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Oritavancin Program Results

July 2nd 2013

Presenters

Greg Moeck PhD | Background and rationale
Dimitri Goundis DPhil | Clinical program results
Clive Meanwell MD PhD | Discussion

Oritavancin

Overview of the development program

- Background and Rationale — Greg Moeck
- Phase III Clinical Studies — Dimitri Goundis
  - Objectives
  - Patients and Methods
  - Results
  - Conclusions
- Discussion — Clive Meanwell

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Oritavancin Program Results

Background and Rationale

Greg Moeck PhD

Background

Staphylococcus aureus including MRSA infections

478,000 hospitalizations in U.S. hospitals 2007

- 278,000 related to MRSA
- 64% of *S. aureus* infections in U.S. ICUs were MRSA by 2004

94,000 persons first invasive MRSA - 19,000 died 2005

14 million outpatient healthcare visits for suspected *S. aureus* skin and soft tissue infections in US 2005

Klein E et al. *Emerging Infectious Diseases.* 2007;13:1840-6
Klevens RM et al. *Clinical Infectious Diseases* 2006;42:389-91
Klevens et al. *Journal of the American Medical Association* 2007;298(15):1763-1771
Hersh AL et al. *Arch Intern Med*. 2008;168:1585-91

Background

Oritavancin

Bacteriocidal lipoglycopeptide antibiotic for IV use

Three mechanisms of action:

- Inhibits two key steps of cell wall synthesis:
  - Transglycosylation
  - Transpeptidation
- Disrupts bacterial membrane integrity

Differentiated from vancomycin

- Increased potency and expanded Gram-positive spectrum
- Concentration-dependence

Background

Oritavancin

High level potency against important G+ organisms

	MIC_{90} (µg/mL)			
Pathogen	**Oritavancin**	Vancomycin	Daptomycin	Linezolid
S. aureus	**0.06**	1	0.5	2
MSSA	**0.06**	1	0.5	2
MRSA	**0.06**	1	0.5	1
β streptococci	**0.12**	0.5	0.25	1
E. faecalis	**0.06**	2	1	2
E. faecium	**0.06**	>16	2	2

US and European isolates collected between 2010-2012

Concentration-dependent killing

In vitro time-kill study with *S. aureus*

Effect on NRS384 CA-MRSA (USA300)

