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## Effectiveness and safety of dalbavancin in France: a prospective, multicentre cohort study

Johan Courjon, Eric Senneville, Hajnal-Gabriela Illes, Patricia Pavese, David Boutoille, Frederic C Daoud, Nathalie Dunkel, Pierre Tattevin

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1 **Effectiveness and safety of dalbavancin in France: a prospective, multicenter cohort study**

2

3 Johan Courjon<sup>a</sup>, Eric Senneville<sup>b</sup>, Hajnal-Gabriela Illes<sup>c,1</sup>, Patricia Pavese<sup>d</sup>, David Boutoille<sup>e</sup>,

4 Frederic C Daoud<sup>f</sup>, Nathalie Dunkel<sup>g</sup>, Pierre Tattevin<sup>h</sup>

5

6 <sup>a</sup>Université Côte d'Azur, CHU Nice, Nice, France, Infectious disease unit, 151 Route de St Antoine,

7 06200 Nice, courjon.j@chu-nice.fr

8 <sup>b</sup>Infectious Diseases Department, Gustave Dron Hospital, 155 Rue du Président Coty, 59200

9 Tourcoing, France, esenneville@ch-tourcoing.fr

10 <sup>c</sup>Infectious Disease Unit, Hospital of Mont-de-Marsan, 417 Avenue Pierre de Coubertin BP, 40024

11 Mont-de-Marsan, France

12 <sup>1</sup>Present address: Infectious Disease Unit, Private Hospital Francheville, Périgueux, France,

13 hajnal\_gabriela.illes@yahoo.fr

14 <sup>d</sup>Infectious Diseases Department, Grenoble Alpes University Hospital, Boulevard de la Chantourne,

15 38700 La Tronche, France, ppavese@chu-grenoble.fr

16 <sup>e</sup>Department of Infectious Disease and CIC-UIC 1413 INSERM, Nantes University Hospital, 5 Allée de

17 l'Île Gloriette, 44093 Nantes, France, david.boutoille@chu-nantes.fr

18 <sup>f</sup>INSERM U1219 BPH, Université de Bordeaux, 33076 Bordeaux, France, frederic.daoud-pineau@u-

19 bordeaux.fr

20 <sup>g</sup>ADVANS PHARMA Switzerland, Rue de Jargonant 2, 1207 Geneva, Switzerland

21 Nathalie.Dunkel@advanzpharma.com

22 <sup>h</sup>Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital, 2 Rue Henri le

23 Guilloux, 35033 Rennes, France, pierre.tattevin@chu-rennes.fr

24 **Corresponding author:** Johan Courjon, Université Côte d'Azur, CHU Nice, Nice, France, Infectious  
25 disease unit, 151 Route de St Antoine, 06200 Nice. courjon.j@chu-nice.fr; Tel.: +33-(0)49-203-5461

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28

29 **Abstract**

30 Dalbavancin is a lipoglycopeptide antibiotic approved for the treatment of acute bacterial skin and  
31 skin structure infections. However, several studies suggested that it is mostly used for off-label  
32 indications. This prospective, observational, multicenter study conducted in France from September  
33 2018 to April 2020 aimed to describe the use of dalbavancin in patients who received at least 1 dose  
34 of the antibiotic. The primary outcome was the clinical response at 30 days after the last dalbavancin  
35 dose.

36 A total of 151 patients in 16 centers were included in this study. The main infection sites were bone  
37 and joint infections (55.0%), multisite infections (15.9%), and vascular infections (14.6%), and the  
38 primary pathogens were coagulase-negative staphylococci (N=82), *Staphylococcus aureus* (N=51),  
39 and enterococci (N=27). Most patients (71.5%) received 3 previous antibiotic treatments. The  
40 number of dalbavancin injections per patient was 1 in 26 patients (17.2%), 2 in 95 patients (62.9%), 3  
41 in 17 patients (11.3%), and more than 3 in 13 patients (8.6%), with a mean cumulative dose of 3,089  
42  $\pm$  1,461 mg per patient. Among the 129 patients with a complete follow-up, clinical success was  
43 achieved in 119 patients (92.2%). At least 1 adverse event was reported in 67 patients (44.4%),  
44 including 12 (7.9%) patients with dalbavancin-related adverse events.

45 The results of the study showed that dalbavancin is mostly used for off-label indications and in  
46 heavily pre-treated patients in France. The clinical response at 30 days after the last dose was  
47 favorable in most patients, with a good safety profile.

48 clinicaltrials.gov identifier: NCT03726216

49 **Keywords:** Antibiotics, Dalbavancin, Effectiveness, Off-label, Safety

50 **Abbreviations**

51 ABSSSI, acute bacterial skin and skin structure infection; AE, adverse event; MIC, minimum inhibitory  
52 concentration; SD, standard deviation

## 53 1. Introduction

54 Intensive and inappropriate antibiotic use leads to the emergence and spread of antimicrobial  
55 resistance [1]. The estimated number of infections related to antibiotic-resistant bacteria in 2015 in  
56 Europe was over 670,000, resulting in more than 33,000 deaths [2]. The World Health Organization  
57 therefore adopted a global action plan to address antimicrobial resistance, with 5 main objectives  
58 among which: “to optimize the use of antimicrobial medicines in human and animal health and to  
59 develop the economic case for sustainable investment that takes account of the needs of countries  
60 and to increase investment in new medicines, diagnostic tools, vaccines, and other interventions.”  
61 [3].

