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Cadazolid for the treatment of Clostridium difficile infection: results of two double-blind, double-dummy, non-inferiority, randomised controlled phase 3 trials

Supplementary material

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IMPACT 1

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IMPACT 2

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2. List of full inclusion and exclusion criteria

Inclusion criteria:

Eligible patients were required to have fulfilled all of the following inclusion criteria:

1. Signed informed consent prior to any study-mandated procedure.
2. Male or female[1,2] ≥18 years of age at the screening visit.
3. A diagnosis of mild–moderate or severe CDI (first occurrence or first recurrence within 3 months of randomisation) with:
    - Diarrhoea, defined as a change in bowel habits with >3 UBMs, in the 24 h prior to randomisation AND
    - Positive C. difficile Glutamate dehydrogenase (GDH) and toxin A and/or B stool test, on the same sample collected no more than 72 h prior to randomisation using an enzyme immunoassay (EIA) test approved by the sponsor (Quik Chek Complete; additional EIAs were approved by the sponsor if used as standard of care, full list in table).

C. Diff GDH Antigen EIA Test Name	**Manufacturer**
C. DIFF QUIK CHEK®	TechLab
C. DIFF CHEK®-60	TechLab
BD Culturette™ CDT™	Becton Dickinson
ImmunoCard® C. difficile EIA	Meridian
VIDAS C. difficile GDH	Biomerieux
Premier® C. difficile GDH	Meridian

Exclusion criteria

Eligible patients were required to have had none of the following exclusion criteria:

1. More than one previous episode of CDAD in the 3-month period prior to randomisation.
2. Fulminant or life-threatening CDAD. If in the judgment of the investigator there was a suspicion of fulminant or life-threatening CDAD, the presence of any of the following criteria during the 72 h period prior to randomisation and related to the fulminant or life-threatening CDAD episode excluded the potential patient from the study:
    - Septic shock – a systolic blood pressure (SBP) < 90 mmHg or a mean arterial pressure < 70 mmHg in the absence of other causes of hypotension and that persisted despite adequate fluid resuscitation
    - Peritonitis
    - Ileus
    - Toxic megacolon
    - Significant dehydration based on investigator judgment

[1] Non-pregnant women of childbearing potential:

A woman was considered to be of childbearing potential unless she met at least one of the following criteria:

- Previous bilateral salpingo-oophorectomy or hysterectomy;
- Premature ovarian failure confirmed by a health care professional;
- XY genotype, Turner syndrome, uterine agenesis;
- Postmenopausal, defined as 12 consecutive months with no menses without an alternative medical cause (ICH M3 definition).

[2] A non-pregnant woman of childbearing potential was eligible only if:

- The absence of pregnancy was confirmed by a negative urine (or plasma/serum) pregnancy test at Visit 1.
- She agreed to use one of the following methods of contraception from Visit 1 until 7 days after study treatment discontinuation: Condoms, diaphragm or contraceptive sponge if used in combination with a spermicide; Intra-uterine devices; Injectable contraceptive agents, levonorgestrel implants, or transdermal contraceptive hormone patches. If a hormonal contraceptive was chosen, it was required to be taken for at least 1 month prior to randomisation. Alternatively a sterilization method (tubal ligation or partner's vasectomy) was considered acceptable, or she was in a situation of abstinence from intercourse with a male partner, when this was in line with the preferred lifestyle of the patient (e.g., homosexual women or women in a religious order – e.g., nuns). In case of oral contraception, an additional method was to be employed, as diarrhoea could affect the effectiveness of the oral contraceptive pill. Rhythm methods or the use of a condom by a male partner alone were not considered as acceptable methods of contraception.

- White blood cells (WBC) count > 30.0 × 109/L
- Core body temperature >40 °C

3. Concurrent immediately life-threatening disease or condition (likelihood of death within 72 h).
4. History of inflammatory colitis (e.g., ulcerative colitis or Crohn's disease, microscopic colitis, collagenous colitis) or chronic abdominal pain or chronic diarrhoea of any aetiology, or known positive diagnostic test for enteropathogens (this criterion was clarified in Protocol Amendment 1 [Table 9-12]).
5. Vomiting or other condition that interfered with the ability to take oral medication or patients with feeding tubes (i.e., when study treatment would have to be given by the feeding tube).
6. Antimicrobial treatment (AMT) active against CDAD administered for >24 h except for metronidazole treatment failures.

