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An open-label study of the pharmacokinetics, safety and tolerability of zibotentan (ZD4054) in subjects with mild, moderate, or severe renal impairment, or normal renal function

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Background: Zibotentan (ZD4054) is a specific ET_A-receptor antagonist being investigated for the treatment of hormone-resistant prostate cancer. As renal clearance accounts for 30–70% of total plasma clearance of zibotentan, excretion may be reduced in patients with renal impairment, leading to greater drug exposure.
Methods: This open-label, single centre study investigated the pharmacokinetics (PK), safety and tolerability of zibotentan in subjects with renal impairment compared with subjects with normal renal function. Subjects were divided into four categories using measured creatinine clearance values based on 24-hour urine collections: severe (<30 ml/min), moderate (⩾30 to <50 ml/min), mild (⩾50 to ⩽80 ml/min) renal impairment, and normal renal function (>80 ml/min). Subjects received a single 10 mg zibotentan dose po and remained resident for PK sampling for 48 hours post dose (day 3), returning for PK sampling at days 4 and 5. Linear regression models were used to obtain the geometric least squares mean ratio and 90% CI of C_{max} and AUC for each renal impairment group compared with the normal group. Point estimates of differences in $t_{1/2}$ were similarly obtained.
Results: 48 subjects received treatment, and all completed the study (normal, n = 18; mild impairment, n = 12; moderate impairment, n = 9; severe impairment, n = 9). In the normal group, gmean C_{max} was 545 ng/ml (CV 23%), gmean AUC was 5485 ng·h/ml (CV 39%), mean $t_{1/2}$ was 10.8 hours (SD 2.7), and mean CL/F was 33 ml/min (SD 14.2). Results for the renal impairment groups are shown in the Table. Zibotentan was well tolerated by all subjects. The most common adverse event was headache (14 [78%], 6 [50%], 5 [56%] and 4 [44%] subjects in the normal, mild, moderate and severe groups, respectively).

PK parameters relative to normal group

	Renal impairment		
	Mild	Moderate	Severe
C_{max} ratio (90% CI)	1.07 (0.97–1.19)	1.09 (0.96–1.24)	1.12 (0.96–1.30)
AUC ratio (90% CI)	1.66 (1.38–1.99)	1.89 (1.50–2.39)	2.17 (1.64–2.86)
$t_{1/2}$ difference, h (90% CI)	1.87 (0.06–3.68)	2.37 (0.08–4.66)	2.87 (0.10–5.64)
CL/F, %	−15%	−39%	−44%

Conclusions: Following a single 10 mg oral dose of zibotentan, there was no significant difference in C_{max} with degree of renal impairment. AUC was higher and $t_{1/2}$ slightly longer in subjects with renal impairment due to the slower clearance of zibotentan. The clinical consequences of reduced clearance in patients with renal impairment will be evaluated as more safety and tolerability data emerge.
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Ascending single-dose study of the safety, tolerability, and pharmacokinetics of bosutinib administered orally with multiple doses of ketoconazole to healthy adult subjects

