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Omadacycline – The First Aminomethylcycline

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Acknowledgments and Disclosures

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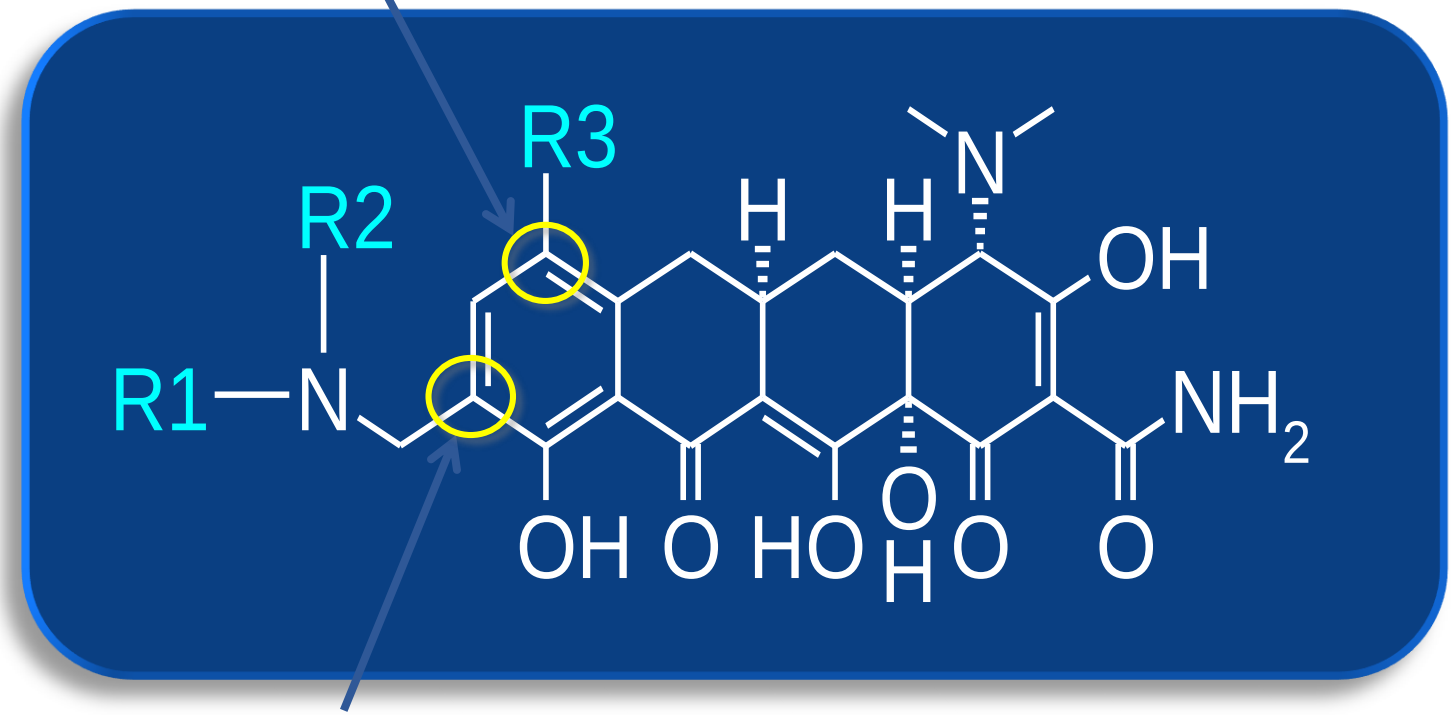
Omadacycline – Investigational Product Overview

Aminomethylcycline

7-Position Modification:
Overcomes Efflux Pump



9-Position Modification:
Overcomes Ribosomal Protection

Key Product Attributes

- Safety and efficacy demonstrated in ABSSSI and CABP
- In-vitro activity against important community pathogens
- Two once-daily formulations – intravenous and oral
- IV and oral formulation with bioequivalence