62 To ensure prevention and treatment of infectious diseases, effective antimicrobials are key [3].

63 Dalbavancin is a semisynthetic lipoglycopeptide antibiotic that is derived from teicoplanin and  
64 disrupts the bacterial cell wall synthesis, resulting in cell death [4]. Its prolonged half-life of 14.5 days  
65 allows an extended interval between doses; dalbavancin is administered intravenously as a single  
66 1,500 mg dose or 1 dose each of 1,000 mg and 500 mg, 1 week apart [4, 5]. Its antibacterial  
67 spectrum is close to that of vancomycin [4].

68 Dalbavancin efficacy was demonstrated for acute bacterial skin and skin structure infections  
69 (ABSSSIs) caused by gram-positive bacteria in large phase III trials [6-8] and for the treatment of  
70 osteomyelitis and *Staphylococcus aureus* bacteremia [9, 10]. Two long-acting lipoglycopeptides have  
71 been approved in Europe for the treatment of ABSSSIs, i.e., dalbavancin and oritavancin [5, 11]. The  
72 pivotal trials that lead to their authorization were non-inferiority trials, as compared to regimens  
73 that include vancomycin [6, 12]. While these trials provide valuable information regarding  
74 tolerability, efficacy data cannot be extrapolated for infections other than ABSSSIs. However, real-  
75 world studies showed that dalbavancin has been used for the treatment of other bacterial  
76 infections, such as bone and joint infections, prosthetic joint infections, osteomyelitis, and  
77 endocarditis [13-18]. Linezolid, also originally approved for ABSSSIs, is a striking example of an

78 antibiotic with extensive off-label use [19], which subsequently required additional research efforts  
79 to characterize its efficacy and tolerability in other indications [20].

80 The aim of this study was therefore to better characterize the use of dalbavancin in France, with a  
81 specific emphasis on its safety.

82

## 83 **2. Materials and methods**

### 84 **2.1. Study design**

85 This was a prospective, observational, multicenter study in France. Physicians who prescribed  
86 dalbavancin or worked in hospitals and clinics that manage complex infections, especially  
87 staphylococcal infections, were contacted by the sponsor via email. The planned number of centers  
88 was 15 to 25. Physicians were asked to record eligible participants in screening logs.

89 Three study periods were defined: the baseline period when the infection was diagnosed, the  
90 treatment period when dalbavancin was administered, and the end of treatment period being up to  
91 30 days after the last dalbavancin injection.

92 At least 2 study visits were planned: the initial visit during which the first dalbavancin dose was  
93 administered and the final visit, which occurred up to 30 days after the last dose was administered.  
94 Interim visits could be planned, especially if multiple doses of dalbavancin were administered.

### 95 **2.2. Study population**

96 Eligible patients were adults  $\geq 18$  years of age at the time of dalbavancin administration. These  
97 patients were registered with the French social security and consented to data collection. Patients  
98 enrolled in a clinical trial with dalbavancin were excluded. Patients were enrolled consecutively  
99 whenever possible.

### 100 **2.3. Study objectives**

101 The study objectives were (1) to determine patient demographic and baseline characteristics,  
102 disease characteristics, and pathogen characteristics; (2) to characterize the routine use of  
103 dalbavancin; (3) to evaluate the effectiveness and the safety of dalbavancin; and (4) to assess  
104 resource utilization.

#### 105 **2.4. Data collection**

106 The following data were collected: (1) patient demographic and baseline characteristics, including  
107 laboratory parameters, comorbidities and Charlson comorbidity index [21], and the presence of a  
108 medical device; (2) primary infectious diagnosis; (3) pathogens, including *in vitro* susceptibility to  
109 dalbavancin whenever possible or susceptibility to vancomycin as a proxy, according to on-site  
110 protocols; (4) antibiotic administration before and during patient management; (5) details on the  
111 dalbavancin treatment, including dose, time between diagnosis and treatment initiation, number of  
112 injections, and interval between doses; (6) total duration of hospital stay; (7) clinical response  
113 (success or failure) with dalbavancin; and (8) adverse events (AEs).

114 Clinical response was assessed at 30 days after the final injection and was defined as a success if the  
115 patient did not need an antibiotic or was switched to an oral antibiotic (except for expected  
116 suppressive treatments), or if the infection had improved clinically at the time of dalbavancin  
117 discontinuation. The clinical response was assessed as a failure if the patient discontinued  
118 dalbavancin treatment because of: (i) an AE or insufficient therapeutic effect, (ii) if the patient was  
119 switched to another intravenous antibiotic, (iii) if the infection had not clinically improved at the  
120 time of dalbavancin discontinuation. Treatment response was undetermined if the information was  
121 unavailable or incomplete.

122 Patient analysis was stratified by infection type: ABSSSI, bacteremia, bone and joint infection,  
123 vascular infection, mediastinitis or pleural/pulmonary infection, and multisite infection, including  
124 infections in distant body locations or infections in adjacent but distinct anatomical structures (e.g.,  
125 soft tissue, muscle, kidney, and circulatory system).

126 Microbiological and antibiotic susceptibility tests were performed according to each hospital's  
127 protocol. When available, dalbavancin minimum inhibitory concentrations (MICs) were reported in  
128 line with national guidelines (Comité de l'Antibiogramme de la Société Française de Microbiologie)  
129 [22]. Otherwise, vancomycin MICs were used as a surrogate indicator of dalbavancin susceptibility.  
130 Breakpoints used were defined by the European Committee on Antimicrobial Susceptibility Testing  
131 [23].

132 AEs were collected in electronic case report forms. They were classified as treatment-emergent if  
133 they occurred between the first dalbavancin dose and the end of the 30-day follow-up period after  
134 the final dalbavancin injection.

