Abstract: 5047
Linezolid Vs Vancomycin In the Treatment of Nosocomial Pneumonia Proven Due to Methicillin-Resistant *Staphylococcus aureus*

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Disclosures – Jean Chastre, MD

- Pfizer
  - Study investigator
  - Consultant
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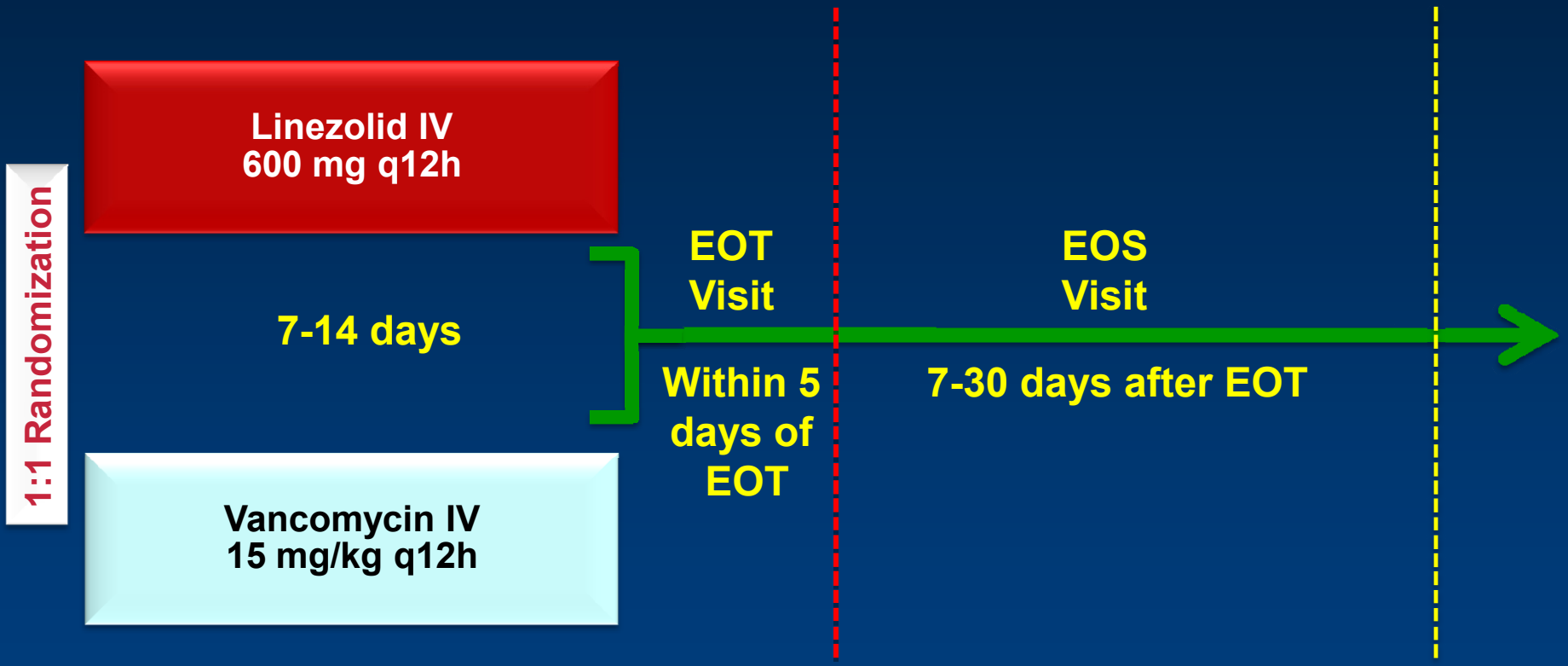
Study Description and Objective

- Phase 4, double-blind, randomized, comparator-controlled, multi-center study:
  - Linezolid compared to vancomycin in subjects with nosocomial pneumonia (including HCAP) caused by culture-proven MRSA
- Vancomycin dose based on weight, CrCl and levels
- Non-inferiority trial with nested superiority hypothesis

Study Overview

- 156 Centers
  - 90 US (58%)
  - 28 EU (18%)
  - 16 Latin America (10%)
  - 13 Asia (8%)
  - 9 Other (6%)
- 1225 Patients enrolled
- 448 culture-positive for MRSA (mITT)
- 348 evaluable at End-of-Study (PP)
  - 339 in primary analysis

Study Design



- Vancomycin dose adjusted by unblinded pharmacist based on renal function and trough concentration
- Initial Cefepime or other Gram-negative coverage (not MRSA active) required

Main Endpoints

Primary

- Clinical response in evaluable MRSA subjects at the End of Study (EOS) visit in Per Protocol Group (PP)

Secondary

- Clinical response at EOS in mITT group
- Clinical response at End of Therapy (EOT) – mITT and PP
- Microbiologic response at EOT and EOS – mITT and PP
- Survival status through 60 days post-treatment
- Safety analyses in the intent-to-treat population (MRSA and non-MRSA)

Clinical Assessments: Definitions

Cure: Resolution of clinical signs and symptoms of pneumonia

- No additional antibiotics required
- 5 days minimum treatment required for success

