Impact of Age and Gender on Efficacy and Safety of Omadacycline versus Moxifloxacin in Community-acquired Bacterial Pneumonia

Poster PA 5465

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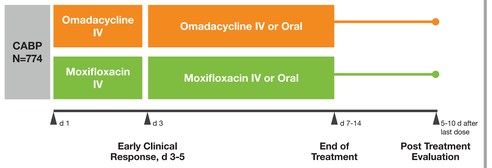
BACKGROUND

- Omadacycline (OMC) is a tetracycline class aminomethylcycline antibiotic that has been developed as a once-daily oral and intravenous monotherapy for acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP).
- *In vitro*, OMC has demonstrated activity against Gram-positive and many Gram-negative aerobes, anaerobes, and atypical bacterial pathogens.[1,2]
- In the Phase 3 **O**madacycline for **P**neumonia **T**reatment **I**n the **C**ommunity (OPTIC) study, OMC displayed non-inferiority to moxifloxacin (MOX) in the treatment of adults with CABP[3]
- Advanced age remains a risk factor for pneumonia,[4] and the pneumonia severity index (PSI or PORT Score) includes both age and gender for predicting mortality.
- Two previous Phase 1, double-blind, placebo-controlled studies have examined the effect of age and gender on the pharmacokinetic (PK) profile of OMC.[5] Dosage adjustments on the basis of age or gender are not required.[5]
- Here we report efficacy outcomes in the OPTIC study by age and gender.

METHODS

Figure 1. OPTIC Study Design



IV = intravenous

- Study design: Multicentre, randomized (1:1), double-blind, noninferiority study comparing OMC and MOX in adults with CABP (NCT02531438, EudraCT #2013-004071-13)
- Treatment: 7-14 days
  - OMC: 100 mg intravenous every 12 hours for 2 doses, then 100 mg intravenous every 24 hours; optional switch to 300 mg oral every 24 hours after ≥3 days
  - MOX: 400 mg intravenous every 24 hours; optional switch to 400 mg oral every 24 hours after ≥3 days
  - Randomization was stratified by PORT Risk Class (II or III/IV), receipt of allowed prior antibiotic, and geographic region
- Eligibility
  - Adults ≥18 years of age with ≥3 symptoms (cough, production of purulent sputum, dyspnea, or pleuritic chest pain); ≥2 abnormal vital signs (fever or hypothermia, SBP <90 mmHg, HR >90 bpm, RR >20 breaths/minute); and ≥1 clinical sign or laboratory finding associated with CABP
    - Up to 25% of individuals were allowed a prior single dose of short-acting antibiotic
  - Exclusions included individuals who received a systemic antibacterial treatment within 72 hours of the first study drug dose or had hospital-acquired pneumonia
- The intent-to-treat (ITT) population included all randomized individuals
- Primary efficacy endpoint
  - Early clinical response (ECR): success was defined as survival with improvement in ≥2 of 4 symptoms and no worsening of any symptom at 72-120 hours after the first study drug dose
- Secondary efficacy endpoint
  - Investigator-assessed clinical response at post therapy evaluation (PTE; 5-10 days after last dose): success was defined as survival and investigator-determined resolution of infection signs and symptoms such that further antibacterial treatment was not needed
- *Ad hoc* analyses of efficacy and safety by age and gender were carried out

RESULTS

- Overall, baseline demographics were comparable between males and females.
  - In the ITT population, males were 53.9% of the OMC group and 56.4% of the MOX group
  - Females in both treatment groups had a higher percentage of mild and moderate renal impairment than males
  - In both treatment groups, a higher percentage of males were PORT Risk Class IV

Table 1. Baseline Demographics by Gender (ITT Population)

	Female			Male		
Characteristic	OMC (N=178)	MOX (N=169)	ALL (N=347)	OMC (N=208)	MOX (N=219)	ALL (N=427)
Age, Years						
Mean (standard deviation)	61.7 (15.5)	64.1 (14.7)	62.9 (15.2)	60.2 (15.0)	60.6 (15.4)	60.4 (15.2)
Median (minimum, maximum)	62 (25, 90)	66 (26, 92)	64 (25, 92)	60 (19, 97)	62 (19, 94)	61 (19, 97)
Body Mass Index, kg/m²						
Mean (standard deviation)	27.78 (6.20)	27.47 (6.11)	27.63 (6.15)	26.77 (5.30)	27.39 (5.55)	27.09 (5.43)
Renal Function, n (%)						
Normal (CrCl >80 mL/min)	79 (44.4)	73 (43.2)	152 (43.8)	108 (51.9)	134 (61.2)	242 (56.7)
Mild impairment (CrCl >50-80 mL/min)	67 (37.6)	57 (33.7)	124 (35.7)	61 (29.3)	62 (28.3)	123 (28.8)
Moderate impairment (CrCl 30-50 mL/min)	32 (18.0)	39 (23.1)	71 (20.5)	38 (18.3)	23 (10.5)	61 (14.3)
Severe impairment (CrCl <30 mL/min)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
PORT Risk Class, n (%)						
I (0≤PORT Score≤50)	2 (1.1)	1 (0.6)	3 (0.9)	0 (0.0)	1 (0.5)	1 (0.2)
II (51≤PORT Score≤70)	32 (18.0)	25 (14.8)	57 (16.4)	23 (11.1)	29 (13.2)	52 (12.2)
III (71≤PORT Score≤90)	108 (60.7)	110 (65.1)	218 (62.8)	119 (57.2)	106 (48.4)	225 (52.7)
IV (91≤PORT Score≤130)	36 (20.2)	33 (19.5)	69 (19.9)	66 (31.7)	82 (37.4)	148 (34.7)
V (PORT Score≥131)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)

