Role of Extended Dosing Interval Antimicrobials in OPAT

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DISCLOSURE

Urania Rappo is an employee of Allergan plc and holds stock in Allergan plc

Overview

- Increasing use of **long-acting antimicrobials and less frequent dosing** in infections requiring prolonged courses of IV antibiotic therapy
  - Osteomyelitis, endocarditis, bacteremia, other infections
- **Dalbavancin:** data from randomized clinical trial using 2-dose regimen for 6 week course; other available data
- **Oritavancin:** available data using extended dosing intervals
- **Teicoplanin:** 3x/week dosing
- **Amikacin:** 3x/week dosing

Dalbavancin

Osteomyelitis in Adults

- Major clinical challenge with potential for poor outcomes, including amputations[1]
- **Diagnosis** by bone biopsy with culture in conjunction with clinical symptoms, elevated inflammatory markers such as CRP, and radiologic findings[2]
- **Debridement** of infected tissue and surgical resection of necrotic bone often needed[2]
- ***Staphylococcus aureus*** most commonly isolated pathogen in adults[1]
- Requires **prolonged (4–6+ weeks) parenteral and oral antibiotics**[3]
  - Antistaphylococcal penicillins (nafcillin/oxacillin), clindamycin, first-generation cephalosporins (cefazolin), and vancomycin are the typical antimicrobials of choice
  - **Increasing incidence of MRSA** and **methicillin-resistant coagulase-negative staphylococci** often require use of vancomycin
    - Vancomycin requires indwelling catheter, monitoring of serum drug levels and careful dose adjustments to maintain appropriate levels in the blood[4]
  - **Better treatment options are needed** which would not require long-term daily IV or oral antibiotics

MRSA=methicillin-resistant *Staphylococcus aureus;* CRP=C-reactive protein

[1] Hatzenbuehler J et al. Am Fam Physician 2011. [2]Kavanaugh et al. Clin Microbiol Rev 2018. [3]Calhoun JH et al. Semin Plast Surg 2009. [4]Rybak MJ et al Clin Infect Dis 2009.

DALBAVANCIN

- A long-acting lipoglycopeptide antibiotic
  - Terminal **half-life of 14.4 days**[1]
  - Structurally related to teicoplanin[2]
- Mechanism of action: inhibits cell wall synthesis
- No known drug-drug interactions
- **Potent** activity against Gram-positive pathogens, including MRSA
  - **MIC_{90} of dalbavancin for *S aureus* (MRSA and MSSA) is 0.06 µg/mL**, with 99.9% of organisms inhibited at 0.12 µg/mL[3,4]
  - 16-fold more potent compared to vancomycin; 8-fold more potent compared to daptomycin[3]
- Extensive clinical trial data
  - 17 Phase 1, 2 Phase 2, and 6 Phase 3 studies
- Approved for the treatment of acute bacterial skin and skin structure infection (ABSSSI) in adults in the United States and European Union as a 30 minute infusion administered as a single dose regimen (1500 mg IV) or as a 2-dose regimen (1000 mg IV followed 1 week later by 500 mg) in 300 mL [1,5]

[1]Dalvance® (dalbavancin) full prescribing information 2016. [2]Economou NJ et al. J Am Chem Soc 2012. [3]Jones RN et al. Diagn Microbiol Infect Dis 2013.
[4]Dunne MW et al. AAC 2015. [5]Xydalba™ (dalbavancin) full prescribing information 2016.

BACKGROUND
Phase 1 Studies on Distribution of Dalbavancin in Bone and Articular Tissue and Extended-Duration Dosing

Dalbavancin Bone Concentrations

- Phase 1 **bone penetration study** evaluated the PK of dalbavancin in **bone & articular tissue** in 30 healthy volunteers who received dalbavancin up to 14 days before elective orthopedic surgery
  - Mean dalbavancin levels in bone were **6.3 µg/g at 12 hours** and were sustained **2 weeks later at 4.1 µg/g**, after a 1000 mg IV infusion
- Mean **bone:plasma AUC penetration** ratio was 13%

	Dalbavancin Concentration (Mean ± SD) at Post-dose Sample Collection Timepoint ‡					
	12 h (0.5 days)	**24 h (1 day)**	**72 h (3 days)**	**168 h (7 days)**	**240 h (10 days)**	**336 h (14 days)**
Plasma, µg/mL*	85.3 ± 18.9 n=31	ND	ND	ND	ND	15.3 ± 4.1 n=31
Synovium, µg/g†	25.0 ± 0 n=3	17.9 ± 7.8 n=3	19.5 ± 4.9 n=3	19.2 ± 8.9 n=4	25.0 ± 0 n=2	15.9 ± 7.9 n=3
Synovial fluid, µg/mL†	22.9 n=1	27.4 ± 10.8 n=4	19.2 ± 4.9 n=3	11.6 ± 3.3 n=2	13.9 ± 1.0 n=3	6.2 ± 1.7 n=2
Bone, µg/g	6.3 ± 3.1 n=5	5.0 ± 3.5 n=5	4.6 ± 3.8 n=5	3.8 ± 2.7 n=5	3.7 ± 2.2 n=5	4.1 ± 1.6 n=5
Skin, µg/g†	19.4 ± 7.9 n=2	12.5 ± 6.5 n=3	13.8 ± 1.4 n=3	15.7 ± 1.0 n=2	21.6 n=1	13.8 ± 2.1 n=2

‡Bone samples and concomitant samples of skin and synovium (and synovial fluid if available) were collected post-dose
*Mean ± SD plasma concentrations in 31 patients at 772 and 1080 h were 6.2 ± 2.4 and 3.4 ± 1.7, respectively. †Concentrations above the upper limit of quantification are reported as 25 µg/unit

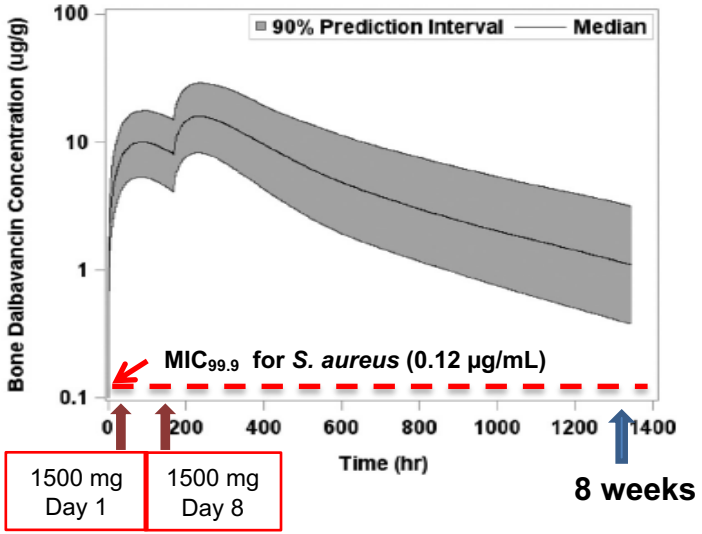
AUC=area under the curve; MIC_{90}=90% minimum inhibitory concentration; ND=not done

From: Dunne MW, et al. Antimicrob Agents Chemother. 2015 Apr;59(4):1849-1855. Copyright © 2015, American Society for Microbiology. All Rights Reserved. doi:10.1128/AAC.04550-14

Pharmacokinetic Modeling for Dose Determination

- Phase 1 study was done to evaluate the PK and safety of dalbavancin dosed as **1000 mg IV** once, then **500 mg weekly** for 7 weeks
- Population PK modeling from these 2 studies (bone penetration study and extended-duration dosing study) led to proposed dalbavancin dosing regimen for osteomyelitis
- A **2-dose, 1500 mg once-weekly regimen** was proposed for osteomyelitis
  - Regimen would provide **tissue exposure at or above dalbavancin $MIC_{99.9}$ of 0.12 µg/mL for *S aureus*** for **up to 8 weeks**
  - While drug concentrations above MIC are reassuring, PK/PD parameter most likely to predict **efficacy** of dalbavancin is **AUC/MIC**
  - 2-dose regimen of **1500 mg on day 1 and day 8** would achieve **similar area under the curve (AUC)** as 1000 mg followed by 4 weekly doses of 500 mg
  - **2-dose regimen more likely** to show **clinical benefit** based on animal studies showing better outcomes when same total dose delivered in **larger** amounts **earlier** and **less frequently**

Simulated mean concentration-time profile in <u>bone</u>
- **1500 mg IV on days 1 and 8**



