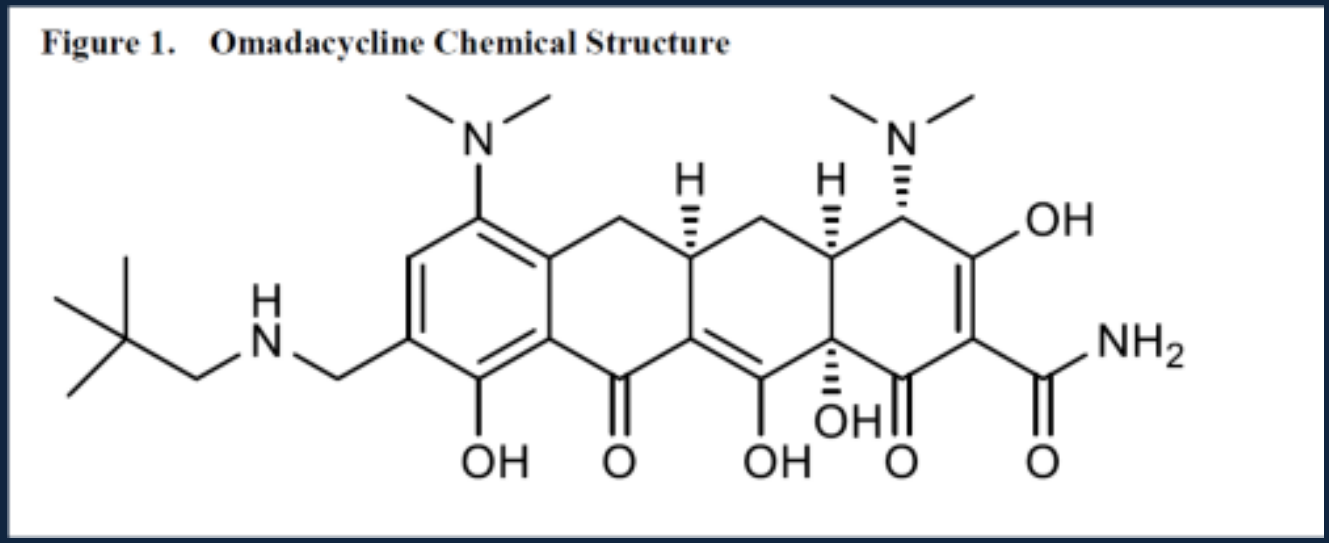
Omadacycline



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Omadacycline (PTK-0796)

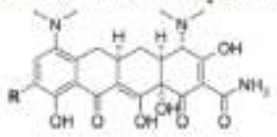
- A semisynthetic tetracycline derived from minocycline that has an aminomethyl group added to the C9 position of the tetracyclic core
- Overcomes efflux systems and ribosomal protection mechanisms that confer resistance to older tetracyclines
- Protein synthesis inhibition
  - Inhibition of the initial codon recognition step of transfer RNA accommodation to the A-Site of the 30S ribosomal subunit

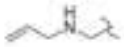
Structure-Activity Relationship of the Aminomethylcyclines and the Discovery of Omadacycline

Laura Honeyman, Mohamed Ismail, Mark L. Nelson, Beena Bhatia, Todd E. Bowser, Jackson Chen, Rachid Mechiche, Kwasi Ohemeng, Atul K. Verma, E. Pat Cannon, Ann Macone, S. Ken Tanaka, Stuart Levy

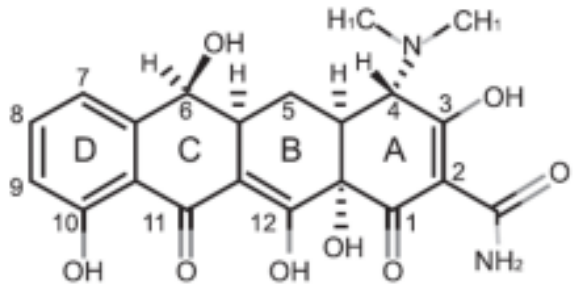
Paratek Pharmaceuticals, Inc., Boston, Massachusetts, USA

TABLE 3 Activities of aminomethylcyclines against tetracycline-resistant Gram-positive bacteria

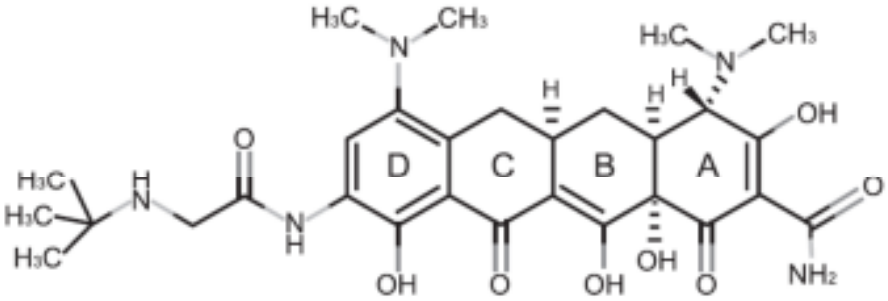


Compound	Structure (R)	MIC (μg/ml) for species and strain type								
		S. aureus			*E. faecalis*			*E. faecium*,	*S. pneumoniae*	
		Wild type[a]	Tet M[b]	Tet K[c]	Wild type[d]	Tet M[e]	Tet L[f]	Tet M + L[g]	Wild type[h]	Tet M[i]
4		4	32	16	4	>64	4	>64	2	4
6		4	4	8	4	4	8	8	1	2
26		1	1	2	2	2	1	2	0.5	0.5
8		1	1	1	1	1	1	1	0.25	0.25
27 (omadacycline)		0.25	0.25	0.25	0.25	0.5	0.5	0.5	<0.06	<0.06
Tetracycline	<0.06	32	>64	0.25	>64	64	>64	<0.06	32	
Minocycline	0.25	2	0.5	0.5	16	0.5	16	<0.06	8	
Tigecycline	0.25	0.25	0.5	0.5	0.5	0.5	0.5	<0.06	<0.06	
Vancomycin	0.5	0.5	0.25	1	1	1	>64	0.25	0.25	
Ciprofloxacin	0.5	16	0.5	1	1	1	1	0.5	0.5	

