Drug Design, Development and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Kimyrsa and Orbactiv – A Tale of Two Formulations

Brittany T Jackson[1], David B Cluck[2], Andrés F Henao-Martínez[3], Daniel B Chastain[4]

[1]Department of Pharmacy, Mount Sinai Morningside, New York, NY, 10025, USA; [2]Department of Pharmacy Practice, Bill Gatton College of Pharmacy East Tennessee State University, Johnson City, TN, 37614, USA; [3]Division of Infectious Diseases, University of Colorado, Anschutz Medical Campus, Aurora, CO, 80045, USA; [4]Department of Clinical and Administrative Pharmacy, University of Georgia College of Pharmacy, Albany, GA, 31701, USA

Correspondence: Brittany T Jackson, Department of Pharmacy, Mount Sinai Morningside, New York, NY, 10025, USA, Email brittany.jackson@mountsinai.org

Abstract: Kimyrsa is a new formulation (NF) of the original formulation of oritavancin ([OF] Orbactiv). Comparatively, the obvious benefit with this product is the shortened infusion time and flexibility with solution compatibility, but otherwise maintains a similar pharmacokinetic and microbiologic profile. At present, the NF lacks significant real-world experience relative to other available lipoglycopeptides and thus its place in therapy remains difficult to predict but would not be expected to be significantly different than its OF.

Keywords: Kimyrsa, Orbactiv, oritavancin, glycopeptides, ABSSSI, soft tissue infections, pharmacokinetics

Introduction

Oritavancin is a semi-synthetic lipoglycopeptide antibiotic for the treatment of Gram-positive bacterial infections and is approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSIs) caused by susceptible Gram-positive organisms. The spectrum of activity of oritavancin includes *Streptococcus* species, *Enterococcus faecalis, E. faecium* (including vancomycin-resistant isolates), *Staphylococcus* species (including *S. aureus*, both methicillin-susceptible [MSSA] and methicillin-resistant [MRSA] isolates), as well as *Clostridium* species.[1] Notably, oritavancin lacks appreciable activity against Gram-negative organisms.

Oritavancin disrupts Gram-positive cell wall membrane integrity, which leads to depolarization, permeabilization, and rapid cell death.[1] It also inhibits the transglycosylation step of cell wall synthesis by binding to the D-ala-D-ala stem termini. Lastly, it inhibits the transpeptidation step of cell wall synthesis by binding to the bridging segment. Due to the ability of oritavancin to bind to D-ala-D-lac, oritavancin retains activity against vancomycin-resistant enterococci (VRE), heteroresistant vancomycin-intermediate *S. aureus* (hVISA), vancomycin-intermediate *S. aureus* (VISA), and vancomycin-resistant *S. aureus* (VRSA). Oritavancin has been successfully used for VRE, though clinical data for many of these multidrug resistant organisms are limited.[2–4]

Despite promising potential, oritavancin is one of three lipoglycopeptides for clinical use (along with dalbavancin and telavancin).[3] The prolonged half-lives of oritavancin and dalbavancin allow for once weekly dosing. In contrast, telavancin requires daily dosing due to its shorter half-life (7 to 9 hours). As such, there was great excitement that oritavancin and dalbavancin could provide a cost-effective approach to avoiding or reducing hospitalization length of stay in patients with ABSSSI. Dalbavancin initially received FDA approval for ABSSSI in May 2014 as a two-dose regimen (1000 mg followed one week later by 500 mg where each dose is infused over 30 minutes).[5]

Shortly thereafter, the FDA approved the original formulation of oritavancin ([OF] Orbactiv) for ABSSSI in August 2014 as a single 1200 mg dose infused over 3 hours.[1,6] Uptake of oritavancin and dalbavancin for ABSSSI was limited by significant costs coupled with the unique administration requirements for each drug (prolonged infusion time and 2-dose regimen, respectively). Moreover, the cost of dalbavancin and oritavancin for ABSSSI, albeit an indication which has many effective drugs, many of which can be administered orally, also limited its clinical utility after approval. In January 2016, the FDA approved a single-dose dalbavancin regimen (1500 mg infused over 30

Received: 5 January 2023
Accepted: 28 February 2023
Published: 9 March 2023

minutes) for ABSSSI based on a pharmacokinetic (PK) study demonstrating similar efficacy and safety outcomes compared to the two-dose regimen.[5,7]

