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► **To cite this version:**

Sophie Reissier, Vincent Cattoir. Streptogramins for the treatment of infections caused by Gram-positive pathogens.. Expert Review of Anti-infective Therapy, 2021, pp.1-13. 10.1080/14787210.2021.1834851 . hal-03000655

**HAL Id: hal-03000655**

**<https://hal.science/hal-03000655>**

Submitted on 5 Feb 2021

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**Streptogramins for the treatment of infections caused by  
Gram-positive pathogens**

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2  
3 **1 Abstract**

4  
5 **2 Introduction:** Streptogramins (pristinamycin and quinupristin-dalfopristin) can be interesting  
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7  
8 **3 options for the treatment of infections due to Gram-positive cocci, especially multidrug-**  
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10 **4 resistant isolates.**

11  
12 **5 Areas covered:** This review provides an updated overview on structural and activity  
13  
14 characteristics, mechanisms of action and resistance, **pharmacokinetic/pharmacodynamic** and  
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16  
17 **7 clinical use of streptogramins.**

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19 **8 Expert opinion:** The streptogramin antibiotics act by inhibition of the bacterial protein  
20  
21  
22 **9 synthesis. They are composed of two chemically distinct compounds, namely type A and type**  
23  
24 **10 B streptogramins, which exert a rapid bactericidal activity against a wide range of Gram-**  
25  
26 **11 positive bacteria (including methicillin-resistant staphylococci and vancomycin-resistant**  
27  
28 **12 enterococci). Several mechanisms of resistance have been identified in staphylococci and**  
29  
30 **13 enterococci but the prevalence of streptogramin resistance among clinical isolates remains**  
31  
32 **14 very low. Even if only a few randomized clinical trials have been conducted, the efficacy of**  
33  
34 **15 pristinamycin has been largely demonstrated with an extensive use for 50 years in France and**  
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36 **16 some African countries. Despite its effectiveness in the treatment of severe Gram-positive**  
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38 **17 bacterial infections demonstrated in several studies and the low rate of reported resistance, the**  
39  
40 **18 clinical use quinupristin-dalfopristin has remained limited, mainly due to its its poor**  
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42 **19 tolerance. Altogether, streptogramins (especially pristinamycin) can be considered as**  
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45  
46 **20 potential alternatives for the treatment of Gram-positive infections.**

## 1. Introduction

Staphylococci, streptococci and enterococci are major Gram-positive bacterial pathogens causing infections both in the community and in hospitals [1]. Methicillin-resistant *Staphylococcus aureus* (MRSA) is still a major cause of nosocomial infections, while the emergence of infections caused by community-acquired MRSA (CA-MRSA) has been reported worldwide, especially in the US [2]. Glycopeptides are the first line antibiotics used to treat MRSA infections, but since 1997, *S. aureus* strains with reduced susceptibility or resistance to glycopeptides have been described and still remain a global concern [3]. Coagulase-negative staphylococci (CoNS) emerged as a major cause of hospital-acquired infections (e.g. catheter-related bacteremia, endocarditis, osteoarticular and neonatal infections) and are often resistant to multiple antibiotics [4–6]. Due to their capacity to acquire and accumulate numerous antibiotic resistance determinants, enterococci, especially vancomycin-resistant *Enterococcus faecium* (VREF), have become major opportunistic pathogens in hospitals, strongly limiting the range of therapeutic options [7]. Even if widespread use of the pediatric pneumococcal conjugate vaccine has significantly decreased morbidity and mortality of infections due to *Streptococcus pneumoniae* in all age groups, there has been an unexpected increase of serotypes uncovered by the vaccine (e.g. 35B) as well as antibiotic-resistant serotypes (e.g. 19A) in some regions [8,9].

Besides the emergence of infections caused by multidrug-resistant (MDR) Gram-positive bacteria, which results in a significant increase of morbidity, mortality, and health cost, there is also a paucity of new antibacterial drugs developed by pharmaceutical companies [10,11]. Therefore, current antimicrobial alternatives for the treatment of severe infections are scarce, taking account into the risk of the emergence of bacterial resistance, the need of intravenous access, side effects and contraindications [12]. Many complex infections due to these MDR microorganisms (such as prosthetic joint infections) also require prolonged antibiotic therapy,

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3 46 with an intravenous-to-oral switch therapy. Oral therapeutic options would be also beneficial,  
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5 47 for the ambulatory treatment of community-acquired infections.  
6

7 48 Streptogramins have been considered as potential alternatives for the treatment of Gram-  
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9  
10 49 positive infections, because of their rapid bactericidal activity against a wide range of Gram-  
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12 50 positive bacteria (including MDR strains), their low prevalence of resistance among clinical  
13  
14 51 isolates, and their good pharmacokinetic properties [13,14]. Streptogramins are also effective  
15  
16 52 against Gram-negative cocci such as *Neisseria spp* or *Moraxella catarrhalis*. To date, two  
17  
18 53 streptogramins are prescribed in human medicine. Oral pristinamycin (formerly RP 7293),  
19  
20 54 commercialized under the name Pyostacine® (Sanofi-Aventis, Gentilly, France), is  
21  
22 55 extensively used for 50 years in France, and is currently used in France, Tunisia and  
23  
24 56 Lithuania. Quinupristin-dalfopristin (formerly RP 59500), marketed under the name  
25  
26 57 Synercid® (Pzifer, New York), is an injectable formulation approved since 1999 and 2000 in  
27  
28 58 the US and Europe, respectively. Quinupristine-dalfopristine is now only used in the US.  
29  
30  
31 59 Another oral streptogramin, NXL 103 (formerly XRP 2868), underwent phase II clinical trial  
32  
33 60 in 2011 but has not been distributed [15]. Of note, virginiamycin, an oral streptogramin, was  
34  
35 61 therapeutically used in France until late 1990s and as a growth promoter for animals in many  
36  
37 62 European countries until early 2000s and currently in the US, China, Japan and Canada [16].  
38  
39 63 Virginiamycin is also used to prevent bacterial contamination in ethanol fuel industry [17].  
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44 64 Several reviews have already been published about streptogramins but they mainly dealt  
45  
46 65 with structure, mode of action or biosynthesis and its regulation [16,18]. Here we have  
47  
48 66 chosen to focus on clinical uses, to synthesize clinical studies on each molecule, current  
49  
50 67 recommendations for use as well as trials about new molecules.  
51

## 52 68 2. Structure

53  
54 69 The streptogramin antibiotics are composed of two chemically distinct compounds, namely  
55  
56 70 type A and type B streptogramins [18]. The type A streptogramins are polyunsaturated cyclic  
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3 71 macrolactones (ca. 500 Da) containing an unusual oxazole ring and a dienyl amide fragment,  
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5 72 whereas type B streptogramins are cyclic hepta- or hexadepsipeptides (ca. 800 Da) with a  
6  
7 73 skeleton of amino acids with variations depending on the compound (**Figure 1**) [18–20].  
8  
9 74 Originally, streptogramins are natural mixtures produced by different members of  
10  
11 75 *Streptomyces* or related genera (**Table 1**) [19,21]. Every antibiotic producer synthesizes a  
12  
13 76 mixture of various A and B components **in different proportions**. For instance, *Streptomyces*  
14  
15 77 *pristinaespiralis* produces a mixture of group B compounds called pristinamycins I  
16  
17 78 (pristinamycin I<sub>A</sub>, pristinamycin I<sub>B</sub>, and pristinamycin I<sub>C</sub> with a ratio of 80-90%, 3-5%, and 2-  
18  
19 79 5%, respectively) and a mixture of group A compounds called pristinamycins II  
20  
21 80 (pristinamycin II<sub>A</sub> and pristinamycin II<sub>B</sub>) [19]. Note that pristinamycin II<sub>A</sub> is predominant in  
22  
23 81 the pristinamycin II mixture. The relative proportion of the different pristinamycin II  
24  
25 82 fermentation products also depends on culture conditions [20]. Finally, the pristinamycin  
26  
27 83 produced by *S. pristinaespiralis* is a mixture of pristinamycin I<sub>A</sub> and pristinamycin II<sub>A</sub> in a  
28  
29 84 30:70 ratio by weight (**Table 1 & Figure 1**) [19,20].

