

## In Vitro Activity of an Oral Streptogramin Antimicrobial, XRP2868, against Gram-Positive Bacteria

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**The comparative in vitro potency of XRP2868, a new oral semisynthetic streptogramin antibiotic, was evaluated against gram-positive bacteria. XRP2868 inhibited all staphylococci at  $\leq 1$   $\mu\text{g/ml}$  and all nonpneumococcal streptococci at  $\leq 0.25$   $\mu\text{g/ml}$  and was fourfold more potent than quinupristin-dalfopristin against *Staphylococcus aureus* and *Enterococcus faecium*.**

Quinupristin-dalfopristin was approved in the United States in 1999 for treatment of infections associated with vancomycin-resistant *Enterococcus faecium* bacteremia and for complicated skin and skin structure infections due to oxacillin-susceptible *Staphylococcus aureus* and *Streptococcus pyogenes*. This agent must be given intravenously, usually by deep-vein catheter because of high rates of venous irritation when administered peripherally (6). One naturally occurring streptogramin mixture, pristinamycin, is available for oral use in France, Belgium, and a few other countries. XRP2868 is an investigational streptogramin antimicrobial with the potential for oral administration. Like quinupristin-dalfopristin, this agent is a 30:70 mixture of a streptogramin B component, RPR202868, and a streptogramin A component, RPR132552 (J. C. Barriere, E. Bacque, N. Berthaud, G. Dutruc-Rooset, G. Doerflinger, and G. Puchault, Abstr. 41st Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-359, 2001). (See reference 5 for structure.)

The new compound was shown to inhibit both *Streptococcus pneumoniae* and *Haemophilus influenzae* at concentrations of 1  $\mu\text{g/ml}$  or less (5). Ninety-five percent of 266 anaerobic gram-positive isolates were susceptible to XRP2868 at  $\leq 0.5$   $\mu\text{g/ml}$  (3). A preliminary report indicated fourfold greater potency than quinupristin-dalfopristin against *S. pyogenes* and twofold greater potency against *S. aureus* (D. Felmingham, M. J. Robbins, J. Shackcloth, C. Dencer, L. J. Williams, C. Couturier, and A. Bryskier, Abstr. 44th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-1410, 2004). The present study was undertaken to explore the activity of XRP2868 and comparators against various gram-positive bacteria.

Approximately 400 isolates of gram-positive bacteria were selected from our collection, stored frozen at  $-80^{\circ}\text{C}$ , to include organisms demonstrating specific resistance traits.

RPR202868, RPR132552, pristinamycin, quinupristin, dalfopristin, quinupristin-dalfopristin (30:70), telithromycin, erythromycin A, and levofloxacin were provided by Aventis Pharma S.A., Romainville, France. XRP2868 was prepared by combin-

ing RPR202868 and RPR132552 in a 30:70 ratio. Doxycycline, amoxicillin, and oxacillin were purchased from Sigma-Aldrich Co. (St. Louis, MO).

Antimicrobial susceptibilities were determined on Mueller-Hinton II agar (Becton, Dickinson & Co., Sparks, MD) (4); this was supplemented with 5% sheep blood for streptococci and diphtheroids. Inocula of approximately  $10^4$  CFU per spot were applied with a multiprong replicator, and the plates were examined for growth after overnight incubation at  $35^{\circ}\text{C}$ . Viridans group streptococci and corynebacteria were incubated in  $\text{CO}_2$ . *S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212 were used for quality control.

XRP2868 inhibited all staphylococci, including three vancomycin-intermediate *S. aureus* isolates and one linezolid-resistant *S. aureus* isolate, and isolates resistant to telithromycin, levofloxacin, or doxycycline, at concentrations of 1  $\mu\text{g/ml}$  or less (Table 1). Based on comparison of MICs for 90% of the strains tested, XRP2868 was fourfold more potent than pristinamycin against oxacillin-susceptible and -resistant *S. aureus* isolates.

