CLOSTRIDIUM DIFFICILE INFECTION (CDI): THE HIDDEN BURDEN
Introduction to Clostridium difficile

- *C. difficile* is a Gram-positive, spore-forming, anaerobic bacillus that was first identified in 1935\(^1\)
- *C. difficile* is the leading cause of infectious nosocomial diarrhoea in industrialised countries\(^2\)
- *C. difficile* passes through a life cycle where it exists in two forms; as vegetative cells and as spores\(^3\)


Vegetative form

Spores surrounding a vegetative cell

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Cycle of infection with *C. difficile*

*C. difficile* spores and vegetative cells are ingested

Most vegetative cells are killed in the stomach, but spores can survive the acid environment

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Key steps in the pathogenesis of CDI

1. Antibacterial therapy
2. Alteration of colonic microflora
3. *C. difficile* exposure and colonisation
4. Release of toxins A and B
5. Colonic mucosal injury and inflammation

Kelly & LaMont. Annu Rev Med 1998;49:375–90. Figure reproduced with permission
Role of host antibody-mediated responses in CDI pathogenesis

Patients with risk factors for CDI, including antibacterial use in hospital setting

Exposure to toxigenic *C. difficile* accompanied by IgG response to toxin A

Exposure to toxigenic *C. difficile* without an IgG response to toxin A

Exposure to non-toxigenic *C. difficile*

Asymptomatically colonised

Asymptomatically colonised

Symptomatic CDI

*C. difficile* negative

CDI, *Clostridium difficile* infection; IgG, Immunoglobulin G antibody


Figure reproduced with permission
Clinical presentation of infection with *C. difficile*

- Asymptomatic colonisation
- Diarrhoea without colitis
  - Watery
  - Mucus but no blood
- Colitis without pseudomembrane formation
- Pseudomembranous colitis
- Fulminant colitis

The incidence of recurrent CDI

Initial episode of CDI

1st recurrence of CDI

Recurrence(s) of CDI

- Up to 25% of patients have recurrent CDI\textsuperscript{1–3}
- \textasciitilde 45–65\% of patients have further recurrences\textsuperscript{4,5}

Risk factors for a recurrence of CDI

• Immunocompromised state¹
• Exposure to other antibacterial agents that disrupt the normal colonic microflora²–⁵
• Renal impairment⁶,⁷
• Aged 65 years or over²,⁴,⁸
• Impaired immune response to C. difficile toxin A²
• Severe underlying disease²
• Prolonged hospitalisation⁸
• ICU stay⁵

Burden of CDI

- Patients with CDI may suffer significant pain and discomfort as a result of their infection.
- Recurrence is common (up to 25%) following treatment with metronidazole and vancomycin\(^1\)\(^{-3}\)
- Mortality rates of 2–7% have been reported in patients with CDI\(^4\),\(^5\)
- CDI imposes a significant economic burden on healthcare systems across Europe, and this is expected to rise over the next four decades\(^6\)

Mortality rates associated with CDI across Europe

Data from a systematic review found the weighted average 30-day mortality from CDI ranged from 3–30%.

Age-specific incidence of CDI and attributable mortality

Risk factors among HSCT recipients for CDI

- Multiple antibiotic courses (cephalosporins, quinolones)$^{1,2}$
- Altered integrity of intestinal mucosa (chemotherapy/total body irradiation)$^{1–3}$
- Source of stem cells: cord blood$^3$
- VRE colonisation$^2$
- Renal impairment$^2$
- Acute graft versus host disease (GvHD)$^{1–3}$
- Immune suppression (pre-engraftment phase)$^{4,5}$
- Diabetes mellitus$^5$
- Prolonged and repeated hospital stays$^{1,4}$

