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An integrated safety analysis of omadacycline in pivotal Phase 3 clinical trials

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Background

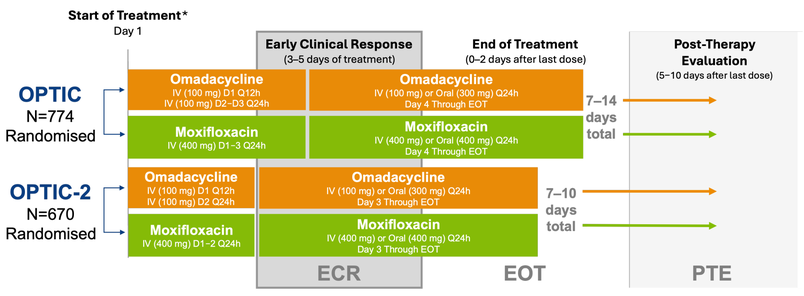
- Omadacycline is a semisynthetic tetracycline-class antibiotic available as once-daily PO and IV formulations, FDA approved for adults with CABP and ABSSSI caused by susceptible microorganisms[1]
- Omadacycline has been evaluated in 4 randomised, double-blind, multicentre Phase 3 clinical trials:
  - OASIS-1 and OASIS-2 in ABSSSI vs linezolid[2,3]
  - OPTIC and OPTIC-2 in CABP vs moxifloxacin[4,5]
  - Treatment regimens were IV-to-oral, except for OASIS-2, which was oral only (**Figure 1**)
- In these pivotal trials, omadacycline was noninferior to the respective comparators for efficacy in ABSSSI and CABP[2–5]

Methods

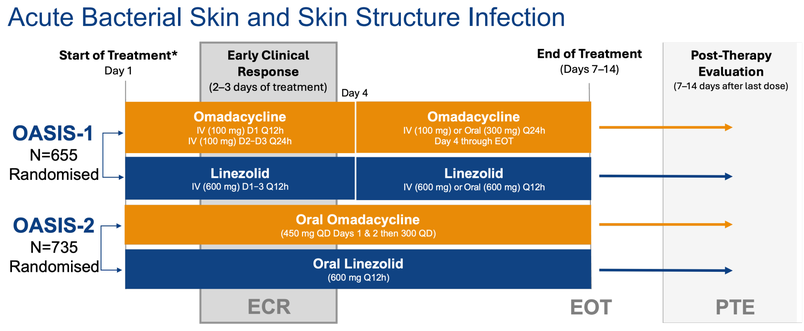
- Data from individual studies were integrated to examine pooled safety
- All safety analyses were performed on the safety population (participants who were randomised and received any amount of study drug)
- TEAEs were recorded through Days 30–37 after first dose of study drug
- TEAEs were examined for select systems/organs (**Additional Information**)

Figure 1: Study designs

Community-Acquired Bacterial Pneumonia



Acute Bacterial Skin and Skin Structure Infection



*Blood was collected at baseline and at PTE for assessment of bacterial pathogens.

CABP

Primary endpoint: Early Clinical Response (ECR) at 72 to 120 hours after administration of the first dose of study drug in the ITT population

Defined as survival with improvement in at least two of four symptoms (cough, sputum production, chest pain, dyspnoea) without deterioration in any of these four symptoms

Secondary endpoint: Clinical Response at the Post Therapy Evaluation (PTE) visit at 5 to 10 days after last dose of study drug in the ITT population

Defined as survival and improvement in signs and symptoms of CABP, based on the clinician's judgment, to the extent that further antibacterial therapy was not necessary

ABSSSI

Primary endpoint: Early Clinical Response (ECR) at 48 to 72 hours after administration of the first dose of study drug in the ITT population

Defined as >20% reduction in lesion size without any reason for failure

Secondary endpoint: Clinical Response at the Post Therapy Evaluation (PTE) visit at 7 to 14 days after last dose of study drug in the ITT population

Defined as survival after completion of study treatment without receiving any alternative antibacterial therapy other than omadacycline, without unplanned major surgical intervention, and sufficient resolution of infection such that further antibacterial therapy was not needed

Objective

Describe the safety parameters of omadacycline across four phase 3, randomised, controlled, multicentre trials

Omadacycline was shown to be safe and well tolerated across four pivotal trials including 1400 participants