30  
31 85 Since a limitation in the clinical use of streptogramins was the poor water solubility, which  
32  
33 86 prevented the availability of an injectable form for the treatment of severe infections, semi-  
34  
35 87 synthetic derivatives were developed in the 1990s from natural pristinamycins (**Table 1**) [19].  
36  
37 88 Quinupristin (RP 57669) and dalfopristin (RP 54476) were obtained after several steps of  
38  
39 89 chemical modifications from pristinamycin II<sub>A</sub> and pristinamycin I<sub>A</sub>, respectively [19]. The  
40  
41 90 streptogramin association selected, comprised quinupristin and dalfopristin combined in a  
42  
43 91 30:70 ratio (w/w) of methane sulfonate salts as RP 59500 (**Figure 1**) [19,20].

### 92 **3. Mechanism of action**

93 Streptogramins A and B act by interfering with bacterial protein synthesis [22,23]. Their  
94  
95 94 bindings to adjacent but distinct regions within the P site of 23S rRNA of the 50S ribosomal  
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97 95 subunit result in synergic inhibiting activity [24]. Due to cooperative binding, streptogramin

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3 96 compounds, which are separately bacteriostatic against most Gram-positive bacteria, act  
4  
5 97 synergistically *in vitro* and *in vivo* and usually become bactericidal when combined [22].  
6

7 98 Type A streptogramins block tRNAs attachment to both A and P sites of the peptidyl-  
9 99 transferase center (PTC), and thus preventing the two early steps of elongation (i.e.  
10 100 aminoacyl-tRNA binding to the A site and peptide bond formation with peptidyl-tRNA at the  
11 101 P site) (Figure 2) [21,22]. Initially, it was thought that streptogramins A were only able to  
12 102 bind to 50S subunits and free 70S ribosomes and not to ribosomes involved into protein  
13 103 synthesis and polysomes [22]. However, it has been demonstrated that streptogramins A also  
14 104 interact with the entrance of the peptide exit tunnel, and likely bind to translating ribosomes  
15 105 [25]. Type B streptogramins share overlapping binding sites with macrolides and  
16 106 lincosamides (domains II and V of the 23S rRNA), and act similarly by inhibiting  
17 107 translocation, preventing polypeptide extension, and triggering the premature release of  
18 108 incomplete protein chains [21,22]. Streptogramins B binding site is located at the entrance to  
19 109 the ribosome tunnel, and does not contact the PTC (Figure 2) [26]. They can interact with  
20 110 ribosomes at any step of protein synthesis, including translating ribosomes and polysomes,  
21 111 inhibiting elongation after a few cycles [22].  
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33 112 In addition, binding of type A streptogramins induces a conformational change in the  
34 113 ribosome near the PTC that subsequently unmask a high-affinity binding site for  
35 114 streptogramins B leading to an increase of their activity by ca. 100-fold [18,21,22]. This  
36 115 synergy in the binding of streptogramins A and B seems to result from a repositioning of a  
37 116 single nucleotide, A2062 (*Escherichia coli* numbering), permitting direct interactions between  
38 117 both compounds [26,27]. Finally, the bactericidal activity of streptogramins may be partially  
39 118 due to the induction of a conformational alteration of U2585, leading to a hydrogen-bond-  
40 119 stabilized distortion of the PTC [26].  
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#### 57 120 4. Antibacterial activity

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3 121 The spectrum of activity of streptogramins includes a broad range of aerobic and anaerobic  
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5 122 Gram-positive bacteria, with a MIC<sub>90</sub> generally  $\leq 1$  mg/l (**Table 2**) [28–33]. They are active  
6  
7 123 against methicillin-susceptible, MRSA and most of *E. faecium* isolates (including VREF)  
8  
9  
10 124 (**Table 2**) [30,34]. Noteworthy, *Enterococcus faecalis* is a gap in the antimicrobial spectrum  
11  
12 125 since this Gram-positive species is intrinsically resistant to type A streptogramins (phenotype  
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14 126 LS<sub>A</sub>, which results in lincosamide and streptogramins A resistance) and to the A plus B  
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16 127 streptogramin combinations, due to the presence of the *lsa(A)* gene [35–37]. Streptogramins  
17  
18 128 are also active against *S. pneumoniae* (regardless of resistance to  $\beta$ -lactams and macrolides),  
19  
20 129  $\beta$ -hemolytic streptococci, viridans streptococci, *Corynebacterium* spp., and *Listeria*  
21  
22 130 *monocytogenes* (**Table 2**) [28,38,39]. In addition, streptogramins exhibit activity against most  
23  
24 131 of Gram-positive anaerobes, such as *Actinomyces* spp., *Clostridium* spp., *Lactobacillus* spp.,  
25  
26 132 *Peptostreptococcus* spp., and *Cutibacterium acnes* (**Table 2**) [33,39]. They are also active  
27  
28 133 against *Mycoplasma* spp., *Ureaplasma urealyticum*, and *Chlamydia* spp. Indeed, European  
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30 134 guidelines about *M. genitalium* infections recommend pristinamycin as third-line therapy in  
31  
32 135 patients failing both azithromycin and moxifloxacin therapy [40,41]. Interestingly, they also  
33  
34 136 have a good activity against fastidious Gram-negative bacteria including *Moraxella*  
35  
36 137 *catarrhalis*, *Neisseria* spp., and *Legionella pneumophila* (**Table 2**) [28,38,39]. Streptogramins  
37  
38 138 have a variable activity against *Bacteroides fragilis* group and other Gram-negative  
39  
40 139 anaerobes. Several strains are resistant and some, like *Fusobacterium* spp. are very  
41  
42 140 susceptible (**Table 2**) [28,39,40]. Finally, Enterobacterales, *Pseudomonas aeruginosa*, and  
43  
44 141 *Acinetobacter* spp. are intrinsically resistant to high levels of streptogramins [28].

51 142 Clinical Laboratory Standards Institute breakpoints for quinupristin-dalfopristin against  
52  
53 143 staphylococci, enterococci, and streptococci are as follows:  $\leq 1$  mg/l, susceptible; 2 mg/l,  
54  
55 144 intermediate; and  $\geq 4$  mg/l, resistant [42]. European Committee of Antimicrobial  
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57 145 Susceptibility Testing breakpoints for quinupristin-dalfopristin are available only for  
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3 146 staphylococci ( $\leq 1$  mg/l, susceptible;  $> 2$  mg/l, resistant) and enterococci ( $\leq 1$  mg/l, susceptible;  
4  
5 147  $> 4$  mg/l, resistant) ([www.eucast.org/](http://www.eucast.org/)). The Antibiogram Committee of the French Society  
6  
7 148 only recommends breakpoints for pristinamycin for Microbiology ([microbiologie.org](http://www.sfm-<br/>8<br/>9<br/>10 149 <a href=)) as follows:  $\leq 1$  mg/l, susceptible and  $> 2$  mg/l, resistant, for staphylococci,  
11  
12 150 enterococci, streptococci (except *S. pneumoniae*), and anaerobes;  $\leq 1$  mg/l, susceptible and  $> 1$   
13  
14 151 mg/l, resistant, for *S. pneumoniae*.

16  
17 152 Streptogramins are usually rapidly bactericidal against methicillin-susceptible  
18  
19 153 staphylococci, streptococci, and pneumococci regardless of erythromycin resistance, with  
20  
21 154 **minimum bactericidal concentration (MBC)** values usually  $\leq 4$ -fold higher than those of MICs  
22  
23 155 [29]. However, the bactericidal activity against staphylococci expressing a constitutive cross-  
24  
25 156 resistance to macrolides, lincosamides, and streptogramins B (like numerous MRSA isolates,  
26  
27 157 see below) is generally altered [43]. For this reason, clindamycin susceptibility has been  
28  
29 158 suggested as a surrogate marker for bactericidal activity of quinupristin-dalfopristin against  
30  
31 159 staphylococci [44,45]. Streptogramins have a bacteriostatic activity against the majority of *E.*  
32  
33 160 *faecium* isolates [39]. Against MRSA, rifampin has been demonstrated to be synergistic with  
34  
35 161 quinupristin-dalfopristin while it has been shown a synergism with doxycycline against VREF  
36  
37 162 [29,46]. Furthermore, the association with doxycycline may prevent or delay the emergence  
38  
39 163 of resistance **in vitro** and **in vivo** among VREF isolates [29,46,47].