4. Anathakrishnan AN. Nat Rev Gastroenterol Hepatol 2011;8:17–26;
### Incidence of CDI in HSCT recipients

<table>
<thead>
<tr>
<th>Author</th>
<th>Transplant type</th>
<th>N</th>
<th>Episodes of diarrhoea&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CDI/episode of diarrhoea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mossad 1996</td>
<td>Auto-HSCT</td>
<td>219</td>
<td>76 (34.7%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Yuen 1998</td>
<td>NS</td>
<td>120</td>
<td>141&lt;sup&gt;c&lt;/sup&gt;</td>
<td>15 (10.6%)</td>
</tr>
<tr>
<td>Avery 2000</td>
<td>Auto-HSCT</td>
<td>80</td>
<td>61 (76.3%)</td>
<td>3 (4.9%)</td>
</tr>
<tr>
<td>Bilgrami 1999</td>
<td>Auto-HSCT</td>
<td>200</td>
<td>NS</td>
<td>15 (7.5%)</td>
</tr>
<tr>
<td>Barton 2001</td>
<td>Auto-HSCT</td>
<td>127</td>
<td>NS</td>
<td>14 (11.0%)</td>
</tr>
<tr>
<td>Gorschluter 2001</td>
<td>NS</td>
<td>371</td>
<td>NS</td>
<td>61 (6.9%)</td>
</tr>
<tr>
<td>Tomblyn 2002</td>
<td>Both</td>
<td>119</td>
<td>109 (91%)</td>
<td>7 (6.4%)</td>
</tr>
<tr>
<td>Jillella 2003</td>
<td>Auto-HSCT</td>
<td>54</td>
<td>15 (27.8%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Arango 2006</td>
<td>Auto-HSCT</td>
<td>242</td>
<td>157 (64.8%)</td>
<td>21 (15.5%)</td>
</tr>
<tr>
<td>Cox 1994</td>
<td>Both</td>
<td>296</td>
<td>150 (50.7%)</td>
<td>6 (4.0%)</td>
</tr>
<tr>
<td>van Kraaj 2000</td>
<td>Both</td>
<td>60</td>
<td>48 (80%)</td>
<td>2 (4.2%)</td>
</tr>
<tr>
<td>Chakrabarti 2000</td>
<td>Allo-HSCT</td>
<td>75</td>
<td>49 (65.3%)</td>
<td>10 (20.4%)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Episodes of diarrhoea per number of patients in the study population;  <sup>b</sup>Total number of infectious complications;  <sup>c</sup>Every patient had at least one episode of diarrhoea;  

* HSCT, haematopoietic stem cell transplantation;  

Epidemiology and outcomes of CDI in HSCT recipients: USA, 2003 to 2008

1-year incidence of CDI by transplant type

- Autologous (N=489) [overall incidence, 6.5%]
- Allogeneic (N=510) [overall incidence, 12.5%]
- All transplants (N=999) [overall incidence, 9.2%]

- Overall CDI incidence did not vary significantly from 2003 to 2008
Timing of CDI by HSCT type

Autologous (N=30)

Allogeneic (N=62)

Day of transplant

Number of cases

Time to CDI (days)

Median time of onset

6.5 days

33 days
Acute GvHD among allogeneic HSCT recipients with and without CDI

The 1-year probability of developing grade 2 or higher gastrointestinal GvHD was 25% in case patients and 4.6% in control patients (log-rank test; p=0.0001)

Cumulative probability of acute GI GvHD (grade 2 or higher)

Time from stem cell transplant (days)

GvHD, graft versus host disease

Survival among allogeneic HSCT recipients with and without CDI

- Median survival was 100 days in patients with CDI vs 41 months in patients without CDI (p=0.01)

The potential rising economic burden of CDI

- Estimates suggest the potential costs associated with management of CDI in Europe are in the region of:

  €3,000 million per year...
  ... and rising

- The problem is expected to increase:
  - By 2050, more than 134 million Europeans will be aged at least 65 years

## Antibacterials and risk of colonisation with *C. difficile*

<table>
<thead>
<tr>
<th>Risk for colonisation with <em>C. difficile</em></th>
<th>Antibacterials</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Clindamycin; second- and third-generation cephalosporins; certain fluoroquinolones</td>
</tr>
<tr>
<td>Medium</td>
<td>Macrolides; amoxicillin/ampicillin; amoxicillin/clavulanic acid</td>
</tr>
<tr>
<td>Low</td>
<td>Aminoglycosides; vancomycin; trimethoprim; tetracyclines; benzylpenicillin; anti-pseudomonal penicillins ± beta-lactamase inhibitor</td>
</tr>
</tbody>
</table>