From: Dunne MW, et al. Antimicrob Agents Chemother. 2015 Apr;59(4):1849-1855. Copyright © 2015, American Society for Microbiology. All Rights Reserved. doi:10.1128/AAC.04550-14

Phase 2 Randomized Clinical Trial in Adults with Osteomyelitis

OBJECTIVE

To describe the efficacy and safety of dalbavancin for the first episode of osteomyelitis in adults

- Known or suspected to be caused by gram-positive pathogens

METHODS

Single-center, randomized, open-label, active-controlled, parallel-group study comparing dalbavancin with standard of care (SOC) therapy in osteomyelitis in adults (NCT02685033)

- Conducted between **March 2016 and December 2017**
- Cherkasy Regional Hospital, 860-bed tertiary teaching hospital in Cherkasy, Ukraine
  - Site had participated in 3 pivotal dalbavancin ABSSSI trials
  - Large orthopedic referral center for 20 regions, would allow enrollment in reasonable timeframe
  - **Bone biopsy with culture** obtained as standard of care in **all patients**

IV=intravenous; SOC=standard of care

KEY INCLUSION CRITERIA

- Diagnosis of **first episode of osteomyelitis** defined as:
  - **Pain or point tenderness** on palpation, or probing to bone

    AND
  - **Elevated CRP** levels

    AND
  - **X-ray or MRI** consistent with osteomyelitis OR Gram-positive cocci documented on baseline Gram-stain from bone specimen

CRP=C-reactive protein; IV=intravenous; MRSA=methicillin-resistant *Staphylococcus aureus;* SOC=standard of care

KEY EXCLUSION CRITERIA

- **>24 hours of IV antibacterial** therapy for osteomyelitis **within 96 hours** of randomization, unless pathogen isolated was documented to be MRSA that was resistant to administered antibiotic
- **Prosthetic material at site of infection** at time of study initiation
- Prior episode of osteomyelitis or failed course of therapy for osteomyelitis
- Osteomyelitis associated with **burn wound**, with **sacral decubitus** ulcer, or with **multiple sites** of osteomyelitis
- **Septic arthritis** that is **non-contiguous** to osteomyelitis diagnosed by isolation of pathogen from synovial fluid culture
- Concomitant **endocarditis** or **necrotizing fasciitis**
- Gram-negative bloodstream infection

Randomization and Intervention

Randomization and treatment

- Two treatment groups randomized in a 7:1 ratio
  - **Dalbavancin 1500 mg** IV on **day 1** and **day 8***
    - 70 patients
  - **SOC antibiotic** for osteomyelitis based on investigator judgment for 4–6 weeks (IV or oral antibiotic allowed)
    - 10 patients
  - Adjunctive **aztreonam** was permitted at randomization for **presumed coinfection with a Gram-negative pathogen** and a switch to an oral antibiotic for Gram-negative coverage was allowed after clinical improvement
  - Patients with Gram-negative pathogens only in bone cultures at baseline were discontinued from study drug per protocol and received Gram-negative coverage, while continuing safety followup in the study

* Dalbavancin dose was adjusted to 1000 mg IV for patients not on dialysis with a creatinine clearance < 30 mL/min

Study Design

EOT: End of treatment; IV: Intravenous

Primary Endpoint

- Clinical response at **Day 42** in the clinically evaluable (**CE) population***
  - **Cure**: Recovery without need for further antibiotic therapy
  - **Failure**: Additional antibiotics required, >6 weeks of antibiotic therapy in comparator arm, new purulence, amputation due to infection progression, **or** death
  - **Indeterminate**: Lost to follow-up or amputation due to vascular insufficiency

CE=clinically evaluable; mITT=modified intent-to-treat

*CE population: subset of mITT population who received ≥1 dose of dalbavancin (or ≥ 2 weeks of comparator), AND ≤ 1 dose of non-study antibiotic for indication other than osteomyelitis

Secondary Endpoints

- Clinical improvement at **Day 21 in the modified intent-to-treat (mITT) population** (excludes patients from whom only Gram-negative pathogen was isolated from blood and/or bone culture):
  - No worsening of pain and/or point tenderness relative to baseline, and improvement in inflammation (also assessed at Day 28)
  - CRP improvement measured at **Day 28**
- Clinical response in the **mITT population:**
  - **Day 42** (6 weeks)
  - **6 months** (Day 180)
  - **1 year** (Day 365)

CRP=C-reactive protein

FOLLOWUP

Safety data collected at each visit

- Baseline, Day 1, Day 8, Day 21, Day 28, Day 42, 6 months, 1 year
  - Included adverse events, physical exam
- Chemistry and hematology: Baseline, Day 8, Day 28
- Inflammatory markers
  - CRP and ESR: Baseline, Day 8, Day 28, Day 42, 6 months

RESULTS

81 patients assessed for eligibility

- One screen failure: did not meet inclusion criteria

80 patients randomized to treatment

- **IV dalbavancin**: 1500 mg on Day 1, 1500 mg on Day 8 (n=70)
  - 67 patients completed both doses of therapy
    - One patient received renal dose reduction per protocol at 1000 mg on Day 1, 1000 mg on Day 8
  - 3 patients discontinued study drug per protocol when baseline bone culture results showed only Gram-negative pathogens; given appropriate Gram-negative antibiotic & continued to follow up for safety visits
- **IV comparator every 12 hours** for 4–6 weeks (n=10)
  - 8 patients completed therapy
    - IV vancomycin alone x 4 weeks (n=3)
    - IV vancomycin x 5-16 days, then IV linezolid or IV levofloxacin to complete 29 days of therapy (n=4)
    - IV vancomycin x 7 days, then IV linezolid plus IV cefotaxime x 43 days (n=1)
  - 2 patients discontinued study drug per protocol when baseline bone culture results showed only Gram-negative pathogens; given appropriate Gram-negative antibiotic & continued to follow up for safety visits

IV=intravenous

Demographics and Medical History (Safety Population)

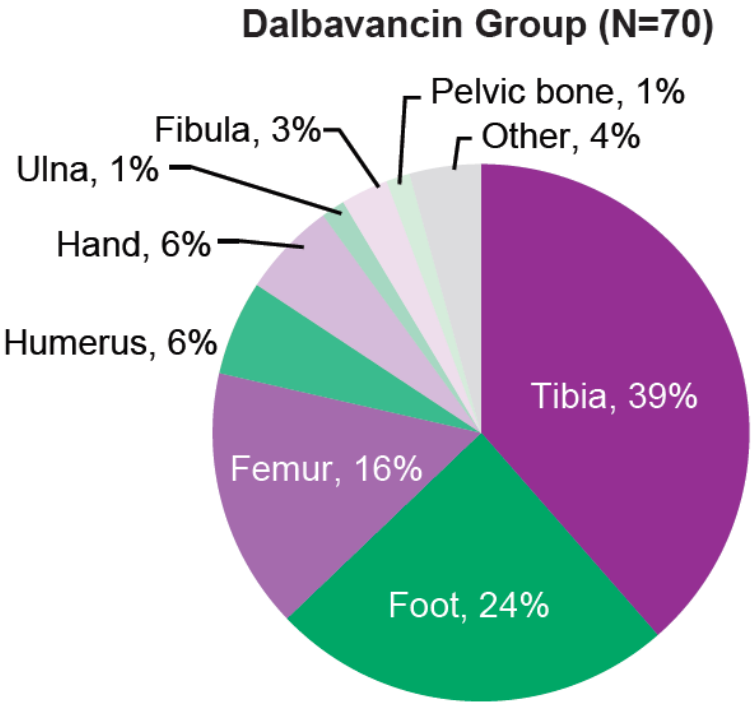
Characteristics	Dalbavancin n=70	Standard of Care n=10
Age, mean ± SD, years (range)	49.2 ± 13.3 (26-79)	54.4 ± 15.3 (29-79)
Male, n (%)	59 (84.3%)	5 (50%)
Race, n (%)		
White	70 (100%)	10 (100%)
Ethnicity, n (%)		
Not Hispanic/Latino	70 (100%)	10 (100%)
Body Mass Index (kg/m^2)		
Mean ± SD	26.1 ± 5.1	30.7 ± 7.4
Median (Min, Max)	24.7 (18.6, 40.1)	33.8 (21.6, 40.3)
Diabetes mellitus, n (%)	10 (14.3%)	5 (50%)
Prior fracture and surgical repair at site	33 (47.1%)	4 (40%)
Debridement with bone culture, n (%)	70 (100%)	10 (100%)
Vacuum-assisted closure of wound, n (%)	8 (11.4%)	3 (30%)
Skin graft, n (%)	1 (1.4%)	1 (10%)
Aztreonam use, n (%)	8 (11.4%)	1 (10%)
Baseline diabetic foot infection, n (%)	4 (5.7%)	1 (10%)

