REVIEW

Oritavancin – A new semisynthetic lipoglycopeptide agent to tackle the challenge of resistant gram positive pathogens

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Abstract: Natural glycopeptide antibiotics like vancomycin and teicoplanin have played a significant role in countering the threat posed by Gram-positive bacterial infections. The emergence of resistance to glycopeptides among enterococci and staphylococci has prompted the search for second-generation drugs of this class and semi-synthetic derivatives are currently under clinical trials. Antimicrobial resistance among Gram-positive organisms has been increasing steadily during the past several decades and the current development of antibiotics falls short of meeting the needs. Oritavancin (LY-333328 diphosphate), a promising novel second-generation semisynthetic lipoglycopeptide, has a mechanism of action similar to that of other glycopeptides. It has concentration-dependent activity against a variety of Gram-positive organisms specially methicillin-resistant *Staphylococcus aureus (MRSA)*, vancomycin-intermediate resistant *Staphylococcus aureus (VISA)*, *Streptococcus pneumoniae* and vancomycin-resistant enterococcus. It is rapidly bactericidal against many species and in particular for enterococci where vancomycin and teicoplanin are only bacteriostatic even against susceptible strains. The pharmacokinetic profile of oritavancin has not been fully described; however, oritavancin has a long half-life of about 195.4 hours and is slowly eliminated by renal means. Oritavancin is not metabolized by the liver in animals. Oritavancin will most probably be prescribed as a once-daily dose and it demonstrates concentration-dependent bactericidal activity. Oritavancin has demonstrated preliminary safety and efficacy in Phase I and II clinical trials. In a Phase III clinical trial, oritavancin has achieved the primary efficacy end point in the treatment of complicated Gram-positive skin and skin-structure infections. To date, adverse events have been mild and limited; the most common being administration site complaints, headache, rhinitis, dry skin, pain, increases in liver transaminases and accumulation of free cholesterol and phospholipids in phagocytic (macrophages) and nonphagocytic (fibroblast) cells. Oritavancin appears to be a promising antimicrobial alternative to vancomycin (with additional activity against Staphylococcus and Enterococcus resistant to vancomycin) for the treatment of complicated Gram-positive skin and skin-structure infections. Additional clinical data are required to fully explore its use.

Keywords: Oritavancin LY-333328 semisynthetic second-generation lipoglycopeptide resistant *Staphylococcus aureus* Gram-positive organisms.

INTRODUCTION

Antimicrobial resistance among gram-positive organisms has been increasing steadily during the past several decades (Anon, 2002; Anon, 1994; Smith *et al*., 1999; Novak *et al*., 1999). Vancomycin remains the mainstay for the treatment of gram-positive infections but unfortunately, resistance continues to emerge in staphylococci and enterococci (Tenover and McDonald, 2005). Few options exist at present for the treatment of resistant gram-positive infections specially Staphylococcus aureus and Enterococcus species. Available antimicrobials that are used to treat resistant gram-positive infections include vancomycin, daptomycin, linezolid, quinupristin-dalfopristin and tigecycline (Bosso, 2005). However, there are limitations such as the lack of oral formulations and resistance to most of these agents. Currently, there is still the need for new agents to treat resistant gram-positive infections. Unfortunately, the number of approved antibiotics has decreased by 56% from 1983-1987 to 1998-2002 (Spellberg *et al*., 2004). At present, only 1.6% of all medications in development by the pharmaceutical companies are antibiotics. The current development of antibiotics falls short of meeting the needs to treat resistant infections in the future (Spelberg *et al*., 2004; Van Bambeke, 2004a; Van Bambeke, 2004b). Therefore, oritavancin which is a new glycopeptide antimicrobial agent with coverage of resistant gram-positive infections would be an important addition to the antimicrobial armamentarium.

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This review describes the most up-to-date data for oritavancin with an emphasis on its history, chemistry, mechanism of action, in vitro activity, pharmacokinetics and pharmacodynamics, clinical efficacy and safety.

History

Oritavancin is a semisynthetic lipoglycopeptide antimicrobial agent originally discovered by Eli Lilly Research Laboratories for use in the treatment of serious infection with resistant gram-positive pathogens (Nicas *et al*., 1996; Schwalbe *et al*., 1996). For the past several years, Intermune owned exclusive rights to this compound and placed a hold on further development of this drug because oritavancin did not fit into the company's core focus areas of pulmonology and hepatology. They were seeking a partner to assume its future development. On 27 December 2005, Targanta Therapeutics acquired the worldwide ownership and exclusivity rights to Oritavancin (http://www.targanta.com/ pipeline/orita vancin.html The Targanta pipeline). This company submitted a new drug application (NDA) with the U.S. Food and Drug Administration (FDA) in February 11, 2008 that includes data from 19 trials for seeking approval of oritavancin (http:// www. drugs.com/nda /oritavancin_080211.html "Drugs.com, Targanta Submits Oritavancin New Drug Application"); in April 2008, the FDA accepted the NDA submission for standard review, establishing an action date of December 8, 2008 (http://www.fdanews.com/newsletter/article?articleId=10 5717&issueId=11481. "FDA News, Targanta to Get FDA Decision by December".). On 9 Dec 2008 the FDA said insufficient data for approval of oritavancin had been provided (http://www.fiercebiotech. com/press-releases/fda-issues-complete-response-letter-oritavancin).

Additionally, Targanta's Marketing Authorization Application (MAA) for oritavancin was submitted and accepted for review by the European Medicines Agency (EMEA) in June 2008 (http://www.pharmaceutical-business-review.com/article_news.asp?guid= BBD6223C-8695-4173-8E37-F4463C61A20E "Pharmaceutical Business Review, EMEA accepts Targanta's oritavancin MAA for review".).

Chemistry

Vancomycin, the first glycopeptide was discovered more than 50 years ago from a soil sample collected on the island of Borneo (Anderson *et al*., 1956-57). Glycopeptides are widely known natural compounds that demonstrate activity against Gram-positive pathogens and are produced by the fermentation process of Actinomycetes (*Nocardia orientalis*; formerly *Amycolatopsis orientalis*)(Anderson *et al*., 1956-57). Oritavancin (LY-333328 diphosphate) (4''R)-22-O-(3-amino-2,3,6-trideoxy-3-C-methyl-alpha-L-arabino-hexopyranosyl)-N3''-[(4-chloro-[1,1'-biphenyl]-4'-yl)methyl] vancomycin diphosphate is a second generation, semisynthetic lipoglycopeptide derived from the glycopeptide family of compounds (Bhavnani *et al*., 2004; Lu *et al*., 2004). The oritavancin structure contains both hydrophobic and lipophilic groups and that's why it is lipoglycopeptide (fig. 1). Oritavancin is the N-alkyl-p-chlorophenylbenzyl derivative of chloroeremomycin, an analogue of vancomycin (Lu *et al*., 2004), whereas, dalbavancin (another glycopeptide) is derived from a teicoplanin-like compound. This structural modification imparts a significant increase in potency against vancomycin-resistant *Enterococci* and vancomycin-intermediate and -resistant *Staphylococcus* compared with vancomycin (Cooper *et al*., 1996; Allen and Nicas, 2003).

