Cardiac Safety of Omadacycline in the IV/Oral Phase 3 Acute Bacterial Skin and Skin Structure Infection (ABSSSI) and in the IV/Oral Phase 3 Community-Acquired Bacterial Pneumonia (CABP) Studies

Poster 1886

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BACKGROUND

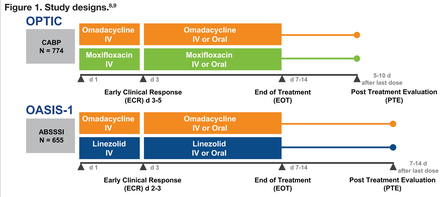
- Omadacycline (OMC) is the first aminomethylcycline in late-stage clinical development
  - Aminomethylcyclines are semisynthetic antibiotics related to the tetracyclines that overcome the 2 main mechanisms of tetracycline resistance, efflux pumps and ribosomal protection[1-3]
- OMC demonstrates potent, broad-spectrum *in vitro* activity against common Gram-positive aerobes (including methicillin- and penicillin-resistant strains), Gram-negative aerobes, anaerobes, and atypical bacterial pathogens[4-3]
- Non-clinical and early clinical studies suggested that OMC had the potential to have a favorable cardiovascular profile
  - OMC had no effect on hERG channel activity or QTc, and demonstrated an overall low potential for cardiac arrhythmia or clinically significant cardiovascular toxicity. OMC inhibited binding of acetylcholine to the M_2-subtype of the muscarinic receptor, resulting in a nonadrenergic, vagolytic effect[6]
  - A phase 1, single-dose, randomized study demonstrated that OMC was associated with asymptomatic increases in heart rate but did not prolong the QT/QTc intervals in healthy adults[7]
- OMC has completed phase 3 clinical development as an intravenous (IV) to once-daily oral monotherapy for community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI). OMC was generally safe and well-tolerated
  - OMC was non-inferior to moxifloxacin (MOX) as an IV to once-daily oral antibiotic for CABP, and was active against the most common CABP pathogens including macrolide-resistant *Streptococcus pneumoniae* (OPTIC)[8]
  - OMC was also non-inferior to linezolid as an IV to once-daily oral antibiotic for ABSSSI, and was active against the most common ABSSSI pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA) (OASIS-1)[9]

OBJECTIVE

- To assess the cardiovascular safety profile of OMC in the phase 3 OPTIC and OASIS-1 studies

METHODS

Figure 1. Study designs.[8,9]



OPTIC Patient Selection[8]

- Key inclusion criteria
  - Qualifying signs, symptoms, and laboratory findings associated with pneumonia
  - Radiographically confirmed pneumonia (new or progressive pulmonary infiltrate(s) on chest x-ray or chest computed tomography consistent with acute bacterial pneumonia within 24 hours prior to the first dose of OMC or MOX)
  - CABP categorized as PORT Risk Class II (≤ 15% of total enrollment), III, or IV at Screening
- Key exclusion criteria
  - ≥ 1 dose(s) of a potentially effective systemic antibacterial treatment within 72 hours prior to the first dose of OMC or MOX
    - Up to 25% of patients were allowed a prior single dose of a short-acting antibiotic
  - Known or suspected hospital-acquired pneumonia or healthcare-associated pneumonia
  - Known history of unstable cardiac disease (eg, unstable angina, myocardial infarction, acute congestive heart failure, or unstable cardiac arrhythmia) within 3 months prior to Screening
  - QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 milliseconds (males) or > 470 milliseconds (females), known long QT syndrome, use of agents with potential proarrhythmic or QT-prolonging effects, and/or present with tachyarrhythmia

OASIS-1 Patient Selection[9]

- Key inclusion criteria
  - Qualifying ABSSSI ≥ 75 cm^2 total surface area of contiguous involved tissue
  - Evidence of a systemic inflammatory response within 24 hours prior to randomization
- Key exclusion criteria
  - Received 1 or more doses of a potentially effective systemic or topical antibacterial treatment within the 72-hour period prior to first dose of study medication
  - Known history of unstable cardiac disease (eg, unstable angina, myocardial infarction, acute congestive heart failure, or unstable cardiac arrhythmia) within 3 months prior to Screening

