

Omadacycline (formerly PTK-0796) In Vitro Spectrum of Activity and Confirmation of Disk Mass Using Fresh Media for MIC Testing

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Abstract

Background: Omadacycline (OMC) is the first aminomethylcycline in development as a once daily oral and IV treatment for skin and soft tissue and respiratory infections. Testing of OMC by MIC methods requires the use of fresh media (less than 12 hours old) since the compound is broken down by oxygen in the media which increases over time. This study was designed to determine the MIC and disk diffusion correlates of omadacycline against approximately 2200 bacterial isolates using a 15 or 30 µg disk mass. Bacterial strains tested included staphylococci, enterococci, streptococci, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Enterobacteriaceae* and non-fermentative Gram-negative bacteria. **Methods:** All strains were tested using the Clinical and Laboratory Standards Institute (CLSI) broth microdilution and disk diffusion guidelines M2-A07 and M7-A08. Both 15 and 30 µg disks were tested on all strains. Disk diffusion and MIC tests were performed using a single inoculum preparation.

Results: The 30 µg disk produced the best separation based on tetracycline class MIC breakpoints and is consistent with other tetracycline class disk mass.

Table 1. Error Rates Omadacycline Disk Diffusion vs MIC

Organism Group (N)	Disk Mass (µg)	Error Rates		
		Very Major ¹ N (%)	Major ² N (%)	Minor ³ N (%)
<i>Staphylococcus aureus</i> (168)	15	0	0	0
	30	0	0	0
<i>Streptococcus pneumoniae</i> (104)	15	0	0	0
	30	0	0	0
<i>Streptococcus</i> spp. (210)	15	0	0	1(0.5)
	30	0	0	0
<i>H. influenzae</i> (105)	15	0	0	0
	30	0	0	0
<i>Moraxella catarrhalis</i> (104)	15	0	0	0
	30	0	0	0
<i>Enterococcus</i> spp. (311)	15	0	0	0
	30	0	0	0
<i>Enterobacteriaceae</i> (768)	15	10 (1.3)	0	58 (7.5)
	30	14 (1.8)	0	59 (7.7)
Non- <i>Enterobacteriaceae</i> Gram negatives (156)	15	0	0	10 (6.4)
	30	1(4.2)	0	14(9)

1. MIC = R, Disk = S 2. MIC = S, Disk = R 3. MIC = S or R, Disk = I or MIC = I, Disk = S or R

Conclusions: For all aerobic Gram positive species, *Moraxella catarrhalis* and *Haemophilus influenzae* disk diffusion error rates were essentially zero with a 30 µg disk when compared to MICs. Error rates varied for *Enterobacteriaceae* spp. (VM Errors primarily in the *Proteus*, *Providencia*, *Morganella* group) and non-fermenters based on species.

Background

Omadacycline is the first aminomethylcycline to enter clinical development. OMC is being developed globally as an intravenous and oral, once daily monotherapy therapy for ABSSSI and CABP. OMC was designed to overcome tetracycline resistance mechanisms and has been shown to have potent in vitro activity and in vivo efficacy against the key pathogens of ABSSSI and CABP, including isolates resistant to standards of care. The IV and oral formulations are bioequivalent and neither shown the dose-limiting nausea and vomiting exhibited by other tetracycline derivatives.

Acknowledgement

This study was sponsored by Paratek Pharmaceuticals

Materials and Methods

- All strains were tested for minimum inhibitory concentrations (MIC) using the CLSI reference broth microdilution (BMD)^{1,2}
- Cation-adjusted Mueller-Hinton broth was used for all MIC tests. This broth was supplemented with 3% lysed horse blood for testing streptococci and made up as haemophilus test media for testing *Haemophilus influenzae*
- DD tests followed the CLSI reference disk diffusion method using Mueller-Hinton, Mueller-Hinton with 5% sheep blood or Haemophilus Test agars³.
- A single inoculum preparation was used for both Disk diffusion (DD) tests and MIC tests.