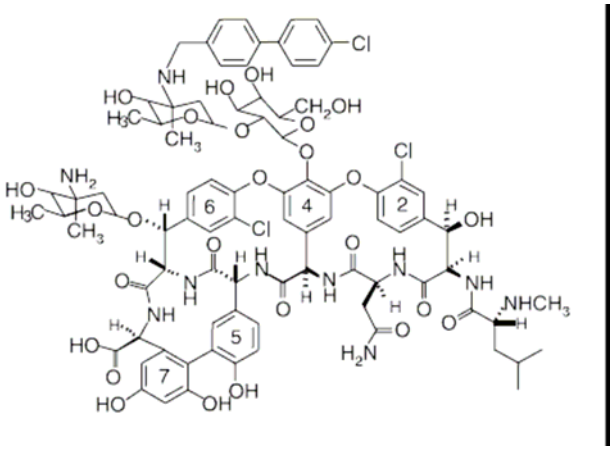

Fig. 1: Chemical Structure of Oritavancin (LY333328) which is the N-alkyl-p-chlorophenylbenzyl derivative of chloroeremomycin, an analogue of vancomycin. Oritavancin's structure is similar to the glycopeptides vancomycin and teicoplanin. However, oritavancin contains an additional unsubstituted sugar and an aromatic lipophilic side chain.

MODE OF ACTION

Oritavancin inhibits bacterial cell wall formation by blocking the transglycosylation step of peptidoglycan synthesis (Malabarba *et al*., 1997). Oritavancin-like peptides (unlike vancomycin-like peptides) have two cell wall binding sites (the pentaglycyl bridging segment as well as the well-known D-alanyl-D-alanine pentapeptide stem terminus) of Gram-positive pathogens, providing a dual mode of action that may account for the enhanced potency of oritavancin against vancomycin-resistant bacteria (Kim *et al*., 2008). The drug is bound to the D-Ala-D-Ala terminus of one stem and is proximate to the bridging pentaglycyl segment that cross-links the two stems (Fig. 2). Structural details of the binding site are revealed in a model of the glycopeptide-peptidoglycan interaction produced by molecular dynamics simulations with internuclear distance restraints determined by solid-state NMR (Cegelski *et al*., 2006). In addition, unlike

vancomycin, oritavancin has a 4-epi-vancosamine sugar which increases dimer formation (Cooper *et al*., 1996) and a chlorobiphenyl side chain, which ensures membrane anchoring (Allen and Nicas, 2003). Oritavancin appears to have multiple mechanisms of action including perturbations of membrane potential (depolarization & increased permeability) and effects on RNA synthesis in addition to the primary mode of action (cell wall synthesis & septum formation) (Belley *et al*., 2008; Arhin *et al*., 2007; Belley *et al*., 2007).

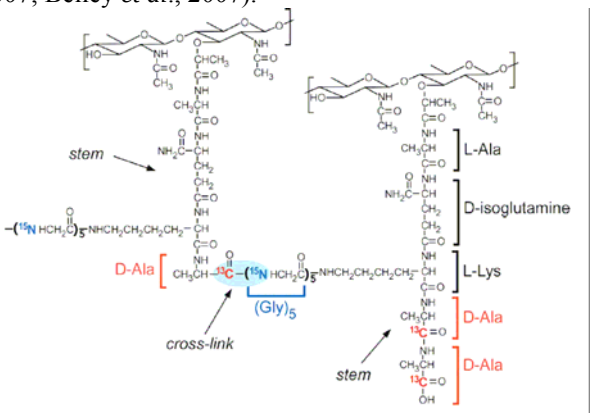

Fig 2: Chemical Structures of two peptidoglycan stems in the cell walls of *S. aureus* grown on media containing D-[1-^{13}C]alanine, [^{15}N]glycine, and an alanine racemase inhibitor (alaphosphin). The stem on the left contains a D-Ala-Gly1 cross-link site (light blue highlight). The bridging pentaglycyl segment is attached by Gly5 to the stem on the right, which ends in a D-Ala-D-Ala oritavancin binding site (From Cegelski *et al*., 2006).

Spectrum of activity and resistance

Oritavancin has demonstrable *in vitro* activity against many Gram-positive (table 1) and anaerobic bacteria. Gram-negative bacteria possess an outer membrane through which glycopeptides are naturally unable to pass (Ward *et al*., 2006).

Oritavancin demonstrates excellent *in vitro* activity against susceptible and multidrug resistant *staphylococci* (Table 2), *enterococci* (Table 3) and *streptococci* (Table 4) (Patel *et al*., 1998; Zeckel *et al*., 2000; Garcia-Garrote *et al*., 1998). Most promising is its activity against vancomycin-resistant *Enterococcus faecium*, *E. faecalis* (including VanA, VanB, and Van C phenotypes) penicillin resistant *Streptococcus pneumonia* and methicillin-resistant *S.aureus* (MRSA) (Schwalbe *et al*., 1996; Biavasco *et al*., 1997; Garcia-Garrote *et al*., 1998; Patel *et al*., 1998; Mezzatesta *et al*., 1998; Zeckel *et al*., 2000; Jones and Barry, 1987; Fasola *et al*., 1996; Noviello *et al*., 2001). The MIC90 values are 0.12µg/ml for MSSA, 0.25µg/ml for MRSA, 0.015µg/ml for vancomycin-susceptible-*E.faecium*, 0.25µg/ml for VR *E. faecium*, 1µg/ml for VR *E. faecalis*.

Activity has also been demonstrated against *Bacillus anthracis* and vancomycin- intermediate and -resistant *S. aureus* (Bozdogan *et al*., 2004; Aeschlimann *et al*., 2000; Heine *et al*., 2001) and MIC values are 0.5-1 µg/ml for VISA and 0.06-0.5µg/ml for VRSA (Draghi *et al*., 2007).

Oritavancin demonstrates *in vitro* activity against anaerobic bacteria including *Propionibacterium acnes*, *Clostridium difficile* and *Clostridium perfringens* (Jones

Table 1: Original (1996) and current (2007) published estimates of *in vitro* activity of oritavancin: MIC_{90} (range)

	Nicas *et al*., 1996*	Schwalbe *et al*., 1996*	Sahm *et al*., 2008; Draghi *et al*., 2007
			2008 ; Arhin et al., 2008)
MSSA	0.5(≤0.063-1)		0.12(≤0.004-2)
MRSA	0.5(≤0.063-0.5)	1(≤0.25-2)	0.25 (≤0.004-4)
MSSE	NR	NR	0.25 (0.008-1)
MRSE	0.5(≤0.13-0.5)	1(≤0.12-1)	0.25 (≤0.004-4)
V susceptible enterococci	1(0.25-2)	NR	0.03 (≤0.0005-0.5)
V non-susceptible enterococci	NR	NR	0.5 (0.015-4)
VRE(van A)	1(0.25-2)	NR	0.5 (0.03-4)
VRE(van B)	1(0.13-1)	NR	NC (0.015-0.03)
VS E. faecium	NR	1(≤0.12-2)	NR
VR E. faecium	NR	0.5(≤0.12-1)	NR
VS E.faecalis	NR	1(≤0.12-2)	NR
VR E.faecalis	NR	2(≤0.12-2)	NR
VRSA	NR	NR	NC (0.12-0.5)
PSSP	0.004	NR	0.004 (≤0.0005-0.25)
PISP	NR	NR	0.008 (≤0.0005-0.5)
PRSP	0.016-0.004	NR	0.008 (0.002-0.015)
S. pyogenes	0.063	NR	0.25 (0.008-0.5)
Lactobacillus spp.	8	NR	8 (0.004-8)
Leuconostoc spp.	4-64	NR	8 (1-8)
Pediococcus spp.	4-8	NR	8 (1-8)

Adapted from Anderson, 2008.
*NB, not using currently recommended laboratory standards; NR, not reported; NC, not calculated since only 7 isolates were tested.