Table 1. OPTIC and OASIS-1 Cardiovascular Safety Assessments

Study Phase	Screening	IV Treatment Phase					IV or PO Treatment Phase						Follow-up Phase	
Study day		Day 1 IV dose 1	Day 1 IV dose 2	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 10	EOT	PTE		Final Follow-up
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG	X	X		X					X		X			
Adverse events	X	X												X

- Vital signs including blood pressure and pulse/heart rate were recorded prior to each dose while the patient was receiving IV treatment. Thereafter, vital signs were recorded at all visits except the final Follow-up visit
  - In addition, for the first 3 IV doses of study medication (t = 0, 12, and 24 hours), heart rate and blood pressure were recorded immediately before the first infusion, within 30 to 90 minutes after the start of the first infusion, and 3.5 to 5.5 hours after the start of the first infusion
- Reading and interpretation of ECGs was performed centrally
- ECG parameters and vital signs were analyzed separately in OPTIC and OASIS-1 using descriptive statistics

RESULTS

- Patient demographics were generally balanced between treatment arms in OPTIC and OASIS-1
  - Patients enrolled in OPTIC were older than patients enrolled in OASIS-1

Table 2. OPTIC Patient Demographics (Safety Population)

	Omadacycline (n = 382)	Moxifloxacin (n = 388)	All Patients (N = 770)
Gender, n (%)			
Female	177 (46.3)	169 (43.6)	346 (44.9)
Male	205 (53.7)	219 (56.4)	424 (55.1)
Race, n (%)			
White	353 (92.4)	355 (91.5)	708 (91.9)
Black or African American	11 (2.9)	7 (1.8)	18 (2.3)
Asian	17 (4.5)	18 (4.6)	35 (4.5)
American Indian or Alaska Native	0	2 (0.5)	2 (0.3)
Other	1 (0.3)	6 (1.5)	7 (0.9)
Age, mean (SD), years	60.9 (15.1)	62.1 (15.2)	61.5 (15.2)
> 65 years	152 (39.4)	172 (44.3)	324 (41.9)
BMI, mean (SD), kg/m^2	27.2 (5.8)	27.4 (5.8)	27.3 (5.8)

Table 3. OASIS-1 Patient Demographics (Safety Population)

	Omadacycline (n = 323)	Linezolid (n = 322)	All Patients (N = 645)
Gender, n (%)			
Female	120 (37.2)	109 (33.9)	229 (35.5)
Male	203 (62.8)	213 (66.1)	416 (64.5)
Race, n (%)			
White	294 (91.0)	300 (93.2)	594 (92.1)
Black or African American	16 (5.0)	8 (2.5)	24 (3.7)
Asian	1 (0.3)	2 (0.6)	3 (0.5)
American Indian or Alaska Native	7 (2.2)	5 (1.6)	12 (1.9)
Other	5 (1.5)	7 (2.1)	12 (1.8)
Age, mean (SD), years	46.9 (15.45)	46.6 (15.30)	46.8 (15.36)
> 65 years	36 (11.1)	32 (9.9)	68 (10.5)
BMI, mean (SD), kg/m^2	28.0 (6.33)	28.1 (6.23)	28.1 (6.28)

- Consistent with their older age and comorbidities, more patients in OPTIC had a medical history of cardiac disorders compared to patients in OASIS-1

Table 4. OPTIC Cardiac Disorders History (≥ 1% Patients; Safety Population)

