The Good, the Bad and the Ugly: Fidaxomicin

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Disclosures

I have received consultancy and advisory fees, honoraria and expenses payments from Astellas Pharma and from Genentech.

July 5, 2012 8:00 AM | Financial | Regulatory | Pharmaceuticals Products

SAVE

DIFICID™ (fidaxomicin), a first-in-class antibiotic, now approved in Canada to treat C. difficile, a serious and life-threatening infection

TORONTO, July 5, 2012 /CNW/ - Optimer Pharmaceuticals Canada, Inc. announced today the approval of DIFICID (fidaxomicin) by Health Canada for the treatment of *Clostridium difficile* infection (CDI) in patients 18 years of age and older. DIFICID was approved in Canada on a priority basis recognizing the critical need for new options to treat this

Optimer Pharmaceuticals, Inc. (NASDAQ: OPTR) and Astellas Pharma Europe Ltd., Astellas Pharma Inc. (Tokyo: 4503) announced today that the European Commission

...rketing Authorization for DIFICLIR™ (fidaxomicin)
...m difficile Infections

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FDA NEWS RELEASE

For Immediate Release: May 27, 2011
Media Inquiries: Morgan Liscinsky, 301-796-0397, morgan.liscinsky@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

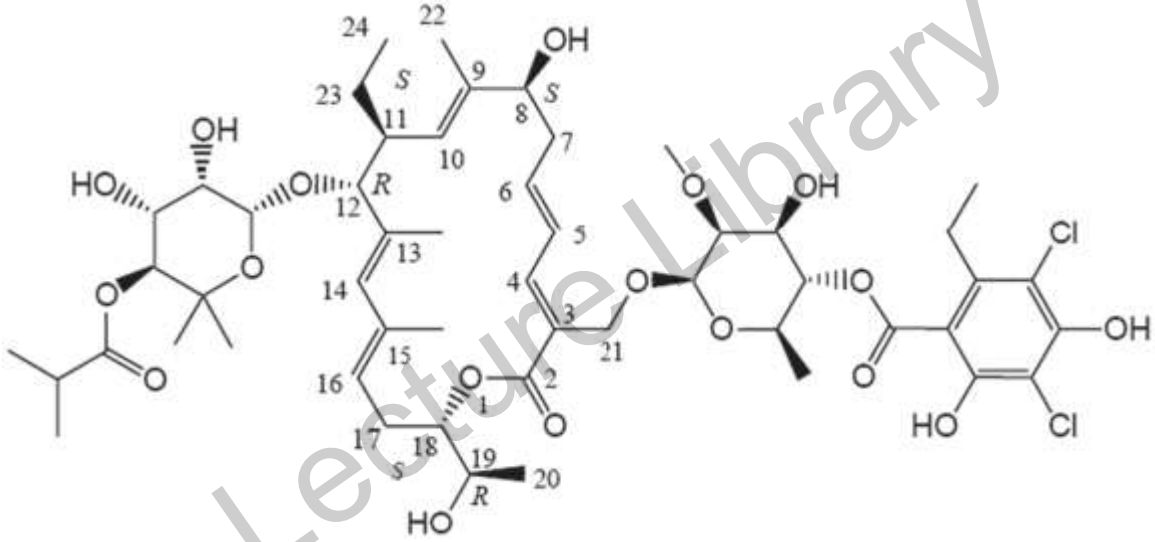
FDA approves treatment for *Clostridium difficile* infection

The U.S. Food and Drug Administration today approved Dificid (fidaxomicin) tablets for the trea...

Outline

- Mechanism of action
- Spectrum of activity and resistance
- Pharmacokinetic and Pharmacodynamic considerations
- Clinical trial data for efficacy
- Safety tolerability
- Place in practice

Fidaxomicin - nature and mechanism of action



- Formerly tiacumicin B, Opt-80, PAR-101
- Macrocyclic actinobacterial[1,2] fermentation product
- Targets bacterial RNA polymerase

- Unique binding site involved in promoter recognition.
  - Narrow spectrum of activity
  - Absence of cross-resistance
  - Bactericidal activity
- Additional mechanisms of action
  - Inhibits sporulation
  - Inhibits spore outgrowth[3]
  - Inhibits toxin production[4]

1. Miller M. Expert Opin Pharmacother 2010;11:1569–78;
2. Swanson RN, et al. Antimicrobial Agents Chemother 1991;35:1108–11;
3. Allen CA et al Antimicrob Agents Chemother 2013;57:664-67.
4. Babakhani F et al J Antimicorob Chemother 2014;68:515-22.

Spectrum of activity

- A narrow-spectrum antibiotic
  - Most potent suppression of Clostridial RNA polymerases
  - Moderate to good activity against Staphylococci and enterococci
    - Including MRSA and VRE
  - No activity against Gram-negative organisms or yeasts
- Less impact on the faecal flora than vancomycin and metronidazole
  - c/w vancomycin in terms of suppressing bacteroides[1]
  - c/w vancomycin and metronidazole in terms of selecting for VRE[2]

1. Louie TJ et al. Antimicrobial Agents Chemother 2009;53:261-63;
2. Nerandzic MM, et al. Clin Infect Dis. 2012; Suppl 2:S121-6.