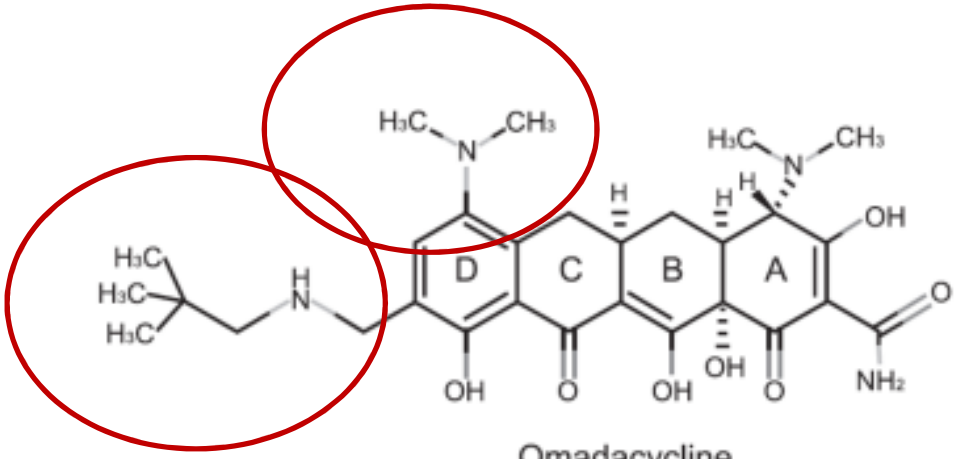
AAC 2015



Tetracycline



Tigecycline



Omadacycline

Spectrum of Activity

- a broad-spectrum agent active against gram-positive organisms, including vancomycin-resistant *Enterococcus* (VRE) and methicillin-resistant *Staphylococcus aureus*; gram-negative organisms, including some extended-spectrum b-lactamase (ESBL)-producing Enterobacteriaceae and *Acinetobacter baumannii*; atypicals; and anaerobes

In Vitro and *In Vivo* Antibacterial Activities of Omadacycline, a Novel Aminomethylcycline

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TABLE 1 *In vitro* activity of omadacycline against tetracycline-resistant and -susceptible bacteria

Organism(s)	Tetracycline resistance gene(s)	No. of isolates	MIC range (μg/ml)[a]		
			Omadacycline	Tetracycline	Doxycycline
Staphylococcus aureus	*tet*(M)	19	0.125–1	32–>64	2–16
	tet(K)	5	0.125–0.25	16–32	1–4
		35	≤0.06–0.5	≤0.06–0.25	≤0.06–0.125
Enterococcus faecalis	*tet*(M)	14	0.125–0.5	32–64	4–8
	tet(L)	1	0.25	64	16
	tet(M), *tet*(L)	3	0.5	>64	16
	tet(S)	1	0.25	32	2
		11	0.25–0.5	≤0.06–0.25	≤0.06–0.125
Enterococcus faecium	*tet*(M)	13	0.125–0.5	32–64	2–8
	tet(M), *tet*(L)	2	0.25	>64	8–16
	tet(K)	1	0.12	32	4
	tet(O)	1	0.12	32	4
		8	0.125–0.5	0.125–0.25	≤0.06
Streptococcus pneumoniae	*tet*(M)	22	≤0.06	4–64	2–4
		18	≤0.06–0.25	≤0.06–0.25	≤0.06–0.25
Beta-hemolytic streptococci[b]	*tet*(M)	17	≤0.06–0.5	4–64	2–16
	tet(O)	4	≤0.06–0.25	32–64	8
		26	≤0.06–0.5	≤0.06–0.125	≤0.06
Escherichia coli	*tet*(A)	4	2	64–>64	16
		17	0.5–2	0.5–2	0.5–1

AAC 2014

FDA Identified Interpretive Criteria

Minimum Inhibitory Concentrations (mcg/mL)			
Pathogen	**S**	**I**	**R**
Enterobacteriaceae [a,†]	≥ 4	8	≤ 16
Staphylococcus aureus (including methicillin-resistant isolates)	≥ 0.5	1.0	≤2.0
Staphylococcus lugdunensis	≥ 0.12	0.25	≤ 0.5
Enterococcus faecalis	≥ 0.25	0.5	≤ 1.0
Streptococcus anginosus group [b]	≥ 0.12	0.25	≤ 0.5
Streptococcus pyogenes	≥ 0.12	0.25	≤0.5
Haemophilus species [b]	≥ 2	4	≤8
Streptococcus pneumoniae	≥ 0.12	0.25	≤ 0.5

Bacteria (No. of Isolates)	Omadacycline			
	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	MIC Range (μg/mL)	% S by CLSI[a]
S. aureus (4215)	0.12	0.25	≤0.015 to 8	98.6
S. aureus MSSA (2777)	0.12	0.25	≤0.015 to 1	99.9
S. aureus MRSA (1438)	0.12	0.25	0.03 to 8	96.1
S. aureus TR (221)[a]	0.12	0.5	0.03 to 2	95.5
E. faecalis (677)	0.12	0.25	≤0.015 to 1	97.2
E. faecalis VS (663)	0.12	0.25	≤0.015 to 1	97.1
E. faecalis VNS (14)	0.12	0.25	≤0.015 to 0.25	100.0
E. faecalis TR (524)[a]	0.12	0.25	≤0.015 to 1	96.4
E. faecium (390)	0.06	0.12	≤0.015 to 8	NA
E. faecium VS (234)	0.06	0.12	≤0.015 to 1	NA
E. faecium VNS (156)	0.06	0.12	≤0.015 to 8	NA
E. faecium TR (217)[a]	0.12	0.12	≤0.015 to 8	NA
S. pneumoniae (1314)	0.06	0.12	≤0.015 to 1	99.7
S. pneumoniae PS (899)	0.06	0.06	≤0.015 to 0.5	99.9
S. pneumoniae PI (263)	0.06	0.12	≤0.015 to 1	98.9
S. pneumoniae PR (152)	0.06	0.12	≤0.015 to 0.12	100.0
S. pneumoniae MR[b] (413)	0.06	0.12	≤0.015 to 1	99.5
S. pneumoniae TR (263)[a]	0.06	0.12	≤0.015 to 1	99.2
S. anginosus group (107)	0.06	0.12	≤0.015 to 0.12	100.0
S. anginosus group TR (34)[a]	0.06	0.12	≤0.015 to 0.12	100.0
β-hemolytic streptococci[c] (966)	0.06	0.12	0.03 to 0.5	NA
β-hemolytic streptococci TR (421)[a]	0.12	0.25	0.03 to 0.5	NA
β-hemolytic streptococci MR[d] (266)	0.12	0.25	0.03 to 0.5	NA

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Gram-positive activity

Table 42. Activity of Omadacycline Against Common Gram-positive Bacterial Pathogens[a]

