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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

H.K. Tomkinson[1], A. Weil[2], E. Engelhardt[2], K. Schmid[2], S. Oliver[1], T. Morris[1], H. Swaisland[1], M. Taboada[1]. *[1]AstraZeneca, Dept of Clinical Development, Macclesfield, United Kingdom; [2]Apex GmbH, Dept of Clinical Operations, Munich, Germany*

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.
Trial sponsored by AstraZeneca (AZ code D4320C00016).

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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

M. El Gaaloul[1], R. Abbas[2], B. Hug[2], C. Leister[2], S. Chalon[1], D. Sonnichsen[2]. *[1]Wyeth Pharmaceuticals, Early Development and Clinical Pharmacology, Paris La Defense, France; [2]Wyeth Pharmaceuticals, Early Development and Clinical Pharmacology, Collegeville PA, USA*

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

S.E. Al-Batran[1], C. Pauligk[1], S. Janowski[1], K. Steinmetz[1], A. Atmaca[1], E. Jäger[1]. *[1]Krankenhaus Nordwest, II. Medizinische Klinik, Frankfurt am Main, Germany*

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

C. Focan[1], F. Kreutz[1], N. Moeneclaey[1], S. Lindemann[2], S. Reif[2], H. Wiesinger[2], M. Kornacker[3]. *[1]CHC-Clinique Saint-Joseph, Medical Oncology, Liège, Belgium; [2]Bayer Schering Pharma, Clinical Pharmacology, Berlin, Germany; [3]Bayer Schering Pharma, Clinical Pharmacology, Wuppertal, Germany*

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

intravenous administration of 28 mg ^{14}C-labelled sagopilone (14 kBq) over a period of 30 min. Pts who appeared to tolerate treatment and to have a clinical benefit were offered further treatment courses with unlabelled sagopilone.
Results: The disposition of sagopilone appears to be multi-exponential, with very rapidly decreasing plasma concentrations after the end of infusion, a high clearcance (83.4 L/h), a high volume of distribution (Vss 4739 L) and a long terminal half-life (68.1 h). The systemic exposure to metabolites was high since parent compound represented only about 5% of the AUC of total radioactivity. Biotransformation of sagopilone was found to be the preferred elimination pathway. Total radioactivity (sagopilone and metabolites) was excreted predominantly in feces, and 11.2% was excreted renally. The bulk of the dose was recovered within a week; by 14 days after administration, 73.5% of the radioactivity had been excreted.
Four pts died during the study because of progression of disease. Ten serious adverse events (SAEs) were reported for three pts; (9 SAEs considered unrelated, 1 SAE (dysphagia) considered unlikely related to study treatment). Most frequent adverse event (AE) was paraesthesia (16 AEs in 5 pts). Responses were measured according to RECIST, one pt obtained a complete (bile duct carcinoma) and one a partial response (rectal cancer).
Conclusions: Sagopilone shows a fast biotransformation and an extensive extravascular distribution. Its long terminal half-life may be attributed to the slow redistribution from tissues. Total radioactivity was excreted predominantly in feces. Tolerability and efficacy are in line with results from clinical trials reported previously.

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Cediranib in combination with mFOLFOX6: results from the cohort expansion phase of a two-part Phase I study

P. LoRusso[1], M. Zalupski[2], S. Desai[2], H.A. Burris[3], P.J. Stella[4], J. Xu[5], Q. Liu[5], B. Mookerjee[5], A.F. Shields[6]. *[1]Wayne State University, Hematology/Oncology Phase I Service, Detroit Michigan, USA; [2]University of Michigan, Ann Arbor, Michigan, USA; [3]Sarah Cannon Cancer Center, Nashville, Tennessee, USA; [4]St Joseph Mercy Hospital, Ypsilanti, Michigan, USA; [5]AstraZeneca, Wilmington, Delaware, USA; [6]Karmanos Cancer Institute, Detroit, Michigan, USA*