C. difficile susceptibility

- Clinical breakpoints not established.
- MIC_{90} of clinical isolates typically 0.125-0.5ug/ml (range <0.001 – 1ug/ml)[1,2].
- Susceptibility consistent across different NAP/REA/Ribotypes
  - 1 dilution higher MIC_{90} for NAP1/BI/027 strains in phase III trials[3].
- Faecal concentrations ~100-1000x higher[3].
- No evidence for effect of MIC on treatment response.

1. Hecht et al. Antimicrob Agents Chemother 2007;51:2716–19;
2. Karlowsky et al. Antimicrob Agents Chemother 2008;52:4163–5
3. Louie et al. N Engl J Med 2011;364:422–31.

C. difficile resistance

- Very low propensity to resistance development[1]
- Mutational resistance rates ~10^{-9}
- May be selected out *in vitro*[2]
- Fidaxomicin resistant isolates of *C. difficile* have not been identified from clinical specimens
- Single isolate MIC of 16ug/ml in a patient experiencing recurrence in phase III trials[2].

1. Swanson et al. Antimicrob Agents Chemother 1991;35:1108–11
2. Babakhan F et al ECCMID 2012 Development of resistance in C.difficile with fidaxomicin, vancomycin, and rifaximin
2. Goldstein EJ et al Antimicrob Agent Chemother 2011;55:5194-99

Fidaxomicin – pharmacokinetics

- Negligible systemic absorption[1]
  - Plasma levels often below quantifiable limits
  - Mean plasma level 23 ng/ml during treatment of *C. difficile* infection[2].
  - No evidence of accumulation
- Intestinal hydrolysis to active metabolite OP-1118
- Eliminated completely in faeces
- Very little data on systemic elimination
  - No dose reductions required based on age, gender, renal or hepatic dysfunction.
  - Manufacturer advises avoid in severe renal / liver disease, pregnancy and breast-feeding.

1. Shue YK, et al. Antimicrob Agents Chemother 2008;52:1391–5;
2. Louie et al. N Engl J Med 2011;364:422–31

Fidaxomicin – pharmacodynamics

- Substrate of P-glycoprotein efflux systems in the GI tract[1,2]
  - Potential for increased absorption of fidaxomicin with inhibitors such as ciclosporin, azoles, macrolides.
  - Potential for reduced elimination of digoxin
  - Co-administration studies suggest effects are not clinically significant
- No apparent interactions with cytochrome P450 isoenzymes.

1. Shue YK, et al.. *Antimicrob Agents Chemother*. 2008;52:1391–1395.
2. European Medicines Agency, European Public Assessment Report for Fidaxomicin, 19 Dec 2011.

Antimicrobial Agents and Chemotherapy, Jan. 2009, p. 223–228
0066-4804/09/$08.00+0 doi:10.1128/AAC.01442-07

Clinical Outcomes, Safety, and Pharmacokinetics of OPT-80 in a Phase 2 Trial with Patients with *Clostridium difficile* Infection[▽]

T. Louie,[1]* M. Miller,[2] C. Donskey,[3] K. Mullane,[4] and E. J. C. Goldstein[5]

Fidaxomicin
50 mg, 100 mg or
200 mg bid

Baseline assessment

10 days of treatment

Assessment at end of treatment

6-week follow-up

Assessment at end of study

Inclusion criteria:
- Proven CDI
- First episode or first recurrence

Exclusion criteria:
- Severe or life-threatening disease
- Concomitant antibiotics

Primary outcome measures
- Clinical cure or failure
- Time to resolution of diarrhoea
- Total relief of symptoms of CDI