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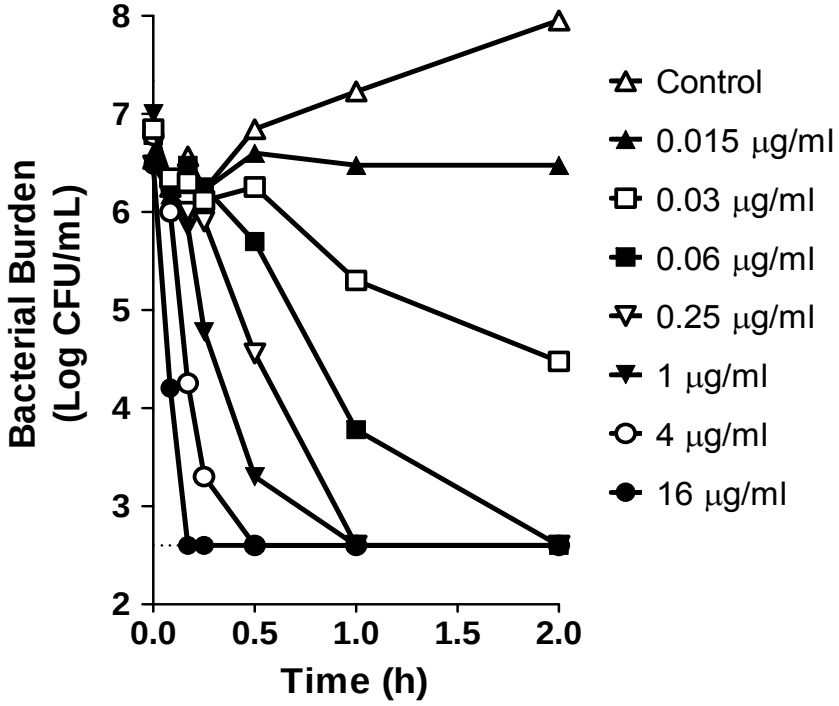
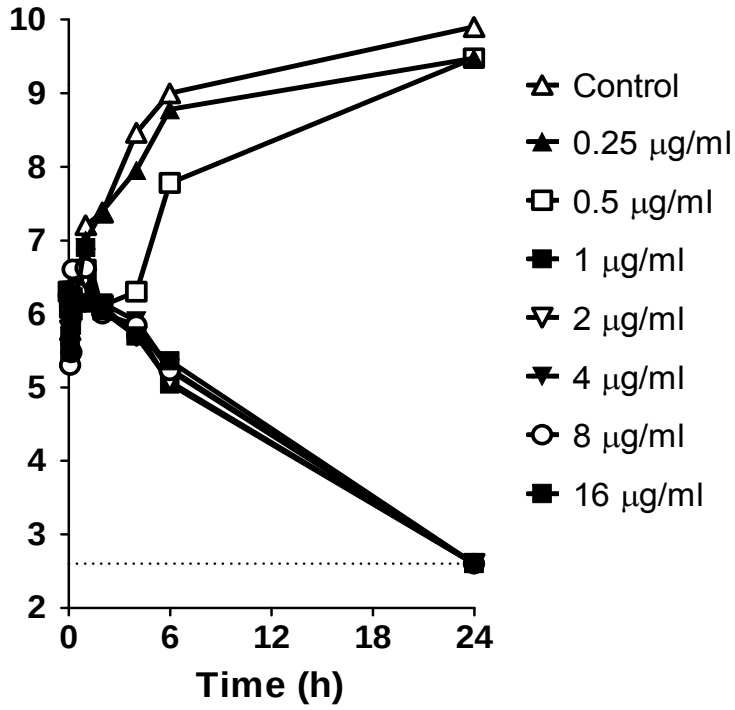


