A phase I and pharmacokinetic study of LAF389 administered to patients with advanced cancer

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LAF389 is a synthetic analogue of bengamide B, a natural product isolated from Jaspidae sponges. LAF389 has both antiproliferative and antiangiogenetic properties, and preclinical investigations showed a broad antitumour activity. This clinical trial aimed to determine the safety and pharmacokinetic profile of LAF389 administered as a slow intravenous injection for 3 consecutive days every 3 weeks in patients with advanced solid tumours. Eight dose levels were tested: 1, 2.5, 5, 10, 15, 30, 25 and 20 mg/day. A total of 33 patients, median age 52 years (range 33–72), with refractory solid tumours were enroled, 19 men and 14 women with a median World Health Organization performance status of 1 (0–4). Seventy-eight cycles of treatment have been administered (mean 2.5, range 1–10). Four cardiovascular dose-limiting toxicities were reported at 30 mg (2/2 patients) and 25 mg (2/9 patients), eight additional patients at various dose levels had (cardio)vascular toxicity, probably drug related, and one patient died owing to pulmonary embolism at the 5 mg dose. No objective responses were recorded. Pharmacokinetic parameters were variable, although linear and without obvious accumulation from cycle I to cycle II. LAF389 dose escalation was terminated owing to occurrence of unpredictable cardiovascular events. This, associated with the lack of clinical activity, did not warrant further investigation of this agent. *Anti-Cancer Drugs* 18:219–225 © 2007 Lippincott Williams & Wilkins.

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Introduction

LAF389 is a structurally novel synthetic analogue of bengamide B, one of a family of natural products isolated from Jaspidae sponges indigenous to the Fiji Islands. Bengamides have been described to have antiproliferative properties, but their mechanism of action and molecular target(s) are currently unknown. Bengamide B was evaluated in the NCI 60 cell line in-vitro anticancer screen and found to have a unique in-vitro antitumour profile compared with the standard agent database of antitumour compounds [1]. The bengamides produce cell cycle arrest at both the G_0/G_1 and G_2/M interfaces after apoptosis. The intracellular molecular target of LAF389 has been extensively investigated through proteome analysis and both isoforms of human methionine aminopeptidase have been suggested as targets of the compound [2,3]. Nuclear magnetic resonance imaging (MRI) of tumours from animals treated with LAF389 demonstrates a marked inhibition of tumour vascularization. Thus, the activity against tumours *in vivo* is due to the inhibition of proliferation of the tumour cells itself and the inhibition of tumour angiogenesis.

LAF389 is a metabolically labile ester and requires intracellular hydrolysis to its alcohol metabolite, LAF153, for activity. LAF389 is more potent than LAF153, possibly owing to the enhanced entry into cells of LAF389 relative to its metabolite. Both compounds are detectable in plasma and tumour tissue by high-performance liquid chromatography. LAF389 is a potent inhibitor of monolayer cell proliferation in human cell lines. Cytotoxicity is a function of total exposure, but cell death does not require continuous exposure. Combinations of LAF389 with standard cytotoxics were neither synergistic nor antagonistic on human carcinoma cells in culture. LAF389 is active in tumour cell lines unresponsive to some standard cytotoxics and in tumours with different mechanisms of drug resistance. Although LAF389 is a substrate for P-glycoprotein-mediated multidrug resistance *in vitro*, the effect of P-glycoprotein overexpression on in-vitro growth inhibition by LAF389 is significantly less than the effect on paclitaxel growth inhibition.

Animal studies have demonstrated that repeat bolus administrations of LAF389 were effective and well tolerated in a wide variety of schedules. Significant tumour growth inhibition was observed in a panel of six different human solid tumour xenografts and increased with the frequency of administration. The schedule

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chosen for preclinical efficacy and toxicology testing was a daily × 3 bolus intravenous injection followed by a 7-day treatment-free interval, repeated for three cycles. The main systemic toxicities to be anticipated from LAF389 were reversible myelosuppression (mainly lymphopenia), and effects on other rapidly proliferating tissues like the gastrointestinal tract, the skin, the male reproductive organs, the liver and the bladder. Cardiovascular effects were observed in telemetered rats and anesthetized dogs, showing transiently reduced blood pressure and increased heart rates in the absence of consistent electrocardiogram (ECG) changes. In rats, elimination of LAF389 is mainly mediated by metabolism. Excretion of the parent compound and its metabolite(s) is nearly complete within 72 h, and it occurs in roughly similar proportions via the renal and biliary routes.

