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Integrated Safety Summary of Omadacycline: A Novel Aminomethylcycline Antibiotic

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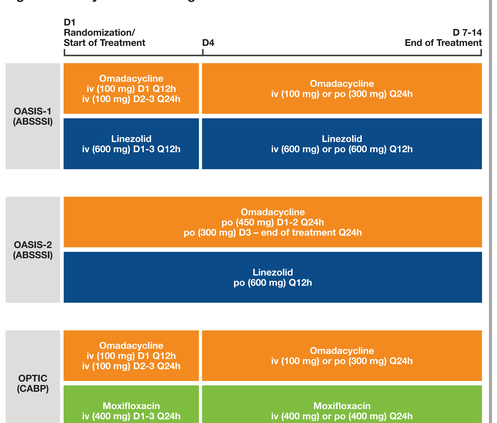
BACKGROUND

- Omadacycline (OMC) is a semisynthetic antibacterial derived from the tetracycline class of antibiotics and classified as an aminomethylcycline[1,2]
- OMC circumvents tetracycline-specific resistance, including efflux and ribosomal protection[3]
- OMC has demonstrated *in vitro* activity against Gram-positive aerobes, many Gram-negative aerobes, anaerobes, and atypical bacterial pathogens[4,5]
- OMC inhibits carbamylcholine binding to the M_2 subtype of the muscarinic acetylcholine receptor, resulting in a maximum concentration (C_{max})-related vagolytic effect and a transient, generally asymptomatic increase in heart rate (HR), primarily observed in healthy volunteers exposed to OMC (12-17 beats per min [bpm] for 100-200 mg intravenous [iv] doses)
- OMC has no effect on the QTc interval (negative thorough QTc study)
- OMC has been studied as a once-daily iv and oral (po) monotherapy for acute bacterial skin and skin structure infections (ABSSSI)[6,7] and community-acquired bacterial pneumonia (CABP)[8]
- We present an integrated review of the safety results from three randomized, double-blind, multicenter Phase 3 studies, including two ABSSSI studies (**O**madacycline in **A**cute **S**kin and skin structure **I**nfections **S**tudy [OASIS-1 and OASIS-2]) and one CABP study (**O**madacycline for **P**neumonia **T**reatment **I**n the **C**ommunity [OPTIC])[6,7,8]

METHODS

- All analyses were performed on the safety population consisting of all subjects who were randomized and received any amount of study drug
- In the ABSSSI studies the comparator study drug was linezolid (LZD) and in the CABP study the comparator study drug was moxifloxacin (MOX)
- The total treatment duration in the three Phase 3 studies was 7-14 days with the treatment regimens shown in **Fig. 1**

Figure 1. Study Treatment Regimens



ABSSSI = acute bacterial skin and skin structure infection; CABP = community-acquired bacterial pneumonia; D = day; *iv* = intravenous; po = oral

METHODS

- Treatment-emergent adverse events (TEAEs) were recorded through Days 30-37 after first dose of study drug
  - TEAE defined as any adverse event that newly appeared, increased in frequency, or worsened in severity on or after initiation of study drug treatment
  - Determined number and percentage of subjects who experienced a TEAE in each group by MedDRA system organ class and preferred term
- Grades of laboratory values were determined based on the modified Division of Microbiology and Infectious Diseases criteria, Nov 21, 2007
- An extensive monitoring program utilizing electrocardiograms (ECGs) to measure HR changes pre- and post- Day 1 (ie, dose 1) and Day 2 (ie, dose 3) iv dosing time points in the OASIS-1 and OPTIC studies was implemented
  - This ECG sampling approach (30 min pre- and 30-90 min post-OMC infusion) was chosen to include time points that would most closely represent C_{max} exposure to OMC

RESULTS

- This pooled analysis is based on 2,150 subjects enrolled and treated in the three Phase 3 studies
  - 705 subjects received the combined iv and po OMC regimen for the treatment of ABSSSI (n=323) and CABP (n=382) in the OASIS-1 and OPTIC studies, respectively
  - 368 subjects received the po-only OMC regimen for the treatment of ABSSSI in the OASIS-2 study
- Mean days of total therapy was 8-10 days (**Table 1**)
  - Duration of iv, po, and total therapy was similar between OMC and comparator in each study

Table 1. Study Drug Exposure in the ABSSSI and CABP Phase 3 Studies (Safety Population)

	OASIS-1		OASIS-2		OPTIC	
Parameter	OMC N=323	LZD N=322	OMC N=368	LZD N=367	OMC N=382	MOX N=388
Days of iv Therapy						
n	323	322	NA	NA	382	388
Mean (SD)	4.4 (1.96)	4.4 (2.11)	NA	NA	5.7 (2.51)	5.7 (2.94)
Days of po Therapy						
n	286	283	368	367	295	294
Mean (SD)	4.0 (1.33)	5.4 (1.71)	8.2 (2.77)	8.0 (2.98)	5.1 (1.93)	5.2 (2.04)
Total Days on Therapy						
Mean (SD)	9.2 (2.76)	9.1 (2.85)	8.2 (2.77)	8.0 (2.98)	9.6 (2.88)	9.6 (2.94)