Table 2: Current estimates of *in vitro* activity of oritavancin against staphylococci: MIC_{90} (range)

Pathogen	n	Oritavancin	Vancomycin	Teicoplanin	Linezolid	Daptomycin	Quinupristin/ dalfopristin
S. aureus							
All	5008	0.12	1	2	0.5	0.5	
		(≤0.004-4)	(≤0.25-2)	(≤0.25-4)	(≤0.25-4)	(≤0.12-2)	(≤0.12-4)
MS	2518≤	0.12	1	1	2	0.5	0.5
		(≤0.004-2)	(≤0.25-2)	(≤0.25-4)	(≤0.25-4)	(≤0.12-2)	(≤0.12-2)
MR	2490	0.25	1	1	2	0.5	1
		(≤0.004-4)	(≤0.25-2)	(≤0.25-4)	(≤0.25-4)	(≤0.12-2)	(≤0.12-4)
MDR	1941	0.25	1	1	2	0.5	1
		(≤0.004-4)	(≤0.25-2)	(≤0.25-4)	(≤0.25-4)	(≤0.12-2)	(≤0.12-4)
VISA	13	1	NR	NR	NR	NR	NR
		(0.5-1)	NR	NR	NR	NR	NR
VRSA	5	NC	NR	NR	NR	NR	NR
		(0.12-0.5)	NR	NR	NR	NR	NR
CoNS							
All	862	0.25	2	4	1	0.5	0.25
		(≤0.004-1)	(≤0.25-4)	(0.25-16)	(≤0.25-8)	(≤0.12-2)	(≤0.12-1)
MS	213	0.25	2	4	1	0.5	0.25
		(≤0.008-1)	(≤0.25-2)	(0.25-8)	(≤0.25-2)	(≤0.12-1)	(≤0.12-1)
MR	649	0.25	2	4	1	0.5	0.25
		(≤0.004-1)	(≤0.25-4)	(0.25-16)	(≤0.25->8)	(≤0.12-2)	(≤0.12-1)
MDR	529	0.25	2	4	1	0.5	0.25
		(≤0.015-1)	(≤0.25-2)	(0.25-16)	(≤0.25->8)	(≤0.12-2)	(≤0.12-1)

Adapted from Anderson, 2008

NR, not reported; NC, not calculated since only 5 isolates were tested; MS, methicillin/oxacillin-susceptible; MR, methicillin/oxacillin-resistant; MDR, multidrug-resistant(resistant to ≥3 agents including ciprofloxacin, clindamycin, erythromycin, gentamicin, oxacillin, trimethoprim-sulfamethoxazole); VISA, vancomycin-intermediate *S. aureus*; VRSA, vancomycin-resistant *S. aureus*; CoNS, coagulase-negative staphylococci.

Table 3: Current estimates of *in vitro* activity of oritavancin against enterococci: MIC_{90} (range)

Pathogen	n	Oritavancin	Vancomycin	Teicoplanin	Linezolid	Daptomycin
E. faecalis						
All	909	0.12	2	0.25	2	2
		(≤0.0005-4)	(0.5->256)	(0.03-256)	(0.25-32)	(0.25->4)
Van S	850	0.06	2	0.25	2	2
		(≤0.0005-0.5)	(0.5-4)	(0.03-2)	(0.25-32)	(0.25->4)
Van NS	59	1	>256	256	2	2
		(0.015-4)	(8->256)	(0.12-256)	(0.15-16)	(0.5->4)
VanA	48	1	>256	256	2	2
		(0.03-4)	(>256->256)	(32-256)	(0.15-16)	(0.5->4)
VanB	7	NC	NC	NC	NC	NC
		(0.015-0.03)	(32->256)	(0.12-0.5)	(1-2)	(0.5-2)
E. faecium						
All	389	0.25	>256	128	2	4
		(≤0.0005-2)	(0.03->256)	(≤0.015->256)	(≤0.12-16)	(≤0.12->4)
Van S	120	0.015	1	1	2	4
		(≤0.0005-0.06)	(0.03-4)	(≤0.015-8)	(≤0.12-4)	(≤0.12->4)
Van NS	269	0.25	>256	128	2	4
		(≤0.0005-2)	(8->256)	(0.12->256)	(0.05-16)	(≤0.12->4)
VanA	234	0.25	>256	128	2	4
		(0.004-2)	(32->256)	(32->256)	(0.5-8)	(1->4)
VanB	24	0.03	256	4	2	2
		(0.004-0.06)	(64->256)	(0.12-8)	(1-16)	(0.25->4)

Adapted from Anderson, 2008

Van, vancomycin; S, susceptible; NS, nonsusceptible; VanA and VanB are vancomycin resistance phenotypes; NC, not calculated since only 7 isolates were tested.

et al., 1997; Sillerstrom *et al*., 1999; Barry *et al*., 2001; Goldstein *et al*., 2003a; Goldstein *et al*., 2003b; Citron *et al*., 2005) (table 5). It has modest activity against *Lactobacillus*, *Leuconostoc* and *Pediococcus*.

It does not have activity against Gram-negative organisms such as *Escherichia coli, Pseudomonas aeruginosa* and *Acinetobacter spp., Haemophilus influenzae* (Moeck *et al*., 2007). Naturally occurring oritavancin resistance

among *S. aureus* has not been described but moderate level of oritavancin (MIC 8-16 µg/ml) resistance to VanA- and VanB-type *enterococci* were selected *in vitro* by mutation in Vans sensor gene, other gene-encoded ligases and unknown mechanisms (Arthur *et al*., 1999).

Table 4: Current estimates of *in vitro* activity of oritavancin against streptococci: MIC_{90} (range)

Pathogen	n	Oritavancin	Vancomycin
S. pneumoniae			
All	1010	0.008	0.25
		(≤0.0005-0.5)	(≤0.06-0.5)
Pen S	646	0.004	0.25
		(≤0.0005-0.25)	(≤0.06-0.5)
Pen I	216	0.008	0.25
		(≤0.0005-0.5)	(0.12-0.5)
Pen R	148	0.008	0.5
		(≤0.0005-0.015)	(0.25-0.5)
Non-MDR	768	0.004	0.25
		(≤0.0005-0.5)	(≤0.06-0.5)
MDR	242	0.008	0.5
		(≤0.0005-0.015)	(0.25-0.5)
*S. pyogenes**	287	0.25	0.25
		(0.008-0.5)	(0.25-0.5)
*S. agalactiae**	101	0.12	0.5
		(0.03-0.5)	(0.25-0.5)

Adapted from Anderson, 2008

Pen S, penicillin-susceptible; Pen I, penicillin-intermediate; Pen R, penicillin resistant; MDR, multidrug-resistant (resistant to ≥3 agents such as ciprofloxacin, clindamycin, erythromycin, gentamicin, oxacillin, trimethoprim-sulfamethoxazole). *One-third nonsusceptible to erythromycin.

Pharmacokinetics

Oritavancin is supplied as a freeze-dried powder (100 mg of oritavancin base per vial, Targanta Therapeutics, Indianapolis, IN, USA) containing 65-70% active drug and 30-35% mannitol, to be administered by intravenous (i.v.) route after reconstitution with sterile water for injection and subsequent dilution in 5% dextrose injection. Oritavancin is administered by i.v. infusions (Karaoui *et al.,* 2013; Bouza and Burillo, 2010) and it is immediately available to the central compartment. Oritavancin is administered in combination with a carrier, which can include water, dextrose, ethanol, polyethylene glycol (PEG) among many others (Lehoux *et al.*, 2011). In a single dose (0.02-0.5 mg/kg) open label, dose escalation study on healthy human subjects of oritavancin infused over 1 hr, kinetics appeared to be linear (Bhavnani *et al*., 2004). Mean C_{max} ±SD for the 0.5 mg/kg dose was 6.3±1.24 µg/ml. The mean ±SD of the plasma terminal half-life was 195.4±47.9 hrs (Bhavnani *et al*., 2004). In this experiment, oritavancin diphosphate was administered in a solution of 5% dextrose in water. In another study by Bhavnani *et al*, oritavancin at a dose of 5-10 mg/kg/day in patients with *S. aureus* bacteremia, the mean C_{max}±SD was 82±27 mg/l and median C_{max} was 80 (range 39-172) mg/l (Bhavnani *et al*., 2004).

