

Anti-Infective Advisory Committee

**November 19, 2008
(Afternoon Session)**

**Targanta Therapeutics, Corp.
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Questions to the AIDAC**

ORITAVANCIN
NDA 22,153

PRESENTATION BY
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FDA
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OUTLINE

- Background
- PK Characteristics
- Study Descriptions
- Comparison of Doses in ARRI and ARRD
- Efficacy Results
- Safety Results
- Issues for Discussion

BACKGROUND

- Proposed Indication: Treatment of adults with complicated Skin and Skin Structure Infections (cSSSI) caused by susceptible isolates of the Gram-positive organisms including methicillin-resistant *Staphylococcus aureus*.
- Dosage: The proposed dose regimen for oritavancin is 200 mg (300 mg for patients weighing >110 kg) daily for 3 to 7 days.

PK characteristics of oritavancin

- Linear at doses ranging from 0.05 mg/kg to 10 mg/kg and at fixed doses ranging from 100 mg to 800 mg
- Declined to <11% of the maximum concentration within the first 24 hours
- No substantial accumulation in C_{\max} after 10 days (30% ↑) ~3 fold accumulation in C_{\min} for 10 days
- V_d of ~100L, distributes into phagocytic cells
- Oritavancin is not metabolized
- <5% of the dose is excreted in urine and <1% in feces after 14 days
- Terminal half-life is approximately 320 hours
- Blood samples to determine oritavancin concentration in plasma collected up to 14 days in Phase 1 studies

Studies

- **Study ARRI** was a Phase 3, randomized, double-blind, multicenter study in patients with cSSSI.
- Patients were randomly assigned to receive 200 mg oritavancin intravenously once daily (300 mg for patients weighing more than 110 kg [242 lbs]) followed by oral placebo, or 15 mg/kg vancomycin intravenously twice daily (or less in patients with reduced creatinine clearance) followed by oral cephalexin (1 gram twice daily) in a ratio of two oritavancin patients to one vancomycin patient.
- Randomization was stratified by disease category (wound infection, major abscess, or cellulitis).

Studies (cont)

- **Study ARRD** was a Phase 3, randomized, double-blind, multicenter study in patients with cSSSI.
- This study was a three-arm study - Oritavancin IV 3.0 mg/kg QD (max dose 400 mg) vs. Oritavancin IV 1.5 mg/kg QD vs. Vancomycin IV 15 mg/kg q12 hrs, followed by Cephalexin PO (one or two 500 mg capsules BID).
- Treatment duration was 3-7 day for the two oritavancin arms and 10-14 days for the vancomycin arm.

Comparison of Doses between ARRI and ARRD

Mean comparisons

- Data analyzed using only the ARRD 3.0 mg/kg arm, as virtually the entire 1.5 mg/kg arm will have a lower dose than 200 mg
- In ARRI, patients who weighed ≤ 110 kg received a 200 mg fixed dose, and patients who weighed > 110 kg received a 300 mg fixed dose

