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Clinical Pharmacological Review of Cefepime/Taniborbactam: A New Type β-lactamase Inhibitor Complex Formulation

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Abstract:

Bacterial resistance is increasing exponentially worldwide, especially in carbapenem-resistant Gram-negative bacteria, but effective therapeutic drugs are very limited. Taniborbactam is a novel cyclic borate ester β-lactamase inhibitor. It has a strong inhibitory effect on serine and metallo-β-lactamases (Ambler classes A, B, C, and D). Currently, taniborbactam is combined with cefepime for new drug development, with the potential to address this medication demand. This article provides a review of the mechanism, pharmacodynamics, and pharmacokinetic clinical studies of cefepime/taniborbactam.

Keywords:

β-lactamases
Cefepime
Taniborbactam
Pharmacodynamics
Pharmacokinetics

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1. Introduction

Infections caused by carbapenem-resistant Gram-negative bacteria (CR-GNB) pose a significant challenge in clinical anti-infective treatment, with limited options for antimicrobial agents. The primary mechanism of resistance of CR-GNB to antimicrobial agents is the production of carbapenemases. Therefore, the development of new drugs that inhibit the activity of carbapenemases represents an important direction in antimicrobial research and development. Currently, the novel β-lactamase inhibitors available for clinical use include avibactam, vaborbactam, and relebactam, which target class A *Klebsiella pneumoniae* Carbapenemase (KPC) and certain class D oxacillinases (OXA), but do not inhibit class B metallo-β-lactamases (MBL) [1]. Taniborbactam, first disclosed as a patented product by Venatorx Pharmaceuticals in 2014 [2], exhibits broad inhibitory activity against carbapenemases, including MBLs. Its combination with cefepime as a new antimicrobial agent for the treatment of CR-GNB infections has garnered significant clinical attention. This review summarizes the clinical pharmaceutical research

on cefepime/taniborbactam.

2. Development and mechanism of action of taniborbactam

Taniborbactam (VNRX-5133) is a boron-containing β-lactamase inhibitor developed by Venatorx Pharmaceuticals in the United States [2]. Its chemical structure is (3R)-3-[[2-[trans-4-[(2-aminoethyl)amino] cyclohexyl]acetyl]amino]-3,4-dihydro-2-hydroxy-2H-1,2-benzoxaborole-8-carboxylic acid (**Figure 1**), with a molecular formula of C19H28BN3O5 and a relative molecular weight of 389.2. Taniborbactam exhibits broad inhibitory activity against β-lactamases, including class A, C, and D serine-β-lactamases (SBLs) as well as some class B MBLs, such as Verona integron-encoded metallo-β-lactamase (VIM) and New Delhi metallo-β-lactamase (NDM). However, it has poor inhibitory activity against imipenem (IMP) [3]. Currently, five Phase I clinical studies [4–8] and one Phase III clinical study [9] have been completed for this drug, and a new Phase III clinical study was initiated in December 2023 [10].

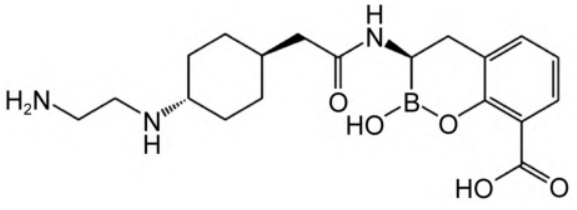

Figure 1. Chemical structure of taniborbactam [2].

Taniborbactam can mimic the intermediates of the hydrolysis process of β-lactamases by serine-based and zinc-based enzymes, thereby inhibiting the activity of β-lactamases [11]. The mechanism of action of taniborbactam primarily involves the formation of a reversible covalent bond with the serine residue, resulting in slow dissociation and prolonged residence time at the active site (half-life of 30 to 105 minutes), thus inhibiting the activity of SBLs. Its inhibition of MBLs is achieved through the interaction of boron with the active zinc site, inducing a narrowing of the active site cleft and forming a more stable enzyme-inhibitor complex. It exerts direct inhibitory effects on NDM and VIM by competing with their substrates for binding [12]. According to a study by Ono *et al.* (2024) [13], the effective binding of taniborbactam to NDM-1 is mediated by K224 and E149 (an amino acid side chain located near the active zinc site). Hydrogen bonding with K224 and E149, followed by the interaction of boron with the active zinc site, produces inhibition of NDM-1. However, the homologous residue of E149 in IMP-1 is D149, and its shorter aspartic acid side chain (by one carbon) compared to glutamic acid may prevent taniborbactam from forming a hydrogen bond with D149, suggesting a reason for taniborbactam's failure to inhibit IMP-1.