Results

Figure 1. Omadacycline MIC µg/mL vs. Omadacycline 30 µg Zone Diameter (mm) *Enterococcus faecalis* (n=153) and *Enterococcus faecium* (n=157) Strains Combined (n=310)

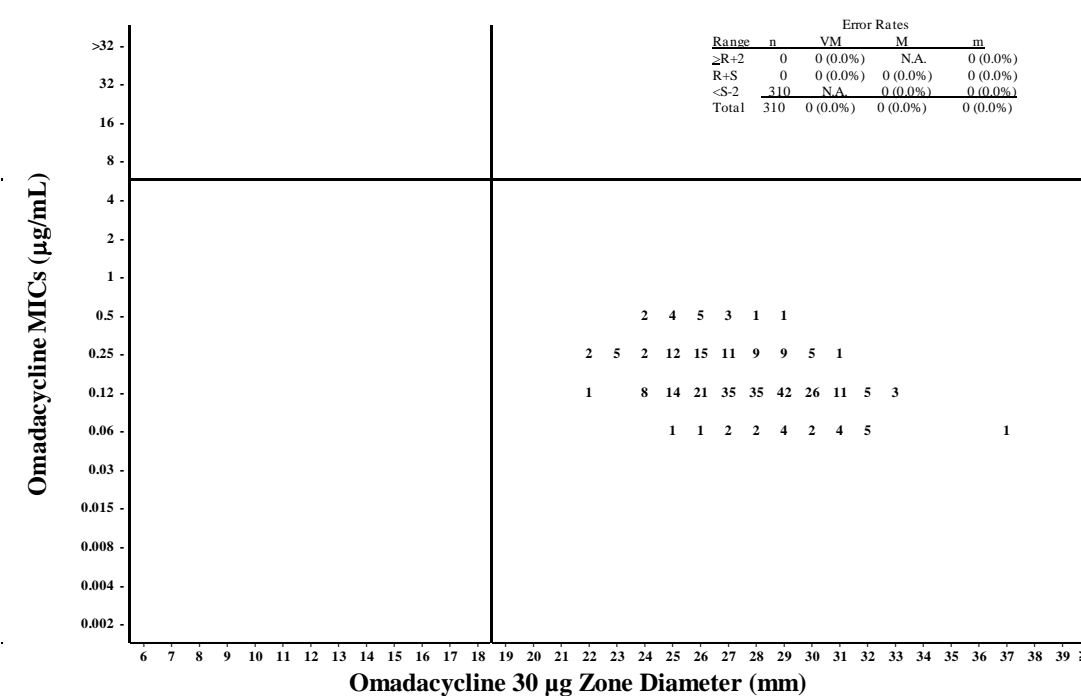


Figure 2. Omadacycline MIC µg/mL vs. Omadacycline 30 µg Zone Diameter (mm) *Staphylococcus aureus* methicillin S (n=52), methicillin R (n=111) and vancomycin I or R (n=5) Strains Combined (n=168)