There are noteworthy differences between dalbavancin and oritavancin. Dalbavancin elimination includes renal (33% as unchanged drug) and non-renal pathways.[8] Dose adjustments are required in patients with renal dysfunction due to reduced clearance. Alternatively, oritavancin is primarily eliminated through the reticuloendothelial system,[9] which may negate dose adjustments in patients with renal dysfunction though more data are needed.[1] Infusion-related reactions have been reported for dalbavancin and oritavancin, however, the risk may be higher with oritavancin due to structural similarities with vancomycin.[3,10] Dalbavancin and oritavancin share a similar spectrum of activity with a notable exception for VRE. Dalbavancin is active against VRE expressing vanB and vanC, but not vanA,[11] whereas oritavancin retains activity against vanA- and vanB-mediated isolates.[12] Resistance to both dalbavancin and oritavancin has been reported, but is uncommon in clinical settings.[13]

While oritavancin and dalbavancin are available as single-dose regimens for ABSSSI, the significantly shorter infusion time of dalbavancin may be preferred by providers and patients. Recently, a new formulation of oritavancin, Kimyrsa (NF), was developed to be infused over 1 hour and approved by the FDA for ABSSSI on March 12, 2021.[14] The purpose of this review is to evaluate the efficacy and safety data for the NF.

Clinical Efficacy and Safety of Oritavancin

Oritavancin was compared to vancomycin in two multicenter randomized, double-blind, controlled trials for the treatment of ABSSSIs (SOLO I and SOLO II).[15,16] Adult patients were eligible for inclusion if their ABSSSI was suspected or proven to be caused by a Gram-positive pathogen and would require at least 7 days of intravenous therapy. Patients were randomized 1:1 to receive a single 1200 mg dose of oritavancin infused over 3 hours (n = 978) or IV vancomycin (either 1 g fixed dose or weight based at 15 mg/kg every 12 hours) for 7 to 10 days (n = 981). Most participants were White or Caucasian (64.4% vs 64.3%) male (65.3% vs 65.6%) patients with cellulitis (39.6% vs 40.8%) or an abscess (31.5% vs 30.6%) in both groups. A Gram-positive organism was isolated from 63% of participants from each group. Of these, *S. aureus* was identified in 76% and 75% of the oritavancin and vancomycin groups, respectively, though less than 50% were MRSA (44% and 43%, respectively).

In the modified intent to treat populations from SOLO I and SOLO II, 82.3% and 80.1% of patients in the oritavancin groups versus 78.9% and 82.9% of patients in the vancomycin groups achieved early clinical response, which was defined as a composite of the cessation of spread or reduction in lesion size, absence of fever, and no rescue antibacterial drug at 48 to 72 hours. Based on these findings, oritavancin met the predetermined non-inferiority criteria against vancomycin. Similar findings were observed among patients with MRSA isolated (80.8% and 82% in the oritavancin groups vs 80% and 81.2% in the vancomycin groups). Clinical success at 14 to 21 days was observed in 79.6% and 82.7% of the oritavancin groups compared to 80.0% and 80.5% of the vancomycin groups.

At least 1 treatment-emergent adverse event occurred in a similar proportion of participants randomized to oritavancin (60.0% and 50.9%) and vancomycin (63.8% and 50.2%) in both SOLO I and SOLO II. Nausea and headache were reported most often by patients in the oritavancin groups (SOLO I: 11% and 7.2%; SOLO II: 8.9% vs 7.0%) and vancomycin groups (SOLO I: 8.9% and 7.9%; SOLO II: 12% vs 5.6%). Infusion-related reactions were only reported in SOLO I and occurred in 4% of patients treated with oritavancin compared to 7.1% treated with vancomycin. Though, these adverse events seldom led to study drug discontinuation (3.8% and 3.6% vs 5.8% and 2.6%, respectively). Notably, the first dose of vancomycin was infused over 3 hours to maintain study blinding, whereas subsequent doses were infused over a minimum of 1 hour.