#### 164 **5. Mechanisms of resistance to streptogramins A and B**

165 Most Gram-negative bacteria are intrinsically resistant to streptogramins, owing to the low  
166 permeability of the outer membrane and active efflux mechanisms. As already mentioned,  
167 type A and B streptogramins are chemically unrelated and have different binding sites on the  
168 ribosome. Therefore, different mechanisms will confer resistance to each type of  
169 streptogramins. In Gram-positive organisms, a variety of mechanisms confer resistance to  
170 either the A or the B component, including modifying enzymes, and modification or

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3 171 protection of the ribosomal target (**Table 3, Figure 3**)  
4  
5 172 (<http://faculty.washington.edu/marilynr/>) [20,21,48–51].  
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8 173 The alteration of the ribosomal target is the most common resistance mechanism to type B  
9  
10 174 streptogramins [20,21,49–51]. It is mainly due to the post-transcriptional modification of the  
11  
12 175 23S rRNA (domain V) by an rRNA methylase encoded by *erm* genes (**Table 3**) [20,21,24,49–  
13  
14 176 51]. Plasmid-borne or transposable *erm* genes encode a ribosomal methylase that mono- or  
15  
16 177 dimethylates the N<sup>6</sup> of A2058 (*E. coli* numbering) of the 23S rRNA. This methylation leads to  
17  
18 178 an alteration of binding of streptogramins B to their target, knowing that the A2058 is the  
19  
20 179 binding site not only for streptogramins B but also for macrolides and lincosamides, which  
21  
22 180 have partially overlapping binding sites. This is the reason why this modification confers  
23  
24 181 cross-resistance to macrolides, lincosamides, and streptogramins B (the so-called MLS<sub>B</sub>  
25  
26 182 phenotype) [20]. To date, more than 40 different *erm* genes have been described  
27  
28 183 (<http://faculty.washington.edu/marilynr/>) [48,50–55]. Expression of MLS<sub>B</sub> resistance can be  
29  
30 184 constitutive or inducible [20]. In inducible resistance, only the use of erythromycin (and other  
31  
32 185 14- and 15-membered macrolides) is prohibited, clindamycin and streptogramins B are  
33  
34 186 remain active. When *erm* genes are expressed constitutively, they confer cross-resistance both  
35  
36 187 to macrolides, clindamycin, and streptogramins B. Mutations of 23S rRNA and L22  
37  
38 188 ribosomal proteins, which lead to resistance to streptogramins B, have also been reported,  
39  
40 189 particularly in *S. pneumoniae* (**Table 3**) [20,48,56].  
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46 190 Other mechanisms affecting the activity of type B streptogramins are enzymatic  
47  
48 191 modification (hydrolysis) and ribosome protection. Lyases and lactonases, enzymes encoded  
49  
50 192 by *vgb* genes, could inactivate streptogramins B (**Table 3**) [20,21,48,50,51]. They cause a  
51  
52 193 cleavage of the ester linkage leading to a linearization of the molecule. A Low-level of  
53  
54 194 resistance to streptogramins B, mediated by ribosomal protection through acquisition of *msr*-  
55  
56 195 like genes, is described in staphylococci, streptococci, or enterococci [57].  
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3 196 Drug modification and target modification or protection account for resistance to  
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5 197 streptogramins A [20,21,48–51]. Ribosomal methylation, occurring at a different site than the  
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7 198 A2058 previously mentioned, may confer resistance to type-A streptogramins. Initially  
9  
10 199 identified in staphylococcal isolates from animal sources, the ribosomal methylation  
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12 200 mechanism has been also detected in human *S. aureus* clinical isolates [58–63]. The  
13  
14 201 resistance is due to the production of the Cfr protein that methylates the 23S rRNA at the  
16  
17 202 A2503 residue (*E. coli* numbering) (Table 3) [64]. Interestingly, Cfr is responsible for a  
18  
19 203 cross-resistance to five different antibiotic families: phenicols, lincosamides, oxazolidinones,  
20  
21 204 pleuromutilins, and streptogramins A (the so-called PhLOPS<sub>A</sub> phenotype) [65]. Usually found  
23  
24 205 on plasmids, the *cfr* gene has also been reported to be encoded on chromosomes [61,66]. Type  
25  
26 206 A streptogramins can be inactivated through the O-acetylation by acetyltransferases encoded  
27  
28 207 by *vat* genes (Table 3) [20,21,49–51]. *Vat* enzymes add an acetyl group from acetyl-CoA to  
29  
30 208 the second hydroxyl of type A streptogramins. Several proteins belonging to the ABC  
31  
32 209 proteins family including Lsa and Vga proteins are responsible for streptogramin A resistance  
33  
34 210 in *E. faecalis* and staphylococci through ribosomal protection [48,57,67]. Mutations in *eat(A)*,  
35  
36 211 which is coding for a ABC protein and conferred acquired LS<sub>A</sub> resistance, has also described  
37  
38 212 in *E. faecium* [68].

## 213 6. Consequences of resistance mechanisms on synergism between streptogramins A and 214 B

215 In staphylococci, it is possible to select *in vitro* some mutants resistant to quinupristin-  
216 dalfopristin, but the frequency remains low ( $10^{-8}$  to  $10^{-9}$ ) [29]. However, a higher rate of  
217 selection has been demonstrated in *E. faecium* [29]. Because of the synergism, acquisition of  
218 resistance to each streptogramin type might have no or only partial negative impact on the  
219 antimicrobial activity of the combination [20]. Actually, most staphylococcal clinical isolates  
220 that express complete resistance to the combination harbour several streptogramin resistance

221 genes such as *vat(A)*, *vgb(A)*, *vga(A)*, *vga(B)* or *vat(B)* [16,48]. In these isolates, *vat(A)*,  
222 *vgb(A)*, and *vga(A)* or *vga(B)* and *vat(B)* genes are often associated on plasmids of 26-40 kb  
223 and 50-90 kb, respectively [69]. Although streptogramin-resistant clinical isolates of *S. aureus*  
224 and *E. faecium* containing such plasmids have already spread, their prevalence remains low  
225 [69]. Resistance to the B component of streptogramins due to the constitutive MLS<sub>B</sub>  
226 phenotype is widespread in staphylococci and streptococci [20,48]. It has been early shown  
227 that the synergism between type A and B components is maintained against clinical isolates of  
228 staphylococci and streptococci constitutively resistant to macrolides. The original observation  
229 of synergy preservation was done with pristinamycin, and was confirmed for quinupristin-  
230 dalfopristin [70,71]. Conservation of synergism is likely due to the unique and synergic mode  
231 of action of streptogramins (see above). However, as previously mentioned, the *in vitro*  
232 bactericidal activity of the combination is altered in staphylococci expressing the MLS<sub>B</sub>  
233 constitutive phenotype. Three studies using an experimental model of aortic endocarditis in  
234 rabbit or in rat indicated decreased *in vivo* efficacy of quinupristin-dalfopristin against MLS<sub>B</sub>-  
235 resistant strains of *S. aureus* and *E. faecium* [72–74]. In one study, failure was imputed to the  
236 short plasmatic half-life of dalfopristin, highlighting the importance of the individual kinetics  
237 of each component of the combination [74]. Another study showed a maintained *in vivo*  
238 efficacy of quinupristin-dalfopristin against a *S. aureus* strain constitutively expressing an  
239 *erm(A)* gene [75]. Unfortunately, no large clinical studies are available to provide a definitive  
240 answer.

241 When strains express the inducible MLS<sub>B</sub> phenotype, they remain susceptible to  
242 clindamycin and type B streptogramins. However, concern over the possibility of selection of  
243 constitutive mutants resistant to clindamycin during therapy has led to discourage clinicians  
244 from prescribing streptogramin antibiotics. Similarly, the capacity of type B streptogramins to  
245 select constitutively resistant mutants was described [70]. However, the emergence of mutants

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3 246 was prevented *in vitro* if the cultures were exposed to type A streptogramins, suggesting that  
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5 247 such mutants were unlikely to be selected *in vivo* when applying the streptogramin  
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8 248 combination [70].

## 9 10 249 **7. Epidemiology of resistance**

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12 250 Although rare, resistance to streptogramins has been reported in *E. faecium* isolates  
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14 251 recovered from patients treated with quinupristin-dalfopristin [49,76]. This resistance was  
15  
16 252 associated with clinical failure and persistent VREF infections in almost all cases [49]. Other  
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18 253 streptogramin-resistant *E. faecium* isolates have also been recovered from humans in Europe  
19  
20 254 and in the US [77]. The rate of resistance to quinupristin-dalfopristin is usually  $\leq 10\%$  but  
21  
22 255 higher rates have been reported in Europe (up to 30%) [78–80]. A major concern is the  
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24 256 resistance among *E. faecium* isolates from animal sources that appears to be more common  
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26 257 (up to 100%) [49]. This is likely related to the extensive use of streptogramins in animal  
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28 258 husbandry (as growth factors) and veterinary medicine [16]. Whereas virginiamycin is still  
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30 259 approved by the US FDA to promote growth and prevent or control disease in chickens,  
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32 260 turkeys, swine, and cattle, it has been banned since 1999 in Europe [16]. The emergence of  
33  
34 261 streptogramin-resistant *E. faecium* isolates seems to be substantially the result of  
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36 262 virginiamycin use in animals and the transfer of streptogramin resistance via food to humans  
37  
38 263 [49,81]. In staphylococci (MRSA and CoNS), prevalence of resistance to quinupristin-  
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40 264 dalfopristin remains very low ( $< 1\%$ ) [82].