## 135 **2.5. Statistical analysis**

136 The study was descriptive and sample size calculations were based on the assumption of a 90% cure  
137 rate of ABSSSIs. A sample size of 150 patients (i.e., 135 cured patients) was calculated to estimate a  
138 90% cure rate with an exact 2-sided 95% confidence interval with a precision of  $\pm 5\%$  (0.84–0.94).  
139 Three study populations were defined: the total population, i.e., all patients included in the study,  
140 the eligible population, i.e., all patients meeting the inclusion criteria, and the safety population, i.e.,  
141 all patients having received at least 1 dose of dalbavancin.

142 Continuous variables were described by mean  $\pm$  standard deviation (SD) or median and quartiles 1  
143 and 3. Categorical variables were described by the total and percentage of each response. The  
144 statistical analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC,  
145 USA).

## 146 **2.6. Ethical considerations**

147 This study complied with French regulations on patient observational clinical studies and with the  
148 Declaration of Helsinki. The protocol was approved by the French National Authority for Health  
149 (DEMESP/SEM/AA/MPI/TD/KLF/18.0221), received institutional review board approval (CPP



150 AU1420), and was registered with the competent authority in 2018 (n°ID-RCB 2018-A005080-50). It  
151 complied with regulations on data protection (CNIL MR-3 approval n° 2152768 v 0). The study was  
152 registered at clinicaltrials.gov (NCT03726216) and a substantial amendment was approved in 2019.  
153 Patients signed a non-objection form.

154

### 155 **3. Results**

#### 156 **3.1. Center and patient selection**

157 Thirty-five centers were contacted. Eighteen centers accepted to participate, of which 16 centers  
158 recruited patients (**Figure 1**). Among the participating centers, 78% were university hospitals. Eighty-  
159 three percent of recruiting physicians were infectious diseases specialists.

160 From September 2018 to April 2020, 178 patients who received at least 1 dose of dalbavancin were  
161 identified. Of these, 27 declined or could not sign the consent form, resulting in 151 eligible patients  
162 of whom 9 were lost to follow-up (6.0%) and 8 died (5.3%). The causes of death were septic shock  
163 (N=2), pulmonary aspiration (N=1), acute renal failure (N=1), cutaneous T-cell lymphoma (N=1),  
164 acute pulmonary edema (N=1), status epilepticus due to cerebral metastases (N=1), and  
165 undetermined (N=1).

#### 166 **3.2. Demographic and baseline characteristics**

167 The demographic and baseline characteristics of the study population are presented in **Table 1**. The  
168 mean age at study entry was 66 years (SD ± 16), and a majority of study participants were male  
169 (62.3%) (**Table 1**).

#### 170 **3.3. Indications and microorganisms**

171 Most infections were categorized as bone and joint infections (55.0%), followed by multisite  
172 infections (15.9%), and vascular infections (14.6%; 21 cases of endocarditis and 1 case of arteritis)

173 (Table 2). Among the 21 infective endocarditis cases, 4/21 (19.0%) occurred in patients with  
174 prosthetic valves. Ten infections (6.6%) were categorized as ABSSSI only (Table 2). More than half of  
175 the patients (56.3%) had a medical device-related infection, and 44.4% of patients had an infection  
176 on orthopedic implants (Table 2). A total of 253 pathogens were identified in 140 patients. The main  
177 pathogens were coagulase-negative staphylococci (N=82), *S. aureus* (N=51), enterococci (N=27), and  
178 *Corynebacterium striatum* (N=13) (Table 2). Most infections were monomicrobial (54.3%) (Table 2).  
179 Among the 137 strains tested for vancomycin susceptibility, 4 were resistant (2 strains of *S.*  
180 *epidermidis* and 2 strains of *Enterococcus gallinarum*), while the 29 strains tested for dalbavancin  
181 were susceptible. Three vancomycin-resistant strains were isolated in patients with polymicrobial  
182 infections with susceptible strains. The clinical responses of these patients were all successful after  
183 administration of 3,000 mg or 4,500 mg of dalbavancin. One vancomycin-resistant strain was  
184 monomicrobial, with a successful outcome after administration of 3,000 mg of dalbavancin. All  
185 patients with strains not covered by dalbavancin received additional concomitant antibiotics.

### 186 3.4. Antibiotic administration before and during patient management

187 Most patients received several prior antibiotic treatments for infections targeted by dalbavancin.  
188 Twelve patients (8.0%) received dalbavancin as first-line treatment, while 108 patients (71.5%)  
189 received 3 previous lines of treatment (Table 3). The median duration between the diagnosis and  
190 the initiation of dalbavancin was 29 days (Table 3). Among the 151 patients, 30.5% were treated  
191 with dalbavancin as a monotherapy. The main indications for the use of dalbavancin in association  
192 with another antibacterial treatment were multisite infections (21/24, 87.5%) and bone and joint  
193 infections (54/83, 65.1%) (Supplementary Table 1). The proportion of participants receiving  
194 combination treatment gradually increased with the number of previous antibacterial regimens:  
195 from 2/12 (16.7%) when dalbavancin was prescribed as first-line treatment, to 86/108 (79.6%) when  
196 it was first prescribed as fourth-line treatment (Supplementary Table 2). The concomitant antibiotics  
197 were primarily daptomycin (9.6%), linezolid (7.7%), and rifampicin (7.4%).