	Patients, n (%)	
	Omadacycline (n = 382)	Moxifloxacin (n = 388)
Cardiac disorders	**110 (28.8)**	**119 (30.7)**
Atrial fibrillation	39 (10.2)	35 (9.0)
Coronary artery disease	35 (9.2)	33 (8.5)
Cardiac failure	28 (7.3)	26 (6.7)
Myocardial ischemia	24 (6.3)	27 (7.0)
Cardiac failure chronic	22 (5.8)	20 (5.2)
Myocardial infarction	15 (3.9)	12 (3.1)
Angina pectoris	10 (2.6)	7 (1.8)
Cardiac failure congestive	6 (1.6)	6 (1.5)
Acute myocardial infarction	5 (1.3)	1 (0.3)
Hypertensive heart disease	5 (1.3)	5 (1.3)
Mitral valve incompetence	5 (1.3)	5 (1.3)
Aortic valve incompetence	3 (0.8)	4 (1.0)
Left ventricular hypertrophy	2 (0.5)	4 (1.0)

Table 5. OASIS-1 Cardiac Disorders History (≥ 1% Patients; Safety Population)

	Patients, n (%)	
	Omadacycline (n = 323)	Linezolid (n = 322)
Cardiac disorders	**31 (9.6)**	**28 (8.7)**
Atrial fibrillation	6 (1.9)	6 (1.9)
Cardiac failure chronic	6 (1.9)	3 (0.9)
Myocardial ischemia	5 (1.5)	5 (1.6)
Myocardial infarction	1 (0.3)	4 (1.2)

Treatment Exposure

- Treatment exposure was similar in both arms in OPTIC and OASIS-1
  - OPTIC
    - OMC—mean, 9.6 days IV and PO total; 5.7 days IV; 5.1 days PO
    - MOX—mean, 9.6 days IV and PO total; 5.7 days IV; 5.2 days PO
  - OASIS-1
    - OMC—mean, 9.2 days IV and PO total; 4.4 days IV; 5.5 days PO
    - LZD—mean, 9.1 days IV and PO total; 4.4 days IV; 5.4 days PO

RESULTS

- No clinically relevant differences between treatment arms in cardiovascular TEAEs in OPTIC or OASIS-1

Table 6. OPTIC Cardiac Disorder TEAEs (Safety Population)

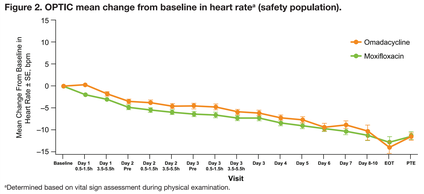
	Patients, n (%)	
	Omadacycline (n = 382)	Moxifloxacin (n = 388)
Cardiac disorders	**15 (3.9)**	**20 (5.2)**
Tachycardia	4 (1.0)	3 (0.8)
Atrial fibrillation	3 (0.8)	1 (0.3)
Cardiac failure	3 (0.8)	3 (0.8)
Acute myocardial infarction	2 (0.5)	0
Cardiogenic shock	2 (0.5)	1 (0.3)
Atrial flutter	1 (0.3)	0
Cardiac arrest	1 (0.3)	0
Cardio-respiratory arrest	1 (0.3)	0
Congestive cardiomyopathy	1 (0.3)	0
Extrasystoles	1 (0.3)	0
Myocardial ischemia	1 (0.3)	2 (0.5)
Stress cardiomyopathy	1 (0.3)	0
Angina pectoris	0	2 (0.5)
Aortic valve stenosis	0	1 (0.3)
Atrioventricular block first degree	0	1 (0.3)
Bradycardia	0	2 (0.5)
Cardiac failure congestive	0	1 (0.3)
Cardiomegaly	0	1 (0.3)
Mitral valve incompetence	0	1 (0.3)
Palpitations	0	1 (0.3)
Pericardial effusion	0	1 (0.3)
Right ventricular failure	0	1 (0.3)
Ventricular extrasystoles	0	1 (0.3)

Table 7. OASIS-1 Cardiac Disorder TEAEs (Safety Population)

