterial action exerted by cadazolid. In addition, it weakly inhibits bacterial DNA synthesis. Locher et al. carried out a series of in-vitro tests to study the mechanism of action of cadazolid.¹⁹

Using a macromolecular labelling assay, the site of action of cadazolid in the bacterial cell was investigated by monitoring its inhibitory action on incorporation of labelled macromolecules; i.e., L-leucine (protein synthesis), adenine (nucleic acid synthesis), and N-acetyl-D-glucosamine (cell wall synthesis). Also, its influence on transcription and translation was determined by cell-free coupled transcription/translation assays (CFTA) and on DNA supercoiling and decatenation by DNA topoisomerase assays. It was found that cadazolid displayed potent protein synthesis inhibition when compared with DNA synthesis inhibition in both quinolone-resistant and linezolid-resistant *C. difficile* strains.¹⁹

Cadazolid inhibited in-vitro translation in CFTA with potency much superior to linezolid. It showed demonstrable inhibition of *E. coli* DNA gyrase and topoisomerase IV. However, it failed to show measurable inhibition of *C. difficile* DNA gyrase. On antibiotic susceptibility tests, *C. difficile* strains had much lower MIC (0.125 to 0.5 µg/ml) for cadazolid when compared with other antibiotics.¹⁵ The potency of cadazolid was higher than that of linezolid (8– to 64–fold), ciprofloxacin (64–fold), and moxifloxacin (8– to 64–fold). Nosocomial outbreaks of CDI with increase in mortality, relapses, complications intensive care admission, and surgical intervention have been reported from Canada, the United States, and several European countries in the last decade.^{7,8} The majority of the *C. difficile* isolates associated with these outbreaks belonged to ribotype 027

and toxinotype III. This new strain characteristically displayed enhanced production of toxin A and toxin B associated with *tcdC* gene mutation. High-level fluoroquinolone resistance has been frequently reported.⁸ Multilocus variable-number tandem repeat analyses (MLVA), microarray analyses, restriction endonuclease analyses (REA), pulsed-field gel electrophoresis, toxin gene polymorphism typing, and ribotyping were used extensively for typing and this emerging strain was designated as BI/NAP1/027.¹ The superior antimicrobial activity of cadazolid was also demonstrated in time kill assays. They showed more than a $3 \times \log_{10}$ CFU reduction within 24 hours for wild strains as well as hypervirulent and quinolone-resistant strains. In contrast, in the case of vancomycin the initial rate of killing was slow and $3 \times \log_{10}$ CFU reduction was not achieved.¹⁵

Cadazolid showed potent biological effects on *C. difficile* toxin and spore formation.¹⁵ Inhibition of toxin production was reported even at a lower concentration (0.25xMIC) and reached maximum potency at 1x and 4xMIC concentration. In contrast, only 4xMIC concentration of linezolid was inhibitory to *C. difficile* toxin, while other anti-*C. difficile* antibiotics showed no effect. Interestingly, moxifloxacin and vancomycin were found to increase toxin formation at sub-MIC concentration. While vancomycin at 0.5 and 1xMIC concentration failed to inhibit or delay spore formation, cadazolid markedly inhibited sporulation at sub-growth-inhibitory (0.5xMIC) concentrations and delayed new spore formation for up to five days at 1xMIC.

Effect on intestinal microbiota

Chilton et al. studied the interplay between antibiotics, intestinal microflora, and *C. difficile* using a triple-stage chemostat-based human gut model.²⁰ The chemostat was inoculated with *C. difficile*-negative pooled faecal samples. On reaching the steady-state of microbial population, the system was inoculated with 10^7 CFU spores of *C. difficile* and was exposed to clindamycin to simulate the intestinal microenvironment as in CDI. Once *C. difficile* toxin production was high, cadazolid was instilled for seven days at high- and low-dose regimens (250 mg/L or 750 mg/L twice daily). Cadazolid concentration and cytotoxin titres were monitored for 14 days. It was found that cadazolid maintained a high concentration (50–100-fold supra-MIC) for 14 days post-dosing, which resulted in rapid reduction of viable counts of *C. difficile* and cytotoxin titres. Although *Bifidobacterium* counts decreased, other beneficial gut flora remained unaffected.²⁰ Furthermore, there was no evidence of repopulation (recurrence) of *C. difficile* in this experiment.

