Subject Number	47031012
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-005813
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Dyspepsia, Abdominal pain upper (7x)
AE(s) Leading to Discontinuation	Abdominal pain upper

A 49-year-old Chinese male was diagnosed with hepatocellular carcinoma on 28 Jan 2010. Significant medical history included cholelithiasis, gastrointestinal hemorrhage, hepatitis B, and hepatic cirrhosis. Previous anticancer therapies included high intensity focused ultrasound and transcatheter arterial chemoembolization. Prior and concomitant medications included ammonium bicarbonate w/cephaelis sp, bisacodyl, calcium polystyrene sulfonate, chlorphenamine, ciprofloxacin, diosmectite, entecavir, enzymes w/vitamins, famotidine, filgrastim, furosemide, hyoscine, lactulose, levothyroxine, loperamide, megestrol, metoclopramide, pantoprazole, paracetamol, phytomenadione, prednisolone, pyridoxine, ranitidine, sodium chloride, spironolactone, tramadol, and valsartan. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at diaphragm; lung mass, and inferior vena cava clot. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 31 Dec 2014 (Day 1), treatment with study drug was initiated.

On 08 Apr 2015 (Day 99), the subject was hospitalized for dyspepsia (Grade 2). The subject was treated with pantoprazole. On 09 Apr 2015 (Day 100), the subject recovered from dyspepsia and was discharged from the hospital. The study drug dose did not change. The Investigator considered dyspepsia serious and not related to the study drug.

On 23 Dec 2015 (Day 358), the subject was hospitalized for upper abdominal pain (Grade 3) associated with vomiting, diarrhea, and abdominal tenderness. Abdominal x-ray ruled out dilated bowel; renal function tests and laboratory tests were normal. The subject was treated with hyoscine, loperamide, and metoclopramide. The study drug dose did not change. On 24 Dec 2015 (Day 359), the subject recovered from upper abdominal pain and was discharged from the hospital. The Investigator considered upper abdominal pain serious and not related to the study drug.

On 01 Jan 2016 (Day 367), the subject was again hospitalized for upper abdominal pain (Grade 3) associated with vomiting. Abdominal x-ray ruled out dilated bowel. The subject was treated with metoclopramide and hyoscine. The study drug dose did not change. On 02 Jan 2016 (Day 368), the subject recovered from this event and was discharged from the hospital. The Investigator considered upper abdominal pain serious and not related to the study drug.

On 10 Jan 2016 (Day 376), the subject was again hospitalized for upper abdominal pain (Grade 3) associated with vomiting and diarrhea. Chest x-ray showed clear lungs and abdominal

x-ray ruled out dilated bowel. The subject was treated with paracetamol. The study drug dose did not change. On 11 Jan 2016 (Day 377), the subject recovered from the event and was discharged from the hospital. The Investigator considered this event serious and not related to the study drug.

On 07 Mar 2016 (Day 433), the subject was hospitalized for upper abdominal pain (Grade 3) with intermittent periumbilical pain with vomiting (Grade 1) and diarrhea (Grade 1). Abdominal x-ray ruled out dilated bowel. Treatment was not provided. The study drug dose did not change. On the same day (Day 433), the subject recovered from vomiting and diarrhea and on 09 Mar 2016 (Day 435), the subject recovered from upper abdominal pain. The Investigator considered upper abdominal pain serious and not related to the study drug; vomiting and diarrhea nonserious and not related to the study drug.

On 01 Apr 2016 (Day 458), the subject was hospitalized for upper abdominal pain (Grade 2) with upper abdominal pain radiating upwards to the chest, diarrhea (Grade 1), and vomiting (Grade 1) of coffee ground/fresh blood. The subject was afebrile and had BP of 140/75 mmHg. An abdominal x-ray showed prominent bowel loops and chest x-ray was normal. The subject was treated with metoclopramide. On 01 Apr 2016 (Day 458), the subject recovered from vomiting and diarrhea. On 06 Apr 2016 (Day 463), the subject recovered from upper abdominal pain and was discharged from the hospital. The study drug dose did not change. The Investigator considered upper abdominal pain serious and not related to the study drug; vomiting and diarrhea nonserious and not related to the study drug.

On 23 Apr 2016 (Day 480), the subject was again hospitalized for upper abdominal pain (Grade 2). Abdominal x-ray showed prominent gastric bubble, no dilated bowel, and no free gas. Chest x-ray showed clear lungs and no gas under diaphragm. Ultrasound of abdomen showed ascites. Treatment was not provided. The study drug dose did not change. On 25 Apr 2016 (Day 482), the subject recovered from upper abdominal pain and was discharged from the hospital. The Investigator considered upper abdominal pain serious and not related to the study drug.

On 02 May 2016 (Day 489), the subject was again hospitalized for upper abdominal pain (Grade 2). Abdominal x-ray showed prominent loops at central abdomen with air-fluid levels; chest x-ray showed clear lungs; ultrasound of abdomen showed ascites. The subject was treated with tramadol. The outcome of the event was unknown. On 05 Jul 2016 (Day 553), the subject was withdrawn from the study due to upper abdominal pain and received the last dose of the study drug on the same day (Day 553). The Investigator considered upper abdominal pain serious and not related to the study drug.

Subject Number	48011002
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01423-CLI-MY
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Dehydration, Gastric ulcer, Seborrhoeic dermatitis, Intertrigo

A 78-year-old Chinese male was diagnosed with hepatocellular carcinoma on 21 Nov 2013. Significant medical history included gouty arthritis, hepatitis B, and hypertension. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included amlodipine, celecoxib, cetirizine, chloramphenicol, cloxacillin, colchicine, diclofenac, fobancort, furosemide, meloxicam, miconazole, other emollients and protectives (aqueous cream), pantoprazole, potassium permanganate, sodium chloride, spironolactone, telmisartan, and tramadol. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left lobes of the liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

On 19 Dec 2013 (Day 1), treatment with study drug was initiated.