Findings from SOLO I and SOLO II were replicated in CHROME, a retrospective observational registry that included 112 patients with ABSSSI from 8 study sites.[17] Similar to SOLO I and SOLO II, most participants were White or Caucasian (91.7%) male (53.6%) patients, of which cellulitis and cutaneous abscesses were most common (67% and 21.4%, respectively). Almost all patients experienced resolution of clinical signs and symptoms (92.8%) and microbiologic eradication (90%). Treatment-related adverse events were reported in 4.5% of patients, but none led to drug discontinuation. Of these, two participants experienced infusion-related reactions, whereby the infusion was briefly interrupted (15–30 minutes) to allow administration of supportive care (eg, diphenhydramine, acetaminophen, etc.), before restarting the infusion at a slower rate (initially administered over 3 hours; reduced to 4 to 5.5 hours).

Based on the findings from SOLO I, SOLO II, and CHROME, oritavancin was demonstrated to be an acceptable single-dose alternative to multidose regimens for the treatment of ABSSSIs in adult patients. Although oritavancin has

only received FDA-approval for ABSSSIs, previous reports have also demonstrated treatment success for off-label uses including bacteremia, osteomyelitis, and endovascular infections.[17–20] In addition, oritavancin has been associated with reduced length of stay and therefore lower costs in comparison to standard therapies.[20,21]

Repurposing Orbactiv as Kimyrsa

Oritavancin was reformulated as the NF to address many of the issues associated with the OF. (Table 1). First, the NF formulation uses 2-hydroxypropyl-β-cyclodextrin (HPβCD), a solubility enhancer, which prevents precipitation of oritavancin at high concentrations. This allows a significant decrease in the volume required for infusion (from 1000 mL to 250 mL). HPβCD is eliminated in the urine, which may accumulate in patients with renal dysfunction.[22] However, the amount of HPβCD in the NF is lower than that found in other medications (2.4 grams in the NF vs 8 grams in itraconazole).[23] In addition, HPβCD is well tolerated compared to older cyclodextrins, so the risk of potential toxicities is thought to be negligible.[24] Second, the NF is compatible with and can be administered in 5% dextrose in sterile water (D5W) or 0.9% sodium chloride (Table 1). The OF is only compatible with D5W and each 1200 mg dose of the OF provides 50 g of dextrose.[1,22] Lastly, and perhaps most importantly, the infusion time was dramatically shortened to 1 hour with the NF, whereas the OF requires administration over 3 hours to minimize infusion-related reactions. A benefit of shorter infusion times with the NF is decreasing the time patients spend receiving the infusion which decreases chair time and allows for more patients to receive antimicrobial therapies. In addition, these modifications may allow for greater utilization of the NF in patients who are volume-restricted, have poorly controlled diabetes mellitus, or are at risk for dysglycemia.

Pharmacokinetics and Safety of Kimyrsa Vs Orbactiv

The NF was evaluated in a randomized, open-label, multicenter study to evaluate the relative exposure compared to the OF. Adults with ABSSSI suspected or confirmed to be caused by a Gram-positive pathogen were randomized 1:1 to receive a single 1200 mg IV infusion of oritavancin as a 1-hour infusion (NF) or a 3-hour infusion (OF) to compare the relative area-under-the-curve (AUC). Patients were excluded if they had 1) an infection involving or near a prosthetic device, 2) an infection due to dermatologic diseases, 3) decubitus or ischemic ulcers, 4) diabetic foot infections, 5) necrotizing infections, 6) catheter-related infections, 7) bacteremia at the time of enrollment, or 8) severe sepsis or shock.[25]

Table 1 Comparison of Orbactiv to Kimyrsa

	Orbactiv[1]	**Kimyrsa**[22]
Formulation	400 mg of lyophilized powder in a single-dose vial Inactive ingredients: mannitol (200 mg) and phosphoric acid (to adjust pH 3.1 to 4.3)	1200 mg of lyophilized powder in a single-dose vial Inactive ingredients: HPβCD (2400 mg), mannitol (800 mg) and phosphoric acid or sodium hydroxide (to adjust pH 4.0 to 6.0)
Dose	1200 mg IV	1200 mg IV
Infusion time	3 hours	1 hour
Preparation	Each vial is reconstituted with SWFI and further diluted with D5W for IV infusion Final volume: 1000 mL of D5W	Each vial is reconstituted with SWFI and further diluted with NS or D5W for IV infusion Final volume: 250 mL of NS or D5W
Stability	Use within 6 hours when stored at room temperature, within 12 hours if refrigerated	Use within 4 hours when stored at room temperature, within 12 hours if refrigerated
Cost per 1200 mg dose (average wholesale price, USD)[39]	3939.60	6036.62
Comments	Incompatible with NS (precipitate formation)	Compatible with D5W or NS

Abbreviations: D5W, 5% dextrose in sterile water; HPβCD, hydroxypropyl-β-cyclodextrin; IV, intravenous; NS, normal saline; SWFI, sterile water for injection; USD, US dollars.

