Subject ID:	**10022005**
Age:	49 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	8 mg QD, Dose-escalation component (Phase 1; Group 2)
Current medical conditions:	Caries, constipation, cough, esophageal varix, hypoalbuminemia, inferior vena cava thrombosis, liver cirrhosis, muscle pain, pharyngitis
Concomitant medications:	Azulene, beclomethasone dipropionate, betamethasone butyrate propionate, betamethasone valerate, bifidobacterium, cefdinir, cefditoren pivoxil, dequalinium chloride, dextromethorphan hydrobromide hydrate, diclofenac sodium, diflorasone diacetate, livact, famotidine, furosemide, gentamicin sulfate, hachiazule, indometacin, influenza HA vaccine "SEIKEN", ketoprofen, lidocaine hydrochloride, loperamide hydrochloride, loxoprofen sodium hydrate, magnesium oxide, pl granule, human plasma protein fraction, sodium polyacrylate, roihi, spironolactone, tetracycline hydrochloride, urea, ursodeoxycholic acid, tokuhon, zinc oxide
Reason for narrative:	
Nonfatal SAE(s)	Tumour haemorrhage
Relationship to study drug:	Not related

AE Description:

09 Nov 2009	Informed consent was obtained.
22 Nov 2011	The subject started the study medication. (The last dose of administration was on 21 Dec 2012.)
16 Jan 2013	The subject developed left flank pain; voltaren tablets (diclofenac sodium) were administered, but were not effective.
17 Jan 2013 (SAE Start Date)	The event of left flank pain had not improved. The subject was urgently hospitalised due to a suspected tumor hemorrhage (adrenal gland). A CT showed tumor hemorrhage. On an unknown date, the subject underwent TAE of the left adrenal arteries (superior and middle). Hemoglobin decreased from 11.1 to 7.7, indicating anemia. The subject received a blood transfusion and morphine injection was administered for pain.
19 Jan 2013	Hb decreased to 7.7 again. Blood transfusion was performed. Hb did not decrease (10.4 on 28 Jan 2013).
22 Jan 2013	Injection of morphine was changed to oral Opso (morphine hydrochloride hydrate) as needed for pain on 22 Jan 2013 and good control was achieved. After TAE, he had pyrexia on consecutive days. The pyrexia was treated with loxoprofen.

30 Jan 2013 The subject was discharged from the hospital with recovery from the tumour hemorrhage.

Investigator's comment:

Since liver cancer metastasised to the adrenal glands, the adrenal hemorrhage was due to aggravation of the underlying disease. Further, since the study medication had stopped 1 month prior to the event. Therefore the event was considered not related to study drug.

Follow up information received as above. No change to previous Sponsor medical assessment of causality. Study drug had been discontinued 28 days prior to tumour haemorrhage and the event is therefore considered not related.

Subject ID:	**10012002**
Age:	58 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Dose-escalation component (Phase 1; Group 2)
Current medical conditions:	Hepatitis B virus
Concomitant medications:	Betamethasone d-chlorpheniramine maleate, diphenhydramine, entecavir hydrate, livact
Reason for narrative:	
Nonfatal SAE(s)	Hepatic encephalopathy
Relationship to study drug:	Possibly related

AE Description:

Dec 2003	The subject was diagnosed with hepatocellular carcinoma.
12 Mar 2010	The subject consented to participate in the clinical study.
15 Mar 2010	Informed consent was obtained.
23 Mar 2010	The subject enrolled into the clinical study.
24 Mar 2010	The subject started the study medication (12 mg/body/day).
02 Apr 2010	The subject received last dose of study medication. Neither disturbed consciousness nor findings indicative of hepatic encephalopathy were confirmed.
03 Apr 2010 (SAE Start Date)	The subject fell during a night shift. He responded to be being called; however, experienced disturbed consciousness. Flapping tremors were confirmed, and he was diagnosed as having hepatic encephalopathy (hepatic dysfunction/hepatic failure = Grade 4). A CT scan was performed urgently and revealed no intracranial lesions. An abdominal CT scan confirmed a portal vein tumor embolus and aggravated thrombus. As a result, it was determined to be the progression of cancer and he was withdrawn from the clinical study. Fatigue (Grade 3) and anorexia (Grade 3) were also observed.
07 Apr 2010	Based on laboratory data, the hepatic dysfunction (T-Bil, ammonia) tended to improve (hepatic dysfunction/hepatic failure = Grade 0). Although the subject's ammonia level was high at 133 μg/dL, his consciousness was clear. In addition, the clinical symptoms improved; therefore the subject was considered recovered from the event.

Investigator's comment:
The administration of the study drug was initiated from 24 Mar 2010, and no specific side effects were confirmed. On 03 Apr 2010 (Day 11) flapping tremors occurred, and the level of his ammonia was high at 126 μg/dL; consequently, a diagnosis of Grade 3 hepatic encephalopathy was made. An abdominal CT scan confirmed a portal vein tumor embolus and aggravated thrombus, and a decreased portal blood flow was considered to have caused hepatic encephalopathy. As a result, the aggravation of the original lesion was likely to have induced the event. However, the event occurred while the study drug was being administered and so it has been assessed that the causal relationship between the event and the study drug cannot be ruled out.

Subject ID:	**10022002**
Age:	66 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Dose-escalation component (Phase 1; Group 2)
Current medical conditions:	Cataract, cirrhosis, constipation, edema, esophageal varices, hernia inguinalis, hypothyroidism, insomnia, pollen allergy, pruritus, reflux esophagitis
Concomitant medications:	Human serum albumin, dimethyl isopropylazulene, baclofen, lac-B, chlorpromazine hydrochloride, livact, furosemide, ketoprofen, levothyroxine sodium hydrate, magnesium oxide, menturm, metoclopramide, naproxen, acetaminophen, pirenoxine, sodium rabeprazole, sennoside, spironolactone, ursodeoxycholic acid, zolpidem tartrate
Reason for narrative:	
Nonfatal SAE(s)	Tumour haemorrhage
Relationship to study drug:	Not related

AE Description:

Feb 2009	The subject was diagnosed with hepatocellular carcinoma.
14 Oct 2010	The subject started the study medication (12 mg/day).
23 Nov 2010	The subject received his last dose of the study medication (12 mg/day).
08 Dec 2010	An imaging test revealed progression of disease (PD). The subject was withdrawn from the study.
15 Dec 2010 (SAE Start Date)	As the subject had a tendency of low haemoglobin and ascites, routine tests were performed. Blood test revealed low level of hemoglobin at 6.5 g/dL. Abdominal puncture showed hemorrhagic ascites, and tumor haemorrhage was suspected. The subject was admitted to the hospital. A transcatheter arterial embolization at two medial branches of A4 and A3 was performed for hemostasis. Transfusion with four units of packed red blood cells was performed. The subject experienced pyrexia with a temperature of 39.0 °C. It was thought pyrexia occurred along with post-transcatheter arterial embolization management. No focus to suspect infection was identified.
16 Dec 2010	The subject experienced abdominal pain. Blood test showed hemoglobin of 9.3 g/dL. The hemorrhage ceased.
18 Dec 2010	Pyrexia, liver function and renal function tended to improve. The subject's haemoglobin level was 8.7 g/dL, and no haemorrhaging seemed to occur.
20 Dec 2010	The subject experienced intense bloating. Ascites puncture was performed and 800 mL of fluid was drained. Hemoglobin level was 9.3 g/dL.