On 28 Dec 2013 (Day 10), the subject was hospitalized for dehydration (Grade 3) and gastric ulcer (Grade 2). On 29 Dec 2013 (Day 11), the subject experienced peripheral edema of the leg (Grade 1). Gastroscopy confirmed pre-pyloric ulcer and laboratory tests showed sodium 114 mmol/L (NR: 136 – 145), potassium 4.9 mmol/L (NR: 3.6 – 5.2), total bilirubin 61 umol/L (NR: 3 – 17), creatinine 149 umol/L (NR: 80 – 132), albumin 24 g/L (NR: 35 – 50), absolute neutrophils count 12.35 x10^9/L (NR: 2 – 7), Hgb 110 g/L (NR: 130 – 170), and WBC 15.3 x10^9/L (NR: 4 – 10). On 01 Jan2014 (Day 14), the study drug was interrupted due to dehydration, gastric ulcer, and peripheral edema of the leg. The subject was treated with pantoprazole and sodium chloride. On 06 Jan 2014 (Day 19), the subject experienced non-malignant ascites (Grade 1), and severity of peripheral edema of the leg worsened to Grade 2. On 27 Jan 2014 (Day 40), severity of peripheral edema of the leg improved to Grade 1. On the same day (Day 40), the subject recovered from dehydration and gastric ulcer. On 07 Feb 2014 (Day 51), the study drug was resumed at a reduced dose of 4 mg/day due to peripheral edema of the leg, dehydration, gastric ulcer, and ascites. The subject was recovering from peripheral edema of leg. The subject did not recover from ascites. The Investigator considered dehydration serious and probably related to the study drug; gastric ulcer serious and possibly related to the study drug; peripheral edema of the leg nonserious and possibly related to the study drug; ascites nonserious and probably related to the study drug.

On 10 Apr 2014 (Day 113), tumor response assessment showed disease progression. On 08 May 2014 (Day 141), subject was withdrawn from the study due to disease progression and received the last dose of the study drug on 07 May 2014 (Day 140).

On 16 May 2014 (Day 149), the subject was hospitalized for intertrigo (Grade 3) and seborrheic dermatitis (Grade 3) described as erythematous patches over arms and legs with weeping,

crusting, and pustules; diagnosis was confirmed by an excision skin biopsy. The subject was found with extensive rash covering 50% of the body surface area and cracked skin with erythema at the angle of the mouth. The subject's eyes and genitalia were spared. The subject was treated with cloxacillin, cetirizine, chloramphenicol, fobancort, miconazole, meloxicam, other emollients and protectives (aqueous cream), and potassium permanganate. The subject was recovering from these events. The Investigator considered seborrheic dermatitis and intertrigo serious and probably related to the study drug.

On 08 Jul 2014 (Day 202, 62 days after the last dose), the subject died due to disease progression. Autopsy was not performed.

Subject Number	48011004
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-006170
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Diarrhea, Hyperkalaemia

A 64-year-old Asian male was diagnosed with hepatocellular carcinoma on 10 Aug 2014. Significant medical history included diabetes mellitus, hypercholesterolemia, hypertension, and hepatic cirrhosis. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included enalapril, furosemide, human insulin, human mixtard, intravenous solutions – lytic cocktail (calcium gluconate, dextrose 50%, insulin), loperamide, metformin, propranolol, and simvastatin. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right lobe of liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

On 18 Sep 2014 (Day 1), treatment with study drug was initiated.

On 04 Apr 2015 (Day 199), the subject experienced diarrhea (Grade 3) with watery stool, which was persistent since 05 Mar 2015 (Day 169) as Grade 1. The subject was treated with loperamide. On 08 Apr 2015 (Day 203), the subject was hospitalized for diarrhea. On 12 Apr 2015 (Day 207), the study drug was interrupted due to diarrhea. On 14 Apr 2015 (Day 209), the subject recovered from diarrhea. On 15 Apr 2015 (Day 210), the study drug was resumed at same dose of 12 mg/day. On 16 Apr 2015 (Day 211), laboratory tests were performed and showed potassium 6.3 mmol/L (NR: not provided), sodium 132 mmol/L (NR: not provided), and creatinine 130 umol/L (NR: not provided). On 16 Apr 2015 (Day 211), the subject was diagnosed with hyperkalemia (Grade 3) and was treated with intravenous solutions – lytic cocktail (calcium gluconate, dextrose 50%, insulin). On 17 Apr 2015 (Day 212), the study drug was interrupted due to hyperkalemia. On the same day (Day 212), repeat potassium showed 4.5 mmol/L (NR: not provided) and the subject recovered from hyperkalemia. On 20 Apr 2015 (Day 215), the films for tumor assessments were re-evaluated; the tumor response was initially assessed as partial response on 04 Mar 2015 (Day 168). After the re-evaluation, the subject was confirmed to have disease progression and was withdrawn from the study on the 20 Apr 2015 (Day 215). The subject received the last dose of the study drug on 16 Apr 2015 (Day 211). On 24 Apr 2015 (Day 219), the subject was discharged from the hospital. The Investigator considered diarrhea serious and probably related to study drug; hyperkalemia serious and possibly related to study drug.

On 19 Jul 2015 (Day 305, 94 days after the last dose), the subject died due to disease progression.

Subject Number	48041001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01394-CLI-MY
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Scrotal infection

A 66-year-old Chinese male was diagnosed with hepatocellular carcinoma on 13 Jun 2012. Significant medical history included diabetes mellitus type 2, hypertension, duodenal ulcer, hepatic cirrhosis, and esophageal varices. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included bromhexine, ceftriaxone, chlorphenamine, cloxacillin, felodipine, furosemide, fusidic acid, human insulin, human mixtard, hydrocortisone, insulin, lactulose, lovastatin, other emollients and protective (aqueous cream), pantoprazole, neurobion, papain, propranolol, spironolactone, tramadol, and vitamins. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left lobe of the liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

On 08 Oct 2013 (Day 1), treatment with study drug was initiated.

On 18 Oct 2013 (Day 11), subject experienced hypertension (Grade 3) with BP of 166/86 mmHg and was treated with felodipine. On 22 Oct 2013 (Day 15), subject experienced proteinuria (Grade 2) with urine protein dipstick 3+ and 24h urine protein 2.3792 g/24hr. On 28 Oct 2013 (Day 21), subject was hospitalized for scrotal infection (Grade 3) with oozy erythematous scrotal swelling. The subject also experienced ascites (Grade 2), increased weight (Grade 2) with body weight of 90 kg (Baseline: 81 kg), and pedal edema (Grade 1). Laboratory tests showed albumin 31 g/L (NR: 35 – 55) and blood culture and sensitivity did not show any specific growth of organism. On 28 Oct 2013 (Day 21), the study drug was interrupted due to scrotal infection, proteinuria, ascites, pedal edema, and increased weight. The subject was treated with furosemide, spironolactone, cloxacillin, tramadol, papain, hydrocortisone, and ceftriaxone. On 06 Nov 2013 (Day 30), hypertension improved to Grade 1. On 20 Nov 2013 (Day 44), the subject recovered from scrotal infection, ascites, increased weight, and pedal edema and did not recover from hypertension and proteinuria. On the same day (Day 44), the study drug was resumed at a reduced dose of 8 mg/day due to proteinuria. The Investigator considered scrotal infection serious and possibly related to study drug; hypertension, proteinuria, ascites, increased weight, and pedal edema nonserious and probably related to study drug.