The OF was compounded using three single-use vials (1200 mg total) containing 400 mg of oritavancin diphosphate (as the free base) and the inactive component mannitol. Each vial was reconstituted using sterile water for injection and further diluted in D5W to a total volume of 1000 mL for infusion over 3 hours. Alternatively, NF was prepared using a single vial which contained 1200 mg of oritavancin. Vials were reconstituted with sterile water for injection and further diluted in 0.9% normal saline to a total volume of 250 mL for infusion over 1 hour.[25]

Plasma samples for PK analyses were collected prior to and at the end of the infusion (1 hour or 3 hours), then at 3 hours for participants who received NF, and up to 168 hours after the start of the infusion. PK parameters, including C_{max}, T_{max}, and AUC from time 0 to 72 hours postdose (AUC_{0-72}) and 0 to 168 hours postdose (AUC_{0-168}), were evaluated in both groups. Safety and tolerability were also assessed through day 15 of follow-up.

After enrollment, 50 patients were randomized to the NF and 52 to OF. Of the 102 who were enrolled in the study, two participants randomized to OF discontinued the study due to hypersensitivity reactions while another withdrew because vascular access could not be obtained. Most participants identified as non-Hispanic (58% vs 59.6%), White or Caucasian (92% vs 86.5%), male (60% vs 71.2%) patients. Types of ABSSSIs were reported overall, whereby cutaneous abscesses (44.1%) and cellulitis (29.4%) were most common. Body weight and BMI were higher in the NF group (88.7 ± 26.9 kg and 29.7 ± 8.5 kg/m^2) compared to the OF group (80.8 ± 19.5 kg and 27.3 ± 6.0 kg/m^2).[25] Medical and surgical history were reported as "balanced" between each group, though further data were not provided despite more than 50% of each group being considered overweight.[26]

The mean C_{max} was 1.3-fold higher and the median T_{max} was approximately 2 hours faster after administration of NF, likely due to the shorter infusion time. The mean AUC_{0-72}, which is associated with antimicrobial activity, and the mean AUC_{0-168} were similar in both groups. Geometric means were calculated from participants with plasma concentrations obtained based on protocol specifications. Patients were not included in this analysis if the plasma concentration results were unavailable or not collected within the protocol-defined time window. The mean AUC_{0-72} and mean AUC_{0-168} were 1410 h·μg/mL and 1680 h·μg/mL from 43 and 42 patients in the NF group compared to 1290 h·μg/mL and 1580 h·μg/mL from 44 and 42 patients in the OF group, respectively. In addition, the AUC values evaluated in this study were similar compared with previous AUC results from Phase 3 studies in patients with ABSSSI.[25]

Treatment-emergent adverse events were reported in 48% of participants treated with the NF and 59.6% treated with OF, of which 22% and 38.5% were study-drug related, respectively. Pruritus and diarrhea were most common and reported by 2% and 3% of the NF group versus 7% and 5% of the OF group. A higher proportion of patients treated with NF experienced chills and pyrexia during or immediately after the infusion compared to those treated with the OF (6% vs 1.9%, respectively), though it is unclear how long patients were monitored after the infusion. However, fewer patients randomized to the NF experienced a treatment-emergent adverse event that led to study drug discontinuation (4% v 5.8%). Notably, two patients in each group experienced infusion-related reactions (4% vs 3.8%). One patient developed a hypersensitivity reaction several hours after receiving the NF, which was alleviated with diphenhydramine. The other patient experienced an infusion-related reaction during the NF infusion whereby the infusion was interrupted for 13 minutes to allow administration of diphenhydramine before completing the infusion. Of those who experienced infusion-related reactions with the OF, one patient developed pruritus and hives, but was able to complete the infusion following administration of diphenhydramine, while the other experienced an acute allergic reaction (grade 3, severe) leading to cessation of the study drug.