Propensity to develop resistance

The major concern limiting the therapeutic prospect of an antibiotic is its tendency to induce resistance among pathogenic microbes with continuous use. Spontaneous mutations play an essential role in antimicrobial resistance. Locher et al. measured the spontaneous resistance frequencies in *C. difficile* strains.¹⁹ Fidaxomicin and moxifloxacin had moderately high resistance frequencies (10^{-7} to 10^{-8}) in comparison to cadazolid, linezolid, and vancomycin. Cadazolid showed very low resistance frequencies ($<10^{-10}$), minimal increase in MIC after one to three selection steps and lack of cross-resistance with other antibiotics used in CDI. It also displayed good activity against fidaxomicin- and moxifloxacin-nonsusceptible strains.¹⁹

Therapeutic efficacy, safety and tolerability

The pharmacokinetic profile and safety of cadazolid have been investigated in animal studies and human clinical trials. In one animal study, cadazolid was found to substantially prevent mortality and diarrhoea associated with CDI in mice and hamsters in a dose-dependent manner in comparison to the control animals.¹⁵ However, the results were found more reproducible in mice experiments than in hamsters. There was significant reduction in the risk of death in mice by 56, 96, and 95 per cent at 0.1, 1, and 10 mg/kg doses, respectively, during the monitoring period of 18 days.¹⁵ Although the overall rates of survival were comparable to vancomycin at the same doses, cadazolid decreased risk of death in infected mice during the monitoring period of 18 days indicating its sustained treatment effect.

Currently, there are six clinical trials for cadazolid (Table 1). Out of these, four are also registered in the US Clinical trials registry.²¹⁻²⁴ The results of phase I clinical trials evaluating the tolerability and pharmacokinetics of cadazolid following single ascending doses (SAD) and multiple ascending doses (MAD) are now available.¹⁶ The results of phase III studies are yet to be published.

In a phase I study, oral doses of cadazolid between 30mg and 3,000 mg were tested in a total of 64 healthy male subjects and cadazolid was well tolerated up to 3,000mg twice daily for 10 days. In a SAD study, 40 subjects were selected into five treatment groups consisting of eight subjects each, for administering a single dose of cadazolid of 30mg, 100mg, 300mg, 1,000mg, and 3,000mg, respectively.¹⁶ In each group, six subjects received cadazolid and the remaining two received a placebo. Likewise, the MAD study had three treatment groups (300mg, 1,000mg, and 3,000mg) of eight subjects, of which six in each group

were administered with oral cadazolid twice daily for 10 days.¹⁶ Headache and diarrhoea were the commonest adverse effects. Three out of 40 participants reported diarrhoea in the SAD study and one had loss of appetite in the MAD study. No dose-limiting adverse reaction was noted. The low plasma concentration of cadazolid (3.3 to 6.9ng/ml) is attributed to its poor intestinal absorption and consequently, its pharmacokinetic properties were detected only in the higher single dose groups and in all multiple dose groups on the 10th day. The mean $t_{1/2}$ in 300mg, 1,000mg, and 3,000mg SAD treatment groups were 2.85, 3.58, and 12.85 hours, respectively. Although food was found to increase the rate of absorption ($t_{1/2}$ in 300mg group in fed state was 6.5 hours), plasma levels remained low. After a single dose of 30, 100, 300, or 1,000mg, cadazolid remained detectable in plasma for two, four, six, and eight hours, respectively.¹¹ With multiple doses, plasma levels reached steady state after 3–4 days. The mean $t_{1/2}$ in 300mg, 1,000mg, and 3,000 mg MAD treatment groups on the 10th day were 14.04, 14.19, and 13.02 hours respectively. The antibiotic showed biphasic elimination with a slow second phase from eight hours post-dose. Cadazolid was found to have predominant faecal excretion (81–93.5 per cent) in unchanged form. The faecal recovery of unchanged drug was highest at 24 hours post-dose. Only a minor fraction of administered dose (<0.015 per cent) was recovered from the urine.

A multi-centre, double-blind, randomised phase II clinical trial was conducted to evaluate the efficacy, safety, and tolerability of 10-day, twice daily oral cadazolid therapy in 84 CDI patients.^{21,25} However, unlike the phase I study, here 250mg, 500mg, or 1,000mg doses were evaluated in three treatment groups. Cadazolid was comparable or superior to vancomycin for the key endpoints (i.e., clinical cure rates and sustained cure rates) with lower recurrence rates for all three doses. Currently, two phase III clinical trials (NCT01987895 and NCT01983683) under an IMPACT program are in the recruiting phase. Approximately 1,280 subjects worldwide are expected to enrol for these studies.²⁵