All of the nonpneumococcal streptococci, including penicillin-resistant isolates of viridans group streptococci and isolates with quinupristin-dalfopristin MICs as high as 4  $\mu\text{g/ml}$ , were inhibited by XRP2868 at 0.25  $\mu\text{g/ml}$  or less. MICs of XRP2868 for 90% of the strains of streptococci tested were at least fourfold lower than those of quinupristin-dalfopristin. Blood supplementation did not affect the activities of XRP2868, RPR202868, or RPR132552 against control strains. Over the entire study, the modal MICs (and MIC ranges) of XRP2868 and of the components, respectively, against control strains were as follows: against *E. faecalis* ATCC 29212, 1  $\mu\text{g/ml}$  (0.5 to 2  $\mu\text{g/ml}$ ), 8  $\mu\text{g/ml}$  (4 to 8  $\mu\text{g/ml}$ ), and 128  $\mu\text{g/ml}$  (128  $\mu\text{g/ml}$ ); against *S. aureus* ATCC 29213, 0.12  $\mu\text{g/ml}$  ( $\leq 0.06$  to 0.12  $\mu\text{g/ml}$ ), 16  $\mu\text{g/ml}$  (16 to 32  $\mu\text{g/ml}$ ), and 0.5  $\mu\text{g/ml}$  (0.25 to 0.5  $\mu\text{g/ml}$ ). With  $\text{CO}_2$  incubation, MICs of the XRP2868 components were within these ranges for both QC strains. With  $\text{CO}_2$  incubation, MICs of XRP2868 were 1 dilution above the modal MIC against *E. faecalis* ATCC 29212 and 1 dilution below the modal MIC against *S. aureus* ATCC 29213.

The in vitro potency of XRP2868 was approximately fourfold greater than that of quinupristin-dalfopristin against 95 isolates of *E. faecium*, with median MICs of 0.12 and 0.5  $\mu\text{g/ml}$ ,

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TABLE 1. Comparative in vitro potency of XRP2868 against gram-positive bacteria

Organism (no. of isolates) and agent	MIC ( $\mu\text{g/ml}$ )		
	Range	50% of isolates	90% of isolates
<b>Oxacillin-susceptible <i>Staphylococcus aureus</i> (30)</b>			
XRP2868	0.06–0.25	0.12	0.12
RPR202868	16–>128	16	32
PRP132552	0.25–0.5	0.5	0.5
Quinu-Dalfo <sup>a</sup>	0.12–0.5	0.25	0.5
Quinupristin	0.5–64	2	2
Dalfopristin	4.0–8	8	8
Pristinamycin	$\leq 0.06$ –1	0.25	0.5
Erythromycin A	0.25–>128	0.25	>128
Telithromycin	$\leq 0.03$ –>128	0.06	0.12
Levofloxacin	0.12–64	0.25	0.25
Doxycycline	$\leq 0.06$ –2	0.25	0.25
Oxacillin	0.25–1	0.5	0.5
<b>Oxacillin-resistant <i>Staphylococcus aureus</i><sup>b</sup> (45)</b>			
XRP2868	0.06–0.5	0.25	0.5
RPR202868	16–>128	>128	>128
PRP132552	0.25–2	0.5	1
Quinu-Dalfo	0.12–1	0.5	1
Quinupristin	0.5–128	64	128
Dalfopristin	4–>128	8	8
Pristinamycin	0.25–2	1	2
Erythromycin A	0.25–>128	>128	>128
Telithromycin	$\leq 0.03$ –>128	>128	>128
Levofloxacin	0.25–>128	16	64
Doxycycline	$\leq 0.06$ –16	0.25	4
Oxacillin	4–>128	>128	>128
<b><i>Staphylococcus epidermidis</i> (14)</b>			
XRP2868	0.06–1	0.06	0.5
RPR202868	8–>128	16	>128
PRP132552	0.12–4	0.12	4
Quinu-Dalfo	$\leq 0.06$ –0.5	0.12	0.25
Quinupristin	0.12–32	0.12	8
Dalfopristin	1.0–16	2	8
Pristinamycin	$\leq 0.06$ –2	0.12	1
Erythromycin A	$\leq 0.06$ –>128	0.12	>128
Telithromycin	$\leq 0.03$ –>128	$\leq 0.03$	>128
Levofloxacin	0.12–16	0.25	8
Doxycycline	$\leq 0.06$ –1	0.25	1
Oxacillin	$\leq 0.06$ –32	0.12	32
<b><i>Enterococcus faecalis</i><sup>c</sup> (24)</b>			
XRP2868	0.12–2	1	2
RPR202868	4–>128	16	>128
PRP132552	8–>128	128	>128
Quinu-Dalfo	1.0–32	8	16
Quinupristin	4–>128	16	64
Dalfopristin	128–>128	>128	>128
Pristinamycin	0.5–16	2	4
Erythromycin A	1–>128	8	>128
Telithromycin	$\leq 0.03$ –4	0.06	2
Levofloxacin	0.5–128	2	128
Doxycycline	0.12–32	8	16
Amoxicillin	0.25–2	0.5	1
<b><math>\beta</math>-Lactamase-positive <i>Enterococcus faecalis</i> (6)</b>			
XRP2868	1.0–2	1	
RPR202868	16–>128	>128	
PRP132552	128–>128	>128	
Quinu-Dalfo	8.0–16	8	
Quinupristin	32–128	64	
Dalfopristin	>128	>128	
Pristinamycin	2.0–8	8	
Erythromycin A	8–>128	>128	
Telithromycin	0.06–4	2	
Levofloxacin	1	1	
Doxycycline	8.0–16	8	
Amoxicillin	0.5–1	1	
<b><i>Enterococcus faecalis</i> (VanA) (10)</b>			
XRP2868	1	1	1

