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Clostridium difficile: Options for Treating the Failing Patient Fidaxomicin and Other Antibiotic Strategies

Oliver A. Cornely MD, FIDSA, FACP

Dept. I for Internal Medicine

Infectious Diseases

Centre for Clinical Trials & Translation

BMBF 01KN1106

CECAD – Cluster of Excellence

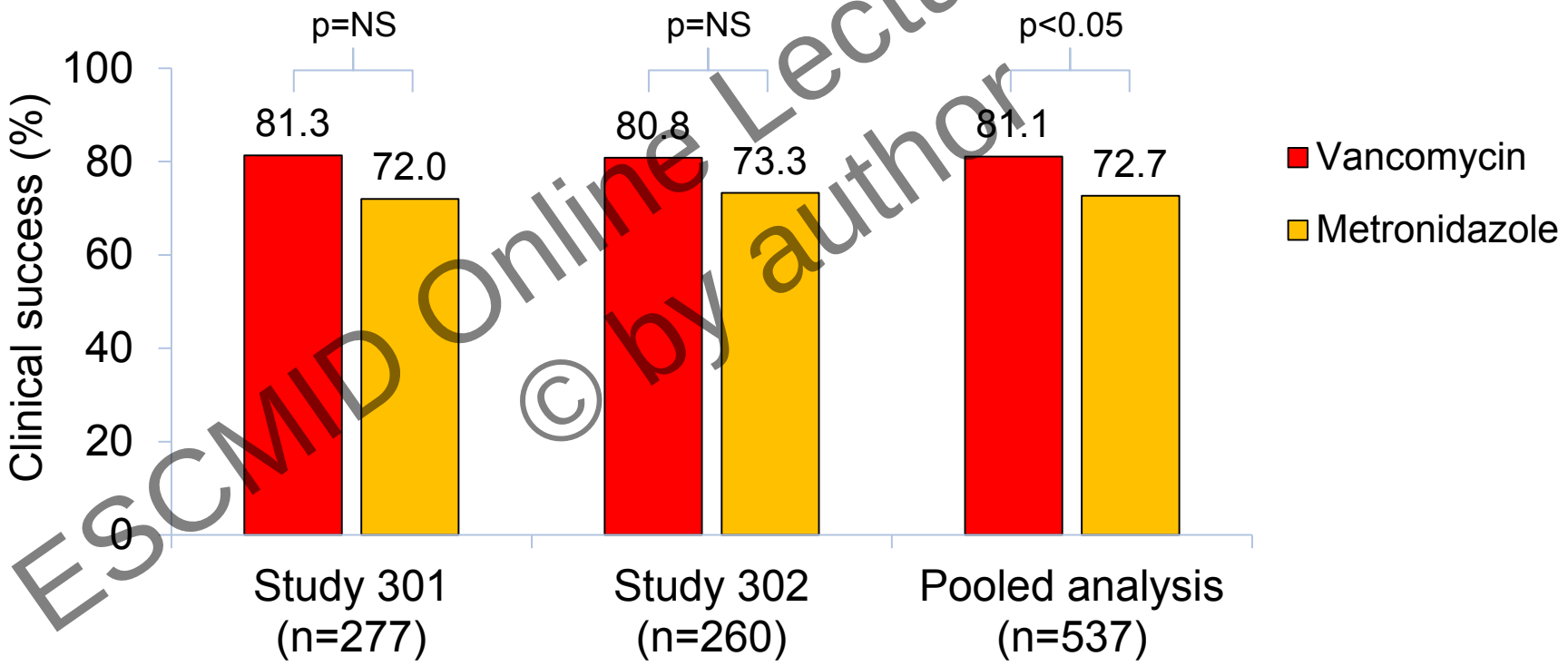
University of Cologne

Transparency Declaration

- German Federal Ministry of Research and Education
  (BMBF 01KN1106, 01KN0706, 01GH1001E, 01EZ0931)
- German Research Foundation (DFG)
- German Center for Infection Research (DZIF)
- German José Carreras Leukaemia Foundation
- European Commission (FP7, IMI)
- European Organization for Research and Treatment of Cancer (EORTC)
- European Society for Clinical Microbiology and Infectious Diseases (ESCMID)
- European Confederation of Medical Mycology (ECMM)
- Research Grants, Trial Design, or Speaker for:
  3M, Actelion, Astellas, Basilea, Bayer, Biocryst, Celgene, F2G, Gilead, GSK, Menarini, Merck Serono, MSD, Miltenyi, Novartis, Optimer, Pfizer, Quintiles, Sanofi Pasteur, Viropharma.

Rates of Clinical Success for Metronidazole and Vancomycin

Rates of clinical success in two identical multicentre, randomised, double-blind, parallel-group trials

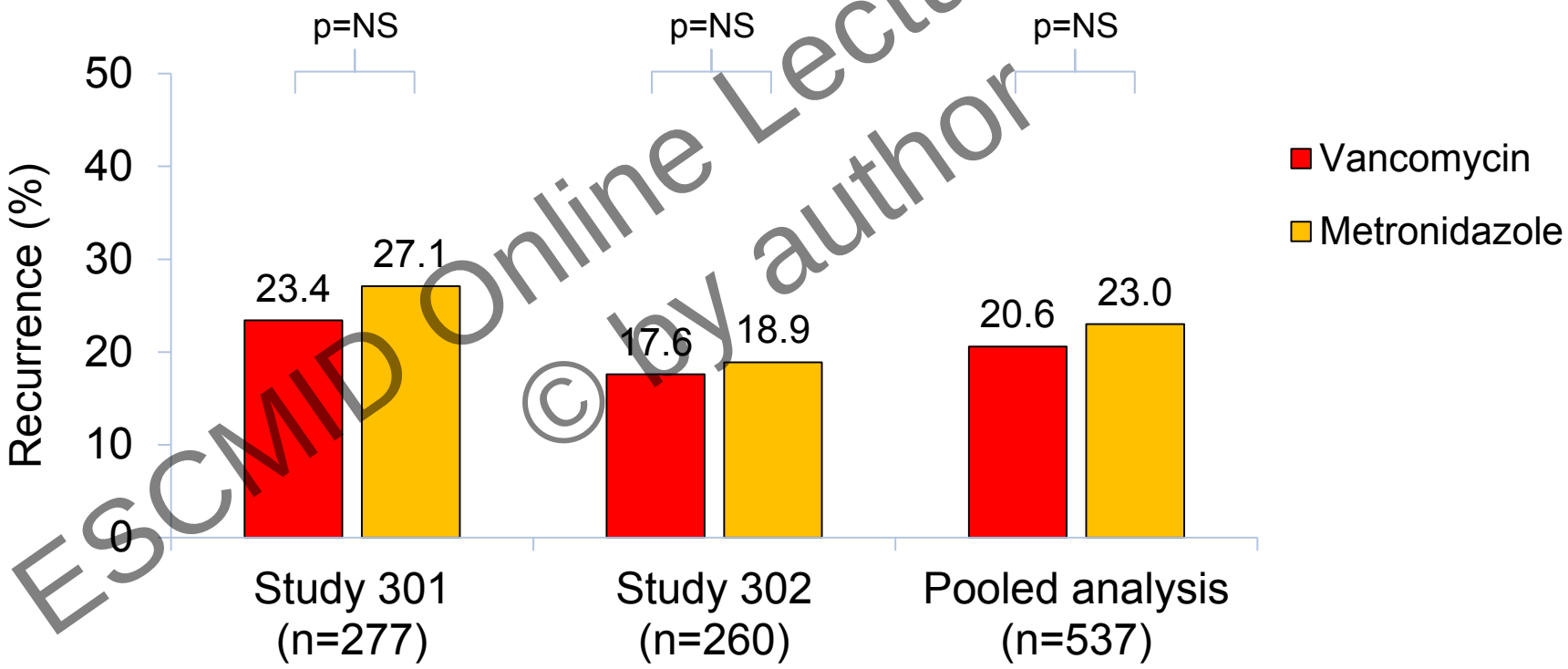


Clinical success was defined as diarrhoea resolution and absence of severe abdominal discomfort due to CDI on Day 10;
NS, not significant

Johnson et al. ID Week 2012, San Diego, USA; 818.