On 28 Jan 2014 (Day 113), tumor response assessment showed disease progression.

On 04 Feb 2014 (Day 120), the subject experienced worsened proteinuria (Grade 3) with 24h urine protein 3.938 g/24hr. On 08 Feb 2014 (Day 124), the study drug was interrupted. On 13 Feb 2014 (Day 129), the severity of proteinuria improved to Grade 2 with 24h urine protein 1.836 g/24hr. The subject was recovering from proteinuria. The Investigator considered this event nonserious and probably related to study drug.

On 14 Feb 2014 (Day 130), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on 07 Feb 2014 (Day 123).

On 20 Dec 2014 (Day 439, 316 days after the last dose), the subject died due to unknown cause.

Subject Number	48051003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-002610
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Intracranial tumour haemorrhage

A 52-year-old Asian female was diagnosed with hepatocellular carcinoma on 08 May 2013. Significant medical history included bronchial asthma, diabetes mellitus, gastritis, hepatic steatosis, hepatitis B, hyperlipidemia, hypertension, menopause, secondary polycythemia, and hysterectomy (total abdominal hysterectomy). Previous anticancer therapies included hepatectomy (2x) and transcatheter arterial chemoembolization. Prior and concomitant medications included actifed, ascorbic acid, celecoxib, activated charcoal, cinnarizine, dexamethasone, esomeprazole, human insulin, hyoscine, insulin, lovastatin, magnesium trisilicate, meloxicam, metformin, metoclopramide, neurobion, omeprazole, paracetamol, phenytoin, ranitidine, salbutamol, sodium chloride, telmisartan, tenofovir, tramadol, and triamcinolone. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right lobe of liver (segment 6), mass at left lingular lobe of lung, and right portal vein thrombus. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 03 Mar 2014 (Day 1), treatment with study drug was initiated.

On 16 Oct 2014 (Day 228), tumor response assessment showed disease progression.

On 09 Dec 2014 (Day 282), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on the same day (Day 282).

On 14 Dec 2014 (Day 287), the subject was hospitalized for intracranial tumor hemorrhage (Grade 2), and presented with episodes of seizures. Treatment included dexamethasone and phenytoin. On 17 Dec 2014 (Day 290), CT scan of brain showed hyperdense left frontal lobe lesion suggestive of brain metastases. On 18 Dec 2014 (Day 291), the subject recovered from intracranial tumor hemorrhage and was discharged from the hospital. The Investigator considered intracranial tumor hemorrhage serious and not related to study drug but related to disease progression.

On 28 Jan 2015 (Day 332, 50 days after the last dose), the subject died due to disease progression.

Subject Number	48051005
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-005426
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Duodenal ulcer haemorrhage, Duodenal ulcer

A 51-year-old Asian male was diagnosed with hepatocellular carcinoma on 02 Nov 2012. Significant medical history included chronic hepatitis B, esophageal varices, gastritis, and hepatic cirrhosis. Previous anticancer therapy included hepatectomy, transcatheter arterial chemoembolization, and ultrasound guided percutaneous ethanol injection. Prior and concomitant medications included amoxicillin, clarithromycin, esomeprazole, folic acid, iron, metoclopramide, pantoprazole, propranolol, and tenofovir. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left lobe of liver, multiple lesions across liver, mass at left upper lung lobe, right lower lung lobe mass, and multiple lung masses. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 04 Jul 2014 (Day 1), treatment with study drug was initiated.

On 12 Mar 2015 (Day 252), the subject experienced duodenal ulcer hemorrhage (Grade 3) with Hgb 75 g/L (NR: 125 – 170). Treatment included folic acid and iron. On 19 Mar 2015 (Day 259), the study drug was interrupted due to duodenal ulcer hemorrhage. Due to the persistence of duodenal ulcer hemorrhage and duodenal ulcer (Grade 2), the subject was hospitalized on 27 Mar 2015 (Day 267). The esophagogastroduodenoscopy confirmed duodenal ulcer. Treatment included amoxicillin, clarithromycin, esomeprazole, and pantoprazole. On 27 Mar 2015 (Day 267), the subject was transfused with two pints of packed RBC and one pint of packed RBC on 28 Mar 2015 (Day 268) and repeat Hgb was 89 g/L (NR: 100 – 180). On 02 Apr 2015 (Day 273), the subject was discharged from the hospital. On 09 Apr 2015 (Day 280), the subject recovered from duodenal ulcer hemorrhage and did not recover from duodenal ulcer. On 14 Apr 2015 (Day 285), repeat esophagogastroduodenoscopy showed that the duodenal ulcer had not recovered completely. The subject was re-hospitalized for observation of duodenal ulcer and was treated with pantoprazole. On 15 Apr 2015 (Day 286), the subject was planned to be discharged from the hospital and no further information was provided. The Investigator considered duodenal ulcer hemorrhage and duodenal ulcer serious and not related to study drug.

On 08 Jun 2015 (Day 340), tumor response assessment showed disease progression. On 09 Jun 2015 (Day 341), esophagogastroduodenoscopy showed that duodenal ulcer was still present and infiltration of tumor into duodenum was observed. On 09 Jun 2015 (Day 341), the subject was withdrawn from the study due to disease progression and received the last dose on 18 Mar 2015 (Day 258).

On 03 Sep 2015 (Day 427, 169 days after the last dose), the subject died due to disease progression.

Arm: Sorafenib

Subject Number	10031009
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-007995
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Acute kidney injury
AE(s) Leading to Discontinuation	Acute kidney injury

A 64-year-old Chinese male was diagnosed with hepatocellular carcinoma on 15 Jan 2014. Significant medical history included hepatitis B, hypertension, pruritus, and seasonal allergy. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included acetylsalicylic acid, antacids (maalox), ascorbic acid, atenolol, cetirizine, colecalciferol, desloratadine, diphenhydramine, enoxaparin, fish oil, glucose, hydroxyzine, hyzaar, insulin lispro, iron, lactulose, loratadine, losartan, magnesium chloride, magnesium hydroxide, nifedipine, nortase, prednisone, sodium bicarbonate, sodium chloride, and tenoretic. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe and lymphadenopathies at gastrohepatic and porta-hepatis lymph nodes. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 01 Apr 2014 (Day 1), treatment with study drug was initiated.