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TABLE 1—Continued

Organism (no. of isolates) and agent	MIC ( $\mu\text{g/ml}$ )		
	Range	50% of isolates	90% of isolates
RPR202868	16–64	32	64
PRP132552	64–>128	128	>128
Quinu-Dalfo	4.0–8	8	8
Quinupristin	16–64	32	64
Dalfopristin	>128	>128	>128
Pristinamycin	2.0–4	4	4
Erythromycin A	4–>128	>128	>128
Telithromycin	$\leq 0.03$ –1.0	0.25	0.5
Levofloxacin	1.0–2	1	2
Doxycycline	0.12–16	16	16
Amoxicillin	0.5–2	0.5	1
<i>Enterococcus faecalis</i> (VanB) (23)			
XRP2868	0.5–4	2	2
RPR202868	4–>128	>128	>128
PRP132552	64–>128	128	128
Quinu-Dalfo	4.0–32	16	32
Quinupristin	8–>128	64	128
Dalfopristin	>128	>128	>128
Pristinamycin	2.0–8	8	8
Erythromycin A	4–>128	>128	>128
Telithromycin	$\leq 0.03$ –8	8	8
Levofloxacin	0.5–32	1	32
Doxycycline	0.12–64	16	32
Amoxicillin	0.5–4	1	1
<i>Enterococcus faecium</i> <sup>d</sup> (30)			
XRP2868	$\leq 0.06$ –1	0.12	0.5
RPR202868	2–>128	>128	>128
PRP132552	0.25–128	0.5	32
Quinu-Dalfo	0.5–2	0.5	1
Quinupristin	2–>128	64	128
Dalfopristin	2–>128	4	128
Pristinamycin	0.12–2	0.25	0.5
Erythromycin A	1–>128	>128	>128
Telithromycin	$\leq 0.03$ –8	2	8
Levofloxacin	1–128	4	8
Doxycycline	$\leq 0.06$ –32	0.12	32
Amoxicillin	0.12–64	32	64
<i>Enterococcus faecium</i> <sup>e</sup> (VanA) (32)			
XRP2868	$\leq 0.06$ –8	0.12	1
RPR202868	2–>128	>128	>128
PRP132552	0.25–128	0.25	64
Quinu-Dalfo	0.5–32	0.5	8
Quinupristin	2–>128	128	>128
Dalfopristin	2–>128	4	>128
Pristinamycin	0.25–32	0.25	4
Erythromycin A	2–>128	>128	>128
Telithromycin	$\leq 0.03$ –64	8	16
Levofloxacin	2–>128	64	128
Doxycycline	$\leq 0.06$ –32	0.12	16
Amoxicillin	16–128	64	128
<i>Enterococcus faecium</i> <sup>f</sup> (VanB) (31)			
XRP2868	0.06–2	0.12	1
RPR202868	2–>128	>128	>128
PRP132552	$\leq 0.06$ –64	0.5	16
Quinu-Dalfo	0.25–16	0.5	4
Quinupristin	4–>128	128	>128
Dalfopristin	1–128	4	64
Pristinamycin	0.12–4	0.25	2
Erythromycin A	2–>128	>128	>128
Telithromycin	$\leq 0.03$ –8	4	8
Levofloxacin	2–128	32	128
Doxycycline	$\leq 0.06$ –32	16	32
Amoxicillin	4–128	64	64
<i>Enterococcus faecium</i> (vanD) (2)			
XRP2868	$\leq 0.06$		
RPR202868	>128		