We performed this study to determine the safety profile and the maximum tolerated dose (MTD) of LAF389 as a single agent and to determine the pharmacokinetic (PK) profile of LAF389 and its metabolite(s). We intended also to assess the extraction flow product of tumour vasculature reflecting both vascular permeability and microvascular density using dynamic contrast-enhanced (DCE)-MRI, in patients treated at the MTD. A secondary objective was to evaluate preliminary antitumour activity of LAF389.

Patients and methods

Study design

This was an open-label, multicenter, noncomparative, dose-escalation study designed to characterize the safety, tolerability and PK profile of LAF389, and to determine the MTD.

The dosing regimen chosen for this study was a slow bolus injection on days 1, 2 and 3, followed by a treatment-free interval of 18 days to allow the observation of and the recovery from toxicities, such as myelosuppression, as anticipated from animal toxicology studies. On the basis of 1/10 the dose below STD in the dog, the starting dose was 1.0 mg per day for 3 days. The dose-escalation followed predefined dose levels on the basis of a modified continuous reassessment method [4–8]. Each treatment cycle was 21 days and the treatment cycles were repeated until dose limiting toxicity (DLT) or disease progression, whichever occurred first. Further, tested doses were 2.5, 5, 10, 15, 30, 25 and 20 mg/day. For the purpose of dose finding, three patients were assigned sequentially to a cohort. An evaluable patient was one who completed the first cycle or discontinued during the first cycle owing to dose-limiting toxicity. Doses were escalated until the first occurrence of grade 3 (G3) or grade 4 (G4) toxicity during the first 3 weeks of treatment. The MTD was defined to be the highest dose of LAF389 administered for at least one treatment cycle in which not more than 30% of the patients experience DLT. DLTs were defined as G4 neutropenia or leucopenia, thrombocytopenia with platelet count $< 20\,000\,mm^3$ or $< 100\,000\,mm^3$ for more than 2 weeks and any G3 or G4 nonhaematological toxicities except for alopecia and nausea and vomiting responsive to antiemetics.

Assessment of the extraction flow product of tumour vasculature was planned at the MTD: DCE-MRI scans were to be performed twice before treatment, on days 7 and 21 of cycles I and II, and as indicated. These included T1 and T2 weighted images of measurable disease and a DCE study of a representative lesion. The study was conducted in two centres (Belgium and The Netherlands) after local ethical committee approval, according to Good Clinical Practice and in agreement with the latest revision of the Declaration of Helsinki.

Patient selection

Adult patients with a histological or cytological diagnosis of advanced cancer (excluding leukemia), for whom no standard therapy exists. They should have a World Health Organization performance status of ≤ 2 with an anticipated life expectancy of at least 3 months. Patients with impaired gastrointestinal, hepatic, renal, cardiac or neurological functions were excluded. Patients with haemoglobin < 6 g/dl, neutrophils $< 1.0 \times 10^9$/l or platelets $< 100 \times 10^9$/l were also excluded. Patients with bleeding disorders or on anticoagulant drugs or patients with significant concomitant diseases (e.g. uncontrolled infections, psychiatric disorders) that may cause unacceptable safety risks for exposure to an investigational drug or that make compliance with the protocol impossible were also excluded. Known brain metastases and known HIV infection were additional exclusion criteria. Pregnant or breastfeeding women or adults of reproductive potential not employing an effective method of birth control, were excluded too. All patients were requested to give written informed consent to participate in this study.

Drug

LAF389 was provided by Novartis Pharma (Basel, Switzerland) as a clear colourless solution of 30 mg/ml in propylene glycol/ethanol (70/30) sterile concentrate, presented as a 1.0 ml solution in a 2.0 ml vial. The content of each vial was diluted 30 times, by adding of 29 ml physiological saline to obtain a final concentration of 1 mg/ml. LAF389 was administered by a suitable syringe pump either via a peripheral venous infusion or a central indwelling catheter as a slow bolus injection of 10, 20 or 30 min, depending on the dose level. The dose was not adjusted for surface area or body weight. LAF389 is light sensitive and was kept protected from light at all times, including during administration.