41  
42 265 Despite the longstanding oral use of streptogramins in France, the frequency of resistance  
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44 266 to pristinamycin remains low in *S. aureus* and CoNS (usually  $< 5\text{--}10\%$ ) [83]. In North  
45  
46 267 America, resistance to quinupristin-dalfopristin has been infrequently observed, where more  
47  
48 268 than 98% of *S. aureus* (including CA-MRSA) and CoNS isolates are entirely susceptible  
49  
50 269 [44,78,79,84–86]. Although macrolide resistance in  $\beta$ -hemolytic streptococci is common,  
51  
52 270 high-level streptogramin resistance has not been reported yet. However, several *S. agalactiae*  
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3 271 isolates from New Zealand and USA expressed *lsa(C)* or *lsa(E)* genes and expressed LS<sub>A</sub>  
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5 272 phenotype [87,88]. Among pneumococci and viridans streptococci, resistance to quinupristin-  
6  
7 273 dalfopristin is very uncommon, with more than 99% and 97% of susceptible strains,  
8  
9 274 respectively [84,86]. In France, all strains of *S. pneumoniae* isolated in adults and children  
10  
11 275 were susceptible to pristinamycin in 2016 [89].

## 14 276 **8. Pharmacokinetics and Pharmacodynamics**

16  
17 277 The two main components of pristinamycin (i.e. PI<sub>A</sub> and PII<sub>A</sub>) exhibit nearly parallel  
18  
19 278 plasma kinetics (**Table 4**) [90]. They are both quite rapidly absorbed, especially with  
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21 279 concomitant food intake ( $t_{max}$ , 1 h vs. 3 h) [90]. Although few data on its metabolism are  
22  
23 280 available, pristinamycin is mainly eliminated in the bile and poorly penetrates into **cerebral**  
24  
25 281 **spinal fluid**. Only scarce data are available on the diffusion in other biological fluids and into  
26  
27 282 tissues, in particular bone.

28  
29 283 Due to its minimal oral absorption, quinupristin-dalfopristin is only administered  
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31 284 intravenously, at a fixed 30:70 ratio. A linear relationship between dose and maximum plasma  
32  
33 285 concentration ( $C_{max}$ ) has been observed [29,91]. The main pharmacokinetic parameters after a  
34  
35 286 single 7.5 mg/kg infusion over 1 h are shown in **Table 4** [29,91]. After multiple doses (7.5  
36  
37 287 mg/kg q8h or q12h), steady state is achieved by day 2 and there is an increase of ca. 20% in  
38  
39 288  $C_{max}$  and AUC for both components [29,91]. Quinupristin exhibits higher, although moderate,  
40  
41 289 protein binding than dalfopristin (**Table 4**) [29,91]. Both quinupristin and dalfopristin  
42  
43 290 distribute well into tissues, such as kidneys, liver, spleen, salivary glands, and into white  
44  
45 291 blood cells, but the penetration into the CSF is poor [29,91]. Extravascular penetration into  
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47 292 blister fluid is approximately 40% of that of the plasma [29,91]. The diffusion of radiolabeled  
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49 293 quinupristin and dalfopristin, alone or in combination, in aortic vegetations from experimental  
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51 294 endocarditis in rabbits was also evaluated [92]. Quinupristin was homogeneously distributed  
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53 295 throughout the vegetations whereas dalfopristin showed a decreasing gradient of  
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3 296 concentration between the periphery and the core of the vegetation. Both compounds are  
4  
5 297 rapidly metabolized via non-enzymatic reactions [29,91]. Quinupristin is converted in two  
6  
7 298 active metabolites; a glutathione-conjugated compound (RP 69012) and a cysteine-conjugated  
9  
10 299 compound (RPR 100391) whereas dalfopristin is hydrolyzed to the natural pristinamycin II<sub>A</sub>  
11  
12 300 (RP 12536). Importantly, these metabolites exhibit antibacterial activity similar to that of the  
13  
14 301 parental compounds. Quinupristin-dalfopristin is hepatically cleared and excreted through the  
16  
17 302 biliary tract (**Table 4**) [29,91]. Quinupristin and dalfopristin exhibit a biphasic elimination,  
18  
19 303 and distribution half-life ( $t_{1/2}$ ) values of their metabolites are slightly longer ( $\times 1.1-1.5$ )  
20  
21 304 [29,91]. After administration of multiples doses, clearance of quinupristin-dalfopristin is  
23  
24 305 decreased by ca. 20%. Age, gender, and obesity appear to have no clinically significant  
25  
26 306 impact [29,91]. Finally, no dosage adjustments are necessary in patients with renal  
27  
28 307 impairment (including those under hemodialysis) and mild-to-moderate hepatic disease  
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31 308 [29,91]. The ratio AUC to MIC (AUC/MIC) seems to be the most predictive PK/PD  
32  
33 309 parameter of quinupristin-dalfopristin for antibacterial activity against *S. aureus* and *S.*  
34  
35 310 *pneumoniae* [91]. In addition, this association possesses an extended post-antibiotic effect  
37  
38 311 (PAE) against most of Gram-positive pathogens, which varies from approximately 4 to 5 h (at  
39  
40 312 4-fold MIC) in *S. aureus* and *S. epidermidis* [29]. At 4-fold MIC, a prolonged PAE is also  
42  
43 313 observed for *S. pneumoniae* (ca. 8 h), *S. pyogenes* (ca. 9-10 h), and *S. agalactiae* (ca. 7 h)  
44  
45 314 [29]. Finally, it has a PAE around 4-5 h (at 4-fold MIC) against *E. faecium*, even if it may be  
46  
47 315 as short as 0.2-1 h for some VREF strains [29,91].

## 49 316 **9. Clinical use**

51 317 Even if there are only a few randomized clinical trials to support the use of pristinamycin,  
53  
54 318 oral and topical preparations have been used in some European countries (particularly in  
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56 319 France) for more than 50 years, its efficacy has been largely demonstrated in humans  
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58 320 throughout this long period of time. In France, pristinamycin is primarily indicated for the  
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3 321 management of staphylococcal and streptococcal infections in adults (2-3 g/day) and children  
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5 322 (50 mg/kg/day): sinusitis, bronchopulmonary and skin infections. Two double-blind  
6  
7 323 randomized multicenter studies have demonstrated the non-inferiority of pristinamycin versus  
8  
9 324 cefuroxime axetil in the treatment of acute sinusitis in adults (**Table 5**) [93,94]. Two large  
10  
11 325 multicenter studies have also validated the use of pristinamycin in the treatment of  
12  
13 326 community-acquired pneumonia and another in **chronic obstructive pulmonary disease** acute  
14  
15 327 exacerbations (**Table 5**) [95–97]. A multicenter phase IV french study comparing the efficacy  
16  
17 328 of pristinamycin (2g x 2 per day for 2 days then 1g x 3 per day for 5 to 7 days) versus  
18  
19 329 amoxicillin (1g x 3 per day for 7 to 9 days) in adults with acute community acquired  
20  
21 330 pneumonia is currently undergoing ([www.clinicaltrials.gov](http://www.clinicaltrials.gov); NCT02332577). Several  
22  
23 331 prospective studies have also demonstrated that pristinamycin was a good alternative to treat  
24  
25 332 skins infections, such as erysipelas and superficial pyodermas (**Table 5**)[98–101].  
26  
27 333 Pristinamycin is not recommended as a first-line treatment for osteo-articular and bone joint  
28  
29 334 infections but several retrospective studies have described its clinical utility for (success rate  
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31 335 ca. 70%) [13,102,103]. Pristinamycin was also effective for MDR Gram-positive infections  
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33 336 treatment, especially MRSA (success rates ca. 80%) [102,104–106]. Several studies showed  
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35 337 that pristinamycin might be useful in management of *Mycoplasma genitalium* infections  
36  
37 338 [107,108]. Since 2016, European guidelines recommended to use pristinamycin as a third-line  
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39 339 treatment after azithromycin and moxifloxacin treatment failure for *M. genitalium* infections,  
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41 340 an important sexually transmitted pathogen responsible for both male and female genital tract  
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43 341 disease [40]. Finally, In 2016, Teng *et al.* demonstrated that pristinamycin was a good  
44  
45 342 alternative to treat infections due to resistant Gram-positive bacteria in patients with cancer  
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47 343 [14].