27 Dec 2010	Ascites with tendency of dehydration was observed. Fluid replacement was continued because the subject had still been able to eat only a small amount of food.
28 Dec 2010	The subject was suffering from severe ascites and a puncture was performed. 2000 mL of haemorrhagic ascitic fluid was drained, the density of which was lighter than the previous time.
31 Dec 2010	The subject was still suffering from ascites, and a repeat puncture was performed, from which 2500 mL was drained. Hemoglobin level was 9.9 g/dL.
03 Jan 2011	PS3.
05 Jan 2011	Ascites puncture was performed and 2500 mL of ascites was drained with light red color. The subject will receive best supportive care.

Investigator's comment:
It was assumed that hemorrhagic ascites occurred due to bleeding from the ruptured hepatocellular carcinoma that was rapidly enlarged during a follow-up period after the subject was evaluated as progression of disease on the study drug. Causal relationship between the study drug and the event was deniable. Aggravation of underlying disease was evaluated as cause of event. No Progression of anemia noted. Change in property of ascitic fluid represented haemorrhage from hepatocellular carcinoma was resolved.

Subject ID:	**20013005**
Age:	37 years
Sex:	Female
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	Cancer pain, hepatitis B virus, urinary calculosis
Concomitant medications:	Diclofenac sodium, difluprednate, domperidone, entecavir hydrate, famotidine, indometacin, levothyroxine sodium hydrate, loxoprofen sodium hydrate, magnesium oxide, morphine hydrochloride hydrate, nadifloxacin, oxycodone hydrochloride, Rohto antibacterial eyewash, urea
Reason for narrative:	
Nonfatal SAE(s)	Hypoglycaemia
Relationship to study drug:	Not related

AE Description:

Apr 2010	The subject was diagnosed with advanced hepatocellular carcinoma.
27 Aug 2010	Informed consent was obtained.
01 Sep 2010	The subject started the study medication (12 mg).
22 Dec 2010	The subject was withdrawn from the study owing to progression of disease.
07 Jan 2011	Oral administration of sorafenib tosilate was initiated for the next treatment.
12 Jan 2011	A blood test showed the aggravation of hepatic failure; hence sorafenib tosilate was interrupted.
21 Jan 2011 (SAE Start Date)	The reporting physician got a phone call saying that the subject scarcely moved and was sluggish from the morning at home. The subject was transported to hospital by ambulance, and her consciousness level at arrival was 300. A blood sugar test revealed hypoglycaemia and glucose sugar fluid replacement was started. After the replacement was started, she recovered her consciousness, and the BS level increased to 167 mg/dL. The subject was hospitalized.
25 Jan 2011	Hypoglycaemia was observed and glucose sugar fluid replacement was continued for 24 hours although there was no finding in the subject's symptoms.
27 Jan 2011	The subject was discharged from hospital according to her family's request and would be treated at home by a doctor.
14 Feb 2011	The subject died at home.

Investigator's comment:
The subject was withdrawn from the study owing to progression of disease on 22 Dec 2010. Afterwards, she was admitted to the hospital for hypoglycaemia during receiving follow-up. The event was due to hepatic failure caused by the aggravation of the underlying disease. The causal relationship between the event and the study drug can be ruled out.

Subject ID:	**20013006**
Age:	77 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	Diabetes mellitus, gastritis, liver cirrhosis, pleural effusion, prostate hypertrophy
Concomitant medications:	Famotidine, lactulose, mosapride citrate hydrate, nateglinide, sennoside
Reason for narrative:	
Nonfatal SAE(s)	Hepatic encephalopathy
Relationship to study drug:	Probably related

AE Description:

Dec 2002	The subject was diagnosed with hepatocellular carcinoma.
01 Feb 2011	Informed consent was obtained.
07 Feb 2011	The subject enrolled into the clinical study.
08 Feb 2011	The subject started the study medication (12 mg/day).
10 Feb 2011	The subject received his last dose of the study medication before onset of the event.
11 Feb 2011 (SAE Start Date)	The subject had an abnormal behaviour and experienced a “flapping” tremor. A blood test was performed which showed an increase in liver enzymes, biliary enzymes and ammonia. The subject was diagnosed with Grade 3 hepatic encephalopathy. Morihepamin (amino acid) administration started intravenously. The subject’s ammonia level was 183 µg/dL.
17 Feb 2011	The subject’s ammonia level was restored to 67 µg/dL and his liver enzymes and biliary enzyme values improved. Morihepamin treatment was discontinued.
18 Feb 2011	Grade 0 hepatic encephalopathy. The study medication was resumed at a reduced dosage of 8 mg/day.

Investigator’s comment:

After receiving the study drug, he experienced hepatic encephalopathy with the increase in the ammonia value, which improved owing to the interruption of the drug. Hence the study drug was related to the event.

Subject ID:	**20023002**
Age:	59 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	Constipation, gastric ulcer, gingivitis, hepatitis B, hypertension, insomnia, tinea, tinea unguium
Concomitant medications:	Amlodipine besilate, azithromycin hydrate, betamethasone butyrate propionate, bifonazole, candesartan cilexetil, cefcapene pivoxil hydrochloride hydrate, cefmetazole sodium, diphenhydramine, entecavir hydrate, fexofenadine hydrochloride, heparinoid, ketoconazole, loxoprofen sodium hydrate, magnesium oxide, metoclopramide, nitrazepam, omeprazole, oseltamivir phosphate, PL granule, acetaminophen, prochlorperazine, sennoside A B, stronger neo minophagen C, urea, varenicline tartrate
Reason for narrative:	
Nonfatal SAE(s)	Lymphoma
Relationship to study drug:	Not related

AE Description:

23 Mar 2011	The subject started study medication.
13 Jun 2012	Study medication was discontinued due to imaging showing progressive disease. The subject visited a nearby clinic (division of dentistry, internal medicine) due to maxillary pain and gingival swelling.
20 Jun 2012	Antibiotic drug was initiated.
25 Jun 2012	The subject visited the oral surgery and underwent ultrasonography and an MRI. Ultrasonography showed a 70% probability that he had pus.
27 Jun 2012 (SAE Start Date)	A medical examination was performed revealing swelling in left cervical lymph nodes.
30 Jun 2012	The possibility of tumour formation was explained as a result of MRI.
02 Jul 2012	The subject was admitted to participate in another study. An MRI was performed and revealed a mass extending from the left cervical region to the pharynx.
05 Jul 2012	The subject visited the division of head and neck in the investigator's hospital. He underwent a biopsy of oropharynx.
12 Jul 2012	Biopsy detected malignant lymphoma.
13 Jul 2012	The subject was transferred to the hematology and internal medicine unit.

Investigator's comment:
Although biopsy was performed on 05 Jul 2012, and 27 Jun 2012 (the date when the swelling in the left cervical lymph nodes was noted) regarded as the onset date of malignant lymphoma. The study drug, an angiogenesis inhibitor, had been found to have no effects inducing gene mutation in nonclinical studies; therefore, the mechanism of action of the study drug was not believed to cause malignant lymphoma. Consequently, the relationship between the event and the study drug was excluded. Although the subject had not yet recovered from the event, he was started on treatment in other department; thus, no further follow-up of this subject was required.