Safety and toxicity evaluation

Safety assessments consisted of monitoring and recording all adverse events and serious adverse events, the regular monitoring of haematology, blood chemistry, coagulation tests and urine values, the regular measurements of vital signs, and the performance of physical examinations. All concomitant medications were documented. A baseline chest radiograph and radiological assessment of tumour lesions were also performed. ECG monitoring was recorded during infusion and for 6 h after completion of each injection for cycles I and II, and if indicated, also during further cycles. Clinical and laboratory toxicity was assessed using the National Cancer Institute Common Toxicity Criteria (CTC) version 2.0.

Efficacy

Tumour responses were assessed by computed tomography scans every two cycles (every 6 weeks), complemented by serum tumour markers, which were followed during each cycle for patients showing raised levels. Response was classified according to Southwestern Oncology Group criteria. To characterize the antiangiogenetic activity of LAF389 and PK/progressive disease relationships, DCE-MRI was planned at the MTD. DCE-MRI can determine the vascular perfusion and permeability characteristics of tumours of patients with metastatic lesions more than 3 cm in the maximum dimension by providing data concerning the extraction flow product of tumour vasculature. Successful anti-angiogenesis will reduce both vascular perfusion and permeability, causing a decrease in the peak and rate of contrast enhancement.

Pharmacokinetics

Blood and plasma samples for drug-level analysis and PK analysis of LAF398 and its metabolite LAF153 were taken at the following time points: on day 1 of cycles I and II before the start of injection, immediately before or at the stop of injection at 5, 15, 30 min and 1, 2, 4, 8 and 24 h (just before the second dose) after the stop of injection. On day 3 of cycle I, samples were taken at the same time points and an extra sample 48 h after the stop of injection.

The LAF389 and LAF153 concentration–time data were analyzed for basic parameters by noncompartmental methods using the software package WinNonlin V 3.2 from Pharsight Corporation (Novartis Pharmaceuticals Corp., East Hanover, New Jersey, USA): maximum drug concentration (C_{max}), time to the maximum concentration (t_{max}), area under the concentration–time curve (AUC), half-life ($t_{1/2}$), total clearance (CL) and volume of distribution (V_z). Terminal half-life and PK parameters depending on the terminal elimination rate constant ($AUC_{infinity}$, CL, V_z) were estimated only if the square of the correlation coefficient of the linear regression to the ln(concentration) versus time plot was ≥ 0.8. The dependence of the PK parameters from the dose and the ratio of blood to plasma PK parameters were assessed.

Results

Patient characteristics

A total of 33 patients entered the study at three institutions from May 2000 to April 2002. Demographic characteristics at baseline, cohort allocation and duration of treatment are summarized in Table 1. The most frequent malignancies were colorectal carcinoma ($n = 4$), melanoma ($n = 4$) and lung carcinoma ($n = 3$). Bile duct, pancreatic and thyroid carcinoma were represented by two patients each. All patients, except two (one at 15 mg and one at 20 mg), received previous chemotherapy. Other previous treatments were surgery in 13 patients, radiotherapy in 10 patients and immunotherapy in two patients. The mean number of cycles administered was 2.5. One patient received 10 cycles, with a first cycle of 30 mg, and thereafter 15 mg (days 1 and 2) and 30 mg (day 3) per cycle. The most frequently reported reason for discontinuation was lack of efficacy ($n = 25$).

Toxicity

Out of the 33 patients, 31 (93.9%) reported adverse events (AE). Only two patients, enroled in the 2.5 mg and in the 10 mg cohorts, respectively, experienced no AE. The most frequent adverse experiences were fatigue, nausea, anorexia, dyspnoea and visual disturbances. Severe AEs (CTC grade ≥ 3) are presented in Table 2. Four DLTs were reported at 30 mg (2/2 patients) and 25 mg (2/9 patients): grade 3 vaso-motor reaction with headache, flushing and stiffness of the hands (30 mg), grade 4 hypertensive crisis with grade 3 papillary oedema (30 mg), grade 3 macula oedema (25 mg) and grade 3 hypertension (25 mg). After these DLTs, we reduced the dose from 30 to 25 mg and eventually to 20 mg/day. In all cases, the toxicities were reversible. Angina pectoris was reported as a serious adverse event at 25 mg. Incidences of one or a combination of the following signs of (cardio)vascular toxicity were reported in a total of eight patients at doses ≥ 5 mg, grade 1–2, likely to be drug related: blurred vision, supraventricular arrhythmia, atrioventricular heart block and hypotension. In addition, one unexpected sudden death with an equivocal relationship to treatment occurred in a patient at 5 mg who died on day 12 of cycle I, possibly owing to pulmonary embolism. Other nonhaematological toxicities assessed as drug related included fatigue, taste disturbance, stomatitis, nausea, vomiting and anorexia in 18 patients. These were generally mild to moderate. Haematological toxicity was reported in only five patients: one grade 3 febrile neutropenia (10 mg/day), two grade 3 anaemia and three grade 2 anaemia (1, 2.5, 10, 20 and 25 mg/day, respectively). None were considered to be related to LAF389. Two deaths unrelated to treatment were also reported at 25 mg/day: both patients died owing to progressive