Species	No. Isolates	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)[b]
Staphylococcus aureus (MSSA)	1206	0.12	0.12
Staphylococcus aureus (MRSA)	942	0.12	0.12
Coagulase–negative staphylococci[c]	320	0.12	0.5
Enterococcus faecalis (VSE)	607	0.06	0.12
Enterococcus faecalis (VRE)	29	0.06	0.12
Enterococcus faecium (VSE)	74	0.06	0.12
Enterococcus faecium (VRE)	167	0.06	0.25
Streptococcus pneumoniae	1012	0.06	0.12
Streptococcus pneumoniae (PRSP)	33	0.06	0.12
Streptococcus pyogenes	286	0.06	0.06
Streptococcus agalactiae	261	0.12	0.12
Viridans group streptococci[d]	106	0.06	0.12
Staphylococcus saprophyticus (MR)	7	--	Range: 0.06 - 0.25

Gram-negative activity

Table 43. Activity of Omadacycline Against Common Gram-negative Bacterial Pathogens[a]

Species	No. Isolates	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)[b]
Haemophilus influenzae	4,683	1	2
Moraxella catarrhalis[c]	408	0.25	0.25
Citrobacter freundii[c]	86	1	4
Escherichia coli	14,091	1	2
Enterobacter aerogenes[c]	248	1	4
Enterobacter cloacae	2,703	2	>4
Klebsiella pneumoniae	6,792	2	>4
Morganella morganii[c]	175	4	32
Proteus mirabilis[c]	463	16	>32
Proteus vulgaris[c]	60	8	16
Providencia stuartii[c]	41	16	>32
Salmonella spp.	249	2	4
Serratia marcescens[c]	364	4	8
Pseudomonas aeruginosa[c]	1986	32	> 32
Acinetobacter baumannii	2,754	2	8
Burkholderia cepacia species complex[d]	8	--	Range: 0.5 - 4
Stenotrophomonas maltophilia	1,023	2	8

Bacteria (No. of Isolates)	Omadacycline			
	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC Range (µg/mL)	% S by CLSI[b]
Enterobacteriaceae (8345)	1	8	0.12 to 32	NA
Enterobacteriaceae CNS (1439)	2	8	0.12 to 32	NA
Enterobacteriaceae TR (2737)[a]	2	16	0.12 to 32	NA
E. coli (3541)	0.5	2	0.12 to 32	NA
E. coli CS (3030)	0.5	2	0.12 to 32	NA
E. coli CNS (511)	1	2	0.12 to 32	NA
E. coli TR (1272)[a]	1	4	0.12 to 32	NA
K. pneumoniae (1771)	2	8	0.25 to 32	89.7
K. pneumoniae CS (1264)	1	4	0.25 to 32	94.7
K. pneumoniae CNS (507)	2	8	0.25 to 32	77.1
K. pneumoniae TR (430)[a]	4	16	0.5 to 32	67.7
K. oxytoca (423)	1	2	0.25 to 32	NA
K. oxytoca TR (30)[a]	2	16	0.25 to 32	NA
E. cloacae spp. complex (752)	2	4	0.25 to 32	93.6
E. cloacae spp. complex CS (542)	2	4	0.5 to 32	95.0
E. cloacae spp. complex CNS (210)	2	4	0.25 to 32	90.0
E. cloacae spp. complex TR (87)[a]	4	16	1 to 32	69.0
Other *Enterobacter* spp. (250)	1	4	0.5 to 16	NA
Other *Enterobacter* spp. TR (17)[a]	16	16	2 to 16	NA
Citrobacter spp. (354)	1	4	0.25 to 16	NA
Citrobacter spp. TR (23)[a]	4	8	0.5 to 8	NA
P. mirabilis (463)	16	>32	2 to 32	NA
P. mirabilis TR (458)[a]	16	>32	2 to 32	NA
Proteus spp. IP (317)	8	32	0.5 to 32	NA
Proteus spp. IP, TR (169)[a]	8	32	0.5 to 32	NA
H. influenzae (803)	1	1	0.12 to 16	99.4
H. influenzae BLP (201)	1	1	0.25 to 4	99.0
H. influenzae BLN (602)	1	1	0.12 to 16	99.5
M. catarrhalis (408)	0.25	0.25	0.06 to 0.5	NA

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PK parameters

$t_{1/2}$	16h
Protein binding	21%
Bioavailability fasting	35% (no food 6h before-2h after)

Table 2. Pharmacokinetic Parameters of Omadacycline After Single and Multiple Doses