Subject ID:	**20033003**
Age:	61 years
Sex:	Female
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	Asomnia, bronchial asthma, chronic gastritis, chronic hepatitis B, gall stone, neck stiffness, portal hypertension
Concomitant medications:	Bfluid, brotizolam, ciclesonide, entecavir hydrate, lansoprazole, nifedipine, acetoaminophen, pranlukast hydrate, serevent rotadisk, sennoside, urea, zolpidem tartrate
Reason for narrative:	
Nonfatal SAE(s)	Hepatic encephalopathy, Portal vein thrombosis
Relationship to study drug:	Not related (Hepatic encephalopathy, Portal vein thrombosis)

AE Description:

20 Dec 2010	The subject was diagnosed with recurrence of hepatocellular carcinoma.
18 Jan 2011	Informed consent was obtained.
04 Feb 2011	The subject started the study medication (Day 1 of Cycle 1, 12 mg/day).
17 Feb 2011 (SAE Start Date)	The Day 15 of Cycle 1; the subject was suspected to have hepatic encephalopathy and underwent a blood test, which showed that her serum ammonia value increased to 207 μg/dL. The subject was given a diagnosis of hepatic encephalopathy (Grade 2). The subject was admitted to the hospital and started receiving intravenous transfusion including a drip infusion of amino acid injection (Terufis) (drug for hepatic failure). The study drug was interrupted.
18 Feb 2011	Hepatic encephalopathy was improving (Grade 1).
19 Feb 2011	Although hepatic encephalopathy improved, the transfusion was maintained.
21 Feb 2011	The transfusion was completed, and the hepatic encephalopathy resolved.
25 Feb 2011	The study mediation was reintroduced at a reduced dosage of 8 mg/day.
02 Mar 2011	The subject received Day 1 Cycle 2 of the study medication at 8 mg/day.
03 Mar 2011 (SAE Start Date)	The subject's discharge was scheduled for 07 Mar 2011. A CT examination revealed portal vein thrombosis. Ascites was also observed.

04 Mar 2011	Administration of diuretic drug(s) (furosemide) and branched-chain amino acid fluids (hepan ED) was initiated.
07 Mar 2011	The ascites persisted, so the subject's hospitalization was prolonged.
08 Mar 2011	Therapy with intravenous, danaparoid sodium (2500 units/day) and anthrobin P for injection (1500 units/day) was started, for which concomitant medications are prohibited; therefore, the administration of the study medication was discontinued.
12 Mar 2011	The administration of anthrobin P for injection was ended.
14 Mar 2011	A CT scan revealed no change in the ascites or portal vein thrombosis.
22 Mar 2011	The administration of danaparoid sodium was ended.
23 Mar 2011	A CT scan showed that the ascites had improved and the blood flow in the portal vein had slightly increased. Lymph node metastases were noted.
24 Mar 2011	Warfarin was initiated (2.0 mg/day).
28 Mar 2011	INR 1.47. The dose of warfarin was increased (3.0 mg/day) because of insufficient efficacy.
04 Apr 2011	INR 2.85. The daily dose of warfarin was reduced to 2.5 mg/day.
07 Apr 2011	A CT scan confirmed increased blood flow in the portal vein.
08 Apr 2011	INR 2.79. The subject recovered from the event and the daily dose of warfarin was reduced to 2.25 mg/day. The subject was discharged from hospital.

Investigator's comment:

The event developed after the start of the study drug; therefore, causal relationship with the study drug cannot be ruled out. Although she is in the hospital at the time of the report, the event had resolved; the reporting physician completes the report.

The subject's portal vein thrombosis was associated with cirrhosis and progressed; thus, the causal relationship between the study drug and the portal vein thrombosis can be ruled out. The seriousness of the event is considered to be serious since her hospitalization was prolonged due to the event.

Subject ID:	**20043001**
Age:	76 years
Sex:	Female
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	Constipation, edema-leg, hypertension, hyperuricemia, hypokalemia, osteoarthritis, renal atrophy, shoulder pain
Concomitant medications:	Allopurinol, ambroxol hydrochloride, dimethyl isopropylazulene, betamethasone, betamethasone sodium phosphate, bifidobacterium, calcium polystyrene sulfonate, carbazochrome sodium sulfonate hydrate, celestamine, ascorbic acid calcium pantothenate, dextromethorphan hydrobromide hydrate, difluprednate, domiphen bromide, Biofermln-R, L-isoleucine, L-leucine L-varine, furosemide, ketoprofen, levofloxacin hydrate, lidocaine, loxoprofen sodium hydrate, loxoprofen sodium hydrate, magnesium oxide, methyl salicylate, montelukast sodium, nifedipine, omeprazole, PL granule, acetaminophen, prednisolone, rokitamycin, sennnoside A B, sodium gualenate hydrate, sofalcone, teprenone, triamcinolone acetonide, Tsukushi AM powder, tulobuterol
Reason for narrative:	
Nonfatal SAE(s)	Angina pectoris
Relationship to study drug:	Probably related

AE Description:

The subject started the study medication on 25 Jan 2011 and received it until 06 Apr 2012.

06 Apr 2012 (SAE Start Date)	A routine ECG (performed on Cycle 16 examinations) showed negative inversion of the T-wave at leads V1 to 4. The subject had felt pain while walking over the preceding week, but had experienced no problems when not walking. A cardiovascular consultation was arranged.
10 Apr 2012	A follow-up ECG was performed which showed positive T-wave conversion. Myocardial scintigraphy was performed on 12 Apr 2012, though the results were not reported.
17 Apr 2012	Based on an ultrasound cardiography, it was thought more likely the subject had angina pectoris. The subject was treated with aspirin and clopidogrel sulphate. The treating cardiologist requested that the study subinvestigator withdraw the subject from the study.

24 Apr 2012	The subject was admitted to hospital for a coronary angiogram, which was performed the next day (25 Apr 2012). The angiogram showed 90% stenosis of the left anterior descending coronary artery (LAD [segment 7]).
26 Apr 2012	The subject was discharged from hospital.
02 May 2012	She returned to hospital as an outpatient and admission was planned for 10 May 2012 for her to undergo a percutaneous coronary intervention. The procedure was delayed, however, because the subject had lower limb oedema. Pulmonary congestion (present on an X-ray) and congestive heart failure were also noted.
11 May 2012	No cardiac event (chest symptoms) was occurred. The subject's urinary status was favourable the next day (12 May 2012).
13 May 2012	The subject complained of leg pain and crystal arthritis was suspected. A stool test was positive for occult faecal blood.
14 May 2012	The subject's leg pain remained unchanged.
15 May 2012	She underwent an upper gastrointestinal endoscopy which revealed chronic gastritis.
16 May 2012	A lower gastrointestinal endoscopy showed polyps which required follow-up examination. No obvious source of bleeding was identified, and the subject's leg oedema disappeared.
18 May 2012	The subject underwent the delayed percutaneous coronary intervention. A bare metal stent was placed.
19 May 2012	A tendency towards anaemia was noted and the subject received two units of concentrated red blood cells.
20 May 2012	The subject's hospitalisation was prolonged because of the follow-up required for her anaemia.
21 May 2012	No specific changes were noted and the subject was scheduled to be discharged the next day (22 May 2012), with a follow-up visit planned for a week later.
29 May 2012	The subject had a cardiovascular follow-up and had no chest symptoms or changes in her leg oedema.
08 Jun 2012	A gastrointestinal follow-up and a further cardiovascular follow-up on 12 Jun 2012 were unremarkable.
15 Jun 2012	The subject's angina of effort was considered to be improving.

Investigator's comment:
The causal relationship between angina of effort and the study drug cannot be excluded since the event occurred after administration of the study drug and there were case reports of ischaemic heart disease. The subject was hospitalised for CAG on 24 Apr 2012; therefore the event was determined to be an SAE. Interaction among drugs during administration can be excluded. Symptoms subsequently improved after PCI on 18 May 2012; therefore the outcome of the event was "recovering".