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49 344 Quinupristin-dalfopristin was firstly investigated on an emergency-use basis in the  
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51 345 treatment of infections attributable to MDR Gram-positive bacteria, such as MRSA and  
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3 346 VREF [29]. Its efficacy in the treatment of MRSA infections was documented in case reports,  
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5 347 a comparative pilot study and two phase III studies, with clinical success rates consistently  
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7 348 higher than 60% (**Table 5**) [29,109]. In a small single-blind randomized study, quinupristin-  
8  
9 349 dalfopristin has been also found to achieve similar response rates to vancomycin for the  
10  
11 350 treatment of catheter-related bloodstream infections (**Table 5**) [110]. The efficacy of  
12  
13 351 quinupristin-dalfopristin in the treatment of VREF infections was determined in three large  
14  
15 352 prospective phase III studies, with clinical and bacteriological success rates between 50 and  
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17 353 70% (**Table 5**) [111–113]. The overall response rates varied according to the site of infection  
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19 354 (<45% for endocarditis, intra-abdominal and intravascular infections) [111]. It is important to  
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21 355 note that the treatment with quinupristin-dalfopristin may also favor an *E. faecalis*  
22  
23 356 superinfection, because of the antimicrobial spectrum of quinupristin-dalfopristin excluded *E.*  
24  
25 357 *faecalis* [111]. Two large randomized open multicenter trials have compared quinupristin-  
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27 358 dalfopristin with standard therapy in patients suffering from presumed Gram-positive  
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29 359 complicated skin and soft-tissue infections (SSSIs) with similar clinical and bacteriological  
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31 360 success rates in the two groups (**Table 5**) [29,114]. For the treatment of nosocomial  
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33 361 pneumonia, the efficacy of quinupristin-dalfopristin plus aztreonam versus vancomycin plus  
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35 362 aztreonam was tested in a randomized, non-blind, multicenter study, and the equivalence of  
36  
37 363 the two antimicrobial regimens was demonstrated (**Table 5**) [115]. Quinupristin-dalfopristin  
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39 364 was also used successfully to treat a variety of infections, such as cellulitis, catheter-related  
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41 365 bacteremia, osteomyelitis, peritonitis, septic arthritis/bursitis, and wound infections [29].  
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43 366 Finally, a single study has reported a clinical benefit (favorable clinical and microbiological  
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45 367 response rates at 69% and 78%, respectively) in pediatric patients with severe Gram-positive  
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47 368 infections [116]. Since 1999, the association quinupristin-dalfopristin is approved by the USA  
48  
49 369 FDA for complicated SSSIs caused by oxacillin-susceptible *S. aureus* and *S. pyogenes*. In  
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51 370 1999, quinupristin-dalfopristin was also approved for the treatment of severe infections due to  
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3 371 VREF associated with bacteremia, but approval was removed by USA FDA in 2010. In 2015,  
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5 372 European Society of Cardiology recommended to use quinupristin-dalfopristin to treat  
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7 373 infective endocarditis due to aminoglycosides, beta-lactams and vancomycin resistant *E.*  
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9 374 *faecium* [117]. The efficacy of the streptogramin combination in infections due to  
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11 375 clindamycin-resistant staphylococci (mostly hospital-acquired MRSA) remains controversial.  
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13 376 The recommended dosages of quinupristin-dalfopristin are 7.5 mg/kg every 12 h for  
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15 377 complicated SSTIs and 7.5 mg/kg every 8 h for VRE infections (IV infusion over 1 h).

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17 378 Another oral streptogramin have been developed, named NXL103. Two multicenter,  
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19 379 randomized, phase II clinical trials have been conducted in 2007 and 2009 (Table 5). The first  
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21 380 one evaluated NXL103 efficacy, safety and tolerance for the treatment of community-  
22  
23 381 acquired pneumonia in adults ([www.clinicaltrials.gov](http://www.clinicaltrials.gov), NCT00653172). The second one  
24  
25 382 evaluated NXL103 to treat acute bacterial skin infections ([www.clinicaltrials.gov](http://www.clinicaltrials.gov),  
26  
27 383 NCT00949130). Those two studies were stopped in 2009 and 2010 respectively. No clinical  
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29 384 data has been published since then.

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## 36 386 **10. Adverse effects and drug interactions**

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38 387 Pristinamycin is generally well tolerated, with gastrointestinal disturbances (incidence ca.  
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40 388 7-25%) being the most frequent adverse events (nausea, vomiting, diarrhea), while some skin  
41  
42 389 rashes, arthralgia or myalgia have been also reported [13,94,118].

43  
44 390 The two major adverse effects of quinupristin-dalfopristin are venous intolerance  
45  
46 391 (incidence>50%), and arthralgia or myalgia (incidence, 2-30%), which can be severe [39].  
47  
48 392 Administration of quinupristin-dalfopristin requires the presence of a central venous catheter  
49  
50 393 because of venous toxicity, which is an important limitation to its use [39]. Other common  
51  
52 394 adverse events (incidence, 2-4%) include nausea, vomiting, diarrhea, and rash [39].  
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54 395 Biologically, an elevation of conjugated bilirubin may be observed [39]. Quinupristin and  
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3 396 dalfopristin are inhibitors of CYP3A4 and consequently drug interaction is observed with  
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5 397 ciclosporin, midazolam, nifedipine, tamoxifen, and terfenadine [39,91].  
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## 8 398 **11. Conclusion**

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10 399 Streptogramin antibiotics are a combination of chemically unrelated compounds, namely  
11  
12 400 type A and type B streptogramins, which act synergistically by inhibiting protein synthesis.  
13  
14 401 Although the streptogramin compounds are separately bacteriostatic, the combination usually  
15  
16 402 becomes bactericidal. Their spectrum of activity includes a broad range of aerobic and  
17  
18 403 anaerobic Gram-positive bacteria, but also most of fastidious Gram-negative and atypical  
19  
20 404 bacteria. This synergism also allows overcoming certain mechanisms of resistance to the  
21  
22 405 individual components of the combination and may explain low rates of resistance reported so  
23  
24 406 far. To date, two streptogramins are available in human medicine, oral pristinamycin, and  
25  
26 407 quinupristin-dalfopristin, an injectable formulation approved since 1999 and 2000 in the US  
27  
28 408 and Europe, respectively. **In this study we have synthesized all the clinical studies evaluating**  
29  
30 409 **these antibiotics.** Finally, virginiamycin, an oral streptogramin, was therapeutically used in  
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32 410 France until late 1990s and as a growth promoter for animals in many European countries  
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34 411 until early 2000s and currently in the US.  
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3 413 **Expert opinion**  
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5 414 Pristinamycin and quinupristin-dalfopristin are the two streptogramins used in human  
6  
7 415 medicine. They are a combination of two compounds that are bacteriostatic separately **but**  
8  
9 416 **have bactericidal activity when used synergistically**. The mechanism of the synergy is unique  
10  
11 417 and based on a stable ribosome conformational change provoked by the binding of  
12  
13 418 streptogramins A that unmasks a high-affinity binding site for streptogramins B. Using  
14  
15 419 combined antimicrobials to achieve synergism and enhance antimicrobial activity is not a new  
16  
17 420 concept. This notion has already proven to be correct for antimicrobial combinations  
18  
19 421 developed as a single drug such as trimethoprim combined with sulfamethoxazole  
20  
21 422 (cotrimoxazole), which sequentially inhibit two **different enzymatic** steps of the same  
22  
23 423 metabolic pathway (i.e. synthesis of folic acids). In addition, if the synergism is conserved  
24  
25 424 despite resistance to one of the components, this should avoid resistance to the combination.  
26  
27 425 The value of the synergy strategy has been highlighted by the maintained **in vitro** activity of  
28  
29 426 the streptogramin combination against most strains that are resistant to either type of  
30  
31 427 streptogramins and by the low frequency of resistant isolates in France despite the use of  
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33 428 pristinamycin for more than 50 years.

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35 429 Nonetheless, an important issue for clinical use of streptogramins is the specific  
36  
37 430 pharmacokinetics of each component of the combination that needs to reach the bacterial  
38  
39 431 pathogen at the site of infection in a ratio allowing synergism. This is particularly true for  
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41 432 strains that are resistant to one of the streptogramin components.