Table 5: *In vitro* activity (µg/mL) of oritavancin against Gram-positive anaerobic bacteria

Antimicrobial agent	Minimum Inhibitory Concentration (µg/mL)		
Organism (No.)	Range	50%*	90%*
Clostridium perfringens (28)			
Oritavancin	0.25-1	0.5	1
Vancomycin	0.25-0.5	0.25	0.5
Clindamycin	≤0.03-4	0.5	2
Metronidazole	0.5-8	2	4
Propionibacterium acnes (11)			
Oritavancin	0.125-0.25	0.125	0.25
Vancomycin	0.25-0.5	0.25	0.5
Clindamycin	≤0.03-0.06	0.06	0.06
Metronidazole	>64	>64	>64
Peptostreptococcus anaerobius (15)			
Oritavancin	0.06-0.5	0.125	0.25
Vancomycin	0.06-0.5	0.25	0.5
Clindamycin	≤0.03-0.5	0.06	0.5
Metronidazole	0.125->64	1	64
Peptoniphilus asaccharolyticus (17)			
Oritavancin	≤0.03-0.5	0.25	0.5
Vancomycin	0.06-0.5	0.06	0.25
Clindamycin	≤0.03->64	0.125	>64
Metronidazole	0.25-4	1	2
Finegoldia magna (12)			
Oritavancin	≤0.03-0.25	0.06	0.25
Vancomycin	0.05-0.25	0.25	0.25
Clindamycin	≤0.03->64	0.125	8
Metronidazole	0.06-2	0.5	0.5
Micromonas micros (15)			
Oritavancin	≤0.03-0.5	0.125	0.25
Vancomycin	0.5-1	0.5	0.5
Clindamycin	≤0.03-4	0.25	1
Metronidazole	0.25->64	0.5	64
Anaerococcus prevotti (16)			
Oritavancin	≤0.03-1	≤0.03	0.25
Vancomycin	0.06-1	0.25	1
Clindamycin	≤0.03->64	0.06	0.5
Metronidazole	0.125->64	1	4

Adapted from Citron *et al*., 2005

*Concentrations at which 50% and 90% of strains tested were inhibited.

Oritavancin is ~ 90% bound to plasma protein (Rowe and rown, 2001). In a study by Van Bambeke *et al*, oritavancin preferentially accumulates in macrophages as shown byhigh intracellular: extracellular concentration ratio, reaching ≤350 times the extracellular concentration (Van Bambeke *et al*., 2004). Oritavancin also distributes into blister fluid and reached maximal concentration in blister fluid at 10±6.05 and 9.5±3.67 hr following the administration of oritavancin 200 & 800 mg, respectively, which is 8 &11 times lower than plasma, respectively. Blister AUC_{0-24} was 5 times lower (90.7±35.7 and 208±76.7 µg.h/ml) in both oritavancin 200 and 800mg

groups, respectively (Fetterly *et al*., 2005). A recent study in volunteers demonstrated that oritavancin reaches high concentrations not only in epithelial lining fluid but also in alveolar macrophages (Rodvold *et al*., 2004).

In a study of the effects of oritavancin on *Clostridium difficile* germination in hamsters, oritavancin was formulated in 85% PEG 400 in water, and was dosed at 50mg/kg orally (Freeman *et al*., 2012). In this experiment, all hamsters (n=22) treated with oritavancin prior to *C. difficile* spore exposure survived for the length of the trial (20 days), with no signs of spore germination or toxin production. By contrast hamsters pretreated with clindamycin (n=10) or vancomycin (n=22) prior to *C. difficile* inoculation died within 6 days.

Oritavancin has also been compared to vancomycin as a treatment for clindamycin-induced *C. difficile* (PCR ribotype 027) infection in *in-vitro* gut models over 7 days (Bains *et al.*, 2008), and over a 4 day course (Chilton *et al.*, 2012) where oritavancin was prepared as a 0.002% (v/v in distilled water) polysorbate-80 preparation (as previously described by Bains *et al*., 2008), and administered 2 times per day for 4 days at 64mg/ml in both trials. It was shown that oritavancin was effective against *C. difficile* spores, where vancomycin was not, and it was suggested that a 4 day course of oritavancin may be preferable to longer exposures of vancomycin since it resulted in decreased negative effects on normal intestinal flora (Chilton *et al.,* 2008). The 4 day course of oritavancin had similar effects on the levels of indigenous microflora as the previously studied 7 day trial performed by Bains *et al* (Chilton *et al*., 2008).

Unlike most antibiotics (personal communication with Dr. Caroline Chilton), in the process of measuring antimicrobial concentrations in gut models, oritavancin was not filtered, since it tends to adhere to cellulose acetate filters (Freeman *et al*., 2012).

Limited information on the metabolism and excretion of oritavancin are available. Oritavancin is not metabolized and is slowly eliminated from the body as unchanged drug (Bhavnani *et al*., 2004; www.sec.gov/Archives/ edgar/data/1398161/000119312508067341/d10k.htm).
Renal clearance was approximately 0.457ml/min. Less than 5% and 1% of administered dose were recovered in the urine and faeces, respectively, after 7 days. Fecal oritavancin levels were undetectable in nearly 50% healthy human subjects (Bhavnani *et al*., 2004). In clinical trials to date, oritavancin has not required monitoring of blood levels for the purpose of adjusting the blood level of the antibiotic due to hepatic or renal insufficiency (www.sec.gov/Archives/edgar/data/1398 161/000119312508067341/d10k.htm).

Some pertinent data on pharmacokinetic parameters of oritavancin are incorporated in table 6.

Efficacy studies/profile

Oritavancin demonstrates concentration-dependent bactericidal activity against *S. aureus* (MRSA,VISA), *S. pneumoniae* and vancomycin resistant *Enterococcus* (Allen and Nicas, 2003; Patel *et al*., 1998; Aeschlimann *et al*., 2000). The parameter that best predicts oritavancin efficacy is the ratio between the free Cmax concentration and the minimal inhibitory concentration (MIC) of the offending organism (Boylan *et al*., 2003). Time-kill studies compared the bactericidal activity of *S. aureus* (MSSA, MRSA, coagulase-negative SA), oritavancin demonstrated killing at 3hr. At 24hr, oritavancin was bactericidal against all strains tested (Lin *et al*., 2005). In another study, oritavancin 5mg/kg/day demonstrate rapid bactericidal activity against VISA and MRSA (Aeschlimann *et al*., 2000). Additional favorable pharmacodynamic properties of oritavancin include longer post-antibiotic effects and synergistic effects with ampicillin or gentamicin (Lefort *et al*., 2000; Baltch *et al*., 1998). The length of post-antibiotic effects is concentration-dependent and significantly longer in *Enterococci* than in *Staphylococci* (Mercier *et al*., 1997; Baltch *et al*., 1998). Activity against stationary-phase bacteria and biofilms was documented with *S. aureus* including MRSA and VRSA strains (Belley *et al*., 2009).