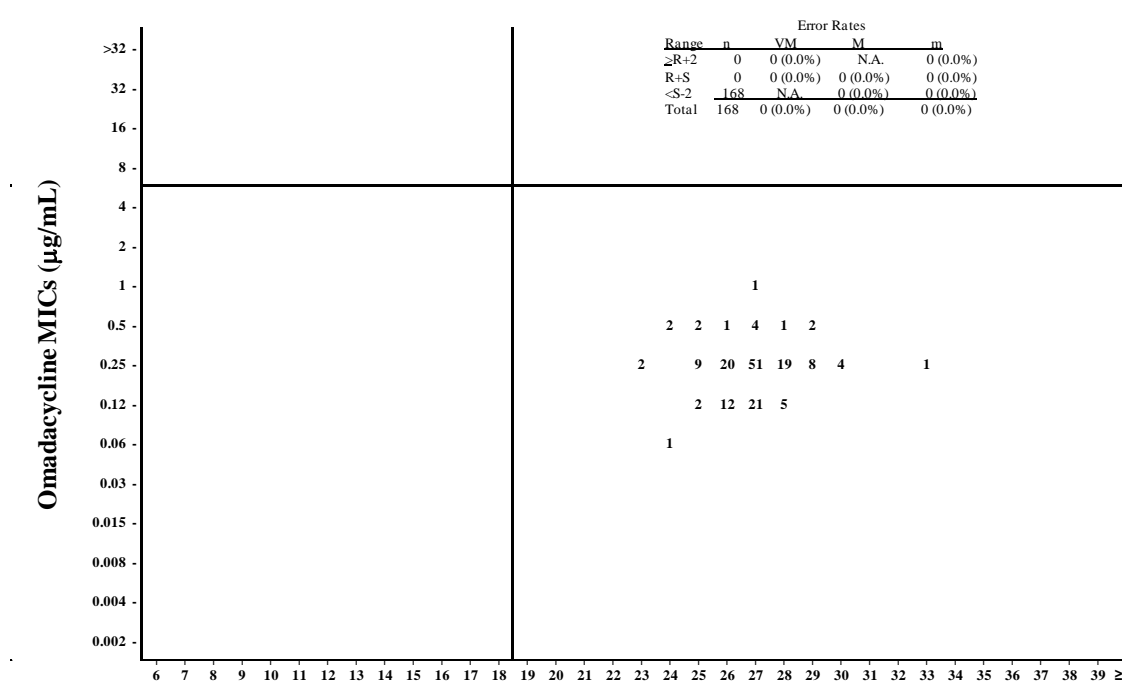


Figure 3. Omadacycline MIC µg/mL vs. Omadacycline 30 µg Zone Diameter (mm) All *Enterobacteriaceae* Strains Combined (n=768)

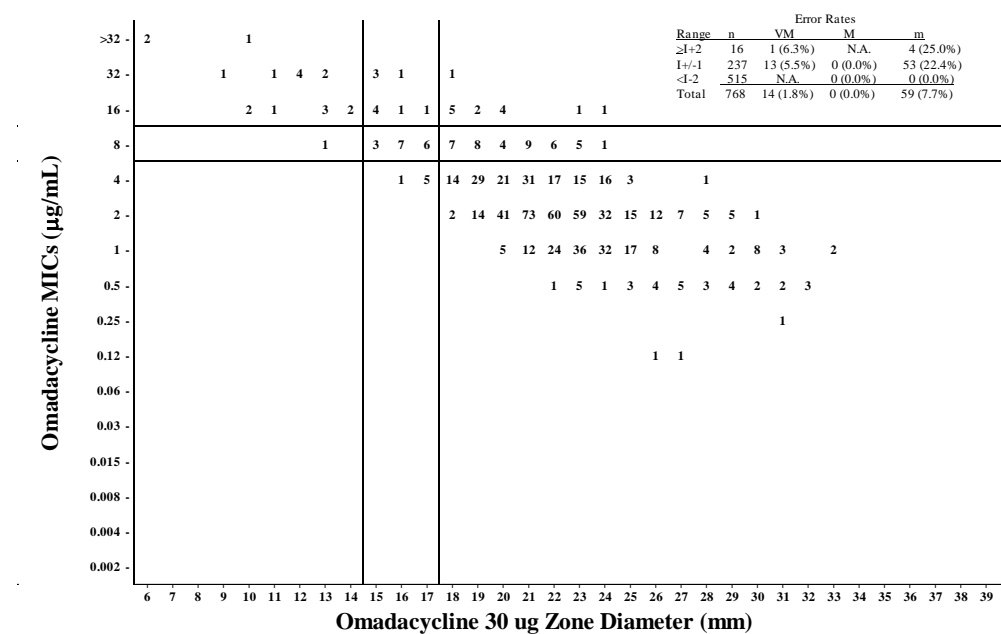


Figure 4. Omadacycline MIC µg/mL vs. Omadacycline 30 µg Zone Diameter (mm) *Escherichia coli* (n=203)