3. Pharmacodynamics (PD) studies of cefepime/taniborbactam

Current research indicates that taniborbactam exhibits good *in vitro* antibacterial activity against carbapenemase-producing Enterobacteriaceae and carbapenem-resistant *Pseudomonas aeruginosa*.

A Spanish study showed that among 67 meropenem-resistant Enterobacteriaceae isolates investigated, cefepime/taniborbactam demonstrated antibacterial activity against 94% of the resistant strains (minimum inhibitory concentration (MIC) > 8 $mg \cdot L^{-1}$), including strains producing KPC, OXA-48, and MBL enzymes [14]. In strains producing OXA-48 and MBL enzymes, cefepime/taniborbactam exhibited superior antibacterial activity compared to ceftazidime/avibactam, ceftolozane/tazobactam, imipenem/relebactam, and meropenem/vaborbactam (**Table 1**). A study by Mushtaq *et al.* (2021) [15] demonstrated that the combination of 4 $mg \cdot L^{-1}$ taniborbactam with cefepime could reduce the MIC values of KPC-producing Enterobacteriaceae from >128 $mg \cdot L^{-1}$ to 2 $mg \cdot L^{-1}$ and those of VIM-producing Enterobacteriaceae from >128 $mg \cdot L^{-1}$ to 8 $mg \cdot L^{-1}$. Piccirilli *et al.* (2021) [16] conducted an *in vitro* study on 26 MBL-producing Enterobacteriaceae isolates, including 13 *Escherichia coli*, 8 *Klebsiella pneumoniae*, 2 *Enterobacter cloacae*, and 3 *Citrobacter freundii*. The combination of taniborbactam (4 $mg \cdot L^{-1}$) with cefepime showed antibacterial activity against isolates producing VIM-1, VIM-2, VIM-4, VIM-19, NDM-1, NDM-5, and NDM-7, restoring the activity of cefepime against NDM-producing strains. However, it had no significant antibacterial effect on isolates producing IMP-1 and IMP-4 (**Table 2**). Another study indicated that cefepime/

Table 1. Activity of cefepime/taniborbactam and comparators against meropenem-resistant strains [14]

Carbapenemase (type)	FEP			FTB			CZA		
	MIC_{50} ($mg \cdot L^{-1}$)	MIC_{90} ($mg \cdot L^{-1}$)	Sensitivity rate (%)	MIC_{50} ($mg \cdot L^{-1}$)	MIC_{90} ($mg \cdot L^{-1}$)	Sensitivity rate (%)	MIC_{50} ($mg \cdot L^{-1}$)	MIC_{90} ($mg \cdot L^{-1}$)	Sensitivity rate (%)
Enterobacteriales (*n* = 247)	32	> 32	15.8	0.5/4	4/4	97.6	1/4	> 32/4	80.6
MER-R [27.1% (67/247)]	> 32	> 32	4.5	2/4	8/4	94.0	2/4	> 32/4	73.1
KPC (35/67)	> 32	> 32	0	2/4	8/4	94.3	2/4	8/4	94.3
OXA-48 (15/67)	16	> 32	20.0	4/4	8/4	100	1/4	2/4	93.3
VIM, NDM, IMP (16/67)	> 32	> 32	0	2/4	16/4	**87.5**	> 32/4	> 32/4	12.5
Pseudomonas (*n* = 170)	32	> 32	20.0	8/4	32/4	67.6	8/4	> 32/4	61.2
MER-R [71.8% (122/170)]	32	> 32	10.7	8/4	32/4	63.9	8/4	> 32/4	51.6
GES (30/122)	> 32	> 32	0	8/4	8/4	93.9	4/4	8/4	96.7
VIM (49/122)	> 32	> 32	13.0	8/4	> 32/4	61.2	> 32/4	> 32/4	14.3
Non-carbapenemase (43/122)	32	> 32	16.3	16/4	32/4	46.5	8/4	> 32/4	62.8
Carbapenemase (type)	**CT**			**IMR**			**MEV**		
	MIC_{50} ($mg \cdot L^{-1}$)	MIC_{90} ($mg \cdot L^{-1}$)	Sensitivity rate (%)	MIC_{50} ($mg \cdot L^{-1}$)	MIC_{90} ($mg \cdot L^{-1}$)	Sensitivity rate (%)	MIC_{50} ($mg \cdot L^{-1}$)	MIC_{90} ($mg \cdot L^{-1}$)	Sensitivity rate (%)
Enterobacteriales (*n* = 247)	> 32/4	> 32/4	11.7	1/4	8/4	71.7	1/8	16/8	89.1
MER-R [27.1% (67/247)]	> 32/4	> 32/4	3.0	2/4	> 32/4	53.7	4/8	> 32/8	62.7
KPC (35/67)	> 32/4	> 32/4	0	0.5/4	2/4	97.1	0.5/8	4/8	100
OXA-48 (15/67)	> 32/4	> 32/4	13.3	2/8	> 32/4	0	> 32/8	> 32/8	6.7
VIM, NDM, IMP (16/67)	> 32/4	> 32/4	0	8/4	> 32/4	12.5	16/8	> 32/8	31.2
Pseudomonas (*n* = 170)	8/4	> 32/4	34.7	16/4	> 32/4	37.1	32/8	> 32/8	32.9
MER-R [71.8% (122/170)]	8/4	> 32/4	17.2	32/4	> 32/4	16.4	> 32/8	> 32/8	8.2
GES (30/122)	8/4	8/4	0	32/4	32/4	0	> 32/8	> 32/8	0
VIM (49/122)	> 32/4	> 32/4	0	> 32/4	> 32/4	0	> 32/8	> 32/8	4.1
Non-carbapenemase (43/122)	8/4	> 32/4	48.8	4/4	32/4	46.5	16/8	> 32/8	18.6

