strain of Acinetobacter baumannii, Hornsey et al. demonstrated that telavancin and colistin in combination was significantly more active than either drug used alone.

As daptomycin does not appear to pose a risk for nephrotoxicity, it is unfortunate that we observed no synergy and a high rate of antagonism (41.2%) in the colistin + daptomycin combinations. To our knowledge, this has not been reported by other workers. Körber-Irrgang et al. reported no antagonism when testing the combination against 10 P. aeruginosa strains using Mueller–Hinton broth supplemented with 50 mg/L calcium. In time-kill studies that involved testing colistin + daptomycin against 15 clinical A. baumannii isolates, Malmberg et al. reported an increase in the initial kill rate (1–4 h) in 13 of the 15 strains compared with colistin alone. They used Mueller–Hinton II broth and agar, which is cation adjusted to a standard calcium ion concentration of 25 mg/L (C. Malmberg, Antibiotic Research Unit, Uppsala University and Uppsala Academic Hospital, Uppsala, Sweden, personal communication).

We wonder if the antagonism we found with colistin + daptomycin is genuine or is perhaps artefact of the method used to assess this combination. Daptomycin Etests incorporate a constant level of 50 mg/L calcium along the antimicrobial gradient, which is required for optimal activity of the daptomycin. Calcium is known to have an inhibitory effect on polymyxins.

It is possible, therefore, that direct contact with the calcium from the daptomycin Etest is inhibiting the colistin. This would decrease the availability of colistin for antimicrobial action, resulting in elevation of the MIC, which is borne out by the MIC50/90 of colistin when combined with daptomycin. Whether this explains the antagonism we observed or whether it is indeed genuine remains to be seen. Until this can be resolved, we would urge caution in the selection of methodology for testing colistin + daptomycin combinations.

### Table 1. Results of testing colistin in combination with telavancin and daptomycin using Etest against 17 strains of *P. aeruginosa*

<table>
<thead>
<tr>
<th>Combination</th>
<th>Synergy, FICI ≤0.5</th>
<th>No interaction, FICI &gt;0.5–4.0</th>
<th>Antagonism, FICI ≥4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colistin + telavancin</td>
<td>1 (5.9%)</td>
<td>16 (94.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Colistin + daptomycin</td>
<td>0 (0%)</td>
<td>10 (58.8%)</td>
<td>7 (41.2%)</td>
</tr>
</tbody>
</table>

### References

### Pharmacokinetics of oral isavuconazole in a patient after Roux-en-Y gastric bypass surgery

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**Sir,**

This is a report describing pharmacokinetic aspects of an orally administered azole antifungal agent, in particular of the investigational agent isavuconazole, in a patient after Roux-en-Y gastric bypass surgery. The patient gave written consent for publication of their medical details.
A 47-year-old patient had undergone a laparoscopic Roux-en-Y gastric bypass surgery in 2007 for weight reduction. In October 2013, type 2 diabetes mellitus was diagnosed in the setting of an admission for hyperglycaemic hyperosmolar non-ketotic syndrome. During this admission the patient complained about cough that was productive of greyish sputum. Chest CT revealed a cavitary left upper lobe lung mass measuring 9 × 6 × 10 cm and a mass-like area of consolidation within the left lower lobe. Bronchoalveolar lavage and sputum cultures grew 1+ of *Rhizopus* species. The MICs of amphotericin B and posaconazole for the organism were 1 and 0.5 mg/L, respectively (University of Texas Health Science Center at San Antonio reference laboratory; testing according to CLSI M38-A2). The patient was started on 7.5 mg/kg AmBisome every 24 h and underwent left pneumonectomy. Histopathology showed angioinvasive mucormycosis disrupting the pleural surface, and the pulmonary artery and bronchial margin had acute inflammatory changes without fungal elements. The left lower lobe histopathology was consistent with multifocal bronchopneumonia without visualization of fungal elements. Post-surgical pleural fluid samples were negative for growth of *Rhizopus* spp. AmBisome treatment was complicated by type 1 renal tubular acidosis with significant electrolyte wasting and worsening renal function, leading to a dose reduction to 5 mg/kg at week 4 of treatment. Transition to 200 mg of posaconazole by mouth four times daily was attempted while the patient was maintained on AmBisome; however, trough levels of posaconazole were only 0.17 mg/L after 10 days of treatment, well below the MIC for the organism. Since the patient was not on any medications that interfered with the pharmacokinetics of posaconazole and had maintained strict adherence to posaconazole intake with fatty meals, it was thought that, in addition to the known poor absorption of the oral formulation of posaconazole, a reduced gastric acid environment and accelerated intestinal transit time secondary to gastric bypass were causative. Further, worsening renal function required AmBisome discontinuation at week 8 of treatment.