Notably, one patient enrolled in the study had a history of renal dysfunction (baseline serum creatinine of 2.5 mg/dL). Though the authors do not explicitly state which formulation the patient received, they noted no evidence of nephrotoxicity associated with HPβCD observed in the study.[25]

PK exposures and safety outcomes reported in this study led to FDA approval of the NF for adult patients with ABSSSI.[14]

Kimyrsa in the Clinical Realm

The NF is an attractive agent due to the shorter infusion time, flexibility with the diluent, and a lower volume to be infused. This formulation exhibits similar PK exposures compared to OF[25] and would be expected to have similar efficacy. However, limited data are available with the NF and efficacy outcomes were not directly assessed in the open label study.

In addition, PK exposure and safety findings observed with the NF may not be generalizable to patients at greatest risk for ABSSSIs (patients with obesity, hepatic disease, renal dysfunction, vascular insufficiency, etc.) due to the lack of

data describing baseline characteristics.[27] While HPβCD is thought to pose minimal risk for patients with renal dysfunction, these expectations are extrapolated from other medications as only one patient with renal dysfunction was included in the open label study and it was unclear if the patient received the NF or OF.

The economic advantages associated with OF should also be observed with the NF. An additional benefit of the NF over the OF and dalbavancin is that the NF was granted "pass-through" status on October 1, 2021 by the Centers for Medicare and Medicaid Services (CMS) in the outpatient setting. Notably, there are no additional data available describing the use of the NF outside of the treatment for ABSSSI. Further investigation is warranted to assess efficacy outcomes in patients treated with NF for invasive Gram-positive infections (eg, bacteremia, osteomyelitis, infective endocarditis) in the setting of increasing antimicrobial resistance as well as to improve patient compliance, convenience, and lower health-care costs. Favorable outcomes have been reported in following treatment with one or more doses of the OF for complicated Gram positive infections, but are limited due to small patient populations and lack of comparator groups.[28–30] Additionally, multi-dose dalbavancin for complicated infections caused by *Staphylococcus* species and *Streptococcus* species is supported by more robust data,[28,31,32] some of which included matched cohorts and comparator groups.[33–36] As such, the OF may be most useful against complicated infections caused by *Enterococcus* species, particularly VRE.[18,37] Perhaps, the NF can replace the OF, though it is unclear how the NF and OF will coexist going forward. As such, data are needed to clarify utilization, and potential treatment-related adverse events, of the NF in lieu of the OF. Recently, a new Healthcare Common Procedure Coding System (HCPCS) code was established to differentiate the NF (J2406) from the OF (J2407) since these are "theoretically" not bioequivalent.[38]