Recurrence of CDI

• Recurrence of CDI has been identified by ESCMID as the most important problem in the treatment of CDI\textsuperscript{1}
• CDI recurrence is common, occurring in up to 25% of cases within 30 days following treatment\textsuperscript{2–4}
• Recurrence appears to be related to a combination of:\textsuperscript{5}
  – A failure to re-establish the colonic microflora
  – The presence in the intestines of spores of \textit{C. difficile}
  – A sub-optimal host immune response to the infecting organism and its toxins

\textsuperscript{1} Bauer et al. Clin Microbiol Infect 2009;15:1067–79;
\textsuperscript{4} Bouza et al. Clin Microbiol Infect 2008;14(Suppl 7):S103–4;
CURRENT MANAGEMENT OF CLOSTRIDIUM DIFFICILE INFECTION (CDI)
ESCMID recommended diagnostic algorithm for CDI

Toxin detection or bacterial detection

EIA to detect TcdA and TcdB

- +
  - No CDI

EIA to detect GDH, or real-time PCR to detect TcdB

- - +
  - No CDI
  - C. difficile toxins are not detectable in faeces but C. difficile is present; CDI cannot be excluded

EIA to detect GDH, or real-time PCR to detect TcdB, or cytotoxicity assay

- +
  - CDI is diagnosed

High clinical suspicion: toxigenic culture

- -
  - CDI is diagnosed

EIA to detect TcdA, and TcdB, or cytotoxicity assay

- +
  - CDI is diagnosed


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Pharmacotherapy of CDI: First episode

- Aim of treatment is to eradicate *C. difficile* from the intestines and promote restoration of the normal colonic microflora
- Cessation of antibacterial therapy, if possible, is usually the first step

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ESCMID recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-severe first episode</td>
<td>• Metronidazole 500 mg tid orally for 10 days*</td>
</tr>
<tr>
<td>Severe first episode</td>
<td>• Vancomycin 125 mg qid orally for 10 days</td>
</tr>
<tr>
<td></td>
<td>• IV metronidazole 500 mg tid for 10 days plus intracolonic vancomycin 500 mg in 100 mL saline every 4–12 hours and/or vancomycin 500 mg qid by nasogastric tube if oral therapy impossible</td>
</tr>
</tbody>
</table>

*IV if oral therapy is not possible

Pharmacotherapy of CDI: First recurrence

- ESCMID has identified recurrence as being the most important problem in the treatment of CDI
  - Up to 25% of patients suffer a recurrence within 30 days following treatment
- ESCMID recommends treating a first recurrence as a first episode unless the disease has progressed from non-severe to severe

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</tr>
<tr>
<td></td>
<td>vancomycin 500 mg qid by nasogastric tube if oral therapy</td>
</tr>
<tr>
<td></td>
<td>impossible</td>
</tr>
</tbody>
</table>

*IV if oral therapy is not possible

Pharmacotherapy of CDI: Second and later recurrences

- ESCMID recommends treating second or later recurrences in the same way as severe first recurrence
  - With the option of using tapered or pulsed dosing regimens

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ESCMID recommended treatment</th>
</tr>
</thead>
</table>
| Second and later recurrences     | Vancomycin 125 mg qid orally for at least 10 days
|                                  | • Consider tapering vancomycin dose by decreasing daily dose with 125 mg every 3 days
|                                  | • Consider pulse dosing with vancomycin 125 mg every 3 days for 3 weeks
|                                  | IV metronidazole 500 mg tid for 10–14 days plus retention enema of vancomycin 500 mg in 100 mL saline every 4–12 hours and/or vancomycin 500 mg qid by nasogastric tube if oral therapy impossible |

ESCMID recommendations for surgical intervention

- In the minority (<5%) of patients who develop fulminant colitis, surgical intervention (colectomy) may be needed.
- Surgical intervention carries a high rate of mortality.
- Optimal timing for colectomy has not been established.
- Current guidelines recommend intervention before:
  - The disease becomes too severe
  - Serum lactate levels exceed 5 mmol/L