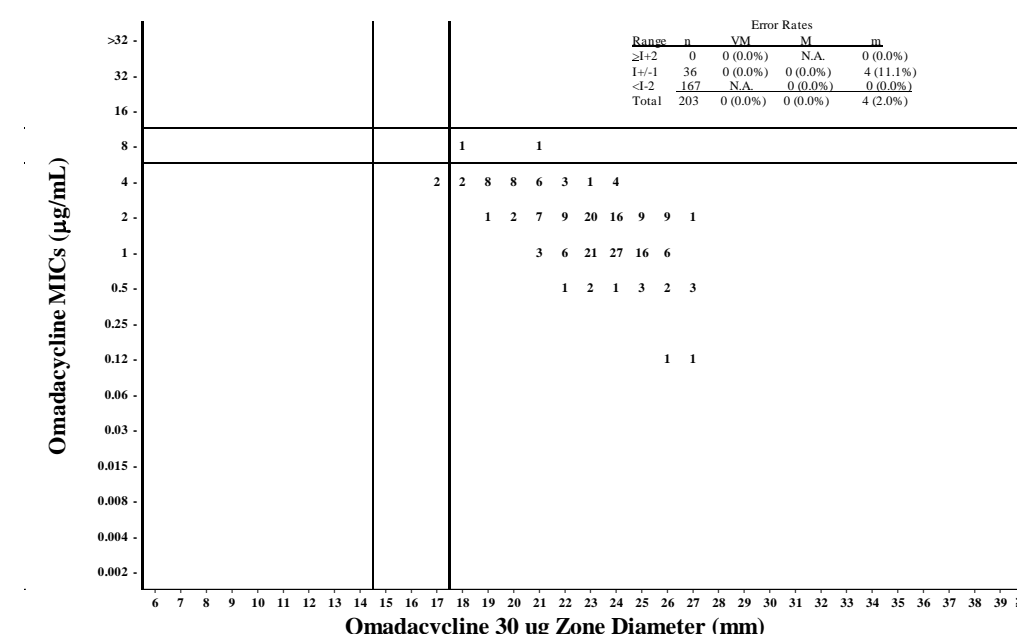


Figure 5. Omadacycline MIC µg/mL vs. Omadacycline 30 µg Zone Diameter (mm) *Klebsiella pneumoniae* (n=204)

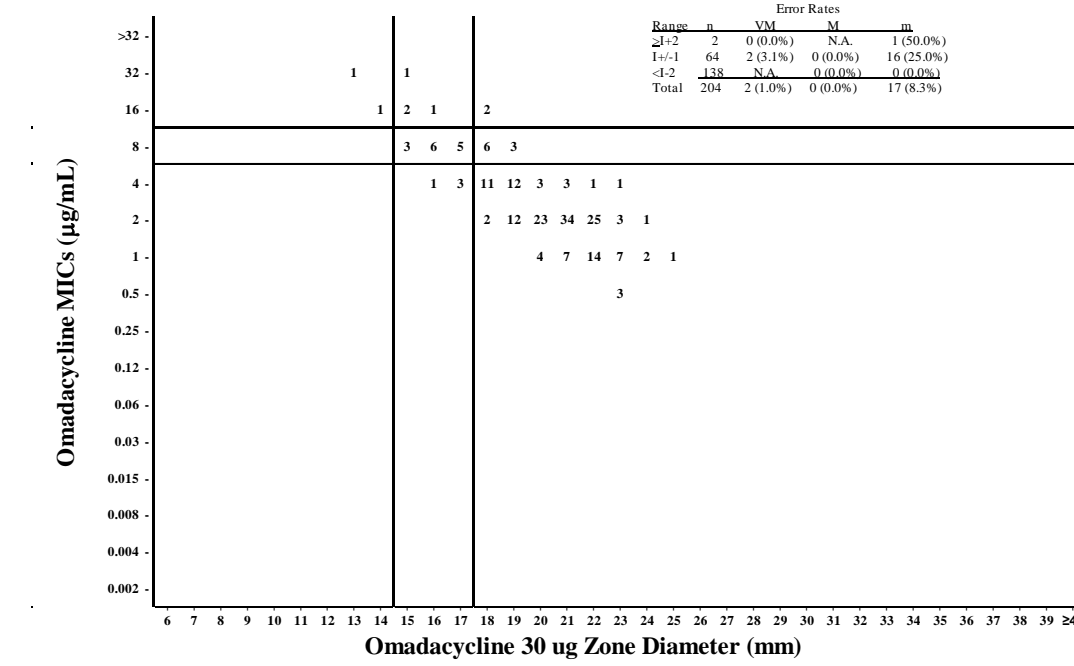


Figure 6. Omadacycline MIC µg/mL vs. Omadacycline 30 µg Zone Diameter (mm) *Streptococcus pneumoniae* (n=104)

