Omadacycline Exposure After a Light Meal

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Background

Omadacycline is a novel aminomethylcycline antibiotic approved to treat adults with community-acquired bacterial pneumonia (CABP) or acute bacterial skin and skin structure infection (ABSSSI)[1]

Patients taking omadacycline are instructed to fast for 4 h before and 2 h after oral dosing (no dairy products, antacids, or multivitamins for 4 h)[1]

The effect of a light meal on omadacycline pharmacodynamics (PD) is unknown

Methods

A phase 1, open-label, single sequence study enrolled 12 participants who received a single oral 300 mg dose of omadacycline while fasting and approximately 60–90 min after having orange juice and toast[2]

Washout period: ≥4 days between the last dose in one period and the first dose in the next period

Concentration–time profiles for Days 2 and 5 for 5-day dosing regimens were simulated from Day 1 data

Regimens: A: 300 mg QD Days 1–5; **B:** 600 mg Day 1, then 300 mg QD Days 2–5; **C:** 450 mg QD Days 1–2, then 300 mg QD Days 3–5; **D:** 450 mg QD Days 1–5

Unbound plasma areas under the curve (*f*AUC; based on 20% plasma protein binding of omadacycline) to minimum inhibitory concentration (MIC) ratio targets were simulated for each regimen using the MIC that inhibits 90% (MIC_{90}) of isolates[3]

- **MIC_{90}:** *Staphylococcus aureus* 0.25 mg/L, *Streptococcus pyogenes* 0.12 mg/L, and *Streptococcus pneumoniae* 0.12 mg/L[3]

Efficacy targets were previously derived from *in vivo* models. Stasis targets for common ABSSSI pathogens *S. aureus* (median target = 21.9) and *S. pyogenes* (median target = 33.3) and a 1-log_{10} reduction target for a common CABP pathogen, *S. pneumoniae*, (median target = 17.4) were applied to simulated exposures[4,5]

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Effect of a Light Meal on the Pharmacodynamics of Omadacycline

Objectives

To simulate the effect of a light meal on omadacycline PD using phase 1 study data

To compare simulated omadacycline exposures to efficacy targets for common ABSSSI and CABP pathogens *S. aureus*, *S. pyogenes*, and *S. pneumoniae*

Conclusions

Omadacycline exposures remained above efficacy targets for key ABSSSI and CABP pathogens for all regimens except regimen A on Day 2 in fed state against *S. aureus*, which then exceeded the target on Day 5

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Results

All four regimens exceeded median *f*AUC/MIC_{90} ratio targets for stasis against *S. aureus* and *S. pyogenes* and 1-log_{10} reduction for *S. pneumoniae*, except for Regimen A on Day 2 in a fed state against *S. aureus*, which increased above the target by Day 5

		*f*AUC/MIC_{90}			
		Day 2		Day 5	
Pathogen	Regimen*	Fasted	Fed	Fasted	Fed
S. aureus		**Median target for stasis = 21.9**			
	A: 300 mg	27.2	20.0	31.5	25.1
	B: 600/300 mg	38.2	28.2	32.2	25.7
	C: 450/300 mg	36.4	26.8	32.7	26.1
	D: 450 mg	36.4	26.8	42.1	33.5
S. pyogenes		**Median target for stasis = 33.3**			
	A: 300 mg	54.4	40.0	63.0	50.2
	B: 600/300 mg	76.4	56.4	64.4	51.4
	C: 450/300 mg	72.8	53.6	65.4	52.2
	D: 450 mg	72.8	53.6	84.2	67.0
S. pneumoniae		**Median target for 1-log_{10} reduction = 17.4**			
	A: 300 mg	54.4	40.0	63.0	50.2
	B: 600/300 mg	76.4	56.4	64.4	51.4
	C: 450/300 mg	72.8	53.6	65.4	52.2
	D: 450 mg	72.8	53.6	84.2	67.0

*Regimens were **A:** 300 mg QD Days 1–5; **B:** 600 mg Day 1, then 300 mg QD Days 2–5; **C:** 450 mg QD Days 1–2, then 300 mg QD Days 3–5; and **D:** 450 mg QD Days 1–5. Omadacycline MIC for *S. aureus*: MIC_{90}: 0.25 mg/L and *Streptococcus* spp.: MIC_{90}: 0.12 mg/L

*f*AUC/MIC ratios were approximately 25% lower on Days 2 and 5 after a light meal compared with fasted

Ratios increased with simulated higher doses or loading doses

Similar increases were observed regardless of the loading dose strategy employed

References

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