18 Aug 2010	Due to worsening of facial oedema and oedema of the limbs, the study medication was put on hold. The subject's urea nitrogen and creatine levels increased, and he experienced a decrease in renal function characterized by reduced urine output, nausea and vomiting. Chest imaging detected a mild accumulation of pleural effusion.
19 Aug 2010	Reduced urine output persisted and urethral catheterization was started.
20 Aug 2010	An echocardiogram was performed which revealed no deterioration of cardiac functioning.
23 Aug 2010	A urine sample was collected which showed a urine creatinine level of 52.4 mg/dL, a daily amount of creatinine emission of 0.9 g/dL and a creatinine clearance adjusted value of 43.0 mL/min. It was noted that the edema and the subject's general condition improved slightly.
30 Aug 2010	The subject's oedema and general condition improved and the study medication was resumed with a dose reduction to 8 mg/day.
31 Aug 2010	The subject's general condition improved and he was discharged on his own request.
13 Sep 2010	The subject had experienced a feeling of abdominal fullness, loss of appetite and constipation. An abdominal echo revealed moderate ascites and worsening renal function. The study medication was again put on hold.
24 Sep 2010	A CT scan was performed – tumor size was stable without change in mass.
27 Sep 2010	Renal function was improving, so the study medication was resumed at 4 mg/day. The subject's weight on this day was 60.0 kg.
04 Oct 2010	Facial and limb oedema was noted. An abdominal echo detected massive ascites. The study medication was discontinued at the subject's request. The subject was treated with two tablets of spironolactone and monitored. The subject's weight remained at 60.0 kg.
18 Oct 2010	The subject's facial oedema had disappeared but persisted slightly on the limbs. The subject's weight had decreased to 56.3 kg.
05 Nov 2010	The subject's oedema of the lower left limbs resolved. Urine protein improved with a +2 qualitative increase.
15 Nov 2010	Hospital admission was postponed at the subject's request, and he presented able to walk. The subject's next treatment was considered but this was postponed. The subject's weight had decreased to 54.3 kg.
24 Nov 2010	The subject's next treatment was planned on 25 Nov 2010.
26 Nov 2010	During follow-up investigation no lower limb oedema or ascites were observed. The subject was withdrawn from the study.

Investigator's comment:
Mild diabetic nephropathy had occurred before the subject started this clinical study. However after this study was started, Urinary nitrogen and creatinine levels gradually increased and a decreased in renal function occurred. After cessation of the drug, levels of renal function improved. However after reintroduction of the drug, worsening renal function, oedema and ascites were noted. Thus a causal association between the drug and the event was considered undeniable. Symptoms improved as of 26 Nov 2010 and the subject's condition was stabilized. However it was assumed no further remission of the event was expected because mild renal disorder had already been noted before this study was started. The next treatment was started on 26 Nov 2010 and further follow-up investigation of this study was considered difficult. Thus this study was ended.

Subject ID:	**20113005**
Age:	73 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	Erythema, hyperthyroidism, osteoporosis, alopecia, cancer pain, constipation, esophageal varices, gastritis, hepatitis C virus, hypertension
Concomitant medications:	Bfluid, amlodipine besilate, cefazolin sodium, dextromethorphan hydrobromide hydrate, livact, furosemide, ketoprofen, lactec, loxoprofen sodium hydrate, Neolamin 3B, magnesium oxide, menatetrenone, Soldem 3AG, sennoside, spironolactone, thiamazole, Tukushi, urea
Reason for narrative:	
Nonfatal SAE(s)	Oesophageal varices haemorrhage
Relationship to study drug:	Not related

AE Description:

17 Sep 2004	The subject was diagnosed with carcinoma hepatocellular.
28 Sep 2010	Informed consent was obtained.
19 Oct 2010	A CT scan performed revealed oesophageal varices, for which endovenous laser treatment was started.
26 Oct 2010	The subject underwent endoscopy to confirm the site of performance, and no remaining oesophageal varices were found.
29 Oct 2010	The subject started study medication.
13 May 2011 (SAE Start Date)	The subject visited the physician's hospital for Day 1 of the Cycle 8. The subject received the scheduled dose of study medication. After the medical examination, the subject vomited blood at the parking lot of the hospital. The subject was transported to the outpatient department of internal medicine. Subsequently, the subject experienced several episodes of hematemesis, facial pallor, and loss of consciousness. An endoscopy performed revealed rupture of the oesophageal varices. The subject was urgently hospitalized and endovenous laser treatment was conducted at five points. The subject's condition stabilized but later (around 22:20) the subject vomited blood again and underwent urgent endoscopy, which revealed a deviation of the endovenous laser band at one point. Endovenous laser treatment was conducted again, and hemostasis was confirmed.
14 May 2011	His hemoglobin value decreased for which intravenous ferric oxide saccharate (40 mg 2 mL) was started. The study medication was interrupted for observation.

17 May 2011	An upper gastrointestinal endoscopy showed white moss was attached to the endovenous laser sites. The event was considered as resolved.
20 May 2011	The subject was scheduled to be discharged and the study medication was due to restarted on 21 May 2011.