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TABLE 1—Continued

Organism (no. of isolates) and agent	MIC ( $\mu\text{g/ml}$ )		
	Range	50% of isolates	90% of isolates
PRP132552	0.25		
Quinu-Dalfo	0.5		
Quinupristin	64		
Dalfopristin	2		
Pristinamycin	0.25		
Erythromycin A	>128		
Telithromycin	2, 4		
Levofloxacin	2		
Doxycycline	$\leq 0.06, 4$		
Amoxicillin	32, 64		
<i>Enterococcus avium</i> (10)			
XRP2868	0.5–1	0.5	1
RPR202868	1–>128	4	>128
PRP132552	>128	>128	>128
Quinu-Dalfo	1.0–8	2	4
Quinupristin	0.25–64	1	64
Dalfopristin	>128	>128	>128
Pristinamycin	0.5–2	0.5	2
Erythromycin A	0.12–>128	0.25	>128
Telithromycin	$\leq 0.03$ –2	$\leq 0.03$	1
Levofloxacin	2	2	2
Doxycycline	0.12–64	16	32
Amoxicillin	0.25–0.5	0.5	0.5
<i>Enterococcus casseliflavus</i> (15)			
XRP2868	0.5	0.5	0.5
RPR202868	8	8	8
PRP132552	64–>128	128	>128
Quinu-Dalfo	2.0–4	2	4
Quinupristin	8.0–16	8	16
Dalfopristin	>128	>128	>128
Pristinamycin	0.5–1	1	1
Erythromycin A	2.0–8	4	4
Telithromycin	$\leq 0.03$ –0.06	0.06	0.06
Levofloxacin	1.0–8	4	4
Doxycycline	$\leq 0.06$ –0.25	0.25	0.25
Amoxicillin	0.25–1	0.5	1
<i>Enterococcus gallinarum</i> (15)			
XRP2868	0.25–0.5	0.25	0.5
RPR202868	4.0–32	8	8
PRP132552	128–>128	>128	>128
Quinu-Dalfo	2	2	2
Quinupristin	4.0–32	8	8
Dalfopristin	>128	>128	>128
Pristinamycin	0.5	0.5	0.5
Erythromycin A	0.12–>128	0.5	2
Telithromycin	$\leq 0.03$ –2	$\leq 0.03$	0.06
Levofloxacin	1.0–4	2	2
Doxycycline	0.12–32	0.25	16
Amoxicillin	0.5–1	1	1
<i>Enterococcus raffinosus</i> (10)			
XRP2868	$\leq 0.06$ –0.5	0.5	0.5
RPR202868	2–>128	2	>128
PRP132552	0.5–>128	>128	>128
Quinu-Dalfo	0.5–4	2	4
Quinupristin	1–>128	1	64
Dalfopristin	4–>128	>128	>128
Pristinamycin	0.25–2	1	2
Erythromycin A	0.12–>128	0.25	>128
Telithromycin	$\leq 0.03$ –4	$\leq 0.03$	2
Levofloxacin	1.0–16	2	4
Doxycycline	0.12–16	2	16
Amoxicillin	8.0–64	16	64
<i>Streptococcus pyogenes</i> (27)			
XRP2868	$\leq 0.06$	$\leq 0.06$	$\leq 0.06$
RPR202868	1.0–4	2	4
PRP132552	$\leq 0.06$ –0.25	$\leq 0.06$	0.12

