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

Johan Courjon[a], Eric Senneville[b], Hajnal-Gabriela Illes[c,1], Patricia Pavese[d], David Boutoille[e], Frederic C Daoud[f], Nathalie Dunkel[g], Pierre Tattevin[h]

[a]Université Côte d'Azur, CHU Nice, Nice, France, Infectious disease unit, 151 Route de St Antoine, 06200 Nice, courjon.j@chu-nice.fr

[b]Infectious Diseases Department, Gustave Dron Hospital, 155 Rue du Président Coty, 59200 Tourcoing, France, esenneville@ch-tourcoing.fr

[c]Infectious Disease Unit, Hospital of Mont-de-Marsan, 417 Avenue Pierre de Coubertin BP, 40024 Mont-de-Marsan, France

[1]Present address: Infectious Disease Unit, Private Hospital Francheville, Périgueux, France, hajnal_gabriela.illes@yahoo.fr

[d]Infectious Diseases Department, Grenoble Alpes University Hospital, Boulevard de la Chantourne, 38700 La Tronche, France, ppavese@chu-grenoble.fr

[e]Department of Infectious Disease and CIC-UIC 1413 INSERM, Nantes University Hospital, 5 Allée de l'Île Gloriette, 44093 Nantes, France, david.boutoille@chu-nantes.fr

[f]INSERM U1219 BPH, Université de Bordeaux, 33076 Bordeaux, France, frederic.daoud-pineau@u-bordeaux.fr

[g]ADVANZ PHARMA Switzerland, Rue de Jargonnant 2, 1207 Geneva, Switzerland Nathalie.Dunkel@advanzpharma.com

[h]Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital, 2 Rue Henri le Guilloux, 35033 Rennes, France, pierre.tattevin@chu-rennes.fr

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

Abstract

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

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

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

clinicaltrials.gov identifier: NCT03726216

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

Abbreviations

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

1. Introduction

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

To ensure prevention and treatment of infectious diseases, effective antimicrobials are key [3]. Dalbavancin is a semisynthetic lipoglycopeptide antibiotic that is derived from teicoplanin and disrupts the bacterial cell wall synthesis, resulting in cell death [4]. Its prolonged half-life of 14.5 days allows an extended interval between doses; dalbavancin is administered intravenously as a single 1,500 mg dose or 1 dose each of 1,000 mg and 500 mg, 1 week apart [4, 5]. Its antibacterial spectrum is close to that of vancomycin [4].

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

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

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

2. Materials and methods

2.1. Study design

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

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

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

2.2. Study population

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

2.3. Study objectives

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

2.4. Data collection

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

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

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

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

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

2.5. Statistical analysis

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

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

2.6. Ethical considerations

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

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

3. Results

3.1. Center and patient selection

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

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

3.2. Demographic and baseline characteristics

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

3.3. Indications and microorganisms

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

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

3.4. Antibiotic administration before and during patient management

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

3.5. Dalbavancin treatment

The mean cumulative dose of dalbavancin per patient was 3,089 mg (SD ± 1,461 mg), including 89 patients (58.9%) who received 3,000 mg (**Table 3** and **Supplementary Figure 1**). Three patients (2.0%) received 1,000 mg, the lowest dose, and 1 patient (0.7%) received 12,000 mg, the highest dose. The distribution of dose administration is presented in **Supplementary Figure 1**, and the cumulative dose by indication in **Supplementary Figure 2A**. More than half of the patients (62.9%) received 2 injections of dalbavancin, and 17.2% received 1 injection. The maximum number of injections was 9 for a patient with a bone and joint infection (**Table 3**). For patients receiving multiple injections (N=125), the median interval between 2 injections was 7 days (**Table 3**). **Supplementary Figure 2B** shows the total treatment duration with dalbavancin by indication.

For the 129 patients with a reported clinical outcome, the mean follow-up duration from the baseline visit to the last follow-up visit or final visit was 55 days (SD ± 37).

3.6. Hospitalization

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

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

The effectiveness (success or failure) was determined in 129 (85.4%) patients with a complete follow-up. The clinical response was categorized as a success in 119 patients (92.2%; 95% confidence interval 86.2%–93.2%). A stratification by indication and by line of treatment is presented in **Table 4**.