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Omadacycline Selected Spectrum of Activity by Indication

Skin Pathogens			CABP Pathogens			UTI and Gram (-) Pathogens		
	N	MIC_{90}		N	MIC_{90}		N	MIC_{90}
S. aureus	2,050	0.25	*S. pneumoniae*	605	0.06	*E. coli*	1,692	2
MRSA	920	0.25	Pen-R (≥2)	74	0.12	ESBL	308	2
Tetracycline-R	70	0.5	Tetracycline-R	119	0.12	*K. pneumoniae*	941	4
β-hemolytic strep	541	0.12	Macrolide-R	267	0.12	ESBL	164	8
Viridans group strep	106	0.12	*H. influenzae*	445	1	*E. cloacae* sp.	429	4
E. faecalis	328	0.25	*β-lactamase +*	141	2	*Citrobacter* sp.	210	2
E. faecium	167	0.12	*β-lactamase -*	304	1	*A. baumannii*	144	8
VRE	112	0.12	*M. catarrhalis*	246	0.25			
			L. pneumophila	90	0.25			
			Chlamydophila	5	0.12-0.25			
			M. pneumoniae	28	0.25			

JMI 2016 North American Surveillance, Data on File; J Dubois et al. 2016 abstract 1248 ECCMID Amsterdam, NL;
M Hammerschlag, SUNY Downstate Medical Center, Data on File; Waites KB, et al. 2016. Antimicrob Agents Chemother 60:7502–7504

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Omadacycline – Pharmacokinetics/Pharmacodynamics

- Oral Bioavailability: ~35%
  - Oral absorption is negatively affected by food (<6 h before or < 2 h after oral dose administration; no Ca^{++} containing products for 4 h after oral dose)
- Large Volume of distribution, implying extensive tissue distribution
  - e.g. Alveolar Cell/Plasma partition ratio of 25
- Steady-state exposure (AUC) of 300 mg oral q24 h = 100 mg iv q24 h ~=10 µg·h/mL
  - AUC/MIC 14.9 to 38.7 for *Streptococcus pneumoniae* and *E. coli*
  - AUC/MIC 37.8 to 81.8 for *Staphylococcus aureus and Klebsiella pneumoniae*
- Elimination half-live is between 14-24 h - amenable to q24 h dosing
- Eliminated: ~63-73% of the bioavailable dose is via biliary excretion and ~27-37% via renal excretion
  - Not metabolized
  - No dose adjustments for age, gender, and renal or hepatic impaired subjects
  - Steady-state urine concentration for 300 mg and 450 mg QD range from 18-48 ug/mL
- No QTc effect
- Low potential for DDI

Villano S et. al, Future Microbiol 2016; 11:1421-1434

Omadacycline - Clinical Development Program and Dosing

	Research	Pre-Clinical	Phase 1	Phase 2	Phase 3	NDA
Omadacycline	ABSSI (IV to Oral) – QIDP + SPA ✓					
	CABP (IV to Oral) – QIDP + SPA ✓					
	ABSSSI (Oral Only) – QIDP ✓					
	UTI (Oral & IV) – QIDP					

		Day 1		Day 2		Day 3		Day 4 and beyond
		0h	12h	24h	36h	48h	60h	
OASIS-1 (ABSI-1108)	Omadacycline	100 mg IV	100 mg IV	100mg IV	---	100mg IV	---	After Day 3: either 100 mg IV or 300 mg oral once daily
OPTIC (CABP-1200)	Omadacycline	100 mg IV	100 mg IV	100 mg IV	---	100 mg IV	---	After Day 3: either 100 mg IV or 300 mg oral once daily
OASIS-2 (ABSI-16301)	Omadacycline	450 mg Oral		450 mg Oral	---	300 mg Oral	---	After Day 2: 300 mg oral once daily

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Omadacycline - Most Frequent TEAEs (>2%)