On 23 Jun 2015 (Day 449), the subject experienced vomiting, fatigue and shortness of breath and was hospitalized with a diagnosis of acute kidney injury (Grade 4). On 24 Jun 2015 (Day 450), the study drug was interrupted due to acute kidney injury. Laboratory tests showed potassium 6.5 mmol/L (NR: 3.2 – 4.9), creatinine 565.76 umol/L (NR: 53.04 – 114.92), and BUN 61.404 mmol/L (NR: 2.499 – 6.426). Chest x-ray showed clear lung fields with no acute cardiopulmonary processes. Electrocardiogram showed sinus bradycardia with tall T-waves and normal P-R interval. The subject underwent hemodialysis and was treated with glucose, insulin lispro, sodium bicarbonate, sodium chloride, and lactulose. On 03 Jul 2015 (Day 459), the subject recovered from acute kidney injury. On 10 Jul 2015 (Day 466), the subject was withdrawn from the study due to acute kidney injury and received the last dose of study drug on 23 Jun 2015 (Day 449). The Investigator considered acute kidney injury serious and not related to the study drug.

On 15 Oct 2015 (Day 563, 114 after the last dose), the subject died due to unknown reason.

Subject Number	10031025
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-013223
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Enterocolitis, Abdominal pain

A 49-year-old African American male was diagnosed with hepatocellular carcinoma on 23 May 2015. Significant medical history included abdominal rigidity, back pain, constipation, flatulence, hepatitis B, spinal laminectomy, and neuralgia (neuropathic pain-feet). Previous anticancer therapy included radiotherapy to T7 vertebral lesion. Prior and concomitant medications included ciprofloxacin, docusate, dronabinol, entecavir, famotidine, gabapentin, hydromorphone, lactulose, lisinopril, metronidazole, morphine, oxycocet, oxycodone, and senna alexandrina. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left and right liver lobes, and right portal vein; bilateral adrenal, T7 vertebral, and lung masses. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 22 Jul 2015 (Day 1), treatment with study drug was initiated.

On 17 Dec 2015 (Day 149), the subject was hospitalized for enterocolitis (Grade 3) with symptoms of abdominal pain, watery diarrhea, nonbloody vomiting, chills, nausea, and decreased oral intake. Abdominal CT scan showed mild abdominal colonic wall thickening consistent with inflammatory colitis. Blood culture was negative for any growth. The subject was treated with ciprofloxacin and metronidazole. On 18 Dec 2015 (Day 150), the study drug was interrupted due to enterocolitis. On 19 Dec 2015 (Day 151), the subject recovered from enterocolitis and was discharged from the hospital. On 20 Dec 2015 (Day 152), the study drug was resumed at the same dose. The Investigator considered enterocolitis serious and not related to the study drug.

On 25 Dec 2015 (Day 157), the subject was hospitalized for abdominal pain (Grade 3). Computerized tomography scan of the chest, abdomen, and pelvis showed extensive wall thickening involving few small bowel loops with less wall thickening involving the colon, numerous bilateral pulmonary nodules, new mild abdominal ascites, and trace pleural effusion. Laboratory tests showed AST 63 U/L (NR: 1 – 50), ALP 146 U/L (NR: 30 – 110), and ALT 56 U/L (NR: 1 – 53). The subject was treated with oxycodone. On 27 Dec 2015 (Day 159), the study drug was interrupted due to abdominal pain. On 30 Dec 2015 (Day 162), the subject recovered from abdominal pain and was discharged from the hospital. On 31 Dec 2015 (Day 163), the study drug was resumed at the same dose. The Investigator considered abdominal pain serious and not related to the study drug.

On 01 Mar 2016 (Day 224), tumor response assessment showed disease progression. On 02 Mar 2016 (Day 225), the subject was withdrawn from study due to disease progression and received the last dose of the study drug on the same day (Day 225).

Subject Number	10101013
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-006646
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Peritoneal haemorrhage
AE(s) Leading to Discontinuation	Peritoneal haemorrhage

A 65-year-old white female was diagnosed with hepatocellular carcinoma on 16 Mar 2015. Significant medical history included dyspnea, fatigue, and hepatitis C. Previous anticancer therapies included wedge resection of right middle and right lower lobes of lung. Prior and concomitant medications included calcium gluconate, ciprofloxacin, dextrose in lactated ringer's, flebobag ring lactate, human albumin, hydromorphone, insulin lispro, loperamide, metoclopramide, morphine, ondansetron, oxycodone, phytomenadione, sodium chloride, tramadol, and vitamin k. At Screening, tumor assessments of target/non-target lesions via MRI showed lesion at left liver lobe; CT scan showed innumerable bilateral pulmonary nodules. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 27 Apr 2015 (Day 1), treatment with study drug was initiated.

On 02 May 2015 (Day 6), the subject was hospitalized for peritoneal hemorrhage (Grade 4) and the subject also experienced fatigue (Grade 1), and pyrexia (Grade 1) with temperature 101.0 °F. Laboratory tests showed Hgb 133 g/L (NR: 121 – 151). On 06 May 2015 (Day 10), CT scan of the abdomen showed rupture of hepatocellular carcinoma with a large volume of hemoperitoneum. Visceral angiogram showed disrupted vasculature and heterogeneous blush in the left hemi liver compatible with ruptured HCC. The subject was transfused with packed red blood cells and underwent transcatheter arterial chemoembolization. The subject was treated with human albumin, calcium gluconate, ciprofloxacin, dextrose in lactated ringer's, metoclopramide, morphine, sodium chloride, ondansetron, vitamin k, hydromorphone, sodium chloride, insulin lispro, flebobag ring lactate, oxycodone, and tramadol. On 07 May 2015 (Day 11), the subject experienced chills (Grade 1), dyspnea (Grade 1), and abdominal pain (increased abdominal pain related to hemoperitoneum; Grade 2). Laboratory tests showed Hgb 78 g/L, INR 1.59 (NR: 0.9 – 1.2), creatinine 174.148 umol/L (NR: 53.04 – 114.92), AST 5176 U/L (NR: 11 – 47), and ALT 2641 U/L (NR: 7 – 53). On 07 May 2015 (Day 11), the subject was withdrawn from the study due to peritoneal hemorrhage and received the last dose of study drug on 06 May 2015 (Day 10). On 11 May 2015 (Day 15), the subject recovered from pyrexia. On 12 May 2015 (Day 16), the subject recovered from peritoneal hemorrhage and the severity of fatigue worsened to Grade 2. On 18 May 2015 (Day 22), the laboratory tests showed INR 1.3 (NR: 0.9 – 1.1), creatinine 44 umol/L (NR: 62 – 124), AST 52 U/L (NR:10 – 36), ALT 69 U/L (NR: 10 – 33). On 06 Jul 2015 (Day 71), the subject recovered from abdominal pain. The subject did not recover from dyspnea, fatigue, and chills. The Investigator considered peritoneal hemorrhage serious and possibly related to the study drug and related to disease progression; abdominal pain nonserious and possibly related to the study drug and related to disease progression; pyrexia nonserious and possibly related to the study drug;

fatigue nonserious and not related to the study drug but related to disease progression; chills and dyspnea nonserious and not related to the study drug.