3. Results of the treatment re-extension period

IMPACT 1

A total of 49 subjects were screened for enrolment into the re-treatment extension, of which 47 (16 previously randomised to cadazolid and 31 previously randomised to vancomycin) were enrolled and received open-label cadazolid. In the re-treatment extension with cadazolid, the re-treatment clinical cure rate was 89.4% (42/47 subjects). Of the re-treatment clinically cured subjects, nine (21.4%) had a recurrence. The re-treatment sustained cure rate was 63.8% (30/47 subjects). The median duration of study treatment in the re-treatment period was 10 days. The nature of adverse events was similar to that seen in the main study.

IMPACT 2

A total of 40 subjects were screened for enrolment into the re-treatment extension, of which, 36 (16 previously randomised to cadazolid and 20 previously randomised to vancomycin) were enrolled and received open-label cadazolid. In the re-treatment extension with cadazolid, the re-treatment clinical cure rate was 97.2% (35/36 subjects). Of the re-treatment clinically cured subjects, five (14.3%) had a recurrence. The re-treatment sustained cure rate was 75.0% (27/36 subjects). The median duration of study treatment in the re-treatment period was 10 days. The nature of adverse events was similar to that seen in the main study.

4. List of Data and Safety Monitoring Committee Members

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Robin Patel	Mayo Clinic, Rochester, MN, US
Tim Planche	St. George's University, London, UK
David DeMets	University of Minnesota, MN, US

5. List of investigator-assessed cure and failure criteria

Cure was qualified by any of the following criteria (or more than one criterion):

- Patient required no additional CDAD therapy or faecal microbial therapy between first dose of study treatment up to and including 2 days after EOT.
- Patient had ≤3 UBMs for 2 consecutive days on therapy and maintained for 2 days after EOT.
- Patient had a marked reduction in the number of UBMs (in the opinion of the investigator).
- Patient had stable and improved CDAD signs and symptoms (other than diarrhoea – e.g., abdominal pain, fever), or other criteria (e.g., WBC elevation [not due to a clear alternative aetiology]).

Failure was qualified by any of the following criteria (or more than one criterion):

- Patient required additional CDAD therapy or FMT between first dose of study treatment up to and including 2 days after EOT.
- Patient did not have ≤3 UBMs for 2 consecutive days on therapy and maintained for 2 days after EOT.
- Patient did not have a marked reduction in the number of unformed stools (in the opinion of the investigator).

Patient had worsened CDAD signs and symptoms (other than diarrhoea – e.g., abdominal pain, fever), or other criteria (e.g., WBC elevation [not due to a clear alternative aetiology]).

6. Statistical methods for the meta-analysis of epidemic strains

A meta-analysis was conducted on all patients confirmed at baseline to have CDI with epidemic strains of C. difficile identified in baseline stool samples by PCR ribotyping with the objective to demonstrate superiority of cadazolid versus vancomycin on the sustained cure rate. Data from IMPACT 1 and IMPACT 2 were pooled using a fixed effects meta-analysis to examine the treatment effect of cadazolid versus vancomycin on the

difference in proportions for sustained cure. A Cochran's Q test was used to examine the between-studies heterogeneity with a two-sided p-value.

7. List of Steering Committee Members

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8. Supplementary tables and figures

Supplementary tables

Table S1: Stratified sensitivity analysis of clinical cure by episode type and geographical region