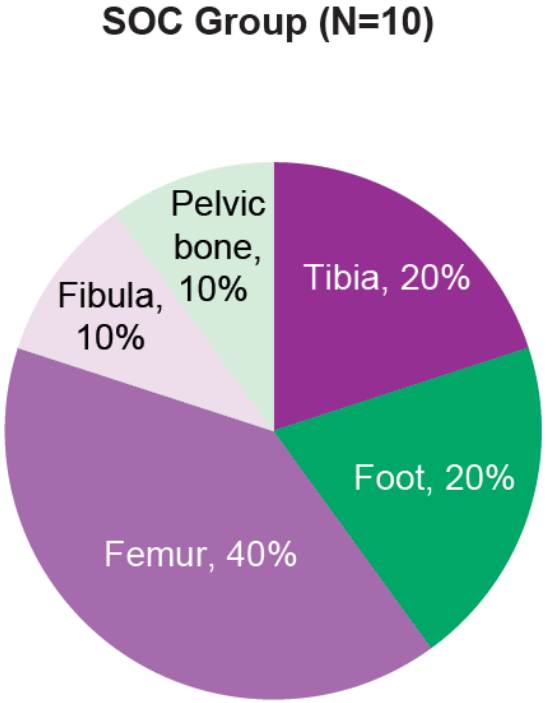
SD: Standard Deviation

KEY BASELINE CHARACTERISTICS

- **All patients in both study arms had baseline debridement with bone culture and histology**
- ***Staphylococcus aureus*: pathogen most commonly isolated from bone**
  - 60% of dalbavancin patients
  - 60% of SOC patients

Site of Osteomyelitis





Most common sites in both groups:

- **Tibia**
- **Foot**
- **Femur**

"Other" sites include patella (n=1), clavicle (n=1), finger (n=1)

Patient Baseline Characteristics (Safety Population)

Characteristics	Dalbavancin n=70	SOC n=10
Baseline CRP, mg/L*		
Mean ± SD	43.9 ± 54.8	20.4 ± 11.4
Median (Min, Max)	24 (12, 192)	18 (12, 48)
Baseline ESR, mm/h†		
Mean ± SD	33.2 ± 17.6	30.6 ± 18.2
Median (Min, Max)	34 (2, 70)	24 (12, 65)
Baseline bacteremia, n (%)		
MSSA	2 (3%)	0
Coagulase-negative Staphylococci	2 (3%)	1 (10%)
Baseline bone histology		
Acute inflammatory cells	56 (80%)	8 (80%)
Necrotic bone	43 (61.4%)	6 (60%)
Edema	11 (15.7%)	4 (40%)
Granulations	8 (11.4%)	1 (10%)
Vascular congestion	4 (5.7%)	0

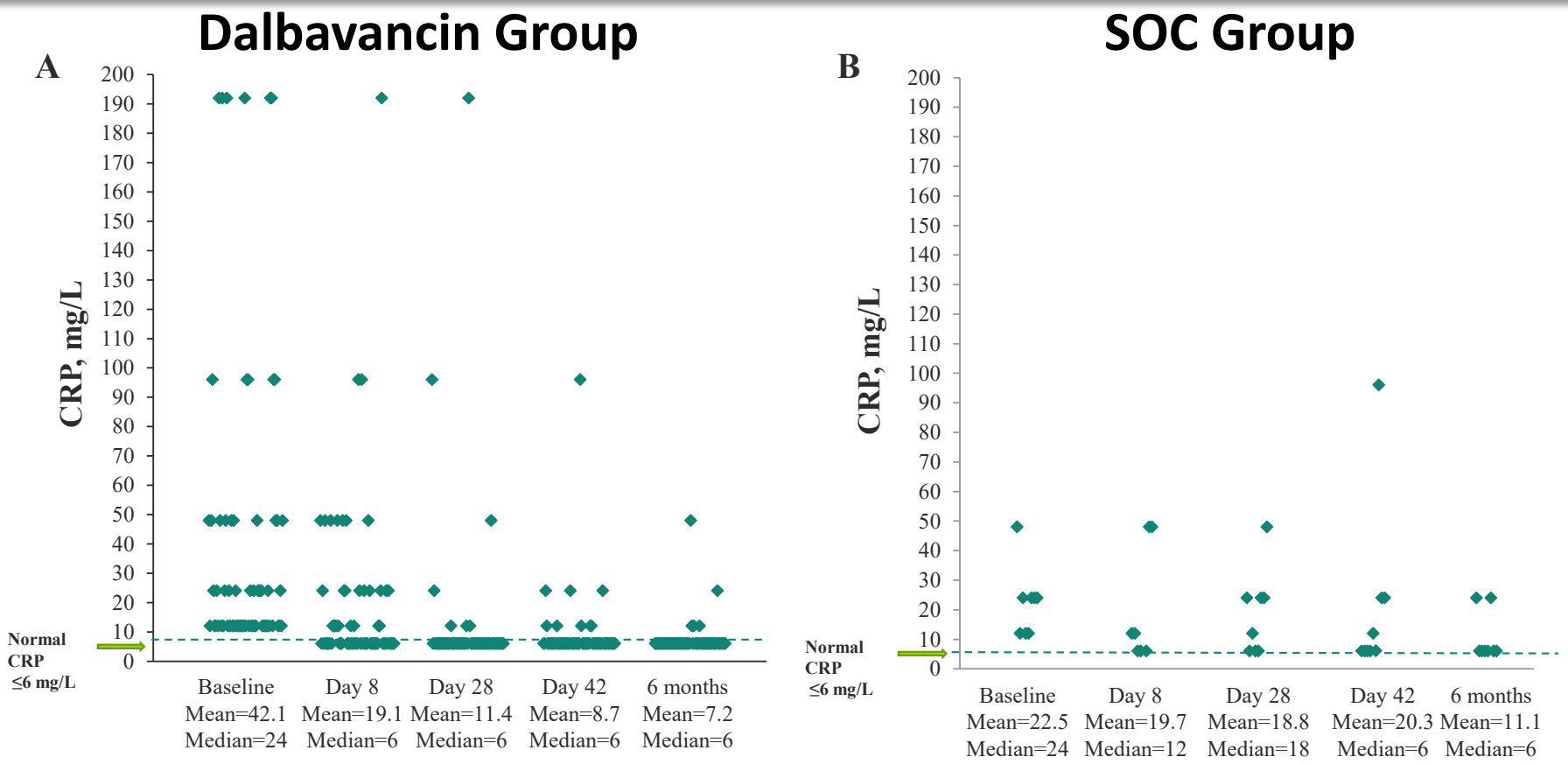
CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; MSSA=methicillin-susceptible *S aureus*; SOC=standard of care.
*CRP normal range=0–6 mg/L. †ESR normal range = 1–10 mm/h.

Baseline Pathogens (Safety Population)