Subject ID:	**20053001**
Age:	61 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	Allergy for contrast medium, diabetes mellitus, gingivitis, liver cirrhosis type B
Concomitant medications:	Alprostadil alfadex, ambroxol hydrochloride, amlodipine besilate, dimethyl isopropylazulene, betamethasone butyrate propionate, bifidobacterium, carbazochrome sodium sulfonate hydrate, L-carbocisteine, cefditoren pivoxil, cefotiam hexetil hydrochloride, cetirizine hydrochloride, codeine phosphate hydrate, diclofenac sodium, diphenhydramine laurylsulfate, furosemide, gentamicin sulfate, heparinoid, scopolamine butylbromide, levofloxacin hydrate, loxoprofen sodium hydrate, metoclopramide hydrochloride, mometasone furoate hydrate, montelukast, mosapride citrate hydrate, PL, acetaminophen, sodium rabeprazol, rebamipide, roxithromycin, sodium gualenate hydrate, spironolactone, sulfadiazine silver, tranexamic acid, urea
Reason for narrative:	
Nonfatal SAE(s)	Hepatic encephalopathy
Relationship to study drug:	Possibly related

AE Description:

13 Jun 2007	The subject was diagnosed with hepatocellular carcinoma.
12 Oct 2010	The subject started the study medication (12 mg).
12 Jan 2011	The subject's study medication dose changed (8 mg) due to decreased platelet counts.
27 Jul 2011	The subject consulted the reporting physician, and no specific findings were observed. Although an "MRI (08 Jul 2011) showed a worsening finding, a CT scan (21 Jul 2011) revealed no aggravation" leading to a decision of continuing on the clinical study.
29 Jul 2011 (SAE Start Date)	The subject's spouse reported on the phone in the evening that something was wrong with the subject. Mild clouding of consciousness was present. The subject was hospitalized. The study medication was discontinued. NH_3 level: 134. The subject was diagnosed with hepatic encephalopathy.
30 Jul 2011	The subject discontinued eating and fluids (aminoleban injection [amino acids, vitamins, minerals, etc]) were initiated instead. NH_3 level: 221.

03 Aug 2011	NH_3 level: 71. His consciousness level was normal with restriction of protein and control of defecation. In the evening, he resumed eating a protein-restricted diet. Administration of fluids stopped.
08 Aug 2011	He was discharged from the hospital.

Investigator's comment:
The causal relationship between the event and study medication was considered as possibly related and hepatic encephalopathy was Grade 3. Aggravation of his underlying disease could not be excluded; however, the event occurred while the study drug was being administered. Thus, the causal relationship to the study drug was classified as "possible".

Subject ID:	**20053002**
Age:	79 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	Allergy for contrast medium, blindness, constipation, gastritis, hypertension, liver cirrhosis, osteoporosis, esophageal varices
Concomitant medications:	Berizym, alendronate sodium hydrate, amlodipine besilate, betamethasone butyrate propionate, bifidobacterium, codeine phosphate hydrate, famotidine, levofloxacin hydrate, loperamide hydrochloride, loxoprofen sodium hydrate, PL, pyridoxal phosphate hydrate, seirogan, sennoside, sodium gualenate hydrate, sodium picosulfate hydrate, trimebutine maleate, urea, ursodeoxycholic acid, Rinderon-VG
Reason for narrative:	
Nonfatal SAE(s)	Oedema peripheral
Relationship to study drug:	Possibly related

AE Description:

Jan 2003	The subject was diagnosed with hepatocellular carcinoma.
20 Oct 2010	The subject started the study medication at a dose of 12 mg (body weight was 53.5 kg).
06 Nov 2010	The dosage of the study medication was reduced to 8 mg due to generalized malaise and anorexia.
26 Feb 2011	The subject developed sporadic diarrhea.
25 Apr 2011	The subject experienced diarrhea for several days and was instructed to interrupt the study medication.
28 Apr 2011	The subject presented to the hospital due to the diarrhea. His body weight had increased by 5.2 kg (48.3 kg on 21 Apr 2011 to 53.5 kg on 28 Apr 2011). There was no oedema or abdominal distension. CT scan was negative for ascites.
03 May 2011 (SAE Start Date)	The subject presented to the emergency department with marked oedema of the lower limbs and was treated with furosemide 20 mg and spironolactone 25 mg.
06 May 2011	The subject attended a follow-up appointment where his body weight had increased by another 4.5 kg to 58.0 kg. No change in the oedema was noted. Abdominal distension was positive, and human serum albumin and furosemide were administered intravenously. Both furosemide and spironolactone doses were increased to 2-fold.

07 May 2011	The subject resumed treatment with the study medication at a further reduced dosage (4 mg).
09 May 2011	The subject was admitted to hospital as planned and received treatment for oedema. The subject was treated with furosemide and potassium canrenoate.
11 May 2011	The subject's body weight had decreased to 51.4 kg and oedema remained on the dorsum of the foot.
15 May 2011	The subject's oedema showed an improvement and the subject's weight had decreased further to 48.7 kg. Oral and intravenous diuretic medications were completed.
17 May 2011	The study medication was resumed at the 4 mg dose and the subject was considered recovered from the event.
20 May 2011	The subject was discharged.

Investigator's comment:
The subject had maintained good liver function capacity graded as Child-A after administration of study medication. However ascites and oedema at lower limbs developed independently regardless of fluctuation in blood test results. So causal relationship between the study drug and event could not be ruled out considering the half-life of the study drug.

Subject ID:	**20053003**
Age:	74 years
Sex:	Female
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	Esophageal varices, hypokalemia, hypothyroidism, liver cirrhosis, reflux esophagitis
Concomitant medications:	Human serum albumin, amlodipine besilate, camostat mesilate, livact, filgrastim, furosemide, lactec, lansoprazole, levothyroxine sodium hydrate, loperamide hydrochloride, pyridoxal phosphate hydrate, spironolactone, neo-minophagen C (SNMC), sulpiride, tiquizium bromide, urea, ursodeoxycholic acid
Reason for narrative:	
Nonfatal SAE(s)	Oedema peripheral
Relationship to study drug:	Possibly related

AE Description:

Jun 2007	The subject was diagnosed with carcinoma hepatocellular.
09 Feb 2011	The subject started study medication at a dose of 12 mg once daily.
06 Mar 2011	Study medication daily dose was reduced to 8 mg/day due to a decreased platelet count.
01 Jul 2011	Study medication daily dose was further reduced to 4 mg/day because of generalized malaise.
25 Aug 2011	The subject had frequent diarrhoea which was controlled by changing the dose of loperamide hydrochloride from administered as required to twice daily.
09 Feb 2012	The subject's oedema of the lower limb occurred which was improved with the administration of human serum albumin and furosemide.
22 Mar 2012	The subject's diarrhoea aggravated so loperamide hydrochloride was increased to 3 mg TID. Study medication was held the following day.
29 Mar 2012 (SAE Start Date)	The subject's body weight had increased from 37.8 kg on 22 Mar 2012 to 44.5 kg on 29 Mar 2012. Marked oedema of the lower limbs and ascites was also noted.
30 Mar 2012	The subject was admitted to hospital for treatment of edema. The subject's body weight was 45.4 kg. Intravenous drips of human serum albumin, furosemide and potassium canrenoate were started.
05 Apr 2012	The subject's body weight was 42.0 kg. The intravenous drip medications did not improve the edema and ascites completely. The subject was withdrawn from the study given her overall status.

25 Apr 2012	The subject's condition was tendency improved and her body weight was at 41.4 kg.
27 Apr 2012	The subject was discharged from hospital.