Table 6: Some pharmacokinetic parameters of oritavancin

Pharmacokinetic parameter	Result
C_{max}(µg/ml)*(Owen *et al.,* 2004)	29
C_{min}(µg/ml)* (Owen *et al.,* 2004)	2.2
AUC_{0-24}(µg.h/ml)* (Owen *et al.,* 2004)	166
V_{dss}(l/kg)#(Chien *et al.,* 1998)	0.65-1.92
Cl(ml/kg/min)# (Chien *et al.,* 1998)	0.0547-0.138
Protein binding(%) (Rowe and Brown, 2001)	90
Mean Plasma Terminal half-life(h) (Karaoui *et al.,* 2013)	195.4

*Bayesian modeling using oritavancin 200mg. #Values for doses of oritavancin 0.5-3 mg/kg in healthy volunteers(n=8).

A. In animal models of infection-The efficacy of oritavancin has been demonstrated in animal models of endocarditis caused by vancomycin susceptible or resistant *Enteroc-occus faecalis* (Lefort *et al*., 2000) or MRSA (Kaatz *et al*., 1998), models of meningitis caused by *pneumococci* susceptible or resistant to β-lactams (even though the concentration in CSF is only 5% of the serum level) (Gerber *et al*., 2001; Cabellos *et al*., 2003). Models of central venous catheter associated infection by vanco-mycin resistant *Enterococcus faecium* (Rupp *et al*., 2001).

In MRSA endocarditis model in rabbit (Kaatz *et al*., 1998), there were no differences between the two groups and on day 4, all of the cultures were negative. In *Enterococcus faecalis* endocarditis model (Lefort *et al*., 2000; Saleh-Mghir *et al*., 1999), oritavancin was active against glycopeptide-susceptible and -resistant (vanA and vanB) strains of *Enterococcus faecalis*. When combined

with gentamicin, oritavancin displayed more bactericidal activity (Lefort *et al*., 2000).

In rabbit model of meningitis caused by *pneumococci* susceptible or resistant to β-lactams, oritavancin 10mg/kg was as effective as ceftriaxone in reducing bacterial loads (Gerber *et al*., 2001).

In rat model of central venous catheter associated infection by vancomycin resistant *Enterococcus faecium*, >87% had *Enterococcus* on the catheter tips of the untreated rats compared with only 12.5% of those that received oritavancin. Bacteraemia was not identified in any of the treated rats compared with 75% of those left untreated (Rupp *et al*., 2001).

B. Clinical Studies-Due to multiple changes of ownership, clinical development of oritavancin has been slowed down. Data from the phase III studies currently under review by regulatory authorities is not publicly available. There have been two published abstracts presented in poster form at ICAAC 2001 (Wasilewski *et al*., 2001) and ICAAC 2003 (Giamarellou *et al*., 2003) which have evaluated the efficacy of oritavancin for the treatment of complicated Gram-positive skin and soft tissue infections. The ICAAC 2001 (Wasilewski *et al*., 2001) a double blind, randomised Phase II/III study, comparing oritavancin 1.5 (n=173) or 3 (n=169) mg/kg IV for 3-7 days followed by oral placebo or with vancomycin 15 mg/kg for 3-7 days followed by oral cephalexin for a total course of 10-14 days. Both dosing arms of oritavancin were noninferior to vancomycin-cephalexin, with clinical response (cure or improvement) rates at first follow up were 62, 65 and 65 %, respectively and bacteriologic response (eradication, presumed eradication, colonization) were 72, 75, and 76% respectively. None of these differences were statistically significant but needed shorter treatment duration (low and high dose oritavancin arms at 5.3 and 5.7 days respectively verses 11.9 days for vancomycin-cephalexin).

In ICAAC 2003 (Giamarellou *et al*., 2003) Phase III study, 1246 patients with complicated skin and soft tissue infections were randomized to oritavancin 200mg IV daily injection for 3-7 days followed by oral placebo or vancomycin at 15mg/kg twice daily for 3-7days followed by cephalexin 1gm twice daily for a total course of 10-14 days. Clinical response (cure or improvement) rates at first follow up were 79 % for oritavancin and 76% for vancomycin group and bacteriologic response (eradication, presumed eradication, colonization) were 75 and 73% respectively and was not statistically significant. Clinical outcome at late follow up of the successful patients was >98% in both treatment arms.

Safety profile

No specific or life threatening side effects were observed in two randomized, double blind, multicentric clinical trials on oritavancin (Wasilewski *et al*., 2001; Giamarellou *et al*., 2003). Adverse effects were similar between oritavancin and vancomycin (followed by oral cephalexin) in one Phase III clinical trial (Wasilewski *et al*., 2001). The most common adverse events were headache, nausea, vomiting, diarrhea, sleep disturbances, embolism/thrombosis and injection site reaction. Statistical differences in adverse events were oedema and tremor which were more common with the higher dose of oritavancin and pulmonary embolism/thrombosis which was more common in the vancomycin group (Ambrose *et al*., 2007).

In a second Phase III trial, adverse effects were greater in vancomycin (with follow up cephalexin) group than oritavancin group (58 vs 47%, respectively) (Giamarellou *et al*., 2003). None of these differences were statistically significant except pruritus (itching) (table 7). When safety data were combined for both trials, a significant lower percentage of patients required discontinuation due to adverse events in the oritavancin arm versus the vancomycin-cephalexin arm (1.8 vs 4.8%;p=0.003).

Table 7: Safety results from the ICAAC 2003 Phase III Study: Adverse events in ≥2% of patients in the ICAAC 2003 Phase III Study (Giamarellou *et al*., 2003).

	Oritavancin 200 mg/day (n=831)	Vancomycin 15 mg/kg twice daily (n=415)
Headache	4.9%	5.8%
Nausea	4.2%	4.8%
Vomiting	3.7%	4.6%
Abscess	3.6%	5.1%
Constipation	3.5%	1.9%
Phlebitis	3.2%	2.7%
Dizziness	3.2%	1.7%
Insomnia	2.9%	5.1%
Diarrhea	2.5%	3.9%
Pruritus*	2.0%	8.0%

*P< 0.001.

Safety was also reported in two pharmacokinetic studies (Bhavnani *et al*., 2004; Fetterly *et al*., 2005). There were no serious adverse events or death during study. The most common adverse events were headache, rhinitis, dry skin and pain. Five subjects experienced transient elevation in liver transaminase (AST and/or ALT) (Bhavnani *et al*., 2004) and one subject experienced injection site thrombosis (Fetterly *et al*., 2005). There were no abnormalities in aPTT or bleeding time, renal indices and hearing (Bhavnani *et al*., 2004). Neither study reported any anaphylaxis or anaphylactoid reaction.

Due to its exceptional level of cellular accumulation as demonstrated *in vitro* (in models of cultured phagocytic and nonphagocytic cells (Van Bambeke *et al*., 2004c) as well as *in vivo* (in alveolar macrophages of volunteers (Rodvold *et al*., 2004), it may cause cellular toxicity.

When cultured cells are exposed to oritavancin, they show morphological alterations characterized by the presence of large vacuoles with heterogenous content associated with an increase in polar lipid cell content (Van Bambeke *et al*., 2005). As the extracellular oritavancin dose increased, the uptake of cholesterol was ~3.5-fold greater than control values in both cell types and was primarily (85%) of the free form. The accumulation was reversible after removal from exposure to oritavancin. The uptake of phospholipids was 1.5-fold greater than control but only partially reversed after removal from exposure to oritavancin. Excessive free cholesterol uptake in cells can cause cellular toxicity and death (Tabas, 2002). These observations provide a rationale for revisiting animal safety data in order to establish the potential toxicological significance of oritavancin.