On 02 Jul 2015 (Day 67), tumor response assessment showed disease progression.

On 11 Feb 2016 (Day 291, 281 days after the last dose), the subject died due to disease progression.

Subject Number	10121004
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-005841
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Spinal fracture, Diarrhoea

A 68-year-old white female was diagnosed with hepatocellular carcinoma on 22 Mar 2013. Significant medical history included drug hypersensitivity (allergy to codeine, quinolone, and sulfa drugs), contrast media allergy (allergy to iodinated radiocontrast dyes), allergy to nickel, anemia, appendectomy, arthritis, facial paralysis, blepharoplasty, mammoplasty, carpal tunnel syndrome, joint arthroplasty (carpometacarpal arthroplasty), cellulitis, spinal fusion surgery, cholecystectomy, chronic low back pain, congestive cardiac failure, depression, eczema, empyema, fatigue, hepatitis C, hypertension, hypothyroidism, cyst removal (incision of left index finger and wrist cyst), insomnia, intermittent constipation, device related infection (intermittent infections of prosthetic right knee joint), urinary incontinence, arthralgia (knee pain), breast cyst excision (left breast), peripheral edema (lower extremity), nausea, obesity, oral lichen planus, hysterectomy (partial), pneumonia, recurrent infections of the right knee, pulmonary resection (right middle partial lobectomy, lung), rosacea, tonsillectomy, total right knee arthroplasty, and abdominoplasty. Previous anticancer therapies included high frequency ablation and radioembolization. Prior and concomitant medications included amlodipine, azelaic acid, betamethasone, cadexomer iodine, calcitonin, celecoxib, cyclobenzaprine, docusate, doxycycline, famotidine, fluocinonide, hydrocortisone, lansoprazole, levothyroxine, lomotil, loperamide, lorazepam, magic mouthwash, methylphenidate, methylprednisolone, metronidazole, miconazole, nystatin, omeprazole, ondansetron, oxycodone, paracetamol, phentermine, potassium, prednisone, prochlorperazine, sodium chloride, torasemide, trazodone, vancomycin, and zolpidem. At Screening, tumor assessments of target/non-target lesions via MRI showed lesions at the right lobe of liver, multiple liver lesions, portal vein tumor thrombus, and porta-hepatis lymphadenopathy; CT scan showed left mediastinal lymphadenopathy. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 02 Jun 2014 (Day 1), treatment with study drug was initiated.

On 16 Jun 2014 (Day 15), the subject experienced oral lichen planus (worsening oral mucositis with lichen planus; Grade 3). On 30 Jun 2014 (Day 29), the subject experienced fatigue (Grade 2), increased blood bilirubin (Grade 2), and bullous dermatitis (Grade 2). Laboratory tests showed total bilirubin 30.3 umol/L (NR: 0 – 18.8) and potassium 3.3 mmol/L (NR: 3.5 – 5). The subject was treated with methylphenidate, potassium, prednisone, and magic mouthwash. On 01 Jul 2014 (Day 30), the study drug was interrupted due to increased blood bilirubin, bullous dermatitis, oral lichen planus, and fatigue. On 07 Jul 2014 (Day 36), the subject recovered from oral lichen planus. On 15 Jul 2014 (Day 44), the subject recovered from increased blood bilirubin. On 16 Jul 2014 (Day 45), the study drug was resumed at reduced dose of 600 mg/day due to fatigue and oral lichen planus. The subject did not recover from fatigue and bullous dermatitis. The Investigator considered oral lichen planus nonserious and possibly

related to study drug; fatigue and bullous dermatitis nonserious and probably related to study drug; increased blood bilirubin nonserious and not related to study drug.

On 18 Jun 2014 (Day 17), the subject experienced rash (skin rash; Grade 1). On 12 Aug 2014 (Day 72), rash worsened to Grade 2. The subject was treated with hydrocortisone. On the same day (Day 72), the study drug was interrupted due to rash. On 25 Aug 2014 (Day 85), the subject recovered from the event. On 26 Aug 2014 (Day 86), the study drug was resumed at reduced dose of 400 mg/day due to rash. The Investigator considered rash nonserious and possibly related to study drug.

On 11 Mar 2015 (Day 283), the subject experienced a fall (Grade 1) and post-traumatic pain (back pain secondary to fall; Grade 2). On 08 Apr 2015 (Day 311), the subject was hospitalized for spinal fracture (vertebral traumatic fracture; Grade 2) and also experienced back pain (related to vertebral traumatic fracture; Grade 2). Treatment included oxycodone, calcitonin, and paracetamol. On the same day (Day 311), the study drug was interrupted due to these events. On 09 Apr 2015 (Day 312), CT scan of lumbar spine confirmed traumatic fracture likely secondary to fall and nuclear magnetic resonance imaging of lumbar spine showed L2 compression fracture. The subject was advised to wear thoracolumbosacral orthosis brace at all times. On 10 Apr 2015 (Day 313), the subject was diagnosed with Clostridium difficile infection (Grade 2) which was confirmed by Clostridium difficile test. The subject was treated with vancomycin. The study drug remained interrupted due to Clostridium difficile infection. On 10 Apr 2015 (Day 313), the subject recovered with sequelae from spinal fracture and back pain and was discharged from the hospital. On 15 Apr 2015 (Day 318), the study drug was resumed at the same dose. On 03 Jun 2015 (Day 367), a repeat enteric pathogen bacterial culture test and Clostridium difficile toxin were negative and the subject recovered from Clostridium difficile infection. The subject did not recover from post-traumatic pain. The Investigator considered spinal fracture serious and not related to study drug; fall, post-traumatic pain, back pain, and Clostridium difficile infection nonserious and not related to study drug.

On 24 May 2015 (Day 357), the subject experienced diarrhea (Grade 3) which started as Grade 2 on 01 Dec 2014 (Day 183). On 03 Jun 2015 (Day 367), the subject was hospitalized for diarrhea and also experienced metabolic encephalopathy (Grade 2) and decreased weight (Grade 3) with weight of 70.5 kg (Baseline: 90.1 kg). Treatment included lomotil and loperamide. On 03 Jun 2015 (Day 367), the study drug was interrupted due to diarrhea and metabolic encephalopathy. On 05 Jun 2015 (Day 369), the subject recovered from metabolic encephalopathy and diarrhea, and was discharged from the hospital. The subject did not recover from decreased weight. The Investigator considered diarrhea serious and possibly related to study drug; decreased weight and metabolic encephalopathy nonserious and possibly related to study drug.