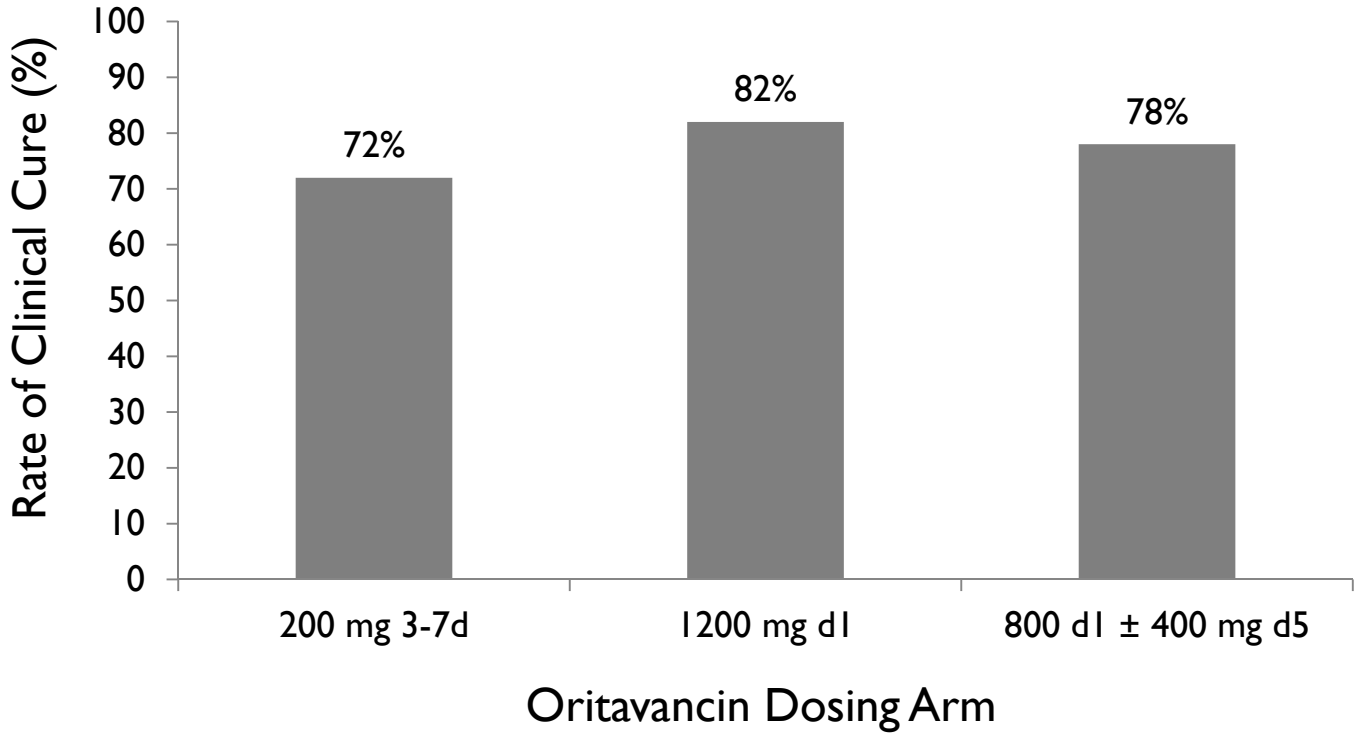
Vancomycin



Clinical proof of concept

SIMPLIFI Phase II Study in ABSSSI

Clinical cure in clinically evaluable patients



Dunbar et al. AAC 2011; 55: 3476-84

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Phase III Clinical Studies

Dimitri Goundis DPhil

Oritavancin Phase III Clinical Studies

SOLO program overview

Two identical double-blind randomized controlled studies

ABSSSI due to gram positive organisms including MRSA

Active comparator – vancomycin

Recruitment in United States, Europe and Asia

Protocols based on current regulatory guidance

Non-inferiority design

Oritavancin Phase III Clinical Studies

Primary objectives of both studies for FDA | EMA

FDA: To determine non-inferiority for the primary efficacy outcome (as defined by the cessation of spread or reduction in size of the baseline lesion, absence of fever and no rescue antibiotic medication) at Early Clinical Evaluation (ECE) at 48 to 72 hours with single dose IV oritavancin compared with IV vancomycin for 7 to 10 days in the modified intent-to-treat (mITT) population

EMA: To determine non-inferiority for the investigator-assessed clinical cure of treatment with single-dose IV oritavancin compared with IV vancomycin for 7 to 10 days at the post-therapy evaluation (PTE) visit in the mITT population

Oritavancin Phase III Clinical Studies

Patient eligibility criteria

- At least 18 years of age
- Suspected or proven gram-positive pathogen
- Requiring at least 7 days of IV therapy
- ABSSSI
  - Wound infections (either traumatic or surgical in origin)
  - Cellulitis/erysipelas
  - Major cutaneous abscess
- Each lesion at least 75 cm^2
- Signs and symptoms of systemic inflammation.

Oritavancin Phase III Clinical Studies

Treatment randomization

1:1 ratio

Oritavancin: Single 1200 mg IV dose of oritavancin followed by IV placebo for 7 to 10 days

Vancomycin: 1 g or 15 mg/kg, every 12 hours for 7 to 10 days

Aztreonam and metronidazole were permitted for gram-negative and anaerobic coverage, respectively.