Table 1 Demographic characteristics at baseline and duration of treatment by cohort

	Cohort 1 (1 mg)	Cohort 2 (2.5 mg)	Cohort 3 (5 mg)	Cohort 4 (10 mg)	Cohort 5 (15 mg)	Cohort 6 (30 mg)	Cohort 7 (20 mg)	Cohort 8 (25 mg)	Total
No. of patients	$n=3$	$n=3$	$n=4$	$n=5$	$n=4$	$n=2$	$n=3$	$n=9$	$n=33$
Sex: male/female	0/3	1/2	4/0	2/3	1/3	2/0	2/1	7/2	19/14
Age[a] (years)	53 (44–68)	48 (40–56)	42.2 (35–53)	64 (54–72)	58 (40–72)	49 (45 –53)	56.6 (57–64)	44.8 (33–70)	51.9 (33–72)
	66 (58–79)	72 (64–83)	68.2 (64–73)	61.8 (46–75)	85.8 (70–117)	84.5 (79–90)	66.3 (62–71)	67.3 (54–92)	71.5 (46–117)
	166 (154–174)	167.6 (165–170)	177.7 (169–185)	163.8 (153–180)	167.5 (150–185)	182.5 (180–185)	161.6 (155–170)	171.2 (156–184)	169.7 (150–185)
WHO performance status 0/1/2/3/4	1/0/1/0/1[b]	1/2/0/0/0	0/4/0/0/0	0/5/0/0/0	2/2/0/0/0	0/2/0/0/0	0/1/2/0/0	4/1/4/0/0	8/17/7/0/1
No. of cycles									
total/cohort	6	10	8	9	14	11	5	15	78
mean/patient (range)	2 (1–3)	3.3 (2–6)	2 (1–4)	1.8 (1–2)	3.5 (2–8)	5.5 (1–10)	1.6 (1–2)	1.6 (1–4)	2.5 (1–10)µ

[a]Mean (range).
[b]This patient at WHO performance status 4 was paraplegic.

disease on day 20 of cycle I and after discontinuation of treatment at the end of cycle I, respectively.

Antitumour activity

No complete or partial responses were reported. Two patients with thyroid carcinoma had stable disease. In one patient, stable disease was maintained for 10 cycles before progression. Both patients were treated at 15 mg, but one was initially dosed at 30 mg for one cycle. In four patients, response was not assessable.

Owing to early discontinuation of the study (before reaching MTD), no DCE-MRI has been performed.

Pharmacokinetics

LAF389 disappears very rapidly from plasma and blood. Its metabolite LAF153 persisted longer and at higher concentrations than LAF389. Pharmacokinetic parameters are very variable and it is difficult to give good estimates. The half-life of LAF389 is probably less than 1 h, but some patients displayed half-lives of several hours. Whole-blood and plasma half-lives for the parent compound are similar. The half-life of LAF153 is around 8 h, but individual values ranged from less than 1 h to more than 50 h. The relationship between AUC and dose in plasma and blood of LAF389 and its metabolite LAF153 are shown in Figs 1 and 2, respectively. The data of C_{max} versus dose are similar (not shown) owing to the good correlation between C_{max} and AUC ($P < 0.0001$, linear fit). A clear increase in exposure with increasing dose is observed. On the basis of AUC there is no obvious accumulation of LAF389 within a treatment cycle (day 1 to day 3) or from cycle I to cycle II. At lower doses, plasma and blood levels decreased on day 3 when compared with day 1 in cycle I. They were approximately comparable between cycle I day 1 and cycle II day 1. At doses ≥ 5 mg, no decrease was observed and AUC levels on cycle I day 3 were similar or higher than on day 1. The decrease of LAF389 levels on cycle I day 3 at lower doses appeared to be compensated, at least partially, by an increase in LAF153 concentrations. At higher doses, however, when no decrease in LAF389 on cycle I day 3 was observed compared with cycle I day 1, LAF153 AUC still increased. This was most likely due to a carryover on cycle I day 3 from the previous doses.