198 **3.5. Dalbavancin treatment**

199 The mean cumulative dose of dalbavancin per patient was 3,089 mg (SD  $\pm$  1,461 mg), including 89  
200 patients (58.9%) who received 3,000 mg (**Table 3** and **Supplementary Figure 1**). Three patients  
201 (2.0%) received 1,000 mg, the lowest dose, and 1 patient (0.7%) received 12,000 mg, the highest  
202 dose. The distribution of dose administration is presented in **Supplementary Figure 1**, and the  
203 cumulative dose by indication in **Supplementary Figure 2A**. More than half of the patients (62.9%)  
204 received 2 injections of dalbavancin, and 17.2% received 1 injection. The maximum number of  
205 injections was 9 for a patient with a bone and joint infection (**Table 3**). For patients receiving  
206 multiple injections (N=125), the median interval between 2 injections was 7 days (**Table 3**).  
207 **Supplementary Figure 2B** shows the total treatment duration with dalbavancin by indication.  
208 For the 129 patients with a reported clinical outcome, the mean follow-up duration from the  
209 baseline visit to the last follow-up visit or final visit was 55 days (SD  $\pm$  37).

210 **3.6. Hospitalization**

211 The median duration of hospitalization was 19 days (N=148), with a median of 7 days (N=132) of  
212 hospitalization on dalbavancin treatment (**Table 3** and **Supplementary Figure 3**). Seven patients  
213 were treated in the intensive care unit, with a median duration of hospitalization of 76 days (**Table**  
214 **3**).

215 **3.7. Clinical response in patients with a complete follow-up**

216 The effectiveness (success or failure) was determined in 129 (85.4%) patients with a complete  
217 follow-up. The clinical response was categorized as a success in 119 patients (92.2%; 95% confidence  
218 interval 86.2%–93.2%). A stratification by indication and by line of treatment is presented in **Table 4**.  
219 Among the 8 patients who received dalbavancin for ABSSEI, 7 (87.5%) achieved clinical success. The  
220 clinical success of dalbavancin treatment for off-label indications was  $\geq$ 80.0%, with a 100.0% success  
221 rate for bacteremia, vascular infections, and multisite infections, an 80.0% success rate for

222 mediastinitis or pleural/pulmonary infections, and an 89.2% success rate for bone and joint  
223 infections (**Table 4**).

224 Of the 10 patients (7.8%) with a clinical failure, 8 had a bone and joint infection, 1 had mediastinitis,  
225 and 1 had an ABSSSI (**Table 4**). The patient with an ABSSSI received dalbavancin as second-line  
226 treatment, and the patient with mediastinitis received it as fourth-line treatment. Six patients with a  
227 bone and joint infection received dalbavancin as fourth line treatment; the 2 remaining patients as  
228 third-line treatment. Baseline susceptibility testing was performed for 8 patients with a clinical  
229 failure. All strains were susceptible to either vancomycin or dalbavancin.

230 The 10 patients who received dalbavancin as first-line treatment achieved clinical success. When  
231 administered as second-, third-, and fourth-line treatment, 93.3%, 85.7%, and 92.2% of patients  
232 achieved clinical success, respectively (**Table 4**).

### 233 **3.8. Safety**

234 Sixty-seven patients (44.4%) developed a total of 125 AEs, of which 120 were classified as treatment-  
235 emergent AEs (**Table 5**). Thirty-one patients (20.5%) experienced 44 serious treatment-emergent  
236 AEs, and 7 patients had a fatal outcome post-treatment not deemed related to dalbavancin (**Table**  
237 **5**). Twelve patients (7.9%) reported 14 AEs assessed as related to dalbavancin (**Table 5**). Two serious  
238 related AEs (syncope and hypotension) were reported for the same patient and required immediate  
239 discontinuation of dalbavancin. Both were resolved without sequelae.

### 240 **4. Discussion**

241 The results of the present study indicate that dalbavancin is effective and well tolerated for the  
242 treatment of ABSSSIs as well as for off-label indications, including bacteremia, vascular infections,  
243 mediastinitis or pleural/pulmonary infections, multisite infections, and bone and joint infections.

244 Dalbavancin treatment is mostly used for off-label indications in France as 6.6% of patients included  
245 in this study were treated for ABSSSIs only. These results are aligned with other European real-world

246 observational studies in Austria, Spain, and Germany where dalbavancin was used to treat ABSSSIs in  
247 10.9% (11/101), 21.7% (15/69), and 33.3% (3/9) of patients, respectively [14, 24, 25]. However, there  
248 are no adapted protocols for the off-label use of dalbavancin, resulting in a heterogenic use of this  
249 antibiotic in France and other European countries [14, 16, 24, 25]. Additional studies to evaluate  
250 dalbavancin safety and efficacy in the identified off-label indications are therefore needed. In the  
251 context of bone and joint infections, a pharmacokinetic analysis was performed based on a  
252 predefined target of  $fAUC_{24h}/MIC > 111.1$ . This analysis indicated that creatinine clearance would be  
253 the main factor to select between 1,000 and 1,500 mg for the second injection, using therapeutic  
254 drug monitoring based on trough plasma concentration to tailor optimal doses and intervals for the  
255 following injections [26]. As shown in **Supplementary Figure 2B**, the median time between first and  
256 second injection was 12 days for bone and joint infections in our study, with increasing use of  
257 therapeutic drug monitoring thereafter.

258 This study showed an effectiveness of 92.2% at 30 days after the last dose of dalbavancin, regardless  
259 of the indication. These results are in line with previous European observational studies [14, 24, 25].  
260 In an Austrian study with 94 evaluable patients, the clinical success at 90 days after treatment was  
261 89.4% [14]. A Spanish study conducted over a 12-month period reported an effectiveness of 84.1%  
262 in 69 patients [24]. In another study conducted in Germany (N=9), the clinical success was 83.3% at  
263 30 days after the last dalbavancin dose [25]. These data suggest that dalbavancin treatment is  
264 effective for a broad range of infections with gram-positive bacteria.

265 This study also reported that dalbavancin is well tolerated, when used for both on- and off-label  
266 indications, which is in line with the results reported for other European territories [14-18, 24, 25].