Oritavancin Phase III Clinical Studies

Pre-specified endpoints (mITT)

Early – at 48-72 hours (ECE)

- **FDA primary composite outcome**
  - Cessation of spread or reduction in size of baseline lesion
  - Absence of fever
  - No rescue antibiotic medication
- **FDA exploratory outcome**
  - At least 20% reduction in lesion area

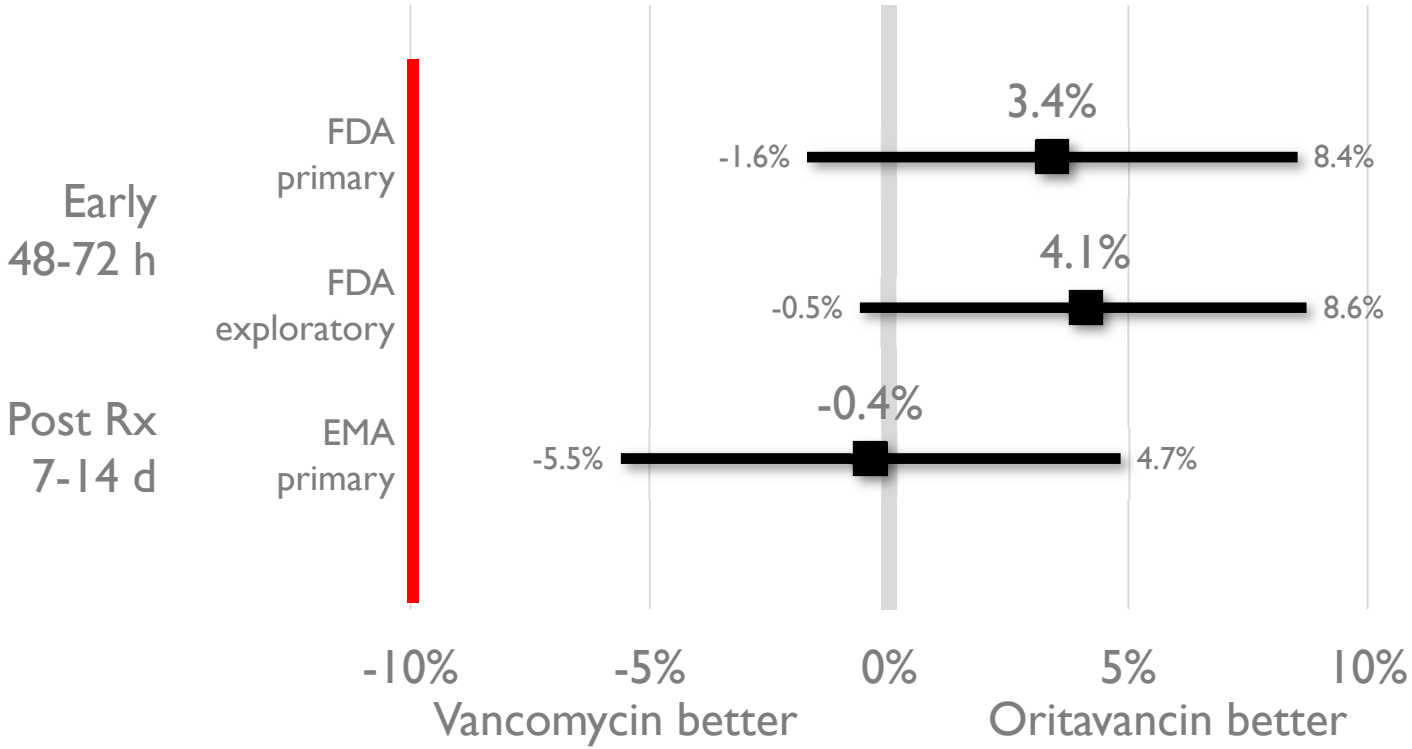
Post-treatment 7-14 days (PTE)

- **EMA primary composite outcome**
  - Investigator-assessed clinical cure

Oritavancin Phase III Clinical Studies

SOLO-I: primary efficacy (N = 954)