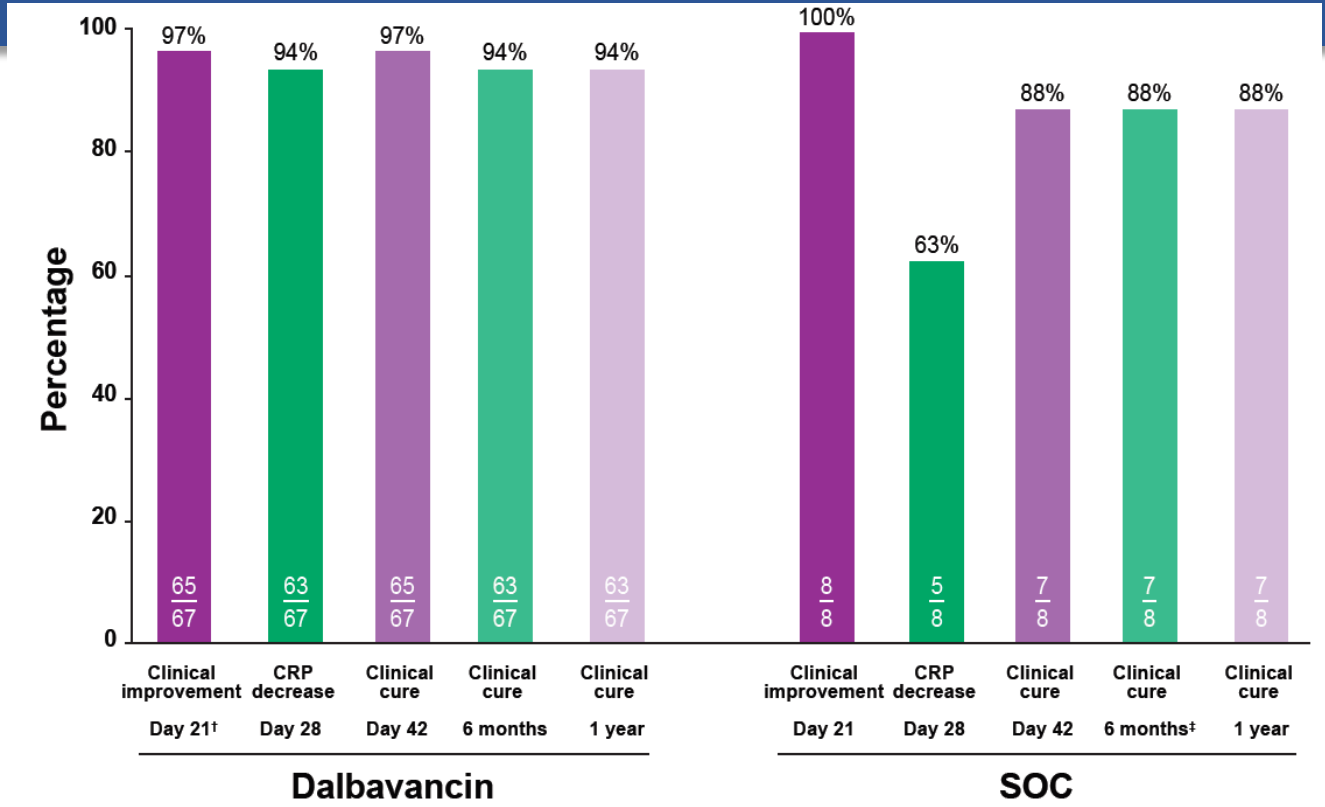
Pathogens in Bone, n (%)*	Dalbavancin n=70	SOC n=10
MSSA	38 (54.3%)	5 (50%)
MRSA	4 (5.7%)	1 (10%)
Coagulase-negative Staphylococci		
Staphylococcus epidermidis	6 (8.6%)	2 (20%)
Staphyloccocus haemolyticus	4 (5.7%)	0
Staphylococcus hominis	2 (2.9%)	0
Staphylococcus pasteuri	1 (1.4%)	0
Staphylococcus simulans	1 (1.4%)	0
Enterococci		
Enterococcus faecalis	7 (10%)	1 (10%)
Enterococcus faecium	1 (1.4%)	0
Anaerobes	9 (12.9%)	0
Streptococci		
Streptococcus agalactiae	1 (1.4%)	1 (10%)
Streptococcus dysgalactiae	1 (1.4%)	0
Streptococcus pyogenes	1 (1.4%)	0
Other Gram-positive pathogens		
Corynebacterium striatum	2 (2.9%)	1 (10%)
Aerococcus viridans	1 (1.4%)	0
***Globicatella* species**	1 (1.4%)	0
Micrococcus luteus	1 (1.4%)	0
Mixed (Gram-positives and aerobic Gram-negatives)	11 (15.7%)	2 (20%)
Gram-negative pathogens only†	3 (4.3%)	2 (20%)
No growth‡	5 (7.1%)	0

MRSA=methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-susceptible *S aureus*; SOC=standard of care.
*Categories are not mutually exclusive. †3 patients in dalbavancin arm and 2 patients in SOC arm were premature discontinuations from study drug due to only Gram-negative pathogens isolated from bone culture. ‡5 patients in dalbavancin arm had no growth on bone biopsy; histology results showed necrotic bone in 3/5 (60%) and acute inflammatory cells in 2/5 (40%)

CRP (mITT Population)



Clinical Outcomes (mITT Population*)



mITT=modified intent-to-treat; SOC=standard of care

*3 patients on dalbavancin and 2 on SOC had only Gram-negative pathogens isolated from bone cultures and were excluded from mITT population and efficacy analyses, per protocol.

†2 patients on dalbavancin were lost to followup before Day 21 visit; both had clinical improvement (decreased pain and point tenderness) at Day 8 visit. ‡1 patient on SOC was lost to followup before 6 month visit; he was a clinical cure at Day 42 visit

Hospital Stay and Antibiotic Treatment (mITT Population)

Outcome	Dalbavancin n=67	SOC n=8
Length of hospital stay, days		
Mean ± SD	15.8 ± 7.1	33.3 ± 14.2
Median (Min, Max)	15.0 (8, 38)	30.5 (11, 56)
Days of IV antibiotic treatment		
Mean ± SD	2.0 ± 0	31.6 ± 7.0
Median (Min, Max)	2 (2, 2)	29 (29, 49)
Total IV infusion duration, hours		
Mean ± SD	1.0 ± 0.02*	101.3 ± 20.8
Median (Min, Max)	1.0 (1.0, 1.1)*	112.6 (66.9, 113.3)

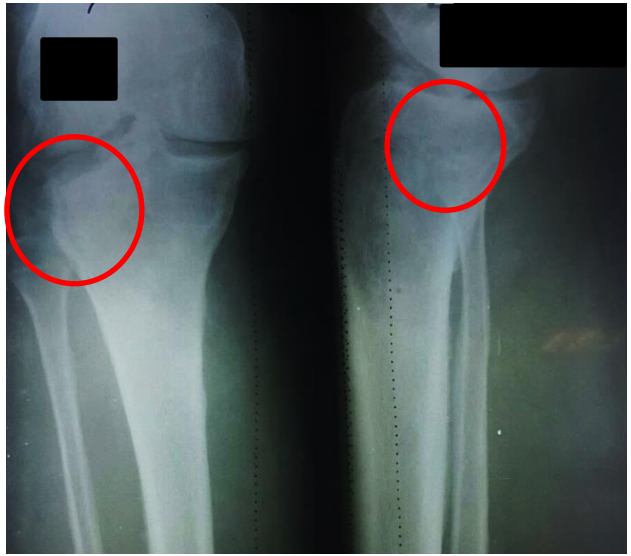
IV=intravenous; mITT=modified intent-to-treat; SD=standard deviation

* All patients in mITT population received both doses of dalbavancin at Day 1 and Day 8 visits (over approximately 30 minutes [range 29-32 minutes]).

Dalbavancin Patient with Right Tibia Osteomyelitis

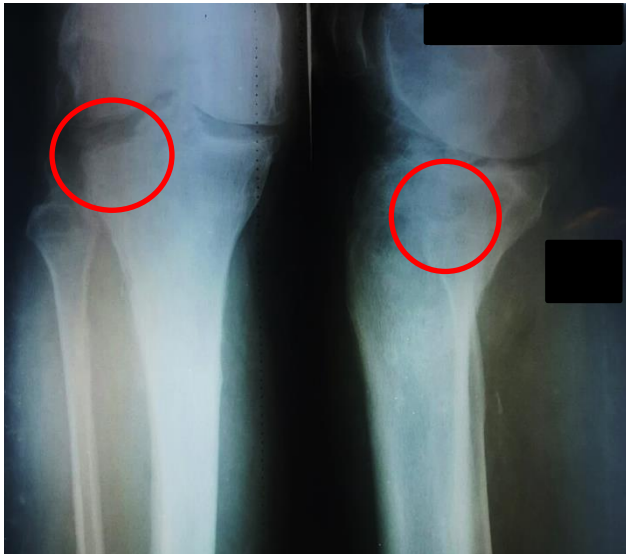
Pathogen: MSSA in Bone Culture & Blood Culture

Baseline: CRP 192 mg/L



Baseline X-ray: Periosteal reaction in area of **right tibia external condyle,** with sites of **sequestration** and **bone defect**. Signs of deforming arthrosis of the right knee joint

Day 42: CRP 6 mg/L



Day 42 X-ray: No signs of periosteal reaction or sequestration.