Note: MER - Meropenem; FEP - Cefepime; FTB - Cefepime/Taniborbactam; CZA - Ceftazidime/Avibactam; CT - Ceftolozane/Tazobactam; IMR - Imipenem/Relebactam; MEV - Meropenem/Vaborbactam.

Table 2. *In vitro* antibacterial activity of β-lactam and β-lactam/β-lactamase inhibitors against 26 strains of MBLs-producing Enterobacteriaceae [16]

Clinical isolates	Encoding	β-lactamase type	MIC/mg·L^{-1}						
			AMX	AMC	MEM	FEP	CAZ	CAZ/AVI	FTB
Escherichia coli/VIM-1	AQ-2	B	> 512	256	> 128	> 1024	> 1024	> 1024	0.5
Escherichia coli/VIM-1	AQ-5	B	> 512	256	> 128	> 1024	> 1024	> 1024	0.5
Escherichia coli/VIM-1	AQ-28	B	> 512	256	> 128	> 1024	> 1024	> 1024	0.5
Citrobacter freundii/VIM-1	AQ-24	B	> 512	256	> 128	> 1024	> 1024	> 1024	1.0
Klebsiella pneumoniae/VIM-1	AQ-88	B	> 512	256	> 128	> 1024	> 1024	> 1024	2.0
Klebsiella pneumoniae/VIM-1	AQ-90	B	> 512	256	> 128	> 1024	> 1024	> 1024	2.0
Klebsiella pneumoniae/VIM-1	AQ-95	B	> 512	256	> 128	> 1024	> 1024	> 1024	2.0
Enterobacter cloacae/VIM-2	AQ-102	B	> 512	256	> 128	> 1024	> 1024	128	0.25
Enterobacter cloacae/VIM-2	AQ-100	B	> 512	256	> 128	> 1024	> 1024	128	0.25
Escherichia coli/VIM-4	AQ-33	B	> 512	256	> 128	> 1024	> 1024	> 1024	0.5
Escherichia coli/VIM-19	AQ-32	B	> 512	256	> 128	> 1024	> 1024	256	0.12
Escherichia coli/IMP-1/CMY-2	AQ-41	B/C	> 512	256	> 128	> 1024	> 1024	> 1024	128
Klebsiella pneumoniae/IMP-4/SHV-12	AQ-45	B/A	> 512	256	> 128	> 1024	> 1024	> 1024	128
Citrobacter freundii/NDM-1	AQ-25	B	> 512	256	> 128	> 1024	> 1024	> 1024	0.12
Citrobacter freundii/NDM-1	AQ-23	B	> 512	256	> 128	> 1024	> 1024	> 1024	0.12
Escherichia coli/NDM-1	AQ-7	B	> 512	256	> 128	> 1024	> 1024	> 1024	4.0
Escherichia coli/NDM-1	AQ-11	B	> 512	256	> 128	> 1024	> 1024	> 1024	4.0
Escherichia coli/NDM-1	AQ-22	B	> 512	256	> 128	> 1024	> 1024	> 1024	0.25
Escherichia coli/NDM-1-CTX-M-15	AQ-92	B/A	> 512	256	> 128	> 1024	> 1024	> 1024	1.0
Klebsiella pneumoniae/NDM-1	AQ-12	B	> 512	256	> 128	> 1024	> 1024	> 1024	1.0
Klebsiella pneumoniae/NDM-1	AQ-15	B	> 512	256	> 128	> 1024	> 1024	> 1024	1.0
Klebsiella pneumoniae/NDM-1/OXA-181	AQ-17	B/D	> 512	256	> 128	> 1024	> 1024	> 1024	1.0
Klebsiella pneumoniae/NDM-1/OXA-232	AQ-18	B/D	> 512	256	> 128	> 1024	> 1024	> 1024	0.5
Escherichia coli/NDM-5	AQ-44	B	> 512	256	> 128	> 1024	> 1024	> 1024	4.0
Escherichia coli/NDM-5	AQ-39	B	> 512	256	> 128	> 1024	> 1024	> 1024	4.0
Escherichia coli/NDM-7	AQ-42	B	> 512	256	> 128	> 1024	> 1024	> 1024	1.0