On 08 Jul 2015 (Day 402), the subject withdrew consent from the study and received the last dose on 02 Jun 2015 (Day 366).

Subject Number	10161005
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-010797
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Pathological fracture, Tumour pain
AE(s) Leading to Discontinuation	Pathological fracture, Tumour pain

A 58-year-old white female was diagnosed with hepatocellular carcinoma on 14 Oct 2014. Significant medical history included abdominal pain, decreased appetite, anxiety, right eye operation, intervertebral disc operation, intervertebral disc compression, constipation, hepatitis C, hysterectomy, hepatic cirrhosis, nausea, psoriasis, eye injury (right eye injury), muscle strain (right shoulder strain), blindness unilateral (right eye), tobacco user, and uterine leiomyoma. Previous anticancer therapies included transcatheter arterial chemoembolization (2x). Prior and concomitant medications included alprazolam, bactrim, cefalexin, docusate, dronabinol, enoxaparin, fentanyl, hydromorphone, lactulose, magnesium sulfate, nicotine, ondansetron, oxycodone, pantoprazole, potassium, propofol, and sodium chloride. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left and right liver lobes. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 08 May 2015 (Day 1), treatment with study drug was initiated.

On 21 May 2015 (Day 14), the subject experienced increased hepatic enzyme (Grade 1) with ALP 219 U/L (NR: 30 – 115), ALT 118 U/L (NR: 10 – 33), and AST 189 U/L (NR: 10 – 36). On 25 May 2015 (Day 18), the subject experienced palmar-plantar erythrodysesthesia syndrome (Grade 3) and oral mucosal blistering (Grade 3). On 26 May 2015 (Day 19), the study drug was interrupted due to increased hepatic enzyme, palmar-plantar erythrodysesthesia syndrome, and oral mucosal blistering. On 28 May 2015 (Day 21), increased hepatic enzymes worsened to Grade 3 and repeat laboratory tests showed ALP 212 U/L, ALT 193 U/L, and AST 258 U/L. On 05 Jun 2015 (Day 29), the subject recovered from palmar-plantar erythrodysesthesia syndrome and oral mucosal blistering. On the same day (Day 29), the study drug resumed at a reduced dose of 600 mg/day due to palmar-plantar erythrodysesthesia syndrome. The subject did not recover from increased hepatic enzyme. The Investigator considered increased hepatic enzyme, palmar-plantar erythrodysesthesia syndrome, and oral mucosal blistering nonserious and probably related to the study drug.

On 15 Jun 2015 (Day 39), the subject experienced another episode of palmar-plantar erythrodysesthesia syndrome (Grade 2). On 16 Jun 2015 (Day 40), the study drug was interrupted due to this event. On 18 Jun 2015 (Day 42), the subject recovered from this event and the study drug was resumed at a reduced dose of 400 mg/day due to palmar-plantar erythrodysesthesia syndrome. The Investigator considered this event nonserious and probably related to the study drug.

On 25 Sep 2015 (Day 141), the subject was hospitalized for pathological fracture (right humerus metastatic hepatocellular carcinoma lesion; Grade 3), and tumor pain

(RUE pain R/T right humeral lesion/tumor; Grade 3). Nuclear magnetic resonance imaging of right shoulder showed heterogeneous lesion of the visualized right humeral shaft demonstrating mild extraosseous soft tissue component in the medial upper arm highly suggestive of malignancy, which may be a primary bone malignancy or an osseous metastasis. Nuclear magnetic resonance imaging of humerus showed large enhancing mass lesion of the proximal humeral diaphysis with no displaced pathologic fracture. On the same day (Day 141), tumor response assessment showed disease progression. The subject was treated with enoxaparin, oxycodone, and hydromorphone. On 28 Sep 2015 (Day 144), the subject was withdrawn from the study due to pathological fracture, and tumor pain and received the last dose of the study drug on the same day (Day 144). On 06 Oct 2015 (Day 152), the subject had biopsy of the right proximal humerus which showed positive for metastatic hepatocellular carcinoma and underwent an intramedullary rod insertion. On 26 Oct 2015 (Day 172), the subject recovered from tumor pain and pathological fracture. On 23 Nov 2015 (Day 200), the subject had palliative radiation therapy to right humerus. The Investigator considered pathological fracture and tumor pain serious and not related to study drug but related to disease progression.

On 16 Mar 2016 (Day 314, 170 days after the last dose), the subject died due to disease progression.

Subject Number	12011006
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01567-CLI-JP
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Pyrexia

A 69-year-old Japanese male was diagnosed with hepatocellular carcinoma in Nov 2012. Significant medical history included carotid arteriosclerosis, hypertension, and hepatitis B (post infection with HBV). Previous anticancer therapies included hepatectomy, and transcatheter arterial chemoembolization (5x). Prior and concomitant medications included acetylsalicylic acid, albumin tannate, amlodipine, berberine, cefoperazone, diazepam, dimeticone, drugs for functional gastrointestinal disorder, enterococcus faecalis, enzymes (excelase combination tablets), lidocaine, loperamide, magnesium oxide, pronase, rabeprazole, scopolia carniolica, sodium bicarbonate, urea, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left liver lobe and diaphragm. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 14 Aug 2014 (Day 1), treatment with study drug was initiated.

On 29 Aug 2014 (Day 16), the subject experienced pyrexia (Grade 1) with body temperature of 38 – 39 ºC while in the clinic. Laboratory tests showed CRP 16.5 mg/L (NR: 0 – 5) and WBC 3.8 x10^9/L (NR: 3.7 – 11). On 01 Sep 2014 (Day 19), the subject was hospitalized for pyrexia and was treated with cefoperazone. Repeat laboratory tests showed CRP 90.7 mg/L (NR: 0 – 3) and WBC 4.5 x10^9/L (NR: 3.5 – 9.7). The study drug was interrupted due to pyrexia. On 05 Sep 2014 (Day 23), the study drug was resumed at the same dose. On 10 Sep 2014 (Day 28), the subject recovered from pyrexia. Laboratory tests showed CRP 11.7 mg/L (NR: 0 – 5) and WBC 3.5 x10^9/L (NR: 3.7 – 11). On the same day (Day 28), the subject was discharged from the hospital. The Investigator considered pyrexia serious and not related to study drug.

On 28 Oct 2014 (Day 76), the subject experienced diarrhea (Grade 2). Treatment included Enterococcus faecalis, berberine, scopolia carniolica, albumin tannate, and loperamide. On 28 Apr 2015 (Day 258), diarrhea improved to Grade 1. On the same day (Day 258), the study drug was reduced to a dose of 400 mg/day due to this event. On 29 Jun 2015 (Day 320), the subject recovered from diarrhea. The Investigator considered diarrhea nonserious and possibly related to the study drug.