Investigator's comment:
The oesophageal varices rupture is likely due to the subject's underlying hepatic condition. The investigator considered the causal relationship between the study medication and the reported event as "not related".

Subject ID:	**20123001**
Age:	49 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	B type chronic hepatits, constipation, gastritis, insomnia
Concomitant medications:	Amlodipine besilate, soldem 3A, entecavir hydrate, fexofenadine hydrochloride, garenoxacin mesilate hydrate, azulene sulfonate sodium hydrate L-gluta, huscode, loxoprofen sodium hydrate, olmesartan medoxomil, PL, acetaminophen, sennoside, triamcinolone acetonide, zolpidem tartrate
Reason for narrative:	
Nonfatal SAE(s)	Gastritis
Relationship to study drug:	Not related

AE Description:

13 Oct 2010	The subject started study medication.
19 Jan 2011 (SAE Start Date)	The subject presented to the hospital on Day 15 of Cycle 4 with cold-like symptoms such as cough and nasal discharge. Fexofenadine hydrochloride was administered to treat upper respiratory inflammation and the subject went home at 11:00. At around 12:00, the subject suddenly experienced epigastric pain outside the subject's home and then returned to the hospital. A CT scan confirmed neither ruptured hepatoma nor acute pancreatitis. An upper gastrointestinal endoscope revealed mild gastric mucosal reddening. The subject was admitted because of follow-up for abdominal symptom. 15 mg of pentazocine and 500 mL of Veen-F were administered to treat epigastric pain. Acetate ringer's solution, 20 mg of famotidine, 20 mg of scopolamine butylbromide and 500 mL of glucose-electrolyte fluid was started. Meanwhile, 3 × 100 mg tablets divided into three daily doses of rebamipide was initiated. Vital signs on admission were body temperature 36.8 °C, HR 94 and BP 140/78 mmHg. The epigastric pain was relieved owing to analgesic.
20 Jan 2011	The epigastric pain disappeared and he remained without symptoms and signs. The subject was scheduled to pay the next visit on 02 Feb 2011 and was discharged from the hospital.
02 Feb 2011	The subject presented for his scheduled Cycle 5, Day 1 visit. Mild epigastric pain persisted, but oral intake was good and his pain score was 10 Feb 2011. Oral rebamipide and famotidine therapy was maintained and the subject's condition continued to be monitored.

16 Feb 2011	The subject presented for his scheduled Cycle 5, Day 15 visit. The epigastric pain had disappeared and the subject had no digestive symptoms such as nausea or vomiting. Due to the improved symptoms both rebamipide and famotidine were withdrawn.
17 Feb 2011	The subject was considered to have recovered from the event.

Investigator's comment:
The subject's condition was stable after the start of the study drug. Epigastric pain appeared suddenly on 19 Jan 2011. Upper gastrointestinal endoscopy revealed mild gastritis and abdominal CT angiography found no obvious causative abnormality. The symptom was abating by itself and was not exacerbated owing to usual administration of the study drug on the morning of 20 Jan 2011. Although the specific cause cannot be decided, the reporting physician considered that the event occurred accidentally because the symptom did not worsen after he took the study drug as usual. Consequently, causal relationship with the study drug can be ruled out.

Subject ID:	**20123002**
Age:	70 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	Diabetes, hepatits C virus, hypertension, hypoacusis, hypothyroidism, osteoporosis, pruritus
Concomitant medications:	Aminoleban EN, candesartan cilexetil, livact, insulin lispro, levothyroxine sodium hydrate, magnesium oxide, menatetrenone, nifedipine, sennoside, urea
Reason for narrative:	
Nonfatal SAE(s)	Proteinuria, Renal impairment
Relationship to study drug:	Probably related (Proteinuria, Renal impairment)

AE Description:

15 Dec 2010	The subject started study medication.
28 Dec 2010	After discharge from hospital.
05 Jan 2011 (SAE Start Date)	An abdominal ultrasound was performed and a moderate volume of ascites detected at liver surface, Morrison's pouch and Douglas's pouch. With consideration of proteinuria of 4+, a 2.2 kg increase in weight and difficulty of oral intake, the subject was hospitalized for management of ascities. An aggravation of the underlying disease was considered as a contributing factor. The administration of study medication was interrupted.
07 Jan 2011	The subject's body weight was 54 kg. Oedema persisted. The subject was treated with 10 mg of Lasix granules (40 mg/G furosemide) and 25 mg one tablet of adalactalone. The subject had persistent watery diarrhea and 330 mg of magnesium oxide and sennoside were discontinued in the evening.
11 Jan 2011	Uric acid was improved to (2+) and the subject lost 5 kg of body weight since admission to hospital and now weighed 50 kg. Oedema at the dorsum of the foot was mild and oral intake became better. The subject was discharged and scheduled to follow-up on 18 Jan 2011. At this appointment an examination will be made whether study medication will be reintroduced. The subject's body temperature was 35.7 °C, heart rate 64/min and blood pressure 124/78 mmHg.
14 Jan 2011	The subject's furosemide and adalactalone treatments were discontinued.
18 Jan 2011	There was improvement including no oedema of the lower legs and proteinuria +1, so the study medication was resumed at a reduced dose of 8 mg/day.