Background: Cediranib (RECENTIN™) is a highly potent and selective oral VEGF signaling inhibitor. Recent trials have shown that combining a VEGF signaling inhibitor with chemotherapy provides clinical benefit in patients with advanced cancers. In part 1 of this two-part study (study codes NCT00502567; 2171IL/0008), cediranib was evaluated with various chemotherapy regimens, including mFOLFOX6 (Shields AF *et al. J Clin Oncol* 2007;25(18S):abst 3544). Here we report results of an expansion cohort of patients treated with cediranib and mFOLFOX6 from part 2 of the study.
Materials and Methods: Cediranib 30 mg was given once daily with mFOLFOX6 every 2 weeks, at four centers in the USA. The primary objective was to determine the safety and tolerability of cediranib in combination with mFOLFOX6. A preliminary evaluation of efficacy (RECIST) was a secondary objective.
Results: In total, 47 patients received treatment. The most common primary tumor types were colorectal cancer (CRC) and pancreas (both n = 11), and biliary tract (n = 7). The mean (range) number of prior therapies was 1.7 (0–7). No unexpected adverse events (AEs) were observed, and the tolerability of cediranib with mFOLFOX6 was consistent with the known safety profiles for the individual treatments. The most common AEs irrespective of causality were fatigue (n = 35), diarrhea (n = 33), nausea (n = 32) and peripheral neuropathy (n = 31). Hypertension (n = 11, grade 3)/fatigue (n = 5, all grade 3) and neutropenia (n = 7, grade 3; n = 5, grade 4)/fatigue (n = 6, all grade 3) were the most common CTC grade $\geqslant$3 cediranib- and mFOLFOX6-related AEs, respectively. All hypertension AEs were considered manageable and none has led to permanent discontinuation of study treatment. The majority (75%) of patients had a dose reduction/pause. Of the 44 patients evaluable for efficacy, five (11%) experienced a best response of partial response; stable disease was observed in a further 23 (52%) patients. The overall median progression-free survival was 6.9 months (95% confidence interval: 4.7, 8.8).
Conclusions: In this group of heavily pretreated patients, combination treatment with cediranib 30 mg and mFOLFOX6 demonstrated encouraging preliminary evidence of antitumor activity with manageable AEs. Cediranib 20 mg in combination with FOLFOX/XELOX is currently in Phase III development in first-line CRC.

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Phase I dose-escalation study of continuous oral treatment with the angiokinase inhibitor BIBF 1120 in patients with advanced solid tumors

H. Kaneda[1], I. Okamoto[1], T. Satoh[1], T. Arao[1], K. Nishio[1], A. Sarashina[2], K. Konishi[2], P. Stopfer[3], R. Kaiser[4], K. Nakagawa[1]. *[1]Kinki University School of Medicine, Osakasayama City, Osaka, Japan; [2]Nippon Boehringer Ingelheim Co. Ltd., Medical Development Division, Tokyo, Japan; [3]Boehringer Ingelheim Pharma GmbH & Co. KG, Department of Drug Metabolism and Pharmacokinetics, Biberach, Germany; [4]Boehringer Ingelheim Pharma GmbH & Co. KG, Clinical Research/Oncology, Biberach, Germany*