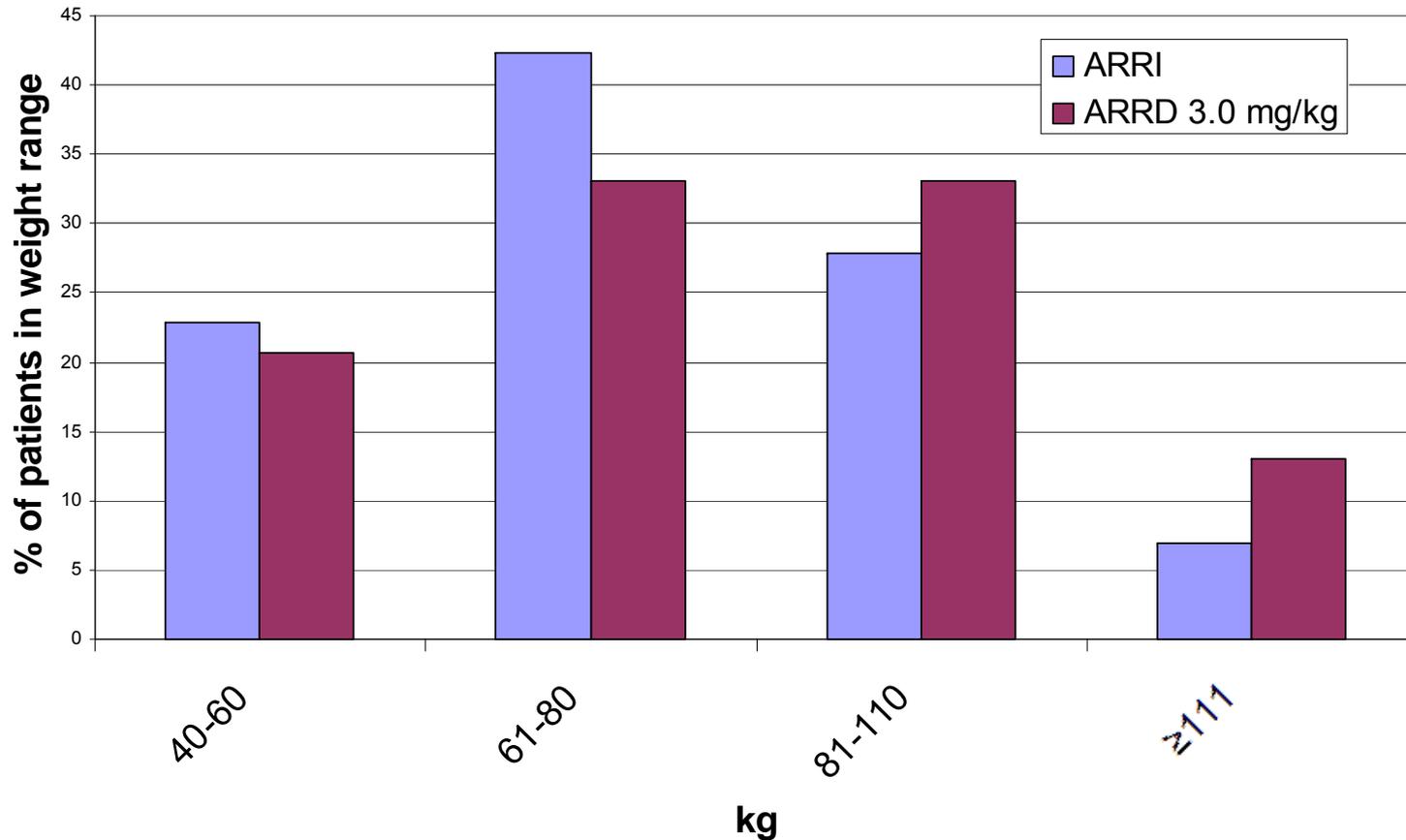
Comparison of Doses in ARRI and ARRD

	ARRI	ARRD
N of patients		
49 - 110 kg	734	139
111 - 122 kg	28	4
Dose (Mean)		
49 - 110 kg	200 mg	224 mg
111 - 122 kg	300 mg	349 mg
Range		
49 - 110 kg	200 mg	147 - 330 mg
111 - 122 kg	300 mg	333 - 366 mg

Percent of patients in ARRD who received a dose within X% of ARRI

% of ARRI Dose	Dose Range (49 - 110 kg) (111 – 122 kg)	% of patients in ARRD dosed within this range	% of patients in ARRD dosed at \leq higher dose bound
10%	180 – 220 mg	21.3%	42.0%
	270 – 330 mg		
15%	170 – 230 mg	34.9%	48.5%
	255 – 345 mg		
20%	160 – 240 mg	47.9%	55.6%
	240 – 360 mg		

Comparison of patient weight distribution in ARRD 3.0 mg/kg and ARRI



ARRI and ARRD comparison conclusions

- On average, patients in ARRD 3.0 mg/kg received a higher dose and had higher exposures as compared to patients in ARRI
- Any differences in efficacy for oritavancin between ARRD 3.0 mg/kg group and ARRI fixed dose group are not due to patients in ARRD 3.0 mg/kg receiving a lower dose

Efficacy Endpoint

STUDY ARRI

- The primary efficacy endpoint was the Sponsor-Defined Clinical Outcome (SDCO) at the First Follow-up Visit (TOC visit).
- The non-inferiority margin (NI) used in this study was 10%.