Adverse Events

Characteristic	Dalbavancin n=70	SOC n=10
Patients experiencing ≥ 1 of the following:		
TEAE	10 (14.3%)	0
TEAE leading to premature discontinuation of study drug	0	0
Drug-related TEAE	1 (1.4%)	0
Serious TEAE	2 (2.9%)†	0

TEAE=treatment-emergent adverse event

†Both serious TEAEs were not related to study drug and occurred after Day 42 (primary endpoint)

DISCUSSION

- Most patients had a **Gram-positive organism** isolated from bone (89% in dalbavancin group, 80% in SOC group) consistent with previous literature
- **High clinical cure rates** in dalbavancin group at **day 42** (97% in CE, mITT and micro-mITT populations), sustained **through 1 year**
- Patients in **dalbavancin** group had **total IV duration of 1 hour** vs **SOC** group with average **duration of 101.3 hours** per patient

Dalbavancin Osteomyelitis Study Summary

- **Long half-life** of dalbavancin and its high bone penetration after a short treatment regimen allows once-weekly dosing and maintains serum concentrations above the MIC_{90} for most Gram-positive pathogens, including *S aureus* over at least 6 weeks
- **Good bone penetration** of dalbavancin after a short dosing regimen is relevant for osteomyelitis
- The 2-dose, once-weekly regimen may offer advantages to patients and physicians
  - Eliminates need for prolonged IV access
  - Optimizes adherence for infection requiring treatment duration of 4–6 weeks
  - Brief 2-dose regimen may be suitable for **outpatient setting**, eg emergency rooms, infusion centers and hospital outpatient departments
- Dalbavancin was **well tolerated** in this adult population
- Outcomes at 6 weeks, 6 months, and 1 year suggest that treatment of adult osteomyelitis with a 2-dose, weekly regimen of dalbavancin shows a **favourable and durable clinical benefit**

IV=intravenous; MIC_{90}=90% minimum inhibitory concentration

ADDITIONAL DATA ON DALBAVANCIN IN OSTEOMYELITIS

- Findings from randomized clinical trial **consistent with efficacy of dalbavancin in other reports**
  - Animal model with MRSA sternal osteomyelitis[1]
- Observations of **high response rates** in treatment of osteomyelitis with dalbavancin
  - Case report of multiple weekly dosing of dalbavancin for **native vertebral osteomyelitis with MRSA** bacteremia (1000 mg IV weekly x 2 wks, followed by 500 mg weekly x 6 wks, plus daily oral rifampin)[2]
  - Case report of weekly dalbavancin in **deep sternal wound infection with MRSA** after coronary artery bypass surgery (1500 mg IV with repeat dose of 1500 mg IV after 2 wks) [3]
  - Multicenter retrospective review of **31 patients with gram-positive osteomyelitis** treated with weekly dalbavancin from 3 U.S. hospitals[4]
    - **90% success**; no adverse events related to dalbavancin
    - 5 patient admissions were prevented; these patients received entire course in outpatient setting
    - Remaining 26 patients received 1st dose of dalbavancin at discharge and then completed any weekly doses as outpatients
      - Dalbavancin doses ranged from 500 to 1500 mg/dose, and number of doses varied from single dose to 14 doses based on rate of improvement, duration of therapy remaining and other factors; median duration of prior antibiotics: 20 days (range 2-55 days)
      - Mean reduction in LOS: 28 ± 10 days per patient
      - Estimated total cost-savings of $649,954

[1]Barnea Y et al. J Antimicrob Chemother 2016.
[2]Almangour TA et al. Am J Case Rep 2017.
[3]Guzek A et al. J Cardiothorac Surg 2018.
[4] Almangour TA et al. Diagn Microbiol Infect Dis 2018.

DALBAVANCIN IN OTHER INFECTIONS

- Retrospective study of adults treated with dalbavancin for **various infections** in 29 institutions in **Spain**[1]
  - **69 patients** received dalbavancin as weekly regimen
  - Most common infections: prosthetic joint infection, acute bacterial skin and skin structure infection, osteomyelitis, catheter-related bacteremia and endocarditis
    - Dalbavancin dose: most common 1000 mg IV followed by 500 mg weekly to cover 14-42 days (n=40), or 1500 mg alone (n=17)
    - 97.1% received dalbavancin as 2nd line therapy, after median 18 days of antibiotics
    - Dalbavancin given for median 21 days (range 7-168); 36% on concomitant antibiotic
  - Overall 84% success; 10 of the 11 clinical failures due to inadequate source control
  - Reduced hospital stay by 1160 days
  - 50 of 69 patients were treated in outpatient setting
  - Overall cost reduction at €211 481, or €3064 per patient

[1]Bouza E et al. Int J Antimicrob Agents 2018.

DALBAVANCIN IN ENDOCARDITIS AND BACTEREMIA

- Retrospective study of adults treated with dalbavancin for **gram-positive infective endocarditis** (IE) in University Hospital of **Vienna** as weekly or q 2 week regimen[1]
  - **27 patients**: 16 native valve IE, 6 prosthetic valve IE, 5 cardiac-device IE
    - Dalbavancin dose
      - 1000 mg followed by 500 mg weekly (n=9), or
      - 1500 mg followed by 1000 mg every 2 wks (n=18)
    - Median duration of dalbavancin: 6 weeks (range 1-30 weeks)
  - 93% microbiological and clinical success
  - 23 of the 27 patients were treated in OPAT setting

- Case reports of successful treatment of **bacteremia** with dalbavancin
  - **MSSA bacteremia** due to septic phlebitis treated with dalbavancin 1000 mg on discharge and 500 mg as outpatient 1 week later; had received prior therapy with 6 days of cefazolin[2]
  - PICC-line associated bacteremia with **vancomycin-susceptible *Enterococcus faecalis*** treated with 1500 mg single dose of dalbavancin in outpatient infusion center in intravenous drug user[3]

[1]Tobudic S et al. Clin Infect Dis 2018. [2]Cho JC et al. Clin Pharm Ther 2015. [3]Jones BM et al. Int J Infect Dis 2018.

Oritavancin

ORITAVANCIN BACKGROUND

- Semisynthetic **lipoglycopeptide** approved for **acute bacterial skin and skin structure infection (ABSSSI) in US and EU; launched in US**[1]
  - **1200 mg** dose as a **3-hour** infusion (in **1000 mL**)
  - Active against gram-positive bacteria including *S. aureus* (MSSA, MRSA) and *Enterococcus* spp.
  - Terminal half-life of **10.2 days**
  - Drug-drug interactions
    - Nonspecific weak **inhibitor** (CYP2C9 and CYP2C19)
    - **Weak inducer** (CYP3A4 and CYP2D6)
    - Avoid oritavancin with drugs with narrow therapeutic window that are predominantly metabolized by one of the affected CYP450 enzymes
  - Interference with **coagulation tests**: artificially prolongs aPTT (up to 120h), PT/INR (up to 12h) and ACT (up to 24h)
    - Use of IV heparin contraindicated for 120h (5 days) after oritavancin
    - Patients on warfarin should be monitored for bleeding

[1]Orbactiv® (oritavancin) full prescribing information, 2018.

ORITAVANCIN DATA IN OTHER INFECTIONS

- **Case report** of successful treatment of **MSSA osteomyelitis** with multiple doses of weekly oritavancin (1200 mg 2 days before surgery to remove infected tibial nail, then 1200 mg weekly x 6 wks)[1]
  - Supported by rabbit study showing bone concentrations above MIC_{90} for *S. aureus* (0.06 µg/mL) for 7 days[2]

- **Retrospective review** of oritavancin at **US medical center** for multiple doses[3]
  - **17 patients** treated for osteomyelitis, surgical site infection, intravascular infections and pneumonia (empiric therapy n=5, definitive/targeted therapy n=12)
    - Oritavancin dose per institutional protocol: initiated at 1200 mg, then 800 mg weekly or 1200 mg every 9-12 days (range 2-18 doses)
  - All had clinical success or improvement
  - 4 patients had adverse event requiring discontinuation of oritavancin

[1]Delaportas DJ et al. Pharmacotherapy 2017. [2]Lehoux D et al. Antimicrob Agents Chemother 2015. [3]Schulz LT et al. Pharmacotherapy 2017.

ORITAVANCIN DATA IN OTHER INFECTIONS

- **Retrospective review in US** center of patients treated with oritavancin for **indication other than ABSSSI**[1]
  - **10 patients** treated primarily for bacteremia with MSSA, group B *Streptococcus* with endocarditis, CoNS, vancomycin-susceptible *Enterococcus*
    - Oritavancin dose: 1200 mg x 1 (n=9); 1200 mg x 3 every 14-19 days (n=1)
  - 70% success; all patients had prior antibiotics before oritavancin and combination therapy with other antibiotics

- **Case report** of oritavancin in **vancomycin-resistant *Enterococcus faecium*** prosthetic valve endocarditis[2]
  - Oritavancin dose: 1200 mg every other day x 3 doses, then 1200 mg weekly x 6 wks; 8 days later, reinitiated after recurrence of VRE bacteremia at 1200 mg twice weekly, underwent valve replacement and continued 1200 mg twice weekly x 10 wks post-op

[1]Stewart CL et al. Infect Dis Ther 2017.

