1343

CLEARANCE OF *STAPHYLOCOCCUS AUREUS* BACTEREMIA IN PATIENTS TREATED WITH DALBAVANCIN

Michael Dunne, MD, Sailaja Puttagunta, MD

Durata Therapeutics, Inc., Branford, CT, USA

ABSTRACT

Background: Dalbavancin is a lipoglycopeptide being studied for treatment of acute bacterial skin and skin structure infections (ABSSSI). It has potent activity against gram positive pathogens associated with ABSSSI including both methicillin sensitive and methicillin resistant *S. aureus*. We examined the clearance of bacteremia in four clinical studies of dalbavancin including three phase 3 trials in skin and skin structure infections and one phase 2 catheter related infection study.

Methods: Patients in whom *S. aureus* was identified in blood cultures taken at the baseline visit were selected for further assessment. Clearance of bacteremia is provided for those patients with at least one of the required follow-up post-baseline blood cultures. Comparators included vancomycin and linezolid (cSSSI).

Results: All patients with *S. aureus* bacteremia treated with dalbavancin for whom follow-up blood culture results were available cleared their bacteremia. One case of persistent bacteremia was from a patient treated with vancomycin. Both patients treated with linezolid cleared their bacteremia.

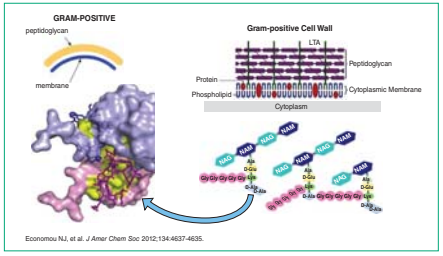
Documented clearance of *S. aureus* bacteremia		
Infection	**Dalbavancin**	**Comparator**
ABSSSI		
DISCOVER 1	3/3	2/3
DISCOVER 2	7/7	6/6
Catheter related bloodstream infection	10/10	9/9
cSSSI	4/4	2/2
Total	24/24 (100%)	19/20 (95%)

Conclusion: All patients treated with dalbavancin who had a *S. aureus* bacteremia associated with either a catheter or a skin infection and had follow up blood cultures available for evaluation in this series of clinical trials were documented to have had clearance of their bloodstream infection.

BACKGROUND

- Dalbavancin is a second generation semi-synthetic lipoglycopeptide antibiotic structurally related to teicoplanin.
- Its *in vitro* activity has been substantiated in various animal models of infection and it possesses a pharmacokinetic (PK) profile which allows once-weekly intravenous (IV) dosing.
- 21 studies (for a total of 3442 subjects) have been conducted and completed with dalbavancin: 14 phase 1 clinical pharmacology studies in 431 subjects, 2 phase 2 studies (CRBSI and skin and skin structure infection [SSSI]) in 136 subjects), and 5 phase 3 studies (ABSSSI/cSSSI, uSSSI) in 2875 subjects.

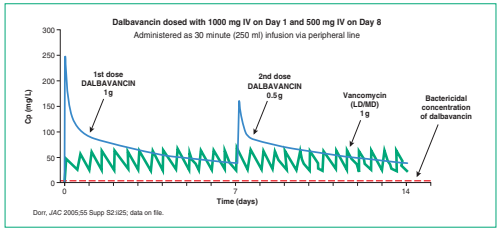
Figure 1. Dalbavancin Mechanism of Action



Economou NJ, et al. *J Amer Chem Soc* 2012;134:4637-4635.

- The mechanism of action of dalbavancin involves the interruption of cell wall synthesis by binding to the terminal D-alanyl-D-alanine of the stem peptide in nascent cell wall peptidoglycan, thereby preventing cross-linking (transpeptidation and transglycosylation) of disaccharide subunits resulting in bacterial cell death.

Figure 2. Dalbavancin: Once-Weekly Dosing Regimen



Dorr, *JAC* 2005;55 Supp S2:ii25; data on file.