Baseline Demographics

ARRI

	ITT		CE	
Demographics	Oritavancin N=831 n (%)	Vancomycin N=415 n (%)	Oritavancin N=675 n (%)	Vancomycin N=328 n (%)
Sex				
Male	463 (55.7)	230 (55.4)	370 (54.8)	176 (53.7)
Female	368 (44.3)	185 (44.6)	305 (45.2)	152 (46.3)
Ethnic Origin				
Caucasian	413 (49.7)	208 (50.1)	351 (52.0)	172 (52.4)
African Descent	174 (20.9)	87 (21.0)	142 (21.0)	69 (21.0)
Hispanic	119 (14.3)	54 (13.0)	87 (12.9)	34 (10.4)
Other	125 (15.0)	66 (15.9)	95 (14.1)	53 (16.2)
Age (years)				
Mean (\pm SD)	48.0 (16.95)	48. (16.77)	48.2 (17.05)	49.4 (16.32)

Success/Cure Rates at TOC Visit

Study ARRI

Efficacy Endpoint/ Patient Population	Oritavancin n/N (%)	Vancomycin n/N (%)	Difference (95% CI)
Sponsor-Defined Clinical Outcome			
ITT	594/831 (71.5%)	284/415 (68.4%)	3.0 (-2.4, 8.5)*
CE	530/675 (78.5%)	249/328 (75.9%)	2.6 (-3.0, 8.2)
Investigator-Defined Clinical Outcome			
ITT	608/831 (73.2%)	291/415 (70.1%)	3.0 (-2.3, 8.4)
CE	534/675 (79.1%)	254/328 (77.4%)	1.7 (-3.8, 7.1)

*The 99.875% CI (equivalent to that from two studies) would be (-5.9, 12)

Sponsor-Defined Clinical Outcome with Identified Baseline Pathogens (MITT Population) Study ARRI

Organism	Oritavancin n/N (%)	Vancomycin n/N (%)
<i>Staphylococcus aureus</i> (All)	303/429 (70.6%)	158/222 (71.2%)
Methicillin-sensitive (MSSA)	219/286 (76.6%)	116/156 (74.4%)
Methicillin-resistant (MRSA)	66/118 (55.9%)	36/53 (67.9%)
<i>Streptococcus pyogenes</i>	74/96 (77.1%)	36/62 (58.1%)
<i>Streptococcus agalactiae</i>	20/35 (57.1%)	6/8 (75%)
<i>Streptococcus anginosus</i> group	25/38 (65.8%)	13/19 (68.4%)
Other <i>Streptococcus</i> spp	21/28 (75.0%)	12/21 (57.1%)
<i>Enterococcus faecalis</i>	23/34 (67.6%)	16/24 (66.7%)

Efficacy Endpoint (cont)

Study ARRD

- The primary efficacy endpoint was the Investigator-Defined Clinical Outcome (IDCO) at the TOC Visit.
- The efficacy analysis methods used in this study were the same as in Study ARRI except for the non-inferiority margin.
- The non-inferiority margin (NI) used in this study was 15%.

Multiplicity Issues in the primary analysis

- **Study ARRD** compared the efficacy results of the twooritavancin regimens with theoritavancin treatment.
- Multiplicity could be an issue if the intent of this study was to determine which or both the twooritavancin regimens were non-inferior to the vancomycin treatment.
- The sponsor calculated the 95% CI for the success rate differences between treatment groups which will not address this potential multiplicity issue.
- Thus, the 97.5% CI were calculated for the rate differences to adjust for this potential multiplicity issue.

