Omadacycline Gastrointestinal Effects – an Integrated Safety Analysis from the Phase 3 ABSSSI and CABP Studies

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Abstract 2181

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BACKGROUND

- Nausea and vomiting are well-known effects of the tetracycline class[1]
- Omadacycline (OMC) is the first aminomethylcycline antibiotic in late-stage clinical development as once-daily intravenous (iv) and oral (po) monotherapy for acute bacterial skin and skin structure infections (ABSSSI)[2,3] and community-acquired bacterial pneumonia (CABP)[4]
- OMC demonstrates potent *in vitro* activity against Gram-positive and many Gram-negative pathogens, as well as anaerobic and atypical bacterial pathogens[5,6]
- Here, we present the gastrointestinal (GI) safety profile of iv and po OMC monotherapy from two Phase 3 ABSSSI studies (**O**madacycline in **A**cute **S**kin and skin structure **I**nfections **S**tudy, OASIS-1 and OASIS-2) and one Phase 3 CABP study (**O**madacycline for **P**neumonia **T**reatment **I**n the **C**ommunity, OPTIC)

METHODS

Population Pooling

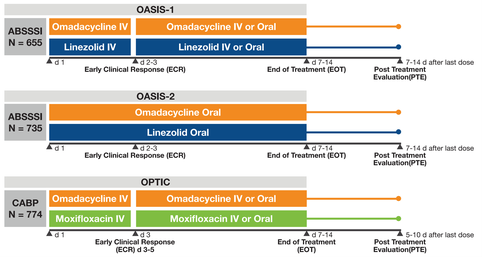
- For the Phase 3 studies, the integrated analysis of OMC safety data includes pooled data from
  - Two Phase 3 studies in ABSSSI: ABSI-1108 (OASIS-1) and ABSI-16301 (OASIS-2)
  - One Phase 3 study in CABP: CABP-1200 (OPTIC)
- Overall, 2150 total subjects were enrolled and treated
  - These studies included a total of:
    - 705 subjects who received the combined iv and po OMC regimen
    - 368 subjects who received the po-only OMC regimen for the treatment of ABSSSI

Analysis of GI Treatment-emergent Adverse Events

- All analyses were performed on the safety population, defined as subjects who were randomized and received study drug
- A treatment-emergent adverse event (TEAE) was defined as any adverse event that newly appeared, increased in frequency, or worsened in severity on or after the initiation of active study drug
- The number and percentage of subjects reporting a TEAE in each treatment group was tabulated by system organ class and preferred term

Study Designs

Figure 1. Study Design of Phase 3 Clinical Studies



RESULTS

Completion of Study and Study Treatment

- Completion of the study treatment was accomplished by 976 (91.0%), 603 (87.5%), and 346 (89.2%) of subjects in the OMC, linezolid (LZD), and moxifloxacin (MOX) groups, respectively
- Completion of the study (eg. subjects that completed the study, received at least one dose of the study drug, and completed end of treatment, post-treatment evaluation/test-of-cure, and follow-up) was accomplished by 971 (90.5%), 604 (87.7%), and 362 (93.3%) of subjects in the OMC, LZD, and MOX groups, respectively