CONCLUSIONS

Oritavancin is a rapidly bactericidal agent with an extended spectrum of action against Gram-positive organisms (MRSA, VISA, VRSA and VRE) that includes activity against high level vancomycin resistance mediated by both vanA and vanB genotype. Its multiple mechanism of antibacterial action, long duration of post antibiotic effect with excellent activity against stationary phase bacteria and biofilms, synergism with penicillin and aminoglycosides, are important attributes that increase the rate of bacterial killing. Its concentration-dependent activity, long half-life, and high plasma protein binding make daily dosing feasible. Although its overall side effects profile is favourable, there are some concerns that lysosomal oritavancin accumulation, particularly in macrophage-rich reticuloendothelial cells (liver) may lead to toxicity.

Despite the remarkable properties, the use of this potent agent should be restricted to severe infection caused by resistant or poorly sensitive Gram-positive organisms, to limit the risk of potential selection of resistance. Additional clinical data are required to fully assess its use. Large clinical studies (including safety studies) will aid in positioning this compound in the arsenal of new anti-Gram-positive agents.

REFERENCES

Aeschlimann JR, Allen GP, Hershberger E and Rybak MJ (2000). Activities of LY333328 and vancomycin administered alone or in combination with gentamicin against three strains of vancomycin-intermediate *Staphylococcus aureus* in an in vitro pharmacodynamic infection model. *Antimicrob. Agents Chemother.,* **44**(11): 2991-2998.

Allen NE and Nicas TI (2003). Mechanism of action of oritavancin and related glycopeptide antibiotics. *FEMS Microbiol. Rev.,* **26**: 511-532.

Ambrose PG, Bhavnani SM, Rubino CM, Louie A, Gumbo T, Forrest A and Drusano GL (2007). Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. *Clin. Infect. Dis.,* **44**(1): 79-86.

Anderson DL (2008). Oritavancin for skin infections. *Drugs Today,* **44**(8): 563-575.

Anderson RC, Worth HM, Harris PN and Chen KK (1956-1957). Vancomycin, a new antibiotic IV. Pharmacologic and toxicologic studies. *Antibiot. Annu.,* 75-81.

Anon (1994). Summary of notifiable diseases, United States, *MMWR Morb. Mortal.Wkly. Rep.,* **43**(53): 1-80.

Anon (2002). *Staphylococcus aureus* resistant to vancomycin-United States. *MMWR Morb. Mortal. Wkly. Rep.*, **51**(26): 565-567.

Arhin FF, Sarmiento I, Parr TR Jr and Moeck G (2007). Mechanisms of action of oritavancin in *Staphylococcus aureus* (abstr) C1-1471. *In*: Proceedings of the 47th International Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago, IL, 17-20 September 2007. American Society of Microbiology, USA.

Arhin FF, Sarmiento I, Parr TR Jr and Moeck G (2008). Activity of oritavancin against *Staphylococcus aureus* isolates that show heterogeneous resistance to vancomycin (abstr). *In*: Proceedings of the 18th European Congress of Microbiology and Infectious Diseases (ECCMID), April 19-22 Barcelona, 2008. *Clin. Microbial Infect,* 14 (Abstracts Issue), p.584.

Arthur M, Depardieu F, Reynolds P and Courvalin P (1999). Moderate-level resistance to glycopeptide LY333328 mediated by genes of the vanA and vanB clusters in enterococci. *Antimicrob. Agents Chemother.,* **43**: 1875-80.

Baines SD, O'Connor R, Saxton K, Freeman J and Wilcox MH (2008). Comparison of oritavancin versus vancomycin as treatments for clindamycin-induced *Clostridium difficili* PCR ribotype 027 infection in a human gut model. *J. Antimicrob. Chemother.*, **62**(5): 1078-1085.

Baltch AL, Smith RP, Ritz WJ and Bopp LH (1998). Comparison of inhibitory and bactericidal activities and postantibiotic effects of LY333328 and ampicillin used singly and in combination against vancomycin-resistant *Enterococcus faecium, Antimicrob. Agents Chemother.,* **42**: 2564-2568.

Barry AL, Fuchs PC and Brown SD (2001). In vitro activities of daptomycin against 2,789 clinical isolates from 11 North American medical centers. *Antimicrob. Agents Chemother.,* **45**(6): 1919-1922.

Belley A, Harris B, Beveridge T, Beveridge T, Parr TR and Moeck G (2008). Cell wall and membrane effects of oritavancin on *Staphylococcus aureus* and *Enterococcus faecalis* (abstr) *Clin Microbiol Infect. In*: Proceedings of the 18th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)

(April 19-22, Barcelona) 2008, 14 (Abstracts Issue): Abst., p.537.

Belley A, Harris B, Beveridge T, Parr TR and Moeck G (2007). Differential targeting of cell wall assembly systems by oritavancin (abstr). *In*: Proceedings of the 47th International Conference on Antimicrobial Agents and Chemotherapy (ICAAC), (Sept 17-20, Chicago) 2007, American Society of Microbiology, Abst C1-1472.

Belley A, Neesham-Grenon E, McKay G, Arhin FF, Harris R, Beveridge T, Parr TR Jr and Moeck G (2009). Oritavancin Kills Stationary-Phase and Biofilm *Staphylococcus aureus* cells *in vitro*. *Antimicrob. Agents Chemother.,* **53**: 918-925.

Bhavnani SM, Owen JS, Loutit JS, Porter SB and Ambrose PG (2004). Pharmacokinetics, safety, and tolerability of ascending single intravenous doses of oritavancin administered to healthy human subjects. *Diagn. Microbiol. Infect. Dis.,* **50**: 95-102.

Biavasco F, Vignaroli C, Lupidi R, Manso E, Facinelli B and Varaldo PE (1997). In vitro antibacterial activity of LY333328 a new semisynthetic glycopeptide. *Antimicrob. Agents Chemother.,* **41**: 2165-2172.

Bosso JA (2005). The antimicrobial armamentarium: evaluating current and future treatment options and *Pharmacotherapy,* **25**(10-2): 55-62.

Bouza E and Burillo A (2010). Oritavancin: A novel lipoglycopeptide active against gram-positive pathogens including multiresistant strains. *Int. J. Antimicrob. Agents.,* **36**: 401-407.

Boylan CJ, Campanale K, Iversen PW, Phillips DL, Zecke ML and Parr TR (2003). Pharmacodynamics of oritavancin (LY333328) in a neutropenic-mouse thigh model of *Staphylococcus aureus* infection. *Antimicrob. Agents Chemother.,* **47**: 1700-1706.

Bozdogan B, Ednie L, Credito K, Kosowska K and Appelbaum PC (2004). Derivatives of a vancomycin-resistant *Staphylococcus aureus* strain isolated at Hershey Medical Center, *Antimicrob. Agents Chemother.,* **48**(12): 4762-4765.

Cabellos C, Fernàndez A, Maiques JM, Tubau F, Ardanuy C, Viladrich PF, Liñares J and Gudiol F (2003). Experimental study of LY333328 (oritavancin), alone and in combination, in therapy of cephalosporin-resistant pneumococcal meningitis. *Antimicrob. Agents Chemother.,* **47**(6): 1907-1911.

Cegelski L, Dirk S, Mehta AK, Kulp DW, Axelsen PH and Schaefer J (2006). Conformational and quantitative characterization of oritavancin-peptidoglycan complexes in whole cells of *Staphylococcus aureus* by *in vivo* ^{13}C and ^{15}N labeling. *J. Mol. Biol.,* **357**: 1253-1262.

Chien J, Allerheiligen S, Phillips DL, Cerimele B and Thomasson HR (1998). Safety and pharmacokinetics of single intravenous doses of LY 333328 diphosphate (glycopeptide) in healthy men (abstr). *In:* 38th International Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Diego, USA, American Society of Microbiology: A-55.

