

DALBAVANCIN VS LINEZOLID FOR TREATMENT OF ACUTE BACTERIAL INFECTIONS OF THE SKIN: A COMPARISON OF EARLY AND STANDARD OUTCOME MEASURES IN STUDY VER001-9

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ABSTRACT

Objectives: FDA Draft Guidance for treatment of skin infections has recommended the implementation of an outcome assessment at 48–72 hours post baseline of the cessation of spread plus resolution of elevated temperatures as the primary point for comparisons in noninferiority studies, rather than the test of cure historically measured post therapy. We performed a retrospective analysis of this new endpoint in a previously completed registrational trial and compared the outcome to the protocol prespecified primary endpoint of clinical response at Day 28.

Methods: The primary endpoint at Day 28 was originally defined in the clinically evaluable population which was then further analyzed in subgroups of patients meeting the newly defined FDA inclusion criteria (surface area of lesion >75cm²; one sign of either fever, elevated white blood cell count or bacteremia) as well as the early response endpoint at Day 3/4 (lesion size the same or smaller relative to baseline and temperature <37.6°C).

Results: The difference in response rates between the dalbavancin and linezolid treated patients was similar in all analyses of early response based on lesion size and temperature compared to the historical assessment of clinical response at the end of therapy. The early response point estimates that include temperature assessments were lower than the overall clinical response at end of therapy. The difference in cure rates between treatment regimens as assessed by the early response endpoint did not further differentiate between those regimens relative to the cure rates determined by clinical response at the end of therapy.

Conclusions: Dalbavancin noninferiority relative to linezolid as assessed by the prespecified primary analysis is reinforced with an early responder analysis performed at Day 3/4, with very similar differences in the point estimate regardless of outcome measure.

OBJECTIVES

- Perform a retrospective analysis of the performance of the new FDA Draft Guidance early responder endpoint in a previously completed registrational trial of complicated skin and skin structure infections (SSSI) (new FDA terminology: Acute Bacterial SSSI, ABSSSI)
- Compare the outcome of that early responder analysis to the protocol's pre-specified primary endpoint of clinical response at the Test-of-Cure (TOC) visit at Study Day 28
- Compare the early responder analysis results to FDA's proposed assessment of Clinical Response at End of Treatment (EOT)

METHODS

Study Design and Treatments:

- Randomized, double-blind study conducted in 7 countries from January 2003 through May 2004
- Patients randomized 2:1 to receive either of the following:
 - Dalbavancin, 1000-mg on day 1 followed by 500-mg on day 8, with a possible switch to oral placebo
 - Linezolid 600 mg intravenously every 12 h, with a possible switch to orally administered linezolid for 14 days

Primary Endpoint:

- Protocol-specified primary endpoint: Clinical success in the clinically evaluable (CE) population at Day 28, the TOC visit (i.e., signs and symptoms of SSSI improved so no further antibacterial therapy warranted)
 - Clinically evaluable patients received at least 72 h of treatment with the blinded study medication, did not have an indeterminate clinical response, and fulfilled all other protocol requirements relating to concurrent use of antibacterials, surgical intervention of the SSSI, and efficacy-related inclusion/exclusion criteria
 - For this reanalysis, the primary endpoint in the CE population was further analyzed in subgroups of patients meeting the newly defined FDA inclusion criteria, specifically: surface area of lesion >75 cm² or >50 cm² if on face AND one sign of either fever, elevated white blood cell count or bacteremia
- FDA early response endpoint: Success at Day 3 or 4, defined as an ABSSSI lesion size the same or smaller than at baseline (i.e., "cessation of lesion spread") and temperature <37.6°C
 - The analysis population was the intent-to-treat (ITT) population excluding patients with missing data for the skin lesion size
 - Failures included death or receipt of another potentially effective antibiotic
 - For this re-analysis, patients with missing data for skin lesion size or temperature were removed from the analysis
- Data are shown for the population defined by the new FDA inclusion criteria
- The Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for an early response or non-response was calculated using the EOT response in the original analysis as the gold standard