- Nausea and vomiting were the most common TEAEs, and most were mild in nature
- TEAEs were consistent with the known profile of omadacycline and the tetracycline class

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Abbreviations

ABSSSI, acute bacterial skin and skin structure infection; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CABP, community-acquired bacterial pneumonia; ECR, Early Clinical Response; EOT, end of treatment; FDA, [US] Food and Drug Administration; ITT, intent-to-treat; IV, intravenous; OMC, omadacycline; PO, oral; PTE, Post Therapy Evaluation; q##h, every ## h; qd, once daily; SD, standard deviation; TEAE, treatment-emergent adverse event

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Results

- A total of 2818 participants were treated
  - 1409 received omadacycline (1041 in IV-to-oral studies; 368 in oral-only ABSSSI study)
  - Mean (SD) age was 53.5 (16.9) y
  - 58.8% were male
  - Mean (SD) duration of therapy was 9.0 (2.7) d
- TEAEs were reported by 42.8% of the omadacycline group, 41.2% of the linezolid group, and 36.8% of the moxifloxacin group (**Table 1**)
  - Discontinuation for a TEAE occurred in 3.0%, 1.5%, and 4.9% of participants, respectively, in the omadacycline, linezolid, and moxifloxacin groups
- The most frequently reported TEAEs for omadacycline were nausea (11.5%), vomiting (6.3%), ALT increased (3.4%), and headache (3.1%; **Table 2**)
- Nausea and vomiting were more frequently associated with oral versus IV route of administration (**Table 3**)

Table 1: TEAEs, pooled safety population

Parameter / Category n (%)	Omadacycline (n=1409)	Linezolid (n=689)	Moxifloxacin (n=720)
Any TEAE	603 (42.8)	284 (41.2)	265 (36.8)
Drug-related TEAE	245 (17.4)	111 (16.1)	91 (12.6)
Serious TEAE	56 (4.0)	13 (1.9)	41 (5.7)
Drug-related serious TEAE	3 (0.2)	1 (0.1)	2 (0.3)
TEAE leading to death	14 (1.0)	3 (0.4)	10 (1.4)
TEAE leading to discontinuation of study drug	42 (3.0)	10 (1.5)	35 (4.9)
Serious TEAE leading to discontinuation of study drug	20 (1.4)	5 (0.7)	16 (2.2)

Table 2: TEAEs ≥2% in any treatment group

Parameter / Category n (%)	Omadacycline (n=1409)	Linezolid (n=689)	Moxifloxacin (n=720)
Nausea	162 (11.5)	60 (8.7)	26 (3.6)
Vomiting	89 (6.3)	27 (3.9)	7 (1.0)
ALT increased	48 (3.4)	25 (3.6)	19 (2.6)
Headache	43 (3.1)	21 (3.0)	20 (2.8)
AST increased	40 (2.8)	24 (3.5	14 (1.9)
Wound infection	30 (2.1)	22 (3.2)	0
Cellulitis	28 (2.0)	23 (3.3)	0
Infusion site extravasation	28 (2.0)	19 (2.8)	0
Diarrhoea	26 (1.8)	20 (2.9)	41 (5.7)
Insomnia	16 (1.1)	6 (0.9)	15 (2.1)
Abscess, limb	13 (0.9)	20 (2.9)	0

Table 3: Nausea and vomiting TEAEs by omadacycline administration route

	3 IV-to-oral[a] trials		3 IV-to-oral trials[a] & 1 oral-only trial[b]
n (%)	IV period (n=1041)	Oral period (n=762)	Oral period (n=1130)
Nausea	17 (1.6)	34 (4.5)	145 (12.8)
Vomiting	11 (1.1)	16 (2.1)	78 (6.9)

[a] In the IV-to-oral trials (OPTIC and OPTIC-2 in CABP, OASIS-1 in ABSSSI), the loading dose was 100 mg IV q12h on Day 1; the maintenance dose was 100 mg IV qd or 300 mg PO qd thereafter (oral option was available on or after Day 4 of treatment [Day ≥3 in OPTIC-2]).
[b] In the oral-only OASIS-2 trial in ABSSSI, the loading dose on Days 1 and 2 was 450 mg PO qd omadacycline; the maintenance dose on Days 3 through EOT was 300 mg PO qd.

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