Investigator's comment:
Child-B with hepatic functional reserve was favorably maintained despite administration of study medication. However it was assumed the study drug was causally related because ascites and edema at lower limbs solely occurred regardless of the laboratory result of blood test. Although she still had oedema in the lower limb, it was tendency improved compared to the time of admission so she was discharged from the hospital. The symptoms were stable so follow-up was not needed after the final observation.

Subject ID:	**20063001**
Age:	55 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	Allergic diathesis, asthma, constipation, gastric ulcer, hypertension, pruritus, shoulder arthritis
Concomitant medications:	Alosenn, cavadesartan cilexetil, solita-T 3G, chlorpheniramine maleate, famotidine, fluorometholone, furosemide, heparinoid ointment, levocabastine hydrochloride, loxoprofen sodium hydrate, magnesium oxide, nifedipine, salbutamol sulfate
Reason for narrative:	
Nonfatal SAE(s)	Syncope
Relationship to study drug:	Probably related

AE Description:

2003	The subject was diagnosed with hepatocellular carcinoma.
09 Dec 2010	The subject consented to participate in the study and was screened.
17 Dec 2010	The subject started the study medication (12 mg/day).
20 Dec 2010	The subject experienced elevated blood pressure and pain in the shoulder joints to the occipital region. This was treated with antihypertensive drugs and loxoprofen sodium hydrate.
07 Jan 2011	The subject experienced symptoms including blurred vision, out-of-focus vision and lightheadedness.
21 Jan 2011	The subject experienced a feeling of fatigue.
26 Jan 2011 (SAE Start Date)	The subject reported having lost consciousness and falling at the train station on his way to hospital for his Cycle 2, Day 15 visit, though he continued walking to hospital following the fall and experienced no subsequent abnormalities. The subject's sight was still "dim" on arrival and symptoms included fatigue and loss of appetite. The subject was nevertheless hospitalised to undergo detailed examination regarding his loss of consciousness and for his condition to be monitored. ECG performed showed normal results. Treatment was initiated with transfusion of 500 mL/day of "solita-T No.3G" (an electrolyte fluid, with 7.5% sugar added).
27 Jan 2011	The subject had experienced loss of consciousness and loss of appetite with a decreased platelet count and decreased haemoglobin. The study medication was therefore put on hold.
28 Jan 2011	The study medication was resumed at a reduced daily dosage of 8 mg/day.

29 Jan 2011	Blood pressure was stable. It was noted that therapy with cavadesartan cilexetil was reduced to 8 mg/day.
31 Jan 2011	The subject had an MRI of the brain which showed normal results.
01 Feb 2011	"solita-T No.3G" therapy was discontinued.
03 Feb 2011	Furosemide therapy was withdrawn.
04 Feb 2011	The subject's fatigue and "dim" sight were persisting.
09 Feb 2011	On Cycle 3, Day 1 the subject underwent clinical examinations and CT scans.
10 Feb 2011	The subject was discharged from hospital.

Investigator's comment:
Because symptoms including stuffy head persisted after the subject lost consciousness, the reporting physician considered that the subject needed to be observed in the hospital. Hence loss of consciousness was reported as a SAE. Loss of consciousness developed after the study drug was started and did not recur after the dose reduction; therefore a causal relationship cannot be ruled out.

Subject ID:	**20063003**
Age:	62 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	A-V block, arrhythmia, diabetes, esophageal varices, hemorrhoids, hepatitis C, hypertension, pain shoulder
Concomitant medications:	Allopurinol, amlodipine besilate, betamethasone butyrate propionate, betamethasone valerate, bifidobacterium, cavadesartan cilexetil, clobetasol propionate, clobetasone butyrate, dextromethorphan hydrobromide hydrate, diflorasone diacetate, famotidine, furosemide, glimepiride, heparinoid ointment, insulin glargine, levothyroxine sodium, loperamide hydrochloride, losartan potassium, loxoprofen sodium hydrate, metoclopramide, mosapride citrate, neriproct, ofloxacin, spironolactone, ursodeoxycholic acid, voglibose
Reason for narrative:	
Nonfatal SAE(s)	Hypoalbuminaemia, Hepatic encephalopathy
Relationship to study drug:	Possibly related (Hypoalbuminaemia, Hepatic encephalopathy)

AE Description:

On an unspecified date in 2004, the subject was diagnosed with carcinoma hepatocellular.

02 Feb 2011	The subject started the study medication (12 mg/day).
03 Aug 2011	The study medication was interrupted due to a decreased platelet count.
04 Aug 2011	The study medication was restarted at a reduced dose (8 mg/day).
16 Aug 2011 (SAE Start Date)	The albumin level had decreased to 2.6 g/dL. The investigator reported that subsequent changes in the albumin level ranged from 2.7 to 3.0 g/dL.
04 Sep 2011	A CT showed right pleural effusion (nonmalignant).
21 Nov 2011	A CT showed an increase in the right pleural effusion, which was treated with furosemide and spironolactone. Albumin level was 2.6 g/dL. Furthermore human serum albumin and furosemide were administered from 21 Nov 2011 to 21 Dec 2011.
21 Dec 2011	The albumin level was 2.5 g/dL.
05 Jan 2012	A CT showed no change in the pleural effusion and albumin was 2.3 g/dL. Human serum albumin and furosemide were administered.
18 Jan 2012	The albumin level was 2.5 g/dL and therefore human serum albumin and furosemide were once again administered.

23 Jan 2012	The pleural effusion was concluded to be due to hypoalbuminaemia. On the same day, the subject was admitted to hospital for treatment of the event hypoalbuminaemia. Repeated daily administration of human serum albumin (from 23 Jan 2012 to 25 Jan 2012, and from 01 Feb 2012 to 03 Feb 2012) and furosemide (from 23 Jan 2012 to 03 Feb 2012) were initiated. Furthermore the subject was given Kindavate ointment (clobetasone butyrate) due to a skin eruption.
28 Jan 2012	The subject presented with persisted diarrhoea (watery stools) and an accumulation of gas prior to the hospital admission.
29 Jan 2012	Oral Lac-B (bifidobacterium) was started.
30 Jan 2012	Urinary acid was 9.2 mg/dL, which was treated with Zyloric (allopurinol).
02 Feb 2012	Oral Lopemin (loperamide hydrochloride) was started. Although pleural effusion had remained at one fourth of the right lobe, subjective symptoms had improved.
04 Feb 2012	The subject was improving and was discharged from hospital.
18 Feb 2012	The subject experienced trembling of the upper extremities. The study medication, furosemide and spironolactone were discontinued.
19 Feb 2012 (SAE Start Date)	The subject was taken to the emergency room by ambulance due to general weakness and anorexia. Upon investigation flapping tremor and hyperammonemia (161 μg/dL) were noted. Therefore the subject was diagnosed with hepatic encephalopathy, which resulted in hospitalisation. The subject was only allowed fluids, not food. Fluid replacement included soldem 3A (until 27 Feb 2012), riboflavin, ascorbic acid, pyridoxal phosphate hydrate, thiamine chloride hydrochloride and lactated ringer's solution (until 22 Feb 2012).
20 Feb 2012	The subject received solita-T No. 4 for transfusion and mecobalamin intravenously (until 22 Feb 2012).
21 Feb 2012	The subject received lactulose for treating hyperammonemia.
23 Feb 2012	The subject resumed his diet.
27 Feb 2012	A chest X-ray showed a very small amount of pleural effusion and therefore the study medication was restarted at a reduced dose of 4 mg/day.
28 Feb 2012	No tremor was noted and the subject was "clearly conscious".
29 Feb 2012	The subject recovered from the event hepatic encephalopathy and was discharged from hospital.