Note: AMX - Amoxicillin; AMC - Amoxicillin-Clavulanic Acid; MEM - Meropenem; FEP - Cefepime; CAZ - Ceftazidime; AVI - Avibactam; FTB – Cefepime / Taniborbactam.

taniborbactam exhibited good *in vitro* antibacterial activity against NDM-producing *Escherichia coli* isolates. Some NDM-5-producing *Escherichia coli* isolates had MIC values > 8 $mg \cdot L^{-1}$, which may be due to mutations in penicillin-binding protein 3 (PBP3) caused by amino acid insertions [17].

Studies by Kloezen *et al.* (2021) [18] have shown that taniborbactam restores the antibacterial activity of cefepime against carbapenem-resistant *Pseudomonas aeruginosa*, reducing the MIC values of cefepime against strains producing AmpC- and VIM. An *in vitro* study in Spain demonstrated that among 122 isolates of meropenem-resistant *Pseudomonas aeruginosa*, cefepime/taniborbactam exhibited antibacterial activity against 63.9% of the resistant strains, particularly showing higher activity against 30 strains producing the Guiana extended-spectrum β-lactamase (GES) [14]. Among these resistant strains, cefepime/taniborbactam (MIC ≤ 8/4 $mg \cdot L^{-1}$) showed higher antibacterial activity compared to ceftazidime/avibactam, ceftolozane/tazobactam, imipenem/relebactam, and meropenem/vaborbactam. Additionally, among 43 carbapenemase-non-producing resistant *Pseudomonas aeruginosa* strains, the antibacterial activity of cefepime/taniborbactam was comparable to that of ceftolozane/tazobactam and imipenem/relebactam, and higher than meropenem/vaborbactam (**Table 1**).

4. Pharmacokinetic (PK) and PD studies of cefepime/taniborbactam in animal models

In a neutropenic mouse thigh infection model, dose-ranging studies of taniborbactam revealed that increasing its dosing concentration enhances the antibacterial activity of cefepime against KPC-, OXA-, and ESBL-producing Gram-negative bacteria. The dosing frequency did not affect cefepime's antibacterial activity [19], suggesting that the PK/PD parameter most relevant to taniborbactam's inhibitory activity may be fAUC0-24/MIC. Increasing the dose of taniborbactam can enhance its enzyme-inhibiting effect. Human simulation studies showed that cefepime/taniborbactam (2/0.5 g, q8h, 2-hour infusion) has good *in vivo* antibacterial activity against carbapenem-resistant strains. In vivo studies conducted in mouse models of complex urinary tract infection (cUTI) [20] and pneumonia [21] demonstrated that cefepime/taniborbactam exhibits significant antibacterial activity against SBLs-producing Enterobacteriaceae (including CTX-M, KPC, OXA-48), AmpC-type *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*. A dosing regimen of 2/0.5 g, q8h is suggested. In a bacteremia model of mice infected with *Escherichia coli* (NDM-1) or *Klebsiella pneumoniae* (KPC-2, VIM-4, CMY-4), taniborbactam reduced the ED_{50} of cefepime by approximately 5 times [22]. These findings can guide the selection of dosing regimens for humans.