[2]Johnson JA et al. Open Forum Infect Dis 2015.

Teicoplanin

TEICOPLANIN CHARACTERISTICS

- Glycopeptide antibiotic approved and available in EU, indicated for
  - **Parenteral** treatment
    - Complicated skin and soft tissue infections
    - Bone and joint infections
    - Hospital acquired pneumonia, community-acquired pneumonia
    - Complicated urinary tract infections
    - Infective endocarditis
    - Peritonitis associated with continuous ambulatory peritoneal dialysis
    - Bacteraemia with any of the above
  - **Oral** treatment for *Clostridium difficile* infection-associated diarrhoea and colitis
- Active against **Gram-positive** bacteria, including *S. aureus*, coagulase-negative staphylococci, *Enterococcus* spp., *Streptococcus* spp., Gram-positive anaerobes
- Elimination **half-life** varies from **4-7 days**

Targocid (teicoplanin) SPC 2017.

TEICOPLANIN DOSAGE GUIDELINES IN OPAT

- Teicoplanin useful for OPAT due to long half-life[1]
  - Since 2000: 2x/week (twice-weekly) or 3x/week (thrice-weekly) dosing used by Glasgow OPAT service, usually combined with a 2nd active oral agent
  - Study analyzed routinely generated teicoplanin concentration data from OPAT clinic in Glasgow, using a population pharmacokinetic approach
    - Data from 94 patients for model development and 36 patients for validation
  - Dosage guidelines developed for **thrice-weekly** dosing
    - Success rates of **91% in deep-seated infections** (primarily bone & joint, endocarditis) and **95% in other infections** (primarily cellulitis and wound infections)

[1]Lamont E. et al. J Antimicrob Chemother 2009.

NHS Tayside guidelines for bone and joint infections: thrice-weekly teicoplanin dosing

1. Loading dose – Doses should be given 24 hourly for the first 3 days

Target **Trough Concentration**	**Ideal Body Weight (kg)*** see IBW guidance		
	40-59	60-79	>80
20-30mg/L			
CLCR<60ml/min	1000mg	1200mg	1400mg
CLCR>60ml/min	1200mg	1400mg	1600mg

*Use Actual Body weight if lower than Ideal Body Weight

2. Maintenance doses – doses should be given three times weekly on Mon, Wed and Fri.

CrCLml/min (Use ABW to calculate CrCl) **							
<25	25-40	41-54	55-74	75-89	90-104	105-120	>120
Target Trough Concentration 20-30mg/L							
400mg	600mg	800mg	1000mg	1200mg	1400mg	1600mg	1800mg

** CrCl = $\frac{(140-\text{age}) \times \text{weight (kg)}}{\text{Serum creatinine}} \times$ (1.23 male or 1.04 female)

[NB: Serum creatinine in µmol/L]

https://www.nhstaysideadtc.scot.nhs.uk/Antibiotic%20site/pdf%20docs/Teicoplanin%20three%20times%20weekly.pdf

Targocid (teicoplanin) SPC 2017. Lamont E. et al. J Antimicrob Chemother 2009.

NHS Tayside guidelines (Cont'd): Monitoring

Dosing regime above aims to achieve a trough of 20-30mg/L
BEFORE 6th dose (e.g. 15 -30 mins before) check trough Teicoplanin level

↓

Adjust maintenance dose based on Teicoplanin level or renal function
NB: Teicoplanin levels may take 7 to 10 days to be reported

↓

Teicoplanin Level (mg/L)	Action
<10	Recheck CrCL as per above table
10-20	Consider increasing dose to achieve trough 20-30mg/L
20-30	No dose adjustment. Recheck levels after 1 week
>30	Decrease frequency of dosing – give SAME dose twice weekly. Recheck levels after 1 week. Recheck CrCL

NB: Add RIFAMPICIN 450mg bd to regime if Prosthetic joint/implant/graft in situ. Check for Rifampicin sensitivity – if resistant seeks ID/Micro advice. Rifampicin should be prescribed after consideration of co-morbidities, potential hypersensitivity and drug interactions.

https://www.nhstaysideadtc.scot.nhs.uk/Antibiotic%20site/pdf%20docs/Teicoplanin%20three%20times%20weekly.pdf

Targocid (teicoplanin) SPC 2017.
Lamont E. et al. J Antimicrob Chemother 2009.

TEICOPLANIN COST-MINIMIZATION ANALYSIS

- Retrospective audit of 55 treatment episodes of bone and joint infections
- Mean cost of care with **teicoplanin**
  - Ambulatory setting **£1749.15**
  - In-patient setting **£11400**
  - Hypothetical treatment with oral linezolid in home setting £2546
- Parenteral teicoplanin delivered by **specialist outpatient service** associated with **lower financial costs** vs in-patient care or hypothetical oral linezolid

Nathwani D et al. J Antimicrob Chemother 2003

Amikacin

AMIKACIN CHARACTERISTICS

- Semi-synthetic, **aminoglycoside** antibiotic[1]
  - Bactericidal
  - Indicated in short-term treatment of **serious infections** due to susceptible **Gram-negative** bacteria; may at times be indicated for known or suspected **staphylococcal disease**
  - Broad spectrum of Gram-negative organisms, including *Pseudomonas aeruginosa*, *E. coli*, and some Gram-positive organisms, including *Staphylococcus aureus*, and some MRSA
  - Intramuscular or intravenous administration
  - Elimination **half-life**: **2-3 hours**
  - Special warnings: potential **ototoxicity** and **nephrotoxicity**
- **Active** against **Mycobacteria**[2,3]
  - **Thrice-weekly** dosing as add-on therapy for
    - **Fibrocavitary or severe** lung disease, in combination with a 3-drug regimen (eg azithromycin plus rifampicin plus ethambutol)
    - **Mycobacterium avium complex** lung infections with cavitary disease or macrolide resistance (if amikacin MIC ≤ 64 mcg/mL) for first 8-16 weeks of therapy

[1]Amikacin SPC 2015. [2]Haworth CS et al. Thorax 2017 [3]Kasperbauer S et al. Uptodate.com 2018

THRICE-WEEKLY AMIKACIN

- Study compared incidence of nephrotoxicity and ototoxicity with daily vs thrice-weekly amikacin in MDR-tuberculosis or complicated non-tuberculous mycobacterial infection
  - Patients randomized to IV amikacin, streptomycin or kanamycin
    - 15 mg/kg **daily (Mon-Fri)** or
    - 25 mg/kg **3 times/week**
  - In the group randomized to IV amikacin 3x/week (n=11), median duration of therapy was 23 weeks (range 2-43 weeks)
  - **Size of dosage** and **frequency** not associated with ototoxicity, vestibular toxicity or nephrotoxicity
    - Amikacin, streptomycin and kanamycin can be administered either daily or 3x/week without affecting likelihood of toxicity

Peloquin CA et al. Clin Infect Dis 2004

THRICE WEEKLY IV AMIKACIN IN *M. ABSCESSUS*

- Limited options for ***Mycobacterium abscessus*** **pulmonary disease**, especially in outpatient settings
  - Among parenteral antibiotics, IV amikacin considered one of the most active vs *M. abscessus*
- **Retrospective case series** of **13 outpatients** with *M. abscessus* pulmonary disease treated with IV amikacin
  - IV amikacin was added 6.1 months (on average) after start of anti-mycobacterial therapy
    - IV amikacin administered for median duration of 4 months (range 3-9 months)
  - Starting dose of IV amikacin 15 mg/kg 3x/week, with dose adjustment based on trough
    - More than half the patients had dose reduction; median dose decreased to 12.5 (8.3-16.2) mg/kg
- Addition of IV amikacin 3x/week led to
  - Sputum conversion in 10 of 13 patients, including 8 who continued to have negative sputum status >1 year after the end of amikacin treatment
  - No severe adverse events, such as ototoxicity, vestibular toxicity and renal toxicity
    - Attributed to lower starting dose of amikacin and dose reduction based on troughs

