**Introduction**

Omadacycline is a potent aminomethylcycline antibiotic with activity against Gram-positive bacteria, including MSSA/MRSA and *S. pneumoniae*, Gram-negative bacteria, and atypical bacteria. It is currently in phase 3 clinical trials for acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. We have used a well validated, clinically reflective model of the human gut to investigate the effects of omadacycline exposure on the normal gut microbiota, and subsequent potential for induction of simulated *C. difficile* infection (CDI).

**Methods**

A triple stage chemostat gut model was inoculated with a pooled human faecal slurry (n=5) from healthy volunteers (age ≥60 years) and left for 2 weeks to allow bacterial populations to equilibrate. The model was challenged with 10^10 cfu/mL *C. difficile* spores (ribotype 027) on days 14 and 21. Omadacycline instillation (430 mg/L, once daily, for 7 days) commenced on day 21. The model was observed for a further three weeks post-antimicrobial (days 28-49). Gut microbiota populations and *C. difficile* total viable counts and spore counts were enumerated daily by culture on selective and non-selective agars. Toxin was detected by cell cytotoxicity assay (vero cells), and antimicrobial concentrations were measured by large plate bioassay using *Kocuria rhizophila* ATCC 9341 as the indicator organism.

**Figure 1 - Schematic diagram showing the gut model experimental timeline**

- **Antibiotic**
- **CD Spores**
- **Inoculation with faecal slurry**

Period A: CD Spores
Period B: CD Spores + Antibiotic
Period C: Inoculation with faecal slurry
Period D: Inoculation with faecal slurry + Antibiotic

**Discussion**

- Despite causing extensive disruption to the gut microbiota, omadacycline exposure did not induce any signs of simulated CDI within the in vitro human gut model.
- Simulated CDI in the gut model is characterised by a detectable vegetative cell population (an increase in total viable counts vs spore counts) and detectable toxin. Population changes included a rise in the proportion of spores.
- Toxin was detected throughout the experiment in all three vessels.
- There was no evidence of simulated CDI and no changes in gut microbiota, omadacycline exposure did not induce any signs of simulated CDI within the in vitro human gut model.

**Figure 2A - Mean facultative anaerobic gut microflora populations (log_{10} cfu/mL) in Vessel 3 of the gut model.**

Periods A-D are defined in Figure 1

**Figure 2B - Mean obligate anaerobic gut microflora populations (log_{10} cfu/mL) in Vessel 3 of the gut model.**

Periods A-D are defined in Figure 1

**Figure 3 - Mean *C. difficile* total viable counts and spore counts (log_{10} cfu/mL), toxin titre and Omadacycline concentration in Vessel 3 of the gut model.**

Periods A-D are defined in Figure 1

**Results**

Some fluctuation in gut microbiota were observed in the early days of the experiment until a steady state was achieved (Period A, Fig. 2A and 2B). Prior to antimicrobial exposure (Periods A and B), gut microbiota populations were stable (Fig. 2A and 2B). Minor fluctuations in Bifidobacteria populations were observed at the end of period A (Fig. 2B), but these had recovered prior to antibiotic instillation.

Omadacycline instillation caused immediate substantial changes to the microbiota (Fig. 2A and 2B). Declines were observed in populations of:
- Clostridia (~6 log_{10} cfu/mL)
- Bifidobacteria (~6 log_{10} cfu/mL),
- *B. fragilis* grsp species (~3 log_{10} cfu/mL),
- *Lactobacillus* spp. (~2 log_{10} cfu/mL),
- Enterococcus spp. (~4 log_{10} cfu/mL),
- *Kocuria* spp.

Population changes included a rise in the proportion of spores.

**References**