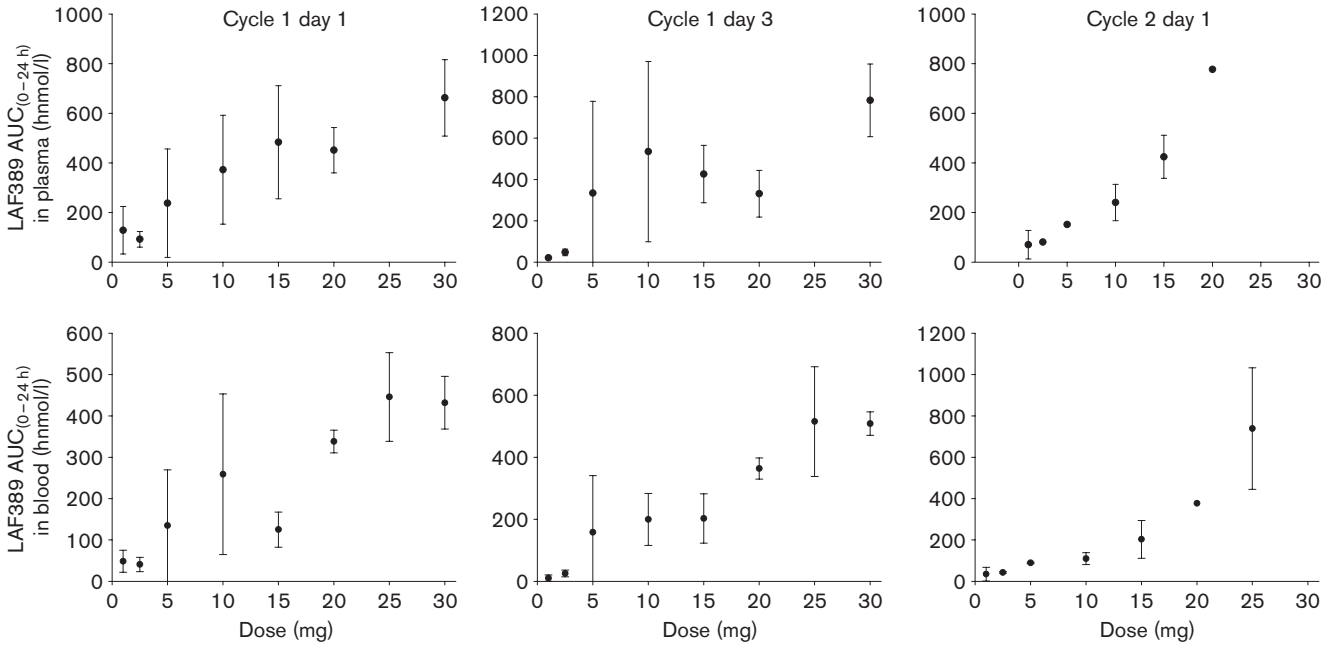
The blood to plasma distribution is shown in Table 3. LAF389 does not distribute substantially to blood cells as the ratio was close to a normal haematocrit and constant across doses. LAF153, however, showed higher whole-blood than plasma concentrations, particularly at lower doses. At doses ≥ 5 mg, concentrations were higher in plasma than in blood, probably indicating a saturable distribution into blood cells. In conclusion, there appears to be no unexpected drug accumulation on the basis of plasma levels. Whole blood showed a similar behaviour than plasma.