On 19 May 2015 (Day 279), tumor response assessment showed disease progression, and the subject was withdrawn from the study due to disease progression. The subject received the last dose of study drug on 18 May 2015 (Day 278).

Subject Number	12031010
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-013124
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Ascites, Cataract

A 63-year-old Japanese male was diagnosed with hepatocellular carcinoma on 05 Sep 2011. Significant medical history included cataract, cholelithiasis, chronic hepatitis C, colon adenoma, diabetes mellitus, diabetic retinopathy, lithotripsy, hyperplastic cholecystopathy, gastritis, hepatic cirrhosis, hypertension, hypoalbuminemia, hypokalemia, hemorrhoids, cerebellar infarction, atrial fibrillation, pheochromocytoma, thyroid mass, urinary calculus, and vitrectomy. Previous anticancer therapies included transcatheter arterial chemoembolization and high frequency ablation. Prior and concomitant medications included allopurinol, betamethasone, bromfenac, cefazolin, difluprednate, dimeticone, falkamin, fluorometholone, furosemide, gatifloxacin, glycyrrhizic acid, influenza vaccine, insulin detemir, insulin glargine, insulin lispro, levofloxacin, lidocaine, loperamide, mydrin p, nifedipine, olmesartan, pa, phenylephrine, potassium, pronase, rabeprazole, ropivacaine, sodium bicarbonate, solita-t1, spironolactone, tolvaptan, torasemide, urea, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right, quadrate, and left liver lobes. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

On 25 Sep 2014 (Day 1), treatment with study drug was initiated.

On 08 Oct 2014 (Day 14), the subject experienced proteinuria (Grade 2) and hypertension (Grade 3). Urine protein dipstick was 3+ and blood pressure was 172/99 mmHg. The subject was treated with nifedipine and olmesartan. The subject did not recover from hypertension and proteinuria. The Investigator considered hypertension and proteinuria nonserious and probably related to the study drug.

On 15 Jul 2015 (Day 294), the subject experienced increased blood creatinine (Grade 1) with creatinine 95.472 umol/L (NR: 53.04 – 88.4). On 12 Aug 2015 (Day 322), the subject experienced peripheral edema (edema legs; Grade 1). The subject was treated with torasemide, spironolactone, and furosemide. The subject did not recover from increased blood creatinine and peripheral edema. The Investigator considered increased blood creatinine nonserious and possibly related to the study drug; peripheral edema nonserious and probably related to the study drug.

On 21 Aug 2015 (Day 331), the subject experienced ascites (unspecified; Grade 2) confirmed by routine abdominal CT scan. On 20 Nov 2015 (Day 422), the study drug was reduced to a dose of 400 mg/day due to ongoing proteinuria and ascites. Repeat laboratory tests showed urine protein dipstick 4+, albumin 32 g/L (NR: 35 – 55), BUN 11.78 mmol/L (NR: 1.78 – 7.14), and creatinine 141 umol/L (NR: 62 – 124). On 21 Dec 2015 (Day 453), the subject was hospitalized for ascites and was treated with olmesartan, furosemide, spironolactone, and tolvaptan. On 09 Jan 2016 (Day 472), the subject was recovering from ascites and was

discharged from the hospital. The Investigator considered ascites serious and probably related to the study drug; proteinuria nonserious and probably related to the study drug.

On 16 Mar 2016 (Day 539), the subject had cataract (left cataract aggravated; Grade 3) and was hospitalized on 28 Mar 2016 (Day 551). Treatment included gatifloxacin, betamethasone, bromfenac, mydrin P, lidocaine, levofloxacin, phenylephrine, ropivacaine, solita-t1, cefazolin, and fluorometholone. The subject underwent cataract operation. On 02 Apr 2016 (Day 556), the subject recovered from cataract and was discharged from the hospital. The Investigator considered cataract serious and not related to the study drug.

On 04 Apr 2016 (Day 558), tumor response assessment showed disease progression. On 20 Apr 2016 (Day 574), the subject was withdrawn from the study due to disease progression. The subject received the last dose of study drug on 19 Apr 2016 (Day 573).

On 18 Jul 2016 (Day 663, 90 days after the last dose), the subject died due to unknown reason.

Subject Number	12041006
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-001316
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Gastric haemorrhage, Pleural effusion
AE(s) Leading to Discontinuation	General physical health deterioration

A 71-year-old Japanese female was diagnosed with hepatocellular carcinoma on 27 Jul 2005. Significant medical history included chronic hepatitis C, diabetes mellitus, and esophageal varices. Previous anticancer therapy included radiofrequency ablation and transcatheter arterial chemoembolization. Prior and concomitant medications included alginic acid, carbohydrates w/potassium chloride/sodium, chlorpromazine, cobamamide, difluprednate, dimeticone, furosemide, glimepiride, guaiazulene, human albumin, hyoscine, lidocaine, loperamide, omeprazole, prochlorperazine, pronase, rabeprazole, ramelteon, ranitidine, ringer-lactatis, risperidone, scopolia carniolica, sodium bicarbonate, sodium chloride, solita-t1, spironolactone, trazodone, unacid, urea, ursodeoxycholic acid, and voglibose. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right and quadrate liver lobes. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

On 06 Mar 2014 (Day 1), treatment with study drug was initiated.

On 01 Apr 2014 (Day 27), the subject experienced decreased appetite (Grade 1) and on 08 Apr 2014 (Day 34) the study drug was interrupted. On 30 Apr 2014 (Day 56), the subject recovered and on 01 May 2014 (Day 57) the study drug was resumed at a reduced dose of 400 mg/day due to decreased appetite. The Investigator considered decreased appetite nonserious and possibly related to study drug.