Table 1. Pivotal Efficacy Studies Conducted During Phase 2/3 Development of Dalbavancin

Study Number and Title	Treatment	Total Dosed	Enrolled in Dalbavancin group	Bacteremia in Dalbavancin Patients
Pivotal Phase 3 Efficacy Studies				
VER001-9 A phase 3, randomized, double-blind, multi-center study to evaluate the safety and efficacy of dalbavancin versus linezolid in the treatment of complicated skin and soft tissue infections with suspected or confirmed gram-positive bacterial pathogens.	**IV Dalbavancin:** 1000 mg on Day 1, 500 mg on Day 8, possible switch to oral placebo q12h, treatment duration 14 days. **IV Linezolid:** 600 mg q12h. Possible switch to oral linezolid 600 mg q12h, treatment duration 14 days.	854	571 (71 at 1000 mg) (500 at 1500 mg)	12
DUR001-301 A phase 3, randomized, double-blind, double-dummy study to compare the efficacy and safety of dalbavancin to a comparator regimen (vancomycin with possible switch to oral linezolid) for the treatment of acute bacterial skin and skin structure infections.	**IV Dalbavancin:** 1000 mg on Day 1, 500 mg on Day 8, IV placebo q12h to match vancomycin, possible switch to oral placebo q12h after 3 days of IV therapy, treatment duration 10–14 days. **IV Comparator:** IV vancomycin 1000 mg or 15 mg/kg q12h, IV placebo to match dalbavancin, possible switch to oral linezolid 600 mg q12h after 3 days of IV vancomycin therapy, treatment duration 10–14 days.	568	288	8
DUR001-302 A phase 3, randomized, double-blind, double-dummy study to compare the efficacy and safety of dalbavancin to a comparator regimen (vancomycin with possible switch to oral linezolid) for the treatment of acute bacterial skin and skin structure infections.	**IV Dalbavancin:** 1000 mg on Day 1, 500 mg on Day 8, IV placebo q12h to match vancomycin, possible switch to oral placebo q12h after 3 days of IV therapy, treatment duration 10–14 days. **IV Comparator:** IV vancomycin 1000 mg or 15 mg/kg q12h, IV placebo to match dalbavancin, possible switch to oral linezolid 600 mg q12h after 3 days of IV vancomycin therapy, treatment duration 10–14 days.	735	371	21
Supporting Efficacy Studies				
VER001-4 A phase 2, randomized, open-label, multi-center study to evaluate the safety and efficacy of dalbavancin versus vancomycin in the treatment of catheter-related bloodstream infections with suspected or confirmed gram-positive bacterial pathogens.	**IV Dalbavancin:** Weekly: 1000 mg on Day 1, 500 mg on Day 8 (n=33). Daily: 650 mg on Day 1, 65 mg on Days 2–14 (this arm was discontinued) [n=7]. 780 mg [n=1], 845 mg [n=1], 1000 mg [n=3], 1170 mg [n=1], 1500 mg [n=34]. **IV Comparator:** : IV vancomycin: 1000 mg q12h, or dose-adjusted for renal impairment. Could switch to IV nafcillin or oxacillin 2 g q4h or q6h after pathogen identification and susceptibility testing.	74	40	26
VER001-5 A phase 2, pilot, randomized, open label, multi-center study to evaluate the safety and efficacy of dalbavancin versus investigator/physician-designated comparator in skin and soft tissue infection.	**IV Dalbavancin:** Single dose [n=20]: 1100 mg on Day 1; Multiple dose [n=21]: 1000 mg on Day 1, 500 mg on Day 8. 1000 mg [n=1], 1100 mg [n=20], 1500 mg [n=20]. **IV Comparator:** Standard Antibiotic Therapy: as defined by investigator prior to randomization, given for 7 to 21 days.	62	41	0
VER001-8 A phase 3, randomized, double-blind, multi-center study to evaluate the safety and efficacy of dalbavancin versus cefazolin in the treatment of uncomplicated skin and soft tissue infection with suspected or confirmed gram-positive bacterial pathogens.	**IV Dalbavancin:** 1000 mg on Day 1, option to add 500 mg dose on Day 8, possible switch to oral placebo q8h, treatment duration 7 or 14 days. 1000 mg [n=273], 1500 mg [n=94]. **IV Comparator:** IV Cefazolin: 500 mg q8h, possible switch to oral cephalexin 500 mg q6h, treatment duration 7 or 14 days.	553	367	3
VER001-16 A phase 3, randomized, open-label, multi-center study to evaluate the safety and efficacy of dalbavancin vs. vancomycin in the treatment of complicated or uncomplicated skin and soft tissue infections with suspected or confirmed methicillin resistant *Staphylococcus aureus* (MRSA).	**IV Dalbavancin:** 1000 mg on Day 1, 500 mg on Day 8 (optional for uSSSI), 1000 mg [n=50], 1500 mg [n=57]. **IV Comparator:** IV Vancomycin: 1000 mg q12h, or dose-adjusted for renal impairment; possible switch to oral therapy for 14 days. Possible switch to cephalexin 500 mg q6h if subject did not have MRSA.	156	107	1
Total		**3002**	**1785**	**71**