Table 2 Incidence of grade 3–4 adverse events (all cycles)

	Cohort 1 (1 mg)	Cohort 2 (2.5 mg)	Cohort 3 (5 mg)	Cohort 4 (10 mg)	Cohort 5 (15 mg)	Cohort 6 (30 mg)	Cohort 7 (20 mg)	Cohort 8 (25 mg)	Total
No. of patients	$n=3$	$n=3$	$n=4$	$n=5$	$n=4$	$n=2$	$n=3$	$n=9$	$n=33$
Neuropathy	0	0	0	0	0	1	0	1	2
Dyspnoea	1	0	0	1	0	0	2	1	5
Abdominal pain or cramps	1	0	1	0	0	0	0	0	2
Anorexia	0	0	0	1	0	0	0	2	3
Nausea	1	0	0	1	0	0	0	1	3
Vomiting	1	0	0	0	0	0	0	0	1
Fatigue	0	1	1	0	1	0	0	0	3
Hypertension	0	0	0	0	0	1	0	1	2
Ocular/visual	0	0	0	0	0	1	1	1	3
Thrombosis/embolism	0	0	1	0	0	1	0	0	2
Pleural effusion (nonmalignant)	0	0	0	0	0	0	1	0	1
Dysphagia	0	0	0	0	0	0	0	1	1
Myalgia	0	0	0	0	0	0	0	1	1
Tachycardia	0	0	0	0	0	0	0	1	1
Constipation/obstruction	1	0	1	0	0	0	0	0	2
Dehydration	0	0	0	0	0	0	0	1	1
Cardiovascular/general	0	0	0	0	0	0	0	1	1
Pain	0	0	0	0	0	0	0	1	1
Haemoglobin	0	$1+1^a$	1^a	$3+1^a$	$1+1^a$	1^a	$1+1^a$	$2+1^a$	15
Lymphocytes	1	1	0	0	0	0	0	1	3
SGOT (ASAT)	0	0	1	0	1	0	0	0	2
Bilirubin	0	0	0	1	1	0	0	0	2
Febrile neutropenia	0	0	0	1	0	0	0	0	1

Serum Glutamic Oxaloacetic Transaminase (SGOT); ASAT, aspartate aminotransferase.
[a]Present at baseline.