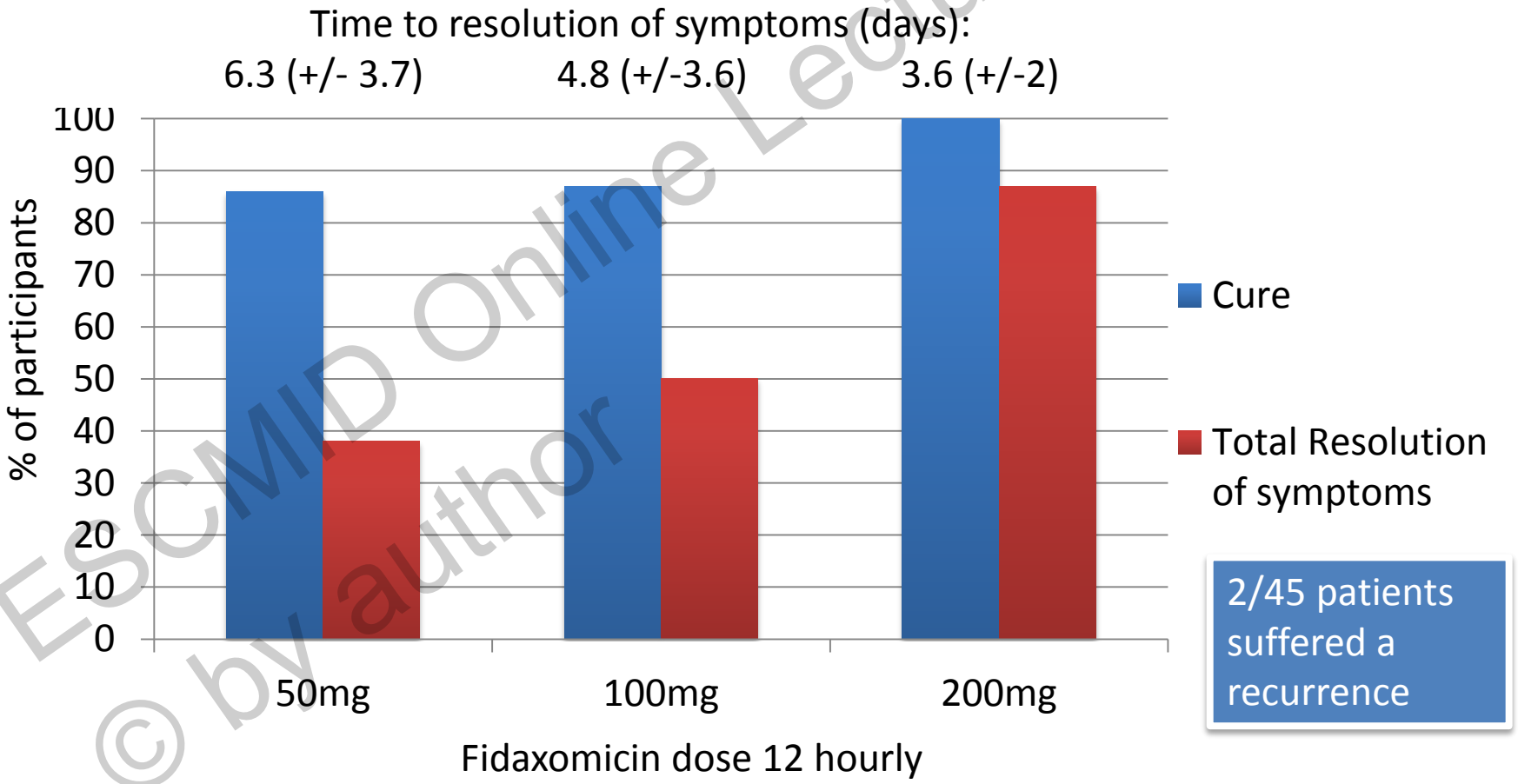
Secondary outcome measure
- Recurrence

Antimicrobial Agents and Chemotherapy, Jan. 2009, p. 223–228
0066-4804/09/$08.00+0 doi:10.1128/AAC.01442-07

Clinical Outcomes, Safety, and Pharmacokinetics of OPT-80 in a Phase 2 Trial with Patients with *Clostridium difficile* Infection▽

T. Louie,[1]* M. Miller,[2] C. Donskey,[3] K. Mullane,[4] and E. J. C. Goldstein[5]

49 patients enrolled; 45 patients evaluated



ORIGINAL ARTICLE

Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

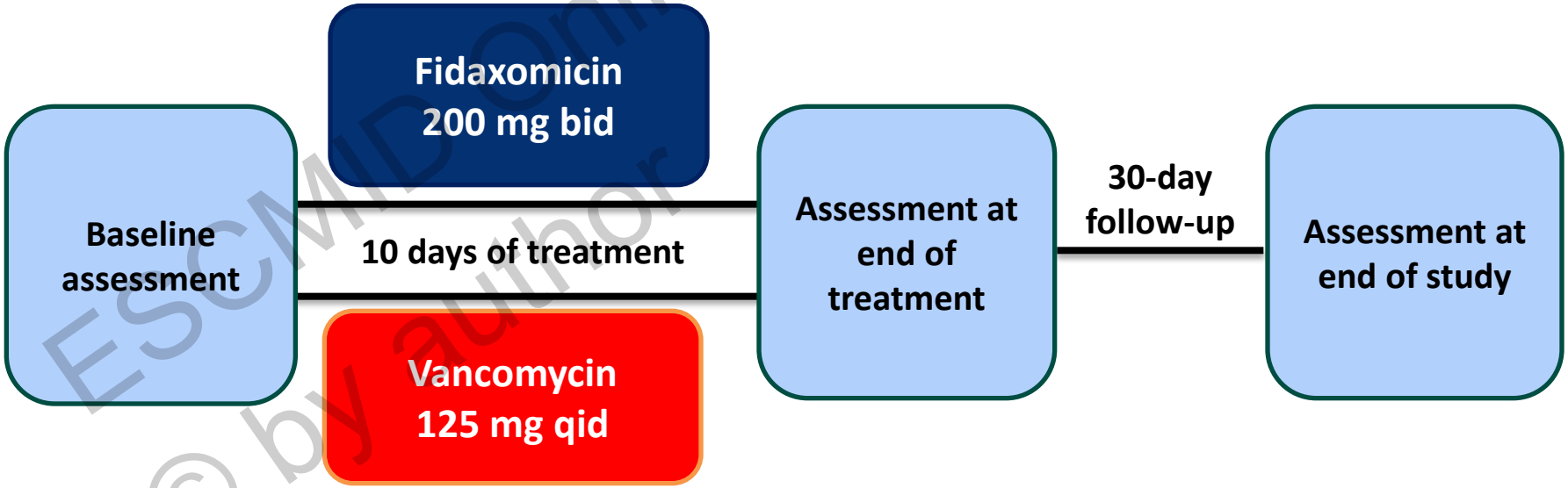
Thomas J. Louie, M.D., Mark A. Miller, M.D., Kathleen M. Mullane, D.O., Karl Weiss, M.D., Arnold Lentnek, M.D., Yoav Golan, M.D., Sherwood Gorbach, M.D., Pamela Sears, Ph.D., and Youe-Kong Shue, Ph.D., for the OPT-80-003 Clinical Study Group*

Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial

Oliver A Cornely, Derrick W Crook, Roberto Esposito, André Poirier, Michael S Somero, Karl Weiss, Pamela Sears, Sherwood Gorbach, for the OPT-80-004 Clinical Study Group

Phase III clinical trials of fidaxomicin

	Size and setting	Comparison	Primary endpoint	Secondary endpoints
OPT-80-003 Louie TJ NEJM 2011[1]	n=629 in North America	Fidaxomicin 200 mg bid vs vancomycin 125 mg qid	Clinical cure (resolution of diarrhoea) at end of treatment	1. Recurrence at 30 days 2. Time to resolution of diarrhoea 3. Sustained response 'global cure' at 30 days
OPT-80-004 Cornely OA Lancet Infect Dis 2012[2]	n=535 in Europe and North America			



1. Louie TJ, et al. NEJM 2011;364:422–31;
2. Cornely OA, et al. Lancet Infect Dis. 2012 Apr;12(4):281-9.

Phase III clinical trials of fidaxomicin

Inclusion criteria

- Confirmed diagnosis of *C. difficile* infection
- First episode or first recurrence

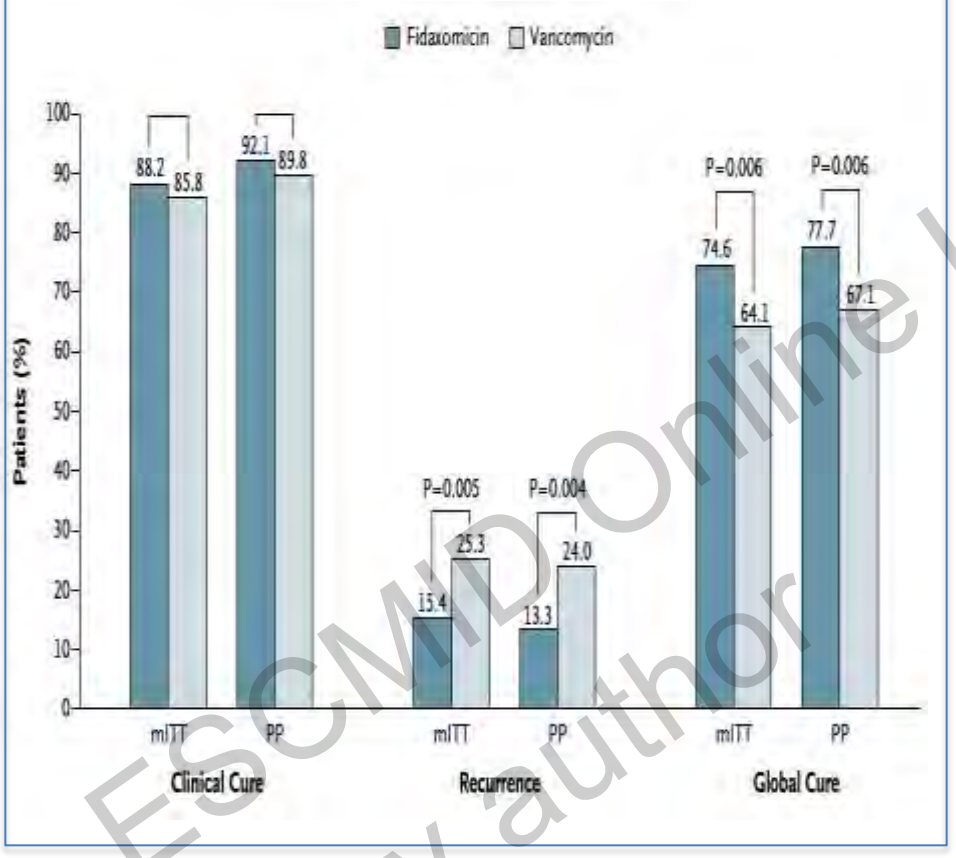
Exclusion criteria

- Life-threatening or fulminant disease
- Toxic megacolon
- >1 previous episode of *C. difficile* infection in last 3 months
- Inflammatory bowel disease