- Overall, baseline demographics were comparable between age groups.
  - In the ITT population, subjects ≥65 years of age were 42.2% of the OMC group and 47.2% of the MOX group
    - Subjects ≥75 years of age were 22.0% of the OMC group and 22.7% of the MOX group
  - Subjects ≥65 years old had decreased renal function compared with subjects <65 years old
  - Renal insufficiency was greatest in subjects ≥75 years old (48.0%, mild renal impairment; 42.8%, moderate renal impairment)
  - PORT Risk Class distribution was higher in subjects ≥65 years old; this is not unexpected given the age criteria for the PORT scoring system

Table 2. Baseline Demographics by Age (ITT Population)

	<65 Years			≥65 Years		
Characteristic	OMC (N=223)	MOX (N=205)	ALL (N=428)	OMC (N=163)	MOX (N=183)	ALL (N=346)
Gender, n (%)						
Female	99 (44.4)	78 (38.0)	177 (41.4)	79 (48.5)	91 (49.7)	170 (49.1)
Male	124 (55.6)	127 (62.0)	251 (58.6)	84 (51.5)	92 (50.3)	176 (50.9)
BMI, kg/m²						
Mean (standard deviation)	26.94 (6.14)	27.49 (6.07)	27.20 (6.11)	27.64 (5.15)	27.35 (5.47)	27.49 (5.31)
Renal Function, n (%)						
Normal (CrCl >80 mL/min)	161 (72.2)	163 (79.5)	324 (75.7)	26 (16.0)	44 (24.0)	70 (20.2)
Mild impairment (CrCl >50-80 mL/min)	46 (20.6)	37 (18.0)	83 (19.4)	82 (50.3)	82 (44.8)	164 (47.4)
Moderate impairment (CrCl 30-50 mL/min)	16 (7.2)	5 (2.4)	21 (4.9)	54 (33.1)	57 (31.1)	111 (32.1)
Severe impairment (CrCl <30 mL/min)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)
PORT Risk Class, n (%)						
I (0≤PORT Score≤50)	2 (0.9)	2 (1.0)	4 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
II (51≤PORT Score≤70)	52 (23.3)	46 (22.4)	98 (22.9)	3 (1.8)	8 (4.4)	11 (3.2)
III (71≤PORT Score≤90)	140 (62.8)	127 (62.0)	267 (62.4)	87 (53.4)	89 (48.6)	176 (50.9)
IV (91≤PORT Score≤130)	29 (13.0)	30 (14.6)	59 (13.8)	73 (44.8)	85 (46.4)	158 (45.7)
V (PORT Score≥131)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)

RESULTS

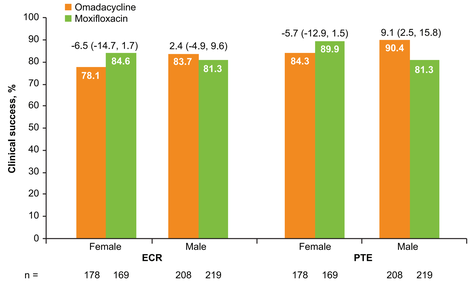
Table 3. Most Common Pathogens by Gender or Age Identified from Blood Specimens, Respiratory Specimens, Urinary Antigen Tests, and/or Serology (microITT Population)