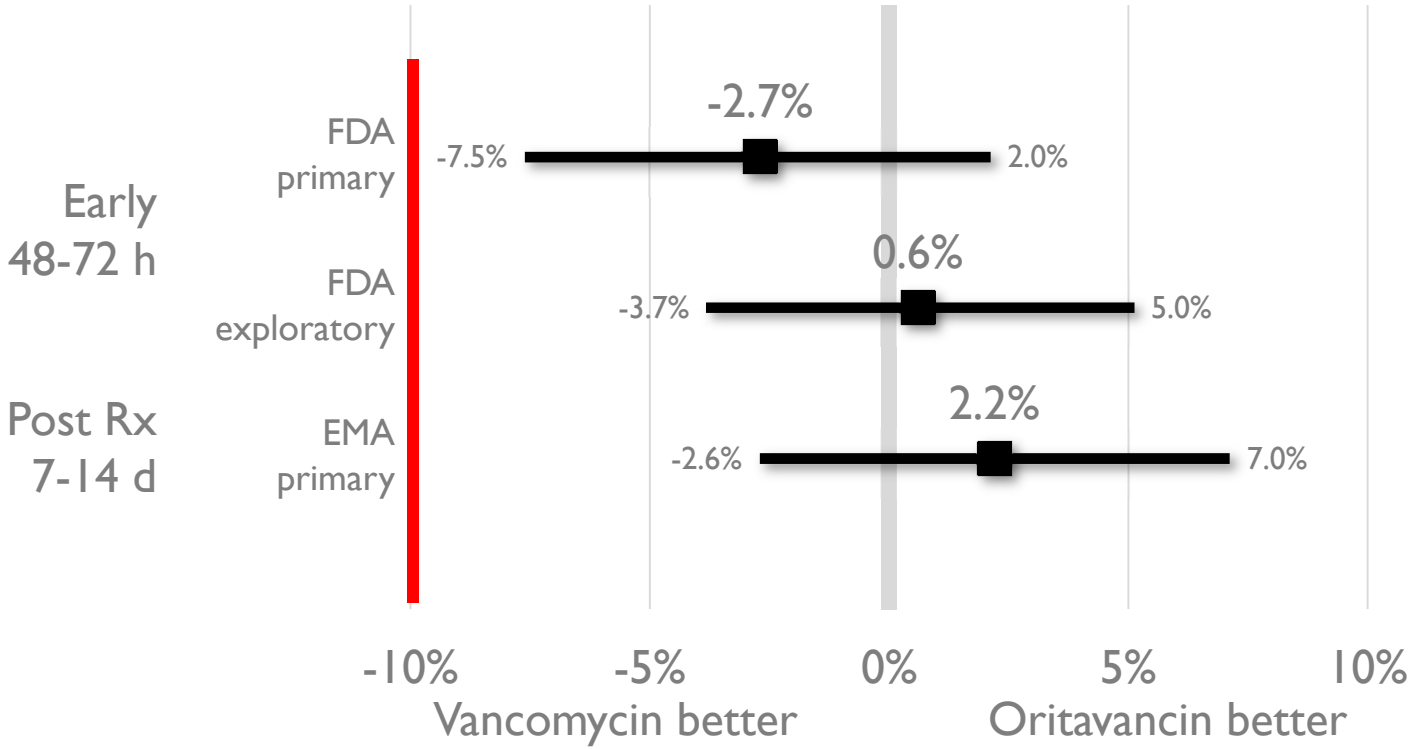
Non-inferiority margin of -10% was met



Oritavancin Phase III Clinical Studies

SOLO-II: primary efficacy (N = 1,005)