		Cadazolid N, n (%)	Vancomycin N, n (%)	% difference cadazolid – vancomycin (95% CI)
IMPACT 1 mITT	CDI episode type			-1.5 (-7.2, 4.2)
	First occurrence	238, 198 (83.2)	253, 213 (84.2)	
	First recurrence	64, 55 (85.9)	65, 58 (89.2)	
	Geographical region			-1.4 (-7.0, 4.2)
	USA	101, 80 (79.2)	108, 83 (76.9)	
	Canada	83, 73 (88.0)	88, 77 (87.5)	
	Europe	111, 95 (85.6)	117, 107 (91.5)	
	Rest of the world	7, 5 (71.4)	5, 4 (80.0)	
IMPACT 1 PP	CDI episode type			-4.1 (-9.1, 0.9)
	First occurrence	220, 192 (87.3)	227, 208 (91.6)	
	First recurrence	62, 55 (88.7)	61, 56 (91.6)	
	Geographical region			-4.0 (-8.9, 0.9)
	USA	90, 77 (85.6)	95, 80 (84.2)	
	Canada	83, 73 (88.0)	82, 77 (92.9)	
	Europe	102, 92 (90.2)	106, 103 (97.2)	
	Rest of the world	7, 5 (71.4)	5, 4 (80.0)	
IMPACT 2 mITT	CDI episode type			-4.7 (-10.7, 1.3)
	First occurrence	235, 191 (81.3)	246, 209 (85.0)	
	First recurrence	55, 44 (80.0)	55, 49 (89.1)	
	Geographical region			-4.7 (-10.6, 1.2)
	USA	102, 72 (70.6)	107, 89 (83.2)	
	Canada	15, 12 (80.0)	16, 16 (100.0)	
	Europe	121, 106 (87.6)	124, 111 (89.5)	
	Rest of the world	52, 45 (86.5)	54, 42 (77.8)	
IMPACT 2 PP	CDI episode type			-4.9 (-10.3, 0.6)
	First occurrence	200, 173 (86.5)	209, 192 (91.9)	
	First recurrence	47, 41 (87.2)	50, 45 (90.0)	
	Geographical region			-5.2 (-10.5, 0.1)
	USA	83, 65 (78.3)	92, 83 (90.2)	
	Canada	15, 12 (80.0)	15, 15 (100.0)	
	Europe	110, 100 (90.9)	105, 101 (96.2)	
	Rest of the world	39, 37 (94.9)	47, 38 (80.9)	

CI, confidence interval; N, total number of patients within subgroup level in the treatment group; n, total number of responders, mITT, modified intent-to-treat analysis; PP, per-protocol analysis
Confidence intervals calculated using Wald method

Table S2: CDI DaySyms™ PRO

Domains	IMPACT 1			IMPACT 2		
	N (Cad, Van)	Treatment difference (change from baseline) Mean (95% CI)	p-value	N (Cad, Van)	Treatment difference (change from baseline) Mean (95% CI)	p-value
Diarrhoea symptoms	228, 234	0.002 (-0.20; 0.20)	0.9814	209, 223	-0.044 (-0.26; 0.17)	0.6871
Abdominal symptoms	227, 234	0.087 (-0.07; 0.25)	0.2879	209, 223	0.025 (-0.15; 0.20)	0.7833
Systemic/other symptoms	227, 234	0.050 (-0.09; 0.19)	0.4880	209, 223	0.061 (-0.09; 0.21)	0.4145

Cad, cadazolid; CI, confidence limits, Van, vancomycin.

Table S3: Recurrence rates (mITT)

	IMPACT 1		IMPACT 2	
	Cadazolid (n=302)	Vancomycin (n=318)	Cadazolid (n=290)	Vancomycin (n=301)
Clinical cure (n)	253	271	235	258
Recurrence (n)	38	58	37	46
Recurrence rate, % (95% CI)	15.0 (11.1; 19.9)	21.4 (16.9; 26.7)	15.7 (11.6; 20.9)	17.8 (13.6; 23.0)

CI, confidence limits; mITT, modified intent-to-treat analysis set.