Rates of Recurrence for Metronidazole and Vancomycin

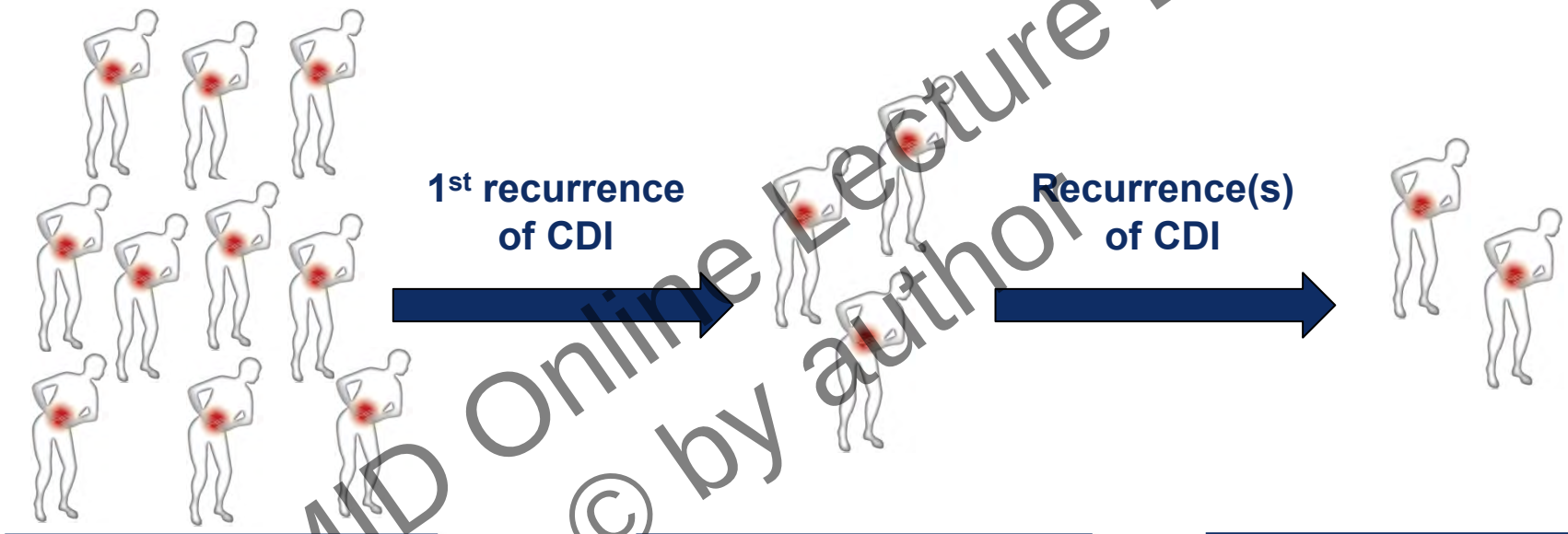
Rates of recurrence in two identical multicentre, randomised, double-blind, parallel-group trials



NS, not significant

Johnson et al. ID Week 2012, San Diego, USA; 818.

The Incidence of Recurrent *C. difficile* Infection



1. Louie et al. N Engl J Med 2011;364:422–31;
2. Lowy et al. N Engl J Med 2010;362:197–205;
3. Bouza et al. Clin Microbiol Infect 2008;4(Suppl. 7):S103–4;
4. McFarland et al. Am J Gastroenterol 2002;97:1969–75;
5. McFarland et al. JAMA 1994;271:1913–8.
6. Johnson et al. ID Week 2012, San Diego, USA; 818.

ESCMID Guideline on CDAD 2009
First Recurrence

Diagnosis	ESCMID recommended treatment
Non-severe first recurrence	• Metronidazole 500 mg tid orally for 10 days*
Severe first recurrence	• Vancomycin 125 mg qid orally for 10 days • 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