28 Jan 2011	The study medication was discontinued based on the results of a test on 26 Jan 2011 which showed proteinuria 3+.
02 Feb 2011	An unscheduled test showed proteinuria of 2+. There was no subjective change in the subject's symptoms so the study medication was resumed at 8 mg/day.
16 Mar 2011	The subject had oedema in the lower legs on an unscheduled examination. His weight was 54.1 kg. The study medication was suspended.
30 Mar 2011	His weight was 52.3 kg, representing an improvement. The subject's lower leg oedema decreased, so the study medication was resumed at 8 mg/day.
22 Apr 2011	The study medication was suspended because the results of a test on 20 Apr 2011 showed proteinuria +3.
27 Apr 2011	The subject made an unscheduled hospital visit. An in-hospital test showed proteinuria 2+, so the study medication was resumed at 8 mg/day.
11 May 2011	The results of a test on 02 May 2011 showed proteinuria 3+. Although not required by the protocol, the study medication was suspended for the subject's safety.
18 May 2011	The subject's proteinuria had improved to 2+, so the study medication was resumed at a reduced dose of 4 mg/day.
04 Apr 2012	Proteinuria 3+ was detected and the study medication was suspended. The subject's body weight was 51.1 kg.
18 Apr 2012	The subject's weight was 51.5 kg. His lower leg oedema and abdominal bloating decreased and his proteinuria improved to 2+. The study medication was resumed at 4 mg/day.
16 May 2012	The subject's weight had increased by 1.5 kg to 53.0 kg. He had abdominal bloating, so the dose of furosemide was increased to 60 mg/day and Aldactone-A was increased to 50 mg/day.
31 May 2012	The results of a CT scan on 02 May 2011 were confirmed, with evidence of involvement of another tumour in the liver. The subject was therefore withdrawn from the study, according to the protocol.
01 Jun 2012	The subject took his last dose of the study medication, which the investigator ordered to be discontinued as from 02 Jun 2012. The subject's proteinuria on discontinuation was 3+.
27 Jun 2012	On follow-up the subject had proteinuria 2+, a BUN level of 30 mg/dL, creatinine level of 1.34 mg/dL (central test), good food intake and no abdominal bloating or facial oedema. The oedema in his lower legs had almost disappeared and his body weight was 48.2 kg. Although the subject had not fully recovered, the reported events were confirmed to have improved and his symptoms were stable. Therefore no further follow-up was arranged.

Investigator's comment:
Abnormal levels of laboratory tests as well as symptoms associated to renal function appeared after the study drug was started. Thus causal relationships between the study drug and events were not deniable. The subject's status was confirmed about 30 days after the study drug was discontinued. Although it was not as good as recovery, it was confirmed to be improved and the symptoms were also confirmed to be stable. Therefore follow-up was terminated based on the study protocol.

Subject ID:	**21013002**
Age:	69 years
Sex:	Male
Race:	Asian (Korean)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	Musculoskeletal pain (chest), pain (right shoulder), pain (back), tinnitus, contrast agent allergy, headache, hearing disturbance, hypertension, right flank pain, sputum
Concomitant medications:	Amitriptyline, amlodipine, bromhexine, chlorpheniramine, dihydrocodeine bitartrate, fentanyl propanamide, hydrochlorothiazide, hydrocortisone sodium succinate, codeine/acetaminophen/ibuprofen, morphine, piperacillin/tazobactam, red blood cell
Reason for narrative:	
Nonfatal SAE(s)	Haemoptysis
Relationship to study drug:	Not related

AE Description:

01 May 2003	The subject was diagnosed with hepatocellular carcinoma.
26 Mar 2011	The subject started the study medication. Multiple medications were administered concomitantly.
27 Mar 2011 (SAE Start Date)	The subject had his last dose of the study medication. He experienced hemoptysis at home, the subject visited the emergency room. The subject's blood pressure was 147/90 mmHg, pulse rate 85 beats/min, respiratory 24 rpm, body temp 36.0°C. Lab value showed WBC $13.3\times10^3/mm^3$, Hb 14.5 g/dL, Platelet $18.9\times10^4/mm^3$, E-ANC $10250/mm^3$, AST (SGOT) 70 IU/L, ALT (SGPT) 19 IU/L, Bilirubin total 1.6 mg/dL, Bilirubin, direct 0.4 mg/dL, CRP (quant) 2.04 mg/dL. Treatment included tranexamic acid, blood transfusion, antibiotics (Tazocin), tranexamic acid and oxygen. Bronchial arteriography showed much enlarged vessels with abnormal pulmonary staining. The right and left bronchial arteries were embolized.
28 Mar 2011	The study drug was discontinued due to the event. The subject had fever and chest pain and was treated with antibiotics and painkillers.
08 Apr 2011	The subject was removed from the study.
13 Apr 2011	The subject recovered from the event and was discharged from hospital with good clinical condition.

Investigator's comment:

The hemoptysis was not suspected to be related to the study medication.