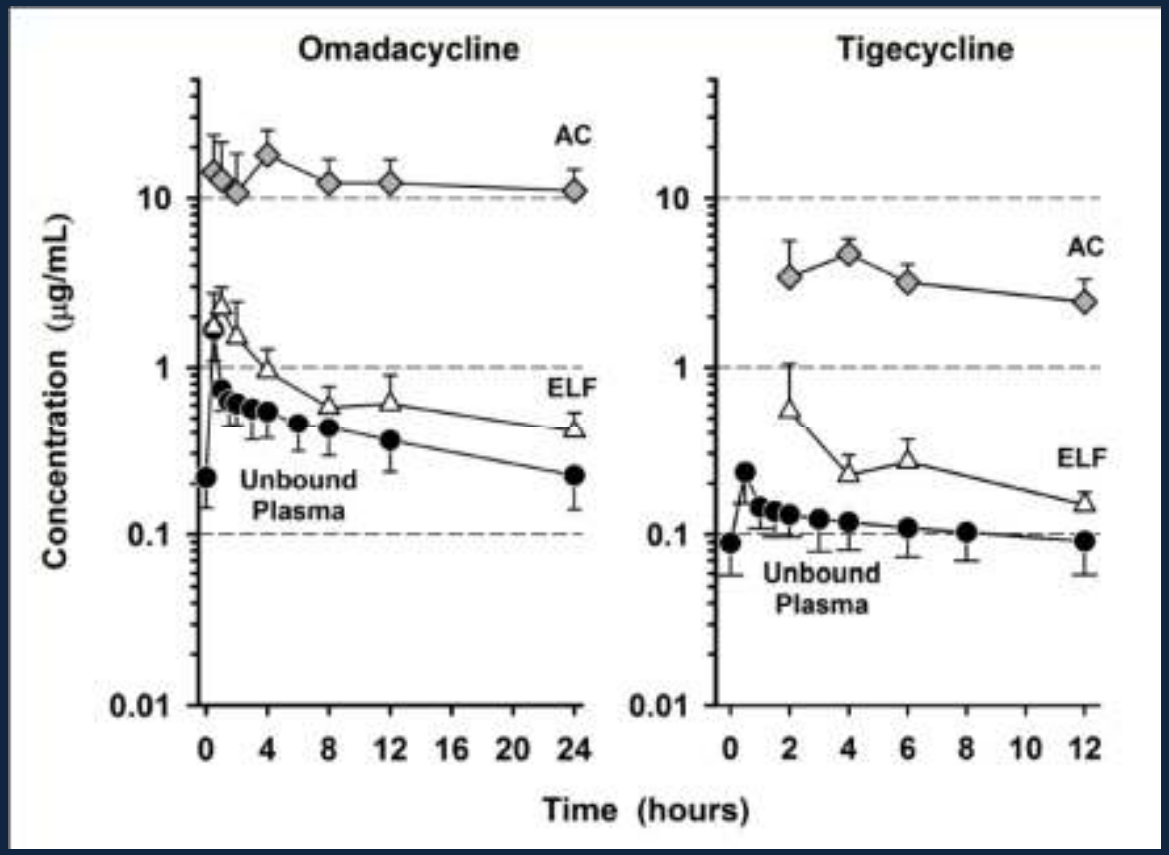
Dosage (mg)	Intravenous		Oral	
	100 mg iv Single Dose	100 mg iv Steady State	300 mg Oral Single Dose	300 mg Oral Steady State
N	63	41	103	43
C_{max} (mg/L)	1.51 (38.6)	2.12 (32.0)	0.55 (26.7)	0.95 (44.2)
CL_{total} (L/h)[a]	11.2 (23.8)	8.8 (25.2)	34.6 (30.9)	NR
T ½ (h)	16.2 (14.7)	16.0 (21.7)	15.0 (16.5)	15.5 (10.7)
T_{max} (h)	0.55 (0.25, 0.68)	0.50 (0, 1.0)	2.50 (1.0, 4.1)	2.50 (0, 8.0)
AUC (h-mg/L)[b]	9.36 (22.1)	12.14 (26.6)	9.4 (27.2)	11.16 (44.9)
Vd (L)	256 (25.6)	190 (27.7)	794 (23.6)	NR

Data presented as mean (CV%)

a. CL/F for oral

b. $AUC_{0\text{-inf}}$ for single dose or $AUC_{0\text{-}24}$ for steady state

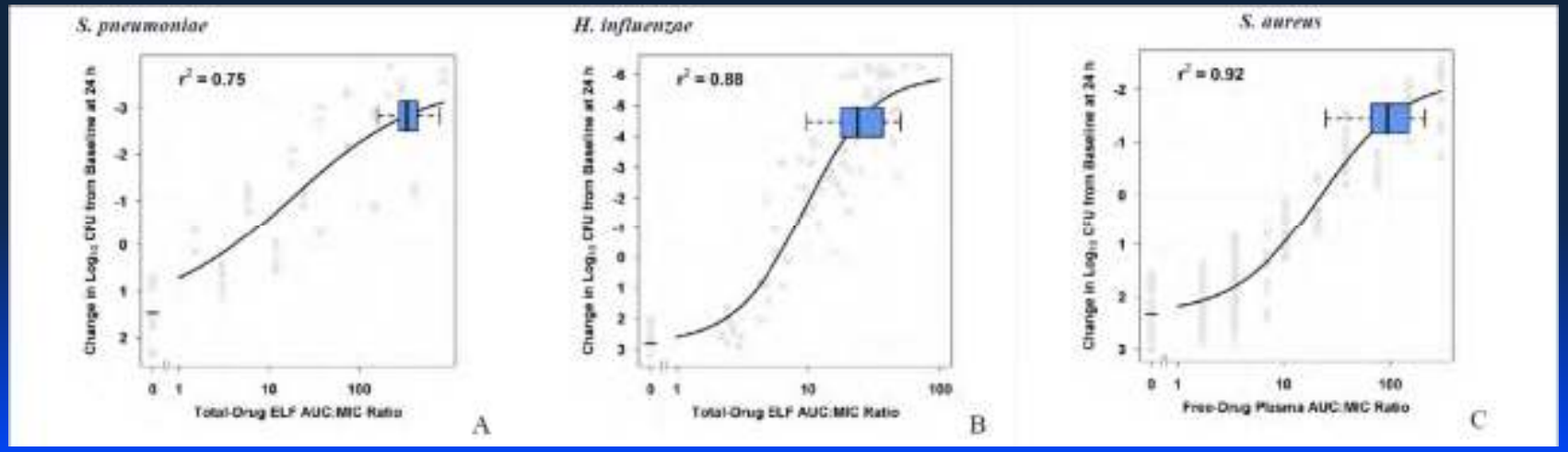
AUC = area under the concentration-time curve, C_{max} = peak plasma concentration, CL_{total} = total clearance, CV% = percentage coefficient of variance, iv = intravenous, NR = not reported, V_d = volume of distribution, $T_{½}$ = half-life, T_{max} = time to maximum concentration.



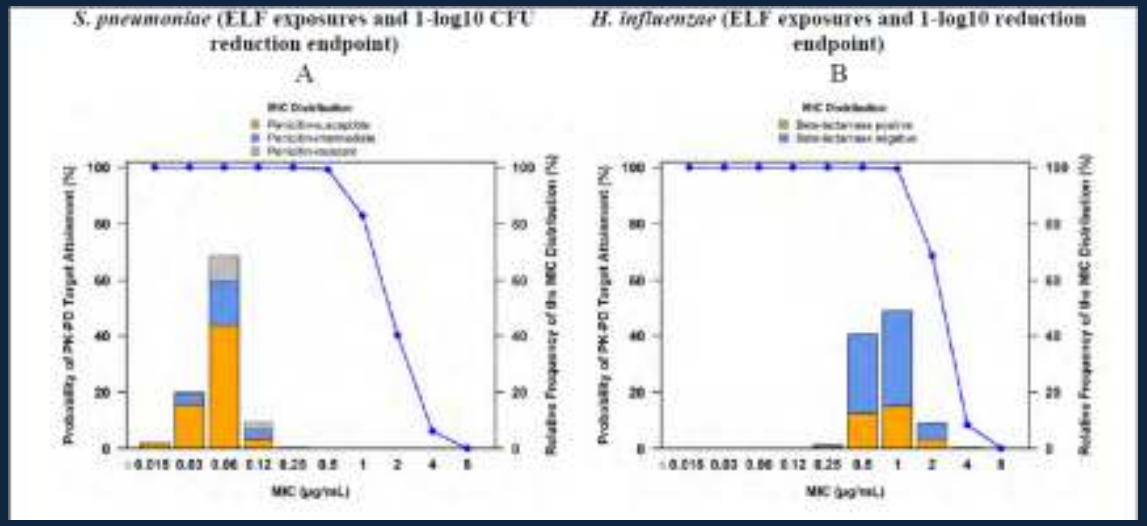
- Alveolar cells concentration 26 -fold higher than in plasma
- ELF concentration 1.5 -fold higher than in plasma
- No metabolism; Eliminated as the parent drug through
  - Biliary excretion (81%)
  - Renal elimination (14%)
- Dose adjustment not required for either hepatic or renal impairment