	Female		Male		<65 Years		≥65 Years	
Baseline Pathogen	OMC (N=91) n (%)	MOX (N=79) n (%)	OMC (N=113) n (%)	MOX (N=103) n (%)	OMC (N=120) n (%)	MOX (N=97) n (%)	OMC (N=84) n (%)	MOX (N=85) n (%)
Gram-positive Bacteria (Aerobes)	28 (30.8)	26 (32.9)	33 (29.2)	30 (29.1)	36 (30.0)	27 (27.8)	25 (29.8)	29 (34.1)
Streptococcus pneumoniae[a]	18 (19.8)	14 (17.7)	25 (22.1)	20 (19.4)	26 (21.7)	19 (19.6)	17 (20.2)	15 (17.6)
MDRSP	3 (3.3)	3 (3.8)	4 (3.5)	3 (2.9)	3 (2.5)	4 (4.1)	4 (4.8)	2 (2.4)
PSSP	11 (12.1)	9 (11.4)	15 (13.3)	13 (12.6)	13 (10.8)	16 (16.5)	13 (15.5)	6 (7.1)
Macrolide resistant	4 (4.4)	2 (2.5)	6 (5.3)	3 (2.9)	6 (5.0)	4 (4.1)	4 (4.8)	1 (1.2)
Staphylococcus aureus	6 (6.6)	7 (8.9)	5 (4.4)	4 (3.9)	6 (5.0)	4 (4.1)	5 (6.0)	7 (8.2)
Gram-negative Bacteria (Aerobes)	31 (34.1)	26 (32.9)	48 (42.5)	42 (40.8)	39 (32.5)	33 (34.0)	40 (47.6)	35 (41.2)
Escherichia coli	1 (1.1)	3 (3.8)	5 (4.4)	4 (3.9)	3 (2.5)	2 (2.1)	3 (3.6)	5 (5.9)
Haemophilus influenzae	16 (17.6)	7 (8.9)	16 (14.2)	9 (8.7)	17 (14.2)	8 (8.2)	15 (17.9)	8 (9.4)
Haemophilus parainfluenzae	2 (2.2)	5 (6.3)	16 (14.2)	12 (11.7)	13 (10.8)	11 (11.3)	5 (6.0)	6 (7.1)
Klebsiella pneumoniae	8 (8.8)	3 (3.8)	5 (4.4)	10 (9.7)	5 (4.2)	6 (6.2)	8 (9.5)	7 (8.2)
Atypical Pathogens[b]	31 (34.1)	28 (35.4)	42 (37.2)	36 (35.0)	45 (37.5)	37 (38.1)	28 (33.3)	27 (31.8)
Legionella pneumophila[c]	11 (12.1)	15 (19.0)	18 (15.9)	13 (12.6)	21 (17.5)	15 (15.5)	8 (9.5)	13 (15.3)
Chlamydophila pneumoniae[d]	6 (6.6)	3 (3.8)	9 (8.0)	11 (10.7)	8 (6.7)	9 (9.3)	7 (8.3)	5 (5.9)
Mycoplasma pneumoniae[d]	14 (15.4)	13 (16.5)	21 (18.6)	16 (15.5)	21 (17.5)	16 (16.5)	14 (16.7)	13 (15.3)

MDRSP = multi-drug resistant *Streptococcus pneumoniae*; PSSP = penicillin-susceptible *Streptococcus pneumoniae*
[a]Overall tabulation of *Streptococcus pneumoniae* included identification from urinary antigen only and identification from culture
[b]For identification by serology, considers only a positive convalescent serology as positive
[c]*Legionella pneumophila* was identified by urinary antigen or serology
[d]*Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* were identified by serology

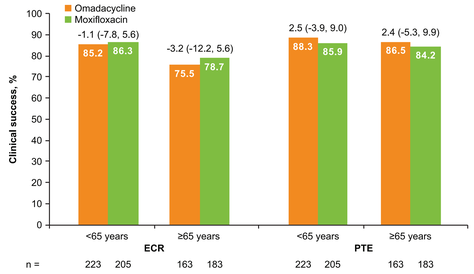
- Both ECR and PTE rates were higher in males in the OMC group
- ECR rates were higher in subjects <65 years of age, whereas PTE rates were comparable between the age strata
  - Clinical success in subjects ≥75 years old: ECR OMC 76.5%, ECR MOX 77.3%; PTE OMC 89.4%, PTE MOX 81.8%

Figure 2. Clinical Success by Gender at ECR and PTE (ITT Population)



RESULTS

Figure 3. Clinical Success by Age at ECR and PTE (ITT Population)



- Treatment-emergent adverse events (TEAEs) were more frequent in older subjects
- In the OMC group, TEAEs were more frequent in females (46.9%) than in males (36.1%)
  - Nausea and vomiting were slightly higher in females than in males

Table 4. Treatment-emergent Adverse Events by Gender (Safety Population)

	Female		Male	
	OMC (N=177)	MOX (N=169)	OMC (N=205)	MOX (N=219)
Total TEAEs, n	199	207	177	254
Subjects with at least one AE, n (%)	88 (49.7)	85 (50.3)	82 (40.0)	115 (52.5)
TEAEs, n (%)	83 (46.9)	80 (47.3)	74 (36.1)	108 (49.3)
Drug-related TEAEs, n (%)	22 (12.4)	35 (20.7)	17 (8.3)	34 (15.5)
Severe TEAEs, n (%)	12 (6.8)	10 (5.9)	13 (6.3)	16 (7.3)
Serious TEAEs, n (%)	12 (6.8)	12 (7.1)	11 (5.4)	14 (6.4)
Subjects who died, n (%)	3 (1.7)	2 (1.2)	5 (2.4)	2 (0.9)