*IV if oral therapy is not possible

ESCMID Guideline on CDAD 2009
Second or Later Recurrence / ≥3rd Episode

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

Diagnosis	ESCMID recommended treatment

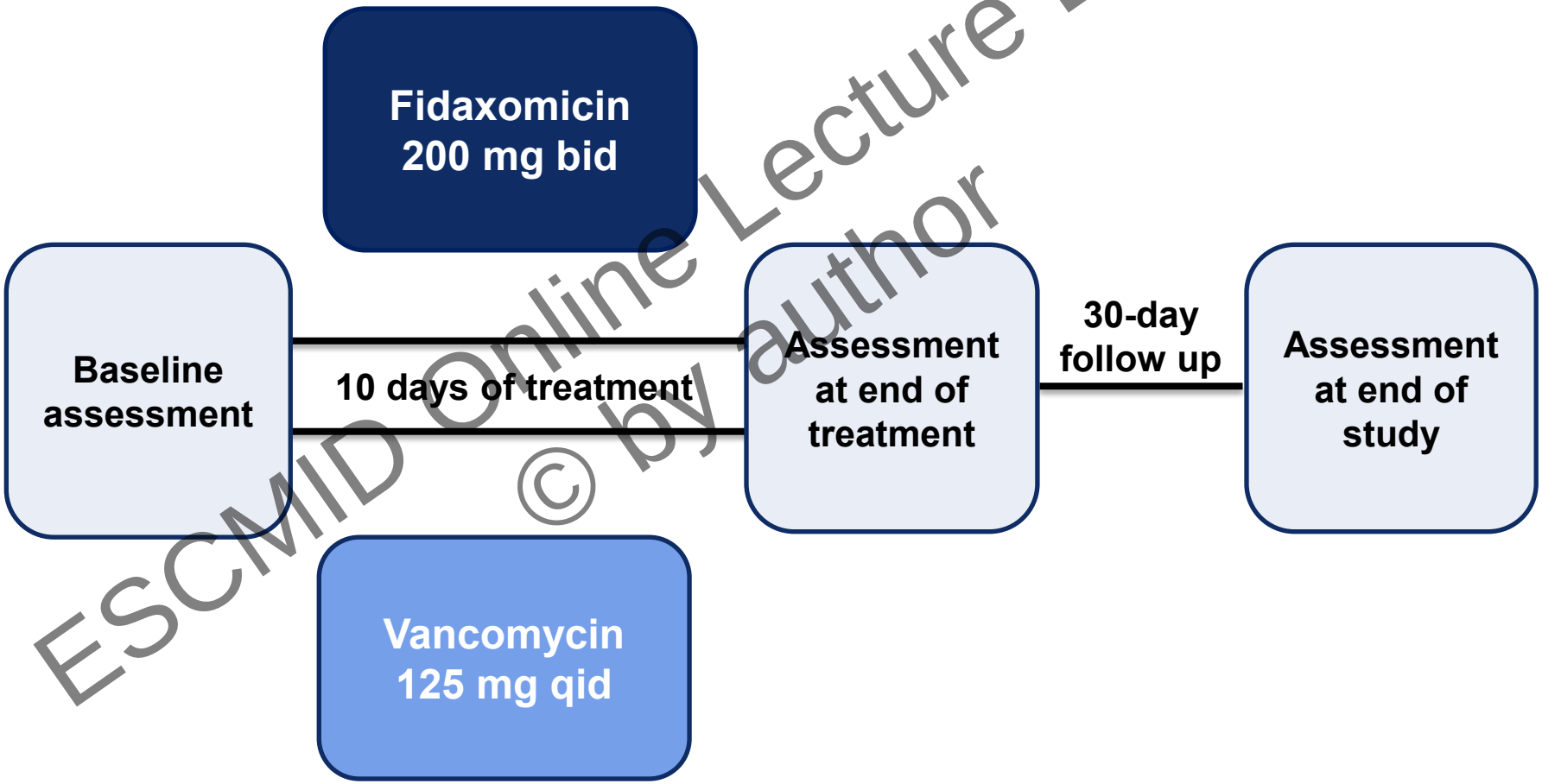
Second and later recurrences	• Vancomycin 125 mg qid orally for at least 10 days
	  • Consider tapering vancomycin dose by decreasing daily dose with 125 mg every 3 days
	  • Consider pulse dosing with vancomycin 125 mg every 3 days for 3 weeks
	• IV metronidazole 500 mg tid for 10–14 days plus retention 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

Bauer et al. Clin Microbiol Infect 2009;15:1067–79.

New Antibiotic Management Options for CDAD

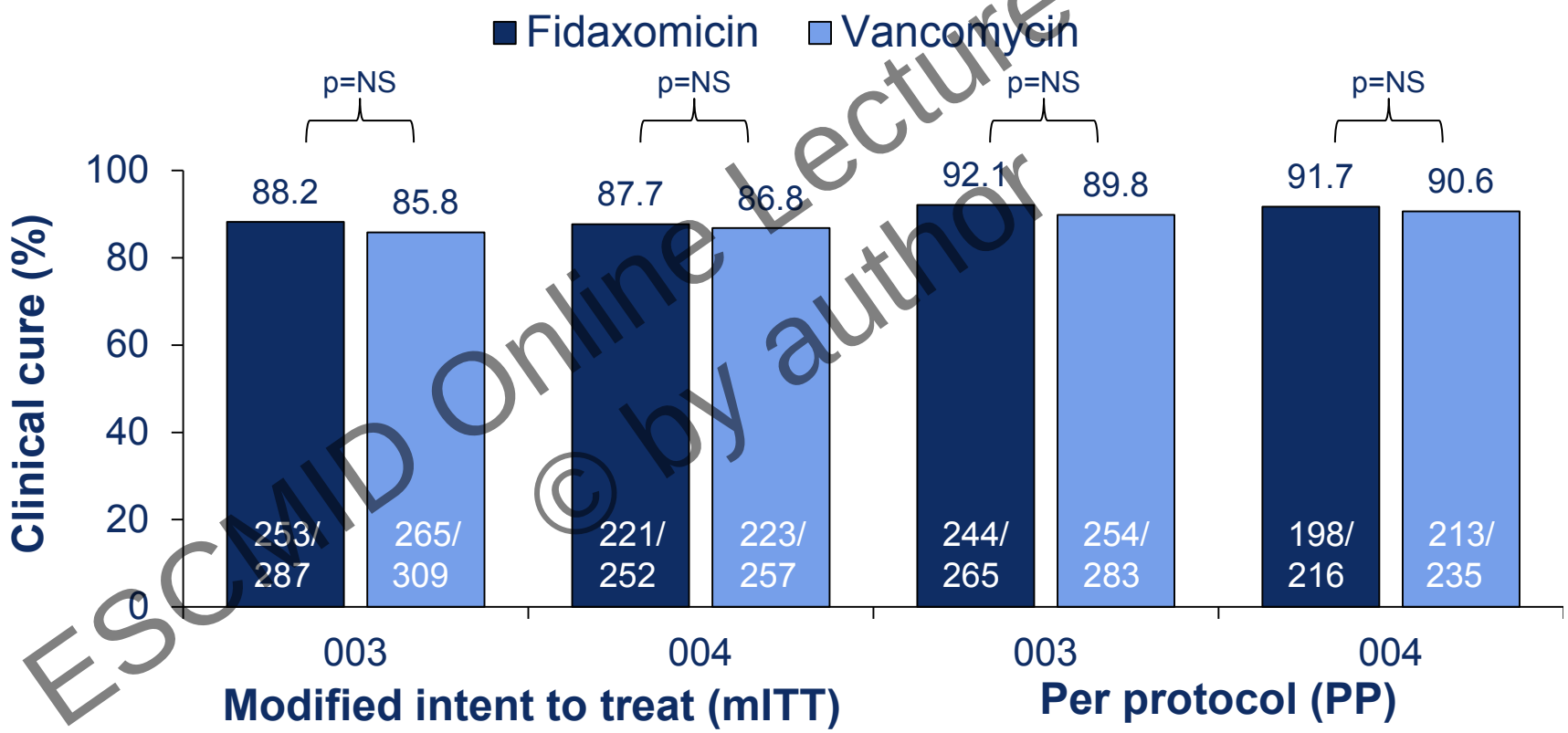
- **Fidaxomicin** **Licensed for CDAD**
- Bacitracin Licensed for topical use
- Fusidic acid Licensed for topical use
- Nitazoxanide Evaluated as antiparasitic
- Ramoplanin Licensed in the US for VRE infections
- Rifaximin Licensed for traveller´s diarrhea
- Tigecycline Licensed for complicated BSSSI & abdominal infections
- Teicoplanin Licensed for gram-positive infections
- Cadazolid Phase II / EUDRA-CT 2010-020941-29
- Surotomycin Phase III / EUDRA-CT 2012-000252-34

Phase 3 registration trials: Study design



Louie et al. N Engl J Med 2011;364:422–31;
Cornely et al. Lancet Infect Dis 2012;12:281–9.