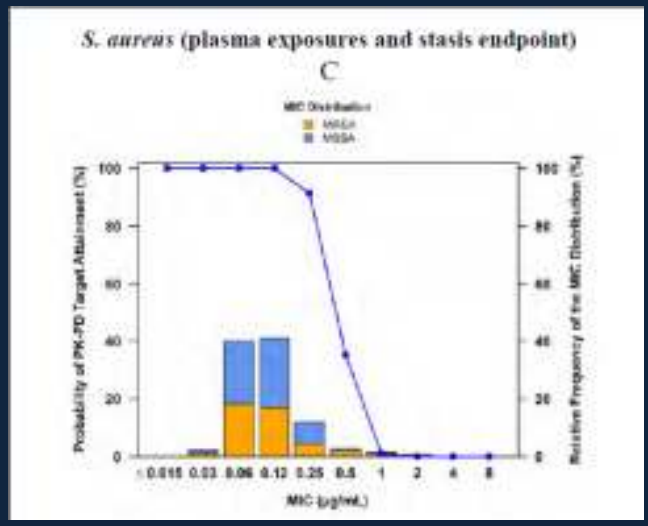
AUC/MIC best PK/PD parameter to predict efficacy

Organism	Infection Model (Exposure Matrix)	Magnitude of AUC/MIC Ratio by Endpoint		
		Net Bacterial Stasis	1-$\log_{10}$ CFU Reduction	2-$\log_{10}$ CFU Reduction
S. pneumoniae	Lung (ELF)	16.00 (14.2, 17.8)	13.3 (6.00, 17.6)[b]	23.20 (17.3, 47.3)
S. pneumoniae	Thigh (plasma)	31.2 (17.5, 53.4)	65.8 (30.4, 83.0)[b]	Not available
H. influenzae	in vitro (ELF)	6.91 (4.38, 8.76)	8.91 (5.44,11.60)	11.1 (6.72, 15.5)
S. aureus	Thigh (plasma)	21.9 (13.8, 51.1)	57.7 (32.2, 302.5)	Not available



Percent Probabilities of PK/PD Target Attainment by MIC on Days 1-2 for *S. pneumoniae*, *H. influenzae*, and *S. aureus* Among Simulated Patients after the Omadacycline iv-to-po Dosing Regimen





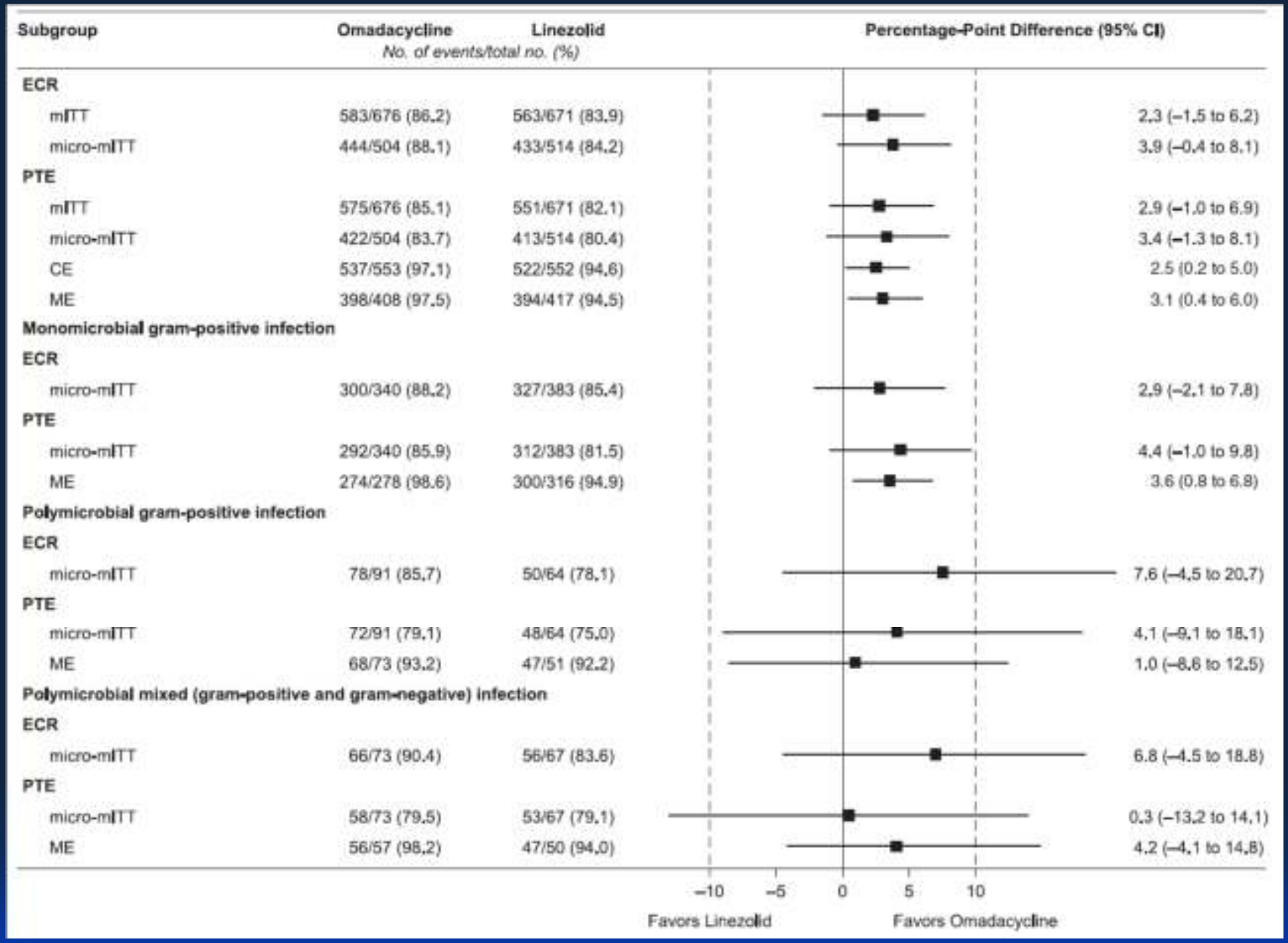
Two ABSSSI phase 3 clinical trials

- OASIS 1 study compared intravenous to oral omadacycline with linezolid for 7 to 14 days for the treatment of ABSSSIs due to gram-positive pathogens in 627 adults.
- The number of patients with an abscess was capped at 30%.
- The primary endpoint was early clinical response, defined as ≥20% reduction in lesion size at 48 to 72 hours of therapy.
- OASIS 2 study similar to OASIS 1 design, but compared oral-only omadacycline with linezolid in 720 adults