Table 5. Treatment-emergent Adverse Events by Age (Safety Population)

	<65 Years		≥65 Years	
	OMC (N=221)	MOX (N=205)	OMC (N=161)	MOX (N=183)
Total TEAEs, n	165	211	211	250
Subjects with at least one AE, n (%)	89 (40.3)	99 (48.3)	81 (50.3)	101 (55.2)
TEAEs, n (%)	77 (34.8)	89 (43.4)	80 (49.7)	99 (54.1)
Drug-related TEAEs, n (%)	21 (9.5)	28 (13.7)	18 (11.2)	41 (22.4)
Severe TEAEs, n (%)	7 (3.2)	12 (5.9)	18 (11.2)	14 (7.7)
Serious TEAEs, n (%)	7 (3.2)	11 (5.4)	16 (9.9)	15 (8.2)
Subjects who died, n (%)	0 (0)	0 (0)	8 (5.0)	4 (2.2)

Table 6. Frequent Treatment-emergent Adverse Events by Gender (Safety Population; 2% Cutoff)

	Female			Male	
Preferred Term	OMC (N=177) n (%)	MOX (N=169) n (%)	Preferred Term	OMC (N=205) n (%)	MOX (N=219) n (%)
Nausea	9 (5.1)	16 (9.5)	Alanine aminotransferase increased	8 (3.9)	15 (6.8)
Hypertension	8 (4.5)	5 (3.0)	Constipation	6 (2.9)	5 (2.3)
Vomiting	7 (4.0)	6 (3.6)	Lung neoplasm	6 (2.9)	1 (0.5)
Alanine aminotransferase increased	6 (3.4)	3 (1.8)	Aspartate aminotransferase Increased	5 (2.4)	11 (5.0)
Headache	6 (3.4)	3 (1.8)	Gamma-glutamyltransferase increased	5 (2.4)	5 (2.3)
Insomnia	6 (3.4)	3 (1.8)	Insomnia	4 (2.0)	5 (2.3)
Influenza	5 (2.8)	0 (0.0)	Diarrhoea	2 (1.0)	18 (8.2)
Gamma-glutamyltransferase increased	5 (2.8)	3 (1.8)	Chronic obstructive pulmonary disease	2 (1.0)	5 (2.3)
Anaemia	4 (2.3)	2 (1.2)	Nausea	0 (0.0)	5 (2.3)
Diarrhoea	2 (1.1)	13 (7.7)			
Clostridium difficile infection	0 (0.0)	4 (2.4)			

RESULTS

Table 7. Frequent Treatment-emergent Adverse Events by Age (Safety Population; 2% Cutoff)

	<65 Years			≥65 Years	
Preferred Term	OMC (N=221) n (%)	MOX (N=205) n (%)	Preferred Term	OMC (N=161) n (%)	MOX (N=183) n (%)
Alanine aminotransferase increased	9 (4.1)	11 (5.4)	Constipation	6 (3.7)	5 (2.7)
Gamma-glutamyltransferase increased	8 (3.6)	7 (3.4)	Vomiting	6 (3.7)	4 (2.2)
Hypertension	7 (3.2)	5 (2.4)	Renal Cyst	6 (3.7)	0 (0.0)
Insomnia	6 (2.7)	1 (0.5)	Hypertension	6 (3.7)	6 (3.3)
Headache	5 (2.3)	4 (2.0)	Anaemia	5 (3.1)	3 (1.6)
Nausea	4 (1.8)	7 (3.4)	Nausea	5 (3.1)	14 (7.7)
Aspartate aminotransferase increased	4 (1.8)	9 (4.4)	Alanine aminotransferase increased	5 (3.1)	7 (3.8)
Diarrhoea	2 (0.9)	14 (6.8)	Hypokalaemia	4 (2.5)	4 (2.2)
Rash	1 (0.5)	5 (2.4)	Lung neoplasm	4 (2.5)	1 (0.5)
			Insomnia	4 (2.5)	7 (3.8)
			Aspartate aminotransferase increased	4 (2.5)	5 (2.7)
			Aortic arteriosclerosis	4 (2.5)	2 (1.1)
			Chronic obstructive pulmonary disease	3 (1.9)	4 (2.2)
			Diarrhoea	2 (1.2)	17 (9.3)

CONCLUSIONS

- Omadacycline and moxifloxacin showed similar efficacy in the treatment of CABP regardless of age or gender
- Omadacycline was safe and well tolerated in both males and females, and in younger (<65) and older (≥65) adults

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