	Patients, n (%)	
	Omadacycline (n = 323)	Linezolid (n = 322)
Cardiac disorders	**4 (1.2)**	**3 (0.9)**
Atrial fibrillation	2 (0.6)	0
Sinus bradycardia	1 (0.3)	0
Sinus tachycardia	1 (0.3)	0
Cardiac arrest	0	1 (0.3)
Cardiac failure	0	1 (0.3)
Cardiac failure congestive	0	1 (0.3)
Myocardial ischemia	0	1 (0.3)

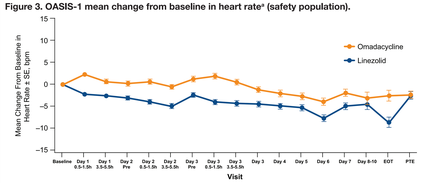
- Small but not clinically relevant differences in changes in heart rate were reported between treatment arms in OPTIC or OASIS-1

Figure 2. OPTIC mean change from baseline in heart rate[a] (safety population).



[a]Determined based on vital sign assessment during physical examination.

Figure 3. OASIS-1 mean change from baseline in heart rate[a] (safety population).

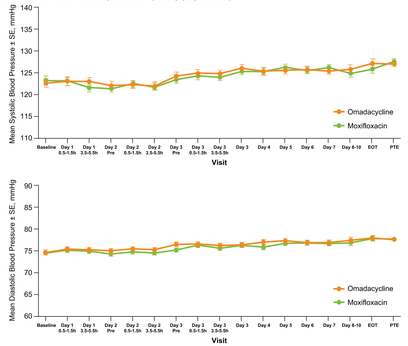


[a]Determined based on vital sign assessment during physical examination.

RESULTS

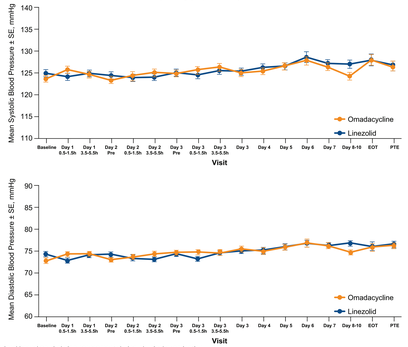
- No clinically relevant differences between treatment arms in blood pressure in OPTIC or OASIS-1

Figure 4. OPTIC mean blood pressure[a] (safety population).



[a]Determined based on vital sign assessment during physical examination.

Figure 5. OASIS-1 mean blood pressure[a] (safety population).



[a]Determined based on vital sign assessment during physical examination.

- Clinically notable changes in vital signs were well balanced between treatments in OPTIC and OASIS-1

Table 8. OPTIC Summary of Clinically Notable Changes in Heart Rate and Blood Pressure (Safety Population)

	Patients, n (%)	
	Omadacycline (n = 382)	Moxifloxacin (n = 388)
Patients with heart rate value at any post-baseline visit		
Heart rate ≥ 120 bpm	21 (5.5)	22 (5.7)
Patients with heart rate value at baseline and any post-baseline visit		
Heart rate ≥ 120 bpm and increase of ≥ 15 bpm	5 (1.3)	8 (2.1)
Systolic blood pressure ≥ 180 mm Hg	11 (2.9)	8 (2.1)
Patients with systolic blood pressure value at baseline and any post-baseline visit		
Systolic blood pressure ≥ 180 mm Hg and increase of ≥ 20 mm Hg	9 (2.4)	6 (1.5)
Patients with diastolic blood pressure value at baseline and any post-baseline visit		
Diastolic blood pressure ≥ 105 mm Hg and increase of ≥ 15 mm Hg	7 (1.8)	5 (1.3)

RESULTS

Table 9. OASIS-1 Summary of Clinically Notable Changes in Heart Rate and Blood Pressure (Safety Population)