Design of Omadacycline Pivotal, Double-blind Phase 3 Studies OASIS-1 and OASIS-2

ECR 48 to 72 h After the First Infusion of the Test Article in OASIS-1 and OASIS-2 (mITT Population)

Primary Efficacy Outcome	Omadacycline n (%)	Linezolid n (%)	Difference (95% CI)
OASIS-1	**N = 316**	**N = 311**	
Clinical success	268 (84.8)	266 (85.5)	-0.7 (-6.3, 4.9)
Clinical failure or indeterminate	48 (15.2)	45 (14.5)	
Clinical failure	23 (7.3)	19 (6.1)	
Indeterminate	25 (7.9)	26 (8.4)	
OASIS-2	**N = 360**	**N = 360**	
Clinical success	315 (87.5)	297 (82.5)	5.0 (-0.2, 10.3)
Clinical failure or indeterminate	45 (12.5)	63 (17.5)	
Clinical failure	26 (7.2)	32 (8.9)	
Indeterminate	19 (5.3)	31 (8.6)	



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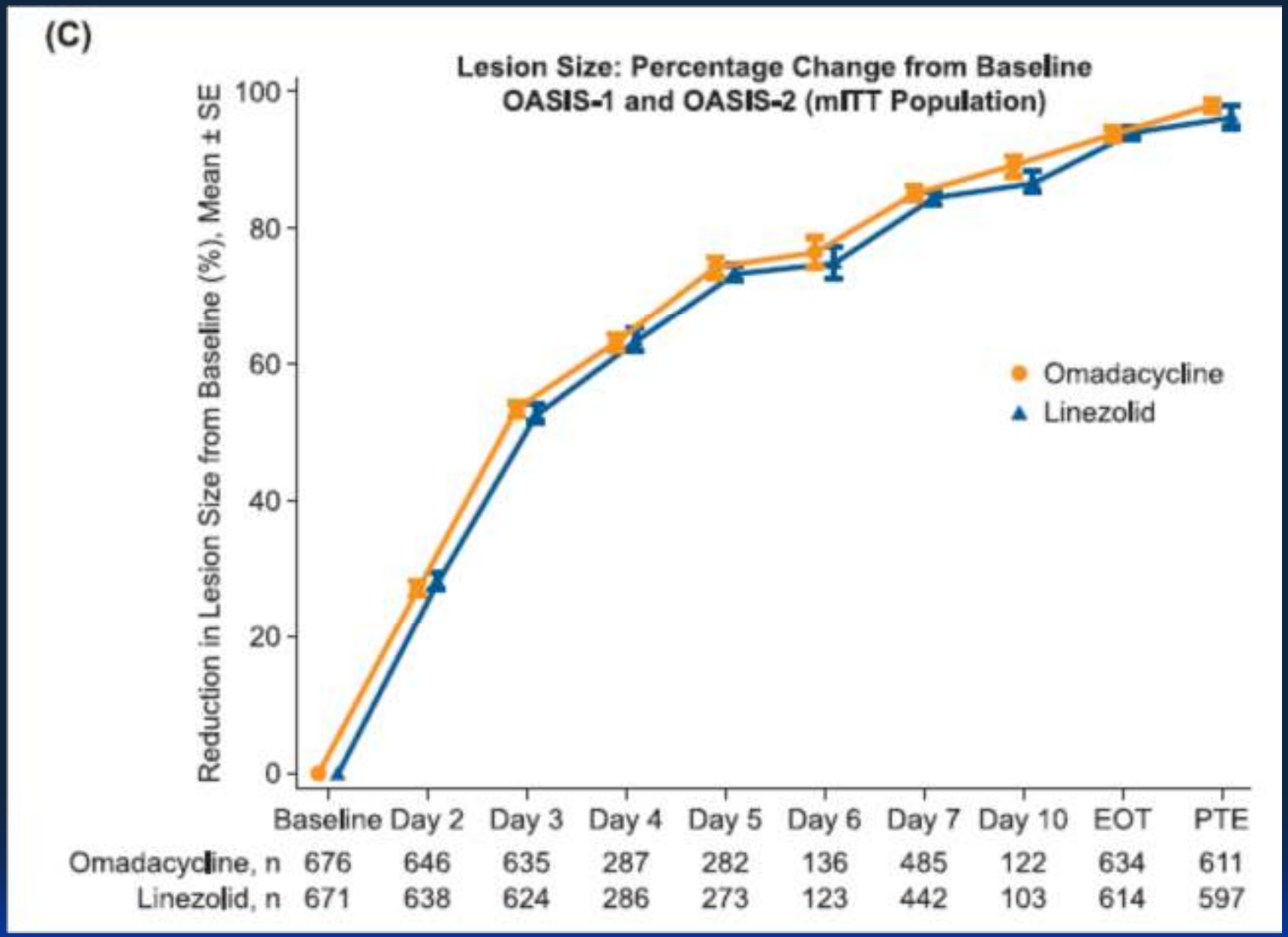

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CABP phase 3 clinical trial

- OPTIC trial compared omadacycline with moxifloxacin for the treatment of CABP for 7 to 14 days in 774 adults.
- Patients enrolled required hospitalization for moderate to severe infection that was radiographically confirmed.
- The primary endpoint was early clinical success, defined as at least 1 level of improvement on a scale of absent, mild, moderate, or severe in at least 2 CABP symptoms (cough, sputum production, pleuritic chest pain, dyspnea) without worsening of any other CABP symptoms

The NEW ENGLAND JOURNAL of MEDICINE

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Omadacycline for Community-Acquired Bacterial Pneumonia