Chilton CH, Freeman, J, Crowther SL, Todhunter SL and Wilcox MH (2012). Effectiveness of a short (4 day) course of oritavancin in the treatment of simulated *Clostridium difficile* infection using a human gut model. *J. Antimicrob Chemother*., **67**: 2434-2437.

Citron DM, Kwok YY and Appleman MD (2005). *In vitro* activity of oritavancin (LY 333328), vancomycin, clindamycin, and metronidazole against *Clostridium perfringens*, *Propionibacterium acnes* and anerobic Gram-positive cocci. *Anaerobe*, **11**: 93-95.

Cooper RDG, Snyder NJ, Zweifel MJ, Staszak MA, Wilkei SC, Nicas TI, Mullen DL, Butler TF, Rodriguez MJ, Huff BE and Thompson RC (1996). Reductive alkylation of glycopeptide antibiotics: synthesis and antibacterial activities. *J. Antibiot* (Tokyo), **49**: 575-581.

Draghi D, Moeck G, Thornsberry C and Sahm DF (2007). Comparative in vitro potency of oritavancin, teicoplanin and vancomycin against glycopeptide-susceptible and resistant Gram positive organisms (abstr) *In*: Proceedings of the 43rd International Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago., IL, USA, 17-20 September 2007, American Society of Microbiology.

Draghi DC, Moeck G, Arhin FF, Pillar C and Sahm DF (2008). Anti-enterococcal and anti-streptococcal activity profile of oritavancin in Europe (abstr). *In*: Proceedings of the 18th European Congress of Microbiology and Infectious Diseases (ECCMID), April 19-22 Barcelona, 2008. *Clin. Microbial Infect.,* 14 (Abstracts Issue): P538.

Fasola E, Spangler SK, Ednie LM, Jacobs MR, Bajaksouzian S and Appelbaum PC (1996). Comparative activities of LY333328, a new glycopeptide, against penicillin-susceptible and resistant pneumococci, *Antimicrob. Agents Chemother.,* **40**: 2661-2663.

Fetterly GJ, Ong CM, Bhavnani SM, Loutit JS, Porter SB, Morello LG, Ambrose PG and Nicolau DP (2005). Pharmacokinetics of oritavancin in plasma and skin blister fluid following administration of a 200-milligram dose for 3 days or a single 800-milligram dose. *Antimicrob. Agents Chemother.,* **49**: 148-152.

Freeman J, Marquis M, Crowther GS, Todhunter SL, Fawley WN, Chilton CH, Moeck G, Lehoux D and Wilcox MH (2012). Oritavancin does not induce *Clostridium difficile* germination and toxin production in hamsters or a human gut model. *J. Antimicrob. Chemother*., **67**(12): 2919-2926.

Garcia-Garrote F, Cercenado C, Alcala L and Bouza E (1998). *In vitro* activity of the new glycopeptide LY333328 against multipleresistant gram-positive isolates. *Antimicrob. Agents Chemother.,* **42**: 2452-2455.

Gerber J, Smirnov A, Wellmer A, Ragheb J, Prange J, Schütz E, Wettich K, Kalich S, Nau R(2001). Activity of LY333328 in experimental meningitis caused by a *Streptococcus pneumoniae* strain susceptible to penicillin. *Antimicrob. Agents Chemother.,* **45**: 2169-2172.

Giamarellou H, O'Riordan W, Harris H, Owen S, Porter S and Loutit J (2003). Phase 3 trial comparing 3-7 days of oritavancin vs.10-14 days of vancomycin/cephalexin in the treatment of patients with complicated skin and skin structure infections (cSSSI) (abstr). *In*: Proceedings of the 43rd International Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago, IL, September 14-17, 2003. Washington, D.C: American Society for Microbiology: L-739a.

Goldstein EJ, Citron DM, Merriam CV, Warren Y, Tyrrell K and Fernandez HT (2003). *In vitro* activities of Dalbavancin and nine comparator against anaerobic Gram-positive species and corynebacteria. *Antimicrob. Agents Chemother.,* **47**:1968-1971.

Goldstein EJ, Citron DM, Merriam CV, Warren Y, Tyrrell K, Fernandez HT (2003). *In vitro* activities of daptomycin, vancomycin, quinupristin-dalfopristin, linezolid, and five other antimicrobials against 307 Gram-positive anaerobic and 31 Corynebacterium clinical isolates. *Antimicrob. Agents Chemother.,* **47**: 337-341.

Heine HS, Dicks R and Andrews G (2001). *In vitro* activity of oritavancin (LY333328), levofloxacin, meropenem, GAR936 and linezolid against strains of *Bacillus anthracis* (abstr) Abstr. *In*: Proceedings of the 41st International Conference of Antimicrobial Agents and Chemotherapy (ICAAC), American Society of Microbiology, Washington, DC: E-524, p.173.

Jones RN, Barrett MS and Erwin ME (1997). In vitro activity and spectrum of LY333328, a novel glycopeptide derivative. *Antimicrob. Agents Chemother.,* **41**: 488-493.

Jones RN and Barry AL (1987). Antimicrobial activity and spectrum of LY146032, a lipopeptide antibiotic, including susceptibility testing recommendations. *Antimicrob. Agents Chemother.,* **31**(4): 625-629.

Kaatz GW, Seo SM, Aeschlimann JR, Houlihan HH, Mercier RC and Rybak MJ (1998). Efficacy of LY333328 against experimental methicillin-resistant *Staphylococcus aureus* endocarditis. *Antimicrob. Agents Chemother.,* **42**: 981-983.

Kaatz GW, Seo SM, Aeschlimann JR, Houlihan HH, Mercier RC and Rybak MJ (1998). Efficacy of LY333328 against experimental methicillin-resistant *Staphylococcus aureus* endocarditis. *Antimicrob. Agents Chemother.,* **42**: 981-983.

Karaoui LR, El-Lababidi R and Chahine EB (2013). Oritavancin: An investigational lipoglycopeptide antibiotic. *Am. J. Health-Syst. Pharm.,* **70**: 23-33.

Kim SJ, Cegelski L,Stueber D, Singh M, Dietrich E, Tanaka KS, Parr TR, Far AR and Schaefer J (2008). Oritavancin exhibits dual mode of action to inhibit cell-wall biosynthesis in *Staphylococcus aureus. J. Mol. Biol.,* **377**(1): 281-293.

Lefort A, Saleh-Mghir A, Garry L, Carbon C and Fantin B (2000). Activity of LY333328 combined with gentamicin in vitro and in rabbit experimental endocarditis due to vancomycin-susceptible or resistant *Enterococcus faecalis. Antimicrob. Agents Chemother.,* **44**: 3017-3021.

Lefort AA, Saleh-Mghir L, Garry C, Carbon C and Fantin B (2000). Activity of LY333328 combined with gentamicin *in vitro* and in rabbit experimental endocarditis due to vancomycin-susceptible or resistant *Enterococcus faecalis. Antimicrob. Agents Chemother.,* **44**: 3017-3021.

Lehoux D, Parr TR, Moeck G and Etienne P (2011). Methods of treatment using single doses of oritavancin. Targanta Therapeutics Corp., accessed 31 October 2012 <http://www.faqs.org/patents/app/20110201546 >

Lin G, Credito K, Ednie LM and Appelbaum PC (2005). Antistaphylococcal activity of dalbavancin, an experimental glycopeptide. *Antimicrob. Agents Chemother.,* **49**(2): 770-772.

Lu W, Oberthür M, Leimkuhler C, Tao J, Kahne D and Walsh CT (2004). Characterization of a regiospecific epivancosaminyl transferase GtfA and enzymatic reconstitution of the antibiotic chloroeremomycin. *Proc. Natl. Acad. Sci. USA.,* **101**(13): 4390-4395.