Among the 8 patients who received dalbavancin for ABSSSI, 7 (87.5%) achieved clinical success. The clinical success of dalbavancin treatment for off-label indications was ≥80.0%, with a 100.0% success rate for bacteremia, vascular infections, and multisite infections, an 80.0% success rate for

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

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

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

3.8. Safety

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

4. Discussion

The results of the present study indicate that dalbavancin is effective and well tolerated for the treatment of ABSSSIs as well as for off-label indications, including bacteremia, vascular infections, mediastinitis or pleural/pulmonary infections, multisite infections, and bone and joint infections. Dalbavancin treatment is mostly used for off-label indications in France as 6.6% of patients included in this study were treated for ABSSSIs only. These results are aligned with other European real-world

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

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

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

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

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

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

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

5. Conclusions

The results of the present study indicate that dalbavancin was mostly used off-label in heavily pre-treated patients in France. The clinical success rate was high in ABSSSI (87.5%) and in off-label indications (≥80.0%), while the AE rate was low. These results are in line with previously published data from other European countries, indicating that dalbavancin treatment is effective and well 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.

Acknowledgements

The authors would like to thank the patients for their contribution to this registry as well as Universal Medica and the International Clinical Trials Association. They thank all investigators and supporting staff at the participating sites for their collaboration in the study, in particular Dr. Catherine Lechiche, Dr. Frédéric-Antoine Dauchy, Dr. Jérome Dimet, Dr. Benjamin Davido, Dr. François Goehringer, Prof. Firouzé Banisadr, Dr. Yann Gérard, and Dr. Lydie Khatchatourian for their involvement in the study conduct. The authors thank Anaïs Lorne for study oversight and for reviewing the paper, and Edwige Yon for statistical support. The authors would also like to thank Tina Van den Meersche (Akkodis Belgium, on behalf of ADVANZ PHARMA) for providing medical writing support.

Declarations

Funding: This study was sponsored by ADVANZ PHARMA Switzerland Sàrl, a company of the ADVANZ PHARMA group, previously known as Correvio International. The content of this article is solely the responsibility of the authors. Neither honoraria nor payments were made for authorship.

Competing interests: Johan Courjon received consulting fees from Menarini and personal fees from Advanz Pharma. Eric Senneville received consulting fees from Advanz Pharma, BioMérieux, Menarini, Shionogi and Pfizer. Hajnal-Gabriela Illes received personal fees from Advanz Pharma, ViiV and Pfizer. Nathalie Dunkel is an employee of Advanz Pharma. Pierre Tattevin received consulting fees from Advanz Pharma, Menarini, Shionogi and Pfizer. David Boutoille received consulting fees from Advanz Pharma and MSD. Patricia Pavese and Frederic C Daoud declare no conflict of interest.

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

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

List of contributions

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

Data statement

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

References

[1] Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. PT 2015;40:277-83.

[2] Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis 2019;19:56-66. 10.1016/s1473-3099(18)30605-4

[3] World Health Organization. Global action plan on antimcrobial resistance. https://www.who.int/publications/i/item/9789241509763; 2015 [accessed 30 September 2022].

[4] Smith JR, Roberts KD, Rybak MJ. Dalbavancin: A Novel Lipoglycopeptide Antibiotic with Extended Activity Against Gram-Positive Infections. Infect Dis Ther 2015;4:245-58. 10.1007/s40121-015-0077-7

[5] European Medicines Agency. Xydalba. Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/xydalba-epar-product-information_en.pdf; 2015 [accessed 30 September 2022].