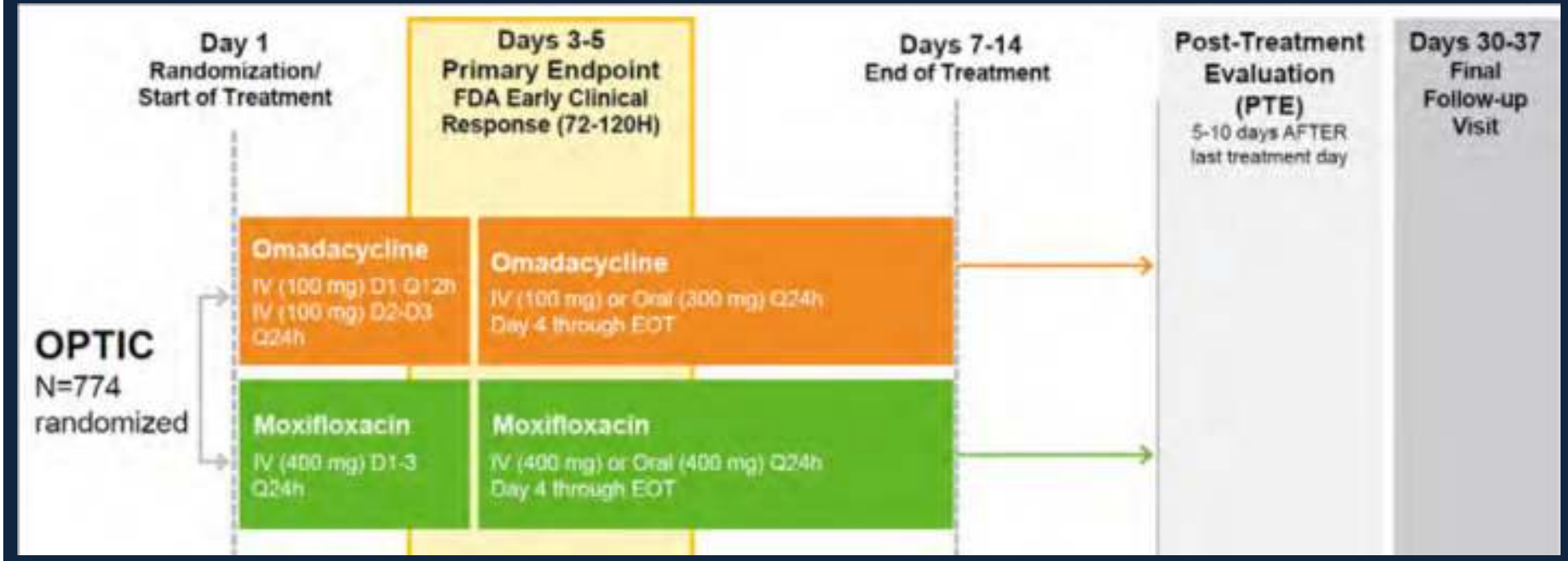
Roman Stets, M.D., Ph.D., Monica Popescu, M.D., Jason R. Gasink, M.D., Ismail Mitha, M.D., William Short, M.D., Andrzej Madej, M.D., Ph.D., Courtney Kirsch, B.S., Anita T. Das, Ph.D., Lynn Gurtler-Ryan, Ph.D., Judith N. Steenbergen, Ph.D., Amy Manley, B.S., Paul B. Eckburg, M.D., Evan Tzanis, B.S., Paul C. McGovern, M.D., and Evan Loh, M.D.

Table 1. Baseline Demographic and Clinical Characteristics in the Intention-to-Treat Population.*

Characteristic	Omadacycline (N=386)	Moxifloxacin (N=388)
Median age (range) — yr	61 (19–97)	63 (19–94)
Age >65 yr — no. (%)	152 (39.4)	172 (44.3)
Male sex — no. (%)	208 (53.9)	219 (56.4)
Race — no. (%)†		
White	356 (92.2)	355 (91.5)
Black	11 (2.8)	7 (1.8)
Asian	17 (4.4)	18 (4.6)
Other	2 (0.5)	8 (2.1)
Geographic region — no. (%)		
Western Europe or North America	91 (23.6)	92 (23.7)
Eastern Europe	249 (64.5)	248 (63.9)
Rest of world	46 (11.9)	48 (12.4)
Body-mass index‡	27.2±5.8	27.4±5.8
Creatinine clearance — no. (%)		
>80 ml/min	187 (48.4)	207 (53.4)
>50–80 ml/min	128 (33.2)	119 (30.7)
30–50 ml/min	70 (18.1)	62 (16.0)
<30 ml/min	1 (0.3)	0
Current smoker — no. (%)	105 (27.2)	82 (21.1)
Past smoker — no. (%)	76 (19.7)	79 (20.4)
Previous lung infection — no. (%)	48 (12.4)	37 (9.5)
Mild-to-moderate COPD — no. (%)§	57 (14.8)	51 (13.1)
Symptomatic asthma with wheezing — no. (%)	18 (4.7)	20 (5.2)
PSI score¶	83.2±16.5	84.0±16.0
PSI risk class — no. (%)¶		
II	55 (14.2)	54 (13.9)
III	227 (58.8)	216 (55.7)
IV	102 (26.4)	115 (29.6)
Modified ATS criteria for severe CABP — no./total no. (%)‖	44/368 (12.0)	53/370 (14.3)
Antibiotics before randomization — no. (%)**	89 (23.1)	90 (23.2)
Bacteremia — no. (%)	15 (3.9)	18 (4.6)