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43 433 Pristinamycin is mainly used in France until now to treat sinusitis, bronchopulmonary and  
44  
45 434 skin infections due to streptococci or staphylococci. This antibiotic is easy to use because of  
46  
47 435 its non-invasive route of administration, oral or topical. In addition, pristinamycin is well  
48  
49 436 tolerated with few side effects; it also has few interactions with other drugs and is  
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51 437 inexpensive. **Currently, pristinamycin is recommended to treat sinusitis, bronchopulmonary**  
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3 438 infections and skin infections due to streptococci or staphylococci. *M. genitalium* is an  
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5 439 important sexually transmitted pathogen responsible for both male and female genital tract  
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7 440 disease. Recently, the interest of pristinamycin in the treatment of infections due to this  
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9 441 pathogen have been demonstrated and European guidelines recommend to use pristinamycin  
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11 442 as a third-line treatment after azithromycin and moxifloxacin treatment failure for *M.*  
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13 443 *genitalium* infections. Moreover, this antibiotic has been described to be a good alternative to  
14  
15 444 treat infections due to resistant Gram-positive bacteria in patients with cancer in an Australian  
16  
17 445 study.

21 446 Quinupristin-dalfopristin, an injectable streptogramin, was the first to be developed  
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23 447 internationally. Despite its effectiveness in the treatment of severe Gram-positive bacterial  
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25 448 infections demonstrated in several studies, and the low rate of reported resistance, the  
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27 449 penetration of this molecule into the antibiotic market has remained limited. This can be  
28  
29 450 probably explained in part by the mode of administration, which requires a central venous  
30  
31 451 catheter. The low use of this antibiotic can likely also be explained by the high prevalence of  
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33 452 side effects, namely venous intolerance and the risk of thrombophlebitis. Studies to decrease  
34  
35 453 the toxicity of this molecule would be interesting, in order to make it more accessible and  
36  
37 454 easy to use. Currently marketed in North America, its high cost also represents a barrier to its  
38  
39 455 use.

44 456

#### 47 **Financial & competing interests disclosure**

48  
49 458 The authors have no other relevant affiliations or financial involvement with any  
50  
51 459 organization or entity with a financial interest in or financial conflict with the subject matter  
52  
53 460 or materials discussed in the manuscript.

54  
55 461 No writing assistance was utilized in the production of this manuscript.

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3 463 **Key issues**  
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- 5 464 • Streptogramins are a bactericidal combination of two compounds, streptogramins A  
6 and B that act synergistically by inhibition of bacterial protein synthesis.  
7  
8 465  
9  
10 466 • Two streptogramins (pristinamycin and quinupristin-dalfopristin) are currently used in  
11 human medicine.  
12 467  
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14 468 • Streptogramins exhibit a rapid bactericidal activity against a wide range of Gram-  
15 positive bacteria (including multidrug-resistant isolates)  
16 469  
17  
18 470 • Several mechanisms of resistance have been identified in staphylococci and  
19 enterococci but their prevalence among clinical isolates remains very low  
20 471  
21  
22 472 • The efficacy of pristinamycin has been largely demonstrated due to its extensive use  
23 for 50 years in France and some African countries.  
24 473  
25  
26 474 • The clinical use quinupristin-dalfopristin has remained limited, mainly due to its poor  
27 tolerance  
28 475  
29  
30 476 • Streptogramins (especially pristinamycin) can be considered as potential alternatives  
31 for the treatment of Gram-positive infections  
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3 841 **Legends of the figures**  
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5 842 **Figure 1.** Structure of streptogramins A (right) and B (left).  
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7 843  
8 844 **Figure 2.** Mechanism of action of streptogramins. (A) Normal protein elongation; attachment  
9 845 of tRNAs to the peptidyl transferase center (PTC) and elongation of polypeptide chain. Then,  
10 846 the peptide exits through the peptide exit tunnel. (B) Streptogramins could blocked tRNA  
11 847 attachment and prevent early steps of elongation, or interact with the peptide exit tunnel.  
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13 849 **Figure 3.** Mechanisms of resistance to streptogramins A and B  
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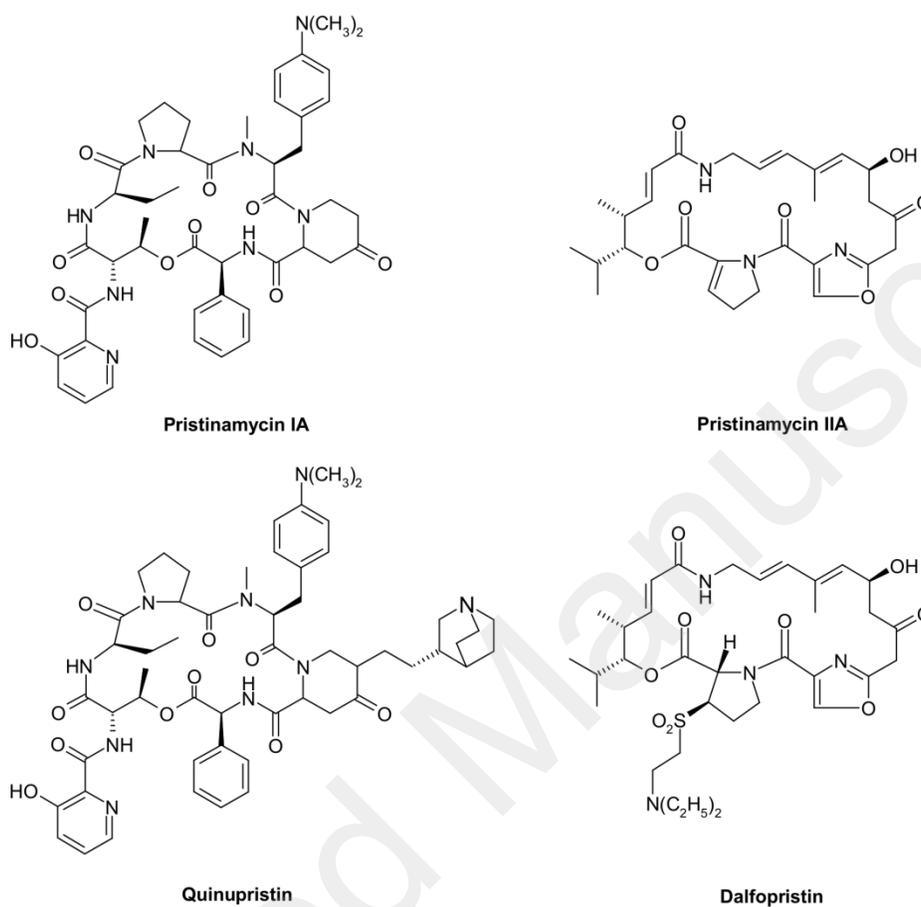


Figure 1

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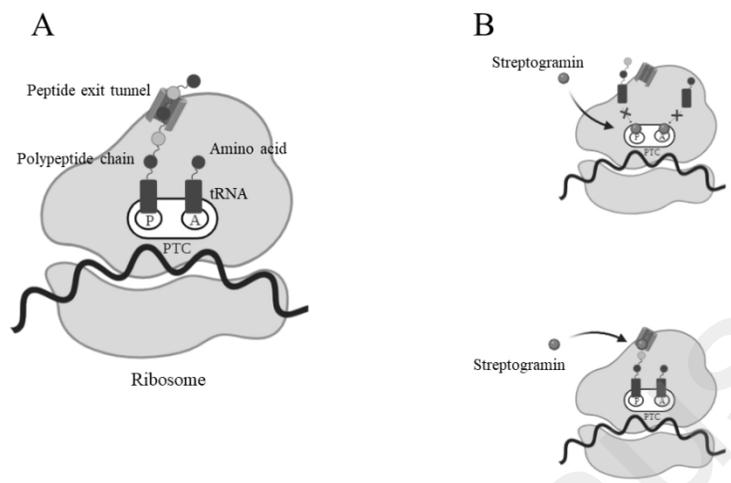