Future prospects

It is evident from the currently available data that cadazolid is one of the promising future treatment options for CDI. Its low plasma concentration and narrow antimicrobial spectrum of activity precludes its wider use in systemic and polymicrobial infections. This selective distribution of cadazolid increases its bioavailability at the site of CDI. Since the liver and kidneys have a minimal role in its metabolism and excretion, cadazolid may be safer than other antibiotics

in patients with decreased hepatic and renal functions.¹⁶ Furthermore, its antimicrobial action on *C. difficile* without adversely affecting normal intestinal microbiota is a considerable advantage over several other antibiotics.²⁰ *C. difficile* cytotoxins have an essential role in pathogenesis, whereas its spores are considered responsible for high recurrence rates.^{15,26}

Unlike other antibiotics used in CDI, cadazolid substantially inhibits toxin production and sporulation even at low (sub-MIC) concentration.¹⁵ Consequently, it is likely to prevent recurrent CDI more effectively. Its novel molecular structure, dual mechanism of action (strong inhibition of protein synthesis and weak inhibition of DNA synthesis) and lower propensity to develop resistance are other potential advantages. However, there are certain aspects of cadazolid that are yet to be explored. There are no data concerning its use in CDI patients with extraintestinal lesions; it is unlikely to be effective in extraintestinal CDI. Also, its teratogenic potential is unknown. Intestinal inflammation is a common feature of CDI and it may affect the absorption of cadazolid. Hence, there is a need to study its absorption from the inflamed gut and consequent plasma concentrations in human patients to standardise therapeutic regimens.

Conclusion

Cadazolid is a novel hybrid of oxazolidinone and quinolone antibiotics. It was found to have potent antimicrobial action for *C. difficile* without the major limitations (i.e., high recurrence, risk of resistance development, and intestinal dysbiosis) of antibiotics currently in use for CDI. With further clinical development cadazolid and other compounds of this class may emerge as primary therapeutic choices for CDI in near future. However, further studies are essential to define its clinical utility.

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PEER REVIEW

Not commissioned.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

Table 1: Clinical trials of cadazolid

Trial numbers NCT Number (Phase)	Official title	Inclusion criteria	Exclusion criteria	Primary outcomes	Secondary outcomes
AC-061-101 (Phase I)	A Phase I, double-blind, placebo-controlled study to investigate the safety, tolerability, and pharmacokinetics (including food Interaction) of single ascending doses of ACT-179811 in healthy male subjects	Non-smoking, healthy male subjects of any ethnic origin aged between 45 and 65 years with a body mass index between 18 and 32 kg/m ²	Use of any antibiotic within the previous three months	Pharmacokinetics, safety, and tolerability of cadazolid in healthy male subjects following single ascending doses.	
AC-061-102 (Phase I)	A phase 1, double-blind, placebo-controlled, randomised, multiple-ascending-dose study to investigate the safety, tolerability, and pharmacokinetics of ACT-179811 in healthy male subjects	Non-smoking, healthy male subjects of any ethnic origin aged between 45 and 65 years with a body mass index between 18 and 32 kg/m ²	Use of any antibiotic within the previous three months	Pharmacokinetics, safety, and tolerability of cadazolid in healthy male subjects following multiple ascending doses	
AC-061-103 NCT02053181 (Phase I)	A phase 1, open-label, single oral dose study to investigate the pharmacokinetics, safety, and tolerability of cadazolid in patients with severe <i>Clostridium difficile</i> Infection (CDI)	<ul style="list-style-type: none"> * Signed informed consent prior to any study-mandated procedure * Non-pregnant females were to remain non-pregnant for one month after the end of the study. * Subjects with severe CDAD * Received oral vancomycin or oral/intravenous (i.v.) metronidazole therapy for the treatment of CDAD 	<ul style="list-style-type: none"> * Known hypersensitivity to any excipients of the drug formulation. * Clinical evidence of any relevant disease other than CDAD and/or existence of any surgical or medical condition that might interfere with the absorption, distribution, metabolism, or excretion of the study drug. * Veins unsuitable for i.v. puncture on either arm (e.g., veins that are difficult to locate, access, or puncture; veins with a tendency to rupture during or after puncture). * Subjects with rare hereditary fructose intolerance, glucose-galactose malabsorption, saccharase-isomaltase deficiency, or previously undiagnosed diabetes mellitus. * Subjects who have a life-threatening condition, which may be related to CDAD or other underlying 	<ul style="list-style-type: none"> * Maximum plasma concentration (C_{max}) * Time to reach maximum plasma concentration (t_{max}) * Area under the plasma concentration-time curve * Unchanged cadazolid in urine up to Day 7 * Unchanged cadazolid in faeces up to Day 7 	<ul style="list-style-type: none"> * Change from baseline up to Day 7 in systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, and body weight * Change from baseline up to Day 7 in heart rate, PQ interval, QRS duration, QT interval, QT interval according to Bazett's correction (QTcB) and QT interval according to Fridericia's correction (QTcF) * Frequency of treatment-emergent ECG abnormalities from up to Day 7