NA = not applicable; SD = standard deviation

- Study treatment completion was ~90% (treatment group range 87-91%)
- Study completion was ~90% (treatment group range 88-93%)
- Demographics of the ABSSSI and CABP populations are described in **Table 2**
- An overview of adverse events is provided in **Table 3**
- TEAEs occurred in similar numbers of OMC, LZD, and MOX subjects
- Serious TEAEs and discontinuations due to TEAEs or serious TEAEs were low
- TEAEs graded as severe occurred in 1.7% OMC and 2.5% LZD subjects in the ABSSSI studies and in 6.5% OMC and 6.7% MOX subjects in the CABP study

RESULTS

Table 2. Subject Demographics in the ABSSSI and CABP Phase 3 Studies (Safety Population)

	ABSSSI Studies			CABP Study		
Characteristic	OMC (N=691)	LZD (N=689)	Total (N=1380)	OMC (N=382)	MOX (N=388)	Total (N=770)
Age, Years						
Mean (SD)	44.7 (14.2)	45.5 (14.2)	45.1 (14.2)	60.9 (15.2)	62.1 (15.2)	61.5 (15.2)
Min, max	18.0, 88.8	18.0, 90.0	18.0, 90.0	19.0, 97.0	19.0, 94.0	19.0, 97.0
Sex, n (%)						
Female	246 (35.6)	256 (37.2)	502 (36.4)	177 (46.3)	169 (43.6)	346 (44.9)
Male	445 (64.4)	433 (62.8)	878 (63.6)	205 (53.7)	219 (56.4)	424 (55.1)
Race, n (%)						
White	621 (89.9)	641 (93.0)	1262 (91.4)	353 (92.4)	355 (91.5)	708 (91.9)
Non-white	70 (10.1)	48 (7.0)	118 (8.6)	29 (7.6)	33 (8.5)	62 (8.1)
Ethnicity, n (%)						
Hispanic or Latino	238 (34.3)	247 (35.8)	485 (35.1)	8 (2.1)	14 (3.6)	22 (2.9)
Not Hispanic or Latino	449 (65.0)	440 (63.9)	889 (64.4)	370 (96.9)	370 (95.4)	740 (96.1)
Not reported	4 (0.6)	2 (0.3)	6 (0.4)	4 (1.0)	4 (1.0)	8 (1.0)
BMI, kg/m²						
<25	260 (37.6)	245 (35.6)	505 (36.6)	147 (38.5)	145 (37.4)	292 (37.9)
25-30	221 (32.0)	243 (35.3)	464 (33.6)	131 (34.3)	135 (34.8)	266 (34.5)
>30	210 (30.4)	200 (29.1)	410 (29.7)	104 (27.2)	108 (27.8)	212 (27.5)

ABSSSI = acute bacterial skin and skin structure infection; BMI = body mass index; CABP = community-acquired bacterial pneumonia; max = maximum; min = minimum; SD = standard deviation

Table 3. Overview of Treatment-emergent Adverse Events in the ABSSSI and CABP Phase 3 Studies (Safety Population)

Parameter, n (%)	OMC (N=1073)	LZD (N=689)	MOX (N=388)
Subjects with any TEAE	510 (47.5)	284 (41.2)	188 (48.5)
Serious TEAE	39 (3.6)	13 (1.9)	26 (6.7)
TEAE leading to premature discontinuation of study drug	33 (3.1)	10 (1.5)	27 (7.0)
Serious TEAE leading to premature discontinuation of study drug	16 (1.5)	5 (0.7)	11 (2.8)
Deaths	9 (0.8)	3 (0.4)	4 (1.0)

TEAE = treatment-emergent adverse event

- Gastrointestinal events, in particular nausea and vomiting, were the most frequently observed TEAEs (**Table 4**)
  - Higher rates of nausea and vomiting events occurred with the oral-only OMC regimen used in OASIS-2; the majority of these events occurred during the loading dose phase on Days 1 and 2 of treatment, when 450 mg was given daily
  - Except for 1 episode, all events of nausea and vomiting were of mild or moderate intensity, and only four OMC subjects (0.4%) discontinued due to nausea and vomiting
  - Diarrhea rates were low (at 2%) and no OMC subject developed *Clostridium difficile* infection compared with eight (2.1%) MOX subjects
- Most infusion-site extravasation events were observed in OASIS-1, where ABSSSI subjects with iv drug use had iv access difficulties
- Rates of infection TEAEs were similar across treatment groups
  - Wound infection, cellulitis, and subcutaneous abscess occurred only in ABSSSI subjects
  - In CABP, infection TEAEs occurred at rates <2% (OMC 1.6%, MOX 3.6%)