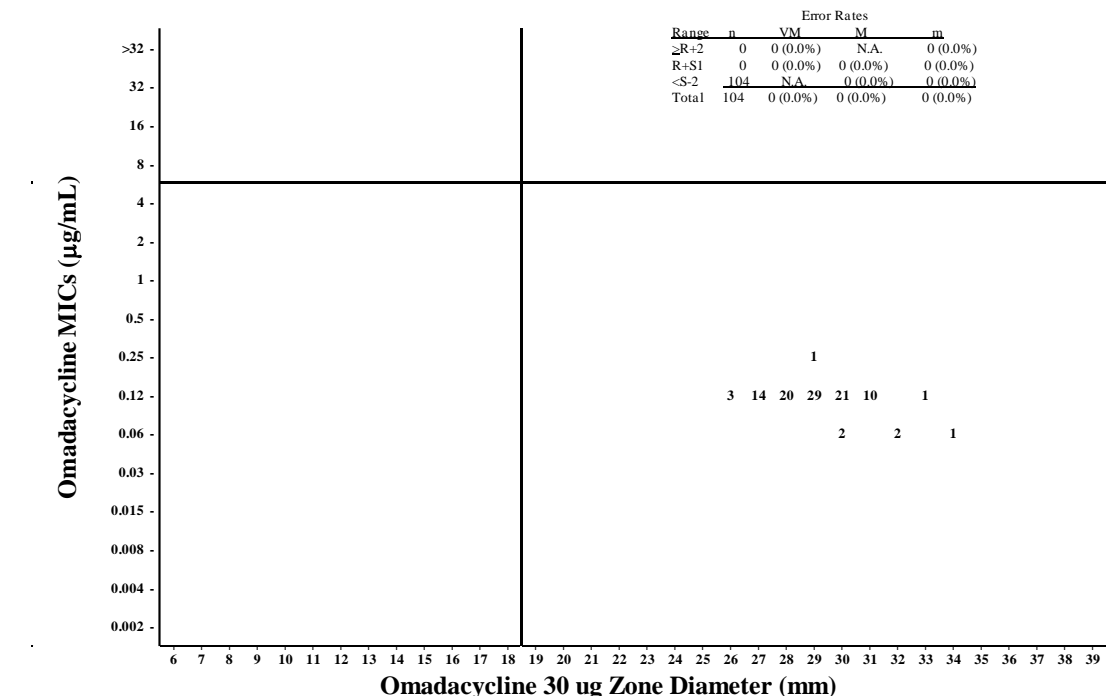


Figure 7. Omadacycline mg/mL vs. Omadacycline 30 µg Zone Diameter (mm) *Streptococcus* other than *S. pneumoniae* (n=210)