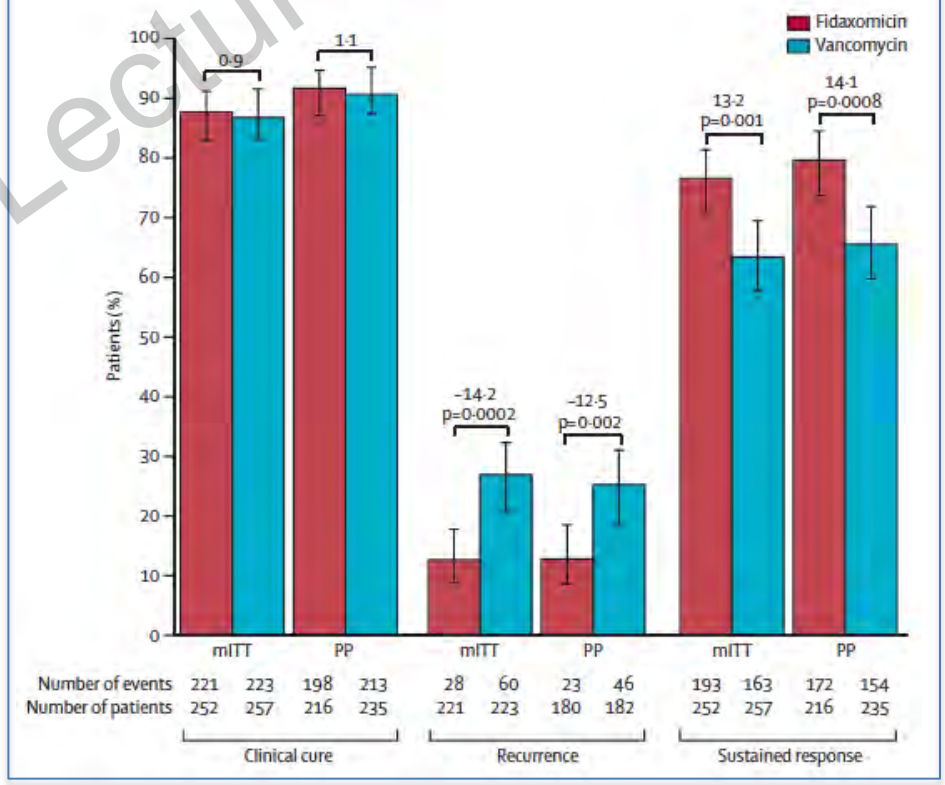
1. Louie TJ, et al. NEJM 2011;364:422–31;
2. Cornely OA, et al. Lancet Infect Dis. 2012 Apr;12(4):281-9.

Phase III clinical trials of fidaxomicin

OPT-80-003



OPT-80-004



1. Louie TJ, et al. NEJM 2011;364:422–31;
2. Cornely OA, et al. Lancet Infect Dis. 2012 Apr;12(4):281-9.

Safety and tolerability

	Fidaxomicin (%)	Vancomycin (%)	p
Any adverse event	**62.3**	**60.4**	**0.62**
Abdominal pain	3.0	2.2	0.62
Chills	0.3	2.5	0.004
Diarrhoea	3.0	3.7	0.66
Dizziness	4.0	1.2	0.04
Nausea	10.3	8.7	0.40
Vomiting	6.0	4.3	0.50
Pneumonia	2	1.5	0.79
Rash	3	0.6	0.003
Urinary Tract Infection	4	3.7	1.00
Any serious adverse event	**25.0**	**24.1**	**0.85**
Laboratory abnormalities	4.7	1.2	0.015
Anaphylaxis	0.3	0	0.48

Louie TJ, et al. NEJM 2011;364:422–31.

Hypersensitivity Reactions Associated With Fidaxomicin Use

Dmitri E. Iarikov, John Alexander, and Sumathi Nambiar

Division of Anti-Infective Products, Food and Drug Administration, Silver Spring, Maryland

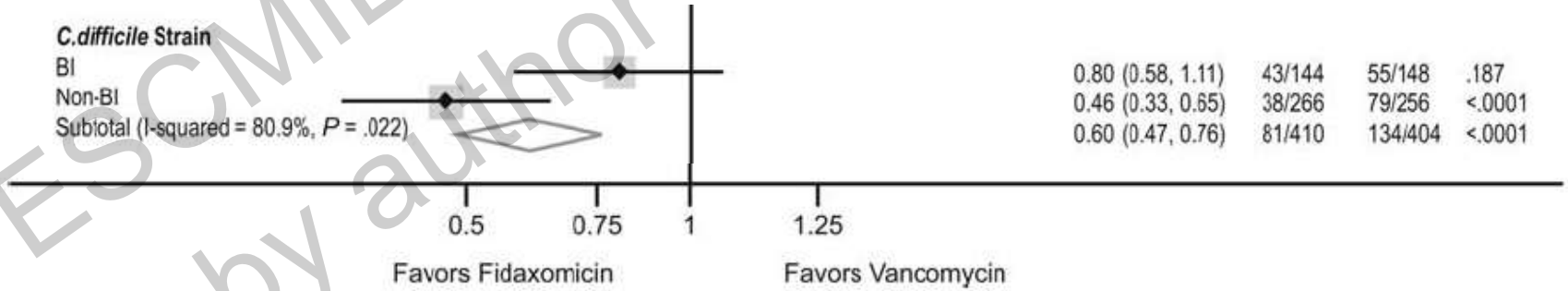
Clinical Infectious Diseases 2014;58(4):537–9

- 12 cases of hypersensitivity reactions identified in post marketing reports
- 6 involved facial / tongue swelling, 4 diffuse rash
- 3 patients with previous macrolide allergies
- Labelling revised in 2013 to advise caution in patients with history of macrolide allergy.
- Systemic reactions to oral vancomycin as also been reported[2].

1. Larikov DE et al Clin Infect Dis 2014;58:537-9
2. Bosse D et al Infection 2013; 41:579-82.

Impact of strain type (NAP1/BI/027)

	NA Trial (OPT-80-003)		NA and EU Trial (OPT-80-004)	
	Fidaxomicin	Vancomycin	Fidaxomicin	Vancomycin
Clinical cure				
027	59/75 (79%)	67/83 (80%)	54/65 (83%)	50/60 (83%)
Non-027	117/125 (94%)	121/132 (92%)	120/131 (92%)	106/121 (88%)
Recurrence				
027	16/59 (27%)	14/67 (21%)	12/54 (22%)	19/50 (38%)
Non-027	12/117 (10%)	34/121 (28%)	11/120 (9.2%)	29/106 (27%)



Persistent diarrhoea, recurrence or death through day 40.