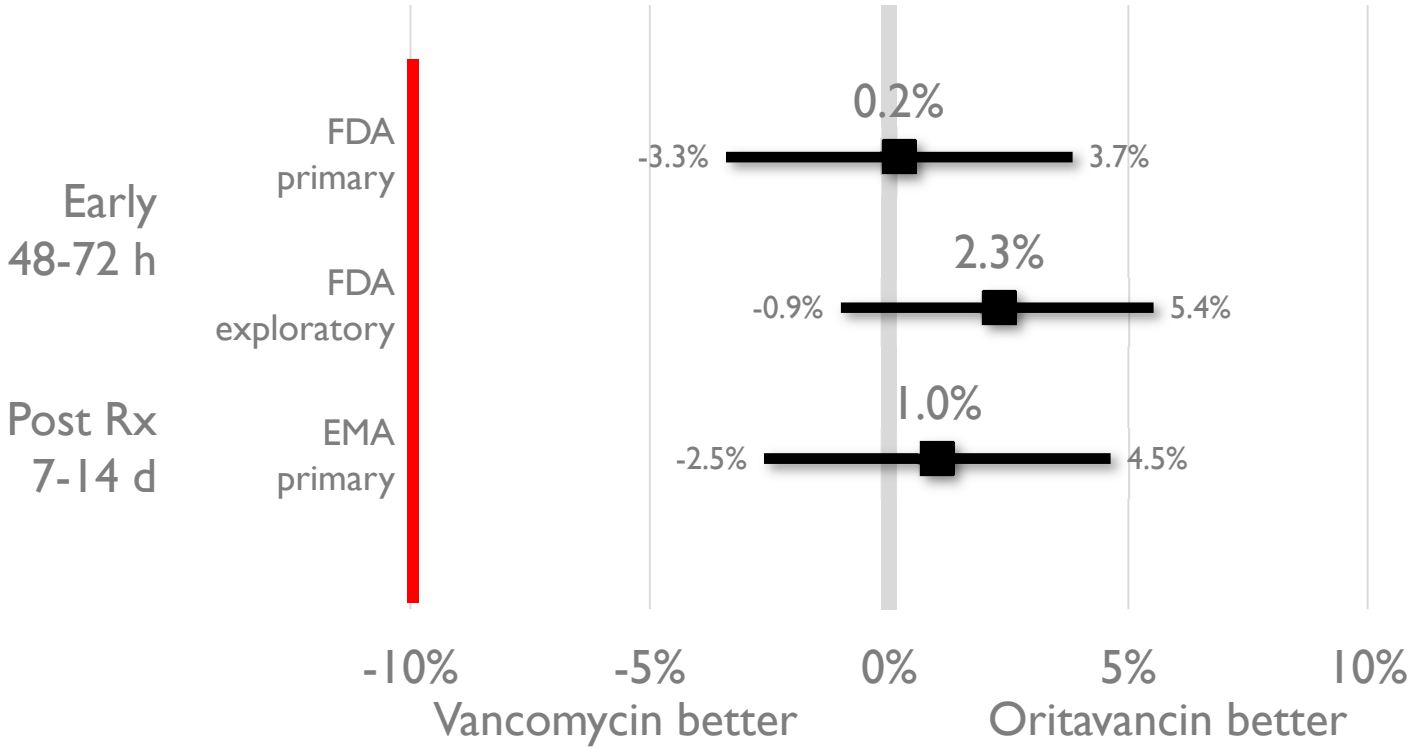
Non-inferiority margin of -10% was met



Oritavancin Phase III Clinical Studies

Combined: primary efficacy (N = 1,959)