RESULTS

Liver Safety

- TEAEs related to liver transaminase increases were similar between OMC and comparators
- Four subjects (two OMC, two MOX) had increases in alanine aminotransferase (ALT) or aspartate aminotransferase resulting in discontinuation of study drug
- Post-baseline ALT >3×upper limit of normal in 4.3% OMC, 4.1% LZD, and 4.5% MOX subjects
- The number of subjects with a two-grade increase from baseline in ALT was 3.9% OMC, 3.6% LZD, and 5.5% MOX
- No cases of Hy's law were detected in subjects treated with OMC, LZD, or MOX

Table 4. Most Frequent TEAEs (≥2% Subjects in OMC Group by Preferred Term) in the ABSSSI and CABP Phase 3 Studies (Safety Population)

System Organ Class with Preferred Term, n (%)	OMC (N=1073)	LZD (N=689)	MOX (N=388)
Gastrointestinal disorders	241 (22.5)	103 (14.9)	70 (18.0)
Nausea	160 (14.9)	60 (8.7)	21 (5.4)
Vomiting	89 (8.3)	27 (3.9)	6 (1.5)
Diarrhea	26 (2.4)	20 (2.9)	31 (8.0)
General disorders and administration-site conditions	70 (6.5)	42 (6.1)	18 (4.6)
Infusion-site extravasation	28 (2.6)	19 (2.8)	0 (0.0)
Infections	132 (12.3)	92 (13.4)	41 (10.6)
Wound	30 (2.8)	22 (3.2)	0 (0.0)
Cellulitis	28 (2.6)	24 (3.5)	0 (0.0)
Subcutaneous abscess	23 (2.1)	27 (3.9)	0 (0.0)
Investigations	93 (8.7)	56 (8.1)	46 (11.9)
ALT increased	42 (3.9)	25 (3.6)	18 (4.6)
AST increased	33 (3.1)	24 (3.5)	14 (3.6)
Nervous system disorders	49 (4.6)	32 (4.6)	12 (3.1)
Headache	31 (2.9)	21 (3.0)	5 (1.3)

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Adverse Events Related to the Tetracycline Class

- TEAEs related to the tetracycline class were infrequent in OMC subjects
- Fungal infections occurred in 1.0% OMC, 0.9% LZD, and 1.3% MOX subjects
- No cases of phototoxicity were reported for any study drug
- Vestibular disorder TEAEs including dizziness and vertigo were observed in 0.8% OMC, 0.9% LZD, and 1.0% MOX subjects
- No pill esophagitis was reported with po OMC administration
- One case of mild chronic pancreatitis was reported in an OMC patient (max post-baseline lipase 68 U/L)
  - Worst post-baseline median (min, max) change in lipase was 9.40 U/L (-173.4, 291.4) OMC, 6.00 U/L LZD (-124.3, 2213.2), and 13.00 U/L MOX (-78.0, 672.0)
  - 5.9% OMC, 4.1% LZD, and 5.8% MOX subjects had a two-grade increase from baseline in lipase

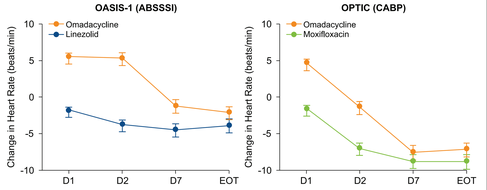
Cardiac Safety

- No changes in QTcF were observed in OMC while an increase in median QTcF values was seen in the MOX group (median change presented)
  - OMC: 0.0 msec (dose 1) and 0.0 msec (dose 3)
  - LZD: 4.0 msec (dose 1) and 4.0 (msec (dose 3)
  - MOX: 5.0 msec (dose 1) and 10.0 msec (dose 3)
- Cardiac TEAEs occurred in 2.1% OMC, 0.4% LZD, and 5.2% MOX subjects
  - Atrial fibrillation occurred in 0.5% OMC, 0.0% LZD, and 0.3% MOX subjects
  - Tachycardia occurred in 0.5% OMC, 0.0% LZD, and 0.8% MOX subjects
- Serious cardiac TEAEs occurred in 0.5% OMC, 0.3% LZD, and 0.5% MOX subjects

RESULTS

- The mean HR changes (± SEM) from baseline on Day 1 and Day 2 are shown for OASIS-1 and OPTIC in **Fig. 2**
- The data demonstrate an approximate mean change in HR of 5 bpm post first dose on Day 1 for OMC with a reduction in the mean change from baseline HR over time, concordant with the clinical improvement in both treatment groups

Figure 2. Heart Rate: Mean Change (bpm±SEM) from Baseline



ABSSSI = acute bacterial skin and skin structure infection; CABP = community-acquired bacterial pneumonia; D = Day; EOT = End of Treatment

CONCLUSIONS

- This integrated analysis of the three ABSSSI and CABP Phase 3 studies demonstrates that omadacycline is safe and well tolerated
- Nausea and vomiting were the most common adverse events but were not treatment limiting in the vast majority of subjects
- The majority of TEAEs in all treatment groups were considered mild or moderate in intensity and there was a low rate of study drug discontinuation
- Observed adverse events were consistent with the known adverse effect profile of the tetracycline class
- Omadacycline causes non-clinically relevant increases in HR

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