Conclusion

The NF is a welcome "upgrade", but this new formulation still possesses many of the shortcomings associated with the OF. Based on similar PK exposures, efficacy outcomes following treatment with the NF "should" be comparable to the OF, but efficacy data are unavailable for ABSSSIs or invasive Gram-positive infections. Ideally, the NF could replace the OF to provide a more convenient option against complicated infections, though additional data are needed.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Orbactiv [package insert]. Lincolnshire, IL . Melinta Therapeutics. LLC; 2021.
2. Brade KD, Rybak JM, Rybak MJ. Oritavancin: a new lipoglycopeptide antibiotic in the treatment of gram-positive infections. *Infect Dis Ther*. 2016;5(1):1–15. doi:10.1007/s40121-016-0103-4
3. Zhanel GG, Calic D, Schweizer F, et al. New lipoglycopeptides: a comparative review of dalbavancin, oritavancin and telavancin. *Drugs*. 2010;70(7):859–886. doi:10.2165/11534440-000000000-00000
4. Zhanel GG, Schweizer F, Karlowsky JA. Oritavancin: mechanism of action. *Clin Infect Dis*. 2012;54(Suppl 3):S214–219. doi:10.1093/cid/cir920
5. Drugs.com. Dalvance FDA approval history; 2014. Available from: https://www.drugs.com/history/dalvance.html. Accessed November 29, 2022.
6. Drugs.com. Orbactiv FDA approval history; 2014. Available from: https://www.drugs.com/history/orbactiv.html. Accessed November 29, 2022.
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(5):545–551. doi:10.1093/cid/civ982
8. Marbury T, Dowell JA, Seltzer E, Buckwalter M. Pharmacokinetics of dalbavancin in patients with renal or hepatic impairment. *J Clin Pharmacol*. 2009;49(4):465–476. doi:10.1177/0091270008330162
9. Rubino CM, Van Wart SA, Bhavnani SM, Ambrose PG, McCollam JS, Forrest A. Oritavancin population pharmacokinetics in healthy subjects and patients with complicated skin and skin structure infections or bacteremia. *Antimicrob Agents Chemother*. 2009;53(10):4422–4428. doi:10.1128/AAC.00231-09
10. Panicker N, Chandni V, Lakshmi Prasanna VM, et al. Drugs-associated with red man syndrome: an integrative approach using disproportionality analysis and Pharmip. *J Clin Pharm Ther*. 2022;47(10):1650–1658. doi:10.1111/jcpt.13716
11. Saravolatz LD, Billeter M, Zervos MJ, Chen AY, Dalovisio JR, Kurukularatne C. Dalbavancin: a novel once-weekly lipoglycopeptide antibiotic. *Clinical Infectious Diseases*. 2008;46(4):577–583. doi:10.1086/526772
12. Saleh-Mghir A, Lefort A, Petegnief Y, et al. Activity and diffusion of LY333328 in experimental endocarditis due to vancomycin-resistant Enterococcus faecalis. *Antimicrob Agents Chemother*. 1999;43(1):115–120. doi:10.1128/AAC.43.1.115