OASIS-1 (ABSSSI)

	Omadacycline (N=323) n (%)	Linezolid (N=322) n (%)
Subjects with any TEAE	**156 (48.3)**	**147 (45.7)**
Nausea	40 (12.4)	32 (9.9)
Vomiting	17 (5.3)	16 (5.0)
Diarrhea	7 (2.2)	10 (3.1)
Infusion site extravasation[a]	28 (8.7)	19 (5.9)
ALT increased	9 (2.8)	14 (4.3)
AST increased	8 (2.5)	12 (3.7)
Subcutaneous abscess	17 (5.3)	19 (5.9)
Cellulitis	15 (4.6)	15 (4.7)
Wound Infection	8 (2.5)	5 (1.6)
Pruritus	7 (2.2)	0 (0.0)
Headache	10 (3.1)	13 (4.0)

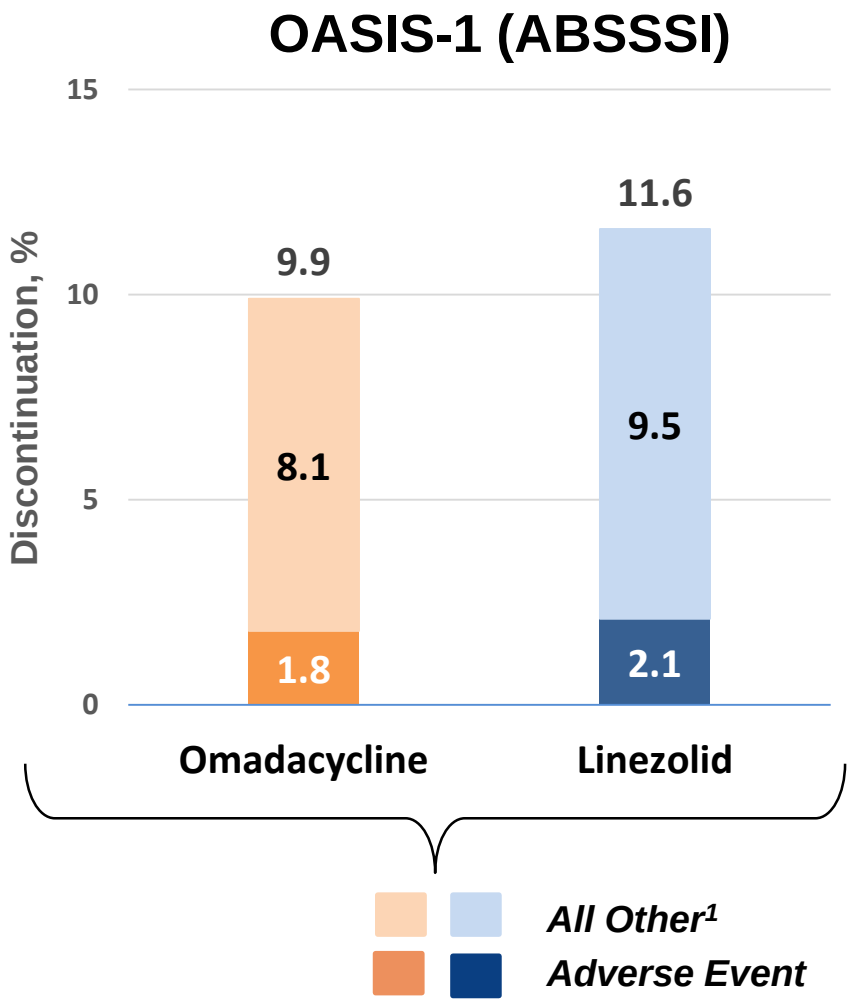
OPTIC (CABP)