		<ul style="list-style-type: none"> * Ability to communicate well with the investigator in the local language, and to understand and comply with the requirements of the study. 	<ul style="list-style-type: none"> illness. * Any clinically relevant electrocardiogram (ECG) abnormality at screening. * Subjects who were unable to swallow or have difficulty swallowing. * Subjects with vomiting, ileus or not passing stool. * Likelihood of death within 72 hours from any cause. * Life-threatening or fulminant CDAD (White blood cell count $>30 \times 10^9/L$; temperature $>40^\circ C$; or septic shock, peritoneal signs or significant dehydration). * History of ulcerative colitis or Crohn's disease. * Loss of 250ml or more of blood within three months prior to screening. * Positive results from the hepatitis serology, except for vaccinated subjects, at screening. * Positive results from the human immunodeficiency virus (HIV) serology at screening. * Legal incapacity or limited legal capacity at screening. * Any circumstances or conditions, which, in the opinion of the investigator, may affect full participation in the study or compliance with the protocol. 		
AC-061A201 NCT01222702 (Phase II)	Multi-centre, double-blind, randomised, active reference, parallel group study to evaluate the efficacy, safety, and tolerability of three doses of ACT-179811 in subjects with <i>Clostridium difficile</i> Infection	<ul style="list-style-type: none"> * Male or female * At least 18 years old * CDI 1st occurrence or 1st recurrence 	<ul style="list-style-type: none"> * Concurrent life threatening condition * Concomitant antimicrobial treatment for CDI * Concomitant treatment with another investigational drug 	Clinical cure rate after treatment of ACT-179811 (cadazolid).	Disease recurrence rate following treatment with ACT-179811 (cadazolid).
AC-061A301 NCT01987895 (Phase III)	A multi-centre, randomised, double-blind study to compare the efficacy and safety of cadazolid versus vancomycin in subjects With <i>Clostridium difficile</i> -associated diarrhoea (CDAD)	<ul style="list-style-type: none"> * Signed informed consent * Male or female ≥ 18 years of age. Females of childbearing potential must agree to use an adequate and reliable method of contraception 	<ul style="list-style-type: none"> * More than one previous episode of CDAD in the three-month period prior to randomisation. * Evidence of life-threatening or fulminant CDAD. * Likelihood of death within 72 hours from any cause. * History of inflammatory colitides, chronic abdominal pain, or chronic diarrhoea. * Antimicrobial treatment active against CDAD administered for >24 hours except for 	Clinical cure at end of treatment (resolution of diarrhea and no additional CDAD treatment.)	<ul style="list-style-type: none"> * Sustained cure (clinical cure and no recurrence). * Time to resolution of diarrhoea * CDAD Symptoms

		<ul style="list-style-type: none"> * Subject with a diagnosis of mild-moderate or severe CDAD 	<ul style="list-style-type: none"> metronidazole treatment failures * Known hypersensitivity or contraindication to study drugs, oxazolidinones, or quinolones. * Unable or unwilling to comply with all protocol requirements. 		
<p>AC-061A302 NCT01983683</p> <p>(Phase III)</p>	<p>A multi-centere randomised, double-blind study to compare the efficacy and safety of cadazolid versus vancomycin in subjects With Clostridium difficile-associated diarrhoea (CDAD)</p>	<ul style="list-style-type: none"> * Signed informed consent. * Male or female ≥ 18 years of age. Females of childbearing potential must agree to use an adequate and reliable method of contraception * Subject with a diagnosis of mild-moderate or severe CDAD 	<ul style="list-style-type: none"> * More than one previous episode of CDAD in the three-month period prior to randomisation. * Evidence of life-threatening or fulminant CDAD. * Likelihood of death within 72 hours from any cause. * History of inflammatory colitides, chronic abdominal pain, or chronic diarrhoea. * Antimicrobial treatment active against CDAD administered for >24 hours except for metronidazole treatment failures * Known hypersensitivity or contraindication to study drugs, oxazolidinones, or quinolones. * Unable or unwilling to comply with all protocol requirements. 	<ul style="list-style-type: none"> * Clinical cure at end of treatment (resolution of diarrhoea and no additional CDAD treatment). 	<ul style="list-style-type: none"> * Sustained cure (clinical cure and no recurrence). * Time to resolution of diarrhoea * CDAD Symptoms