[6] Boucher HW, Wilcox M, Talbot GH, Puttagunta S, Das AF, Dunne MW. Once-weekly dalbavancin versus daily conventional therapy for skin infection. N Engl J Med 2014;370:2169-79. 10.1056/NEJMoa1310480

[7] Dunne MW, Puttagunta S, Giordano P, Krievins D, Zelasky M, Baldassarre J. A Randomized Clinical Trial of Single-Dose Versus Weekly Dalbavancin for Treatment of Acute Bacterial Skin and Skin Structure Infection. Clin Infect Dis 2016;62:545-51. 10.1093/cid/civ982

[8] Jauregui LE, Babazadeh S, Seltzer E, Goldberg L, Krievins D, Frederick M, et al. Randomized, double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of complicated skin and skin structure infections. Clin Infect Dis 2005;41:1407-15. 10.1086/497271

[9] Rappo U, Puttagunta S, Shevchenko V, Shevchenko A, Jandourek A, Gonzalez PL, et al. Dalbavancin for the Treatment of Osteomyelitis in Adult Patients: A Randomized Clinical Trial of Efficacy and Safety. Open Forum Infect Dis 2018;6:ofy331. 10.1093/ofid/ofy331

[10] Gonzalez PL, Rappo U, Akinapelli K, McGregor JS, Puttagunta S, Dunne MW. Outcomes in Patients with Staphylococcus aureus Bacteremia Treated with Dalbavancin in Clinical Trials. Infect Dis Ther 2022;11:423-34. 10.1007/s40121-021-00568-7

[11] European Medicines Agency. Tenkasi. Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/tenkasi-previously-orbactiv-epar-product-information_en.pdf; 2015 [accessed 23 June 2023].

[12] Lodise TP, Redell M, Armstrong SO, Sulham KA, Corey GR. Efficacy and Safety of Oritavancin Relative to Vancomycin for Patients with Acute Bacterial Skin and Skin Structure Infections (ABSSSI) in the Outpatient Setting: Results From the SOLO Clinical Trials. Open Forum Infect Dis 2017;4:ofw274. 10.1093/ofid/ofw274

[13] Dinh A, Duran C, Pavese P, Khatchatourian L, Monnin B, Bleibtreu A, et al. French national cohort of first use of dalbavancin: A high proportion of off-label use. Int J Antimicrob Agents 2019;54:668-72. 10.1016/j.ijantimicag.2019.08.006

[14] Wunsch S, Krause R, Valentin T, Prattes J, Janata O, Lenger A, et al. Multicenter clinical experience of real life Dalbavancin use in gram-positive infections. Int J Infect Dis 2019;81:210-4. 10.1016/j.ijid.2019.02.013

[15] Illes H-G, Lupu A, Loutfi B, Hoskovec C, Rogero J-M, Delbast L, et al. Efficacy and safety of dalbavancin monotherapy as salvage treatment for bone and joint infection. Clinical Medicine Research 2022;11:74-80. 10.11648/j.cmr.20221103.16

[16] Matt M, Duran C, Courjon J, Lotte R, Le Moing V, Monnin B, et al. Dalbavancin treatment for prosthetic joint infections in real-life: a national cohort study and literature review. J Glob 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/jbji-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; 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

Characteristic at baseline		N
Age (years)		
Mean ± SD	66 ± 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 ± SD, kg	78.0 ± 16.6	110
Mean BMI ± SD, kg/m^2	27.6 ± 6.1	103
Mean body temperature ± SD, °C	36.9 ± 0.5	135
Biological analyses, mean ± SD		
White blood cells, /mm^3	7,803 ± 3,600	118
Neutrophils, /mm^3	5,401 ± 3,175	108
C-reactive protein, mg/L	46.6 ± 54.5	102
Creatinine clearance, mL/min	78 ± 38	147
Serum creatinine, µmol/L	103.8 ± 94.7	115
Comorbidities		
Charlson comorbidity index ± SD	4 ± 3	151
Mean number of major comorbidities ± SD	6 ± 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

Table 2 Infection characteristics and pathogens at baseline

Characteristic	**N=151**
Infection type, n (%)	
Bone and joint infection	83 (55.0)
Multisite infection[a]	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)
Characteristic	**N'=253**
Pathogens, n' (%)[b]	
Staphylococcus epidermidis	56 (22.1)
Staphylococcus aureus	51 (20.2)
Enterococcus faecalis	18 (7.1)
Corynebacterium striatum	13 (5.1)
Enterococcus faecium	7 (2.8)
Cutibacterium acnes	6 (2.4)
Pseudomonas aeruginosa	6 (2.4)
Escherichia coli	5 (2.0)
Klebsiella pneumoniae	5 (2.0)
Proteus mirabilis	5 (2.0)
Methicillin-resistant *Staphylococcus aureus*	5 (2.0)
Staphylococcus capitis	5 (2.0)
Staphylococcus haemolyticus	5 (2.0)