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TABLE 1—Continued

Organism (no. of isolates) and agent	MIC ( $\mu\text{g/ml}$ )		
	Range	50% of isolates	90% of isolates
Quinu-Dalfo	0.25–1	0.25	0.5
Quinupristin	0.25–8	0.5	2
Dalfopristin	0.5–4	1	4
Pristinamycin	$\leq 0.06$ –0.12	0.12	0.12
Erythromycin A	$\leq 0.06$ –8	$\leq 0.06$	$\leq 0.06$
Telithromycin	$\leq 0.03$ –0.5	$\leq 0.03$	$\leq 0.03$
Levofloxacin	0.25–2	0.5	2
Doxycycline	$\leq 0.06$ –16	0.12	0.25
Amoxicillin	$\leq 0.06$ –0.5	$\leq 0.06$	$\leq 0.06$
<i>Streptococcus agalactiae</i> (15)			
XRP2868	$\leq 0.03$ –0.06	0.06	0.06
RPR202868	4.0–16	8	16
PRP132552	$\leq 0.06$ –0.12	0.12	0.12
Quinu-Dalfo	0.5–2	1	2
Quinupristin	16–64	32	32
Dalfopristin	2.0–8	4	8
Pristinamycin	0.12–0.25	0.25	0.25
Erythromycin A	$\leq 0.06$ –8	$\leq 0.06$	0.12
Telithromycin	$\leq 0.03$ –0.25	$\leq 0.03$	$\leq 0.03$
Levofloxacin	0.5–2	1	1
Doxycycline	0.12–32	32	32
Amoxicillin	$\leq 0.06$ –0.12	0.12	0.12
Group C + group G streptococci (15)			
XRP2868	$\leq 0.06$ –0.25	0.12	0.25
RPR202868	2.0–16	4	4
PRP132552	0.12–1	0.25	1
Quinu-Dalfo	0.5–2	1	1
Quinupristin	1.0–32	8	32
Dalfopristin	4.0–16	4	16
Pristinamycin	0.12–0.5	0.25	0.5
Erythromycin A	$\leq 0.06$ –>128	0.12	>128
Telithromycin	$\leq 0.03$ –0.06	$\leq 0.03$	0.06
Levofloxacin	0.25–2	0.5	1
Doxycycline	0.12–32	0.25	32
Amoxicillin	$\leq 0.06$	$\leq 0.06$	$\leq 0.06$
Viridans group streptococci <sup>g</sup> (20)			
XRP2868	0.06–0.25	0.12	0.25
RPR202868	2.0–128	8	16
PRP132552	$\leq 0.06$ –128	8	64
Quinu-Dalfo	0.12–4	1	4
Quinupristin	4.0–128	32	128
Dalfopristin	1.0–>128	128	>128
Pristinamycin	0.25–1	0.5	0.5
Erythromycin A	$\leq 0.06$ –>128	1	32
Telithromycin	$\leq 0.03$ –2	0.06	0.5
Levofloxacin	0.5–2	1	1
Doxycycline	<0.06–16	0.12	2
Amoxicillin	<0.06–16	1	4
<i>Corynebacterium jeikeium</i> (10)			
XRP2868	$\leq 0.03$ –0.25	$\leq 0.03$	0.25
RPR202868	16–64	16	16
PRP132552	$\leq 0.06$ –1	$\leq 0.06$	1
Quinu-Dalfo	$\leq 0.06$ –1.0	0.25	0.5
Quinupristin	4.0–32	32	32
Dalfopristin	0.25–8	1	8
Pristinamycin	0.12–0.5	0.12	0.5
Erythromycin A	0.25–64	8	32
Telithromycin	$\leq 0.03$ –0.12	0.06	0.12
Levofloxacin	0.25–8	0.5	8
Doxycycline	$\leq 0.06$ –4	0.25	0.5
Amoxicillin	0.5–>128	64	128

<sup>a</sup> Quinu-Dalfo, quinupristin-dalfopristin (30:70).<sup>b</sup> Includes three vancomycin-intermediate isolates and one linezolid-resistant isolate.<sup>c</sup> Includes three linezolid-resistant isolates.<sup>d</sup> Includes one linezolid-resistant isolate.<sup>e</sup> Includes two linezolid-resistant and three quinupristin-dalfopristin-resistant isolates.<sup>f</sup> Includes three quinupristin-dalfopristin-resistant isolates.<sup>g</sup> *S. mitis* (7 isolates), *S. sanguis* (5 isolates), *S. salivarius* (4 isolates), and *S. anginosus* group (4 isolates).