267 The main strength of this study was the prospective, standardized collection of data in multiple  
268 centers across France (representing both university and non-university hospitals) with expertise in  
269 complex infections. This was also one of the largest prospective studies on dalbavancin so far, with  
270 few patients lost to follow-up. In addition, the enrolled patients were representative for the current

271 prescribing pattern of dalbavancin in France as this was an observational study with less stringent  
272 criteria than a randomized controlled trial.

273 The main limitation of the study was the follow-up of 30 days after the last dalbavancin  
274 administration as the study was designed for ABSSSI. This follow-up may not be sufficient to  
275 determine the effectiveness for certain other indications (e.g., bone and joint infections). Indeed,  
276 Matt et al. recorded a 47% success rate among 17 prosthetic joint infections managed with  
277 dalbavancin after on average 2 prior antibiotic treatment strategies and a median follow-up of 299  
278 days [16]. Moreover, resistance data after dalbavancin treatment for patients with clinical failure  
279 were not collected nor documented, and no causal associations could be made due to the  
280 descriptive nature of the study. Despite its limitations, the present study provides valuable  
281 information on the current use and outcomes of dalbavancin treatment.

282 As previously reported [13], in our opinion, dalbavancin may be of interest for gram-positive  
283 infections other than ABSSSIs, either as single-drug regimen or in combination, with the following  
284 assets as compared to alternative regimens: (1) secure treatment adherence, (2) no requirement of  
285 central venous access, (3) good safety profile, (4) early discharge for management as outpatient, and  
286 (5) activity on most multi-resistant gram-positive bacteria. The latter is typically true for device-  
287 related multi-resistant coagulase-negative staphylococcal infections, with treatment options often  
288 restricted. Dalbavancin is also suitable for *vanB* vancomycin-resistant enterococci [27].

## 289 **5. Conclusions**

290 The results of the present study indicate that dalbavancin was mostly used off-label in heavily pre-  
291 treated patients in France. The clinical success rate was high in ABSSSI (87.5%) and in off-label  
292 indications ( $\geq 80.0\%$ ), while the AE rate was low. These results are in line with previously published  
293 data from other European countries, indicating that dalbavancin treatment is effective and well  
294 tolerated when used for the treatment of ABSSSIs and off-label indications, including bacteremia,

295 vascular infections, mediastinitis or pleural/pulmonary infections, multisite infections, and bone and  
296 joint infections.

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307

308 **Declarations**

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315 Pfizer. Nathalie Dunkel is an employee of Advanz Pharma. Pierre Tattevin received consulting fees  
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317 Advanz Pharma and MSD. Patricia Pavese and Frederic C Daoud declare no conflict of interest.

318 **Ethical Approval:** This study complied with French regulations on patient observational clinical  
319 studies and with the Declaration of Helsinki. The protocol was approved by the French National  
320 Authority for Health (DEMESP/SEM/AA/MPI/TD/KLF/18.0221), received institutional review board  
321 approval (CPP AU1420), and was registered with the competent authority in 2018 (n°ID-RCB 2018-



322 A005080-50). It complied with regulations on data protection (CNIL MR-3 approval n° 2152768 v 0).  
323 The study was registered at [clinicaltrials.gov](https://clinicaltrials.gov) (NCT03726216) and a substantial amendment was  
324 approved in 2019. Patients signed a non-objection form.

325

### 326 **List of contributions**

327 All authors conceptualized the presented work. Johan Courjon, Eric Senneville, Hajnal-Gabriela Illes,  
328 Patricia Pavese, David Bouteille, and Pierre Tattevin were involved in the study conduct. Frederic C  
329 Daoud analyzed the data. All authors read and approved the final manuscript.

330

### 331 **Data statement**

332 The study information is available at <https://www.clinicaltrials.gov/> (NCT03726216). The data that  
333 support the findings of this study are available from the corresponding author, upon reasonable  
334 request.

335

336

337 **References**

- 338 [1] Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. *PT* 2015;40:277-83.
- 339 [2] Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable  
340 deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the  
341 EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis*  
342 2019;19:56-66. 10.1016/s1473-3099(18)30605-4
- 343 [3] World Health Organization. Global action plan on antimicrobial resistance.  
344 <https://www.who.int/publications/i/item/9789241509763>; 2015 [accessed 30 September 2022].
- 345 [4] Smith JR, Roberts KD, Rybak MJ. Dalbavancin: A Novel Lipoglycopeptide Antibiotic with Extended  
346 Activity Against Gram-Positive Infections. *Infect Dis Ther* 2015;4:245-58. 10.1007/s40121-015-0077-  
347 7
- 348 [5] European Medicines Agency. Xydalba. Summary of product characteristics.  
349 [https://www.ema.europa.eu/en/documents/product-information/xydalba-epar-product-](https://www.ema.europa.eu/en/documents/product-information/xydalba-epar-product-information_en.pdf)  
350 [information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/xydalba-epar-product-information_en.pdf); 2015 [accessed 30 September 2022].
- 351 [6] Boucher HW, Wilcox M, Talbot GH, Puttagunta S, Das AF, Dunne MW. Once-weekly dalbavancin  
352 versus daily conventional therapy for skin infection. *N Engl J Med* 2014;370:2169-79.  
353 10.1056/NEJMoa1310480
- 354 [7] Dunne MW, Puttagunta S, Giordano P, Krievins D, Zelasky M, Baldassarre J. A Randomized Clinical  
355 Trial of Single-Dose Versus Weekly Dalbavancin for Treatment of Acute Bacterial Skin and Skin  
356 Structure Infection. *Clin Infect Dis* 2016;62:545-51. 10.1093/cid/civ982
- 357 [8] Jauregui LE, Babazadeh S, Seltzer E, Goldberg L, Krievins D, Frederick M, et al. Randomized,  
358 double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the  
359 treatment of complicated skin and skin structure infections. *Clin Infect Dis* 2005;41:1407-15.  
360 10.1086/497271

