DAV132, developed to prevent side effects of antibiotics in the gut flora: results of a pilot cross-over study in healthy volunteers

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OBJECTIVES
The objective of this first study in man (DAV132-CL-1001) was to demonstrate the site-specific delivery of the anti-diarrhoeal DAV132. To this end, we undertook a pharmaco-kinetic study in which DAV132 was co-administered orally to healthy volunteers (HV) with two probe drugs: (i) amoxicillin which is absorbed proximally in the small intestine, and (ii) sulfapyridine, in which the amino bond linking sulfapyridine to 5-aminoacetylsaliclylic acid is cleaved by enzymes produced in the caecum by the commensal flora leading to the rapid absorption of sulfapyridine in the large intestine.

RESULTS
18 HV (10/8 M/F; 20-37 y: BMI: 19.1-27.0 kg/m²) were included from Feb to Apr 2013.
None reported AE were related or possibly related to DAV132. One female subject had inter-menstrual bleeding in period receiving FAC and oral contraceptives: this event was possibly related to FAC. Intestinal bleeding is a known adverse effect of activated charcoal when simultaneously administered with oral contraceptives.

Table: Effect of DAV132 on PK parameters of amoxicillin and sulfapyridine vs Control

<table>
<thead>
<tr>
<th></th>
<th>DAV132 vs Control</th>
<th>% reduction</th>
<th>90% CI</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Amoxicillin</td>
<td></td>
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<tr>
<td>AUC (mg·h/L)</td>
<td>16.3 (13.2-18.8)</td>
<td>18.1 (14.3-23.7)</td>
<td>50% (0.054-0.044)</td>
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<tr>
<td>Cmax (mg/L)</td>
<td>7.87 (6.76-9.72)</td>
<td>7.53 (6.5-9.28)</td>
<td>50% (0.031-0.047)</td>
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<tr>
<td>t_max (h)</td>
<td>1.00 (0.75-1.50)</td>
<td>1.00 (0.75-2.00)</td>
<td></td>
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<tr>
<td>Tmax (h)</td>
<td>1.03 (1.00-1.08)</td>
<td>1.00 (1.00-2.08)</td>
<td></td>
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<tr>
<td>Sulfapyridine</td>
<td></td>
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<tr>
<td>AUC (mg·h/L)</td>
<td>146.6 (105.2-201)</td>
<td>202.1 (127.8-300)</td>
<td>50% (0.051)</td>
<td></td>
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<tr>
<td>Cmax (mg/L)</td>
<td>8.09 (6.24-10.5)</td>
<td>11.7 (8.24-19.7)</td>
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</table>

Fig 1: Effect of DAV132 on serum concentrations of amoxicillin vs FAC and Control

Fig 2: Effect of DAV132 on serum concentrations of sulfapyridine vs FAC and Control

CONCLUSIONS
The results of this study show that:
- The PK characteristics of amoxicillin and sulfapyridine attest that they must have been respectively absorbed in the duodenum-jejunum and the proximal colon, as reported in the literature.
- DAV132 efficiently released its absorbent in the distal part of the small intestine (ileum) or in the caecum, where it is able to adsorb molecules without interfering with their absorption in the proximal small intestine.
- 4 doses of DAV132 given within 24h are well tolerated. DAV132 can be given with molecules absorbed in the proximal small intestine, such as antibiotics, oral contraceptives, without affecting their plasma PK in a clinically relevant manner.

The further clinical development of DAV132 will allow to demonstrate:
- The ability of DAV132 to prevent the side effects of systemic antibiotic treatments on the gut flora, such as the emergence and dissemination of resistance, and the onset of C. difficile associated diarrhoea.
- The safe administration of DAV132 with concomitant orally administered drugs.

REFERENCES