Malabarba A, Nicas TI and Thompson RC (1997). Structural modifications of glycopeptide antibiotics. *Med. Res. Rev.,* **17**(1): 69-137.

Mercier RC, Houlihan HH and Rybak MJ (1997). Pharmacodynamic evaluation of a new glycopeptide, LY333328, and in vitro activity against *Staphylococcus aureus* and *Enterococcus faecium. Antimicrob. Agents Chemother.,* **41**: 1307-1312.

Mezzatesta ML, Bonfiglio G, DeAngelis L, Stefani S and Russo G (1998). Study on the *in vitro* activity of LY333328 against gram-positive cocci (letter). *J. Antimicrob. Chemother.,* **42**: 266-268.

Moeck G, Draghi, DC, Arhin FF and Sahm DF (2007). In vitro activity profile of oritavancin against a broad spectrum of aerobic and anaerobic pathogens (abstr). *In*: Proceedings of the 47th International Conference on Antimicrobial Agents and Chemotherapy (ICAAC) (Sept 17-20, Chicago) Washington D.C, American Society of Microbiology, USA: E-1612.

Nicas TI, Mullen DL, Flokowitsch JE, Preston DA, Snyder NJ, Zweifel MJ, Wilkie SC, Rodriguez MJ, Thompsom RC and Cooper Rd (1996). Semisynthetic glycopeptide antibiotics derived from LY264826 active against vancomycin-resistant enterococci. *Antimicrob. Agents Chemother.,* **40**: 2194-2199.

Novak R, Henriques B, Charpentier E, Normark S and Tuomanen E (1999). Emergence of vancomycin tolerance in *Streptococcus pneumoniae* (comments). *Nature*, **399**(6736): 590-593.

Noviello S, Ianniello F and Esposito S (2001). *In vitro* activity of LY333328 (oritavancin) against gram-positive aerobic cocci and synergy with ciprofloxacin against enterococci. *J. Antimicrob. Chemother.,* **48**: 283-286.

Owen JS, Bhavnani SM, Fielder-Kelly J, Loutit JS and Porter SB (2004). Population pharmacokinetics of oritavancin (abstr). *In*: Proceedings of the 44th International Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Washington D.C, American Society of Microbiology, USA: A-20.

Patel R, Rouse MB, Piper KE, Cockerill FR 3rd and Steckelberg JM (1998). *In vitro* activity of LY333328 against vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae. Diagn. Microbiol. Infect. Dis.,* **30**(2): 89-92.

Patel R, Rouse MS, Piper KE, Cockerill FR 3rd and Steckelberg JM (1998). *In vitro* activity of LY333328 against vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae. Diagn. Microbiol. Infect. Dis.,* **30**(2): 89-92.

Rodvold KA, Gotfried MH, Loutit JS and Porter SB (2004). Plasma and intrapulmonary concentrations of oritavancin and vancomycin in normal healthy adults (abstract). *Clin. Microbiol. Infect.,* **10**: 0254.

Rowe PA and Brown TJ (2001). Protein binding of ^{14}C-oritavancin (abstr). *In*: Program and abstracts of the 41st International Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago, IL, December 16-19, Washington, D.C: American Society for Microbiology: A-2193

Rupp ME, Fey PD and Longo GM (2001). Effect of LY333328 against vancomycin-resistant *Enterococcus faecium* in a rat central venous catheter-associated infection model. *J. Antimicrob. Chemother.,* **47**: 705-707.

Saleh-Mghir A, Lefort A, Petegnief Y, Dautrey S, Vallois JM, Le Guludec D, Carbon C and Fantin B (1999). Activity and diffusion of LY333328 in experimental endocarditis due to vancomycin-resistant *Enterococcus faecalis*.*Antimicrob. Agents Chemother.,***43**(1):115-120.

Sahm D, Moeck G, Pillar C, Arhin F and Draghi D (2008). In vitro activity profile of oritavancin against resistant staphylococcal populations from a recent surveillance initiative in Europe (abstr). *In*: Proceedings of the 18th European Congress of Microbiology and Infectious Diseases (ECCMID), April 19-22 Barcelona, 2008, *Clin. Microbial Infect.,* 14 (Abstracts Issue): p.539.

Schwalbe RS, McIntosh AC, Qaiyumi S, Johnson JA, Furness KM, Holloway WJ and Steele-Moore L (1996). *In vitro* activity of LY333328, an investigational glycopeptide antibiotic, against enterococci and staphylococci. *Antimicrob. Agents Chemother.,* **40**(10): 2416-2419.

Sillerstrom E, Wahlund E and Nord CE (1999). *In vitro* activity of LY333328 against anaerobic gram-positive bacteria. *J. Chemother.,* **11**: 90-92.

Smith TL, Pearson ML, Wilcox KR, Cruz C, Lancaster MV, Robinson-Dunn B, Tenover FC, Zervos MJ, Band JD, White E and Jarvis WR (1999). Emergence of vancomycin resistance in *Staphylococcus aureus*. Glycopeptide-intermediate *Staphylococcus aureus* Working Group (comment). *N. Engl. J. Med.,* **340**(17): 493-501.

Spellberg B, Powers JH, Brass EP, Miller LG and Edwards JE Jr (2004). Trends in antimicrobial drug development: Implications for the future. *Clin. Infect. Dis.,* **38**(9): 1279-1286.

Tabas I (2002). Consequences of cellular cholesterol accumulation: Basic concepts and physiological implications. *J. Clin. Investig.,* **110**: 905-911.

Tenover FC and McDonald LC (2005). Vancomycin-resistant staphylococci and enterococci: Epidemiology and control. *Curr. Opin. Infect. Dis.,* **18**(4): 300-305.

Van Bambeke F (2004a). Glycopeptides in clinical development: Pharmacological profile and clinical perspectives. *Curr. Opin. Pharmacol.,* **4**(5): 471-478.

Van Bambeke F, Carryn S, Seral C, Chanteux H, Tyteca D, Mingeot-Leclercq MP and Tulkens PM (2004c). Cellular pharmacokinetics and pharmacodynamics of the glycopeptide antibiotic oritavancin (LY333328) in a model of J774 mouse macrophages. *Antimicrob. Agents Chemother.,* **48**: 2853-2860.

Van Bambeke F, Saffran J, Mingeot-Leclercq MP and Tulkens PM (2005). Mixed-lipid storage disorder induced in macrophages and fibroblasts by oritavancin (LY333328), a new glycopeptide antibiotic with exceptional cellular accumulation. *Antimicrob. Agents Chemother.,* **49**(5): 1695-1700.

Van Bambeke F, Van Laethem Y, Courvalin P and Tulkens PM (2004b). Glycopeptide antibiotics: From conventional molecules to new derivatives. *Drugs,* **64**(9): 913-936.

Ward KE, Mersfelder TL and LaPlante KL (2006). Oritavancin-an investigational glycopeptide antibiotic. *Expert Opin. Investig. Drugs,* **15**(4): 417-429.

Wasilewski M, Disch D, McGill J, Harris H, O'Riordan W, Zeckel M (2001). Equivalence of shorter course therapy with oritavancin vs. vancomycin/cephalexin in complicated skin/skin structure infections (CSSI) (late-breaking abstr) *In*: Program andAbstracts of the 41st International Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago, IL, December 16-9, 2001.Washington, D.C: American Society of Microbiology, 2001.

Zeckel ML, Preston DA and Allen BS (2000). *In vitro* activities of LY333328 and comparative agents against nosocomial gram-positive pathogens collected in a 1997 global surveillance study. *Antimicrob. Agents Chemother.,* **44**: 1370-1374.