RESULTS

Table 1. Demographics and Baseline Characteristics*

	Dalbavancin (N=135)	Linezolid (N=85)
Age (years)		
n	135	85
Mean	47.10	47.00
SD	15.430	16.410
Median	46.00	45.00
Min, Max	19, 82	18, 90
Gender		
Male, n (%)	88 (65.2)	49 (57.6)
Female, n (%)	47 (34.8)	36 (42.4)
Race/Ethnicity		
Caucasian, n (%)	92 (68.1)	61 (71.8)
African American, n (%)	13 (9.6)	6 (7.1)
Asian, n (%)	0 (0.0)	2 (2.4)
Hispanic/Latino, n (%)	28 (20.7)	15 (17.6)
Other, n (%)	2 (1.5)	1 (1.2)
BMI (kg/m²)		
n	133	84
Mean	33.25	31.32
SD	11.134	9.730
Median	30.30	29.60
Min, Max	17.10, 72.90	13.40, 66.60

*FDA-defined population, i.e. with lesion >75 cm² and one systemic sign

Table 2. Description and Location of the ABSSSI

	Dalbavancin (N=135)	Linezolid (N=85)
Type of Infection		
Cellulitis	52 (38.5)	29 (34.1)
Major abscess	51 (37.8)	27 (31.8)
Wound infection	20 (14.8)	14 (16.5)
Traumatic wound infection	10 (7.4)	7 (8.2)
Surgical site wound infection	10 (7.4)	7 (8.2)
Other deep soft tissue infection	12 (8.9)	15 (17.6)
Anatomical Site of Infection		
Head/neck	2 (1.5)	1 (1.2)
Face	2 (1.5)	3 (3.5)
Chest	2 (1.5)	2 (2.4)
Abdomen	9 (6.7)	10 (11.8)
Hand	7 (5.2)	8 (9.4)
Arm (upper and lower)	27 (20.0)	12 (14.1)
Foot	9 (6.7)	6 (7.1)
Leg (upper and lower)	51 (37.8)	35 (41.2)
Groin	7 (5.2)	6 (7.1)
Buttock	17 (12.6)	3 (3.5)
Back	4 (3.0)	3 (3.5)

Table 3. ABSSSI Measurements at Baseline

	Dalbavancin (N=135)	Linezolid (N=85)
Length (cm)		
n	135	85
Mean	24.71	21.46
SD	20.517	11.270
Median	20.00	19.00
Min, Max	5.50, 200.00	7.00, 70.00
Width (cm)		
n	135	85
Mean	19.07	16.98
SD	16.869	12.127
Median	14.00	13.00
Min, Max	5.00, 150.00	2.00, 63.00
Area (cm²)		
n	135	85
Mean	769.90	438.64
SD	2670.872	559.298
Median	264.00	252.00
Min, Max	72.0, 30000.00	56.00, 2767.10

Table 5. FDA Primary Outcome Measure: Cessation of Skin Lesion Spread and Afebrile

Timepoint	Analysis Population	Endpoint	Dalbavancin, n/N (%)	Linezolid, n/N (%)	Difference, 95% CI
Day 3/4	Clinically evaluable	Cessation of spread + afebrile	283/340 (83.2)	155/178 (87.1)	-3.8 (-10.6, 2.9)
		Cessation of spread	312/340 (91.8)	165/178 (92.7)	-0.9 (-6.2, 4.3)
	+ >75 cm ² lesions*	Cessation of spread + afebrile	212/258 (82.2)	109/135 (80.7)	1.4 (-7.3, 10.1)
		Cessation of spread	237/258 (91.9)	121/135 (89.6)	2.2 (-4.5, 8.9)
		Cessation of spread + afebrile	103/135 (76.3)	67/85 (78.8)	-2.5 (-14.8, 9.7)
		Cessation of spread	120/135 (88.9)	76/85 (89.4)	-0.5 (-9.9, 8.9)
Day 28	Clinically evaluable	Clinical response at test of cure	386/434 (88.9)	206/226 (91.2)	-2.2 (-7.3, 2.9)

*Includes facial lesions >50 cm²

Table 6. Reasons for Non-Response FDA Primary Efficacy Outcome Measure

Reason	Dalbavancin (N=135) n (%)	Linezolid (N=85) n (%)
Nonresponders, N1	32	18
Increase in lesion size	9 (28.1)	7 (38.9)
Increase by >0–5%	0 (0.0)	1 (5.6)
Increase by >5–10%	1 (3.1)	0 (0.0)
Increase by >10–15%	1 (3.1)	0 (0.0)
Increase by >20%	7 (21.9)	6 (33.3)
Temperature of >37.6°C	23 (71.9)	14 (77.8)
Death	1 (3.1)	0 (0.0)
Received systemic antibiotic with gram-positive activity	8 (25.0)	4 (22.2)