Extracted from Crook D et al Clin Infect Dis 2012;55:S93-103

Impact of concomitant antibiotics during treatment of *C. difficile* infection

Efficacy of fidaxomicin vs vancomycin as therapy for *Clostridium difficile* infection in individuals taking concomitant antibiotics for other infections, Mullane KM, et al. Clin Infect Dis 2011; N = 1,142			
	No CA	CA	Significance
Clinical cure			
All	**92.6%**	**84.4%**	**<0.01**
Recurrence rate			
All	17.6%	23.2%	0.08

Mullane KM, et al. Clin Infect Dis 2011;53:440–7.

CA, concomitant antibiotics

What about patients who continue concomitant antibiotics during CDI treatment?

Efficacy of fidaxomicin vs vancomycin as therapy for *Clostridium difficile* infection in individuals taking concomitant antibiotics for other infections, Mullane KM Clin Infect Dis 2011 N = 1,164					
	No CA		CA		Significance
Clinical cure					
All	**92.6%**		**84.4%**		**<0.01**
Vancomycin	92.8%	NS	79.4%	P=0.04	
Fidaxomicin	92.3%		90.0%		
Recurrence rate					
All	17.6%		23.2%		0.08
Vancomycin	23.1%	P<0.01	29.2%	P=0.05	
Fidaxomicin	11.0%		16.9%		

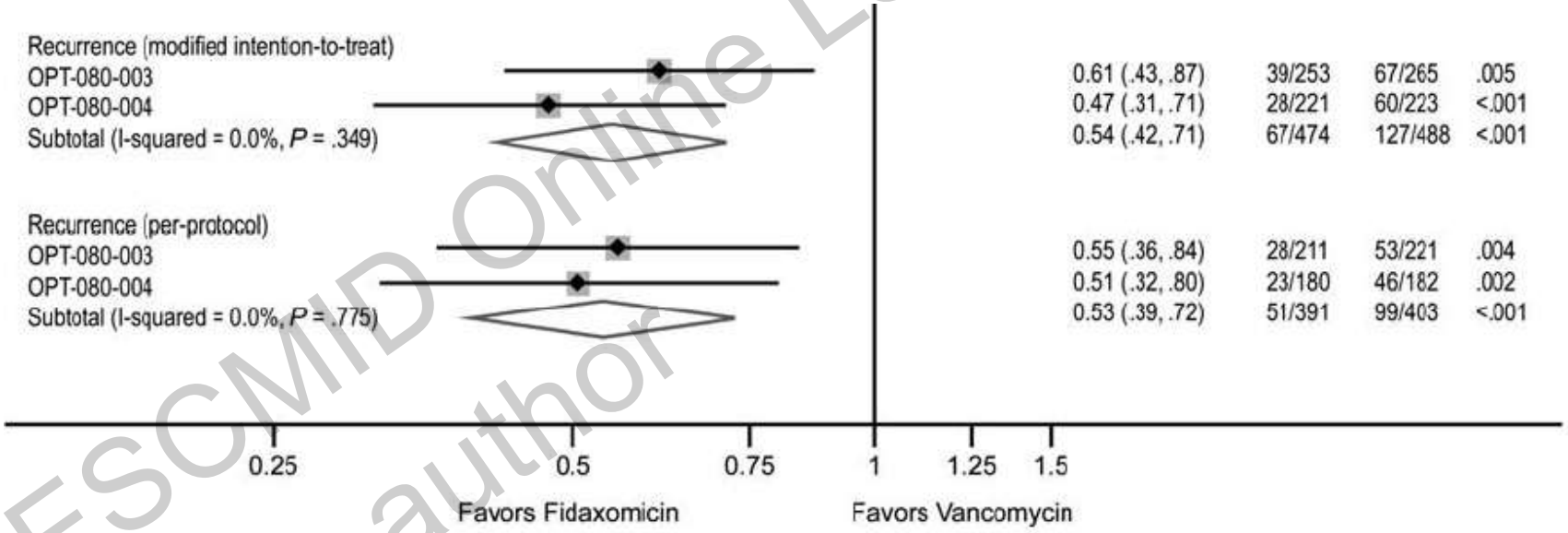
Mullane KM, et al. Clin Infect Dis 2011;53:440–7.

Fidaxomicin and *C. difficile* recurrence

Is it worth (quite) a few dollars (or Euros) more…?