Figure 2

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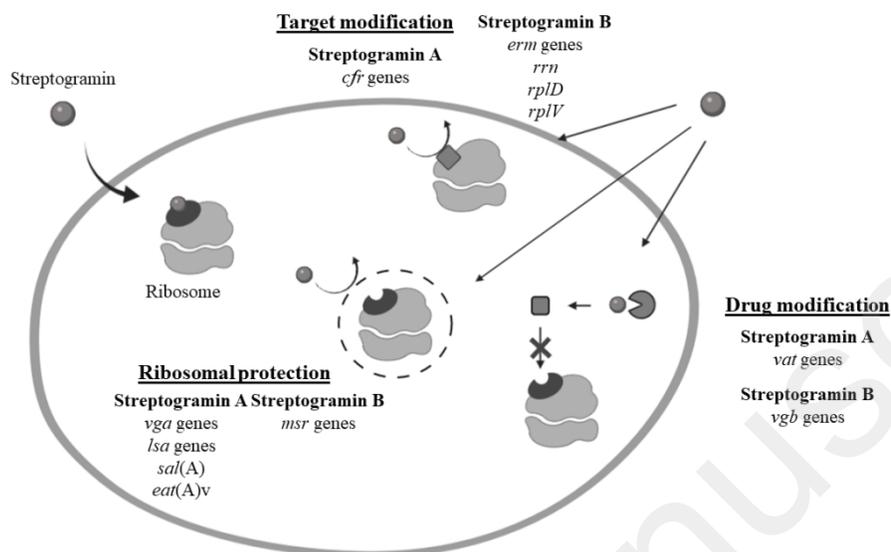


Figure 3

338x190mm (96 x 96 DPI)

**Table 1:** Examples of streptogramins [19,20].

Streptogramins	Individual components		Producing organism
	A	B	
<b>Natural products</b>			
Madumycin	Madumycin II	Madumycin I	<i>Actinomadura flava</i>
Mikamycin	Mikamycin A	Mikamycin B	<i>Streptomyces mitakaensis</i>
Pristinamycin	Pristinamycin II <sub>A</sub> , II <sub>B</sub> , II <sub>C</sub> , II <sub>D</sub> , II <sub>E</sub> , II <sub>F</sub> , II <sub>G</sub>	Pristinamycin I <sub>A</sub> , I <sub>B</sub> , I <sub>C</sub> , I <sub>D</sub> , I <sub>E</sub> , I <sub>F</sub> , I <sub>G</sub> , I <sub>H</sub> , I <sub>I</sub>	<i>Streptomyces pristinaespiralis</i>
Synergistin	Synergistin A1, A2	Synergistin B1, B2, B3	
Vernamycin	Vernamycin A	Vernamycin B ( $\alpha$ , $\beta$ , $\gamma$ , $\delta$ )	<i>Streptomyces olivaceus</i>
Virginiamycin	Virginiamycin M1, M2	Virginiamycin S1, S2, S3, S4, S5	<i>Streptomyces loidensis Streptomyces virginiae</i>
<b>Semisynthetic derivatives</b>			
Quinupristin-dalfopristin (RP 59500)	Dalfopristin (RP 54476)	Quinupristin (RP 57669)	-
Linopristin-flopristin (XRP 2868)	Flopristin (RPR 132552)	Linopristin (RPR 202868)	-

**Table 2:** Comparative in vitro activity (MIC in mg/l) of quinupristin-dalfopristin, and pristinamycin against Gram-positive bacteria [31-40].

Bacterial species (no. of tested isolates) <sup>a</sup>	Quinupristin-Dalfopristin			Pristinamycin		
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	MIC <sub>50</sub>	MIC <sub>90</sub>
MS <i>Staphylococcus aureus</i> (30)	0.12-0.5	0.25	0.5	≤0.06-1	0.25	0.5
MR <i>Staphylococcus aureus</i> (45)	0.12-1	0.5	1	0.25-2	1	2
<i>Staphylococcus epidermidis</i> (14)	≤0.06-0.12	0.12	0.25	≤0.06-2	0.12	1
VS <i>Enterococcus faecalis</i> (24)	1-32	8	16	0.5-16	2	4
VanA <i>Enterococcus faecalis</i> (10)	4	8	8	2-4	4	4
VanB <i>Enterococcus faecalis</i> (23)	4-32	16	32	2-8	8	8
VS <i>Enterococcus faecium</i> (30)	0.5-2	0.5	1	0.12-2	0.25	0.5
VanA <i>Enterococcus faecium</i> (32)	0.5-32	0.5	8	0.25-32	0.25	4
VanB <i>Enterococcus faecium</i> (31)	0.25-16	0.5	4	0.12-4	0.25	2
PS <i>Streptococcus pneumoniae</i> (86)	≤0.06-1	0.5	0.5	0.12-0.5	0.25	0.25
PI <i>Streptococcus pneumoniae</i> (81)	0.12-1	0.5	1	0.12-1	0.25	0.5
PR <i>Streptococcus pneumoniae</i> (94)	0.12-1	0.5	1	0.12-1	0.25	0.5
ES <i>Streptococcus pneumoniae</i> (141)	≤0.06-1	0.5	0.5	0.12-0.5	0.25	0.25
ER <i>Streptococcus pneumoniae</i> (120)	0.25-1	0.5	1	0.12-1	0.25	0.5
<i>Streptococcus pyogenes</i> (27)	0.25-1	0.25	0.5	≤0.06-0.12	0.12	0.12
<i>Streptococcus agalactiae</i> (15)	0.5-2	1	2	0.12-0.25	0.25	0.25
Viridans streptococci (20)	0.12-4	1	4	0.25-1	0.5	0.5
<i>Listeria monocytogenes</i> (23)	0.5-1	1	1	0.25-0.5	0.5	0.5
<i>Corynebacterium jeikeium</i> (10)	≤0.06-1	0.25	0.5	0.12-0.5	0.12	0.5
<i>Actinomyces israelii</i> (13)	0.12-0.5	0.25	0.25	≤0.03-0.12	0.12	0.12
<i>Actinomyces odontolyticus</i> (10)	0.12-0.5	0.25	0.25	≤0.03-0.12	≤0.03	0.12
<i>Clostridium difficile</i> (14)	0.25-2	0.25	1	0.12-16	0.12	4
<i>Clostridium perfringens</i> (12)	0.12-0.5	0.25	0.25	0.12	0.12	0.12
<i>Fingoldia magna</i> (11) <sup>b</sup>	0.25-0.5	0.25	0.5	0.06-0.12	0.12	0.12
<i>Cutibacterium acnes</i> (10)	≤0.03-0.5	0.12	0.12	≤0.03-0.12	≤0.03	≤0.03
BLN <i>Haemophilus influenzae</i> (50)	1-8	2	4	0.5-2	1	2
BLP <i>Haemophilus influenzae</i> (79)	0.25-8	4	4	0.12-4	1	2
BLNAR <i>Haemophilus influenzae</i> (21)	1-8	2	4	0.25-4	1	1
BLN <i>Haemophilus parainfluenzae</i> (18)	1-16	8	16	0.5-8	4	4
BLP <i>Haemophilus parainfluenzae</i> (8)	2-32	8	16	1-8	4	4
<i>Moraxella catarrhalis</i> (30)	0.25-2	1	1	0.06-0.5	0.25	0.5
<i>Bordetella pertussis</i> (10)	0.12-0.25	-	-	0.06	-	-
<i>Neisseria meningitidis</i> (20)	0.06-1	0.25	0.5	0.03-0.25	0.06	0.12
<i>Neisseria gonorrhoeae</i> (30)	0.12-4	0.5	1	0.06-1	0.12	0.5
<i>Bacteroides fragilis</i> group (100)	0.25-4	2	2	0.5-8	2	4
<i>Bacteroides</i> spp. (50)	0.03-2	0.125	1	0.06-4	0.25	2
<i>Fusobacterium</i> spp. (40)	0.06-0.12	0.06	0.12	0.06-2	0.06	0.5
<i>Mycoplasma pneumoniae</i> (20)	0.03-0.5	0.12	0.25	0.12-0.5	0.25	0.5
<i>Mycoplasma hominis</i> (20)	0.25-4	1	2	0.25-2	0.5	0.5
<i>Ureaplasma urealyticum</i> (19)	0.5-2	1	2	0.25-2	0.5	2
<i>Legionella</i> spp. (20)	0.25-1	0.5	0.5	0.03-0.12	0.06	0.12
<i>Chlamydophila pneumoniae</i> (5)	2-4	-	-	0.5-1	-	-
<i>Chlamydia trachomatis</i> (10)	0.5-1	-	-	0.12-0.25	-	-

<sup>a</sup>ER: Erythromycin-resistant; ES: Erythromycin-susceptible; MR: Methicillin-resistant; MS: Methicillin-susceptible; PI: Penicillin-intermediate; PR: Penicillin-resistant; PS: Penicillin-susceptible; VS: Vancomycin-susceptible; BLN: β-lactamase-negative; BLNAR: β-lactamase-negative ampicillin-resistant; BLP: β-lactamase-positive.

<sup>b</sup>Formerly *Peptostreptococcus magnus*.