13. Tran TT, Gomez Villegas S, Aitken SL, et al. New perspectives on antimicrobial agents: long-acting lipoglycopeptides. *Antimicrob Agents Chemother*. 2022;66(6):e0261420. doi:10.1128/aac.02614-20
14. FDA. FDA U.S. Food & drug administration NDA approval for Kimyrsa; 2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/214155Orig1s000ltr.pdf. Accessed November 29, 2022.
15. Corey GR, Kabler H, Mehra P, et al. Single-dose oritavancin in the treatment of acute bacterial skin infections. *N Engl J Med*. 2014;370(23):2180–2190. doi:10.1056/NEJMoa1310422
16. Corey GR, Good S, Jiang H, et al. Single-dose oritavancin versus 7–10 days of vancomycin in the treatment of gram-positive acute bacterial skin and skin structure infections: the SOLO II noninferiority study. *Clin Infect Dis*. 2015;60(2):254–262. doi:10.1093/cid/ciu778
17. Redell M, Sierra-Hoffman M, Assi M, et al. The CHROME study, a real-world experience of single- and multiple-dose oritavancin for treatment of gram-positive infections. *Open Forum Infect Dis*. 2019;6(11):ofz479. doi:10.1093/ofid/ofz479
18. Scoble PJ, Reilly J, Tillotson GS. Real-world use of oritavancin for the treatment of osteomyelitis. *Drugs Real World Outcomes*. 2020;7(Suppl 1):46–54. doi:10.1007/s40801-020-00194-8
19. Van Hise NW, Chundi V, Didwania V, et al. Treatment of acute osteomyelitis with once-weekly oritavancin: a two-year, multicenter, retrospective study. *Drugs Real World Outcomes*. 2020;7(Suppl 1):41–45. doi:10.1007/s40801-020-00195-7
20. Brownell LE, Adamsick ML, McCreary EK, et al. Clinical outcomes and economic impact of oritavancin for gram-positive infections: a single academic medical center health system experience. *Drugs Real World Outcomes*. 2020;7(Suppl 1):13–19. doi:10.1007/s40801-020-00192-w
21. Saddler K, Zhang J, Sul J, et al. Improved economic and clinical outcomes with oritavancin versus a comparator group for treatment of acute bacterial skin and skin structure infections in a community hospital. *PLoS One*. 2021;16(3):e0248129. doi:10.1371/journal.pone.0248129
22. Kimyrsa [package insert]. Lincolnshire, IL . Morristown, NJ: Melinta Therapeutics, LLC; 2021.
23. Buchanan CM, Buchanan NL, Edgar KJ, et al. Pharmacokinetics of itraconazole after intravenous and oral dosing of itraconazole-cyclodextrin formulations. *J Pharm Sci*. 2007;96(11):3100–3116. doi:10.1002/jps.20878
24. Gadade DD, Pekamwar SS. Cyclodextrin based nanoparticles for drug delivery and theranostics. *Adv Pharm Bull*. 2020;10(2):166–183. doi:10.34172/apb.2020.022
25. Hoover RK, Krsak M, Molina KC, Shah K, Redell M. Kimyrsa, an oritavancin-containing product: clinical study and review of properties. *Open Forum Infect Dis*. 2022;9(5):ofac090. doi:10.1093/ofid/ofac090
26. CDC. Defining adult overweight & obesity; 2022. Available from: https://www.cdc.gov/obesity/basics/adult-defining.html#:~:text=If%20your%20BMI%20is%20less,falls%20within%20the%20obesity%20range. Accessed November 29, 2022.
27. Kaye KS, Petty LA, Shorr AF, Zilberberg MD. Current epidemiology, etiology, and burden of acute skin infections in the United States. *Clin Infect Dis*. 2019;68(Suppl 3):S193–s199. doi:10.1093/cid/ciz002
28. Thomas G, Henao-Martínez AF, Franco-Paredes C, Chastain DB. Treatment of osteoarticular, cardiovascular, intravascular-catheter-related and other complicated infections with dalbavancin and oritavancin: a systematic review. *Int J Antimicrob Agents*. 2020;56(3):106069. doi:10.1016/j.ijantimicag.2020.106069
29. Chastain DB, Davis A. Treatment of chronic osteomyelitis with multidose oritavancin: a case series and literature review. *Int J Antimicrob Agents*. 2019;53(4):429–434. doi:10.1016/j.ijantimicag.2018.11.023
30. Schulz LT, Dworkin E, Dela-Pena J, Rose WE. Multiple-dose oritavancin evaluation in a retrospective cohort of patients with complicated infections. *Pharmacotherapy*. 2018;38(1):152–159. doi:10.1002/phar.2057
31. Veve MP, Patel N, Smith ZA, Yeager SD, Wright LR, Shorman MA. Comparison of dalbavancin to standard-of-care for outpatient treatment of invasive Gram-positive infections. *Int J Antimicrob Agents*. 2020;56(6):106210. doi:10.1016/j.ijantimicag.2020.106210
32. Tobudic S, Forstner C, Burgmann H, et al. Dalbavancin as primary and sequential treatment for gram-positive infective endocarditis: 2-year experience at the general hospital of Vienna. *Clin Infect Dis*. 2018;67(5):795–798. doi:10.1093/cid/ciy279
33. Rappo U, Puttagunta S, Shevchenko V, et al. Dalbavancin for the treatment of osteomyelitis in adult patients: a randomized clinical trial of efficacy and safety. *Open Forum Infect Dis*. 2019;6(1):ofy331. doi:10.1093/ofid/ofy331
34. Raad I, Darouiche R, Vazquez J, et al. Efficacy and safety of weekly dalbavancin therapy for catheter-related bloodstream infection caused by gram-positive pathogens. *Clin Infect Dis*. 2005;40(3):374–380. doi:10.1086/427283
35. Cain AR, Bremmer DN, Carr DR, et al. Effectiveness of dalbavancin compared with standard of care for the treatment of osteomyelitis: a real-world analysis. *Open Forum Infect Dis*. 2022;9(2):ofab589. doi:10.1093/ofid/ofab589
36. Antosz K, Al-Hasan MN, Lu ZK, et al. Clinical utility and cost effectiveness of long-acting lipoglycopeptides used in deep-seated infections among patients with social and economic barriers to care. *Pharmacy*. 2021;10:1. doi:10.3390/pharmacy10010001
37. Johnson JA, Feeney ER, Kubiak DW, Corey GR. Prolonged use of oritavancin for vancomycin-resistant enterococcus faecium prosthetic valve endocarditis. *Open Forum Infect Dis*. 2015;2(4):ofv156. doi:10.1093/ofid/ofv156
38. Centers for Medicare & Medicaid Services (CMS). Healthcare Common Procedure Coding System (HCPCS) application summaries and coding decisions second quarter 2021 coding cycle for drug and biological products; 2021.
39. Lexicomp. Oritavancin, Lexicomp; 2022.