Clinical limitations associated with current treatments for CDI

• Although metronidazole and vancomycin are effective in a first episode of CDI, therapy remains suboptimal

• Among the most significant drawbacks of current therapy for CDI are:
  – Rates of treatment failure with metronidazole of approximately 18%\(^1\)
  – Rates of recurrent infection following treatment with metronidazole and vancomycin of up to 25% within 30 days following treatment\(^2–4\)
  – Risk of overgrowth of vancomycin-resistant enterococci (VRE) in patients who are already colonised with VRE\(^5\)

Rates of treatment failure with metronidazole


Note: the dates relate to the year of publication not the year of the study
ND: no data
Rates of disease recurrence with metronidazole and vancomycin


Note: the dates relate to the year of publication not the year of the study
Rationale for a new treatment

• CDI remains a disease for which there are significant unmet needs e.g.:
  – Therapy to provide sustained clinical cure (defined as clinical cure without recurrence)
  – Therapy to reduce recurrence (relapse and/or reinfection)
  – Better identification of patients at risk of recurrence or those for whom the impact of recurrence would be most dramatic

• A new agent that effectively treats an acute episode of CDI but also markedly reduces recurrence would represent a significant therapeutic advance
Fidaxomicin (DIFICLIR™) chemical structure

- First in a new class of antibacterials known as macrocycles
- Fermentation product from *Dactylosporangium aurantiacum*
- Unsaturated 18-membered macrocyclic core with two highly functionalised sugars as side chains
- Main metabolite of fidaxomicin is the hydrolysis product, OP-1118

Summary

• Fidaxomicin is the first member of the new class of macrocyclic antibacterials which targets bacterial DNA-dependent RNA polymerase
• Systemic absorption of fidaxomicin is low
• Fidaxomicin undergoes metabolism to the active metabolite, OP-1118
• Fidaxomicin is excreted in the faeces with near-complete faecal recovery of parent drug or its metabolite OP-1118
  – Most drug remains in the gastrointestinal tract, the prime site of drug exposure
  – Faecal concentrations far exceed the MIC$_{90}$ for C. difficile
• No dose adjustment is necessary when fidaxomicin is co-administered with drugs that are CYP substrates
• No dose adjustment is necessary in older patients (≥65 years) undergoing treatment for CDI with fidaxomicin
Activity against other Gram-positive bacteria

• Fidaxomicin is not significantly active against *Streptococcus* spp.
  – MICs are typically in the range of 16–128 μg/mL\(^1\)
• Fidaxomicin has MICs in the range of 2–16 μg/mL against *Enterococcus* spp.
  – Fidaxomicin is 2–4-fold less active against *Enterococci* than vancomycin (MIC range 0.5–4 μg/mL\(^1\))
  – This more modest activity of fidaxomicin against *Enterococci* may prove beneficial in reducing colonisation with VRE\(^2\)

Low risk of acquisition of VRE

Comparative effects of fidaxomicin and vancomycin on acquisition of VRE

Post-antibiotic effect

• Due to the rapid transit time in the bowel associated with severe diarrhoea there is a risk that a drug is eliminated from the bowel before the next dose is given.

• Antibacterials with a prolonged PAE may have the potential to provide antibacterial activity against *C. difficile* even in the absence of therapeutic concentrations:
  – This may offer protection between doses.
  – A prolonged PAE may also permit less frequent dosing.

• PAE for fidaxomicin was 5.5 h vs. 1.5–3 h for vancomycin.

Inhibition of *C. difficile* sporulation

Effect of exposure to fidaxomicin or vancomycin on sporulation by *C. difficile* strain ATCC 43255

![Graph showing sporulation inhibition](image)

- **Control (no drug)**
- **Fidaxomicin (1/4 x MIC)**
- **Vancomycin (1/4 x MIC)**

Gomez et al. ICAAC 2011;C1-632.