Namkoong H et al. BMC Infect Dis 2016

SUMMARY: ANTIMICROBIALS WITH LESS FREQUENT DOSING

- **Dalbavancin**
  - **Osteomyelitis**
    - **Randomized clinical trial (n=80)**: dalbavancin weekly x 2 (1500 mg IV on day 1 and day 8) for at least 6 weeks of coverage (n=70), vs SOC antibiotic x 4-6 weeks (n=10)
      - High clinical cure rates in dalbavancin group at day 42 (97%), through 1 year, with LOS reduction
    - **Multicenter retrospective review in US (n=31):** 90% success with LOS reduction and cost savings
    - **Case reports** of successful treatment with weekly dalbavancin
  - **Various infections**
    - **Multicenter retrospective review in Spain (n=69)**: 84% success with LOS reduction and cost savings
    - **Retrospective review in Vienna (n=27):** gram-positive endocarditis; 93% success with mostly OPAT
    - **Case reports** of successful treatment in bacteremia

- **Oritavancin**
  - **Osteomyelitis**
    - **Case report** of successful treatment with multiple weekly doses
  - **Various infections**
    - **Retrospective review in US (n=17):** all had clinical success or improvement; 4 discontinued drug due to AE
    - **Retrospective review in US (n=10):** 70% success
    - **Case report** of use in VRE prosthetic valve endocarditis

SUMMARY (CONT'D)

- **Teicoplanin**
  - **3x/week dosing guidelines** developed from routine clinical data in **Glasgow OPAT clinic**
    - 91% success in deep-seated infections; 95% success in other infections
  - **Bone & joint** infections--**NHS Tayside** guidelines
    - Loading dose every 24h x 3 days, then maintenance doses 3x/week (M/W/F)
    - Trough before 6th dose; goal trough 20-30 mg/L

- **Amikacin IV**
  - 3x/week dosing vs daily dosing in MDR-tuberculosis or complicated NTM infection
    - Amikacin daily as 15 mg/kg (n=11) or 3x/week as 25 mg/kg (n=11) did not affect likelihood of toxicity
  - **Retrospective review (n=13 outpatients)** in *M. abscessus* pulmonary disease
    - Lower starting dose 3x/week as 15 mg/kg with dose adjustment based on trough: fewer severe AEs

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Thank You!

Backup Slides

DALBAVANCIN PK STUDY IN BONE

Phase 1 study of dalbavancin in **bone and synovial tissue**

- Adults undergoing elective orthopedic surgery (22 knee replacements, 8 hips)
  - Assigned to 1 of 6 cohorts (5 patients per cohort)
    - Subjects received a **single dose of 1000 mg of dalbavancin** at appropriate timepoint before surgery
    - **Tissue** sampling at **12h, 24h, 3 days, 7 days, 10 days, 14 days** POST-DOSE
    - **Plasma** PK sampling in all subjects: **1h, 4h, 12h, 14 days, 30 days, 45 days** POST-DOSE
    - 31 subjects, 30 evaluable bone samples
    - Mean conc of dalbavancin in **bone** at **12h post-dose: 6.3 mcg/g**, and at **14 days: 4.1 mcg/g**
      - Remained >10-fold above MIC90 of S. aureus (0.06 mcg/mL) through final sample collection at 14 days

Dunne et al. AAC 59:1849-1855.

Dalbavancin PK study: Extended-Duration Dosing

Phase 1 Study evaluated 18 subjects in 3 cohorts (6 patients per cohort)

Cohort 1

- **4 weekly dalbavancin doses** (1000 mg D1, then 500 mg weekly x 3), cumulative dose of **2500 mg**

Cohort 2

- **6 weekly dalbavancin doses** (1000 mg D1, then 500 mg weekly x 5), cumulative dose of **3500 mg**

Cohort 3

- **8 weekly dalbavancin doses** (1000 mg D1, then 500 mg weekly x 7), cumulative dose of **4500 mg**

Plasma PK sampling

- Plasma PK sampling on D1 (multiple timepoints post-dose) and pre- & post dosing on D8, D15, time of last dose at D22 (cohort 1), D36 (cohort 2), D50 (cohort 3), and also at 4 weeks after intense PK sampling

Dunne et al. AAC 59:1849-1855.

Dalbavancin Dosing Regimens

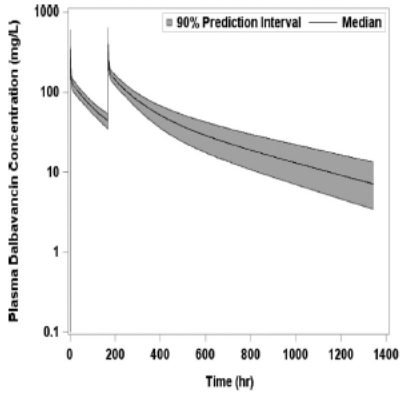
Based on 2 Phase 1 studies in healthy adults and population PK modeling

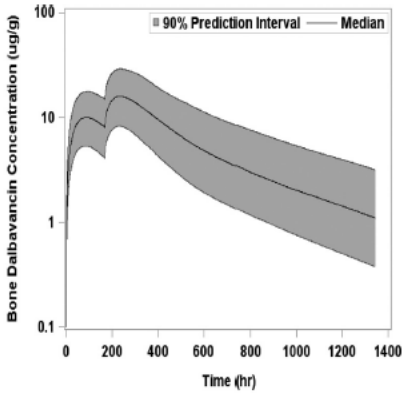
- Proposed dosing regimen for **osteomyelitis**
  - Two 1500 mg IV infusions 1 week apart (D1, D8)
    - Dalbavancin exposure at or above the S. aureus MIC99.9 for dalbavancin of 0.12 mcg/mL for entire treatment duration (8 weeks)
  - 1500 mg regimen on D1 & D8 (cum dose 3000 mg) expected to achieve AUC similar to 1000 mg D1, followed by 500 mg weekly x 4 (cum dose 3000 mg)
  - 2 dose regimen (1500 mg D1 & D8) over 2 weeks selected over regimen with same cum dose of 3000 mg over 1 month (1000 mg D1, 500 mg weekly x 4 on D8, D15, D22, D29)
    - Better outcomes observed if same total dose delivered in larger amounts earlier and less frequently in animal studies
    - With translation of animal data to humans, anticipate that 2-dose 1500 mg regimen → more likely to achieve success

Dunne et al. AAC 2015; 59:1849-1855
Andes et al. AAC 2007; 51:1633-1642

Dalbavancin Plasma & Bone PK Modeling: Similar exposures through 8 Weeks with 3000 mg cumulative dose

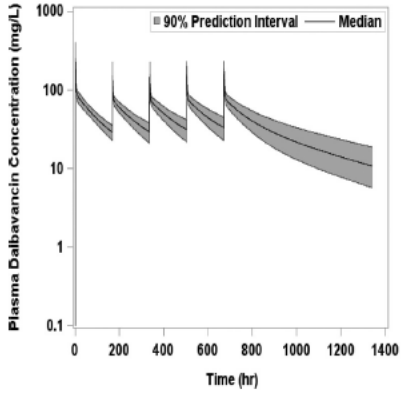
PLASMA
2 dose regimen
(1500 mg D1/D8)

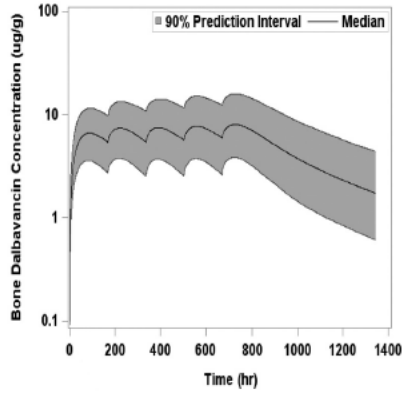




BONE LEVELS
2 dose regimen
(1500 mg D1/D8)

PLASMA
5 dose regimen
(1000 mg D1,
500 mg
D8/D15/D22/D29)