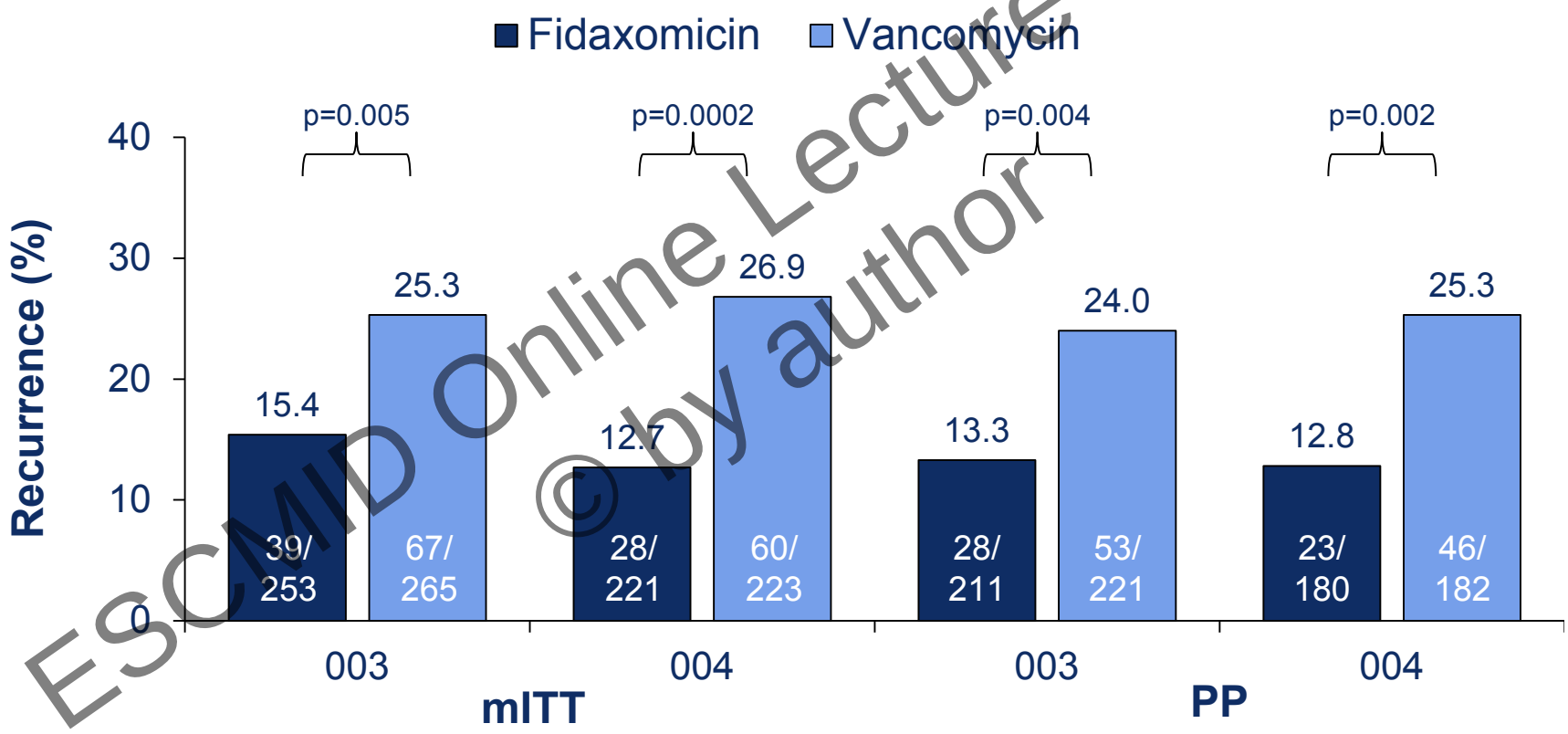
Rates of clinical cure



mITT: Patients underwent randomisation and received ≥1 dose of study medication;
PP: Patients in the mITT population who received ≥3 days of study medication (in cases of failure) or ≥8 days (in cases of clinical cure) with documented adherence to study protocol and who underwent EOT evaluation

Louie et al. N Engl J Med 2011;364:422–31;
Cornely et al. Lancet Infect Dis 2012;12:281–9.

Rates of recurrence



Louie et al. N Engl J Med 2011;364:422–31;
Cornely et al. Lancet Infect Dis 2012;12:281–9.

Fidaxomicin versus Vancomycin Phase III Stratum with Prior Episode

Treatment of First Recurrence of *Clostridium difficile* Infection: Fidaxomicin Versus Vancomycin

Oliver A. Cornely,[1] Mark A. Miller,[2] Thomas J. Louie,[3,4] Derrick W. Crook,[5,6] and Sherwood L. Gorbach[7,8]

[1]Department I of Internal Medicine, Clinical Trials Centre Cologne, ZKS Köln, BMBF 01KN1106, Center for Integrated Oncology CIO Köln Bonn, and Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases, University of Cologne, Germany; [2]Division of Infectious Diseases, Jewish General Hospital, McGill University, Montreal, Quebec, Canada; [3]Department of Medicine, and [4]Department of Microbiology-Immunology and Infectious Diseases, University of Calgary, Alberta, Canada; [5]Nuffield Department of Clinical Medicine, Oxford University, [6]NIHR Oxford Biomedical Research Centre, John Radcliffe Hospital, United Kingdom; [7]Optimer Pharmaceuticals, Inc., San Diego, California, and [8]Tufts University School of Medicine, Boston, Massachusetts

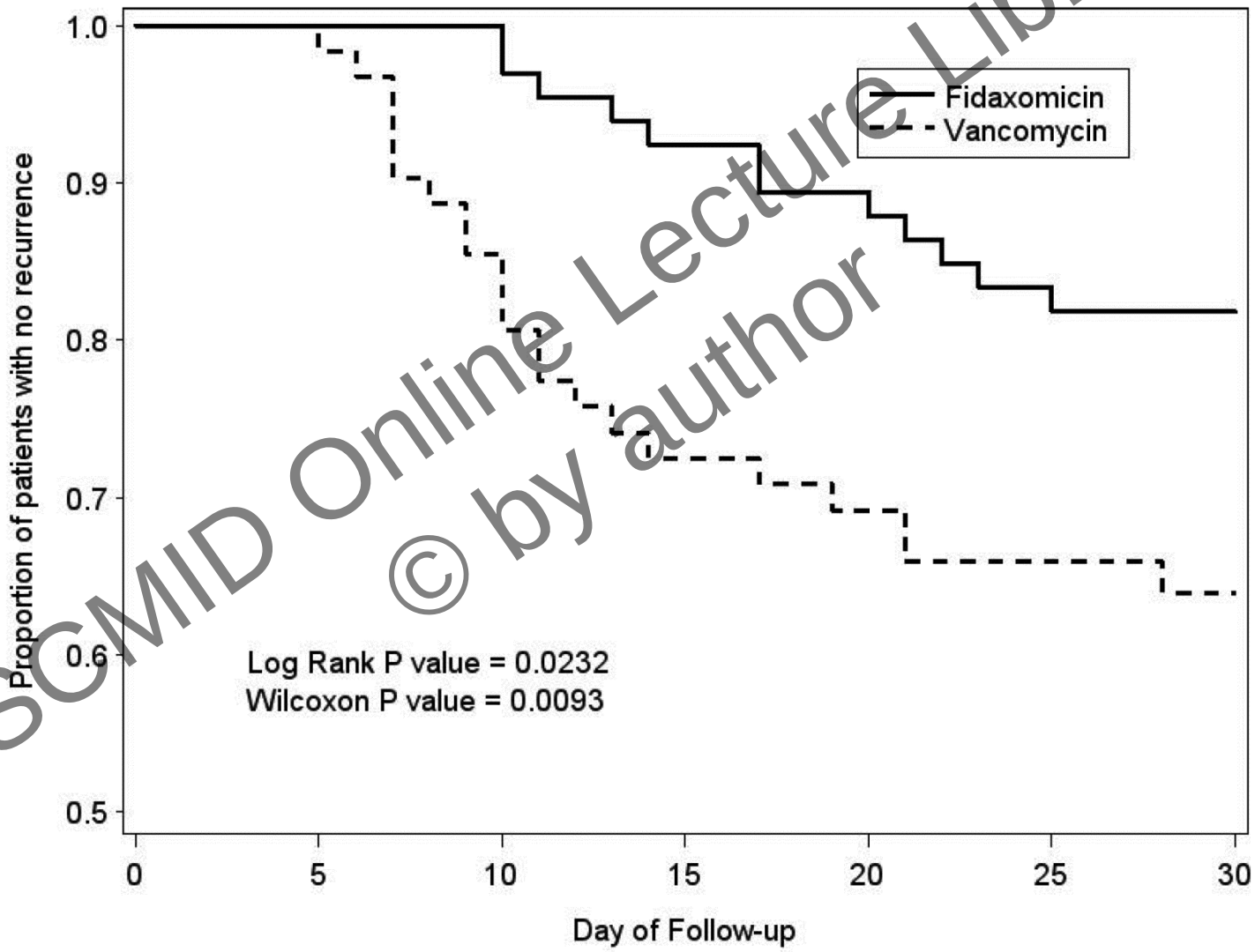
Cornely OA et al. Clin Infect Dis 2012.