Figure reproduced with permission
Inhibition of *C. difficile* toxin production

Effect of exposure to fidaxomicin and vancomycin on *C. difficile* toxin production

- Control (no drug)
- Fidaxomicin (1/4 x MIC)
- Fidaxomicin (1/8 x MIC)
- Vancomycin (1/4 x MIC)

Sims et al. ICAAC 2011;C1-634.
Emergence of resistance to fidaxomicin

- Low propensity for resistance development\(^1\)
- Low frequency of spontaneous resistance (FSR)\(^2\)
  - FSR for fidaxomicin and vancomycin at 8 × MIC: \(<1.41 \times 10^{-9}\) to \(<4.13 \times 10^{-9}\)
- No MIC shift seen after 12 serial passages\(^3\)
- No shifts in MIC developed during fidaxomicin therapy in either of the phase 3 trials\(^3,4\)
- No cross-resistance with existing classes of antibacterial agents\(^2\)

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2. Astellas Pharma Europe Ltd. Data on file, FDX/11/0024/EU;
3. Astellas Pharma Europe Ltd. Data on file, FDX/11/0009/EU;
CLINICAL EFFICACY OF FIDAXOMICIN IN CDI
Phase 3 registration trials: Study design

Fidaxomicin 200 mg bid

Baseline assessment

10 days of treatment

Assessment at end of treatment

Assessment at end of study

Vancomycin 125 mg qid

30-day follow up

## Phase 3 registration trials: Inclusion/exclusion criteria

### Inclusion criteria
- Adult (≥16 years)
- Confirmed diagnosis of CDI:
  - Diarrhoea defined as >3 UBM in a 24-hour period
  - Presence of *C. difficile* toxins A or B in stool within 48 hours of randomisation
- Primary episode or first recurrence of CDI

### Exclusion criteria
- Life-threatening or fulminant CDI
- Toxic megacolon
- Previous exposure to fidaxomicin
- >1 recurrence or relapse within 3 months
- Concurrent antibacterial therapy with likely effectiveness in treating CDI such as oral vancomycin,* metronidazole,* bacitracin or fusidic acid
- Crohn's disease or ulcerative colitis
- Use of antidiarrhoeal drugs such as loperamide

UBM = unformed bowel movement

*≤4 doses and ≤24 hours of pre-treatment allowed
## Phase 3 registration trials: Endpoints

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRIMARY ENDPOINT</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical cure</td>
<td>• Resolution of diarrhoea (≤3 UBM/day for two consecutive days)</td>
</tr>
<tr>
<td></td>
<td>• Maintenance of resolution for the duration of therapy</td>
</tr>
<tr>
<td></td>
<td>• No further requirement for therapy from Day 2 following EOT</td>
</tr>
<tr>
<td><strong>SECONDARY ENDPOINTS</strong></td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>• Reappearance of &gt;3 diarrhoeal stools per 24-hour period within 30 days of cessation of therapy</td>
</tr>
<tr>
<td></td>
<td>• The presence of <em>C. difficile</em> toxin A or B, or both, in stool</td>
</tr>
<tr>
<td></td>
<td>• The need for re-treatment for CDI</td>
</tr>
<tr>
<td>Time to resolution of diarrhoea</td>
<td>• Time elapsing from start of treatment to resolution of diarrhoea (first of two consecutive days of ≤3 UBM that are sustained through EOT)</td>
</tr>
<tr>
<td>Sustained clinical cure</td>
<td>• Clinical cure without recurrence during the 30-day follow-up period</td>
</tr>
</tbody>
</table>