Baseline Demographics

ARRD

	ITT			CE		
	Oritavancin		Vancomycin	Oritavancin		Vancomycin
Demographics	1.5 mg/kg N=173 (%)	3.0 mg/kg N=169 (%)	N=175 (%)	1.5 mg/kg N=136 (%)	3.0 mg/kg N=128 (%)	N=130 (%)
Sex						
Male	109 (63.0)	106 (62.7)	166 (66.3)	82 (60.3)	74 (57.8)	87 (66.9)
Female	64 (37.0)	63 (37.3)	59 (33.7)	54 (39.7)	54 (42.2)	43 (33.1)
Ethnic Origin						
Caucasian	97 (56.1)	95 (56.2)	106 (60.6)	75 (55.1)	72 (56.3)	82 (63.1)
African Descent	21 (12.1)	23 (13.6)	13 (7.4)	15 (11.0)	14 (10.9)	10 (7.7)
Hispanic	49 (28.3)	49 (29.0)	51 (29.1)	41 (30.1)	41 (32.0)	34 (26.2)
Other	6 (3.5)	2 (1.2)	5 (2.9)	5 (3.7)	1 (0.8)	4 (3.1)
Age (years)	48.6	49.3	48.6	48.3	50.6	48.3
Mean (±SD)	(15.60)	(15.74)	(16.29)	(14.56)	(15.58)	(16.17)

Success/Cure Rates at TOC Visit

Study ARRD

Efficacy endpoint/ Patient Population	Oritavancin 1.5 mg/kg n/N (%)	Oritavancin 3.0 mg/kg n/N (%)	Vancomycin n/N (%)	Difference 1.5 mg/kg (97.5% CI)	Difference 3.0 mg/kg (97.5% CI)
Sponsor-Defined Clinical Outcome					
ITT	98/173 (56.6%)	95/169 (56.2%)	101/175 (57.7%)	-1.1 (-13,10.8)	-1.5 (-13.5, 10.5)
CE	98/136 (72.1%)	94/128 (73.4%)	98/130 (75.4%)	-3.3 (-15.4, 8.8)	-1.9 (-14.1, 10.2)
Investigator- Defined Clinical Outcome					
ITT	101/173 (58.4%)	97/169 (57.4%)	106/175 (60.6%)	-2.2 (-14,9.6)	-3.2 (-15,8.7)
CE	100/136 (73.5%)	95/128 (74.2%)	100/130 (76.9%)	-3.4 (-15.2, 8.5)	-2.7 (-14.7, 9.3)

Sponsor-Defined Clinical Outcome with Identified Baseline Pathogens (MITT Population) Study ARRD

Organism	ORI 1.5 mg/kg n/N (%)	ORI 3.0 mg/kg n/N (%)	Vancomycin n/N (%)
<i>Staphylococcus aureus</i> (ALL)	36/68 (52.9%)	34/63 (54%)	37/65 (56.9%)
Methicillin-sensitive (MSSA)	22/37 (59.5%)	22/43 (51.2%)	26/47 (55.3%)
Methicillin-resistant (MRSA)	8/20 (40%)	10/16 (62.5%)	8/14 (57.1%)
<i>Streptococcus pyogenes</i>	5/14 (35.7%)	9/14 (64.3%)	11/20 (55.0%)

**Cure Rates for Sponsor-Defined Clinical Outcome at Test-of-Cure Visit by
Disease Category: Intent-to-Treat Population (ITT)**

Disease Category	Oritavancin n/N (%)		Vancomycin n/N (%)
Study ARRI			
Wound Infection	183/265 (69.1%)		90/139 (64.7%)
Major Abscess	263/366 (71.9%)		121/177 (68.4%)
Cellulitis	148/200 (74%)		73/99 (73.7%)
Study ARRD	1.5 mg/kg n/N (%)	3.0 mg/kg n/N (%)	
Wound Infection	21/35 (60%)	20/34 (58.8%)	20/38 (52.6%)
Major Abscess	37/66 (56.1%)	36/61 (59.0%)	40/64 (62.5%)
Cellulitis	40/72 (55.6%)	39/74 (52.7%)	41/73 (56.2%)

Safety

- The NDA database included 2176 individuals who received eitheroritavancin or a comparator.
- **1540 individuals** (225 subjects and 1315 patients) received **oritavancin** and 636 (12 subjects and 624 patients) received vancomycin.
- In the two phase 3 studies (ARRI and ARRD), there were **1173** oritavancin-treated patients, and **590** vancomycin-treated patients.
- In study ARRI, 831 patients received oritavancin and 415 patients received vancomycin.
- In study ARRD, 342 patients received oritavancin and 175 patients received vancomycin.
- In the oritavancin group, 173 patients received oritavancin 1.5 mg/kg and 169 patients received oritavancin 3.0 mg/kg.

