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P0281 Staphylococcal-selective antibiotic afabicin preserves the human gut microbiota

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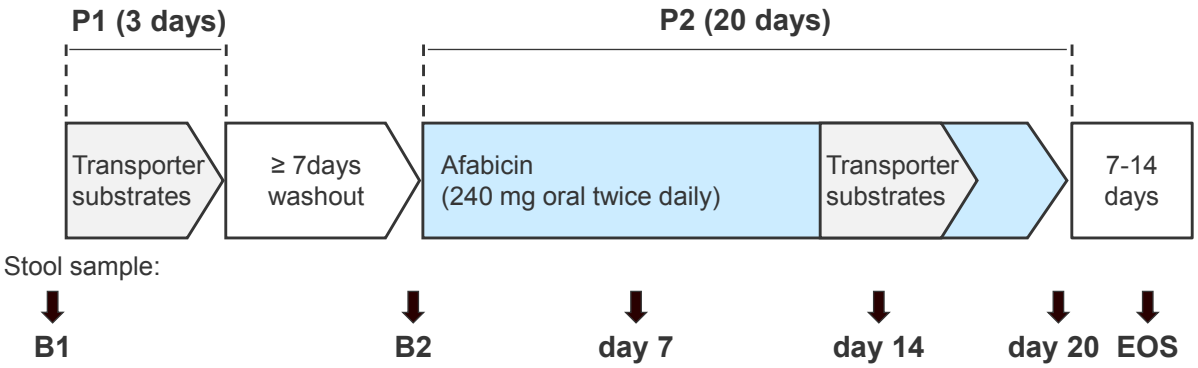
Background: Afabicin (Debio 1450) is an antibiotic candidate in phase II clinical development for intravenous and oral treatment of staphylococcal infections. It specifically targets *Staphylococcus* by inhibiting FabI, an enzyme essential for fatty acid synthesis in this genus. We have recently shown that, unlike broad-spectrum antibiotics, oral afabicin did not induce gut microbiota dysbiosis in mice. The aim of this study was to assess the effect of a 20-day oral afabicin administration on the human gut microbiota within a phase I drug-drug interaction study (EudraCT: 2015-001525-17) using 16S rDNA taxonomic metasequencing and qPCR.

Materials/methods: Sixteen healthy subjects received oral afabicin for 20 days at a recommended therapeutic dose (240 mg twice daily). The study sequence and sampling time points are shown in Fig.1. As an exploratory analysis, stool samples were collected at two baselines (B1, B2), on treatment days 7, 14, 20, and at the end of study (EOS). Total fecal DNA was extracted. The hypervariable V3 and V4 16S rRNA gene region was sequenced using Illumina MiSeq platform and taxonomic classification was obtained using a bioinformatic pipeline based on Mothur software. The level of total bacteria and *Clostridum difficile* was measured by 16S rDNA and species-specific qPCR, respectively.

Results: Gut microbiota richness (Chao index) and diversity (Shannon index) remained unchanged throughout the entire study. Afabicin did not induce any significant changes in the fecal microbial composition at the phylum, family and genus level at any study point. Although the total bacterial abundance did not differ before and after afabicin administration (B1 and B2 *vs* EOS), a significant increase was noted on day 7 and 20 *vs* B2 ($519\pm293 \times 10^9$, $545\pm378 \times 10^9$ *vs* $298\pm191 \times 10^9$ copies/g of stool, respectively, $p<0.05$; mean±SD) followed by a decrease from day 20 to EOS ($545\pm378 \times 10^9$ *vs* $289\pm 243 \times 10^9$ copies/g, respectively, $p<0.05$). *C. difficile* was undetectable in any sample.

Conclusions: Oral afabicin administered for 20 days at recommended therapeutic dose did not cause significant changes in the composition of human gut microbiota. This result supports the development of targeted antibiotherapy to treat staphylococcal infections as it may reduce antibiotic-associated complications such as antibiotic-associated diarrhea and *C. difficile* infections.

Figure 1


P1 (3 days)
P2 (20 days)
Transporter substrates
≥ 7days washout
Afabicin (240 mg oral twice daily)
Transporter substrates
7-14 days
Stool sample:
B1
B2
day 7
day 14
day 20
EOS