UBM = unformed bowel movement
Astellas Pharma Europe Ltd. Data on file, FDX/11/0012/EU;
Astellas Pharma Europe Ltd. Data on file, AI/11/0003/EU.
# Demographic and baseline clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study 003</th>
<th></th>
<th>Study 004</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fidaxomicin (N=287)</td>
<td>Vancomycin (N=309)</td>
<td>Fidaxomicin (N=252)</td>
<td>Vancomycin (N=257)</td>
</tr>
<tr>
<td>Mean age (SD), years</td>
<td>60.3 (± 16.9)</td>
<td>62.9 (± 16.9)</td>
<td>64.3 (± 17.9)</td>
<td>62.5 (± 18.4)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>57.1</td>
<td>54.7</td>
<td>58.7</td>
<td>63.0</td>
</tr>
<tr>
<td>Mean number UBM per day (SD)</td>
<td>8.1 (± 4.2)</td>
<td>8.3 (± 5.4)</td>
<td>7.5 (± 4.4)</td>
<td>7.4 (± 4.4)</td>
</tr>
<tr>
<td>Inpatient (%)</td>
<td>58.2</td>
<td>60.5</td>
<td>69.0</td>
<td>67.3</td>
</tr>
<tr>
<td>Previous metronidazole failure (%)</td>
<td>4.5</td>
<td>5.5</td>
<td>4.8</td>
<td>3.1</td>
</tr>
<tr>
<td>Treatment for <em>C. difficile</em> in previous 24 hours (%)</td>
<td>38.3</td>
<td>39.8</td>
<td>38.4</td>
<td>38.1</td>
</tr>
<tr>
<td>Previous episode of CDI (%)</td>
<td>16.7</td>
<td>17.5</td>
<td>15.9</td>
<td>14.0</td>
</tr>
<tr>
<td>BI/NAP1/027 strain* (%)</td>
<td>37.5</td>
<td>38.6</td>
<td>33.2</td>
<td>33.1</td>
</tr>
</tbody>
</table>

*Percentages based on patients with typed isolates only (study 003, n=415; study 004, n=377)

Rates of recurrence

Astellas Pharma Europe Ltd. Data on file, FDX/11/0012/EU;
Astellas Pharma Europe Ltd. Data on file, AI/11/0004/EU.
## Disease severity at baseline

<table>
<thead>
<tr>
<th>Baseline disease severity, n %</th>
<th>Study 003</th>
<th></th>
<th>Study 004</th>
<th></th>
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</tr>
<tr>
<td>Mild</td>
<td>64 (22.3)</td>
<td>80 (25.9)</td>
<td>77 (30.6)</td>
<td>95 (37.0)</td>
</tr>
<tr>
<td>Moderate</td>
<td>111 (38.7)</td>
<td>106 (34.3)</td>
<td>82 (32.5)</td>
<td>73 (28.4)</td>
</tr>
<tr>
<td>Severe</td>
<td>112 (39.0)</td>
<td>123 (39.8)</td>
<td>90 (35.7)</td>
<td>88 (34.2)</td>
</tr>
</tbody>
</table>

Baseline disease severity categories defined as: Mild, 4–5 UBM/day or WBC ≤12,000/mm³; Moderate, 6–9 UBM/day or WBC 12,001–15,000 mm³; Severe, ≥10 UBM/day or WBC ≥15,001/mm³.
Rates of sustained clinical cure

Astellas Pharma Europe Ltd. Data on file, FDX/11/0012/EU;
Astellas Pharma Europe Ltd. Data on file, AI/11/0004/EU.
Rates of clinical cure

Astellas Pharma Europe Ltd. Data on file, FDX/11/0012/EU;
Astellas Pharma Europe Ltd. Data on file, AI/11/0004/EU.
Clinical cure in patients on concomitant antibiotics

Effect of concomitant antibiotics on sustained clinical cure

Data from pooled analysis

Recurrence in patients with renal impairment

Data from pooled analysis

Astellas Pharma Europe Ltd. Data on file, FDX/11/0013/EU.
Summary (1)

- Fidaxomicin is non-inferior to vancomycin in the treatment of CDI and achieves similar clinical cure rates.
- High rates of clinical cure and low rates of recurrence with fidaxomicin translate into clinically significant improvements in sustained clinical cure compared with vancomycin.
- Fidaxomicin is significantly more effective than vancomycin in reducing recurrence of CDI, achieving a 47% reduction relative to vancomycin.
- Fidaxomicin is the first antibacterial to demonstrate lower recurrence rates for CDI versus vancomycin.
# Time to resolution of diarrhoea

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</tbody>
</table>

- No statistically significant differences between treatments with respect to time to resolution of diarrhoea

---


Data from mITT population
Time to resolution of diarrhoea in patients with cancer