Investigator's comment:

The subject was urgently hospitalised for treating hepatic encephalopathy. Clinical findings and laboratory test data (AST, ALT) showed no aggravation of the underlying disease (liver failure). Prior to the onset of hepatic encephalopathy, pleural effusion occurred due to hypoalbuminaemia (causality to the study drug was not excluded). The subject received human serum albumin and diuretic agent as treatment for pleural effusion, which might have been responsible for hepatic encephalopathy. Hepatic encephalopathy occurred during the study drug treatment period; therefore a direct relationship to the study medication could not be excluded.

The subject experienced hypoalbuminaemia-related effusion, which resulted in hospitalisation for treatment. Whilst neither marked aggravation of the underlying disease on CT nor changes in the laboratory data (AST, ALT) was observed. Only the albumin level had decreased, therefore it was suggested that an aggravation of the underlying disease was not the sole cause of hypoalbuminaemia. Further side effects, including anorexia and proteinuria were likely to be responsible for hypoalbuminaemia. However direct relationship to the study medication could not be excluded.

Subject ID:	**20063004**
Age:	71 years
Sex:	Female
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	Duodenal ulcer, gastritis, hepatitis C, hypertension, insomnia, osteoporosis, peripheral circulatory disturbance
Concomitant medications:	Human serum albmin, alfacalcidol, amlodipine besilate, calcium L-aspartate hydrate, betamethasone valerate, bisacodyl, bofutsushosan, brotizolam, diflorasone diacetate, famotidine, furosemide, isosorbide dinitrate, ketoprofen, olmesartan medoxomil, omeprazole sodium, rebamipide, tocopherol acetate, ursodeoxycholic acid
Reason for narrative:	
Nonfatal SAE(s)	Renal impairment, Cholecystitis acute
Relationship to study drug:	Probably related (Renal impairment), Possibly related (Cholecystitis acute)

AE Description:

Apr 2011	The subject was diagnosed with hepatocellular carcinoma.
22 Jun 2011	The subject started the study medication (12 mg/day).
06 Jul 2011 (SAE Start Date)	The subject's creatinine level was at 1.2 mg/dL.
14 Jul 2011	The study medication was interrupted due to a decreased platelet count and increased creatinine value.
20 Jul 2011	The dosage of the study medication was restarted at a reduced dose (8 mg/day).
03 Aug 2011	An increased creatinine value of 2.2 mg/dL was observed.
04 Aug 2011	She was hospitalized and the administration of the study drug was interrupted due to an increased creatinine value.
04 Aug 2011	The subject received solita-T No. 1 (until 17 Aug 2011).
05 Aug 2011	The subject received human serum albumin (until 10 Aug 2011).
15 Aug 2011	Creatinine was 1.1 mg/dL. A computed tomogram was performed.
16 Aug 2011	Study medication was reintroduced at 8 mg/day.
17 Aug 2011	The subject's blood pressure increased.
18 Aug 2011	Amlodipine besilate was interrupted on 18 Aug 2011 and restarted on 22 Sep Aug 2011.
22 Aug 2011	Creatinine was 1.5 mg/dL. Study medication was interrupted on 23 Aug 2011.
23 Aug 2011	Amlodipine besilate was increased to 7.5 mg.

24 Aug 2011	Creatinine increased, which became an SAE; however, after study medication was decreased to 4 mg/day, creatinine was stable without problems. Study medication restarted at 4 mg/ day.
25 Aug 2011	Creatinine was 1.4 mg/dL.
26 Aug 2011	She was considered to have improved and was discharged from hospital.
12 Sep 2011 (SAE Start Date)	–
13 Sep 2011	She complained of pain in the lower right abdomen and was urgently examined on 12 Sep 2011. Acute cholecystitis was diagnosed based on results of examinations such as ultrasonography. She was expected to be treated while being hospitalized, and the reported event was determined to be an SAE. She had experienced queasiness and vomiting since 12 Sep 2011 and the symptoms had persisted. These symptoms were judged to have been caused by the acute cholecystitis. CRP was 4.2 mg/dL. She was hospitalized immediately. The administration of the study medication was interrupted (the subject having received her last dose on 24 Nov 2011). A drip infusion of solita-T No. 1 and cefotiam hydrochloride was initiated.
14 Sep 2011	The subject had no abdominal pains.
16 Sep 2011	The solita-T No. 1 was stopped and meals resumed the following day.
18 Sep 2011	The subject's blood pressure decreased and amlodipine besilate was discontinued.
20 Sep 2011	Cefotiam hydrochloride was withdrawn and the study medication was resumed on 21 Sep 2011 at the previous dose of 4 mg/day.
22 Sep 2011	The subject's blood pressure was found to have increased and amlodipine besilate was resumed.
23 Sep 2011	The subject was discharged from hospital, being considered to have recovered from her acute cholecystitis.

Investigator's comment:

Increase in creatinine and renal impairment occurred after oral administration of the study drug was started. Although these events remitted once while the subject was undergoing cessation of the study drug, increase in creatinine reoccurred after the study drug was resumed at the reduced dose. This event was reported as a SAE because creatinine increased to 2.2 mg/dL on 03 Aug 2011 and that required hospital admission for work-up and treatment. In addition, a nephrologist also evaluated this event as possible renal impairment induced by drug. The causal relationship between the event and the study drug cannot be ruled out based on the information received so far.

The subject was urgently hospitalized to receive treatment for acute cholecystitis; thus, the acute cholecystitis was reported as a SAE. The causal relationship between the study drug and the event cannot be ruled out as the event occurred while the study drug was being administered.

Subject ID:	**20073007**
Age:	62 years
Sex:	Female
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	Abdominal pain
Concomitant medications:	Amlodipine besilate, lac-B, calcium lactate, unisia, candesartan cilexetil, carbocysteine, dextromethorphan hydrobromide hydrate, diclofenac sodium, diclofenac, scopolamine butylbromide, Juzentaihoto (chinese herbal medicine), loxoprofen sodium, magnesium oxide, omeprazole, pentazocine hydrochloride, prochlorperazine, rebamipide, sennoside, trichlormethiazide
Reason for narrative:	
Nonfatal SAE(s)	Jaundice cholestatic, Cancer pain
Relationship to study drug:	Not related (Jaundice cholestatic, Cancer pain)

AE Description:

On an unknown date, the subject was diagnosed with carcinoma hepatocellular.

25 Dec 2010	Study medication was started at 12 mg/day.
09 Jan 2011	Study medication was interrupted (until 14 Jan 2011).
15 Jan 2011	Study medication daily dose was reduced to 8 mg/day.
19 Mar 2011	Study medication was interrupted (until 01 Apr 2011).
02 April 2011	Study medication was further reduced to 4 mg/day.
11 Jun 2011 (SAE Start Date)	The subject was hospitalized with obstructive jaundice, and an endoscopic nasobillary drainage was performed until 22 Jun 2011 and her symptoms temporarily subsided.
18 Jun 2011	The subject underwent stent treatment. The stent treatment showed a positive result. It was reported that “inflammation” was also improving.
20 Jun 2011 (SAE Start Date)	The subject experienced cancer pain.
22 Jun 2011	The subject was discharged from the hospital.
23 Jun 2011	The subject took the study medication and she showed a temporal improvement in her symptoms. The last dose of study medication was received on 23 Jun 2011, as the subject experienced vomiting caused by an opioid that was used to treat cancer pain on 24 Jun 2011, and therefore she was unable to continue to receive the study medication.
05 Jul 2011	Her condition was “not well”, and there was no improvement in obstructive jaundice. The subject was then removed from the study.