Table 8. Percent Change from Baseline in Lesion Area for Responders by Infection Type

Reason	Cellulitis (N=81)	Major Abscess (N=78)	Wound Infection (N=34)	Other Infection Type (N=27)
Responders, N1	61 (75.3%)	68 (87.2%)	21 (61.8%)	20 (74.1%)
No change	3 (4.9%)	1 (1.5%)	3 (14.3%)	0 (0%)
>0–5% decrease	4 (6.6%)	0 (0%)	0 (0%)	0 (0%)
>5–10% decrease	3 (4.9%)	2 (2.9%)	0 (0%)	1 (5.0%)
>10–15% decrease	3 (4.9%)	1 (1.5%)	0 (0%)	0 (0%)
>15–20% decrease	0 (0%)	3 (4.4%)	1 (4.8%)	1 (5.0%)
>20% decrease	48 (78.7%)	61 (89.7%)	17 (81.0%)	18 (90%)

Table 4. Systemic Signs of ABSSSI at Baseline

	Dalbavancin (N=135)	Linezolid (N=85)
Temperature (°C)		
N1	135	85
Mean	37.99	37.96
SD	0.770	0.891
Median	38.20	38.10
Min, Max	36.20, 39.90	35.90, 40.80
Temperature (≥38°C), n (%)	81 (60.0)	50 (58.8)
WBC Count (cells/mm³)		
N1	133	83
Mean	14.07	14.10
SD	5.517	5.192
Median	13.30	13.80
Min, Max	2.90, 34.80	4.50, 35.30
WBC Count >12,000 cells/mm ³ , n (%)	98 (73.7)	61 (73.5)
Bands (%)		
N1	66	33
Mean	3.70	6.30
SD	8.930	8.240
Median	0.00	1.00
Min, Max	0.00, 50.00	0.00, 24.00
Bands ≥10%, n (%)	9 (13.6)	10 (30.3)

Table 9. Mean Change from Baseline in Lesion Area by Infection Type

	All Patients (N=220)
Cellulitis	
n	81
Mean	-266.55
SD	476.772
Median	-144.00
Min, Max	-2070.00, 873.80
Mean % reduction from baseline	55.2
Major Abscess	
n	78
Mean	-133.87
SD	156.99
Median	-97.50
Min, Max	-652.00, 679.00
Mean % reduction from baseline	63.2
Wound Infection	
n	34
Mean	-220.65
SD	297.248
Median	-94.60
Min, Max	-1089.00, 64.00
Mean % reduction from baseline	57.8
Other Deep Soft Tissue Infection	
n	27
Mean	-194.11
SD	395.147
Median	-96.25
Min, Max	-1720.00, 786.00
Mean % reduction from baseline	61.8

Table 10. Early Response at Day 3/4 vs. Clinical Response at End of Therapy

	All Treated (N=220)	
	Clinical Success at EOT (N1=187)	Clinical Failure at EOT (N1=33)
Early Clinical Response		
Responder, n/N1 (%)	154 (70.0%)	16 (7.3%)
Nonresponder, n/N1 (%)	33 (15.0%)	17 (7.7%)

CONCLUSIONS

- Dalbavancin noninferiority relative to linezolid as assessed by the prespecified primary analysis is reinforced with an early responder analysis performed at Day 3/4, with very similar differences in the point estimate regardless of outcome measure.
- The addition of resolution of fever to the early response definition did not further differentiate between treatment regimens beyond lesion measurement alone.
- Most patients who were an early responder were also a clinical success at EOT (PPV of response at Day 3/4=90.6%). However, most patients who were an early nonresponder became a clinical success at EOT (NPV of non-response at Day 3/4=34%).
- In our analysis, the early response endpoint had limitations, specifically a low NPV.
- A validated measure of response at EOT and TOC that is acceptable to FDA and other regulatory agencies would be more intuitive to clinicians and more relevant to patients.

REFERENCES

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