361 [9] Rappo U, Puttagunta S, Shevchenko V, Shevchenko A, Jandourek A, Gonzalez PL, et al.  
362 Dalbavancin for the Treatment of Osteomyelitis in Adult Patients: A Randomized Clinical Trial of  
363 Efficacy and Safety. *Open Forum Infect Dis* 2018;6:ofy331. 10.1093/ofid/ofy331  
364 [10] Gonzalez PL, Rappo U, Akinapelli K, McGregor JS, Puttagunta S, Dunne MW. Outcomes in  
365 Patients with Staphylococcus aureus Bacteremia Treated with Dalbavancin in Clinical Trials. *Infect*  
366 *Dis Ther* 2022;11:423-34. 10.1007/s40121-021-00568-7  
367 [11] European Medicines Agency. Tenkasi. Summary of product characteristics.  
368 [https://www.ema.europa.eu/en/documents/product-information/tenkasi-previously-orbactiv-epar-](https://www.ema.europa.eu/en/documents/product-information/tenkasi-previously-orbactiv-epar-product-information_en.pdf)  
369 [product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/tenkasi-previously-orbactiv-epar-product-information_en.pdf); 2015 [accessed 23 June 2023].  
370 [12] Lodise TP, Redell M, Armstrong SO, Sulham KA, Corey GR. Efficacy and Safety of Oritavancin  
371 Relative to Vancomycin for Patients with Acute Bacterial Skin and Skin Structure Infections (ABSSSI)  
372 in the Outpatient Setting: Results From the SOLO Clinical Trials. *Open Forum Infect Dis*  
373 2017;4:ofw274. 10.1093/ofid/ofw274  
374 [13] Dinh A, Duran C, Pavese P, Khatchatourian L, Monnin B, Bleibtreu A, et al. French national  
375 cohort of first use of dalbavancin: A high proportion of off-label use. *Int J Antimicrob Agents*  
376 2019;54:668-72. 10.1016/j.ijantimicag.2019.08.006  
377 [14] Wunsch S, Krause R, Valentin T, Prattes J, Janata O, Lenger A, et al. Multicenter clinical  
378 experience of real life Dalbavancin use in gram-positive infections. *Int J Infect Dis* 2019;81:210-4.  
379 10.1016/j.ijid.2019.02.013  
380 [15] Illes H-G, Lupu A, Loutfi B, Hoskovec C, Rogero J-M, Delbast L, et al. Efficacy and safety of  
381 dalbavancin monotherapy as salvage treatment for bone and joint infection. *Clinical Medicine*  
382 *Research* 2022;11:74-80. 10.11648/j.cmr.20221103.16  
383 [16] Matt M, Duran C, Courjon J, Lotte R, Le Moing V, Monnin B, et al. Dalbavancin treatment for  
384 prosthetic joint infections in real-life: a national cohort study and literature review. *J Glob*  
385 *Antimicrob Resist* 2021;25:341-5. 10.1016/j.jgar.2021.03.026

386 [17] Tobudic S, Forstner C, Burgmann H, Lagler H, Ramharter M, Steininger C, et al. Dalbavancin as  
387 Primary and Sequential Treatment for Gram-Positive Infective Endocarditis: 2-Year Experience at the  
388 General Hospital of Vienna. Clin Infect Dis 2018;67:795-8. 10.1093/cid/ciy279

389 [18] Tobudic S, Forstner C, Burgmann H, Lagler H, Steininger C, Traby L, et al. Real-world experience  
390 with dalbavancin therapy in gram-positive skin and soft tissue infection, bone and joint infection.  
391 Infection 2019;47:1013-20. 10.1007/s15010-019-01354-x

392 [19] Theil C, Schmidt-Braekling T, Gosheger G, Schwarze J, Dieckmann R, Schneider KN, et al. Clinical  
393 use of linezolid in periprosthetic joint infections - a systematic review. J Bone Jt Infect 2020;6:7-16.  
394 10.5194/jbj-6-7-2020

395 [20] Jean SS, Liu IM, Hsieh PC, Kuo DH, Liu YL, Hsueh PR. Off-label use versus formal  
396 recommendations of conventional and novel antibiotics for the treatment of infections caused by  
397 multidrug-resistant bacteria. Int J Antimicrob Agents 2023;61:106763.  
398 10.1016/j.ijantimicag.2023.106763

399 [21] Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin  
400 Epidemiol 1994;47:1245-51. 10.1016/0895-4356(94)90129-5

401 [22] Société Française de Microbiologie. Comité de l'antibiogramme de la Société Française de  
402 Microbiologie. Recommandations 2021 V.1.0 Avril. <http://sante.rns.tn/images/eucastcasfm2021.pdf>;  
403 2021 [accessed 30 September 2022].

404 [23] European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for  
405 interpretation of MICs and zone diameters Version 12.0, valid from 2022-01-01.  
406 [https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST\\_files/Breakpoint\\_tables/v\\_12.0 Breakp  
407 oint Tables.pdf](https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_12.0_Breakpoint_Tables.pdf); 2022 [accessed 30 September 2022].