Investigator's comment:
The aggravation of lymph node metastasis led to biliary tract obstruction and triggered obstructive jaundice; therefore, the causal relationship between obstructive jaundice and the drug can be ruled out.

The events cancer pain is considered related to the underlying disease and not related to the study medication.

Subject ID:	**20083005**
Age:	66 years
Sex:	Female
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	Constipation, gastritis, hypertension, knee joint pain
Concomitant medications:	Amlodipine besilate, diphenhydramine, epinastine, Biofermin, loperamide, loxoprofen, olmesartan medoxomil, pancreatin, rabeprazole, Sahne cream, senna
Reason for narrative:	
Nonfatal SAE(s)	Cholecystitis
Relationship to study drug:	Possibly related

AE Description:

Aug 2006	The subject was diagnosed with carcinoma hepatocellular.
31 May 2011	Informed consent was obtained.
16 Jun 2011	The subject started the study medication (12 mg/day).
06 Jul 2011	Due to a decrease in platelets (nonserious), the dose of the study medication was reduced to 8 mg/day.
20 May 2012 (SAE Start Date)	The subject's condition was poor and she experienced nausea (nonserious).
21 May 2012	The subject experienced nonserious gastralgia and right flank pain. The subject repeatedly vomited after each meal.
23 May 2012	The subject underwent a CT and blood tests. She was diagnosed with cholecystitis and was urgently hospitalised. Bfluid, Physio, Vitamedin, Wystal, and omeprazole were administered.
28 May 2012	An abdominal ultrasonography was performed. Blood tests were performed and medication was switched from Wystal (sulbactam sodium) to Meropenem (meropenem trihydrate).
30 May 2012	An upper gastrointestinal endoscopy, blood tests and electrocardiogram were performed.
31 May 2012	A CT was performed. The event of cholecystitis was reported as "ongoing".
01 Jun 2012	All intravenous drip medications were discontinued and administration with Urso (ursodesoxycholic acid) was started.
04 Jun 2012	Blood tests were performed.
05 Jun 2012	Study medication was resumed at the same dose as before (8 mg/day).
09 Jun 2012	The subject was discharged from hospital.
11 Jul 2012	Event of cholecystitis was reported as "resolved".

Investigator's comment:
Although cholecystitis may be due to suspected biliary sludge, the causal relationship between the event and the study drug cannot be excluded since the drug has been taken for nearly a year.

Subject ID:	**20103003**
Age:	75 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	Cataract, hyperglycemia, insomnia, viral hepatitis
Concomitant medications:	Amlodipine besilate, amoxicillin hydrate (AMPC), betamethasone butyrate propionate, betamethasone valerate, brotizolam, buprenorphine hydrochloride, cefazolin sodium, cefdinir, diazepam, dicrofenac sodium, diphenhydramine, epinastin hydrochloride, heparin sodium, iomeprol, isosorbide dinitrate, levothyroxine sodium hydrate, lidocaine hydrochloride, locobase repair milk, loxoprofen sodium hydrate, lysozyme hydrochloride, magnesium oxide, mepivacaine hydrochloride, metoclopramide, acetaminophen, pirenoxine, salicylic acid, isotonic sodium chloride solution, Solita-T No.1, Solita-T No.3, teprenone, ursodeoxycholic acid
Reason for narrative:	
Nonfatal SAE(s)	Acute coronary syndrome, Cardiac tamponade
Relationship to study drug:	Probably related (Acute coronary syndrome), Not related (Cardiac tamponade)

AE Description:

Sep 2006	The subject was diagnosed with advanced carcinoma hepatocellular.
06 Jan 2011	The subject consented to participate in the study, and a screening test was initiated: 12-lead electrocardiogram (ECG) normal (HR: 58/min, QT: 375 ms); first blood pressure 143/62 mmHg; second blood pressure 141/68 mmHg.
18 Jan 2011	Study medication was started (12 mg/day).
26 Jan 2011	Amlodipine besilate was started due to occurrence of blood pressure increased (Grade 2). After treatment of amlodipine, his blood pressure was stabilized and no abnormal finding was observed in electrocardiogram. He discontinued amlodipine treatment on 15 Jun 2011.
16 Mar 2011	The study medication was interrupted for six days due to Grade 2 anorexia and tiredness. The study medication resumed on 22 Mar 2011 at a reduced dose of 8 mg/day.
11 May 2011	The subject developed hand-foot skin reaction (Grade 2) and the study drug was again interrupted for six days.
17 May 2011	The subject restarted study medication (8 mg/day).

24 May 2011 (SAE Start Date)	A 12-lead ECG revealed the subject had a complete left bundle branch block (HR: 52/min, QT 438 ms). The subject was sent to the cardiovascular department, neither the ultrasonic cardiogram nor a chest X-ray showed specific abnormalities with his cardiac function, the subject did not display any subjective symptoms.
30 May 2011	The subject started to wear a Holter ECG monitor, the next day (31 Mar 2011) the results were analyzed and a diagnosis of complete left bundle branch block was confirmed. 12-lead ECG (HR: 58/min, QT: 417 ms).
01 Jun 2011	A coronary CT angiography was performed, which revealed findings of 50% or more stenosis in the root 6 of the left anterior descending coronary, which was considered to be due to plaque. No apparent narrowing was observed in the right coronary artery or the left circumflex coronary artery.
07 Jun 2011	12-lead ECG (HR: 54/min, QT: 383 ms). The left bundle branch block disappeared and narrow QRS appeared. V1-4 shown negative T-wave and he was suspected to have ischemic cardiac disease. No elevated cardiac enzymes were detected.
08 Jun 2011	A 12-lead electrocardiogram revealed a complete left bundle branch block (heart rate: 60/min and QT 425 ms). He discontinued study medication.
13 Jun 2011	A coronary angiography (CAG) was carried out, which showed significant stenotic lesions in the proximal LAD (75% stenosis), proximal LCx (75% stenosis), and proximal HL (90% stenosis). These finding were suggestive of unstable plaque at the legion around HL.
14 Jun 2011	Treatment was required for his coronary stenosis, so he was withdrawn from the clinical study due to safety reasons. An antiplatelet agent and revascularisation was required for severe stenosis of legion around left main coronary.
15 Jun 2011	Acetylsalicylic acid was started for prophylaxis of thrombosis. His blood pressure was stabilized.
23 Jun 2011	Clopidogrel and pitavastatin were started to stabilize plaque.
27 Jun 2011	Percutaneous coronary revascularisation was performed at lesions around LAD, HL and LCx. At 18:30 he received intravenous administration of heparin and solita-T No. 3.