Background: BIBF 1120 (Vargatef™*) is a potent, orally available tyrosine kinase inhibitor (vascular endothelial growth factor receptor 1/2/3, platelet-derived growth factor receptor α/β and fibroblast growth factor receptor 1/3) that suppress tumor growth by angiogenesis inhibition.
Method: This study was designed to determine the safety, tolerability, maximum tolerated dose (MTD), pharmacokinetics (PK) and preliminary efficacy of BIBF 1120 in advanced solid tumors. BIBF 1120 (150–250 mg) was given orally twice-daily by continuous 4-week dosing in one cycle.
Results: Twenty-one patients (11 males, 10 females, median age 62 years, range 41–81, ECOG performance status of 0–1) were treated at doses of 150 mg bid (n = 3), 200 mg bid (n = 12) and 250 mg bid (n = 6). Dose-limiting toxicities (DLTs) of reversible Grade 3/4 elevated liver enzymes occurred in three out of 12 patients at 200 mg bid and three out of six patients at 250 mg bid; 200 mg bid was determined as the MTD. Most of the reported adverse events were of CTC Grade 1 or 2 gastrointestinal disorders (e.g. diarrhea, abdominal pain, nausea and vomiting) which were seen in 85.7% of patients. No treatment-related deaths were reported. Best overall response was stable disease, seen in 16 (76.2%) patients, and median progression-free survival was 113 days (95% CI: 77–119 days). At the MTD of BIBF 1120, maximum plasma concentrations (C_{max}) of BIBF 1120 were reached at approximately 3 hours after dosing (range 1.98–4.00 hours); gMean C_{max} and $C_{max,ss}$ = 52.0 and 67.6 ng/mL. The gMean exposure (AUC_{0-24} and $AUC_{0-24,ss}$) to BIBF 1120 was 312 and 595 ng·h/mL. The gMean exposure (AUC_{0-12} and $AUC_{0-12,ss}$) to BIBF 1120 was 233 and 423 ng·h/mL; $t_{1/2} \approx$ 10.2–19.9 hours. The gMean values of accumulation ratios were 1.2–1.7. Pharmacokinetic analysis indicated that BIBF 1120 steady state was reached after 8 days of bid dosing, and C_{max} and AUC increased with increased dose within the dose range tested.
Conclusion: BIBF 1120 at 200 mg bid continuous dosing was well tolerated and appeared to provide some clinical benefit, and is therefore considered the recommended dose for continuous daily treatment for patients with advanced solid tumors. An international, randomized, placebo-controlled Phase III trial program, LUME-Lung, of BIBF 1120 in combination with standard 2nd-line NSCLC therapies is now recruiting patients.
*Trade name not FDA approved.

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The pharmacokinetic effect of the specific ETA receptor antagonist zibotentan (ZD4054) on CYP3A4 activity using midazolam as a probe in healthy male volunteers

J. Kemp[1], H.K. Tomkinson[1], D. Mazur[2], T. Wollseifen[2], T. Morris[1], M. Taboada[1], S. Oliver[1]. *[1]AstraZeneca, Dept of Clinical Development, Macclesfield, United Kingdom; [2]PAREXEL International GmbH, Klinikum Neukölln, Berlin, Germany*

Background: Zibotentan (ZD4054) is a small-molecule, ET_A-receptor specific antagonist being investigated for the treatment of hormone-resistant prostate cancer. In this study, the known CYP3A4 substrate midazolam was used as a probe to evaluate the potential of zibotentan to inhibit the CYP3A4 metabolic pathway.
Methods: This was an open-label, randomized, single centre, two-period, crossover trial in healthy male volunteers. Subjects were randomized 1:1 to receive the following sequence or its opposite: 7 days' once-daily oral zibotentan 10 mg with a single oral dose of midazolam 7.5 mg on day 6; $\geqslant$7 days' washout; a single oral dose of midazolam 7.5 mg. Blood samples for midazolam pharmacokinetics (PK) were collected pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24 and 30 hours post midazolam dose. Results of AUC and C_{max} were expressed as the ratio of geometric least square means (GLSMean) and 90% confidence intervals (CI) for midazolam + zibotentan:midazolam alone. An interaction between zibotentan and midazolam was predefined to have occurred if the upper 90% CI was greater than 1.5.
Results: A total of 12 subjects participated (mean age 49 years, range 32–59), with six subjects in each sequence cohort. All subjects completed the study and results from all subjects are included in the analysis. Steady-state levels of zibotentan were achieved over 7 days. Steady-state zibotentan