5. PK studies of cefepime/taniborbactam in humans

PK studies of taniborbactam in healthy subjects [23] showed that the C_{max} of taniborbactam after single-day administration (750 mg, q8h) was (39,122 ± 23.7) $ng \cdot mL^{-1}$, with an AUC of (11,914 ± 18.0) $ng \cdot h \cdot mL^{-1}$. For multiple-day administration (750 mg, q8h), the C_{max} was (38,778 ± 18.2) $ng \cdot mL^{-1}$, and the AUC was (139,518 ± 21.6) $ng \cdot h \cdot mL^{-1}$. The volume of distribution (V_z) was (37.4 ± 19.9) L, the half-life (t1/2) was (4.7 ± 15.4) h, and the renal clearance at steady state (CLr,ss) was (5.2 ± 28.6) $L \cdot h^{-1}$. Approximately 90% of taniborbactam was excreted unchanged in urine (**Table 3**). Based on the evaluation of blood urea nitrogen, serum creatinine, glomerular filtration rate, and tubular epithelial cell casts, there was no evidence of nephrotoxicity with cefepime/taniborbactam. There were no significant differences in C_{max} and T_{max} between single and multiple-day administrations of taniborbactam. The AUC was higher after multiple-day administration, and both C_{max} and AUC increased with higher dosing.

Dowell *et al.* (2022) [24] studied both healthy subjects and subjects with renal impairment, showing that the PK profiles of cefepime and taniborbactam are generally similar. At a dose of 2/0.5 g for cefepime/taniborbactam, the renal clearance (CLR) was essentially the same for healthy subjects and those with mild renal impairment, at (4.37 ± 17.8) and (4.23 ± 22.7) $L \cdot h^{-1}$, respectively. For subjects with moderate renal impairment, CLR was (1.59 ± 21.0) $L \cdot h^{-1}$, and for those with severe renal impairment, CLR was (0.76 ± 120.3) $L \cdot h^{-1}$. All renal impairment groups showed significantly increased AUC,

Table 3. PK parameters of taniborbactam at different doses [23] (mean ± SD)

Parameter	Days of administration (ration/d)	Dose of taniborbactam		
		250 mg, q8h	500 mg, q8h	750 mg,q8h
C_{max}/ng·mL^{-1}	1	10544 ± 18.3	25778 ± 15.2	39122 ± 23.7
	10	11188 ± 16.5	26533 ± 13.0	38778 ± 18.2
T_{max} /h	1	2.0 (2.0, 2.1)	2.0 (2.0, 2.1)	2.0 (2.0, 2.3)
	10	2.0 (2.0, 2.1)	2.0 (2.0, 2.3)	2.0 (2.0, 2.3)
AUC/ng·h·mL^{-1}	1	34447 ± 17.2	81890 ± 14.7	119140 ± 18.0
	10	41563 ± 15.1	89103 ± 13.8	139518 ± 21.6
V_z/L	10	36.0 ± 28.3	39.8 ± 14.3	37.4 ± 19.9
CL_{ss}/L·h^{-1}	10	6.2 ± 15.9	5.7 ± 12.6	5.6 ± 21.1
$t_{1/2}$/h	10	4.1 ± 29.3	4.9 ± 13.3	4.7 ± 15.4
Ae/mg	10	211.0 ± 11.8	462.2 ± 10.2	692.2 ± 21.7
Fe/%	10	84.4 ± 11.8	92.4 ± 10.2	92.3 ± 21.7
$CL_{R.ss}$/L·h^{-1}	10	5.2 ± 17.3	5.3 ± 14.2	5.2 ± 28.6

Table 4. PK parameters of cefepime/taniborbactam in subjects with different renal functions [24] (mean ± SD)