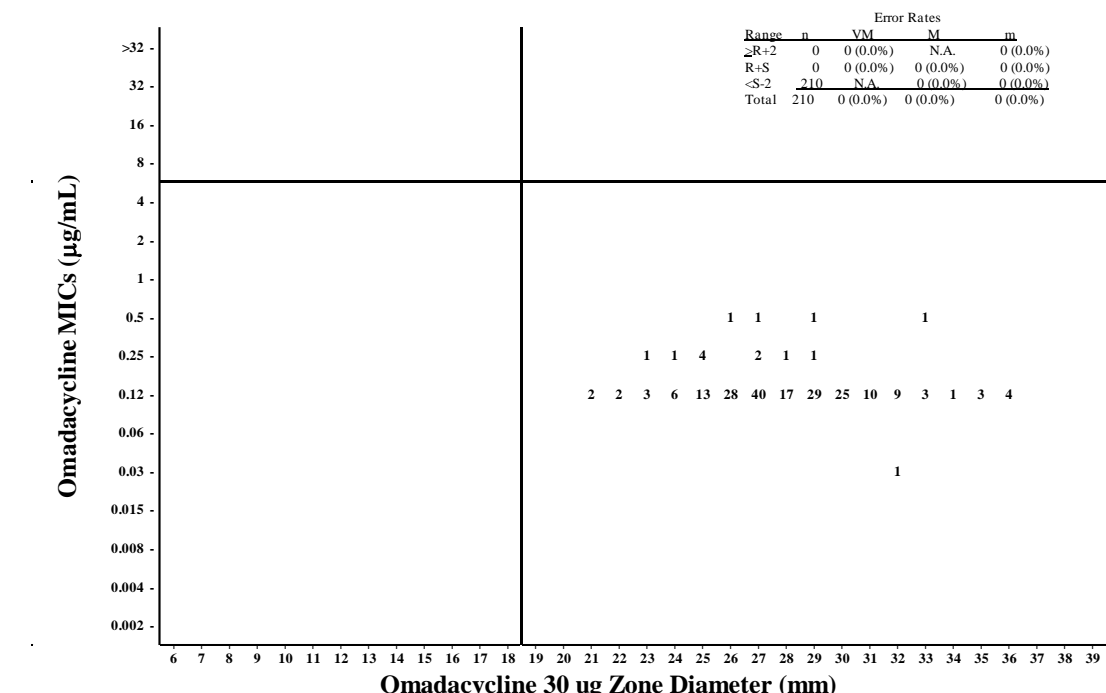


Figure 8. Omadacycline MIC µg/mL vs. Omadacycline 30 µg Zone Diameter (mm) *Haemophilus influenzae* (n=105)

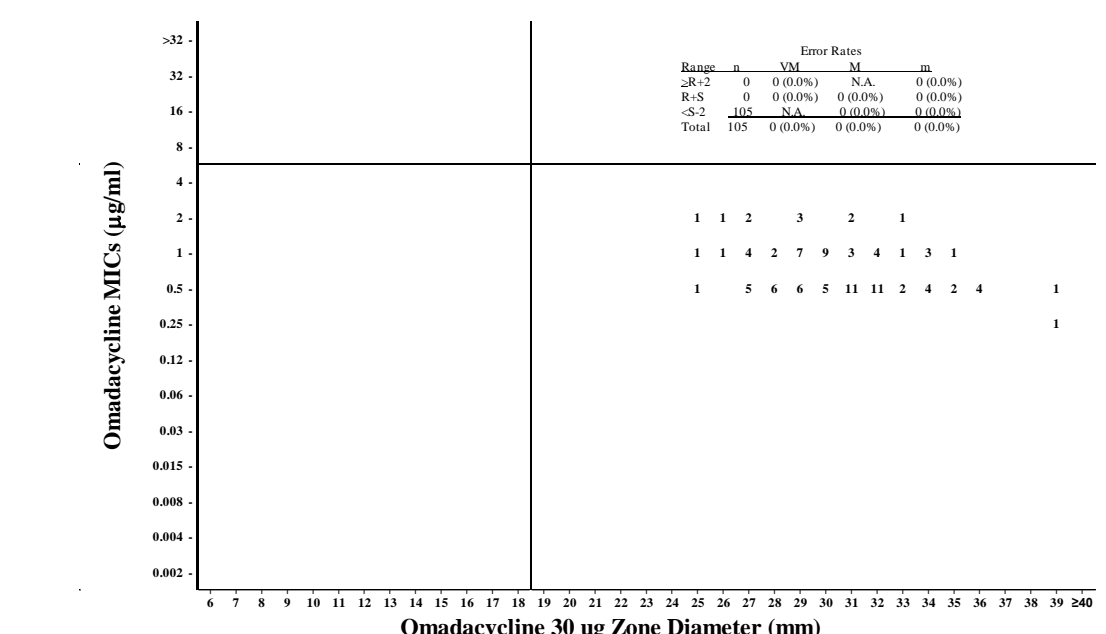


Figure 9. Omadacycline MIC µg/mL vs. Omadacycline 30 µg Zone Diameter (mm) *Moraxella catarrhalis* (n=105)