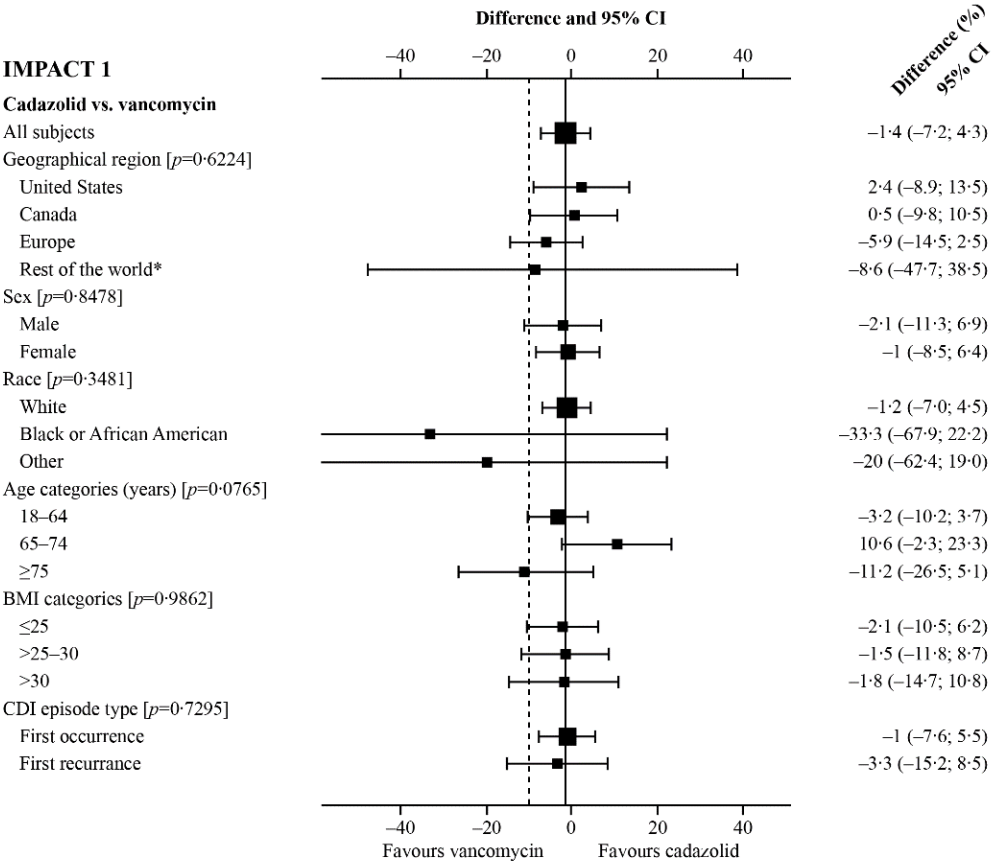
Table S4: Demographic characteristics of patients in the hypervirulent meta-analysis

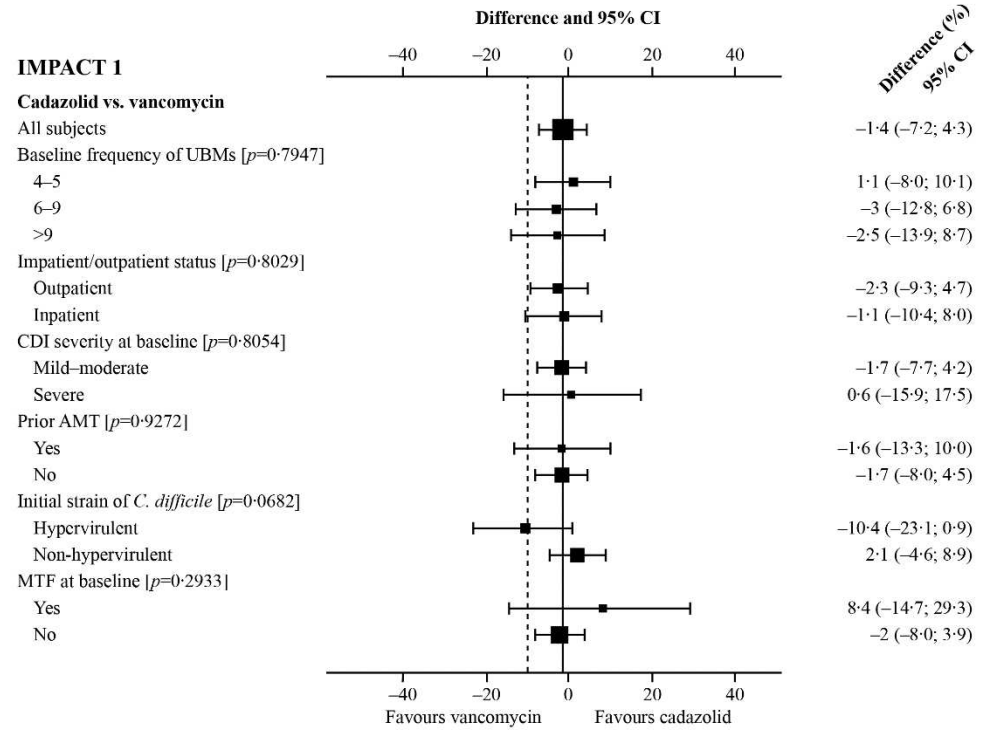
		IMPACT 1 and IMPACT 2 (pooled data)		
		Cadazolid N=133	Vancomycin N=170	Total N=303
Demographic characteristics, n (%)	Female	82 (61.7)	98 (57.6)	180 (59.4)
	Age 18–64 years	65 (48.9)	95 (55.9)	160 (52.8)
	Age 65–74 years	29 (21.8)	27 (15.9)	56 (18.5)
	Age ≥75 years	39 (29.3)	48 (28.2)	87 (28.7)
	White	130 (97.7)	158 (92.9)	288 (95.0)
Geographical regions, n (%)	USA	31 (23.3)	49 (28.8)	80 (26.4)
	Canada	13 (9.8)	21 (12.4)	34 (11.2)
	Europe	85 (63.9)	95 (55.9)	180 (59.4)
	Rest of world	4 (3.0)	5 (2.9)	9 (3.0)
CDI episode type, n (%)	First occurrence	100 (75.2)	130 (76.5)	230 (75.9)
	First recurrence	33 (24.8)	40 (23.5)	73 (24.1)
Hypervirulent ribotype at baseline, n (%)	027	119 (89.5)	144 (84.7)	263 (86.8)
	078	12 (9.0)	24 (14.1)	36 (11.9)
	244	2 (1.5)	2 (1.2)	4 (1.3)
CDI severity, n (%)	Severe	28 (21.1)	35 (20.6)	63 (20.8)
	Mild-moderate	94 (70.7)	124 (72.9)	218 (71.9)
	Unable to determine	11 (8.3)	11 (6.5)	22 (7.3)
MTF at baseline, n (%)	Yes	9 (6.8)	15 (8.8)	24 (7.9)