Improvement: Improvement in 2 or more clinical S/S of pneumonia

- No additional MRSA-active antibiotics required (used only at the EOT)

Failure (one of the following):

- Persistence or progression of clinical signs/symptoms of pneumonia after at least 2d (48h) of treatment
- Progression of radiographic abnormalities
- Development of new pulmonary or extrapulmonary findings consistent with active infection

Unknown: Extenuating circumstances precluded classification to one of the above

Those who received antibiotics active in-vitro against their specific MRSA for any reason were considered failures (and carried forward as failures)

Analysis Sets

Intent-to-treat (ITT)

- All subjects who received at least 1 dose of study drug
- Included non-MRSA patients
- Safety analysis only

Modified intent-to-treat (mITT)

- ITT subjects who received at least 1 dose of study drug and had a positive baseline MRSA culture

Per protocol (PP)

- Key inclusion/exclusion criteria
- Adequate compliance
- No prohibited concomitant meds
- EOT/EOS visits within windows

Patient Characteristics: PP

	Linezolid n=172 n (%)	Vancomycin n=176 n (%)
Sex		
Male (%)	116 (67.4)	112 (63.6)
Female (%)	56 (32.6)	64 (36.4)
Race:		
White (%)	119 (69.2)	112 (63.6)
Black (%)	18 (10.5)	28 (15.9)
Asian (%)	27 (15.7)	28 (15.9)
Ventilated at Baseline	125 (68.3)	140 (74.5)
Bacteremic at Baseline	10 (5.5)	20 (10.6)
Mean	Linezolid n=172	Vancomycin n=176
Age (years)	60.7	61.6
Weight (kg)	78.1	76.5
Baseline Apache II Score (s.e.)	17.2 (0.5)	17.4 (0.5)
Baseline modified CPIS Score (s.e.)	9.7 (0.2)	9.4 (0.2)

Vancomycin Trough Plasma Concentrations: PP

Treatment Day	n	Mean concentration (μg/mL)	Median concentration (μg/mL)	Concentration range (μg/mL)
3	140	14.1	12.3	2.8 – 50.8
6	90	16.9	14.7	2.7 – 45.0
9	33	17.4	16.1	2.0 – 46.9

As a double-blind study, only the research pharmacist and unblinded monitor were aware of the levels

Primary Efficacy Endpoint: Per Protocol (PP) at End of Study (EOS)

	Linezolid n (%)	Vancomycin n (%)	P-Value	95% CI
Subjects	165 (100)	174 (100)		
Success/Cure	95 (57.6)	81 (46.6)	0.042	0.5%, 21.6%
Failure	70 (42.4)	93 (53.4)		
Unknown*	7	2		

*Excluded from analysis.

Secondary Efficacy Point: mITT at EOS

	Linezolid n=186 n (%)	Vancomycin n=205 n (%)	P-Value	95% CI
Success/Cure	102 (54.8)	92 (44.9)	0.049	0.1%, 19.8%
Failure	84 (45.2)	113 (55.1)		
Unknown*	38	19		

*Excluded from analysis

Secondary Efficacy Endpoint: PP at EOT

	Linezolid n=180 n (%)	Vancomycin n=186 n (%)	P-Value	95% CI
Success (Cure + Improvement)	150 (83.3)	130 (69.9)	0.002	4.9%. 22.0%
Failure	30 (16.7)	56 (30.1)		
Unknown*	3	2		

*Excluded from analysis.

Secondary Efficacy Point: mITT at EOT

	Linezolid n=201 n (%)	Vancomycin n=214 n (%)	P-Value	95% CI
Success (Cure + Improvement)	161 (80.1)	145 (67.8)	0.004	4.0%, 20.7%
Failure	40 (19.9)	69 (32.2)		
Unknown*	23	10		

*Excluded from analysis

Clinical Response by Maximum Vancomycin Trough Concentrations at Either Day 3, 6, or 9 (mITT at EOS)

	0-11.35 (μg/mL) n=41 n (%)	>11.35-15 (μg/mL) n=42 n (%)	>15-22.2 (μg/mL) n=36 n (%)	>22.2 (μg/mL) n=38 n (%)
Success	20 (48.8)	20 (47.6)	17 (47.2)	17 (44.7)
Failure	21 (51.2)	22 (52.4)	19 (52.8)	21 (55.3)

As a double-blind study, only the research pharmacist and unblinded monitor were aware of the assignment.