28 Jun 2011 (SAE Start Date)	The subject experienced a decrease in urinary output and blood pressure. Fluid infusion was administered and he was observed. After 11:00 am he experienced chest pain and a 12-lead electrocardiogram revealed ST elevation. Nitroglycerin was administered. A cardiac echo revealed a 10 to 15 mm sized pericardial fluid accumulation. He was diagnosed with cardiac tamponade and pericardial drainage was performed. Whilst he was being treated, SpO_2 was decreased to 93% and oxygen therapy was started. The continuous heparin drip was discontinued. His general condition was managed. 25 mL of bloody fluid was withdrawn from the drain. Pericarditis was considered to have occurred due to cardiac tamponade. An intravenous drip of cefazolin was administered due to the continuous drainage that had been performed.
29 Jun 2011	The subject had a CT of the head due to the vomiting which had started the day before. No intracranial findings were suggestive to a marked hemorrhage and hematoma. A coronary angiography was performed to identify origin of hemorrhage. A slight amount of bloody serous fluid from the pericardial drain was found. Vital signs were stabilized and no chest symptoms were noted. Loxoprofen was administered for pericarditis.
30 Jun 2011	The pericardial drain was removed.
01 Jul 2011	An electrocardiogram showed an improvement in ST. Oxygen therapy was consequently discontinued.
05 Jul 2011	A chest X-ray performed showed oedema at lower limb and small amount of pleural effusion associated with no cardiac tamponade and furosemide and spironolactone was administered.
06 Jul 2011	A cardiac echo detected only a small amount of pericardial fluid and no pendulate motion was noted. No abnormal wall motion was noted. The monitoring of the electrocardiogram was turned off. Pericarditis was improved and Loxoprofen was discontinued.
09 Jul 2011	The oedema of the lower limbs improved.
11 Jul 2011	An electrocardiogram showed further improvement in ST elevation. A chest X-ray revealed remission of pleural effusion and cardiac enlargement. He had no chest pains and his body condition was stabilized.
13 Jul 2011	Diuretic agents; furosemide and spironolactone, and pitavastatin were discontinued.
14 Jul 2011	He was transferred to the department of gastroenterological medicine for the treatment of hepatocellular carcinoma. A complication occurred after PCI resolved and cardiac function was stabilized. The subject was able to discharge and considered to be recovered.

Investigator's comment:

When the confirmed diagnosis of acute coronary syndromes (ACS) was made therefore name of event was revised from complete left bundle branch block to acute coronary syndromes (ACS). Although cause or period of plaque formation was undefined, it was assumed existing plaque was destabilized because of administration of study drug that triggered transient complete left bundle branch block caused by ischemia. Causal relationship to the study drug was strongly suspected because left bundle branch block resolved after discontinuation of the study drug. It was unlikely that the study drug directly affected to the impulse conducting system and caused problem (complete left bundle branch block). PCI was performed for treating event. Although post PCI complication of cardiac tamponade occurred, the outcome of the event was favorable. Although at least one year of antiplatelet therapy with acetylsalicylic acid and clopidogrel was required for preventing late thrombosis, the subject's cardiac function improved (this diagnosis was made by a cardiologist) and therefore the follow-up investigation of this study ended with this report.

Cardiac tamponade is considered not related to the study medication based on current information reported. It may have been a complication of some unspecified intervention used to treat coronary artery disease.

Subject ID:	**20103004**
Age:	75 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	Cataract, chronic gastritis, diabetes, esophageal varices, hypertension, insomnia, prostatic hypertrophy, reflux esophagitis, spondylosis deformans, viral hepatitis
Concomitant medications:	Amlodipine besilate, bisacodyl, brotizolam, chlorpromazine hydrochloride, glimepiride, ketoprofen, lansoprazole, miglitol, SM combination powder, urea
Reason for narrative:	
Nonfatal SAE(s)	Hepatic encephalopathy
Relationship to study drug:	Possibly related

AE Description:

Nov 2005	The subject was diagnosed with hepatocellular carcinoma.
03 Feb 2011	The subject consented to participate in the study.
17 Feb 2011	The subject started the study medication (12 mg/day).
10 Mar 2011	The subject was discharged from hospital.
11 Mar 2011 (SAE Start Date)	The subject started vomiting from the evening.
12 Mar 2011	The subject started to experience a mild tremor in his hand was and was dropping objects.
13 Mar 2011	The subject had been constipated since discharge and had produced only a “banana-sized” hard stool.
14 Mar 2011	The subject was reported to be lusterless. Upon reporting of the earlier symptoms to his physician by a family member, the subject was advised to attend his hospital immediately. Upon presentation, the subject was found to have decreased awareness of his surroundings, apathy, an unsteady gait, a “flapping” tremor and an increased ammonia level of 130 μg/dL. The subject was diagnosed with hepatic encephalopathy (Grade 3) and admitted. It was thought possible that the subject’s constipation led to the hepatic encephalopathy, but a causal relationship with the study medication could not be ruled out. The study medication was interrupted and the subject was treated with an injection of “Aminoleban” (an amino acid for the treatment of hepatic encephalopathy) and 60 mL/day of oral lactulose. The subject started to experience vomiting in the evening.

15 Mar 2011	The subject had difficulty in waking up and was lethargic over the course of the day. The subject opened his eyes when addressed and was able to comply with easy instructions, but fell asleep easily. The subject's ammonia level increased to 141 μg/dL and he was observed continuously. The subject received two enemas and produced stools in response to each.
16 Mar 2011	The subject was lethargic without stimulation, but opened his eyes and spoke when in company. The flapping tremor persisted, and he produced another stool with a further enema. The subject's ammonia level decreased to 94 μg/dL, and his symptoms were improving. The subject had a CT angiogram of the head and no indication of cerebral metastasis or cerebral haemorrhage was observed.
17 Mar 2011	The subject's consciousness level was clear, although his movement and speech were slow. The earlier flapping tremor was not observed and Aminoleban and lactulose therapies were maintained.
22 Mar 2011	The level of ammonia was 32 μg/dL. This suggested hyperammonemia improved. The subject had no flapping tremor.
25 Mar 2011	The subject had no problem with his course. With discontinuation of intravenous drip of amino-acid formulation, the event was recovered. Cessation of the drug was continued because of follow-up of the subject. The study drug was scheduled to be restarted on the next Monday 28 Mar 2011.
28 Mar 2011	The subject claimed his withdrawal of this study; and the process of ending this study was proceeded.

Investigator's comment:

After the discharge, his dietary intake decreased and hepatic encephalopathy developed with his poor defecation. The symptom improved immediately owing to the defecation control after admitting to the hospital. Although relationship with the study drug could not be ruled out, it was probably due to his living conditions.

Subject ID:	**20113001**
Age:	77 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	Cataract, constipation, diabetes, glaucoma, hepatitis C virus, hyperlipidemia, hypertension, neuropathy of left arm and leg, retinopathy
Concomitant medications:	Amlodipine besilate, cyanocobalamin, furosemide, insulin human (genetical recombination), magnesium oxide, nifedipine, nipradilol, pirenoxine, pravastatin sodium, sennoside
Reason for narrative:	
Nonfatal SAE(s)	Renal impairment
Relationship to study drug:	Probably related

AE Description:

Dec 2002	The subject was diagnosed with carcinoma hepatocellular.
21 Jul 2010	Informed consent was obtained from the subject, who was given a diagnosis of progressive hepatoarcinoma.
02 Aug 2010	The subject started study medication (Cycle 1) after hospital admission.
06 Aug 2010	The subject experienced an increase in blood pressure whish was assumed to be influenced by the study drug. An oral hypotensor was administered.
11 Aug 2010 (SAE Start Date)	The subject developed symptoms of eyelid oedema and erythema. The subject was diagnosed with a renal disorder.
12 Aug 2010	The subject's eyelid oedema was slightly reduced. The subject was allowed to continue as an outpatient.
16 Aug 2010	The subject experienced weight gain and edema of the face and limbs. An abdominal echo was performed which detected ascites around the liver and abdominal cavity. The subject was treated with intravenous potassium canrenoate and furosemide.
17 Aug 2010	The subject fell beside his bed which resulted in mobility of the lower limb being impaired. He complained of abnormalities in his lower extremities. A CT scan and an MRI scan were performed and revealed no findings such as cerebral infarction, intercranial density or any marked abnormal findings in the major cerebral artery. Although the cause of the event was unknown; it was determined that he required prolonged hospitalisation since he was suspected of having hepatic edema.