Fig. 1

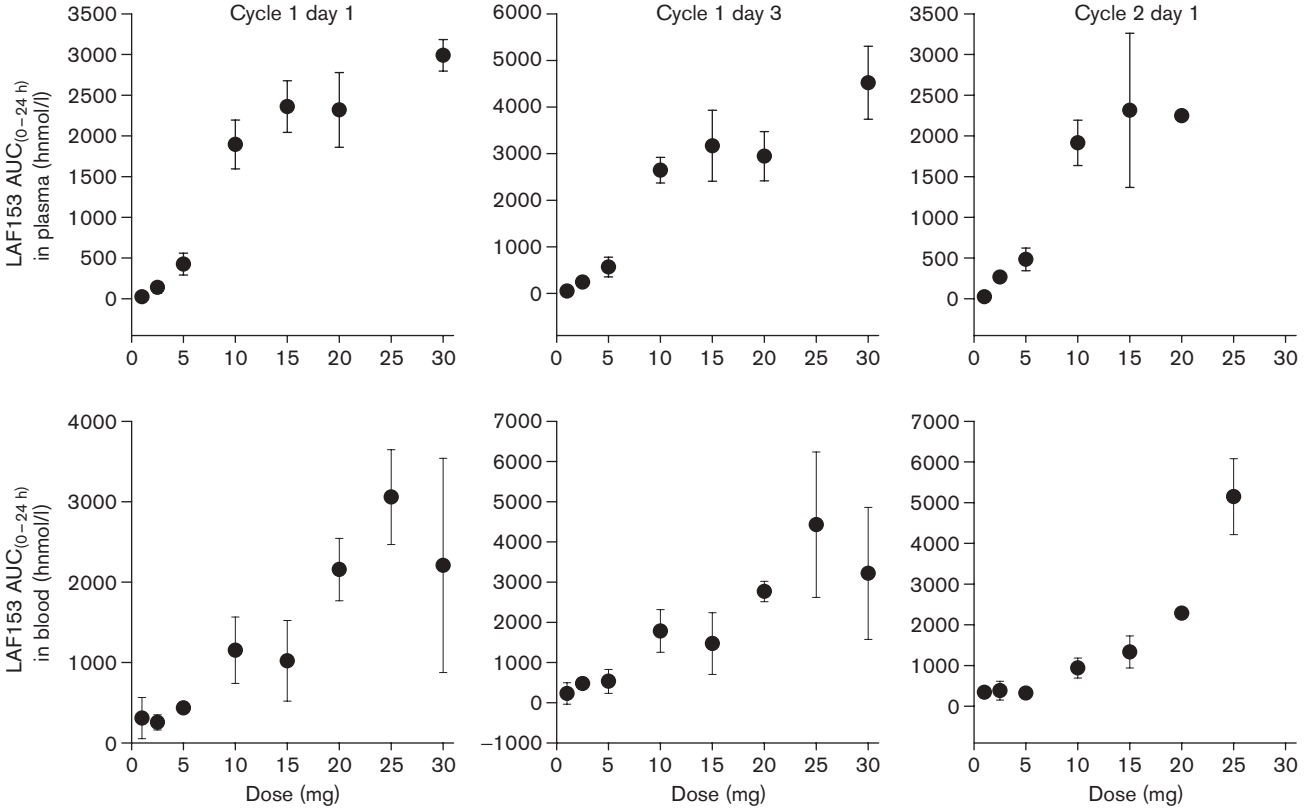


$AUC_{(0-24\,h)}$ versus dose of LAF389 in plasma and blood. AUC, area under curve.

Conclusion

LAF389 was well tolerated up to doses of 15 mg/day, as a bolus injection on 3 consecutive days every 3 weeks. The side effects were mild to moderate and predominantly nonhaematological. Furthermore, at the dose levels of 30, 25 and 20 mg a day, the majority of adverse events observed were of a nature to be expected in this population of patients with advanced solid malignancies, although it is

Fig. 2



$AUC_{(0-24\,h)}$ versus dose of LAF153 in plasma and blood. AUC, area under curve.

Table 3 **Blood to plasma ratio of $AUC_{(0-24\,h)}$**

Dose[a]	Cycle	Day	*n*	LAF389		LAF153	
				Mean	SD	Mean	SD
1	1	1	3	0.49	0.32	11.77	9.75
1	1	3	2	0.54	0.57	3.63	1.66
1	2	1	2	0.45	0.10	14.16	0.15
2.5	1	1	2	0.44	0.04	2.38	2.16
2.5	1	3	3	0.53	0.11	2.05	0.90
2.5	2	1	3	0.53	0.02	1.38	0.74
5	1	1	3	0.53	0.08	0.90	0.19
5	1	3	4	0.58	0.14	0.87	0.24
5	2	1	2	0.59	0.05	0.70	0.23
10	1	1	5	0.86	0.78	0.60	0.19
10	1	3	5	0.56	0.37	0.68	0.20
10	2	1	4	0.46	0.09	0.49	0.10
15	1	1	4	0.27	0.05	0.42	0.18
15	1	3	4	0.49	0.21	0.44	0.18
15	2	1	4/3	1.50	1.96	0.44	0.04
20	1	1	3	0.78	0.20	0.93	0.05
20	1	3	2	0.92	0.05	0.95	0.09
30	1	1	1	0.68	0.25	0.72	0.40
30	1	3	1	0.66	0.10	0.69	0.24

AUC, area under curve.
[a]Note: no measurements were performed in plasma at the dose level of 25 mg.

possible that LAF389 may have contributed to an increased frequency and/or severity of these events. The underlying disease could easily lead to symptoms such as fatigue, nausea, dyspnoea and anorexia, or to laboratory toxicities such as elevated liver function tests. The four DLTs at 30 and 20 mg, on the other hand, were of great concern, and most likely drug-related (cardio)vascular events such as vaso-motor signs, hypertensive crises with papillary oedema and macula oedema. In addition eight patients had (cardio)vascular toxicity, probably drug related, like blurred vision, supraventricular arrhythmia, atrioventricular heart block or hypotension and one patient died owing to pulmonary embolism. These events were not predicted by preclinical testing, only minor cardiovascular effects were observed in rats and dogs, showing transiently reduced blood pressure and increased heart rates in the absence of consistent ECG changes. These high incidences of (cardio)vascular signs were also described in the other phase 1 study in patients with advanced B-malignancies in a total of three patients treated at doses ≥ 10 mg/day. The overall risk of serious cardiovascular events in the course of treatment with LAF389 appears excessively high as compared with the anticipated patient benefit (no objective responses seen). Consequently, in the absence of clear signals of clinical activity, the investigators and the sponsor agreed on the early termination of the LAF389 project on safety grounds.

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