Fidaxomicin and recurrence

- Halving of recurrence risk with fidaxomicin
- Huge potential cost-benefit implications



Reported recurrence rates with metronidazole and vancomycin therapy

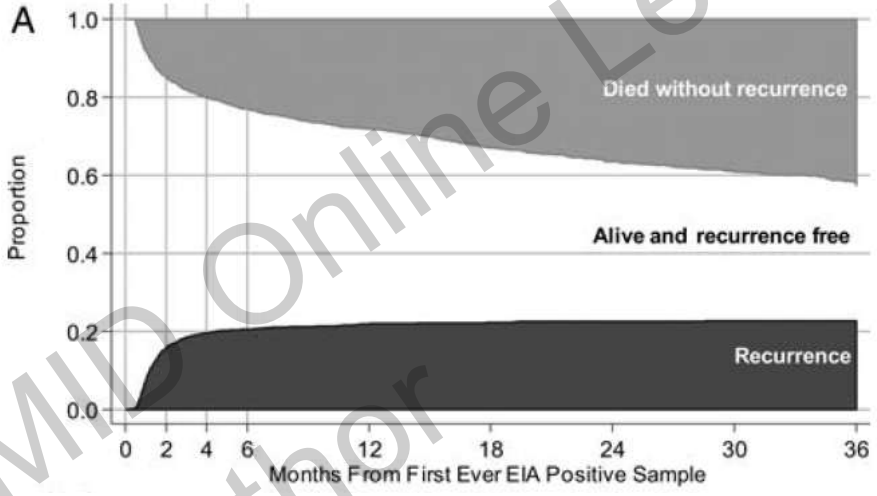
Studies	Treatment failures [n/total (%)]	Recurrences [n/total (%)]	Duration of follow up (days)	Percentage failure plus recurrence
Metronidazole				
Cherry et al, 1982[59]	0/13	2/13 (15%)	30	15%
Teasley et al, 1983[47]	2/42 (5%)	2/39 (5%)	21	10%
Olson et al, 1994[4]	14/632 (2%)	39/632 (6%)	30	8%
Wenisch et al, 1996[60]	2/31 (6%)	5/31 (16%)	30	22%
Kyne et al, 2001[5]	..	22/44 (50%)	60	..
Fernandez et al, 2004[61]	38/99 (38%)	..	..	..
Musher et al, 2005[8]	46/207 (22%)	58/207 (28%)	90	50%
Pepin et al, 2005[9]	178/1123 (16%)	243/845 (29%)	60	45%
Vancomycin				
Bartlett et al, 1980[62]	3/79 (4%)	11/79 (14%)	30	18%
Silva et al, 1981[53]	0/16	2/16 (13%)	42	13%
Teasley et al, 1983[47]	0/52	6/51 (12%)	21	12%
Bartlett, 1984[48]	6/189 (3%)	46/189 (24%)	25	27%
Young et al, 1985[56]	8/42 (19%)	11/30 (37%)	30	56%
Dudley et al, 1986[57]	0/15	3/15 (20%)	60	20%
de Lalla et al, 1989[63]	2/25 (8%)	3/25 (12%)	30	20%
Fekety et al, 1989[55]	0/46	9/46 (20%)	42	20%
de Lalla et al, 1992[58]	0/20	4/20 (20%)	30	20%
Olson et al, 1994[4]	1/122 (1%)	12/122 (10%)	30	11%
Wenisch et al, 1996[60]	2/31 (6%)	5/31 (16%)	30	22%
Pepin et al, 2005[9]	..	31/112 (28%)	60	..
Metronidazole and vancomycin				
McFarland et al, 1994[64]	8/33 (24%)	8/33 (24%)	60	48%
Nair et al, 1998[49]	9/36 (25%)	7/36 (19%)	90	44%
Noren et al, 2004[65]	..	68/267 (25%)	60	..

Table: **Studies of antibiotic treatment in CDAD: treatment failure and recurrences**

Aslam S Lancet Infect Dis. 2005 Sep;5(9):549-57

How often and when do recurrences occur?

- Eyre et al 2012[1]
  - 1191 adult inpatients completing CDI treatment
  - 22% recurrence