**Table 3:** Mechanisms of resistance to streptogramins in Gram-positive bacteria (<http://faculty.washington.edu/marilynr/>) [20, 21, 24, 48-68].

Resistance mechanism	Gene(s)	Resistance phenotype <sup>a</sup>	Main bacterial species
<b>Streptogramins A</b>			
Ribosomal methylation	<i>cfr</i> , <i>cfr</i> (B), <i>cfr</i> (D)	PhLOPS <sub>A</sub>	<i>Staphylococcus</i> spp., <i>Streptococcus</i> spp., <i>Enterococcus</i> spp.
Acetylation	<i>vat</i> (A)-(E), <i>vat</i> (G),	S <sub>A</sub>	<i>Staphylococcus</i> spp., <i>Enterococcus</i> spp.
Ribosomal protection	<i>vga</i> (A)-(E), <i>vga</i> (A) <sub>v</sub> , <i>vga</i> (A) <sub>LC</sub> <i>lsa</i> (A)-(C) <sup>c</sup> , <i>lsa</i> (E)	S <sub>A</sub> LS <sub>A</sub> LS <sub>A</sub>	<i>Staphylococcus</i> spp., <i>Enterococcus</i> spp. <i>Staphylococcus</i> spp. <i>Staphylococcus</i> spp., <i>Streptococcus</i> spp., <i>Enterococcus</i> spp.
	<i>sal</i> (A) <i>eat</i> (A) <sub>v</sub>	LS <sub>A</sub> LS <sub>A</sub>	<i>Staphylococcus sciuri</i> <i>Enterococcus faecium</i>
<b>Streptogramins B</b>			
Ribosomal methylation	<i>erm</i> genes <sup>b</sup>	MLS <sub>B</sub>	<i>Staphylococcus</i> spp., <i>Streptococcus</i> spp., <i>Enterococcus</i> spp., <i>Cutibacterium acnes</i>
Ribosomal mutation	<i>rrn</i> (23S rRNA) <i>rplD</i> (L4 protein) <i>rplV</i> (L22 protein)	MLS <sub>B</sub> M MS <sub>B</sub>	<i>Streptococcus pneumoniae</i> <i>Streptococcus pneumoniae</i> <i>Staphylococcus aureus</i> , <i>Streptococcus pneumoniae</i>
Hydrolysis	<i>vgb</i> (A), <i>vgb</i> (B)	S <sub>B</sub>	<i>Staphylococcus</i> spp., <i>Enterococcus faecium</i>
Ribosomal protection	<i>msr</i> (A)-(D), <i>msr</i> (F)-(H)	MS <sub>B</sub>	<i>Staphylococcus</i> spp., <i>Streptococcus</i> spp., <i>Enterococcus</i> spp., <i>Micrococcus</i> spp.

<sup>a</sup> L: Lincosamides; M: Macrolides; O: Oxazolidinones; P: Pleuromutilins; Ph: Phenicols; S<sub>A</sub>: Streptogramins A; S<sub>B</sub>: Streptogramins B.

<sup>b</sup> *erm*(A)-(C), *erm*(F), *erm*(Q), *erm*(T), *erm*(X), *erm*(Y), *erm*(34), *erm*(43)-(45), *erm*(48), *erm*(50)

<sup>c</sup> *lsa*(C) is associated with a "LS<sub>A</sub>P" resistance phenotype

**Table 4:** Main pharmacokinetic parameters of streptogramins after a single dose [29, 90-92].

Parameter <sup>a</sup>	Pristinamycin (2 g, PO)		Quinupristin-Dalfopristin (30:70) (7.5 mg/kg, IV)	
	PI <sub>A</sub>	PII <sub>A</sub>	Quinupristin	Dalfopristin
C <sub>max</sub> (mg/L)	0.8	0.6	2.3-2.7	6.1-8.2
t <sub>max</sub> (h)	3.2	3.1	0.9	1.1
AUC (mg•h/L)	2.2	1.2	2.7-3.3	6.5-7.7
t <sub>1/2</sub> (h)	4	2.8	0.9-1.3	0.7-1.1
CL (L/h/kg)	-	-	0.7-0.9	0.7-0.8
V <sub>d</sub> (L/kg)	-	-	0.45	0.24
PB (%)	40-45	70-80	55-78	11-26
FE (%)	-	-	75	77
UE (%)	-	-	15	19

<sup>a</sup>AUC: area under the concentration-time curve; CL: Systemic clearance; C<sub>max</sub>: Maximal plasma concentration; FE: Excretion in the faeces; IV: Intravenous; PB: Protein binding; PO: per os; t<sub>1/2</sub>: Plasmatic half-life; UE: Excretion in the urine; V<sub>d</sub>: Volume of distribution.

**Table 5:** Main clinical trials assessing the efficacy of pristinamycin [93-101] and quinupristin-dalfopristin [109-115].

Reference	No. of patients	Drug and dosage <sup>b</sup>	Duration (days)	Results (%) <sup>c</sup>	
				Clinical success	Bacteriologic success
<b>Acute sinusitis</b>					
Pessey et al. [93]	160	PRI 2g/d	7-9	73-84	-
	148	CXM 500 mg/d	8-10	75-87	-
Gehanno et al. [94]	250	PRI 2 g/d	4	87-91	87
	235	CXM 500 mg/d	5	86-91	88
<b>Community-acquired pneumonia</b>					
Poirier et al. [96]	92	PRI 2 g/d	10-14	84-85	-
	88	AMC 2 g/d	10-14	84	-
Trémolières et al. [95]	170	PRI 3 g/d	7-10	80-88	82
	169	AMX 3 g/d	7-10	83-88	88
<b>Acute exacerbations of COPD<sup>a</sup></b>					
Léophonte et al. [97]	239	PRI 3 g/d	4	87	85
	236	AMC 2 g/d	8	88	78
<b>Skin and soft-tissue infections</b>					
Bernard et al. [98]	42	PRI 3 g/d	up to 10	86	-
Bernard et al. [99]	151	PRI 2 g/d	10	87	-
	142	OXA 2 g/d	10	90	-
Bernard et al. [100]	138	PRI 2-3 g/d	14	65-81	-
	150	PG 10-20 MIU/d - PV 3-6 MIU/d	14	53-67	-
Chosidow et al. [101]	163		14	81	-
	171	PRI 2 g/d CLO 2 g/d	14	83	-
<b>MRSA infections</b>					
Drew et al. [109]	90	QD 7.5 mg/kg q8h	28	74-76	67-71
<b>Catheter-related staphylococcal bacteremia</b>					
Raad et al. [110]	11	QD 5 mg/kg q8h	7	27-50	-
	15	QD 7.5 mg/kg q8h	7	27-57	-
	13	VA 1 g q12h	1	15-50	-
<b>VRE infections</b>					
Linden et al. [111]	396	QD 7.5 mg/kg q8h	20	51-69	60-68
Moellering et al. [113]	396	QD 7.5 mg/kg q8h or q12h	14	55-74	61
Raad et al. [112]	21	QD 7.5 mg/kg q8h	11	43	71
	19	LIN 600 mg q12h	15	58	89
<b>Complicated SSSTIs</b>					
Nichols et al. [114]	450	QD 7.5 mg/kg q12h	7	68	46-66
	443	OXA 2 g q6h, VAN 1 g q12h, or CFZ 1 g q8h	8	71	48-73
<b>Nosocomial pneumonia</b>					
Fagon et al. [115]	150	QD 7.5 mg/kg q8h + ATM 2 g	10	43-56	53-59
	148	q8h	9	45-58	55-64
		VAN 1 g q12h + ATM 2 g q8h			
<b>Community acquired pneumonia</b>					
Not published (NCT00653172)	302	NXL103 500 mg q12h NXL103 600 mg q12h Comparator q12h	NA	NA	NA
<b>Acute bacterial skin infections</b>					

Not published (NCT00949130)	180	NXL103 q12h LIN q12h	7-14 7-14	NA	NA
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<sup>a</sup>COPD: Chronic obstructive pulmonary disease.

<sup>b</sup>AMC: Amoxicillin-clavulanate; AMX: Amoxicillin; ATM: Aztreonam; CFZ: cefazolin; CLO: Cloxacillin; CXM: Cefuroxime axetil; LIN: Linezolid; OXA: Oxacillin; PG: Penicillin G; PV: Penicillin V; PRI: Pristinamycin; QD: Quinupristin-dalfopristin; VAN: Vancomycin

<sup>c</sup>Success rates observed in per-protocol and/or intention-to-treat populations (end of treatment and/or follow-up).

NA: not available.