408 [24] Bouza E, Valerio M, Soriano A, Morata L, Carus EG, Rodríguez-González C, et al. Dalbavancin in  
409 the treatment of different gram-positive infections: a real-life experience. Int J Antimicrob Agents  
410 2018;51:571-7. 10.1016/j.ijantimicag.2017.11.008

411 [25] Hanses F, Dolff S, Trauth J, Seimetz M, Hagel S. A Multicentre, Prospective, and Retrospective  
412 Registry to Characterize the Use, Effectiveness, and Safety of Dalbavancin in German Clinical  
413 Practice. *Antibiotics (Basel)* 2022;11:563. 10.3390/antibiotics11050563

414 [26] Cojutti PG, Tedeschi S, Gatti M, Zamparini E, Meschiari M, Siega PD, et al. Population  
415 Pharmacokinetic and Pharmacodynamic Analysis of Dalbavancin for Long-Term Treatment of  
416 Subacute and/or Chronic Infectious Diseases: The Major Role of Therapeutic Drug Monitoring.  
417 *Antibiotics (Basel)* 2022;11. 10.3390/antibiotics11080996

418 [27] Kresken M, Klare I, Wichelhaus TA, Wohlfarth E, Layer-Nicolaou F, Neumann B, et al.  
419 Glycopeptide resistance in *Enterococcus* spp. and coagulase-negative staphylococci from  
420 hospitalised patients in Germany: occurrence, characteristics and dalbavancin susceptibility. *J Glob*  
421 *Antimicrob Resist* 2022;28:102-7. 10.1016/j.jgar.2021.12.016

422

423 **Tables**424 **Table 1** Demographic and baseline characteristics of the study population

<b>Characteristic at baseline</b>		<b>N</b>
Age (years)		
Mean $\pm$ SD	66 $\pm$ 16	151
Range	18–91	151
Sex, n (%)		
Male	94 (62.3)	151
Female	57 (37.7)	151
Pregnancy, n (%)	0 (0.0)	151
Breastfeeding, n (%)	0 (0.0)	151
Mean weight $\pm$ SD, kg	78.0 $\pm$ 16.6	110
Mean BMI $\pm$ SD, kg/m <sup>2</sup>	27.6 $\pm$ 6.1	103
Mean body temperature $\pm$ SD, °C	36.9 $\pm$ 0.5	135
Biological analyses, mean $\pm$ SD		
White blood cells, /mm <sup>3</sup>	7,803 $\pm$ 3,600	118
Neutrophils, /mm <sup>3</sup>	5,401 $\pm$ 3,175	108
C-reactive protein, mg/L	46.6 $\pm$ 54.5	102
Creatinine clearance, mL/min	78 $\pm$ 38	147
Serum creatinine, $\mu$ mol/L	103.8 $\pm$ 94.7	115
Comorbidities		
Charlson comorbidity index $\pm$ SD	4 $\pm$ 3	151
Mean number of major comorbidities $\pm$ SD	6 $\pm$ 5	151
Renal failure, n (%)	37 (24.5)	151
Hemodialysis, n (%)	6 (4.0)	150
Oxygen therapy, n (%)	11 (8.0)	137

425 N, total number of patients with available data; SD, standard deviation; n (%), number (percentage)

426 of patients in the specified category; BMI, body mass index

427

428 **Table 2** Infection characteristics and pathogens at baseline

<b>Characteristic</b>	<b>N=151</b>
Infection type, n (%)	
Bone and joint infection	83 (55.0)
Multisite infection <sup>a</sup>	24 (15.9)
Vascular infection	22 (14.6)
ABSSSI only	10 (6.6)
Bacteremia only	7 (4.6)
Mediastinitis or pleural/pulmonary infection	5 (3.3)
Infection on medical device, n (%)	
None	66 (43.7)
Orthopedic implant	67 (44.4)
Unspecified	8 (5.3)
Vascular access device	7 (4.6)
Aortic or vascular implant	3 (2.0)
Documented infections, n (%)	140 (92.7)
Monomicrobial infections, n (%)	82 (54.3)
Polymicrobial infections, n (%)	58 (38.4)
<b>Characteristic</b>	<b>N'=253</b>
Pathogens, n' (%) <sup>b</sup>	
<i>Staphylococcus epidermidis</i>	56 (22.1)
<i>Staphylococcus aureus</i>	51 (20.2)
<i>Enterococcus faecalis</i>	18 (7.1)
<i>Corynebacterium striatum</i>	13 (5.1)
<i>Enterococcus faecium</i>	7 (2.8)
<i>Cutibacterium acnes</i>	6 (2.4)
<i>Pseudomonas aeruginosa</i>	6 (2.4)
<i>Escherichia coli</i>	5 (2.0)
<i>Klebsiella pneumoniae</i>	5 (2.0)
<i>Proteus mirabilis</i>	5 (2.0)
Methicillin-resistant <i>Staphylococcus aureus</i>	5 (2.0)
<i>Staphylococcus capitis</i>	5 (2.0)
<i>Staphylococcus haemolyticus</i>	5 (2.0)

429 N, total number of patients; n (%), number (percentage) of patients in the specified category;

430 ABSSSI, acute bacterial skin and skin structure infections; N', total number of identified pathogens; n'

431 (%), number (percentage) of pathogens in the specified category

432 <sup>a</sup>Multisite infections include infections in distant body locations and/or infections in adjacent but

433 distinct anatomical structures (e.g., soft tissue, muscle, kidney, and circulatory system)

434 <sup>b</sup>Identified in 140 patients; strains identified at least 5 times are reported