On 20 Oct 2014 (Day 229), the subject experienced nausea (Grade 2), decreased appetite (Grade 2) and was treated with prochlorperazine. On 21 Oct 2014 (Day 230), study drug was interrupted due to nausea and decreased appetite. On 28 Oct 2014 (Day 237), the subject was hospitalized for gastric hemorrhage (Grade 3) confirmed by upper gastrointestinal tract endoscopy. On the same day (Day 237), the subject also experienced general physical health deterioration (Grade 3) and the severity of nausea improved to Grade 1. Laboratory test showed Hgb 70 g/L (NR: 120 – 150). The subject underwent red blood cell transfusion and was treated with sodium chloride, ringer-lactatis, omeprazole, solita-t1, carbohydrates w/potassium chloride/sodium, alginic acid, and rabeprazole. On 29 Oct 2014 (Day 238), the subject recovered from nausea. On 03 Nov 2014 (Day 243), the subject experienced pleural effusion (Grade 2) confirmed by chest x-ray. On 07 Nov 2014 (Day 247), the subject underwent aspiration of pleural cavity and was treated with oxygen supplementation, furosemide, and spironolactone. On 11 Nov 2014 (Day 251), the subject experienced pneumonia (Grade 2) and the subject was treated with unacid. On the same day (Day 251), the subject was withdrawn from the study due to general physical health deterioration secondary to clinical disease progression and received the last dose of study drug on 20 Oct 2014 (Day 229). On 14 Nov 2014 (Day 254), the subject's decreased appetite improved to Grade 1. The subject did not recover from gastric hemorrhage,

pleural effusion, decreased appetite, pneumonia, and general physical health deterioration. On 18 Nov 2014 (Day 258), tumor response assessment showed disease progression. The Investigator considered gastric hemorrhage and pleural effusion serious and not related to study drug; nausea nonserious and possibly related to study drug; general physical health deterioration nonserious and not related to study drug; decreased appetite, pneumonia nonserious and not related to study drug.

On 22 Sep 2015 (Day 566, 337 days after the last dose), the subject died due to disease progression.

Subject Number	12061005
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-000425
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Drug eruption, Haemoglobin decreased
AE(s) Leading to Discontinuation	Drug eruption

A 70-year-old Japanese male was diagnosed with hepatocellular carcinoma on 16 May 2012. Significant medical history included gastrectomy, chronic gastritis, contrast media allergy, eczema asteatotic, gastric ulcer, gastroesophageal varices, hepatitis C, hyperuricemia, hepatic cirrhosis, and hypertonic bladder. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included allopurinol, amphotericin b, carbohydrates w/potassium chloride/sodium, diclofenac, fexofenadine, rabeprazole, triamcinolone, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via MRI showed lesions at right and left lobes of the liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 6.

On 10 Sep 2014 (Day 1), treatment with study drug was initiated.

On 22 Sep 2014 (Day 13), the subject was hospitalized for drug eruption (Grade 2) described as erythema all over the body. The subject was treated with fluid replacement. On 23 Sep 2014 (Day 14), the study drug was interrupted due to drug eruption. On 25 Sep 2014 (Day 16), the subject experienced decreased platelet count (Grade 1) with platelet count 80 x10^9/L (NR: 125 – 375) and on the following day (Day 17), the subject experienced oral candidiasis (Grade 2). The subject was treated with carbohydrates w/potassium chloride/sodium, and amphotericin b gargle and study drug remained interrupted due to oral candidiasis. On 03 Oct 2014 (Day 24), the subject was withdrawn from the study due to drug eruption. The subject received the last dose of the study drug on 22 Sep 2014 (Day 13). On 03 Oct 2014 (Day 24), the subject recovered from drug eruption, decreased platelet count with platelet count 152 x10^9/L (NR: 141 – 327), and oral candidiasis. On 06 Oct 2014 (Day 27), the subject's hospitalization was prolonged due to decreased hemoglobin (Grade 2) with Hgb 88 g/L (NR: 125 – 170). On 07 Oct 2014 (Day 28), the subject recovered from decreased hemoglobin with Hgb 99 g/L (NR: 130 – 170). The Investigator considered drug eruption serious and probably related to the study drug; decreased hemoglobin serious and possibly related to the study drug; decreased platelet count and oral candidiasis nonserious and probably related to the study drug.

On 07 Feb 2016 (Day 516, 503 days after the last dose), the subject died due to disease progression.

Subject Number	12061007
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-003373
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Plasma cell myeloma, Hepatic function abnormal

A 67-year-old Japanese male was diagnosed with hepatocellular carcinoma on 12 Dec 2013. Significant medical history included cholecystectomy, chronic hepatitis, gastric polyps, hypertension, hyperuricemia, large intestinal polypectomy, hepatic cirrhosis, and benign monoclonal hypergammaglobulinemia. Previous anticancer therapies included hepatectomy and transcatheter arterial chemoembolization. Prior and concomitant medications included amlodipine, buprenorphine, diclofenac, dimeticone, febuxostat, gentamicin, heparinoid, hyoscine, lansoprazole, lidocaine, losartan, loxoprofen, ms onshippu, prednisolone, pregabalin, teprenone, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left liver lobe. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 6.

On 26 Nov 2014 (Day 1), treatment with study drug was initiated.

On 07 Jan 2015 (Day 43), the subject experienced abnormal hepatic function (Grade 2). Laboratory tests showed ALP 132 U/L (NR: 43 – 115), ALT 108 U/L (NR: 10 – 40), AST 219 U/L (NR: 10 – 43), and GGT 313 U/L (NR: 10 – 49). On the same day (Day 43), the study drug was reduced to a dose of 400 mg/day due to abnormal hepatic function. The subject did not recover from this event. The Investigator considered abnormal hepatic function nonserious and possibly related to the study drug.

On 15 Jan 2015 (Day 51), the subject had bone marrow biopsy for suspected multiple myeloma which showed 5.2% of plasma cell count; flow cytometry showed clonal plasma cells, hypocellular bone marrow, with plasma cells expressing abnormal surface markers. Laboratory tests showed IgA 58.5 mg/dL (NR: 110 – 410) and IgG 4212 mg/dL (NR: 870 – 1700). On 19 Jan 2015 (Day 55), laboratory tests showed RBC 2.79 x10^12/L (NR: 4 – 5.6), WBC 3.4 x10^9/L (NR: 3.7 – 11), Hgb 106 g/L (NR: 125 – 170), platelet count 109 x10^9/L (NR: 125 – 375), and creatinine 53 umol/L (NR: 62 – 124). On 22 Jan 2015 (Day 58), the subject was diagnosed with plasma cell myeloma (multiple myeloma; Grade 1). No treatment was provided. The study drug dose was not changed. The subject did not recover from this event. The Investigator considered plasma cell myeloma serious (important medical event) and not related to the study drug.

On 19 Feb 2015 (Day 86), the study drug was interrupted due to abnormal hepatic function (Grade 2). On 23 Feb 2015 (Day 90), abdominal ultrasound showed multiple hyperechoic masses and space occupying lesions, no abnormalities in gallbladder, pancreas or kidney, and mild splenomegaly. On 02 Mar 2015 (Day 97), the severity of abnormal hepatic function worsened to Grade 3. Laboratory tests showed total bilirubin 53.01 umol/L (NR: 5.13 – 18.81), ALT 753 U/L (NR: 8 – 42), and AST 1074 U/L (NR: 13 – 33). A CT scan of abdomen showed