Given these circumstances, FDA authorization under the Emergency Investigational New Drug programme (EIND#120969) and authorization from our internal review board were obtained to treat the patient with oral isavuconazole, a broad-spectrum antifungal drug with in vitro and in vivo activity against a broad range of yeasts and moulds. Isavuconazonium (BAL 8557), a prodrug of isavuconazole (BAL 4815), is highly water soluble and rapidly cleaved into isavuconazole after oral or intravenous administration. The bioavailability of oral isavuconazole independent of food and gastric pH in healthy volunteers suggested that the pharmacokinetic characteristics of orally administered isavuconazole might provide a viable treatment option for this patient. The MIC of isavuconazole for the *Rhizopus* sp. isolate was 0.5 mg/L (University of Texas Health Science Center at San Antonio reference laboratory; testing according to CLSI M38-A2).

The patient received a 3 day loading dose of oral isavuconazole (200 mg three times per day) followed by 200 mg per day. Isavuconazole concentrations in plasma were measured using a validated HPLC MS/MS method with a lower limit of detection of 5 μg/L. Plasma concentrations obtained on day 7 of therapy (Table 1) were found to be below the mean trough level of 3.458 mg/L and the mean Cmax of 5.817 mg/L found in healthy volunteers at that dose. Assuming that the patient’s more rapid intestinal transit was leading to reduced bioavailability, the isavuconazole dose was increased to 200 mg every 12 h. This resulted in trough levels above the target concentration of 3 mg/L (Table 1). With the exception of mild nausea, isavuconazole was well tolerated during the 4 months of administration and the patient had no evidence of fungal recurrence on repeat bronchoscopy and CT imaging at the end of the treatment course. The patient had a baseline elevated alkaline phosphatase between 250 and 370 IU/L (normal range 34–104 IU/L) for 12 months preceding isavuconazole administration, and a diagnostic liver biopsy had been planned but was postponed in the light of the pulmonary mucormycosis diagnosis. Alkaline phosphatase fluctuated between 300 and 445 IU/L on isavuconazole treatment, with normal transaminase and bilirubin levels. Per year, an estimated 220 000 bariatric surgical procedures are performed in the USA, with Roux-en-Y gastric bypass surgery being the most common procedure. This operation reduces the size of the stomach, limits the acid environment and bypasses the absorptive duodenal segment, leading to decreased or increased bioavailability of drugs, depending on their physico-chemical properties.

Mucormycosis is an emerging, life-threatening, rapidly progressive angioinvasive fungal disease. Among 929 reported cases of mucormycosis in the literature, diabetic patients represented 36% of the total population, with an overall mortality of 44%. If feasible, timely surgical resection and treatment with amphotericin B formulations is the mainstay of therapy. To date, salvage therapy is limited to oral posaconazole, but case reports of successful treatment with isavuconazole have been published. For patients having had Roux-en-Y gastric bypass surgery, oral isavuconazole may be an alternative, based on its food- and pH-independent high oral bioavailability; however, a higher dose may be required. Given the rising number of Roux-en-Y gastric bypass surgeries per year, patients requiring antifungal treatment will be emerging. The availability of pharmacokinetic data on oral antifungals is crucial for their treatment outcome.

### Acknowledgements

Astellas provided isavuconazole and facilitated susceptibility and drug level testing. I am thankful to Marie Rosenfeld, Laura Kovanda, Bob Townsend and Bernie Zeiher at Astellas Pharma Global Development, Inc. for the support provided to treat this patient.

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**Table 1.** Isavuconazole (BAL 4815) plasma levels during treatment

<table>
<thead>
<tr>
<th>Study day</th>
<th>Oral dose</th>
<th>Sampling day and time</th>
<th>Isavuconazole level (μg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3</td>
<td>200 mg every 8 h</td>
<td>day 7: trough</td>
<td>1048.56</td>
</tr>
<tr>
<td>4–16</td>
<td>200 mg every 24 h</td>
<td>2 h post-dose</td>
<td>2324.16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 h post-dose</td>
<td>2418.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 h post-dose</td>
<td>1852.20</td>
</tr>
<tr>
<td>17–48</td>
<td>200 mg every 12 h</td>
<td>day 27: trough</td>
<td>4432.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 h post-dose</td>
<td>6057.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 h post-dose</td>
<td>5749.32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 h post-dose</td>
<td>5405.08</td>
</tr>
<tr>
<td></td>
<td>day 41: trough</td>
<td>4970.67</td>
<td></td>
</tr>
<tr>
<td></td>
<td>day 48: trough</td>
<td>4273.56</td>
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</table>
Funding
This study was conducted as part of our routine work. Astellas provided isavuconazole and drug level testing free of charge.

Transparency declarations
None to declare.

References