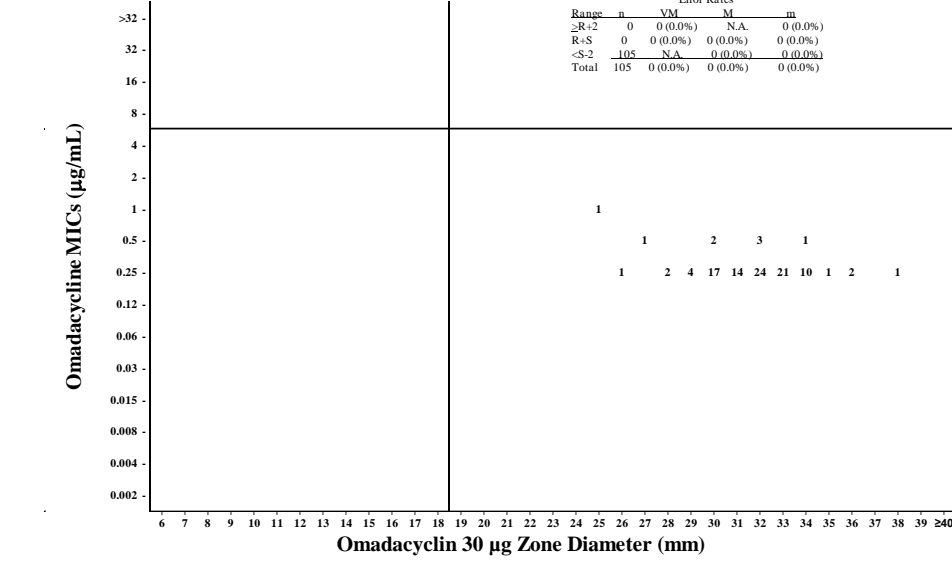
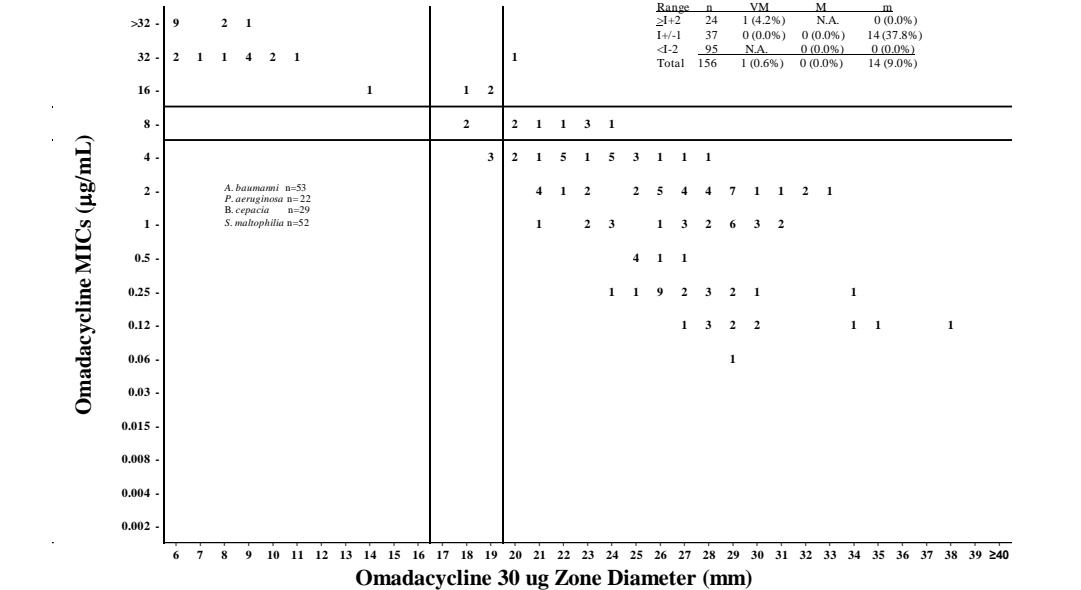


Figure 10. Omadacycline MIC mg/mL vs. Omadacycline 30 µg Zone Diameter (mm) All Non-*Enterobacteriaceae* Combined (n=156)



Summary

- Omadacycline has broad spectrum activity with potent activity against the primary pathogens causing acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia.
- There was no evidence of a resistant subpopulation amongst the highly susceptible species, while some *Enterobacteriaceae* and *P. aeruginosa* were not susceptible to OMC.
- Fresh media is important for broth dilution testing.
- Zone diameters correlate well with MICs.
- The 30 µg disk was chosen based on testing 15, 30, and 60 µg disk masses giving the best dynamic range without overly large zones against highly susceptible organisms.

References

- Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Eighth Edition, M07-A8 Vol. 29 No. 2, January 2009, Clinical Laboratory Standards Institute, Wayne PA.
- Performance Standards for Antimicrobial Susceptibility Testing; Nineteenth Informational Supplement, M100-S19 Vol 28 No. 1, January 2009, Clinical Laboratory Standards Institute, Wayne, PA.
- Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard, M02-A10 Vol 29 No. 1, January 2009. Clinical Laboratory Standards Institute, Wayne PA.