Deaths

- A total of 74 deaths (66 during study and 8 post-study) occurred among oritavancin- and vancomycin-treated patients in the cSSSI and Phase 2 ITT populations.
- Of 1173 oritavancin patients, 19 (1.6%) died in the “during study” period. For the majority (73.6% [14 of 19]) of these patients, the adverse events that led to death occurred in the “post study drug” period while in 2 cases, the adverse events that led to patient death occurred in the “during IV therapy” period.
- Of 590 vancomycin patients, 12 (2.0%) died in the “during study” period. For 5 of these patients (41.7% [5 of 12]), the adverse events that led to death occurred in the “post study drug” period while in 3 cases, the adverse events that led to patient death occurred in the “during IV therapy” period
- Overall, the vast majority of deaths were found to be related to the underlying medical conditions of the patients.

Serious Adverse Events

- Oritavancin and vancomycin-treated cSSSI patients with serious adverse event (SAE) during the Phase 3 studies (9.1% [107 of 1173 for oritavancin]; 11.4% [67 of 590 for vancomycin]).
- Oritavancin and vancomycin-treated cSSSI patients with investigator-assessed SAE as related to study drug (0.9% [10 of 1173 for oritavancin]; 1.2% [7 of 590 for vancomycin]).

Selected Serious Adverse Events in cSSSI patients

Serious AE	Oritavancin n (%)	Vancomycin n (%)
Cellulitis	10 (0.9%)	3 (0.5%)
Abscess	7 (0.6%)	2 (0.3%)
Sepsis	7 (0.6%)	3 (0.5%)
Abscess Limb	6 (0.5%)	1 (0.2%)
Osteomyelitis	5 (0.4%)	0
Septic Shock	4 (0.3%)	0
Myocardial Infarction	3 (0.3%)	1 (0.2%)
Cardiac Arrest	3 (0.3%)	4 (0.7%)
Cardio-respiratory Arrest	3 (0.3%)	1 (0.2%)
Chest Pain	3 (0.3%)	1 (0.2%)
Pyrexia	2 (0.2%)	3 (0.5%)
Pulmonary embolism	1 (0.1%)	4 (0.7%)
Vomiting	1 (0.1%)	4 (0.7%)

Discontinuations of Study Drug

- In **Study ARRI**, 11.4% (95/831) of the oritavancin group and 12.5% (52/415) of the vancomycin group discontinued treatment with study drug.

Discontinuations

	ITT		CE	
	Oritavancin N (%)	Vancomycin N (%)	Oritavancin N (%)	Vancomycin N (%)
ARRI				
N	831	415	675	328
Discontinued	95 (11.4)	52 (12.5)	63 (9.3)	41 (12.5)
Lack of Efficacy	32 (3.9)	12 (2.9)	28 (4.1)	12 (3.7)
Death	0	1 (0.2)	0	1 (0.3)
Adverse Event	16 (1.9)	20 (4.8)	14 (2.1)	18 (5.5)
Other	47 (5.7)	19 (4.6)	21 (3.1)	10 (3.0)

Discontinuations of Study Drug (cont)

- In **Study ARRD**, 29.2% (100/342) of all patients given oritavancin discontinued treatment with study drug (27.2% for oritavancin 1.5 mg/kg, 31.4% for oritavancin 3.0 mg/kg) as compared to 27.4% for vancomycin-treated patients.