Stets R. 2019

Design of Omadacycline Pivotal, Double-blind Phase 3 Study OPTIC



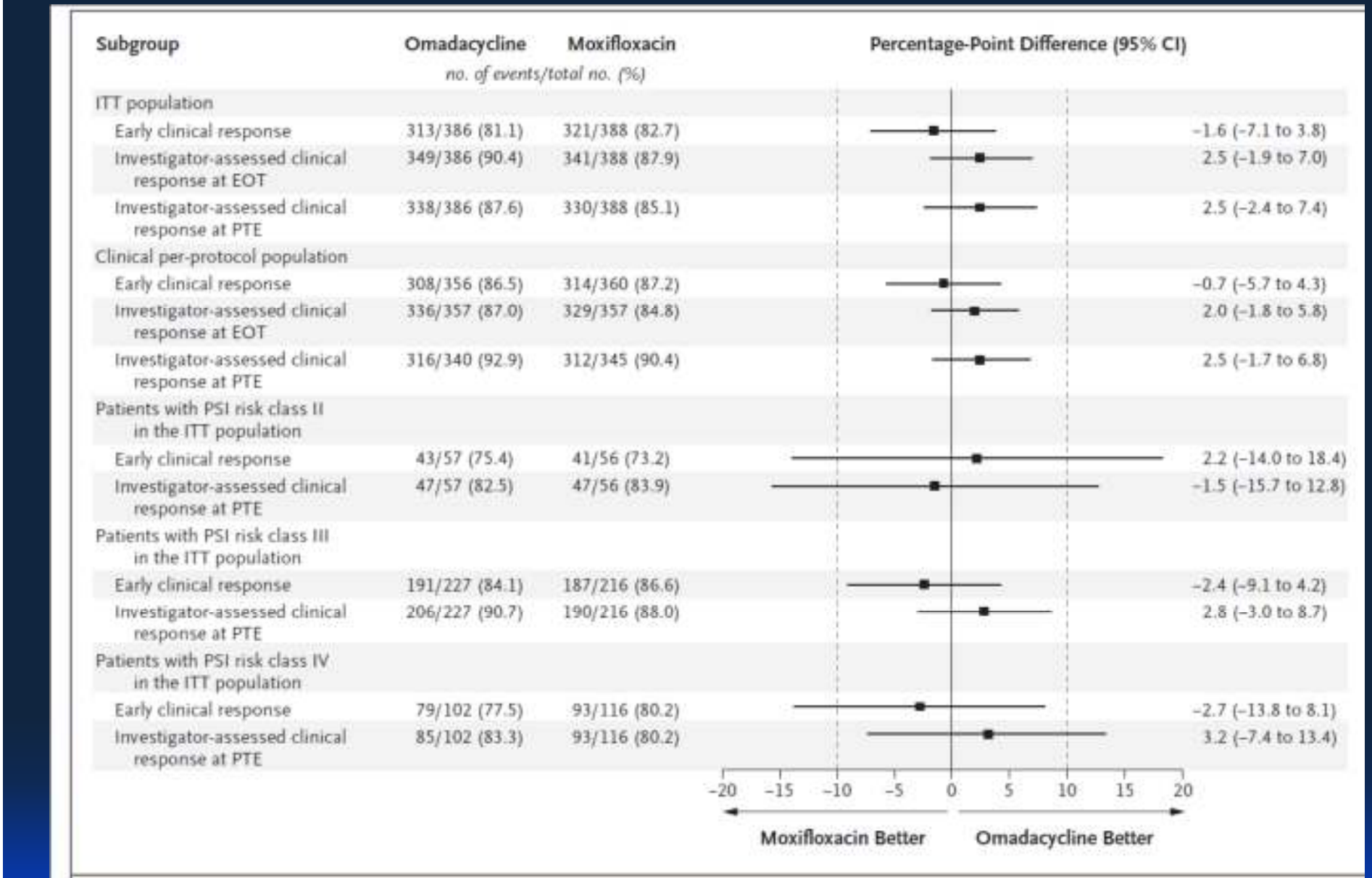


Figure 2. Forest Plot of Primary and Secondary End Points.

Table 2. Investigator-Assessed Clinical Response at the Post-Treatment Evaluation According to Pathogen Detected at Baseline (Microbiologic Intention-to-Treat Population).*

Pathogen Detected at Baseline	Omadacycline (N=204)		Moxifloxacin (N=182)	
	Patients with Pathogen	Patients with Clinical Response	Patients with Pathogen	Patients with Clinical Response
	no.	*no. (%)*	*no.*	*no. (%)*
Gram-positive aerobic bacteria	61	52 (85)	56	49 (88)
Streptococcus pneumoniae†	43	37 (86)	34	31 (91)
Penicillin-susceptible	26	23 (88)	22	21 (95)
Macrolide-resistant	10	10 (100)	5	5 (100)
Tetracycline-resistant	16	14 (88)	17	13 (76)
Staphylococcus aureus‡	11	8 (73)	11	9 (82)
Gram-negative aerobic bacteria	79	67 (85)	69	56 (81)
Haemophilus influenzae	32	26 (81)	16	16 (100)
H. parainfluenzae	18	15 (83)	17	13 (76)
Klebsiella pneumoniae	13	10 (77)	13	11 (85)
Atypical bacteria, SAP definition of positivity§	118	109 (92)	106	97 (92)
Mycoplasma pneumoniae¶	70	66 (94)	57	50 (88)
Legionella pneumophila‖	37	35 (95)	37	36 (97)
Chlamydia pneumoniae¶	28	25 (89)	28	25 (89)
Atypical bacteria, conservative definition of positivity**	73	66 (90)	64	58 (91)
M. pneumoniae¶	35	31 (89)	29	25 (86)
L. pneumophila‖	29	27 (93)	28	27 (96)
C. pneumoniae¶	15	14 (93)	14	13 (93)

Table 3. Adverse Events That Emerged after Treatment Initiation (Safety Population).*

Type of Event	Omadacycline (N=382)	Moxifloxacin (N=388)
	no. of patients (%)	
Any adverse event	157 (41.1)	188 (48.5)
Treatment-related adverse event†	39 (10.2)	69 (17.8)
Severe adverse event	25 (6.5)	26 (6.7)
Serious adverse event	23 (6.0)	26 (6.7)
Treatment discontinuation for adverse event	21 (5.5)	27 (7.0)
Death	8 (2.1)	4 (1.0)
Adverse events that occurred in >2% of patients in either group		
ALT increased	14 (3.7)	18 (4.6)
Hypertension	13 (3.4)	11 (2.8)
γ-Glutamyltransferase increased	10 (2.6)	8 (2.1)
Insomnia	10 (2.6)	8 (2.1)
Vomiting	10 (2.6)	6 (1.5)
Constipation	9 (2.4)	6 (1.5)
Nausea	9 (2.4)	21 (5.4)
AST increased	8 (2.1)	14 (3.6)
Headache	8 (2.1)	5 (1.3)
Diarrhea‡	4 (1.0)	31 (8.0)

Warning and adverse events

- Mortality Imbalance in Patients with CABP: In the CABP trial, mortality rate of 2% was observed in NUZYRA-treated patients
- The most common adverse reactions (incidence ≥2%) are
  - nausea, vomiting, infusion site reactions, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased, hypertension, headache, diarrhea, insomnia, and constipation

Summary Omadacycline

- A new generation tetracycline
  - IV and oral formulations
- Preserve activity against many resistant organisms
- Excellent activity against respiratory pathogens and against gram-positive organisms
- Some activity against GNR
- High efficacy and tolerability in in CABP and ABSSSI trials
- Gained FDA approval for the above indications