435

436 **Table 3** Dalbavancin treatment

<b>Treatment characteristic</b>	
Dalbavancin treatment line, n (%) (N=151)	
1 <sup>st</sup> line	12 (8.0)
2 <sup>nd</sup> line	16 (10.6)
3 <sup>rd</sup> line	15 (9.9)
4 <sup>th</sup> line	108 (71.5)
Duration between diagnosis and treatment, days (N=150)	
Median (Q1–Q3)	29 (13–60)
Treatment regimen, n (%) (N=151)	
1 injection	26 (17.2)
2 injections	95 (62.9)
3 injections	17 (11.3)
4 injections	5 (3.3)
5 injections	3 (2.0)
6 injections	3 (2.0)
7 injections	0 (0.0)
8 injections	1 (0.7)
9 injections	1 (0.7)
Interval between injections, days (N=125)	
Median (Q1–Q3)	7 (3–20.7)
Cumulative dose administered, mg (N=150)	
Mean ± SD	3,089 ± 1,461
Hospitalization, days	
Length of stay, median (Q1–Q3) (N=148)	19.0 (5.0–35.5)
Length of stay on dalbavancin, median (Q1–Q3) (N=132)	6.8 (2.0–16.3)
Length of stay in intensive care unit, median (Q1–Q3) (N=7)	76.0 (38.0–146.0)

437 n (%), number (percentage) of patients in the specified category; N, total number of patients; Q1,

438 first quartile; Q3, third quartile; SD, standard deviation

439



440 **Table 4** Effectiveness in patients with a complete follow-up by indication and line of treatment

441 (N=129)

<b>Indication, n (%)</b>	<b>Success</b>	<b>Failure</b>
ABSSSI only	7 (87.5)	1 (12.5)
Bacteremia only	4 (100.0)	0 (0.0)
Vascular infection	19 (100.0)	0 (0.0)
Mediastinitis or pleural/pulmonary infection	4 (80.0)	1 (20.0)
Multisite infection	19 (100.0)	0 (0.0)
Bone and joint infection <sup>a</sup>	66 (89.2)	8 (10.8)
<b>Total</b>	<b>119 (92.2)</b>	<b>10 (7.8)</b>
<b>Treatment line, n (%)</b>		
1 <sup>st</sup> line	10 (100.0)	0 (0.0)
2 <sup>nd</sup> line	14 (93.3)	1 (6.7)
3 <sup>rd</sup> line	12 (85.7)	2 (14.3)
4 <sup>th</sup> line	83 (92.2)	7 (7.8)

442 N, total number of patients; n (%), number (percentage) of patients in the specified category;

443 ABSSSI, acute bacterial skin and skin structure infection

444 <sup>a</sup>61 patients had a bone and joint infection on a material, with 46 successes and 7 failures (8 were

445 undetermined or could not be assessed)

446

447 **Table 5** Number and percentages of patients reporting at least 1 adverse event with related adverse  
 448 events' characteristics according to MedDRA

<b>Type of AE</b>	<b>Number of patients N=151</b>	<b>Number of events</b>
<b>Any AE, n (%)</b>	67 (44.4)	125
<b>TEAEs, n (%)</b>	65 (43.0)	120
<b>Serious</b>	31 (20.5)	44
<b>Fatal</b>	7 (4.6)	7
<b>Related AEs, n (%)</b>	12 (7.9)	14
<b>Type by MedDRA Preferred Term</b>		
<b>Blood and lymphatic system disorders</b>		
Eosinophilia	1 (0.7)	1
<b>Gastrointestinal disorders</b>		
Diarrhea	1 (0.7)	1
Nausea	2 (1.3)	2
<b>General disorders and administration site conditions</b>		
Asthenia	2 (1.3)	2
Chills	1 (0.7)	1
<b>Musculoskeletal and connective tissue disorders</b>		
Arthralgia	1 (0.7)	1
<b>Nervous system disorders</b>		
Dysgeusia	1 (0.7)	1
Syncope <sup>a</sup>	1 (0.7)	1
<b>Skin and subcutaneous tissue disorders</b>		
Pruritus	2 (1.3)	2
Vascular purpura	1 (0.7)	1
<b>Vascular disorders</b>		
Hypotension <sup>a</sup>	1 (0.7)	1

449 N, total number of patients; AE, adverse event; n (%), number (percentage) of patients in the  
 450 specified category; TEAE, treatment-emergent adverse event; MedDRA, Medical Dictionary for  
 451 Regulatory Activities

452 <sup>a</sup>Two related AEs (syncope and hypotension, observed in the same patient) were reported as serious

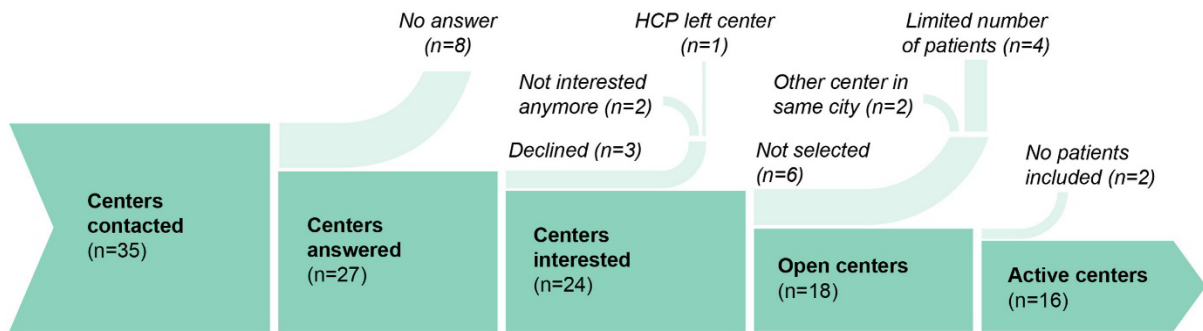
453

454 **Figures**

455 **Figure 1** Recruitment of centers and reasons for exclusion

456 HCP, health care professional; n, number of centers in the specified category

457



458