Discontinuations

	ITT			CE		
	Oritavancin N (%)		Vanco N (%)	Oritavancin N(%)		Vanco N (%)
ARRD	1.5 mg/kg	3.0 mg/kg		1.5 mg/kg	3.0 mg/kg	
N	173	169	175	136	128	130
Discontinued	47 (27.2)	53 (31.4)	48 (27.4)	22 (16.2)	23 (18.0)	17 (13.1)
Lack of Efficacy	8 (4.6)	12 (7.1)	6 (3.4)	8 (5.9)	11 (8.6)	5 (3.8)
Death	0	0	0	0	0	0
Adverse Event	6 (3.5)	13 (7.7)	13 (7.4)	0	4 (3.1)	3 (2.3)
Other	33 (19.1)	28 (16.6)	29 (16.6)	14 (10.3)	8 (6.3)	9 (6.9)

Injection site vein toleration of oritavancin

- Phase 1, single-center, randomized, double-blinded, crossover design study to establish the injection site vein toleration of oritavancin.
- The primary objective of this study was to assess the injection site vein toleration of oritavancin after two single, sequential intravenous doses of oritavancin (200 mg and 800 mg or 800 mg and 200 mg) separated by 14 days via peripheral intravenous catheters in healthy male subjects.
- Fifteen (15) healthy men were enrolled and 13 subjects completed the study.

Results

- 24 adverse events were reported by 8 subjects.
- Injection site reactions and adverse events related to injection site were experienced by 5 subjects after oritavancin infusion.
- Three subjects (Subject Nos. 002, 009, and 011, [3 of 14 subjects, 21%]) experienced injection site phlebitis after receiving the 800 mg dose of oritavancin.
- Two subjects (Subject Nos. 001 and 004, [2 of 14 subjects, 14%]) experienced injection site reactions excluding injection site phlebitis including edema, erythema, swelling, and tenderness after receiving the 200 mg dose of oritavancin.

Results (cont)

- Subject No 010 (1 of 15 subjects; 6.7%) experienced extravasation of the IV fluid into the subcutaneous tissue resulting in erythema, pain, and swelling during his first infusion bag (~20 mg oritavancin infused). This occurred during infusion of the 400 mg dose.
- Two subjects experienced probable histamine-like infusion reactions after their first exposure of 800 mg of oritavancin. Symptoms included mild urticaria, mild sensation of puffiness in face, and moderate hypotension.

Treatment-Emergent ADR of Special Interest in Phase 3 Studies

- I.V. infusion site phlebitis was reported in 1.6% (19/1173) oritavancin patients compared to 1.5% (9/590) vancomycin patients.
- Infusion site pain was reported in 1.7% (20/1173) oritavancin patients compared to 1.9% (11/590) vancomycin patients.
- Pruritus was reported in 1.6% (19/1173) oritavancin patients compared to 5.4% (32/590) vancomycin patients.

Issues for Discussion

1. Does study ARRI independently provide evidence of the effectiveness of oritavancin for cSSSI? Please vote Yes/No and in your response, discuss the following:
 - The primary outcome and 95% and 99.875% CIs for the study
 - Outcomes for patients with known baseline pathogens, particularly MRSA
2. Does study ARRD independently provide evidence of the effectiveness of oritavancin for cSSSI? Please vote Yes/No and in your response, discuss the following:
 - The primary outcome and 97.5% CI for the study
 - The weight-based dosing regimen used in study ARRD
3. Do the data presented demonstrate the safety and effectiveness of oritavancin for the treatment of cSSSI? Please vote Yes/No.
 - If your answer is yes, are there any specific issues that should be addressed in labeling?
 - If your answer is no, what additional data/studies are needed?

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Questions

1. Does study ARRI independently provide evidence of the effectiveness of oritavancin for cSSSI? Please vote Yes/No and in your response, discuss the following:
 - The primary outcome and 95% and 99.875% CIs for the study
 - Outcomes for patients with known baseline pathogens, particularly MRSA
2. Does study ARRD independently provide evidence of the effectiveness of oritavancin for cSSSI? Please vote Yes/No and in your response, discuss the following:
 - The primary outcome and 97.5% CI for the study
 - The weight-based dosing regimen used in study ARRD
3. Do the data presented demonstrate the safety and effectiveness of oritavancin for the treatment of cSSSI? Please vote Yes/No.
 - If your answer is yes, are there any specific issues that should be addressed in labeling?
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