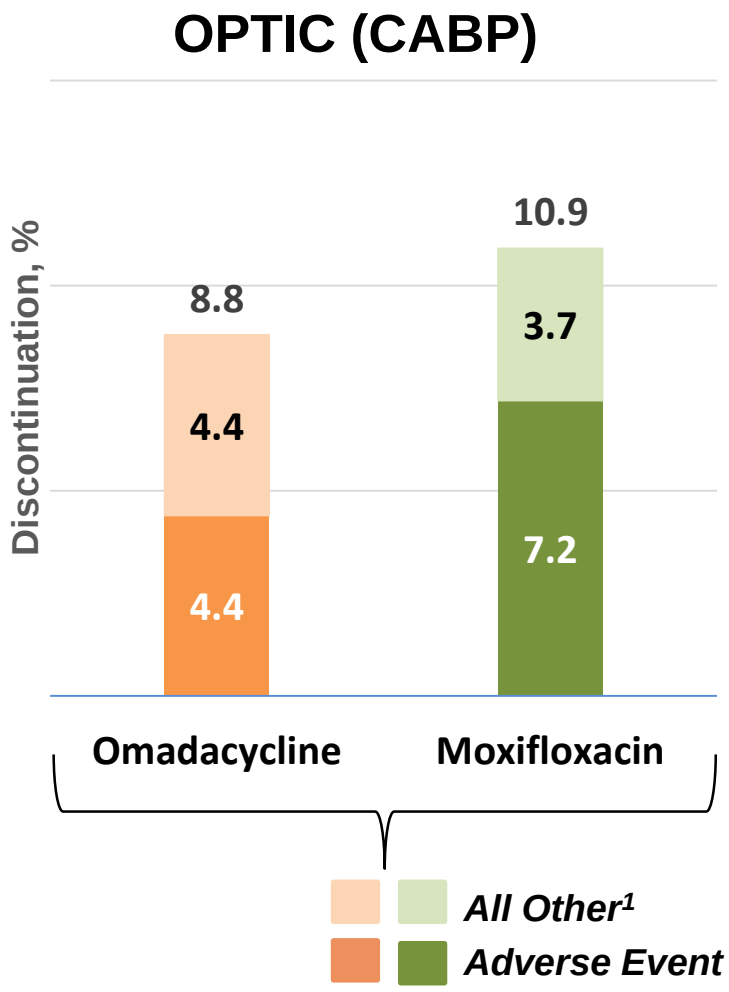
	Omadacycline (N=382) n (%)	Moxifloxacin (N=388) n (%)
Subjects with any TEAE	**157 (41.1)**	**188 (48.5)**
Vomiting	10 (2.6)	6 (1.5)
Nausea	9 (2.4)	21 (5.4)
Constipation	9 (2.4)	6 (1.5)
Diarrhea[b]	4 (1.0)	31 (8.0)
ALT increased	14 (3.7)	18 (4.6)
GGT increased	10 (2.6)	8 (2.1)
AST increased	8 (2.1)	14 (3.6)
Hypertension	13 (3.4)	11 (2.8)
Insomnia	10 (2.6)	8 (2.1)
Headache	8 (2.1)	5 (1.3)

[a] **Events were reported as IV site infiltration, due to difficulty in finding reliable venous access sites.**

[b] **8 cases of *C.difficile* infection in the moxifloxacin arm**

Omadacycline - Premature Discontinuation from Study Treatment





[1] All Other: Lost to Follow-up, Withdrawal by Subject, Physician Decision, Death, Other

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Omadacycline - Liver Chemistry