Parameter	Normal renal function	Renal impairment		
		Mild	Moderate	Severe
Cefepime				
C_{max}/μg·mL^{-1}	102 ± 25.3	101 ± 19.4	124 ± 20.6	129 ± 21.8
AUC/μg·h·mL^{-1}	343 ± 13.2	418 ± 9.0	913 ± 20.0	1589 ± 69.0
$t_{1/2}$/h	2.53 ± 0.53	3.03 ± 0.39	5.53 ± 1.34	10.12 ± 5.16
V_Z/L	20.2 ± 20.5	20.0 ± 21.2	16.3 ± 25.6	16.4 ± 21.1
CL/L·h^{-1}	5.65 ± 13.8	4.61 ± 11.6	2.09 ± 23.2	1.23 ± 66.6
Taniborbactam				
C_{max}/μg·mL^{-1}	22.0 ± 11.2	22.8 ± 22.6	26.9 ± 24.1	27.9 ± 21.7
AUC/μg·h·mL^{-1}	83.6 ± 11.4	97.4 ± 11.5	225 ± 22.5	445 ± 79.3
$t_{1/2}$/h	10.2 ± 2.6	19.5 ± 9.9	17.6 ± 2.6	21.3 ± 10.1
V_Z/L	82.0 ± 33.4	123.0 ± 59.5	53.1 ± 35.6	31.5 ± 43.5
CL/L·h^{-1}	5.79 ± 11.7	4.95 ± 13.9	2.12 ± 25.8	1.10 ± 76.7
CL_R/L·h^{-1}	4.37 ± 17.8	4.23 ± 22.7	1.59 ± 21.0	0.76 ± 120.3

C_{max}, and $t_{1/2}$ compared to the normal group (**Table 4**). For patients with reduced renal function, increased plasma concentrations, prolonged drug half-life, and varying degrees of renal damage, adjustments to the dosing of cefepime and taniborbactam are necessary.

6. Phase III clinical study of cefepime/taniborbactam

There is limited clinical research data available for cefepime/taniborbactam. Currently, a Phase III double-blind, randomized controlled clinical study (NCT03840148) [9] has been completed to evaluate the clinical efficacy, safety, and tolerability of cefepime/taniborbactam (2 g/0.5 g, q8h) compared to meropenem (1 g, q8h) in the treatment of cUTI. This study defines microbiological eradication as <1000 CFU/mL for Gram-negative bacteria, and clinical resolution as the resolution or return to baseline of symptoms of urinary tract infection. The observation period ranged from 7 to 14 days of treatment up to 28 to 35 days of follow-up. Results from various observation stages showed that the cefepime/taniborbactam treatment group was superior to the meropenem treatment group in both microbiological and clinical outcomes (**Table 5**) [25].

Regarding adverse events that occurred during treatment, the study showed that the most common symptoms were headache and diarrhea, with a rate of 35.5% in the cefepime/taniborbactam group and 29.0% in the meropenem group. The safety and tolerability of cefepime/taniborbactam were good, and its safety profile was similar to that of meropenem [25].

7. Summary

In summary, taniborbactam exhibits good inhibitory activity against carbapenemases. As a novel β-lactam/β-lactamase inhibitor combination, cefepime/taniborbactam demonstrates strong antibacterial activity against CR-GNB, providing a new treatment option for clinical use. Currently, the available research data is limited, and further studies are needed on the *in vitro* antibacterial activity of cefepime/taniborbactam against a larger sample size of clinically isolated strains, as well as on the types of infections treated, efficacy, and safety in clinical settings.

Table 5. Comparison of the efficacy of cefepime/taniborbactam and meropenem [25]

Outcome measures	Number of effective patients / Total number of patients (Effective rate, %)		Treatment difference (%) (95% CI)
	Cefepime / Taniborbactam	Meropenem	
Primary outcome measures			
Composite success in cure trial	207/293 (70.6)	83/143 (58.0)	12.6 (3.1–22.2)
Microbiology	229/293 (78.2)	95/143 (66.4)	11.7 (2.9–21.0)
Clinical	251/293 (85.7)	116/143 (81.1)	4.5 (-2.6–12.6)
Secondary outcome measures			
Composite success at the end of treatment	261/293 (89.1)	123/143 (86.0)	3.1 (-3.2–10.4)
Microbiology	284/293 (96.9)	139/143 (97.2)	-0.3 (-3.5–4.1)
Clinical	265/293 (90.4)	127/143 (88.8)	1.6 (-4.1–8.5)
Composite success during later follow-up	187/293 (63.8)	74/143 (51.7)	12.1 (2.2–21.9)
Microbiology	207/293 (70.6)	90/143 (62.9)	7.7 (-1.6–17.3)
Clinical	238/293 (81.2)	102/143 (71.3)	9.9 (1.5–18.8)

Disclosure statement

The authors declare no conflict of interest.

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