METHODS

- Patients enrolled in the ABSSSI, cSSSI and CRBSI studies were included in this analysis.
- Blood cultures were drawn at Baseline (prior to study drug treatment) from 2 different anatomical sites and not through an existing intravascular line.
- If positive at Baseline, blood cultures were to be repeated every 48–72 hours until negative.
- If clinically indicated, blood cultures were to be collected at time of treatment discontinuation or for determination of treatment failure.
- Patients in whom *S. aureus* was identified in blood cultures taken at the baseline visit were selected for further assessment.
- Clearance of bacteremia is provided for those patients with at least one of the required follow-up post-baseline blood cultures.

RESULTS

Table 2. Documented Clearance and Clinical Outcome of *S. aureus* Bacteremia

	Dalbavancin		Comparator	
Infection	**Clearance of bacteremia[1]**	**Clinical success at EOT[2]**	**Clearance of bacteremia[1]**	**Clinical success at EOT[2]**
ABSSSI				
DISCOVER 1	3/3	2/3	2/3	3/3
DISCOVER 2	7/7	5/6	6/6	5/6
cSSSI	4/4	3/4	2/2	2/2
Catheter related bloodstream infection	10/10	9/9	9/9	8/12
Total	**24/24 (100%)**	**19/22 (86.4%)**	**19/20 (95%)**	**18/23 (78.3%)**

EOT = End of Treatment
[1] Patients with follow-up blood culture [post-baseline)
[2] Clinically evaluable population (those with missing data excluded from analysis) of patients with a positive blood culture at baseline

Table 3. Documented Clearance and Clinical Outcome of all Gram Positive Bacteremia

	Dalbavancin		Comparator	
Infection	**Clearance of bacteremia[1]**	**Clinical success at EOT[2]**	**Clearance of bacteremia[1]**	**Clinical success at EOT[2]**
ABSSSI				
DISCOVER 1	5/5	4/8	3/4	6/6
DISCOVER 2	17/17	15/20	9/10	10/13
cSSSI	12/12	8/10	6/6	4/5
Catheter related bloodstream infection	24/24	24/24	23/25	26/28
VER001-8	2/2	2/2	0/1	0
VER001-16	1/1	1/1	0	0

EOT = End of Treatment
[1] Patients with follow-up blood culture [post-baseline)
[2] Clinically evaluable population (those with missing data excluded from analysis) of patients with a positive blood culture at baseline

DISCUSSION

- None of the clinical failures in the dalbavancin group was a result of persistent underlying bacteremia
- Among the reasons for clinical failure were:
  - physician's reluctance to treat the bacteremia in the context of a clinical trial leading to discontinuation from blinded study drug therapy
  - Lack of resolution of underlying skin infection
  - Associated adverse event
  - Considered indeterminate due to presence of gram-negative bacteremia at baseline
- 61/71 (86%) of patients had follow up blood cultures available for assessment

CONCLUSIONS

- A total of 71 patients treated with dalbavancin in the clinical development program had baseline gram-positive bacteremia
- All patients in the dalbavancin group with baseline gram-positive bacteremia, including those with *S. aureus*, who had follow-up blood cultures available had documented clearance of their bacteremia and clinical outcome rates at EOT similar to comparators
- These data support the use of dalbavancin in patients with skin infections who also have a bacteremia at baseline

Presented at IDWeek 2013, October 2–6, 2013, San Francisco, California, USA.
Research funding provided by Durata Therapeutics, Inc.