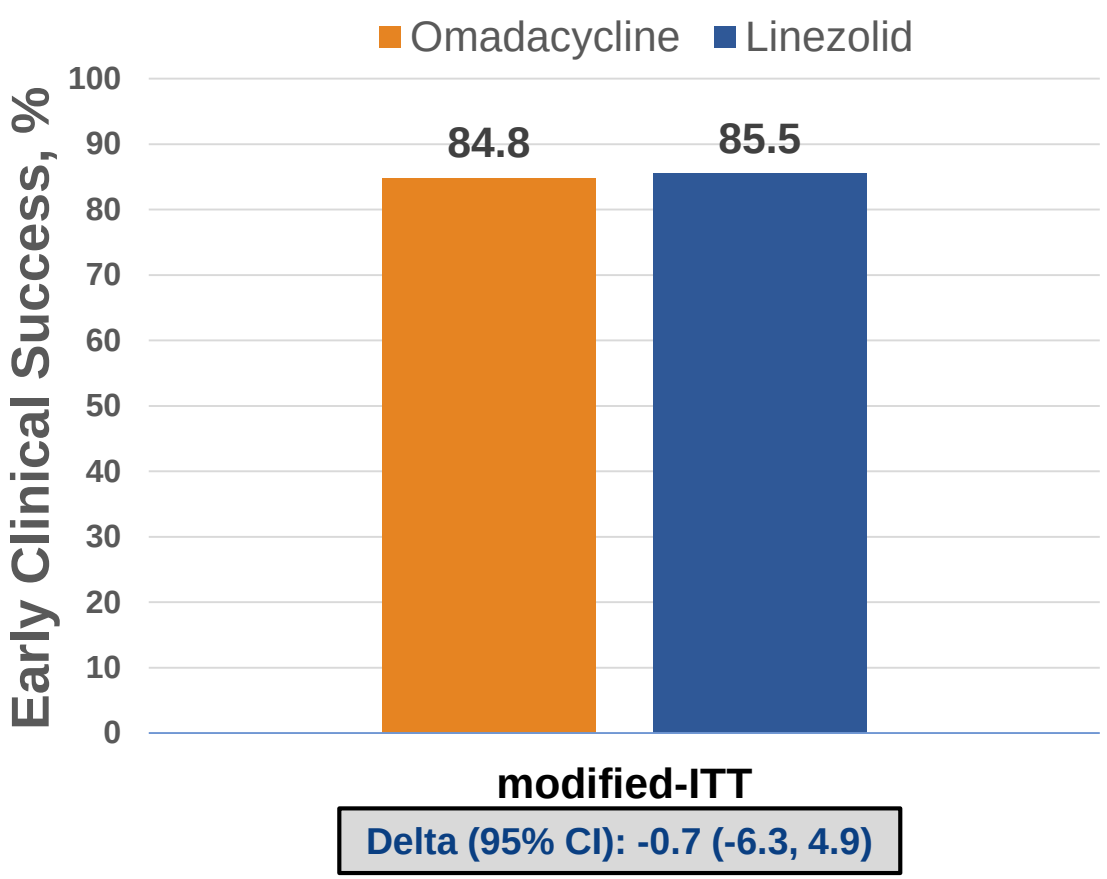
No Drug-Induced Liver Injury (i.e. No Hy's Law Cases)

		OASIS-1 (ABSSSI)		OPTIC (CABP)	
Lab parameter[a]		**OMC**	**LZD**	**OMC**	**MOX**
ALT (U/L)	n[b]	240	251	281	295
	> 3x ULN	3 (1.3)	5 (2.0)	7 (2.5)	11 (3.7)
	> 5x ULN	3 (1.3)	2 (0.8)	2 (0.7)	1 (0.3)
	>10x ULN	1 (0.4)	1 (0.4)	2 (0.7)	0
AST (U/L)	n[b]	263	281	323	328
	> 3x ULN	3 (1.1)	6 (2.1)	5 (1.5)	5 (1.5)
	> 5x ULN	2 (0.8)	3 (1.1)	3 (0.9)	1 (0.3)
	>10x ULN	0	0	1 (0.3)	0
TB (umol/L)	n[b]	296	296	333	343
	>1.5x ULN	2 (0.7)	1 (0.3)	1 (0.3)	6 (1.7)
	> 2x ULN	1 (0.3)	1 (0.3)	1 (0.3)	4 (1.2)