TABLE 2. Activity of XRP2868 and its components against six isolates of *E. faecium* resistant to quinupristin-dalfopristin

Strain	MIC ( $\mu\text{g/ml}$ )					
	Q-D <sup>a</sup>	XRP2868	Dalfopristin	RPR132552	Quinupristin	RPR202868
A4077	4	1	>128	64	>128	>128
A2603	4	1	64	8	32	16
A4208	4	1	64	16	>128	>128
A2414	8	1	128	16	32	>128
A4192	16	2	64	16	32	16
A2735	32	8	>128	64	>128	>128

<sup>a</sup> Q-D, quinupristin-dalfopristin.

respectively. Six of the 95 isolates were included in this study because of known resistance to quinupristin-dalfopristin (MICs, 4 to 32  $\mu\text{g/ml}$ ) (2). Against these isolates, MICs of XRP2868 (1 to 8  $\mu\text{g/ml}$ ) were four- to eightfold lower than those of quinupristin-dalfopristin. For each of these isolates, the potency of the streptogramin A component of XRP2868 (i.e., RPR132552 alone) was always greater than that of dalfopristin, while the potency of the streptogramin B component of XRP2868 (RPR202868 alone) could be less than, equal to, or greater than that of quinupristin (Table 2). This finding suggests that the greater potency of the streptogramin A component of the new antimicrobial is the major determinant of the superior potency of XRP2868 compared with quinupristin-dalfopristin against strains resistant to the latter.

Quinupristin-dalfopristin is poorly active against *E. faecalis* (1). The gene *lsa*, determining a predicted ABC protein homologue, has been associated with dalfopristin resistance and appears intrinsic to the species (7). In our study, only 1 of 63 isolates of *E. faecalis* was inhibited by quinupristin-dalfopristin at a concentration within the susceptible range (1  $\mu\text{g/ml}$ ). In contrast, 39 isolates (62%) of *E. faecalis* (as well as all isolates of *E. avium*, *E. casseliflavus*, *E. gallinarum*, and *E. raffinosus*) were inhibited by XRP2868 at concentrations of  $\leq 1$   $\mu\text{g/ml}$ . Differential activities of the streptogramin B components can be dismissed as an explanation for the superior potency of XRP2868 against this species, because comparison of MIC<sub>50</sub>s reveals that quinupristin is at least as potent as, if not more potent than, RPR202868.

The streptogramin A component of XRP2868, RPR132552, does appear to be marginally more potent than dalfopristin, and this may offer an explanation for the superior potency of the new drug against *E. faecalis*. It is possible that RPR132552 is inferior to dalfopristin as a substrate for efflux; alternatively, the increase in binding of the streptogramin B component attributed to conformational changes induced by the streptogramin A component, which is postulated to explain the synergistic activities of quinupristin and dalfopristin, may be greater when ribosomes are exposed to RPR132552 compared with dalfopristin.

In summary, the results of this study show that the investigational streptogramin antimicrobial XRP2868 inhibits a broad range of gram-positive bacteria. It is at least as potent as quinupristin-dalfopristin against oxacillin-susceptible and -resistant *S. aureus* strains, and it is fourfold more potent than the oral streptogramin pristinamycin against these organisms. In addition, XRP2868 is more potent than many of the comparator agents against nonpneumococcal streptococci and *E. faecium*, including strains resistant to vancomycin or quinupristin-dalfopristin. Whether the enhanced potency of this streptogramin against *E. faecalis*, compared with quinupristin-dalfopristin, will prove clinically useful remains to be shown. However, this observation suggests that the mechanisms of action and patterns of resistance to XRP2868 and quinupristin-dalfopristin merit further investigation.

An oral antimicrobial agent with the spectrum of XRP2868 could prove useful for step-down therapy following parenteral treatment of infections due to hospital-associated multidrug-resistant strains of staphylococci or enterococci and might also be an attractive alternative oral agent for the treatment of infections due to community-associated strains of oxacillin-resistant *S. aureus*. The greater potency of XRP2868 against nonpneumococcal streptococci and pneumococci (5), compared with quinupristin-dalfopristin, might further enhance its appeal for treatment of infections in which streptococci must also be targeted.

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