N, total number of patients; n (%), number (percentage) of patients in the specified category; ABSSSI, acute bacterial skin and skin structure infections; N', total number of identified pathogens; n' (%), number (percentage) of pathogens in the specified category

[a]Multisite infections include infections in distant body locations and/or infections in adjacent but distinct anatomical structures (e.g., soft tissue, muscle, kidney, and circulatory system)

[b]Identified in 140 patients; strains identified at least 5 times are reported

436 **Table 3** Dalbavancin treatment

Treatment characteristic	
Dalbavancin treatment line, n (%) (N=151)	
1st line	12 (8.0)
2nd line	16 (10.6)
3rd line	15 (9.9)
4th 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

Table 4 Effectiveness in patients with a complete follow-up by indication and line of treatment (N=129)

Indication, n (%)	**Success**	**Failure**
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[a]	66 (89.2)	8 (10.8)
Total	119 (92.2)	10 (7.8)
Treatment line, n (%)		
1st line	10 (100.0)	0 (0.0)
2nd line	14 (93.3)	1 (6.7)
3rd line	12 (85.7)	2 (14.3)
4th line	83 (92.2)	7 (7.8)

N, total number of patients; n (%), number (percentage) of patients in the specified category; ABSSSI, acute bacterial skin and skin structure infection

[a]61 patients had a bone and joint infection on a material, with 46 successes and 7 failures (8 were undetermined or could not be assessed)

447 **Table 5** Number and percentages of patients reporting at least 1 adverse event with related adverse

448 events' characteristics according to MedDRA

Type of AE	Number of patients N=151	Number of events
Any AE, n (%)	67 (44.4)	125
TEAEs, n (%)	65 (43.0)	120
Serious	31 (20.5)	44
Fatal	7 (4.6)	7
Related AEs, n (%)	12 (7.9)	14
Type by MedDRA Preferred Term		
Blood and lymphatic system disorders		
Eosinophilia	1 (0.7)	1
Gastrointestinal disorders		
Diarrhea	1 (0.7)	1
Nausea	2 (1.3)	2
General disorders and administration site conditions		
Asthenia	2 (1.3)	2
Chills	1 (0.7)	1
Musculoskeletal and connective tissue disorders		
Arthralgia	1 (0.7)	1
Nervous system disorders		
Dysgeusia	1 (0.7)	1
Syncope[a]	1 (0.7)	1
Skin and subcutaneous tissue disorders		
Pruritus	2 (1.3)	2
Vascular purpura	1 (0.7)	1
Vascular disorders		
Hypotension[a]	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 [a]Two related AEs (syncope and hypotension, observed in the same patient) were reported as serious

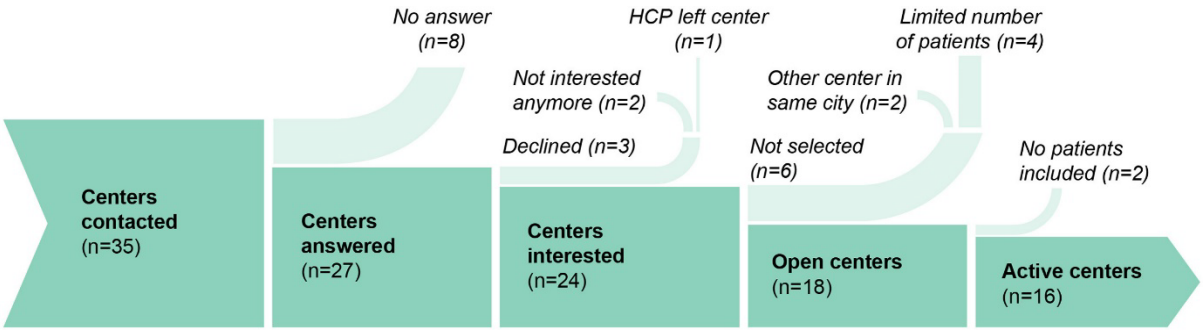
453

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