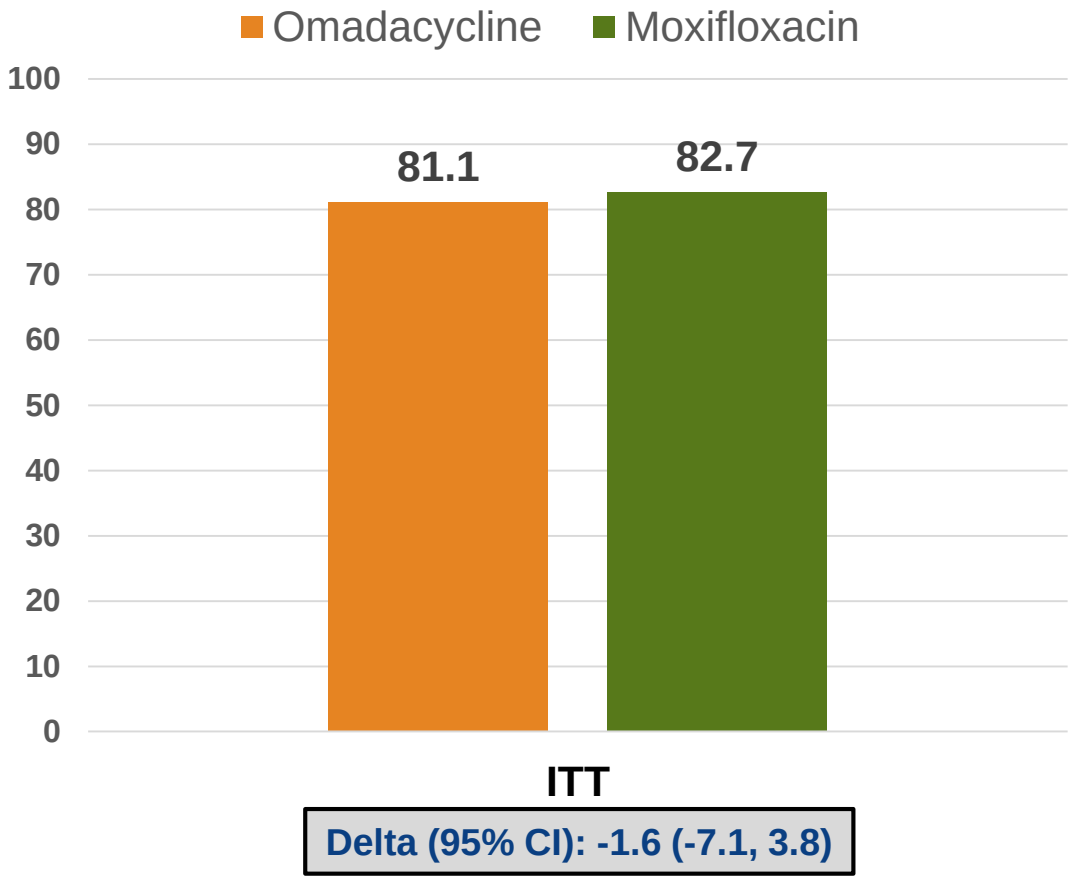
[a] Worst post-baseline value; [b] Number of patients with normal range at baseline

Omadacycline Efficacy – Early Clinical Response (FDA)

OASIS-1 (ABSSSI)



OPTIC (CABP)