Log-rank p-value = 0.0450

Proportion of subjects with ≤3 UBM/day

Time to resolution of diarrhoea (hours)

Fidaxomicin (n=87)
Vancomycin (n=96)

Data from pooled analysis;
UBM, unformed bowel movement

Cornely OA, et al. Poster presented at ASCO 2012; 41F.
Summary (2)

- Consistent with the results for the whole study population, the benefits in recurrence and sustained clinical cure rates for fidaxomicin versus vancomycin were also seen in patients aged ≥65 years.
- Fidaxomicin is as effective as vancomycin in patients infected with the hypervirulent 027 strain of C. difficile.
- In a subpopulation analysis of patients receiving concomitant antibacterial therapy, those treated with fidaxomicin exhibited significantly better rates of clinical cure versus those treated with vancomycin.
- Fidaxomicin treatment was associated with significantly lower rates of recurrence compared with vancomycin in patients who received concomitant antibacterials.
- Fidaxomicin achieved significantly greater rates of sustained clinical cure for CDI in patients who received concomitant antibacterial therapy.
- Treatment with fidaxomicin was associated with significantly lower rates of recurrence of CDI compared to vancomycin in patients with various levels of renal impairment.
- Patients with recurrent CDI treated with fidaxomicin were significantly less likely to experience another recurrence of CDI versus those treated with vancomycin.
SAFETY AND TOLERABILITY OF FIDAXOMICIN
## Overview of AEs in phase 3 trials

<table>
<thead>
<tr>
<th>Type of event, n (%)</th>
<th>Fidaxomicin (N=564)</th>
<th>Vancomycin (N=583)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>373 (66.1)</td>
<td>372 (63.8)</td>
</tr>
<tr>
<td>Study drug related AE</td>
<td>60 (10.6)</td>
<td>65 (11.1)</td>
</tr>
<tr>
<td>AEs leading to discontinuation of study drug or discontinuation from the study</td>
<td>45 (8.0)</td>
<td>49 (8.4)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>145 (25.7)</td>
<td>135 (23.2)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>36 (6.4)</td>
<td>38 (6.5)</td>
</tr>
</tbody>
</table>

Pooled data from phase 3 trials

Astellas Pharma Europe Ltd. Data on file, FDX/11/0015/EU.
## Most common AEs

<table>
<thead>
<tr>
<th>Preferred AE term, n (%)</th>
<th>Fidaxomicin (N=564)</th>
<th>Vancomycin (N=583)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>373 (66.1)</td>
<td>372 (63.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>56 (9.9)</td>
<td>58 (9.9)</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>40 (7.1)</td>
<td>35 (6.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>35 (6.2)</td>
<td>25 (4.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>34 (6.0)</td>
<td>34 (5.8)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>32 (5.7)</td>
<td>18 (3.1)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>17 (3.0)</td>
<td>26 (4.5)</td>
</tr>
</tbody>
</table>

Pooled data from phase 3 trials

Astellas Pharma Europe Ltd. Data on file, FDX/11/0015/EU.
Summary (1)

• Consistent with the results for the whole study population, the benefits in recurrence and sustained clinical cure rates for fidaxomicin vs vancomycin were also seen in patients aged ≥65 years¹

• In a subpopulation analysis of patients receiving concomitant antibacterial therapy, those treated with fidaxomicin exhibited significantly better rates of clinical cure vs those treated with vancomycin²

• Fidaxomicin achieved significantly greater rates of sustained clinical cure for CDI in patients who received concomitant antibacterial therapy²

1. Astellas Pharma Europe Ltd. Data on file, FDX/13/0001/EU;
Summary (2)

• Fidaxomicin was non-inferior to vancomycin for the clinical cure of CDI in patients with all levels of renal impairment¹

• Fidaxomicin resulted in lower rates of CDI recurrence than vancomycin in patients with renal impairment, although statistical significance was only reached for patients with mild renal impairment¹

• Consistent with the results for the whole study population, the benefits in recurrence and sustained clinical cure rates for fidaxomicin vs vancomycin were also seen in patients with cancer²

1. Astellas Pharma Europe Ltd. 2012 Data on file, FDX/12/0007/EU;