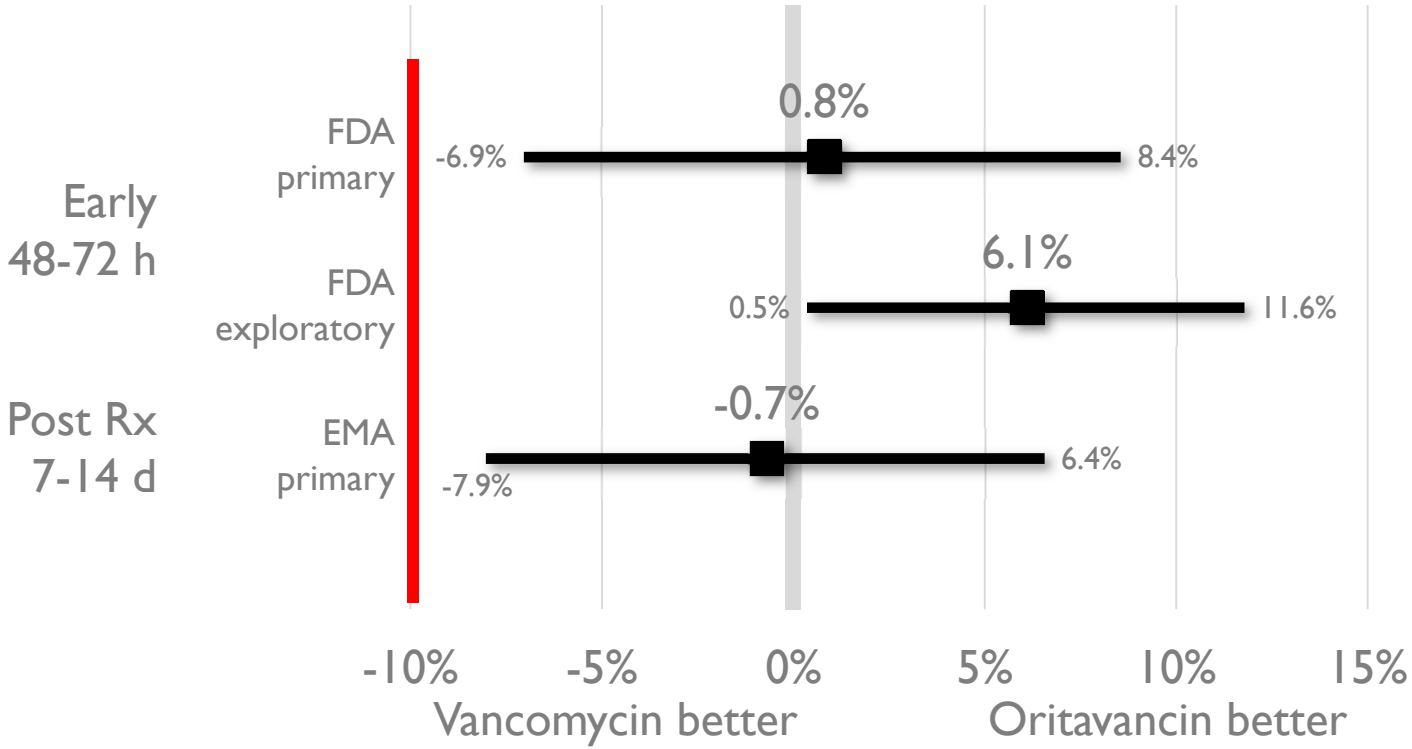
Non-inferiority margin of -10% was met



Oritavancin Phase III Clinical Studies

Combined MRSA: primary efficacy (N = 405)

Non-inferiority margin of -10% was met



Oritavancin Phase III Clinical Studies

Adverse events including 60-day follow-up period

Favorable comparative results

	SOLO-I		SOLO-II		COMBINED	
	N = 954		N = 1,005		N = 1,959	
	ORIT	VANC	ORIT	VANC	ORIT	VANC
Any AE	60%	64%	51%	50%	55%	57%
TEAEs	23%	31%	22%	26%	22%	28%
Discontinued due to AEs	4%	6%	4%	3%	4%	4%

Summary

Oritavancin met all prespecified objectives

In two double-blind, randomized, active controlled ABSSSI trials, oritavancin given as a single IV dose:

- Demonstrated clinical non-inferiority to vancomycin given intravenously twice daily for 7-10 days
- Was effective in MRSA infections
- Was associated with favorable safety results

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Discussion

Clive Meanwell MD PhD