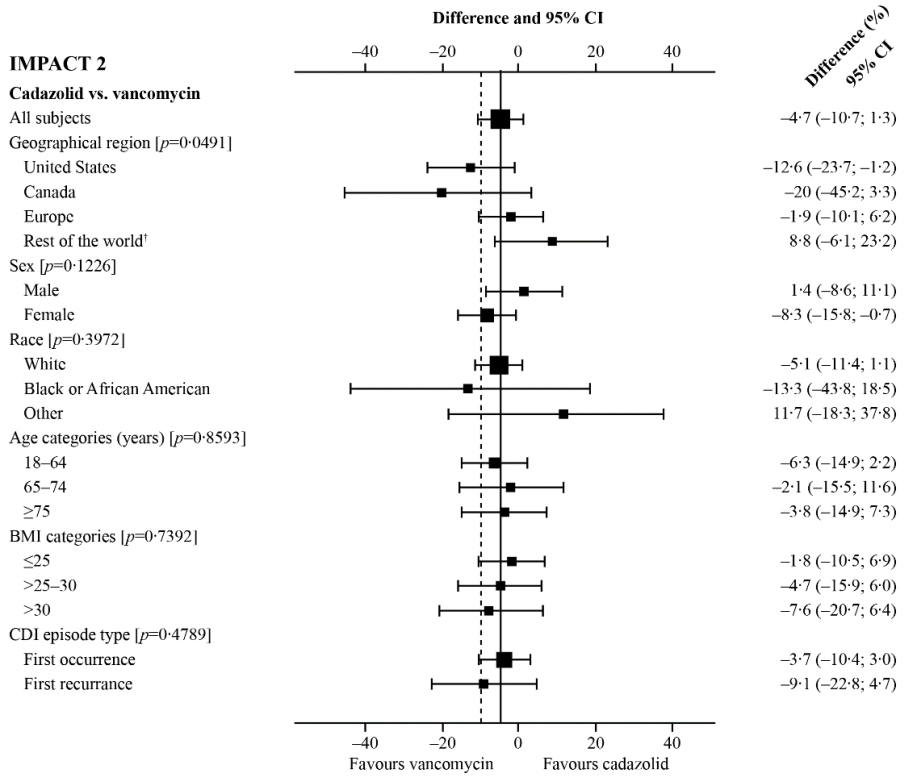
CDI, Clostridium difficile infection; MTF, metronidazole treatment failure.