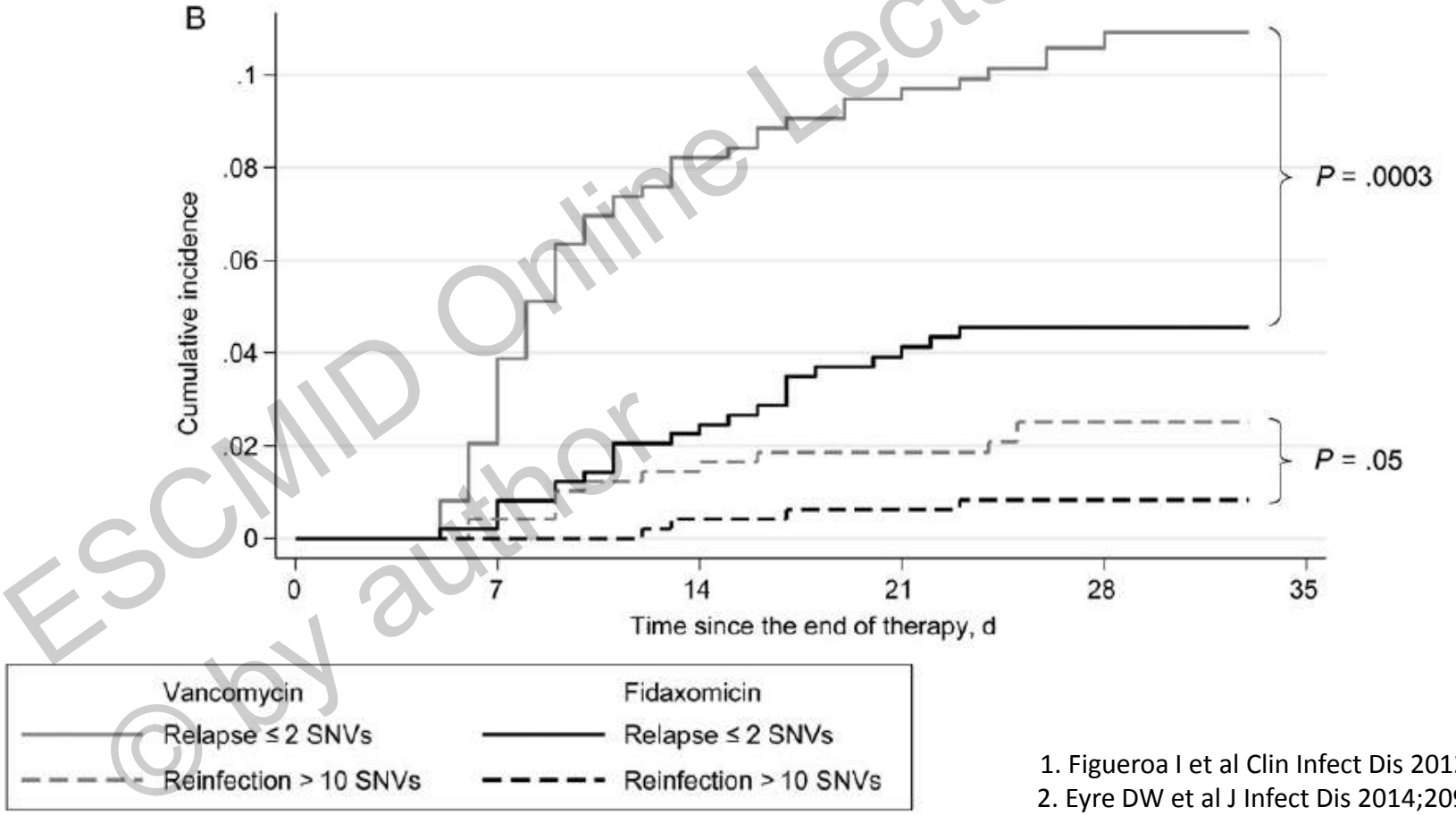


- Islam et al 2014[2]
  - 312 adult inpatients completing CDI treatment
  - 10.3% recurrence at 28 days after completing treatment

1. Eyre DW et al Clin Infect Dis. 2012; 55 Suppl 2:S77-87
2. Islam J et al J Hosp Infect. 2013 Sep;85(1):17-21

Recurrence, relapse or reinfection

- 16-50% of symptomatic recurrences are in fact re-infections[1].
- Recurrence rates may fall as rates of infection and transmission decline



1. Figueroa I et al Clin Infect Dis 2012;55:S104-9
2. Eyre DW et al J Infect Dis 2014;209:1446-517.

Economic issues

Drug	Cost (standard 10 day oral course)	
Metronidazole	£100	€120
Vancomycin injection (given orally)	£100	€120
Vancomycin capsules	£300	€360
Fidaxomicin	£1350	€1650

Economic analysis

- Several attempts at economic analysis with conflicting results
- Limited by lack of good data on resource use and quality of life impacts related to recurrent *C. difficile* infection
- Highlight sensitivity of models to[1,2]:
  - Prevalence of NAP1/BI/027 strains: need for strain typing? Need for better strain-specific data?
  - Local re-infection and relapse rates
  - Prevalence of risk factors for recurrent disease[3,4]
    - Age, severity of illness, concomitant antibiotics
    - E.g. ATLAS score[4]
  - Healthcare systems factors
    - Ability to realize cost savings or opportunity benefits

No prospective studies establishing or implementing stratification approach to fidaxomicin treatment

1. Stranges Pm et al Value Health 2013;16:297-304
2. Bartsch SM et al Clin Infect Dis 2013; 57:555-61.
3. Eyre DW et al Clin Infect Dis 2012;55:S77-87.
4. Miller MA et al. BMC Inf ect Dis 2013 ;13:148

ORIGINAL ARTICLE 10.1111/1469-0691.12418

European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection

S. B. Debast[1], M. P. Bauer[2], E. J. Kuijper[3], on behalf of the Committee*

1) Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, Departments of 2) Infectious Diseases and 3) Medical Microbiology, Centre for Infectious Diseases, Leiden University Medical Centre, Leiden, the Netherlands

Summary of recommendations from ESCMID for oral treatment of *C. difficile* Infection. Strength of recommendation A-E and Strength of evidence I-III)

Indication	Recommendation
First episode, non-severe	Metronidazole (A-I) Vancomycin (B-I) Fidaxomicin (B-1)
First episode, Severe	Vancomycin (A-I) Fidaxomicin (B-I) – no evidence supporting use in life-threatening disease
First recurrence (or risk of) recurrent infection	Fidaxomicin (B-I) Vancomycin (B-I) Metronidazole (C-1)
Multiple Recurrent infection	Fidaxomicin (B-II)* Vancomycin (B-II) (then pulse or taper)*

*faecal transplantation probably preferable to either approach

In conclusion

- Fidaxomicin is a potent, reliable and specific treatment for *C. difficile* infection
- Two well conducted clinical trials demonstrate it is a safe and effective treatment for *C. difficile* infection
  - Equivalent to vancomycin for early cure
  - Superior to vancomycin for recurrence and sustained cure
- Cost-effectiveness remains to be established
  - Likely to be determined by local patient, treatment and healthcare system factors
- Future studies need to establish costs of recurrent C. difficile infection more accurately and evaluate risk stratification of patients.