Efficacy – Rates of 2nd Recurrence

Endpoint	Fidaxomicin	Vancomycin	P Value
Cured and evaluated for recurrence	n = 66	n = 62	
Recurrence within 14 days of follow-up	5/66 (7.6%)	17/62 (27.4%)	.003
No recurrence within 14 days	n = 61	n = 45	
Recurrence from 15 to 28 days	8/61 (13.1%)	5/45 (11.1%)	
Censored at 28 days (no recurrence)	53/66 (80.3%)	40/62 (64.5%)	

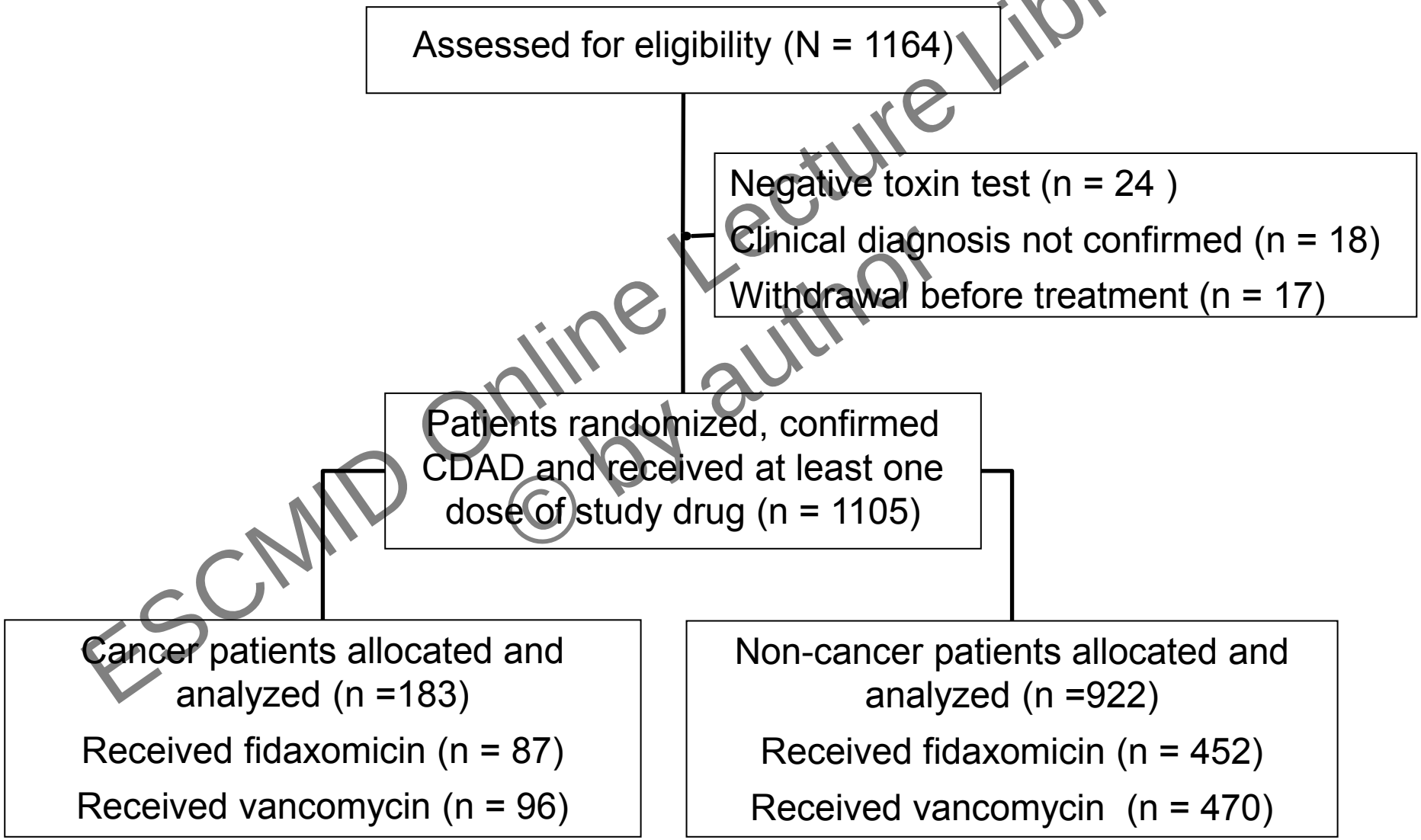
Cornely OA et al. Clin Infect Dis 2012.