Subject Demographics

Table 1. Subject demographics in the ABSSSI and CABP Phase 3 studies

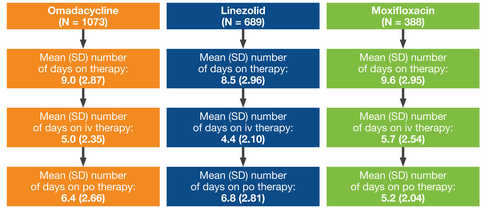
	ABSSSI Studies			CABP Study		
Characteristics	OMC (N = 691)	LZD (N = 689)	All (N = 1380)	OMC (N = 382)	MOX (N = 388)	All (N = 770)
Sex, n (%)						
n	691	689	1380	382	388	770
Female	246 (35.6)	256 (37.2)	502 (36.4)	177 (46.3)	169 (43.6)	346 (44.9)
Male	445 (64.4)	433 (62.8)	878 (63.6)	205 (53.7)	219 (56.4)	424 (55.1)
Categorical age (years), n (%)						
n	691	689	1380	382	388	770
18-65	641 (92.8)	637 (92.5)	1278 (92.6)	232 (60.7)	216 (55.7)	448 (58.2)
65-75	32 (4.6)	26 (3.8)	58 (4.2)	76 (19.9)	89 (22.9)	165 (21.4)
BMI (kg/m²)						
n	691	689	1380	382	388	770
< 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)

Subject Exposure to iv and po Treatment

- In the OASIS-1 and OPTIC studies, 62.3% (OMC), 64.3% (LZD), and 62.6% (MOX) of subjects received 4-8 days of iv therapy (**Figure 2**)
- In the OASIS-1 study, 64.3% (OMC) and 66.1% (LZD) of subjects received 4 – 6 days of po therapy
- In the OPTIC study, 96.2% (OMC) and 94.9% (MOX) of subjects received 1 – 7 days of po therapy
- Subjects in the OASIS-2 study received po OMC or LZD, only
- The mean number of days subjects received iv therapy in the OASIS-1 and OPTIC studies was comparable: 5.0 days for OMC, 4.4 days for LZD, and 5.7 days for MOX
- The mean number of days subjects received po therapy was comparable: 6.4 days for OMC, 6.8 days for LZD, and 5.2 days for MOX

RESULTS

Figure 2. Mean Number of Days on iv/po Therapy in the ABSSSI and CABP Phase 3 Studies



GI Treatment-emergent Adverse Event Rates

- Overall rates of GI TEAEs were 22.5%, 14.9%, and 18.0% for subjects receiving OMC, LZD, and MOX, respectively
- Nausea, vomiting, and diarrhea were the only TEAEs occurring in ≥ 2% of subjects (**Table 2**)

Table 2. GI TEAEs in the ABSSSI and CABP Phase 3 Studies

TEAE	Omadacycline N = 1073 n (%)	Linezolid N = 689 n (%)	Moxifloxacin N = 388 n (%)
Nausea	160 (14.9)	60 (8.7)	21 (5.4)
Vomiting	89 (8.3)	27 (3.9)	6 (1.5)
Diarrhea	16 (2.4)	20 (2.9)	31 (8.0)

Nausea and vomiting TEAEs

- The numbers of subjects experiencing nausea and vomiting in the iv to po studies were comparable (**Table 3**)
- In the po-only OASIS-2 study, a higher percentage of subjects showed nausea and vomiting TEAEs compared with subjects receiving LZD
  - Onset of nausea and vomiting mostly occurred during the first 2 days of treatment, when subjects received an OMC "loading dose" of 450 mg
- In the Phase 3 ABSSSI studies, iv drug using (IVDU) subjects treated with omadacycline showed more nausea and vomiting TEAEs, compared with non-IVDU subjects (**Table 4**)

Table 3. Nausea and Vomiting TEAEs During iv and po Omadacycline Treatment

TEAE	CABP iv/po		ABSSSI iv/po		ABSSSI po only	
	iv (N = 382)	po (N = 295)	iv (N = 323)	po (N = 286)	po (D1 – D2) (N = 368)	po (D3 – EOT) (N = 368)
Nausea, n (%)	2 (0.5)	7 (2.4)	14 (4.3)	26 (9.1)	93 (25.3)	15 (4.1)
Vomiting, n (%)	7 (1.8)	3 (1.0)	4 (1.2)	13 (4.5)	46 (12.5)	15 (4.1)

Table 4. Nausea and Vomiting TEAEs in IVDU Subjects Treated with Omadacycline in the ABSSSI Studies