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Background: Bosutinib (BOSU), a potent dual inhibitor of Src and Abl tyrosine kinases, is in development for treatment of chronic myelogenous leukemia. The objective of this study was to combine BOSU, a CYP3A4 substrate, and ketoconazole (KETO), a potent CYP3A4 inhibitor, under fed conditions in order to evaluate the safety and tolerability of supratherapeutic exposures of BOSU in healthy adults.
Methods: This randomized, double-blind, sequential-group study was conducted in 48 healthy males aged between 18−50 years. Daily doses of 400 mg KETO were administered on day −1 in the evening and on the morning of days 1 to 4. Single ascending oral doses (SAD) of BOSU 100, 200, 300, 400, 500, or 600 mg (6 subjects per dose cohort) or placebo (2 subjects per dose cohort) were administered concomitantly after consumption of a high-fat breakfast on the morning of day 1. Serial blood samples were collected for pharmacokinetic (PK) analysis and laboratory tests. Dose proportionality of bosutinib C_{max} and AUC_{∞} was evaluated using a power model. Safety assessments included physical examination, vital signs, and electrocardiograms (ECG).
Results: The study was completed by 48 subjects. The most commonly reported treatment emergent adverse events (TEAEs) were headache (62.5%), nausea (22.9%), diarrhea (18.8%), dizziness (14.6%), and vomiting (10.4%). All TEAEs were mild to moderate in severity. No trends of clinical importance were noted in clinical laboratory results, ECG results, or vital signs. No serious AEs were reported during this study. BOSU absorption was relatively slow, with a median t_{max} of 5 to 11 hours. Mean BOSU C_{max} following single ascending doses of 100 to 600 mg BOSU ranged from 58.4 ng/mL (SD = 13.3; 100-mg dose) to 426 ng/mL (SD = 100; 600-mg dose). For these same respective doses, mean AUC ranged from 2980 ng × h/mL (SD = 802) to 23,000 ng × h/mL (SD = 4020). The mean elimination half-life of BOSU ranged from 38 to 52 hours.
Conclusions: Single oral doses up to 600 mg BOSU administered with food and multiple doses of 400 mg KETO were safe and showed acceptable tolerability in healthy subjects. PK exposures of BOSU increased with increasing dose in a linear and dose proportional fashion after oral doses of BOSU co-administered with KETO under fed conditions. A supratherapeutic C_{max} level was achieved to support future investigation of the potential effect of BOSU on cardiac repolarization in healthy subjects.

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RAD001 plus mitomycin C, every three weeks in previously treated patients with advanced gastric cancer or cancer of the esophagogastric junction – preliminary results of a Phase I study

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Background: The mTOR pathway could be potential target in the treatment of gastric cancer. This study was designed to determine the maximum-tolerated-dose and preliminary safety and efficacy of the mTOR inhibitor RAD001 in combination with mitomycin C in patients with previously treated advanced gastric cancer.
Methods: In this dose-escalation phase I trial, patients received mitomycin C at 5 mg/m^2 i.v. every 3 weeks combined with escalated doses of oral RAD001 (starting with 5 mg/day) once daily in 3-week cycles. Patients were investigated for safety every week and for efficacy every 6 weeks.
Results: 11 patients (3 male, 8 female) have been included so far. All patients were pretreated with a platinum-based chemotherapy, and 9/11 had also received docetaxel. Treatment cohorts were: 5 mg/day, 3 patients; 7.5 mg/day, 3 patients; and 10 mg/day, 5 patients. Median treatment duration was 46 days (range, 8 to 91 days). There were no dose limiting toxicities, until dose escalation of RAD001 was stopped at the 10 mg/day dose. The only grade 3−4 toxicity observed was leukopenia in 9% of patients. Frequent grade 1−2 toxicities with possible relationship were mucositis 64%, leukopenia 64%, nausea 54%, thrombocytopenia 45%, fatigue 27%, and diarrhea 18%. Only mucositis and leukopenia were associated with higher dose levels. Two (22%) of 9 evaluable patients experienced a major response (both liver metastases), two patients were not evaluable for efficacy at the time of the analysis, and the rest of the patients had disease progression. Responses were independently confirmed.
Conclusions: Oral RAD001 up to 10 mg once daily can be safely combined with mitomycin C at 5 mg/m^2 every 3 weeks in previously treated patients with advanced gastric cancer. The achievement of major responses with the combination in this heavily pretreated population is encouraging.

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Mass balance study of the novel epothilone compound sagopilone in patients with advanced solid tumours

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Background: Sagopilone is an enantiomerically pure, synthetic analogue of the microtubule stabilizer epothilone B. It has shown remarkable anti-tumor activity in various multi-drug resistant tumor models. Preliminary results from phase II trials show efficacy in ovarian and prostate cancer and in malignant melanoma.
Material and Methods: This single center mass-balance study was conducted in 7 patients (pts) with histologically confirmed solid tumors, pretreated with a median of 3 chemotherapy regimen. During treatment course 1, blood, urine and fecal samples were collected and analyzed over a period of 14 days to measure total radioactivity and sagopilone following