Fidaxomicin versus Vancomycin Efficacy – Time to 2nd Recurrence



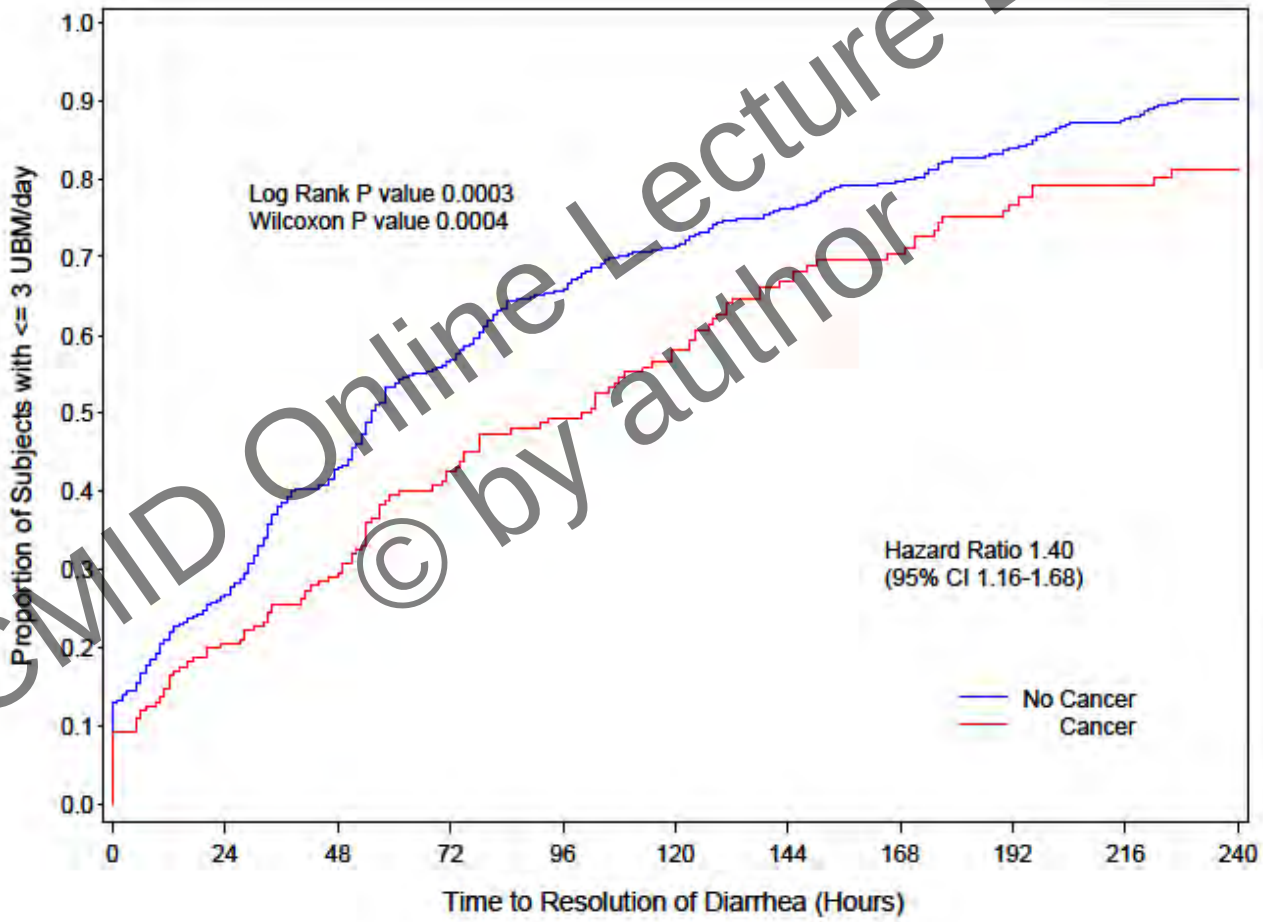
Cornely OA et al. Clin Infect Dis 2012.

Special Populations at Risk: CDAD in Cancer Patients



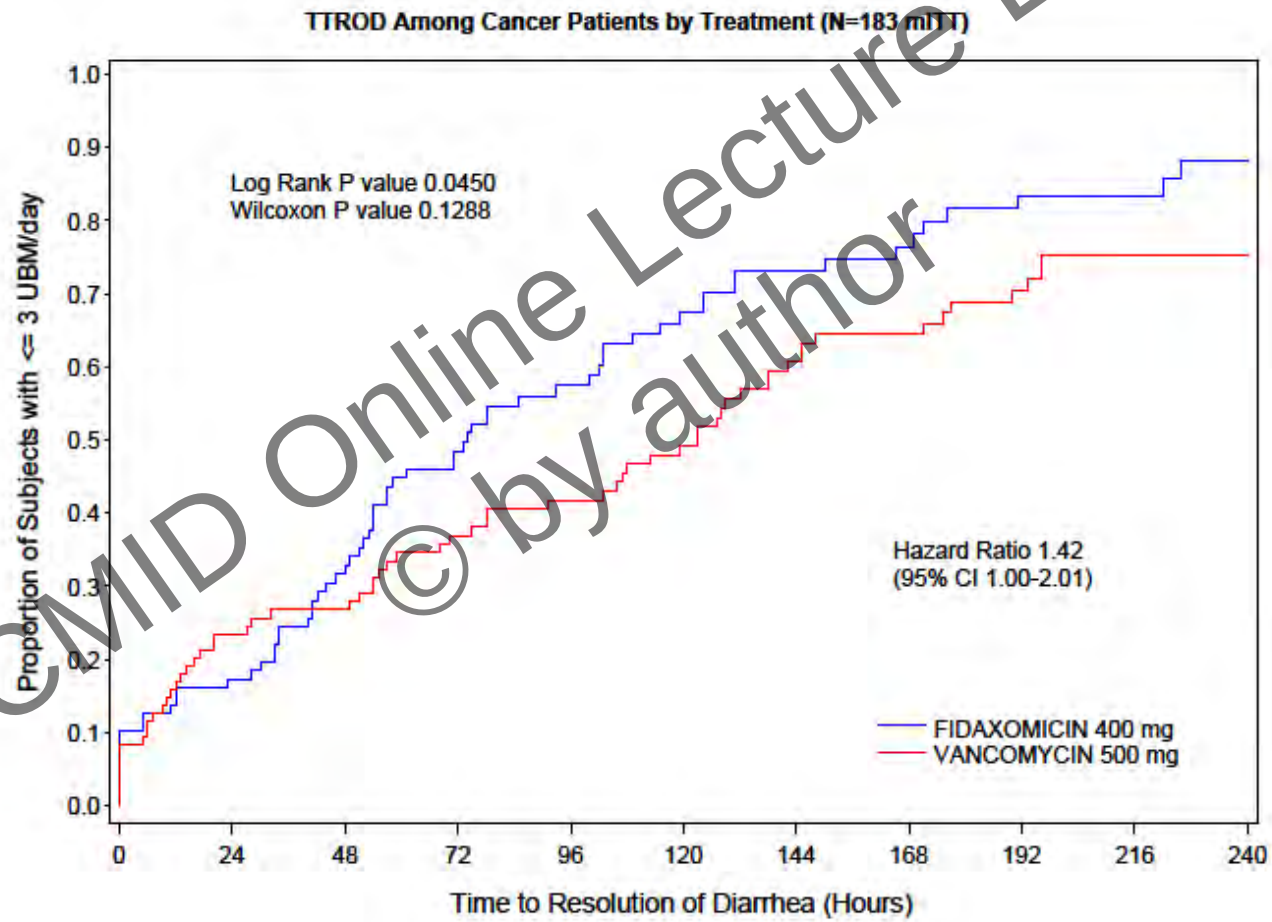
Cornely OA et al. J Clin Oncol (in press).

Impact of Cancer on Time to Resolution of Diarrhea (TTROD)



Cornely OA et al. J Clin Oncol (in press).

TTROD in Cancer Patients by Treatment



Cornely OA et al. J Clin Oncol (in press).