TEAE	OASIS-1 (iv/po) (N = 323)		OASIS-2 (po only) (N = 368)		OASIS-1 + OASIS-2 (N = 691)	
	IVDU (N = 155)	Non-IVDU (N = 168)	IVDU (N = 256)	Non-IVDU (N = 112)	IVDU (N = 411)	Non-IVDU (N = 280)
Nausea, n (%)	24 (15.5%)	16 (9.5%)	84 (32.8%)	27 (24.1%)	108 (26.3%)	43 (15.4%)
Vomiting, n (%)	11 (7.1%)	6 (3.6%)	47 (18.4%)	15 (13.4%)	58 (14.1%)	21 (7.5%)

RESULTS

TEAEs by Sex, Age, and BMI

- In the Phase 3 studies, there were no overall differences in GI TEAEs between sexes, ages, or BMI groups (**Figures 3-5**)
  - Older subjects had less nausea, but this is due to the younger age group in the OASIS-2 study, where rates of nausea were higher

Figure 3. GI TEAEs by Sex

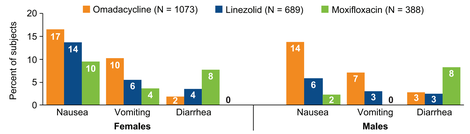


Figure 4. GI TEAEs by Age

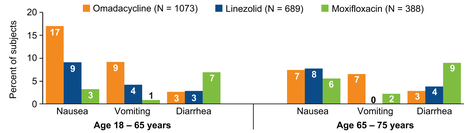
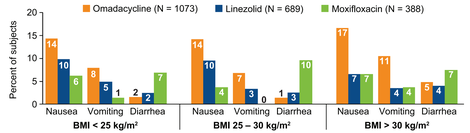


Figure 5. GI TEAEs by BMI



Discontinuation of the Study Drug

- All GI TEAEs, except 1 OMC and 1 LZD subject with vomiting, were mild or moderate
- GI TEAEs leading to the discontinuation of the study drug occurred equally across all treatment groups (**Table 5**)
- Discontinuations related to GI TEAEs in OMC subjects were due to nausea and vomiting

Table 5. GI TEAEs Leading to Treatment Discontinuation in OASIS-1, OASIS-2 and OPTIC Studies

Subjects with at least one TEAE leading to premature discontinuation of the study drug	Omadacycline (N = 1073) n (%)	Linezolid (N = 689) n (%)	Moxifloxacin (N = 388) n (%)
Gastrointestinal disorders	4 (0.4)	1 (0.1)	2 (0.5)
Vomiting	4 (0.4)	0	0
Nausea	2 (0.2)	1 (0.1)	0
Hematemesis	1 (0.1)	0	0
Diarrhea	0	0	1 (0.3)
Constipation	0	1 (0.1)	0
Dyspepsia	0	0	1 (0.3)

RESULTS

- TEAEs associated with *Clostridium difficile* infection did not occur in any OMC-treated subjects across all studies to date, comparable to LZD
  - However, 8 (2.1%) of subjects receiving MOX developed *C difficile* infections
  - Risk difference (95% confidence interval) OMC – MOX: -2.1 (-3.48, -0.65)

CONCLUSIONS

- Frequency and severity of GI TEAEs was comparable between all 3 treatment groups
- Overall nausea and vomiting TEAEs were more frequent in OMC-treated subjects, but were not treatment limiting
  - The frequency of nausea and vomiting in OMC-treated subjects were similar to comparator in the iv to po studies and more frequent than comparator during the first two days of the OASIS-2 oral study, when the subjects received a "loading dose" of OMC (450 mg)
- No clinically meaningful differences in nausea or vomiting were seen by subject sex, age or BMI
- OMC-treated subjects had fewer diarrhea TEAEs and no cases of *C difficile* infection, in contrast to subjects treated with MOX
- The data demonstrate that OMC is safe and well-tolerated
  - GI TEAEs were consistent with the known profile of the tetracycline class

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