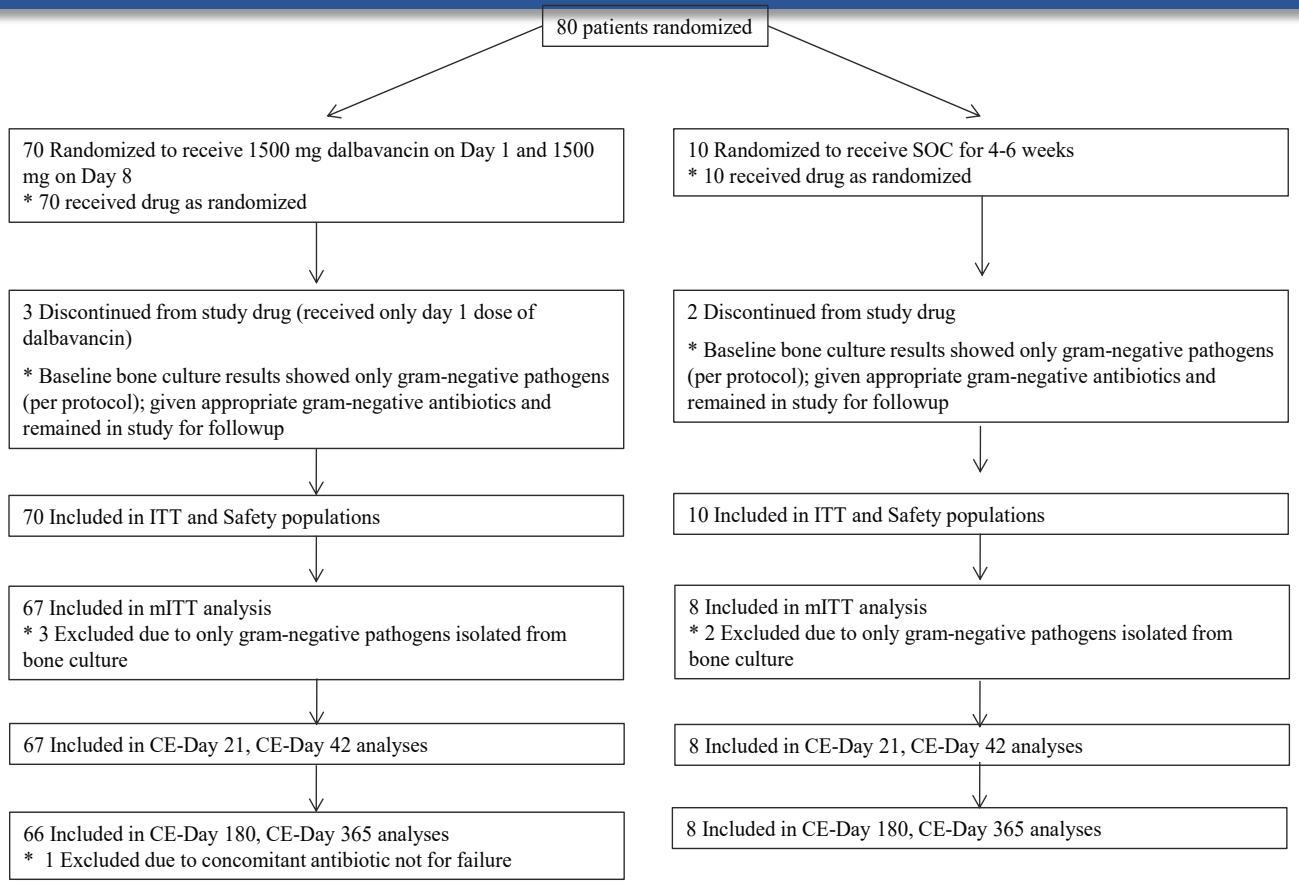




BONE LEVELS
5 dose regimen (1000
mg D1, 500 mg
D8/D15/D22/D29)

Dunne et al. AAC 59:1849-1855.

Patient Disposition



TREATMENT REGIMENS FOR SOC GROUP

Regimen (every 12 hours)	SOC (n=10)	Baseline Pathogen(s) in Bone
Vancomycin IV x 29–30 d (D1–29 or D1–30)	3 (30%)	*Corynebacterium striatum* (n=1); *Staphylococcus epidermidis* (n=1); MSSA + *Enterococcus faecalis* (n=1)[a]
Vancomycin IV x 5 d (D1–5); linezolid IV x 25 d (D5–29)	1 (10%	MSSA + *Staphylococcus epidermidis* + *Streptococcus agalactiae*
Vancomycin IV x 6 d (D1–6); linezolid IV x 24 d (D6–29)[b]	1 (10%)	MRSA + *Klebsiella pneumoniae* + *Proteus mirabilis*
Vancomycin IV x 8 d (D1–8); levofloxacin IV x 22 d (D8–29)	1 (10%)	MSSA
Vancomycin IV x 16 d (D1–16); levofloxacin IV x 15 d (D15–29)	1 (10%)	MSSA
Vancomycin IV × 7 d (D1–7); linezolid IV + cefotaxime IV x 43 d (D7–49)[c]	1 (10%)	MSSA + *Pseudomonas aeruginosa* + *Raoultella planticola* + *Serratia marcescens*
Excluded from mITT (only Gram-negatives in bone)		
Vancomycin IV x 16 d (D1–16); amikacin IV x 13 d (D8–20)[d,e]	1 (10%)	*Klebsiella pneumoniae* + *Proteus mirabilis*
Vancomycin IV x 5 d (D1–5); IV ceftriaxone x 25 d (D4–29)[d]	1 (10%)	*Enterobacter cloacae complex* + *Escherichia coli* + *Klebsiella oxytoca*

IV=intravenous; d=days; D=Study Day. MRSA=methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-susceptible *S. aureus*; SOC=standard of care; mITT=modified intent-to-treat
[a]**Indeterminate** at 6 months and 1 year due to **loss to followup**. [b]Received adjunctive **aztreonam**. [c]**Clinical failure at day 42** due to receipt of **antibiotics > 6 weeks**. [d]Discontinued study drug per protocol when baseline bone culture results showed only gram-negative pathogens; given appropriate gram-negative antibiotic. [e]Withdrew from study on day 20 (withdrew consent)

Baseline pathogens in mixed infection: Gram-Positive + Gram-Negative Aerobes in bone (safety population)

Baseline Pathogen, by Patient	Site	Clinical Response at Day 42
Dalbavancin Group		
1. MSSA, *Escherichia coli* (plus anaerobes *Bacteroides fragilis, Peptoniphilus harei*)	Hand	Cure
2. Enterococcus faecalis, Enterobacter cloacae complex (plus anaerobe *Prevotella intermedia*)	Tibia	Cure
3. MSSA, *E. faecalis, E. coli, K. pneumoniae* (plus anaerobes *Bacteroides fragilis, Bacteroides vulgatus*)	Diabetic foot	Cure
4. Staphylococcus haemolyticus, Streptococcus dysgalactiae, Escherichia coli, Klebsiella pneumoniae	Foot (not diabetic)	Cure
5. MSSA, *M. morganii, P. mirabilis* (plus anaerobes *B. thetaiotaomicron, Porphyromonas asaccharolytica*)	Foot (not diabetic)	Cure
6. MSSA, *Morganella morganii* (plus anaerobe *Finegoldia magna)*	Foot (not diabetic)	Cure
7. S. epidermidis, E. faecalis, Escherichia hermannii, Pluralibacter gergoviae, Raoultella planticola	Diabetic Foot	Cure
8. MSSA, *Staphylococcus haemolyticus, Acinetobacter calcoaceticus*	Patella	Cure
9. Staphylococcus simulans, Pseudomonas aeruginosa	Tibia	Cure
10. MSSA, *Pseudomonas aeruginosa*	Femur	Cure
11. MSSA, *Enterobacter cloacae complex* (plus anaerobes *Peptoniphilus harei, Prevotella disiens*)	Foot (not diabetic)	Cure

MRSA=methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-susceptible *S. aureus*; SOC=standard of care

BASELINE PATHOGENS IN MIXED INFECTION (CON'D)

Baseline Pathogen, by Patient	Site	Clinical Response at Day 42
SOC Group 1. MSSA, *Pseudomonas aeruginosa, Raoultella planticola, Serratia marcescens* 2. MRSA, *Klebsiella pneumoniae*, *Proteus mirabilis*	Tibia Femur	Failure Cure

MRSA=methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-susceptible *S. aureus*; SOC=standard of care

BASELINE PATHOGENS (SAFETY POPULATION): MUTUALLY EXCLUSIVE CATEGORIES

Pathogens in Bone, n (%)	Dalbavancin (n=70)	SOC (n=10)
Monomicrobial Gram-positive infection	**44 (62.9%)**	**4 (40%)**
MSSA	27 (38.6%)	2 (20%)
MRSA	4 (5.7%)	0
Coagulase-negative Staphylococci	6 (8.6%)	1 (10%)
Enterococci	2 (2.9%)	0
Streptococci	1 (1.4%)	0
Other Gram-positive pathogens	4 (5.7%)	1 (10%)
Polymicrobial infection	**18 (25.7%)**	**4 (40%)**
Polymicrobial Gram-positive infection	4 (5.7%)	2 (20%)
Mixed Gram-positive and aerobic Gram-negative infection ± anaerobes	11 (15.7%)	2 (20%)
Mixed Gram-positive and anaerobic infection	3 (4.3%)	0
Gram-negative infection only	**3 (4.3%)**	**2 (20%)**
No growth	**5 (7.1%)**	**0**