Rifaximin "Chaser"

J Antimicrob Chemother 2011; **66**: 2850–2855
doi:10.1093/jac/dkr377 Advance Access publication 21 September 2011

Journal of Antimicrobial Chemotherapy

A randomized, double-blind, placebo-controlled pilot study to assess the ability of rifaximin to prevent recurrent diarrhoea in patients with *Clostridium difficile* infection

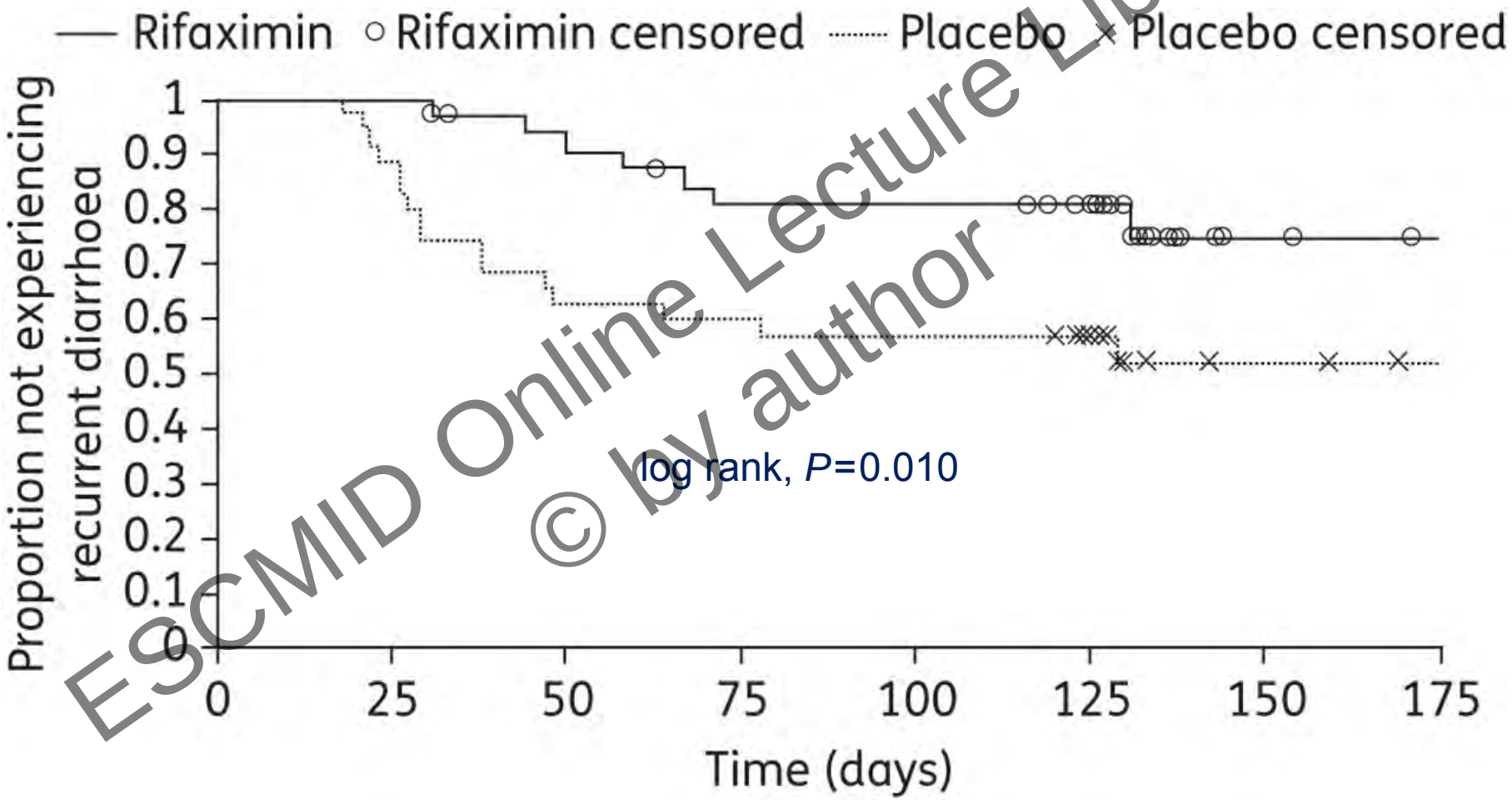
Kevin W. Garey[1–3]*, Shashank S. Ghantoji[2], Dhara N. Shah[1,3], Musarat Habib[1], Vaneet Arora[1], Zhi-Dong Jiang[2] and Herbert L. DuPont[1–4]

[1]University of Houston College of Pharmacy, 1441 Moursund Street, Houston, TX 77030, USA; [2]University of Texas School of Public Health, 1200 Herman Pressler, Houston, TX 77030, USA; [3]St Luke's Episcopal Hospital, 6720 Bertner Ave., Houston, TX 77030, USA; [4]Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA

- Rifaximin 400 mg TID or placebo for 20 days immediately after CDAD treatment
- 6-7 previous episodes
- last antibiotic: 82% metronidazole, 18% vancomycin

Garey KW et al. J Antimicrob Chemoth 2011.

Time from Starting CDAD Treatment to Recurrence of Diarrhoea (Not Necessarily CDAD)



N=68

Garey KW et al. J Antimicrob Chemoth 2011.

Update of the ESCMID treatment guidance document for *Clostridium difficile* infection

S. Debast, M. Bauer and E. Kuijper
(Executive committee)

F. Allerberger, B. Guery, J. Coia, O.A. Cornely, D. Nathwani, T. Noren, B. Oleson, E. Rakoczi, T. Welte, A. Widmer, M. Wilcox
(Expert Panel)

Treatment guideline summary: recommendations (4)

C. First recurrence or risk for recurrent disease

Antibiotic treatment

- Metronidazole po 500 mg tid 10 - 14 days (B-I)
- Vancomycin 125 mg qid 10 days (B-I)
- Fidaxomicin po 200 mg bid for 10-14 days (B-I)

Cornely et al. (2012) Clin. Inf. Dis. 55 (suppl 2): S154–S161.

Babakhani et al. (2013) Fidaxomicin inhibits toxin production in Clostridium difficile, J. Antimicrob. Chemother. 68: 515-522.