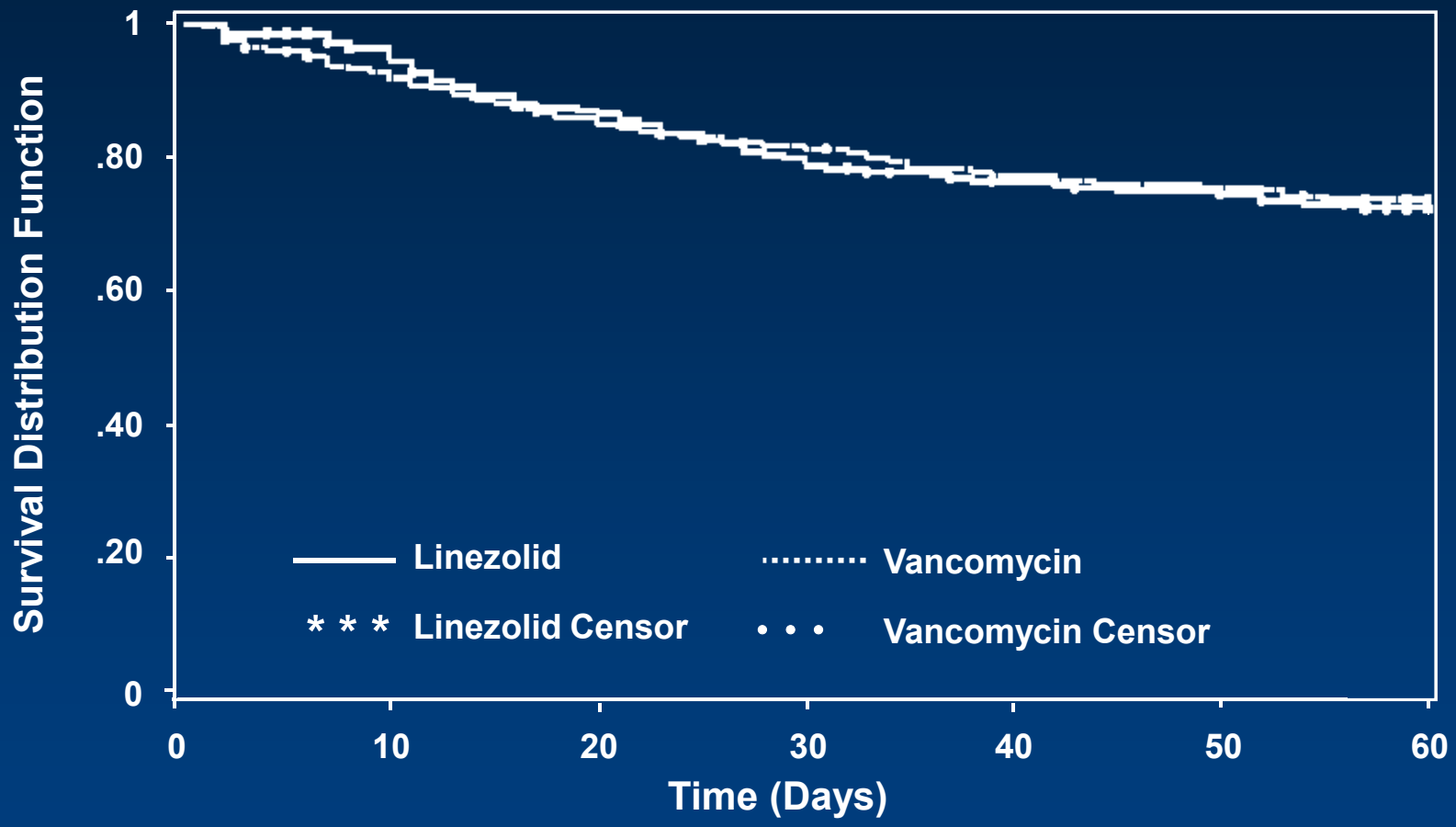
Microbiological Response at EOT: PP

	Per Protocol	
	Linezolid n=182 n (%)	Vanco n=188 n (%)
Subjects in analysis	182 (100)	188 (100)
Success	149 (81.9)	114 (60.6)
Eradication	76	59
Presumed eradication	73	55
Failure	33 (18.1)	74 (39.4)
Persistence	16	50
Presumed persistence	17	24
Missing/indeterminate	1	0

*Missing and indeterminate excluded from analysis

PP EOT Success: p-value = <0.001 95% CI (12.3%, 30.2%)

Mortality: Kaplan-Meier Plot – 60 Days: mITT



94 subject deaths (15.7%) in linezolid arm
100 subject deaths (17.0%) in vancomycin arm

Adverse Events* of Interest
All Causality: ITT

Adverse Event	Linezolid n=597 n (%)	Vancomycin n=587 n (%)
Anemia	30 (5.2)	42 (7.2)
Renal failure/azotemia	23 (3.8)	42 (7.2)
Cardiac arrest	11 (1.8)	13 (2.2)
Thrombocytopenia	8 (1.3)	13 (2.2)
Pancreatitis	5 (0.8)	1 (0.2)
Polyneuropathy	2 (0.3)	0
Neutropenia	2 (0.3)	1 (0.2)
Pancytopenia	2 (0.3)	1 (0.2)
Acute myocardial infarction	0	2 (0.3)
Paresthesia	0	1 (0.2)

*Investigator reported Events to study safety database

Conclusions

- For the primary endpoint, clinical response in PP at EOS, linezolid achieved a statistically significantly higher success rate compared to vancomycin
- Similar results were observed for clinical and microbiological response at EOS and EOT in both PP and mITT populations
- Overall, linezolid demonstrated an acceptable safety and tolerability profile for the treatment of proven MRSA nosocomial pneumonia

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