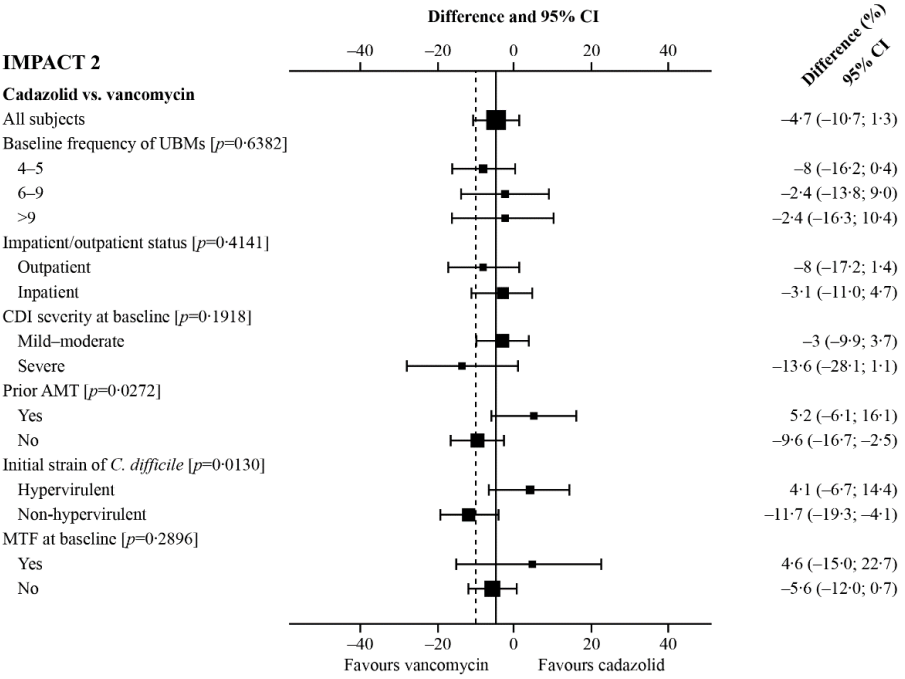
Supplementary figures

Figure S1: Clinical cure rate by subgroup (mITT) in the IMPACT 1 and IMPACT 2 trials



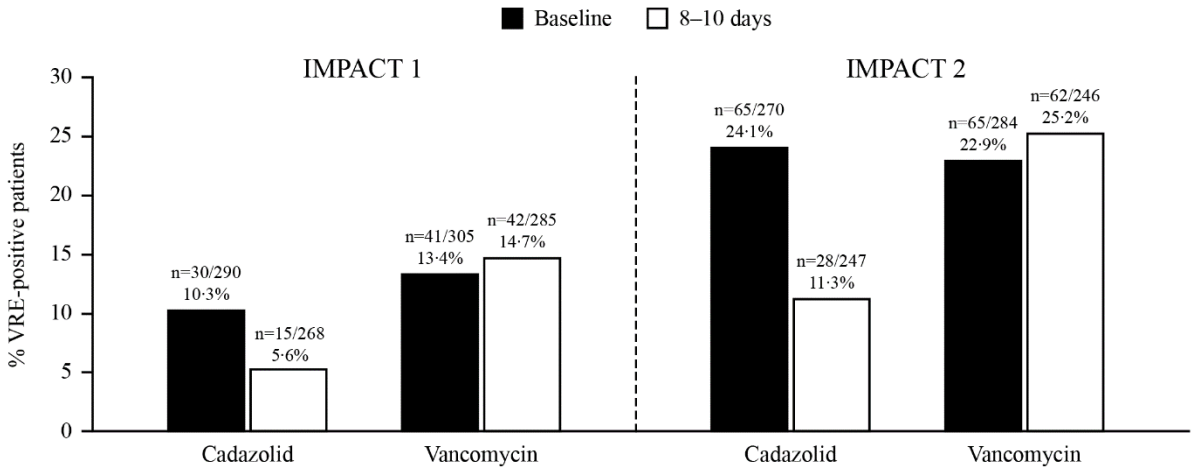






Rest of world: For IMPACT 1: Australia, Brazil, Peru. For IMPACT 2: Argentina, Brazil, Chile, Israel, Republic of Korea.
The solid vertical line references the overall treatment effect and the dotted vertical line represents the non-inferiority margin of -10%.
AMT, Antimicrobial treatment active against CDI; CI, confidence limits; MTF, faecal microbiota transplant; mITT, modified intent-to-treat analysis set, UBM, unformed bowel movements.

Figure S2: VRE carriage (mITT)



VRE, vancomycin-resistant enterococci.