Allen et al. (2013) ***Both Fidaxomicin and Vancomycin Inhibit Outgrowth of*** *Clostridium difficile Spores, Antimicrob. Agents Chemother. 57: 664-667*

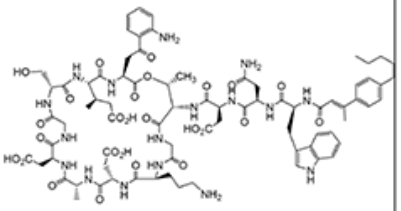
Louie et al. (2012) Fidaxomicin preserves the intestinal microbiome during and after treatment of Clostridium difficile infection (CDI) and reduces both toxin reexpression and recurrence of CDI, Clin. Inf. Dis. 55 (Suppl 2): S141

Surotomycin- A Lipopeptide

Surotomycin Overview

CUBIST PHARMACEUTICALS

Compound



Mechanism of Action

- Disruption of membrane potential

Stage

- Phase 3

In vitro Microbiology

C. difficile	MIC_{90} = 0.5µg/mL; includes NAP1 isolates
Selectivity	No activity against enteric Gram-negative including bacteroides *spp.* Minimal vs. G(+) gut flora
Cidality	Rapid killing of vegetative cells (>3log in 24 hrs); includes NAP1 isolates
Resistance (*C. difficile*)	Low resistance incidence

Pharmacokinetics

- Low oral bioavailability < 1% (healthy rats and dogs)

Phase 2 Efficacy

- Similar cure rates to vancomycin
- Lower recurrence rates vs. vancomycin; 250 mg BID dose statistically superior

Commercial Outlook

- Growing CDAD market merits new agents
- Disease severity and recurrence rates are increasing
- Estimate global peak annual sales, in the range of $400-500 million, assuming clinical and regulatory success

IP Protection

- US patent protection through at least Dec 2020 (composition)
- Additional pending patent protection pending (composition through Dec 2029 if issued; formulation through May 2032 if issued)

http://www.cubist.com/products/cdad

Surotomycin – Efficacy and Safety of CB-183,315 for the Treatment of CDI

The drug
- Surotomycin, lipopeptide derived from daptomycin
- in vitro activity against *C. difficile*

Objective
Efficacy, safety and tolerability of surotomycin in patients with CDAD

Methods
- Phase 2, randomised, controlled, double-blind, multicenter
- adults with diarrhoea + pos. *C. difficile* toxin test
- received p.o. SUR 125, or 250 mg BID or vancomycin (125 mg QID) for 10 days
- 1° end point was clinical response
- 2° end point was recurrence within 4 weeks

Results
N=209

Registration

Funding
Cubist Pharmaceuticals Inc.

Surotomycin – Efficacy and Safety of CB-183,315 for the Treatment of CDI

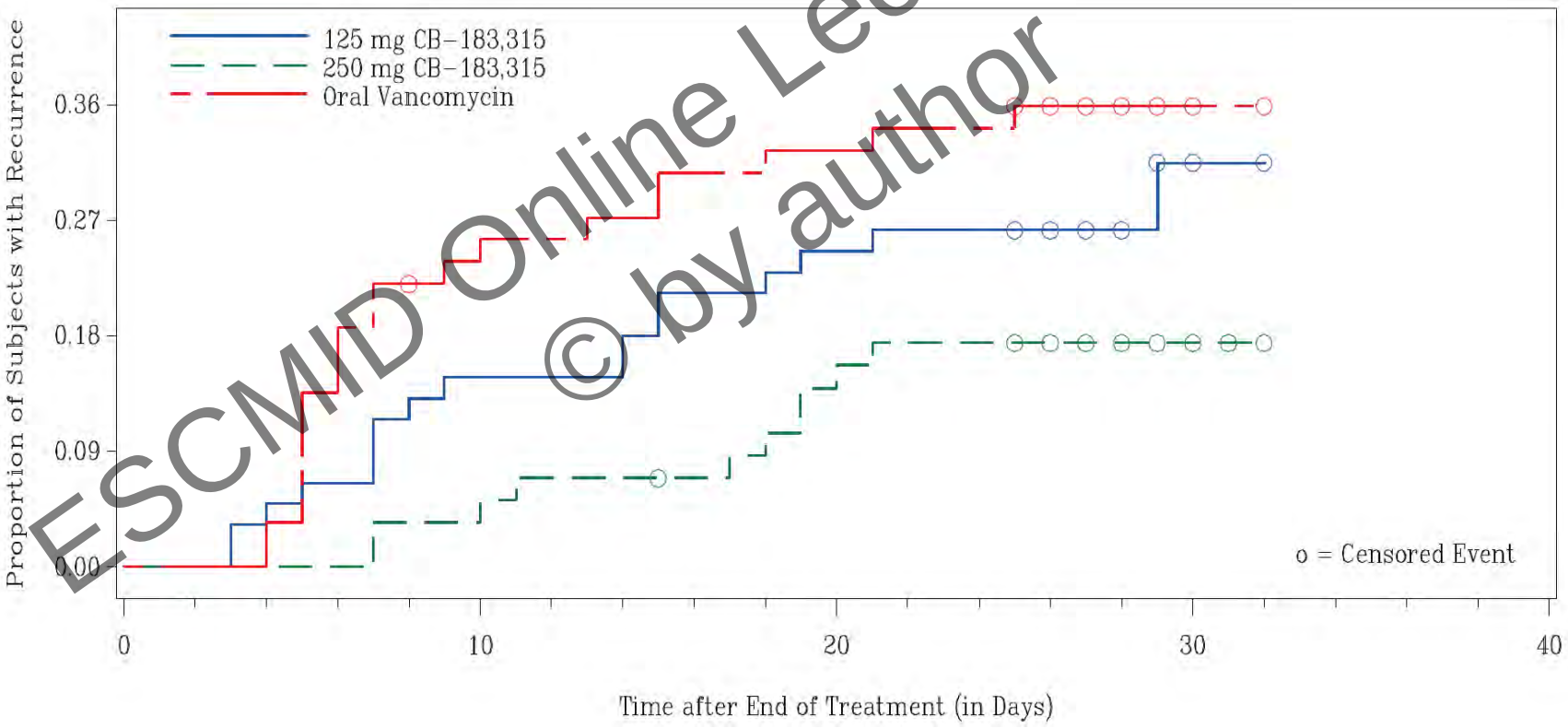
Outcome	CB-183,315 125 mg BID	CB-183,315 250 mg BID	Vancomycin 125 mg QID
Cure Rate	61/66 (92.4%)	58/67 (86.6%)	59/66 (89.4%)
Recurrence Rate	17/61 (27.9%)	10/58 (17.2%)	21/59 (35.6%)
Sustained Cure Rate	44/66 (66.7%)	47/67 (70.1%)	37/66 (56.1%)

Patino H et al. ICAAC 2011 Chicago K-205a.

Surotomycin Compared to Vancomycin
Time to Recurrence of Diarrhea After Treatment

(N=178)

Comparison	P-Values Log-Rank	Wilcoxon
125 mg versus Oral Vancomycin	0.287	0.216
250 mg versus Oral Vancomycin	0.014	0.007
125 mg versus 250 mg	0.159	0.148



Cadazolid – Late Breaker Poster LB 2956 Phase 2 Study Versus Vancomycin

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The drug
- Cadazolid, oxazolidinone with a fluoroquinolone moiety
- in vitro activity against *C. difficile*

Objective
Efficacy, safety and tolerability of cadazolid in subjects with CDAD

Methods
- Multicentre, double-blind, double-dummy, active comparator, randomised, dose-finding, parallel-group, phase 2 study
- adults with 1st occurrence or 1st recurrence
- diarrhoea + pos. *C. difficile* toxin test
- received p.o. CDZ 250, 500 or 1000 mg BID or vancomycin (125 mg QID) for 10 days

Results
N=84

Registration
EUDRA-CT 2010-020941-29 & NCT01222702

Funding
Actelion Pharmaceuticals Ltd.

Cadazolid – Late Breaker Poster LB 2956 Phase 2 Study Versus Vancomycin

Clinical cure rate, recurrence rate and sustained cure rate (mITT set)

Louie T et al. ECCMID 2013, Berlin, LB 2956.