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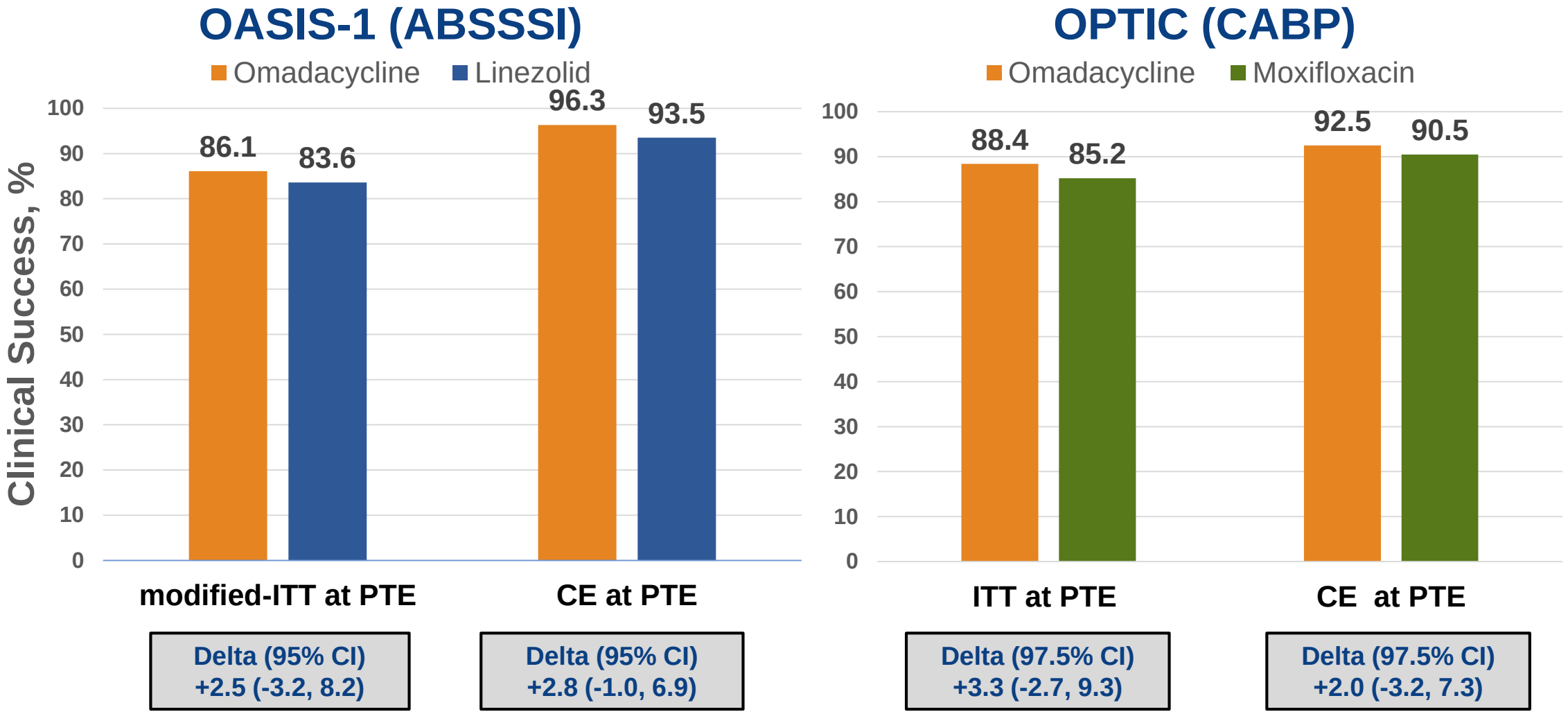
Omadacycline Efficacy – Post Treatment Evaluation (EMA)



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Omadacycline OASIS 1 and OPTIC Summary

- Robust and consistent efficacy observed for omadacycline across all three studies
  - Omadacycline met ALL primary and secondary FDA and EMA endpoints in each study
- Omadacycline was generally safe and well-tolerated
  - Low discontinuation rate for patients on omadacycline and comparators
  - No cases of *Clostridium difficile* infection to date in the clinical development program
  - Post-baseline changes in liver chemistries similar for omadacycline and comparators
    - No evidence of drug induced liver injury (Hy's Law)
- NDA submission on track for finalization1Q2018
  - Two formulations (IV and oral)
  - Two indications (ABSSSI and CABP)

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