	Patients, n (%)	
	Omadacycline (n = 323)	Linezolid (n = 322)
Patients with heart rate value at any post-baseline visit		
Heart rate ≥ 120 bpm	5 (1.5)	6 (1.9)
Patients with heart rate value at baseline and any post-baseline visit		
Heart rate ≥ 120 bpm and increase of ≥ 15 bpm	5 (1.5)	6 (1.9)
Systolic blood pressure ≥ 180 mm Hg	5 (1.5)	12 (3.7)
Patients with systolic blood pressure value at baseline and any post-baseline visit		
Systolic blood pressure ≥ 180 mm Hg and increase of ≥ 20 mm Hg	4 (1.2)	11 (3.4)
Patients with diastolic blood pressure value at baseline and any post-baseline visit		
Diastolic blood pressure ≥ 105 mm Hg and increase of ≥ 15 mm Hg	6 (1.9)	9 (2.8)

- OMC did not affect ECG parameters in the OPTIC study
  - Mean ΔQTcF was within 0.8 to 1.8 msec after the first and before the third dose of OMC, and mean ΔPR and ΔQRS were negligible across study visits
  - MOX, with a known and well-described effect on cardiac repolarization, served as a positive control regarding QT prolongation with mean ΔQTcF of 5.8 and 11.1 msec after the first and third dose, respectively[10]

Table 10. OPTIC Summary of Clinically Notable Changes in ECG Values (Safety Population)

	Patients, n (%)	
	Omadacycline (n = 352)	Moxifloxacin (n = 368)
Number of patients with both a baseline and post-baseline QTcF value	**354**	**360**
Patients with baseline QTcF ≤ 450 and any post-baseline QTcF > 450 ms	42 (11.9)	79 (21.9)
Patients with baseline QTcF ≤ 500 and any post-baseline QTcF > 500 ms	6 (1.7)	4 (1.1)
Maximum increase from baseline ≥ 30 and ≤ 60 ms	67 (18.9)	104 (28.9)
Maximum increase from baseline > 60 ms	10 (2.8)	14 (3.9)
Maximum post-baseline value > 450 ms and increase from baseline > 30 ms	24 (6.8)	48 (13.3)
Maximum post-baseline value > 500 ms and increase from baseline > 30 ms	5 (1.4)	4 (1.1)
Number of patients with a post-baseline QTcF value	**359**	**367**
Maximum post-baseline value > 450 to ≤ 480 ms	47 (13.1)	95 (25.9)
Maximum post-baseline value > 480 to ≤ 500 ms	9 (2.5)	13 (3.5)
Maximum post-baseline value > 500 ms	7 (1.9)	7 (1.9)

- No clinically relevant differences between treatment arms in ECG values in OASIS-1

Table 11. OASIS-1 Summary of Clinically Notable Changes in ECG Values (Safety Population)

	Patients, n (%)	
	Omadacycline (n = 323)	Linezolid (n = 322)
Patients with baseline QTcF ≤ 450 and any post-baseline QTcF > 450 ms	**23 (7.1)**	**29 (9.0)**
Patients with baseline QTcF ≤ 500 and any post-baseline QTcF > 500 ms	**1 (0.3)**	**2 (0.6)**
Number of patients with both a baseline and post-baseline QTcF value	**317**	**319**
Maximum increase from baseline ≥ 30 and ≤ 60 ms	26 (8.2)	42 (13.2)
Maximum increase from baseline > 60 ms	1 (0.3)	4 (1.3)
Maximum post-baseline value > 450 ms and increase from baseline > 30 ms	3 (0.9)	13 (4.1)
Maximum post-baseline value > 500 ms and increase from baseline > 30 ms	1 (0.3)	2 (0.6)
Number of patients with a post-baseline QTcF value	**322**	**321**
Maximum post-baseline value > 450 to ≤ 480 ms	34 (10.6)	35 (10.9)
Maximum post-baseline value > 480 to ≤ 500 ms	1 (0.3)	8 (2.5)
Maximum post-baseline value > 500 ms	3 (0.9)	3 (0.9)

CONCLUSIONS

- Omadacycline was not associated with clinically relevant changes in cardiac safety, heart rate, blood pressure, or ECG values in OPTIC or OASIS-1
  - Moxifloxacin was associated with changes in QTc values in OPTIC

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